



Silver-Mediated Trifluoromethoxylation of Aryl Nucleophiles and Synthesis of 3-Deoxy-3-Fluoromorphine

Citation

Liang, Theresa. 2012. Silver-Mediated Trifluoromethoxylation of Aryl Nucleophiles and Synthesis of 3-Deoxy-3-Fluoromorphine. Doctoral dissertation, Harvard University.

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SILVER-MEDIATED TRIFLUOROMETHOXYLATION OF ARYL NUCLEOPHILES AND SYNTHESIS OF 3-DEOXY-3-FLUOROMORPHINE

Abstract

Fluorine incorporation has become increasingly important in pharmaceutical applications. Upon fluorination and incorporation of fluorinated moieties such as trifluoromethoxy groups, many small molecules become more bioavailable and metabolically stable and additionally can better cross the blood-brain-barrier. This thesis describes the development of a method mediated by silver salts for the synthesis of pharmaceutical-like trifluoromethoxylated compounds via C–OCF₃ bond formation. Additionally, the synthesis of 3-deoxy-3-fluoromorphine via late-stage fluorination of morphine is described as well as in vitro and in vivo evaluation of 3-deoxy-3-fluoromorphine as a potential analgesic.

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Note

Portions of this thesis have been taken from the following publications:

1. Huang, C.; Liang, T.; Harada, S.; Lee, E.; Ritter, T. Silver-Mediated Trifluoromethoxylation of Aryl Stannanes and Arylboronic Acids. *J. Am. Chem. Soc.* 2011, *133*, 13308.
2. Liang, T.; Ritter, T. Progress and Advances in the Incorporation of Fluorine and Fluorinated Functional Groups. *Angew. Chem. Int. Ed.* In preparation.
3. Liang, T.; Ritter, T. Synthesis of Fluorides. In *Comprehensive Organic Synthesis 2e*. In preparation.

Acknowledgements

I have been very blessed by the people in my life during my graduate studies. Many people have contributed to the success of my graduate career and for that I am extremely grateful. I would first like to say though that without God's provision, protection, and blessing, none of this would be possible and I thank Him first and foremost for allowing me to embark on this journey.

I am extremely grateful my adviser, Tobias Ritter, who has taught me how to not fear taking risks, both in research and in life, and to pursue projects that would really make an impact in science. I also thank him for being so patient these past five years as I learned how to think critically about science and also for his guidance, both academically and personally, along the way. He is an adviser that I can have genuine and honest conversations with and a leader that truly desires to be the best he can be for his students. Additionally, a hearty thank you to Eric Jacobsen and Ted Betley for being on my thesis committee and their open-door policy for me to drop by and ask questions.

I am also very grateful to have such a motivated and helpful research group, especially in the last six months of my graduate studies. I would like to thank all Ritter group members past and present especially 310 Mallinkrodt baymates (and adopted baymates) Jessica Wu, Christian Kuttruff, Pingping Tang, Ville Olsson, Jean Reynaud, Charles Reese, Anthony Mazzotti, Greg Boursalian (go Bears!), Nicky Stephenson, Kangsang Lee, Jennifer Murphy, Filippo Sladojevich, and Kasia Hojczyk. I would be remiss not to specifically thank Pingping who has been such a great mentor in the lab and has patiently helped me without reservation in my research. Mike Campbell and Sarah Parker have both made the lab an enjoyable place to work, especially during the beginning years of the group. Additionally, undergrads Weike Wang and Allie Strom were such a joy to work with and have been very close and intimate friends of mine, supporting me throughout the journey. Thank you all for making my Harvard experience so wonderfully memorable and for providing a home away from home.

For the trifluoromethoxylation project, I would like to acknowledge Chenghong Huang, Eunsung Lee, and Shinji Harada for their contributions to the project. I would also like to thank Dr. Aron Lichtman for his work on the in vivo studies for the morphine project. Additionally, Dr. Jianren Mao and Dr. Luke Wang have offered their invaluable advice and support for the morphine project as well.

On a more personal note, I would like to thank the Harvard Graduate Christian Fellowship as well as Citylife Presbyterian Church for being such supportive communities and additionally for all the help (moving around the dorms, listening to practice talks, etc.) and personal growth (bible studies, accountability, and of course fun!) both groups have provided. Every individual in both communities has left a profound impact on me and I will never forget the love, generosity, and support you have all shown me. From those groups, I would like to especially thank Grace Chen, Gary Sing, Catherine Con, Minju Kim, and Bo Zhu for spending time with me, encouraging me, and being amazing brothers and sisters!

Other people I would like to thank include Sirinya Matchacheep and Philippe de Rouffignac for their love and hospitality and for being my second family here in Cambridge. Additionally, the Dunster community especially Art Bartolozzi, Chris Allison, Grecia Gonzalez, and Aixin Wang has provided a wonderful second home to come back to after finishing up in lab each day these past three years. Thank you guys for being so spectacular!

Most importantly, I would like to thank my parents and my brother Andrew for being the best family a girl can ask for. Thank you for loving me when I act unlovable and for listening to me complain about research not progressing and about graduate school woes. To my parents, thank you for teaching me about the most important things in life, especially about God's faithfulness in my moments of doubt. Without you both, I would never have come to make the most important decision in my life—entrusting my future and beyond to my Lord and Savior—and I thank you for that.

List of Abbreviations

Å: angstrom
Ac: acetyl
Ad: adamantyl
Ar: aryl
Bn: benzyl
Boc: *N-tert*-butoxycarbonyl
BOX: bisoxazoline ligand
Bu: butyl
Bz: benzoyl
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
DMF: *N,N*-dimethylformamide
DMSO: dimethylsulfoxide
equiv: equivalent
Et: ethyl
EtOH: ethanol
EWG: electron-withdrawing group
F-TEDA-BF₄: 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
F-TEDA-PF₆: 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate)
h: hour
i.p.: intraperitoneal
*i*Pr: isopropyl
*i*PrOH: isopropanol
L: ligand
*m*CPBA: *meta*-chloroperoxybenzoic acid
Me: methyl
MeCN: acetonitrile
min: minute
Mor: morphine
MPE: maximal possible effect
MTBE: methyl *tert*-butyl ether
*n*BuLi: *n*-butyl lithium
NFSI: *N*-fluorobis(phenylsulfonyl)imide
nM: nanomolar
NMP: *N*-methylpyrrolidine
Ph: phenyl
PTFE: polytetrafluoroethylene
py: pyridine
R: general substituent
rgt: reagent
SEM: standard error of the mean
S_N1: first-order nucleophilic substitution
S_N2: second-order nucleophilic substitution
S_NAr: nucleophilic aromatic substitution
TADDOL: $\alpha,\alpha,\alpha,\alpha$ -tetraaryl-1,3-dioxolane-4,5-dimethanol
*t*Bu: *tert*-butyl
TEDA: triethylenediamine
Tf: trifluoromethanesulfonyl
THF: tetrahydrofuran
Veh: vehicle
X: anionic counterion, typically halide anion

Isaiah 43:1-7 (NIV)

¹ But now, this is what the Lord says—
 he who created you, Jacob,
 he who formed you, Israel:
“Do not fear, for I have redeemed you;
I have summoned you by name; you are mine.
² When you pass through the waters,
 I will be with you;
and when you pass through the rivers,
 they will not sweep over you.
When you walk through the fire,
 you will not be burned;
the flames will not set you ablaze.
³ For I am the Lord your God,
the Holy One of Israel, your Savior;
I give Egypt for your ransom,
Cush and Seba in your stead.
⁴ Since you are precious and honored in my sight,
 and because I love you,
I will give people in exchange for you,
nations in exchange for your life.
⁵ Do not be afraid, for I am with you;
I will bring your children from the east
 and gather you from the west.
⁶ I will say to the north, ‘Give them up!’
and to the south, ‘Do not hold them back.’
Bring my sons from afar
and my daughters from the ends of the earth—
⁷ everyone who is called by my name,
 whom I created for my glory,
 whom I formed and made.”

For my Redeemer, forever my first Love

1. Introduction

1.1. Importance of fluorine incorporation

Pharmaceuticals,¹ agrochemicals,² new materials³ such as electronic/optoelectronic materials (electroluminescent diodes or liquid crystals),^{3a-d} polymers (Teflon or elastomers),^{3e-h} and metal-organic frameworks,^{3d} as well as positron emission tomography⁴ have benefited from fluorine incorporation. Over the past thirty years; the number of fluorinated pharmaceuticals has grown to 20% of all developed drugs^{1f} while fluorinated agrochemicals^{1e} consist of up to 30% of all agrochemicals developed, compared to 4% in the late 1970s.^{2b}

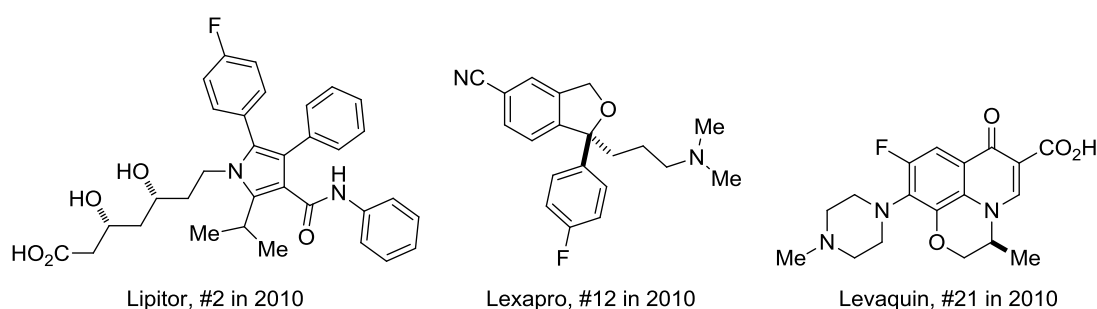


Figure 1. Selected fluorinated brand-name drugs and their ranking by retail sales in the United States for 2010⁵

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⁵ Ranking taken from: <http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster> (downloaded 07/18/2012)

1.1.1. Fluorine incorporation for medicinal chemistry applications

Fluorine can provide many beneficial properties when incorporated into a molecule. As the most electronegative element of the periodic table, fluorine can increase the Brønsted acidity of nearby functional groups thereby allowing for the modulation of the pK_a of the functional group.^{1f,6} This is especially useful in medicinal chemistry to attenuate the basicity of amines or other basic residues that can hinder membrane penetration due to protonation at physiological pH.⁷ Upon fluorine incorporation, arenes are reported to show increased lipophilicity,^{6,8} which has been advantageously used in drug development.^{1a,c,d,f,g,i} Fluorination and incorporation of fluorinated moieties such as $-CF_3$, $-OCF_3$, and $-SCF_3$ groups typically lead to increased bioavailability and blood-brain-barrier penetrability.⁹ Additionally, the high electronegativity of fluorine contributes to the polar nature of carbon–fluorine bonds and the interaction of the bond with hydrogen bond donors¹⁰ (the existence of a genuine hydrogen bond with the fluorinated moiety in molecules is under debate),¹¹ other fluorinated compounds,^{12,3c,d,h} polar functional groups such as carbonyls,¹³ and hydrophobic moieties.¹ The polar nature of the carbon–fluorine bond additionally contributes to its

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¹¹ (a) Schneider, H. J. *Chem. Sci.* 2012, **3**, 1381. (b) Dunitz, J. D. *ChemBioChem* 2004, **5**, 614.

¹² Berkessel, A.; Adrio, J. A.; Huettnerich, D.; Neudorfl, J. M. *J. Am. Chem. Soc.* 2006, **128**, 8421.

¹³ (a) Olsen, J. A.; Banner, D. W.; Seiler, P.; Sander, U. O.; D'Arcy, A.; Stihle, M.; Muller, K.; Diederich, F. *Angew. Chem. Int. Ed.* 2003, **42**, 2507. (b) Hof, F.; Scofield, D. M.; Schweizer, W. B.; Diederich, F. *Angew. Chem. Int. Ed.* 2004, **43**, 5056. (c) Olsen, J.; Seiler, P.; Wagner, B.; Fischer, H.; Tschopp, T.; Obst-Sander, U.; Banner, D. W.; Kansy, M.; Muller, K.; Diederich, F. *Org. Biomol. Chem.* 2004, **2**, 1339. (d) Olsen, J. A.; Banner, D. W.; Seiler, P.; Wagner, B.; Tschopp, T.; Obst-Sander, U.; Kansy, M.; Muller, K.; Diederich, F. *ChemBioChem* 2004, **5**, 666. (e) Paulini, R.; Muller, K.; Diederich, F. *Angew. Chem. Int. Ed.* 2005, **44**, 1788.

bond strength^{1h,14} making carbon–fluorine bonds difficult to fragment. Most fluorinated compounds, but not all,¹⁵ exhibit increased metabolic stability by impedance of undesired oxidative metabolism pathways.¹⁶

Although fluorine is often used as an isostere for hydrogen in medical chemistry, the van der Waals radius of fluorine is more similar to oxygen (1.47 Å versus 1.52 Å for oxygen and 1.20 Å for hydrogen).¹⁷ Exploiting the steric likeness of oxygen and fluorine, alkenyl fluorides have been investigated as isosteres for amide bonds in peptides.¹⁸ Fluorine incorporation has been shown to increase binding affinity to target systems¹⁹ probably due to advantageous polar interactions,²⁰ however, in many cases this phenomenon is empirically observed and rationalized ex post facto and cannot be predicted or designed a priori. Additionally, fluorinated compounds can be strategically used as transition state inhibitors (i.e. inhibitors that react with the target system and are trapped as the covalently linked inhibitor–target complex), which advantageously use the fluorinated moiety to halt further reactivity in the

¹⁴ Peters, D. *J. Chem. Phys.* 1963, **38**, 561.

¹⁵ For examples in which fluorination does not increase metabolic stability, please see: (a) Kaufman, S. *Biochim. Biophys. Acta* 1961, **51**, 619. (b) Guroff, G.; Daly, J. W.; Jerina, D. M.; Renson, J.; Witkop, B.; Udenfrie, S. *Science* 1967, **157**, 1524.

¹⁶ (a) Barnette, W. E. *Crit. Rev. Biochem.* 1984, **15**, 201. (b) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* 1997, **40**, 1347. (c) VanHeek, M.; France, C. F.; Compton, D. S.; McLeod, R. L.; Yumibe, N. P.; Alton, K. B.; Sybertz, E. J.; Davis, H. R. *J. Pharmacol. Exp. Ther.* 1997, **283**, 157. (d) Clader, J. W. *J. Med. Chem.* 2004, **47**, 1.

¹⁷ Bondi, A. *J. Phys. Chem.* 1964, **68**, 441.

¹⁸ Bartlett, P. A.; Otake, A. *J. Org. Chem.* 1995, **60**, 3107.

¹⁹ (a) Piepenbrink, K. H.; Borbulevych, O. Y.; Sommese, R. F.; Clemens, J.; Armstrong, K. M.; Desmond, C.; Do, P.; Baker, B. M. *Biochem. J* 2009, **423**, 353. (b) Burke, T. R.; Ye, B.; Yan, X. J.; Wang, S. M.; Jia, Z. C.; Chen, L.; Zhang, Z. Y.; Barford, D. *Biochemistry* 1996, **35**, 15989. (c) DerHovanessian, A.; Doyon, J. B.; Jain, A.; Rablen, P. R.; Sapse, A. M. *Org. Lett.* 1999, **1**, 1359. (d) Doyon, J. B.; Jain, A. *Org. Lett.* 1999, **1**, 183. (e) Kim, C. Y.; Chang, J. S.; Doyon, J. B.; Baird, T. T.; Fierke, C. A.; Jain, A.; Christianson, D. W. *J. Am. Chem. Soc.* 2000, **122**, 12125. (f) Kim, C. Y.; Chandra, P. P.; Jain, A.; Christianson, D. W. *J. Am. Chem. Soc.* 2001, **123**, 9620. (g) Abbate, F.; Casini, A.; Scozzafava, A.; Supuran, C. T. *J. Enzyme Inhib. Med. Chem.* 2003, **18**, 303. (h) Chou, Y. L.; Davey, D. D.; Eagen, K. A.; Griedel, B. D.; Karanjawala, R.; Phillips, G. B.; Sacchi, K. L.; Shaw, K. J.; Wu, S. C.; Lentz, D.; Liang, A. M.; Trinh, L.; Morrissey, M. M.; Kochanny, M. J. *Bioorg. Med. Chem. Lett.* 2003, **13**, 507. (i) Koga, H.; Itoh, A.; Murayama, S.; Suzue, S.; Irikura, T. *J. Med. Chem.* 1980, **23**, 1358. (j) Kotoris, C. C.; Chen, M. J.; Taylor, S. D. *Bioorg. Med. Chem. Lett.* 1998, **8**, 3275. (k) Domagala, J. M.; Hanna, L. D.; Heifetz, C. L.; Hutt, M. P.; Mich, T. F.; Sanchez, J. P.; Solomon, M. *J. Med. Chem.* 1986, **29**, 394. (l) Domagala, J. M.; Heifetz, C. L.; Mich, T. F.; Nichols, J. B. *J. Med. Chem.* 1986, **29**, 445. (m) Grunewald, G. L.; Seim, M. R.; Lu, J.; Makboul, M.; Criscione, K. R. *J. Med. Chem.* 2006, **49**, 2939. (n) Roth, B. D.; Ortwine, D. F.; Hoefle, M. L.; Stratton, C. D.; Sliskovic, D. R.; Wilson, M. W.; Newton, R. S. *J. Med. Chem.* 1990, **33**, 21.

²⁰ DiMagno, S. G.; Sun, H. *Curr. Top. Med. Chem.* 2006, **6**, 1473.

target system.^{1c} Likewise, fluorinated functional groups such as monofluoromethyl and difluoromethyl groups have been used as pseudo-oxygen replacements in molecules such as nucleotides, phosphate esters, and sulphate esters.²¹ Difluoromethyl moieties can act as electrophilic alkylating agents and inhibit target systems via irreversible alkylation.²²

1.1.2. Fluorination with fluorine-18 for positron emission tomography (PET)

Positron emission tomography (PET) is the molecular imaging of in vivo processes via detection of positron decay of radioactively tagged molecules called radiotracers.^{4a-d} There is continual growing interest in using fluorine-18, the radioactive isotope of sole naturally occurring fluorine isotope fluorine-19, in radiochemistry due to the convenient half-life time of 110 minutes. Methods to introduce fluorine-18 into molecules should occur, if not at the last step, at the latest stage of the radiotracer synthesis as possible. Ideally, the time used to synthesize, purify, and formulate radiotracers for injection should take less than two half-life cycles. The method for fluorine-18 introduction should be highly efficient at nanomolar concentrations such that picomolar amounts of radiotracers can be obtained, which is often difficult; thus, a 10³- or 10⁴-fold excess of the unlabeled precursor is often times used to facilitate the reaction. Multiple fluorinated and non-fluorinated products can arise from non-selective and inefficient radiofluorination reagent reactivity, especially for electrophilic radiofluorination methods. This phenomenon is undesirable because of difficulties in separating the fluorinated products from each other and non-fluorinated products from the fluorinated products. A minimally water-sensitive method that allows for the efficient incorporation of high specific activity ¹⁸F as one single ¹⁸F-fluorinated product would provide the ideal radiofluorination reaction.

Nucleophilic methods for the incorporation of ¹⁸F

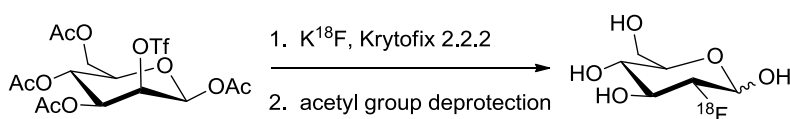
Fluorine-18 is synthesized by the bombardment of oxygen-18-enriched water with protons to afford wet ¹⁸F-fluoride in high specific activity (¹⁸F/¹⁹F is >100:1). Desolvation of wet ¹⁸F-fluoride to anhydrous ¹⁸F-fluoride is difficult

²¹ (a) Blackburn, G. M.; Perree, T. D.; Rashid, A.; Bisbal, C.; Lebleu, B. *Chem. Scri.* 1986, **26**, 21. (b) Phillion, D. P.; Cleary, D. G. *J. Org. Chem.* 1992, **57**, 2763. (c) Berkowitz, D. B.; Shen, Q. R.; Maeng, J. H. *Tetrahedron Lett.* 1994, **35**, 6445. (d) Berkowitz, D. B.; Bose, M. *J. Fluorine Chem.* 2001, **112**, 13. (e) Lapierre, J.; Ahmed, V.; Chen, M. J.; Ispahany, M.; Guillemette, J. G.; Taylor, S. D. *Bioorg. Med. Chem. Lett.* 2004, **14**, 151. (f) Burke, T. R., Jr. *Curr. Top. Med. Chem.* 2006, **6**, 1465.

²² Hanson, S. R.; Whalen, L. J.; Wong, C.-H. *Biorg. Med. Chem.* 2006, **14**, 8386.

due to strong hydrogen bonding interaction of the fluoride with water,²³ deterring use of anhydrous ^{18}F -fluoride for PET chemistry. In theory, the maximum achievable yield with high specific activity fluorine-18 is 100%. ^{18}F -Fluoride can be diluted with ^{19}F -fluorine gas to generate an ^{18}F -enriched electrophilic fluorinating reagent but would result in low specific activity reagent due ^{18}F dilution with ^{19}F . Reactions with high specific activity ^{18}F are thus more desirable.

Radiofluorinations with ^{18}F -fluoride is the most common for substitution reactions that occur on alkyl or aryl substrates and is dependent on leaving group ability as well as activation by EWGs of the alkane or arene. Because generation of ^{18}F -fluoride occurs in aqueous conditions, cryptands along with alkali salts are typically used to increase fluoride nucleophilicity^{4d} (nucleophilicity is diminished via hydrogen bonding²³). Reactions solvents are chosen such that $\text{S}_{\text{N}}2$ -type and $\text{S}_{\text{N}}\text{Ar}$ -type reactions are facilitated with the most commonly used solvents being polar aprotic solvents DMF, DMSO, and acetonitrile. Alkyl halides or sulfonates (such as triflates) are substituted via $\text{S}_{\text{N}}2$ reaction with activated ^{18}F -fluoride with no additional EWGs required unlike with nucleophilic aromatic substitution. ^{18}F -Fluoride is basic when rendered more nucleophilic with cryptands and alkali salts,^{4d} making protic and some electrophilic functional groups incompatible and leading to elimination side reactions. *Tert*-butanol may be used to temper the basicity of ^{18}F -fluoride for aliphatic substitution reactions without excessively losing the nucleophilicity of the fluoride.²⁴ The most commonly produced radiotracer for imaging, 2-deoxy-2- ^{18}F fluoro-D-glucose (^{18}F FDG), can be made via ^{18}F -fluoride substitution of the triflate leaving group (Scheme 1).²⁵



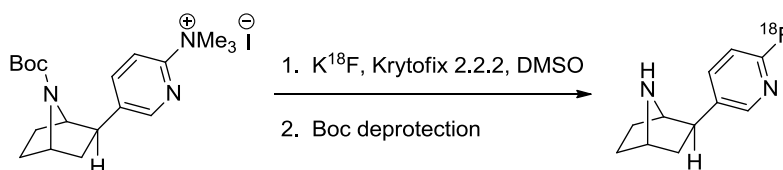
Scheme 1. Nucleophilic radiochemical fluorination with ^{18}F -fluoride to afford ^{18}F FDG

²³ Emsley, J. *Chem. Soc. Rev.* 1980, 9, 91.

²⁴ (a) Kim, D. W.; Ahn, D.-S.; Oh, Y.-H.; Lee, S.; Kil, H. S.; Oh, S. J.; Lee, S. J.; Kim, J. S.; Ryu, J. S.; Moon, D. H.; Chi, D. Y. *J. Am. Chem. Soc.* 2006, 128, 16394. (b) Kim, D. W.; Jeong, H.-J.; Litn, S. T.; Sohn, M.-H.; Katzenellenbogen, J. A.; Chi, D. Y. *J. Org. Chem.* 2008, 73, 957.

²⁵ Hamacher, K.; Coenen, H. H.; Stocklin, G. *J. Nucl. Med.* 1986, 27, 235.

Nucleophilic aromatic substitution with ^{18}F -fluoride can be used to synthesize ^{18}F -labelled arenes.²⁶ Substrates that undergo $\text{S}_{\text{N}}\text{Ar}$ -type substitutions generally require at least one EWG on the arene ortho or para to the leaving group, which can be nitro, trialkylammonium, halide, or sulfonate leaving groups, and substantial heating, even microwave heating in some instances. Use of polar aprotic solvents is especially important for $\text{S}_{\text{N}}\text{Ar}$ reactions, which is drastically impacted by the nucleophilicity of the fluoride. Nicotinic acetylcholine receptor radioligands have been synthesized via nucleophilic aromatic substitution (Scheme 2).²⁷



Scheme 2. Nucleophilic aromatic substitution with ^{18}F -fluoride

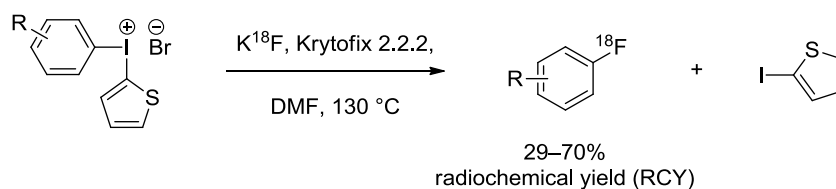
Diaryliodonium salts have also been fluorinated with ^{18}F -fluoride²⁸ with arene selectivity based on electronics (the more electron-poor arene is fluorinated) and sterics (*ortho*-substituted arenes are more susceptible to fluorination) (Scheme 3). Currently, 2-thiophene can be advantageously used as a dummy ligand on iodine.^{28b} The counterion of the iodonium salts also have an effect on the yield of fluorination—the more dissociative and non-nucleophilic counteranions promote higher radiochemical yields (decay-corrected yields, radiochemical yields of 10–50% are useful for imaging). With *ortho*-substituted substrates, the radiochemical yield can be as high as ~60%. The major drawback to this approach with diaryliodonium salts is that complex, natural product-like substrates are difficult to synthesize as diaryliodonium salts with the current methodologies available. The synthesis of aryl iodonium salts often employs oxidants such as *m*CPBA or peroxydisulfate salts and strong acids such as sulfuric acid and triflic acid.²⁹

²⁶ (a) Attina, M.; Cacace, F.; Wolf, A. P. *J. Chem. Soc., Chem. Commun.* 1983, 108. (b) Angelini, G.; Speranza, M.; Wolf, A. P.; Shiue, C. Y. *J. Fluorine Chem.* 1985, 27, 177.

²⁷ Ding, Y. S.; Gatley, S. J.; Fowler, J. S.; Volkow, N. D.; Aggarwal, D.; Logan, J.; Dewey, S. L.; Liang, F.; Carroll, F. I.; Kuhar, M. J. *Synapse* 1996, 24, 403.

²⁸ (a) Pike, V. W.; Aigbirhio, F. I. *J. Chem. Soc., Chem. Commun.* 1995, 2215. (b) Ross, T. L.; Ermert, J.; Hocke, C.; Coenen, H. H. *J. Am. Chem. Soc.* 2007, 129, 8018.

²⁹ Merritt, E. A.; Olofsson, B. *Angew. Chem. Int. Ed.* 2009, 48, 9052.



Scheme 3. Nucleophilic radiochemical fluorination of aryl(2-thienyl)iodonium bromides

Electrophilic methods for the incorporation of ^{18}F

Electrophilic radiofluorination reactions with low specific activity ^{18}F -fluorine gas have a highest achievable yield of 50% due to dilution of ^{18}F with ^{19}F . Many other ^{18}F -electrophilic fluorinating reagents have been synthesized from ^{18}F -fluorine gas such as ^{18}F -acetyl hypofluorite,³⁰ ^{18}F -xenon difluoride,³¹ ^{18}F -*N*-fluorosulfonamide or imide reagents,³² ^{18}F -*N*-fluoropyridinium salts,³³ and ^{18}F -TEDA salts.³⁴ Electrophilic radiofluorination approaches with the aforementioned reagents are hindered by the use of low specific activity fluorinating reagents. Electrophilic radiofluorination via direct, non-specific fluorination of substrates such as alkenes³⁵ for the synthesis of [^{18}F]FDG and related sugars as well as arenes³⁶ for the synthesis of [^{18}F]fluoro-3,4-dihydroxy phenylalanine ([^{18}F]F-DOPA) commonly leads to multiple fluorinated products and does not demonstrate functional group tolerance. Radiochemical fluorodemetalation has also been used for aryl organometallic reagents,^{32a} aryl silanes,³⁷ and aryl

³⁰ (a) Chirakal, R.; Firnau, G.; Couse, J.; Garnett, E. S. *Int. J. Appl. Radiat. Isot.* 1984, **35**, 651. (b) Namavari, M.; Bishop, A.; Satyamurthy, N.; Bida, G.; Barrio, J. R. *Appl. Radiat. Isot.* 1992, **43**, 989.

³¹ (a) Frame, H. D.; Huston, J. L.; Sheft, I. *Inorg. Chem.* 1969, **8**, 1549. (b) Firnau, G.; Chirakal, R.; Sood, S.; Garnett, E. S. *J. Labelled Compd. Radiopharm.* 1981, **18**, 7. (c) Shiue, C. Y.; To, K. C.; Wolf, A. P. *J. Labelled Compd. Radiopharm.* 1983, **20**, 157. (d) Chirakal, R.; Firnau, G.; Couse, J.; Garnett, E. S. *Int. J. Appl. Radiat. Isot.* 1984, **35**, 651. (e) Aigbirhio, F. I.; Pike, V. W.; Smith, R. G.; Ramsden, C. A. *J. Nucl. Med.* 1998, **39**, 231P. (f) Vasdev, N.; Pointner, B. E.; Chirakal, R.; Schrobilgen, G. J. *J. Am. Chem. Soc.* 2002, **124**, 12863.

³² (a) Satyamurthy, N.; Bida, G. T.; Phelps, M. E.; Barrio, J. R. *Appl. Radiat. Isot.* 1990, **41**, 733. (b) Teare, H.; Robins, E. G.; Arstad, E.; Luthra, S. K.; Gouverneur, V. *Chem. Commun.* 2007, 2330.

³³ Oberdorfer, F.; Hofmann, E.; Maier-Borst, W. *J. Labelled Compd. Radiopharm.* 1988, **35**, 999.

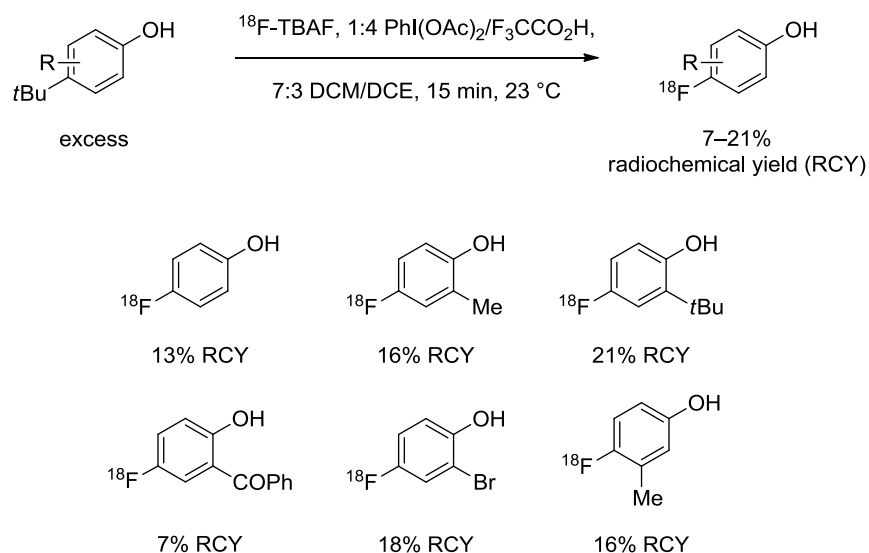
³⁴ Teare, H.; Robins, E. G.; Kirjavainen, A.; Forsback, S.; Sandford, G.; Solin, O.; Luthra, S. K.; Gouverneur, V. *Angew. Chem. Int. Ed.* 2010, **49**, 6821.

³⁵ Ido, T.; Wan, C. N.; Casella, V.; Fowler, J. S.; Wolf, A. P.; Reivich, M.; Kuhl, D. E. *J. Labelled Compd. Radiopharm.* 1978, **14**, 175.

³⁶ Firnau, G.; Garnett, E. S.; Chirakal, R.; Sood, S.; Nahmias, C.; Schrobilgen, G. *Appl. Radiat. Isot.* 1986, **37**, 669.

³⁷ (a) Diraddo, P.; Diksic, M.; Jolly, D. *J. Chem. Soc., Chem. Commun.* 1984, 159. (b) Speranza, M.; Shiue, C. Y.; Wolf, A. P.; Wilbur, D. S.; Angelini, G. *J. Fluorine Chem.* 1985, **30**, 97.

stannanes³⁸ and can afford better fluorination selectivity but requires the use of toxic precursor molecules such as stannanes. Oxidative fluorination of *p-tert*-butylphenols with replacement of the *p-tert*-butyl group with ¹⁸F-fluoride is possible in the presence of iodobenzene diacetate and trifluoroacetic acid in dichloromethane (Scheme 4).³⁹ The isolated fluorination radiochemical yields for various *p-tert*-butylphenol can range from 7–21% and tolerates a wide range of electronically-diverse *ortho*-substituents including halides, other *tert*-butyl groups, carbonyls, and olefins.



Scheme 4. Oxidative radiochemical fluorination of *p-tert*-butyl phenols with ¹⁸F-fluoride

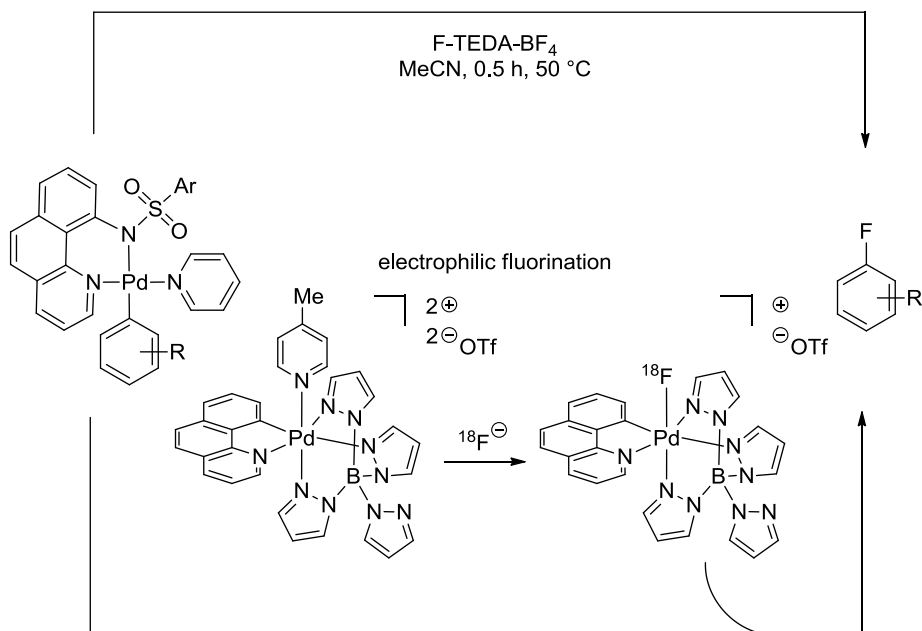
A novel approach to electrophilic radiofluorination involves the umpolung of ¹⁸F-fluoride with a Pd(IV) complex (Scheme 5).⁴⁰ The Pd(IV) complex is an efficient scavenger of fluoride and can be used for the radiochemical fluorination of benzoquinolylsulfonamide Pd(II) complexes to afford ¹⁸F-labeled arenes. Direct S_N2 transfer and an electron-coupled fluoride transfer have both been proposed as possible reaction pathways. An advantage of using this method is that ¹⁸F-fluoride can be incorporated into high complexity arenes and also high specific activity electrophilic radiochemical fluorination can be achieved in up to 33% radiochemical yield. Additionally, the

³⁸ (a) Adam, M. J.; Pate, B. D.; Ruth, T. J.; Berry, J. M.; Hall, L. D. *J. Chem. Soc., Chem. Commun.* 1981, 733. (b) Adam, M. J.; Ruth, T. J.; Jivan, S.; Pate, B. D. *J. Fluorine Chem.* 1984, 25, 329. (c) Namavari, M.; Bishop, A.; Satyamurthy, N.; Bida, G.; Barrio, J. R. *Appl. Radiat. Isot.* 1992, 43, 989.

³⁹ Gao, Z.; Lim, Y. H.; Tredwell, M.; Li, L.; Verhoog, S.; Hopkinson, M.; Kaluza, W.; Collier, T. L.; Passchier, J.; Huiban, M.; Gouverneur, V. *Angew. Chem. Int. Ed.* 2012, 6733.

⁴⁰ Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker, J. M.; Ritter, T. *Science* 2011, 334, 639.

Pd(IV)-[^{18}F] complex is not water-sensitive and is also thermally stable at room temperature. *Ortho*-substituted arenes are currently not viable substrates for this radiochemical fluorination.



Scheme 5. Synthesis of ^{18}F -labelled aryl fluorides with an electrophilic ^{18}F -Pd(IV) fluorinating reagent

1.2. Fluorination

Fluorine is the most electronegative element and thus is difficult to oxidize by one electron to fluoronium (“ F^+ ”); thus, oxidation of fluoride to “ F^+ ” is difficult transformation. As the thirteenth most abundant element in the earth’s crust, fluorine exists as fluoride.⁴¹ This has direct implications in the chemistry that nature uses for fluorine incorporation—the few naturally occurring fluorinated molecules⁴¹ such as fluoroacetate are enzymatically synthesized in nature with fluoride.⁴² This is not the case with other halogens such as iodide⁴³ or bromide,⁴⁴ which can accomplish iodination and bromination with an electrophilic haloperoxidase. Fluoride also forms strong

⁴¹ Harper, D. B.; O'Hagan, D. *Natural Product Reports* 1994, 11, 123.

⁴² (a) Sanada, M.; Miyano, T.; Iwadare, S.; Williamson, J. M.; Arison, B. H.; Smith, J. L.; Douglas, A. W.; Liesch, J. M.; Inamine, E. *J. Antibiot.* 1986, 39, 259. (b) Reid, K. A.; Hamilton, J. T. G.; Bowden, R. D.; O'Hagan, D.; Dasaradhi, L.; Amin, M. R.; Harper, D. B. *Microbiology-UK* 1995, 141, 1385.

⁴³ Kupper, F. C.; Schweigert, N.; Gall, E. A.; Legendre, J. M.; Vilter, H.; Kloareg, B. *Planta* 1998, 207, 163.

⁴⁴ Slebodnick, C.; Hamstra, B. J.; Pecoraro, V. L. Modeling the biological chemistry of vanadium: structural and reactivity studies elucidating biological function. In *Metal Sites in Proteins and Models: Phosphatases, Lewis Acids and Vanadium*; Hill, H. A. O.; Sadler, P. J.; Thomson, A. J., Eds.; Springer-Verlag: Berlin, 1997; Vol. 89, pp 51-108.

hydrogen bonds⁴⁵ that diminish its nucleophilicity; in the laboratory setting, nucleophilic and anhydrous sources of fluoride have been established for use in reactions.

Fluorination reactions investigated in the laboratory have utilized both nucleophilic and electrophilic fluorination approaches to afford fluorinated materials. Many different fluoride sources exist, ranging from metal fluoride salts to organic nucleophilic fluorinating reagents. Highly nucleophilic fluoride sources tend to deliver small unsolvated, densely charged fluoride anions that correspondingly are basic. For certain substrates, this basicity is problematic because undesired side products result from deprotonation with fluoride.

The direct chemical oxidation of fluoride to electrophilic fluorine, as mentioned previously, cannot occur due to the highly negative oxidation potential value of fluoride. Conceptually, the closest example of this type of transformation would be oxidative electron-transfer coupled with fluoride incorporation. Electrophilic fluorination approaches involve the use of fluorine gas and various electrophilic fluorinating reagents. Most electrophilic fluorinating reagents are ultimately derived from fluorine gas, the strongest elemental oxidizing agent known, synthesized by electrolysis of potassium bifluoride in hydrogen fluoride.⁴⁶ Direct use of fluorine gas as the oxidant even with specialized equipment, training, and protocols is hazardous due to the dangers of improper handling—fluorine gas is fatal if inhaled. Use of less-oxidizing electrophilic fluorinating reagents has facilitated the development of more functional group tolerant fluorination methods encompassing a broader substrate scope.

1.2.1. Electrophilic fluorination

Electrophilic fluorination was first reported with highly oxidizing fluorinating reagents such as fluorine gas, hypofluorites, fluoroxysulfates, and perchloryl fluoride that are explosive if handled incorrectly. Xenon difluoride was examined as a more stable electrophilic fluorination source; however, it still displayed uncontrollable reactivity to many functional groups. The development of crystalline, benchtop-stable fluorinating reagents such as *N*-fluorobis(phenyl)sulfonimide (NFSI)⁴⁷ and related analogs,⁴⁸ *N*-fluoropyridinium salts,⁴⁹ and 1-chloromethyl-4-

⁴⁵ Emsley, J. *Chem. Soc. Rev.* 1980, 9, 91.

⁴⁶ Villalba, G.; Ayres, R. U.; Schroder, H. *J. Ind. Ecol.* 2007, 11, 85.

⁴⁷ Differding, E.; Ofner, H. *Synlett* 1991, 187.

⁴⁸ (a) Barnette, W. E. *J. Am. Chem. Soc.* 1984, 106, 452. (b) Differding, E.; Lang, R. W. *Tetrahedron Lett.* 1988, 29, 6087. (c) Differding, E.; Lang, R. W. *Helv. Chim. Acta* 1989, 72, 1248. (d) Davis, F. A.; Han, W. *Tetrahedron Lett.*

fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF₄)⁵⁰ was crucial for the development of selective, functional group tolerant fluorination methods (Figure 2). Even though *N*-fluoro reagents can formally behave as source of fluoronium ("F⁺"), the N-F bonds are polarized toward fluorine, with partial negative charge on fluorine. Because the $\sigma^*_{\text{N-F}}$ orbital on the nitrogen are sterically not accessible, the nucleophiles attack at the $\sigma^*_{\text{N-F}}$ orbital on fluorine. Possibly due to the small orbital coefficient of the $\sigma^*_{\text{N-F}}$ on fluorine and the low energy level of the $\sigma^*_{\text{N-F}}$ orbital, other reactions such as single-electron transfer can compete with electrophilic fluorination. The process in which these oxidants mediate the two-electron oxidation is under discussion; two single-electron transfers or concerted two-electron transfer for fluorination both have been proposed.⁵¹

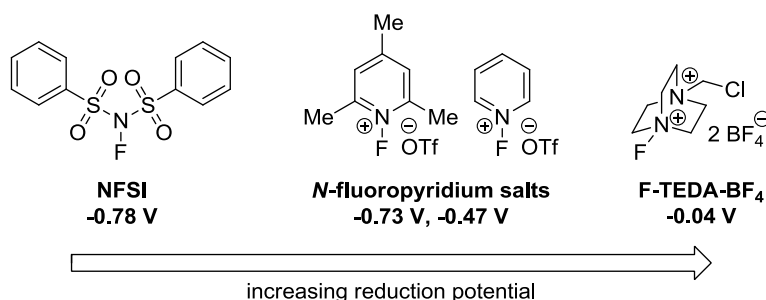


Figure 2. Comparison of the redox potential of crystalline, bench-top stable fluorinating reagents

1.2.1.1. Electrophilic fluorination for the synthesis of fluorinated arenes

Originally, aromatic fluorination was accomplished with fluorine gas, acetyl hypofluorite, and xenon difluoride by functionalization of toxic or moisture-sensitive aryl nucleophiles and later shifted to less-basic, less-toxic main group aryl nucleophiles. The development of transition-metal-based fluorination methods provides functional group

1991, **32**, 1631. (e) Differding, E.; Ofner, H. *Synlett* 1991, 187. (f) Resnati, G.; Desmarteau, D. D. *J. Org. Chem.* 1991, **56**, 4925. (g) Davis, F. A.; Zhou, P.; Murphy, C. K. *Tetrahedron Lett.* 1993, **34**, 3971.

⁴⁹ (a) Umemoto, T.; Kawada, K.; Tomita, K. *Tetrahedron Lett.* 1986, **27**, 4465. (b) Umemoto, T.; Tomita, K. *Tetrahedron Lett.* 1986, **27**, 3271. (c) Tomita, K.; Kawada, K.; Umemoto, T. *J. Fluorine Chem.* 1987, **35**, 52. (d) Umemoto, T.; Tomita, K. *J. Fluorine Chem.* 1987, **35**, 14. (e) Umemoto, T.; Tomizawa, G. *Tetrahedron Lett.* 1987, **28**, 2705. (f) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* 1990, **112**, 8563. (g) Umemoto, T.; Harasawa, K.; Tomizawa, G.; Kawada, K.; Tomita, K. *Bull. Chem. Soc. Jpn.* 1991, **64**, 1081. (h) Umemoto, T.; Tomizawa, G. *J. Org. Chem.* 1995, **60**, 6563. (i) Umemoto, T.; Nagayoshi, M.; Adachi, K.; Tomizawa, G. *J. Org. Chem.* 1998, **63**, 3379.

⁵⁰ Banks, R. E.; Mohialdinkhaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. *J. Chem. Soc., Chem. Commun.* 1992, 595.

⁵¹ (a) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* 1996, **96**, 1737. (b) Nyffeler, P. T.; Duron, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C. H. *Angew. Chem. Int. Ed.* 2005, **44**, 192.

tolerant fluorination of pre-functionalized aryl nucleophiles. Current investigations are focused on the development of functional group tolerant, direct conversion of the C–H bonds of arenes to the corresponding C–F bonds with predictable regioselectivity.

