



Catalytic, Stereoselective Fluorination Reactions

Citation

Mennie, Katrina Marie. 2019. Catalytic, Stereoselective Fluorination Reactions. Doctoral dissertation, Harvard University, Graduate School of Arts & Sciences.

Link

<http://nrs.harvard.edu/urn-3:HUL.InstRepos:41121278>

Terms of use

This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material (LAA), as set forth at

<https://harvardwiki.atlassian.net/wiki/external/NGY5NDE4ZjgzNTc5NDQzMGIzZWZhMGFIOWI2M2EwYTg>

Accessibility

<https://accessibility.huit.harvard.edu/digital-accessibility-policy>

Share Your Story

The Harvard community has made this article openly available.
Please share how this access benefits you. [Submit a story](#)

Catalytic, Stereoselective Fluorination Reactions

A dissertation presented

by

Katrina Marie Mennie

to

The Department of Chemistry and Chemical Biology

in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

in the subject of

Chemistry

Harvard University

Cambridge, Massachusetts

September 2018

© 2018 Katrina Marie Mennie

All rights reserved.

Catalytic, Stereoselective Fluorination Reactions**Abstract**

In Chapter 1, we describe a general strategy for 1,3-oxidation of cyclopropanes using aryl iodine(I–III) catalysis, with emphasis on 1,3-difluorination reactions. These reactions make use of practical, commercially available reagents and can engage a variety of substituted cyclopropane substrates. Analysis of crystal and solution structures of several of the products reveals the consistent effect of 1,3-difluorides in dictating molecular conformation through dipole minimization effects. Stereochemical analysis of the 1,3-difluorination reaction suggests a mechanism of cyclopropane activation by I^{III} analogous to that of alkene activation by I^{III}. The generality of this catalytic, cyclopropane C–C bond activation strategy for 1,3-difunctionalization is demonstrated in the synthesis of 1,3-fluoroacetoxy, 1,3-diol, 1,3-amino alcohol and 1,3-diamine products.

In Chapter 2, we report the stereoselective synthesis of *syn*-β-fluoroaziridine building blocks *via* chiral aryl iodide-catalyzed fluorination of allylic amines. This method employs HF–pyridine as a nucleophilic fluoride source together with *m*CPBA as a stoichiometric oxidant and affords access to aryethylamine derivatives featuring fluorine-containing stereocenters with high diastereo- and enantioselectivity. Catalyst-controlled diastereoselectivity in the fluorination of chiral allylic amines enables the preparation of highly enantioenriched 1,3-difluoro-2-amines bearing three contiguous stereocenters. This enantioselective, catalytic method is applied successfully to other classes of multifunctional alkene substrates to afford *anti*-β-fluoropyrrolidines as well as a variety of 1,2-oxyfluorinated products.

Finally, in Chapter 3, we discuss a strategy for asymmetric catalysis of carbocationic rearrangements using alkyl iodanes as stereodefined carbocation surrogates. This approach is demonstrated within the context of Wagner-Meerwein rearrangements of β -cumyl-, β -*t*-butyl and β -*i*-propyl-substituted styrenes. Using a nucleophilic fluoride source, this method affords access to highly enantioenriched 1,3-difluorinated products. Hammett, kinetic isotope effect and computational studies reveal that the enantiodetermining step can vary between intermolecular fluoride attack and intramolecular 1,2-migration depending on the nature of the migrating group. As a competition between external and internal nucleophilic attack is prevalent in iodine(III)-mediated difunctionalization reactions of alkenes, these studies also potentially provide general insight into the mechanisms involved in iodine(III) chemistry.

Table of Contents

Abstract	iii
Table of Contents	v
Acknowledgments	vii
List of Abbreviations	ix
Chapter 1. Catalytic 1,3-Difunctionalization <i>via</i> Oxidative C–C Bond Activation	1
1.1 Introduction	1
1.1.1 Electrophilic Addition to Cyclopropanes	2
1.1.2 Conformational Properties of 1,3-Difunctionalized Molecules	9
1.2 Development of Catalytic 1,3-Difunctionalization Reactions of	
Cyclopropanes	11
1.2.1 Development of a Catalytic 1,3-Difluorination Reaction	11
1.2.2 Stereochemical Analysis of the 1,3-Difluorination Reaction	17
1.2.3 Computational Modeling of Cyclopropane Activation by I ^{III}	18
1.2.4 Conformational Analysis of 1,3-Difluorinated Molecules	19
1.2.5 Extension of the 1,3-Difluorination Reaction Protocol	20
1.2.6 Development of General 1,3-Oxidation of Cyclopropanes	21
1.3 Conclusion	24
1.4 Experimental Section	25
Chapter 2. Catalytic Diastereo- and Enantioselective Fluoroamination of	
Alkenes	146
2.1 Introduction	146
2.1.1 Physical and Biological Properties of β -Fluoroamines	147

2.1.2 Fluoroamination of Alkenes	148
2.2 Development of Enantioselective Fluoroamination Reactions	157
2.2.1 Development of a β -Fluoroaziridination Reaction	157
2.2.2 Extension of the Fluoroamination Reaction Protocol	163
2.2.3 Development of Enantioselective 1,2-Oxyfluorination Reactions	165
2.3 Conclusion	167
2.4 Experimental Section	168
Chapter 3. Asymmetric Fluorinative Wagner–Meerwein Rearrangements Catalyzed by Hypervalent Iodine	307
3.1 Introduction	307
3.1.1 The Wagner–Meerwein Rearrangement	308
3.1.2 Catalytic, Enantioselective Semi-Pinacol Rearrangements	309
3.1.3 Mechanistic Questions in Enantioselective Hypervalent Iodine Chemistry	312
3.2 Development and Mechanistic Study of Catalytic, Enantioselective Fluorinative Wagner–Meerwein Rearrangements	314
3.2.1 Reaction Development	314
3.2.2 Hammett, Kinetic Isotope Effect and Computational Studies	318
3.3 Conclusion	328
3.4 Experimental Section	330

Acknowledgements

I would first like to express my sincere gratitude to my advisor, Professor Eric Jacobsen, for his mentorship, patience and support over the past four years. Eric's curiosity, scientific rigor and openness to new ideas have made his laboratory a truly unique place in which to develop as a scientist, and it has been my great privilege to learn from him.

I would also like to thank the rest of my thesis committee: Professor Emily Balskus and Professor Theodore Betley, not only for their encouragement and insight, but also for challenging me to think more deeply and critically about my research.

I am extremely fortunate to have benefited from a number of very productive and enjoyable collaborations over the past few years. Dr. Steven Banik took me under his wing in my younger graduate student days and was instrumental in my development as an independent scientist. His scientific legacy to the Jacobsen Group is incontrovertible, and I am sure that great things await him in his future career. It was also my great pleasure to collaborate with and mentor a number of younger students. Elaine Reichert joined me at the start of the fluoroamination project. It was very gratifying to witness her growth as a scientist, and her quirky personality definitely added a certain *je ne sais quoi* to the lab. Hayden Sharma helped transform the Wagner–Meerwein rearrangement project into something beyond what I had initially envisaged thanks to his thoughtful analysis and mechanistic insightfulness. His enthusiasm, effervescence and unique sense of humor made working together a very rewarding experience.

The Jacobsen Group is an eclectic cast of characters, and it has been my honor to learn from them as scientists and get to know them as people. Samuel Levi, affectionately dubbed 'chatterbox', was my classmate and good friend. Over the last four years, I have greatly

appreciated his infectious passion for science as well as his gregarious (and rather mischievous) nature. A mutual love for obscure trivia and macabre sense of humor made overlapping with Andrew Bendelsmith a great pleasure. I have always been struck by not only his encyclopedic knowledge of chemistry but also his selfless desire to teach and help others. Prithvi Vangal, aka ‘Peepers’, was a constant source of optimism and fun. I could always count on him to make me smile and I greatly enjoyed sharing a bay with him.

The support and encouragement of my family (Mum, Dad, Ross and Penny) have been of huge importance to me, not only throughout my graduate career but also throughout my entire life. My Mum, in particular, has been extraordinary in terms of her love and sacrifice. Without her, this thesis would not have been possible.

List of Abbreviations

A	neighboring group
$[\alpha]_D^T$	specific rotation at T (°C) and 589 nm
Å	Angstrom
A _{1,3}	1,3-allylic
Ac	acetyl
acac	acetylacetonate
<i>anti</i>	L., against, opposite
Ar	aryl
aq.	aqueous
B3LYP	Becke-3-Lee-Yang-Parr
BAr ^F	tetrakis[(3,5-trifluoromethyl)phenyl]borate
BC	bathocuproine
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bu	butyl
cal	calorie
°C	degrees Celsius
<i>cis</i>	L., on the same side
COMU	(1-Cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate
Cy	cyclohexyl

D	deuterium, after solvent = solvent- d_n
δ	chemical shift in parts per million
dba	dibenzylideneacetone
DCM	dichloromethane
DCE	1,2-dichloroethane
DEPT	distortionless enhancement by polarization transfer
(DHQ) ₂ PHAL	hydroquinine 1,4-phthalazinediyl diether
DIAD	diisopropyl azodicarboxylate
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
d.r.	diastereomeric ratio
E	energy, electrophile
<i>E</i>	Ger., entgegen
EDC	<i>N</i> -(3-dimethylaminopropyl)- <i>N</i> -ethylcarbodiimide
EDG	electron-donating group
e.e.	enantiomeric excess
<i>ent</i>	enantiomeric
equiv	equivalent
e.r.	enantiomeric ratio
ESI	electrospray ionization

Et	ethyl
EWG	electron-withdrawing group
g	gram
<i>g</i>	<i>gauche</i>
G	Gibbs free energy
GC	gas chromatography
h	hour
H	enthalpy
HOBt	1-hydroxybenzotriazole hydrate
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
Hz	Hertz
<i>i</i>	iso
IR	infrared
<i>J</i>	coupling constant
<i>k</i>	rate constant
K	Kelvin
KIE	kinetic isotope effect
λ	wavelength
LUMO	LUMO
<i>m</i>	<i>meta</i>
M	molarity
M06-2X	Minnesota 2006 hybrid meta density functional theory

<i>m</i> CPBA	3-chloroperbenzoic acid
Me	methyl
min.	minute(s)
mol	molar
MQF	multiple-quantum filtered
M _r	relative molecular mass
Ms	mesyl
MS	mass spectroscopy
<i>n</i>	<i>normal</i>
NMR	Nuclear Magnetic Resonance
Ns	nosyl
Nu	nucleophile
<i>o</i>	<i>ortho</i>
[O]	oxidant
OTf	triflate
<i>p</i>	<i>para</i>
Ph	phenyl
pin	pinacolato
Piv	pivaloate
Pr	propyl
pyr	pyridine
<i>R</i>	rectus
rt	room temperature

s	second
S	entropy
<i>S</i>	sinister
sat.	saturated
SM	starting material
S _N 1	unimolecular nucleophilic substitution
S _N 2	bimolecular nucleophilic substitution
<i>syn</i>	D., with, together
t	time
<i>t</i>	<i>tert</i> , tertiary
t _R	retention time
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBS	<i>tert</i> -butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
Tol	tolyl
TLC	thin-layer chromatography
<i>trans</i>	L., on the opposite side
Ts	tosyl
UV	ultraviolet

V	volume
wt. %	percentage by weight
Z	Ger., zusammen

Chapter 1

Catalytic 1,3-Difunctionalization *via* Oxidative C–C Bond Activation

1.1 Introduction

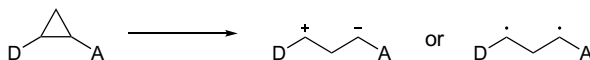
Electronegative substituents arrayed in 1,3-relationships along saturated carbon frameworks can exert strong influence over molecular conformation due to dipole minimization effects. Simple and general methods for the incorporation of such functional group relationships could thus provide a valuable tool for modulating molecular shape. Described in this chapter is a general strategy for the 1,3-oxidation of cyclopropanes based on aryl iodine(I–III) catalysis, with emphasis on 1,3-difluorination reactions. These reactions make use of practical, commercially available reagents and can engage a variety of substituted cyclopropane substrates. Analysis of crystal and solution structures of several of the products reveals the consistent effect of 1,3-difluorides in dictating molecular conformation. Stereochemical analysis of the 1,3-difluorination reaction suggests a mechanism of cyclopropane activation by I^{III} analogous to that of alkene activation by I^{III}. The generality of this catalytic, cyclopropane C–C bond activation strategy for 1,3-difunctionalization is demonstrated in the synthesis of 1,3-fluoroacetoxy, 1,3-diol, 1,3-amino alcohol and 1,3-diamine products.

1.1.1 Electrophilic Addition to Cyclopropanes

In an effort to develop efficient and general methods for the installation of 1,3-difunctionality, we undertook an investigation of the strategies employed for the direct activation of substituted cyclopropanes.

Cyclopropanes can undergo a variety of transformations due to the high strain energy and unique bonding imposed by the three-membered ring. The high strain energy of cyclopropanes (27.4–29.0 kcal/mol)¹ is the result of a combination of torsional strain due to unavoidable eclipsing interactions and bond-angle strain; it is this high energy content that renders most ring-opening reactions of cyclopropanes thermodynamically downhill. Cyclopropane C–C bonds have significant π -type character,² making them analogous, in some respects, to the C=C bonds of alkenes.

The majority of approaches to cyclopropane ring opening have relied on vicinal donor–acceptor (DA) substitution on the strained ring (Scheme 1.1).³



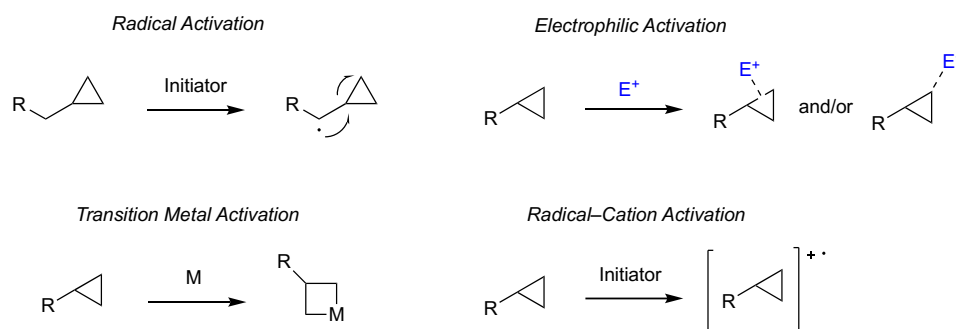
Scheme 1.1 Ring opening of DA cyclopropanes.

¹ Khoury, P.R.; Goddard, J.D.; Tam, W. *Tetrahedron* **2004**, *60*, 8103–8112.

² A number of molecular orbital models have been proposed in order to account for the unique bonding of cyclopropanes. For Walsh’s model, which describes the C–C bonds as linear combinations of three sp^2 -type orbitals, see: (a) Walsh, A.D. *Trans. Faraday Soc.* **1949**, *45*, 179–190. For the Coulson-Moffitt model, which argues for the formation of “bent banana bonds” from sp^3 hybrids with enhanced p-type character, see: (b) Coulson, C.A.; Moffitt, W.E. *J. Chem. Phys.* **1947**, *15*, 151. For a review discussing both models, see: (c) de Meijere, A. *Angew. Chem. Int. Ed.* **1979**, *18*, 809–886. For a more recent computational analysis using valence bond theory, see: (d) Hamilton, J.G.; Palke, W.E. *J. Am. Chem. Soc.* **1993**, *115*, 4159–4164.

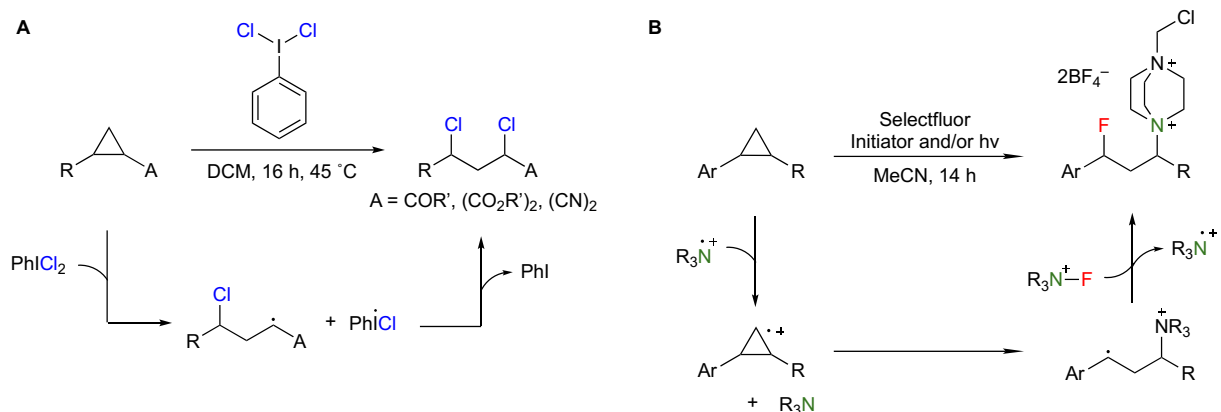
³ For representative reviews, see: (a) Grover, H.K.; Emmett, M.R.; Kerr, M.A. *Org. Biomol. Chem.* **2015**, *13*, 655–671. (b) Schneider, T.F.; Kaschel, J.; Werz, D.B. *Angew. Chem. Int. Ed.* **2014**, *53*, 5504–5523. (c) Cavitt, M.A.; Phun, L.H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804–818. (d) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196.

Strategies for non-DA cyclopropane functionalization have invoked radical,⁴ electrophilic, transition metal⁵ and radical-cation activation (Scheme 1.2).



Scheme 1.2 Strategies for non-DA cyclopropane functionalization.

For example, 1,3-dichlorination of acceptor cyclopropanes using iodobenzene dichloride as a Cl_2 source has been reported to proceed *via* a radical mechanism (Scheme 1.3A).⁶ A catalytic method that achieves 1,3-aminofluorination of arylcyclopropanes with Selectfluor through the intermediacy of radical cations has also been reported recently (Scheme 1.3B).⁷



Scheme 1.3 A) An example of I(III)-mediated ring opening of acceptor cyclopropanes. **B)** An example of 1,3-aminofluorination of arylcyclopropanes *via* radical cations.

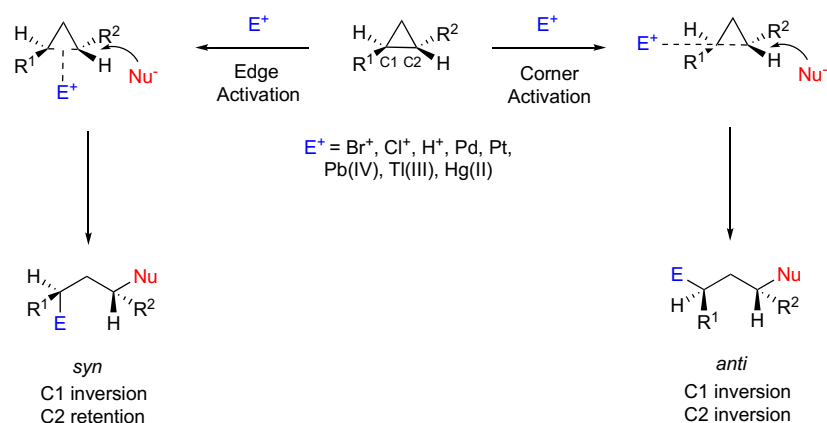
⁴ (a) Nonhebel, D.C. *Chem. Soc. Rev.* **1993**, 22, 347–359. (b) Bowry, V.W.; Lusztyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* **1991**, 113, 5687–5698.

⁵ Souillart, L.; Cramer, N. *Chem. Rev.* **2015**, 115, 9410–9464.

⁶ Garye, L.K.; Barkawitz, P.; Jones, P.G.; Werz, D.B. *Org. Lett.* **2014**, 16, 5804–5807.

⁷ Pitts, C.R.; Ling, B.; Snyder, J.A.; Bragg, A.E.; Lectka, T. *J. Am. Chem. Soc.* **2016**, 138, 6598–6609.

Electrophilic addition to non-DA cyclopropanes has been the subject of much study as it represents one of the few ways to achieve oxidative functionalization of C–C bonds. However, rather than developing general and practical synthetic methods that capitalize on this reactivity, research in this particular area has largely focused on understanding the subtle nuances regarding the mechanism of ring opening.⁸ Two intermediates have been advanced to explain the relative stereochemical outcomes of stereospecific, electrophilic additions to substituted cyclopropanes. In an *edge* activation mechanism, the electrophile interacts with the degenerate HOMOs of the cyclopropane *orthogonally* to the C–C bond (Scheme 1.4, left). Subsequent nucleophilic ring opening of the activated cyclopropane results in inversion of stereochemistry at the carbon (C2) undergoing nucleophilic attack and retention of stereochemistry at the carbon (C1) forming a bond to the electrophile. In a *corner* activation mechanism, the electrophile interacts with the degenerate HOMOs *collinearly* with the C–C bond, resulting in inversion of stereochemistry at both carbons upon nucleophilic attack (Scheme 1.4, right).



Scheme 1.4 Mechanisms of stereospecific, electrophilic addition to substituted cyclopropanes. Non-stereospecific ionization mechanisms are not considered explicitly in this scheme but can be significant contributors in electrophilic additions to cyclopropanes.

⁸ For a review, see: DePuy, C.H. *Top. Curr. Chem.* **1973**, *40*, 73–101.

These mechanisms represent limiting scenarios that have been challenging to distinguish experimentally. For example, Lambert and co-workers proposed that corner activation was the predominant mechanism in the polar 1,3-dibromination of *trans*-cyclopropane-1,1,2,3-*d*₄ (Scheme 1.5A) as only products of inversion were obtained. These results suggest against edge activation and ionization mechanisms because the formation of products of both inversion and retention would be expected in those cases.⁹ However, as Lambert and co-workers realized, this analysis does not account for differential isotope effects between nucleophilic attack at CHD and CD₂. In a subsequent study of the polar 1,3-dichlorination and 1,3-dibromination of *cis*-cyclopropane-1,2,3-*d*₃, conformational analysis using variable temperature ¹H NMR and *ab initio* calculations at the MP4(FC)/6-311G** level identified the product of a net inversion-retention process as the major 1,3-dihalogenated product (Scheme 1.5B).¹⁰ This is outcome is most consistent with edge activation of the cyclopropane by the molecular halogen.^{11,12} More recent higher-level studies (B3LYP/6-31G*) have corroborated this conclusion, indicating that an edge-activated bromonium species is lower in energy than a corner-activated species.¹³ These studies also identified a concerted cycloaddition transition state in the 1,3-dibromination of cyclopropane, although experimental validation has, as yet, not been obtained.

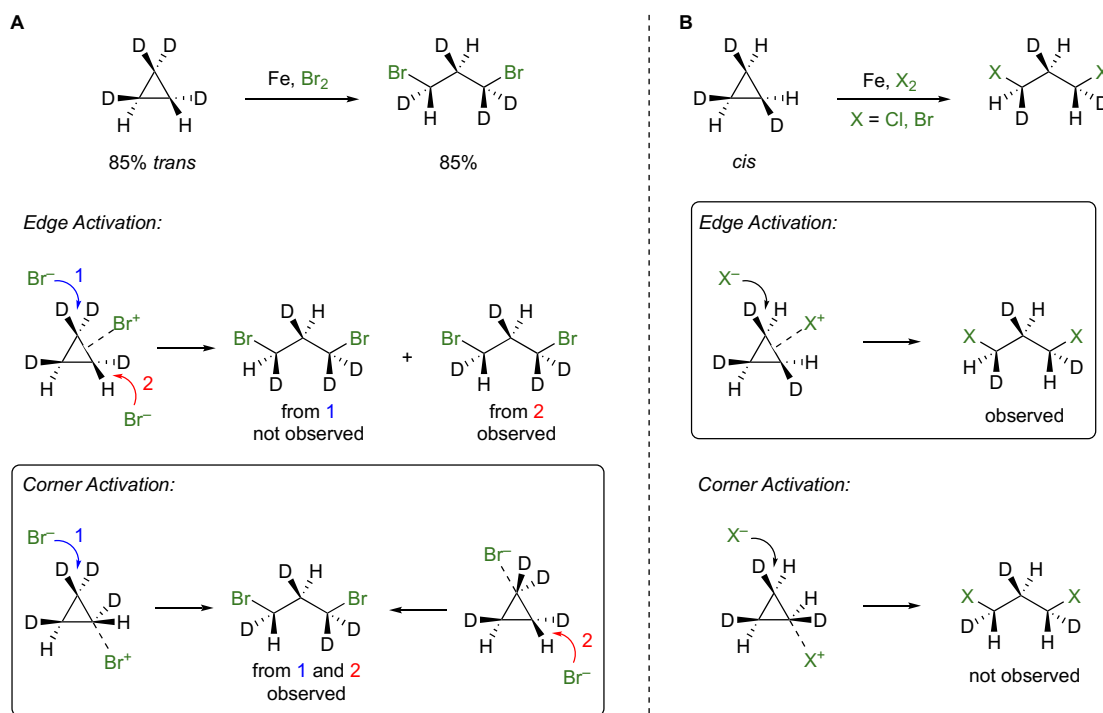
⁹ Lambert, J.B.; Schulz Jr., W.J.; Mueller, P.H.; Kobayashi, K. *J. Am. Chem. Soc.* **1984**, *106*, 792–793.

¹⁰ Lambert, J.B.; Chelius, E.C.; Schulz Jr., W.J.; Carpenter, N.E. *J. Am. Chem. Soc.* **1990**, *112*, 3156–3162.

¹¹ For a study that proposes edge activation by dihaloiodates, see: *Russ. J. Org. Chem.* **2011**, *47*, 340–354.

¹² For a recent example of electrophilic activation of cyclopropanes for intramolecular bromocyclization, see: Rösner, C.; Hennecke, U. *Org. Lett.* **2015**, *17*, 3226–3229.

¹³ Coxon, J.M.; Smith, W.B. *J. Org. Chem.* **2000**, *65*, 2192–2194.



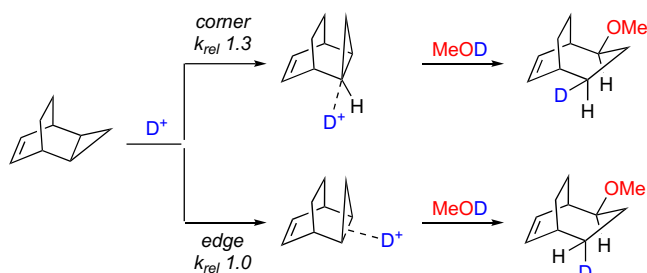
Scheme 1.5 **A)** Initial experiments suggesting a corner activation mechanism for polar 1,3-dibromination of cyclopropanes. **B)** A more rigorous study indicating an edge activation mechanism for polar 1,3-dihalogenation of cyclopropanes.

Studies of cyclopropane activation by other electrophiles have proven similarly ambiguous, suggesting that there is no general rule for edge or corner activation of cyclopropanes. For example, Coxon and co-workers demonstrated that both activation modes are viable in the deuteration of *exo*-tricyclo[3.2.2.0^{2,4}]non-6-ene (Scheme 1.6).¹⁴ Both *syn*- and *anti*-addition products were obtained in a 1.3:1 ratio. Exclusive inversion of stereochemistry at the carbon undergoing nucleophilic attack was observed, which is inconsistent with a non-stereospecific ionization mechanism. Additional studies have provided indirect evidence for both edge¹⁵ and corner¹⁶ protonation mechanisms.

¹⁴ Burritt, A.; Coxon, J.M.; Steel, P.J. *J. Org. Chem.* **1995**, *60*, 7670–7673.

¹⁵ Lee, C.C.; Vassie, S.; Ko, E.C.F. *J. Am. Chem. Soc.* **1972**, *94*, 8931–8932.

¹⁶ (a) Koch, W.; Liu, B. *J. Am. Chem. Soc.* **1989**, *111*, 3479–3480. (b) DePuy, C.H.; Andrist, A.H.; Fünfschilling, P.C. *J. Am. Chem. Soc.* **1974**, *96*, 948–950.



Scheme 1.6 Both corner and edge activation mechanisms are viable in the deuteration of *exo*-tricyclo[3.2.2.0^{2,4}]non-6-ene.

The subtle differences between a symmetrical corner-activated intermediate and an asymmetrical corner-activated intermediate add yet another layer of complexity (Figure 1.1). In the symmetrical corner activation mechanism, the nucleophile attacks the position that bears the greatest positive charge; thus, in this scenario, nucleophilic attack is the selectivity-determining step. However, in the asymmetrical corner activation mechanism, electrophilic activation determines the bond to be broken, effectively removing nucleophilic attack as the selectivity-determining step.

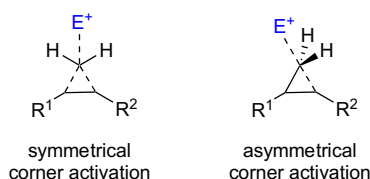
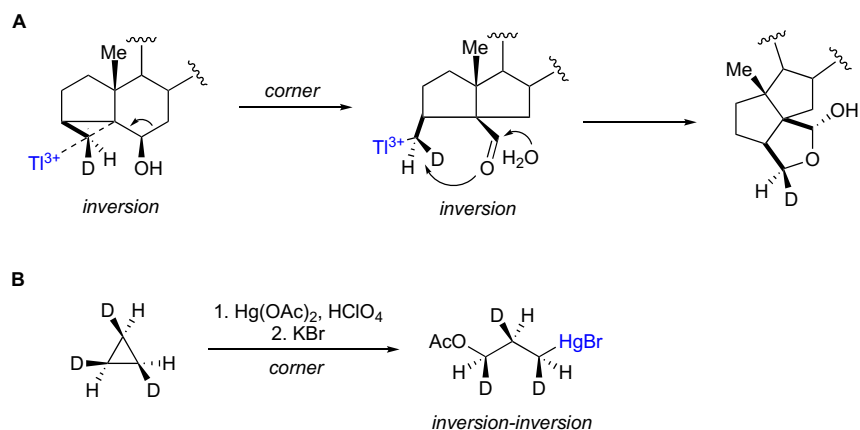


Figure 1.1 Symmetrical and asymmetrical corner activation of substituted cyclopropanes.

Protonation reactions of substituted cyclopropanes have been studied both experimentally and computationally; in these reactions, Wiberg and co-workers suggest that carbocationic intermediates are mainly responsible for the stereochemical outcomes.¹⁷ Their study indicates that while the nucleophile preferentially attacks the position that best stabilizes positive charge, protonation of the cyclopropane to form the putative carbocationic intermediate is not necessarily selective.

¹⁷ Wiberg, K.B.; Kass, S.R. *J. Am. Chem. Soc.* **1985**, *107*, 988–995.

Beyond halogenation and protonation, the stereochemical outcomes of cyclopropane activation by other electrophiles have also been reported. While electrophiles such as Ti(III) ¹⁸ and Hg(II) ¹⁹ have been found to prefer corner activation (Scheme 1.7A and Scheme 1.7B), Pd can access either mechanistic pathway.²⁰



Scheme 1.7 A) Corner activation by Ti(III) . B) Corner activation by Hg(II) .

The factors that favor either corner or edge activation are not well understood. Coxon and co-workers proposed a molecular orbital model,²¹ which argues that H^+ , Br^+ and $^+\text{HgOAc}$ prefer corner activation due to better orbital overlap in σ -type complexes (Figure 1.2A). Edge activation is less favored due to suboptimal overlap with the unsymmetrical HOMO of cyclopropane. For electrophiles that can interact with the LUMO of cyclopropane, such as transition metals with d orbitals, edge activation is favored (Figure 1.2B).

¹⁸ Kočovský, P.; Pour, M.; Gogol, A.; Hanuš, V.; Smrčina, M. *J. Am. Chem. Soc.* **1990**, *112*, 6735–6737.

¹⁹ (a) Lambert, J.B.; Chelius, E.C.; Bible Jr., R.H.; Hajd, E. *J. Am. Chem. Soc.* **1991**, *113*, 1331–1334. (b) Coxon, J.M.; Steel, P.J.; Whittington, B.I. *J. Org. Chem.* **1989**, *54*, 1383–1391.

²⁰ (a) Blomberg, M.R.A; Sigbahn, P.E.M.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1987**, *109*, 4450–4456. (b) Ahmad, M.; Bäckvall, J.E.; Nordberg, R.E.; Norin, T.; Strömberg, S. *J. Chem. Soc., Chem. Commun.* **1982**, 321–323. (c) Bäckvall, J.-E.; Björkman, E.E.; Pettersson, L.; Siegbahn, P.; Strich, A. *J. Am. Chem. Soc.* **1985**, *107*, 7408–7412.

²¹ Coxon, J.M.; Steel, P.J.; Whittington, B.I. *J. Am. Chem. Soc.* **1988**, *110*, 2988–2990.

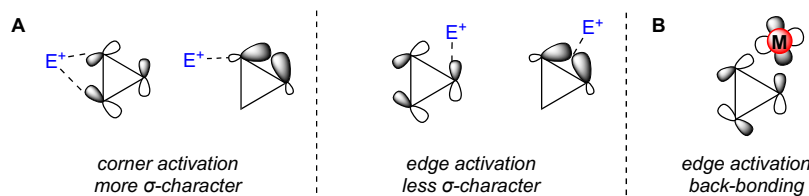


Figure 1.2 A) Coxon's model implicating orbital overlap in dictating corner activation. B) Coxon's model implicating orbital overlap in dictating edge activation.

However, this model only applies to unsubstituted cyclopropanes, as the orbital coefficients shift with substitution. Furthermore, this model does not account for situations in which edge activation is preferred to, or competitive with, corner activation, such as in halogenation reactions and certain protonation reactions. Thus, no general conceptual approach has been advanced which is truly predictive for all cases, perhaps reflecting the relatively low energetic barriers for competitive mechanisms in electrophilic additions to cyclopropanes.

1.1.2 Conformational Properties of 1,3-Difunctionalized Molecules

The strategic disposition of substituents in 1,3-relationships is a well-established tool for influencing the conformation of organic molecules. Control elements such as *syn*-pentane²² and $A_{1,3}$ interactions,²³ which rely on minimization of steric repulsion between 1,3-substituents, are the most familiar, and are broadly exploited in molecular design. Dipole minimization, although considerably less developed as a design strategy, can provide biasing effects of similar magnitude in structures possessing electronegative functional groups disposed in a 1,3-manner (Figure 1.3A). For example, 1,3-difluorides have been shown to display a strong bias to adopting

²² (a) Hoffman, R.W. *Angew. Chem. Int. Ed.* **1992**, 31, 1124–1134. (b) Tsuzuki, S.; Schafer, L.; Goto, H.; Jemmis, E.D.; Hosoya, H.; Siam, K.; Tanabe, K.; Osawa, E. *J. Am. Chem. Soc.* **1991**, 113, 4665–4671.

²³ (a) Hoffman, R.W. *Chem. Rev.* **1989**, 89, 1841–1860. (b) Hoffman, R.W. *Angew. Chem. Int. Ed.* **2000**, 39, 2054–2070.

dipole-minimized conformations.²⁴ Indeed, the minimization of electrostatic repulsion between C–F bonds in a 1,3-relationship has been implicated as the dominant feature in controlling the conformation of multivicinal fluoride systems (Figure 1.3B).²⁵

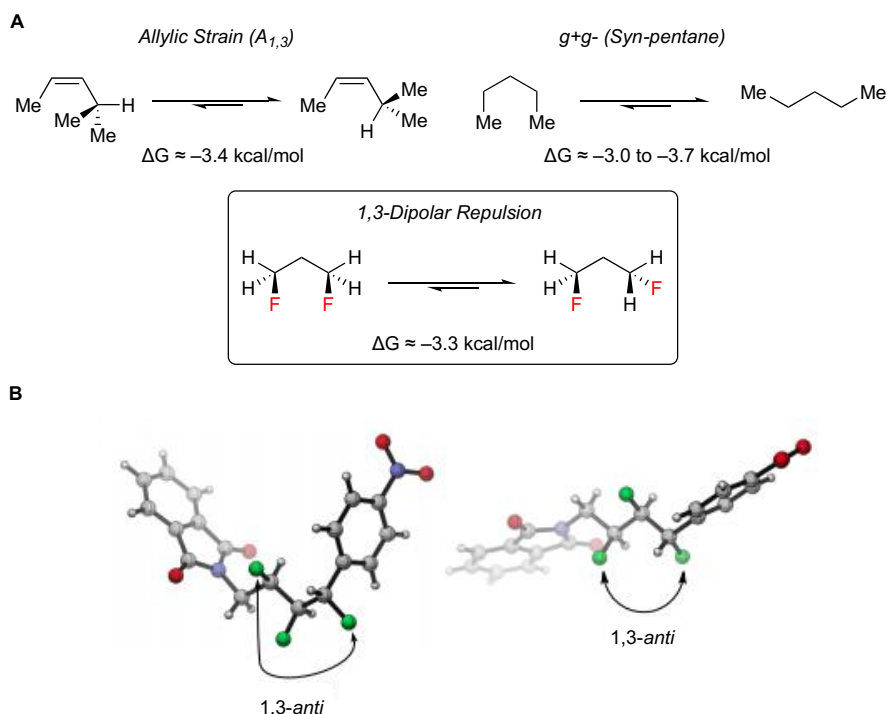


Figure 1.3 **A)** Conformational properties of 1,3-difunctionalized compounds. **B)** X-ray crystal structures of 1,2,3-trifluoride diastereomers displaying a 1,3-dipole-minimized conformation.

²⁴ For the initial investigation of this phenomenon, see: (a) Wu, D.; Tian, A.; Sun, H. *J. Phys. Chem.* **1998**, *102*, 9901–9905. For a review discussing dipole minimization of 1,3-difluorides, see: (b) O’Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308–319.

²⁵ For representative studies, see: (a) Nicoletti, M.; O’Hagan, D.; Slawin, A.M.Z. *J. Am. Chem. Soc.* **2005**, *127*, 482–483. (b) Hunter, L.; Slawin, A.M.Z.; Kirsch, P.; O’Hagan, D. *J. Am. Chem. Soc.* **2006**, *128*, 16422–16423. (c) Hunter, L.; Slawin, A.M.Z.; Kirsch, P.; O’Hagan, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 7887–7890. (d) Hunter, L.; Kirsch, P.; Slawin, A.M.Z.; O’Hagan, D. *Angew. Chem. Int. Ed.* **2009**, *48*, 5457–5460. (e) Brunet, V.A.; Slawin, A.M.Z.; O’Hagan, D. *Beilstein J. Org. Chem.* **2009**, *5*, 61. (f) Farran, D.; Slawin, A.M.Z.; Kirsch, P.; O’Hagan, D. *J. Org. Chem.* **2009**, *74*, 7168–7171. (g) Cheerlavanha, R.; Lawer, A.; Cagnes, M.; Bhadbhade, M.; Hunter, L. *Org. Lett.* **2013**, *15*, 5562–5565. For a recent report, see: (h) Scheidt, F.; Selter, P.; Satschi, N.; Holland, M.C.; Dudenko, D.V.; Daniliuc, C.; Mück-Lichtenfeld, C.; Hansen, M.R.; Gilmour, R. *Chem. Eur. J.* **2017**, *23*, 6142–6149.

1.2 Development of Catalytic 1,3-Difunctionalization Reactions of Cyclopropanes²⁶

1.2.1 Development of a Catalytic 1,3-Difluorination Reaction

Installation of conformational control elements often calls for multi-step synthetic sequences but has emerged as an important pursuit in molecular design.²⁷ Thus, simple and general methods for the incorporation of 1,3-difunctionality could provide a valuable tool for modulating molecular shape.

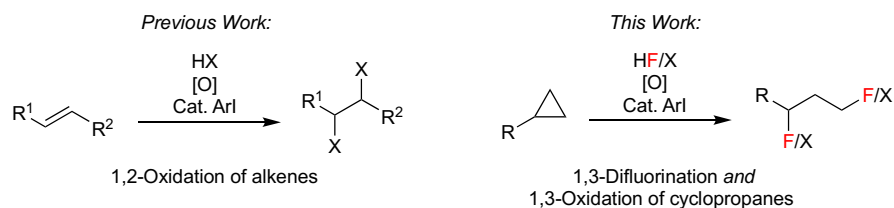
We and others have developed oxidative 1,2-difunctionalization reactions of alkenes based on aryl iodine(I–III) catalysis,^{28,29} and we hypothesized that the alkene-like π -donating properties of unactivated cyclopropanes could promote 1,3-oxidation reactions by similar mechanisms (Scheme 1.8).

²⁶ This work was performed in collaboration with Dr. Steven M. Banik. Portions of this chapter have been adapted from Banik, S.M.; Mennie, K.M.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2017**, *139*, 9152–9155 © American Chemical Society 2017, and Chapter 6 of “I. Chiral Squaramide Catalysts for Lewis Acid Activation in Asymmetric Catalysis. II. Catalytic, Stereoselective Difluorination Reactions”, © Dr. Steven M. Banik and Harvard University.

²⁷ For a recent example of synthetic efforts to harness *syn*-pentane interactions, see: Burns, M.; Essafi, S.; Bame, J.R.; Bull, S.P.; Webster, M.P.; Balieu, S.; Dale, J.W.; Butts, C.P.; Harvey, J.N.; Aggarwal, V.K. *Nature* **2014**, *513*, 183–188.

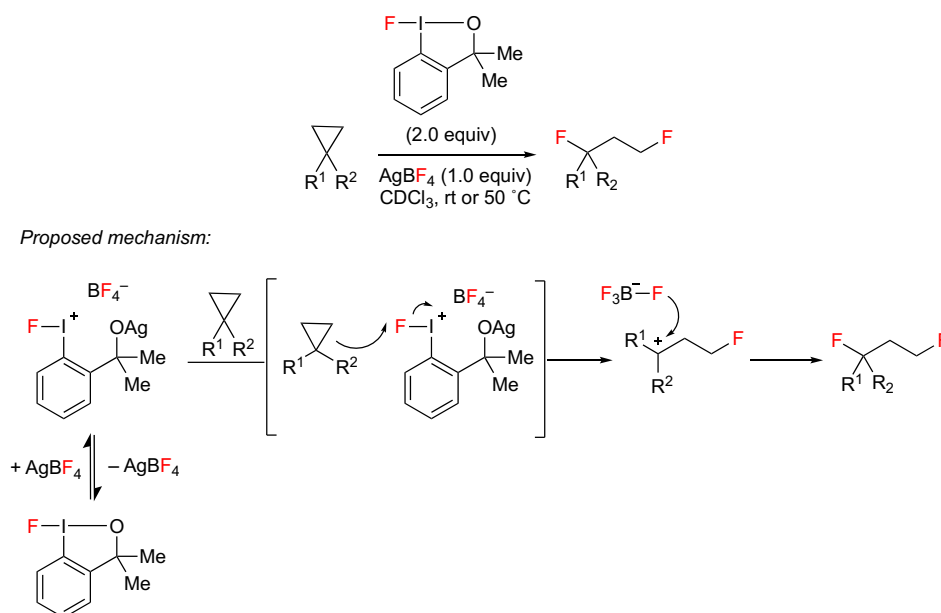
²⁸ For a comprehensive review, see: Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016**, *116*, 3328–3435.

²⁹ For representative examples of oxidative 1,2-difunctionalization of alkenes using aryl iodine(I–III) catalysis, see: (a) Gelis, C.; Dumoulin, A.; Bekkaye, M.; Neuville, L.; Masson, G. *Org. Lett.* **2017**, *19*, 278–281. (b) Muñiz, K.; Barreiro, L.; Romero, R.M.; Martínez, C. *J. Am. Chem. Soc.* **2017**, *139*, 4354–4357. (c) Haubenreisser, S.; Wöste, T.; Martínez, C.; Ishihara, K.; Muñiz, K. *Angew. Chem., Int. Ed.* **2016**, *55*, 413–417. (d) Banik, S.M.; Medley, J.W.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2016**, *138*, 5000–5003. (e) Molnar, I.G.; Gilmour, R. *J. Am. Chem. Soc.* **2016**, *138*, 5004–5007. (f) Wöste, T.H.; Muñiz, K. *Synthesis* **2016**, *48*, 816–827. (h) Woerly, E.M.; Banik, S.M.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2016**, *138*, 13858–13861. (i) Mizar, P.; Laverny, A.; El-Sherbini, M.; Farid, U.; Brown, M.; Malmedy, F.; Wirth, T. *Chem. - Eur. J.* **2014**, *20*, 9910–9913. (j) Suzuki, S.; Kamo, T.; Fukushi, K.; Hiramatsu, T.; Tokunaga, E.; Dohi, T.; Kita, Y.; Shibata, N. *Chem. Sci.* **2014**, *5*, 2754–2760. (k) Martín Romero, R.; Wöste, T.H.; Muñiz, K. *Chem. - Asian J.* **2014**, *9*, 972–983. (l) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073–2085.



Scheme 1.8 The alkene-like π -donating properties of unactivated cyclopropanes can promote 1,3-oxidation reactions.

Indeed, in the course of our studies, Szábo and co-workers demonstrated that 1,1-disubstituted cyclopropanes undergo 1,3-difluorination in the presence of stoichiometric iodine(III) reagents together with stoichiometric AgBF_4 (Scheme 1.9).³⁰ The proposed mechanism for this transformation invokes an iodonium-fluoride species as an electrophilic fluorinating reagent that is attacked by a nucleophilic 1,1-disubstituted cyclopropane to generate a tertiary carbocation.

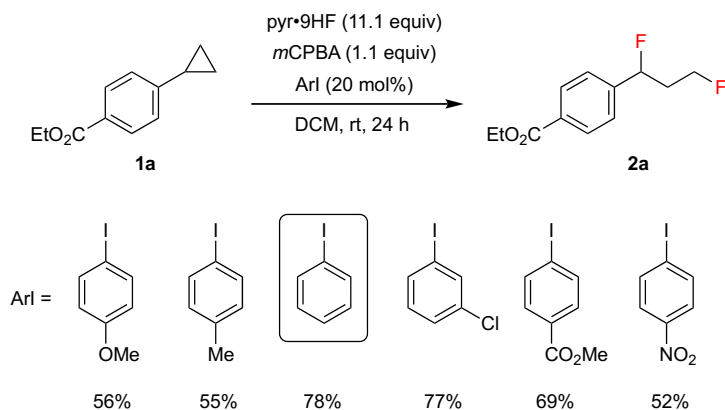


Scheme 1.9 A stoichiometric 1,3-difluorination reaction recently developed by Szábo and co-workers.

³⁰ Ilchenko, N.O.; Hedberg, M.; Szábo, K. *Chem. Sci.* **2017**, 8, 1056–1061.

However, recent mechanistic evidence and computational work have suggested the iodonium-fluoride species is electrophilic at iodine rather than fluorine.³¹

We initiated experimental efforts toward catalytic 1,3-difluorination of substituted cyclopropanes using *m*CPBA as a stoichiometric oxidant, HF–pyridine as a nucleophilic fluoride source and acidic promoter, and commercially available aryl iodides as catalysts.³² With this reagent protocol, the carboethoxy-substituted arylcyclopropane **1a** was converted to the corresponding 1,3-difluorination product in the presence of a variety of electron rich and electron deficient aryl iodides (Scheme 1.10). In contrast, cyclopropylbenzene and more electron-rich analogs decomposed to uncharacterized products. Iodobenzene afforded the highest yields in the difluorination of **1a**, and thus this simplest of potential aryl iodide catalysts was selected for further investigation of the reaction scope.³³



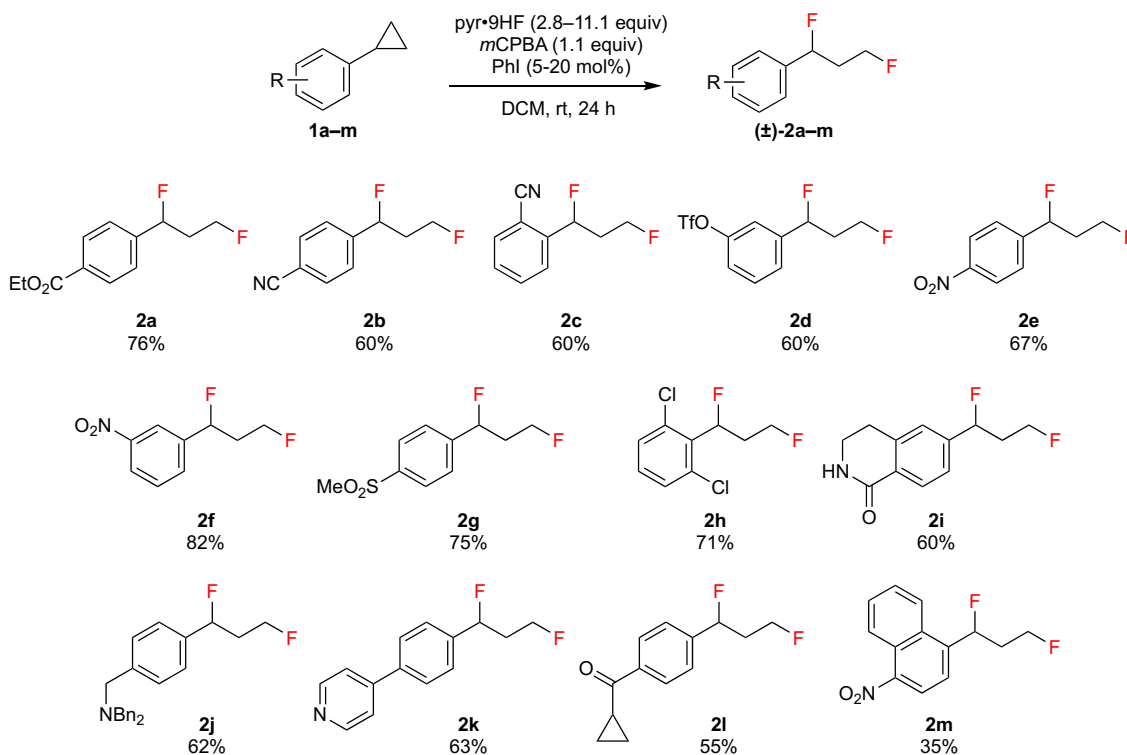
Scheme 1.10 Catalyst optimization studies.

³¹ (a) Yan, T.; Zhou, B.; Xue, X.-S.; Cheng, J.-P. *J. Org. Chem.* **2016**, *81*, 9006–9011. (b) Zhou, B.; Yan, T.; Xue, X.-S.; Cheng, J.-P. *Org. Lett.* **2016**, *18*, 6128–6131.

³² For condition optimization in the closely related 1,2-difluorination reaction of alkenes, see Chapter 2 of “I. Chiral Squaramide Catalysts for Lewis Acid Activation in Asymmetric Catalysis. II. Catalytic, Stereoselective Difluorination Reactions”, © Dr. Steven M. Banik and Harvard University.

³³ A relatively high concentration of HF–pyridine is needed for the 1,3-difluorination reaction to occur in the presence of 2,5-Me₂C₆H₃IF₂. No increase in efficiency was observed by increasing the loading of PhI above 20 mol%.

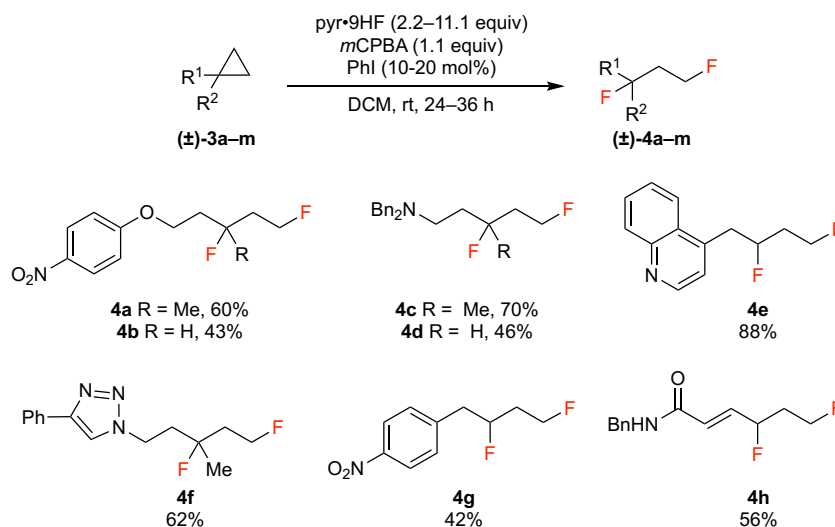
In general, aryl cyclopropanes bearing electron-withdrawing substituents were useful substrates in the catalytic reaction, undergoing regioselective difluorination in moderate-to-good yields (Scheme 1.11). Substrates bearing amine substituents (**1j**) and *N*-heterocycles (**1k**) also underwent successful difluorination, by virtue of the basic groups undergoing *in situ* protection *via* protonation by HF. The reaction was chemoselective for the most electron rich cyclopropane in **1l**, providing **2l** as the only detectable 1,3-difluorinated product. Cyclopropanes featuring extended aromatic rings, however, were not well tolerated under the reaction conditions, likely due to competitive oxidative side reactions (**2m**).



Scheme 1.11 Substrate scope for 1,3-difluorination of aryl cyclopropanes.

Non-conjugated monosubstituted cyclopropanes also underwent oxidation under the catalytic conditions (Scheme 1.12). Increased catalyst loadings (20 mol%) were required for non-conjugated cyclopropane substrates due to competitive hydrofluorination, a known reaction of

HF–pyridine and aliphatic cyclopropanes.³⁴ Substrates containing ether (**4a**, **4b**) and amine (**4c**, **4d**) functionality underwent difluorination in good yields. 1,1-Disubstituted cyclopropanes were converted to the corresponding 1,3-difluorinated products more cleanly in higher yields relative to the monosubstituted analogues (**4a**, **4c** vs. **4b**, **4d**). The compatibility of basic nitrogen functionality with the acidic, oxidizing conditions was further demonstrated by the isolation of quinoline **4e** and triazole **4f** in good yields. Subjection of β -cyclopropyl acrylamide **3h** to the reaction conditions resulted ring-opening 1,3-difluorination to afford **4h**, with no detectable difluorination of the alkene.



Scheme 1.12 Substrate scope for 1,3-difluorination of aryl cyclopropanes.

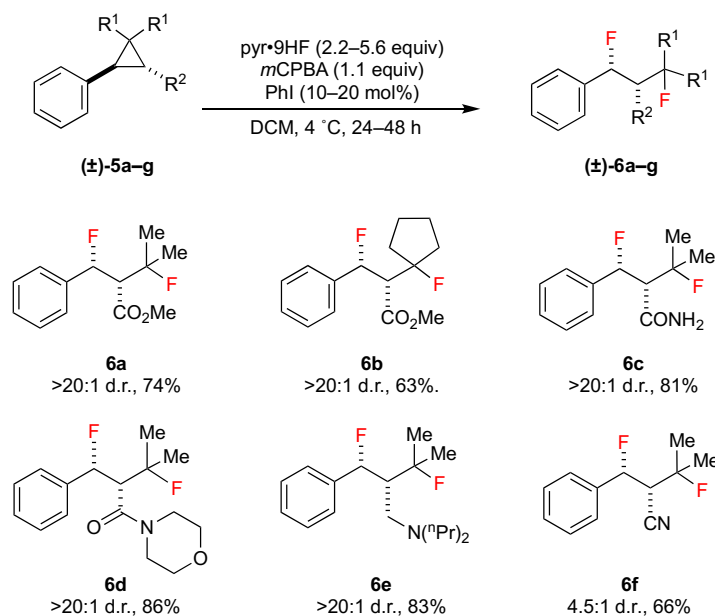
In contrast to the established effectiveness of chiral aryl iodide catalysts in enantioselective fluorofunctionalizations of alkenes,^{29d,h,35} only very low levels of enantiocontrol were observed in the corresponding 1,3-difluorination of cyclopropanes such as **1a** with a variety of catalysts (see Experimental Section). One possible explanation for these observations is asymmetrical edge coordination of the catalyst to the cyclopropane; this would displace the

³⁴ Olah, G.A.; Nojima, M.; Kerekes, I. *Synthesis* **1973**, 12, 779–780.

³⁵ Banik, S.M.; Medley, J.W.; Jacobsen, E.N. *Science* **2016**, 353, 51–54.

stereochemical information of the catalyst from the site of C–F bond formation, thereby resulting in a smaller energetic bias in a selectivity-determining C–F bond-forming step. Alternatively, given that selectivity-determining corner activation has been observed with substituted cyclopropanes,¹⁸ it is possible that, on coordination to the homobenzylic position of the cyclopropane, the catalyst would not be able to effectively distinguish between the benzylic proton and the arene, and yet represent the selectivity-determining step.

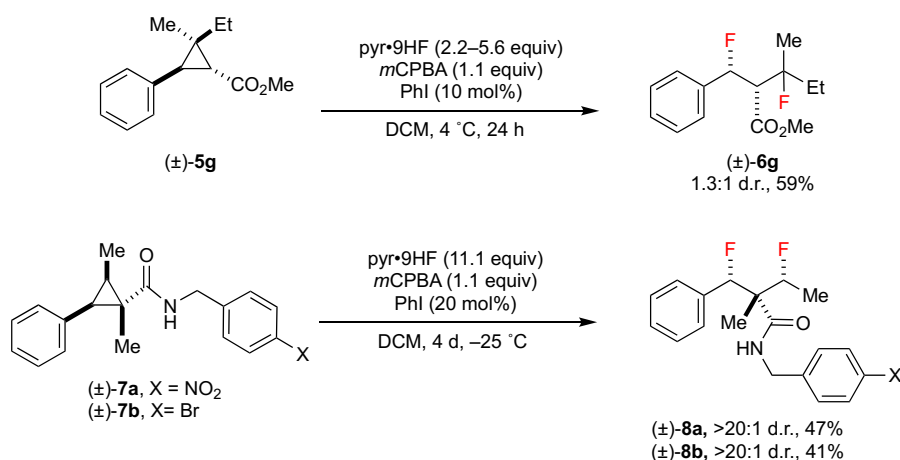
While the identification of effective chiral catalysts for enantioselective 1,3-difluorination reactions will demand further effort, we found that stereochemically complex 1,3-difluorination products could be accessed effectively with achiral aryl iodide catalysts from readily accessible chiral cyclopropanes. For example, tetrasubstituted substrates **5a–e** underwent difluorination stereospecifically in the presence of iodobenzene (>20:1 d.r., Scheme 1.13). Cyclopropane **5f** underwent difluorination to afford a mixture of diastereomers, as this substrate required the use of higher concentrations of pyr•9HF (5.6 equiv) to reach complete conversion.



Scheme 1.13 Stereospecific 1,3-difluorination reactions.

1.2.2 Stereochemical Analysis of the 1,3-Difluorination Reaction

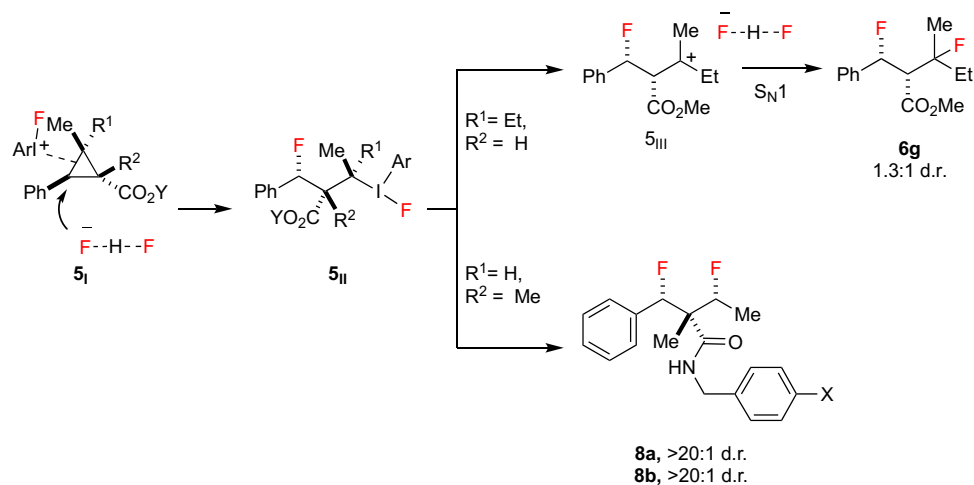
To gain insight into the stereospecificity of both C–F bond-forming steps, cyclopropanes **5g** and **7a–b** were subjected to the catalytic fluorination conditions (Scheme 1.14). Whereas **5g** underwent ring opening to provide **6g** as a 1.3:1 mixture of diastereomers, the less highly substituted substrates **7a–b** underwent stereospecific difluorination to afford diastereomerically pure products. The relative configuration of the two fluoride-bearing stereocenters in **8b** was determined to be *syn* via X-ray diffraction analysis of a crystalline derivative.



Scheme 1.14 Evaluation of the stereospecificity of both C–F bond forming steps.

The divergent stereochemical behavior observed between **5g** and **7a–b** can be rationalized according to the mechanism outlined in Scheme 1.15. The first C–F bond formation is proposed to occur *via* regioselective invertive ring opening at the most electrophilic benzylic position to afford fluoroiodinated species **5II**. In the case of the fully substituted intermediate ($R^1 = \text{Et}$), ionization of the C–I^{III} bond appears to be facile and yields tertiary carbocation **5III**, which can be trapped by fluoride non-stereospecifically in an S_N1 process. In the case of the secondary intermediate ($R^1 = \text{H}$), concerted, invertive fluoride substitution appears to be favored, leading to stereospecific formation of the *syn* product. The relative stereochemistry observed in **8** is consistent with edge activation of cyclopropanes by I^{III} in a manner analogous to the activation

of alkenes by I^{III} . The stereospecificity observed in the difluorination reactions described above represents an important practical feature of this electrophilic catalytic system.



Scheme 1.15 Mechanistic proposals for the divergent stereochemical outcomes observed between substrates **5** and **6**.

1.2.3 Computational Modeling of Cyclopropane Activation by I^{III}

The putative intermediate formed by complexation of phenyl cyclopropane to $[PhIF]^+$ was modeled computationally using density functional theory (Figure 1.4).³⁶ Consistent with the observed reaction outcomes, the HOMO of the complex is predicted to correspond to a dative edge interaction between the cyclopropane and the electrophilic I^{III} center, while the LUMO is anti-bonding and reveals the electrophilic nature of the cyclopropane ring carbons. While both the benzylic or homobenzylic carbons bear significant coefficients in the LUMO for fluoride attack, the selective attack at the benzylic position may be ascribed to electrostatic effects. Similar HOMO and LUMO models have been developed for acylium ion additions to cyclopropanes.³⁷

³⁶ These calculations were performed at the B3LYP/6-31+G(d,p)/SDD(I) level of theory.

³⁷ Audran, G.; Brémond, P.; Marque, S.R.A.; Siri, D. *Tetrahedron Lett.* **2016**, 57, 1743–1749.

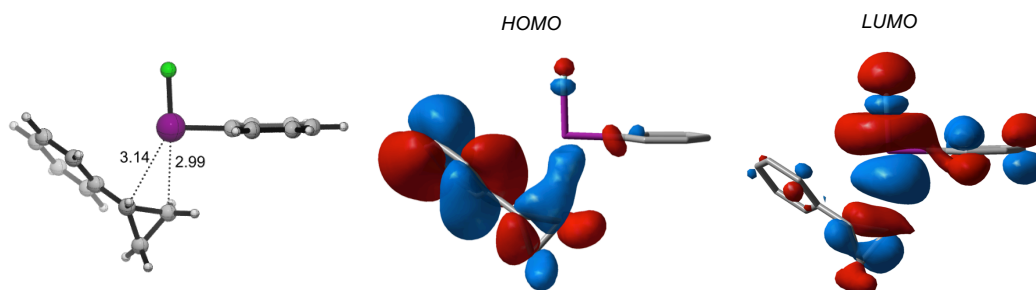


Figure 1.4 Computational modeling of a cyclopropane–aryl iodonium(III) complex.

1.2.4 Conformational Analysis of 1,3-Difluorinated Molecules

X-ray crystal structures were obtained for compounds **4a**, **4h**, **6c** and **6d**. In all cases, the molecules adopt solid-state conformations wherein the 1,3-difluoro substituents are oriented in the *gauche-gauche* relationships that minimize dipolar interactions (Figure 1.5).

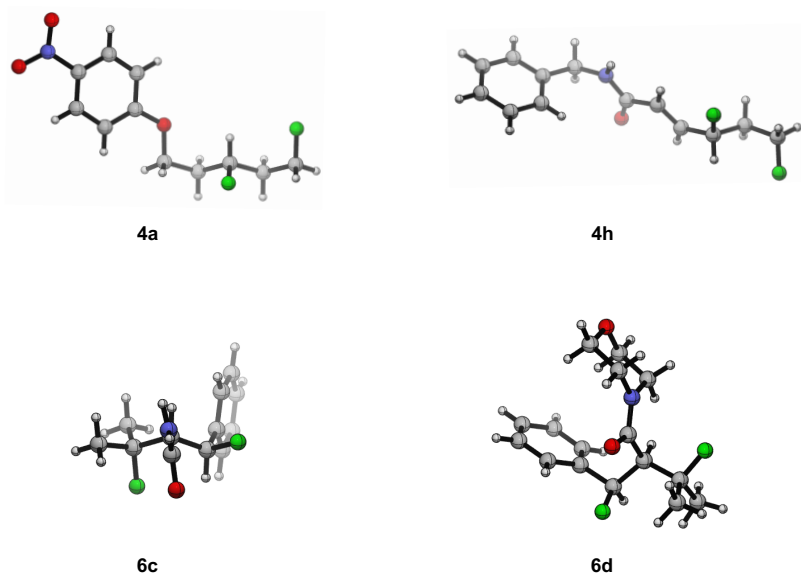


Figure 1.5 X-ray crystal structures of 1,3-difluorides.

Both **6a** and **6e** were found to adopt similar 1,3-dipolar minimized conformations in solution, as determined by vicinal H–F NMR coupling constants ($^3J_{\text{H-F}}$, Figure 1.6). These findings add to the growing body of crystallographic and solution state data demonstrating that

fluorides disposed in a 1,3-relationship impose strong conformational biases to saturated, acyclic carbon frameworks.

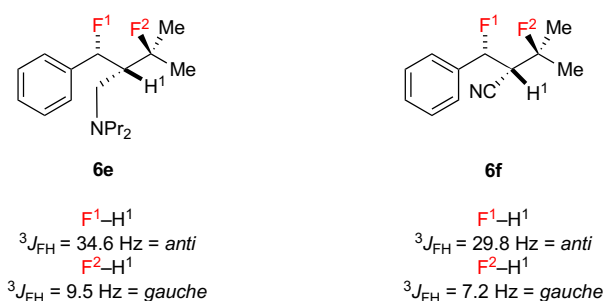
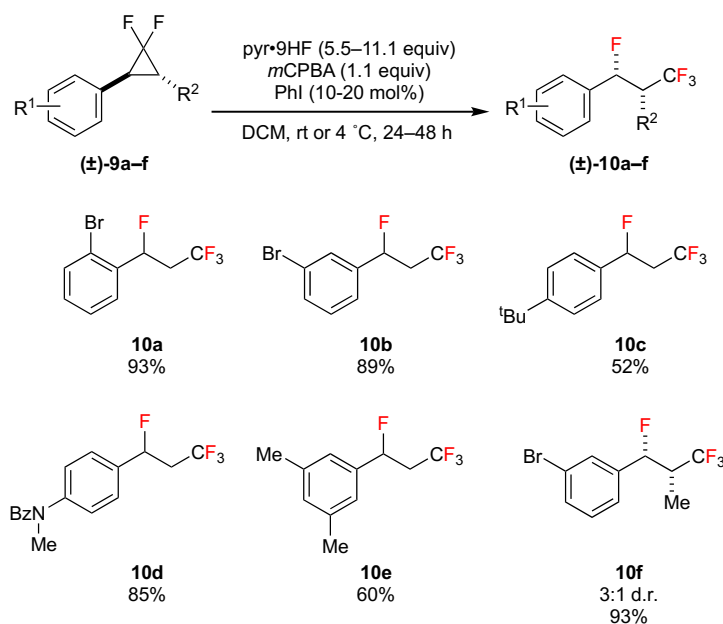


Figure 1.6 ^1H NMR conformational analysis of 1,3-difluorides.

1.2.5 Extension of the 1,3-Difluorination Reaction Protocol

The catalytic ring-opening difluorination protocol could be applied successfully to 1,1-difluorocyclopropane substrates, affording products corresponding formally to alkene 1,2-fluorotrifluoromethylation (Scheme 1.16). Several substituted 1,1-difluoroarylcyclopropanes were transformed to fluorotrifluoromethylated products **10a–f** in good-to-excellent yields. 1,1-Difluorocyclopropanes have been calculated to possess very high ring strain energies (ca. 40 kcal/mol),³⁸ and this is proposed to offset the expected deactivating inductive effect of fluorine substitution on the cyclopropane ring and enable the 1,3-difluorination reaction. Large excesses of $\text{pyr} \bullet 9\text{HF}$ (5.6–11.1 equiv) were required to achieve complete substrate conversion. Thus, only modest diastereoselectivity (3:1) was observed in the ring opening of the substituted cyclopropane **5g**, consistent with similar results obtained with **5f** under strongly acidic conditions (*vide supra*).

³⁸ Bach, R.D.; Dmitrenko, O. *J. Org. Chem.* **2002**, 67, 3884–3896.



Scheme 1.16 1,3-Difluorination of 1,1-difluorocyclopropanes.

1.2.6 Development of General 1,3-Oxidation of Cyclopropanes

In light of the great importance of direct, catalytic 1,2-oxidation reactions of alkenes, analogous 1,3-oxidation reactions of cyclopropanes to install functional groups such as 1,3-diols,^{39,40} 1,3-amino alcohols⁴¹ and 1,3-diamines⁴² would be of considerable synthetic interest. We found that the protocol for the catalytic 1,3-fluorination reaction of cyclopropanes could be adapted in a straightforward manner to allow the introduction of other electronegative groups, thereby providing an expedient method for the installation of 1,3-difunctionality. For example,

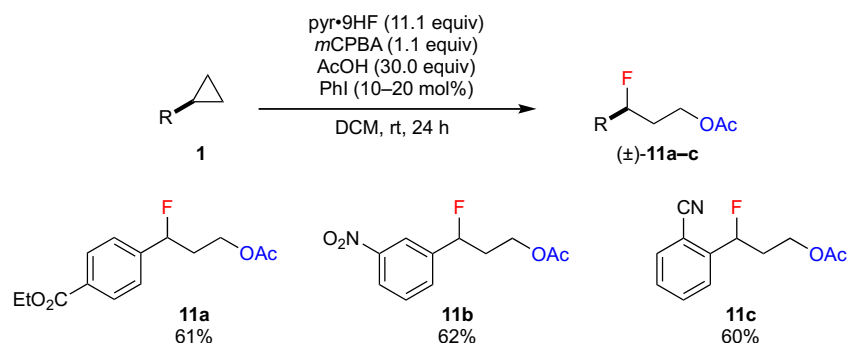
³⁹ For reviews on the synthesis of 1,3-diols, see: (a) Bode, S.E.; Wolberg, M.; Miller, M. *Synthesis* **2006**, 4, 557–588. (b) Oishi, T.; Nakata, T. *Synthesis* **1990**, 8, 635–645.

⁴⁰ Omura, S.; Tanaka, H. In *Macrolide Antibiotics: Chemistry, Biology, and Practice*, Omura, S., Ed; Academic Press: New York, 1984.

⁴¹ For examples of natural products with 1,3-amino alcohols, see: (a) Pinder, A.R. *Nat. Prod. Rep.* **1992**, 9, 491–504. (b) Plunkett, A.O. *Nat. Prod. Rep.* **1994**, 11, 581–590. (c) Kozikowski, A.P.; Chen, Y.-Y. *J. Org. Chem.* **1981**, 46, 5248–5250. (d) Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, 104, 6465–6466. For a review on application of 1,3-amino alcohols in asymmetric organic synthesis, see: (e) Lait, S.M, Rankic, D.A.; Key, B.A. *Chem. Rev.* **2007**, 107, 767–796

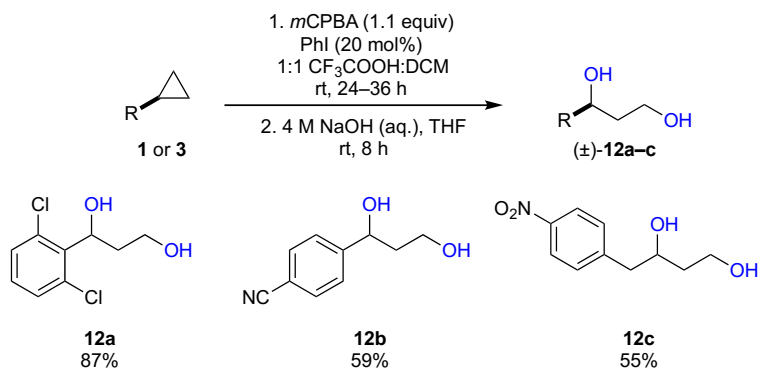
⁴² Ji, X.; Huang, H. *Org. Biomol. Chem.* **2016**, 14, 10557–10566.

introduction of excess acetic acid to the 1,3-difluorination conditions led to the formation of fluoroacetoxylation products (**11a–c**) in good yields and with complete regioselectivity (Scheme 1.17).



Scheme 1.17 Synthesis of 1,3-fluoroacetoxylation products using acetic acid as a co-solvent.

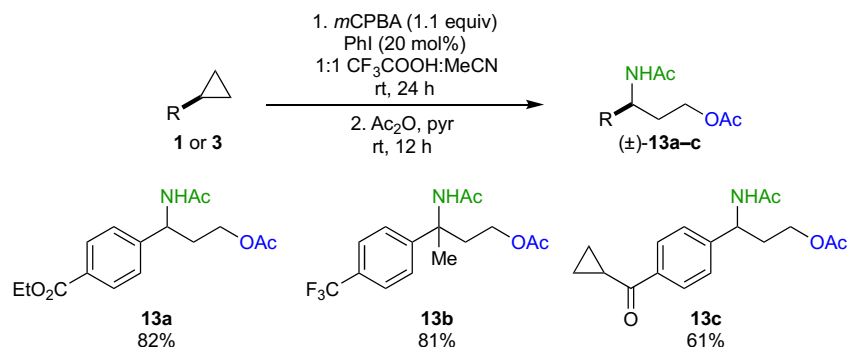
Net 1,3-dihydroxylation of cyclopropanes was achieved using trifluoroacetic acid instead of hydrofluoric acid as the acidic promoter and nucleophile (Scheme 1.18). This reaction directly resulted in the formation of 1,3-trifluoroacetoxylation products, which readily hydrolyze to provide 1,3-diols from cyclopropanes in moderate-to-excellent yields (**12a–c**).



Scheme 1.18 Synthesis of 1,3-diols using trifluoroacetic acid as a co-solvent followed by hydrolysis.

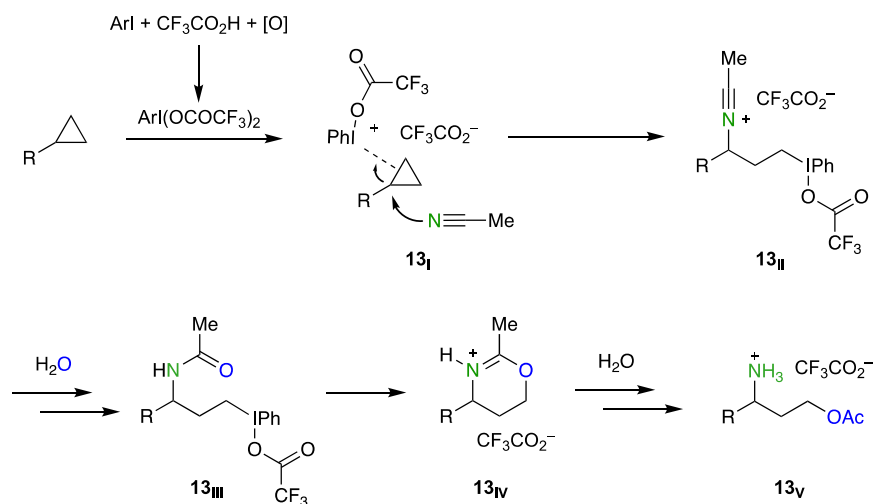
When the same reactions of cyclopropanes and trifluoroacetic acid were conducted in acetonitrile, 1,3-amino alcohols were obtained with complete regioselectivity and in good yields (Scheme 1.19, **13a–c**). The formation of 1,3-amino alcohol products in this reaction suggests

Ritter-type substitution reactions are available to the highly electrophilic species generated under I^{III} catalysis.



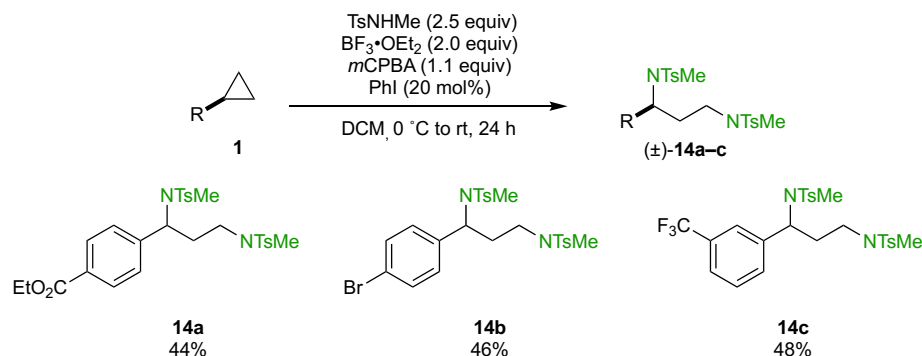
Scheme 1.20 Synthesis of 1,3-amino alcohols using trifluoroacetic acid and acetonitrile as co-solvents.

The observed regiochemical outcome is proposed to arise *via* the mechanism outlined in Scheme 1.20. Initial attack by acetonitrile in **13_I** results in nitrilium **13_{II}**, which undergoes rapid hydrolysis to afford **13_{III}**. Subsequent attack by the amide at the C–I(III) bond provides cyclic intermediate **13_{IV}**, which undergoes hydrolysis to arrive at **13_V**.



Scheme 1.20 Proposed mechanism to account for regioselectivity in 1,3-oxyamination of cyclopropanes.

Catalytic 1,3-cyclopropane oxidation could also be applied to the synthesis of 1,3-diamine products (Scheme 1.21). These reactions require $\text{BF}_3 \cdot \text{OEt}_2$ as a stoichiometric activator with a sulfonamide nitrogen source and proceed in moderate yield (**14a–c**).



Scheme 1.21 Synthesis of 1,3-diamines using *p*-tolylmethanesulfonamide and $\text{BF}_3 \cdot \text{OEt}_2$.

1.3 Conclusion

The discovery of a direct, catalytic method for the construction of 1,3-difluorinated compounds introduces a new tool for the modulation of molecular conformation. Generalization of this cyclopropane C–C bond activation strategy holds promise for accessing a variety of 1,3-oxidation patterns, as demonstrated here in the synthesis of 1,3-fluoroacetoxy, 1,3-diol, 1,3-amino alcohol, and 1,3-diamine products. Challenges remain in obtaining high levels of enantioselectivity in these reactions with chiral catalysts. While an appropriate catalyst has not been identified, a more fundamental mechanistic issue that precludes effective enantioinduction cannot be excluded.

1.4 Experimental Section

General experimental procedures. All reactions for the preparation of substrates were performed in standard, dry glassware fitted with rubber septa under an inert atmosphere of nitrogen unless otherwise described. All difluorination reactions were performed in low-density polyethylene tubes sealed with a low-density polyethylene cap under an atmosphere of air. Reported concentrations refer to solution volumes at room temperature. Concentration of organic solutions under reduced pressure was performed using house vacuum (ca. 40 mm Hg) at 30 °C. Column chromatography was performed with ZEOprep® 60 (40–63 micron) silica gel from American Scientific. Thin layer chromatography (TLC) was used for reaction monitoring and product detection was performed using pre-coated glass plates covered with 0.20 mm silica gel with fluorescent indicator; plates were visualized by exposure to UV light ($\lambda_{\text{ex}} = 254 \text{ nm}$) or by staining with potassium permanganate or ninhydrin.

CAUTION: Pyridine•9HF is a corrosive and toxic substance that will etch glassware. Safe handling can be conducted with plastic syringes and metal needles, with NaHCO_3 (aq.) or NaOH (aq.) employed to quench excess HF. Though reactions should not be conducted in glassware when employing pyridine•9HF, glassware may be used to quench reactions provided sufficient quantities of base are present. Always handle pyridine•9HF while wearing gloves and in a fumehood. As a precautionary measure, have calcium gluconate gel nearby and apply immediately and liberally on skin exposed to HF.

Materials. Reagents were purchased in reagent grade from commercial suppliers and used as received, unless otherwise described. Anhydrous solvents (benzene, dichloromethane, diethyl ether, *N,N*-dimethylformamide, tetrahydrofuran, and toluene) were prepared by passing the

solvent through an activated alumina column. Triethylamine and diisopropylethylamine were distilled over calcium hydride at atmospheric pressure.

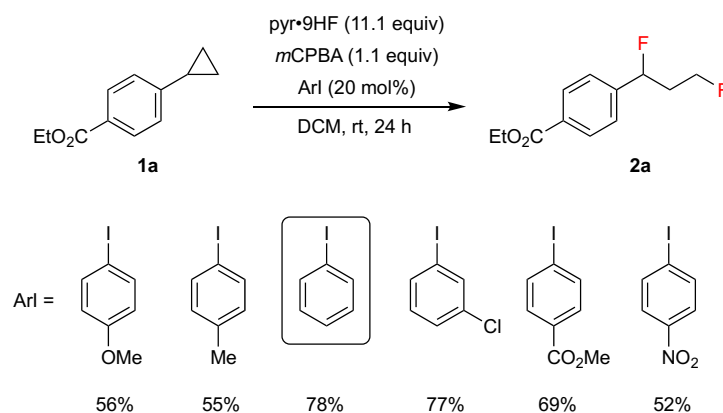
Instrumentation. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on an Inova-500 spectrometer, are reported in parts per million downfield from tetramethylsilane, and are referenced to the residual protium resonances of the NMR solvent (CDCl_3 : 7.26 [CHCl_3]). Proton-decoupled carbon-13 nuclear magnetic resonance (^{13}C $\{^1\text{H}\}$ NMR) spectra were recorded on an Inova-500 spectrometer, are reported in parts per million downfield from tetramethylsilane, and are referenced to the carbon resonances of the NMR solvent (CDCl_3 : 77.16). Chemical shifts for fluorine-19 nuclear magnetic resonance (^{19}F NMR) were recorded on an Inova-500 spectrometer and are reported in parts per million downfield from chlorotrifluoromethane, and are referenced to the fluorine resonance of chlorotrifluoromethane ($\delta = 0$). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sext = sextet, sept = septet, m = multiplet), coupling constants in Hertz (Hz), integration. Infrared spectra were recorded using a Bruker Tensor 27 FT-IR spectrometer. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad). High-resolution mass spectrometric data were obtained on an Agilent 6210 time-of-flight HPLC/MS spectrometer (ESI-TOF). Low-resolution mass spectrometric data were obtained on a Waters Quattro Micro GCMS (EI^+). High-resolution GC-MS analysis was performed using Thermo Scientific TRACE 1310 Gas Chromatograph equipped with a Thermo Scientific Q Exactive Orbitrap mass spectrometry system. GC analysis was performed using an Agilent 7890A GC system using commercially available columns. Chiral HPLC analysis was performed using an Agilent 1200

series quaternary HPLC system using commercially available CHIRALCEL analytical columns (4.6 x 250 mm).

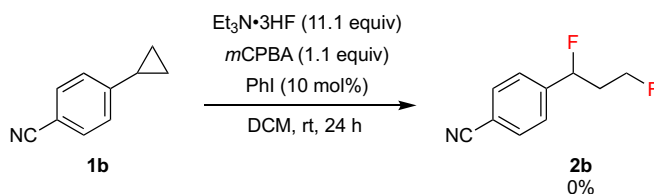
Optimization and Control Experiments

General procedure for catalyst and reaction condition optimization:

Catalyst (10.4 μmol , 20.0 mol%), *m*-chloroperbenzoic acid (*m*CPBA, 77% by weight, 12.8 mg, 57.2 μmol , 1.10 equiv), **1a** (9.9 mg, 52.0 μmol , 1.00 equiv), dodecane (11.4 μL , 52.0 μmol , 1.00 equiv) and dichloromethane (0.30 mL) were combined in a polyethylene tube at room temperature. Pyridinium poly(hydrogen fluoride) (pyr•9HF, 0.140 mL, 0.58 mmol, 11.1 equiv) was added *via* micropipette. The reaction was stirred for 24 hours at room temperature. The reaction was cooled to $-78\text{ }^{\circ}\text{C}$ and basic alumina (approximately 750 mg) was added slowly. The reaction was allowed to warm to room temperature with stirring and was filtered. The crude mixture was analyzed by GC to determine the conversion and yield of product.

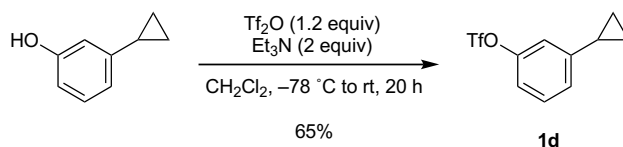


Scheme S1.1 Catalyst optimization.



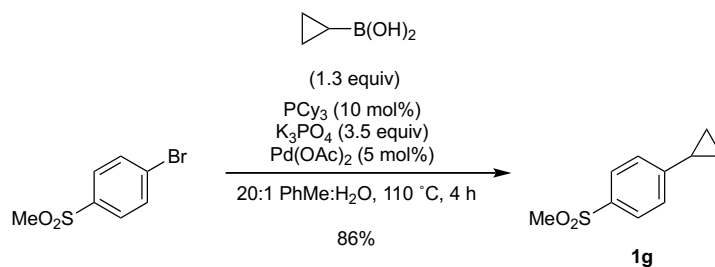
Scheme S1.2 $\text{Et}_3\text{N}\cdot 3\text{HF}$ as a fluoride source.

Synthesis of Substrates

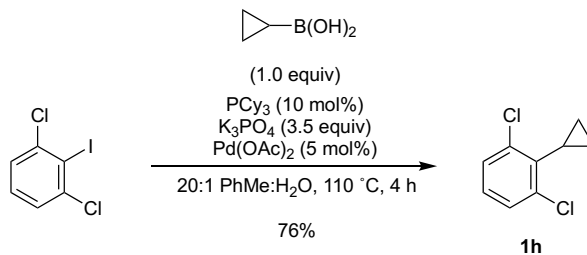


To a solution of 3-cyclopropylphenol ⁴³ (1.35 g, 10.1 mmol, 1.00 equiv) in anhydrous dichloromethane (12 mL) at -78°C was added triethylamine (2.80 mL, 20.1 mmol, 2.00 equiv) followed by triflic anhydride (1.0 M in dichloromethane, 12 mL, 12 mmol, 1.2 equiv). The resulting mixture was allowed to warm to room temperature and stirred for 20 hours. The reaction mixture was quenched with water (20 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered, concentrated under reduced pressure and purified by flash column chromatography on silica gel (0% to 1% diethyl ether in hexanes) to provide **1d** as a colorless oil (1.73 g, 65%). ^1H NMR (500 MHz, CDCl_3) δ 7.31 (t, $J = 8.0$ Hz, 1H), 7.09 (d, $J = 8.0$ Hz, 1H), 7.05 (dd, $J = 8.0, 2.0$ Hz, 1H), 6.97 (t, $J = 2.0$ Hz, 1H), 1.94 (ddd, $J = 13.4, 8.5, 5.1$ Hz, 1H), 1.08–1.02 (m, 2H), 0.76–0.70 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 150.0 (s), 147.6 (s), 130.0 (s), 125.8 (s), 118.9 (q, $J = 321.0$ Hz, 1H), 118.7 (s), 118.1 (s), 15.4 (s), 9.9 (s); ^{19}F NMR (470.4 MHz, CDCl_3) δ -73.0; FTIR (thin film) ν 3012 (w), 1615 (m), 1419 (s), 1203 (s), 936 (s), 603 (s) cm^{-1} ; GCMS (EI^+) Calc'd for $\text{C}_{10}\text{H}_9\text{F}_3\text{O}_2\text{S}$ $[\text{M}]^+$: 266.0; found 266.0. Note: HRMS was not possible for this compound.

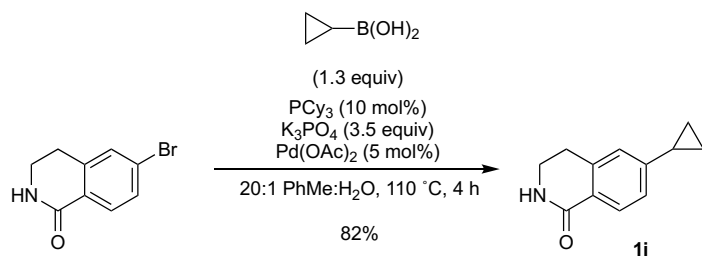
⁴³ Woo, B.Y.; Sim, S-Y; Kim, Y.; Shin, S.S.; Kim, J.K.; Lee, K-W; Kim, D.H.; Lim, K.M.; Moh, J-H; Jeong, Y.S.; Choi, J.K.; Koh, H.J.; Lee, J.; Kim, H.; Yoon, J.H.; Li, F.; Kim, J-S; Suh, Y-G PCT Int. Appl., 2010002209, 07 Jan 2010.



To a solution of 1-bromo-4-(methanesulfonyl)benzene (1.41 g, 6.00 mmol, 1.00 equiv) in 20:1 toluene:water (30 mL) was added potassium phosphate tribasic (4.46 g, 21.0 mmol, 3.50 equiv), cyclopropylboronic acid (670 mg, 7.80 mmol, 1.30 equiv), tricyclohexylphosphine (171 mg, 0.610 mmol, 10 mol%) and palladium(II) acetate (67.4 mg, 0.300 mmol, 5.0 mol%). The resulting mixture was heated to 110 °C. After 4 hours, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL) and washed with water (100 mL). The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 40% ethyl acetate in hexanes) to give **1g** as a pale yellow solid (1.01 g, 86%). ^1H NMR (500 MHz, CDCl_3) δ 7.75 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 2.99 (s, 3H), 1.92 (m, 1H), 1.05 (m, 2H), 0.74 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 151.2, 137.2, 127.3, 126.2, 44.6, 15.6, 10.7; FTIR (thin film) ν 3002 (w), 1596 (m), 1288 (s), 1139 (s), 776 (s), 524 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{10}\text{H}_{12}\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 197.0631; found 197.0629.

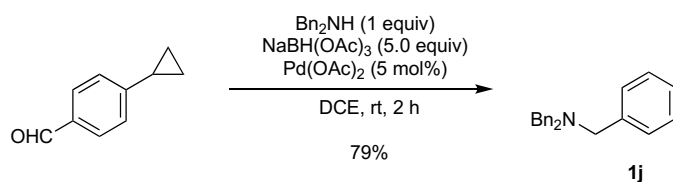


To a solution of 2-iodo-1,3-dichlorobenzene (1.35 g, 5.00 mmol, 1.00 equiv) in 20:1 toluene:water (25 mL) was added potassium phosphate tribasic (3.71 g, 17.5 mmol, 3.50 equiv), cyclopropylboronic acid (430 mg, 5.00 mmol, 1.00 equiv), tricyclohexylphosphine (140 mg, 0.500 mmol, 10 mol%) and palladium(II) acetate (55.6 mg, 0.250 mmol, 5.0 mol%). The resulting mixture was heated to 110 °C. After 4 hours, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL) and washed with water (100 mL). The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes) to give **1h** as a colorless oil (711 mg, 76%). ¹H NMR (500 MHz, CDCl₃) δ 7.26 (d, *J* = 8.1 Hz, 2H), 7.10–7.05 (m, 1H), 1.81–1.73 (m, 1H), 1.18–1.05 (m, 2H), 0.80–0.60 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 138.0, 137.9, 128.3, 127.9, 13.4, 9.4; FTIR (thin film) ν 3010 (w), 1557 (m), 1428 (s), 1195 (m), 774 (s) cm⁻¹; HRGCMS (EI⁺) Calc'd for C₉H₈Cl₂ [M]⁺: 185.9998; found 185.9996.

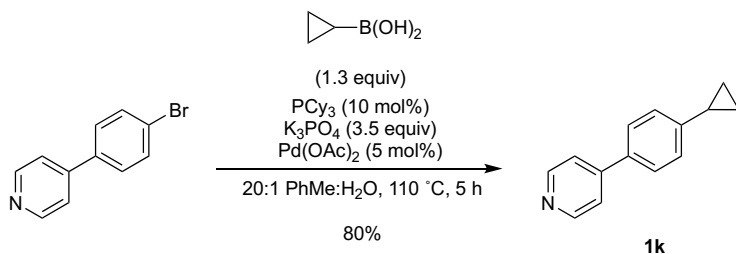


To a solution of 6-bromo-3,4-dihydro-2H-isoquinolin-1-one (500 mg, 2.21 mmol, 1.00 equiv) in 20:1 toluene:water (9 mL) was added potassium phosphate tribasic (1.60 g, 7.54 mmol, 3.50 equiv), cyclopropylboronic acid (260 mg, 2.88 mmol, 1.30 equiv), tricyclohexylphosphine (62.0 mg, 0.221 mmol, 10 mol%), and palladium(II) acetate (25.0 mg, 0.114 mmol, 5.0 mol%). The resulting mixture was heated to 110 °C. After 4 hours, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (50 mL) and washed with water (50 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over

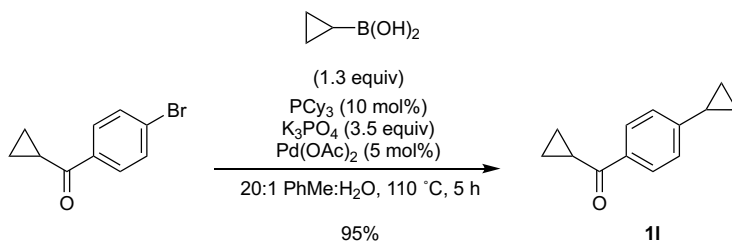
MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 100% ethyl acetate in hexanes) to give **1i** as a white solid (339 mg, 82%). ¹H NMR (500 MHz, CDCl₃) δ 7.93 (d, *J* = 7.8 Hz, 1H), 7.03–6.97 (m, 1H), 6.88 (s, 1H), 6.66 (br. s, 1H), 3.57–3.50 (m, 2H), 2.97–2.90 (m, 2H), 1.95–1.85 (m, 1H), 1.05–0.95 (m, 2H), 0.80–0.70 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 166.8, 149.2, 139.0, 128.3, 126.4, 124.4, 124.3, 40.5, 28.7, 15.8, 10.2; FTIR (thin film) ν 3208 (w), 1663 (s), 1613 (m), 1477 (m), 1338 (m) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₄H₁₃N [M+H]⁺: 196.1121; found 196.1117.



To a solution of 4-cyclopropylbenzaldehyde (700 mg, 4.79 mmol, 1.00 equiv) and dibenzylamine (0.920 mL, 4.79 mmol, 1.00 equiv) in anhydrous 1,2-dichloroethane (16 mL) was added sodium triacetoxyborohydride (5.07 g, 23.9 mmol, 5.00 equiv). The resulting suspension was stirred at room temperature for 2 hours and quenched with sat. NaHCO₃ (aq.) (20 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered, concentrated under reduced pressure and purified by flash column chromatography on silica gel (0% to 10% diethyl ether in hexanes) to give **1j** as a waxy solid (1.24 g, 79%). ¹H NMR (500 MHz, CDCl₃) δ 7.57–7.51 (m, 4H), 7.48–7.39 (m, 6H), 7.38–7.31 (m, 2H), 7.19–7.12 (m, 2H), 3.71–3.62 (m, 6H), 2.03–1.95 (m, 1H), 1.08–1.01 (m, 2H), 0.83–0.77 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 142.6, 139.8, 136.7, 128.8, 128.3, 126.9, 125.6, 57.9, 57.7, 15.3, 9.3; FTIR (thin film) ν 3025 (w), 2791 (w), 1494 (m), 1122 (m), 806 (m) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₂₄H₂₅N [M+H]⁺: 328.2060; found 328.2074.

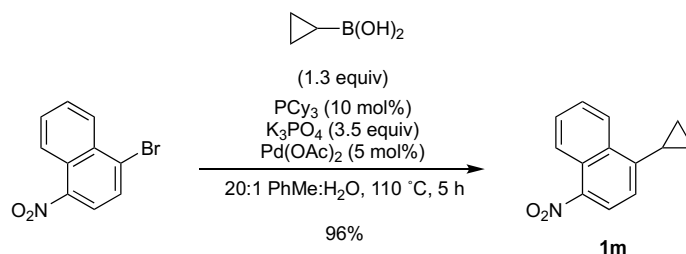


To a solution of 4-(4-bromophenyl)pyridine (1.17 g, 5.00 mmol, 1.00 equiv) in 20:1 toluene:water (25 mL) was added potassium phosphate tribasic (3.71 g, 17.5 mmol, 3.50 equiv), cyclopropylboronic acid (560 mg, 6.52 mmol, 1.30 equiv), tricyclohexylphosphine (140 g, 0.500 mmol, 10 mol%) and palladium(II) acetate (55.6 mg, 0.250 mmol, 5.0 mol%). The resulting mixture was heated to 110 °C. After 5 hours, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL) and washed with water (100 mL). The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 30% diethyl ether in dichloromethane) to give **1k** as a yellow solid (780 mg, 80%). ¹H NMR (500 MHz, CDCl₃) δ 8.65–8.60 (m, 2H), 7.57–7.47 (m, 4H), 7.18 (d, *J* = 8.1 Hz, 2H), 1.99–1.91 (m, 1H), 1.10–0.95 (m, 2H), 0.76–0.70 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 150.1, 147.9, 145.4, 134.9, 126.7, 126.2, 121.2, 15.2, 9.7; FTIR (thin film) ν 1609 (w), 1051 (w), 807 (s), 726 (w), 513 (w) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₄H₁₃N [M+H]⁺: 196.1121; found 196.1117.



To a solution of 4-bromophenyl cyclopropyl ketone (500 mg, 2.22 mmol, 1.00 equiv) in 20:1 toluene:water (10.5 mL) was added potassium phosphate tribasic (1.65 g, 7.77 mmol,

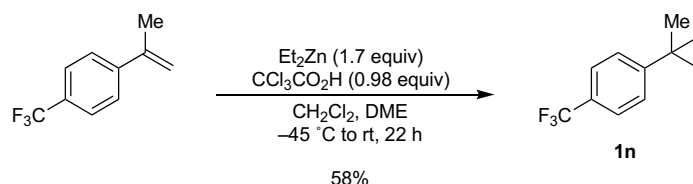
3.50 equiv), cyclopropylboronic acid (246 mg, 2.89 mmol, 1.30 equiv), tricyclohexylphosphine (62.0 mg, 0.220 mmol, 10 mol%) and palladium(II) acetate (25.0 mg, 0.110 mmol, 5.0 mol%). The resulting mixture was heated to 110 °C. After 5 hours, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (50 mL) and washed with water (50 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 30% diethyl ether in hexanes) to give **11** as a white solid (393 mg, 95%). ¹H NMR (500 MHz, CDCl₃) δ 7.90 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 2.63 (tt, *J* = 7.8, 4.4 Hz, 1H), 1.93 (tt, *J* = 8.3, 4.9 Hz, 1H), 1.23–1.15 (m, 2H), 1.09–1.01 (m, 2H), 1.01–0.94 (m, 2H), 0.81–0.71 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 200.0, 150.0, 135.4, 128.3, 125.5, 16.9, 15.8, 11.5, 10.4; FTIR (thin film) ν 3007 (w), 1658 (s), 1385 (s), 1220 (s), 990 (s), 698 (s), 523 (s) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₃H₁₄O [M+H]⁺: 187.1117; found 187.1121.



To a solution of 1-bromo-4-nitronaphthalene⁴⁴ (700 mg, 2.78 mmol, 1.00 equiv) in 20:1 toluene:water (14 mL) was added potassium phosphate tribasic (2.06 g, 9.73 mmol, 3.50 equiv), cyclopropylboronic acid (310 mg, 3.61 mmol, 1.30 equiv), tricyclohexylphosphine (78.0 mg, 0.280 mmol, 10 mol%) and palladium(II) acetate (31.0 mg, 0.140 mmol, 5.0 mol%). The resulting mixture was heated to 110 °C. After 5 hours, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL) and washed with water (100 mL). The aqueous

⁴⁴ Manna, S.; Maity, S.; Rana, S.; Agasti, S.; Maiti, D. *Org. Lett.* **2012**, *14*, 1736–1739.

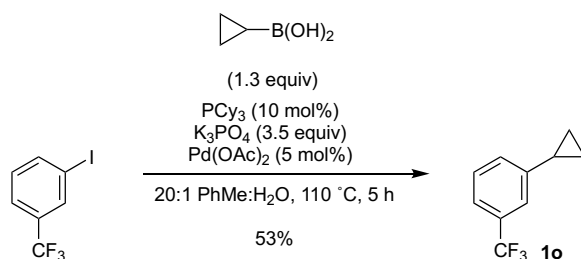
layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 20% diethyl ether in hexanes) to give **1m** as a yellow oil (570 mg, 96%). ¹H NMR (500 MHz, CDCl₃) δ 8.60 (d, *J* = 8.5 Hz, 1H), 8.54 (d, *J* = 8.5 Hz, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.76–7.65 (m, 2H), 7.30 (d, *J* = 7.8 Hz, 1H), 2.48–2.36 (m, 1H), 1.25–1.15 (m, 2H), 0.87–0.80 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 147.1, 145.1, 134.1, 128.9, 127.1, 125.1, 125.0, 123.9, 123.5, 121.9, 13.9, 7.5; FTIR (thin film) ν 3009 (w), 1736 (w), 1511 (s), 1333 (m), 764 (m) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₁H₁₁NO₂ [M+H]⁺: 214.0863; found 214.0868.



To anhydrous dichloromethane (7.5 mL) was added diethylzinc (1.0 M in hexanes, 7.5 mL, 7.5 mmol, 1.7 equiv). The solution was cooled down to −45 °C. A solution of diiodomethane (1.2, 3.3 mmol, 2 equiv) in anhydrous dichloromethane (3.7 mL) was added. After stirring for one hour at −40 °C, a solution of trichloroacetic acid (120 mg, 0.734 mmol, 0.098 equiv) and DME (0.4 mL) in anhydrous dichloromethane (3.7 mL), The reaction mixture was warmed to −10 °C and stirred at that temperature for one hour. A solution of 1-(prop-1-en-2-yl)-4-(trifluoromethyl)benzene⁴⁵ (838 mg, 4.50 mmol, 1.00 equiv) was added as a solution in dichloromethane (3.7 mL). The reaction was warmed to room temperature and stirred for 20 hours. Sat. NH₄Cl (aq.) (10 mL) was added. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated under reduced pressure and purified by flash column

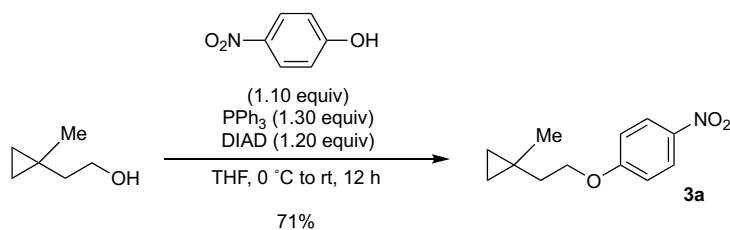
⁴⁵ Cussó, O.; Ribas, X.; Lloret-Fillol, J.; Costas, M. *Angew. Chem. Int. Ed.* **2015**, *84*, 2729–2733.

chromatography on silica gel (0% to 10% diethyl ether in hexanes) to give **1n** as a colorless oil (527 mg, 58%). ¹H NMR (500 MHz, CDCl₃) δ 7.52 (d, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 1.43 (s, 3H), 0.92–0.88 (m, 2H), 0.83–0.79 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 151.4, 127.8 (q, *J* = 32.1 Hz), 126.9, 125.2 (q, *J* = 3.7 Hz), 124.5 (q, *J* = 271.6 Hz), 25.3, 19.8, 16.4; ¹⁹F NMR (470.4 MHz, CDCl₃) δ -62.3 (s); FTIR (thin film) ν 2927 (w), 1619 (w), 1326 (s), 1068 (m), 844 (w) cm⁻¹; HRGCMS (EI⁺) Calc'd for C₁₁H₁₁F₃ [M]⁺: 200.0807; found 200.0807

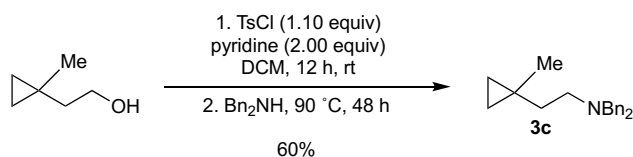


To a solution of 3-iodobenzotrifluoride (721 μL, 5.00 mmol, 1.00 equiv) in 20:1 toluene:water (25 mL) was added potassium phosphate tribasic (3.71 g, 17.5 mmol, 3.50 equiv), cyclopropylboronic acid (560 mg, 6.52 mmol, 1.30 equiv), tricyclohexylphosphine (140 g, 0.500 mmol, 10 mol%) and palladium(II) acetate (55.6 mg, 0.250 mmol, 5.0 mol%). The resulting mixture was heated to 110 °C. After 5 hours, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL) and washed with water (100 mL). The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes) to give **1o** as a colorless oil (495 mg, 53%). ¹H NMR (500 MHz, CDCl₃) δ 7.46–7.42 (m, 1H), 7.41–7.35 (m, 2H), 7.29–7.24 (m, 1H), 1.98 (tt, *J* = 8.5, 5.1 Hz, 1H), 1.09–1.02 (m, 2H), 0.83–0.71 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 145.2, 130.8 (q, *J* = 32.1 Hz), 129.1, 128.8, 124.5 (q, *J* = 272.1 Hz), 122.8, 122.3, 15.5, 9.6; ¹⁹F NMR (470.4 MHz, CDCl₃) δ -62.7 (s); FTIR (thin film) ν

3012 (w), 1443 (w), 1323 (s), 1118 (s), 910 (m), 699 (s) cm^{-1} ; HRGCMS Calc'd for $\text{C}_{10}\text{H}_9\text{F}_3$ $[\text{M}]^+$: 186.0651; found 186.0649.



To a solution of 2-(1-methylcyclopropyl)ethanol⁴⁶ (900 mg, 9.00 mmol, 1.00 equiv), 4-nitrophenol (1.38 g, 9.90 mmol, 1.10 equiv), and triphenylphosphine (3.07 g, 11.7 mmol, 1.30 equiv) in tetrahydrofuran (90 mL) cooled to 0 °C was added diisopropyl azodicarboxylate (2.14 mL, 10.8 mmol, 1.20 equiv) over 30 minutes. The reaction was allowed to warm to room temperature overnight. The reaction was then concentrated under reduced pressure, and the residue was purified by flash column chromatography (0 to 20% diethyl ether in hexanes) to give **3a** as a colorless oil (1.41 g, 71%). ^1H NMR (500 MHz, CDCl_3) δ 8.19–8.14 (m, 2H), 6.95–6.90 (m, 2H), 4.14 (t, $J = 7.1$ Hz, 2H), 1.75 (t, $J = 7.1$ Hz, 2H), 1.09 (s, 3H), 0.38–0.28 (m, 4H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 164.2, 141.4, 125.9, 114.5, 67.7, 38.3, 23.1, 13.2, 13.0; FTIR (thin film) ν 2947 (w), 1591 (m), 1497 (m), 1470 (m), 1330 (s), 1255 (s), 1110 (m), 843 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{12}\text{H}_{15}\text{NO}_3$ $[\text{M}+\text{Na}]^+$: 244.0939; found 244.0944

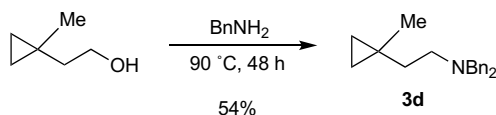


To a solution of 2-(1-methylcyclopropyl)ethanol⁴⁷ (248 mg, 2.48 mmol, 1.00 equiv) and 4-toluenesulfonyl chloride (519 mg, 2.73 mmol, 1.10 equiv) in anhydrous dichloromethane (4.3

⁴⁶ Hahn, M.; Lampe, T.; Stasch, J-P; Schlemmer, K-H; Wunder, F.; Li, V M-J; Becker, E-M; Stoll, F.; Knorr, A.; Woltering, E. PCT Int. Appl., 2012139888, 18 Oct 2012.

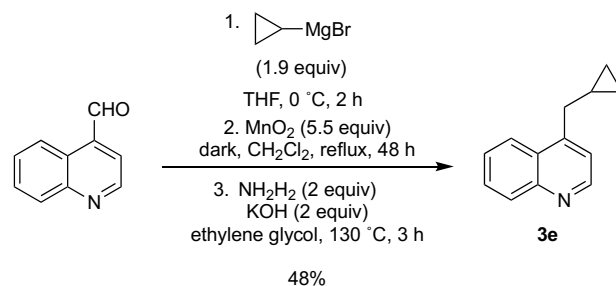
⁴⁷ Yuk, I. H.; Purkey, H.; O'Brien, T. Patent Application Number PCT/US2015/021040 (March 17, 2015).

mL) was added pyridine (400 μ L, 4.96 mmol, 2.00 equiv). The reaction mixture was stirred overnight, and then diluted with dichloromethane (20 mL) and water (20 mL). The organic layer was separated and washed with 1 M HCl (aq.) (10 mL), dried with MgSO_4 , filtered, and concentrated under reduced pressure to give a colorless oil which solidified on standing. To this solid was added dibenzylamine (1.93 mL), and the resulted mixture was heated to 90 $^{\circ}\text{C}$ for 48 hours. Upon cooling, the reaction mixture was purified by flash column chromatography (0% to 10% diethyl ether in hexanes) to give **3c** as a colorless oil (416 mg, 60% over two steps). ^1H NMR (500 MHz, CDCl_3) δ 7.45–7.30 (m, 8H), 7.27–7.24 (m, 2H), 3.60 (s, 4H), 2.61–2.56 (m, 2H), 1.56–1.45 (m, 2H), 0.95 (s, 3H), 0.27–0.18 (m, 4H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 140.1, 128.9, 128.3, 126.9, 58.5, 51.6, 36.5, 23.1, 14.2, 13.1; FTIR (thin film) ν 2793 (w), 1427 (m), 1125 (m), 733 (s), 696 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{20}\text{H}_{25}\text{N}$ $[\text{M}+\text{H}]^+$: 280.2060; found 280.2073.



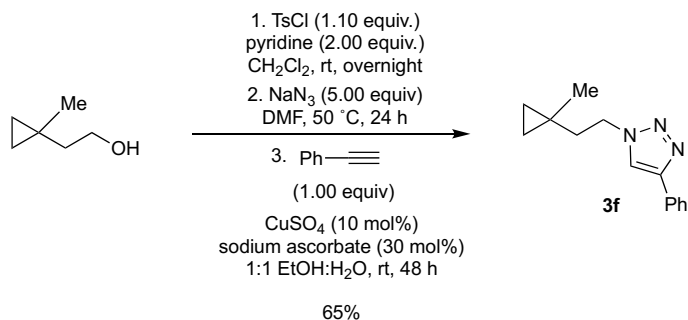
A solution of 2-cyclopropylethyl 4-methylbenzenesulfonate⁴⁸ (835 mg, 3.48 mmol, 1.00 equiv) and dibenzylamine (2.7 mL) was heated to 90 $^{\circ}\text{C}$ for 48 hours. Upon cooling, the reaction mixture was purified by flash column chromatography (0% to 10% diethyl ether in hexanes) to give **3d** as a colorless oil (499 mg, 54%). ^1H NMR (500 MHz, CDCl_3) δ 7.43–7.20 (m, 10H), 3.59 (s, 4H), 2.55 (app. t, J = 7.3 Hz, 2H), 1.43 (dt, J = 7.8, 7.3 Hz, 2H), 0.75–0.63 (m, 1H), 0.42–0.35 (m, 2H), 0.00–0.05 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 140.3, 128.9, 128.3, 126.9, 58.5, 53.7, 32.6, 9.3, 4.6; FTIR (thin film) ν 2921 (w), 2793 (w), 1452 (w), 731 (m), 697 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{13}\text{H}_{16}\text{F}_2\text{O}_2$ $[\text{M}+\text{Na}]^+$: 266.1903; found 266.1910.

⁴⁸ Clapham, K.M.; Bardos, J.; Finlay, M.; Raymond V.; Golding, B.T.; Griffen, E.J.; Griffin, R.J.; Hardcastle, I.R.; Menear, K.A.; Ting, A.; Turner, P.; Young, G.L.; Cano, C. *Bioorganic Med. Chem. Lett.* **2011**, 21, 966–970.



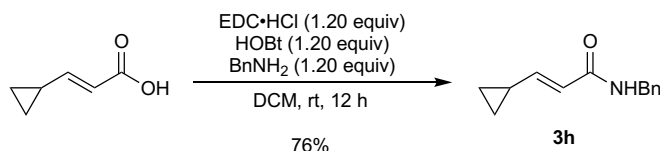
To a solution of 4-quinolinecarboxaldehyde (1.62 g, 10.3 mmol, 1.00 equiv) in anhydrous tetrahydrofuran at 0 °C was added cyclopropylmagnesium bromide (0.5 M in tetrahydrofuran, 40 mL, 20 mmol, 2 equiv) dropwise. After stirring for 2 hours at 0 °C, the reaction mixture was quenched with water (20 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered, concentrated and purified by flash column chromatography on silica gel (0% to 50% ethyl acetate in dichloromethane) to provide cyclopropyl(quinolin-4-yl)methanol as an orange, viscous oil. To a solution of this oil in dichloromethane (40 mL) was added manganese(IV) oxide (4.93 g, 56.7 mmol, 5.50 equiv). The resulting suspension was stirred in the dark under reflux for 48 hours. Upon cooling, the reaction mixture was filtered through celite and concentrated under reduced pressure to give cyclopropyl(quinolin-4-yl)methanone as a colorless oil. Ethylene glycol (4.9 mL) was added to this oil followed by 50% hydrazine hydrate (aq.) (1.28 mL, 20.6 mmol, 2.00 equiv), and 85% potassium hydroxide (1.37 g, 20.6 mmol, 2.00 equiv). The reaction mixture was heated to 130 °C. After 3 hours, the reaction mixture was cooled to room temperature, diluted with diethyl ether (200 mL), washed with water (4 × 100 mL) and brine (50 mL), dried over Na₂SO₄, filtered, concentrated under reduced pressure and purified by flash column chromatography on silica gel (0% to 100% diethyl ether in hexanes) to give **3e** as a yellow oil (910 mg, 48% over three steps). ¹H NMR (500 MHz, CDCl₃) δ 8.76 (d, *J* = 4.1 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.63–7.56 (m, 1H), 7.47–7.40 (m, 1H),

7.31–7.25 (m, 1H), 2.86 (d, $J = 6.8$ Hz, 2H), 1.09–0.97 (m, 1H), 0.56–0.48 (m, 4H), 0.20–0.13 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 150.2, 148.0, 147.6, 130.0, 128.8, 127.6, 126.1, 123.3, 120.2, 36.0, 10.0, 5.0; FTIR (thin film) ν 3002 (w), 1591 (m), 1508 (m), 1018 (m), 752 (s), 416 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{13}\text{H}_{13}\text{N}$ $[\text{M}+\text{H}]^+$: 184.1121; found 184.1120.



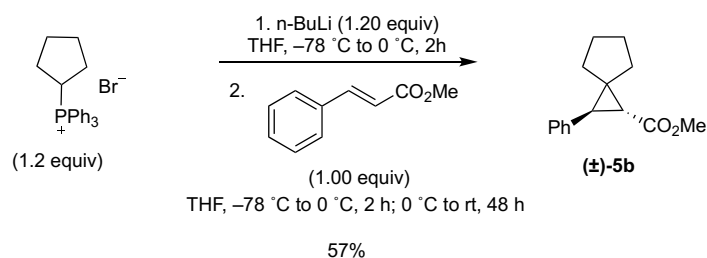
To a solution of 2-(1-methylcyclopropyl)ethanol (622 mg, 6.21 mmol, 1.00 equiv) and 4-toluenesulfonyl chloride (1.30 g, 6.84 mmol, 1.10 equiv) in anhydrous dichloromethane (4.3 mL) was added pyridine (1.00 mL, 12.4 mmol, 2.00 equiv). The reaction mixture was stirred overnight, and then diluted with dichloromethane (80 mL) and water (80 mL). The organic layer was separated and washed with 1 M HCl (aq.) (40 mL), dried with MgSO_4 , filtered, and concentrated under reduced pressure to give a colorless oil which solidified on standing. To a solution of this solid in *N,N*-dimethylformamide (6.5 mL) was added sodium azide (2.02 g, 31.1 mmol, 5.00 equiv). The resulting suspension was heated to 50 °C for 24 hours. Upon cooling, the reaction mixture was diluted with diethyl ether (100 mL), washed with water (5×100 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give 1-(2-azidoethyl)-1-methylcyclopropane as a colorless oil. To a solution of this oil and phenylacetylene (0.680 mL, 6.21 mmol, 1.00 equiv) in 1:1 ethanol:water (50 mL) was added copper(II) sulfate (99.0 mg, 0.620 mmol, 10 mol%) and sodium ascorbate (370 mg, 1.86 mmol, 30 mol%). The resulting suspension was stirred at room temperature. After 48 h, the reaction mixture was diluted with diethyl ether (200 mL), washed with water (3×100 mL), dried over

Na₂SO₄, filtered and concentrated to give **3f** as a pale yellow solid (920 mg, 65% over two steps). ¹H NMR (500 MHz, CDCl₃) δ 7.85–7.80 (m, 2H), 7.74 (s, 1H), 7.43–7.37 (m, 2H), 7.33–7.28 (m, 1H), 4.50–4.45 (m, 2H), 1.89–1.84 (m, 2H), 1.10 (s, 3H), 0.30–0.20 (m, 4H); ¹³C NMR (125.7 MHz, CDCl₃) δ 147.8, 130.9, 129.0, 128.2, 125.8, 119.8, 48.7, 40.1, 22.4, 13.3, 12.8; FTIR (thin film) ν 3081 (w), 1610 (w), 1462 (m), 1102 (m), 765 (s), 692 (s), 515 (m) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₄H₁₇N₃ [M+H]⁺: 228.1495; found 228.1506.

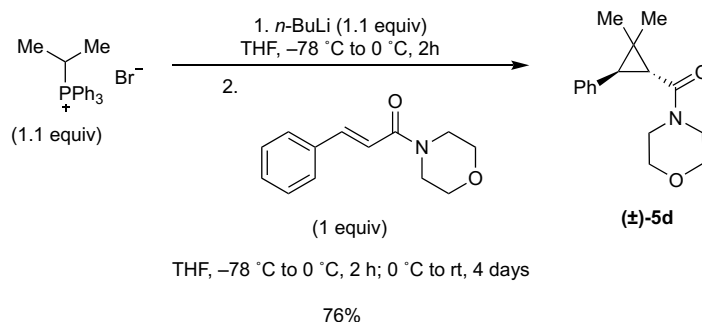


To a solution of 3-(cyclopropyl)acrylic acid⁴⁹ (400 mg, 3.57 mmol, 1.00 equiv), EDC·HCl (820 mg, 4.28 mmol, 1.20 equiv), and HOBT (660 mg, 4.28 mmol, 1.20 equiv) in dichloromethane (10.0 mL) was added benzylamine (0.470 mL, 4.28 mmol, 1.20 equiv). After stirring overnight at room temperature, the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (10% to 50% ethyl acetate in hexanes) to give **3h** as a white solid (543 mg, 76%). ¹H NMR (500 MHz, CDCl₃) δ 7.30–7.17 (m, 5H), 7.00 (br. t, *J* = 5.4 Hz, 1H), 6.26 (dd, *J* = 15.1, 10.2 Hz, 1H), 5.95 (d, *J* = 15.1 Hz, 1H), 4.36 (d, *J* = 5.9 Hz, 2H), 1.51–1.39 (m, 1H), 0.94–0.77 (m, 2H), 0.58–0.43 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 166.3, 149.2, 138.6, 128.4, 127.5, 127.1, 120.7, 43.2, 14.0, 8.2; FTIR (thin film) ν 3291 (m), 1664 (s), 1545 (s), 1167 (m), 873 (s), 581 (m) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₃H₁₅NO [M+H]⁺: 202.1226; found 202.1225.

⁴⁹ Baker, R.K.; Parsons, W.H.; Ruprecht, K. Patent Application Number PCT/US2000/005214 (March 1, 2000).

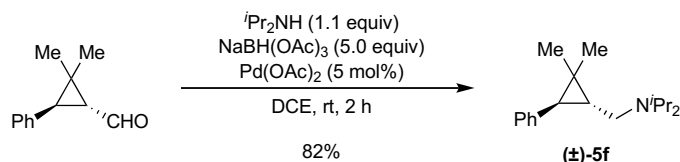


To a suspension of cyclopentyl(triphenyl)phosphonium bromide (3.46 g, 8.41 mmol, 1.20 equiv) in anhydrous tetrahydrofuran (20 mL) at $-78\text{ }^{\circ}\text{C}$ was added dropwise *n*-BuLi (2.50 M in hexanes, 3.40 mL, 8.50 mmol, 1.20 equiv). The reaction mixture was allowed to warm to $0\text{ }^{\circ}\text{C}$, stirred for 30 minutes until a red solution was formed, and cooled back down to $-78\text{ }^{\circ}\text{C}$. A solution of methyl *trans*-cinnamate (1.14 g, 7.00 mmol, 1.00 equiv) was added. The reaction mixture was allowed to warm to $0\text{ }^{\circ}\text{C}$, stirred for 2 h and then warmed to room temperature. After 48 hours, the reaction mixture was quenched with 1 M HCl (aq.) (50 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether ($3 \times 100\text{ mL}$). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting oily residue was diluted with dichloromethane (200 mL). 77% *m*-chloroperbenzoic acid (2.35 g, 10.5 mmol, 1.50 equiv) was added and the reaction mixture was stirred at room temperature for 2 hours, washed with sat. $\text{Na}_2\text{S}_2\text{O}_3$ (aq.) (50 mL), sat. NaHCO_3 (aq.) (50 mL) and brine (50 mL), dried over Na_2SO_4 , filtered, concentrated under reduced pressure and purified by flash column chromatography on silica gel (0% to 10% diethyl ether in hexanes) to give ($\pm$)-**5b** as a white solid (1.10 g, 57%). ^1H NMR (500 MHz, CDCl_3) δ 7.35–7.10 (m, 5H), 3.74 (s, 3H), 2.81 (d, $J = 5.9\text{ Hz}$, 1H), 2.19 (d, $J = 5.9\text{ Hz}$, 1H), 2.00–1.30 (m, 8H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 172.9, 137.7, 128.2, 128.01, 126.3, 51.3, 40.4, 37.8, 32.7, 31.6, 31.2, 26.1, 25.9; FTIR (thin film) ν 2951 (m), 1725 (s), 1439 (m), 1151 (s), 698 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{15}\text{H}_{18}\text{O}_2$ $[\text{M}+\text{H}]^+$: 231.1380; found 231.1375.

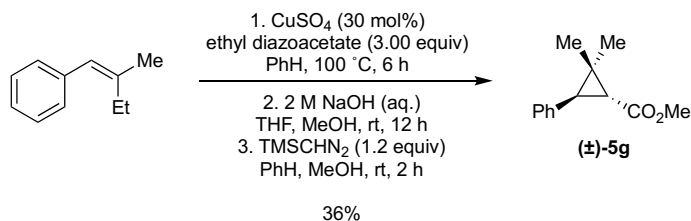


To a suspension of isopropyltriphenylphosphonium iodide (2.63 g, 6.08 mmol, 1.10 equiv) in anhydrous tetrahydrofuran (18 mL) at $-78\text{ }^{\circ}\text{C}$ was added dropwise *n*-BuLi (2.50 M in hexanes, 2.50 mL, 6.25 mmol, 1.10 equiv). The reaction mixture was allowed to warm to $0\text{ }^{\circ}\text{C}$, stirred for 30 minutes until a red solution was formed, and cooled back down to $-78\text{ }^{\circ}\text{C}$. A solution of (*E*)-1-morpholino-3-phenylprop-2-en-1-one⁵⁰ (1.20 g, 5.52 mmol, 1.00 equiv) was added. The reaction mixture was allowed to warm to $0\text{ }^{\circ}\text{C}$, stirred for 2 hours and then warmed to room temperature. After 4 days, the reaction mixture was quenched with 1 M HCl(aq.) (50 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether ($3 \times 100\text{ mL}$). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , filtered, concentrated under reduced pressure and purified by flash column chromatography on silica gel (0% to 100% ethyl acetate in hexanes) to give ($\pm$)-**5d** as a white solid (1.24 g, 76%). ^1H NMR (500 MHz, CDCl_3) δ 7.35–7.28 (m, 2H), 7.27–7.19 (m, 3H), 3.92–3.52 (m, 8H), 2.83 (d, $J = 5.8\text{ Hz}$, 1H), 1.99 (d, $J = 5.8\text{ Hz}$, 1H), 1.28 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 169.3, 137.9, 128.9, 128.0, 126.1, 67.1, 67.0, 46.0, 42.3, 34.2, 32.0, 26.7, 21.5, 21.4; FTIR (thin film) ν 2855 (w), 1635 (s), 1581 (s), 1236 (s), 699 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{16}\text{H}_{21}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 260.1645; found 260.1648.

⁵⁰ Castral, T.C.; Matos, A.P.; Monteiro, J.L.; Araujo, F.M.; Bondancia, T.M.; Batista-Pereira, L.G.; Fernandes, J.B.; Vieira, P.C.; da Silva, M.F.G.F.; Corrêa, A.G. *J. Agric. Food Chemistry* **2011**, *59*, 4822–4827.



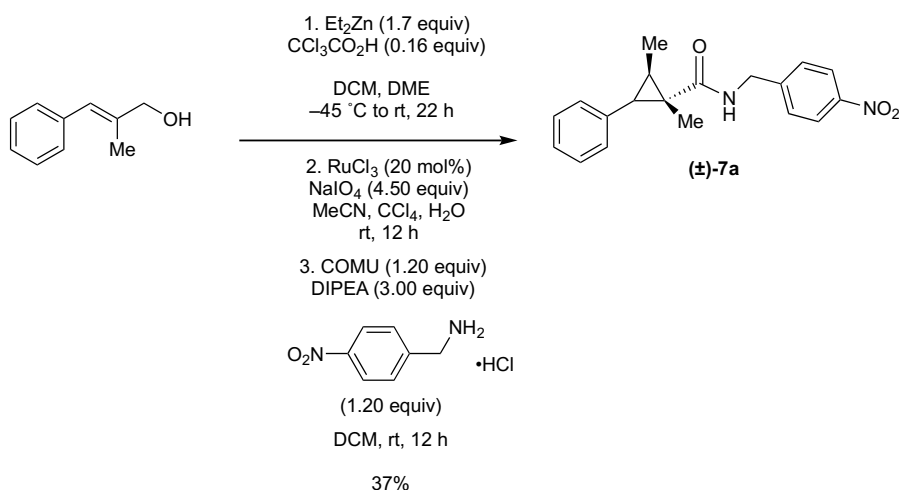
To a solution of 2,2-dimethyl-3-phenylcyclopropane-1-carbaldehyde⁵¹ (690 mg, 3.97 mmol, 1.00 equiv) and dipropylamine (0.60 mL, 4.28 mmol, 1.10 equiv) in anhydrous 1,2-dichloroethane (14 mL) was added sodium triacetoxyborohydride (4.24 g, 20.0 mmol, 5.00 equiv). The resulting suspension was stirred at room temperature for 2 hours and quenched with sat. NaHCO₃ (aq.) (20 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered, concentrated under reduced pressure and purified by flash column chromatography on silica gel (0% to 30% diethyl ether in hexanes) to give (±)-5e as a colorless oil (840 mg, 82%). ¹H NMR (500 MHz, CDCl₃) δ 7.28–7.10 (m, 5H), 2.65 (ddd, *J* = 44.7, 13.2, 6.2 Hz, 2H), 2.51–2.40 (m, 4H), 1.62–1.43 (m, 5H), 1.23–1.15 (m, 4H), 0.91–0.76 (m, 9H); ¹³C NMR (125.7 MHz, CDCl₃) δ 140.1, 128.8, 127.9, 125.6, 55.9, 53.9, 35.4, 35.3, 27.0, 23.0, 22.0, 20.4, 12.1; FTIR (thin film) ν 2957 (m), 1455 (m), 1068 (m), 698 (s) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₈H₂₉N [M+H]⁺: 260.2373; found 260.2365.



To a mixture of (Z)-(2-methylbut-1-en-1-yl)benzene (355 mg, 2.43 mmol, 1.00 equiv) and CuSO₄ (116 mg, 0.730 mmol, 30 mol%) in benzene (4.0 mL) heated to 100 °C was added ethyl diazoacetate (85%, 978 mg, 7.28 mmol, 3.00 equiv) in benzene (1.30 mL) dropwise over 6

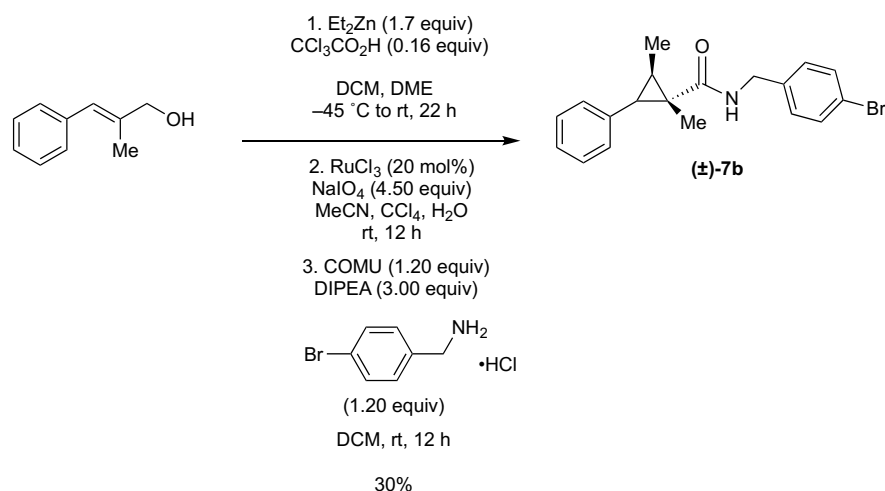
⁵¹ Harvey, A.; Avery, T.; Paul, D.; Ripper, J.; Huff, B.; Singh, R.; Scheffer, L.; Joseph, C.; Morice, C.; Giethlen, B. PCT Int. Appl., 2014019023, 06 Feb 2014.

hours. After cooling to room temperature, the reaction mixture was filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (0% to 20% diethyl ether in hexanes) to give a mixture of diastereomeric cyclopropanes. This mixture (343 mg) was dissolved in a 1:1:1 mixture of tetrahydrofuran, methanol, and 2 M NaOH (aq.) (10.2 mL) and stirred overnight at room temperature. The reaction mixture was acidified with 1 M HCl (aq.) to pH=2 and extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried with MgSO₄ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (0% to 50% diethyl ether in hexanes) to give a single diastereomer of carboxylic acid; the other diastereomer was recovered as the ethyl ester. The resulting carboxylic acid (200.0 mg, 0.980 mmol, 1.00 equiv) was dissolved in benzene (4.8 mL) and methanol (2.0 mL), and (trimethylsilyl)diazomethane (2.0 M in hexanes, 0.59 mL, 1.2 mmol, 1.2 equiv) was added slowly over 15 minutes. The resulting solution was stirred for 2 hours, then quenched by addition of HCl (2.0 M in diethyl ether, 1.0 mL). The mixture was concentrated under reduced pressure and the resulting residue purified by flash column chromatography (0% to 20% diethyl ether in hexanes) to give pure (±)-**5g** as a single diastereomer (189 mg, 36% over three steps). A single crystal suitable for X-ray diffraction analysis was grown by slow evaporation from hexanes. ¹H NMR (500 MHz, CDCl₃) δ 7.30–7.14 (m, 5H), 3.73 (s, 3H), 2.75 (d, *J* = 5.9 Hz, 1H), 1.98 (d, *J* = 5.9 Hz, 1H), 1.35 (s, 3H), 1.24 (dq, *J* = 14.2, 7.3 Hz, 1H), 1.05–0.95 (m, 1H), 0.84 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (125.7 MHz, CDCl₃) δ 173.0, 137.4, 129.0, 128.3, 126.5, 51.8, 38.6, 34.6, 30.6, 28.5, 17.5, 10.8; FTIR (thin film) ν 2965 (w), 1725 (s), 1439 (m), 1162 (s), 770 (m), 699 (s) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₄H₁₈O₂ [M+H]⁺: 219.1280; found 219.1384.



To anhydrous dichloromethane (9.0 mL) was added diethylzinc (1.0 M in hexanes, 9.0 mL, 9.0 mmol, 1.7 equiv). The solution was cooled down to -45°C . A solution of 1,1-diiodoethane (5.00 g, 17.7 mmol, 3.31 equiv) in anhydrous dichloromethane (4.0 mL) was added. After stirring for one hour at -40°C , a solution of trichloroacetic acid (143 mg, 0.875 mmol, 0.164 equiv) and DME (0.48 mL) in anhydrous dichloromethane (4.0 mL), The reaction mixture was warmed to -10°C and stirred at that temperature for one hour. A solution of *trans*-2-methyl-3-phenyl-2-propen-1-ol (0.77 mL, 5.35 mmol, 1.00 equiv) was added as a solution in dichloromethane (4.0 mL). The reaction was warmed to room temperature and stirred for 20 hours. Sat. NH_4Cl (aq.) (10 mL) was added. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3×20 mL). The combined organic layers were dried over MgSO_4 , filtered, concentrated under reduced pressure and purified by flash column chromatography on silica gel (10% to 70% diethyl ether in hexanes) to give a colorless oil (600 mg). 250 mg of this oil was dissolved in a 1:1:2.25 mixture of acetonitrile, carbon tetrachloride, and water (8.0 mL). The mixture was rapidly stirred, and RuCl_3 hydrate (59.0 mg, 0.28 mmol, 20 mol%) and sodium periodate (1.37 g, 6.39 mmol, 4.50 equiv) were added, and the mixture was further stirred for 12 hours. The organic layer was separated and the aqueous layer was extracted with ethyl acetate

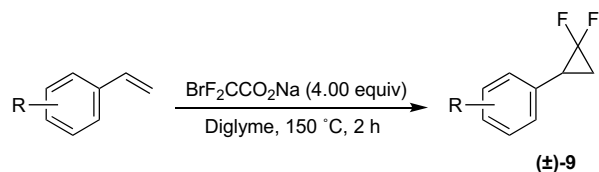
(100 mL). The combined organic layers were dried with MgSO_4 , filtered, concentrated under reduced pressure and purified by flash column chromatography (20% to 90% diethyl ether in hexanes). To a solution of 135 mg of the resulting viscous residue (0.710 mmol) in anhydrous dichloromethane (7.0 mL) was added 4-nitrobenzylamine hydrochloride (161 mg, 0.85 mmol, 1.20 equiv), (1-cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU, 365 mg, 0.85 mmol, 1.20 equiv), and diisopropylethylamine (372 μL , 2.13 mmol, 3.00 equiv). The reaction mixture was stirred for 12 hours at room temperature, then concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (20% to 100% diethyl ether in hexanes) to give ($\pm$)-**7a** as a colorless oil which solidified on standing (200 mg, 37% over three steps, single diastereomer). ^1H NMR (500 MHz, CDCl_3) δ 8.19 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H), 7.33–7.28 (m, 2H), 7.25–7.20 (m, 1H), 7.19–7.14 (m, 2H), 6.44–6.31 (br. m, 1H), 4.61 (d, J = 5.9 Hz, 2H), 2.86 (d, J = 9.8 Hz, 1H), 1.91 (dq, J = 9.8, 6.8 Hz, 1H), 1.13 (s, 3H), 1.09 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 176.1, 147.5, 146.5, 135.8, 131.0, 128.5, 126.7, 124.1, 43.6, 32.7, 26.8, 24.4, 11.6, 10.2; FTIR (thin film) ν 3347 (w), 2929 (w), 1636 (m), 1515 (s), 1343 (s), 701 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 325.1547; found 325.1550.



To anhydrous dichloromethane (9.0 mL) was added a solution of diethylzinc (1.0 M in hexanes, 9.0 mL, 9.0 mmol, 1.7 equiv). The solution was cooled down to $-45\text{ }^{\circ}\text{C}$. A solution of 1,1-diiodoethane (5.00 g, 17.7 mmol, 3.31 equiv) in anhydrous dichloromethane (4.0 mL) was added. After stirring for one hour at $-40\text{ }^{\circ}\text{C}$, a solution of trichloroacetic acid (143 mg, 0.875 mmol, 0.164 equiv) and DME (0.48 mL) in anhydrous dichloromethane (4.0 mL), The reaction mixture was warmed to $-10\text{ }^{\circ}\text{C}$ and stirred at that temperature for one hour. A solution of *trans*-2-methyl-3-phenyl-2-propen-1-ol (0.77 mL, 5.35 mmol, 1.00 equiv) was added as a solution in dichloromethane (4.0 mL). The reaction was warmed to room temperature and stirred for 20 hours. Sat. NH_4Cl (aq.) (10 mL) was added. The organic layer was separated, and the aqueous layer was extracted with diethyl ether ($3 \times 20\text{ mL}$). The combined organic layers were dried over MgSO_4 , filtered, concentrated under reduced pressure and purified by flash column chromatography on silica gel (10% to 70% diethyl ether in hexanes) to give a colorless oil (600 mg). 250 mg of this oil was dissolved in in a 1:1:2.25 mixture of acetonitrile, carbon tetrachloride, and water (8.0 mL). The mixture was rapidly stirred, and RuCl_3 hydrate (59.0 mg, 0.28 mmol, 20 mol%) and sodium periodate (1.37 g, 6.39 mmol, 4.50 equiv) were added, and the mixture was further stirred for 12 hours. After 12 hours, the reaction was quenched with 1 M HCl (aq.) (20 mL) and diluted with diethyl ether (100 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were dried with MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (20% to 90% diethyl ether in hexanes). To 240 mg of the resulting viscous residue (1.26 mmol) in dichloromethane (12.6 mL) was added methyl 4-bromobenzylamine hydrochloride (336 mg, 1.51 mmol, 1.20 equiv), (1-cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU,

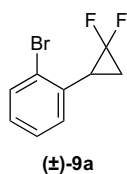
647 mg, 1.51 mmol, 1.20 equiv), and diisopropylethylamine (635 μ L, 4.53 mmol, 3.00 equiv). The reaction mixture was stirred for 12 hours at room temperature, then concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (20% to 100% diethyl ether in hexanes) to give ($\pm$)-**7b** as a colorless oil (331 mg, 30% over three steps, single diastereomer). ^1H NMR (500 MHz, CDCl_3) δ 8.00 (d, J = 8.1 Hz, 2H), 7.45–7.17 (m, 7H), 6.52–6.45 (br. m, 1H), 4.56 (d, J = 5.6 Hz, 2H), 3.91 (s, 3H), 2.85 (d, J = 9.8 Hz, 1H), 1.95–1.86 (m, 1H), 1.12 (s, 3H), 1.08 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 175.7, 166.9, 144.1, 135.8, 130.9, 130.0, 129.2, 128.3, 127.5, 126.4, 52.1, 43.7, 32.3, 26.6, 24.0, 11.3, 10.0; FTIR (thin film) ν 3348 (w), 2930 (w), 1729 (w), 1635 (s), 1526 (s), 1013 (s), 701 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{21}\text{H}_{23}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 338.1751; found 338.1756.

