On the Development of Pseudoephenamine and Its Applications in Asymmetric Synthesis

A dissertation presented

by

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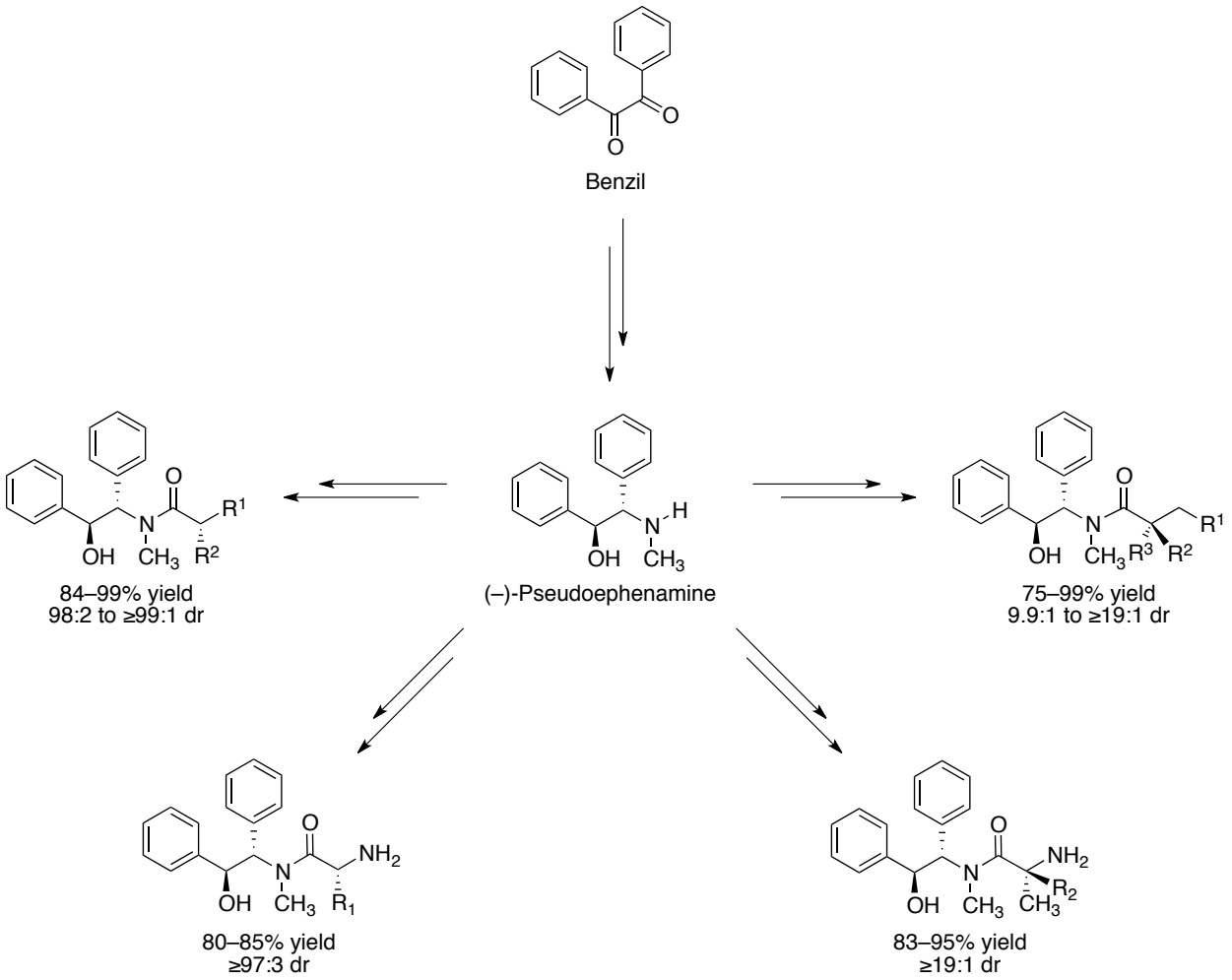
Abstract

Pseudoephedrine is well established as a chiral auxiliary in the alkylation of amide enolates to form tertiary and quaternary carbon stereocenters. However, due to its facile transformation into the illegal narcotic methamphetamine, pseudoephedrine is either illegal or highly regulated in many countries, which limits its use in academic and industrial settings. To address this issue, pseudoephenamine has been developed as a replacement for pseudoephedrine in organic synthesis. This new auxiliary suffers no regulatory issues and exhibits several practical advantages over pseudoephedrine, including the high diastereoselectivities observed in alkylation reactions forming quaternary carbon stereocenters, the propensity for pseudoephenamine amides to be free-flowing crystalline solids, and the sharp, well-defined peaks that typically compose the ^{1}H NMR spectra of these amides.

This thesis details the development of pseudoephenamine, including its application to the synthesis of several chiral building blocks bearing tertiary and quaternary carbon stereocenters. In addition, the use of pseudoephenamine to direct the alkylative construction of α-methyl α-amino acids is described. Finally, a simple, scalable synthesis of pseudoephenamine is reported which enables the production of this auxiliary from inexpensive starting materials on large scale.


Benzil
(–)-Pseudoephenamine
84–99% yield
98:2 to ≥99:1 dr
75–99% yield
9.9:1 to ≥19:1 dr
80–85% yield
≥97:3 dr
83–95% yield
≥19:1 dr

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For my family.

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First and foremost, I would like to thank my thesis advisor, Andy Myers, whose guidance and patience has enabled me to complete this journey. I have learned a great deal from Andy about the proper way to conduct research in synthetic organic chemistry, and I will keep those lessons with me as I move forward. I must also pay special thanks to Dave Evans, whose candor and advice in committee meetings and private communications has exceeded expectations. Similarly, Alan Saghatelian has been a valued confidant and friend whose willingness to extend a helping hand has been very much appreciated. I would also like to thank Tobias Ritter for his helpful discussions in committee meetings.

Through all of its permutations, the Myers group has remained a wonderful place to conduct research. In roughly chronological order: I would like to thank Jason Brubaker for giving me a crash course in proper laboratory techniques, including my first (and only) lesson in column chromatography. Miriam Quintal helped me find my feet in the Myers lab and was of great assistance as I started on my first project. Peter Wright and I joined the Myers group on the same day, and he was an excellent colleague and friend throughout our tenure together. I thank Dave Kummer for teaching me both how to titrate *n*-butyllithium underwater and how to monopolize rotovaps in a time of crisis. On a related note, I must thank Alec Flyer for teaching me how to deal with Dave Kummer and for his lessons on pronunciation. I would be remiss if I didn't acknowledge Landy Blasdel and Jakub Švenda for their friendship and good spirits during their time in lab. DongEun Lee was a remarkably kind baymate who put up with my (many) neuroses for far too long. Similarly, Herschel Mukherjee's willingness to listen to my rants and to read a portion of this thesis was very much appreciated. Marvin Morales was a very helpful project partner, and none of the work that follows would be possible without him. Tommy Magauer was

and continues to be a great friend who is irrevocably linked to many of my best memories from grad school. Finally, I must thank Cedric Hugelshofer for being a terrific project partner who was willing to listen to my seemingly random procedural suggestions and even try them out every once in a while.

I would also like to also thank the many members of the chemistry department who have supported my research: Wendy Huntington, Chris Perry, Susan Kinsella, Bill Collins, Shaw Huang, Shao-Liang Zheng, and especially Derek Barton.

Lastly, I would like to thank Reed Alexander, Doris Jurisson, and Olivia Alexander for their kindness and support. You accepted a wayward cousin into your family, and I will never be able to repay your generosity.

List of Abbreviations

Å	ångström
Ac	acetyl
Bn	benzyl
Boc	*tert*-butylcarbonate
Bu	butyl
c	concentration (g/100 mL)
Cbz	carboxybenzyl
cis	*L.*, on the same side
Cp	cyclopentadienyl
DIBAL-H	diisobutylaluminum hydride
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
dr	diastereomeric ratio
DTBAD	di-*tert*-butyl azodicarboxylate
E	*Ger.*, entgegen
ee	enantiomeric excess
ent	enantiomer
equiv	equivalent
Et	ethyl
FTIR	Fourier transform infrared
g	gram
h	hour

HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
Hz	hertz
J	coupling constant (in Hz)
LAB	lithium amidiotrihydroborate
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
M	molar (mols/liter)
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mmol	millimole
mol	mole
MS	molecular sieves
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
OMs	mesylate
PDC	pyruvate decarboxylase
Ph	phenyl
PMP	*para*-methoxyphenyl
ppm	parts per million

R	rectus (Cahn-Ingold-Prelog system)
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
R_f	retention factor
S	sinister (Cahn-Ingold-Prelog system)
t-BuLi	*tert*-butyllithium
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
trans	*L.*, across
Ts	tosyl
UV	ultraviolet
Z	*Ger.*, zusammen

Chapter 1

On the Use of Pseudoephedrine as a Chiral Auxiliary

Introduction

Pseudoephedrine (**1**) is an amphetamine alkaloid first isolated from the leaves of *Ephedra vulgaris* in 1889.[1] While the leaves and stems of the *Ephedra* plant were traditionally prescribed as a stimulant or an antiasthmatic,[2] pseudoephedrine is today marketed primarily as a decongestant in over-the-counter medications such as Sudafed®, Claritin-D®, and Zyrtec-D®. Notoriously, pseudoephedrine is easily transformed into methcathinone (**2**) or methamphetamine (**3**) by oxidation or reduction, respectively, of the benzylic alcohol of the natural product (Figure 1.1).

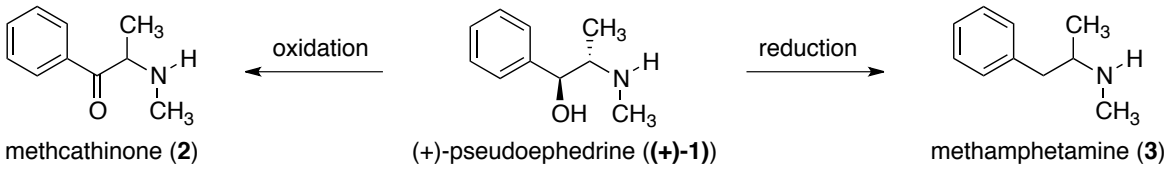

Figure 1.1 Modification of pseudoephedrine to give methcathinone or methamphetamine.

Because both methcathinone and methamphetamine are highly addictive, illegal psychostimulants,[3] pseudoephedrine is itself illegal or highly regulated in many countries.[4] In spite of this, pseudoephedrine is manufactured in multi-ton amounts annually in a process that involves a reductive coupling of pyruvate (**4**) and benzaldehyde mediated by the enzyme pyruvate decarboxylase (PDC) followed by reductive amination with methylamine to give the

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[1] Chen, K. K.; Kao, C. H. *J. Am. Pharm. Assoc.* **1926**, *15*, 625–639.

[2] Abourashed, E. A.; El-Alfy, A. T.; Khan, I.A.; Walker, L. *Phytother. Res.* **2003**, *17*, 703–712.

[3] Methcathinone is classified as a Schedule I illegal drug by the UN Convention on Psychotropic Substances, while methamphetamine is classified as a Schedule II illegal drug by the same governing body.

[4] For example, pseudoephedrine is illegal in Mexico, Japan, and Colombia, and it is highly regulated by law in the United States and Australia. It is a Table 1 precursor under the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances and is a banned item on the World Anti-Doping Agency list.

final amino alcohol (Figure 1.2).[5] The following sections describe reported methodologies that utilize pseudoephedrine as a chiral auxiliary. For the sake of brevity, other applications of pseudoephedrine are not discussed.

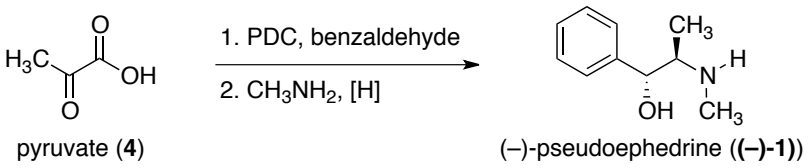

Figure 1.2 Industrial synthesis of (–)-pseudoephedrine.

Stereocontrolled Alkylation of Pseudoephedrine Amide Enolates

The group of Andrew G. Myers first reported the use of pseudoephedrine as a chiral auxiliary in the mid-1990s.[6] In their initial reports, highly practical methods for the synthesis and stereocontrolled alkylation of pseudoephedrine amides to form tertiary carbon stereocenters were disclosed.[7] The general protocol for these reactions involved enolization of the pseudoephedrine amides with lithium diisopropylamide (LDA) in the presence of lithium chloride followed by alkylation with an appropriate alkyl halide to produce highly diastereomerically-enriched products in high yield (Scheme 1.1).[8] Lithium chloride was found to be an essential additive to

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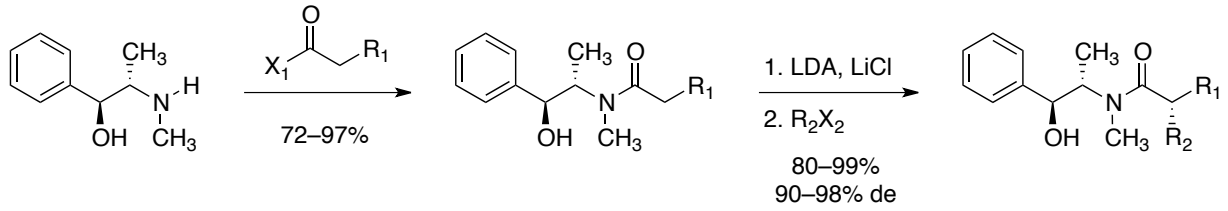
[5] Oliver, A. L.; Anderson, B. N.; Roddick, F. A. *Adv. Microb. Physiol.* **1999**, *41*, 1–45.

[6] The use of ephedrine as a chiral auxiliary in the alkylation of amide enolates was reported nearly two decades earlier: a) Larcheveque, M.; Ignatova, E.; Cuvigny, T. *Tetrahedron Lett.* **1978**, *41*, 3961–3964. b) Larcheveque, M.; Ignatova, E.; Cuvigny, T. *J. Organomet. Chem.* **1979**, *177*, 5–15.

[7] a) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361–9362. b) Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428–2440. c) Myers, A. G.; Yang, B.H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511. d) Myers, A.G.; McKinstry, L.; Barbay, J.K.; Gleason, J.L. *Tetrahedron Lett.* **1998**, *39*, 1335–1338.

[8] Pseudoephedrine amide enolate alkylation chemistry has been extended to a protocol featuring pseudoephedrine affixed to a resin support: a) Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *Org. Lett.* **2002**, *4*, 4583–4585. b) Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *J. Org. Chem.* **2004**, *69*, 790–801.

promote efficient alkylations, though it had no observed effect on the diastereoselectivity of the reactions.[9]



Scheme 1.1 Synthesis of pseudoephedrine amides followed by stereocontrolled amide enolate alkylation. X_1 = RCH_2CO_2, Cl, *t*-$BuCO_2$, OCH_3. R_1 = alkyl, aryl, Cl, F. R_2 = alkyl, benzyl, allyl, BOM. X_2 = I, Br.

Monosubstituted epoxides were also reported to be effective electrophiles in pseudoephedrine amide enolate alkylations, though the stereochemistry of the epoxide had a notable impact on the yield and diastereoselectivity of the reaction.[1b] The stereochemically matched alkylation is shown in Scheme 1.2. Interestingly, alkylations employing these electrophiles proceeded with opposite enolate π-facial selectivity in comparison to those utilizing alkyl halide electrophiles.[10] A stereochemical model illustrating the different selectivities in the alkylation of pseudoephedrine amide enolates with either alkyl halides or epoxides is presented in Figure 1.3.

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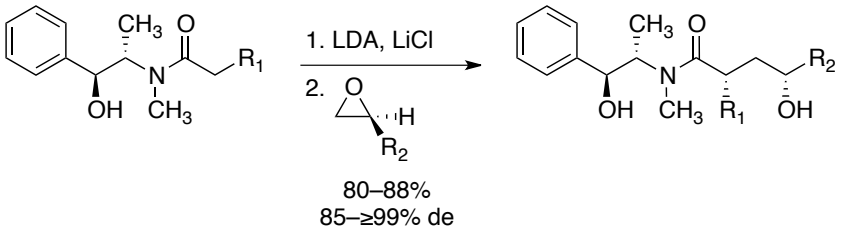
[9] For a discussion on the role of lithium chloride in enolate alkylation reactions, see: (a) Seebach, D.; Bossler, H.; Gründler, H.; Shoda, S. -I. *Helv. Chim. Acta* **1991**, *74*, 197–224. (b) Miller, S. A.; Griffiths, S. L.; Seebach, D. *Helv. Chim. Acta* **1993**, *76*, 563–595. (c) Bossler, H. G.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 1124–1165.

[10] Opposite π-facial selectivity for alkyl halides and epoxides has also been observed in the stereocontrolled alkylation of prolinol amide enolates: Askin, D.; Volante, R. P.; Ryan, K. M.; Reamer, R. A.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 4245–4248.



Scheme 1.2 Stereocontrolled alkylation of pseudoephedrine amide enolates with epoxide electrophiles. $R_1 = CH_3$, Bn. $R_2 = CH_3$, Ph, CH_2OBn, CH_2OTBS.

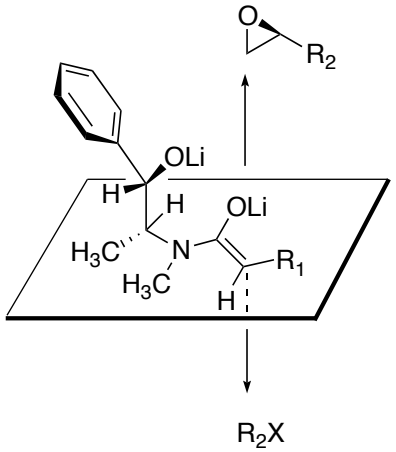


Figure 1.3 Stereochemical model for the observed diastereoselectivity in pseudoephedrine amide enolate alkylations. Alkyl halides approach the enolate from the bottom of face of the enolate, while epoxides approach from the top face.

More recently, Myers and co-workers extended the above enolization-alkylation procedure to the synthesis of quaternary carbon stereocenters,[11] and the developed protocol was applicable to the synthesis of α-methyl quaternary amides from the corresponding α-methyl disubstituted pseudoephedrine amides.[12] As part of the study, matched and mismatched amide diastereomers

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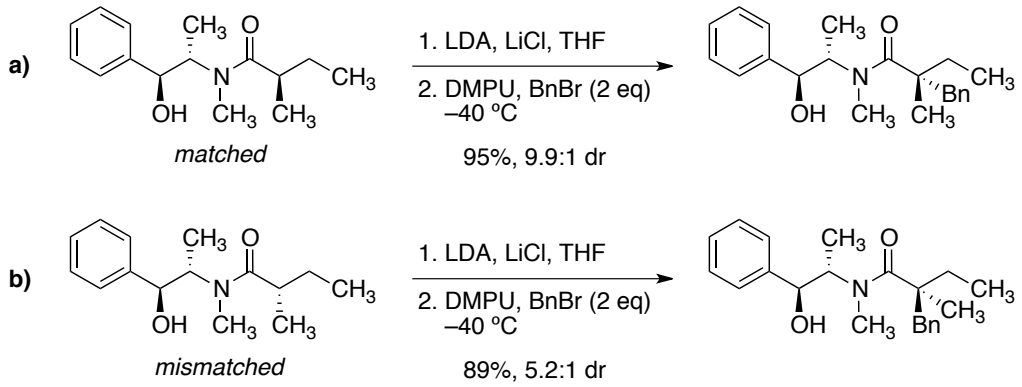
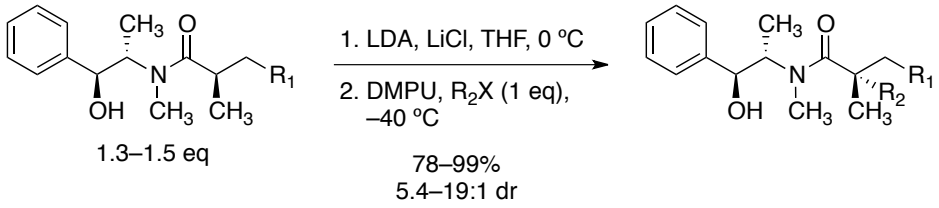
[11] Kummer, D. A.; Chain, W. J.; Morales, M. R.; Quiroga, O.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 13231–13233.

[12] A single example of the enolization-alkylation of an α-phenyl pseudoephedrine amide was also reported, though the broad utility of such a substrate in enolization-alkylation reactions was not demonstrated. See Scheme 1.7 for transformations of this substrate.

were identified,[13] with the diastereomer featuring a 1,4-*anti* relationship between the α-methyl group of the amide and the *C*-methyl group of pseudoephedrine proving to be the matched substrate (Scheme 1.3). Additional reaction optimizations included the use of DMPU as additive to promote efficient alkylation and the use of the electrophile as the limiting reagent in the reaction, which resulted in formation of products with greater diastereoselectivity. The utility of this protocol was demonstrated in the syntheses of a variety of α-quaternary amides in good to excellent yield and good to excellent diastereoselectivity (Scheme 1.4).



Scheme 1.3 Enolization-alkylation of α-methyl pseudoephedrine amides demonstrating a) matched alkylations and b) mismatched alkylations to form quaternary carbon stereocenters.



Scheme 1.4 Enolization-alkylation of α-methyl pseudoephedrine amides to produce quaternary carbon stereocenters. R_1 = ethyl, propyl, vinyl, phenyl. R_2 = alkyl, allyl, benzyl. X = Br, I.

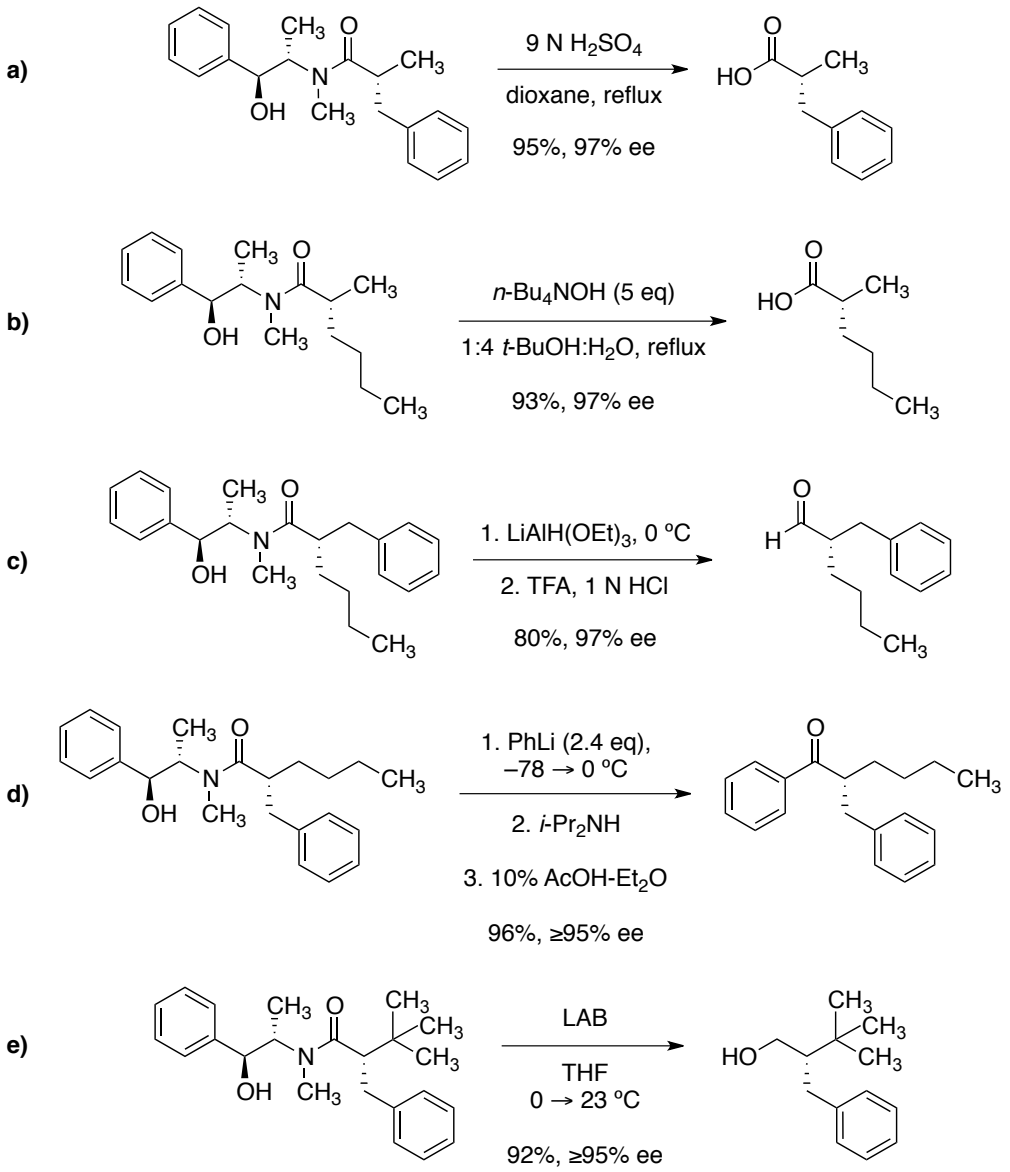
A key aspect of this methodology is the efficient transformation of pseudoephedrine amide alkylation products to a variety of enantiomerically-enriched compounds. As exemplified by the

[13] Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, III, L. A.; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46,* 245–264.

reactions shown in Scheme 1.5, pseudoephedrine amides are readily hydrolyzed to carboxylic acids (via either acidic or basic hydrolysis), reduced to aldehydes (by Brown's aluminum hydride reagent),[14] transformed into ketones (by addition of an organolithium reagent), and reduced to primary alcohols (by lithium amidotrihydroborate, LAB).[15] The yields for these reactions are typically quite high, and the products are isolated with little to no erosion of enantioenrichment in the products. In addition, the auxiliary may be recovered in high yield.

[14] Brown, H. C.; Tsukamoto, A. *J. Am. Chem. Soc.* **1964**, *86*, 1089–1095.

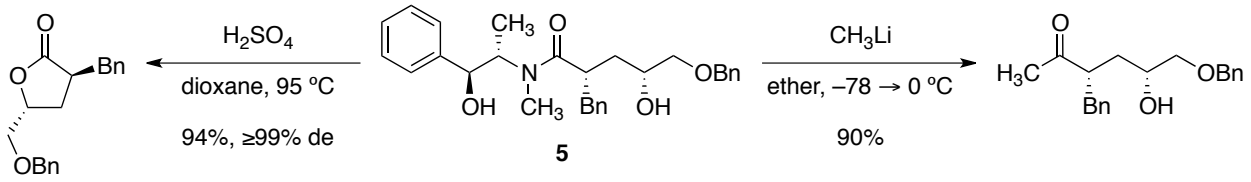
[15] Myers, A. G.; Yang, B. H. Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623–3626.



Scheme 1.5 Representative transformations of pseudoephedrine amide alkylation products. a) Acidic hydrolysis to carboxylic acids. b) Basic hydrolysis to carboxylic acids. c) Reduction to aldehydes. d) Formation of ketones. e) Reduction to primary alcohols.

The γ-hydroxy pseudoephedrine amides obtained by alkylation of pseudoephedrine amide enolates with monosubstituted epoxides were also converted to synthetically useful intermediates. As demonstrated with amide **5** below, hydrolysis of the γ-hydroxy amides resulted in auxiliary cleavage with concomitant cyclization to provide diastereomerically-enriched γ-

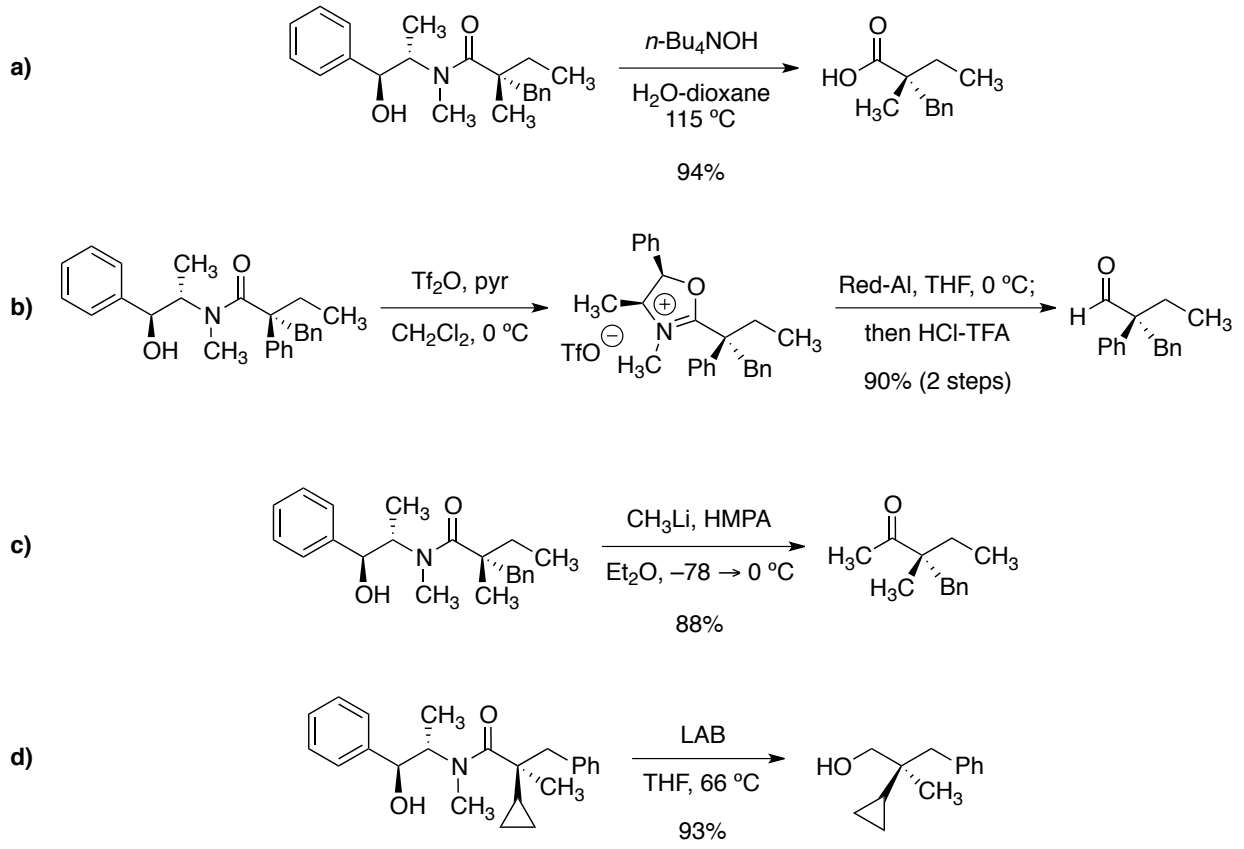
lactones, while treatment of the amides with methyllithium yielded the corresponding methyl ketones (Scheme 1.6).



Scheme 1.6 Representative transformations of γ-hydroxy pseudoephedrine amides.

As with pseudoephedrine amides bearing a tertiary center at the α-position, α-quaternary pseudoephedrine amides are also easily transformed into carboxylic acids, aldehydes, ketones, and primary alcohols, albeit with the slightly different reaction conditions shown in Scheme 1.7. Of particular interest in this set of transformations is the reduction of α-quaternary pseudoephedrine amides to obtain α-quaternary aldehydes, which proceeds through an oxazolinium triflate intermediate (Scheme 1.7b). Triflates of this type, which are the product of an intramolecular cyclization of the amide functional group onto the secondary alcohol of the auxiliary after activation with triflic anhydride, have been shown to be a useful diagnostic tool for the determination of the diastereomeric enrichment of a pseudoephedrine amide, since the rigid oxazolinium triflate eliminates the amide bond rotational isomerism that often complicates the ^{1}H NMR spectra of these amides.[16]

[16] Chain, W. J.; Myers, A. G. *Org. Lett.* **2007**, *9*, 355–357.



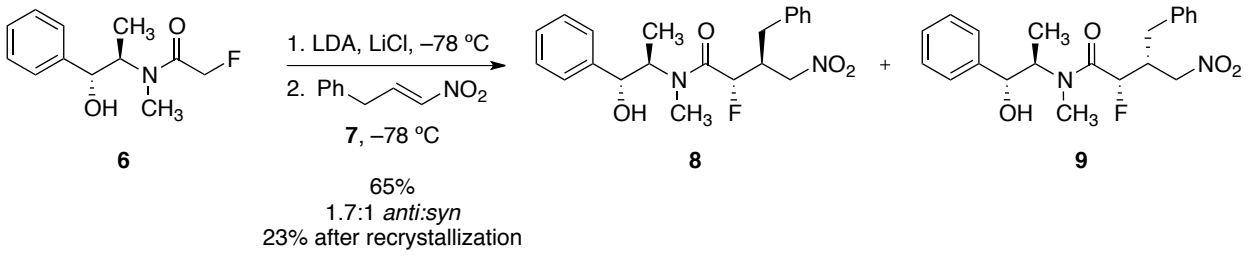
Scheme 1.7 Transformations of α-quaternary pseudoephedrine amides. a) Hydrolysis to carboxylic acids. b) Reduction to aldehydes proceeding through an oxazolinium triflate intermediate. c) Addition of organolithium reagents to produce ketones. d) Reduction with lithium amidotrihydroborate to obtain primary alcohols.

Use of Pseudoephedrine to Direct Asymmetric Michael Reactions

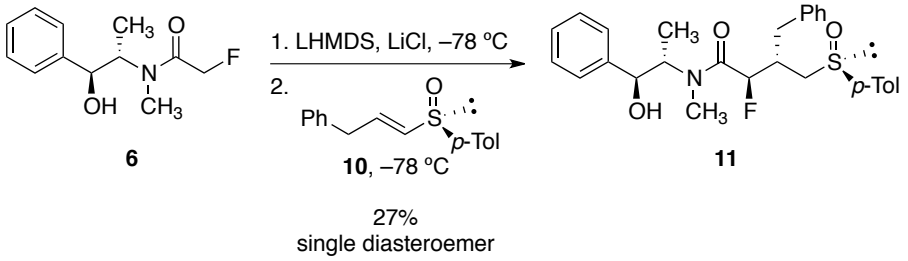
The Michael addition of a pseudoephedrine amide enolate to an α,β-unsaturated acceptor was first reported by Myers and co-workers in the context of the synthesis of a series of HIV protease inhibitors.[17] In this study, the enolate derived from (*R*,*R*)-pseudoephedrine α-fluoroacetamide **6** was treated with nitroalkene **7** to give a 1.7:1 mixture of diastereomers favoring the *anti* diastereomer **8** (Scheme 1.8). The reaction proved to be scalable, providing more than 5 g (23% yield) of the desired *anti* isomer after recrystallization. Use of vinyl sulfoxide **10** as the Michael acceptor was also demonstrated in the synthesis of α-fluoro amide

[17] Myers, A. G.; Barbay, J. K.; Zhong, B. *J. Am. Chem. Soc.* **2001**, *123*, 7207–7219.

10, which was formed as a single diastereomer with opposite *anti*-selectivity to amide **8** (Scheme 1.9)



Scheme 1.8 Pseudoephedrine-directed Michael reaction of amide **6** and nitroalkene **7.**

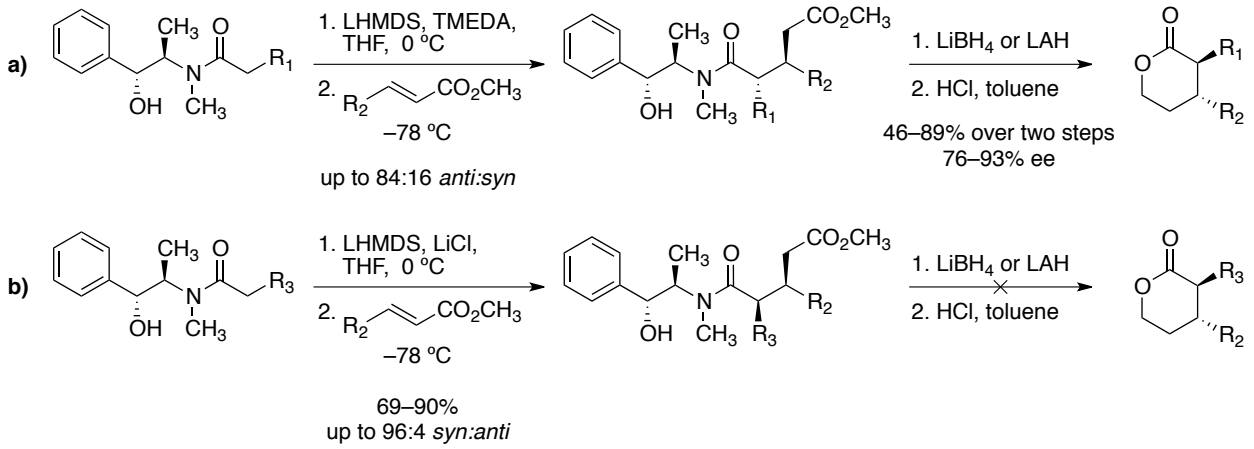


Scheme 1.9 Pseudoephedrine-directed Michael reaction using vinyl sulfoxide **10** as the Michael acceptor.

Smitrovich et al. later expanded the utility of pseudoephedrine amide enolates in Michael addition reactions in their pursuit of diastereomerically-enriched 3,4-*trans* δ-lactones.[18] Interestingly, their reports included methods allowing access to both *anti* and *syn* Michael adducts (Scheme 1.10). In the *anti*-selective protocol, α-aryl pseudoephedrine amides were treated with lithium hexamethyldisilazide (LHMDS) in the presence of tetramethylethylenediamine (TMEDA), and the resulting enolates were trapped with a variety of α,β-unsaturated methyl esters. Alternatively, use of lithium chloride in place of TMEDA resulted in the formation of the *syn* diastereomer as the major product. The authors concluded that the use

[18] a) Smitrovich, J. H.; Boice, G. N.; Qu, C.; DiMichele, L.; Nelson, T. D.; Huffman, M. A.; Murry, J.; McNamara, J.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1963–1966. b) Smitrovich, J. H.; DiMichele, L.; Qu, C.; Boice, G. N.; Nelson, T. D.; Huffman, M. A.; Murry, J. *J. Org. Chem.* **2004**, *69*, 1903–1908.

of LiCl switches the favored enolate π-facial selectivity in the Michael addition – the Michael acceptor approaches from the top enolate π-face in the presence of LiCl, while it approaches from the bottom face in the presence of TMEDA. The subsequent sequence involving selective reduction of the methyl ester followed by acidic hydrolysis/lactonization was found to be successful only with the *anti* Michael adducts, and no alternative transformations for these stereochemically-rich amides were disclosed.



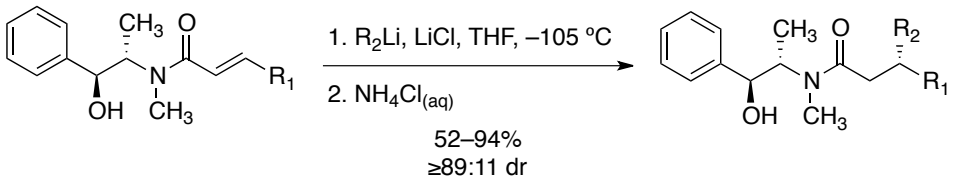
Scheme 1.10 Michael reactions of pseudoephedrine amide enolates with α,β-unsaturated methyl esters. a) *Anti*-selective reactions conducted in the presence of TMEDA. b) *Syn*-selective reactions conducted in the presence of LiCl. R_1 = aryl. R_2 = alkyl, alkyl ether, aryl, 3° amine. R_3 = alkyl, aryl.

In addition to the use of pseudoephedrine amide enolates as nucleophiles in Michael reactions, pseudoephedrine has also been shown to effectively direct the conjugate addition of metallated nucleophiles to α,β-unsaturated pseudoephedrine amides.[19] Dolores Badía and co-workers first demonstrated this methodology in their synthesis of both highly enantio- and diastereomerically enriched carboxylic acids and alcohols.[20] Initially, it was demonstrated that β-

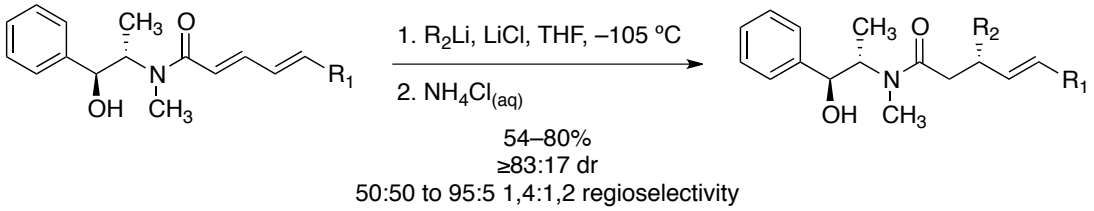
[19] The conjugate addition of Grignard reagents to α,β-unsaturated ephedrine amides has been reported to proceed with moderate yields and excellent diastereoselectivities: Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1981**, 913–916.

[20] a) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Iza, A.; Uria, U. *Org. Lett.* **2006**, *8*, 2535–2538. b) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Uria, U.; Iza, A. *J. Org. Chem.* **2006**, *71*, 7763–7772.

substituted α,β-unsaturated pseudoephenamine amides were able to direct the regio- and diastereoselective 1,4-addition of organolithium reagents to the β-position of the amide while completely avoiding formation of the 1,2-addition product,[21] provided that the temperature of the reaction was kept at –105 ºC. Despite the low reaction temperature, the addition was found to be remarkably efficient, with conjugate addition of even bulky organolithium reagents such as *t*-BuLi occurring in good to excellent yield with high diastereoselectivity (Scheme 1.11). This methodology was extended to the 1,4-addition of organolithium reagents in α,β,γ,δ-unsaturated pseudoephedrine amides, though the yield and regioselectivity suffered in this class of substrates due to competing 1,2-addition (Scheme 1.12).[22]



Scheme 1.11 Diastereoselective conjugate addition of organolithium reagents to β-substituted α,β-unsaturated pseudoephedrine amides. R_1 = methyl, ethyl, *n*-propyl, *t*-butyl, phenyl. R_2 = *i*-propyl, *n*-butyl, *t*-butyl, phenyl.



Scheme 1.12 Diastereoselective 1,4-addition of organolithium reagents to α,β,γ,δ-unsaturated pseudoephedrine amides. R_1 = H, methyl. R_2 = ethyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl, *n*-hexyl, $TMSCH_2$, phenyl.

Recognizing that the conjugate addition of organolithium reagents to α,β-unsaturated pseudoephenamine amides results in the formation of a stereodefined amide enolate, Badía et al.

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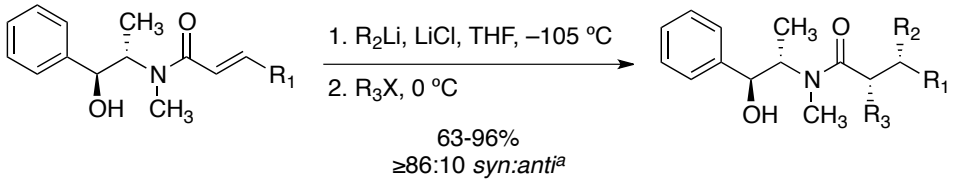
[21] Use of methyllithium resulted in exclusive 1,2-addition to give the corresponding methyl ketone.

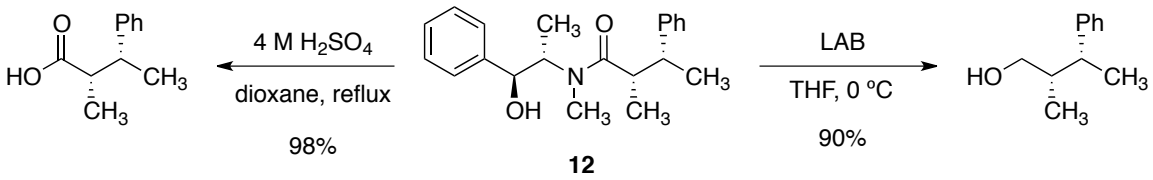
[22] Ocejo, M.; Carrillo, L.; Badía, D.; Vicario, J. L.; Fernández, N.; Reyes, E. *J. Org. Chem.* **2009**, *74*, 4404–4407.

utilized this transient enolate in a conjugate addition-alkylation protocol to synthesize *syn* α,β-dialkyl pseudoephedrine amides in good yield.[20] As with the conjugate addition reactions described above, the initial addition of the organolithium reagent was conducted at –105 ºC, while the alkylation step was conducted at 0 ºC and exhibited excellent diastereoselectivity (Scheme 1.13).



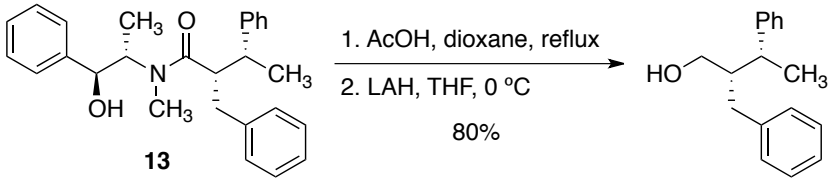
Scheme 1.13 Conjugate addition alkylation protocol to produce *syn* α,β-dialkyl pseudoephedrine amides. R_1 = methyl, ethyl, *n*-propyl, *t*-Bu. R_2 = *n*-Bu, phenyl. R_3 = methyl, ethyl, allyl, benzyl. X = Br, I. [a] Represents the ratio of the major product diastereomers.

Protocols for the basic hydrolysis and LAB reduction of the aforementioned conjugate addition products are represented by the transformations of amide **12** below (Scheme 1.14). In all cases, yields for the hydrolyses (≥75%) and reductions (≥65%) were generally high, and no loss of enantio- or diastereoenrichment was reported. For substrates such as amide **13** bearing larger alkyl groups at the α-position, LAB reduction to the primary alcohol was found to be sluggish or unsuccessful, and a second protocol involving *N→O* acyl transfer[23] and subsequent LAH reduction was also developed (Scheme 1.15).



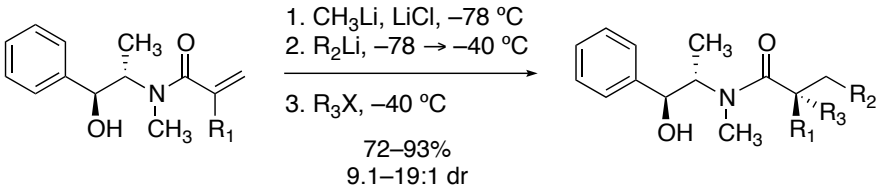
Scheme 1.14 Representative acidic hydrolysis and LAB reduction of conjugate addition-alkylation product **12**.

[23] The tendency of ephedrine and pseudoephedrine amides to undergo *N→O* acyl transfer under acidic conditions has been reported: Welsh, L. H. *J. Am. Chem. Soc.* **1947**, *69*, 128–136.



Scheme 1.15 Reduction of amide **13** to the corresponding primary alcohol via acetic acid promoted *N*→*O* acyl transfer followed by reduction of the resulting ester with LAH.

Myers et al. have adapted the above conjugate-addition alkylation protocol in a method for the stereocontrolled synthesis of quaternary carbon stereocenters (Scheme 1.16).[11] Utilizing pseudoephedrine acrylamides with varying alkyl substituents at the α-position, a wide variety of organolithium reagents, including *t*-BuLi, were shown to add to *s*-cis conformer of the acrylamides to give a stereodefined enolate that could be trapped with an electrophile to give quaternary carbon stereocenters in good yield and diastereoselectivity. This method serves as a companion protocol to the enolization-alkylation strategy shown in Scheme 1.4, and the amide products obtained through this process can be transformed into the corresponding carboxylic acids, aldehydes, ketones, and alcohols using the reactions shown in Scheme 1.7.

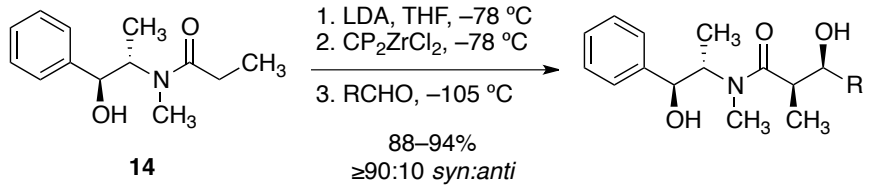


Scheme 1.16 Conjugate addition-alkylation of α-alkyl pseudoephedrine acrylamides to obtain quaternary carbon stereocenters. R_1 = methyl, ethyl, *i*-propyl, cyclopropyl. R_2 = *n*-butyl, *t*-butyl, phenyl, heteroaryl. R_3 = methyl, allyl, benzyl. X = Br, I.

Use of Pseudoephedrine to Direct Asymmetric Aldol and Mannich Reactions

In addition to their work with conjugate addition reactions, Badía and co-workers were also the first to study asymmetric aldol and Mannich reactions using pseudoephedrine as a chiral auxiliary. Their initial reports focused on the aldol reaction of (+)-pseudoephedrine

propionamide (**14**) with achiral aldehydes. They investigated the use of the lithium enolate derived from **14** as the nucleophile in the reaction, but this invariably led to low diastereoselectivity (65:35 *syn*:*anti* at –105 ºC).[24] However, transmetallation to the zirconium enolate using Cp_2ZrCl_2 resulted in a much more selective reaction (≥90:10 *syn*:*anti*) with both aliphatic and aromatic aldehydes (Scheme 1.17).[25] Notably, the *syn* selectivity increased with the steric bulk of the aldehydes (90:10 for R = CH_3 vs. >99:1 for R = *t*-Bu).



Scheme 1.17 Pseudoephedrine-directed aldol reaction of propionamide **14**. R = methyl, ethyl, *i*-propyl, *t*-butyl, phenyl.

Attempts were made to extend this methodology to the use of pseudoephedrine acetamide (**15**) as the nucleophile in the aldol reaction, but they were met with mixed results. Aldol reactions between **15** and achiral aldehydes were universally unselective.[26] However, high diastereoselectivity was observed in the aldol reaction between **15** and Garner's aldehyde[27] (**16**, Scheme 1.18).[28] Buoyed by this success, the aldol reaction between **15** and other chiral aldehydes bearing α-heteroatoms was investigated.[29] While no generally applicable method was developed, efficient reactions were observed between pseudoephedrine acetamide and chiral aldehydes bearing Boc-protected secondary amines at the α-position when lithium chloride was used as an

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[24] Vicario, J. L.; Badía, D.; Domínguez, E.; Carrillo, L. *Tetrahedron Lett*. **1998**, *39*, 9267–9270.

[25] Vicario, J. L.; Badía, D.; Domínguez, E.; Rodríguez, M.; Carrillo, L. *J. Org. Chem*. **2000**, *65*, 3754–3760.

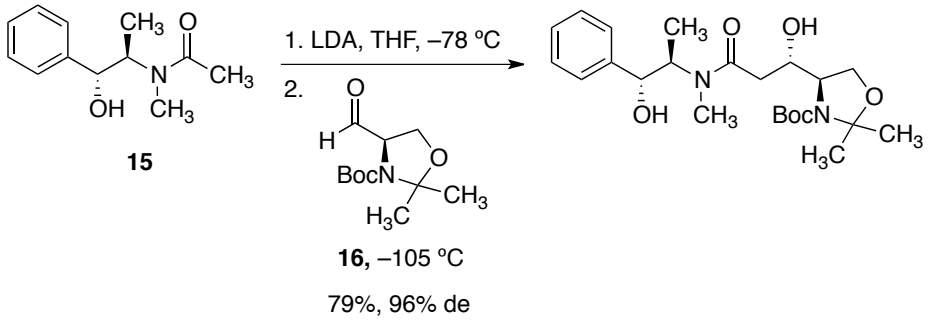
[26] Rodriguez, M.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Biomol. Chem*. **2005**, *3*, 2026–2030.

[27] Garner, P.; Ramakanth, S. *J. Org. Chem*. **1986**, *51*, 2609–2612.

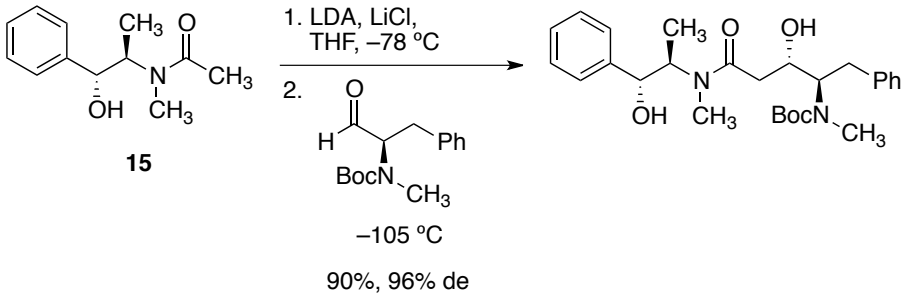
[28] Vicario, J. L.; Rodriquez, M.; Badía, D.; Carrillo, L.; Reyes, E. *Org. Lett*. **2004**, *6*, 3171–3174.

[29] Ocejo, M.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E. *J. Org. Chem*. **2011**, *76*, 460–470.

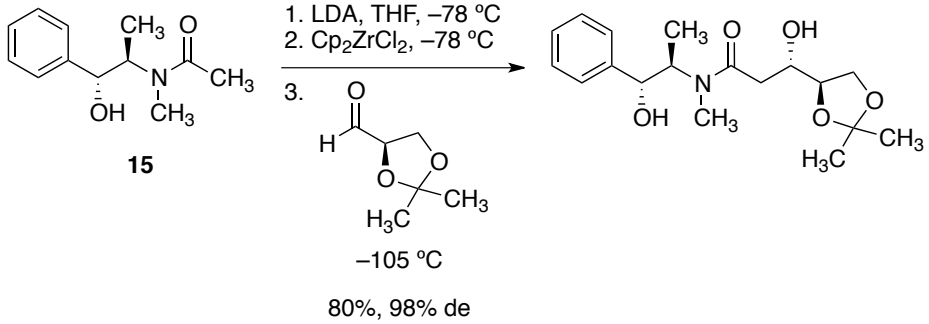
additive (Scheme 1.19). In addition, the acetonide derived from (*R*)-glyceraldehyde was a suitable electrophile if the lithium enolate derived from **15** was transmetallated with Cp_2ZrCl_2 prior to addition of the aldehyde (Scheme 1.20).



Scheme 1.18 Aldol reaction between (–)-pseudoephedrine acetamide (**15**) and Garner's aldehyde **(16)**.

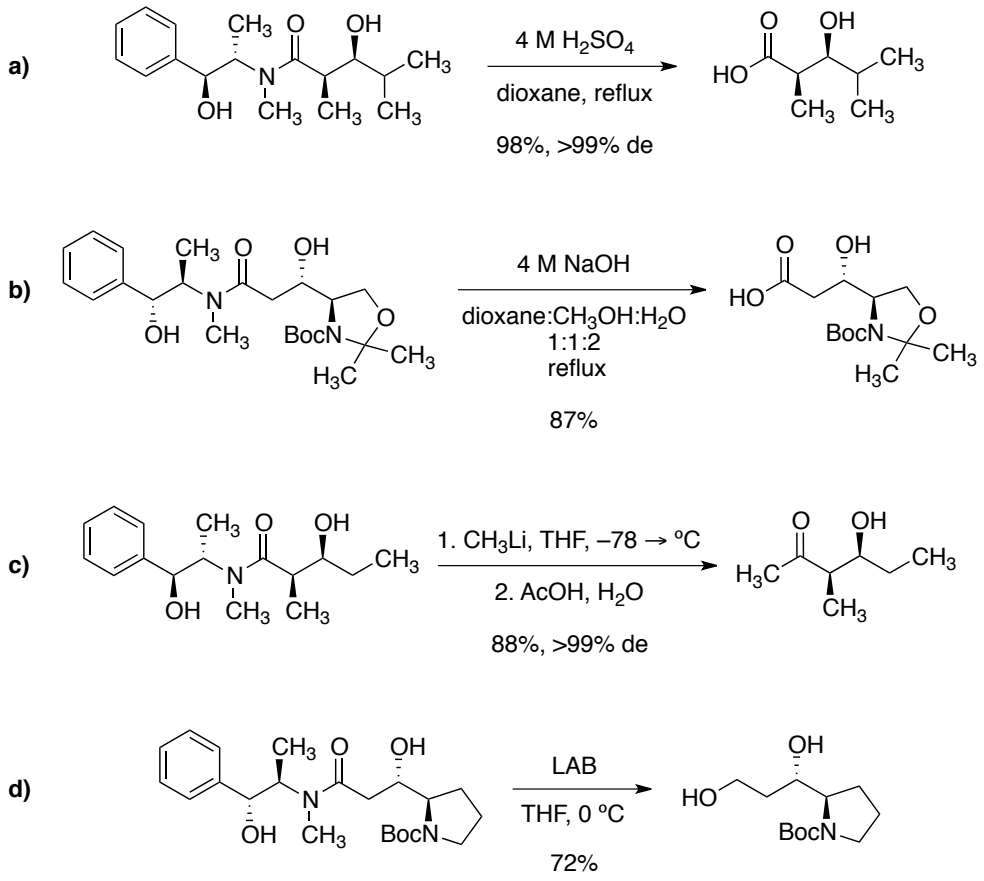


Scheme 1.19 Aldol reaction between **15** and a chiral aldehyde bearing a Boc-protected secondary amine.



Scheme 1.20 Aldol reaction between **15** and the acetonide of (*R*)-glyceraldehyde.

It was also shown that these aldol products could be transformed to a number of diastereomerically-enriched synthetic intermediates, including carboxylic acids, ketones, primary alcohols, and derivatives thereof. Representative examples are presented in Scheme 1.21.

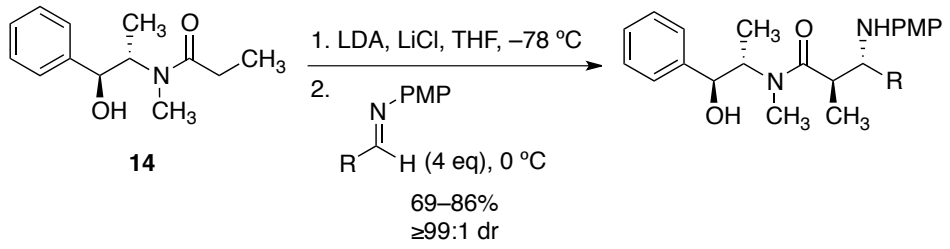


Scheme 1.21 Transformations of β-hydroxy pseudoephedrine amides. a) Acidic hydrolysis. b) Basic hydrolysis. c) Ketone formation. d) LAB reduction.

Extension of the above methodology to include imines as electrophiles required slight modification of the reaction conditions. In the case of non-enolizable imines, it was found that lithium chloride was required as an additive – the absence of the lithium salt resulted in no conversion of the starting material.[30] In addition, a large excess of the PMP-protected imine was required for good conversion of the amide starting material. Badía and co-workers attribute both of these requirements to the decreased electrophilicity of imines in comparison to aldehydes. Conducting the Mannich reactions under these conditions, a number of aryl and heteroaryl imines, in addition to pivaldimine, proved to be suitable electrophiles in the reaction with

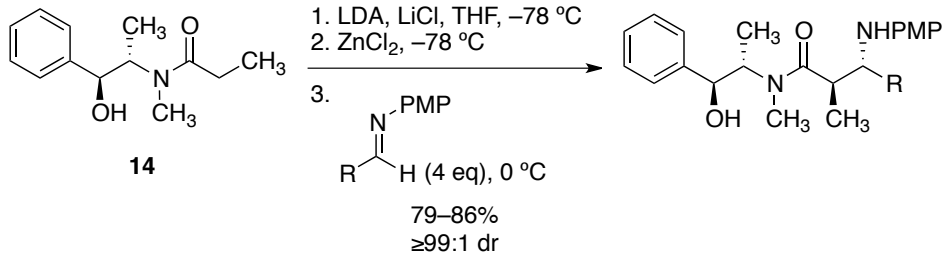
[30] Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 9030–9032.

propionamide **14** (Scheme 1.22). Note that these reactions favor the *anti* Mannich adduct as opposed to the *syn* products favored in the aldol reactions described above.



Scheme 1.22 Mannich reactions of propionamide **14** with non-enolizable imines. R = aryl, heteroaryl, *t*-Bu.

Under the above conditions, Mannich reactions conducted with enolizable imines simply returned unreacted starting material and polymerized imine by-products, indicating that the enolate was deprotonating the imine partner instead of acting as a nucleophile. Transmetallation of the lithium enolate to the zinc enolate with $ZnCl_2$ prior to addition of the imine was found to circumvent this problem, and the reaction was then compatible with alkyl imine substrates (Scheme 1.23).[31]



Scheme 1.23 Mannich reactions of propionamide **15** with enolizable imines. R = methyl, ethyl, *i*-propyl.

The hydrolysis-esterification of the protected β-amino amides was shown to be a useful transformation, though isolation of the intermediate β-amino acids was not reported (Scheme 1.24). β-lactam synthesis from the isolated esters was also demonstrated.[32]

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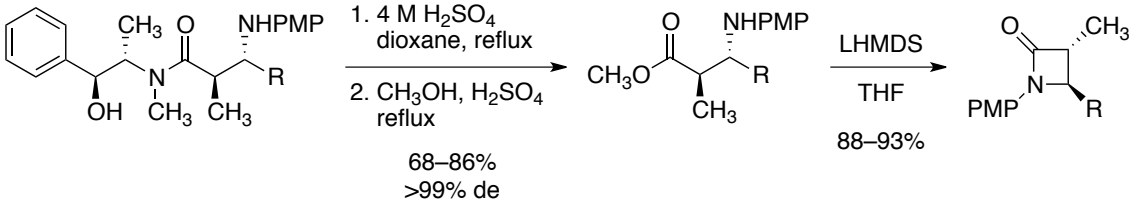
[31] Vicario, J. L.; Badía, D.; Carrillo. L. *Org. Lett.* **2001**, *3*, 773–776.

[32] Iza, A.; Vicario, J. L.; Carrillo, L.; Badía, D. *Synthesis* **2006**, *23*, 4065–4074.



Scheme 1.24 Transformations of β-amino pseudoephedrine amides. R = alkyl, aryl.

Pseudoephenamine-Directed Synthesis of α-, β-, and γ-Amino Acids

Concurrent with their work on the alkylation of pseudoephedrine amides to form tertiary carbon stereocenters, the Myers group also investigated the use of pseudoephedrine glycinamide (**17**) as a precursor for the synthesis of α-amino acids. Prepared either by acylation of pseudoephenamine with the mixed anhydride prepared from *N*-Boc glycine and pivaloyl chloride (followed by deprotection of the amino group after acylation) or by direct reaction of the lithium amide of pseudoephedrine with glycine methyl ester,[33] glycinamide **17** was found to undergo highly diastereoselective alkylation reactions with a wide variety of electrophiles to prepare both natural and non-natural amino acids (Scheme 1.25).[34,35] Using dihalide electrophiles, it was also possible to prepare cyclic α-amino acid derivatives (Scheme 1.26). In addition, pseudoephedrine sarcosinamide (**18**) was shown to be a suitable substrate for the synthesis of *N*-methyl amino acids (Scheme 1.27), although *N*-methylethanolamine was required as an additive in this case to ensure high diastereoselectivity in the alkylations.

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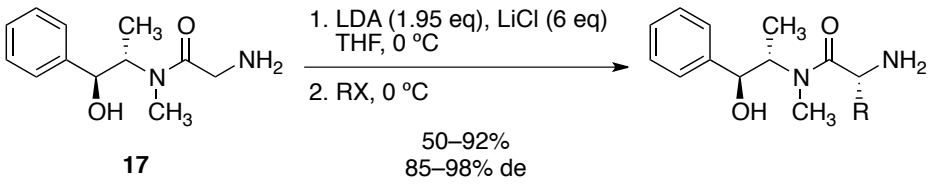
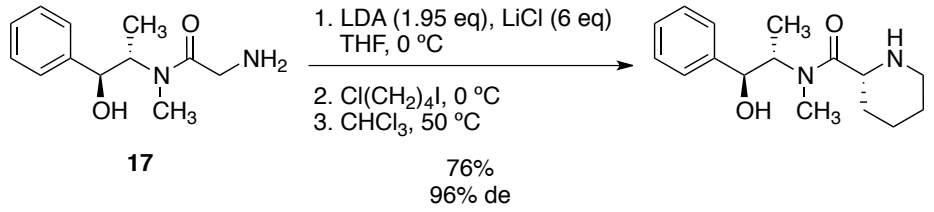
[33] Myers, A. G.; Yoon, T.; Gleason, J. L. *Tetrahedron Lett*. **1995**, *36*, 4555–4558.

[34] a) Myers, A. G.; Gleason, J. L.; Yoon, T. *J. Am. Chem. Soc*. **1995**, *117*, 8488–8489. b) Myers, A.G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc*. **1997**, *119*, 656–673.

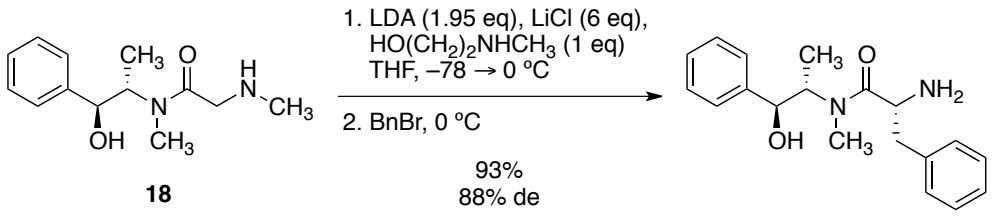
[35] The alkylation of *N*-Boc pseudoephedrine glycinamide was also reported. See reference 33b.



Scheme 1.25 Alkylation of pseudoephedrine glycinamide **17** to give α-amino acids. R = alkyl, allyl, aryl, heteroaryl. X = Cl, Br, I, OMs, OTf.



Scheme 1.26 Preparation of a cyclic α-amino amide from pseudoephedrine glycinamide **17**.

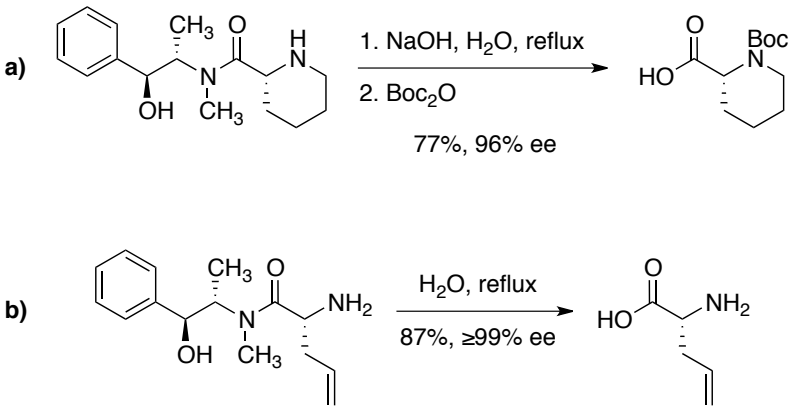


Scheme 1.27 Representative alkylation of pseudoephedrine sarcosinamide **18**.

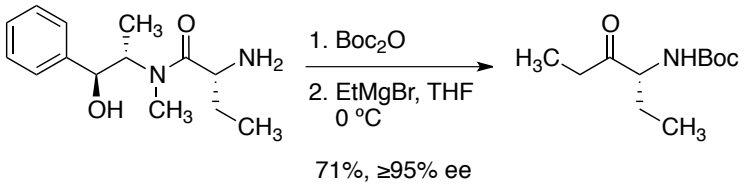
In reactions of both glycinamide **17** and sarcosinamide **18**, the use of lithium chloride as a reaction additive was found to be essential to the attainment of both efficient and highly diastereoselective alkylations. It was also determined that the use of 1.95 equivalents of base was optimal to prevent deleterious side reactions resulting in the liberation of pseudoephedrine. This procedure was later adapted to allow the use of pseudoephedrine glycinamide hydrate (**17**·H_2O) as the starting material, thereby eliminating the need to scrupulously dry the hygroscopic glycinamide **17**.[36]

[36] Myers, A. G.; Schnider, P.; Kwon, S.; Kung, D. W. *J. Org. Chem.* **1999**, *64*, 3322–3327.

A number of procedures for hydrolysis of the above glycinamide alkylation products were developed, including basic hydrolysis with subsequent protection of the amino group and salt-free hydrolysis in water.[37] Representative examples of these procedures are presented in Scheme 1.28. Additionally, the synthesis of *N*-Boc α-amino ketones by addition of organolithium or Grignard reagents was also reported (Scheme 1.29).[38] Little to no epimerization of the α-tertiary stereocenter was observed in these reactions, and the chiral auxiliary was typically recovered in high yield.



Scheme 1.28 Hydrolysis of α-amino pseudoephedrine amides. a) Hydrolysis under basic conditions followed by *N*-Boc carbamate formation. b) Hydrolysis under salt-free conditions.



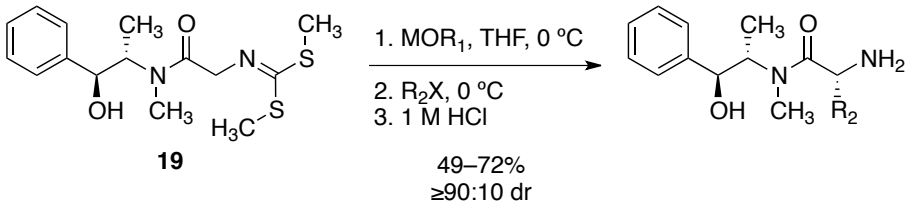
Scheme 1.29 Synthesis of *N*-Boc α-amino ketones.

Other methods for the synthesis of α-amino acids have been reported. Nájera et al. described the use of pseudoephedrine glycinamide dithioiminocarbonate (**19**, Scheme 1.30) as an

[37] Hydrolysis of *N*-Boc and *N*-Fmoc amides was also reported. See reference 25b.

[38] Myers, A. G.; Yoon, T. *Tetrahedron Lett*. **1995**, *36*, 9429–9432.

alternative substrate for alkylation reactions to obtain amino acid derivatives.[39] The primary advantage of this platform is the use of milder bases (metal alkoxides) to generate the enolate of the glycinamide. Unfortunately, the yields of the alkylation products are notably lower than those obtained with the glycinamide **17** above, and the diastereoselectivities of the alkylations were slightly lower, though it should be noted that lithium chloride was not employed as an additive in these reactions. The α-amino amides obtained were hydrolyzed as described above to yield the corresponding amino acids.



Scheme 1.30 Alkylation of dithioiminocarbonate **19**. M = Li, Na, K. R_1 = Et, *t*-Bu. R_2 = methyl, ethyl, allyl, benzyl. X = Br, I.

The Badía group has developed two methods for the synthesis of α-amino acids. In the first method, enolates derived from α-aryl pseudoephedrine amides were trapped diastereoselectively with di-*tert*-butyl azodicarboxylate (DTBAD) to give the *bis*-Boc hydrazine, which was deprotected with TFA and hydrogenated in the presence of Raney nickel to give the α-amino amide.[40] These amides were shown to hydrolyze under acidic conditions to give the corresponding amino acids (Scheme 1.31).[41]

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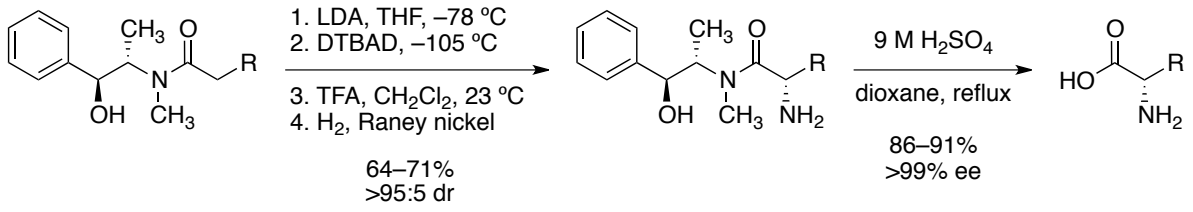
[39] Guillena, G.; Nájera, C. *Tetrahedron: Asymmetry* **2001**, *12*, 181–183.

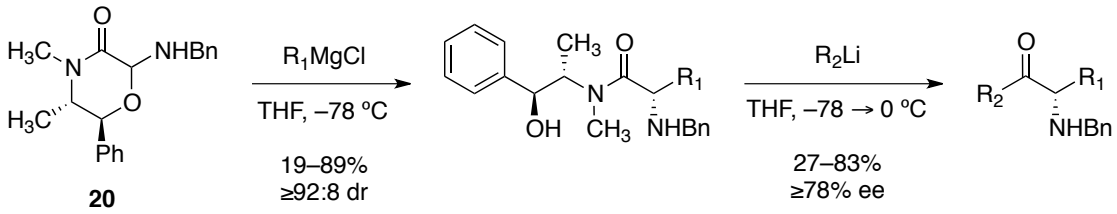
[40] Similar amination of *N*-methyl ephedrine ester enolates and oxazolidinone imide enolates with DTBAD has been reported: a) Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394–6395. b) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395–6397.

[41] a) Anakabe, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; Yoldi, V. *Eur. J. Org. Chem.* **2001**, 4343–4352. b) Vicario, J. L.; Badía, D.; Carrillo, L.; Anakabe, E. *Tetrahedron: Asymmetry* **2002**, *13*, 745–751.



Scheme 1.31 Amination and hydrolysis of α-aryl pseudoephedrine amides.

The second protocol employed the pseudoephedrine-derived cyclic aminal **20** as an electrophile in reactions with Grignard reagents.[42] This method proceeded with notably lower yields and diastereoselectivities in comparison to the previously described methods. The amides obtained in these reactions were hydrolyzed as shown in Scheme 1.31 above, or they were treated with organolithium reagents to access the *N*-benzyl α-amino ketones, as shown in Scheme 1.32 below.



Scheme 1.32 Synthesis of *N*-benzyl α-amino ketones via the electrophilic glycine aminal **20**.

Two methods for the synthesis of β-amino acids using pseudoephedrine as a chiral auxiliary have been reported. Lum and co-workers described the alkylation of pseudoephedrine β-alaninamide **21**.[43] While the alkylation of this amide was successful, the diastereoselectivity of the alkylation was not reported due to difficulties in the determination of the dr of the alkylation products, and the selectivity must be inferred from the enantiomeric excesses of the amino acids isolated after hydrolysis in water (Scheme 1.33).

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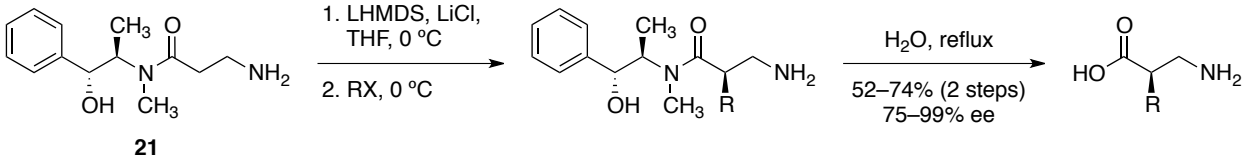
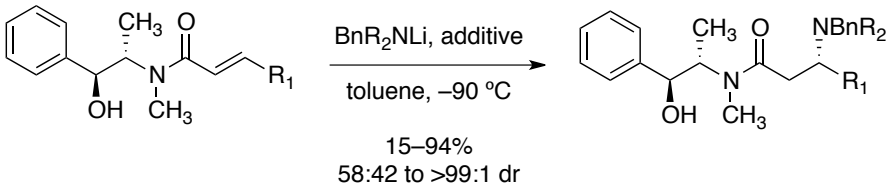
[42] Ruiz, N.; Vicario, J. L. Badía, D.; Carrillo, L.; Alonso, B. *Org. Lett.* **2008**, *10*, 2613–2616.

[43] Nagula, G.; Huber, V. J.; Lum, C.; Goodman, B. A. *Org. Lett.* **2000**, *2*, 3527–3529.



Scheme 1.33 Stereocontrolled synthesis of β-amino acids via alkylation of pseudoephedrine β-amino alaninamide (**21**).

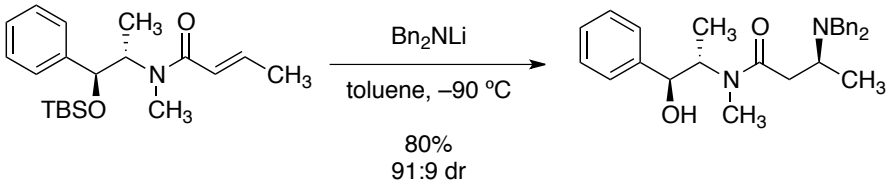
In addition to their study of pseudoephedrine amide Mannich reactions described above, the Badía group also reported the synthesis of β-amino acids through the aza-Michael addition of nitrogen nucleophiles to α,β-unsaturated pseudoephedrine amides.[44] Unfortunately, the yields and diastereoselectivities observed with this methodology varied significantly with the substituent at the β-position of the amide (Scheme 1.34). The best result was obtained in the conjugate addition of Bn_2NLi to pseudoephedrine crotonyl amide ($R_1 = CH_3$) in the absence of additives (85% yield, >99:1 dr), but the yields and selectivities for larger substituents at R_1 were markedly lower. During the course of these investigations, it was found that protection of the hydroxyl group of the auxiliary as an alkyl or silyl ether led to a reversal of selectivity in the conjugate addition, with the products of these reactions favoring the opposite β-epimer than the one shown in Scheme 1.34. While interesting, the yields and selectivities obtained with these protected substrates were lower than those obtained with the unprotected amides (Scheme 1.35).



Scheme 1.34 Aza-Michael addition of lithium amides to α,β-unsaturated pseudoephedrine amides. R_1 = methyl, ethyl, *n*-propyl, *i*-propyl, *t*-butyl, phenyl. R_2 = benzyl, methyl. Additive = none, TMEDA, TMEDA with CuI.

---

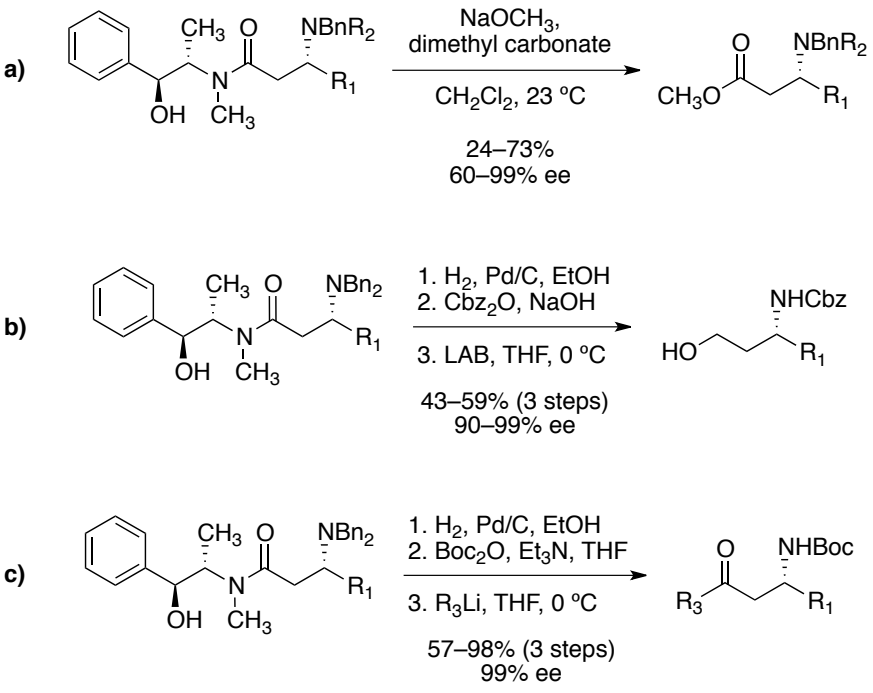
[44] a) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2004**, *69*, 2588–2590. b) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L.; Ruiz, N. *J. Org. Chem.* **2005**, *70*, 8790–8800.



Scheme 1.35 Representative aza-Michael addition of lithium dibenzylamide to TBS-protected pseudoephedrine crotonylamide. Note the reversal of diastereoselectivity in comparison to the Michael additions of Scheme 1.34.

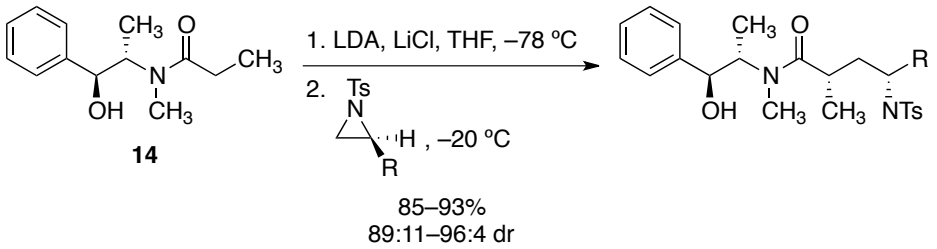
Despite the low selectivities of the aza-Michael additions, the diastereomers isolated from the reactions could be separated, and a number of protocols were developed to transform the Michael adducts to synthetically useful compounds. In contrast to the above report from Lum and co-workers, hydrolysis of these β-amino amides was unsuccessful under acidic or basic hydrolysis conditions, with the reactions suffering from low yields (15–35%).[45] To avoid the issues associated with hydrolysis, conditions for the direct methanolysis of the amides were developed, and the methyl esters were isolated in variable yields with varying levels of enantioenrichment (Scheme 1.36). LAB reduction of the *N*-benzyl amides were complicated by the low enantiomeric excesses of the products. By switching protecting groups from *N*-benzyl to *N*-Cbz, the yield of the LAB reduction could be dramatically improved (90–99% yield for the reduction step, Scheme 1.36). Finally, the direct formation of ketones from the *N*-benzyl amides was troubled by unreactive starting material, a problem that was solved by switching protecting groups from *N*-benzyl to *N*-Boc. With these new substrates, the desired amino ketones were obtained in good to excellent yield with high levels of enantioenrichment (Scheme 1.36).

[45] It should be noted that Badía et al. only reported hydrolysis reactions with *N*-benzyl amides, whereas Lum and co-workers hydrolyzed unprotected β-amino amides.



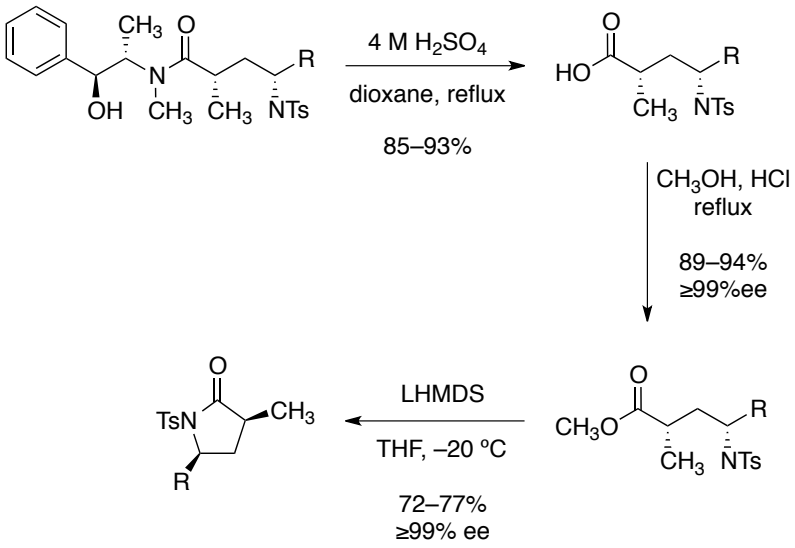
Scheme 1.36 Transformations of protected β-amino amides. a) Formation of methyl esters. b) LAB reduction of *N*-Cbz β-amino amides. c) Ketone formation using *N*-Boc amino amides. R_1 = methyl, ethyl, *n*-propyl, *i*-propyl, *t*-butyl, phenyl. R_2 = benzyl, methyl. R_3 = methyl, ethyl, *i*-propyl, *n*-butyl, phenyl.

Lastly, the Badía group also developed a method for the synthesis of γ-amino acids via the nucleophilic opening of chiral monosubstituted *N*-tosyl aziridines with pseudoephedrine propionamide enolates. These reactions closely mirrored the epoxide opening reactions described by Myers et al., with the aziridines approaching the same enolate π-face as epoxides. Additionally, reactions with aziridines displayed the same matched and mismatched pairs as epoxide opening reactions. When these reactions were conducted with the matched pairs, the alkylations proceeded in excellent yields with high diastereoselectivities (Scheme 1.37). Lithium chloride was required for these reactions, as the absence of this additive resulted in complete recovery of starting material.



Scheme 1.37 Stereocontrolled opening of *N*-tosyl aziridines with pseudoephedrine propionamide. R = methyl, *i*-propyl, benzyl, phenyl.

The resulting γ-amino amides were efficiently transformed to γ-amino acids, γ-amino esters, and chiral pyrrolidinones in sequence (Scheme 1.37). These reactions were all high yielding and did not result in any loss of enantioenrichment.



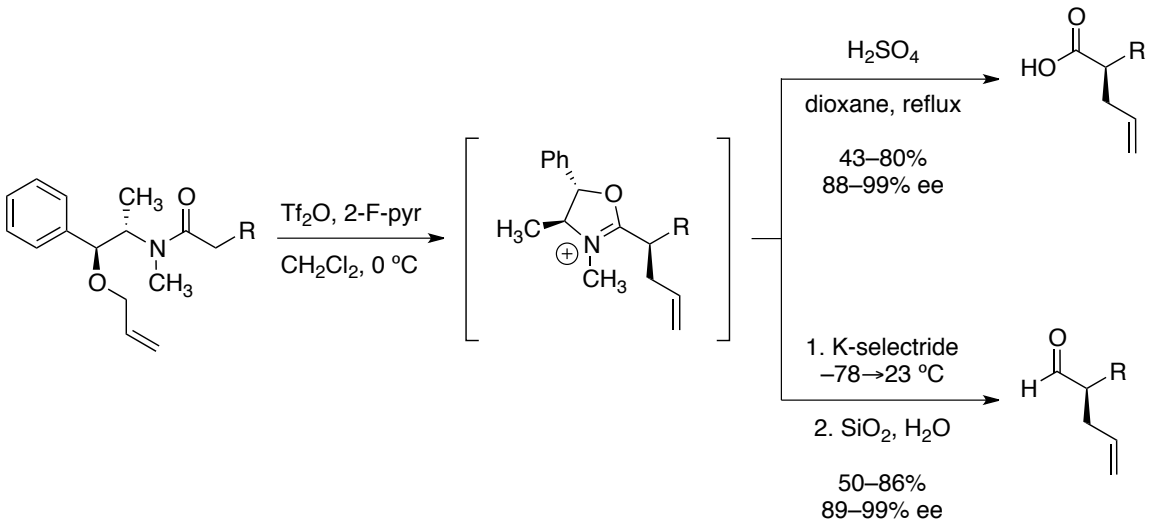
Scheme 1.38 Transformations of γ-amino amides. R = methyl, *i*-propyl, benzyl, phenyl.

Pseudoephedrine-Directed Asymmetric Claisen Rearrangement

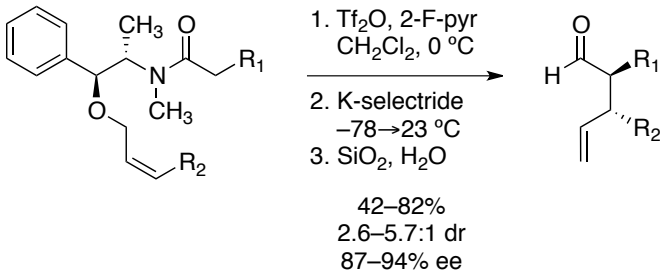
Maulide et al. have studied the Claisen rearrangement of activated allyl ethers, most recently using pseudoephedrine to direct an asymmetric variant of this important sigmatropic rearrangement.[46] Using *O*-allyl pseudoephedrine amides, a Claisen rearrangement was initiated

[46] Peng, B.; Geerdink, D.; Maulide, N. *J. Am. Chem. Soc.* **2013**, *135*, 14968–14971.

by treatment of the amides with triflic anhydride in the presence of 2-fluoropyridine. It is noteworthy that the diastereoselectivity of the rearrangement was opposite to that obtained in Myers' asymmetric allylation of pseudoephedrine amide enolates. The rearrangement products were not isolated, and were instead subjected to either acidic hydrolysis or reduction conditions to obtain carboxylic acids and aldehydes, respectively (Scheme 1.38). These sigmatropic rearrangement conditions were tolerant of functional groups that would be problematic in pseudoephedrine amide enolate allylation reactions, including nitriles, esters, ketones, and terminal alkynes. The rearrangement also worked with substituted olefins to give α- and β-branched aldehydes with moderate diastereoselectivity and high enantiomeric excess (Scheme 1.39).



Scheme 1.39 Stereocontrolled Claisen rearrangement of *O*-allyl pseudoephedrine amides followed by acidic hydrolysis or reduction. R = alkyl (including nitrile, ester, ketone, alkyne, and alkene functional groups), alkyl ethers, benzyl.



Scheme 1.40 Diastereoselective Claisen rearrangement of substituted *O*-(*Z*)-crotyl pseudoephedrine amides followed by reduction to the corresponding aldehydes. R_1 = alkyl. R_2 = alkyl.

Chapter 2

On the Development of Pseudoephenamine

Introduction

Given the broad utility of pseudoephedrine summarized in Chapter 1, it would be beneficial to the field of organic chemistry to develop an analogue of pseudoephedrine that exhibits or expands its capabilities as a chiral auxiliary while avoiding its regulatory issues. To that end, Marvin Morales, a graduate student in the Myers group, prepared a number of pseudoephedrine analogues focused primarily on substitutions of the phenyl ring of pseudoephedrine (analogues **22**–**24**), though he also prepared an analogue replacing the *C*-methyl group with a phenyl group (pseudoephenamine[47] (**25**), Figure 2.1).[48]

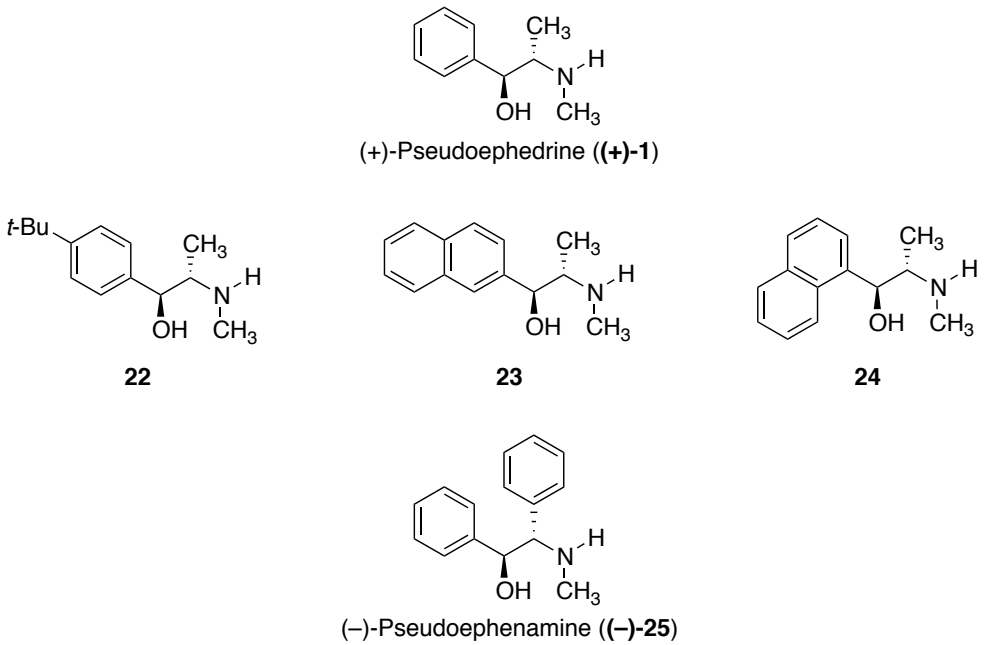


Figure 2.1 Potential pseudoephedrine analogues.

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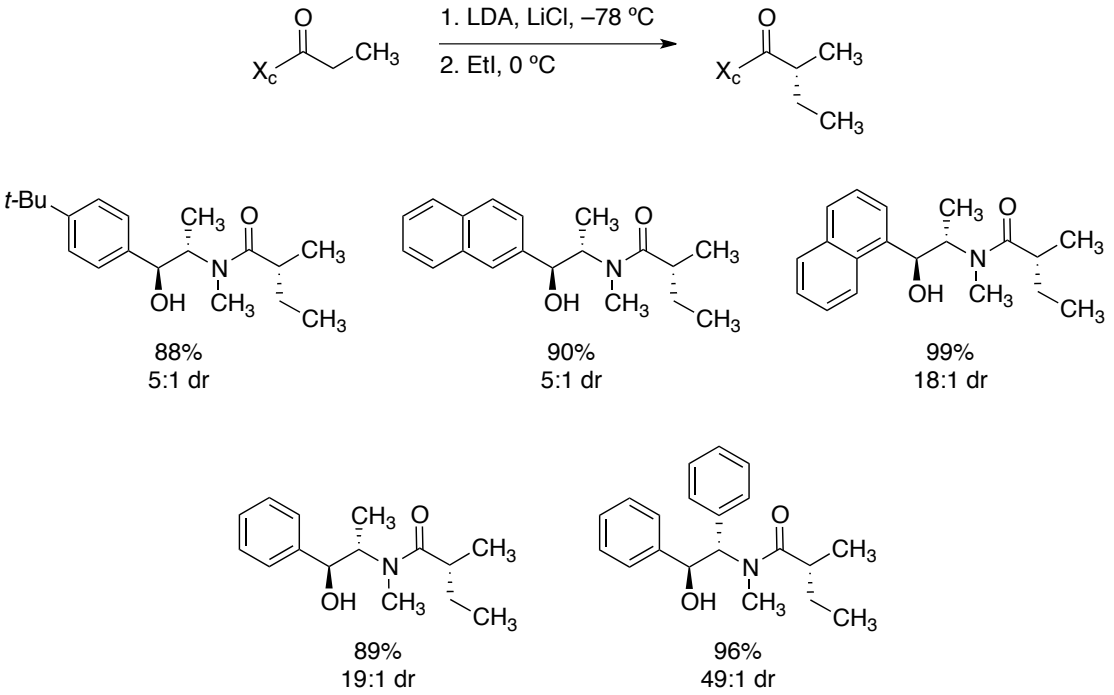
[47] The name pseudoephenamine is derived from the term ephenamine, which was used in the Federal Registrar (June 7, 1951) to describe (1*R*,2*S*)-2-methylamino-1,2-diphenylethanol in a salt form of penicillin G.