Traditional electrophilic fluorination methods with main-group elements

Aryl carbon–fluorine bonds can be constructed via reaction of an aryl nucleophile with an electrophilic fluorinating reagent. Fluorination via electrophilic aromatic substitution to directly functionalize C–H bonds of arene is challenging when compared to other halogenations, possibly due to electronegative fluorine atom disfavoring the rate-limiting formation of the Wheland⁵² intermediate. Arylmethyl reagents including aryltin,⁵³ -mercury,⁵⁴ lead,⁵⁵ -germanium,⁵⁶ -silicon,⁵⁷ and -boron⁵⁸ can react with fluorine gas, xenon difluoride, hypofluorites, and fluoroxy-sulfates to afford fluorinated arenes; however, the substrate scope is limited due to the high reactivity of the reagents, often resulting in unselective fluorination. On the other hand, aryl nucleophiles with more electropositive

⁵² Wheland, G. W. *J. Am. Chem. Soc.* 1942, **64**, 900.

⁵³ (a) Adam, M. J.; Pate, B. D.; Ruth, T. J.; Berry, J. M.; Hall, L. D. *J. Chem. Soc., Chem. Commun.* 1981, 733. (b) Adam, M. J.; Berry, J. M.; Hall, L. D.; Pate, B. D.; Ruth, T. J. *Can. J. Chem.* 1983, **61**, 658. (c) Adam, M. J.; Ruth, T. J.; Jivan, S.; Pate, B. D. *J. Fluorine Chem.* 1984, **25**, 329. (d) Bryce, M. R.; Chambers, R. D.; Mullins, S. T.; Parkin, A. *J. Fluorine Chem.* 1984, **26**, 533. (e) Bryce, M. R.; Chambers, R. D.; Mullins, S. T.; Parkin, A. *J. Chem. Soc., Chem. Commun.* 1986, 1623. (f) Coenen, H. H.; Moerlein, S. M. *J. Fluorine Chem.* 1987, **36**, 63. (g) Hodson, H. F.; Madge, D. J.; Widdowson, D. A. *Synlett* 1992, 831. (h) Matthews, D. P.; Miller, S. C.; Jarvi, E. T.; Sabol, J. S.; McCarthy, J. R. *Tetrahedron Lett.* 1993, **34**, 3057. (i) Tius, M. A.; Kawakami, J. K. *Tetrahedron* 1995, **51**, 3997. (j) Tius, M. A.; Kawakami, J. K. *Synth. Commun.* 1992, **22**, 1461. (k) Tius, M. A. *Tetrahedron* 1995, **51**, 6605.

⁵⁴ (a) Bryce, M. R.; Chambers, R. D.; Mullins, S. T.; Parkin, A. *J. Fluorine Chem.* 1984, **26**, 533. (b) Visser, G. W. M.; Vonhalteren, B. W.; Herscheid, J. D. M.; Brinkman, G. A.; Hoekstra, A. *J. Chem. Soc., Chem. Commun.* 1984, 655. (c) Visser, G. W. M.; Bakker, C. N. M.; Vonhalteren, B. W.; Herscheid, J. D. M.; Brinkman, G. A.; Hoekstra, A. *J. Org. Chem.* 1986, **51**, 1886. (d) Butin, K. P.; Kiselev, Y. M.; Magdesieva, T. V.; Reutov, O. A. *J. Organomet. Chem.* 1982, **235**, 127.

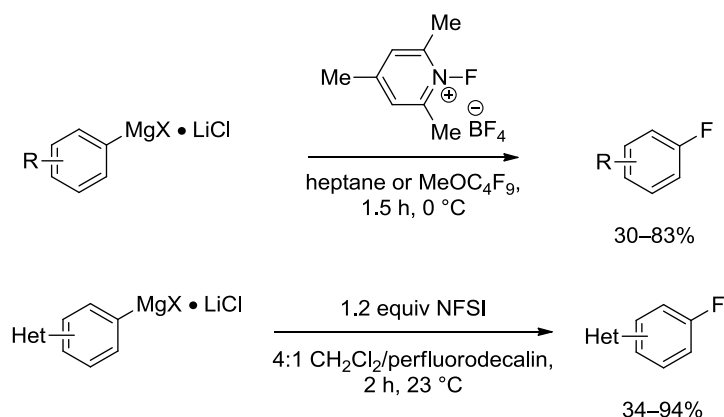
⁵⁵ (a) De Meio, G. V.; Pinhey, J. T. *J. Chem. Soc., Chem. Commun.* 1990, 1065. (b) De Meio, G. V.; Morgan, J.; Pinhey, J. T. *Tetrahedron* 1993, **49**, 8129. (c) Adam, M. J.; Berry, J. M.; Hall, L. D.; Pate, B. D.; Ruth, T. J. *Can. J. Chem.* 1983, **61**, 658.

⁵⁶ Coenen, H. H.; Moerlein, S. M. *J. Fluorine Chem.* 1987, **36**, 63.

⁵⁷ (a) Diraddo, P.; Diksic, M.; Jolly, D. *J. Chem. Soc., Chem. Commun.* 1984, 159. (b) Speranza, M.; Shiue, C. Y.; Wolf, A. P.; Wilbur, D. S.; Angelini, G. *J. Fluorine Chem.* 1985, **30**, 97. (c) Lothian, A. P.; Ramsden, C. A. *Synlett* 1993, 753. (d) Coe, P. L.; Stuart, A. M.; Moody, D. J. *J. Fluorine Chem.* 1998, **92**, 27. (e) Stuart, A. M.; Coe, P. L.; Moody, D. J. *J. Fluorine Chem.* 1998, **88**, 179. (f) Tredwell, M.; Gouverneur, V. *Org. Biomol. Chem.* 2006, **4**, 26.

⁵⁸ (a) Grushin, V. V.; Kantor, M. M.; Tolstaya, T. P.; Shcherbina, T. M. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1984, **33**, 2130. (b) Diorazio, L. J.; Widdowson, D. A.; Clough, J. M. *Tetrahedron* 1992, **48**, 8073. (c) Cazorla, C.; Metay, E.; Andrioletti, B.; Lemaire, M. *Tetrahedron Lett.* 2009, **50**, 3936.

metals, such as aryllithium reagents,⁵⁹ can react with less reactive electrophilic fluorinating reagents, such as *N*-fluorinated reagents. Such basic nucleophiles can undergo single electron transfer and result in protodemetalation byproducts. Fluorination of Grignard reagents with electrophilic *N*-fluorinated reagents is the most reliable method with basic aryl nucleophiles but demonstrates a narrow substrate scope due to the basicity and nucleophilicity of the arylmagnesium reagents (Scheme 6).^{59a, 60} Through appropriate choice of solvent and reagents, undesired protodemetalation products can be minimized.⁶⁰



Scheme 6. Synthesis of aryl fluorides from aryl Grignard reagents

Transition-metal-mediated or -catalyzed electrophilic fluorination

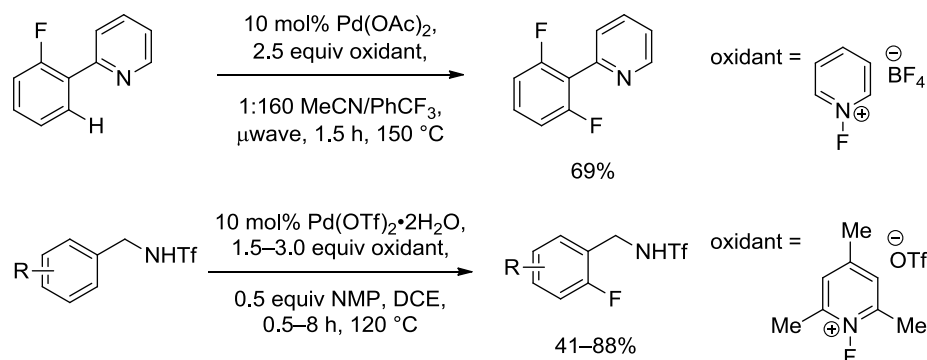
In the past decade, functional-group tolerant and regioselective fluorination with redox active transition metals has been investigated. In contrast to main group organometallic fluorination, transition-metal-mediated electrophilic fluorination often forms metal–carbon bond via transmetalation or direct C–H metalation, followed with oxidation at the metal center with an electrophilic fluorinating reagent. Depending on the reaction conditions, oxidation can result in formation of a monometallic high valent intermediate⁶¹ or a high valent multi-metallic complex.⁶² In both instances, aryl fluoride products are produced upon reductive elimination.

⁵⁹ (a) DeYoung, J.; Kawa, H.; Lagow, R. J. *J. Chem. Soc., Chem. Commun.* 1992, 811. (b) Snieckus, V.; Beaulieu, F.; Mohri, K.; Han, W.; Murphy, C. K.; Davis, F. A. *Tetrahedron Lett.* 1994, **35**, 3465. (c) Slocum, D. W.; Shelton, P.; Moran, K. M. *Synthesis* 2005, 3477.

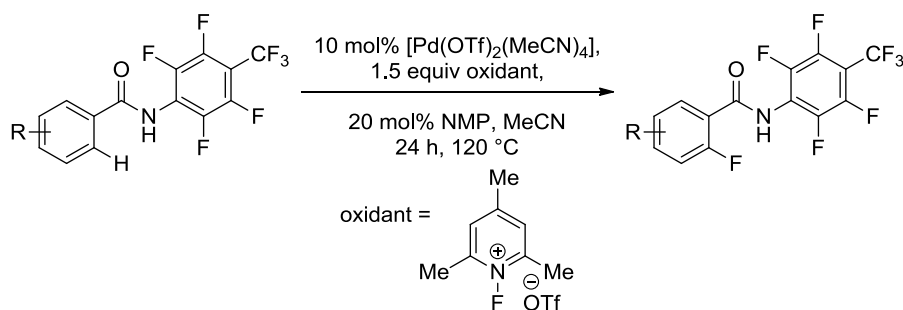
⁶⁰ (a) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* 2010, **49**, 2219. (b) Yamada, S.; Gavryushin, A.; Knochel, P. *Angew. Chem. Int. Ed.* 2010, **49**, 2215. (c) Anbarasan, P.; Neumann, H.; Beller, M. *Chem. Asian J.* 2010, **5**, 1775.

⁶¹ (a) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* 2008, **130**, 13285. (b) Stowers, K. J.; Sanford, M. S. *Org. Lett.* 2009, **11**, 4584.

The first transition-metal-catalyzed aromatic fluorination reactions were developed by means of utilizing an *ortho*-directing group (Scheme 7).⁶³ Direct C–H fluorination is desirable, but the necessity of directing groups limits the structural diversity of the substrates that can be fluorinated. An additional challenge was to prevention of double fluorination at both *ortho* positions on an arene without *ortho* or *meta* substituents. Double fluorination was addressed with a benzoic acid-derived, weakly coordinating anionic *ortho*-directing group *N*-perfluorotolylamide that allows for rapid displacement of the monofluorinated product by the substrate, thus affording high selectivity for monofluorination (Scheme 8).⁶⁴



Scheme 7. *N*-directed Pd-catalyzed fluorination of arenes



Scheme 8. *N*-Perfluorotolylamide-directed Pd-catalyzed fluorination of arenes

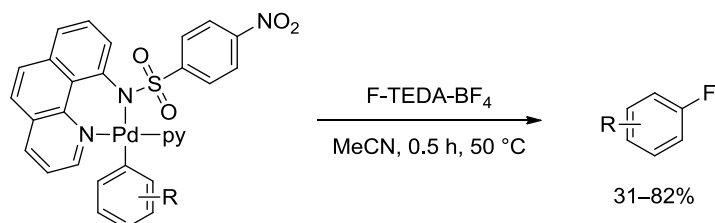
Arylboronic acids have been used to synthesize Pd(II) aryl benzoquinoline-sulfonamide complexes that undergo fluorination with F-TEDA-BF₄ in the presence of functional groups ranging from aldehydes to phenols (Scheme

⁶² (a) Powers, D. C.; Xiao, D. Y.; Geibel, M. A. L.; Ritter, T. *J. Am. Chem. Soc.* 2010, **132**, 14530. (b) Powers, D. C.; Ritter, T. *Nat. Chem.* 2009, **1**, 302.

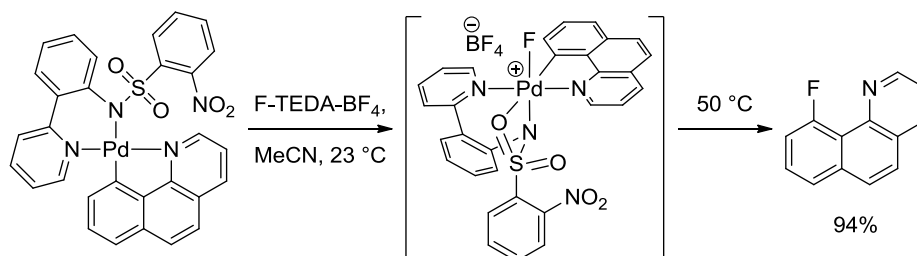
⁶³ (a) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* 2006, **128**, 7134. (b) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* 2009, **131**, 7520.

⁶⁴ Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* 2011, **50**, 9081.

9);⁶⁵ however, stoichiometric amounts of Pd complex are needed for the transformation of arylboronic acids to aryl fluorides. Mechanistic studies on the oxidation of the benzoquinoline phenylpyridinesulfonamide palladium(II) complex with F-TEDA-BF₄ support the presence of a distinct intermediary κ^2 -sulfonamide Pd(IV) species that undergoes reductive elimination to make aryl carbon–fluorine bonds (Scheme 10).⁶⁶



Scheme 9. Fluorination of Pd(II) benzoquinolyl sulfoamide complexes with F-TEDA-BF₄



Scheme 10. Reductive elimination from Pd(IV) phenylpyridyl sulfonamide complexes

Silver-mediated fluorination of aryl stannanes,⁶⁷ boronic acids,⁶⁸ and silanes⁶⁹ has been proposed to proceed through multi-metallic, high valent silver species obtained by oxidation of silver(I) complexes with F-TEDA-PF₆ and followed by reductive elimination. Multi-metallic redox synergy of silver may enable fluorination of aryl stannanes and boronic acids at 23 °C. This method displays a broad substrate scope—nitrogenous heteroaryl and mesityl nucleophiles as well as nucleophiles containing electron-rich, electron-poor, electrophilic, and protic functional groups can be successfully fluorinated—to afford fluorinated complex natural product-derived products (Scheme

⁶⁵ Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem. Int. Ed.* 2008, **47**, 5993.

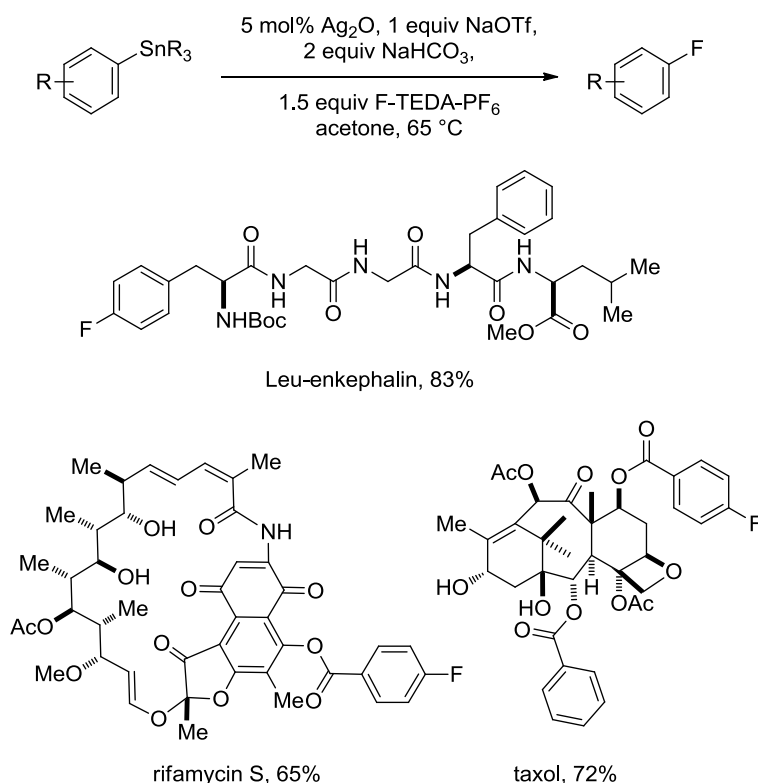
⁶⁶ (a) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* 2008, **130**, 10060. (b) Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P.; Goddard, W. A., III; Ritter, T. *J. Am. Chem. Soc.* 2010, **132**, 3793.

⁶⁷ Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* 2009, **131**, 1662.

⁶⁸ Furuya, T.; Ritter, T. *Org. Lett.* 2009, **11**, 2860.

⁶⁹ Tang, P.; Ritter, T. *Tetrahedron* 2011, **67**, 4449.

11).⁷⁰ Although the silver catalyzed fluorination of aryl stannanes requires the synthesis of toxic aryl stannanes, it displays the broadest substrate scope and functional group tolerance in the field.



Scheme 11. Ag-catalyzed fluorination of complex aryl stannanes (names of products refer to non-fluorinated parent structure)

1.2.1.2. Electrophilic fluorination for the synthesis of aliphatic fluorides

Nucleophiles employed in aliphatic electrophilic fluorination reactions are often stabilized carbanions, such as those derived from β -ketocarbonyl compounds. Other methods for the synthesis of aliphatic fluorides can involve fluorination and nucleophile addition cascades across double bonds.⁷¹ Enantioselective variants for both fluorination of C–H acidic substrates and fluorination-addition cascades have been reported and can be promoted with Lewis acids, organocatalysts, or phase-transfer catalysts. Aliphatic C–F bond forming reactions via radicals have been

⁷⁰ Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* 2010, **132**, 12150.

⁷¹ (a) Wu, T.; Yin, G.; Liu, G. *J. Am. Chem. Soc.* 2009, **131**, 16354. (b) Dilman, A. D.; Belyakov, P. A.; Struchkova, M. I.; Arkhipov, D. E.; Korlyukov, A. A.; Tartakovsky, V. A. *J. Org. Chem.* 2010, **75**, 5367. (c) Qiu, S.; Xu, T.; Zhou, J.; Guo, Y.; Liu, G. *J. Am. Chem. Soc.* 2010, **132**, 2856. (d) Peng, H.; Liu, G. *Org. Lett.* 2011, **13**, 772. (e) Xu, T.; Liu, G. *Synlett* 2012, 955.

disclosed and can provide a substrate scope complementary to more commonly used nucleophilic or electrophilic fluorination reactions, making further development in this field desirable.

Electrophilic fluorination of acidic C–H bonds in methylene and methyne units

α -Fluorination of carbonyls, α' -ketocarbonyls, and related carbonyl derivatives with strongly oxidizing fluorinating reagents including gaseous fluorine,⁷² hypofluorite,⁷³ perchloryl fluoride,⁷⁴ fluoroxysulfate,⁷⁵ and XeF₂⁷⁶ generally give undesired α,α -difluorinated products in addition to the α -monofluorinated products.^{74a,76} Less reactive, more functional group tolerant electrophilic fluorinating reagents like *N*-fluoropyridinium salts, NFSI, and F-TEDA-BF₄ have been used to selectively α -monofluorinate carbonyl derivatives without providing difluorinated products.^{49a,b,e,h,51,77} The asymmetric α -fluorination of carbonyl substrates was explored first with chiral electrophilic fluorinating reagents^{48b,c,78} and later with chiral catalysts for the generation of chiral enolate intermediates.

Many methods have exploited the two-point binding of dicarbonyl compounds to chiral Lewis acid complexes to control enantioselective fluorination. Asymmetric fluorination of β -ketoesters was achieved with titanium-TADDOLate-based catalysts (Scheme 12),⁷⁹ Cu(II)- (Scheme 13)⁸⁰ and Ni(II)-BOX complexes (Scheme 14),⁸¹

⁷² (a) Purrington, S. T.; Lazaridis, N. V.; Bumgardner, C. L. *Tetrahedron Lett.* 1986, 27, 2715. (b) Chambers, R. D.; Hutchinson, J. *J. Fluorine Chem.* 1998, 89, 229.

⁷³ (a) Middleton, W. J.; Bingham, E. M. *J. Am. Chem. Soc.* 1980, 102, 4845. (b) Middleton, W. J.; Bingham, E. M. *J. Am. Chem. Soc.* 1980, 102, 4845.

⁷⁴ (a) Inman, C. E.; Oesterling, R. E.; Tyczkowski, E. A. *J. Am. Chem. Soc.* 1958, 80, 6533. (b) Gershon, H.; Schulman, S. G.; Spevack, A. D. *J. Med. Chem.* 1967, 10, 536. (c) Sheppard, W. A. *Tetrahedron Lett.* 1969, 10, 83. (d) Shapiro, B. L.; Chrysam, M. M. *J. Org. Chem.* 1973, 38, 880.

⁷⁵ (a) Stavber, S.; Zupan, M. *J. Chem. Soc., Chem. Commun.* 1981, 795.

⁷⁶ Zajc, B.; Zupan, M. *J. Org. Chem.* 1982, 47, 573.

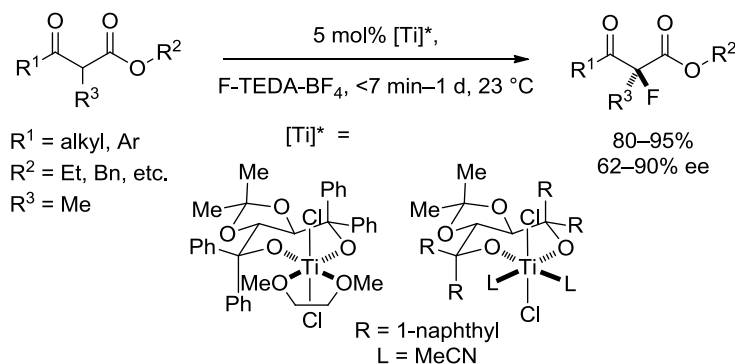
⁷⁷ (a) Lal, G. S. *J. Org. Chem.* 1993, 58, 2791. (b) Davis, F. A.; Han, W.; Murphy, C. K. *J. Org. Chem.* 1995, 60, 4730. (c) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* 2004, 37, 31.

⁷⁸ Cahard, D.; Audouard, C.; Plaquevent, J. C.; Roques, N. *Org. Lett.* 2000, 2, 3699.

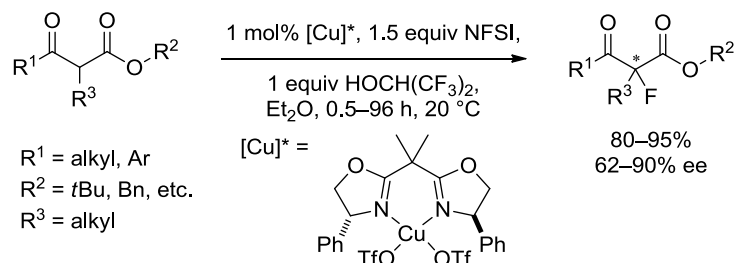
⁷⁹ (a) Hintermann, L.; Togni, A. *Angew. Chem. Int. Ed.* 2000, 39, 4359. (b) Hintermann, L.; Perseghini, M.; Togni, A. *Beil. J. Org. Chem.* 2011, 7, 1421. (c) Piana, S.; Devillers, I.; Togni, A.; Rothlisberger, U. *Angew. Chem. Int. Ed.* 2002, 41, 979. (d) Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A. *Org. Lett.* 2003, 5, 1709. (e) Bertogg, A.; Hintermann, L.; Huber, D. P.; Perseghini, M.; Sanna, M.; Togni, A. *Helv. Chim. Acta* 2012, 95, 353.

⁸⁰ Ma, J. A.; Cahard, D. *Tetrahedron: Asymmetry* 2004, 15, 1007.

chiral bis(imino)bis(phosphine)ruthenium(II) complexes (Scheme 15),⁸² and scandium binaphthylphosphate complexes.⁸³ The Ni-catalyzed reaction (10 mol% catalyst) has demonstrated the broadest substrate scope so far, and allows for α -fluorination of a variety of β -ketoesters and *N*-Boc-protected amides⁸¹ in 71–93% yield and 83–99% ee. The catalytic enantioselective α -fluorination of α -substituted methyl, *tert*-butyl malonate was accomplished via chiral Lewis acid catalysis with Zn(II) acetate, (*R,R*)-4,6-dibenzofurandiyl-2,2'-bis(4-phenyloxazoline) ligand, and NFSI.⁸⁴ This approach, however, was specifically optimized for the malonate substrate en route to the enantioselective synthesis of fluorinated β -lactams.



Scheme 12. Ti-catalyzed asymmetric α -fluorination of β -ketoesters



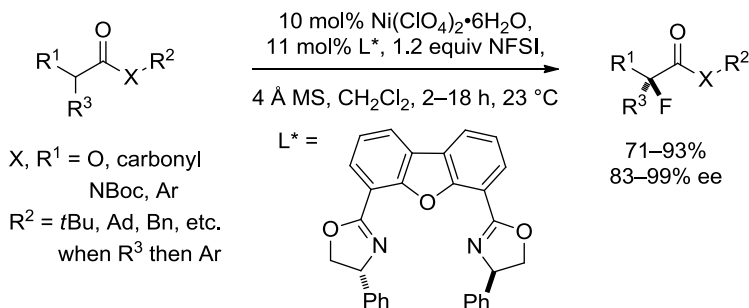
Scheme 13. Cu-catalyzed asymmetric α -fluorination of β -ketoesters

⁸¹ Shibata, N.; Kohno, J.; Takai, K.; Ishimaru, T.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew. Chem. Int. Ed.* 2005, **44**, 4204.

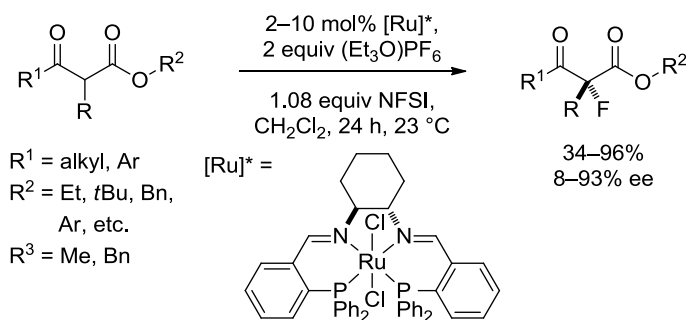
⁸² (a) Althaus, M.; Becker, C.; Togni, A.; Mezzetti, A. *Organometallics* 2007, **26**, 5902. (b) Althaus, M.; Togni, A.; Mezzetti, A. *J. Fluorine Chem.* 2009, **130**, 702.

⁸³ Suzuki, S.; Furuno, H.; Yokoyama, Y.; Inanaga, J. *Tetrahedron: Asymmetry* 2006, **17**, 504.

⁸⁴ Reddy, D. S.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew. Chem. Int. Ed.* 2008, **47**, 164.



Scheme 14. Ni-catalyzed asymmetric α -fluorination of β -ketoesters and *N*-Boc oxindoles



Scheme 15. Ru-catalyzed asymmetric α -fluorination of β -ketoesters

Chiral Pd-BINAP complexes catalyze the enantioselective fluorination of α -ketoesters,⁸⁵ β -ketoesters (Scheme 16),⁸⁶ β -ketophosphonates,⁸⁷ oxindoles (Scheme 17),⁸⁸ and α -ester lactones/lactams.⁸⁹ The use of chiral palladium complexes was particularly successful for the α -fluorination of acyclic α -ketoesters, cyclic and acyclic *tert*-butyl β -ketoester as well as oxindoles α -substituted with an electronically diverse range of aryl and alkyl groups.^{85,86,88} Chiral palladium-bound enolates are proposed to induce facial selectivity; stronger bonds between the palladium complex and the oxindole, α -ketoester, or β -ketoester enolate, respectively, may explain the higher enantiomeric excess as compared to those obtained for β -ketophosphonates or α -ester lactones/lactams.

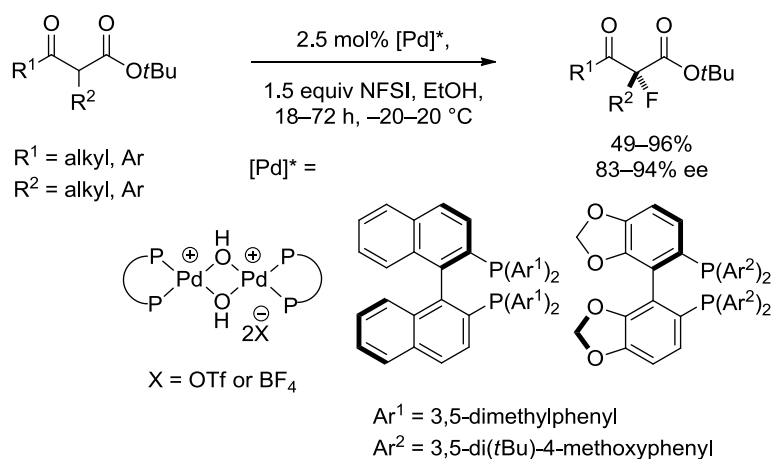
⁸⁵ Suzuki, S.; Kitamura, Y.; Lectard, S.; Hamashima, Y.; Sodeoka, M. *Angew. Chem. Int. Ed.* 2012, **51**, 4581.

⁸⁶ (a) Hamashima, Y.; Yagi, K.; Takano, H.; Tamas, L.; Sodeoka, M. *J. Am. Chem. Soc.* 2002, **124**, 14530. (b) Hamashima, Y.; Takano, H.; Hotta, D.; Sodeoka, M. *Org. Lett.* 2003, **5**, 3225.

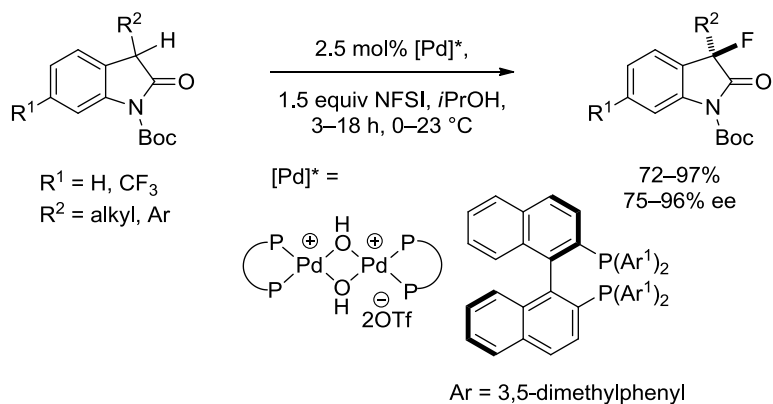
⁸⁷ (a) Hamashima, Y.; Suzuki, T.; Shimura, Y.; Shimizu, T.; Umebayashi, N.; Tamura, T.; Sasamoto, N.; Sodeoka, M. *Tetrahedron Lett.* 2005, **46**, 1447. (b) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Tsuchiya, Y.; Moriya, K.-i.; Goto, T.; Sodeoka, M. *Tetrahedron* 2006, **62**, 7168.

⁸⁸ Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* 2005, **127**, 10164.

⁸⁹ Suzuki, T.; Goto, T.; Hamashima, Y.; Sodeoka, M. *J. Org. Chem.* 2007, **72**, 246.



Scheme 16. Pd-catalyzed asymmetric α -fluorination of β -ketoesters



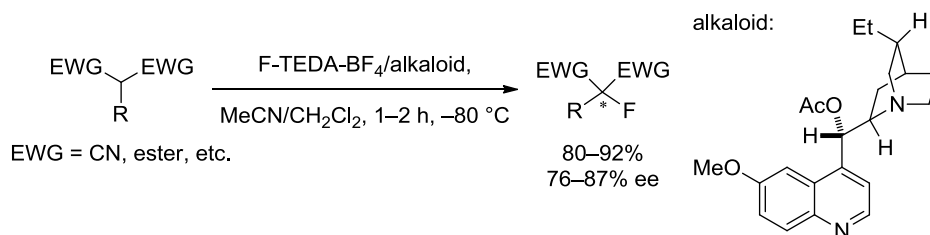
Scheme 17. Pd-catalyzed asymmetric α -fluorination of oxindoles.

Organocatalysts provide enantioinduction by participating as a chiral fluorinating reagent or by activating of the substrate to generate a chiral nucleophile during the course of the reaction. The chiral fluorinating reagent approach is challenging in that potential background reaction with achiral fluorinating reagents leads to a racemic mixture. Catalytic asymmetric fluorination via chiral fluorinated organocatalysts intermediates has been challenging to accomplish but can be achieved with fluorinating reagents such as NFSI at temperatures $\leq 0^\circ\text{C}$.

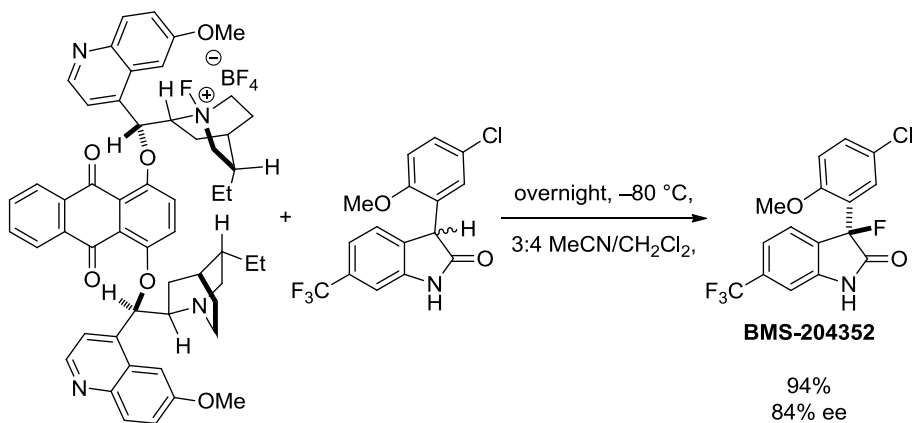
Cinchona alkaloids have been used to enantioselectively fluorinate nucleophiles in the presence of achiral fluorinating reagent. Enantioselective fluorination of the activated methyne groups was accomplished using stoichiometric amounts of cinchona alkaloid derivatives (Scheme 18).⁹⁰ Cinchona alkaloids have also been used to

⁹⁰ Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* 2000, 122, 10728.

mediate enantioselective α -fluorination of silylenol ethers, α,α -cyanoester C-H acids, β -ketoesters, and oxindoles.⁹¹ The methodology was applied to the synthesis of BMS-204352 (Scheme 19).⁹² Cinchona-alkaloid-derived thiourea catalyst have also been used to enantioselectively α -fluorinate β -ketoesters.⁹³ The substrate scope with cinchona alkaloids when compared to the Lewis acid-catalyzed approach for β -ketoesters and oxindoles is rather limited; however, with cinchona alkaloids, silylenol ethers can be enantioselectively α -fluorinated, which is not possible with the Lewis acid-catalyzed two-point binding approach.



Scheme 18. Enantioselective cinchona-alkaloid-mediated fluorination of C-H acidic substrates



Scheme 19. Enantioselective α -fluorination of oxindoles mediated by *N*-fluoroammonium salts of cinchona alkaloids

Enantioselective organocatalytic α -fluorination of aldehydes was accomplished by Enders,⁹⁴ MacMillan (Scheme 20),⁹⁵ Jørgensen (Scheme 20),⁹⁶ and Barbas (Scheme 21);⁹⁷ similarly, enantioselective α -fluorination of ketones has

⁹¹ Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* 2001, **123**, 7001.

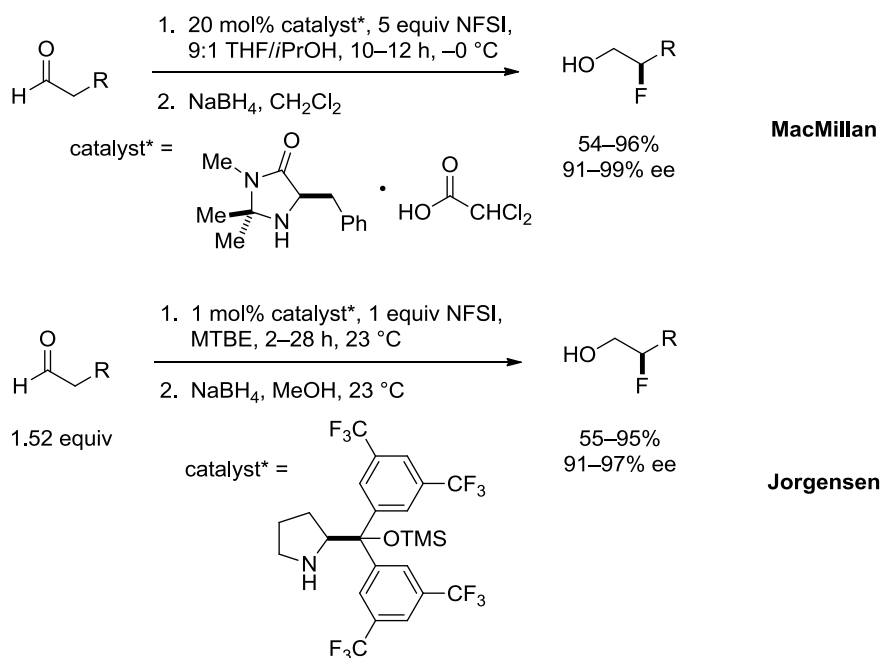
⁹² Shibata, N.; Ishimaru, T.; Suzuki, E.; Kirk, K. L. *J. Org. Chem.* 2003, **68**, 2494.

⁹³ Xu, J.; Hu, Y.; Huang, D.; Wang, K.-H.; Xu, C.; Niu, T. *Adv. Synth. Catal.* 2012, **354**, 515.

⁹⁴ Enders, D.; Huttl, M. R. M. *Synlett* 2005, 991.

⁹⁵ Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* 2005, **127**, 8826.

been accomplished with enamine catalysis.⁹⁸ The method described by MacMillan demonstrates a broader substrate scope; the method described by Jørgensen uses lower catalyst loading and does not require five equivalents of NFSI. Branched aldehyde substrates for enantioselective α -fluorination are currently challenging; Barbas reported 98–99% yield but only 45–66% ee for such substrates. The fluorinated aldehyde products are especially useful for the synthesis of enantiopure β -fluoroamines, which can be accomplished by a chiral sulfinylimine condensation, directed reduction sequence of the enantioenriched fluorinated aldehyde.⁹⁹



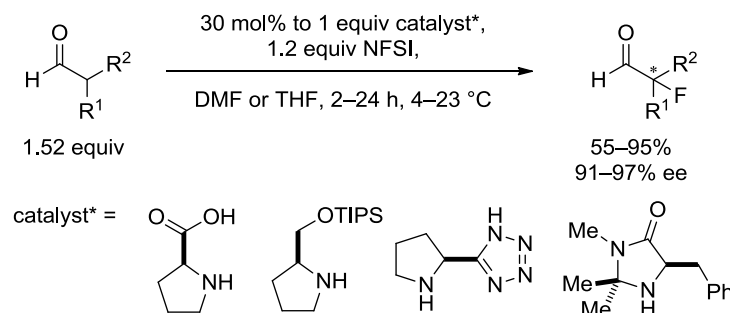
Scheme 20. Organocatalytic asymmetric α -fluorination of aldehydes

⁹⁶ Marigo, M.; Fielenbach, D. I.; Branton, A.; Kjoersgaard, A.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* 2005, **44**, 3703.

⁹⁷ Steiner, D. D.; Mase, N.; Barbas, C. F. *Angew. Chem. Int. Ed.* 2005, **44**, 3706.

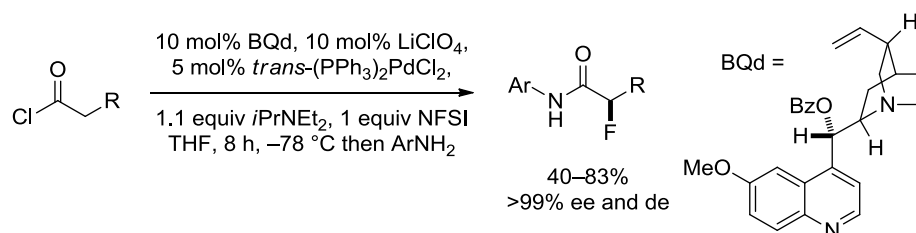
⁹⁸ Kwiatkowski, P.; Beeson, T. D.; Conrad, J. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* 2011, **133**, 1738.

⁹⁹ Schulte, M. L.; Lindsley, C. W. *Org. Lett.* 2011, **13**, 5684.



Scheme 21. Organocatalytic asymmetric α -fluorination of aldehydes

The enantioselective α -fluorination of acid chlorides was accomplished by combining a palladium catalyst, a chiral nucleophile, and an alkali metal (Scheme 22).¹⁰⁰ The cinchona alkaloid-based nucleophile reacts with the acid chloride in the presence of the palladium catalyst to generate a chiral zwitterion amide–enolate intermediate. Both catalysts work cooperatively such that a chiral enolate can be generated for fluorination. The alkali metal catalyst is hypothesized to play a role in the activation of NFSI through chelation of the sulfonyl oxygens with the cation, thus activating the reagent for nucleophilic attack by the chiral enolate. After fluorination, addition of an amine nucleophile affords the α -fluorinated amide product in >99% ee and de. Thiourea catalysts derived from cinchona alkaloids can also be used as synergistic bifunctional catalysts for the asymmetric α -fluorination of cyclic and acyclic β -ketoesters with NFSI.¹⁰¹ The catalyst is able to act as a base (via the quinuclidine moiety) and also as a hydrogen-bond donor (via the thiourea moiety), and is proposed to have proper hydrogen-bonding interactions with the substrate and NFSI to afford good enantioselectivity.



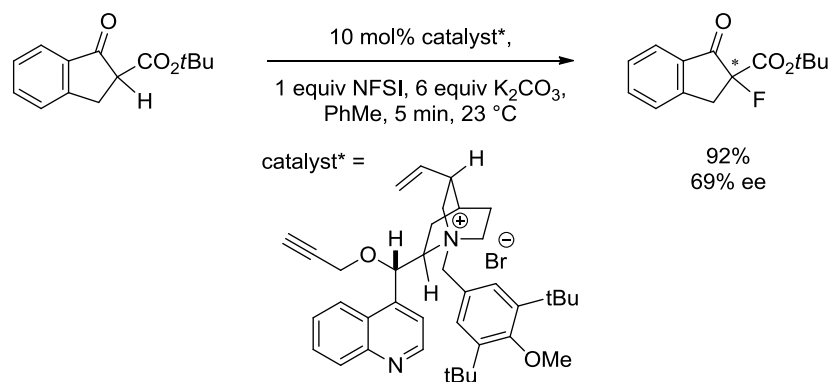
Scheme 22. Organocatalytic asymmetric α -fluorination of acid chlorides

Phase-transfer catalysis (PTC) for enantioselective fluorination can often benefit from simple operation procedures and high yield and enantioselectivity. The formation of a tight chiral ion pair is important for enantioinduction;

¹⁰⁰ Erb, J.; Paull, D. H.; Dudding, T.; Belding, L.; Lectka, T. *J. Am. Chem. Soc.* 2011, **133**, 7536.

¹⁰¹ Xu, J.; Hu, Y.; Huang, D.; Wang, K.-H.; Xu, C.; Niu, T. *Adv. Synth. Catal.* 2012, **354**, 515.

thus, solvents in which the ion pairs remain associated such as dichloromethane and toluene are preferred for PTC. Chiral quaternary ammonium salts have been used as cationic phase-transfer catalysts for enantioselective fluorination of β -ketoesters with ion pairing between the enolate and chiral ammonium counterion (Scheme 23).¹⁰² The α -fluorination of β -ketoesters is reported in 69% ee or less, most likely resulting from poor ion pairing between the chiral ammonium salt and the enolate or fast α -fluorination background reaction.



Scheme 23. Enantioselective α -fluorination of β -ketoesters with quaternary ammonium salts

A non-traditional approach to chiral allylic fluorides and chiral propargylic fluorides utilizes organocatalysis to facilitate the asymmetric fluorination step with subsequent olefination or introduction of the propargyl group (Scheme 24).¹⁰³ The organocatalytic approach can give >90% ee by avoiding the S_N1 racemization pathway that encumbers chiral allylic alcohol fluorination; however, it can only afford ethynyl-substituted propargylic fluorides and α,β -unsaturated ester allylic fluorides (Scheme 24). Fluorination of α -methylstyrene can occur via oxidative fluorination of the allylic C–H bond with a *N*-fluoropyridinium salt promoted by catalytic amounts of ytterbium(III) triflate.¹⁰⁴ Electrophilic fluorodesilylation of allenyl and allylsilanes was reported to yield propargylic and allylic fluoride products.¹⁰⁵ Acyclic secondary allylic fluorides can be prepared via a cross-metathesis–electrophilic

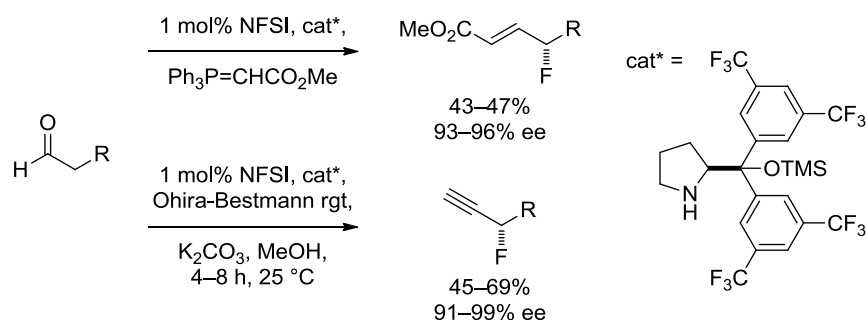
¹⁰² Kim, D. Y.; Park, E. J. *Org. Lett.* 2002, **4**, 545.