General Procedure for the Synthesis of gem-Difluorocyclopropanes:

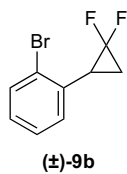


To a solution of substituted styrene (6.50 mmol, 1.00 equiv) in anhydrous diglyme (20 mL) at 150 $^\circ\text{C}$ was added a solution of $\text{BrF}_2\text{CCO}_2\text{Na}$ ⁵² (5.16 g, 26.00 mmol, 4.00 equiv) in anhydrous diglyme (15 mL). The resulting suspension was stirred at 150 $^\circ\text{C}$ for 2 hours. Upon cooling, the reaction mixture was diluted with diethyl ether (150 mL), washed with H_2O (5×50 mL), dried over Na_2SO_4 , filtered, concentrated under reduced pressure and purified by flash column chromatography on silica gel (hexanes).

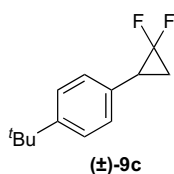
⁵² Li, Q *et al. Journal of Fluorine Chemistry* **2014**, 163, 38–41.



Prepared according to the general procedure. 2-Bromostyrene (0.81 mL, 6.5 mmol) was reacted to give (±)-9a as a colorless oil (1.24 g, 82%). ¹H NMR (500 MHz, CDCl₃) δ 7.61 (d, *J* = 7.6 Hz, 1H), 7.33–7.13 (m, 3H), 2.89 (q, *J* = 11.0 Hz, 1H), 1.95–1.84 (m, 1H), 1.68–1.57 (m, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 133.7, 132.8, 129.3, 129.1, 127.5, 126.3, 112.6 (dd, *J* = 287.0, 283.1 Hz), 28.1 (t, *J* = 12.0 Hz), 16.8 (t, *J* = 11.0 Hz); ¹⁹F NMR (470.4 MHz, CDCl₃) δ -126.8 (dtd, *J* = 153.8, 11.9, 3.6 Hz, 1F), -140.8 (ddd, *J* = 153.8, 12.5, 4.8 Hz, 1F); FTIR (thin film) ν 3061 (w), 1568 (m), 1470 (s), 1228 (s), 1021 (s), 748 (s), 445 (m) cm⁻¹; HRGCMS (EI⁺) Calc'd for C₉H₇F₂Br [M]⁺: 232.9774; found 232.9772.

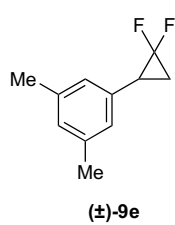


Prepared according to the general procedure. 3-Bromostyrene (0.85 mL, 6.5 mmol) was reacted to give (±)-9b as a colorless oil (950 mg, 66%). ¹H NMR (500 MHz, CDCl₃) δ 7.45–7.27 (m, 2H), 7.24–7.14 (m, 2H), 2.72 (td, *J* = 12.3, 8.2 Hz, 1H), 1.85 (tdd, *J* = 12.2, 7.8, 4.9 Hz, 1H), 1.63 (dtd, *J* = 12.5, 8.2, 3.8 Hz); ¹³C NMR (125.7 MHz, CDCl₃) δ 136.1, 131.3, 130.5, 130.1, 126.9, 122.6, 112.3 (t, *J* = 284.1 Hz), 26.8 (t, *J* = 11.5 Hz), 17.3 (t, *J* = 10.5 Hz); ¹⁹F NMR (470.4 MHz, CDCl₃) δ -126.0 (dtd, *J* = 154.4, 12.5, 3.6 Hz, 1F), -142.1 (ddd, *J* = 154.4, 12.5, 4.8 Hz); FTIR (thin film) ν 3066 (w), 1567 (s), 1228 (s), 1020 (s), 778 (s), 476 (m) cm⁻¹; HRGCMS (EI⁺) Calc'd for C₉H₇F₂Br [M]⁺: 232.9773; found 232.9772.



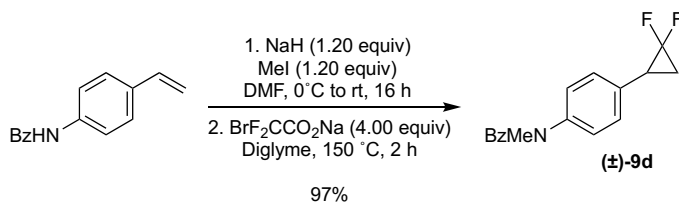
Prepared according to the general procedure. 4-tert-Butylstyrene (1.19 mL, 6.50 mmol) was reacted to give (±)-9c as a colorless oil (1.26 g, 92%). ¹H NMR (500 MHz, CDCl₃) δ 7.47 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 2.81 (td, *J* = 12.5, 8.1 Hz, 1H), 1.87 (tdd, *J* = 12.5, 7.8, 4.6 Hz, 1H), 1.68 (dtd, *J* = 12.2, 8.1, 3.9 Hz, 1H), 1.43 (s, 9H); ¹³C NMR (125.7 MHz, CDCl₃) δ 150.3, 130.8, 127.8, 125.6, 112.9 (q, *J* =

284.6 Hz), 34.6, 31.5, 27.0 (t, $J = 11.3$ Hz), 17.2 (t, $J = 10.5$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -125.9 (dtd, $J = 153.5, 13.1, 3.6$ Hz, 1F), -142.4 (ddd, $J = 153.5, 13.1, 4.8$ Hz, 1F); FTIR (thin film) ν 2963 (m), 1520 (s), 1269 (s), 932 (s), 550 (m) cm^{-1} ; HRGCMS (EI^+) Calc'd for $\text{C}_{13}\text{H}_{16}\text{F}_2$ $[\text{M}]^+$: 211.1293; found 211.1293



Prepared according to the general procedure. 1,3-Dimethyl-5-vinylbenzene⁵³ (610 mg, 4.61 mmol) was reacted to give (±)-9e as a colorless oil (550 g, 65%).

^1H NMR (500 MHz, CDCl_3) δ 6.98 (br, s, 1H), 6.92 (br. s, 2H), 2.74 (td, $J = 12.6, 8.3$ Hz, 1H), 2.38 (s, 6H), 1.82 (tdd, $J = 12.2, 7.6, 4.9$ Hz, 1H), 1.66 (dtd, $J = 12.4, 8.2, 3.9$ Hz, 1H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 138.1, 133.6, 129.0, 126.0, 112.8 (t, $J = 286.5$ Hz), 27.3 (t, $J = 11.5$ Hz), 21.3, 16.9 (t, $J = 10.5$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -125.8 (dtd, $J = 153.2, 12.5, 3.6$ Hz, 1F), -142.3 (ddd, $J = 153.2, 12.5, 4.8$ Hz, 1F); FTIR (thin film) ν 2920 (w), 1607 (m), 1318 (m), 1209 (s), 1012 (m), 843 (m) cm^{-1} ; HRGCMS (EI^+) Calc'd for $\text{C}_{11}\text{H}_{12}\text{F}_2$ $[\text{M}]^+$: 182.0902; found 182.0900.

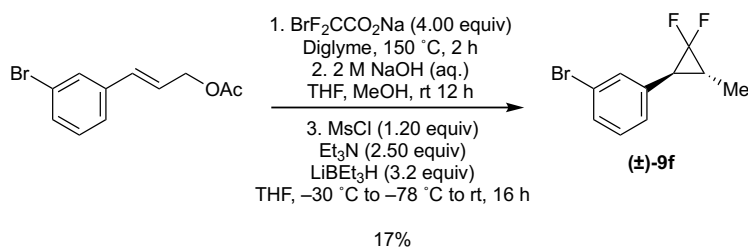


To a solution of *N*-(4-vinylphenyl)benzamide⁵⁴ (2.23 g, 9.99 mmol, 1.00 equiv) in anhydrous dimethylformamide (25 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 480 mg, 12.00 mmol, 1.20 equiv). The resulting suspension was stirred at that temperature for 30 mins before the addition of iodomethane (0.75 mL, 12.1 mmol, 1.20 equiv). The reaction

⁵³ Haubenreisser, S.; Wöste, T.H.; Martinez, C.; Ishihara, K.; Muñiz, K. *Angew. Chem. Int. Ed.* **2016**, *55*, 413–417.

⁵⁴ Shah, P. N., Min, J., Kim, H-J, Park, S-Y, Lee, J-S *Macromolecules* **2011**, *44*, 7917–7925.

mixture was allowed to warm to room temperature and stirred under N_{2(g)}. After 16 hours, the reaction was quenched with water (50 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water (50 mL) and brine (4 × 100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *N*-methyl-*N*-(4-vinylphenyl)benzamide as a colorless viscous oil. This oil was then subjected to the general procedure with the following modification: flash column chromatography was conducted with 0% to 10% ethyl acetate in dichloromethane. Excess diglyme was removed by vacuum distillation to provide (±)-**9d** as a waxy solid (2.78 g, 97%). ¹H NMR (500 MHz, CDCl₃) δ 7.38–7.00 (m, 9H), 3.52 (s, 3H), 2.69 (q, *J* = 12.2 Hz, 1H), 1.87–1.76 (m, 1H), 1.62–1.53 (m, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 170.5, 143.8, 135.8, 131.9, 129.6, 128.7, 128.6, 127.7, 126.8, 112.3 (dd, *J* = 287.5, 283.6 Hz), 38.3, 26.6 (t, *J* = 11.5 Hz), 17.1 (t, *J* = 10.5 Hz); ¹⁹F NMR (470.4 MHz, CDCl₃) δ -126.0 (dtd, *J* = 154.4, 13.1, 4.2 Hz, 1F), -142.5 (ddd, *J* = 153.8, 12.5, 4.8 Hz, 1F); FTIR (thin film) ν 3030 (w), 1638 (s), 1363 (s), 933 (m), 697 (s) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₇H₁₅F₂NO [M+H]⁺: 288.1194; found 288.1209.



(±)-**9f**: To 3-bromocinnamyl acetate⁵⁵ (1.49 g, 5.80 mmol, 1.00 equiv) in anhydrous diglyme (29 mL) at 150 °C was added a solution of BrF₂CCO₂Na (4.56 g, 23.2 mmol, 4.00 equiv) in anhydrous diglyme (58 mL). The resulting suspension was stirred at 150 °C for 12 hours. Upon cooling, the reaction mixture was diluted with diethyl ether (250 mL), washed with H₂O (5 ×

⁵⁵ Robbins, D.W., Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, 52, 933–937.

50 mL), dried over MgSO₄, filtered, concentrated under reduced pressure and purified by flash column chromatography on silica gel (0% to 5% diethyl ether in hexanes). To the resulting colorless oil was added 2 M NaOH (aq.) (9.0 mL), tetrahydrofuran (9.0 mL), and methanol (9.0 mL), and the reaction was stirred at room temperature. After 12 hours, 100 mL diethyl ether was added, and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3 × 50 mL), and the combined organic layers were dried with MgSO₄, filtered, and concentrated under reduced pressure. To 670 mg of the resulting residue was added triethylamine (911 μL, 6.60 mmol, 2.50 equiv) and tetrahydrofuran (16.0 mL). The reaction mixture was cooled to -30 °C, and methanesulfonyl chloride (244 μL, 3.15 mmol, 1.20 equiv) was added. The reaction mixture was stirred at -30 °C for 4 hours and cooled to -78 °C. To the reaction was added LiBEt₃H (1.0 M in tetrahydrofuran, 8.4 mL, 3.2 equiv), and the reaction was allowed to warm to room temperature over 12 hours. After 12 hours, the reaction was cooled to 0 °C, and a 10:1 mixture of 1 M NaOH and 30% H₂O₂ (aq.) (10 mL) was added dropwise. The resulting biphasic solution was stirred at reflux for 1 hour, cooled, and the organic layer was separated. The aqueous layer was further extracted with diethyl ether (50 mL). The organic layers were dried with MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexanes) to give (±)-**9f** as a colorless oil (251 mg, 17% over 3 steps as a single diastereomer). ¹H NMR (500 MHz, CDCl₃) δ 7.39 (ddd, *J* = 7.8, 2.0, 1.0 Hz, 1H), 7.35 (s, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 2.25 (dd, *J* = 12.6, 7.7 Hz, 1H), 1.89–1.78 (m, 2H), 1.35 (ddd, *J* = 6.6, 2.4, 1.2 Hz, 3H); ¹³C NMR (125.7 MHz, CDCl₃) δ 136.8, 131.1, 130.2, 130.1, 126.7, 114.4 (t, *J* = 289.4 Hz), 33.7 (t, *J* = 11.3 Hz), 24.8 (t, *J* = 10.1 Hz), 11.5; ¹⁹F NMR (470.4 MHz, CDCl₃) δ -137.1–138.2 (m); FTIR (thin film)

ν 2975 (w), 1483 (m), 1305 (m), 1266 (m), 1022 (m) cm^{-1} ; HRGCMS (EI^+) Calc'd for $\text{C}_{10}\text{H}_9\text{BrF}_2$

$[\text{M}]^+$: 245.9850; found 245.9851.

Procedures for 1,3-Difunctionalization

General Procedure A: A low-density polyethylene tube with a stir bar was charged with substituted cyclopropane (1.04 mmol, 1.00 equiv), iodobenzene (12.0 μ L, 0.10 mmol, 10 mol%) and dichloromethane (6.0 mL), and the resulting mixture was vigorously stirred. Pyridinium poly(hydrogen fluoride) (pyr•9HF, 2.72 mL, 104 mmol, 100 equiv HF) was added *via* plastic syringe followed by *m*-chloroperbenzoic acid (*m*CPBA, 77% by weight, 256 mg, 1.14 mmol, 1.10 equiv). The tube was sealed with a low-density polyethylene snap top. After 24 hours at room temperature, the reaction mixture was transferred to a rapidly stirring suspension of basic alumina (15 g) in diethyl ether (100 mL) at -78°C . The slurry was allowed to warm to room temperature and filtered through a basic alumina plug, washing with diethyl ether (200 mL). The filtrate was concentrated under reduced pressure.

General Procedure B: A low density polyethylene tube with a stir bar was charged with substituted cyclopropane (1.04 mmol, 1.00 equiv), iodobenzene (12.0 μ L, 0.100 mmol, 10.0 mol%) and dichloromethane (6.0 mL), and acetic acid (1.79 mL, 31.2 mmol, 30.0 equiv) and the resulting mixture was vigorously stirred. Pyridinium poly(hydrogen fluoride) (pyr•9HF, 2.72 mL, 104 mmol, 100 equiv HF) was added *via* plastic syringe followed by *m*-chloroperbenzoic acid (*m*CPBA, 77% by weight, 0.256 g, 1.14 mmol, 1.10 equiv). The tube was sealed with a low-density polyethylene snap top. After 24 hours at room temperature, the reaction mixture was transferred to a rapidly stirring suspension of basic alumina (15 g) in diethyl ether (100 mL) at -78°C . The slurry was allowed to warm to room temperature and filtered through a basic alumina plug, washing with diethyl ether (200 mL). The filtrate was concentrated under reduced pressure, dissolved in dichloromethane (150 mL) and washed with

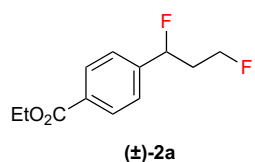
sat. NaHCO_3 (aq.) (75 mL). The organic layer was dried with MgSO_4 , filtered, and concentrated under reduced pressure.

General Procedure C: A 20 mL scintillation vial with a stir bar was charged with substituted cyclopropane (1.04 mmol, 1.00 equiv), iodobenzene (42.0 mg, 0.200 mmol, 20.0 mol%), *m*-chloroperbenzoic acid (*m*CPBA, 77% by weight, 256 mg, 1.14 mmol, 1.10 equiv), dichloromethane (2.0 mL) and trifluoroacetic acid (2.0 mL), and the resulting mixture was stirred vigorously. After 36 hours at room temperature, the reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in tetrahydrofuran (8.0 mL) and 1 M NaOH (aq.) (4 mL) and stirred. After 8 hours, ethyl acetate (50 mL) and water (10 mL) were added. The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (3×50 mL). The combined organic layers were dried with Na_2SO_4 , filtered, and concentrated under reduced pressure.

General Procedure D: A scintillation vial with a stir bar was charged with substituted cyclopropane (1.04 mmol, 1.00 equiv), iodobenzene (24.0 μL , 0.200 mmol, 20.0 mol%) and 1:1 trifluoroacetic acid:acetonitrile (4.0 mL). *m*-Chloroperbenzoic acid (*m*CPBA, 77% by weight, 256 mg, 1.14 mmol, 1.10 equiv) was added, and the reaction was stirred for 36 h. The reaction was concentrated, basified with sat. NaHCO_3 (aq.), extracted with Et_2O (3×15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. This crude residue was dissolved in pyridine (5 mL). Acetic anhydride (0.98 mL, 10.4 mmol, 10 equiv) was added and the reaction was stirred at room temperature for 12 h. The reaction mixture was diluted in diethyl ether (50 mL), washed with 1 M HCl (aq.) (3×10 mL), sat. NaHCO_3 (aq.)

(3 x 10 mL) and brine (10 mL), concentrated and purified by silica gel column chromatography (0% to 10% methanol in dichloromethane).

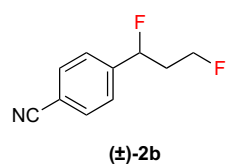
General Procedure E: A scintillation vial with a stir bar was charged with substituted cyclopropane (1.04 mmol, 1.00 equiv), iodobenzene (24.0 μ L, 0.200 mmol, 20.0 mol%), *N*-methyl-*p*-toluenesulfonamide (482 mg, 2.60 mmol, 2.50 equiv), *m*-chloroperbenzoic acid (*m*CPBA, 77% by weight, 256 mg, 1.14 mmol, 1.10 equiv) and dichloromethane (3.0 mL). The resulting solution was cooled down to 0 °C. Boron trifluoride diethyl etherate (BF₃•OEt₂, 256 μ L, 2.07 mmol, 2.00 equiv) was added dropwise, and the reaction mixture was left to warm to room temperature while stirring for 24 h. The reaction mixture was diluted with diethyl ether (40 mL), washed with sat. NaHCO₃ (aq.) (3 x 10 mL) and brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure.



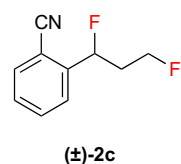
Prepared according to general procedure A using ethyl 4-cyclopropylbenzoate (**1a**, 198 mg, 1.04 mmol). After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to

10% diethyl ether in hexanes) to give (±)-**2a** as a colorless oil (180 mg, 76%). ¹H NMR (500 MHz, CDCl₃) δ 8.05 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 5.68 (ddd, *J* = 47.8, 8.5, 4.6 Hz, 1H), 4.76–4.43 (m, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 2.31–2.10 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (125.7 MHz, CDCl₃) δ 166.1, 144.4 (d, *J* = 19.6 Hz), 130.7 (d, *J* = 1.4 Hz), 129.9, 125.2 (d, *J* = 7.2 Hz), 90.1 (dd, *J* = 172.5, 4.8 Hz), 79.7 (dd, *J* = 165.8, 4.8 Hz), 61.1, 38.2 (dd, *J* = 23.5, 19.6 Hz), 14.3; ¹⁹F NMR (470.4 MHz, CDCl₃) δ -182.4 (ddd, *J* = 47.1, 30.4, 16.1 Hz, 1F), -222.6 (tdd, *J* = 47.1, 31.0, 20.3 Hz, 1F); FTIR (thin film) ν 2980 (w), 1715 (s), 1272 (s),

1105 (s), 704 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{12}\text{H}_{14}\text{F}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 229.1035; found 229.1042.

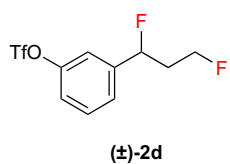


Prepared according to general procedure A using 4-cyclopropylbenzonitrile (**1b**, 149 mg, 1.04 mmol). After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 10% diethyl ether in hexanes) to give (±)-**2b** as a colorless oil (113 mg, 60%). ^1H NMR (500 MHz, CDCl_3) δ 7.67 (d, $J = 8.1$ Hz, 2H), 7.45 (d, $J = 8.1$ Hz, 2H), 5.77–5.61 (m, 1H), 4.77–4.44 (m, 2H), 2.32–2.11 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 144.7 (d, $J = 19.6$ Hz), 132.5, 125.9 (d, $J = 7.2$ Hz), 118.4, 112.3 (d, $J = 1.4$ Hz), 89.6 (dd, $J = 173.9, 4.3$ Hz), 79.4 (dd, $J = 165.8, 4.3$ Hz), 38.1 (dd, $J = 23.5, 20.1$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -183.8– -184.2 (m, 1F), -222.3– -222.8 (m, 1F); FTIR (thin film) ν 2974 (w), 2230 (m), 1391 (m), 1033 (s), 831 (s), 565 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{10}\text{H}_9\text{F}_2\text{N}$ $[\text{M}+\text{H}]^+$: 182.0766; found 182.0784.

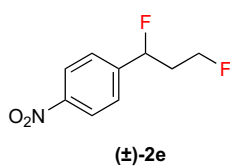


Prepared according to general procedure A using 2-cyclopropylbenzonitrile (**1c**, 149 mg, 1.04 mmol). After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 10% diethyl ether in hexanes) to give (±)-**2c** as a colorless oil (115 mg, 61%). ^1H NMR (500 MHz, CDCl_3) δ 7.72–7.58 (m, 3H), 7.50–7.43 (m, 1H), 6.05–5.90 (m, 1H), 4.81–4.53 (m, 2H), 2.45–2.25 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 142.9 (d, $J = 20.6$ Hz), 133.2 (d, $J = 22.9$ Hz), 129.03 (d, $J = 1$ Hz), 126.2 (d, $J = 8.6$ Hz), 116.7, 109.7 (d, $J = 5.3$ Hz), 88.7 (dd, $J = 174.9, 4.8$ Hz), 79.4 (dd, $J = 166.7, 3.8$ Hz), 37.4 (dd, $J = 23.5, 20.1$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -182.9– -183.3 (m, 1F), -222.0– -

222.4 (m, 1F); FTIR (thin film) ν 2971 (w), 2228 (w), 1036 (m), 905 (s), 725 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{10}\text{H}_9\text{F}_2\text{N}$ $[\text{M}+\text{H}]^+$: 182.0766; found 182.0780.

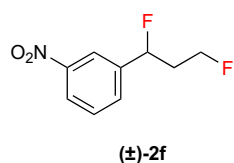


Prepared according to general procedure A using 3-cyclopropylphenyl trifluoromethanesulfonate (**1d**, 277 mg, 1.04 mmol). After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 5% dichloromethane in hexanes) to give (±)-**2d** as a colorless oil (221 mg, 70%). ^1H NMR (500 MHz, CDCl_3) δ 7.53–7.46 (m, 1H), 7.41–7.36 (m, 1H), 7.32–7.25 (m, 2H), 5.78–5.62 (m, 1H), 4.79–4.46 (m, 2H), 2.37–2.13 (m, 1H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 149.9, 142.8 (d, J = 20.6 Hz), 130.7, 125.3 (d, J = 7.2 Hz), 121.4, 118.9 (q, J = 320.5 Hz), 118.5 (d, J = 8.1 Hz), , 89.5 (dd, J = 173.9, 4.8 Hz), 79.6 (dd, J = 165.8, 4.8 Hz), 38.3 (dd, J = 23.5, 19.6 Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -72.9 (s, 3F), -182.07 (ddd, J = 46.5, 30.4, 16.1 Hz, 1F), -222.5–222.9 (m, 1F); FTIR (thin film) ν 2979 (w), 1421 (s), 1206 (s), 1138 (s), 856 (s), 604 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{10}\text{H}_9\text{F}_5\text{O}_3\text{S}$ $[\text{M}+\text{Na}]^+$: 327.0085; found 327.0073.

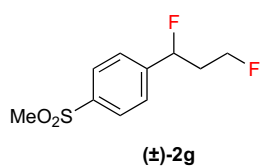


Prepared according to general procedure A using 1-cyclopropyl-4-nitrobenzene (**1e**, 170 mg, 1.04 mmol) with the following modifications: dichloromethane was omitted; 5.0 mol% of iodobenzene was used instead. After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 20% diethyl ether in hexanes) to give (±)-**2e** as a colorless oil (140 mg, 67%). ^1H NMR (500 MHz, CDCl_3) δ 8.23 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 5.84–5.77 (m, 1H), 5.71 (dd, J = 8.3, 4.9 Hz, 1H), 4.80–4.45 (m, 2H), 2.35–2.15 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 148.0, 146.8 (d, J = 20.1 Hz), 126.2 (d, J = 7.7 Hz), 124.0, 89.6 (dd, J = 174.4, 3.8 Hz), 79.5 (dd, J = 165.8, 4.8 Hz), 38.3 (dd, J = 23.0, 20.1 Hz); ^{19}F NMR (470.4 MHz, CDCl_3) -183.9– -184.2

(m, 1F), -222.4– -222.7 (m, 1F); FTIR (thin film) ν 2974 (w), 1608 (m), 1519 (s), 1740 (s), 1344 (s), 1014 (s), 850 (s), 687 (s), 517 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_9\text{H}_9\text{F}_2\text{NO}_2$ $[\text{M}+\text{H}]^+$: 202.0674; found 202.0678.

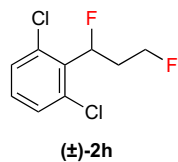


Prepared according to general procedure A using 1-cyclopropyl-3-nitrobenzene (**1f**, 170 mg, 1.04 mmol) with the following modification: dichloromethane was omitted. After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 25% diethyl ether in hexanes) to give (±)-**2f** as a colorless oil (171 mg, 82%). ^1H NMR (500 MHz, CDCl_3) δ 8.22–8.13 (m, 2H), 7.71–7.65 (m, 1H), 7.61–7.54 (m, 1H), 5.82–5.66 (m, 1H), 4.79–4.47 (m, 2H), 2.38–2.16 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 148.4, 141.7 (d, $J = 20.6$ Hz), 131.4 (d, $J = 7.2$ Hz), 129.8, 123.4, 120.8 (d, $J = 8.1$ Hz), 89.5 (dd, $J = 173.9, 4.3$ Hz), 79.5 (dd, $J = 166.2, 4.8$ Hz), 38.0 (dd, $J = 23.5, 19.6$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -181.8– -181.2 (m, 1F), -222.3– -222.8 (m, 1F); FTIR (thin film) ν 2976 (w), 1531 (s), 1350 (s), 1033 (m), 737 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_9\text{H}_9\text{F}_2\text{NO}_2$ $[\text{M}+\text{H}]^+$: 202.0674; found 202.0675.

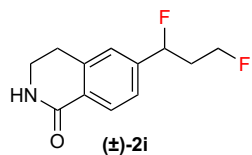


Prepared according to general procedure A using 1-cyclopropyl-4-(methanesulfonyl)benzene (**1g**, 204 mg, 1.04 mmol). After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 100% diethyl ether in hexanes) to give (±)-**2g** as a white solid (183 mg, 75%). ^1H NMR (500 MHz, CDCl_3) δ 7.93 (d, $J = 8.4$ Hz, 2H), 7.52 (d, $J = 8.4$ Hz, 2H), 5.87–5.63 (m, 1H), 4.74–4.43 (m, 2H), 3.02 (s, 3H), 2.29–2.12 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 145.6 (d, $J = 19.6$ Hz), 140.6 (d, $J = 1.4$ Hz), 127.8, 126.1 (d, $J = 7.2$ Hz), 89.6 (dd, $J = 173.4, 4.3$ Hz), 79.5

(dd, $J = 165.8, 4.8$ Hz), 44.4, 38.1 (d, $J = 23.5, 19.6$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -183.7– -184.0 (m, 1F), -222.3– -222.8 (m, 1F); FTIR (thin film) ν 2974 (w), 1603 (w), 1305 (s), 1148 (s), 956 (s), 727 (s), 545 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{10}\text{H}_{12}\text{F}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 235.0599; found 235.0609.

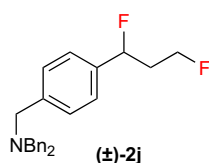


Prepared according to general procedure A using 1,3-dichloro-2-cyclopropylbenzene (**1h**, 195 mg, 1.04 mmol). After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 20% dichloromethane in hexanes) to give (±)-**2h** as a colorless oil (166 mg, 71%). ^1H NMR (500 MHz, CDCl_3) δ 7.35–7.30 (m, 2H), 7.22 (t, $J = 8.5$ Hz, 1H), 6.36 (ddd, $J = 46.6, 9.8, 4.2$ Hz, 1H), 4.82–4.61 (m, 2H), 2.83–2.20 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 134.6 (d, $J = 3.4$ Hz), 133.5 (d, $J = 18.2$ Hz), 130.2 (d, $J = 1.4$ Hz), 129.6, 87.5 (dd, $J = 175.8, 4.8$ Hz), 80.0 (dd, $J = 166.7, 4.8$ Hz), 34.2 (d, $J = 23.0, 20.1$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -192.0 (ddd, $J = 46.5, 29.8, 11.3$ Hz, 1F), -227.4 (tdd, $J = 47.1, 32.8, 19.1$ Hz, 1F); FTIR (thin film) ν 2973 (w), 1564 (m), 1475 (m), 1034 (m), 905 (s), 727 (s) cm^{-1} ; HRGCMS (EI^+) Calc'd for $\text{C}_9\text{H}_8\text{Cl}_2\text{F}_2$ $[\text{M}]^+$: 223.9966; found 223.9966.



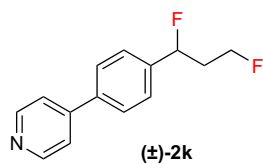
Prepared according to general procedure A using 6-cyclopropyl-3,4-dihydroisoquinolin-1(2H)-one (**1i**, 97.4 mg, 0.52 mmol) with the following modification: 20.0 mol% of iodobenzene was used instead. After work-up, the crude residue was purified by flash column chromatography on silica gel (5% to 50% diethyl ether in hexanes) to give (±)-**2i** as a white solid (70.3 mg, 60%). ^1H NMR (500 MHz, CDCl_3) δ 8.06 (d, $J = 8.0$ Hz, 1H), 7.45 (br. s, 1H), 7.30 (d, $J = 8.0$ Hz, 1H), 7.21 (s, 1H), 5.66 (ddd, $J =$

48.1, 8.5, 4.6 Hz, 1H), 4.78–4.43 (m, 2H), 3.63–3.52 (m, 2H), 3.03–2.99 (t, $J = 6.6$ Hz, 2H), 2.36–2.10 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 166.3, 143.6 (d, $J = 19.6$ Hz), 139.5, 129.3, 128.4, 124.3 (d, $J = 7.2$ Hz), 124.1 (d, $J = 7.2$ Hz), 90.2 (dd, $J = 172.5, 4.3$ Hz), 79.8 (dd, $J = 165.8, 4.3$ Hz), 40.1, 38.2 (dd, $J = 23.5, 19.6$ Hz), 28.4; ^{19}F NMR (470.4 MHz, CDCl_3) δ -181.9 (ddd, $J = 47.1, 31.0, 15.5$ Hz, 1F), -222.5 (tdd, $J = 46.5, 31.0, 20.9$ Hz, 1F); HRMS (ESI-TOF) Calc'd for $\text{C}_{12}\text{H}_{13}\text{F}_2\text{NO}$ $[\text{M}+\text{H}]^+$: 226.1038; found 226.1045.

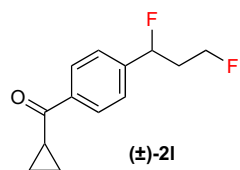


Prepared according to general procedure A using *N,N*-dibenzyl-1-(4-cyclopropylphenyl)methanamine (**1j**, 341 mg, 1.04 mmol) with the following modifications: 25 equiv of HF were used instead; after 24 h, 4 M NaOH (aq.)

(100 mL) was added to the reaction mixture at -78 °C instead of basic alumina. The mixture was allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted with 1:1 ethyl acetate:diethyl ether (3×100 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , filtered, concentrated under reduced pressure. After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 10% diethyl ether in hexanes) to give (**±**)-**2j** as a colorless oil (236 mg, 62%). ^1H NMR (500 MHz, CDCl_3) δ 7.45–7.20 (m, 14H), 5.63 (ddd, $J = 47.4, 8.8, 3.9$ Hz, 1H), 4.70 (dtd, $J = 47.0, 8.8, 3.9$ Hz, 1H), 4.52 (ddt, $J = 46.5, 10.3, 4.9$ Hz, 1H), 3.57 (s, 6H), 2.45–2.10 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 140.6 (d, $J = 2.3$ Hz), 139.7, 129.1, 128.9, 128.5, 127.1, 125.7, 125.7, 90.8 (dd, $J = 171.1, 5.8$ Hz), 80.3 (dd, $J = 165.3, 4.6$ Hz), 58.18, 57.8, 38.3 (dd, $J = 24.3, 19.7$); ^{19}F NMR (470.4 MHz, CDCl_3) -177.3 (ddd, $J = 46.5, 31.0, 14.3$ Hz, 1F), -222.6 (tdd, $J = 47.7, 31.0, 20.3$ Hz, 1F); FTIR (thin film) ν 2924 (w), 2795 (w), 1029 (m), 745 (m), 698 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{24}\text{H}_{25}\text{F}_2\text{N}$ $[\text{M}+\text{H}]^+$: 366.2028; found 366.2036.

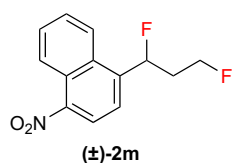


Prepared according to general procedure A using 4-(4-cyclopropylphenyl)pyridine (**1k**, 203 mg, 1.04 mmol) with the following modifications: 25 equiv of HF and 20.0 mol% of iodobenzene were used instead; after 24 h, 4 M NaOH (aq.) (100 mL) was added to the reaction mixture at $-78\text{ }^{\circ}\text{C}$ instead of basic alumina. The mixture was allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted with 1:1 ethyl acetate:diethyl ether ($3 \times 100\text{ mL}$). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , filtered, concentrated under reduced pressure. After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 10% methanol in dichloromethane) to give (±)-**2k** as a colorless oil (153 mg, 63%). ^1H NMR (500 MHz, CDCl_3) δ 8.90–8.45 (br. s, 2H), 7.68–7.62 (m, 2H), 7.53–7.43 (m, 4H), 5.7 (ddd, $J = 47.6, 9.0, 3.9\text{ Hz}$, 1H), 4.80–4.46 (m, 2H), 2.42–2.14 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 150.4, 147.7, 140.5 (d, $J = 19.6\text{ Hz}$), 138.5 (d, $J = 1.9\text{ Hz}$), 127.4, 126.3 (d, $J = 7.2\text{ Hz}$), 121.7, 90.3 (dd, $J = 171.5, 4.8\text{ Hz}$), 79.9 (dd, $J = 165.3, 4.3\text{ Hz}$), 38.2 (dd, $J = 24.0, 19.6\text{ Hz}$); ^{19}F NMR (470.4 MHz, CDCl_3) δ -184.6 (ddd, $J = 48.3, 31.0, 14.3\text{ Hz}$, 1F), -227.7 (tdd, $J = 47.1, 31.0, 20.7\text{ Hz}$, 1F); FTIR (thin film) ν 2973 (w), 1677 (s), 1489 (m), 1034 (m), 812 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{14}\text{H}_{13}\text{F}_2\text{N}$ $[\text{M}+\text{H}]^+$: 234.1089; found 234.1099.

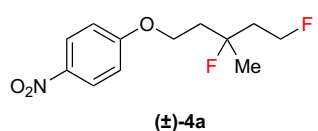


Prepared according to general procedure A using cyclopropyl(4-cyclopropylphenyl)methanone (**1l**, 194 mg, 1.04 mmol). After work-up, the crude residue was purified by flash column chromatography on silica gel (5% to 35% diethyl ether in hexanes) to give (±)-**2l** as a colorless oil (128 mg, 55%). ^1H NMR (500 MHz, CDCl_3) δ 8.04 (d, $J = 7.8\text{ Hz}$, 2H), 7.46 (d, $J = 8.3\text{ Hz}$, 2H), 5.73 (ddd, $J = 47.4, 8.3,$

4.4 Hz, 1H), 4.72 (dtd, $J = 47.0, 8.8, 3.9$ Hz, 1H), 4.54 (ddt, $J = 46.5, 9.8, 4.9$ Hz, 1H), 2.67 (tt, $J = 7.8, 4.9$ Hz, 1H), 2.41–2.12 (m, 2H), 1.28–1.23 (m, 2H), 1.11–1.01 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 200.3, 144.3 (d, $J = 19.2$ Hz), 138.3, 128.6, 125.5 (d, $J = 7.7$ Hz), 90.2 (dd, $J = 3.8, 172.5$), 79.9 (dd, $J = 169.6, 3.8$), 38.4 (dd, $J = 24.0, 20.1$), 17.5, 12.0; ^{19}F NMR (470.4 MHz, CDCl_3) -182.4 (ddd, $J = 47.7, 31.0, 16.7$ Hz, 1F), -222.6 (tdd, $J = 46.6, 31.0, 20.3$, 1F); FTIR (thin film) ν 2973 (w), 1667 (s), 1740 (s), 1224 (s), 992 (s), 727 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{13}\text{H}_{14}\text{F}_2\text{O}$ $[\text{M}+\text{H}]^+$: 225.1085; found 225.1085.

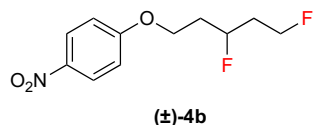


Prepared according to general procedure A using 1-cyclopropyl-4-nitronaphthalene (**1m**, 222 mg, 1.04 mmol). After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 10% diethyl ether in hexanes) to give (±)-**2m** as a yellow oil (91.4 mg, 35%). ^1H NMR (500 MHz, CDCl_3) δ 8.51 (d, $J = 8.5$ Hz, 1H), 8.16 (d, $J = 7.8$ Hz, 1H), 7.98 (d, $J = 8.5$ Hz, 1H), 7.76–7.63 (m, 3H), 6.52–6.36 (m, 1H), 4.94–4.57 (m, 2H), 2.58–2.16 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 147.2, 142.1 (d, $J = 18.2$ Hz), 130.2 (d, $J = 3.8$ Hz), 129.2, 128.1, 125.2, 124.0, 123.2, 123.1, 121.1 (d, $J = 12.9$ Hz), 87.8 (dd, $J = 174.4, 3.8$ Hz), 79.9 (dd, $J = 165.8, 2.9$ Hz), 38.1 (dd, $J = 23.5, 20.1$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -191.3– -191.7 (m, 1F), -226.9– -227.3 (m, 1F); FTIR (thin film) ν 2972 (w), 1515 (s), 1336 (m), 1042 (m), 764 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{13}\text{H}_{11}\text{F}_2\text{NO}_2$ $[\text{M}+\text{H}]^+$: 252.0831; found 252.0839.

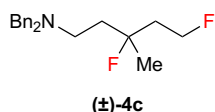


Prepared according to general procedure A using 1-(2-(1-methylcyclopropyl)ethoxy)-4-nitrobenzene (**3a**, 230 mg, 1.04 mmol) with the following modifications: 20 equiv of HF and 20.0 mol% of iodobenzene were used

instead. After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 30% diethyl ether in hexanes) to give ($\pm$)-**4a** as a white solid (162 mg, 60%). ^1H NMR (500 MHz, CDCl_3) δ 8.18–8.12 (m, 2H), 6.95–6.90 (m, 2H), 4.63 (dt, $J = 47.3, 5.9$ Hz, 1H), 4.21 (t, $J = 6.6$ Hz, 2H), 2.30–2.04 (m, 2H), 1.46 (d, $J = 22.0$ Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 163.7, 141.6, 125.9, 114.5, 94.8 (dd, $J = 169.6, 2.9$ Hz), 79.8 (dd, $J = 164.8, 7.2$ Hz), 64.3 (d, $J = 6.2$ Hz), 40.4 (dd, $J = 23.0, 19.2$ Hz), 38.8 (d, $J = 22.5$ Hz), 25.0 (dd, $J = 24.4, 1.0$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -145.0–-145.4 (m, 1F), -218.2 (tt, $J = 47.7, 26.8$ Hz, 1F); FTIR (thin film) ν 2980 (w), 1592 (s), 1339 (s), 1111 (s), 845 (s), 729 (s), 650 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{12}\text{H}_{15}\text{F}_2\text{NO}_3$ $[\text{M}+\text{H}]^+$: 260.1093; found 260.1088.

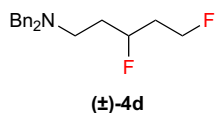


Prepared according to general procedure A using 1-(2-cyclopropylethoxy)-4-nitrobenzene (**3b**, 216 mg, 1.04 mmol) with the following modifications: 20 equiv of HF and 20.0 mol% of iodobenzene were used instead. After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 30% diethyl ether in hexanes) to give ($\pm$)-**4b** as a white solid (110 mg, 43%). A single crystal for X-ray diffraction analysis was grown by slow evaporation from hexanes. ^1H NMR (500 MHz, CDCl_3) δ 8.20–8.15 (m, 2H), 6.98–6.92 (m, 2H), 5.05–4.87 (m, 1H), 4.72–4.52 (m, 2H), 4.26–4.15 (m, 2H), 2.21–1.95 (m, 4H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 163.8, 141.7, 126.0, 114.5, 87.3 (dd, $J = 168.6, 3.8$ Hz), 79.9 (dd, $J = 164.8, 4.8$ Hz), 64.5 (d, $J = 4.8$ Hz), 36.2–35.9 (t, $J = 20.6$ Hz), 34.8 (d, $J = 20.6$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -187.2– -187.6 (m, 1F), -221.6 (tdd, $J = 47.1, 31.0, 20.3$ Hz, 1F); FTIR (thin film) ν 2969 (w), 1592 (s), 1257 (s), 1109 (s), 844 (s), 657 (s), 499 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{11}\text{H}_{13}\text{F}_2\text{NO}_3$ $[\text{M}+\text{H}]^+$: 246.0931; found 246.0936.



Prepared according to general procedure A using *N,N*-dibenzyl-2-(1-methylcyclopropyl)ethan-1-amine (**3c**, 291 mg, 1.04 mmol) with the following

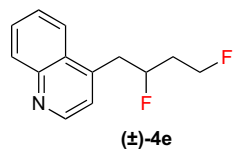
modifications: 20 equiv of HF and 20.0 mol% of iodobenzene were used instead. After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 10% diethyl ether in hexanes) to give (±)-**4c** as a colorless oil (231 mg, 70%). ¹H NMR (500 MHz, CDCl₃) δ 7.48–7.34 (m, 8H), 7.33–7.27 (m, 2H), 4.69–4.45 (m, 2H), 3.65 (s, 4H), 2.67–2.61 (m, 2H), 2.08–1.87 (m, 2H), 1.34 (d, *J* = 22.0 Hz, 3H); ¹³C NMR (125.7 MHz, CDCl₃) δ 139.7, 129.0, 127.1, 95.7 (dd, *J* = 168.6, 3.8), 80.0 (dd, *J* = 163.9, 6.7 Hz), 58.5, 48.1 (d, *J* = 6.7 Hz), 40.0 (dd, *J* = 23.0, 19.2 Hz), 37.2 (d, *J* = 22.0 Hz), 24.9 (dd, *J* = 24.9 Hz); ¹⁹F NMR (470.4 MHz, CDCl₃) -143.6 (oct, *J* = 20.3 Hz, 1F), -218.7 (tt, *J* = 47.7, 26.2 Hz, 1F); FTIR (thin film) ν 2798 (w), 1494 (m), 1003 (m), 733 (s), 697 (m) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₂₀H₂₅F₂N [M+H]⁺: 318.2028; found 318.2038.



Prepared according to general procedure A using *N,N*-dibenzyl-2-cyclopropylethan-1-amine (**3d**, 276 mg, 1.04 mmol) with the following

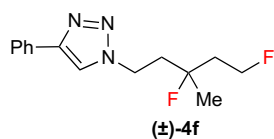
modifications: 20 equiv of HF and 20.0 mol% of iodobenzene were used instead. After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 10% diethyl ether in hexanes) to give (±)-**4d** as a colorless oil (145 mg, 46%). ¹H NMR (500 MHz, CDCl₃) δ 7.45–7.32 (m, 8H), 7.31–7.24 (m, 2H), 4.90–4.70 (m, 1H), 4.67–4.44 (m, 2H), 3.62 (s, 4H), 2.70–2.56 (m, 2H), 2.03–1.69 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ 139.7, 129.0, 128.4, 127.1, 89.2 (dd, *J* = 167.7, 4.8), 80.3 (dd, *J* = 164.8, 4.8 Hz), 58.7, 49.5 (dd, *J* = 4.8 Hz), 36.1 (app. t, *J* = 20.1 Hz), 33.2 (d, *J* = 20.1 Hz); ¹⁹F NMR (470.4 MHz, CDCl₃) -184.3– -184.7 (m,

1F), -221.4– -221.8 (m, 1F); FTIR (thin film) ν 2799 (w), 1452 (m), 1028 (m), 732 (s), 697 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{19}\text{H}_{24}\text{F}_2\text{N}$ $[\text{M}+\text{H}]^+$: 304.1871; found 304.1866.



Prepared according to general procedure A using 4-(cyclopropylmethyl)quinoline (**3e**, 191 mg, 1.04 mmol) with the following modification: dichloromethane was omitted; 20.0 mol% of iodobenzene was

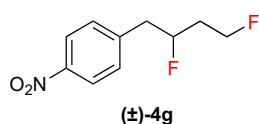
used instead. After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 60% diethyl ether in hexanes) to give (±)-**4e** as a brown oil (203 mg, 88%). ^1H NMR (500 MHz, CDCl_3) δ 8.82–8.75 (m, 1H), 8.10 (d, $J = 8.4$ Hz, 1H), 7.92 (d, $J = 8.4$ Hz, 1H), 7.70–7.61 (m, 1H), 7.54–7.47 (m, 1H), 7.26–7.20 (m, 1H), 5.11–4.92 (m, 1H), 4.66–4.45 (m, 2H), 3.42–3.23 (m, 2H), 2.16–1.88 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 149.9, 148.3, 142.8 (d, $J = 3.8$ Hz), 130.2, 129.3, 127.6, 126.8, 123.4, 122.3, 89.4 (dd, $J = 173.9, 4.3$ Hz), 79.7 (dd, $J = 165.3, 4.8$ Hz), 37.5 (d, $J = 22.0$ Hz), 36.0 (t, $J = 22.0$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -180.8– -181.3 (m, 1F), -221.57 (tdd, $J = 47.1, 32.8, 20.3$ Hz, 1F); FTIR (thin film) ν 3035 (w), 1593 (m), 1509 (m), 1033 (s), 760 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{13}\text{H}_{13}\text{F}_2\text{N}$ $[\text{M}+\text{H}]^+$: 222.1089; found 222.1085.



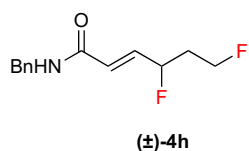
Prepared according to general procedure A using 1-(2-(1-methylcyclopropyl)ethyl)-4-phenyl-1H-1,2,3-triazole (**3f**, 236 mg, 1.04 mmol) with the following modifications: 20 equiv of HF and 20.0

mol% of iodobenzene were used instead. After work-up, the crude residue was purified by flash column chromatography on silica gel (20% to 100% diethyl ether in hexanes) to give (±)-**4f** as a white solid (171 mg, 62%). ^1H NMR (500 MHz, CDCl_3) δ 7.84–7.74 (m, 3H), 7.41–7.36 (m,

2H), 7.33–7.27 (m, 1H), 4.66–4.43 (m, 4H), 2.40–2.22 (m, 2H), 2.05 (ddt, $J = 27.8, 18.6, 5.9$, 2H), 1.41 (d, $J = 22.0$ Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 147.9, 130.7, 128.9, 128.2, 125.7, 119.9, 94.5 (dd, $J = 169.6, 1.9$ Hz), 79.7 (dd, $J = 165.8, 7.7$ Hz), 45.6 (d, $J = 5.7$ Hz), 40.2 (ddd, $J = 23.0, 9.7, 9.6$ Hz), 24.5 (d, $J = 25.9$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3) -146.7 (oct, $J = 21.5$ Hz, 1F), -218.0 (tt, $J = 47.7, 27.4$ Hz, 1F); FTIR (thin film) ν 2981 (w), 1610 (m), 1385 (m), 911 (s), 694 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{14}\text{H}_{17}\text{F}_2\text{N}_3$ $[\text{M}+\text{H}]^+$: 266.1463; found 266.1472.

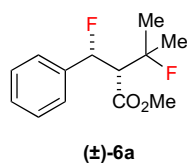


Prepared according to general procedure A using 1-(cyclopropylmethyl)-4-nitrobenzene (**3g**, 184 mg, 1.04 mmol) with the following modifications: 20 equiv of HF and 20.0 mol% of iodobenzene were used instead. After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 10% diethyl ether in hexanes) to give (±)-**4g** as a colorless oil (94.0 mg, 42%). ^1H NMR (500 MHz, CDCl_3) δ 8.15 (d, $J = 7.6$ Hz, 2H), 7.40 (d, $J = 7.6$ Hz, 2H), 5.02–4.83 (m, 1H), 4.70–4.50 (m, 2H), 2.99–2.86 (m, 2H), 2.02–1.73 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 147.0, 144.6 (d, $J = 2.9$ Hz), 130.4, 123.7, 89.9 (dd, $J = 173.0, 3.8$ Hz), 79.8 (dd, $J = 165.3, 4.8$ Hz), 41.3 (d, $J = 21.1$ Hz), 35.7 (t, $J = 20.6$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -183.1– -183.6 (m, 1F), -221.6 (tdd, $J = 47.1, 32.8, 19.7$ Hz, 1F); FTIR (thin film) ν 2971 (w), 1605 (m), 1517 (s), 1345 (s), 1035 (m), 745 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{10}\text{H}_{11}\text{F}_2\text{NO}_2$ $[\text{M}+\text{H}]^+$: 216.0831; found 216.0838.



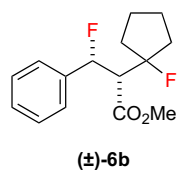
Prepared according to general procedure A using (E)-N-benzyl-3-cyclopropylacrylamide (**3h**, 209 mg, 1.04 mmol) with the following modifications: 20 equiv of HF and 20 mol% of iodobenzene were used

instead; the reaction mixture was stirred for 36 hours. After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 10% diethyl ether in dichloromethane) to give **4h** as a white solid (139 mg, 56%). A single crystal for X-ray diffraction analysis was grown by vapor diffusion of hexanes into an ethyl acetate solution containing ($\pm$)-**4h**. ^1H NMR (500 MHz, CDCl_3) δ 7.38–7.23 (m, 5H), 6.84 (ddd, J = 21.0, 15.6, 4.4 Hz, 1H), 6.28 (br. s., 1H), 6.17–6.11 (m, 1H), 5.37–5.19 (m, 1H), 4.71–4.46 (m, 2H), 4.49 (d, J = 5.9 Hz, 2H), 2.47–1.92 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 164.8, 140.7 (d, J 17.2 Hz), 138.1, 128.9, 128.0, 127.8, 123.7 (d, J = 9.6 Hz), 88.1 (dd, J = 173.4, 4.8 Hz), 79.5 (165.8, 4.8 Hz), 43.9, 36.0 (t, J = 19.6 Hz); ^{19}F NMR (470.4 MHz, CDCl_3) -187.5 (dddd, J = 47.7, 31.0, 21.5, 16.7 Hz, 1F), -222.4 (tdd, J = 47.7, 32.2, 20.3 Hz, 1F); FTIR (thin film) ν 3293 (m), 1626 (m), 1585 (s), 1267 (m), 986 (m), 695 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{13}\text{H}_{15}\text{F}_2\text{NO}$ $[\text{M}+\text{H}]^+$: 240.1194; found 240.1199.

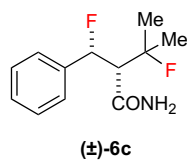


Prepared according to general procedure A using methyl 2,2-dimethyl-3-phenylcyclopropane-1-carboxylate (($\pm$)-**5a**, 212 mg, 1.04 mmol) with the following modifications: 20 equiv of HF were used instead; the reaction mixture was stirred at 4 °C instead of room temperature. The diastereomeric ratio of the crude residue after work-up was determined to be >20:1 by ^1H and ^{19}F NMR analysis. Purification of this residue by flash column chromatography on silica gel (0% to 30% diethyl ether in hexanes) gave ($\pm$)-**6a** as a colorless oil (186 mg, 74%). ^1H NMR (500 MHz, CDCl_3) δ 7.43–7.33 (m, 5H), 5.85 (dd, J = 45.4, 6.8 Hz, 1H), 3.69 (s, 3H), 3.31 (ddd, J = 18.1, 9.8, 6.8 Hz, 1H), 1.42 (d, J = 3.9 Hz, 3H), 1.37 (d, J = 3.4 Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 169.9–169.8 (m), 137.9 (d, J = 21.1 Hz), 129.3 (d, J = 1.9 Hz), 128.8, 126.6 (d, J = 6.7 Hz), 94.5 (dd, J = 170.6, 4.8 Hz), 91.9

(dd, $J = 175.4, 5.8$ Hz), 61.6–61.2 (app. t, $J = 23.0$ Hz), 52.1, 26.3 (d, $J = 24.0$ Hz), 25.6 (dd, $J = 24.0, 1.9$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3) -133.0 (sptd, $J = 22.6, 9.5$ Hz, 1F), -175.0 (dd, $J = 45.3, 17.9$ Hz, 1F); FTIR (thin film) ν 2988 (w), 2953 (w), 1740 (s), 1168 (m), 700 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{14}\text{H}_{13}\text{N}$ $[\text{M}+\text{H}]^+$: 265.1011; found 265.1007.

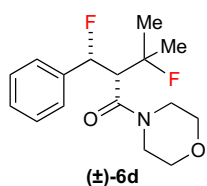


Prepared according to general procedure A using methyl 2-phenylspiro[2.4]heptane-1-carboxylate ((±)-5b, 240 mg, 1.04 mmol) with the following modifications: 20 equiv of HF were used instead; the reaction mixture was stirred at 4 °C instead of room temperature. The diastereomeric ratio of the crude residue after work-up was determined to be >20:1 by ^1H and ^{19}F NMR analysis. Purification of this residue by flash column chromatography on silica gel (0% to 10% diethyl ether in hexanes) gave (±)-6b as a white solid (176 mg, 63%). ^1H NMR (500 MHz, CDCl_3) δ 7.43–7.34 (m, 5H), 5.91 (dd, $J = 45.4, 8.3$ Hz, 1H), 3.73 (s, 3H), 3.43–3.29 (m, 1H), 2.20–1.15 (m, 8H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 170.3 (dd, $J = 5.8, 1.9$ Hz), 129.3 (d, $J = 2.4$ Hz), 128.6, 127.0 (d, $J = 6.2$ Hz), 104.2 (dd, $J = 180.6, 7.2$ Hz), 92.5 (dd, $J = 172.5, 5.3$ Hz), 59.3 (dd, $J = 24.4, 23.0$ Hz), 37.4 (d, $J = 23.0$ Hz), 36.3 (dd, $J = 23.5, 1.4$ Hz), 23.6, 23.0; ^{19}F NMR (470.4 MHz, CDCl_3) δ -144.8– -145.3 (m, 1F), -172.0 (dd, $J = 45.3, 13.7$ Hz, 1F); FTIR (thin film) ν 2954 (w), 1436 (s), 1166 (m), 699 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{15}\text{H}_{18}\text{F}_2\text{O}_2$ $[\text{M}+\text{Na}]^+$: 286.1613; found 286.1624.



Prepared according to general procedure A using (E)-2,2-dimethyl-3-phenylcyclopropane-1-carboxamide ((±)-5c, 197 mg, 1.04 mmol) with the following modifications: 20 equiv of HF were used instead; the reaction mixture

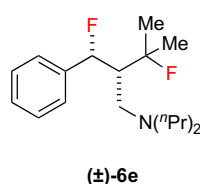
was stirred at 4 °C instead of room temperature. The diastereomeric ratio of the crude residue after work-up was determined to be >20:1 by ^1H and ^{19}F NMR analysis. Purification of this residue by flash column chromatography on silica gel (0% to 20% diethyl ether in dichloromethane) gave ($\pm$)-**6c** as a white solid (191 mg, 81%). A single crystal suitable for X-ray diffraction analysis was grown by vapor diffusion of hexanes into an isopropyl alcohol/ethyl acetate (1:1) solution containing ($\pm$)-**6c**. ^1H NMR (500 MHz, CDCl_3) δ 7.40–7.30 (m, 5H), 6.15 (br. s, 1H), 6.04 (br. s, 1H), 5.95 (dd, J = 46.4, 45.4 Hz, 1H), 3.03 (ddd, J = 23.9, 14.6, 4.9 Hz, 1H), 1.49 (d, J = 6.3 Hz, 3H), 1.45 (d, J = 7.3 Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 171.0 (d, J = 7.7 Hz), 137.8 (d, J = 20.1 Hz), 129.0, 128.8, 126.2 (d, J = 7.7 Hz), 94.9 (dd, J = 171.5, 3.8 Hz), 91.6 (dd, J = 175.4, 4.8 Hz), 61.9 (t, J = 22.0 Hz), 26.4 (d, J = 24.0 Hz), 25.8 (dd, J = 24.0, 1.9 Hz); ^{19}F NMR (470.4 MHz, CDCl_3) -136.0– -136.5 (m, 1F), -182.5– -183.0 (m, 1F); FTIR (thin film) ν 3195 (w), 1667 (s), 1409 (m), 1236 (m), 910 (m), 698 (s), 602 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{12}\text{H}_{15}\text{F}_2\text{NO}$ $[\text{M}+\text{H}]^+$: 228.1194; found 228.1194.



Prepared according to general procedure A using (E)-2,2-dimethyl-3-phenylcyclopropyl(morpholino)methanone (($\pm$)-**5d**, 270 mg, 1.04 mmol) with the following modification: 20 equiv of HF were used instead; the reaction

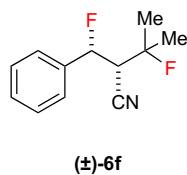
mixture was stirred at 4 °C instead of room temperature; the reaction mixture was stirred for 48 hours instead. The diastereomeric ratio of the crude residue after work-up was determined to be >20:1 by ^1H and ^{19}F NMR analysis. Purification of this residue by flash column chromatography on silica gel (0% to 2.5% methanol in dichloromethane) gave ($\pm$)-**6d** as a white solid (266 mg, 86%). A single crystal suitable for X-ray diffraction analysis was grown by vapor diffusion of pentanes into a diethyl ether solution containing ($\pm$)-**6d**. ^1H NMR (500 MHz, CDCl_3) δ 7.41–

7.30 (m, 5H), 5.89 (dd, $J = 44.9, 6.6$ Hz, 1H), 3.66–3.18 (m, 9H), 1.40 (d, $J = 22.2$ Hz, 3H), 1.33 (d, $J = 23.4$ Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 167.5 (d, $J = 9.6$ Hz), 137.8 (d, $J = 20.1$ Hz), 129.3 (d, $J = 1.9$ Hz), 128.7, 126.7 (d, $J = 6.7$ Hz), 95.7 (dd, $J = 168.2, 6.7$ Hz), 92.6 (dd, $J = 175.4, 5.3$ Hz), 66.8, 66.4, 55.2 (t, $J = 24.0$ Hz), 46.9, 42.4, 26.1 (d, $J = 24.0$ Hz), 25.6 (d, $J = 24.0$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -127.6– -128.2 (m, 1F), -173.8 (dd, $J = 44.1, 16.7$ Hz, 1F); FTIR (thin film) ν 2979 (w), 1636 (s), 1436 (m), 114 (s), 647 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{16}\text{H}_{21}\text{F}_2\text{NO}_2$ $[\text{M}+\text{H}]^+$: 298.1613; found 298.1611.



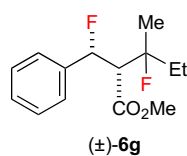
Prepared according to general procedure A using *N*-(((*E*)-2,2-dimethyl-3-phenylcyclopropyl)methyl)-*N*-propylpropan-1-amine ((±)-5e, 270 mg, 1.04 mmol) with the following modifications: 20 equiv of HF and 20.0 mol%

of iodobenzene were used instead; the reaction mixture was stirred at 4 °C instead of room temperature; the reaction mixture was stirred for 48 hours instead. The diastereomeric ratio of the crude residue after work-up was determined to be >20:1 by ^1H and ^{19}F NMR analysis. Purification of this residue by flash column chromatography on silica gel (0% to 2.5% methanol in dichloromethane) gave (±)-6e as a colorless oil (257 mg, 83%). ^1H NMR (500 MHz, CDCl_3) δ 7.41–7.25 (m, 5H), 6.11 (d, $J = 47.8$ Hz, 1H), 2.57–1.93 (m, 7H), 1.61–1.51 (m, 6H), 1.32–1.13 (m, 4H), 0.76–0.70 (m, 6H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 140.8 (d, $J = 21.1$ Hz), 128.1 (d, $J = 1.9$ Hz), 127.3, 124.7 (d, $J = 9.6$ Hz), 98.1 (dd, $J = 167.2, 1.0$ Hz), 91.9 (dd, $J = 176.8, 8.6$ Hz), 55.7, 52.6 (t, $J = 18.7$ Hz), 49.3 (t, $J = 8.4$ Hz), 28.1 (d, $J = 23.5$ Hz), 23.8 (dd, $J = 24.9, 3.8$ Hz), 19.5, 12.0; ^{19}F NMR (470.4 MHz, CDCl_3) δ -129.5 (sptdd, $J = 23.0, 9.5, 4.2$ Hz, 1F), -200.0 (dd, $J = 47.7, 34.6$ Hz, 1F); FTIR (thin film) ν 2959 (m), 1451 (m), 1175 (m), 906 (s), 700 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{18}\text{H}_{29}\text{F}_2\text{N}$ $[\text{M}+\text{H}]^+$: 298.2341; found 298.2348.



Prepared according to general procedure A using (E)-2,2-dimethyl-3-phenylcyclopropane-1-carboxamide ((±)-**5f**, 178 mg, 1.04 mmol) with the following modification: 50 equiv of HF were used instead; the reaction mixture

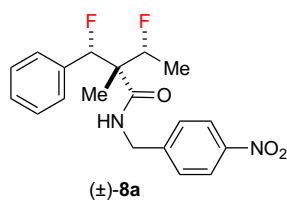
was stirred at 4 °C instead of room temperature. The diastereomeric ratio of the crude residue after work-up was determined to be 4.5:1 by ^1H and ^{19}F NMR analysis. Purification of this residue by flash column chromatography on silica gel (0% to 20% diethyl ether in dichloromethane) gave (±)-**6e** as a colorless oil (144 mg, 66%). The diastereomeric ratio of the purified product was determined to be >20:1 by ^1H and ^{19}F NMR analysis. ^1H NMR (500 MHz, CDCl_3) δ 7.34–7.24 (m, 5H), 5.73 (dd, J = 45.9, 0.7 Hz, 1H), 2.99 (ddd, J = 29.5, 8.1, 1.0 Hz, 1H), 1.60–1.47 (m, 6H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 136.8 (d, J = 21.2 Hz), 129.5 (d, J = 1.0 Hz), 128.9, 125.0, 115.1 (dd, J = 11.3, 5.0 Hz), 94.3 (dd, J = 177.3, 1.0 Hz), 88.2 (dd, J = 184.5, 5.3 Hz), 50.8 (dd, J = 29.7, 21.1 Hz), 27.1, (dd, J = 23.5, 1.4 Hz), 24.1, (dd, J = 23.5, 3.8 Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -138.4 (sptd, J = 22.0, 9.0 Hz, 1F), -184.8 (dd, J = 45.9, 29.8 Hz, 1F); FTIR (thin film) ν 2991 (w), 1455 (m), 1146 (m), 860 (m), 715 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{12}\text{H}_{13}\text{F}_2\text{N}$ $[\text{M}+\text{Na}]^+$: 232.0908; found 232.0908.



Prepared according to general procedure A using (±)-**5g** (114 mg, 0.520 mmol) with the following modifications: 20 equiv of HF were used instead; the reaction mixture was stirred at 4 °C instead of room temperature. The diastereomeric ratio

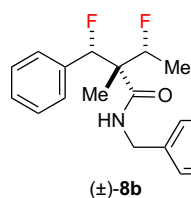
of the crude residue after work-up was determined to be 1.3:1 by ^1H and ^{19}F NMR analysis. Purification of this residue by flash column chromatography on silica gel (0% to 10% diethyl ether in hexanes) gave (±)-**6g** as a colorless oil (78.0 mg, 59%, 1.1:1 d.r.). ^1H NMR (500 MHz, CDCl_3) δ (Two diastereomers, 1.1:1 d.r. *denotes select minor diastereomer resonances) 7.45–

7.30 (m, 5H), 5.93* (dd, $J = 45.4, 6.1$ Hz, 1H), 5.79 (dd, $J = 44.9, 7.32$ Hz, 1H), 3.71 (s, 3H), 3.67* (s, 3H), 3.44–3.36 (m, 2H), 3.37–3.28* (m, 2H), 1.83–1.70 (m, 1H), 1.62–1.45 (m, 1H), 1.48 (d, $J = 22.0$ Hz, 3H), 1.37* (d, $J = 22.5$ Hz, 3H), 0.91* (t, $J = 7.3$ Hz, 3H), 0.88 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ (Two diastereomers) 171.1 (dd, $J = 5.8, 2.9$ Hz), 170.0 (dd, $J = 13.4, 2.9$ Hz), 138.4 (d, $J = 20.1$ Hz), 137.6 (d, $J = 20.1$ Hz), 129.5 (d, $J = 2.9$ Hz), 129.0 (d, $J = 1.9$ Hz), 128.8, 128.6, 126.8 (d, $J = 5.7$ Hz), 126.3 (d, $J = 6.7$ Hz), 96.3 (ddd, $J = 174.4, 8.6, 3.8$ Hz), 91.9 (ddd, $J = 174.4, 51.7, 7.7$ Hz), 60.3–59.7 (m), 52.1, 52.0, 31.6 (dd, $J = 114.0, 23.0$), 22.0 (dd, $J = 34.5, 24.0$ Hz), 7.4 (d, $J = 5.7$ Hz), 7.3 (d, $J = 5.7$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ (*Denotes minor diastereomer) -144.7– -145.1* (m, 1F), -146.5– -146.9 (m, 1F), -172.1* (dd, $J = 45.3, 16.7$ Hz), -176.6 (dd, $J = 46.5, 20.2$ Hz); FTIR (thin film) ν 2951 (w), 1738 (s), 1436 (m), 1165 (s), 971 (m), 700 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{14}\text{H}_{18}\text{F}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 279.1167; found 279.1165.

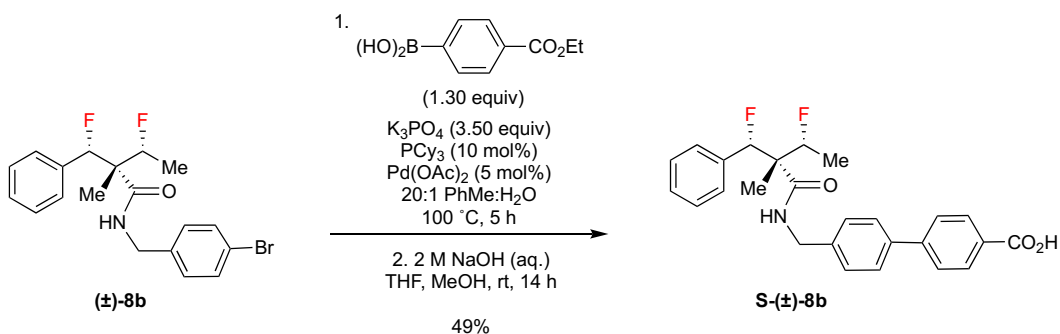


Prepared according to general procedure A using (±)-**7a** (156 mg, 0.480 mmol, 1.00 equiv) with the following modifications: 20.0 mol% iodobenzene was used instead; the reaction mixture was stirred at -25°C ; the reaction mixture was stirred for 4 days instead. The diastereomeric ratio of the crude residue after work-up was determined to be >20:1 by ^1H and ^{19}F NMR. Purification of this residue by flash column chromatography on silica gel (10% to 80% diethyl ether in hexanes) gave (±)-**8a** as a white solid (82.0 mg, 47%, >20:1 d.r.). ^1H NMR (500 MHz, CDCl_3) δ 8.18 (d, $J = 8.8$ Hz, 2H), 7.48 (d, $J = 8.8$ Hz, 2H), 7.43–7.30 (m, 5H), 6.85–6.71 (br. m, 1H), 5.92 (d, $J = 44.9$ Hz, 1H), 4.67 (ddd, $J = 77.1, 15.6, 5.9$ Hz, 2H), 4.53 (dq, $J = 47.3, 6.8$ Hz, 1H), 1.31 (ddd, $J = 25.1, 6.3, 1.0$ Hz, 3H), 1.03 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 171.3, 146.5, 146.2,

135.1 (d, $J = 21.1$ Hz), 129.2, 128.5, 128.4, 126.9 (d, $J = 7.7$ Hz), 124.1, 95.5 (dd, $J = 179.2, 6.7$ Hz), 93.1 (dd, $J = 171.5, 6.7$ Hz), 55.4 (dd, $J = 23.0, 15.8$ Hz), 43.3, 16.2 (d, $J = 22.0$ Hz), 13.0 (app. t, $J = 4.8$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3) -174.2 (sxttd, $J = 25.0, 7.2$ Hz, 1F), -188.5 (d, $J = 44.1$, 1F); FTIR (thin film) ν 3369 (w), 2990 (w), 1655 (m), 1518 (s), 1344 (s), 734 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{19}\text{H}_{20}\text{F}_2\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 363.1515; found 363.1530.

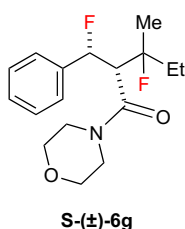


Prepared according to general procedure A using (±)-**7b** (186 mg, 0.520 mmol, 1.00 equiv) with the following modifications: 20.0 mol% of iodobenzene was used instead; the reaction mixture was stirred at -25 °C instead at room temperature; the reaction mixture was stirred for 4 days instead. The diastereomeric ratio of the crude residue after work-up was determined to be >20:1 by ^1H and ^{19}F NMR. Purification of this residue by flash column chromatography on silica gel (10% to 80% diethyl ether in hexanes) gave (±)-**8b** as a white solid (84.5 mg, 41%, >20:1 d.r.). ^1H NMR (500 MHz, CDCl_3) δ 7.55–7.19 (m, 9H), 7.42–7.28 (m, 7H), 6.74–6.58 (br. m, 1H), 5.90 (d, $J = 44.9$ Hz, 1H), 4.65–4.44 (m, 3H), 1.32 (dd, $J = 25.4, 6.3$ Hz, 3H), 1.04 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 170.9, 135.2 (d, $J = 21.1$ Hz), 131.9, 129.6, 129.0, 128.4, 128.3, 126.9 (d, $J = 8.1$ Hz), 121.4, 95.4 (dd, $J = 178.7, 5.9$ Hz), 93.0 (dd, $J = 171.5, 6.2$ Hz), 55.1 (dd, $J = 23.0, 15.8$ Hz), 43.3, 16.1 (d, $J = 22.5$ Hz), 12.9; ^{19}F NMR (470.4 MHz, CDCl_3) -174.4 (sxttd, $J = 25.6, 6.6$ Hz, 1F), -188.7 (d, $J = 44.7$ Hz, 1F); FTIR (thin film) ν 3369 (w), 1655 (s), 1262 (m), 1011 (s), 704 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{19}\text{H}_{20}\text{BrF}_2\text{NO}$ $[\text{M}+\text{Na}]^+$: 418.0589; found 418.0586.



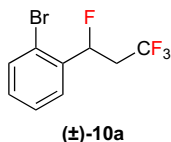
To a solution of 53.1 mg of **(±)-8b** (0.134 mmol, 1.00 equiv) in 20:1 toluene:water (1.9 mL) was added potassium phosphate tribasic (99.5 mg, 0.469 mmol, 3.50 equiv), 4-ethoxycarbonylphenylboronic acid (35.1 mg, 0.174 mmol, 1.30 equiv), tricyclohexylphosphine (3.70 mg, 0.0134 mmol, 10 mol%) and palladium(II) acetate (1.50 mg, 0.00670 mmol, 5.0 mol%). The resulting mixture was heated to 110 °C. After 5 hours, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL) and washed with water (100 mL). The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 70% diethyl ether in hexanes) to give a colorless oil. A solution of 32.4 mg of this oil in 1:1:1 2 M NaOH (aq.):THF:CH₃OH (1.5 mL) was stirred for 14 h at room temperature. The aqueous layer was acidified with 1 M HCl (aq.) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄ and concentrated to give **S-(±)-8b** as a white solid (29.0 mg, 49% over 2 steps). A crystal suitable for X-ray diffraction was obtained by slow evaporation from a methanol/diethyl ether solution of **S-(±)-8b**. ¹H NMR (500 MHz, CDCl₃) δ 8.25–8.14 (m, 2H), 7.74–7.58 (m, 4H), 7.48–7.35 (m, 7H), 6.71–6.62 (m, 1H), 5.93 (d, *J* = 44.9 Hz, 1H), 4.76–4.45 (m, 3H), 1.36 (dd, *J* = 24.5, 7.0 Hz, 3H), 1.07 (s, 3H); ¹³C NMR (125.7 MHz, CDCl₃) δ 171.3, 171.0, 146.0, 139.2, 138.7, 135.3 (d, *J* = 21.1

Hz), 130.9, 129.0, 128.5, 128.4, 128.3, 127.8, 127.2, 126.9 (d, $J = 7.7$ Hz), 95.1 (dd, $J = 178.8$, 5.8 Hz), 93.1 (dd, $J = 171.5$, 5.8 Hz), 70.7, 43.7, 16.2 (d, $J = 22.5$ Hz), 13.0; ^{19}F NMR (470.4 MHz, CDCl_3) -174.3 (sxt, $J = 25.0$, 6.0 Hz, 1F), -188.6 (d, $J = 44.7$ Hz, 1F); FTIR (thin film) ν 2924 (w), 1686 (m), 1005 (m), 728 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{26}\text{H}_{25}\text{F}_2\text{NO}_3$ $[\text{M}+\text{H}]^+$: 438.1875; found 438.1883.



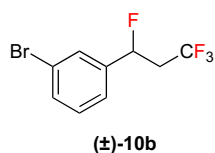
Prepared according to general procedure A using **S-(±)-5g** (54.5 mg, 0.520 mmol) with the following modifications: 20 equiv of HF were used instead; the reaction mixture was stirred at 4 °C instead of room temperature. The diastereomeric ratio of the crude residue after work-up was determined to be 1:1

by ^1H and ^{19}F NMR analysis and the yield to be 28% by ^{19}F NMR analysis using trifluorotoluene as an internal standard.

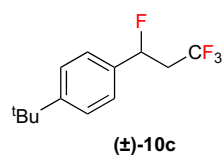


Prepared according to general procedure A using 1-bromo-2-(2,2-difluorocyclopropyl)benzene ((±)-**9a**, 242 mg, 1.04 mmol). After work-up, the

crude residue was purified by flash column chromatography on silica gel (hexanes) to give (±)-**10a** as a colorless oil (262 mg, 93%). ^1H NMR (500 MHz, CDCl_3) δ 7.61–7.53 (m, 2H), 7.43 (td, $J = 7.6$, 1.2 Hz, 1H), 7.26 (td, $J = 7.8$, 1.7 Hz, 1H), 6.11 (ddd, $J = 47.1$, 9.3, 2.2 Hz, 1H), 2.81–2.58 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 137.5 (d, $J = 21.2$ Hz), 133.1, 130.7, 128.2 (d, $J = 1.0$ Hz), 126.8 (d, $J = 11.0$ Hz), 125.2 (q, $J = 277.9$ Hz), 120.3 (d, $J = 5.3$ Hz), 87.5 (dq, $J = 177.7$, 3.4 Hz), 40.4 (tdd, $J = 28.8$, 28.8, 24.4 Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -64.4 (q, $J = 10.1$ Hz, 3F), -184.2– -184.5 (m, 1F); FTIR (thin film) ν 1572 (w), 1389 (m), 1135 (s), 753 (s), 450 (m) cm^{-1} ; HRGCMS (EI^+) Calc'd for $\text{C}_9\text{H}_7\text{F}_4\text{Br}$ $[\text{M}]^+$: 269.9662; found 269.9661.

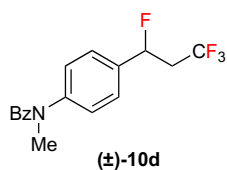


Prepared according to general procedure A using 1-bromo-3-(2,2-difluorocyclopropyl)benzene ((±)-**9b**, 242 mg, 1.04 mmol). After work-up, the crude residue was purified by flash column chromatography on silica gel (hexanes) to give (±)-**10b** as a colorless oil (251 mg, 89%). ¹H NMR (500 MHz, CDCl₃) δ 7.56–7.49 (m, 2H), 7.33–7.25 (m, 2H), 5.73 (ddd, *J* = 47.6, 9.3, 2.7 Hz, 1H), 2.88–2.73 (m, 1H), 2.64–2.45 (m, 1H); ¹³C NMR (125.7 MHz, CDCl₃) 140.2 (d, *J* = 19.6 Hz), 132.5 (d, *J* = 1.4 Hz), 130.6, 128.7 (d, *J* = 7.7 Hz), 125.1 (qd, *J* = 277.4, 2.4 Hz), 124.1 (d, *J* = 6.7 Hz), 123.1, 87.4 (dq, *J* = 177.3, 3.4 Hz), 41.6 (qd, *J* = 28.8, 24.9 Hz); ¹⁹F NMR (470.4 MHz, CDCl₃) δ –64.2 (td, *J* = 10.1, 7.7 Hz, 3F), –177.4 (dddq, *J* = 47.1, 31.6, 16.1, 7.8 Hz, 1F); FTIR (thin film) ν 2951 (w), 1575 (w), 1250 (s), 1128 (s), 784 (m), 611 (m) cm^{–1}; HRGCMS (EI⁺) Calc'd for C₉H₇F₄Br [M]⁺: 269.9662; found 269.9662.



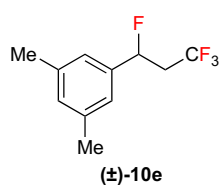
Prepared according to general procedure A using 1-(*tert*-butyl)-4-(2,2-difluorocyclopropyl)benzene ((±)-**9c**, 219 mg, 1.04 mmol) with the following modifications: 50.0 mL of dichloromethane and 20.0 mol% of iodobenzene were used instead; the reaction mixture was stirred at 4 °C instead of room temperature. After work-up, the crude residue was purified by flash column chromatography on silica gel (hexanes) to give (±)-**10c** as a colorless oil (134 mg, 52%). ¹H NMR (500 MHz, CDCl₃) δ 7.45–7.41 (m, 2H), 7.31–7.27 (m, 2H), 5.74 (ddd, *J* = 48.1, 9.5, 2.7 Hz, 1H), 2.94–2.44 (m, 2H), 1.33 (s, 9H); ¹³C NMR (125.7 MHz, CDCl₃) δ 152.6, 135.0 (d, *J* = 19.7 Hz), 126.0, 125.4 (q, *J* = 277.1 Hz), 125.5 (d, *J* = 6.2 Hz), 88.2 (dd, *J* = 174.5, 3.8 Hz), 41.5 (qd, *J* = 28.8, 25.9 Hz), 34.8, 31.4; ¹⁹F NMR (470.4 MHz, CDCl₃) δ –64.3 (app. q, *J* = 9.5 Hz, 3F), –173.8 (dddq, *J* = 47.7, 31.0, 16.1,

8.3 Hz, 1F); FTIR (thin film) ν 2965 (w), 1281 (m), 1252 (m), 1134 (s), 1114 (m) cm^{-1} ; HRGCMS (EI⁺) Calc'd for C₁₃H₁₆F₄ [M]⁺: 248.1183; found 248.1184.



Prepared according to general procedure A using *N*-(4-(2,2-difluorocyclopropyl)phenyl)-*N*-methylbenzamide ((±)-9d, 189 mg, 1.04 mmol). After work-up, the crude residue was purified by flash column

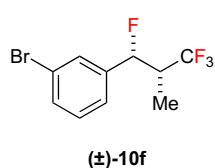
chromatography on silica gel (0% to 50% diethyl ether in dichloromethane) to give (±)-10d as a colorless oil (288 mg, 85%). ¹H NMR (500 MHz, CDCl₃) δ 7.32–7.08 (m, 9H), 5.70 (ddd, *J* = 47.6, 9.0, 3.2 Hz, 1H), 3.51 (m, 3H), 2.87–2.42 (m, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 170.4, 145.8 (d, *J* = 2.4 Hz), 135.9 (d, *J* = 20.1 Hz), 135.7, 130.0, 128.8, 127.3, 126.4 (d, *J* = 6.2 Hz), 125.0 (qd, *J* = 276.9, 2.4 Hz), 87.6 (dq, *J* = 175.3, 3.4 Hz), 41.4 (dq, *J* = 27.3, 28.8 Hz), 38.4; ¹⁹F NMR (470.4 MHz, CDCl₃) δ -64.1 (dt, *J* = 7.8, 3.6 Hz, 3F), -175.5– -175.7 (m, 1F); FTIR (thin film) ν 2926 (w), 1643 (s), 1494 (m), 1254 (s), 1132 (s), 886 (m), 592 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for C₁₇H₁₅F₄NO [M+H]⁺: 326.1163; found 326.1174.



Prepared according to general procedure A using 1-(2,2-difluorocyclopropyl)-3,5-dimethylbenzene ((±)-9e, 299 mg, 1.04 mmol) with the following modifications: 50.0 mL of dichloromethane and 20.0 mol% of iodobenzene

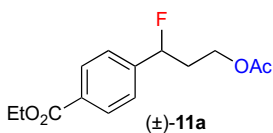
were used instead; the reaction mixture was stirred at 4 °C instead of room temperature. After work-up, the crude residue was purified by flash column chromatography on silica gel (hexanes) to give (±)-10e as a colorless oil (137 mg, 60%). ¹H NMR (500 MHz, CDCl₃) δ 7.05 (s, 1H), 6.99 (s, 2H), 5.71 (ddd, *J* = 48.1, 9.5, 2.7 Hz, 1H), 2.93–2.45 (m, 2H), 2.37 (s, 6H); ¹³C NMR (125.7 MHz, CDCl₃) δ 138.7, 138.0 (d, *J* = 19.2 Hz), 130.9 (d, *J* = 1.9 Hz), 125.4 (q, *J* =

278.8 Hz), 123.3 (d, $J = 6.7$ Hz), 88.4 (dq, $J = 174.9, 3.4$ Hz), 41.7 (qd, $J = 28.3, 25.4$ Hz), 21.4; ^{19}F NMR (470.4 MHz, CDCl_3) -64.3 (q, $J = 9.5$ Hz, 3F), -175.0 (dddq, $J = 48.3, 30.1, 16.1, 8.3$ Hz, 1F); FTIR (thin film) ν 2923 (w), 1279.1 (m), 1248 (m), 1126 (s), 855 (m) cm^{-1} ; HRGCMS (EI^+) Calc'd for $\text{C}_{11}\text{H}_{12}\text{F}_4$ $[\text{M}]^+$: 220.0870; found 220.0868.



Prepared according to general procedure A using 1-bromo-3-((E)-2,2-difluoro-3-methylcyclopropyl)benzene ((±)-9f, 257 mg, 1.04 mmol) with the following modification: 50 equiv of HF were used instead. The diastereomeric ratio of

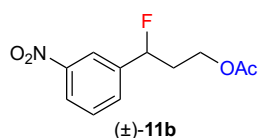
the crude residue after work-up was determined to be 3:1 by ^1H and ^{19}F NMR analysis. Purification of this residue by flash column chromatography on silica gel (hexanes) gave (±)-10f as a colorless oil (169 mg, 57%). The diastereomeric ratio of the purified product was determined to be >20:1 by ^1H and ^{19}F NMR analysis. ^1H NMR (500 MHz, CDCl_3) δ 7.58–7.50 (m, 2H), 7.34–7.25 (m, 2H), 5.45 (dd, $J = 46.4, 8.3$ Hz, 1H), 2.89–2.74 (m, 1H), 0.96 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 138.9 (d, $J = 20.6$ Hz), 132.6 (d, $J = 1.9$ Hz), 130.4, 129.9 (d, $J = 6.7$ Hz), 126.7 (qd, $J = 280.3, 1.9$ Hz), 125.5 (d, $J = 6.2$ Hz), 122.9, 92.0 (dd, $J = 179.2, 2.4$ Hz), 43.8 (qd, $J = 25.9, 23.0$ Hz), 10.0; ^{19}F NMR (470.4 MHz, CDCl_3) δ -69.4 (dd, $J = 11.9, 8.3$ Hz, 3F), -173.2 (dquin, $J = 46.5, 12.5$ Hz, 1F); FTIR (thin film) ν 2995 (w), 1574 (m), 1127 (s), 1023 (m), 785 (m) cm^{-1} ; HRGCMS (EI^+) Calc'd for $\text{C}_{10}\text{H}_9\text{BrF}_4$ $[\text{M}]^+$: 283.9818; found 283.9818.



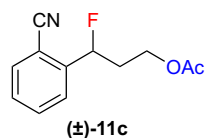
Prepared according to general procedure B using ethyl 4-cyclopropylbenzoate (1a, 198 mg, 1.04 mmol). After work-up, the crude

residue was purified by flash column chromatography on silica gel (0% to 30% diethyl ether in

hexanes) to give ($\pm$)-**11a** as a colorless oil (170 mg, 61%). ^1H NMR (500 MHz, CDCl_3) δ 8.02 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 5.60 (ddd, J = 47.8, 8.3, 3.9 Hz, 1H), 4.34 (q, J = 6.8 Hz, 2H), 4.27–4.12 (m, 2H), 2.31–2.04 (m, 2H), 2.01 (s, 3H), 1.36 (t, J = 6.83 Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 170.9, 166.2, 144.5 (d, J = 19.2 Hz), 130.1, 129.9, 125.2 (d, J = 7.7 Hz), 90.9 (d, J = 172.5 Hz), 61.2, 60.2 (d, J = 4.8 Hz), 36.4 (d, J = 24.0 Hz), 20.9, 14.4; ^{19}F NMR (470.4 MHz, CDCl_3) -181.4 (ddd, J = 47.7, 31.0, 16.7 Hz); FTIR (thin film) ν 2981 (w), 1715 (s), 1367 (m), 1178 (s), 1042 (s), 858 (m), 674 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{14}\text{H}_{17}\text{FO}_4$ $[\text{M}+\text{H}]^+$: 269.1184; found 269.1178.

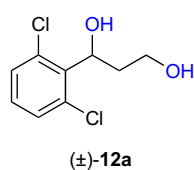


Prepared according to general procedure B using 1-cyclopropyl-3-nitrobenzene (**1f**, 170 mg, 1.04 mmol). After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 40% diethyl ether in hexanes) to give ($\pm$)-**11b** as a colorless oil (156 mg, 62%). ^1H NMR (500 MHz, CDCl_3) δ 8.21–8.15 (m, 2H), 7.69–7.65 (m, 1H), 7.59–7.55 (m, 1H), 5.68 (ddd, J = 47.3, 8.8, 3.9 Hz, 1H), 4.30–4.17 (m, 2H), 2.35–2.10 (m, 2H), 2.04 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 170.9, 148.5, 141.9 (d, J = 20.1 Hz), 131.5 (d, J = 7.7 Hz), 129.9, 123.5, 120.6 (d, J = 7.7 Hz), 90.3 (d, J = 174.4 Hz), 60.5 (d, J = 4.8 Hz), 36.4 (d, J = 23.0 Hz), 21.0; ^{19}F NMR (470.4 MHz, CDCl_3) -181.0 (ddd, J = 47.7, 32.2, 16.7 Hz); FTIR (thin film) ν 2967 (w), 1734 (s), 1530 (s), 1349 (s), 1227 (s), 1043 (s), 809 (m), 737 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{11}\text{H}_{12}\text{FNO}_4$ $[\text{M}+\text{H}]^+$: 242.0823; found 242.0821.

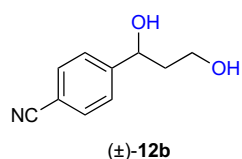


Prepared according to general procedure B using 2-cyclopropylbenzonitrile (**1c**, 145 mg, 1.04 mmol) with the following modifications: 20.0 mol% of

iodobenzene and 20 equiv of acetic acid were used instead. The reaction was allowed to stir for 24 hours. After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 40% diethyl ether in hexanes) to give ($\pm$)-**11c** as a colorless oil (138 mg, 60%). ^1H NMR (500 MHz, CDCl_3) δ 7.67–7.51 (m, 4H), 7.41 (t, J = 7.6 Hz, 1H), 5.90 (ddd, J = 46.9, 8.3, 4.2 Hz, 1H), 4.26–4.15 (m, 2H), 2.33–2.11 (m, 2H), 2.01 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 170.1, 143.2 (d, J = 20.6 Hz), 133.3, 133.0, 129.0 (d, J = 1.4 Hz), 126.1 (d, J = 8.6 Hz), 116.6, 109.7 (d, J = 5.3 Hz), 89.2 (d, J = 174.9 Hz), 59.8 (d, J = 3.8 Hz), 36.0 (d, J = 24.0 Hz), 20.8; ^{19}F NMR (470.4 MHz, CDCl_3) -183.1 (ddd, J = 47.7, 31.0, 17.9 Hz); FTIR (thin film) ν 2966 (w), 2226 (w), 1736 (s), 1366 (m), 1226 (s), 1045 (s), 764 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{12}\text{H}_{12}\text{FNO}_2$ $[\text{M}+\text{Na}]^+$: 244.0744; found 244.0744.

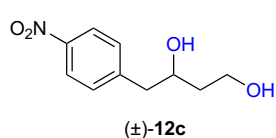


Prepared according to general procedure C using 1,3-dichloro-2-cyclopropylbenzene (**1h**, 98.0 mg, 0.520 mmol). After work-up, the crude residue was purified by flash column chromatography on silica gel (10% to 80% ethyl acetate in hexanes) to give ($\pm$)-**12a** as a viscous, colorless oil (100 mg, 87%). ^1H NMR (500 MHz, CDCl_3) δ 7.31–7.26 (m, 2H), 7.15–7.10 (m, 1H), 5.65 (dd, J = 9.9, 4.3 Hz, 1H), 3.92–3.82 (m, 2H), 3.60–3.15 (br. s, 1H), 2.75–1.85 (m, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 137.5, 134.3, 129.6, 129.1, 70.9, 61.0, 37.1; FTIR (thin film) ν 3358 (br. s), 2953 (w), 1561 (m), 1436 (w), 1038 (s), 764 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_9\text{H}_{10}\text{Cl}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 221.0131; found 221.0121.

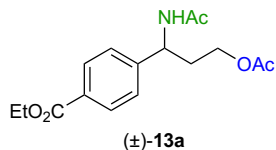


Prepared according to general procedure C using 4-cyclopropylbenzonitrile (**1b**, 149 mg, 1.04 mmol). After work-up, the crude residue was purified by

flash column chromatography on silica gel (20% to 100% ethyl acetate in hexanes) to give ($\pm$)-**12b** as a viscous, colorless oil (107 mg, 59%). ^1H NMR (500 MHz, CDCl_3) δ 7.58 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 4.96 (t, J = 6.1 Hz, 1H), 4.25–3.95 (br. s, 1H), 3.84–3.75 (m, 2H), 3.30–2.85 (br. s, 1H), 1.93–1.82 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 150.0, 132.3, 126.4, 118.9, 110.9, 73.2, 60.9, 40.2; FTIR (thin film) ν 3362 (br. s), 2229 (m), 1644 (m), 1049 (s), 723 (s), 563 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{10}\text{H}_{11}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 178.0863; found 178.0860.

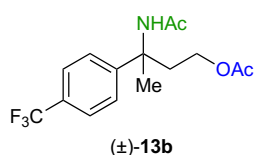


Prepared according to general procedure C using 1-(cyclopropylmethyl)-4-nitrobenzene (**3g**, 184 mg, 1.04 mmol) with the following modifications: the reaction was stirred for 24 hours before concentrating the reaction mixture. The hydrolysis was conducted on this residue with a 1:1 mixture of tetrahydrofuran and 2 M NaOH (5 mL). After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 10% methanol in dichloromethane) to give ($\pm$)-**12c** as a viscous, colorless oil (121 mg, 55%). ^1H NMR (500 MHz, CDCl_3) δ 8.11 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 4.17–4.03 (m, 1H), 3.90–3.71 (m, 2H), 3.29 (br. s, 1H), 2.85 (d, J = 6.3 Hz, 2H), 2.85 (br. s, 1H), 1.79–1.61 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 146.8, 146.7, 130.5, 123.7, 72.2, 61.4, 44.0, 38.0; FTIR (thin film) ν 3335 (br. s), 2940 (w), 1599 (m), 1512 (s), 1342 (s), 1051 (m), 699 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{10}\text{H}_{13}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 212.0917; found 212.0919.

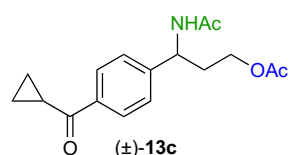


Prepared according to general procedure D using ethyl 4-cyclopropylbenzoate (**1a**, 198 mg, 1.04 mmol) to give ($\pm$)-**13a** as a yellow oil (262 mg, 82%). ^1H NMR (500 MHz, CDCl_3) δ 7.96 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 6.53 (d, J = 8.1 Hz, 1H), 5.16–5.08 (m, 1H), 4.33 (q, J = 7.2 Hz,

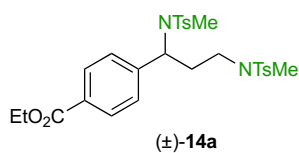
2H), 4.10–3.95 (m, 2H), 2.11–2.04 (m, 2H), 1.99 (s), 1.95 (s), 1.35 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 171.0, 169.7, 166.3, 146.7, 130.1, 129.8, 126.5, 61.5, 61.1, 50.6, 34.8, 23.3, 21.0, 14.4; FTIR (thin film) ν 3275 (w), 1716 (s), 1368 (m), 1276 (s), 709 (w) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{16}\text{H}_{21}\text{NO}_5$ $[\text{M}+\text{Na}]^+$: 330.1312; found 330.1319.



Prepared according to general procedure D using **1l** (104 mg, 0.52 mmol) to give (±)-**13b** as a colorless oil (134 mg, 81%). ^1H NMR (500 MHz, CDCl_3) δ 7.54 (d, $J = 8.3$ Hz, 2H), 7.40 (d, $J = 8.3$ Hz, 2H), 6.63 (s, 1H), 4.07–3.99 (m, 2H), 2.43–2.05 (m, 2H), 1.99 (s, 3H), 1.94 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 171.0, 169.5, 149.4, 128.9 (q, $J = 32.1$ Hz), 125.4 (q, $J = 3.6$ Hz), 125.4, 124.1 (q, $J = 271.6$ Hz), 60.9, 57.6, 39.8, 26.5, 23.9, 20.9; ^{19}F NMR (470.4 MHz, CDCl_3) -62.5; FTIR (thin film) ν 3295 (w), 1737 (m), 1327 (s), 1114 (s), 841 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{15}\text{H}_{18}\text{F}_3\text{NO}_3$ $[\text{M}+\text{Na}]^+$: 340.1131; found 340.1139.

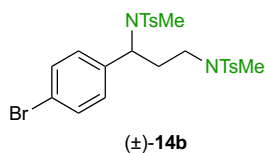


Prepared according to general procedure D using **1n** (194 mg, 1.04 mmol) to give (±)-**13c** as a yellow oil (192 mg, 61%). ^1H NMR (500 MHz, CDCl_3) δ 7.99 (d, $J = 8.3$ Hz, 2H), 7.39 (d, $J = 8.3$ Hz, 2H), 6.18–6.08 (m, 1H), 5.17 (q, $J = 7.6$ Hz, 1H), 4.14–4.00 (m, 2H), 2.68–2.60 (m, 1H), 2.17–2.10 (m, 2H), 2.02 (s, 3H), 2.00 (s, 3H), 1.27–1.18 (m, 2H), 1.04 (dq, $J = 7.4, 3.6$ Hz, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 200.2, 171.1, 169.6, 146.5, 137.4, 128.7, 126.7, 61.3, 50.7, 34.8, 23.4, 21.0, 17.3, 11.8; FTIR (thin film) ν 3277 (w), 1654 (s), 1541 (m), 1227 (s), 993 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{17}\text{H}_{21}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 304.1543; found 304.1544.



Prepared according to general procedure E using ethyl 4-cyclopropylbenzoate (**1a**, 198 mg, 1.04 mmol). After work-up, the crude residue was purified by flash column chromatography on silica gel (10% to

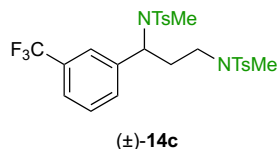
70% diethyl ether in hexanes) to give (±)-**14a** as a viscous, yellow oil (255 mg, 44%). ¹H NMR (500 MHz, CDCl₃) δ 7.95 (d, *J* = 8.1 Hz, 2H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.33–7.22 (m, 6H), 5.15 (t, *J* = 7.7 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 3.10–3.01 (m, 1H), 2.96–2.87 (m, 1H), 2.73 (s, 3H), 2.65 (s, 3H), 2.42 (s, 3H), 2.41 (s, 3H), 2.30–2.20 (m, 1H), 2.15–2.03 (m, 1H), 1.40 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (125.7 MHz, CDCl₃) δ 166.1, 143.5, 142.3, 136.8, 134.2, 130.1, 129.7, 127.9, 127.3, 127.1, 61.0, 57.3, 48.0, 35.6, 29.6, 29.0, 21.5, 14.3; FTIR (thin film) ν 2979 (w), 1713 (s), 1275 (s), 911 (s), 546 (s) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₂₈H₃₄N₂O₆S₂ [M+H]⁺: 559.1931; found 559.1933



Prepared according to general procedure E using 1-bromo-4-cyclopropylbenzene (205 mg, 1.04 mmol). After work-up, the crude residue was purified by flash column chromatography on silica gel (10% to

70% diethyl ether in hexanes) to give (±)-**14b** as a viscous, yellow oil (270 mg, 46%). ¹H NMR (500 MHz, CDCl₃) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 5.03 (apparent t, *J* = 7.7 Hz, 1H), 3.02 (ddd, *J* = 14.0, 9.7, 6.0 Hz, 1H), 2.90 (ddd, *J* = 14.0, 9.6, 4.9 Hz, 1H), 2.72 (s, 3H), 2.62 (s, 3H), 2.43 (s, 3H), 2.42 (s, 3H), 2.23–2.13 (m, 1H), 2.11–2.01 (m, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 143.5, 143.4, 136.9, 136.4, 134.3, 131.6, 129.7, 129.7, 127.3, 127.1, 122.1, 57.1, 48.0, 35.6, 29.7, 28.9, 21.5; FTIR (thin film) ν 2925 (w), 1597 (w),

1332 (s), 1156 (s), 814 (m), 547 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{25}\text{H}_{29}\text{N}_2\text{O}_4\text{S}_2$ $[\text{M}+\text{H}]^+$: 565.0839; found 565.0825.

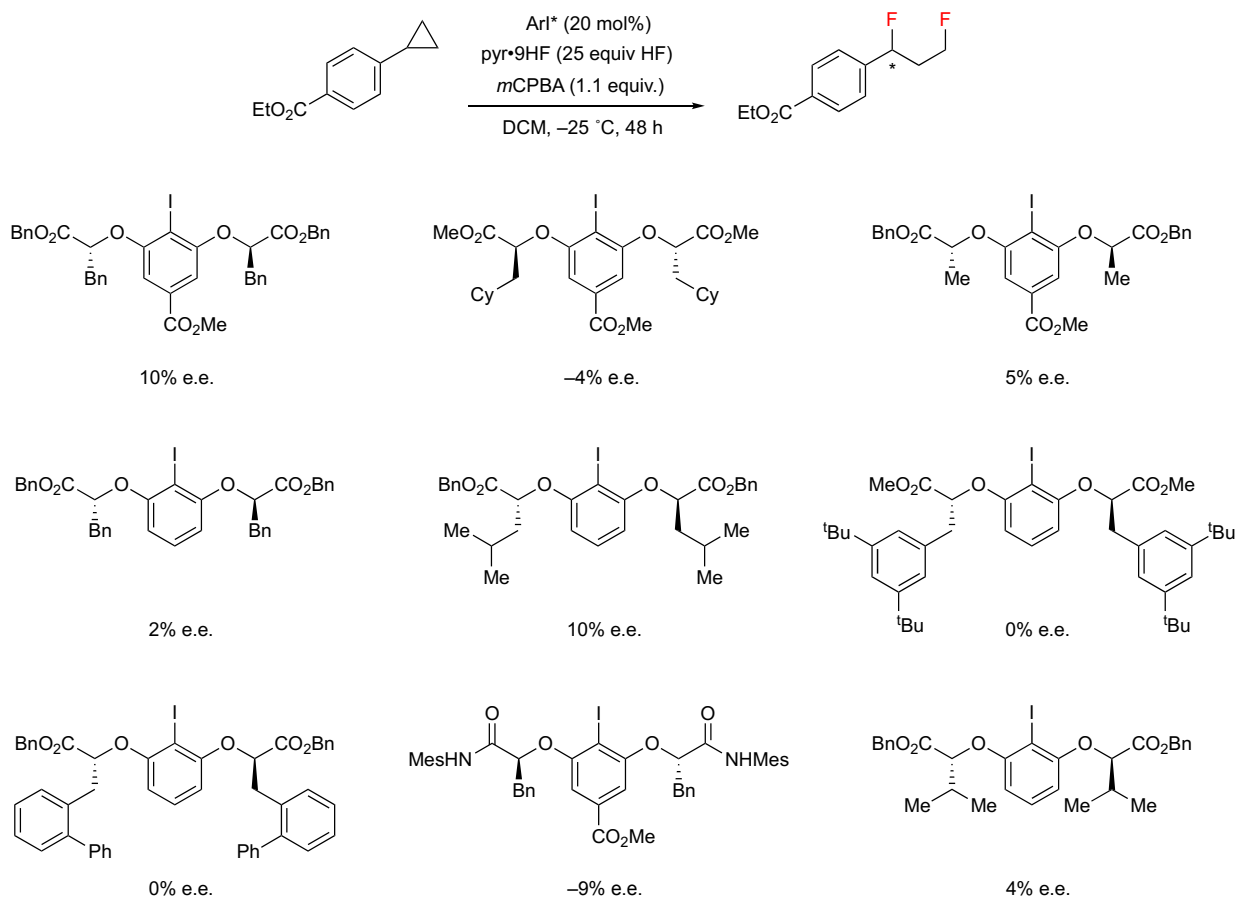


Prepared according to general procedure E using 1-(cyclopropyl)-3-(trifluoromethyl)benzene (**10**, 194 mg, 1.04 mmol). After work-up, the crude residue was purified by flash column chromatography on silica gel (0% to 50% diethyl ether in hexanes) to give (**±**)-**14c** as a colorless viscous oil (277 mg, 48%). ^1H NMR (500 MHz, CDCl_3) δ 7.65–7.61 (m, 4H), 7.52–7.47 (m, 1H), 7.41 (d, $J = 5.4$ Hz, 2H), 7.31 (d, $J = 7.8$ Hz, 2H), 7.28–7.24 (m, 2H), 7.18 (s, 1H), 5.14–5.08 (m, 1H), 3.11 (ddd, $J = 14.9, 9.5, 6.1$ Hz, 1H), 2.95 (ddd, $J = 14.0, 9.5, 5.1$ Hz, 1H), 2.76 (s, 3H), 2.66 (s, 3H), 2.43 (s, 3H), 2.41 (s, 3H), 2.29–2.13 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 143.7, 143.6, 138.5, 136.8, 134.3, 131.2, 130.8 (q, $J = 32.6$ Hz), 129.8, 129.7, 129.2, 127.4, 127.0, 124.9 (q, $J = 3.6$ Hz), 124.8 (q, $J = 3.6$ Hz), 123.9 (q, $J = 272.6$ Hz), 57.4, 48.1, 35.8, 29.9, 29.1, 21.5, 21.4; ^{19}F NMR (470.4 MHz, CDCl_3) δ -62.7; FTIR (thin film) ν 2926 (w), 1598 (w), 1156 (s), 906 (m), 731 (s), 546 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{26}\text{H}_{29}\text{F}_3\text{N}_2\text{O}_4\text{S}_2$ $[\text{M}+\text{H}]^+$: 555.1594; found 555.1588.

Enantioselective Reaction.

Catalyst (10.4 μmol , 20.0 mol%), *m*-chloroperbenzoic acid (*m*CPBA, 77% by weight, 12.8 mg, 57.2 μmol , 1.10 equiv), **1a** (9.9 mg, 52.0 μmol , 1.00 equiv), dodecane (11.4 μL , 52.0 μmol , 1.00 equiv) and dichloromethane (0.30 mL) were combined in a polyethylene tube and cooled to -78 $^\circ\text{C}$. Pyridinium poly(hydrogen fluoride) ($\text{pyr}\cdot 9\text{HF}$, 0.028 mL, 1.0 mmol, 20 equiv HF) was added *via* micropipette. The reaction was stirred for 48 hours at -25 $^\circ\text{C}$. The reaction was cooled

to $-78\text{ }^{\circ}\text{C}$, and slowly added to a basic alumina slurry (approximately 750 mg in 2 mL dichloromethane). The mixture was allowed to warm to room temperature with stirring and was filtered. The crude mixture was analyzed by GC to determine starting material conversion and the yield of product as well as chiral HPLC using a CHIRALCEL OD-H column to determine enantiomeric excess.



Scheme S1.3 Effect of catalyst structure on enantioselectivity of 1,3-difluorination reaction of **1a**.

Computational Studies

Calculations were performed at Harvard University on the Odyssey research computing cluster using the Gaussian 09 program.⁵⁶ The B3LYP density functional was employed with the Stuttgart–Dresden (SDD) ECP for iodine. The 6-31+G(d,p) basis set was used. Default optimization convergence criteria, tight SCF convergence criteria, and default integration settings were used. All stationary points were verified by frequency calculations using the rigid-rotor/harmonic-oscillator assumption, and minima were characterized by the absence of any imaginary frequencies. Distances are reported in units of angstroms (Å).

Charge = 1 Multiplicity = 1

Electronic Energy (AU)= -691.53850472

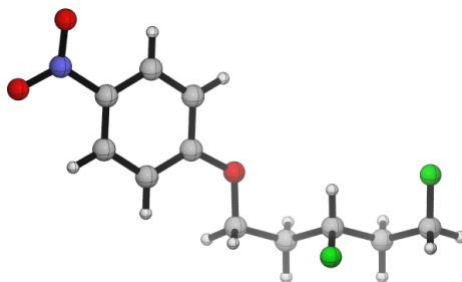
Solvent: gas phase

Imaginary Frequencies: 0

⁵⁶ Gaussian 09, Revision A.02, Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G.A.; Akatsuji, H.; Caricato, M.; Li, X.; Hratchian, H.P.; Izmaylov, A.F.; Bloino, J.; Zheng, G.; Sonnenberg, J.L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery Jr., J.A.; Peralta, J.E.; Ogliaro, F.; Bearpark, M.; Heyd, J.J.; Brothers, E.; Kudin, K.N.; Staroverov, V.N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J.C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J.M.; Klene, M.; Knox, J.E.; Cross, J.B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R.E.; Yazyev, O.; Austin, A.J.; Cammi, R.; Pomelli, C.; Ochterski, J.W.; Martin, R.L.; Morokuma, K.; Zakrzewski, V.G.; Voth, G.A.; Salvador, P.; Dannenberg, J.J.; Dapprich, S.; Daniels, A.D.; Farkas, O.; Foresman, J.B.; Ortiz, J.V.; Cioslowski, J.; Fox, D.J. Gaussian, Inc., Wallingford CT, 2009.

C	4.79647	0.2811	0.2542
C	3.98446	0.14538	1.39769
C	2.063	-0.19667	0.00712
C	4.19761	0.17451	-1.01679
H	4.42995	0.22525	2.38492
H	4.80906	0.27664	-1.90849
I	0.00874	-0.60476	-0.17600
F	0.22545	-2.5835	-0.16878
C	-3.39425	-0.30141	-1.03961
C	-2.97313	0.78326	-0.24546
C	-3.4877	0.89905	1.05896
C	-4.39961	-0.03605	1.5473
C	-4.8139	-1.10816	0.74658
C	-4.31211	-1.23653	-0.54884
H	-3.03509	-0.39075	-2.06255
H	-3.19237	1.72777	1.69704
H	-4.79388	0.07397	2.55296
H	-5.52824	-1.82989	1.12997
H	-4.63506	-2.05659	-1.18272
C	-2.00745	1.76343	-0.82052
C	-1.9558	3.19737	-0.41142
C	-0.79557	2.34127	0.04078
H	-1.74968	1.57443	-1.85976
H	-2.65052	3.52609	0.35523
H	-1.75173	3.92903	-1.18701
H	0.16185	2.5273	-0.43679
H	-0.76131	2.11186	1.10164
C	2.61909	-0.09516	1.29144
H	2.01144	-0.20558	2.18305
C	2.83522	-0.06594	-1.15713
H	2.39346	-0.15457	-2.14377
H	5.85001	0.44199	0.34936

X-Ray Crystallographic Information Data for (±)-4b



A crystal mounted on a diffractometer was analyzed at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II CCD diffractometer ($\text{MoK}\alpha$ radiation, $\lambda=0.71073$ Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 0.5° scans in ω at 28° in 2θ . Data integration down to 0.78 Å resolution was carried out using SAINT V8.37⁵⁷ with reflection spot size optimization. Absorption corrections were made with the program SADABS.⁵⁹ The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods against F^2 using SHELXT-2014⁵⁸ and SHELXL-2014⁵⁹ with OLEX 2 interface.⁶⁰ Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table S1.1, and geometric parameters are shown in Table S1.2. The Ortep plots were produced with the SHELXL-2014 program.

⁵⁷ Bruker AXS APEX3. Bruker AXS: Madison, WI, 2014.

⁵⁸ Sheldrick, G.M. *Acta Cryst.* **2015**, *A71*, 3–8.

⁵⁹ Sheldrick, G.M. *Acta Cryst.* **2015**, *C71*, 3–8.

⁶⁰ Dolomanov, O.V., Bourhis, L.J., Gildea, R.J., Howard, J.A.K., Puschmann, H. *J. Appl. Cryst.* **2009**, *42*, 339–341.

Table S1.1 Experimental details.**Crystal data**

Chemical formula	C ₁₁ H ₁₃ F ₂ NO ₃
M_r	245.22
Crystal system, space group	Triclinic, $P-1$
Temperature (K)	100
a, b, c (Å)	4.6385 (6), 9.6361 (13), 13.1145 (17)
α, β, γ (°)	103.819 (2), 95.249 (2), 95.137 (2)
V (Å ³)	563.05 (13)
Z	2
Radiation type	Mo $K\alpha$
μ (mm ⁻¹)	0.13
Crystal size (mm)	0.18 × 0.08 × 0.06

Data collection

Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan <i>SADABS</i>
$T_{\min}, T_{\max}$	0.829, 0.862
No. of measured, independent and observed [$I > 2s(I)$] reflections	7614, 2474, 2054
R_{int}	0.021
$(\sin \theta/\lambda)_{\text{max}}$ (Å ⁻¹)	0.641

Refinement

$R[F^2 > 2s(F^2)], wR(F^2), S$	0.033, 0.093, 1.06
No. of reflections	2474
No. of parameters	154
H-atom treatment	H-atom parameters constrained
$D\rho_{\text{max}}, D\rho_{\text{min}}$ (e Å ⁻³)	0.29, -0.23

Table S1.2 Geometric parameters (Å, °).

F1—C9	1.4217 (13)	C3—H3	0.9500
F2—C11	1.4072 (16)	C6—C1	1.3879 (16)
O1—C4	1.3530 (13)	C6—H6	0.9500
O1—C7	1.4382 (13)	C8—C9	1.5123 (16)
O2—N1	1.2287 (13)	C8—H8A	0.9900
O3—N1	1.2286 (14)	C8—H8B	0.9900
N1—C1	1.4583 (15)	C9—C10	1.5117 (16)
C4—C3	1.3969 (16)	C9—H9	1.0000
C4—C5	1.3982 (16)	C1—C2	1.3806 (16)
C7—C8	1.5099 (15)	C2—H2	0.9500
C7—H7A	0.9900	C10—C11	1.5061 (18)
C7—H7B	0.9900	C10—H10A	0.9900
C5—C6	1.3748 (16)	C10—H10B	0.9900
C5—H5	0.9500	C11—H11A	0.9900
C3—C2	1.3847 (16)	C11—H11B	0.9900
C4—O1—C7	118.14 (8)	C9—C8—H8B	108.8
O3—N1—O2	123.00 (10)	H8A—C8—H8B	107.7
O3—N1—C1	118.66 (10)	F1—C9—C10	107.74 (9)
O2—N1—C1	118.34 (10)	F1—C9—C8	107.93 (9)
O1—C4—C3	124.59 (10)	C10—C9—C8	113.23 (10)
O1—C4—C5	115.12 (10)	F1—C9—H9	109.3
C3—C4—C5	120.28 (10)	C10—C9—H9	109.3
O1—C7—C8	106.72 (9)	C8—C9—H9	109.3
O1—C7—H7A	110.4	C2—C1—C6	121.89 (11)
C8—C7—H7A	110.4	C2—C1—N1	119.43 (10)
O1—C7—H7B	110.4	C6—C1—N1	118.67 (10)
C8—C7—H7B	110.4	C1—C2—C3	119.34 (11)
H7A—C7—H7B	108.6	C1—C2—H2	120.3
C6—C5—C4	120.13 (10)	C3—C2—H2	120.3

C6—C5—H5	119.9	C11—C10—C9	113.76 (10)
C4—C5—H5	119.9	C11—C10—H10A	108.8
C2—C3—C4	119.43 (11)	C9—C10—H10A	108.8
C2—C3—H3	120.3	C11—C10—H10B	108.8
C4—C3—H3	120.3	C9—C10—H10B	108.8
C5—C6—C1	118.91 (11)	H10A—C10—H10B	107.7
C5—C6—H6	120.5	F2—C11—C10	109.14 (10)
C1—C6—H6	120.5	F2—C11—H11A	109.9
C7—C8—C9	113.82 (9)	C10—C11—H11A	109.9
C7—C8—H8A	108.8	F2—C11—H11B	109.9
C9—C8—H8A	108.8	C10—C11—H11B	109.9
C7—C8—H8B	108.8	H11A—C11—H11B	108.3
C7—O1—C4—C3	-1.51 (15)	C5—C6—C1—N1	-177.36 (10)
C7—O1—C4—C5	177.62 (9)	O3—N1—C1—C2	-12.04 (16)
C4—O1—C7—C8	177.41 (9)	O2—N1—C1—C2	168.73 (10)
O1—C4—C5—C6	-179.56 (10)	O3—N1—C1—C6	167.08 (11)
C3—C4—C5—C6	-0.39 (16)	O2—N1—C1—C6	-12.15 (16)
O1—C4—C3—C2	-179.76 (10)	C6—C1—C2—C3	-0.98 (17)
C5—C4—C3—C2	1.15 (16)	N1—C1—C2—C3	178.11 (10)
C4—C5—C6—C1	-1.03 (16)	C4—C3—C2—C1	-0.47 (17)
O1—C7—C8—C9	65.43 (12)	F1—C9—C10—C11	-59.99 (13)
C7—C8—C9—F1	61.93 (12)	C8—C9—C10—C11	-179.27 (10)
C7—C8—C9—C10	-178.90 (10)	C9—C10—C11—F2	-59.52 (14)
C5—C6—C1—C2	1.74 (17)		

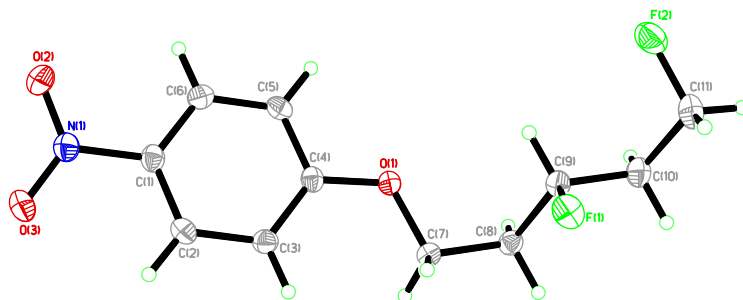
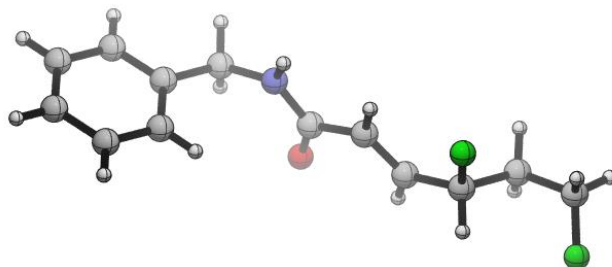


Figure S1.1 Perspective views showing 50% probability displacement.

X-Ray Crystallographic Information Data for (±)-4h



A crystal mounted on a diffractometer was analyzed at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II DUO CCD diffractometer ($\text{CuK}\alpha$ radiation, $\lambda=1.54178$ Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 1.0° scans in ω at -30° , -55° , -80° , 30° , 55° , 80° and 115° in 2θ . Data integration down to 0.84 Å resolution was carried out using SAINT V8.34 C with reflection spot size optimization. Absorption corrections were made with the program SADABS. The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods against F^2 using SHELXT-2014 and SHELXL-2014 with OLEX 2 interface. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table S1.3, geometric parameters are shown in Table S1.4. The Ortep plots were produced with the SHELXL-2014 program.

Table S1.3 Experimental details.

Crystal data

Chemical formula	$\text{C}_{26}\text{H}_{30}\text{F}_4\text{N}_2\text{O}_2$
M_r	478.52

Crystal system, space group	Monoclinic, $P2_1$
Temperature (K)	100
a, b, c (Å)	5.55621 (10), 26.2064 (5), 8.18405 (15)
β (°)	92.4361 (8)
V (Å ³)	1190.59 (4)
Z	2
Radiation type	Cu $K\alpha$
μ (mm ⁻¹)	0.89
Crystal size (mm)	$0.20 \times 0.18 \times 0.16$
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan <i>SADABS</i>
$T_{\min}, T_{\max}$	0.818, 0.864
No. of measured, independent and observed [$I > 2s(I)$] reflections	29655, 4006, 3890
R_{int}	0.028
$(\sin \theta/\lambda)_{\max}$ (Å ⁻¹)	0.596
Refinement	
$R[F^2 > 2s(F^2)], wR(F^2), S$	0.033, 0.096, 1.07
No. of reflections	4006
No. of parameters	315
No. of restraints	1
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$D\rho_{\max}, D\rho_{\min}$ (e Å ⁻³)	0.24, -0.25
Absolute structure	Flack x determined using 1728 quotients $[(I^+)-(I^-)]/[(I^+)+(I^-)]$ (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	0.00 (4)

Table S1.4 Geometric parameters (Å, °).

F1—C11	1.404 (2)	F3—C31	1.404 (2)
F2—C13	1.402 (3)	F4—C33	1.400 (3)
O1—C8	1.241 (3)	O2—C28	1.238 (3)
N1—C8	1.332 (3)	N2—C28	1.334 (3)
N1—C7	1.456 (3)	N2—C27	1.469 (3)
N1—H1	0.88 (3)	N2—H2A	0.92 (2)
C1—C2	1.387 (3)	C21—C22	1.387 (3)
C1—C6	1.392 (3)	C21—C26	1.396 (3)
C1—H1A	0.9500	C21—H21	0.9500
C2—C3	1.389 (3)	C22—C23	1.384 (3)
C2—H2	0.9500	C22—H22	0.9500
C3—C4	1.385 (3)	C23—C24	1.385 (3)
C3—H3	0.9500	C23—H23	0.9500
C4—C5	1.390 (3)	C24—C25	1.385 (3)
C4—H4	0.9500	C24—H24	0.9500
C5—C6	1.398 (3)	C25—C26	1.388 (3)
C5—H5	0.9500	C25—H25	0.9500
C6—C7	1.514 (3)	C26—C27	1.511 (3)
C7—H7A	0.9900	C27—H27A	0.9900
C7—H7B	0.9900	C27—H27B	0.9900
C8—C9	1.490 (3)	C28—C29	1.487 (3)
C9—C10	1.325 (3)	C29—C30	1.325 (3)
C9—H9	0.9500	C29—H29	0.9500
C10—C11	1.494 (3)	C30—C31	1.493 (3)
C10—H10	0.9500	C30—H30	0.9500
C11—C12	1.516 (3)	C31—C32	1.514 (3)
C11—H11	1.0000	C31—H31	1.0000
C12—C13	1.506 (3)	C32—C33	1.505 (3)

C12—H12A	0.9900	C32—H32A	0.9900
C12—H12B	0.9900	C32—H32B	0.9900
C13—H13A	0.9900	C33—H33A	0.9900
C13—H13B	0.9900	C33—H33B	0.9900
C8—N1—C7	123.11 (17)	C28—N2—C27	122.79 (17)
C8—N1—H1	116.1 (16)	C28—N2—H2A	114.8 (15)
C7—N1—H1	120.5 (16)	C27—N2—H2A	122.2 (15)
C2—C1—C6	120.87 (18)	C22—C21—C26	120.22 (18)
C2—C1—H1A	119.6	C22—C21—H21	119.9
C6—C1—H1A	119.6	C26—C21—H21	119.9
C1—C2—C3	120.12 (19)	C23—C22—C21	120.58 (19)
C1—C2—H2	119.9	C23—C22—H22	119.7
C3—C2—H2	119.9	C21—C22—H22	119.7
C4—C3—C2	119.6 (2)	C22—C23—C24	119.4 (2)
C4—C3—H3	120.2	C22—C23—H23	120.3
C2—C3—H3	120.2	C24—C23—H23	120.3
C3—C4—C5	120.27 (19)	C23—C24—C25	120.12 (19)
C3—C4—H4	119.9	C23—C24—H24	119.9
C5—C4—H4	119.9	C25—C24—H24	119.9
C4—C5—C6	120.57 (19)	C24—C25—C26	120.96 (19)
C4—C5—H5	119.7	C24—C25—H25	119.5
C6—C5—H5	119.7	C26—C25—H25	119.5
C1—C6—C5	118.6 (2)	C25—C26—C21	118.7 (2)
C1—C6—C7	119.53 (18)	C25—C26—C27	120.35 (19)
C5—C6—C7	121.89 (18)	C21—C26—C27	120.98 (18)
N1—C7—C6	113.53 (16)	N2—C27—C26	111.73 (16)
N1—C7—H7A	108.9	N2—C27—H27A	109.3
C6—C7—H7A	108.9	C26—C27—H27A	109.3
N1—C7—H7B	108.9	N2—C27—H27B	109.3
C6—C7—H7B	108.9	C26—C27—H27B	109.3

H7A—C7—H7B	107.7	H27A—C27—H27B	107.9
O1—C8—N1	123.76 (19)	O2—C28—N2	123.57 (19)
O1—C8—C9	121.79 (18)	O2—C28—C29	121.49 (18)
N1—C8—C9	114.45 (17)	N2—C28—C29	114.94 (17)
C10—C9—C8	121.38 (18)	C30—C29—C28	120.80 (18)
C10—C9—H9	119.3	C30—C29—H29	119.6
C8—C9—H9	119.3	C28—C29—H29	119.6
C9—C10—C11	125.44 (19)	C29—C30—C31	125.87 (19)
C9—C10—H10	117.3	C29—C30—H30	117.1
C11—C10—H10	117.3	C31—C30—H30	117.1
F1—C11—C10	109.72 (17)	F3—C31—C30	109.72 (17)
F1—C11—C12	107.38 (17)	F3—C31—C32	107.52 (17)
C10—C11—C12	113.11 (18)	C30—C31—C32	113.02 (18)
F1—C11—H11	108.8	F3—C31—H31	108.8
C10—C11—H11	108.8	C30—C31—H31	108.8
C12—C11—H11	108.8	C32—C31—H31	108.8
C13—C12—C11	112.65 (18)	C33—C32—C31	112.12 (18)
C13—C12—H12A	109.1	C33—C32—H32A	109.2
C11—C12—H12A	109.1	C31—C32—H32A	109.2
C13—C12—H12B	109.1	C33—C32—H32B	109.2
C11—C12—H12B	109.1	C31—C32—H32B	109.2
H12A—C12—H12B	107.8	H32A—C32—H32B	107.9
F2—C13—C12	109.8 (2)	F4—C33—C32	109.94 (19)
F2—C13—H13A	109.7	F4—C33—H33A	109.7
C12—C13—H13A	109.7	C32—C33—H33A	109.7
F2—C13—H13B	109.7	F4—C33—H33B	109.7
C12—C13—H13B	109.7	C32—C33—H33B	109.7
H13A—C13—H13B	108.2	H33A—C33—H33B	108.2
C6—C1—C2—C3	0.2 (3)	C26—C21—C22— C23	-0.8 (3)

C1—C2—C3—C4	0.1 (3)	C21—C22—C23— C24	0.8 (3)
C2—C3—C4—C5	-0.6 (3)	C22—C23—C24— C25	0.0 (3)
C3—C4—C5—C6	0.8 (3)	C23—C24—C25— C26	-0.9 (3)
C2—C1—C6—C5	0.0 (3)	C24—C25—C26— C21	0.9 (3)
C2—C1—C6—C7	178.37 (17)	C24—C25—C26— C27	-177.90 (17)
C4—C5—C6—C1	-0.4 (3)	C22—C21—C26— C25	-0.1 (3)
C4—C5—C6—C7	-178.80 (18)	C22—C21—C26— C27	178.75 (17)
C8—N1—C7—C6	110.2 (2)	C28—N2—C27— C26	111.7 (2)
C1—C6—C7—N1	153.00 (18)	C25—C26—C27— N2	89.6 (2)
C5—C6—C7—N1	-28.7 (3)	C21—C26—C27— N2	-89.2 (2)
C7—N1—C8—O1	-0.7 (3)	C27—N2—C28—O2	-1.0 (3)
C7—N1—C8—C9	179.83 (18)	C27—N2—C28— C29	179.07 (18)
O1—C8—C9—C10	2.7 (3)	O2—C28—C29— C30	1.7 (3)
N1—C8—C9—C10	-177.9 (2)	N2—C28—C29— C30	-178.4 (2)
C8—C9—C10—C11	-179.8 (2)	C28—C29—C30— C31	-179.8 (2)
C9—C10—C11—F1	5.6 (3)	C29—C30—C31—F3	5.2 (3)
C9—C10—C11—C12	-114.3 (2)	C29—C30—C31— C32	-114.7 (2)
F1—C11—C12—C13	67.2 (2)	F3—C31—C32—C33	67.5 (2)
C10—C11—C12— C13	-171.61 (19)	C30—C31—C32— C33	-171.26 (19)

C11—C12—C13—F2	67.7 (3)	C31—C32—C33—F4	67.6 (2)

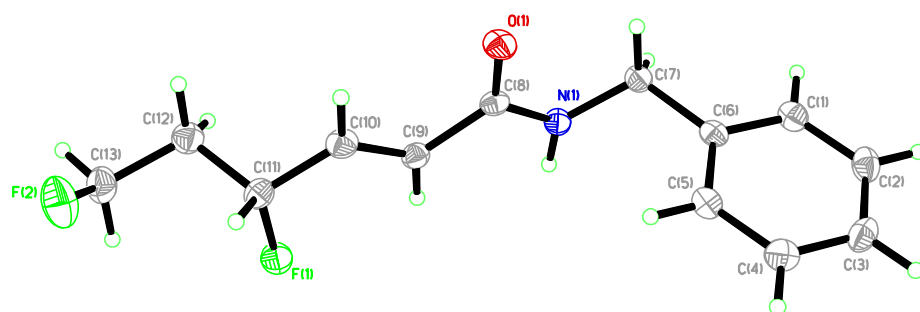
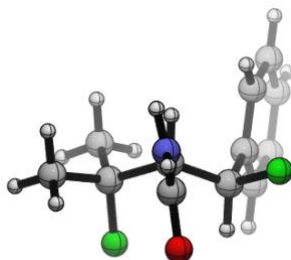


Figure S1.2 Perspective views showing 50% probability displacement.

X-Ray Crystallographic Information Data for (±)-6c



X-ray Crystallography: A crystal mounted on a diffractometer was analyzed at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II DUO CCD diffractometer ($\text{CuK}\alpha$ radiation, $\lambda=1.54178$ Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 1.0° scans in ω at -30° , -55° , -80° , 30° , 55° , 80° and 115° in 2θ . Data integration down to 0.84 Å resolution was carried out using SAINT V8.34 C with reflection spot size optimization. Absorption corrections were made with the program SADABS. The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods against F^2 using SHELXT-2014 and SHELXL-2014 with OLEX 2 interface. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table S1.5, geometric parameters are shown in Table S1.6. The Ortep plots produced with the SHELXL-2014 program.

Table S1.5 Experimental details.

Crystal data

Chemical formula	$\text{C}_{12}\text{H}_{15}\text{F}_2\text{NO}$
M_r	227.25
Crystal system, space group	Orthorhombic, $Pbcn$
Temperature (K)	100
a, b, c (Å)	15.5514 (6), 16.0433 (6), 9.9222 (4)

$V(\text{\AA}^3)$	2475.55 (17)
Z	8
Radiation type	Cu $K\alpha$
μ (mm ⁻¹)	0.83
Crystal size (mm)	0.09 × 0.01 × 0.01
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan <i>SADABS</i>
$T_{\min}, T_{\max}$	0.699, 0.864
No. of measured, independent and observed [I > 2s(I)] reflections	30666, 2199, 1719
R_{int}	0.075
$(\sin \theta/\lambda)_{\max}$ (Å ⁻¹)	0.596
Refinement	
$R[F^2 > 2s(F^2)], wR(F^2), S$	0.088, 0.210, 1.09
No. of reflections	2199
No. of parameters	155
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$D\rho_{\max}, D\rho_{\min}$ (e Å ⁻³)	0.25, -0.17

Table S1.6 Geometric parameters (Å, °).

F1—C7	1.424 (5)	C5—H5	0.9500
F2—C10	1.420 (5)	C6—C7	1.506 (5)
O1—C9	1.230 (5)	C7—C8	1.521 (6)
N1—C9	1.300 (6)	C7—H7	1.0000
N1—H1A	0.91 (4)	C8—C9	1.547 (5)
N1—H1B	0.90 (5)	C8—C10	1.548 (6)
C1—C6	1.368 (6)	C8—H8	1.0000
C1—C2	1.388 (6)	C10—C11	1.500 (6)
C1—H1	0.9500	C10—C12	1.521 (5)
C2—C3	1.357 (7)	C11—H11A	0.9800

C2—H2	0.9500	C11—H11B	0.9800
C3—C4	1.359 (8)	C11—H11C	0.9800
C3—H3	0.9500	C12—H12A	0.9800
C4—C5	1.408 (7)	C12—H12B	0.9800
C4—H4	0.9500	C12—H12C	0.9800
C5—C6	1.383 (6)		
C9—N1—H1A	131 (2)	C7—C8—C9	106.4 (3)
C9—N1—H1B	120 (3)	C7—C8—C10	114.7 (4)
H1A—N1—H1B	109 (4)	C9—C8—C10	111.4 (3)
C6—C1—C2	121.2 (4)	C7—C8—H8	108.0
C6—C1—H1	119.4	C9—C8—H8	108.0
C2—C1—H1	119.4	C10—C8—H8	108.0
C3—C2—C1	119.5 (5)	O1—C9—N1	123.8 (4)
C3—C2—H2	120.2	O1—C9—C8	119.5 (4)
C1—C2—H2	120.2	N1—C9—C8	116.7 (4)
C2—C3—C4	120.9 (5)	F2—C10—C11	107.3 (4)
C2—C3—H3	119.6	F2—C10—C12	106.4 (4)
C4—C3—H3	119.6	C11—C10—C12	110.2 (4)
C3—C4—C5	119.9 (5)	F2—C10—C8	107.1 (3)
C3—C4—H4	120.0	C11—C10—C8	111.8 (4)
C5—C4—H4	120.0	C12—C10—C8	113.7 (4)
C6—C5—C4	119.4 (5)	C10—C11—H11A	109.5
C6—C5—H5	120.3	C10—C11—H11B	109.5
C4—C5—H5	120.3	H11A—C11—H11B	109.5
C1—C6—C5	119.1 (4)	C10—C11—H11C	109.5
C1—C6—C7	119.9 (4)	H11A—C11—H11C	109.5
C5—C6—C7	121.0 (4)	H11B—C11—H11C	109.5
F1—C7—C6	106.5 (3)	C10—C12—H12A	109.5
F1—C7—C8	106.1 (3)	C10—C12—H12B	109.5
C6—C7—C8	116.6 (3)	H12A—C12—H12B	109.5
F1—C7—H7	109.2	C10—C12—H12C	109.5
C6—C7—H7	109.2	H12A—C12—H12C	109.5
C8—C7—H7	109.2	H12B—C12—H12C	109.5

C6—C1—C2—C3	0.7 (7)	C6—C7—C8—C9	-166.9 (4)
C1—C2—C3—C4	-0.5 (8)	F1—C7—C8—C10	-172.3 (3)
C2—C3—C4—C5	0.0 (8)	C6—C7—C8—C10	69.4 (5)
C3—C4—C5—C6	0.5 (8)	C7—C8—C9—O1	-54.3 (5)
C2—C1—C6—C5	-0.3 (6)	C10—C8—C9—O1	71.4 (5)
C2—C1—C6—C7	177.1 (4)	C7—C8—C9—N1	124.1 (4)
C4—C5—C6—C1	-0.3 (7)	C10—C8—C9—N1	-110.2 (4)
C4—C5—C6—C7	-177.6 (4)	C7—C8—C10—F2	46.5 (4)
C1—C6—C7—F1	-59.9 (5)	C9—C8—C10—F2	-74.4 (4)
C5—C6—C7—F1	117.4 (4)	C7—C8—C10—C11	163.7 (4)
C1—C6—C7—C8	58.1 (6)	C9—C8—C10—C11	42.8 (5)
C5—C6—C7—C8	-124.6 (5)	C7—C8—C10—C12	-70.7 (5)
F1—C7—C8—C9	-48.6 (4)	C9—C8—C10—C12	168.4 (4)

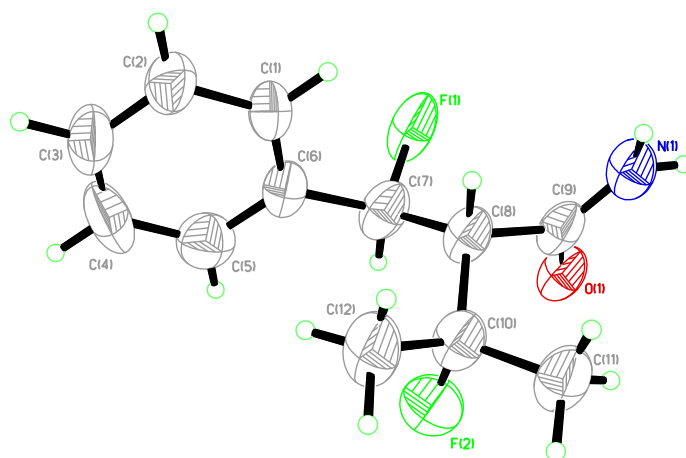
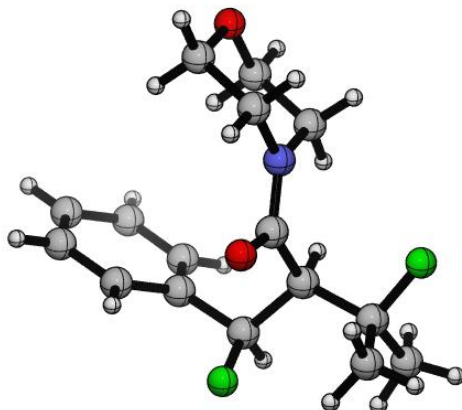


Figure S1.3 Perspective views showing 50% probability displacement.

X-Ray Crystallographic Information Data for (±)-6d



A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II DUO CCD diffractometer ($\text{CuK}\alpha$ radiation, $\lambda=1.54178$ Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 1.0° scans in ω at -30° , -55° , -80° , 30° , 55° , 80° and 115° in 2θ . Data integration down to 0.84 Å resolution was carried out using SAINT V8.34 C with reflection spot size optimization. Absorption corrections were made with the program SADABS. The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods against F^2 using SHELXT-2014 and SHELXL-2014 with OLEX 2 interface. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table S1.7, and geometric parameters are shown in Table S1.8. The Ortep plots were produced with the SHELXL-2014 program.

Table S1.7 Experimental details.

Crystal data

Chemical formula	$\text{C}_{16}\text{H}_{21}\text{F}_2\text{NO}_2$
M_r	297.34

Crystal system, space group	Monoclinic, $P2_1$
Temperature (K)	100
a, b, c (Å)	18.7446 (5), 11.0884 (4), 14.2531 (4)
β (°)	90.3646 (16)
V (Å ³)	2962.41 (16)
Z	8
Radiation type	Cu $K\alpha$
μ (mm ⁻¹)	0.87
Crystal size (mm)	0.16 × 0.12 × 0.10
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan <i>SADABS</i>
$T_{\min}, T_{\max}$	0.687, 0.864
No. of measured, independent and observed [I $> 2s(I)$] reflections	82778, 10133, 9563
R_{int}	0.048
$(\sin \theta/\lambda)_{\max}$ (Å ⁻¹)	0.599
Refinement	
$R[F^2 > 2s(F^2)], wR(F^2), S$	0.068, 0.202, 1.09
No. of reflections	10133
No. of parameters	858
No. of restraints	376
H-atom treatment	H-atom parameters constrained
$D\rho_{\max}, D\rho_{\min}$ (e Å ⁻³)	0.30, -0.28
Absolute structure	Twinning involves inversion, so Flack parameter cannot be determined

Table S1.8 Geometric parameters (Å, °).