[48] Morales, M. R. (2012) *Pseudoephenamine: A Practical Chiral Auxiliary for Asymmetric Synthesis*. Ph.D. Thesis, Harvard University.

In alkylation reactions using the propionamide derivatives of these pseudoephedrine analogues, it was found that the pseudoephenamine amide enolate was alkylated with notably higher diastereoselectivity compared to the other pseudoephedrine analogues (Scheme 2.1).



Scheme 2.1 Alkylation of pseudoephedrine propionamide analogues with ethyl iodide.

Based on these results, pseudoephenamine was selected as promising replacement for pseudoephedrine, and, as the following sections will illustrate, pseudoephenamine has been found to hold several advantages over pseudoephedrine. In addition to the lack of government regulation of the auxiliary and any of its precursors or derivatives, asymmetric alkylation reactions employing pseudoephenamine proceed with equal or greater diastereoselectivity in comparison to the corresponding alkylation reactions of pseudoephedrine amide enolates, with notable enhancement in the diastereoselectivities of alkylation reactions forming quaternary carbon stereocenters. More practically, pseudoephenamine amides are typically free-flowing crystalline solids (making them easy to manipulate), and the ^{1}H NMR spectra of these amides

exhibit sharp, well-defined peaks, whereas the rotational isomerism present in pseudoephedrine amides leads to broad peaks that make spectra interpretation and assignment more difficult.

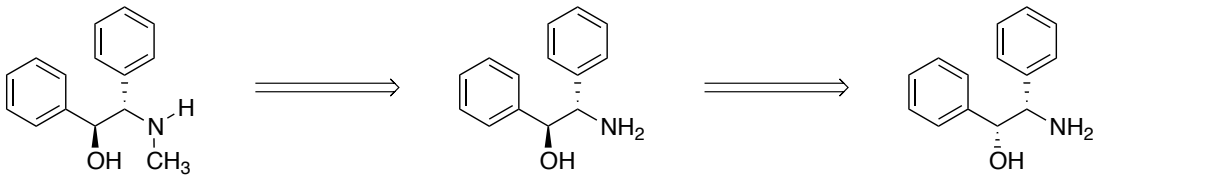
First-Generation Synthesis of Pseudoephenamine

Due to pseudoephenamine's present lack of commercial availability, it was necessary to develop a synthesis of both enantiomers of the auxiliary.[49] The most direct precursor to pseudoephenamine (alternatively, (+)-(1*R*,2*R*)-2-methylamino-1,2-diphenylethanol or (–)-(1*S*,2*S*)-2-methylamino-1,2-diphenylethanol) is the desmethyl amino alcohol of proper stereochemistry (i.e. (+)-(1*R*,2*R*)-1,2-diphenyl-2-aminoethanol [**(+)-26**] or (–)-(1*S*,2*S*)-1,2-diphenyl-2-aminoethanol [**(–)-26**], respectively, Scheme 2.2). Unfortunately, the cost of these amino alcohols is prohibitively high for large-scale production of pseudoephenamine, though the cost of the ephenamine diastereomers of the amino alcohol (i.e. (+)-(1*S*,2*R*)-1,2-diphenyl-2-aminoethanol [**(+)-27**] or (–)-(1*R*,2*S*)-1,2-diphenyl-2-aminoethanol [**(–)-27**], respectively) are more reasonable.[50]

---

[49] For previous syntheses of pseudoephenamine, see: a) Yamashita, J.; Kawahara, H.; Ohashi, S.; Honda, Y.; Kenmotsu, T.; Hashimoto, H. *Tech. Rep. Tohoku University* **1983**, *48*, 211–219. b) Meyers, A.I.; Marra, J.M. *Tetrahedron Lett.* **1985**, *26*, 5863–5866. c) Lou, R.; Mi, A.; Jiang, Y.; Qin, Y.; Li, Z.; Fu, F.; Chan, A.S.C. *Tetrahedron* **2000**, *56*, 5857–5863.

[50] Currently, (–)-(1*S*,2*S*)-1,2-diphenyl-2-aminoethanol is available from Sigma-Aldrich, LLC at a cost of $112 for 500 mg, and (–)-(1*R*,2*S*)-1,2-diphenyl-2-aminoethanol is available from Ace Synthesis, LLC at a cost of $550 for 100 g.



(–)-pseudoephenamine **(–)-25** | (–)-(1*S*,2*S*)-1,2-diphenyl-2-aminoethanol **(–)-26** | (–)-(1*R*,2*S*)-1,2-diphenyl-2-aminoethanol **(–)-27**

Scheme 2.2 Retrosynthesis of (–)-pseudoephenamine.

Fortunately, robust chemistry for the conversion of **(+)-** or **(–)-27** to **(+)-** or **(–)-26**, respectively, was developed by Max Tishler and coworkers at Merck in the early 1950s,[51] and it was this chemistry that formed the foundation of the first-generation synthesis of pseudoephenamine, which is outlined in Scheme 2.3.[52,53,54]

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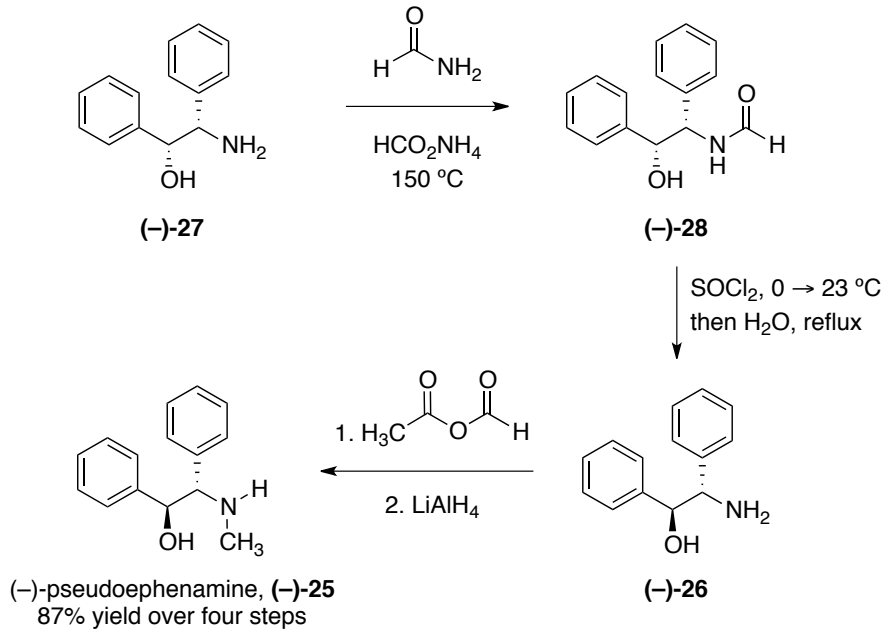
[51] Weijlard, J.; Pfister III, K.; Swanezy, E. F.; Robinson, C. A.; Tishler, M. *J. Am. Chem. Soc.* **1951,** *73*, 1216–1218.

[52] For the first synthesis of (1*R*,2*R*)- and (1*S*,2*S*)-1,2-diphenyl-2-aminoethanol, see: a) Erlenmeyer, E. *Annalen.* **1899**, *307*, 113–137. b) Erlenmeyer, E. *Chem. Ber.* **1899**, *32*, 2377–2378. c) Erlenmeyer, E.; Arnold, A. *Justus Liebigs Ann. Chem.* **1904**, *337*, 307–328.

[53] For the use of (1*R*,2*S*)- and (1*S*,2*R*)-1,2-diphenyl-2-aminoethanol in chiral auxiliaries, see: a) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103–1104. b) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547–1557. c) Williams, R. M.; Fegley, G. J.; *J. Am. Chem. Soc.* **1991**, *113*, 8796–8806. d) Williams, R. M.; Im, M. *J. Am. Chem. Soc.* **1991**, *113*, 9276–9286. e) Williams, R. M.; Zhai, W.; Aldous, D. J.; Aldous, S. C. *J. Org. Chem.* **1992**, *57*, 6527–6532.

[54] For selected other uses of 1,2-diphenyl-2-aminoethanol in asymmetric synthesis, see: a) Hashimoto, Y.; Takaoki, K.; Sudo, A.; Ogasawara, T.; Saigo, K. *Chem. Lett.* **1995**, 235–236. b) Hirayama, L. C.; Gamsey, S.; Knueppel, D.; Steiner, D.; DeLaTorre, K.; Singaram, B. *Tetrahedron Lett.* **2005**, *46*, 2315–2318. c) Clayden, J.; Parris, S.; Cabedo, N.; Payne, A. H.; *Angew. Chem. Int. Ed.* **2008**, *47*, 5060–5062. d) Mahadik, G. S.; Knott, S. A.; Szczepura, L. F.; Peters, S. J.; Standard, J. M.; Hitchcock, S. R.; *J. Org. Chem.* **2009**, *74*, 8164–8173. e) Seashore-Ludlow, B.; Villo, P.; Häcker, C.; Somfai, P. *Org. Lett.* **2010**, *12*, 5274–5277.

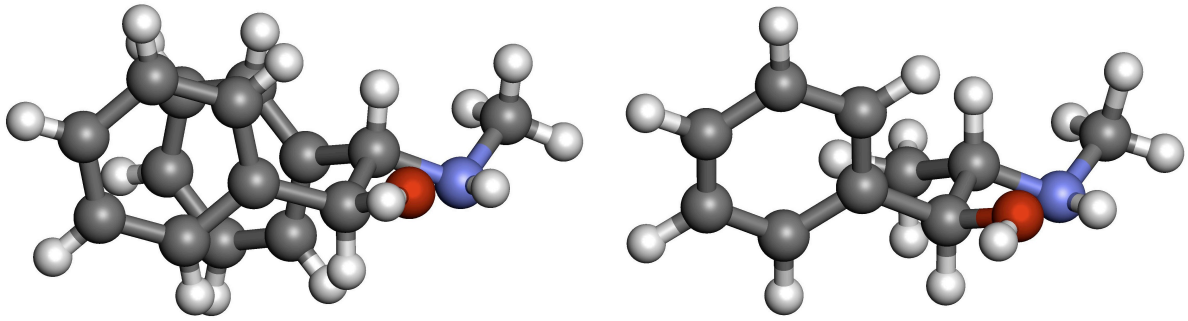


Scheme 2.3 First-generation synthesis of (–)-pseudoephenamine.

As reported by Tishler et al., formylation of **(–)-27** in warm, neat formamide produces the *N*-formyl adduct **(–)-28**, though it was necessary in the present work to include ammonium formate (0.2 equiv) in the reaction mixture to ensure maximum yield of **(–)-28** with minimal by-products. Activation of the benzylic alcohol of formamide **(–)-28** with thionyl chloride promoted invertive displacement of the secondary hydroxyl group by the *N*-formyl group, and the resulting oxazoline was hydrolyzed in refluxing water to give amino alcohol **(–)-26** as a single diastereomer after recrystallization from ethanol. It should be noted that this recrystallization was the only purification necessary in this synthesis. Formylation of **(–)-26** with acetic formic anhydride followed by reduction of the resulting formamide with lithium aluminum hydride (LAH) gave pseudoephenamine in 87% yield over four steps.[55] Using this process, (+)- and (–)-pseudoephenamine were routinely synthesized on 20–40 g scale, and the final auxiliary could be recrystallized from hot ethanol to produce large, orthorhombic crystals. These crystals were

[55] Effenberger, F.; Gutterer, B.; Jäger, J. *Tetrahedron: Asymmetry* **1997**, *8*, 459–467.

suitable for X-ray crystallographic analysis, and, as shown in Figure 2.2, pseudoephenamine was found to adopt a remarkably similar conformation to pseudoephedrine in the solid state.



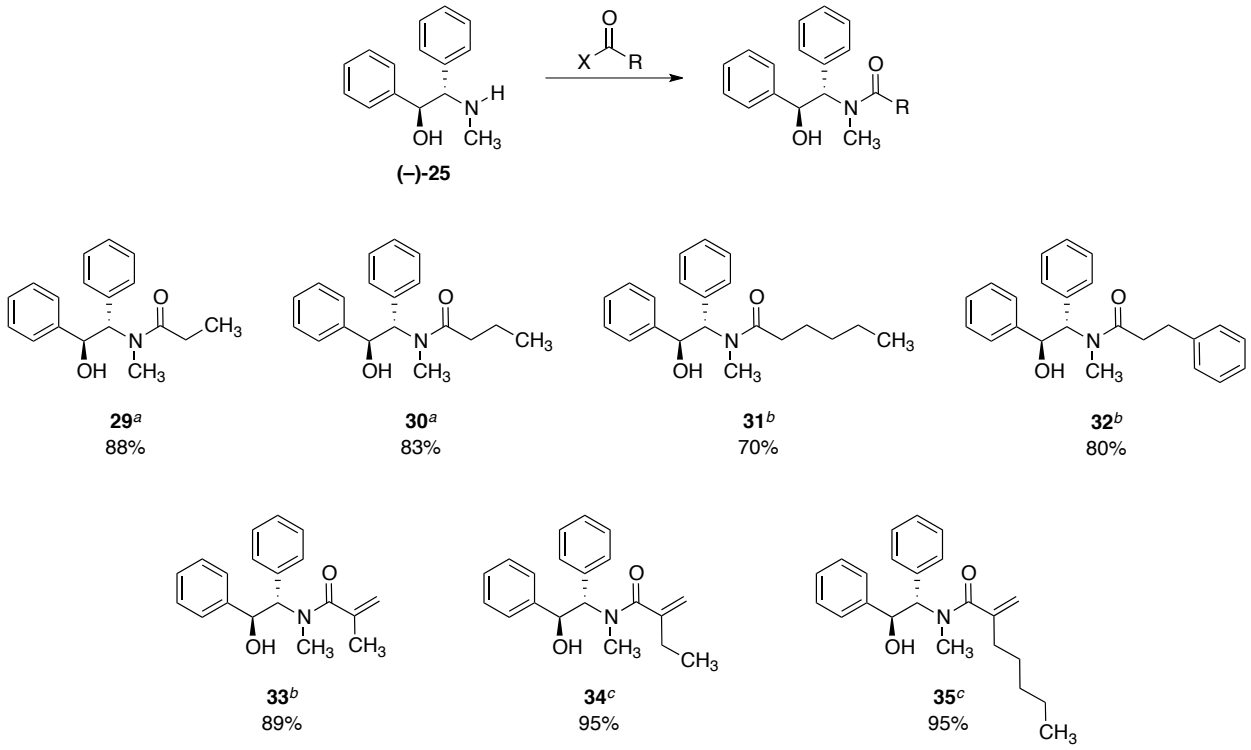
(–)-pseudoephenamine **(+)pseudoephedrine**

Figure 2.2 Comparison of the X-ray crystal structures of (–)-pseudoephenamine (left) and (+)-pseudoephedrine (right).[56]

Synthesis of Pseudoephenamine Amides

Pseudoephenamine amides were conveniently prepared by coupling of the auxiliary with carboxylic acids or by acylation with the appropriate carboxylic acid chloride or anhydride, and the amides synthesized as part of this work are presented in Scheme 2.4. All amides save for acrylamides **34** and **35** were crystalline solids that were typically purified by recrystallization (see Experimental Information for details).

[56] a) The pseudoephedrine crystal structure was obtained from the Cambridge Crystallographic Database (PSEPED01). Mathew, M.; Palenik, G. J. *Acta Crystallogr., Sect. B.* **1977**, *33*, 1016–1022. b) The hydrogen atoms of the benzene ring of pseudoephedrine were regenerated at idealized positions using DS Visualizer. Allen, F. H. *Acta Crystallogr., Sect. B.* **2002**, *58*, 380–388.

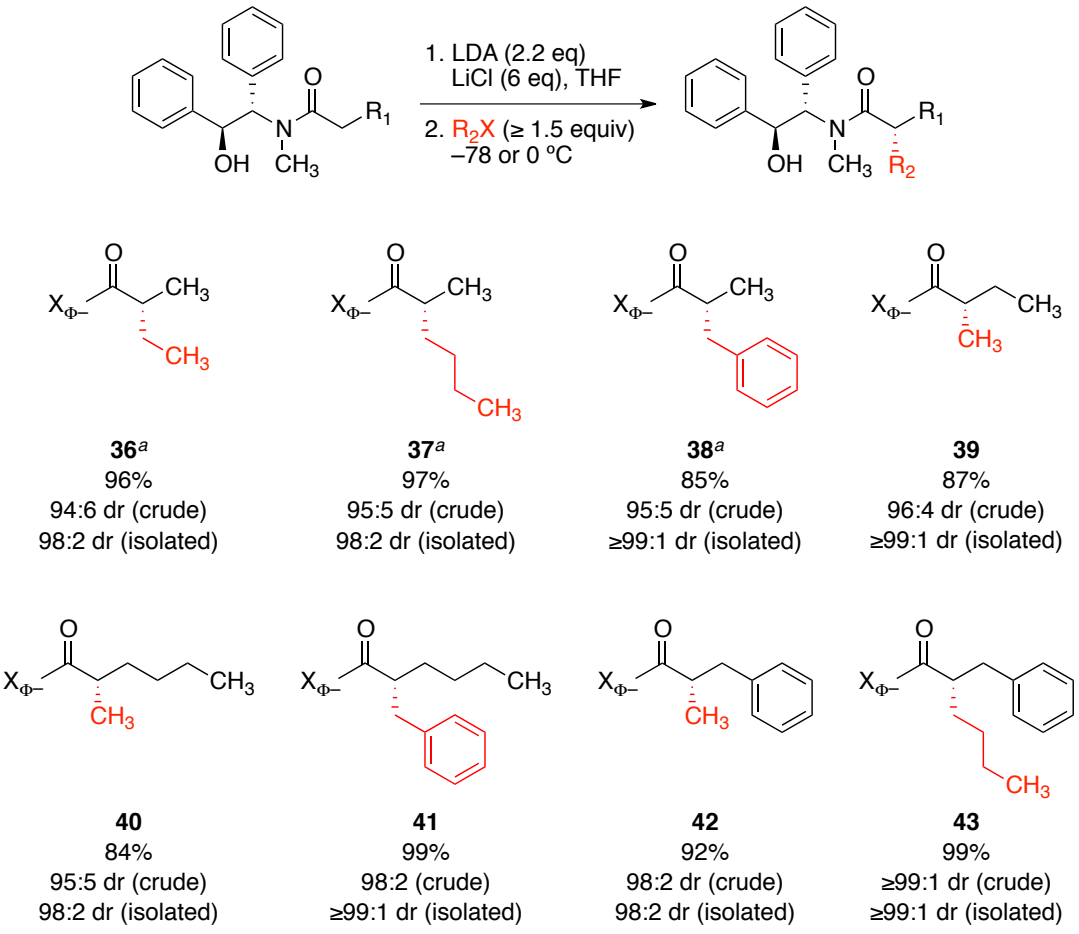


Scheme 2.4 Synthesis of pseudoephenamine amides. X = OH, Cl, RCO_2. [a] Prepared from the corresponding carboxylic acid anhydride. [b] Prepared from the corresponding carboxylic acid chloride. [c] Prepared from the corresponding carboxylic acid.

Stereocontrolled Alkylation of Pseudoephenamine Amides

Enolization and alkylation of pseudoephenamine amides was found to work very well under the conditions that were previously developed for the enolization and alkylation of pseudoephedrine amides. Generally, pseudoephenamine amide enolates were generated with lithium diisopropylamide (LDA, 2.2 equiv) in tetrahydrofuran (THF) at –78 ºC in the presence of lithium chloride (6 equiv). However, pyridine was required as a co-solvent (1:1 THF:pyridine) when using pseudoephenamine propionamide (**29**) due to the low solubility of this amide in THF alone. In any case, addition of the desired alkyl halide (1.5–4.0 equiv) to the enolate solution at –78 ºC or 0 ºC led to the formation of alkylated products in 84–99% yield (Scheme 2.5). The crude amides were of high diastereomeric purity (≥94:6 dr, as measured by HPLC analysis of the

crude product or ^{1}H NMR analysis of the oxazolinium triflate derivatives[15]), though the products were often further enriched upon purification by recrystallization or column chromatography (≥98:2 dr). The yields and diastereoselectivities observed in these alkylations were comparable to the corresponding alkylation reactions employing pseudoephedrine, and the majority of the alkylation products were solids.



Scheme 2.5 Alkylation of pseudoephenamine amide enolates. X = Br, I. [a] Pyridine was required as a co-solvent with THF (1:1).

As demonstrated by the reactions illustrated above, alkylation of pseudoephenamine amide enolates proceeds with the same diastereofacial selectivity observed in the alkylation of pseudoephedrine amide enolates (Figure 2.3a). Thus, when drawn in an extended zig-zag

conformation, the proximal phenyl ring of the auxiliary and the newly introduced alkyl group exhibit a 1,4-*syn* relationship (Figure 2.3b).

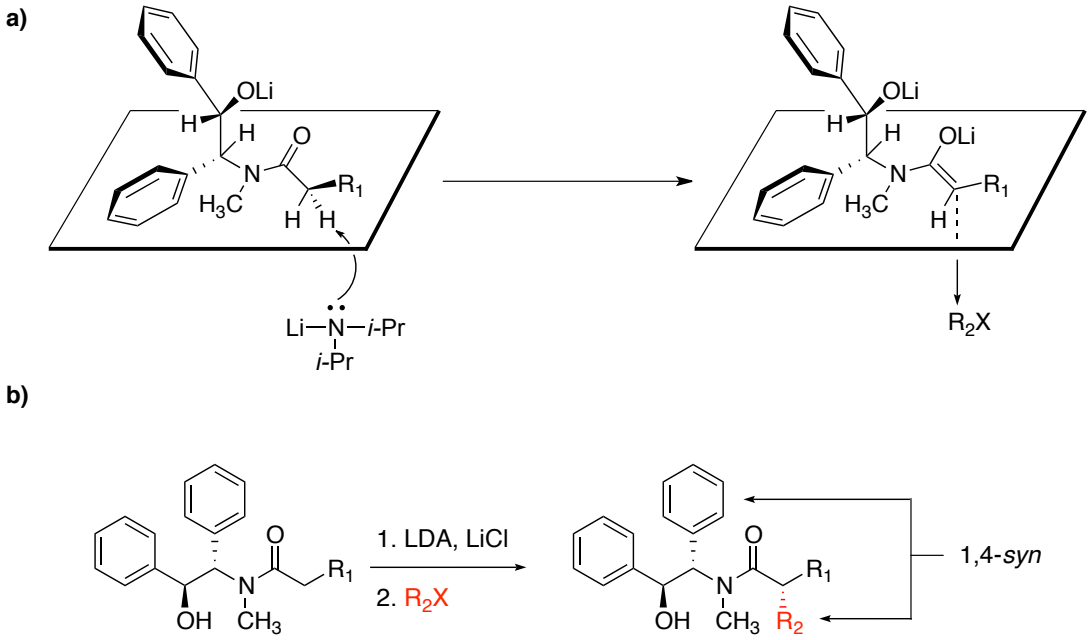
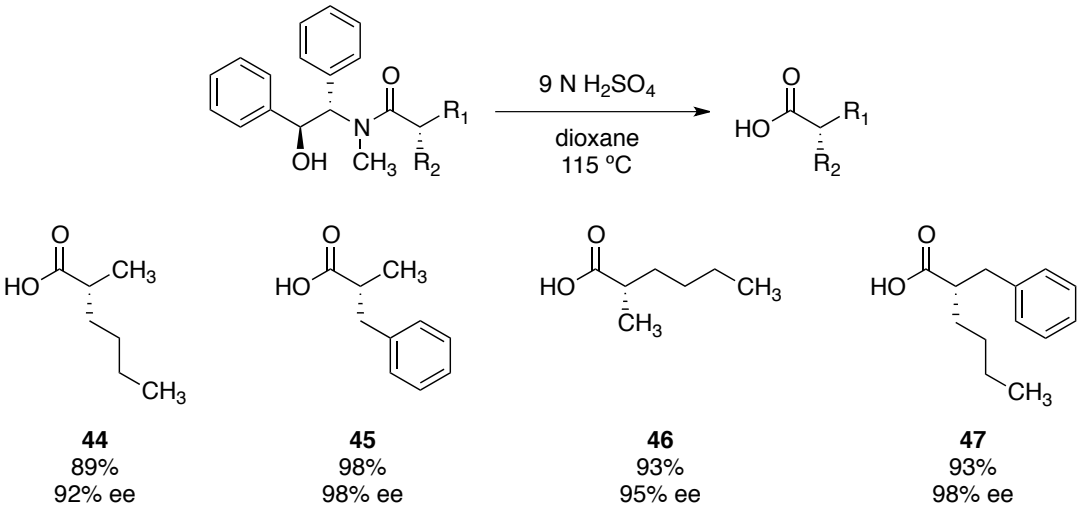


Figure 2.3 Guides for the observed diastereoselectivity in pseudoephenamine amide enolate alkylations. a) Stereochemical model for the selectivity of amide deprotonation and alkylation using alkyl halides as electrophiles. b) Mnemonic to predict the stereochemical outcome of pseudoephenamine-directed alkylation reactions.

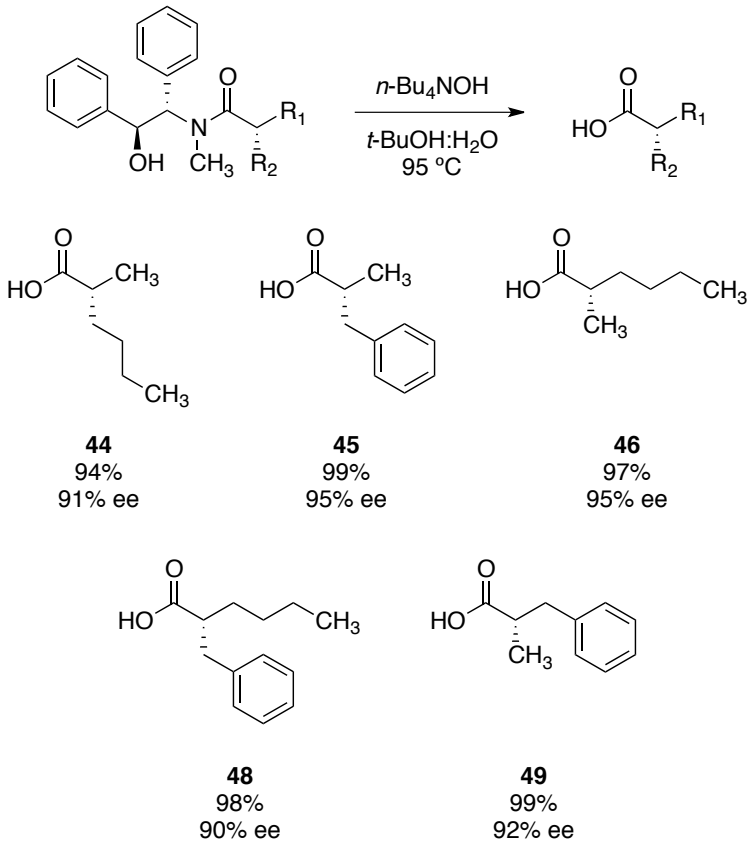
Transformations of Pseudoephenamine Amides

The utility of pseudoephedrine alkylation chemistry is due in large part to the fact that pseudoephedrine amides are easily converted to enantioenriched carboxylic acids, aldehydes, ketones, and primary alcohols. Fortunately, pseudoephenamine amides exhibit largely the same reactivity under identical conditions. As summarized in Schemes 2.6 and 2.7, pseudoephedrine amide alkylation products were easily converted to carboxylic acids under acid or basic conditions, to ketones upon treatment with an appropriate organolithium reagent, and to primary alcohols when reduced by LAB. The products of these reactions were isolated in high yield with little to no loss of enantioenrichment.

Acidic Hydrolysis:

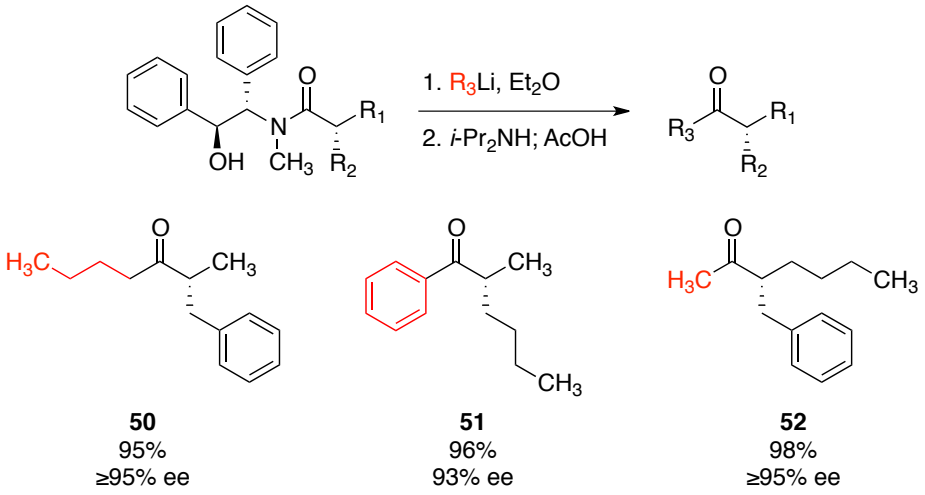


Basic Hydrolysis:

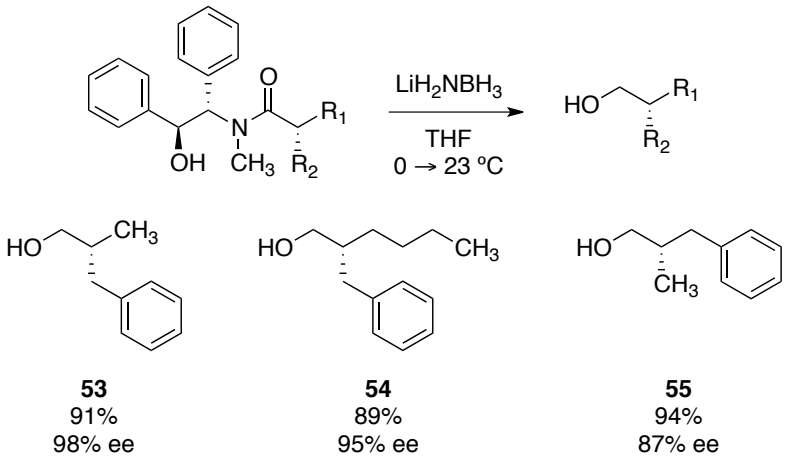


Scheme 2.6 Hydrolysis of pseudoephenamine amides under acidic and basic conditions.

Ketone Synthesis:



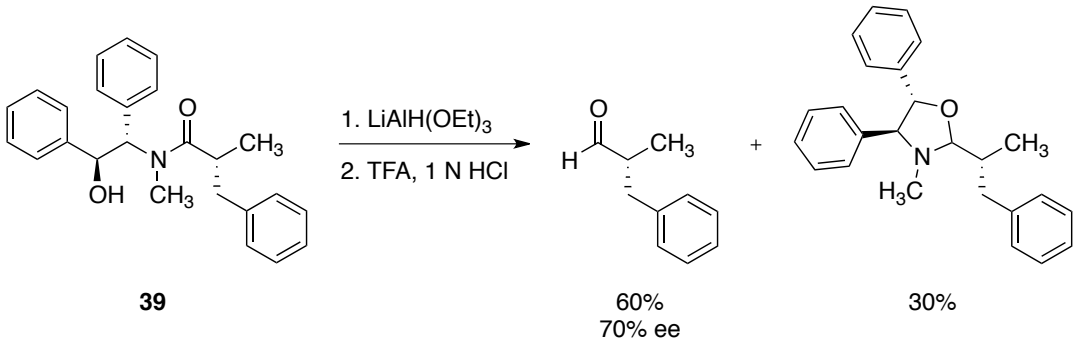
Alcohol Synthesis:



Scheme 2.7 Synthesis of ketones and primary alcohols from the corresponding pseudoephenamine amides.

One reaction of pseudoephedrine amides that does not translate to pseudoephenamine amides is the lithium triethoxyaluminum hydride reduction to the corresponding aldehyde. With pseudoephedrine amides, this reaction typically provides the desired aldehydes in 70–80% yield and 90–98% ee. However, reduction of similar pseudoephenamine amides is hampered by low yields (due to the stability of the isolable aminal intermediate produced during the course of the

reaction) and loss of enantioenrichment, as shown in Scheme 2.8. Efforts to improve this reaction have been unsuccessful.

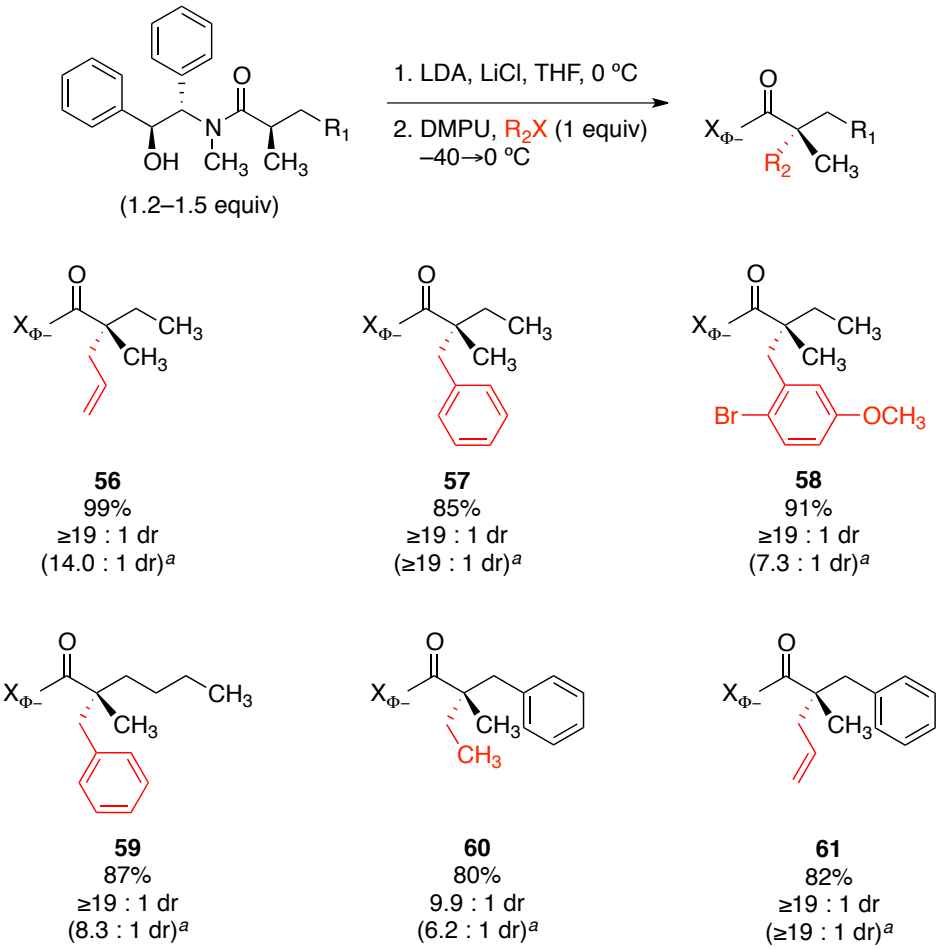


Scheme 2.8 Representative pseudoephenamine amide reduction to the corresponding aldehyde. The reaction is complicated by loss of enantioenrichment in the aldehyde and diminished yield due to the stability of the intermediate cyclic aminal.

Stereocontrolled Synthesis of Quaternary Carbon Stereocenters

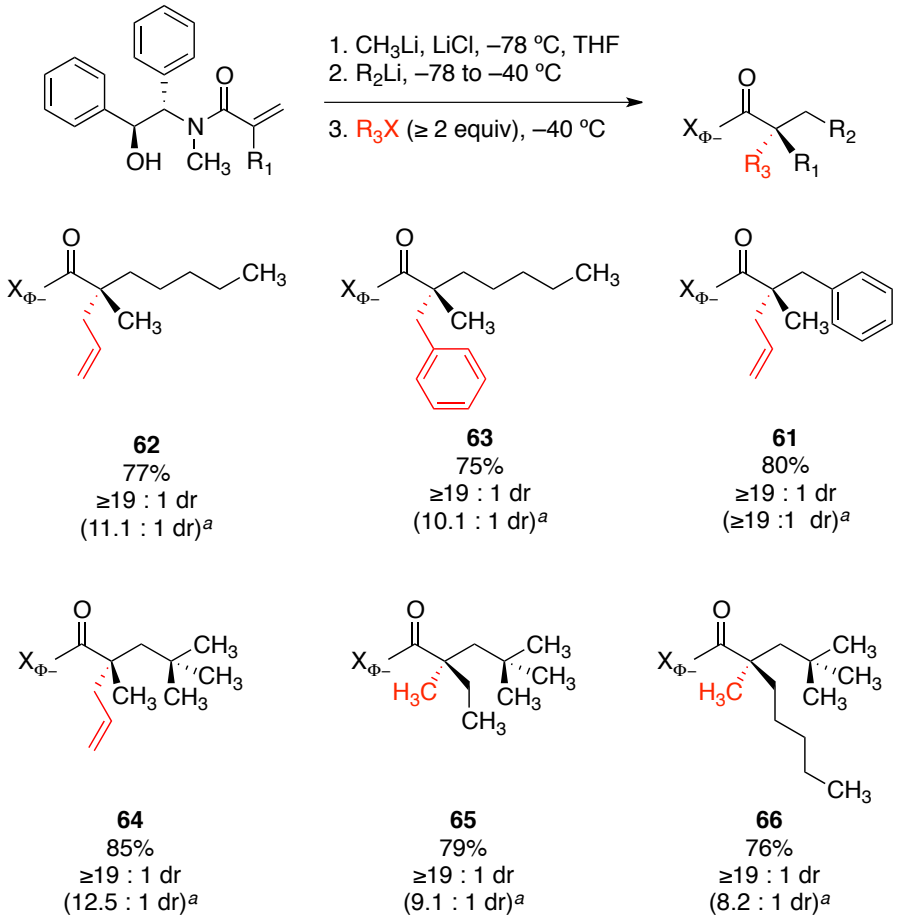
In the synthesis of quaternary carbon stereocenters, pseudoephenamine amide enolates undergo alkylation with significantly enhanced diastereoselectivity compared to the corresponding reactions using pseudoephedrine. Two methods were employed for the synthesis of quaternary centers, utilizing protocols that closely mirrored those used with pseudoephedrine. In the first method, sequential enolization-alkylation of matched α-methyl pseudoephenamine amides provided α,α-disubstituted amides in high yield and high diastereoselectivity (Scheme 2.9). The lone exception to this trend was the alkylation of amide **39** with ethyl iodide, which gave in the desired product in 9.9:1 dr.[57] Note that this protocol used the electrophile as the limiting reagent, as the yield of the reactions was lower when conducted with limiting nucleophile.

[57] The diastereomers of this product were easily separated using radial chromatography, which was enabled by the high UV activity of the chiral auxiliary.



Scheme 2.9 Enolization-alkylation of α-methyl pseudoephenamine amides to form quaternary carbon stereocenters. X = Br, I. [a] Diastereomeric ratios in parentheses correspond to the analogous transformations with pseudoephedrine.

The second method for the formation of quaternary centers involved the conjugate addition of organolithium reagents to α-alkyl pseudoephenamine acrylamides. As with the preceding reactions involving pseudoephedrine, this protocol was successful even when using *t*-BuLi as the nucleophile in the reaction, and the diastereoselectivities observed in these reactions were universally high (Scheme 2.10).



Scheme 2.10 Conjugate addition-alkylation of α-alkyl pseudoephenamine acrylamides. X = Br, I. [a] Diastereomeric ratios in parentheses correspond to the analogous transformations with pseudoephedrine.

A stereochemical model for the formation of quaternary carbon stereocenters by either of the above methods is presented in Figure 2.4. To summarize, deprotonation of α-methyl pseudoephenamine amides occurs from the bottom face of the molecule, and the electrophile subsequently approaches the enolate from the same face. Similarly, the conjugate addition protocol produces a (*Z*)-enolate that is alkylated from the bottom face of the substrate.

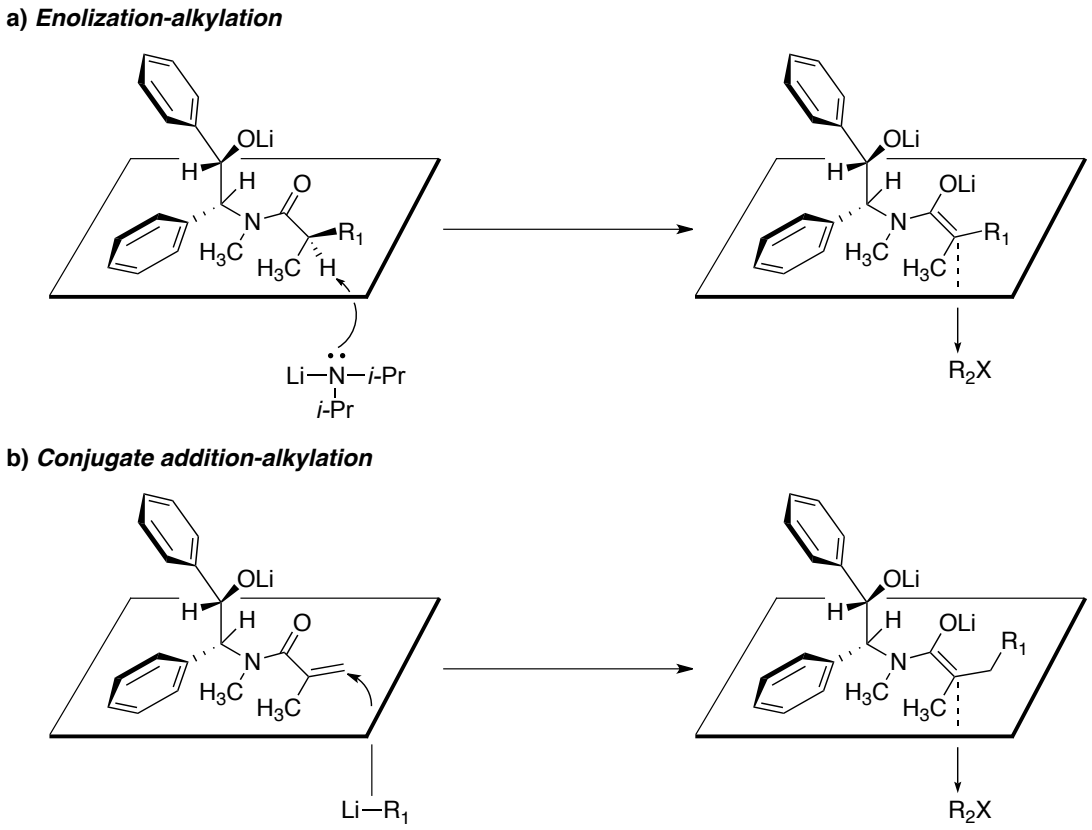


Figure 2.4 Model for the observed diastereoselectivity in alkylation reactions forming quaternary carbon stereocenters. a) Enolization-alkylation of α-methyl pseudoephenamine amides. b) Conjugate addition-alkylation of α-alkyl pseudoephenamine amides.

Both protocols for quaternary center formation provided crude material that was exceptionally clean, and the products appeared to exist in a single rotomeric form by ^{1}H NMR. These two factors allowed for the assessment of the diastereoselectivity of the alkylation reactions by examination of the ^{1}H NMR spectra of the crude products, though the selectivity could also be confirmed by formation of the oxazolinium triflate derivatives.[16] Additionally, the α,α-disubstituted amide products isolated in these reactions were solids, whereas the corresponding pseudoephedrine amide products were typically oils. Combined with the high

diastereoselectivity of the alkylation reactions, these factors make pseudoephenamine a superior chiral auxiliary for the stereocontrolled formation of quaternary carbon stereocenters.[58]

[58] For a compelling illustration of the superior utility of pseudoephenamine versus pseudoephedrine in the alkylative construction of quaternary centers within a complex series of alkaloids, see: Medley, J. W.; Movassaghi, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 4572–4576.

Experimental Information

General experimental procedures: All reactions were performed in flame-dried glassware fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 35 °C at 40 mmHg. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25-mm, 60-Å pore size, 230−400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), then were stained by submersion in aqueous potassium permanganate solution (KMnO4), followed by brief heating on a hot plate (215 °C, 10−15 s). Flash column chromatography was performed as described by Still et al.,[59] employing silica gel (60 Å, standard grade) purchased from Dynamic Adsorbents.

Materials: Commercial solvents and reagents were used as received with the following exceptions. *N,N*-diisopropylamine was distilled from calcium hydride under an atmosphere of dinitrogen at 760 mmHg. 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) was distilled from calcium hydride under reduced pressure (0.1 mmHg) and stored under argon. Dichloromethane, ethyl ether, and tetrahydrofuran were purified by the method of Pangborn et al.[60] Lithium chloride was dried at 150 °C under vacuum (0.1 mmHg) for 12 h and stored in a drying oven at 150 °C (760 mmHg); the hot dried solid was flame dried under vacuum (0.1 mmHg) for 2−3 min immediately prior to use. Benzyl bromide, allyl bromide, iodobutane, iodoethane, and iodomethane were filtered through a column of oven-dried basic alumina, neat,

[59] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

[60] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F.J. *Organometallics*. **1996**, *15*, 1518–1520.

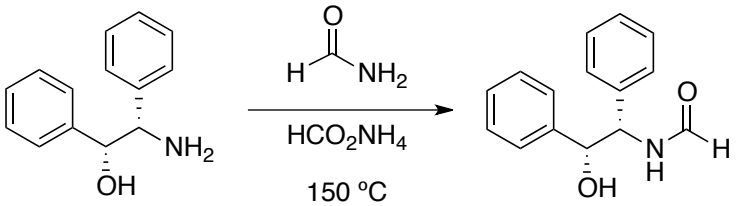
immediately prior to use. The molarity of solutions of *n-butyllithium, t-butyllithium,* methyllithium, and phenyllithium was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[61]

Instrumentation: Proton nuclear magnetic resonance spectra (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian INOVA 500 (500 MHz/125 MHz) or Varian INOVA 600 (600 MHz/150 MHz) NMR spectrometers at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHC1_3$: δ 7.26). Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonance of the NMR solvent ($CDC1_3$: δ 77.0). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, dq= doublet of quartets, dquint = doublet of quintets, sxt = sextet, m = multiplet, br = broad, app = apparent), integration, and coupling constant (J) in Hertz (Hz). Infrared (IR) spectra were obtained using a Shimadzu 8400S FT-IR spectrophotometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), and intensity of absorption (s = strong, m = medium, br = broad). Gas chromatogram retention times were acquired using a Shimadzu GC-2014 instrument equipped with a Restek Rt-βDEXsm chiral column (30m, 0.25 mm ID, 0.25 μm df). HPLC retention times were acquired using a Beckman System Gold instrument equipped with a Chiracel OD-H column (5 mm particle size, 4.6 mm x 250 mm). Optical rotations were determined using a JASCO P-2000 digital polarimeter equipped with a sodium lamp source (589 nm). Reported readings are the average of three measurements

[61] Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879–1880.

for each sample. Melting points were determined using a Thomas Scientific capillary melting point apparatus. High-resolution mass spectra were obtained at the Harvard University Mass Spectrometry Facility. X-ray crystallographic analyses were performed at the Harvard University X-Ray Crystallographic Laboratory by Dr. Shao-Liang Zheng.

Effect of formamide source on the formylation of (–)-(1*R*,2*S*)-1,2-diphenylaminoethanol:



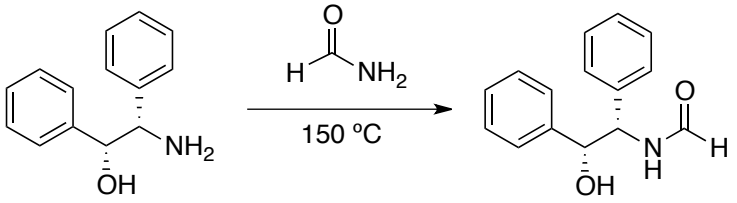
(–)-27 **(–)-28**

97%

***N*-[(1*S*,2*R*)-2-hydroxy-1,2-diphenylethyl]formamide ((–)-28)**

A 1-L round-bottom flask was charged with (–)-(1*R*,2*S*)-2-amino-1,2-diphenylethanol (43.4 g, 203 mmol, 1 equiv), ammonium formate (2.57 g, 40.7 mmol, 0.20 equiv), and formamide (162 mL, 4.07 mol, 20.0 equiv) at 23 °C. The reaction mixture was warmed to 150 °C, affording a clear solution. After 2 h, heating was discontinued and the product solution was allowed to cool to 23 °C, whereupon solidification occurred. The white solid product was suspended in water (200 mL) and the solids were collected by vacuum filtration, rinsing with two 100-mL portions of water. The washed solid was suction-dried for 1 h then was transferred to an empty 2-L round-bottom flask and dried under reduced pressure affording formamide **(–)-28** as a white solid (47.5 g, 97%, mp = 198–199 °C). TLC (80% ethyl acetate–hexanes): R_f = 0.32 (UV, $KMnO_4$). ^{1}H NMR (4.5:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, DMSO-d_6), δ: 8.54 (d, 1H, *J* = 9.5 Hz), 8.15* (t, 1H, 10.8 Hz), 7.89 (s, 1H), 7.73* (d, 1H, *J* = 11.0 Hz), 7.36-7.19 (m, 10H), 5.52 (d, 1H, *J* = 4.5 Hz), 5.47* (d, 1H, *J* = 4.5 Hz), 5.02 (dd, 1H, *J* = 9.0, 6.5 Hz), 4.77 (app t, 1H, *J* = 5.5 Hz), 4.71* (dd, 1H, *J* = 8.0, 4.5 Hz), 4.55* (app t, 1H, *J* = 9.0 Hz). ^{13}C NMR (6:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, DMSO-d_6), δ: 164.1*, 160.0, 142.8*, 142.7, 140.9*, 140.0, 128.2, 127.9*, 127.8*, 127.7*, 127.6, 127.5, 127.2*, 127.0, 126.9*,

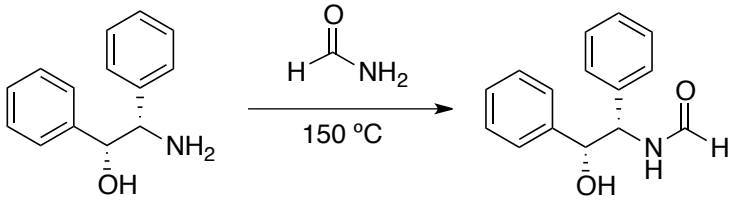
126.8, 126.7, 75.5*, 74.9, 61.6*, 56.9. FTIR (neat), cm^{-1}: 3132 (br), 3064, 3030, 1671 (m), 1453 (m). HRMS (ESI): Calcd for $(C_{15}H_{15}NO_2 + H)^+$: 242.1176. Found: 242.1177.



(–)-27 **(–)-28**

***N*-[(1*S*,2*R*)-2-hydroxy-1,2-diphenylethyl]formamide ((–)-28)**

A 1-L round-bottom flask was charged with (–)-(1*R*,2*S*)-2-amino-1,2-diphenylethanol (40.2 g, 189 mmol, 1 equiv) and formamide (150 mL, 3.77 mol, 20.0 equiv) from a fresh bottle (shown by ^{13}C NMR analysis to be pure) at 23 °C. The reaction mixture was warmed to 150 °C, resulting in a clear solution that gradually became yellow. After 2.5 h, heating was discontinued and the product solution was allowed to cool to 23 °C, whereupon solidification occurred. The yellow solid product was suspended in water (200 mL) and the solids were collected by vacuum filtration, rinsing with two 100-mL portions of water. The washed solid was suction-dried for 1 h then was transferred to a flask and dried under reduced pressure. The solid was recrystallized from hot ethanol (90 °C, 700 mL) to afford formamide **(–)-28** as a white solid (33.6 g, 74%).

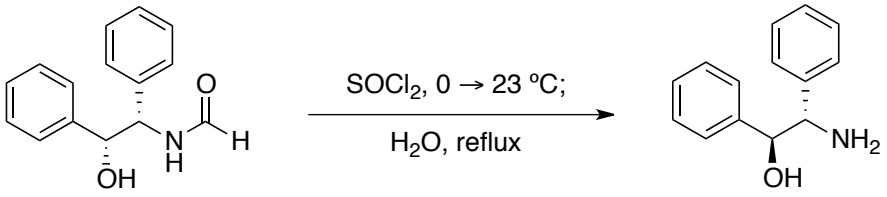


(–)-27 **(–)-28**

***N*-[(1*S*,2*R*)-2-hydroxy-1,2-diphenylethyl]formamide ((–)-28)**

A 1-L round-bottom flask was charged with (–)-(1*R*,2*S*)-2-amino-1,2-diphenylethanol (40.7 g, 191 mmol, 1 equiv) and formamide (152 mL, 3.82 mol, 20.0 equiv) from an old bottle (EM Science, shown by ^{13}C NMR analysis to contain a ~5% formate impurity) at 23 °C. The reaction mixture was warmed to 150 °C, producing a clear solution. After 3 h, heating was discontinued and the product solution was allowed to cool to 23 °C, whereupon solidification occurred. The white solid product was suspended in water (200 mL) and the solids were collected by vacuum filtration, rinsing with two 100-mL portions of water. The washed solid was suction-dried for 1 h then was transferred to a flask and dried under reduced pressure affording formamide **(–)-28** as a white solid (44.6 g, 98%).

Synthesis of (1S,2S)-pseudoephenamine:

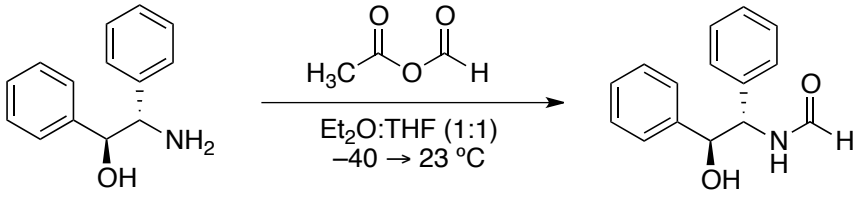


(–)-28 92% **(–)-26**

(–)-(1*S*,2*S*)-2-amino-1,2-diphenylethanol ((–)-26)

A 2-L round-bottom flask was charged with formamide **(–)-28** (44.6 g, 185 mmol, 1 equiv) then was cooled to 0 °C. Thionyl chloride (94.0 mL, 1.30 mol, 7.00 equiv) was added and the resulting clear, yellow solution was stirred for 10 min at 0 °C and for 30 min at 23 °C. Ice (1070 g) was added slowly (Caution: HCl gas evolution!). A white solid precipitated. After fitting with a reflux condenser the flask was warmed to 120 °C. The resulting clear solution was stirred for 2 h at 120 °C. The reaction flask was allowed to cool to 23 °C, during which time the solution became opaque. Once cool, 5 N aqueous sodium hydroxide solution (1 L) was added to the solution, leading to the precipitation of an off-white solid. The suspension was stirred for 30 min at 23 °C. The solids were collected by vacuum filtration, rinsing with two 200-mL portions of water. The washed solid was suction-dried for 1 h then was transferred to a 500-mL flask. The solid was dried under reduced pressure. The dried pale-green solid was recrystallized from hot absolute ethanol (140 mL, 80 °C). A second batch of crystals was collected to give optically pure amino alcohol **(–)-26** was a white, crystalline solid (36.1 g, 92%, mp = 106–108 °C, $[\alpha]_D^{25}$ = –121.69, *c* 1.12, EtOH). TLC (80% ethyl acetate–hexanes): R_f = 0.13, streak (UV, $KMnO_4$). ^{1}H NMR (600 MHz, $CDCl_3$), δ: 7.12–7.31 (m, 10H), 4.65 (d, 1H, *J* = 6.4 Hz), 3.99 (d, 1H, *J* = 6.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 142.4, 141.7, 128.3, 128.0, 127.3, 127.3, 127.0, 126.5,

78.0, 82.5. FTIR (neat), cm^{-1}: 2928 (m), 2868, 1603, 1493, 1452 (m). HRMS (ESI): Calcd for $(C_{14}H_{15}NO + H)^+$: 214.1226. Found: 214.1221.

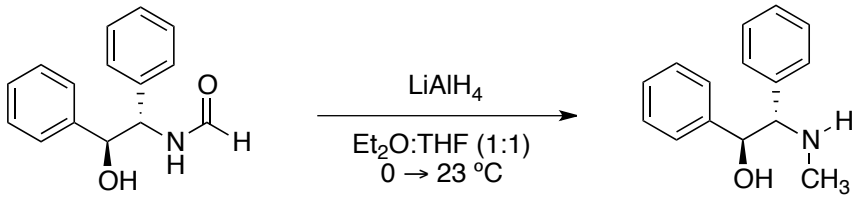


(–)-26 99% **(–)-94**

***N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]formamide ((–)-94)**

A mixture of acetic anhydride (28.9 mL, 306 mmol, 2.00 equiv) and formic acid (12.9 mL, 337 mmol, 2.10 equiv) was heated for 1 h at 60 ºC then was cooled to 23 ºC. The cooled solution was added by cannula to a solid mixture of (–)-(1*S*,2*S*)-2-amino-1,2-diphenylethanol (32.6 g, 153 mmol, 1 equiv) in a 1:1 mixture of ether (392 mL) and tetrahydrofuran (392 mL) at –40 ºC. The resulting clear, colorless solution was stirred for 45 min at –40 ºC and for 1.75 h at 23 ºC. The reaction mixture was poured into 2 N aqueous sodium hydroxide solution (750 mL), and the layers were separated. The organic layer was washed with 2 N aqueous sodium hydroxide solution (750 mL) and saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford formamide **(–)-94** as a white solid (36.5 g, 99%, mp = 104-105 ºC). TLC (80% ethyl acetate–hexanes): R_f = 0.36 (UV, $KMnO_4$). ^{1}H NMR (9:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, DMSO-d_6), δ: 8.58 (d, 1H, J = 9.3 Hz), 8.17* (t, 1H, J = 10.7 Hz), 7.97 (s, 1H), 7.86* (d, 1H, J = 11.2 Hz), 7.35 (d, 2H, J = 7.8 Hz), 7.33–7.29 (m, 2H), 7.27 (td, 4H, J = 7.3, 3.4 Hz), 7.23–7.12 (m, 3H), 5.62 (m, 1H), 5.03 (dd, 1H, J = 9.3, 3.9 Hz), 4.81 (t, 1H, J = 4.2 Hz), 4.72* (t, 1H, J = 5.6 Hz), 4.58* (dd, 1H, J = 9.8, 6.4 Hz). ^{13}C NMR (8:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, DMSO-d_6), δ: 164.6*, 160.7, 143.1, 142.8*, 141.4, 140.6*, 127.9*, 127.8, 127.7*, 127.6, 127.5*, 127.3, 126.9, 126.8*, 126.7,

126.5, 75.7*, 75.1, 62.5*, 57.4. FTIR (neat), cm^{-1}: 3300 (br), 3036, 2876, 1661 (s), 1496 (m). HRMS (ESI): Calcd for $(C_{15}H_{15}NO_2 + Na)^+$: 264.0995. Found: 264.1002.



(–)-(1*S*,2*S*)-pseudoephenamine ((–)-25)

Solid lithium aluminum hydride (11.6 g, 302 mmol, 2.00 equiv) was added carefully in three portions (2.90 g, 2.90 g, 5.90 g; Caution: gas evolution!) to an ice-cooled solution of formamide **(–)-94** (36.4 g, 151 mmol, 1 equiv) in a 1:1 mixture of ether (472 mL) and tetrahydrofuran (472 mL). The resulting grey slurry was stirred for 10 min at 0 ºC and for 22 h at 23 ºC. The reaction mixture was cooled to 0 ºC, and excess hydride was quenched by sequential, dropwise addition of water (12 mL), 2 N aqueous sodium hydroxide solution (24 mL), and water (36 mL).[62] The slurry was poured into half-saturated aqueous sodium chloride solution (900 mL), and the layers were separated. The aqueous layer was extracted with two 900-mL portions of ether. The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford (–)-(1*S*,2*S*)-pseudoephenamine as a white solid (33.6 g, 98%, mp = 105–107 ºC, $[\alpha]_D^{25}$ = –104.24, *c* 0.990, EtOH). Recrystallization of the solid product (1.00 g) from hot absolute ethanol yielded large orthorhombic crystals (mp = 109–110 ºC, $[\alpha]_D^{25}$ = –110.5, *c* 1.05, EtOH). TLC (80% ethyl acetate–hexanes): R_f = 0.25 (UV, $KMnO_4$). ^{1}H NMR (600 MHz, $CDCl_3$), δ: 7.25–7.14 (m, 6H), 7.13–7.07 (m, 2H), 7.03 (d, 2H, *J* = 6.7 Hz), 4.57 (d, 1H, *J* = 8.5 Hz), 3.49 (d, 1H, *J* = 8.5 Hz), 2.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 141.3, 139.5, 128.1, 127.8, 127.3, 127.3, 126.8, 77.7, 72.3, 34.2. FTIR (neat), cm^{-1}: 3317, 3065,

[62] Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis.* **1967**, 581–595.

3033, 2803, 1453 (m). HRMS (ESI): Calcd for $(C_{15}H_{17}NO + Na)^+$: 250.1202. Found: 250.1205. Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16; found: C, 79.28; H, 7.57; N, 6.11.

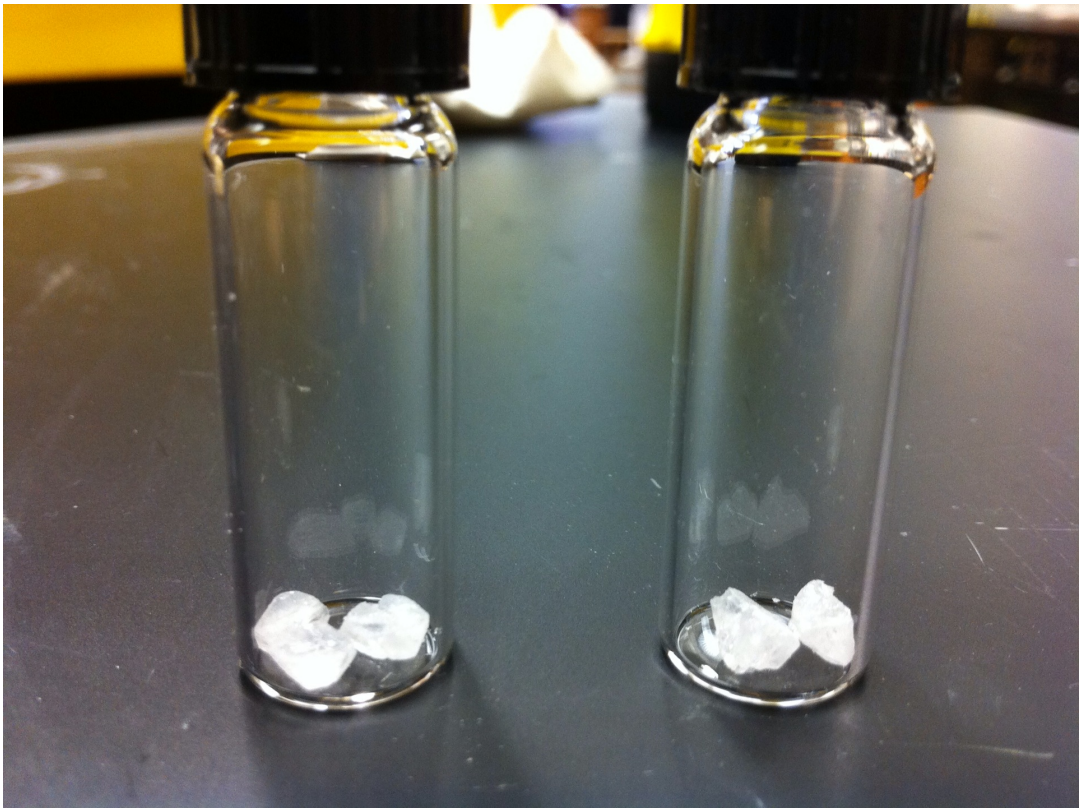
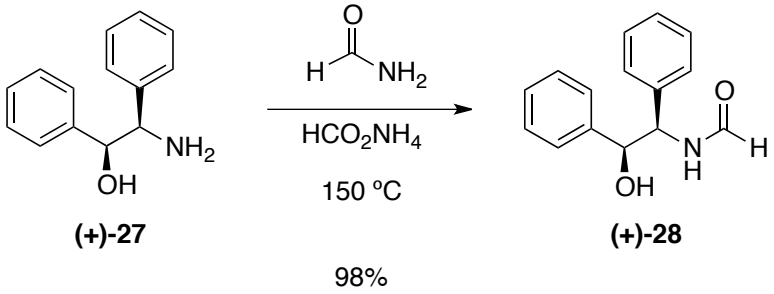


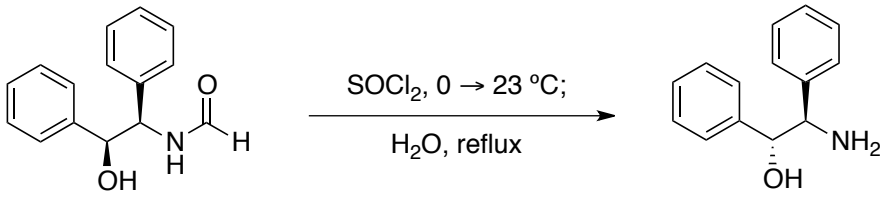
Image 2.1 Large, orthorhombic crystals of (–)-(1*S*,2*S*)-pseudoephenamine (left) and (+)-(1*R*,2*R*)-pseudoephenamine obtained after recrystallization from hot ethanol.

Synthesis of (1*R*,2*R*)-pseudoephenamine:



***N*-[(1*R*,2*S*)-2-hydroxy-1,2-diphenylethyl]formamide ((+)-28)**

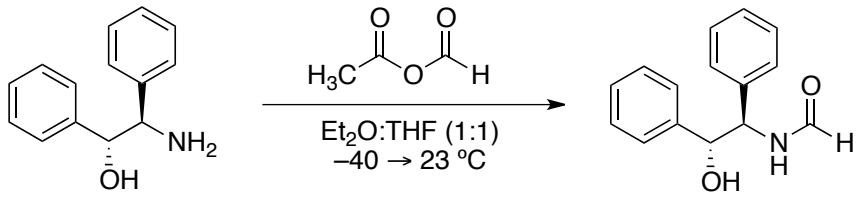
A 500-mL round-bottom flask was charged with (+)-(1*S*,2*R*)-2-amino-1,2-diphenylethanol (30.0 g, 141 mmol, 1 equiv), ammonium formate (1.77 g, 28.1 mmol, 0.20 equiv), and formamide (112 mL, 2.81 mol, 20.0 equiv) at 23 °C. The reaction mixture was warmed to 150 °C, affording a clear, pale-yellow solution. After 50 min, heating was discontinued and the product solution was allowed to cool to 23 °C, whereupon solidification occurred. The white solid product was suspended in water (300 mL) and the solids were collected by vacuum filtration, rinsing with two 200-mL portions of water. The washed solid was suction-dried for 1 h then was transferred to an empty 2-L round-bottom flask and dried under reduced pressure affording formamide **(+)-28** as a white solid (33.4 g, 98%, mp = 194–196 °C). The characterization data obtain for formamide **(+)-28** were identical to those of formamide **(–)-28.**



(+)-28 92% **(+)-26**

(1*R*,2*R*)-(+)-2-amino-1,2-diphenylethanol ((+)-26)

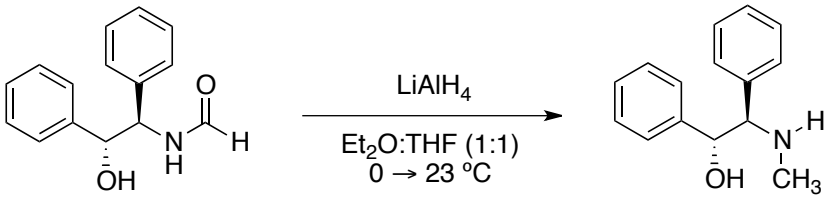
A 2-L round-bottom flask was charged with formamide **(+)-28** (33.4 g, 138 mmol, 1 equiv) then was cooled to 0 ºC. Thionyl chloride (70.4 mL, 969 mmol, 7.00 equiv) was added and the resulting clear, yellow solution was stirred for 10 min at 0 ºC and for 30 min at 23 ºC. Ice (830 g) was added slowly (Caution: HCl gas evolution!). A white solid precipitated. After fitting with a reflux condenser the flask was warmed to 125 ºC. The resulting clear solution was stirred for 2 h at 125 ºC. The reaction flask was allowed to cool to 23 ºC, during which time the solution became opaque. Once cool, 5 N aqueous sodium hydroxide solution (850 mL) was added to the solution, leading to the precipitation of an off-white solid. The suspension was stirred for 30 min at 23 ºC. The solids were collected by vacuum filtration, rinsing with two 150-mL portions of water. The washed solid was suction-dried for 1 h then was transferred to a 500-mL flask. The solid was dried under reduced pressure. The dried pale-green solid was recrystallized from hot absolute ethanol (120 mL, 80 ºC) to give optically pure amino alcohol **(+)-26** as a white, crystalline solid after two recrystallizations (27.0 g, 92%, mp = 104–106 ºC, $[\alpha]_D^{25}$ = +121.2, *c* 1.15, EtOH). The characterization data obtain for amino alcohol **(+)-26** were identical to those of amino alcohol **(–)-26**.



(+)-26 99% **(+)-94**

***N*-[(1*R*,2*R*)-2-hydroxy-1,2-diphenylethyl]formamide ((+)-94)**

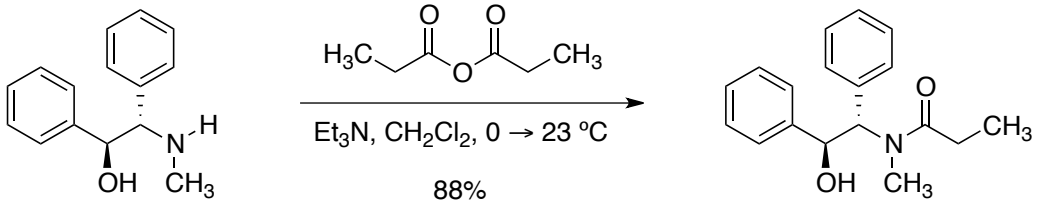
A mixture of acetic anhydride (18.6 mL, 197 mmol, 2.00 equiv) and formic acid (8.31 mL, 217 mmol, 2.10 equiv) was heated for 1 h at 60 ºC then was cooled to 23 ºC. The cooled solution was added by cannula to a solid mixture of (+)-(1*R*,2*R*)-2-amino-1,2-diphenylethanol (21.0 g, 98.0 mmol, 1 equiv) in a 1:1 mixture of ether (490 mL) and tetrahydrofuran (490 mL) at –40 ºC. The resulting clear, colorless solution was stirred for 45 min at –40 ºC and for 1.5 h at 23 ºC. The reaction mixture was poured into 2 N aqueous sodium hydroxide solution (400 mL), and the layers were separated. The organic layer was washed with 2 N aqueous sodium hydroxide solution (400 mL) and saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford formamide **(+)-94** as a white solid (23.6 g, 99%, mp = 101-103 ºC). The characterization data obtain for formamide **(+)-94** were identical to those of formamide **(–)-94**.



(+)-(1*R*,2*R*)-pseudoephenamine ((+)-25)

Solid lithium aluminum hydride (7.42 g, 196 mmol, 2.00 equiv) was added carefully in three portions (2.00 g, 2.00 g, 3.40 g; Caution: gas evolution!) to an ice-cooled solution of formamide **(+)-94** (23.6 g, 98.0 mmol, 1 equiv) in a 1:1 mixture of ether (306 mL) and tetrahydrofuran (306 mL). The resulting grey slurry was stirred for 10 min at 0 ºC and for 20.5 h at 23 ºC. The reaction mixture was cooled to 0 ºC, and excess hydride was quenched by sequential, dropwise addition of water (8 mL), 2 N aqueous sodium hydroxide solution (16 mL), and water (24 mL).[1] The slurry was poured into half-saturated aqueous sodium chloride solution (600 mL), and the layers were separated. The aqueous layer was extracted with two 400-mL portions of ether. The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford (+)-(1*R*,2*R*)-pseudoephenamine as a white solid (21.5 g, 97%) Recrystallization of the solid product from hot absolute ethanol (80 ºC, 40 mL) yields large orthorhombic crystals (15.3 g, 71%, mp = 109–110 ºC, $[\alpha]_D^{25}$ = +110.0, *c* 1.15, EtOH). The characterization data obtain for (+)-(*R*,*R*)-pseudoephenamine were indentical to those of (–)-(1*S*,2*S*)-pseudoephenamine.

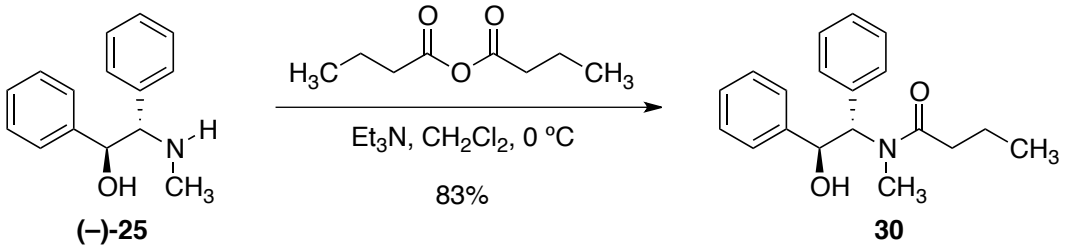
Synthesis of Pseudoephenamine Amides:



(*S*,*S*)-*N*-(2-hydroxy-1,2-diphenylethyl)-*N*-methylpropionamide (29)

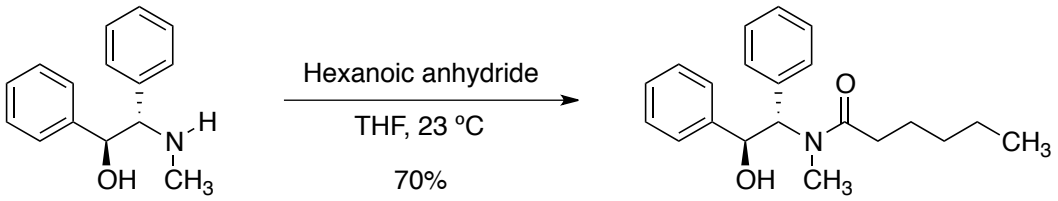
Propionic anhydride (9.64 mL, 74.8 mmol, 1 equiv) was added to a solution of (–)-(1*S*,2*S*)-pseudoephenamine (17.0 g, 74.8 mmol, 1 equiv) and triethylamine (12.5 mL, 89.8 mmol, 1.20 equiv) in dichloromethane (150 mL) at 0 ºC. The reaction mixture was stirred for 10 min at 0 ºC, then for 35 min at 23 ºC. Excess propionic anhydride was quenched by the addition of water (50 mL). The resulting biphasic mixture was partitioned between water (100 mL) and dichloromethane (650 mL), and the layers were separated. The organic layer was washed sequentially with half-saturated aqueous sodium bicarbonate solution (2 x 100 mL) and 1 N aqueous hydrochloric acid solution (2 x 100 mL). The organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated, affording a white solid. Recrystallization of the product from hot toluene (800 mL, 100 ºC) provided the propionamide **29** as a white crystalline solid (18.7 g, 88%, mp = 188-190 ºC). TLC (80% Ethyl acetate–hexanes): R_f = 0.59 (UV, $KMnO_4$). ^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.42-7.16 (m, 10H), 5.64 (d, 1H, *J* = 8.5 Hz), 5.36 (d, 1H, *J* = 8.5 Hz), 5.11* (d, 1H, *J* = 7.5 Hz), 3.89 (br s, 1H), 2.98* (s, 3H), 2.86 (s, 3H), 2.44-2.27 (m, 2H), 1.13 (t, 3H, *J* = 7.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 176.0, 141.8, 137.0, 128.4, 128.4, 128.3, 127.7, 127.5, 126.7, 73.9, 65.9, 34.1, 27.5, 9.2. FTIR (neat), cm^{-1}: 3366 (br), 2940,

1724, 1597 (s), 1454 (m), 1288 (m), 1069 (s). HRMS (ESI): Calcd for $(C_{18}H_{21}NO_2 + Na)^+$: 306.1465. Found: 306.1465.



***N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*-methylbutyramide (30)**

Butyric anhydride (1.2 mL, 7.1 mmol, 1.1 equiv) was added to a solution of (–)-(1*S*,2*S*)-pseudoephenamine (1.5 g, 6.6 mmol, 1 equiv) and triethylamine (1.1 mL, 7.9 mmol, 1.2 equiv) in dichloromethane (13 mL) at 0 ºC. The reaction mixture was stirred for 1 h at 0 ºC. Excess butyric anhydride was quenched by the addition of water (5 mL). The resulting biphasic mixture was partitioned between water (10 mL) and dichloromethane (20 mL), and the layers were separated. The organic layer was washed sequentially with half-saturated aqueous sodium bicarbonate solution (2 x 10 mL) and 1 N aqueous hydrochloric acid solution (2 x 10 mL). The organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated, affording a white solid. Recrystallization of the product from hot toluene (14 mL, 100 ºC) provided the butyramide **30** as a white crystalline solid (1.6 g, 83%, mp = 133-135 ºC). TLC (60% Ethyl acetate–hexanes): R_f = 0.45 (UV, $KMnO_4$). ^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.46-7.18 (m, 10H), 5.63 (d, 1H, *J* = 8.0 Hz), 5.40* (d, 1H, *J* = 7.0 Hz), 5.36 (d, 1H, *J* = 8.0 Hz), 5.12* (d, 1H, *J* = 7.5 Hz), 2.96* (s, 3H), 2.86 (s, 3H), 2.37-2.17 (m, 2H), 1.69-1.60 (m, 2H), 0.94 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 175.3, 141.9, 137.1, 128.4, 128.38, 128.35, 127.6, 127.5, 126.7, 73.9, 65.9, 36.2, 34.4, 18.4, 13.9. FTIR (neat), cm^{-1}: 3356 (br), 2958, 1616 (m), 1452, 1063, 908 (m). HRMS (ESI): Calcd for $(C_{19}H_{23}NO_2 + Na)^+$: 320.1621. Found: 320.1612.

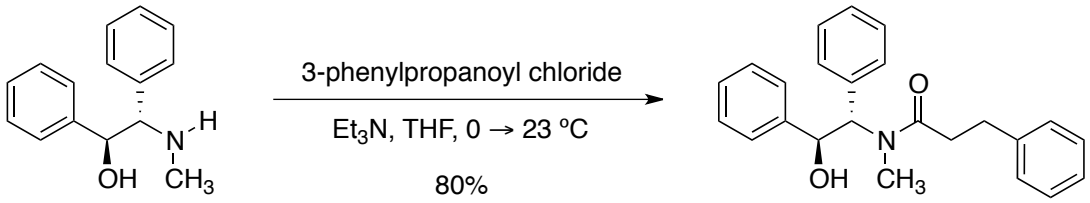


(–)-25 **31**

***N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*-methylhexanamide (31)**

Hexanoic anhydride (7.63 mL, 33.0 mmol, 1.07 equiv) was added to a solution of (–)-(1*S*,2*S*)-pseudoephenamine (7.02 g, 30.9 mmol, 1 equiv) in tetrahydrofuran (64.3 mL) at 23 °C. The reaction mixture was stirred for 1.5 h at 23 °C. Excess hexanoic anhydride was quenched by the addition of saturated aqueous sodium bicarbonate solution (39 mL). The resulting biphasic mixture was then partitioned between ethyl acetate (200 mL) and water (140 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 140 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. Recrystallization of the product from a mixture of hexanes:dichloromethane (8:1, 90 mL, 70 °C) provided the hexanamide **31** as a white solid (6.32 g, 63%, mp = 88–90 °C). A second crop was obtained providing an additional 0.75 g of product (70% total yield). TLC (60% ethyl acetate–hexanes): R_f = 0.48 (UV, $KMnO_4$). ^{1}H NMR (6.5:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.38 (d, 2H, *J* = 7.8 Hz), 7.17–7.34 (m, 8H), 5.62 (d, 1H, *J* = 7.8 Hz), 5.32–5.42 (m, 1H), 5.12* (d, 1H, *J* = 7.3 Hz), 4.01 (d, 1H, *J* = 5.4 Hz), 2.96* (s, 1H), 2.85 (s, 1H), 2.15–2.39 (m, 2H), 1.49–1.68 (m, 2H), 1.19–1.38 (m, 4H), 0.90 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR (10:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, $CDCl_3$), δ: 175.3, 174.3*, 141.8, 141.2*, 137.1, 128.5*, 128.4*, 128.3, 128.2, 128.1*, 127.6*, 127.5, 127.4, 126.9*, 126.7, 73.7, 73.4*, 65.4*, 65.3, 34.1, 34.0*, 33.2*, 31.6*, 31.5, 24.9*, 24.6,

22.4, 13.9. FTIR (neat), cm^{-1}: 3374 (br), 2957, 1607 (s), 1454 (m), 1063 (m). HRMS (ESI): Calcd for $(C_{21}H_{27}NO_2 + H)^+$: 326.2115. Found: 326.2109.

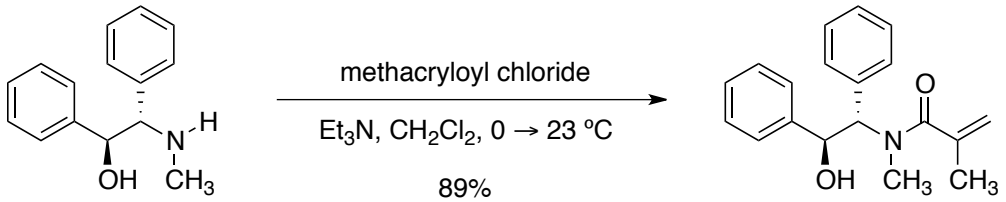


(–)-25 **32**

***N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*-methyl-3-phenylpropanamide (32)**

3-Phenylpropanoyl chloride (6.07 mL, 40.9 mmol, 1.15 equiv) was added dropwise to a solution of (–)-(1*S*,2*S*)-pseudoephenamine (8.08 g, 35.5 mmol, 1 equiv) and triethylamine (6.44 mL, 45.2 mmol, 1.30 equiv) in tetrahydrofuran (85 mL) at 0 ºC. The resulting white suspension was stirred for 10 min at 0 ºC, then for 30 min at 23 ºC. Excess acid chloride was quenched by the addition of water (7 mL). The resulting biphasic mixture was partitioned between ethyl acetate (210 mL) and saturated aqueous sodium chloride solution (70.0 mL), and the layers were separated. The organic layer was washed with saturated aqueous sodium chloride solution (2 x 100 mL). The organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated, affording a white solid. Recrystallization of the product from hot toluene (56 mL, 110 ºC) provided the phenylpropanamide **32** as a white crystalline solid (9.51 g, 74%, mp = 147–149 ºC). A second crop was obtained providing an additional 0.77 g of product (80% total yield). TLC (60% ethyl acetate–hexanes): R_f = 0.39 (UV, $KMnO_4$). ^{1}H NMR (5:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.36 (d, 2H, *J* = 7.3 Hz), 7.11–7.32 (m, 13H), 5.71 (d, 1H, *J* = 7.8 Hz), 5.29–5.39 (m, 1H), 5.06* (d, 1H, *J* = 7.3 Hz), 3.77 (d, 1H, *J* = 6.4 Hz), 2.89–3.01 (m, 2H), 2.82 (s, 3H), 2.54–2.70 (m, 2H), 2.44–2.53* (m, 2H). ^{13}C NMR (6:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, $CDCl_3$), δ: 174.1, 173.2*, 141.7, 141.5*, 141.3*, 141.1, 137.0, 128.5*, 128.4, 128.3, 128.2, 128.2*, 128.1*, 127.6*, 127.6, 127.4, 126.9*, 126.8, 126.0*, 125.9, 73.5, 73.4*, 65.4*, 64.8, 35.9, 35.1*, 33.5, 31.4*, 31.0,

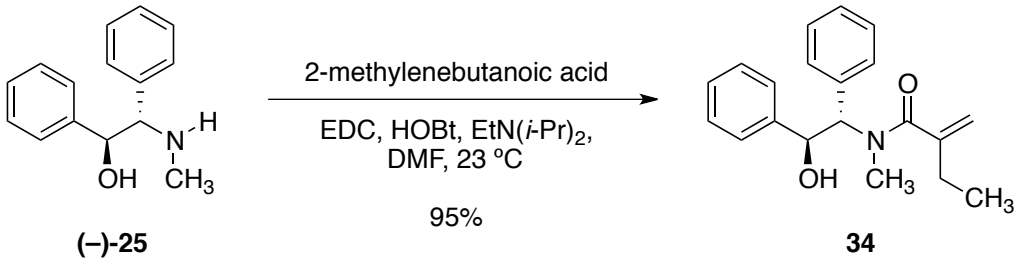
30.0*. FTIR (neat), cm^{-1}: 3385 (br), 3028, 1601 (s), 1452 (m), 1068 (m). HRMS (ESI): Calcd for $(C_{24}H_{25}NO_2 + H)^+$: 360.1958. Found: 360.1954.



(–)-25 **33**

***N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*-methylmethacrylamide (33)**

Methacryloyl chloride (946 μL, 9.68 mmol, 1.10 equiv) was added to a solution of (–)-(1*S*,2*S*)-pseudoephenamine (2.00 g, 8.80 mmol, 1 equiv) and triethylamine (1.60 mL, 11.4 mmol, 1.30 equiv) in dichloromethane (22 mL) at 0 °C. The white suspension was stirred for 5 min at 0 °C, then for 55 min at 23 °C. Excess acid chloride was quenched by the addition of water (14 mL). The layers of the resulting biphasic mixture were separated. The aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (10→50% ethyl acetate–hexanes) to provide acrylamide **33** as a white crystalline solid (2.31 g, 89%, mp = 141–143 °C). TLC (60% ethyl acetate–hexanes): R_f = 0.32 (UV, $KMnO_4$). ^{1}H NMR (2.5:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.37–7.49 (m, 2H), 7.16–7.37 (m, 8H), 5.31–5.56 (m, 2H), 5.21* (br s, 1H), 5.14 (br s, 1H), 5.04* (br s, 1H), 4.89 (br s, 1H), 4.29 (d, 1H, *J* = 5.4 Hz), 3.05* (br s, 3H), 2.87 (br s, 3H), 2.26* (br s, 3H), 1.89 (br s, 3H). ^{13}C NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, $CDCl_3$), δ: 174.3, 141.7, 140.8, 136.6, 128.4, 128.2, 128.1, 127.9*, 127.5, 127.1*, 126.5, 73.6, 72.7*, 66.7*, 65.6, 36.0, 28.7*, 20.9*, 19.8. FTIR (neat), cm^{-1}: 3356 (br), 3032, 1599 (s), 1452 (m), 1087 (m). HRMS (ESI): Calcd for ($C_{19}H_{21}NO_2$ + Na)$^+$: 318.1465. Found: 318.1460.

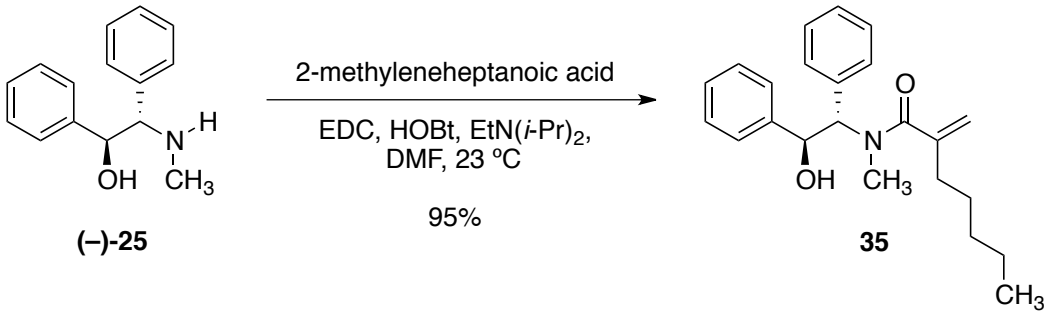


(–)-25 **34**

***N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*-methyl-2-methylenebutanamide (34)**

N,*N*-Diisopropylethylamine (4.11 mL, 23.5 mmol, 3.00 equiv), 1-hydroxybenzotriazole hydrate (1.32 g, 8.62 mmol, 1.10 equiv), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (1.65 g, 8.62 mmol, 1.10 equiv) were added sequentially to a solution of (–)-(1*S*,2*S*)-pseudoephenamine (2.14 g, 9.41 mmol, 1.20 equiv) and 2-methylenebutanoic acid (785 mg, 7.84 mmol, 1 equiv) in *N*,*N*-dimethylformamide (15.7 mL) at 23 °C. The resulting yellow solution was stirred for 15 h at 23 °C. The reaction mixture was partitioned between ethyl acetate (15 mL) and water (40 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 15 mL). The combined organic extracts were washed sequentially with 1 N aqueous hydrochloric acid solution (2 x 20 mL) and half-saturated aqueous sodium chloride solution (2 x 20 mL). The washed organic solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (50% ethyl acetate–hexanes) to afford acrylamide **34** as a clear, colorless syrup (2.31 g, 95%). TLC (30% ethyl acetate–hexanes): R_f = 0.12 (UV, $KMnO_4$). ^{1}H NMR (4.5:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.43 (d, 2H, *J* = 7.3 Hz), 7.37–7.15 (m, 8H), 5.51 (d, 1H, *J* = 6.8 Hz), 5.43 (t, 1H, *J* = 7.3 Hz), 5.35* (br s, 1H), 5.20* (br s, 1H), 5.13 (br s, 1H), 5.06* (br s, 1H), 4.87 (s, 1H), 4.28 (br d, 1H, *J* = 6.4 Hz), 3.09* (br s, 3H), 2.86 (s, 3H), 2.17–2.38 (m, 2H), 2.10* (br s, 2H), 1.13* (br s, 3H), 1.03 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR (2.5:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, $CDCl_3$), δ: 173.9, 146.7*, 146.3, 141.7, 141.5*,

136.6*, 136.7, 128.1, 128.0, 127.9, 127.4*, 127.3*, 127.3*, 127.2, 126.9, 126.8*, 126.3, 73.0, 72.3*, 66.7*, 64.1, 35.3, 28.7*, 26.4, 26.3*, 11.3. FTIR (neat), cm^{-1}: 3373 (br), 2923, 1739, 1602 (s), 1451 (m). HRMS (ESI): Calcd for $(C_{20}H_{23}NO_2 + H)^+$: 310.1802. Found: 310.1812.

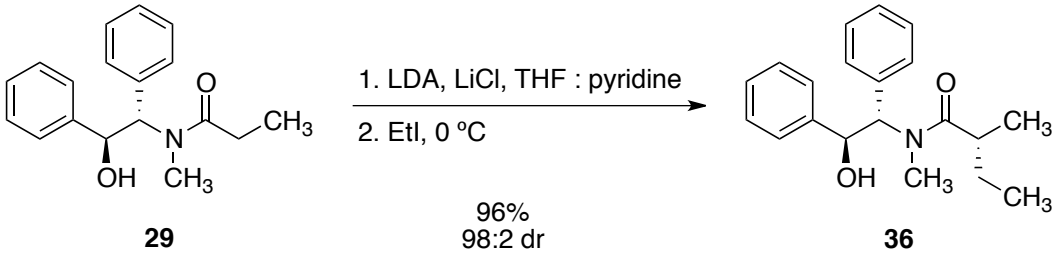


***N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*-methyl-2-methyleneheptanamide (35)**

N,*N*-Diisopropylethylamine (2.13 mL, 12.2 mmol, 3.00 equiv), 1-hydroxybenzotriazole hydrate (685 mg, 4.47 mmol, 1.10 equiv), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (858 mg, 4.47 mmol, 1.10 equiv) were added sequentially to a solution of (–)-(1*S*,2*S*)-pseudoephenamine (1.11 g, 4.88 mmol, 1.20 equiv) and 2-methyleneheptanoic acid (785 mg, 7.84 mmol, 1 equiv) in *N*,*N*-dimethylformamide (15.7 mL) at 23 °C. The resulting yellow solution was stirred for 15 h at 23 °C. The reaction mixture was partitioned between ethyl acetate (15 mL) and water (40 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 15 mL). The combined organic extracts were washed sequentially with 1 N aqueous hydrochloric acid solution (2 x 20 mL) and half-saturated aqueous sodium chloride solution (2 x 20 mL). The washed organic solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (30→50% ethyl acetate–hexanes) to afford acrylamide **35** as a clear, colorless syrup (1.35 g, 95%). TLC (30% ethyl acetate–hexanes): R_f = 0.21 (UV, $KMnO_4$). ^{1}H NMR (5.2:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.43 (d, 2H, *J* = 7.3 Hz), 7.38–7.15 (m, 8H), 5.51 (d, 1H, *J* = 7.5 Hz), 5.43 (t, 1H, *J* = 7.5 Hz), 5.35* (br s, 1H), 5.19* (br s, 1H), 5.13 (br s, 1H), 5.04* (br s, 1H), 4.88 (s, 1H), 4.34 (br d, 1H, *J* = 6.4 Hz), 3.10* (br s, 3H), 2.86 (s, 3H), 2.22 (t, 2H, *J* = 7.6 Hz), 2.11* (br s, 2H), 1.53* (br s, 2H), 1.40 (br s, 2H), 1.30 (br s, 4H), 0.88 (t, 3H, *J* = 6.4 Hz). ^{13}C NMR (4.5:1 rotamer ratio, asterisk denotes minor

rotamer peaks, 125 MHz, $CDCl_3$), δ: 174.1, 174.0*, 145.7*, 145.3, 141.78, 141.3*, 136.9*, 136.7, 128.3, 128.2*, 128.1, 127.8*, 127.4, 127.4, 127.0*, 126.4, 114.1, 113.8*, 73.4, 72.89*, 68.7*, 65.3, 36.1, 33.8, 31.3, 28.9*, 26.9, 22.3, 13.8. FTIR (neat), cm^{-1}: 3378 (br), 2931, 1741, 1602 (s), 1452 (m). HRMS (ESI): Calcd for $(C_{23}H_{29}NO_2 + H)^+$: 352.2271. Found: 352.2279.