¹⁰³ Jiang, H.; Falcicchio, A.; Jensen, K. L.; Paixao, M. W.; Bertelsen, S.; Jorgensen, K. A. *J. Am. Chem. Soc.* 2009, **131**, 7153.

¹⁰⁴ Yamanaka, M.; Arisawa, M.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* 2002, **43**, 2403.

¹⁰⁵ (a) Carroll, L.; Pacheco, M. C.; Garcia, L.; Gouverneur, V. *Chem. Commun.* 2006, 4113. (b) Giuffredi, G.; Bobbio, C.; Gouverneur, V. *J. Org. Chem.* 2006, **71**, 5361. (c) Lam, Y. H.; Bobbio, C.; Cooper, I. R.; Gouverneur, V. *Angew. Chem. Int. Ed.* 2007, **46**, 5106. (d) Lam, Y. h.; Hopkinson, M. N.; Stanway, S. J.; Gouverneur, V. *Synlett* 2007, 3022. (e) Purser, S.; Odell, B.; Claridge, T. D. W.; Moore, P. R.; Gouverneur, V. *Chem. Eur. J.* 2006, **12**, 9176. (f) Purser, S.; Wilson, C.; Moore, P. R.; Gouverneur, V. *Synlett* 2007, 1166. (g) Teare, H.; Huguet, F.; Tredwell, M.; Thibaudeau, S.; Luthra, S.; Gouverneur, V. *ARKIVOC* 2007, **10**, 232. (h) Teare, H.; Robins, E. G.;

fluorodesilylation sequence.¹⁰⁶ Chiral tertiary allylic fluorides have been prepared via cinchona alkaloid-mediated electrophilic fluorodesilylation.¹⁰⁷



Scheme 24. Enantioselective synthesis of propargyl and allylic fluoride with organocatalysis

Fluorination–nucleophile addition cascades across double bonds

For activated alkenes like enamines, fluorination can occur without catalysts; for example, fluorocyanation of enamines is hypothesized to occur via electrophilic fluorination of the enamine with NFSI followed by trapping of the iminium intermediate with cyanide.^{71b} With unactivated alkenes, fluorination–nucleophile addition reactions need to be assisted by a catalyst. Both the intramolecular aminofluorination of unactivated alkenes (Scheme 25)^{71a} and the intermolecular aminofluorination of styrenes (Scheme 25)^{71c} were facilitated by the use of palladium catalysts. Although both reactions accomplish aminofluorination of alkenes, different approaches and reaction mechanisms are hypothesized for each case. The intramolecular variant utilizes an iodine(III) oxidant coupled with fluoride to accomplish the oxidative fluorination of the resultant complex after the intramolecular amino–palladation step with the alkene. For the intermolecular case with styrenyl substrates, fluoro–palladation with NFSI and the active Pd catalyst is proposed to occur first, followed by oxidation to a putative Pd(IV) species, and subsequent reductive elimination to form the carbon–nitrogen bond. The reactivity of high valent transition-metal complexes to induce C–F reductive elimination at sp^3 carbon centers.¹⁰⁸ has also been investigated with Pt(IV) complexes.^{108c}

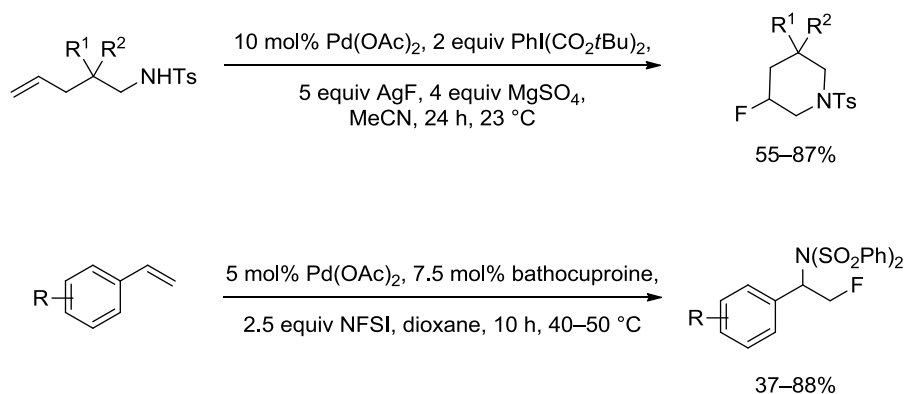
Årstad, E.; Luthra, S. K.; Gouverneur, V. *Chem. Commun.* 2007, 2330. (i) Tredwell, M.; Gouverneur, V. *Org. Biomol. Chem.* 2006, 4, 26. (k) Tredwell, M.; Tenza, K.; Pacheco, M. C.; Gouverneur, V. *Org. Lett.* 2005, 7, 4495.

¹⁰⁶ Thibaudeau, S.; Gouverneur, V. *Org. Lett.* 2003, 5, 4891.

¹⁰⁷ Greedy, B.; Paris, J. M.; Vidal, T.; Gouverneur, V. *Angew. Chem. Int. Ed.* 2003, 42, 3291.

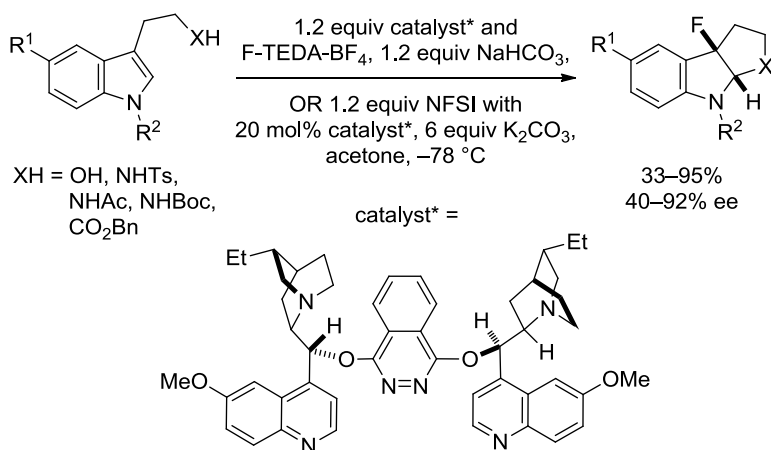
¹⁰⁸ (a) Mankad, N. P.; Toste, F. D. *Chem. Sci.* 2012, 3, 72. (b) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* 2006, 128, 7134. (c) Racowski, J. M.; Gary, J. B.; Sanford, M. S. *Angew. Chem. Int. Ed.* 2012, 51, 3414.

Oxidation of stoichiometric alkyl Au(I) complexes with XeF₂ to Au(III) intermediates followed by reductive elimination also affords the corresponding aliphatic fluorides.^{108a} The propensity for β-hydride elimination with Au(III) complexes and the use of XeF₂ has limited the substrate scope to mostly β,β-disubstituted alkanes.



Scheme 25. (top) Intramolecular Pd-catalyzed aminofluorocyclization of alkene sulfonamides
(bottom) Intermolecular aminofluorination of styrenes with NFSI

For enantioselective fluorocyclization of indole substrates mediated or catalyzed by cinchona alkaloids, the enantioselectivity is proposed to arise from the chiral fluorinating reagent generated by reaction of the fluorinating reagent with the cinchona alkaloid catalyst (Scheme 26).¹⁰⁹

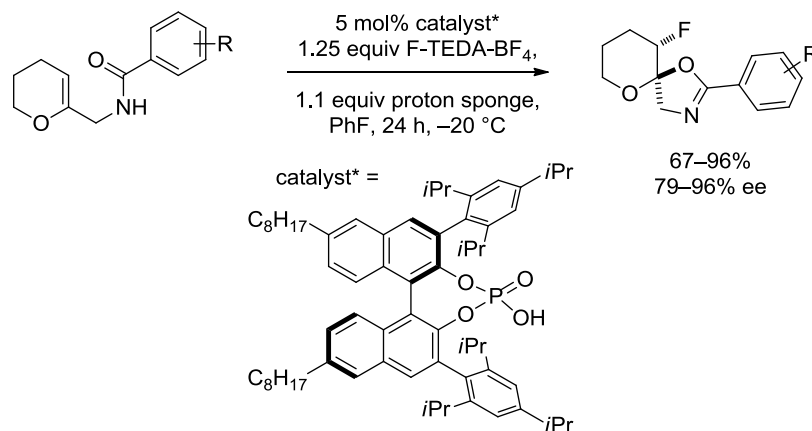


Scheme 26. Enantioselective fluorocyclizations mediated and catalyzed by cinchona alkaloids

Enantioselective fluoro-spiro cyclization reactions via chiral anionic PTC have been reported (Scheme 27) by using chiral anion pairing with cationic F-TEDA to provide a source of chiral electrophilic fluorinating reagent.¹¹⁰ Because

¹⁰⁹ Lozano, O.; Blessley, G.; del Campo, T. M.; Thompson, A. L.; Giuffredi, G. T.; Bettati, M.; Walker, M.; Borman, R.; Gouverneur, V. *Angew. Chem. Int. Ed.* 2011, 50, 8105.

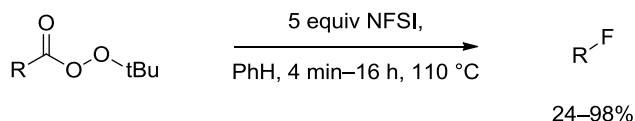
the F-TEDA-BF₄ is sparingly soluble in the solvent, resulting in a negligible rate of background reaction, the chiral anion acts as a shuttle to solubilize the cationic F-TEDA as a chiral fluorinating reagent in the fluorination-spiro cyclization reaction. Enantiomeric excess of 79–96% can be achieved using this approach. Similarly, with chiral anionic PTC, enamines can be enantioselectively fluorinated to afford α -fluoroimines.¹¹¹



Scheme 27. Enantioselective spiro-cyclizations via chiral anionic PTC

1.2.1.3. Fluorination via radical mechanisms

The N–F bonds in electrophilic fluorinating reagents have relatively low bond dissociation energies (2.84 V for *N*-fluorosultam).¹¹² Under either photolysis or thermolysis, a variety of *tert*-butyl alkylperoxoates afforded the corresponding alkyl fluorides upon treatment with NFSI (Scheme 28).¹¹³ The generality of this reaction was not reported and primary alkyl fluoride formation was not efficient which supports a mechanism via radicals.



Scheme 28. Fluorination of *tert*-butyl alkylperoxoates with NFSI

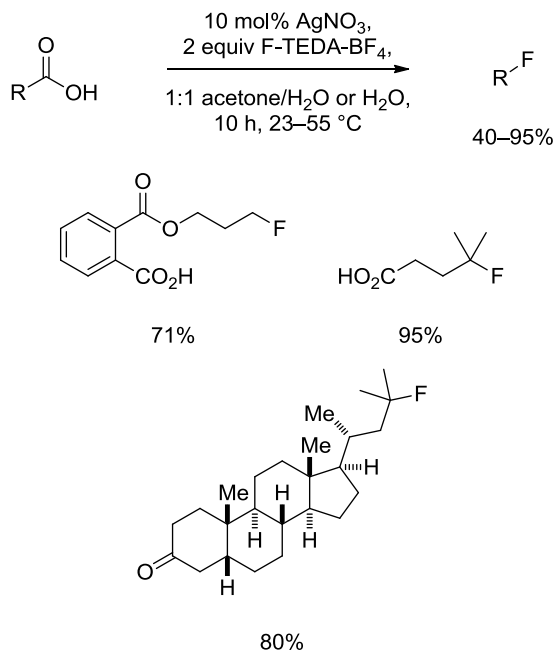
¹¹⁰ Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* 2011, **334**, 1681.

¹¹¹ Phipps, R. J.; Hiramatsu, K.; Toste, F. D. *J. Am. Chem. Soc.* 2012, **134**, 8376.

¹¹² Andrieux, C. P.; Differding, E.; Robert, M.; Saveant, J. M. *J. Am. Chem. Soc.* 1993, **115**, 6592.

¹¹³ Rueda-Becerril, M.; Chatalova Sazepin, C.; Leung, J. C. T.; Okbinoglu, T.; Kennepohl, P.; Paquin, J.-F.; Sammis, G. M. *J. Am. Chem. Soc.* 2012, **134**, 4026.

More recently silver-catalyzed decarboxylative fluorination of secondary and tertiary aliphatic carboxylic acids with F-TEDA-BF₄ was reported (Scheme 29).¹¹⁴ This approach is complementary to traditional nucleophilic fluorination reactions with DAST-type reagents. Involvement of Ag-mediated decarboxylation to form an alkyl radical during the reaction was demonstrated, but the detailed mechanism for the key C–F bond formation is still indeterminate.



Scheme 29. Ag-catalyzed decarboxylative fluorination of aliphatic carboxylic acids with F-TEDA

1.2.2. Nucleophilic fluorination

The challenges associated with nucleophilic fluorination ultimately derive from the high electronegativity of fluorine, which contributes to the high kinetic barriers in forming carbon–fluorine bond despite the thermodynamic driving force of forming the strongest carbon–heteroatom bond. Propensity of fluoride to form strong hydrogen bonds²³ attenuates its nucleophilicity under standard reaction conditions. Rigorous exclusion of potential hydrogen bond donors can make fluoride nucleophilic but also basic which often leads to side reactions.

Use of alkali metal fluoride salts is desirable due to low cost especially compared to electrophilic fluorinating reagents.¹¹⁵ The strong lattice energy of such salts makes them weak nucleophiles and poorly soluble in organic

¹¹⁴ Yin, F.; Wang, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* 2012, 10401.

¹¹⁵ McPake, C. B.; Sandford, G. *Org. Process Res. Dev.* 2012, 16, 844.

solvents. Crown ethers in combination with alkali metal fluorides such as 18-crown-6 can be used to increase solubility of fluoride salts such as KF and therefore often increases reactivity.¹¹⁶ Aprotic solvents especially polar aprotic solvents^{116b,117} are preferred for nucleophilic fluorination such that nucleophilicity of fluoride anions is not attenuated by hydrogen bonding interactions; however, consequently fluoride is highly basic and leads to elimination byproducts. The addition of tertiary alcohols such as *tert*-butanol²⁴ has been shown to retain the fluoride nucleophilicity while diminishing fluoride basicity, thereby reducing undesired byproduct formation. Tetrabutylammonium difluorotriphenylsilicate (TBAT), tetramethylammonium fluoride (TMAF), and tetrabutylammonium fluoride (TBAF) are commonly used soluble inorganic fluoride sources but generally exhibit lower nucleophilicity.

Fluorodeoxygenation of carbon centers commonly requires specialized fluorinating reagents that are dually used for oxygen activation/deoxygenation and as the fluoride source. Various aryl and aminosulfur trifluorides¹¹⁸ and derivatives thereof as well as 2,2-difluoroimidazoline-type reagents¹¹⁹ participate in fluorodeoxygenation reactions. Several hydrogen fluoride-based reagents¹²⁰ have been developed to assist sulfur displacement with fluoride in fluorodesulfurization reactions. Electrochemical fluorination with alkali metal-fluorides has been explored as an approach for the synthesis of organofluorides.¹²¹ Catalysis has enabled many nucleophilic fluorination reactions that are otherwise kinetically difficult to accomplish; uncatalyzed nucleophilic aromatic fluorination is problematic for electron-rich substrates because the rate-determining step is typically the addition of fluoride to form a

¹¹⁶ (a) Liotta, C. L.; Harris, H. P. *J. Am. Chem. Soc.* 1974, *96*, 2250. (b) Clark, J. H. *Chem. Rev.* 1980, *80*, 429.

¹¹⁷ Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Am. Chem. Soc.* 2002, *124*, 10278.

¹¹⁸ (a) Sheppard, W. A. *J. Am. Chem. Soc.* 1960, *82*, 4751. (b) Sheppard, W. A. *J. Am. Chem. Soc.* 1962, *84*, 3058. (c) Markovskij, L. N.; Pashinnik, V. E.; Kirsanov, A. V. *Synthesis* 1973, 787. (d) Middleton, W. J. *J. Org. Chem.* 1975, *40*, 574. (e) Mange, K. C.; Middleton, W. J. *J. Fluorine Chem.* 1989, *43*, 405. (f) Messina, P. A.; Mange, K. C.; Middleton, W. J. *J. Fluorine Chem.* 1989, *42*, 137. (g) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozone, F. M. *Chem. Commun.* 1999, 215. (h) Bi, X. *Synlett* 2006, 2515. (i) Umemoto, T.; Singh, R. P.; Xu, Y.; Saito, N. *J. Am. Chem. Soc.* 2010, *132*, 18199. (j) Singh, R. P.; Umemoto, T. *J. Org. Chem.* 2011, *76*, 3113.

¹¹⁹ (a) Hayashi, H.; Sonoda, H.; Fukumura, K.; Nagata, T. *Chem. Commun.* 2002, 1618. (b) Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* 2011, *133*, 11482.

¹²⁰ (a) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* 1979, *44*, 3872. (b) Olah, G. A.; Li, X. Y.; Wang, Q.; Prakash, G. K. S. *Synthesis* 1993, 693. (c) York, C.; Prakash, G. K. S.; Olah, G. A. *Tetrahedron* 1996, *52*, 9. (d) Bucsi, I.; Torok, B.; Marco, A. I.; Rasul, G.; Prakash, G. K. S.; Olah, G. A. *J. Am. Chem. Soc.* 2002, *124*, 7728. (e) Haufe, G. *J. Prakt. Chem.* 1996, *338*, 99. (f) Yoshiyama, T.; Fuchigami, T. *Chem. Lett.* 1992, 1995. (g) Fuchigami, T.; Fujita, T. *J. Org. Chem.* 1994, *59*, 7190.

¹²¹ Sawamura, T.; Takahashi, K.; Inagi, S.; Fuchigami, T. *Angew. Chem. Int. Ed.* 2012, *51*, 4413.

Meisenheimer-type complex.¹²² Additionally, chiral transition-metal complexes and organocatalysts can be used for nucleophilic fluorination reactions to afford enantioenriched fluorinated compounds.

1.2.2.1. Nucleophilic fluorination for the synthesis of fluorinated arenes

S_NAr reactions are currently used on an industrial scale in the Halex process,¹²³ although one or more electron-withdrawing groups on the arene are typically required. Aromatic substitution, catalyzed and non-catalyzed, is one of the most direct methods for nucleophilic fluorination at this time with control of regioselectivity. Improvement in the substrate scope is desirable because nucleophilic fluorination is preferred both on industrial scale for cost efficiency and for radiochemical fluorination methods in positron emission tomography imaging because of the availability of ¹⁸F-fluoride.

Traditional nucleophilic fluorination methods with main group elements

Balz and Schiemann first developed the nucleophilic fluorination of arenes via thermal decomposition of aryl diazonium tetrafluoroborate salts in 1927,¹²⁴ a process which was improved.¹²⁵ Displacement of chloride in 1-chloro-2,4-dinitrobenzene under forcing conditions with anhydrous potassium fluoride (the Halex process) was developed in 1936¹²⁶ followed by fluorodenitration of arenes, by *ipso*-attack at the carbon bearing the nitro group (Scheme 30).¹²⁷ More recent work in this area has allowed for the fluorination of electron-poor, chloro-, nitro-, or trimethylammoniumarenes with anhydrous tetrabutylammonium fluoride at room temperature in up to >95% yield.¹²⁸ Aryl fluorides can be accessed from reaction of aryl bromides with anhydrous tetramethylammonium

¹²² Meisenheimer, J. *Justus Liebigs Ann. Chem.* 1902, 323, 205.

¹²³ Langlois, B.; Gilbert, L.; Forat, G. Fluorination of aromatic compounds by halogen exchange with fluoride anions ("Halex" reaction). In *Industrial Chemistry Library*; Jean-Roger, D.; Serge, R., Eds.; Elsevier: Amsterdam, 1996; Vol. 8, pp 244-293.

¹²⁴ Balz, G.; Schiemann, G. *Ber. Dtsch. Chem. Ges.* 1927, 60, 1186.; the Wallach reaction reported prior to the Balz-Schiemann reaction involves the fluorination of aryl triazenes via diazonium intermediates: Wallach, O. *Justus Liebigs Ann. Chem.* 1886, 235, 233.

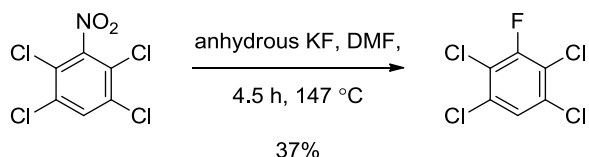
¹²⁵ Finger, G. C.; Oesterling, R. E. *J. Am. Chem. Soc.* 1956, 78, 2593.

¹²⁶ Gottlieb, H. B. *J. Am. Chem. Soc.* 1936, 58, 532.

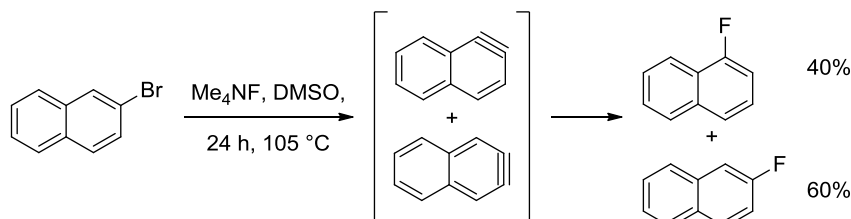
¹²⁷ Finger, G. C.; Kruse, C. W. *J. Am. Chem. Soc.* 1956, 78, 6034.

¹²⁸ Sun, H.; DiMagno, S. G. *Angew. Chem. Int. Ed.* 2006, 45, 2720.

fluoride; however, the process actually occurs through fluoride trapping of aryne intermediates generated from the elimination of the bromide with the strongly basic anhydrous fluoride and therefore provides a mixture of regioisomers (Scheme 31).¹²⁹ Other approaches that have been explored involve two-step nucleophilic fluorodemetalation of toxic organothallium(III) substrates¹³⁰ as well as diaryliodonium substrates.¹³¹ Although simple fluorinated arenes can be synthesized with some of the aforementioned reactions, even on industrial processes,¹²³ none of these methods are tolerant of many functional groups or exhibit broad substrate scope such that densely functionalized substrates may be nucleophilically fluorinated.



Scheme 30. Nucleophilic aromatic substitution with KF



Scheme 31. Fluorination of naphthyl bromide via aryne intermediates

Transition-metal-catalyzed nucleophilic fluorination

Transition-metal-catalyzed cross-coupling with fluoride as nucleophile has been investigated with late transition metals such as nickel, copper, ruthenium, rhodium, palladium, iridium, and platinum.¹³² Reductive elimination from

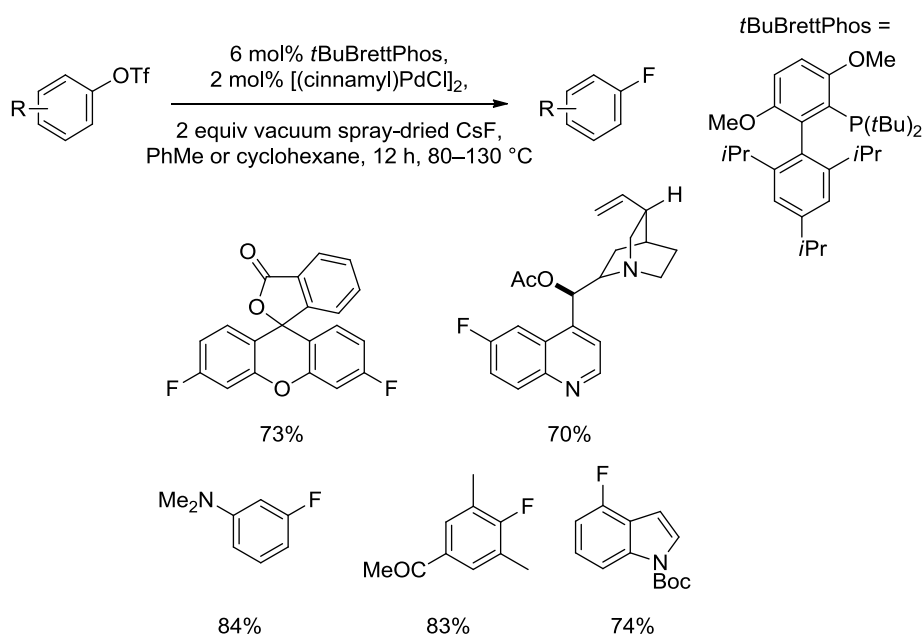
¹²⁹ Grushin, V. V.; Marshall, W. J. *Organometallics* 2008, 27, 4825.

¹³⁰ (a) Taylor, E. C.; Bigham, E. C.; Johnson, D. K.; McKillop, A. *J. Org. Chem.* 1977, 42, 362. (b) Gun'kin, I. F.; Pankst'yanov, A. Y.; Popova, S. S.; Kleimenova, V. I. *Russ. J. Gen. Chem.* 2000, 70, 37.

¹³¹ Vanderpuy, M. J. *Fluorine Chem.* 1982, 21, 385.

¹³² (a) Barthazy, P.; Hintermann, L.; Stoop, R. M.; Worle, M.; Mezzetti, A.; Togni, A. *Helv. Chim. Acta* 1999, 82, 2448. (b) Barthazy, P.; Stoop, R. M.; Worle, M.; Togni, A.; Mezzetti, A. *Organometallics* 2000, 19, 2844. (c) Grushin, V. V. *Chem. Eur. J.* 2002, 8, 1006. (d) Yandulov, D. V.; Tran, N. T. *J. Am. Chem. Soc.* 2007, 129, 1342. (e) Grushin, V. V.; Marshall, W. J. *Organometallics* 2007, 26, 4997. (f) Watson, D. A.; Su, M. J.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* 2009, 325, 1661. (g) Grushin, V. V. *Acc. Chem. Res.* 2010, 43, 160. (h) Casitas, A.; Canta, M.; Sola, M.; Costas, M.; Ribas, X. *J. Am. Chem. Soc.* 2011, 133, 19386. (i) Noel, T.; Maimone, T. J.; Buchwald, S. L. *Angew. Chem. Int. Ed.* 2011, 50, 8900. (j) Zhao, S.-B.; Wang, R.-Y.;

Pd(II) is challenging because a stable fluoride-bridge dimer complex formation is favored due to the high basicity of the fluoride ligand. Cross-coupling fluorination of aryl triflates with fluoride via palladium catalysis (Scheme 32)^{132f, 133} was developed with the key use of bulky monodentate phosphine ligand *t*BuBrettPhos that afford mononuclear, tri-coordinate palladium(II) complexes positioned for successful C–F reductive elimination. This method displays a broad substrate scope and tolerates nucleophilic functional groups that are often not tolerated in electrophilic fluorination methods due to competing fluorination of the nucleophile. Protic functional groups are not yet tolerated under the reaction conditions and constitutional isomers were formed in some cases, which may result from the use of basic fluoride salts.¹³³



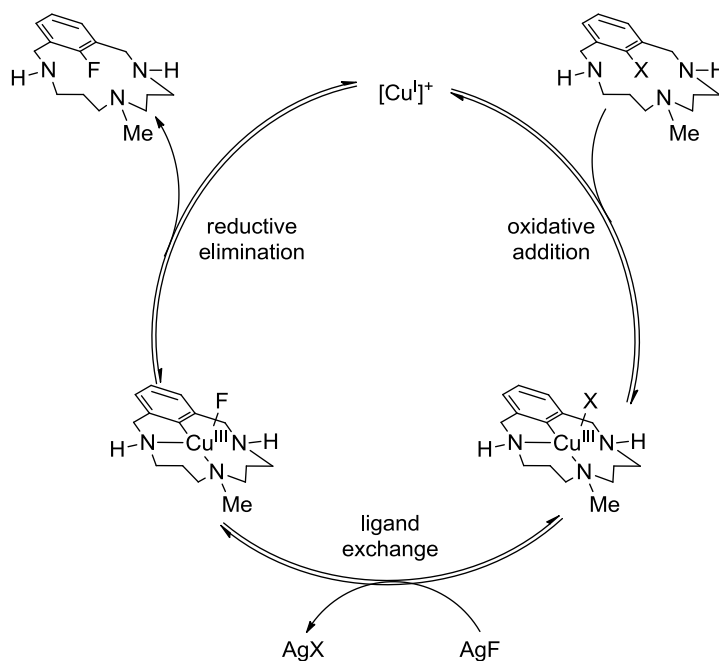
Scheme 32. Pd-catalyzed cross-coupling of aryl triflates with CsF

An oxidative addition—C–F reductive elimination sequence was established via a Cu(I)-Cu(III) cycle using a contrived substrate that allowed for isolation of the intermediates (Scheme 33).^{132h} Oxidative addition of copper(I) into the aryl halide supported by the tris(amine) ligand generates a copper(III) complex which upon ligand metathesis with silver fluoride gives a copper(III) fluoride complex that undergoes reductive elimination to extrude

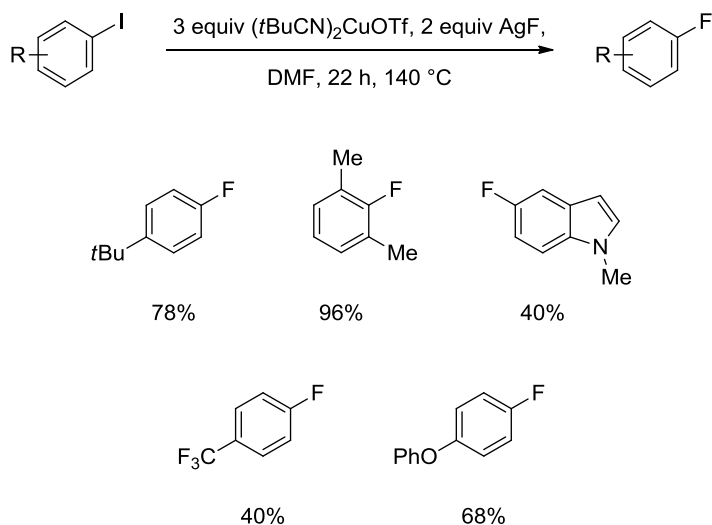
Nguyen, H.; Becker, J. J.; Gagne, M. R. *Chem. Commun.* 2012, 48, 443. (k) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* 2012, 10795.

¹³³ Maimone, T. J.; Milner, P. J.; Kinzel, T.; Zhang, Y.; Takase, M. K.; Buchwald, S. L. *J. Am. Chem. Soc.* 2011, 133, 18106.

the aryl fluoride product. Copper-mediated fluorination of aryl iodides was subsequently reported with 3 equivalents of copper(I) complex and AgF (Scheme 34).^{132k}



Scheme 33. Cu-catalyzed halide exchange on arenes with AgF

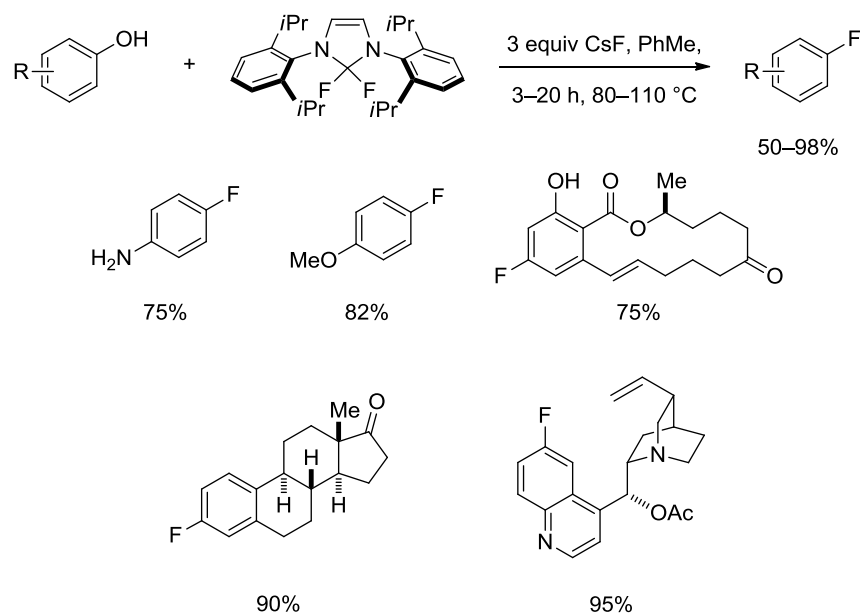


Scheme 34. Cu-mediated fluorination of aryl iodides with AgF

Nucleophilic aromatic deoxyfluorination

The ability to directly substitute the hydroxy group in phenols with fluoride avoids pre-functionalization of the phenol. Catechol can be monodeoxyfluorinated by oxidation of the catechol to the *ortho*-quinone followed by

nucleophilic fluorination with Deoxo-Fluor[®].¹³⁴ This oxidation-fluorination method affords a mixture of *ortho*-fluorinated phenol isomers. One of the first examples of deoxyfluorination of nitro-substituted phenol was accomplished with *N,N'*-dimethyl-2,2-difluoroimidazolidine.^{119a} A general method for the *ipso*-deoxyfluorination of phenols was subsequently accomplished with the sterically hindered difluoroimidazole reagent shown in Scheme 35 (PhenoFluor[®]) and cesium fluoride.^{119b} Electron-poor, -neutral, and -rich aryl fluorides in addition to heteroaromatic fluorides can be synthesized from the corresponding phenol precursors using this method but requires a stoichiometric amount of the reagent.



Scheme 35. Deoxyfluorination of phenols with PhenoFluor[®]

1.2.2.2. Nucleophilic fluorination for the synthesis of aliphatic fluorides

Through appropriate selection of fluoride source, leaving group, and solvent, nucleophilic fluorination at a primary carbon center is well established.¹³⁵ Nucleophilic fluorination at a secondary or tertiary carbon center is inherently more difficult. Deoxyfluorination with sulphur tetrafluoride or derivatives thereof can afford fluoride from

¹³⁴ Nemoto, H.; Nishiyama, T.; Akai, S. *Org. Lett.* 2011, **13**, 2714.

¹³⁵ (a) Liotta, C. L.; Harris, H. P. *J. Am. Chem. Soc.* 1974, **96**, 2250. (b) Gerstenberger, M. R. C.; Haas, A. *Angew. Chem. Int. Ed.* 1981, **20**, 647. (c) Ishikawa, N.; Kitazume, T.; Yamazaki, T.; Mochida, Y.; Tatsuno, T. *Chem. Lett.* 1981, 761. (d) Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* 1984, **49**, 3216. (e) Shimizu, M.; Nakahara, Y.; Yoshioka, H. *Tetrahedron Lett.* 1985, **26**, 4207. (f) Pilcher, A. S.; Ammon, H. L.; Deshong, P. *J. Am. Chem. Soc.* 1995, **117**, 5166.

secondary or tertiary carbinols, but competing elimination¹³⁶ and rearrangement^{136, 137} reactions are often problematic. Halofluorination of alkenes were accomplished via treatment of the alkene with *N*-iodosuccinimide and tetraalkylammonium hydrogen fluoride.¹³⁸ Epoxide¹³⁹ and aziridine¹⁴⁰ openings with fluoride afford vicinal fluoroalcohols and fluoroamines respectively which have been elaborated to multivincinal multi-fluoroalkanes.¹⁴¹

Deoxy/dethiofluorination via nucleophilic fluorination

Carbonyl compounds were first converted to geminal difluoromethylene functional groups with sulphur tetrafluoride.¹⁴² The toxicity and volatility of sulfur tetrafluoride discouraged its use and lead to the use of less volatile reagents such as aryl and aminosulfur trifluorides.¹¹⁸ Diethylaminosulfur trifluoride (DAST)^{136,143} has most commonly been used to fluorinate oxygenated (carbonyl, hydroxyl) or sulfur-containing (thiocarbonyl, sulfide) substrates.^{118c,144} The mechanism of DAST-mediated fluorination is proposed to be initiated by a nucleophilic attack

¹³⁶ Middleton, W. J. *J. Org. Chem.* 1975, **40**, 574.

¹³⁷ Ye, C. F.; Shreeve, J. M. *J. Fluorine Chem.* 2004, **125**, 1869.

¹³⁸ Kuroboshi, M.; Hiyama, T. *Tetrahedron Lett.* 1991, **32**, 1215.

¹³⁹ (a) Hamatani, T.; Matsubara, S.; Matsuda, H.; Schlosser, M. *Tetrahedron* 1988, **44**, 2875. (b) Nicoletti, M.; O'Hagan, D.; Slawin, A. M. Z. *J. Am. Chem. Soc.* 2005, **127**, 482. (c) Hunter, L.; O'Hagan, D.; Slawin, A. M. Z. *J. Am. Chem. Soc.* 2006, **128**, 16422. (d) Hunter, L.; O'Hagan, D. *Org. Biomol. Chem.* 2008, **6**, 2843.

¹⁴⁰ (a) Noritake, S.; Shibata, N.; Kawai, H.; Pandey, M. K.; Nakamura, S.; Toru, T. *Heterocycl. Commun.* 2009, **15**, 105. (b) Duthion, B.; Pardo, D. G.; Cossy, J. *Org. Lett.* 2010, **12**, 4620. (c) Alvernhe, G.; Lacombe, S.; Laurent, A. *Tetrahedron Lett.* 1980, **21**, 289.

¹⁴¹ (a) Hunter, L.; O'Hagan, D. *Org. Biomol. Chem.* 2008, **6**, 2843. (b) O'Hagan, D. *J. Org. Chem.* 2012, **77**, 3689.

¹⁴² (a) Smith, W. C.; Tullock, C. W.; Muetterties, E. L.; Hasek, W. R.; Fawcett, F. S.; Engelhardt, V. A.; Coffman, D. D. *J. Am. Chem. Soc.* 1959, **81**, 3165. (b) Hasek, W. R.; Smith, W. C.; Engelhardt, V. A. *J. Am. Chem. Soc.* 1960, **82**, 543.

¹⁴³ Middleton, W. J.; Bingham, E. M. *Organic Syntheses* 1988, **50**, 440.

¹⁴⁴ (a) Tewson, T. J.; Welch, M. J. *J. Org. Chem.* 1978, **43**, 1090. (b) Boulton, K.; Cross, B. E. *J. Chem. Soc., Perkin Trans. 1* 1979, 1354. (c) Middleton, W. J.; Bingham, E. M. *J. Org. Chem.* 1980, **45**, 2883. (d) Castillon, S.; Dessingues, A.; Faghhi, R.; Lukacs, G.; Olesker, A.; Thang, T. T. *J. Org. Chem.* 1985, **50**, 4913. (e) Posner, G. H.; Haines, S. R. *Tetrahedron Lett.* 1985, **26**, 5. (f) Hudlicky, M. *J. Fluorine Chem.* 1987, **36**, 373. (g) Pansare, S. V.; Vederas, J. C. *J. Org. Chem.* 1987, **52**, 4804. (h) Ratcliffe, A. J.; Warner, I. *Tetrahedron Lett.* 1995, **36**, 3881. (i) Hagele, G.; Haas, A. *J. Fluorine Chem.* 1996, **76**, 15. (j) Shellhamer, D. F.; Anstine, D. T.; Gallego, K. M.; Ganesh, B. R.; Hanson, A. A.; Hanson, K. A.; Henderson, R. D.; Prince, J. M.; Heasley, V. L. *J. Chem. Soc., Perkin Trans. 2* 1995, 861. (k) Hagele, G.; Haas, A. *J. Fluorine Chem.* 1996, **76**, 15. (l) Shellhamer, D. F.; Briggs, A. A.; Miller, B. M.; Prince, J. M.; Scott, D. H.; Heasley, V. L. *J. Chem. Soc., Perkin Trans. 2* 1996, 973. (m) Kirihaara, M.; Niimi, K.; Momose, T. *Chem. Commun.* 1997, 599. (n) Kirihaara, M.; Niimi, K.; Okumura, M.; Momose, T. *Chem. Pharm. Bull.* 2000, **48**, 220. (o) Ferreira, S. B. *Synlett* 2006, 1130. (p) Das, S.; Chandrasekhar, S.; Yadav, J. S.; Gree, R. *Tetrahedron Lett.* 2007, **48**, 5305.

of a hydroxyl group to the sulphur atom of DAST to form an alkoxyaminodifluorosulfane intermediate¹⁴⁵ that is activated for a S_N2 attack by fluoride. In some cases, however, fluoride attack afford products consistent with an S_N1 intermediate.^{144l} Additional drawbacks of DAST include moisture sensitivity as well as potential explosion upon heating.^{118f}

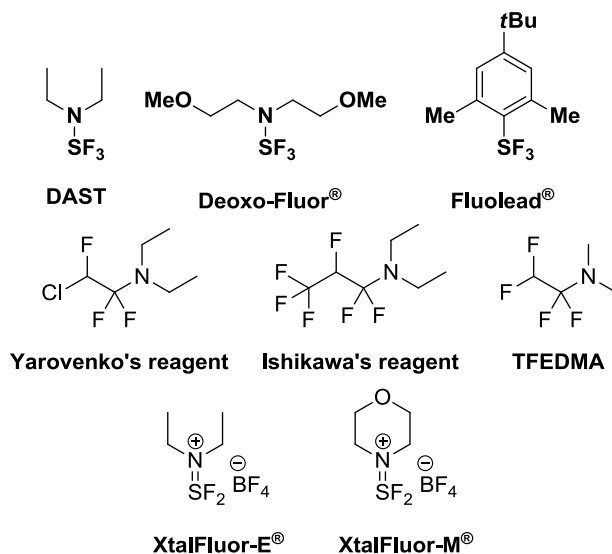


Figure 3. A selection of nucleophilic fluorinating reagents

Besides with DAST, deoxyfluorination and dethiofluorination can be accomplished with many different fluoride sources (Figure 3): pyridinium poly(hydrogen fluoride) (Olah's reagent),¹⁴⁶ nitrosonium tetrafluoroborate/pyridinium poly(hydrogen fluoride),¹⁴⁷ triethylamine tris(hydrogen fluoride) (TREAT•HF),¹⁴⁸ perfluoro-1-butanefluoride (PFSF),¹⁴⁹ sulfonyl fluoride/TREAT•HF mixture (Scheme 36),¹⁵⁰ Yarovenko's reagent,¹⁵¹ Ishikawa's reagent,¹⁵² TFEDMA,¹⁵³ *N,N'*-dimethyl-2,2,-difluoroimidazolidine,^{119a} 4-morpholinosulfur

¹⁴⁵ Sutherland, A.; Vederas, J. C. *Chem. Commun.* 1999, 1739.

¹⁴⁶ (a) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* 1979, **44**, 3872. (b) Olah, G. A.; Li, X. Y.; Wang, Q.; Prakash, G. K. S. *Synthesis* 1993, 693. (c) Bucsi, I.; Torok, B.; Marco, A. I.; Rasul, G.; Prakash, G. K. S.; Olah, G. A. *J. Am. Chem. Soc.* 2002, **124**, 7728.

¹⁴⁷ York, C.; Prakash, G. K. S.; Olah, G. A. *Tetrahedron* 1996, **52**, 9.

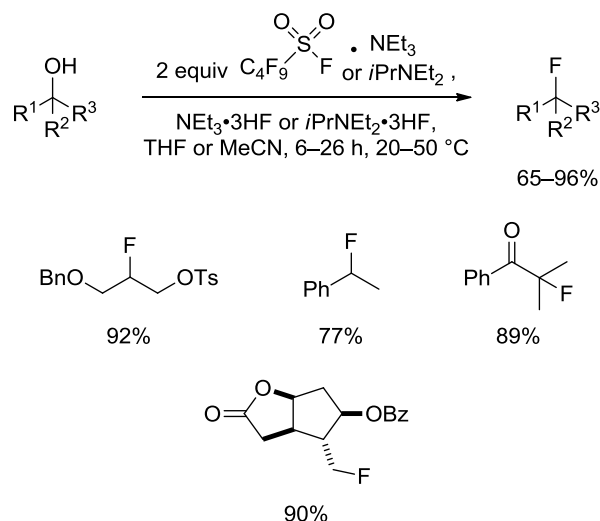
¹⁴⁸ Haufe, G. *J. Prakt. Chem.* 1996, **338**, 99.

¹⁴⁹ Bennua-Skalmowski, B.; Vorbrüggen, H. *Tetrahedron Lett.* 1995, **36**, 2611.

¹⁵⁰ Yin, J. J.; Zarkowsky, D. S.; Thomas, D. W.; Zhao, M. M.; Huffman, M. A. *Org. Lett.* 2004, **6**, 1465.

¹⁵¹ Yarovenko, N. N.; Raksha, M. A. *Zh. Obshch. Khim.* 1959, **29**, 2159.

trifluoride,^{118e,154} Deoxo-Fluor[®],^{118g,155} bromine trifluoride,¹⁵⁶ and 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead[®]).^{118j} Deoxo-Fluor[®] has been the most commonly used reagent for fluorination reactions and is considered a safer, more thermally stable alternative to DAST but is similarly moisture-sensitive and prone to decomposition to generate toxic HF. Likewise, Olah's reagent exhibits corrosive properties and toxicity due to presence of HF; TREAT•HF has been used as a less hazardous replacement and is mild enough to be used in borosilicate glassware.



Scheme 36. Deoxyfluorination of various alcohols with perfluorobutanesulfonyl fluoride-trialkylamine adduct and TREAT•HF

¹⁵² Takaoka, A.; Iwakiri, H.; Ishikawa, N. *Bull. Chem. Soc. Jpn.* 1979, **52**, 3377.

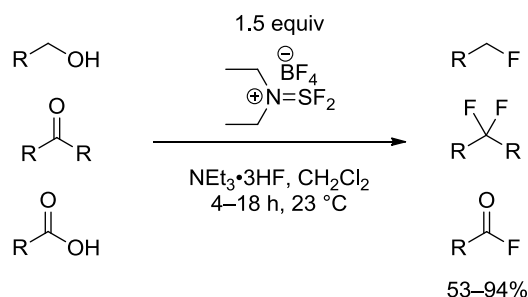
¹⁵³ Petrov, V. A.; Swearingen, S.; Hong, W.; Chris Petersen, W. *J. Fluorine Chem.* 2001, **109**, 25.