F1—C7	1.422 (7)	F5—C47	1.359 (8)
F2—C14	1.447 (7)	F6—C54	1.410 (8)
O1—C12	1.410 (8)	O5—C51	1.395 (9)
O1—C11	1.463 (8)	O5—C52	1.442 (9)

O2—C9	1.229 (8)	O6—C49	1.217 (7)
N1—C9	1.353 (8)	N3—C49	1.345 (8)
N1—C13	1.453 (9)	N3—C50	1.425 (9)
N1—C10	1.501 (8)	N3—C53	1.481 (9)
C1—C6	1.360 (9)	C41—C42	1.385 (9)
C1—C2	1.392 (9)	C41—C46	1.402 (9)
C1—H1	0.9500	C41—H41	0.9500
C2—C3	1.355 (10)	C42—C43	1.377 (10)
C2—H2	0.9500	C42—H42	0.9500
C3—C4	1.375 (10)	C43—C44	1.389 (9)
C3—H3	0.9500	C43—H43	0.9500
C4—C5	1.386 (9)	C44—C45	1.384 (9)
C4—H4	0.9500	C44—H44	0.9500
C5—C6	1.411 (9)	C45—C46	1.368 (9)
C5—H5	0.9500	C45—H45	0.9500
C6—C7	1.496 (8)	C46—C47	1.531 (8)
C7—C8	1.520 (9)	C47—C48	1.548 (9)
C7—H7	1.0000	C47—H47	1.0000
C8—C14	1.544 (8)	C48—C49	1.527 (8)
C8—C9	1.550 (9)	C48—C54	1.547 (8)
C8—H8	1.0000	C48—H48	1.0000
C10—C11	1.495 (9)	C50—C51	1.536 (10)
C10—H10A	0.9900	C50—H50A	0.9900
C10—H10B	0.9900	C50—H50B	0.9900
C11—H11A	0.9900	C51—H51A	0.9900
C11—H11B	0.9900	C51—H51B	0.9900
C12—C13	1.493 (10)	C52—C53	1.523 (9)
C12—H12A	0.9900	C52—H52A	0.9900
C12—H12B	0.9900	C52—H52B	0.9900
C13—H13A	0.9900	C53—H53A	0.9900
C13—H13B	0.9900	C53—H53B	0.9900
C14—C15	1.509 (9)	C54—C56	1.506 (9)
C14—C16	1.517 (9)	C54—C55	1.514 (10)

C15—H15A	0.9800	C55—H55A	0.9800
C15—H15B	0.9800	C55—H55B	0.9800
C15—H15C	0.9800	C55—H55C	0.9800
C16—H16A	0.9800	C56—H56A	0.9800
C16—H16B	0.9800	C56—H56B	0.9800
C16—H16C	0.9800	C56—H56C	0.9800
C21—C22	1.3900	C61—C62	1.3900
C21—C26	1.3900	C61—C66	1.3900
C21—H21	0.9500	C61—H61	0.9500
C22—C23	1.3900	C62—C63	1.3900
C22—H22	0.9500	C62—H62	0.9500
C23—C24	1.3900	C63—C64	1.3900
C23—H23	0.9500	C63—H63	0.9500
C24—C25	1.3900	C64—C65	1.3900
C24—H24	0.9500	C64—H64	0.9500
C25—C26	1.3900	C65—C66	1.3900
C25—H25	0.9500	C65—H65	0.9500
C26—C27	1.490 (11)	C66—C67	1.534 (14)
C27—F3	1.433 (14)	C67—F7	1.377 (13)
C27—C28	1.515 (14)	C67—C68	1.547 (16)
C27—H27	1.0000	C67—H67	1.0000
C28—C29	1.535 (15)	C68—C69	1.501 (17)
C28—C34	1.543 (13)	C68—C74	1.518 (16)
C28—H28	1.0000	C68—H68	1.0000
C29—O4	1.250 (13)	C69—O8	1.289 (19)
C29—N2	1.360 (13)	C69—N4	1.328 (16)
N2—C33	1.466 (13)	N4—C70	1.450 (16)
N2—C30	1.516 (13)	N4—C73	1.485 (14)
C30—C31	1.484 (16)	C70—C71	1.532 (17)
C30—H30A	0.9900	C70—H70A	0.9900
C30—H30B	0.9900	C70—H70B	0.9900
C31—O3	1.439 (17)	C71—O7	1.376 (18)
C31—H31A	0.9900	C71—H71A	0.9900

C31—H31B	0.9900	C71—H71B	0.9900
O3—C32	1.434 (15)	O7—C72	1.439 (16)
C32—C33	1.513 (15)	C72—C73	1.521 (16)
C32—H32A	0.9900	C72—H72A	0.9900
C32—H32B	0.9900	C72—H72B	0.9900
C33—H33A	0.9900	C73—H73A	0.9900
C33—H33B	0.9900	C73—H73B	0.9900
C34—F4	1.439 (13)	C74—F8	1.394 (15)
C34—C35	1.508 (16)	C74—C76	1.501 (18)
C34—C36	1.533 (17)	C74—C75	1.517 (18)
C35—H35A	0.9800	C75—H75A	0.9800
C35—H35B	0.9800	C75—H75B	0.9800
C35—H35C	0.9800	C75—H75C	0.9800
C36—H36A	0.9800	C76—H76A	0.9800
C36—H36B	0.9800	C76—H76B	0.9800
C36—H36C	0.9800	C76—H76C	0.9800
C21A—C22A	1.3900	C61A—C62A	1.3900
C21A—C26A	1.3900	C61A—C66A	1.3900
C21A—H21A	0.9500	C61A—H61A	0.9500
C22A—C23A	1.3900	C62A—C63A	1.3900
C22A—H22A	0.9500	C62A—H62A	0.9500
C23A—C24A	1.3900	C63A—C64A	1.3900
C23A—H23A	0.9500	C63A—H63A	0.9500
C24A—C25A	1.3900	C64A—C65A	1.3900
C24A—H24A	0.9500	C64A—H64A	0.9500
C25A—C26A	1.3900	C65A—C66A	1.3900
C25A—H25A	0.9500	C65A—H65A	0.9500
C26A—C27A	1.496 (18)	C66A—C67A	1.521 (12)
C27A—F3A	1.46 (2)	C67A—F7A	1.383 (12)
C27A—C28A	1.53 (2)	C67A—C68A	1.545 (14)
C27A—H27A	1.0000	C67A—H67A	1.0000
C28A—C34A	1.541 (19)	C68A—C69A	1.482 (16)
C28A—C29A	1.56 (2)	C68A—C74A	1.532 (14)

C28A—H28A	1.0000	C68A—H68A	1.0000
C29A—O4A	1.23 (2)	C69A—O8A	1.286 (18)
C29A—N2A	1.36 (2)	C69A—N4A	1.315 (15)
N2A—C33A	1.43 (2)	N4A—C70A	1.448 (14)
N2A—C30A	1.52 (2)	N4A—C73A	1.473 (14)
C30A—C31A	1.49 (2)	C70A—C71A	1.541 (14)
C30A—H30C	0.9900	C70A—H70C	0.9900
C30A—H30D	0.9900	C70A—H70D	0.9900
C31A—O3A	1.48 (2)	C71A—O7A	1.392 (14)
C31A—H31C	0.9900	C71A—H71C	0.9900
C31A—H31D	0.9900	C71A—H71D	0.9900
O3A—C32A	1.42 (2)	O7A—C72A	1.456 (16)
C32A—C33A	1.51 (2)	C72A—C73A	1.502 (16)
C32A—H32C	0.9900	C72A—H72C	0.9900
C32A—H32D	0.9900	C72A—H72D	0.9900
C33A—H33C	0.9900	C73A—H73C	0.9900
C33A—H33D	0.9900	C73A—H73D	0.9900
C34A—F4A	1.450 (19)	C74A—F8A	1.441 (13)
C34A—C35A	1.51 (2)	C74A—C76A	1.494 (17)
C34A—C36A	1.52 (2)	C74A—C75A	1.516 (16)
C35A—H35D	0.9800	C75A—H75D	0.9800
C35A—H35E	0.9800	C75A—H75E	0.9800
C35A—H35F	0.9800	C75A—H75F	0.9800
C36A—H36D	0.9800	C76A—H76D	0.9800
C36A—H36E	0.9800	C76A—H76E	0.9800
C36A—H36F	0.9800	C76A—H76F	0.9800
C12—O1—C11	110.0 (5)	C51—O5—C52	112.5 (6)
C9—N1—C13	131.6 (5)	C49—N3—C50	120.7 (5)
C9—N1—C10	117.6 (6)	C49—N3—C53	127.4 (6)
C13—N1—C10	110.2 (5)	C50—N3—C53	111.9 (6)
C6—C1—C2	120.3 (6)	C42—C41—C46	120.0 (6)
C6—C1—H1	119.8	C42—C41—H41	120.0
C2—C1—H1	119.8	C46—C41—H41	120.0

C3—C2—C1	121.1 (7)	C43—C42—C41	120.5 (6)
C3—C2—H2	119.5	C43—C42—H42	119.8
C1—C2—H2	119.5	C41—C42—H42	119.8
C2—C3—C4	119.7 (6)	C42—C43—C44	119.7 (6)
C2—C3—H3	120.1	C42—C43—H43	120.1
C4—C3—H3	120.1	C44—C43—H43	120.1
C3—C4—C5	120.2 (6)	C45—C44—C43	119.3 (6)
C3—C4—H4	119.9	C45—C44—H44	120.3
C5—C4—H4	119.9	C43—C44—H44	120.3
C4—C5—C6	119.7 (6)	C46—C45—C44	121.7 (6)
C4—C5—H5	120.1	C46—C45—H45	119.1
C6—C5—H5	120.1	C44—C45—H45	119.1
C1—C6—C5	118.9 (5)	C45—C46—C41	118.7 (6)
C1—C6—C7	123.3 (6)	C45—C46—C47	120.0 (5)
C5—C6—C7	117.8 (5)	C41—C46—C47	121.3 (6)
F1—C7—C6	108.9 (5)	F5—C47—C46	110.8 (5)
F1—C7—C8	110.9 (5)	F5—C47—C48	111.3 (5)
C6—C7—C8	111.4 (5)	C46—C47—C48	111.7 (5)
F1—C7—H7	108.5	F5—C47—H47	107.6
C6—C7—H7	108.5	C46—C47—H47	107.6
C8—C7—H7	108.5	C48—C47—H47	107.6
C7—C8—C14	113.9 (5)	C49—C48—C54	110.8 (5)
C7—C8—C9	111.2 (5)	C49—C48—C47	109.3 (5)
C14—C8—C9	112.2 (5)	C54—C48—C47	115.9 (5)
C7—C8—H8	106.3	C49—C48—H48	106.8
C14—C8—H8	106.3	C54—C48—H48	106.8
C9—C8—H8	106.3	C47—C48—H48	106.8
O2—C9—N1	124.1 (6)	O6—C49—N3	120.6 (6)
O2—C9—C8	117.9 (6)	O6—C49—C48	121.8 (6)
N1—C9—C8	117.9 (6)	N3—C49—C48	117.6 (5)
C11—C10—N1	110.5 (6)	N3—C50—C51	110.0 (6)
C11—C10—H10A	109.6	N3—C50—H50A	109.7
N1—C10—H10A	109.6	C51—C50—H50A	109.7

C11—C10—H10B	109.6	N3—C50—H50B	109.7
N1—C10—H10B	109.6	C51—C50—H50B	109.7
H10A—C10—H10B	108.1	H50A—C50—H50B	108.2
O1—C11—C10	110.7 (5)	O5—C51—C50	110.3 (6)
O1—C11—H11A	109.5	O5—C51—H51A	109.6
C10—C11—H11A	109.5	C50—C51—H51A	109.6
O1—C11—H11B	109.5	O5—C51—H51B	109.6
C10—C11—H11B	109.5	C50—C51—H51B	109.6
H11A—C11—H11B	108.1	H51A—C51—H51B	108.1
O1—C12—C13	112.8 (6)	O5—C52—C53	110.1 (6)
O1—C12—H12A	109.0	O5—C52—H52A	109.6
C13—C12—H12A	109.0	C53—C52—H52A	109.6
O1—C12—H12B	109.0	O5—C52—H52B	109.6
C13—C12—H12B	109.0	C53—C52—H52B	109.6
H12A—C12—H12B	107.8	H52A—C52—H52B	108.1
N1—C13—C12	110.8 (6)	N3—C53—C52	109.5 (6)
N1—C13—H13A	109.5	N3—C53—H53A	109.8
C12—C13—H13A	109.5	C52—C53—H53A	109.8
N1—C13—H13B	109.5	N3—C53—H53B	109.8
C12—C13—H13B	109.5	C52—C53—H53B	109.8
H13A—C13—H13B	108.1	H53A—C53—H53B	108.2
F2—C14—C15	105.2 (5)	F6—C54—C56	105.9 (5)
F2—C14—C16	105.8 (5)	F6—C54—C55	105.0 (5)
C15—C14—C16	112.4 (6)	C56—C54—C55	112.6 (6)
F2—C14—C8	102.2 (5)	F6—C54—C48	104.8 (5)
C15—C14—C8	111.9 (5)	C56—C54—C48	116.6 (5)
C16—C14—C8	117.7 (6)	C55—C54—C48	110.9 (6)
C14—C15—H15A	109.5	C54—C55—H55A	109.5
C14—C15—H15B	109.5	C54—C55—H55B	109.5
H15A—C15—H15B	109.5	H55A—C55—H55B	109.5
C14—C15—H15C	109.5	C54—C55—H55C	109.5
H15A—C15—H15C	109.5	H55A—C55—H55C	109.5
H15B—C15—H15C	109.5	H55B—C55—H55C	109.5

C14—C16—H16A	109.5	C54—C56—H56A	109.5
C14—C16—H16B	109.5	C54—C56—H56B	109.5
H16A—C16—H16B	109.5	H56A—C56—H56B	109.5
C14—C16—H16C	109.5	C54—C56—H56C	109.5
H16A—C16—H16C	109.5	H56A—C56—H56C	109.5
H16B—C16—H16C	109.5	H56B—C56—H56C	109.5
C22—C21—C26	120.0	C62—C61—C66	120.0
C22—C21—H21	120.0	C62—C61—H61	120.0
C26—C21—H21	120.0	C66—C61—H61	120.0
C23—C22—C21	120.0	C61—C62—C63	120.0
C23—C22—H22	120.0	C61—C62—H62	120.0
C21—C22—H22	120.0	C63—C62—H62	120.0
C22—C23—C24	120.0	C64—C63—C62	120.0
C22—C23—H23	120.0	C64—C63—H63	120.0
C24—C23—H23	120.0	C62—C63—H63	120.0
C23—C24—C25	120.0	C65—C64—C63	120.0
C23—C24—H24	120.0	C65—C64—H64	120.0
C25—C24—H24	120.0	C63—C64—H64	120.0
C26—C25—C24	120.0	C64—C65—C66	120.0
C26—C25—H25	120.0	C64—C65—H65	120.0
C24—C25—H25	120.0	C66—C65—H65	120.0
C25—C26—C21	120.0	C65—C66—C61	120.0
C25—C26—C27	118.7 (7)	C65—C66—C67	118.4 (7)
C21—C26—C27	121.2 (7)	C61—C66—C67	121.5 (7)
F3—C27—C26	110.0 (9)	F7—C67—C66	110.9 (10)
F3—C27—C28	112.7 (10)	F7—C67—C68	109.6 (10)
C26—C27—C28	110.1 (9)	C66—C67—C68	113.9 (10)
F3—C27—H27	108.0	F7—C67—H67	107.4
C26—C27—H27	108.0	C66—C67—H67	107.4
C28—C27—H27	108.0	C68—C67—H67	107.4
C27—C28—C29	112.7 (11)	C69—C68—C74	111.4 (13)
C27—C28—C34	113.1 (9)	C69—C68—C67	111.1 (13)
C29—C28—C34	110.6 (9)	C74—C68—C67	117.9 (11)

C27—C28—H28	106.7	C69—C68—H68	105.1
C29—C28—H28	106.7	C74—C68—H68	105.1
C34—C28—H28	106.7	C67—C68—H68	105.1
O4—C29—N2	121.2 (10)	O8—C69—N4	117.9 (13)
O4—C29—C28	119.1 (10)	O8—C69—C68	119.5 (12)
N2—C29—C28	119.6 (11)	N4—C69—C68	122.5 (14)
C29—N2—C33	128.0 (10)	C69—N4—C70	123.4 (12)
C29—N2—C30	119.3 (10)	C69—N4—C73	124.9 (12)
C33—N2—C30	112.6 (9)	C70—N4—C73	111.7 (10)
C31—C30—N2	107.6 (13)	N4—C70—C71	109.4 (11)
C31—C30—H30A	110.2	N4—C70—H70A	109.8
N2—C30—H30A	110.2	C71—C70—H70A	109.8
C31—C30—H30B	110.2	N4—C70—H70B	109.8
N2—C30—H30B	110.2	C71—C70—H70B	109.8
H30A—C30—H30B	108.5	H70A—C70—H70B	108.2
O3—C31—C30	110.8 (11)	O7—C71—C70	113.0 (14)
O3—C31—H31A	109.5	O7—C71—H71A	109.0
C30—C31—H31A	109.5	C70—C71—H71A	109.0
O3—C31—H31B	109.5	O7—C71—H71B	109.0
C30—C31—H31B	109.5	C70—C71—H71B	109.0
H31A—C31—H31B	108.1	H71A—C71—H71B	107.8
C32—O3—C31	112.2 (10)	C71—O7—C72	112.8 (11)
O3—C32—C33	112.3 (12)	O7—C72—C73	112.1 (10)
O3—C32—H32A	109.2	O7—C72—H72A	109.2
C33—C32—H32A	109.2	C73—C72—H72A	109.2
O3—C32—H32B	109.2	O7—C72—H72B	109.2
C33—C32—H32B	109.2	C73—C72—H72B	109.2
H32A—C32—H32B	107.9	H72A—C72—H72B	107.9
N2—C33—C32	108.1 (10)	N4—C73—C72	109.0 (11)
N2—C33—H33A	110.1	N4—C73—H73A	109.9
C32—C33—H33A	110.1	C72—C73—H73A	109.9
N2—C33—H33B	110.1	N4—C73—H73B	109.9
C32—C33—H33B	110.1	C72—C73—H73B	109.9

H33A—C33—H33B	108.4	H73A—C73—H73B	108.3
F4—C34—C35	106.8 (11)	F8—C74—C76	105.0 (11)
F4—C34—C36	105.6 (9)	F8—C74—C75	104.5 (11)
C35—C34—C36	112.3 (10)	C76—C74—C75	111.5 (12)
F4—C34—C28	102.7 (9)	F8—C74—C68	106.4 (10)
C35—C34—C28	110.6 (11)	C76—C74—C68	113.2 (11)
C36—C34—C28	117.7 (11)	C75—C74—C68	115.3 (12)
C34—C35—H35A	109.5	C74—C75—H75A	109.5
C34—C35—H35B	109.5	C74—C75—H75B	109.5
H35A—C35—H35B	109.5	H75A—C75—H75B	109.5
C34—C35—H35C	109.5	C74—C75—H75C	109.5
H35A—C35—H35C	109.5	H75A—C75—H75C	109.5
H35B—C35—H35C	109.5	H75B—C75—H75C	109.5
C34—C36—H36A	109.5	C74—C76—H76A	109.5
C34—C36—H36B	109.5	C74—C76—H76B	109.5
H36A—C36—H36B	109.5	H76A—C76—H76B	109.5
C34—C36—H36C	109.5	C74—C76—H76C	109.5
H36A—C36—H36C	109.5	H76A—C76—H76C	109.5
H36B—C36—H36C	109.5	H76B—C76—H76C	109.5
C22A—C21A—C26A	120.0	C62A—C61A—C66A	120.0
C22A—C21A— H21A	120.0	C62A—C61A— H61A	120.0
C26A—C21A— H21A	120.0	C66A—C61A— H61A	120.0
C23A—C22A—C21A	120.0	C63A—C62A—C61A	120.0
C23A—C22A— H22A	120.0	C63A—C62A— H62A	120.0
C21A—C22A— H22A	120.0	C61A—C62A— H62A	120.0
C24A—C23A—C22A	120.0	C62A—C63A—C64A	120.0
C24A—C23A— H23A	120.0	C62A—C63A— H63A	120.0
C22A—C23A— H23A	120.0	C64A—C63A— H63A	120.0

C23A—C24A—C25A	120.0	C63A—C64A—C65A	120.0
C23A—C24A— H24A	120.0	C63A—C64A— H64A	120.0
C25A—C24A— H24A	120.0	C65A—C64A— H64A	120.0
C26A—C25A—C24A	120.0	C66A—C65A—C64A	120.0
C26A—C25A— H25A	120.0	C66A—C65A— H65A	120.0
C24A—C25A— H25A	120.0	C64A—C65A— H65A	120.0
C25A—C26A—C21A	120.0	C65A—C66A—C61A	120.0
C25A—C26A—C27A	118.1 (13)	C65A—C66A—C67A	121.4 (6)
C21A—C26A—C27A	121.9 (13)	C61A—C66A—C67A	118.6 (6)
F3A—C27A—C26A	108.1 (16)	F7A—C67A—C66A	110.2 (8)
F3A—C27A—C28A	110.4 (16)	F7A—C67A—C68A	109.5 (9)
C26A—C27A—C28A	112.0 (17)	C66A—C67A—C68A	113.2 (9)
F3A—C27A—H27A	108.8	F7A—C67A—H67A	107.9
C26A—C27A— H27A	108.8	C66A—C67A— H67A	107.9
C28A—C27A— H27A	108.8	C68A—C67A— H67A	107.9
C27A—C28A—C34A	115.0 (16)	C69A—C68A—C74A	112.9 (13)
C27A—C28A—C29A	108.8 (18)	C69A—C68A—C67A	110.4 (11)
C34A—C28A—C29A	114.5 (17)	C74A—C68A—C67A	115.5 (9)
C27A—C28A— H28A	105.9	C69A—C68A— H68A	105.7
C34A—C28A— H28A	105.9	C74A—C68A— H68A	105.7
C29A—C28A— H28A	105.9	C67A—C68A— H68A	105.7
O4A—C29A—N2A	126 (2)	O8A—C69A—N4A	119.3 (12)
O4A—C29A—C28A	117.2 (18)	O8A—C69A—C68A	117.6 (11)
N2A—C29A—C28A	115.8 (19)	N4A—C69A—C68A	122.9 (13)
C29A—N2A—C33A	133.7 (19)	C69A—N4A—C70A	126.1 (11)
C29A—N2A—C30A	112.8 (17)	C69A—N4A—C73A	121.3 (11)

C33A—N2A—C30A	112.7 (15)	C70A—N4A—C73A	112.6 (9)
C31A—C30A—N2A	112 (2)	N4A—C70A—C71A	107.7 (9)
C31A—C30A—H30C	109.3	N4A—C70A—H70C	110.2
N2A—C30A—H30C	109.3	C71A—C70A—H70C	110.2
C31A—C30A— H30D	109.3	N4A—C70A—H70D	110.2
N2A—C30A—H30D	109.3	C71A—C70A— H70D	110.2
H30C—C30A— H30D	108.0	H70C—C70A— H70D	108.5
O3A—C31A—C30A	109.8 (18)	O7A—C71A—C70A	112.1 (10)
O3A—C31A—H31C	109.7	O7A—C71A—H71C	109.2
C30A—C31A—H31C	109.7	C70A—C71A—H71C	109.2
O3A—C31A—H31D	109.7	O7A—C71A—H71D	109.2
C30A—C31A— H31D	109.7	C70A—C71A— H71D	109.2
H31C—C31A— H31D	108.2	H71C—C71A— H71D	107.9
C32A—O3A—C31A	111.7 (18)	C71A—O7A—C72A	110.8 (10)
O3A—C32A—C33A	112 (2)	O7A—C72A—C73A	110.2 (11)
O3A—C32A—H32C	109.2	O7A—C72A—H72C	109.6
C33A—C32A—H32C	109.2	C73A—C72A—H72C	109.6
O3A—C32A—H32D	109.2	O7A—C72A—H72D	109.6
C33A—C32A— H32D	109.2	C73A—C72A— H72D	109.6
H32C—C32A— H32D	107.9	H72C—C72A— H72D	108.1
N2A—C33A—C32A	110.6 (19)	N4A—C73A—C72A	109.3 (10)
N2A—C33A—H33C	109.5	N4A—C73A—H73C	109.8
C32A—C33A—H33C	109.5	C72A—C73A—H73C	109.8
N2A—C33A—H33D	109.5	N4A—C73A—H73D	109.8
C32A—C33A— H33D	109.5	C72A—C73A— H73D	109.8
H33C—C33A— H33D	108.1	H73C—C73A— H73D	108.3

F4A—C34A—C35A	106.9 (19)	F8A—C74A—C76A	105.8 (10)
F4A—C34A—C36A	104.9 (16)	F8A—C74A—C75A	102.2 (9)
C35A—C34A—C36A	113.3 (18)	C76A—C74A—C75A	114.9 (11)
F4A—C34A—C28A	101.8 (16)	F8A—C74A—C68A	103.6 (9)
C35A—C34A—C28A	112 (2)	C76A—C74A—C68A	118.4 (11)
C36A—C34A—C28A	117 (2)	C75A—C74A—C68A	109.9 (10)
C34A—C35A— H35D	109.5	C74A—C75A— H75D	109.5
C34A—C35A—H35E	109.5	C74A—C75A—H75E	109.5
H35D—C35A—H35E	109.5	H75D—C75A—H75E	109.5
C34A—C35A—H35F	109.5	C74A—C75A—H75F	109.5
H35D—C35A—H35F	109.5	H75D—C75A—H75F	109.5
H35E—C35A—H35F	109.5	H75E—C75A—H75F	109.5
C34A—C36A— H36D	109.5	C74A—C76A— H76D	109.5
C34A—C36A—H36E	109.5	C74A—C76A—H76E	109.5
H36D—C36A—H36E	109.5	H76D—C76A—H76E	109.5
C34A—C36A—H36F	109.5	C74A—C76A—H76F	109.5
H36D—C36A—H36F	109.5	H76D—C76A—H76F	109.5
H36E—C36A—H36F	109.5	H76E—C76A—H76F	109.5
C6—C1—C2—C3	0.2 (11)	C46—C41—C42— C43	-0.5 (10)
C1—C2—C3—C4	0.5 (11)	C41—C42—C43— C44	0.5 (11)
C2—C3—C4—C5	-1.1 (11)	C42—C43—C44— C45	0.4 (11)
C3—C4—C5—C6	1.1 (10)	C43—C44—C45— C46	-1.2 (10)
C2—C1—C6—C5	-0.2 (9)	C44—C45—C46— C41	1.1 (10)
C2—C1—C6—C7	177.6 (6)	C44—C45—C46— C47	-178.0 (6)
C4—C5—C6—C1	-0.5 (9)	C42—C41—C46— C45	-0.2 (10)
C4—C5—C6—C7	-178.3 (6)	C42—C41—C46— C47	178.9 (6)

C1—C6—C7—F1	24.2 (8)	C45—C46—C47—F5	-157.7 (6)
C5—C6—C7—F1	-158.0 (5)	C41—C46—C47—F5	23.1 (9)
C1—C6—C7—C8	-98.5 (7)	C45—C46—C47— C48	77.6 (8)
C5—C6—C7—C8	79.3 (7)	C41—C46—C47— C48	-101.5 (7)
F1—C7—C8—C14	58.8 (7)	F5—C47—C48—C49	-68.7 (6)
C6—C7—C8—C14	-179.7 (5)	C46—C47—C48— C49	55.7 (7)
F1—C7—C8—C9	-69.1 (6)	F5—C47—C48—C54	57.2 (7)
C6—C7—C8—C9	52.4 (7)	C46—C47—C48— C54	-178.4 (5)
C13—N1—C9—O2	-173.5 (7)	C50—N3—C49—O6	2.6 (9)
C10—N1—C9—O2	-2.9 (10)	C53—N3—C49—O6	-175.5 (6)
C13—N1—C9—C8	8.8 (10)	C50—N3—C49— C48	-177.5 (5)
C10—N1—C9—C8	179.5 (5)	C53—N3—C49— C48	4.4 (9)
C7—C8—C9—O2	57.0 (8)	C54—C48—C49— O6	-73.3 (7)
C14—C8—C9—O2	-71.8 (8)	C47—C48—C49— O6	55.5 (7)
C7—C8—C9—N1	-125.2 (6)	C54—C48—C49— N3	106.9 (6)
C14—C8—C9—N1	106.0 (6)	C47—C48—C49— N3	-124.3 (6)
C9—N1—C10—C11	-117.8 (6)	C49—N3—C50— C51	-122.2 (6)
C13—N1—C10— C11	54.7 (7)	C53—N3—C50— C51	56.2 (8)
C12—O1—C11— C10	58.2 (7)	C52—O5—C51— C50	58.9 (8)
N1—C10—C11—O1	-56.5 (7)	N3—C50—C51—O5	-57.5 (8)
C11—O1—C12— C13	-58.4 (7)	C51—O5—C52— C53	-58.4 (9)
C9—N1—C13—C12	117.4 (8)	C49—N3—C53— C52	122.7 (7)

C10—N1—C13— C12	-53.8 (8)	C50—N3—C53— C52	-55.6 (8)
O1—C12—C13—N1	57.3 (8)	O5—C52—C53—N3	54.5 (8)
C7—C8—C14—F2	173.2 (5)	C49—C48—C54—F6	-60.6 (6)
C9—C8—C14—F2	-59.4 (6)	C47—C48—C54—F6	174.3 (5)
C7—C8—C14—C15	61.0 (8)	C49—C48—C54— C56	56.1 (8)
C9—C8—C14—C15	-171.6 (6)	C47—C48—C54— C56	-69.1 (8)
C7—C8—C14—C16	-71.5 (8)	C49—C48—C54— C55	-173.3 (6)
C9—C8—C14—C16	55.9 (8)	C47—C48—C54— C55	61.5 (8)
C26—C21—C22— C23	0.0	C66—C61—C62— C63	0.0
C21—C22—C23— C24	0.0	C61—C62—C63— C64	0.0
C22—C23—C24— C25	0.0	C62—C63—C64— C65	0.0
C23—C24—C25— C26	0.0	C63—C64—C65— C66	0.0
C24—C25—C26— C21	0.0	C64—C65—C66— C61	0.0
C24—C25—C26— C27	-176.4 (10)	C64—C65—C66— C67	-178.1 (10)
C22—C21—C26— C25	0.0	C62—C61—C66— C65	0.0
C22—C21—C26— C27	176.3 (11)	C62—C61—C66— C67	178.0 (11)
C25—C26—C27—F3	-160.1 (8)	C65—C66—C67—F7	-156.1 (9)
C21—C26—C27—F3	23.5 (13)	C61—C66—C67—F7	25.9 (14)
C25—C26—C27— C28	75.1 (12)	C65—C66—C67— C68	79.6 (12)
C21—C26—C27— C28	-101.2 (11)	C61—C66—C67— C68	-98.4 (11)
F3—C27—C28—C29	-69.1 (12)	F7—C67—C68—C69	-71.3 (14)
C26—C27—C28—	54.1 (13)	C66—C67—C68—	53.6 (15)

C29		C69	
F3—C27—C28—C34	57.2 (14)	F7—C67—C68—C74	58.9 (16)
C26—C27—C28—C34	-179.6 (9)	C66—C67—C68—C74	-176.2 (10)
C27—C28—C29—O4	51.2 (16)	C74—C68—C69—O8	-78 (2)
C34—C28—C29—O4	-76.5 (16)	C67—C68—C69—O8	55 (2)
C27—C28—C29—N2	-125.0 (13)	C74—C68—C69—N4	105 (2)
C34—C28—C29—N2	107.4 (14)	C67—C68—C69—N4	-121 (2)
O4—C29—N2—C33	-175.4 (14)	O8—C69—N4—C70	4 (3)
C28—C29—N2—C33	1 (2)	C68—C69—N4—C70	179.8 (15)
O4—C29—N2—C30	2 (2)	O8—C69—N4—C73	-173.8 (15)
C28—C29—N2—C30	178.2 (11)	C68—C69—N4—C73	2 (3)
C29—N2—C30—C31	-119.7 (14)	C69—N4—C70—C71	-122 (2)
C33—N2—C30—C31	58.2 (14)	C73—N4—C70—C71	55.5 (15)
N2—C30—C31—O3	-57.8 (16)	N4—C70—C71—O7	-55.4 (16)
C30—C31—O3—C32	59.4 (18)	C70—C71—O7—C72	55.2 (16)
C31—O3—C32—C33	-57.2 (16)	C71—O7—C72—C73	-55.1 (16)
C29—N2—C33—C32	122.1 (16)	C69—N4—C73—C72	122.0 (19)
C30—N2—C33—C32	-55.6 (15)	C70—N4—C73—C72	-55.7 (15)
O3—C32—C33—N2	54.3 (15)	O7—C72—C73—N4	53.9 (15)
C27—C28—C34—F4	174.4 (10)	C69—C68—C74—F8	-54.8 (15)
C29—C28—C34—F4	-58.1 (12)	C67—C68—C74—F8	175.1 (10)
C27—C28—C34—C35	60.9 (15)	C69—C68—C74—C76	-169.5 (12)
C29—C28—C34—	-171.7 (11)	C67—C68—C74—	60.3 (17)

C35		C76	
C27—C28—C34— C36	-70.1 (14)	C69—C68—C74— C75	60.5 (16)
C29—C28—C34— C36	57.3 (14)	C67—C68—C74— C75	-69.6 (15)
C26A—C21A— C22A—C23A	0.0	C66A—C61A— C62A—C63A	0.0
C21A—C22A— C23A—C24A	0.0	C61A—C62A— C63A—C64A	0.0
C22A—C23A— C24A—C25A	0.0	C62A—C63A— C64A—C65A	0.0
C23A—C24A— C25A—C26A	0.0	C63A—C64A— C65A—C66A	0.0
C24A—C25A— C26A—C21A	0.0	C64A—C65A— C66A—C61A	0.0
C24A—C25A— C26A—C27A	-179.4 (19)	C64A—C65A— C66A—C67A	179.4 (9)
C22A—C21A— C26A—C25A	0.0	C62A—C61A— C66A—C65A	0.0
C22A—C21A— C26A—C27A	179 (2)	C62A—C61A— C66A—C67A	-179.4 (9)
C25A—C26A— C27A—F3A	-158.9 (14)	C65A—C66A— C67A—F7A	-16.6 (12)
C21A—C26A— C27A—F3A	22 (2)	C61A—C66A— C67A—F7A	162.8 (8)
C25A—C26A— C27A—C28A	79 (2)	C65A—C66A— C67A—C68A	106.5 (9)
C21A—C26A— C27A—C28A	-100.1 (19)	C61A—C66A— C67A—C68A	-74.1 (11)
F3A—C27A— C28A—C34A	61 (2)	F7A—C67A— C68A—C69A	74.8 (13)
C26A—C27A— C28A—C34A	-178.3 (17)	C66A—C67A— C68A—C69A	-48.7 (14)
F3A—C27A— C28A—C29A	-69 (2)	F7A—C67A— C68A—C74A	-54.8 (13)
C26A—C27A— C28A—C29A	52 (2)	C66A—C67A— C68A—C74A	-178.2 (9)
C27A—C28A—	63 (3)	C74A—C68A—	70 (2)

C29A—O4A		C69A—O8A	
C34A—C28A— C29A—O4A	-67 (3)	C67A—C68A— C69A—O8A	-61 (2)
C27A—C28A— C29A—N2A	-126 (2)	C74A—C68A— C69A—N4A	-107 (2)
C34A—C28A— C29A—N2A	104 (3)	C67A—C68A— C69A—N4A	122.4 (19)
O4A—C29A— N2A—C33A	-176 (3)	O8A—C69A— N4A—C70A	-179.3 (14)
C28A—C29A— N2A—C33A	13 (4)	C68A—C69A— N4A—C70A	-3 (3)
O4A—C29A— N2A—C30A	-7 (5)	O8A—C69A— N4A—C73A	0 (3)
C28A—C29A— N2A—C30A	-178 (2)	C68A—C69A— N4A—C73A	176.0 (14)
C29A—N2A— C30A—C31A	-120 (3)	C69A—N4A— C70A—C71A	-125.2 (18)
C33A—N2A— C30A—C31A	52 (3)	C73A—N4A— C70A—C71A	55.5 (13)
N2A—C30A— C31A—O3A	-52 (3)	N4A—C70A— C71A—O7A	-57.1 (13)
C30A—C31A— O3A—C32A	57 (3)	C70A—C71A— O7A—C72A	59.6 (14)
C31A—O3A— C32A—C33A	-59 (3)	C71A—O7A— C72A—C73A	-59.3 (14)
C29A—N2A— C33A—C32A	117 (3)	C69A—N4A— C73A—C72A	123.4 (17)
C30A—N2A— C33A—C32A	-52 (3)	C70A—N4A— C73A—C72A	-57.2 (14)
O3A—C32A— C33A—N2A	56 (3)	O7A—C72A— C73A—N4A	56.6 (14)
C27A—C28A— C34A—F4A	174.1 (16)	C69A—C68A— C74A—F8A	62.3 (12)
C29A—C28A— C34A—F4A	-59 (2)	C67A—C68A— C74A—F8A	-169.3 (9)
C27A—C28A— C34A—C35A	60 (3)	C69A—C68A— C74A—C76A	-54.3 (15)
C29A—C28A—	-172.6 (19)	C67A—C68A—	74.1 (14)

C34A—C35A		C74A—C76A	
C27A—C28A— C34A—C36A	-72 (2)	C69A—C68A— C74A—C75A	170.9 (11)
C29A—C28A— C34A—C36A	55 (2)	C67A—C68A— C74A—C75A	-60.7 (13)

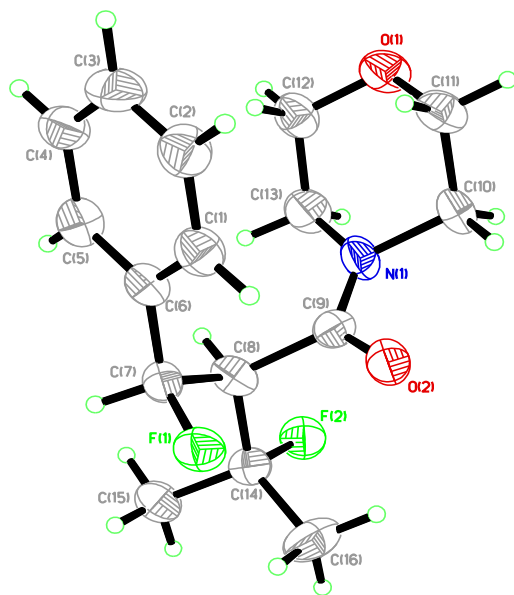
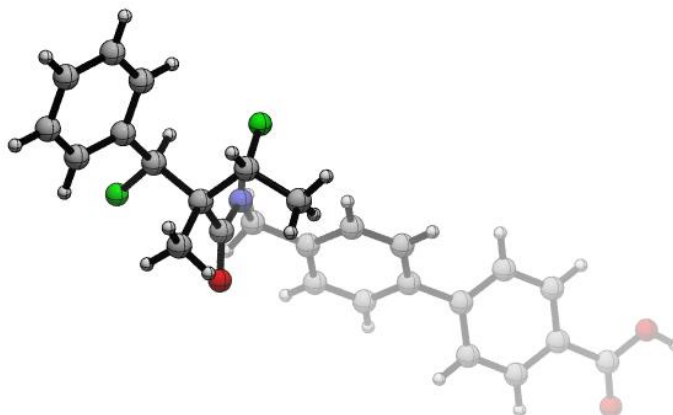


Figure S1.4 Perspective views showing 50% probability displacement.

X-Ray Crystallographic Information Data for S-(±)-8a



A crystal mounted on a diffractometer was analyzed at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II DUO CCD diffractometer ($\text{CuK}\alpha$ radiation, $\lambda=1.54178$ Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 1.0° scans in ω at -30° , -55° , -80° , 30° , 55° , 80° and 115° in 2θ . Data integration down to 0.84 Å resolution was carried out using SAINT V8.35 A with reflection spot size optimization. Absorption corrections were made with the program SADABS. The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods against F^2 using SHELXT-2014 and SHELXL-2014 with OLEX 2 interface. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table S1.9, geometric parameters are shown in Table S1.10. The Ortep plots were produced with the SHELXL-2014 program.

Table S1.9 Experimental details.

Crystal data

Chemical formula	$\text{C}_{26}\text{H}_{25}\text{F}_2\text{NO}_3$
M_r	437.47
Crystal system, space group	Orthorhombic, $Pbcn$

Temperature (K)	100
a, b, c (Å)	19.3979 (12), 7.6403 (6), 33.4046 (19)
V (Å ³)	4950.8 (6)
Z	8
Radiation type	Cu $K\alpha$
μ (mm ⁻¹)	0.72
Crystal size (mm)	0.18 × 0.08 × 0.06
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan <i>SADABS</i>
$T_{\min}, T_{\max}$	0.695, 0.864
No. of measured, independent and observed [I > 2s(I)] reflections	35641, 4354, 2942
R_{int}	0.107
($\sin \theta/\lambda$) _{max} (Å ⁻¹)	0.596
Refinement	
$R[F^2 > 2s(F^2)], wR(F^2), S$	0.074, 0.193, 1.06
No. of reflections	4354
No. of parameters	299
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$D\rho_{\text{max}}, D\rho_{\text{min}}$ (e Å ⁻³)	0.37, -0.28

Table S1.10 Geometric parameters (Å, °).

F1—C17	1.399 (5)	C12—H12	0.9500
F2—C24	1.426 (4)	C13—H13	0.9500
O1—C1	1.301 (5)	C14—H14A	0.9900
O1—H1	0.95 (6)	C14—H14B	0.9900
O2—C1	1.238 (4)	C15—C16	1.544 (5)
O3—C15	1.226 (4)	C16—C24	1.525 (5)
N1—C15	1.339 (5)	C16—C17	1.546 (5)
N1—C14	1.451 (5)	C16—C26	1.559 (5)

N1—H1A	0.72 (3)	C17—C18	1.506 (5)
C1—C2	1.478 (5)	C17—H17	1.0000
C2—C3	1.380 (5)	C18—C23	1.386 (7)
C2—C7	1.395 (5)	C18—C19	1.392 (7)
C3—C4	1.387 (5)	C19—C20	1.424 (8)
C3—H3	0.9500	C19—H19	0.9500
C4—C5	1.397 (5)	C20—C21	1.377 (10)
C4—H4	0.9500	C20—H20	0.9500
C5—C6	1.390 (5)	C21—C22	1.362 (9)
C5—C8	1.480 (5)	C21—H21	0.9500
C6—C7	1.391 (5)	C22—C23	1.392 (7)
C6—H6	0.9500	C22—H22	0.9500
C7—H7	0.9500	C23—H23	0.9500
C8—C13	1.393 (5)	C24—C25	1.513 (5)
C8—C9	1.396 (5)	C24—H24	1.0000
C9—C10	1.386 (5)	C25—H25A	0.9800
C9—H9	0.9500	C25—H25B	0.9800
C10—C11	1.384 (5)	C25—H25C	0.9800
C10—H10	0.9500	C26—H26A	0.9800
C11—C12	1.389 (5)	C26—H26B	0.9800
C11—C14	1.513 (4)	C26—H26C	0.9800
C12—C13	1.383 (5)		
C1—O1—H1	111 (4)	O3—C15—C16	121.7 (3)
C15—N1—C14	121.5 (3)	N1—C15—C16	117.0 (3)
C15—N1—H1A	121 (3)	C24—C16—C15	112.2 (3)
C14—N1—H1A	118 (3)	C24—C16—C17	110.4 (3)
O2—C1—O1	122.6 (3)	C15—C16—C17	108.0 (3)
O2—C1—C2	121.3 (3)	C24—C16—C26	107.8 (3)
O1—C1—C2	116.1 (3)	C15—C16—C26	108.1 (3)
C3—C2—C7	119.8 (3)	C17—C16—C26	110.4 (3)
C3—C2—C1	119.2 (3)	F1—C17—C18	108.5 (3)
C7—C2—C1	121.0 (3)	F1—C17—C16	107.2 (3)
C2—C3—C4	120.2 (4)	C18—C17—C16	116.1 (3)

C2—C3—H3	119.9	F1—C17—H17	108.3
C4—C3—H3	119.9	C18—C17—H17	108.3
C3—C4—C5	120.8 (4)	C16—C17—H17	108.3
C3—C4—H4	119.6	C23—C18—C19	120.7 (4)
C5—C4—H4	119.6	C23—C18—C17	121.1 (4)
C6—C5—C4	118.6 (3)	C19—C18—C17	118.2 (4)
C6—C5—C8	121.8 (3)	C18—C19—C20	117.9 (6)
C4—C5—C8	119.6 (3)	C18—C19—H19	121.1
C5—C6—C7	120.9 (3)	C20—C19—H19	121.1
C5—C6—H6	119.6	C21—C20—C19	120.1 (7)
C7—C6—H6	119.6	C21—C20—H20	119.9
C6—C7—C2	119.8 (3)	C19—C20—H20	119.9
C6—C7—H7	120.1	C22—C21—C20	121.3 (6)
C2—C7—H7	120.1	C22—C21—H21	119.4
C13—C8—C9	118.3 (3)	C20—C21—H21	119.4
C13—C8—C5	121.8 (3)	C21—C22—C23	119.7 (6)
C9—C8—C5	119.9 (3)	C21—C22—H22	120.2
C10—C9—C8	121.0 (3)	C23—C22—H22	120.2
C10—C9—H9	119.5	C18—C23—C22	120.3 (5)
C8—C9—H9	119.5	C18—C23—H23	119.9
C11—C10—C9	120.4 (3)	C22—C23—H23	119.9
C11—C10—H10	119.8	F2—C24—C25	108.2 (3)
C9—C10—H10	119.8	F2—C24—C16	107.6 (3)
C10—C11—C12	118.8 (3)	C25—C24—C16	115.3 (3)
C10—C11—C14	117.9 (3)	F2—C24—H24	108.5
C12—C11—C14	123.3 (3)	C25—C24—H24	108.5
C13—C12—C11	121.2 (3)	C16—C24—H24	108.5
C13—C12—H12	119.4	C24—C25—H25A	109.5
C11—C12—H12	119.4	C24—C25—H25B	109.5
C12—C13—C8	120.3 (3)	H25A—C25—H25B	109.5
C12—C13—H13	119.8	C24—C25—H25C	109.5
C8—C13—H13	119.8	H25A—C25—H25C	109.5
N1—C14—C11	115.7 (3)	H25B—C25—H25C	109.5

N1—C14—H14A	108.4	C16—C26—H26A	109.5
C11—C14—H14A	108.4	C16—C26—H26B	109.5
N1—C14—H14B	108.4	H26A—C26—H26B	109.5
C11—C14—H14B	108.4	C16—C26—H26C	109.5
H14A—C14—H14B	107.4	H26A—C26—H26C	109.5
O3—C15—N1	121.3 (3)	H26B—C26—H26C	109.5
O2—C1—C2—C3	5.8 (6)	C14—N1—C15— C16	-170.6 (3)
O1—C1—C2—C3	-173.9 (4)	O3—C15—C16— C24	118.6 (4)
O2—C1—C2—C7	-172.1 (4)	N1—C15—C16— C24	-61.9 (4)
O1—C1—C2—C7	8.2 (6)	O3—C15—C16— C17	-119.5 (4)
C7—C2—C3—C4	-0.4 (6)	N1—C15—C16— C17	60.0 (4)
C1—C2—C3—C4	-178.4 (4)	O3—C15—C16— C26	-0.1 (5)
C2—C3—C4—C5	1.2 (7)	N1—C15—C16— C26	179.5 (3)
C3—C4—C5—C6	-1.7 (6)	C24—C16—C17—F1	175.3 (3)
C3—C4—C5—C8	178.3 (4)	C15—C16—C17—F1	52.4 (4)
C4—C5—C6—C7	1.4 (5)	C26—C16—C17—F1	-65.5 (4)
C8—C5—C6—C7	-178.6 (3)	C24—C16—C17— C18	-63.3 (5)
C5—C6—C7—C2	-0.7 (5)	C15—C16—C17— C18	173.8 (4)
C3—C2—C7—C6	0.2 (6)	C26—C16—C17— C18	55.9 (5)
C1—C2—C7—C6	178.0 (3)	F1—C17—C18—C23	31.8 (5)
C6—C5—C8—C13	-41.4 (5)	C16—C17—C18— C23	-88.9 (5)
C4—C5—C8—C13	138.6 (4)	F1—C17—C18—C19	-147.7 (4)
C6—C5—C8—C9	138.1 (4)	C16—C17—C18— C19	91.6 (5)
C4—C5—C8—C9	-41.9 (5)	C23—C18—C19—	2.3 (7)

		C20	
C13—C8—C9—C10	1.2 (5)	C17—C18—C19—C20	-178.2 (4)
C5—C8—C9—C10	-178.3 (3)	C18—C19—C20—C21	-2.0 (9)
C8—C9—C10—C11	-0.7 (5)	C19—C20—C21—C22	0.8 (11)
C9—C10—C11—C12	-1.0 (5)	C20—C21—C22—C23	0.3 (10)
C9—C10—C11—C14	174.9 (3)	C19—C18—C23—C22	-1.2 (7)
C10—C11—C12—C13	2.2 (5)	C17—C18—C23—C22	179.3 (4)
C14—C11—C12—C13	-173.4 (3)	C21—C22—C23—C18	-0.1 (8)
C11—C12—C13—C8	-1.7 (5)	C15—C16—C24—F2	69.2 (4)
C9—C8—C13—C12	0.0 (5)	C17—C16—C24—F2	-51.3 (4)
C5—C8—C13—C12	179.5 (3)	C26—C16—C24—F2	-172.0 (3)
C15—N1—C14—C11	-87.0 (4)	C15—C16—C24—C25	-51.6 (4)
C10—C11—C14—N1	156.0 (3)	C17—C16—C24—C25	-172.1 (3)
C12—C11—C14—N1	-28.3 (5)	C26—C16—C24—C25	67.2 (4)
C14—N1—C15—O3	8.9 (5)		

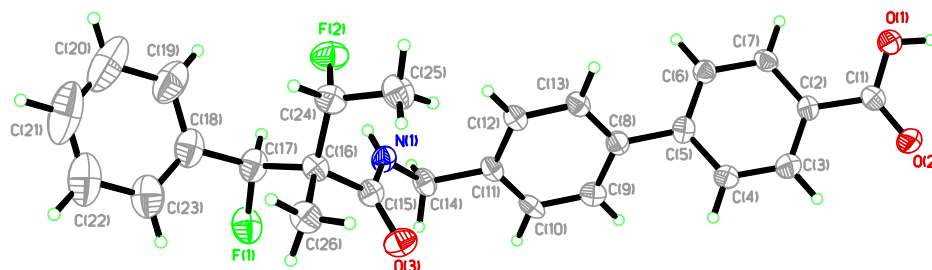
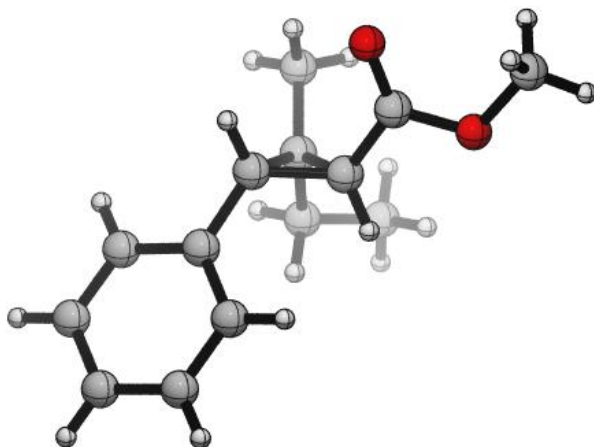


Figure S1.5 Perspective views showing 50% probability displacement.

X-Ray Crystallographic Information Data for (±)-5g



A crystal mounted on a diffractometer was analyzed at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II CCD diffractometer (MoK α radiation, λ =0.71073 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 0.5° scans in ω at 28° in 2θ . Data integration down to 0.78 Å resolution was carried out using SAINT V8.37A¹³ with reflection spot size optimization. Absorption corrections were made with the program SADABS.¹³ The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods against F^2 using SHELXT-2014¹⁴ and SHELXL-2014¹⁵ with OLEX 2 interface.¹⁶ Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table S1.11, and geometric parameters are shown in Table S1.12. The Ortep plots were produced with the SHELXL-2014 program.

Table S1.11. Experimental details.

Crystal data

Chemical formula	C ₁₄ H ₁₈ O ₂
M_r	218.28
Crystal system, space group	Monoclinic, $P2_1/n$

Temperature (K)	100
a, b, c (Å)	13.2420 (8), 5.8519 (4), 15.6972 (10)
b (°)	91.8329 (11)
V (Å ³)	1215.77 (14)
Z	4
Radiation type	Mo $K\alpha$
μ (mm ⁻¹)	0.08
Crystal size (mm)	0.24 × 0.18 × 0.10
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan <i>SADABS</i>
$T_{\min}, T_{\max}$	0.834, 0.862
No. of measured, 19967, 2679, 2298 independent and observed [I > 2s(I)] reflections	
R_{int}	0.036
($\sin \theta/\lambda$) _{max} (Å ⁻¹)	0.641
Refinement	
$R[F^2 > 2s(F^2)], wR(F^2), S$	0.035, 0.091, 1.03
No. of reflections	2679
No. of parameters	148
H-atom treatment	H-atom parameters constrained
$D\rho_{\text{max}}, D\rho_{\text{min}}$ (e Å ⁻³)	0.28, -0.19

Table S1.12. Geometric parameters (Å, °).

O1—C10	1.3492 (13)	C8—C11	1.5131 (15)
O1—C14	1.4482 (12)	C8—C12	1.5173 (14)
O2—C10	1.2080 (13)	C8—C9	1.5390 (15)
C1—C2	1.3901 (15)	C9—C10	1.4804 (14)
C1—C6	1.3999 (15)	C9—H9	1.0000
C1—H1	0.9500	C11—H11A	0.9800
C2—C3	1.3887 (16)	C11—H11B	0.9800
C2—H2	0.9500	C11—H11C	0.9800
C3—C4	1.3886 (16)	C12—C13	1.5257 (16)

C3—H3	0.9500	C12—H12A	0.9900
C4—C5	1.3953 (15)	C12—H12B	0.9900
C4—H4	0.9500	C13—H13A	0.9800
C5—C6	1.3939 (16)	C13—H13B	0.9800
C5—H5	0.9500	C13—H13C	0.9800
C6—C7	1.4977 (15)	C14—H14A	0.9800
C7—C8	1.5125 (14)	C14—H14B	0.9800
C7—C9	1.5134 (15)	C14—H14C	0.9800
C7—H7	1.0000		
C10—O1—C14	115.16 (8)	C10—C9—C8	120.29 (9)
C2—C1—C6	121.04 (10)	C7—C9—C8	59.40 (7)
C2—C1—H1	119.5	C10—C9—H9	115.2
C6—C1—H1	119.5	C7—C9—H9	115.2
C3—C2—C1	120.13 (10)	C8—C9—H9	115.2
C3—C2—H2	119.9	O2—C10—O1	123.07 (10)
C1—C2—H2	119.9	O2—C10—C9	126.68 (10)
C4—C3—C2	119.44 (10)	O1—C10—C9	110.25 (9)
C4—C3—H3	120.3	C8—C11—H11A	109.5
C2—C3—H3	120.3	C8—C11—H11B	109.5
C3—C4—C5	120.45 (10)	H11A—C11—H11B	109.5
C3—C4—H4	119.8	C8—C11—H11C	109.5
C5—C4—H4	119.8	H11A—C11—H11C	109.5
C6—C5—C4	120.61 (10)	H11B—C11—H11C	109.5
C6—C5—H5	119.7	C8—C12—C13	113.26 (9)
C4—C5—H5	119.7	C8—C12—H12A	108.9
C5—C6—C1	118.33 (10)	C13—C12—H12A	108.9
C5—C6—C7	122.82 (10)	C8—C12—H12B	108.9
C1—C6—C7	118.85 (10)	C13—C12—H12B	108.9
C6—C7—C8	122.08 (9)	H12A—C12—H12B	107.7
C6—C7—C9	121.05 (9)	C12—C13—H13A	109.5
C8—C7—C9	61.14 (7)	C12—C13—H13B	109.5
C6—C7—H7	114.2	H13A—C13—H13B	109.5
C8—C7—H7	114.2	C12—C13—H13C	109.5

C9—C7—H7	114.2	H13A—C13—H13C	109.5
C7—C8—C11	117.69 (9)	H13B—C13—H13C	109.5
C7—C8—C12	118.82 (9)	O1—C14—H14A	109.5
C11—C8—C12	115.48 (9)	O1—C14—H14B	109.5
C7—C8—C9	59.46 (7)	H14A—C14—H14B	109.5
C11—C8—C9	119.46 (9)	O1—C14—H14C	109.5
C12—C8—C9	114.45 (9)	H14A—C14—H14C	109.5
C10—C9—C7	120.18 (9)	H14B—C14—H14C	109.5
C6—C1—C2—C3	-0.83 (16)	C6—C7—C9—C10	-138.41 (10)
C1—C2—C3—C4	0.63 (16)	C8—C7—C9—C10	109.50 (11)
C2—C3—C4—C5	0.13 (16)	C6—C7—C9—C8	112.09 (11)
C3—C4—C5—C6	-0.70 (16)	C7—C8—C9—C10	-109.33 (11)
C4—C5—C6—C1	0.50 (15)	C11—C8—C9—C10	-2.69 (15)
C4—C5—C6—C7	179.75 (10)	C12—C8—C9—C10	140.39 (10)
C2—C1—C6—C5	0.26 (15)	C11—C8—C9—C7	106.64 (11)
C2—C1—C6—C7	-179.03 (10)	C12—C8—C9—C7	-110.28 (10)
C5—C6—C7—C8	97.90 (13)	C14—O1—C10—O2	-0.37 (15)
C1—C6—C7—C8	-82.84 (13)	C14—O1—C10—C9	178.87 (8)
C5—C6—C7—C9	24.61 (15)	C7—C9—C10—O2	-12.31 (17)
C1—C6—C7—C9	-156.14 (9)	C8—C9—C10—O2	57.68 (15)
C6—C7—C8—C11	139.95 (10)	C7—C9—C10—O1	168.49 (9)
C9—C7—C8—C11	-109.58 (10)	C8—C9—C10—O1	-121.53 (10)
C6—C7—C8—C12	-7.54 (15)	C7—C8—C12—C13	-145.62 (10)
C9—C7—C8—C12	102.93 (11)	C11—C8—C12—C13	66.20 (13)
C6—C7—C8—C9	-110.47 (11)	C9—C8—C12—C13	-78.39 (12)

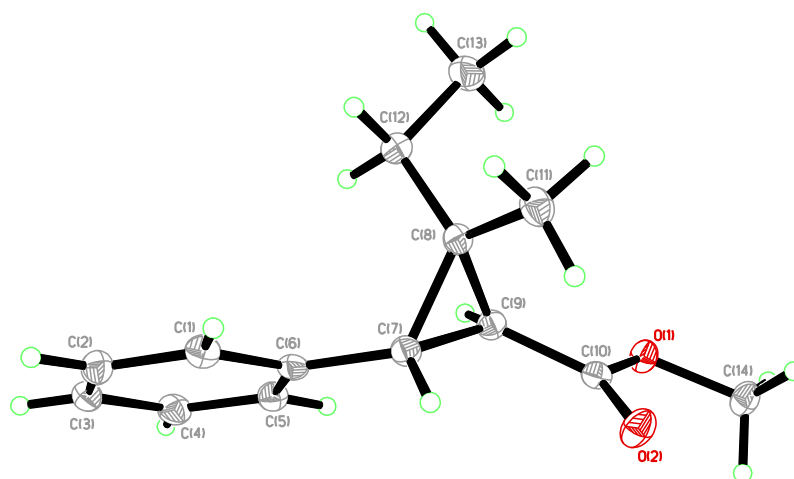
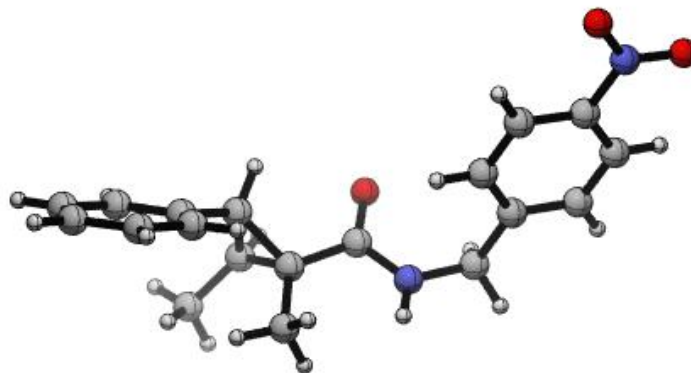


Figure S1.6 Perspective views showing 50% probability displacement.

X-Ray Crystallographic Information Data for (±)-7a



A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II DUO CCD diffractometer ($\text{CuK}\alpha$ radiation, $\lambda=1.54178$ Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 1.0° scans in ω at -30° , -55° , -80° , 30° , 55° , 80° and 115° in 2θ . Data integration down to 0.84 Å resolution was carried out using SAINT V8.34 C with reflection spot size optimization. Absorption corrections were made with the program SADABS. The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods against F^2 using SHELXT-2014 and SHELXL-2014 with OLEX 2 interface. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table S1.13, geometric parameters are shown in Table S1.14. The Ortep plots were produced with the SHELXL-2014 program.

Table S1.13 Experimental details.

Crystal data

Chemical formula	$\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3$
M_r	324.37
Crystal system, space group	Triclinic, $P-1$

Temperature (K)	100
a, b, c (Å)	9.6923 (3), 11.9153 (4), 16.0313 (6)
α, β, γ (°)	85.039 (2), 80.408 (2), 70.1280 (18)
V (Å ³)	1715.93 (10)
Z	4
Radiation type	Cu $K\alpha$
μ (mm ⁻¹)	0.69
Crystal size (mm)	0.20 × 0.12 × 0.06
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan <i>SADABS</i>
$T_{\min}, T_{\max}$	0.694, 0.864
No. of measured, independent and observed [I $> 2\sigma(I)$] reflections	25274, 5823, 5040
R_{int}	0.041
$(\sin \theta/\lambda)_{\max}$ (Å ⁻¹)	0.596
Refinement	
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.037, 0.102, 1.04
No. of reflections	5823
No. of parameters	445
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$D\rho_{\max}, D\rho_{\min}$ (e Å ⁻³)	0.20, -0.20

Table S1.14 Geometric parameters (Å, °).

O1—C10	1.2400 (15)	O4—C30	1.2401 (15)
O2—N2	1.2273 (16)	O5—N4	1.230 (2)
O3—N2	1.2308 (16)	O6—N4	1.226 (2)
N1—C10	1.3469 (17)	N3—C30	1.3463 (17)
N1—C11	1.4486 (17)	N3—C31	1.4453 (17)
N1—H1	0.843 (18)	N3—H3A	0.852 (18)
N2—C15	1.4651 (18)	N4—C35	1.467 (2)

C1—C2	1.392 (2)	C21—C22	1.384 (2)
C1—C6	1.396 (2)	C21—C26	1.395 (2)
C1—H1A	0.9500	C21—H21	0.9500
C2—C3	1.377 (3)	C22—C23	1.382 (3)
C2—H2	0.9500	C22—H22	0.9500
C3—C4	1.382 (3)	C23—C24	1.378 (3)
C3—H3	0.9500	C23—H23	0.9500
C4—C5	1.393 (2)	C24—C25	1.381 (2)
C4—H4	0.9500	C24—H24	0.9500
C5—C6	1.390 (2)	C25—C26	1.390 (2)
C5—H5	0.9500	C25—H25	0.9500
C6—C7	1.497 (2)	C26—C27	1.4932 (19)
C7—C8	1.5088 (19)	C27—C28	1.5064 (18)
C7—C9	1.5372 (17)	C27—C29	1.5299 (17)
C7—H7	1.0000	C27—H27	1.0000
C8—C18	1.507 (2)	C28—C38	1.5020 (19)
C8—C9	1.5274 (18)	C28—C29	1.5345 (17)
C8—H8	1.0000	C28—H28	1.0000
C9—C10	1.4965 (18)	C29—C30	1.4971 (18)
C9—C19	1.5140 (17)	C29—C39	1.5144 (16)
C11—C12	1.5127 (18)	C31—C32	1.5123 (19)
C11—H11A	0.9900	C31—H31A	0.9900
C11—H11B	0.9900	C31—H31B	0.9900
C12—C13	1.3877 (19)	C32—C33	1.3923 (19)
C12—C17	1.3993 (19)	C32—C37	1.393 (2)
C13—C14	1.383 (2)	C33—C34	1.389 (2)
C13—H13	0.9500	C33—H33	0.9500
C14—C15	1.383 (2)	C34—C35	1.374 (2)
C14—H14	0.9500	C34—H34	0.9500
C15—C16	1.383 (2)	C35—C36	1.384 (2)
C16—C17	1.383 (2)	C36—C37	1.382 (2)
C16—H16	0.9500	C36—H36	0.9500
C17—H17	0.9500	C37—H37	0.9500

C18—H18A	0.9800	C38—H38A	0.9800
C18—H18B	0.9800	C38—H38B	0.9800
C18—H18C	0.9800	C38—H38C	0.9800
C19—H19A	0.9800	C39—H39A	0.9800
C19—H19B	0.9800	C39—H39B	0.9800
C19—H19C	0.9800	C39—H39C	0.9800
C10—N1—C11	121.34 (11)	C30—N3—C31	121.00 (10)
C10—N1—H1	120.4 (11)	C30—N3—H3A	121.9 (11)
C11—N1—H1	117.4 (11)	C31—N3—H3A	116.6 (11)
O2—N2—O3	123.20 (12)	O6—N4—O5	123.27 (15)
O2—N2—C15	118.46 (12)	O6—N4—C35	118.27 (16)
O3—N2—C15	118.34 (12)	O5—N4—C35	118.46 (16)
C2—C1—C6	120.72 (15)	C22—C21—C26	120.54 (15)
C2—C1—H1A	119.6	C22—C21—H21	119.7
C6—C1—H1A	119.6	C26—C21—H21	119.7
C3—C2—C1	120.53 (18)	C23—C22—C21	120.13 (16)
C3—C2—H2	119.7	C23—C22—H22	119.9
C1—C2—H2	119.7	C21—C22—H22	119.9
C2—C3—C4	119.51 (17)	C24—C23—C22	119.79 (15)
C2—C3—H3	120.2	C24—C23—H23	120.1
C4—C3—H3	120.2	C22—C23—H23	120.1
C3—C4—C5	120.08 (16)	C23—C24—C25	120.27 (15)
C3—C4—H4	120.0	C23—C24—H24	119.9
C5—C4—H4	120.0	C25—C24—H24	119.9
C6—C5—C4	121.17 (16)	C24—C25—C26	120.77 (15)
C6—C5—H5	119.4	C24—C25—H25	119.6
C4—C5—H5	119.4	C26—C25—H25	119.6
C5—C6—C1	117.94 (14)	C25—C26—C21	118.46 (13)
C5—C6—C7	118.48 (14)	C25—C26—C27	121.40 (13)
C1—C6—C7	123.44 (13)	C21—C26—C27	120.14 (13)
C6—C7—C8	121.76 (12)	C26—C27—C28	122.43 (11)
C6—C7—C9	123.52 (11)	C26—C27—C29	121.20 (11)
C8—C7—C9	60.18 (8)	C28—C27—C29	60.71 (8)

C6—C7—H7	113.7	C26—C27—H27	114.1
C8—C7—H7	113.7	C28—C27—H27	114.1
C9—C7—H7	113.7	C29—C27—H27	114.1
C18—C8—C7	122.55 (13)	C38—C28—C27	122.38 (12)
C18—C8—C9	121.11 (12)	C38—C28—C29	121.22 (11)
C7—C8—C9	60.83 (8)	C27—C28—C29	60.40 (8)
C18—C8—H8	114.1	C38—C28—H28	114.2
C7—C8—H8	114.1	C27—C28—H28	114.2
C9—C8—H8	114.1	C29—C28—H28	114.2
C10—C9—C19	118.05 (11)	C30—C29—C39	117.55 (11)
C10—C9—C8	112.60 (11)	C30—C29—C27	114.11 (10)
C19—C9—C8	119.85 (11)	C39—C29—C27	120.87 (11)
C10—C9—C7	113.00 (10)	C30—C29—C28	112.95 (10)
C19—C9—C7	120.87 (11)	C39—C29—C28	119.23 (11)
C8—C9—C7	58.99 (8)	C27—C29—C28	58.89 (8)
O1—C10—N1	120.81 (12)	O4—C30—N3	121.24 (12)
O1—C10—C9	121.84 (11)	O4—C30—C29	121.63 (11)
N1—C10—C9	117.35 (11)	N3—C30—C29	117.12 (11)
N1—C11—C12	114.28 (11)	N3—C31—C32	115.88 (11)
N1—C11—H11A	108.7	N3—C31—H31A	108.3
C12—C11—H11A	108.7	C32—C31—H31A	108.3
N1—C11—H11B	108.7	N3—C31—H31B	108.3
C12—C11—H11B	108.7	C32—C31—H31B	108.3
H11A—C11—H11B	107.6	H31A—C31—H31B	107.4
C13—C12—C17	119.22 (12)	C33—C32—C37	119.15 (13)
C13—C12—C11	121.69 (12)	C33—C32—C31	122.65 (12)
C17—C12—C11	119.10 (12)	C37—C32—C31	118.16 (12)
C14—C13—C12	121.17 (13)	C34—C33—C32	120.50 (14)
C14—C13—H13	119.4	C34—C33—H33	119.8
C12—C13—H13	119.4	C32—C33—H33	119.8
C13—C14—C15	118.16 (13)	C35—C34—C33	118.67 (14)
C13—C14—H14	120.9	C35—C34—H34	120.7
C15—C14—H14	120.9	C33—C34—H34	120.7

C14—C15—C16	122.42 (13)	C34—C35—C36	122.39 (13)
C14—C15—N2	117.95 (13)	C34—C35—N4	119.26 (15)
C16—C15—N2	119.63 (13)	C36—C35—N4	118.35 (14)
C17—C16—C15	118.59 (13)	C37—C36—C35	118.31 (14)
C17—C16—H16	120.7	C37—C36—H36	120.8
C15—C16—H16	120.7	C35—C36—H36	120.8
C16—C17—C12	120.43 (13)	C36—C37—C32	120.97 (13)
C16—C17—H17	119.8	C36—C37—H37	119.5
C12—C17—H17	119.8	C32—C37—H37	119.5
C8—C18—H18A	109.5	C28—C38—H38A	109.5
C8—C18—H18B	109.5	C28—C38—H38B	109.5
H18A—C18—H18B	109.5	H38A—C38—H38B	109.5
C8—C18—H18C	109.5	C28—C38—H38C	109.5
H18A—C18—H18C	109.5	H38A—C38—H38C	109.5
H18B—C18—H18C	109.5	H38B—C38—H38C	109.5
C9—C19—H19A	109.5	C29—C39—H39A	109.5
C9—C19—H19B	109.5	C29—C39—H39B	109.5
H19A—C19—H19B	109.5	H39A—C39—H39B	109.5
C9—C19—H19C	109.5	C29—C39—H39C	109.5
H19A—C19—H19C	109.5	H39A—C39—H39C	109.5
H19B—C19—H19C	109.5	H39B—C39—H39C	109.5
C6—C1—C2—C3	2.3 (3)	C26—C21—C22— C23	-0.4 (3)
C1—C2—C3—C4	-1.9 (3)	C21—C22—C23— C24	1.6 (3)
C2—C3—C4—C5	0.2 (3)	C22—C23—C24— C25	-0.9 (3)
C3—C4—C5—C6	1.3 (3)	C23—C24—C25— C26	-0.9 (2)
C4—C5—C6—C1	-0.9 (2)	C24—C25—C26— C21	2.0 (2)
C4—C5—C6—C7	174.97 (14)	C24—C25—C26— C27	-178.69 (13)
C2—C1—C6—C5	-0.9 (2)	C22—C21—C26— C25	-1.3 (2)

C2—C1—C6—C7	-176.54 (15)	C22—C21—C26— C27	179.34 (14)
C5—C6—C7—C8	66.25 (17)	C25—C26—C27— C28	123.00 (14)
C1—C6—C7—C8	-118.10 (16)	C21—C26—C27— C28	-57.68 (18)
C5—C6—C7—C9	139.31 (14)	C25—C26—C27— C29	50.03 (18)
C1—C6—C7—C9	-45.0 (2)	C21—C26—C27— C29	-130.65 (14)
C6—C7—C8—C18	2.96 (19)	C26—C27—C28— C38	-0.10 (19)
C9—C7—C8—C18	-110.22 (14)	C29—C27—C28— C38	110.23 (13)
C6—C7—C8—C9	113.19 (13)	C26—C27—C28— C29	-110.33 (13)
C18—C8—C9—C10	-143.39 (13)	C26—C27—C29— C30	-144.50 (12)
C7—C8—C9—C10	104.10 (12)	C28—C27—C29— C30	103.23 (12)
C18—C8—C9—C19	2.31 (19)	C26—C27—C29— C39	4.59 (19)
C7—C8—C9—C19	-110.20 (13)	C28—C27—C29— C39	-107.68 (13)
C18—C8—C9—C7	112.51 (15)	C26—C27—C29— C28	112.27 (14)
C6—C7—C9—C10	146.22 (13)	C38—C28—C29— C30	142.70 (12)
C8—C7—C9—C10	-103.41 (12)	C27—C28—C29— C30	-105.22 (12)
C6—C7—C9—C19	-1.9 (2)	C38—C28—C29— C39	-1.65 (18)
C8—C7—C9—C19	108.49 (14)	C27—C28—C29— C39	110.43 (13)
C6—C7—C9—C8	-110.37 (15)	C38—C28—C29— C27	-112.08 (14)
C11—N1—C10—O1	-4.55 (19)	C31—N3—C30—O4	-6.39 (18)
C11—N1—C10—C9	176.54 (11)	C31—N3—C30—	172.23 (11)

		C29	
C19—C9—C10—O1	-176.65 (12)	C39—C29—C30— O4	-176.18 (12)
C8—C9—C10—O1	-30.28 (16)	C27—C29—C30— O4	-26.00 (17)
C7—C9—C10—O1	34.28 (17)	C28—C29—C30— O4	38.83 (16)
C19—C9—C10—N1	2.24 (17)	C39—C29—C30— N3	5.21 (17)
C8—C9—C10—N1	148.61 (11)	C27—C29—C30— N3	155.38 (11)
C7—C9—C10—N1	-146.83 (11)	C28—C29—C30— N3	-139.78 (11)
C10—N1—C11— C12	-94.51 (14)	C30—N3—C31— C32	84.11 (14)
N1—C11—C12— C13	14.07 (17)	N3—C31—C32— C33	-9.34 (17)
N1—C11—C12— C17	-166.09 (11)	N3—C31—C32— C37	172.99 (11)
C17—C12—C13— C14	1.26 (19)	C37—C32—C33— C34	0.82 (19)
C11—C12—C13— C14	-178.90 (12)	C31—C32—C33— C34	-176.82 (12)
C12—C13—C14— C15	-0.16 (19)	C32—C33—C34— C35	-0.4 (2)
C13—C14—C15— C16	-0.9 (2)	C33—C34—C35— C36	-0.1 (2)
C13—C14—C15— N2	178.63 (11)	C33—C34—C35— N4	-179.49 (12)
O2—N2—C15—C14	-0.81 (18)	O6—N4—C35—C34	178.96 (14)
O3—N2—C15—C14	179.19 (12)	O5—N4—C35—C34	-1.0 (2)
O2—N2—C15—C16	178.72 (12)	O6—N4—C35—C36	-0.5 (2)
O3—N2—C15—C16	-1.27 (19)	O5—N4—C35—C36	179.59 (14)
C14—C15—C16— C17	0.8 (2)	C34—C35—C36— C37	0.0 (2)
N2—C15—C16— C17	-178.72 (12)	N4—C35—C36— C37	179.46 (12)

C15—C16—C17— C12	0.3 (2)	C35—C36—C37— C32	0.4 (2)
C13—C12—C17— C16	-1.35 (19)	C33—C32—C37— C36	-0.86 (19)
C11—C12—C17— C16	178.81 (12)	C31—C32—C37— C36	176.89 (11)

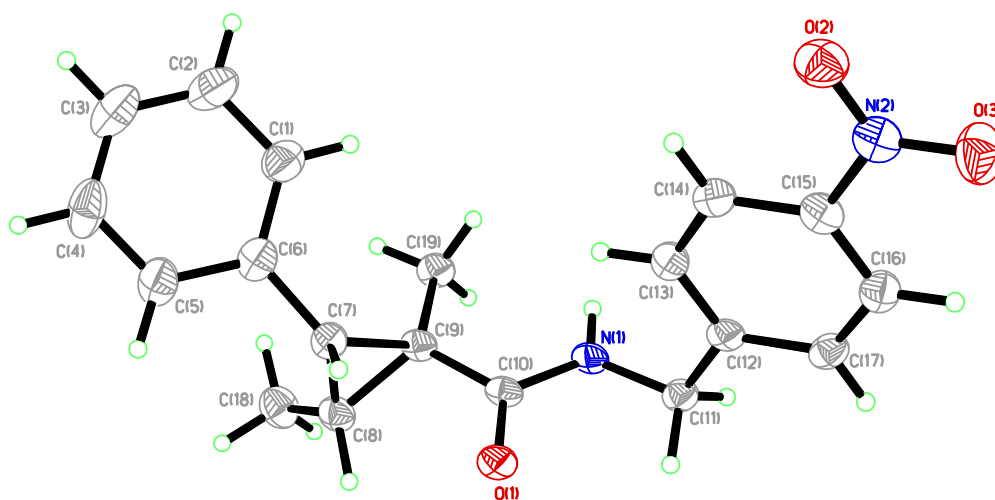


Figure S1.7 Perspective views showing 50% probability displacement.

Chapter 2

Catalytic Diastereo- and Enantioselective Fluoroamination of Alkenes

2.1 Introduction

The unique ability of fluorine substituents to modulate the physical and biological properties of organic molecules¹ has inspired widespread efforts to develop methods for the selective construction of C–F bonds.² Given the crucial importance of basic nitrogen groups in bioactive compounds, the stereoselective construction of vicinal fluoroamines has emerged as a particularly promising direction in organofluorine chemistry. Described in this chapter is the stereoselective synthesis of *syn*- β -fluoroaziridine building blocks *via* chiral aryl iodide-catalyzed fluorination of allylic amines. This method employs HF–pyridine as a nucleophilic fluoride source together with *m*CPBA as a stoichiometric oxidant and affords access to aryloethylamine derivatives featuring fluorine-containing stereocenters with high diastereo- and

¹ For some leading reviews, see: (a) Gillis, E.P.; Eastman, K.J.; Hill, M.D.; Donnelly, D.J.; Meanwell, N.A. *J. Med. Chem.* **2015**, *58*, 8315–8359. (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J.L.; del Pozo, C.; Sorochinsky, A.E.; Fustero, S.; Soloshonok, V.A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432–2506. (c) Purser, S.; Moore, P.R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330. (d) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359–4369.

² For some leading reviews, see: a) Yang, X.; Wu, T.; Phipps, R.J.; Toste, F.D. *Chem Rev.* **2015**, *115*, 826–870. (b) Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal.* **2011**, *352*, 2708–2732.

enantioselectivity. Catalyst-controlled diastereoselectivity in the fluorination of chiral allylic amines enables the preparation of highly enantioenriched 1,3-difluoro-2-amines bearing three contiguous stereocenters. This enantioselective, catalytic reaction protocol is applied successfully to other classes of multifunctional alkene substrates to afford *anti*- β -fluoropyrrolidines, as well as a variety of 1,2-oxyfluorinated products.

2.1.1 Physical and Biological Properties of β -Fluoroamines

β -Fluoroamines are privileged motifs in medicinal chemistry. In addition to improving metabolic stability, β -fluorine-substitution lowers the pK_a of amines,³ which in turn improves biological activity,⁴ bioavailability⁵ and lipophilicity ($\log D$).⁶ As a result, β -fluoroamines have become increasingly prevalent in bioactive compounds and drugs (Figure 2.1A). For instance, introduction of a stereodefined β -fluorine in the piperidine ring of MK-0731 was found to attenuate the basicity of the amine while reducing cellular efflux by *P*-glycoprotein and improving metabolic stability.⁷ The β -fluoroamine Sofosbuvir is an RNA polymerase inhibitor

³ Morgenthaler, M.; Schweizer, E.; Hoffmann-Roder, A.; Benini, F.; Martin, R.E.; Jaeschke, G.; Wagner, B.; Fisher, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Muller, K. *Chem Med Chem.* **2007**, *2*, 1100–1115.

⁴ Donetti, A.; Cereda, E.; Ezhaya, A.; Micheletti, R. *J. Med. Chem.* **1989**, *32*, 957–961.

⁵ van Niel, M.B.; Coliins, I.; Beer, M.S.; Broughton, H.B.; Cheng, S.K.; Goodacre, S.C.; Heald, A.; Locker, K.L.; MacLeod, A.M.; Morrison, D.; Moyes, C.R.; O'Connor, D.; Pike, A.; Rowley, M.; Russell, M.G.; Sohal, B.; Stanton, J.A.; Thomas, S.; Verrier, H.; Watt, A.P.; Castro, J.L. *J. Med. Chem.* **1999**, *42*, 20187–2104.

⁶ Böhm, H.J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *Chembiochem.* **2004**, *5*, 637–643.

⁷ Morgenthaler, M. *et al. J. Med. Chem.* **2008**, *51*, 4239–4252.

used in the treatment of hepatitis C.⁸ In addition, strategic incorporation of fluorine-bearing stereocenters into β -peptide structures has been demonstrated to induce powerful and predictable conformational effects (Figure 2.1B).⁹

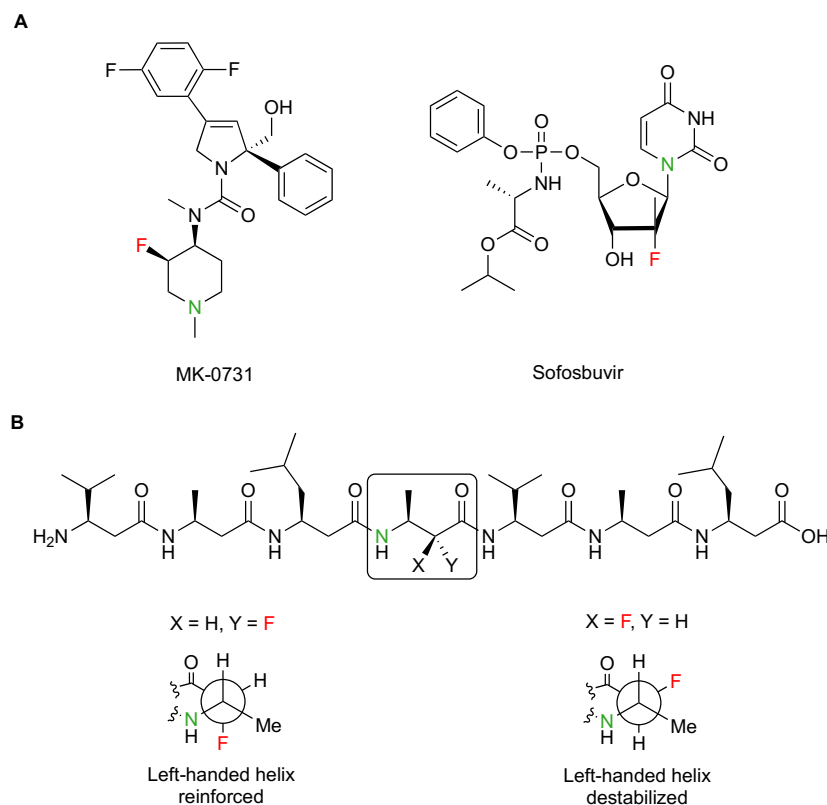


Figure 2.1 A) Bioactive compounds featuring the β -fluoroamine motif. B) Conformational effects of fluorine-substitution in β -peptides.

2.1.2 Fluoroamination of Alkenes

As a result of the unique properties of β -fluoroamines, the development of efficient methodologies for their synthesis represents an important goal in organic chemistry.¹⁰ Traditional

⁸ Clark, J.L.; Hollecker, L.; Mason, J.C.; Stuyver, L.J.; Tharnish, P.M.; Lostia, S.; McBrayer, T.R.; Schinazi, R.F.; Watanabe, K.A.; Otto, M.J.; Furman, P.A.; Stec, W.J.; Patterson, S.E.; Pankiewicz, K.W. *J. Med. Chem.* **2005**, 48, 5504–5508.

⁹ (a) Seebach, D.; Dubost, E.; Mathad, R.I.; Jaun, B.; Limbach, M.; Löweneck, M.; Flögel, O.; Gardiner, J.; Capone, S.; Beck, A.K.; Widmer, H.; Langenegger, D.; Monna, D.; Hoyer, D. *Helv. Chim. Acta.* **2008**, 91, 1736–1786. (b) Mathad, R.I.; Gessier, F.; Seebach, D.; Jaun, B. *Helv. Chim. Acta* **2005**, 88, 266–280.

access to β -fluoroamines from alkenes, however, usually requires multi-step transformations and suffers from low efficiency (Scheme 2.1). For example, nucleophilic fluorination of amino alcohols (Scheme 2.1A) is often plagued by rearrangement and dehydration side-reactions.¹¹ Ring opening of aziridines with nucleophilic fluoride sources (Scheme 2.1B) generates β -fluoroamines with moderate regioselectivities.¹² Other methods to access β -fluoroamines involve the fluorination of unsaturated amines (Scheme 2.1C), such as the α -fluorination of imines,¹³ the electrophilic fluorination of enamines,¹⁴ enamides¹⁵ and indoles¹⁶ as well as the hydrofluorination of allylic amines.¹⁷ A more recent approach to the synthesis of β -fluoroamines

¹⁰ For a review, see: Chen, G.; Liu, G. *Eur. J. Org. Chem.* **2015**, 4295–4309.

¹¹ For reviews, see: (a) Singh, R.P.; Shreeve, J.M. *Synthesis* **2002**, 17, 2561–2578. For selected examples, see: (b) Nicolaou, K.C.; Ladduwahetty, T.; Randall, J.L.; Chucholowski, A. *J. Am. Chem. Soc.* **1986**, 108, 2466–2467. (c) Duthion, B.; Pardo, D.G.; Cossy, J. *Org. Lett.* **2010**, 12, 4620–4623. (d) Anxionnat, B.; Robert, B.; George, P.; Ricci, G.; Perrin, M.-A.; Pardo, D.G.; Cossy, J. *J. Org. Chem.* **2012**, 77, 6087–6099. *J. Org. Chem.*, **2012**, 77, 4177–4183. (e) Nielsen, M.K.; Ugaz, C.R.; Li, W.; Doyle, A. *J. Am. Chem. Soc.* **2015**, 137, 9571–9574.

¹² (a) Alvenrhe, G.M.; Lacombe, S.; Laurent, A.J.; *Tetrahedron Lett.* **1980**, 21, 289–293. (b) Malik, G.; Estéoule, A.; Retailleau, P.; Dauban, P. *J. Org. Chem.* **2011**, 76, 7438–7448. (c) Kalow, J.A.; Schmitt, D.E.; Doyle, A.G. *J. Org. Chem.* **2012**, 77, 4177–4183.

¹³ (a) Verniest, G.; Van Hende, E.; Surmont, R.; De Kimpe, N. *Org. Lett.* **2006**, 8, 4767–4770. (b) Fadeyi, O.O.; Lindsley, C.W. *Org. Lett.* **2009**, 11, 943–946. (c) Han, X.; Kwiatkowski, J.; Xue, F.; Huang, K.-W.; Lu, Y. *Angew. Chem. Int. Ed.* **2009**, 48, 7604–7607. (d) Pan, P.; Zhao, Y.; Ma, T.; Yang, Y.; Liu, H.; Jiang, Z.; Tan, C.-H. *Chem. Eur. J.* **2010**, 16, 779–782.

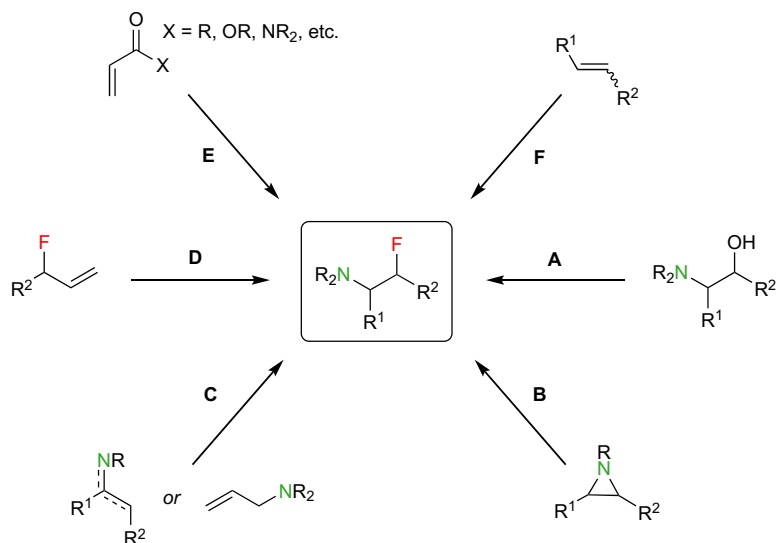
¹⁴ Dilman, A.D.; Belyakov, P.A.; Struchkova, M.I.; Arkhipov, D.E.; Korlyukov, A.A.; Tartakovsky, V.A. *J. Org. Chem.* **2010**, 75, 5367–5370.

¹⁵ (a) Honjo, T.; Phipps, R.J.; Raunivar, V.; Toste, F.D. *Angew. Chem. Int. Ed.* **2012**, 51, 9684–9688. (b) Phipps, R.J.; Hiramatsu, K.; Toste, F.D. *J. Am. Chem. Soc.* **2012**, 134, 8376–8379.

¹⁶ Lozano, O.; Blessley, G.; Matrinez del Campo, T.; Thompson, A.L.; Giuffredi, G.T.; Bettati, M.; Walker, M.; Borman, R.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2011**, 50, 8105–8109.

¹⁷ Thibaudeau, S.; Martin-Mingot, A.; Jouannetaud, M.-P.; Karam, O.; Zunino, F. *Chem. Commun.* **2007**, 3198–3200.

includes the hydroamination of allylic fluorides (Scheme 2.1D).¹⁸ Formal fluoroamination of activated α,β -unsaturated systems by a cascade Michael addition and electrophilic fluorination sequence (Scheme 2.1E) is well established.¹⁹ However, selective and efficient access to β -fluoroamines *via* direct fluoroamination of unactivated alkenes (Scheme 2.1F) has proven more challenging.²⁰



Scheme 2.1 Synthetic approaches to β -fluoroamines.

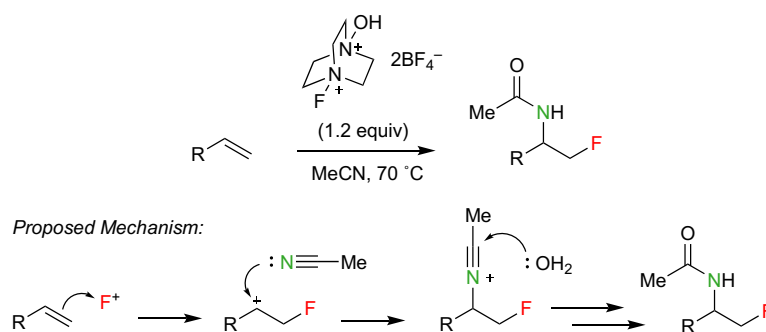
Stavner and co-workers developed the first example of an intermolecular fluoroamination of alkenes using 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2] octane bis(tetrafluoroborate) as an electrophilic fluorine source and acetonitrile as a nitrogen nucleophile (Scheme 2.2).²¹ Fluoroacetamides were obtained in good yields *via* Ritter-type reactivity.

¹⁸ Combettes, L.E.; Schuler, M.; Patel, R.; Bonillo, B.; Odell, B.; Thompson, A.L.; Claridge, T.D.W.; Gouverneur, V. *Chem. Eur. J.* **2012**, *18*, 13126–13132.

¹⁹ (a) Andrews, P.C.; Bhaskar, V.; Bromfield, K.M.; Dodd, A.M.; Duggan, P.J.; Duggan, S.A.M.; McCarthy, T.D. *Synlett* **2004**, 791–794. (b) Appayee, C.; Brenner-Moyer, S.E. *Org. Lett.* **2010**, *12*, 3356–3359

²⁰ Kong, W.; Merino, E.; Nevado, C. *Chimica* **2014**, *68*, 430–435.

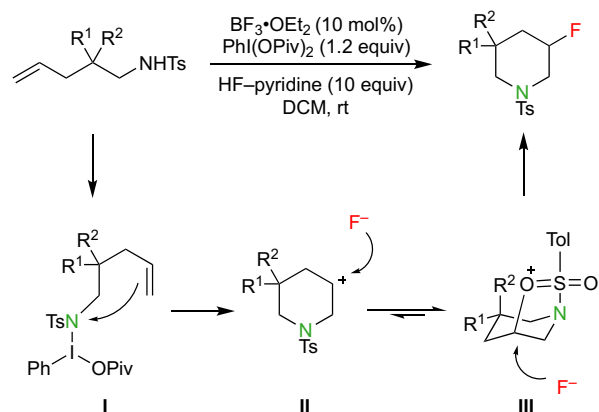
²¹ Stavner, S.; Pecn, T.S.; Papež, M.; Zupan, M. *Chem. Commun.* **1996**, 2247–2248.



Scheme 2.2 Ritter-type fluoroamination of alkenes.

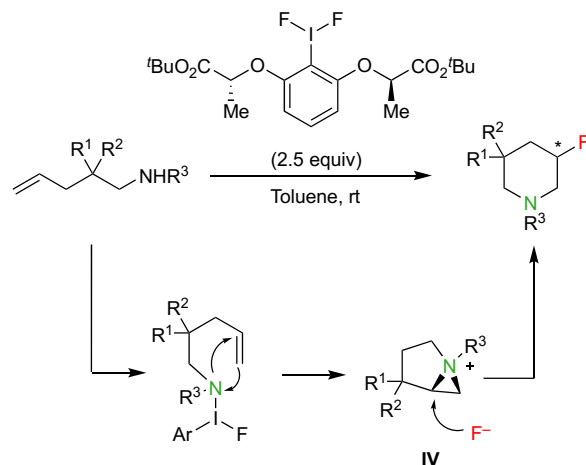
Metal-free approaches to fluoroamination of unactivated alkenes typically involve the use of hypervalent iodine(III) reagents.²² For example, Li and co-workers reported intramolecular fluoroamination of *N*-tosyl pentenamines to generate β -fluoropiperidines with high regio- and stereoselectivity promoted by $\text{PhI}(\text{OPiv})_2$, HF –pyridine and $\text{BF}_3 \cdot \text{OEt}_2$ (Scheme 2.3A).^{22a} The authors proposed a mechanism in which the sulfonamide nitrogen is oxidized by the hypervalent iodine to form electrophilic species **I**, which subsequently undergoes nucleophilic attack by the alkene to generate carbocationic intermediate **II**. Stabilization of this intermediate *via* neighboring group participation by the tosyl group to form **III** is followed by stereospecific displacement by fluoride to arrive at the *cis*-product exclusively. For substrates bearing a quaternary β -carbon, the axial alkyl group prevents the formation of **III**, producing a non-selective *cis/trans* mixture of products.

²² For selected examples, see: (a) Wang, Q.; Zhong, W.; Wei, X.; Ning, M.; Meng, X.; Li, Z. *Org. Biomol. Chem.* **2012**, *10*, 8566–8569. (b) Suzuki, S.; Kamo, T.; Fukushi, K.; Hiramatsu, T.; Tokunaga, E.; Dohi, T.; Kita, Y.; Shibata, N. *Chem. Sci.* **2014**, *5*, 2754–2760. (c) Cui, J.; Jia, Q.; Feng, R.-Z.; Liu, S.-S.; He, T.; Zhang, C. *Org. Lett.* **2014**, *16*, 1818–1821. (d) Kong, W.; Feige, P.; de Haro, T.; Nevado, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 2469–2473. (e) Chen, H.; Kaga, A.; Chiba, S. *Org. Biomol. Chem.* **2016**, *14*, 5481–5485.



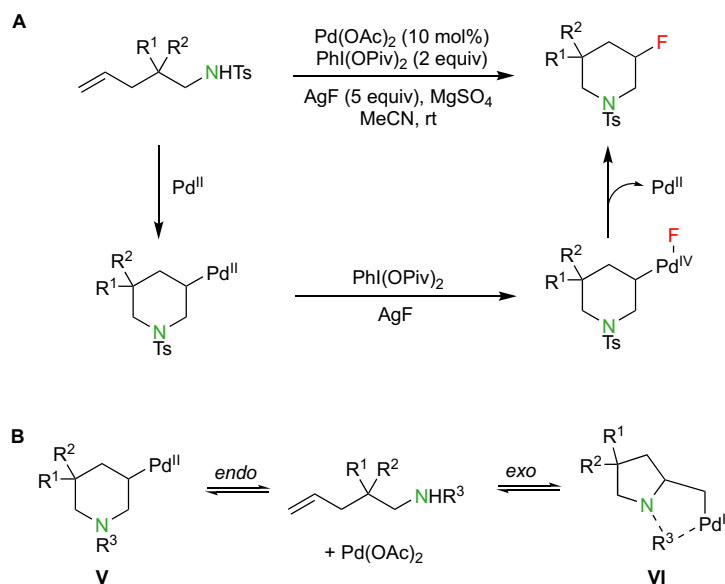
Scheme 2.3 Synthesis of β -fluoropiperidines *via* hypervalent iodine(III)-mediated intramolecular fluoroamination of alkenes.

An enantioselective version of this reaction was reported by Nevado and co-workers using a lactate-based iodonium difluoride (Scheme 2.4). The reaction protocol could also be extended to β -fluoroazepanes using a catalytic amount of a Lewis acidic gold complex. However, only terminal alkenes with diaromatic substituents were suitable for enantioinduction. Based on control experiments and deuterium labeling studies, the authors proposed a mechanism invoking the formation of aziridinium intermediate **IV** followed by fluoride attack at the more substituted carbon to give the *endo* product.



Scheme 2.4 Enantioselective intramolecular fluoroamination of alkenes promoted by I^{III} .

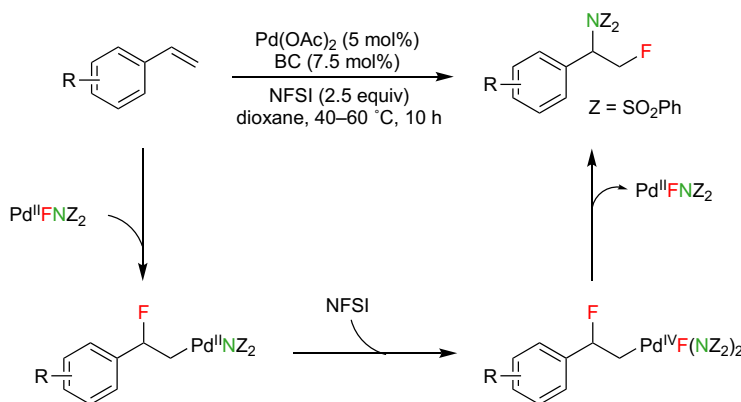
Transition-metal catalysis has also been applied to fluoroamination of alkenes. For example, Liu and co-workers reported a palladium-catalyzed 6-*endo*-selective intramolecular fluoroamination of unsaturated *N*-sulfonamides using AgF as the fluorine donor and PhI(OPiv)₂ as the stoichiometric oxidant (Scheme 2.5A).²³ The authors proposed a mechanism in which *trans*-aminopalladation of the alkene forms secondary alkyl-Pd(II) intermediate **V**. Oxidation with PhI(OPiv)₂ delivers a Pd(IV)–F species, which is then proposed to undergo reductive elimination to form the C(sp³)–F bond. A competitive S_N2-type mechanism operating on the Pd(II) intermediate, however, cannot be ruled out. Interestingly, a switch in regioselectivity from 6-*endo* to 5-*exo* cyclization was observed when a chelating group [C(O)NR₂] was installed on the nitrogen (Scheme 2.5B). Deuterium-labeling experiments indicated that, in this case, a kinetically favored *trans*-aminopalladation takes place to give primary alkyl-Pd(II) species **VI** stabilized by the chelating group, which then undergoes the oxidative fluorination reaction.



Scheme 2.5 **A)** Palladium-catalyzed intramolecular fluoroamination of alkenes. **B)** Chelating nitrogen protecting groups favor 5-*exo* cyclization.

²³ Wu, T.; Yin, G.; Liu, G. *J. Am. Chem. Soc.* **2009**, *131*, 8708–8713.

A palladium-catalyzed intermolecular fluoroamination reaction of styrenes was developed by the same group using *N*-fluorobenzenesulfonimide (NFSI) as the source of both nitrogen and fluorine (Scheme 2.6).²⁴ Mechanistic studies suggested a Pd^{II}/Pd^{IV} catalytic cycle involving fluoropalladation of the alkene by a F–Pd(II) species. Oxidation by NFSI to give a Pd(IV) intermediate followed by reductive elimination would deliver the observed product. Similar conditions were employed for an intramolecular version of this reaction.²⁵



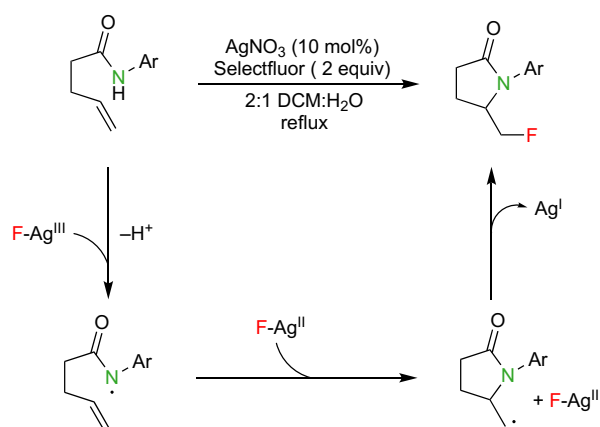
Scheme 2.6 Palladium-catalyzed intermolecular fluoroamination of styrenes.

Li and co-workers have reported a silver-catalyzed process for fluoroamination of unactivated alkenes using Selectfluor as both the fluorine source and oxidant (Scheme 2.7).²⁶ A series of *N*-arylpent-4-enamides underwent 5-*exo* cyclization/fluorination to give fluorinated lactams. The authors proposed a radical fluorination pathway involving an amidyl radical cyclization reaction, followed by fluorination with Selectfluor.

²⁴ Qiu, S.; Xu, T.; Zhou, J.; Guo, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 2856–2857.

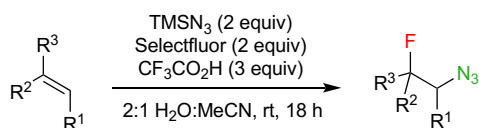
²⁵ Wu, T.; Yin, G.; Liu, G. *J. Am. Chem. Soc.* **2009**, *131*, 16354–16355.

²⁶ Li, Z.; Song, L.; Li, C. *J. Am. Chem. Soc.* **2013**, *135*, 4640–4643.



Scheme 2.7 Silver-catalyzed radical fluoroamination of alkenes.

A similar strategy, not requiring a silver catalyst, has also been employed for the azidofluorination of alkenes (Scheme 2.8).²⁷

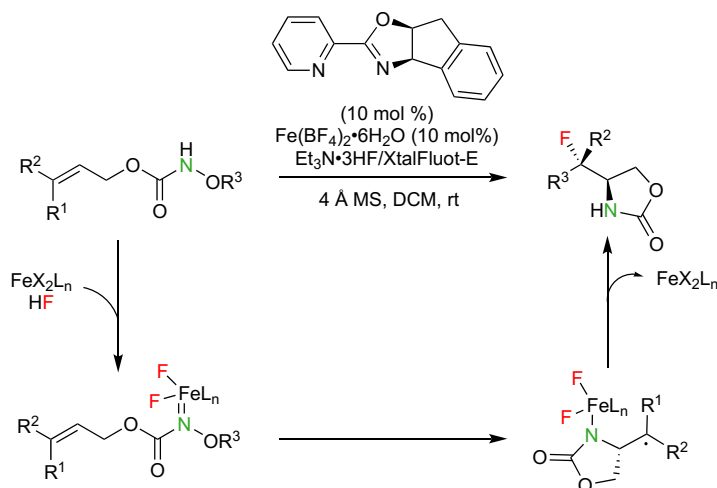


Scheme 2.8 Radical azidofluorination of unactivated alkenes.

In addition to catalysis by noble metals, fluoroamination of alkenes by cheap earth-abundant metals has also attracted considerable attention. For example, Xu and co-workers have reported iron-catalyzed inter- and intramolecular fluoroamination reactions of unfunctionalized alkenes using $\text{Et}_3\text{N}\cdot 3\text{HF}$ as the fluorine source (Scheme 2.9).²⁸ Preliminary studies demonstrate that enantioinduction is possible using a chiral catalyst and that both an iron-nitrenoid and carbocationic species may be reactive intermediates.

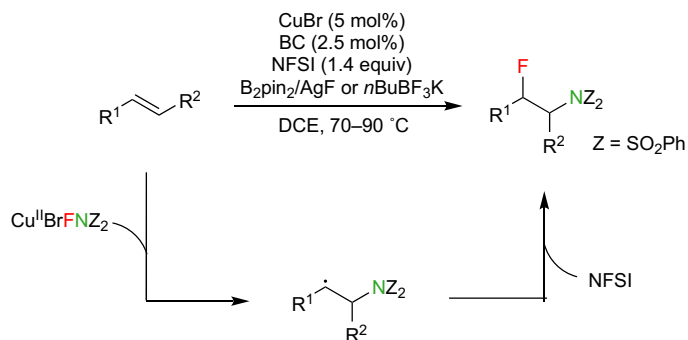
²⁷ Li, Z.; Zhang, C.; Zhu, L.; Liu, C.; Li, C. *Org. Chem. Front.* **2014**, *1*, 100–104.

²⁸ (a) Lu, D.-F.; Liu, S.-S.; Zhu, C.-L.; Yuan, B.; Xu, H. *Org. Lett.* **2014**, *53*, 11079–11083. (b) Lu, D.-F.; Zhu, C.-L.; Sear, J.D.; Xu, H. *J. Am. Chem. Soc.* **2016**, *138*, 11360–11367.



Scheme 2.9 Iron-catalyzed intramolecular fluoroamination of alkenes.

Finally, a copper-catalyzed process for the fluoroamination of styrenes with NFSI has been reported by Zhang and co-workers (Scheme 2.10).²⁹ This reaction afforded fluoroaminated products with high regioselectivities opposite to that observed for palladium-catalyzed and non-catalyzed processes. Mechanistic studies revealed that a radical mechanism is operative.



Scheme 2.10 Copper-catalyzed fluoroamination of alkenes.

²⁹ Zhang, H.; Song, Y.; Zhao, J.; Zhang, J.; Zhang, Q. *Angew. Chem. Int. Ed.* **2014**, 53, 11079–11083.

2.2 Development of Enantioselective Fluoroamination Reactions³⁰

2.2.1 Development of a β -Fluoroaziridination Reaction

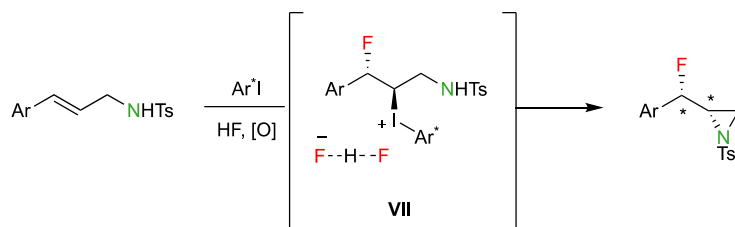
We and others have developed a variety of oxidative fluorofunctionalization reactions of alkenes based on aryl iodine(I–III) catalysis.^{31,32} In the presence of even weakly nucleophilic groups proximal to the alkene, the C(sp³)–I(III) intermediate that is proposed to be generated after initial fluoride addition (e.g., **VII**, Scheme 2.11) can be intercepted either temporarily or permanently to give rise to a variety of different pathways and products. This principle has been exploited with C₂-symmetric aryl iodide catalysts in the highly enantioselective syntheses of *anti*-1,2-difluorinated cinnamamides,^{32d} 4-fluoroisochromanones^{32h} and β,β -difluoroarylethanes.³²ⁱ We hypothesized that enantioenriched *syn*- β -fluoroaziridines might be generated in an analogous manner by trapping the key ArI(III) intermediate **VII** with appropriately positioned nitrogen nucleophiles (Scheme 2.11). This methodology would provide access to versatile precursors to β -fluoroamines, as the strained aziridine may be engaged in

³⁰ This work was performed in collaboration with Dr. Steven M. Banik and Elaine C. Reichert. Portions of this chapter have been adapted from Mennie, K.M.; Banik, S.M.; Reichert, E.C.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2018**, *140*, 4797–4802 © American Chemical Society 2018.

³¹ For a comprehensive review, see: Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016**, *116*, 3328–3435.

³² For representative examples of oxidative difunctionalization of alkenes using aryl iodine(I–III) catalysis, see: (a) Gelis, C.; Dumoulin, A.; Bekkaye, M.; Neuville, L.; Masson, G. *Org. Lett.* **2017**, *19*, 278–281. (b) Muñiz, K.; Barreiro, L.; Romero, R.M.; Martínez, C. *J. Am. Chem. Soc.* **2017**, *139*, 4354–4357. (c) Haubenreisser, S.; Wöste, T.; Martínez, C.; Ishihara, K.; Muñiz, K. *Angew. Chem., Int. Ed.* **2016**, *55*, 413–417. (d) Banik, S.M.; Medley, J.W.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2016**, *138*, 5000–5003. (e) Molnar, I.G.; Gilmour, R. *J. Am. Chem. Soc.* **2016**, *138*, 5004–5007. (f) Wöste, T.H.; Muñiz, K. *Synthesis* **2016**, *48*, 816–827. (h) Woerly, E.M.; Banik, S.M.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2016**, *138*, 13858–13861. (i) Banik, S.M.; Medley, J.W.; Jacobsen, E.N. *Science* **2016**, *353*, 51–54. (j) Mizar, P.; Laverny, A.; El-Sherbini, M.; Farid, U.; Brown, M.; Malmedy, F.; Wirth, T. *Chem. - Eur. J.* **2014**, *20*, 9910–9913. (k) Suzuki, S.; Kamo, T.; Fukushi, K.; Hiramatsu, T.; Tokunaga, E.; Dohi, T.; Kita, Y.; Shibata, N. *Chem. Sci.* **2014**, *5*, 2754–2760. (l) Martín Romero, R.; Wöste, T.H.; Muñiz, K. *Chem. - Asian J.* **2014**, *9*, 972–983. (m) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073–2085.

regioselective ring opening with a wide variety of nucleophiles.³³ We describe here the successful development and application of this principle to the highly stereoselective fluoroaziridination of cinnamyl amine derivatives, and elaboration of the products to a variety of novel fluorinated phenethylamine derivatives.³⁴



Scheme 2.11 β -Fluoroaziridination *via* sulfonamide trapping of a C(sp³)-I(III) intermediate.

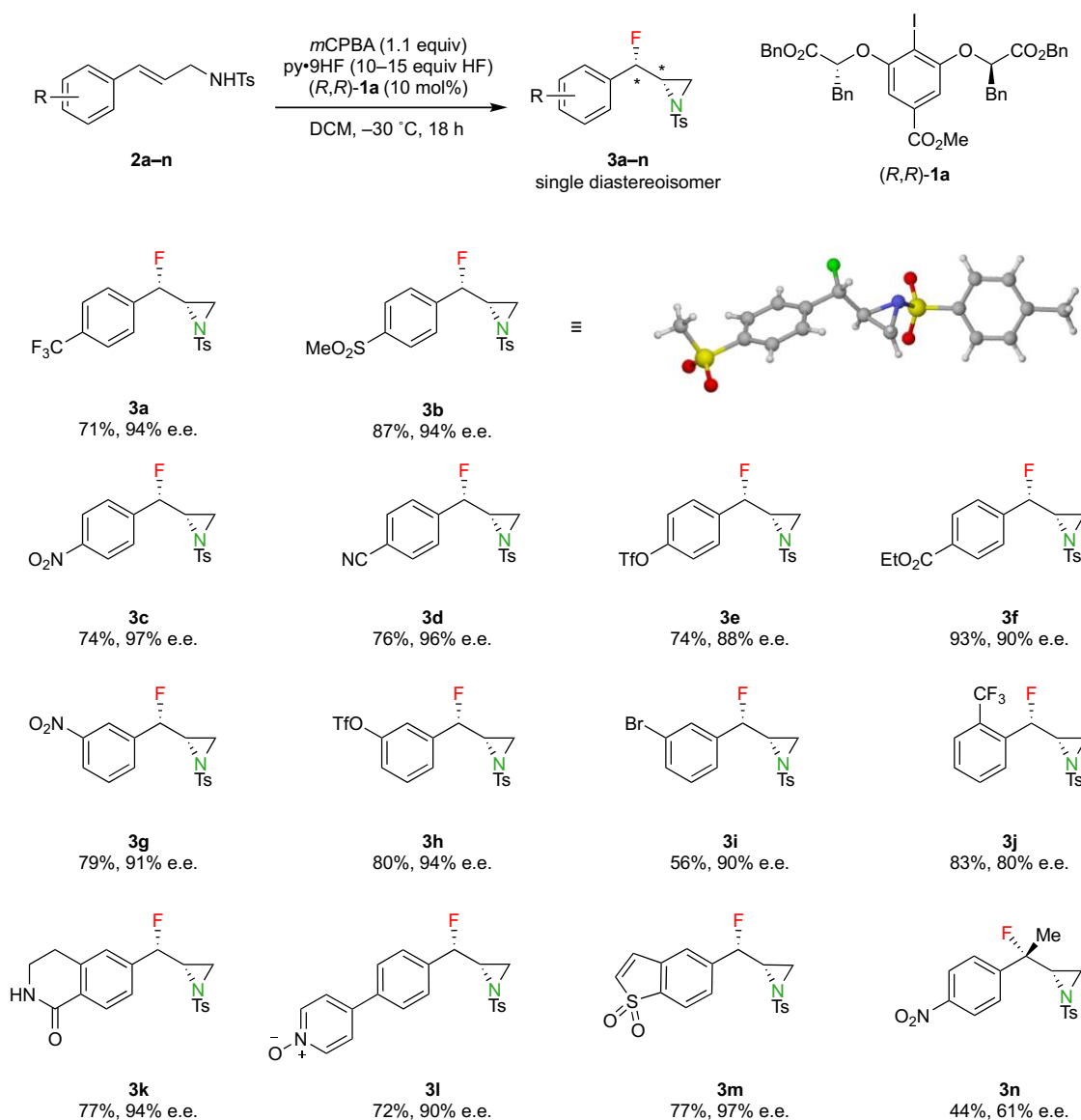
Cinnamyl tosylamide derivative **2a** was evaluated as a model substrate in the proposed fluoroaziridination reaction. Investigation of a variety of reagent combinations and experimental protocols led to the identification of optimal conditions similar to those reported in our previously described alkene 1,1-difluorination and fluorolactonization reactions (see Experimental Section).^{32h,i} Thus, in the presence of chiral aryl iodide catalysts, *m*CPBA as a stoichiometric oxidant and HF–pyridine as a nucleophilic fluoride source and acidic promoter, **2a** was observed to undergo selective oxidation to generate the corresponding β -fluoroaziridine product (**3a**) as a single detectable diastereoisomer. Catalyst **1a** proved superior with respect to both yield and enantioselectivity (94% e.e.) among all the chiral aryl iodides that were evaluated (see Experimental Section). Judicious optimization of HF loading (15 equiv HF) and temperature (−30 °C) proved crucial for obtaining the desired aziridine product in high yield; at higher HF loadings and/or temperatures, the 1,3-difluoride product resulting from opening of the putative

³³ Yudin, A. K. *Aziridines and Epoxides in Organic Synthesis*. Wiley-VCH, February 2006.

³⁴ (a) Trachsel, D. *Drug Testing and Analysis* **2012**, 4, 577–590. (b) Nichols, D.E. *Journal of Pharmaceutical Sciences* **1981**, 70, 839–849.

aziridinium ion intermediate was obtained. Sulfonamides proved to be uniquely effective in the fluoroaziridination reaction, as carbonyl-based protecting groups (amides, carbamates) led to the formation of 1,2-oxy-fluorinated products instead. Variation of the sulfonyl-protecting group had no effect on the enantioselectivity of the reaction, but the toluenesulfonamides generally afforded the highest yields (see Experimental Section) and were therefore selected for further investigation of substrate scope.

A variety of electron-deficient cinnamyl tosylamides were found to undergo clean conversion to the corresponding β -fluoroaziridine products (**3a–m**) as single diastereoisomers and with high enantioselectivity (Scheme 2.12). The *syn* relative stereochemistry of the products was established by X-ray crystallographic analysis of **3b** and is consistent with the intermediacy of a fluoroiodinated adduct (**VII**, Scheme 2.11). Substrates bearing electron-donating substituents were poor substrates for the fluoroaziridination reaction (*vide infra*), but it proved possible to generate products bearing *O*-aryl substituents by employing triflate-protected derivatives (**3e** and **3h**). This result bears significance given the prevalence of 3- and 4-hydroxy-substitution patterns in biologically important aryethylamines. Trisubstituted cinnamyl tosylamides proved less effective as substrates, as reflected by the tertiary fluoride **3n** being isolated in moderate yield and enantiomeric excess.



Scheme 2.12 Evaluation of substrate scope for electron-deficient cinnamyl tosylamides.

Substrates lacking electron-withdrawing substituents were found to undergo a phenonium ion rearrangement pathway to afford 1,1-difluoromethylated products in competition with the desired fluoroaziridination reaction (Figure 2.2).³²ⁱ For example, nearly exclusive formation of the 1,1-difluoromethylated product was observed in the case of the unsubstituted phenyl substrate (R = H). Indeed, a good correlation between the electronic properties of the substituents (σ^+) and the selectivity for the desired product was observed.

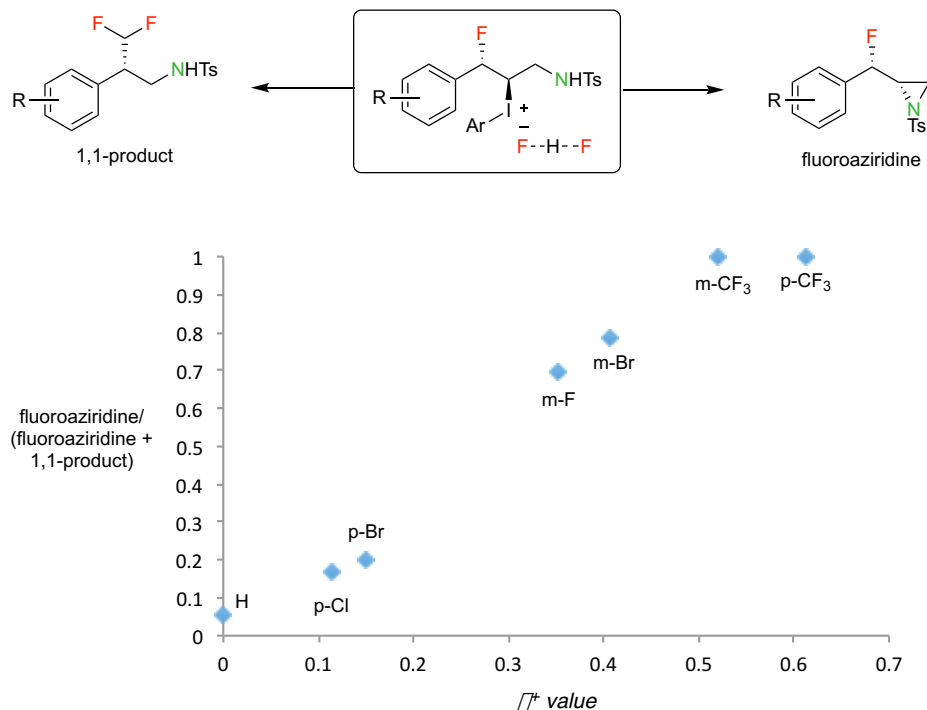
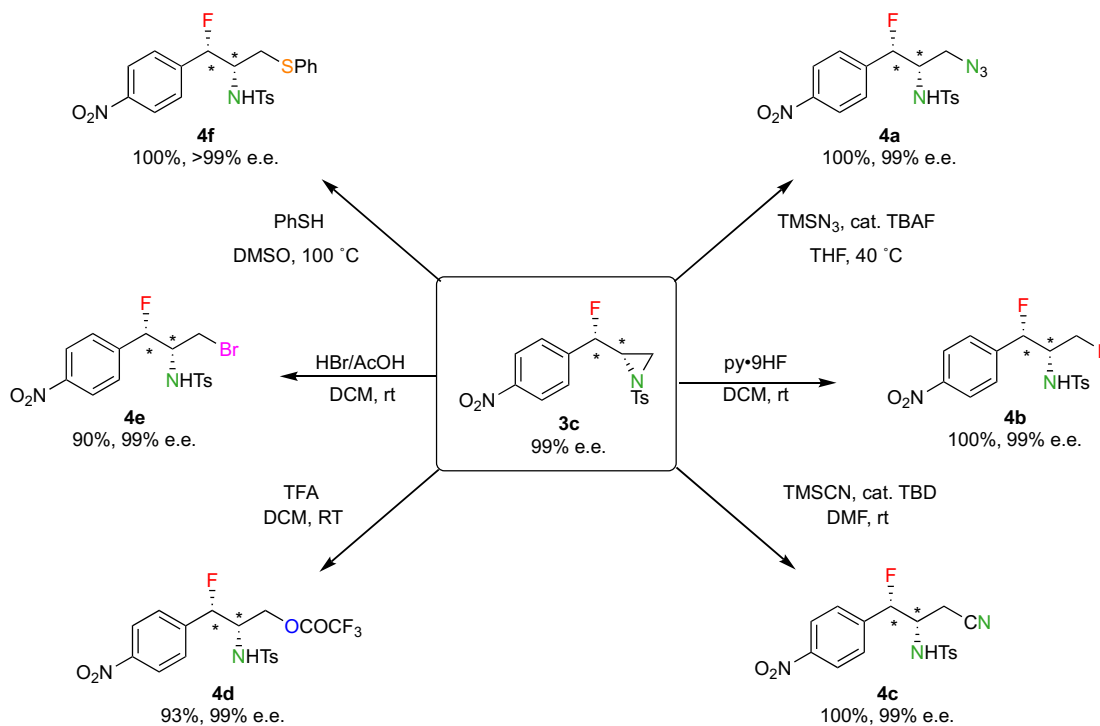


Figure 2.2 Product selectivity as a function of substituent. The ratio of fluoroaziridine product yield to the sum of fluoroaziridine and 1,1-difluoromethylated product yields was determined by ^{19}F NMR analysis of the crude mixture.

The β -fluoroaziridine product **3c** was selected as a model for synthetic elaboration studies. We found that ring opening with different classes of nucleophiles could be effected smoothly to yield a variety of β -fluoro-arylethyl amine products in excellent yields and without compromise of enantiomeric integrity (Scheme 2.13). Fluoride opening could be accomplished by simply subjecting **3c** to HF–pyridine at room temperature to yield the corresponding 1,3-difluoride (**4a**). Treatment of **3c** with other strong Brønsted acids such as hydrobromic and trifluoroacetic acid also resulted in clean ring opening, affording **4b** and **4c** respectively. In contrast, strongly basic nucleophiles were found to promote elimination pathways predominantly. In accordance with literature precedent, regioselective ring opening of **3c** with trimethylsilyl azide and trimethylsilylcyanide in the presence of catalytic base was observed to

yield **4d** and **4e** respectively,³⁵ while **4f** was obtained in quantitative yield by heating **3c** with thiophenol in dimethyl sulfoxide.³⁶



Scheme 2.13 Synthetic elaboration studies. Reactions of fluoroaziridine **3c** (upgraded to 99% e.e. by recrystallization).

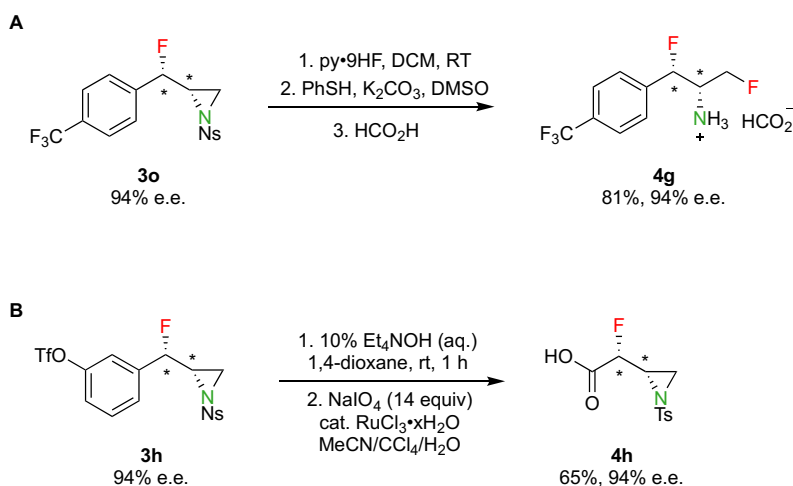
While removal of tosyl protecting groups is generally challenging, preparation, elaboration and deprotection of the analogous nosyl derivatives (e.g. **3o**) proved straightforward (Scheme 2.14A).³⁷ While the fluoroaziridination reaction was restricted to cinnamyl amine derivatives, the aromatic group in **3h** could be degraded oxidatively to a functional carboxylic acid handle³⁸ in a simple two-step sequence (Scheme 2.14B).

³⁵ Wu, J.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **2000**, 65, 1344–1348.

³⁶ Wu, J.; Sun, X.; Sun, W. *Org. Biomol. Chem.* **2006**, 4, 4231–4235.

³⁷ Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, 36, 6373–6374.

³⁸ Nunez, M.T.; Martin, V.S. *J. Org. Chem.* **1990**, 55, 1928–1932.

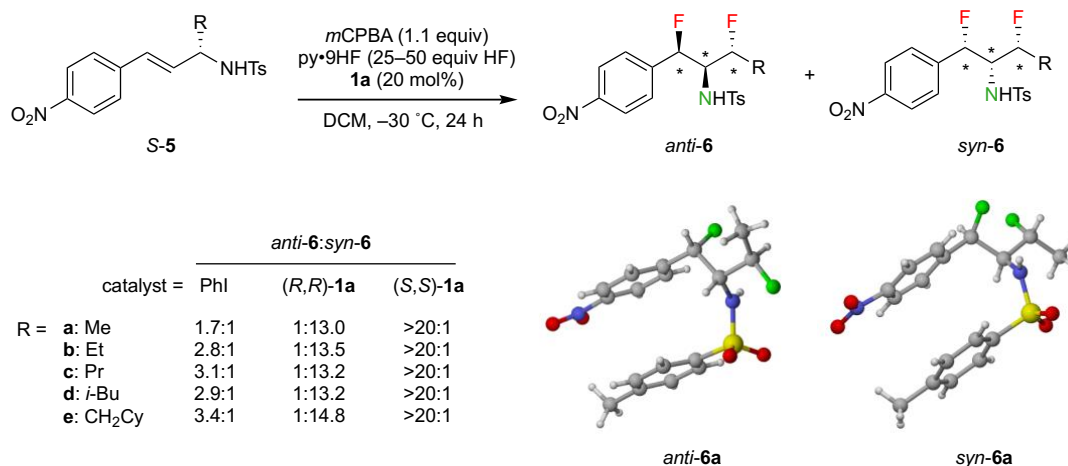


Scheme 2.14 Synthetic elaboration studies. **A)** Deprotection of nosyl fluoroaziridine **3o**. **B)** Oxidative degradation of aromatic group in **3h** to a functional carboxylic acid handle.

2.2.2 Extension of the Fluoroamination Reaction Protocol

1,3-Difluorides (**6a–e**) bearing three contiguous stereocenters were generated when the reaction protocol was applied to chiral substrates bearing an aliphatic allylic substituent, as in **5a** (Scheme 2.15). Higher HF loadings (25–50 equiv HF) were required to achieve full conversion of the starting material, and under these conditions the fluoride addition products were obtained exclusively. Completely regioselective ring opening of the putative 1,2-disubstituted aziridinium ion intermediate was observed, presumably due to the β -fluorine inductively deactivating ring opening at the homobenzylic position. The degree and sense of diastereoselectivity in the reaction was found to be subject to high levels of catalyst control. In the presence of an achiral catalyst such as iodobenzene, subjection of enantiopure **5a** to the fluoroaziridination protocol resulted in generation of the 1,3-difluoride **6a** in low, 1.7:1 d.r. (*anti/syn*). In contrast, chiral catalyst **1a** promoted formation of either diastereomer of **6a** with high selectivity depending on the enantiomer of catalyst employed. Consistent results were obtained in the catalyst-controlled difluorination of other substituted cinnamyl sulfonamides (**5b–5e**). X-Ray crystal structure

analyses of both diastereomers of **6a** revealed that the alkyl chains adopt dramatically different conformations in the solid state to minimize unfavorable dipolar interactions between the 1,3-difluoro substituents. These observations add to the increasing body of evidence that 1,3-difluorides can serve as potentially valuable conformational control elements.³⁹

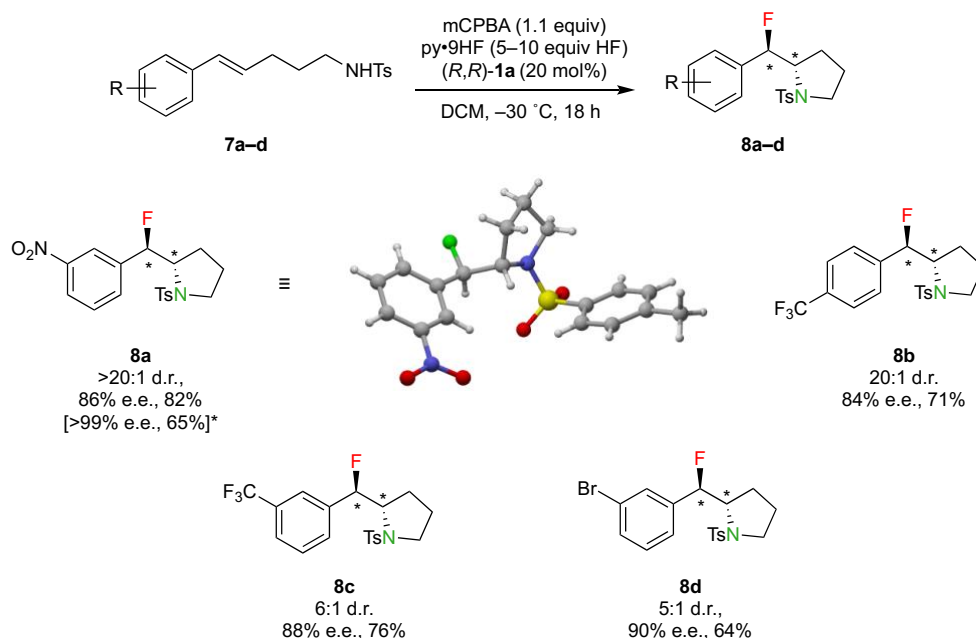


Scheme 2.15 Formation of 1,3-difluoro-2-amines bearing three contiguous stereocenters from enantioenriched allylic sulfonamides.

Variation of the spacing between the alkene and the sulfonamide was examined with an interest in generating fluorinated *N*-heterocycles of varying size. Substrates bearing either two or four methylene groups between the alkene and sulfonamide did not form the desired 4- or 6-membered *N*-heterocycles. Instead, low reactivity and conversion of the starting material to multiple uncharacterized fluorinated products were observed. In contrast, the fluoroamination protocol was applied successfully to the formation of 5-membered *N*-heterocycles (**8a–d**, Scheme 2.16). Notable in this reaction is the switch in diastereoselectivity to give *anti*-1,2-fluoroaminated products, as compared to the *syn*-1,2-fluoroaminated products from the β -fluoroaziridination reaction. The strong dependence of product diastereoselectivity on the electronic nature of the styrenyl arene also stands in contrast to the β -fluoroaziridination reaction.

³⁹ For a review discussing 1,3-difluoride dipole minimization, see: O'Hagan, D. *Chem. Soc. Rev.* **2008**, 37, 308–319.

The fluoroaziridination and fluoropyrrolidination reactions must therefore proceed by fundamentally different mechanisms, yet both pathways can be promoted with high enantioselectivity using the same aryl iodide catalyst **1a**.

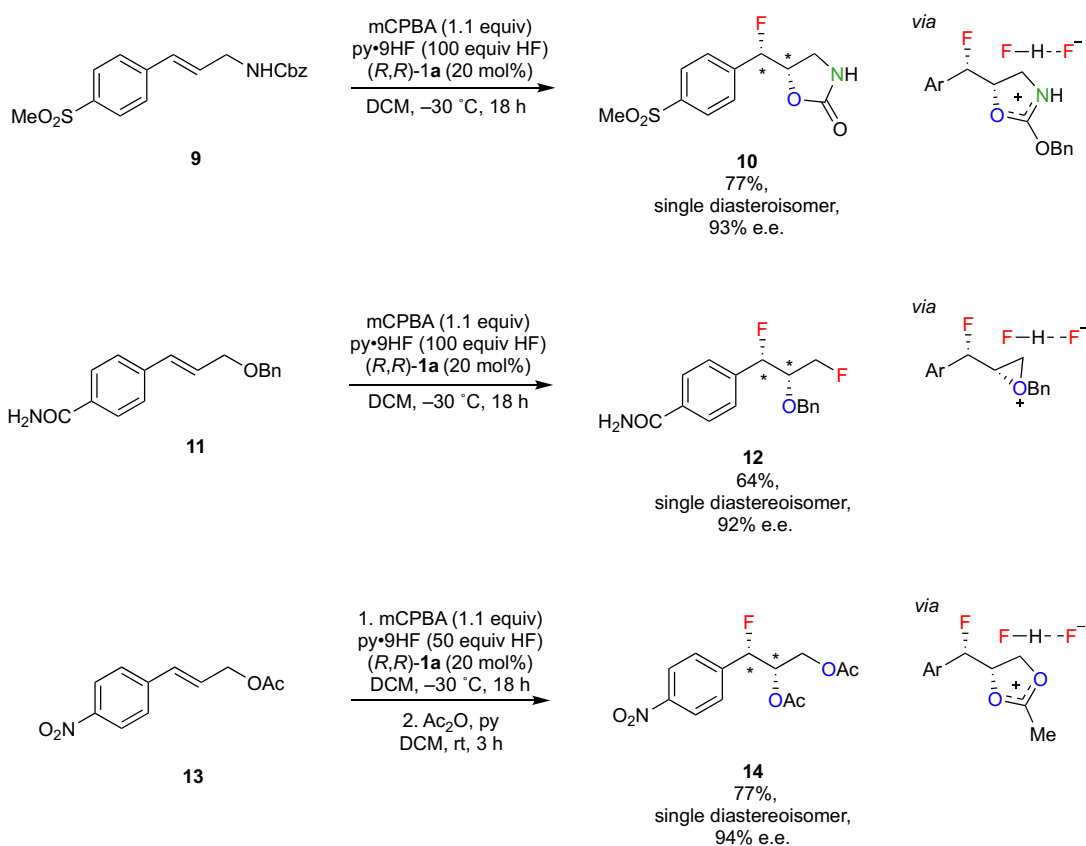


Scheme 2.16 Fluoroamination of bis-homoallylic sulfonamides results in the formation of the corresponding *anti*-β-fluoro-pyrrolidines. *Yield and e.e. of **8a** following recrystallization.

2.2.3 Development of Enantioselective 1,2-Oxyfluorination Reactions

For several classes of cinnamyl derivatives, neighboring group participation by *O*-centered functional groups was found to result in stereoselective generation of oxyfluorinated products. Benzyl ether **9** underwent a fluorinative rearrangement reaction to generate 1,3-difluoride **10**, consistent with formation and fluorinative ring opening of the corresponding oxiranium ion intermediate. As noted above, allylic amine substrates bearing carbonyl-containing nitrogen protecting groups such as carbamates and acetamides were found to undergo cyclization *via* reaction at the carbonyl oxygen rather than the nitrogen, resulting in the formation of a

variety of novel 1,2-oxyfluorinated products (Scheme 2.17). For example, when the reaction protocol was applied to Cbz-protected cinnamyl amine **11**, formal 1,2-oxyfluorination of the alkene was observed to generate the cyclic carbamate **12** as a single observable diastereoisomer in good yield and in 93% e.e. Allylic acetates such as **13** were observed to react *via* an analogous pathway, resulting in the formation of a mixture of hydroxy and acetoxy products that presumably arise from hydrolytic ring opening of an acetoxonium ion intermediate. Treatment of the product mixture with acetic anhydride yielded the corresponding 1-fluoro-2,3-diacetoxyated product **14** in good yield and as a single observable diastereoisomer in 94% e.e.



Scheme 2.17 Catalytic diastereo- and enantioselective 1,2-oxyfluorination reactions.

2.3 Conclusion

The catalytic enantioselective fluorofunctionalization reactions described in this chapter provide access to a variety of new fluorine-containing chiral compounds with potentially unique conformational and functional properties. Evaluating and exploiting the utility of these polyfunctional fluorinated compounds would represent interesting future directions for this project.

1.4 Experimental Section

General experimental procedures. All reactions for the preparation of substrates were performed in standard, dry glassware fitted with rubber septa under an inert atmosphere of nitrogen unless otherwise described. All difluorination reactions were performed in low density polyethylene tubes sealed with a low-density polyethylene cap under an atmosphere of air. Reported concentrations refer to solution volumes at room temperature. Concentration of organic solutions under reduced pressure was performed using house vacuum (ca. 40 mm Hg) at 30 °C. Column chromatography was performed with ZEOprep® 60 (40–63 micron) silica gel from American Scientific. Thin layer chromatography (TLC) was used for reaction monitoring and product detection was performed using pre-coated glass plates covered with 0.20 mm silica gel with fluorescent indicator; plates were visualized by exposure to UV light ($\lambda_{\text{ex}} = 254 \text{ nm}$) or by staining with potassium permanganate or ninhydrin.

CAUTION: Pyridine•9HF is a corrosive and toxic substance that will etch glassware. Safe handling can be conducted with plastic syringes and metal needles, with NaHCO_3 (aq.) or NaOH (aq.) employed to quench excess HF. Though reactions should not be conducted in glassware when employing pyridine•9HF, glassware may be used to quench reactions provided sufficient quantities of base are present. Always handle pyridine•9HF while wearing gloves and in a fumehood. As a precautionary measure, have calcium gluconate gel nearby and apply immediately and liberally on skin exposed to HF.

Materials. Reagents were purchased in reagent grade from commercial suppliers and used as received, unless otherwise described. Anhydrous solvents (benzene, dichloromethane, diethyl ether, *N,N*-dimethylformamide, tetrahydrofuran, and toluene) were prepared by passing the

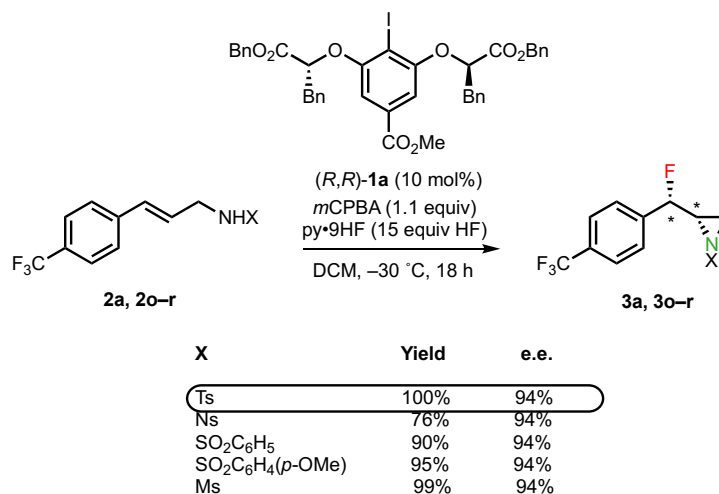
solvent through an activated alumina column. Triethylamine and diisopropylethylamine were distilled over calcium hydride at atmospheric pressure.