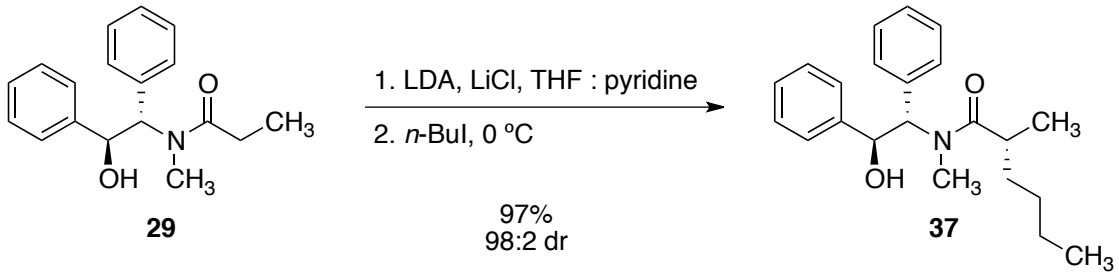
Synthesis of α,α-disubstituted pseudoephenamine amides:



(*R*)-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylbutanamide (36)

N,*N*-Diisopropylamine (3.35 mL, 23.9 mmol, 2.26 equiv) was added by syringe to a stirring suspension of lithium chloride (2.69 g, 63.5 mmol, 6.00 equiv) in tetrahydrofuran (21 mL) at 23 °C. The resulting slurry was cooled to –78 °C. A freshly titrated solution of *n*-butyllithium in hexanes (2.50 M, 9.36 mL, 2.21 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 °C (5 min), then was cooled to –78 °C. An ice-cooled solution of amide **29** (3.00 g, 10.6 mmol, 1 equiv) in pyridine (26 mL) was added by cannula. The transfer was quantitated with tetrahydrofuran (5 mL). The reaction mixture was stirred for 1 h at –78 °C, for 15 min at 0 °C, and for 5 min at 23 °C, then was cooled to 0 °C, whereupon iodoethane (2.13 mL, 26.5 mmol, 2.50 equiv) was added. After 55 min, aqueous ammonium chloride solution (1.5 mL) was added to the ice-cold product mixture. The biphasic mixture was partitioned between ethyl acetate (80 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (100 mL). The layers were separated. The aqueous layer was extracted with two 50-mL portions of ethyl acetate. The combined organic extracts were washed with water (60 mL). The washed organic solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (30→50% ethyl acetate–hexanes) to provide amide **36** as a pale yellow oil, which solidified upon standing after 3–4 days (3.15 g, 96%). The diastereomeric ratio of the

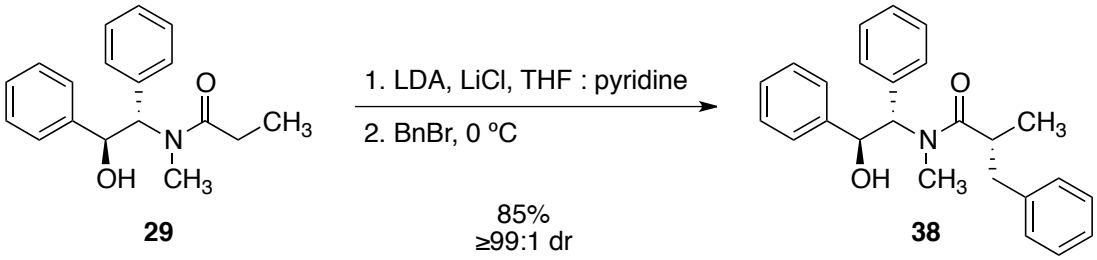
purified product was determined to be 98:2 dr by chiral HPLC analysis (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R (major, amide **36**) = 20.7 min, t_R (minor, amide **39**) = 24.9 min). TLC (60% Ethyl acetate–hexanes): R_f = 0.50 (UV, $KMnO_4$). ^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.46-7.16 (m, 10H), 5.66 (d, 1H, *J* = 8.0 Hz), 5.55* (d, 1H, *J* = 8.0 Hz), 5.38 (d, 1H, *J* = 7.5 Hz), 5.22* (d, 1H, *J* = 7.0 Hz), 4.32* (br s, 1H), 4.12 (br s, 1H), 3.00* (s, 3H), 2.89 (s, 3H), 2.58 (sxt, 1H, *J* = 6.8 Hz), 1.75-1.61 (m, 1H), 1.43-1.32 (m, 1H), 1.08 (d, 3H, *J* = 7.0 Hz), 1.03* (d, 3H, *J* = 6.5 Hz), 0.84 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 178.9, 141.9, 137.2, 128.5, 128.3, 128.2, 127.6, 127.5, 126.6, 73.8, 65.9, 38.2, 34.5, 26.9, 17.0, 11.9. FTIR (neat), cm^{-1}: 3379 (br), 2967, 1616 (s), 1452, 1082, 908 (s). HRMS (ESI): Calcd for $(C_{20}H_{25}NO_2 + H)^+$: 312.1958. Found: 312.1964.



(*R*)-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylhexanamide (37)

N,*N*-Diisopropylamine (3.35 mL, 23.9 mmol, 2.26 equiv) was added by syringe to a stirring suspension of lithium chloride (2.69 g, 63.5 mmol, 6.00 equiv) in tetrahydrofuran (26 mL) at 23 °C. The resulting slurry was cooled to –78 °C. A freshly titrated solution of *n*-butyllithium in hexanes (2.50 M, 9.36 mL, 2.21 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 °C (5 min), then was cooled to –78 °C. An ice-cooled solution of amide **29** (3.00 g, 10.6 mmol, 1 equiv) in pyridine (23 mL) was added by cannula. The transfer was quantitated with tetrahydrofuran (5 mL). The reaction mixture was stirred for 1 h at –78 °C, for 15 min at 0 °C, and for 5 min at 23 °C, then was cooled to 0 °C, whereupon 1-iodobutane (3.01 mL, 26.5 mmol, 2.50 equiv) was added. After 1.2 h, aqueous ammonium chloride solution (1.5 mL) was added to the ice-cold product mixture. The biphasic mixture was partitioned between ethyl acetate (80 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (100 mL). The layers were separated. The aqueous layer was extracted with two 50-mL portions of ethyl acetate. The combined organic extracts were washed with water (60 mL). The washed organic solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (30→50% ethyl acetate–hexanes) to provide amide **37** as a pale yellow oil, which solidified upon standing after 4–5 days (3.49 g, 97%). The diastereomeric ratio of the purified product was determined to be 98:2 dr by chiral HPLC analysis (Chiralcel OD-H, 95:5

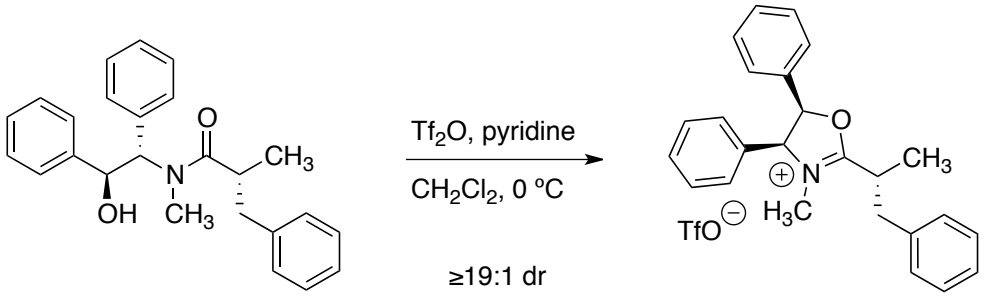
hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R (major, amide **37**) = 16.5 min, t_R (minor, amide **40**) = 21.8 min). TLC (60% Ethyl acetate–hexanes): R_f = 0.64 (UV, $KMnO_4$). ^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.45-7.19 (m, 10H), 5.61 (d, 1H, *J* = 8.0 Hz), 5.53* (d, 1H, *J* = 7.5 Hz), 5.38 (t, 1H, *J* = 7.2 Hz), 5.22* (d, 1H, *J* = 8.0 Hz), 4.32* (br s, 1H), 4.22 (d, 1H, *J* = 6.0 Hz), 3.01* (s, 3H), 2.88 (s, 3H), 2.64 (sxt, 1H, *J* = 6.9 Hz), 1.66-1.58 (m, 1H), 1.36-1.22 (m, 3H), 1.21-1.13 (m, 2H), 1.07 (d, 3H, *J* = 7.0 Hz), 1.03* (d, 3H, *J* = 7.0 Hz), 0.87 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 179.1, 142.0, 137.2, 128.4, 128.3, 128.2, 127.5, 127.4, 126.6, 73.8, 66.2, 36.5, 34.7, 33.7, 29.6, 22.2, 17.3, 13.9. FTIR (neat), cm^{-1}: 3365 (br), 2930, 1618 (s), 1452, 1069. HRMS (ESI): Calcd for $(C_{22}H_{29}NO_2 + H)^+$: 340.2271. Found: 340.2274.



(*R*)-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethyl-3-phenylpropanamide (38)

N,*N*-Diisopropylamine (5.59 mL, 39.9 mmol, 2.26 equiv) was added by syringe to a stirring suspension of lithium chloride (4.49 g, 106 mmol, 6.00 equiv) in tetrahydrofuran (40 mL) at 23 °C. The resulting slurry was cooled to –78 °C. A freshly titrated solution of *n*-butyllithium in hexanes (2.40 M, 16.3 mL, 2.21 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 °C (5 min), then was cooled to –78 °C. An ice-cooled solution of amide **29** (5.00 g, 17.6 mmol, 1 equiv) in pyridine (44 mL) was added by cannula. The transfer was quantitated with tetrahydrofuran (5 mL). The reaction mixture was stirred for 1 h at –78 °C, for 15 min at 0 °C, and for 5 min at 23 °C, then was cooled to 0 °C, whereupon benzyl bromide (3.14 mL, 26.5 mmol, 1.50 equiv) was added. After 30 min, saturated aqueous ammonium chloride solution (1.5 mL) was added to the ice-cold product mixture. The biphasic mixture was partitioned between ethyl acetate (130 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (160 mL). The layers were separated. The aqueous layer was extracted with two 80-mL portions of ethyl acetate. The combined organic extracts were washed with water (100 mL). The washed organic solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (10→70% ethyl acetate–hexanes) to provide amide **38** as a pale orange solid (6.36 g, 97%). The purified product was recrystallized from toluene (25 mL, 100 °C) affording a white crystalline solid (5.08 g, 77%, mp = 128-129 °C). A second crop was

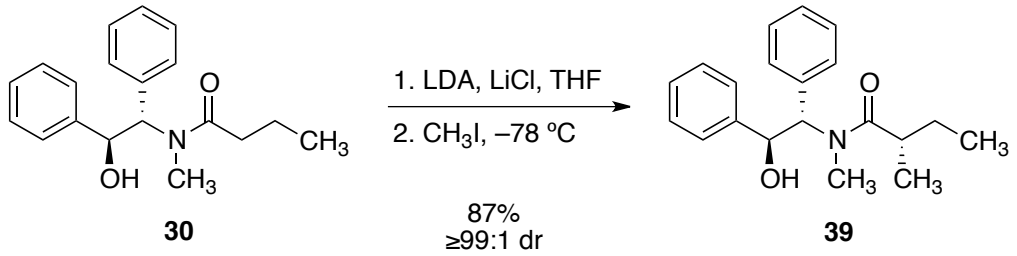
obtained providing an additional 0.55 g of product (85% total yield). The product **38** (26.0 mg, 0.07 mmol, 1 equiv) was silylated with a mixture of chlorotrimethylsilane (24.7 μL, 0.19 mmol, 2.80 equiv) and triethylamine (34.9 μL, 0.25 mmol, 3.60 equiv) in dichloromethane (1 mL) at 23 ºC for 10 min, and chiral HPLC analysis of the resulting trimethylsilyl ether established that amide **38** was of ≥99:1 dr (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R (minor, amide **42**) = 5.82 min, t_R (major, amide **38**) = 7.28 min). This diastereomeric ratio was confirmed by ^{1}H NMR analysis of the corresponding oxazolinium triflate (see below). TLC (60% Ethyl acetate–hexanes): R_f = 0.56 (UV, $KMnO_4$). ^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.44-6.98 (m, 15H), 5.68 (d, 1H, *J* = 7.0 Hz), 5.35 (t, 1H, *J* = 7.0 Hz), 5.21* (dd, 1H, *J* = 7.5, 3.5 Hz), 5.02* (d, 1H, *J* = 8.5 Hz), 3.58 (br s, 1H), 3.12-3.04* (m, 1H), 3.03-2.88 (m, 2H), 2.70 (s, 3H), 2.62 (dd, 1H, *J* = 12.0, 5.0 Hz), 1.09 (d, 3H, *J* = 6.5 Hz), 1.05* (d, 3H, *J* = 6.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 177.9, 141.7, 140.0, 136.9, 129.0, 128.4 (2), 128.3, 128.2, 127.6, 127.3, 126.6, 126.1, 73.7, 64.5, 40.2, 38.8, 33.9, 17.6. FTIR (neat), cm^{-1}: 3371 (br), 3028, 1618 (s), 1452, 1080, 908 (s). HRMS (ESI): Calcd for $(C_{25}H_{27}NO_2 + H)^+$: 374.2115. Found: 374.2116.



38 **95**

Oxazolinium triflate (95)

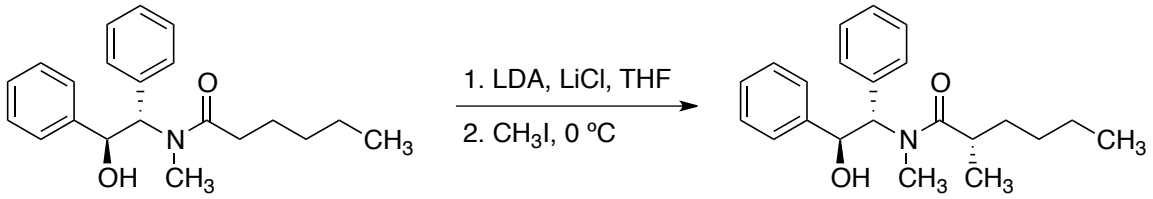
Trifluoromethanesulfonic anhydride (18.9 μL, 0.112 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of the α-tertiary amide **38** (21.0 mg, 0.056 mmol, 1 equiv) and pyridine (13.6 μL, 0.169 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 3 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.90* (t, 1H, *J* = 6.0 Hz), 8.55* (t, 1H, *J* = 7.75 Hz), 8.06* (t, 1H, *J* = 6.5 Hz), 7.41-6.83 (m, 15H), 6.03 (d, 1H, *J* = 11.0 Hz), 3.55-3.47 (m, 2H), 3.23 (s, 3H), 2.95 (dd, 1H, *J* = 8.5, 4.5 Hz), 1.56 (d, 3H, *J* = 7.0 Hz).



(*S*)-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylbutanamide (39)

N,*N*-Diisopropylamine (1.07 mL, 7.57 mmol, 2.25 equiv) was added by syringe to a stirring suspension of lithium chloride (0.86 g, 20.2 mmol, 6.00 equiv) in tetrahydrofuran (10 mL) at 23 °C. The resulting slurry was cooled to –78 °C. A freshly titrated solution of *n*-butyllithium in hexanes (2.40 M, 2.80 mL, 2.00 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 °C (5 min), then was cooled to –78 °C. An ice-cooled solution of amide **30** (1.00 g, 3.36 mmol, 1 equiv) in tetrahydronfuran (12 mL) was added by cannula. The transfer was quantitated with tetrahydrofuran (2 mL). The reaction mixture was stirred for 1 h at –78 °C, for 15 min at 0 °C, and for 5 min at 23 °C, then was cooled to 0 °C, whereupon iodomethane (0.63 mL, 10.1 mmol, 3.00 equiv) was added. After 1 h, aqueous ammonium chloride solution (2 mL) was added to the ice-cold product mixture. The biphasic mixture was partitioned between ethyl acetate (20 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (30 mL). The layers were separated. The aqueous layer was extracted with two 20-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (30→40% ethyl acetate–hexanes) to provide amide **39** as a white solid (0.91 g, 87%, mp = 89-90 °C). The diastereomeric ratio of the purified product was determined to be ≥99:1 dr by chiral HPLC analysis (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R (minor, amide **36**) = 21.1 min, t_R (major, amide **39**) =

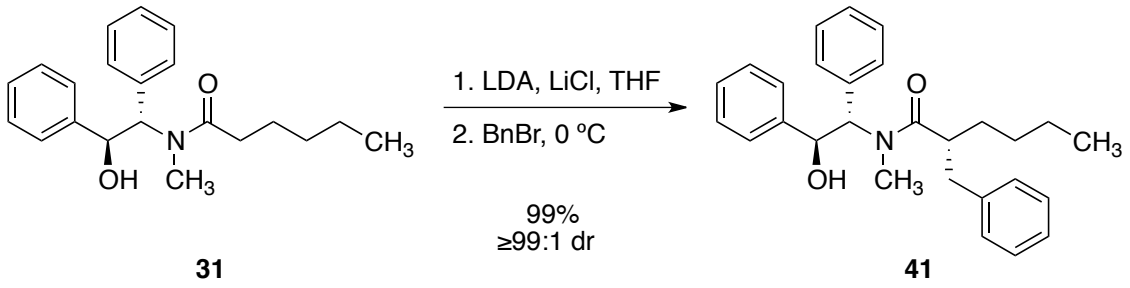
25.3 min). TLC (60% Ethyl acetate–hexanes): R_f = 0.63 (UV, $KMnO_4$). ^1H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.46-7.18 (m, 10H), 5.54 (d, 1H, *J* = 7.5 Hz), 5.40 (d, 1H, *J* = 7.0 Hz), 5.21* (d, 1H, *J* = 7.5 Hz), 4.31 (br s, 1H), 3.02* (s, 3H), 2.87 (s, 3H), 2.57 (sxt, 1H, *J* = 6.8 Hz), 1.81-1.63 (m, 1H), 1.45-1.30 (m, 1H), 1.03 (d, 3H, *J* = 6.5 Hz), 0.84 (t, 3H, *J* = 7.7 Hz), 0.79 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 178.9, 142.0, 137.2, 128.4, 128.3, 128.2, 127.5, 127.4, 126.6, 73.9, 66.7, 38.3, 35.1, 26.9, 17.1, 11.9. FTIR (neat), cm^{-1}: 3363 (br), 2965, 1616 (s), 1450, 1082, 910. HRMS (ESI): Calcd for $(C_{20}H_{25}NO_2 + H)^+$: 312.1958. Found: 312.1969.



(*S*)-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylhexanamide (40)

N,*N*-Diisopropylamine (3.02 mL, 21.2 mmol, 2.26 equiv) was added by syringe to a stirring suspension of lithium chloride (2.38 g, 56.2 mmol, 6.00 equiv) in tetrahydrofuran (20 mL) at 23 ºC. The resulting slurry was cooled to –78 ºC. A freshly titrated solution of *n*-butyllithium in hexanes (2.53 M, 8.19 mL, 2.21 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 ºC (5 min) before cooling to –78 ºC. An ice-cooled solution of amide **31** (3.05 g, 9.37 mmol, 1 equiv) in tetrahydrofuran (20 mL with 6.9 mL rinse) was added by cannula. The reaction mixture was stirred for 1 h at –78 ºC, for 15 min at 0 ºC, and for 5 min at 23 ºC, then was cooled to 0 ºC, whereupon iodomethane (2.34 mL, 37.5 mmol, 4.00 equiv) was added. After 40 min, saturated aqueous ammonium chloride solution (2 mL) was added to the ice-cold product mixture. The resulting biphasic mixture was partitioned between ethyl acetate (80 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (100 mL). The layers were separated. The aqueous layer was extracted with two 60-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (5→40% ethyl acetate–hexanes) to provide amide **40** as an off-white solid (2.86 g, 90%). The diastereomeric ratio of the purified product was determined to be 95:5 by chiral HPLC analysis (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R(minor) = 16.3 min, t_R(major) = 20.0 min). The purified product was recrystallized from hot

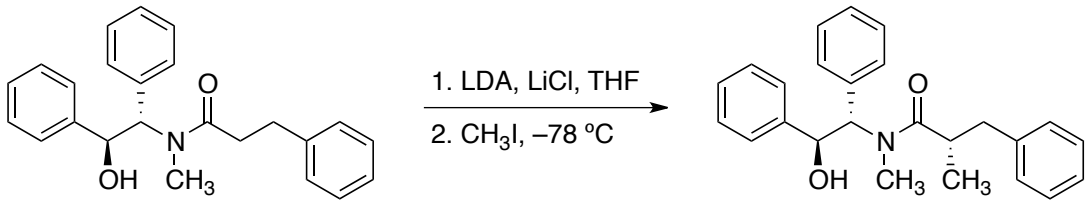
ether–hexanes (1:7, 10 mL, 40 ºC) to provide amide **40** as an off-white crystalline solid (2.42 g, 76%, mp = 77–79 ºC). A second crop was obtained providing an additional 0.26 g of amide **40** (84% total yield). The diastereomeric ratio of the recrystallized product was determined to be 98:2 by chiral HPLC analysis (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R(minor, amide **37**) = 17.2 min, t_R(major, amide **40**) = 21.6 min). TLC (30% ethyl acetate–benzene): R_f = 0.45 (UV, $KMnO_4$). ^{1}H NMR (10:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.40 (d, 2H, *J* = 7.6 Hz), 7.19–7.36 (m, 8H), 5.53 (d, 1H, *J* = 7.0 Hz), 5.34-5.44 (m, 1H), 5.19* (d, 1H, *J* = 7.3 Hz), 4.36 (br s, 1H), 3.02* (s, 3H), 2.87 (s, 3H), 2.63 (sxt, 1H, *J* = 6.7 Hz), 1.59–1.70 (m, 1H), 1.22–1.39 (m, 3H), 1.10–1.22 (m, 2H), 1.07* (d, 3H, *J* = 6.7 Hz), 1.03 (d, 3H, *J* = 6.7 Hz), 0.87 (t, 3H, *J* = 7.3 Hz), 0.80* (t, 3H, *J* = 6.9 Hz). ^{13}C NMR (10:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, $CDCl_3$), δ: 178.7, 1778.1*, 141.9, 141.4*, 137.4*, 137.3, 128.3*, 128.2, 128.1, 128.1*, 128.0, 127.9*, 127.5*, 127.3, 127.2, 126.9*, 126.4, 73.6, 73.3*, 65.8, 65.4*, 36.3, 35.6*, 34.8, 34.1*, 33.4, 30.1*, 29.4, 22.6, 22.5*, 17.3*, 17.2, 13.9, 13.8*. FTIR (neat), cm^{-1}: 3354 (br), 2931, 1618 (s), 1450 (m). HRMS (ESI): Calcd for $(C_{22}H_{29}NO_2 + H)^+$: 340.2271. Found: 340.2261.



(*R*)-2-benzyl-*N*-[(1S,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*-methylhexanamide (41)

N,*N*-Diisopropylamine (2.97 mL, 20.8 mmol, 2.26 equiv) was added by syringe to a stirring suspension of lithium chloride (2.35 g, 55.3 mmol, 6.00 equiv) in tetrahydrofuran (20 mL) at 23 °C. The resulting slurry was cooled to –78 °C. A freshly titrated solution of *n*-butyllithium in hexanes (2.53 M, 8.05 mL, 2.21 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 °C (5 min) before cooling to –78 °C. An ice-cooled solution of amide **31** (3.00 g, 9.22 mmol, 1 equiv) in tetrahydrofuran (20 mL with 6.1 mL rinse) was added via cannula. The reaction mixture was stirred for 1 h at –78 °C, for 15 min at 0 °C, and for 5 min at 23 °C, then was cooled to 0 °C, whereupon benzyl bromide (1.65 mL, 13.8 mmol, 1.50 equiv) was added. After 1.3 h, saturated aqueous ammonium chloride solution (2 mL) was added to the ice-cold product mixture. The resulting biphasic mixture was partitioned between ethyl acetate (80 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (100 mL). The layers were separated. The aqueous layer was extracted with two 60-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was recrystallized from hot ethyl acetate–hexanes (1:1, 10 mL, 70 °C) to provide amide **41** as a white crystalline solid (3.35 g, 88%, mp = 112–114 °C). A second crop was obtained providing an additional 0.47 g of amide **41** (99% total yield). The diastereomeric ratio of the purified product was determined to be ≥99:1 by chiral HPLC analysis (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220

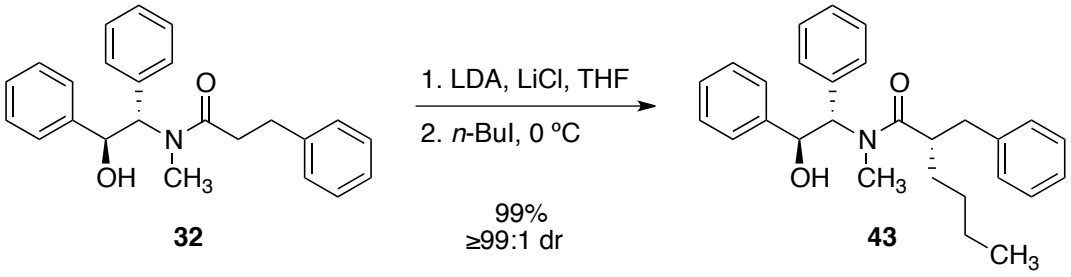
nm, t_R(major, amide **41**) = 25.1 min, t_R(minor, amide **43**) = not observed). TLC (50% ethyl acetate–hexanes): R_f = 0.57 (UV, $KMnO_4$). ^{1}H NMR (12:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.39* (m, 2H), 7.35 (d, 2H, *J* = 7.3 Hz), 7.3* (m, 2H), 7.23–7.28 (m, 2H), 7.10–7.22 (m, 9H), 6.97–7.03 (m, 2H), 6.90–6.96* (m, 2H), 5.79 (d, 1H, *J* = 7.6 Hz), 5.31 (t, 1H, *J* = 7.2 Hz), 4.97* (dd, 1H, *J* = 9.1, 4.9 Hz), 4.73* (d, 1H, *J* = 9.4 Hz), 3.42 (br s, 1H), 3.15* (s, 3H), 2.92–3.00 (m, 1H), 2.85–2.92 (m, 1H), 2.72 (dd, 1H, *J* = 13.0, 4.8 Hz), 2.64 (s, 3H), 1.60–1.71 (m, 1H), 1.41–1.50 (m, 1H), 1.14–1.33 (m, 4H), 0.87 (t, 3H, *J* = 7.2 Hz), 0.66* (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (10:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, $CDCl_3$), δ: 177.3, 176.9*, 141.7, 140.8*, 140.5*, 139.9*, 137.8*, 136.9, 129.2*, 128.9, 128.5*, 128.3, 128.2, 128.19, 127.9*, 127.8*, 127.5*, 127.4, 127.1, 127.0*, 126.6, 126.3*, 125.9, 73.9*, 73.3, 66.7*, 63.2, 47.6*, 44.2, 39.3*, 39.0, 33.2, 32.8, 32.6*, 29.9*, 29.4*, 29.2, 22.7, 22.6*, 13.8, 13.7*. FTIR (neat), cm^{-1}: 3356 (br), 2929, 1616 (s), 1446 (m). HRMS (ESI): Calcd for $(C_{28}H_{33}NO_2 + H)^+$: 416.2584. Found: 416.2580.



(*S*)-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethyl-3-phenylpropanamide (42)

N,*N*-Diisopropylamine (1.76 mL, 12.4 mmol, 2.26 equiv) was added by syringe to a stirring suspension of lithium chloride (1.39 g, 32.8 mmol, 6.00 equiv) in tetrahydrofuran (10 mL) at 23 °C. The resulting slurry was cooled to –78 °C. A freshly titrated solution of *n*-butyllithium in hexanes (2.46 M, 4.92 mL, 2.21 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 °C (5 min) before cooling to –78 °C. An ice-cooled solution of amide **32** (1.97 g, 5.47 mmol, 1 equiv) in tetrahydrofuran (13 mL with 4.0 mL rinse) was added by cannula. The reaction mixture was stirred for 1 h at –78 °C, for 15 min at 0 °C, and for 5 min at 23 °C, then was cooled to 0 °C, whereupon iodomethane (1.37 mL, 19.5 mmol, 2.50 equiv) was added. After 2 h, saturated aqueous ammonium chloride solution (2 mL) was added to the ice-cold product mixture. The resulting biphasic mixture was partitioned between ethyl acetate (80 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (100 mL). The layers were separated. The aqueous layer was extracted with two 60-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (5→50% ethyl acetate–hexanes) to provide amide **42** as a white solid (1.88 g, 92%). The product **42** (21.1 mg, 0.06 mmol, 1 equiv) was silylated with a mixture of chlorotrimethylsilane (20.2 μL, 0.16 mmol, 2.80 equiv) and triethylamine (28.3 μL, 0.20 mmol, 3.60 equiv) in dichloromethane (1 mL) at 23 °C for 10 min, and chiral HPLC analysis of the

resulting trimethylsilyl ether established that amide **42** was of 98:2 dr (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R (minor, amide **38**) = 5.82 min, t_R (major, amide **42**) = 7.28 min). TLC (30% ethyl acetate–hexanes) R_f = 0.41 (UV, $KMnO_4$). ^{1}H NMR (6:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.43 (d, 2H, *J* = 7.3 Hz), 7.33 (t, 4H, *J* = 7.8 Hz), 7.13–7.30 (m, 9H), 6.82* (d, 2H, *J* = 7.3 Hz), 5.49 (d, 1H, *J* = 7.3 Hz), 5.32–5.41 (m, 1H), 5.19* (d, 1H, *J* = 7.6 Hz), 4.52 (d, 1H, *J* = 5.3 Hz), 3.07–3.19* (m, 2H), 2.98–3.06 (m, 2H), 2.94* (s, 3H), 2.82 (s, 3H), 2.61–2.71 (m, 1H), 1.09 (d, 3H, *J* = 6.4 Hz). ^{13}C NMR (10:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, $CDCl_3$), δ: 177.9, 177.2*, 141.7, 141.4*, 140.2*, 139.8, 136.9*, 136.8, 129.0*, 128.9, 128.5*, 128.3, 128.2, 128.17*, 128.1, 128.0*, 127.9*, 127.9, 127.3, 127.3*, 127.2, 127.0*, 126.5, 126.1, 126.0*, 73.5, 72.9*, 67.0, 65.2*, 40.9*, 39.7, 38.8, 38.4*, 35.0, 17.9*, 17.3. FTIR (neat), cm^{-1}: 3360 (br), 3028, 1620 (s), 1452 (m). HRMS (ESI): Calcd for $(C_{25}H_{27}NO_2 + H)^+$: 374.2115. Found: 374.2105.

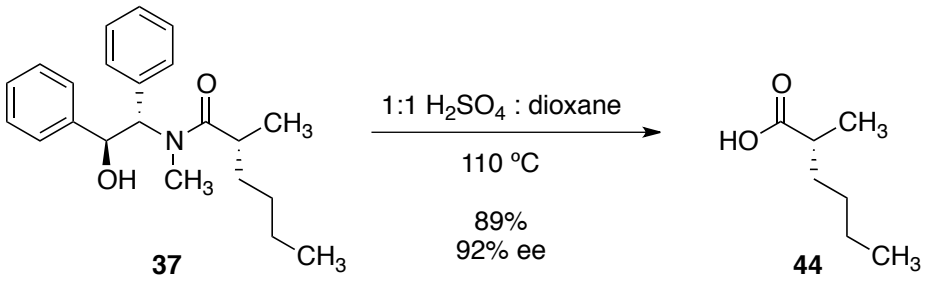


(*S*)-2-benzyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*-methylhexanamide (43)

N,*N*-Diisopropylamine (2.51 mL, 17.6 mmol, 2.26 equiv) was added by syringe to a stirring suspension of lithium chloride (1.98 g, 46.7 mmol, 6.00 equiv) in tetrahydrofuran (20 mL) at 23 °C. The resulting slurry was cooled to –78 °C. A freshly titrated solution of *n*-butyllithium in hexanes (2.53 M, 6.80 mL, 2.21 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 °C (5 min) before cooling to –78 °C. An ice-cooled solution of amide **32** (2.80 g, 7.79 mmol, 1 equiv) in tetrahydrofuran (13 mL with 5.9 mL rinse) was added by cannula. The reaction mixture was stirred for 1 h at –78 °C, for 15 min at 0 °C, and for 5 min at 23 °C, then was cooled to –78 °C, whereupon 1-iodobutane (2.22 mL, 19.5 mmol, 2.50 equiv) was added, and the reaction mixture was warmed to 0 °C. After 3 h, saturated aqueous ammonium chloride solution (2 mL) was added to the ice-cold product mixture. The resulting biphasic mixture was partitioned between ethyl acetate (80 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (100 mL). The layers were separated. The aqueous layer was extracted with two 60-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (5→40% ethyl acetate–hexanes) to provide amide **43** as a white solid (3.20 g, 99%, mp = 109–111 °C). The diastereomeric ratio of the purified product was determined to be ≥99:1 by chiral HPLC analysis (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R(major, amide

43) = 5.73 min, t_R(minor, amide **41**) = 7.32 min). TLC (50% ethyl acetate–benzene): R_f = 0.41 (UV, $KMnO_4$). ^{1}H NMR (10:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.37 (d, 2H, *J* = 7.6 Hz), 7.23–7.31 (m, 4H), 7.05–7.23 (m, 9H), 7.03* (d, 1H, *J* = 6.7 Hz), 6.70* (d,, 1H, *J* = 7.6 Hz), 5.58 (d, 1H, *J* = 8.20 Hz), 5.18–5.28 (m, 1H), 5.15 (d, 1H, *J* = 8.5 Hz), 3.87 (br s, 1H), 2.98* (s, 3H), 2.89–2.96 (m, 2H), 2.64–2.76 (m, 4H), 1.54–1.67 (m, 1H), 1.38–1.49 (m, 1H), 1.28–1.38* (m, 2H), 1.17–1.28 (m, 2H), 1.07–1.16 (m, 2H), 0.91* (t, 3H, *J* = 7.0 Hz), 0.82 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR (10:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, $CDCl_3$), δ: 177.6, 176.8*, 141.6, 141.1*, 140.3*, 139.9, 136.9*, 136.82, 129.0*, 128.9, 128.5*, 128.4, 128.2, 128.2, 128.1, 128.1*, 127.9*, 127.4, 127.28, 127.1*, 126.7, 126.2, 125.9*, 73.4*, 73.3*, 66.4, 65.6*, 44.6, 44.2*, 38.8, 38.5*, 34.3, 32.7, 32.2*, 29.7*, 29.4, 22.9*, 22.7, 14.0*, 13.8. FTIR (neat), cm^{-1}: 3362 (br), 2929, 1620 (s), 1452 (m). HRMS (ESI): Calcd for $(C_{28}H_{33}NO_2 + H)^+$: 416.2584. Found: 416.2576.

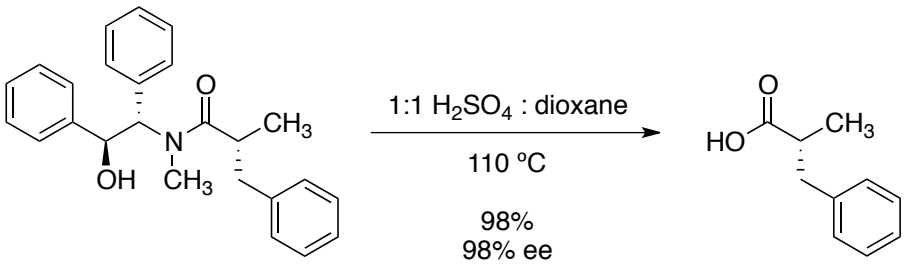
Acidic hydrolysis to form carboxylic acids:



(*R*)-2-methylhexanoic acid (44)

A biphasic solution of amide **37** (250 mg, 0.736 mmol, 1 equiv) in dioxane (1.2 mL) and 9 N aqueous sulfuric acid solution (1.2 mL) was heated for 5.5 h at 115 °C and then cooled to 0 °C. The pH of the mixture was adjusted to pH ≥ 10 by the slow addition of 5 N aqueous sodium hydroxide solution, and the resulting mixture was partitioned between water (10 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL). The aqueous layer was acidified to pH ≤ 1 by the slow addition of 9 N aqueous sulfuric acid solution. The resulting acidic aqueous layer was extracted with dichloromethane (3 x 20 mL). The latter organic extracts were combined and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford acid **44** as a clear liquid (85.0 mg, 89%). Coupling of acid **44** (25.0 mg, 0.192 mmol, 1 equiv) with (*R*)-(α-methylbenzyl)amine (29.3 μL, 0.230 mmol, 1.20 equiv) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (55.2 mg, 0.288 mmol, 1.50 equiv), 1-hydroxybenzotriazole hydrate (38.9 mg, 0.288 mmol, 1.50 equiv), and triethylamine (107 μL, 0.768 mmol, 4.00 equiv) in *N*,*N*-dimethylformamide (640 μL) at 23 °C for 20 h gave the corresponding (*R*)-(α-methylbenzyl)amide which was analyzed by chiral capillary GC to establish an ee of 92% for acid **44** (Restek Rt-βDEXsm column, 30 m, 0.23 mm ID, oven temperature 190 °C, t_R (minor) = 5.6 min, t_R (major) = 5.9 min). The characterization data

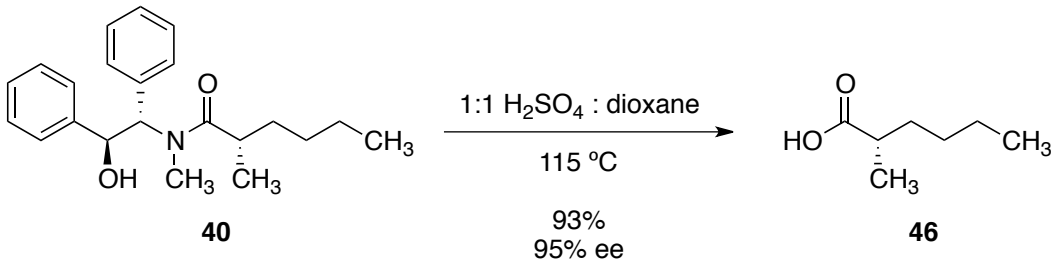
obtained for acid **44** were in agreement with values previously reported.[7c]



38 **45**

(*R*)-2-methyl-3-phenylpropanoic acid (45)

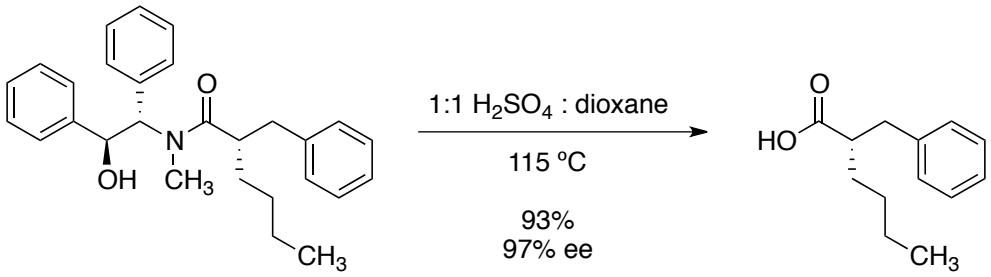
A biphasic solution of amide **38** (500 mg, 1.34 mmol, 1 equiv) in dioxane (2.1 mL) and 9 N aqueous sulfuric acid solution (2.1 mL) was heated for 5.3 h at 115 °C and then cooled to 0 °C. The pH of the mixture was adjusted to pH ≥ 10 by the slow addition of 5 N aqueous sodium hydroxide solution, and the resulting mixture was partitioned between water (10 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL). The aqueous layer was acidified to pH ≤ 1 by the slow addition of 9 N aqueous sulfuric acid solution. The resulting acidic aqueous layer was extracted with dichloromethane (3 x 20 mL). The latter organic extracts were combined and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford acid **45** as a clear liquid (216 mg, 98%). Coupling of acid **45** (25.0 mg, 0.152 mmol, 1 equiv) with (*R*)-(α-methylbenzyl)amine (23.0 μL, 0.183 mmol, 1.20 equiv) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (43.8 mg, 0.228 mmol, 1.50 equiv), 1-hydroxybenzotriazole hydrate (30.9 mg, 0.228 mmol, 1.50 equiv), and triethylamine (85.0 μL, 0.609 mmol, 4.00 equiv) in *N*,*N*-dimethylformamide (500 μL) at 23 °C for 20 h gave the corresponding (*R*)-(α-methylbenzyl)amide which was analyzed by chiral capillary GC to establish an ee of 98% for acid **45** (Restek Rt-βDEXsm column, 30 m, 0.23 mm ID, oven temperature 190 °C, t_R (major) = 22.0 min, t_R (minor) = 24.8 min). The characterization data obtained for acid **45** were in agreement with values previously reported.[7c]



40 **46**

(*S*)-2-methylhexanoic acid (46)

A biphasic solution of amide **40** (213 mg, 0.629 mmol, 1 equiv) in 1,4-dioxane (1.0 mL) and 9 N aqueous sulfuric acid solution (1.0 mL) was heated for 6 h at 115 ºC and then cooled to 0 ºC. The pH of the mixture was adjusted to pH ≥ 10 by the slow addition of 5 N aqueous sodium hydroxide solution, and the resulting mixture was partitioned between water (10 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL). The aqueous layer was acidified to pH ≤ 1 by the slow addition of 9 N aqueous sulfuric acid solution. The resulting acidic aqueous layer was extracted with dichloromethane (3 x 20 mL). The latter organic extracts were combined and dried over anhydrous sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford acid **46** as a clear liquid (75.9 mg, 93%). Coupling of acid **46** (32.8 mg, 0.252 mmol, 1 equiv) with (*R*)-(α-methylbenzyl)amine (38.5 μL, 0.302 mmol, 1.20 equiv) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (72.4 mg, 0.378 mmol, 1.50 equiv), 1-hydroxybenzotriazole hydrate (57.9 mg, 0.378 mmol, 1.50 equiv), and triethylamine (140 μL, 1.01 mmol, 4.00 equiv) in *N*,*N*-dimethyformamide (500 μL) at 23 ºC for 20 h gave the corresponding (*R*)-(α-methylbenzyl)amide which was analyzed by chiral capillary GC to establish an ee of 97% for acid **46** (Restek Rt-βDEXsm column, 30 m, 0.23 mm ID, oven temperature 190 ºC, t_R(minor) = 5.57 min, t_R(major) = 5.91 min). The characterization data obtained for acid **46** were in agreement with values previously reported.[7c]

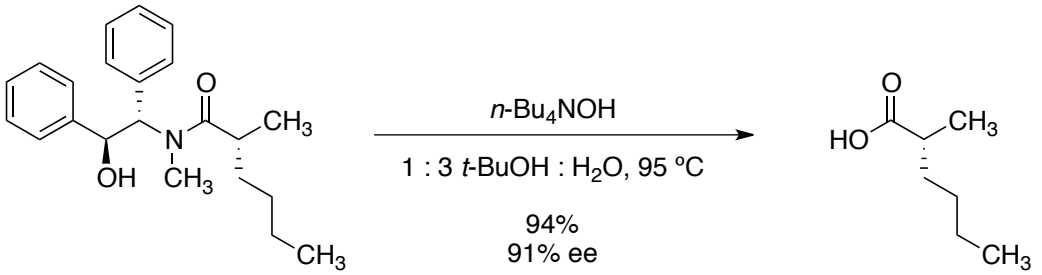


43 **47**

(*S*)-2-benzylhexanoic acid (47)

A biphasic solution of amide **43** (198 mg, 0.476 mmol, 1 equiv) in 1,4-dioxane (1.0 mL) and 9 N aqueous sulfuric acid solution (1.0 mL) was heated for 9 h at 115 °C and then cooled to 0 °C. The pH of the mixture was adjusted to pH ≥ 10 by the slow addition of 5 N aqueous sodium hydroxide solution, and the resulting mixture was partitioned between water (10 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL). The aqueous layer was acidified to pH ≤ 1 by the slow addition of 9 N aqueous sulfuric acid solution. The resulting acidic aqueous layer was extracted with dichloromethane (3 x 20 mL). The latter organic extracts were combined and dried over anhydrous sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford acid **47** as a clear liquid (91.0 mg, 93%). Coupling of acid **47** (24.7 mg, 0.120 mmol, 1 equiv) with (*R*)-(α-methylbenzyl)amine (18.3 μL, 0.144 mmol, 1.20 equiv) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (34.4 mg, 0.180 mmol, 1.50 equiv), 1-hydroxybenzotriazole hydrate (27.5 mg, 0.180 mmol, 1.50 equiv), and triethylamine (66.8 μL, 0.479 mmol, 4.00 equiv) in *N*,*N*-dimethyformamide (500 μL) at 23 °C for 20 h gave the corresponding (*R*)-(α-methylbenzyl)amide, which was analyzed by chiral capillary GC to establish an ee of 97% for acid **47** (Restek Rt-βDEXsm column, 30 m, 0.23 mm ID, oven temperature 190 °C, t_R(minor) = 45.8 min, t_R(major) = 47.9 min). The characterization data obtained for acid **47** were in agreement with values previously reported.[7c]

Basic hydrolysis to form carboxylic acids:

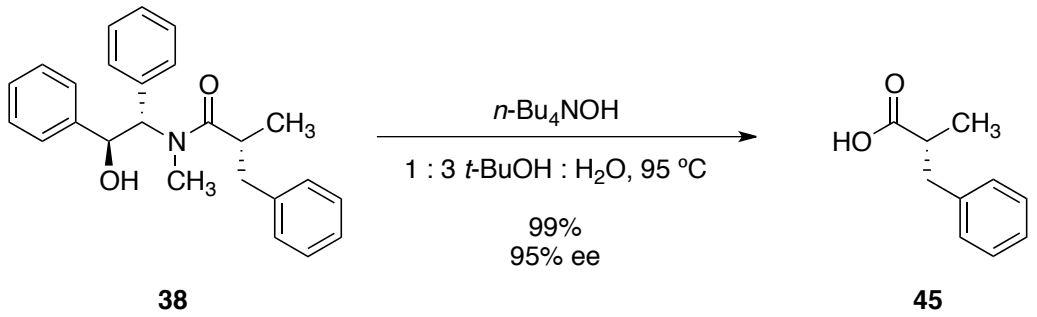


37 **44**

(*R*)-2-methylhexanoic acid (44)

An aqueous solution of tetra-*n*-butylammonium hydroxide (40% w/w, 4.83 mL, 7.36 mmol, 5.00 equiv) was added in one portion to a stirring biphasic mixture of amide **37** (500 mg, 1.47 mmol, 1 equiv) in *tert*-butyl alcohol (5 mL) and water (15 mL). The resulting biphasic mixture was stirred for 24 h at 95 ºC and then cooled to 23 ºC. The biphasic mixture was partitioned between 0.5 N aqueous sodium hydroxide solution (200 mL) and ether (30 mL). The layers were separated. The aqueous layer was extracted with two 30-mL portions of ether. The aqueous layer was acidified to pH ≤ 1 by the addition of 3 N aqueous hydrochloric acid solution. The resulting acidic aqueous solution was saturated with sodium chloride and then extracted with three 40-mL portions of ether. The combined organic extracts were washed with water (15 mL) and then dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford acid **44** as a clear liquid (180 mg, 94%). Coupling of acid **44** (25.0 mg, 0.192 mmol, 1 equiv) with (*R*)-(α-methylbenzyl)amine (29.3 μL, 0.230 mmol, 1.20 equiv) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (55.2 mg, 0.288 mmol, 1.50 equiv), 1-hydroxybenzotriazole hydrate (38.9 mg, 0.288 mmol, 1.50 equiv), and triethylamine (107 μL, 0.768 mmol, 4.00 equiv) in *N*,*N*-dimethylformamide (640 μL) at 23 ºC for 20 h gave the corresponding (*R*)-(α-methylbenzyl)amide which was analyzed by chiral

capillary GC to establish an ee of 91% for acid **44** (Restek Rt-βDEXsm column, 30 m, 0.23 mm ID, oven temperature 190 ºC, t_R (minor, amide) = 5.6 min, t_R (major, amide) = 5.9 min). The characterization data obtained for acid **44** were in agreement with values previously reported.[7c]

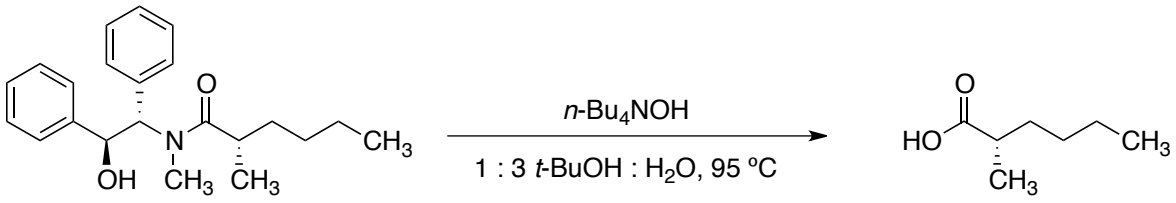


38 **45**

(*R*)-2-methyl-3-phenylpropanoic acid (45)

An aqueous solution of tetra-*n*-butylammonium hydroxide (40% w/w, 4.39 mL, 6.69 mmol, 5.00 equiv) was added in one portion to a stirring biphasic mixture of amide **38** (500 mg, 1.34 mmol, 1 equiv) in *tert*-butyl alcohol (5 mL) and water (15 mL). The resulting biphasic mixture was stirred for 24 h at 95 ºC and then cooled to 23 ºC. The biphasic mixture was partitioned between 0.5 N aqueous sodium hydroxide solution (200 mL) and ether (30 mL). The layers were separated. The aqueous layer was extracted with two 30-mL portions of ether. The aqueous layer was acidified to pH ≤ 1 by the addition of 3 N aqueous hydrochloric acid solution. The resulting acidic aqueous solution was saturated with sodium chloride and then extracted with three 35-mL portions of ether. The combined organic extracts were washed with water (15 mL) and then dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford acid **45** as a clear liquid (219 mg, 99%). Coupling of acid **45** (25.0 mg, 0.152 mmol, 1 equiv) with (*R*)-(α-methylbenzyl)amine (23.0 μL, 0.183 mmol, 1.20 equiv) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (43.8 mg, 0.228 mmol, 1.50 equiv), 1-hydroxybenzotriazole hydrate (30.9 mg, 0.228 mmol, 1.50 equiv), and triethylamine (85.0 μL, 0.609 mmol, 4.00 equiv) in *N*,*N*-dimethylformamide (500 μL) at 23 ºC for 20 h gave the corresponding (*R*)-(α-methylbenzyl)amide which was analyzed by chiral capillary GC to establish an ee of 95% for acid **45** (Restek Rt-βDEXsm column, 30 m, 0.23 mm

ID, oven temperature 190 ºC, t_R (major, amide) = 22.0 min, t_R (minor, amide) = 24.8 min). The characterization data obtained for acid **45** were in agreement with values previously reported.[7c]

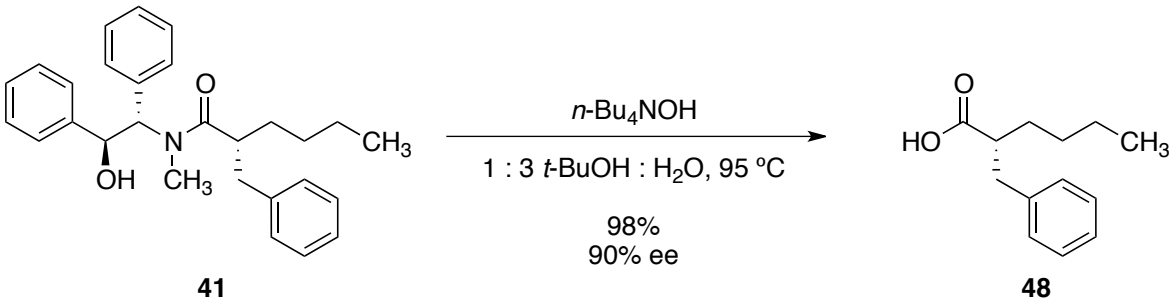


40 **46**

(*S*)-2-methylhexanoic acid (46)

An aqueous solution of tetra-*n*-butylammonium hydroxide (40% w/w, 4.84 mL, 7.39 mmol, 5.00 equiv) was added in one portion to a stirring biphasic solution of amide **40** (501 mg, 1.48 mmol, 1 equiv) and in *tert*-butyl alcohol (5.5 mL) and water (16.5 mL). The resulting biphasic mixture was stirred for 24 h at 95 ºC and then cooled to 23 ºC. The biphasic mixture was partitioned between 0.5 N aqueous sodium hydroxide solution (200 mL) and ether (30 mL). The layers were separated. The aqueous layer was extracted with two 30-mL portions of ether. The aqueous layer was acidified to pH ≤ 1 by addition of 3 N aqueous hydrochloric acid solution. The acidic aqueous solution was extracted with three 30-mL portions of ether. These combined organic extracts were washed sequentially with water (15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford acid **46** as a clear, colorless liquid (187 mg, 97%). Coupling of acid **46** (32.1 mg, 0.247 mmol, 1 equiv) with (*R*)-(α-methylbenzyl)amine (37.7 μL, 0.296 mmol, 1.20 equiv) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (70.9 mg, 0.370 mmol, 1.50 equiv), 1-hydroxybenzotriazole hydrate (56.6 mg, 0.370 mmol, 1.50 equiv), and triethylamine (137 μL, 0.986 mmol, 4.00 equiv) in *N*,*N*-dimethyformamide (500 μL) at 23 ºC for 20 h gave the corresponding (*R*)-(α-methylbenzyl)amide, which was analyzed by chiral capillary GC to establish an ee of 95% for acid **46** (Restek Rt-βDEXsm column, 30 m, 0.23 mm ID, oven

temperature 190 ºC, t_R(minor) = 5.59 min, t_R(major) = 5.93 min). The characterization data obtained for acid **46** were in agreement with values previously reported.[7c]

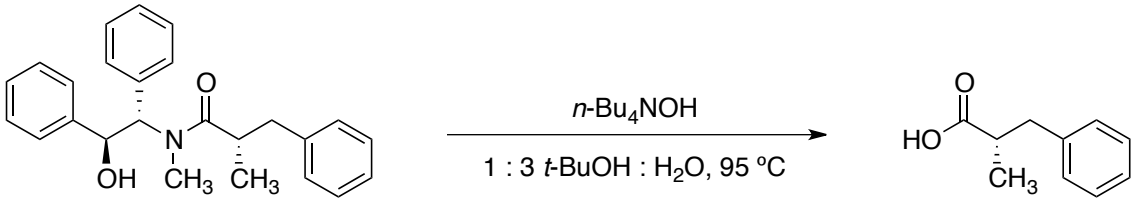


41 **48**

(*R*)-2-benzylhexanoic acid (48)

An aqueous solution of tetra-*n*-butylammonium hydroxide (40% w/w, 3.95 mL, 6.03 mmol, 5.00 equiv) was added in one portion to a stirring biphasic solution of amide **41** (501 mg, 1.21 mmol, 1 equiv) and in *tert*-butyl alcohol (4.5 mL) and water (13.5 mL). The resulting biphasic mixture was stirred for 20 h at 95 ºC and then cooled to 23 ºC. The mixture was partitioned between 0.5 N aqueous sodium hydroxide solution (200 mL) and ether (30 mL). The layers were separated. The aqueous layer was extracted with two 30-mL portions of ether. The aqueous layer was acidified to pH ≤ 1 by addition of 3 N aqueous hydrochloric acid solution. The acidic aqueous solution was extracted with three 30-mL portions of ether. These combined organic extracts were washed sequentially with water (15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford acid **48** as a clear, colorless liquid (245 mg, 98%). Coupling of acid **48** (26.2 mg, 0.127 mmol, 1 equiv) with (*R*)-(α-methylbenzyl)amine (19.4 μL, 0.152 mmol, 1.20 equiv) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (36.5 mg, 0.191 mmol, 1.50 equiv), 1-hydroxybenzotriazole hydrate (29.2 mg, 0.191 mmol, 1.50 equiv), and triethylamine (70.8 μL, 0.508 mmol, 4.00 equiv) in *N*,*N*-dimethyformamide (500 μL) at 23 ºC for 20 h gave the corresponding (*R*)-(α-methylbenzyl)amide, which was analyzed by chiral capillary GC to establish an ee of 90% for acid **48** (Restek Rt-βDEXsm column, 30 m, 0.23 mm ID, oven temperature 190 ºC, t_R(major) =

45.9 min, t_R(minor) = 47.8 min). The characterization data obtained for acid **48** were in agreement with values previously reported.[7c]



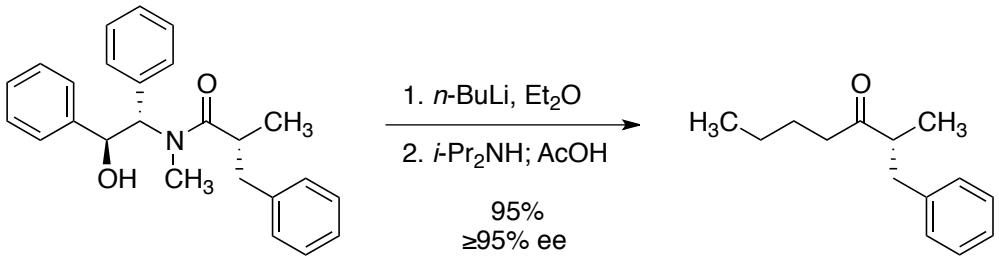
42 **49**

(*S*)-2-methyl-3-phenylpropanoic acid (49)

An aqueous solution of tetra-*n*-butylammonium hydroxide (40% w/w, 4.50 mL, 6.86 mmol, 5.00 equiv) was added in one portion to a stirring biphasic solution of amide **42** (512 mg, 1.37 mmol, 1 equiv) and in *tert*-butyl alcohol (5.17 mL) and water (15.5 mL). The resulting biphasic mixture was stirred for 24 h at 95 ºC and then cooled to 23 ºC. The mixture was partitioned between 0.5 N aqueous sodium hydroxide solution (200 mL) and ether (30 mL). The layers were separated. The aqueous layer was extracted with two 30-mL portions of ether. The aqueous layer was acidified to pH ≤ 1 by addition of 3 N aqueous hydrochloric acid solution. The acidic aqueous solution was extracted with three 30-mL portions of ether. These combined organic extracts were washed sequentially with water (15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford acid **49** as a clear, colorless liquid (224 mg, 99%). Coupling of acid **49** (31.3 mg, 0.191 mmol, 1 equiv) with (*R*)-(α-methylbenzyl)amine (29.1 μL, 0.229 mmol, 1.20 equiv) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (54.8 mg, 0.286 mmol, 1.50 equiv), 1-hydroxybenzotriazole hydrate (43.8 mg, 0.286 mmol, 1.50 equiv), and triethylamine (106 μL, 0.762 mmol, 4.00 equiv) in *N*,*N*-dimethyformamide (500 μL) at 23 ºC for 20 h gave the corresponding (*R*)-(α-methylbenzyl)amide, which was analyzed by chiral capillary GC to establish an ee of 92% for acid **49** (Restek Rt-βDEXsm column, 30 m, 0.23 mmID, oven temperature 190 ºC, t_R(minor) =

22.0 min, t_R(major) = 24.9 min). The characterization data obtained for acid **49** were in agreement with values previously reported.[7c]

Addition of organolithium reagents to form ketones:

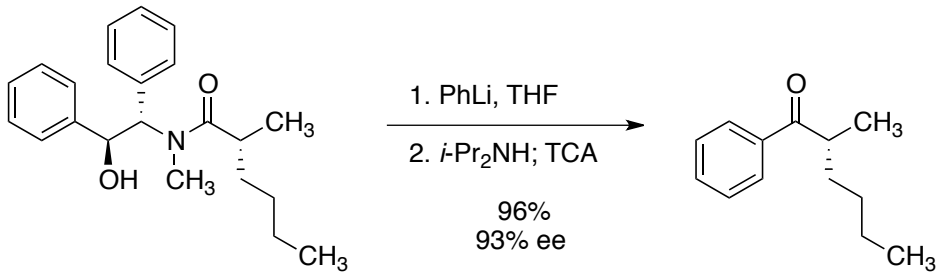


38 **50**

(*R*)-2-methyl-1-phenylheptan-3-one (50)

Amide **38** (500 mg, 1.34 mmol, 1 equiv) was suspended in toluene (10 mL). The suspension was warmed to 70 ºC to dissolve the amide, and the resulting solution was concentrated under reduced pressure. The reaction flask was flushed with dry argon, ether (10.5 mL) was added, and the resulting suspension was cooled to –78 ºC. A freshly titrated solution of *n*-butyllithium in hexanes (2.40 M, 1.34 mL, 2.40 equiv) was added by syringe, and the mixture was warmed to 0 ºC and held at that temperature for 20 min. Excess *n*-butyllithium was quenched at 0 ºC by the addition of *N*,*N*-diisopropylamine (0.188 mL, 1.34 mmol, 1 equiv). After 15 min, a solution of acetic acid in ether (20% v/v, 10 mL) was added. The mixture was partitioned between ethyl acetate (20 mL) and water (20 mL). The layers were separated. The aqueous layer was extracted with two 20-mL portions of dichloromethane. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (2→5% ethyl acetate–hexanes) to afford ketone **50** as a clear, colorless liquid (261 mg, 95%). Solid lithium aluminum hydride (13.9 mg, 0.367 mmol, 1.50 equiv) was added to a solution of ketone **50** (50.0 mg, 0.245 mmol, 1 equiv) in ether (490 μL) at 0 ºC for 25 min to afford a mixture of diastereomeric alcohols. Acylation of the mixture of diastereomeric alcohols (7.50 mg, 0.036 mmol, 1 equiv) with (*R*)- or (S)-Mosher acid chloride (20.4 μL, 0.109 mmol, 3.00 equiv) in the presence of 4-(dimethylamino)-pyridine (22.2

mg, 0.182 mmol, 5.00 equiv) and triethylamine (25.3 μL, 0.182 mmol, 5.00 equiv) in dichloromethane (1 mL) at 23 ºC for 20 min, followed by ^{1}H-NMR analysis of the corresponding Mosher ester derivatives, established that ketone **50** was of ≥95% ee. The characterization data obtained for ketone **50** were in agreement with values previously reported.[7c]

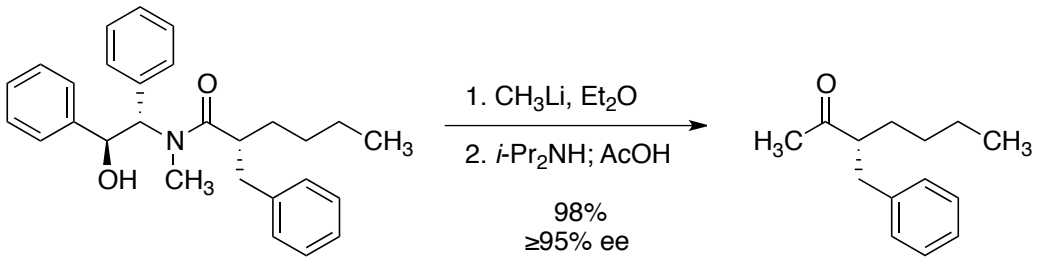


37 **51**

(*R*)-2-methyl-1-phenylhexan-1-one (51)

Amide **37** (200 mg, 0.589 mmol, 1 equiv) was dissolved in toluene (5 mL). The solution was warmed to 70 ºC and then was concentrated under reduced pressure. The reaction flask was flushed with dry argon, tetrahydrofuran (10 mL) was added, and the resulting solution was cooled to –78 ºC. A freshly titrated solution of phenyllithium in di-*n*-buytl ether (1.80 M, 0.982 mL, 3.00 equiv) was added by syringe, and the mixture was stirred for 20 min at 0 ºC and for 10 min at 23 ºC. Excess phenyllithium was quenched at 0 ºC by the addition of *N*,*N*-diisopropylamine (83.0 μL, 0.589 mmol, 1.00 equiv). After 15 min, a solution of trichloroacetic acid in ether (10% v/v, 10 mL) was added. The mixture was partitioned between ethyl acetate (40 mL) and saturated aqueous sodium bicarbonate solution (50 mL). The layers were separated. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate solution (50 mL) and water (50 mL). The washed organic extract was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (0→5% ethyl acetate–hexanes) to afford ketone **51** as a pale yellow liquid (109 mg, 96%). Solid lithium aluminum hydride (12.0 mg, 0.315 mmol, 1.50 equiv) was added to a solution of ketone **51** (40.0 mg, 0.210 mmol, 1 equiv) in ether (500 μL) at 0 ºC for 25 min to afford a mixture of diastereomeric alcohols. Acylation of the mixture of diastereomeric alcohols (10.0 mg, 0.052 mmol, 1 equiv) with (*R*)- or (S)-Mosher acid chloride (29.1 μL, 0.156 mmol, 3.00 equiv) in the presence of 4-(dimethylamino)-pyridine (31.8 mg, 0.260 mmol, 5.00

equiv) and triethylamine (36.2 μL, 0.260 mmol, 5.00 equiv) in dichloromethane (1 mL) at 23 ºC for 20 min, followed by ^{1}H-NMR analysis of the corresponding Mosher ester derivatives, established that ketone **51** was of ≥93% ee. The characterization data obtained for ketone **51** were in agreement with values previously reported.[7c]



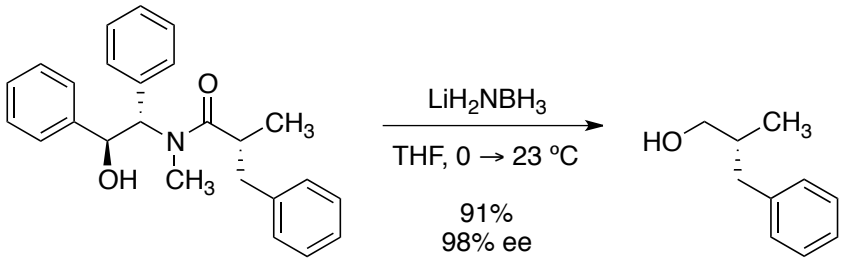
41 **52**

(*R*)-3-benzylheptan-2-one (52)

Amide **41** (203 mg, 0.489 mmol, 1 equiv) was suspended in toluene (4 mL). The suspension was warmed to 70 ºC to dissolve the amide, and the resulting solution was concentrated under reduced pressure. The reaction flask was flushed with dry argon, ether (5.0 mL) was added, and the resulting suspension was cooled to –78 ºC. A freshly titrated solution of methyllithium in diethoxymethane (2.85 M, 515 μL, 3.00 equiv) was added by syringe, and the mixture was stirred for 30 min to 0 ºC and for 10 min at 23 ºC. Excess methyllithium was quenched at 0 ºC by the addition of *N*,*N*-diisopropylamine (68.6 μL, 0.489 mmol, 1 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 10 mL) was added. The mixture was partitioned between ethyl acetate (40 mL) and saturated aqueous sodium bicarbonate solution (50 mL). The layers were separated. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate solution (25 mL), water (25 mL), and saturated aqueous sodium chloride solution (25 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (1→5% ethyl acetate–hexanes) to afford ketone **52** as a clear, colorless liquid (97.5 mg, 98%). Solid lithium aluminum hydride (13.4 mg, 0.325 mmol, 1.50 equiv) was added to a solution of ketone **52** (48.0 mg, 0.235 mmol, 1 equiv) in ether (940 μL) at 0 ºC for 30 min to afford a mixture of diastereomeric alcohols. Acylation of the mixture of diastereomeric alcohols (10.0 mg, 0.048 mmol, 1 equiv) with (*R*)- or (S)-Mosher acid chloride (36.7 μL, 0.145 mmol,

3.00 equiv) in the presence of 4-(dimethylamino)-pyridine (29.6 mg, 0.242 mmol, 5.00 equiv) and triethylamine (34.0 μL, 0.242 mmol, 5.00 equiv) in dichloromethane (1.5 mL) at 23 ºC for 10 h, followed by ^{1}H-NMR analysis of the corresponding Mosher ester derivatives, established that ketone **52** was of ≥95% ee. The characterization data obtained for ketone **52** were in agreement with values previously reported.[7c]

Reduction with lithium amidotrihydroborate to form primary alcohols:

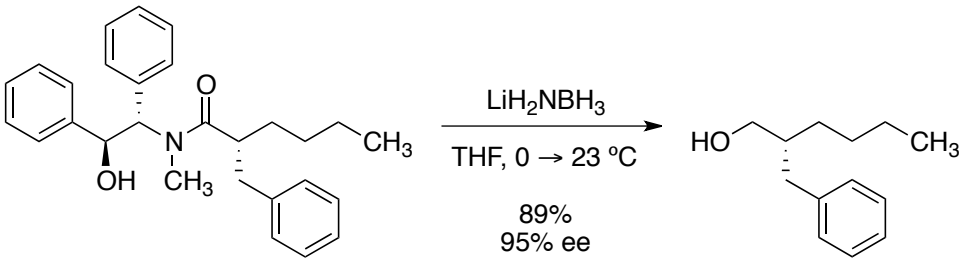


38 **53**

(*R*)-2-methyl-3-phenylpropan-1-ol (53)

A freshly titrated solution of *n*-butyllithium in hexanes (2.40 M, 2.18 mL, 3.90 equiv) was added by syringe to a stirring solution of *N*,*N*-diisopropylamine (0.79 mL, 5.62 mmol, 4.20 equiv) in tetrahydrofuran (5.6 mL) at –78 ºC. The resulting solution was stirred at –78 ºC for 10 min, then was warmed to 0 ºC and held at that temperature for 10 min. Borane-ammonia complex (90%, 184 mg, 5.35 mmol, 4.00 equiv) was added in one portion, and the suspension was stirred at 0 ºC for 15 min and then was warmed to 23 ºC. After 15 min, the solution was cooled to 0 ºC. A solution of amide **38** (500 mg, 1.34 mmol, 1 equiv) in tetrahydrofuran (3.4 mL, followed by a 0.6-mL rinse) was added via cannula. The reaction mixture was allowed to warm to 23 ºC. After 1 h, the reaction mixture was cooled in an ice-bath and 3 N aqueous hydrochloric acid solution (15 mL) was added carefully (Caution: evolution of dihydrogen). After stirring for 30 min at 0 ºC the product solution was extracted with four 20-mL portions of ether. The combined organic extracts were washed sequentially with 3 N aqueous hydrochloric acid solution (15 mL), 2 N aqueous sodium hydroxide solution (15 mL), and saturated aqueous sodium chloride solution (15 mL). The washed organic extracts were dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (40→60% ether-pentane) to afford alcohol **53** as a clear liquid (183 mg, 91%).

Chiral HPLC analysis (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R (minor, alcohol **55**) = 8.23 min, t_R (major, alcohol **53**) = 9.57 min) of alcohol **53** established that alcohol **53** was of 98% ee. The characterization data obtained for alcohol **53** were in agreement with values previously reported.[7c]

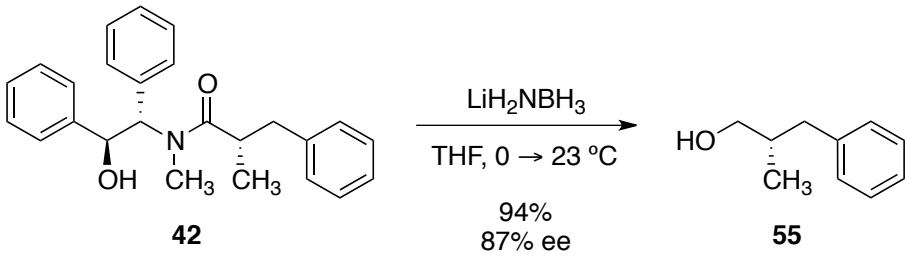


41 **54**

(*R*)-2-benzylhexan-1-ol (54)

A freshly titrated solution of *n*-butyllithium in hexanes (2.46 M, 767 μL, 3.90 equiv) was added by syringe to a stirring solution of *N*,*N*-diisopropylamine (290 μL, 2.03 mmol, 4.20 equiv) in tetrahydrofuran (1.4 mL) at –78 °C. The resulting solution was stirred at –78 °C for 10 min, then was warmed to 0 °C and held at that temperature for 10 min. Borane–ammonia complex (90%, 66.4 mg, 1.93 mmol, 4.00 equiv) was added in one portion, and the suspension was stirred at 0 °C for 15 min and then was warmed to 23 °C. After 15 min, the solution was cooled to 0 °C. A solution of amide **41** (201 mg, 0.484 mmol, 1 equiv) in tetrahydrofuran (1.0 mL, followed by a 1.0 mL rinse) was added via cannula. The reaction mixture was allowed to warm to 23 °C. After 1.5 h, the reaction mixture was cooled in an ice-bath and 3 N aqueous hydrochloric acid solution (6 mL) was added carefully (Caution: evolution of dihydrogen). After stirring for 30 min at 0 °C, the product solution was extracted with four 10-mL portions of ether. The combined organic extracts were washed sequentially with 3 N aqueous hydrochloric acid solution (10 mL), 2 N aqueous sodium hydroxide solution (6 mL), and saturated aqueous sodium chloride solution (6 mL). The washed organic extracts were dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel pre-treated with 20% triethylamine–hexanes (20% ethyl acetate–hexanes) to afford alcohol **54** as a clear, colorless liquid (82.5 mg, 89%). Chiral HPLC analysis

(Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R (minor) = 6.68 min, t_R (major, alcohol **54**) = 8.12 min) of alcohol **54** established that alcohol **54** was of 95% ee. The characterization data obtained for alcohol **54** were in agreement with values previously reported.[7c]



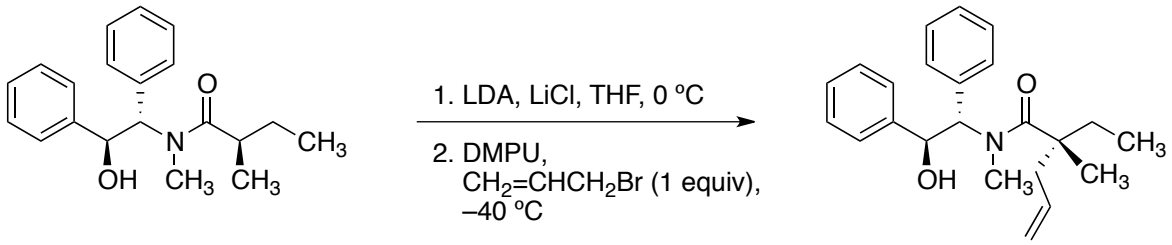
42 **55**

(*S*)-2-methyl-3-phenylpropan-1-ol (55)

A freshly titrated solution of *n*-butyllithium in hexanes (2.45 M, 2.21 mL, 3.90 equiv) was added by syringe to a stirring solution of *N*,*N*-diisopropylamine (830 μL, 5.83 mmol, 4.20 equiv) in tetrahydrofuran (5.0 mL) at –78 ºC. The resulting solution was stirred at –78 ºC for 10 min, then was warmed to 0 ºC and held at that temperature for 10 min. Borane–ammonia complex (90%, 190 mg, 5.55 mmol, 4.00 equiv) was added in one portion, and the suspension was stirred at 0 ºC for 15 min and then was warmed to 23 ºC. After 15 min, the solution was cooled to 0 ºC. A solution of amide **42** (518 mg, 1.39 mmol, 1 equiv) in tetrahydrofuran (4.0 mL, followed by a 0.91 mL rinse) was added via cannula. The reaction mixture was allowed to warm to 23 ºC. After 1 h, the reaction mixture was cooled in an ice-bath and 3 N aqueous hydrochloric acid solution (15 mL) was added carefully (Caution: evolution of dihydrogen). After stirring for 30 min at 0 ºC, the product solution was extracted with four 20-mL portions of ether. The combined organic extracts were washed sequentially with 3 N aqueous hydrochloric acid solution (15.0 mL), 2 N aqueous sodium hydroxide solution (15 mL), and saturated aqueous sodium chloride solution (15 mL). The organic solution was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel pre-treated with 20% triethylamine–hexanes (25% ethyl acetate–hexanes) to afford alcohol **55** as a clear, colorless liquid (195 mg, 94%). Chiral HPLC analysis (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R (major, alcohol **55**) = 8.40 min, t_R (minor,

alcohol **53**) = 9.97 min) of alcohol **55** established that alcohol **55** was of 87% ee. The characterization data obtained for alcohol **55** were in agreement with values previously reported.[7c]

Enolization–alkylation of α,α-disubstituted pseudoephenamine amides depicted in Table 2:

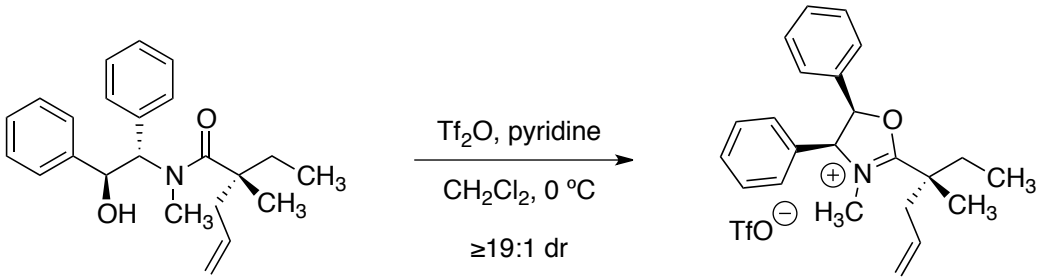


36 **56**

(*R*)-2-ethyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylpent-4-enamide (56)

N,*N*-Diisopropylamine (131 μL, 0.938 mmol, 2.92 equiv) was added by syringe to a stirring suspension of lithium chloride (123 mg, 2.89 mmol, 9.00 equiv) in tetrahydrofuran (600 μL) at 23 °C. The resulting slurry was cooled to –78 °C. A freshly titrated solution of *n*-butyllithium in hexanes (2.38 M, 394 μL, 2.92 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 °C (5 min), then was cooled to –78 °C. An ice-cooled solution of amide **36** (150 mg, 0.482 mmol, 1.50 equiv) in tetrahydrofuran (600 μL) was then added by syringe. The transfer was quantitated with tetrahydrofuran (400 μL). The reaction mixture was stirred for 3 h at 0 °C. The yellow heterogeneous mixture was cooled to –40 °C, then DMPU (146 μL, 1.21 mmol, 3.76 equiv) was added by syringe and stirring was continued for 15 min at –40 °C, whereupon allyl bromide (28.0 μL, 0.321 mmol, 1 equiv) was added by syringe. The mixture was stirred for 5 h at –40 °C, then saturated aqueous ammonium chloride solution (1.5 mL) was added and the biphasic mixture was warmed to 23 °C. The biphasic mixture was partitioned between ethyl acetate (20 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (30 mL). The layers were separated. The aqueous layer was extracted with two 20-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The

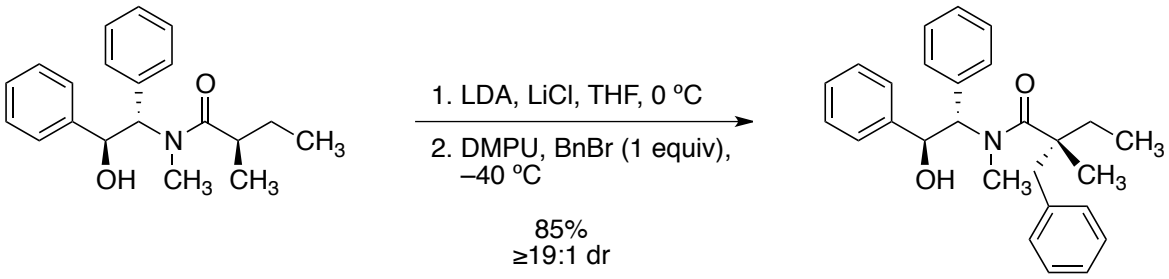
residue was purified by flash column chromatography (10→50% ethyl acetate–hexanes) to provide amide **56** as a white solid (113 mg, 99%). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below). TLC (40% Ethyl acetate–hexanes): R_f = 0.69 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.45-7.16 (m, 10H), 5.87 (d, 1H, *J* = 9.5 Hz), 5.85-5.75 (m, 1H), 5.32 (dd, 1H, *J* = 9.0, 7.0 Hz), 5.13-5.05 (m, 2H), 3.77 (d, 1H, *J* = 5.5 Hz), 2.97 (s, 3H), 2.59 (dd, 1H, *J* = 14.0, 6.5 Hz), 2.23 (dd, 1H, *J* = 14.0, 7.5 Hz), 1.77 (dq, 1H, *J* = 14.5, 7.5 Hz), 1.52 (dq, 1H, *J* = 15.0, 7.5 Hz), 1.23 (s, 3H), 0.80 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 178.2, 141.8, 136.9, 134.7, 128.9, 128.3, 128.2, 127.6, 127.5, 127.1, 117.7, 73.0, 66.0, 47.4, 43.7, 33.5, 31.6, 23.9, 8.9. FTIR (neat), cm^{-1}: 3406 (br), 2974, 1601 (s), 1452, 1080, 912. HRMS (ESI): Calcd for $(C_{23}H_{29}NO_2 + H)^+$: 352.2271. Found: 352.2263.



56 **96**

Oxazolinium triflate (96)

Trifluoromethanesulfonic anhydride (19.0 μL, 0.114 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of the α-quaternary amide **56** (20.0 mg, 0.057 mmol, 1 equiv) and pyridine (14.0 μL, 0.171 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 3 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.92* (t, 1H, *J* = 5.9 Hz), 8.57* (t, 1H, *J* = 8.1 Hz), 8.08* (t, 1H, *J* = 6.6 Hz), 7.24-7.12 (m, 6H), 6.98-6.91 (m, 4H), 6.89 (d, 1H, *J* = 11.0 Hz), 6.34 (d, 1H, *J* = 10.5 Hz), 5.99-5.88 (m, 1H), 5.44-5.27 (m, 2H), 3.50 (s, 3H), 2.79 (dd, 1H, *J* = 14.5, 7.5 Hz), 2.63 (dd, 1H, *J* = 14.0, 6.5 Hz), 2.17 (dq, 1H, *J* = 14.5, 7.5 Hz), 1.91 (dq, 1H, *J* = 15.5, 8.0 Hz), 1.64 (s, 3H), 1.19 (t, 3H, *J* = 7.5 Hz).

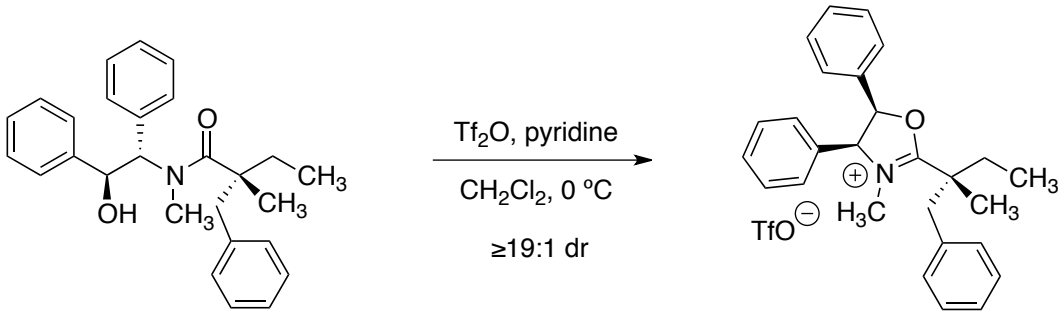


36 **57**

(*R*)-2-benzyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylbutanamide (57)

N,*N*-Diisopropylamine (113 μL, 0.952 mmol, 2.28 equiv) was added by syringe to a stirring suspension of lithium chloride (124 mg, 2.92 mmol, 7.00 equiv) in tetrahydrofuran (700 μL) at 23 °C. The resulting slurry was cooled to –78 °C. A freshly titrated solution of *n*-butyllithium in hexanes (2.38 M, 400 μL, 2.28 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 °C (5 min), then was cooled to –78 °C. An ice-cooled solution of amide **36** (156 mg, 0.501 mmol, 1.20 equiv) in tetrahydrofuran (600 μL) was then added by syringe. The transfer was quantitated with tetrahydrofuran (400 μL). The reaction mixture was stirred for 3 h at 0 °C. The yellow heterogeneous mixture was cooled to –40 °C, then DMPU (164 μL, 1.35 mmol, 3.25 equiv) was added by syringe and stirring was continued for 15 min at –40 °C, whereupon benzyl bromide (50.0 μL, 0.417 mmol, 1 equiv) was added by syringe. The mixture was stirred for 1.25 h at –40 °C, then saturated aqueous ammonium chloride solution (1.5 mL) was added and the biphasic mixture was warmed to 23 °C. The biphasic mixture was partitioned between ethyl acetate (20 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (30 mL). The layers were separated. The aqueous layer was extracted with two 20-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (10→50% ethyl acetate–hexanes) to provide amide **57** as an off-white solid (143 mg, 85%). The diastereomeric

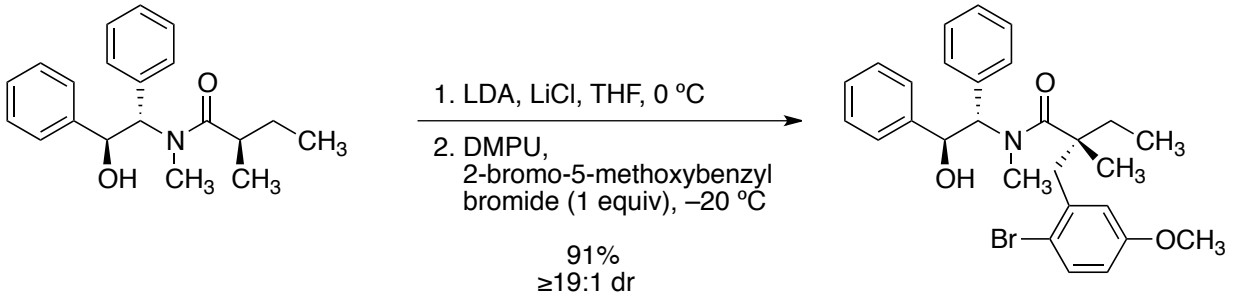
ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below). TLC (40% Ethyl acetate–hexanes): R_f = 0.69 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.46-7.08 (m, 15H), 5.85 (d, 1H, *J* = 9.0 Hz), 5.33 (dd, 1H, *J* = 9.5, 7.0 Hz), 3.69 (d, 1H, *J* = 6.0 Hz), 3.12 (d, 1H, *J* = 14.0 Hz), 2.94 (s, 3H), 2.81 (d, 1H, *J* = 13.5 Hz), 1.93 (dq, 1H, *J* = 14.5, 7.5 Hz), 1.42 (dq, 1H, *J* = 15.0, 7.5 Hz), 1.20 (s, 3H), 0.81 (t, 3H, *J* = 7.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 178.5, 141.9, 137.9, 136.8, 130.5, 129.1, 128.4, 128.2, 128.0, 127.7, 127.6, 127.1, 126.4, 73.3, 66.3, 48.8, 45.3, 33.7, 32.2, 23.6, 9.0. FTIR (neat), cm^{-1}: 3404 (br), 2970, 1601 (s), 1452, 1080, 908. HRMS (ESI): Calcd for $(C_{27}H_{31}NO_2 + H)^+$: 402.2428. Found: 402.2423.



57 **97**

Oxazolinium triflate (97)

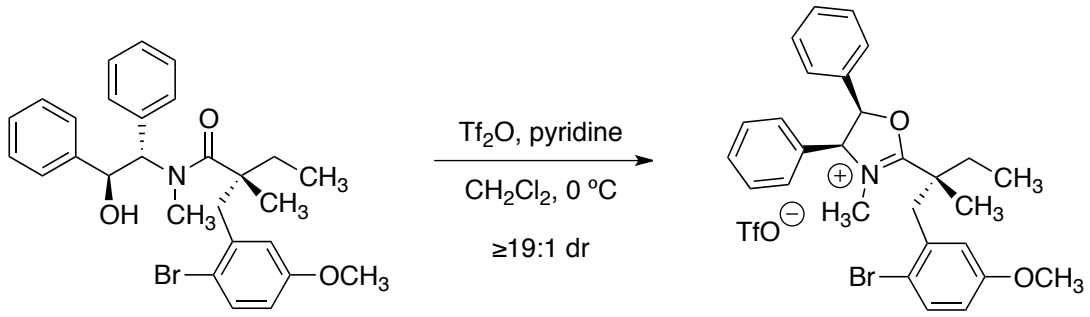
Trifluoromethanesulfonic anhydride (17.0 μL, 0.100 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of the α-quaternary amide **57** (20.0 mg, 0.050 mmol, 1 equiv) and pyridine (12.0 μL, 0.149 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 3 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.88* (d, 1H, *J* = 4.9 Hz), 8.47* (t, 1H, *J* = 7.8 Hz), 7.99* (t, 1H, *J* = 7.1 Hz), 7.54-7.03 (m, 14H), 6.87-6.80 (m, 2H), 6.41 (d, 1H, *J* = 11.5 Hz), 3.36 (s, 3H), 3.29 (d, 1H, *J* = 14.5 Hz), 3.22 (d, 1H, *J* = 14.0 Hz), 2.30 (dq, 1H, *J* = 14.5, 7.5 Hz), 1.83 (dq, 1H, *J* = 15.0, 7.5 Hz), 1.67 (s, 3H), 1.24 (t, 3H, *J* = 7.7 Hz).



(*R*)-2-(2-bromo-5-methoxybenzyl)-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylbutanamide (58)

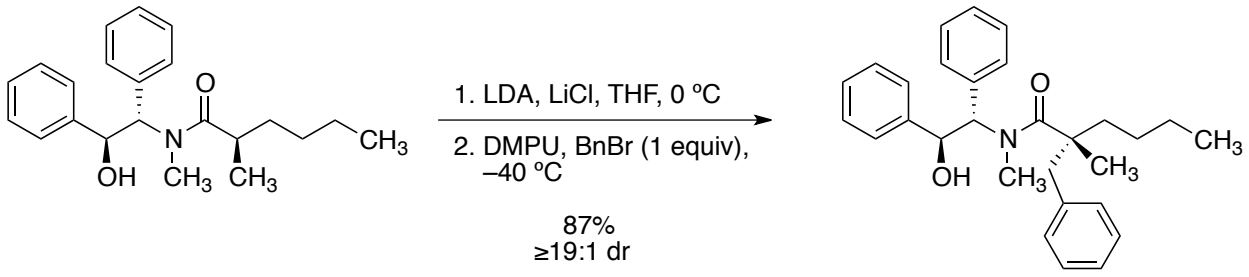
N,*N*-Diisopropylamine (176 μL, 1.25 mmol, 2.93 equiv) was added by syringe to a stirring suspension of lithium chloride (163 mg, 3.85 mmol, 9.00 equiv) in tetrahydrofuran (700 μL) at 23 °C. The resulting slurry was cooled to –78 °C. A freshly titrated solution of *n*-butyllithium in hexanes (2.38 M, 527 μL, 2.93 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 °C (5 min), then was cooled to –78 °C. An ice-cooled solution of amide **36** (200 mg, 0.642 mmol, 1.50 equiv) in tetrahydrofuran (600 μL) was then added by syringe. The transfer was quantitated with tetrahydrofuran (400 μL). The reaction mixture was stirred for 3 h at 0 °C. The yellow heterogeneous mixture was cooled to –20 °C, then DMPU (194 μL, 1.60 mmol, 3.74 equiv) was added by syringe and stirring was continued for 15 min at –20 °C, whereupon 2-bromo-5-methoxybenzyl bromide (120 mg, 0.428 mmol, 1 equiv) in THF (500 μL) was added by syringe. The mixture was stirred for 2 h at –20 °C, then saturated aqueous ammonium chloride solution (1.5 mL) was added and the biphasic mixture was warmed to 23 °C. The biphasic mixture was partitioned between ethyl acetate (20 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (30 mL). The layers were separated. The aqueous layer was extracted with two 20-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography

(10→40% ethyl acetate–hexanes) to provide amide **58** as a white foam/solid (198 mg, 91%). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below).TLC (40% Ethyl acetate–hexanes): R_f = 0.59 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.42-7.41 (m, 1H), 7.30-7.17 (m, 10H), 6.96 (d, 1H, *J* = 3.0 Hz), 6.64 (dd, 1H, *J* = 9.0, 3.0 Hz), 5.94 (d, 1H, *J* = 9.5 Hz), 5.34 (d, 1H, *J* = 9.0 Hz), 3.73 (s, 3H), 3.27 (d, 1H, 15.0 Hz), 3.12 (d, 1H, *J* = 15.0 Hz), 3.03 (s, 3H), 2.02 (sxt, 1H, *J* = 7.5 Hz), 1.51 (sxt, 1H, *J* =7.5 Hz), 1.24 (s, 3H), 0.80 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 178.5, 158.6, 141.9, 138.8, 136.8, 133.3, 128.9, 128.4, 128.3, 127.8, 127.6, 127.1, 117.6, 116.6, 113.6, 73.3, 66.1, 55.4, 49.2, 43.4, 33.8, 32.2, 23.2, 9.0. FTIR (neat), cm^{-1}: 3402 (br), 2969, 1597 (m), 1471 (m), 1384, 1240 (m). HRMS (ESI): Calcd for $(C_{28}H_{32}BrNO_3 + H)^+$: 510.1638. Found: 510.1631.



Oxazolinium triflate (98)

Trifluoromethanesulfonic anhydride (13.2 μL, 0.078 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of the α-quaternary amide **58** (20.0 mg, 0.039 mmol, 1 equiv) and pyridine (9.47 μL, 0.118 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 3 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.91* (d, 1H, *J* = 5.0 Hz), 8.56* (t, 1H, *J* = 8.0 Hz), 8.07* (t, 1H, *J* = 7.0 Hz), 7.55 (d, 1H, *J* = 9.0 Hz), 7.22-7.11 (m, 8H), 6.97-6.96 (m, 1H), 6.94 (d, 1H, *J* = 3.5 Hz), 6.90-6.87 (m,2H), 6.79, (dd, 1H, *J* = 8.5, 3.0 Hz), 6.37 (d, 1H, *J* = 10.5 Hz), 3.83 (s, 3H), 3.51 (s, 3H), 3.50 (d, 1H, *J* = 14.0 Hz), 3.44 (d, 1H, *J* = 14.0 Hz), 2.40 (sxt, 1H, *J* = 7.3 Hz), 1.85 (sxt, 1H, *J* = 7.3 Hz), 1.68 (s, 3H), 1.21 (t, 3H, *J* = 7.3 Hz).