¹⁵⁴ Surmont, R.; Verniest, G.; De Groot, A.; Thuring, J. W.; De Kimpe, N. *Adv. Synth. Catal.* 2010, **352**, 2751.

¹⁵⁵ (a) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonc, F. M.; Cheng, H. S. *J. Org. Chem.* 1999, **64**, 7048. (b) Lal, G. S.; Lobach, E.; Evans, A. *J. Org. Chem.* 2000, **65**, 4830. (c) Singh, R. P.; Shreeve, J. M. *Org. Lett.* 2001, **3**, 2713. (d) Singh, R. P.; Shreeve, J. M. *Synthesis* 2002, 2561. (e) Singh, R. P.; Shreeve, J. M. *J. Fluorine Chem.* 2002, **116**, 23. (f) Singh, R. P.; Twamley, B.; Shreeve, J. M. *J. Org. Chem.* 2002, **67**, 1918. (g) Singh, R. P.; Shreeve, J. M. *J. Org. Chem.* 2003, **68**, 6063. (h) Krow, G. R.; Lin, G. L.; Moore, K. P.; Thomas, A. M.; DeBrosse, C.; Ross, C. W.; Ramjit, H. G. *Org. Lett.* 2004, **6**, 1669. (i) Chang, Y.; Tewari, A.; Adi, A.-I.; Bae, C. *Tetrahedron* 2008, **64**, 9837.

¹⁵⁶ (a) Sasson, R.; Hagooly, A.; Rozen, S. *Org. Lett.* 2003, **5**, 769. (b) Rozen, S. *Acc. Chem. Res.* 2005, **38**, 803. (c) Hagooly, Y.; Rozen, S. *J. Org. Chem.* 2008, **73**, 6780. (d) Hagooly, Y.; Sasson, R.; Welch, M. J.; Rozen, S. *Eur. J. Org. Chem.* 2008, 2875. (e) Cohen, O.; Hagooly, Y.; Rozen, S. *Tetrahedron* 2009, **65**, 1361. (f) Hagooly, Y.; Cohen, O.; Rozen, S. *Tetrahedron Lett.* 2009, **50**, 392.

Development of non-explosive crystalline, less moisture-sensitive deoxyfluorinating reagent XtalFluor-E[®] (diethylaminodifluorosulfonium tetrafluoroborate)¹⁵⁷ and related reagents¹⁵⁸ has resulted in fluorodeoxygenation with less byproducts (Scheme 37). Unlike DAST or Deoxo-Fluor[®], addition of amine hydrogen fluoride such as triethylamine tris(hydrogen fluoride) is required as a fluoride source for fluorination with XtalFluor-type reagents because after addition of the alcohol to XtalFluor, the diethylamino group is fully protonated and release the fluoride does not occur. Instead of adding an external fluoride source, addition of DBU can also promote release of fluoride by deprotonation of ammonium.



Scheme 37. Deoxyfluorination of alcohols, carbonyls, and carboxylic acids with XtalFluor-E[®]

Preparation of propargylic and allylic fluorides

The synthesis of propargylic fluorides can be accomplished via deoxyfluorination of propargylic alcohols with DAST¹⁵⁹ or fluorination of variety of activated propargylic substrates¹⁶⁰ such as propargylic mesylates and silylethers. Commonly used fluoride sources besides DAST for the synthesis of propargylic fluorides include

¹⁵⁷ Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; LaFlamme, F.; L'Heureux, A. *Org. Lett.* 2009, **11**, 5050.

¹⁵⁸ L'Heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; LaFlamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. *J. Org. Chem.* 2010, **75**, 3401.

¹⁵⁹ Middleton, W. J. *J. Org. Chem.* 1975, **40**, 574.

¹⁶⁰ (a) Haloui, E.; Nasr, C. B.; Canet, D. *J. Mol. Struct.* 1982, **95**, 231. (b) Kornilov, A. M.; Sorochinskii, A. E.; Kukhar, V. P. *Zh. Org. Khim* 1989, **25**, 2520. (c) Khanous, A.; Gorgues, A.; Cousseau, J. *J. Fluorine Chem.* 1990, **49**, 401. (d) Asai, T.; Morizawa, Y.; Shimada, T.; Nakayama, T.; Urushihara, M.; Matsumura, Y.; Yasuda, A. *Tetrahedron Lett.* 1995, **36**, 273. (e) Matsumura, Y.; Asai, T.; Shimada, T.; Nakayama, T.; Urushihara, M.; Morizawa, Y.; Yasuda, A.; Yamamoto, T.; Fujitani, B.; Hosoki, K. *Chem. Pharm. Bull.* 1995, **43**, 353. (f) Matsumura, Y.; Shimada, T.; Nakayama, T.; Urushihara, M.; Asai, T.; Morizawa, Y.; Yasuda, A. *Tetrahedron* 1995, **51**, 8771. (g) Benayoud, F.; deMendonca, D. J.; Digits, C. A.; Moniz, G. A.; Sanders, T. C.; Hammond, G. B. *J. Org. Chem.* 1996, **61**, 5159. (h) Matsumura, Y.; Nakano, T.; Asai, T.; Morizawa, Y.; Yasuda, A. *ACS Symp. Ser.* 1996, **639**, 83. (i) Matsumura, Y.; Shimada, T.; Wang, S. Z.; Asai, T.; Morizawa, Y.; Yasuda, A. *Bull. Chem. Soc. Jpn.* 1996, **69**, 3523. (j) Shimizu, M.; Kanemoto, S.; Nakahara, Y. *Heterocycles* 2000, **52**, 117.

SF₄,^{160b,g,161} dialkylaminosulfur trifluorides,^{160d-f,i} Yarovenko's reagent,¹⁶² and Ghosez's reagent (*N,N*-diisopropyl-1-fluoro-2-methylpropenamine).¹⁶³ For the synthesis of chiral propargylic fluorides, Grée used chiral propargylic alcohols and introduced fluoride via S_N2 displacement.¹⁶⁴ This approach is substrate dependent as many chiral propargylic alcohols can give enantiomeric excess-eroded or racemized products through alternate S_N1 pathways. Most reported methods utilize nucleophilic fluorination to give propargylic fluorides; Hammond¹⁶⁵ and Gouverneur¹⁶⁶ have investigated electrophilic fluorination routes to propargylic fluorides.

Middleton first reported the dehydroxyfluorination of allylic alcohols with DAST,¹⁵⁹ which later was used to study the fluorination of allylic alcohol substrates containing different substituents and substitution patterns.¹⁶⁷ Complexation of the double bonds using stoichiometric amount of rhenium¹⁶⁸ and iron¹⁶⁹ complexes were developed for allylic alcohols and dienols, respectively. This strategy successfully prevented transposition of the double bonds with complete retention of the stereochemistry of deoxyfluorination but the use of stoichiometric amounts of transition-metal complex as well as additional protection-deprotection steps has limited utility of the complexation

¹⁶¹ Dear, R. E. A.; Gilbert, E. E. *J. Org. Chem.* 1968, **33**, 819.

¹⁶² Zakharkin, L. I.; Kvasov, B. A.; Lebedev, V. N. *Zh. Obshch. Khim.* 1971, **41**, 2694.

¹⁶³ Tietze, L. F.; Bothe, U.; Schuberth, I. *Chem. Eur. J.* 2000, **6**, 836.

¹⁶⁴ (a) Grée, D.; Madiot, V.; Grée, R. *Tetrahedron Lett.* 1999, **40**, 6399. (b) Madiot, V.; Grée, D.; Grée, R. *Tetrahedron Lett.* 1999, **40**, 6403. (c) Madiot, V.; Lesot, P.; Grée, D.; Courtieu, J.; Grée, R. *Chem. Commun.* 2000, 169. (d) Prakesch, M.; Grée, D.; Grée, R. *J. Org. Chem.* 2001, **66**, 3146. (e) Prakesch, M.; Grée, D.; Grée, R. *Acc. Chem. Res.* 2002, **35**, 175. (f) Prakesch, M.; Kerouredan, E.; Grée, D.; Grée, R.; DeChancie, J.; Houk, K. N. *J. Fluorine Chem.* 2004, **125**, 537. (g) Manthathi, V. L.; Murthy, A. S. K.; Caijo, F.; Drouin, D.; Lesot, P.; Grée, D.; Grée, R. *Tetrahedron: Asymmetry* 2006, **17**, 2306.

¹⁶⁵ (a) Zapata, A. J.; Gu, Y.; Hammond, G. B. *J. Org. Chem.* 2000, **65**, 227. (b) Wang, Z.; Gu, Y.; Zapata, A. J.; Hammond, G. B. *J. Fluorine Chem.* 2001, **107**, 127.

¹⁶⁶ Carroll, L.; Pacheco, M. C.; Garcia, L.; Gouverneur, V. *Chem. Commun.* 2006, 4113.

¹⁶⁷ (a) Blackburn, G. M.; Kent, D. E. *J. Chem. Soc., Chem. Commun.* 1981, 511. (b) Blackburn, G. M.; Kent, D. E. *J. Chem. Soc., Perkin Trans. 1* 1986, 913. (c) Boukerb, A.; Grée, D.; Laabassi, M.; Grée, R. *J. Fluorine Chem.* 1998, **88**, 23. (d) Hammond, G. B.; deMendonca, D. J. *J. Fluorine Chem.* 2000, **102**, 189. (e) Grée, D.; Vallerie, L.; Grée, R.; Toupet, L.; Washington, I.; Pelicier, J. P.; Villacampa, M.; Pérez, J. M.; Houk, K. N. *J. Org. Chem.* 2001, **66**, 2374.

¹⁶⁸ Legoupy, S.; Crévisy, C.; Guillemin, J. C.; Grée, R. *J. Fluorine Chem.* 1999, **93**, 171.

¹⁶⁹ Grée, D. M.; Kermarrec, C. J. M.; Martelli, J. T.; Grée, R. L.; Lellouche, J. P.; Toupet, L. J. *J. Org. Chem.* 1996, **61**, 1918.

approach. Besides DAST, other fluoride sources can be used, for example, bis(dialkylamino)sulfur difluorides,^{159,170} Yarovenko's reagent,¹⁷¹ Ghosez's reagent,¹⁷² and IF₅ in NEt₃•3HF.¹⁷³ Other activated allylic substrates besides allylic alcohols were also employed.¹⁷⁴ An attractive route to allylic fluorides is the Tsuji-Trost-type fluoride displacement of a leaving group catalyzed by a transition-metal complex. As fluoride serves as a better leaving group than the typically used acetate in the Tsuji-Trost reaction,¹⁷⁵ selection of an appropriate leaving group is important. Cinnamyl allylic carbonates can be transformed to terminal allylic fluorides via palladium catalysis¹⁷⁶ as well as secondary and tertiary allylic fluorides from allylic trichloroacetamides under iridium catalysis (Scheme 38).¹⁷⁷ The enantioselective fluorination of cyclic¹⁷⁸ and acyclic (Scheme 39)¹⁷⁹ allylic chlorides in the presence of a chiral Pd catalyst was reported; from acyclic (linear) allylic chlorides, branched or linear allylic fluorides can be synthesized. The selectivity reported for the linear allylic chloride substrates is for branched products and is >20:1 for most substrates. Additionally, a variety of functional groups can be tolerated; however, this method requires the use of three equivalents of silver fluoride.

¹⁷⁰ (a) Poulter, C. D.; Wiggins, P. L.; Plummer, T. L. *J. Org. Chem.* 1981, **46**, 1532. (b) Mann, J.; Smith, G. P. *J. Chem. Soc., Perkin Trans. 1* 1991, 2884.

¹⁷¹ (a) Cross, B. E.; Hendley, P. *J. Chem. Soc., Perkin Trans. 1* 1975, 2523. (b) Banks, R. E.; Cross, B. E. *J. Chem. Soc., Perkin Trans. 1* 1977, **5**, 512. (c) Banks, R. E.; Bateson, J. H.; Cross, B. E.; Erasmussen, A. *J. Chem. Res., Synop.* 1980, **2**, 46. (d) Kozikowski, A. P.; Wu, J. P. *Tetrahedron Lett.* 1990, **31**, 4309.

¹⁷² Munyemana, F.; Frisque-Hesbain, A. M.; Devos, A.; Ghosez, L. *Tetrahedron Lett.* 1989, **30**, 3077.

¹⁷³ Yoneda, N.; Fukuhara, T. *Chem. Lett.* 2001, 222.

¹⁷⁴ (a) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* 1979, **44**, 3872. (b) Villieras, J.; Rambaud, M. *Synthesis* 1982, 924. (c) Mann, J.; Pietrzak, B. *J. Chem. Soc., Perkin Trans. 1* 1983, 2681. (d) Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* 1984, **49**, 3216. (e) Bannai, K.; Toru, T.; Ōba, T.; Tanaka, T.; Okamura, N.; Watanabe, K.; Hazato, A.; Kurozumi, S. *Tetrahedron* 1986, **42**, 6735. (f) Ichihara, J.; Matsuo, T.; Hanafusa, T.; Ando, T. *J. Chem. Soc., Chem. Commun.* 1986, 793. (g) Ichikawa, J.; Sugimoto, K. i.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* 1987, 1985. (h) Bhadury, P. S.; Pandey, M.; Jaiswal, D. K. *J. Fluorine Chem.* 1995, **73**, 185. (i) Ichihara, J.; Takai, Y.; Hanafusa, T.; Tomioka, K. *J. Fluorine Chem.* 1995, **71**, 131. (j) Albanese, D.; Landini, D.; Penso, M. *J. Org. Chem.* 1998, **63**, 9587. (k) Guijarro, D.; Yus, M. *J. Organomet. Chem.* 2001, **624**, 53.

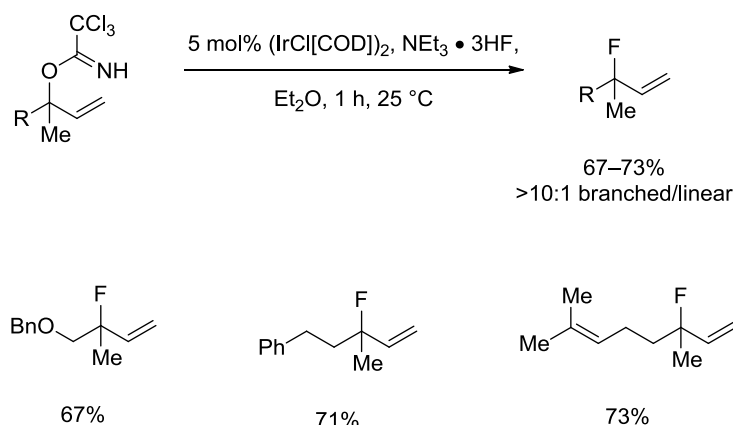
¹⁷⁵ Hazari, A.; Gouverneur, V.; Brown, J. M. *Angew. Chem. Int. Ed.* 2009, **48**, 1296.

¹⁷⁶ Hollingworth, C.; Hazari, A.; Hopkinson, M. N.; Tredwell, M.; Benedetto, E.; Huiban, M.; Gee, A. D.; Brown, J. M.; Gouverneur, V. *Angew. Chem. Int. Ed.* 2011, **50**, 2613.

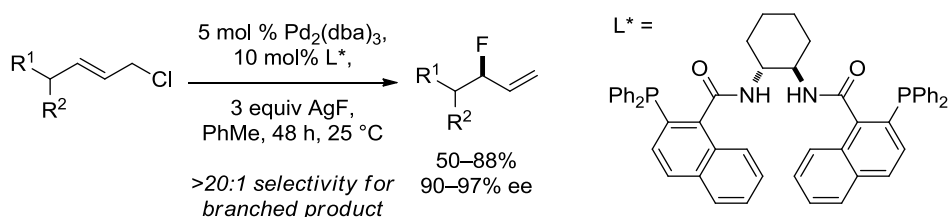
¹⁷⁷ Topczewski, J. J.; Tewson, T. J.; Nguyen, H. M. *J. Am. Chem. Soc.* 2011, **133**, 19318.

¹⁷⁸ Katcher, M. H.; Doyle, A. G. *J. Am. Chem. Soc.* 2010, **132**, 17402.

¹⁷⁹ Katcher, M. H.; Sha, A.; Doyle, A. G. *J. Am. Chem. Soc.* 2011, **133**, 15902.



Scheme 38. Ir-catalyzed fluorination of allylic trichloroacetamidates



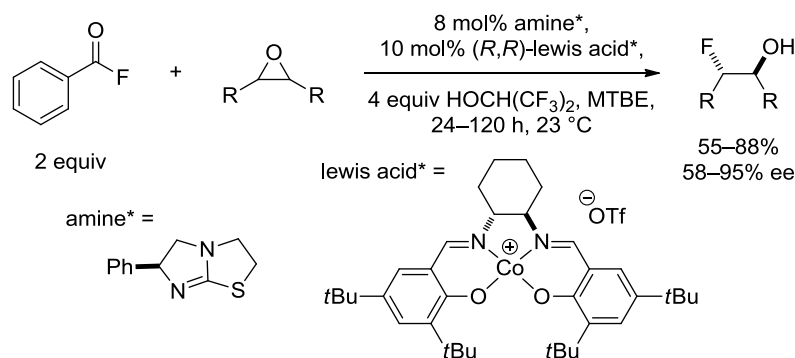
Scheme 39. Pd-catalyzed enantioselective synthesis of branched allylic fluorides

Fluoride addition olefins and epoxides

In addition to S_N2 reactions, fluoride addition to olefins can occur through bromofluorination of olefins, which can be done efficiently on large scale to afford simple fluorinated aliphatic products.^{120e} Epoxide opening with fluoride can provide access to secondary or tertiary fluorinated aliphatic molecules as well. Asymmetric opening of *meso*-epoxides with fluoride was first reported with stoichiometric amounts of chiral Lewis acid complexes¹⁸⁰ and later with a Co(III)-salen catalyst (Scheme 40)¹⁸¹ for non-linear *meso*-epoxides and terminal epoxides. In situ fluoride release from benzoyl fluoride was employed to suppress background reactions and catalyst inhibition. Mechanistic studies suggest that the rate-determining epoxide opening proceeds via a bimetallic complex, which led to the design of a more efficient dimeric catalyst with two cobalt-salen complexes tethered together (Scheme 40).

¹⁸⁰ (a) Bruns, S.; Haufe, G. *J. Fluorine Chem.* 2000, **104**, 247. (b) Haufe, G.; Bruns, S. *Adv. Synth. Catal.* 2002, **344**, 165.

¹⁸¹ (a) Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* 2010, **132**, 3268. (b) Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* 2011, **133**, 16001.



Scheme 40. Co(III)-catalyzed asymmetric opening of *meso*-epoxides with fluoride

1.3. Trifluoromethoxylation

Trifluoromethoxylated molecules have been used as agrochemicals, pharmaceuticals, and electro-optical materials.¹⁸² The increase in lipophilicity¹⁸³ from trifluoromethoxy group incorporation has made this functional group an attractive substituent to use in medicinal chemistry. Additionally, the ability to induce molecular conformation changes with the trifluoromethoxy substituent, which in arenes sits orthogonal to the plane of the arene¹⁸⁴ compared to a methoxy group which normally rests in plane of the arene, attests to the added value of trifluoromethoxy group incorporation into molecules.

The formation of the oxygen–CF₃ bond as well as the carbon–OCF₃ bond has been difficult to accomplish for two main reasons: reactivity of the trifluoromethylating reagents with carbon sites of the oxygenated nucleophile leading to formation of byproducts and the thermal instability of many trifluoromethoxide salts. Consequently, many nucleophilic fluorodesulfurization and fluorodeoxygenation of functionalized alcohols and phenols have been established for the synthesis of trifluoromethyl ethers whereas fewer methods for the formation of oxygen–CF₃ and carbon–OCF₃ bonds have been successfully accomplished. Most approaches for the synthesis of trifluoromethyl ethers have low functional group tolerance because of the use of hydrogen fluoride, Lewis acids, or thermally unstable, reactive trifluoromethylating reagents. Synthesis of aryl trifluoromethyl ethers via O-trifluoromethylation of phenols has not been a successful approach due to carbon trifluoromethylation side reactions or use of impractical

¹⁸² Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* 2005, 105, 827.

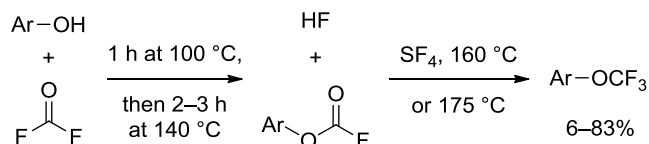
¹⁸³ Jeschke, P.; Baston, E.; Leroux, F. R. *Mini-Rev. Med. Chem.* 2007, 7, 1027.

¹⁸⁴ Bohm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Muller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* 2004, 5, 637.

reaction conditions with thermally unstable *O*-(trifluoromethyl)dibenzofuranium reagents. In contrast, *O*-trifluoromethylation of primary and secondary alcohols with thermally stable Togni reagent affords the desired trifluoromethyl ethers.

1.3.1. Aryl trifluoromethyl ethers

Nucleophilic fluorination of phenols functionalized as aryl trichloromethyl ethers,¹⁸⁵ aryl chlorothionoformates,^{185b, 186} phenyl fluoroformates,¹⁸⁷ and aryl xanthates¹⁸⁸ constitutes most of the methods developed for the synthesis of trifluoromethoxyarenes. The development of a broad substrate scope, functional group tolerant method with the phenol functionalization-fluorination approach has yet to come due to the use of HF and antimony-based Lewis acids. Aryl trichloromethyl ethers^{185b,189} synthesized in situ¹⁹⁰ or prior to the reaction by chlorination of the aryl methyl ether^{185b,c,f} as well as aryl chlorothionoformates^{185b,186} can be nucleophilically fluorinated with hydrogen fluoride,^{185e} SbF₅,^{185g} SbF₃ in the presence of SbF₅,^{185a,b,f} and molybdenum hexafluoride.¹⁸⁶ Likewise, phenol fluoroformates can be treated with SbF₃ or SF₄/HF to afford desired trifluoromethoxyarenes (Scheme 41).¹⁸⁷ Furthermore, aryl xanthates were used as substrates for fluorodesulfurization with HF/pyridine and dibrominated hydantoin (Scheme 42).^{188a} These aforementioned reactions conditions cannot be used to synthesize complex, functionalized trifluoromethoxyarenes.



Scheme 41. Synthesis of aryl trifluoromethyl ethers via fluoroformate intermediates

¹⁸⁵ (a) Yagupolskii, L. M. *Dokl. Akad. Nauk S.S.S.R.* 1955, **105**, 100. (b) Yarovenko, N. N.; Vasileva, A. S. *Zh. Obshch. Khim.* 1958, **28**, 2502. (c) Yagupolskii, L. M.; Troitskaya, V. I. *Zh. Obshch. Khim.* 1961, **31**, 915. (d) Louw, R.; Franken, P. W. *Chem. Ind. (London)* 1977, 127. (e) Feiring, A. E. *J. Org. Chem.* 1979, **44**, 2907. (f) Yagupolskii, L. M.; Orda, V. V. *Zh. Obshch. Khim.* 1964, **34**, 1979. (g) Salome, J.; Mauger, C.; Brunet, S.; Schanen, V. *J. Fluorine Chem.* 2004, **125**, 1947.

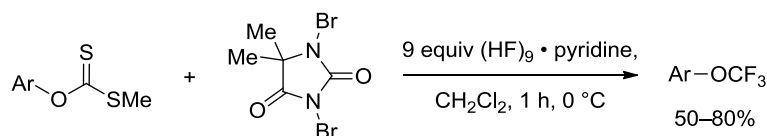
¹⁸⁶ Mathey, F.; Bensoam, J. *Tetrahedron Lett.* 1973, 2253.

¹⁸⁷ Sheppard, W. A. *J. Org. Chem.* 1964, **29**, 1.

¹⁸⁸ (a) Kuroboshi, M.; Suzuki, K.; Hiyama, T. *Tetrahedron Lett.* 1992, **33**, 4173. (b) Ben-David, I.; Rechavi, D.; Mishani, E.; Rozen, S. *J. Fluorine Chem.* 1999, **97**, 75. (c) Kanie, K.; Tanaka, Y.; Suzuki, K.; Kuroboshi, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* 2000, **73**, 471.

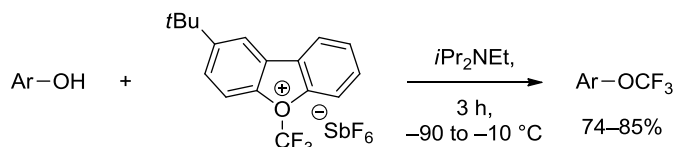
¹⁸⁹ Louw, R.; Franken, P. W. *Chem. Ind. (London)* 1977, 127.

¹⁹⁰ Feiring, A. E. *J. Org. Chem.* 1979, **44**, 2907.

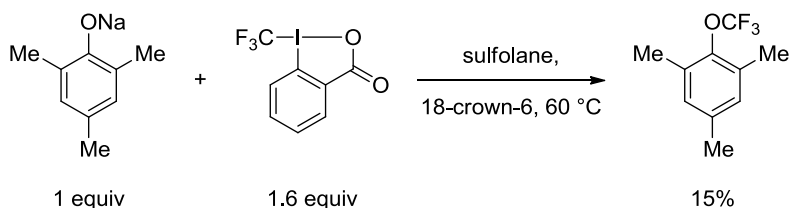


Scheme 42. Synthesis of aryl trifluoromethyl ethers by fluorodesulfurization of aryl xanthates

Simple phenol derivatives can undergo trifluoromethylation with *O*-(trifluoromethyl)dibenzofuranium reagents in the presence of alkyl amine bases to afford simple trifluoromethoxyarenes (Scheme 43).¹⁹¹ The reagent requires photochemical decomposition of the trifluoromethoxybiaryl diazonium salt at -100 to -90 °C to generate the active *O*-(trifluoromethyl)dibenzofuranium reagent. Trifluoromethylation of phenols with Togni reagent II was investigated but *O*-trifluoromethylation only occurred with 2,4,6-trimethylphenol in 15% yield along with carbon trifluoromethylation products (Scheme 44).¹⁹²



Scheme 43. *O*-Trifluoromethylation of phenols to afford aryl trifluoromethyl ethers



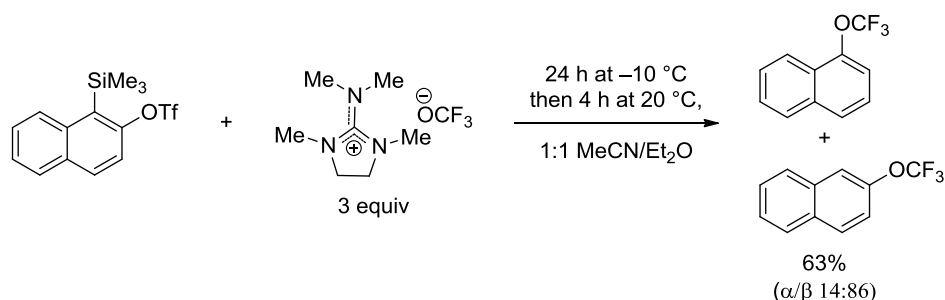
Scheme 44. *O*-Trifluoromethylation of phenols with Togni reagent II

The use of trifluoromethoxide anion to form the aryl carbon–oxygen bond has not been as widely explored as other approaches. S_NAr reaction with trifluoromethoxide was attempted but does not occur; S_NAr with fluoride abstraction from trifluoromethoxide to generate volatile carbonyl difluoride occurs instead to afford aryl fluorides.¹⁹³ Phenyl and naphthyl carbon–OCF₃ formation occurred when trifluoromethoxide anion was added into the corresponding benzyne to afford aryl trifluoromethyl ethers (Scheme 45).¹⁹³

¹⁹¹ Umemoto, T.; Adachi, K.; Ishihara, S. *J. Org. Chem.* 2007, **72**, 6905.

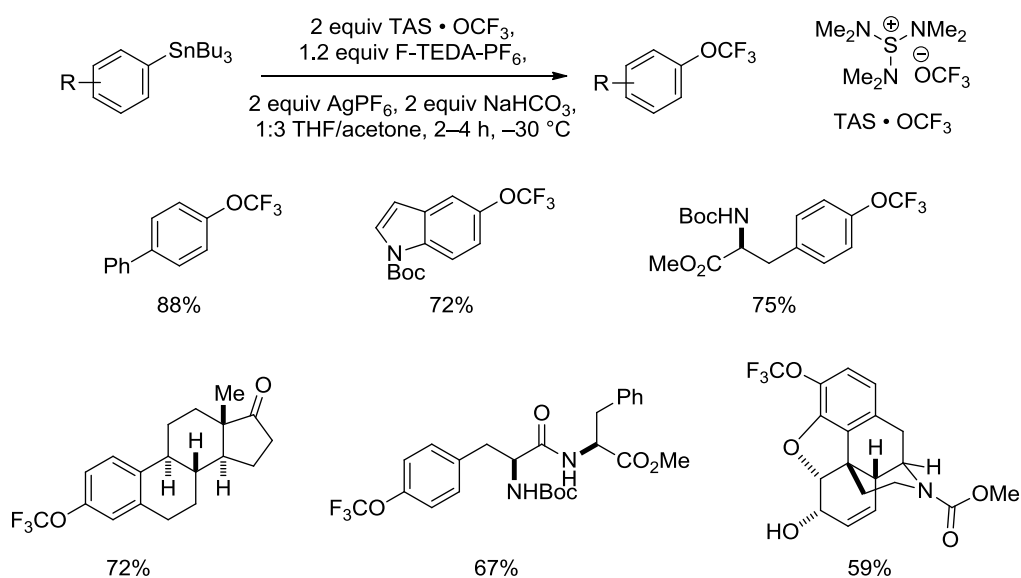
¹⁹² Stanek, K.; Koller, R.; Togni, A. *J. Org. Chem.* 2008, **73**, 7678.

¹⁹³ Kolomeitsev, A. A.; Vorobyev, M.; Gillandt, H. *Tetrahedron Lett.* 2008, **49**, 449.



Scheme 45. Trifluoromethoxide anion addition to *ortho*-trimethylsilylnaphthyl triflate via aryne intermediate

With silver salts, aryl stannanes and boronic acids can undergo cross-coupling with tris(dimethylamino)sulfonium trifluoromethoxide to afford functionalized aryl trifluoromethyl ethers (Scheme 46).¹⁹⁴ This method affords the cross-coupling products of complex, functionalized aryl stannanes with trifluoromethoxide but is limited to non-heteroaryl nucleophiles and additionally cannot tolerate nucleophilic amine and protic substituents.



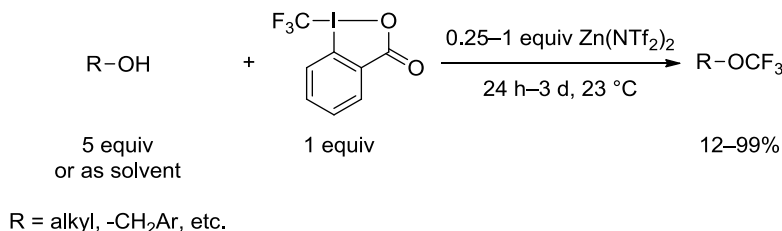
Scheme 46. Ag-mediated cross-coupling of aryl stannanes with trifluoromethoxide salt

1.3.2. Aliphatic trifluoromethyl ethers

Alkyl trifluoromethyl ethers can be synthesized via the trifluoromethylation of alcohols or displacement of a leaving group on alkyl electrophiles by trifluoromethoxide anion. Primary and secondary alcohols can be

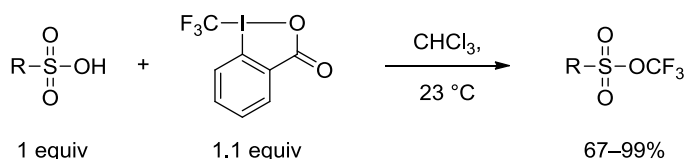
¹⁹⁴ Huang, C.; Liang, T.; Harada, S.; Lee, E.; Ritter, T. *J. Am. Chem. Soc.* 2011, **133**, 13308.

trifluoromethylated with Togni reagent in the presence of $\text{Zn}(\text{NTf}_2)_2$ (Scheme 47).¹⁹⁵ The soluble zinc catalyst with non-nucleophilic triflimide anions is proposed to activate Togni reagent for attack by coordinating to the carboxy group of the reagent.



Scheme 47. O-Trifluoromethylation of alcohols with Togni reagent II

Ring-opening polymerization of tetrahydrofuran in the presence of Lewis or Brønsted acids and Togni reagent II affords trifluoromethyl ethers¹⁹⁶ while additionally Togni reagent II reacts with sulfonic acids to afford O-trifluoromethylated sulfonic acids (Scheme 48).¹⁹⁷ 2-Phenylethanol, *n*-decanol, and (2-naphthyl)methanol were reported to react with *O*-(trifluoromethyl)dibenzofuranium reagents (shown in Scheme 43 with phenols) to afford the corresponding trifluoromethylated alcohols.¹⁹¹ Analogous to the method for the fluorination of aryl xanthates,^{188a} alkyl xanthates were treated with BrF_3 to afford alkyl trifluoromethyl ethers¹⁹⁸ while simple alkyl triflates can be substituted with trifluoromethoxide anion to afford alkyl trifluoromethyl ethers as well (Scheme 49).¹⁹³



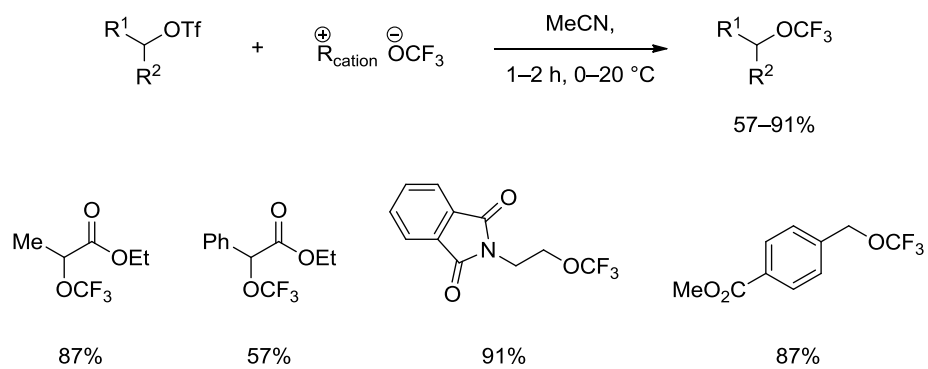
Scheme 48. O-Trifluoromethylation of sulfonic acids with Togni reagent II

¹⁹⁵ Koller, R.; Stanek, K.; Stolz, D.; Aardoom, R.; Niedermann, K.; Togni, A. *Angew. Chem. Int. Ed.* 2009, **48**, 4332.

¹⁹⁶ Fantasia, S.; Welch, J. M.; Togni, A. *J. Org. Chem.* 2010, **75**, 1779.

¹⁹⁷ Koller, R.; Huchet, Q.; Battaglia, P.; Welch, J. M.; Togni, A. *Chem. Commun.* 2009, 5993.

¹⁹⁸ Ben-David, I.; Rechavi, D.; Mishani, E.; Rozen, S. *J. Fluorine Chem.* 1999, **97**, 75.



Scheme 49. Synthesis of trifluoromethyl ethers via displacement of alkyl triflates with trifluoromethoxide salts

2. Results and Discussion

2.1. Silver-mediated trifluoromethoxylation of aryl nucleophiles¹

Silver salts are used to catalyze chemical transformations spanning asymmetric catalysis² to C–H functionalization.³ Much of the homogenous silver reaction chemistry for organic transformations involve the use of silver(I) as Lewis acids or as a one-electron chemistry participant.^{2–4} Examples of redox participation of homogenous high valent silver intermediates are rare compared to abundance of silver(I) chemistry that has been developed. Silver-catalyzed aziridination⁵ as well as C–H amidation⁶ and amination,⁷ have been reported with disilver complexes and are postulated to proceed via high valent silver intermediates. Putative Ag(II)–Ag(II) intermediates have also been suggested in the aminofluorination of allenes catalyzed by AgNO₃.⁸ A silver-mediated trifluoromethoxylation reaction of aryl nucleophiles with trifluoromethoxide salt **1** (Figure 4) has been developed and is postulated to occur through high valent silver intermediates as proposed for the analogous fluorination reaction of aryl stannanes.⁹ The general approach for the trifluoromethoxylation of aryl nucleophiles is summarized in Figure 4.

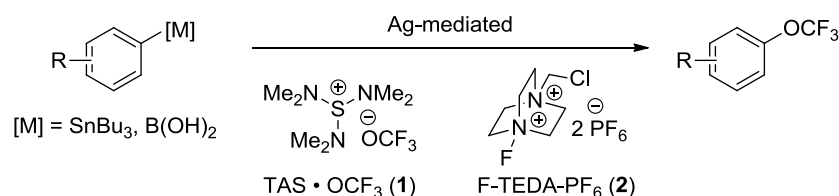


Figure 4. Ag-mediated trifluoromethoxylation of aryl nucleophiles

¹ Huang, C.; Liang, T.; Harada, S.; Lee, E.; Ritter, T. *J. Am. Chem. Soc.* 2011, **133**, 13308.

² For a review on asymmetric silver-catalyzed reactions, please see Naodovic, M.; Yamamoto, H. *Chem. Rev.* 2008, **108**, 3132.

³ For reviews on silver-catalyzed C–H functionalization reactions, please see: (a) Diaz-Requejo, M. M.; Perez, P. J. *Chem. Rev.* 2008, **108**, 3379. (b) Yamamoto, Y. *Chem. Rev.* 2008, **108**, 3199.

⁴ (a) Harmata, M. *Silver in Organic Chemistry*, John Wiley & Sons: Hoboken, NJ, 2010. (b) Weibel, J. M.; Blanc, A.; Pale, P. *Chem. Rev.* 2008, **108**, 3149.

⁵ Cui, Y.; He, C. *J. Am. Chem. Soc.* 2003, **125**, 16202.

⁶ Cui, Y.; He, C. *Angew. Chem. Int. Ed.* 2004, **43**, 4210.

⁷ Li, Z.; Capretto, D. A.; Rahaman, R.; He, C. *Angew. Chem. Int. Ed.* 2007, **46**, 5184.

⁸ Xu, T.; Mu, X.; Peng, H.; Liu, G. *Angew. Chem. Int. Ed.* 2011, **50**, 8176.

⁹ For discussions on bimetallic high valent silver intermediates proposed in silver-mediated aryl stannane fluorination, please see: Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* 2009, **131**, 1662.

2.1.1. Design of the silver-mediated trifluoromethoxylation reaction

Methods to synthesize aryl trifluoromethyl ethers have mainly relied on pre-functionalization of phenols as aryl trichloromethyl ethers,¹⁰ aryl chlorothionoformates,¹¹ phenyl fluoroformates,¹² and aryl xanthates¹³ followed with exhaustive nucleophilic fluorination at the carbonyl carbon with various harsh fluorinating reagents such as SF₄ and HF to afford the trifluoromethoxy group (for other methods, please see Chapter 1.3). Cross-coupling reactions have been strategically used to form aryl carbon–heteroatom bonds¹⁴ and have resulted in successful formation of aryl C–N, C–O, C–S, and C–F bonds. Transition-metal–mediated cross-coupling was proposed as an alternative to traditional methods for the synthesis of aryl trifluoromethyl ethers from an aryl equivalent and a trifluoromethoxy group source. One possible combination involves the oxidative cross-coupling of aryl nucleophiles with trifluoromethoxide; however, this cross-coupling reaction would most likely need to occur below room temperature because trifluoromethoxide reversibly decomposes to fluoride and carbonyl difluoride (b.p. –84 °C) above room temperature.¹⁵ Additionally, β -fluoride elimination¹⁶ from transition-metal–trifluoromethoxide complexes could also potentially obstruct successful aryl carbon–OCF₃ bond formation. Reductive elimination of C–OCF₃ is considered more difficult than reductive elimination of C–OCH₃ due to the inductively electron-withdrawing nature of the

¹⁰ (a) Yagupolskii, L. M. *Dokl. Akad. Nauk S.S.S.R.* 1955, **105**, 100. (b) Yarovenko, N. N.; Vasileva, A. S. *Zh. Obshch. Khim.* 1958, **28**, 2502. (c) Yagupolskii, L. M.; Troitskaya, V. I. *Zh. Obshch. Khim.* 1961, **31**, 915. (d) Louw, R.; Franken, P. W. *Chem. Ind. (London)* 1977, 127. (e) Feiring, A. E. *J. Org. Chem.* 1979, **44**, 2907. (f) Yagupolskii, L. M.; Orda, V. V. *Zh. Obshch. Khim.* 1964, **34**, 1979. (g) Salome, J.; Mauger, C.; Brunet, S.; Schanen, V. *J. Fluorine Chem.* 2004, **125**, 1947.

¹¹ (a) Yarovenko, N. N.; Vasileva, A. S. *Zh. Obshch. Khim.* 1958, **28**, 2502. (b) Mathey, F.; Bensoam, J. *Tetrahedron Lett.* 1973, 2253.

¹² Sheppard, W. A. *J. Org. Chem.* 1964, **29**, 1.

¹³ (a) Kuroboshi, M.; Suzuki, K.; Hiyama, T. *Tetrahedron Lett.* 1992, **33**, 4173. (b) Ben-David, I.; Rechavi, D.; Mishani, E.; Rozen, S. *J. Fluorine Chem.* 1999, **97**, 75. (c) Kanie, K.; Tanaka, Y.; Suzuki, K.; Kuroboshi, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* 2000, **73**, 471.

¹⁴ For reviews on aryl carbon–heteroatom bond formation, please see: (a) Muci, A. R.; Buchwald, S. L. Practical Palladium Catalysts for C–N and C–O Bond Formation. In *Cross-Coupling Reactions*; Miyaura, N., Ed.; Top. Curr. Chem.; Springer Publishing: New York, 2002; 219, 131. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* 2003, **42**, 5400. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* 2004, **248**, 2337. (d) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* 2004, **346**, 1599. (e) Hartwig, J. F. *Nature* 2008, **455**, 314. (f) Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* 2009, **48**, 6954. (g) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* 2011, **473**, 470.

¹⁵ (a) Taylor, S. L.; Martin, J. C. *J. Org. Chem.* 1987, **52**, 4147. (b) Kolomeitsev, A. A.; Vorobyev, M.; Gillandt, H. *Tetrahedron Lett.* 2008, **49**, 449.

¹⁶ (a) Kraft, B. M.; Lachicotte, R. J.; Jones, W. D. *Organometallics* 2002, **21**, 727. (b) Fout, A. R.; Scott, J.; Miller, D. L.; Bailey, B. C.; Pink, M.; Mindiola, D. J. *Organometallics* 2009, **28**, 331.

fluorine in the trifluoromethoxy group, as observed in cross-coupling with weaker nucleophiles.¹⁷ Identification of a transition metal capable of accomplishing difficult aryl carbon–OCF₃ bond formation at ≤ 25 °C was key for the successful development of oxidative cross-coupling between aryl nucleophiles and trifluoromethoxide.

Aryl carbon–fluorine bonds have been difficult to form through cross-coupling reactions with transition metals due to difficulties in reductive elimination.¹⁸ Our research group has advantageously utilized the reactivity of silver salts to mediate the fluorination of aryl stannanes,⁹ aryl boronic acids,¹⁹ and aryl silanes,²⁰ which can be accomplished at room temperature with stannanes and boronic acids. Additionally, silver catalysis allowed for the development of the most functional group tolerant fluorination method with the broadest substrate scope to date for the synthesis of complex aryl fluorides.²¹ These silver-mediated and -catalyzed fluorination reactions are hypothesized to proceed via high valent multi-metallic silver complexes generated upon oxidation of the aryl silver complex from transmetalation of the aryl nucleophile to silver (Figure 5). This proposed multi-metallic silver redox activity is rationalized to be the enabling factor for aryl carbon–fluorine bond formation at 23 °C and may be a consequence of synergistic metal–metal interactions that can lower activation barriers, as identified for bimetallic catalysis.²² Thus, the synergistic reactivity of high valent silver for fluorination offered a promising avenue to explore trifluoromethoxylation.

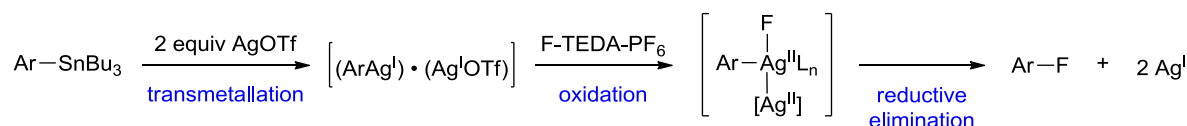


Figure 5. Proposed mechanism for the Ag-mediated fluorination of aryl stannanes to afford aryl fluorides

¹⁷ Hartwig, J. F. *Acc. Chem. Res.* 1998, *31*, 852.

¹⁸ (a) Grushin, V. V. *Chem. Eur. J.* 2002, *8*, 1006. (b) Yandulov, D. V.; Tran, N. T. *J. Am. Chem. Soc.* 2007, *129*, 1342. (c) Grushin, V. V.; Marshall, W. J. *Organometallics* 2007, *26*, 4997-5002.

¹⁹ Furuya, T.; Ritter, T. *Org. Lett.* 2009, *11*, 2860.

²⁰ Tang, P.; Ritter, T. *Tetrahedron* 2011, *67*, 4449.

²¹ Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* 2010, *132*, 12150.

²² (a) Powers, D. C.; Ritter, T. *Nature Chemistry* 2009, *1*, 302. (b) Powers, D. C.; Benitez, D.; Tkatchouk, E.; Goddard, W. A.; Ritter, T. *J. Am. Chem. Soc.* 2010, *132*, 14092. (c) Powers, D. C.; Ritter, T. *Acc. Chem. Res.* 2012, *45*, 840.