Instrumentation. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on an Inova-500 spectrometer, are reported in parts per million downfield from tetramethylsilane, and are referenced to the residual protium resonances of the NMR solvent (CDCl_3 : 7.26 [CHCl_3]). Proton-decoupled carbon-13 nuclear magnetic resonance (^{13}C $\{^1\text{H}\}$ NMR) spectra were recorded on an Inova-500 spectrometer, are reported in parts per million downfield from tetramethylsilane, and are referenced to the carbon resonances of the NMR solvent (CDCl_3 : 77.16). Chemical shifts for fluorine-19 nuclear magnetic resonance (^{19}F NMR) were recorded on an Inova-500 spectrometer and are reported in parts per million downfield from chlorotrifluoromethane and are referenced to the fluorine resonance of chlorotrifluoromethane ($\delta = 0$). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sext = sextet, sept = septet, m = multiplet), coupling constants in Hertz (Hz), integration. Infrared spectra were recorded using a Bruker Tensor 27 FT-IR spectrometer. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad). High-resolution mass spectrometric data were obtained on an Agilent 6210 time-of-flight HPLC/MS spectrometer (ESI-TOF). Low-resolution mass spectrometric data were obtained on a Waters Quattro Micro GCMS (EI^+). Chiral HPLC analysis was performed using an Agilent 1200 series quaternary HPLC system using commercially available CHIRALCEL analytical columns (4.6 x 250 mm).

Optimization Experiments

General procedure for *N*-protecting group optimization

Catalyst (*R,R*)-**1a**³²ⁱ (8.0 mg, 5.20 μ mol, 10.0 mol%), *p*-trifluoromethyl-cinnamyl sulfonamide (52.0 μ mol, 1.00 equiv) and dichloromethane (0.30 mL) were combined in a polyethylene tube. The reaction mixture was cooled to -78 $^{\circ}$ C. Pyridinium poly(hydrogen fluoride) (pyr•9HF, 70% hydrogen fluoride by weight, 21 μ L, 15 equiv hydrogen fluoride) was added via micropipette followed by *m*-chloroperbenzoic acid (*m*CPBA, 77% by weight, 12.8 mg, 57.2 μ mol, 1.10 equiv). The reaction was warmed to -30 $^{\circ}$ C and stirred for 18 hours at that temperature. The reaction was cooled to -78 $^{\circ}$ C and basic alumina (approximately 400 mg) was added slowly. The reaction was allowed to warm to room temperature with stirring and was filtered. The crude mixture was analyzed by ^{1} H NMR using mesitylene as an internal standard to determine the yield of product and by chiral HPLC to determine the enantioselectivity.

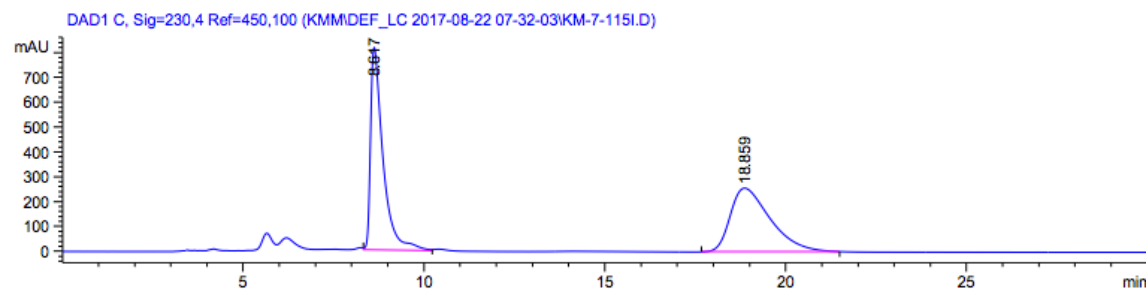


Scheme S2.1 *N*-Protecting group optimization.

X = Ts (3a)

94% e.e., chiral HPLC (OJ-H, 50% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230$ nm); $t_R(\text{minor})$ = 8.4 min, $t_R(\text{major})$ = 17.7 min.

Racemic sample:

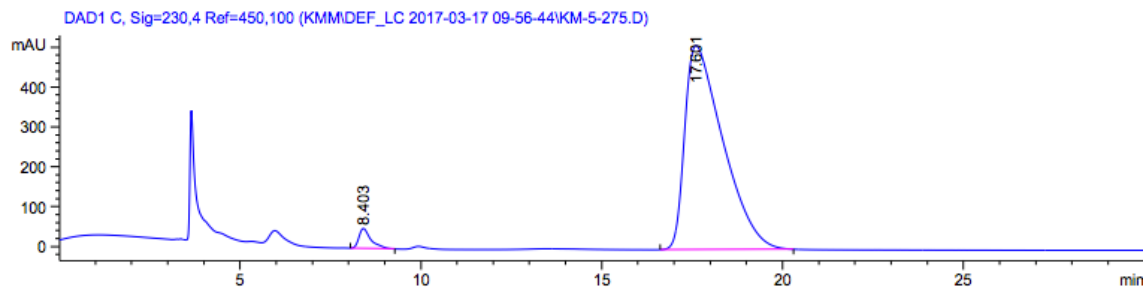


Signal 3: DAD1 C, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.617	VB	0.3503	1.95753e4	814.81110	49.8014
2	18.859	BB	1.1274	1.97315e4	256.50644	50.1986

Totals : 3.93067e4 1071.31754

Enriched sample:



Signal 3: DAD1 C, Sig=230,4 Ref=450,100

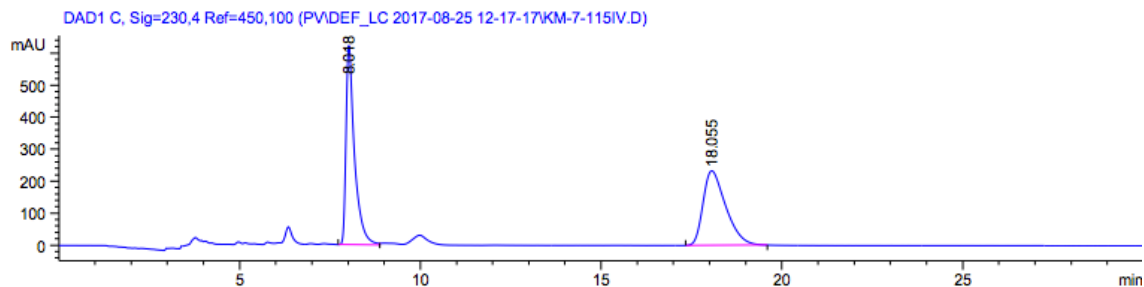
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.403	BB	0.3418	1155.48096	49.95803	2.9786
2	17.601	BB	1.0699	3.76372e4	511.83502	97.0214

Totals : 3.87927e4 561.79305

X = Ns (3o)

94% e.e., chiral HPLC (OJ-H, 50% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230$ nm); $t_R(\text{major})$
= 7.1 min, $t_R(\text{minor}) = 18.3$ min.

Racemic sample:

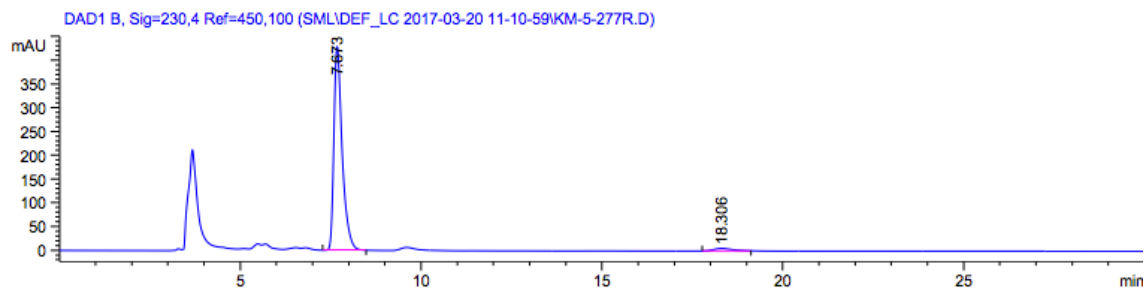


Signal 3: DAD1 C, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.018	VV	0.2370	1.01980e4	622.86884	50.0240
2	18.055	BB	0.6560	1.01882e4	233.07854	49.9760

Totals : 2.03862e4 855.94737

Enriched sample:



Signal 2: DAD1 B, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.673	VB	0.2378	6832.35889	429.04306	97.2353
2	18.306	BB	0.5252	194.26431	5.38117	2.7647

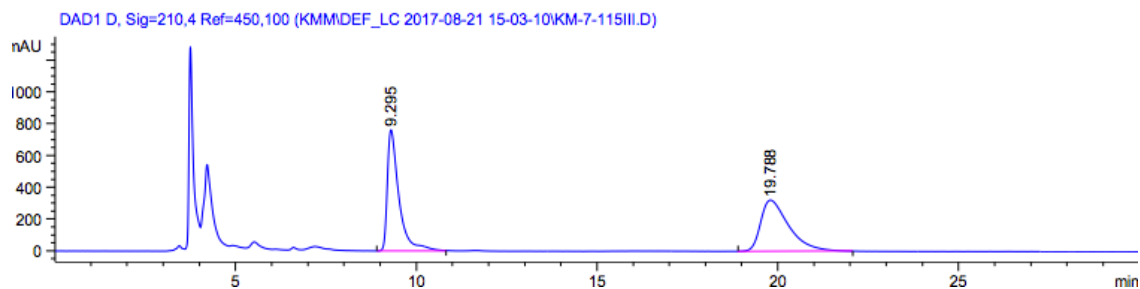
Totals : 7026.62320 434.42423

X = SO₂C₆H₅ (3p)

94% e.e., chiral HPLC (OJ-H, 50% isopropanol in hexanes, 1.0 mL/min, λ = 210 nm); t_R(minor)

= 8.9 min, t_R(major) = 19.1 min.

Racemic sample:

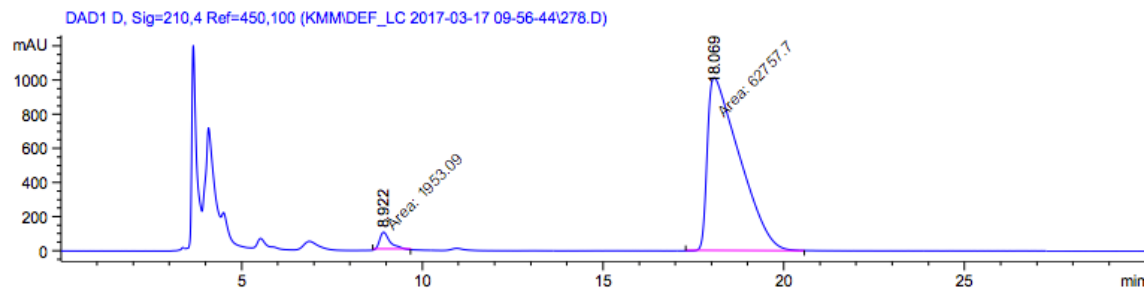


Signal 4: DAD1 D, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.295	BV	0.3346	1.73198e4	763.76923	49.8517
2	19.788	BB	0.7452	1.74228e4	322.03442	50.1483

Totals : 3.47426e4 1085.80365

Enriched sample:



Signal 4: DAD1 D, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.922	MM	0.3280	1953.08704	99.22910	3.0182
2	18.069	MM	1.0308	6.27577e4	1014.73376	96.9818

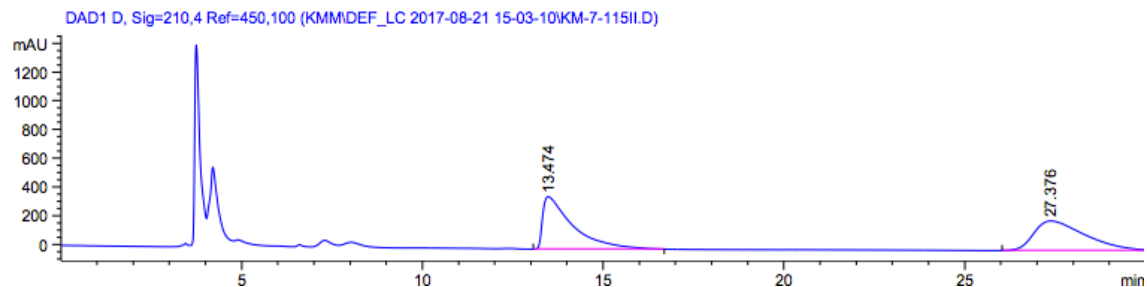
Totals : 6.47108e4 1113.96287

X = SO₂C₆H₄(*p*-OMe) (3q)

94% e.e., chiral HPLC (OJ-H, 50% isopropanol in hexanes, 1.0 mL/min, λ = 210 nm); t_R(minor)

= 14.2 min, t_R(major) = 25.6 min.

Racemic sample:

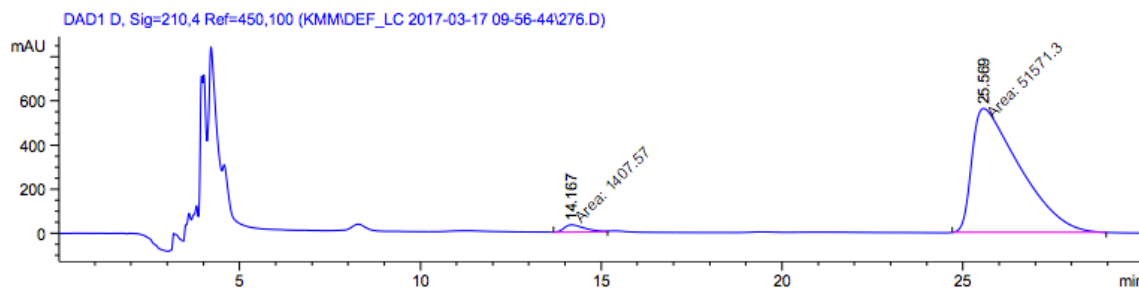


Signal 4: DAD1 D, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.474	BB	0.7661	2.11041e4	364.19147	51.1759
2	27.376	VBA	1.1700	2.01342e4	204.97517	48.8241

Totals : 4.12383e4 569.16664

Enriched sample:



Signal 4: DAD1 D, Sig=210,4 Ref=450,100

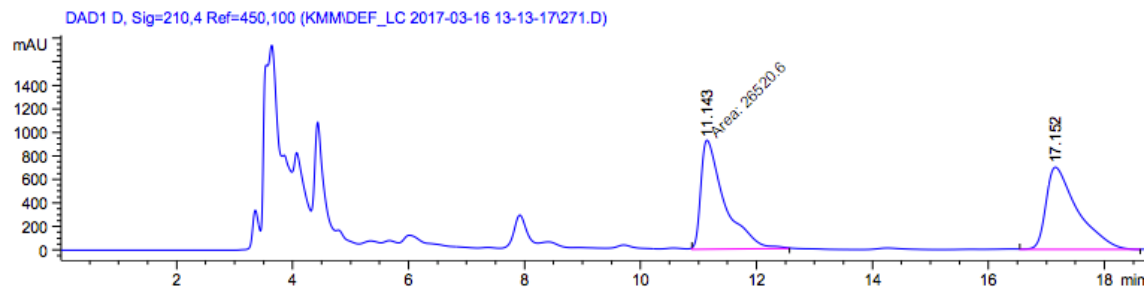
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.167	MM	0.6997	1407.57104	33.52897	2.6569
2	25.569	MM	1.5284	5.15713e4	562.36053	97.3431

Totals : 5.29789e4 595.88951

X = Ms (3r)

94% e.e., chiral HPLC (OJ-H, 50% isopropanol in hexanes, 1.0 mL/min, $\lambda = 210$ nm); t_R (minor)
= 11.4 min, t_R (major) = 17.1 min.

Racemic sample:

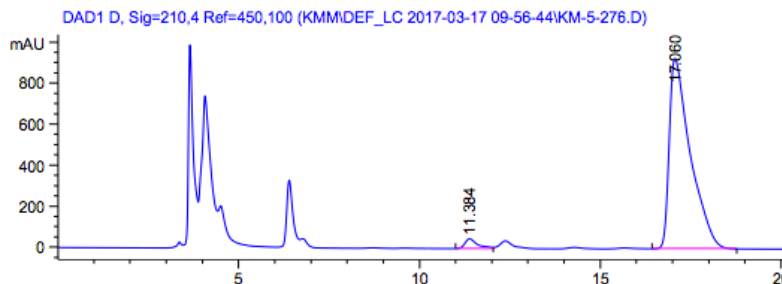


Signal 4: DAD1 D, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.143	MM	0.4756	2.65206e4	929.37671	50.0303
2	17.152	VV	0.5513	2.64885e4	700.32471	49.9697

Totals : 5.30091e4 1629.70142

Enriched sample:



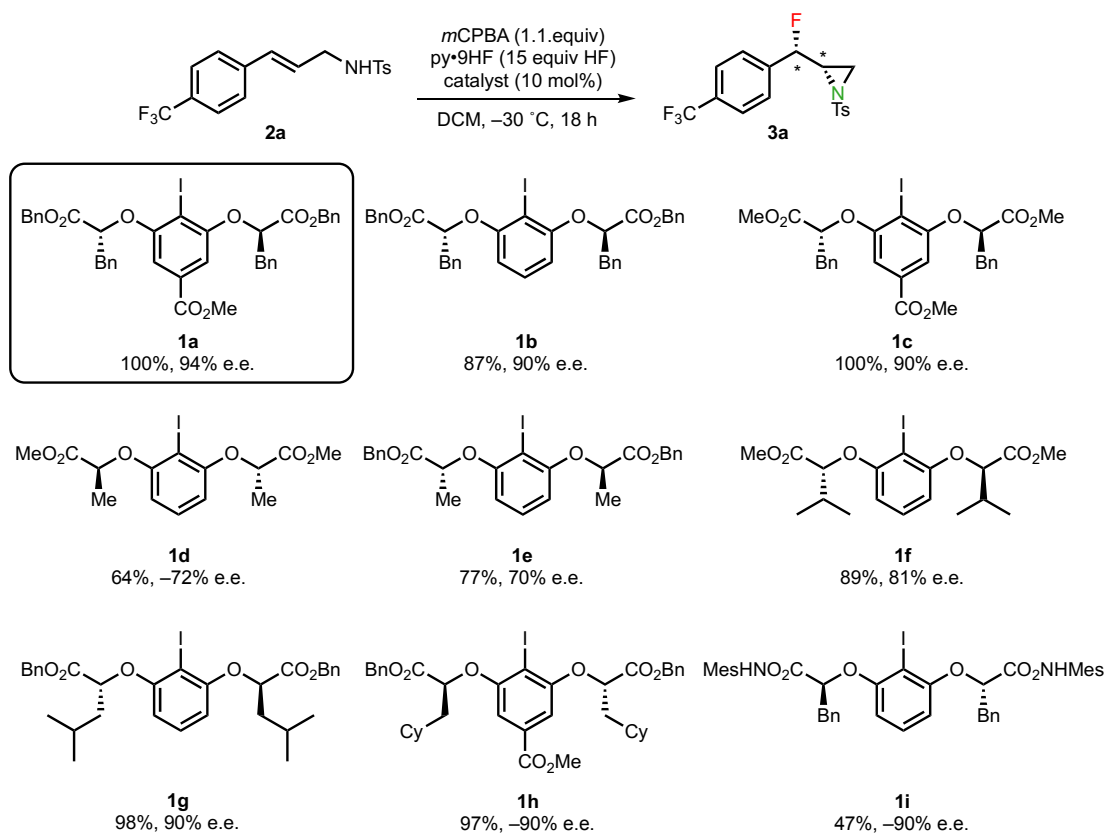
Signal 4: DAD1 D, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.384	BV	0.3592	1177.55298	47.84172	3.0421
2	17.060	VB	0.5720	3.75315e4	927.64667	96.9579

Totals : 3.87090e4 975.48839

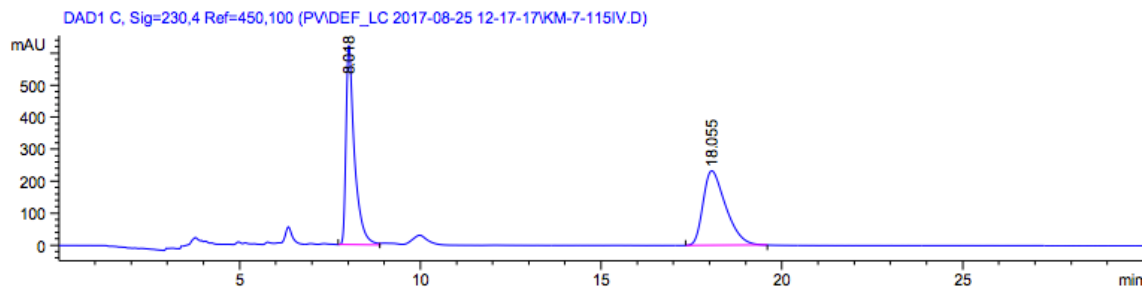
General procedure for catalyst optimization

Catalyst (**1a–i**, 5.2 μmol , 10.0 mol%), *p*-trifluoromethyl-cinnamyl tosylamide (**2a**, 17.8 mg, 52.0 μmol , 1.00 equiv) and DCM (0.30 mL) were combined in a polyethylene tube. The reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$. Pyridinium poly(hydrogen fluoride) (pyr•9HF, 70% hydrogen fluoride by weight, 21 μL , 15 equiv HF) was added *via* micropipette followed by *m*CPBA (77% by weight, 12.8 mg, 57.2 μmol , 1.10 equiv). The reaction was warmed to $-30\text{ }^{\circ}\text{C}$ and stirred for 18 hours. The reaction was cooled to $-78\text{ }^{\circ}\text{C}$ and basic alumina (approximately 750 mg) was added slowly. The reaction was allowed to warm to room temperature with stirring and was filtered. The crude mixture was analyzed by ^1H NMR using mesitylene as an internal standard to determine the yield of product and by chiral HPLC to determine the enantioselectivity.



Scheme S2.2 Catalyst optimization

Racemic sample:



Signal 3: DAD1 C, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.018	VV	0.2370	1.01980e4	622.86884	50.0240
2	18.055	BB	0.6560	1.01882e4	233.07854	49.9760

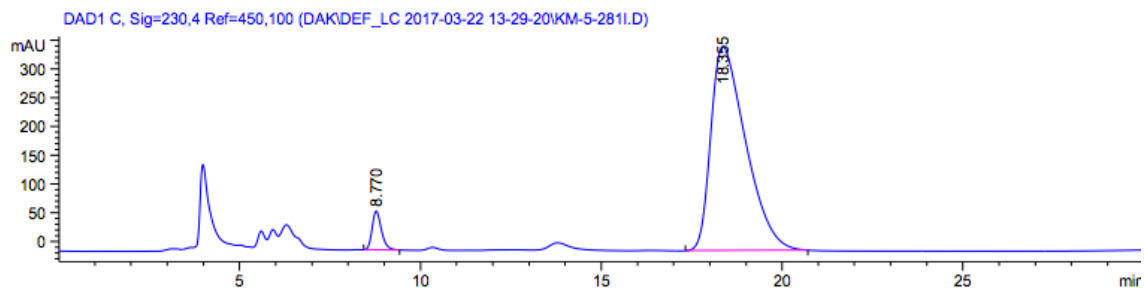
Totals : 2.03862e4 855.94737

Catalyst 1b

90% e.e., chiral HPLC (OJ-H, 50% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230$ nm); t_R (minor)

= 8.8 min, t_R (major) = 18.4 min.

Enriched sample:



Signal 3: DAD1 C, Sig=230,4 Ref=450,100

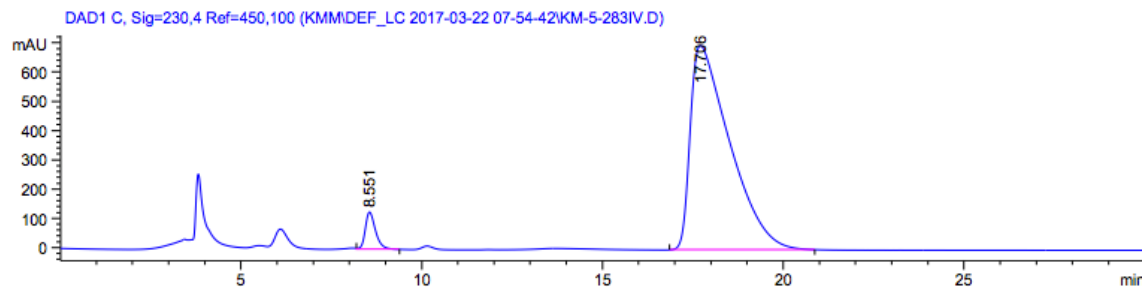
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.770	BB	0.2757	1213.22131	67.48472	4.8392
2	18.355	BB	1.0173	2.38577e4	355.32098	95.1608

Totals : 2.50710e4 422.80570

Catalyst **1c**

90% e.e., chiral HPLC (OJ-H, 50% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230$ nm); $t_R(\text{minor})$ = 8.6 min, $t_R(\text{major})$ = 17.8 min.

Enriched sample:



Signal 3: DAD1 C, Sig=230,4 Ref=450,100

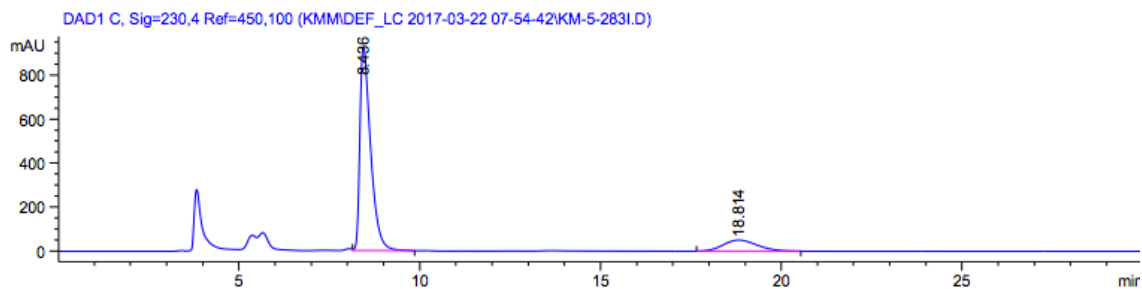
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.551	VB	0.3020	2536.97534	127.57331	4.5663
2	17.706	BB	1.0779	5.30214e4	698.23096	95.4337

Totals : 5.55584e4 825.80427

Catalyst **1d**

–72% e.e., chiral HPLC (OJ-H, 50% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230$ nm); $t_R(\text{major})$ = 8.5 min, $t_R(\text{minor})$ = 18.8 min.

Enriched sample:



Signal 3: DAD1 C, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.436	VB	0.3109	1.91469e4	927.42902	85.2549
2	18.814	BB	0.9450	3311.52393	50.23888	14.7451

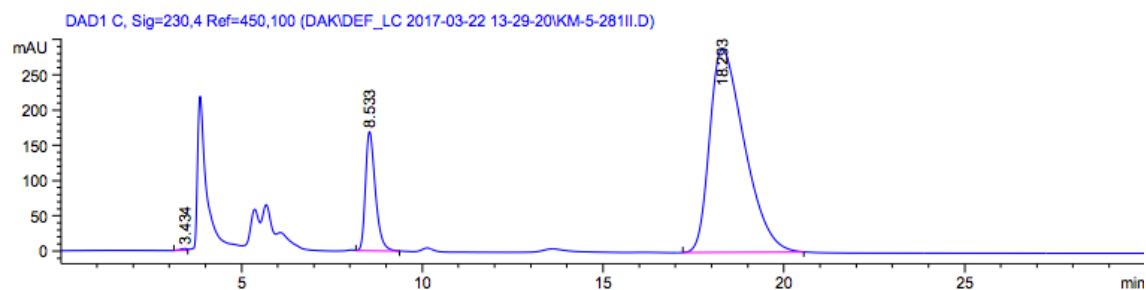
Totals : 2.24585e4 977.66790

Catalyst 1e

70% e.e., chiral HPLC (OJ-H, 50% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230$ nm); t_R (minor)

= 8.5 min, t_R (major) = 18.3 min.

Enriched sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.434	BV	0.1567	37.35361	3.14161	0.1649
2	8.533	VB	0.2937	3248.10229	169.38814	14.3349
3	18.293	BB	1.0055	1.93732e4	289.22510	85.5002

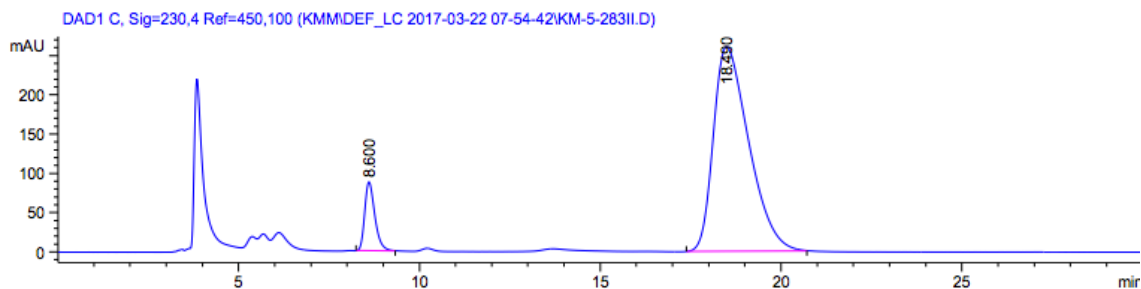
Totals : 2.26587e4 461.75485

Catalyst 1f

81% e.e., chiral HPLC (OJ-H, 50% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230$ nm); t_R (minor)

= 8.6 min, t_R (major) = 18.5 min.

Enriched sample:



Signal 3: DAD1 C, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.600	BB	0.2998	1710.93127	87.63212	8.8052
2	18.490	BB	1.0313	1.77199e4	260.59326	91.1948

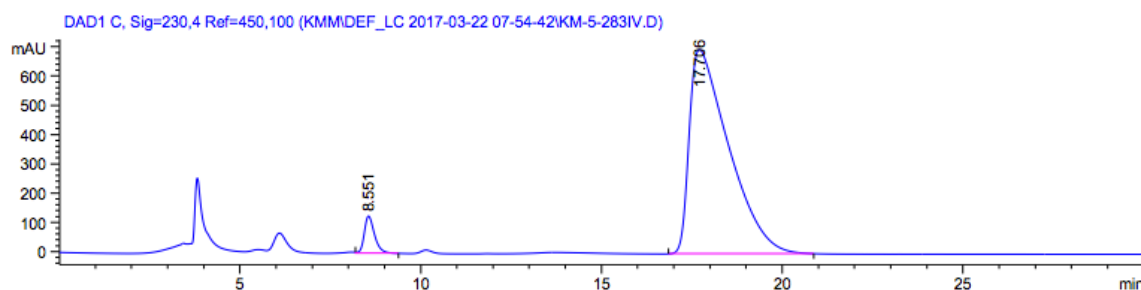
Totals : 1.94309e4 348.22538

Catalyst **1g**

90% e.e., chiral HPLC (OJ-H, 50% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230$ nm); t_R (minor)

= 8.6 min, t_R (major) = 17.8 min.

Enriched sample:



Signal 3: DAD1 C, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.551	VB	0.3020	2536.97534	127.57331	4.5663
2	17.706	BB	1.0779	5.30214e4	698.23096	95.4337

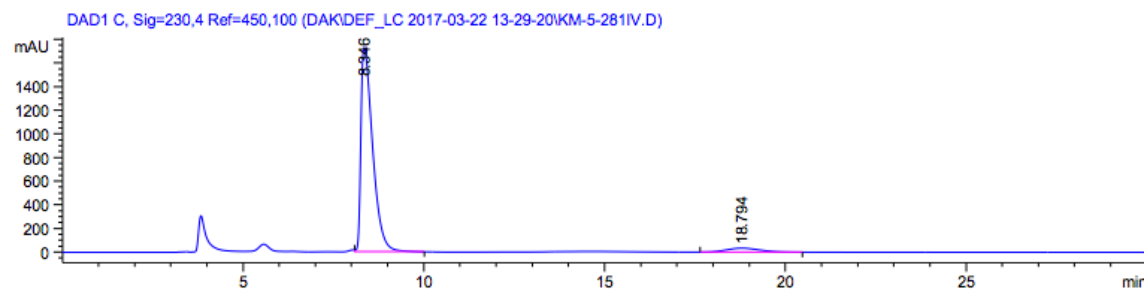
Totals : 5.55584e4 825.80427

Catalyst **1h**

–90% e.e., chiral HPLC (OJ-H, 50% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230$ nm); t_R (major)

= 8.3 min, t_R (minor) = 18.8 min.

Enriched sample:



Signal 3: DAD1 C, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.346	VB	0.3451	3.89807e4	1728.34973	94.7775
2	18.794	BB	0.9057	2147.95630	33.33636	5.2225

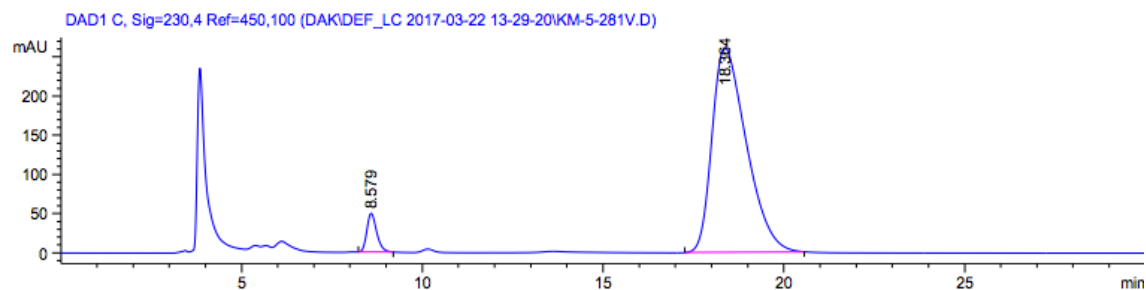
Totals : 4.11286e4 1761.68610

Catalyst 1i

–90% e.e., chiral HPLC (OJ-H, 50% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230$ nm); t_R (major)

= 8.3 min, t_R (minor) = 18.8 min.

Enriched sample:



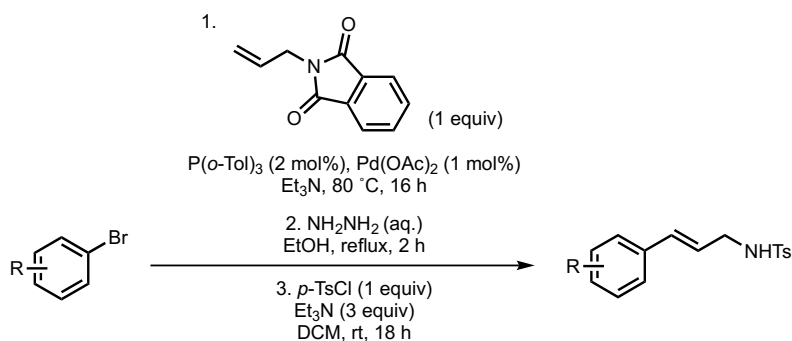
Signal 3: DAD1 C, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.579	BB	0.2904	941.48804	49.37883	5.1649
2	18.364	BB	0.9916	1.72872e4	261.39069	94.8351

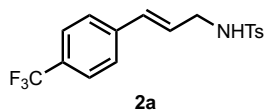
Totals : 1.82287e4 310.76952

Synthesis of Substrates

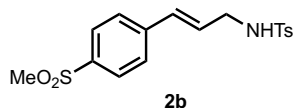
General Procedure A:



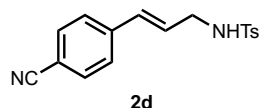
To a suspension of aryl bromide (5.50 mmol, 1 equiv), 2-allylisoindoline-1,3-dione (1.03 g, 5.50 mmol, 1.0 equiv) and tri(*o*-tolyl)phosphine (33.5 mg, 0.11 mmol, 2 mol%) in anhydrous triethylamine (4.0 mL) was added palladium(II) acetate (12.7 mg, 0.057 mmol, 1 mol%). The reaction mixture was stirred at 80 °C for 16 hours. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (100 mL), washed with water (20 mL), dried over NaSO_4 , filtered and concentrated under reduced pressure. The crude residue was added to a solution of ethanol (40 mL) and hydrazine hydrate (~80% in water, 2 mL) and heated under reflux for 2 hours. After cooling, the suspension was filtered, washing with cold ethanol. The filtrate was concentrated under reduced pressure, re-dissolved in ethyl acetate (50 mL), washed with 1 M NaOH (aq.) (2 x 20 mL) and brine (10 mL), dried over NaSO_4 , filtered and concentrated under reduced pressure. The crude residue was dissolved in dichloromethane (22 mL). Triethylamine (2.3 mL, 16.5 mmol, 3 equiv) followed by *p*-toluenesulfonyl chloride (1.05 g, 5.50 mmol, 1 equiv). The resulting solution was stirred at room temperature. After 18 hours, the reaction mixture was washed with brine (10 mL), dried over NaSO_4 , filtered and concentrated under reduced pressure.



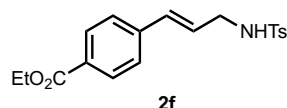
Prepared according to general procedure A using 1-bromo-4-(trifluoromethyl)benzene (0.77 mL, 5.50 mmol). The crude residue was purified by silica gel column chromatography (10 to 100% ethyl acetate in hexanes) to give **2a** (1.45 g, 74% overall yield) as a yellow solid. ^1H NMR (500 MHz, CDCl_3): δ 7.80 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.3 Hz, 2H), 7.41–7.27 (m, 4H), 6.48 (dd, J = 15.9, 1.6 Hz, 1H), 6.12 (dt, J = 15.9, 6.1 Hz, 1H), 5.20 (t, J = 6.3 Hz, 1H), 3.78 (td, J = 6.2, 1.6 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 143.8, 139.8, 137.1, 131.4, 129.9, 129.7 (q, J = 32.3 Hz), 127.3, 127.2, 126.7, 125.6 (q, J = 3.8 Hz), 124.2 (q, J = 271.8 Hz), 83.39–74.57 (m), 45.3, 21.5; ^{19}F NMR (470.4 MHz, CDCl_3): δ -62.6 (s); FTIR (thin film) ν 3259 (w), 1715 (w), 1370 (s), 1159 (s), 906 (s), 728 (s), 552 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{17}\text{H}_{16}\text{F}_3\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 356.0927; found 356.0920.



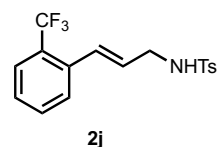
Prepared according to general procedure A using 4-bromophenyl methyl sulfone (1.29 g, 5.50 mmol). The crude residue was purified by silica gel column chromatography (10 to 100% ethyl acetate in hexanes) to give **2b** (1.38 g, 68% overall yield) as a yellow solid. ^1H NMR (500 MHz, CDCl_3): δ 7.88–7.69 (m, 4H), 7.33 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.47 (dd, J = 15.9, 1.9 Hz, 1H), 6.17 (ddd, J = 16.0, 6.8, 5.1 Hz, 1H), 5.28 (t, J = 6.3 Hz, 1H), 3.75 (td, J = 6.2, 1.6 Hz, 2H), 3.03 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 143.7, 141.8, 139.2, 137.1, 130.7, 129.9, 129.0, 127.7, 127.3, 127.1, 45.1, 44.6, 21.6; FTIR (thin film) ν 3270 (br. s), 1596 (m), 1294 (s), 1146 (s), 959 (m), 550 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{17}\text{H}_{19}\text{NO}_4\text{S}_2$ $[\text{M}+\text{H}]^+$: 366.0828; found 366.0826.



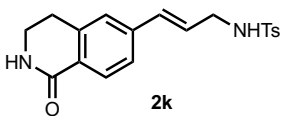
Prepared according to general procedure A using 4-bromobenzonitrile (1.00 g, 5.50 mmol). The crude residue was purified by silica gel column chromatography (10 to 100% ethyl acetate in hexanes) to give **2d** (1.43 g, 81% overall yield) as a yellow solid. ¹H NMR (500 MHz, CDCl₃): δ 7.74 (d, *J* = 8.3 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.22 (dd, *J* = 8.1, 4.9 Hz, 3H), 6.41 (d, *J* = 15.9 Hz, 1H), 6.11 (dt, *J* = 15.9, 6.0 Hz, 1H), 5.54 (t, *J* = 6.3 Hz, 1H), 3.84–3.59 (m, 1H), 2.32 (s, 2H); ¹³C NMR (125.7 MHz, CDCl₃): δ 143.5, 140.8, 136.9, 132.2, 130.6, 129.7, 128.6, 127.1, 126.8, 118.8, 110.6, 44.9, 21.4; FTIR (thin film) ν 3272 (br. s), 2225 (m), 1604 (m), 1322 (s), 1153 (s), 661 (s), 549 (s) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₇H₁₆N₂O₂S [M+H]⁺: 313.1005; found 313.1004.



Prepared according to general procedure A using ethyl 4-bromobenzoate (0.9 mL, 5.50 mmol). The crude residue was purified by silica gel column chromatography (10 to 100% ethyl acetate in hexanes) to give **2f** (1.52 g, 77% overall yield) as a white solid. ¹H NMR (500 MHz, CDCl₃): δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.87–7.70 (m, 2H), 7.46–7.18 (m, 4H), 6.65–6.35 (m, 1H), 6.13 (ddd, *J* = 16.0, 6.8, 5.5 Hz, 1H), 4.90 (t, *J* = 6.3 Hz, 1H), 4.56–4.16 (m, 2H), 4.01–3.59 (m, 2H), 2.42 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 2H); ¹³C NMR (125.7 MHz, CDCl₃): δ 166.4, 143.7, 140.6, 137.2, 132.0, 130.0, 129.9, 129.8, 127.3, 127.1, 126.4, 61.1, 45.4, 21.6, 14.5; FTIR (thin film) ν 3241 (m), 1697 (s), 1293 (s), 1154 (s), 981 (m), 581 (s) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₉H₂₁NO₄S [M+H]⁺: 360.1264; found 360.1261.



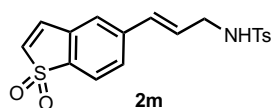
Prepared according to general procedure A using 1-bromo-2-(trifluoromethyl)benzene (0.75 mL, 5.50 mmol). The crude residue was purified by silica gel column chromatography (10 to 100% ethyl acetate in hexanes) to give **2j**

 **2k**

Prepared according to general procedure A using 6-bromo-3,4-dihydroisoquinolin-1(2H)-one (1.24 g, 5.50 mmol). The crude residue was purified by recrystallization from methanol to give **2k** (1.18 g, 60% overall yield) as a white solid. ^1H NMR (500 MHz, DMSO- d_6): δ 7.93–7.82 (m, 2H), 7.76 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.27–7.22 (m, 1H), 7.19 (s, 1H), 6.65–6.36 (m, 1H), 6.16 (dt, J = 15.9, 5.9 Hz, 1H), 3.59 (s, 2H), 3.35 (dt, J = 6.7, 3.2 Hz, 2H), 2.85 (t, J = 6.5 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (125.7 MHz, DMSO- d_6): δ 64.3, 142.6, 139.6, 139.4, 137.9, 130.3, 129.6, 128.4, 127.8, 127.4, 126.6, 125.0, 124.4, 45.5, 44.5, 27.7, 20.9; FTIR (thin film) ν 1653 (s), 1156 (s), 845 (m), 550 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$: 357.1267; found 357.1273.

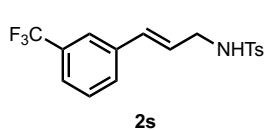


was added and the reaction mixture was stirred at room temperature. After 16 hours, the reaction mixture was washed with sat. NaHCO₃ (aq.) (3 x 10 mL) and brine (10 mL), dried over NaSO₄, filtered, concentrate under reduced pressure and purified by silica gel column chromatography (0 to 10% methanol in dichloromethane) to give **2l** (1.15 g, 55%) as white solid. ¹H NMR (500 MHz, CD₃OD): δ 8.35 (d, *J* = 7.3 Hz, 2H), 7.86 (d, *J* = 7.3 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.39–7.34 (m, 2H), 6.50 (d, *J* = 16.0 Hz, 1H), 6.16 (dt, *J* = 15.8, 6.1 Hz, 1H), 3.70 (dd, *J* = 6.1, 1.6 Hz, 2H), 2.39 (s, 3H); ¹³C NMR (125.7 MHz, 5% CD₃CO₂D/CDCl₃): δ 143.5, 141.9, 139.7, 137.9, 137.2, 134.5, 131.4, 129.8, 127.4, 127.2, 126.8, 126.7, 123.5, 45.2, 21.6; FTIR (thin film) ν 3051 (br. s), 1711 (br. s), 1479 (m), 1155 (s), 844 (m), 569 (m) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₂₁H₂₀N₂O₃S [M+H]⁺: 381.1267; found 381.1261.

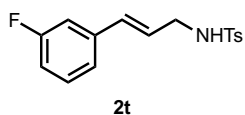


Prepared according to general procedure A using 5-bromobenzo[*b*]thiophene (1.17 g, 5.50 mmol). The crude residue was dissolved in dichloromethane (22 mL). *m*CPBA (77% by weight, 2.70 g, 11.0 mmol, 1.0 equiv) was added and the reaction mixture was stirred at room temperature. After 16 hours, the reaction mixture was washed with sat. NaHCO₃ (aq.) (3 x 10 mL) and brine (10 mL), dried over NaSO₄, filtered, concentrate under reduced pressure and purified by silica gel column chromatography (10 to 100% ethyl acetate in hexanes) to give **2m** (1.49, 72%) as white solid. ¹H NMR (500 MHz, 10% CD₃OD/CDCl₃): δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.24–7.08 (m, 5H), 6.64 (d, *J* = 6.9 Hz, 1H), 6.34 (d, *J* = 15.9 Hz, 1H), 6.05 (dt, *J* = 15.9, 5.9 Hz, 1H), 3.70 (s, 1H), 3.59 (dd, *J* = 5.9, 1.6 Hz, 2H), 2.26 (s, 3H); ¹³C NMR (125.7 MHz, 10% CD₃OD/CDCl₃): δ 143.5, 142.3, 136.9, 134.8, 132.5, 131.8, 130.8, 129.9, 129.6, 129.1, 128.5, 126.9, 122.9, 121.3,

44.6, 21.2; FTIR (thin film) ν 3279 (br. m), 1599 (w), 1291 (s), 1138 (s), 730 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{18}\text{H}_{17}\text{NO}_4\text{S}_2$ $[\text{M}+\text{H}]^+$: 376.0672; found 376.0666.

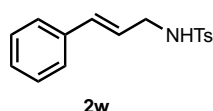


Prepared according to general procedure A using 1-bromo-3-(trifluoromethyl)benzene (0.77 mL, 5.50 mmol). The crude residue was purified by silica gel column chromatography (10 to 100% ethyl acetate in hexanes) to give **2s** (1.41 g, 72% overall yield) as a white solid. ^1H NMR (500 MHz, CDCl_3): δ 7.80 (dd, J = 8.1, 1.3 Hz, 2H), 7.48–7.44 (m, 1H), 7.42–7.36 (m, 3H), 7.27 (d, J = 7.6 Hz, 2H), 6.45 (dd, J = 15.9, 1.5 Hz, 1H), 6.06 (dtd, J = 15.9, 6.2, 1.2 Hz, 1H), 5.35 (t, J = 6.2 Hz, 1H), 3.96–3.62 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 43.7, 137.2, 137.1, 131.3, 130.9 (q, J = 32.1 Hz), 129.8, 129.7, 127.3, 124.3 (q, J = 3.8 Hz), 123.9 (q, J = 272.3 Hz), 123.0 (q, J = 3.9 Hz), 45.2, 21.4; ^{19}F NMR (470.4 MHz, CDCl_3): δ -62.87 (s); FTIR (thin film) ν 3277 (br. s), 1598 (w), 1328 (s), 1154 (s), 965 (m), 661 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{17}\text{H}_{16}\text{F}_3\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 356.0927; found 356.0923.



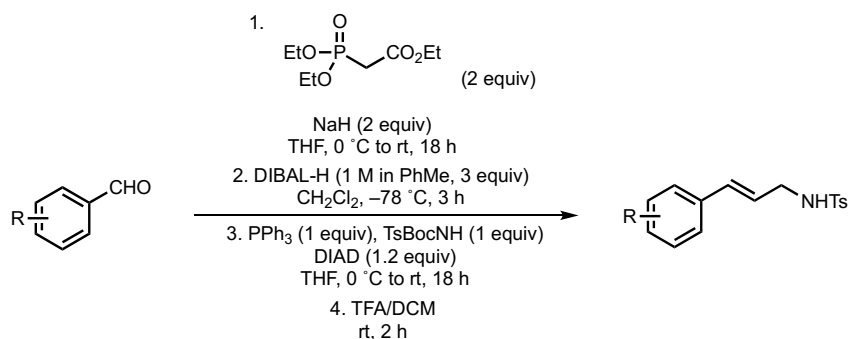
Prepared according to general procedure A using 1-bromo-3-fluorobenzene (0.77 mL, 5.50 mmol). The crude residue was purified by silica gel column chromatography (10 to 100% ethyl acetate in hexanes) to give **2t** (1.68 g, 78% overall yield) as a white solid. ^1H NMR (500 MHz, CDCl_3): δ 7.79 (d, J = 8.3 Hz, 2H), 7.37–7.15 (m, 3H), 7.09–6.79 (m, 3H), 6.38 (d, J = 15.8 Hz, 1H), 5.98 (dt, J = 15.9, 6.2 Hz, 1H), 5.25 (t, J = 6.2 Hz, 1H), 3.74 (td, J = 6.2, 1.6 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 163.0 (d, J = 245.2 Hz), 143.6, 138.6 (d, J = 8.0 Hz), 137.1, 131.6 (d, J = 2.8 Hz), 130.0 (d, J = 8.4 Hz), 129.8, 127.3, 125.8, 122.4 (d, J = 3.0 Hz), 114.6 (d, J = 21.4 Hz), 112.8 (d, J = 22.0 Hz), 45.2,

21.5; ^{19}F NMR (470.4 MHz, CDCl_3): δ -113.36 (td, J = 9.1, 5.9 Hz); FTIR (thin film) ν 3275 (br. s), 1583 (m), 1092 (s), 964 (m), 661 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{16}\text{H}_{16}\text{FNO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 306.0959; found 306.0953.



Prepared according to general procedure A using bromobenzene (0.77 mL, 5.50 mmol). The crude residue was purified by silica gel column chromatography (10 to 100% ethyl acetate in hexanes) to give **2w** (1.19 g, 75% overall yield) as a white solid. ^1H NMR (500 MHz, CDCl_3): δ 7.79 (d, J = 8.3 Hz, 2H), 7.32–7.17 (m, 7H), 6.43 (dd, J = 15.8, 1.6 Hz, 1H), 6.00 (dtd, J = 15.9, 6.4, 1.7 Hz, 1H), 5.04 (t, J = 6.4 Hz, 1H), 3.74 (td, J = 6.3, 1.6 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 143.6, 137.2, 136.2, 133.0, 129.8, 128.6, 127.9, 127.3, 126.5, 124.2, 45.5, 21.6; FTIR (thin film) ν 3278 (br. s), 1598 (w), 1324 (m), 1157 (s), 967 (m), 493 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{16}\text{H}_{17}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 288.1053; found 288.1047.

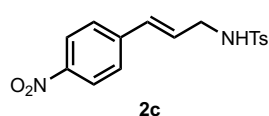
General Procedure B:



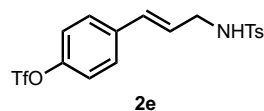
To a solution of triethyl phosphonoacetate (2.78 mL, 14.0 mmol, 2.0 equiv) in anhydrous tetrahydrofuran (28 mL) at 0 °C was added sodium hydride (60% by weight, 560 mg, 14.0 mmol, 2.0 equiv). The reaction mixture was stirred at that temperature for 30 minutes before the

addition of benzaldehyde (7.00 mmol, 1.0 equiv) as a solution in tetrahydrofuran (5 mL). The resulting solution was allowed to warm to room temperature. After 18 hours, the reaction mixture was quenched with 1 M HCl (aq.) (10 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over NaSO₄, filtered and concentrate under reduced pressure. The crude residue was dissolved in anhydrous dichloromethane (28 mL) and cooled to -78 °C. Diisobutylaluminum hydride (1.0 M in toluene, 21.0 mmol, 3.0 equiv) was added dropwise, and reaction mixture was stirred at -78 °C for 3 hours. The reaction was quenched with a 1:1 mixture of 4 M NaOH (aq.) and sat. Rochelle salt solution (aq.) (20 mL), and the reaction mixture was allowed to warm to room temperature. The organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 40 mL). The combined organic layers were washed with brine (20 mL), dried over NaSO₄, filtered and concentrated under reduced pressure. The crude residue was dissolved in anhydrous tetrahydrofuran (28 mL) at 0 °C. Triphenylphosphine (1.84 g, 7.00 mmol, 1.0 equiv) and *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (1.90 g, 7.00 mmol, 1.0 equiv) were added followed by diisopropyl azodicarboxylate (1.65 mL, 8.40 mmol, 1.2 equiv). The reaction mixture was allowed to warm to room temperature. After 18 hours, the reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (10 to 100% diethyl ether in hexanes). To a solution of the retrieved compound in dichloromethane (8 mL) was added trifluoroacetic acid (2 mL). The reaction mixture was stirred at room temperature for 2 hours. 1 M NaOH (aq.) was added until the pH registered as neutral. The organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The

combined organic layers were washed with brine (10 mL), dried over NaSO₄, filtered and concentrated under reduced pressure.

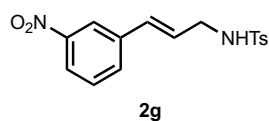


Prepared according to general procedure B using 4-nitrobenzaldehyde (1.06 mg, 7.00 mmol) to give **2c** (1.83 g, 79% overall yield) as a yellow solid. ¹H NMR (500 MHz, CDCl₃): δ 8.11 (d, *J* = 8.9 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.32–7.24 (m, 1H), 6.53 (d, *J* = 16.0 Hz, 1H), 6.22 (dt, *J* = 15.9, 6.0 Hz, 1H), 5.21 (t, *J* = 6.3 Hz, 1H), 3.80 (td, *J* = 6.1, 1.6 Hz, 2H), 2.40 (s, 2H); ¹³C NMR (125.7 MHz, CDCl₃): δ 147.1, 143.8, 142.8, 137.0, 130.5, 129.9, 129.6, 127.3, 127.0, 124.0, 45.1, 21.6; FTIR (thin film) ν 3279 (br. m), 1597 (m), 1515 (s), 1341 (s), 1158 (s), 551 (m) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₆H₁₆N₂O₄S [M+H]⁺: 333.0904; found 333.0915.

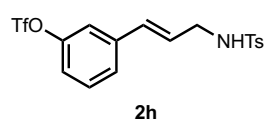


Prepared according to general procedure B using 4-formylphenyl trifluoromethanesulfonate⁴⁰ (1.78 g, 7.00 mmol) to give **2e** (2.04 g, 67% overall yield). ¹H NMR (500 MHz, CDCl₃): δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 4H), 7.17 (d, *J* = 8.7 Hz, 2H), 6.44 (d, *J* = 15.9 Hz, 1H), 6.04 (ddd, *J* = 15.9, 6.5, 5.7 Hz, 1H), 5.22 (t, *J* = 6.2 Hz, 1H), 3.76 (td, *J* = 6.2, 1.4 Hz, 2H), 2.39 (s, 3H); ¹³C NMR (125.7 MHz, CDCl₃): δ 148.9, 143.8, 137.1, 136.8, 129.9, 128.1, 127.2, 126.7, 121.5, 118.8 (q, *J* = 321.0 Hz), 45.2, 21.5; ¹⁹F NMR (470.4 MHz, CDCl₃): δ -72.8 (s); FTIR (thin film) ν 3274 (br. m), 1598 (w), 1500 (m), 1422 (s), 1093 (s), 885 (s), 551 (m) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₇H₁₆F₃NO₅S₂ [M+H]⁺: 436.0495; found 436.0490.

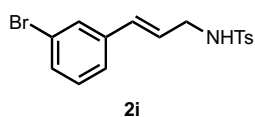
⁴⁰ Gasparini, F.; Inderbitzin, W.; Francotte, E.; Lecis, G.; Richert, P.; Dragic, Z.; Kuhn, R.; Flor, P.J. *Bioorganic & Medicinal Chemistry Letters* **2000**, *10*, 1241–1244.



Prepared according to general procedure B using 3-nitrobenzaldehyde (1.06 mg, 7.00 mmol) to give **2g** (1.74 g, 75% overall yield) as a yellow solid. ^1H NMR (500 MHz, CDCl_3): δ 8.03 (d, J = 8.3 Hz, 1H), 7.99 (s, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.3 Hz, 1H), 7.46–7.39 (m, 1H), 7.29 (d, J = 8.3 Hz, 2H), 6.49 (d, J = 15.9 Hz, 1H), 6.25–6.08 (m, 1H), 5.30 (s, 1H), 4.14–3.28 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 148.5, 143.8, 138.1, 137.1, 132.3, 130.3, 129.9, 129.5, 127.9, 127.3, 122.4, 121.0, 45.0, 21.5; FTIR (thin film) ν 3279 (br. s), 1598 (w), 1526 (s), 1350 (s), 1157 (s), 815 (m), 550 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 333.0904; found 333.0900.



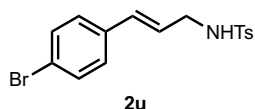
Prepared according to general procedure B using 3-formylphenyl trifluoromethanesulfonate⁴¹ (1.78 g, 7.00 mmol) to give **2h** (2.16 g, 67% overall yield) as white solid. ^1H NMR (500 MHz, CDCl_3): δ 7.79 (d, J = 8.3 Hz, 2H), 7.34 (t, J = 8.0 Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.26–7.20 (m, 1H), 7.16–7.07 (m, 2H), 6.43 (dd, J = 15.9, 1.7 Hz, 1H), 6.06 (dt, J = 15.8, 6.1 Hz, 1H), 5.26 (t, J = 6.3 Hz, 1H), 3.77 (td, J = 6.2, 1.6 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 149.9, 143.8, 139.1, 137.1, 130.7, 130.4, 129.9, 127.3, 127.3, 126.4, 120.3, 119.0, 118.8 (q, J = 321.1 Hz), 45.1, 21.5; ^{19}F NMR (470.4 MHz, CDCl_3): δ -72.9 (s); FTIR (thin film) ν 3277 (br. m), 1599 (w), 1419 (s), 1208 (s), 844 (s), 571 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{17}\text{H}_{16}\text{F}_3\text{NO}_5\text{S}_2$ $[\text{M}+\text{H}]^+$: 436.0495; found 436.0487.



Prepared according to general procedure B using 3-bromobenzaldehyde (1.30 g, 7.00 mmol) to give **2i** (1.95 g, 76% overall yield) as a white solid. ^1H NMR (500 MHz, CDCl_3): δ 7.79 (d, J = 8.3 Hz, 2H), 7.38–7.25 (m, 4H), 7.17–7.08 (m, 2H),

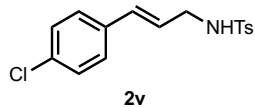
⁴¹ Hackenberger, D.; Song, B.; Gruenberg, M.F.; Farsadpour, S.; Menges, F.; Kelm, H.; Gross, C.; Wolff, T.; Niedner-Schatteburg, G.; Thiel, W.R.; Goossen, L.J. *ChemCatChem* **2015**, 7, 3579–3588.

6.34 (dd, $J = 15.9, 1.6$ Hz, 1H), 5.97 (dt, $J = 15.9, 6.2$ Hz, 1H), 5.21 (t, $J = 6.3$ Hz, 1H), 3.75 (td, $J = 6.2, 1.6$ Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 143.7, 138.5, 137.2, 131.3, 130.7, 130.1, 129.8, 129.3, 127.3, 126.0, 125.2, 122.7, 45.2, 21.6; FTIR (thin film) ν 3274 (br. s), 1592 (w), 1323 (m), 1154 (s), 814 (m), 572 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{16}\text{H}_{16}\text{BrNO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 366.0158; found 366.0149.



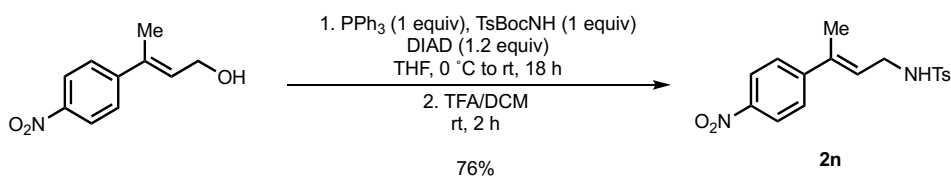
Prepared according to general procedure B using 4-bromobenzaldehyde (1.30 g, 7.00 mmol) to give **2u** (2.07 g, 81% overall yield) as a white solid.

^1H NMR (500 MHz, CDCl_3): δ 7.77 (d, $J = 8.3$ Hz, 2H), 7.38 (d, $J = 8.5$ Hz, 2H), 7.27 (d, $J = 7.8$ Hz, 2H), 7.07 (d, $J = 8.5$ Hz, 2H), 6.36 (dd, $J = 15.9, 1.8$ Hz, 1H), 5.99 (dtd, $J = 15.8, 6.2, 1.5$ Hz, 1H), 5.08 (s, 1H), 3.74–3.70 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 143.6, 137.1, 135.2, 131.7, 129.8, 127.3, 125.2, 121.7, 45.4, 21.6; FTIR (thin film) ν 3260 (br. s), 1598 (w), 1487 (m), 1320 (m), 1156 (s), 811 (m), 575 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{16}\text{H}_{16}\text{BrNO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 365.0080; found 365.0078.



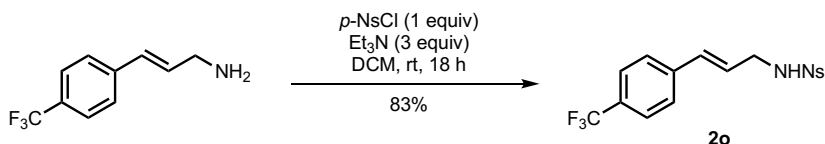
Prepared according to general procedure B using 4-chlorobenzaldehyde (1.30 g, 7.00 mmol) to give **2v** (1.87 g, 83% overall yield) as a white solid.

^1H NMR (500 MHz, CDCl_3): δ 7.81–7.76 (m, 2H), 7.30–7.26 (m, 2H), 7.25–7.21 (m, 2H), 7.18–7.11 (m, 2H), 6.38 (dd, $J = 15.8, 1.7$ Hz, 1H), 6.11–5.82 (m, 1H), 5.10 (s, 1H), 3.71–3.75 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 43.6, 137.1, 134.8, 133.5, 131.7, 129.8, 128.7, 127.7, 127.3, 125.0, 45.4, 21.6; FTIR (thin film) ν 3275 (br. s), 1597 (w), 1491 (s), 1154 (s), 967 (m), 550 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{16}\text{H}_{16}\text{ClNO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 321.0585; found 321.0585.



(*E*)-3-(4-Nitrophenyl)but-2-en-1-ol⁴² (965 g, 5.00 mmol, 1.0 equiv) was dissolved in anhydrous tetrahydrofuran (50 mL) at 0 °C. Triphenylphosphine (1.32 g, 5.00 mmol, 1.0 equiv) and *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (1.36 g, 5.00 mmol, 1.0 equiv) were added followed by diisopropyl azodicarboxylate (1.18 mL, 6.0 mmol, 1.2 equiv). The reaction mixture was allowed to warm to room temperature. After 18 hours, the reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (10 to 100% diethyl ether in hexanes). To a solution of the retrieved compound in dichloromethane (8 mL) was added trifluoroacetic acid (2 mL). The reaction mixture was stirred at room temperature for 2 hours. 1 M NaOH (aq.) was added until the pH registered as neutral. The organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, concentrated under reduced pressure and purified by silica gel column chromatography (10 to 100% diethyl ether in hexanes) to give **2n** (1.32 g, 76%) as a yellow solid. ¹H NMR (500 MHz, CDCl₃): δ 8.08 (d, *J* = 8.7 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.37–7.25 (m, 4H), 5.77–5.71 (m, 1H), 5.37 – 5.31 (m, 1H), 3.89–3.74 (m, 2H), 2.40 (s, 3H), 1.97 (s, 3H); ¹³C NMR (125.7 MHz, CDCl₃): δ 148.9, 146.9, 143.7, 137.1, 137.0, 129.8, 127.3, 126.5, 126.4, 123.5, 41.7, 21.6, 15.9; FTIR (thin film) ν 3277 (br. m), 1595 (m), 1512 (s), 1341 (s), 1155(s), 666 (m) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₇H₁₈N₂O₄S [M+H]⁺: 347.1060; found 347.1054.

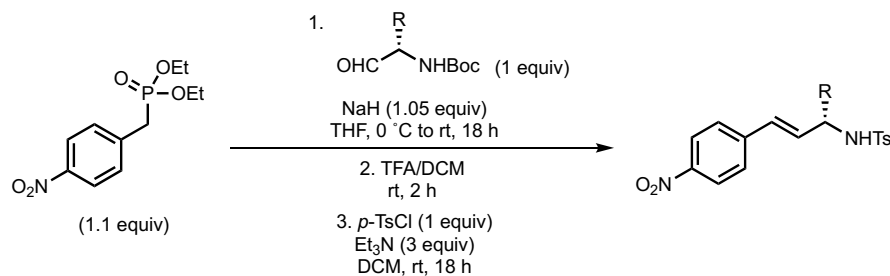
⁴² Li, J-Q; Liu, J.; Krajangsri, S.; Chumnanvej, N.; Singh, T.; Andersson, P.G. *ACS Catalysis* **2016**, 6, 8342–8349.



To a solution of (*E*)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-amine⁴³ (302 mg, 1.50 mmol, 1 equiv) in dichloromethane (7.5 mL) was added triethylamine (0.63 mL, 4.50 mmol, 3 equiv) followed by 4-nitrobenzenesulfonyl chloride (332 mg, 1.50 mmol, 1 equiv). The reaction mixture was allowed to stir at room temperature overnight before being quenched by 1 M HCl (aq.) (3 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered, concentrated under reduced pressure and purified by silica gel column chromatography (20 to 70% ethyl acetate in hexanes) to give **2o** (481 mg, 83%) as a yellow solid. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.37 (d, *J* = 7.8 Hz, 2H), 8.16-8.10 (m, 2H), 8.10-8.04 (m, 2H), 7.56 (d, *J* = 7.8 Hz, 2H), 6.59 (d, *J* = 16.4 Hz, 1H), 6.38-6.29 (m, 1H), 4.83-4.72 (m, 1H), 3.78-3.67 (m, 2H); ¹³C NMR (125.7 MHz, DMSO-*d*₆): δ ¹³C NMR (DMSO-*d*₆) 156.2, 149.5, 146.4, 142.8, 130.6, 129.5, 128.2, 127.1, 124.6, 123.8, 123.7 (q, *J* = 272.4 Hz), 44.6; ¹⁹F NMR (CDCl₃) -62.8 (s); HRMS (ESI-TOF) Calc'd for C₁₆H₁₃F₃N₂O₄S [M+H]⁺: 387.0632; found 387.0630.

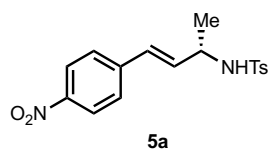
⁴³ Chen, C.; Jin, S.; Zhang, Z.; Wei, B.; Wang, H.; Zhang, K.; Lv, H.; Dong, X-H; Zhang, X. *J. Am. Chem. Soc.* **2016**, *138*, 9017–9020.

General Procedure C:



To a solution of diethyl (4-nitrobenzyl)phosphonate ⁴⁴ (901 mg, 3.30 mmol, 1.1 equiv) in anhydrous tetrahydrofuran (12 mL) at 0 °C was added sodium hydride (60% by weight, 119 mg, 2.99 mmol, 1.0 equiv). The reaction mixture was allowed to stir at 0 °C for 30 minutes before the addition of a solution of aldehyde (3.00 mmol, 1 equiv). The reaction mixture was allowed to warm to room temperature. After 18 hours, the reaction was quenched with 1 M HCl (aq.) (10 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over NaSO_4 , filtered and concentrated under reduced pressure. The crude residue was dissolved in dichloromethane (6 mL) was added trifluoroacetic acid (1.5 mL). The reaction mixture was stirred at room temperature for 2 hours. 1 M NaOH (aq.) was added until the pH registered as neutral. The organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over NaSO_4 , filtered and concentrated under reduced pressure. The crude residue was dissolved in dichloromethane (15 mL). Triethylamine (1.26 mL, 9.00 mmol, 3 equiv) followed by *p*-toluenesulfonyl chloride (573 mg, 3.00 mmol, 1 equiv). The resulting solution was stirred at room temperature. After 18 hours, the reaction mixture was washed with brine (10 mL), dried over NaSO_4 , filtered and concentrated under reduced pressure.

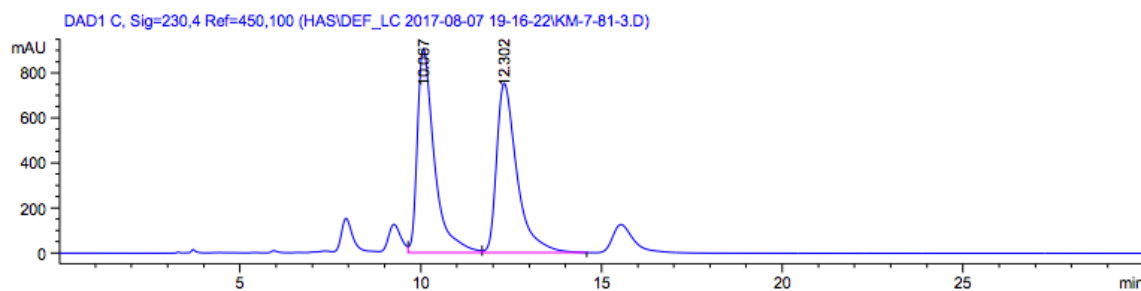
⁴⁴ Pankova, A.S.; Sorokina, M.V.; Kuznetsov, M.A. *Tetrahedron Letters* **2015**, 56, 5381–5385.



Prepared according to general procedure C using Boc-L-alaninal (520 mg, 3.00 mmol) followed by purification by silica gel column chromatography (10 to 100% diethyl ether in hexanes) to give **5a** as a yellow solid (823 mg, 72% overall yield). ¹H NMR (500 MHz, CDCl₃): δ 8.14–8.03 (m, 2H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.36–7.15 (m, 4H), 6.40 (d, *J* = 15.9 Hz, 1H), 6.16–6.01 (m, 1H), 5.38 (d, *J* = 7.7 Hz, 1H), 4.24–3.99 (m, 1H), 2.33 (s, 3H), 1.27 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (125.7 MHz, CDCl₃): δ 147.0, 143.6, 143.0, 138.0, 135.4, 129.7, 128.4, 127.3, 127.0, 123.9, 51.6, 21.6 (d, *J* = 17.2 Hz); FTIR (thin film) ν 3271 (br. m), 1595 (m), 1512 (s), 1339 (s), 1147 (s), 814 (s), 663 (s) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₇H₁₈N₂O₄S [M+H]⁺: 347.1060; found 347.1054; [α]_D²⁴ = –169° (c 1.0, CHCl₃).

98% e.e., chiral HPLC (OD-H, 30% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm); t_R(major) = 10.0 min, t_R(minor) = 12.4 min.

Racemic sample:

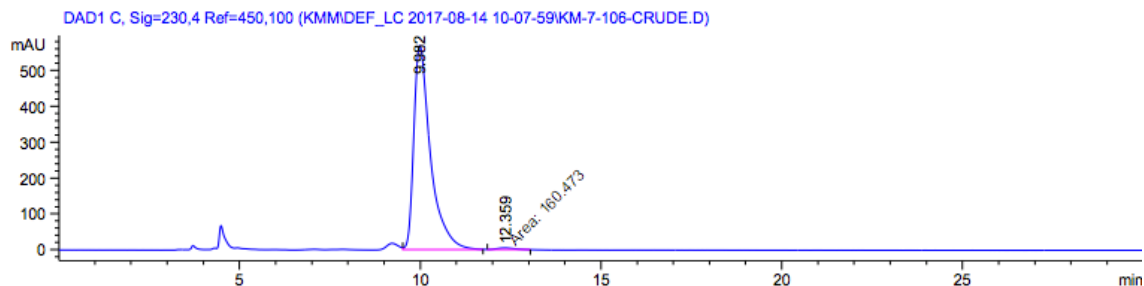


Signal 3: DAD1 C, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.067	VV	0.4907	2.97686e4	907.42834	50.2442
2	12.302	VB	0.5870	2.94793e4	752.63397	49.7558

Totals : 5.92479e4 1660.06232

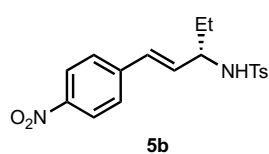
Enriched sample:



Signal 3: DAD1 C, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.982	VB	0.4816	1.84537e4	570.11945	99.1379
2	12.359	MM	0.5673	160.47330	4.71452	0.8621

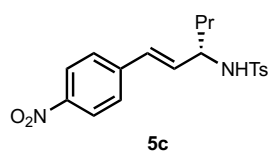
Totals : 1.86141e4 574.83396



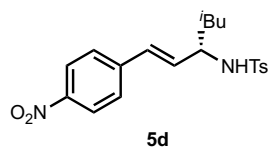
Prepared according to general procedure C using (S)-tert-butyl 1-oxobutan-2-ylcarbamate⁴⁵ (562 mg, 3.00 mmol) followed by purification by silica gel column chromatography (10 to 100% diethyl ether in

hexanes) to give **5b** as a yellow solid (756 mg, 70% overall yield). ¹H NMR (500 MHz, CDCl₃): δ 8.06 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 6.30 (d, *J* = 15.9 Hz, 1H), 5.97 (dd, *J* = 15.9, 7.4 Hz, 1H), 5.47 (d, *J* = 8.0 Hz, 1H), 4.05–3.61 (m, 1H), 2.27 (s, 3H), 1.81–1.36 (m, *J* = 6.9 Hz, 2H), 0.85 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (125.7 MHz, CDCl₃): δ 146.9, 143.4, 143.0, 138.1, 134.1, 129.6, 129.3, 127.3, 126.9, 123.8, 57.6, 28.6, 21.4, 10.0; FTIR (thin film) ν 3274 (br. m), 1595 (m), 1339 (s), 663 (s) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₈H₂₀N₂O₄S [M+H]⁺: 361.1217; found 361.1216; [α]_D²⁴ = −142.7° (c 1.0, CH₃CN).

⁴⁵ Banner, D.; Haap, W.; Kuhn, B.; Luebbers, T.; Peters, J-U; Schulz-Gasch, T. PCT Int. Appl., 2013076063, 30 May 2013.



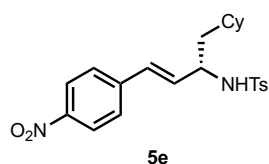
Prepared according to general procedure C using carbamic acid, [(1S)-1-formylbutyl], 1,1-dimethylethyl ester⁴⁶ (604 mg, 3.00 mmol) followed by purification by silica gel column chromatography (10 to 100% diethyl ether in hexanes) to give **5c** as a yellow solid (764 mg, 68% overall yield). ¹H NMR (500 MHz, CDCl₃): δ 8.06 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 7.7 Hz, 2H), 6.29 (dd, *J* = 16.0, 0.9 Hz, 1H), 5.97 (dd, *J* = 15.9, 7.5 Hz, 1H), 5.39 (d, *J* = 8.3 Hz, 1H), 4.00–3.87 (m, 1H), 2.27 (s, 3H), 1.63–1.45 (m, 2H), 1.42–1.18 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (125.7 MHz, CDCl₃): δ 146.9, 143.4, 143.0, 138.1, 134.4, 129.6, 129.1, 127.3, 126.9, 123.8, 56.0, 37.7, 21.5, 18.7, 13.7; FTIR (thin film) ν 3275 (br. m), 1596 (m), 1340 (s), 1158 (s), 667 (m) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₉H₂₂N₂O₄S [M+H]⁺: 375.1373; found 375.1375; [α]_D²⁴ = -122° (c 1.0, CH₃CN).



Prepared according to general procedure C using commercially available tert-butyl [(1S)-1-formyl-3-methylbutyl]carbamate (646 mg, 3.00 mmol) followed by purification by silica gel column chromatography (10 to 100% diethyl ether in hexanes) to give **5d** as a yellow solid (862 mg, 74% overall yield). ¹H NMR (500 MHz, CDCl₃): δ 8.07 (d, *J* = 8.7 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.18–7.14 (m, 2H), 6.29 (d, *J* = 15.9 Hz, 1H), 5.93 (dd, *J* = 15.9, 7.6 Hz, 1H), 5.30 (d, *J* = 8.0 Hz, 1H), 4.07–3.93 (m, 1H), 2.26 (s, 3H), 1.72–1.59 (m, 1H), 1.51–1.42 (m, 1H), 1.42–1.31 (m, 1H), 0.83 (dd, *J* = 17.8, 6.6 Hz, 6H); ¹³C NMR (125.7 MHz, CDCl₃): δ 146.9, 143.4, 143.0, 138.2, 134.5, 129.6, 129.0, 127.4, 126.9, 123.8, 54.6, 44.8, 24.4, 22.5, 22.2, 21.5; FTIR

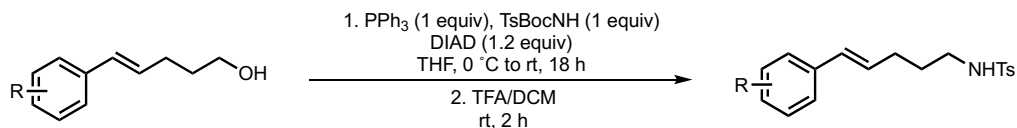
⁴⁶ Catalano, J.G.; Deaton, D.N.; Furfine, E.S.; Hassell, A.M.; McFayden, R.B.; Miller, A.B.; Miller, L.R.; Shewchuk, L.M.; Willard Jr., D.H.; Wright, L.L. *Bioorganic & Medicinal Chemistry Letters*, **2004**, *14*, 275–278.

(thin film) ν 2956 (br. m), 1596 (m), 1367(s), 663 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 389.1530; found 389.1531; $[\alpha]_{\text{D}}^{27} = -60.3^\circ$ (c 1.0, CH_3CN).



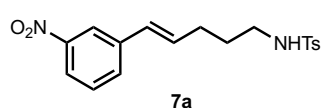
Prepared according to general procedure C using commercially available tert-butyl *N*-(1-cyclohexyl-3-oxopropan-2-yl)carbamate (766 mg, 3.00 mmol) followed by purification by silica gel column chromatography (10 to 100% diethyl ether in hexanes) to give **5e** as a yellow solid (913 mg, 71% overall yield). ^1H NMR (500 MHz, CDCl_3): δ 8.13–8.03 (m, 2H), 7.74 (d, $J = 8.3$ Hz, 2H), 7.23 (d, $J = 8.7$ Hz, 2H), 7.18 (d, $J = 7.9$ Hz, 2H), 6.33 (d, $J = 15.8$ Hz, 1H), 5.97 (ddd, $J = 15.9, 7.3, 0.8$ Hz, 1H), 5.21 (d, $J = 7.8$ Hz, 1H), 4.10–3.92 (m, 1H), 2.28 (s, 3H), 1.74–0.67 (m, 13H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 146.9, 143.4, 143.1, 138.1, 134.9, 129.6, 128.8, 127.4, 126.9, 123.8, 53.7, 43.4, 33.7, 33.3, 32.8, 26.4, 26.2, 26.0, 21.5; FTIR (thin film) ν 2921 (br. m), 1596 (m), 1339 (s), 1157 (s), 667 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 429.1843; found 429.1838; $[\alpha]_{\text{D}}^{24} = -83.3^\circ$ (c 1.0, CH_3CN).

General Procedure D:

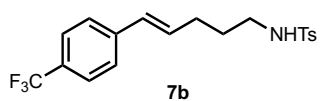


Alcohol (5.00 mmol, 1.0 equiv) was dissolved in anhydrous tetrahydrofuran (25 mL) at 0 °C. Triphenylphosphine (1.32 g, 5.00 mmol, 1.0 equiv) and *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (1.36 g, 5.00 mmol, 1.0 equiv) were added followed by diisopropyl azodicarboxylate (1.18 mL, 6.0 mmol, 1.2 equiv). The reaction mixture was allowed to warm to room temperature. After 18 hours, the reaction mixture was concentrated under reduced pressure

and purified by silica gel column chromatography (10 to 100% diethyl ether in hexanes). To a solution of the retrieved compound in dichloromethane (8 mL) was added trifluoroacetic acid (2 mL). The reaction mixture was stirred at room temperature for 2 hours. 1 M NaOH (aq.) was added until the pH registered as neutral. The organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over NaSO₄, filtered and concentrated under reduced pressure.



Prepared according to general procedure D using (*E*)-5-(3-nitrophenyl)pent-4-en-1-ol⁴⁷ (1.04 g, 5.00 mmol) followed by purification by silica gel column chromatography (10 to 100% diethyl ether in hexanes) to give **7a** (1.41 g, 78%) as a yellow solid. ¹H NMR (500 MHz, CDCl₃): δ 8.11 (s, 1H), 8.05–7.99 (m, 2H), 7.82–7.72 (m, 4H), 7.62–7.55 (m, 2H), 7.49–7.40 (m, 2H), 7.30 (m, 5H), 6.38 (dd, *J* = 15.9, 1.5 Hz, 2H), 6.31–6.18 (m, 2H), 5.16–5.09 (m, 3H), 3.06–2.94 (m, 5H), 2.41 (s, 6H), 2.32–2.23 (m, 5H), 1.76–1.63 (m, 6H); ¹³C NMR (125.7 MHz, CDCl₃): δ 148.6, 143.5, 139.3, 137.0, 132.6, 132.0, 129.8, 129.4, 128.86, 127.2, 121.7, 120.5, 42.5, 29.8, 28.9, 21.6; FTIR (thin film) ν 3281 (br. m), 1654 (w), 1524 (s), 1153 (s), 965 (m), 550 (s) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₈H₂₀N₂O₄S [M+H]⁺: 361.1217; found 361.1210.

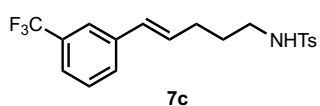


Prepared according to general procedure D using (*E*)-5-(4-(trifluoromethyl)phenyl)pent-4-en-1-ol⁴⁸ (1.15 g, 5.00 mmol) followed by purification by silica gel column chromatography (10 to 80% diethyl ether in hexanes) to give **7d** (1.55 g, 81%) as a white solid. ¹H NMR (500 MHz, CDCl₃): δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.50

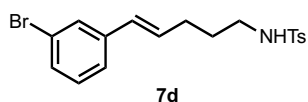
⁴⁷ Belanger, G.; Levesque, F.; Paquet, J.; Barbe, G. *J. Org. Chem.* **2005**, *70*, 291–296.

⁴⁸ Denmark, S.E.; Burk, M.T. *Org. Lett.* **2012**, *14*, 256–259.

(d, $J = 8.2$ Hz, 2H), 7.35 (d, $J = 8.1$ Hz, 2H), 7.27 (d, $J = 8.1$ Hz, 2H), 6.35 (d, $J = 15.9$ Hz, 1H), 6.19 (dt, $J = 15.8, 6.9$ Hz, 1H), 5.55 (t, $J = 6.2$ Hz, 1H), 2.99 (q, $J = 6.7$ Hz, 2H), 2.37 (s, 3H), 2.30 – 2.17 (m, 2H), 1.68 (p, $J = 7.1$ Hz, 2H); ^{19}F NMR (470.4 MHz, CDCl_3): δ -62.3 (s); ^{13}C NMR (125.7 MHz, CDCl_3): δ 143.4, 141.0, 136.9, 132.1, 129.7, 129.6, 128.6 (q, $J = 32.2$ Hz), 127.1, 126.1, 125.3 (q, $J = 3.9$ Hz), 123.9 (q, $J = 272.3$ Hz), 42.5, 29.8, 28.8, 21.4; HRMS (FIA) Calc'd for $\text{C}_{19}\text{H}_{20}\text{F}_3\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 384.1240; found 384.1237.

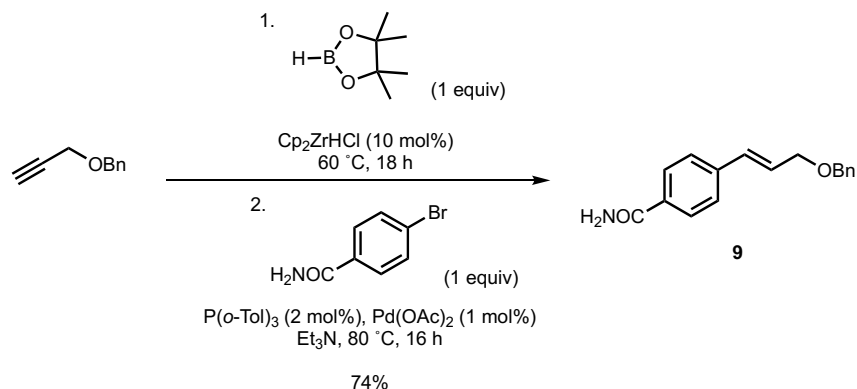


Prepared according to general procedure D using (*E*)-5-(3-(trifluoromethyl)phenyl)pent-4-en-1-ol (1.15 g, 5.00 mmol) followed by purification by silica gel column chromatography (10 to 80% diethyl ether in hexanes) to give **7c** (1.44 g, 75%) as a white solid. ^1H NMR (500 MHz, CDCl_3): δ 7.78 (d, $J = 8.3$ Hz, 2H), 7.50 (s, 1H), 7.47 – 7.41 (m, 3H), 7.38 (d, $J = 7.7$ Hz, 1H), 7.28 (d, $J = 8.0$ Hz, 2H), 6.44 – 6.27 (m, 1H), 6.15 (dt, $J = 15.8, 6.9$ Hz, 1H), 5.23 (t, $J = 6.2$ Hz, 1H), 2.98 (q, $J = 6.7$ Hz, 2H), 2.38 (s, 3H), 2.23 (qd, $J = 7.2, 1.4$ Hz, 2H), 1.66 (p, $J = 7.1$ Hz, 2H); ^{19}F NMR (470.4 MHz, CDCl_3): δ -62.70; ^{13}C NMR (125.7 MHz, CDCl_3): δ 143.5, 138.3, 136.9, 131.2, 130.9 (q, $J = 32.1$ Hz), 129.8, 129.7, 129.2, 129.0, 127.2, 123.6 (q, $J = 3.8$ Hz), 123.9 (q, $J = 272.3$ Hz), 122.6 (q, $J = 3.8$ Hz), 42.5, 29.8, 29.0, 21.5; HRMS (FIA) Calc'd for $\text{C}_{19}\text{H}_{20}\text{F}_3\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 384.1240; found 384.1239.



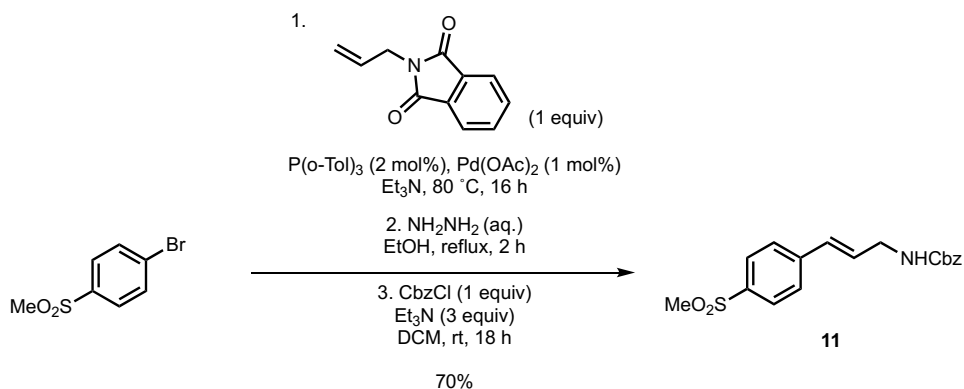
Prepared according to general procedure D using (*E*)-5-(3-bromophenyl)pent-4-en-1-ol (1.21 g, 5.00 mmol) followed by purification by silica gel column chromatography (10 to 80% diethyl ether in hexanes) to give **7d** (1.64 g, 83%) as a white solid. ^1H NMR (500 MHz, CDCl_3): δ 7.76 (d, $J = 8.2$ Hz, 2H), 7.34 (d, J

= 1.9 Hz, 1H), 7.27 – 7.17 (m, 3H), 7.12 (dt, J = 7.9, 1.3 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 6.16 (d, J = 15.8 Hz, 1H), 6.00 (dt, J = 15.8, 6.9 Hz, 1H), 5.64 (t, J = 6.1 Hz, 1H), 2.92 (q, J = 6.7 Hz, 2H), 2.31 (s, 3H), 2.22 – 2.05 (m, 2H), 1.59 (p, J = 7.1 Hz, 2H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 143.1, 139.5, 136.7, 130.7, 129.8, 129.5, 129.1, 128.5, 126.9, 124.5, 122.4, 42.2, 29.5, 28.6, 21.3; HRMS (FIA) Calc'd for $\text{C}_{18}\text{H}_{20}\text{BrNO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 394.0471; found 394.0464.



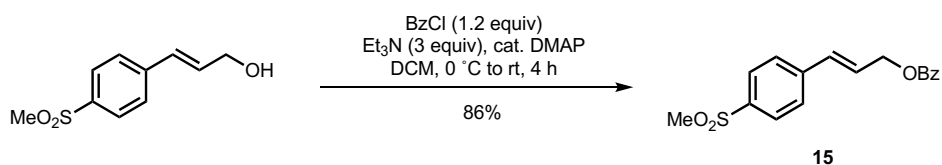
A mixture of benzyl propargyl ether (0.80 mL, 5.50 mmol, 1 equiv), pinacol borane (0.80 mL, 5.50 mmol, 1 equiv) and bis(cyclopentadienyl)zirconium(IV) chloride hydride (142 mg, 0.55 mmol, 10 mol%) was stirred at 60 °C for 18 hours and then flushed through a plug of silica with diethyl ether. To this crude residue was added 4-bromophenyl methyl sulfone (1.29 g, 5.50 mmol), tri(*o*-tolyl)phosphine (33.5 mg, 0.11 mmol, 2 mol%) and anhydrous triethylamine (4.0 mL) followed by palladium(II) acetate (12.7 mg, 0.057 mmol, 1 mol%). The reaction mixture was stirred at 80 °C for 16 hours. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (100 mL), washed with water (20 mL), dried over NaSO_4 , filtered, concentrated under reduced pressure and purified by silica gel column chromatography (20 to 100% ethyl acetate in hexanes) to give **9** (1.09 g, 74%) as a yellow solid. ^1H NMR (500 MHz, CDCl_3): δ 7.77 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H), 7.42–7.34 (m, 4H), 7.34–7.28 (m, 1H), 6.72–6.63 (m, 1H), 6.43 (ddd, J = 16.0, 6.0, 5.4 Hz, 1H), 4.59 (s, 2H), 4.22 (dd, J = 5.8, 1.5 Hz, 2H); ^{13}C NMR (125.7 MHz, 10% $\text{CD}_3\text{OD}/\text{CDCl}_3$): δ 69.9, 140.6,

138.1, 132.2, 131.3, 128.6, 128.0, 127.9, 127.9, 126.7, 72.6, 70.6; FTIR (thin film) ν 2531 (br. m), 2350 (br. m), 1623 (s), 1114 (m), 697 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{17}\text{H}_{17}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 268.1332; found 268.1339.



To a suspension of 4-bromophenyl methyl sulfone (1.29 g, 5.50 mmol), 2-allylisindoline-1,3-dione (1.03 g, 5.50 mmol, 1.0 equiv) and tri(*o*-tolyl)phosphine (33.5 mg, 0.11 mmol, 2 mol%) in anhydrous triethylamine (4.0 mL) was added palladium(II) acetate (12.7 mg, 0.057 mmol, 1 mol%). The reaction mixture was stirred at 80 °C for 16 hours. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (100 mL), washed with water (20 mL), dried over NaSO_4 , filtered and concentrated under reduced pressure. The crude residue was added to a solution of ethanol (40 mL) and hydrazine hydrate (~80% in water, 2 mL) and heated under reflux for 2 hours. After cooling, the suspension was filtered, washing with cold ethanol. The filtrate was concentrated under reduced pressure, re-dissolved in ethyl acetate (50 mL), washed with 1 M NaOH (aq.) (2 x 20 mL) and brine (10 mL), dried over NaSO_4 , filtered and concentrated under reduced pressure. The crude residue was dissolved in dichloromethane (22 mL). Triethylamine (2.3 mL, 16.5 mmol, 3 equiv) followed by benzyl chloroformate (0.79 mL, 5.50 mmol, 1 equiv). The resulting solution was stirred at room temperature. After 18 hours, the reaction mixture was washed with brine (10 mL), dried over NaSO_4 , filtered, concentrated under reduced pressure and purified by silica gel column

chromatography (0 to 10% methanol in dichloromethane) to give **11** (1.33 g, 70%) as a white solid. ^1H NMR (500 MHz, CDCl_3): δ 7.83 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 7.40–7.29 (m, 5H), 6.52 (d, J = 16.0 Hz, 1H), 6.42 – 6.28 (m, 1H), 5.25–5.20 (m, 1H), 5.17–5.09 (m, 2H), 4.00 (dd, J = 8.3, 3.7 Hz, 2H), 3.01 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 156.5, 142.2, 139.0, 136.5, 130.7, 129.4, 128.6, 128.3, 128.2, 127.7, 127.1, 66.9, 44.6, 42.9; FTIR (thin film) ν 3358 (br. s), 1703 (m), 1144 (s), 764 (m), 535 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{18}\text{H}_{19}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 346.1108; found 346.1113.

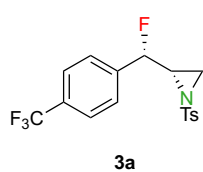


To a solution of (*E*)-3-(4-(methylsulfonyl)phenyl)prop-2-en-1-ol⁴⁹ (1.06 g, 5.00 mmol, 1 equiv) in dichloromethane at 0 °C was added triethylamine (2.09 mL, 15.0 mmol, 3.0 equiv), a catalytic amount of 4-dimethylaminopyridine and benzoyl chloride (0.70 mL, 6.00 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 4 hours and then washed with water (10 mL), dried over NaSO_4 , filtered, concentrated under reduced pressure and purified by silica gel column chromatography (10 to 100% diethyl ether in hexanes) to give **15** (1.36 g, 86%) as a yellow solid. ^1H NMR (500 MHz, CDCl_3): δ 8.12–8.06 (m, 2H), 7.90 (d, J = 8.4 Hz, 2H), 7.63–7.57 (m, 3H), 7.47 (t, J = 7.8 Hz, 2H), 6.85–6.75 (m, 1H), 6.62–6.52 (m, 1H), 5.03 (dd, J = 5.9, 1.5 Hz, 2H), 3.05 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 167.6, 142.1, 138.8, 134.2, 131.6, 130.5, 129.6, 128.6, 127.6, 127.2, 127.0, 44.6, 41.8; FTIR (thin film) ν 2925 (w), 1638 (m), 1293 (s), 1143 (s), 957 (m), 540 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{17}\text{H}_{16}\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 317.0842; found 317.0836.

⁴⁹ Li, F.; Wang, Z-H; Zhao, L.; Xiong, F-J; He, Q-Q; Chen, F-E *Tetrahedron: Asymmetry* **2011**, 22, 1337–1341.

Synthesis of Products

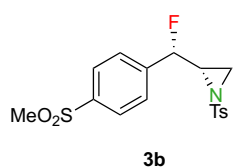
To a solution of substrate (0.52 mmol, 1 equiv) and catalyst (*R,R*)-**1a** (40.0 mg, 0.052 mmol, 10 mol%) in dichloromethane (3 mL) in a low-density polyethylene tube at -78°C was added HF–pyridine (py•9HF, 70% hydrogen fluoride by weight, 210 μL , 15 equiv hydrogen fluoride) followed by *m*CPBA (77% by weight, 128 mg, 0.57 mmol, 1.1 equiv). The reaction mixture was warmed to -30°C and stirred at that temperature for 16 hours. The heterogeneous mixture was transferred carefully into a vigorously stirred suspension of basic alumina (4.0 g) in dichloromethane at -78°C . The resulting suspension was allowed to warm to room temperature and filtered, washing with 200 mL dichloromethane. The combined filtrate was concentrated under reduced pressure.



Prepared according to the general procedure using **2a** (185 mg, 0.52 mmol).

After work-up, the crude residue was purified by silica gel column chromatography (10 to 30% diethyl ether in hexanes) to give **3a** (138 mg,

71%) as a white solid in 94% e.e. ^1H NMR (500 MHz, CDCl_3): δ 7.65 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 5.40 (dd, J = 45.8, 4.5 Hz, 1H), 3.12 (ddt, J = 15.8, 7.1, 4.3 Hz, 1H), 2.81 (dd, J = 7.2, 1.9 Hz, 1H), 2.47 (d, J = 4.3 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 145.1, 140.1 (d, J = 21.6 Hz), 134.4, 131.0 (q, J = 32.1 Hz), 129.7, 128.0, 126.0 (d, J = 7.0 Hz), 125.5 (d, J = 3.8 Hz), 123.9 (q, J = 272.3 Hz), 89.7 (d, J = 181.2 Hz), 42.8 (d, J = 25.9 Hz), 29.4 (d, J = 7.1 Hz), 21.6; ^{19}F NMR (470.4 MHz, CDCl_3): δ -62.7, -188.7 (dd, J = 45.7, 15.8 Hz); FTIR (thin film) ν 2934 (w), 1596 (w), 1319 (s), 1064 (s), 683 (s), 520 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{17}\text{H}_{15}\text{F}_4\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 374.0832; found 374.0830; $[\alpha]_{\text{D}}^{25} = +13.9^{\circ}$ (c 1.0, CH_3CN)



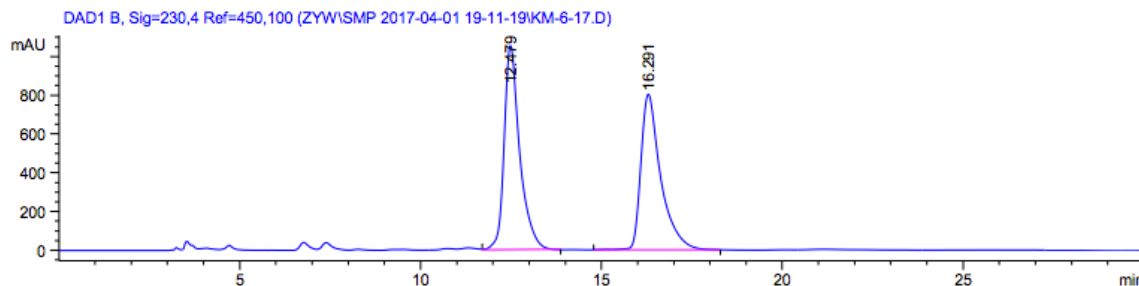
Prepared according to the general procedure using **2b** (190 mg, 0.52 mmol).

After work-up, the crude residue was purified by silica gel column chromatography (dichloromethane) to give **3b** (173 mg, 87%) as a white

solid in 94% e.e. Crystals of **3b** were grown by allowing a hot solution of the compound in ethyl acetate cool to room temperature. ^1H NMR (500 MHz, CDCl_3): δ 7.81 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 5.44 (dd, J = 45.9, 4.5 Hz, 1H), 3.14 (ddt, J = 15.7, 7.0, 4.4 Hz, 1H), 3.02 (s, 3H), 2.80 (d, J = 7.1, 1H), 2.48–2.45 (m, 4H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 145.4, 142.1 (d, J = 21.6 Hz), 141.1, 134.2, 129.9, 128.0, 127.7, 126.7 (d, J = 7.2 Hz), 89.6 (d, J = 181.9 Hz), 44.6, 42.4 (d, J = 26.3 Hz), 29.6 (d, J = 6.9 Hz), 21.8; ^{19}F NMR (470.4 MHz, CDCl_3): δ -188.9 (dd, J = 45.9, 15.5 Hz); FTIR (thin film) ν 2926 (w), 1597 (w), 1307 (s), 1161 (s), 941 (m), 564 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{17}\text{H}_{18}\text{FNO}_4\text{S}_2$ $[\text{M}+\text{H}]^+$: 384.0734; found 384.0730; $[\alpha]_{\text{D}}^{27} = +18.8^\circ$ (c 1.0, CH_3CN).

94% e.e., chiral HPLC (AD-H, 40% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm); t_{R} (major) = 12.4 min, t_{R} (minor) = 16.3 min.

Racemic sample:

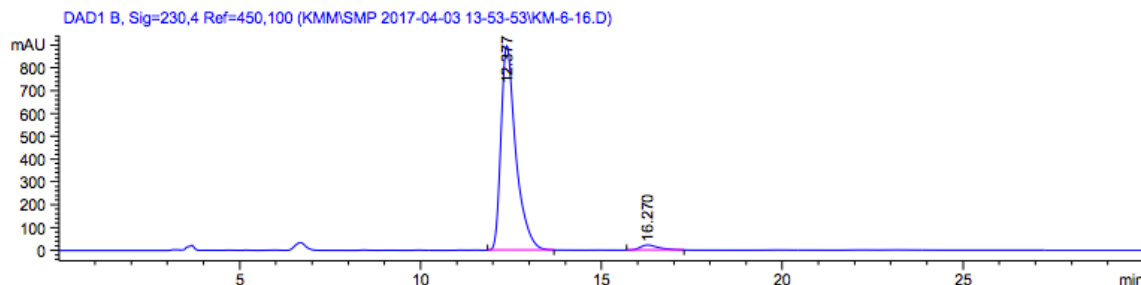


Signal 2: DAD1 B, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.479	VB	0.4436	3.15563e4	1053.15369	50.7936
2	16.291	BB	0.5603	3.05703e4	802.69446	49.2064

Totals : 6.21266e4 1855.84814

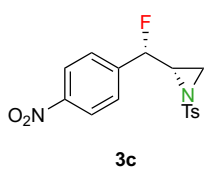
Enriched sample:



Signal 2: DAD1 B, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.377	BB	0.4251	2.55935e4	896.32416	96.9632
2	16.270	BB	0.5404	801.55267	22.03313	3.0368

Totals : 2.63950e4 918.35729



Prepared according to the general procedure using **2c** (173 mg, 0.52 mmol).

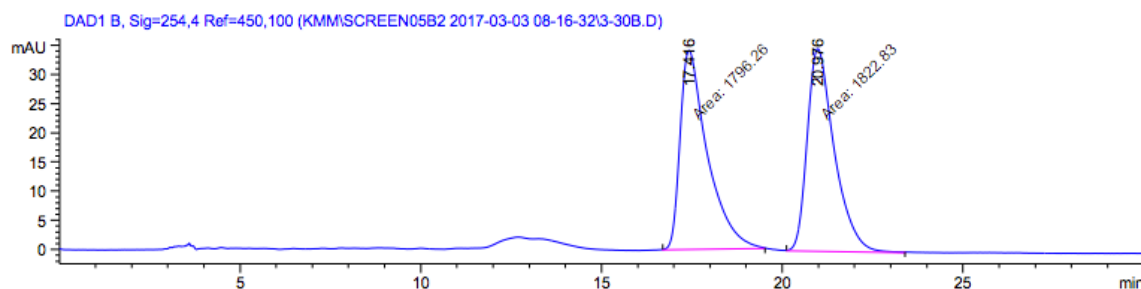
After work-up, the crude residue was purified by silica gel column chromatography (dichloromethane to give **3c** (135 mg, 74%) as a white solid

in 97% e.e. **3c** in 99% ee was obtained following precipitation of the compound from dichloromethane/hexanes. ¹H NMR (500 MHz, CDCl₃): δ 8.02 (d, *J* = 8.6 Hz, 2H), 7.64–7.57 (m, 2H), 7.38–7.32 (m, 2H), 7.21–7.16 (m, 2H), 5.52 (dd, *J* = 45.8, 3.7 Hz, 1H), 3.10 (dddt, *J* = 15.4, 7.0, 4.2, 2.1 Hz, 1H), 2.82 (d, *J* = 7.1 Hz, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.64–7.57 (m, 1H), 7.38–7.32 (m, 2H), 7.21–7.16 (m, 2H), 5.52 (dd, *J* = 45.8, 3.7 Hz, 1H), 3.10 (dddt, *J* = 15.4, 7.0, 4.2, 2.1 Hz, 1H), 2.82 (d, *J* = 7.1 Hz, 1H), 2.53 (d, *J* = 4.3 Hz, 1H), 2.38 (s, 3H); ¹³C NMR

(125.7 MHz, CDCl₃): δ 148.0, 145.3, 143.1 (d, J = 21.7 Hz), 134.2, 129.7, 128.1, 126.5 (d, J = 7.3 Hz), 123.7, 88.8 (d, J = 182.8 Hz), 42.6 (d, J = 25.2 Hz), 29.5 (d, J = 7.3 Hz), 21.6; ¹⁹F NMR (470.4 MHz, CDCl₃): δ -191.6 (dd, J = 45.5, 17.1 Hz); FTIR (thin film) ν 2923 (w), 1595 (w), 1519 (s), 1319 (s), 1158 (s), 727 (s), 563 (m) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₆H₁₅FN₂O₄S [M+H]⁺: 351.0809; found 351.0808; [α]_D²⁴ = +6.0° (c 1.0, CH₃CN).

97% e.e., chiral HPLC (OD-H, 30% isopropanol in hexanes, 1.0 mL/min, λ = 254 nm); t_R (major) = 17.8 min, t_R (minor) = 22.4 min.

Racemic sample:

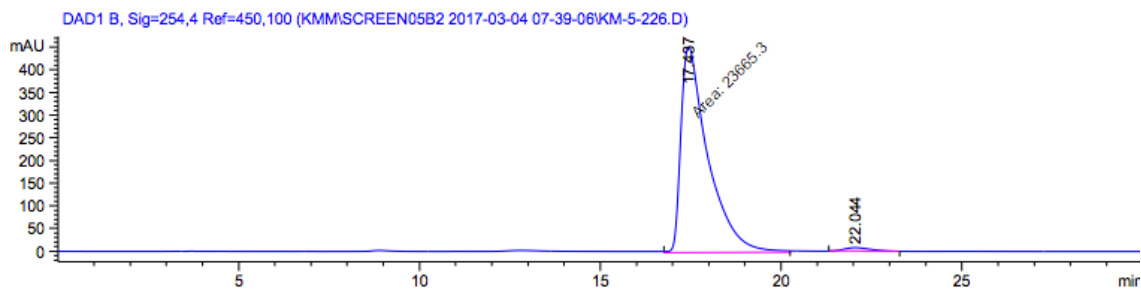


Signal 2: DAD1 B, Sig=254,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.416	MM	0.8773	1796.26318	34.12587	49.6330
2	20.976	MM	0.8735	1822.82703	34.77885	50.3670

Totals : 3619.09021 68.90472

Enriched sample:

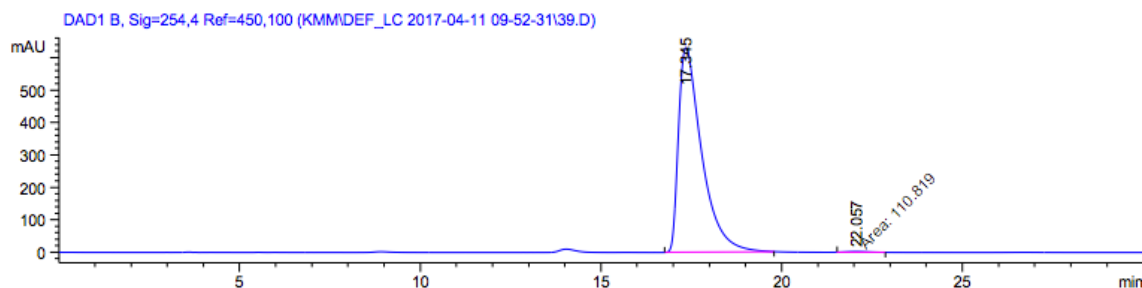


Signal 2: DAD1 B, Sig=254,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.437	MM	0.8680	2.36653e4	454.40854	98.3205
2	22.044	BB	0.6873	404.23941	7.89612	1.6795

Totals : 2.40695e4 462.30466

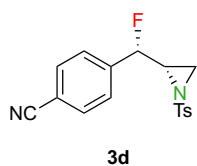
Upgraded (99% e.e.) sample:



Signal 2: DAD1 B, Sig=254,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.345	BB	0.6671	2.81967e4	631.22870	99.6085
2	22.057	MM	0.7423	110.81932	2.48825	0.3915

Totals : 2.83075e4 633.71694



Prepared according to the general procedure using **2d** (162 mg, 0.52 mmol).

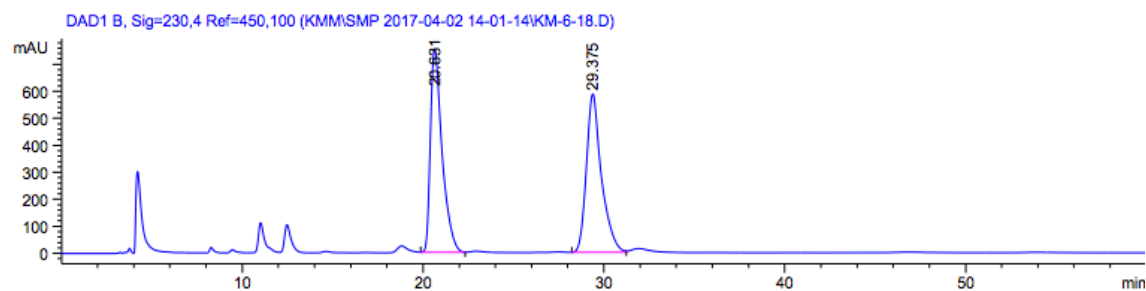
After work-up, the crude residue was purified by silica gel column chromatography (10 to 40% diethyl ether in hexanes) to give **3d** (131 mg, 76%)

as a white solid in 96% e.e. ^1H NMR (500 MHz, CDCl_3): δ 7.62 (d, J = 8.3 Hz, 2H), 7.51–7.47 (m, 2H), 7.33–7.28 (m, 2H), 7.25–7.20 (m, 2H), 5.43 (dd, J = 45.8, 4.3 Hz, 1H), 3.09 (ddt, J = 16.4, 7.1, 4.3 Hz, 1H), 2.79 (dd, J = 7.1, 1.9 Hz, 1H), 2.50–2.44 (m, 4H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 145.2, 141.2 (d, J = 21.7 Hz), 134.2, 132.3, 129.7, 128.0, 126.3 (d, J = 7.3 Hz), 118.3, 112.7, 89.2 (d, J = 182.1 Hz), 42.5 (d, J = 25.5 Hz), 29.5 (d, J = 7.2 Hz), 21.7; ^{19}F NMR (470.4 MHz, CDCl_3): δ -190.6 (dd, J = 45.8, 16.5 Hz); FTIR (thin film) ν 3060 (w), 2227 (m), 1595

(m), 1415 (s), 977 (s), 562 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{17}\text{H}_{15}\text{FN}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 331.0911; found. 331.0905; $[\alpha]_{\text{D}}^{25} = +29.2^\circ$ (c 1.0, CH_3CN)

96% e.e., chiral HPLC (AD-H, 20% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230$ nm); $t_{\text{R}}(\text{major}) = 20.6$ min, $t_{\text{R}}(\text{minor}) = 29.1$ min.

Racemic sample:

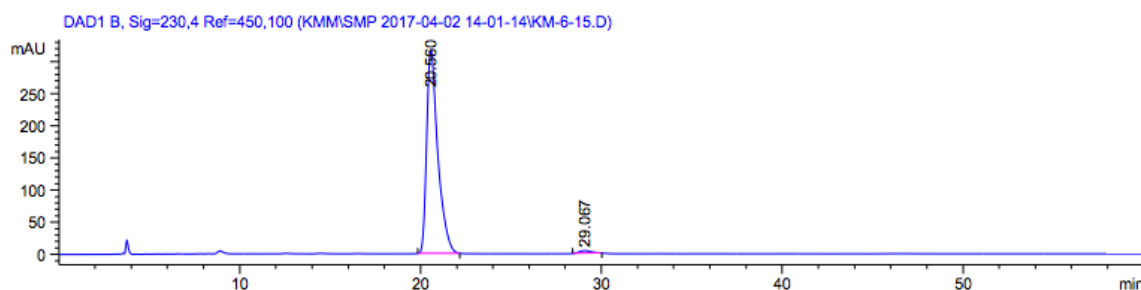


Signal 2: DAD1 B, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.631	BB	0.6713	3.38637e4	754.92334	50.0459
2	29.375	BB	0.8364	3.38015e4	586.50360	49.9541

Totals : 6.76652e4 1341.42694

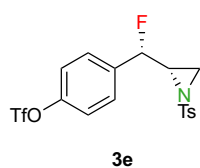
Enriched sample:



Signal 2: DAD1 B, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.560	BB	0.6383	1.36080e4	317.32004	98.4951
2	29.067	BB	0.6358	207.91110	4.31747	1.5049

Totals : 1.38159e4 321.63751



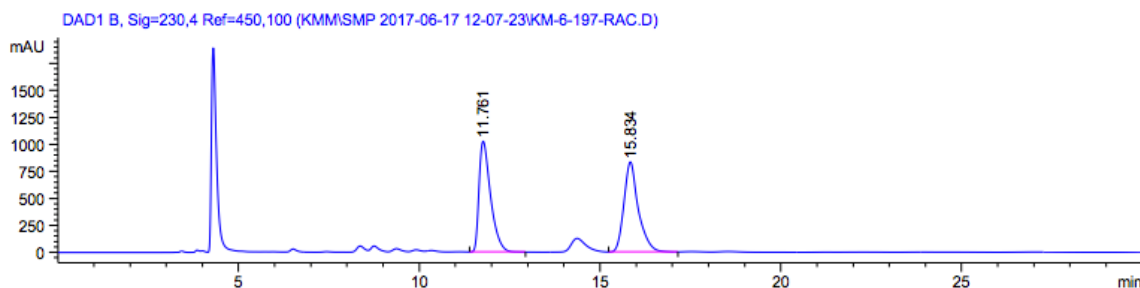
Prepared according to the general procedure using **2e** (226 mg, 0.52 mmol).

After work-up, the crude residue was purified by silica gel column chromatography (10 to 50% diethyl ether in hexanes) to give **3e** (174 mg, 74%)

as a white solid in 88% e.e. ^1H NMR (500 MHz, CDCl_3): δ 7.72 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.22–7.16 (m, 2H), 5.33 (dd, J = 45.8, 4.7 Hz, 1H), 3.15 (ddt, J = 14.4, 7.1, 4.7 Hz, 1H), 2.79 (dd, J = 7.2, 2.1 Hz, 1H), 2.45 (s, 3H), 2.41 (d, J = 4.5 Hz, 1H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 149.4, 145.0, 139.1 (d, J = 22.0 Hz), 134.2, 130.6, 129.8, 128.0, 125.6 (d, J = 6.8 Hz), 121.7, 118.8 (d, J = 7.8 Hz), 118.7 (q, J = 320.6 Hz), 89.5 (d, J = 181.5 Hz), 42.3 (d, J = 26.5 Hz), 29.5 (d, J = 7.1 Hz), 21.6; ^{19}F NMR (470.4 MHz, CDCl_3): δ -73.0, -185.1 (dd, J = 45.9, 14.5 Hz); FTIR (thin film) ν 1598 (w), 1503 (m), 1419 (s), 1135 (s), 883 (s), 529 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{17}\text{H}_{15}\text{F}_4\text{NO}_5\text{S}_2$ $[\text{M}+\text{H}]^+$: 454.0401; found 454.0391. $[\alpha]_{\text{D}}^{23} = +16.3^\circ$ (c 1.0, CHCl_3).

88% e.e., chiral HPLC (AD-H, 20% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm); t_{R} (major) = 11.8 min, t_{R} (minor) = 15.9 min.

Racemic sample:

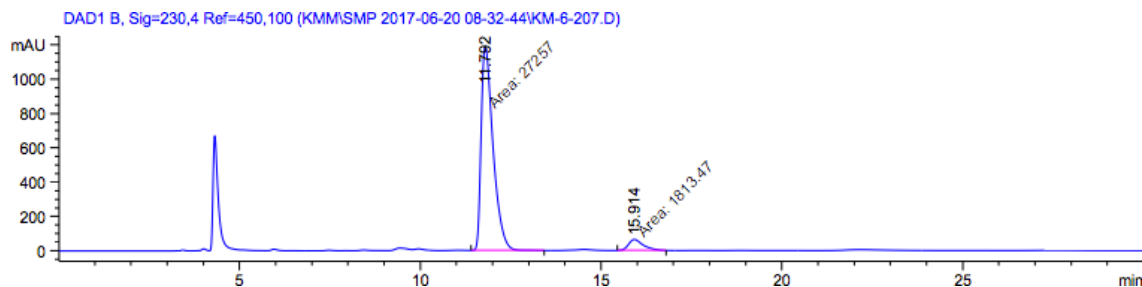


Signal 2: DAD1 B, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.792	MM	0.3815	2.72570e4	1190.68335	93.7618
2	15.914	MM	0.4711	1813.46936	64.15755	6.2382

Totals : 2.90705e4 1254.84090

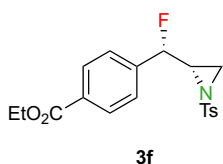
Enriched sample:



Signal 2: DAD1 B, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.792	MM	0.3815	2.72570e4	1190.68335	93.7618
2	15.914	MM	0.4711	1813.46936	64.15755	6.2382

Totals : 2.90705e4 1254.84090



Prepared according to the general procedure using **2f** (187 mg, 0.52 mmol).

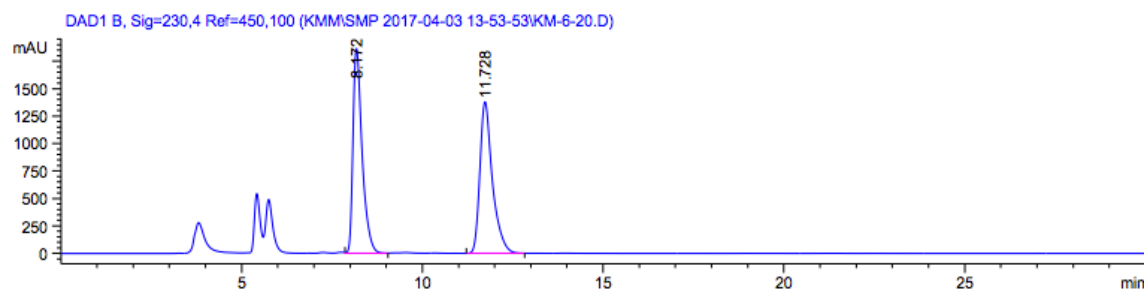
After work-up, the crude residue was purified by silica gel column chromatography (10 to 40% diethyl ether in hexanes) to give **3f** (183 mg, 93%) as a white solid in 90% e.e.

¹H NMR (500 MHz, CDCl₃): δ 7.93–7.88 (m, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 7.24–7.18 (m, 2H), 5.38 (dd, *J* = 46.0, 4.7 Hz, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 3.13 (ddt, *J* = 15.0, 7.3, 4.5 Hz, 1H), 2.81 (dd, *J* = 7.2, 2.0 Hz, 1H), 2.47 (d, *J* = 4.4 Hz, 1H), 2.40 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (125.7 MHz, CDCl₃): δ 165.9, 144.9, 140.8 (d, *J* = 21.4 Hz), 134.3, 130.9, 129.7, 129.6, 128.0, 125.5 (d, *J* = 6.9 Hz), 90.1 (d, *J* = 180.8 Hz), 61.2, 42.7 (d, *J* = 26.2 Hz), 29.4 (d, *J* = 7.2 Hz), 21.6, 14.4; ¹⁹F NMR (470.4 MHz, CDCl₃): δ -188.09 (dd, *J* = 45.9, 15.2 Hz); FTIR (thin film) ν 2982 (br. w), 1714 (s), 1273 (s),

1090 (s), 724 (s), 564 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{19}\text{H}_{20}\text{FNO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 378.1170; found 378.1168; $[\alpha]_{\text{D}}^{25} = +13.1^\circ$ (c 1.0, CH_3CN).

90% e.e., chiral HPLC (AD-H, 40% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230$ nm); $t_{\text{R}}(\text{major}) = 8.2$ min, $t_{\text{R}}(\text{minor}) = 11.8$ min.

Racemic sample:

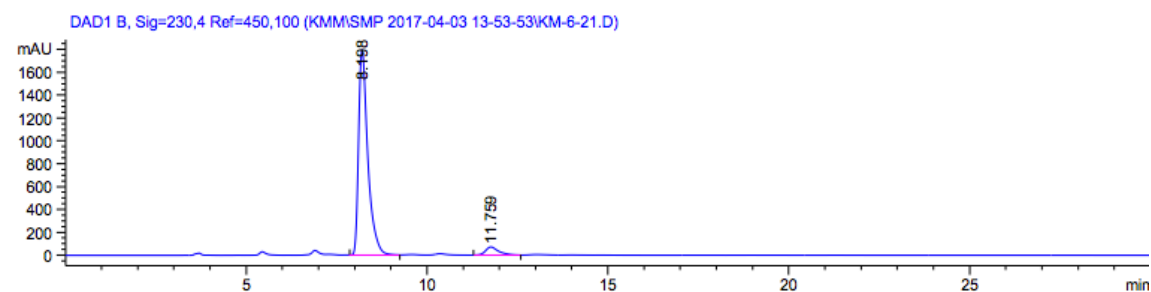


Signal 2: DAD1 B, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.172	VB	0.2651	3.27591e4	1863.62451	49.6587
2	11.728	BB	0.3569	3.32093e4	1379.49377	50.3413

Totals : 6.59684e4 3243.11829

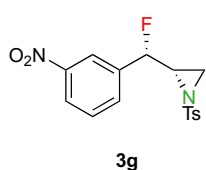
Enriched sample:



Signal 2: DAD1 B, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.198	VB	0.2679	3.20187e4	1796.49976	94.7411
2	11.759	BB	0.3681	1777.29785	70.98157	5.2589

Totals : 3.37960e4 1867.48132



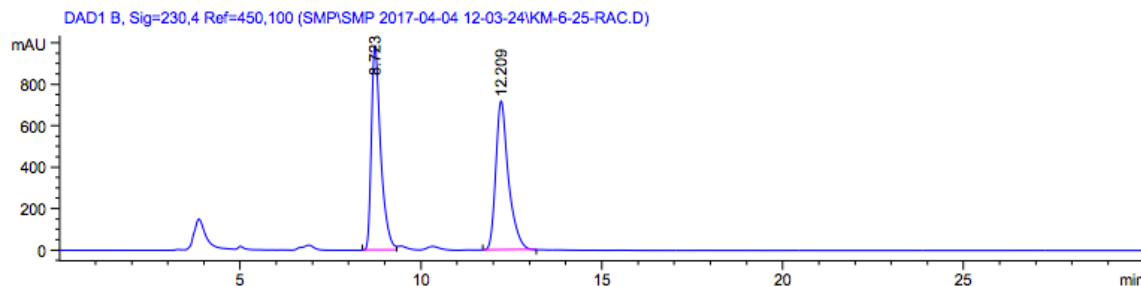
Prepared according to the general procedure using **2g** (173 mg, 0.52 mmol).

After work-up, the crude residue was purified by silica gel column chromatography (dichloromethane) to give **3g** (144 mg, 79%) as a white solid

in 91% e.e. ^1H NMR (500 MHz, CDCl_3): δ 8.12 (ddd, $J = 8.2, 2.3, 1.1$ Hz, 1H), 8.04 (t, $J = 0.7$ Hz, 1H), 7.64 (d, $J = 8.4$ Hz, 2H), 7.57 (ddd, $J = 7.8, 1.8, 1.0$ Hz, 1H), 7.51–7.43 (m, 1H), 7.18 (dd, $J = 8.7, 0.7$ Hz, 2H), 5.51 (dd, $J = 45.5, 4.2$ Hz, 1H), 3.13 (ddt, $J = 16.5, 7.1, 4.2$ Hz, 1H), 2.84 (dd, $J = 7.1, 1.8$ Hz, 1H), 2.51 (d, $J = 4.3$ Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 148.1, 145.0, 138.3 (d, $J = 22.3$ Hz), 134.1, 131.6 (d, $J = 6.8$ Hz), 129.7, 129.6, 127.9, 123.6, 120.9 (d, $J = 7.7$ Hz), 88.7 (d, $J = 182.2$ Hz), 42.5 (d, $J = 25.4$ Hz), 29.5 (d, $J = 7.2$ Hz), 21.6; ^{19}F NMR (470.4 MHz, CDCl_3): δ -189.8 (dd, $J = 45.5, 16.7$ Hz); FTIR (thin film) ν 3093 (w), 1569 (w), 1530 (s), 1159 (s), 915 (s), 725 (s), 537 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{16}\text{H}_{15}\text{FN}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 351.0809; found 351.0808; $[\alpha]_{\text{D}}^{25} = -20.1^\circ$ (c 1.0, CH_3CN).

91% e.e., chiral HPLC (AD-H, 40% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230$ nm); t_{R} (major) = 8.7 min, t_{R} (minor) = 12.2 min.

Racemic sample:

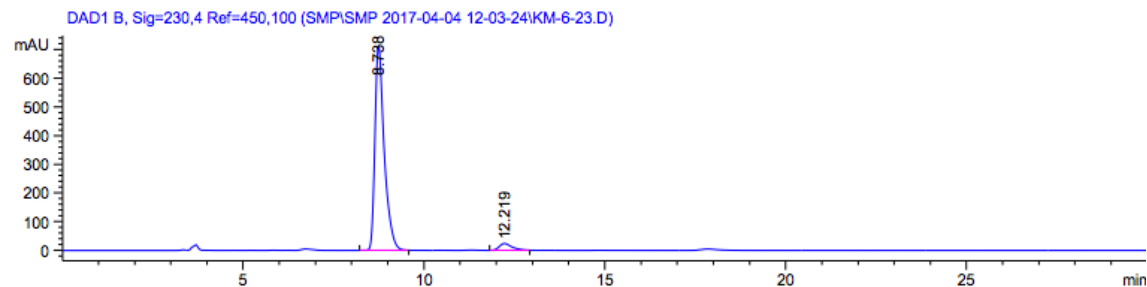


Signal 2: DAD1 B, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.723	BV	0.2672	1.76847e4	986.33575	50.2257
2	12.209	BB	0.3606	1.75258e4	718.56067	49.7743

Totals : 3.52105e4 1704.89642

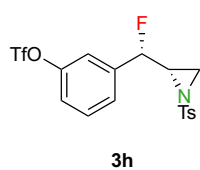
Enriched sample:



Signal 2: DAD1 B, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.738	BB	0.2663	1.27388e4	713.42920	95.5959
2	12.219	BB	0.3618	586.87427	23.95986	4.4041

Totals : 1.33257e4 737.38906



Prepared according to the general procedure using **2h** (226 mg, 0.52 mmol).

After work-up, the crude residue was purified by silica gel column chromatography (10 to 50% diethyl ether in hexanes) to give **3h** (189 mg, 80%)

as a white solid in 94% e.e. ^1H NMR (500 MHz, CDCl_3): δ 7.73–7.67 (m, 2H), 7.35 (t, J = 8.0 Hz, 1H), 7.26 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.2 Hz, 1H), 7.16 (s, 1H), 5.38 (dd, J = 45.6, 4.7 Hz, 1H), 3.13 (ddt, J = 15.0, 7.3, 4.5 Hz, 1H), 2.79 (dd, J = 7.1, 1.9 Hz, 1H), 2.48 – 2.36 (m, 4H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 149.5, 145.0, 139.1 (d, J = 21.9 Hz), 134.2, 130.6, 129.8, 128.0, 125.64 (d, J = 6.7 Hz), 121.7, 118.8 (d, J = 7.9 Hz), 118.7 (q, J = 320.5 Hz), 89.5 (d, J = 181.6 Hz), 42.3 (d, J = 26.5 Hz), 29.5 (d, J = 6.8 Hz), 21.6; ^{19}F NMR (470.4 MHz, CDCl_3): δ -73.0, -187.3 (dd, J = 45.7, 14.8 Hz); FTIR (thin film) ν 1616 (w), 1421 (s), 1209 (s), 713 (s), 474

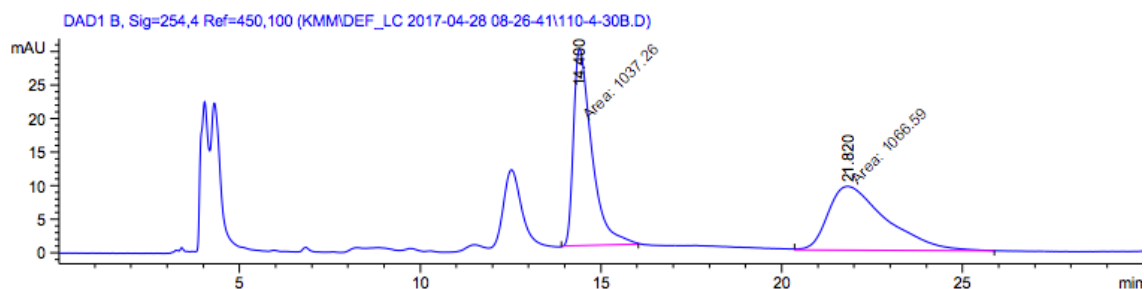
(m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{17}\text{H}_{15}\text{F}_4\text{NO}_5\text{S}_2$ $[\text{M}+\text{H}]^+$: 454.0401; found 454.0394.

$[\alpha]_{\text{D}}^{24} = -3.1^\circ$ (c 1.0, CHCl_3).

94% e.e., chiral HPLC (OJ-H, 30% isopropanol in hexanes, 1.0 mL/min, $\lambda = 254$ nm); $t_{\text{R}}(\text{major})$

= 12.3 min, $t_{\text{R}}(\text{minor}) = 21.8$ min.

Racemic sample:

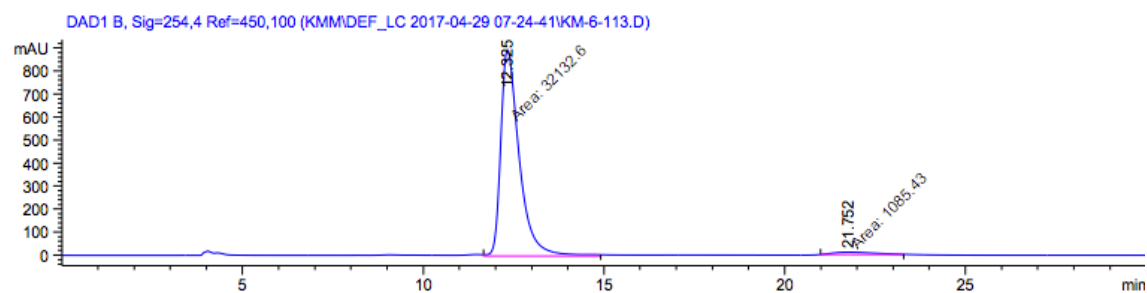


Signal 2: DAD1 B, Sig=254,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.400	MM	0.5888	1037.25598	29.35960	49.3028
2	21.820	MM	1.8643	1066.59009	9.53506	50.6972

Totals : 2103.84607 38.89466

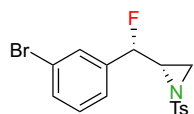
Enriched sample:



Signal 2: DAD1 B, Sig=254,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.325	MM	0.5972	3.21326e4	896.72174	96.7324
2	21.752	MM	1.4931	1085.42749	12.11568	3.2676

Totals : 3.32180e4 908.83742



3i

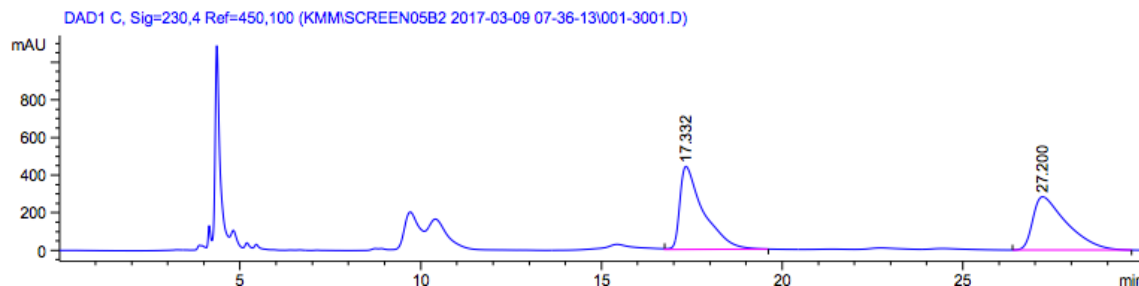
Prepared according to the general procedure using **2i** (190 mg, 0.52 mmol).

After work-up, the crude residue was purified by silica gel column chromatography (0 to 25% diethyl ether in hexanes) to give **3i** (112 mg, 56%)

as a colorless oil in 90% e.e. ^1H NMR (500 MHz, CDCl_3): δ 7.76–7.67 (m, 2H), 7.45–7.39 (m, 1H), 7.37 (s, 1H), 7.27 (d, $J = 8.1$ Hz, 2H), 7.21–7.12 (m, 2H), 5.25 (dd, $J = 45.8, 5.0$ Hz, 1H), 3.12 (ddt, $J = 14.2, 6.9, 4.6$ Hz, 1H), 2.81 (dd, $J = 7.2, 2.1$ Hz, 1H), 2.53–2.37 (m, 4H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 144.9, 138.3 (d, $J = 21.6$ Hz), 134.3, 132.0, 130.2, 129.8, 128.9 (d, $J = 7.3$ Hz), 128.0, 124.3 (d, $J = 6.7$ Hz), 122.8, 90.1 (d, $J = 181.2$ Hz), 42.7 (d, $J = 26.8$ Hz), 29.6 (d, $J = 7.2$ Hz), 21.8; ^{19}F NMR (470.4 MHz, CDCl_3): δ -185.6 (dd, $J = 45.8, 14.4$ Hz); FTIR (thin film) ν 2924 (w), 1597 (w), 1324 (m), 1159 (s), 724 (m), 600 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{16}\text{H}_{15}\text{BrFNO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 384.0064; found 384.0060; $[\alpha]_{\text{D}}^{25} = +0.9^\circ$ (c 1.0, CH_3CN).

90% e.e., chiral HPLC (OJ-H, 30% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230$ nm); t_{R} (minor) = 17.6 min, t_{R} (major) = 26.8 min.

Racemic sample:

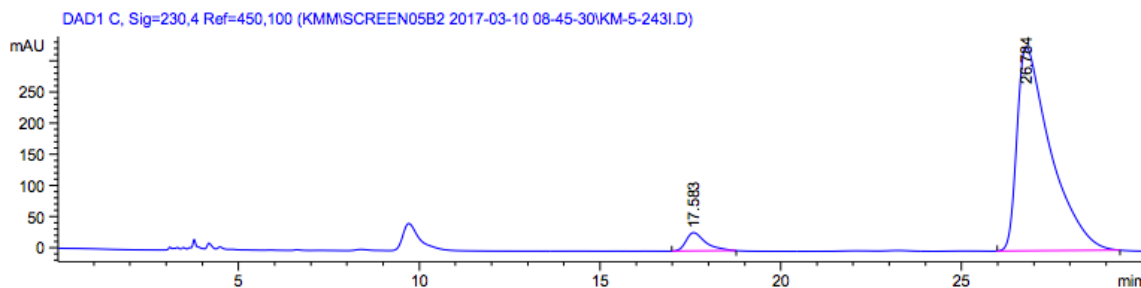


Signal 3: DAD1 C, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.332	VB	0.6411	2.00325e4	441.74008	52.0870
2	27.200	BB	0.9356	1.84272e4	283.03888	47.9130

Totals : 3.84597e4 724.77896

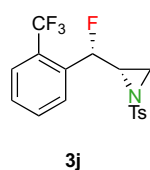
Enriched sample:



Signal 3: DAD1 C, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.583	BB	0.5589	1132.05652	29.55073	5.0693
2	26.784	BB	0.9175	2.11996e4	328.25854	94.9307

Totals : 2.23316e4 357.80927



Prepared according to the general procedure using **2j** (185 mg, 0.52 mmol). After

work-up, the crude residue was purified by silica gel column chromatography (0 to

15% diethyl ether in hexanes) to give **3j** (161 mg, 83%) as a colorless oil in 80%

e.e. ¹H NMR (500 MHz, CDCl₃): δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.55 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.51

(dd, *J* = 7.2, 1.9 Hz, 1H), 7.39–7.30 (m, 2H), 7.20–7.14 (m, 2H), 5.86–5.67 (m, 1H), 3.14 (ddt, *J*

= 17.3, 7.3, 4.2 Hz, 1H), 2.79 (dd, *J* = 7.2, 1.9 Hz, 1H), 2.54 (d, *J* = 4.4 Hz, 1H), 2.38 (s, 3H);

¹³C NMR (125.7 MHz, CDCl₃): δ 144.7, 134.8 (d, *J* = 22.5 Hz), 134.3, 132.3, 129.7, 128.8 (d, *J*

= 1.9 Hz), 128.5 (d, *J* = 8.7 Hz), 128.0, 125.4 (q, *J* = 5.7 Hz), 124.0 (q, *J* = 273.6 Hz), 85.7 (dd, *J*

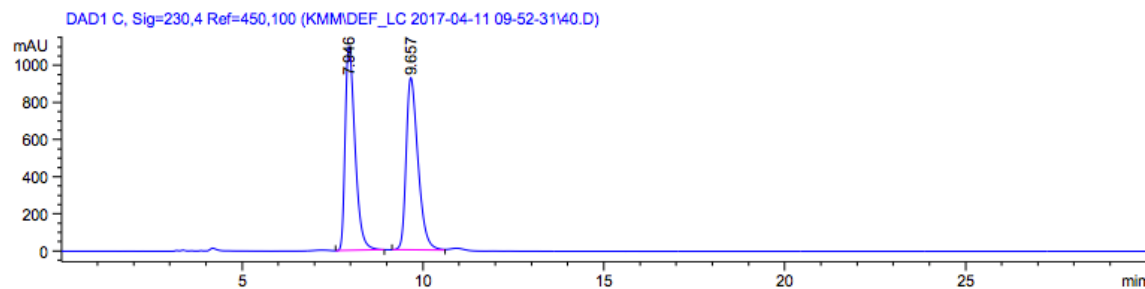
= 178.4, 2.6 Hz), 42.7 (d, *J* = 25.4 Hz), 29.8 (d, *J* = 7.2 Hz), 21.6; ¹⁹F NMR (470.4 MHz,

CDCl₃): δ -57.93 (s, 3F), -185.14 (dd, *J* = 44.9, 17.3 Hz, 1F); FTIR (thin film) ν 1597 (w), 1312

(s), 1159 (s), 941 (m), 716 (s), 563 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{17}\text{H}_{15}\text{F}_4\text{NO}_5\text{S}_2$ $[\text{M}+\text{H}]^+$: 374.0832; found 374.0826. $[\alpha]_{\text{D}}^{23} = +6.8^\circ$ (c 1.0, CHCl_3).