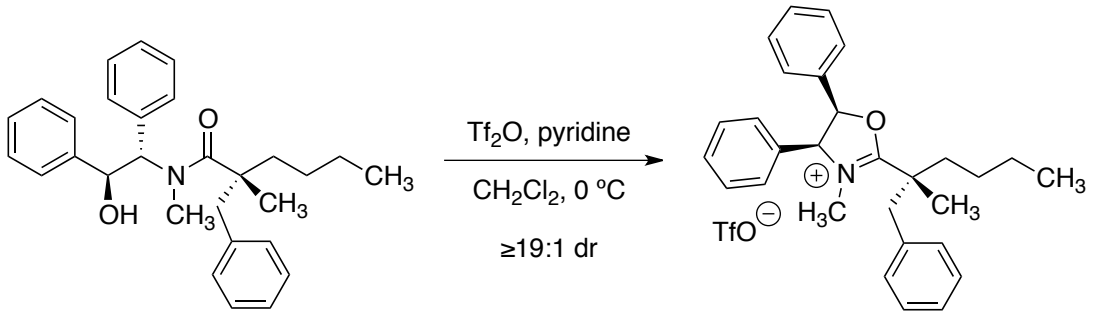


37 **59**

(*R*)-2-benzyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylhexanamide (59)

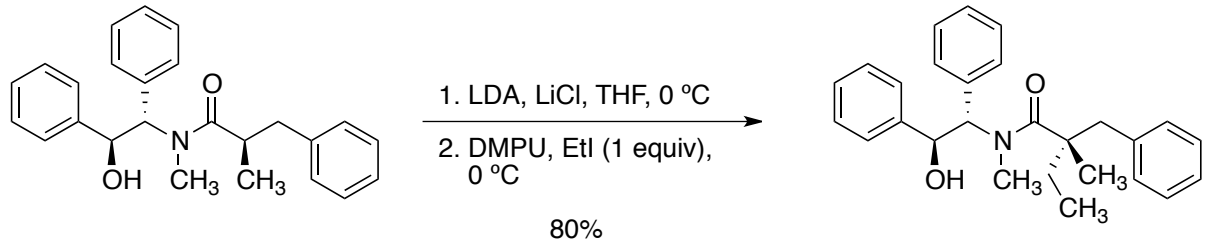
N,*N*-Diisopropylamine (161 μL, 1.15 mmol, 2.93 equiv) was added by syringe to a stirring suspension of lithium chloride (150 mg, 3.53 mmol, 9.00 equiv) in tetrahydrofuran (800 μL) at 23 °C. The resulting slurry was cooled to –78 °C. A freshly titrated solution of *n*-butyllithium in hexanes (2.38 M, 484 μL, 2.93 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 °C (5 min), then was cooled to –78 °C. An ice-cooled solution of amide **37** (200 mg, 0.589 mmol, 1.50 equiv) in tetrahydrofuran (700 μL) was then added by syringe. The transfer was quantitated with tetrahydrofuran (500 μL). The reaction mixture was stirred for 3 h at 0 °C. The yellow heterogeneous mixture was cooled to –40 °C, then DMPU (178 μL, 1.47 mmol, 3.74 equiv) was added by syringe and stirring was continued for 15 min at –40 °C, whereupon benzyl bromide (46.7 μL, 0.393 mmol, 1 equiv) was added by syringe. The mixture was stirred for 3.5 h at –40 °C, then saturated aqueous ammonium chloride solution (1.5 mL) was added and the biphasic mixture was warmed to 23 °C. The biphasic mixture was partitioned between ethyl acetate (20 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (30 mL). The layers were separated. The aqueous layer was extracted with two 20-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (10→30% ethyl acetate–hexanes) to

provide amide **59** as an off-white solid (147 mg, 87%). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below). TLC (40% Ethyl acetate–hexanes): R_f = 0.81 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.41-7.15 (m, 15H), 5.84 (d, 1H, *J* = 9.0 Hz), 5.32 (d, 1H, *J* = 9.0 Hz), 3.13 (d, 1H, *J* = 13.5 Hz), 2.81 (d, 1H, *J* = 13.5 Hz), 1.84 (dt, 1H, *J* = 13.0, 4.0 Hz), 1.34 (dt, 1H, *J* = 12.5, 4.0 Hz), 1.28-1.22 (m 2H), 1.20 (s, 3H), 1.09-1.04 (m, 2H), 0.81 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 178.7, 141.9, 137.8, 136.8, 130.4, 129.1, 128.4, 128.2, 128.0, 127.7, 127.6, 127.1, 126.4, 73.2, 66.4, 48.4, 45.6, 39.4, 33.7, 26.7, 24.3, 23.3, 13.9. FTIR (neat), cm^{-1}: 3410 (br), 2956, 1601 (m), 1452, 1078, 908. HRMS (ESI): Calcd for $(C_{29}H_{35}NO_2 + H)^+$: 430.2741. Found: 430.2735.



Oxazolinium triflate (99)

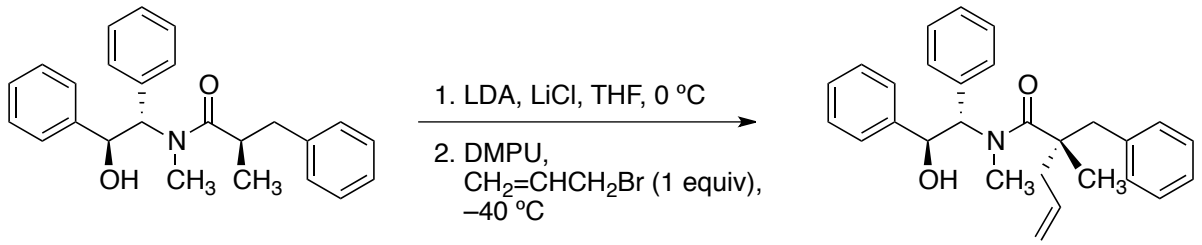
Trifluoromethanesulfonic anhydride (15.7 μL, 0.093 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of the α-quaternary amide **99** (20.0 mg, 0.047 mmol, 1 equiv) and pyridine (11.3 μL, 0.140 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 3 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.88* (t, 1H, *J* = 6.1 Hz), 8.56* (t, 1H, *J* = 7.7 Hz), 8.06* (t, 1H, *J* = 6.5 Hz), 7.47-7.08 (m, 14H), 6.86 (d, 1H, *J* = 6.5 Hz), 6.81 (d, 1H, *J* = 11.0 Hz), 6.37 (d, 1H, *J* = 10.5 Hz), 3.34 (s, 3H), 3.29 (d, 1H, *J* = 14.0 Hz), 3.21 (d, 1H, *J* = 14.0 Hz), 2.19 (dt, 1H, *J* = 14.0, 3.2 Hz), 1.75 (dt, 1H, *J* = 13.8, 4.3 Hz), 1.67 (s, 3H), 1.60-1.44 (m, 4H), 0.99 (t, 3H, *J* = 7.0 Hz).



(*S*)-2-benzyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylbutanamide (60)

N,*N*-Diisopropylamine (110 μL, 0.784 mmol, 2.93 equiv) was added by syringe to a stirring suspension of lithium chloride (102 mg, 2.41 mmol, 9.00 equiv) in tetrahydrofuran (500 μL) at 23 °C. The resulting slurry was cooled to –78 °C. A freshly titrated solution of *n*-butyllithium in hexanes (2.38 M, 330 μL, 2.93 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 °C (5 min), then was cooled to –78 °C. An ice-cooled solution of amide **38** (150 mg, 0.402 mmol, 1.50 equiv) in tetrahydrofuran (500 μL) was then added by syringe. The transfer was quantitated with tetrahydrofuran (340 μL). The reaction mixture was stirred for 3 h at 0 °C. Then, DMPU (121 μL, 1.00 mmol, 3.74 equiv) was added by syringe and stirring was continued for 15 min at 0 °C, whereupon iodoethane (21.5 μL, 0.268 mmol, 1 equiv) was added by syringe. The mixture was stirred for 18.5 h at 0 °C, then saturated aqueous ammonium chloride solution (1.5 mL) was added and the biphasic mixture was warmed to 23 °C. The biphasic mixture was partitioned between ethyl acetate (20 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (30 mL). The layers were separated. The aqueous layer was extracted with two 20-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (10→50% ethyl acetate–hexanes) to provide amide **60** as a yellow semi-solid (89.0 mg, 83%, mixture of diastereomers). The diastereomeric ratio of the purified product was determined to be

9.9:1 by ^{1}H NMR analysis. The diastereomers were separated by radial chromatography (10→30% ethyl acetate–hexanes) to provide amide **60** as a clear, colorless semi-solid (77.0 mg, 71%) and amide **57** as a white solid (6.0 mg, 6%). TLC (40% Ethyl acetate–hexanes): R_f = 0.65 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.40-7.03 (m, 15H), 5.92 (d, 1H, *J* = 9.0 Hz), 5.31 (d, 1H, *J* = 9.0 Hz), 3.73 (br, 1H), 3.09 (d, 1H, *J* = 14.0 Hz), 2.96 (s, 3H), 2.73 (d, 1H, *J* = 13.5 Hz), 2.03 (app sxt, 1H, *J* = 7.2 Hz), 1.45 (app sxt, 1H, *J* = 7.2 Hz), 1.21 (s, 3H), 0.94 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 178.7, 141.9, 137.8, 136.5, 130.4, 129.4, 128.4, 128.3, 128.0, 127.7, 127.1, 126.4, 73.3, 66.0, 49.0, 44.9, 33.1, 32.8, 23.8, 9.2. FTIR (neat), cm^{-1}: 3404 (br), 2974, 1601 (s), 1452 (m), 1386, 1078 (m). HRMS (ESI): Calcd for $(C_{27}H_{31}NO_2 + H)^+$: 402.2428. Found: 402.2419.

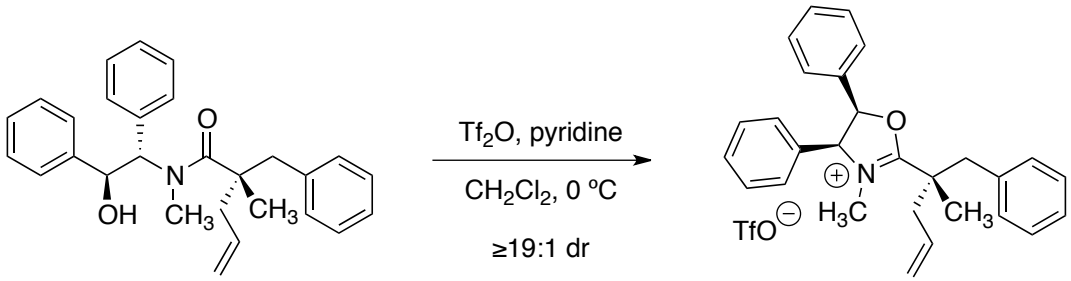


38 82% ≥19:1 dr **61**

(*S*)-2-benzyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylpent-4-enamide (61)

N,*N*-Diisopropylamine (110 μL, 0.785 mmol, 2.54 equiv) was added by syringe to a stirring suspension of lithium chloride (102 mg, 2.41 mmol, 7.80 equiv) in tetrahydrofuran (500 μL) at 23 °C. The resulting slurry was cooled to –78 °C. A freshly titrated solution of *n*-butyllithium in hexanes (2.38 M, 330 μL, 2.54 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 °C (5 min), then was cooled to –78 °C. An ice-cooled solution of amide **38** (150 mg, 0.402 mmol, 1.30 equiv) in tetrahydrofuran (500 μL) was then added by syringe. The transfer was quantitated with tetrahydrofuran (340 μL). The reaction mixture was stirred for 3 h at 0 °C. The yellow heterogeneous mixture was cooled to –40 °C, then DMPU (121 μL, 1.00 mmol, 3.25 equiv) was added by syringe and stirring was continued for 15 min at –40 °C, whereupon allyl bromide (27.0 μL, 0.309 mmol, 1 equiv) was added by syringe. The mixture was stirred for 1.3 h at –40 °C, then saturated aqueous ammonium chloride solution (1.5 mL) was added and the biphasic mixture was warmed to 23 °C. The biphasic mixture was partitioned between ethyl acetate (20 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (30 mL). The layers were separated. The aqueous layer was extracted with two 20-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (10→50% ethyl acetate–hexanes) to provide amide **61** as a pale-yellow semi-solid (105 mg, 82%). The diastereomeric ratio of the

purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below). TLC (40% Ethyl acetate–hexanes): R_f = 0.72 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.43-7.01 (m, 15H), 5.91-5.79 (m, 2H), 5.32 (dd, 1H, *J* = 9.0, 6.0 Hz), 5.17-5.07 (m, 2H), 3.64 (d, 1H, *J* = 5.0 Hz), 3.12 (d, 1H, *J* = 14.0 Hz), 2.96 (s, 3H), 2.85-2.73 (m, 2H), 2.19 (dd, 1H, *J* = 15.0, 8.0 Hz), 1.24 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 177.8, 141.6, 137.3, 136.4, 134.5, 130.3, 129.3, 128.3, 128.2, 128.1, 127.7, 127.6, 127.2, 126.5, 118.1, 73.0, 66.2, 48.4, 44.9, 44.6, 33.3, 24.1. FTIR (neat), cm^{-1}: 3416 (br), 3030, 1603 (m), 1452, 1076, 910. HRMS (ESI): Calcd for $(C_{28}H_{31}NO_2 + H)^+$: 414.2428. Found: 414.2426.

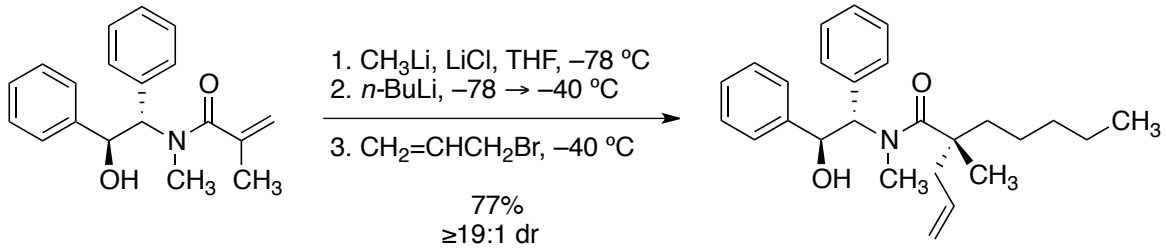


61 **100**

Oxazolinium triflate (100)

Trifluoromethanesulfonic anhydride (16.0 μL, 0.097 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of the α-quaternary amide **61** (20.0 mg, 0.048 mmol, 1 equiv) and pyridine (12.0 μL, 0.145 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 3 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.83* (d, 1H, *J* = 4.9 Hz), 8.42-8.29* (m, 1H), 7.89* (dd, 1H, *J* = 6.3, 7.3 Hz), 7.52-6.78 (m, 15H), 6.73 (d, 1H, *J* = 11.0 Hz), 6.38 (d, 1H, *J* = 10.5 Hz), 5.98 (m, 1H), 5.45-5.33 (m, 2H), 3.45 (s, 3H), 3.41 (d, 1H, *J* = 14.0 Hz), 3.15 (d, 1H, *J* = 14.5 Hz), 3.00 (dd, 1H, *J* = 14.5, 8.0 Hz), 2.61 (dd, 1H, *J* = 14.5, 6.5 Hz), 1.65 (s, 3H).

Conjugate addition–alkylation of α-alkyl-α,β α-unsaturated pseudoephenamine amides:

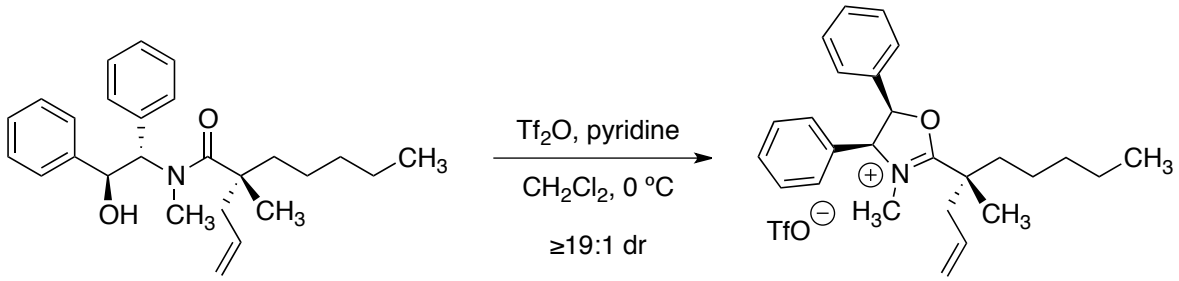


33 **62**

(*R*)-2-allyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylheptanamide (62)

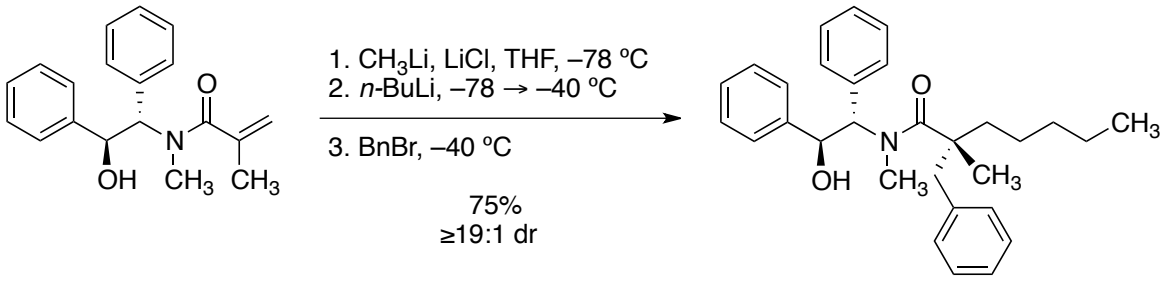
A freshly titrated solution of methyllithium in diethoxymethane (2.93 M, 610 μL, 1.00 equiv) was added by syringe to a stirring suspension of amide **33** (528 mg, 1.79 mmol, 1 equiv) and lithium chloride (455 mg, 10.7 mmol, 6.00 equiv) in tetrahydrofuran (8.93 mL) at –78 °C. After stirring for 10 min at –78 °C, a freshly titrated solution of *n*-butyllithium in hexanes (2.50 M, 858 μL, 1.20 equiv) was added by syringe. The resulting solution was stirred for 10 min at –78 °C and for 10 min at –40 °C, whereupon allyl bromide (464 μL, 5.36 mmol, 3.00 equiv) was added by syringe. The mixture was stirred for 3 h at –40 °C, then saturated aqueous ammonium chloride (2 mL) was added and the biphasic mixture was warmed to 23 °C. The biphasic mixture was partitioned between ethyl acetate (60 mL) and 0.5 N aqueous hydrochloric acid solution (20 mL). The layers were separated. The organic layer was washed sequentially with 0.5 N aqueous hydrochloric acid solution (2 x 20 mL) and saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (5→25% ethyl acetate–hexanes) to afford amide **62** as a clear, colorless oil (544 mg, 77%). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below). TLC (30% ethyl acetate–hexanes): R_f = 0.48 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.42 (d, 2H, J = 7.3 Hz),

7.32–7.16 (m, 8H), 5.94–5.71 (m, 2H), 5.31 (dd, 1H, J = 8.8, 6.8 Hz), 5.13–5.01 (m, 2H), 3.76 (br s, 1H), 2.96 (s, 3H), 2.58 (dd, 1H, J = 14.2, 6.8 Hz), 2.23 (dd, 1H, J = 14.2, 7.3 Hz), 1.68 (td, 1H, J = 13.1, 4.2 Hz), 1.49–1.38 (m, 1H), 1.34–0.99 (m, 9H), 0.82 (t, 3H, J = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 177.7, 141.7, 137.0, 134.5, 128.6, 128.0, 127.9, 127.3, 127.2, 126.8, 117.4, 72.7, 65.4, 46.8, 43.8, 38.6, 33.4, 32.1, 24.4, 23.9, 22.2, 13.8. FTIR (neat), cm^{-1}: 3396 (br), 2927 (m), 1603 (s), 1455 (m), 1376. HRMS (ESI): Calcd for $(C_{26}H_{35}NO_2 + H)^+$: 394.2741. Found: 394.2740.



Oxazolinium triflate (101)

Trifluoromethanesulfonic anhydride (29.5 μL, 0.175 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of α-quaternary amide **62** (34.5 mg, 0.088 mmol, 1 equiv) and pyridine (21.3 μL, 0.263 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 2 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.88* (d, 2H, *J* = 5.4 Hz), 8.60* (t, 1H, *J* = 7.8 Hz), 8.10* (t, 2H, *J* = 7.1 Hz), 7.23–7.08 (m, 6H), 7.00–6.93 (m, 2H), 6.91 (d, 2H, *J* = 6.8 Hz), 6.85 (d, 1H, *J* = 10.7 Hz), 6.30 (d, 1H, *J* = 10.7 Hz), 5.98–5.86 (m, 1H), 5.40–5.27 (m, 2H), 3.48 (s, 3H), 2.78 (dd, 1H, *J* = 14.4, 7.6 Hz), 2.62 (dd, 1H, *J* = 14.4, 7.1 Hz), 2.12–1.99 (m, 1H), 1.85–1.71 (m, 1H), 1.64 (s, 3H), 1.57–1.46 (m, 2H), 1.45–1.30 (m, 4H), 0.92 (t, 3H, *J* = 6.8 Hz).

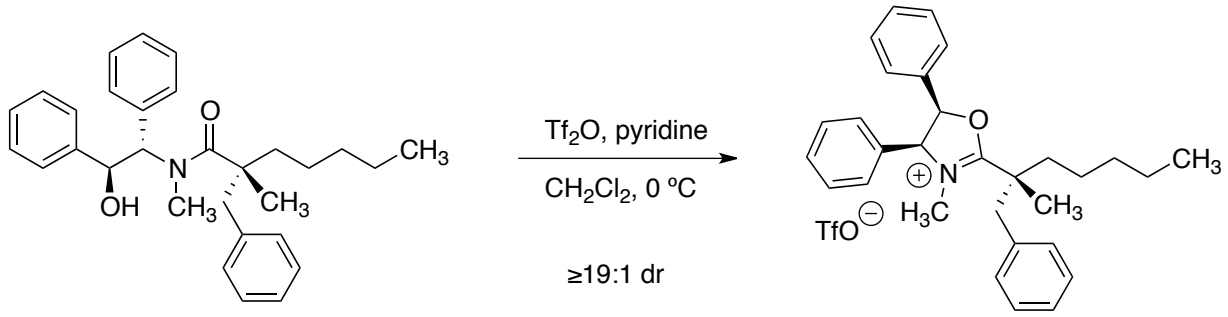


33 **63**

(*R*)-2-benzyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylheptanamide (63)

A freshly titrated solution of methyllithium in diethoxymethane (2.67 M, 630 μL, 1.00 equiv) was added by syringe to a stirring suspension of amide **33** (496 mg, 1.68 mmol, 1 equiv) and lithium chloride (428 mg, 10.1 mmol, 6.00 equiv) in tetrahydrofuran (8.40 mL) at –78 °C. After stirring for 10 min at –78 °C, a freshly titrated solution of *n*-butyllithium in hexanes (2.45 M, 823 μL, 1.20 equiv) was added by syringe. The resulting solution was stirred for 10 min at –78 °C and for 10 min at –40 °C, whereupon benzyl bromide (600 μL, 5.04 mmol, 3.00 equiv) was added by syringe. The mixture was stirred for 1 h at –40 °C, then saturated aqueous ammonium chloride (2 mL) was added and the biphasic mixture was warmed to 23 °C. The biphasic mixture was partitioned between ethyl acetate (60 mL) and 0.5 N aqueous hydrochloric acid solution (20 mL). The layers were separated. The organic layer was washed sequentially with 0.5 N aqueous hydrochloric acid solution (2 x 20 mL) and saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (5→45% ethyl acetate–hexanes) to afford amide **63** as a white, crystalline solid (560 mg, 75%, mp = 80-82 °C). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below). TLC (40% ethyl acetate–hexanes): R_f = 0.60 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.40 (d, 2H, J = 7.3

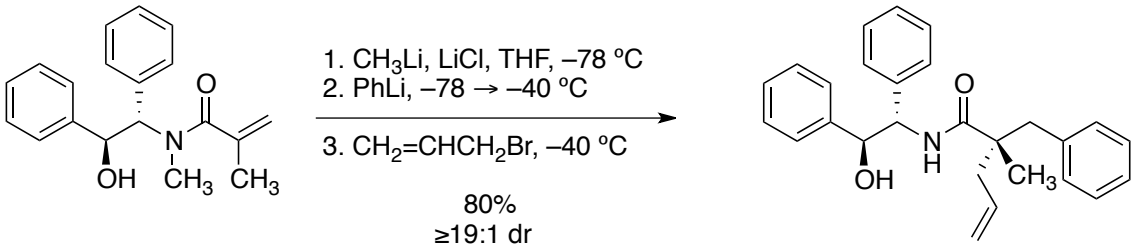
Hz), 7.09–7.31 (m, 13H), 5.85 (d, 1H, *J* = 8.8 Hz), 5.32 (dd, 1H, *J* = 9.0, 7.1 Hz), 3.70 (d, 1H, *J* = 4.9 Hz), 3.12 (d, 1H, *J* = 13.7 Hz), 3.94 (s, 3H), 2.81 (d, 1H, *J* = 13.7 Hz), 1.83 (td, 1H, *J* = 13.1, 3.7 Hz), 1.00–1.41 (m, 11H), 0.82 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 178.5, 141.9, 137.8, 136.8, 136.5, 130.4, 129.0, 128.2, 128.1, 127.9, 127.6, 127.5, 127.0, 126.3, 73.1, 66.1, 48.3, 45.5, 39.6, 33.6, 32.3, 24.3, 24.2, 22.4, 14.0. FTIR (neat), cm^{-1}: 3402 (br), 2929, 1602 (s), 1452 (m). HRMS (ESI): Calcd for $(C_{30}H_{37}NO_2 + H)^+$: 444.2897. Found: 444.2896.



63 **102**

Oxazolinium triflate (102)

Trifluoromethanesulfonic anhydride (19.8 μL, 0.118 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of α-quaternary amide **63** (26.1 mg, 0.059 mmol, 1 equiv) and pyridine (14.3 μL, 0.177 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 2 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.88* (br s, 2H), 8.45* (br s, 1H), 7.98* (br d, 2H, *J* = 6.3 Hz), 7.46 (t, 2H, *J* = 7.3 Hz), 7.37 (t, 1H, *J* = 7.3 Hz), 7.29 (d, 2H, *J* = 7.3 Hz), 7.03–7.23 (m, 6H), 6.87 (d, 2H, *J* = 7.3 Hz), 6.76–6.84 (m, 3H), 6.36 (d, 1H, *J* = 11.2 Hz), 3.32 (s, 3H), 3.28 (d, 1H, *J* = 13.7 Hz), 3.20 (d, 1H, *J* = 14.2 Hz), 2.12–2.23 (m, 1H), 1.74 (td, 1H, *J* = 13.3, 4.6 Hz), 1.67 (s, 3H), 1.45–1.63 (m, 2H), 1.33–1.45 (m, 4H), 0.93 (t, 3H, *J* = 6.8 Hz).

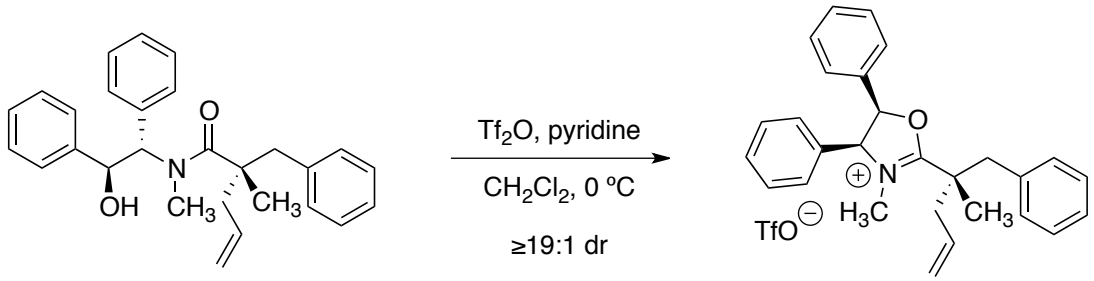


33 **61**

(*S*)-2-benzyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylpent-4-enamide (61)

A freshly titrated solution of methyllithium in diethoxymethane (2.67 M, 629 μL, 1.00 equiv) was added by syringe to a stirring suspension of amide **33** (496 mg, 1.68 mmol, 1 equiv) and lithium chloride (427 mg, 10.1 mmol, 6.00 equiv) in tetrahydrofuran (8.40 mL) at –78 °C. After stirring for 10 min at –78 °C, a freshly titrated solution of phenyllithium in di-*n*-butyl ether (1.61 M, 1.23 mL, 1.20 equiv) was added by syringe. The resulting solution was stirred for 10 min at –78 °C and for 10 min at –40 °C, whereupon allyl bromide (436 μL, 5.04 mmol, 3.00 equiv) was added by syringe. The mixture was stirred for 6 h at –40 °C, then saturated aqueous ammonium chloride (2 mL) was added and the biphasic mixture was warmed to 23 °C. The biphasic mixture was partitioned between ethyl acetate (25 mL) and half-saturated aqueous sodium chloride solution (50 mL). The layers were separated. The aqueous layer was extracted with two 25-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (5→40% ethyl acetate–hexanes) to afford amide **61** as a clear, colorless glaze (556 mg, 80%). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below). TLC (40% ethyl acetate–hexanes): R_f = 0.49 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.39 (d, 3H, J = 7.3 Hz), 7.12–7.33 (m, 9H), 6.98–7.07 (m, 3H), 5.75–5.93 (m, 2H), 5.31 (dd, 1H, J = 9.3, 6.4 Hz), 5.05–5.18 (m, 2H), 3.64 (br s, 1H), 3.11 (d, 1H, J = 14.2 Hz), 2.95

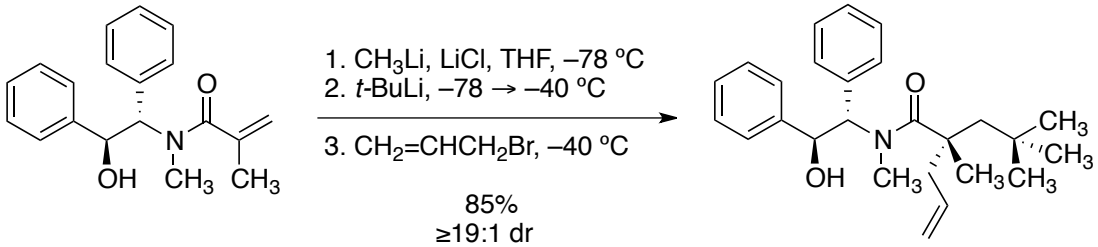
(s, 3H), 2.70–2.84 (m, 2H), 2.18 (dd, 1H, J = 14.7, 7.3 Hz), 2.01–2.08 (m, 1H), 1.23 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 177.5, 141.6, 137.2, 136.4, 134.3, 130.2, 129.1, 128.1, 128.1, 127.9, 127.5, 127.4, 127.0, 126.3, 117.9, 72.8, 65.8, 48.2, 44.7, 44.3, 33.1, 23.9. FTIR (neat), cm^{-1}: 3406 (br), 3030, 1602 (s), 1452 (m). HRMS (ESI): Calcd for $(C_{28}H_{31}NO_2 + H)^+$: 414.2428. Found: 414.2421.



61 **103**

Oxazolinium triflate (103)

Trifluoromethanesulfonic anhydride (22.5 μL, 0.133 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of α-quaternary amide **61** (27.6 mg, 0.067 mmol, 1 equiv) and pyridine (16.2 μL, 0.200 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 2 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.82* (br s, 2H), 8.27* (br s, 1H), 7.83* (br s, 2H), 7.43 (t, 2H, *J* = 7.3 Hz), 7.29–7.39 (m, 3H), 7.15–7.21 (m, 1H), 7.06–7.15 (m, 5H), 6.77–6.92 (m, 4H), 6.66 (d, 1H, *J* = 10.7 Hz), 6.32 (d, 1H, *J* = 11.2 Hz), 5.91–6.04 (m, 1H), 5.32–5.44 (m, 2H), 3.45 (s, 3H), 3.40 (d, 1H, *J* = 13.7 Hz), 3.15 (d, 1H, *J* = 14.2 Hz), 3.02 (dd, 1H, *J* = 14.6, 7.9 Hz), 2.59 (dd, 1H, *J* = 14.9, 6.6 Hz), 1.63 (s, 3H).

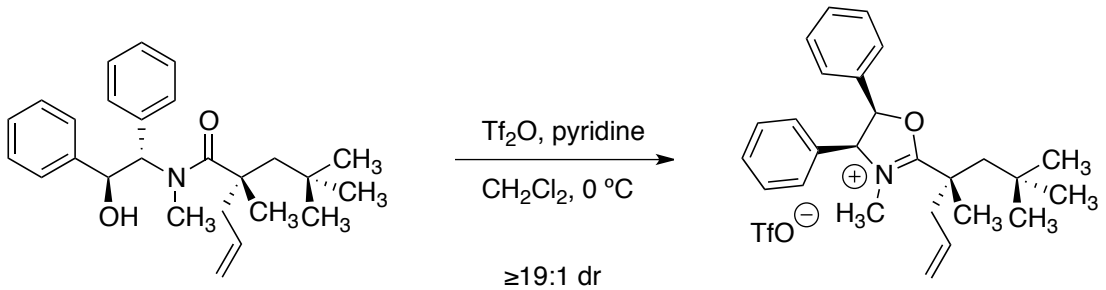


33 **64**

(*S*)-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethyl-2-neopentylpent-4-enamide (64)

A freshly titrated solution of methyllithium in diethoxymethane (2.67 M, 250 μL, 1.00 equiv) was added by syringe to a stirring suspension of amide **33** (197 mg, 0.669 mmol, 1 equiv) and lithium chloride (170 mg, 4.01 mmol, 6.00 equiv) in tetrahydrofuran (3.34 mL) at –78 °C. After stirring for 10 min at –78 °C, a freshly titrated solution of *tert*-butyllithium in pentane (1.71 M, 469 μL, 1.20 equiv) was added by syringe. The resulting solution was stirred for 10 min at –78 °C and for 10 min at –40 °C, whereupon allyl bromide (174 μL, 2.01 mmol, 3.00 equiv) was added by syringe. The mixture was stirred for 6 h at –40 °C, then saturated aqueous ammonium chloride (2 mL) was added and the biphasic mixture was warmed to 23 °C. The biphasic mixture was partitioned between ethyl acetate (60 mL) and 0.5 N aqueous hydrochloric acid solution (20 mL). The layers were separated. The organic layer was washed sequentially with 0.5 N aqueous hydrochloric acid solution (2 x 20 mL) and saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (5→45% ethyl acetate–hexanes) to afford amide **64** as a white, crystalline solid (224 mg, 85%, mp = 90-92 °C). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below). TLC (40% ethyl acetate–hexanes): R_f = 0.48 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.37 (d, 2H, J = 7.3 Hz), 7.12–7.28 (m, 8H), 6.04 (d, 1H, J = 9.8 Hz), 5.89 (ddt, 1H, J = 17.1, 10.0, 7.0, 7.0 Hz), 5.27

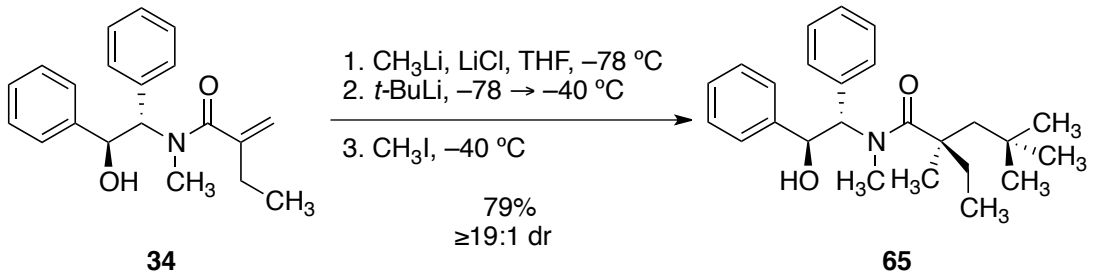
(dd, 1H, J = 10.0, 5.6 Hz), 5.06–5.19 (m, 2H), 3.36 (d, 1H, J = 4.9 Hz), 3.06 (s, 3H), 2.68 (dd, 1H, J = 14.4, 7.0 Hz), 2.21 (dd, 1H, J = 14.4, 7.1 Hz), 1.87 (d, 1H, J = 15.1 Hz), 1.46 (d, 1H, J = 15.1 Hz), 1.37 (s, 3H), 0.85 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 178.3, 141.4, 135.8, 134.6, 129.6, 128.2, 128.0, 127.6, 127.4, 117.9, 72.9, 65.1, 52.1, 48.0, 46.4, 32.5, 32.0, 31.2, 26.7. FTIR (neat), cm^{-1}: 3394 (br), 2951, 1599 (s), 1454 (m). HRMS (ESI): Calcd for $(C_{26}H_{35}NO_2 + H)^+$: 394.2741. Found: 394.2735.



64 **104**

Oxazolinium triflate (104)

Trifluoromethanesulfonic anhydride (22.4 μL, 0.133 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of α-quaternary amide **64** (26.2 mg, 0.067 mmol, 1 equiv) and pyridine (16.2 μL, 0.200 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 2 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.84* (d, 2H, *J* = 5.3 Hz), 8.54* (t, 1H, *J* = 7.8 Hz), 8.04* (t, 2H, *J* = 7.0 Hz), 7.10–7.21 (m, 6H), 7.00 (d, 4H, *J* = 5.3 Hz), 6.76 (d, 1H, *J* = 11.1 Hz), 6.46 (d, 1H, *J* = 11.4 Hz), 5.88–6.00 (m, 1H), 5.32–5.43 (m, 2H), 3.49 (s, 3H), 2.83 (dd, 1H, *J* = 14.6, 8.2 Hz), 2.59 (dd, 1H, *J* = 14.6, 6.2 Hz), 2.24 (d, 1H, *J* = 15.2 Hz), 1.78 (d, 1H, *J* = 15.2 Hz), 1.74 (s, 3H), 1.13 (s, 9H).

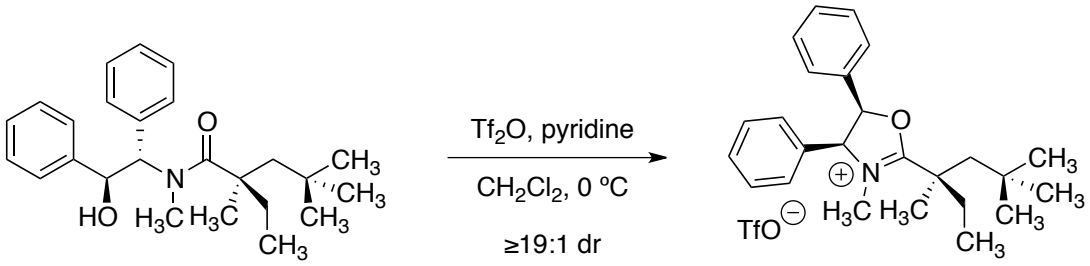


34 **65**

(*R*)-2-ethyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2,4,4-tetramethylpentanamide (65)

A freshly titrated solution of methyllithium in diethoxymethane (2.84 M, 569 μL, 1.00 equiv) was added by syringe to a stirring suspension of amide **34** (500 mg, 1.62 mmol, 1 equiv) and lithium chloride (411 mg, 9.70 mmol, 6.00 equiv) in tetrahydrofuran (8.08 mL) at –78 °C. After stirring for 10 min at –78 °C, a freshly titrated solution of *tert*- butyllithium in pentane (1.41 M, 1.37 mL, 1.20 equiv) was added by syringe. The resulting solution was stirred for 10 min at –78 °C and for 10 min at –40 °C, whereupon iodomethane (404 μL, 6.46 mmol, 4.00 equiv) was added by syringe. The mixture was stirred for 4 h at –40 °C, then saturated aqueous ammonium chloride (2 mL) was added and the biphasic mixture was warmed to 23 °C. The biphasic mixture was partitioned between ethyl acetate (50 mL) and half-saturated aqueous sodium chloride solution (75 mL). The layers were separated. The aqueous layer was extracted with two 50-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (5→35% ethyl acetate–hexanes) to afford amide **65** as an off-white solid (487 mg, 79%, mp = 85-86 °C). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below). TLC (30% ethyl acetate–hexanes): R_f = 0.46 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.37 (d, 2H, *J* = 7.3 Hz), 7.29–7.24 (m, 2H), 7.24–7.12 (m, 6H), 5.91 (d, 1H, *J* = 9.8 Hz), 5.31 (dd, 1H, *J* = 9.8, 6.4 Hz), 3.89 (d, 1H, *J* = 6.4 Hz), 3.01 (s, 3H), 1.93 (d,

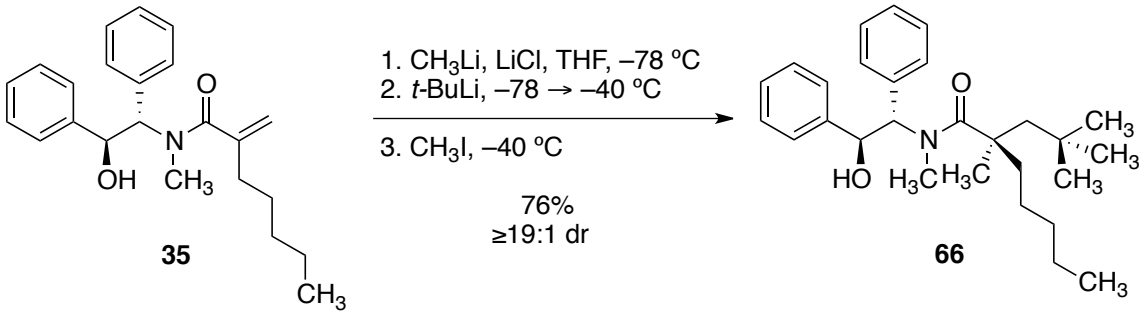
1H, J = 14.7 Hz), 1.82 (dq, 1H, J = 14.3, 7.3 Hz), 1.48 (d, 1H, J = 15.1 Hz), 1.43–1.30 (m, 4H), 0.99 (s, 9H), 0.72 (t, 3H, J = 7.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 179.7, 142.0, 136.4, 129.6, 128.2, 128.1, 127.6, 127.5, 127.2, 73.5, 66.1, 52.9, 48.3, 34.2, 33.4, 32.1, 31.4, 25.6, 8.5. FTIR (neat), cm^{-1}: 3374 (br), 2923 (s), 2853 (m), 1741 (m), 1602 (m). HRMS (ESI): Calcd for $(C_{25}H_{35}NO_2 + Na)^+$: 404.2560. Found: 404.2560.



65 **105**

Oxazolinium triflate (105)

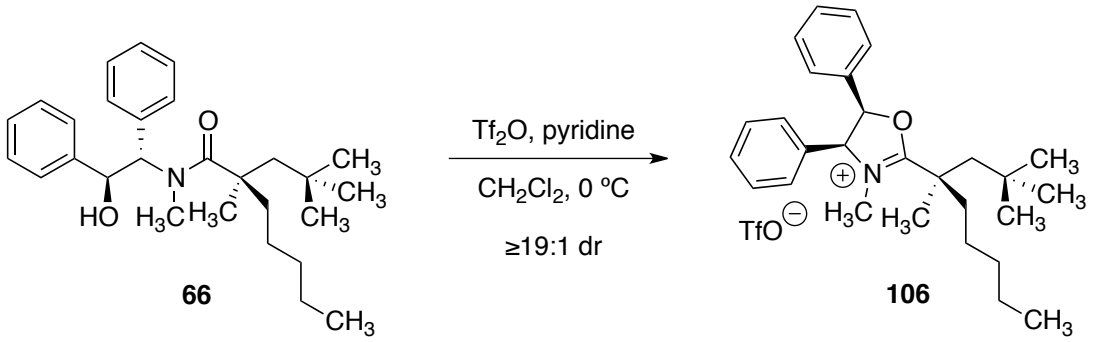
Trifluoromethanesulfonic anhydride (21.5 μL, 0.128 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of α-quaternary amide **65** (24.4 mg, 0.064 mmol, 1 equiv) and pyridine (15.5 μL, 0.192 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 2 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (asterisk denotes pyridinium ion peaks, 600 MHz, $CDCl_3$), δ: 8.85* (d, 2H, *J* = 5.3 Hz), 8.64–8.57* (m, 1H), 8.10* (t, 2H, *J* = 6.7 Hz), 7.23–7.16 (m, 3H), 7.16–7.10 (m, 3H), 7.01 (dd, 2H, *J* = 6.3, 2.3 Hz, 2H), 6.94 (d, 2H, *J* = 6.2 Hz), 6.75 (d, 1H, *J* = 10.8 Hz), 6.45 (d, 1H, *J* = 10.8 Hz), 3.53 (s, 3H), 2.25 (dq, 1H, *J* = 14.2, 7.3 Hz), 2.07 (d, 1H, *J* = 15.2 Hz), 1.91 (dq, 1H, *J* = 14.1, 7.3 Hz), 1.85 (d, 1H, *J* = 14.9 Hz), 1.69 (s, 3H), 1.18 (t, 3H, *J* = 7.5 Hz), 1.10 (s, 9H).



(*R*)-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethyl-2-neopentylheptanamide (66)

A freshly titrated solution of methyllithium in diethoxymethane (2.84 M, 501 μL, 1.00 equiv) was added by syringe to a stirring suspension of amide **35** (500 mg, 1.42 mmol, 1 equiv) and lithium chloride (362 mg, 8.54 mmol, 6.00 equiv) in tetrahydrofuran (7.11 mL) at –78 °C. After stirring for 10 min at –78 °C, a freshly titrated solution of *tert*- butyllithium in pentane (1.41 M, 1.21 mL, 1.20 equiv) was added by syringe. The resulting solution was stirred for 10 min at –78 °C and for 10 min at –40 °C, whereupon iodomethane (445 μL, 7.11 mmol, 5.00 equiv) was added by syringe. The mixture was stirred for 6 h at –40 °C, then saturated aqueous ammonium chloride (2 mL) was added and the biphasic mixture was warmed to 23 °C. The biphasic mixture was partitioned between ethyl acetate (50 mL) and half-saturated aqueous sodium chloride solution (75 mL). The layers were separated. The aqueous layer was extracted with two 50-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (5→35% ethyl acetate–hexanes) to afford amide **66** as an off-white solid (461 mg, 76%, mp = 99-101 °C). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below). TLC (30% ethyl acetate–hexanes): R_f = 0.55 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.37 (d, 2H, *J* = 7.3 Hz), 7.30–7.11 (m, 8H), 5.94 (d, 1H, *J* = 10.3 Hz), 5.30 (dd, 1H, *J* = 9.8, 6.4 Hz, 1H), 3.85 (d, 1H, *J* = 6.4 Hz, 1H), 3.00 (s, 3H), 1.94 (d, 1H, *J* =

14.7 Hz), 1.77–1.66 (m, 1H), 1.48 (d, 1H, J = 15.1 Hz), 1.37 (s, 3H), 1.34–1.03 (m, 6H), 0.99 (s, 9H), 0.95–0.85 (m, 1H), 0.79 (t, 3H, J = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 179.8, 142.0, 136.4, 129.6, 128.2, 128.0, 127.6, 127.5, 127.2, 73.4, 65.9, 53.2, 48.1, 41.8, 33.2, 32.4, 32.1, 31.4, 26.4, 23.6, 22.5, 14.0. FTIR (neat), cm^{-1}: 3350 (br), 2959 (m), 2934 (m), 1679 (m), 1608 (s). HRMS (ESI): Calcd for $(C_{28}H_{41}NO_2 + H)^+$: 424.3210. Found: 424.3211.



Oxazolinium triflate (106)

Trifluoromethanesulfonic anhydride (19.1 μL, 0.114 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of α-quaternary amide **66** (24.1 mg, 0.057 mmol, 1 equiv) and pyridine (13.8 μL, 0.171 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 2 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.90* (d, 2H, *J* = 5.9 Hz), 8.85* (t, 2H, *J* = 5.9 Hz), 8.60* (t, 1H, *J* = 7.8 Hz), 8.42* (t, 1H, *J* = 7.8 Hz, 1H), 8.09* (t, 2H, *J* = 6.8 Hz), 8.01* (t, 2H, *J* = 6.8 Hz), 7.24–7.10 (m, 6H), 7.04–6.97 (m, 2H), 6.93 (d, 2H, *J* = 6.4 Hz), 6.72 (d, 1H, *J* = 10.7 Hz), 6.41 (d, 1H, *J* = 10.7 Hz), 3.53 (s, 3H), 2.20–2.01 (m, 2H), 1.92–1.77 (m, 2H), 1.71 (s, 3H), 1.64–1.51 (m, 1H), 1.49–1.33 (m, 5H), 1.10 (s, 9H), 0.93 (t, 3H, *J* = 6.6 Hz).

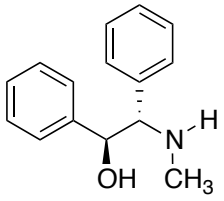
X-ray Data:

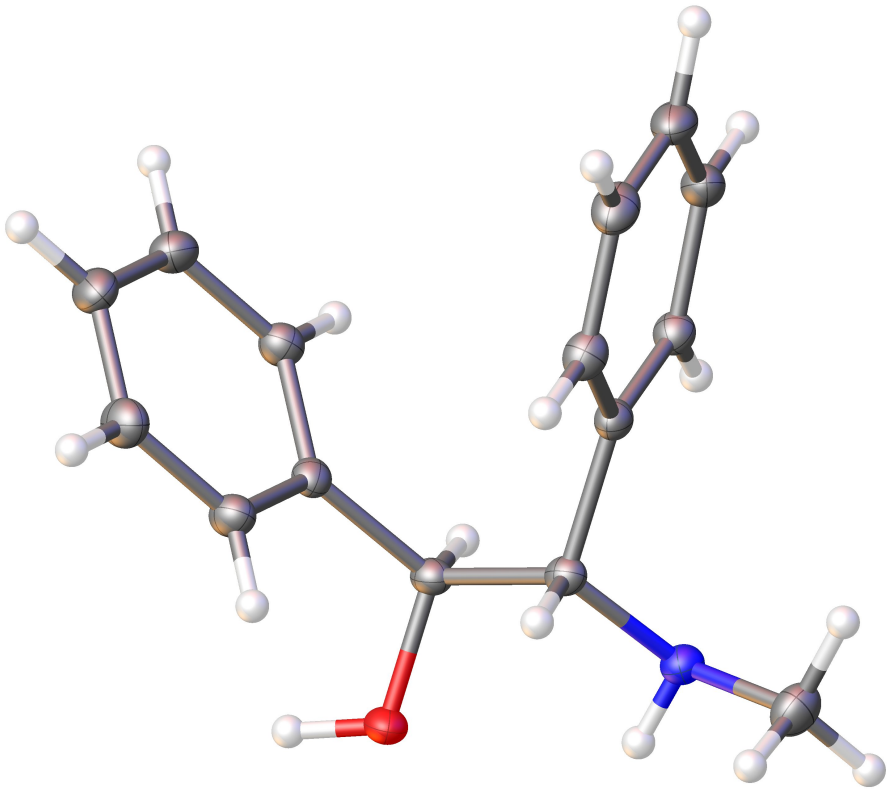
X-ray Crystallographic Laboratory

Harvard University

Structure Report

Shao-Liang Zheng





CCDC Deposition Number: CCDC 867287

X-Ray Crystallography: A crystal was mounted on a diffractometer; data was collected at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II CCD diffractometer (Mo_{K_α} radiation, λ=0.71073 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 0.5° scans in ω at 28° in 2θ. Data integration down to 0.74 Å resolution was carried out using SAINT V7.46 A [63] with reflection spot size optimization. Absorption corrections were made with the program SADABS . The structure was solved by the direct methods procedure and refined by least-squares methods on F^2 using SHELXS-97 and SHELXL-97[64] with OLEX 2 interface.[65] Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table 1, and geometric parameters are shown in Table 2, and hydrogen-bond parameters are listed in Table 3. The Ortep plots produced with SHELXL-97 program, and the other drawings were produced with Accelrys DS Visualizer 2.0.[66]

Table 2.1: Experimental details

Crystal data	
Chemical formula	$C_{15}H_{17}NO$
M_r	227.30
Crystal system, space group	ORTHORHOMBIC, $P2_12_12_1$
Temperature (K)	100
a, b, c (Å)	9.2424 (4), 10.2613 (4), 13.3610 (5)
V (Å^3)	1267.14 (9)

[63] Bruker AXS APEX II, Bruker AXS, Madison, Wisconsin, 2009.

[64] Sheldrick, G. M. *Acta Cryst*. **2008**, *A64*, 112–122.

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

[66] Accelrys DS Visualizer v2.0.1, Accelrys Software. Inc., 2007.

Table 2.1 (continued)

Z	4
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.07
Crystal size (mm)	0.28 × 0.22 × 0.12
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector diffractometer
Absorption correction	Multi-scan *SADABS*
T_{min}, T_{max}	0.980, 0.991
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	57307, 3279, 3090
R_{int}	0.063
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.034, 0.084, 1.08
No. of reflections	3279
No. of parameters	163
No. of restraints	0
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $Å^{-3}$)	0.22, -0.21
Absolute structure	Flack H D (1983), Acta Cryst. A39, 876-881
Flack parameter	-1.3 (11)

Computer programs: *APEX2* v2009.3.0 (Bruker-AXS, 2009), *SAINT* 7.46A (Bruker-AXS, 2009), *SHELXS97* (Sheldrick, 2008), *SHELXL97* (Sheldrick, 2008), Bruker *SHELXTL* (Sheldrick, 2008).

Table 2.2: Geometric parameters (Å, º)

C1—C2	1.3904 (16)	C9—C10	1.3916 (16)
C1—C6	1.3937 (16)	C9—C14	1.3957 (15)
C1—H1	0.9500	C10—C11	1.3893 (17)
C2—C3	1.3923 (17)	C10—H10	0.9500
C2—H2	0.9500	C11—C12	1.3907 (19)
C3—C4	1.3915 (18)	C11—H11	0.9500
C3—H3	0.9500	C12—C13	1.3850 (17)
C4—C5	1.3913 (16)	C12—H12	0.9500
C4—H4	0.9500	C13—C14	1.3900 (16)

Table 2.2 (continued)

C5—C6	1.3949 (15)	C13—H13	0.9500
C5—H5	0.9500	C14—H14	0.9500
C6—C7	1.5141 (15)	C15—N1	1.4717 (15)
C7—O1	1.4287 (13)	C15—H15A	0.9800
C7—C8	1.5402 (15)	C15—H15B	0.9800
C7—H7	1.0000	C15—H15C	0.9800
C8—N1	1.4719 (13)	N1—H1A	0.861 (16)
C8—C9	1.5185 (14)	O1—H1B	0.915 (19)
C8—H8	1.0000		
C2—C1—C6	120.69 (11)	C7—C8—H8	108.5
C2—C1—H1	119.7	C10—C9—C14	118.66 (10)
C6—C1—H1	119.7	C10—C9—C8	120.24 (10)
C1—C2—C3	119.90 (11)	C14—C9—C8	120.83 (10)
C1—C2—H2	120.1	C11—C10—C9	121.14 (11)
C3—C2—H2	120.1	C11—C10—H10	119.4
C4—C3—C2	119.71 (11)	C9—C10—H10	119.4
C4—C3—H3	120.1	C10—C11—C12	119.68 (11)
C2—C3—H3	120.1	C10—C11—H11	120.2
C5—C4—C3	120.30 (11)	C12—C11—H11	120.2
C5—C4—H4	119.9	C13—C12—C11	119.69 (11)
C3—C4—H4	119.9	C13—C12—H12	120.2
C4—C5—C6	120.23 (11)	C11—C12—H12	120.2
C4—C5—H5	119.9	C12—C13—C14	120.51 (11)
C6—C5—H5	119.9	C12—C13—H13	119.7
C1—C6—C5	119.18 (10)	C14—C13—H13	119.7
C1—C6—C7	120.57 (10)	C13—C14—C9	120.31 (10)
C5—C6—C7	120.23 (10)	C13—C14—H14	119.8
O1—C7—C6	112.79 (9)	C9—C14—H14	119.8
O1—C7—C8	106.82 (9)	N1—C15—H15A	109.5
C6—C7—C8	111.13 (9)	N1—C15—H15B	109.5
O1—C7—H7	108.7	H15A—C15—H15B	109.5
C6—C7—H7	108.7	N1—C15—H15C	109.5
C8—C7—H7	108.7	H15A—C15—H15C	109.5
N1—C8—C9	112.67 (9)	H15B—C15—H15C	109.5
N1—C8—C7	108.48 (8)	C15—N1—C8	112.70 (9)

Table 2.2 (continued)

C9—C8—C7	110.13 (9)	C15—N1—H1A	107.9 (11)
N1—C8—H8	108.5	C8—N1—H1A	104.7 (10)
C9—C8—H8	108.5	C7—O1—H1B	111.0 (12)
C6—C1—C2—C3	0.09 (18)	C6—C7—C8—C9	-51.88 (11)
C1—C2—C3—C4	-0.04 (18)	N1—C8—C9—C10	-132.90 (10)
C2—C3—C4—C5	0.00 (18)	C7—C8—C9—C10	105.84 (11)
C3—C4—C5—C6	-0.01 (18)	N1—C8—C9—C14	53.05 (13)
C2—C1—C6—C5	-0.09 (17)	C7—C8—C9—C14	-68.21 (12)
C2—C1—C6—C7	178.27 (10)	C14—C9—C10—C11	0.41 (17)
C4—C5—C6—C1	0.06 (16)	C8—C9—C10—C11	-173.76 (10)
C4—C5—C6—C7	-178.32 (11)	C9—C10—C11—C12	0.47 (18)
C1—C6—C7—O1	49.41 (14)	C10—C11—C12—C13	-0.54 (18)
C5—C6—C7—O1	-132.24 (10)	C11—C12—C13—C14	-0.28 (18)
C1—C6—C7—C8	-70.52 (13)	C12—C13—C14—C9	1.18 (17)
C5—C6—C7—C8	107.83 (11)	C10—C9—C14—C13	-1.23 (16)
O1—C7—C8—N1	60.98 (10)	C8—C9—C14—C13	172.90 (10)
C6—C7—C8—N1	-175.62 (9)	C9—C8—N1—C15	75.81 (12)
O1—C7—C8—C9	-175.29 (8)	C7—C8—N1—C15	-162.00 (9)

Table 2.3: Hydrogen-bond parameters

D—H···*A*	*D*—H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*—H···*A* (°)
N1—H1A···O1	0.861 (16)	2.316 (15)	2.7970 (13)	115.5 (12)
O1—H1B···N1^{i}	0.915 (19)	1.94 (2)	2.8449 (13)	170.7 (17)

Symmetry code(s): (i) *x*-1/2, -*y*+1/2, -*z*+1.

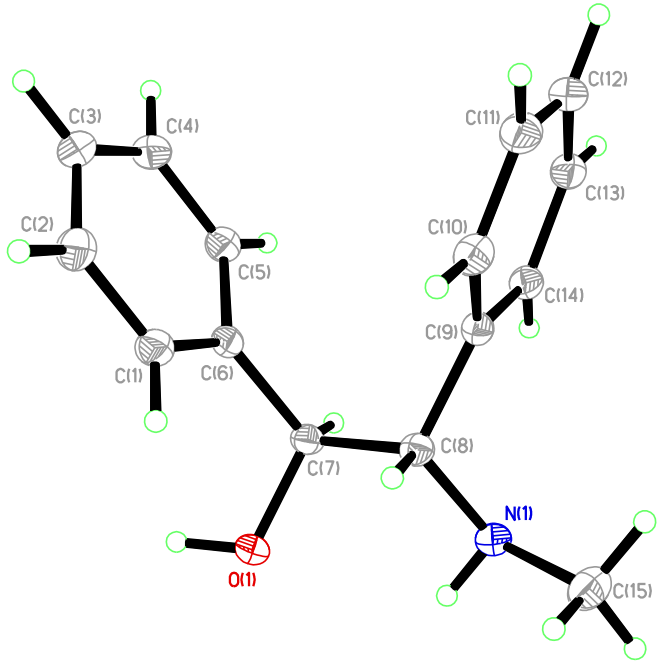


Figure 2.5: Perspective views showing 50% probability displacement.

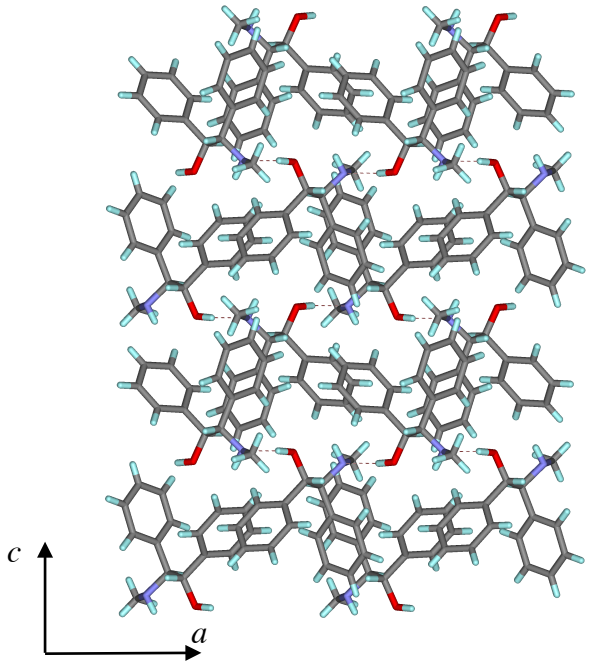


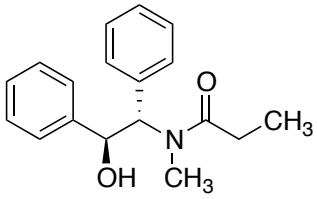
Figure 2.6: Three-dimensional supramolecular architecture viewed along the *b*-axis direction.

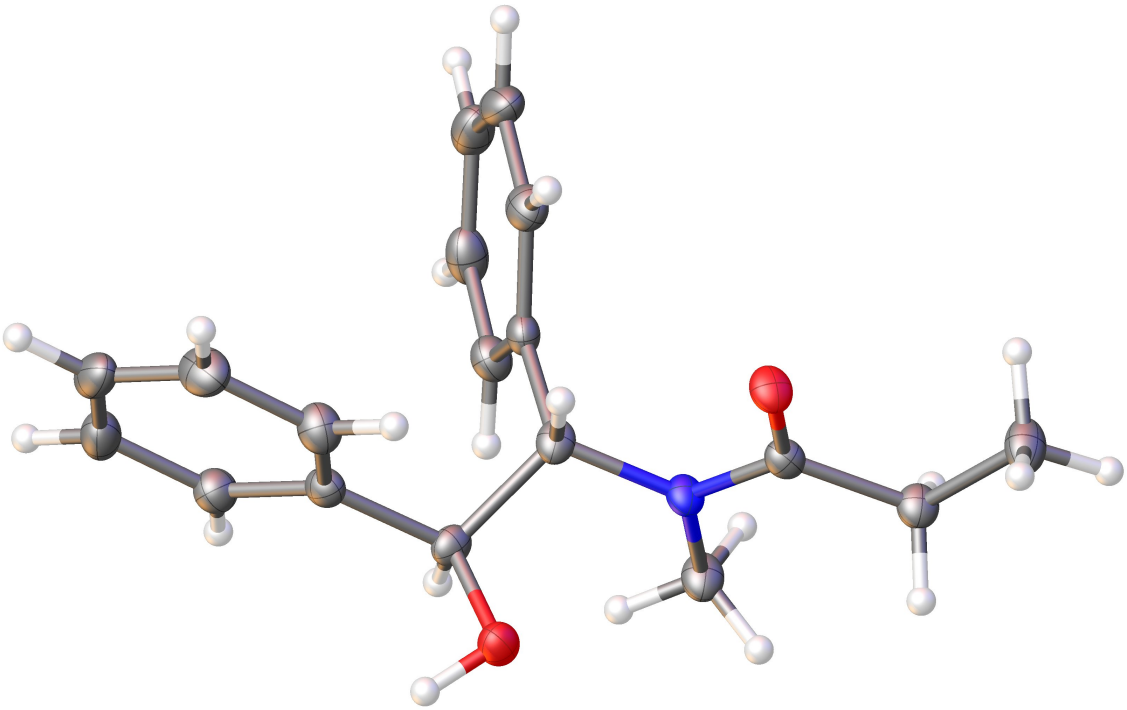
X-ray Crystallographic Laboratory

Harvard University

Structure Report

Shao-Liang Zheng





CCDC Deposition Number: CCDC 867288

X-Ray Crystallography: A crystal was mounted on a diffractometer; data was collected at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II DUO CCD diffractometer ($Cu_{K\alpha}$ radiation, λ=1.54178 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 1.0° scans in ω at 30°, 55°, 80° and 105° in 2θ. Data integration down to 0.84 Å resolution was carried out using SAINT V7.46 A with reflection spot size optimisation. Absorption corrections were made with the program SADABS. The structure was solved by the direct methods procedure and refined by least-squares methods on F^2 using SHELXS-97 and SHELXL-97. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table 1, geometric parameters are shown in Table 2 and hydrogen-bond parameters listed in Table 3. The Ortep plots produced with SHELXL-97 program, and the other drawings were produced with Accelrys DS Visualizer 2.0.

Table 2.4: Experimental details

	VI-114
Crystal data	
Chemical formula	$C_{18}H_{21}NO_2$
M_r	283.36
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	100
a, b, c (Å)	6.9181 (4), 14.5010 (9), 15.1962 (8)
V (Å^3)	1524.47 (15)
Z	4
Radiation type	Cu $K\alpha$
μ (mm^{-1})	0.63
Crystal size (mm)	0.40 × 0.02 × 0.01
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector diffractometer

Table 2.4 (continued)

Absorption correction	Multi-scan *SADABS*
T_{min}, T_{max}	0.786, 0.992
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	16296, 2590, 2339
R_{int}	0.080
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.049, 0.127, 1.06
No. of reflections	2590
No. of parameters	196
No. of restraints	0
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.25, -0.25
Absolute structure	Flack H D (1983), Acta Cryst. A39, 876-881
Flack parameter	0.3 (3)

Computer programs: *APEX2* v2009.3.0 (Bruker-AXS, 2009), *SAINT* 7.46A (Bruker-AXS, 2009), *SHELXS97* (Sheldrick, 2008), *SHELXL97* (Sheldrick, 2008), Bruker *SHELXTL*.

Table 2.5: Geometric parameters (Å, º)

O1—C7	1.427 (2)	C9—C14	1.384 (3)
O1—H1	0.94 (3)	C9—C10	1.392 (3)
O2—C16	1.236 (3)	C10—C11	1.402 (3)
N1—C16	1.344 (3)	C10—H10	0.9500
N1—C15	1.460 (3)	C11—C12	1.377 (4)
N1—C8	1.479 (3)	C11—H11	0.9500
C1—C6	1.387 (3)	C12—C13	1.378 (4)
C1—C2	1.394 (3)	C12—H12	0.9500
C1—H1A	0.9500	C13—C14	1.394 (3)
C2—C3	1.378 (3)	C13—H13	0.9500
C2—H2	0.9500	C14—H14	0.9500
C3—C4	1.381 (4)	C15—H15A	0.9800
C3—H3	0.9500	C15—H15B	0.9800
C4—C5	1.401 (3)	C15—H15C	0.9800
C4—H4	0.9500	C16—C17	1.522 (3)

Table 2.5 (continued)

C5—C6	1.387 (3)	C17—C18	1.516 (3)
C5—H5	0.9500	C17—H17A	0.9900
C6—C7	1.523 (3)	C17—H17B	0.9900
C7—C8	1.530 (3)	C18—H18A	0.9800
C7—H7	1.0000	C18—H18B	0.9800
C8—C9	1.525 (3)	C18—H18C	0.9800
C8—H8	1.0000		
C7—O1—H1	104.1 (19)	C9—C10—C11	119.7 (2)
C16—N1—C15	121.89 (17)	C9—C10—H10	120.2
C16—N1—C8	118.83 (16)	C11—C10—H10	120.2
C15—N1—C8	119.02 (16)	C12—C11—C10	120.5 (2)
C6—C1—C2	120.6 (2)	C12—C11—H11	119.7
C6—C1—H1A	119.7	C10—C11—H11	119.7
C2—C1—H1A	119.7	C11—C12—C13	120.0 (2)
C3—C2—C1	120.2 (2)	C11—C12—H12	120.0
C3—C2—H2	119.9	C13—C12—H12	120.0
C1—C2—H2	119.9	C12—C13—C14	119.7 (2)
C2—C3—C4	119.8 (2)	C12—C13—H13	120.2
C2—C3—H3	120.1	C14—C13—H13	120.2
C4—C3—H3	120.1	C9—C14—C13	121.1 (2)
C3—C4—C5	120.2 (2)	C9—C14—H14	119.5
C3—C4—H4	119.9	C13—C14—H14	119.5
C5—C4—H4	119.9	N1—C15—H15A	109.5
C6—C5—C4	120.1 (2)	N1—C15—H15B	109.5
C6—C5—H5	119.9	H15A—C15—H15B	109.5
C4—C5—H5	119.9	N1—C15—H15C	109.5
C1—C6—C5	119.11 (19)	H15A—C15—H15C	109.5
C1—C6—C7	120.52 (18)	H15B—C15—H15C	109.5
C5—C6—C7	120.36 (18)	O2—C16—N1	122.31 (19)
O1—C7—C6	112.27 (16)	O2—C16—C17	121.07 (18)
O1—C7—C8	106.80 (16)	N1—C16—C17	116.63 (17)
C6—C7—C8	110.15 (17)	C18—C17—C16	112.66 (18)
O1—C7—H7	109.2	C18—C17—H17A	109.1
C6—C7—H7	109.2	C16—C17—H17A	109.1
C8—C7—H7	109.2	C18—C17—H17B	109.1

Table 2.5 (continued)

N1—C8—C9	110.84 (16)	C16—C17—H17B	109.1
N1—C8—C7	112.62 (16)	H17A—C17—H17B	107.8
C9—C8—C7	112.77 (17)	C17—C18—H18A	109.5
N1—C8—H8	106.7	C17—C18—H18B	109.5
C9—C8—H8	106.7	H18A—C18—H18B	109.5
C7—C8—H8	106.7	C17—C18—H18C	109.5
C14—C9—C10	119.0 (2)	H18A—C18—H18C	109.5
C14—C9—C8	118.75 (18)	H18B—C18—H18C	109.5
C10—C9—C8	122.3 (2)		
C6—C1—C2—C3	0.2 (3)	C6—C7—C8—C9	-62.3 (2)
C1—C2—C3—C4	-0.3 (3)	N1—C8—C9—C14	-105.6 (2)
C2—C3—C4—C5	-0.2 (4)	C7—C8—C9—C14	127.1 (2)
C3—C4—C5—C6	0.7 (3)	N1—C8—C9—C10	73.4 (2)
C2—C1—C6—C5	0.4 (3)	C7—C8—C9—C10	-53.9 (3)
C2—C1—C6—C7	-178.5 (2)	C14—C9—C10—C11	1.5 (3)
C4—C5—C6—C1	-0.8 (3)	C8—C9—C10—C11	-177.58 (19)
C4—C5—C6—C7	178.1 (2)	C9—C10—C11—C12	-0.7 (3)
C1—C6—C7—O1	-121.5 (2)	C10—C11—C12—C13	-0.5 (3)
C5—C6—C7—O1	59.6 (3)	C11—C12—C13—C14	0.9 (3)
C1—C6—C7—C8	119.6 (2)	C10—C9—C14—C13	-1.0 (3)
C5—C6—C7—C8	-59.2 (2)	C8—C9—C14—C13	178.03 (19)
C16—N1—C8—C9	101.2 (2)	C12—C13—C14—C9	-0.2 (3)
C15—N1—C8—C9	-73.0 (2)	C15—N1—C16—O2	-180.0 (2)
C16—N1—C8—C7	-131.42 (19)	C8—N1—C16—O2	6.0 (3)
C15—N1—C8—C7	54.4 (2)	C15—N1—C16—C17	0.0 (3)
O1—C7—C8—N1	49.1 (2)	C8—N1—C16—C17	-174.00 (17)
C6—C7—C8—N1	171.31 (16)	O2—C16—C17—C18	-7.4 (3)
O1—C7—C8—C9	175.49 (16)	N1—C16—C17—C18	172.61 (19)

Table 2.6: Hydrogen-bond parameters

D—H···*A*	*D*—H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*—H···*A* (°)
O1—H1···O2^{i}	0.94 (3)	1.90 (3)	2.801 (2)	162 (3)

Symmetry code(s): (i) *x*-1/2, -*y*+1/2, -*z*+1.

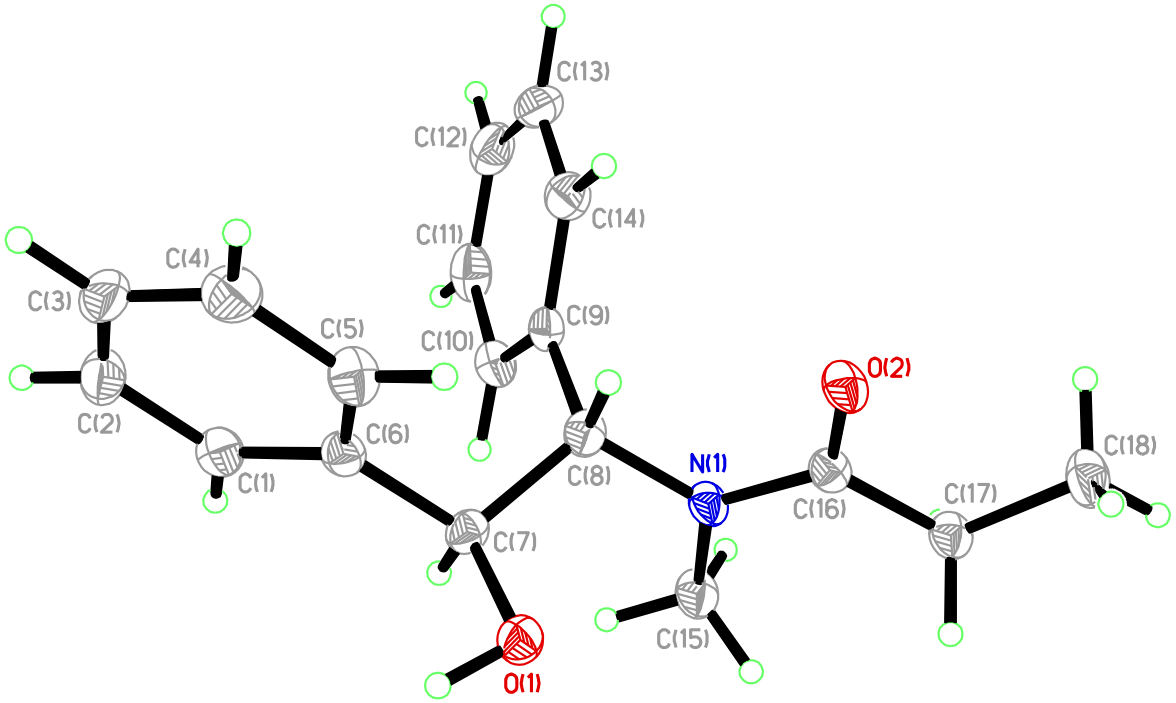


Figure 2.7: Perspective views showing 50% probability displacement.

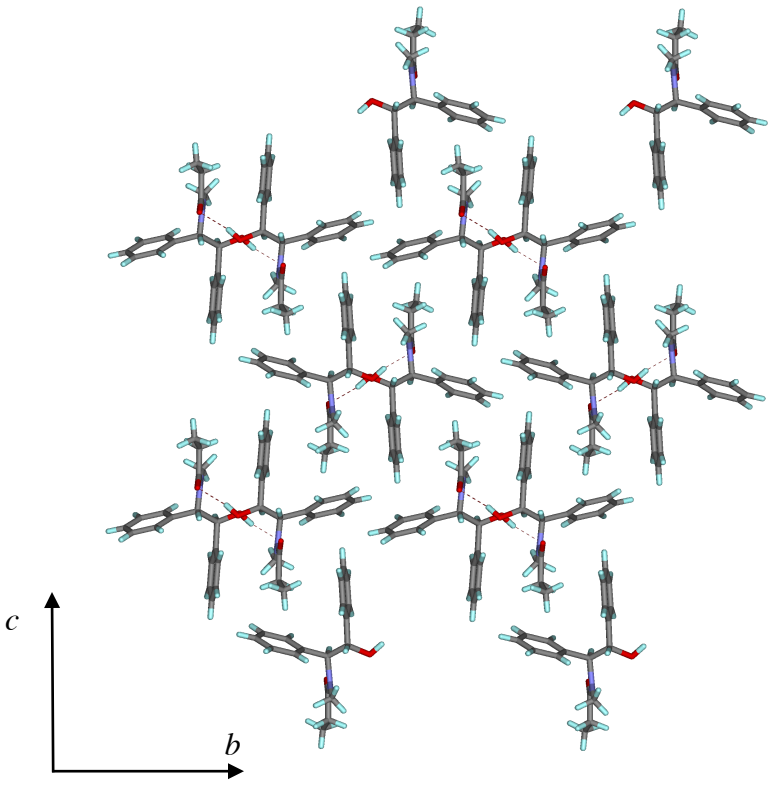
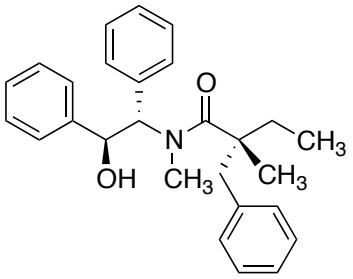


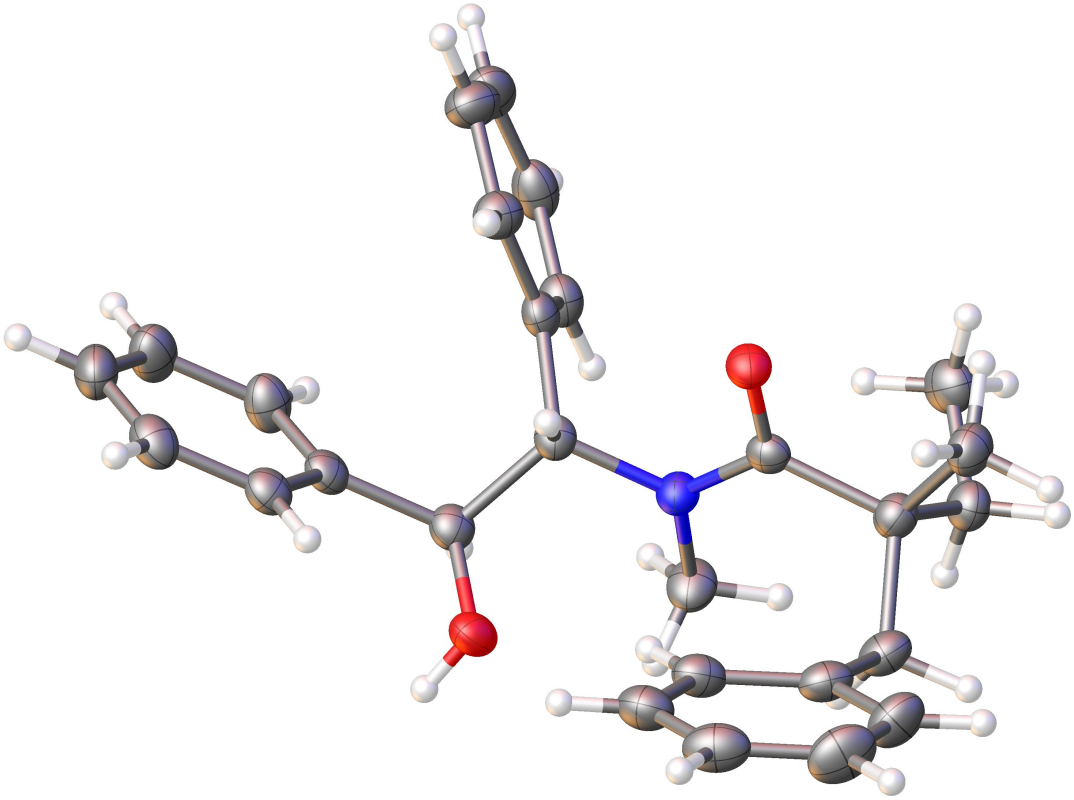
Figure 2.8: Three-dimensional supramolecular architecture viewed along the *a*-axis direction.

X-ray Crystallographic Laboratory
Harvard University

Structure Report

Shao-Liang Zheng





CCDC Deposition Number: CCDC 867290

X-Ray Crystallography: A crystal was mounted on a diffractometer; data was collected at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II DUO CCD diffractometer ($Cu_{K\alpha}$ radiation, λ=1.54178 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 1.0° scans in ω at 30°, 55°, 80° and 105° in 2θ. Data integration down to 0.84 Å resolution was carried out using SAINT V7.46 A with reflection spot size optimisation. Absorption corrections were made with the program SADABS. The structure was solved by the direct methods procedure and refined by least-squares methods on F^2 using SHELXS-97 and SHELXL-97. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table 1, geometric parameters are shown in Table 2 and hydrogen-bond parameters listed in Table 3. The Ortep plots produced with SHELXL-97 program, and the other drawings were produced with Accelrys DS Visualizer 2.0.

Table 2.7: Experimental details

	VI-136
Crystal data	
Chemical formula	$C_{27}H_{31}NO_2$
M_r	401.53
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	100
a, b, c (Å)	9.5300 (2), 9.9323 (2), 24.1764 (5)
V (Å^3)	2288.41 (8)
Z	4
Radiation type	Cu $K\alpha$
μ (mm^{-1})	0.56
Crystal size (mm)	0.38 × 0.32 × 0.16
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector diffractometer

Table 2.7 (continued)

Absorption correction	Multi-scan *SADABS*
T_{min}, T_{max}	0.814, 0.915
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	31684, 3953, 3930
R_{int}	0.032
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.025, 0.065, 1.06
No. of reflections	3953
No. of parameters	279
No. of restraints	0
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.16, -0.14
Absolute structure	Flack H D (1983), Acta Cryst. A39, 876-881
Flack parameter	0.01 (15)

Computer programs: *APEX2* v2009.3.0 (Bruker-AXS, 2009), *SAINT* 7.46A (Bruker-AXS, 2009), *SHELXS97* (Sheldrick, 2008), *SHELXL97* (Sheldrick, 2008), Bruker *SHELXTL*.

Table 2.8 Geometric parameters (Å, º)

O1—C7	1.4192 (14)	C14—H14	0.9500
O1—H1	0.852 (17)	C15—C16	1.5523 (15)
O2—C15	1.2326 (13)	C16—C25	1.5382 (16)
N1—C15	1.3579 (14)	C16—C17	1.5547 (16)
N1—C24	1.4610 (14)	C16—C26	1.5571 (16)
N1—C8	1.4863 (13)	C17—C18	1.5162 (17)
C1—C2	1.3843 (17)	C17—H17A	0.9900
C1—C6	1.3891 (16)	C17—H17B	0.9900
C1—H1A	0.9500	C18—C19	1.3922 (18)
C2—C3	1.3859 (18)	C18—C23	1.3938 (18)
C2—H2	0.9500	C19—C20	1.385 (2)
C3—C4	1.382 (2)	C19—H19	0.9500
C3—H3	0.9500	C20—C21	1.382 (2)
C4—C5	1.3870 (18)	C20—H20	0.9500
C4—H4	0.9500	C21—C22	1.3809 (19)
C5—C6	1.3899 (16)	C21—H21	0.9500

Table 2.8 (continued)

C5—H5	0.9500	C22—C23	1.3865 (18)
C6—C7	1.5176 (15)	C22—H22	0.9500
C7—C8	1.5444 (15)	C23—H23	0.9500
C7—H7	1.0000	C24—H24A	0.9800
C8—C9	1.5166 (15)	C24—H24B	0.9800
C8—H8	1.0000	C24—H24C	0.9800
C9—C10	1.3889 (16)	C25—H25A	0.9800
C9—C14	1.3909 (16)	C25—H25B	0.9800
C10—C11	1.3912 (17)	C25—H25C	0.9800
C10—H10	0.9500	C26—C27	1.5224 (16)
C11—C12	1.382 (2)	C26—H26A	0.9900
C11—H11	0.9500	C26—H26B	0.9900
C12—C13	1.385 (2)	C27—H27A	0.9800
C12—H12	0.9500	C27—H27B	0.9800
C13—C14	1.3871 (17)	C27—H27C	0.9800
C13—H13	0.9500		
C7—O1—H1	106.8 (11)	C25—C16—C15	106.88 (9)
C15—N1—C24	125.37 (9)	C25—C16—C17	108.36 (9)
C15—N1—C8	115.87 (9)	C15—C16—C17	111.47 (9)
C24—N1—C8	118.75 (9)	C25—C16—C26	107.70 (10)
C2—C1—C6	120.78 (11)	C15—C16—C26	113.26 (9)
C2—C1—H1A	119.6	C17—C16—C26	108.97 (9)
C6—C1—H1A	119.6	C18—C17—C16	116.83 (9)
C1—C2—C3	120.23 (12)	C18—C17—H17A	108.1
C1—C2—H2	119.9	C16—C17—H17A	108.1
C3—C2—H2	119.9	C18—C17—H17B	108.1
C4—C3—C2	119.42 (12)	C16—C17—H17B	108.1
C4—C3—H3	120.3	H17A—C17—H17B	107.3
C2—C3—H3	120.3	C19—C18—C23	117.76 (11)
C3—C4—C5	120.32 (12)	C19—C18—C17	120.61 (11)
C3—C4—H4	119.8	C23—C18—C17	121.56 (10)
C5—C4—H4	119.8	C20—C19—C18	121.09 (13)
C4—C5—C6	120.63 (12)	C20—C19—H19	119.5
C4—C5—H5	119.7	C18—C19—H19	119.5
C6—C5—H5	119.7	C21—C20—C19	120.48 (12)

Table 2.8 (continued)

C1—C6—C5	118.61 (11)	C21—C20—H20	119.8
C1—C6—C7	120.42 (10)	C19—C20—H20	119.8
C5—C6—C7	120.96 (11)	C22—C21—C20	119.19 (13)
O1—C7—C6	112.28 (9)	C22—C21—H21	120.4
O1—C7—C8	105.45 (8)	C20—C21—H21	120.4
C6—C7—C8	111.35 (9)	C21—C22—C23	120.43 (13)
O1—C7—H7	109.2	C21—C22—H22	119.8
C6—C7—H7	109.2	C23—C22—H22	119.8
C8—C7—H7	109.2	C22—C23—C18	121.04 (11)
N1—C8—C9	113.22 (9)	C22—C23—H23	119.5
N1—C8—C7	111.18 (9)	C18—C23—H23	119.5
C9—C8—C7	111.84 (8)	N1—C24—H24A	109.5
N1—C8—H8	106.7	N1—C24—H24B	109.5
C9—C8—H8	106.7	H24A—C24—H24B	109.5
C7—C8—H8	106.7	N1—C24—H24C	109.5
C10—C9—C14	118.79 (11)	H24A—C24—H24C	109.5
C10—C9—C8	119.51 (10)	H24B—C24—H24C	109.5
C14—C9—C8	121.54 (10)	C16—C25—H25A	109.5
C9—C10—C11	120.53 (11)	C16—C25—H25B	109.5
C9—C10—H10	119.7	H25A—C25—H25B	109.5
C11—C10—H10	119.7	C16—C25—H25C	109.5
C12—C11—C10	120.21 (12)	H25A—C25—H25C	109.5
C12—C11—H11	119.9	H25B—C25—H25C	109.5
C10—C11—H11	119.9	C27—C26—C16	114.91 (9)
C11—C12—C13	119.60 (12)	C27—C26—H26A	108.5
C11—C12—H12	120.2	C16—C26—H26A	108.5
C13—C12—H12	120.2	C27—C26—H26B	108.5
C12—C13—C14	120.22 (12)	C16—C26—H26B	108.5
C12—C13—H13	119.9	H26A—C26—H26B	107.5
C14—C13—H13	119.9	C26—C27—H27A	109.5
C13—C14—C9	120.61 (12)	C26—C27—H27B	109.5
C13—C14—H14	119.7	H27A—C27—H27B	109.5
C9—C14—H14	119.7	C26—C27—H27C	109.5
O2—C15—N1	119.39 (10)	H27A—C27—H27C	109.5
O2—C15—C16	118.29 (9)	H27B—C27—H27C	109.5
N1—C15—C16	122.30 (9)		

Table 2.8 (continued)

C6—C1—C2—C3	0.16 (18)	C12—C13—C14—C9	0.05 (18)
C1—C2—C3—C4	0.45 (19)	C10—C9—C14—C13	-1.72 (17)
C2—C3—C4—C5	-0.3 (2)	C8—C9—C14—C13	173.68 (10)
C3—C4—C5—C6	-0.4 (2)	C24—N1—C15—O2	172.01 (11)
C2—C1—C6—C5	-0.85 (17)	C8—N1—C15—O2	-7.62 (15)
C2—C1—C6—C7	-179.78 (10)	C24—N1—C15—C16	-9.95 (16)
C4—C5—C6—C1	0.96 (18)	C8—N1—C15—C16	170.42 (9)
C4—C5—C6—C7	179.88 (11)	O2—C15—C16—C25	1.24 (14)
C1—C6—C7—O1	25.95 (14)	N1—C15—C16—C25	-176.82 (10)
C5—C6—C7—O1	-152.95 (11)	O2—C15—C16—C17	119.47 (11)
C1—C6—C7—C8	-92.03 (12)	N1—C15—C16—C17	-58.59 (13)
C5—C6—C7—C8	89.07 (13)	O2—C15—C16—C26	-117.20 (11)
C15—N1—C8—C9	82.28 (11)	N1—C15—C16—C26	64.74 (13)
C24—N1—C8—C9	-97.38 (12)	C25—C16—C17—C18	58.31 (13)
C15—N1—C8—C7	-150.83 (9)	C15—C16—C17—C18	-59.03 (13)
C24—N1—C8—C7	29.52 (13)	C26—C16—C17—C18	175.24 (10)
O1—C7—C8—N1	56.00 (11)	C16—C17—C18—C19	-106.39 (13)
C6—C7—C8—N1	178.02 (9)	C16—C17—C18—C23	76.85 (14)
O1—C7—C8—C9	-176.35 (8)	C23—C18—C19—C20	1.36 (19)
C6—C7—C8—C9	-54.33 (12)	C17—C18—C19—C20	-175.52 (13)
N1—C8—C9—C10	-129.15 (10)	C18—C19—C20—C21	-1.4 (2)
C7—C8—C9—C10	104.31 (11)	C19—C20—C21—C22	0.4 (2)
N1—C8—C9—C14	55.49 (13)	C20—C21—C22—C23	0.70 (19)
C7—C8—C9—C14	-71.06 (13)	C21—C22—C23—C18	-0.73 (18)
C14—C9—C10—C11	1.89 (17)	C19—C18—C23—C22	-0.30 (17)
C8—C9—C10—C11	-173.61 (11)	C17—C18—C23—C22	176.55 (11)
C9—C10—C11—C12	-0.39 (19)	C25—C16—C26—C27	-82.93 (12)
C10—C11—C12—C13	-1.29 (19)	C15—C16—C26—C27	35.03 (14)
C11—C12—C13—C14	1.46 (19)	C17—C16—C26—C27	159.72 (10)

Table 2.9: Hydrogen-bond parameters

D—H···*A*	*D*—H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*—H···*A* (°)
O1—H1···O2^{i}	0.852 (17)	1.828 (17)	2.6791 (11)	175.8 (16)

Symmetry code(s): (i) -*x*+1, *y*+1/2, -*z*+1/2.

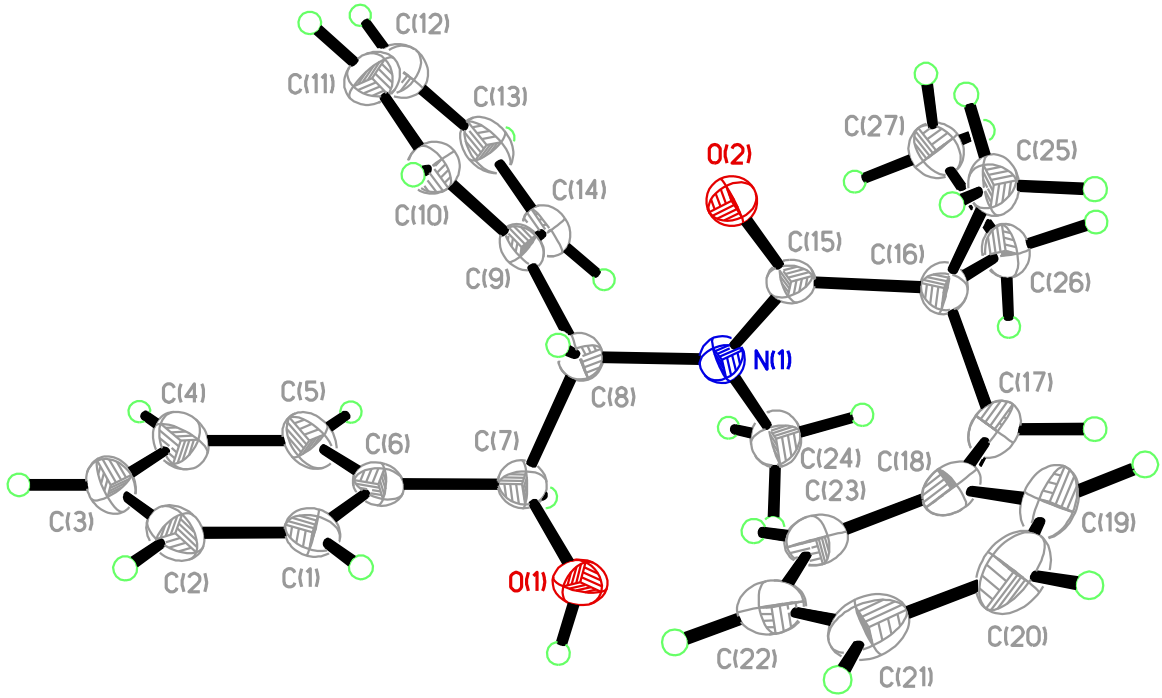


Figure 2.9: Perspective views showing 50% probability displacement.