The envisioned system for the silver(I)-mediated trifluoromethoxylation of aryl nucleophiles is outlined in Figure 6. Transmetalation of the aryl nucleophile to silver(I) would give aryl silver complexes adducted with one or more additional silver(I) species. Subsequent oxidation with an oxidant such as F-TEDA salts would then give a high valent multi-metallic silver complex that could undergo fluoride ligand exchange with trifluoromethoxide to arrive at a silver-trifluoromethoxide complex. Reductive elimination from this multi-metallic high valent silver-trifluoromethoxide complex would then afford the trifluoromethoxy arene. With this design in mind, aryl stannanes would be treated with a silver(I) salt, F-TEDA-PF₆, and a trifluoromethoxide salt to afford trifluoromethoxy arenes.²³

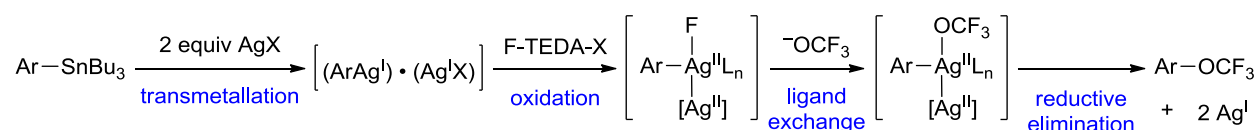


Figure 6. Envisioned reaction mechanism for Ag-mediated trifluoromethoxylation of aryl stannanes

Trifluoromethyl trifluoromethanesulfonate¹⁵ (**3**) was identified as a “masked” source of trifluoromethoxide anion (Figure 7). Trifluoromethoxide can be liberated with addition of a nucleophile, most commonly fluoride, to afford trifluoromethoxide ion-paired with the countercation accompanying the fluoride. Without a stabilizing countercation, trifluoromethoxide readily decomposes to fluoride and carbonyl difluoride.¹⁵ Different trifluoromethoxide salts can be synthesized in situ with different fluoride sources and evaluated for the trifluoromethoxylation reaction.

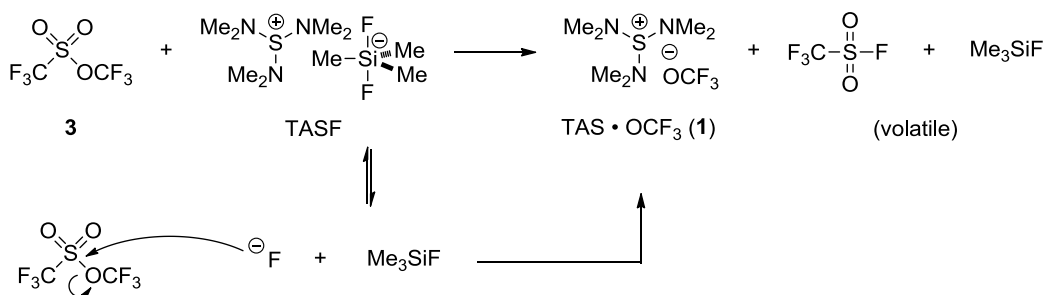


Figure 7. Liberation of trifluoromethoxide with fluoride source TASF to generate trifluoromethoxide salt **1**

²³ Professor Tobias Ritter and Mr. Chenghong Huang conceived the design of this method while Mr. Chenghong Huang discovered the first silver-mediated trifluoromethoxylation reaction of aryl stannanes and performed all initial reaction optimization (not discussed in thesis).

2.1.2. Optimization of the trifluoromethoxylation reaction

The reaction conditions for the trifluoromethoxylation reaction were optimized with substrate 4-fluorophenyl tributylstannane (4) and monitored by ^{19}F NMR spectroscopy with 3-nitrofluorobenzene as an internal standard. The products formed from the reaction include trifluoromethoxylated product 5 as well as fluorinated product 6, biaryl homo-coupling 7, hydroxylation product 8, and protodestannylated product 9 (Figure 8). The mass balance of the starting material was unidentified fluorinated byproducts.

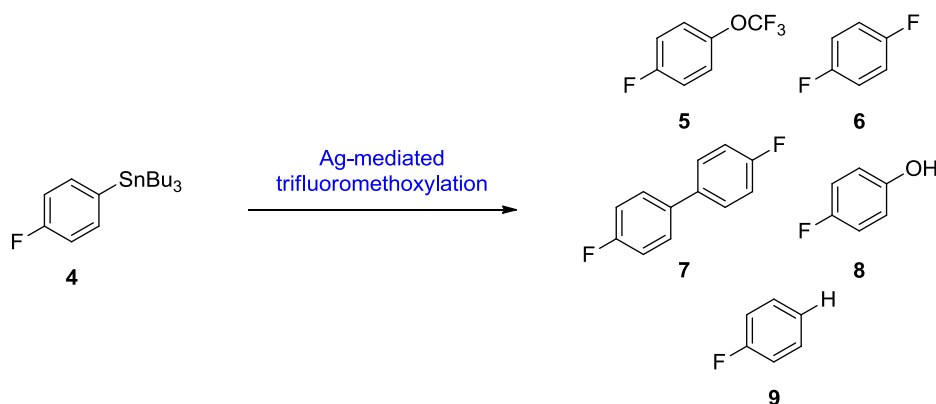


Figure 8. Main products formed from the Ag-mediated trifluoromethoxylation reaction

Effect of fluoride source on trifluoromethoxylation

The source of fluoride for in situ trifluoromethoxide salt generation was optimized (Table 1). As shown in Table 1, the identity of the trifluoromethoxide salt was imperative for trifluoromethoxylation. Salts with larger organic cations afforded higher yields than inorganic cations. This phenomenon is hypothesized to come from the stability of the trifluoromethoxide salt; unstable salts may decompose prior to participation in the course of the reaction. TASF was the best fluoride source screened and thus it was used as the fluoride source in subsequent optimizations.

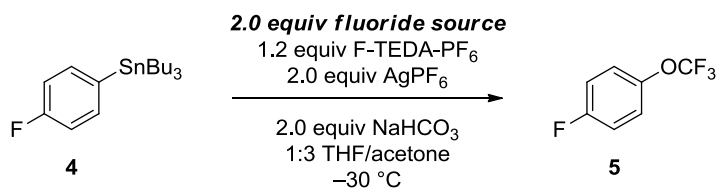


Table 1. Effect of fluoride source on percent yield of trifluoromethoxylation

	 -117.0 ppm	 -121.7 ppm	 -118.0 ppm	 -128.4 ppm	 -115.4 ppm
KF	<1	28	<1	8	<1
CsF	3	25	<1	<1	3
AgF	<1	18	<1	<1	<1
TMAF	16	35	<1	<1	<1
TASF	41	2	1	<1	<1
TBAT	18	2	<1	<1	10

Effect of silver salt on trifluoromethoxylation

Different silver salts were evaluated for the trifluoromethoxylation reaction (Table 2). As shown in Table 2, the choice of silver salt was less critical for trifluoromethoxylation. Although the silver salt producing the highest yield of trifluoromethoxylated product 5 was AgSbF₆, trifluoromethoxylation with AgSbF₆ afforded multiple additional uncharacterized broad fluorine signals in the ¹⁹F NMR spectrum while AgPF₆ afford the second highest trifluoromethoxylation yield without additional fluorine signals. Use of AgOTf led to mostly fluorinated product 6, which was the optimized silver salt reported for the silver-mediated fluorination of aryl stannanes.⁹ Subsequent optimization of the trifluoromethoxylation reaction was performed with AgPF₆ as the silver salt of choice.

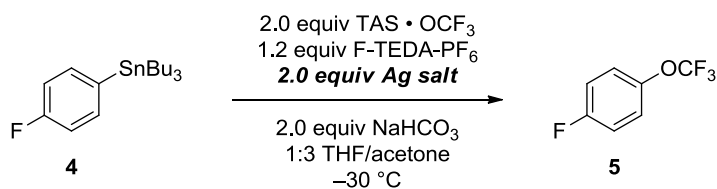


Table 2. Effect of silver salt on percent yield of trifluoromethoxylation

	 -117.0 ppm	 -121.7 ppm	 -118.0 ppm	 -128.4 ppm	 -115.4 ppm
AgOTf	<1	22	<1	5	<1
Ag ₂ O	15	8	7	<1	8
AgNO ₃	29	6	7	<1	8
AgBF ₄	32	4	2	<1	2
AgSbF ₆ ²⁴	44	<1	<1	<1	<1
AgPF ₆	41	2	1	<1	<1

Effect of solvent on trifluoromethoxylation

Different solvents and solvent combinations were evaluated for optimization of the trifluoromethoxylation reaction (Table 3). Table 3 shows critical dependence of the trifluoromethoxylation reaction on solvent. Acetone was found to decompose TAS • OCF₃, which explains the lack of successful trifluoromethoxylation (see Chapter 2.1.3 for decomposition studies of TAS • OCF₃). Use of only THF does not afford products in general most likely due to F-TEDA-PF₆ not dissolving in THF. A 1:3 mixture of THF/acetone was found to be the optimal solvent mixture screened; a potential explanation for this observation is that addition of THF in a 1:3 ratio to acetone slows down the decomposition of TAS • OCF₃ but still allows for trifluoromethoxylation to proceed. Both acetonitrile and acetone promote the formation of fluorination product 6. A 1:3 mixture of THF/acetone was used in subsequent optimization reactions.

²⁴ Trifluoromethoxylation with AgSbF₆ afforded multiple additional uncharacterized broad fluorine signals in the ¹⁹F NMR spectrum.

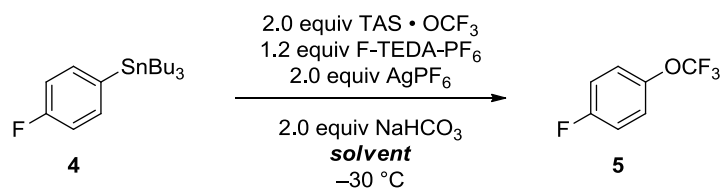


Table 3. Effect of solvent on percent yield of trifluoromethoxylation

	 -117.0 ppm	 -121.7 ppm	 -118.0 ppm	 -128.4 ppm	 -115.4 ppm
MeCN	6	19	2	<1	3
DMF	<1	<1	<1	<1	<1
acetone	<1	23	2	1	<1
THF	<1	<1	<1	<1	<1
1:3 THF/acetone	41	2	1	<1	<1

Effect of temperature on trifluoromethoxylation

A range of reaction temperatures were evaluated for the trifluoromethoxylation reaction (Table 4). Fluorination yields decrease as reaction temperature is decreased; however, trifluoromethoxylation yields peak at $-50\text{ }^\circ\text{C}$ and then fall at $-70\text{ }^\circ\text{C}$. This observation may be explained by our hypothesized mechanism for silver-mediated trifluoromethoxylation, which proposes the oxidation of the arylsilver species with F-TEDA- PF_6 followed by fluoride ligand exchange with trifluoromethoxide. At temperatures lower than $-50\text{ }^\circ\text{C}$, it is possible that ligand exchange is too slow for productive trifluoromethoxylation to proceed while fluorination pathways are also suppressed. The temperature chosen for further optimization of the trifluoromethoxylation reaction was $-30\text{ }^\circ\text{C}$ because the ratio of trifluoromethoxylated product 5 versus the sum of all byproducts was 8.2:1 at $-30\text{ }^\circ\text{C}$ compared to 7.5:1 at $-50\text{ }^\circ\text{C}$.

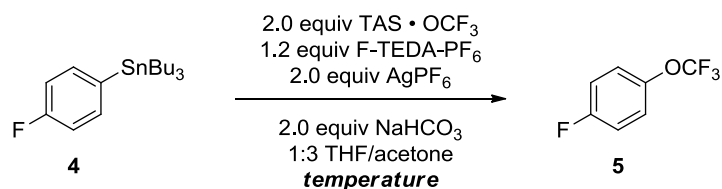


Table 4. Effect of temperature on percent yield of trifluoromethoxylation

	 -117.0 ppm	 -121.7 ppm	 -118.0 ppm	 -128.4 ppm	 -115.4 ppm
25 °C	21	16	2	<1	3
0 °C	15	5	1	<1	<1
-30 °C ²⁵	41	2	1	<1	<1
-50 °C ²⁵	68	2	3	<1	<1
-70 °C	18	<1	1	<1	<1

Effect of additives on trifluoromethoxylation

The effect of additives on the yield for trifluoromethylation was evaluated (Table 5). With the addition of NaOTf, an increase of undesired fluorinated product 6 was observed along with 1% formation of trifluoromethoxylated product 5. The triflate counterion seems to play an important role in facilitating fluorination but the role has not been clearly established. The use of sodium bicarbonate is important for trifluoromethoxylation. Sodium bicarbonate was chosen as an additive based on the empirical observation of protodestannylation suppression in the silver-catalyzed fluorination of aryl stannanes.^{21,26}

²⁵ The ratio of trifluoromethoxylated product to byproducts is superior at -30 °C than at -50 °C (8.2:1 versus 7.5:1). With other substrates, suppressed byproduct formation was also empirically observed at -30 °C compared to at -50 °C. Accordingly, -30 °C was chosen as the general trifluoromethoxylation reaction temperature such that byproduct formation could be minimized.

²⁶ Special acknowledgement to Dr. Pingping Tang who suggested the additive from his own work on the silver-catalyzed fluorination of aryl stannanes

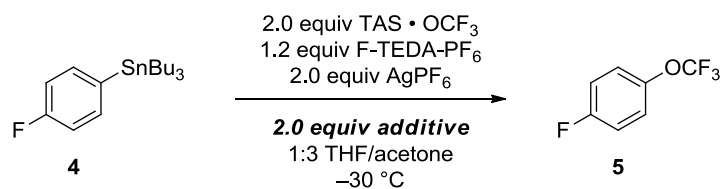
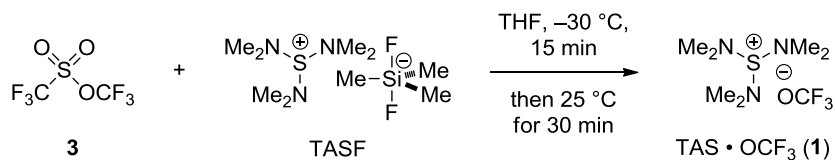


Table 5. Effect of additives on percent yield of trifluoromethoxylation

none	1	6	2	12	<1
NaOTf	1	37	<1	13	<1
Na ₂ CO ₃	1	9	<1	14	<1
NaHCO ₃	41	2	1	<1	<1

2.1.3. Identification of the trifluoromethoxide salt

Trifluoromethoxide salt **1** was typically prepared in situ during the course of the reaction outside of the glovebox. For characterization purposes and decomposition studies, **1** was synthesized, isolated, and purified within a glovebox (Scheme 50).²⁷ The decomposition of **1** at 45 °C was monitored with 3-nitrofluorobenzene as an internal standard by ¹⁹F NMR spectroscopy to afford carbonyl difluoride (COF₂) and an unknown byproduct within 15 min at 45 °C as shown in Figure 9 (vide infra).



Scheme 50. Synthesis of **1** from **3** and TASF for characterization and decomposition studies

²⁷ See Experimental Section (Chapter 4.1) for detailed procedures. Dr. Eunsung Lee synthesized and isolated **1** for characterization and decomposition purposes according to literature precedent: Farnham, W. B.; Smart, B. E.; Middleton, W. J.; Calabrese, J. C.; Dixon, D. A. *J. Am. Chem. Soc.* 1985, *107*, 4565.

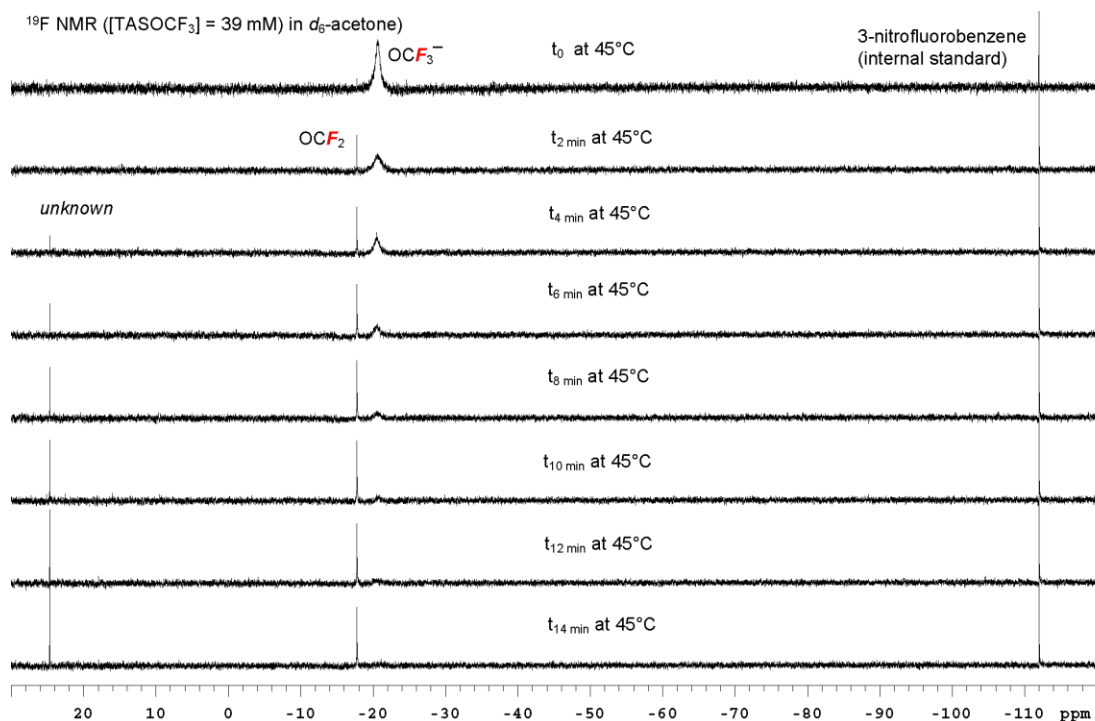


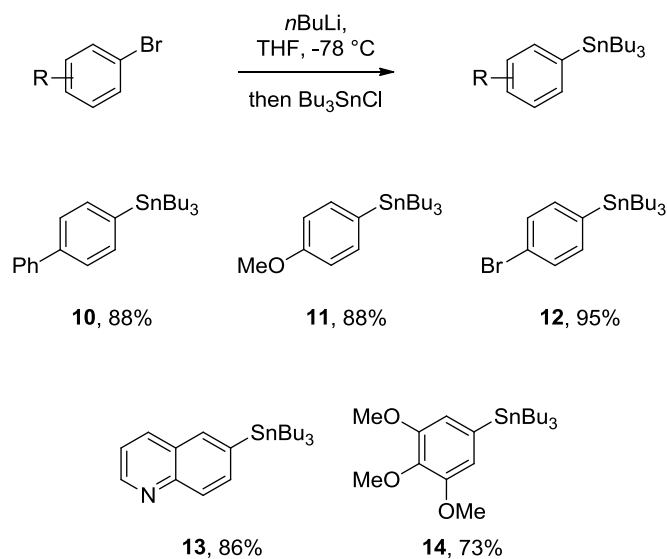
Figure 9. ^{19}F NMR spectrum of the decomposition of $\text{TAS} \cdot \text{OCF}_3$ (1) to carbonyl difluoride at 45 °C

2.1.4. Synthesis of complex, functionalized aryl stannanes

After reaction optimization, the substrate scope was evaluated. Aryl stannanes of various complexities were synthesized and subjected to the optimized trifluoromethoxylation reaction conditions. Methods for the synthesis of aryl stannanes can be divided into two main classes: (1) functionalization of aryl lithium or Grignard-type reagents (usually generated from the corresponding aryl halides) with an electrophilic trialkylstannane source such as tributyltin chloride, suitable for arenes containing non-electrophilic, base insensitive functional groups; (2) functionalization of aryl halides and sulfonates with tributylstannyl groups via cross-coupling with transition-metals, suitable for complex, functionalized arenes.

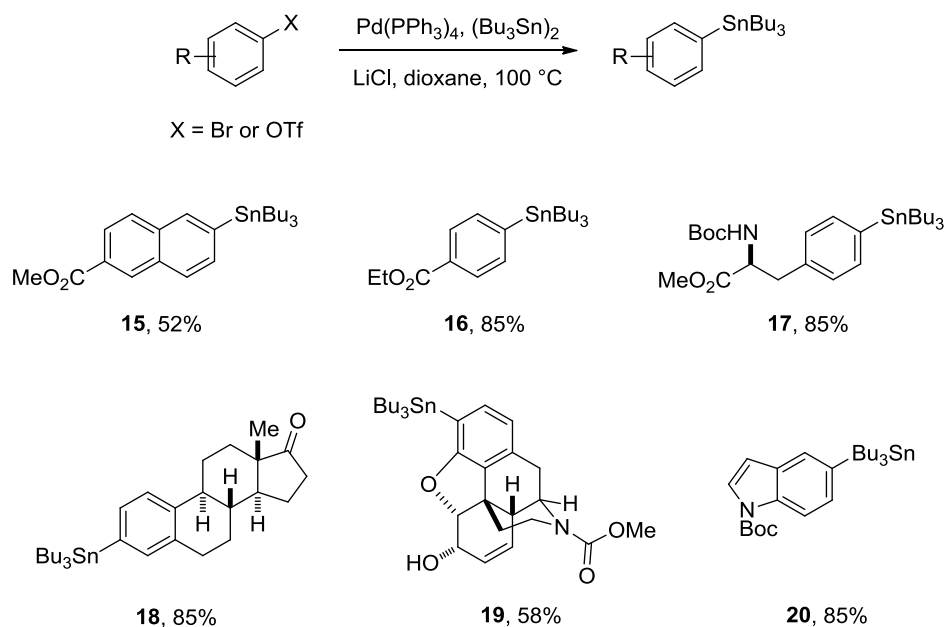
Simple aryl stannanes containing non-electrophilic, base insensitive functional groups shown in Scheme 51 were synthesized via lithiation of the aryl bromide with *n*BuLi followed by reaction with tributyltin chloride.²⁸

²⁸ 14 was synthesized by Mr. Chenghong Huang, 10–13 were synthesized according to procedures described within the group



Scheme 51. Synthesis of simple aryl stannane via lithiation-stannylation route

Complex, functionalized aryl stannanes shown in Scheme 52 were synthesized by Pd-catalyzed cross-coupling of aryl halides or sulfonates with hexabutylditin.²⁹ Other aryl stannanes were prepared according to literature precedent and are described and referenced in Experimental (Chapter 4.1).

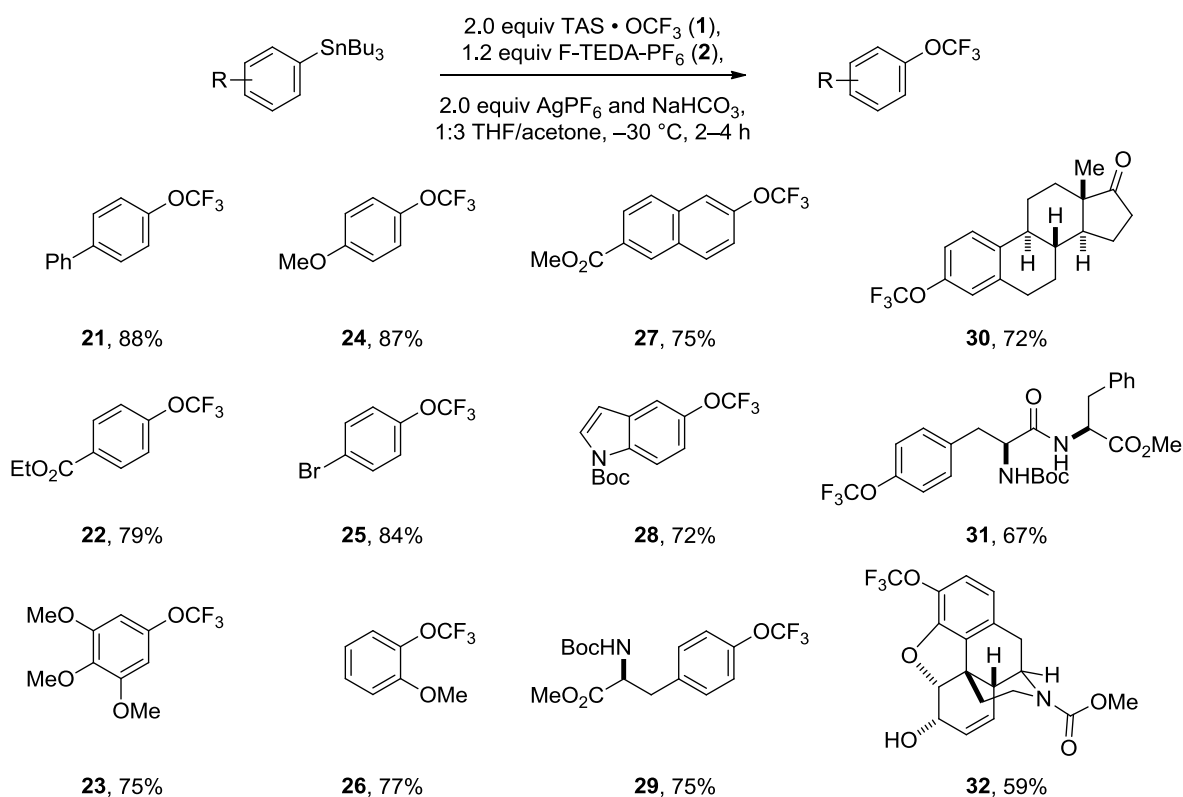


Scheme 52. Synthesis of functionalized aryl stannanes via Pd-catalyzed stannylation of aryl bromides or triflates

²⁹ **15** was synthesized by Mr. Chenghong Huang while **16**, **17**, **18**, and **20** were synthesized according to procedures described within the group

2.1.5. Trifluoromethoxylation of aryl stannanes¹

After synthesizing desired aryl stannanes 10–20, the stannanes were trifluoromethoxylated using the optimized reaction conditions (Scheme 53).³⁰ TAS • OCF₃ (1) was generated in situ in the presence of NaHCO₃ and the stannane of interest at –30 °C by addition of trifluoromethyl trifluoromethanesulfonate (3) to a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) in anhydrous THF. A solution of AgPF₆ and F-TEDA-PF₆ in dry acetone was added dropwise to the prior described suspension at –30 °C and then stirred at –30 °C for 2–4 hours. As shown in Scheme 53, electron-rich, neutral, and poor aryl stannanes were trifluoromethoxylated in 75–88% yield. Stannane 19 was added dropwise as a solution in dry acetone as the last operation in the sequence due to potential reaction of TASF with stannane 19. As discussed in Chapter 2.1.2, solvent and TAS • OCF₃ (1) significantly impact the yield; deviations from optimized conditions leads to byproducts resulting from fluorodestannylation, hydroxydestannylation, protodestannylation, and biaryl formation via homocoupling. Trifluoromethoxylation of stannane 19 afforded 59% trifluoromethoxylation yield in addition to 24% and 10% of the corresponding fluorodestannylated and protodestannylated product.



Scheme 53. Ag-mediated trifluoromethoxylation of aryl stannanes (percentages are isolated yields)

³⁰ Yields for trifluoromethoxylated products 21–23 and 27–30 were obtained by Mr. Chenghong Huang

When 6-(tributylstannyl)quinoline was subjected the standard trifluoromethoxylation conditions, <1% yield was obtained by ^{19}F NMR spectroscopy. One possible explanation for this phenomenon is the stabilization of the putative high valent silver species via coordination of the quinolyl nitrogen lone pair³¹ and potentially breaking the Ag–Ag interaction necessary for reductive elimination (Figure 10), leading to decomposition of the trifluoromethoxide-silver complex.

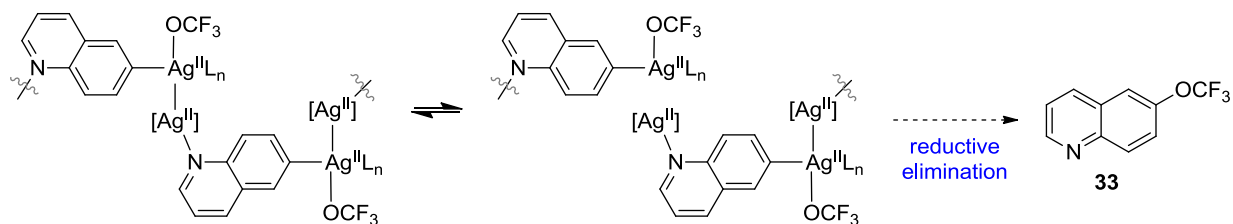
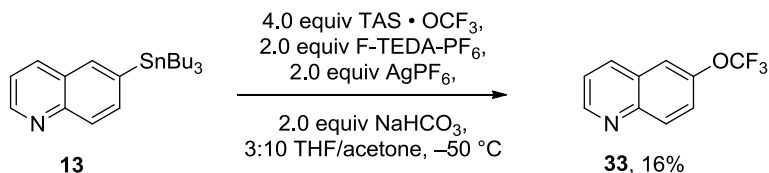


Figure 10. Potential coordination of quinolyl nitrogen disfavoring reductive elimination

Lowering the reaction temperature to $-50\text{ }^{\circ}\text{C}$ while concurrently increasing the amount of $\text{TAS} \cdot \text{OCF}_3$ (1) to four equivalents and F-TEDA-PF_6 to two equivalents afforded 6-trifluoromethoxyquinoline in 16% yield (Scheme 54). Nitrogenous heteroaryl substrates remain a limitation for this trifluoromethoxylation method.



Scheme 54. Ag-mediated trifluoromethoxylation of 6-(tributylstannyl)quinoline (13)

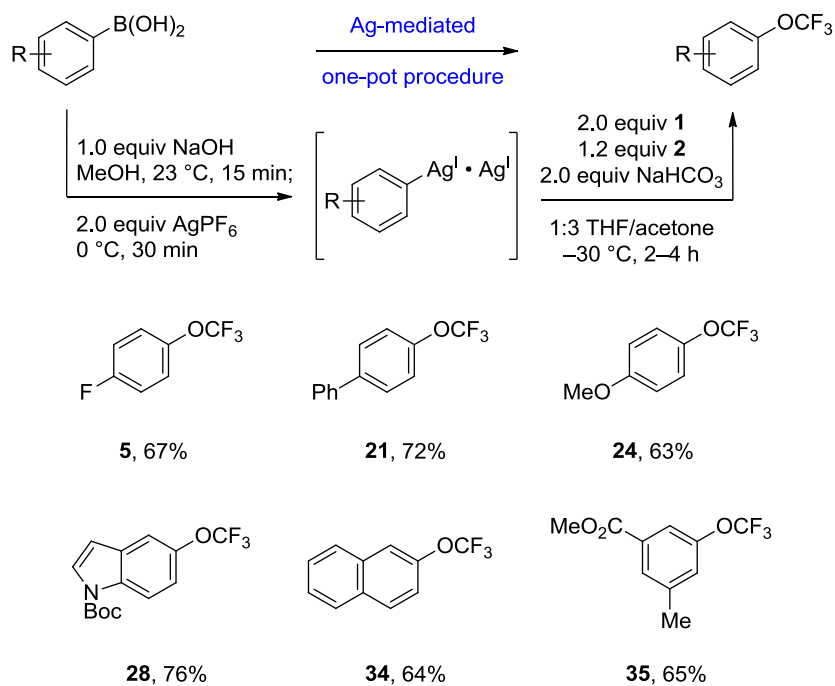
2.1.6. Trifluoromethoxylation of boronic acids^{1,32}

Commercially available arylboronic acids were treated with one equivalent of NaOH in MeOH at $23\text{ }^{\circ}\text{C}$ and then reacted with two equivalents of silver hexafluorophosphate at $0\text{ }^{\circ}\text{C}$ to afford the putative aryl silver complex shown in Scheme 55. After evaporation of MeOH and co-evaporation with THF , $\text{TAS} \cdot \text{OCF}_3$ (1) was generated in situ in anhydrous THF at $-30\text{ }^{\circ}\text{C}$ by addition of trifluoromethyl trifluoromethanesulfonate (3) to a thick suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF). A solution of F-TEDA-PF_6 was added at $-30\text{ }^{\circ}\text{C}$ to

³¹ For discussions of of high valent silver stabilization by nitrogenous ligands, please see: (a) Po, H. N. *Coord. Chem. Rev.* 1976, 20, 171. (b) Levason, W.; Spicer, M. D. *Coord. Chem. Rev.* 1987, 76, 45.

³² The trifluoromethoxylation of arylboronic acids was discovered by Dr. Shinji Harada. Compounds 21, 24, and 28 were synthesized by Dr. Shinji Harada and compounds 5, 34, and 35 were synthesized by Dr. Eunsung Lee.

the prior solution and reacted for 1 hour at $-30\text{ }^{\circ}\text{C}$. Typically, trifluoromethoxylation reactions with arylboronic acids afford yields lower than with aryl stannanes.



Scheme 55. Ag-mediated trifluoromethoxylation of arylboronic acids

2.2. Synthesis of 3-deoxy-3-fluoromorphine

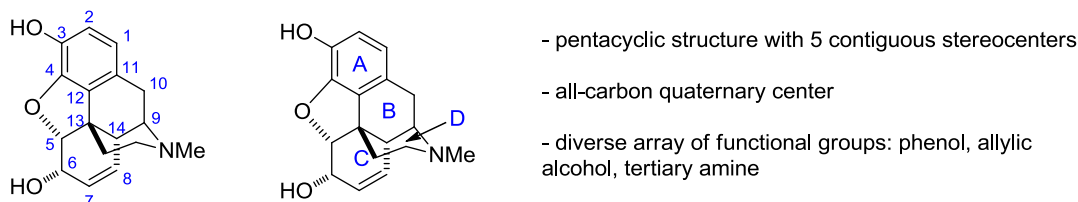


Figure 11. Morphine structural numbering of the carbon framework and ring nomenclature

Since its isolation in 1805, morphine (shown in Figure 11) has been used as an analgesic for relief from severe pain associated with cancer and surgical operations.³³ Along with analgesia, morphine elicits side effects such as respiratory depression, constipation, nausea, tolerance, and addiction due to unselective agonism of μ -opioid receptors thus compromising its use as a clinical treatment for chronic pain.³⁴ Morphine metabolism limits its bioavailability via enzymatic glycosylation by glycoprotein UGT2B7 at the phenol to morphine-3-glucuronide (M3G, 50%), a biologically inactive metabolite excreted through the kidneys, and at the allylic alcohol to morphine-6-glucuronide (M6G, 10%), a biologically active metabolite that cannot effectively penetrate the blood-brain barrier (Figure 12).³⁵

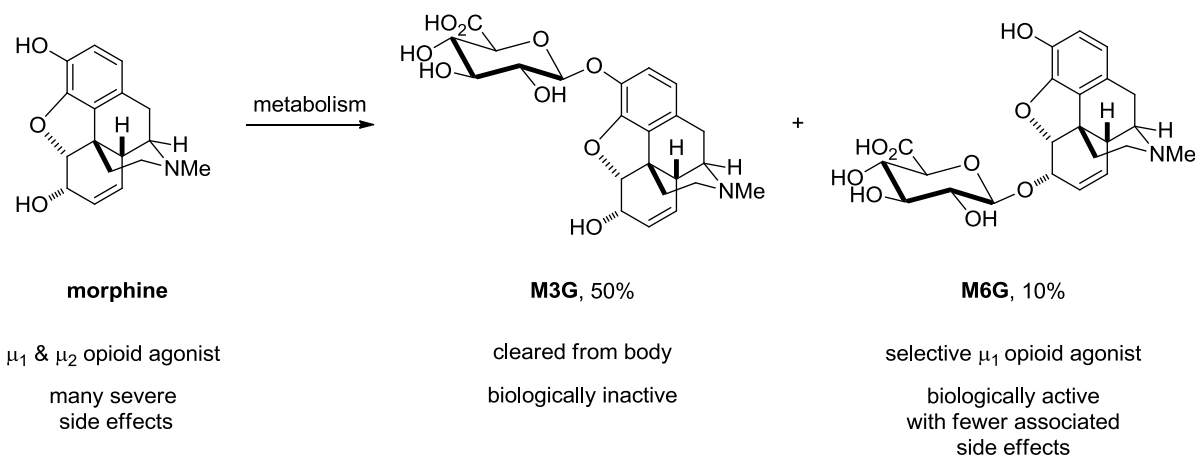


Figure 12. Metabolism of morphine to M3G and M6G in humans

³³ Eguchi, M. *Med. Res. Rev.* 2004, 24, 182.

³⁴ (a) Kantor, T. G.; Hopper, M.; Laska, E. *J. Clin. Pharmacol.* 1981, 21, 1. (b) Lotsch, J.; Geisslinger, G. *Clin. Pharmacokinet.* 2001, 40, 485.

³⁵ (a) Lotsch, J.; Stockmann, A.; Kobal, G.; Brune, K.; Waibel, R.; Schmidt, N.; Geisslinger, G. *Clin. Pharmacol. Ther.* 1996, *60*, 316. (b) Kilpatrick, G. J.; Smith, T. W. *Med. Res. Rev.* 2005, *25*, 521. (c) Wittwer, E.; Kern, S. E. *AAPS Journal* 2006, *8*, E348.

Glucuronidation can occur after entry into the brain³⁶ with an enzyme that also glucuronidates congeners such as codeine, indicating promiscuity for the functional group identity at the 3 position.³⁷ Although the phenol at the 3 position has been implicated in hydrogen bonding at the receptor pocket,³⁸ oxycodone and dihydrocodeine with methoxy substituents at the 3 position show analgesic activity^{38a, 39} with studies showing that these parent compounds and not the O-demethylated metabolites are responsible for pharmacological activity.⁴⁰ With the rationale that fluorine is an isostere to a hydroxyl group⁴¹ and can also participate in polar interactions,⁴² replacement of the hydroxyl at the 3 position of morphine is expected to block metabolism⁴³ at the 3 position and prevent formation of the biologically inactive metabolite M3G, which would lead to a therapeutic with better bioavailability (Figure 13). Additionally, fluorination of morphine to afford 3-deoxy-3-fluoromorphine may provide a therapeutic with better pharmacological properties than morphine.⁴⁴

³⁶ Wahlstrom, A.; Winblad, B.; Bixo, M.; Rane, A. *Pain* 1988, **35**, 121.

³⁷ Radominska-Pandya, A.; Little, J. M.; Czernik, P. J. *Curr. Drug Metab.* 2001, **2**, 283. (b) Coffman, B. L.; King, C. D.; Rios, G. R.; Tephly, T. R. *Drug Metab. Dispos.* 1998, **26**, 73.

³⁸ (a) Thompson, C. M.; Wojno, H.; Greiner, E.; May, E. L.; Rice, K. C.; Selley, D. E. *J. Pharmacol. Exp. Ther.* 2004, **308**, 547. (b) Chen, Z. R.; Irvine, R. J.; Somogyi, A. A.; Bochner, F. *Life Sci.* 1991, **48**, 2165.

³⁹ (a) Kalso, E. *J. Pain Symptom Manage.* 2005, **29**, S47. (b) Bostrom, E.; Hammarlund-Udenaes, M.; Simonsson, U. S. H. *Anesthesiology* 2008, **108**, 495.

⁴⁰ (a) (b) Wilder-Smith, C. H.; Hufschmid, E.; Thormann, W. *Br. J. Clin. Pharmacol.* 1998, **45**, 575.

⁴¹ Bondi, A. *J. Phys. Chem.* 1964, **68**, 441.

⁴² (a) Berkessel, A.; Adrio, J. A.; Huettenhain, D.; Neudorfl, J. M. *J. Am. Chem. Soc.* 2006, **128**, 8421. (b) Anton, D. *Adv. Mater.* 1998, **10**, 1197. (c) Cametti, M.; Crousse, B.; Metrangolo, P.; Milani, R.; Resnati, G. *Chem. Soc. Rev.* 2012, **41**, 31. (d) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. *Chem. Soc. Rev.* 2011, **40**, 3496. (e) Hoffmann-Roeder, A.; Schweizer, E.; Egger, J.; Seiler, P.; Obst-Sander, U.; Wagner, B.; Kansy, M.; Banner, D. W.; Diederich, F. *ChemMedChem* 2006, **1**, 1205. (f) Biffinger, J. C.; Kim, H. W.; DiMaggio, S. G. *ChemBioChem* 2004, **5**, 622. (g) Kim, C. Y.; Chandra, P. P.; Jain, A.; Christianson, D. W. *J. Am. Chem. Soc.* 2001, **123**, 9620.

⁴³ For an example of fluorine introduction blocking glucuronidation, please see: Kanou, M.; Saeki, K.; Kato, T. A.; Takahashi, K.; Mizutani, T. *Fundam. Clin. Pharmacol.* 2002, **16**, 513.

⁴⁴ For discussions on how fluorination can beneficially alter pharmacokinetics and pharmacodynamics, please see: (a) Smart, B. E. *J. Fluorine Chem.* 2001, **109**, 3. (b) Ismail, F. M. D. *J. Fluorine Chem.* 2002, **118**, 27. (c) Bohm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Muller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* 2004, **5**, 637. (d) Ojima, I. *ChemBioChem* 2004, **5**, 628. (e) Kirk, K. L. *Curr. Top. Med. Chem.* 2006, **6**, 1447. (f) Muller, K.; Faeh, C.; Diederich, F. *Science* 2007, **317**, 1881. (g) Hagmann, W. K. *J. Med. Chem.* 2008, **51**, 4359. (h) Kirk, K. L. *Org. Process Res. Dev.* 2008, **12**, 305. (i) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* 2008, **37**, 320.

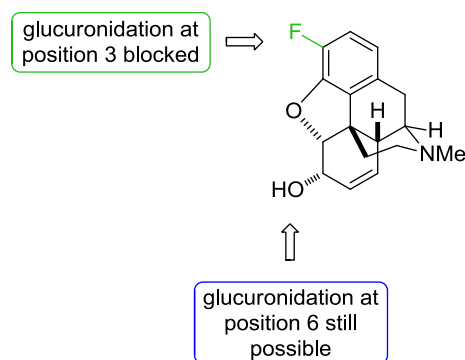


Figure 13. Expected metabolism of 3-deoxy-3-fluoromorphine

Carbon–fluorine bond replacement of the phenol at the 3 position in morphine is not trivial. Many past total syntheses of morphine utilize the phenol or phenol equivalents to direct the construction of the carbon scaffold of morphine (Figure 14).⁴⁵ As such, prior syntheses do not allow for access of 3-deoxy-fluoromorphine by a simple switch of starting materials to the fluorinated analogs, meaning a new total synthesis using fluorinated starting materials would need to be conceived. Designing a new synthesis would not expediently access 3-deoxy-3-fluoromorphine for in vitro and in vivo studies; the most expedient approach would involve direct deoxyfluorination of morphine or late-stage fluorination of a substrate derived from morphine.

⁴⁵ For prior total syntheses and formal syntheses of morphine, please see: (a) Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* 1956, **78**, 1380. (b) Evans, D. A.; Mitch, C. H.; Thomas, R. C.; Zimmerman, D. M.; Robey, R. L. *J. Am. Chem. Soc.* 1980, **102**, 5955. (c) Rice, K. C. *J. Org. Chem.* 1980, **45**, 3135. (d) Toth, J. E.; Fuchs, P. L. *J. Org. Chem.* 1987, **52**, 473. (e) Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* 1992, **114**, 9688. (f) Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* 1993, **115**, 11028. (g) Mulzer, J.; Durner, G.; Trauner, D. *Angewandte Chemie-International Edition in English* 1996, **35**, 2830. (h) Mulzer, J.; Bats, J. W.; List, B.; Opatz, T.; Trauner, D. *Synlett* 1997, 441. (i) Trauner, D.; Bats, J. W.; Werner, A.; Mulzer, J. *J. Org. Chem.* 1998, **63**, 5908. (j) White, J. D.; Hrnčiar, P.; Stappenbeck, F. *J. Org. Chem.* 1999, **64**, 7871. (k) Nagata, H.; Miyazawa, N.; Ogasawara, K. *Chem. Commun.* 2001, 1094. (l) Taber, D. F.; Neubert, T. D.; Rheingold, A. L. *J. Am. Chem. Soc.* 2002, **124**, 12416. (m) Trost, B. M.; Tang, W. P. *J. Am. Chem. Soc.* 2002, **124**, 14542. (n) Trost, B. M.; Tang, W. P.; Toste, F. D. *J. Am. Chem. Soc.* 2005, **127**, 14785. (o) Uchida, K.; Yokoshima, S.; Kan, T.; Fukuyama, T. *Org. Lett.* 2006, **8**, 5311. (p) Omori, A. T.; Finn, K. J.; Leisch, H.; Carroll, R. J.; Hudlicky, T. *Synlett* 2007, 2859. (q) Tanimoto, H.; Saito, R.; Chida, N. *Tetrahedron Lett.* 2008, **49**, 358. (r) Varin, M.; Barre, E.; Iorga, B.; Guillou, C. *Chem. Eur. J.* 2008, **14**, 6606. (s) Leisch, H.; Omori, A. T.; Finn, K. J.; Gilmet, J.; Bissett, T.; Ilceski, D.; Hudlicky, T. *Tetrahedron* 2009, **65**, 9862. (t) Stork, G.; Yamashita, A.; Adams, J.; Schulte, G. R.; Chesworth, R.; Miyazaki, Y.; Farmer, J. J. *J. Am. Chem. Soc.* 2009, **131**, 11402. (u) Uchida, K.; Yokoshima, S.; Kan, T.; Fukuyama, T. *Heterocycles* 2009, **77**, 1219. (v) Koizumi, H.; Yokoshima, S.; Fukuyama, T. *Chem. Asian J.* 2010, **5**, 2192. (w) Erhard, T.; Ehrlich, G.; Metz, P. *Angew. Chem. Int. Ed.* 2011, **50**, 3892.