80% e.e., chiral HPLC (OJ-H, 30% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230 \text{ nm}$); $t_{\text{R}}(\text{minor}) = 8.0 \text{ min}$, $t_{\text{R}}(\text{major}) = 9.6 \text{ min}$.

Racemic sample:

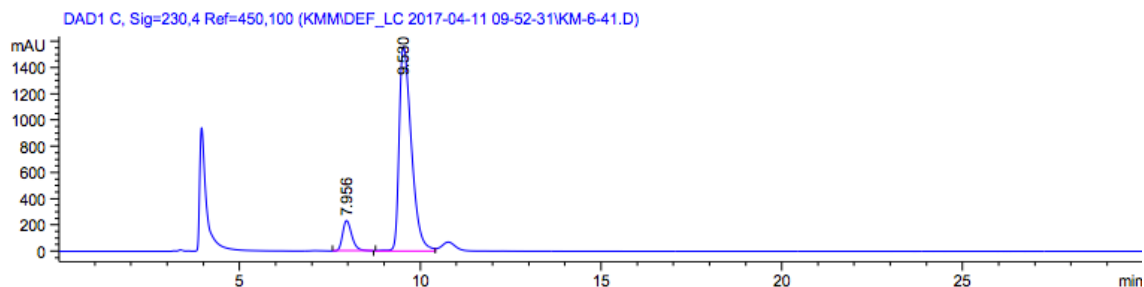


Signal 3: DAD1 C, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.946	VB	0.2909	2.08105e4	1099.03418	49.4876
2	9.657	BV	0.3490	2.12415e4	928.29474	50.5124

Totals : 4.20520e4 2027.32892

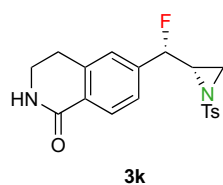
Enriched sample:



Signal 3: DAD1 C, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.956	VB	0.2766	4179.44287	231.53537	10.2289
2	9.530	BV	0.3606	3.66799e4	1558.64014	89.7711

Totals : 4.08593e4 1790.17551



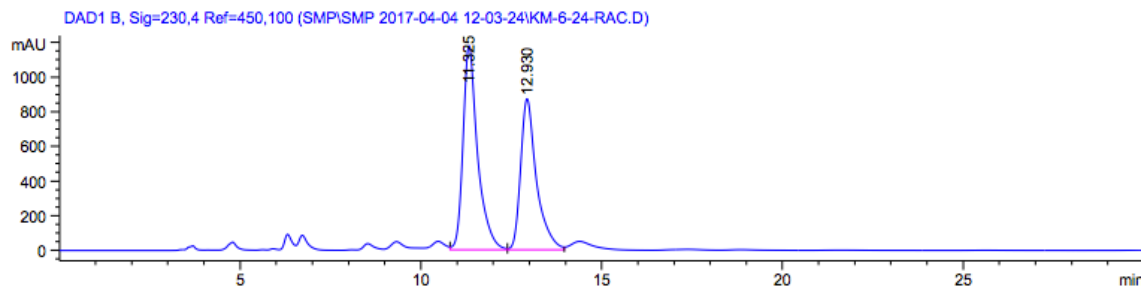
Prepared according to the general procedure using **2k** (185 mg, 0.52 mmol).

After work-up, the crude residue was purified by silica gel column chromatography (20 to 100% ethyl acetate in hexanes) to give **3k** (150 mg,

77%) as a white solid in 94% e.e. ^1H NMR (500 MHz, CDCl_3): δ 7.91 (d, J = 8.0 Hz, 1H), 7.67 (dd, J = 8.3, 1.6 Hz, 2H), 7.45 (s, 1H), 7.21 (d, J = 7.7 Hz, 2H), 7.16 (d, J = 8.1 Hz, 1H), 7.10 (s, 1H), 5.29 (dd, J = 46.1, 5.0 Hz, 1H), 3.52 (dt, J = 7.3, 3.6 Hz, 2H), 3.19–3.08 (m, 1H), 2.87 (t, J = 6.9 Hz, 2H), 2.77 (dd, J = 7.2, 2.3 Hz, 1H), 2.46 – 2.32 (m, 4H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 166.0, 144.9, 140.0 (d, J = 21.0 Hz), 139.3, 134.2, 129.6, 129.5, 128.1, 127.9, 124.3 (dd, J = 38.4, 6.9 Hz), 90.5 (d, J = 180.6 Hz), 42.7 (d, J = 26.7 Hz), 39.9, 29.5 (d, J = 7.4 Hz), 28.1, 21.6; ^{19}F NMR (470.4 MHz, CDCl_3): δ -186.0 (dd, J = 46.3, 14.2 Hz); FTIR (thin film) ν 3207 (br. s), 1665 (s), 1323 (s), 1159 (s), 908 (s), 710 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{19}\text{H}_{19}\text{FN}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$: 375.1173; found 375.1177; $[\alpha]_{\text{D}}^{25}$ = +1.3° (c 1.0, CH_3CN).

94% e.e., chiral HPLC (AD-H, 40% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm); t_{R} (major) = 11.3 min, t_{R} (minor) = 13.0 min.

Racemic sample:

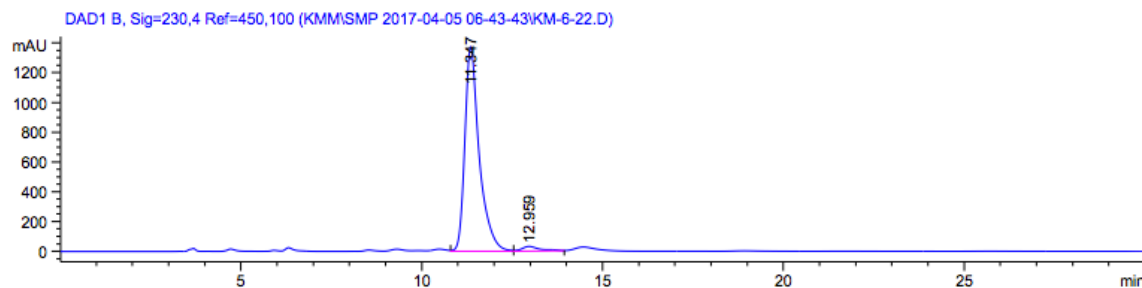


Signal 2: DAD1 B, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.325	VV	0.4126	3.32390e4	1180.19873	55.3532
2	12.930	VV	0.4499	2.68099e4	873.84082	44.6468

Totals : 6.00490e4 2054.03955

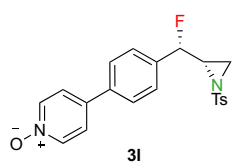
Enriched sample:



Signal 2: DAD1 B, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.347	VV	0.4088	3.80237e4	1374.08093	96.8467
2	12.959	VV	0.5457	1238.01978	32.25899	3.1533

Totals : 3.92617e4 1406.33992



Prepared according to the general procedure using **21** (98.9 mg, 0.26 mmol).

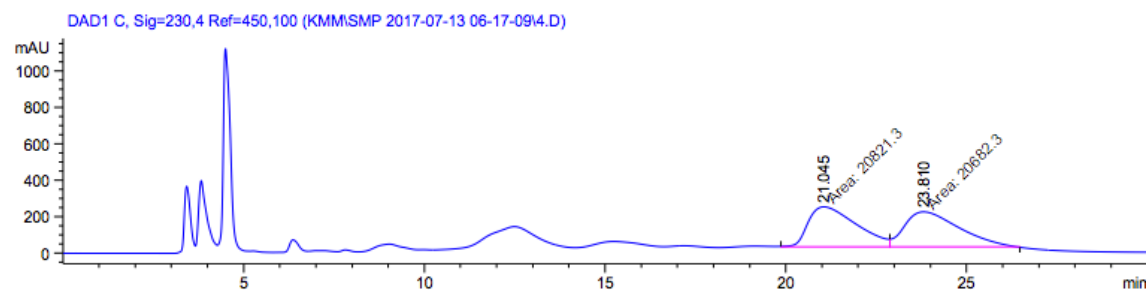
After work-up, the crude residue was purified by silica gel column chromatography (0 to 10% methanol in dichloromethane) to give **31**

(74.6 mg, 72%) as a yellow solid in 90% e.e. ¹H NMR (500 MHz, CDCl₃): δ 8.28 (d, *J* = 7.2 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.57–7.47 (m, 4H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.32–7.24 (m, 2H), 5.32 (dd, *J* = 46.0, 5.4 Hz, 1H), 3.21 (dddd, *J* = 12.9, 7.1, 5.5, 4.4 Hz, 1H), 2.77 (dd, *J* = 7.1, 2.2 Hz, 1H), 2.41 (d, *J* = 4.3 Hz, 1H), 2.36 (s, 3H); ¹³C NMR (125.7 MHz, CDCl₃): δ 144.9, 139.5, 137.8, 137.0 (d, *J* = 21.3 Hz), 136.9, 134.5, 129.7, 128.1, 127.0 (d, *J* = 6.5 Hz), 126.6, 123.7, 90.9 (d, *J* = 179.8 Hz), 42.5 (d, *J* = 27.6 Hz), 29.8 (d, *J* = 6.9 Hz), 21.7; ¹⁹F NMR (470.4 MHz, CDCl₃): δ -183.29 (dd, *J* = 46.0, 13.2 Hz); FTIR (thin film) ν 3379 (br. s), 1597 (w), 1478 (m),

1243 (m), 1160 (s), 728 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{21}\text{H}_{19}\text{FN}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$: 399.1173; found 399.1166. $[\alpha]_{\text{D}}^{23} = +51.9^\circ$ (c 1.0, CHCl_3).

90% e.e., chiral HPLC (OJ-H, 50% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230$ nm); $t_{\text{R}}(\text{minor}) = 21.9$ min, $t_{\text{R}}(\text{major}) = 23.9$ min.

Racemic sample:

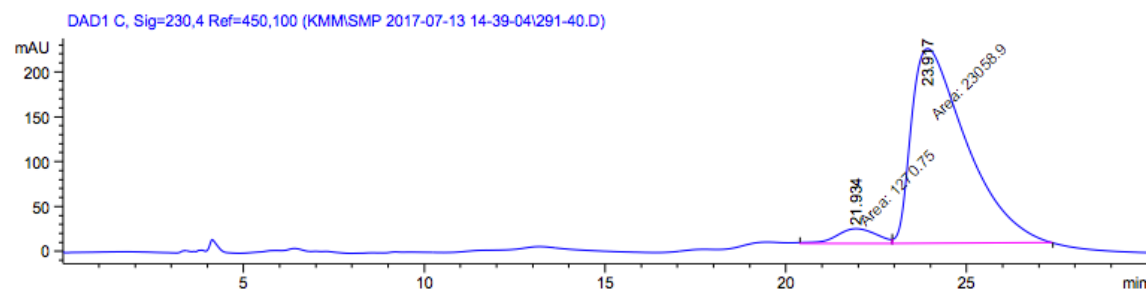


Signal 3: DAD1 C, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.045	MM	1.5611	2.08213e4	222.28683	50.1675
2	23.810	MM	1.7709	2.06823e4	194.65215	49.8325

Totals : 4.15036e4 416.93898

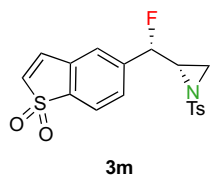
Enriched sample:



Signal 3: DAD1 C, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.934	MM	1.2837	1270.75439	16.49884	5.2231
2	23.917	MM	1.7708	2.30589e4	217.02835	94.7769

Totals : 2.43297e4 233.52719



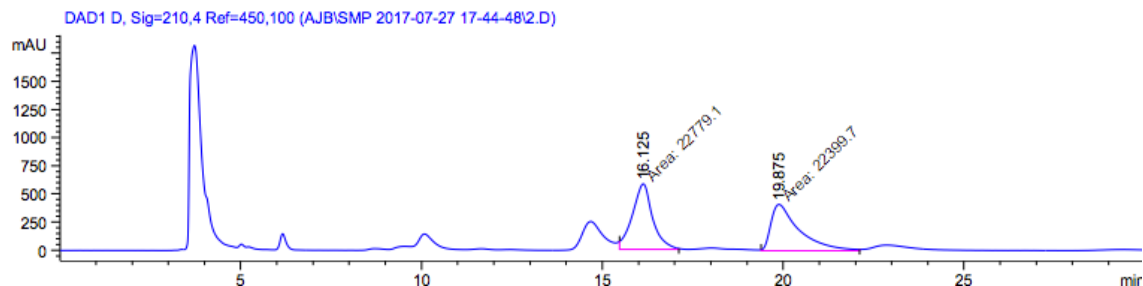
Prepared according to the general procedure using **2m** (195 mg, 0.52 mmol).

After work-up, the crude residue was purified by silica gel column chromatography (10 to 100% diethyl ether in hexanes) to give **3m** (158 mg,

77%) as a white solid in 97% e.e. ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 7.76 (d, $J = 7.8$ Hz, 1H), 7.61 (d, $J = 8.3$ Hz, 2H), 7.56–7.48 (m, 2H), 7.45–7.37 (m, 2H), 7.32–7.24 (m, 2H), 5.67 (dd, $J = 45.8, 4.7$ Hz, 1H), 3.33–3.26 (m, 1H), 2.77 (dd, $J = 7.3, 2.1$ Hz, 1H), 2.64 (d, $J = 4.3$ Hz, 1H), 2.36 (d, $J = 1.9$ Hz, 3H); ^{13}C NMR (125.7 MHz, $\text{DMSO}-d_6$): δ 144.8, 142.5 (d, $J = 21.2$ Hz), 136.3, 133.7, 132.5, 131.5 (d, $J = 3.8$ Hz), 129.7, 128.2 (d, $J = 7.4$ Hz), 127.6, 123.0 (d, $J = 7.2$ Hz), 121.0, 89.1 (d, $J = 178.2$ Hz), 42.5 (d, $J = 23.9$ Hz), 29.2 (d, $J = 7.9$ Hz), 21.1; ^{19}F NMR (470.4 MHz, $\text{DMSO}-d_6$): δ -188.86 (dd, $J = 45.7, 16.7$ Hz); FTIR (thin film) ν 1298 (s), 1158 (s), 914 (m), 726 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{18}\text{H}_{16}\text{FNO}_4\text{S}_2$ $[\text{M}+\text{H}]^+$: 394.0578; found 394.0573. $[\alpha]_{\text{D}}^{24} = -0.97^\circ$ (c 1.0, CH_2Cl_2).

97% e.e., chiral HPLC (AD-H, 40% isopropanol in hexanes, 1.0 mL/min, $\lambda = 210$ nm); t_{R} (major) = 16.5 min, t_{R} (minor) = 21.0 min.

Racemic sample:

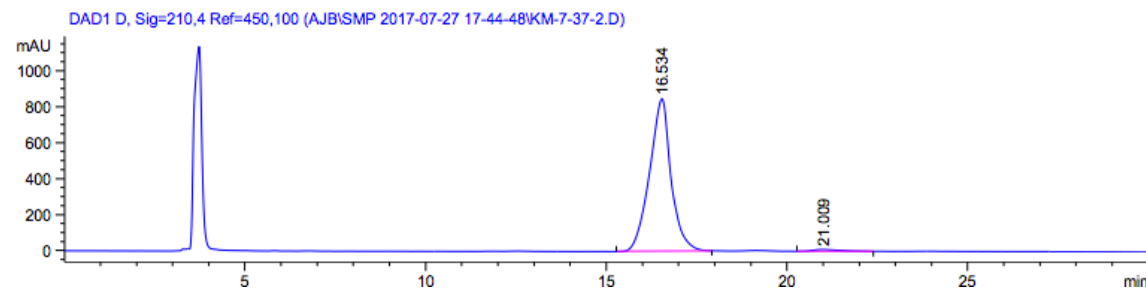


Signal 4: DAD1 D, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.125	MM	0.6514	2.27791e4	582.78949	50.4199
2	19.875	MM	0.9080	2.23997e4	411.14539	49.5801

Totals : 4.51788e4 993.93488

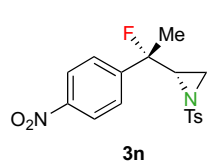
Enriched sample:



Signal 4: DAD1 D, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.534	VB	0.5802	3.50054e4	846.99823	98.4646
2	21.009	BV	0.6358	545.83673	10.17539	1.5354

Totals : 3.55513e4 857.17362



Prepared according to the general procedure using **2n** (180 mg, 0.52 mmol)

with the following modification: 10 equiv of HF were used instead. After

work-up, the crude residue was purified by silica gel column chromatography

(dichloromethane) to give **3n** (83.4 mg, 44%) as a white solid in 61% e.e. ^1H NMR (500 MHz,

CDCl_3): δ 7.98 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.9 Hz, 2H), 7.14 (d, J

= 8.1 Hz, 2H), 3.05 (ddd, J = 16.2, 7.0, 4.2 Hz, 1H), 2.80 (dd, J = 7.0, 1.1 Hz, 1H), 2.43 (d, J =

4.2 Hz, 1H), 2.36 (s, 3H), 1.71 (d, J = 22.4 Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 147.9,

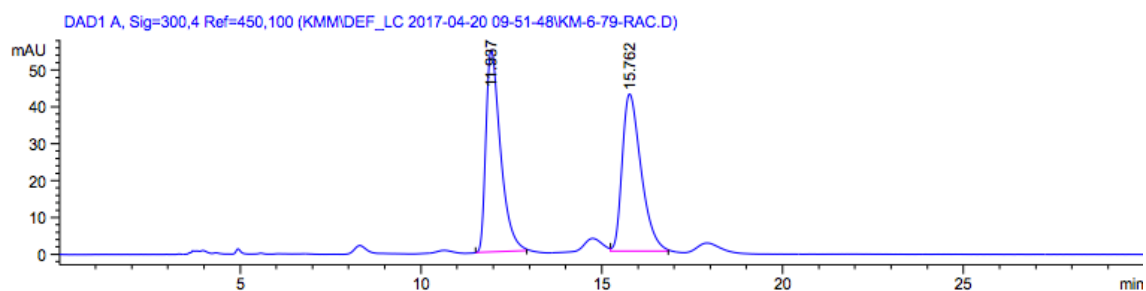
147.6 (d, J = 29.9 Hz), 145.2, 134.3, 129.6, 128.0, 125.5 (d, J = 9.6 Hz), 123.4 (d, J = 1.8 Hz),

92.7 (d, J = 181.2 Hz), 46.0 (d, J = 26.9 Hz), 29.6 (d, J = 6.5 Hz), 24.5 (d, J = 24.1 Hz), 21.6; ^{19}F

NMR (470.4 MHz, CDCl₃): δ -159.6 (dd, J = 22.4, 16.2 Hz); FTIR (thin film) ν 3084 (w), 1598 (w), 1522 (m), 1409 (m), 1161 (s), 733 (m) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₇H₁₇FN₂O₄S [M+H]⁺: 365.0966; found 365.0960. $[\alpha]_D^{24}$ = -2.3° (c 1.0, CHCl₃).

61% e.e., chiral HPLC (OD-H, 30% isopropanol in hexanes, 1.0 mL/min, λ = 300 nm); t_R (major) = 11.9 min, t_R (minor) = 15.7 min.

Racemic sample:

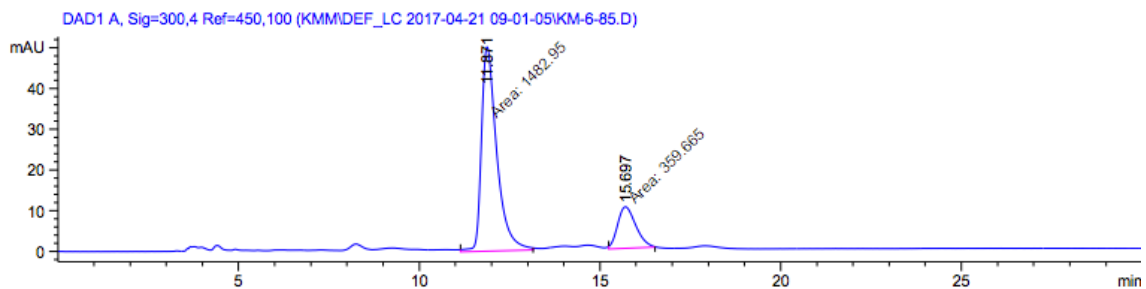


Signal 1: DAD1 A, Sig=300,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.937	BB	0.4267	1545.68359	54.86849	49.9175
2	15.762	VB	0.5542	1550.79480	42.65345	50.0825

Totals : 3096.47839 97.52195

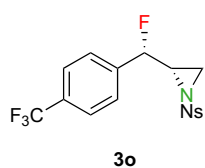
Enriched sample:



Signal 1: DAD1 A, Sig=300,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.871	MM	0.4928	1482.94702	50.15132	80.4807
2	15.697	MM	0.5861	359.66513	10.22727	19.5193

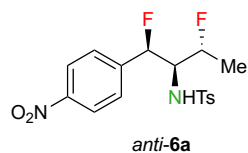
Totals : 1842.61215 60.37860



Prepared according to the general procedure using **2o** (402 mg, 1.04 mmol).

After work-up, the crude residue was purified by silica gel column chromatography (dichloromethane) to give **3o** (235 mg, 56%) as a white solid

in 94% e.e. ^1H NMR (600 MHz, CDCl_3): δ 8.31 (d, J = 8.9 Hz, 2H), 8.03 (d, J = 8.8 Hz, 2H), 7.61–7.50 (m, 2H), 7.44–7.35 (m, 2H), 5.38 (dd, J = 45.9, 5.1 Hz, 1H), 3.27 (dddd, J = 14.3, 7.2, 5.1, 4.4 Hz, 1H), 2.94 (ddd, J = 7.2, 2.2, 0.6 Hz, 1H), 2.57 (d, J = 4.5 Hz, 1H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 150.90, 143.28, 139.74 (d, J = 21.5 Hz), 131.0 (q, J = 32.1 Hz), 129.4, 126.0 (d, J = 7.1 Hz), 125.8 (q, J = 3.8 Hz), 124.3, 124.0 (q, J = 273.6 Hz), 90.1 (d, J = 181.7 Hz), 43.6 (d, J = 26.4 Hz), 30.3 (d, J = 7.6 Hz); ^{19}F NMR (470.4 MHz, CDCl_3): δ -62.86, -187.28 (dd, J = 45.8, 14.4 Hz); HRMS (ESI-TOF) Calc'd for $\text{C}_{16}\text{H}_{12}\text{F}_4\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 405.0527; found 405.0532; $[\alpha]_{\text{D}}^{24} = +10.1^\circ$ (c 1.0, CH_3CN).

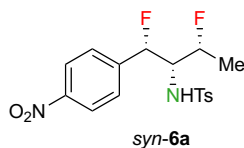


Prepared according to the general procedure using **5a** (180 mg, 0.52 mmol)

with the following modification: 25 equiv of HF and 20 mol% of catalyst (*S,S*)-**1a**³²ⁱ were used instead. The diastereomeric ratio (d.r.) of the crude

residue was determined to be >20:1 by ^{19}F NMR. The crude residue was purified by silica gel column chromatography (10 to 40% diethyl ether in hexanes) to give *anti*-**6a** (156 mg, 78%) as a white solid in >20:1 d.r. Crystals of *anti*-**6a** were grown by vapor diffusion of pentane into a solution of the compound in ethyl acetate. ^1H NMR (500 MHz, CDCl_3): δ 7.82 (d, J = 8.7 Hz,

2H), 7.18 (t, $J = 8.6$ Hz, 4H), 6.91 (d, $J = 8.0$ Hz, 2H), 5.87 (d, $J = 45.4$ Hz, 1H), 4.77 (ddq, $J = 47.0, 8.7, 6.3$ Hz, 1H), 3.91–3.53 (m, 1H), 2.24 (s, 3H), 1.47 (dd, $J = 25.1, 6.3$ Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 147.4, 143.9 (d, $J = 21.2$ Hz), 143.3, 138.5, 129.3, 126.1, 125.9 (d, $J = 9.1$ Hz), 123.3 (d, $J = 1.9$ Hz), 90.1 (dd, $J = 157.3, 3.9$ Hz), 88.7 (dd, $J = 151.6, 3.8$ Hz), 62.3 (dd, $J = 25.8, 19.2$ Hz), 50.5–48.1 (m), 21.1, 18.1 (d, $J = 21.7$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3): δ -177.7–178.1 (m), -203.4 (ddd, $J = 45.5, 29.3, 5.0$ Hz); FTIR (thin film) ν 3246 (br. w), 1605 (w), 1514 (s), 1161 (s), 478 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{17}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 385.1028; found 385.1022. $[\alpha]_{\text{D}}^{24} = -21.5^\circ$ (c 1.0, CHCl_3).



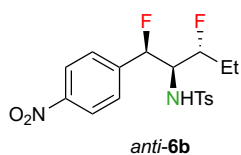
Prepared according to the general procedure using **5a** (180 mg, 0.52 mmol)

with the following modification: 50 equiv of HF and 20 mol% of catalyst

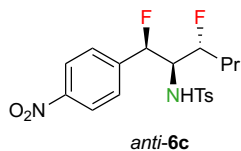
(*R,R*)-**1a** were used instead. The diastereomeric ratio (d.r.) of the crude

residue was determined to be 13:1 by ^{19}F NMR. The crude residue was purified by silica gel column chromatography (10 to 40% diethyl ether in hexanes) to give *syn*-**6a** (138 mg, 69%) as a white solid in >20:1 d.r. Crystals of *syn*-**6a** were grown by vapor diffusion of pentane into a solution of the compound in ethyl acetate. ^1H NMR (500 MHz, CDCl_3): δ 7.99 (d, $J = 8.8$ Hz, 2H), 7.46 (d, $J = 8.3$ Hz, 2H), 7.31 (d, $J = 8.8$ Hz, 2H), 7.08 (d, $J = 7.9$ Hz, 2H), 5.70 (dd, $J = 45.8, 3.9$ Hz, 1H), 4.77 (ddd, $J = 46.2, 6.4, 3.4$ Hz, 1H), 3.73 (dddd, $J = 22.1, 18.2, 6.0, 2.6$ Hz, 1H), 2.32 (s, 3H), 1.36 (dd, $J = 24.6, 6.4$ Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 147.8, 143.6, 143.5 (d, $J = 21.1$ Hz), 129.5, 126.6, 126.4 (d, $J = 8.3$ Hz), 123.5, 91.1 (dd, $J = 181.1, 2.6$ Hz), 89.2 (d, $J = 173.0$ Hz), 61.5–59.7 (m), 21.3, 17.0 (d, $J = 22.2$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3): δ -182.4–183.0 (m), -192.7 (ddd, $J = 45.6, 21.7, 3.9$ Hz); FTIR (thin film) ν 3250 (br.

w), 1608 (w), 1345 (s), 1160 (s), 815 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{17}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 385.1028; found 385.1022; $[\alpha]_{\text{D}}^{25} = +40.4^\circ$ (c 1.0, CH_3OH).

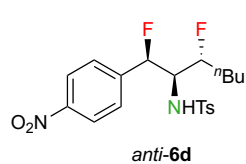


Prepared according to the general procedure using **5b** (187 mg, 0.52 mmol) with the following modification: 25 equiv of HF and 20 mol% of catalyst (*S,S*)-**1a** were used instead. The diastereomeric ratio (d.r.) of the crude residue was determined to be >20:1 by ^{19}F NMR. The crude residue was purified by silica gel column chromatography (10 to 40% diethyl ether in hexanes) to give *anti*-**6b** (176 mg, 85%) as a white solid in >20:1 d.r. ^1H NMR (500 MHz, 10% $\text{CD}_3\text{OD}/\text{CDCl}_3$): δ 7.77 (d, $J = 8.3$ Hz, 2H), 7.15 (d, $J = 8.7$ Hz, 2H), 7.13 (d, $J = 7.9$ Hz, 2H), 6.88 (d, $J = 7.9$ Hz, 2H), 5.84 (d, $J = 45.3$ Hz, 1H), 4.48 (dtd, $J = 47.6, 8.9, 2.7$ Hz, 1H), 3.72 (dt, $J = 29.4, 8.0$ Hz, 1H), 2.21 (s, 3H), 2.02–1.80 (m, 1H), 1.75–1.58 (m, 1H), 0.99 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125.7 MHz, 10% $\text{CD}_3\text{OD}/\text{CDCl}_3$): δ 147.3, 144.0 (d, $J = 21.1$ Hz), 143.2, 138.5, 129.2, 126.0, 125.8 (d, $J = 9.1$ Hz), 123.2 (d, $J = 1.7$ Hz), 93.2 (dd, $J = 176.7, 3.2$ Hz), 90.1 (dd, $J = 179.3, 4.7$ Hz), 60.9 (dd, $J = 25.7, 19.4$ Hz), 24.8 (d, $J = 20.6$ Hz), 21.0, 9.2 (d, $J = 4.3$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3): δ -188.84 (dddt, $J = 45.4, 37.0, 17.2, 7.5$ Hz), -204.14 (ddd, $J = 45.4, 28.6, 6.9$ Hz); FTIR (thin film) ν 2961 (br. w), 1521 (s), 1158 (s), 543 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{18}\text{H}_{20}\text{F}_2\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 399.1185; found 399.1196; $[\alpha]_{\text{D}}^{24} = -22.6^\circ$ (c 1.0, CH_3CN).



Prepared according to the general procedure using **5c** (195 mg, 0.52 mmol) with the following modification: 25 equiv of HF and 20 mol% of catalyst (*S,S*)-**1a** were used instead. The diastereomeric ratio (d.r.) of the crude residue was determined to be >20:1 by ^{19}F NMR. The crude residue was purified by silica gel

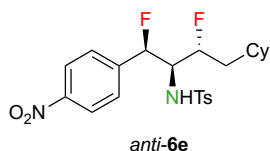
column chromatography (10 to 40% diethyl ether in hexanes) to give *anti*-**6c** (165 mg, 77%) as a white solid in >20:1 d.r. ¹H NMR (500 MHz, 10% CD₃OD/CDCl₃): δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 5.90 (d, *J* = 45.5 Hz, 1H), 4.60 (dtd, *J* = 47.7, 9.1, 2.5 Hz, 1H), 3.86–3.63 (m, 1H), 2.27 (s, 3H), 1.93–1.32 (m, 4H), 0.90 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (125.7 MHz, 10% CD₃OD/CDCl₃): δ 147.1, 144.1 (d, *J* = 21.0 Hz), 142.9, 138.7, 129.0, 125.9, 125.8, 123.0 (d, *J* = 1.7 Hz), 91.6 (d, *J* = 176.0 Hz), 90.0 (dd, *J* = 179.6, 4.6 Hz), 61.1 (dd, *J* = 25.7, 19.3 Hz), 33.5 (d, *J* = 20.2 Hz), 20.7, 18.1 (d, *J* = 3.4 Hz), 13.3; ¹⁹F NMR (470.4 MHz, CDCl₃): δ -187.11–187.49 (m), -203.61–203.89 (m); FTIR (thin film) ν 1517(s), 1332 (s), 852 (s), 533 (s) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₉H₂₂F₂N₂O₄S [M+H]⁺: 413.1341; found 413.1349; [α]_D²⁴ = -10.9° (c 1.0, CH₃CN).



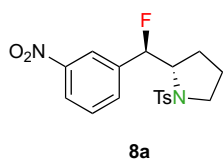
Prepared according to the general procedure using **5d** (202 mg, 0.52 mmol) with the following modification: 25 equiv of HF and 20 mol% of catalyst (*S,S*)-**1a** were used instead. The diastereomeric ratio (d.r.) of the crude

residue was determined to be >20:1 by ¹⁹F NMR. The crude residue was purified by silica gel column chromatography (10 to 40% diethyl ether in hexanes) to give *anti*-**6d** (184 mg, 83%) as a white solid in >20:1 d.r. ¹H NMR (500 MHz, 10% CD₃OD/CDCl₃): δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 5.90 (d, *J* = 45.4 Hz, 1H), 4.67 (dddd, *J* = 48.2, 10.6, 8.4, 2.5 Hz, 1H), 3.72 (dt, *J* = 30.0, 8.2 Hz, 1H), 2.27 (s, 3H), 1.92–1.77 (m, 1H), 1.67–1.47 (m, 2H), 0.90 (dd, *J* = 6.7, 2.1 Hz, 6H); ¹³C NMR (125.7 MHz, 10% CD₃OD/CDCl₃): δ 147.2, 144.0 (d, *J* = 21.2 Hz), 143.0, 138.6, 129.1, 125.9, 125.9, 123.1, 91.96–90.37 (m), 90.37–88.54 (m), 61.50 (dd, *J* = 25.6, 19.1 Hz), 40.41 (d, *J* = 20.0 Hz), 24.40 (d, *J* = 2.2 Hz), 23.13, 21.07, 20.84; ¹⁹F NMR (470.4 MHz, CDCl₃): δ -186.44 (dddt, *J* = 50.1,

42.4, 16.0, 8.2 Hz), -203.15 (ddd, $J = 45.3, 28.9, 7.2$ Hz); FTIR (thin film) ν 3371 (w), 1597 (w), 1518 (s), 1155 (s), 533 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{20}\text{H}_{24}\text{F}_2\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 427.1498; found 427.1496; $[\alpha]_{\text{D}}^{24} = -6.05^\circ$ (c 1.0, CH_3CN).



Prepared according to the general procedure using **5e** (223 mg, 0.52 mmol) with the following modification: 25 equiv of HF and 20 mol% of catalyst (*S,S*)-**1a** were used instead. The diastereomeric ratio (d.r.) of the crude residue was determined to be >20:1 by ^{19}F NMR. The crude residue was purified by silica gel column chromatography (10 to 40% diethyl ether in hexanes) to give *anti*-**6e** (189 mg, 78%) as a white solid in >20:1 d.r. ^1H NMR (500 MHz, 10% $\text{CD}_3\text{OD}/\text{CDCl}_3$): δ 7.85 (d, $J = 8.8$ Hz, 2H), 7.21 (d, $J = 4.4$ Hz, 2H), 7.19 (d, $J = 3.9$ Hz, 2H), 6.94 (d, $J = 8.3$ Hz, 2H), 5.87 (d, $J = 45.4$ Hz, 1H), 4.81–4.54 (m, 1H), 3.67 (dtd, $J = 29.1, 8.3, 1.6$ Hz, 1H), 2.25 (s, 3H), 1.85–0.71 (m, 13H); ^{13}C NMR (125.7 MHz, 10% $\text{CD}_3\text{OD}/\text{CDCl}_3$): δ 147.4, 144.0 (d, $J = 21.1$ Hz), 143.3, 138.5, 129.3, 126.1, 125.9 (d, $J = 9.1$ Hz), 123.3 (d, $J = 1.7$ Hz), 93.4–88.0 (m), 61.6 (dd, $J = 25.4, 19.1$ Hz), 39.3 (d, $J = 20.0$ Hz), 34.0, 33.9, 32.1, 26.4, 26.1 (d, $J = 31.3$ Hz), 21.1; ^{19}F NMR (470.4 MHz, 10% $\text{CD}_3\text{OD}/\text{CDCl}_3$): δ -185.61–185.99 (m), -203.12 (ddd, $J = 45.4, 28.8, 7.5$ Hz); FTIR (thin film) ν 1523 (s), 1447 (m), 1161 (s), 542 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{23}\text{H}_{28}\text{F}_2\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 467.1811; found 467.1817; $[\alpha]_{\text{D}}^{24} = -6.5^\circ$ (c 1.0, CH_3CN).

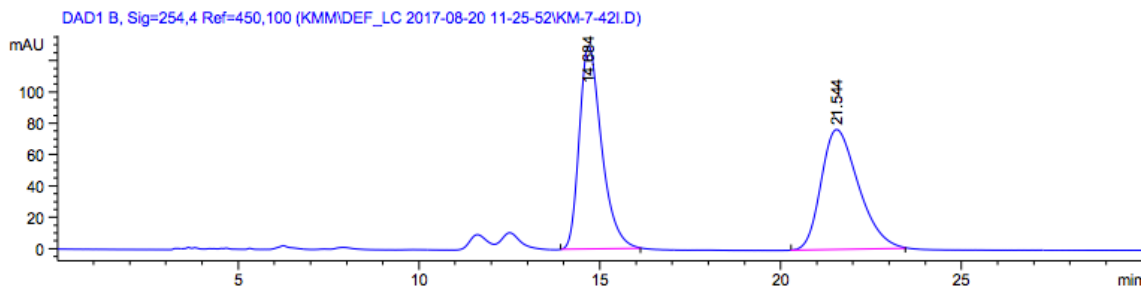


Prepared according to the general procedure using **7a** (187 mg, 0.52 mmol) with the following modification: 10 equiv of HF was used instead. After work-up, the crude residue was purified by silica gel column chromatography

(0 to 30% diethyl ether in hexanes) to give **8a** (161 mg, 82%) as a white solid in 86% e.e. Crystals of **8a** were grown by vapor diffusion of pentane into a solution of the compound in ethyl acetate. These crystals were filtered and dried *in vacuo* to give **8a** in >99% e.e. (128 mg, 65%). ¹H NMR (500 MHz, CDCl₃): δ 8.26–8.10 (m, 1H), 7.79–7.65 (m, 2H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 6.07 (dd, *J* = 47.6, 2.1 Hz, 1H), 3.90 (ddt, *J* = 27.9, 5.4, 2.8 Hz, 1H), 3.55–3.39 (m, 1H), 3.23 (dt, *J* = 10.2, 6.9 Hz, 1H), 2.41 (s, 2H), 2.02–1.83 (m, 1H), 1.64–1.48 (m, 1H), 1.49–1.32 (m, 1H); ¹³C NMR (125.7 MHz, CDCl₃): δ 148.5, 144.0, 139.9 (d, *J* = 21.2 Hz), 134.4, 131.2 (d, *J* = 8.2 Hz), 130.0, 129.8, 127.5, 123.2, 120.0 (d, *J* = 9.9 Hz), 94.5 (d, *J* = 183.7 Hz), 64.4 (d, *J* = 22.2 Hz), 49.5, 24.8 (d, *J* = 2.1 Hz), 21.6; ¹⁹F NMR (470.4 MHz, CDCl₃): δ -202.5 (dd, *J* = 47.6, 28.0 Hz); FTIR (thin film) ν 3091 (w), 1598 (w), 1531 (s), 1400 (s), 1156 (s), 588(s) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₈H₁₉FN₂O₄S [M+H]⁺: 379.1122; found 379.1115; [α]_D²⁴ = -120° (c 1.0, CHCl₃).

86% e.e., chiral HPLC (AS-H, 50% isopropanol in hexanes, 1.0 mL/min, λ = 254 nm); t_R(minor) = 14.9 min, t_R(major) = 21.4 min.

Racemic sample:

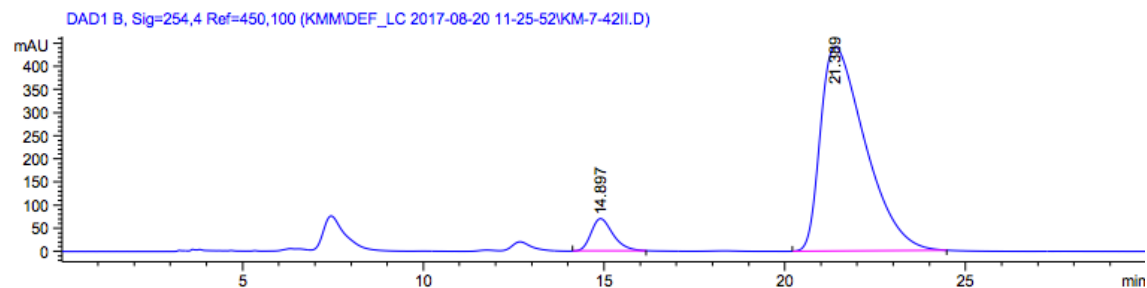


Signal 2: DAD1 B, Sig=254,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.684	BB	0.6498	5586.34180	129.87555	50.3545
2	21.544	BB	1.0773	5507.68604	76.56126	49.6455

Totals : 1.10940e4 206.43681

Enriched sample:

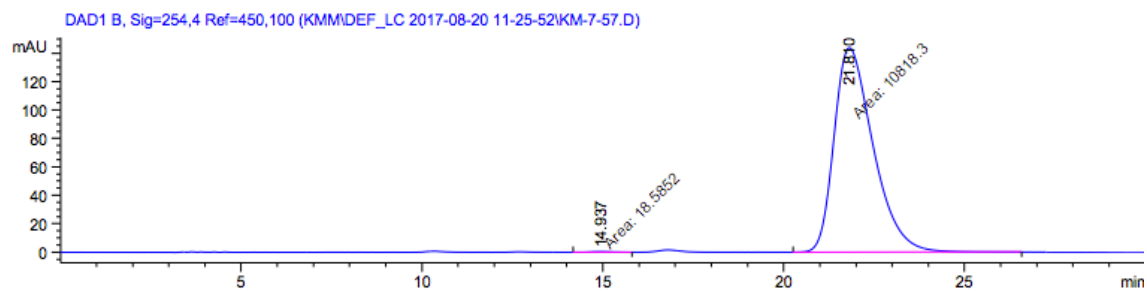


Signal 2: DAD1 B, Sig=254,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.897	BB	0.6486	2964.25171	69.91708	7.2321
2	21.389	BB	1.2659	3.80234e4	441.88013	92.7679

Totals : 4.09877e4 511.79721

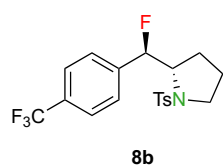
Upgraded (>99% e.e.) sample:



Signal 2: DAD1 B, Sig=254,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.937	MM	0.7423	18.58518	4.17295e-1	0.1715
2	21.810	MM	1.2532	1.08183e4	143.87566	99.8285

Totals : 1.08369e4 144.29295

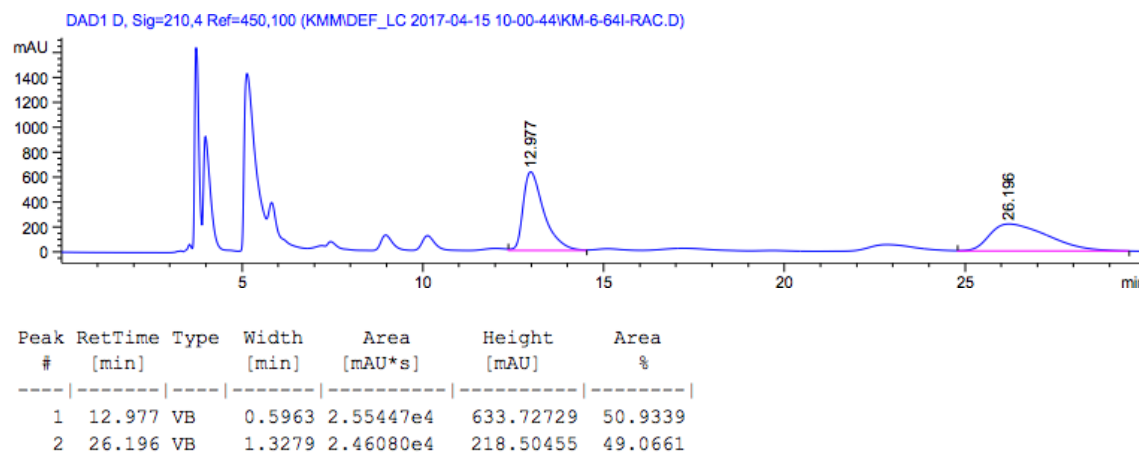


Prepared according to the general procedure using **7b** (199 mg, 0.52 mmol) with the following modification: 10 equiv of HF was used. After work-up, the crude residue was purified by silica gel column chromatography (0 to 20%

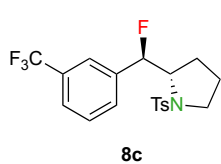
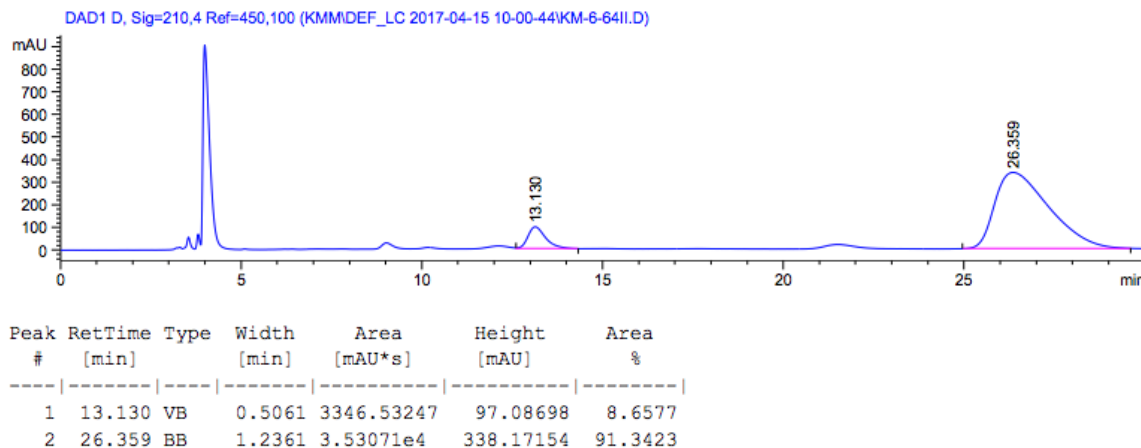
diethyl ether in hexanes) to give **8b** (148 mg, 71%) as a white solid in 84% ee. The d.r. of the crude mixture was determined to be 20:1 d.r. ¹H NMR (500 MHz, CDCl₃): δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.10 (d, *J* = 48.0 Hz, 1H), 3.88 (dddd, *J* = 29.3, 8.7, 3.7, 1.8 Hz, 1H), 3.56 – 3.43 (m, 1H), 3.23 (dt, *J* = 10.1, 7.0 Hz, 1H), 2.42 (s, 3H), 2.00 – 1.84 (m, 2H), 1.51 (tdd, *J* = 12.5, 6.8, 3.4 Hz, 1H), 1.36 (pd, *J* = 9.7, 8.3, 6.4 Hz, 1H); ¹⁹F NMR (470.4 MHz, CDCl₃): δ -62.6 (s, 3F), -204.48 (dd, *J* = 48.2, 29.2 Hz, 1F); ¹³C NMR (125.7 MHz, CDCl₃): δ 144.0, 141.8 (d, *J* = 20.5 Hz), 134.5, 130.4 (q, *J* = 32.5 Hz), 130.0, 127.6, 125.6 (dd, *J* = 4.1, 1.6 Hz), 125.3 (d, *J* = 8.9 Hz), 124.0 (q, *J* = 273.6 Hz), 95.1 (d, *J* = 182.7 Hz), 64.6 (d, *J* = 21.6 Hz), 49.5, 24.9 (d, *J* = 2.0 Hz), 24.8 (d, *J* = 5.5 Hz), 21.6; HRMS (FIA) Calc'd for C₁₉H₁₉F₄NO₂S [M+H]⁺: 402.1145; found 402.1143.

84% ee, Chiral HPLC (AS-H, 10% isopropanol in hexanes, 1.0 mL/min, λ = 210 nm); *t_R*(minor) = 13.1 min, *t_R*(major) = 26.3 min.

Racemic sample:



Enriched sample:

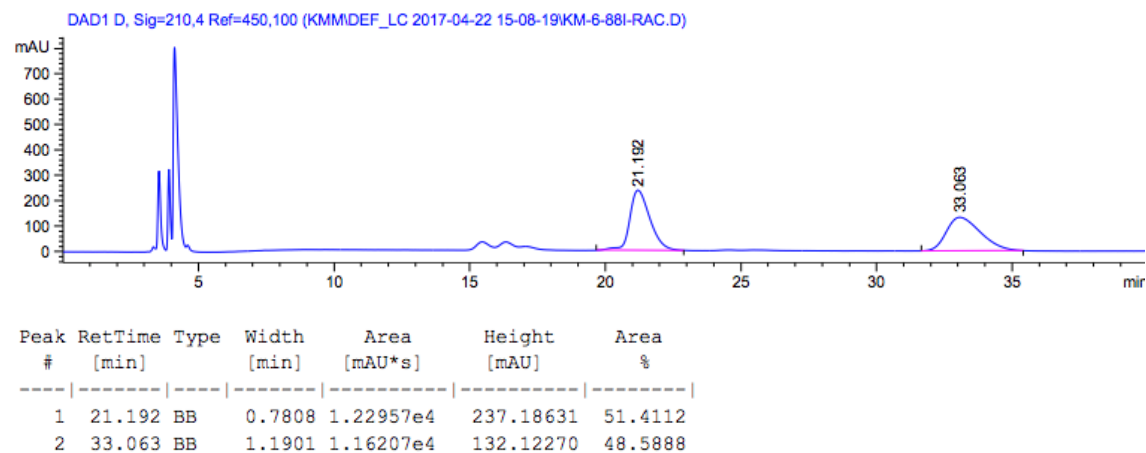


Prepared according to the general procedure using **7c** (199 mg, 0.52 mmol) with the following modification: 10 equiv of HF was used instead. After work-up, the crude residue was purified by silica gel column chromatography

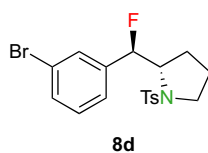
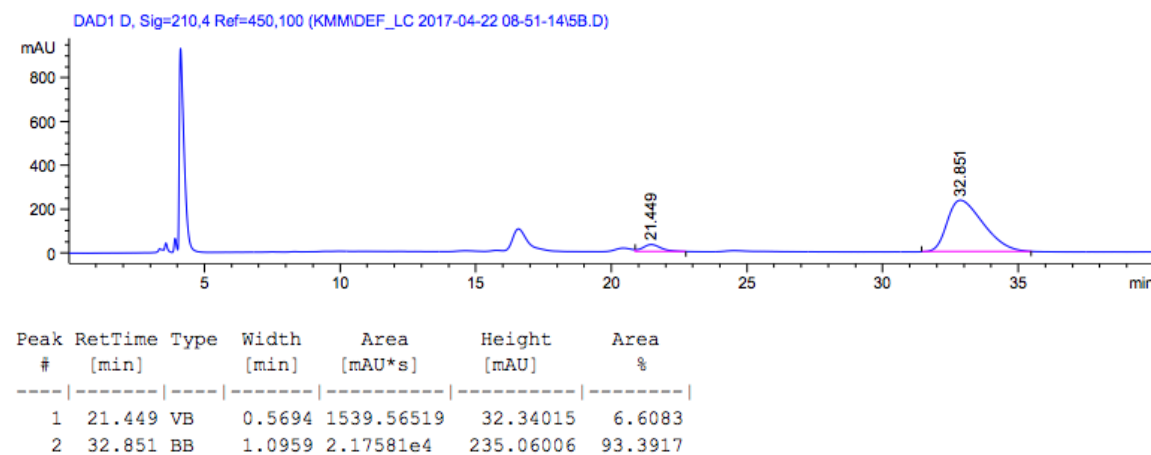
(0 to 20% diethyl ether in hexanes) to give **8c** (159 mg, 76%) as a white solid in 88% e.e. The d.r. of the crude mixture was determined to be 6:1 d.r. ¹H NMR (500 MHz, CDCl₃): δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.64 – 7.48 (m, 4H), 7.37 – 7.29 (m, 2H), 6.09 (dd, *J* = 47.8, 1.8 Hz, 1H), 3.89 (dddd, *J* = 29.1, 8.8, 3.5, 1.9 Hz, 1H), 3.48 (ddd, *J* = 10.0, 6.9, 5.2 Hz, 1H), 3.24 (dt, *J* = 10.0, 7.0 Hz, 1H), 2.42 (s, 3H), 2.01 – 1.85 (m, 2H), 1.60 – 1.48 (m, 1H), 1.44 – 1.33 (m, 1H); ¹⁹F NMR (470.4 MHz, CDCl₃): δ -62.7 (s, 3F), -203.9 (dd, *J* = 47.9, 29.2 Hz, 1F); ¹³C NMR (125.7 MHz, CDCl₃): δ 144.0, 138.9 (d, *J* = 20.7 Hz), 134.6, 131.1 (q, *J* = 32.4, 31.9 Hz), 130.0, 129.2 (d, *J* = 1.6 Hz), 128.4 (d, *J* = 8.2 Hz), 127.6, 125.5–124.6 (m), 124.0 (q, *J* = 273.6 Hz), 121.8 (dq, *J* = 7.8, 3.9 Hz), 95.0 (d, *J* = 182.9 Hz), 64.6 (d, *J* = 21.8 Hz), 49.6, 25.0 (d, *J* = 2.1 Hz), 24.8 (d, *J* = 5.5 Hz), 21.6; HRMS (FIA) Calc'd for C₁₉H₁₉F₄NO₂S [M+H]⁺: 402.1145; found 402.1143.

88% e.e., chiral HPLC (AS-H, 5% isopropanol in hexanes, 1.0 mL/min, λ = 210 nm); t_R(minor) = 21.5 min, t_R(major) = 32.9 min.

Racemic sample:



Enriched sample:



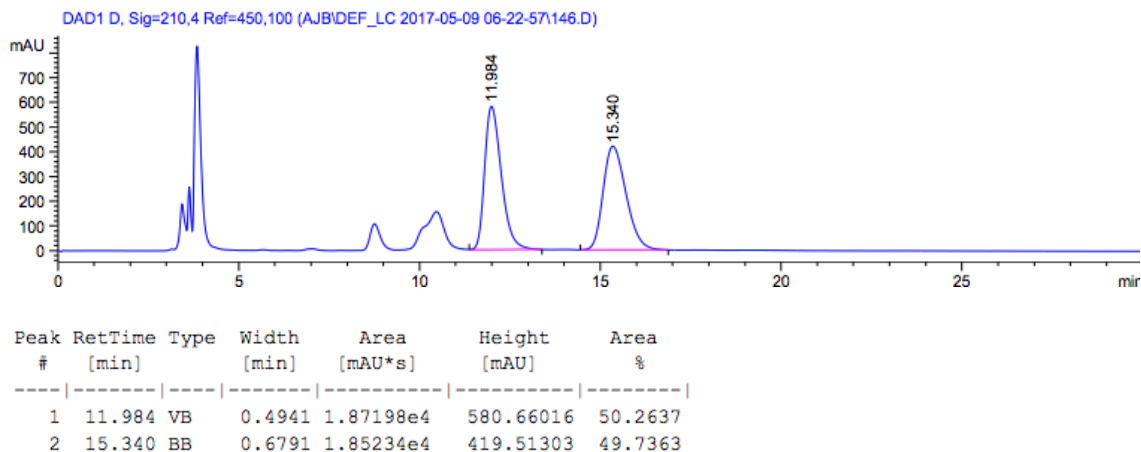
Prepared according to the general procedure using **7d** (205 mg, 0.52 mmol) with the following modification: 5 equiv of HF was used instead. After work-up, the crude residue was purified by silica gel column chromatography (0 to

20% diethyl ether in hexanes) to give **8d** (137 mg, 64%) as a white solid in 90% e.e. The d.r. of the crude mixture was determined to be 5:1 d.r. ¹H NMR (500 MHz, CDCl₃): δ 7.80 – 7.69 (m, 2H), 7.50 (d, *J* = 1.9 Hz, 1H), 7.45 (dt, *J* = 6.9, 2.1 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.29 – 7.23 (m, 2H), 6.01 (dd, *J* = 47.9, 1.8 Hz, 1H), 3.88 (dddd, *J* = 29.6, 9.0, 3.7, 1.8 Hz, 1H), 3.53 – 3.44

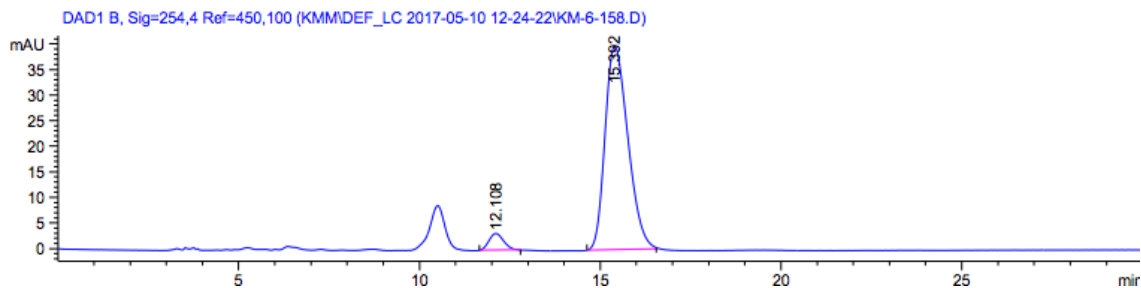
(m, 1H), 3.23 (dt, $J = 10.3, 7.2$ Hz, 1H), 2.43 (s, 3H), 2.05 – 1.85 (m, 2H), 1.55 – 1.51 (m, 1H), 1.45 – 1.31 (m, 1H); ^{19}F NMR (470.4 MHz, CDCl_3): δ -203.9 (dd, $J = 47.8, 29.5$ Hz); ^{13}C NMR (125.7 MHz, CDCl_3): δ 143.9, 140.2 (d, $J = 20.6$ Hz), 134.8, 131.4, 130.3, 130.0, 128.0 (d, $J = 9.5$ Hz), 127.6, 123.6 (d, $J = 8.5$ Hz), 94.9 (d, $J = 183.1$ Hz), 64.7 (d, $J = 21.7$ Hz), 49.6, 25.0 (d, $J = 2.3$ Hz), 24.8 (d, $J = 5.5$ Hz), 21.7; HRMS (FIA) Calc'd for $\text{C}_{18}\text{H}_{19}\text{BrFNO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 412.0377; found 412.0363.

90% e.e., chiral HPLC (AS-H, 30% isopropanol in hexanes, 1.0 mL/min, $\lambda = 210$ nm); $t_{\text{R}}(\text{minor}) = 12.1$ min, $t_{\text{R}}(\text{major}) = 15.4$ min.

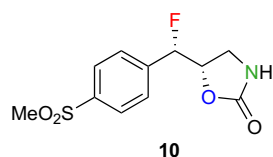
Racemic sample:



Enriched sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.108	BB	0.3898	92.86687	3.26500	5.0325
2	15.392	BB	0.6688	1752.48083	39.86847	94.9675

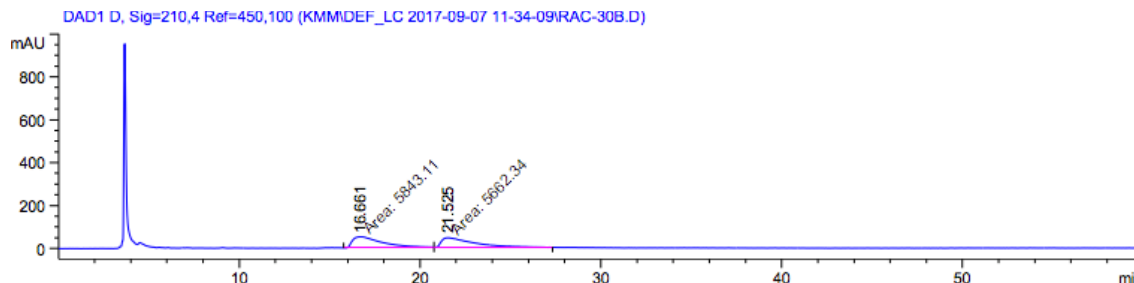


Prepared according to the general procedure using **9** (180 mg, 0.52 mmol) with the following modification: 100 equiv of HF and 20 mol% of catalyst (*R,R*)-**1a** were used instead. After work-up, the crude residue was purified

by silica gel column chromatography (0 to 2% methanol in dichloromethane) to give **10** (109 mg, 77%) as a white solid in 93% e.e. Crystals of **10** were grown by slow cooling of a solution of the compound in ethyl acetate. ¹H NMR (500 MHz, CDCl₃): δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.72–7.56 (m, 2H), 5.65 (dd, *J* = 45.0, 3.5 Hz, 1H), 5.17 (s, 1H), 4.96 (dddd, *J* = 18.9, 9.5, 6.3, 3.5 Hz, 1H), 3.89–3.46 (m, 2H), 3.08 (s, 3H); ¹³C NMR (125.7 MHz, 10% CD₃OD/CDCl₃): δ 159.3, 140.9 (d, *J* = 13.0 Hz), 140.8 (d, *J* = 13.0 Hz), 127.6, 127.2 (d, *J* = 7.5 Hz), 91.5 (d, *J* = 182.4 Hz), 76.6 (d, *J* = 23.2 Hz), 44.1, 41.4 (d, *J* = 4.7 Hz); ¹⁹F NMR (470.4 MHz, CDCl₃): δ -193.99 (dd, *J* = 45.2, 20.6 Hz); FTIR (thin film) ν 1749 (s), 1410 (m), 1090 (s), 766 (m) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₁H₁₂FNO₄S [M+H]⁺: 274.0544; found 274.0555; [α]_D²⁴ = +38.2° (c 1.0, CH₃OH).

93% e.e., chiral HPLC (IA, 30% isopropanol in hexanes, 1.0 mL/min, λ = 210 nm); t_R(major) = 16.3 min, t_R(minor) = 23.8 min.

Racemic sample:

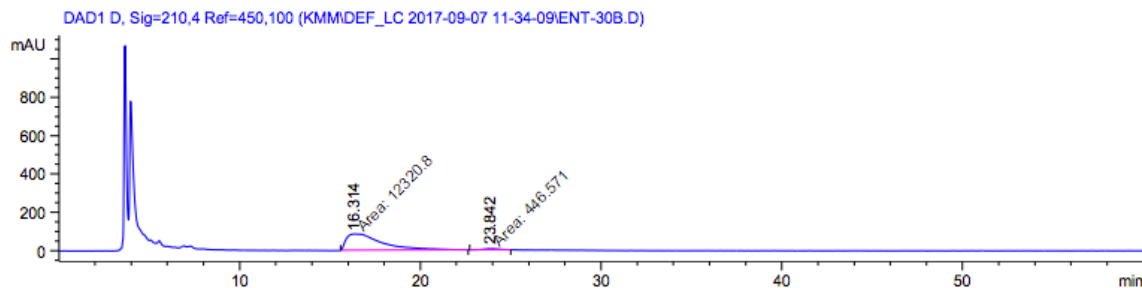


Signal 4: DAD1 D, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.661	MM	1.9167	5843.11377	50.80884	50.7856
2	21.525	MM	2.0973	5662.34033	44.99783	49.2144

Totals : 1.15055e4 95.80667

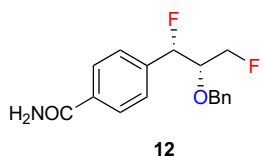
Enriched sample:



Signal 4: DAD1 D, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.314	MM	2.3692	1.23208e4	86.67197	96.5022
2	23.842	MM	1.0891	446.57083	6.83378	3.4978

Totals : 1.27674e4 93.50574



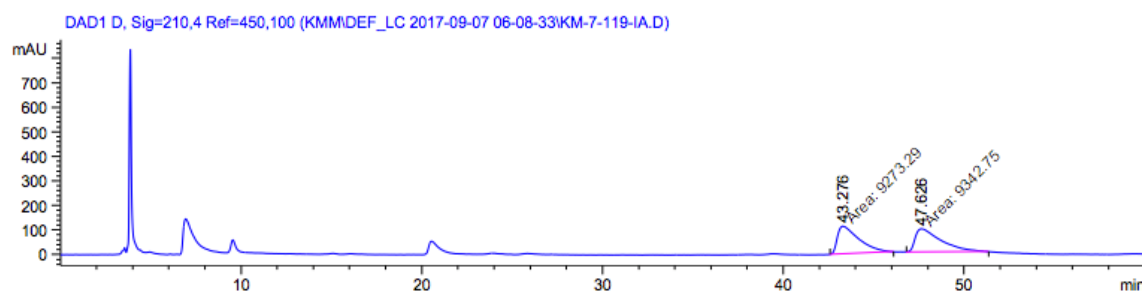
Prepared according to the general procedure using **11** (187 mg, 0.52 mmol) with the following modification: 100 equiv of HF and 20 mol% of catalyst (*R,R*)-**1a** were used instead. After work-up, the crude

residue was purified by silica gel column chromatography (10 to 100% diethyl ether in hexanes) to give **12** (159 mg, 64%) as a white solid in 92% e.e. Absolute configuration was assigned by analogy to an X-ray crystal structure of **4a**. ¹H NMR (500 MHz, CDCl₃): δ 7.83 (d, *J* = 7.8 Hz, 2H), 7.51–7.41 (m, 2H), 7.32–7.27 (m, 3H), 7.23–7.18 (m, 2H), 6.10 (br. s, 1H), 5.80 (br. s, 1H), 5.67 (dd, *J* = 45.9, 4.6 Hz, 1H), 4.68–4.47 (m, 3H), 4.32 (ddd, *J* = 46.9, 9.9, 5.3 Hz, 1H), 3.91 (dddt, *J* = 19.6, 17.6, 5.4, 4.6 Hz, 1H); ¹³C NMR (125.7 MHz, CDCl₃): δ 169.3, 140.5 (d, *J* =

20.6 Hz), 137.4, 133.9, 128.6, 128.1, 127.7, 126.4 (d, $J = 7.7$ Hz), 92.4 (dd, $J = 178.9, 6.5$ Hz), 82.1 (dd, $J = 172.3, 6.3$ Hz), 79.4 (dd, $J = 22.1, 19.5$ Hz), 73.9; ^{19}F NMR (470.4 MHz, CDCl_3): δ -194.57 (dd, $J = 46.0, 19.5$ Hz), -230.43 (td, $J = 46.9, 17.5$ Hz); FTIR (thin film) ν 3369 (br. s), 3176 (br. s), 1651 (s), 1394 (m), 1119 (m), 695 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{17}\text{H}_{17}\text{F}_2\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 274.0544; found 274.0555; $[\alpha]_{\text{D}}^{24} = +13.3^\circ$ (c 1.0, CH_3CN).

92% e.e., chiral HPLC (IA, 5% isopropanol in hexanes, 1.0 mL/min, $\lambda = 210$ nm); $t_{\text{R}}(\text{minor}) = 43.9$ min, $t_{\text{R}}(\text{major}) = 46.6$ min.

Racemic sample:

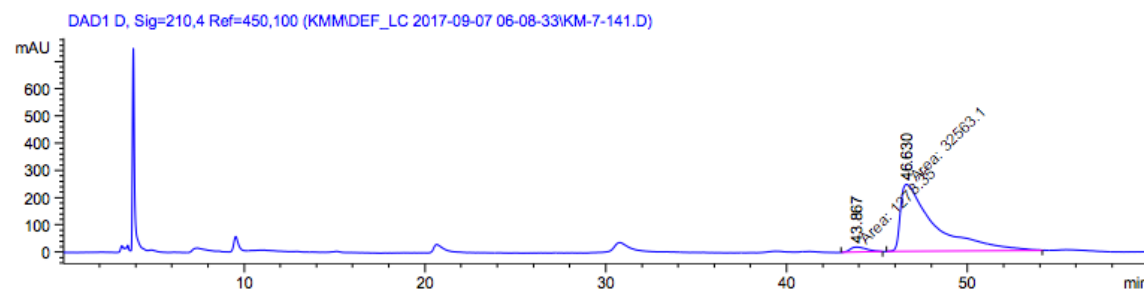


Signal 4: DAD1 D, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	43.276	MM	1.3718	9273.28711	112.66366	49.8134
2	47.626	MM	1.6608	9342.74512	93.75551	50.1866

Totals : 1.86160e4 206.41917

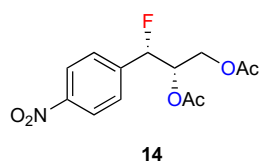
Enriched sample:



Signal 4: DAD1 D, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	43.867	MM	1.1051	1278.34875	19.27968	3.7775
2	46.630	MM	2.2030	3.25631e4	246.35051	96.2225

Totals : 3.38414e4 265.63019



Prepared according to the general procedure using **13** (187 mg, 0.52 mmol)

with the following modification: 100 equiv of HF and 20 mol% of catalyst

(*R,R*)-**1a** were used instead. After work-up, the crude residue was purified

by silica gel column chromatography (10 to 100% diethyl ether in hexanes) to give **14** (120 mg,

77%) as a white solid in 94% e.e. The absolute configuration was assigned by analogy to an X-

ray crystal structure of **16**. ¹H NMR (500 MHz, CDCl₃): δ 8.32–8.12 (m, 2H), 7.61–7.41 (m,

2H), 5.74 (dd, *J* = 45.9, 4.0 Hz, 1H), 5.51–5.34 (m, 1H), 4.39 (ddd, *J* = 11.9, 4.7, 1.0 Hz, 1H),

4.03 (dd, *J* = 11.9, 6.5 Hz, 1H), 2.03 (s, 3H), 1.95 (s, 3H); ¹³C NMR (125.7 MHz, CDCl₃): δ

170.4, 169.7, 148.3, 142.5 (d, *J* = 20.8 Hz), 126.9 (d, *J* = 7.9 Hz), 123.8, 90.8 (d, *J* = 182.1 Hz),

71.8 (d, *J* = 21.2 Hz), 61.8 (d, *J* = 6.2 Hz), 20.7, 20.5; ¹⁹F NMR (470.4 MHz, CDCl₃): δ -195.72

(dd, *J* = 46.0, 22.9 Hz); FTIR (thin film) ν 1742 (s), 1523 (s), 1212 (s), 1043 (s), 721 (m) cm⁻¹;

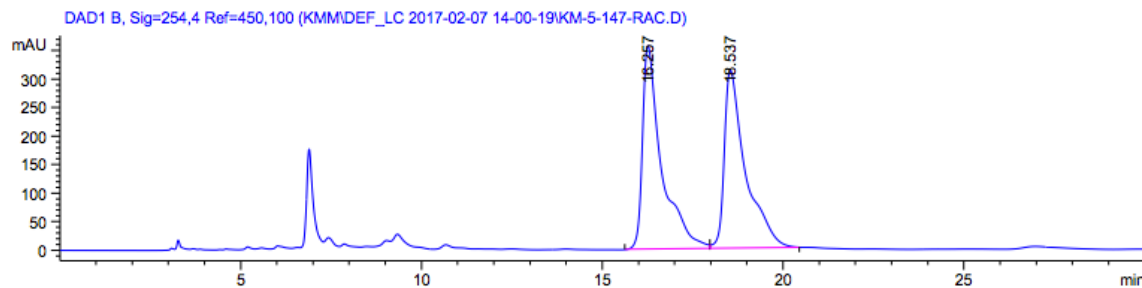
HRMS (ESI-TOF) Calc'd for C₁₃H₁₄FNO₆ [M+H]⁺: 300.0878; found 300.0893; [α]_D²⁶ = +1.4° (c

1.0, CH₃CN).

94% e.e., chiral HPLC (whelk, 10% isopropanol in hexanes, 1.0 mL/min, λ = 254 nm); t_R(minor)

= 17.1 min, t_R(major) = 18.9 min.

Racemic sample:

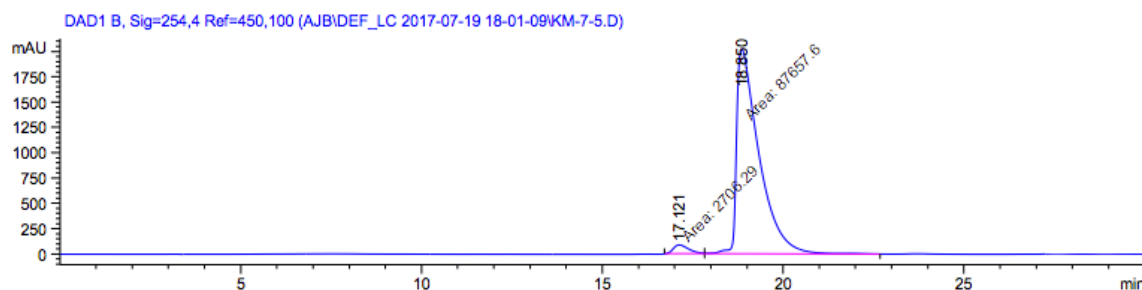


Signal 2: DAD1 B, Sig=254,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.257	BV	0.5212	1.31420e4	357.23099	50.6881
2	18.537	VB	0.5814	1.27852e4	312.45844	49.3119

Totals : 2.59273e4 669.68942

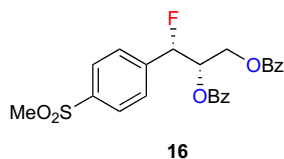
Enriched sample:



Signal 2: DAD1 B, Sig=254,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.121	MM	0.5083	2706.29297	88.74250	2.9949
2	18.850	MM	0.7215	8.76576e4	2024.92297	97.0051

Totals : 9.03639e4 2113.66547

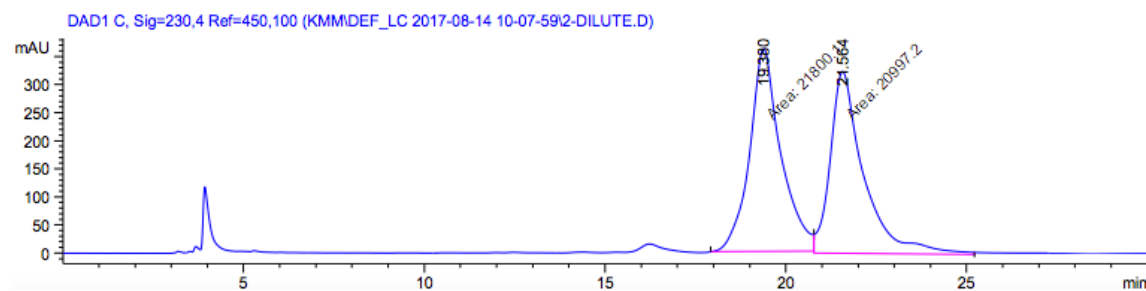


Prepared according to the general procedure using **15** (187 mg, 0.52 mmol) with the following modification: 100 equiv of HF and 20 mol% of catalyst (*R,R*)-**1a** were used instead. After work-up, the crude residue was purified by silica gel column chromatography (10 to 100% diethyl ether in

hexanes) to give **16** (173 mg, 73%) as a white solid in 94% e.e. Crystals of **16** were grown by vapor diffusion of pentane into a solution of the compound in ethyl acetate. ^1H NMR (500 MHz, CDCl_3): δ 8.03–7.86 (m, 6H), 7.69–7.61 (m, 2H), 7.58–7.51 (m, 2H), 7.45–7.37 (m, 4H), 6.07–5.82 (m, 2H), 4.74 (ddd, $J = 11.9, 4.7, 0.9$ Hz, 1H), 4.49 (dd, $J = 11.9, 6.4$ Hz, 1H), 2.97 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 165.9, 165.2, 141.5 (d, $J = 20.6$ Hz), 141.1, 133.6, 133.4, 129.8, 129.7, 129.2, 128.9, 128.6, 128.5, 127.8, 127.0 (d, $J = 7.8$ Hz), 91.1 (d, $J = 182.1$ Hz), 72.4 (d, $J = 22.0$ Hz), 62.3 (d, $J = 5.8$ Hz), 44.3; ^{19}F NMR (470.4 MHz, CDCl_3): δ -194.0 (dd, $J = 45.6, 21.2$ Hz); FTIR (thin film) ν 3064 (w), 1720 (s), 1451 (w), 1150 (s), 909 (m), 708 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{24}\text{H}_{21}\text{FO}_6\text{S}$ $[\text{M}+\text{H}]^+$: 457.1116; found 457.1107. $[\alpha]_{\text{D}}^{24} = +20.8^\circ$ (c 1.0, CH_3OH).

94% e.e., chiral HPLC (AD-H, 30% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230$ nm); $t_{\text{R}}(\text{minor}) = 19.9$ min, $t_{\text{R}}(\text{major}) = 21.8$ min.

Racemic sample:

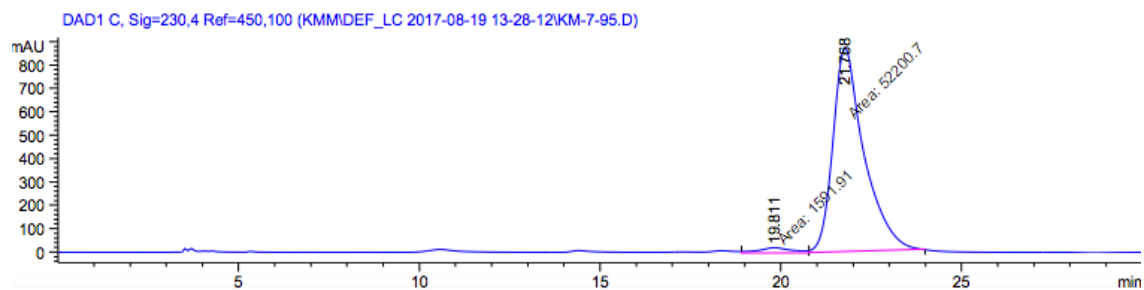


Signal 3: DAD1 C, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.380	MM	1.0044	2.18001e4	361.76038	50.9380
2	21.564	MM	1.0784	2.09972e4	324.51047	49.0620

Totals : 4.27972e4 686.27084

Enriched sample:

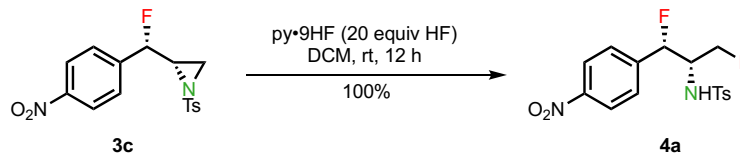


Signal 3: DAD1 C, Sig=230,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.811	MM	1.1281	1591.90503	23.51830	2.9593
2	21.768	MM	0.9961	5.22007e4	873.43707	97.0407

Totals : 5.37926e4 896.95537

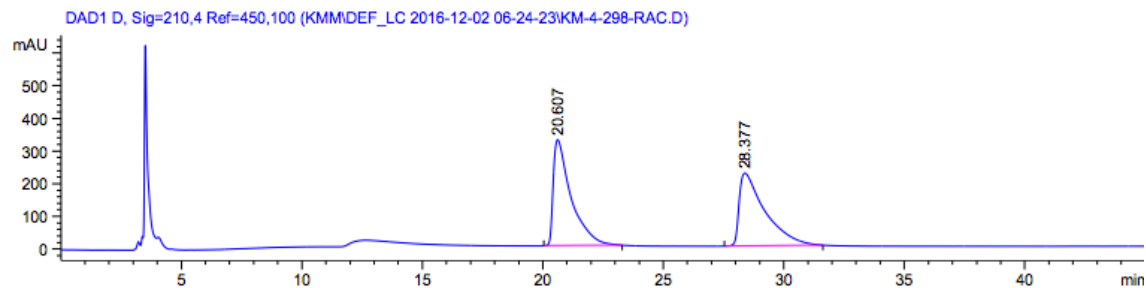
Synthetic Elaboration Studies



To a solution of **3c** (65.0 mg, 0.186 mmol, 1 equiv) in dichloromethane (1 mL) in a low-density polyethylene tube was added HF–pyridine (py•9HF, 70% hydrogen fluoride by weight, 100 μ L, 20 equiv hydrogen fluoride). The reaction mixture was stirred at room temperature for 12 hours. The heterogeneous mixture was transferred carefully into a vigorously stirred suspension of basic alumina (0.5 g) in dichloromethane at -78 $^{\circ}\text{C}$. The resulting suspension was allowed to warm to room temperature and filtered, washing with 10 mL dichloromethane. The combined filtrate was concentrated under reduced pressure to give **4a** as a white solid (68.6 mg, 100%). Crystals of **4a** were grown by vapor diffusion of pentane into a solution of the compound in ethyl acetate. ^1H NMR (500 MHz, 10% $\text{CD}_3\text{OD}/\text{CDCl}_3$): δ 7.99 (d, $J = 8.7$ Hz, 2H), 7.37 (d, $J = 8.2$ Hz, 2H), 7.27 (d, $J = 8.7$ Hz, 2H), 7.06 (d, $J = 8.7$ Hz, 2H), 5.83 (d, $J = 45.6$ Hz, 1H), 4.96 (d, $J = 9.5$ Hz, 1H), 4.72–4.45 (m, 2H), 3.90–3.72 (m, 1H), 2.35 (s, 3H); ^{13}C NMR (125.7 MHz, 10% $\text{CD}_3\text{OD}/\text{CDCl}_3$): δ 147.5, 143.5, 143.3 (d, $J = 21.1$ Hz), 137.2, 129.3, 126.4, 126.0 (d, $J = 8.6$ Hz), 123.3, 89.8 (dd, $J = 180.1, 2.4$ Hz), 80.8 (dd, $J = 176.3, 4.3$ Hz), 56.9 (dd, $J = 22.0, 20.6$ Hz), 21.1; ^{19}F NMR (470.4 MHz, 10% $\text{CD}_3\text{OD}/\text{CDCl}_3$): -203.2 (dd, $J = 45.3, 25.6$ Hz, 1F), -223.2 (td, $J = 46.7, 10.7$ Hz, 1F); FTIR (thin film) ν 3281 (br. m), 1790 (w), 1522 (s), 1346 (s), 1160 (s), 548 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{16}\text{H}_{16}\text{F}_2\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 371.0872; found 371.0866; $[\alpha]_{\text{D}}^{26} = +33.45^{\circ}$ (c 1.0, CH_3CN).

99% e.e., chiral HPLC (Whelk, 10% isopropanol in hexanes, 1.0 mL/min, $\lambda = 210$ nm); $t_{\text{R}}(\text{minor}) = 21.0$ min, $t_{\text{R}}(\text{major}) = 26.8$ min.

Racemic sample:

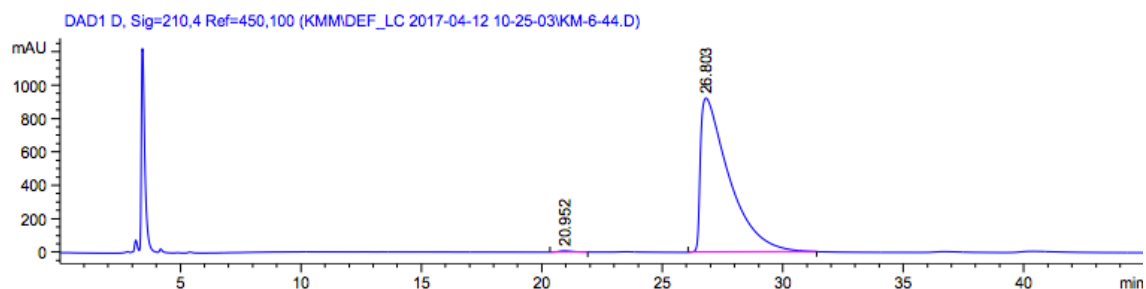


Signal 4: DAD1 D, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.607	BB	0.7391	1.67828e4	324.67023	50.2482
2	28.377	BB	1.0231	1.66170e4	223.05663	49.7518

Totals : 3.33998e4 547.72685

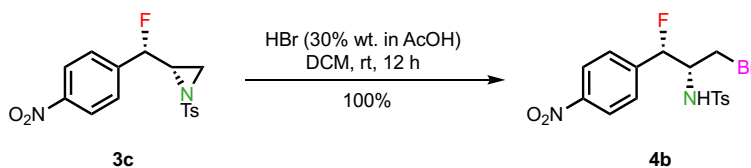
Enriched sample:



Signal 4: DAD1 D, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.952	BB	0.4807	307.36530	7.61842	0.3997
2	26.803	BB	1.0921	7.65846e4	922.89575	99.6003

Totals : 7.68920e4 930.51417

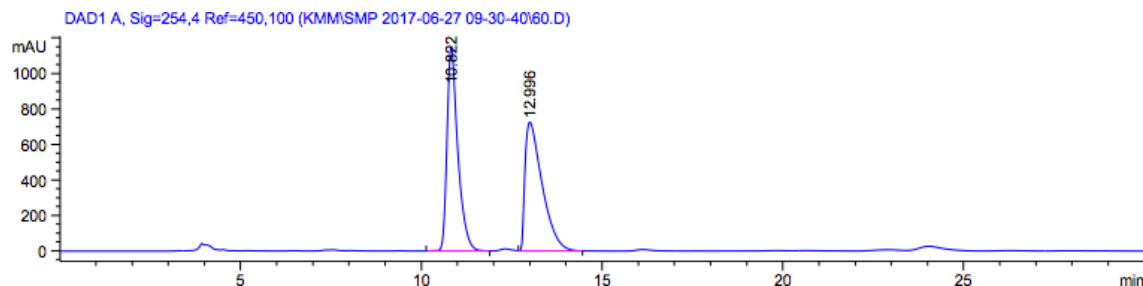


To a solution of **3c** (65.0 mg, 0.186 mmol, 1 equiv) in dichloromethane (1 mL) was added hydrobromic acid (33 wt. % in acetic acid, 1 mL). The reaction mixture was stirred at room

temperature for 12 hours. The solution was transferred carefully into a vigorously stirred suspension of basic alumina (0.5 g) in dichloromethane at -78°C . The resulting suspension was allowed to warm to room temperature and filtered, washing with 10 mL 1:1 diethyl ether:dichloromethane. The combined filtrate was concentrated under reduced pressure to give **4b** as an orange solid (80.0 mg, 100%). ^1H NMR (500 MHz, CDCl_3): δ 7.99 (d, $J = 8.6$ Hz, 2H), 7.39–7.33 (m, 2H), 7.26 (d, $J = 8.6$ Hz, 2H), 7.05 (d, $J = 7.9$ Hz, 2H), 6.07 (d, $J = 44.6$ Hz, 1H), 4.90 (d, $J = 9.3$ Hz, 1H), 3.77–3.66 (m, 1H), 3.66–3.56 (m, 2H), 2.35 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 147.67, 144.12, 142.96 (d, $J = 19.8$ Hz), 136.4, 129.7, 127.1, 126.1 (d, $J = 6.6$ Hz), 123.6, 90.3 (d, $J = 180.7$ Hz), 59.1 (d, $J = 19.6$ Hz), 31.6, 21.4; ^{19}F NMR (470.4 MHz, CDCl_3): δ -202.6 (dd, $J = 45.6, 23.1$ Hz); FTIR (thin film) ν 3274 (br. m), 1608 (w), 1522 (s), 1157 (s), 946 (m), 548 (s) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{16}\text{H}_{16}\text{BrFN}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 431.0071; found 431.0066; $[\alpha]_{\text{D}}^{25} = +14.2^{\circ}$ (c 1.0, CH_3OH).

99% e.e., chiral HPLC (AD-H, 20% isopropanol in hexanes, 1.0 mL/min, $\lambda = 254$ nm); $t_{\text{R}}(\text{minor}) = 10.9$ min, $t_{\text{R}}(\text{major}) = 13.4$ min.

Racemic sample:

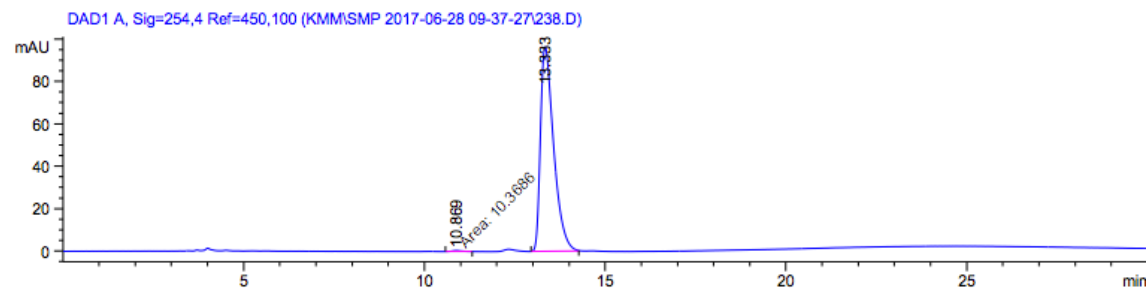


Signal 1: DAD1 A, Sig=254,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.822	BB	0.3083	2.39347e4	1152.55505	50.0350
2	12.996	VB	0.4959	2.39012e4	726.38916	49.9650

Totals : 4.78360e4 1878.94421

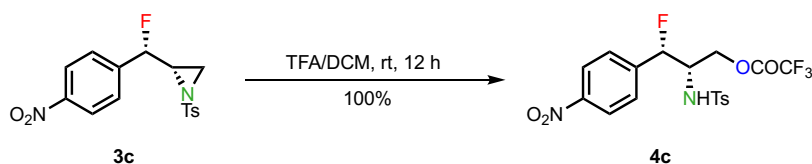
Enriched sample:



Signal 1: DAD1 A, Sig=254,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.869	MM	0.3400	10.36864	5.08316e-1	0.4226
2	13.333	BB	0.3839	2442.94775	96.32810	99.5774

Totals : 2453.31639 96.83642

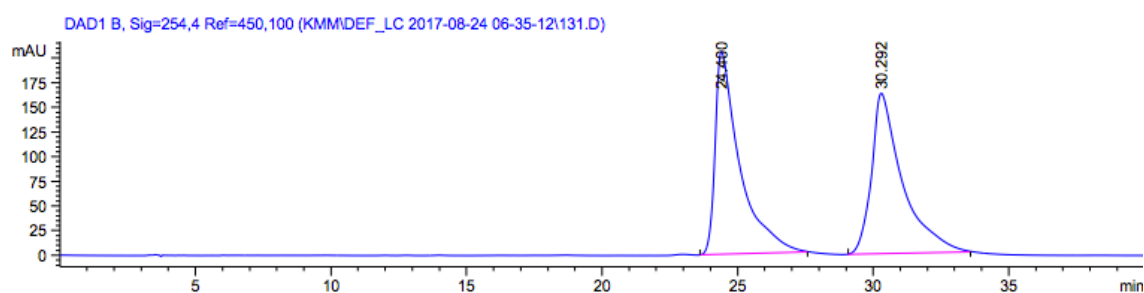


To a solution of **3c** (65.0 mg, 0.186 mmol, 1 equiv) in dichloromethane (1 mL) was added trifluoroacetic acid (0.5 mL). The reaction mixture was stirred at room temperature for 12 hours, concentrated under reduced pressure to give **4c** as a white solid (86.2 mg, 100%). ¹H NMR (500 MHz, CDCl₃): δ 7.94 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 1H), 5.76 (dd, *J* = 45.5, 2.1 Hz, 1H), 5.55 (d, *J* = 9.3 Hz, 1H), 4.78–4.35 (m, 2H), 4.18–3.90 (m, 1H), 2.34 (s, 3H); ¹³C NMR (125.7 MHz, CDCl₃): δ 157.0 (q, *J* = 43.3 Hz), 147.9, 144.3, 142.2 (d, *J* = 20.8 Hz), 136.5, 129.7, 126.7, 125.9 (d, *J* = 9.0 Hz), 123.6 (d, *J* = 1.5 Hz), 121.1–109.0 (m), 90.4 (d, *J* = 181.5 Hz), 66.0 (d, *J* = 3.9 Hz), 56.1 (d, *J* = 20.7 Hz), 21.4; ¹⁹F

NMR (470.4 MHz, CDCl₃): δ -74.7 (s, 3F), -201.6 (dd, J = 45.5, 25.9 Hz, 1F); FTIR (thin film) ν 3277 (br. w), 1788 (m), 1523 (m), 1151 (s), 733 (m) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₈H₁₆F₄N₂O₆S [M+H]⁺: 465.0738; found 465.0749; $[\alpha]_D^{25}$ = +20.8° (c 1.0, CH₃OH).

99% e.e., chiral HPLC (OJ-H, 40% isopropanol in hexanes, 1.0 mL/min, λ = 254 nm); t_R (minor) = 22.8 min, t_R (major) = 30.4 min.

Racemic sample:

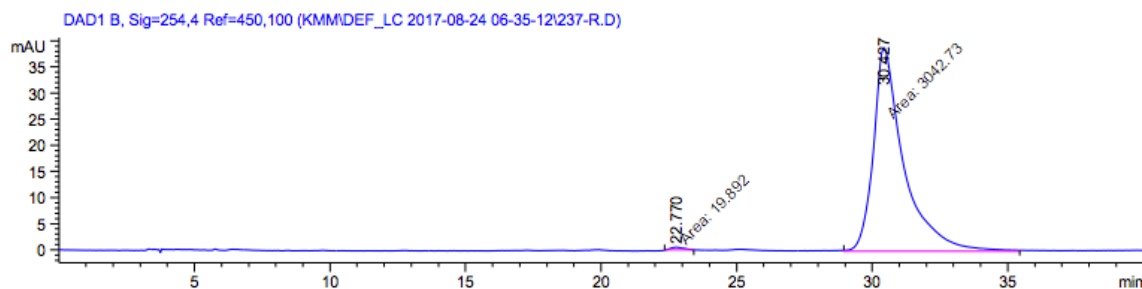


Signal 2: DAD1 B, Sig=254,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.400	BB	0.8763	1.30050e4	205.51227	50.2024
2	30.292	BB	1.0910	1.29001e4	162.69958	49.7976

Totals : 2.59051e4 368.21185

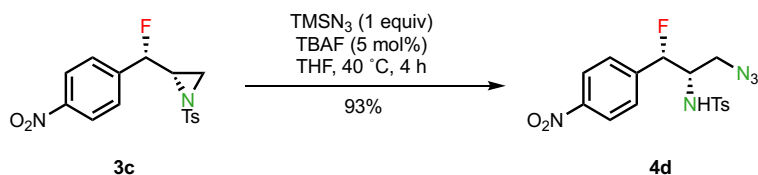
Enriched sample:



Signal 2: DAD1 B, Sig=254,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.770	MM	0.5845	19.89203	5.67209e-1	0.6495
2	30.427	MM	1.3026	3042.73462	38.93262	99.3505

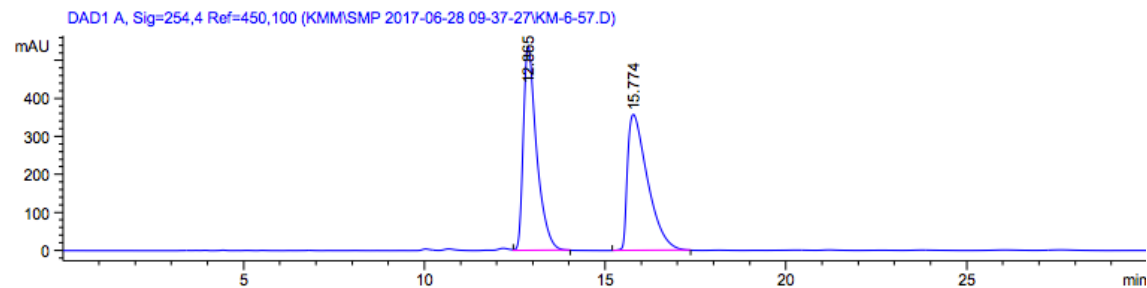
Totals : 3062.62665 39.49983



To a solution of **3c** (65.0 mg, 0.186 mmol, 1 equiv) in anhydrous tetrahydrofuran (2.1 mL) under nitrogen atmosphere was added azidotrimethylsilane (25.0 μL , 0.188 mmol, 1.0 equiv) followed by tetrabutylammonium fluoride (1.0 M in THF, 8.9 μL , 5 mol%). The reaction mixture was warmed to 40 $^\circ\text{C}$ and stirred for 4 hours. After cooling to room temperature, the solution was filtered through a plug of silica, washing with diethyl ether. The filtrate was concentrated under reduced pressure to give **4d** as a white solid (66.6 mg, 93%). ^1H NMR (500 MHz, CD_3CN): δ 7.95 (d, J = 8.6 Hz, 2H), 7.53–7.23 (m, 4H), 7.09 (d, J = 7.9 Hz, 2H), 6.11 (s, 1H), 5.78 (d, J = 45.5 Hz, 1H), 3.88–3.73 (m, 1H), 3.54 (ddd, J = 64.3, 12.7, 6.8 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (125.7 MHz, CD_3CN): δ 148.6, 144.57 (d, J = 20.8 Hz), 144.2, 138.9, 130.3, 127.3, 127.3, 124.1, 58.38 (d, J = 20.7 Hz), 53.16 (d, J = 3.9 Hz), 21.3; ^{19}F NMR (470.4 MHz, CD_3CN): δ -200.8–201.2 (m); FTIR (thin film) ν 3259 (m), 2108 (s), 1521 (s), 1346 (s), 1159 (s), 562 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{16}\text{H}_{16}\text{FN}_5\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 394.0980; found 394.0971; $[\alpha]_{\text{D}}^{25}$ = +47.2 $^\circ$ (c 1.0, CH_3OH).

99% e.e., chiral HPLC (AD-H, 20% isopropanol in hexanes, 1.0 mL/min, λ = 254 nm); t_{R} (minor) = 12.2 min, t_{R} (major) = 16.1 min.

Racemic sample:

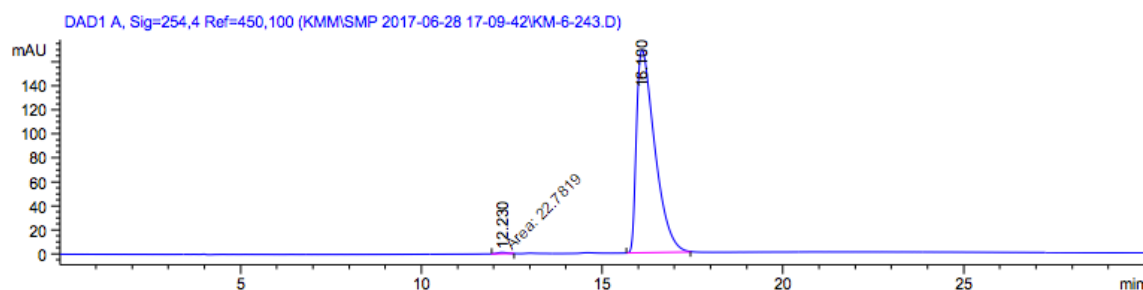


Signal 1: DAD1 A, Sig=254,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.865	VB	0.3801	1.37566e4	538.43182	49.8704
2	15.774	BB	0.5865	1.38281e4	358.09665	50.1296

Totals : 2.75847e4 896.52847

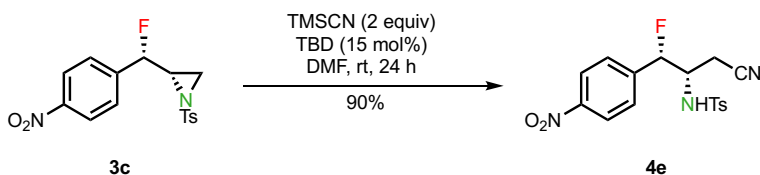
Enriched sample:



Signal 1: DAD1 A, Sig=254,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.230	MM	0.3299	22.78185	1.15102	0.3807
2	16.100	BB	0.5378	5961.09375	168.88438	99.6193

Totals : 5983.87560 170.03540

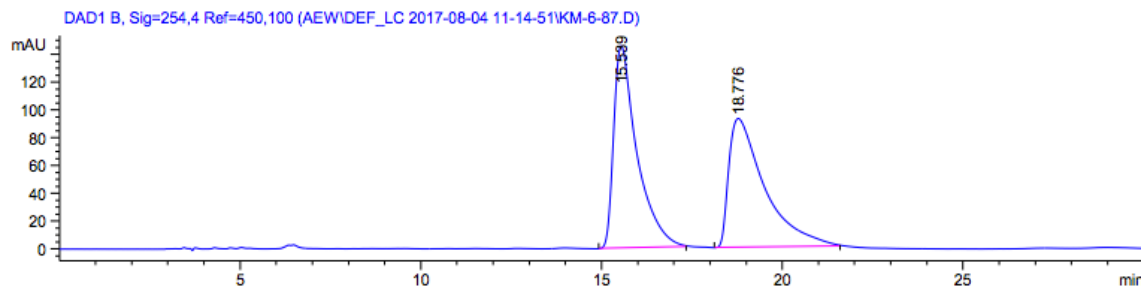


To a solution of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (3.8 mg, 0.027 mmol, 15 mol%) in anhydrous dimethylformamide (0.6 mL) was added **3c** (65.0 mg, 0.186 mmol, 1 equiv) followed

by trimethylsilyl cyanide (47.0 μ L, 0.376 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature. After 24 hours, the solution was diluted with diethyl ether (10 mL) and washed with 1 M HCl (aq.) (5 mL), water (3 x 5 mL) and brine (5 mL), dried over NaSO₄, filtered and concentrated under reduced pressure to **4e** as a white solid (63.2 mg, 90%). ¹H NMR (500 MHz, CDCl₃): δ 7.94 (d, J = 8.3 Hz, 2H), 7.44–7.32 (m, 4H), 7.26 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 7.9 Hz, 1H), 5.83 (dd, J = 45.6, 2.2 Hz, 1H), 5.63 (d, J = 9.3 Hz, 1H), 3.90 (dddd, J = 25.2, 10.4, 8.0, 3.4 Hz, 1H), 3.16–2.81 (m, 2H), 2.35 (s, 3H); ¹³C NMR (125.7 MHz, CDCl₃): δ 147.9, 144.5, 142.0 (d, J = 20.9 Hz), 136.2, 129.7, 126.7, 125.9 (d, J = 8.8 Hz), 123.6, 116.4, 91.8 (d, J = 182.4 Hz), 54.8 (d, J = 20.9 Hz), 22.4 (d, J = 3.7 Hz), 21.4; ¹⁹F NMR (470.4 MHz, CDCl₃): δ -201.0 (dd, J = 45.6, 25.9 Hz); FTIR (thin film) ν 3270 (br. m), 1609 (w), 1523 (s), 1346 (s), 1158 (s), 732 (m) cm⁻¹; HRMS (ESI-TOF) Calc'd for C₁₇H₁₆FN₃O₄S [M+H]⁺: 378.0918; found 378.0914; [α]_D²⁵ = +21.4° (c 1.0, CH₃OH).

99% e.e., chiral HPLC (AD-H, 20% isopropanol in hexanes, 1.0 mL/min, λ = 254 nm); t_R (minor) = 15.3 min, t_R (major) = 17.7 min.

Racemic sample:

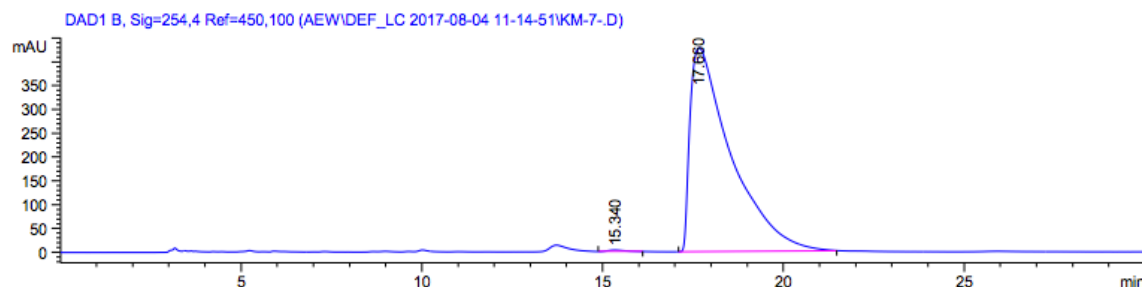


Signal 2: DAD1 B, Sig=254,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.539	BB	0.6484	6524.58691	145.71365	50.4887
2	18.776	BB	0.9749	6398.27490	92.74018	49.5113

Totals : 1.29229e4 238.45383

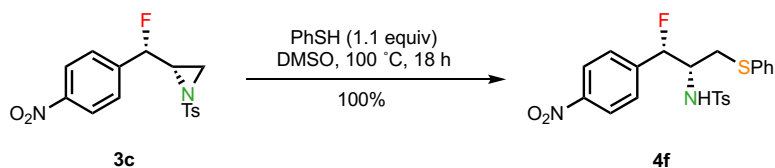
Enriched sample:



Signal 2: DAD1 B, Sig=254,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.340	BB	0.4146	104.34280	3.11625	0.3078
2	17.660	BB	1.1266	3.37971e4	428.31116	99.6922

Totals : 3.39015e4 431.42741

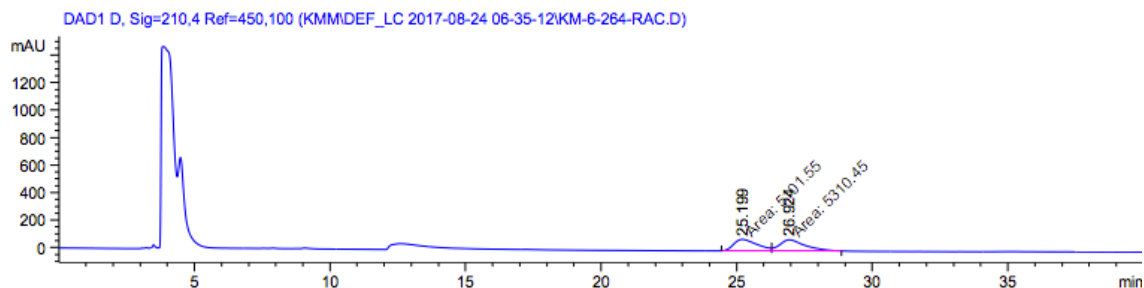


To a solution of **3c** (65.0 mg, 0.186 mmol, 1 equiv) in dimethyl sulfoxide (0.36 mL) was added thiophenol (21.6 μ L, 0.210 mmol, 1.1 equiv). The reaction mixture was heated to 100 °C for 18 hours. After cooling to room temperature, the crude mixture was purified by silica gel column chromatography (10 to 100% diethyl ether in hexanes) to give **4f** as a white solid (85.7 mg, 100%). ¹H NMR (500 MHz, CDCl₃): δ 7.88 (d, J = 8.8 Hz, 2H), 7.47–7.42 (m, 2H), 7.41–7.35 (m, 2H), 7.34–7.28 (m, 1H), 7.16 (dd, J = 8.3, 1.8 Hz, 2H), 7.07 (dd, J = 8.8, 1.9 Hz, 2H), 6.93 (dd, J = 8.2, 1.9 Hz, 2H), 6.13 (d, J = 45.2 Hz, 1H), 5.28 (dd, J = 9.4, 2.1 Hz, 1H), 3.63–3.32 (m,

2H), 3.34–3.08 (m, 1H), 2.31 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 147.5, 143.9, 143.7 (d, J = 21.0 Hz), 136.2, 133.6, 123.0, 129.5, 129.4, 127.2, 126.8, 125.6 (d, J = 9.0 Hz), 123.3 (d, J = 1.7 Hz), 90.0 (d, J = 180.7 Hz), 57.0 (d, J = 20.8 Hz), 35.0, 21.4; ^{19}F NMR (470.4 MHz, CDCl_3): δ -204.2 (dd, J = 45.1, 26.6 Hz); FTIR (thin film) ν 3272 (br. m), 1607 (w), 1523 (s), 1344 (s), 1158 (s), 742 (m) cm^{-1} ; HRMS (ESI-TOF) Calc'd for $\text{C}_{22}\text{H}_{21}\text{FN}_2\text{O}_4\text{S}_2$ $[\text{M}+\text{H}]^+$: 461.1000; found 461.0993; $[\alpha]_{\text{D}}^{25} = +53.2^\circ$ (c 1.0, CH_3OH).

99% e.e., chiral HPLC (AD-H, 10% isopropanol in hexanes, 1.0 mL/min, λ = 210 nm); t_{R} (major) = 25.2 min, t_{R} (minor) = 28.3 min.

Racemic sample:

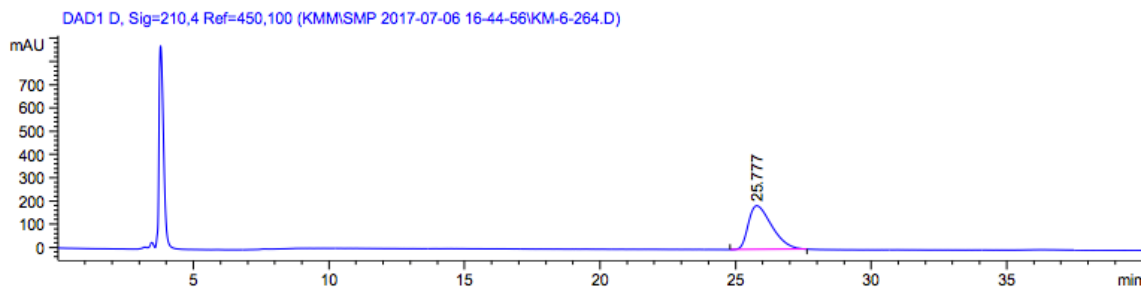


Signal 4: DAD1 D, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.199	MM	1.0066	5101.55322	84.47024	48.9969
2	26.924	MM	1.0829	5310.44678	81.72871	51.0031

Totals : 1.04120e4 166.19895

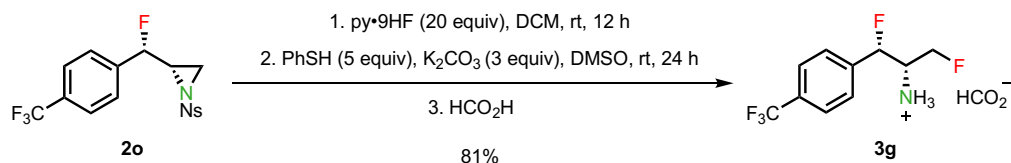
Enriched sample:



Signal 4: DAD1 D, Sig=210,4 Ref=450,100

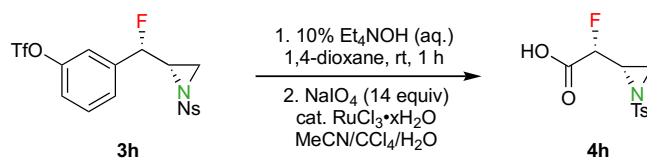
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.777	BB	0.8456	1.13442e4	188.10159	100.0000

Totals : 1.13442e4 188.10159



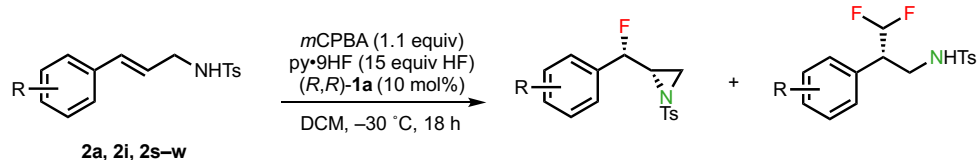
To a solution of **3o** (75.2 mg, 0.186 mmol, 1 equiv) in dichloromethane (1 mL) in a low-density polyethylene tube was added HF–pyridine (py•9HF, 70% hydrogen fluoride by weight, 100 μ L, 20 equiv hydrogen fluoride). The reaction mixture was stirred at room temperature for 12 hours. The heterogeneous mixture was transferred carefully into a vigorously stirred suspension of basic alumina (0.5 g) in dichloromethane at -78 °C. The resulting suspension was allowed to warm to room temperature and filtered, washing with 10 mL dichloromethane. The combined filtrate was concentrated under reduced pressure. The crude residue was dissolved in DMSO (0.37 mL) to which thiophenol (95.5 μ L, 0.93 mmol, 5 equiv) and potassium carbonate (129 mg, 0.93 mmol, 5 equiv) were added. The reaction mixture was stirred at room temperature. After 24 h, the crude mixture was purified by silica gel column chromatography (0% to 5% CH₃OH/CH₂Cl₂) followed by prep HPLC (0% to 50% (0.1% HCO₂H (aq.))/CH₃CN) to give **4g** (43.0 mg, 81%) as a white solid. ¹H NMR (600 MHz, CDCl₃): δ 8.01 (s, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 7.9 Hz, 2H), 5.60 (dd, J = 46.9, 5.2 Hz, 1H), 4.49 (dddd, J = 46.9, 9.5, 5.4, 1.8 Hz, 1H), 4.34 (ddd, J = 46.8, 9.5, 4.8 Hz, 1H), 3.38 (br. s, 1H), 3.38–3.23 (m, 1H); ¹³C NMR (125.7 MHz, CDCl₃): δ 163.8, 141.0 (d, J = 20.6 Hz), 131.2 (q, J = 32.6 Hz), 126.3 (d, J = 7.7 Hz), 125.8 (q, J = 3.8 Hz), 123.7 (q, J = 272.3 Hz), 93.1 (dd, J = 175.0, 2.8 Hz), 83.5 (dd, J = 171.2, 6.2 Hz), 56.4 (dd, J = 22.5, 19.2 Hz); ¹⁹F NMR (470.4 MHz, CDCl₃): δ -62.8 (s, 3H), -196.5 (dd, J = 47.1, 19.7 Hz,

1H), -230.4 (td, $J = 47.1, 19.1$ Hz, 1H); HRMS (ESI-TOF) Calc'd for $C_{11}H_{12}F_2NO_2$ $[M-HCO_2^-]$: 240.0806; found 240.0807; $[\alpha]_D^{25} = +13.8^\circ$ (c 1.0, CH_3CN).



To a solution of **3h** (84.3 mg, 0.186 mmol, 1 equiv) in 1,4-dioxane (1.10 mL) was added 10% Et_4NOH (aq.) (0.55 mL). The reaction mixture was stirred at room temperature. After 1 h, the reaction was quenched with 1 M HCl (aq.) (0.5 mL). Diethyl ether (5 mL) was added, and the aqueous and organic layers were separated. The aqueous layer was extracted with diethyl ether (3 x 5 mL), washed with brine (2 mL), dried over Na_2SO_4 , filtered and concentrated to give a colorless oil. The crude residue was dissolved in acetonitrile (0.5 mL) and carbon tetrachloride (0.5 mL). Water (1.0 mL), sodium periodate (557 mg, 2.60 mmol, 14 equiv) and a catalytic amount of ruthenium(III) chloride hydrate were added. The reaction mixture was allowed to stir at room temperature under air. After 18 h, diethyl ether (5 mL) was added, and the aqueous and organic layers were separated. The aqueous layer was extracted with diethyl ether (3 x 5 mL), washed with brine (2 mL), dried over Na_2SO_4 , filtered, concentrated and purified by prep HPLC (H_2O/CH_3CN) to give **4h** as a colorless oil (33.0 mg, 65%). ^1H NMR (600 MHz, $CDCl_3$): δ 8.20–7.90 (br. s, 1H), 7.83 (d, $J = 7.9$ Hz, 2H), 7.35 (d, $J = 7.9$ Hz, 2H), 4.85 (dd, $J = 47.4, 5.0$ Hz, 1H), 3.36–3.17 (m, 1H), 2.81 (d, $J = 7.3$ Hz, 1H), 2.51 (d, $J = 4.1$ Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 170.48 (d, $J = 25.0$ Hz), 145.42, 133.98, 129.94, 128.37, 85.51 (d, $J = 192.4$ Hz), 38.93 (d, $J = 23.5$ Hz), 29.75 (d, $J = 7.8$ Hz), 21.83; ^{19}F NMR (470.4 MHz, $CDCl_3$): δ -198.7 (d, $J = 43.5$ Hz); HRMS (ESI-TOF) Calc'd for $C_{11}H_{12}F_5NO_2$ $[M-H]$: 272.0398; found 272.0410.

Competition between Aziridinium versus Phenonium Ion Formation



To a solution of substrate (0.104 mmol, 1 equiv) and catalyst **1a** (8.0 mg, 0.0104 mmol, 10 mol%) in dichloromethane (0.6 mL) in a low-density polyethylene tube at $-78\text{ }^{\circ}\text{C}$ was added HF-pyridine (py·9HF, 70% hydrogen fluoride by weight, 42 μL , 15 equiv hydrogen fluoride) followed by *m*CPBA (77% by weight, 25.6 mg, 0.114 mmol, 1.1 equiv). The reaction mixture was warmed to $-30\text{ }^{\circ}\text{C}$ and stirred at that temperature for 16 hours. The heterogeneous mixture was transferred carefully into a vigorously stirred suspension of basic alumina (400 mg) in dichloromethane at $-78\text{ }^{\circ}\text{C}$. The resulting suspension was allowed to warm to room temperature and filtered, washing with 20 mL dichloromethane. The combined filtrate was concentrated under reduced pressure. The ratio of fluoroaziridine product yield [NHTs] to the combined fluoroaziridine and 1,1-difluoro-product yield [NHTs + Ar] was determined by ^{19}F NMR analysis of the crude mixture.

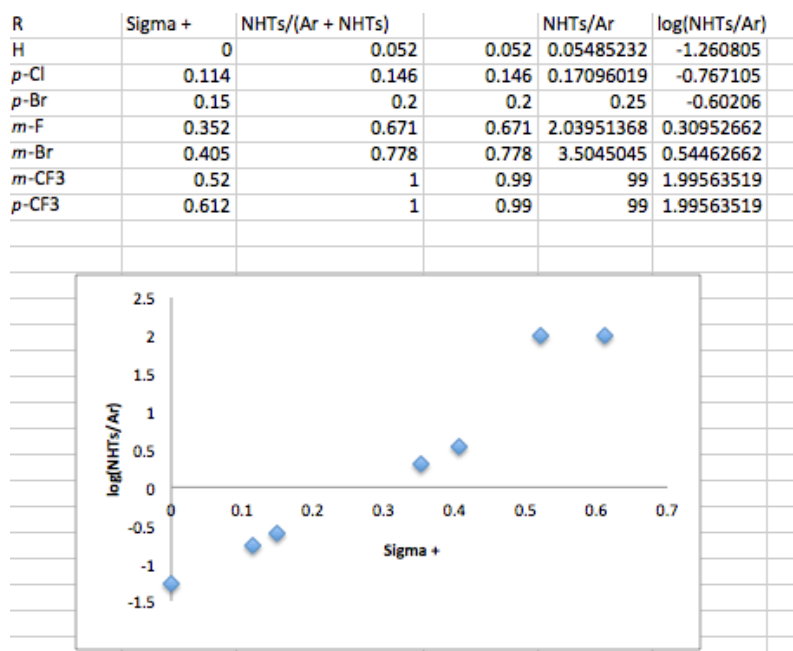
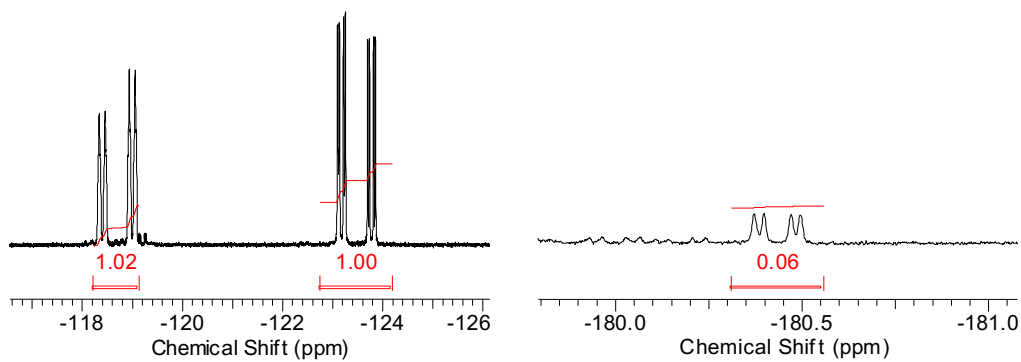


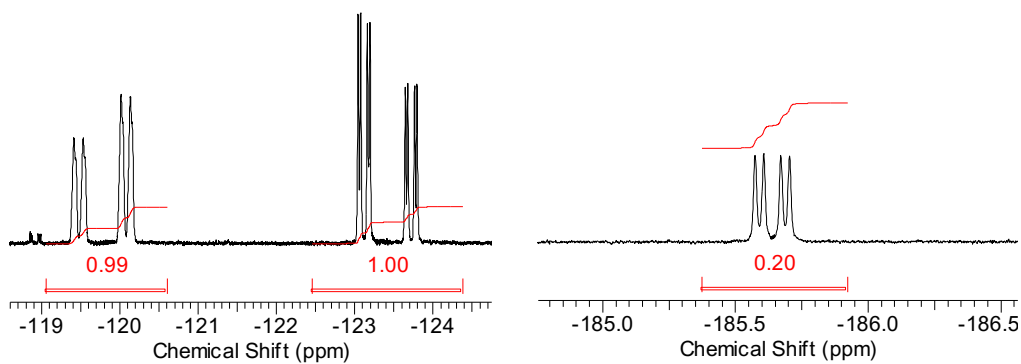
Figure S2.1 Hammett plot of the product selectivity for fluoroaziridine versus 1,1-product as a function of substituent. For the *m*-CF₃ and *p*-CF₃ derivatives, the reactions were completely selective (>99:1) for the fluoroaziridine. The points on the plot depict the lower boundaries for the value of $\log ([\text{NHTs}]/[\text{Ar}])$.

^{19}F NMR
145.7 Hz
 CDCl_3

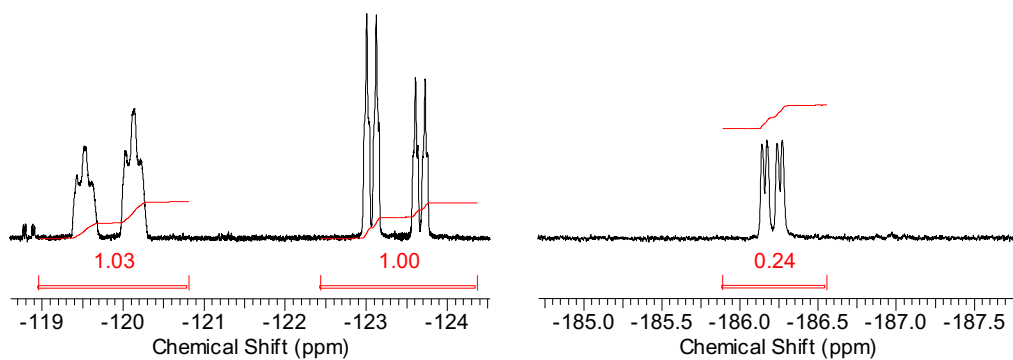
R = H:



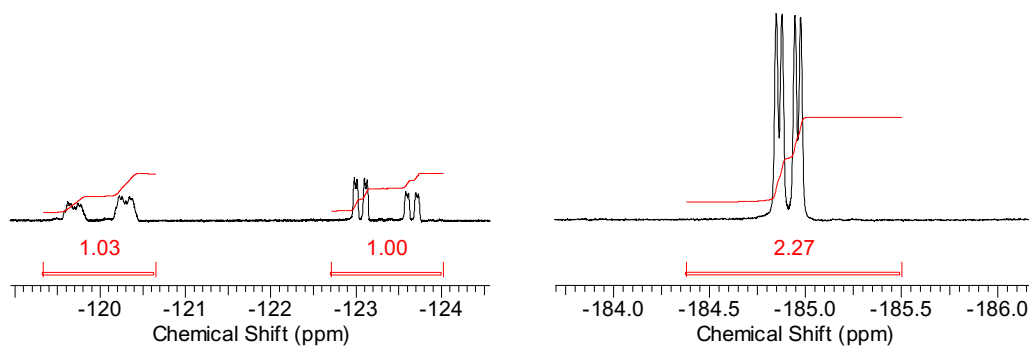
R = *p*-Cl:



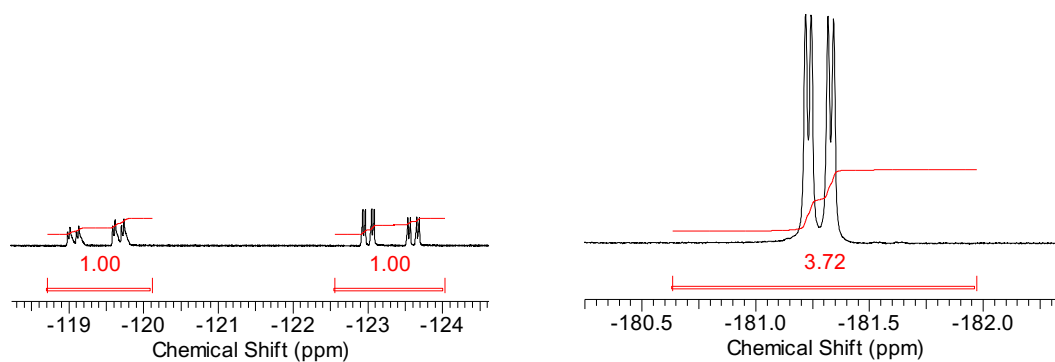
R = *p*-Br



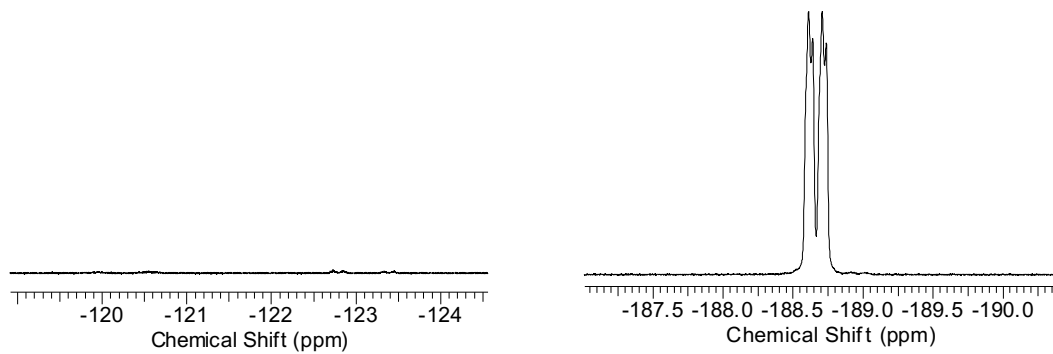
R = *m*-F



R = *m*-Br

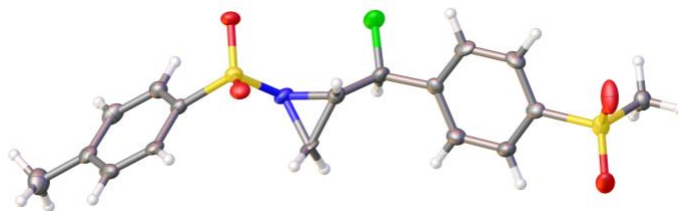


R = *m*-CF₃



X-ray Crystallography Information

X-Ray Crystallographic Information Data for 3b



X-Ray Crystallography: A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II CCD diffractometer (MoK α radiation, λ =0.71073 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 0.5° scans in ω at 28° in 2θ . Data integration down to 0.84 Å resolution was carried out using SAINT V8.37A with reflection spot size optimization.⁵⁰ Absorption corrections were made with the program TWINABS. The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods again F^2 using SHELXT-2014⁵¹ and SHELXL-2014⁵² with OLEX 2 interface.⁵³ Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table S2.1, and geometric parameters are shown in Table S2.2. The Ortep plots produced with

⁵⁰ Bruker AXS APEX3, Bruker AXS, Madison, Wisconsin, **2016**.

⁵¹ Sheldrick, G.M. *Acta Cryst.* **2015**, *A71*, 3–8.

⁵² Sheldrick, G.M. *Acta Cryst.* **2015**, *C71*, 3–8.

⁵³ Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. *J. Appl. Cryst.* **2009**, *42*, 339–341.

SHELXL-2014 program, and the other drawings were produced with Accelrys DS Visualizer 2.0.⁵⁴

Table S2.1 Experimental details.

Crystal data

Chemical formula	C ₁₇ H ₁₈ FNO ₄ S ₂
M_r	383.44
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	100
a, b, c (Å)	5.5270 (4), 8.6617 (6), 36.032 (3)
V (Å ³)	1725.0 (2)
Z	4
Radiation type	Mo $K\alpha$
μ (mm ⁻¹)	0.34
Crystal size (mm)	0.10 × 0.02 × 0.01

Data collection

Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan <i>SADABS</i>
$T_{\min}, T_{\max}$	0.833, 0.862
No. of measured, independent and observed [I $> 2s(I)$] reflections	29926, 3065, 2507
R_{int}	0.130
$(\sin \theta/\lambda)_{\max}$ (Å ⁻¹)	0.596

Refinement

$R[F^2 > 2s(F^2)], wR(F^2), S$	0.068, 0.129, 1.17
No. of reflections	3065
No. of parameters	228
H-atom treatment	H-atom parameters constrained
$D\rho_{\max}, D\rho_{\min}$ (e Å ⁻³)	0.36, -0.45

⁵⁴ Accelrys DS Visualizer v2.0.1, Accelrys Software. Inc., **2007**.

Absolute structure Flack x determined using 795 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).

Absolute structure parameter 0.11 (8)

Table 2.2 Geometric parameters (Å, °).

S1—O2	1.428 (5)	C6—H6	0.9500
S1—O1	1.434 (5)	C7—C8	1.379 (9)
S1—N1	1.659 (6)	C8—C9	1.389 (9)
S1—C10	1.743 (7)	C8—H8	0.9500
S2—O3	1.428 (6)	C9—H9	0.9500
S2—O4	1.438 (6)	C10—C15	1.387 (9)
S2—C17	1.737 (7)	C10—C11	1.391 (10)
S2—C7	1.779 (7)	C11—C12	1.382 (10)
F1—C3	1.410 (7)	C11—H11	0.9500
N1—C1	1.481 (8)	C12—C13	1.375 (10)
N1—C2	1.482 (8)	C12—H12	0.9500
C1—C2	1.480 (9)	C13—C14	1.395 (10)
C1—H1A	0.9900	C13—C16	1.506 (10)
C1—H1B	0.9900	C14—C15	1.384 (9)
C2—C3	1.504 (9)	C14—H14	0.9500
C2—H2	1.0000	C15—H15	0.9500
C3—C4	1.505 (10)	C16—H16A	0.9800
C3—H3	1.0000	C16—H16B	0.9800
C4—C5	1.381 (10)	C16—H16C	0.9800
C4—C9	1.383 (9)	C17—H17A	0.9800
C5—C6	1.384 (10)	C17—H17B	0.9800
C5—H5	0.9500	C17—H17C	0.9800
C6—C7	1.378 (9)		
O2—S1—O1	117.8 (3)	C5—C6—H6	120.7
O2—S1—N1	111.7 (3)	C6—C7—C8	121.5 (6)
O1—S1—N1	104.8 (3)	C6—C7—S2	118.7 (5)

O2—S1—C10	109.0 (3)	C8—C7—S2	119.7 (5)
O1—S1—C10	109.6 (3)	C7—C8—C9	118.9 (6)
N1—S1—C10	102.8 (3)	C7—C8—H8	120.6
O3—S2—O4	119.7 (4)	C9—C8—H8	120.6
O3—S2—C17	107.9 (4)	C4—C9—C8	120.7 (6)
O4—S2—C17	109.1 (4)	C4—C9—H9	119.6
O3—S2—C7	107.8 (3)	C8—C9—H9	119.6
O4—S2—C7	107.0 (3)	C15—C10—C11	120.3 (7)
C17—S2—C7	104.2 (3)	C15—C10—S1	120.0 (5)
C1—N1—C2	59.9 (4)	C11—C10—S1	119.6 (5)
C1—N1—S1	117.3 (5)	C12—C11—C10	118.7 (7)
C2—N1—S1	114.1 (4)	C12—C11—H11	120.6
C2—C1—N1	60.1 (4)	C10—C11—H11	120.6
C2—C1—H1A	117.8	C13—C12—C11	122.3 (7)
N1—C1—H1A	117.8	C13—C12—H12	118.8
C2—C1—H1B	117.8	C11—C12—H12	118.8
N1—C1—H1B	117.8	C12—C13—C14	118.1 (7)
H1A—C1—H1B	114.9	C12—C13—C16	122.7 (7)
C1—C2—N1	60.0 (4)	C14—C13—C16	119.2 (7)
C1—C2—C3	121.2 (6)	C15—C14—C13	121.0 (7)
N1—C2—C3	113.4 (6)	C15—C14—H14	119.5
C1—C2—H2	116.5	C13—C14—H14	119.5
N1—C2—H2	116.5	C14—C15—C10	119.6 (7)
C3—C2—H2	116.5	C14—C15—H15	120.2
F1—C3—C2	106.8 (5)	C10—C15—H15	120.2
F1—C3—C4	108.3 (6)	C13—C16—H16A	109.5
C2—C3—C4	113.2 (6)	C13—C16—H16B	109.5
F1—C3—H3	109.4	H16A—C16—H16B	109.5
C2—C3—H3	109.4	C13—C16—H16C	109.5
C4—C3—H3	109.4	H16A—C16—H16C	109.5
C5—C4—C9	119.0 (6)	H16B—C16—H16C	109.5
C5—C4—C3	118.7 (6)	S2—C17—H17A	109.5
C9—C4—C3	122.3 (6)	S2—C17—H17B	109.5

C4—C5—C6	121.4 (7)	H17A—C17—H17B	109.5
C4—C5—H5	119.3	S2—C17—H17C	109.5
C6—C5—H5	119.3	H17A—C17—H17C	109.5
C7—C6—C5	118.5 (7)	H17B—C17—H17C	109.5
C7—C6—H6	120.7		
O2—S1—N1—C1	30.2 (6)	C17—S2—C7—C6	99.6 (6)
O1—S1—N1—C1	158.9 (5)	O3—S2—C7—C8	34.4 (6)
C10—S1—N1—C1	-86.5 (5)	O4—S2—C7—C8	164.4 (5)
O2—S1—N1—C2	-37.0 (5)	C17—S2—C7—C8	-80.1 (6)
O1—S1—N1—C2	91.6 (5)	C6—C7—C8—C9	-1.0 (10)
C10—S1—N1—C2	-153.8 (5)	S2—C7—C8—C9	178.7 (6)
S1—N1—C1—C2	-103.4 (5)	C5—C4—C9—C8	0.1 (10)
N1—C1—C2—C3	-100.8 (7)	C3—C4—C9—C8	-179.1 (6)
S1—N1—C2—C1	108.8 (5)	C7—C8—C9—C4	0.4 (10)
C1—N1—C2—C3	113.7 (6)	O2—S1—C10—C15	-10.4 (6)
S1—N1—C2—C3	-137.5 (5)	O1—S1—C10—C15	-140.6 (5)
C1—C2—C3—F1	142.5 (6)	N1—S1—C10—C15	108.3 (6)
N1—C2—C3—F1	74.5 (7)	O2—S1—C10—C11	167.2 (5)
C1—C2—C3—C4	-98.4 (7)	O1—S1—C10—C11	36.9 (7)
N1—C2—C3—C4	-166.4 (6)	N1—S1—C10—C11	-74.1 (6)
F1—C3—C4—C5	-162.0 (6)	C15—C10—C11— C12	0.7 (10)
C2—C3—C4—C5	79.7 (8)	S1—C10—C11—C12	-176.9 (5)
F1—C3—C4—C9	17.3 (9)	C10—C11—C12— C13	-0.2 (11)
C2—C3—C4—C9	-101.1 (7)	C11—C12—C13— C14	-0.3 (10)
C9—C4—C5—C6	0.0 (10)	C11—C12—C13— C16	-179.8 (7)
C3—C4—C5—C6	179.2 (7)	C12—C13—C14— C15	0.4 (10)
C4—C5—C6—C7	-0.6 (11)	C16—C13—C14— C15	179.9 (6)
C5—C6—C7—C8	1.1 (10)	C13—C14—C15—	0.1 (10)

		C10	
C5—C6—C7—S2	-178.6 (5)	C11—C10—C15— C14	-0.6 (10)
O3—S2—C7—C6	-145.9 (6)	S1—C10—C15—C14	176.9 (5)
O4—S2—C7—C6	-15.8 (7)		

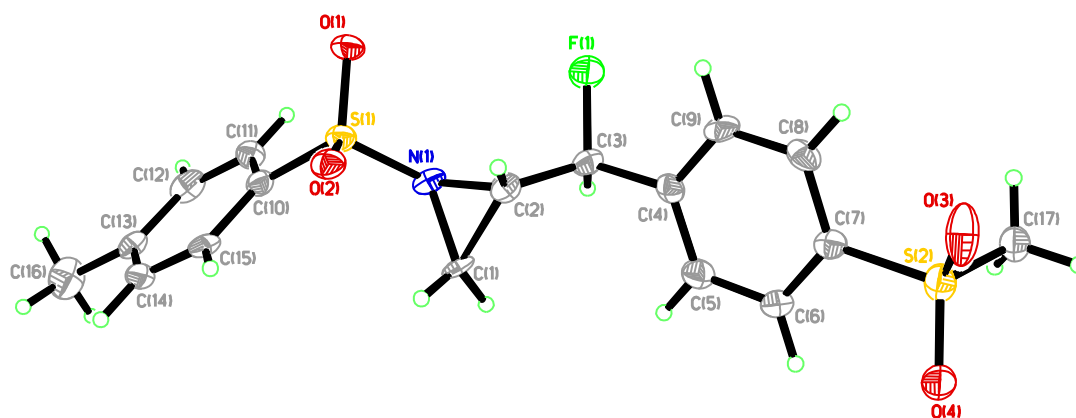


Figure S2.2 Perspective views showing 50% probability displacement.

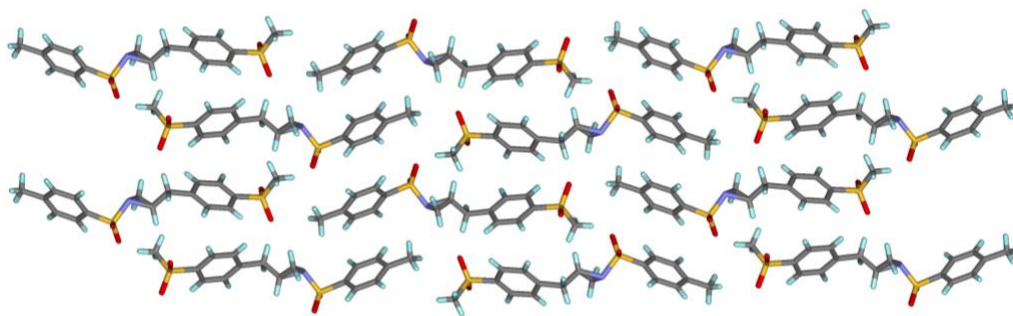
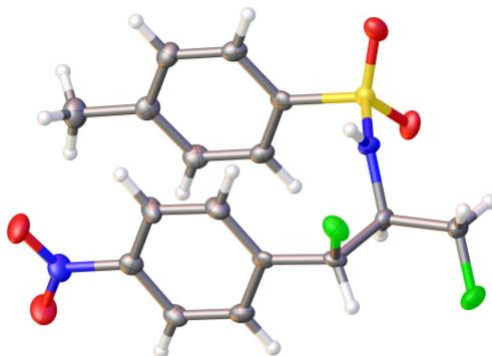


Figure S2.3 Three-dimensional supramolecular architecture viewed along the *a*-axis direction.

X-Ray Crystallographic Information Data for 4a



X-ray Crystallography: A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II DUO CCD diffractometer ($\text{CuK}\alpha$ radiation, $\lambda=1.54178$ Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 1.0° scans in ω at -30° , -55° , -80° , 30° , 55° , 80° and 115° in 2θ . Data integration down to 0.84 Å resolution was carried out using SAINT V8.37 A with reflection spot size optimization. Absorption corrections were made with the program SADABS. The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods again F^2 using SHELXT-2014 and SHELXL-2014 with OLEX 2 interface. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table S2.3, geometric parameters are shown in Table S2.4 and hydrogen-bond parameters are listed in Table S2.5. The Ortep plots produced with SHELXL-2014 program, and the other drawings were produced with Accelrys DS Visualizer 2.0.

Table S2.3 Experimental details.