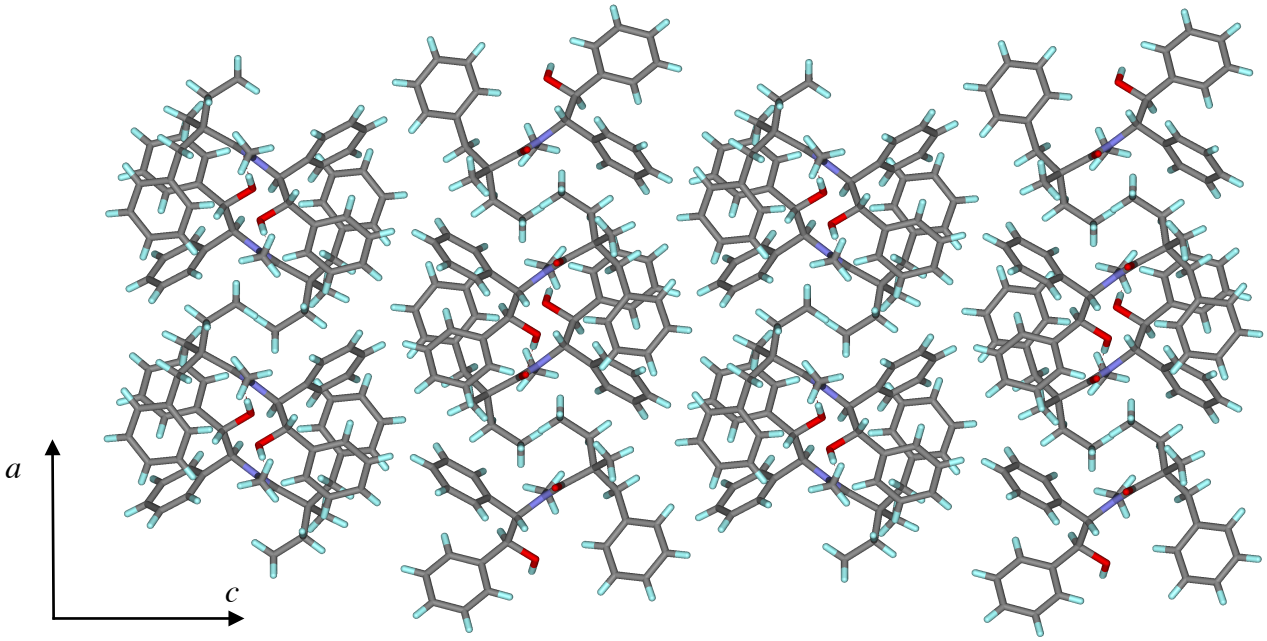
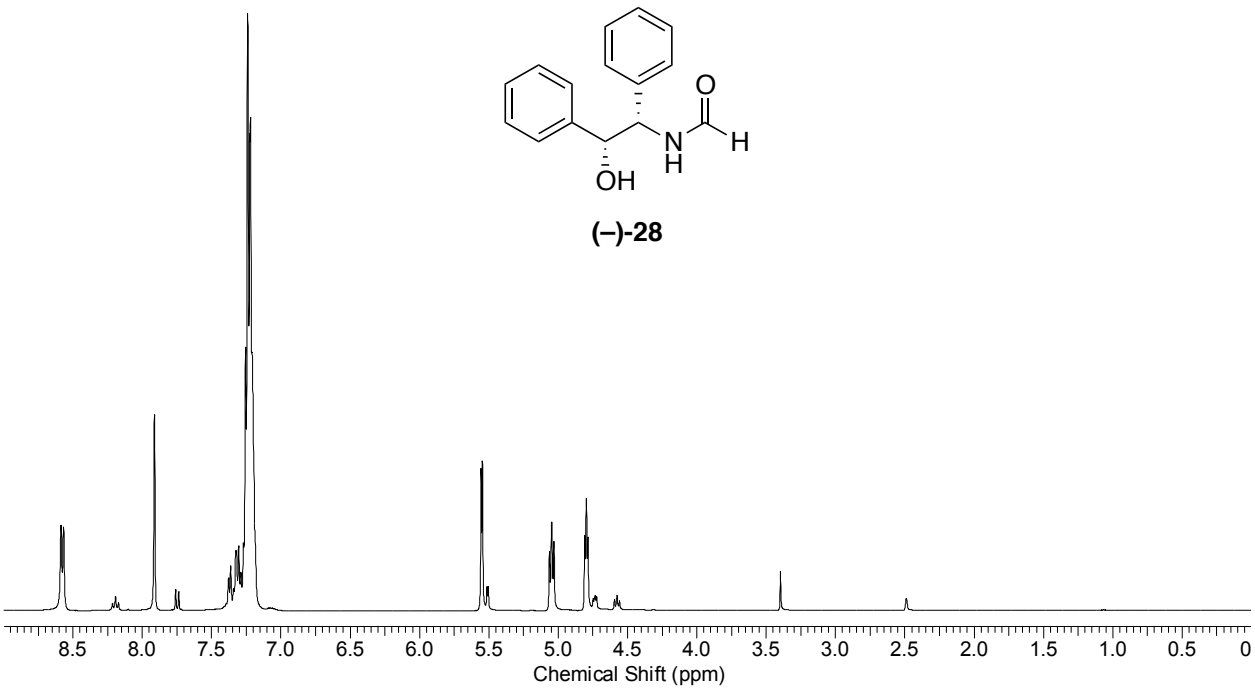
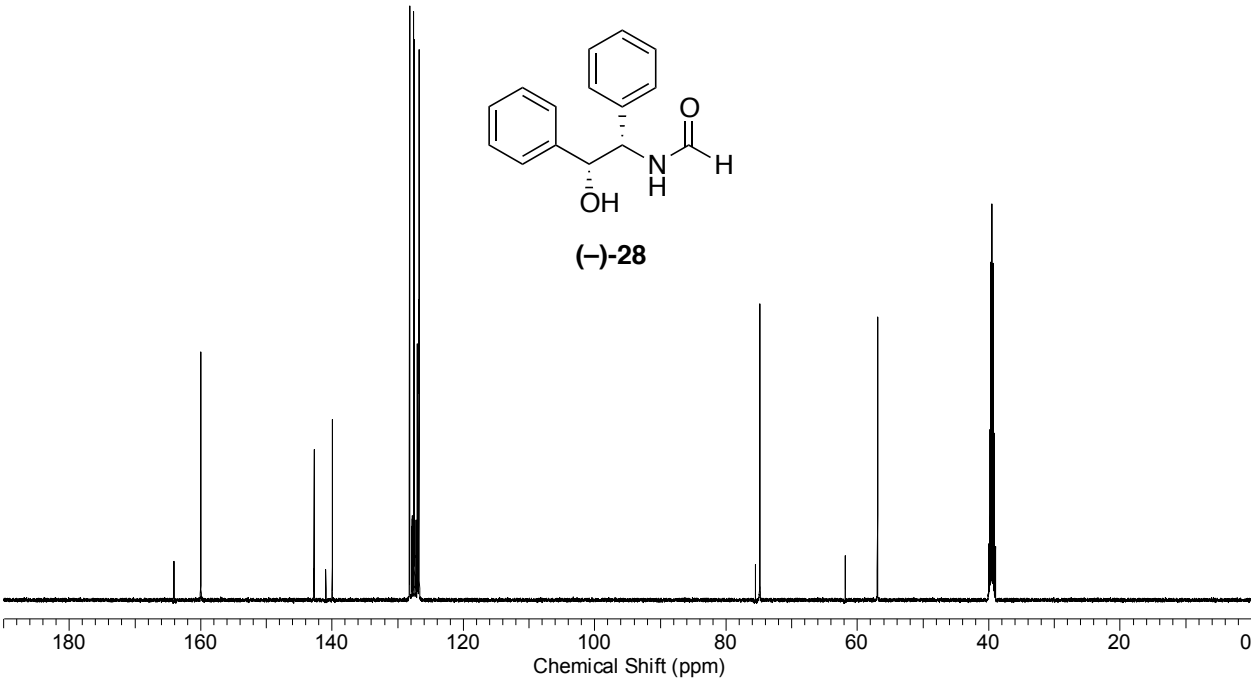


Figure 2.10: Three-dimensional supramolecular architecture viewed along the *b*-axis direction.

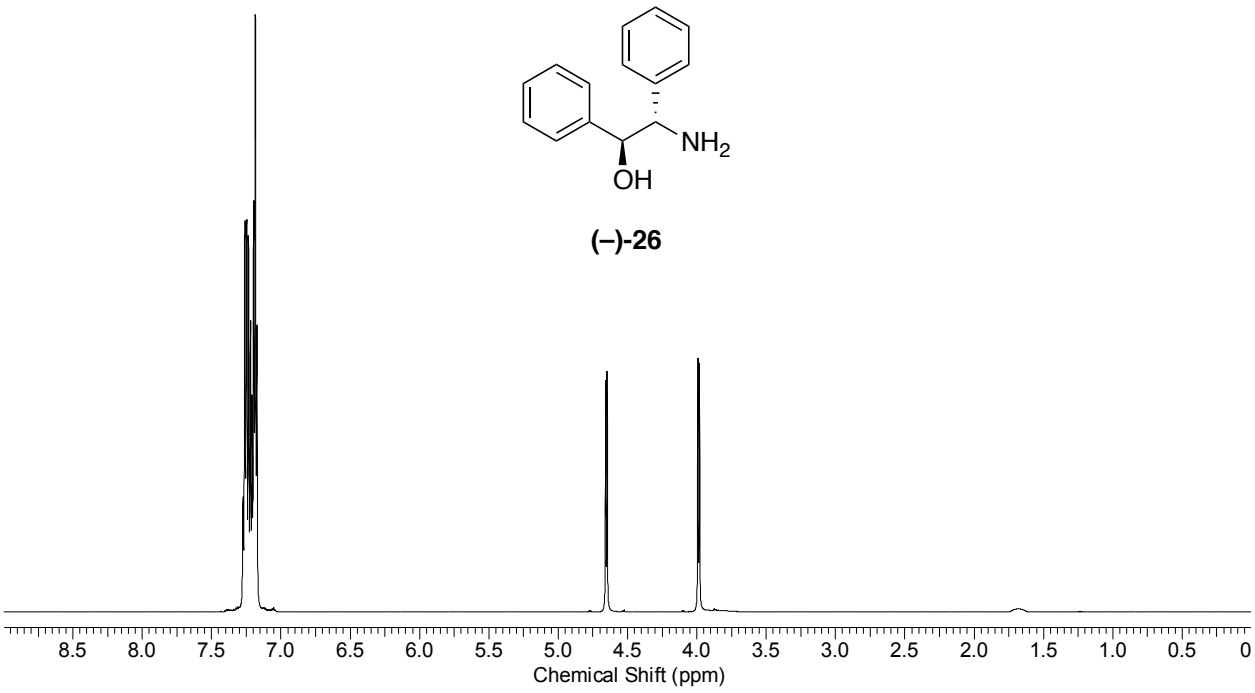
[1]H and [13]C NMR Spectra:



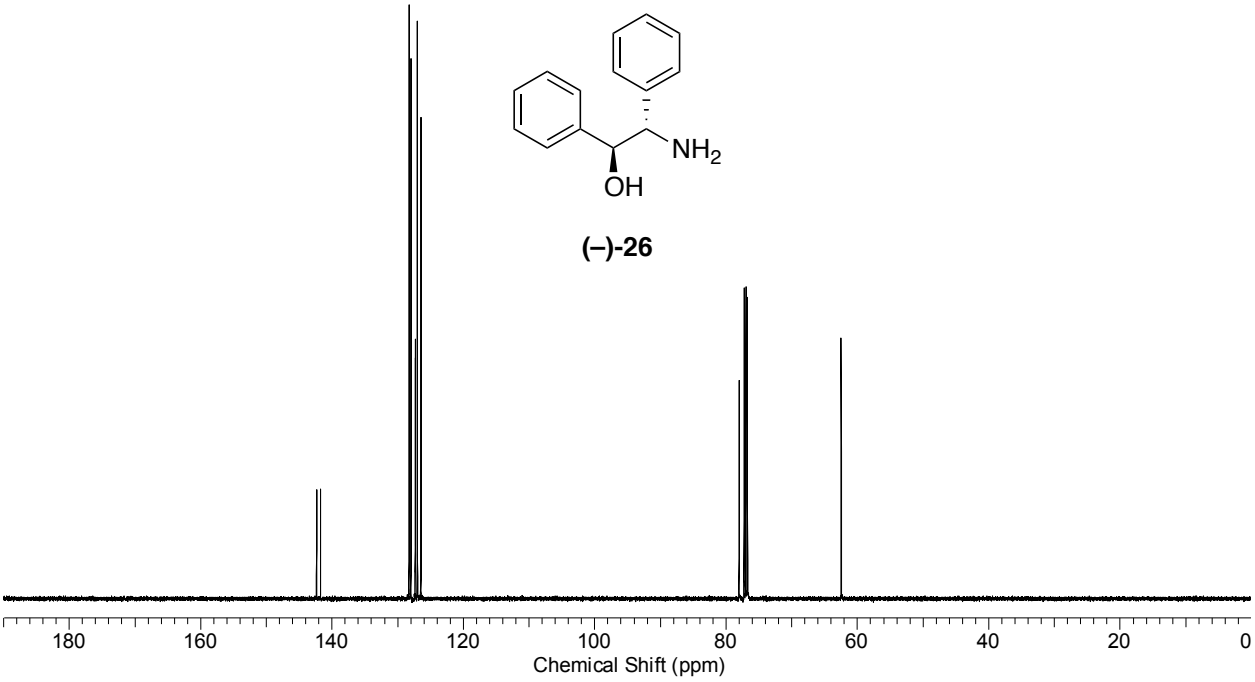
(–)-28



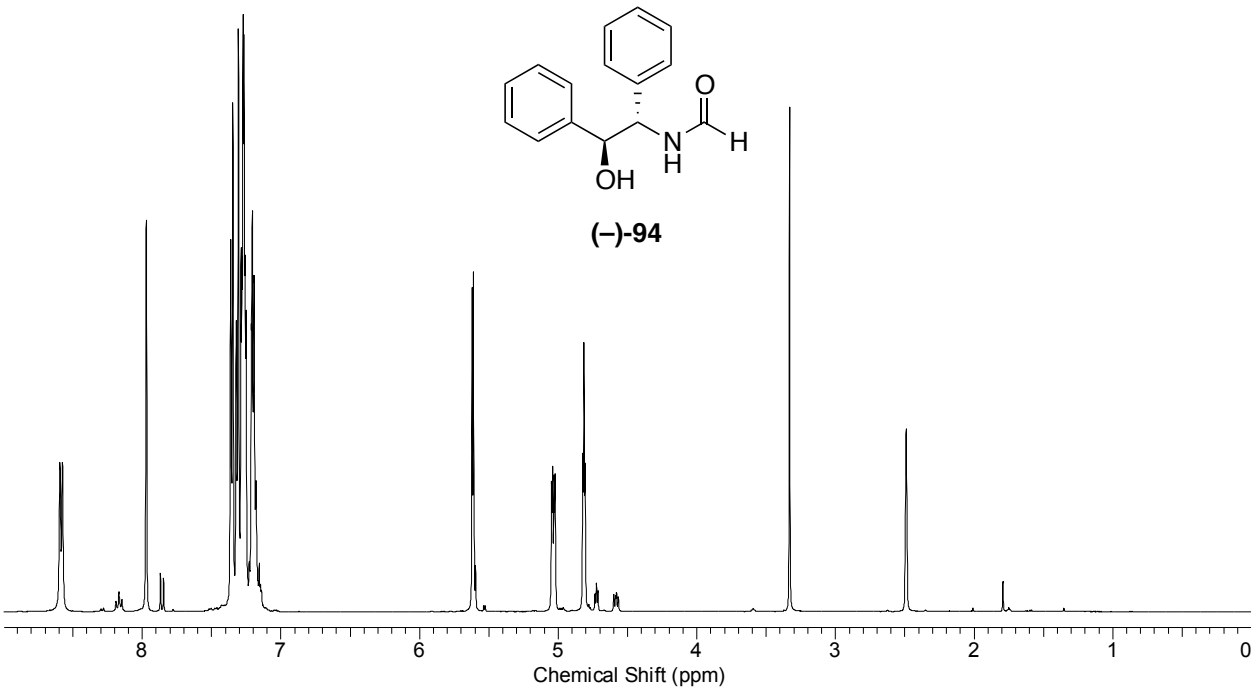
(–)-28


NH2
OH
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

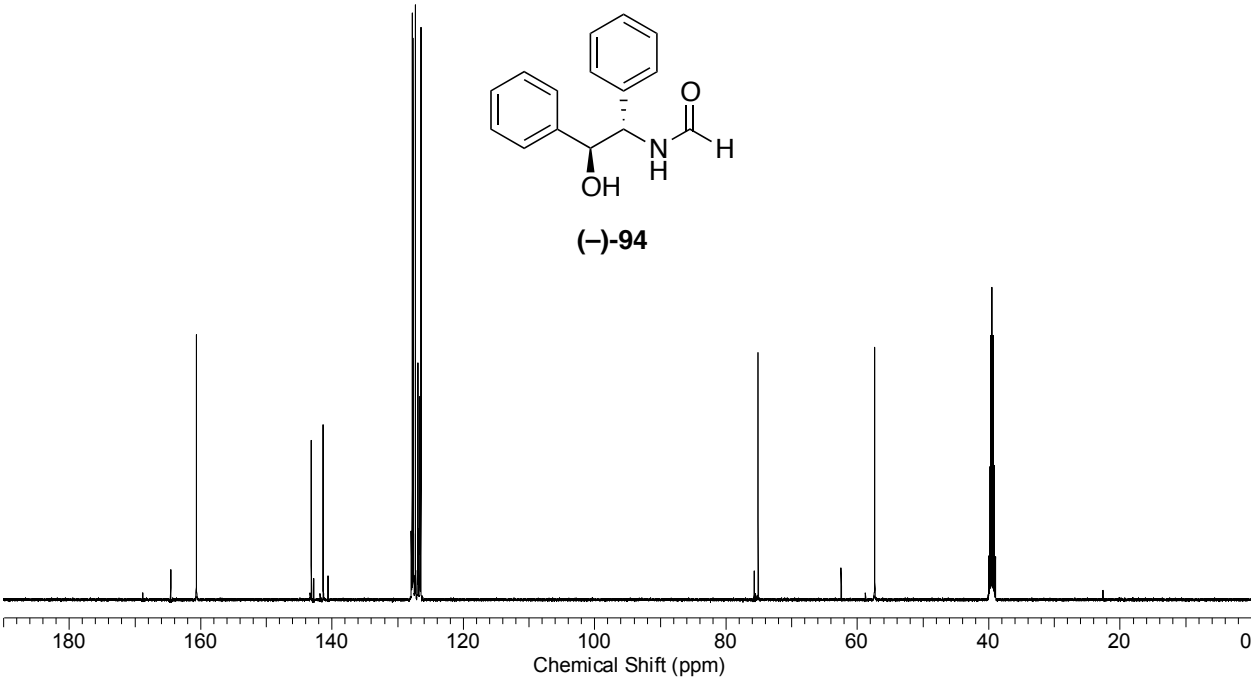
(–)-26


NH2
OH
180 160 140 120 100 80 60 40 20 0
Chemical Shift (ppm)

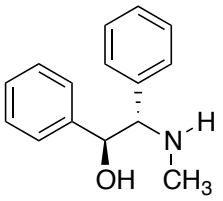
(–)-26


O
N
H
H
OH
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

(–)-94

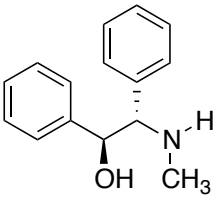

O
N
H
H
OH
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

(–)-94


H
N
OH
CH3

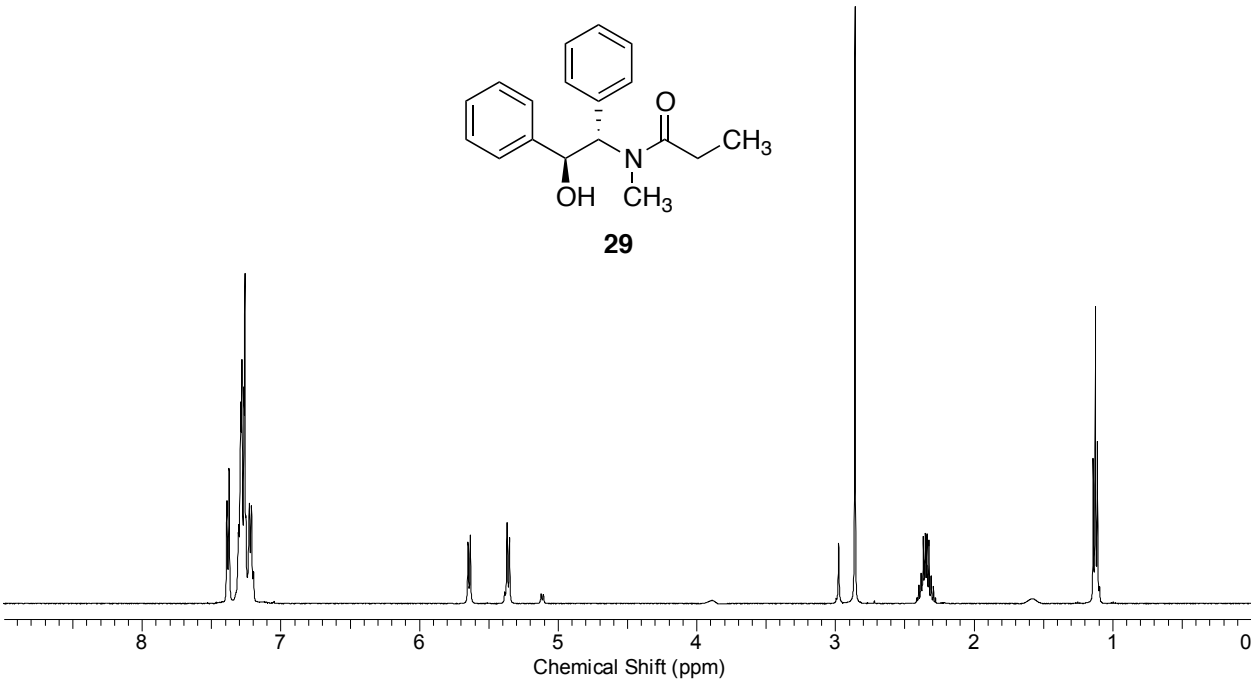
(–)-25

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

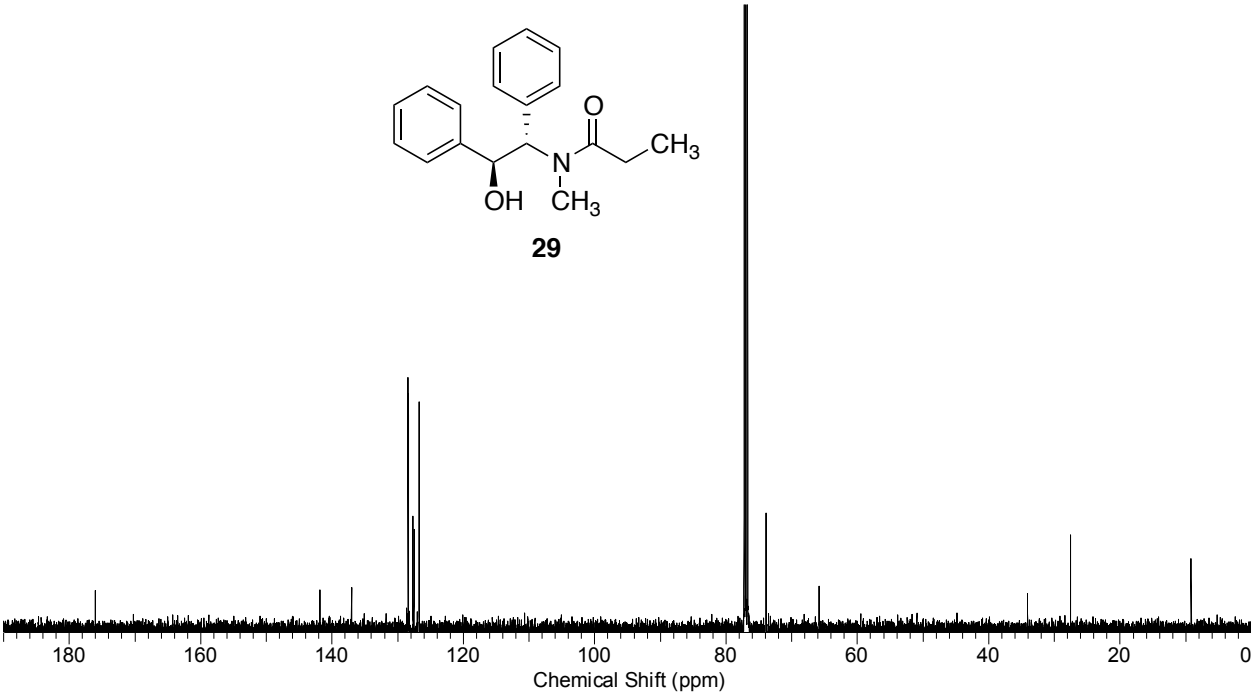

H
N
OH
CH3

(–)-25

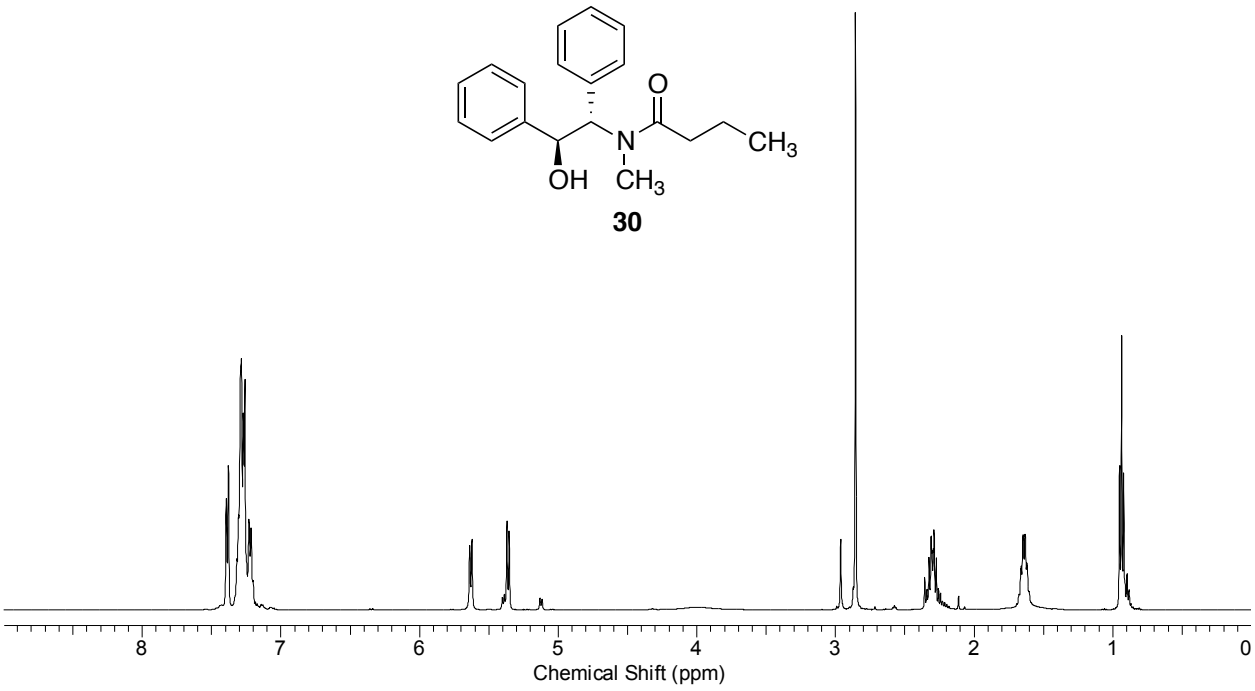
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


O
CH3
N
OH
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

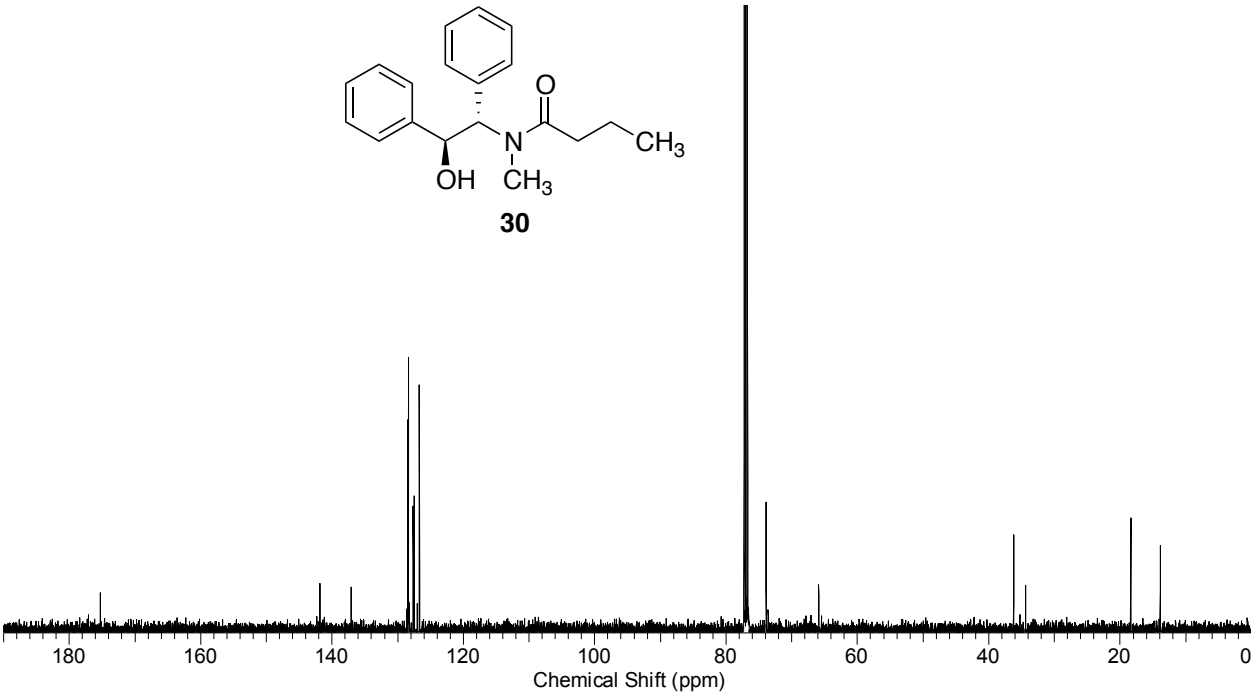
29


O
CH3
N
OH
CH3
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

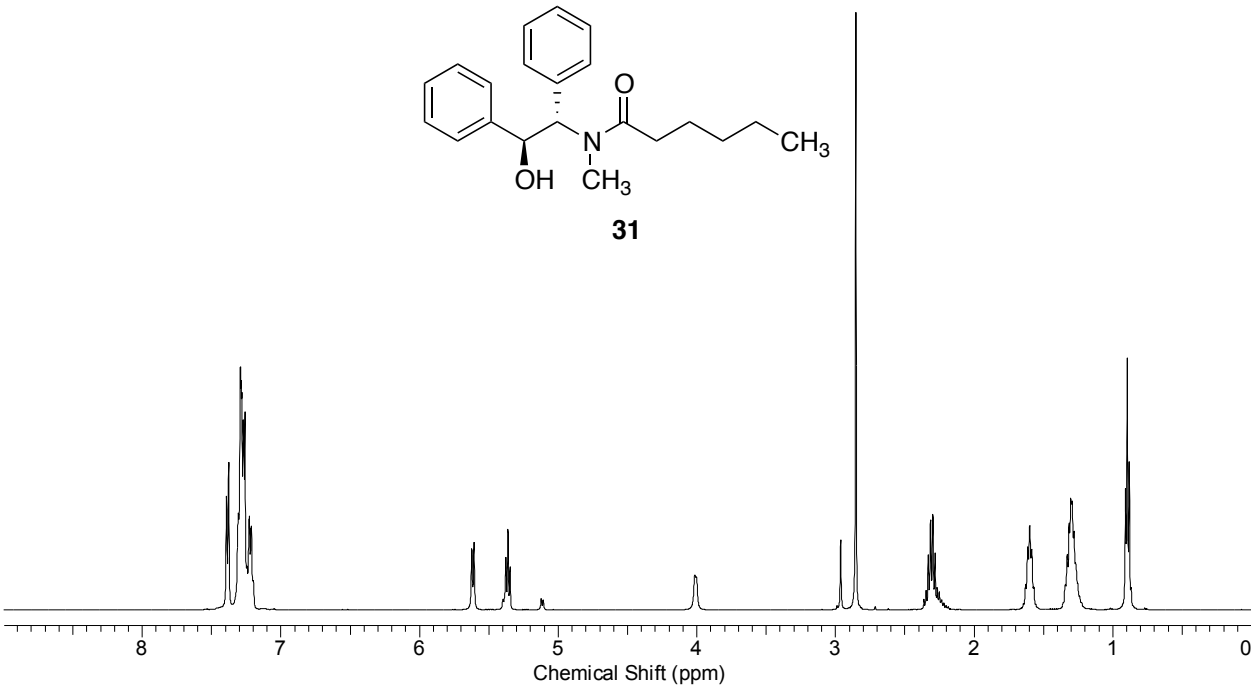
29


O
N
CH3
OH
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

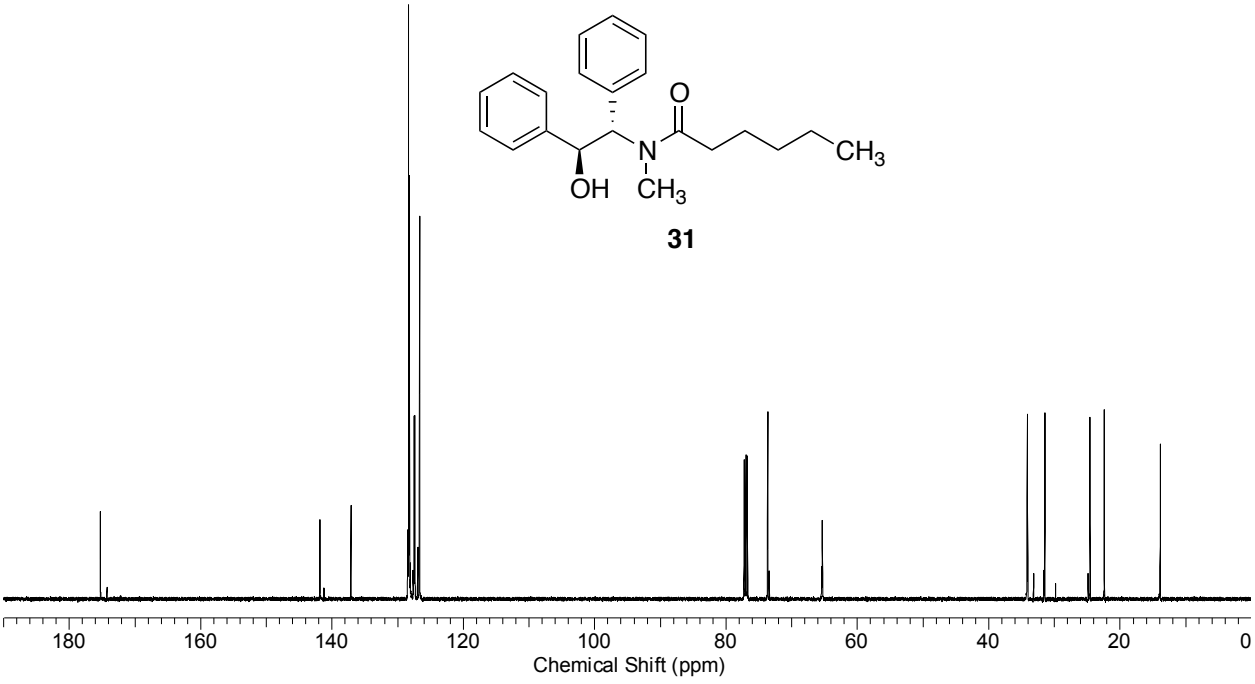
30


O
N
CH3
OH
CH3
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

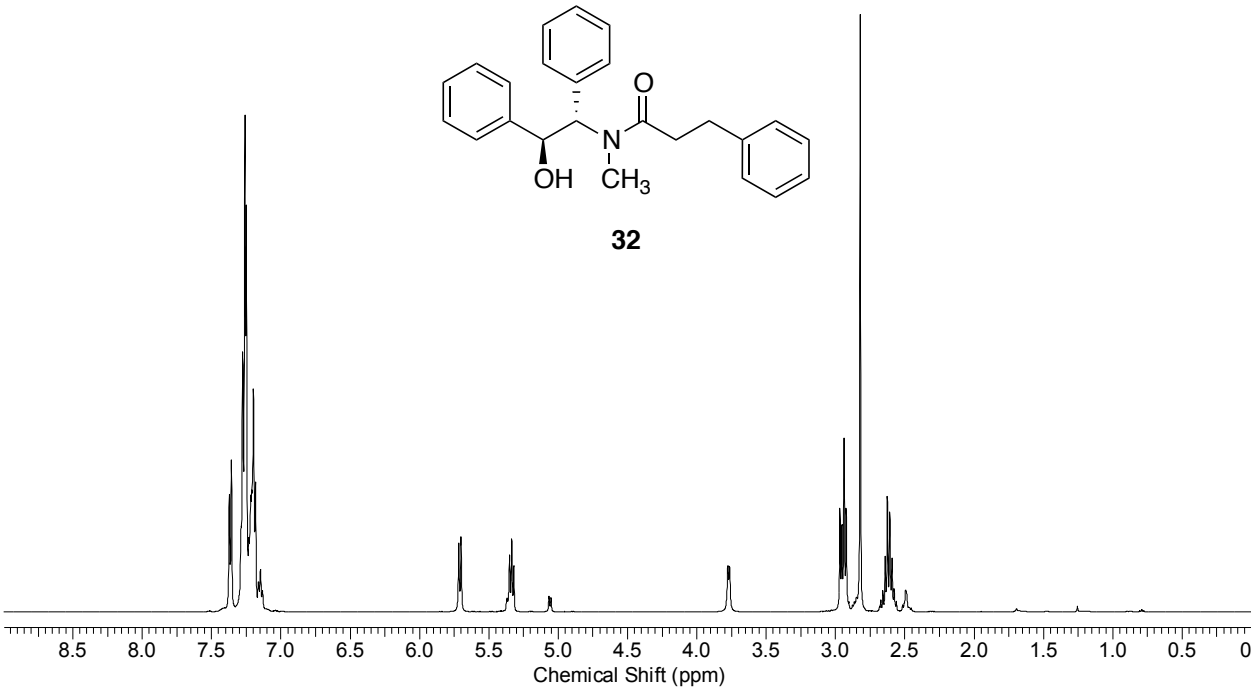
30


O
N
CH3
OH
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

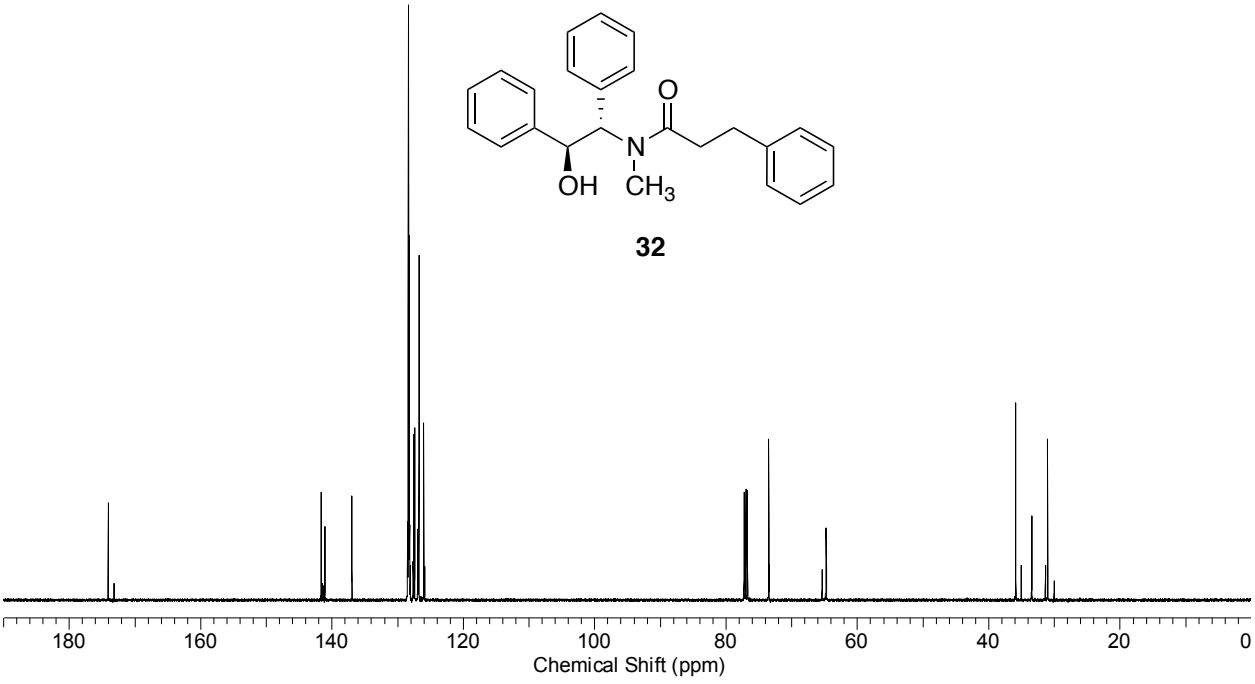
31


O
N
CH3
OH
CH3
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

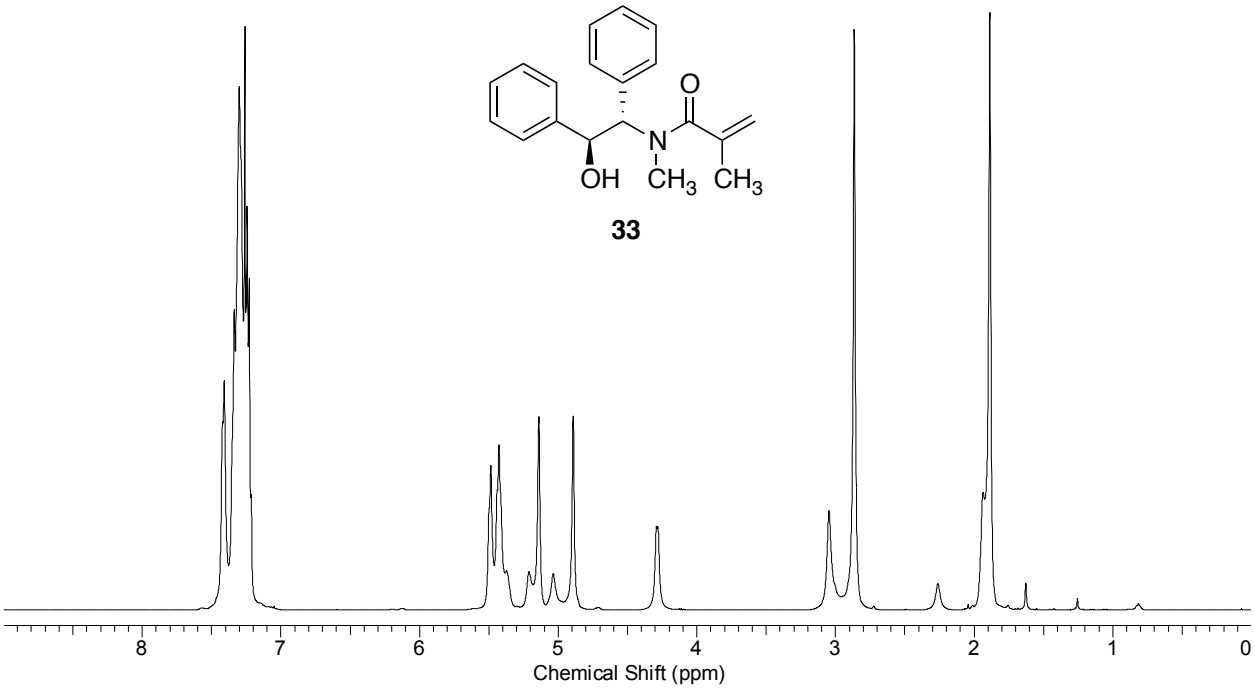
31


O
N
OH
CH3
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

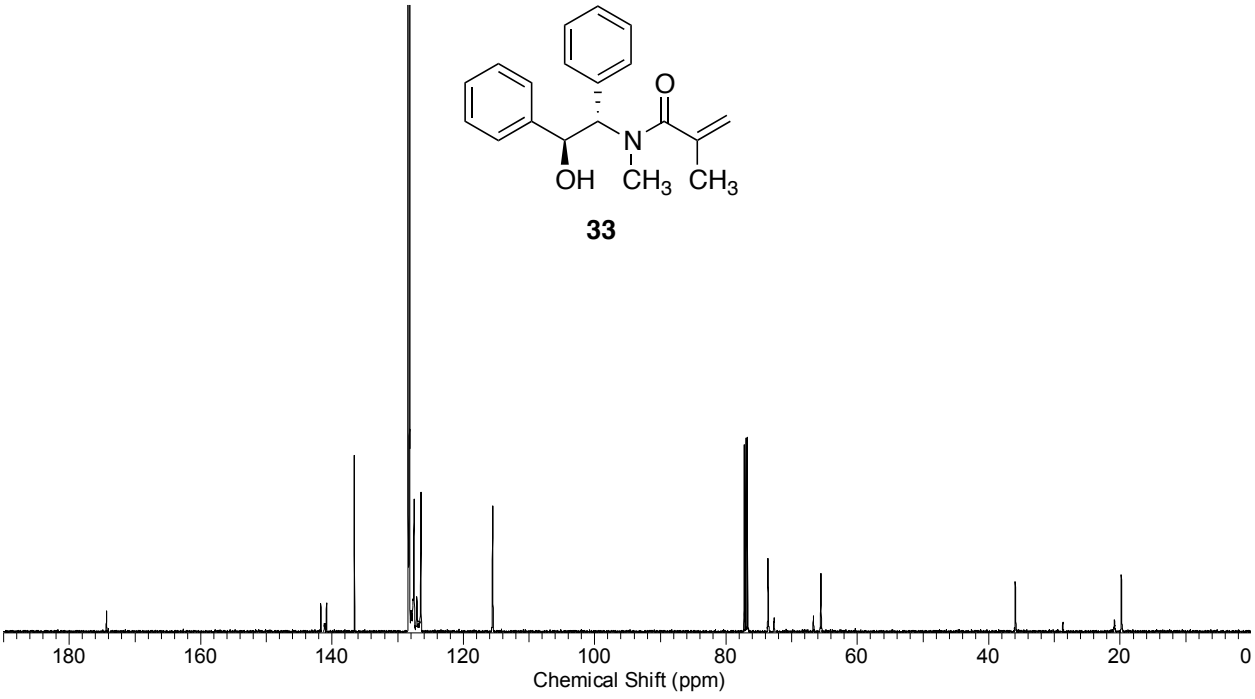
32


O
N
OH
CH3
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

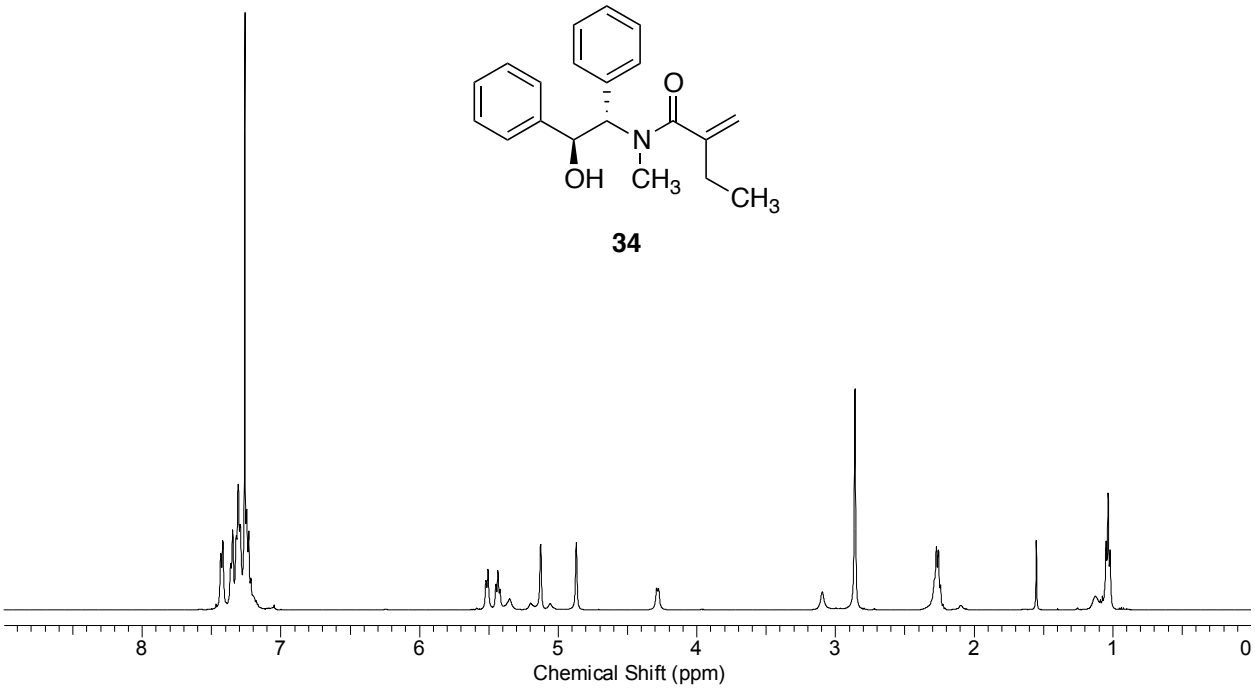
32


O
N
OH
CH3
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

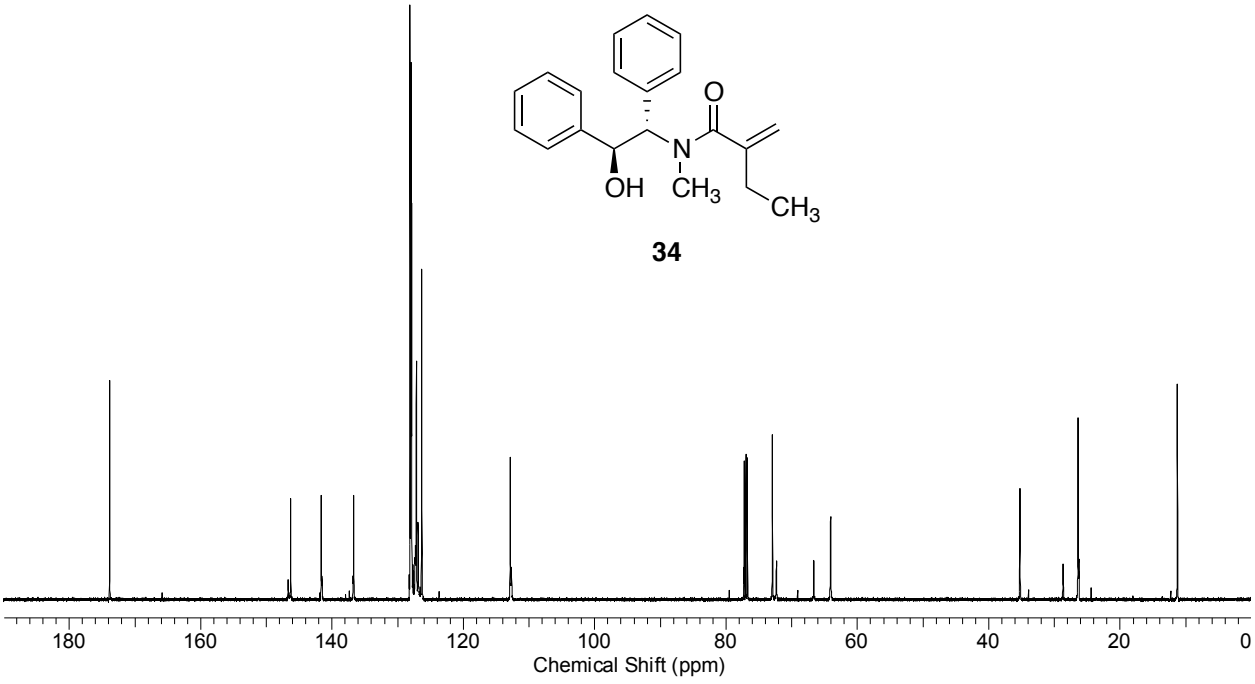
33


O
N
OH
CH3
CH3
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

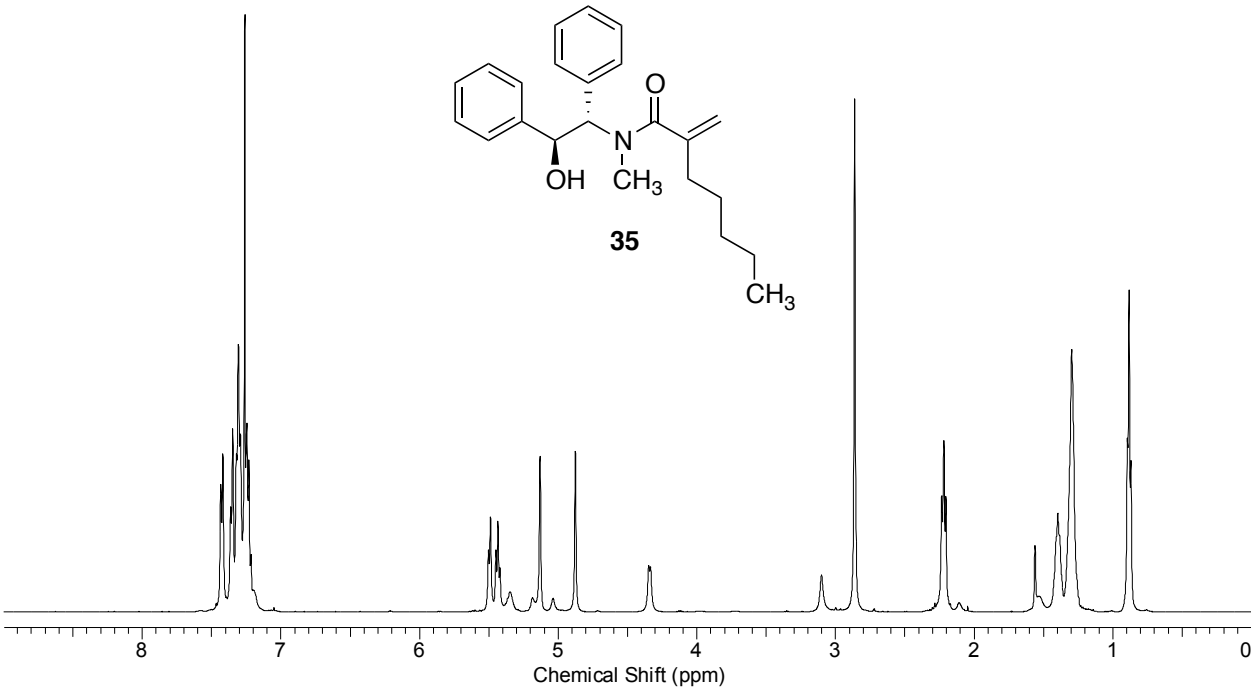
33

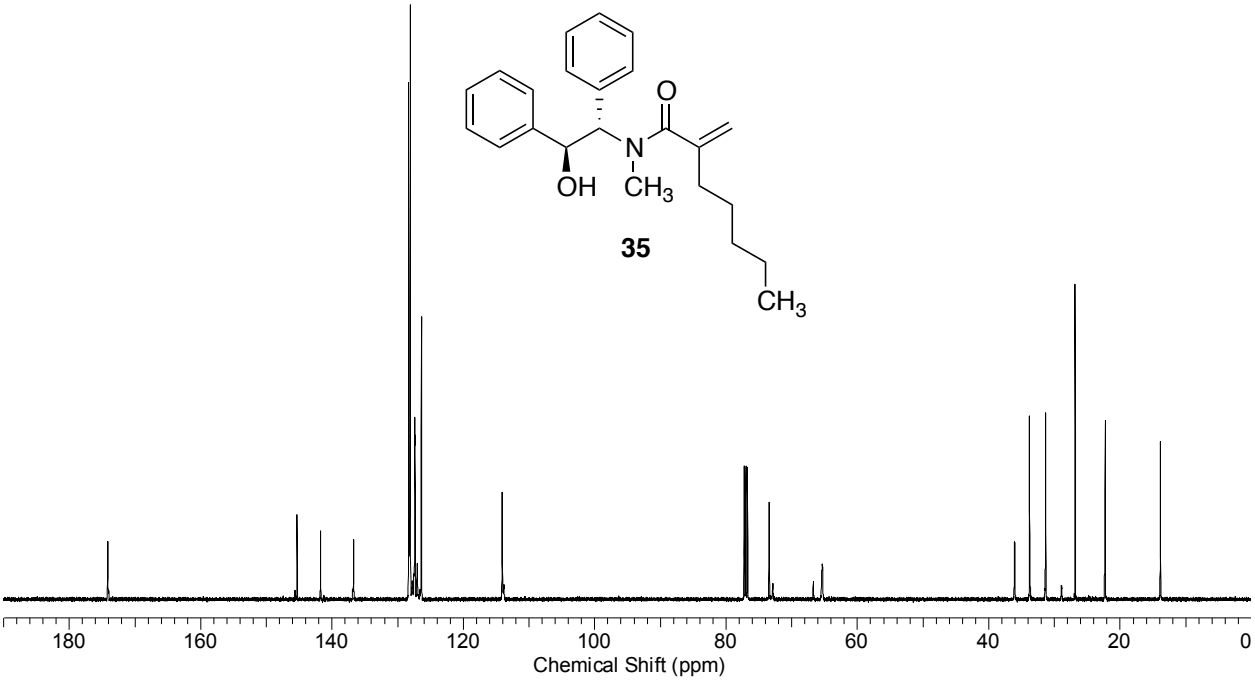

O
N
OH
CH3
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

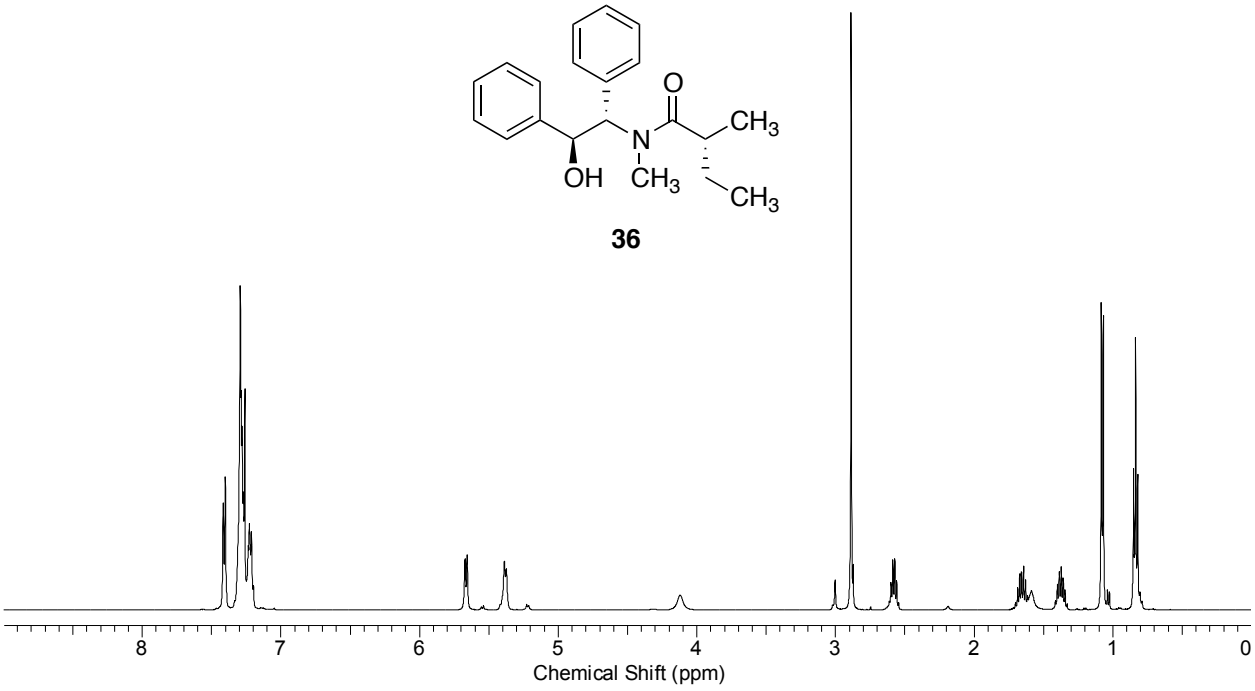
34


O
N
OH
CH3
CH3
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

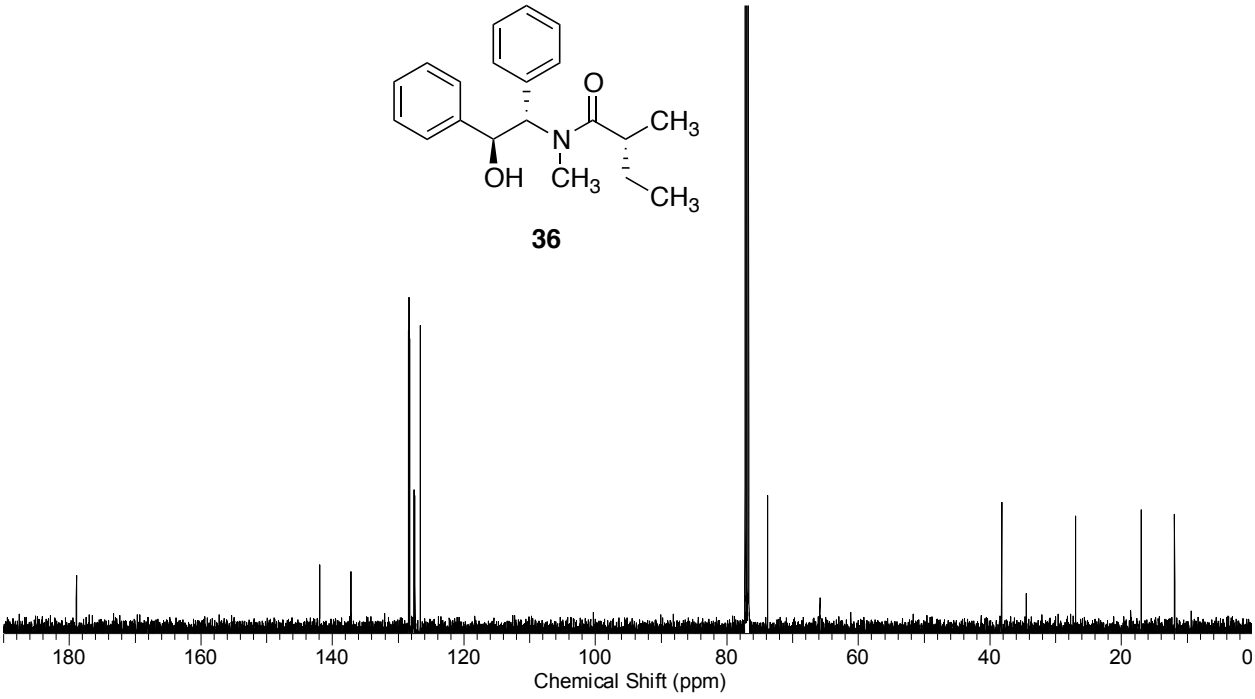
34


O
N
OH
CH3
CH3
35
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

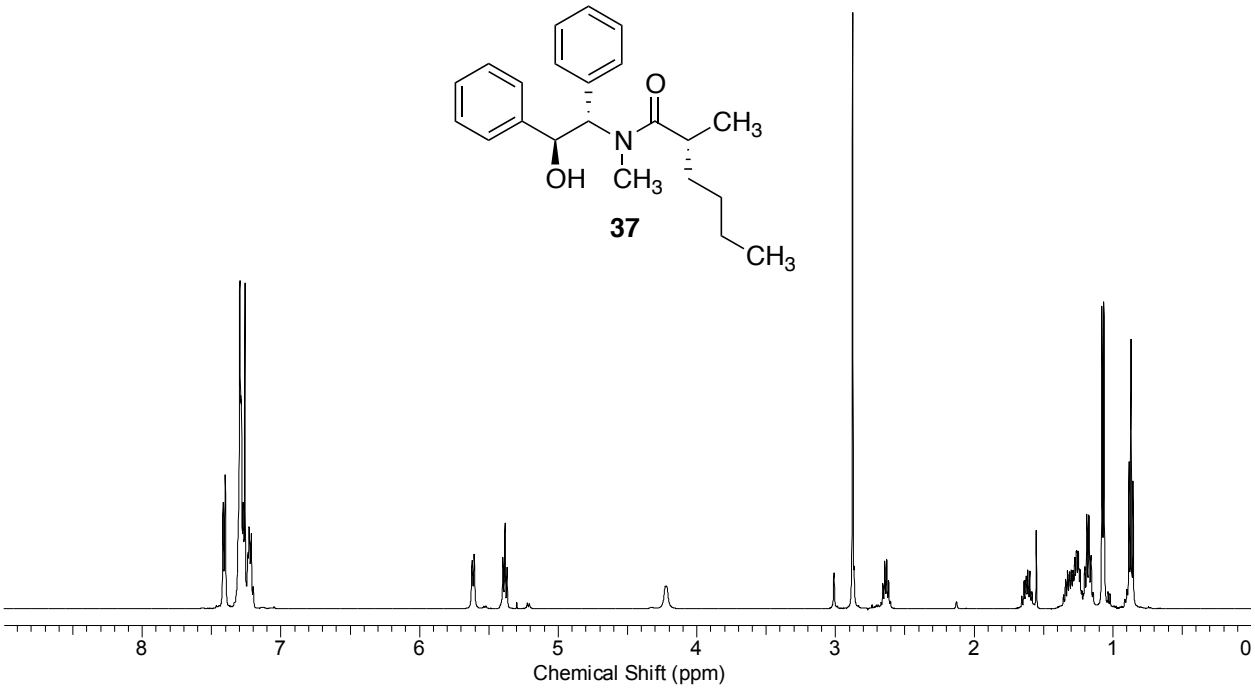

O
N
OH
CH3
CH3
35
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


O
CH3
N
OH
CH3
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

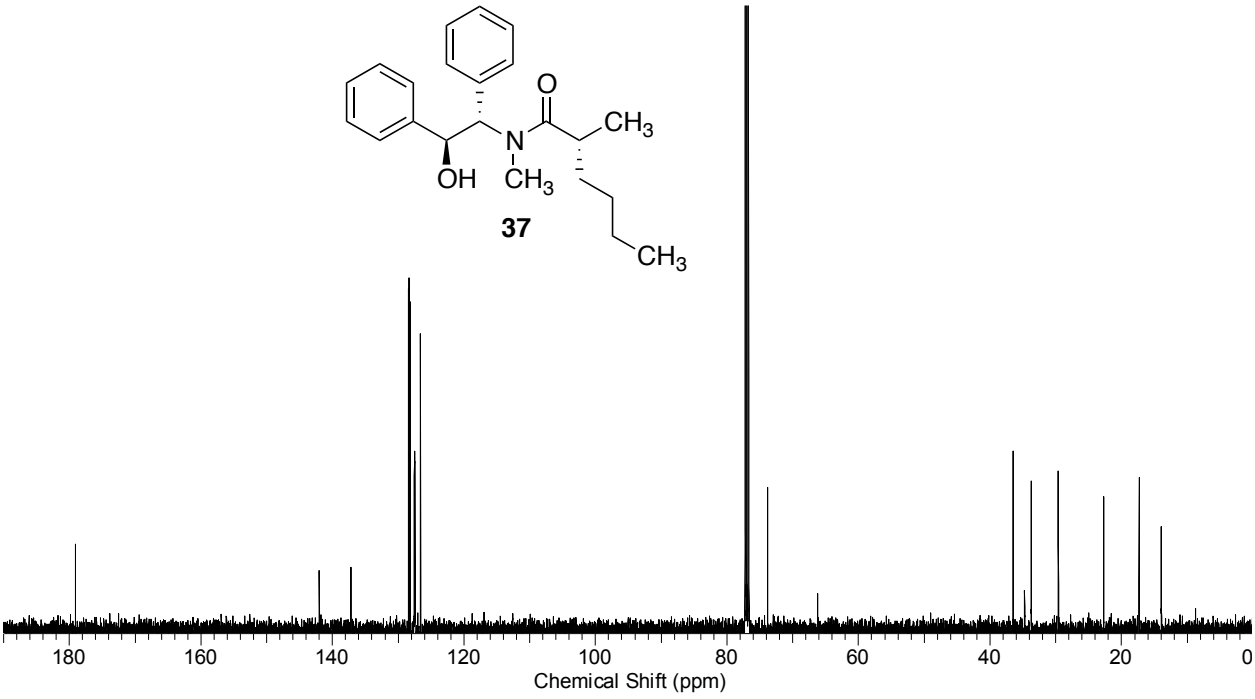
36


O
CH3
N
OH
CH3
CH3
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

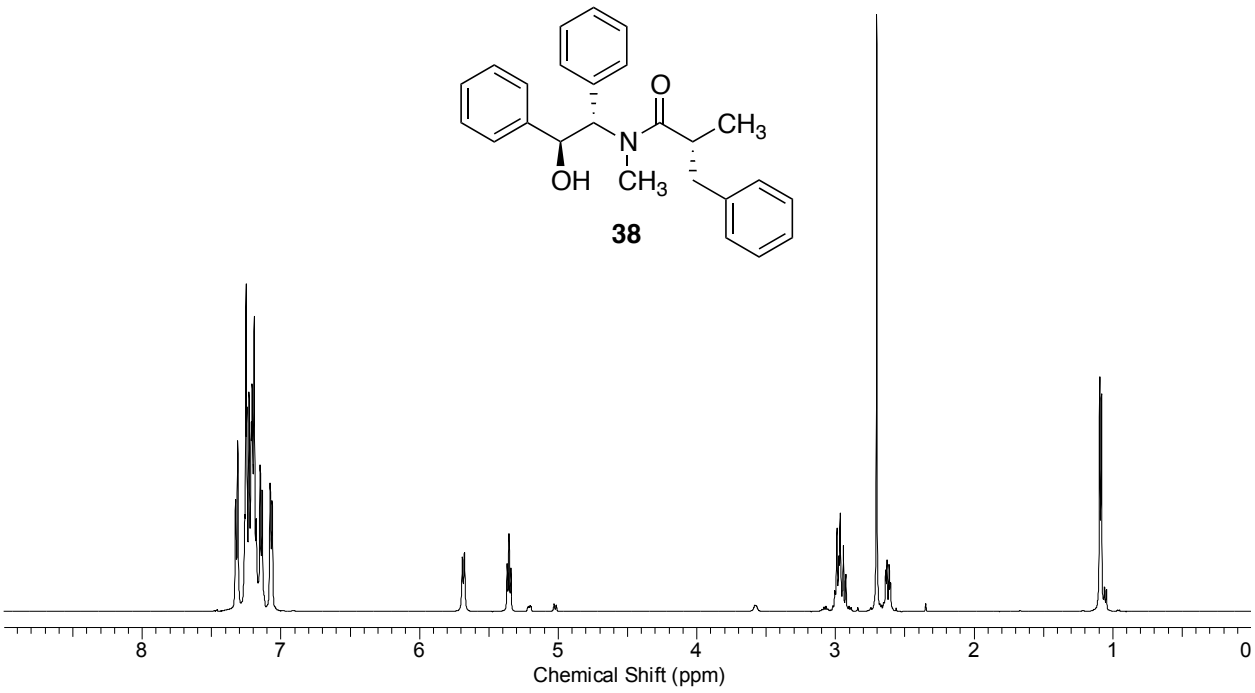
36

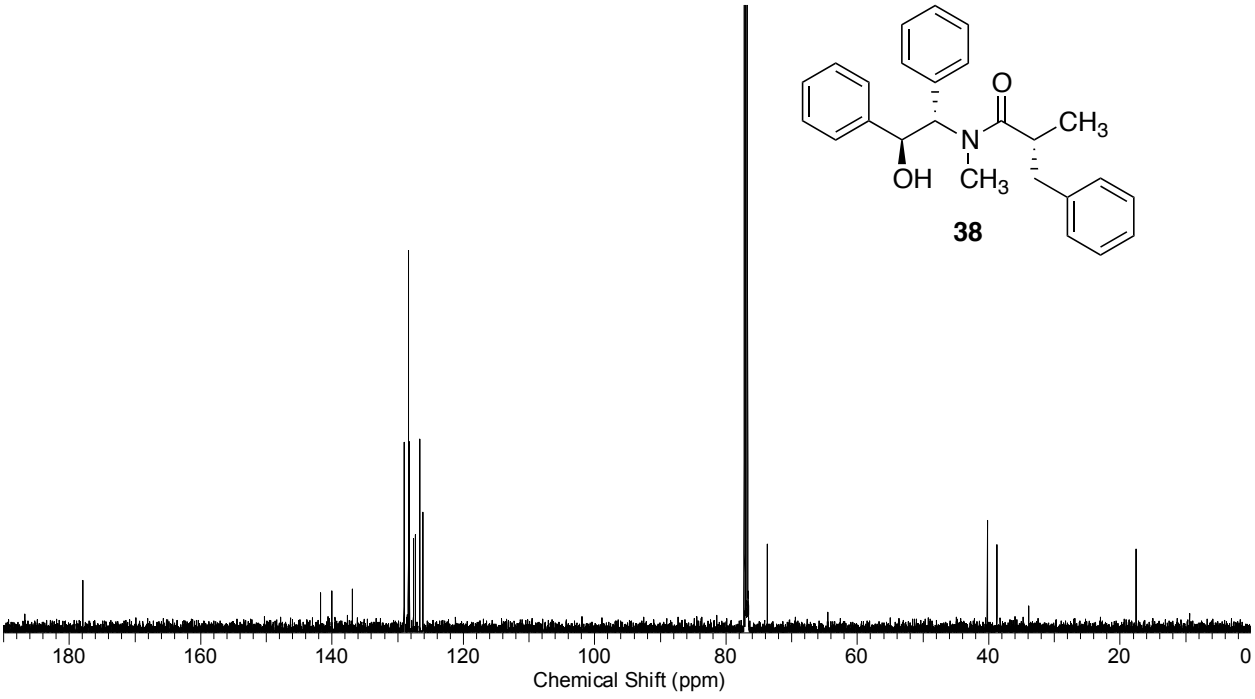

O
CH3
N
OH
CH3
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

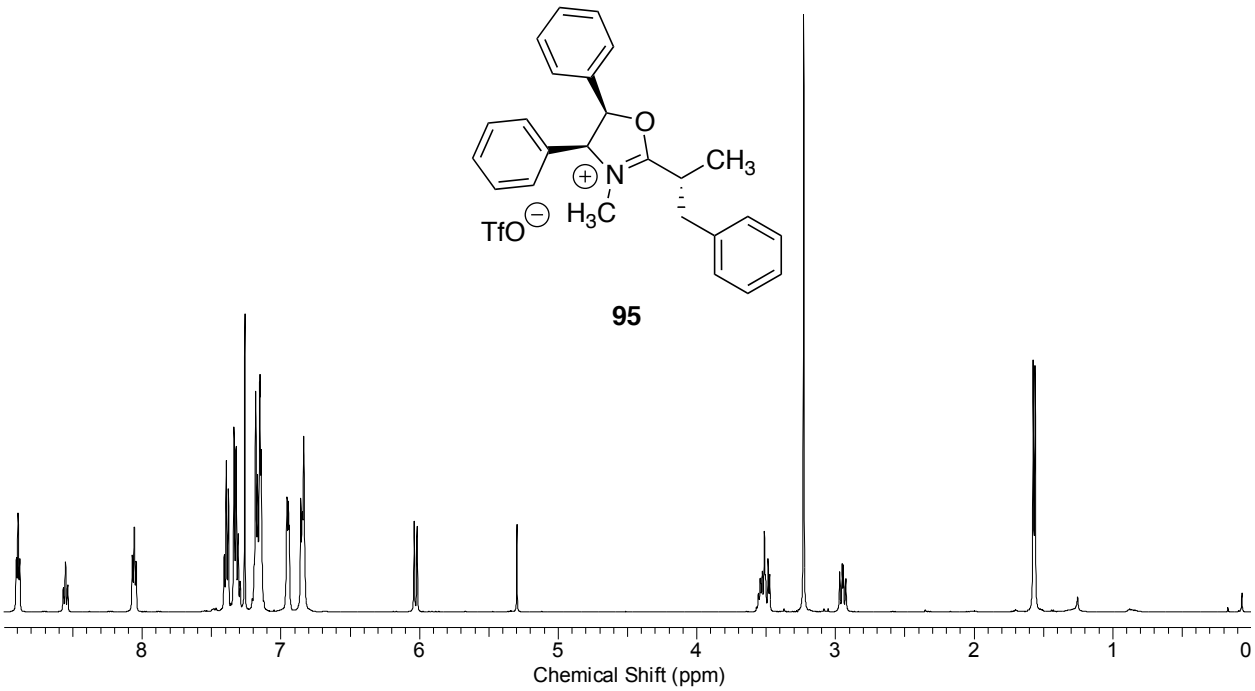
37


O
CH3
N
OH
CH3
CH3
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

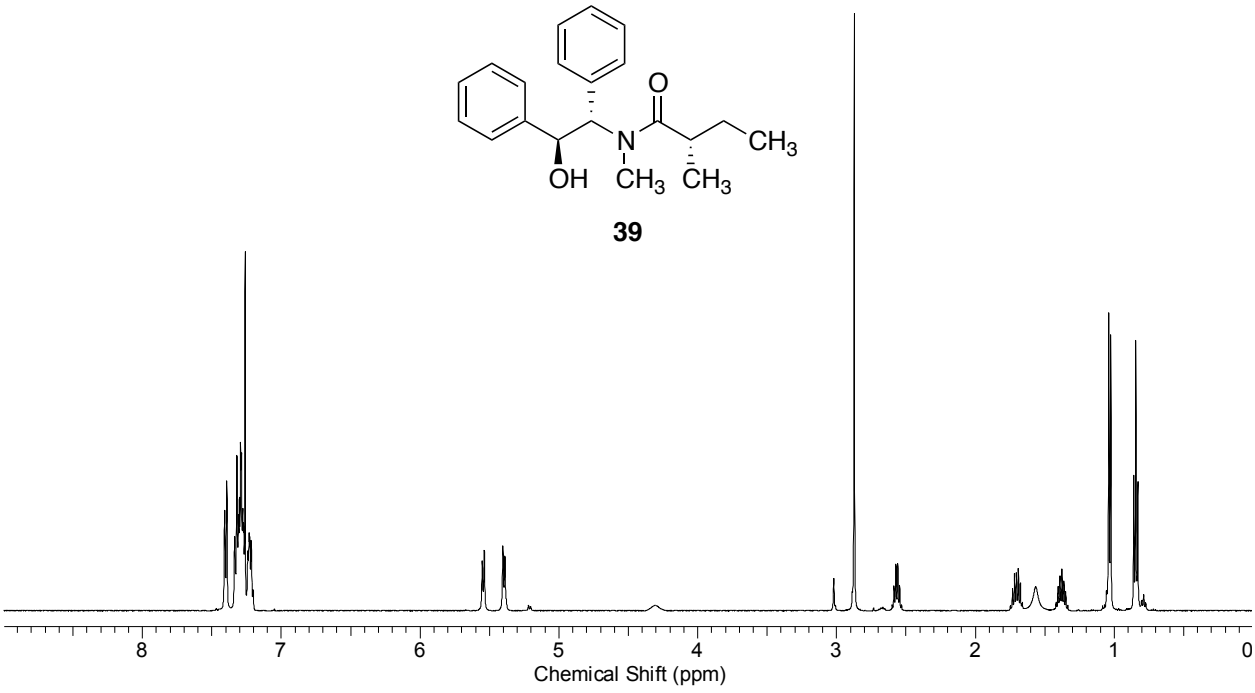
37


O
CH3
N
OH
CH3
38
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

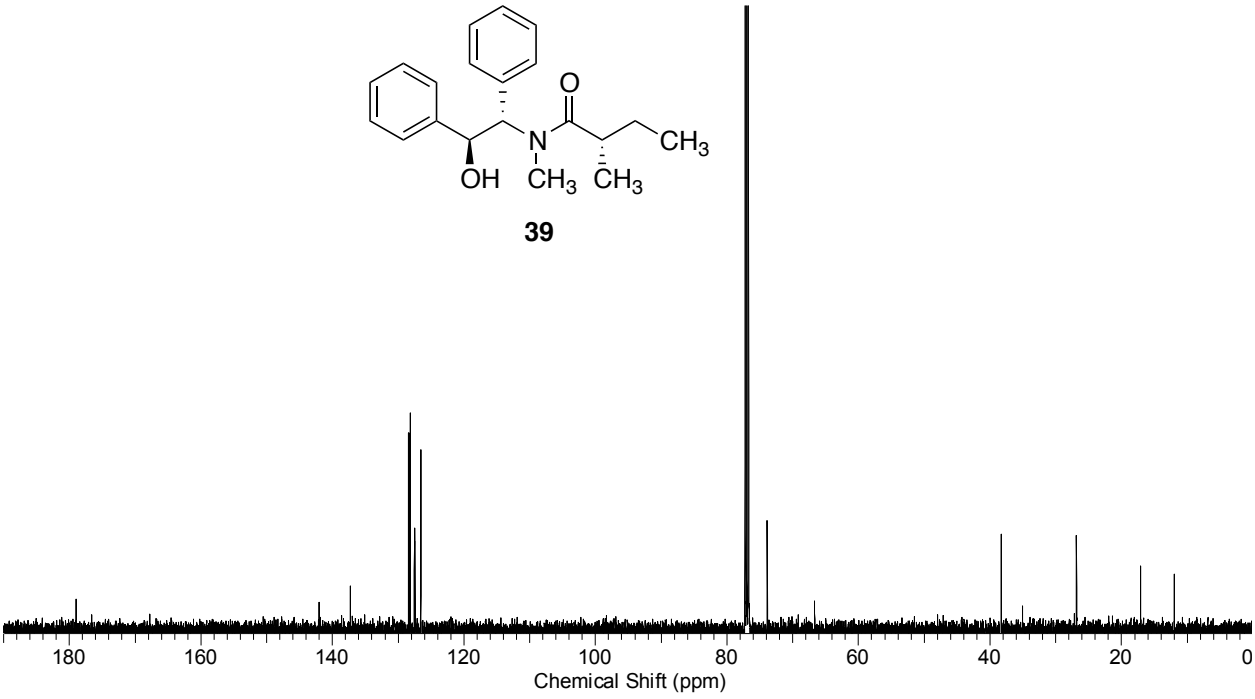

O
CH3
N
OH
CH3
38
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)