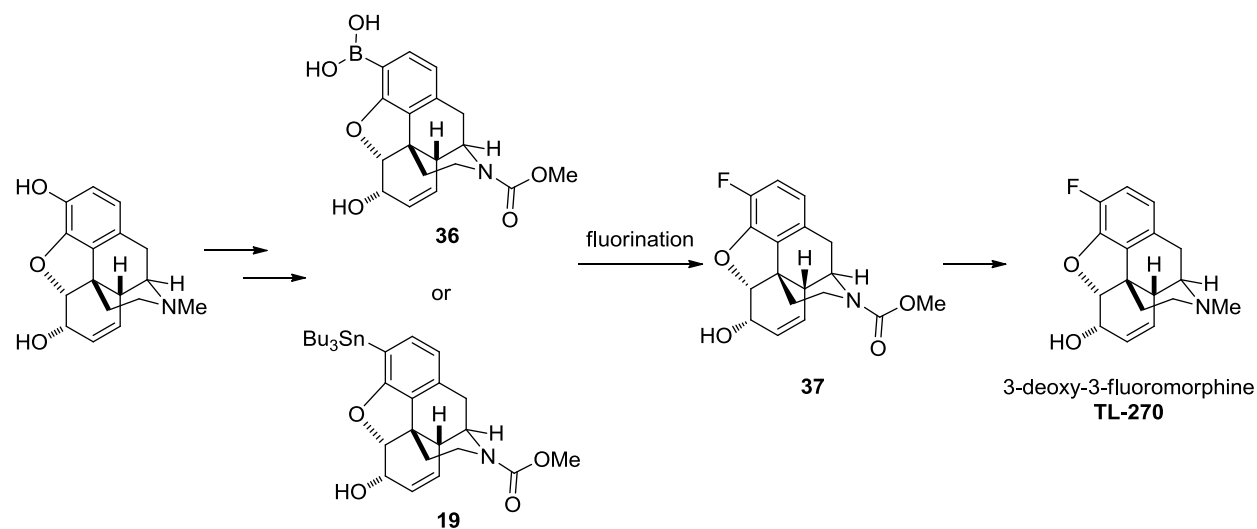
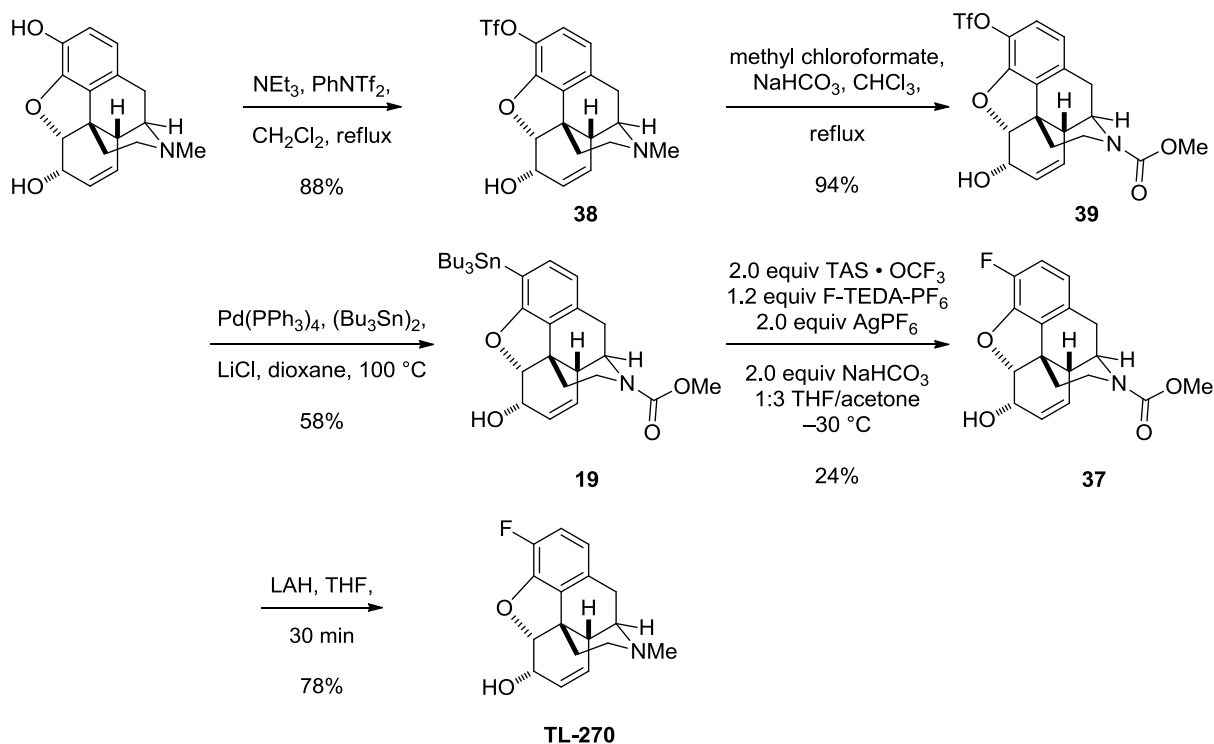


Figure 15. Original proposed route to 3-deoxy-3-fluoromorphine

To our surprise, when the products of the trifluoromethoxylation of stannane **19** were obtained, we observed fluorination product **37** in 24% yield. The formation of **37** is intriguing mainly because the analogous silver-mediated fluorination reaction of substrate **19** afforded no desired fluorinated product. This phenomenon may be due to the occurrence of a different fluorination pathway during the trifluoromethoxylation reaction; potentially, exogenous fluoride liberated from ligand exchange with trifluoromethoxide may be assisting in carbon–fluorine bond formation. With **37** in hand, we proceeded to synthesize 3-deoxy-3-fluoromorphine and other fluorinated morphine derivatives for *in vitro* and *in vivo* studies.



Scheme 56. Synthetic route to 3-deoxy-3-fluoromorphine (TL-270) from morphine

The full synthetic route to TL-270 is summarized in Scheme 56. Morphine was first functionalized at the 3 position with *N*-phenylbis(trifluoromethane)sulfonamide as trifluoromethanesulfonate **38** and subsequently demethylated at the tertiary amine with concurrent protection as the methyl carbamate with methyl chloroformate to afford **39**. Pd-catalyzed stannylation of **39** with hexabutylditin afforded stannane **19** which upon trifluoromethoxylation conditions produced fluorinated product **37** in 24% yield. Reduction of the carbamate group in **37** with lithium aluminum hydride afforded the final desired product TL-270.

2.2.2. Biological activity

In vitro studies have shown that the concentrations necessary for agonist-stimulated binding for oxycodone was three to eight times higher than that of morphine.⁴⁸ Additionally, the morphine affinity for the μ -opioid receptor in vitro is twenty-six times higher than for oxycodone.^{48b} Despite this, the observed potency when administered to

⁴⁸ (a) Thompson, C. M.; Wojno, H.; Greiner, E.; May, E. L.; Rice, K. C.; Selley, D. E. *J. Pharmacol. Exp. Ther.* 2004, **308**, 547. (b) Peckham, E. M.; Traynor, J. R. *J. Pharmacol. Exp. Ther.* 2006, **316**, 1195. (c) Lalovic, B.; Kharasch, E.; Hoffer, C.; Risler, L.; Liu-Chen, L. Y.; Shen, D. D. *Clin. Pharmacol. Ther.* 2006, **79**, 461.

postoperative patients intravenously was equivalent for both oxycodone and morphine.⁴⁹ This discrepancy between oxycodone and morphine in vitro and in vivo has been investigated through rat model studies of blood versus brain concentrations of opiate drugs and demonstrated that oxycodone was two to three times higher in concentration in the brain than in blood⁵⁰ while the concentration of morphine in the brain is two to three times less than in blood.⁵¹ Thus, blood-brain barrier transport plays an important role in in vivo potency and cannot simply be established with in vitro IC₅₀ (concentration causing a half-maximal inhibition of control specific binding) or EC₅₀ values (concentration causing a half-maximal effect response), as demonstrated with oxycodone and morphine.^{51c}

First, in vitro cellular functional assays were performed by Cerep to confirm that TL-270 functions as an agonist of the μ -opioid receptor and not as an antagonist. The agonist response rate reported by Cerep was 70.3% with rat recombinant CHO (Chinese hamster ovary) cells. Response rates greater than 50% are considered significant effects for test compounds and generally the cut-off value for further investigation. In vitro binding assays performed by Cerep were then used to determine IC₅₀ values of TL-270. The IC₅₀ value as reported by Cerep for TL-270 was 8.0×10^{-7} M or 800 nM. When compared to the literature IC₅₀ values for morphine of 53 nM,⁵² TL-270 is about ten-fold less effective than morphine at providing inhibition. This observance is similar to the three to eight-fold concentration difference observed for agonist-stimulated binding of oxycodone and morphine. Subsequent in vivo studies of brain-plasma partitioning with fasted male Sprague-Dawley rats with injections at 0.952 mg/kg intravenously (i.v.) and 4.78 mg/kg per oreo (p.o. or orally) demonstrated that partitioning was 2.91 times greater in the brain than in the plasma after four hours. With the aforementioned in vitro data, an antinociceptive study was next logical step for the determination of in vivo potency of TL-270.

The antinociceptive effects of TL-270 were evaluated by Lichtman and coworkers with traditional warm water tail withdrawal and hotplate assays of nociception. In addition, the mice were observed for Straub tail, an opioid sensitive measure in which the tail stands up at a near 90 degree angle. The results of the antinociceptive tests are

⁴⁹ Silvasti, M.; Rosenberg, P.; Seppala, T.; Svartling, N.; Pitkanen, M. *Acta Anaesthesiol. Scand.* 1998, **42**, 576.

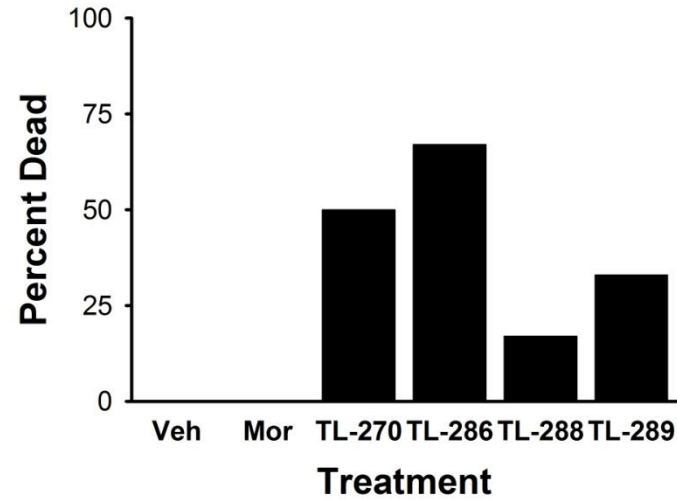
⁵⁰ Bostrom, E.; Simonsson, U. S. H.; Hammarlund-Udenaes, M. *Drug Metab. Dispos.* 2006, **34**, 1624.

⁵¹ (a) Letrent, S. P.; Pollack, G. M.; Brouwer, K. R.; Brouwer, K. L. R. *Drug Metab. Dispos.* 1999, **27**, 827. (b) Tunblad, K.; Jonsson, E. N.; Hammarlund-Udenaes, M. *Pharm. Res.* 2003, **20**, 618. (c) Bostrom, E.; Hammarlund-Udenaes, M.; Simonsson, U. S. H. *Anesthesiology* 2008, **108**, 495.

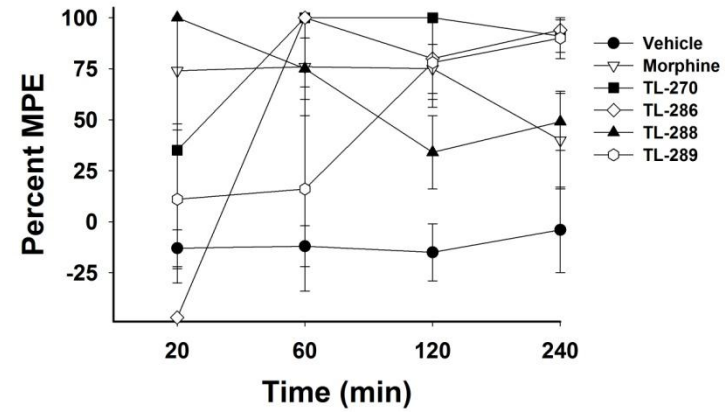
⁵² Inturrisi, C. E.; Schultz, M.; Shin, S.; Umans, J. G.; Angel, L.; Simon, E. J. *Life Sci.* 1983, **33**, 773.

depicted in Figure 16 (page 71). As indicated in Figure 16A, 100 mg/kg of each TL compound produced some lethality within minutes of administration, most likely from respiratory depression, in contrast to no lethality being observed for the saline or morphine groups. The time courses of the antinociceptive effects of surviving mice are shown in Figure 16B (hotplate) and Figure 16C (tail withdraw) while Figure 16D depicts the percentage of surviving mice showing straub tail. Figure 16B shows that at 100 mg/kg TL-270 exhibits a response greater than morphine with an induction period of 60 minutes while for the tail withdraw test (Figure 16C), TL-270 at 100 mg/kg exhibits a response comparable to morphine with loss of efficacy after 120 minutes. While TL-270 indicates good response, loss of efficacy of TL-270 over 120 minutes in the straub tail tests has discouraged further development of TL-270 as a therapeutic.

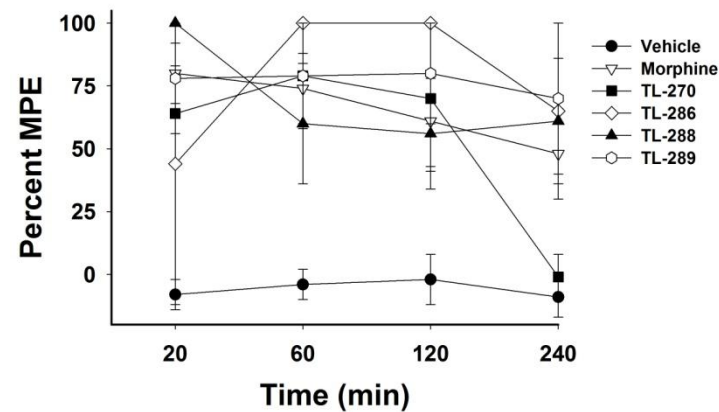
A



B



C



D

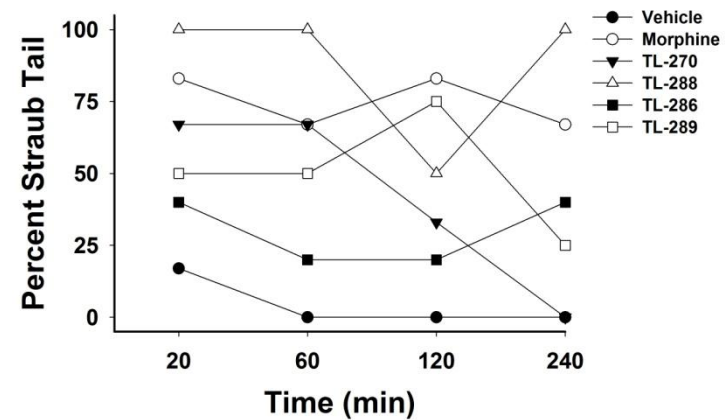


Figure 16. Mice were given an i.p. injection of TL-270 (100 mg/kg), TL-286 (100 mg/kg), TL-288 (100 mg/kg), TL-289 (100 mg/kg), morphine (20 mg/kg), or saline (n = 6 mice/group). The time course for nociceptive behavior (hotplate and tail withdrawal assays) and straub tail were evaluated over a 4 h period. *Panel A.* Percentage of lethality in each group. The respective numbers of deaths for the TL-270 (100 mg/kg), TL-286 (100 mg/kg), TL-288 (100 mg/kg), and TL-289 (100 mg/kg) conditions were 3 of 6, 4 of 6, 1 of 6, and 2 of 6. *Panel B.* Time course of hotplate antinociception in surviving mice. *Panel C.* Time course of tail withdrawal antinociception in surviving mice. *Panel D.* Time course of straub tail in surviving mice. Values represent mean (panels A-D) and error bars represent SEM (panels B & C)

3. Conclusion and Outlook

In summary, a novel silver-mediated cross-coupling reaction has been developed for the trifluoromethoxylation of aryl stannanes and arylboronic acids. While the use of aryl stannanes and low trifluoromethoxylation yields for nitrogenous heterocyclic substrates are limitations, this method establishes a proof of principle that aryl trifluoromethyl ethers can be synthesized via a cross-coupling approach, specifically oxidative cross-coupling of aryl nucleophiles with trifluoromethoxide. The use of silver salts as well as more stable $\text{TAS} \cdot \text{OCF}_3$ trifluoromethoxide salt has enabled challenging aryl carbon– OCF_3 bond formation. Future endeavors for the synthesis of aryl trifluoromethyl ethers should focus on developing operationally simple, functional group tolerant methods using benign aryl substrates such as aryl halides and boronic acids with bench-top stable trifluoromethoxide salts or trifluoromethoxide precursors.

Additionally, 3-deoxy-3-fluoromorphine was synthesized via late-stage fluorination methods starting from morphine. The potential of 3-deoxy-3-fluoromorphine as a therapeutic was assessed with in vitro and in vivo studies. While 3-deoxy-3-fluoromorphine localizes in the brain of male Sprague-Dawley rats three times higher than in plasma after four hours, in vivo studies showed the loss of antinociceptive effects after 120 minutes. Future work in analgesics development should focus on creating therapeutics that have prolonged efficacy without side effects such as respiratory depression, constipation, nausea, tolerance, and addiction.

4. Experimental

Materials and Methods

All reactions were carried out under an inert nitrogen atmosphere unless otherwise indicated. Dichloromethane was dried by passage through alumina.¹ Except as indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography (TLC) using EMD TLC plates pre-coated with 250 μm thickness silica gel 60 F254 plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained using ceric ammonium molybdate or potassium permanganate stain. Flash chromatography was performed on Dynamic Adsorbents Silica Gel 40–63 μm particle size using a forced flow of eluent at 0.3–0.5 bar pressure.² Concentration under reduced pressure was performed by rotary evaporation at 25–30 °C (and at 5 °C when specified) at appropriate pressure. Purified compounds were further dried under vacuum (0.01–0.2 Torr depending on volatility of compound). NMR spectra were recorded on a Varian Mercury 400 (400 MHz for ^1H , 100 MHz for ^{13}C , and 375 MHz for ^{19}F acquisitions) or Unity/Inova 500 (500 MHz for ^1H , 125 MHz for ^{13}C , and 470 MHz for ^{19}F acquisitions). ^{13}C NMR spectra are recorded ^1H decoupled. ^{19}F NMR spectra are recorded ^1H coupled. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CDCl_3 , 23 °C, ^1H NMR: 7.26 ppm, ^{13}C NMR: 77.16 ppm).² Data is reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants in Hz; integration. High-resolution mass spectra were obtained on Jeol AX-505 or SX-102 spectrometers at the Harvard University Mass Spectrometry Facilities. Anhydrous THF was obtained by distillation over sodium/benzophenone. Dry acetone was obtained by distillation over B_2O_3 . Triethylamine and *N,N*-diisopropylethylamine were distilled over calcium hydride. *n*-Butyllithium, tris(dimethylamino)sulfonium difluorotrimethylsilicate, silver hexafluorophosphate, tetrakis(triphenylphosphine)palladium, lithium chloride, hexabutyliditin, 1,4-dioxane (anhydrous, 99.8% in Sure/SealTM), 4-(dimethylamino)pyridine, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), 1-hydroxybenzotriazole (HOBt), *N*-phenylbis(trifluoromethane)sulfonimide, and methyl chloroformate were purchased from Aldrich and used as received. Sodium bicarbonate and sand were purchased from Mallinckrodt Chemicals and used as received. 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), ammonium hexafluorophosphate,

¹ Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* 1996, 15, 1518.

² Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, 43, 2923.

and tributyltin chloride were purchased from Alfa Aesar and used as received. Trifluoromethanesulfonic acid was purchased from Oakwood Products, Inc. and used as received. Phosphorus pentoxide was purchased from Acros Organics and used as received. NMR spectroscopic data of known compounds correspond to the data given in the appropriate references. Arylstannanes were prepared and used within 1 week and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate)³ was prepared and used within one month for the trifluoromethoxylation reactions.

Experimental procedures and compound characterization

4.1. Ag-mediated trifluoromethoxylation of aryl stannanes and arylboronic acids

General procedure for the trifluoromethoxylation of aryl stannanes

To a 25 mL oven-dried two-neck round-bottom flask charged with a magnetic bar, tris(dimethylamino)sulfonium difluorotrimethylsilicate (222 mg, 1.00 mmol, 2.00 equiv) in an one dram vial (prepared in a glove box), sodium bicarbonate (84.0 mg, 1.00 mmol, 2.00 equiv), and aryl stannane (0.500 mmol, 1.00 equiv) were added under low nitrogen flow. Anhydrous THF (2.00 mL) was added to the flask at –30 °C under nitrogen flow using a 3 mL syringe. Trifluoromethyl trifluoromethanesulfonate (**3**) (0.450 g, 0.300 mL, 2.10 mmol, 4.10 equiv) in a Schlenk flask cooled to –50 °C under nitrogen flow was subsequently added using a 1 mL syringe (cooled by crushed dry ice wrapped in aluminum foil) while the suspension was stirred vigorously at –30 °C. The reaction mixture was stirred at –30 °C for 30 minutes and then a solution of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate)³ (**2**) (282 mg, 0.600 mmol, 1.20 equiv) and silver hexafluorophosphate (252 mg, 1.00 mmol, 2.00 equiv) in dry acetone (6.0 mL) cooled to –30 °C (prepared in a glovebox in a 25 mL round-bottom flask) was added by cannula. The reaction mixture was stirred for 2 to 4 hours in the dark and then warmed to 23 °C. The reaction mixture was filtered through a pad of celite eluting with CH₂Cl₂ and the filtrate concentrated in vacuo. The residue was purified via column chromatography on silica gel to afford the desired trifluoromethoxylated compound.

Note 1: Most reagents were stored in a glovebox for optimal results. The reaction could also be performed without the use of a glovebox when fresh reagents were used.

³ Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* 2009, *131*, 1662.

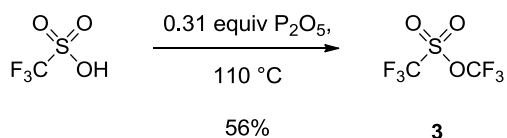
Note 2: The use of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluoro-phosphate) (2)³ gave highest results. The reaction can also be performed with commercially available 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) but yields are generally around 10% lower.

General procedure for the trifluoromethoxylation of arylboronic acids

To an anhydrous solution sodium hydroxide in methanol (1.00 N, 0.500 mL, 1.00 equiv) in an oven-dried 4 dram vial with a resealable PTFE/silicone disc charged with a magnetic bar was added under nitrogen flow arylboronic acid (0.500 mmol, 1.00 equiv) at 23 °C and stirred for 15 minutes. The reaction mixture was then cooled to 0 °C and silver hexafluorophosphate (252 mg, 1.00 mmol, 2.00 equiv) (prepared in an oven-dried 0.5 dram vial in a glovebox) was added quickly and the suspension was stirred for 30 minutes at 0 °C. The solvent was removed under reduced pressure at 0 °C and the residual methanol removed under reduced pressure by co-evaporation with anhydrous THF (2 × 0.500 mL). To the residue was added tris(dimethylamino)sulfonium difluorotrimethylsilicate (276 mg, 1.00 mmol, 2.00 equiv) and sodium bicarbonate (84.0 mg, 1.00 mmol, 2.00 equiv) (prepared in a one dram vial in a glove box) and then anhydrous THF (2.0 mL) was added to the mixture at –30 °C. Trifluoromethyl trifluoromethanesulfonate (3) (0.600 g, 0.400 mL, 2.80 mmol, 5.50 equiv) in a Schlenk flask cooled to –50 °C under nitrogen flow was subsequently added using a 1 mL syringe, cooled by crushed dry ice wrapped in aluminum foil, to the suspension stirring vigorously at –30 °C. The suspension was stirred at –30 °C for 30 minutes. A solution of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2)³ (282 mg, 0.600 mmol, 1.20 equiv) in dry acetone (6.0 mL) cooled to –30 °C was added to the prior suspension. The resulting suspension was then stirred for 1 hour and filtered through a pad of celite eluting with CH₂Cl₂ and the filtrate concentrated in vacuo. The residue was purified via column chromatography to afford the desired trifluoromethoxylated compound.

Note 1: Most reagents were stored in a glovebox for optimal results. The reaction could also be performed without the use of a glovebox when fresh reagents were used.

Note 2: Although arylboronic acids are generally preferred reagents over aryl stannanes, for the trifluoromethoxylation reaction reported here we generally recommend the stannane version of the method due to a simpler procedure and higher observed yields in general.



Trifluoromethyl trifluoromethanesulfonate⁴ (3)

Note: Trifluoromethyl trifluoromethanesulfonate (3) is commercially available from Oakwood Products, Inc.⁵. It can be prepared in 80% yield by a procedure published by Taylor and Martin in one step from trifluoromethanesulfonic anhydride and SbF₅ as a catalyst.⁶ We recommend the procedure by Taylor and Martin but provide an additional procedure that affords the product in lower yield (56%). The method presented here however does not require the use of SbF₅:

A 250-mL round-bottomed flask charged with a magnetic stir bar, 30-cm Vigreux column, and 100-mL round-bottomed receiving flask were dried in an oven for 12 hours at 135 °C. The system was assembled while the glass was hot and cooled under vacuum to 25 °C and then backfilled with N₂ and kept under a N₂ atmosphere. To the dry 250-mL round-bottomed flask charged with a magnetic stir bar was added sequentially sand (10.0 g), phosphorous pentoxide (25.0 g, 180 mmol, 0.310 equiv), and trifluoromethanesulfonic acid (50.0 mL, 84.8 g, 565 mmol, 1.00 equiv). The receiving flask was cooled to –78 °C. The reaction mixture was stirred at room temperature for 3 hours, then heated until reaching 110 °C (30 °C every 15 minutes) for a total of 8 hours. The distillate collected in the 100-mL round-bottomed Schlenk flask was then sealed and attached to a N₂ line. To the 100-mL round-bottomed flask at 0 °C was added a precooled solution of 3 M KOH (50 mL) at 0 °C. To the 100-mL round-bottomed flask at 0 °C was attached a short-path distillation apparatus with a 100-mL round-bottomed Schlenk flask as the collection flask was cooled to –78 °C. The 100-mL round-bottomed flask was warmed with a water bath to 25 °C and the distillate collected via short-path distillation in the 100-mL round-bottomed Schlenk flask cooled to –78 °C. The 100-mL round-bottomed Schlenk flask was then sealed after all the distillate was collected, allowed to warm to 25 °C, and attached to a vacuum transfer apparatus with a 50-mL long-bodied Schlenk flask. The vacuum transfer apparatus was flamed dried under vacuum and allowed to cool to 25 °C. The distillate was then transferred via vacuum transfer at 0 °C (frozen solid with liquid nitrogen first, then during vacuum transfer allowed to warm to

⁴ Nofle, R. E.; Cady, G. H. *Inorg. Chem.* 1965, 4, 1010.

⁵ <http://www.oakwoodchemical.com/p-59367-062235.aspx> (downloaded 07/16/2011)

⁶ Taylor, S. L.; Martin, J. C. *J. Org. Chem.* 1987, 52, 4147.

0 °C) over 15 minutes and the liquid collected in the 50-mL long-bodied Schlenk flask, cooled with liquid nitrogen, to give 34.5 g of the target compound as a colorless liquid (56%). The compound was stored in the 50-mL long-bodied Schlenk flask at –20 °C.

NMR Spectroscopy: ^{13}C NMR (100 MHz, CDCl_3 , 23 °C, δ): 118.8 (q, J = 273 Hz), 118.4 (q, J = 320 Hz). ^{19}F NMR (375 MHz, CDCl_3 , 23 °C, δ): –73.5 (q, J = 4.5 Hz), –52.9 (q, J = 3.0 Hz). The previously reported spectroscopic data are ^{19}F NMR (CFCl_3 , 23 °C, δ): –74.0 (q, J = 3.5 Hz), –53.3 (q, J = 3.5 Hz).⁶

Tris(dimethylamino)sulfonium trifluoromethoxide⁷ ($\text{TAS} \cdot \text{OCF}_3$) (1)

Typically, 1 was prepared in situ outside a glovebox (vide infra). For characterization purposes, we also synthesized it independently as follows:

All manipulations were carried out in a dry box under a N_2 atmosphere. To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) (330 mg, 1.20 mmol, 1.00 equiv) in anhydrous THF (12 mL) in a 20 mL vial with a resealable PTFE/silicone disc at –30 °C was added trifluoromethyl trifluoromethanesulfonate (3) (0.392 g, 0.261 mL, 1.80 mmol, 1.5 equiv) using a syringe (both 3 and the syringe were cooled to –30 °C). The suspension was stirred vigorously at –30 °C and at 23 °C for 15 min and 30 min, respectively. The suspension was filtered off and washed with THF (3×3 mL) to afford 243 mg of the title compound as a colorless solid (82% yield).

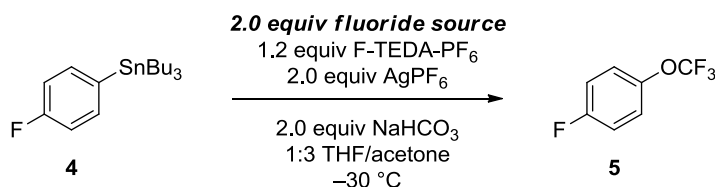
NMR Spectroscopy: ^1H NMR (500 MHz, CD_2Cl_2 , 23 °C, δ): 2.93 (s, 18H). ^{13}C NMR (125 MHz, CD_2Cl_2 , 23 °C, δ): 38.7. ^{19}F NMR (470 MHz, CD_2Cl_2 , 23 °C, δ): –20.5 (s, br). These spectroscopic data correspond to the reported data in reference.^{7b}

Decomposition study of $\text{TAS} \cdot \text{OCF}_3$ (1)

In a glove box, 0.60 mL of d_6 -acetone was added to a J. Y. tube, which contained $\text{TAS} \cdot \text{OCF}_3$ (1) (5.9 mg, 24 μmol) and 3-nitrofluorobenzene (1.0 μL) at 0 °C. The solution was warmed to 23 °C and immediately placed into the

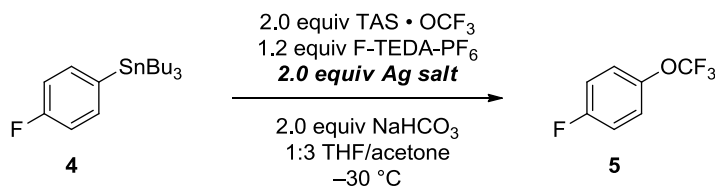
⁷ (a) Kolomeitsev, A. A.; Vorobyev, M.; Gillandt, H. *Tetrahedron Lett.* 2008, 49, 449. (b) Farnham, W. B.; Smart, B. E.; Middleton, W. J.; Calabrese, J. C.; Dixon, D. A. *J. Am. Chem. Soc.* 1985, 107, 4565.

NMR machine and the ^{19}F NMR resonances followed by ^{19}F NMR spectroscopy at 45 °C. $\text{TAS} \cdot \text{OCF}_3$ was completely decomposed to difluorophosgene (COF_2) and an unknown byproduct within 15 min at 45 °C.



Effect of fluoride source on the yield of Ag-mediated trifluoromethoxylation reaction

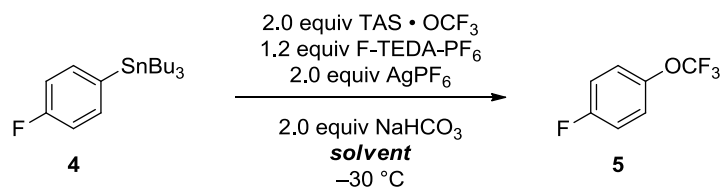
To a suspension of fluoride source (0.400 mmol, 2.00 equiv), sodium bicarbonate (33.6 mg, 0.400 mmol, 2.00 equiv), and (4-fluorophenyl)tributylstannane³ (**4**) (77.0 mg, 0.200 mmol, 1.00 equiv) in anhydrous THF (0.800 mL) at $-30\text{ }^\circ\text{C}$ was added trifluoromethyl trifluoromethanesulfonate (**3**) (0.18 g, 0.12 mL, 0.83 mmol, 4.1 equiv), and the suspension was stirred vigorously. The reaction mixture was stirred at $-30\text{ }^\circ\text{C}$ for 30 minutes, then a solution cooled to $-30\text{ }^\circ\text{C}$ of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (**2**) (113 mg, 0.240 mmol, 1.20 equiv) and silver hexafluorophosphate (101 mg, 0.400 mmol, 2.00 equiv) in dry acetone (2.4 mL) was added. The reaction mixture was stirred for 2 hours in the dark, then warmed to $23\text{ }^\circ\text{C}$. To the reaction mixture was added 3-nitrofluorobenzene (20.0 μL , 0.188 mmol, 0.939 equiv). The yield was determined by comparing the integration of the ^{19}F NMR (375 MHz, acetone- d_6 , $23\text{ }^\circ\text{C}$) resonance of 1-fluoro-4-(trifluoromethoxy)benzene (-117.0 ppm , -59.9 ppm), 1,4-difluorobenzene (-121.7 ppm), 4,4'-difluorobiphenyl (-118.0 ppm), 4-fluorophenol (-128.4 ppm), and fluorobenzene (-115.4 ppm) with that of 3-nitrofluorobenzene (-112.0 ppm). Yields are reported as percentages (by ^{19}F NMR).



Effect of Ag salt on the yield of Ag-mediated trifluoromethoxylation reaction

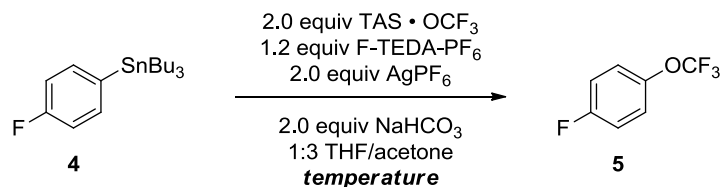
To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (110 mg, 0.400 mmol, 2.00 equiv), sodium bicarbonate (33.6 mg, 0.400 mmol, 2.00 equiv), and (4-fluorophenyl)tributylstannane³ (**4**) (77.0 mg, 0.200 mmol, 1.00 equiv) in anhydrous THF (0.800 mL) at $-30\text{ }^\circ\text{C}$ was added trifluoromethyl trifluoromethanesulfonate (**3**) (0.18 g, 0.12 mL, 0.83 mmol, 4.1 equiv), and the suspension was stirred vigorously. The reaction mixture was

stirred at $-30\text{ }^{\circ}\text{C}$ for 30 minutes, then a solution cooled to $-30\text{ }^{\circ}\text{C}$ of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (113 mg, 0.240 mmol, 1.20 equiv) and silver salt (0.400 mmol, 2.00 equiv) in dry acetone (2.4 mL) was added. The reaction mixture was stirred for 2 hours in the dark, then warmed to $23\text{ }^{\circ}\text{C}$. To the reaction mixture was added 3-nitrofluorobenzene (20.0 μL , 0.188 mmol, 0.939 equiv). The yield was determined by comparing the integration of the ^{19}F NMR (375 MHz, acetone- d_6 , $23\text{ }^{\circ}\text{C}$) resonance of 1-fluoro-4-(trifluoromethoxy)benzene (-117.0 ppm , -59.9 ppm), 1,4-difluorobenzene (-121.7 ppm), 4,4'-difluorobiphenyl (-118.0 ppm), 4-fluorophenol (-128.4 ppm), and fluorobenzene (-115.4 ppm) with that of 3-nitrofluorobenzene (-112.0 ppm). Yields are reported as percentages (by ^{19}F NMR).



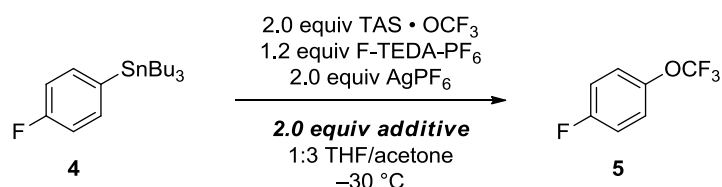
Effect of solvent on the yield of Ag-mediated trifluoromethoxylation reaction

To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (110 mg, 0.400 mmol, 2.00 equiv), sodium bicarbonate (33.6 mg, 0.400 mmol, 2.00 equiv), and (4-fluorophenyl)tributylstannane³ (4) (77.0 mg, 0.200 mmol, 1.00 equiv) in anhydrous solvent (0.800 mL) at $-30\text{ }^{\circ}\text{C}$ was added trifluoromethyl trifluoromethanesulfonate (3) (0.18 g, 0.12 mL, 0.83 mmol, 4.1 equiv), and the suspension was stirred vigorously. The reaction mixture was stirred at $-30\text{ }^{\circ}\text{C}$ for 30 minutes, then a solution cooled to $-30\text{ }^{\circ}\text{C}$ of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (113 mg, 0.240 mmol, 1.20 equiv) and silver hexafluorophosphate (101 mg, 0.400 mmol, 2.00 equiv) in anhydrous solvent (2.4 mL) was added. The reaction mixture was stirred for 2 hours in the dark, then warmed to $23\text{ }^{\circ}\text{C}$. To the reaction mixture was added 3-nitrofluorobenzene (20.0 μL , 0.188 mmol, 0.939 equiv). The yield was determined by comparing the integration of the ^{19}F NMR (375 MHz, acetone- d_6 , $23\text{ }^{\circ}\text{C}$) resonance of 1-fluoro-4-(trifluoromethoxy)benzene (-117.0 ppm , -59.9 ppm), 1,4-difluorobenzene (-121.7 ppm), 4,4'-difluorobiphenyl (-118.0 ppm), 4-fluorophenol (-128.4 ppm), and fluorobenzene (-115.4 ppm) with that of 3-nitrofluorobenzene (-112.0 ppm). Yields are reported as percentages (by ^{19}F NMR).



Effect of temperature on the yield of Ag-mediated trifluoromethoxylation reaction

To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (110 mg, 0.400 mmol, 2.00 equiv), sodium bicarbonate (33.6 mg, 0.400 mmol, 2.00 equiv), and (4-fluorophenyl)tributylstannane³ (4) (77.0 mg, 0.200 mmol, 1.00 equiv) in anhydrous THF (0.800 mL) at the corresponding temperature was added trifluoromethyl trifluoromethanesulfonate (3) (0.18 g, 0.12 mL, 0.83 mmol, 4.1 equiv), and the suspension was stirred vigorously. The reaction mixture was stirred at the corresponding temperature for 30 minutes, then a solution cooled to the corresponding temperature of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (113 mg, 0.240 mmol, 1.20 equiv) and silver hexafluorophosphate (101 mg, 0.400 mmol, 2.00 equiv) in dry acetone (2.4 mL) was added. The reaction mixture was stirred for 2 hours in the dark, then warmed to 23 °C. To the reaction mixture was added 3-nitrofluorobenzene (20.0 μ L, 0.188 mmol, 0.939 equiv). The yield was determined by comparing the integration of the ¹⁹F NMR (375 MHz, acetone-*d*₆, 23 °C) resonance of 1-fluoro-4-(trifluoromethoxy)benzene (−117.0 ppm, −59.9 ppm), 1,4-difluorobenzene (−121.7 ppm), 4,4'-difluorobiphenyl (−118.0 ppm), 4-fluorophenol (−128.4 ppm), and fluorobenzene (−115.4 ppm) with that of 3-nitrofluorobenzene (−112.0 ppm). Yields are reported as percentages (by ¹⁹F NMR).

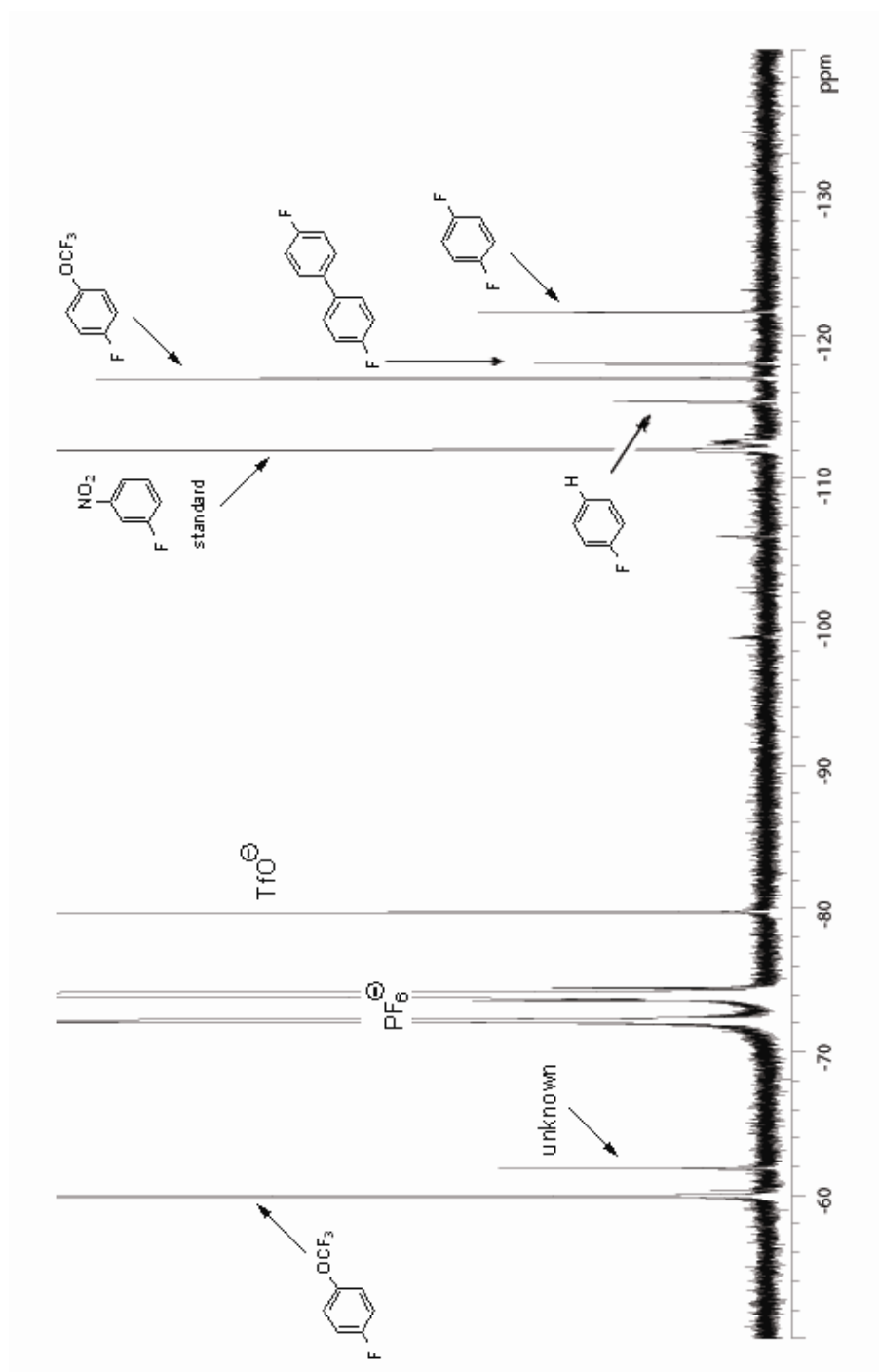


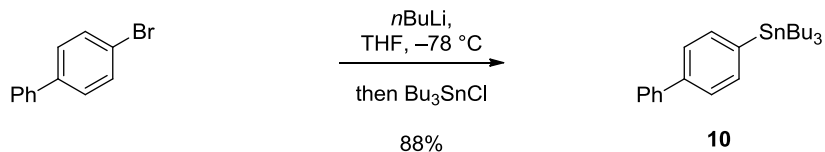
Effect of additives on the yield of Ag-mediated trifluoromethoxylation reaction

To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (110 mg, 0.400 mmol, 2.00 equiv), additive (0.400 mmol, 2.00 equiv), and (4-fluorophenyl)tributylstannane³ (4) (77.0 mg, 0.200 mmol, 1.00 equiv) in anhydrous THF (0.800 mL) at −30 °C was added trifluoromethyl trifluoromethanesulfonate (3) (0.18 g, 0.12 mL, 0.83 mmol, 4.1 equiv), and the suspension was stirred vigorously. The reaction mixture was stirred at −30 °C for 30 minutes, then a solution cooled to −30 °C of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (113 mg, 0.240 mmol, 1.20 equiv) and silver hexafluorophosphate (101 mg, 0.400

mmol, 2.00 equiv) in dry acetone (2.4 mL) was added. The reaction mixture was stirred for 2 hours in the dark, then warmed to 23 °C. To the reaction mixture was added 3-nitrofluorobenzene (20.0 μ L, 0.188 mmol, 0.939 equiv). The yield was determined by comparing the integration of the ^{19}F NMR (375 MHz, acetone- d_6 , 23 °C) resonance of 1-fluoro-4-(trifluoromethoxy)benzene (−117.0 ppm, −59.9 ppm), 1,4-difluorobenzene (−121.7 ppm), 4,4'-difluorobiphenyl (−118.0 ppm), 4-fluorophenol (−128.4 ppm), and fluorobenzene (−115.4 ppm) with that of 3-nitrofluorobenzene (−112.0 ppm). Yields are reported as percentages (^{19}F NMR).