Crystal data

Chemical formula	C ₁₆ H ₁₆ F ₂ N ₂ O ₄ S
M_r	370.37
Crystal system, space group	Monoclinic, $P2_1$
Temperature (K)	100
a, b, c (Å)	13.7281 (5), 7.7633 (3), 15.1716 (5)
β (°)	96.176 (2)
V (Å ³)	1607.53 (10)
Z	4
Radiation type	Cu $K\alpha$
μ (mm ⁻¹)	2.23
Crystal size (mm)	0.24 × 0.10 × 0.01
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan <i>SADABS</i>
$T_{\min}, T_{\max}$	0.815, 0.864
No. of measured, independent and observed [I > 2 $\sigma(I)$] reflections	27659, 5129, 4476
R_{int}	0.085
$(\sin \theta/\lambda)_{\max}$ (Å ⁻¹)	0.595
Refinement	
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.064, 0.174, 1.14
No. of reflections	5129
No. of parameters	455
No. of restraints	1
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$D\rho_{\max}, D\rho_{\min}$ (e Å ⁻³)	0.46, -0.64
Absolute structure	Flack x determined using 1569 quotients $[(I^+)-(I^-)]/[(I^+)+(I^-)]$ (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	0.01 (3)

Table S2.4 Geometric parameters (Å, °).

S1—O3	1.425 (5)	S2—O7	1.431 (5)
S1—O4	1.432 (4)	S2—O8	1.438 (4)
S1—N2	1.606 (6)	S2—N4	1.618 (6)
S1—C10	1.762 (7)	S2—C30	1.778 (7)
F1—C7	1.418 (6)	F3—C27	1.414 (6)
F2—C9	1.410 (8)	F4—C29	1.395 (9)
O1—N1	1.245 (7)	O5—N3	1.233 (7)
O2—N1	1.223 (7)	O6—N3	1.228 (7)
N1—C3	1.463 (9)	N3—C23	1.468 (9)
N2—C8	1.463 (8)	N4—C28	1.456 (9)
N2—H2	0.8698	N4—H4A	0.8575
C1—C2	1.372 (10)	C21—C22	1.381 (10)
C1—C6	1.393 (9)	C21—C26	1.395 (9)
C1—H1	0.9500	C21—H21	0.9500
C2—C3	1.379 (9)	C22—C23	1.382 (9)
C2—H2A	0.9500	C22—H22	0.9500
C3—C4	1.392 (9)	C23—C24	1.387 (9)
C4—C5	1.379 (10)	C24—C25	1.370 (9)
C4—H4	0.9500	C24—H24	0.9500
C5—C6	1.410 (9)	C25—C26	1.401 (9)
C5—H5	0.9500	C25—H25	0.9500
C6—C7	1.499 (9)	C26—C27	1.500 (10)
C7—C8	1.507 (10)	C27—C28	1.525 (9)
C7—H7	1.0000	C27—H27	1.0000
C8—C9	1.524 (9)	C28—C29	1.522 (9)
C8—H8	1.0000	C28—H28	1.0000
C9—H9A	0.9900	C29—H29A	0.9900
C9—H9B	0.9900	C29—H29B	0.9900
C10—C15	1.395 (9)	C30—C31	1.387 (9)
C10—C11	1.397 (9)	C30—C35	1.392 (9)
C11—C12	1.378 (10)	C31—C32	1.383 (10)
C11—H11	0.9500	C31—H31	0.9500

C12—C13	1.401 (9)	C32—C33	1.392 (10)
C12—H12	0.9500	C32—H32	0.9500
C13—C14	1.397 (9)	C33—C34	1.400 (10)
C13—C16	1.511 (10)	C33—C36	1.507 (10)
C14—C15	1.371 (10)	C34—C35	1.367 (10)
C14—H14	0.9500	C34—H34	0.9500
C15—H15	0.9500	C35—H35	0.9500
C16—H16A	0.9800	C36—H36A	0.9800
C16—H16B	0.9800	C36—H36B	0.9800
C16—H16C	0.9800	C36—H36C	0.9800
O3—S1—O4	120.2 (3)	O7—S2—O8	119.8 (3)
O3—S1—N2	106.4 (3)	O7—S2—N4	107.1 (3)
O4—S1—N2	106.4 (3)	O8—S2—N4	106.0 (3)
O3—S1—C10	107.5 (3)	O7—S2—C30	107.4 (3)
O4—S1—C10	108.0 (3)	O8—S2—C30	107.7 (3)
N2—S1—C10	107.8 (3)	N4—S2—C30	108.5 (3)
O2—N1—O1	123.3 (6)	O6—N3—O5	123.2 (6)
O2—N1—C3	118.5 (5)	O6—N3—C23	119.4 (6)
O1—N1—C3	118.3 (5)	O5—N3—C23	117.4 (5)
C8—N2—S1	124.7 (4)	C28—N4—S2	124.3 (4)
C8—N2—H2	117.9	C28—N4—H4A	130.9
S1—N2—H2	115.4	S2—N4—H4A	104.3
C2—C1—C6	120.7 (6)	C22—C21—C26	120.0 (6)
C2—C1—H1	119.7	C22—C21—H21	120.0
C6—C1—H1	119.7	C26—C21—H21	120.0
C1—C2—C3	119.0 (6)	C21—C22—C23	118.4 (6)
C1—C2—H2A	120.5	C21—C22—H22	120.8
C3—C2—H2A	120.5	C23—C22—H22	120.8
C2—C3—C4	122.2 (6)	C22—C23—C24	122.9 (7)
C2—C3—N1	118.5 (6)	C22—C23—N3	118.7 (6)
C4—C3—N1	119.2 (6)	C24—C23—N3	118.3 (6)
C5—C4—C3	118.4 (6)	C25—C24—C23	118.3 (6)

C5—C4—H4	120.8	C25—C24—H24	120.8
C3—C4—H4	120.8	C23—C24—H24	120.8
C4—C5—C6	120.3 (6)	C24—C25—C26	120.3 (6)
C4—C5—H5	119.9	C24—C25—H25	119.8
C6—C5—H5	119.9	C26—C25—H25	119.8
C1—C6—C5	119.3 (6)	C21—C26—C25	120.1 (7)
C1—C6—C7	121.5 (5)	C21—C26—C27	121.0 (6)
C5—C6—C7	119.2 (6)	C25—C26—C27	118.8 (6)
F1—C7—C6	108.4 (5)	F3—C27—C26	109.2 (5)
F1—C7—C8	106.1 (5)	F3—C27—C28	106.1 (5)
C6—C7—C8	115.0 (6)	C26—C27—C28	113.9 (6)
F1—C7—H7	109.1	F3—C27—H27	109.2
C6—C7—H7	109.1	C26—C27—H27	109.2
C8—C7—H7	109.1	C28—C27—H27	109.2
N2—C8—C7	111.2 (5)	N4—C28—C29	108.1 (6)
N2—C8—C9	107.3 (5)	N4—C28—C27	110.1 (5)
C7—C8—C9	112.1 (6)	C29—C28—C27	112.2 (6)
N2—C8—H8	108.7	N4—C28—H28	108.8
C7—C8—H8	108.7	C29—C28—H28	108.8
C9—C8—H8	108.7	C27—C28—H28	108.8
F2—C9—C8	107.7 (5)	F4—C29—C28	108.5 (6)
F2—C9—H9A	110.2	F4—C29—H29A	110.0
C8—C9—H9A	110.2	C28—C29—H29A	110.0
F2—C9—H9B	110.2	F4—C29—H29B	110.0
C8—C9—H9B	110.2	C28—C29—H29B	110.0
H9A—C9—H9B	108.5	H29A—C29—H29B	108.4
C15—C10—C11	120.2 (6)	C31—C30—C35	121.3 (6)
C15—C10—S1	120.5 (5)	C31—C30—S2	118.6 (5)
C11—C10—S1	119.2 (5)	C35—C30—S2	120.0 (5)
C12—C11—C10	120.0 (6)	C32—C31—C30	118.5 (6)
C12—C11—H11	120.0	C32—C31—H31	120.7
C10—C11—H11	120.0	C30—C31—H31	120.7
C11—C12—C13	120.3 (6)	C31—C32—C33	121.7 (6)

C11—C12—H12	119.8	C31—C32—H32	119.2
C13—C12—H12	119.8	C33—C32—H32	119.2
C14—C13—C12	118.7 (6)	C32—C33—C34	117.8 (7)
C14—C13—C16	120.8 (6)	C32—C33—C36	121.1 (7)
C12—C13—C16	120.5 (6)	C34—C33—C36	121.1 (7)
C15—C14—C13	121.6 (6)	C35—C34—C33	121.8 (6)
C15—C14—H14	119.2	C35—C34—H34	119.1
C13—C14—H14	119.2	C33—C34—H34	119.1
C14—C15—C10	119.2 (6)	C34—C35—C30	118.8 (6)
C14—C15—H15	120.4	C34—C35—H35	120.6
C10—C15—H15	120.4	C30—C35—H35	120.6
C13—C16—H16A	109.5	C33—C36—H36A	109.5
C13—C16—H16B	109.5	C33—C36—H36B	109.5
H16A—C16—H16B	109.5	H36A—C36—H36B	109.5
C13—C16—H16C	109.5	C33—C36—H36C	109.5
H16A—C16—H16C	109.5	H36A—C36—H36C	109.5
H16B—C16—H16C	109.5	H36B—C36—H36C	109.5
O3—S1—N2—C8	-157.7 (5)	O7—S2—N4—C28	-149.4 (5)
O4—S1—N2—C8	-28.4 (6)	O8—S2—N4—C28	-20.4 (6)
C10—S1—N2—C8	87.3 (6)	C30—S2—N4—C28	95.0 (6)
C6—C1—C2—C3	0.7 (11)	C26—C21—C22— C23	1.0 (11)
C1—C2—C3—C4	-2.8 (11)	C21—C22—C23— C24	-1.0 (12)
C1—C2—C3—N1	175.8 (6)	C21—C22—C23— N3	-178.0 (6)
O2—N1—C3—C2	169.3 (7)	O6—N3—C23—C22	163.0 (8)
O1—N1—C3—C2	-10.8 (10)	O5—N3—C23—C22	-18.4 (11)
O2—N1—C3—C4	-12.1 (10)	O6—N3—C23—C24	-14.1 (11)
O1—N1—C3—C4	167.8 (7)	O5—N3—C23—C24	164.4 (7)
C2—C3—C4—C5	2.5 (11)	C22—C23—C24— C25	0.3 (12)
N1—C3—C4—C5	-176.0 (6)	N3—C23—C24—	177.3 (7)

		C25	
C3—C4—C5—C6	-0.3 (11)	C23—C24—C25— C26	0.3 (11)
C2—C1—C6—C5	1.5 (10)	C22—C21—C26— C25	-0.4 (11)
C2—C1—C6—C7	-179.4 (6)	C22—C21—C26— C27	179.0 (7)
C4—C5—C6—C1	-1.7 (10)	C24—C25—C26— C21	-0.3 (11)
C4—C5—C6—C7	179.2 (6)	C24—C25—C26— C27	-179.7 (7)
C1—C6—C7—F1	32.5 (9)	C21—C26—C27—F3	24.0 (9)
C5—C6—C7—F1	-148.4 (6)	C25—C26—C27—F3	-156.6 (6)
C1—C6—C7—C8	-86.0 (7)	C21—C26—C27— C28	-94.4 (7)
C5—C6—C7—C8	93.1 (7)	C25—C26—C27— C28	85.0 (8)
S1—N2—C8—C7	-133.3 (5)	S2—N4—C28—C29	104.5 (6)
S1—N2—C8—C9	103.8 (6)	S2—N4—C28—C27	-132.7 (5)
F1—C7—C8—N2	-52.4 (7)	F3—C27—C28—N4	-54.6 (7)
C6—C7—C8—N2	67.3 (6)	C26—C27—C28— N4	65.6 (7)
F1—C7—C8—C9	67.7 (6)	F3—C27—C28—C29	65.8 (7)
C6—C7—C8—C9	-172.5 (5)	C26—C27—C28— C29	-174.0 (5)
N2—C8—C9—F2	-179.7 (5)	N4—C28—C29—F4	-177.2 (5)
C7—C8—C9—F2	57.9 (6)	C27—C28—C29—F4	61.2 (7)
O3—S1—C10—C15	162.7 (6)	O7—S2—C30—C31	-21.2 (6)
O4—S1—C10—C15	31.6 (7)	O8—S2—C30—C31	-151.5 (5)
N2—S1—C10—C15	-83.0 (6)	N4—S2—C30—C31	94.2 (6)
O3—S1—C10—C11	-18.9 (6)	O7—S2—C30—C35	158.6 (5)
O4—S1—C10—C11	-150.0 (5)	O8—S2—C30—C35	28.3 (7)
N2—S1—C10—C11	95.4 (6)	N4—S2—C30—C35	-86.0 (6)
C15—C10—C11— C12	1.0 (10)	C35—C30—C31— C32	-1.1 (10)
S1—C10—C11—C12	-177.3 (5)	S2—C30—C31—C32	178.7 (5)

C10—C11—C12—C13	-0.2 (10)	C30—C31—C32—C33	0.1 (11)
C11—C12—C13—C14	-0.4 (11)	C31—C32—C33—C34	0.5 (11)
C11—C12—C13—C16	179.4 (7)	C31—C32—C33—C36	-178.1 (7)
C12—C13—C14—C15	0.1 (11)	C32—C33—C34—C35	-0.1 (11)
C16—C13—C14—C15	-179.7 (7)	C36—C33—C34—C35	178.4 (7)
C13—C14—C15—C10	0.7 (11)	C33—C34—C35—C30	-0.8 (11)
C11—C10—C15—C14	-1.3 (10)	C31—C30—C35—C34	1.4 (11)
S1—C10—C15—C14	177.0 (5)	S2—C30—C35—C34	-178.4 (6)

Table S2.5 Hydrogen-bond parameters.

$D-H\cdots A$	$D-H$ (Å)	$H\cdots A$ (Å)	$D\cdots A$ (Å)	$D-H\cdots A$ (°)
N2—H2 $\cdots$ O8	0.87	2.13	2.968 (6)	161.7
N4—H4A $\cdots$ O1 ⁱ	0.86	2.24	3.086 (7)	171.4

Symmetry code(s): (i) $-x+1, y+1/2, -z$.

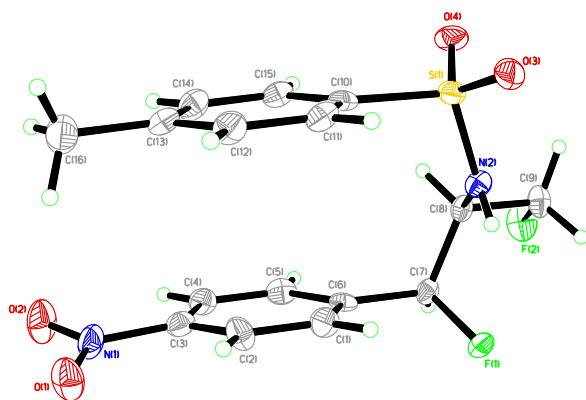


Figure S2.4 Perspective views showing 50% probability displacement.

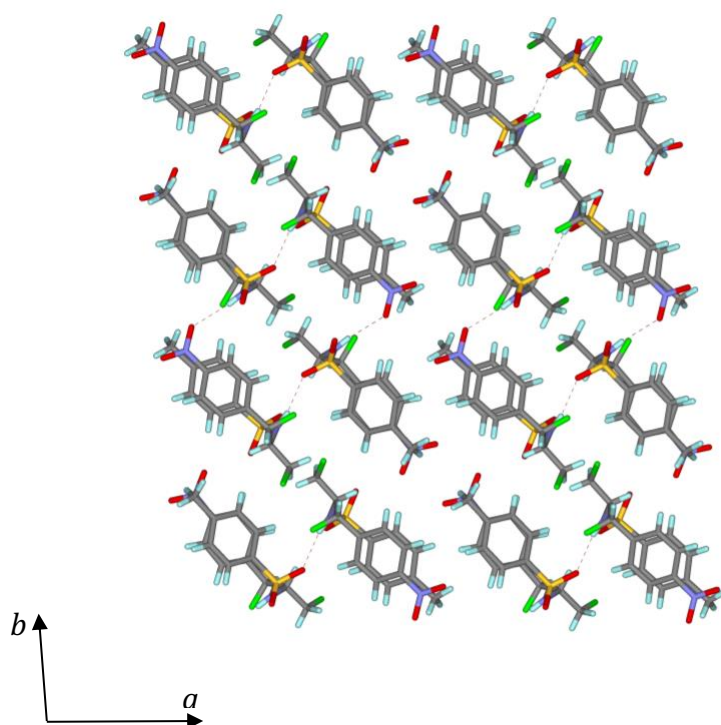
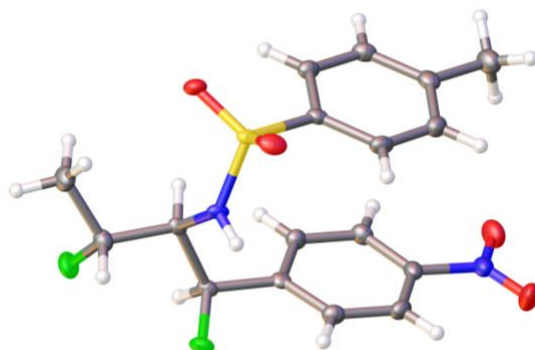


Figure S2.5 Three-dimensional supramolecular architecture viewed along the *c*-axis direction.

X-Ray Crystallographic Information Data for *anti*-6a



X-ray Crystallography: A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II CCD diffractometer (MoK α radiation, $\lambda=0.71073$ Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 0.5° scans in ω at 28° in 2θ . Data integration down to 0.78 Å resolution was carried out using SAINT V8.37A with reflection spot size optimization. Absorption corrections were made with the program SADABS. The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods against F^2 using SHELXT-2014 and SHELXL-2014 with OLEX 2 interface. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table S2.6, geometric parameters are shown in Table S2.7 and hydrogen-bond parameters are listed in Table S2.8. The Ortep plots produced with SHELXL-2014 program, and the other drawings were produced with Accelrys DS Visualizer 2.0.

Table S2.6 Experimental details.

Crystal data

Chemical formula	C ₁₇ H ₁₈ F ₂ N ₂ O ₄ S
M_r	384.39
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	100
a, b, c (Å)	7.5617 (3), 9.7752 (5), 23.9131 (10)
V (Å ³)	1767.59 (14)
Z	4
Radiation type	Mo $K\alpha$
μ (mm ⁻¹)	0.23
Crystal size (mm)	0.18 × 0.14 × 0.10

Data collection

Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan <i>SADABS</i>
$T_{\min}, T_{\max}$	0.809, 0.862
No. of measured, independent and observed [I $> 2s(I)$] reflections	22510, 3906, 3600
R_{int}	0.032
$(\sin \theta/\lambda)_{\max}$ (Å ⁻¹)	0.642

Refinement

$R[F^2 > 2s(F^2)], wR(F^2), S$	0.032, 0.075, 1.06
No. of reflections	3906
No. of parameters	241
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$D\rho_{\max}, D\rho_{\min}$ (e Å ⁻³)	0.33, -0.33
Absolute structure	Flack x determined using 1437 quotients $[(I^+)-(I^-)]/[(I^+)+(I^-)]$ (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	-0.01 (2)

Table S2.7 Geometric parameters (Å, °).

S1—O3	1.4320 (17)	C7—H7	1.0000
S1—O4	1.4388 (16)	C8—C9	1.534 (3)
S1—N2	1.6108 (18)	C8—H8	1.0000
S1—C11	1.765 (2)	C9—C10	1.505 (3)
F1—C7	1.415 (2)	C9—H9	1.0000
F2—C9	1.405 (3)	C10—H10A	0.9800
O1—N1	1.229 (3)	C10—H10B	0.9800
O2—N1	1.228 (3)	C10—H10C	0.9800
N1—C3	1.469 (3)	C11—C12	1.392 (3)
N2—C8	1.453 (3)	C11—C16	1.393 (3)
N2—H2	0.83 (3)	C12—C13	1.383 (4)
C1—C2	1.374 (3)	C12—H12	0.9500
C1—C6	1.397 (3)	C13—C14	1.395 (4)
C1—H1	0.9500	C13—H13	0.9500
C2—C3	1.385 (3)	C14—C15	1.395 (3)
C2—H2A	0.9500	C14—C17	1.509 (4)
C3—C4	1.378 (4)	C15—C16	1.387 (3)
C4—C5	1.389 (3)	C15—H15	0.9500
C4—H4	0.9500	C16—H16	0.9500
C5—C6	1.389 (3)	C17—H17A	0.9800
C5—H5	0.9500	C17—H17B	0.9800
C6—C7	1.504 (3)	C17—H17C	0.9800
C7—C8	1.528 (3)		
O3—S1—O4	119.99 (10)	N2—C8—H8	108.8
O3—S1—N2	104.82 (10)	C7—C8—H8	108.8
O4—S1—N2	107.62 (10)	C9—C8—H8	108.8
O3—S1—C11	108.22 (11)	F2—C9—C10	108.1 (2)
O4—S1—C11	106.10 (10)	F2—C9—C8	107.10 (18)
N2—S1—C11	109.91 (10)	C10—C9—C8	115.0 (2)
O2—N1—O1	123.5 (2)	F2—C9—H9	108.8
O2—N1—C3	118.2 (2)	C10—C9—H9	108.8

O1—N1—C3	118.3 (2)	C8—C9—H9	108.8
C8—N2—S1	124.67 (15)	C9—C10—H10A	109.5
C8—N2—H2	119.2 (19)	C9—C10—H10B	109.5
S1—N2—H2	114.0 (18)	H10A—C10—H10B	109.5
C2—C1—C6	120.3 (2)	C9—C10—H10C	109.5
C2—C1—H1	119.9	H10A—C10—H10C	109.5
C6—C1—H1	119.9	H10B—C10—H10C	109.5
C1—C2—C3	118.5 (2)	C12—C11—C16	120.8 (2)
C1—C2—H2A	120.8	C12—C11—S1	119.42 (17)
C3—C2—H2A	120.8	C16—C11—S1	119.73 (18)
C4—C3—C2	122.7 (2)	C13—C12—C11	119.1 (2)
C4—C3—N1	119.0 (2)	C13—C12—H12	120.5
C2—C3—N1	118.2 (2)	C11—C12—H12	120.5
C3—C4—C5	118.2 (2)	C12—C13—C14	121.4 (2)
C3—C4—H4	120.9	C12—C13—H13	119.3
C5—C4—H4	120.9	C14—C13—H13	119.3
C4—C5—C6	120.2 (2)	C15—C14—C13	118.6 (2)
C4—C5—H5	119.9	C15—C14—C17	120.5 (2)
C6—C5—H5	119.9	C13—C14—C17	120.9 (2)
C5—C6—C1	120.0 (2)	C16—C15—C14	121.0 (2)
C5—C6—C7	121.7 (2)	C16—C15—H15	119.5
C1—C6—C7	118.2 (2)	C14—C15—H15	119.5
F1—C7—C6	108.65 (18)	C15—C16—C11	119.2 (2)
F1—C7—C8	106.70 (17)	C15—C16—H16	120.4
C6—C7—C8	114.91 (18)	C11—C16—H16	120.4
F1—C7—H7	108.8	C14—C17—H17A	109.5
C6—C7—H7	108.8	C14—C17—H17B	109.5
C8—C7—H7	108.8	H17A—C17—H17B	109.5
N2—C8—C7	110.47 (18)	C14—C17—H17C	109.5
N2—C8—C9	108.84 (18)	H17A—C17—H17C	109.5
C7—C8—C9	110.97 (18)	H17B—C17—H17C	109.5
O3—S1—N2—C8	170.18 (18)	C6—C7—C8—N2	-57.0 (2)

O4—S1—N2—C8	41.4 (2)	F1—C7—C8—C9	-57.3 (2)
C11—S1—N2—C8	-73.7 (2)	C6—C7—C8—C9	-177.83 (19)
C6—C1—C2—C3	-0.3 (4)	N2—C8—C9—F2	-170.71 (18)
C1—C2—C3—C4	-1.6 (4)	C7—C8—C9—F2	-48.9 (2)
C1—C2—C3—N1	178.0 (2)	N2—C8—C9—C10	69.1 (2)
O2—N1—C3—C4	-2.6 (3)	C7—C8—C9—C10	-169.1 (2)
O1—N1—C3—C4	177.1 (2)	O3—S1—C11—C12	35.1 (2)
O2—N1—C3—C2	177.8 (2)	O4—S1—C11—C12	165.13 (18)
O1—N1—C3—C2	-2.5 (3)	N2—S1—C11—C12	-78.8 (2)
C2—C3—C4—C5	1.8 (4)	O3—S1—C11—C16	-142.08 (18)
N1—C3—C4—C5	-177.8 (2)	O4—S1—C11—C16	-12.1 (2)
C3—C4—C5—C6	-0.1 (4)	N2—S1—C11—C16	103.99 (19)
C4—C5—C6—C1	-1.8 (4)	C16—C11—C12— C13	-0.2 (3)
C4—C5—C6—C7	175.9 (2)	S1—C11—C12—C13	-177.43 (19)
C2—C1—C6—C5	2.0 (4)	C11—C12—C13— C14	-0.2 (4)
C2—C1—C6—C7	-175.8 (2)	C12—C13—C14— C15	0.3 (4)
C5—C6—C7—F1	-14.4 (3)	C12—C13—C14— C17	-178.7 (2)
C1—C6—C7—F1	163.30 (19)	C13—C14—C15— C16	0.0 (4)
C5—C6—C7—C8	105.0 (2)	C17—C14—C15— C16	179.0 (2)
C1—C6—C7—C8	-77.3 (3)	C14—C15—C16— C11	-0.4 (3)
S1—N2—C8—C7	129.16 (18)	C12—C11—C16— C15	0.6 (3)
S1—N2—C8—C9	-108.77 (19)	S1—C11—C16—C15	177.74 (18)
F1—C7—C8—N2	63.5 (2)		

Table S2.8 Hydrogen-bond parameters.

$D-H\cdots A$	$D-H$ (Å)	$H\cdots A$ (Å)	$D\cdots A$ (Å)	$D-H\cdots A$ (°)

N2—H2 $\cdots$ O4 ⁱ	0.83 (3)	2.08 (3)	2.903 (2)	169 (3)

Symmetry code(s): (i) $-x+1, y+1/2, -z+1/2$.

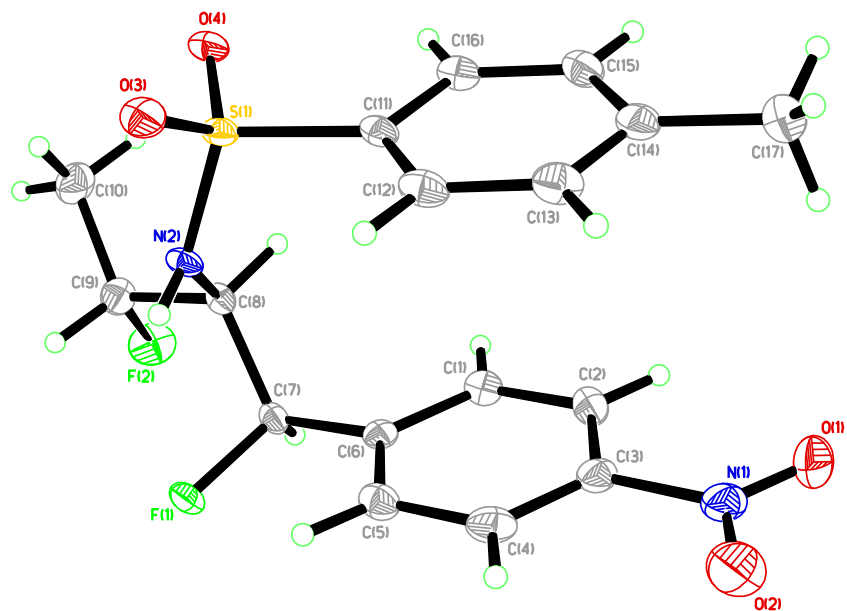


Figure S2.6 Perspective views showing 50% probability displacement.

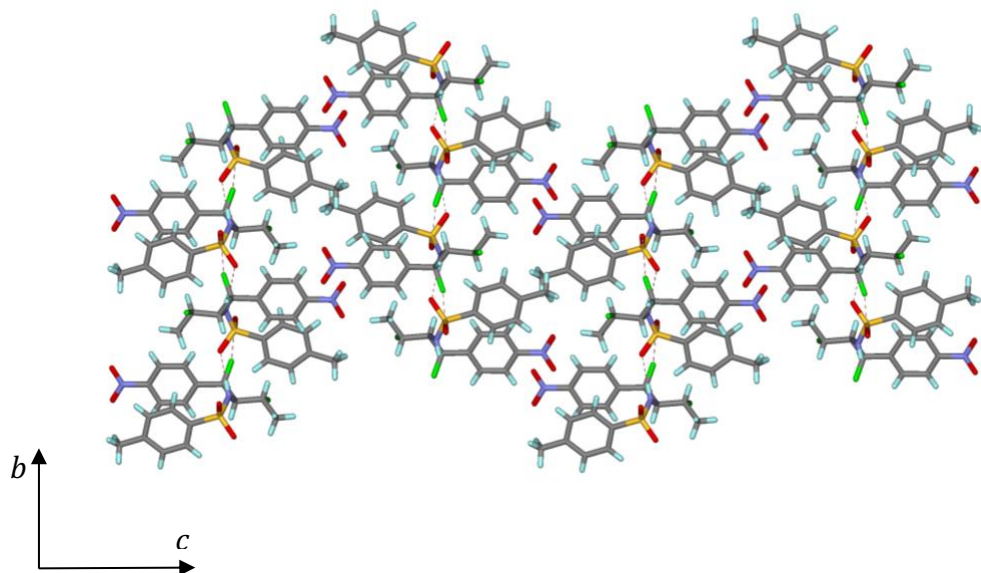
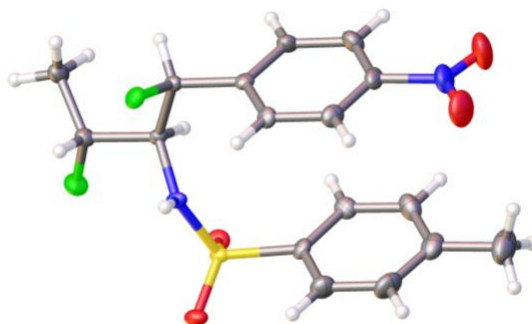


Figure S2.7 Three-dimensional supramolecular architecture viewed along the a -axis direction.

X-Ray Crystallographic Information Data for *syn*-6a



X-ray Crystallography: A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II CCD diffractometer (MoK α radiation, $\lambda=0.71073$ Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 0.5° scans in ω at 28° in 2θ . Data integration down to 0.78 Å resolution was carried out using SAINT V8.37A with reflection spot size optimization. Absorption corrections were made with the program SADABS. The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods again F^2 using SHELXT-2014 and SHELXL-2014 with OLEX 2 interface. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table S2.9, geometric parameters are shown in Table S2.10, and hydrogen bond parameters are listed in Table S2.11. The Ortep plots produced with SHELXL-2014 program, and the other drawings were produced with Accelrys DS Visualizer 2.0.

Table S2.9 Experimental details.

Crystal data

Chemical formula	C ₁₇ H ₁₈ F ₂ N ₂ O ₄ S
M_r	384.39
Crystal system, space group	Monoclinic, $P2_1$

Temperature (K)	100
a, b, c (Å)	7.8163 (5), 9.2956 (6), 12.4965 (8)
α (°)	98.9206 (10)
V (Å ³)	896.98 (10)
Z	2
Radiation type	Mo $K\alpha$
μ (mm ⁻¹)	0.23
Crystal size (mm)	0.24 × 0.18 × 0.15
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan <i>SADABS</i>
$T_{\min}, T_{\max}$	0.760, 0.801
No. of measured, independent and observed [I $> 2s(I)$] reflections	18368, 3934, 3786
R_{int}	0.039
$(\sin \theta/\lambda)_{\text{max}}$ (Å ⁻¹)	0.641
Refinement	
$R[F^2 > 2s(F^2)], wR(F^2), S$	0.030, 0.078, 1.04
No. of reflections	3934
No. of parameters	241
No. of restraints	1
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$D\rho_{\text{max}}, D\rho_{\text{min}}$ (e Å ⁻³)	0.35, -0.20
Absolute structure	Flack x determined using 1695 quotients $[(I^+)-(I^-)]/[(I^+)+(I^-)]$ (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	0.04 (3)

Table S2.10 Geometric parameters (Å, °).

S1—O4	1.4376 (19)	C7—H7	1.0000

S1—O3	1.4402 (19)	C8—C9	1.533 (3)
S1—N2	1.603 (2)	C8—H8	1.0000
S1—C13	1.771 (3)	C9—C10	1.495 (4)
F1—C7	1.414 (3)	C9—H9	1.0000
F2—C9	1.408 (3)	C10—H10A	0.9800
O1—N1	1.226 (4)	C10—H10B	0.9800
O2—N1	1.238 (4)	C10—H10C	0.9800
N1—C3	1.476 (3)	C11—C12	1.381 (4)
N2—C8	1.458 (3)	C11—C16	1.390 (5)
N2—H2	0.79 (3)	C11—H11	0.9500
C1—C2	1.384 (4)	C12—C13	1.397 (4)
C1—C6	1.390 (4)	C12—H12	0.9500
C1—H1	0.9500	C13—C14	1.394 (4)
C2—C3	1.384 (4)	C14—C15	1.382 (4)
C2—H2A	0.9500	C14—H14	0.9500
C3—C4	1.380 (4)	C15—C16	1.393 (4)
C4—C5	1.385 (4)	C15—H15	0.9500
C4—H4	0.9500	C16—C17	1.513 (4)
C5—C6	1.398 (4)	C17—H17A	0.9800
C5—H5	0.9500	C17—H17B	0.9800
C6—C7	1.507 (3)	C17—H17C	0.9800
C7—C8	1.528 (3)		
O4—S1—O3	119.41 (11)	N2—C8—H8	109.1
O4—S1—N2	106.72 (11)	C7—C8—H8	109.1
O3—S1—N2	107.25 (11)	C9—C8—H8	109.1
O4—S1—C13	106.51 (12)	F2—C9—C10	109.0 (2)
O3—S1—C13	107.36 (11)	F2—C9—C8	106.71 (19)
N2—S1—C13	109.33 (11)	C10—C9—C8	114.7 (2)
O1—N1—O2	124.0 (3)	F2—C9—H9	108.8
O1—N1—C3	118.1 (3)	C10—C9—H9	108.8
O2—N1—C3	117.8 (3)	C8—C9—H9	108.8
C8—N2—S1	126.63 (17)	C9—C10—H10A	109.5

C8—N2—H2	118 (2)	C9—C10—H10B	109.5
S1—N2—H2	115 (2)	H10A—C10—H10B	109.5
C2—C1—C6	120.3 (3)	C9—C10—H10C	109.5
C2—C1—H1	119.9	H10A—C10—H10C	109.5
C6—C1—H1	119.9	H10B—C10—H10C	109.5
C3—C2—C1	117.9 (3)	C12—C11—C16	121.2 (3)
C3—C2—H2A	121.0	C12—C11—H11	119.4
C1—C2—H2A	121.0	C16—C11—H11	119.4
C4—C3—C2	123.2 (2)	C11—C12—C13	119.4 (3)
C4—C3—N1	117.8 (2)	C11—C12—H12	120.3
C2—C3—N1	119.0 (3)	C13—C12—H12	120.3
C3—C4—C5	118.5 (2)	C14—C13—C12	120.3 (2)
C3—C4—H4	120.7	C14—C13—S1	120.73 (19)
C5—C4—H4	120.7	C12—C13—S1	118.9 (2)
C4—C5—C6	119.5 (2)	C15—C14—C13	119.0 (3)
C4—C5—H5	120.3	C15—C14—H14	120.5
C6—C5—H5	120.3	C13—C14—H14	120.5
C1—C6—C5	120.6 (2)	C14—C15—C16	121.6 (3)
C1—C6—C7	119.0 (2)	C14—C15—H15	119.2
C5—C6—C7	120.4 (2)	C16—C15—H15	119.2
F1—C7—C6	108.9 (2)	C11—C16—C15	118.4 (3)
F1—C7—C8	106.48 (18)	C11—C16—C17	121.0 (3)
C6—C7—C8	113.34 (19)	C15—C16—C17	120.6 (3)
F1—C7—H7	109.3	C16—C17—H17A	109.5
C6—C7—H7	109.3	C16—C17—H17B	109.5
C8—C7—H7	109.3	H17A—C17—H17B	109.5
N2—C8—C7	109.34 (19)	C16—C17—H17C	109.5
N2—C8—C9	109.40 (19)	H17A—C17—H17C	109.5
C7—C8—C9	110.80 (19)	H17B—C17—H17C	109.5
O4—S1—N2—C8	-147.6 (2)	C6—C7—C8—N2	58.2 (3)
O3—S1—N2—C8	-18.5 (2)	F1—C7—C8—C9	59.1 (2)
C13—S1—N2—C8	97.6 (2)	C6—C7—C8—C9	178.8 (2)

C6—C1—C2—C3	-0.6 (4)	N2—C8—C9—F2	-62.9 (3)
C1—C2—C3—C4	0.1 (4)	C7—C8—C9—F2	176.5 (2)
C1—C2—C3—N1	178.8 (3)	N2—C8—C9—C10	176.4 (2)
O1—N1—C3—C4	172.5 (3)	C7—C8—C9—C10	55.7 (3)
O2—N1—C3—C4	-5.6 (4)	C16—C11—C12— C13	-0.1 (5)
O1—N1—C3—C2	-6.3 (4)	C11—C12—C13— C14	-1.9 (4)
O2—N1—C3—C2	175.7 (3)	C11—C12—C13— S1	176.3 (2)
C2—C3—C4—C5	0.5 (4)	O4—S1—C13— C14	156.4 (2)
N1—C3—C4—C5	-178.2 (2)	O3—S1—C13— C14	27.4 (2)
C3—C4—C5—C6	-0.5 (4)	N2—S1—C13— C14	-88.6 (2)
C2—C1—C6—C5	0.7 (4)	O4—S1—C13— C12	-21.7 (2)
C2—C1—C6—C7	-178.5 (2)	O3—S1—C13— C12	-150.7 (2)
C4—C5—C6—C1	-0.1 (4)	N2—S1—C13— C12	93.2 (2)
C4—C5—C6—C7	179.0 (2)	C12—C13—C14— C15	2.2 (4)
C1—C6—C7—F1	-153.5 (2)	S1—C13—C14— C15	-175.9 (2)
C5—C6—C7—F1	27.4 (3)	C13—C14—C15— C16	-0.7 (4)
C1—C6—C7—C8	88.2 (3)	C12—C11—C16— C15	1.5 (4)
C5—C6—C7—C8	-90.9 (3)	C12—C11—C16— C17	-178.1 (3)
S1—N2—C8—C7	-130.93 (19)	C14—C15—C16— C11	-1.2 (4)
S1—N2—C8—C9	107.6 (2)	C14—C15—C16— C17	178.5 (3)
F1—C7—C8—N2	-61.6 (2)		

Table S2.11 Hydrogen-bond parameters.

$D-H\cdots A$	$D-H$ (Å)	$H\cdots A$ (Å)	$D\cdots A$ (Å)	$D-H\cdots A$ (°)
$N2-H2\cdots O3^i$	0.79 (3)	2.05 (3)	2.827 (3)	167 (3)

Symmetry code(s): (i) $-x+1, y+1/2, -z+1$.

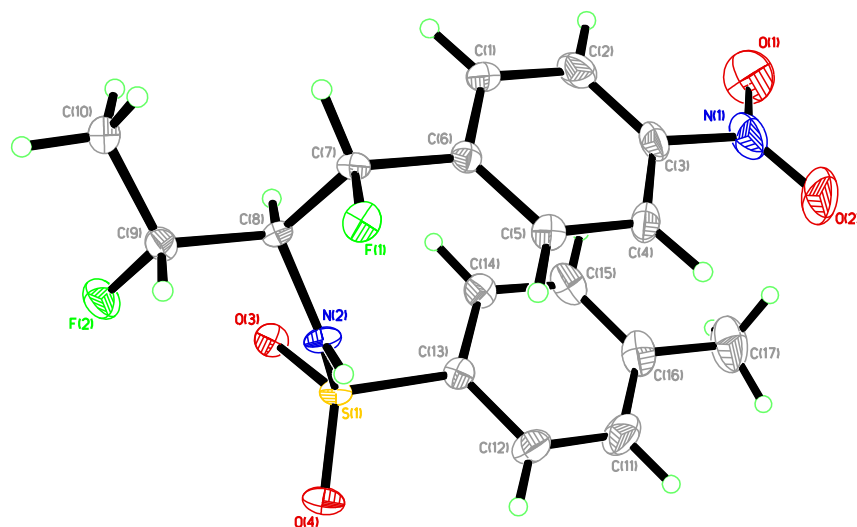


Figure S2.8 Perspective views showing 50% probability displacement.

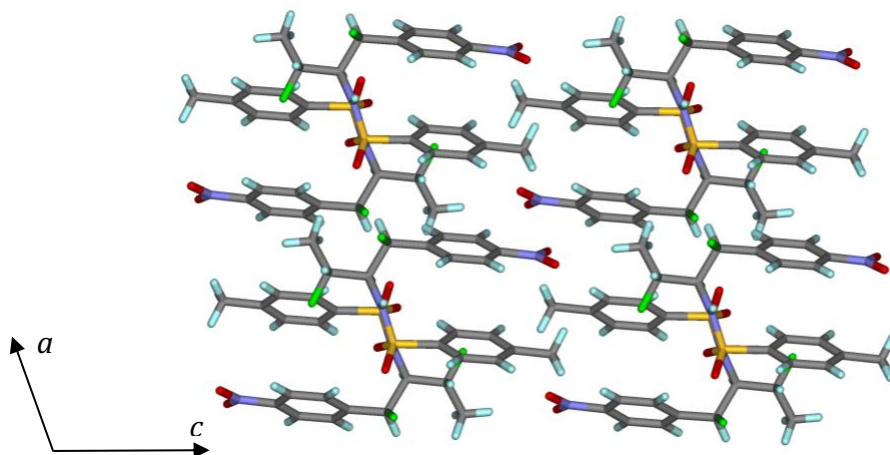
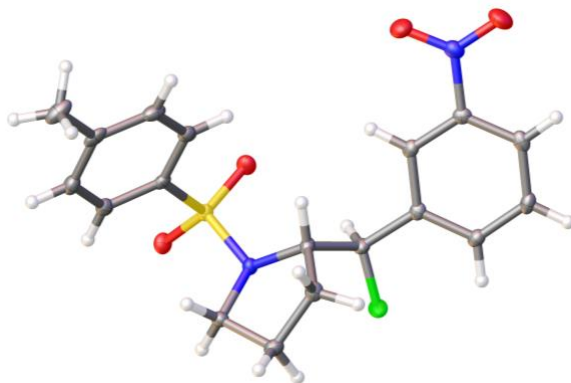


Figure S2.9 Three-dimensional supramolecular architecture viewed along the b -axis direction.

X-Ray Crystallographic Information Data for 8a



X-ray Crystallography: A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II CCD diffractometer (MoK α radiation, λ =0.71073 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 0.5° scans in ω at 28° in 2θ . Data integration down to 0.78 Å resolution was carried out using SAINT V8.37A with reflection spot size optimization. Absorption corrections were made with the program SADABS. The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods against F^2 using SHELXT-2014 and SHELXL-2014 with OLEX 2 interface. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table S2.12, and geometric parameters are shown in Table S2.13. The Ortep plots produced with SHELXL-2014 program, and the other drawings were produced with Accelrys DS Visualizer 2.0.

Table S2.12 Experimental details.

Crystal data

Chemical formula	C ₁₈ H ₁₉ FN ₂ O ₄ S
M_r	378.41
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	100

a, b, c (Å)	7.4092 (7), 10.2119 (9), 22.525 (2)
V (Å ³)	1704.3 (3)
Z	4
Radiation type	Mo $K\alpha$
μ (mm ⁻¹)	0.23
Crystal size (mm)	0.24 × 0.18 × 0.12

Data collection

Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan <i>SADABS</i>
$T_{\min}, T_{\max}$	0.746, 0.801
No. of measured, independent and observed [I $> 2s(I)$] reflections	19152, 3766, 3651
R_{int}	0.025
$(\sin \theta/\lambda)_{\max}$ (Å ⁻¹)	0.641

Refinement

$R[F^2 > 2s(F^2)], wR(F^2), S$	0.031, 0.077, 1.10
No. of reflections	3766
No. of parameters	236
H-atom treatment	H-atom parameters constrained
$D\rho_{\max}, D\rho_{\min}$ (e Å ⁻³)	0.38, -0.28
Absolute structure	Flack x determined using 1497 quotients [(I^+)-(I^-)]/[(I^+)+(I^-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	-0.024 (19)

Table S2.13 Geometric parameters (Å, °).

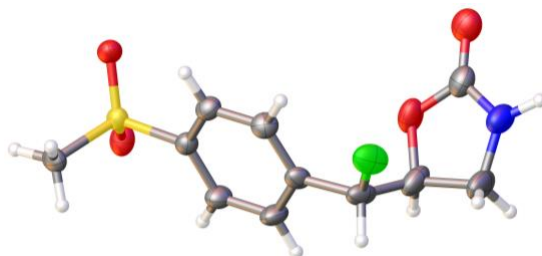
S1—O4	1.4306 (17)	C8—H8	1.0000
S1—O3	1.4370 (17)	C9—C10	1.530 (3)
S1—N2	1.632 (2)	C9—H9A	0.9900
S1—C12	1.765 (2)	C9—H9B	0.9900
F1—C7	1.406 (3)	C10—C11	1.521 (3)

O1—N1	1.225 (3)	C10—H10A	0.9900
O2—N1	1.225 (3)	C10—H10B	0.9900
N1—C2	1.474 (3)	C11—H11A	0.9900
N2—C8	1.482 (3)	C11—H11B	0.9900
N2—C11	1.482 (3)	C12—C13	1.387 (3)
C1—C2	1.376 (3)	C12—C17	1.395 (3)
C1—C6	1.397 (3)	C13—C14	1.382 (3)
C1—H1	0.9500	C13—H13	0.9500
C2—C3	1.387 (3)	C14—C15	1.391 (3)
C3—C4	1.388 (3)	C14—H14	0.9500
C3—H3	0.9500	C15—C16	1.396 (4)
C4—C5	1.394 (3)	C15—C18	1.503 (3)
C4—H4	0.9500	C16—C17	1.384 (4)
C5—C6	1.391 (3)	C16—H16	0.9500
C5—H5	0.9500	C17—H17	0.9500
C6—C7	1.505 (3)	C18—H18A	0.9800
C7—C8	1.528 (3)	C18—H18B	0.9800
C7—H7	1.0000	C18—H18C	0.9800
C8—C9	1.535 (3)		
O4—S1—O3	120.35 (10)	C10—C9—C8	104.71 (18)
O4—S1—N2	106.78 (10)	C10—C9—H9A	110.8
O3—S1—N2	106.19 (10)	C8—C9—H9A	110.8
O4—S1—C12	107.70 (10)	C10—C9—H9B	110.8
O3—S1—C12	108.86 (11)	C8—C9—H9B	110.8
N2—S1—C12	106.11 (11)	H9A—C9—H9B	108.9
O2—N1—O1	124.0 (2)	C11—C10—C9	103.97 (18)
O2—N1—C2	117.97 (19)	C11—C10—H10A	111.0
O1—N1—C2	118.0 (2)	C9—C10—H10A	111.0
C8—N2—C11	111.28 (18)	C11—C10—H10B	111.0
C8—N2—S1	117.76 (15)	C9—C10—H10B	111.0
C11—N2—S1	118.14 (14)	H10A—C10—H10B	109.0
C2—C1—C6	118.7 (2)	N2—C11—C10	102.67 (17)

C2—C1—H1	120.6	N2—C11—H11A	111.2
C6—C1—H1	120.6	C10—C11—H11A	111.2
C1—C2—C3	123.4 (2)	N2—C11—H11B	111.2
C1—C2—N1	118.0 (2)	C10—C11—H11B	111.2
C3—C2—N1	118.6 (2)	H11A—C11—H11B	109.1
C2—C3—C4	117.4 (2)	C13—C12—C17	120.7 (2)
C2—C3—H3	121.3	C13—C12—S1	119.24 (17)
C4—C3—H3	121.3	C17—C12—S1	119.94 (17)
C3—C4—C5	120.6 (2)	C14—C13—C12	119.4 (2)
C3—C4—H4	119.7	C14—C13—H13	120.3
C5—C4—H4	119.7	C12—C13—H13	120.3
C6—C5—C4	120.7 (2)	C13—C14—C15	121.1 (2)
C6—C5—H5	119.6	C13—C14—H14	119.4
C4—C5—H5	119.6	C15—C14—H14	119.4
C5—C6—C1	119.1 (2)	C14—C15—C16	118.6 (2)
C5—C6—C7	122.4 (2)	C14—C15—C18	120.7 (2)
C1—C6—C7	118.4 (2)	C16—C15—C18	120.7 (2)
F1—C7—C6	109.59 (18)	C17—C16—C15	121.2 (2)
F1—C7—C8	108.64 (18)	C17—C16—H16	119.4
C6—C7—C8	113.42 (19)	C15—C16—H16	119.4
F1—C7—H7	108.4	C16—C17—C12	118.9 (2)
C6—C7—H7	108.4	C16—C17—H17	120.5
C8—C7—H7	108.4	C12—C17—H17	120.5
N2—C8—C7	109.29 (18)	C15—C18—H18A	109.5
N2—C8—C9	104.38 (17)	C15—C18—H18B	109.5
C7—C8—C9	115.24 (19)	H18A—C18—H18B	109.5
N2—C8—H8	109.2	C15—C18—H18C	109.5
C7—C8—H8	109.2	H18A—C18—H18C	109.5
C9—C8—H8	109.2	H18B—C18—H18C	109.5
O4—S1—N2—C8	165.87 (16)	S1—N2—C8—C9	143.46 (16)
O3—S1—N2—C8	36.29 (18)	F1—C7—C8—N2	-72.7 (2)
C12—S1—N2—C8	-79.45 (17)	C6—C7—C8—N2	165.16 (19)

O4—S1—N2—C11	-55.83 (18)	F1—C7—C8—C9	44.4 (3)
O3—S1—N2—C11	174.59 (17)	C6—C7—C8—C9	-77.7 (2)
C12—S1—N2—C11	58.86 (18)	N2—C8—C9—C10	19.6 (2)
C6—C1—C2—C3	1.1 (4)	C7—C8—C9—C10	-100.2 (2)
C6—C1—C2—N1	179.1 (2)	C8—C9—C10—C11	-34.1 (2)
O2—N1—C2—C1	5.7 (3)	C8—N2—C11—C10	-23.5 (2)
O1—N1—C2—C1	-174.1 (2)	S1—N2—C11—C10	-164.34 (15)
O2—N1—C2—C3	-176.1 (2)	C9—C10—C11—N2	34.9 (2)
O1—N1—C2—C3	4.1 (3)	O4—S1—C12—C13	22.4 (2)
C1—C2—C3—C4	-0.2 (3)	O3—S1—C12—C13	154.44 (19)
N1—C2—C3—C4	-178.2 (2)	N2—S1—C12—C13	-91.6 (2)
C2—C3—C4—C5	-0.9 (3)	O4—S1—C12—C17	-160.69 (19)
C3—C4—C5—C6	1.1 (4)	O3—S1—C12—C17	-28.7 (2)
C4—C5—C6—C1	-0.2 (3)	N2—S1—C12—C17	85.3 (2)
C4—C5—C6—C7	177.0 (2)	C17—C12—C13— C14	0.4 (4)
C2—C1—C6—C5	-0.9 (3)	S1—C12—C13—C14	177.31 (19)
C2—C1—C6—C7	-178.1 (2)	C12—C13—C14— C15	-0.2 (4)
C5—C6—C7—F1	4.3 (3)	C13—C14—C15— C16	-0.6 (4)
C1—C6—C7—F1	-178.59 (19)	C13—C14—C15— C18	178.1 (2)
C5—C6—C7—C8	125.9 (2)	C14—C15—C16— C17	1.3 (4)
C1—C6—C7—C8	-57.0 (3)	C18—C15—C16— C17	-177.4 (2)
C11—N2—C8—C7	126.3 (2)	C15—C16—C17— C12	-1.1 (4)
S1—N2—C8—C7	-92.7 (2)	C13—C12—C17— C16	0.2 (4)
C11—N2—C8—C9	2.5 (2)	S1—C12—C17—C16	-176.62 (18)

X-Ray Crystallographic Information Data for 12



X-ray Crystallography: A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX DUO CCD diffractometer ($\text{CuK}\alpha$ radiation, $\lambda=1.54178$ Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 1.0° scans in ω at -30° , -55° , -80° , 30° , 55° , 80° and 115° in 2θ . Data integration down to 0.84 Å resolution was carried out using SAINT V8.37 A with reflection spot size optimization. Absorption corrections were made with the program SADABS (Bruker diffractometer, 2015). The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods against F^2 using SHELXT-2014 and SHELXL-2014 with OLEX 2 interface. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table S2.14, geometric parameters are shown in Table S2.15 and hydrogen-bond parameters are listed in Table S2.16. The Ortep plots produced with SHELXL-2014 program, and the other drawings were produced with Accelrys DS Visualizer 2.0.

Table S2.14 Experimental details.

Crystal data

Chemical formula $\text{C}_{11}\text{H}_{12.50}\text{FNO}_{4.25}\text{S}$

M_r 277.78

Crystal system, space group Hexagonal, $P6_2$

Temperature (K)	100
a, c (Å)	17.8047 (4), 6.9972 (2)
V (Å ³)	1920.99 (10)
Z	6
Radiation type	Cu $K\alpha$
μ (mm ⁻¹)	2.48
Crystal size (mm)	0.24 × 0.18 × 0.12
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan <i>SADABS</i>
$T_{\min}, T_{\max}$	0.660, 0.806
No. of measured, independent and observed [I $> 2s(I)$] reflections	14238, 2181, 2133
R_{int}	0.046
$(\sin \theta/\lambda)_{\max}$ (Å ⁻¹)	0.595
Refinement	
$R[F^2 > 2s(F^2)], wR(F^2), S$	0.033, 0.090, 1.07
No. of reflections	2181
No. of parameters	177
No. of restraints	7
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$D\rho_{\max}, D\rho_{\min}$ (e Å ⁻³)	0.30, -0.20
Absolute structure	Flack x determined using 924 quotients $[(I^+)-(I^-)]/[(I^+)+(I^-)]$ (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	-0.021 (19)

Table S2.15 Geometric parameters (Å, °).

S1—O4	1.441 (2)	C5—C6	1.378 (5)
S1—O3	1.445 (2)	C5—C10	1.398 (5)

S1—C11	1.760 (3)	C6—C7	1.386 (5)
S1—C8	1.771 (3)	C6—H6	0.9500
F1—C4	1.405 (4)	C7—C8	1.378 (5)
O1—C1	1.363 (5)	C7—H7	0.9500
O1—C3	1.447 (5)	C8—C9	1.386 (5)
O2—C1	1.214 (5)	C9—C10	1.383 (5)
N1—C1	1.335 (5)	C9—H9	0.9500
N1—C2	1.452 (6)	C10—H10	0.9500
N1—H1	0.95 (7)	C11—H11A	0.9800
C2—C3	1.534 (5)	C11—H11B	0.9800
C2—H2A	0.9900	C11—H11C	0.9800
C2—H2B	0.9900	O1W—O2W	1.0 (2)
C3—C4	1.502 (6)	O1W—H1WA	0.8124
C3—H3	1.0000	O1W—H1WB	0.8201
C4—C5	1.505 (4)	O2W—H2WA	0.7833
C4—H4	1.0000	O2W—H2WB	0.8183
O4—S1—O3	118.24 (14)	C6—C5—C10	120.3 (3)
O4—S1—C11	108.27 (15)	C6—C5—C4	120.8 (3)
O3—S1—C11	108.42 (14)	C10—C5—C4	118.9 (3)
O4—S1—C8	107.82 (14)	C5—C6—C7	120.2 (3)
O3—S1—C8	107.47 (15)	C5—C6—H6	119.9
C11—S1—C8	105.97 (15)	C7—C6—H6	119.9
C1—O1—C3	110.6 (3)	C8—C7—C6	119.1 (3)
C1—N1—C2	112.7 (3)	C8—C7—H7	120.5
C1—N1—H1	115 (3)	C6—C7—H7	120.5
C2—N1—H1	131 (3)	C7—C8—C9	121.7 (3)
O2—C1—N1	129.8 (4)	C7—C8—S1	119.1 (2)
O2—C1—O1	120.7 (3)	C9—C8—S1	119.2 (3)
N1—C1—O1	109.5 (3)	C10—C9—C8	119.0 (3)
N1—C2—C3	101.9 (3)	C10—C9—H9	120.5
N1—C2—H2A	111.4	C8—C9—H9	120.5
C3—C2—H2A	111.4	C9—C10—C5	119.7 (3)

N1—C2—H2B	111.4	C9—C10—H10	120.1
C3—C2—H2B	111.4	C5—C10—H10	120.1
H2A—C2—H2B	109.2	S1—C11—H11A	109.5
O1—C3—C4	108.8 (3)	S1—C11—H11B	109.5
O1—C3—C2	104.4 (3)	H11A—C11—H11B	109.5
C4—C3—C2	114.5 (4)	S1—C11—H11C	109.5
O1—C3—H3	109.7	H11A—C11—H11C	109.5
C4—C3—H3	109.7	H11B—C11—H11C	109.5
C2—C3—H3	109.7	O2W—O1W— H1WA	150.7
F1—C4—C3	108.0 (3)	O2W—O1W—H1WB	96.4
F1—C4—C5	109.2 (3)	H1WA—O1W— H1WB	112.3
C3—C4—C5	113.3 (3)	O1W—O2W— H2WA	173.4
F1—C4—H4	108.7	O1W—O2W—H2WB	77.8
C3—C4—H4	108.7	H2WA—O2W— H2WB	105.9
C5—C4—H4	108.7		
C2—N1—C1—O2	-174.4 (4)	C10—C5—C6—C7	-0.9 (5)
C2—N1—C1—O1	6.4 (5)	C4—C5—C6—C7	175.8 (3)
C3—O1—C1—O2	-179.7 (4)	C5—C6—C7—C8	-1.4 (5)
C3—O1—C1—N1	-0.4 (4)	C6—C7—C8—C9	2.3 (5)
C1—N1—C2—C3	-9.2 (5)	C6—C7—C8—S1	-175.8 (2)
C1—O1—C3—C4	117.4 (3)	O4—S1—C8—C7	151.1 (2)
C1—O1—C3—C2	-5.2 (4)	O3—S1—C8—C7	22.6 (3)
N1—C2—C3—O1	8.2 (5)	C11—S1—C8—C7	-93.2 (3)
N1—C2—C3—C4	-110.6 (4)	O4—S1—C8—C9	-27.1 (3)
O1—C3—C4—F1	-68.6 (3)	O3—S1—C8—C9	-155.6 (3)
C2—C3—C4—F1	47.7 (4)	C11—S1—C8—C9	88.7 (3)
O1—C3—C4—C5	52.6 (4)	C7—C8—C9—C10	-0.7 (5)
C2—C3—C4—C5	168.9 (3)	S1—C8—C9—C10	177.4 (3)
F1—C4—C5—C6	13.7 (4)	C8—C9—C10—C5	-1.6 (5)

C3—C4—C5—C6	-106.8 (4)	C6—C5—C10—C9	2.5 (5)
F1—C4—C5—C10	-169.6 (3)	C4—C5—C10—C9	-174.3 (3)
C3—C4—C5—C10	70.0 (4)		

Table S2.16 Hydrogen-bond parameters.

$D-H\cdots A$	$D-H$ (Å)	$H\cdots A$ (Å)	$D\cdots A$ (Å)	$D-H\cdots A$ (°)
N1—H1 $\cdots$ O1 ⁱ	0.95 (7)	2.68 (5)	3.077 (4)	106 (4)
N1—H1 $\cdots$ O2 ⁱ	0.95 (7)	2.08 (7)	2.978 (5)	158 (5)
C2—H2B $\cdots$ O1 ⁱ	0.99	2.54	3.096 (5)	115.4

Symmetry code(s): (i) $x-y+1, x, z+1/3$.

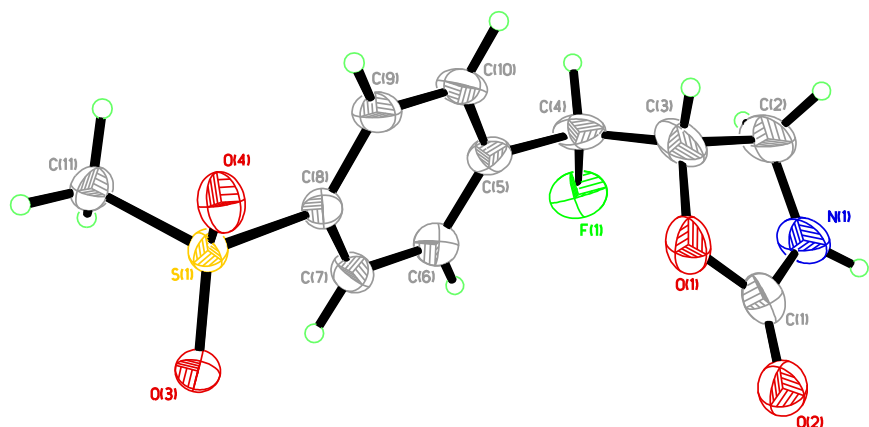


Figure S2.12 Perspective views showing 50% probability displacement.

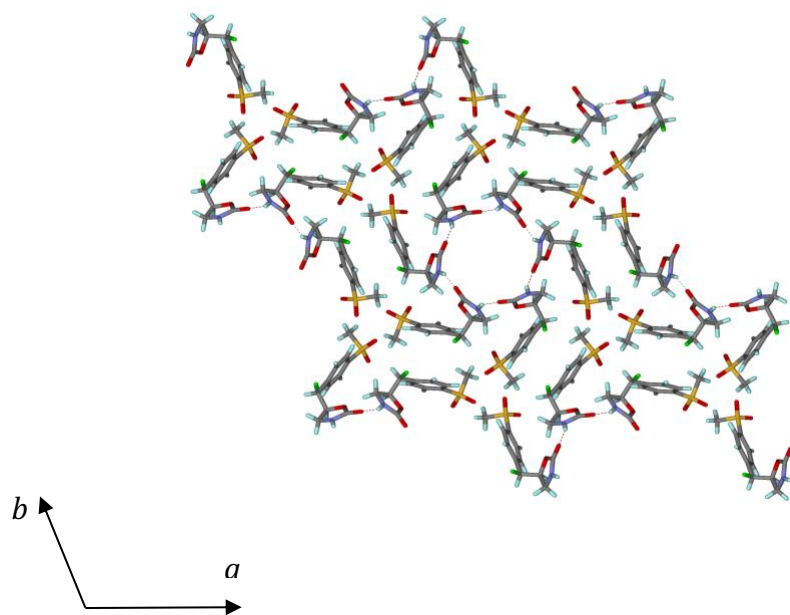
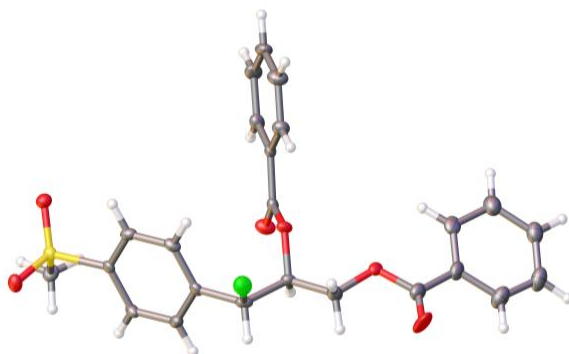


Figure S2.13 Three-dimensional supramolecular architecture viewed along the c -axis direction.

X-Ray Crystallographic Information Data for 16



X-ray Crystallography: A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II CCD diffractometer (MoK α radiation, $\lambda=0.71073$ Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 0.5° scans in ω at 28° in 2θ . Data integration down to 0.78 Å resolution was carried out using SAINT V8.37A with reflection spot size optimization. Absorption corrections were made with the program SADABS. The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods against F^2 using SHELXT-2014 and SHELXL-2014 with OLEX 2 interface. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table S2.17, and geometric parameters are shown in Table S2.19. The Ortep plots produced with SHELXL-2014 program, and the other drawings were produced with Accelrys DS Visualizer 2.0.

Table S2.17 Experimental details.

Crystal data

Chemical formula C₂₄H₂₁FO₆S

M_r 456.47

Crystal system, space group Orthorhombic, $P2_12_12_1$

Temperature (K)	100
<i>a</i> , <i>b</i> , <i>c</i> (Å)	5.2733 (3), 10.7709 (6), 37.817 (2)
<i>V</i> (Å ³)	2147.9 (2)
<i>Z</i>	4
Radiation type	Mo <i>K</i> α
<i>μ</i> (mm ⁻¹)	0.20
Crystal size (mm)	0.18 × 0.04 × 0.02

Data collection

Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan <i>SADABS</i>
<i>T</i> _{min} , <i>T</i> _{max}	0.719, 0.862
No. of measured, independent and observed [<i>I</i> > 2 <i>s</i> (<i>I</i>)] reflections	15038, 4709, 3791
<i>R</i> _{int}	0.051
(sin <i>q</i> / <i>l</i>) _{max} (Å ⁻¹)	0.642

Refinement

<i>R</i> [<i>F</i> ² > 2 <i>s</i> (<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.052, 0.093, 1.08
No. of reflections	4709
No. of parameters	318
No. of restraints	72
H-atom treatment	H-atom parameters constrained
Dρ _{max} , Dρ _{min} (e Å ⁻³)	0.30, -0.35
Absolute structure	Flack <i>x</i> determined using 1250 quotients [(<i>I</i> ⁺)-(<i>I</i> ⁻)]/[(<i>I</i> ⁺)+(<i>I</i> ⁻)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	-0.01 (5)

Table S2.19 Selected geometric parameters (Å, °).

S1—O2	1.440 (2)	C13—H13	0.9500
S1—O1	1.449 (2)	C14—C15	1.375 (6)
S1—C10	1.753 (4)	C14—H14	0.9500

S1—C3	1.778 (3)	C15—C16	1.384 (5)
F1—C7	1.407 (4)	C15—H15	0.9500
O3—C11	1.358 (4)	C16—C17	1.380 (5)
O3—C8	1.439 (4)	C16—H16	0.9500
O4—C11	1.207 (4)	C17—H17	0.9500
C1—C2	1.387 (4)	O5—C18	1.313 (16)
C1—C6	1.389 (5)	C18—O6	1.195 (16)
C1—H1	0.9500	C18—C19	1.483 (17)
C2—C3	1.389 (5)	C19—C20	1.380 (18)
C2—H2	0.9500	C19—C24	1.396 (16)
C3—C4	1.382 (4)	C20—C21	1.394 (16)
C4—C5	1.384 (4)	C20—H20	0.9500
C4—H4	0.9500	C21—C22	1.386 (16)
C5—C6	1.391 (5)	C21—H21	0.9500
C5—H5	0.9500	C22—C23	1.369 (15)
C6—C7	1.514 (4)	C22—H22	0.9500
C7—C8	1.519 (5)	C23—C24	1.387 (16)
C7—H7	1.0000	C23—H23	0.9500
C8—C9	1.510 (4)	C24—H24	0.9500
C8—H8	1.0000	O5A—C18A	1.324 (11)
C9—O5	1.42 (4)	C18A—O6A	1.207 (12)
C9—O5A	1.47 (2)	C18A—C19A	1.486 (13)
C9—H9AA	0.9900	C19A—C20A	1.381 (16)
C9—H9AB	0.9900	C19A—C24A	1.394 (12)
C9—H9BC	0.9900	C20A—C21A	1.390 (12)
C9—H9BD	0.9900	C20A—H20A	0.9500
C10—H10A	0.9800	C21A—C22A	1.378 (12)
C10—H10B	0.9800	C21A—H21A	0.9500
C10—H10C	0.9800	C22A—C23A	1.374 (12)
C11—C12	1.481 (5)	C22A—H22A	0.9500
C12—C17	1.381 (5)	C23A—C24A	1.394 (12)
C12—C13	1.399 (5)	C23A—H23A	0.9500
C13—C14	1.375 (5)	C24A—H24A	0.9500

O2—S1—O1	117.74 (15)	C13—C12—C11	118.4 (3)
O2—S1—C10	108.75 (16)	C14—C13—C12	120.2 (4)
O1—S1—C10	108.67 (16)	C14—C13—H13	119.9
O2—S1—C3	107.73 (14)	C12—C13—H13	119.9
O1—S1—C3	106.87 (14)	C13—C14—C15	120.2 (3)
C10—S1—C3	106.54 (17)	C13—C14—H14	119.9
C11—O3—C8	117.4 (3)	C15—C14—H14	119.9
C2—C1—C6	120.6 (3)	C14—C15—C16	120.2 (4)
C2—C1—H1	119.7	C14—C15—H15	119.9
C6—C1—H1	119.7	C16—C15—H15	119.9
C1—C2—C3	118.9 (3)	C17—C16—C15	119.9 (4)
C1—C2—H2	120.5	C17—C16—H16	120.1
C3—C2—H2	120.5	C15—C16—H16	120.1
C4—C3—C2	121.0 (3)	C16—C17—C12	120.5 (3)
C4—C3—S1	117.8 (3)	C16—C17—H17	119.8
C2—C3—S1	121.1 (2)	C12—C17—H17	119.8
C3—C4—C5	119.7 (3)	C18—O5—C9	116 (3)
C3—C4—H4	120.1	O6—C18—O5	118 (2)
C5—C4—H4	120.1	O6—C18—C19	126 (2)
C4—C5—C6	120.1 (3)	O5—C18—C19	114.6 (19)
C4—C5—H5	120.0	C20—C19—C24	120.1 (16)
C6—C5—H5	120.0	C20—C19—C18	122.1 (18)
C1—C6—C5	119.7 (3)	C24—C19—C18	117.8 (18)
C1—C6—C7	119.1 (3)	C19—C20—C21	119.4 (19)
C5—C6—C7	121.3 (3)	C19—C20—H20	120.3
F1—C7—C6	108.8 (3)	C21—C20—H20	120.3
F1—C7—C8	108.4 (3)	C22—C21—C20	119.4 (17)
C6—C7—C8	113.4 (3)	C22—C21—H21	120.3
F1—C7—H7	108.7	C20—C21—H21	120.3
C6—C7—H7	108.7	C23—C22—C21	121.8 (17)
C8—C7—H7	108.7	C23—C22—H22	119.1
O3—C8—C9	107.6 (3)	C21—C22—H22	119.1

O3—C8—C7	109.4 (3)	C22—C23—C24	118.5 (18)
C9—C8—C7	110.9 (3)	C22—C23—H23	120.7
O3—C8—H8	109.6	C24—C23—H23	120.7
C9—C8—H8	109.6	C23—C24—C19	120.5 (16)
C7—C8—H8	109.6	C23—C24—H24	119.7
O5—C9—C8	110.4 (13)	C19—C24—H24	119.7
O5A—C9—C8	103.8 (8)	C18A—O5A—C9	118.2 (19)
O5—C9—H9AA	109.6	O6A—C18A—O5A	123.3 (17)
C8—C9—H9AA	109.6	O6A—C18A—C19A	123.3 (15)
O5—C9—H9AB	109.6	O5A—C18A—C19A	113.3 (13)
C8—C9—H9AB	109.6	C20A—C19A— C24A	119.4 (12)
H9AA—C9—H9AB	108.1	C20A—C19A— C18A	122.2 (13)
O5A—C9—H9BC	111.0	C24A—C19A— C18A	118.4 (15)
C8—C9—H9BC	111.0	C19A—C20A— C21A	120.1 (13)
O5A—C9—H9BD	111.0	C19A—C20A— H20A	120.0
C8—C9—H9BD	111.0	C21A—C20A— H20A	120.0
H9BC—C9—H9BD	109.0	C22A—C21A— C20A	120.2 (12)
S1—C10—H10A	109.5	C22A—C21A— H21A	119.9
S1—C10—H10B	109.5	C20A—C21A— H21A	119.9
H10A—C10—H10B	109.5	C23A—C22A— C21A	120.2 (12)
S1—C10—H10C	109.5	C23A—C22A— H22A	119.9
H10A—C10—H10C	109.5	C21A—C22A— H22A	119.9
H10B—C10—H10C	109.5	C22A—C23A— C24A	119.8 (12)

O4—C11—O3	123.7 (3)	C22A—C23A— H23A	120.1
O4—C11—C12	125.4 (3)	C24A—C23A— H23A	120.1
O3—C11—C12	110.9 (3)	C19A—C24A— C23A	120.1 (13)
C17—C12—C13	119.1 (3)	C19A—C24A— H24A	120.0
C17—C12—C11	122.5 (3)	C23A—C24A— H24A	120.0
C6—C1—C2—C3	0.0 (5)	C11—C12—C13— C14	178.7 (3)
C1—C2—C3—C4	1.1 (5)	C12—C13—C14— C15	1.2 (5)
C1—C2—C3—S1	-174.7 (3)	C13—C14—C15— C16	-0.3 (6)
O2—S1—C3—C4	27.0 (3)	C14—C15—C16— C17	-0.3 (6)
O1—S1—C3—C4	-100.4 (3)	C15—C16—C17— C12	-0.1 (6)
C10—S1—C3—C4	143.5 (3)	C13—C12—C17— C16	1.0 (5)
O2—S1—C3—C2	-157.1 (3)	C11—C12—C17— C16	-179.3 (3)
O1—S1—C3—C2	75.5 (3)	C8—C9—O5—C18	-150.0 (17)
C10—S1—C3—C2	-40.6 (3)	C9—O5—C18—O6	-21 (3)
C2—C3—C4—C5	-1.2 (5)	C9—O5—C18—C19	167 (4)
S1—C3—C4—C5	174.7 (3)	O6—C18—C19— C20	-158 (6)
C3—C4—C5—C6	0.2 (5)	O5—C18—C19— C20	13 (9)
C2—C1—C6—C5	-0.9 (5)	O6—C18—C19— C24	19 (8)
C2—C1—C6—C7	179.6 (3)	O5—C18—C19— C24	-170 (5)
C4—C5—C6—C1	0.8 (5)	C24—C19—C20— C21	-3 (10)

C4—C5—C6—C7	-179.7 (3)	C18—C19—C20—C21	174 (4)
C1—C6—C7—F1	-143.7 (3)	C19—C20—C21—C22	4 (7)
C5—C6—C7—F1	36.8 (4)	C20—C21—C22—C23	0 (4)
C1—C6—C7—C8	95.6 (4)	C21—C22—C23—C24	-5 (5)
C5—C6—C7—C8	-84.0 (4)	C22—C23—C24—C19	5 (6)
C11—O3—C8—C9	133.9 (3)	C20—C19—C24—C23	-1 (9)
C11—O3—C8—C7	-105.5 (3)	C18—C19—C24—C23	-179 (5)
F1—C7—C8—O3	-60.9 (3)	C8—C9—O5A—C18A	-152.6 (12)
C6—C7—C8—O3	60.0 (4)	C9—O5A—C18A—O6A	17 (2)
F1—C7—C8—C9	57.7 (4)	C9—O5A—C18A—C19A	-166 (3)
C6—C7—C8—C9	178.6 (3)	O6A—C18A—C19A—C20A	-166 (4)
O3—C8—C9—O5	-55.3 (12)	O5A—C18A—C19A—C20A	17 (6)
C7—C8—C9—O5	-175.0 (12)	O6A—C18A—C19A—C24A	14 (6)
O3—C8—C9—O5A	-67.4 (9)	O5A—C18A—C19A—C24A	-164 (3)
C7—C8—C9—O5A	173.0 (8)	C24A—C19A—C20A—C21A	3 (7)
C8—O3—C11—O4	0.8 (4)	C18A—C19A—C20A—C21A	-178 (3)
C8—O3—C11—C12	-179.4 (3)	C19A—C20A—C21A—C22A	-3 (5)
O4—C11—C12—C17	-177.7 (3)	C20A—C21A—C22A—C23A	1 (3)
O3—C11—C12—C17	2.5 (4)	C21A—C22A—C23A—C24A	2 (3)

O4—C11—C12— C13	2.0 (5)	C20A—C19A— C24A—C23A	1 (6)
O3—C11—C12— C13	-177.8 (3)	C18A—C19A— C24A—C23A	-179 (3)
C17—C12—C13— C14	-1.5 (5)	C22A—C23A— C24A—C19A	-3 (4)

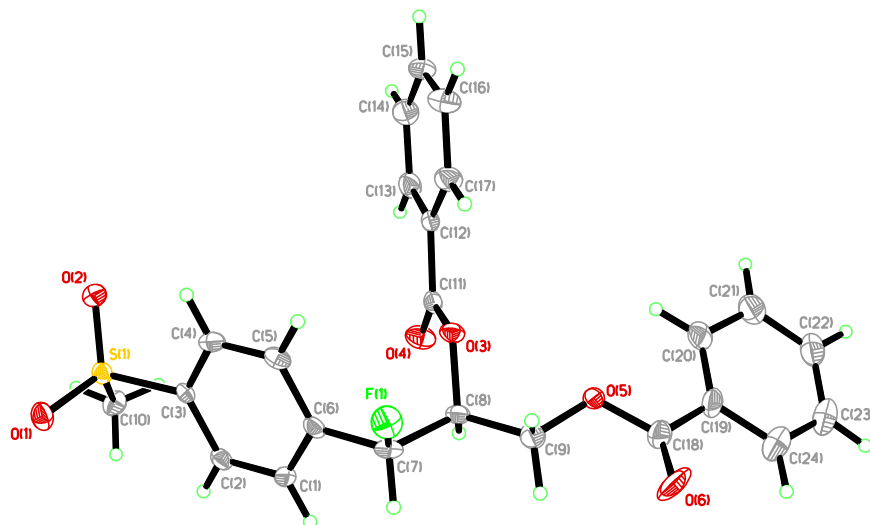


Figure S2.14 Perspective views showing 50% probability displacement.

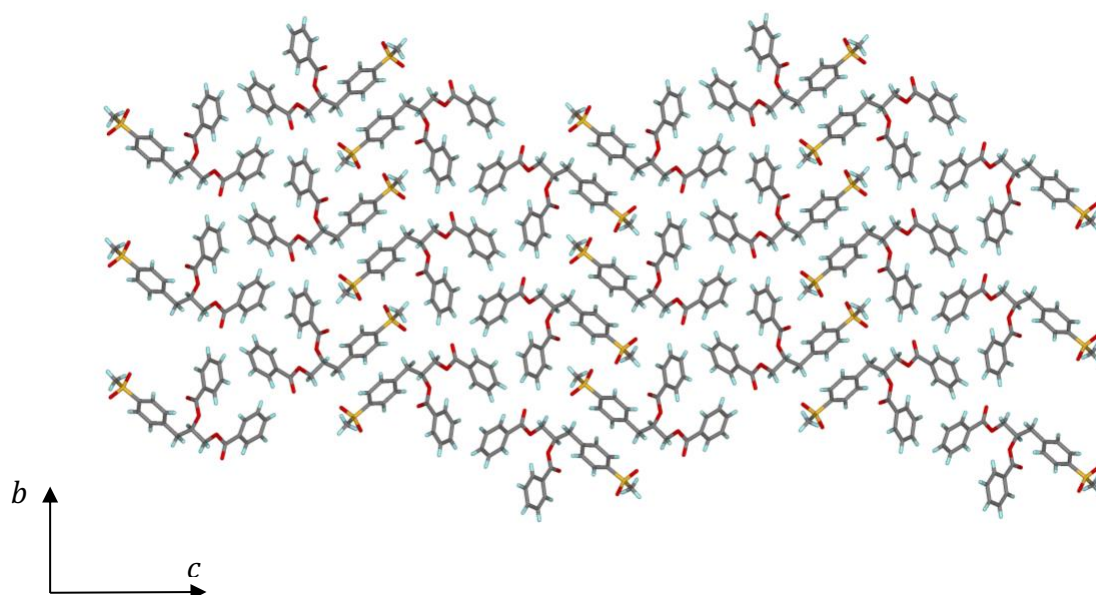


Figure S2.15 Three-dimensional supramolecular architecture viewed along the *a*-axis direction.

Chapter 3

Asymmetric Fluorinative Wagner–Meerwein Rearrangements

Catalyzed by Hypervalent Iodine

3.1 Introduction

Carbocations are highly reactive intermediates that can induce skeletal rearrangements through the migration of strong σ bonds, thus providing a powerful strategy for the construction of complex molecules.^{1,2} However, because the energetic barrier for rearrangements of discrete carbocations is generally low,³ stereochemical control has relied on the use of activated leaving groups as stereodefined carbocation surrogates that can be displaced stereospecifically.⁴

¹ For a review discussing the applications of carbocation chemistry in organic synthesis, see: Naredla, R.R.; Klumpp, D.A. *Chem. Rev.* **2013**, *113*, 6905–6948.

² For selected reviews discussing terpene biosynthesis, see: (a) Cane, D.E. *Chem. Rev.* **1990**, *90*, 1089–1103. (b) Davis, E.M.; Croteau, R. *Top. Curr. Chem.* **2000**, *209*, 53–95. (c) Christianson, D.W. *Chem. Rev.* **2006**, *106*, 3412–3442. (d) Tantillo, D.J. *Chem. Soc. Rev.* **2010**, *39*, 2847–2854.

³ Hong, Y.J.; Tantillo, D.J. *Nat. Chem.* **2014**, *6*, 104–111.

⁴ For selected examples of stereospecific Wagner–Meerwein rearrangements of enantiopure starting materials in targeted syntheses, see: Zubkov, F.I.; Zaytsev, V.P.; Nikitina, E.V.; Khrustalev, V.N.; Gozun, S.V.; Boltukhina, E.V.; Varlamov, A.V. *Tetrahedron* **2011**, *67*, 9148–9163. (b) Cheng, H.; Xu, L.; Chen, D.-L.; Chen, Q.-H.; Wang, F.-P. *Tetrahedron* **2012**, *68*, 1171–1176. (c) Sakurai, J.; Kikuchi, T.; Takahashi, O.; Watanabe, K.; Katoh, T. *Eur. J. Org. Chem.* **2011**, 2948–2957. (d) Suzuki, K.; Takikawa, H.; Hachisu, Y.; Bode, J. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3252–3254.

Efforts to develop catalytic and enantioselective Wagner–Meerwein rearrangements have largely focused on semi-pinacol rearrangements, in which transient, stereodefined electrophiles generated from π -systems induce the stereospecific migration of a C–C or C–H bond concomitant with oxocarbenium ion formation.⁵ In contrast, the development of catalytic and enantioselective Wagner–Meerwein rearrangements involving non-heteroatom-stabilized carbocations has lagged behind. This may be attributed to the two-fold challenge of catalytically generating and stereoselectively controlling highly reactive carbocationic intermediates.

In this chapter, we leverage the high electrophilicity and configurational stability of chiral iodine(III) intermediates generated *via* hypervalent iodine catalysis to induce enantioselective Wagner–Meerwein rearrangements of secondary alkyl carbocation surrogates. Using a nucleophilic fluoride source, this approach affords access to enantioenriched 1,3-difluorides from simple β -substituted styrene precursors through the migration of aryl, methyl, or hydrogen substituents. Hammett, kinetic isotope effect and computational investigations reveal that the enantiodetermining step can vary between intermolecular fluoride attack and intramolecular 1,2-migration depending on the substrate, thereby providing insight into longstanding mechanistic questions in hypervalent iodine chemistry.

3.1.1 The Wagner–Meerwein Rearrangement

The Wagner–Meerwein rearrangement is a 1,2-migration reaction where an aryl, vinyl, alkyl, or hydrogen substituent migrates from one carbon to a neighboring carbocationic center in

⁵ For selected reviews on stereoselective semi-pinacol rearrangements, see: (a) Snape, T.J. *Chem. Soc. Rev.* **2007**, 36, 1823–1842. (b) Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, 111, 7523–7556. (c) Wang, B.; Tu, Y.Q. *Acc. Chem. Res.* **2011**, 44, 1207–1222. (d) Wang, S.-H.; Li, B.-S. *Chem. Commun.* **2014**, 50, 2393–2408.

either a stepwise or concerted mechanism.⁶ The ease with which species migrate varies according to the nature of the reaction and the conditions. However, an approximate ranking is possible based on relative rate data for several rearrangements (Figure 3.1). In general, the substituent that best stabilizes positive charge in the transition state migrates preferentially. Orbital alignment, however, must also be appropriate for migration.

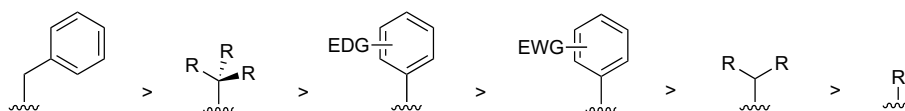


Figure 3.1 Relative migratory aptitudes.

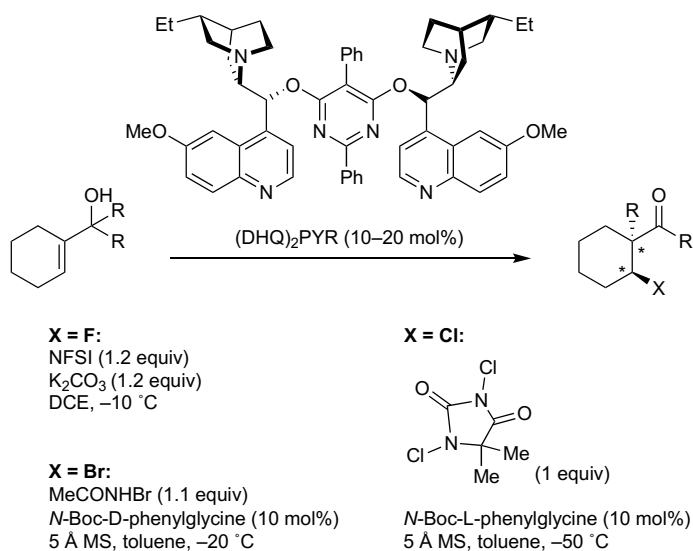
3.1.2 Catalytic, Enantioselective Semi-Pinacol Rearrangements

Towards the development of catalytic and enantioselective Wagner–Meerwein rearrangements, several semi-pinacol variants have been reported.⁵ In these reports, migration is typically induced by activation of an adjacent π -system to generate a carbocationic intermediate. However, the often-weakly electrophilic nature of the metal- and halogen-based activators employed necessitates the use of electron-rich or highly polarized π -systems. As a result of the relatively stabilized nature of the carbocationic intermediates generated prior to migration, only stabilized carbocations (typically by a heteroatom) can be formed upon migration.

For example, Tu and co-workers have reported catalytic and enantioselective halogenation/semi-pinacol rearrangement cascades to generate α -oxaquaternary β -halo-ketones

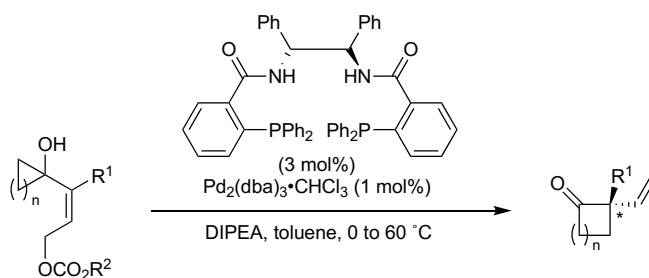
⁶ For an overview of Wagner–Meerwein rearrangements and related reactions, see: (a) Hanson, J.R. In *Comprehensive Organic Synthesis*. (b) Trost, B.M., Fleming, I., Pattenden, G., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 3.1, pp 705–720. (c) Ricknorn, B., *idem.*; Chapter 3.2, pp 721–732, and Chapter 3.3, pp 733–776. (d) Coveney, D.; Chapter 3.4, pp 777–802.

using electrophilic halogen reagents and bis-quinine-derivative (DHQ)₂PYR as the catalyst (Scheme 3.1).⁷



Scheme 3.1 Catalytic, enantioselective halogenation/semi-pinacol rearrangement cascades.

Trost and Yashukata have reported that the complex of Pd(0) with Trost's ligand can catalyze an asymmetric ring expansion-type semi-pinacol rearrangement of allylic cycloalkanols, yielding enantioenriched α -alkyl- α -vinyl cycloketones (Scheme 3.2).⁸

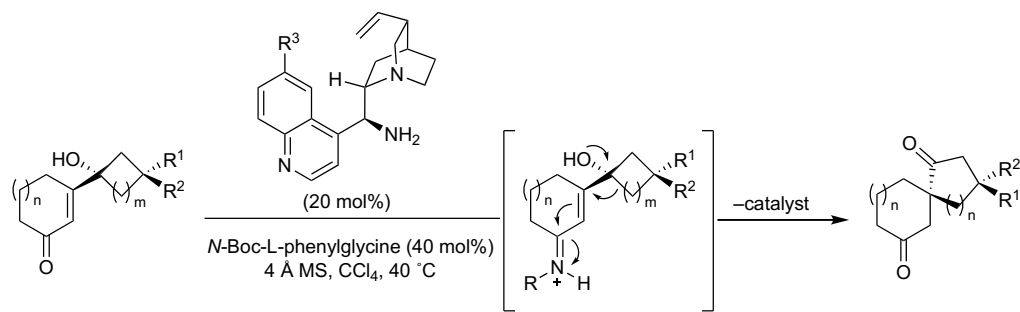


Scheme 3.2 Pd(0)-catalyzed asymmetric semi-pinacol rearrangement of allylic cycloalkanols.

⁷ Chen, Z.-M.; Yang, B.-M.; Chen, Z.-H.; Zhang, Q.-W.; Wang, M.; Tu, Y.-Q. *Chem.-Eur. J.* **2012**, *18*, 12950–12954.

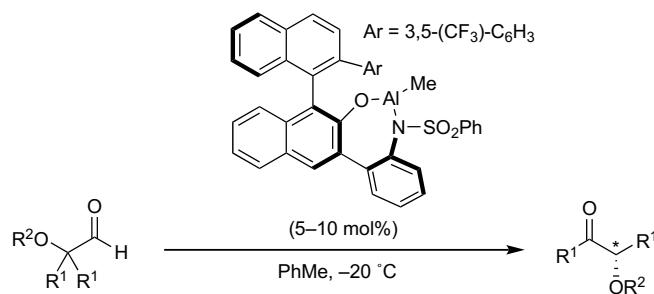
⁸ Trost, B.M.; Yasukata, T. *J. Am. Chem. Soc.* **2001**, *123*, 7162–7163.

An amine-catalyzed asymmetric ring expansion-type rearrangement of cyclic vinylogous α -ket-*tert*-ols to form spirocyclic 1,4-diones was reported by Tu and co-workers (Scheme 3.3).⁹ Formation of a chiral cationic iminium intermediate is invoked followed by a stereospecific semi-pinacol rearrangement.



Scheme 3.3 Amine-catalyzed semi-pinacol rearrangements of vinylogous α -ketols.

Finally, Maruoka and co-workers have disclosed an asymmetric semi-pinacol rearrangement of α,α -disubstituted 2-silyloxyacetaldehydes catalyzed by a chiral organoaluminum Lewis acid (Scheme 3.4).¹⁰ In the proposed mechanism, the Lewis acid complexes to the carbonyl group and induces a 1,2-migration to generate an enantioenriched α -trialkylsiloxy ketone.

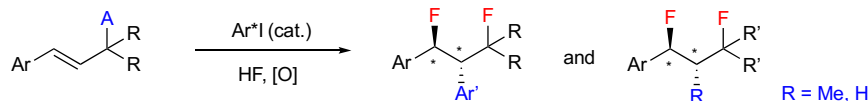


Scheme 3.4 Lewis acid-catalyzed asymmetric acyloin rearrangement of α -siloxy aldehydes.

⁹ Zhang, E.; Fan, C.-A.; Tu, Y.-Q.; Zhang, F.-M.; Song, Y.-L. *J. Am. Chem. Soc.* **2009**, *131*, 14626–14627.

¹⁰ Ooi, T.; Ohmatsu, K.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 2410–2411.

To effect catalytic and enantioselective Wagner–Meerwein rearrangements involving non-heteroatom-stabilized carbocations, we envisioned that a stereodefined carbocation mimic capable of activating electron-poor carbon centers would be required. Towards this end, hypervalent iodine chemistry¹¹ offers a unique opportunity by enabling access to highly reactive, yet configurationally stable, chiral alkyl iodane intermediates *via* enantioselective 1,2-iodofunctionalization of alkenes. Such intermediates are six orders of magnitude more electrophilic than alkyl triflates,^{11b} for example, and can thus generate cationic charge at carbon centers bearing only secondary alkyl substitution or positioned alpha to carbonyl groups. These intermediates display configurational stability uncharacteristic of this reactivity, however, and, in many cases, can be nucleophilically displaced with high levels of stereospecificity. In this chapter, we demonstrate this approach within the context of fluorinative Wagner–Meerwein rearrangements of β -cumyl, *t*-butyl, and *i*-propyl substituted styrenes (Scheme 3.5).



Scheme 3.5 This work: catalytic, enantioselective fluorinative Wagner–Meerwein rearrangements.

3.1.3 Mechanistic Questions in Enantioselective Hypervalent Iodine Chemistry

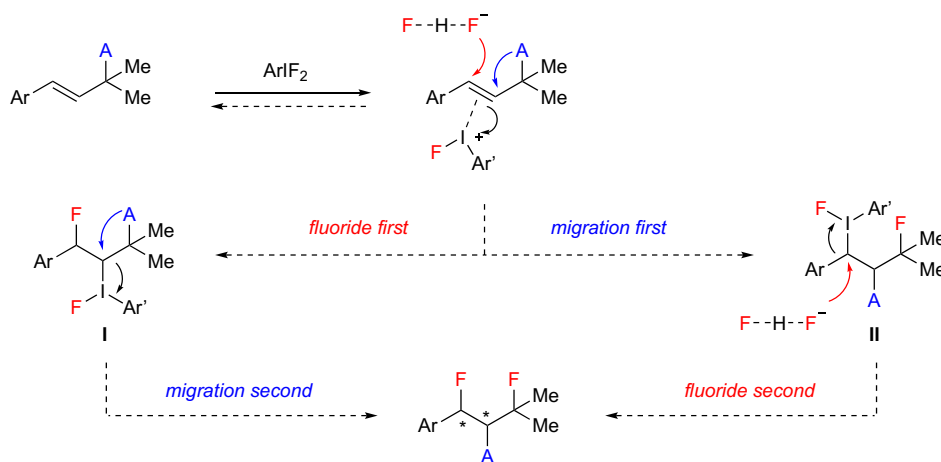
Building on previous work from our group,¹² we anticipated that stereoselective fluorinative Wagner–Meerwein rearrangements of β -substituted styrenes could be achieved

¹¹ For comprehensive reviews, see: (a) Yoshimura, A.; Zhdankin, V.V. *Chem. Rev.* **2016**, *116*, 3328–3435. (b) Ochiai, M. Reactivities, Properties and Structures. In *Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis*; Wirth, T., Ed.; Springer-Verlag: Berlin, Heidelberg, 2003.

¹² (a) Banik, S.M.; Medley, J.W.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2016**, *138*, 5000–5003. (b) Woerly, E.M.; Banik, S.M.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2016**, *138*, 13858–13861. (c) Banik, S.M.; Medley,

through two potential catalytic pathways (Scheme 3.6). In both pathways, oxidation of the aryl iodide catalyst followed by ligand exchange with HF and coordination to the styrene to form a π -complex is proposed. In a “fluoride-first” pathway, exogenous fluoride attacks the π -complex first to generate a chiral alkyl iodane (**I**), which then induces stereospecific 1,2-migration of the adjacent aryl, alkyl or hydrogen substituent. Quenching of the resultant carbocation with fluoride then generates a 1,3-difluoride. Alternatively, in a “migration-first” pathway, the allylic migrating group attacks the π -complex first to form a benzylic iodane and tertiary carbocation (**II**), both of which are attacked by fluoride to generate a 1,3-difluoride.

These two scenarios represent a competition between external and internal nucleophilic attack that is prevalent in many iodine(III)-mediated difunctionalization reactions of alkenes. Although the result of this competition defines the selectivity-determining steps and product outcome, no experimental investigations into the ordering of these events have been reported to date. In the proposed Wagner–Meerwein rearrangements, the ability to vary the nature of the intramolecular trapping group offers a unique opportunity to explore this dichotomy.



Scheme 3.6 Dichotomous mechanistic pathways in iodine(III)-mediated fluorofunctionalization reactions of alkenes.

J.W.; Jacobsen, E.N. *Science* **2016**, 353, 51–54. (d) Mennie, K.M.; Banik, S.M.; Reichert, E.C.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2018**, 140, 4797–4802.

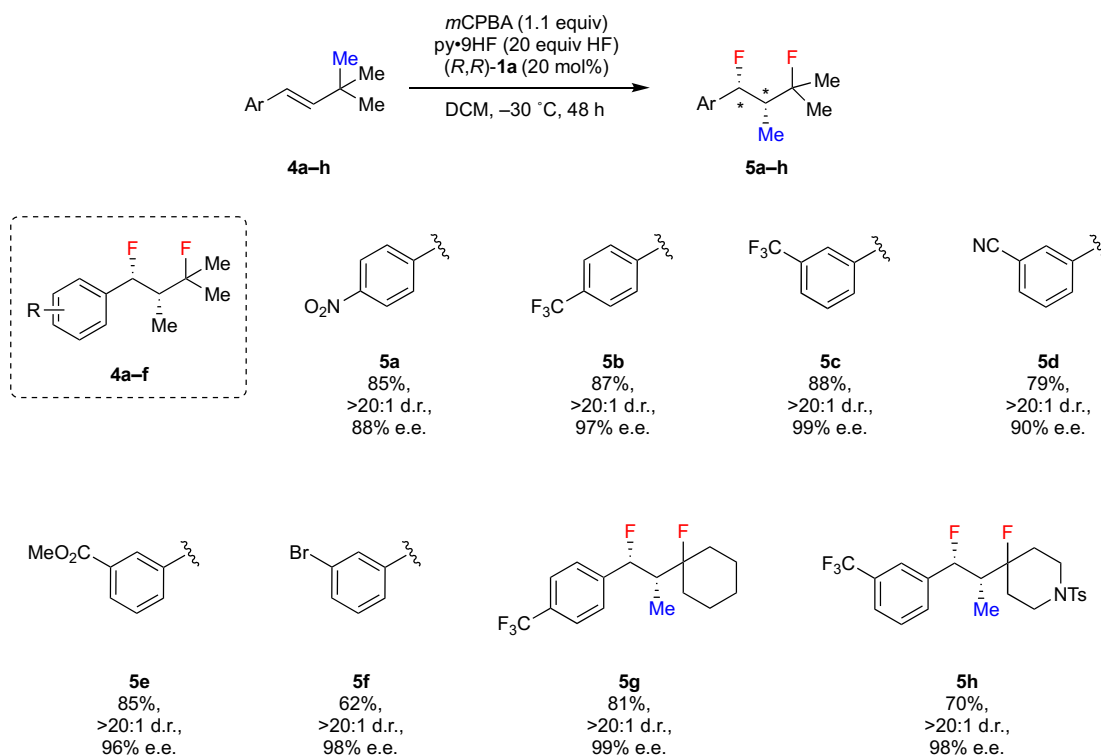
3.2 Development and Mechanistic Study of Catalytic, Enantioselective Fluorinative Wagner–Meerwein Rearrangements¹³

3.2.1 Reaction Development

β -Cumyl styrene derivative **2d** was evaluated as a model substrate for the proposed Wagner–Meerwein rearrangement. Examination of a range of reagent combinations and experimental protocols led to the identification of optimal conditions similar to those reported in our previously described fluorofunctionalization reactions.¹² Thus, in the presence of chiral aryl iodide catalyst **1a**, *m*CPBA as a stoichiometric oxidant, and HF–pyridine (100 equivalents of HF) as a nucleophilic fluoride source and acidic promoter, **2d** was observed to undergo selective oxidation to generate the corresponding 1,3-difluorinated product **3d** in 88% e.e. as the 1,2-*anti*-diastereomer.

A range of migrating and styrenyl arenes was tolerated under the reaction conditions, the corresponding 1,3-difluorinated products (**3a–i**) being formed with high levels of enantioselectivity (Scheme 3.7). Lower loadings of Olah’s reagent (20 equivalents of HF) could be employed for full conversion of substrates bearing electron-neutral/rich migrating arenes. In general, higher levels of enantioselectivity were observed for substrates bearing more electron-deficient migrating groups when similar loadings of HF–pyridine were employed. The level of 1,2-*anti*-diastereoselectivity was found to be highly dependent on the electronics of both the stationary and migrating arenes, decreasing significantly as the migrating arene became more electron-deficient and as the stationary arene became more electron-rich. Both the major 1,2-*anti*- and minor 1,2-*syn*-diastereomers were similarly enantioenriched, suggesting that both products are formed after a common enantiodetermining step.

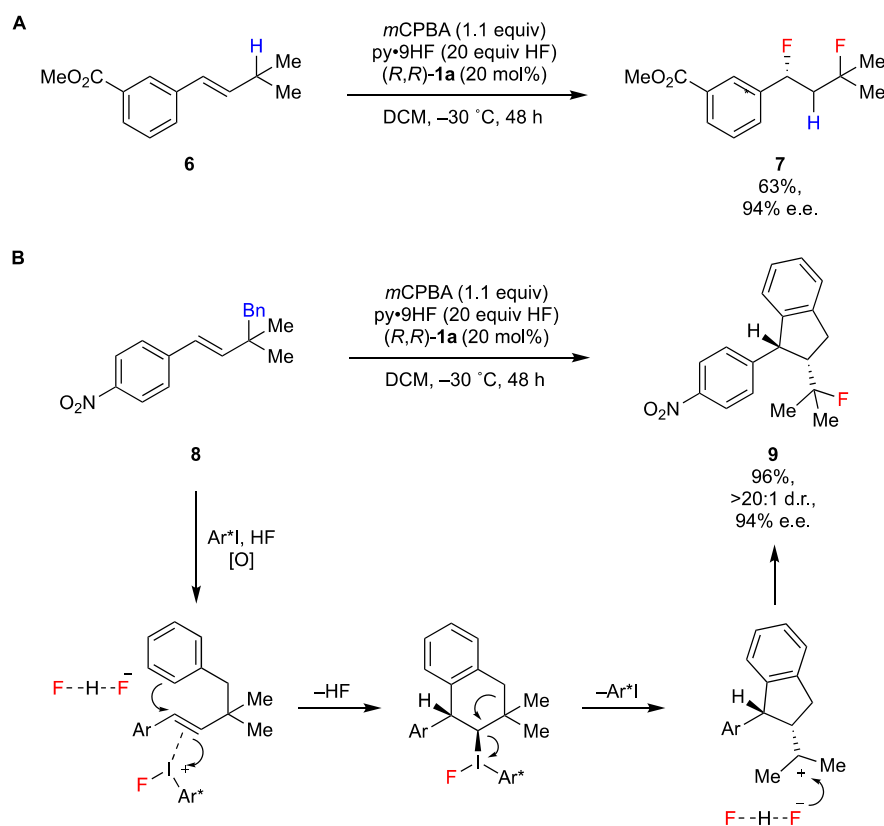
¹³ This work was performed in collaboration with Hayden A. Sharma and Dr. Eugene E. Kwan.



Scheme 3.8 Evaluation of substrate scope for the methyl rearrangement reaction.

In addition, β -*i*-propyl-substituted substrate **6** was found to undergo a selective hydride migration reaction to form 1,3-difluoride **7** in moderate yield and 93% e.e. (Scheme 3.9A). β -Benzyl-substituted styrene **8**, however, did not form the corresponding 1,3-difluorinated product, forming monofluorinated indene **9** instead as a single diastereomer in 94% e.e. (Scheme 3.9B). Formation of this product may be rationalized in terms of a Friedel–Crafts alkylation/Wagner–Meerwein rearrangement cascade. Effective control can thus be achieved for a variety of migrating groups spanning over three orders of migratory aptitude.¹⁴

¹⁴ Saunders, W. H. Jr.; Paine, R. H. *J. Am. Chem. Soc.* **1961**, 83, 882.



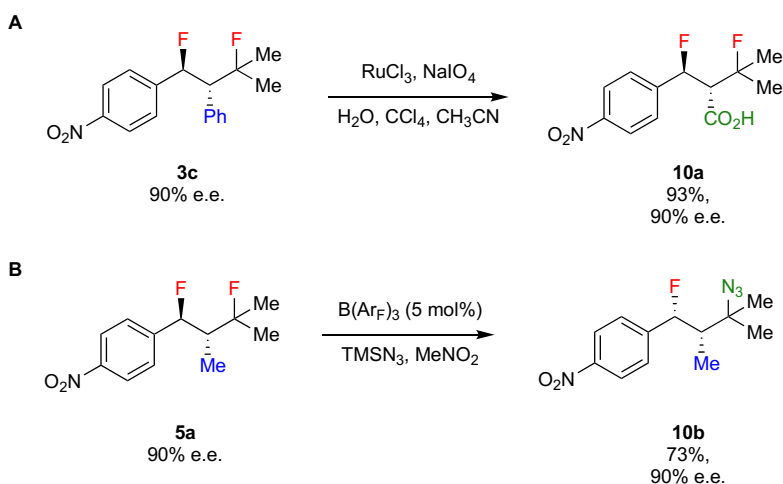
Scheme 3.9 A) 1,3-Hydride migration reaction of β -*t*-butyl-substituted styrenes.
 B) Rearrangement of β -benzyl-substituted styrenes.

The products of these aryl iodide-catalyzed Wagner–Meerwein rearrangements could be elaborated synthetically to yield a number of highly functionalized compounds. For example, chemoselective oxidation of the more electron-rich phenyl ring of **3c** by RuCl₃/NaIO₄ led to generation of a functional carboxylic acid handle¹⁵ between the 1,3-difluoride motif (Scheme 3.10A).¹⁶ In the presence of catalytic BAr_F, the more chemically labile tertiary fluoride in **5a** could be replaced by azide to arrive at a chiral 1,3-fluoroamine motif (Scheme 3.10B).¹⁷

¹⁵ Nunez, M.T.; Martin, V.S. *J. Org. Chem.* **1990**, *55*, 1928–1932.

¹⁶ For a review discussing 1,3-difluoride dipole minimization, see: O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308–319.

¹⁷ Dryzhakov, M.; Richmond, E.; Li, G.; Moran, J. *Journal of Fluorine Chemistry* **2017**, *193*, 45–51.



Scheme 3.10 Product elaboration. **A)** Oxidative degradation of phenyl group in **3c** to functional carboxylic acid handle. **B)** Formation of 1,3-difluoroamine motif from **5a**.

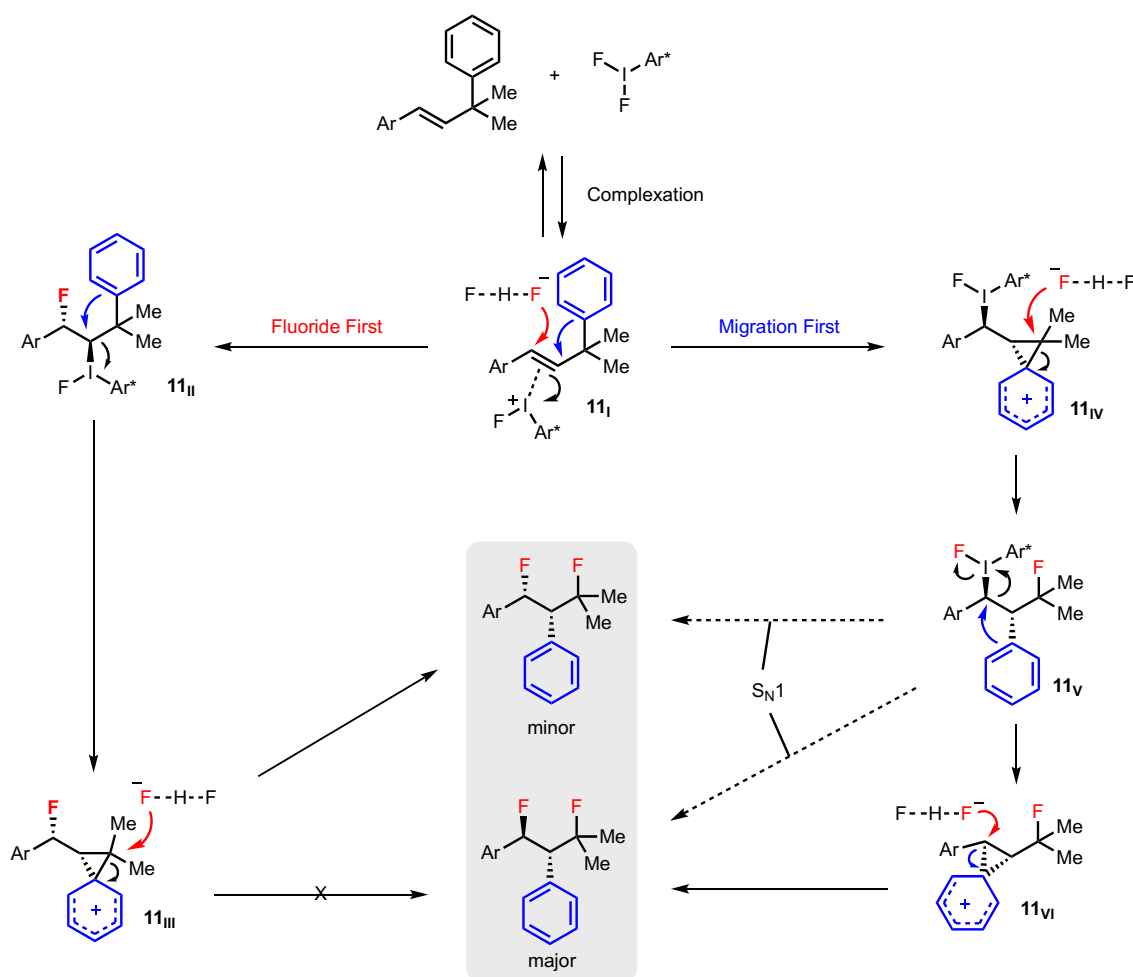
3.2.1 Hammett, Kinetic Isotope Effect and Computational Studies

The results described in this chapter demonstrate that hypervalent iodine species can catalyze a variety of enantioselective fluorinative Wagner–Meerwein rearrangements and may offer a more general approach to the development of catalytic, asymmetric carbocationic rearrangements. In light of the potential applications of this approach as well as the limited reported investigations into the mechanistic features of iodine(III)-mediated fluorofunctionalization reactions of alkenes, we undertook a mechanistic study of the phenyl and methyl rearrangement reactions.

Two plausible mechanistic scenarios for the phenyl rearrangement reaction are proposed based on the fluoride-first and migration-first scenarios (Scheme 3.11). In the fluoride-first scenario, stereoinvertive attack of the styrene–iodonium π -complex (**11i**) by fluoride gives rise to an *anti*-1,2-fluoroiodinated motif (**11ii**). Stereospecific migration of the arene then occurs in two steps *via* formation and fluorinative ring opening of a phenonium intermediate (**11iii**).¹⁸ Fluoride

¹⁸ Cram, D. J. *J. Am. Chem. Soc.* **1949**, *71*, 3863–3870.

delivery occurs at the more substituted position of the phenonium intermediate to furnish the 1,3-difluorinated product. In the migration-first scenario, stereoinvertive attack of the styrene-iodonium π -complex generates a benzylic iodane/phenonium intermediate (**11_{IV}**). Opening of the phenonium ion by fluoride yields **11_V**. Direct displacement of this benzylic iodane by a second fluoride would give rise to a 1,3-difluoride. Alternatively, the benzylic iodane could be intercepted by the migrated arene to form a second phenonium intermediate (**11_{VI}**).¹⁹ Opening of this phenonium ion by fluoride at the benzylic position would also give rise to a 1,3-difluoride.



Scheme 3.11 Possible mechanistic scenarios for the phenyl rearrangement reaction.

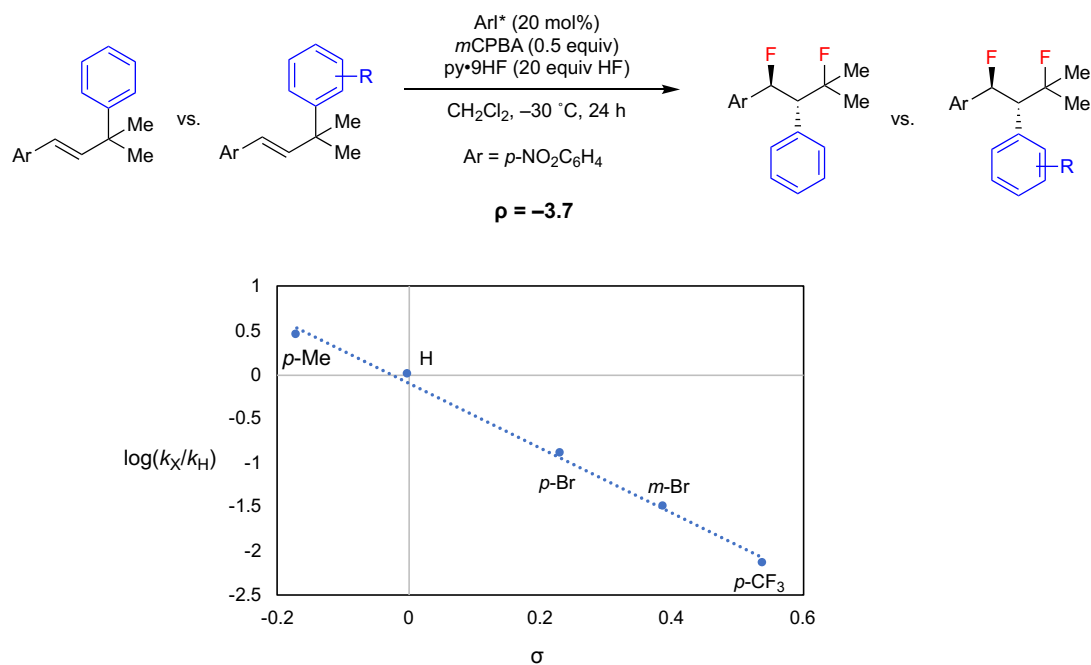
¹⁹ Seminal examples include: (a) Borstein, J.; Borden, M. R.; Nunes, F.; Tarlin, H. I. *J. Am. Chem. Soc.* **1963**, 85, 1609–1615. (b) Carpenter, W. *J. Org. Chem.* **1966**, 31, 2688–2689.

The observed stereochemical outcome, in which the major diastereomer bears an *anti*-1,2-fluoroaryl motif, rules out the proposed fluoride-first mechanism. In contrast, the observed stereochemical outcome can be rationalized with the migration-first mechanism invoking the formation of second phenonium ion intermediate. In this scenario, the minor *syn*-diastereomer might arise from heterolysis of the highly labile benzylic C–I(III) bond in **11v** to form a benzylic carbocation, followed by non-stereospecific fluorination or phenonium formation.^{12c}

In order to validate the proposed migration-first mechanism, we investigated the effect of migrating arene electronics on the rate of substrate consumption. Specifically, we conducted a Hammett analysis comprising a series of one-pot competition experiments between pairs of substrates bearing electronically differentiated migrating arenes. As this experiment involves the competition of substrates in one pot, it served to probe the highest energetic barrier involving the substrate, viz., the substrate-committing step, and neglects potentially higher energetic barriers not involving the substrate, such as catalyst re-oxidation. If either formation of the π -complex or fluoride attack on the π -complex is the substrate-committing step, the electronic nature of the remote migrating arene should have a minimal impact on the rate of that step. However, if arene attack on the π -complex is the substrate-committing step, substrates bearing more electron-rich migrating arenes should be consumed more rapidly as the migrating arene should accumulate significant positive charge during phenonium ion formation.

Analysis of the relative rates of **2a–f** revealed that substrates bearing more electron-rich migrating arenes were indeed consumed more rapidly and correlated well with both σ ($\rho = -3.7$, $R^2 = 0.99$) and σ^+ ($\rho^+ = -2.9$, $R^2 = 0.96$) values (Scheme 3.12). This behavior matches well with that observed for semi-pinacol rearrangements of tetra-aryl diols ($\rho^+ = -3.0$) where arene

migration is involved in the rate-determining step,²⁰ thus validating the proposed migration-first mechanism.



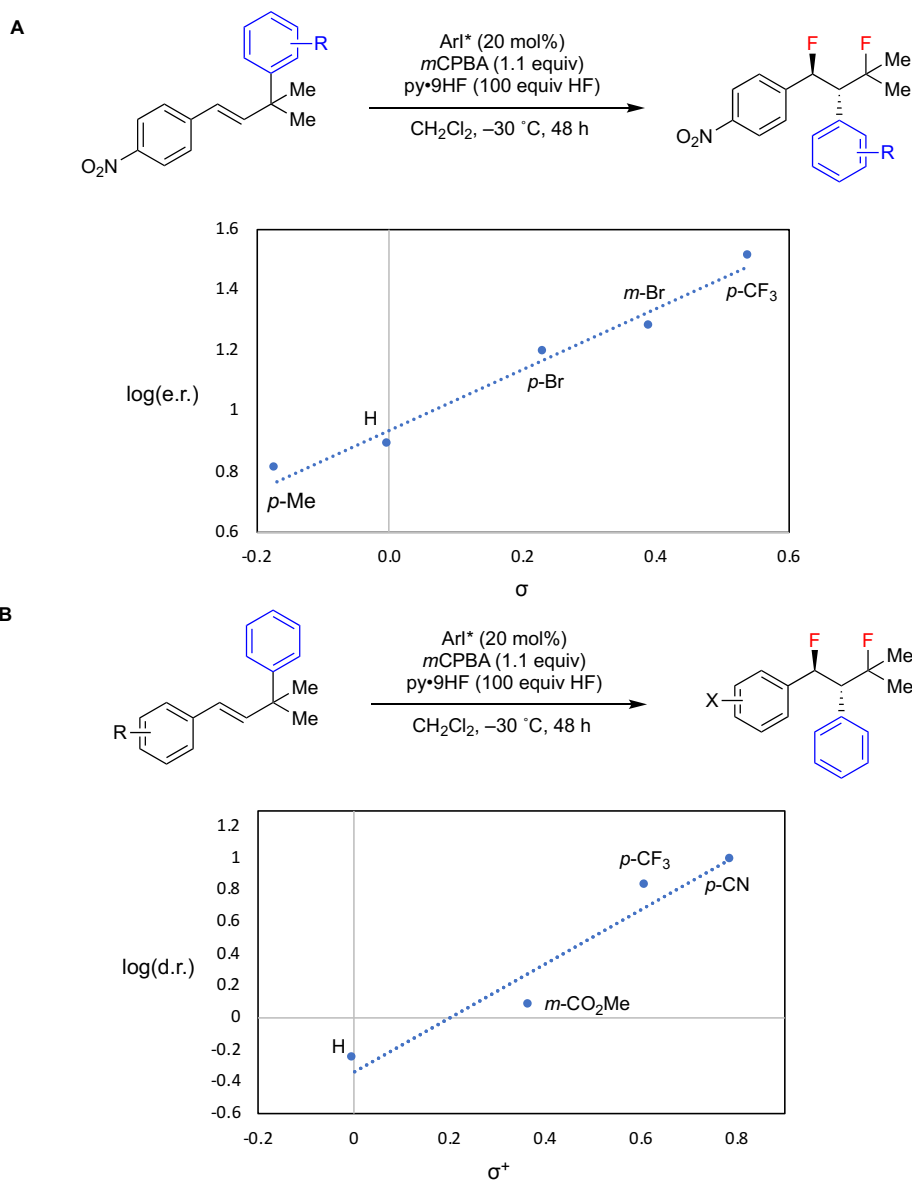
Scheme 3.12 Aryl migration is involved in the substrate-committing step.

Corroborating this conclusion is the small yet significant impact of migrating arene electronics on the enantioselectivity of the reaction, indicating that the migrating arene plays a role in the enantiodetermining step. In general, enantioselectivity increased as the proposed migrating arene became more electron-rich (Scheme 3.13A). In further agreement with the proposed migration-first pathway is the significant impact of styrenyl arene electronics on the diastereoselectivity of the reaction (Scheme 3.13B). Previous studies have suggested that electron-neutral benzylic iodanes readily dissociate to benzylic cations, leading to a loss of stereochemical information through non-stereospecific fluorination.²¹ Thus, in accordance with

²⁰ (a) Bachmann, W.E.; Mosher, F.H. *J. Am. Chem. Soc.* **1932**, *54*, 1124–1133. (b) Bachmann, W.E.; Ferguson, J.W. *J. Am. Chem. Soc.* **1934**, *56*, 2081–2084.

²¹ Banik, S.M.; Mennie, K.M.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2017**, *139*, 9152–9155.

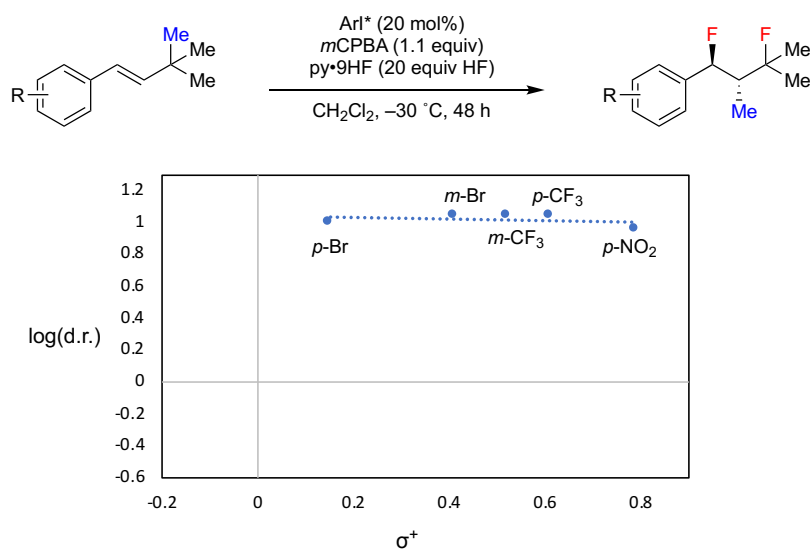
the proposed migration–first mechanism, high diastereoselectivity is only observed for substrates bearing highly electron-deficient styrenyl arenes.



Scheme 3.13 **A)** Effect of migrating arene electronics on e.e. **B)** Effect of styrenyl arene electronics on d.r.

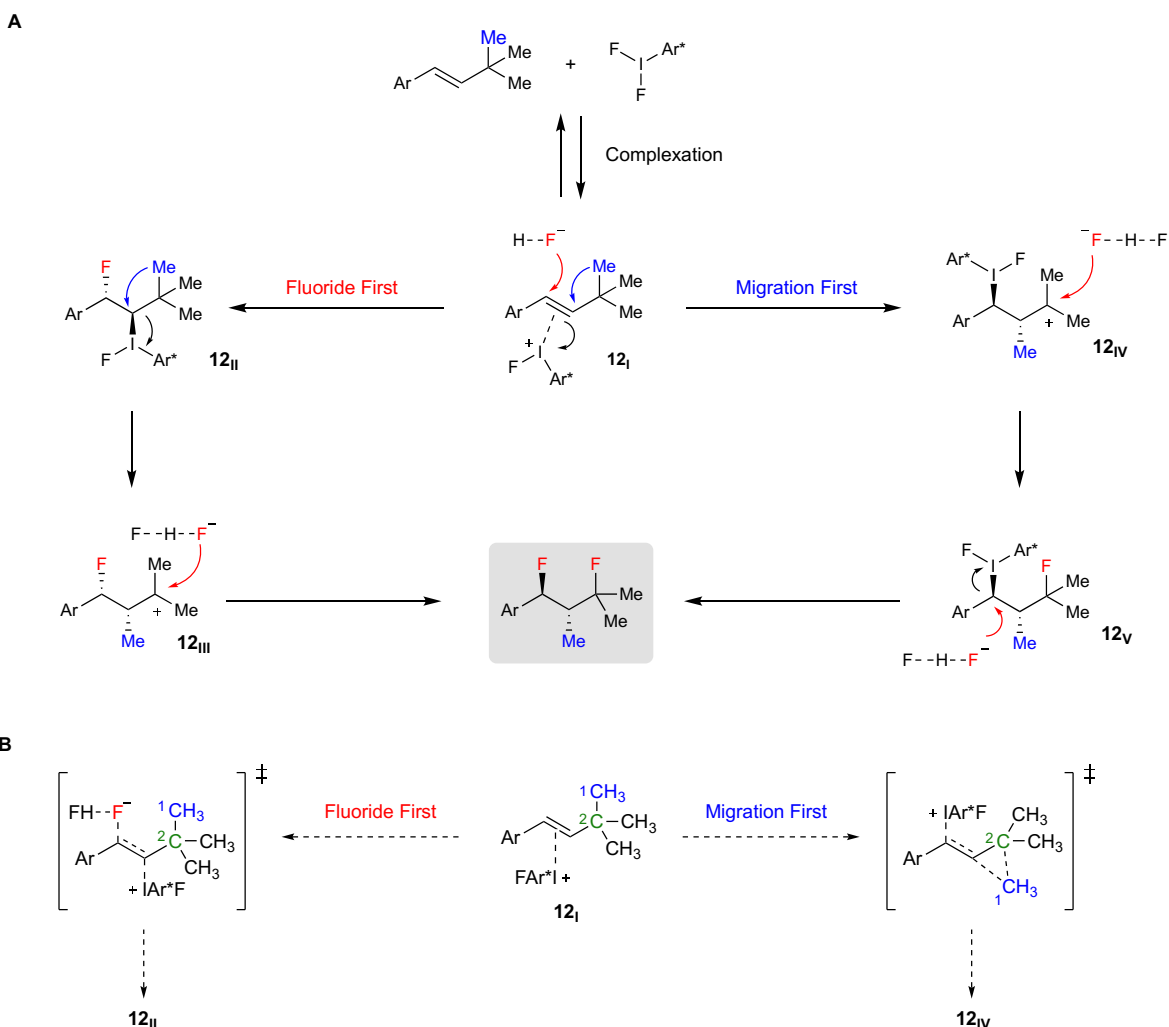
It should be noted, however, that while these data implicate a migration–first pathway, they do not conclusively pinpoint the enantiodetermining step of the phenyl rearrangement reaction, as a significant degree of resonance-stabilized positive charge development might be expected in either the formation or collapse of the phenonium ion intermediate.

In contrast to the aryl rearrangement reaction, the methyl rearrangement reaction involves a significantly less nucleophilic, sp^3 -hybridized migrating group unable to form a bridged phenonium-like intermediate,²⁰ which raises the possibility that methyl migration might not be competitive with fluoride addition. Consistent with this possibility is the minimal effect of styrenyl arene substitution on diastereoselectivity (Scheme 3.14), which stands in contrast to the large impact of this arene on diastereoselectivity in the case of the aryl rearrangement reaction. This contrast suggests against the intermediacy of a benzylic iodane and thus indicates a possible switch in mechanism from the aryl rearrangement reaction.



Scheme 3.14 Effect of styrenyl electronics on d.r. in the methyl rearrangement reaction.

To probe the fluoride-first and migration-first possibilities (Scheme 3.15A), we measured the carbon kinetic isotope effects (KIEs, k_{C12}/k_{C13}) in the reaction. The key difference between the two proposed mechanisms (Scheme 3.15B) is that the bond between C1 and C2 is cleaved during the substrate-committing step in a migration-first mechanism (**12_I** to **12_{IV}**), while no bonds attached to C1 or C2 are broken during the substrate-committing step in a fluoride-first mechanism (**12_I** to **12_{II}**).



Scheme 3.15 **A)** Possible mechanistic scenarios for the methyl rearrangement reaction. **B)** “Fluoride-first” versus “migration-first” transition states.

To measure the primary KIE on the migrating carbon (C1), we carried out an intermolecular competition experiment at natural abundance between substrates with and without an isotopically labeled carbon on the *t*-butyl group (Scheme 3.16). In the case of a migration-first pathway, a significant primary KIE (1.02–1.03) would be expected.²² This is because the presence of an isotopically labeled *t*-butyl would slow the rate of substrate consumption, causing the reaction mixture to become enriched in the isotopically unlabeled product. In contrast, for the fluoride-first pathway, no KIE would be expected. This is because the presence of an isotopically

²² Ando, T.; Yamataka, H.; Kuramochi, J.; Yamawaki, J.; Yukawa, Y. *Tet. Lett.* **1976**, 22, 1879–1880.

labeled *t*-butyl methyl group should have no effect on the rate of substrate consumption, causing no isotopic enrichment of the reaction mixture.

Using fractionation measurements obtained *via* the DEPT method,²³ a KIE value of 0.996²⁴ was observed at *t*-butyl methyl C1 (Scheme 3.16A). This measurement is consistent with a fluoride-first pathway and inconsistent with substrate-committing methyl migration. The lack of a KIE observed at this position stands in contrast to the observation of primary KIEs at the migrating methyl carbon in the rearrangement of neopentyl tosylate systems (1.027), where methyl migration is rate-determining.²² Further corroborating this analysis is the lack of a KIE (0.999)²⁵ observed at allylic C2, which similarly indicates negligible change in the bonding to the central *t*-butyl carbon during the substrate-committing step.

As a control experiment, the KIE at the allylic position was also measured for the aryl rearrangement reaction, where a significant secondary KIE should be observed due to the formation of a phenonium ion intermediate in the substrate-committing step. This value was determined to be 1.007,²⁶ closely matching computed values (B3LYP-D3(BJ)/6-31G*/PCM) for this position in the rearrangement of a neophyl tosylate model system (1.008).²² Thus, the observation that the phenyl rearrangement reaction features a significant secondary KIE at the allylic position while the methyl rearrangement reaction shows no such effect strongly suggests that, in contrast to the aryl rearrangement, methyl migration does not occur during the substrate-committing step.

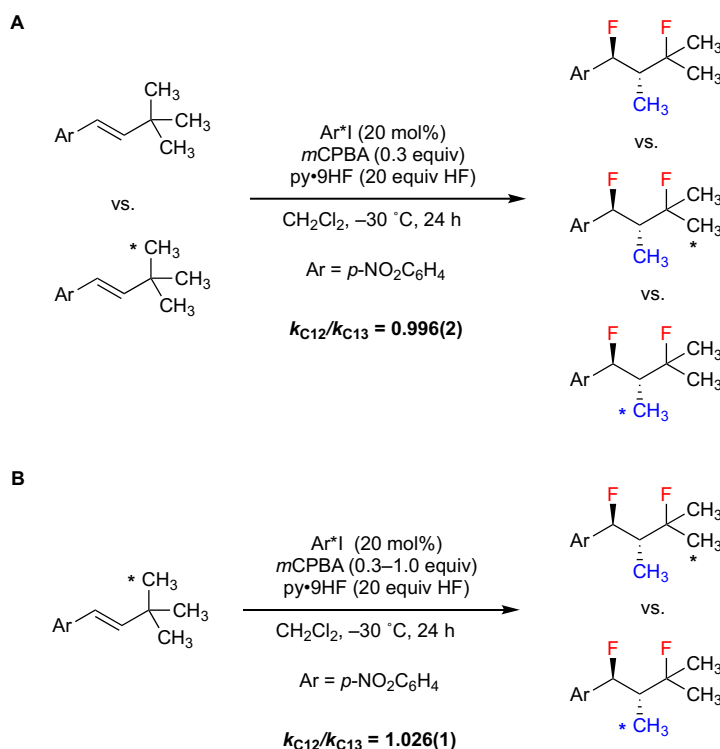
²³ Kwan, E.E.; Park, Y.; Besser, H.A.; Anderson, T.L.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2017**, *139*, 43–46.

²⁴ All intermolecular KIE experiments were run in duplicate, with the results averaged to give the reported KIE value. For this specific experiment, KIE values of 0.991(2) and 1.001(2) were observed.

²⁵ Two independent measurements of 0.996(2) and 1.003(3).

²⁶ Two independent measurements of 1.008(6) and 1.005(7).

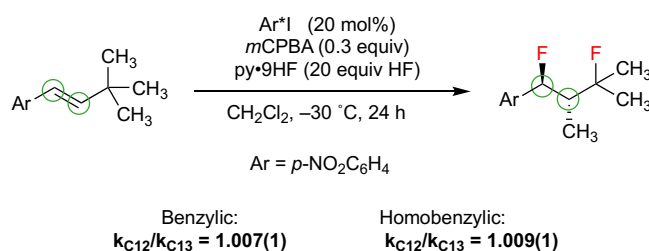
We also considered the possibility that methyl migration might occur *via* an early transition state with minimal C1–C2 bond cleavage, thereby resulting in an insignificant KIE. To observe the isotopic enrichment from this step alone, we designed an intramolecular KIE experiment, which only considers the fate of the naturally isotopically-labeled substrate (Scheme 3.16B). This experiment investigates the relative rate of migration of $^{12}\text{CH}_3$ versus $^{13}\text{CH}_3$ by measuring the ratio of product formed from the migration of $^{12}\text{CH}_3$ (with one $^{12}\text{CH}_3$ and one $^{13}\text{CH}_3$ group left behind) to product formed from the migration of $^{13}\text{CH}_3$ (with two $^{12}\text{CH}_3$ groups left behind). A significant intramolecular KIE value of 1.026 was observed, confirming the presence of a large KIE for the migration step.



Scheme 3.16 A) Methyl migration is not involved in the substrate-committing step. **B)** Control: methyl migration occurs after the substrate-committing step.

While the significant intramolecular KIE indicates that the migration step occurs after the substrate-committing step, the lack of an intermolecular KIE could also be potentially explained

by invoking irreversible styrene–iodonium π -complex formation, which could occur in either the fluoride-first or migration-first pathways. However, substrate-committing complexation is inconsistent with the observation of modest KIE values on the alkene carbons (1.007²⁷ for benzylic, 1.009²⁸ for homobenzylic), which suggest significant rehybridization of the alkene not expected for complexation (Scheme 3.17). For instance, computational modeling of these steps (B3LYP-D3(BJ)/6-31G*/LANL2DZ/PCM) predicts significant KIEs for fluoride attack (1.01–1.02) but not for styrene–iodonium π -complex formation (<1.003). Furthermore, the rate of π -complexation should be similar for both the aryl and methyl rearrangement substrates, as they bear similar styrenyl substitution. Since the aryl rearrangement reaction features a lower energetic barrier to complexation than to aryl migration, the methyl rearrangement reaction should also exhibit facile complexation relative to methyl migration or fluorination, which are both kinetically less favorable than aryl migration. Supporting this claim is the fact that the rate of formation of phenyl product **3c** was observed to significantly outcompete the rate of formation of methyl product **5a** by multiple orders of magnitude in a one-pot competition experiment.



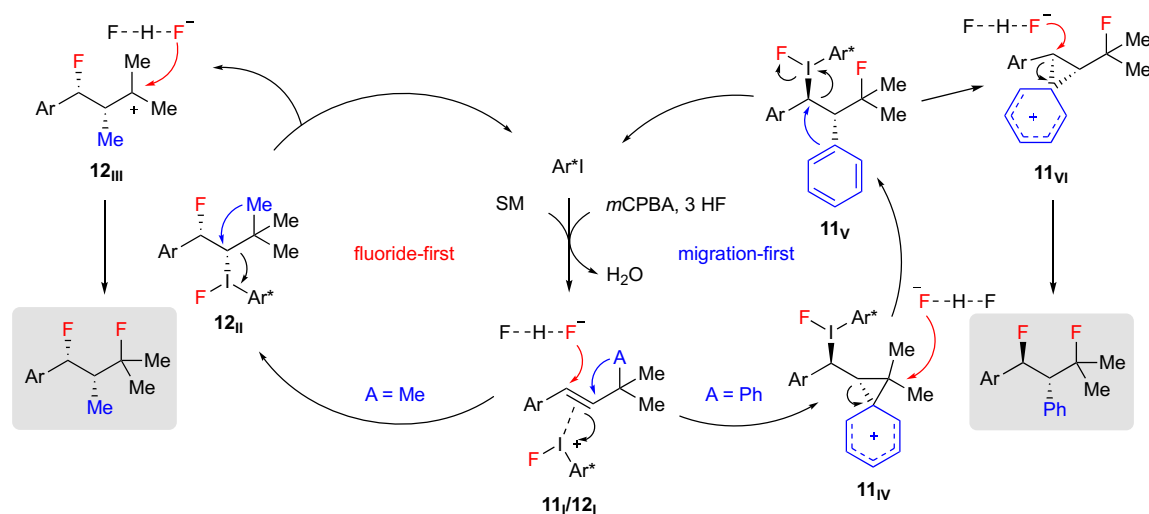
Scheme 3.17 Iodonium–alkene complexation is not involved in the substrate-committing step.

Thus, two distinct catalytic cycles for the methyl and phenyl rearrangements are proposed, consistent with the Hammett and KIE studies discussed above (Scheme 3.18). Beginning from aryl iodide catalyst (*R,R*)-**1a**, oxidation with *m*CPBA and coordination with the

²⁷ Two independent measurements of 1.009(1) and 1.005(1).

²⁸ Two independent measurements of 1.013(1) and 1.006(1).

styrenyl substrate leads to the formation of an styrene–iodonium π -complex. For the methyl rearrangement reaction, complexation is followed by substrate-committing and enantio-determining fluoride attack to deliver a 1,2-fluoriodinated species (**12II**). This highly cationic intermediate induces stereospecific methyl migration, forming a tertiary carbocation (**12III**) that is then quenched with fluoride to deliver the observed *syn*-1,2-fluoromethylated product. Conversely, for the aryl rearrangement reaction, complexation is followed by substrate-committing and enantiodetermining aryl migration: a two-step sequence involving aryl attack of the π -complex to form a phenonium intermediate (**11IV**) followed by ring opening with fluoride to give **11V**. The nascent benzylic iodane is subsequently displaced by the migrated arene to form a second phenonium intermediate (**11VI**), which is then opened at the benzylic position by fluoride to give the observed 1,2-*anti*-fluoromethylated product.



Scheme 3.18 Proposed catalytic cycles for methyl and phenyl rearrangement reactions.

3.3 Conclusion

In conclusion, the high reactivity and configurational stability of alkyl iodane species has enabled the development of catalytic and enantioselective fluorinative Wagner–Meerwein

rearrangements involving non-heteroatom-stabilized carbocations. These transformations afford access to a range of 1,3-difluorinated products in good yields and with high levels of enantio- and diastereoselectivity. Two different yet highly enantioselective substrate-committing steps involving internal and external nucleophilic attack, respectively, were identified. We anticipate that their discovery and characterization will help inform the future design and applications of asymmetric cationic rearrangements and iodine(III)-catalyzed reactions in general.

3.4 Experimental Section

General experimental procedures. All reactions for the preparation of substrates were performed in standard, dry glassware fitted with rubber septa under an inert atmosphere of nitrogen unless otherwise described. All difluorination reactions were performed in low density polyethylene tubes sealed with a low-density polyethylene cap under an atmosphere of air. Reported concentrations refer to solution volumes at room temperature. Concentration of organic solutions under reduced pressure was performed using house vacuum (ca. 40 mm Hg) at 30 °C. Column chromatography was performed with ZEOprep® 60 (40–63 micron) silica gel from American Scientific. Thin layer chromatography (TLC) was used for reaction monitoring and product detection was performed using pre-coated glass plates covered with 0.20 mm silica gel with fluorescent indicator; plates were visualized by exposure to UV light ($\lambda_{\text{ex}} = 254 \text{ nm}$) or by staining with potassium permanganate or ninhydrin.

CAUTION: Pyridine•9HF is a corrosive and toxic substance that will etch glassware. Safe handling can be conducted with plastic syringes and metal needles, with NaHCO_3 (aq.) or NaOH (aq.) employed to quench excess HF. Though reactions should not be conducted in glassware when employing pyridine•9HF, glassware may be used to quench reactions provided sufficient quantities of base are present. Always handle pyridine•9HF while wearing gloves and in a fumehood. As a precautionary measure, have calcium gluconate gel nearby and apply immediately and liberally on skin exposed to HF.