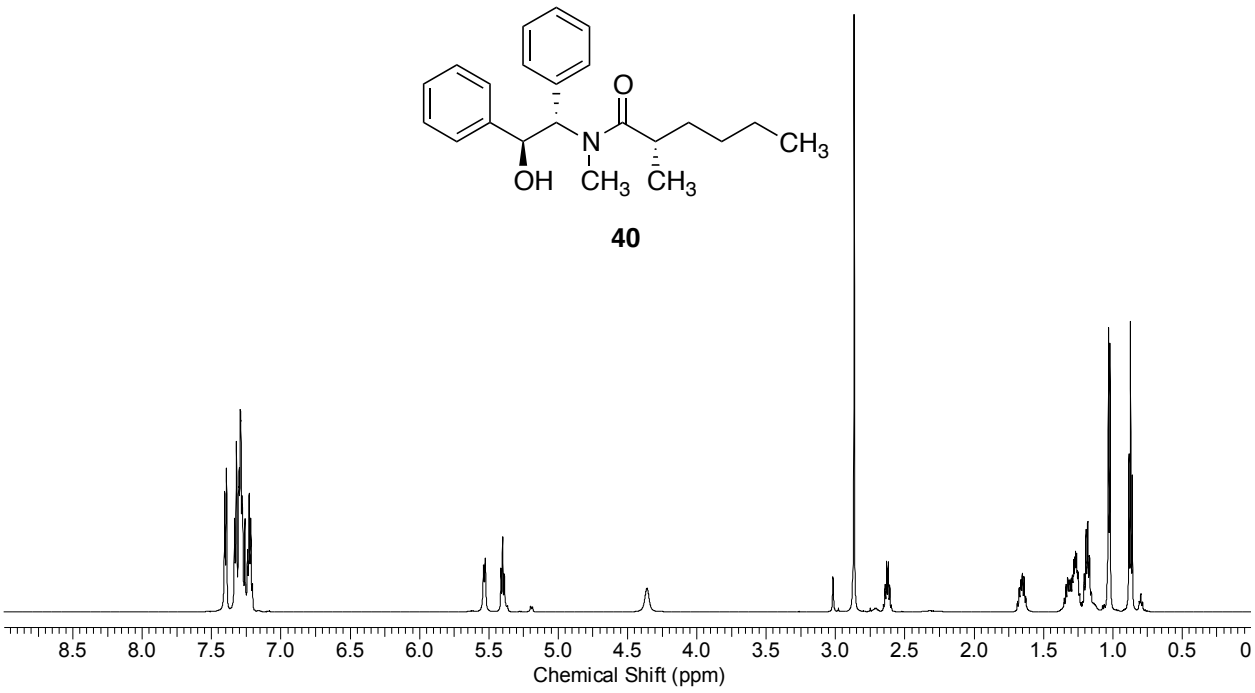
95


O
N
CH3
OH
CH3
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

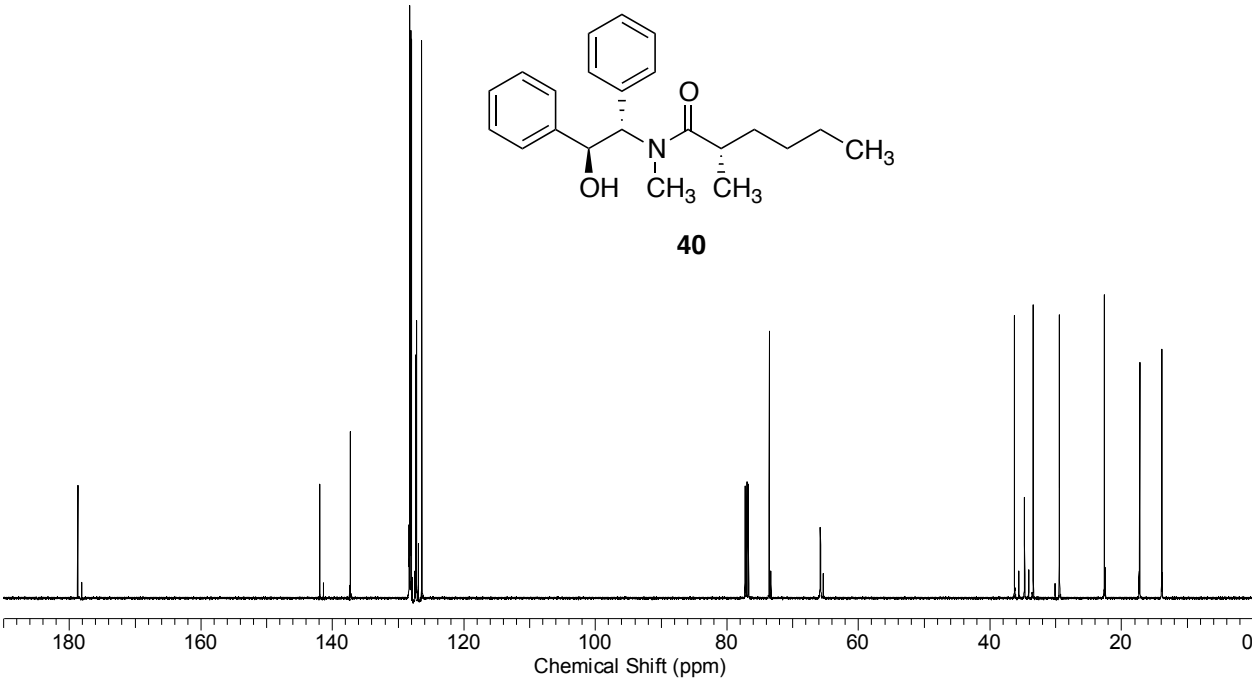
39


O
N
CH3
OH
CH3
CH3
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

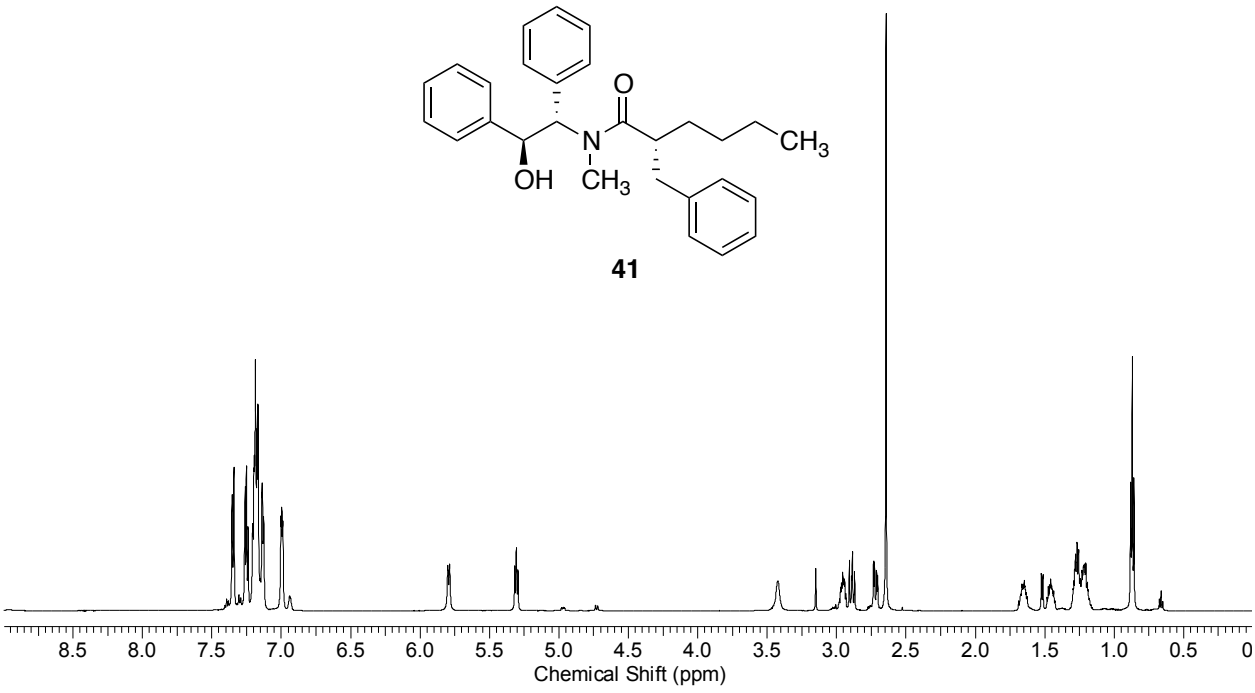
39


O
N
CH3
OH
CH3
CH3
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

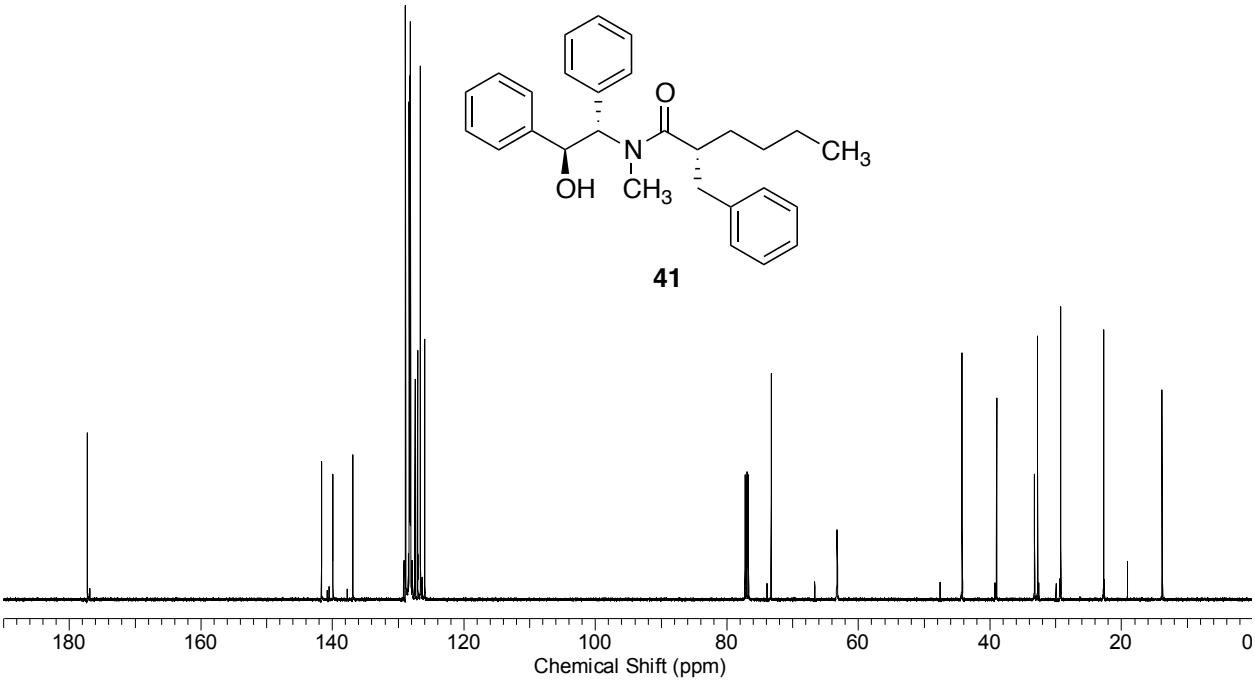
40


O
N
CH3
OH
CH3
CH3
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

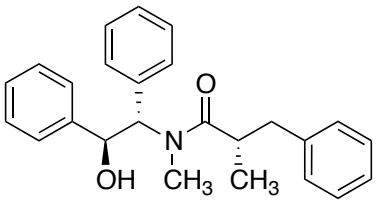
40


O
N
CH3
OH
CH3
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

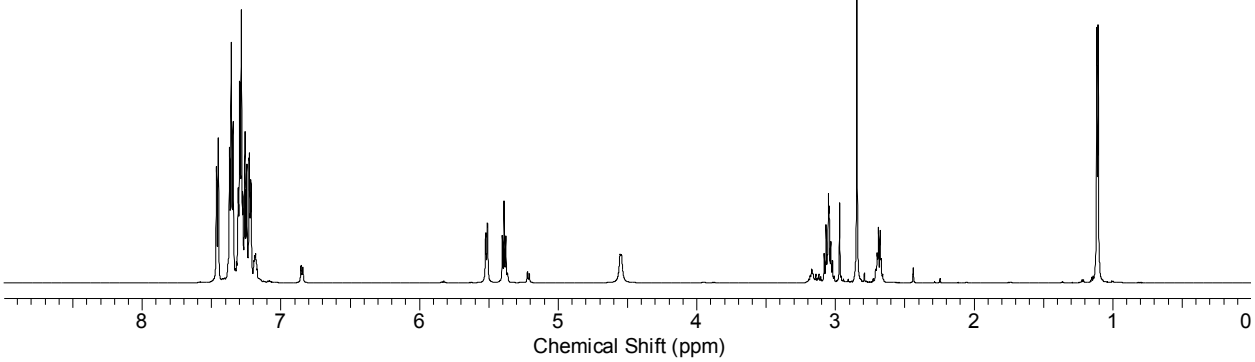
41

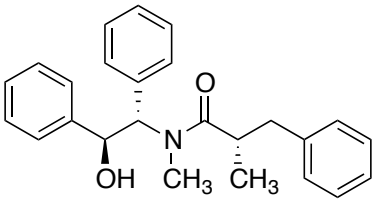

O
N
CH3
OH
CH3
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

41


O
N
OH
CH3
CH3

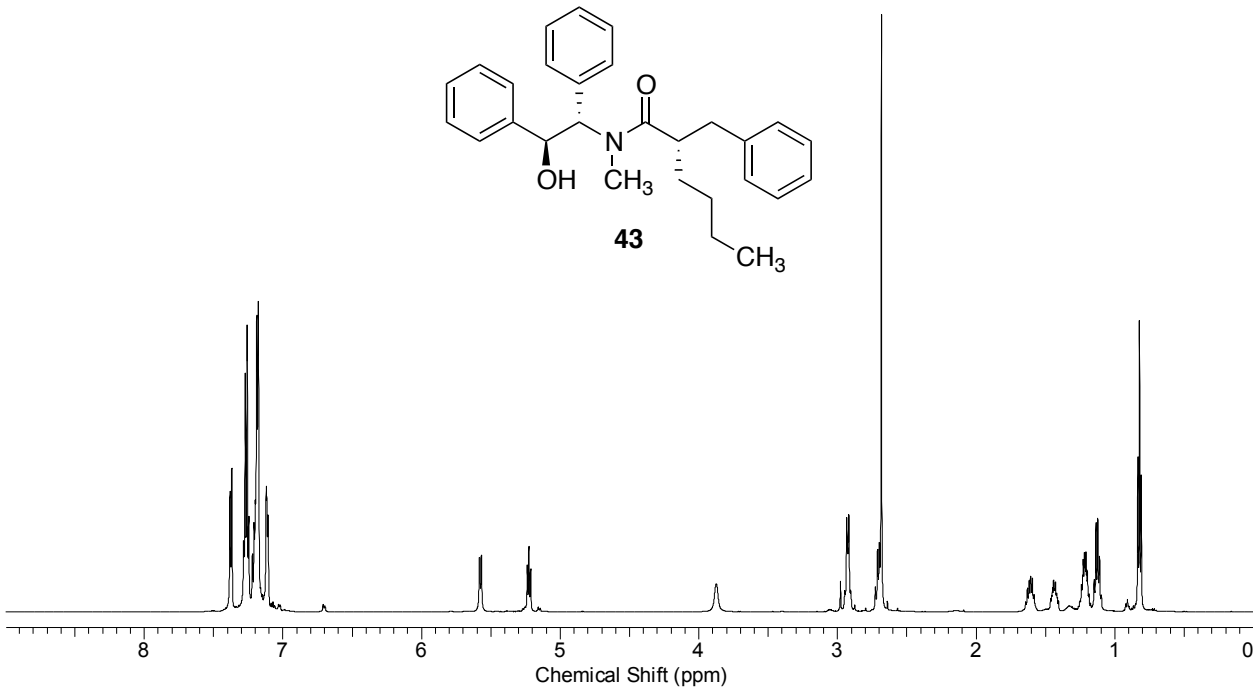
42


8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


O
N
OH
CH3
CH3

42

180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)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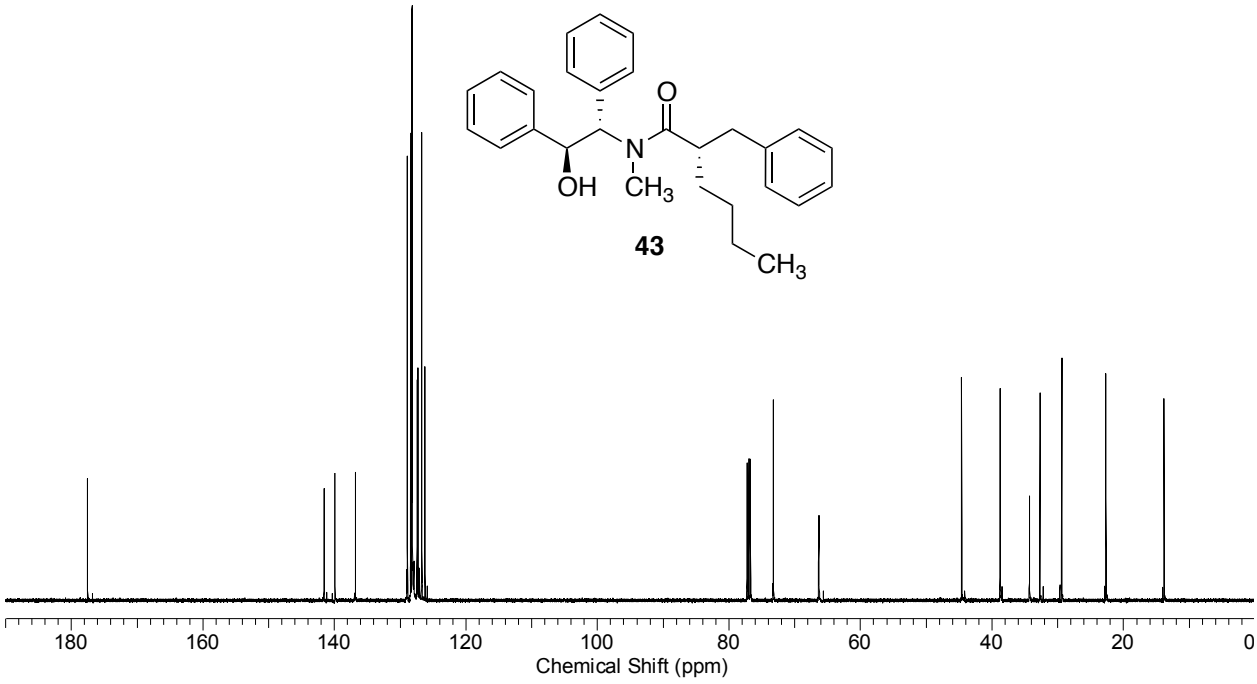
N
OH
CH3
CH3
43
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)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OH
CH3
CH3
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140
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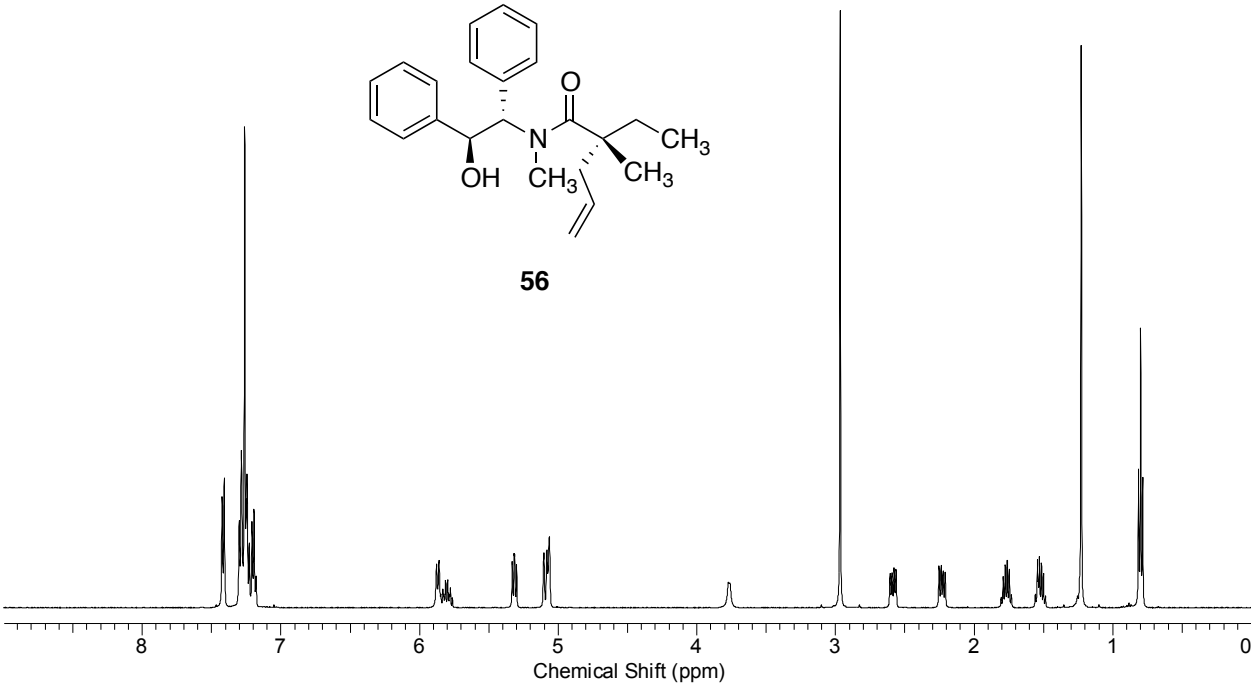
100
80
60
40
20
0
Chemical Shift (ppm)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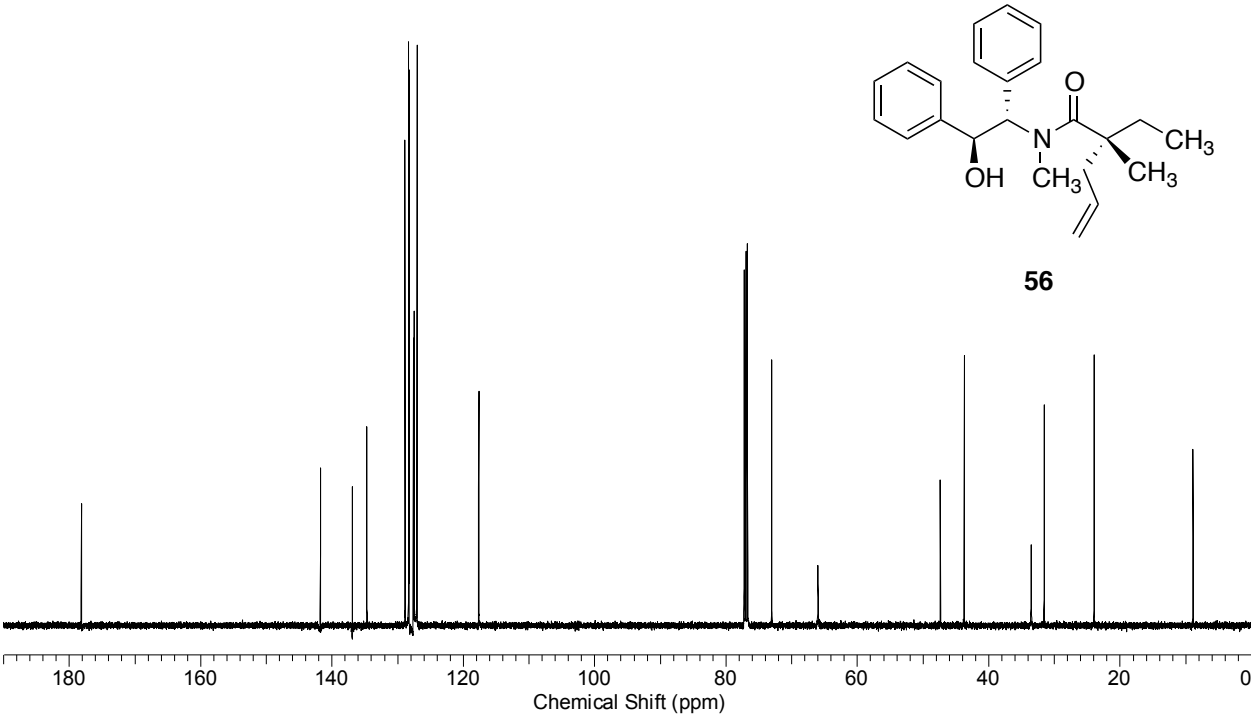
OH
CH3
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

56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CH3
OH
CH3
CH3
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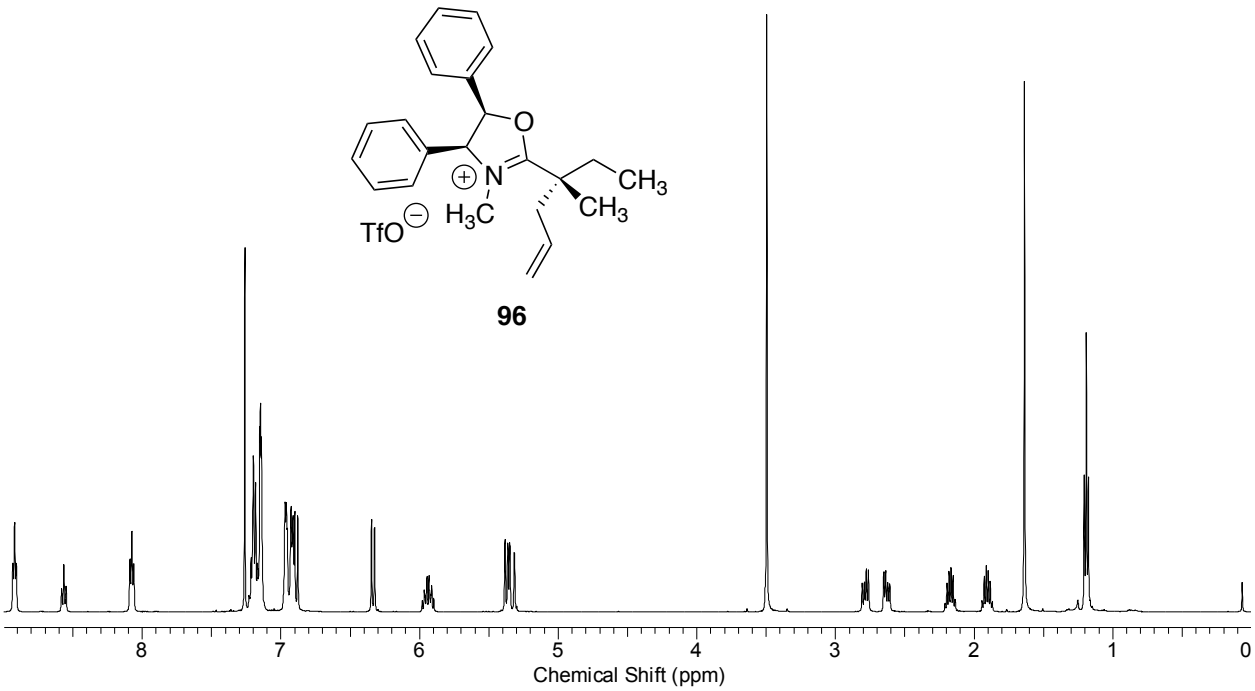
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

56



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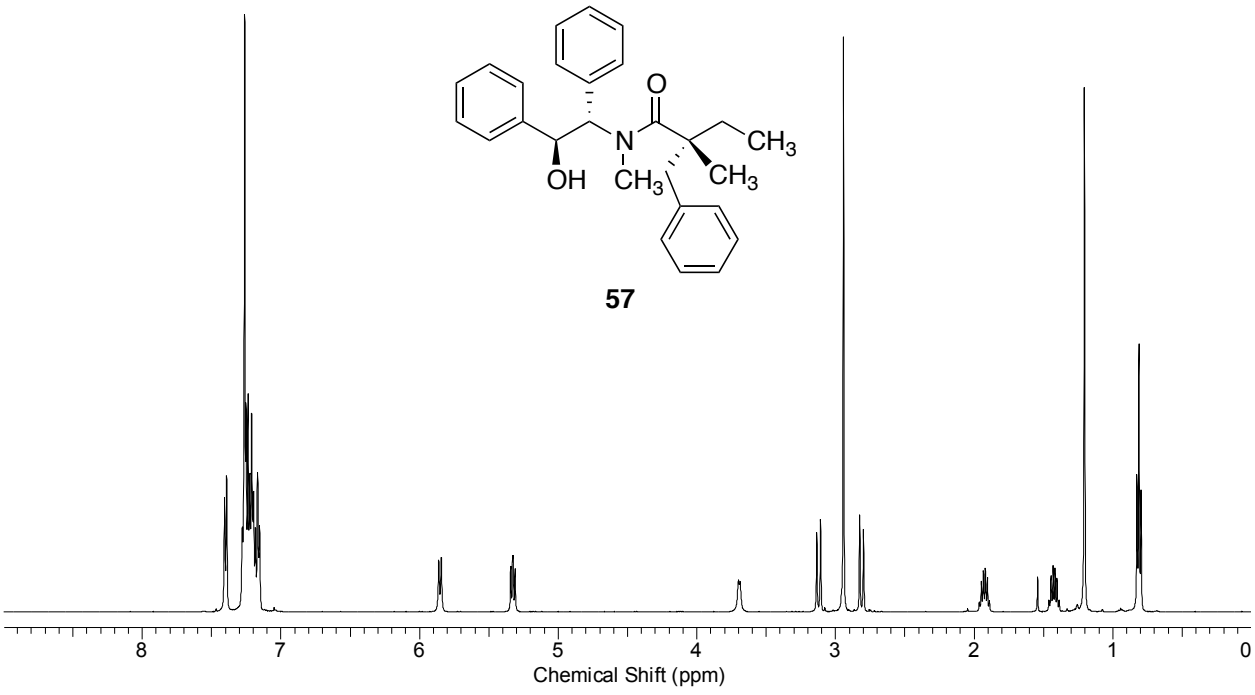
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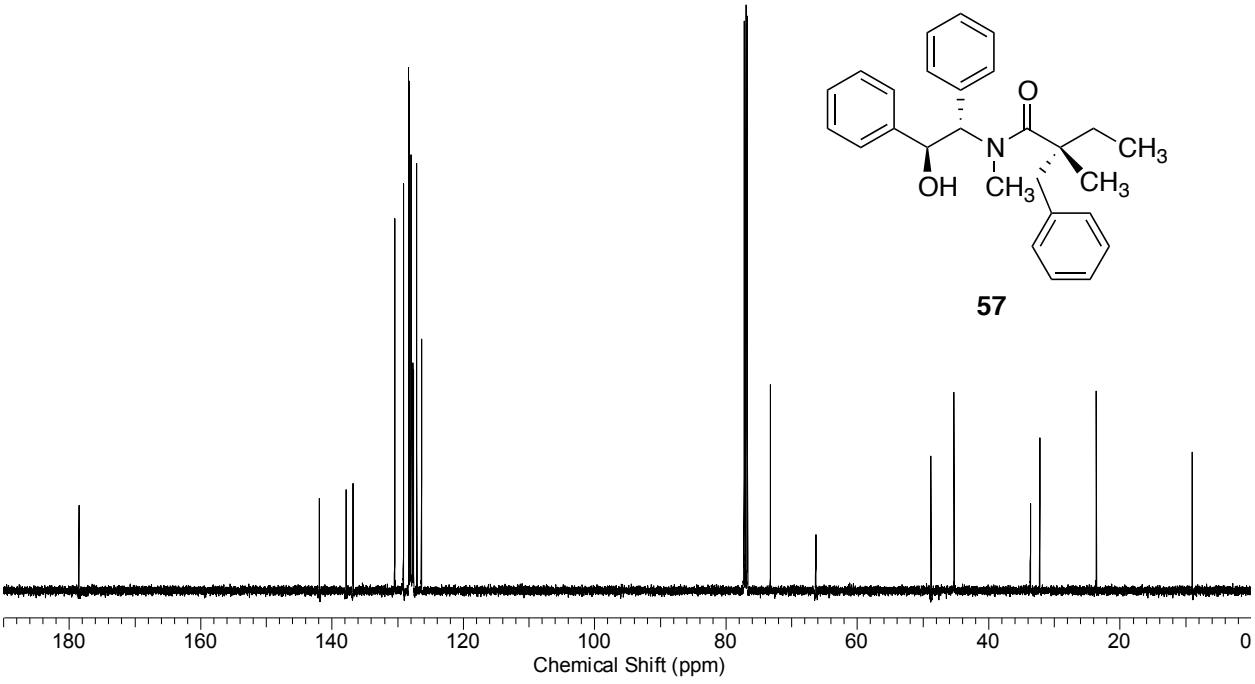
CH3
OH
CH3
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

57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CH3
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100
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20
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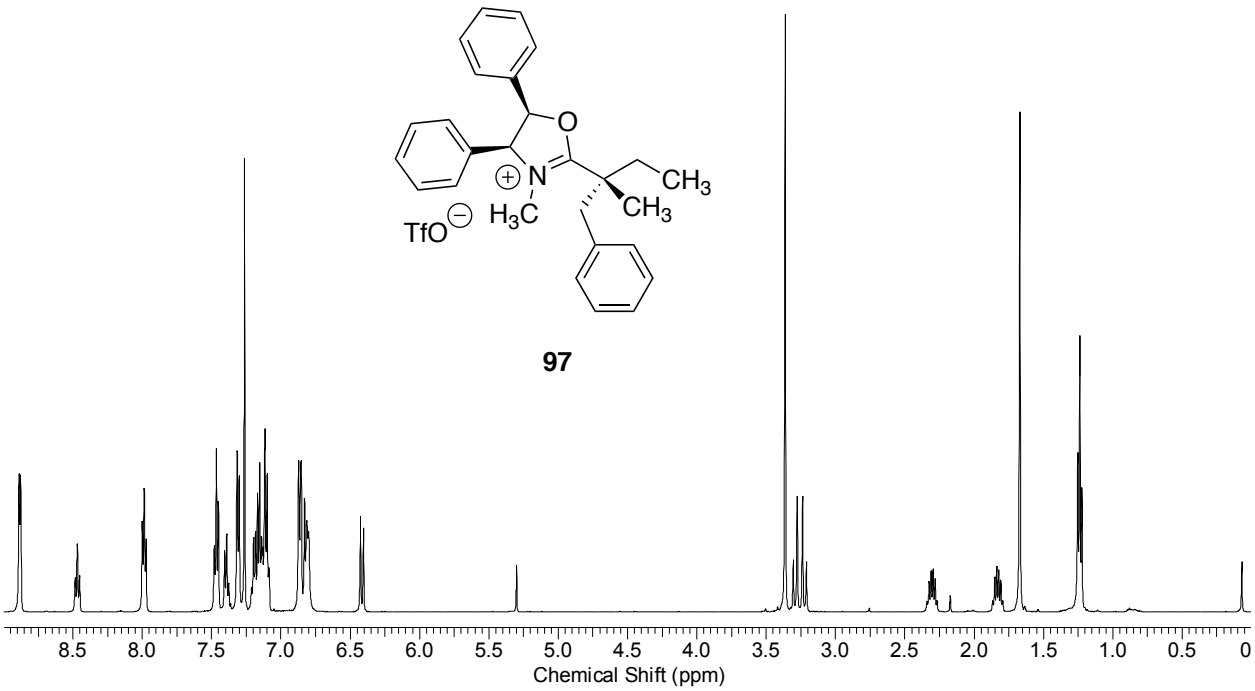
Chemical Shift (ppm)

57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N
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CH3
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TfO
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5.0
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1.5
1.0
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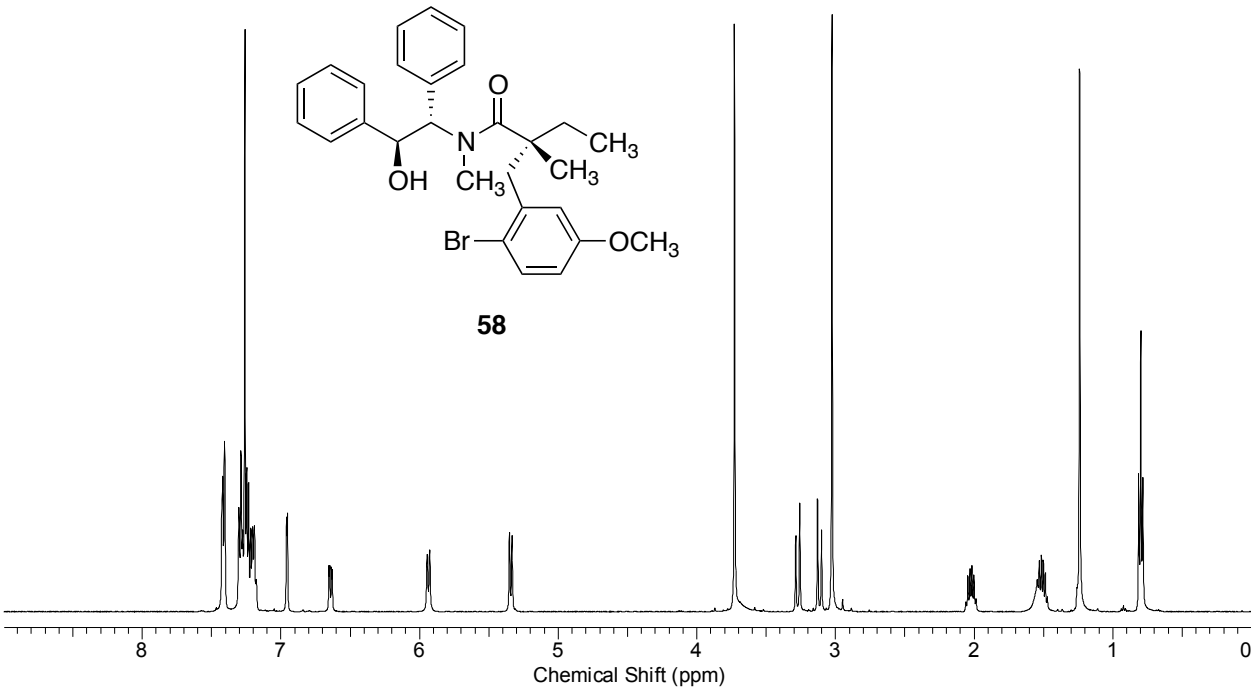
0
Chemical Shift (ppm)

97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N
CH3
CH3
OH
CH3
Br
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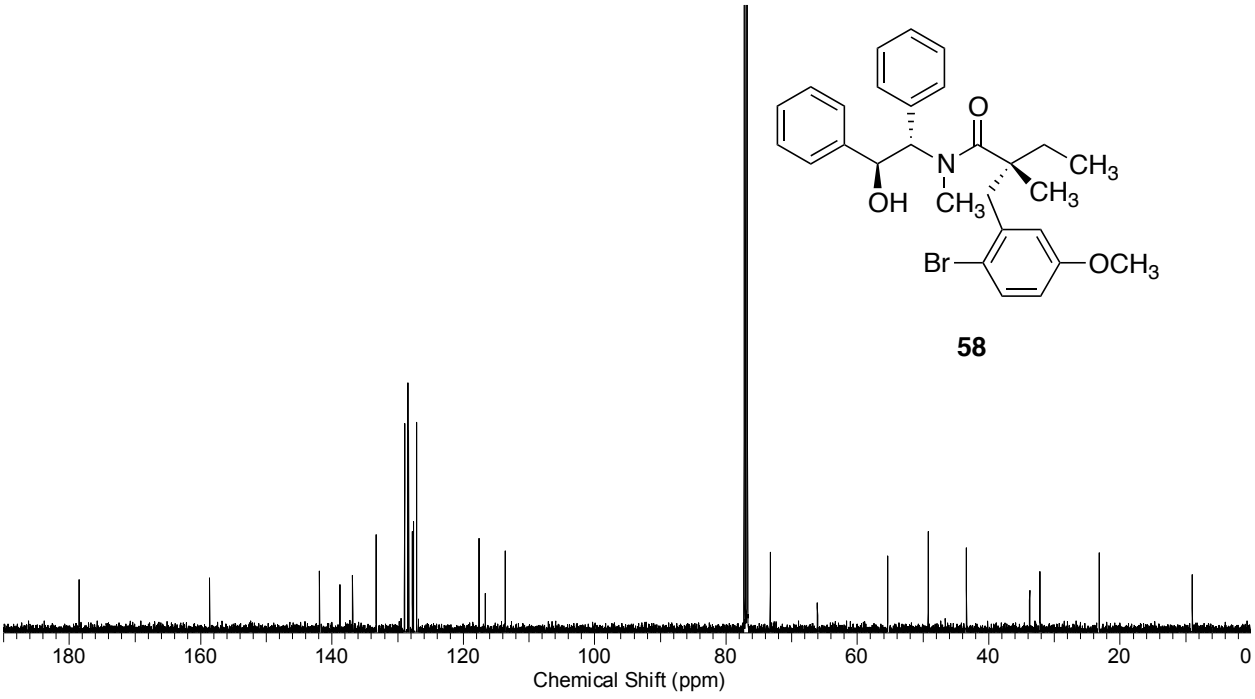
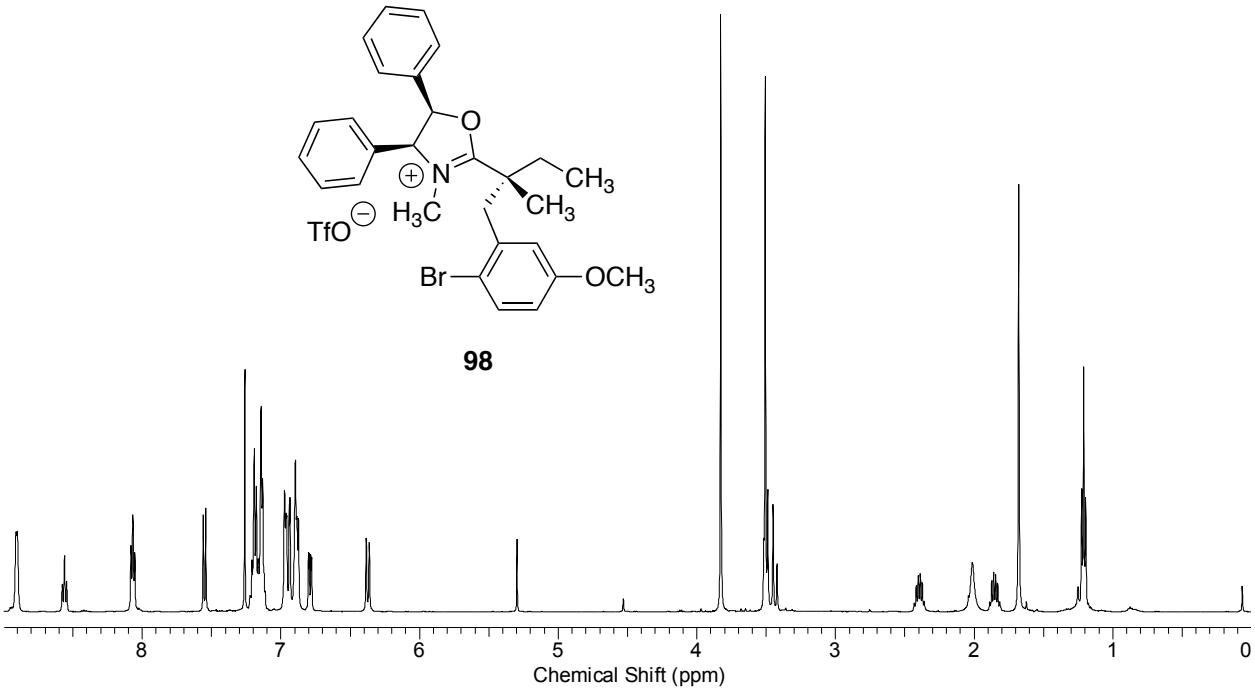
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

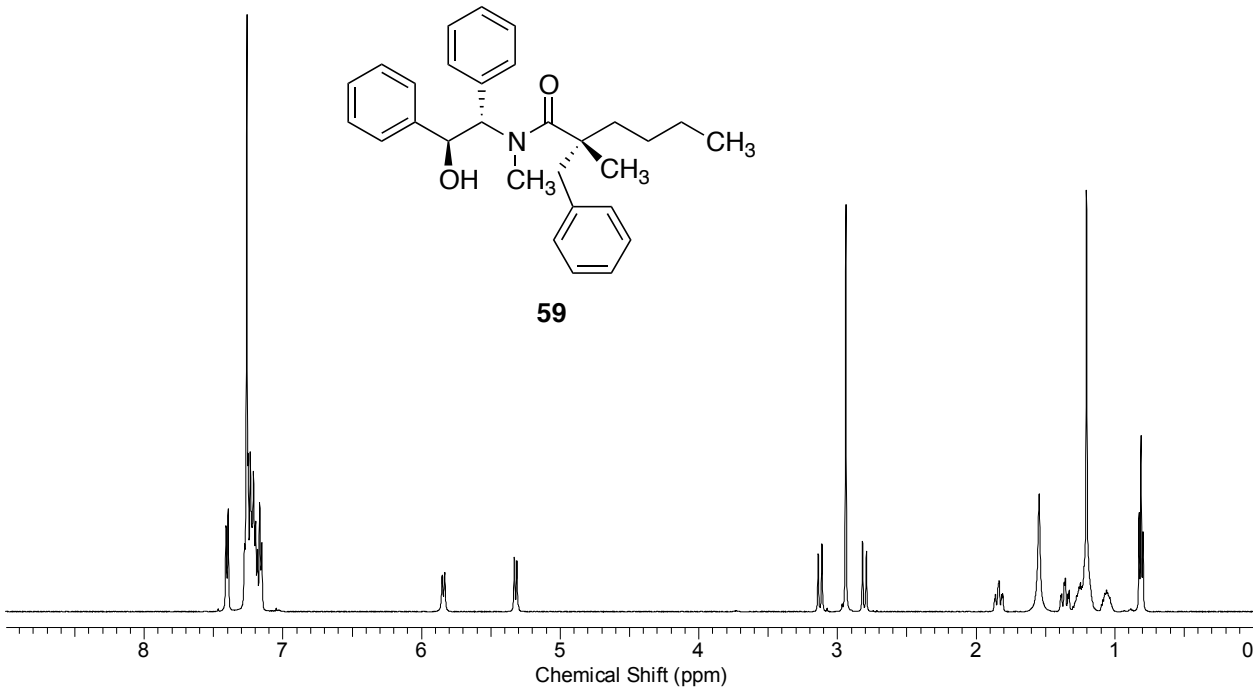
58


O
N
CH3
CH3
OH
CH3
Br
OCH3
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

58



98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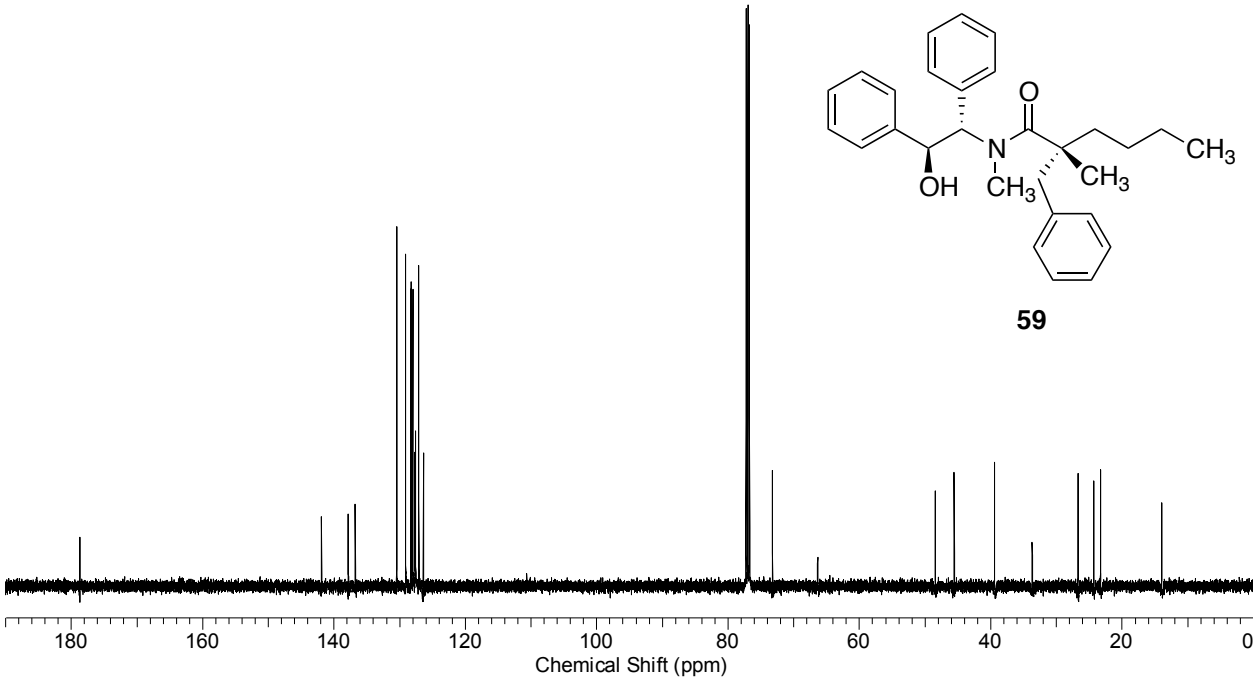
N
OH
CH3
CH3
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

59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OH
CH3
CH3
CH3
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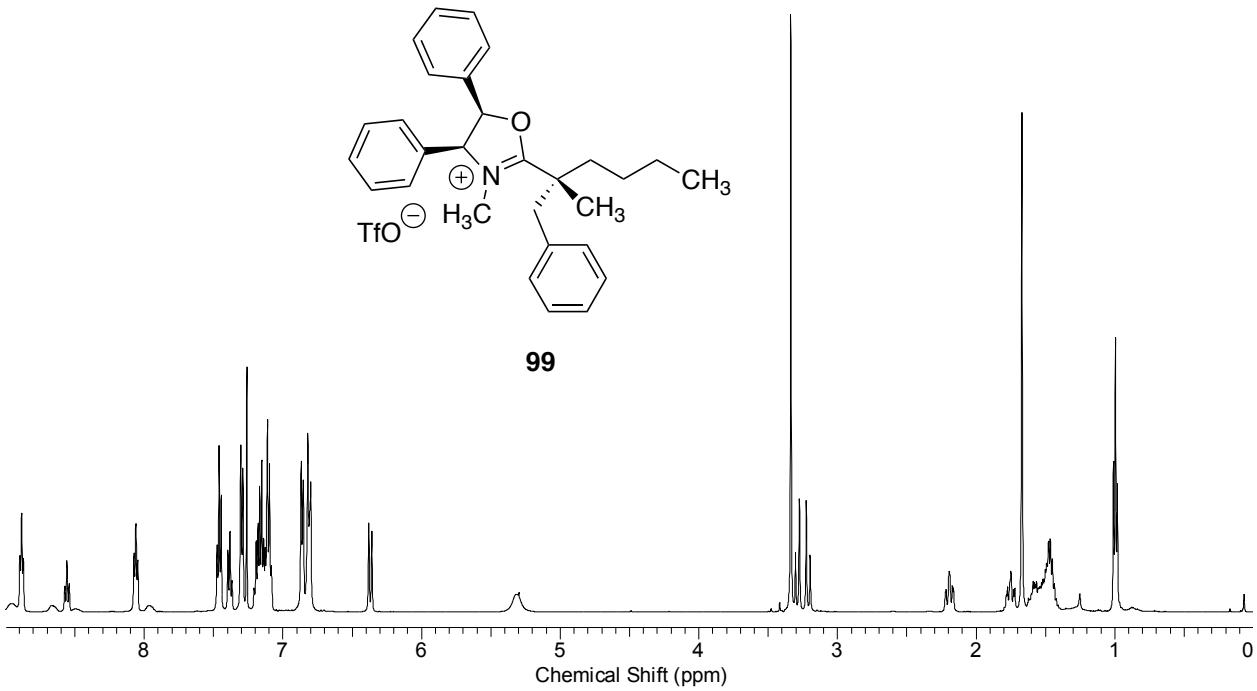
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

59



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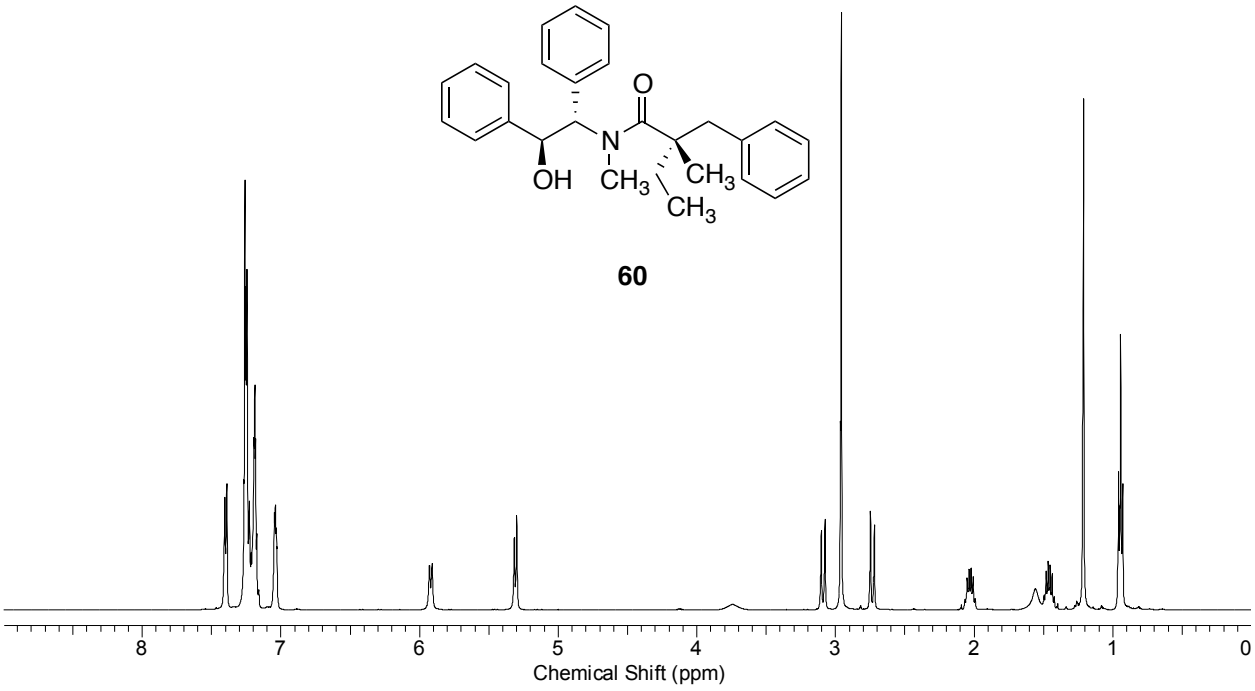
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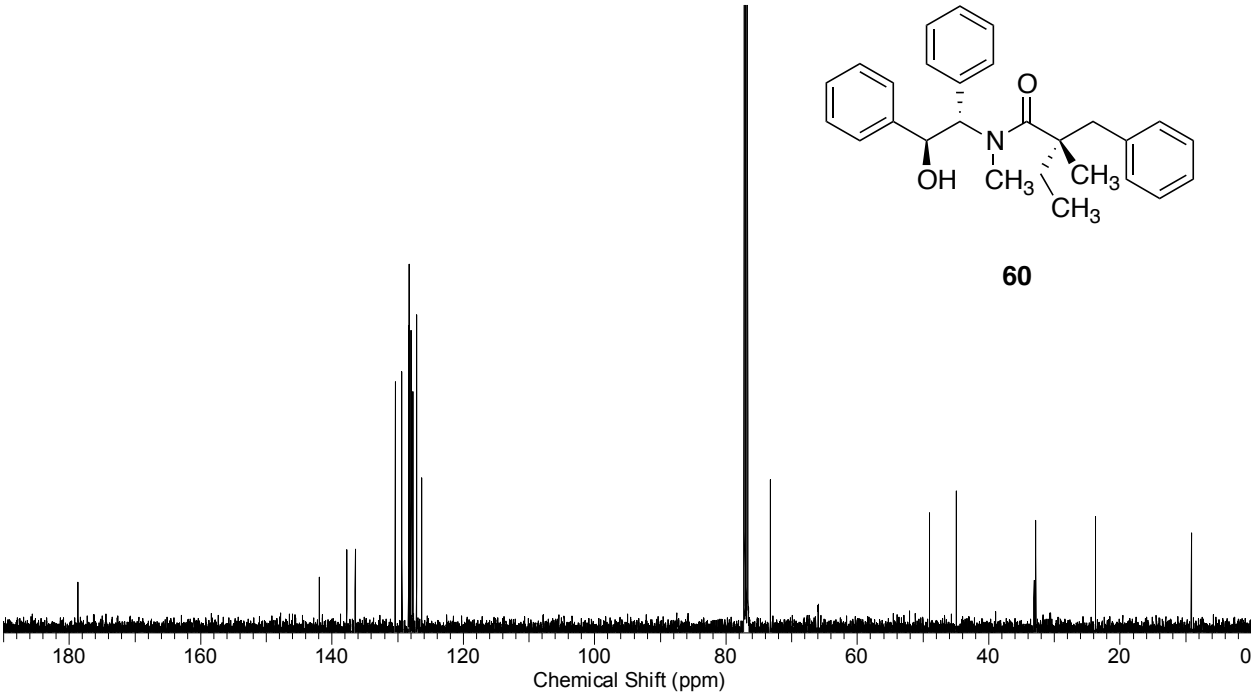
OH
CH3
CH3
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

60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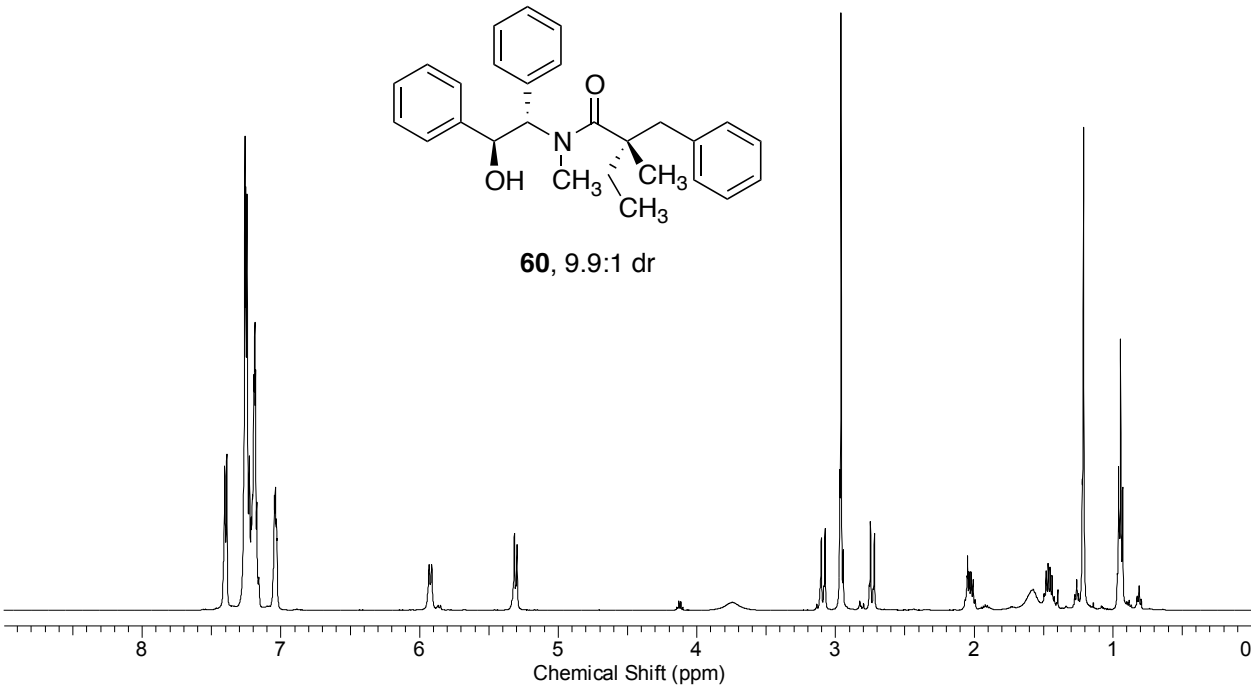
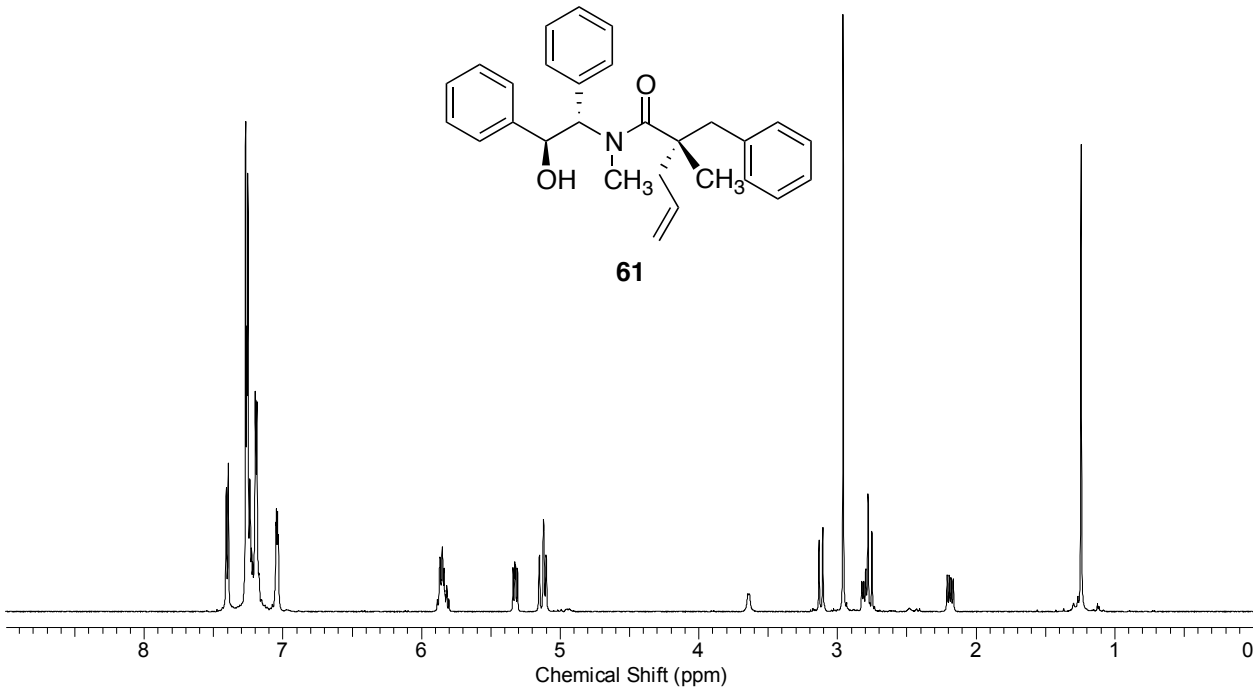
N
OH
CH3
CH3
CH3
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

60



60, 9.9:1 dr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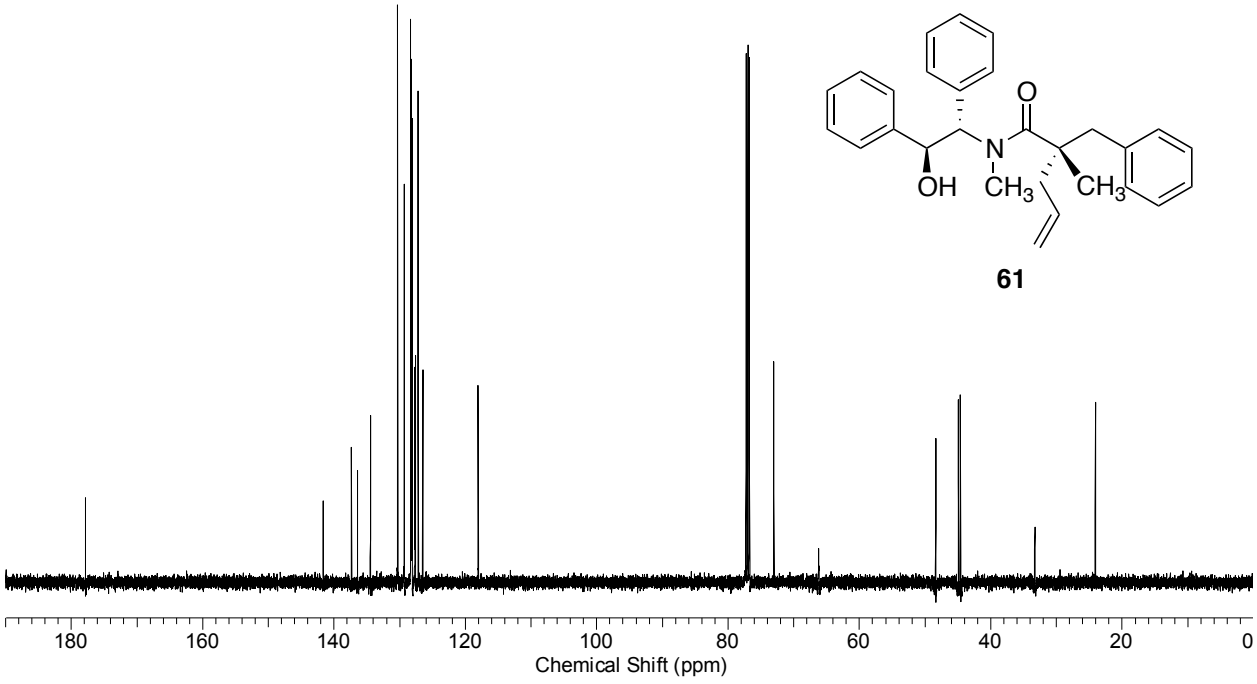
N
OH
CH3
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

61


O
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OH
CH3
CH3
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80
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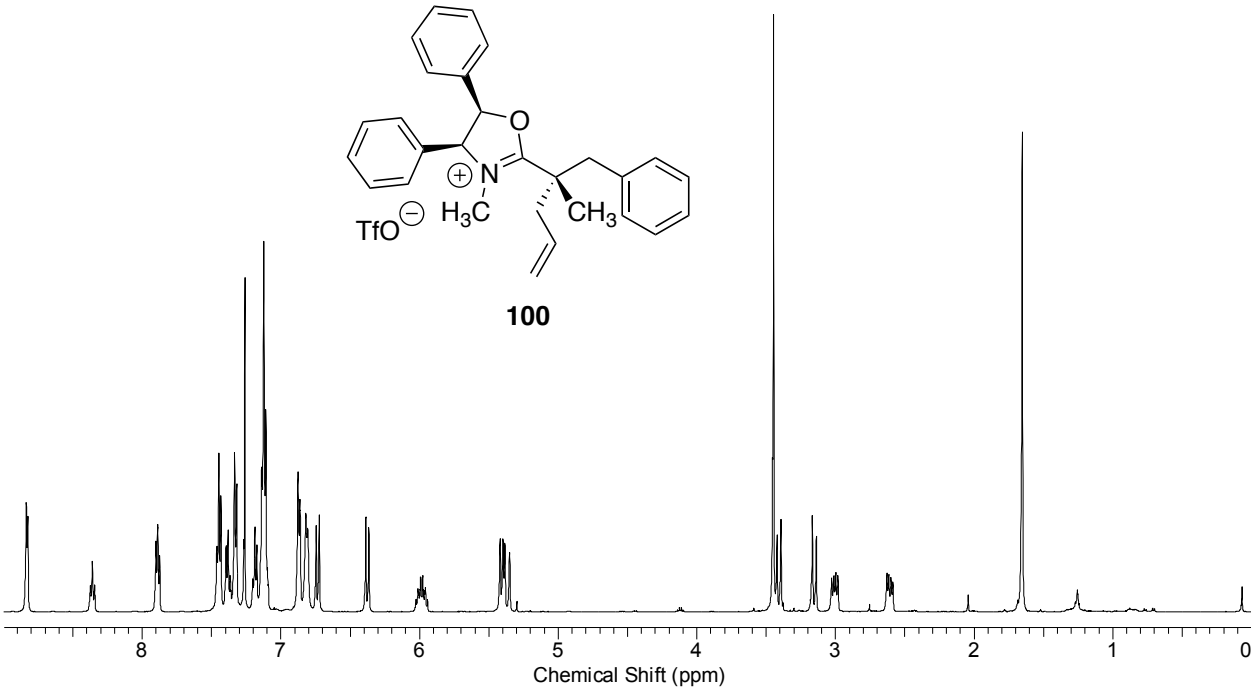
40
20
0
Chemical Shift (ppm)

61



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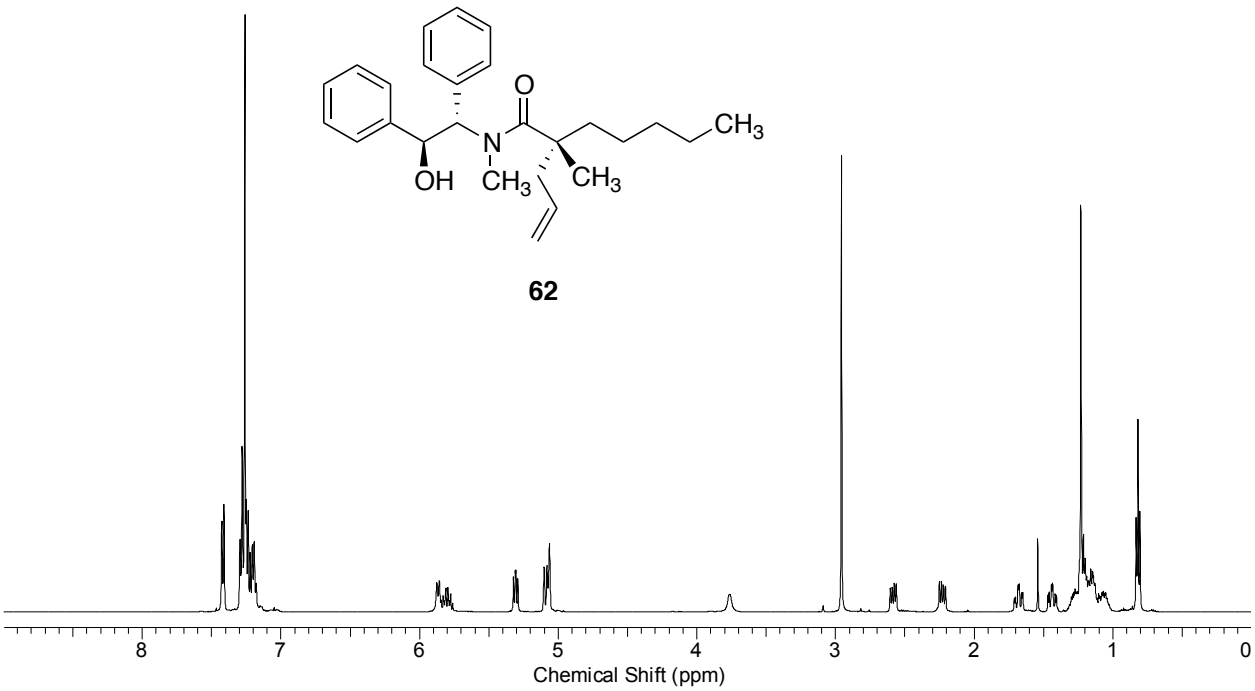
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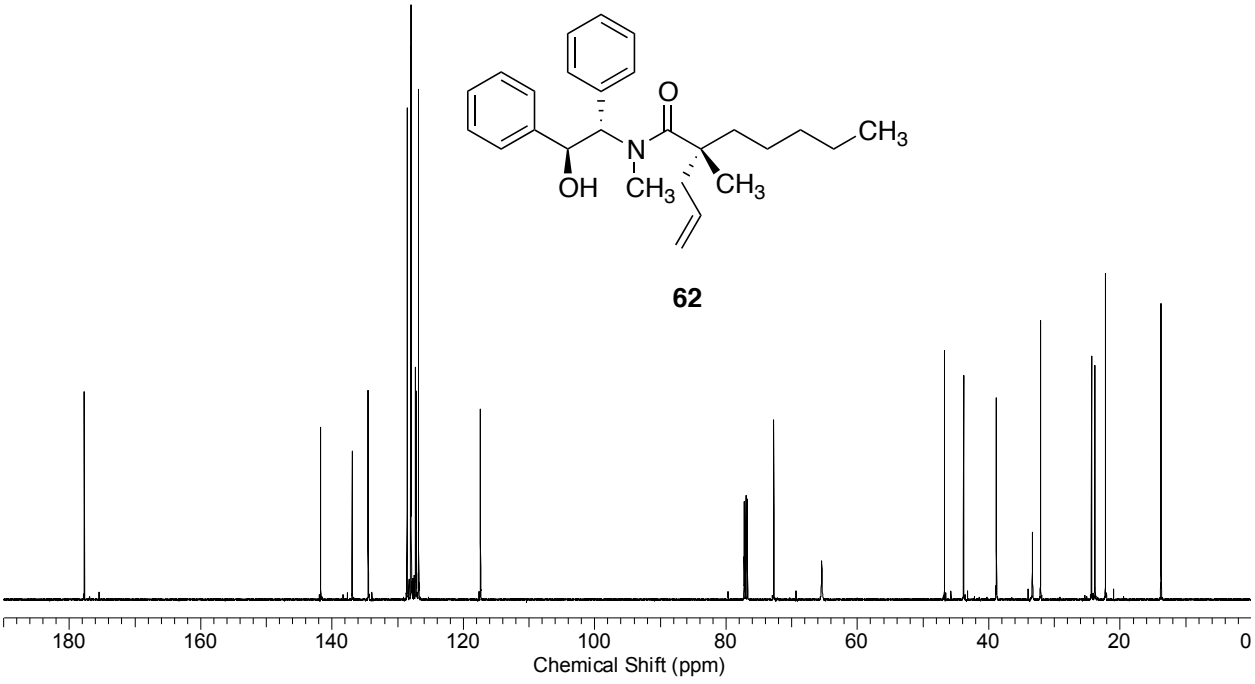
N
CH3
OH
CH3
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

62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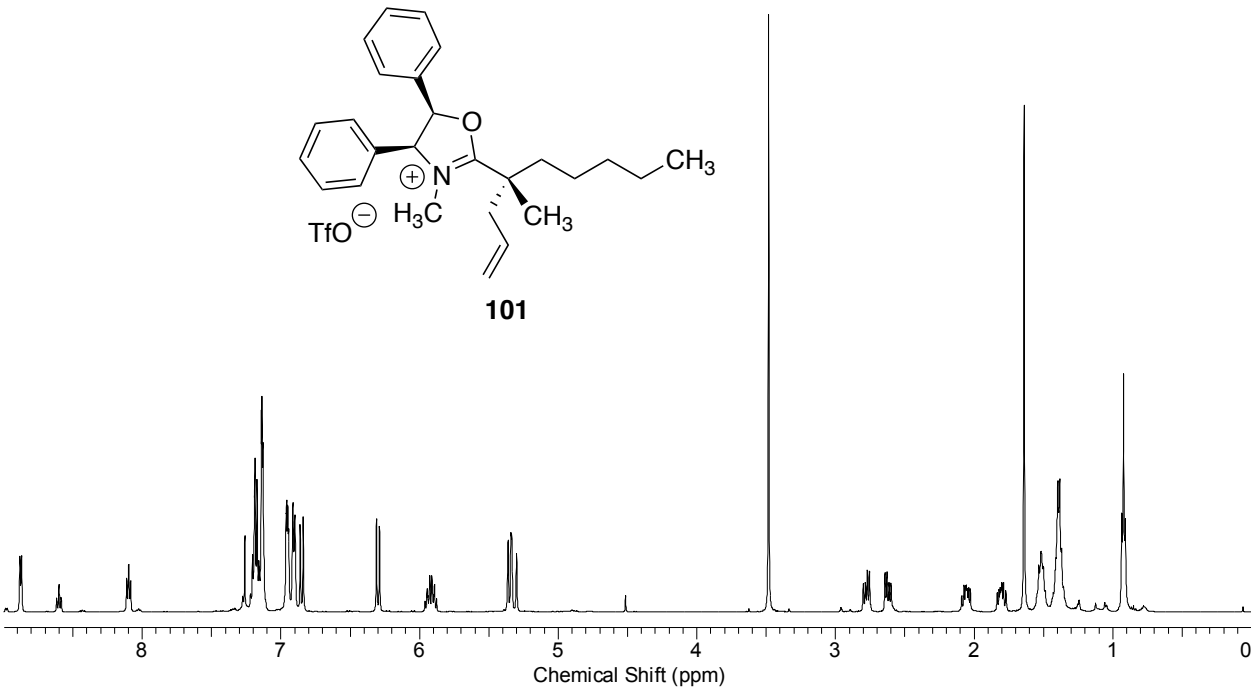
N
CH3
OH
CH3
CH3
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

62



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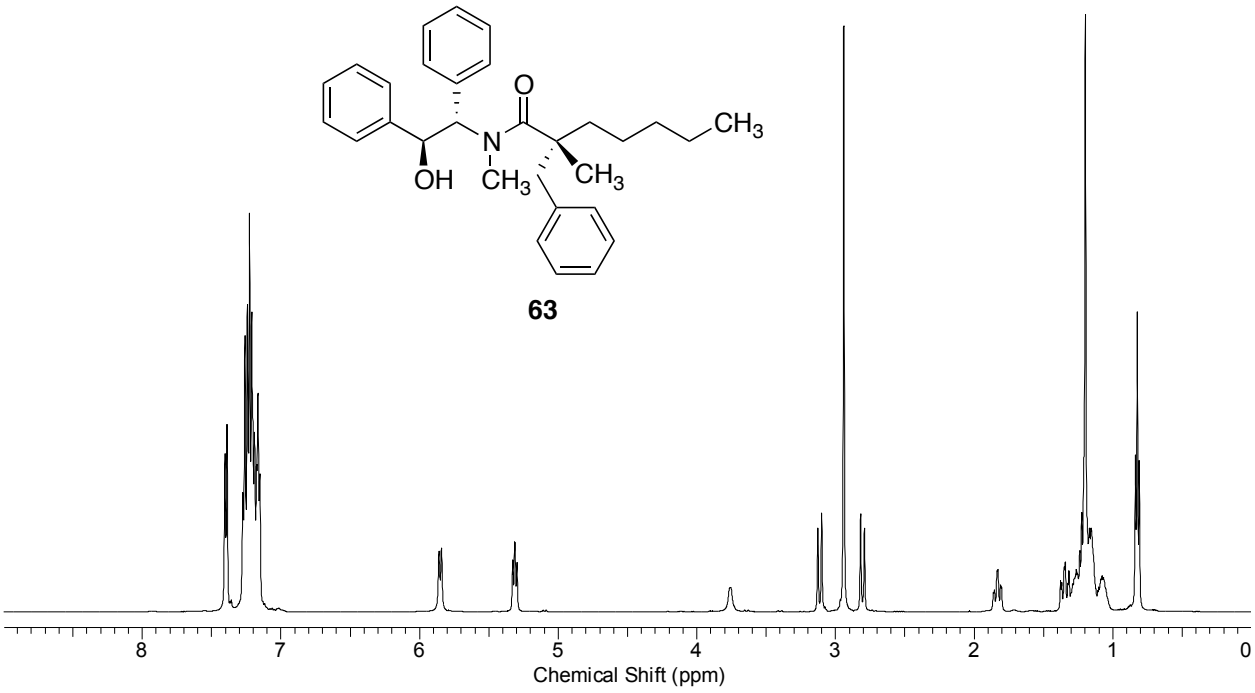
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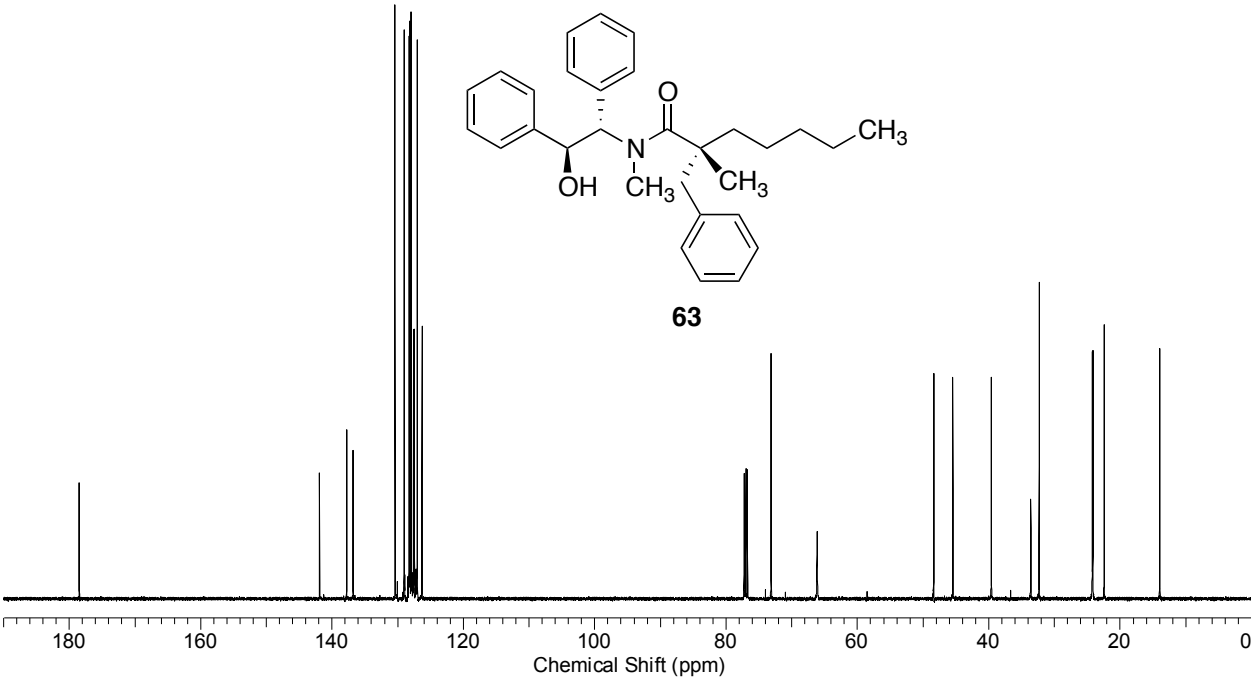
OH
CH3
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

63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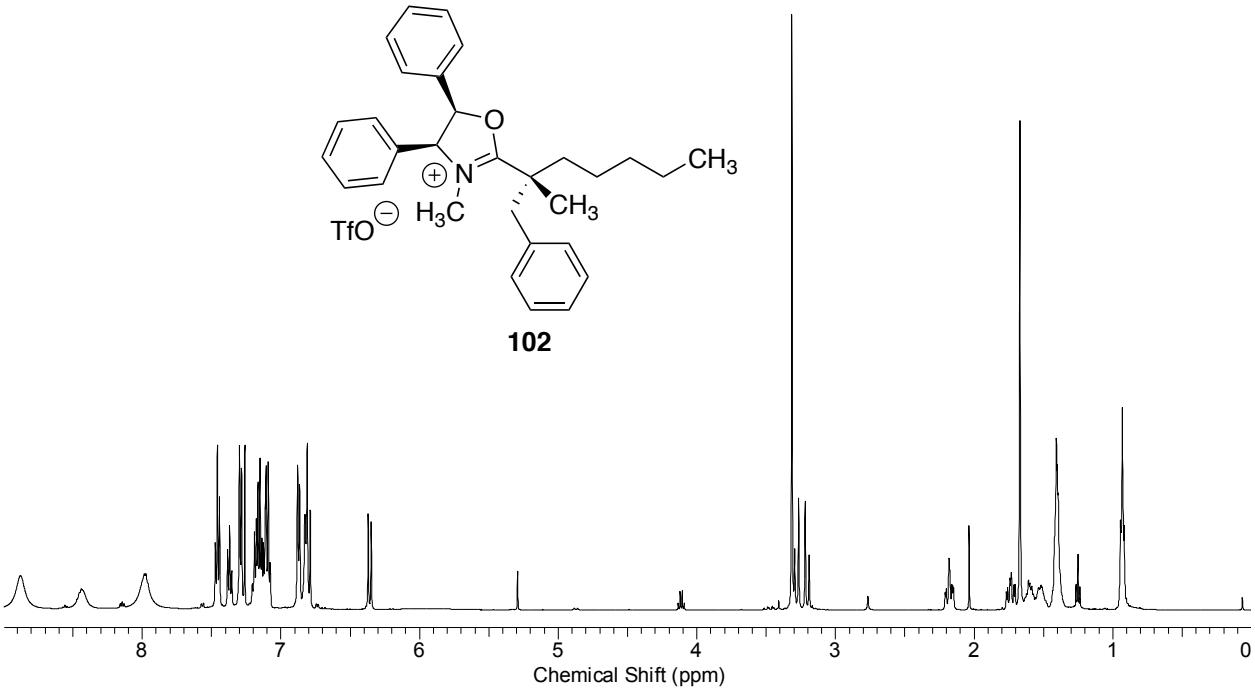
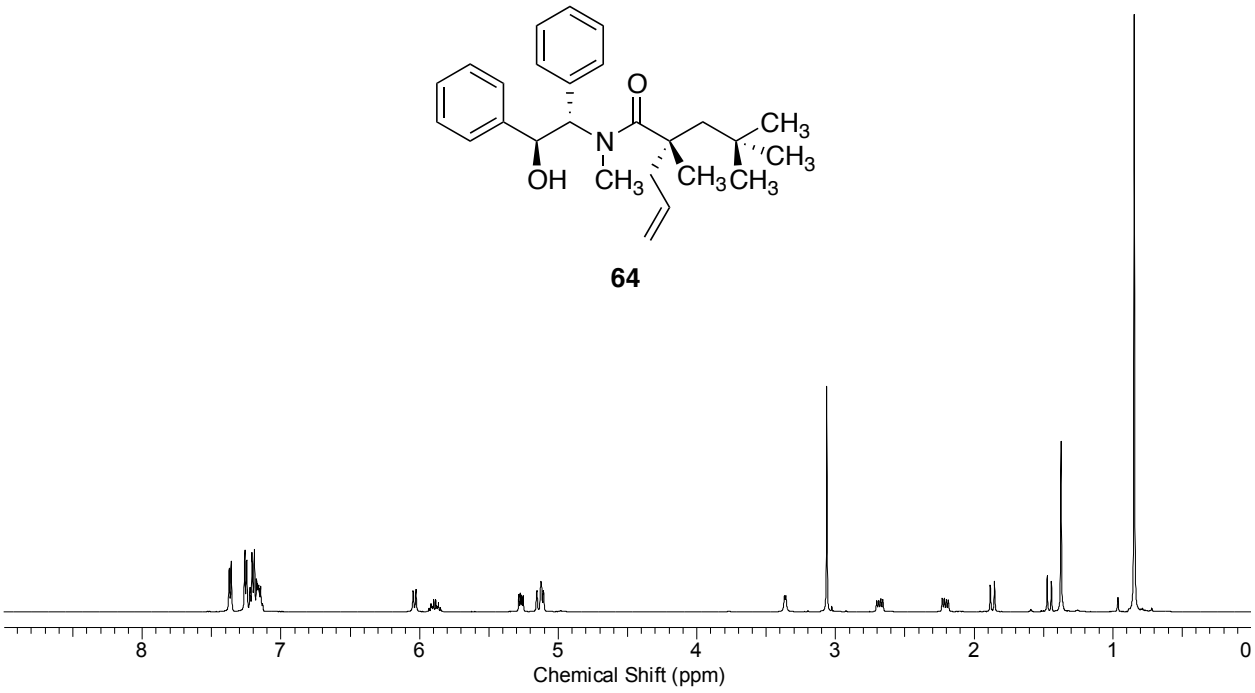
CH3
OH
CH3
CH3
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

63



102


O
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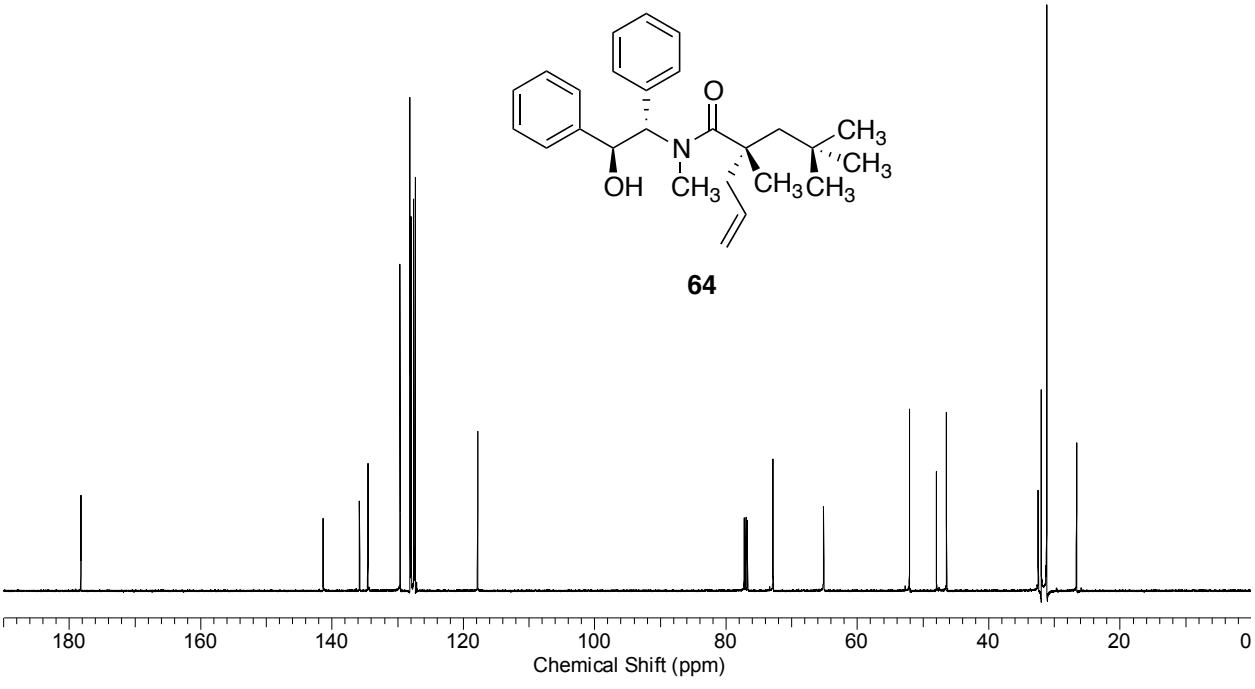
OH
CH3
CH3
CH3
CH3
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

64


O
N
OH
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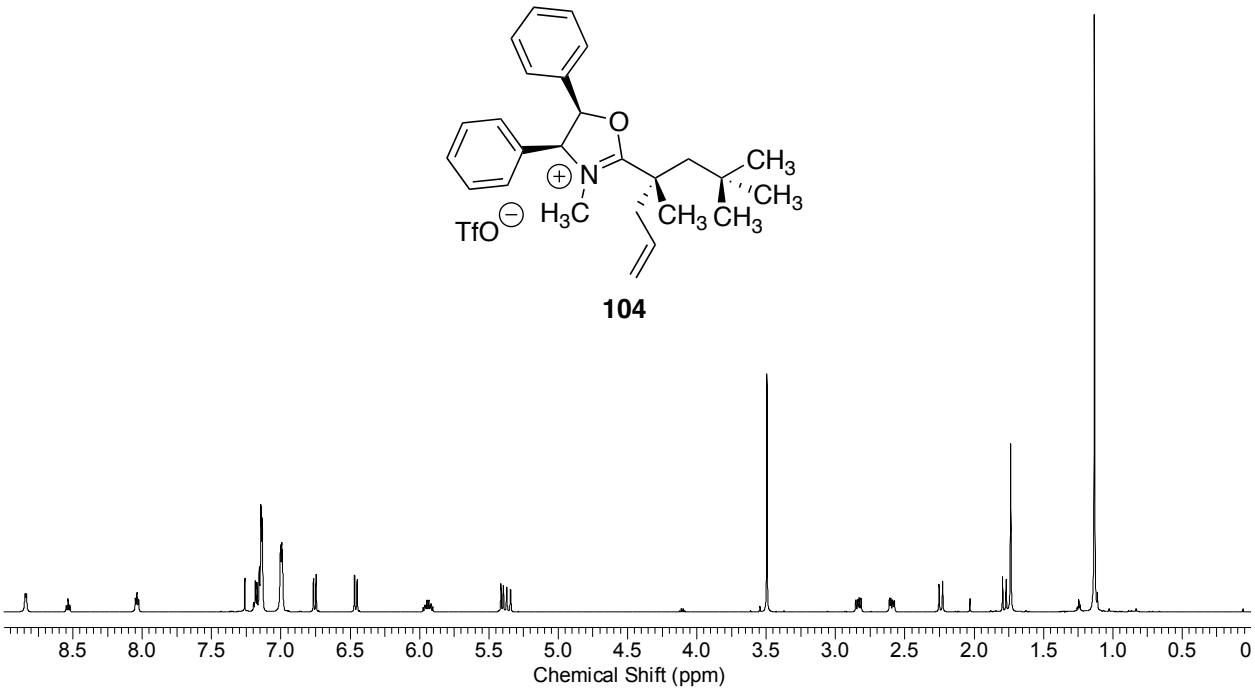
CH3
CH3
CH3
CH3
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

64


O
N
CH3
CH3
CH3
TfO
H3C
CH3 CH3
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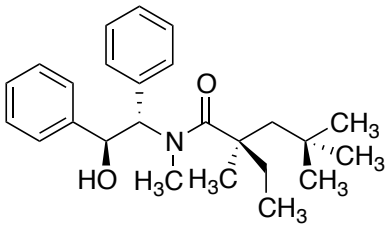
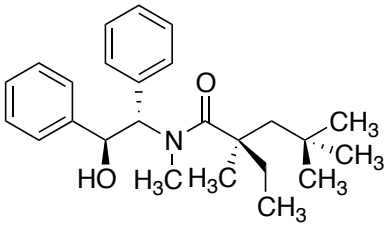
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

104


O
N
HO
H_3C H_3C
CH_3
CH_3
CH_3
CH_3

65

8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


O
N
HO
H_3C H_3C
CH_3
CH_3
CH_3
CH_3

65

180
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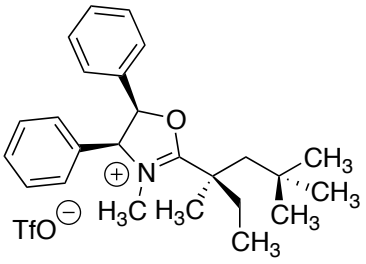
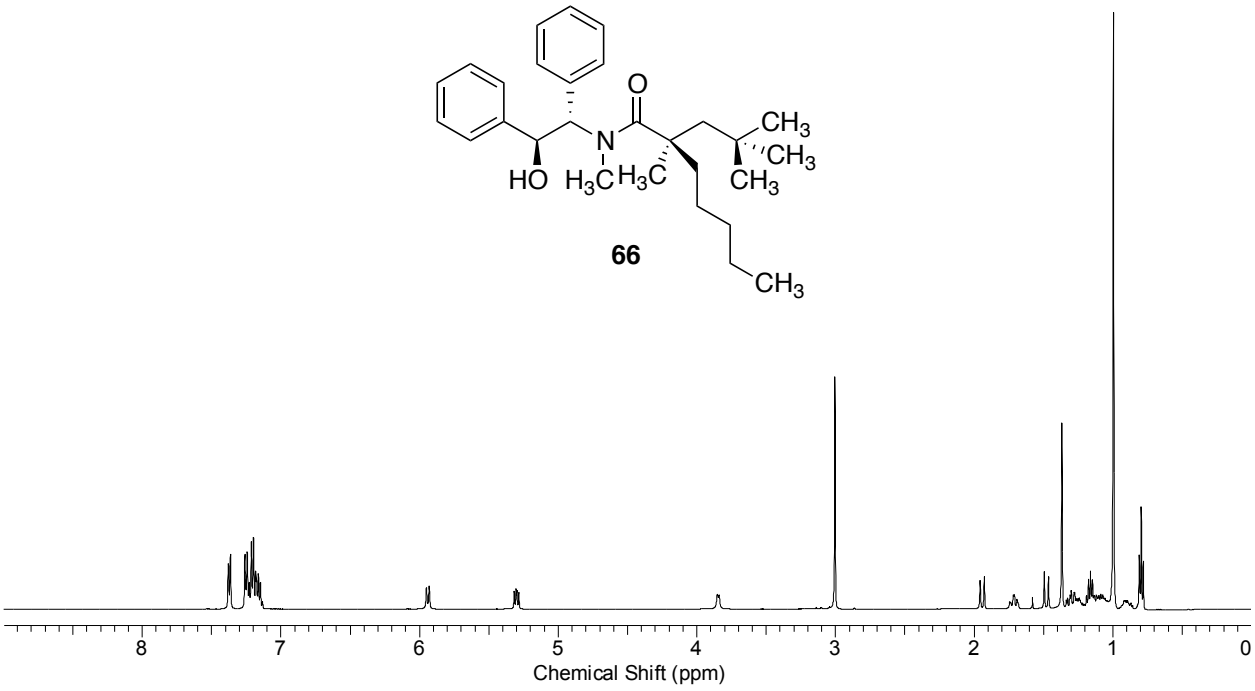
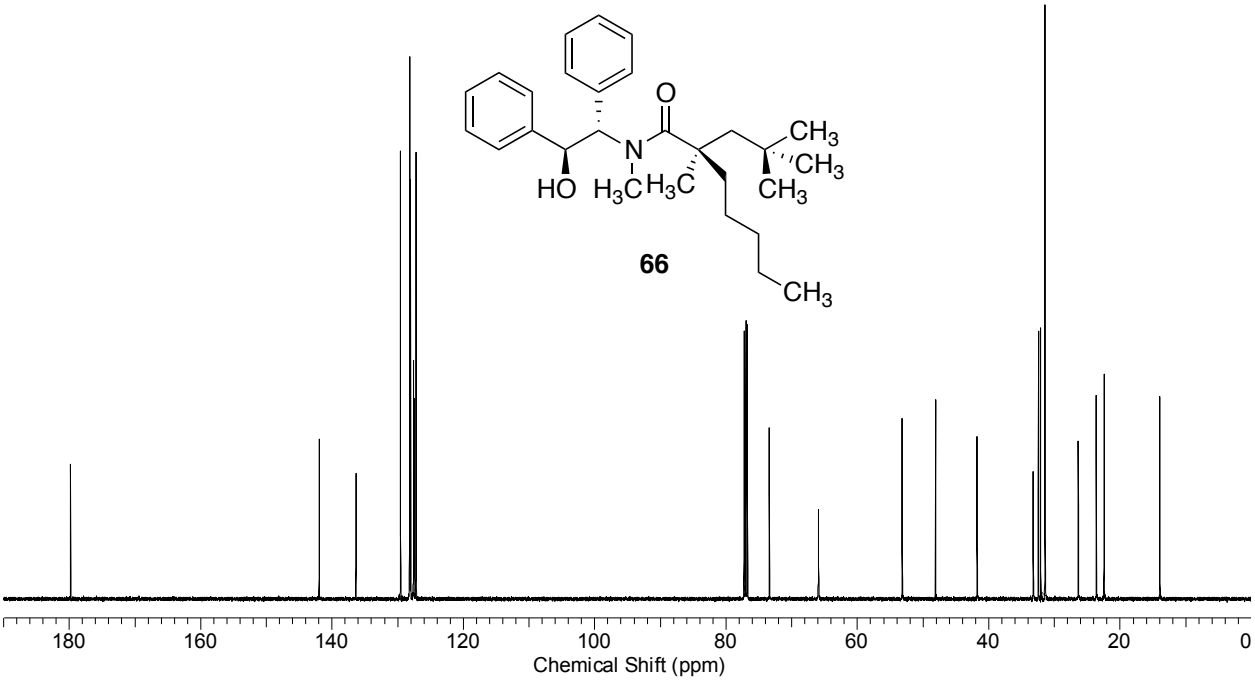
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


O
N
CH_3
CH_3
CH_3
H_3C H_3C
TfO
CH_3

105

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


O
N
HO
H_3C
H_3C
CH_3
CH_3
CH_3
CH_3
66
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


O
N
HO
H_3C
H_3C
CH_3
CH_3
CH_3
CH_3
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180
160
140
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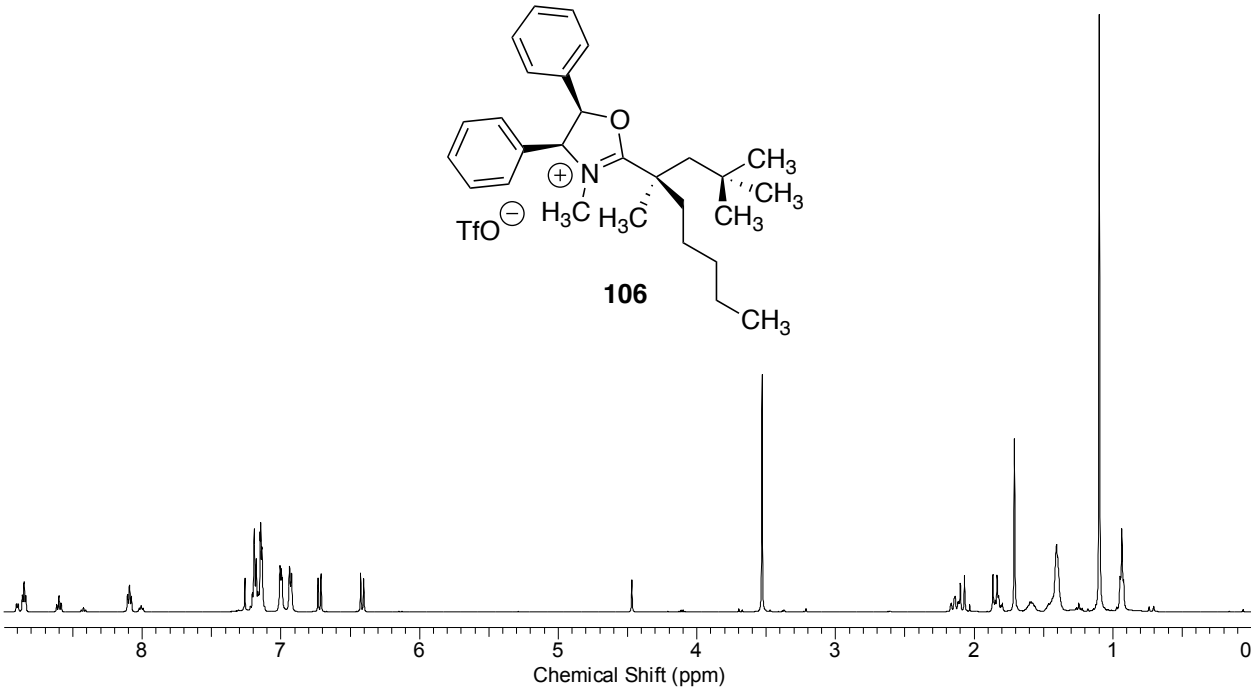
100
80
60
40
20
0
Chemical Shift (ppm)



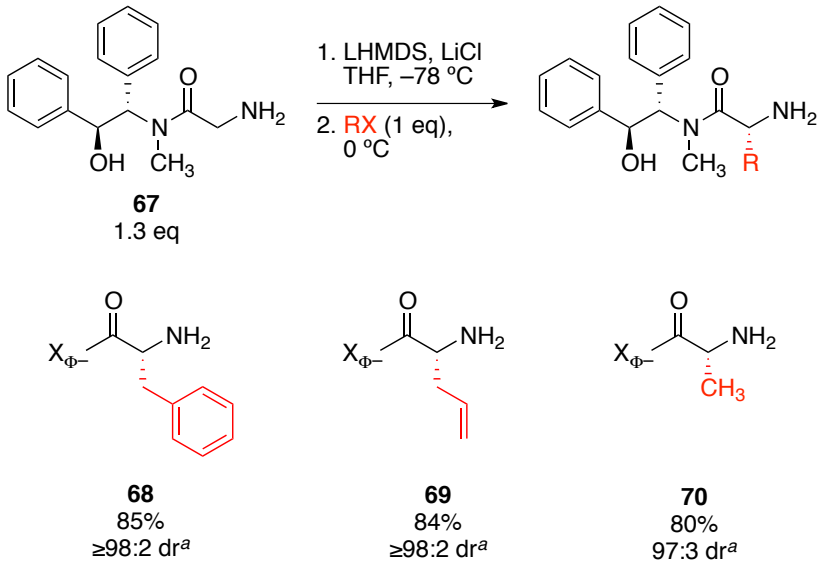
106

Chapter 3

On the Synthesis of α-Methyl α-Amino Acids

Introduction

As discussed in Chapter 1, pseudoephedrine glycinamide serves as a platform for the synthesis of α-amino acids.[34] Similarly, pseudoephenamine glycinamide (**67**) may be employed in the asymmetric synthesis of α-amino amides, with yields and diastereoselectivities comparable to those of the previously reported methodology (Scheme 3.1).



Scheme 3.1 Representative alkylations of pseudoephenamine glycinamide to give α-amino amides. X = Br, I. [a] crude dr.

Following the success of these alkylation reactions, the synthesis of α,α-disubstituted α-amino amides via the alkylation of enolates generated from monosubstituted amino amides was investigated. Such an alkylation is unreported in the pseudoephedrine literature and would represent an advance in the alkylation reactions directed by acyclic chiral auxiliaries. Unfortunately, attempts to alkylate substrates such as **68–70** were unsuccessful; treatment of the monosubstituted α-amino amides with two equivalents of LHMDS or LDA followed by addition of an alkyl halide led to exclusive *N*-alkylation of the substrates, presumably due to the inability of the putative *N*,*O*-dianion to tautomerize to the desired enolate.