Representative ^{19}F NMR spectrum (375 MHz, CDCl_3 , 23 $^\circ\text{C}$) for the trifluoromethoxylation of 4 to give 5

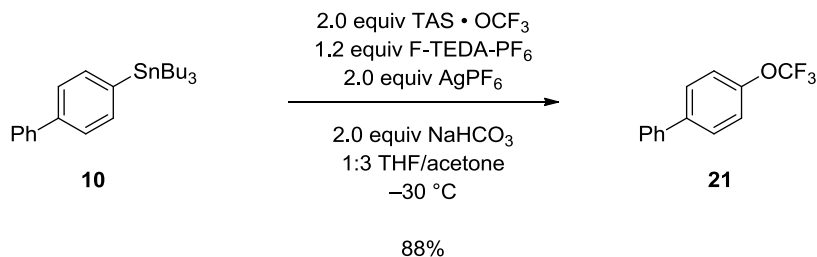




Tributyl(4-biphenyl)stannane³ (10)

To 4-bromobiphenyl (3.00 g, 12.9 mmol, 1.00 equiv) in anhydrous THF (30 mL) at -78°C was added *n*BuLi (2.5 M in hexanes, 5.1 mL, 13 mmol, 1.0 equiv). The reaction mixture was stirred at -78°C for 30 min before the addition of Bu_3SnCl (4.20 g, 3.50 mL, 12.9 mmol, 1.00 equiv). After stirring for 1.0 hr at -78°C , the reaction mixture was warmed to 23°C and the solvent was removed in vacuo. The residue was dissolved in 20 mL of Et_2O and filtered through a plug of neutral alumina. The filtrate was concentrated in vacuo and the residue purified via column chromatography on silica gel eluting with hexanes to afford 3.76 g of the title compound as a colorless oil (88% yield).

$R_f = 0.58$ (hexanes). NMR Spectroscopy: ^1H NMR (400 MHz, CDCl_3 , 23°C , δ): 7.69–7.57 (m, 6H), 7.58–7.51 (m, 2H), 7.44–7.38 (m, 1H), 1.75–1.59 (m, 6H), 1.52–1.40 (m, 6H), 1.27–1.09 (m, 6H), 0.99 (t, $J = 7.3$ Hz, 9H). ^{13}C NMR (100 MHz, CDCl_3 , 23°C , δ): 141.5, 140.0, 137.0, 128.9, 127.3, 127.2, 127.1, 126.8, 29.3, 27.6, 13.9, 9.8. These spectroscopic data correspond to previously reported data.³



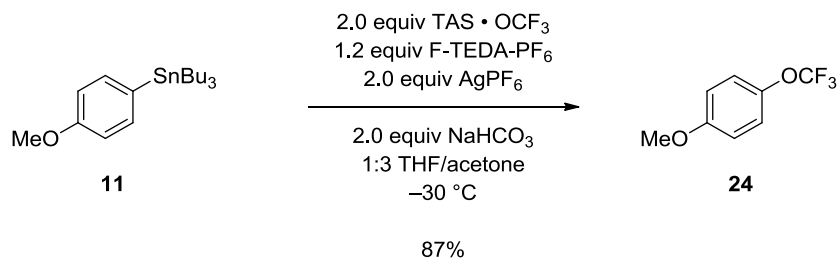
4-(Trifluoromethoxy)biphenyl⁸ (21)

To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (222 mg, 1.00 mmol, 2.00 equiv), sodium bicarbonate (84.0 mg, 1.00 mmol, 2.00 equiv), and tributyl(4-biphenyl)stannane (10) (253 mg, 0.500 mmol, 1.00 equiv) in anhydrous THF (2.00 mL) at -30°C was added trifluoromethyl trifluoromethanesulfonate (3) (0.45 g, 0.30 mL, 2.1 mmol, 4.1 equiv)(0.45 g, 0.30 mL, 2.1 mmol, 4.1 equiv), and the suspension was stirred vigorously. The reaction mixture was stirred at -30°C for 30 minutes, then a solution cooled to -30°C of 1-chloromethyl-4-fluoro-

⁸ Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J. *Nature Chemistry* 2010, 2, 1044.

1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (282 mg, 0.600 mmol, 1.20 equiv) and silver hexafluorophosphate (252 mg, 1.00 mmol, 2.00 equiv) in dry acetone (6.0 mL) was added by cannula. The reaction mixture was stirred for 2.5 hours in the dark, then warmed to 23 °C. The reaction mixture was filtered through a pad of celite eluting with CH₂Cl₂ and the filtrate concentrated in vacuo. The residue was purified via column chromatography on silica gel eluting with hexanes/CH₂Cl₂ 19:1 (v/v) to afford 104 mg of the title compound as a white solid (88% yield).

R_f = 0.53 (hexanes/CH₂Cl₂ 19:1 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 7.64–7.59 (m, 4H), 7.51–7.48 (m, 2 H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃, 23 °C, δ): 148.8 (q, *J* = 2 Hz), 140.1, 140.0, 129.0, 128.6, 127.8, 127.3, 121.4, 120.7 (q, *J* = 256 Hz). ¹⁹F NMR (375 MHz, CDCl₃, 23 °C, δ): –58.2. These spectroscopic data correspond to previously reported data.⁸

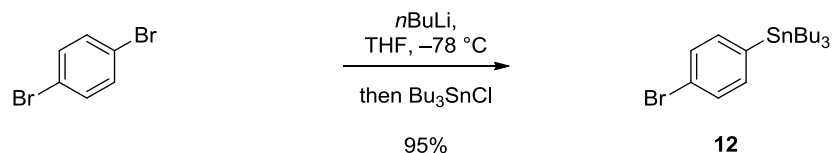


1-Methoxy-4-(trifluoromethoxy)benzene (24)

To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (275 mg, 1.00 mmol, 2.00 equiv), sodium bicarbonate (84.0 mg, 1.00 mmol, 2.00 equiv), and tributyl(4-methoxyphenyl)stannane⁹ (11) (199 mg, 0.500 mmol, 1.00 equiv) in anhydrous THF (2.00 mL) at –30 °C was added trifluoromethyl trifluoromethanesulfonate (3) (0.45 g, 0.30 mL, 2.1 mmol, 4.1equiv), and the suspension was stirred vigorously. The reaction mixture was stirred at –30 °C for 30 minutes, then a solution cooled to –30 °C of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (282 mg, 0.600 mmol, 1.20 equiv) and silver hexafluorophosphate (252 mg, 1.00 mmol, 2.00 equiv) in dry acetone (6.0 mL) was added by cannula. The reaction mixture was stirred for 2 hours in the dark, then warmed to 23 °C. The reaction mixture was filtered through a pad of celite eluting with CH₂Cl₂ and the filtrate concentrated in vacuo at 5 °C. The residue was purified via column chromatography on silica gel eluting with pentane/CH₂Cl₂ 9:1 (v/v) to afford 84 mg of the title compound as a clear liquid (87% yield).

⁹ Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* 2010, *132*, 12150.

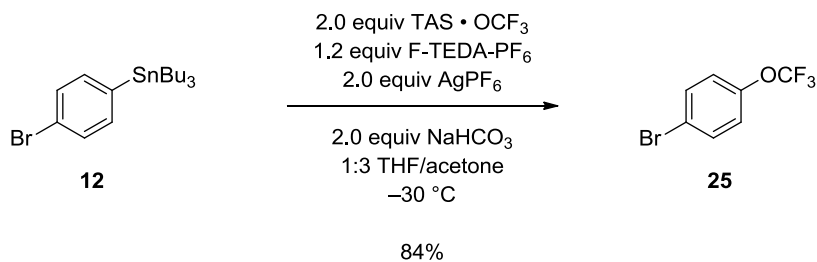
$R_f = 0.48$ (pentane/ CH_2Cl_2 9:1 (v/v)). NMR Spectroscopy: ^1H NMR (500 MHz, CDCl_3 , 23 °C, δ): 7.15 (d, $J = 9.2$ Hz, 2H), 6.89 (dd, $J = 9.2$ Hz, 3.7 Hz, 2H), 3.81 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3 , 23 °C, δ): 158.3, 142.9 (q, $J = 2$ Hz), 122.6, 120.8 (q, $J = 256$ Hz), 114.8, 55.7. ^{19}F NMR (470 MHz, CDCl_3 , 23 °C, δ): -58.9. These spectroscopic data correspond to those obtained from an authentic sample purchased from Strem.



(4-Bromophenyl)tributylstannane (12)

To 1,4-dibromobenzene (1.2 g, 5.0 mmol, 1.0 equiv) in THF (13 mL) at -78 °C was added $n\text{BuLi}$ (1.6 M in hexane, 3.1 mL, 5.0 mmol, 1.0 equiv). The reaction mixture was stirred at -78 °C for 30 min before the addition of Bu_3SnCl (1.6 g, 1.4 mL, 5.0 mmol, 1.0 equiv). After stirring for 1 hr at -78 °C, the reaction mixture was warmed to 23 °C and the solvent was removed in vacuo. The residue was dissolved in 20 mL of Et_2O and filtered through a plug of neutral alumina. The filtrate was concentrated in vacuo and the residue purified via column chromatography on silica gel eluting with hexanes to afford 2.1 g of the title compound as a colorless oil (95% yield).

$R_f = 0.50$ (hexanes). NMR Spectroscopy: ^1H NMR (500 MHz, CDCl_3 , 23 °C, δ): 7.48 (d, $J = 7.8$ Hz, 2H), 7.35 (d, $J = 7.8$ Hz, 2H), 1.59–1.53 (m, 6H), 1.40–1.32 (m, 6H), 1.10–1.07 (m, 6H), 0.92 (t, $J = 7.3$ Hz, 9H). ^{13}C NMR (125 MHz, CDCl_3 , 23 °C, δ): 140.7, 138.0, 131.1, 122.9, 29.2, 27.5, 13.8, 9.8. These spectroscopic data correspond to previously reported data.⁹

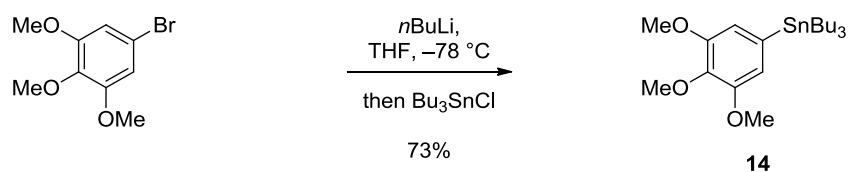


1-Bromo-4-(trifluoromethoxy)benzene (25)

To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (275 mg, 1.00 mmol, 2.00 equiv), sodium bicarbonate (84.0 mg, 1.00 mmol, 2.00 equiv), and (4-bromophenyl)tributylstannane⁹ (12) (223 mg, 0.500 mmol, 1.00 equiv) in anhydrous THF (2.00 mL) at -30 °C was added trifluoromethyl trifluoromethanesulfonate (3) (0.45 g,

0.30 mL, 2.1 mmol, 4.1 equiv), and the suspension was stirred vigorously. The reaction mixture was stirred at -30 °C for 30 minutes, then a solution cooled to -30 °C of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (282 mg, 0.600 mmol, 1.20 equiv) and silver hexafluorophosphate (252 mg, 1.00 mmol, 2.00 equiv) in dry acetone (6.0 mL) was added by cannula. The reaction mixture was stirred for 2.5 hours in the dark, then warmed to 23 °C. The reaction mixture was filtered through a pad of celite eluting with CH_2Cl_2 and the filtrate concentrated in vacuo at 5 °C. The residue was purified via column chromatography on silica gel eluting with pentane/ CH_2Cl_2 1:1 (v/v) to afford 101 mg of the title compound as a clear liquid (84% yield).

$R_f = 0.86$ (pentane/ CH_2Cl_2 1:1 (v/v)). NMR Spectroscopy: ^1H NMR (400 MHz, CDCl_3 , 23 °C, δ): 7.52 (dd, $J = 8.8$ Hz, 1.8 Hz, 2H), 7.10 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3 , 23 °C, δ): 148.4 (q, $J = 2$ Hz), 133.1, 122.9, 120.3, 120.5 (q, $J = 258$ Hz). ^{19}F NMR (375 MHz, CDCl_3 , 23 °C, δ): -58.5 . These spectroscopic data correspond to those obtained from an authentic sample purchased from Strem.



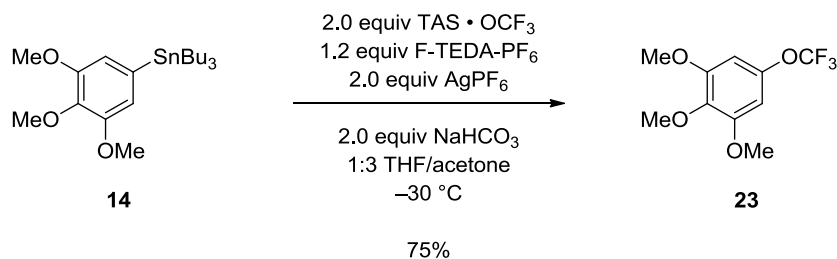
Tributyl(3,4,5-trimethoxyphenyl)stannane¹⁰ (14)

To 5-bromo-1,2,3-trimethoxybenzene (1.2 g, 4.9 mmol, 1.0 equiv), in anhydrous THF (12 mL) at -78 °C was added $n\text{BuLi}$ (2.5 M in hexanes, 2.1 mL, 5.3 mmol, 1.1 equiv). The reaction mixture was stirred at -78 °C for 30 min before the addition of Bu_3SnCl (1.6 g, 1.3 mL, 4.9 mmol, 1.0 equiv). After stirring for 1.0 hr at -78 °C, the reaction mixture was warmed to 23 °C and the solvent was removed in vacuo. The residue was dissolved in 20 mL of Et_2O and filtered through a plug of neutral alumina. The filtrate was concentrated in vacuo and was purified by chromatography on silica gel eluting with hexanes/ EtOAc 5:1 (v/v) to afford 1.6 g of the title compound as a colorless oil (73% yield).

$R_f = 0.47$ (hexanes/ EtOAc 5:1 (v/v)). NMR Spectroscopy: ^1H NMR (400 MHz, CDCl_3 , 23 °C, δ): 6.66 (s, 2H), 3.88(s, 6H), 3.86 (s, 3H), 1.59–1.55 (m, 6H), 1.38–1.33 (m, 6H), 1.09–1.05 (m, 6H), 0.91 (t, $J = 7.2$ Hz, 9H). ^{13}C

¹⁰ Suginome, H.; Orito, K.; Yorita, K.; Ishikawa, M.; Shimoyama, N.; Sasaki, T. *J. Org. Chem.* 1995, *60*, 3052.

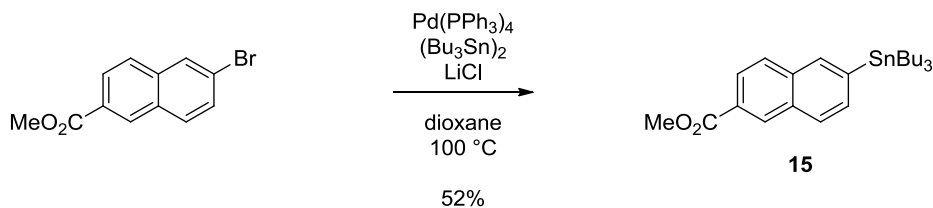
NMR (100 MHz, CDCl₃, 23 °C, δ): 153.0, 138.4, 136.7, 113.0, 60.8, 56.2, 29.2, 27.4, 13.7, 9.9. These spectroscopic data correspond to previously reported data.¹⁰



1,2,3-Trimethoxy-5-(trifluoromethoxy)benzene (23)

To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (275 mg, 1.00 mmol, 2.00 equiv), sodium bicarbonate (84.0 mg, 1.00 mmol, 2.00 equiv), and tributyl(3,4,5-trimethoxyphenyl)stannane¹⁰ (14) (229 mg, 0.500 mmol, 1.00 equiv) in anhydrous THF (2.00 mL) at $-30\text{ }^\circ\text{C}$ was added trifluoromethyl trifluoromethanesulfonate (3) (0.45 g, 0.30 mL, 2.1 mmol, 4.1 equiv), and the suspension was stirred vigorously. The reaction mixture was stirred at $-30\text{ }^\circ\text{C}$ for 30 minutes, then a solution cooled to $-30\text{ }^\circ\text{C}$ of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (282 mg, 0.600 mmol, 1.20 equiv) and silver hexafluorophosphate (252 mg, 1.00 mmol, 2.00 equiv) in dry acetone (6.0 mL) was added by cannula. The reaction mixture was stirred for 4 hours in the dark, then warmed to $23\text{ }^\circ\text{C}$. The reaction mixture was filtered through a pad of celite eluting with CH₂Cl₂ and the filtrate concentrated in vacuo. The residue was purified via column chromatography on silica gel eluting with hexanes/CH₂Cl₂ 1:2 (v/v) to afford 94 mg of the title compound as a clear oil (75% yield).

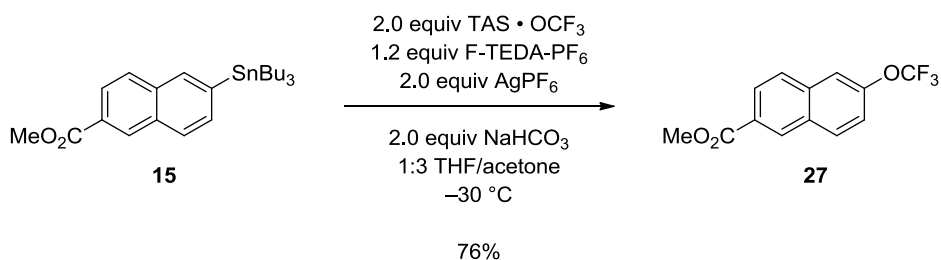
$R_f = 0.28$ (hexanes/CH₂Cl₂ 1:2 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 6.45 (s, 2H), 3.84 (s, 6H), 3.82 (s, 3H). ¹³C NMR (100 MHz, CDCl₃, 23 °C, δ): 153.7, 145.3 (q, $J = 2\text{ Hz}$), 136.8, 120.6 (q, $J = 257\text{ Hz}$), 99.0, 61.0, 56.3. ¹⁹F NMR (470 MHz, CDCl₃, 23 °C, δ): -58.4 . Mass Spectrometry: HRMS-FIA (m/z): Calcd for C₁₀H₁₂F₃O₄ [M + H]⁺, 253.0682. Found, 253.0685.



Methyl 6-(tributylstannyl)-2-naphthoate (15)

To a suspension of lithium chloride (635 mg, 15.0 mmol, 5.00 equiv), hexabutylditin (3.44 g, 3.00 mL, 6.00 mmol, 2.50 equiv), and methyl 6-bromo-2-naphthoate (795 mg, 3.00 mmol, 1.00 equiv) in anhydrous dioxane (30.0 mL) at 25 °C was added palladium tetrakis triphenylphosphine (173 mg, 0.150 mmol, 0.0500 equiv). The reaction mixture was heated to 100 °C and stirred for 12 hours, then cooled to room temperature. The reaction mixture was filtered through a pad of celite eluting with CH_2Cl_2 , and the filtrate concentrated in vacuo. The residue was purified via column chromatography on silica gel eluting with hexanes/EtOAc 3:1 (v/v) to afford 741 mg of the title compound as a clear oil (52% yield).

$R_f = 0.75$ (hexanes/EtOAc 3:1 (v/v)). NMR Spectroscopy: ^1H NMR (400 MHz, CDCl_3 , 23 °C, δ): 8.61 (s, 1H), 8.08 (dd, $J = 8.8$ Hz, 1.6 Hz, 1H), 8.01 (s, 1H), 7.96–7.86 (m, 2H), 7.66 (d, $J = 8.1$ Hz, 1H), 3.99 (s, 3H), 1.70–1.53 (m, 6H), 1.43–1.30 (m, 6H), 1.29–1.09 (m, 6H), 0.93 (t, $J = 7.3$ Hz, 9H). ^{13}C NMR (125 MHz, CDCl_3 , 23 °C, δ): 167.4, 143.7, 136.4, 135.1, 134.0, 132.4, 131.2, 128.1, 127.9, 127.3, 125.2, 52.2, 29.2, 27.5, 13.8, 9.8. Mass Spectrometry: HRMS-FIA (m/z): Calcd for $\text{C}_{24}\text{H}_{37}\text{O}_2\text{Sn}$ [$\text{M} + \text{H}$] $^+$, 477.1810. Found, 477.1795.

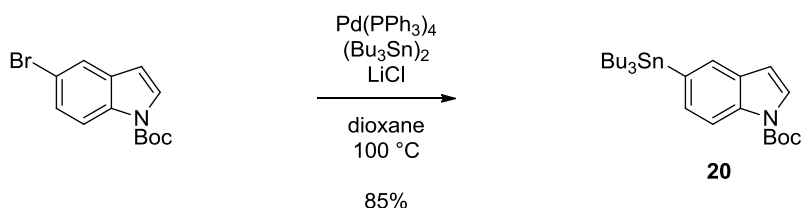


Methyl 6-(trifluoromethoxy)-2-naphthoate (27)

To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (275 mg, 1.00 mmol, 2.00 equiv), sodium bicarbonate (84.0 mg, 1.00 mmol, 2.00 equiv), and methyl 6-(tributylstannyl)-2-naphthoate (15) (238 mg, 0.500 mmol, 1.00 equiv) in anhydrous THF (2.00 mL) at -30°C was added trifluoromethyl trifluoromethanesulfonate (3) (0.45 g, 0.30 mL, 2.1 mmol, 4.1 equiv), and the suspension was stirred vigorously. The reaction mixture was stirred at -30°C for 30 minutes, then a solution cooled to -30°C of 1-chloromethyl-4-fluoro-1,4-

diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (282 mg, 0.600 mmol, 1.20 equiv) and silver hexafluorophosphate (252 mg, 1.00 mmol, 2.00 equiv) in dry acetone (6.0 mL) was added by cannula. The reaction mixture was stirred for 2.5 hours in the dark, then warmed to 23 °C. The reaction mixture was filtered through a pad of celite eluting with CH₂Cl₂ and the filtrate concentrated in vacuo. The residue was purified via column chromatography on silica gel eluting with hexanes/CH₂Cl₂ 1:2 (v/v) to afford 102 mg of the title compound as a clear oil (76% yield).

R_f = 0.52 (hexanes/CH₂Cl₂ 1:2 (v/v)). NMR Spectroscopy: ¹H NMR (400 MHz, CDCl₃, 23 °C, δ): 8.61 (s, 1H), 8.11 (dd, *J* = 8.7 Hz, 1.8 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.86 (d, *J* = 8.7 Hz, 1H), 7.68 (s, 1H), 7.39 (dd, *J* = 9.2 Hz, 1.8 Hz, 1H), 3.99 (s, 3H). ¹³C NMR (100 MHz, CDCl₃, 23 °C, δ): 167.0, 148.7 (q, *J* = 2 Hz), 135.9, 131.7, 130.9, 130.8, 128.2, 128.1, 126.6, 120.9, 120.7 (q, *J* = 257 Hz), 117.8, 52.5. ¹⁹F NMR (375 MHz, CDCl₃, 23 °C, δ): -58.0. Mass Spectrometry: HRMS-FIA (*m/z*): Calcd for C₁₃H₁₀F₃O₃ [M + H]⁺, 271.0577. Found, 271.0573.

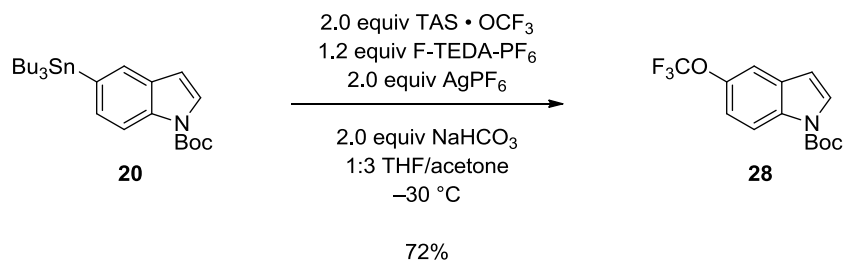


5-Tributylstannyl-*N*-Boc-indole³ (20)

To a suspension of lithium chloride (297 mg, 7.00 mmol, 2.00 equiv), hexabutyltin (3.05 g, 2.65 mL, 5.25 mmol, 1.50 equiv), and 5-bromo-*N*-Boc-indole (1.04 g, 3.50 mmol, 1.00 equiv) in anhydrous dioxane (17.5 mL) at 25 °C was added palladium tetrakis triphenylphosphine (75.0 mg, 0.175 mmol, 0.0500 equiv). The reaction mixture was heated at 100 °C and stirred for 2.5 hours at this temperature, then cooled to room temperature. The reaction mixture was filtered through a pad of celite eluting with CH₂Cl₂, and the filtrate concentrated in vacuo. The residue was purified via column chromatography on silica gel eluting with hexanes/EtOAc 9:1 (v/v) and further purified by evaporation of impurities via kugelrohr at 150 °C at 200 millitorr to afford 1.50 g of the title compound as a clear oil (85% yield).

R_f = 0.50 (hexanes/EtOAc 9:1 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 8.15 (d, *J* = 6.0 Hz, 1H), 7.70 (s, 1H), 7.60 (d, *J* = 3.2 Hz, 1H), 7.44 (d, *J* = 6.0 Hz, 1H), 6.59 (d, *J* = 3.2 Hz, 1H), 1.70 (s, 9H), 1.67–1.55 (m, 6H), 1.43–1.35 (m, 6H), 1.20–1.06 (m, 6H), 0.96 (t, *J* = 6.0 Hz, 9H). ¹³C NMR (100 MHz, CDCl₃, 23 °C,

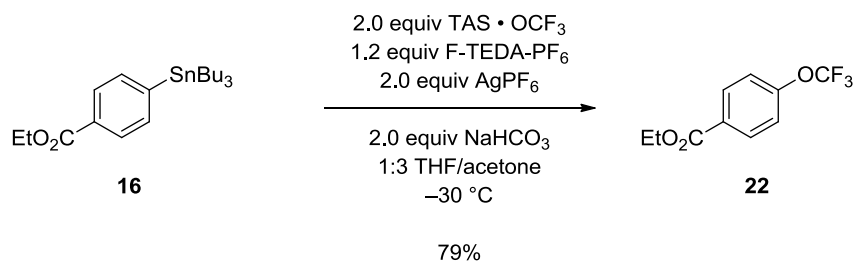
δ): 150.0, 135.4, 132.0, 134.7, 130.8, 129.2, 125.5, 114.9, 107.2, 83.6, 29.3, 28.3, 27.5, 13.8, 9.8. These spectroscopic data correspond to previously reported data.³



5-Trifluoromethoxy-*N*-Boc-indole (28)

To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (275 mg, 1.00 mmol, 2.00 equiv), sodium bicarbonate (84.0 mg, 1.00 mmol, 2.00 equiv), and 5-tributylstannyl-*N*-Boc-indole³ (20) (253 mg, 0.500 mmol, 1.00 equiv) in anhydrous THF (2.00 mL) at $-30\text{ }^\circ\text{C}$ was added trifluoromethyl trifluoromethanesulfonate (3) (0.45 g, 0.30 mL, 2.1 mmol, 4.1 equiv), and the suspension was stirred vigorously. The reaction mixture was stirred at $-30\text{ }^\circ\text{C}$ for 30 minutes, then a solution cooled to $-30\text{ }^\circ\text{C}$ of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (282 mg, 0.600 mmol, 1.20 equiv) and silver hexafluorophosphate (252 mg, 1.00 mmol, 2.00 equiv) in dry acetone (6.0 mL) was added by cannula. The reaction mixture was stirred for 2.5 hours in the dark, then warmed to $23\text{ }^\circ\text{C}$. The reaction mixture was filtered through a pad of celite eluting with CH_2Cl_2 and the filtrate concentrated in vacuo. The residue was purified via column chromatography on silica gel eluting with hexanes/ CH_2Cl_2 1:1 (v/v) to afford 108 mg of the title compound as a clear oil (72% yield).

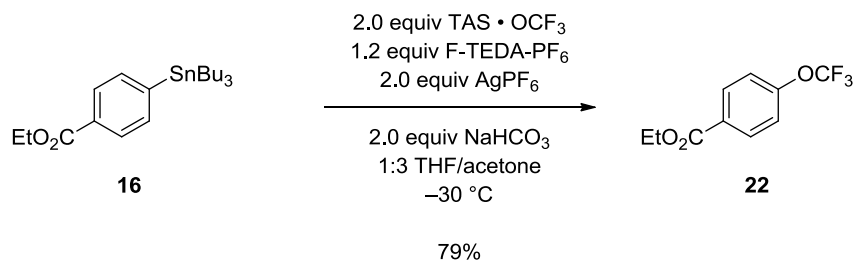
$R_f = 0.70$ (hexanes/ CH_2Cl_2 1:1 (v/v)). NMR Spectroscopy: ^1H NMR (500 MHz, CDCl_3 , $23\text{ }^\circ\text{C}$, δ): 8.17 (d, $J = 7.8$ Hz, 1H), 7.66 (d, $J = 3.4$ Hz, 1H), 7.42 (s, 1H), 7.18 (d, $J = 7.3$ Hz, 1H), 6.57 (d, $J = 3.4$ Hz, 1H), 1.68 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3 , $23\text{ }^\circ\text{C}$, δ): 149.4, 145.0 (q, $J = 2$ Hz), 133.6, 131.3, 127.8, 123.9 (q, $J = 256$ Hz), 117.8, 116.1, 113.4, 107.2, 84.3, 28.3. ^{19}F NMR (375 MHz, CDCl_3 , $23\text{ }^\circ\text{C}$, δ): -58.5 . Mass Spectrometry: HRMS-FIA (m/z): Calcd for $\text{C}_9\text{H}_7\text{F}_3\text{NO}$ [$\text{M} - \text{C}_5\text{H}_9\text{O}_2 (\text{Boc}) + \text{H}$] $^+$, 202.0480. Found, 202.0485.



Ethyl 4-(trifluoromethoxy)benzoate¹¹ (22)

To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (275 mg, 1.00 mmol, 2.00 equiv), sodium bicarbonate (84.0 mg, 1.00 mmol, 2.00 equiv), and ethyl 4-(tributylstannyl)benzoate⁹ (16) (220 mg, 0.500 mmol, 1.00 equiv) in anhydrous THF (2.00 mL) at -30°C was added trifluoromethyl trifluoromethanesulfonate (3) (0.45 g, 0.30 mL, 2.1 mmol, 4.1 equiv), and the suspension was stirred vigorously. The reaction mixture was stirred at -30°C for 30 minutes, then a solution cooled to -30°C of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (282 mg, 0.600 mmol, 1.20 equiv) and silver hexafluorophosphate (252 mg, 1.00 mmol, 2.00 equiv) in dry acetone (6.0 mL) was added by cannula. The reaction mixture was stirred for 2 hours in the dark, then warmed to 23°C . The reaction mixture was filtered through a pad of celite eluting with CH_2Cl_2 and the filtrate concentrated in vacuo at 5°C . The residue was purified via column chromatography on silica gel eluting with pentane/ CH_2Cl_2 1:1 (v/v) to afford 92 mg of the title compound as a light yellow oil (79% yield).

$R_f = 0.89$ (pentane/ CH_2Cl_2 1:1 (v/v)). NMR Spectroscopy: ^1H NMR (400 MHz, CDCl_3 , 23°C , δ): 8.09 (d, $J = 9.2$ Hz, 2H), 7.26 (d, $J = 9.2$ Hz, 2H), 4.39 (q, $J = 7.2$ Hz, 2H), 1.40 (t, $J = 6.8$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3 , 23°C , δ): 165.6, 152.7 (q, $J = 2$ Hz), 131.6, 129.1, 120.5, 120.4 (q, $J = 257$ Hz), 61.4, 14.4. ^{19}F NMR (375 MHz, CDCl_3 , 23°C , δ): -58.1 . These spectroscopic data correspond to previously reported data.¹¹

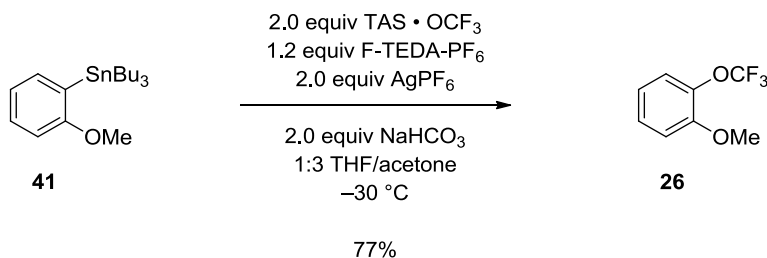


Synthesis of ethyl 4-(trifluoromethoxy)benzoate¹¹ (22) on gram scale

¹¹ Shang, R.; Fu, Y.; Li, J.-B.; Zhang, S.-L.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* 2009, *131*, 5738.

To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (1.65 g, 6.00 mmol, 2.00 equiv), sodium bicarbonate (594 mg, 6.00 mmol, 2.00 equiv), and ethyl 4-(tributylstannyl)benzoate⁹ (16) (1.32 g, 3.00 mmol, 1.00 equiv) in anhydrous THF (12.0 mL) at $-30\text{ }^{\circ}\text{C}$ was added trifluoromethyl trifluoromethanesulfonate (3) (2.6 g, 1.8 mL, 12 mmol, 4.0 equiv), and the suspension was stirred vigorously. The reaction mixture was stirred at $-30\text{ }^{\circ}\text{C}$ for 30 minutes, then a solution cooled to $-30\text{ }^{\circ}\text{C}$ of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (1.69 g, 3.60 mmol, 1.20 equiv) and silver hexafluorophosphate (1.52 mg, 6.00 mmol, 2.00 equiv) in dry acetone (36.0 mL) was added by cannula. The reaction mixture was stirred for 2 hours in the dark, then warmed to $23\text{ }^{\circ}\text{C}$. The reaction mixture was filtered through a pad of celite eluting with CH_2Cl_2 and the filtrate concentrated in vacuo at $5\text{ }^{\circ}\text{C}$. The residue was purified via column chromatography on silica gel eluting with pentane/ CH_2Cl_2 1:1 (v/v) to afford 563 mg of the title compound as a light yellow oil (80% yield).

$R_f = 0.89$ (pentane/ CH_2Cl_2 1:1 (v/v)). NMR Spectroscopy: ^1H NMR (400 MHz, CDCl_3 , $23\text{ }^{\circ}\text{C}$, δ): 8.09 (d, $J = 9.2$ Hz, 2H), 7.26 (d, $J = 9.2$ Hz, 2H), 4.39 (q, $J = 7.2$ Hz, 2H), 1.40 (t, $J = 6.8$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3 , $23\text{ }^{\circ}\text{C}$, δ): 165.6, 152.7 (q, $J = 2$ Hz), 131.6, 129.1, 120.5, 120.4 (q, $J = 257$ Hz), 61.4, 14.4. ^{19}F NMR (375 MHz, CDCl_3 , $23\text{ }^{\circ}\text{C}$, δ): -58.1 . These spectroscopic data correspond to previously reported data.¹¹



1-Methoxy-2-(trifluoromethoxy)benzene¹² (26)

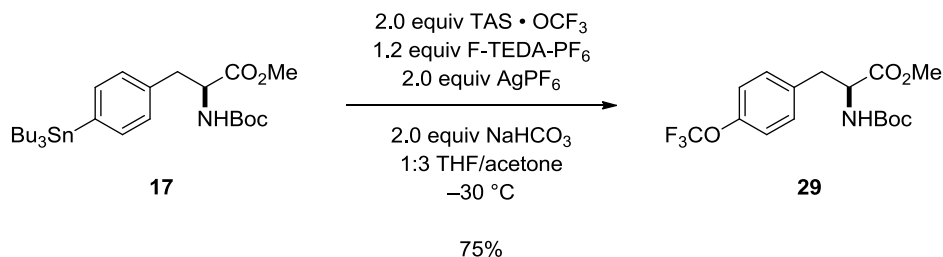
To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (275 mg, 1.00 mmol, 2.00 equiv), sodium bicarbonate (84.0 mg, 1.00 mmol, 2.00 equiv), and tributyl(2-methoxyphenyl)stannane¹³ (41) (199 mg, 0.500 mmol, 1.00 equiv) in anhydrous THF (2.00 mL) at $-30\text{ }^{\circ}\text{C}$ was added trifluoromethyl trifluoromethanesulfonate (3) (0.45 g, 0.30 mL, 2.1 mmol, 4.1 equiv), and the suspension was stirred vigorously. The reaction mixture was stirred at $-30\text{ }^{\circ}\text{C}$ for 30 minutes, then a solution cooled to $-30\text{ }^{\circ}\text{C}$ of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane

¹² Castagnetti, E.; Schlosser, M. *Chem. Eur. J.* 2002, **8**, 799.

¹³ Chun, J.-H.; Lu, S.; Lee, Y.-S.; Pike, V. W. *J. Org. Chem.* 2010, **75**, 3332.

bis(hexafluorophosphate) (2) (282 mg, 0.600 mmol, 1.20 equiv) and silver hexafluorophosphate (252 mg, 1.00 mmol, 2.00 equiv) in dry acetone (6.0 mL) was added by cannula. The reaction mixture was stirred for 2.5 hours in the dark, then warmed to 23 °C. The reaction mixture was filtered through a pad of celite eluting with CH₂Cl₂ and the filtrate concentrated in vacuo at 5 °C. The residue was purified via column chromatography on silica gel eluting with pentane/CH₂Cl₂ 9:1 (v/v) to afford 74 mg of the title compound as a clear oil (77% yield).

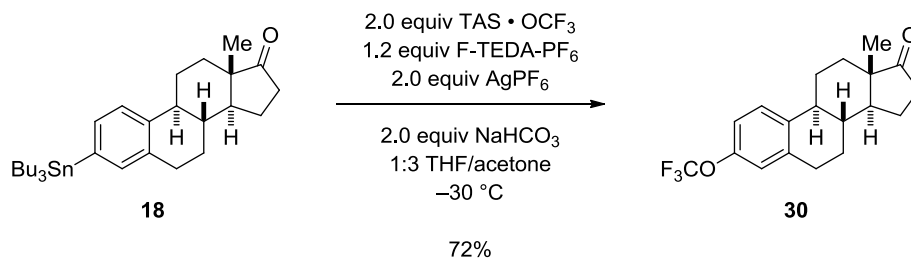
R_f = 0.57 (pentane/CH₂Cl₂ 9:1 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 7.24–7.23 (m, 2H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.93 (t, *J* = 7.8 Hz, 1H), 3.87 (s, 3H). ¹³C NMR (125 MHz, CDCl₃, 23 °C, δ): 152.2, 138.3 (q, *J* = 2 Hz), 128.0, 123.0, 120.8 (q, *J* = 257 Hz), 120.7, 113.1, 56.1. ¹⁹F NMR (470 MHz, CDCl₃, 23 °C, δ): –58.6. These spectroscopic data correspond to previously reported data.¹²



N-Boc-4-(trifluoromethoxy)-*L*-phenylalanine methyl ester (29)

To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (275 mg, 1.00 mmol, 2.00 equiv), sodium bicarbonate (84.0 mg, 1.00 mmol, 2.00 equiv), and *N*-Boc-4-(tributylstannyl)-*L*-phenylalanine methyl ester⁹ (17) (284 mg, 0.500 mmol, 1.00 equiv) in anhydrous THF (2.00 mL) at –30 °C was added trifluoromethyl trifluoromethanesulfonate (3) (0.45 g, 0.30 mL, 2.1 mmol, 4.1 equiv), and the suspension was stirred vigorously. The reaction mixture was stirred at –30 °C for 30 minutes, then a solution cooled to –30 °C of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (282 mg, 0.600 mmol, 1.20 equiv) and silver hexafluorophosphate (252 mg, 1.00 mmol, 2.00 equiv) in dry acetone (6.0 mL) was added by cannula. The reaction mixture was stirred for 2.5 hours in the dark, then warmed to 23 °C. The reaction mixture was filtered through a pad of celite eluting with CH₂Cl₂ and the filtrate concentrated in vacuo. The residue was purified via column chromatography on silica gel eluting with CH₂Cl₂ to afford 136 mg of the title compound as a white solid (75% yield).

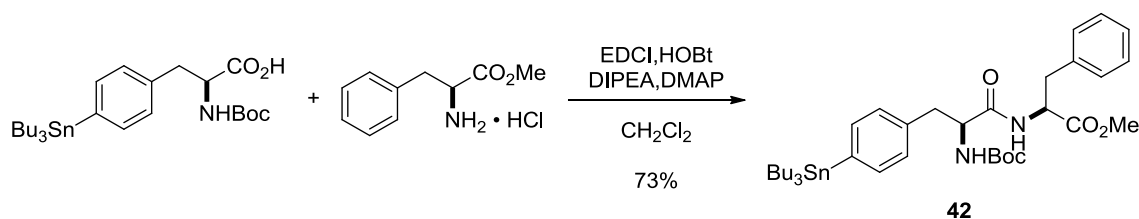
$R_f = 0.29$ (CH_2Cl_2). NMR Spectroscopy: ^1H NMR (500 MHz, CDCl_3 , 23 °C, δ): 7.17–7.12 (m, 4H), 4.99 (d, $J = 7.7$ Hz, 1H), 4.60–4.58 (m, 1H), 3.71 (s, 3H), 3.17–3.00 (m, 1H), 1.41 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3 , 23 °C, δ): 172.2, 155.1, 148.5, 135.0, 130.8, 121.1, 120.6 (q, $J = 255$ Hz), 80.2, 54.4, 52.5, 38.0, 28.4. ^{19}F NMR (470 MHz, CDCl_3 , 23 °C, δ): –58.3. Mass Spectrometry: HRMS-FIA (m/z): Calcd for $\text{C}_{16}\text{H}_{20}\text{F}_3\text{NO}_5\text{Na}$ $[\text{M} + \text{Na}]^+$, 386.1186. Found, 386.1190.



3-Deoxy-3-trifluoromethoxyestrone (30)

To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (275 mg, 1.00 mmol, 2.00 equiv), sodium bicarbonate (84.0 mg, 1.00 mmol, 2.00 equiv), and 3-deoxy-3-(tributylstannyl)estrone⁹ (**18**) (272 mg, 0.500 mmol, 1.00 equiv) in anhydrous THF (2.00 mL) at –30 °C was added trifluoromethyl trifluoromethanesulfonate (**3**) (0.45 g, 0.30 mL, 2.1 mmol, 4.1 equiv), and the suspension was stirred vigorously. The reaction mixture was stirred at –30 °C for 30 minutes, then a solution cooled to –30 °C of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (**2**) (282 mg, 0.600 mmol, 1.20 equiv) and silver hexafluorophosphate (252 mg, 1.00 mmol, 2.00 equiv) in dry acetone (6.0 mL) was added by cannula. The reaction mixture was stirred for 4 hours in the dark, then warmed to 23 °C. The reaction mixture was filtered through a pad of celite eluting with CH_2Cl_2 and the filtrate concentrated in vacuo. The residue was purified via column chromatography on silica gel eluting with CH_2Cl_2 to afford 122 mg of the title compound as a white solid (72% yield).

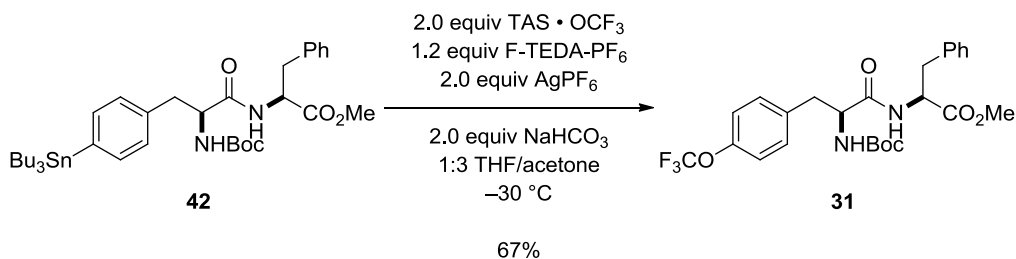
$R_f = 0.42$ (CH_2Cl_2). NMR Spectroscopy: ^1H NMR (500 MHz, CDCl_3 , 23 °C, δ): 7.29 (d, $J = 8.7$ Hz, 1H), 6.99 (d, $J = 8.7$ Hz, 1H), 6.94 (s, 1H), 2.92 (dd, $J = 8.5$ Hz, 3.5 Hz, 2H), 2.51 (dd, $J = 18.5$ Hz, 8.5 Hz, 1H), 2.42–2.39 (m, 1H), 2.30–2.26 (m, 1H), 2.19–2.11 (m, 1H), 2.09–2.02 (m, 2H), 1.99–1.96 (m, 1H), 1.66–1.44 (m, 6H), 0.92 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3 , 23 °C, δ): 220.7, 147.4 (q, $J = 2$ Hz), 138.6, 138.5, 126.8, 121.1, 120.5 (q, $J = 255$ Hz), 118.3, 50.5, 48.0, 44.2, 38.1, 35.9, 31.7, 29.5, 26.4, 25.9, 21.7, 13.9. ^{19}F NMR (375 MHz, CDCl_3 , 23 °C, δ): –58.2. Mass Spectrometry: HRMS-FIA (m/z): Calcd for $\text{C}_{20}\text{H}_{22}\text{F}_3\text{O}_2$ $[\text{M} + \text{H}]^+$, 339.1566. Found, 339.1565.



N-Boc-4-(tributylstannyl)-*L*-phenylalanyl-*L*-phenylalanine methyl ester⁹ (**42**)

To *N*-Boc-4-(tributylstannyl)-*L*-phenylalanine⁹ (422 mg, 0.742 mmol, 1.00 equiv) and *L*-phenylalanine methyl ester hydrochloride (160 mg, 0.742 mmol, 1.00 equiv) in CH₂Cl₂ (30 mL) at 0 °C was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (427 mg, 2.23 mmol, 3.00 equiv), 1-hydroxybenzotriazole (HOBt) (201 mg, 1.49 mmol, 2.00 equiv), *N,N*-diisopropylethylamine (288 mg, 388 μL, 2.23 mmol, 3.00 equiv) and 4-(dimethylamino)pyridine (9.1 mg, 0.074 mmol, 0.10 equiv). After stirring for 1 hr at 0 °C, the reaction mixture was warmed to 23 °C and further stirred for 12 hr. The reaction mixture was quenched with water (10 mL), and CH₂Cl₂ (5 mL) was added. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2 × 5 mL). The combined organic phases were washed with brine (5 mL) and dried (Na₂SO₄). The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc 3:1 (v/v), to afford 389 mg of the title compound as a colorless foam (73% yield).