Materials. Reagents were purchased in reagent grade from commercial suppliers and used as received, unless otherwise described. Anhydrous solvents (benzene, dichloromethane, diethyl ether, *N,N*-dimethylformamide, tetrahydrofuran, and toluene) were prepared by passing the

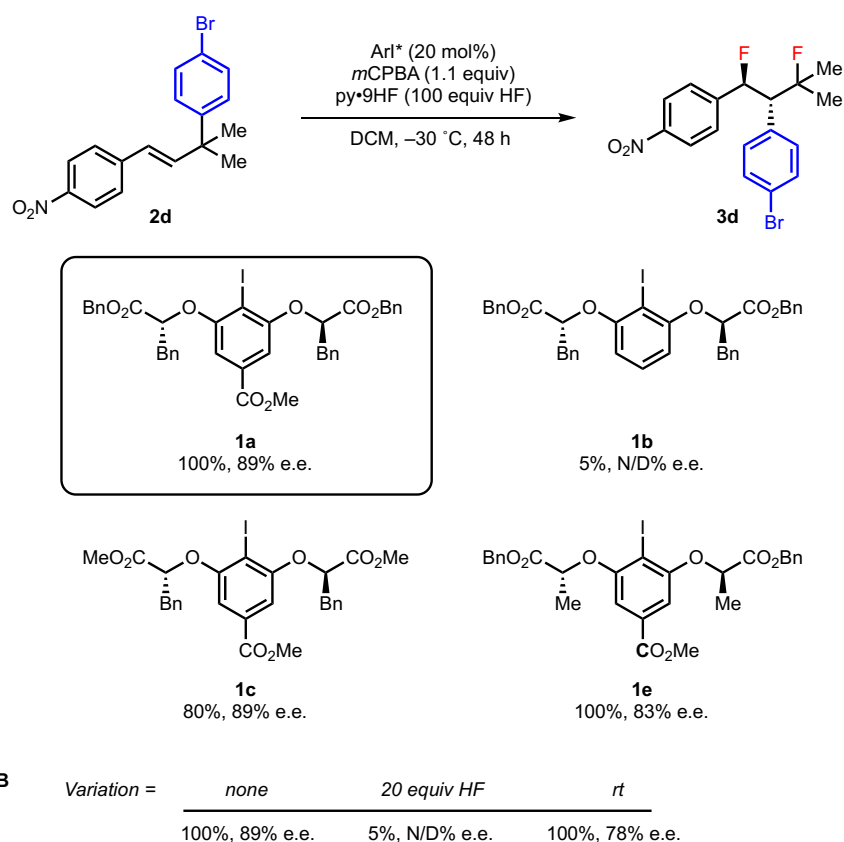
solvent through an activated alumina column. Triethylamine and diisopropylethylamine were distilled over calcium hydride at atmospheric pressure.

Instrumentation. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on an Inova-500 spectrometer, are reported in parts per million downfield from tetramethylsilane, and are referenced to the residual protium resonances of the NMR solvent (CDCl_3 : 7.26 [CHCl_3]). Proton-decoupled carbon-13 nuclear magnetic resonance (^{13}C $\{^1\text{H}\}$ NMR) spectra were recorded on an Inova-500 spectrometer, are reported in parts per million downfield from tetramethylsilane, and are referenced to the carbon resonances of the NMR solvent (CDCl_3 : 77.16). Chemical shifts for fluorine-19 nuclear magnetic resonance (^{19}F NMR) were recorded on an Inova-500 spectrometer and are reported in parts per million downfield from chlorotrifluoromethane and are referenced to the fluorine resonance of chlorotrifluoromethane ($\delta = 0$). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sext = sextet, sept = septet, m = multiplet), coupling constants in Hertz (Hz), integration. High-resolution mass spectrometric data were obtained on an Agilent 6210 time-of-flight HPLC/MS spectrometer (ESI-TOF). High-resolution GC-MS analysis was performed using Thermo Scientific TRACE 1310 Gas Chromatograph equipped with a Thermo Scientific Q Exactive Orbitrap mass spectrometry system. GC analysis was performed using an Agilent 7890A GC system using commercially available columns. Chiral HPLC analysis was performed using an Agilent 1200 series quaternary HPLC system using commercially available CHIRALCEL analytical columns (4.6 x 250 mm).

Optimization Experiments

General procedure for catalyst optimization

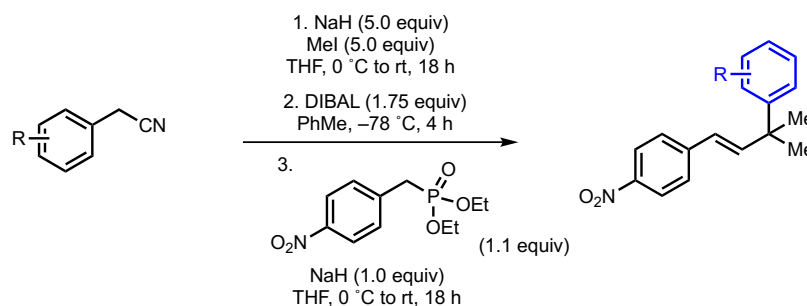
Catalyst (5.20 μmol , 20.0 mol%), cumyl styrene derivative **2d** (18.0 mg, 52.0 μmol , 1.00 equiv) and dichloromethane (0.30 mL) were combined in a polyethylene tube. The reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$. Pyridinium poly(hydrogen fluoride) (pyr•9HF, 70% hydrogen fluoride by weight, 140 μL , 100 equiv hydrogen fluoride) was added *via* micropipette followed by *m*-chloroperbenzoic acid (*m*CPBA, 77% by weight, 12.8 mg, 57.2 μmol , 1.10 equiv). The reaction was warmed to $-30\text{ }^{\circ}\text{C}$ and stirred for 48 hours at that temperature. The reaction was cooled to $-78\text{ }^{\circ}\text{C}$ and basic alumina (approximately 400 mg) was added slowly. The reaction was allowed to warm to room temperature with stirring and was filtered. The crude mixture was analyzed by ^1H NMR using mesitylene as an internal standard to determine the yield of product and by chiral HPLC to determine the enantioselectivity.



Scheme S3.1 A) Catalyst optimization. **B)** Optimization of HF loading and temperature.

Synthesis of Substrates

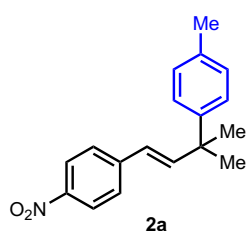
General Procedure A:



To a solution of aryl acetonitrile (5.00 mmol, 1.0 equiv) in anhydrous THF (5 mL) at 0 °C under $N_2(g)$ was added NaH (60% by weight, 1.00 g, 25.0 mmol, 5.0 equiv). The suspension was stirred at 0 °C for 30 mins before the addition of iodomethane (1.55 mL, 25.0 mmol, 5.0 equiv). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with quenched with 1 M HCl(aq.) (5 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with Et₂O (3 x 20 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. To a solution of the crude residue in anhydrous toluene (10 mL) at -78 °C under $N_2(g)$ was added diisobutyl aluminum hydride (1 M in toluene, 8.75 mL, 8.75 mmol, 1.75 equiv). After 4 hours at -78 °C, the reaction mixture was quenched with 1:1 sat. Rochelle salt: ethyl acetate (20 mL) and stirred vigorously for 1 hour. The organic and aqueous layers were separated, and the aqueous layer was extracted with Et₂O (3 x 20 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered, concentrated *in vacuo* and purified by silica gel column chromatography (0 to 30% Et₂O/hexanes). To a solution of diethyl (4-nitrobenzyl)phosphonate²⁹ (1.50 g, 5.50 mmol, 1.1 equiv) in anhydrous tetrahydrofuran (20 mL) at 0 °C was added NaH (60% by weight, 199 mg, 5.00 mmol, 1.0 equiv). The reaction mixture was allowed to stir at 0 °C

²⁹ Pankova, A.S.; Sorokina, M.V.; Kuznetsov, M.A. *Tetrahedron Letters* **2015**, 56, 5381–5385.

for 30 minutes before the addition of a solution of the crude aldehyde in anhydrous THF (2 mL). The reaction mixture was allowed to warm to room temperature. After 18 hours, the reaction was quenched with 1 M HCl(aq.) (5 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over NaSO₄, filtered, concentrated *in vacuo* and purified by silica gel column chromatography (0 to 5% Et₂O/hexanes).

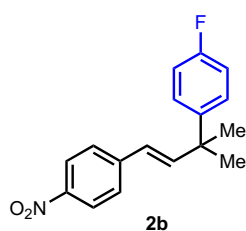


Prepared according to general procedure A using 4-methylbenzyl cyanide

(655 mg, 5.00 mmol) to give **2a** (1.06 g, 75%) as a yellow solid. ¹H NMR

(500 MHz, CDCl₃) δ 8.27 – 8.12 (m, 2H), 7.58 – 7.48 (m, 2H), 7.35 – 7.28 (m, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 6.67 (d, *J* = 16.2 Hz, 1H), 6.50 (d, *J* =

16.1 Hz, 1H), 2.39 (s, 3H), 1.59 (s, 6H); ¹³C NMR (125.7 MHz, CDCl₃) δ 146.6, 145.5, 144.7, 144.5, 135.8, 129.1, 126.7, 126.1, 124.4, 124.0, 40.9, 28.5, 21.0; HRMS (ESI-TOF) Calc'd for C₁₈H₁₉NO₂ [M+H]⁺: 282.1489; found 282.1480.



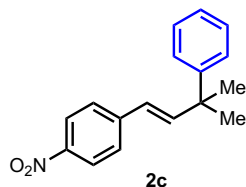
Prepared according to general procedure A using 4-fluorophenylacetonitrile

(676 mg, 5.00 mmol) to give **2b** (1.11 g, 78%) as a yellow solid. ¹H NMR

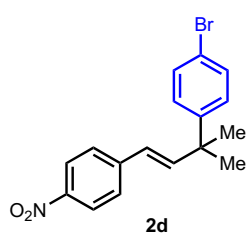
(500 MHz, CDCl₃) δ 8.16 (dd, *J* = 8.8, 1.9 Hz, 2H), 7.56 – 7.45 (m, 2H), 7.34 (ddd, *J* = 9.1, 5.0, 1.8 Hz, 2H), 7.02 (td, *J* = 8.6, 1.8 Hz, 2H), 6.60 (dt,

J = 16.1, 1.4 Hz, 1H), 6.45 (dd, *J* = 16.1, 1.7 Hz, 1H), 1.55 (d, *J* = 1.9 Hz, 6H); ¹³C NMR (125.7 MHz, CDCl₃) δ 161.4 (d, *J* = 245.0 Hz), 146.7, 145.0, 144.2, 143.4 (d, *J* = 3.2 Hz), 127.9 (d, *J* = 7.8 Hz), 126.8, 124.8, 124.1, 115.1 (d, *J* = 20.9 Hz), 40.9, 28.7; ¹⁹F NMR (470.4 MHz, CDCl₃) δ

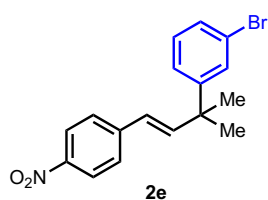
-117.1 (tt, $J = 8.8, 5.3$ Hz); HRMS (ESI-TOF) Calc'd for $C_{17}H_{16}FNO_2$ $[M+H]^+$: 286.1238; found 286.1236.



Prepared according to general procedure A using phenylacetonitrile (586 mg, 5.00 mmol) to give **2c** (949 mg, 71%) as a yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (dd, $J = 8.8, 1.6$ Hz, 2H), 7.52 (dd, $J = 8.7, 1.7$ Hz, 2H), 7.46 – 7.33 (m, 4H), 7.31 – 7.22 (m, 1H), 6.65 (dd, $J = 16.2, 1.5$ Hz, 1H), 6.54 – 6.45 (m, 1H), 1.58 (s, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 147.7, 146.7, 145.4, 144.4, 128.5, 126.8, 126.4, 126.3, 124.6, 124.1, 41.3, 28.5; HRMS (ESI-TOF) Calc'd for $C_{17}H_{17}NO_2$ $[M+H]^+$: 268.1332; found 268.1327.

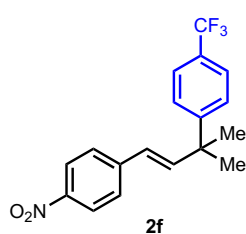


Prepared according to general procedure A using 4-bromophenylacetonitrile (980 mg, 5.00 mmol) to give **2d** (1.25 g, 72%) as a yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, $J = 8.8, 1.9$ Hz, 2H), 7.53 – 7.48 (m, 2H), 7.48 – 7.43 (m, 2H), 7.27 (dd, $J = 8.6, 1.9$ Hz, 2H), 6.59 (dd, $J = 16.1, 1.8$ Hz, 1H), 6.46 (dd, $J = 16.2, 1.8$ Hz, 1H), 1.55 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 146.8, 146.7, 144.5, 144.1, 131.5, 128.2, 126.8, 125.0, 124.0, 120.3, 41.1, 28.5; HRMS (ESI-TOF) Calc'd for $C_{17}H_{16}BrNO_2$ $[M+H]^+$: 346.0437; found 346.0430.



Prepared according to general procedure A using 3-bromophenylacetonitrile (980 mg, 5.00 mmol) to give **2e** (1.32 g, 76%) as a yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, $J = 8.8, 2.1$ Hz, 2H), 7.58 – 7.45 (m, 3H), 7.36 (dd, $J = 7.7, 2.1$ Hz, 1H), 7.30 (dt, $J = 7.9, 1.5$ Hz, 1H), 7.21 (td, J

= 7.9, 2.0 Hz, 1H), 6.64 – 6.53 (m, 1H), 6.52 – 6.39 (m, 1H), 1.53 (s, 6H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 150.2, 146.8, 144.3, 144.0, 130.1, 129.5, 126.8, 125.1, 125.0, 124.0, 122.7, 41.3, 28.4; HRMS (ESI-TOF) Calc'd for $\text{C}_{17}\text{H}_{16}\text{BrNO}_2$ $[\text{M}+\text{H}]^+$: 346.0437; found 346.0427.

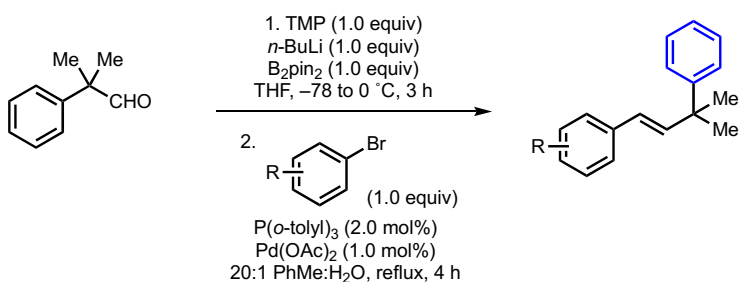


Prepared according to general procedure A using 4-(trifluoromethyl)phenylacetonitrile (926 mg, 5.00 mmol) to give **2f** (1.09 g,

65%) as a yellow solid. ^1H NMR (500 MHz, CDCl_3) δ 8.16 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.2 Hz, 2H), 7.56 – 7.44 (m, J = 8.9, 2.4 Hz, 4H), 6.62 (d,

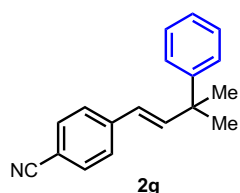
J = 16.2 Hz, 1H), 6.50 (d, J = 16.2 Hz, 1H), 1.59 (s, 6H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 151.9, 146.8, 144.3 – 143.9 (m), 128.6 (q, J = 32.2 Hz), 126.8, 126.7, 125.5 – 125.2 (m), 124.0, 124.1 (q, J = 271.9 Hz), 41.45, 28.37; ^{19}F NMR (470.4 MHz, CDCl_3) δ -62.3 (s); HRMS (ESI-TOF) Calc'd for $\text{C}_{18}\text{H}_{16}\text{F}_3\text{NO}_2$ $[\text{M}+\text{H}]^+$: 336.1206; found 336.1203.

General Procedure B:

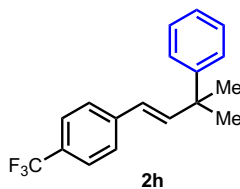


To a solution of 2,2,6,6-tetramethylpiperidine (0.89 mL, 5.25 mmol, 1.0 equiv) in anhydrous THF (14 mL) at 0°C under $\text{N}_{2(\text{g})}$ was added $n\text{-BuLi}$ (2.5 M, 2.1 mL, 5.25 mmol, 1.0 equiv). The resulting solution was stirred at 0°C for 30 mins. A solution of bis(pinacolato)diboron (1.33 g, 5.25 mmol, 1.0 equiv) in anhydrous THF (3 mL) was added and the reaction mixture cooled down to -78°C . A solution of 2-methyl-2-phenylpropanal (778 mg, 5.25 mmol, 1.0 equiv) in

anhydrous THF (3 mL) was added and the reaction mixture was allowed to warm to 0 °C. After 3 hours, the reaction was quenched with 1 M HCl (aq.) (5 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. To a suspension of the crude residue, aryl bromide (5.25 mmol, 1.0 equiv) and tri(*o*-tolyl)phosphine (32.0 mg, 0.105 mmol, 2.0 mol%) in toluene (25 mL) and deionized water (1.25 mL) was added palladium(II) acetate (12.7 mg, 0.0525 mmol, 1.0 mol%). The reaction mixture was stirred under reflux for 4 hours. After cooling down to room temperature, the reaction mixture was filtered through a plug of celite with Et₂O (200 mL), concentrated *in vacuo* and purified by silica gel column chromatography (0 to 5% Et₂O/hexanes).

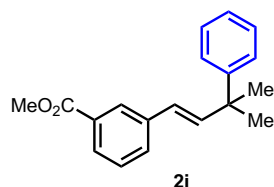


Prepared according to general procedure B using 4-bromobenzonitrile (956 mg, 5.25 mmol) to give **2g** (1.00 g, 77%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.60 (dd, *J* = 8.3, 1.6 Hz, 2H), 7.51 – 7.45 (m, 2H), 7.43 – 7.34 (m, 4H), 7.30 – 7.23 (m, 1H), 6.60 (dd, *J* = 16.2, 1.5 Hz, 1H), 6.44 (dd, *J* = 16.1, 1.4 Hz, 1H), 1.57 (d, *J* = 1.6 Hz, 6H); ¹³C NMR (125.7 MHz, CDCl₃) δ 147.8, 144.3, 142.3, 132.4, 128.4, 126.8, 126.2, 124.9, 119.2, 110.3, 41.2, 28.5; HRMS (ESI-TOF) Calc'd for C₁₈H₁₇N [M+H]⁺: 248.1434; found 248.1434.



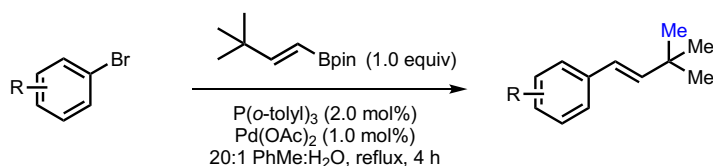
Prepared according to general procedure B using 4-bromobenzotrifluoride (1.18 g, 5.25 mmol) to give **2h** (1.14 g, 75%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.39 – 7.33 (m, 2H), 7.26 (qd, *J* = 7.3, 6.1, 1.3 Hz, 1H), 6.56 (dd, *J* = 16.2,

1.3 Hz, 1H), 6.46 (d, $J = 16.2$ Hz, 1H), 1.56 (d, $J = 1.3$ Hz, 6H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 148.3, 143.1, 141.4, 129.0 (q, $J = 32.4$ Hz), 128.5, 126.5, 126.3, 126.3, 125.6 (q, $J = 3.9$ Hz), 125.2, 124.1 (q, $J = 271.6$ Hz), 41.1, 28.7; ^{19}F NMR (376 MHz, CDCl_3) δ -62.4; HR-GC/MS (EI^+) Calc'd for $\text{C}_{18}\text{H}_{17}\text{F}_3$ $[\text{M}]^+$: 290.1277; found 290.1275.

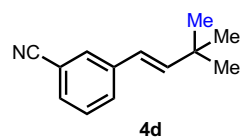


Prepared according to general procedure B using methyl 4-bromobenzoate (1.13 g, 5.25 mmol) to give **2i** (1.12 g, 76%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.21 – 8.08 (m, 1H), 8.00 – 7.88 (m, 1H), 7.66 – 7.55 (m, 1H), 7.53 – 7.34 (m, 5H), 7.30 – 7.24 (m, 1H), 6.58 (d, $J = 16.1$ Hz, 1H), 6.50 (d, $J = 16.2$ Hz, 1H), 3.96 (s, 3H), 1.59 (s, 6H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 167.1, 148.3, 141.5, 138.1, 130.6, 130.5, 128.6, 128.3, 128.1, 127.2, 126.2, 126.1, 125.3, 52.1, 40.9, 28.7; HRMS (ESI-TOF) Calc'd for $\text{C}_{19}\text{H}_{20}\text{O}_2$ $[\text{M}+\text{H}]^+$: 281.1536; found 281.1531.

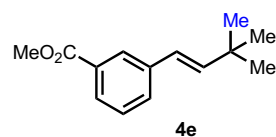
General Procedure C:



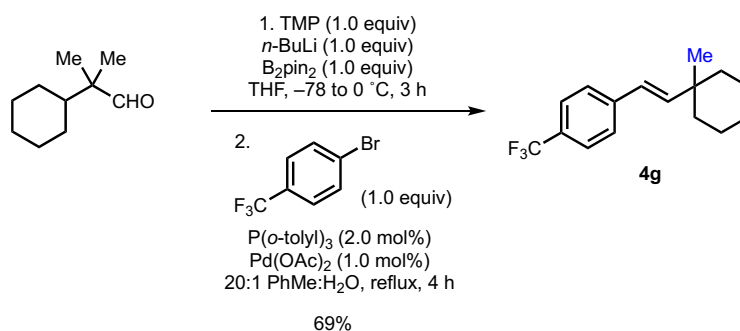
To a suspension of 2-[(1*E*)-3,3-dimethyl-1-buten-1-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.10 g, 5.25 mmol, 1.0 equiv), aryl bromide (5.25 mmol, 1.0 equiv) and tri(*o*-tolyl)phosphine (32.0 mg, 0.105 mmol, 2.0 mol%) in toluene (25 mL) and deionized water (1.25 mL) was added palladium(II) acetate (12.7 mg, 0.0525 mmol, 1.0 mol%). The reaction mixture was stirred under reflux for 4 hours. After cooling to room temperature, the reaction mixture was filtered through a plug of celite with Et_2O (200 mL), concentrated *in vacuo* and purified by silica gel column chromatography (0 to 5% Et_2O /hexanes).



Prepared according to general procedure C using 4-bromobenzonitrile (956 mg, 5.25 mmol) to give **4d** (807 mg, 83%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.58 (d, $J = 1.7$ Hz, 1H), 7.53 (dt, $J = 7.8, 1.6$ Hz, 1H), 7.42 (dt, $J = 7.6, 1.4$ Hz, 1H), 7.35 (t, $J = 7.7$ Hz, 1H), 6.31 (d, $J = 16.2$ Hz, 1H), 6.25 (d, $J = 16.2$ Hz, 1H), 1.12 (d, $J = 1.0$ Hz, 9H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 144.5, 139.2, 130.2, 129.9, 129.3, 129.1, 122.8, 118.8, 112.5, 33.5, 29.3; HRMS (ESI-TOF) Calc'd for $\text{C}_{13}\text{H}_{15}\text{N}$ $[\text{M}+\text{H}]^+$: 186.1277; found 186.1277.

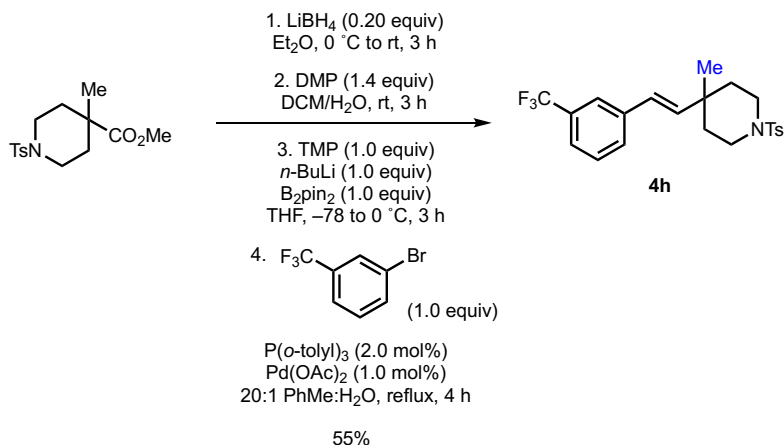


Prepared according to general procedure C using methyl 4-bromobenzoate (1.13 g, 5.25 mmol) to give **4e** (974 mg, 85%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.05 (s, 1H), 7.84 (dd, $J = 7.7, 1.5$ Hz, 1H), 7.50 (ddd, $J = 7.7, 1.9, 1.1$ Hz, 2H), 7.39 – 7.22 (m, 2H), 6.42 – 6.21 (m, 2H), 3.89 (d, $J = 1.1$ Hz, 3H), 1.12 (d, $J = 1.2$ Hz, 9H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 167.0, 143.0, 138.3, 130.4, 130.3, 128.4, 127.7, 127.0, 123.8, 51.9, 33.4, 29.5; HRMS (ESI-TOF) Calc'd for $\text{C}_{14}\text{H}_{18}\text{O}_2$ $[\text{M}+\text{H}]^+$: 219.1380; found 219.1380.



To a solution of 2,2,6,6-tetramethylpiperidine (0.89 mL, 5.25 mmol, 1.0 equiv) in anhydrous THF (14 mL) at 0 °C under $\text{N}_{2(\text{g})}$ was added $n\text{-BuLi}$ (2.5 M, 2.1 mL, 5.25 mmol, 1.0 equiv). The resulting solution was stirred at 0 °C for 30 m. A solution of bis(pinacolato)diboron (1.33 g, 5.25 mmol, 1.0 equiv) in anhydrous THF (3 mL) was added and the reaction mixture cooled down to

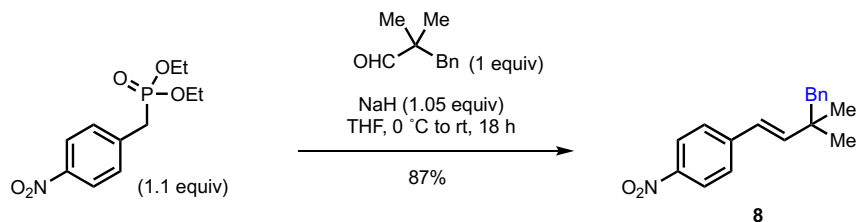
–78 °C. A solution of 1-methyl-cyclohexanecarboxaldehyde (663 mg, 5.25 mmol, 1.0 equiv) in anhydrous THF (3 mL) was added and the reaction mixture was allowed to warm to 0 °C. After 3 hours, the reaction was quenched with 1 M HCl (aq.) (5 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. To a suspension of the crude residue, 4-bromobenzotrifluoride (1.18 g, 5.25 mmol, 1.0 equiv) and tri(*o*-tolyl)phosphine (32.0 mg, 0.105 mmol, 2.0 mol%) in toluene (25 mL) and deionized water (1.25 mL) was added palladium(II) acetate (12.7 mg, 0.0525 mmol, 1.0 mol%). The reaction mixture was stirred under reflux for 4 hours. After cooling to room temperature, the reaction mixture was filtered through a plug of celite with Et₂O (200 mL), concentrated *in vacuo* and purified by silica gel column chromatography (hexanes) to give **4g** (972 mg, 69%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.64 – 7.55 (m, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 6.49 – 6.28 (m, 2H), 1.77 – 1.39 (m, 10H), 1.14 (d, *J* = 2.0 Hz, 3H); ¹³C NMR (125.7 MHz, CDCl₃) δ 144.0, 142.0, 129.1 – 128.3 (m), 126.2, 125.5 (q, *J* = 3.9 Hz), 125.1, 124.1 (q, *J* = 271.6 Hz), 378.0, 36.6, 26.4, 22.6; ¹⁹F NMR (376 MHz, CDCl₃) δ -62.3; HR-GC/MS (EI⁺) Calc'd for C₁₆H₁₉F₃ [M]⁺: 268.1433; found 268.1433.



To a solution of methyl 4-methyl-1-tosylpiperidine-4-carboxylate³⁰ (1.63 g, 5.25 mmol, 1.0 equiv) in anhydrous Et₂O (26 mL) at 0 °C under N_{2(g)} was added lithium borohydride (23.0 mg, 1.06 mmol, 0.20 equiv). The resulting suspension was allowed to warm to room temperature. After 3 hours, the reaction was quenched with 1 M HCl (aq.) (5 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The resulting crude residue was dissolved in dichloromethane (20 mL). Dess-Martin periodinane (3.10 g, 7.31 mmol, 1.4 equiv) and deionized water (0.25 mL) were added. The resulting suspension was stirred at room temperature. After 3 hours, 1:1 sat. Na₂S₂O₃ (aq.):1 M NaOH (aq.) (20 mL) was added. The organic and aqueous layers were separated, and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. To a solution of 2,2,6,6-tetramethylpiperidine (0.89 mL, 5.25 mmol, 1.0 equiv) in anhydrous THF (14 mL) at 0 °C under N_{2(g)} was added *n*-BuLi (2.5 M, 2.1 mL, 5.25 mmol, 1.0 equiv). The resulting solution was stirred at 0 °C for 30 mins. A solution of bis(pinacolato)diboron (1.33 g, 5.25 mmol, 1 equiv) in anhydrous THF (3 mL) was added and the reaction mixture cooled down to -78 °C. A solution of the crude aldehyde (5.25 mmol, 1.0 equiv) in anhydrous THF (3 mL) was added and the reaction mixture was allowed to warm to 0 °C. After 3 hours, the reaction was quenched with 1 M HCl (aq.) (5 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. To a suspension of the crude residue, 4-bromobenzotrifluoride (1.18 g, 5.25 mmol, 1.0 equiv) and tri(*o*-tolyl)phosphine (32.0 mg, 0.105 mmol, 2.0 mol%) in toluene (25 mL) and deionized water (1.25 mL) was added

³⁰ Williamson, P.; Galvan, A.; Gaunt, M.J. *Chem. Sci.* **2017**, 8, 2588–2591.

palladium(II) acetate (12.7 mg, 0.0525 mmol, 1.0 mol%). The reaction mixture was stirred under reflux for 4 hours. After cooling to room temperature, the reaction mixture was filtered through a plug of celite with Et₂O (200 mL), concentrated *in vacuo* and purified by silica gel column chromatography (0 to 30% Et₂O/hexanes) to give **4h** (1.22 g, 55%) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.64 (dd, *J* = 8.2, 1.5 Hz, 2H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 6.30 (d, *J* = 16.4 Hz, 1H), 6.14 (dd, *J* = 16.5, 1.3 Hz, 1H), 3.21 – 2.97 (m, 4H), 2.40 (s, 3H), 1.82 (ddd, *J* = 12.1, 7.3, 4.2 Hz, 2H), 1.62 (ddd, *J* = 12.6, 7.5, 4.2 Hz, 2H), 1.04 (d, *J* = 1.4 Hz, 3H); ¹³C NMR (125.7 MHz, CDCl₃) δ 143.5, 141.0, 133.6, 129.7, 129.0 (q, *J* = 32.4 Hz), 127.7, 126.5, 126.3, 125.5 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 271.8 Hz), 42.7, 36.3, 34.4, 26.0, 21.6; ¹⁹F NMR (470.4 MHz, CDCl₃) δ -62.4; HRMS (ESI-TOF) Calc'd for C₂₂H₂₄F₃NO₂S [M+H]⁺: 424.1553; found 424.1552.



To a solution of diethyl (4-nitrobenzyl)phosphonate (1.50 g, 5.50 mmol, 1.1 equiv) in anhydrous tetrahydrofuran (20 mL) at 0 °C was added NaH (60% by weight, 199 mg, 5.00 mmol, 1.0 equiv). The reaction mixture was allowed to stir at 0 °C for 30 mins before the addition of a solution of α,α-dimethyl-benzenepropanal³¹ (892 mg, 5.50 mmol, 1.0 equiv) in anhydrous THF (3 mL). The reaction mixture was allowed to warm to room temperature. After 18 hours, the reaction was quenched with 1 M HCl (aq.) (5 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over NaSO₄, filtered, concentrated *in*

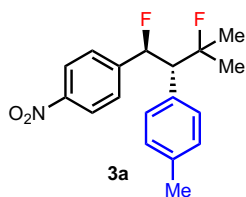
³¹ Abrams, D.J.; West, J.G.; Sorensen, E.J. *Chem. Sci.* **2017**, 8, 1954–1959.

vacuo and purified by silica gel column chromatography (0 to 5% Et₂O/hexanes) to give **8** (1.35 g, 87%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 8.19 – 8.02 (m, 2H), 7.47 – 7.33 (m, 2H), 7.31 – 7.23 (m, 2H), 7.23 – 7.18 (m, 1H), 7.17 – 7.08 (m, 2H), 6.46 (ddd, *J* = 16.2, 3.2, 1.5 Hz, 1H), 6.25 (dt, *J* = 16.2, 2.2 Hz, 1H), 2.71 (t, *J* = 2.1 Hz, 2H), 1.23 – 1.08 (m, 6H); ¹³C NMR (125.7 MHz, CDCl₃) δ 146.3, 145.1, 144.4, 138.1, 130.4, 127.6, 126.4, 126.1, 124.4, 123.8, 49.2, 37.7, 26.5; HRMS (ESI-TOF) Calc'd for C₁₈H₁₉NO₂ [M+H]⁺: 282.1489; found 282.1481.

Synthesis of Products

General Procedure:

To a solution of substrate (0.52 mmol, 1.0 equiv) and catalyst (*R,R*)-**1a** (80.0 mg, 0.104 mmol, 20 mol%) in dichloromethane (3 mL) in a low-density polyethylene tube at $-78\text{ }^{\circ}\text{C}$ was added HF-pyridine (py•9HF, 70% hydrogen fluoride by weight, 1.4 mL, 100 equiv hydrogen fluoride) followed by *m*CPBA (77% by weight, 128 mg, 0.57 mmol, 1.1 equiv). The reaction mixture was warmed to $-30\text{ }^{\circ}\text{C}$ and stirred at that temperature for 48 hours. The heterogeneous mixture was transferred carefully into a vigorously stirred suspension of basic alumina (4.0 g) in dichloromethane at $-78\text{ }^{\circ}\text{C}$. The resulting suspension was allowed to warm to room temperature and filtered, washing with 200 mL dichloromethane. The combined filtrate was concentrated under reduced pressure.



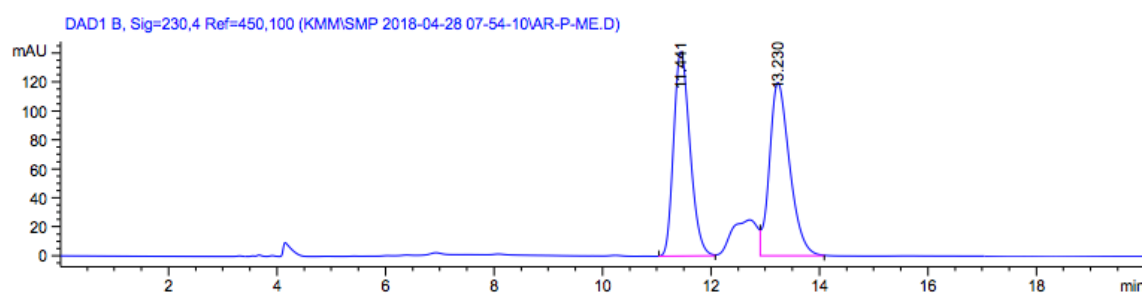
Prepared according to the general procedure using **2a** (146 mg, 0.52 mmol) with the following modification: 20 equiv of HF was used instead. The diastereomeric ratio of the crude residue after work-up was determined to be >20:1 by ^1H and ^{19}F NMR analysis. The crude residue was purified by

silica gel column chromatography (0 to 5% diethyl ether in hexanes) to give **3a** (149 mg, 90%) as a white solid in 90% e.e. ^1H NMR (500 MHz, CDCl_3) δ 7.97 (d, $J = 8.4$ Hz, 2H), 7.21 (d, $J = 8.5$ Hz, 2H), 6.92 (d, $J = 7.8$ Hz, 2H), 6.87 (d, $J = 7.8$ Hz, 2H), 6.02 (dd, $J = 47.0, 9.5$ Hz, 1H), 3.17 (ddd, $J = 22.7, 12.7, 9.5$ Hz, 1H), 2.19 (s, 3H), 1.61 (dd, $J = 21.7, 2.4$ Hz, 3H), 1.30 (d, $J = 21.9$ Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 147.5 (d, $J = 2.3$ Hz), 146.3 (d, $J = 20.7$ Hz), 137.3, 133.4 (d, $J = 8.5$ Hz), 129.7 (d, $J = 2.3$ Hz), 129.3, 127.8 (d, $J = 6.5$ Hz), 123.1, 96.7 (d, $J = 174.4$ Hz), 93.7 (dd, $J = 180.5, 4.7$ Hz), 60.2 (t, $J = 21.0$ Hz), 27.8 (dd, $J = 24.9, 6.8$ Hz), 27.5

(d, $J = 24.3$ Hz), 21.0; ^{19}F NMR (470.4 MHz, CDCl_3) δ -143.6 (dseptd, $J = 22.0, 21.9, 10.0$ Hz, 1F), -168.9 (dt, $J = 47.1, 11.6$ Hz, 1F); HR-GC/MS (EI^+) Calc'd for $\text{C}_{18}\text{H}_{19}\text{F}_2\text{NO}_2$ $[\text{M}]^+$: 319.1378; found 319.1380.

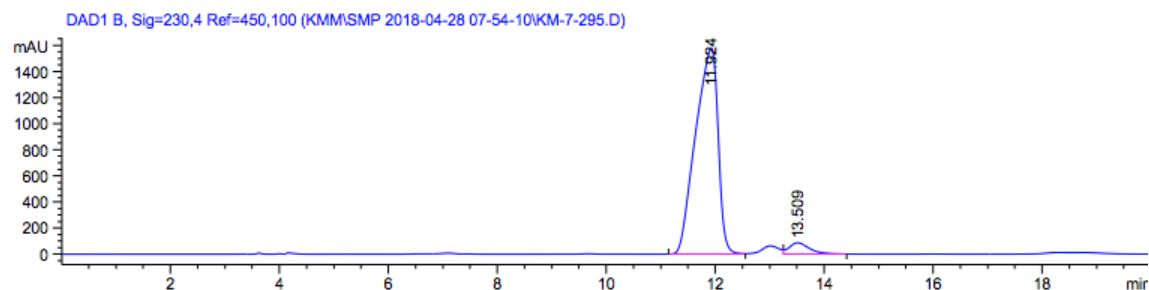
90% e.e., chiral HPLC (OD-H, 1% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230$ nm); $t_{\text{R}}(\text{major}) = 11.9$ min, $t_{\text{R}}(\text{minor}) = 13.5$ min.

Racemic sample:

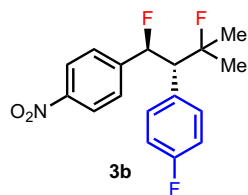


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.441	BB	0.3254	2971.75879	141.25533	49.0018
2	13.230	VB	0.3915	3092.82983	119.69714	50.9982

Enriched sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.924	BV	0.4949	4.53682e4	1580.61670	95.2599
2	13.509	VB	0.3894	2257.51685	86.80167	4.7401

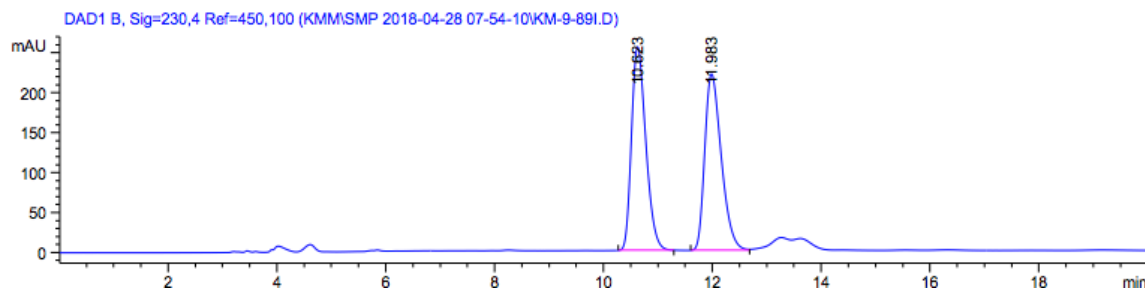


Prepared according to the general procedure using **2b** (148 mg, 0.52 mmol) with the following modification: 20 equiv of HF was used instead. The diastereomeric ratio of the crude residue after work-up was determined to

be >20:1 by ^1H and ^{19}F NMR analysis. The crude residue was purified by silica gel column chromatography (0 to 5% diethyl ether in hexanes) to give **3b** (146 mg, 87%) as a white solid in 93% e.e. ^1H NMR (500 MHz, CDCl_3) δ 8.04 – 7.97 (m, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.99 (dd, J = 8.3, 5.3 Hz, 2H), 6.83 (t, J = 8.8 Hz, 2H), 6.03 (dd, J = 46.8, 9.2 Hz, 1H), 3.22 (ddd, J = 24.3, 13.5, 9.3 Hz, 1H), 1.67 (dd, J = 21.7, 2.7 Hz, 3H), 1.28 (d, J = 21.8 Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 162.0 (d, J = 247.3 Hz), 147.6 (d, J = 2.1 Hz), 145.9 (d, J = 20.9 Hz), 132.5 (dd, J = 9.3, 3.7 Hz), 131.4 (dd, J = 7.9, 3.0 Hz), 127.8 (d, J = 6.5 Hz), 123.3, 115.5 (d, J = 21.3 Hz), 96.6 (d, J = 174.6 Hz), 93.5 (dd, J = 180.7, 4.8 Hz), 59.9 (t, J = 21.2 Hz), 28.0 – 27.3 (m); ^{19}F NMR (470.4 MHz, CDCl_3) δ -114.2 – -114.3 (m, 1F), -145.5 (dseptd, J = 21.8, 21.7, 7.6 Hz, 1F), -168.2 (dt, J = 46.8, 10.9 Hz, 1F); HRMS (ESI-TOF) Calc'd for $\text{C}_{17}\text{H}_{16}\text{F}_3\text{NO}_2$ $[\text{M}+\text{H}]^+$: 324.1206; found 324.1201.

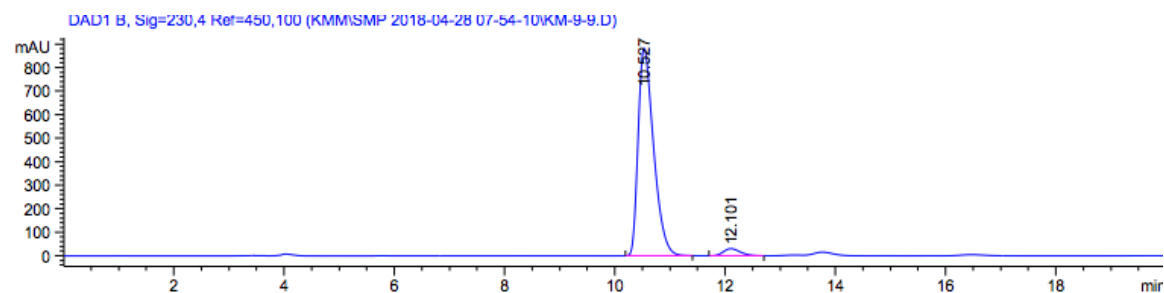
93% e.e., chiral HPLC (OD-H, 2% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm); t_{R} (major) = 10.5 min, t_{R} (minor) = 12.1 min.

Racemic sample:

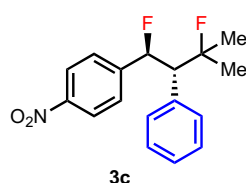


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.623	BB	0.2837	4670.36084	254.91858	50.0604
2	11.983	BB	0.3241	4659.08496	220.83292	49.9396

Enriched sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.527	BB	0.2991	1.71810e4	882.79858	96.3576
2	12.101	BB	0.3318	649.46460	30.33620	3.6424



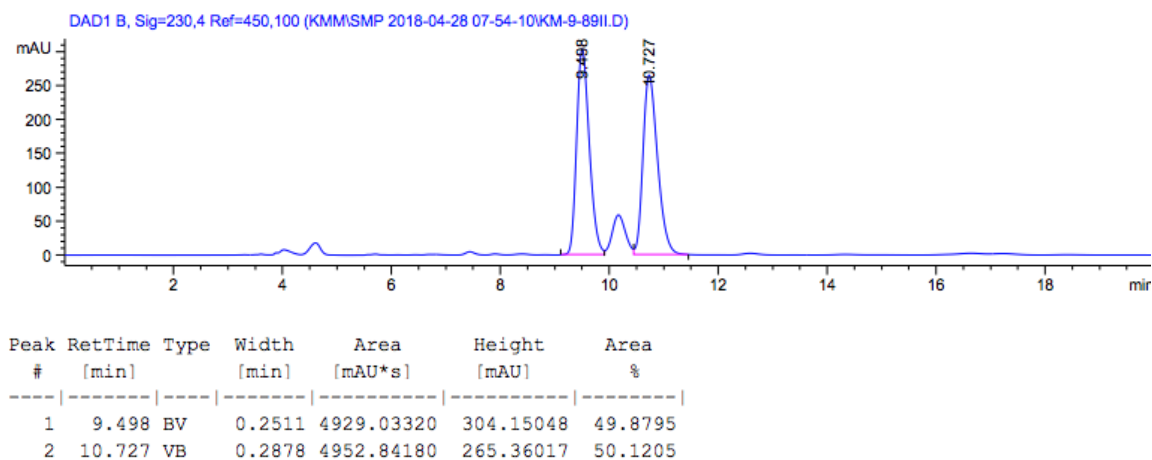
Prepared according to the general procedure using **2c** (139 mg, 0.52 mmol) with the following modification: 20 equiv of HF was used instead. The diastereomeric ratio of the crude residue after work-up was determined to be >20:1 by ¹H and ¹⁹F NMR analysis. The crude residue was purified by silica gel column chromatography (0 to 5% diethyl ether in hexanes) to give **3c** (135 mg, 85%) as a white solid in 94% e.e. Crystals of **3c** were grown by vapor diffusion of pentane into a solution of **3c** in Et₂O.

¹H NMR (500 MHz, CDCl₃) δ 7.99 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.17 – 7.11 (m, 3H), 7.06 – 6.96 (m, 2H), 6.07 (dd, *J* = 47.0, 9.4 Hz, 1H), 3.22 (ddd, *J* = 24.0, 13.0, 9.4 Hz, 1H), 1.67 (dd, *J* = 21.7, 2.5 Hz, 3H), 1.32 (d, *J* = 21.8 Hz, 3H); ¹³C NMR (125.7 MHz, CDCl₃) δ 147.5 (d, *J* = 2.5 Hz), 146.2 (d, *J* = 20.6 Hz), 136.6 (d, *J* = 9.5 Hz), 129.9 (d, *J* = 2.8 Hz), 128.6, 127.8 – 127.6 (m), 123.1, 96.6 (d, *J* = 174.8 Hz), 93.7 (dd, *J* = 180.6, 4.8 Hz), 60.7 (t, *J* = 21.0 Hz), 28.0 – 27.7 (m), 27.8 – 27.5 (m); ¹⁹F NMR (470.4 MHz, CDCl₃) δ -144.2 (septdd, *J* = 22.0,

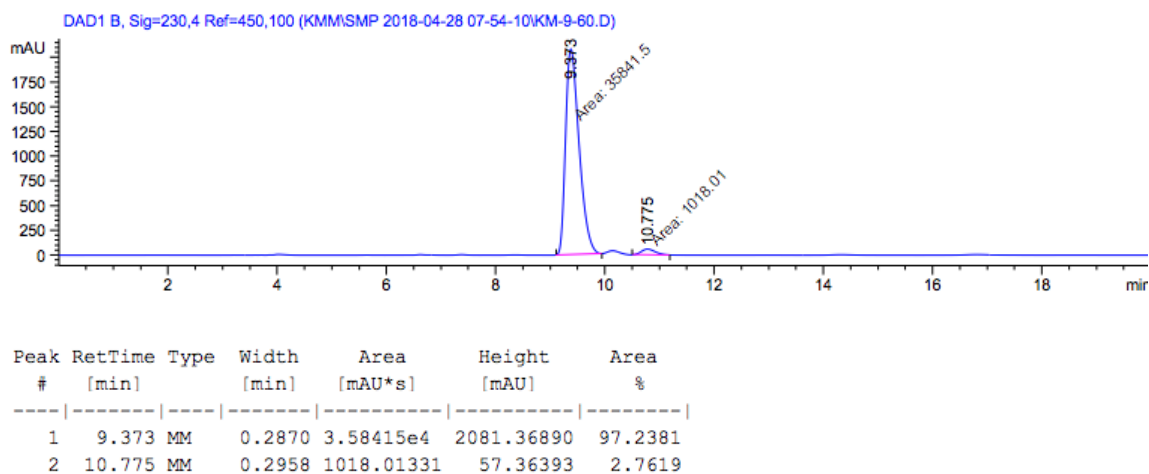
21.9, 9.3 Hz, 1F), -169.0 (dt, $J = 47.1, 11.4$ Hz, 1F); HRMS (ESI-TOF) Calc'd for $C_{17}H_{17}F_2NO_2$
 $[M+Na]^+$: 328.1120; found 328.1104.

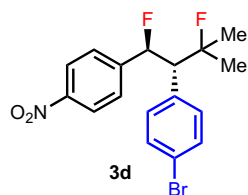
94% e.e., chiral HPLC (OD-H, 2% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230$ nm); t_R (major)
 = 9.4 min, t_R (minor) = 10.8 min.

Racemic sample:



Enriched sample:





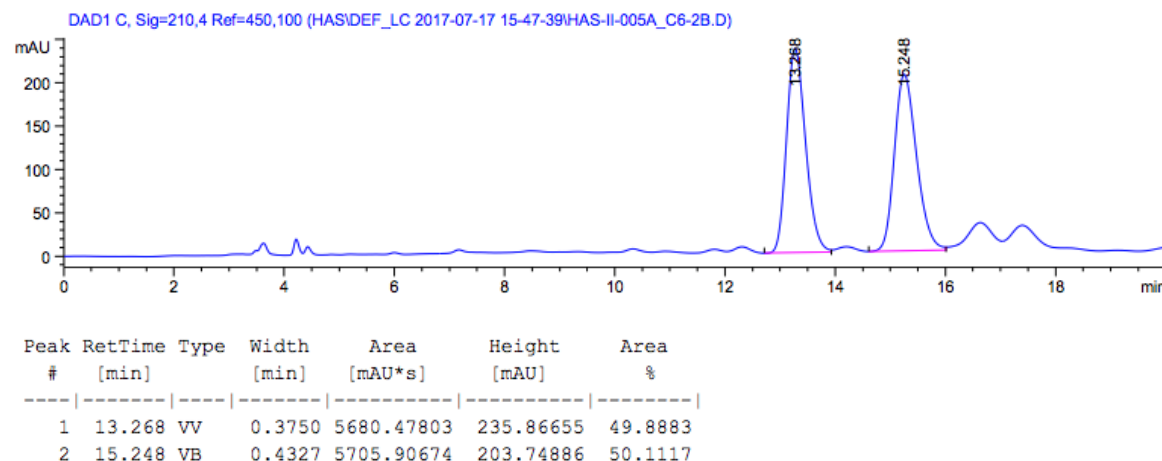
Prepared according to the general procedure using **2d** (180 mg, 0.52 mmol).

The diastereomeric ratio of the crude residue after work-up was determined to be 10:1 by ^1H and ^{19}F NMR analysis. The crude residue was purified by silica gel column chromatography (0 to 5% diethyl ether in hexanes) to give

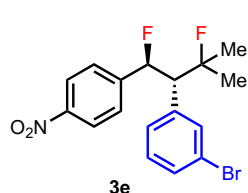
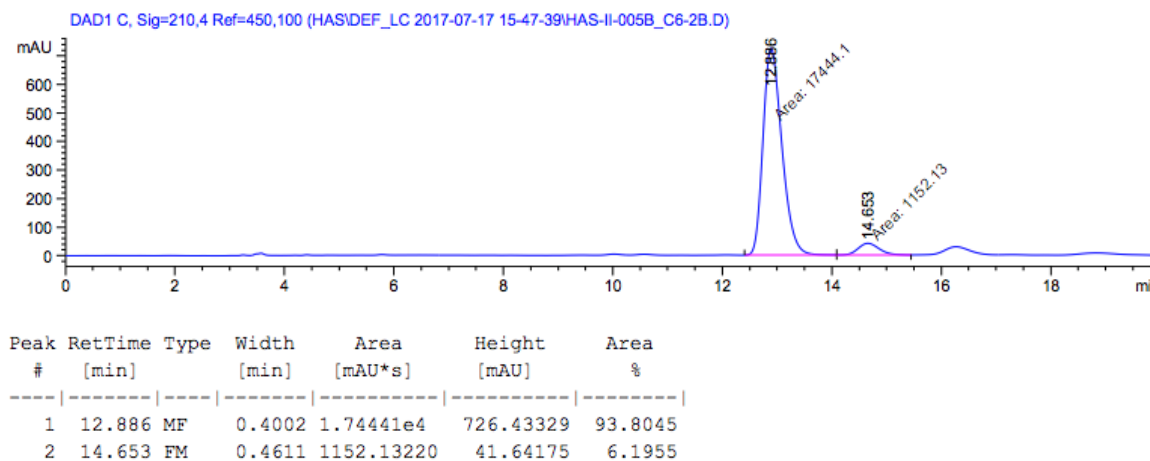
the major diastereomer of **3d** (154 mg, 77%) as a white solid in 88% e.e. The overall yield of both diastereomers was 85%. ^1H NMR (500 MHz, CDCl_3) δ 8.03 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.1 Hz, 2H), 6.04 (dd, J = 46.7, 9.2 Hz, 1H), 3.22 (ddd, J = 23.3, 13.5, 9.2 Hz, 1H), 1.68 (dd, J = 21.7, 2.7 Hz, 3H), 1.29 (d, J = 21.7 Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 147.7, 145.6 (d, J = 20.7 Hz), 135.6 (d, J = 9.1 Hz), 131.7, 131.5 (d, J = 2.7 Hz), 127.8 (d, J = 6.3 Hz), 123.3, 121.7, 96.4 (d, J = 174.9 Hz), 93.2 (dd, J = 180.6, 4.8 Hz), 60.0 (t, J = 21.3 Hz), 27.8 (d, J = 21.3 Hz), 27.7 – 27.4 (m); ^{19}F NMR (470.4 MHz, CDCl_3) δ -145.1 (dseptd, J = 22.1, 22.0, 7.6 Hz, 1F), -168.2 (dt, J = 47.0, 10.3 Hz, 1F); HR-GC/MS (EI^+) Calc'd for $\text{C}_{17}\text{H}_{16}\text{BrF}_2\text{NO}_2$ $[\text{M}]^+$: 383.0327; found 383.0327.

88% e.e., chiral HPLC (OD-H, 2% isopropanol in hexanes, 1.0 mL/min, λ = 210 nm); t_{R} (major) = 12.9 min, t_{R} (minor) = 14.6 min.

Racemic sample:



Enriched sample:



Prepared according to the general procedure using **2e** (180 mg, 0.52 mmol).

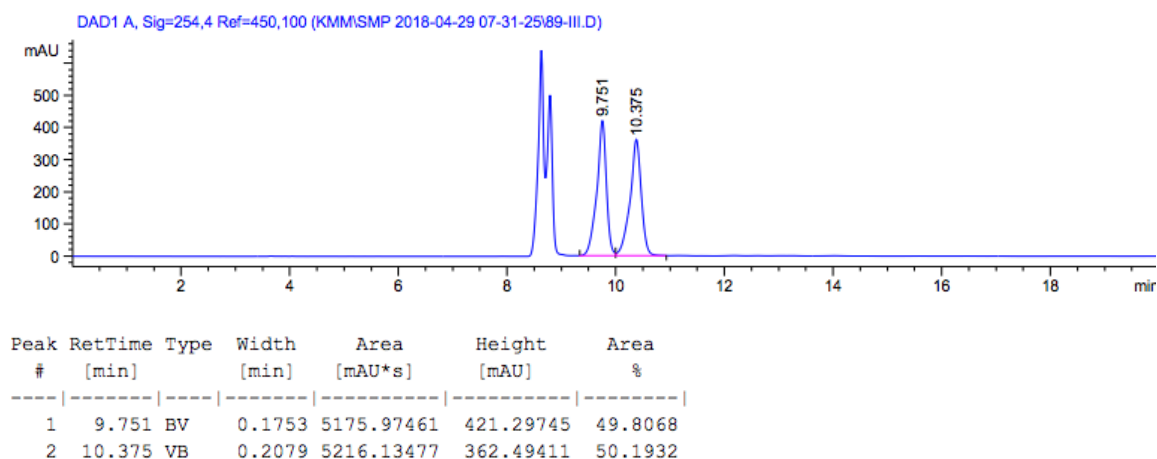
The diastereomeric ratio of the crude residue after work-up was determined

to be 4:1 by ^1H and ^{19}F NMR analysis. The crude residue was purified by

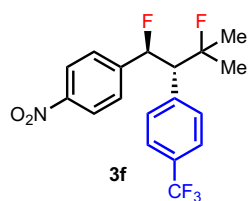
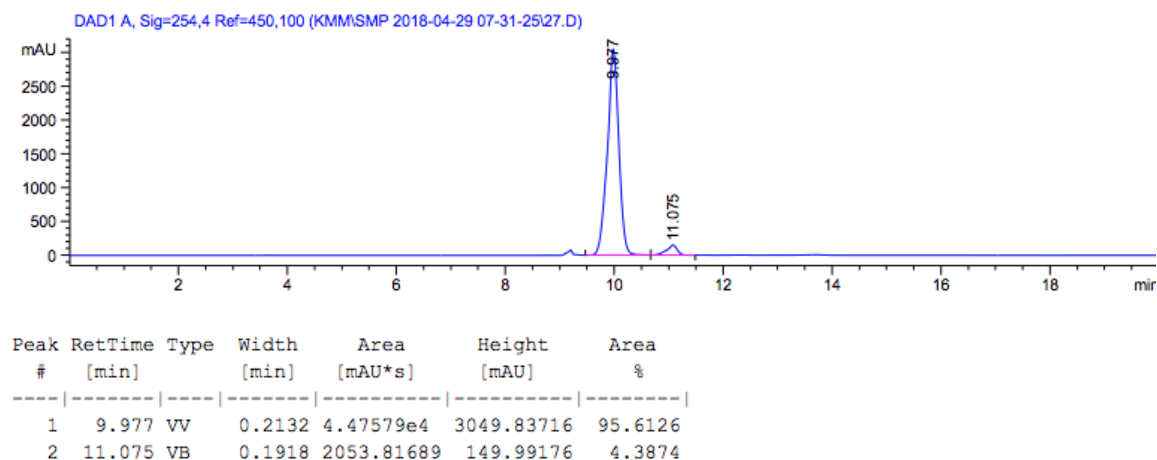
silica gel column chromatography (0 to 5% diethyl ether in hexanes) to give the major diastereomer of **3e** (134 mg, 67%) as a white solid in 91% e.e. The overall yield of both diastereomers was 84%. ^1H NMR (500 MHz, CDCl_3) δ 8.03 (d, J = 8.2 Hz, 2H), 7.31 – 7.18 (m, 4H), 7.01 (t, J = 7.9 Hz, 1H), 6.92 (d, J = 7.7 Hz, 1H), 6.03 (dd, J = 46.6, 9.1 Hz, 1H), 3.29 – 3.08 (m, 1H), 1.68 (dd, J = 21.7, 2.7 Hz, 3H), 1.30 (d, J = 21.7 Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 147.7, 145.6 (d, J = 20.7 Hz), 139.0 (d, J = 8.8 Hz), 132.8 (d, J = 3.3 Hz), 130.9, 130.1, 128.7 (d, J = 2.6 Hz), 127.8 (d, J = 6.4 Hz), 123.4, 122.6, 96.4 (d, J = 175.2 Hz), 93.3 (dd, J = 180.7, 5.0 Hz), 60.7 – 60.1 (m), 27.9 (d, J = 24.8 Hz), 27.8 – 27.5 (m); ^{19}F NMR (470.4 MHz, CDCl_3) δ -145.2 (dseptd, J = 22.1, 22.0, 7.2 Hz, 1F), -168.3 – -168.7 (m, 1F); HRMS (ESI-TOF) Calc'd for $\text{C}_{17}\text{H}_{16}\text{BrF}_2\text{NO}_2$ $[\text{M}+\text{H}]^+$: 384.0405; found 384.0397.

91% e.e., chiral HPLC (OD-H, 2% isopropanol in hexanes, 1.0 mL/min, $\lambda = 254$ nm); t_R (major) = 10.0 min, t_R (minor) = 11.1 min.

Racemic sample:



Enriched sample:



Prepared according to the general procedure using **2f** (174 mg, 0.52 mmol).

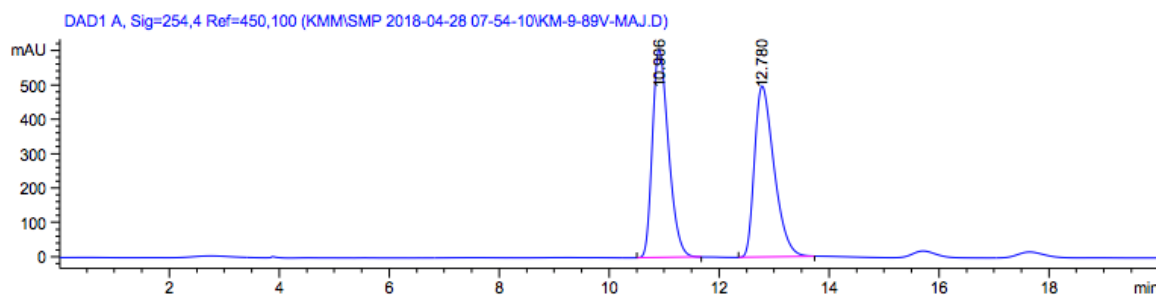
The diastereomeric ratio of the crude residue after work-up was determined to be 2:1 by ^1H and ^{19}F NMR analysis. The crude residue was purified by silica gel column chromatography (0 to 5% diethyl ether in hexanes) to give

the major diastereomer of **3f** (107 mg, 55%) as a white solid in 95% e.e. The overall yield of

both diastereomers was 83%. ^1H NMR (500 MHz, CDCl_3) δ 8.02 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 6.08 (dd, J = 46.6, 9.1 Hz, 1H), 3.31 (ddd, J = 23.4, 13.8, 9.1 Hz, 1H), 1.70 (dd, J = 21.7, 2.7 Hz, 3H), 1.27 (d, J = 21.7 Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 147.8 (d, J = 2.4 Hz), 145.4 (d, J = 20.7 Hz), 140.8 (d, J = 8.7 Hz), 130.4 (d, J = 2.9 Hz), 130.0 (q, J = 32.8 Hz), 127.8 (d, J = 6.3 Hz), 125.5 (d, J = 3.7 Hz), 123.4, 123.9 (q, J = 272.0 Hz), 96.4 (d, J = 175.4 Hz), 93.2 (dd, J = 180.7, 4.9 Hz), 61.5 – 59.5 (m), 28.0 (d, J = 24.4 Hz), 27.6 (dd, J = 24.7, 7.3 Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -62.7 (s, 3F), -145.1 – -145.5 (m, 1F), -168.2 – -168.6 (m, 1F); HR-GC/MS (EI^+) Calc'd for $\text{C}_{18}\text{H}_{16}\text{F}_5\text{NO}_2$ $[\text{M}]^+$: 373.1096; found 373.1094.

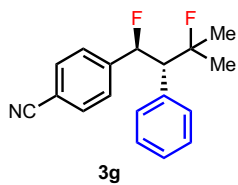
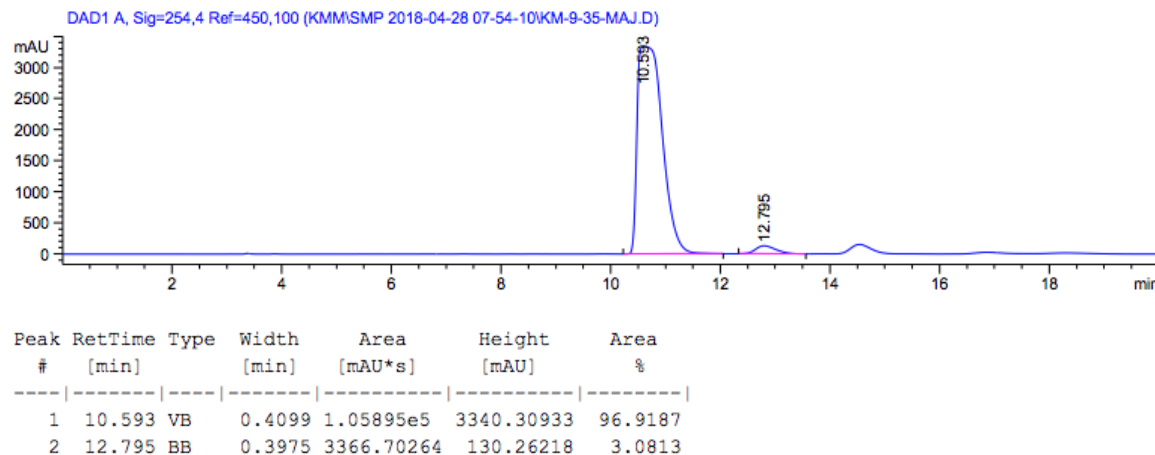
95% e.e., chiral HPLC (OD-H, 2% isopropanol in hexanes, 1.0 mL/min, λ = 254 nm); t_{R} (major) = 10.6 min, t_{R} (minor) = 12.8 min.

Racemic sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.906	BB	0.3136	1.23225e4	605.06677	50.0222
2	12.780	BB	0.3807	1.23116e4	497.51740	49.9778

Enriched sample:



Prepared according to the general procedure using **2g** (129 mg, 0.52 mmol)

with the following modification: 20 equiv of HF was used instead. The

diastereomeric ratio of the crude residue after work-up was determined to be

14:1 by ^1H and ^{19}F NMR analysis. The crude residue was purified by silica

gel column chromatography (0 to 5% diethyl ether in hexanes) to give **3g** (116 mg, 78%) as a

colorless oil in 14:1 d.r and 92% e.e. Major Diastereoisomer: ^1H NMR (500 MHz, CDCl_3) δ 7.42

(d, $J = 8.0$ Hz, 2H), 7.18 – 7.11 (m, 5H), 7.01 – 6.97 (m, 2H), 6.00 (dd, $J = 47.0, 9.5$ Hz, 1H),

3.18 (ddd, $J = 23.7, 12.9, 9.4$ Hz, 1H), 1.65 (dd, $J = 21.7, 2.6$ Hz, 3H), 1.31 (d, $J = 21.8$ Hz, 3H);

^{13}C NMR (125.7 MHz, CDCl_3) δ 144.2 (d, $J = 20.6$ Hz), 136.7 (d, $J = 8.9$ Hz), 131.8, 129.9 (d, J

$= 2.6$ Hz), 128.5, 127.9 – 127.3 (m), 118.6, 112.0 (d, $J = 2.4$ Hz), 96.6 (d, $J = 175.0$ Hz), 93.9

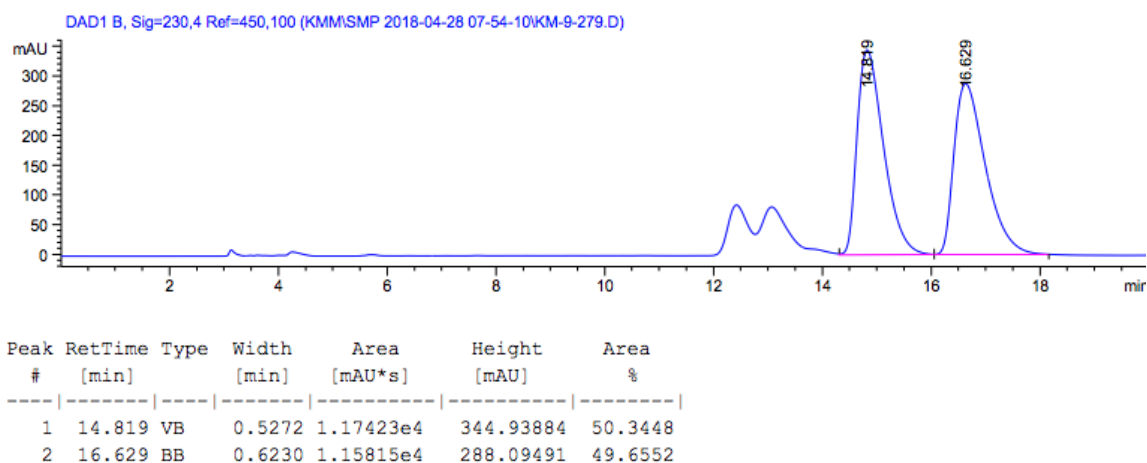
(dd, $J = 180.2, 4.8$ Hz), 60.7 (t, $J = 20.9$ Hz), 28.0 – 27.5 (m); ^{19}F NMR (470.4 MHz, CDCl_3) δ -

144.2 (septdd, $J = 22.5, 22.0, 10.7$ Hz, 1F), -169.2 (dt, $J = 46.9, 11.2$ Hz, 1F); HRMS (ESI-TOF)

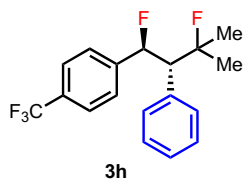
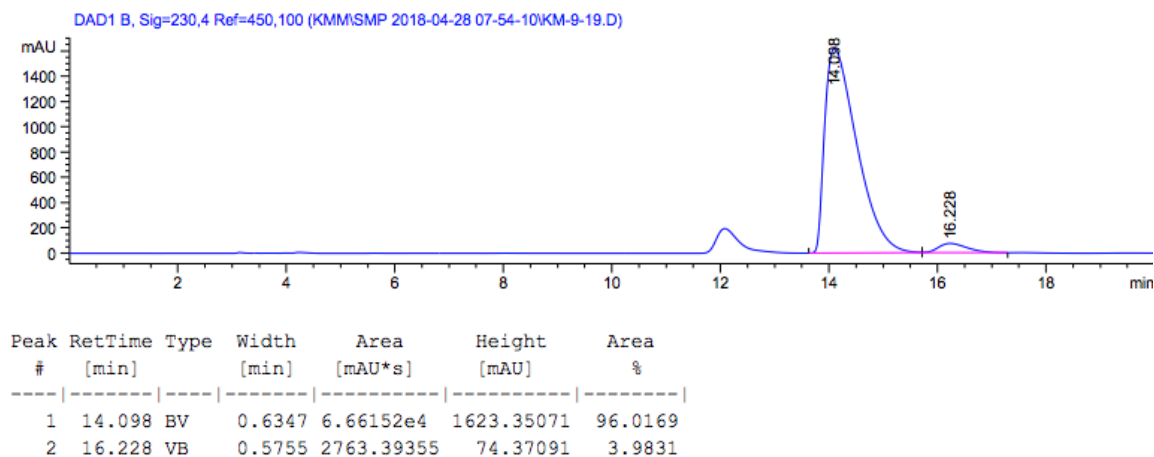
Calc'd for $\text{C}_{18}\text{H}_{17}\text{F}_2\text{N}$ $[\text{M}+\text{H}]^+$: 286.1402; found 286.1402.

92% e.e., chiral HPLC (OD-H, 2% isopropanol in hexanes, 1.0 mL/min, $\lambda = 230$ nm); t_R (major) = 14.1 min, t_R (minor) = 16.2 min.

Racemic sample:



Enriched sample:

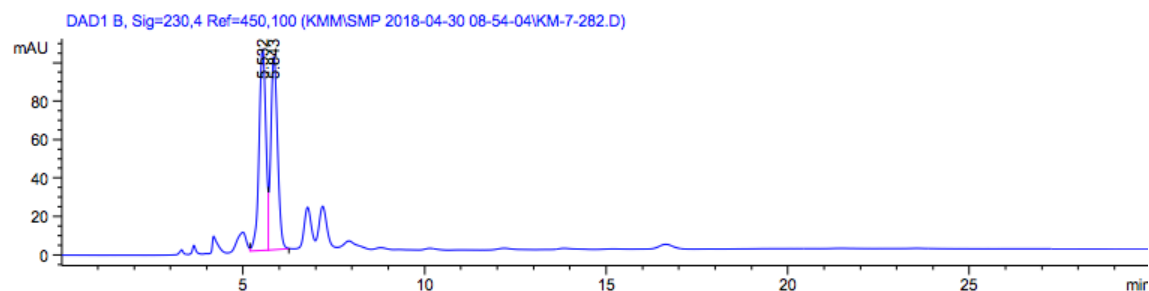


Prepared according to the general procedure using **2h** (151 mg, 0.52 mmol) with the following modification: 20 equiv of HF was used instead. The diastereomeric ratio of the crude residue after work-up was determined to be 5:1 by ^1H and ^{19}F NMR analysis. The crude residue was purified by silica gel column chromatography (0 to 5% diethyl ether in hexanes) to give **3h** (140 mg, 82%) as a colorless oil in

5:1 d.r and 90% ee.. Major Diastereoisomer: ^1H NMR (500 MHz, CDCl_3) δ 7.45 – 7.42 (m, 2H), 7.25 – 7.21 (m, 2H), 7.20 – 7.15 (m, 3H), 7.08 – 7.04 (m, 2H), 6.13 – 6.01 (m, 1H), 3.28 (ddd, J = 23.2, 12.4, 9.5 Hz, 1H), 1.70 (dd, J = 21.6, 2.4 Hz, 3H), 1.38 (d, J = 21.9 Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 143.1 (d, J = 20.6 Hz), 137.0 (d, J = 9.6 Hz), 130.1 (q, J = 32.8 Hz), 130.0 (d, J = 2.4 Hz), 128.5, 127.5, 127.3 (d, J = 6.3 Hz), 125.0 (d, J = 3.8 Hz), 123.9 (q, J = 272.0 Hz), 96.7 (d, J = 174.2 Hz), 94.2 (dd, J = 179.4, 4.8 Hz), 60.8 (t, J = 21.1 Hz), 28.0 – 27.6 (m); ^{19}F NMR (376 MHz, CDCl_3) δ -62.7 (s, 3F), -143.7 (dseptd, J = 21.9, 21.7, 10.9 Hz, 1F), -168.4 (dt, J = 46.8, 11.4 Hz, 1F); HR-GC/MS (EI^+) Calc'd for $\text{C}_{18}\text{H}_{17}\text{F}_5$ $[\text{M}]^+$: 328.1245; found 328.1242.

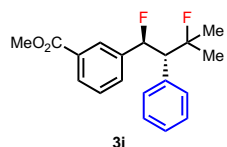
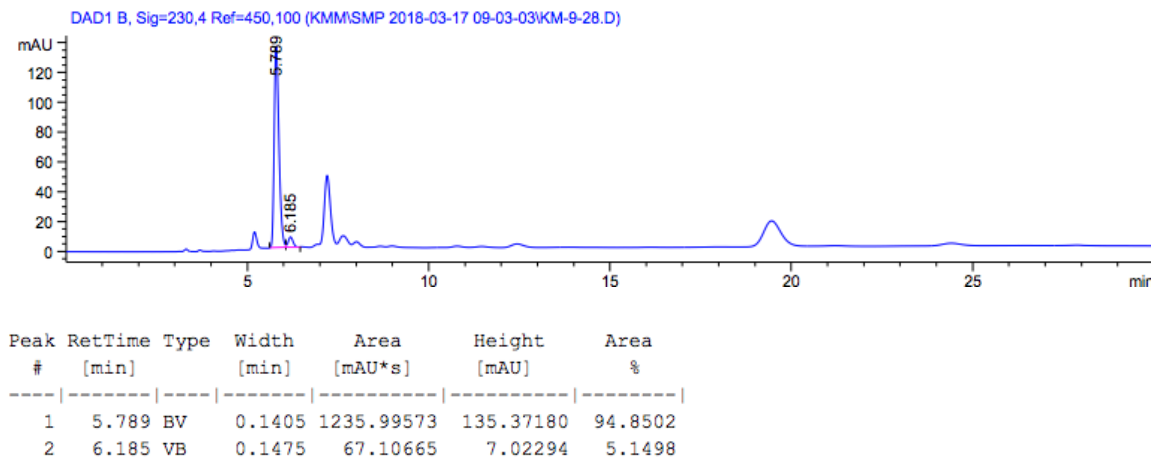
90% e.e., chiral HPLC (OD-H, 0.3% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm); $t_{\text{R}}(\text{major})$ = 5.8 min, $t_{\text{R}}(\text{minor})$ = 6.2 min.

Racemic sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.532	VV	0.2061	1386.68823	104.96294	51.5620
2	5.843	VB	0.1989	1302.67224	100.73479	48.4380

Enriched sample:



Prepared according to the general procedure using **2i** (146 mg, 0.52 mmol)

with the following modification: 20 equiv of HF was used instead. The

diastereomeric ratio of the crude residue after work-up was determined to be

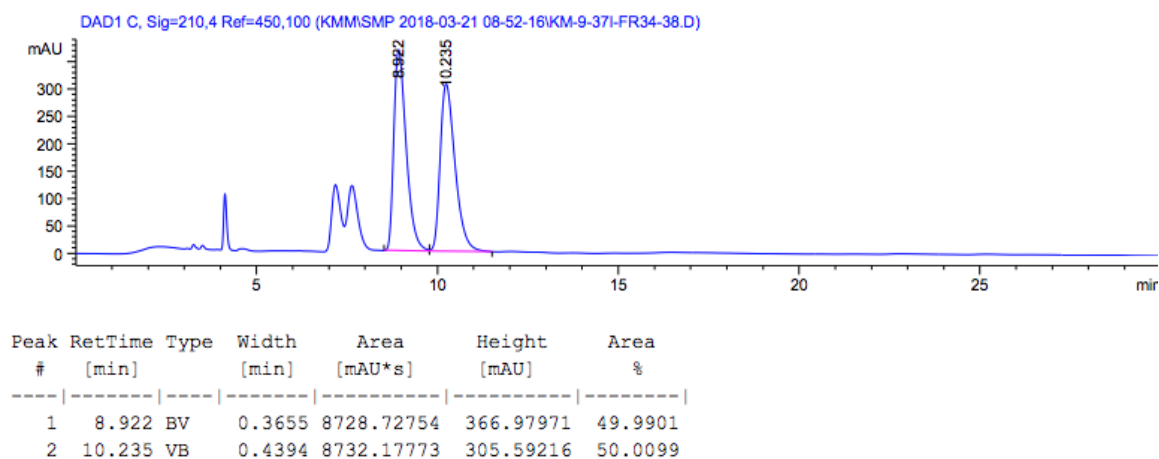
2:1 by ^1H and ^{19}F NMR analysis. The crude residue was purified by silica gel column chromatography (0 to 5% diethyl ether in hexanes) to give **3i** (89 mg, 54%) as a colorless oil in

2:1 d.r and 88% e.e. The overall yield of both diastereomers was 81%. Major Diastereoisomer:

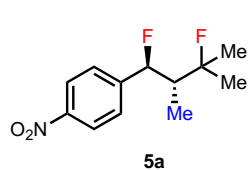
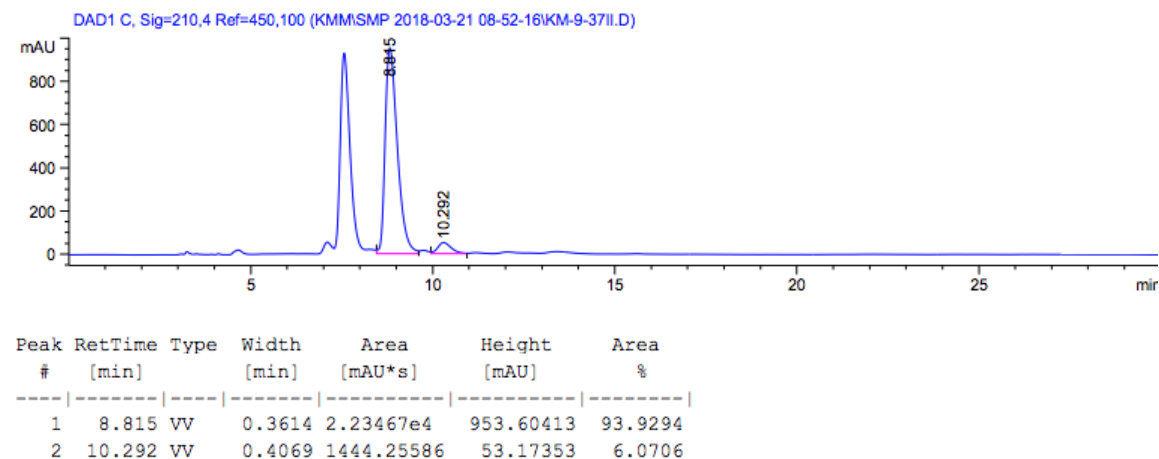
^1H NMR (500 MHz, CDCl_3) δ 7.85 – 7.84 (m, 1H), 7.81 (dd, J = 6.9, 1.7 Hz, 1H), 7.23 – 7.15 (m, 2H), 7.10 (tdd, J = 7.0, 5.6, 2.5 Hz, 3H), 7.01 (d, J = 7.1 Hz, 2H), 6.01 (ddd, J = 46.9, 9.7, 1.2 Hz, 1H), 3.88 (s, 1H), 3.28 (ddd, J = 22.6, 12.4, 9.7 Hz, 1H), 1.66 (d, J = 21.7 Hz, 3H), 1.33 (d, J = 21.8 Hz, 3H); ^{13}C NMR (125/7 MHz, CDCl_3) δ 166.8, 139.6 (d, J = 20.6 Hz), 137.3 (d, J = 9.1 Hz), 131.6 (d, J = 5.7 Hz), 130.1, 130.0 (d, J = 2.4 Hz), 129.4 (d, J = 2.2 Hz), 128.4, 128.2 (d, J = 6.2 Hz), 128.1, 127.3, 96.7 (d, J = 173.2 Hz), 94.4 (dd, J = 178.6, 4.7 Hz), 60.6 (t, J = 21.2 Hz), 52.3, 28.0 – 27.6 (m); ^{19}F NMR (470.4 MHz, CDCl_3) δ -143.8 (septdd, J = 22.1, 22.0, 11.1 Hz, 1F), -166.3 (dt, J = 46.9, 11.2 Hz, 1F); HRMS (ESI-TOF) Calc'd for $\text{C}_{19}\text{H}_{20}\text{F}_2\text{O}_2$ $[\text{M}+\text{Na}]^+$: 341.1324; found 341.1322.

88% e.e., chiral HPLC (AS-H, 1% isopropanol in hexanes, 1.0 mL/min, $\lambda = 210$ nm); t_R (major) = 8.8 min, t_R (minor) = 10.3 min.

Racemic sample:



Enriched sample:



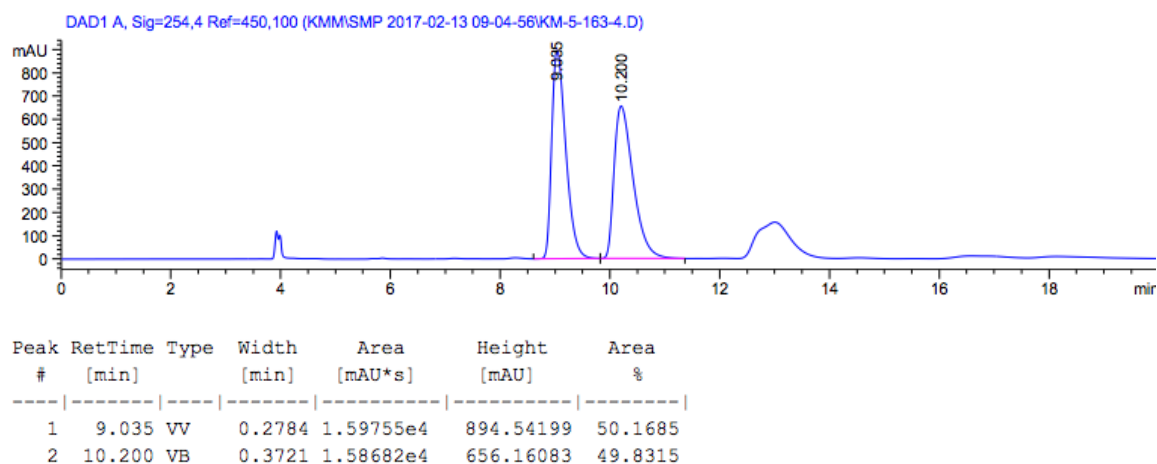
Prepared according to the general procedure using **4a** (107 mg, 0.52 mmol) with the following modification: 20 equiv of HF was used instead. The diastereomeric ratio of the crude residue after work-up was determined to

be >20:1 by ¹H and ¹⁹F NMR analysis. The crude residue was purified by silica gel column chromatography (0 to 5% diethyl ether in hexanes) to give **5a** (108 mg, 85%) as a colorless oil in

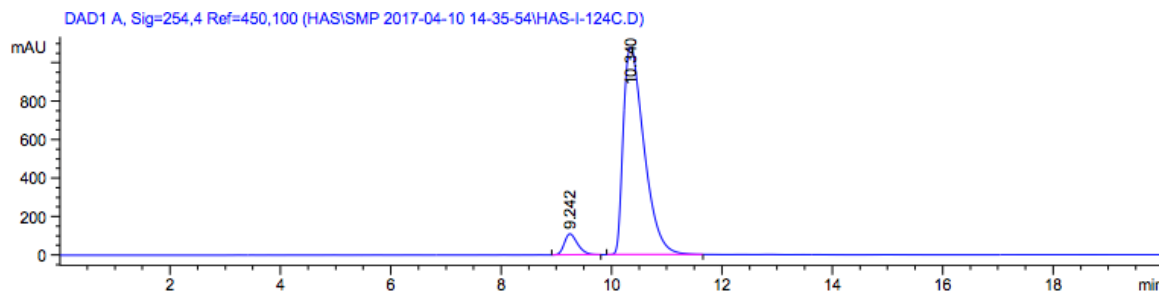
88% e.e. HRMS (ESI-TOF) Calc'd for $C_{12}H_{15}F_2NO_2$ $[M+H]^+$: 244.1144; found 244.1143. ^1H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, $J = 8.7$ Hz, 1H), 7.46 (d, $J = 8.7$ Hz, 1H), 6.04 (d, $J = 48.4$ Hz, 1H), 2.14 – 1.97 (m, 1H), 1.48 (dd, $J = 22.1, 2.0$ Hz, 2H), 1.43 (d, $J = 22.4$ Hz, 2H), 0.84 (dd, $J = 7.3, 1.5$ Hz, 2H); ^{19}F NMR (470.4 MHz, $CDCl_3$) δ -134.1 (heptd, $J = 11.9, 4.6$ Hz), -200.5 (dd, $J = 15.7, 8.9$ Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.6, 125.6, 123.5, 97.4, 90.9, 49.5, 26.6, 23.1, 7.3.

88% e.e., chiral HPLC (OD-H, 2% isopropanol in hexanes, 1.0 mL/min, $\lambda = 254$ nm); t_R (major) = 9.2 min, t_R (minor) = 10.3 min.

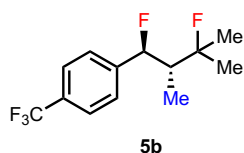
Racemic sample:



Enriched sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.242	BB	0.2583	1835.58813	109.07656	6.1141
2	10.340	BB	0.4026	2.81867e4	1079.62354	93.8859

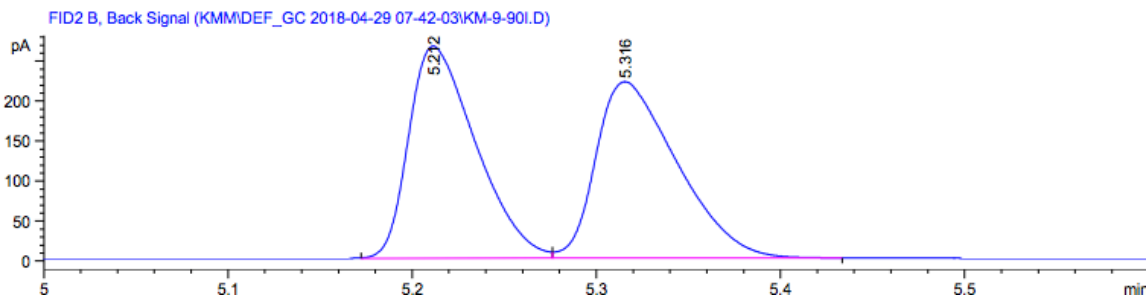


Prepared according to the general procedure using **4b** (119 mg, 0.52 mmol) with the following modification: 20 equiv of HF was used instead. The diastereomeric ratio of the crude residue after work-up was determined to be

>20:1 by ^1H and ^{19}F NMR analysis. The crude residue was purified by silica gel column chromatography (0 to 5% diethyl ether in hexanes) to give **5b** (120 mg, 87%) as a colorless oil in 98% e.e. ^1H NMR (500 MHz, CDCl_3) δ 7.64 (d, $J = 8.2$ Hz, 2H), 7.42 (d, $J = 8.1$ Hz, 2H), 6.03 (d, $J = 48.4$ Hz, 1H), 2.17 – 1.98 (m, 1H), 1.51 (dd, $J = 22.1, 2.0$ Hz, 3H), 1.45 (d, $J = 22.4$ Hz, 3H), 0.87 (dd, $J = 7.3, 1.5$ Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 144.6 (d, $J = 21.6$ Hz), 130.0 (q, $J = 32.4$ Hz), 125.5 – 125.3 (m), 125.2, 125.1, 123.8 (d, $J = 272.0$ Hz), 100.4 – 95.7 (m), 91.3 (dd, $J = 178.9, 7.3$ Hz), 49.8, 26.7 (dd, $J = 24.3, 2.0$ Hz), 23.3 (dd, $J = 25.1, 3.8$ Hz), 7.5 – 7.2 (m); ^{19}F NMR (470.4 MHz, CDCl_3) δ -62.6 (s, 3F), -134.2 (septd, $J = 22.1, 9.7$ Hz, 1F), -200.9 (dd, $J = 48.4, 33.1$ Hz, 1F); HR-GC/MS (EI^+) Calc'd for $\text{C}_{13}\text{H}_{15}\text{F}_5$ $[\text{M}]^+$: 266.1088; found 266.1088.

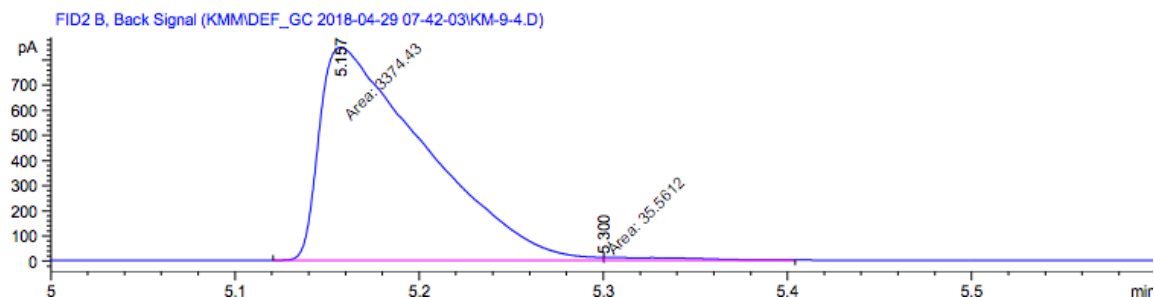
98% e.e., chiral GC (β -Cyclosil, 130 $^\circ\text{C}$, 14 psi); $t_{\text{R}}(\text{major}) = 5.2$ min, $t_{\text{R}}(\text{minor}) = 5.3$ min.

Racemic sample:

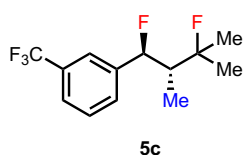


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	5.212	BV	0.0392	671.44733	264.88361	49.77325
2	5.316	VB	0.0479	677.56500	220.42593	50.22675

Enriched sample:



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	5.157	MF	0.0664	3374.43481	846.48456	98.95715
2	5.300	FM	0.0557	35.56116	10.64245	1.04285



Prepared according to the general procedure using **4c** (119 mg, 0.52 mmol) with the following modification: 20 equiv of HF was used instead. The diastereomeric ratio of the crude residue after work-up was determined to be

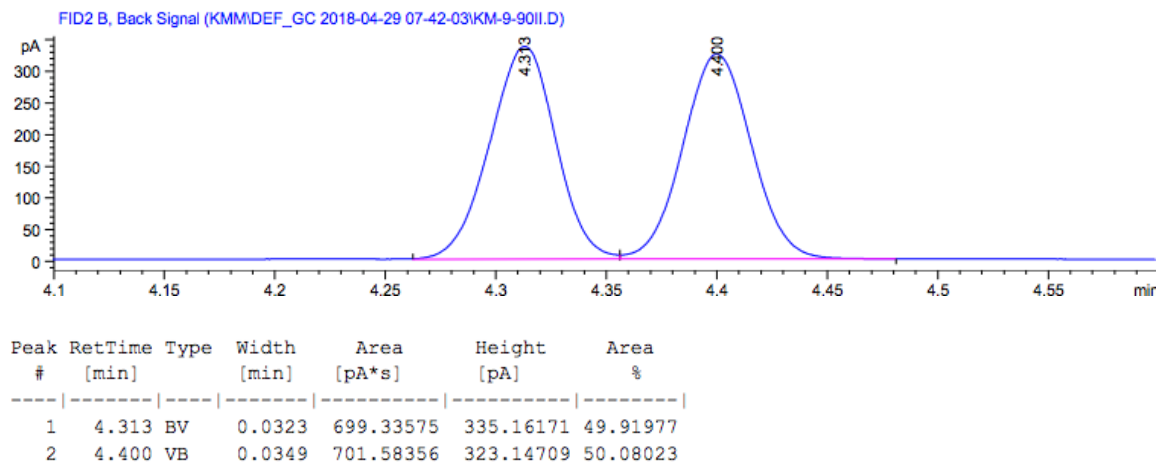
>20:1 by ^1H and ^{19}F NMR analysis. The crude residue was purified by silica gel column chromatography (0 to 5% diethyl ether in hexanes) to give **5c** (121 mg, 88%) as a colorless oil in 99% e.e. ^1H NMR (500 MHz, CDCl_3) δ 7.59 – 7.55 (m, 2H), 7.54 – 7.46 (m, 2H), 6.02 (d, J = 48.2 Hz, 1H), 2.16 – 1.98 (m, 1H), 1.51 (dd, J = 22.1, 1.9 Hz, 3H), 1.45 (d, J = 22.5 Hz, 3H), 0.87 (d, J = 7.2 Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 141.7 (d, J = 21.6 Hz), 131.7 – 130.3 (m), 128.9 (d, J = 2.3 Hz), 128.2 (d, J = 9.5 Hz), 124.2 (q, J = 272.4 Hz), 124.5 (d, J = 3.8 Hz), 121.7 (dd, J = 10.2, 3.8 Hz), 100.7 – 95.4 (m), 91.3 (dd, J = 178.7, 7.3 Hz), 49.7 (t, J = 20.6 Hz), 26.7 (dd, J = 24.2, 2.0 Hz), 23.4 (dd, J = 24.9, 3.8 Hz), 7.4 (t, J = 8.1 Hz); ^{19}F NMR (470.4 MHz,

CDCl₃) δ -62.7 (s, 3F), -134.2 (septd, J = 22.3, 10.0 Hz, 1F), -200.6 (dd, J = 48.2, 33.2 Hz, 1F);

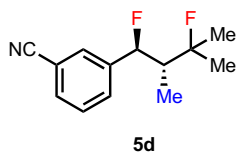
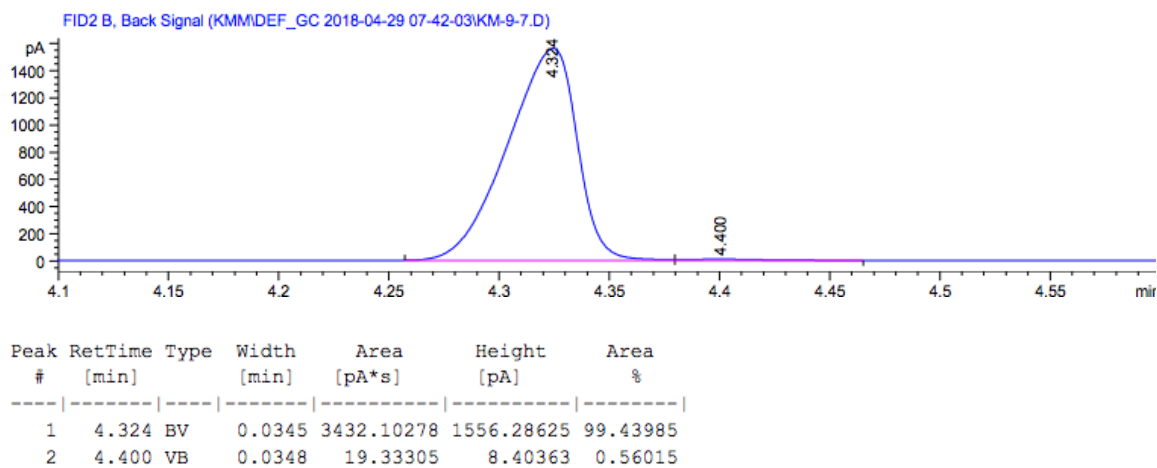
HR-GC/MS (EI⁺) Calc'd for C₁₃H₁₅F₅ [M]⁺: 266.1088; found 266.1089.

99% e.e., chiral GC (β -Cyclosil, 130 °C, 14 psi); t_R (major) = 4.3 min, t_R (minor) = 4.4 min.

Racemic sample:



Enriched Sample:



Prepared according to the general procedure using **4d** (96.3 mg, 0.52 mmol)

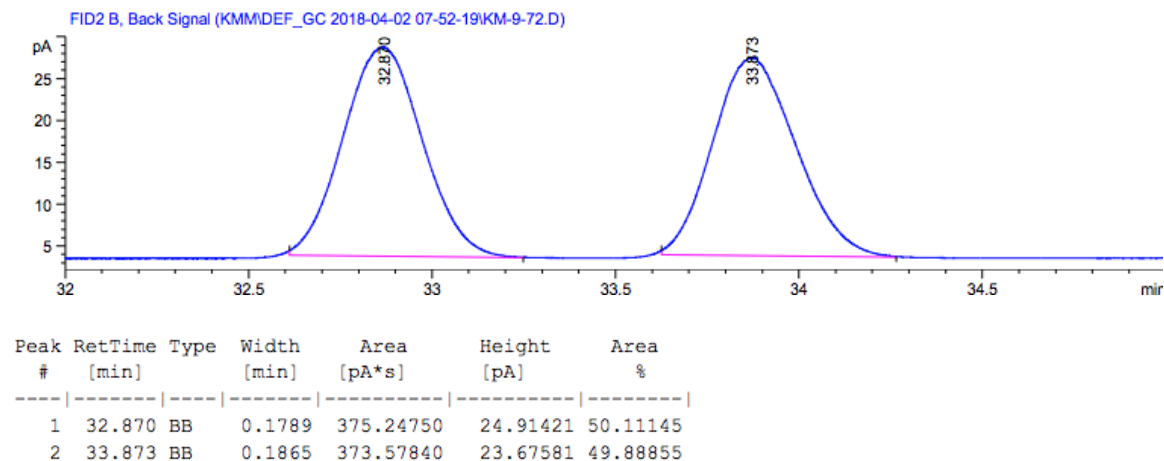
with the following modification: 20 equiv of HF was used instead. The diastereomeric ratio of the crude residue after work-up was determined to be

>20:1 by ¹H and ¹⁹F NMR analysis. The crude residue was purified by silica gel column

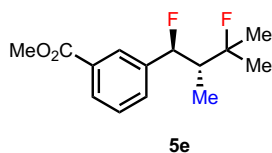
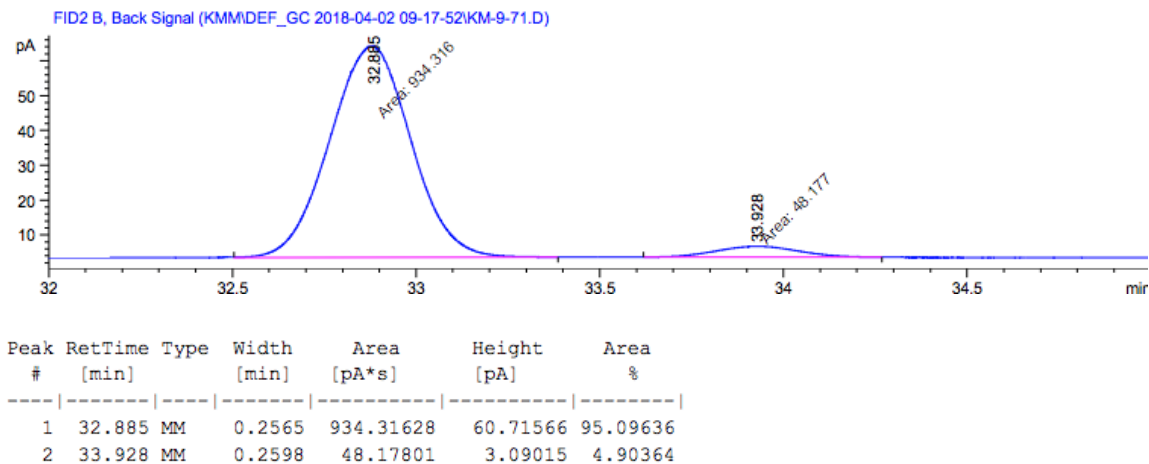
chromatography (0 to 5% diethyl ether in hexanes) to give **5d** (91.7 mg, 79%) as a colorless oil in 90% e.e. ^1H NMR (500 MHz, CDCl_3) δ 7.63 – 7.58 (m, 2H), 7.54 – 7.46 (m, 2H), 5.98 (d, J = 48.1 Hz, 1H), 2.12 – 1.95 (m, 1H), 1.49 (dd, J = 22.2, 2.0 Hz, 3H), 1.43 (d, J = 22.4 Hz, 3H), 0.85 (dd, J = 7.3, 1.4 Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 142.1 (d, J = 21.9 Hz), 131.3, 129.3 (d, J = 1.7 Hz), 129.1 (d, J = 9.1 Hz), 128.4 (d, J = 10.5 Hz), 118.7, 112.7 (d, J = 2.1 Hz), 97.5 (d, J = 166.3 Hz), 90.8 (dd, J = 179.7, 7.3 Hz), 49.6 (t, J = 20.6 Hz), 26.7 (dd, J = 24.5, 1.8 Hz), 23.2 (dd, J = 24.9, 3.7 Hz), 7.4 (t, J = 8.0 Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -134.2 (septd, J = 22.3, 10.2 Hz, 1F), -200.9 (dd, J = 48.3, 32.9 Hz, 1F); HRMS (ESI-TOF) Calc'd for $\text{C}_{13}\text{H}_{15}\text{F}_2\text{N}$ $[\text{M}+\text{H}]^+$: 224.1245; found 224.1245.

90% e.e., chiral GC (β -Cyclosil, 130 °C, 14 psi); $t_{\text{R}}(\text{major})$ = 32.9 min, $t_{\text{R}}(\text{minor})$ = 33.9 min.

Racemic sample:



Enriched sample:

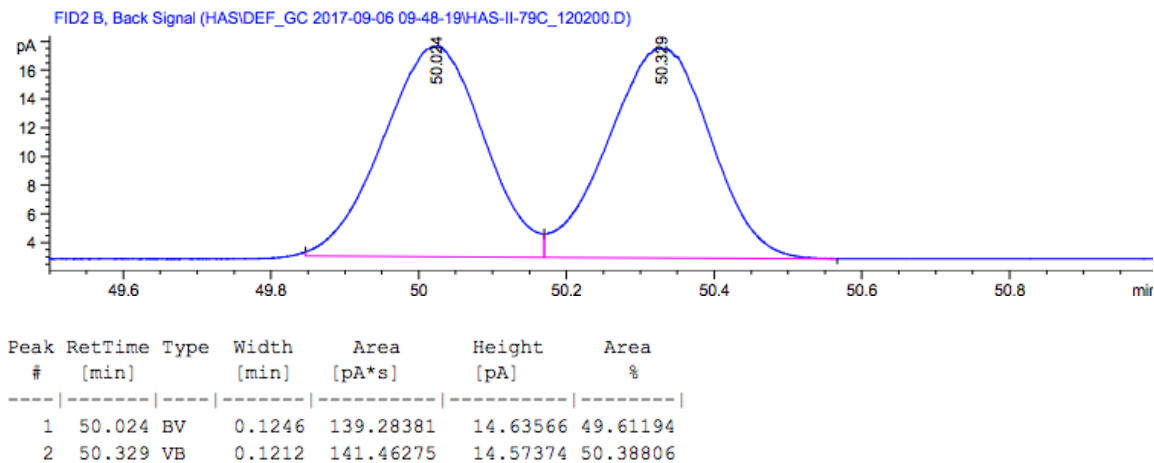


Prepared according to the general procedure using **4e** (114 mg, 0.52 mmol) with the following modification: 20 equiv of HF was used instead. The diastereomeric ratio of the crude residue after work-up was

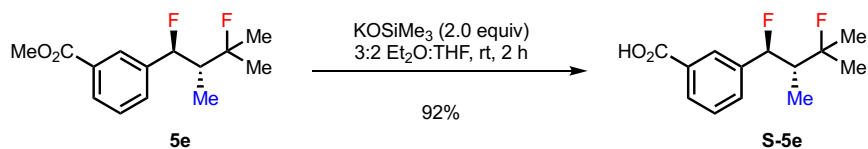
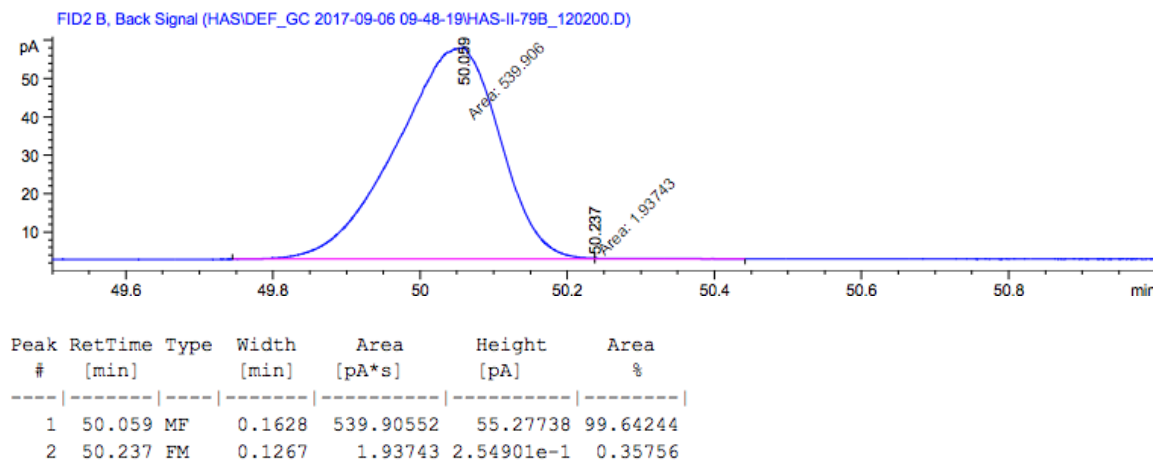
determined to be >20:1 by ^1H and ^{19}F NMR analysis. The crude residue was purified by silica gel column chromatography (0 to 5% diethyl ether in hexanes) to give **5e** (115 mg, 86%) as a colorless oil in 96% e.e. ^1H NMR (500 MHz, CDCl_3) δ 8.09 – 7.89 (m, 2H), 7.51 – 7.47 (m, 1H), 7.44 (t, J = 7.6 Hz, 1H), 5.99 (d, J = 48.2 Hz, 1H), 3.92 (d, J = 1.1 Hz, 3H), 2.18 – 1.95 (m, 1H), 1.51 (d, J = 1.9 Hz, 3H), 1.42 (d, J = 22.2 Hz, 3H), 0.85 (dd, J = 7.2, 1.3 Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 166.9, 141.0 (d, J = 21.5 Hz), 130.4 (d, J = 1.8 Hz), 129.3 (d, J = 9.6 Hz), 128.8, 128.5 (d, J = 1.8 Hz), 125.9 (d, J = 9.6 Hz), 97.6 (d, J = 167.6 Hz), 91.4 (dd, J = 178.3, 7.3 Hz), 52.3, 49.6 (t, J = 20.7 Hz), 26.6 (dd, J = 24.5, 2.0 Hz), 23.5 (dd, J = 24.9, 3.7 Hz), 7.3 (d, J = 7.9 Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -134.3 (septd, J = 22.3, 10.0 Hz), -200.3 (dd, J = 48.2, 33.3 Hz); HR-GC/MS (EI^+) Calc'd for $\text{C}_{14}\text{H}_{18}\text{F}_2\text{O}_2$ $[\text{M}]^+$: 256.1269; found 256.1269.

99% e.e., chiral GC (β -Cyclosil, 120 to 200 °C, 14 psi); t_R (major) = 50.1 min, t_R (minor) = 50.2 min.

Racemic sample:

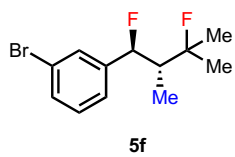


Enriched sample:



To a solution of **5e** (115 mg, 0.45 mmol, 1.0 equiv) in 3:2 Et₂O:THF (4.5 mL) under N_{2(g)} was added potassium trimethylsilanoate (90%, 128 mg, 0.90 mmol, 2.0 equiv). The reaction mixture

was stirred at room temperature. After 2 hours, the reaction was quenched with 1 M HCl (aq.) (2 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with Et₂O (3 x 5 mL). The combined organic layers were washed with brine (2 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give **S-5e** as a white solid (100 mg, 92%). Crystals of **S-5e** were grown by slow evaporation of a solution of **S-5e** in Et₂O/pentane. ¹H NMR (500 MHz, CDCl₃) δ 8.10 – 8.00 (m, 2H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.51 (td, *J* = 7.7, 2.2 Hz, 1H), 6.03 (d, *J* = 48.3 Hz, 1H), 2.20 – 2.01 (m, 1H), 1.52 (d, *J* = 21.9 Hz, 3H), 1.47 (d, *J* = 2.1 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (125.7 MHz, CDCl₃) δ 171.9, 141.2 (d, *J* = 21.6 Hz), 130.3 (d, *J* = 9.4 Hz), 129.5, 128.7, 126.6 (d, *J* = 9.5 Hz), 97.7 (d, *J* = 167.5 Hz), 91.4 (dd, *J* = 178.5, 7.4 Hz), 49.6 (t, *J* = 20.7 Hz), 26.7 (d, *J* = 24.2 Hz), 23.5 (dd, *J* = 25.0, 3.7 Hz), 7.4 (t, *J* = 8.0 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -134.3 (septd, *J* = 22.2, 9.8 Hz, 1F), -200.3 (dd, *J* = 48.2, 33.4 Hz, 1F); HR-GC/MS (EI⁺) Calc'd for C₁₃H₁₆F₂O₂ [M-H]⁻: 241.1046; found 241.1056.

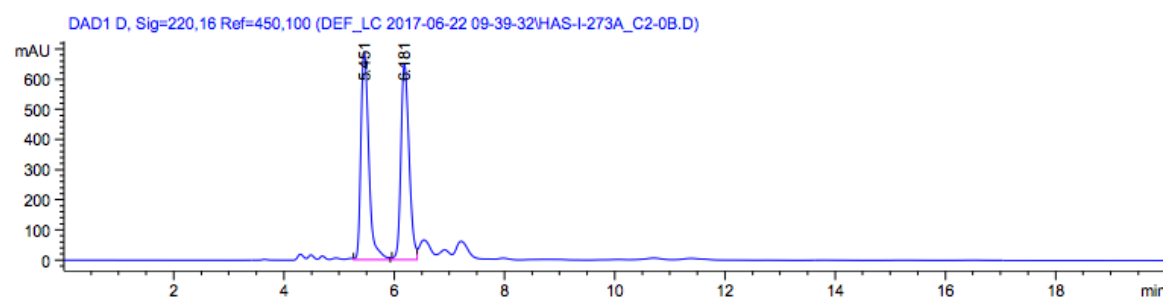


Prepared according to the general procedure using **4f** (124 mg, 0.52 mmol) with the following modification: 20 equiv of HF was used instead. The diastereomeric ratio of the crude residue after work-up was determined to be >20:1 by ¹H and ¹⁹F NMR analysis. The crude residue was purified by silica gel column chromatography (0 to 2% diethyl ether in hexanes) to give **5f** (92.2 mg, 64%) as a colorless oil in 98% e.e. ¹H NMR (500 MHz, CDCl₃) δ 7.49 – 7.38 (m, 2H), 7.29 – 7.16 (m, 2H), 5.92 (d, *J* = 48.3 Hz, 1H), 2.36 – 1.89 (m, 1H), 1.48 (dd, *J* = 22.2, 1.9 Hz, 3H), 1.42 (d, *J* = 22.4 Hz, 3H), 0.86 (dd, *J* = 7.3, 1.4 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 142.9 (d, *J* = 21.5 Hz), 130.7, 130.0 (d, *J* = 1.7 Hz), 127.9 (d, *J* = 10.3 Hz), 123.4 (d, *J* = 9.5 Hz), 122.7 (d, *J* = 2.2 Hz), 97.7 (d, *J* = 167.3 Hz), 91.0 (dd, *J* = 179.0, 7.3 Hz), 49.7 (t, *J* = 20.7 Hz), 29.9, 26.7 (dd, *J* = 24.4, 1.9

Hz), 23.4 (dd, $J = 25.0, 3.7$ Hz), 7.6 – 7.3 (m); ^{19}F NMR (470.4 MHz, CDCl_3) δ -134.3 (septd, $J = 22.3, 10.1$ Hz), -200.3 (dd, $J = 48.3, 33.2$ Hz); HR-GC/MS (EI^+) Calc'd for $\text{C}_{12}\text{H}_{15}\text{BrF}_2$ $[\text{M}]^+$: 276.0320; found 276.0319.

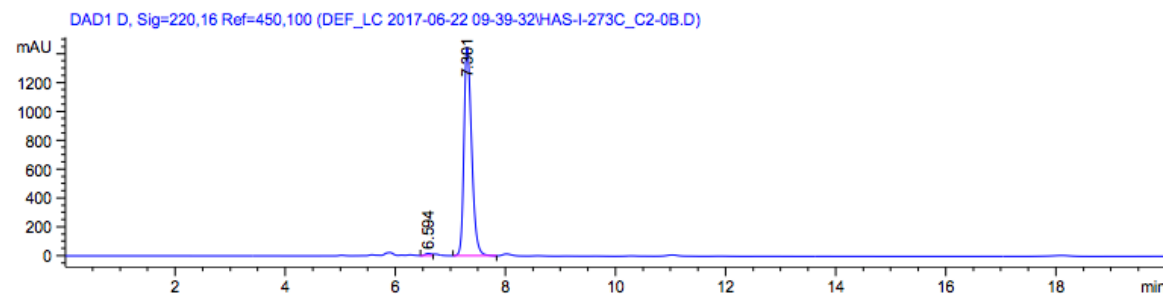
98% e.e., chiral HPLC (IB, 100% hexanes, 1.0 mL/min, $\lambda = 220$ nm); $t_{\text{R}}(\text{minor}) = 6.6$ min, $t_{\text{R}}(\text{major}) = 7.3$ min.

Racemic sample:

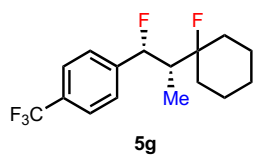


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.451	VB	0.1574	6964.81543	692.16235	50.9396
2	6.181	BV	0.1603	6707.87012	650.69250	49.0604

Enriched sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.594	VV	0.1337	158.18129	17.45622	1.1097
2	7.301	BV	0.1497	1.40962e4	1445.80298	98.8903

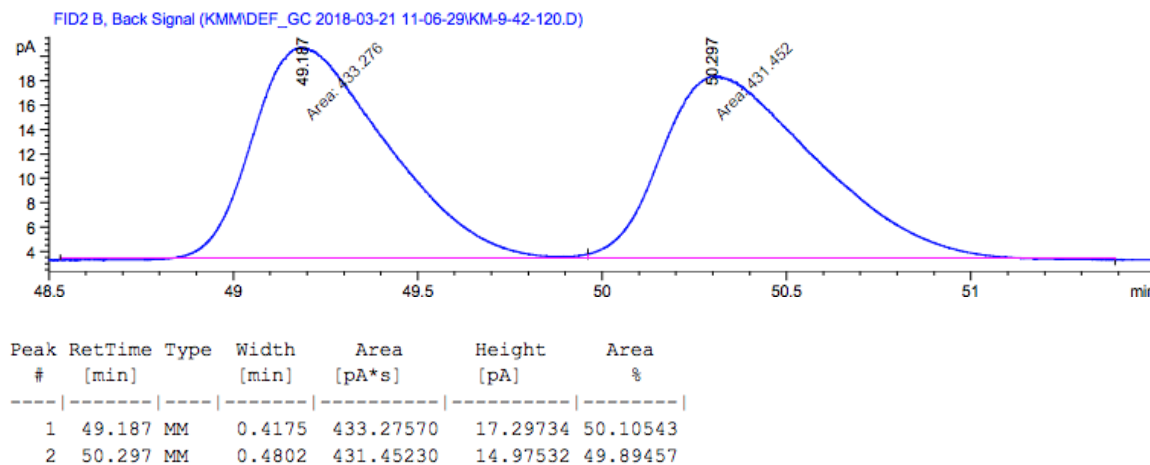


Prepared according to the general procedure using **4g** (140 mg, 0.52 mmol) with the following modification: 20 equiv of HF was used instead. The diastereomeric ratio of the crude residue after work-up was determined to

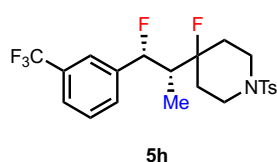
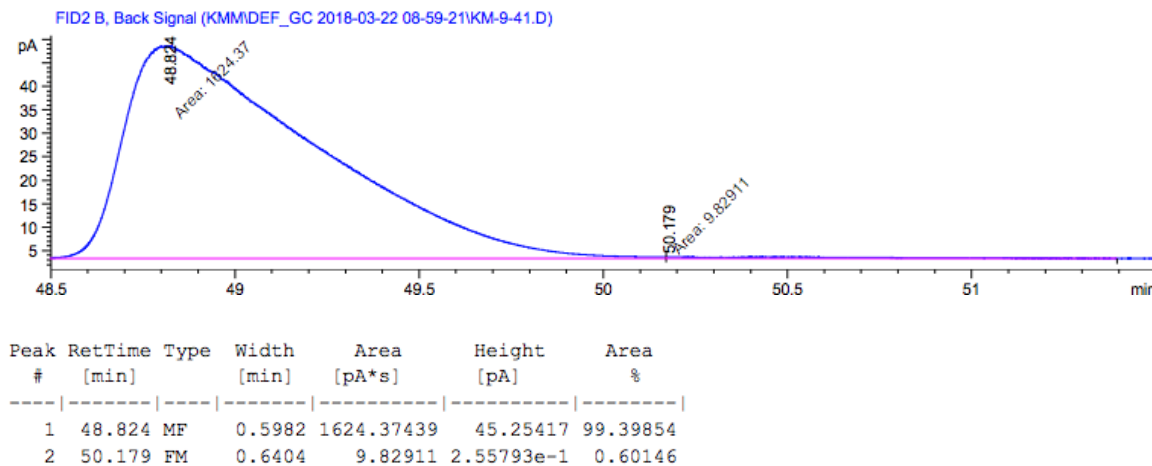
be >20:1 by ^1H and ^{19}F NMR analysis. The crude residue was purified by silica gel column chromatography (0 to 2% diethyl ether in hexanes) to give **5g** (129 mg, 81%) as a colorless oil in 99% e.e. ^1H NMR (500 MHz, CDCl_3) δ 7.64 (d, $J = 8.1$ Hz, 2H), 7.45 (d, $J = 8.1$ Hz, 2H), 5.99 (d, $J = 48.1$ Hz, 1H), 2.25 – 2.03 (m, 3H), 1.85 – 1.56 (m, 5H), 1.51 (dd, $J = 22.0, 3.6$ Hz, 3H), 1.33 – 1.20 (m, 1H), 1.20 – 1.07 (m, 1H), 1.07 – 0.95 (m, 1H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 144.7 (d, $J = 21.5$ Hz), 129.9 (q, $J = 32.3$ Hz), 125.5 – 125.3 (m), 125.3 (d, $J = 9.6$ Hz), 122.1 (d, $J = 272.1$ Hz), 100.2 (dd, $J = 167.1, 2.0$ Hz), 91.8 (dd, $J = 178.8, 2.0$ Hz), 54.7 (dd, $J = 22.0, 20.0$ Hz), 41.6 (d, $J = 23.2$ Hz), 29.3 (d, $J = 49.5$ Hz), 23.34 (dd, $J = 25.5, 4.4$ Hz), 21.7 (d, $J = 3.2$ Hz), 21.3 (dd, $J = 10.2, 6.7$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -62.5 (s, 3F), -129.3 – -129.7 (m, 1F), -198.7 (ddd, $J = 48.3, 35.9, 3.7$ Hz, 1F); HR-GC/MS (EI^+) Calc'd for $\text{C}_{16}\text{H}_{19}\text{F}_5$ $[\text{M}]^+$: 306.1401; found 306.1399.

99% e.e., chiral GC (β -Cyclosil, 120 $^\circ\text{C}$, 14 psi); $t_{\text{R}}(\text{major}) = 48.8$ min, $t_{\text{R}}(\text{minor}) = 50.2$ min.

Racemic sample:



Enriched sample:



Prepared according to the general procedure using **4h** (220 mg,

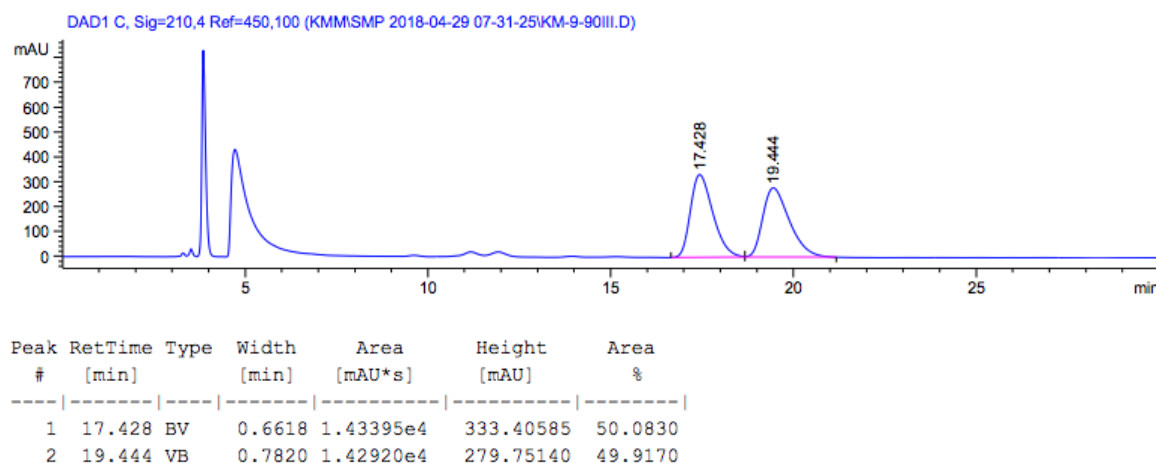
0.52 mmol) with the following modification: 20 equiv of HF was used

instead. The diastereomeric ratio of the crude residue after work-up was

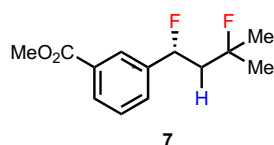
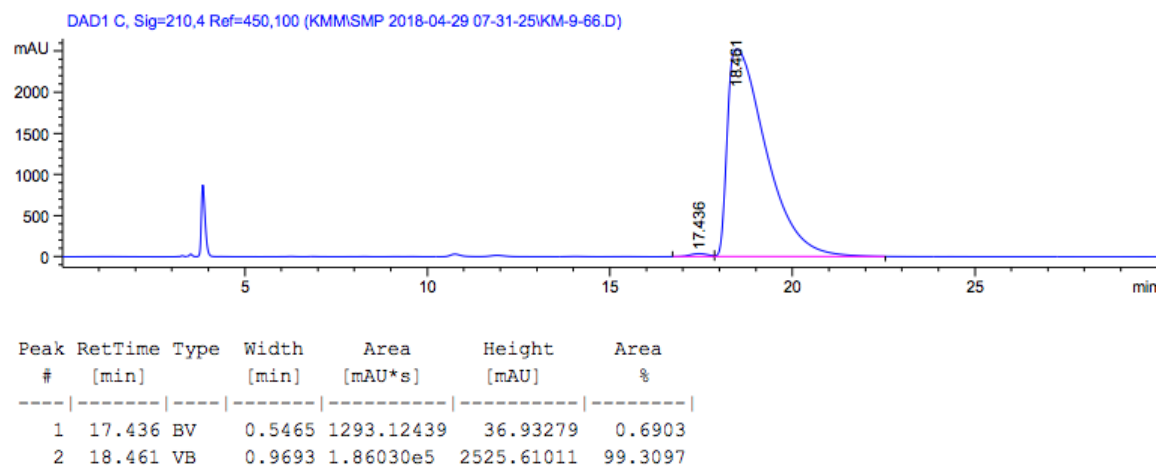
determined to be >20:1 by ^1H and ^{19}F NMR analysis. The crude residue was purified by silica gel column chromatography (0 to 30% diethyl ether in hexanes) to give **5h** (168 mg, 81%) as a white solid in 99% e.e. ^1H NMR (500 MHz, CDCl_3) δ 7.70 – 7.65 (m, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 7.5 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 5.97 (d, J = 48.2 Hz, 1H), 3.76 (dddd, J = 12.1, 9.8, 4.8, 2.2 Hz, 2H), 2.69 – 2.53 (m, 2H), 2.43 (s, 3H), 2.22 – 1.83 (m, 4H), 0.81 (d, J = 7.3 Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 143.8, 143.7 (d), 133.3, 130.0 (q, J = 32.9 Hz), 127.8, 125.4 (d, J = 4.6 Hz), 125.1 (d, J = 9.6 Hz), 124.1 (q, J = 271.8 Hz), 95.2 (d, J = 174.1 Hz), 90.7 (dd, J = 179.3, 7.4 Hz), 48.7 (t, J = 20.3 Hz), 42.2 – 41.8 (m), 33.2 (d, J = 21.2 Hz), 30.5 (dd, J = 21.8, 4.0 Hz), 21.6, 7.0 (t, J = 7.7 Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -62.6 (s, 3F), -160.3 (tq, J = 40.5, 9.4 Hz, 1F), -199.2 (dd, J = 48.2, 33.8 Hz, 1F); HRMS (ESI-TOF) Calc'd for $\text{C}_{22}\text{H}_{24}\text{BrF}_5\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 462.1521; found 462.1520.

99% e.e., chiral HPLC (OD-H, 10% isopropanol in hexanes, 1.0 mL/min, $\lambda = 210$ nm); t_R (major) = 17.4 min, t_R (minor) = 18.5 min.

Racemic sample:



Enriched sample:



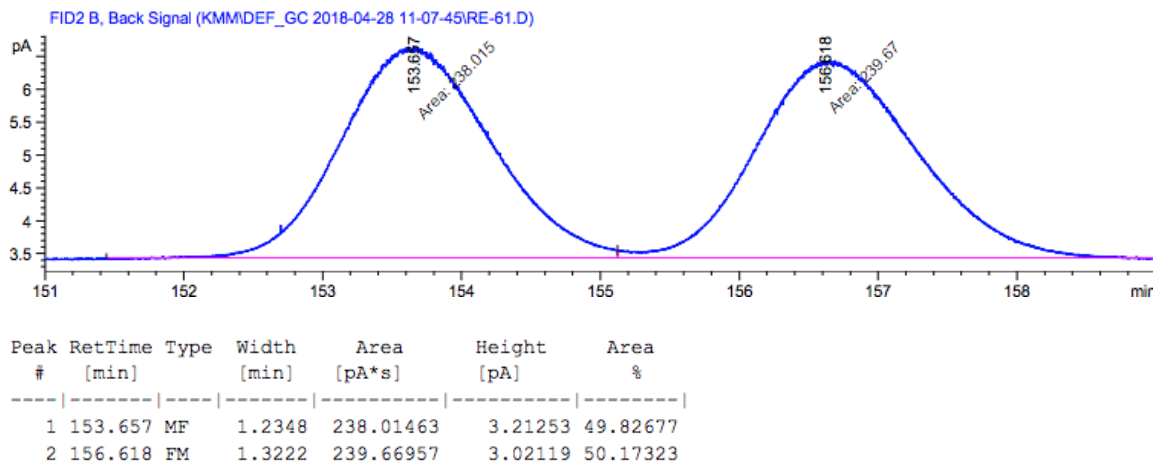
Prepared according to the general procedure using **6** (106 mg, 0.52 mmol) with the following modification: 20 equiv of HF was used instead. The crude residue was purified by silica gel column chromatography (0 to 3%

diethyl ether in hexanes) to give **7** (79.4 mg, 63%) as a colorless oil in 94% e.e. ^1H NMR (500 MHz, CDCl_3) δ 8.04 – 7.98 (m, 2H), 7.55 (ddt, $J = 8.4, 1.9, 0.9$ Hz, 1H), 7.47 (tt, $J = 7.6, 0.9$ Hz,

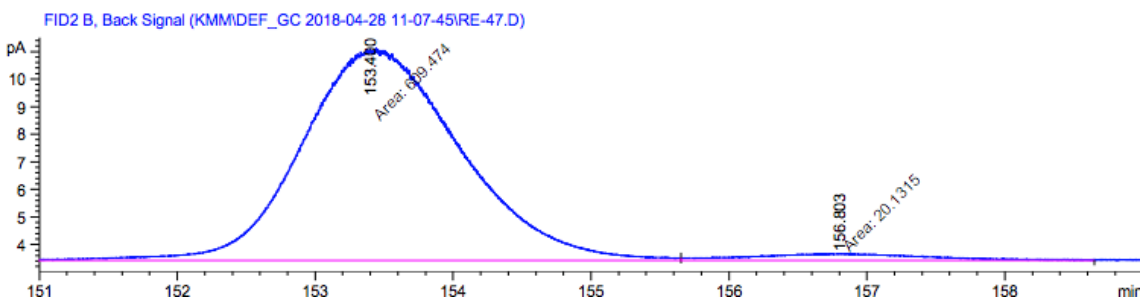
1H), 5.77 (ddd, $J = 48.5, 9.7, 2.1$ Hz, 1H), 3.93 (s, 3H), 2.29 (dddd, $J = 25.4, 18.4, 15.4, 9.7$ Hz, 1H), 2.10 (dddd, $J = 38.1, 15.3, 12.8, 2.1$ Hz, 1H), 1.54 (dd, $J = 21.7, 1.7$ Hz, 3H), 1.45 (d, $J = 21.7$ Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 166.8, 141.1 (d, $J = 20.3$ Hz), 130.7, 130.0 (d, $J = 6.9$ Hz), 129.7 (d, $J = 1.7$ Hz), 128.9, 126.7 (d, $J = 7.1$ Hz), 94.4 (d, $J = 166.6$ Hz), 90.6 (dd, $J = 172.2, 6.0$ Hz), 52.4, 48.8, 28.6 (d, $J = 24.9$ Hz), 26.4 (dd, $J = 24.9, 3.0$ Hz); ^{19}F NMR (470.4 MHz, CDCl_3) δ -136.6 – -137.0 (m, 1F), -173.8 – -174.2 (m, 1F); HRMS (ESI-TOF) Calc'd for $\text{C}_{13}\text{H}_{16}\text{F}_2\text{O}_2$ $[\text{M}+\text{Na}]^+$: 265.1011; found 265.1011.

94% e.e., chiral GC (β -Cyclosil, 100 °C, 14 psi); $t_{\text{R}}(\text{major}) = 153.4$ min, $t_{\text{R}}(\text{minor}) = 156.8$ min.

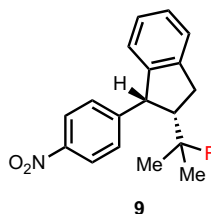
Racemic sample:



Enriched sample:



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	153.400	MF	1.3268	609.47424	7.65578	96.80252
2	156.803	FM	1.4728	20.13149	2.27814e-1	3.19748

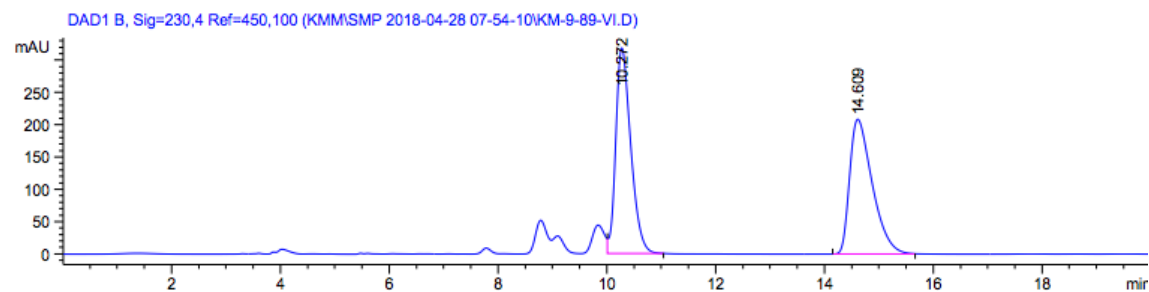


Prepared according to the general procedure using **8** (146 mg, 0.52 mmol) with the following modification: 20 equiv of HF was used instead. The diastereomeric ratio of the crude residue after work-up was determined to be >20:1 by ^1H and ^{19}F NMR analysis. The crude residue was purified by silica

gel column chromatography (0 to 4% diethyl ether in hexanes) to give **9** (149 mg, 96%) as a colorless oil in 94% e.e. Crystals of **9** were grown by slow evaporation of a solution of **9** in Et₂O/pentane. by X. ^1H NMR (500 MHz, CDCl₃) δ 8.18 (d, J = 8.7 Hz, 2H), 7.37 (d, J = 8.7 Hz, 2H), 7.34 – 7.27 (m, 1H), 7.26 – 7.20 (m, 1H), 7.19 – 7.08 (m, 1H), 6.76 (d, J = 7.6 Hz, 1H), 4.57 (d, J = 7.7 Hz, 1H), 3.27 (dd, J = 16.2, 8.9 Hz, 1H), 3.05 (dd, J = 16.2, 8.2 Hz, 1H), 2.95 – 2.76 (m, 1H), 1.39 (d, J = 21.4 Hz, 3H), 1.33 (d, J = 21.5 Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl₃) δ 153.96, 146.66, 145.35, 142.03, 129.41, 127.50, 127.12, 124.97, 124.48, 123.91, 96.79 (d, J = 168.8 Hz), 58.11 (d, J = 21.5 Hz), 52.66 (d, J = 3.7 Hz), 34.11 (d, J = 6.3 Hz), 26.61 (d, J = 24.5 Hz), 24.94 (d, J = 24.5 Hz); ^{19}F NMR (470.4 MHz, CDCl₃) δ -141.4 (septd, J = 21.4, 16.2 Hz); HR-GC/MS (EI⁺) Calc'd for C₁₈H₁₉F₂NO₂ [M]⁺: 319.1378; found 319.1380.

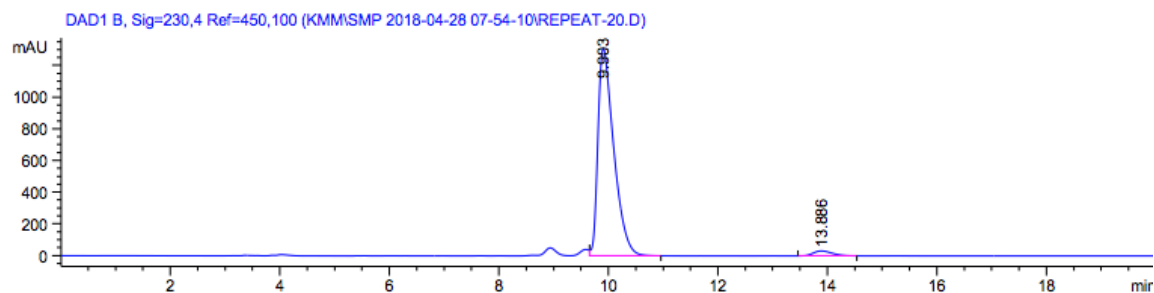
94% e.e., chiral HPLC (OD-H, 2% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm); t_{R} (major) = 10.0 min, t_{R} (minor) = 13.9 min.

Racemic sample:



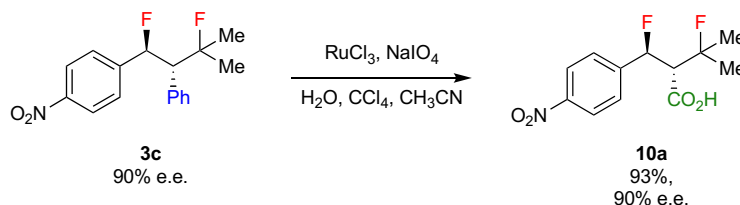
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.272	VB	0.2936	6108.27393	318.73135	50.3399
2	14.609	BB	0.4407	6025.78809	208.80742	49.6601

Enriched sample:

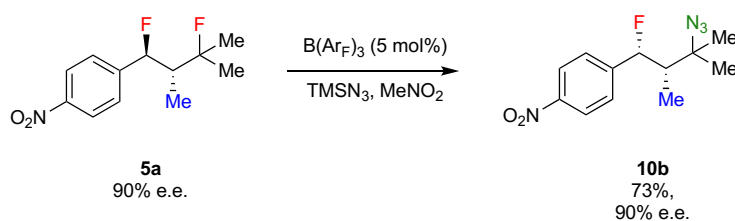


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.903	VB	0.3020	2.62741e4	1310.15796	97.1612
2	13.886	BB	0.3753	767.65558	31.60852	2.8388

Product Elaboration



To a solution of **3c** (76.3 mg, 0.25 mmol, 1.0 equiv) in acetonitrile (0.65 mL) and carbon tetrachloride (0.65 mL) was added water (1.3 mL), sodium periodate (749 mg, 3.49 mmol, 14 equiv) and a catalytic amount of ruthenium(III) chloride hydrate were added. The reaction mixture was allowed to stir at room temperature under air. After 18 h, diethyl ether (10 mL) was added, and the aqueous and organic layers were separated. The aqueous layer was extracted with diethyl ether (3 x 10 mL), washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated to give **10a** as a brown oil (63.5 mg, 93%). ¹H NMR (500 MHz, CDCl₃) δ 8.22 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 5.79 (dd, *J* = 46.7, 10.2 Hz, 1H), 3.27 (td, *J* = 10.0, 7.8 Hz, 1H), 1.76 – 1.54 (m, 6H); ¹³C NMR (125.7 MHz, CDCl₃) δ 174.8 – 172.5 (m), 148.6, 143.6 (d, *J* = 20.4 Hz), 127.9 (d, *J* = 6.2 Hz), 124.0, 95.0 (d, *J* = 174.0 Hz), 90.9 (dd, *J* = 179.9, 7.0 Hz), 61.3 (t, *J* = 24.2 Hz), 28.1 (dd, *J* = 23.9, 4.2 Hz), 25.5 – 23.4 (m); ¹⁹F NMR (470.4 MHz, CDCl₃) δ -133.4 – -133.9 (m, 1F), -179.2 (d, *J* = 46.9 Hz, 1F); HRMS (ESI-TOF) Calc'd for C₁₂H₁₃F₂NO₄ [M-H]⁻: 272.040; found 272.0753.