To prevent this troublesome *N*-alkylation, protection of the amino group as an imine – a strategy with precedent in the synthesis of amino acids[67] – was investigated. After screening a number of imines in the model alkylation of pseudoephenamine alaninamide,[68] it was determined that protection of the amino group as its pivaldimine enabled high-yielding and highly diastereoselective alkylation reactions. As the following sections will illustrate, pseudoephenamine alaninamide pivaldimine now serves as a versatile starting material for the synthesis of α-methyl α-amino acids,[69] which have important applications in many areas of biology.[70,71,72,73]

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[67] For selected uses of imines in the context of enolate alkylations to form amino acids, see: (a) Ojima, I.; Chen, H. C.; Nakahashi, K. *J. Am. Chem. Soc.* **1988**, *110,* 278–281. (b) Ayoub, M.; Chassaing, G.; Loffet, A.; Lavielle, S. *Tetrahedron Lett.* **1995**, *36,* 4069–4072. (c) Meyer, L.; Poirier, J.; Duhamel, P.; Duhamel, L. *J. Org. Chem.* **1998**, *63,* 8094–8095.

[68] Hugelshofer, C. L. (2012) *Synthesis of Quaternary a-Methyl a-Amino Acids by Asymmetric Alkylation of Pseudoephenamine Alaninamide Pivaldimines*. Master's Thesis, Harvard University.

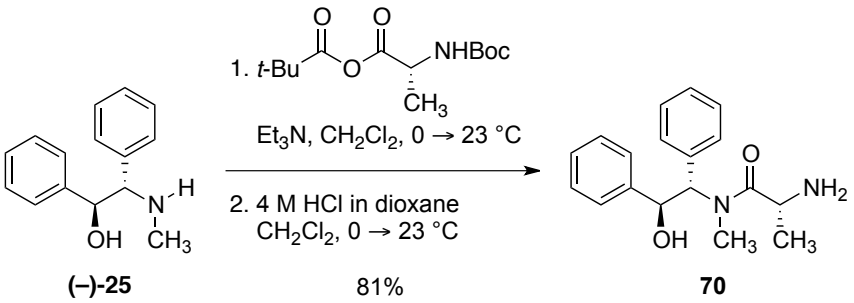
[69] Efforts to extend the present method to alkylate higher α-alkyl pivaldimines (replacing α-methyl with α-benzyl or α-ethyl) were not successful.

[70] This class of amino acids has documented utility in a number of biological applications. In stapled peptides: (a) Schafmeister, C. E.; Po, J.; Verdine, G. L. *J. Am. Chem. Soc.* **2000**, *122,* 5891–5892. (b) Bird, G. H.; Bernal, F.; Pitter, K.; Walensky, L. D. *Models in Enzymology* **2008**, *446,* 369–386. In enzyme inhibition: (c) Sourkes, T. L. *Arch. Biochem. Biophys.* **1945**, *51,* 444. (d) Thaisrivongs, S.; Pals, D. T.; Lawson, J. A.; Turner, S. R.; Harris, D. W. *J. Med. Chem.* **1987**, *30,* 536–541. In small molecule therapeutics: (e) Kelly, T. A.; Jeanfavre, D. D.; McNeil, D. W.; Woska, Jr., J. R.; Reilly, P. L.; Mainolfi, E. A.; Kishimoto, K. M.; Nabozny, G. H.; Zinter, R.; Bormann, B.; Rothlein, R. *J. Immunol.* **1999**, *163,* 5173–5177. In enzyme mechanism elucidation: (f) Fasella, P.; Giartosio, A.; Hammes, G. G. *Biochemistry* **1966**, *5,* 197–202. In the stabilization of peptide secondary structure: (g) Hinds, M. G.; Welsh, J. H.; Brennand, D. M.; Fisher, J.; Glennie, M. J.; Richards, N. G. J.; Turner, D. L.; Robinson, J. A. *J. Med. Chem.* **1991**, *34,* 1777–1789. Imparting resistance to peptide degradation: Khosla, M.C.; Stachowiak, K.; Smeby, R.R.; Bumpus, F.M.; Piriou, F.; Lintner, K.; Fermandjian, S. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78,* 1981.

[71] For recent reviews of the asymmetric synthesis of quaternary α-amino acids, see: (a) Cativiela, C.; Díaz-de-Villegas, M. *Tetrahedron: Asymmetry* **2007**, *18,* 569–623. (b) Cativiela, C.; Ordoñez, M. *Tetrahedron: Asymmetry* **2009**, *20,* 1–63.

Synthesis of Pseudoephenamine Alaninamide Pivaldimine

Synthesis of either diastereomer of (*S*,*S*)-pseudoephenamine alaninamide was achieved in a brief two-step process. First, pseudoephenamine was treated with the mixed anhydride formed from either enantiomer of *N*-Boc alanine and pivaloyl chloride.[74] In the following step, the amino group was deprotected with a solution of hydrochloric acid in dioxane [75] to furnish pseudoephenamine alaninamide (exemplified in the synthesis of (1*S*,2*S*)-pseudoephenamine (*R*)-alaninamide, **70**, Scheme 3.2).



Scheme 3.2 Synthesis of (1*S*,2*S*)-pseudoephenamine (*R*)-alaninamide.

---

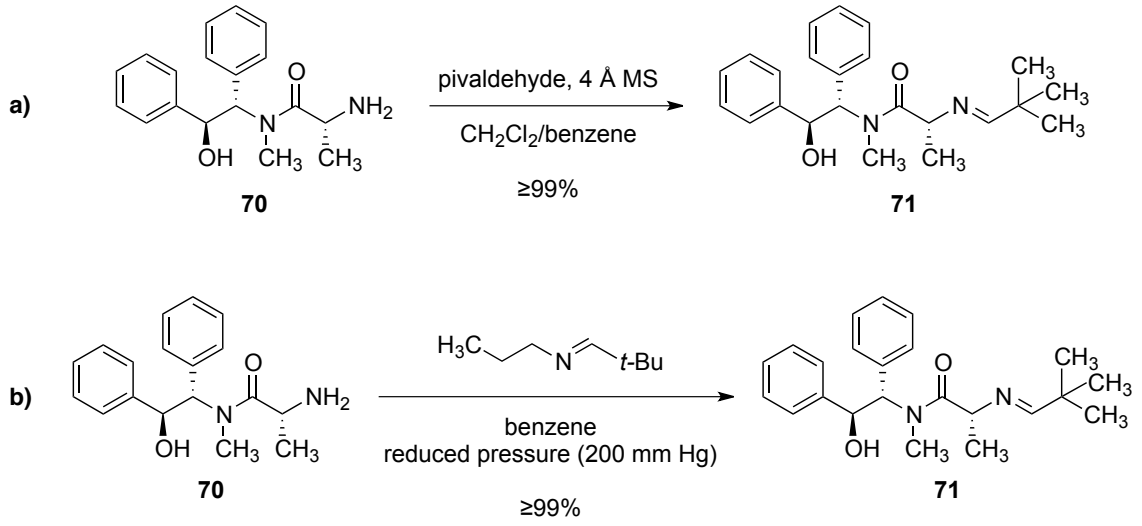
[72] For selected references describing chiral auxiliary-based methods for the asymmetric synthesis of quaternary α-methyl α-amino acids, see: (a) Schöllkopf, U.; Hausberg, H. H.; Hoppe, I.; Segal, M.; Reiter, U. *Angew. Chem. Int. Ed.* **1978**, *17,* 117–119. (b) Seebach, D.; Aebi, J. D.; Naef, R.; Weber, T. *Helv. Chim. Acta* **1985**, *68,* 144–154. (c) Williams, R. M.; Im, J. *J. Am. Chem. Soc.* **1991**, *113,* 9276–9286. (d) Berkowitz, D.B.; Smith, M. K. *J. Org. Chem.* **1995**, *60,* 1233–1238. (e) Alonso, F.; Davies, S. G.; Elend, A. S.; Haggitt, J. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 257–264. (f) Chinchilla, R.; Galindo, N.; Nájera, C. *Synthesis* **1999**, 704–717. (g) Lu, T.; Lin, C. *J. Org. Chem.* **2011**, *76,* 1621–1633.

[73] For selected references describing alternative methods for the asymmetric synthesis of quaternary α-methyl α-amino acids, see: (a) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122,* 5228–5229. (b) Trost, B.M.; Dogra, K. *J. Am. Chem. Soc.* **2002**, *124,* 7256–7257. (c) Vachal, P.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2002**, *124,* 10012–10014. (d) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125,* 5634–5635. (e) Smith, N.D.; Wohlrab, A.M.; Goodman, M. *Org. Lett.* **2005**, *7,* 255–258.

[74] Vaughan, Jr., J. R.; Osato, R. L. *J. Am. Chem. Soc.* **1951**, *73,* 5553–5555.

[75] Peterson, E. A.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2009**, *48*, 6328–6331.

Protection of the amino group of the alaninamides as their pivaldimines was accomplished using one of two different methods. The most direct procedure involved the condensation of pivaldehyde with pseudoephenamine alaninamide in the presence of 4 Å molecular sieves in a mixed solvent of benzene and dichloromethane at 23 ºC (Scheme 3.3a). Conveniently, evaporation of the reaction solvents upon complete reaction followed by heating of the mixture overnight at 35 ºC under reduced pressure (<1 Torr) to remove excess pivaldehyde provided the desired pivaldimine **71** in high yield and in high purity (≥99% yield, ≥95% purity by ^{1}H and ^{13}C NMR). Alternatively, transimination[76] of pivaldehyde *N*-propyl imine with pseudoephenamine alaninamide gave pivaldimine **71** in comparable yield after evaporation of solvent and drying at elevated temperature and reduced pressure (Scheme 3.3b). The pivaldimine obtained using either method could be used in alkylation reactions without further purification.



Scheme 3.3 Synthesis of (1*S*,2*S*)-pseudoephenamine (*R*)-alaninamide pivaldimine by a) direct condensation of pseudoephenamine alaninamide with pivaldehyde or b) transimination with pivaldehyde *N*-propyl imine.

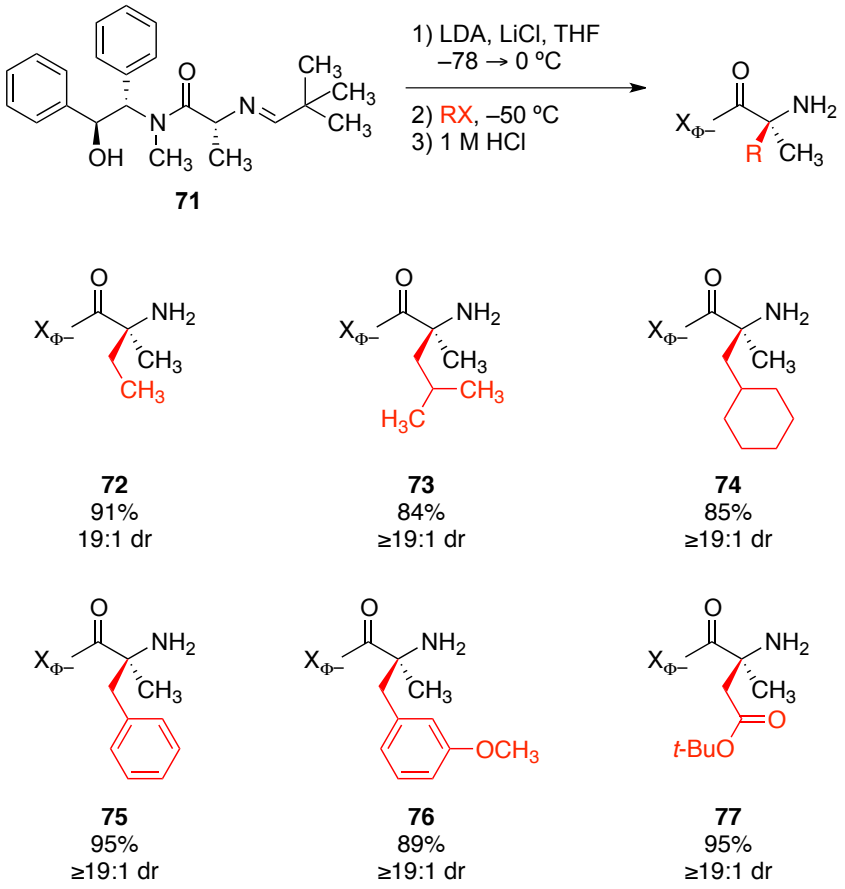
[76] (a) Smith, Jr., G. E. P.; Bergstrom, F. W. *J. Am. Chem. Soc.* **1934**, *56,* 2095–2098. (b) Cordes, E. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1962**, *84,* 826–831. (c) Leach, B. E.; Leussing, D. L. *J. Am. Chem. Soc.* **1971**, *93,* 3377–3384.

Alkylation of Pseudoephenamine Alaninamide Pivaldimine

Due to the possibility of matched and mismatched substrates, alkylation reactions employing both diastereomers of pseudoephenamine alaninamide pivaldimine were investigated. In the general procedure, a solution of either diastereomer of pseudoephenamine alaninamide pivaldimine (1 equiv) in dry tetrahydrofuran (THF) was transferred to a flask containing flame-dried lithium chloride (6.0 equiv), and the resulting slurry was cooled to –78 ºC. A solution of LDA (2.2 equiv) in THF was then added slowly down the side of the flask by cannula or syringe so as to allow the solution of base to cool before reaching the substrate solution. After complete addition and further stirring at –78 ºC for 5 minutes, the reaction flask was transferred to an ice water bath for 10 minutes before cooling to –50 ºC. An electrophile (2.5 equiv) was then added to the cold reaction solution, and the ensuing alkylation reaction was monitored by TLC (reaction times typically ranged from 1.5–3.5 h). When the reaction was judged to be complete, a solution of 1 N hydrochloric acid was added to the reaction mixture to induce hydrolysis of the *tert*-butyl imine function within the alkylated product, which typically occurred in less than 3 h at 23 ºC.

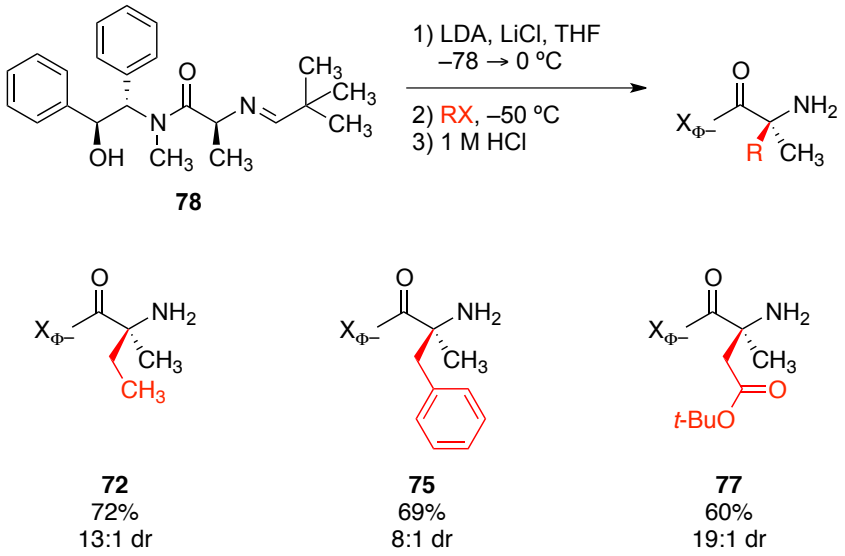
The alkylation reactions of (1*S*,2*S*)-pseudoephenamine (*R*)-alaninamide pivaldimine (**71)** are shown in Scheme 3.4 below. In all cases, diastereoselectivities equaled or exceeded 19:1 dr as determined by ^{1}H NMR analysis, and the solid products were isolated in 83-95% yield after flash-column chromatography. The configuration of benzylation product **75** was established by comparison with a sample of known configuration prepared by an independent route (see Experimental Information). The diastereomer formed arises from replacement of the α-C–H bond by α-C–benzyl with retention of configuration. This alkylation product and two others whose stereochemistry was established unambiguously (compounds **80** and **84** below) were

found to form a homochiral series, and the remaining compounds were presumed to have formed analogously.



Scheme 3.4 Alkylation reactions of (1*S*,2*S*)-pseudoephenamine (*R*)-alaninamide pivaldimine (**71**) to produce α-methyl α-amino amides. X = Br, I, OTf.

Scheme 3.5 summarizes the alkylation reactions of (1*S*,2*S*)-pseudoephenamine (*S*)-alaninamide pivaldimine (**78**) under conditions identical to those used for the alkylation of pivaldimine **71** above. Surprisingly, the major diastereomer obtained in the alkylation of pivaldimine **78** was the same major diastereomer produced in the alkylation of pivaldimine **71**. However, as evidenced by the lower yields and diastereoselectivities observed in these reactions, pivaldimine **78** was the mismatched diastereomer in these alkylations, making pivaldimine **71** the matched substrate.



Scheme 3.5 Alkylation reactions of (1*S*,2*S*)-pseudoephenamine (*S*)-alaninamide pivaldimine (**78**) to produce α-methyl α-amino amides. X = Br, I, OTf.

Given that both the matched and mismatched pivaldimines arrive at the same major diastereomer in the alkylation reactions, it is likely that both alkylations proceed through the same *E*-enolate intermediate upon deprotonation with LDA (Figure 3.1). Interestingly, this implies that deprotonation of pivaldimine **78** must occur along a trajectory impeded by the chiral auxiliary. If this is correct, then formation of the *Z*-enolate from the mismatched substrate must remain a higher energy pathway in spite of the fact that it would arise from deprotonation along a more favorable trajectory. An important factor in this process may be a developing repulsive electronic interaction between the enolate oxygen atom and the α-imino lone pair in the transition state for formation of the *Z*-enolate. The existence of an intermediate *E*-enolate in the alkylation of pivaldimine **71** was confirmed by NOE analysis of a cyclic siloxane obtained by trapping of this enolate with dichlorodiisopropylsilane (Scheme 3.6).

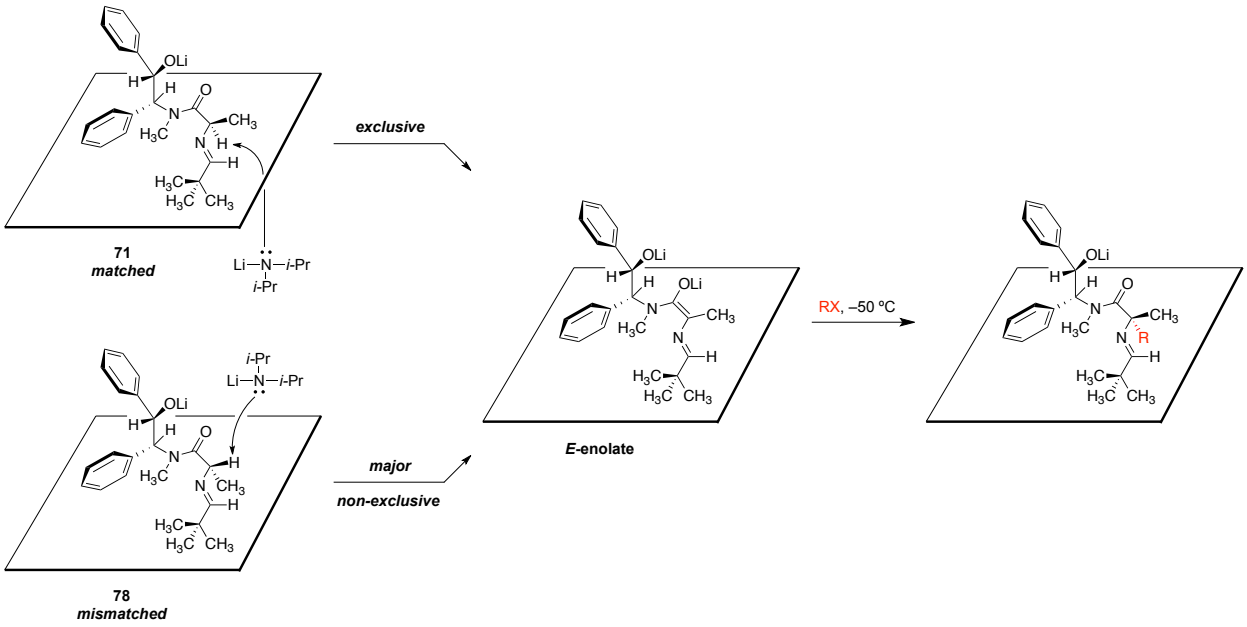
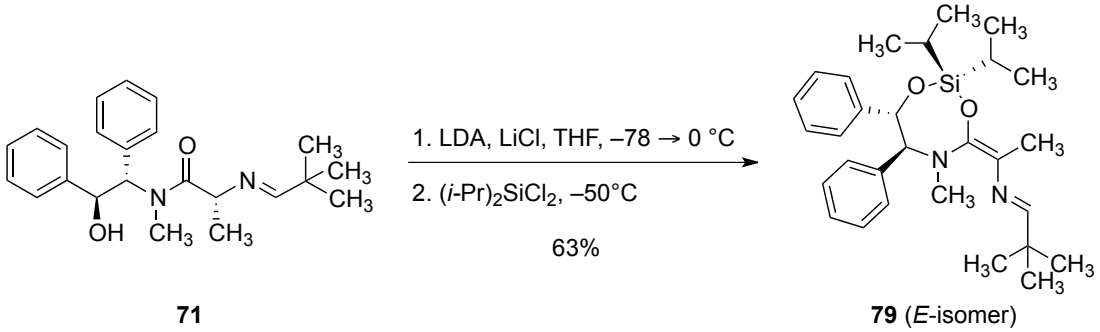


Figure 3.1 Proposed rationale for the stereochemical outcome of the alkylations of the matched and mismatched diastereomers of pseudoephenamine alaninamide pivaldimine.

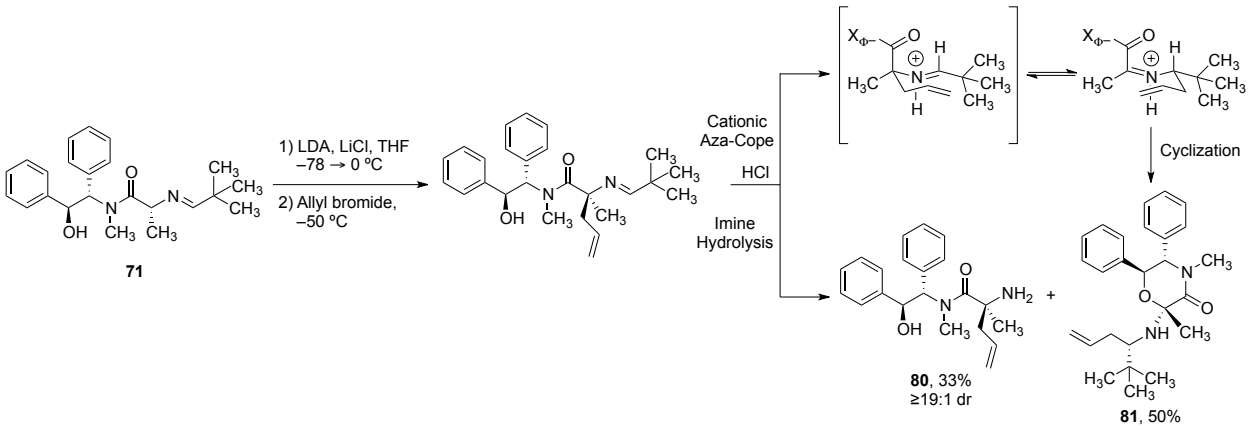


Scheme 3.6 Trapping of the *E*-enoalate of pivaldimine **71** with dichlorodiisopropyl silane.

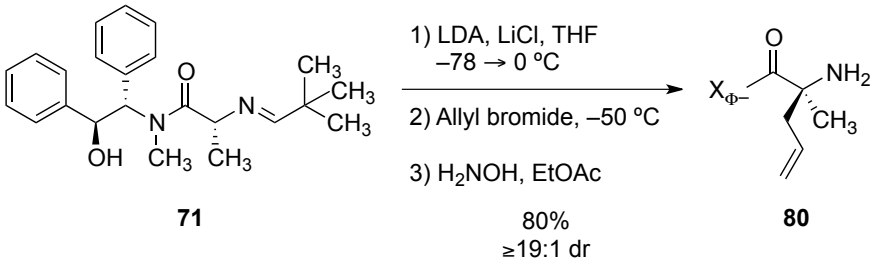
With the matched diastereomer for the alkylation reactions identified, the synthesis of additional substrates was pursued. An interesting transformation was encountered in the allylation of pivaldimine **71**. While the allylation reaction was successful, hydrolysis of the imine functional group under the standard acidic conditions produced a mixture of the desired amide **80** and aminal **81**, which is the by-product of a cationic aza-Cope rearrangement (Scheme 3.7).[77,78]

[77] The structure of aminal **81** was confirmed by X-ray crystallography. See Experimental Information for details.

Cleavage of the imine via transimination with hydroxylamine circumvented this issue and allowed for the isolation of the desired allyl amide in high yield with diastereoselectivity consistent with other matched-case substrates (Scheme 3.8).



Scheme 3.7 Formation of undesired aminal by-product **81** via a cationic aza-Cope rearrangement.

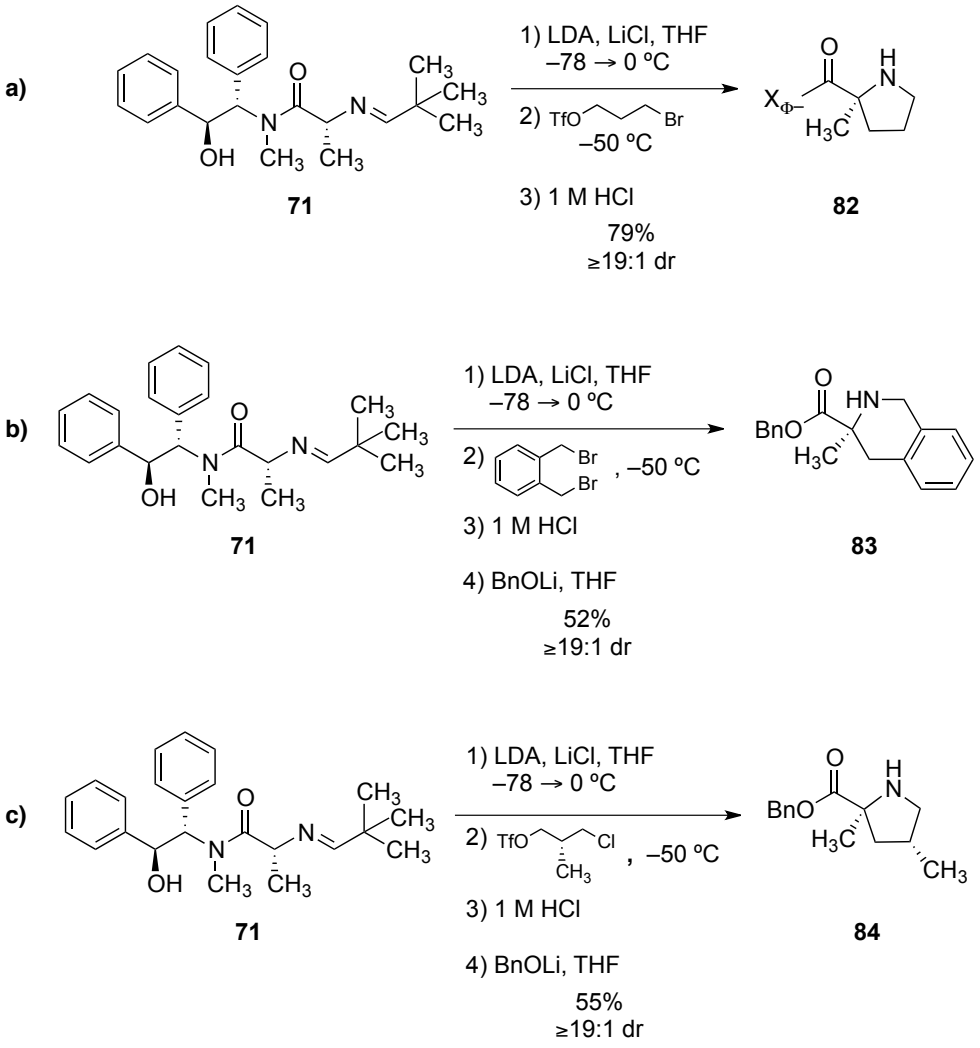


Scheme 3.8 Optimized procedure for the synthesis of α-methyl α-allyl α-amino amide **80**.

As depicted in Scheme 3.9 below, it also proved possible to assemble cyclic α-amino acid derivatives containing an α-quaternary center in a single operation using bis-electrophiles such as (a) 3-bromopropyl trifluoromethanesulfonate, (b) α,α′-dibromo-*o*-xylene, and (c) (*R*)-3-chloro-2-methylpropyl trifluoromethanesulfonate. Due to their chromatographic instability (believed to be a consequence of facile *N*→*O* acyl transfer), products from the latter two

[78] For the use of a chiral auxiliary to direct a similar transfer aminoallylation, see: Sugiura, M.; Mori, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 11038–11039.

alkylations were directly subjected to esterification with lithium benzyloxide prior to purification.[79]

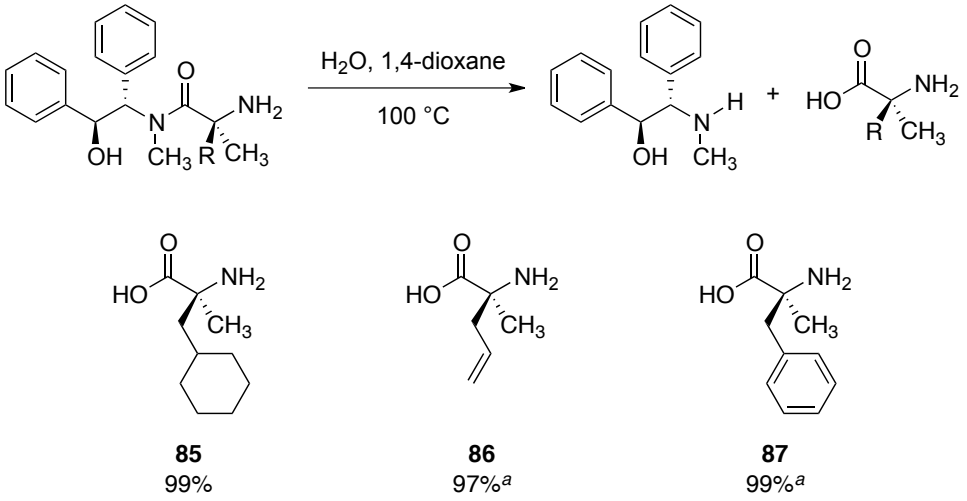


Scheme 3.9 Synthesis of cyclic amino acid derivatives. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude alkylation reaction mixtures.

[79] This protocol was reported for the esterification of oxazolidinone imides: Evans, D. A.; Ennis, M. D.; Mathre, D. J.; *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.

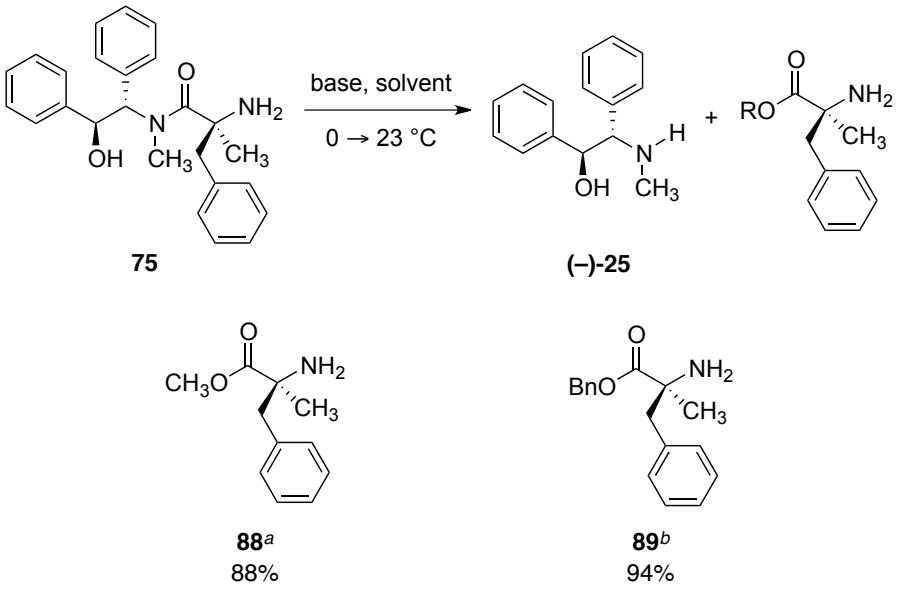
Transformations of α-Methyl α-Amino Pseudoephenamine Amides

Two protocols for the transformation of the α-amino amide alkylation products were developed. Hydrolysis of the α-quaternary α-amino amides to the corresponding α-amino acids was achieved by refluxing in aqueous dioxane (Scheme 3.10). Alternatively, as with the cyclic amino acid derivatives depicted in Scheme 3.9 above, treatment of the α-quaternary α-amino amides with lithium alkoxides provided the α-amino esters directly, as demonstrated with α-methyl phenylalaninamide **75** in Scheme 3.11.[80]



Scheme 3.10 Synthesis of α-methyl quaternary amino acids under salt-free conditions. [a] >98% ee, as determined by chiral HPLC analysis.

[80] Caddick, S.; Parr, N. J.; Pritchard, M. C. *Tetrahedron* **2001**, *57*, 6615–6626.



Scheme 3.11 Synthesis of α-methyl phenylalanine esters. [a] Base = $NaOCH_3$, Solvent = CH_3OH. [b]Base = LiOBn, Solvent = THF.

Experimental Information

General experimental procedures: All reactions were performed in flame-dried glassware fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 35 °C at 40 mmHg. Analytical thin-layer chromatography (TLC) was performed using glass plates precoated with silica gel (0.25-mm, 60-Å pore size, 230–400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), were stained by submersion in aqueous potassium permanganate solution ($KMnO_4$) or ceric ammonium molybdate solution (CAM), and were developed by heating with a heat gun. Flash column chromatography was performed as described by Still et al.,[58] employing silica gel (60 Å, standard grade) purchased from Dynamic Adsorbents. Flash column chromatography using deactivated silica gel was performed by preparing the silica gel slurry with triethylamine (10% v/v in corresponding eluent mixture) and flushing column with the eluent prior to loading the compound on the column.

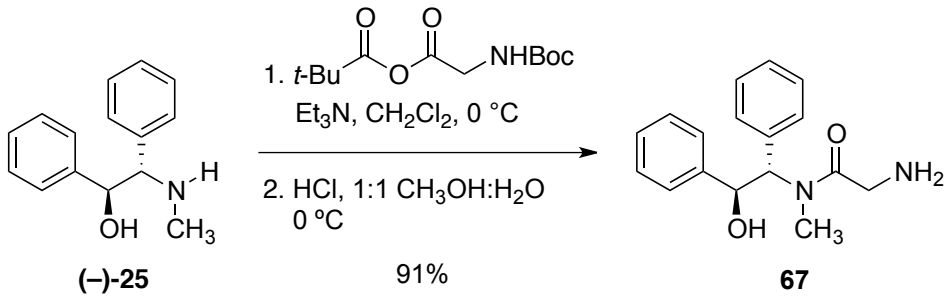
Materials: Commercial solvents and reagents were used as received, with the following exceptions. *N*,*N*-diisopropylamine, dichloromethane, ethyl ether, and tetrahydrofuran were purified by the method of Pangborn et al.[59] Lithium chloride was dried at 150 °C under vacuum (0.1 mmHg) for 12 h and stored in a drying oven at 150 °C (760 mmHg); the hot, dried solid was flame dried under vacuum (0.1 mmHg) for 2–3 min immediately prior to use. 4 Å molecular sieves were stored in a drying oven at 150 °C (760 mmHg) and flame dried under vacuum (0.1 mmHg) for 2-3 min immediately prior to use. Benzyl bromide, *tert*-butyl bromoacetate, 3-

methoxybenzyl bromide, ethyl iodide, methyl iodide, and allyl bromide were filtered neat through a column of oven-dried basic alumina immediately prior to use. The molarity of *n*-butyllithium solutions was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[60]

Instrumentation: Proton nuclear magnetic resonance spectra (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian INOVA 600 (600 MHz/150 MHz), Varian INOVA 500 (500 MHz/125 MHz) or Varian 400 (400 MHz/100 MHz) NMR spectrometers at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, HDO: δ 4.79, CD_2HOD: δ 4.87, THF-d_8: δ 3.58). Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.2, CD_3OD: δ 49.0, THF-d_8: δ 67.6). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, dq= doublet of quartets, dquint = doublet of quintets, sxt = sextet, m = multiplet, br = broad), integration, and coupling constant (J) in Hertz (Hz). Infrared (IR) spectra were obtained using a Shimadzu 8400S FT-IR spectrophotometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), and intensity of absorption (s = strong, m = medium, br = broad). HPLC retention times were acquired using a Beckman System Gold instrument equipped with a Phenomenex Chirex 3126 (D)-penicillamine column (5 μm particle size, 4.6 mm x 50 mm). Melting points were determined using a Thomas Scientific capillary melting point apparatus. High-resolution mass spectra were obtained at the

Harvard University Mass Spectrometry Facility. X-ray crystallographic analysis was performed at the Harvard University X-Ray Crystallographic Laboratory by Dr. Shao-Liang Zheng.

Synthesis of Pseudoephenamine Glycinamide:



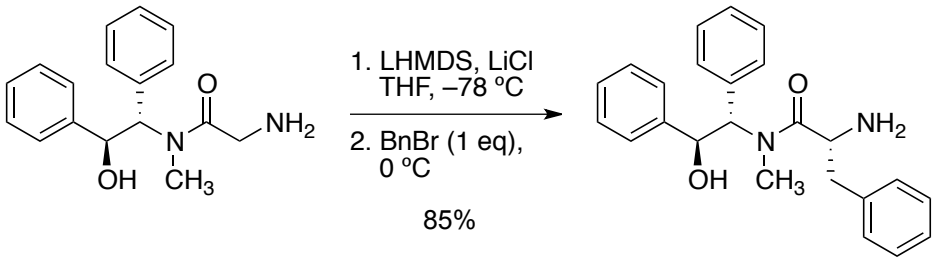
(–)-25 91% 67

2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*-methylacetamide (67)

Trimethylacetyl chloride (7.58 mL, 61.6 mmol, 1.4 equiv) was added dropwise to a stirring solution of *N*-(*tert*-butoxycarbonyl)-glycine (10.79 g, 61.6 mmol, 1.4 equiv) and triethylamine (8.60 mL, 61.5 mmol, 1.40 equiv) in dichloromethane (154 mL) at 0 °C. A white precipitate gradually formed; after 35 min, a second portion of triethylamine (8.60 mL, 61.5 mmol, 1.40 equiv) was added to the reaction mixture, followed by a single portion of (1*S*,2*S*)-pseudoephenamine (10.0 g, 44.0 mmol, 1.00 equiv). Stirring was continued at 0 ºC, and, after 45 min, the solution was concentrated under reduced pressure to give a white syrup. This syrup was partitioned between methanol (75 ml) and water (75 ml). The resulting suspension was cooled to 0 ºC, and concentrated hydrochloric acid (60 ml) was added to the mixture. After stirring for 3 h at 0 ºC, the solution was concentrated to remove the methanol, and the resulting aqueous suspension was cooled to 0 ºC and adjusted to pH 14 using 50% aqueous NaOH solution. The organic material was then extracted from the aqueous solution using dichloromethane (4x50 mL). The combined organic extracts were dried over potassium carbonate, and the dried solution was filtered through a pad of Celite. The organic solution was then concentrated to an off-white solid that was purified by column chromatography (deactivated silica gel, 5→10% methanol-dichloromethane) to produce glycinamide **67** as a white solid (11.4 g, 91%). TLC (10% methanol-dichloromethane, deactivated silica gel): R_f = 0.25 (streak, UV, $KMnO_4$). ^1H NMR

(3.4:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 2H), 7.33 – 7.18 (m, 8H), 5.73 (d, *J* = 8.4 Hz, 1H), 5.36 (m, 1H), 4.99* (d, *J* = 7.9 Hz, 1H), 3.54 – 3.34 (m, 2H), 2.97* (s, 3H), 2.83 (s, 3H). ^{13}C NMR (2.6:1 rotamer ratio, asterisk denotes minor rotamer peaks, 126 MHz, $CDCl_3$) δ 173.72, 173.41*, 141.75, 137.04, 136.48*, 128.43, 128.40, 128.33, 128.32, 128.23, 128.15, 127.81*, 127.70*, 127.55, 127.41, 126.93, 126.90, 72.69, 72.39*, 64.75*, 63.62, 43.28, 43.06*, 30.89, 29.54*. FTIR (neat), cm^{-1}: 3387 (br), 3028 (w), 1606 (s), 1043 (m), 698 (s). HRMS (ESI): Calcd for $(C_{17}H_{20}N_2O_2 + Na)^+$: 307.1417. Found: 307.1428.

Alkylation of Pseudoephenamine Glycinamide:



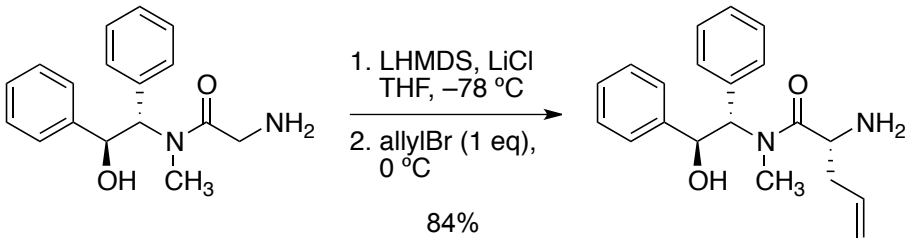
67
1.3 eq

68

(*R*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*-methyl-3-phenylpropanamide (68)

A 10-mL flask was charged with lithium chloride (145 mg, 3.42 mmol, 7.80 equiv), and the salt was flame dried under reduced pressure. Once cool, (*S*,*S*)-pseudoephenamine glycinamide (162 mg, 0.570 mmol, 1.30 equiv) and tetrahydrofuran (2.2 mL) were added to the flask. The glycinamide was allowed to dissolve, and the resulting slurry was cooled to –78 ºC. A freshly prepared solution of lithium hexamethyldisilazide (1 M, 1.13 mL, 1.13 mmol, 2.57 equiv) was then added slowly down the side of the flask in order to allow the solution of base to cool before reaction the reaction slurry. The resulting pale yellow solution was stirred for 10 min at –78 ºC before the solution was warmed to 0 ºC and stirred for 30 min. Benzyl bromide (75 mg, 52.2 µL, 0.439 mmol, 1 equiv) was added to the solution, and the mixture was stirred at 0 ºC for 2 h, after which time 1 M aqueous hydrochloric acid solution (6 mL) was added. The resulting biphasic mixture was allowed to warm to 23 ºC and was transferred to a separatory funnel containing ethyl acetate (10 mL). The layers were separated, and the product was extracted from the organic phase using 1 M aqueous hydrochloric acid solution (3x10 mL). The combined acidic aqueous extracts were cooled to 0 ºC and adjusted to pH 14 by slow addition of 50% aqueous NaOH solution. The organic material was extracted from the resulting basic aqueous solution using dichloromethane (3x10 mL). The organic solution was dried over potassium carbonate. The dried

solution was filtered, and the filtrate was concentrated to a white solid. The crude material was judged to be ≥98:2 dr by HPLC analysis (Chiralpak OD-R, 42% acetonitrile in aqueous pH 2 potassium hexafluorophosphate solution, 1 mL/min, λ = 220 nm, t_R (major) = 6.41 min, t_R (minor) = 9.21 min). The crude amide was purified by column chromatography (deactivated silica gel, 3→7% methanol-dichloromethane) to produce amide **68** as a white solid (148 mg, 91%). The dr of purified **68** was determined to be >99:1 dr by HPLC analysis. TLC (10% methanol-dichloromethane, deactivated silica gel): R_f = 0.51 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H), 7.33 – 7.22 (m, 7H), 7.19 (m, 7H), 7.13 – 7.09 (m, 2H), 6.05 (d, *J* = 8.8 Hz, 1H), 5.29 (d, *J* = 8.8 Hz, 1H), 3.93 (t, *J* = 7.1 Hz, 1H), 2.90 (dd, *J* = 13.2, 7.4 Hz, 1H), 2.80 – 2.75 (dd, *J* = 13.2, 7.4 Hz, 1H), 2.74 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 175.88, 141.60, 137.23, 136.65, 129.14, 128.54, 128.29, 128.14, 128.13, 128.11, 127.52, 127.28, 127.06, 126.40, 72.50, 62.62, 52.98, 41.81, 31.40. HRMS (ESI): Calcd for $(C_{24}H_{26}N_2O_2 + H)^+$: 397.1886. Found: 397.1889.



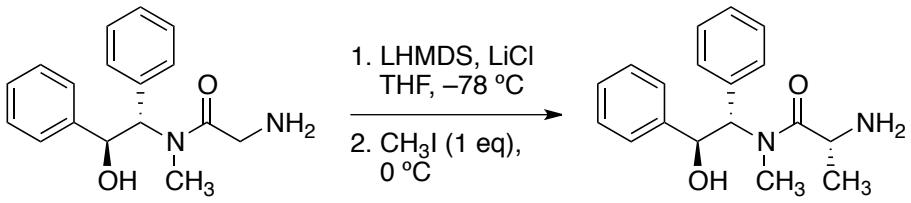
67
1.3 eq

69

(*R*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*-methylpent-4-enamide (69)

A 10-mL flask was charged with lithium chloride (205 mg, 4.84 mmol, 7.80 equiv), and the salt was flame dried under reduced pressure. Once cool, (*S*,*S*)-pseudoephenamine glycinamide (229 mg, 0.806 mmol, 1.30 equiv) and tetrahydrofuran (3.1 mL) were added to the flask. The glycinamide was allowed to dissolve, and the resulting slurry was cooled to –78 ºC. A freshly prepared solution of lithium hexamethyldisilazide (1 M, 1.60 mL, 1.60 mmol, 2.57 equiv) was then added slowly down the side of the flask in order to allow the solution of base to cool before reaction the reaction slurry. The resulting pale yellow solution was stirred for 10 min at –78 ºC before the solution was warmed to 0 ºC and stirred for 30 min. Allyl bromide (75 mg, 53.6 µL, 0.620 mmol, 1 equiv) was added to the solution, and the mixture was stirred at 0 ºC for 2 h, after which time 1 M aqueous hydrochloric acid solution (6 mL) was added. The resulting biphasic mixture was allowed to warm to 23 ºC and was transferred to a separatory funnel containing ethyl acetate (10 mL). The layers were separated, and the product was extracted from the organic phase using 1 M aqueous hydrochloric acid solution (3x10 mL). The combined acidic aqueous extracts were cooled to 0 ºC and adjusted to pH 14 by slow addition of 50% aqueous NaOH solution. The organic material was extracted from the resulting basic aqueous solution using dichloromethane (3x10 mL). The organic solution was dried over potassium carbonate. The dried solution was filtered, and the filtrate was concentrated to a white solid. The crude material was

judged to be ≥98:2 dr by HPLC analysis (Chiralpak OD-R, 35% acetonitrile in aqueous pH 2 potassium hexafluorophosphate solution, 1 mL/min, λ = 220 nm, t_R (major) = 11.3 min, t_R (minor) = 17.2 min). The crude amide was purified by column chromatography (deactivated silica gel, 3→7% methanol-dichloromethane) to produce amide **69** as a white solid (169 mg, 84%). The dr of purified **69** was determined to be >99:1 dr by HPLC analysis. TLC (10% methanol-dichloromethane, deactivated silica gel): R_f = 0.57 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$) 7.42 – 7.37 (m, 6H), 7.32 – 7.27 (m,6), 7.23 (d, *J* = 7.4 Hz, 2H), 5.76 – 5.64 (m, 2H), 5.39 (d, *J* = 8.1 Hz, 1H), 5.13 – 5.03 (m, 2H), 3.73 (dd, *J* = 7.7, 5.0 Hz, 1H), 2.92 (s, 3H), 2.26 (m, 1H), 2.18 – 2.07 (m, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 176.34, 141.61, 136.84, 133.63, 128.46, 128.42, 128.34, 128.28, 127.66, 127.51, 126.98, 126.93, 118.27, 118.25, 72.90, 64.27, 51.24, 39.44, 32.59. HRMS (ESI): Calcd for $(C_{20}H_{24}N_2O_2 + H)^+$: 347.1730. Found: 347.1746.



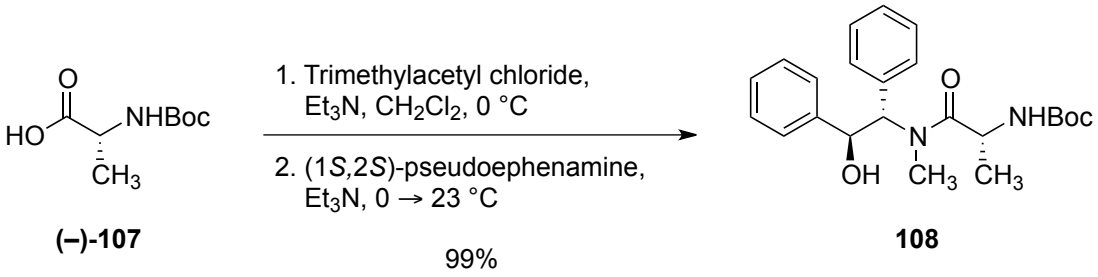
(*R*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*-methylpropanamide (70)

A 10-mL flask was charged with lithium chloride (233 mg, 5.5 mmol, 7.80 equiv), and the salt was flame dried under reduced pressure. Once cool, (*S*,*S*)-pseudoephenamine glycinamide (260 mg, 0.916 mmol, 1.30 equiv) and tetrahydrofuran (3.5 mL) were added to the flask. The glycinamide was allowed to dissolve, and the resulting slurry was cooled to –78 ºC. A freshly prepared solution of lithium hexamethyldisilazide (1 M, 1.81 mL, 1.81 mmol, 2.57 equiv) was then added slowly down the side of the flask in order to allow the solution of base to cool before reaction the reaction slurry. The resulting pale yellow solution was stirred for 10 min at –78 ºC before the solution was warmed to 0 ºC and stirred for 30 min. Methyl iodide (100 mg, 44.1 µL, 0.705 mmol, 1 equiv) was added to the solution, and the mixture was stirred at 0 ºC for 2 h, after which time 1 M aqueous hydrochloric acid solution (6 mL) was added. The resulting biphasic mixture was allowed to warm to 23 ºC and was transferred to a separatory funnel containing ethyl acetate (10 mL). The layers were separated, and the product was extracted from the organic phase using 1 M aqueous hydrochloric acid solution (3x10 mL). The combined acidic aqueous extracts were cooled to 0 ºC and adjusted to pH 14 by slow addition of 50% aqueous NaOH solution. The organic material was extracted from the resulting basic aqueous solution using dichloromethane (3x10 mL). The organic solution was dried over potassium carbonate. The dried solution was filtered, and the filtrate was concentrated to a white solid. The crude material was judged to be 97:3 dr by HPLC analysis (Chiralpak OD-R, 20% acetonitrile in aqueous pH 2

potassium hexafluorophosphate solution, 1 mL/min, λ = 220 nm, t_R (major) = 25.0 min, t_R (minor) = 37.0 min). The crude amide was purified by column chromatography (deactivated silica gel, 5→10% methanol-dichloromethane) to produce amide **70** as a white solid (168 mg, 80%). TLC (10% methanol-dichloromethane, deactivated silica gel): R_f = 0.29 (UV, $KMnO_4$). ^{1}H NMR (10:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 2H), 7.35 – 7.29 (m, 6H), 7.29 – 7.23 (m, 2H), 5.73 (d, *J* = 8.1 Hz, 1H), 5.40 (d, *J* = 8.1 Hz, 1H), 5.38 – 5.37* (m, 1H), 5.17* (d, *J* = 8.0 Hz, 1H), 3.85* (q, *J* = 6.8 Hz, 1H), 3.78 (q, *J* = 6.8 Hz, 1H), 3.09* (s, 3H), 2.93 (s, 3H), 2.39 (br s, 2H), 1.36 – 1.28* (m, 3H), 1.15 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.12, 141.87, 137.04, 128.58, 128.45, 128.41, 127.81, 127.67, 126.91, 73.35, 65.38, 47.61, 33.32, 20.79. FTIR (neat), cm^{-1}: 3030 (m), 2974 (m), 1627 (s), 1452 (m), 1273 (m), 1062 (s). HRMS (ESI): Calcd for $(C_{18}H_{22}N_2O_2 + H)^+$: 299.1761. Found: 299.1755.

Synthesis of Pseudoephenamine Alaninamide Pivaldimines:

Synthesis of Pseudoephenamine Alaninamide Pivaldimines via Pivaldehyde Condensation

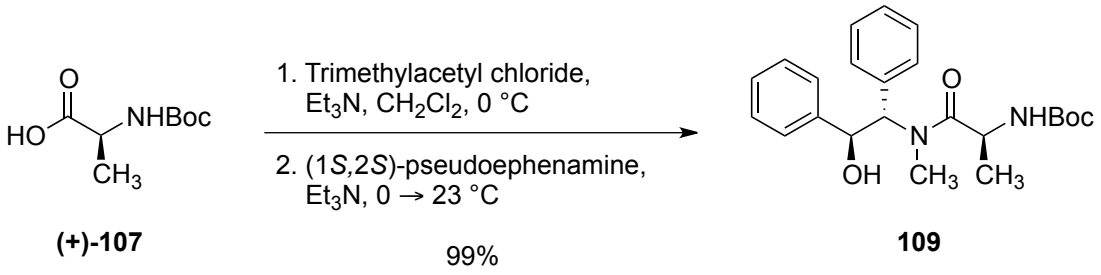


(–)-107 **108**

***Tert*-butyl ((*R*)-1-(((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)(methyl)amino)-1-oxopropan-2-yl)carbamate (108)**

Trimethylacetyl chloride (4.22 mL, 34.3 mmol, 2.60 equiv) was added dropwise to a stirring solution of *N*-(*tert*-butoxycarbonyl)-D-alanine (6.49 g, 34.3 mmol, 2.60 equiv) and triethylamine (4.42 mL, 31.7 mmol, 2.40 equiv) in dichloromethane (88.0 mL) at 0 °C. A white precipitate gradually formed; after 30 min, a second portion of triethylamine (4.42 mL, 31.7 mmol, 2.40 equiv) was added to the reaction mixture, followed by a single portion of (1*S*,2*S*)-pseudoephenamine (3.00 g, 13.2 mmol, 1.00 equiv). Stirring was continued, and, after 12 h, saturated aqueous sodium bicarbonate solution (150 mL) was added. The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 100 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (30→50% ethyl acetate-hexanes) to provide amide **108** as a white foam (5.26 g, 99%). TLC (40% ethyl acetate-hexanes): R_f = 0.55 (UV, $KMnO_4$). ^{1}H NMR (6:1 rotamer ratio, asterisk denotes minor rotamer peaks, 600 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 2H), 7.34 – 7.22 (m, 6H), 7.24 – 7.15 (m, 2H), 5.49 (d, *J* = 7.8 Hz, 1H), 5.39* (d, *J* = 7.2 Hz, 1H), 5.36 (d, *J* = 7.6 Hz, 1H), 5.27* (d, *J* = 8.7 Hz, 1H), 4.87 – 4.77* (m, 1H), 4.58 – 4.50 (m, 1H), 2.90 (s, 3H), 2.88* (s, 3H), 1.42 (s, 9H), 1.38* (s, 9H), 1.10

(d, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.08, 155.50, 141.62, 136.47, 128.88, 128.64, 128.46, 128.25, 127.81, 127.75, 127.33, 126.75, 79.87, 73.49, 67.13, 47.12, 34.70, 28.48, 18.25. FTIR (neat), cm^{-1}: 2980 (m), 1705 (s), 1635 (s), 1454 (s), 1367 (m), 1166 (s). HRMS (ESI): Calcd for $(C_{23}H_{30}N_2O_4 + H)^+$: 399.2286. Found: 399.2312.

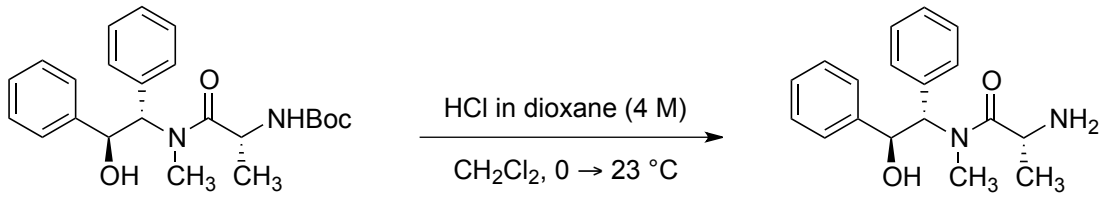


(+)-107 99% **109**

***Tert*-butyl ((*S*)-1-(((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)(methyl)amino)-1-oxopropan-2-yl)-carbamate (109)**

Trimethylacetyl chloride (9.85 mL, 80.0 mmol, 2.60 equiv) was added dropwise to a stirring solution of *N*-(*tert*-butoxycarbonyl)-L-alanine (15.2 g, 80.0 mmol, 2.60 equiv) and triethylamine (10.3 mL, 74.0 mmol, 2.40 equiv) in dichloromethane (200 mL) at 0 °C. A white precipitate gradually formed; after 30 min, a second portion of triethylamine (10.3 mL, 74.0 mmol, 2.40 equiv) was added to the reaction mixture, followed by a single portion of (1*S*,2*S*)-pseudoephenamine (26) (7.00 g, 30.8 mmol, 1.00 equiv). Stirring was continued, and, after 12 h, saturated aqueous sodium bicarbonate solution (200 mL) was added. The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 100 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (30→50% ethyl acetate-hexanes) to provide amide **109** as a white foam (12.3 g, 99%). TLC (40% ethyl acetate-hexanes): R_f = 0.55 (UV, $KMnO_4$). ^{1}H NMR (4:1 rotamer ratio, asterisk denotes minor rotamer peaks, 600 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 2H), 7.33 – 7.17 (m, 8H), 5.74 (d, *J* = 7.4 Hz, 1H), 5.45 (d, *J* = 7.5 Hz, 1H), 5.43* (d, *J* = 8.6 Hz, 1H), 5.24* (d, *J* = 9.0 Hz, 1H), 4.91* (p, *J* = 6.9 Hz, 1H), 4.54 (p, *J* = 7.1 Hz, 1H), 2.98* (s, 3H), 2.96 (s, 3H), 1.45* (s, 9H), 1.43 (s, 9H), 1.33* (d, *J* = 6.9 Hz, 3H), 1.16 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (4:1 rotamer ratio, asterisk denotes minor rotamer peaks, 100 MHz, $CDCl_3$) δ 174.63, 155.34, 141.44, 136.82, 128.77*, 128.72*, 128.68, 128.51, 128.41, 128.16*, 128.08*, 127.95, 127.78, 127.26*, 126.71, 79.68, 73.66, 73.12*, 66.00*, 64.48, 47.06,

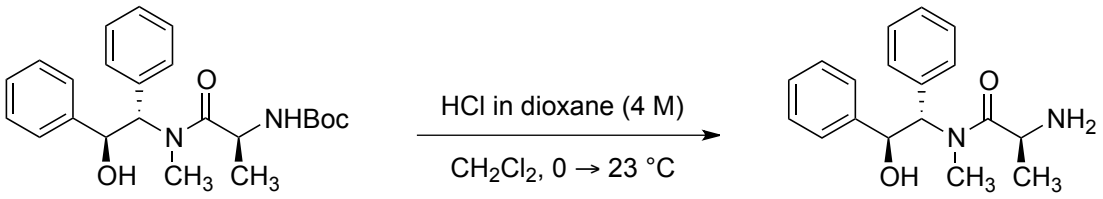
45.78*, 33.48, 29.35*, 28.48, 19.00*, 18.59. FTIR (neat), cm^{-1}: 2980 (m), 1699 (s), 1633 (s), 1494 (s), 1410 (m), 1166 (s). HRMS (ESI): Calcd for $(C_{23}H_{30}N_2O_4 + H)^+$: 399.2286. Found: 399.2306.



108 82% **70**

(*R*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*-methylpropanamide (70)

A solution of hydrogen chloride in dioxane (4 M, 14.4 mL, 57.6 mmol, 4.40 equiv) was added dropwise to a stirring solution of amide **108** (5.20 g, 13.1 mmol, 1.00 equiv) in dichloromethane (29.0 mL) at 0 °C over 2 min. After 5 min, the reaction mixture was allowed to warm to 23 °C. A white precipitate gradually formed, and the resulting suspension was stirred at 23 °C for 2 h, after which time the reaction mixture was brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. Saturated aqueous sodium chloride solution (40 mL) was added, the layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (8% methanol-dichloromethane, triethylamine pretreated silica gel) to provide amide **70** as a white solid (3.21 g, 82%). TLC (10% methanol-dichloromethane): R_f = 0.29 (UV, $KMnO_4$). ^{1}H NMR (10:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 2H), 7.35 – 7.29 (m, 6H), 7.29 – 7.23 (m, 2H), 5.73 (d, *J* = 8.1 Hz, 1H), 5.40 (d, *J* = 8.1 Hz, 1H), 5.38 – 5.37* (m, 1H), 5.17* (d, *J* = 8.0 Hz, 1H), 3.85* (q, *J* = 6.8 Hz, 1H), 3.78 (q, *J* = 6.8 Hz, 1H), 3.09* (s, 3H), 2.93 (s, 3H), 2.39 (br s, 2H), 1.36 – 1.28* (m, 3H), 1.15 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.12, 141.87, 137.04, 128.58, 128.45, 128.41, 127.81, 127.67, 126.91, 73.35, 65.38, 47.61, 33.32, 20.79. FTIR (neat), cm^{-1}: 3030 (m), 2974 (m), 1627 (s), 1452 (m), 1273 (m), 1062 (s). HRMS (ESI): Calcd for $(C_{18}H_{22}N_2O_2 + H)^+$: 299.1761. Found: 299.1755.

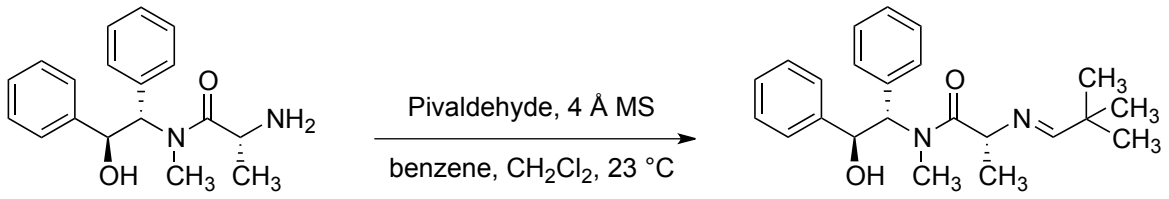


109 **110**

(*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*-methylpropanamide (110)

A solution of hydrogen chloride in dioxane (4 M, 34.2 mL, 137 mmol, 4.40 equiv) was added dropwise to a stirring solution of amide **109** (12.3 g, 30.8 mmol, 1.00 equiv) in dichloromethane (70.0 mL) at 0 °C over 2 min. After 5 min, the reaction mixture was allowed to warm to 23 °C. A white precipitate gradually formed, and the resulting suspension was stirred at 23 °C for 1.5 h, after which time the reaction mixture was brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. Saturated aqueous sodium chloride solution (50 mL) was added, the layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (7% methanol-dichloromethane, triethylamine pretreated silica gel) to provide amide **110** as a white foam (7.40 g, 81%). TLC (10% methanol-dichloromethane): R_f = 0.38 (UV, $KMnO_4$). ^{1}H NMR (4:3 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.35 – 7.20 (m, 8H), 5.75 (d, *J* = 7.7 Hz, 1H), 5.42 (d, *J* = 7.7 Hz, 1H), 5.37 – 5.29* (m, 2H), 3.94* (q, *J* = 6.5 Hz, 1H), 3.73 (q, *J* = 6.8 Hz, 1H), 2.91 (s, 3H), 1.86 (br s, 2H), 1.37* (d, *J* = 6.5 Hz, 3H), 1.18 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (4:3 rotamer ratio, asterisk denotes minor rotamer peaks, 126 MHz, $CDCl_3$) δ 177.49, 175.89*, 142.09*, 141.85, 137.13, 136.37*, 128.74, 128.66, 128.60, 128.58, 128.53, 128.46, 128.37, 127.99, 127.96, 127.73, 127.63, 127.24, 126.74, 73.39, 72.47*, 65.19, 64.15*, 47.46, 46.78*, 32.85, 29.85*, 21.36*, 20.63. FTIR (neat), cm^{-1}: 3030 (m), 2976

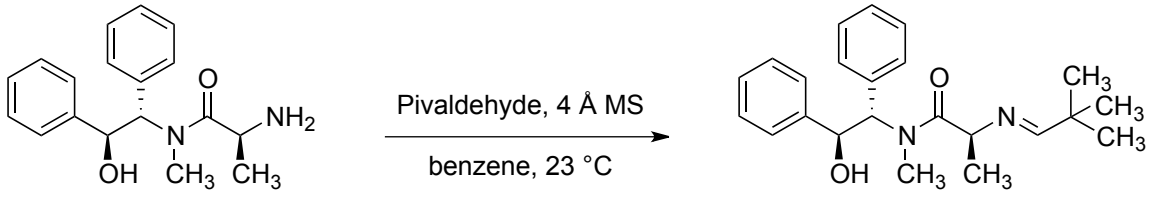
(m), 1627 (s), 1494 (m), 1450 (m). HRMS (ESI): Calcd for $(C_{18}H_{22}N_2O_2 + H)^+$: 299.1761. Found: 299.1770.



(*R*)-2-((*E*)-(2,2-dimethylpropylidene)amino)-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*-methylpropanamide (71)

A 25 mL pear-shaped flask charged with a teflon-coated magnetic stirring bar and 4 Å molecular sieves (20 mg) was flame-dried in vacuo for 3 min. After cooling under vacuum, amide **70** (100 mg, 0.335 mmol, 1.00 equiv), dry benzene (1.20 mL) and dichloromethane (1.00 mL) were added to the flask. Pivaldehyde (74.0 μL, 0.670 mmol, 2.00 equiv) was added to the solution by syringe, and stirring of the reaction mixture was continued at 23 °C for 50 min. The solvent was then evaporated under reduced pressure (ca. 80 mmHg) and the white residue was dried under high vacuum in an oil bath (35 °C) overnight to remove excess pivaldehyde. The *tert*-butyl imine product **71** (123 mg, ≥99%) was used in subsequent alkylation reactions without further purification. ^{1}H NMR (1:1 rotamer ratio, asterisk denotes rotamer peaks, 600 MHz, THF-d_8) δ 7.60 (s, 1H), 7.53 – 7.49 (m, 3H), 7.42 – 7.36 (m, 4H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.25 – 7.13 (m, 7H), 7.11 (t, *J* = 7.3 Hz, 2H), 5.89 (d, *J* = 8.3 Hz, 1H), 5.45 (d, *J* = 5.5 Hz, 1H), 5.31* (d, *J* = 8.3 Hz, 1H), 5.26* (d, *J* = 5.5 Hz, 1H), 4.90 (br s, 1H), 4.75* (br s, 1H), 4.33 (q, *J* = 6.6 Hz, 1H), 4.04* (q, *J* = 6.4 Hz, 1H), 2.94 (s, 3H), 2.75* (s, 3H), 1.18 (d, *J* = 6.7 Hz, 3H), 1.02 (s, 9H), 0.97* (s, 9H), 0.92* (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (1:1 rotamer ratio, asterisk denotes rotamer peaks, 126 MHz, THF) δ 173.12, 172.63, 172.34*, 144.84*, 144.57, 139.85, 139.57*, 130.13, 129.71, 129.18, 128.85, 128.76, 128.42, 128.26, 127.94, 127.76, 74.18, 73.60*, 64.43*, 64.19, 62.23, 37.21, 27.35, 27.15*, 19.27, 18.96*. FTIR (neat), cm^{-1}: 2962 (m),

2235 (s), 2081 (s), 1645 (m), 1099 (s), 1045 (s). HRMS (ESI): Calcd for $(C_{23}H_{30}N_2O_2 + H)^+$: 367.2380. Found: 367.2402.



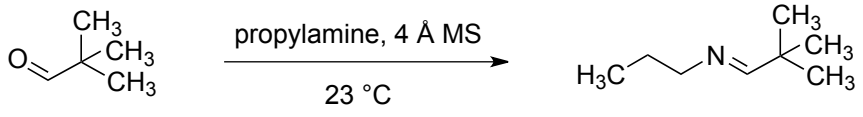
110 **78**

(*S*)-2-((*E*)-(2,2-dimethylpropylidene)amino)-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*-methylpropanamide (78)

A 25 mL pear-shaped flask charged with a teflon-coated magnetic stirring bar and 4 Å molecular sieves (20 mg) was flame-dried in vacuo for 3 min. After cooling under vacuum, amide **110** (100 mg, 0.335 mmol, 1.00 equiv) and dry benzene (2.20 mL) were added to the flask. Pivaldehyde (74.0 μL, 0.670 mmol, 2.00 equiv) was added to the solution by syringe, and stirring of the reaction mixture was continued at 23 °C for 30 min, during which time a white precipitate formed. The solvent was then evaporated under reduced pressure (ca. 80 mmHg) and the white residue was dried under high vacuum in an oil bath (35 °C) overnight to remove excess pivaldehyde. The *tert*-butyl imine product **78** (123 mg, ≥99%) was used in subsequent alkylation reactions without further purification. ^{1}H NMR (4:1 rotamer ratio, asterisk denotes minor rotamer peaks, 600 MHz, THF-d_8) δ 7.65 (s, 1H), 7.41 – 7.37 (m, 2H), 7.37 – 7.31 (m, 2H), 7.24 – 7.14 (m, 4H), 7.14 – 7.07 (m, 2H), 5.97 (d, *J* = 7.5 Hz, 1H), 5.57* (d, *J* = 9.3 Hz, 1H), 5.37 (d, *J* = 7.5 Hz, 1H), 5.21* (d, *J* = 9.1 Hz, 1H), 4.92* (br s, 1H), 4.73 (br s, 1H), 4.70 – 4.64* (m, 1H), 4.37 (q, *J* = 6.6 Hz, 1H), 2.95 (s, 3H), 1.24* (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H), 1.07* (s, 9H), 0.91 (s, 9H). ^{13}C NMR (126 MHz, THF-d_8) δ 172.85, 172.06, 144.59, 140.15, 129.63, 128.82, 128.70, 128.10, 127.89, 127.66, 73.60, 62.99, 62.77, 37.08, 32.24, 27.20, 19.01. FTIR (neat), cm^{-1}: 2962 (m), 2237 (m), 2083 (m), 1645 (s), 1099 (s), 1045 (s). HRMS (ESI): Calcd for $(C_{23}H_{30}N_2O_2 + H)^+$: 367.2380. Found: 367.2384.

Synthesis of Pseudoephenamine Alaninamide Pivaldimines via Transimination:

Synthesis of Transimination Reagent

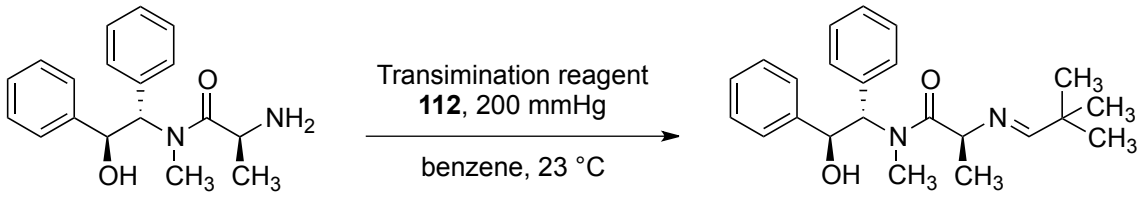


111 **112**

(*E*)-*N*-(2,2-dimethylpropylidene)propan-1-amine (112)

A 50 mL round-bottom flask charged with a teflon-coated magnetic stirring bar and 4 Å molecular sieves (10.0 g) was flame-dried in vacuo for 3 min. After cooling under vacuum, pivaldehyde (12.0 mL, 110 mmol, 1.00 equiv) was added. The mixture was cooled to 0 °C, propylamine (18.2 mL, 221 mmol, 2.00 equiv) was added, and, after 5 min, the reaction mixture was allowed to warm to 23 °C for 1 h. The transimination reagent **112** was directly distilled from the reaction flask (58-62 °C, 100 mmHg) to provide a colorless liquid (13.5 g, 96%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (t, *J* = 1.2 Hz, 1H), 3.32 (td, *J* = 6.9, 1.2 Hz, 2H), 1.59 (h, *J* = 7.3 Hz, 2H), 1.06 (s, 9H), 0.85 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.87, 63.14, 35.97, 27.02, 23.89, 11.58. FTIR (neat), cm^{-1}: 2964 (s), 2931 (m), 1668 (m), 1629 (s), 1284 (m). HRMS (ESI): Calcd for $(C_8H_{17}N + H)^+$: 128.1441 Found: 128.1439.

Pivaldimine Synthesis via Transimination

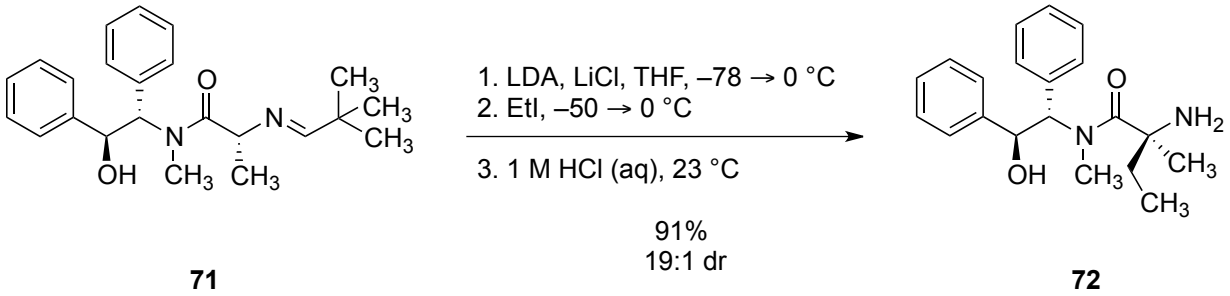


(*S*)-2-((*E*)-(2,2-dimethylpropylidene)amino)-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*-methylpropanamide (78)

Transimination reagent **112** (305 μL, 1.68 mmol, 5.00 equiv) was added to a stirring solution of amide **110** (100 mg, 0.335 mmol, 1.00 equiv) in dry benzene (3.35 mL). The mixture was stirred under reduced pressure (200 mmHg) at 23 °C for 30 min, during which time gas was observed to evolve from the reaction mixture. The solvent was then evaporated under reduced pressure (ca. 80 mmHg) and the white residue was dried under high vacuum in an oil bath (35 °C) overnight to remove excess transimination reagent. The characterization data were in agreement with values for the same *tert*-butyl imine **78** prepared by direct condensation of pivaldehyde with amide **110**, as reported above.

Alkylations of Pseudoephenamine Alaninamide Pivaldimine:

Matched Case

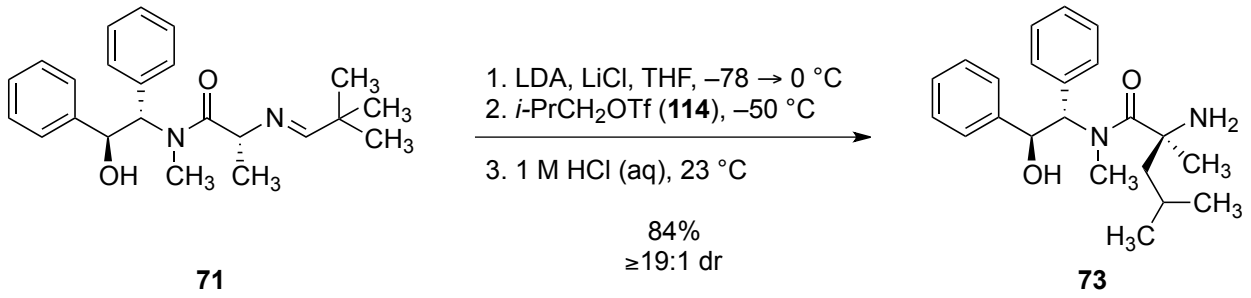


71 **72**

(*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethylbutanamide (72)

A solution of *tert*-butyl imine **71** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to –78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at –78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to –50 °C. After 10 min, ethyl iodide (67.8 μL, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at –50 °C for 30 min, and then was warmed to 0 °C for 3.5 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 1 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined

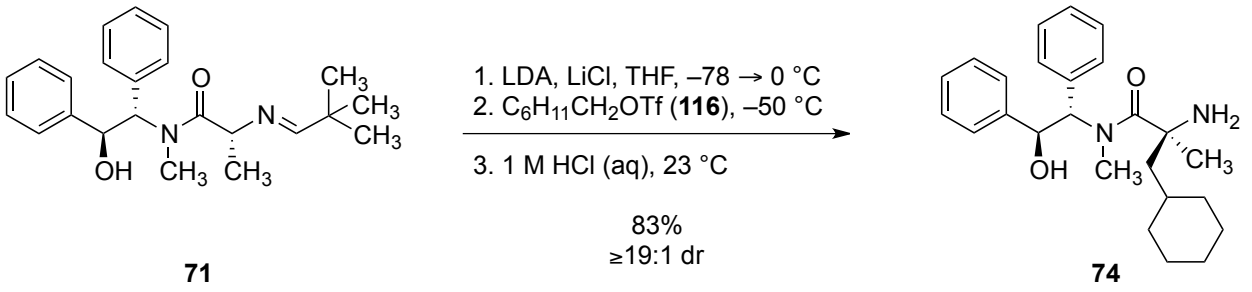
organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (3% methanol-dichloromethane, triethylamine pretreated silica gel) to provide α,α-disubstituted amide **72** as a white solid (100 mg, 91%, mp = 57-58 °C). The diastereomeric ratio of the crude material was determined to be 19:1 by ^{1}H NMR integration. TLC (10% methanol-dichloromethane): R_f = 0.40 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.15 (m, 6H), 7.11 – 7.07 (m, 2H), 7.06 – 7.02 (m, 2H), 5.77 (d, *J* = 7.8 Hz, 1H), 3.93 (d, *J* = 7.8 Hz, 1H), 2.27 (s, 3H), 1.95 (br s, 2H), 1.87 – 1.76 (m, 1H), 1.72 – 1.62 (m, 1H), 1.32 (s, 3H), 0.84 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.69, 138.54, 137.87, 128.52, 128.18, 128.08, 127.99, 127.68, 127.11, 80.48, 69.62, 58.35, 34.52, 33.79, 25.82, 8.52. FTIR (neat), cm^{-1}: 2970 (m), 1732 (s), 1226 (m), 1136 (s), 908 (s). HRMS (ESI): Calcd for $(C_{20}H_{26}N_2O_2 + H)^+$: 327.2074. Found: 327.2075.



(*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2,4-trimethylpentanamide (73)

A solution of *tert*-butyl imine **71** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to –78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at –78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to –50 °C. After 10 min, isobutyl trifluoromethanesulfonate (**114**) (173 mg, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at –50 °C for 1.5 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 4 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (3% methanol-dichloromethane,

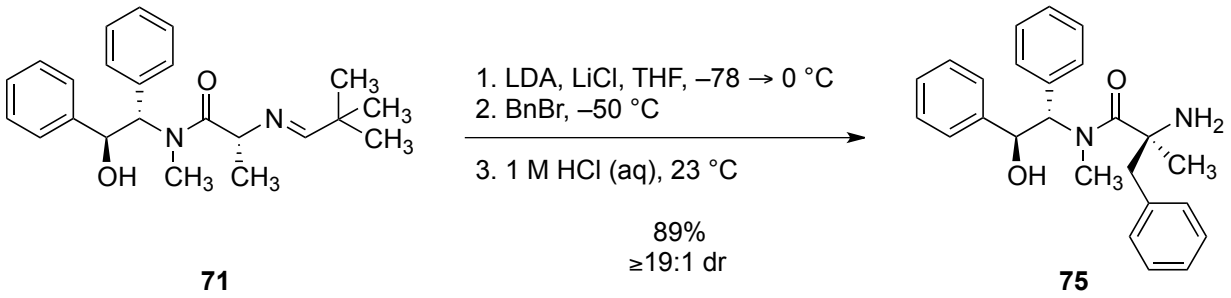
triethylamine pretreated silica gel) to provide α,α-disubstituted amide **73** as a white solid (100 mg, 84%, mp = 59-60 °C). The diastereomeric ratio of the crude material was determined to be ≥19:1 by ^{1}H NMR integration. TLC (10% methanol-dichloromethane): R_f = 0.52 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.14 (m, 6H), 7.11 – 7.05 (m, 2H), 7.04 – 6.99 (m, 2H), 5.73 (d, *J* = 7.9 Hz, 1H), 3.92 (d, *J* = 8.0 Hz, 1H), 2.28 (s, 3H), 1.78 – 1.67 (m, 1H), 1.64 – 1.54 (m, 2H), 1.31 (s, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.43, 138.56, 137.79, 128.62, 128.17, 128.06, 128.01, 127.69, 127.22, 80.77, 69.63, 57.84, 49.35, 34.54, 27.66, 24.70, 24.53, 23.61. FTIR (neat), cm^{-1}: 2955 (m), 1724 (s), 1454 (m), 1207 (m), 1138 (s). HRMS (ESI): Calcd for $(C_{22}H_{30}N_2O_2 + H)^+$: 355.2380. Found: 355.2382.



(*S*)-2-amino-3-cyclohexyl-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethylpropanamide (74)

A solution of *tert*-butyl imine **71** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to –78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at –78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to –50 °C. After 10 min, cyclohexylmethyl trifluoromethanesulfonate (**116**) (207 mg, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at –50 °C for 3 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 12 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (3% methanol-

dichloromethane, triethylamine pretreated silica gel) to provide α,α-disubstituted amide **74** as a white solid (110 mg, 83%, mp = 83-84 °C). The diastereomeric ratio of the crude material was determined to be ≥19:1 by ^{1}H NMR integration. TLC (10% methanol-dichloromethane): R_f = 0.52 (UV, $KMnO_4$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 – 7.13 (m, 6H), 7.10 – 7.07 (m, 2H), 7.05 – 7.00 (m, 2H), 5.74 (d, *J* = 7.8 Hz, 1H), 3.93 (d, *J* = 7.8 Hz, 1H), 2.28 (s, 3H), 1.71 (dd, *J* = 14.1, 6.8 Hz, 1H), 1.65 – 1.57 (m, 7H), 1.54 (dd, *J* = 14.1, 5.2 Hz, 1H), 1.36 (s, 1H), 1.29 (s, 3H), 1.21 – 1.05 (m, 3H), 0.97 – 0.93 (m, 1H), 0.86 – 0.77 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.51, 138.68, 137.79, 128.63, 128.17, 128.06, 128.01, 127.68, 127.27, 80.74, 69.61, 57.74, 48.20, 35.12, 34.57, 34.15, 34.12, 27.75, 26.48, 26.40, 26.27. FTIR (neat), cm^{-1}: 2926 (m), 1730 (s), 1454 (m), 1136 (m), 906 (s). HRMS (ESI): Calcd for $(C_{25}H_{34}N_2O_2 + H)^+$: 395.2700. Found: 395.2720.

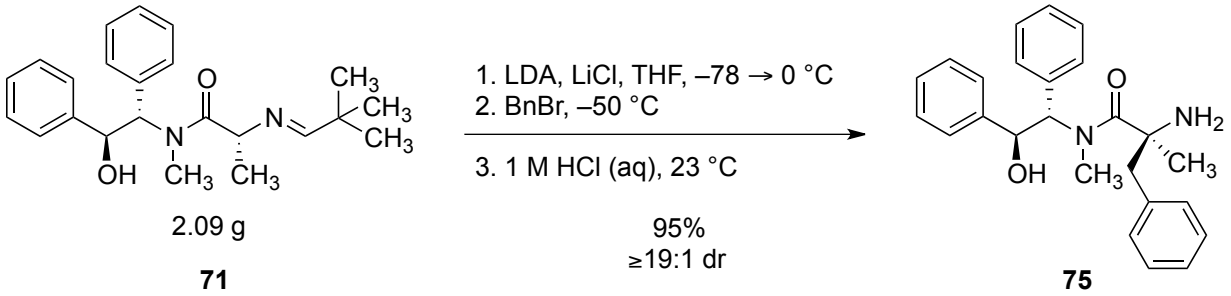


71 **75**

(*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethyl-3-phenylpropanamide (75)

A solution of *tert*-butyl imine **71** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to −78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at −78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to −50 °C. After 10 min, benzyl bromide (100 μL, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at −50 °C for 3.5 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 3 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (2→4% methanol-dichloromethane, triethylamine

pretreated silica gel) to provide α,α-disubstituted amide **75** as a white solid (116 mg, 89%, mp = 111-113 °C). The diastereomeric ratio of the crude material was determined to be ≥19:1 by ^{1}H NMR integration. TLC (10% methanol-dichloromethane): R_f = 0.47 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.15 (m, 6H), 7.13 – 7.05 (m, 2H), 7.04 – 6.98 (m, 2H), 5.79 (d, *J* = 7.6 Hz, 1H), 3.93 (d, *J* = 7.6 Hz, 1H), 3.12 (d, *J* = 13.3 Hz, 1H), 2.85 (d, *J* = 13.3 Hz, 1H), 2.25 (s, 3H), 1.91 (br s, 2H), 1.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.04, 138.35, 137.60, 136.26, 130.20, 128.55, 128.42, 128.23, 128.12, 128.01, 127.77, 127.11, 126.96, 80.62, 69.33, 58.85, 46.72, 34.47, 29.80, 26.30. FTIR (neat), cm^{-1}: 2926 (m), 2852 (m), 1732 (s), 1602 (m), 1454 (s). HRMS (ESI): Calcd for $(C_{25}H_{28}N_2O_2 + H)^+$: 389.2231. Found: 389.2234.



2.09 g

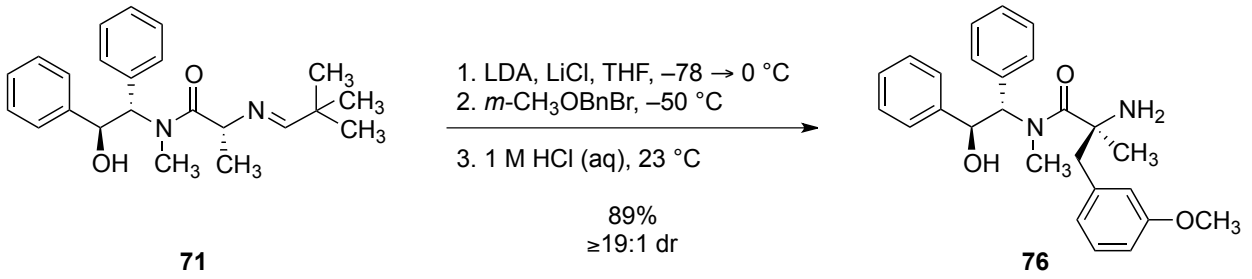
71

75

Larger scale synthesis of (*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethyl-3-phenylpropanamide (75)

A solution of *tert*-butyl imine **71** (2.09 g, 5.70 mmol, 1.00 equiv) in tetrahydrofuran (24.0 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (1.45 g, 34.2 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 7.00 mL). The resulting slurry was cooled to –78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 12.5 μL, 12.5 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask by cannula, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at –78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to –50 °C. After 10 min, benzyl bromide (1.69 mL, 14.2 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at –50 °C for 3.5 h, after which time 1 M aqueous hydrochloric acid solution (100 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 3 h. Ethyl acetate (20 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 30 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 100 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (3% methanol-dichloromethane, triethylamine

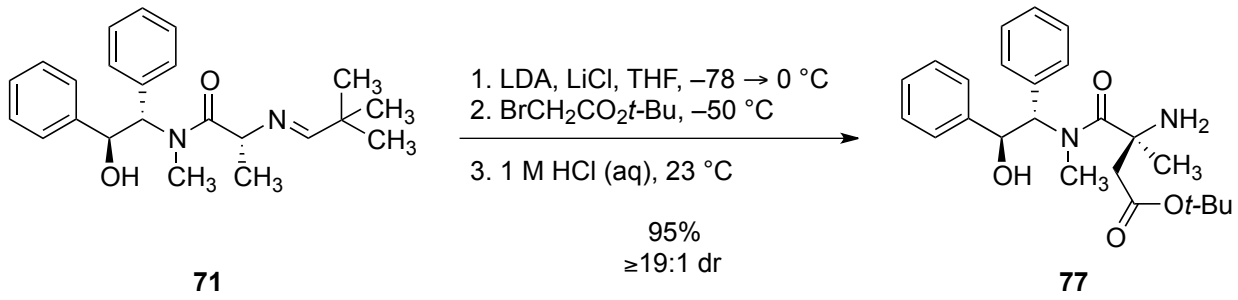
pretreated silica gel) to provide α,α-disubstituted amide **75** as a white solid (2.11 g, 95%). The diastereomeric ratio of the crude material was determined to be ≥19:1 by ^{1}H NMR integration. The characterization data were in agreement with the values for α,α-disubstituted amide **76** prepared on a smaller scale, as reported above.



(*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-3-(3-methoxyphenyl)-*N*,2-dimethylpropanamide (76)

A solution of *tert*-butyl imine **71** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to –78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at –78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to –50 °C. After 10 min, 3-methoxybenzyl bromide (117 μL, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at –50 °C for 3 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 2 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (2→4% methanol-dichloromethane, triethylamine

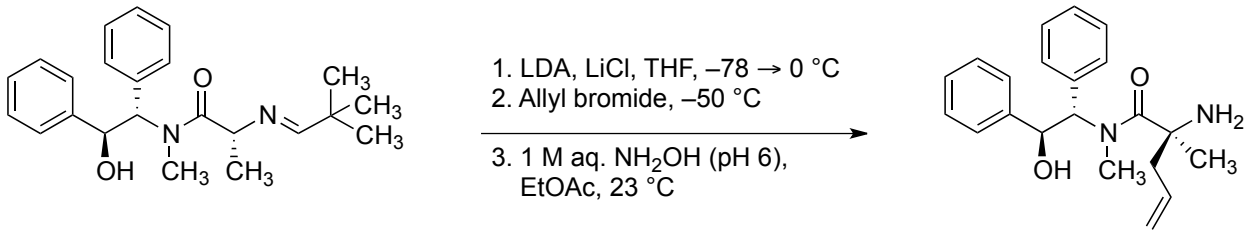
pretreated silica gel) to provide α,α-disubstituted amide **76** as a white solid (125 mg, 89%, mp = 52-53 °C). The diastereomeric ratio of the crude material was determined to be ≥19:1 by ^{1}H NMR integration. TLC (10% methanol-dichloromethane): R_f = 0.53 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.11 (m, 7H), 7.10 – 7.04 (m, 2H), 7.01 – 6.95 (m, 2H), 6.76 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.71 – 6.70 (m, 1H), 6.70 – 6.65 (m, 1H), 5.78 (d, *J* = 7.6 Hz, 1H), 3.92 (d, *J* = 7.7 Hz, 1H), 3.71 (s, 3H), 3.12 (d, *J* = 13.3 Hz, 1H), 2.82 (d, *J* = 13.3 Hz, 1H), 2.25 (s, 3H), 1.84 (br s, 2H), 1.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.15, 159.59, 138.54, 137.89, 137.64, 129.41, 128.55, 128.19, 128.10, 127.98, 127.73, 127.06, 122.48, 115.56, 112.76, 80.66, 69.48, 58.88, 55.20, 46.87, 34.55, 26.55. FTIR (neat), cm^{-1}: 2926 (m), 1732 (m), 1601 (m), 1454 (m), 1263 (m). HRMS (ESI): Calcd for $(C_{26}H_{30}N_2O_3 + H)^+$: 419.2329. Found: 419.2345.



(*S*)-*tert*-butyl 3-amino-4-(((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)(methyl)amino)-3-methyl-4-oxobutanoate (77)

A solution of *tert*-butyl imine **71** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to –78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at –78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to –50 °C. After 10 min, *tert*-butyl bromoacetate (124 μL, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at –50 °C for 2.5 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 1 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (1→2.5% methanol-dichloromethane, triethylamine

pretreated silica gel) to provide α,α-disubstituted amide **77** as a white solid (132 mg, 95%, mp = 83-84 °C). The diastereomeric ratio of the crude material was determined to be ≥19:1 by ^{1}H NMR integration. TLC (8% methanol-dichloromethane): R_f = 0.45 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 – 7.11 (m, 6H), 7.09 – 7.03 (m, 2H), 7.02 – 6.96 (m, 2H), 5.82 (d, *J* = 8.5 Hz, 1H), 3.90 (d, *J* = 8.5 Hz, 1H), 3.00 (d, *J* = 16.6 Hz, 1H), 2.55 (d, *J* = 16.5 Hz, 1H), 2.24 (s, 3H), 2.01 (br s, 2H), 1.46 (s, 9H), 1.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.35, 170.88, 138.64, 137.62, 128.77, 128.09, 127.98, 127.97, 127.63, 127.35, 81.76, 80.97, 69.90, 56.10, 45.63, 34.47, 28.21, 27.02. FTIR (neat), cm^{-1}: 2976 (m), 2793 (m), 1734 (s), 1367 (m), 1153 (s). HRMS (ESI): Calcd for $(C_{24}H_{32}N_2O_4 + H)^+$: 413.2442. Found: 413.2440.



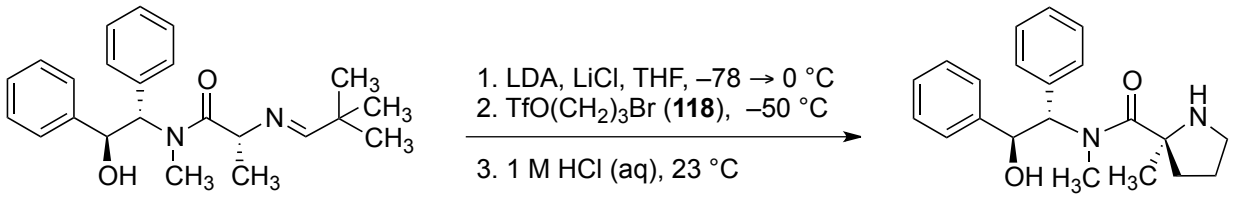
(*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethylpent-4-enamide (80)

A solution of *tert*-butyl imine **71** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to −78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at −78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to −50 °C. After 10 min, allyl bromide (72.6 μg, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at −50 °C for 3 h, after which time water (8 mL) and dichloromethane (10 mL) were added. The layers were separated, the aqueous layer was rapidly extracted with dichloromethane (3 x 20 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was dissolved in ethyl acetate (2 mL) and a stock solution of hydroxylamine hydrochloride in water[81] (5 mL) was added. The biphasic mixture was stirred vigorously at 23 °C for 1.5 h, after which time the aqueous layer was carefully brought to pH 14 by the addition of 2

[81] Prepared by dissolving hydroxylamine hydrochloride (1.39 g) in water (10.0 mL), followed by adjustment of the pH to 6 by the addition of saturated aqueous sodium bicarbonate solution (10.0 mL).