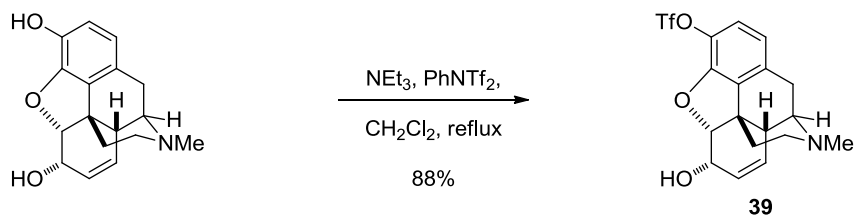
*R*_f = 0.30 (hexanes/EtOAc 3:1 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 7.39 (d, *J* = 7.3 Hz, 2H), 7.23–7.21 (m, 3H), 7.15 (d, *J* = 6.9 Hz, 2H), 6.97 (dd, *J* = 7.3 Hz, 1.8 Hz, 2H), 6.38 (d, *J* = 6.9 Hz, 1H), 4.90 (br s, 1H), 4.80 (br s, 1H), 4.35 (br s, 1H), 3.68 (s, 3H), 3.09–2.99 (m, 4H), 1.55–1.50 (m, 6H), 1.38 (s, 9H), 1.36–1.29 (m, 6H), 1.05–1.01 (m, 6H), 0.87 (t, *J* = 7.3 Hz, 9H). ¹³C NMR (125 MHz, CDCl₃, 23 °C, δ): 171.5, 171.0, 155.4, 140.4, 136.9, 136.2, 135.8, 129.3, 129.1, 129.0, 128.6, 127.2, 80.3, 55.6, 53.4, 52.4, 38.1, 29.1, 28.3, 27.5, 13.8, 9.7. These spectroscopic data correspond to previously reported data.⁹



N-Boc-4-(trifluoromethoxy)-*L*-phenylalanyl-*L*-phenylalanine methyl ester (**31**)

To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (273 mg, 0.992 mmol, 2.00 equiv), sodium bicarbonate (83.0 mg, 0.992 mmol, 2.00 equiv), and *N*-Boc-4-(tributylstannyl)-*L*-phenylalanyl-*L*-phenylalanine methyl ester⁹ (42) (355 mg, 0.496 mmol, 1.00 equiv) in anhydrous THF (2.00 mL) at $-30\text{ }^{\circ}\text{C}$ was added trifluoromethyl trifluoromethanesulfonate (3) (0.45 g, 0.30 mL, 2.1 mmol, 4.1 equiv), and the suspension was stirred vigorously. The reaction mixture was stirred at $-30\text{ }^{\circ}\text{C}$ for 30 minutes, then a solution cooled to $-30\text{ }^{\circ}\text{C}$ of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (282 mg, 0.600 mmol, 1.20 equiv) and silver hexafluorophosphate (252 mg, 1.00 mmol, 2.00 equiv) in dry acetone (6.0 mL) was added by cannula. The reaction mixture was stirred for 2 hours in the dark, then warmed to $23\text{ }^{\circ}\text{C}$. The reaction mixture was filtered through a pad of celite eluting with CH_2Cl_2 and the filtrate concentrated in vacuo. The residue was purified via column chromatography on silica gel eluting with hexanes/acetone 3:1 (v/v) to afford 170 mg of the title compound as a white solid (67% yield).

$R_f = 0.45$ (hexanes/acetone 3:1 (v/v)). NMR Spectroscopy: ^1H NMR (500 MHz, CDCl_3 , $23\text{ }^{\circ}\text{C}$, δ): 7.25–7.23 (m, 3H), 7.20 (d, $J = 8.3\text{ Hz}$, 1H), 7.12 (d, $J = 7.8\text{ Hz}$, 1H), 7.01 (dd, $J = 7.8\text{ Hz}$, 2.0 Hz, 1H), 6.26–6.24 (m, 1H), 4.93–4.91 (m, 1H), 4.78–4.77 (m, 1H), 4.32–4.31 (m, 1H), 3.69 (s, 3H), 3.12–2.99 (m, 5H), 1.40 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3 , $23\text{ }^{\circ}\text{C}$, δ): 171.5, 170.6, 155.4, 148.4, 135.6, 130.9, 129.3, 128.7, 127.3, 120.6 (q, $J = 255\text{ Hz}$), 121.2, 115.6, 80.5, 55.7, 53.3, 52.5, 38.0, 37.8, 28.3. ^{19}F NMR (375 MHz, CDCl_3 , $23\text{ }^{\circ}\text{C}$, δ): -58.3 . Mass Spectrometry: HRMS-FIA (m/z): Calcd for $\text{C}_{25}\text{H}_{30}\text{F}_3\text{N}_2\text{O}_6$ $[\text{M} + \text{H}]^+$, 511.2051. Found, 511.2040.



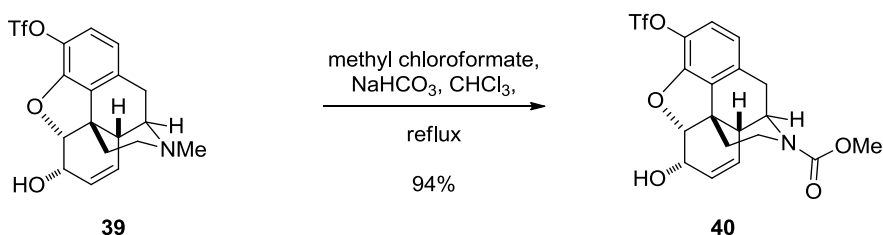
3-(Trifluoromethanesulfonyl)morphine¹⁴ (39)

To morphine (23.7 g, 83.1 mmol, 1.00 equiv) in CH_2Cl_2 (500 mL) was added *N*-phenyltriflimide (30.0 g, 84.0 mmol, 1.01 equiv) and triethylamine (24.8 g, 34.0 mL, 0.245 mol, 2.95 equiv). The reaction mixture was stirred at reflux for 10 hours. The reaction was cooled to $23\text{ }^{\circ}\text{C}$ and diluted with CH_2Cl_2 (250 mL). The organic phase was

¹⁴ Hedberg, M. H.; Johansson, A. M.; Nordvall, G.; Yliniemela, A.; Li, H. B.; Martin, A. R.; Hjorth, S.; Unelius, L.; Sundell, S.; Hacksell, U. *J. Med. Chem.* 1995, **38**, 647.

washed with NaHCO_3 (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×150 mL). The combined organic phases were washed with brine (500 mL) and dried with Na_2SO_4 . The filtrate was concentrated in vacuo and the resulting residue the residue was purified by chromatography on silica gel eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1 (v/v) to afford 30.5 g of the title compound as a light beige solid (88% yield).

$R_f = 0.53$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1 (v/v)). NMR Spectroscopy: ^1H NMR (500 MHz, CDCl_3 , 23 °C, δ): 6.89 (d, $J = 8.4$ Hz, 1H), 6.64 (d, $J = 8.4$ Hz, 1H), 5.72–5.69 (m, 1H), 5.30–5.26 (m, 1H), 5.02 (d, $J = 6.4$ Hz, 1H), 4.24–4.16 (m, 1H), 3.38 (dd, $J = 5.9$ Hz, 3.3 Hz, 1H), 3.08 (d, $J = 18.8$ Hz, 1H), 2.92–2.90 (m, 1H), 2.70 (t, $J = 2.6$ Hz, 1H), 2.61 (dd, $J = 13.2$, Hz, 4.6 Hz, 1H), 2.44 (s, 3H), 2.42–2.28 (m, 2H), 2.10 (dt, $J = 12.4$ Hz, 5.1 Hz, 1H), 1.90 (d, $J = 7.3$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3 , 23 °C, δ): 149.7, 135.8, 133.9, 130.8, 129.7, 128.3, 121.3, 120.4, 118.8 (q, $J = 323$ Hz), 93.7, 66.6, 58.7, 46.2, 43.5, 43.2, 40.6, 35.3, 21.1. ^{19}F NMR (375 MHz, CDCl_3 , 23 °C, δ): –73.4. These spectroscopic data correspond to previously reported data.¹⁴

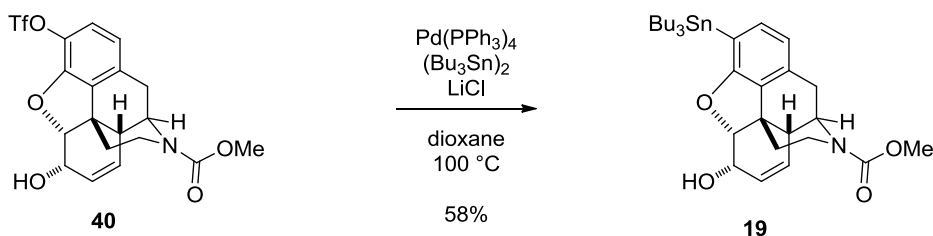


Methyl 3-(trifluoromethanesulfonyl)norfine-2-carboxylate (40)

To 3-(trifluoromethanesulfonyl)morphine¹⁴ (39) (4.50 g, 10.8 mmol, 1.00 equiv) in CHCl_3 (110 mL) was added NaHCO_3 (13.6 g, 0.162 mol, 15.0 equiv) and methyl chloroformate (17.4 g, 14.2 mL, 0.183 mol, 17.0 equiv). The reaction mixture was stirred at reflux for 18 h. The reaction was cooled to 23 °C and quenched with H_2O (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were washed with brine (100 mL) and dried with Na_2SO_4 . The filtrate was concentrated in vacuo and the resulting residue the residue was purified by chromatography on silica gel eluting with hexanes/ EtOAc 2:3 (v/v) to afford 4.67 g of the title compound as a pale yellow solid (94% yield).

$R_f = 0.29$ (hexanes/ EtOAc 2:3 (v/v)). NMR Spectroscopy: ^1H NMR (500 MHz, CDCl_3 , 23 °C, δ): 6.93 (d, $J = 8.3$ Hz, 1H), 6.65 (d, $J = 8.3$ Hz, 1H), 5.76 (d, $J = 9.2$ Hz, 1H), 5.31–5.28 (m, 1H), 5.02 (d, $J = 6.5$ Hz, 1H), 4.85–4.84 (m, 1H), 4.20–4.03 (m, 2H), 3.75 (s, 3H)*, 3.00–2.87 (m, 3H), 2.79 (d, $J = 19.0$ Hz, 1H), 2.57 (s, 1H), 2.00–1.91 (m,

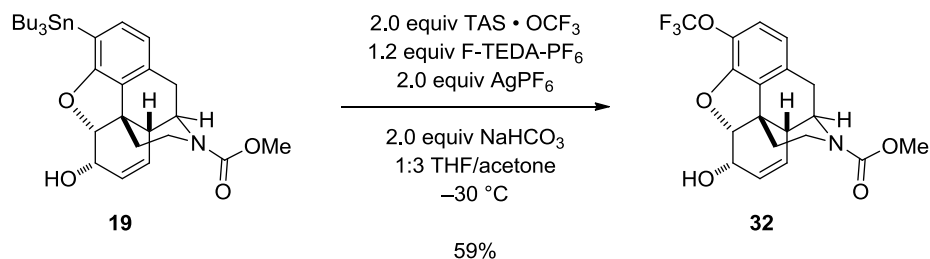
2H). ^{13}C NMR (125 MHz, CDCl_3 , 23 °C, δ): 149.8, 135.0, 134.7, 132.8, 131.0, 127.1, 126.9, 121.8, 120.4, 118.8 (q, $J = 320$ Hz), 93.5, 66.3, 53.0, 50.0, 43.9, 39.6*, 37.3, 35.1, 30.1*. ^{19}F NMR (470 MHz, CDCl_3 , 23 °C, δ): -73.4. Mass Spectrometry: HRMS-FIA (m/z): Calcd for $\text{C}_{19}\text{H}_{18}\text{F}_3\text{NO}_7\text{SnNa}$ $[\text{M} + \text{Na}]^+$, 484.0648. Found, 484.0664. *Two signals attributed to a mixture of rotamers



Methyl 3-deoxy-3-(tributylstannyl)normorphine-carboxylate (19)

To a suspension of lithium chloride (551 mg, 13.0 mmol, 3.00 equiv), hexabutyliditin (5.03 g, 4.38 mL, 8.67 mmol, 2.00 equiv), and methyl 3-(trifluoromethanesulfonyl)normorphine-carboxylate (40) (2.00 g, 4.33 mmol, 1.00 equiv) in anhydrous dioxane (40.0 mL) at 25 °C was added palladium tetrakis triphenylphosphine (250 mg, 0.217 mmol, 0.0500 equiv). The reaction mixture was heated and stirred at 105 °C for 24 hours, then cooled to room temperature. The reaction mixture was filtered through a pad of celite eluting with CH_2Cl_2 , and the filtrate concentrated in vacuo. The residue was purified via column chromatography on silica gel eluting with hexanes/EtOAc 1:1 (v/v) to afford 1.51 g of the title compound as a light yellow oil (58% yield).

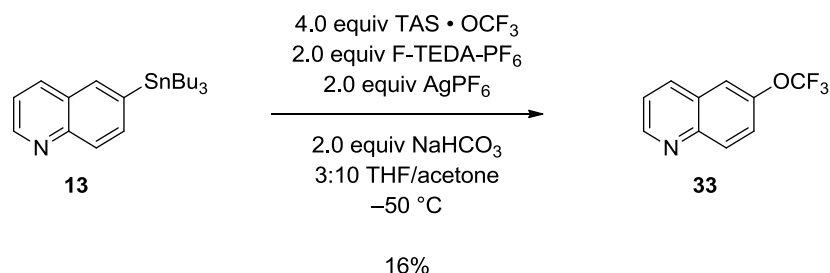
$R_f = 0.85$ (hexanes/EtOAc 2:3 (v/v)). NMR Spectroscopy: ^1H NMR (500 MHz, CDCl_3 , 23 °C, δ): 7.08 (d, $J = 7.3$ Hz, 1H), 6.62 (d, $J = 7.3$ Hz, 1H), 5.72 (d, $J = 9.2$ Hz, 1H), 5.32–5.26 (m, 1H), 4.96 (s (rotamers), 1H), 4.76 (dd, $J = 6.6$ Hz, 1.1 Hz, 1H), 4.18–4.11 (m, 1H), 4.00 (dd, $J = 13.5$ Hz, 4.0 Hz, 1H), 3.73 (s, 3H)*, 3.06–2.69 (m, 4H), 2.53 (s, 1H), 1.96–1.85 (m, 2H), 1.61–1.42 (m, 6H), 1.37–1.24 (m, 6H), 1.15–0.98 (m, 6H), 0.88 (t, $J = 5.3$ Hz, 9H). ^{13}C NMR (100 MHz, CDCl_3 , 23 °C, δ): 165.3, 155.9, 136.2, 134.6, 134.4, 127.3, 126.3, 119.6, 116.4, 89.3, 66.6, 52.9, 50.3, 42.8, 40.1*, 37.6, 35.7, 30.2*, 29.3, 27.4, 13.8, 9.8. Mass Spectrometry: HRMS-FIA (m/z): Calcd for $\text{C}_{30}\text{H}_{45}\text{NO}_4\text{SnNa}$ $[\text{M} + \text{Na}]^+$, 626.2262. Found, 626.2251. *Two signals attributed to a mixture of rotamers



Methyl 3-deoxy-3-(trifluoromethoxy)normorphine-carboxylate (32)

To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (497 mg, 1.80 mmol, 2.00 equiv), and sodium bicarbonate (151 mg, 1.80 mmol, 2.00 equiv) in anhydrous THF (3.60 mL) at -30 °C was added trifluoromethyl trifluoromethanesulfonate (3) (786 mg, 524 μL , 3.6 mmol, 4.0 equiv), and the suspension was stirred vigorously. The reaction mixture was stirred at -30 °C for 30 minutes, then a solution cooled to -30 °C of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (509 mg, 1.08 mmol, 1.20 equiv) and silver hexafluorophosphate (456 mg, 1.80 mmol, 2.00 equiv) in dry acetone (8.0 mL) was added by cannula. Immediately afterwards, a solution of methyl 3-deoxy-3-tributylstannyl-normorphine-carboxylate (19) (543 mg, 0.901 mmol, 1.00 equiv) in dry acetone (2.8 mL) is added dropwise. The reaction mixture was stirred for 4 hours in the dark, then warmed to 23 °C. The reaction mixture was filtered through a pad of celite eluting with CH_2Cl_2 and the filtrate concentrated in vacuo. The residue was purified via column chromatography on silica gel eluting with hexanes/acetone 3:1 (v/v) to afford 212 mg of the title compound as a white foam (59% yield).

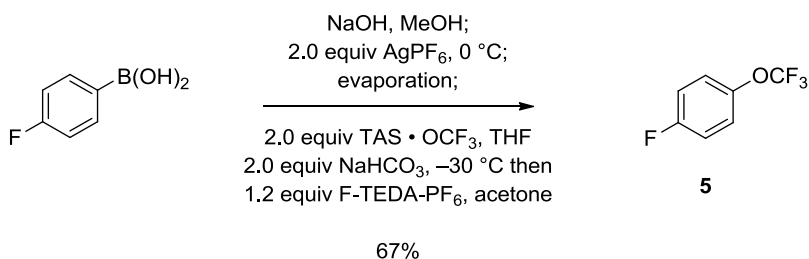
R_f = 0.24 (hexanes/acetone 3:1 (v/v)). NMR Spectroscopy: ^1H NMR (500 MHz, CDCl_3 , 23 °C, δ): 6.94 (d, J = 8.3 Hz, 1H), 6.62 (d, J = 8.3 Hz, 1H), 5.75 (d, J = 8.8 Hz, 1H), 5.31–5.26 (m, 1H), 4.98–4.82 (m, 2H), 4.19–4.02 (m, 2H), 3.73 (s, 3H), 3.02–2.76 (m, 3H), 2.55 (s, 1H), 2.00–1.90 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3 , 23 °C, δ): 155.9, 150.2, 134.4, 133.2, 131.8, 130.5, 127.2, 123.1, 120.8 (q, J = 257 Hz), 120.5, 92.4, 66.2, 53.0, 50.0, 43.6, 39.5*, 37.4, 35.3, 29.9*. ^{19}F NMR (375 MHz, CDCl_3 , 23 °C, δ): -59.2. Mass Spectrometry: HRMS-FIA (m/z): Calcd for $\text{C}_{19}\text{H}_{19}\text{F}_3\text{NO}_5$ $[\text{M} + \text{H}]^+$, 398.1210. Found, 398.1212. *Two signals attributed to a mixture of rotamers



6-(Trifluoromethoxy)quinoline (33)

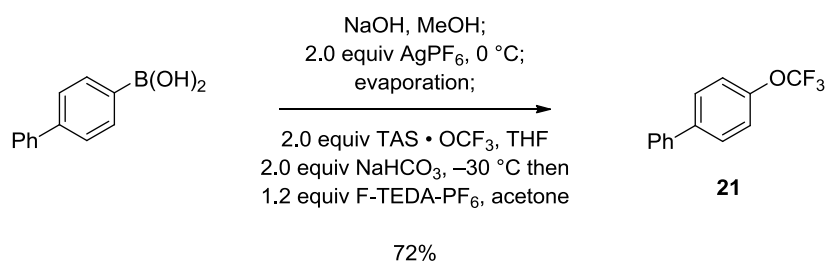
To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (511 mg, 2.00 mmol, 4.00 equiv), and sodium bicarbonate (84.0 mg, 1.00 mmol, 2.00 equiv) in anhydrous THF (2.00 mL) at $-50 \text{ }^\circ\text{C}$ was added trifluoromethyl trifluoromethanesulfonate (3) (600 mg, 400 μL , 2.8 mmol, 5.5 equiv), and the suspension was stirred vigorously. The reaction mixture was stirred at $-50 \text{ }^\circ\text{C}$ for 30 minutes, then a solution of silver hexafluorophosphate (253 mg, 1.00 mmol, 2.00 equiv) in dry acetone (1.25 mL) was added dropwise concurrently as a separate solution of 6-(tributylstannyl)quinoline³ (13) (209 mg, 0.500 mmol, 1.00 equiv) in dry acetone (1.75 mL) was added dropwise at $-50 \text{ }^\circ\text{C}$. A solution of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (471 mg, 1.00 mmol, 2.00 equiv) in dry acetone (3 mL) was then slowly added dropwise over 5 minutes at $-50 \text{ }^\circ\text{C}$. The reaction mixture was stirred for 3 hours in the dark, then warmed to $23 \text{ }^\circ\text{C}$. The reaction mixture was filtered through a pad of celite eluting with CH_2Cl_2 and the filtrate concentrated in vacuo. The residue was purified via column chromatography on silica gel eluting with hexanes/acetone 3:1 (v/v) to afford 15.0 mg of the title compound as a clear oil (14% yield). The experiment was repeated to give 16% yield.

$R_f = 0.40$ (hexanes/acetone 3:1 (v/v)). NMR Spectroscopy: ^1H NMR (400 MHz, CDCl_3 , $23 \text{ }^\circ\text{C}$, δ): 8.96 (d, $J = 2.7 \text{ Hz}$, 1H), 8.19–8.16 (m, 2H), 7.66 (s, 1H), 7.59 (d, $J = 9.2 \text{ Hz}$, 1H), 7.48 (dd, $J = 8.2 \text{ Hz}$, 4.1 Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3 , $23 \text{ }^\circ\text{C}$, δ): 150.8, 147.2, 146.4, 136.3, 131.8, 128.6, 123.9, 122.2, 117.9. The OCF_3 carbon was not observed in the ^{13}C NMR due to insufficient quantity of the product. ^{19}F NMR (375 MHz, CDCl_3 , $23 \text{ }^\circ\text{C}$, δ): -58.2 . Mass Spectrometry: HRMS-FIA (m/z): Calcd for $\text{C}_{10}\text{H}_7\text{F}_3\text{NO}$ $[\text{M} + \text{H}]^+$, 214.0481. Found, 214.0480.



1-Fluoro-4-(trifluoromethoxy)benzene (5)

To a solution of sodium hydroxide in anhydrous methanol (1.00 N, 0.500 mL, 1.00 equiv) at 23 °C was added 4-fluorophenylboronic acid (34) (86.0 mg, 0.500 mmol, 1.00 equiv) and stirred for 15 minutes. The reaction mixture was then cooled to 0 °C and silver hexafluorophosphate (252 mg, 1.00 mmol, 2.00 equiv) was added and the suspension was stirred for 30 minutes at 0 °C. The solvent was removed under reduced pressure at 0 °C, and the residual methanol was removed under reduced pressure by co-evaporation with anhydrous THF (2 × 0.500 mL). To the residue was added anhydrous THF (2.0 mL) and then tris(dimethylamino)sulfonium difluorotrimethylsilicate (276 mg, 1.00 mmol, 2.00 equiv) and sodium bicarbonate (84.0 mg, 1.00 mmol, 2.00 equiv) successively. The reaction was cooled to -30 °C and to the suspension was added trifluoromethyl trifluoromethanesulfonate (3) (0.60 g, 0.40 mL, 2.8 mmol, 5.5 equiv) and the suspension was then stirred at -30 °C for 30 minutes. A solution of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (282 mg, 0.600 mmol, 1.20 equiv.) in dry acetone (6.0 mL) was added. The suspension was stirred for 1 hour and 3-nitrofluorobenzene (20.0 μL, 0.188 mmol) was added to the reaction mixture. The yield (67 %) was determined by comparing integration of the peak of 1-fluoro-4-(trifluoromethoxy)benzene (-117.0 ppm) with that of 3-nitrofluorobenzene (-112.0 ppm).

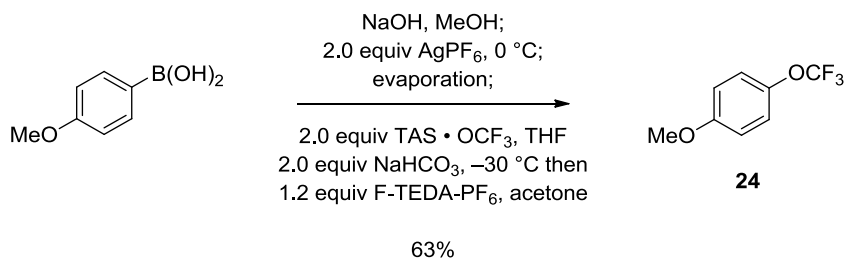


4-(Trifluoromethoxy)biphenyl⁸ (21)

To a solution of sodium hydroxide in anhydrous methanol (1.00 N, 0.500 mL, 1.00 equiv) at 23 °C was added biphenyl boronic acid (99.0 mg, 0.500 mmol, 1.00 equiv) and stirred for 15 minutes. The reaction mixture was then cooled to 0 °C and silver hexafluorophosphate (252 mg, 1.00 mmol, 2.00 equiv) was added and the suspension was

stirred for 30 minutes at 0 °C. The solvent was removed under reduced pressure at 0 °C, and the residual methanol was removed under reduced pressure by co-evaporation with anhydrous THF (2 × 0.500 mL). To the residue was added anhydrous THF (2.0 mL) and then tris(dimethylamino)sulfonium difluorotrimethylsilicate (276 mg, 1.00 mmol, 2.00 equiv) and sodium bicarbonate (84.0 mg, 1.00 mmol, 2.00 equiv) successively. The reaction was cooled to –30 °C and to the suspension was added trifluoromethyl trifluoromethanesulfonate (3) (0.60 g, 0.40 mL, 2.8 mmol, 5.5 equiv) and the suspension was then stirred at –30 °C for 30 minutes. A solution of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (282 mg, 0.600 mmol, 1.20 equiv.) in dry acetone (6.0 mL) was added. The suspension was stirred for 1 hour and then filtered through a pad of celite eluting with CH₂Cl₂ and the filtrate concentrated in vacuo. The residue was purified via column chromatography on silica gel eluting with pentane/CH₂Cl₂ 20:1 (v/v) to afford 86.2 mg of the title compound as a white solid (72% yield).

R_f = 0.53 (hexanes/CH₂Cl₂ 19:1 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 7.64–7.59 (m, 4H), 7.51–7.48 (m, 2 H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃, 23 °C, δ): 148.8 (q, *J* = 2 Hz), 140.1, 140.0, 129.0, 128.6, 127.8, 127.3, 121.4, 120.7 (q, *J* = 256 Hz). ¹⁹F NMR (375 MHz, CDCl₃, 23 °C, δ): –58.2. These spectroscopic data correspond to previously reported data.⁸

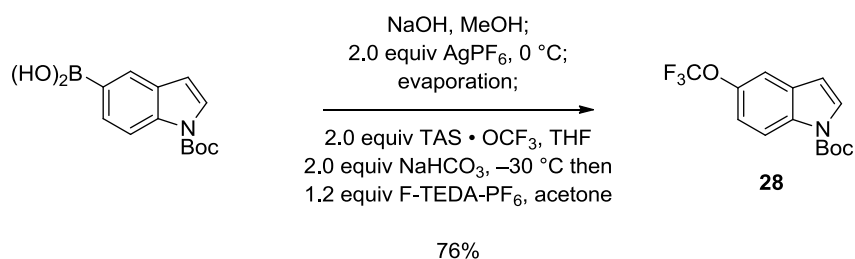


1-Methoxy-4-(trifluoromethoxy)benzene (24)

To a solution of sodium hydroxide in anhydrous methanol (1.00 N, 0.500 mL, 1.00 equiv) at 23 °C was added 4-methoxyphenylboronic acid (76.0 mg, 0.500 mmol, 1.00 equiv) and stirred for 15 minutes. The reaction mixture was then cooled to 0 °C and silver hexafluorophosphate (252 mg, 1.00 mmol, 2.00 equiv) was added and the suspension was stirred for 30 minutes at 0 °C. The solvent was removed under reduced pressure at 0 °C, and the residual methanol was removed under reduced pressure by co-evaporation with anhydrous THF (2 × 0.500 mL). To the residue was added anhydrous THF (2.0 mL) and then tris(dimethylamino)sulfonium difluorotrimethylsilicate (276 mg, 1.00 mmol, 2.00 equiv) and sodium bicarbonate (84.0 mg, 1.00 mmol, 2.00 equiv) successively. The

reaction was cooled to $-30\text{ }^{\circ}\text{C}$ and to the suspension was added trifluoromethyl trifluoromethanesulfonate (3) (0.60 g, 0.40 mL, 2.8 mmol, 5.5 equiv) and the suspension was then stirred at $-30\text{ }^{\circ}\text{C}$ for 30 minutes. A solution of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (282 mg, 0.600 mmol, 1.20 equiv.) in dry acetone (6.0 mL) was added. The suspension was stirred for 1 hour and then filtered through a pad of celite eluting with CH_2Cl_2 and the filtrate concentrated in vacuo. The residue was purified via column chromatography on silica gel eluting with pentane/ Et_2O 5:1 (v/v) to afford 60.5 mg of the title compound as a pale yellow oil (63% yield).

$R_f = 0.48$ (pentane/ CH_2Cl_2 9:1 (v/v)). NMR Spectroscopy: ^1H NMR (500 MHz, CDCl_3 , $23\text{ }^{\circ}\text{C}$, δ): 7.15 (d, $J = 8.5$ Hz, 2H), 6.89 (d, $J = 9.0$ Hz, 2H), 3.81 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3 , $23\text{ }^{\circ}\text{C}$, δ): 158.3, 142.9 (q, $J = 2$ Hz), 122.6, 120.8 (q, $J = 254$ Hz), 114.8, 55.7. ^{19}F NMR (470 MHz, CDCl_3 , $23\text{ }^{\circ}\text{C}$, δ): -58.9 . These spectroscopic data correspond to those obtained from an authentic sample purchased from Strem.

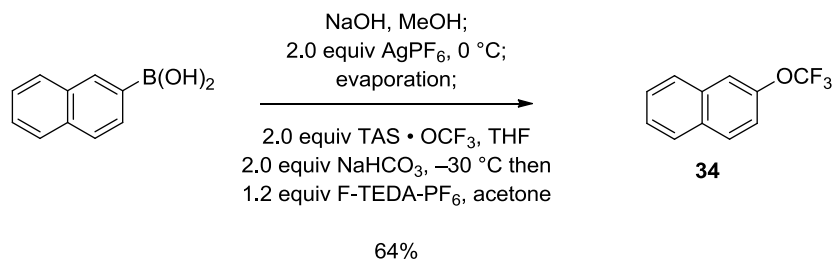


5-Trifluoromethoxy-*N*-Boc-indole (28)

To a solution of sodium hydroxide in anhydrous methanol (1.00 N, 0.500 mL, 1.00 equiv) at $23\text{ }^{\circ}\text{C}$ was added *N*-Boc-indol-5-ylboronic acid (130.5 mg, 0.500 mmol, 1.00 equiv) and stirred for 15 minutes. The reaction mixture was then cooled to $0\text{ }^{\circ}\text{C}$ and silver hexafluorophosphate (252 mg, 1.00 mmol, 2.00 equiv) was added and the suspension was stirred for 30 minutes at $0\text{ }^{\circ}\text{C}$. The solvent was removed under reduced pressure at $0\text{ }^{\circ}\text{C}$, and the residual methanol was removed under reduced pressure by co-evaporation with anhydrous THF (2×0.500 mL). To the residue was added anhydrous THF (2.0 mL) and then tris(dimethylamino)sulfonium difluorotrimethylsilicate (276 mg, 1.00 mmol, 2.00 equiv) and sodium bicarbonate (84.0 mg, 1.00 mmol, 2.00 equiv) successively. The reaction was cooled to $-30\text{ }^{\circ}\text{C}$ and to the suspension was added trifluoromethyl trifluoromethanesulfonate (3) (0.60 g, 0.40 mL, 2.8 mmol, 5.5 equiv) and the suspension was then stirred at $-30\text{ }^{\circ}\text{C}$ for 30 minutes. A solution of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (282 mg, 0.600 mmol, 1.20

equiv.) in dry acetone (6.0 mL) was added. The suspension was stirred for 1 hour and then filtered through a pad of celite eluting with CH₂Cl₂ and the filtrate concentrated in vacuo. The residue was purified via column chromatography on silica gel eluting with pentane/CH₂Cl₂ 10:1 (v/v) to afford 114 mg of the title compound as a pale yellow oil (76% yield).

R_f = 0.70 (hexanes/CH₂Cl₂ 1:1 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 8.17 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 3.4 Hz, 1H), 7.42 (s, 1H), 7.18 (d, *J* = 7.3 Hz, 1H), 6.57 (d, *J* = 3.4 Hz, 1H), 1.68 (s, 9H). ¹³C NMR (125 MHz, CDCl₃, 23 °C, δ): 149.4, 145.0 (q, *J* = 2 Hz), 133.6, 131.3, 127.8, 123.9 (q, *J* = 256 Hz), 117.8, 116.1, 113.4, 107.2, 84.3, 28.3. ¹⁹F NMR (375 MHz, CDCl₃, 23 °C, δ): -58.5. Mass Spectrometry: HRMS-FIA (*m/z*): Calcd for C₉H₇F₃NO [M - C₅H₉O₂ (Boc) + H]⁺, 202.0480. Found, 202.0485.



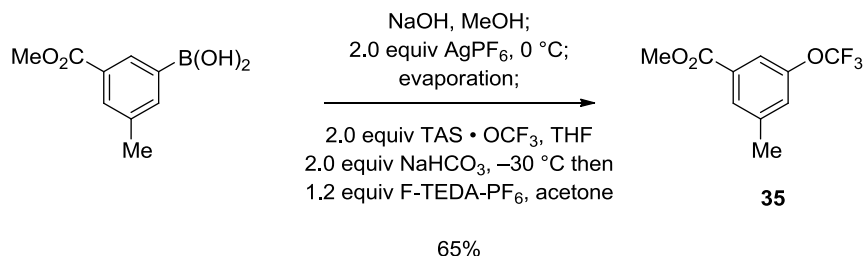
2-(Trifluoromethoxy)naphthalene¹⁵ (34)

To a solution of sodium hydroxide in anhydrous methanol (1.00 N, 0.500 mL, 1.00 equiv) at 23 °C was added 2-naphthylboronic acid (30) (86.0 mg, 0.500 mmol, 1.00 equiv) and stirred for 15 minutes. The reaction mixture was then cooled to 0 °C and silver hexafluorophosphate (252 mg, 1.00 mmol, 2.00 equiv) was added and the suspension was stirred for 30 minutes at 0 °C. The solvent was removed under reduced pressure at 0 °C, and the residual methanol was removed under reduced pressure by co-evaporation with anhydrous THF (2 × 0.500 mL). To the residue was added anhydrous THF (2.0 mL) and then tris(dimethylamino)sulfonium difluorotrimethylsilicate (276 mg, 1.00 mmol, 2.00 equiv) and sodium bicarbonate (84.0 mg, 1.00 mmol, 2.00 equiv) successively. The reaction was cooled to -30 °C and to the suspension was added trifluoromethyl trifluoromethanesulfonate (3) (0.60 g, 0.40 mL, 2.8 mmol, 5.5 equiv) and the suspension was then stirred at -30 °C for 30 minutes. A solution of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (282 mg, 0.600 mmol, 1.20 equiv.) in dry acetone (6.0 mL) was added. The suspension was stirred for 1 hour and then filtered through a pad of

¹⁵ Schlosser, M.; Castagnetti, E. *Eur. J. Org. Chem.* 2001, 3991.

celite eluting with CH₂Cl₂ and the filtrate concentrated in vacuo. The residue was purified via column chromatography on silica gel eluting with pentane/CH₂Cl₂ 9:1 (v/v) to afford 68.2 mg of the title compound as a pale yellow oil (64% yield).

R_f = 0.75 (pentane/CH₂Cl₂ 9:1 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 7.89–7.83 (m, 3H), 7.68 (s, 1H), 7.56–7.52 (m, 2H), 7.35 (d, *J* = 7.3 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃, 23 °C, δ): 147.0 (q, *J* = 2 Hz), 133.7, 131.9, 130.2, 127.9, 127.2, 126.5, 120.8 (q, *J* = 258 Hz), 120.3, 118.3.* ¹⁹F NMR (375 MHz, CDCl₃, 23 °C, δ): –59.2. These spectroscopic data correspond to previously reported data.¹⁵ *Only 9 aromatic carbon signals observed due to overlap of two carbon signals



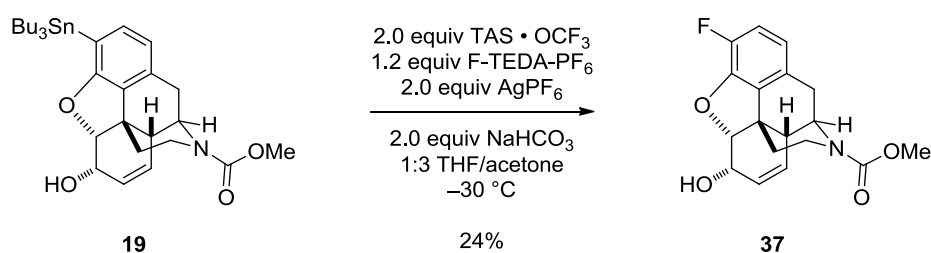
Methyl 3-methyl-5-(trifluoromethoxy)benzoate (35)

To a solution of sodium hydroxide in anhydrous methanol (1.00 N, 0.500 mL, 1.00 equiv) at 23 °C was added 3-methoxycarbonyl-5-methylphenylboronic acid (32) (97.0 mg, 0.500 mmol, 1.00 equiv) and stirred for 15 minutes. The reaction mixture was then cooled to 0 °C and silver hexafluorophosphate (252 mg, 1.00 mmol, 2.00 equiv) was added and the suspension was stirred for 30 minutes at 0 °C. The solvent was removed under reduced pressure at 0 °C, and the residual methanol was removed under reduced pressure by co-evaporation with anhydrous THF (2 × 0.500 mL). To the residue was added anhydrous THF (2.0 mL) and then tris(dimethylamino)sulfonium difluorotrimethylsilicate (276 mg, 1.00 mmol, 2.00 equiv) and sodium bicarbonate (84.0 mg, 1.00 mmol, 2.00 equiv) successively. The reaction was cooled to –30 °C and to the suspension was added trifluoromethyl trifluoromethanesulfonate (3) (0.60 g, 0.40 mL, 2.8 mmol, 5.5 equiv) and the suspension was then stirred at –30 °C for 30 minutes. A solution of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (282 mg, 0.600 mmol, 1.20 equiv.) in dry acetone (6.0 mL) was added. The suspension was stirred for 1 hour and then filtered through a pad of celite eluting with CH₂Cl₂ and the filtrate concentrated in vacuo. The residue was

purified via column chromatography on silica gel eluting with pentane/CH₂Cl₂ 4:1 (v/v) to afford 75.6 mg of the title compound as a colorless oil (65% yield).

R_f = 0.57 (pentane/CH₂Cl₂ 3:1 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 7.80 (s, 1H), 7.69 (s, 1H), 7.22 (s, 1H), 3.93 (s, 3H), 2.43 (s, 3H). ¹³C NMR (125 MHz, CDCl₃, 23 °C, δ): 166.1, 149.3 (q, J = 2 Hz), 140.6, 131.9, 128.8, 126.2, 120.6 (q, J = 258 Hz), 119.3, 52.6, 21.4. ¹⁹F NMR (470 MHz, CDCl₃, 23 °C, δ): -59.4. Mass Spectrometry: HRMS-FIA (m/z): Calcd for C₁₀H₉F₃O₃ [M + H]⁺, 235.0577. Found, 235.0590.

4.2. Synthesis of 3-deoxy-3-fluoromorphine

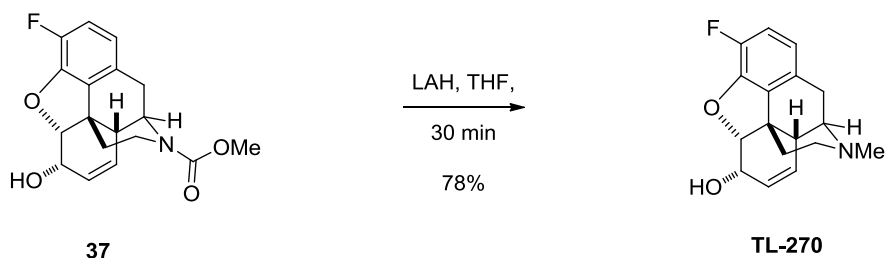


Methyl 3-deoxy-3-fluoro-normorphine-carboxylate (37)

To a suspension of tris(dimethylamino)sulfonium difluorotrimethylsilicate (551 mg, 2.00 mmol, 4.00 equiv), and sodium bicarbonate (84.0 mg, 1.80 mmol, 2.00 equiv) in anhydrous THF (2.00 mL) at -30 °C was added trifluoromethyl trifluoromethanesulfonate (3) (763 mg, 510 μ L, 3.5 mmol, 7.0 equiv), and the suspension was stirred vigorously. The reaction mixture was stirred at -50 °C for 30 minutes, then a solution cooled to -50 °C of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (2) (282 mg, 0.600 mmol, 1.20 equiv) and silver hexafluorophosphate (253 mg, 1.00 mmol, 2.00 equiv) in dry acetone (4.00 mL) was added by cannula. Immediately afterwards, a solution of methyl 3-deoxy-3-tributylstannyl-normorphine-carboxylate (19) (301 mg, 0.500 mmol, 1.00 equiv) in dry acetone (2.00 mL) is added dropwise. The reaction mixture was stirred for 4 hours in the dark, then warmed to 23 °C. The reaction mixture was filtered through a pad of celite eluting with CH₂Cl₂ and the filtrate concentrated in vacuo. The residue was purified via column chromatography on silica gel eluting with hexanes/acetone 3:1 (v/v) and then by prepTLC with EtOAc/hexanes 3:2 (v/v) as the eluent to afford 39.0 mg of the title compound as a clear foam (24% yield).

R_f = 0.29 (EtOAc/hex 3:2 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 6.83 (dd, J = 2.3 Hz, 9.5 Hz, 1H), 6.56 (dd, J = 5.5 Hz, 11.5 Hz, 1H), 5.77 (d, J = 8.5 Hz, 1H), 5.33–5.27 (m, 1H), 4.98–4.82 (m, 2H),

4.22–4.00 (m, 3H), 3.75 (s, 3H),* 3.03–2.73 (m, 3H), 2.55 (s, 1H), 1.99–1.90 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3 , 23 °C, δ): 155.6, 145.6 (d, $J = 244$ Hz), 134.4, 134.2, 131.9, 129.1, 127.0 (d, $J = 19.8$ Hz), 120.3, 116.6 (d, $J = 18.3$ Hz), 92.2, 66.1, 52.9, 50.2, 43.6, 39.6,* 37.3, 34.6, 29.6*. ^{19}F NMR (280 MHz, CDCl_3 , 23 °C, δ): –139.2. Mass Spectrometry: HRMS-FIA (m/z): Calcd for $\text{C}_{18}\text{H}_{18}\text{FNO}_4$ $[\text{M} + \text{H}]^+$, 332.1292. Found, 332.1286. *Two signals attributed to a mixture of rotamers



3-Deoxy-3-fluoromorphine (TL-270)

To methyl 3-deoxy-3-fluoro-normorphine-carboxylate (**37**) (34.5 mg, 0.104 mmol, 1.00 equiv) in THF (0.5 mL) is added lithium aluminum hydride (1.0 M solution in THF) (520 μL , 0.521 mmol, 5.00 equiv). The reaction mixture is stirred for 30 min at 23 °C. The reaction is quenched with 1.0 M solution of Rochelle's salt. The resulting solution is diluted with Et_2O (2 mL) and stirred vigorously overnight. The aqueous layer is extracted with Et_2O (10×1 mL), washed with brine (5 mL), dried (Na_2SO_4), and the filtrate is concentrated in vacuo. The resulting residue is purified by chromatography on silica gel eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1 (v/v) to afford 23.4 mg of the title compound as a white solid (78% yield).

$R_f = 0.05$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1 (v/v)). NMR Spectroscopy: ^1H NMR (500 MHz, CDCl_3 , 23 °C, δ): 6.81 (dd, $J = 8.5$ Hz, 5.35 Hz, 1H), 6.55 (dd, $J = 3.5$ Hz, 3.8 Hz, 1H), 5.71 (dd, $J = 1.5$ Hz, 5.0 Hz, 1H), 5.30–5.28 (m, 1H), 4.95 (d, $J = 6.0$ Hz, 1H), 4.21–4.20 (m, 1H), 3.37 (dd, $J = 3.0$ Hz, 2.8 Hz, 1H), 3.07 (d, $J = 18.5$ Hz, 1H), 2.68 (s, 1H), 2.62 (dd, $J = 4.5$ Hz, 6.0 Hz, 1H), 2.43 (s, 3H), 2.40 (dt, $J = 3.5$ Hz, 12.3 Hz, 6.1 Hz, 1H), 2.31 (dd, $J = 5.5$ Hz, 9.3 Hz, 1H), 2.11 (dt, $J = 5.0$ Hz, 12.4 Hz, 6.1 Hz, 1H), 1.89–1.87 (m, 1H). ^{13}C NMR (125 MHz, CDCl_3 , 23 °C, δ): 146.4 (d, $J = 244$ Hz), 144.3 (d, $J = 10.1$ Hz), 133.26, 133.1 (d, $J = 2.75$ Hz), 130.3, 128.4, 119.8 (d, $J = 4.58$ Hz), 115.97 (d, $J = 17.4$ Hz), 92.4, 66.4, 58.7, 46.2, 43.2, 43.0, 40.7, 35.6, 20.6. ^{19}F NMR (280 MHz, CDCl_3 , 23 °C, δ): –139.8. Mass Spectrometry: HRMS-FIA (m/z): Calcd for $[\text{C}_{17}\text{H}_{18}\text{FNO}_2 + \text{H}]^+$, 288.1394. Found, 288.1396.