To a solution of **5a** (45 mg, 0.185 mmol, 1 equiv) and TMSN₃ (49 μL, 0.37 mmol, 2 equiv) in MeNO₂ (0.093 mL, 2M) was added B(C₅F₅)₃ (4.5 mg, 0.009 mmol, 0.05 equiv). The reaction mixture was stirred for 90 minutes, after which the solution was loaded onto silica using hexanes

and purified by column chromatography using 2% to 6% diethyl ether in hexanes to give **10b** (36.0 mg, 73%). ^1H NMR (500 MHz, CDCl_3) δ 8.23 (t, $J = 9.4$ Hz, 2H), 7.46 (t, $J = 9.1$ Hz, 2H), 6.05 (d, $J = 48.4$ Hz, 1H), 1.88 – 1.71 (m, 1H), 1.42 (d, $J = 2.0$ Hz, 3H), 1.40 (s, 3H), 0.85 (dd, $J = 7.2, 1.6$ Hz, 3H). ^{19}F NMR (470.4 MHz, CDCl_3) δ -200.38 (dt, $J = 31.3, 23.8$ Hz, 1F).

Impact of Styrenyl Arene Electronics on Diastereoselectivity

General procedure

Catalyst (8.0 mg, 10.4 μmol , 20.0 mol%), styrene derivative (52.0 μmol , 1.00 equiv) and dichloromethane (0.30 mL) were combined in a polyethylene tube. The reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$. Pyridinium poly(hydrogen fluoride) (pyr•9HF, 70% hydrogen fluoride by weight, 28 μL , 20 equiv hydrogen fluoride) was added *via* micropipette followed by *m*-chloroperbenzoic acid (*m*CPBA, 77% by weight, 12.8 mg, 57.2 μmol , 1.10 equiv). The reaction was warmed to $-30\text{ }^{\circ}\text{C}$ and stirred for 48 hours at that temperature. The reaction was cooled to $-78\text{ }^{\circ}\text{C}$ and basic alumina (approximately 400 mg) was added slowly. The reaction was allowed to warm to room temperature with stirring and was filtered. The crude mixture was analyzed by ^1H NMR using mesitylene as an internal standard to determine the diastereoselectivity.

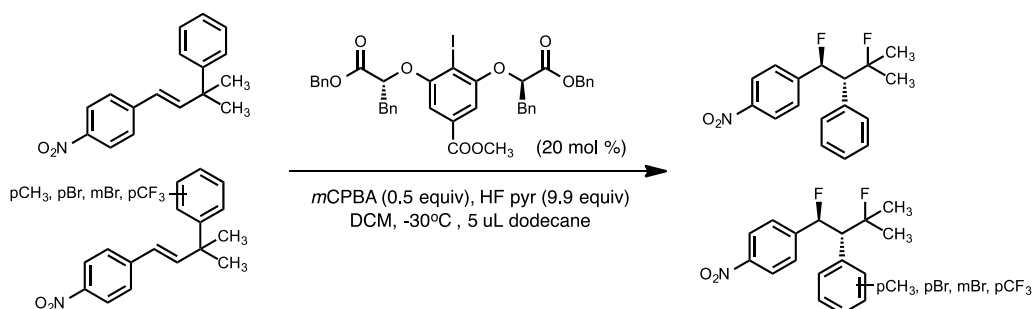
Table S3.1 Effect of styrenyl electronics on d.r. in methyl and aryl rearrangement reactions.

Me shift			
X	sigma+	d.r.	log (d.r.)
<i>p</i> -Br	0.15	10.00	1.00
<i>p</i> -CF ₃	0.61	11.00	1.04
<i>p</i> -NO ₂	0.79	9.00	0.95
<i>m</i> -COOCH ₃	0.37	13.00	1.11
<i>m</i> -CF ₃	0.52	11.00	1.04
<i>m</i> -Br	0.41	11.00	1.04

Ar shift			
X	sigma+	d.r.	log (d.r.)
H	0.00	0.56	-0.26
<i>p</i> -CF ₃	0.61	6.70	0.83
<i>p</i> -NO ₂	0.79	9.80	0.99
<i>m</i> -COOCH ₃	0.37	1.20	0.08

Hammett experiments

To a solution of phenyl-migration-substrate (0.052 mmol, 1 equiv), substituted-aryl-migration-substrate (0.052 mmol, 1 equiv), and (*R,R*)-**1a** (10.4 μ mol, 20 mol%) in dichloromethane (0.3 mL) in a low-density polyethylene tube was added 5 μ L dodecane as an internal standard. This mixture was briefly stirred, and then 10 μ L was removed and diluted with 1 mL of dichloromethane as T_0 for conversion analysis. The mixture was cooled to -78 $^{\circ}$ C, followed by sequential addition of HF-pyridine (py $\cdot$ 9HF, 70% hydrogen fluoride by weight, 140 μ L, 100 equiv hydrogen fluoride) and *m*CPBA (77% by weight, 5 mg, 0.025 mmol, 0.5 equiv). The reaction mixture was warmed to -30 $^{\circ}$ C and stirred at that temperature for 48 hours. The heterogeneous mixture was transferred carefully into a vigorously stirred suspension of basic alumina (1 g) in dichloromethane at -78 $^{\circ}$ C. The resulting suspension was allowed to warm to room temperature and filtered, washing with 10 mL dichloromethane. 2 mL of this solution was removed for GC analysis for the T_f measurement.



Scheme S3.2 Hammett one-pot competition experiment.

All conversions were determined by gas chromatography (achiral GC, 40 to 300 $^{\circ}$ C, ramp = 21 $^{\circ}$ C/min, 14 psi; t_R (Ph) = 7.92 min, t_R (*p*-CH₃Ar) = 7.92 min, t_R (*p*-BrAr) = 8.75 min, t_R (*m*-BrAr) = 8.66 min, t_R (*p*-CF₃Ar) = 7.87 min, t_R (dodecane) = 4.43 min). All samples were acquired with five GC runs, and the integration of relevant peaks was averaged.

Each competition experiment was run in triplicate, and the relative rate was calculated for all three experiments and then averaged. The standard deviation was derived from the spread of values obtained between the three experiments and does not take into account the standard deviation from the measurement itself (the standard deviation between the five GC runs for each experiment), which is negligible. The equation used to determine the relative rate of consumption of the standard phenyl-migration-substrate versus substituted-aryl-migration-substrate was:

$$\frac{k_H}{k_X} = \frac{\ln(1 - F_H)}{\ln((1 - F_H) \left(\frac{R_F}{R_0}\right))}$$

where

$$1 - F = 1 - \text{conversion} = \text{starting material remaining} = \frac{\frac{SM_F}{dod_F}}{\frac{SM_0}{dod_0}}$$

and

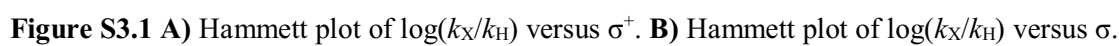
$$\frac{R_F}{R_0} = \frac{\text{ratio of starting material X over starting material H at } T_F}{\text{ratio of starting material X over starting material H at } T_0} = \frac{\frac{[SM_X]_F}{[SM_H]_F}}{\frac{[SM_X]_0}{[SM_H]_0}}$$

and

SM = integral of starting material; *dod* = integral of dodecane internal standard

Table S3.2 Relative Rate Measurements for One-Pot Competition Experiment.

sub.	σ^+	σ	k_X/k_H	$\log(k_X/k_H)$	std. dev.	lower bound	upper bound	log (lower bound)	log (upper bound)
H	0	0	1	0	0	0	0	0	0
<i>p</i> -Br	0.15	0.232	0.103	-0.993	3.63	0.0743	0.161	-1.13	-0.793
<i>m</i> -Br	0.405	0.391	0.0315	-1.50	17.5	0.0203	0.0699	-1.69	-1.15
<i>p</i> -CF ₃	0.612	0.54	0.00721	-2.14	18.3	0.00637	0.00830	-2.19	-2.08
<i>p</i> -Me	0.311	0.170	2.81	0.449	0.218	2.59	3.03	0.413	0.481



Key:	dod = integral of internal standard	pX = integral of substituted aryl migration starting material						
	H = integral of phenyl starting material	F = conversion of starting material = (SMf/dodf)/(Sm0/dod0)						
	kH/kX = relative rate of consumption of H vs X = ln(1-FH)/ln(1-FX)							
	kH/kpBr							
avg	9.8349793							
std dev	1.7289075							
Exp 1	dod	pBr	H		SM left		Relative rates	
To	4486.8	3479.8	4896.6	1 – FH	0.5532032	kH/kpBr	10.8365874	
Tf	8499.25	6241.25	5131.25	1 – FpBr	0.946833			
Exp 2	dod	pBr	H		SM left		Relative rates	
To	2376.75	2210	1911.5	1 – FH	0.4177438	kH/kpBr	11.2658242	
Tf	8596	7397	2888	1 – FpBr	0.9254446			
Exp 3	dod	pBr	H		SM left		Relative rates	
To	6713.75	12380	4711.25	1 – FH	0.8348622	kH/kpBr	7.40252632	
Tf	5349.5	9626.75	3134	1 – FpBr	0.9759128			

	kH/kmBr							
avg	31.793813							
std dev	17.493268							
Exp 1	dod	mBr	H		SM left		Relative rates	
To	1222	1003.25	374.75	1 – FH	0.0526361	kH/kpBr	56.3626788	
Tf	5145	4009	83.05	1 – FmBr	0.9491016			
Exp 2	dod	mBr	H		SM left		Relative rates	
To	3975.25	3980.5	2460	1 – FH	0.441238	kH/kpBr	22.0193206	
Tf	5688.5	5488.25	1553.25	1 – FmBr	0.9635249			
Exp 3	dod	mBr	H		SM left		Relative rates	
To	2031	3609.4	1756.2	1 – FH	0.1330303	kH/kpBr	16.9994407	
Tf	3427.6	5409.8	394.28	1 – FmBr	0.8881084			
	kmBr/kpCF3	kH/kpCF3						
avg	4.36118668	138.65876						
std dev	0.82152552							
Exp 1	dod	pCF3	mBr		SM left		Relative rates	
To	4363.2	3270	981	1 – FmBr	0.7824478	kmBr/kpCF3	3.53966116	
Tf	9161.75	6406.5	1611.75	1 – FpCF3	0.9330389			
Exp 2	dod	pCF3	mBr		SM left		Relative rates	
To	2526.33333	3328	1700.3333	1 – FmBr	0.5505619	kmBr/kpCF3	5.1827122	
Tf	4030.2	4731.6	1493.4	1 – FpCF3	0.8912279			
	kpCH3/kH	kH/kpCH3						
avg	2.81043428	0.3558169						
std dev	0.21817415							
Exp 1	dod	H	pCH3		SM left		Relative rates	
To	5192.66667	8320.3333	6040.3333	1 – FpCH3	0.6685406	kpCH3/kH	2.89955204	
Tf	9391.66667	13097.333	7303.6667	1 – FH	0.870342			
Exp 2	dod	H	pCH3		SM left		Relative rates	
To	1344	1542.6667	1475.3333	1 – FpCH3	0.7641582	kpCH3/kH	3.02169459	
Tf	1425	1496.3333	1195.3333	1 – FH	0.9148306			
Exp 3	dod	H	pCH3		SM left		Relative rates	
To	1676.4	2623.8	1362.8	1 – FpCH3	0.5061742	kpCH3/kH	2.51005621	
Tf	3959.8	4725.2	1629.4	1 – FH	0.7624193			
Summary of rate measurements								
	kH/kpBr	kH/kmBr	kH/kpCF3	kH/kpCH3				
avg	9.83	31.8	139	0.356				
std dev.	1.73	17.5	0.822	0.02				

KIE experiments

Experimental Procedures

Methyl rearrangement reaction

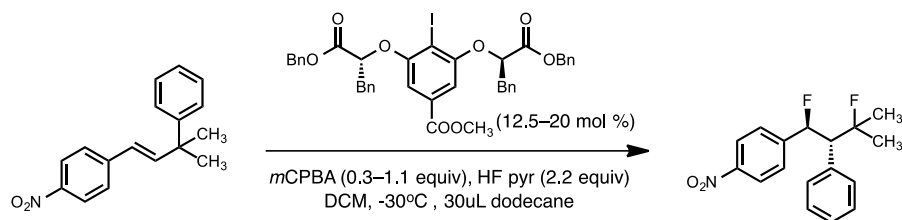
Full conversion:

To a solution of substrate (120mg, 0.58 mmol, 1 equiv) and catalyst (88.0 mg, 0.11 mmol, 20 mol%) in dichloromethane (3.5 mL) in a low-density polyethylene tube at $-78\text{ }^{\circ}\text{C}$ was added HF–pyridine (py•9HF, 70% hydrogen fluoride by weight, 360 μL , 20 equiv hydrogen fluoride) followed by *m*CPBA (77% by weight, 140. mg, 0.63 mmol, 1.1 equiv). The reaction mixture was warmed to $-35\text{ }^{\circ}\text{C}$ and stirred at that temperature for 48 hours. The heterogeneous mixture was transferred carefully into a vigorously stirred suspension of basic alumina (4.0 g) in dichloromethane at $-78\text{ }^{\circ}\text{C}$. The resulting suspension was allowed to warm to room temperature and filtered, washing with 100 mL dichloromethane. The combined filtrate was concentrated under reduced pressure and was purified by silica gel column chromatography (0 to 3.4% diethyl ether in hexanes).

Partial conversion:

To a solution of substrate (330 mg, 1.61 mmol, 1 equiv) and catalyst (154.0 mg, 0.2 mmol, 12.5 mol%) in dichloromethane (11 mL) in a low-density polyethylene tube was added 30 μL dodecane as an internal standard. This mixture was briefly stirred, and then 10 μL was removed as T_0 for conversion analysis. The mixture was cooled to $-78\text{ }^{\circ}\text{C}$, followed by sequential addition of HF–pyridine (py•9HF, 70% hydrogen fluoride by weight, 1.06 mL, 20 equiv hydrogen fluoride) and *m*CPBA (77% by weight, 107 mg, 0.48 mmol, 0.30 equiv). The reaction mixture was warmed to $-30\text{ }^{\circ}\text{C}$ and stirred at that temperature for 48 hours. The heterogeneous mixture

was transferred carefully into a vigorously stirred suspension of basic alumina (10 g) in dichloromethane at $-78\text{ }^{\circ}\text{C}$. The resulting suspension was allowed to warm to room temperature and filtered, washing with 200 mL dichloromethane. 2 mL of this solution was removed for GC analysis for the T_f measurement. The combined filtrate was concentrated under reduced pressure and was purified by silica gel column chromatography (0 to 3.4% diethyl ether in hexanes).



Scheme S3.3 KIE experiments.

Conversion (32.5%, 28.3%) was determined by quantitative gas chromatography spectra (achiral GC, 40 to $300\text{ }^{\circ}\text{C}$, ramp = $21\text{ }^{\circ}\text{C}/\text{min}$, 14 psi; $t_R(\text{starting material}) = 7.92\text{ min}$, $t_R(\text{dodecane}) = 4.43\text{ min}$). All samples were acquired five times, and the integration of relevant peaks was averaged. The equation used to assess conversion was:

$$\text{conversion} = 1 - \frac{\frac{SM_F}{dod_F}}{\frac{SM_0}{dod_0}}$$

Where SM_F = the average integration of the starting material peak at the end of the reaction, SM_0 = the average integration of the starting material peak at the start of the reaction, dod_F = the average integration of the reference peak at the end of the reaction, and dod_0 = the average integration of the reference peak at the start of the reaction.

Phenyl rearrangement reaction

Full conversion:

To a solution of substrate (200mg, 0.75 mmol, 1 equiv) and catalyst (115.0 mg, 0.15 mmol, 20 mol%) in dichloromethane (4.5 mL) in a low-density polyethylene tube at $-78\text{ }^{\circ}\text{C}$ was added HF-pyridine (py•9HF, 70% hydrogen fluoride by weight, 460 μL , 20 equiv hydrogen fluoride) followed by *m*CPBA (77% by weight, 185. mg, 0.82 mmol, 1.1 equiv). The reaction mixture was warmed to $-35\text{ }^{\circ}\text{C}$ and stirred at that temperature for 48 hours. The heterogeneous mixture was transferred carefully into a vigorously stirred suspension of basic alumina (5.0 g) in dichloromethane at $-78\text{ }^{\circ}\text{C}$. The resulting suspension was allowed to warm to room temperature and filtered, washing with 100 mL dichloromethane. The combined filtrate was concentrated under reduced pressure and was purified by silica gel column chromatography (0 to 1.8% diethyl ether in hexanes).

Partial conversion:

To a solution of substrate (600 mg, 2.47 mmol, 1 equiv) and catalyst (230 mg, 0.30 mmol, 12.5 mol%) in dichloromethane (15 mL) in a low-density polyethylene tube was added 100 μL dodecane as an internal standard. This mixture was briefly stirred, and then 15 μL was removed as T_0 for conversion analysis. The mixture was cooled to $-78\text{ }^{\circ}\text{C}$, followed by sequential addition of HF-pyridine (py•9HF, 70% hydrogen fluoride by weight, 1.5mL, 20 equiv hydrogen fluoride) and *m*CPBA (77% by weight, 169 mg, 0.75 mmol, 0.30 equiv). The reaction mixture was warmed to $-30\text{ }^{\circ}\text{C}$ and stirred at that temperature for 48 hours. The heterogeneous mixture was transferred carefully into a vigorously stirred suspension of basic alumina (10 g) in dichloromethane at $-78\text{ }^{\circ}\text{C}$. The resulting suspension was allowed to warm to room temperature

and filtered, washing with 200 mL dichloromethane. 2 mL of this solution was removed for GC analysis for the T_f measurement. The combined filtrate was concentrated under reduced pressure and was purified by silica gel column chromatography (0 to 1.8% diethyl ether in hexanes).

Conversion (26.2%, 23.3%) was determined by quantitative gas chromatography spectra (achiral GC, 40 to 300 °C, ramp = 21 °C/min, 14 psi; t_R (starting material) = 7.92 min, t_R (dodecane) = 4.43 min). All samples were acquired five times, and the integration of relevant peaks was averaged. The equation used to assess conversion is the same as used for analysis of the methyl migration reaction.

NMR Sample Preparation

Methyl rearrangement reaction

4 samples of product were prepared (60 mg of product in 650 μ L of $CDCl_3$ containing 2 mM $Cr(acac)_3$). Two of the samples were full conversion samples ($F = 100\%$) with respect to the starting material and two were partial conversion samples ($F = 32.5\%$ and 28.3%) with respect to the starting material. The samples were prepared in Wilmad 528-PP-9 NMR tubes and subsequently hermetically sealed under air at room temperature.

Phenyl rearrangement reaction

4 samples of product were prepared (120 mg of product in 650 μ L of $CDCl_3$ containing 0.5 mM $Cr(acac)_3$). Two of the samples were full conversion samples ($F = 100\%$) with respect to the starting material and two were partial conversion samples ($F = 26.2\%$ and 23.3%) with respect to

the starting material. The samples were prepared in Wilmad 528-PP-9 NMR tubes and subsequently hermetically sealed under air at room temperature.

Processing Procedure

NMR data were processed using Python and the nmrglue package (www.nmrglue.com). NMR data were collected in blocks of 32 scans in a single experiment using the array command (e.g., `array('nt',6,32,0)` would set up 6 blocks of 32 scans). Each FID was zero-filled to four times the number of complex points, apodized with a line broadening of 0.25 Hz, and Fourier transformed. For each set of FIDs, one spectrum was manually referenced and phased. Regions of integration were defined for each peak for each spectra, as detailed below. The regions were then centered individually on each peak. A first order baseline correction was calculated by fitting a linear function to the non-signal regions and then subtracting it from the entire spectrum. In the case of the ^{19}F spectra, a second-order baseline correction was applied. Signal to noise ratios were calculated for each peak by dividing the signal intensity at half height by the rootmean-square deviation of the signal in a noisy region. Integrals were simply calculated by summing the signal intensities over the peak regions. After the integrals were obtained, KIEs and their associated errors were calculated using an Excel document (in the provided archive file).

Methyl rearrangement integration regions

For the SQUASH-H spectra, regions of integration were defined with widths of 0.120 ppm for the homobenzylic CH. For the SQUASH-F spectra, the region of integration was defined with width 0.090 and 0.120 ppm for the downfield and upfield satellites, respectively, for the allylic C–F. For the ^1H spectra, the region of integration was defined with a width of 0.100 ppm for the

benzylic C–H. For the DEPT spectra, the region of integration was defined with a width of 0.120 ppm for all CH₃ groups. The downfield member of the aryl proton doublet was chosen as the reference peak for the SQUASH-F measurement, and all other peaks were referenced to themselves.

Phenyl rearrangement integration regions

For the SQUASH-F spectra, the region of integration was defined with width 0.100 and 0.175 ppm for the downfield and upfield satellites, respectively. For the ¹⁹F spectra, the region of integration was defined with width 0.900 for the allylic C–F. The downfield member of the aryl proton doublet was chosen as the reference peak for the SQUASH-F measurement, and all other peaks were referenced to themselves.

Calculation of KIEs and Error Bars

For both the aryl and alkyl migration reaction analyses, the KIE was calculated according to:

$$\frac{\log(1 - F)}{\log\left(1 - F \frac{R}{R_0}\right)}$$

where F is the fractional conversion, R is the ¹³C/¹²C ratio in the product, R₀ is the ratio in the starting material, and log refers to the natural logarithm. R₀ is experimentally determined by taking the reaction to 100% conversion and quantitating product because this minimizes errors caused by deviations in response factors. The propagated error in this formula was calculated in Mathematica (using <https://github.com/FlashTek/mathematica-error-propagation>):

$$\sqrt{\frac{(F-1)^2 F^2 R^2 \log^2(1-F) \sigma_{R_0}^2 + (F-1)^2 F^2 R_0^2 \log^2(1-F) \sigma_R^2 + R_0^2 \sigma_F^2 \left((F-1) R \log(1-F) + (R_0 - F R) \log\left(1 - \frac{FR}{R_0}\right) \right)^2}{(F-1)^2 R_0^2 (R_0 - FR)^2 \log^4\left(1 - \frac{FR}{R_0}\right)}}$$

Table S3.4 KIE data for methyl rearrangement reaction.

	relative to itself		relative to itself		relative to itself		relative to aryl	
	benzyle (SQUASH-F)		homobenzyle (SQUASH-H)		sum of methyls (DEPT)		allylic position (SQUASH F)	
INTEGRALS	C12	C13	C12	C13	C12	C13	C12	C13
full A block1	8.7376	9.8426	8.9419	8.8373	85.1412	79.0407	36.3243	10.0455
full B block1	10.2342	11.4098	10.3226	10.3234	94.7573	91.8431	41.497	11.6719
partial A block1	9.0387	10.0394	9.1533	8.9816	85.4997	81.3595	36.7742	10.3004
partial B block1	9.226	10.2742	9.3376	9.2158	87.5041	82.5578	37.6125	10.4789
full A block2	8.565	9.5915	8.6936	8.6297	83.198	78.7504	35.4966	8.7185
full B block2	9.9728	11.1131	9.9907	10.0686	92.0642	90.4279	40.2976	9.9444
partial A block2	8.8475	9.8111	8.8937	8.8177	83.36	81.2239	35.848	8.8617
partial B block2	9.0744	10.0899	9.1068	9.0664	85.6611	82.6506	36.7792	9.0377
full A block3	8.6003	9.6358	8.7186	8.6676	83.5618	78.6076	35.6372	8.7646
full B block3	10.0246	11.1345	10.0246	10.1093	92.1989	90.7197	40.3648	10.026
partial A block3	8.8587	9.8242	8.903	8.8358	83.4884	80.9965	35.8727	8.8777
partial B block3	9.0645	10.0894	9.0885	9.0646	85.5959	82.5309	36.7482	9.0463
block 1	8	10	8	10	8	36	8	10
blocks 2-3	16	10	16	10	16	36	16	16

FRACTIONATION	R = C13/C12	deltaR^2	R = C13/C12	deltaR^2	R = C13/C12	deltaR^2	R = C13/C12	deltaR^2
full A block1	1.1265	3.00E-06	0.9883	8.80E-06	0.9283	1.45E-05	0.2766	1.15E-06
full A block2	1.1198	1.97E-06	0.9926	1.33E-06	0.9465	3.36E-06	0.2456	5.13E-07
full A block3	1.1204	1.28E-06	0.9942	3.15E-06	0.9407	3.67E-06	0.2459	2.32E-07
full B block1	1.1149	1.56E-06	1.0001	2.84E-06	0.9692	1.14E-05	0.2813	5.46E-07
full B block2	1.1143	1.50E-06	1.0078	1.74E-06	0.9822	2.85E-06	0.2468	2.41E-07
full B block3	1.1107	1.23E-06	1.0084	1.77E-06	0.9840	3.32E-06	0.2484	2.90E-07
partial A block1	1.1107	1.40E-06	0.9812	3.34E-06	0.9516	1.22E-05	0.2801	1.04E-06
partial A block2	1.1089	1.06E-06	0.9915	1.90E-06	0.9744	3.41E-06	0.2472	2.76E-07
partial A block3	1.1090	2.19E-06	0.9925	1.29E-06	0.9702	2.99E-06	0.2475	3.01E-07
partial B block1	1.1136	1.70E-06	0.9870	3.95E-06	0.9435	1.40E-05	0.2786	1.95E-06
partial B block2	1.1119	1.14E-06	0.9956	1.43E-06	0.9649	3.86E-06	0.2457	4.53E-07
partial B block3	1.1131	1.55E-06	0.9974	2.94E-06	0.9642	3.10E-06	0.2462	2.82E-07
	R/R0	delta(R/R0)^2	R/R0	delta(R/R0)^2	R/R0	delta(R/R0)^2	R/R0	delta(R/R0)^2
partial A block1	0.9911	2.00E-06	0.9870	6.25E-06	1.0029	2.08E-05	1.0043	1.89E-05
partial B block1	0.9937	2.25E-06	0.9927	6.90E-06	0.9944	2.26E-05	0.9989	3.05E-05
partial A block2	0.9927	1.53E-06	0.9912	2.65E-06	1.0104	5.37E-06	1.0041	7.70E-06
partial B block2	0.9954	1.60E-06	0.9953	2.19E-06	1.0005	5.82E-06	0.9981	1.06E-05
partial A block3	0.9941	1.41E-06	0.9912	2.63E-06	1.0081	6.13E-06	1.0013	9.66E-06
partial B block3	0.9978	1.74E-06	0.9961	4.15E-06	1.0019	5.24E-06	0.9960	6.73E-06
partial A block avg	0.9926	5.49E-07	0.9898	1.28E-06	1.0071	3.59E-06	1.0032	4.03E-06
partial B block avg	0.9956	6.22E-07	0.9947	1.47E-06	0.9989	3.75E-06	0.9977	5.31E-06

	block 1	blocks 2-3		sample	conversion	error		
DEPT	36	36		P1	0.325	0.005		
SQUASH H	10	10		P2	0.283	0.003		
SQUASH F	10	16						
1H	8	16						
error bar interval	0.68							
	benzyllic (SQUASH-F)		homobenzylic (SQUASH-H)		sum of methyhs (DEPT)		allylic position (SQUASH F)	
standard dev	C12	C13	C12	C13	C12	C13	C12	C13
full A block1	0.0087	0.0394	0.0284	0.0653	0.0750	0.9073	0.0210	0.1043
full B block1	0.0103	0.0323	0.0223	0.0409	0.0602	0.8937	0.0213	0.0822
partial A block1	0.0098	0.0293	0.0123	0.0485	0.0743	0.9281	0.0306	0.097
partial B block1	0.0069	0.0314	0.0262	0.0424	0.0537	0.9156	0.0136	0.141
full A block2	0.0073	0.0358	0.0177	0.027	0.0526	0.9045	0.0205	0.099
full B block2	0.013	0.0351	0.0177	0.0374	0.0706	0.9194	0.0342	0.0767
partial A block2	0.0084	0.0265	0.0167	0.0347	0.0584	0.9117	0.0252	0.0732
partial B block2	0.0118	0.0274	0.021	0.0287	0.0689	0.9962	0.0277	0.0962
full A block3	0.0084	0.0285	0.0201	0.0441	0.0569	0.9486	0.0212	0.0667
full B block3	0.0119	0.032	0.0176	0.0379	0.0664	0.9938	0.0271	0.0845
partial A block3	0.0095	0.0388	0.0191	0.0268	0.0714	0.8522	0.0293	0.0763
partial B block3	0.0118	0.0325	0.0181	0.045	0.0519	0.8941	0.0245	0.0758
68% ERR	C12	C13	C12	C13	C12	C13	C12	C13
full A block1	0.0033	0.0147	0.0107	0.0243	0.0284	0.3236	0.0079	0.0388
full B block1	0.0039	0.0120	0.0084	0.0152	0.0228	0.3187	0.0081	0.0306
partial A block1	0.0037	0.0109	0.0047	0.0180	0.0281	0.3310	0.0116	0.0361
partial B block1	0.0026	0.0117	0.0099	0.0158	0.0203	0.3266	0.0052	0.0525
full A block2	0.0019	0.0118	0.0045	0.0089	0.0135	0.1520	0.0053	0.0254
full B block2	0.0033	0.0116	0.0045	0.0124	0.0181	0.1545	0.0088	0.0197
partial A block2	0.0022	0.0088	0.0043	0.0115	0.0150	0.1532	0.0065	0.0188
partial B block2	0.0030	0.0091	0.0054	0.0095	0.0177	0.1674	0.0071	0.0247
full A block3	0.0022	0.0094	0.0052	0.0146	0.0146	0.1594	0.0054	0.0171
full B block3	0.0031	0.0106	0.0045	0.0125	0.0170	0.1670	0.0070	0.0217
partial A block3	0.0024	0.0128	0.0049	0.0089	0.0183	0.1432	0.0075	0.0196
partial B block3	0.0030	0.0108	0.0046	0.0149	0.0133	0.1503	0.0063	0.0194

	benzyllic (SQUASH-F)		homobenzylic (SQUASH-H)		
KIE	KIE	error	KIE	error	
partial A	1.009	0.001	1.013	0.001	$\ln(1-F) / \ln(1 - F R/R0)$
partial B	1.005	0.001	1.006	0.001	$\sqrt{\ln(A/B - 1/C)^2 * \Delta F^2 + D/E}$
average	1.007		1.009		
ERROR CALC	sample 1	sample 2	sample 1	sample 2	
F	0.325	0.283	0.325	0.283	
1-F	0.675	0.717	0.675	0.717	
ΔF^2	2.50E-05	9.00E-06	2.50E-05	9.00E-06	
R/R0	0.9926	0.9956	0.9898	0.9947	
$\Delta(R/R0)^2$	5.49E-07	6.22E-07	1.28E-06	1.47E-06	
A	-3.90E-01	-3.31E-01	-3.89E-01	-3.31E-01	$R/R0 * \ln(1-F)$
w1	6.77E-01	7.18E-01	6.78E-01	7.18E-01	$w1 = 1-F * R/R0$
w2	-3.90E-01	-3.31E-01	-3.88E-01	-3.31E-01	$w2 = \ln(w1)$
B	1.03E-01	7.87E-02	1.02E-01	7.85E-02	$w1 * w2^2$
C	-2.63E-01	-2.37E-01	-2.62E-01	-2.37E-01	$(1-F) * w2$
D	8.95E-09	5.51E-09	2.09E-08	1.30E-08	$F^2 * \ln(1-F)^2 * \Delta(R/R0)^2$
E	1.06E-02	6.19E-03	1.04E-02	6.17E-03	$w1^2 * w2^4$
$(A/B - 1/C)^2 * \Delta F^2$	1.28E-09	1.33E-10	2.48E-09	1.93E-10	conversion-related error
D/E	8.48E-07	8.90E-07	2.00E-06	2.12E-06	fractionation-related error

	sum of methyls (DEPT)		allylic position (SQUASH F)		
KIE	KIE	error	KIE	error	
partial A	0.991	0.002	0.996	0.002	$\ln(1-F) / \ln(1 - F R/R0)$
partial B	1.001	0.002	1.003	0.003	$\text{sqrt}((A/B - 1/C)^2 * \text{delta}F^2 + D/E)$
average	0.996		0.999		
ERROR CALC	sample 1	sample 2	sample 1	sample 2	
F	0.325	0.283	0.325	0.283	
1-F	0.675	0.717	0.675	0.717	
deltaF^2	2.50E-05	9.00E-06	2.50E-05	9.00E-06	
R/R0	1.0071	0.9989	1.0032	0.9977	
delta(R/R0)^2	3.59E-06	3.75E-06	4.03E-06	5.31E-06	
A	-3.96E-01	-3.32E-01	-3.94E-01	-3.32E-01	$R/R0 * \ln(1-F)$
w1	6.73E-01	7.17E-01	6.74E-01	7.18E-01	$w1 = 1 - F * R/R0$
w2	-3.96E-01	-3.32E-01	-3.95E-01	-3.32E-01	$w2 = \ln(w1)$
B	1.06E-01	7.92E-02	1.05E-01	7.90E-02	$w1 * w2^2$
C	-2.68E-01	-2.38E-01	-2.66E-01	-2.38E-01	$(1-F) * w2$
D	5.86E-08	3.32E-08	6.57E-08	4.70E-08	$F^2 * \ln(1-F)^2 * \text{delta}(R/R0)^2$
E	1.12E-02	6.27E-03	1.10E-02	6.24E-03	$w1^2 * w2^4$
(A/B - 1/C)^2 * deltaF^2	1.18E-09	7.78E-12	2.39E-10	3.77E-11	conversion-related error
D/E	5.24E-06	5.29E-06	5.97E-06	7.54E-06	fractionation-related error

Table S3.5 KIE data for phenyl migration reaction.

sample A conversion	0.26		
sample B conversion	0.23		
est. error(conversion)	0.01		
	19F	MQF	
INTEGRALS	12C	13C	
full_A	9.5431	11.2598	
full_B	9.1369	10.7235	
partial_A	8.2175	9.601	
partial_B	8.441	9.8879	
AVERAGES	12C	13C	
partial A	8.2175	9.6010	
partial B	8.4410	9.8879	
full	9.3400	10.9917	
FRACTIONATION	R	R0	R/R0
sample A	1.1684	1.1768	0.9928
sample B	1.1714	1.1768	0.9954

	19F	MQF			
line broadening					
baseline order					
blocks	8	12			
transients/block	8	32			
STDEV	12C	13C	68% ERR	12C	13C
full_A	0.0057	0.1328	full_A	0.002156901	0.039926468
full_B	0.0073	0.1088	full_B	0.002762347	0.032710841
partial_A	0.0081	0.1209	partial_A	0.00306507	0.03634872
partial_B	0.0051	0.1633	partial_B	0.001929859	0.049096327
covs	0.06%	1.18%	AVG 68% ERR	12C	13C
	0.08%	1.01%	partial A	0.0031	0.0363
	0.10%	1.26%	partial B	0.0019	0.0491
	0.06%	1.65%	full	0.0025	0.0365

KIE	KIE	std err	
sample A	1.008	0.006	$\ln(1-F) / \ln(1 - F R/R_0)$
sample B	1.005	0.007	$\sqrt{(A/B - 1/C)^2 \cdot \Delta F^2 + D/E}$
average	1.007		
ERROR CALC			
	sample A	sample B	
R/R0	9.93E-01	9.95E-01	
$(\Delta R/R)^2$	1.45E-05	2.47E-05	$(\text{stderr}(\text{integral1})/\text{integral1})^2 + (\text{stderr}(\text{integral2})/\text{integral2})^2$
$(\Delta R_0/R_0)^2$	1.11E-05	1.11E-05	
$\Delta(R/R_0)^2$	2.56E-05	3.58E-05	$(\Delta R/R)^2 + (\Delta R_0/R_0)^2$
A	-2.99E-01	-3.00E-01	$R/R_0 \cdot \ln(1-F)$
w1	7.42E-01	7.41E-01	$w1 = 1-F \cdot R/R_0$
w2	-2.99E-01	-2.99E-01	$w2 = \ln(w1)$
B	6.61E-02	6.65E-02	$w1 \cdot w2^2$
C	-2.21E-01	-2.22E-01	$(1-F) \cdot w2$
D	1.57E-07	2.19E-07	$F^2 \cdot \ln(1-F)^2 \cdot \Delta(R/R_0)^2$
E	4.37E-03	4.42E-03	$w1^2 \cdot w2^4$
$(A/B - 1/C)^2 \cdot \Delta F^2$	3.60E-09	1.47E-09	conversion-related error
D/E	3.58E-05	4.96E-05	fractionation-related error

Computations

a. General Procedures

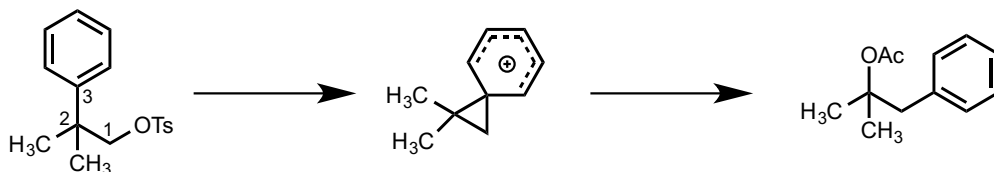
DFT calculations were carried out using Gaussian 16, Revision A.03:

M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016. All stationary points were verified to be true local minima or saddle points by frequency analysis. Where possible, transition states were verified by intrinsic reaction coordinate, growing string, or quasiclassical trajectory analysis.

All stationary points were verified to be true local minima or saddle points by frequency analysis. Where possible, transition states were verified by intrinsic reaction coordinate, growing string, or quasiclassical trajectory analysis.

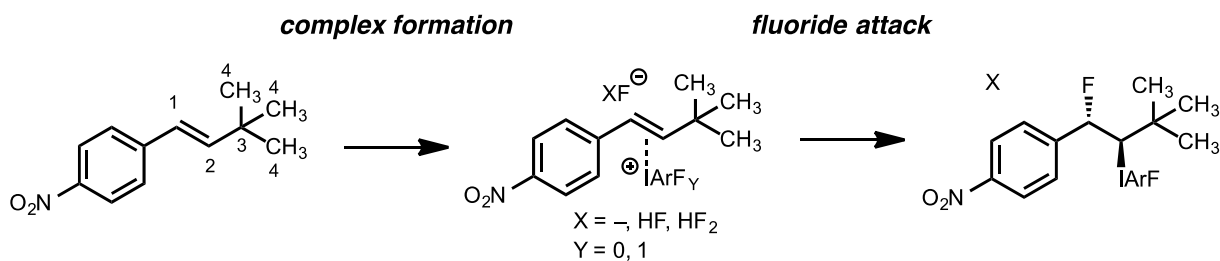
KIEs were calculated using PyQuiver, which is freely available at:

b. Neophyl Tosylate Rearrangement: Summary of Calculations



	1 (C12/C14)	1 (C12/C13)	2 (C12/C13)	3 (C12/C14)	3 (C12/C13)
Experimental	1.093	N/A	N/A	1.023	N/A
Predicted (AcOH activation)	1.092	1.048	1.008	1.044	1.023
Predicted (no activation)	1.083	1.043	1.010	1.051	1.027

c. Pi-complexation vs Fluoride Attack: Summary of Calculations

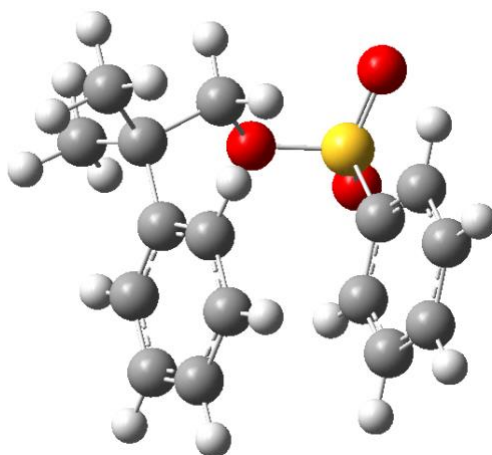


	1	2	3	4
Complex formation	1.002	1.002	1.000	1.000
Fluoride attack (X = -, Y = 0) (TS1)	1.009	1.022	1.003	1.000
Fluoride attack (X = (HF) ₂ , Y = 0) (TS2)	1.020	1.022	1.003	0.999
Fluoride attack (X = -, Y = 1)	1.031	1.018	1.004	1.002

(TS3)				
Fluoride attack (X = (HF), Y =1) (TS4)	1.011	1.022	1.004	1.002

d. Coordinates and Energies

Neophyl phenylate



B3LYP-D3(BJ)/6-31+G(d)/PCM(water)

Charge = 0

Multiplicity = 1

Imaginary Frequencies: 0

Electronic energy: -1244.44169712

Zero-point correction= 0.311065 (Hartree/Particle)

Thermal correction to Energy= 0.329393

Thermal correction to Enthalpy= 0.330338

Thermal correction to Gibbs Free Energy= 0.264122

Sum of electronic and zero-point Energies= -1244.130632

Sum of electronic and thermal Energies= -1244.112304

Sum of electronic and thermal Enthalpies= -1244.111360

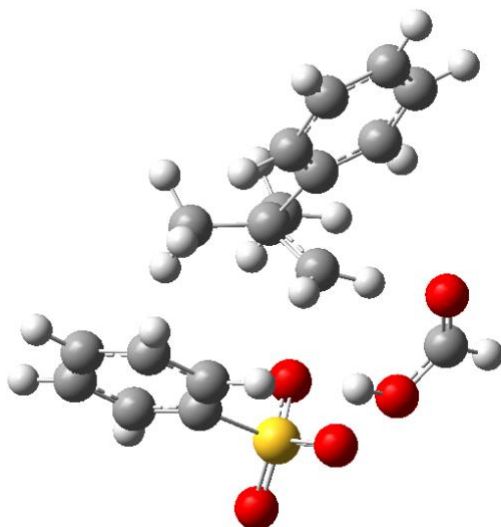
Sum of electronic and thermal Free Energies= -1244.177575

Standard orientation

1 C 0	2.22086900	-0.98807700	0.45885500
2 C 0	3.00703700	-1.73933400	-0.62843500
3 H 0	3.95961900	-1.24034200	-0.83231600
4 H 0	3.22523400	-2.75700300	-0.28766700
5 H 0	2.44621900	-1.81200500	-1.56344800
6 C 0	3.04598900	-1.02345700	1.76446100
7 H 0	2.51558500	-0.56521000	2.60406600
8 H 0	3.28400900	-2.05698200	2.03885300
9 H 0	3.98652200	-0.48204900	1.62294900
10 C 0	0.90866500	-1.73401000	0.73443700
11 H 0	1.09130700	-2.75627800	1.07517800
12 H 0	0.31201700	-1.21088000	1.48545900
13 O 0	0.16179700	-1.81455700	-0.51648500
14 16 0	-1.45988300	-1.81315000	-0.42668200
15 O 0	-1.88229000	-2.11764100	-1.79256900
16 O 0	-1.88316200	-2.66861900	0.68524900
17 C 0	-1.84815200	-0.12322200	-0.04172800
18 C 0	-2.29424400	0.20051900	1.23983300

19 C 0	-1.68889300	0.84293600	-1.03841000
20 C 0	-2.59525100	1.53258200	1.52531000
21 H 0	-2.41226500	-0.57555200	1.98692800
22 C 0	-1.99555200	2.16588600	-0.73770500
23 H 0	-1.33284100	0.56345200	-2.02323500
24 C 0	-2.44885500	2.50899100	0.53940900
25 H 0	-2.94635400	1.80318400	2.51586200
26 H 0	-1.87180200	2.93107000	-1.49635300
27 H 0	-2.68343200	3.54426300	0.76671000
28 C 0	1.89948500	0.46243000	0.07175600
29 C 0	2.16804800	0.97570900	-1.20234900
30 C 0	1.30627800	1.32143100	1.01120600
31 C 0	1.87229600	2.30365200	-1.52357300
32 H 0	2.61708900	0.34467200	-1.96032300
33 C 0	1.01313800	2.64597700	0.69745700
34 H 0	1.06391800	0.95712600	2.00490800
35 C 0	1.29912200	3.14672500	-0.57413900
36 H 0	2.09447700	2.67445400	-2.52047000
37 H 0	0.54991600	3.28388700	1.44408700
38 H 0	1.06827100	4.17871600	-0.82214600

Neophyl phenylate TS (AcOH activation)



B3LYP-D3(BJ)/6-31+G(d)/PCM(water)

Charge = 0

Multiplicity = 1

Imaginary Frequencies: 1

Electronic energy: -1434.17494755

Zero-point correction= 0.342738 (Hartree/Particle)

Thermal correction to Energy= 0.366255

Thermal correction to Enthalpy= 0.367199

Thermal correction to Gibbs Free Energy= 0.285697

Sum of electronic and zero-point Energies= -1433.832209

Sum of electronic and thermal Energies= -1433.808692

Sum of electronic and thermal Enthalpies= -1433.807748

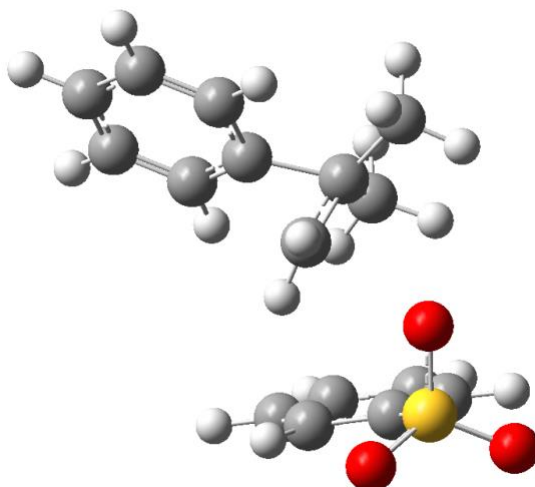
Sum of electronic and thermal Free Energies= -1433.889250

Standard orientation

1 C 0	1.16607200	-0.32363200	1.17173200
2 C 0	0.31040900	-1.45607500	1.72348700
3 H 0	0.87503500	-2.04969400	2.44793900
4 H 0	-0.54933200	-1.00971800	2.22904300
5 H 0	-0.08503300	-2.11350200	0.94786200
6 C 0	1.52893100	0.70649700	2.23426700
7 H 0	2.04472200	1.57465100	1.82390100
8 H 0	0.59584700	1.06312900	2.68006100
9 H 0	2.14249900	0.25327100	3.01775600
10 C 0	0.87071100	0.16293900	-0.14335600
11 H 0	1.21652500	1.13881000	-0.46145900
12 H 0	0.31444500	-0.44194300	-0.84712900
13 O 0	-1.09093500	1.45391000	0.31969200
14 16 0	-2.22531200	1.12661500	-0.65088400
15 O 0	-3.45306800	1.88438500	-0.31836300
16 O 0	-1.77798500	1.20639500	-2.06112200
17 C 0	-2.55417300	-0.60148700	-0.30392600
18 C 0	-2.13451200	-1.58090300	-1.20389000
19 C 0	-3.17074600	-0.94715200	0.90073100
20 C 0	-2.31793900	-2.92807200	-0.88355200
21 H 0	-1.67631700	-1.28542400	-2.14131300
22 C 0	-3.35242800	-2.29330200	1.21215400

23 H 0	-3.50075000	-0.17111300	1.58333500
24 C 0	-2.92067700	-3.28377900	0.32440300
25 H 0	-1.99179000	-3.69607200	-1.57824600
26 H 0	-3.82831000	-2.57078900	2.14774600
27 H 0	-3.05978800	-4.33148900	0.57310900
28 C 0	2.39746200	-0.80470600	0.26775400
29 C 0	2.40699500	-2.10850900	-0.28347100
30 C 0	3.54788200	0.00848200	0.12739200
31 C 0	3.54775800	-2.59755400	-0.90162300
32 H 0	1.52708300	-2.73567100	-0.21478400
33 C 0	4.68365100	-0.48912300	-0.49436700
34 H 0	3.54093100	1.02694500	0.49432900
35 C 0	4.68740700	-1.79203400	-1.00233700
36 H 0	3.55184900	-3.60262600	-1.30927300
37 H 0	5.56368900	0.13742100	-0.59106700
38 H 0	5.57795400	-2.17801700	-1.48842400
39 C 0	1.13396500	4.02872100	0.03522100
40 H 0	1.46368000	5.07599900	0.09379600
41 O 0	1.89010500	3.11962500	-0.26817200
42 O 0	-0.14742600	3.92578600	0.33280900
43 H 0	-0.46808200	2.96733500	0.28449500

Neophyl phenylate TS (no activation)



B3LYP-D3(BJ)/6-31+G(d)/PCM(water)

Charge = 0

Multiplicity = 1

Imaginary Frequencies: 1

Electronic energy: -1244.38277793

Zero-point correction= 0.307383 (Hartree/Particle)

Thermal correction to Energy= 0.326497

Thermal correction to Enthalpy= 0.327442

Thermal correction to Gibbs Free Energy= 0.257948

Sum of electronic and zero-point Energies= -1244.075395

Sum of electronic and thermal Energies= -1244.056280

Sum of electronic and thermal Enthalpies= -1244.055336

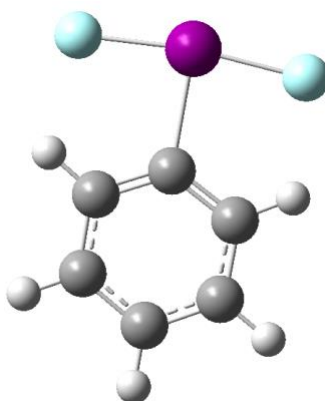
Sum of electronic and thermal Free Energies= -1244.124830

Standard orientation

1 C 0	-1.26176700	-0.72581300	1.08583700
2 C 0	-0.56780500	0.39689900	1.84007600
3 H 0	-1.21321600	0.78503300	2.63274100
4 H 0	0.33482100	-0.02141900	2.29230000
5 H 0	-0.24870900	1.21738300	1.19760400
6 C 0	-1.54644600	-1.93650800	1.95988600
7 H 0	-1.96319900	-2.77881800	1.40535200
8 H 0	-0.59092900	-2.26493900	2.37913900
9 H 0	-2.22061700	-1.67633300	2.78026100
10 C 0	-0.91830800	-0.95165400	-0.28044400
11 H 0	-1.10661700	-1.90316400	-0.75848900
12 H 0	-0.39874100	-0.20129100	-0.85862500
13 O 0	1.31183700	-1.92967100	0.06185300
14 16 0	2.51129500	-1.29348300	-0.58861800
15 O 0	3.78567500	-1.71199700	0.05343100
16 O 0	2.49491000	-1.41638500	-2.07087100
17 C 0	2.33940800	0.46396400	-0.24320200
18 C 0	1.67755800	1.28835400	-1.15582100
19 C 0	2.78806900	0.97341600	0.97675500
20 C 0	1.43946900	2.62593200	-0.83247800
21 H 0	1.36618200	0.88349000	-2.11310500
22 C 0	2.55529300	2.31200700	1.29216100
23 H 0	3.31554800	0.32336800	1.66655500

24 C 0	1.87266700	3.13681900	0.39365300
25 H 0	0.92295200	3.26822400	-1.53957800
26 H 0	2.90301500	2.71113100	2.24040000
27 H 0	1.68705100	4.17684700	0.64457000
28 C 0	-2.51046800	-0.24049900	0.17155800
29 C 0	-2.62198400	1.12152800	-0.20573400
30 C 0	-3.61023200	-1.10558200	-0.05019700
31 C 0	-3.80322900	1.60311200	-0.74633400
32 H 0	-1.78317900	1.79358100	-0.07451300
33 C 0	-4.78838400	-0.61433300	-0.59000800
34 H 0	-3.53996300	-2.15478000	0.20711700
35 C 0	-4.88736700	0.73836300	-0.93367700
36 H 0	-3.88265900	2.64766300	-1.02656500
37 H 0	-5.62911400	-1.28083000	-0.74781300
38 H 0	-5.81157600	1.11898800	-1.35695900

PhIF₂



B3LYP-D3(BJ)/6-31+G(d)+SDD(I) LANL2DZ/PCM(water)

Charge = 0

Multiplicity = 1

Imaginary Frequencies: 0

Electronic energy: -442.63453221

Zero-point correction= 0.094439 (Hartree/Particle)

Thermal correction to Energy= 0.103191

Thermal correction to Enthalpy= 0.104135

Thermal correction to Gibbs Free Energy= 0.058883

Sum of electronic and zero-point Energies= -442.540093

Sum of electronic and thermal Energies= -442.531341

Sum of electronic and thermal Enthalpies= -442.530397

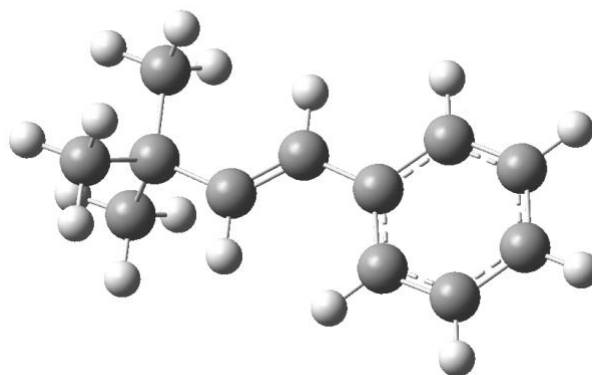
Sum of electronic and thermal Free Energies= -442.575649

Standard orientation

1 C 0	2.87854200	-1.21006200	0.00032200
2 C 0	1.48041000	-1.22427400	0.00030100
3 C 0	0.83201600	0.00018500	0.00014700
4 C 0	1.48059700	1.22457500	-0.00026000
5 C 0	2.87880100	1.21017300	-0.00034700
6 C 0	3.57528600	0.00001000	0.00001700
7 H 0	3.41731300	-2.15268200	0.00053100

8 H 0	0.91424400	-2.14577900	0.00063300
9 H 0	0.91449100	2.14610800	-0.00072200
10 H 0	3.41766600	2.15273500	-0.00070400
11 H 0	4.66081400	-0.00019100	-0.00016700
12 I 0	-1.33056300	-0.00011100	0.00005200
13 O 0	-1.19727800	-2.00506600	-0.00059100
14 O 0	-1.19812100	2.00529200	0.00021500

β -*t*-Butyl-styrene



B3LYP-D3(BJ)/6-31+G(d)/PCM(water)

Charge = 0

Multiplicity = 1

Imaginary Frequencies: 0

Electronic energy: -466.96199742

Zero-point correction= 0.247156 (Hartree/Particle)

Thermal correction to Energy= 0.259360

Thermal correction to Enthalpy= 0.260304

Thermal correction to Gibbs Free Energy= 0.207341

Sum of electronic and zero-point Energies= -466.714841

Sum of electronic and thermal Energies= -466.702638

Sum of electronic and thermal Enthalpies= -466.701693

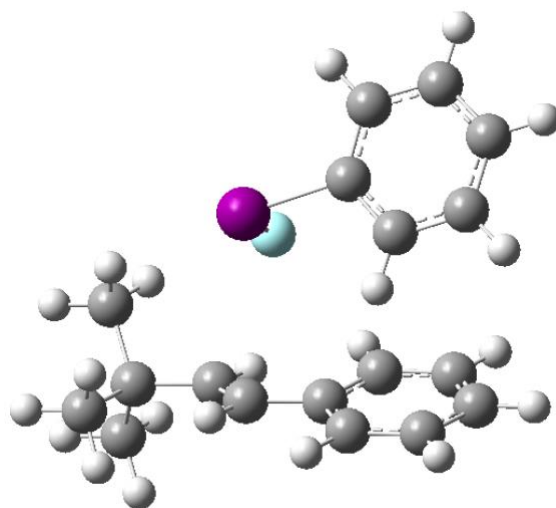
Sum of electronic and thermal Free Energies= -466.754656

Standard orientation

1 C 0	-0.16108400	0.51775000	0.00909500
2 H 0	-0.38522400	1.58244700	0.02440800
3 C 0	-1.17688700	-0.35718700	-0.00586200
4 H 0	-0.96079700	-1.42631800	-0.02389000
5 C 0	1.27616800	0.20304200	0.00493300
6 C 0	2.19890000	1.26413500	0.00011700
7 C 0	1.78417100	-1.11002700	0.00594300
8 C 0	3.57359100	1.02942300	-0.00511900
9 H 0	1.82668500	2.28580500	-0.00001600
10 C 0	3.15606300	-1.34612500	0.00068700
11 H 0	1.10212100	-1.95466700	0.01211400
12 C 0	4.05997700	-0.27862100	-0.00510400
13 H 0	4.26358600	1.86870200	-0.00910900
14 H 0	3.52371800	-2.36862800	0.00175100
15 H 0	5.12964700	-0.46694900	-0.00892200
16 C 0	-2.65624200	-0.03864800	-0.00157200
17 C 0	-3.28647000	-0.70060900	1.24372100

18 H 0	-2.87171000	-0.27491000	2.16422400
19 H 0	-4.37202300	-0.54575700	1.25186800
20 H 0	-3.09859600	-1.78064500	1.25426200
21 C 0	-2.94223800	1.46895700	0.02383800
22 H 0	-2.52213000	1.97067200	-0.85499100
23 H 0	-4.02357300	1.64487200	0.02637400
24 H 0	-2.52277800	1.94068600	0.91942500
25 C 0	-3.28477800	-0.65785000	-1.26947600
26 H 0	-2.86877300	-0.20108800	-2.17440200
27 H 0	-3.09684700	-1.73689300	-1.31647200
28 H 0	-4.37032000	-0.50277300	-1.27383300

β -*t*-Butyl-styrene [PhIF]⁺ complex



B3LYP-D3(BJ)/6-31+G(d)+SDD(I) LANL2DZ/PCM(water)

Charge = 1

Multiplicity = 1

Imaginary Frequencies: 0

Electronic energy: -809.56827749

Zero-point correction= 0.341263 (Hartree/Particle)

Thermal correction to Energy= 0.362605

Thermal correction to Enthalpy= 0.363549

Thermal correction to Gibbs Free Energy= 0.288919

Sum of electronic and zero-point Energies= -809.227014

Sum of electronic and thermal Energies= -809.205672

Sum of electronic and thermal Enthalpies= -809.204728

Sum of electronic and thermal Free Energies= -809.279359

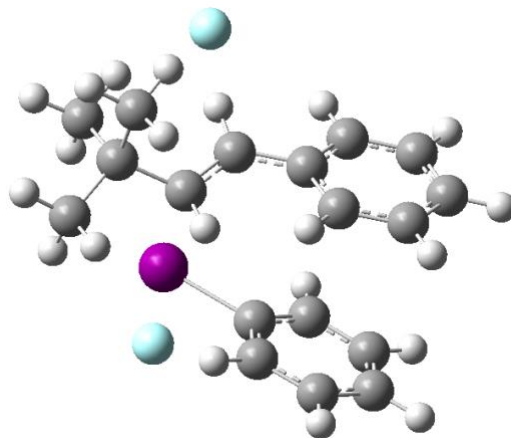
Standard orientation

1 C 0	3.84138000	0.55804800	-0.22058700
2 C 0	2.51356500	0.22801500	-0.47581500
3 C 0	2.09592800	-1.06884400	-0.15316900
4 C 0	2.94254100	-2.04424500	0.39277700
5 C 0	4.26381400	-1.68319500	0.63434300
6 C 0	4.70831800	-0.39004600	0.33119500
7 H 0	4.19209200	1.55762000	-0.45164000
8 H 0	1.83447900	0.95255100	-0.90663400
9 H 0	2.58505600	-3.04086200	0.62120700
10 H 0	4.94587300	-2.41092200	1.06019800
11 H 0	5.74203600	-0.12229600	0.52374100

12 I 0	0.08856200	-1.53956900	-0.47298500
13 C 0	-1.78481000	1.32709100	-0.41836400
14 H 0	-2.07747500	1.31895100	-1.46586800
15 C 0	-2.56047800	0.68792400	0.47944400
16 H 0	-2.29035300	0.72475200	1.53306700
17 C 0	-0.55856000	2.08268400	-0.13256300
18 C 0	0.01737800	2.84778600	-1.16412600
19 C 0	0.08747400	2.06450400	1.11964300
20 C 0	1.17747900	3.59330100	-0.94816900
21 H 0	-0.45878200	2.86018600	-2.14089800
22 C 0	1.24158200	2.81213300	1.33551100
23 H 0	-0.29985400	1.44297400	1.91912700
24 C 0	1.79060200	3.58464200	0.30620500
25 H 0	1.60087900	4.17786700	-1.75947700
26 H 0	1.72567600	2.78058900	2.30705000
27 H 0	2.69458900	4.16088400	0.47802500
28 C 0	-3.83168000	-0.07908100	0.19983000
29 C 0	-4.94655300	0.53133400	1.08076400
30 H 0	-5.12267400	1.57940200	0.81547500
31 H 0	-5.88297000	-0.02106000	0.94278800
32 H 0	-4.67895400	0.48815100	2.14270300
33 C 0	-4.25659700	-0.02494500	-1.27402600
34 H 0	-3.49491800	-0.46036100	-1.93040000

35 H 0	-5.18236700	-0.59287500	-1.41534900
36 H 0	-4.44003500	1.00513500	-1.59859100
37 C 0	-3.62236100	-1.55254800	0.61994500
38 H 0	-4.57271800	-2.09696100	0.58664000
39 H 0	-2.93087400	-2.05816900	-0.06574900
40 H 0	-3.21572500	-1.62792000	1.63345400
41 O 0	-0.45343400	-1.09642500	1.32914800

Fluoride Attack (TS1): β -*t*-Butyl-styrene, $[\text{PhIF}]^+$, F^-



B3LYP-D3(BJ)/6-31+G(d)+SDD(I) LANL2DZ/PCM(water)

Charge = 0

Multiplicity = 1

Imaginary Frequencies: 1

Electronic energy: -909.53582009

Zero-point correction= 0.342134 (Hartree/Particle)

Thermal correction to Energy= 0.364130

Thermal correction to Enthalpy= 0.365074

Thermal correction to Gibbs Free Energy= 0.290183

Sum of electronic and zero-point Energies= -909.193687

Sum of electronic and thermal Energies= -909.171690

Sum of electronic and thermal Enthalpies= -909.170746

Sum of electronic and thermal Free Energies= -909.245637

Standard orientation

1 C 0	3.52743400	-0.93061600	-0.18518600
2 C 0	2.23627000	-1.03225700	-0.70358500
3 C 0	1.19883800	-1.31993600	0.17929300
4 C 0	1.39538200	-1.51452700	1.54322700
5 C 0	2.69730800	-1.41134200	2.03926400
6 C 0	3.75704800	-1.11864900	1.17955200
7 H 0	4.34949300	-0.69248500	-0.85212900
8 H 0	2.05151500	-0.87636100	-1.75920800
9 H 0	0.56966400	-1.74085600	2.20792400
10 H 0	2.87463200	-1.56023300	3.09945900
11 H 0	4.76418400	-1.03231600	1.57436400
12 I 0	-0.76559000	-1.48127400	-0.61123500
13 O 0	-0.04887700	-3.25240900	-1.38849300
14 C 0	-0.75468600	1.41900200	-0.29906700
15 H 0	-1.35142800	1.79589100	-1.13618400
16 C 0	-1.36870600	0.58164700	0.65762400

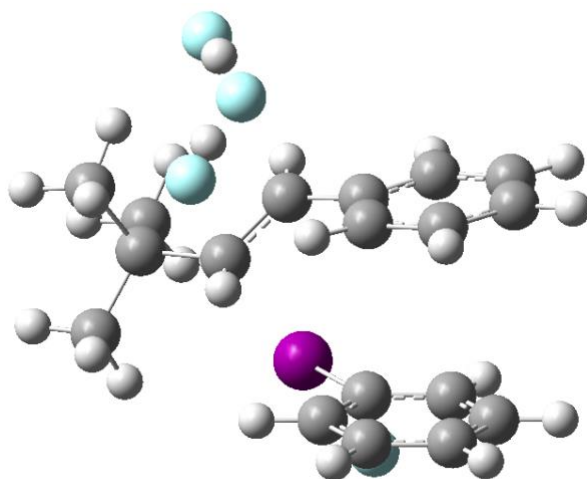
17 H 0	-0.81229800	0.38777400	1.57527500
18 C 0	0.61301600	1.87230000	-0.21389300
19 C 0	1.21801000	2.36713200	-1.39077500
20 C 0	1.37742200	1.82117700	0.97256100
21 C 0	2.55185600	2.75593000	-1.39321500
22 H 0	0.62508300	2.42459700	-2.29832400
23 C 0	2.70693200	2.22090900	0.96982500
24 H 0	0.92519400	1.47977600	1.89598000
25 C 0	3.29864200	2.67873100	-0.21274200
26 H 0	3.01168900	3.12002400	-2.30637700
27 H 0	3.28776800	2.17281700	1.88485800
28 H 0	4.34090600	2.98316300	-0.21164100
29 O 0	-2.28697600	3.18652400	-1.06764200
30 C 0	-2.88415200	0.57256100	0.87694600
31 C 0	-3.18078200	1.91735300	1.58802800
32 H 0	-2.92758800	2.72725700	0.89590200
33 H 0	-4.24590800	1.96690000	1.84729700
34 H 0	-2.60268900	2.01288100	2.51530700
35 C 0	-3.67724400	0.54563800	-0.44027700
36 H 0	-3.46175300	-0.34809100	-1.04124800
37 H 0	-4.75048300	0.52866500	-0.21822300
38 H 0	-3.44048400	1.44987700	-1.01065400
39 C 0	-3.28362500	-0.59619400	1.79113800

40 H 0 -4.34058800 -0.50826300 2.06357400

41 H 0 -3.14673200 -1.56851500 1.30582100

42 H 0 -2.69500200 -0.59518600 2.71659900

Fluoride Attack (TS2): β -*t*-Butyl-styrene, $[\text{PhIF}]^+$, $(\text{FH})_2\text{F}^-$



B3LYP-D3(BJ)/6-31+G(d)+SDD(I) LANL2DZ/PCM(water)

Charge = 0

Multiplicity = 1

Imaginary Frequencies: 1

Electronic energy: -1110.48164926

Zero-point correction= 0.368679 (Hartree/Particle)

Thermal correction to Energy= 0.394367

Thermal correction to Enthalpy= 0.395311

Thermal correction to Gibbs Free Energy= 0.312716

Sum of electronic and zero-point Energies= -1110.112970

Sum of electronic and thermal Energies= -1110.087283

Sum of electronic and thermal Enthalpies= -1110.086338

Sum of electronic and thermal Free Energies= -1110.168933

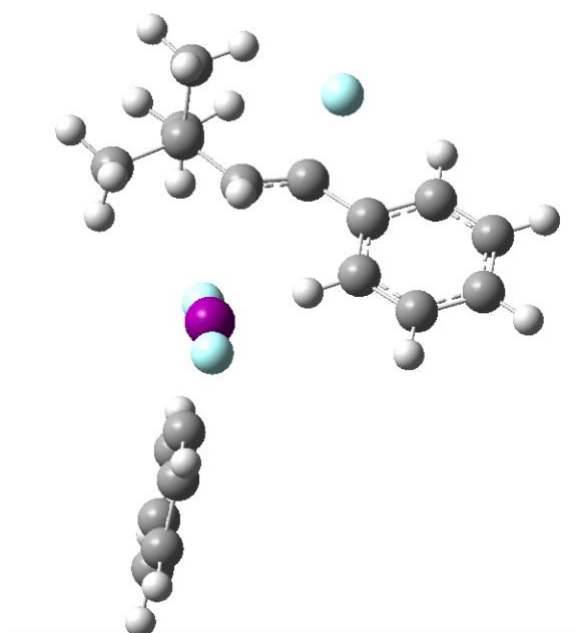
Standard orientation

1 C 0	3.98058400	0.07316100	0.24888100
2 C 0	2.88415100	-0.52218200	-0.37483000
3 C 0	1.80249400	-0.88167100	0.42057100
4 C 0	1.77664800	-0.70696100	1.79876000
5 C 0	2.88909500	-0.11494400	2.40259400
6 C 0	3.98205800	0.27993800	1.63031800
7 H 0	4.83018000	0.38019300	-0.35246300
8 H 0	2.87714700	-0.69710500	-1.44267700
9 H 0	0.93084700	-1.02020900	2.39881100
10 H 0	2.89295100	0.03168200	3.47783200
11 H 0	4.83852300	0.74728300	2.10554600
12 I 0	0.14443500	-1.79720400	-0.56490100
13 O 0	1.62322500	-3.07423200	-1.23727500
14 C 0	-1.12882700	0.85946400	-0.54043300
15 H 0	-1.71584400	0.76981800	-1.44909200
16 C 0	-1.35617400	-0.11717900	0.47421000
17 H 0	-0.83053300	0.07661600	1.40687200
18 C 0	0.08990000	1.64995300	-0.65846800
19 C 0	0.61439800	1.88139800	-1.94250700
20 C 0	0.76619400	2.15565800	0.46778800

21 C 0	1.81616000	2.56737900	-2.09743500
22 H 0	0.08840300	1.49796600	-2.81209300
23 C 0	1.95427300	2.85768600	0.30466000
24 H 0	0.31950500	2.04980900	1.44827900
25 C 0	2.48761500	3.05452800	-0.97332700
26 H 0	2.22509500	2.72586200	-3.09025100
27 H 0	2.47043500	3.24982200	1.17481800
28 H 0	3.42272900	3.59338000	-1.09246200
29 O 0	-2.29928400	2.49022000	0.00388200
30 O 0	-1.68198700	2.35034100	2.35693200
31 H 0	-1.98939800	2.45340300	1.42750000
32 O 0	-3.90400600	1.80779400	-1.66536600
33 H 0	-3.30345100	2.16649900	-0.97253400
34 C 0	-2.71656500	-0.80811100	0.68391300
35 C 0	-3.70108700	0.20470700	1.31827200
36 H 0	-3.98303500	0.96870900	0.59668300
37 H 0	-4.60434400	-0.32950800	1.63398900
38 H 0	-3.25898700	0.69764600	2.18599700
39 C 0	-3.33261000	-1.31310600	-0.63324800
40 H 0	-2.69080100	-2.03295800	-1.15611100
41 H 0	-4.27512500	-1.82761100	-0.41756000
42 H 0	-3.55506100	-0.48185300	-1.30697600
43 C 0	-2.54779900	-1.97422800	1.67737600

44 H 0	-3.52780400	-2.40078700	1.91325900
45 H 0	-1.92356000	-2.78012700	1.28158000
46 H 0	-2.09747600	-1.62676200	2.61470800

Fluoride Attack (TS3): β -*t*-Butyl-styrene, PhIF₂, F⁻



B3LYP-D3(BJ)/6-31+G(d)+SDD(I) LANL2DZ/PCM(water)

Charge = -1

Multiplicity = 1

Imaginary Frequencies: 1

Electronic energy: -1009.51147538

Zero-point correction= 0.343143 (Hartree/Particle)

Thermal correction to Energy= 0.366825

Thermal correction to Enthalpy= 0.367769

Thermal correction to Gibbs Free Energy= 0.287514

Sum of electronic and zero-point Energies= -1009.168332

Sum of electronic and thermal Energies= -1009.144650

Sum of electronic and thermal Enthalpies= -1009.143706

Sum of electronic and thermal Free Energies= -1009.223961

Standard orientation

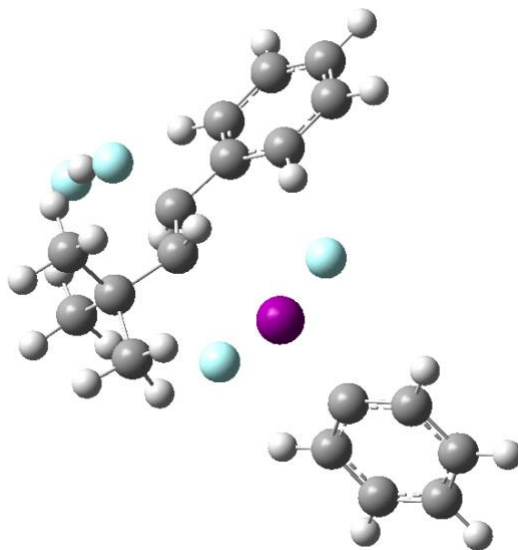
1 C 0	5.07451600	0.13364100	-1.27118200
2 C 0	3.71659700	-0.19558600	-1.20981300
3 C 0	3.00724500	0.11293600	-0.05632000
4 C 0	3.60110200	0.73585000	1.03387300
5 C 0	4.95998000	1.06069100	0.96133500
6 C 0	5.69567100	0.76073500	-0.18797200
7 H 0	5.64523300	-0.10038600	-2.16601900
8 H 0	3.21177400	-0.68295000	-2.03687200
9 H 0	3.01223500	0.95981400	1.91527900
10 H 0	5.44165400	1.54845100	1.80473200
11 H 0	6.75042900	1.01511700	-0.23934200
12 I 0	0.84522300	-0.41829100	0.00200800
13 O 0	1.09078900	-1.21498500	-1.88536300
14 C 0	-2.47524500	-0.07815400	-0.42281300
15 H 0	-2.23334600	-0.34598300	-1.45005300
16 C 0	-1.97135900	-0.94466500	0.56686000
17 H 0	-2.07833800	-0.60157500	1.60008700
18 C 0	-2.48391300	1.40473500	-0.19820800

19 C 0	-3.29275500	2.21675000	-1.01218100
20 C 0	-1.68378500	2.03025000	0.77041200
21 C 0	-3.30315700	3.60239200	-0.86707100
22 H 0	-3.93554700	1.72912400	-1.73477700
23 C 0	-1.70087800	3.41978400	0.92307100
24 H 0	-1.01542200	1.44146200	1.38748100
25 C 0	-2.50683300	4.21406600	0.10641700
26 H 0	-3.93836200	4.20722800	-1.50956700
27 H 0	-1.07024300	3.88132700	1.67897800
28 H 0	-2.51310600	5.29455200	0.22281700
29 C 0	-2.11228000	-2.46035900	0.42092600
30 C 0	-3.55915600	-2.86839100	0.79842400
31 H 0	-4.25773200	-2.28587500	0.19482800
32 H 0	-3.72624600	-3.94451900	0.64304200
33 H 0	-3.75462900	-2.64960300	1.85686900
34 C 0	-1.84292600	-2.91575000	-1.02597400
35 H 0	-0.86065100	-2.58288400	-1.38128600
36 H 0	-1.87881600	-4.01033200	-1.09710500
37 H 0	-2.60351800	-2.51108500	-1.70248600
38 C 0	-1.14790700	-3.19389400	1.37306900
39 H 0	-1.35664000	-4.27157100	1.38487800
40 H 0	-0.10243000	-3.05849500	1.07902800
41 H 0	-1.25745900	-2.82041600	2.39941100

42 O 0 0.87154400 0.41139300 1.85633200

43 O 0 -4.19846000 -0.33553900 -0.76802000

Fluoride Attack (TS4): β -*t*-Butyl-styrene, PhIF_2 , $(\text{FH})\text{F}^-$



B3LYP-D3(BJ)/6-31+G(d)+SDD(I) LANL2DZ/PCM(water)

Charge = -1

Multiplicity = 1

Imaginary Frequencies: 1

Electronic energy: -1109.96436626

Zero-point correction= 0.358013 (Hartree/Particle)

Thermal correction to Energy= 0.383142

Thermal correction to Enthalpy= 0.384086

Thermal correction to Gibbs Free Energy= 0.301348

Sum of electronic and zero-point Energies= -1109.606353

Sum of electronic and thermal Energies= -1109.581224

Sum of electronic and thermal Enthalpies= -1109.580280

Sum of electronic and thermal Free Energies= -1109.663019

Standard orientation

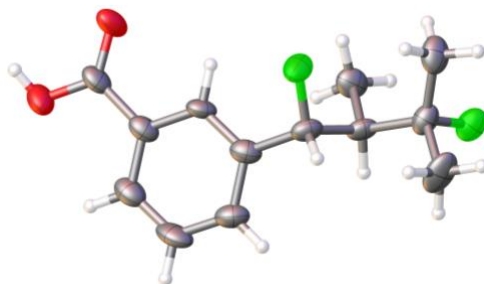
1 C 0	-4.87858500	-0.13217800	1.94301500
2 C 0	-3.55954700	-0.38397400	1.54611700
3 C 0	-3.08477600	0.11710100	0.33417600
4 C 0	-3.93544900	0.86760300	-0.47864600
5 C 0	-5.25434000	1.12347100	-0.08784500
6 C 0	-5.72765000	0.62154000	1.12765400
7 H 0	-5.24471500	-0.52454600	2.88956000
8 H 0	-2.89646600	-0.96777300	2.17499600
9 H 0	-3.57513400	1.26199000	-1.43012000
10 H 0	-5.91021600	1.71016500	-0.72722800
11 H 0	-6.75118200	0.81627900	1.43698300
12 I 0	-0.95133800	-0.15954100	-0.55351200
13 O 0	-0.80309500	-1.16425600	1.21787700
14 C 0	2.12101800	-0.14199700	0.28786600
15 H 0	1.87650300	-0.39923000	1.31690500
16 C 0	1.37449500	-0.97930300	-0.66345400
17 H 0	1.49864400	-0.66322800	-1.70242200
18 C 0	2.21441400	1.34970000	0.12159400
19 C 0	2.90333800	2.05291900	1.12452200
20 C 0	1.68782700	2.05577200	-0.96757800

21 C 0	3.07396700	3.43236300	1.04099700
22 H 0	3.31285400	1.50025700	1.96519000
23 C 0	1.85761500	3.44172100	-1.04357200
24 H 0	1.08497900	1.56151300	-1.72603700
25 C 0	2.55210600	4.13337300	-0.05042300
26 H 0	3.60969800	3.96001900	1.82515400
27 H 0	1.43520500	3.98317100	-1.88596500
28 H 0	2.67938900	5.21018800	-0.11961300
29 C 0	1.52099400	-2.50858200	-0.52059300
30 C 0	2.74798900	-2.95602100	-1.35214900
31 H 0	3.65635600	-2.46327300	-1.00081900
32 H 0	2.88499700	-4.04272000	-1.27750400
33 H 0	2.60995900	-2.70698200	-2.41170700
34 C 0	1.70987800	-2.95415400	0.94194100
35 H 0	0.85206500	-2.63605300	1.53902900
36 H 0	1.78496000	-4.04734200	0.98841900
37 H 0	2.61715100	-2.53785300	1.38770600
38 C 0	0.28368900	-3.23601700	-1.08096200
39 H 0	0.46552400	-4.31669500	-1.12234000
40 H 0	-0.58325200	-3.05725800	-0.43904100
41 H 0	0.04192700	-2.89503800	-2.09475500
42 O 0	-0.60046900	0.79290800	-2.56763500
43 O 0	3.62852100	-0.56530300	0.26689800

44 O 0	3.92859400	-0.73172000	2.71244800
45 H 0	3.94785200	-0.69460900	1.74748700

X-ray Crystallography Information

X-Ray Crystallographic Information Data for 3c



X-ray Crystallography: A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX DUO CCD diffractometer ($\text{CuK}\alpha$ radiation, $\lambda=1.54178$ Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 1.0° scans in ω at -30° , -55° , -80° , 30° , 55° , 80° and 115° in 2θ . Data integration down to 0.84 Å resolution was carried out using SAINT V8.37 A³² with reflection spot size optimization. Absorption corrections were made with the program SADABS.²³ The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods again F^2 using SHELXT-2014³³ and SHELXL-2014³⁴ with OLEX 2 interface³⁵. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table S3.6, geometric parameters are shown in Table S3.7 and hydrogen-

³² Bruker AXS APEX3, Bruker AXS, Madison, Wisconsin, **2016**.

³³ Sheldrick, G.M. *Acta Cryst.* **2015**, *A71*, 3–8.

³⁴ Sheldrick, G.M. *Acta Cryst.* **2015**, *C71*, 3–8.

³⁵ Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Cryst.* **2009**, *42*, 339–341.

bond parameters are listed in Table S3.8. The Ortep plots produced with SHELXL-2014 program, and the other drawings were produced with Accelrys DS Visualizer 2.0.³⁶

Table S3.6 Experimental details.

Crystal data	
Chemical formula	C ₁₃ H ₁₆ F ₂ O ₂
<i>M_r</i>	242.26
Crystal system, space group	Monoclinic, <i>C2</i>
Temperature (K)	100
<i>a</i> , <i>b</i> , <i>c</i> (Å)	12.8574 (6), 6.7912 (3), 28.3419 (13)
<i>b</i> (°)	91.813 (2)
<i>V</i> (Å ³)	2473.5 (2)
<i>Z</i>	8
Radiation type	Cu <i>Kα</i>
<i>μ</i> (mm ⁻¹)	0.90
Crystal size (mm)	0.18 × 0.16 × 0.12
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan <i>SADABS</i>
<i>T_{min}</i> , <i>T_{max}</i>	0.738, 0.864
No. of measured, independent and observed [<i>I</i> > 2 <i>s(I)</i>] reflections	21654, 3881, 3470
<i>R_{int}</i>	0.053
(sin <i>q/l</i>) _{max} (Å ⁻¹)	0.598
Refinement	
<i>R</i> [<i>F</i> ² > 2 <i>s(F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.06, 0.137, 1.09
No. of reflections	3881
No. of parameters	368

³⁶ Accelrys DS Visualizer v2.0.1, Accelrys Software. Inc., **2007**

No. of restraints	30
H-atom treatment	H-atom parameters constrained
$D\rho_{\max}$, $D\rho_{\min}$ ($e \text{ \AA}^{-3}$)	0.40, -0.34
Absolute structure	Flack x determined using 1167 quotients $[(I^+)-(I^-)]/[(I^+)+(I^-)]$ (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	0.03 (14)

Table S3.7 Geometric parameters ($\text{\AA}$, $^\circ$).

F1—C7	1.419 (6)	C28—H28	1.0000
F2—C11	1.429 (6)	C29—H29A	0.9800
O1—C10	1.247 (7)	C29—H29B	0.9800
O2—C10	1.292 (6)	C29—H29C	0.9800
O2—H2	0.8400	C30—O3	1.28 (3)
C1—C6	1.382 (7)	C30—O4	1.303 (18)
C1—C2	1.386 (7)	O4—H4A	0.8400
C1—H1	0.9500	C31—F4	1.437 (13)
C2—C3	1.376 (8)	C31—C32	1.464 (17)
C2—C10	1.490 (8)	C31—C33	1.515 (15)
C3—C4	1.377 (9)	C32—H32A	0.9800
C3—H3	0.9500	C32—H32B	0.9800
C4—C5	1.379 (8)	C32—H32C	0.9800
C4—H4	0.9500	C33—H33A	0.9800
C5—C6	1.402 (8)	C33—H33B	0.9800
C5—H5	0.9500	C33—H33C	0.9800
C6—C7	1.509 (8)	C21A—C26A	1.367 (15)
C7—C8	1.517 (7)	C21A—C22A	1.392 (18)
C7—H7	1.0000	C21A—H21A	0.9500
C8—C9	1.535 (7)	C22A—C23A	1.390 (19)
C8—C11	1.537 (7)	C22A—C30A	1.48 (2)
C8—H8	1.0000	C23A—C24A	1.381 (16)
C9—H9A	0.9800	C23A—H23A	0.9500
C9—H9B	0.9800	C24A—C25A	1.40 (2)

C9—H9C	0.9800	C24A—H24A	0.9500
C11—C12	1.509 (9)	C25A—C26A	1.396 (16)
C11—C13	1.522 (8)	C25A—H25A	0.9500
C12—H12A	0.9800	C26A—C27A	1.519 (14)
C12—H12B	0.9800	C27A—F3A	1.390 (15)
C12—H12C	0.9800	C27A—C28A	1.532 (15)
C13—H13A	0.9800	C27A—H27A	1.0000
C13—H13B	0.9800	C28A—C29A	1.541 (17)
C13—H13C	0.9800	C28A—C31A	1.554 (17)
C21—C22	1.388 (17)	C28A—H28A	1.0000
C21—C26	1.390 (14)	C29A—H29D	0.9800
C21—H21	0.9500	C29A—H29E	0.9800
C22—C23	1.389 (18)	C29A—H29F	0.9800
C22—C30	1.50 (2)	C30A—O3A	1.27 (3)
C23—C24	1.385 (16)	C30A—O4A	1.298 (19)
C23—H23	0.9500	O4A—H4AA	0.8400
C24—C25	1.40 (2)	C31A—F4A	1.415 (14)
C24—H24	0.9500	C31A—C32A	1.474 (18)
C25—C26	1.401 (16)	C31A—C33A	1.484 (17)
C25—H25	0.9500	C32A—H32D	0.9800
C26—C27	1.516 (14)	C32A—H32E	0.9800
C27—F3	1.407 (14)	C32A—H32F	0.9800
C27—C28	1.531 (15)	C33A—H33D	0.9800
C27—H27	1.0000	C33A—H33E	0.9800
C28—C29	1.523 (15)	C33A—H33F	0.9800
C28—C31	1.544 (17)		
C10—O2—H2	109.5	C31—C28—H28	106.0
C6—C1—C2	121.1 (5)	C28—C29—H29A	109.5
C6—C1—H1	119.5	C28—C29—H29B	109.5
C2—C1—H1	119.5	H29A—C29—H29B	109.5
C3—C2—C1	120.0 (6)	C28—C29—H29C	109.5
C3—C2—C10	122.0 (5)	H29A—C29—H29C	109.5

C1—C2—C10	117.8 (5)	H29B—C29—H29C	109.5
C2—C3—C4	119.3 (6)	O3—C30—O4	118 (3)
C2—C3—H3	120.4	O3—C30—C22	123 (4)
C4—C3—H3	120.4	O4—C30—C22	113 (2)
C3—C4—C5	121.5 (6)	C30—O4—H4A	109.5
C3—C4—H4	119.3	F4—C31—C32	105.6 (12)
C5—C4—H4	119.3	F4—C31—C33	105.4 (11)
C4—C5—C6	119.5 (6)	C32—C31—C33	112.0 (11)
C4—C5—H5	120.3	F4—C31—C28	105.1 (9)
C6—C5—H5	120.3	C32—C31—C28	113.7 (10)
C1—C6—C5	118.6 (5)	C33—C31—C28	114.1 (12)
C1—C6—C7	121.4 (5)	C31—C32—H32A	109.5
C5—C6—C7	119.9 (5)	C31—C32—H32B	109.5
F1—C7—C6	107.9 (4)	H32A—C32—H32B	109.5
F1—C7—C8	108.7 (4)	C31—C32—H32C	109.5
C6—C7—C8	114.6 (4)	H32A—C32—H32C	109.5
F1—C7—H7	108.5	H32B—C32—H32C	109.5
C6—C7—H7	108.5	C31—C33—H33A	109.5
C8—C7—H7	108.5	C31—C33—H33B	109.5
C7—C8—C9	111.7 (4)	H33A—C33—H33B	109.5
C7—C8—C11	113.1 (4)	C31—C33—H33C	109.5
C9—C8—C11	112.5 (4)	H33A—C33—H33C	109.5
C7—C8—H8	106.4	H33B—C33—H33C	109.5
C9—C8—H8	106.4	C26A—C21A— C22A	121.6 (14)
C11—C8—H8	106.4	C26A—C21A— H21A	119.2
C8—C9—H9A	109.5	C22A—C21A— H21A	119.2
C8—C9—H9B	109.5	C23A—C22A— C21A	119.3 (17)
H9A—C9—H9B	109.5	C23A—C22A— C30A	118 (2)
C8—C9—H9C	109.5	C21A—C22A—	122 (2)

		C30A	
H9A—C9—H9C	109.5	C24A—C23A— C22A	120.3 (19)
H9B—C9—H9C	109.5	C24A—C23A— H23A	119.8
O1—C10—O2	123.3 (6)	C22A—C23A— H23A	119.8
O1—C10—C2	120.6 (5)	C23A—C24A— C25A	119 (2)
O2—C10—C2	116.1 (5)	C23A—C24A— H24A	120.4
F2—C11—C12	105.6 (5)	C25A—C24A— H24A	120.4
F2—C11—C13	105.4 (4)	C26A—C25A— C24A	120.6 (15)
C12—C11—C13	112.5 (5)	C26A—C25A— H25A	119.7
F2—C11—C8	105.0 (4)	C24A—C25A— H25A	119.7
C12—C11—C8	115.5 (4)	C21A—C26A— C25A	118.7 (12)
C13—C11—C8	111.8 (5)	C21A—C26A— C27A	121.3 (11)
C11—C12—H12A	109.5	C25A—C26A— C27A	120.0 (11)
C11—C12—H12B	109.5	F3A—C27A—C26A	109.2 (10)
H12A—C12—H12B	109.5	F3A—C27A—C28A	109.5 (11)
C11—C12—H12C	109.5	C26A—C27A— C28A	111.0 (10)
H12A—C12—H12C	109.5	F3A—C27A—H27A	109.0
H12B—C12—H12C	109.5	C26A—C27A— H27A	109.0
C11—C13—H13A	109.5	C28A—C27A— H27A	109.1
C11—C13—H13B	109.5	C27A—C28A— C29A	110.4 (10)
H13A—C13—H13B	109.5	C27A—C28A— C31A	112.2 (10)

C11—C13—H13C	109.5	C29A—C28A—C31A	112.7 (11)
H13A—C13—H13C	109.5	C27A—C28A—H28A	107.0
H13B—C13—H13C	109.5	C29A—C28A—H28A	107.0
C22—C21—C26	119.5 (13)	C31A—C28A—H28A	107.0
C22—C21—H21	120.2	C28A—C29A—H29D	109.5
C26—C21—H21	120.2	C28A—C29A—H29E	109.5
C21—C22—C23	121.4 (15)	H29D—C29A—H29E	109.5
C21—C22—C30	117 (2)	C28A—C29A—H29F	109.5
C23—C22—C30	121 (2)	H29D—C29A—H29F	109.5
C24—C23—C22	120.0 (19)	H29E—C29A—H29F	109.5
C24—C23—H23	120.0	O3A—C30A—O4A	123 (4)
C22—C23—H23	120.0	O3A—C30A—C22A	114 (3)
C23—C24—C25	118.5 (19)	O4A—C30A—C22A	116 (2)
C23—C24—H24	120.7	C30A—O4A—H4AA	109.5
C25—C24—H24	120.7	F4A—C31A—C32A	101.7 (12)
C24—C25—C26	121.7 (13)	F4A—C31A—C33A	109.8 (13)
C24—C25—H25	119.1	C32A—C31A—C33A	110.6 (13)
C26—C25—H25	119.1	F4A—C31A—C28A	106.1 (10)
C21—C26—C25	118.7 (11)	C32A—C31A—C28A	116.3 (12)
C21—C26—C27	119.8 (10)	C33A—C31A—C28A	111.6 (12)
C25—C26—C27	121.4 (11)	C31A—C32A—H32D	109.5
F3—C27—C26	108.0 (10)	C31A—C32A—	109.5

		H32E	
F3—C27—C28	107.9 (10)	H32D—C32A— H32E	109.5
C26—C27—C28	112.4 (10)	C31A—C32A— H32F	109.5
F3—C27—H27	109.5	H32D—C32A— H32F	109.5
C26—C27—H27	109.5	H32E—C32A— H32F	109.5
C28—C27—H27	109.5	C31A—C33A— H33D	109.5
C29—C28—C27	112.4 (10)	C31A—C33A— H33E	109.5
C29—C28—C31	113.9 (9)	H33D—C33A— H33E	109.5
C27—C28—C31	111.9 (9)	C31A—C33A— H33F	109.5
C29—C28—H28	106.0	H33D—C33A— H33F	109.5
C27—C28—H28	106.0	H33E—C33A— H33F	109.5
C6—C1—C2—C3	-0.5 (8)	F3—C27—C28— C29	-43.9 (12)
C6—C1—C2—C10	175.5 (5)	C26—C27—C28— C29	75.0 (12)
C1—C2—C3—C4	-0.8 (9)	F3—C27—C28— C31	85.7 (12)
C10—C2—C3—C4	-176.6 (5)	C26—C27—C28— C31	-155.5 (10)
C2—C3—C4—C5	0.8 (9)	C21—C22—C30— O3	19 (10)
C3—C4—C5—C6	0.5 (9)	C23—C22—C30— O3	-164 (6)
C2—C1—C6—C5	1.7 (8)	C21—C22—C30— O4	171 (5)
C2—C1—C6—C7	-175.7 (5)	C23—C22—C30— O4	-12 (9)

C4—C5—C6—C1	-1.7 (9)	C29—C28—C31—F4	-177.1 (10)
C4—C5—C6—C7	175.7 (5)	C27—C28—C31—F4	54.1 (12)
C1—C6—C7—F1	23.0 (7)	C29—C28—C31—C32	-62.2 (15)
C5—C6—C7—F1	-154.4 (5)	C27—C28—C31—C32	169.0 (12)
C1—C6—C7—C8	-98.2 (6)	C29—C28—C31—C33	67.9 (14)
C5—C6—C7—C8	84.4 (6)	C27—C28—C31—C33	-60.9 (14)
F1—C7—C8—C9	-58.1 (5)	C26A—C21A—C22A—C23A	-3 (5)
C6—C7—C8—C9	62.7 (6)	C26A—C21A—C22A—C30A	-175 (5)
F1—C7—C8—C11	69.9 (5)	C21A—C22A—C23A—C24A	-1 (7)
C6—C7—C8—C11	-169.3 (4)	C30A—C22A—C23A—C24A	171 (6)
C3—C2—C10—O1	-173.7 (5)	C22A—C23A—C24A—C25A	5 (8)
C1—C2—C10—O1	10.4 (8)	C23A—C24A—C25A—C26A	-5 (7)
C3—C2—C10—O2	6.3 (8)	C22A—C21A—C26A—C25A	3 (3)
C1—C2—C10—O2	-169.6 (5)	C22A—C21A—C26A—C27A	-177 (2)
C7—C8—C11—F2	176.1 (4)	C24A—C25A—C26A—C21A	1 (4)
C9—C8—C11—F2	-56.3 (6)	C24A—C25A—C26A—C27A	-179 (3)
C7—C8—C11—C12	-68.0 (6)	C21A—C26A—C27A—F3A	19.1 (16)
C9—C8—C11—C12	59.6 (6)	C25A—C26A—C27A—F3A	-160.5 (12)
C7—C8—C11—C13	62.3 (6)	C21A—C26A—C27A—C28A	-101.6 (14)

C9—C8—C11—C13	-170.1 (5)	C25A—C26A— C27A—C28A	78.7 (15)
C26—C21—C22— C23	0 (5)	F3A—C27A— C28A—C29A	-56.2 (14)
C26—C21—C22— C30	177 (5)	C26A—C27A— C28A—C29A	64.4 (15)
C21—C22—C23— C24	0 (7)	F3A—C27A— C28A—C31A	70.5 (13)
C30—C22—C23— C24	-177 (6)	C26A—C27A— C28A—C31A	-168.9 (11)
C22—C23—C24— C25	-2 (7)	C23A—C22A— C30A—O3A	-176 (6)
C23—C24—C25— C26	4 (6)	C21A—C22A— C30A—O3A	-3 (10)
C22—C21—C26— C25	2 (3)	C23A—C22A— C30A—O4A	33 (10)
C22—C21—C26— C27	177 (2)	C21A—C22A— C30A—O4A	-154 (6)
C24—C25—C26— C21	-4 (3)	C27A—C28A— C31A—F4A	42.4 (15)
C24—C25—C26— C27	-180 (3)	C29A—C28A— C31A—F4A	167.8 (11)
C21—C26—C27— F3	-171.2 (10)	C27A—C28A— C31A—C32A	-69.8 (16)
C25—C26—C27— F3	4.6 (16)	C29A—C28A— C31A—C32A	55.6 (16)
C21—C26—C27— C28	70.0 (15)	C27A—C28A— C31A—C33A	162.0 (13)
C25—C26—C27— C28	-114.3 (14)	C29A—C28A— C31A—C33A	-72.5 (16)

Table S3.8 Hydrogen-bond parameters.

$D-H\cdots A$	$D-H$ (Å)	$H\cdots A$ (Å)	$D\cdots A$ (Å)	$D-H\cdots A$ (°)
O2—H2 $\cdots$ O3	0.84	1.92	2.67 (3)	149.1
O2—H2 $\cdots$ O3A	0.84	1.77	2.59 (3)	162.3
O4—H4A $\cdots$ O1	0.84	1.98	2.78 (2)	160.7
O4A—	0.84	1.60	2.42 (2)	166.4

H4AA...O1				

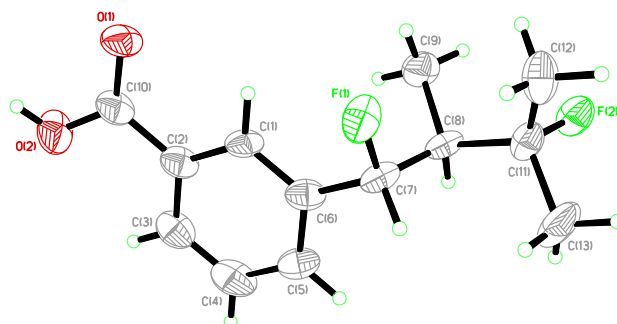


Figure S3.2 Perspective views showing 50% probability displacement.

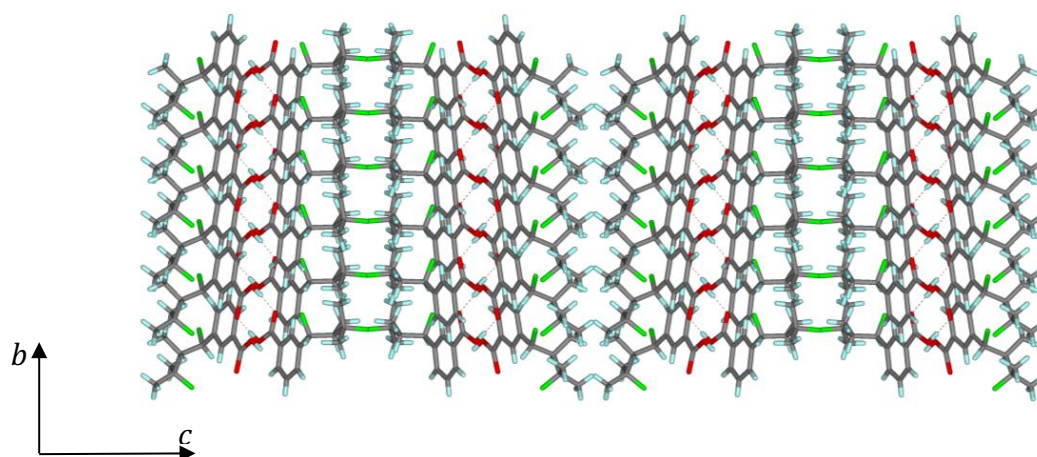
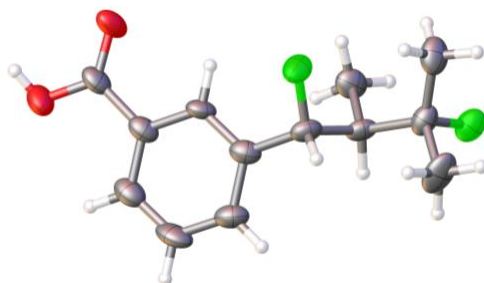


Figure S3.3 Three-dimensional supramolecular architecture viewed along the *a*-axis direction.

X-Ray Crystallographic Information Data for S-5e

X-ray Crystallography:



A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX DUO CCD diffractometer ($\text{CuK}\alpha$ radiation, $\lambda=1.54178$ Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 1.0° scans in ω at -30° , -55° , -80° , 30° , 55° , 80° and 115° in 2θ . Data integration down to 0.84 Å resolution was carried out using SAINT V8.37 A with reflection spot size optimization. Absorption corrections were made with the program SADABS. The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods against F^2 using SHELXT-2014 and SHELXL-2014 with OLEX 2 interface. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table S3.9, geometric parameters are shown in Table S3.10 and hydrogen-bond parameters are listed in Table S3.11. The Ortep plots produced with SHELXL-2014 program, and the other drawings were produced with Accelrys DS Visualizer 2.0.

Table S3.9 Experimental details.

Crystal data

Chemical formula	$\text{C}_{13}\text{H}_{16}\text{F}_2\text{O}_2$
M_r	242.26
Crystal system, space group	Monoclinic, $C2$

Temperature (K)	100
a, b, c (Å)	12.8574 (6), 6.7912 (3), 28.3419 (13)
b (°)	91.813 (2)
V (Å ³)	2473.5 (2)
Z	8
Radiation type	Cu $K\alpha$
μ (mm ⁻¹)	0.90
Crystal size (mm)	0.18 × 0.16 × 0.12
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan <i>SADABS</i>
$T_{\min}, T_{\max}$	0.738, 0.864
No. of measured, independent and observed [I $> 2s(I)$] reflections	21654, 3881, 3470
R_{int}	0.053
$(\sin \theta/\lambda)_{\max}$ (Å ⁻¹)	0.598
Refinement	
$R[F^2 > 2s(F^2)], wR(F^2), S$	0.063, 0.137, 1.09
No. of reflections	3881
No. of parameters	368
No. of restraints	30
H-atom treatment	H-atom parameters constrained
$D\rho_{\max}, D\rho_{\min}$ (e Å ⁻³)	0.40, -0.34
Absolute structure	Flack x determined using 1167 quotients $[(I^+)-(I^-)]/[(I^+)+(I^-)]$ (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	0.03 (14)

Table S3.10 Geometric parameters (Å, °).

F1—C7	1.419 (6)	C28—H28	1.0000

F2—C11	1.429 (6)	C29—H29A	0.9800
O1—C10	1.247 (7)	C29—H29B	0.9800
O2—C10	1.292 (6)	C29—H29C	0.9800
O2—H2	0.8400	C30—O3	1.28 (3)
C1—C6	1.382 (7)	C30—O4	1.303 (18)
C1—C2	1.386 (7)	O4—H4A	0.8400
C1—H1	0.9500	C31—F4	1.437 (13)
C2—C3	1.376 (8)	C31—C32	1.464 (17)
C2—C10	1.490 (8)	C31—C33	1.515 (15)
C3—C4	1.377 (9)	C32—H32A	0.9800
C3—H3	0.9500	C32—H32B	0.9800
C4—C5	1.379 (8)	C32—H32C	0.9800
C4—H4	0.9500	C33—H33A	0.9800
C5—C6	1.402 (8)	C33—H33B	0.9800
C5—H5	0.9500	C33—H33C	0.9800
C6—C7	1.509 (8)	C21A—C26A	1.367 (15)
C7—C8	1.517 (7)	C21A—C22A	1.392 (18)
C7—H7	1.0000	C21A—H21A	0.9500
C8—C9	1.535 (7)	C22A—C23A	1.390 (19)
C8—C11	1.537 (7)	C22A—C30A	1.48 (2)
C8—H8	1.0000	C23A—C24A	1.381 (16)
C9—H9A	0.9800	C23A—H23A	0.9500
C9—H9B	0.9800	C24A—C25A	1.40 (2)
C9—H9C	0.9800	C24A—H24A	0.9500
C11—C12	1.509 (9)	C25A—C26A	1.396 (16)
C11—C13	1.522 (8)	C25A—H25A	0.9500
C12—H12A	0.9800	C26A—C27A	1.519 (14)
C12—H12B	0.9800	C27A—F3A	1.390 (15)
C12—H12C	0.9800	C27A—C28A	1.532 (15)
C13—H13A	0.9800	C27A—H27A	1.0000
C13—H13B	0.9800	C28A—C29A	1.541 (17)
C13—H13C	0.9800	C28A—C31A	1.554 (17)
C21—C22	1.388 (17)	C28A—H28A	1.0000

C21—C26	1.390 (14)	C29A—H29D	0.9800
C21—H21	0.9500	C29A—H29E	0.9800
C22—C23	1.389 (18)	C29A—H29F	0.9800
C22—C30	1.50 (2)	C30A—O3A	1.27 (3)
C23—C24	1.385 (16)	C30A—O4A	1.298 (19)
C23—H23	0.9500	O4A—H4AA	0.8400
C24—C25	1.40 (2)	C31A—F4A	1.415 (14)
C24—H24	0.9500	C31A—C32A	1.474 (18)
C25—C26	1.401 (16)	C31A—C33A	1.484 (17)
C25—H25	0.9500	C32A—H32D	0.9800
C26—C27	1.516 (14)	C32A—H32E	0.9800
C27—F3	1.407 (14)	C32A—H32F	0.9800
C27—C28	1.531 (15)	C33A—H33D	0.9800
C27—H27	1.0000	C33A—H33E	0.9800
C28—C29	1.523 (15)	C33A—H33F	0.9800
C28—C31	1.544 (17)		
C10—O2—H2	109.5	C31—C28—H28	106.0
C6—C1—C2	121.1 (5)	C28—C29—H29A	109.5
C6—C1—H1	119.5	C28—C29—H29B	109.5
C2—C1—H1	119.5	H29A—C29—H29B	109.5
C3—C2—C1	120.0 (6)	C28—C29—H29C	109.5
C3—C2—C10	122.0 (5)	H29A—C29—H29C	109.5
C1—C2—C10	117.8 (5)	H29B—C29—H29C	109.5
C2—C3—C4	119.3 (6)	O3—C30—O4	118 (3)
C2—C3—H3	120.4	O3—C30—C22	123 (4)
C4—C3—H3	120.4	O4—C30—C22	113 (2)
C3—C4—C5	121.5 (6)	C30—O4—H4A	109.5
C3—C4—H4	119.3	F4—C31—C32	105.6 (12)
C5—C4—H4	119.3	F4—C31—C33	105.4 (11)
C4—C5—C6	119.5 (6)	C32—C31—C33	112.0 (11)
C4—C5—H5	120.3	F4—C31—C28	105.1 (9)
C6—C5—H5	120.3	C32—C31—C28	113.7 (10)

C1—C6—C5	118.6 (5)	C33—C31—C28	114.1 (12)
C1—C6—C7	121.4 (5)	C31—C32—H32A	109.5
C5—C6—C7	119.9 (5)	C31—C32—H32B	109.5
F1—C7—C6	107.9 (4)	H32A—C32—H32B	109.5
F1—C7—C8	108.7 (4)	C31—C32—H32C	109.5
C6—C7—C8	114.6 (4)	H32A—C32—H32C	109.5
F1—C7—H7	108.5	H32B—C32—H32C	109.5
C6—C7—H7	108.5	C31—C33—H33A	109.5
C8—C7—H7	108.5	C31—C33—H33B	109.5
C7—C8—C9	111.7 (4)	H33A—C33—H33B	109.5
C7—C8—C11	113.1 (4)	C31—C33—H33C	109.5
C9—C8—C11	112.5 (4)	H33A—C33—H33C	109.5
C7—C8—H8	106.4	H33B—C33—H33C	109.5
C9—C8—H8	106.4	C26A—C21A— C22A	121.6 (14)
C11—C8—H8	106.4	C26A—C21A— H21A	119.2
C8—C9—H9A	109.5	C22A—C21A— H21A	119.2
C8—C9—H9B	109.5	C23A—C22A— C21A	119.3 (17)
H9A—C9—H9B	109.5	C23A—C22A— C30A	118 (2)
C8—C9—H9C	109.5	C21A—C22A— C30A	122 (2)
H9A—C9—H9C	109.5	C24A—C23A— C22A	120.3 (19)
H9B—C9—H9C	109.5	C24A—C23A— H23A	119.8
O1—C10—O2	123.3 (6)	C22A—C23A— H23A	119.8
O1—C10—C2	120.6 (5)	C23A—C24A— C25A	119 (2)
O2—C10—C2	116.1 (5)	C23A—C24A— H24A	120.4
F2—C11—C12	105.6 (5)	C25A—C24A—	120.4

		H24A	
F2—C11—C13	105.4 (4)	C26A—C25A— C24A	120.6 (15)
C12—C11—C13	112.5 (5)	C26A—C25A— H25A	119.7
F2—C11—C8	105.0 (4)	C24A—C25A— H25A	119.7
C12—C11—C8	115.5 (4)	C21A—C26A— C25A	118.7 (12)
C13—C11—C8	111.8 (5)	C21A—C26A— C27A	121.3 (11)
C11—C12—H12A	109.5	C25A—C26A— C27A	120.0 (11)
C11—C12—H12B	109.5	F3A—C27A—C26A	109.2 (10)
H12A—C12—H12B	109.5	F3A—C27A—C28A	109.5 (11)
C11—C12—H12C	109.5	C26A—C27A— C28A	111.0 (10)
H12A—C12—H12C	109.5	F3A—C27A—H27A	109.0
H12B—C12—H12C	109.5	C26A—C27A— H27A	109.0
C11—C13—H13A	109.5	C28A—C27A— H27A	109.1
C11—C13—H13B	109.5	C27A—C28A— C29A	110.4 (10)
H13A—C13—H13B	109.5	C27A—C28A— C31A	112.2 (10)
C11—C13—H13C	109.5	C29A—C28A— C31A	112.7 (11)
H13A—C13—H13C	109.5	C27A—C28A— H28A	107.0
H13B—C13—H13C	109.5	C29A—C28A— H28A	107.0
C22—C21—C26	119.5 (13)	C31A—C28A— H28A	107.0
C22—C21—H21	120.2	C28A—C29A— H29D	109.5
C26—C21—H21	120.2	C28A—C29A— H29E	109.5

C21—C22—C23	121.4 (15)	H29D—C29A— H29E	109.5
C21—C22—C30	117 (2)	C28A—C29A— H29F	109.5
C23—C22—C30	121 (2)	H29D—C29A— H29F	109.5
C24—C23—C22	120.0 (19)	H29E—C29A— H29F	109.5
C24—C23—H23	120.0	O3A—C30A—O4A	123 (4)
C22—C23—H23	120.0	O3A—C30A—C22A	114 (3)
C23—C24—C25	118.5 (19)	O4A—C30A—C22A	116 (2)
C23—C24—H24	120.7	C30A—O4A— H4AA	109.5
C25—C24—H24	120.7	F4A—C31A—C32A	101.7 (12)
C24—C25—C26	121.7 (13)	F4A—C31A—C33A	109.8 (13)
C24—C25—H25	119.1	C32A—C31A— C33A	110.6 (13)
C26—C25—H25	119.1	F4A—C31A—C28A	106.1 (10)
C21—C26—C25	118.7 (11)	C32A—C31A— C28A	116.3 (12)
C21—C26—C27	119.8 (10)	C33A—C31A— C28A	111.6 (12)
C25—C26—C27	121.4 (11)	C31A—C32A— H32D	109.5
F3—C27—C26	108.0 (10)	C31A—C32A— H32E	109.5
F3—C27—C28	107.9 (10)	H32D—C32A— H32E	109.5
C26—C27—C28	112.4 (10)	C31A—C32A— H32F	109.5
F3—C27—H27	109.5	H32D—C32A— H32F	109.5
C26—C27—H27	109.5	H32E—C32A— H32F	109.5
C28—C27—H27	109.5	C31A—C33A— H33D	109.5
C29—C28—C27	112.4 (10)	C31A—C33A—	109.5

		H33E	
C29—C28—C31	113.9 (9)	H33D—C33A— H33E	109.5
C27—C28—C31	111.9 (9)	C31A—C33A— H33F	109.5
C29—C28—H28	106.0	H33D—C33A— H33F	109.5
C27—C28—H28	106.0	H33E—C33A— H33F	109.5
C6—C1—C2—C3	-0.5 (8)	F3—C27—C28— C29	-43.9 (12)
C6—C1—C2—C10	175.5 (5)	C26—C27—C28— C29	75.0 (12)
C1—C2—C3—C4	-0.8 (9)	F3—C27—C28— C31	85.7 (12)
C10—C2—C3—C4	-176.6 (5)	C26—C27—C28— C31	-155.5 (10)
C2—C3—C4—C5	0.8 (9)	C21—C22—C30— O3	19 (10)
C3—C4—C5—C6	0.5 (9)	C23—C22—C30— O3	-164 (6)
C2—C1—C6—C5	1.7 (8)	C21—C22—C30— O4	171 (5)
C2—C1—C6—C7	-175.7 (5)	C23—C22—C30— O4	-12 (9)
C4—C5—C6—C1	-1.7 (9)	C29—C28—C31— F4	-177.1 (10)
C4—C5—C6—C7	175.7 (5)	C27—C28—C31— F4	54.1 (12)
C1—C6—C7—F1	23.0 (7)	C29—C28—C31— C32	-62.2 (15)
C5—C6—C7—F1	-154.4 (5)	C27—C28—C31— C32	169.0 (12)
C1—C6—C7—C8	-98.2 (6)	C29—C28—C31— C33	67.9 (14)
C5—C6—C7—C8	84.4 (6)	C27—C28—C31— C33	-60.9 (14)

F1—C7—C8—C9	-58.1 (5)	C26A—C21A— C22A—C23A	-3 (5)
C6—C7—C8—C9	62.7 (6)	C26A—C21A— C22A—C30A	-175 (5)
F1—C7—C8—C11	69.9 (5)	C21A—C22A— C23A—C24A	-1 (7)
C6—C7—C8—C11	-169.3 (4)	C30A—C22A— C23A—C24A	171 (6)
C3—C2—C10—O1	-173.7 (5)	C22A—C23A— C24A—C25A	5 (8)
C1—C2—C10—O1	10.4 (8)	C23A—C24A— C25A—C26A	-5 (7)
C3—C2—C10—O2	6.3 (8)	C22A—C21A— C26A—C25A	3 (3)
C1—C2—C10—O2	-169.6 (5)	C22A—C21A— C26A—C27A	-177 (2)
C7—C8—C11—F2	176.1 (4)	C24A—C25A— C26A—C21A	1 (4)
C9—C8—C11—F2	-56.3 (6)	C24A—C25A— C26A—C27A	-179 (3)
C7—C8—C11—C12	-68.0 (6)	C21A—C26A— C27A—F3A	19.1 (16)
C9—C8—C11—C12	59.6 (6)	C25A—C26A— C27A—F3A	-160.5 (12)
C7—C8—C11—C13	62.3 (6)	C21A—C26A— C27A—C28A	-101.6 (14)
C9—C8—C11—C13	-170.1 (5)	C25A—C26A— C27A—C28A	78.7 (15)
C26—C21—C22— C23	0 (5)	F3A—C27A— C28A—C29A	-56.2 (14)
C26—C21—C22— C30	177 (5)	C26A—C27A— C28A—C29A	64.4 (15)
C21—C22—C23— C24	0 (7)	F3A—C27A— C28A—C31A	70.5 (13)
C30—C22—C23— C24	-177 (6)	C26A—C27A— C28A—C31A	-168.9 (11)
C22—C23—C24— C25	-2 (7)	C23A—C22A— C30A—O3A	-176 (6)

C23—C24—C25— C26	4 (6)	C21A—C22A— C30A—O3A	-3 (10)
C22—C21—C26— C25	2 (3)	C23A—C22A— C30A—O4A	33 (10)
C22—C21—C26— C27	177 (2)	C21A—C22A— C30A—O4A	-154 (6)
C24—C25—C26— C21	-4 (3)	C27A—C28A— C31A—F4A	42.4 (15)
C24—C25—C26— C27	-180 (3)	C29A—C28A— C31A—F4A	167.8 (11)
C21—C26—C27— F3	-171.2 (10)	C27A—C28A— C31A—C32A	-69.8 (16)
C25—C26—C27— F3	4.6 (16)	C29A—C28A— C31A—C32A	55.6 (16)
C21—C26—C27— C28	70.0 (15)	C27A—C28A— C31A—C33A	162.0 (13)
C25—C26—C27— C28	-114.3 (14)	C29A—C28A— C31A—C33A	-72.5 (16)

Table S3.11 Hydrogen-bond parameters.

$D-H\cdots A$	$D-H$ (Å)	$H\cdots A$ (Å)	$D\cdots A$ (Å)	$D-H\cdots A$ (°)
O2—H2 $\cdots$ O3	0.84	1.92	2.67 (3)	149.1
O2—H2 $\cdots$ O3A	0.84	1.77	2.59 (3)	162.3
O4—H4A $\cdots$ O1	0.84	1.98	2.78 (2)	160.7
O4A— H4AA $\cdots$ O1	0.84	1.60	2.42 (2)	166.4

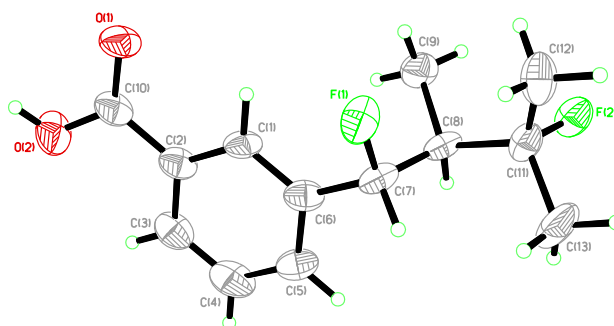


Figure S3.4 Perspective views showing 50% probability displacement.

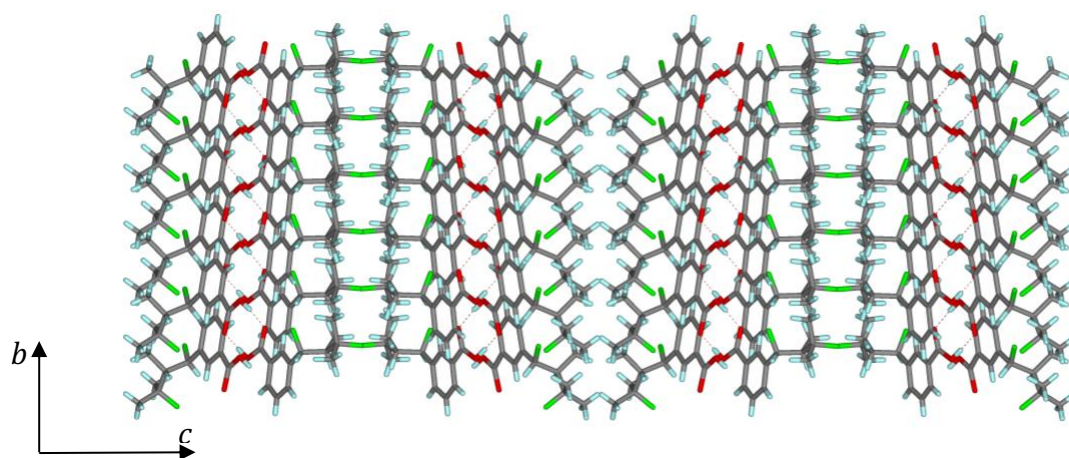
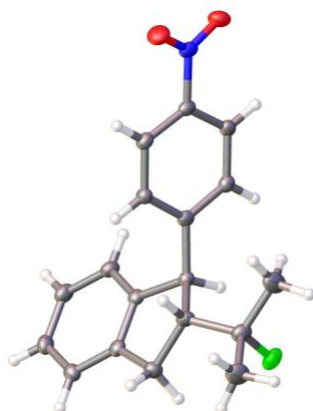


Figure S3.5 Three-dimensional supramolecular architecture viewed along the a -axis direction.

X-Ray Crystallographic Information Data for 7



X-ray Crystallography: A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX DUO CCD diffractometer ($\text{CuK}\alpha$ radiation, $\lambda=1.54178$ Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 1.0° scans in ω at -30° , -55° , -80° , 30° , 55° , 80° and 115° in 2θ . Data integration down to 0.84 Å resolution was carried out using SAINT V8.37 A with reflection spot size optimization. Absorption corrections were made with the program SADABS. The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods against F^2 using SHELXT-2014 and SHELXL-2014 with OLEX 2 interface. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table S3.12, and geometric parameters are shown in Table S3.13. The Ortep plots produced with SHELXL-2014 program, and the other drawings were produced with Accelrys DS Visualizer 2.0.

Table S3.12 Experimental details.

Crystal data

Chemical formula $\text{C}_{18}\text{H}_{18}\text{FNO}_2$

M_r 299.33

Crystal system, space group	Monoclinic, $P2_1$
Temperature (K)	100
a, b, c (Å)	9.4593 (3), 16.9377 (5), 9.6247 (3)
β (°)	97.1568 (13)
V (Å ³)	1530.04 (8)
Z	4
Radiation type	Cu $K\alpha$
μ (mm ⁻¹)	0.76
Crystal size (mm)	0.18 × 0.16 × 0.14
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan <i>SADABS</i>
$T_{\min}, T_{\max}$	0.776, 0.864
No. of measured, independent and observed [$I > 2s(I)$] reflections	46241, 5333, 5195
R_{int}	0.057
$(\sin \theta/\lambda)_{\max}$ (Å ⁻¹)	0.596
Refinement	
$R[F^2 > 2s(F^2)], wR(F^2), S$	0.035, 0.088, 1.06
No. of reflections	5333
No. of parameters	416
No. of restraints	26
H-atom treatment	H-atom parameters constrained
$D\rho_{\max}, D\rho_{\min}$ (e Å ⁻³)	0.54, -0.31
Absolute structure	Flack x determined using 2433 quotients [(I^+)-(I^-)]/[(I^+)+(I^-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	0.01 (6)

Table S3.13 Geometric parameters (Å, °).

F1—C16	1.425 (3)	C22—C23	1.383 (4)
O1—N1	1.225 (3)	C22—H22	0.9500
O2—N1	1.225 (3)	C23—C24	1.380 (4)
N1—C3	1.477 (3)	C24—C25	1.389 (4)
C1—C2	1.390 (4)	C24—H24	0.9500
C1—C6	1.395 (4)	C25—C26	1.389 (4)
C1—H1	0.9500	C25—H25	0.9500
C2—C3	1.382 (4)	C26—C27	1.514 (4)
C2—H2	0.9500	C27—C28	1.517 (4)
C3—C4	1.384 (4)	C27—C35	1.564 (4)
C4—C5	1.381 (4)	C27—H27	1.0000
C4—H4	0.9500	C28—C29	1.382 (4)
C5—C6	1.394 (4)	C28—C33	1.398 (4)
C5—H5	0.9500	C29—C30	1.391 (4)
C6—C7	1.515 (3)	C29—H29	0.9500
C7—C8	1.521 (3)	C30—C31	1.396 (5)
C7—C15	1.564 (3)	C30—H30	0.9500
C7—H7	1.0000	C31—C32	1.390 (5)
C8—C13	1.388 (4)	C31—H31	0.9500
C8—C9	1.390 (4)	C32—C33	1.384 (4)
C9—C10	1.395 (4)	C32—H32	0.9500
C9—H9	0.9500	C33—C34	1.501 (4)
C10—C11	1.393 (4)	C34—C35	1.550 (4)
C10—H10	0.9500	C34—H34A	0.9900
C11—C12	1.386 (4)	C34—H34B	0.9900
C11—H11	0.9500	C35—C36	1.504 (5)
C12—C13	1.391 (4)	C35—C36A	1.64 (2)
C12—H12	0.9500	C35—H35	1.0000
C13—C14	1.504 (4)	C35—H35A	1.0000
C14—C15	1.543 (3)	C36—F2	1.447 (4)
C14—H14A	0.9900	C36—C38	1.516 (5)

C14—H14B	0.9900	C36—C37	1.517 (5)
C15—C16	1.525 (4)	C37—H37A	0.9800
C15—H15	1.0000	C37—H37B	0.9800
C16—C17	1.518 (4)	C37—H37C	0.9800
C16—C18	1.521 (4)	C38—H38A	0.9800
C17—H17A	0.9800	C38—H38B	0.9800
C17—H17B	0.9800	C38—H38C	0.9800
C17—H17C	0.9800	C36A—C37A	1.48 (2)
C18—H18A	0.9800	C36A—F2A	1.52 (2)
C18—H18B	0.9800	C36A—C38A	1.56 (2)
C18—H18C	0.9800	C37A—H37D	0.9800
O3—N2	1.229 (3)	C37A—H37E	0.9800
O4—N2	1.231 (3)	C37A—H37F	0.9800
N2—C23	1.465 (3)	C38A—H38D	0.9800
C21—C22	1.379 (4)	C38A—H38E	0.9800
C21—C26	1.395 (4)	C38A—H38F	0.9800
C21—H21	0.9500		
O2—N1—O1	124.0 (2)	C23—C24—C25	118.2 (2)
O2—N1—C3	117.8 (2)	C23—C24—H24	120.9
O1—N1—C3	118.1 (2)	C25—C24—H24	120.9
C2—C1—C6	121.1 (2)	C26—C25—C24	121.4 (2)
C2—C1—H1	119.5	C26—C25—H25	119.3
C6—C1—H1	119.5	C24—C25—H25	119.3
C3—C2—C1	118.1 (2)	C25—C26—C21	118.4 (2)
C3—C2—H2	121.0	C25—C26—C27	121.0 (2)
C1—C2—H2	121.0	C21—C26—C27	120.6 (2)
C2—C3—C4	122.5 (2)	C26—C27—C28	112.9 (2)
C2—C3—N1	118.9 (2)	C26—C27—C35	116.5 (2)
C4—C3—N1	118.6 (2)	C28—C27—C35	102.1 (2)
C5—C4—C3	118.5 (2)	C26—C27—H27	108.3
C5—C4—H4	120.8	C28—C27—H27	108.3
C3—C4—H4	120.8	C35—C27—H27	108.3

C4—C5—C6	121.1 (2)	C29—C28—C33	120.7 (3)
C4—C5—H5	119.5	C29—C28—C27	128.5 (2)
C6—C5—H5	119.5	C33—C28—C27	110.8 (2)
C5—C6—C1	118.8 (2)	C28—C29—C30	119.2 (3)
C5—C6—C7	121.0 (2)	C28—C29—H29	120.4
C1—C6—C7	120.2 (2)	C30—C29—H29	120.4
C6—C7—C8	112.7 (2)	C29—C30—C31	120.0 (3)
C6—C7—C15	115.4 (2)	C29—C30—H30	120.0
C8—C7—C15	102.41 (19)	C31—C30—H30	120.0
C6—C7—H7	108.7	C32—C31—C30	120.6 (3)
C8—C7—H7	108.7	C32—C31—H31	119.7
C15—C7—H7	108.7	C30—C31—H31	119.7
C13—C8—C9	121.2 (2)	C33—C32—C31	119.1 (3)
C13—C8—C7	111.1 (2)	C33—C32—H32	120.4
C9—C8—C7	127.7 (2)	C31—C32—H32	120.4
C8—C9—C10	118.5 (2)	C32—C33—C28	120.2 (3)
C8—C9—H9	120.8	C32—C33—C34	129.4 (3)
C10—C9—H9	120.8	C28—C33—C34	110.4 (2)
C11—C10—C9	120.3 (2)	C33—C34—C35	103.7 (2)
C11—C10—H10	119.9	C33—C34—H34A	111.0
C9—C10—H10	119.9	C35—C34—H34A	111.0
C12—C11—C10	120.9 (2)	C33—C34—H34B	111.0
C12—C11—H11	119.5	C35—C34—H34B	111.0
C10—C11—H11	119.5	H34A—C34—H34B	109.0
C11—C12—C13	119.0 (2)	C36—C35—C34	112.3 (2)
C11—C12—H12	120.5	C36—C35—C27	115.6 (3)
C13—C12—H12	120.5	C34—C35—C27	104.3 (2)
C8—C13—C12	120.2 (2)	C34—C35—C36A	123.5 (9)
C8—C13—C14	110.6 (2)	C27—C35—C36A	118.7 (9)
C12—C13—C14	129.2 (2)	C36—C35—H35	108.1
C13—C14—C15	103.9 (2)	C34—C35—H35	108.1
C13—C14—H14A	111.0	C27—C35—H35	108.1
C15—C14—H14A	111.0	C34—C35—H35A	102.3

C13—C14—H14B	111.0	C27—C35—H35A	102.3
C15—C14—H14B	111.0	C36A—C35—H35A	102.3
H14A—C14—H14B	109.0	F2—C36—C35	107.0 (3)
C16—C15—C14	113.3 (2)	F2—C36—C38	107.1 (3)
C16—C15—C7	115.3 (2)	C35—C36—C38	111.7 (3)
C14—C15—C7	105.05 (19)	F2—C36—C37	108.8 (3)
C16—C15—H15	107.6	C35—C36—C37	111.0 (3)
C14—C15—H15	107.6	C38—C36—C37	111.1 (3)
C7—C15—H15	107.6	C36—C37—H37A	109.5
F1—C16—C17	106.4 (2)	C36—C37—H37B	109.5
F1—C16—C18	106.6 (2)	H37A—C37—H37B	109.5
C17—C16—C18	110.9 (2)	C36—C37—H37C	109.5
F1—C16—C15	106.8 (2)	H37A—C37—H37C	109.5
C17—C16—C15	113.3 (2)	H37B—C37—H37C	109.5
C18—C16—C15	112.2 (2)	C36—C38—H38A	109.5
C16—C17—H17A	109.5	C36—C38—H38B	109.5
C16—C17—H17B	109.5	H38A—C38—H38B	109.5
H17A—C17—H17B	109.5	C36—C38—H38C	109.5
C16—C17—H17C	109.5	H38A—C38—H38C	109.5
H17A—C17—H17C	109.5	H38B—C38—H38C	109.5
H17B—C17—H17C	109.5	C37A—C36A—F2A	107.2 (19)
C16—C18—H18A	109.5	C37A—C36A—C38A	100.2 (18)
C16—C18—H18B	109.5	F2A—C36A—C38A	110.2 (17)
H18A—C18—H18B	109.5	C37A—C36A—C35	110.4 (16)
C16—C18—H18C	109.5	F2A—C36A—C35	113.7 (14)
H18A—C18—H18C	109.5	C38A—C36A—C35	114.0 (17)
H18B—C18—H18C	109.5	C36A—C37A— H37D	109.5
O3—N2—O4	123.2 (2)	C36A—C37A—H37E	109.5
O3—N2—C23	118.6 (2)	H37D—C37A—H37E	109.5
O4—N2—C23	118.2 (2)	C36A—C37A—H37F	109.5
C22—C21—C26	121.3 (2)	H37D—C37A—H37F	109.5
C22—C21—H21	119.4	H37E—C37A—H37F	109.5

C26—C21—H21	119.4	C36A—C38A—H38D	109.5
C21—C22—C23	118.6 (2)	C36A—C38A—H38E	109.5
C21—C22—H22	120.7	H38D—C38A—H38E	109.5
C23—C22—H22	120.7	C36A—C38A—H38F	109.5
C24—C23—C22	122.1 (2)	H38D—C38A—H38F	109.5
C24—C23—N2	119.4 (2)	H38E—C38A—H38F	109.5
C22—C23—N2	118.4 (2)		
C6—C1—C2—C3	-0.1 (4)	O3—N2—C23—C22	7.9 (3)
C1—C2—C3—C4	-2.2 (4)	O4—N2—C23—C22	-172.8 (2)
C1—C2—C3—N1	177.7 (2)	C22—C23—C24—C25	-1.3 (4)
O2—N1—C3—C2	-167.0 (2)	N2—C23—C24—C25	178.5 (2)
O1—N1—C3—C2	13.2 (3)	C23—C24—C25—C26	0.3 (4)
O2—N1—C3—C4	12.9 (3)	C24—C25—C26—C21	1.3 (4)
O1—N1—C3—C4	-166.9 (2)	C24—C25—C26—C27	179.0 (2)
C2—C3—C4—C5	1.6 (4)	C22—C21—C26—C25	-1.9 (4)
N1—C3—C4—C5	-178.2 (2)	C22—C21—C26—C27	-179.6 (2)
C3—C4—C5—C6	1.3 (4)	C25—C26—C27—C28	-119.7 (3)
C4—C5—C6—C1	-3.4 (4)	C21—C26—C27—C28	57.9 (3)
C4—C5—C6—C7	177.7 (2)	C25—C26—C27—C35	122.6 (3)
C2—C1—C6—C5	2.8 (4)	C21—C26—C27—C35	-59.8 (3)
C2—C1—C6—C7	-178.3 (2)	C26—C27—C28—C29	36.7 (4)
C5—C6—C7—C8	61.5 (3)	C35—C27—C28—C29	162.6 (3)

C1—C6—C7—C8	-117.4 (2)	C26—C27—C28—C33	-145.4 (2)
C5—C6—C7—C15	-55.7 (3)	C35—C27—C28—C33	-19.5 (3)
C1—C6—C7—C15	125.4 (2)	C33—C28—C29—C30	-1.2 (4)
C6—C7—C8—C13	-140.1 (2)	C27—C28—C29—C30	176.5 (3)
C15—C7—C8—C13	-15.5 (3)	C28—C29—C30—C31	0.0 (4)
C6—C7—C8—C9	40.8 (3)	C29—C30—C31—C32	0.6 (5)
C15—C7—C8—C9	165.4 (2)	C30—C31—C32—C33	0.1 (5)
C13—C8—C9—C10	0.3 (4)	C31—C32—C33—C28	-1.4 (4)
C7—C8—C9—C10	179.4 (2)	C31—C32—C33—C34	-179.4 (3)
C8—C9—C10—C11	-0.2 (4)	C29—C28—C33—C32	2.0 (4)
C9—C10—C11—C12	-0.8 (4)	C27—C28—C33—C32	-176.1 (2)
C10—C11—C12—C13	1.6 (4)	C29—C28—C33—C34	-179.6 (2)
C9—C8—C13—C12	0.5 (4)	C27—C28—C33—C34	2.3 (3)
C7—C8—C13—C12	-178.7 (2)	C32—C33—C34—C35	-165.5 (3)
C9—C8—C13—C14	178.8 (2)	C28—C33—C34—C35	16.3 (3)
C7—C8—C13—C14	-0.4 (3)	C33—C34—C35—C36	-153.4 (3)
C11—C12—C13—C8	-1.4 (4)	C33—C34—C35—C27	-27.5 (3)
C11—C12—C13—C14	-179.3 (3)	C33—C34—C35—C36A	-167.2 (10)
C8—C13—C14—C15	16.5 (3)	C26—C27—C35—C36	-84.4 (3)

C12—C13—C14— C15	-165.5 (3)	C28—C27—C35— C36	152.1 (2)
C13—C14—C15— C16	-151.9 (2)	C26—C27—C35— C34	151.8 (2)
C13—C14—C15—C7	-25.3 (3)	C28—C27—C35— C34	28.4 (3)
C6—C7—C15—C16	-87.1 (3)	C26—C27—C35— C36A	-66.2 (9)
C8—C7—C15—C16	150.1 (2)	C28—C27—C35— C36A	170.4 (9)
C6—C7—C15—C14	147.6 (2)	C34—C35—C36—F2	60.1 (3)
C8—C7—C15—C14	24.7 (2)	C27—C35—C36—F2	-59.3 (3)
C14—C15—C16—F1	60.6 (3)	C34—C35—C36— C38	-56.8 (4)
C7—C15—C16—F1	-60.4 (3)	C27—C35—C36— C38	-176.2 (3)
C14—C15—C16— C17	177.5 (2)	C34—C35—C36— C37	178.7 (3)
C7—C15—C16—C17	56.5 (3)	C27—C35—C36— C37	59.2 (4)
C14—C15—C16— C18	-55.9 (3)	C34—C35—C36A— C37A	-162.4 (15)
C7—C15—C16—C18	-176.9 (2)	C27—C35—C36A— C37A	63.2 (19)
C26—C21—C22— C23	0.9 (4)	C34—C35—C36A— F2A	76.9 (17)
C21—C22—C23— C24	0.7 (4)	C27—C35—C36A— F2A	-57.4 (18)
C21—C22—C23— N2	-179.1 (2)	C34—C35—C36A— C38A	-50.5 (19)
O3—N2—C23—C24	-171.9 (2)	C27—C35—C36A— C38A	175.2 (14)
O4—N2—C23—C24	7.3 (3)		

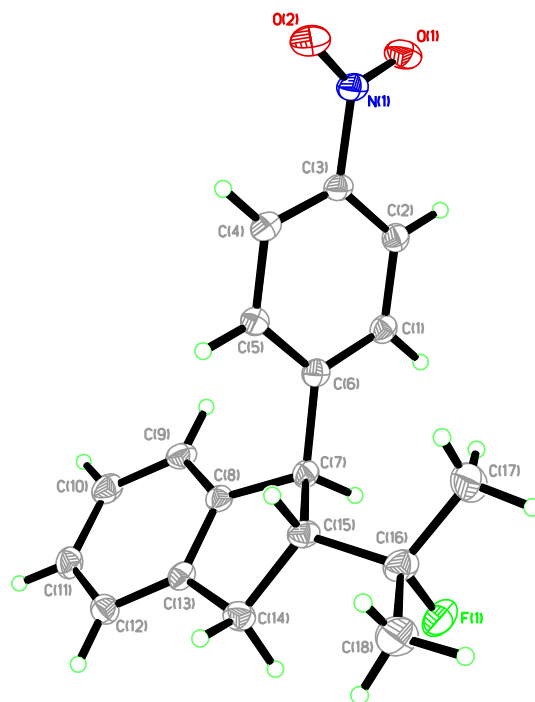


Figure S3.6 Perspective views showing 50% probability displacement.

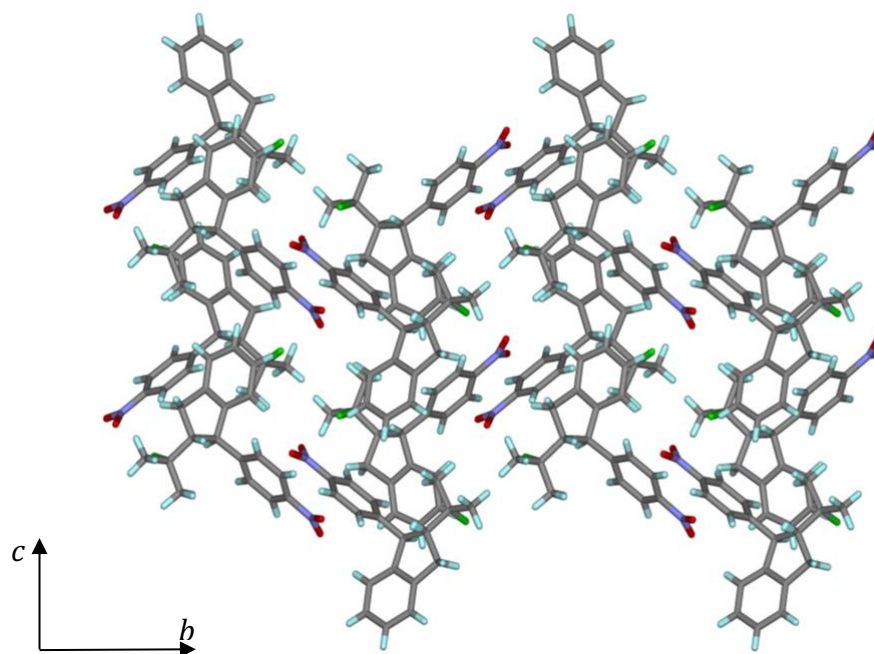


Figure S3.7 Three-dimensional supramolecular architecture viewed along the *a*-axis direction.