M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 40 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (3% methanol-dichloromethane, triethylamine pretreated silica gel) to provide α,α-disubstituted amide **80** as a white solid (91.0 mg, 80%, mp = 62-63 °C). The diastereomeric ratio of the crude material was determined to be ≥19:1 by ^{1}H NMR integration. TLC (10% methanol-dichloromethane): R_f = 0.50 (UV, $KMnO_4$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 – 7.13 (m, 6H), 7.13 – 7.05 (m, 2H), 7.06 – 7.01 (m, 2H), 5.78 (d, *J* = 7.9 Hz, 1H), 5.73 – 5.64 (m, 1H), 5.17 – 5.13 (m, 1H), 5.13 – 5.11 (m, 1H), 3.92 (d, *J* = 8.0 Hz, 1H), 2.59 (dd, *J* = 13.7, 5.9 Hz, 1H), 2.33 (dd, *J* = 14.0, 7.9 Hz, 1H), 2.26 (s, 3H), 1.94 (br s, 2H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.31, 138.44, 137.72, 132.99, 128.55, 128.23, 128.11, 128.07, 127.74, 127.16, 119.52, 80.71, 69.63, 57.62, 45.15, 34.44, 26.21. FTIR (neat), cm^{-1}: 2976 (m), 2793 (m), 1732 (s), 1205 (m), 1136 (s). HRMS (ESI): Calcd for $(C_{21}H_{26}N_2O_2 + H)^+$: 339.2074. Found: 339.2081.

Cyclic Products:

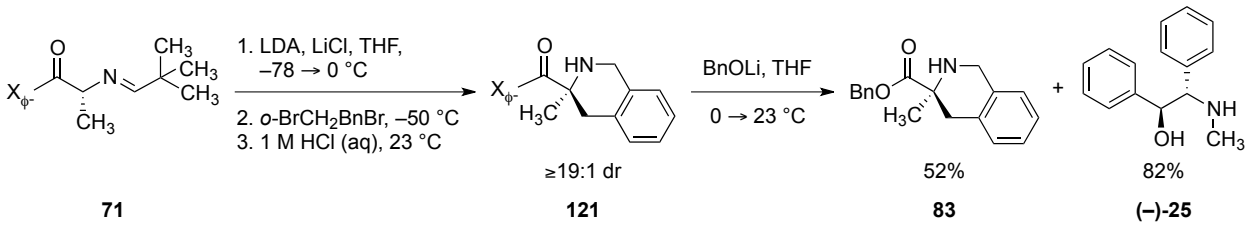


71 **82**

(*S*)-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethylpyrrolidine-2-carboxamide (82)

A solution of *tert*-butyl imine **71** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to –78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at –78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to –50 °C. After 10 min, 3-bromopropyl trifluoromethanesulfonate (**118**) (227 mg, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at –50 °C for 1.5 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 2 h. The mixture was cooled in an ice bath, and the aqueous layer was carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 40 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (3→4% methanol-dichloromethane, triethylamine pretreated silica gel) to provide cyclic α,α-disubstituted amide **82** as a colorless oil (90.0 mg, 79%). The diastereomeric ratio of the crude

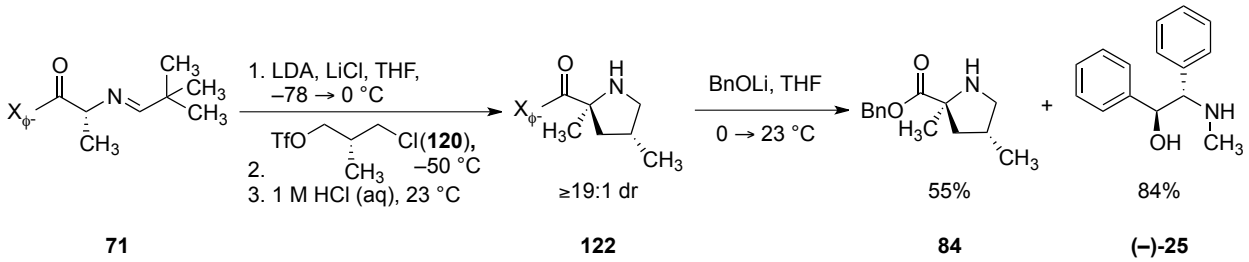
material was determined to be ≥19:1 by ^{1}H NMR integration. TLC (8% methanol-dichloromethane): R_f = 0.31 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.12 (m, 6H), 7.11 – 7.06 (m, 2H), 7.06 – 7.01 (m, 2H), 5.78 (d, *J* = 7.9 Hz, 1H), 3.92 (d, *J* = 7.7 Hz, 1H), 3.02 – 2.90 (m, 2H), 2.27 (s, 3H), 2.26 – 2.21 (m, 1H), 1.90 – 1.79 (m, 1H), 1.79 – 1.66 (m, 2H), 1.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.42, 138.55, 137.77, 128.52, 128.20, 128.12, 128.10, 128.03, 127.71, 127.09, 80.49, 69.68, 65.90, 46.55, 36.94, 34.53, 26.06, 25.27. . FTIR (neat), cm^{-1}: 2976 (m), 1728 (m), 1454 (m), 1170 (m), 1116 (m). HRMS (ESI): Calcd for $(C_{21}H_{26}N_2O_2 + H)^+$: 339.2074. Found: 339.2089.



(2*S*,4*S*)-benzyl 2,4-dimethylpyrrolidine-2-carboxylate (83)

A solution of *tert*-butyl imine **71** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to –78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at –78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to –50 °C. After 10 min, 1,2-bis(bromomethyl)benzene (2 M solution in tetrahydrofuran, 168 μL, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at –50 °C for 2.5 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 3 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was dissolved in tetrahydrofuran (2.60 mL), the resulting solution was cooled to 0 °C, and a freshly prepared solution of lithium phenylmethanolate in

tetrahydrofuran (1 M, 670 μL, 0.670 mmol, 2.00 equiv) was added dropwise to the crude mixture.[77] The solution was warmed to 23 °C for 3 h, after which time water (5 mL) and saturated aqueous sodium chloride solution (5 mL) were added. The aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (10% diethyl ether-dichloromethane, then 1→10% methanol-dichloromethane) to provide (1*S*,2*S*)-pseudoephenamine (62.0 mg, 82%) and benzyl ester **83** as a colorless oil (49.0 mg, 52%). The characterization data for the recovered auxiliary were in agreement with values previously reported. Benzyl ester **83**: The diastereomeric ratio of the crude material prior to cleavage of the auxiliary was determined to be ≥19:1 by ^{1}H NMR integration. TLC (1% methanol-dichloromethane): R_f = 0.29 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 3H), 7.18 – 7.11 (m, 4H), 7.11 – 7.06 (m, 1H), 7.02 – 6.98 (m, 1H), 5.12 (d, *J* = 12.5 Hz, 1H), 5.07 (d, *J* = 12.5 Hz, 1H), 4.13 (d, *J* = 15.9 Hz, 1H), 4.02 (d, *J* = 16.0 Hz, 1H), 3.30 (d, *J* = 16.0 Hz, 1H), 2.82 (d, *J* = 16.0 Hz, 1H), 1.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.91, 135.99, 133.78, 133.20, 129.03, 128.64, 128.24, 127.90, 126.31, 126.27, 126.11, 66.76, 58.22, 45.15, 37.89, 26.40. FTIR (neat), cm^{-1}: 2958 (m), 1728 (s), 1288 (m), 1178 (s), 1105 (s). HRMS (ESI): Calcd for $(C_{18}H_{19}NO_2 + H)^+$: 282.1496. Found: 282.1506.

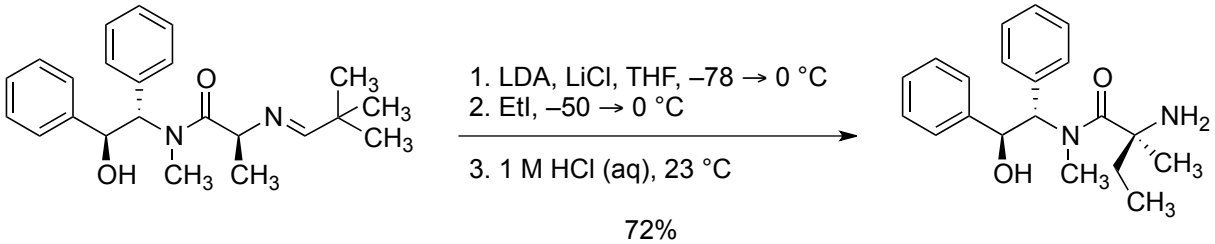


(2*S*,4*R*)-benzyl 2,4-dimethylpyrrolidine-2-carboxylate (84)

A solution of *tert*-butyl imine **71** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to −78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at −78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to −50 °C. After 10 min, triflate **120** (202 mg, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at −50 °C for 2 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 2 h. The mixture was cooled in an ice bath and the aqueous layer was carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 30 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was dissolved in tetrahydrofuran (2.60 mL), the resulting solution was cooled to 0 °C, and a freshly prepared solution of lithium phenylmethanolate in tetrahydrofuran (1 M, 670 μL, 0.670 mmol, 2.00 equiv) was added dropwise to the crude mixture.[77] The solution was warmed to 23 °C for 3 h, after which time water (5 mL) and saturated aqueous sodium

chloride solution (5 mL) were added. The aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (10% diethyl ether-dichloromethane, then 2→10% methanol-dichloromethane) to provide (1*S*,2*S*)-pseudoephenamine (64.0 mg, 84%) and benzyl ester **84** as a colorless oil (43.0 mg, 55%). The characterization data for the recovered auxiliary were in agreement with values previously reported. Benzyl ester **84**: The diastereomeric ratio of the crude material prior to cleavage of the auxiliary was determined to be ≥19:1 by ^{1}H NMR integration, and the relative stereochemistry of the ester product was determined by NOE correlations. TLC (10% methanol-dichloromethane): R_f = 0.54 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H), 5.15 (s, 2H), 3.17 (dd, *J* = 10.2, 7.8 Hz, 1H), 2.52 (dd, *J* = 10.3, 8.1 Hz, 1H), 2.43 (dd, *J* = 12.8, 7.4 Hz, 1H), 2.17 – 2.02 (m, 2H), 1.42 (s, 3H), 1.30 (dd, *J* = 12.8, 10.1 Hz, 1H), 1.01 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.60, 136.12, 128.72, 128.36, 128.03, 66.96, 66.68, 54.07, 45.98, 34.17, 26.60, 18.78. FTIR (neat), cm^{-1}: 2960 (m), 2872 (m), 1726 (s), 1163 (s), 1126 (s). HRMS (ESI): Calcd for $(C_{14}H_{19}NO_2 + H)^+$: 234.1496 Found: 234.1503.

Mismatched Case:

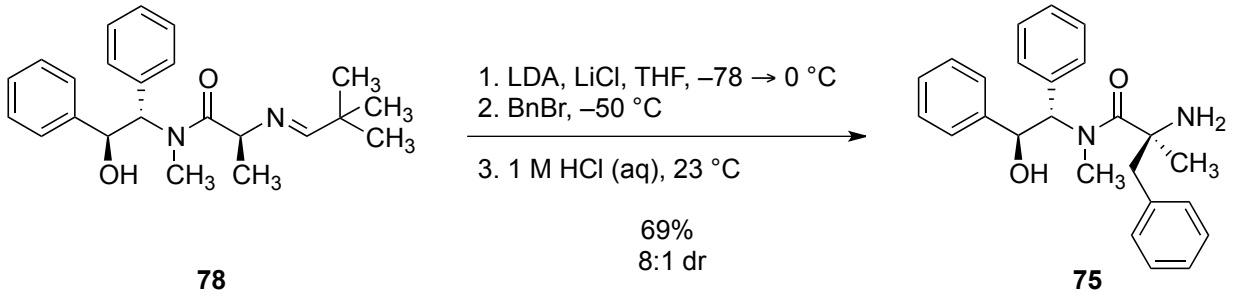


78 **72**

(*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethylbutanamide (72)

A solution of *tert*-butyl imine **78** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to –78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at –78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to –50 °C. After 10 min, ethyl iodide (67.8 μL, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at –50 °C for 30 min, and then was warmed to 0 °C for 4 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 1 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate

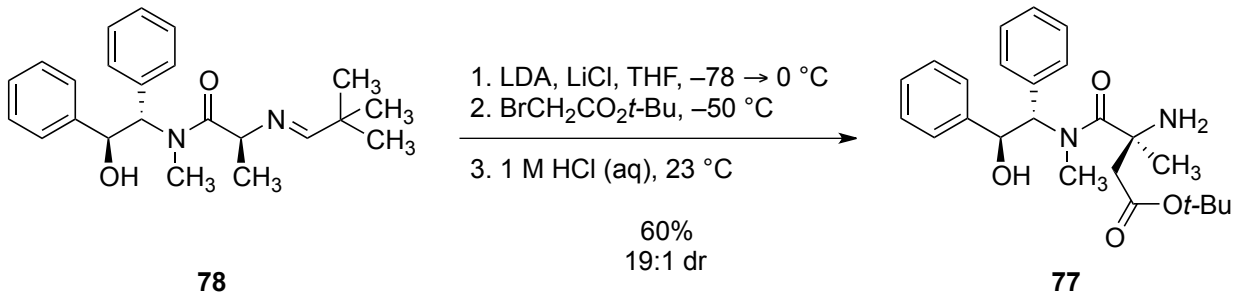
was concentrated. The diastereomeric ratio of the crude material was determined to be 13:1 by ^{1}H NMR integration. The residue was purified by flash chromatography (3% methanol-dichloromethane, triethylamine pretreated silica gel) to provide a 17:1 diastereomeric mixture of diastereomers favoring amide **72** (79 mg, 72%). The characterization data for the major and minor diastereomers were consistent with the values for α,α-disubstituted amide **72** reported above.



(*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethyl-3-phenylpropanamide (75)

A solution of *tert*-butyl imine **78** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to –78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at –78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to –50 °C. After 10 min, benzyl bromide (100 μL, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at –50 °C for 3.5 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 3 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The diastereomeric ratio of the crude material was determined to be 8:1 by ^{1}H NMR integration. The

residue was purified by flash chromatography (3% methanol-dichloromethane, triethylamine pretreated silica gel) to provide a 9:1 diastereomeric mixture of α,α-disubstituted amides **75** and **124** (90 mg, 69%). The characterization data for the major and minor diastereomers were consistent with the values for α,α-disubstituted amides **75** and **124**, respectively.

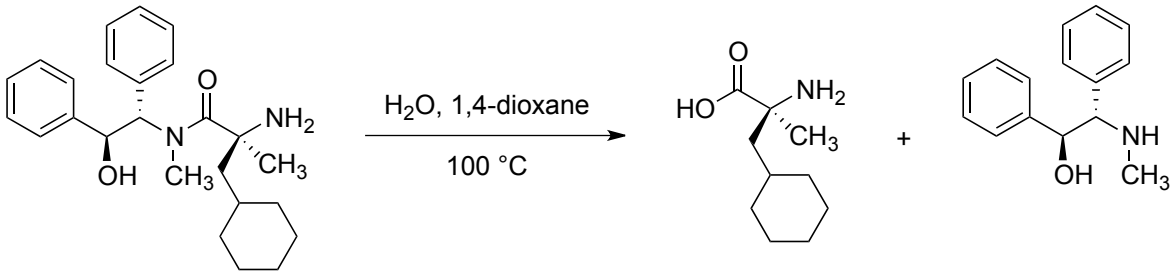


(*S*)-*tert*-butyl 3-amino-4-(((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)(methyl)amino)-3-methyl-4-oxobutanoate (77)

A solution of *tert*-butyl imine **78** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to –78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at –78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to –50 °C. After 10 min, *tert*-butyl bromoacetate (124 μL, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at –50 °C for 2.5 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 1 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The diastereomeric ratio of the crude material was determined to be 19:1 by ^{1}H NMR integration.

The residue was purified by flash chromatography (1→2.5% methanol-dichloromethane, triethylamine pretreated silica gel) to provide α,α-disubstituted amide **77** as a white solid (83 mg, 60%). The characterization data were in agreement with values for the same α,α-disubstituted amide **77** reported above.

Hydrolysis of α-methyl α-amino amides:

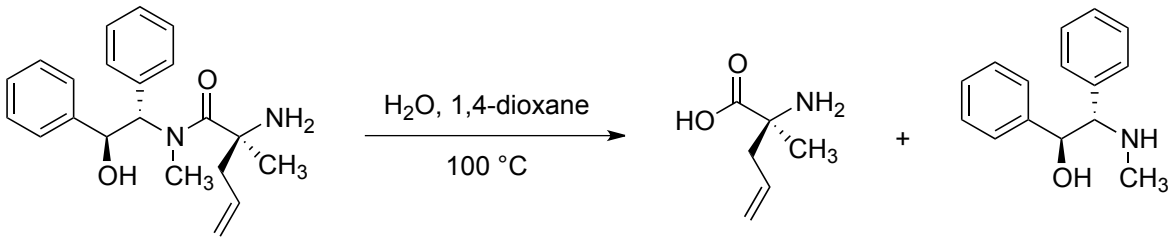


74 **85** **(–)-25**

99% 98%

(*S*)-2-amino-3-cyclohexyl-2-methylpropanoic acid (85)

α,α-disubstituted amide **74** (71.0 mg, 0.180 mol, 1.00 equiv) was dissolved in 1,4-dioxane (900 μL) and water (900 μL) was added. The mixture was refluxed at 100 °C for 2 h, after which time it was cooled to 23 °C and diluted with dichloromethane (3 mL). The layers were separated, and the aqueous solution was extracted with dichloromethane (4 x 7 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to provide (1*S*,2*S*)-pseudoephenamine (40.0 mg, 98%). The aqueous layer was concentrated in vacuo to provide α,α-disubstituted amino acid **85** as a white solid (33.0 mg, 99%)**.** The characterization data for the recovered auxiliary were in agreement with values previously reported.[6] α,α-disubstituted amino acid **85**: ^{1}H NMR (500 MHz, CD_3OD) δ 1.90 – 1.82 (m, 2H), 1.74 – 1.60 (m, 4H), 1.54 (dd, *J* = 14.6, 4.4 Hz, 1H), 1.51 – 1.43 (m, 1H), 1.42 (s, 3H), 1.38 – 1.22 (m, 2H), 1.22 – 1.10 (m, 1H), 1.08 – 0.92 (m, 2H). ^{13}C NMR (126 MHz, CD_3OD) δ 176.85, 61.91, 46.56, 36.17, 34.66, 34.47, 27.40, 27.22, 27.17, 25.02. FTIR (neat), cm^{-1}: 3331 (s), 2945 (m), 2833 (s), 1415 (m), 1024 (s). HRMS (ESI): Calcd for $(C_{10}H_{19}NO_2 + H)^+$: 186.1496. Found: 186.1504.



80 **86** **(–)-25**

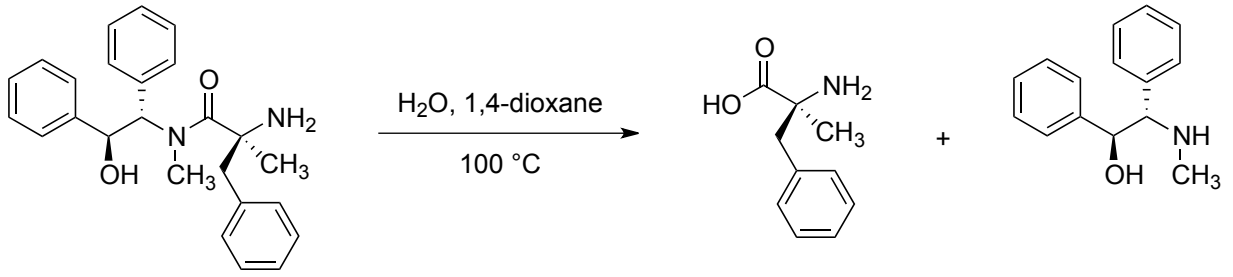
97%, 98% ee 94%

(*S*)-2-amino-2-methylpent-4-enoic acid (86)

α,α-disubstituted amide **80** (70.0 mg, 0.207 mmol, 1.00 equiv) was dissolved in 1,4-dioxane (1.03 mL) and water (1.03 mL) was added. The mixture was refluxed at 100 °C for 1 h, after which time it was cooled to 23 °C and diluted with dichloromethane (3 mL). The layers were separated, and the aqueous solution was extracted with dichloromethane (4 x 7 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to provide (1*S*,2*S*)-pseudoephenamine (44.0 mg, 94%). The aqueous layer was concentrated in vacuo to provide α,α-disubstituted amino acid **86** as a white solid (26.0 mg, 97%)**.** The characterization data for the recovered auxiliary were in agreement with values previously reported. Chiral HPLC analysis (Phenomenex Chirex 3126 (D)-penicillamine, 99:1 aqueous 2 mM copper (II) sulfate solution:*i*-PrOH, 0.5 mL/min, λ = 240 nm, t_R (major, amino acid **86**) = 11.3 min, t_R (minor, amino acid ***ent*-86**) = 15.4 min) of amino acid **86** established that **86** was of 98% ee. The characterization data for α,α-disubstituted amino acid 30 were in agreement with values previously reported:[82] ^{1}H NMR (500 MHz, D_2O) δ 5.81 – 5.68 (m, 1H), 5.34 – 5.22 (m, 2H), 2.65 (dd, *J* = 14.4, 6.6 Hz, 1H), 2.45 (dd, *J* = 14.4, 8.4 Hz, 1H), 1.48 (s, 3H). ^{13}C NMR (126 MHz, D_2O) δ 176.59, 130.80, 121.46, 61.13, 41.57, 22.12. FTIR

[82] Lu, T. J.; Lin, C. K. *J. Org. Chem.* **2011**, *76*, 1621–1633.

(neat), cm^{-1}: 3365 (s), 2839 (m), 2501 (s), 1444 (m), 1014 (s). HRMS (ESI): Calcd for $(C_6H_{11}NO_2 + Na)^+$: 152.0682. Found: 152.0680.



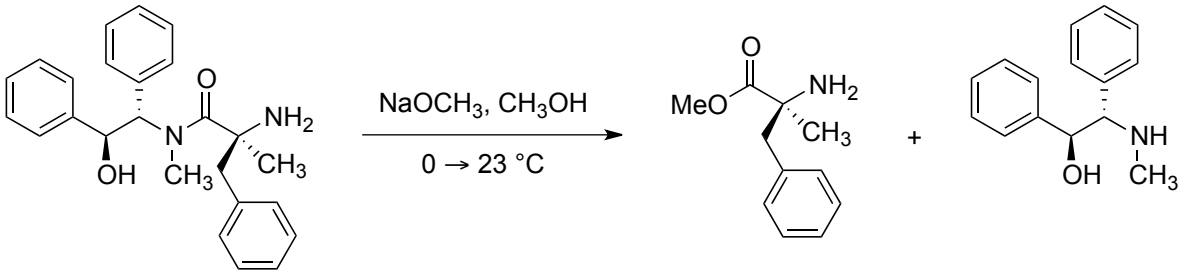
(*S*)-2-amino-2-methyl-3-phenylpropanoic acid (87)

α,α-disubstituted amide **75** (1.00 g, 2.57 mmol, 1.00 equiv) was dissolved in 1,4-dioxane (12.9 mL) and water (12.9 mL) was added. The mixture was refluxed at 100 °C for 3 h, after which time it was cooled to 23 °C and diluted with dichloromethane (30 mL). The layers were separated, and the aqueous solution was extracted with dichloromethane (4 x 30 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to provide (1*S*,2*S*)-pseudoephenamine (583 mg, ≥99%). The aqueous layer was concentrated in vacuo to provide α,α-disubstituted amino acid **87** as a white solid (460 mg, ≥99%)**.** The characterization data for the recovered auxiliary were in agreement with values previously reported.[6] Chiral HPLC analysis (Phenomenex Chirex 3126 (D)-penicillamine, 95:5 aqueous 2 mM copper (II) sulfate solution:*i*-PrOH, 0.5 mL/min, λ = 240 nm, t_R (major, amino acid **87**) = 25.7 min, t_R (minor, amino acid ***ent*-87**) = 39.9 min) of amino acid **87** established that **87** was of 98% ee. The characterization data for α,α-disubstituted amino acid **87** were in agreement with values previously reported:[83] ^{1}H NMR (500 MHz, D_2O) δ 7.43 – 7.34 (m, 3H), 7.29 – 7.24 (m, 2H), 3.30 (d, *J* = 14.2 Hz, 1H), 2.98 (d, *J* = 14.3 Hz, 1H), 1.55 (s, 3H). ^{13}C NMR (100 MHz, D_2O) δ 176.31, 134.31, 130.06, 129.06, 127.93, 62.26, 42.78, 22.48.

[83] Green, J. E.; Bender, D. M.; Jackson, S.; O'Donnell, M. J.; McCarthy, J. R. *Org. Lett.* **2009**, *11*, 807–810.

FTIR (neat), cm^{-1}: 3331 (s), 2945 (s), 2833 (s), 1448 (m), 1022 (s). HRMS (ESI): Calcd for $(C_{10}H_{13}NO_2 + H)^+$: 180.1026. Found: 180.1024.

Esterification of α-methyl α-amino amides:



75 **88** **(–)-25**

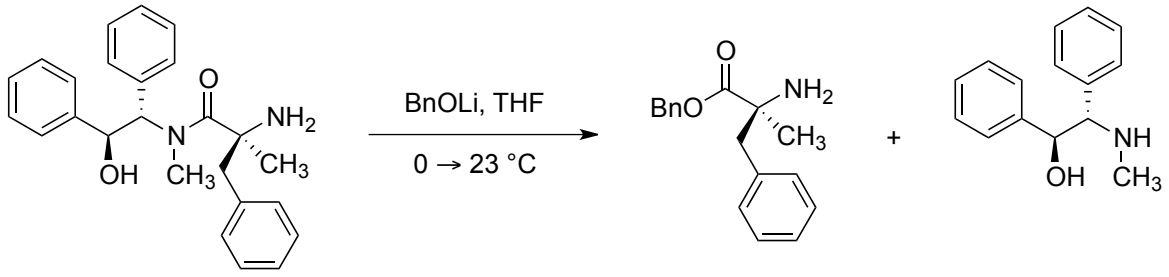
88% 91%

(*S*)-methyl 2-amino-2-methyl-3-phenylpropanoate (88)

Sodium methoxide (0.5 M solution in methanol, 772 μL, 0.386 mmol, 1.00 equiv) was added to a cooled (0 °C) solution of α,α-disubstituted amide **75** (150 mg, 0.386 mmol, 1.00 equiv) in anhydrous methanol (2.40 mL). The mixture was stirred at 23 °C for 3 h, after which time water (4 mL) and saturated aqueous sodium chloride solution (4 mL) were added. The aqueous layer was extracted with dichloromethane (3 x 20 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude residue was purified by flash chromatography (3→10% methanol-dichloromethane) to provide (1*S*,2*S*)-pseudoephenamine (80.0 mg, 91%) and methyl ester **88** as a colorless oil (66.0 mg, 88%). The characterization data for the recovered auxiliary were in agreement with values previously reported. The characterization data for methyl ester **88** were in agreement with values previously reported:[84] TLC (10% methanol-dichloromethane): R_f = 0.56 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 3H), 7.19 – 7.13 (m, 2H), 3.72 (s, 3H), 3.15 (d, *J* = 13.2 Hz, 1H), 2.81 (d, *J* = 13.2 Hz, 1H), 1.58 (br s, 2H), 1.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.67, 136.68, 130.06, 128.47, 127.07, 58.97, 52.23, 47.07, 26.79. FTIR (neat), cm^{-1}: 3030 (m),

[84] Smith, N. D.; Wohlrab, A. M.; Goodman, M. *Org. Lett.* **2005**, *7*, 255–258.

2951 (m), 1732 (s), 1454 (m), 1197 (s). HRMS (ESI): Calcd for $(C_{11}H_{15}NO_2 + H)^+$: 194.1176 Found: 194.1172.



75 **89** **(–)-25**

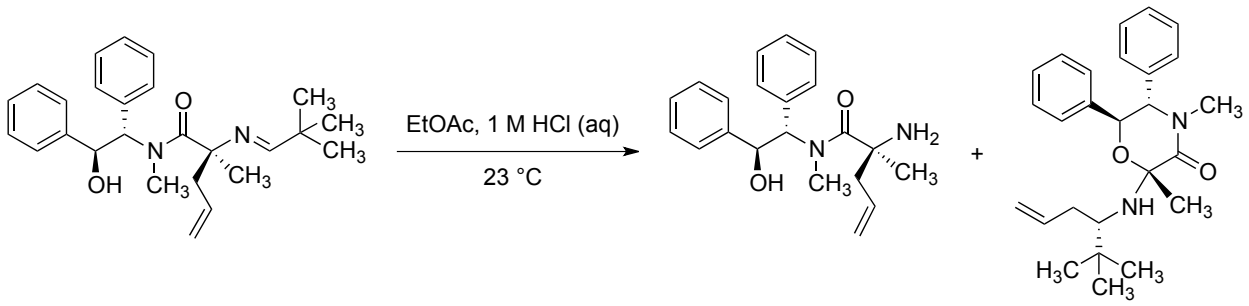
84% 83%

(*S*)-benzyl 2-amino-2-methyl-3-phenylpropanoate (89)

A freshly titrated solution of *n*-butyllithium in hexanes (2.39 M, 113 μL, 1.50 equiv) was added to a cooled (0 °C) solution of benzyl alcohol (37.3 μL, 0.360 mmol, 2.00 equiv) in tetrahydrofuran (200 μL).[5] A solution of α,α-disubstituted amide **75** (70.0 mg, 0.180 mmol, 1.00 equiv) in tetrahydrofuran (800 μL) was transferred to the cold benzyl alkoxide solution via syringe and the transfer was quantitated with tetrahydrofuran (2 x 400 μL). The reaction mixture was stirred at 0 °C for 1 h and then at 23 °C for 1.5 h, after which time water (5 mL) and dichloromethane (5 mL) were added. The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 15 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude residue was purified by flash chromatography (10% diethyl ether-dichloromethane, then 10% methanol-dichloromethane) to provide (1*S*,2*S*)-pseudoephenamine (36.0 mg, 88%) and benzyl ester **89** as a colorless oil (41.0 mg, 84%). The characterization data for the recovered auxiliary were in agreement with values previously reported. Benzyl ester **89**: TLC (40% ethyl acetate-hexanes): R_f = 0.30 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 5H), 7.22 (dd, *J* = 4.8, 1.9 Hz, 3H), 7.12 – 7.06 (m, 2H), 5.13 (s, 2H), 3.15 (d, *J* = 13.2 Hz, 1H), 2.81 (d, *J* = 13.2 Hz, 1H), 1.62 (br s, 2H), 1.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.02, 136.56, 135.78, 130.10,

128.72, 128.50, 128.47, 128.44, 127.01, 67.01, 58.97, 46.95, 26.80. FTIR (neat), cm^{-1}: 3032 (m), 1728 (s), 1496 (m), 1170 (s), 906 (s). HRMS (ESI): Calcd for $(C_{17}H_{19}NO_2 + H)^+$: 270.1489 Found: 270.1497.

Aza-Cope Rearrangement of α-methyl α-allyl pivaldimine:



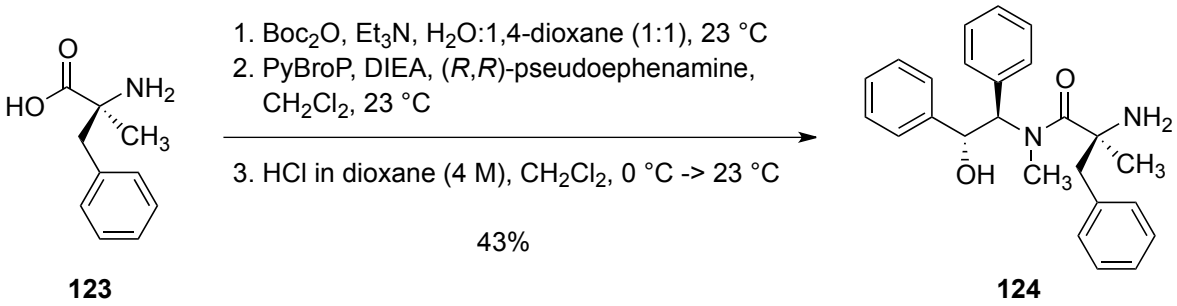
(*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethylpent-4-enamide (80) and (2*R*,5*S*,6*S*)-2-(((*S*)-2,2-dimethylhex-5-en-3-yl)amino)-2,4-dimethyl-5,6-diphenylmorpholin-3-one (81)

Crude allylated imine **125** was obtained via alkylation of *tert*-butyl imine **71** with allyl bromide, similar to the synthesis of α,α-disubstituted amide **80**, with the omission of the final imine hydrolysis step using aqueous hydroxylamine solution. 1 M aqueous hydrochloric acid solution (7 mL) was added to a solution of crude allylated imine **125** (65.0 mg, 0.160 mmol, 1.00 equiv) in ethyl acetate (1.50 mL). The biphasic mixture was stirred vigorously at 23 °C for 3h, after which time ethyl acetate (8 mL) was added. The layers were separated, the organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL), followed by saturated aqueous sodium bicarbonate solution (10 mL). The organic layer was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated. The crude residue was purified by flash chromatography (10% ethyl acetate-hexanes) to provide morpholinone **81** (33.0 mg, 50%) as a colorless solid. The diastereomeric ratio of the crude material was determined to be 7:1 by ^{1}H NMR integration. Morpholinone **81**: TLC (20% ethyl acetate-hexanes): R_f = 0.37 (UV, $KMnO_4$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 – 7.22 (m, 3H), 7.22 – 7.13 (m, 3H), 7.01 – 6.96 (m, 2H), 6.96 – 6.91 (m, 2H), 5.95 – 5.86 (m, 1H), 5.27 (d, *J* = 9.7 Hz, 1H), 4.79 – 4.74 (m, 1H),

4.72 (d, *J* = 10.2 Hz, 1H), 4.48 (d, *J* = 9.8 Hz, 1H), 2.77 (t, *J* = 4.7 Hz, 1H), 2.67 (s, 3H), 2.25 – 2.19 (m, 1H), 2.17 – 2.11 (m, 1H), 2.01 (s, 1H), 1.67 (s, 3H), 0.98 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.02, 138.13, 137.66, 136.46, 128.76, 128.42, 128.25, 128.10, 128.04, 127.80, 114.91, 89.61, 74.51, 70.61, 59.20, 37.54, 35.67, 32.86, 27.59, 24.04. FTIR (neat), cm^{-1}: 2957 (m), 1651 (s), 1477 (m), 1396 (m), 1101 (s). HRMS (ESI): Calcd for $(C_{26}H_{34}N_2O_2 + H)^+$: 407.2693. Found: 407.2707.

The acidic aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 40 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (3% methanol-dichloromethane, triethylamine pretreated silica gel) to provide α,α-disubstituted amide **80** as a white solid (18.0 mg, 33%). The diastereomeric ratio of the crude material was determined to be ≥19:1 by ^{1}H NMR integration and the characterization data were in agreement with values for the same α,α-disubstituted amide **80** reported above.

Synthesis of (*S*)-2-amino-*N*-((1*R*,2*R*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethyl-3-phenyl propanamide for spectroscopic comparison:



123 **124**

(*S*)-2-amino-*N*-((1*R*,2*R*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethyl-3-phenylpropanamide (124)

A solution of commercially available L-α-methylphenylalanine (50.0 mg, 0.279 mmol, 1.00 equiv) in water (1.10 mL) and 1,4-dioxane (1.10 mL) was treated with triethylamine (156 μL, 1.12 mmol, 4.00 equiv) and di-*tert*-butyl dicarbonate (130 μL, 0.558 mmol, 2.00 equiv).[85] The mixture was stirred at 23 °C for 12 h, after which time 1 M aqueous hydrochloric acid solution (2 mL) and ethyl acetate (10 mL) were added. The layers were separated and the organic phase was extracted with saturated aqueous sodium chloride solution (10 mL). The organic layer was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated to provide *N*-(*tert*-butoxycarbonyl)-L-α-methylphenylalanine as a white foam. In the following step, (1*R*,2*R*)-pseudoephenamine (22.4 mg, 0.098 mmol, 1.10 equiv), bromotripyrrolidinophosphonium hexafluorophosphate (28.7 mg, 0.089 mmol, 1.00 equiv) and *N*,*N*-diisopropylethylamine (39.1 μL, 0.224 mmol, 2.50 equiv) were added to a solution of the crude *N*-(*tert*-butoxycarbonyl)-L-α-methylphenylalanine (25.0 mg, 0.089 mmol, 1.00 equiv) in

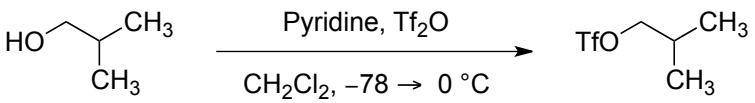
[85] Costanzo, M. J.; Almond, H. R.; Hecker, L. R.; Schott, M. R.; Yabut, S. C.; Zhang, H. C.; Andrade-Gordon, P.; Corcoran, T. W.; Giardino, E. C.; Kauffman, J. A.; Lewis, J. M.; de Garavilla, L.; Haertlein, B. J.; Maryanoff, B. E. *J. Med. Chem.* **2005**, *48*, 1984–2008.

dichloromethane (360 μL).[86,87] The cloudy mixture was stirred at 23 °C for 15 h, after which time dichloromethane (10 mL) and saturated aqueous sodium chloride solution (10 mL) were added. The layers were separated and the organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to provide a colorless oil. A solution of hydrogen chloride in dioxane (4 M, 100 μL, 0.400 mmol, 4.49 equiv) was added dropwise to a solution of this oil in dichloromethane (200 μL) at 0 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C. The mixture was stirred at 23 °C for 1.5 h, after which time the reaction mixture was brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 7 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (5% methanol-dichloromethane) to provide α,α-disubstituted amide **124** as a white foam (15.0 mg, 43%). The ^{1}H NMR, ^{13}C NMR and MS data obtained for α,α-disubstituted amide **124** were consistent with the values for the opposite diastereomer of α,α-disubstituted amide **76** reported above. TLC (10% methanol-dichloromethane): R_f = 0.51 (UV, $KMnO_4$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 – 7.11 (m, 9H), 7.11 – 7.06 (m, 2H), 7.05 – 6.98 (m, 2H), 6.98 – 6.93 (m, 2H), 5.84 (d, *J* = 8.0 Hz, 1H), 3.93 (d, *J* = 8.0 Hz, 1H), 3.08 (d, *J* = 13.3 Hz, 1H), 2.80 (d, *J* = 13.3 Hz, 1H), 2.24 (s, 3H), 1.65 (br s, 2H), 1.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.13, 138.45, 137.31, 130.21, 128.58, 128.33, 128.17, 128.13, 127.71, 127.67, 126.91, 80.44, 69.20, 58.86, 46.59, 34.43, 26.77. FTIR (neat), cm^{-1}: 3030 (m), 2935 (m), 1720 (s), 1454 (s), 1168 (s). HRMS (ESI): Calcd for $(C_{25}H_{28}N_2O_2 + H)^+$: 389.2231. Found: 389.2234.

[86] Coste, J.; Frerot, E.; Jouin, P. *J. Org. Chem.* **1994**, *59*, 2437–2446.

[87] Frerot, E.; Coste, J.; Pantaloni, A.; Dufour, M. N.; Jouin, P. *Tetrahedron* **1991**, *47*, 259–270.

Preparation of Alkyl Triflate Reagents:

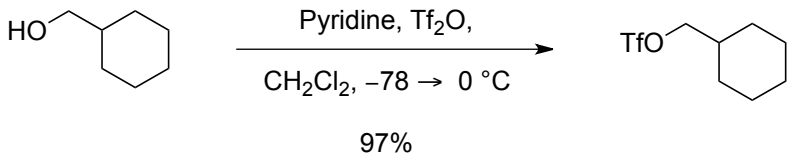


113 77% **114**

Isobutyl trifluoromethanesulfonate (114)

Pyridine (421 μL, 5.20 mmol, 1.20 equiv) was added to a stirring solution of isobutanol (400 μL, 4.33 mmol, 1.00 equiv) in dichloromethane (4.33 mL) at −78 °C.[88] Trifluormethanesulfonic anhydride (739 μL, 4.38 mmol, 1.01 equiv) was added dropwise over 1 min, and stirring was continued at −78 °C for 5 min. The solution was then warmed to 0 °C for 25 min, after which time the mixture was diluted with pentane (10 mL) and cold (0 °C) 1 M aqueous sulfuric acid solution (10 mL). The layers were separated, the organic layer was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the colorless liquid was dried under high vacuum for 30 sec. Triflate **114** (689 mg, 77%) was used in subsequent reactions without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (d, J = 6.4 Hz, 2H), 2.18 – 2.08 (m, 1H), 1.03 (d, J = 6.8 Hz, 6H).

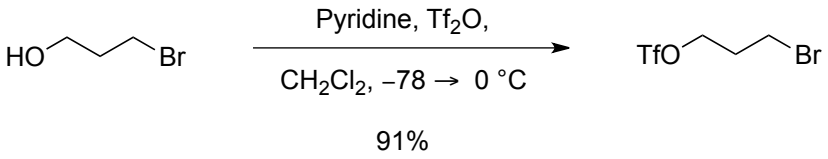
[88] Chi, D. Y.; Kilbourn, M. R.; Katzenellenbogen, J. A.; Welch, M. J. *J. Org. Chem.* **1987**, *52*, 658–664.



115 **116**

Cyclohexylmethyl trifluoromethanesulfonate (116)

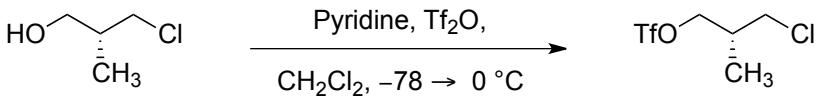
Pyridine (394 μL, 4.88 mmol, 1.20 equiv) was added to a stirring solution of cyclohexanemethanol (500 μL, 4.06 mmol, 1.00 equiv) in dichloromethane (4.06 mL) at –78 °C.[86] Trifluormethanesulfonic anhydride (693 μL, 4.10 mmol, 1.01 equiv) was added dropwise over 1 min, and stirring was continued at –78 °C for 5 min. The solution was then warmed to 0 °C for 25 min, after which time the mixture was diluted with pentane (10 mL) and cold (0 °C) 1 M aqueous sulfuric acid solution (10 mL). The layers were separated, the organic layer was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the light yellow liquid was dried under high vacuum for 30 sec. Triflate **116** (969 mg, 97%) was used in subsequent reactions without further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.33 (d, *J* = 6.1 Hz, 2H), 1.84 – 1.75 (m, 5H), 1.74 – 1.68 (m, 1H), 1.33 – 1.13 (m, 3H), 1.09 – 0.98 (m, 2H).



117 **118**

3-Bromopropyl trifluoromethanesulfonate (118)

Pyridine (268 μL, 3.32 mmol, 1.20 equiv) was added to a stirring solution of 3-bromopropan-1-ol (250 μL, 2.76 mmol, 1.00 equiv) in dichloromethane (2.77 mL) at –78 °C.[116] Trifluormethanesulfonic anhydride (472 μL, 2.79 mmol, 1.01 equiv) was added dropwise over 1 min, and stirring was continued at –78 °C for 5 min. The solution was then warmed to 0 °C for 40 min, after which time the mixture was diluted with pentane (10 mL) and cold (0 °C) 1 M aqueous sulfuric acid solution (10 mL). The layers were separated, the organic layer was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the colorless liquid was dried under high vacuum for 30 sec. Triflate **118** (680 mg, 91%) was used in subsequent reactions without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (t, J = 5.8 Hz, 2H), 3.51 (t, J = 6.2 Hz, 2H), 2.36 (tt, J = 6.1 Hz, J = 6.2 Hz, 2H).



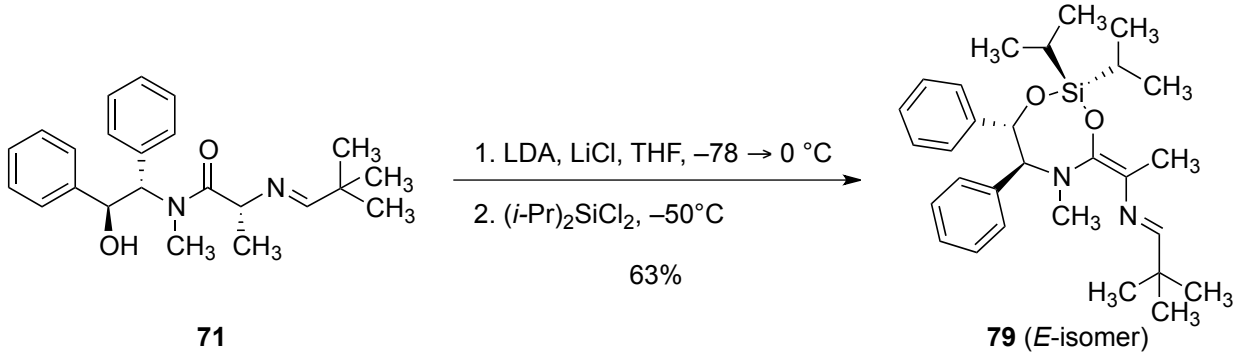
119 **120**

(*R*)-3-Chloro-2-methylpropyl trifluoromethanesulfonate (120)

Pyridine (156 μL, 1.93 mmol, 1.20 equiv) was added to a stirring solution of (*R*)-3-chloro-2-methylpropan-1-ol[89] (175 mg, 1.61 mmol, 1.00 equiv) in dichloromethane (1.61 mL) at −78 °C.[14] Trifluormethanesulfonic anhydride (275 μL, 1.63 mmol, 1.01 equiv) was added dropwise over 1 min, and stirring was continued at −78 °C for 5 min. The solution was then warmed to 0 °C for 30 min, after which time the mixture was diluted with pentane (10 mL) and cold (0 °C) 1 M aqueous sulfuric acid solution (10 mL). The layers were separated, the organic layer was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the light brown liquid was dried under high vacuum for 30 sec. Triflate **120** (265 mg, 68%) was used in subsequent reactions without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (d, *J* = 5.7 Hz, 2H), 3.63 (dd, *J* = 11.4, 4.6 Hz, 1H), 3.54 (dd, *J* = 11.4, 6.2 Hz, 1H), 2.43 – 2.33 (m, 1H), 1.14 (d, *J* = 7.0 Hz, 3H).

[89] Gaucher, A.; Ollivier, J.; Marguerite, J.; Paugam, R.; Salaun, J. *Canadian Journal of Chemistry* **1994**, *72*, 1312–1327.

Pseudoephenamine Alaninamide Pivaldimine Enolate Trapping Experiment:



71 **79** (*E*-isomer)

Cyclic siloxane (79, *E*-isomer)

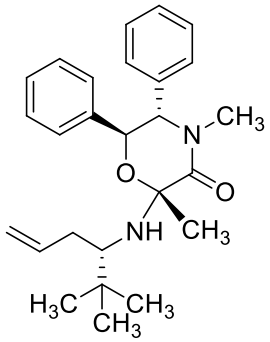
A solution of *tert*-butyl imine **71** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to –78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at –78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to –50 °C. After 10 min, distilled dichlorodiisopropylsilane (84.8 μL, 0.470 mmol, 1.20 equiv) was added by syringe. The mixture was stirred at –50 °C for 2.5 h, then was first concentrated by rotary evaporation (~40 mmHg) at 23 °C, afterwards with a vacuum manifold (1 mmHg) for 30 min at 23 °C. Dry benzene (2 mL) was added to the residue and the resulting suspension was filtered through oven-dried basic alumina, rinsing with additional benzene (5 x 2 mL). The filtrate was concentrated to provide cyclic siloxane **79** as a pale yellow oil (101 mg, 63%). The *E*-geometry of the product was confirmed by a NOE correlation between the protons of the *N*-methyl and *tert*-butyl group. TLC (10% ethyl acetate-hexanes): R_f = 0.42

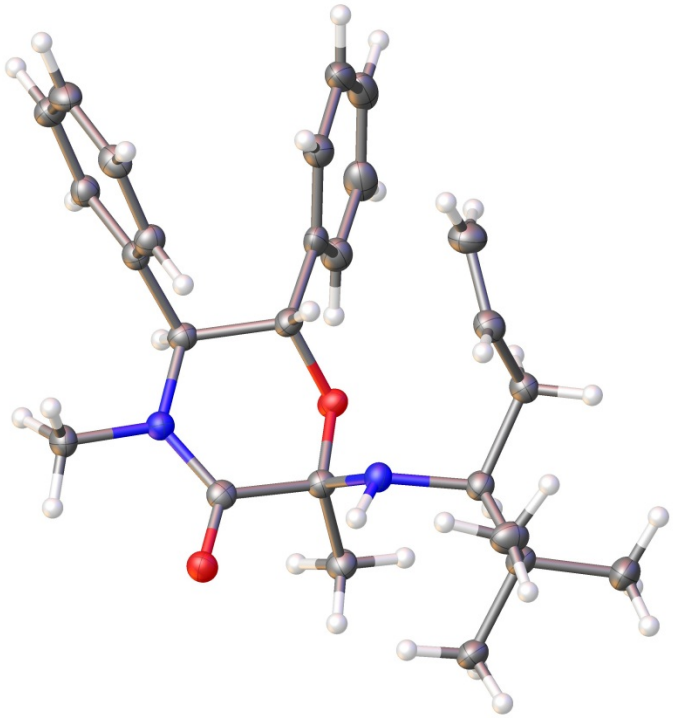
(UV, $KMnO_4$). ^1H NMR (500 MHz, C_6D_6) δ 7.21 – 7.14 (m, 4H), 7.06 – 6.87 (m, 7H), 5.49 (d, *J* = 10.3 Hz, 1H), 4.00 (d, *J* = 10.3 Hz, 1H), 2.95 (s, 3H), 2.07 (s, 3H), 1.34 – 1.13 (m, 14H), 0.87 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 157.97, 150.31, 141.85, 138.18, 129.76, 128.59, 128.35, 128.16, 127.97, 127.66, 127.32, 114.24, 78.02, 75.78, 43.21, 36.63, 27.76, 17.75, 17.57, 17.52, 17.33, 13.78, 13.66, 11.03. FTIR (neat), cm^{-1}: 3036 (m), 1815 (m), 1479 (s), 1035 (m), 812 (m). HRMS (ESI): Calcd for $(C_{29}H_{42}N_2O_2Si + H)^+$: 479.3096. Found: 479.3095.

X-ray Data:

X-ray Crystallographic Laboratory
Harvard University

Structure Report
Shao-Liang Zheng





CCDC Deposition Number: CCDC 961878

X-Ray Crystallography: Data was collected at 180 K from a crystal mounted on a diffractometer. The intensities of the reflections were collected by means of a Bruker APEX II DUO CCD diffractometer ($Cu_{K\alpha}$ radiation, λ=1.54178 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 1.0° scans in ω at 30°, 55°, 80° and 115° in 2θ. Data integration down to 0.84 Å resolution was carried out using SAINT V7.46 A (Bruker diffractometer, 2009) with reflection spot size optimization. Absorption corrections were made with the program SADABS (Bruker diffractometer, 2009). The structure was solved by the direct methods procedure and refined by least-squares methods again F^2 using SHELXS-97 and SHELXL-97 (Sheldrick, 2008). Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table 1, and geometric parameters are shown in Table 2. The Ortep plots produced with SHELXL-97 program, and the other drawings were produced with Accelrys DS Visualizer 2.0 (Accelrys, 2007).

Table 3.1: Experimental details

	(39lpEE)
Crystal data	
Chemical formula	$C_{26}H_{34}N_2O_2$
M_r	406.55
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	100
a, b, c (Å)	9.0583 (2), 14.4124 (4), 17.2685 (4)
V (Å^3)	2254.43 (10)
Z	4
Radiation type	Cu Ka
m (mm^{-1})	0.59
Crystal size (mm)	0.20 × 0.18 × 0.14
Data collection	

Table 3.1 (continued)

Diffractometer	Bruker D8 goniometer with CCD area detector diffractometer
Absorption correction	Multi-scan *SADABS*
T_{min}, T_{max}	0.892, 0.922
No. of measured, independent and observed [$I > 2s(I)$] reflections	33748, 3915, 3894
R_{int}	0.034
(sin q/l)$_{max}$ (Å^{-1})	0.594
Refinement	
$R[F^2 > 2s(F^2)]$, $wR(F^2)$, S	0.027, 0.069, 1.09
No. of reflections	3915
No. of parameters	280
No. of restraints	0
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
Dρ$_{max}$, Dρ$_{min}$ (e Å^{-3})	0.12, -0.19
Absolute structure	Flack H D (1983), Acta Cryst. A39, 876-881
Flack parameter	0.06 (15)

Computer programs: *APEX2* v2009.3.0 (Bruker-AXS, 2009), *SAINT* 7.46A (Bruker-AXS, 2009), *SHELXS97* (Sheldrick, 2008), *SHELXL97* (Sheldrick, 2008), Bruker *SHELXTL* (Sheldrick, 2008).

Table 3.2: Geometric parameters (Å, º)

C1—O1	1.2309 (15)	C12—H12A	0.9800
C1—N1	1.3450 (15)	C12—H12B	0.9800
C1—C2	1.5425 (16)	C12—H12C	0.9800
C2—O2	1.4257 (14)	C13—H13A	0.9800
C2—N2	1.4610 (15)	C13—H13B	0.9800
C2—C5	1.5308 (16)	C13—H13C	0.9800
C3—O2	1.4268 (14)	C14—C19	1.3922 (19)
C3—C14	1.5088 (17)	C14—C15	1.3940 (18)
C3—C4	1.5378 (16)	C15—C16	1.396 (2)
C3—H3	1.0000	C15—H15	0.9500
C4—N1	1.4786 (15)	C16—C17	1.382 (2)
C4—C20	1.5139 (16)	C16—H16	0.9500
C4—H4	1.0000	C17—C18	1.382 (2)
C5—H5A	0.9800	C17—H17	0.9500

Table 3.2 (continued)

C5—H5B	0.9800	C18—C19	1.3863 (19)
C5—H5C	0.9800	C18—H18	0.9500
C6—N2	1.4774 (15)	C19—H19	0.9500
C6—C7	1.5473 (16)	C20—C25	1.3894 (16)
C6—C10	1.5592 (16)	C20—C21	1.3950 (17)
C6—H6	1.0000	C21—C22	1.3831 (18)
C7—C8	1.5031 (17)	C21—H21	0.9500
C7—H7A	0.9900	C22—C23	1.3887 (18)
C7—H7B	0.9900	C22—H22	0.9500
C8—C9	1.3189 (19)	C23—C24	1.3889 (19)
C8—H8	0.9500	C23—H23	0.9500
C9—H9A	0.9500	C24—C25	1.3907 (17)
C9—H9B	0.9500	C24—H24	0.9500
C10—C12	1.5336 (18)	C25—H25	0.9500
C10—C13	1.5377 (17)	C26—N1	1.4642 (15)
C10—C11	1.5420 (17)	C26—H26A	0.9800
C11—H11A	0.9800	C26—H26B	0.9800
C11—H11B	0.9800	C26—H26C	0.9800
C11—H11C	0.9800	N2—H2	0.887 (16)
O1—C1—N1	122.98 (11)	H12A—C12—H12B	109.5
O1—C1—C2	118.09 (10)	C10—C12—H12C	109.5
N1—C1—C2	118.92 (10)	H12A—C12—H12C	109.5
O2—C2—N2	110.74 (9)	H12B—C12—H12C	109.5
O2—C2—C5	103.72 (9)	C10—C13—H13A	109.5
N2—C2—C5	117.14 (10)	C10—C13—H13B	109.5
O2—C2—C1	113.13 (9)	H13A—C13—H13B	109.5
N2—C2—C1	103.61 (9)	C10—C13—H13C	109.5
C5—C2—C1	108.80 (9)	H13A—C13—H13C	109.5
O2—C3—C14	107.78 (10)	H13B—C13—H13C	109.5
O2—C3—C4	108.86 (9)	C19—C14—C15	118.89 (12)
C14—C3—C4	110.85 (9)	C19—C14—C3	120.16 (11)
O2—C3—H3	109.8	C15—C14—C3	120.91 (12)
C14—C3—H3	109.8	C14—C15—C16	119.83 (13)
C4—C3—H3	109.8	C14—C15—H15	120.1
N1—C4—C20	111.62 (9)	C16—C15—H15	120.1

Table 3.2 (continued)

N1—C4—C3	109.16 (9)	C17—C16—C15	120.63 (13)
C20—C4—C3	109.20 (9)	C17—C16—H16	119.7
N1—C4—H4	108.9	C15—C16—H16	119.7
C20—C4—H4	108.9	C18—C17—C16	119.64 (12)
C3—C4—H4	108.9	C18—C17—H17	120.2
C2—C5—H5A	109.5	C16—C17—H17	120.2
C2—C5—H5B	109.5	C17—C18—C19	120.13 (14)
H5A—C5—H5B	109.5	C17—C18—H18	119.9
C2—C5—H5C	109.5	C19—C18—H18	119.9
H5A—C5—H5C	109.5	C18—C19—C14	120.86 (13)
H5B—C5—H5C	109.5	C18—C19—H19	119.6
N2—C6—C7	109.23 (9)	C14—C19—H19	119.6
N2—C6—C10	111.88 (10)	C25—C20—C21	119.19 (11)
C7—C6—C10	116.12 (10)	C25—C20—C4	120.79 (10)
N2—C6—H6	106.3	C21—C20—C4	119.80 (11)
C7—C6—H6	106.3	C22—C21—C20	120.73 (11)
C10—C6—H6	106.3	C22—C21—H21	119.6
C8—C7—C6	116.29 (10)	C20—C21—H21	119.6
C8—C7—H7A	108.2	C21—C22—C23	119.85 (11)
C6—C7—H7A	108.2	C21—C22—H22	120.1
C8—C7—H7B	108.2	C23—C22—H22	120.1
C6—C7—H7B	108.2	C22—C23—C24	119.87 (12)
H7A—C7—H7B	107.4	C22—C23—H23	120.1
C9—C8—C7	124.15 (13)	C24—C23—H23	120.1
C9—C8—H8	117.9	C23—C24—C25	120.18 (11)
C7—C8—H8	117.9	C23—C24—H24	119.9
C8—C9—H9A	120.0	C25—C24—H24	119.9
C8—C9—H9B	120.0	C20—C25—C24	120.17 (11)
H9A—C9—H9B	120.0	C20—C25—H25	119.9
C12—C10—C13	108.94 (11)	C24—C25—H25	119.9
C12—C10—C11	108.40 (10)	N1—C26—H26A	109.5
C13—C10—C11	107.18 (10)	N1—C26—H26B	109.5
C12—C10—C6	114.14 (10)	H26A—C26—H26B	109.5
C13—C10—C6	109.03 (10)	N1—C26—H26C	109.5
C11—C10—C6	108.92 (10)	H26A—C26—H26C	109.5
C10—C11—H11A	109.5	H26B—C26—H26C	109.5

Table 3.2 (continued)

C10—C11—H11B	109.5	C1—N1—C26	118.40 (10)
H11A—C11—H11B	109.5	C1—N1—C4	124.12 (9)
C10—C11—H11C	109.5	C26—N1—C4	117.39 (9)
H11A—C11—H11C	109.5	C2—N2—C6	118.46 (9)
H11B—C11—H11C	109.5	C2—N2—H2	107.5 (10)
C10—C12—H12A	109.5	C6—N2—H2	111.2 (10)
C10—C12—H12B	109.5	C2—O2—C3	113.81 (9)
O1—C1—C2—O2	173.10 (9)	N1—C4—C20—C25	-129.88 (11)
N1—C1—C2—O2	-7.06 (15)	C3—C4—C20—C25	109.33 (12)
O1—C1—C2—N2	-66.92 (12)	N1—C4—C20—C21	55.47 (14)
N1—C1—C2—N2	112.91 (11)	C3—C4—C20—C21	-65.32 (14)
O1—C1—C2—C5	58.40 (13)	C25—C20—C21—C22	-1.21 (18)
N1—C1—C2—C5	-121.77 (11)	C4—C20—C21—C22	173.52 (11)
O2—C3—C4—N1	51.95 (12)	C20—C21—C22—C23	0.67 (18)
C14—C3—C4—N1	170.33 (10)	C21—C22—C23—C24	0.17 (19)
O2—C3—C4—C20	174.23 (9)	C22—C23—C24—C25	-0.44 (19)
C14—C3—C4—C20	-67.39 (12)	C21—C20—C25—C24	0.93 (17)
N2—C6—C7—C8	45.82 (14)	C4—C20—C25—C24	-173.76 (10)
C10—C6—C7—C8	-81.81 (13)	C23—C24—C25—C20	-0.11 (18)
C6—C7—C8—C9	-134.83 (13)	O1—C1—N1—C26	-6.81 (16)
N2—C6—C10—C12	-64.59 (13)	C2—C1—N1—C26	173.36 (10)
C7—C6—C10—C12	61.72 (14)	O1—C1—N1—C4	176.83 (11)
N2—C6—C10—C13	173.35 (10)	C2—C1—N1—C4	-2.99 (16)
C7—C6—C10—C13	-60.34 (13)	C20—C4—N1—C1	-140.09 (11)
N2—C6—C10—C11	56.70 (12)	C3—C4—N1—C1	-19.28 (15)
C7—C6—C10—C11	-176.99 (10)	C20—C4—N1—C26	43.52 (13)
O2—C3—C14—C19	29.45 (14)	C3—C4—N1—C26	164.33 (10)
C4—C3—C14—C19	-89.58 (13)	O2—C2—N2—C6	-70.80 (12)
O2—C3—C14—C15	-152.85 (10)	C5—C2—N2—C6	47.83 (15)
C4—C3—C14—C15	88.12 (13)	C1—C2—N2—C6	167.61 (9)
C19—C14—C15—C16	0.28 (18)	C7—C6—N2—C2	102.53 (12)
C3—C14—C15—C16	-177.46 (11)	C10—C6—N2—C2	-127.49 (11)
C14—C15—C16—C17	-1.58 (19)	N2—C2—O2—C3	-73.16 (11)
C15—C16—C17—C18	1.29 (19)	C5—C2—O2—C3	160.36 (9)
C16—C17—C18—C19	0.3 (2)	C1—C2—O2—C3	42.64 (13)

Table 3.2 (continued)

C17—C18—C19—C14	-1.60 (19)	C14—C3—O2—C2	173.26 (9)
C15—C14—C19—C18	1.30 (18)	C4—C3—O2—C2	-66.44 (12)
C3—C14—C19—C18	179.05 (12)		

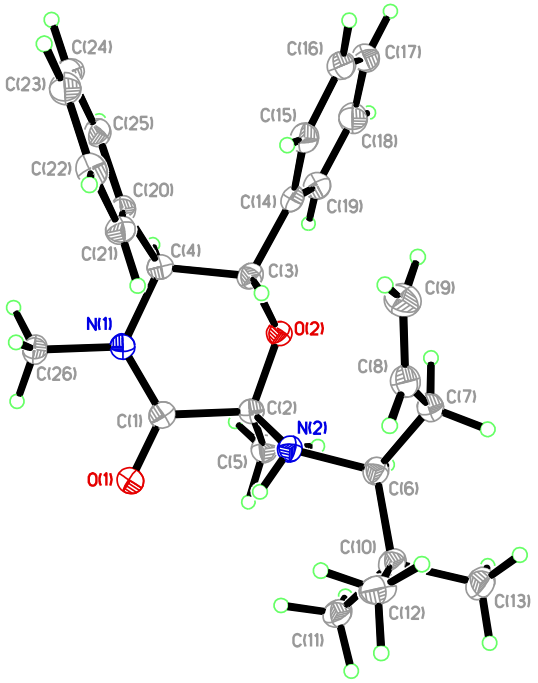


Figure 3.2: Perspective views showing 50% probability displacement.

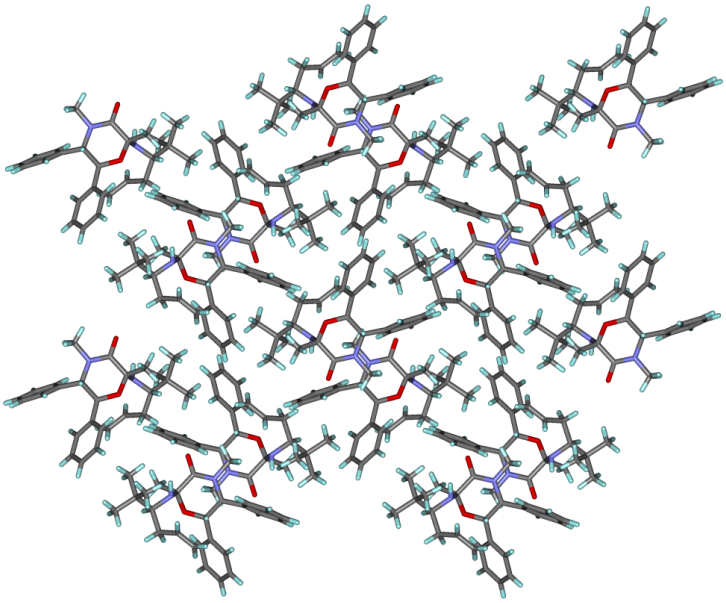
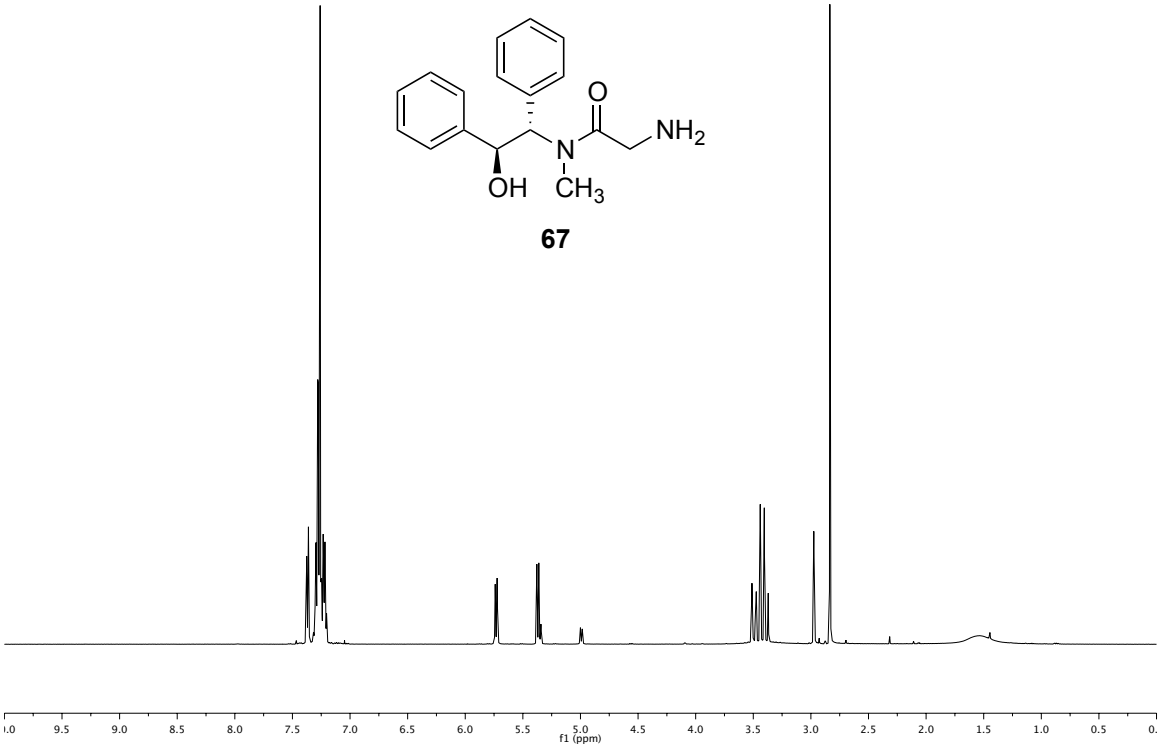


Figure 3.3: Three-dimensional supramolecular architecture viewed along the *a*-axis direction.

[1]H and [13]C NMR Spectra:



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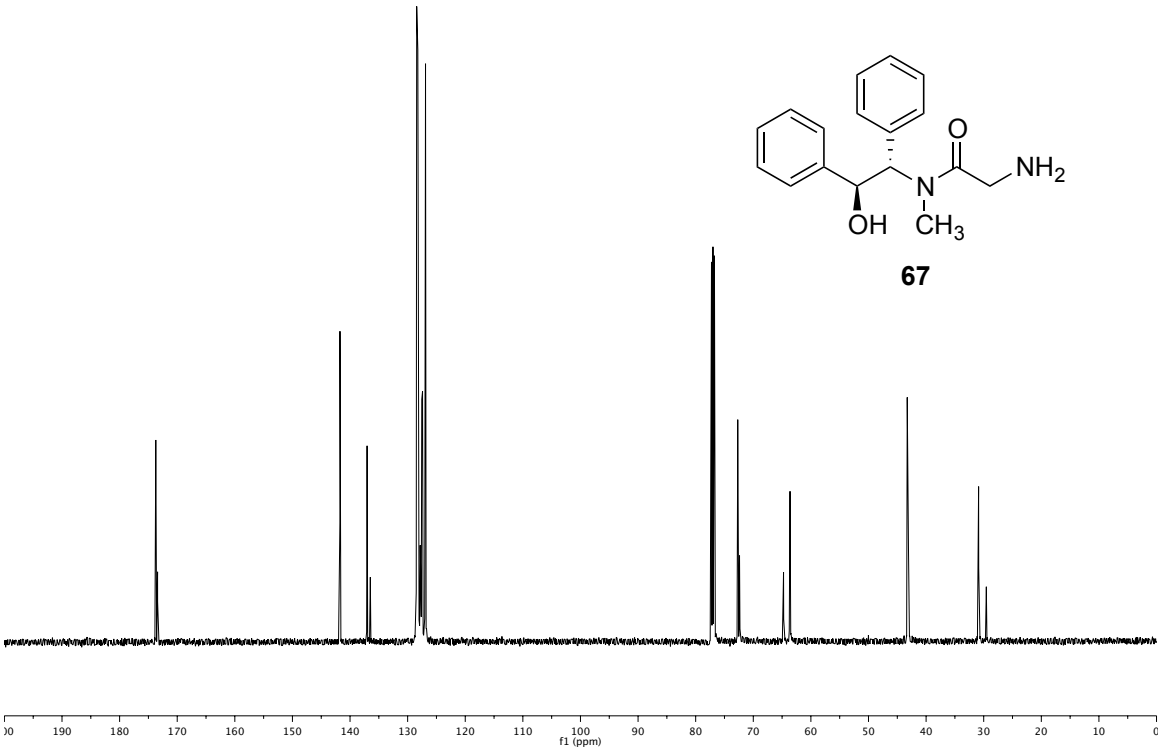

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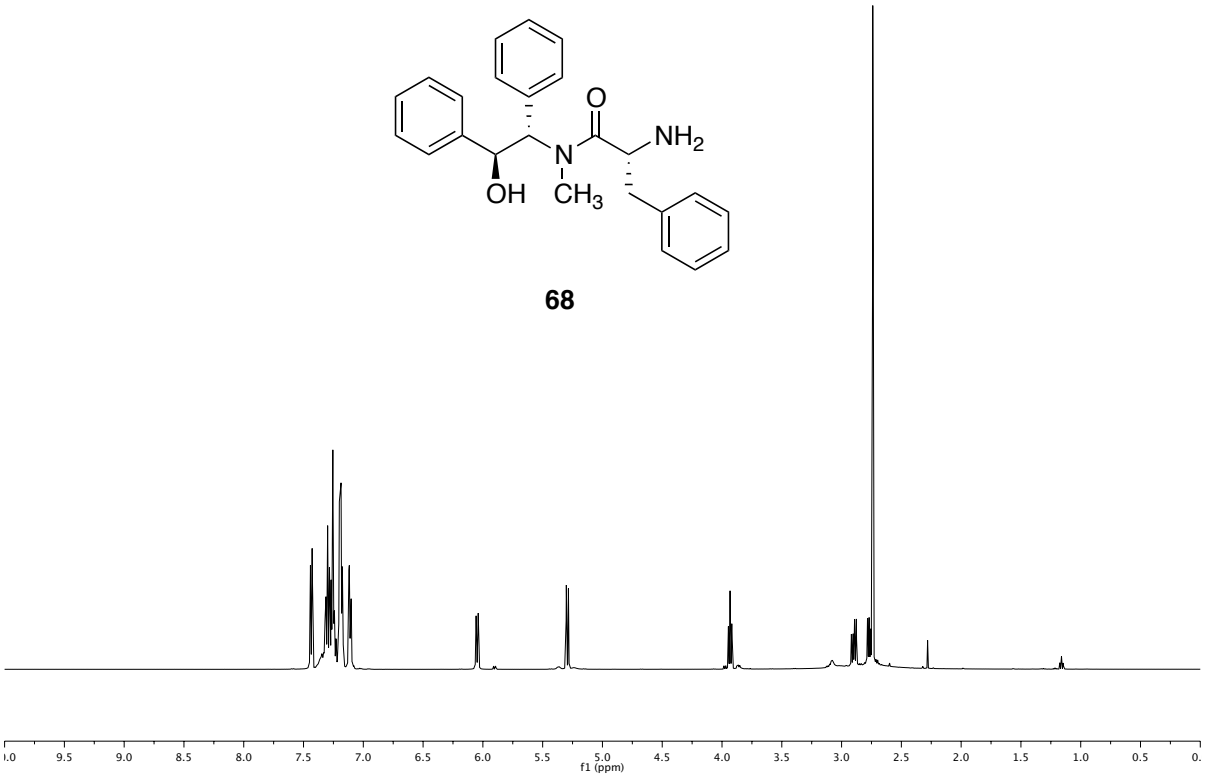

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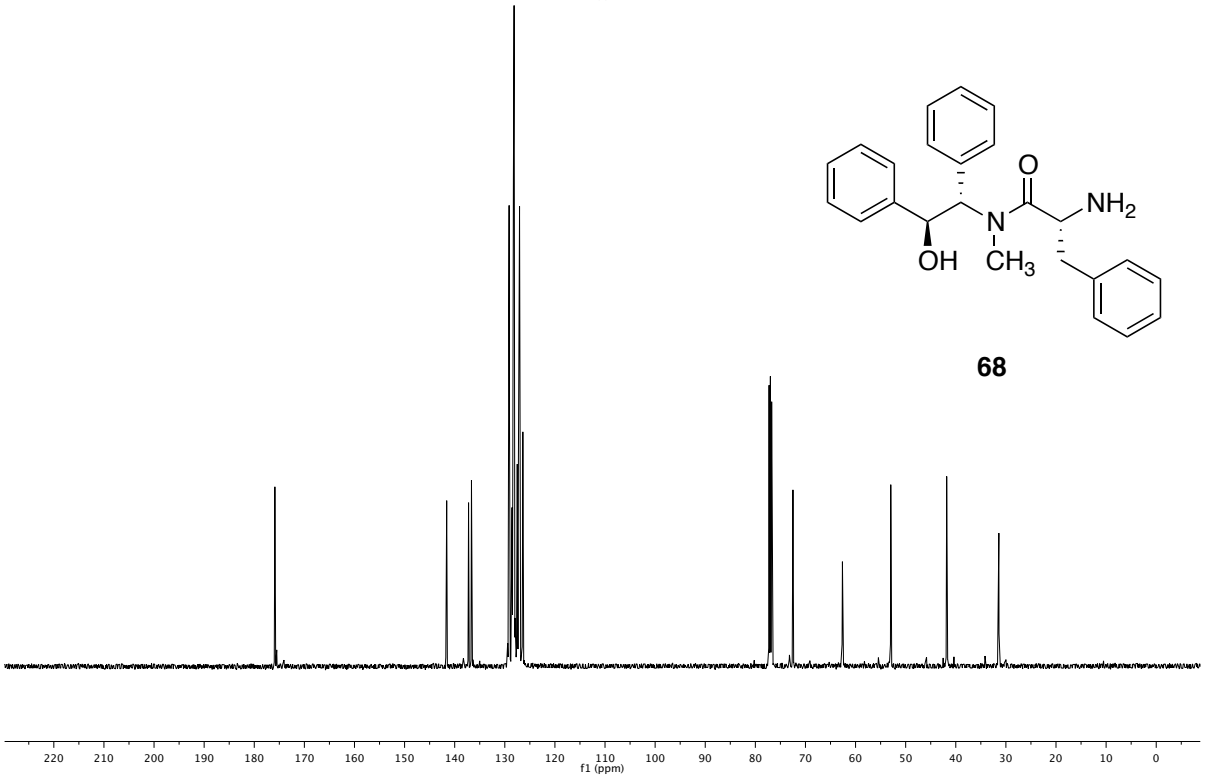

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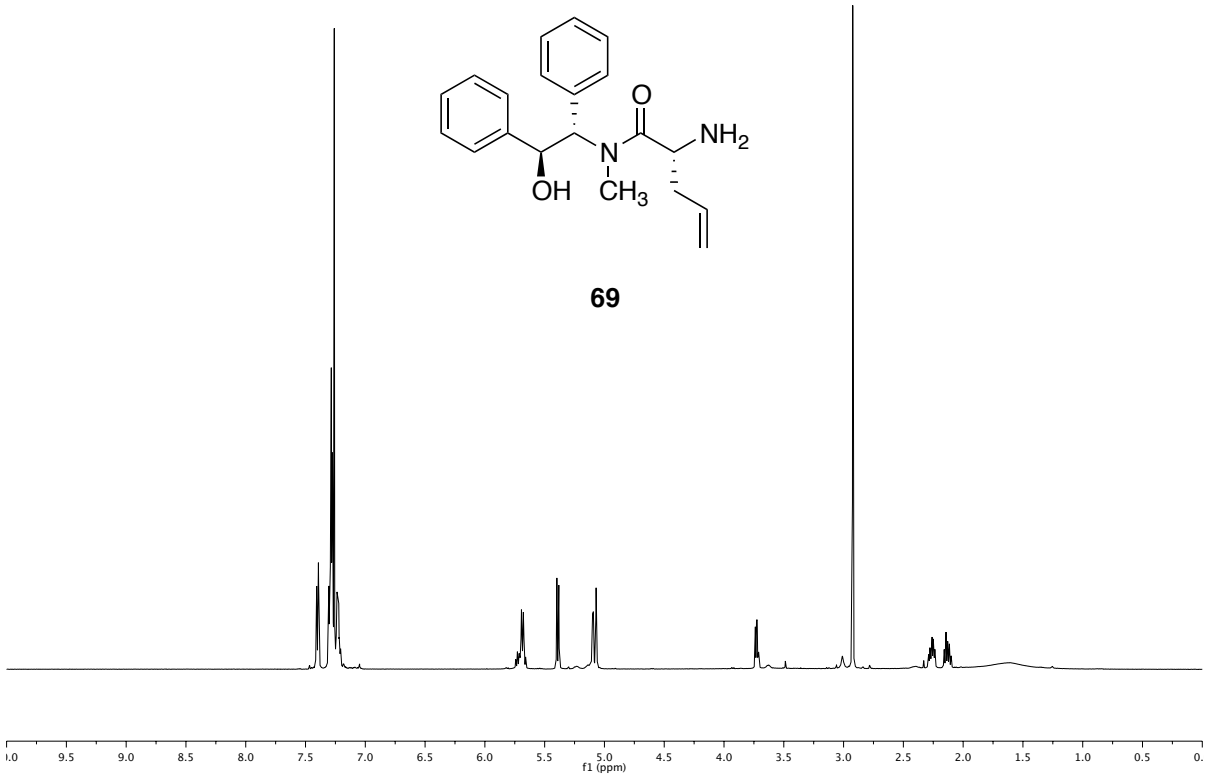

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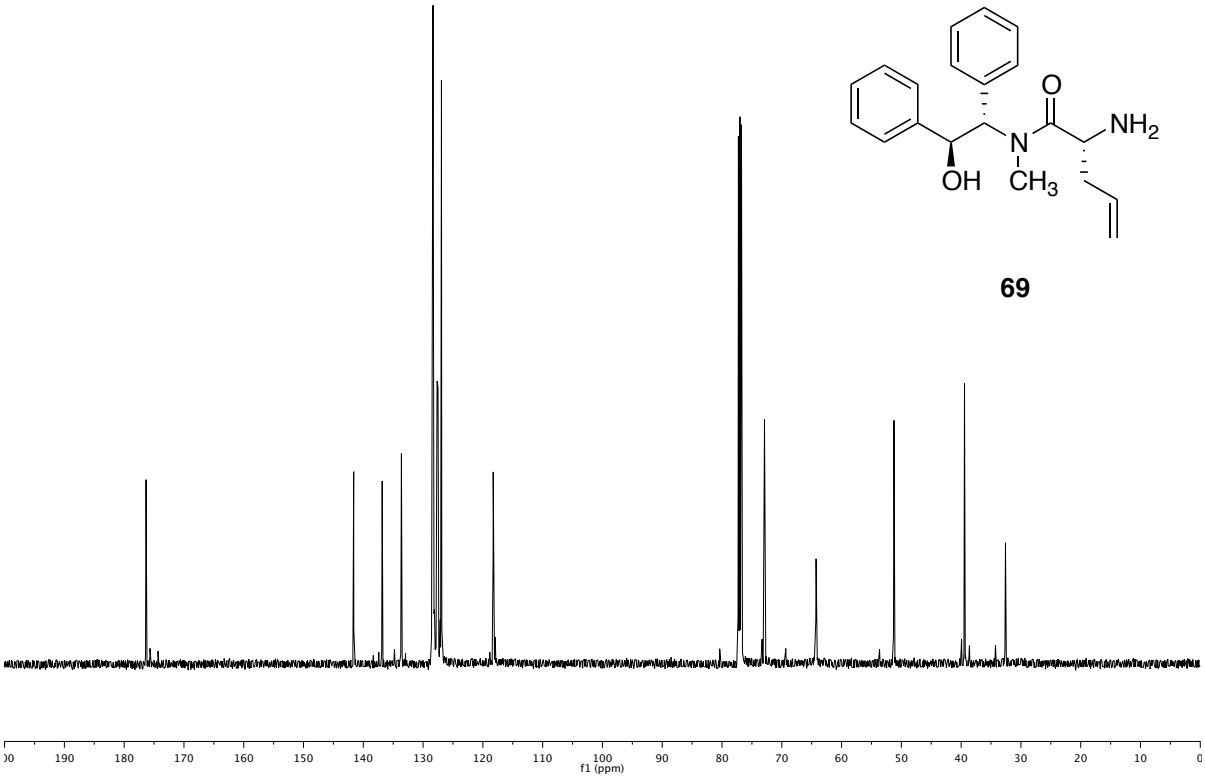

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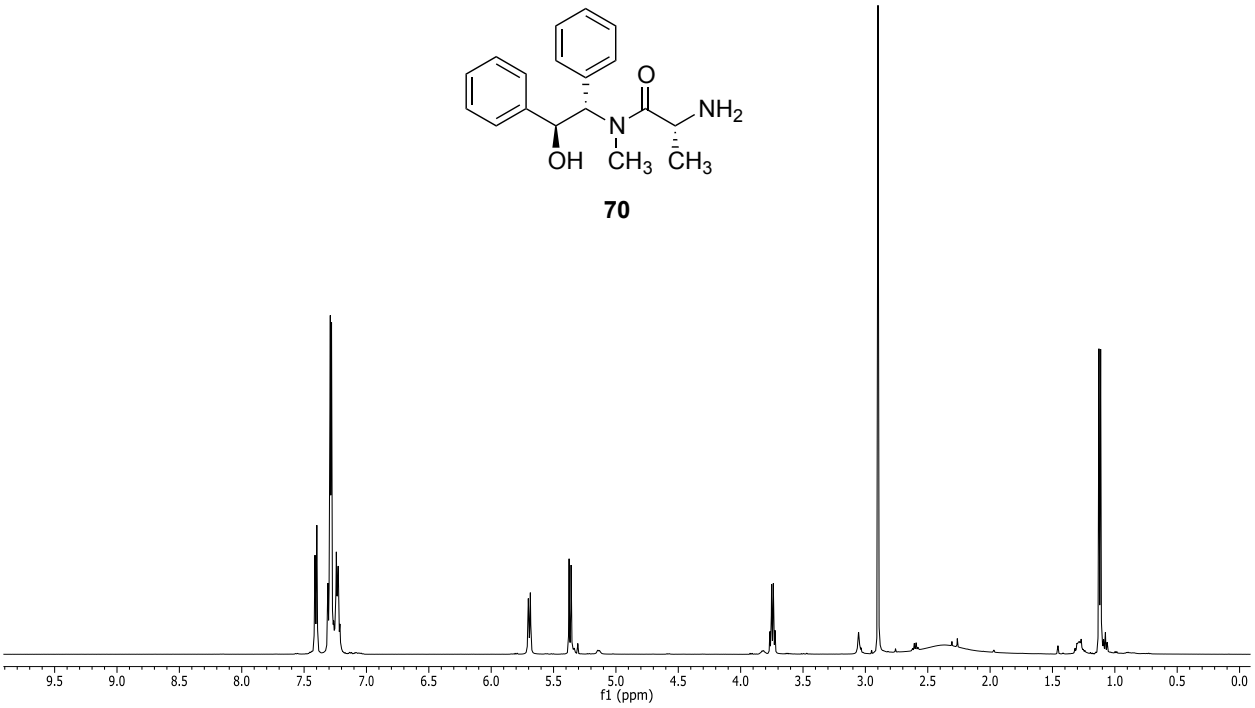
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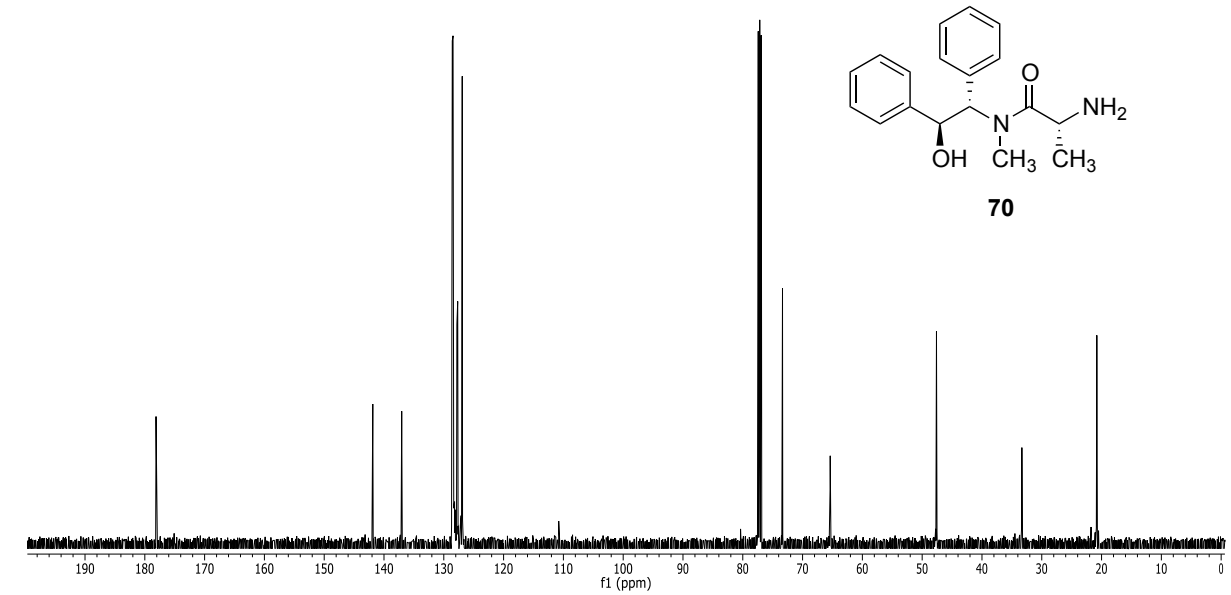
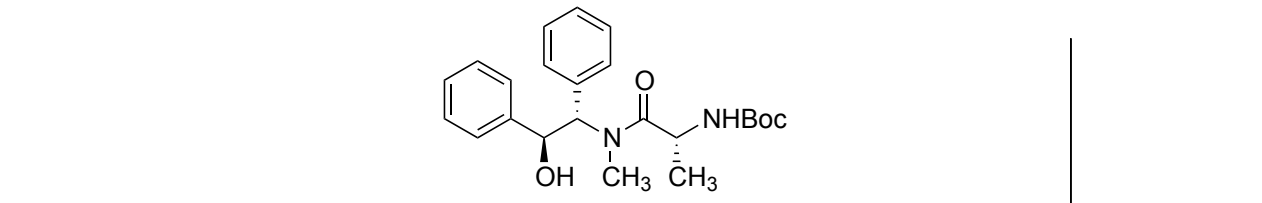
f1 (ppm)

70

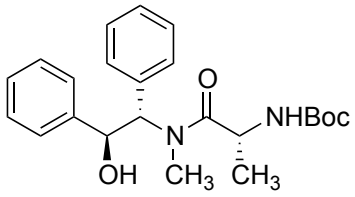

O
NH2
N
OH
CH3
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

70


O
NHBoc
N
OH
CH3
CH3

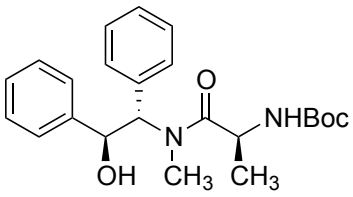
108

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

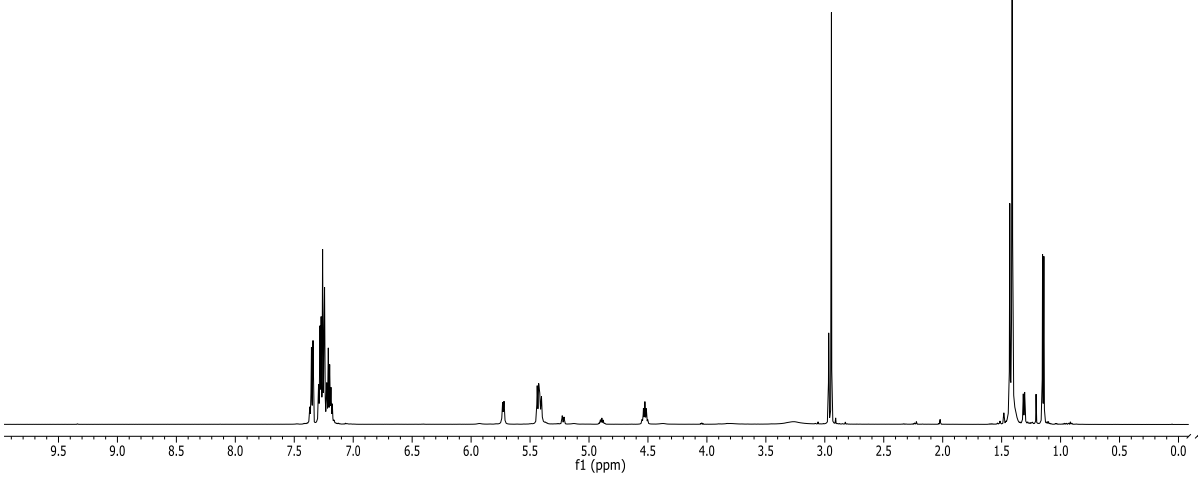

O
NHBoc
N
OH
CH3
CH3

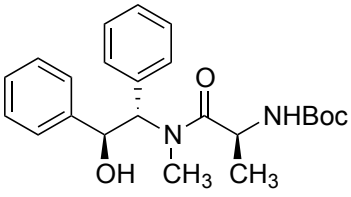
108

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
NHBoc
N
OH
CH3
CH3

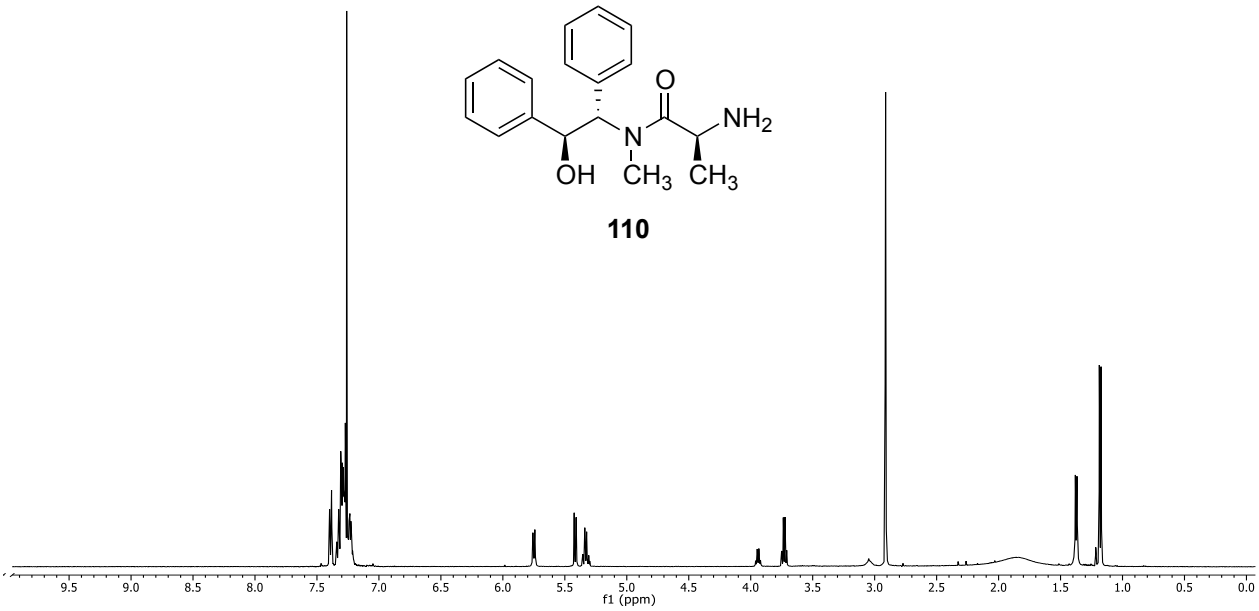
109


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

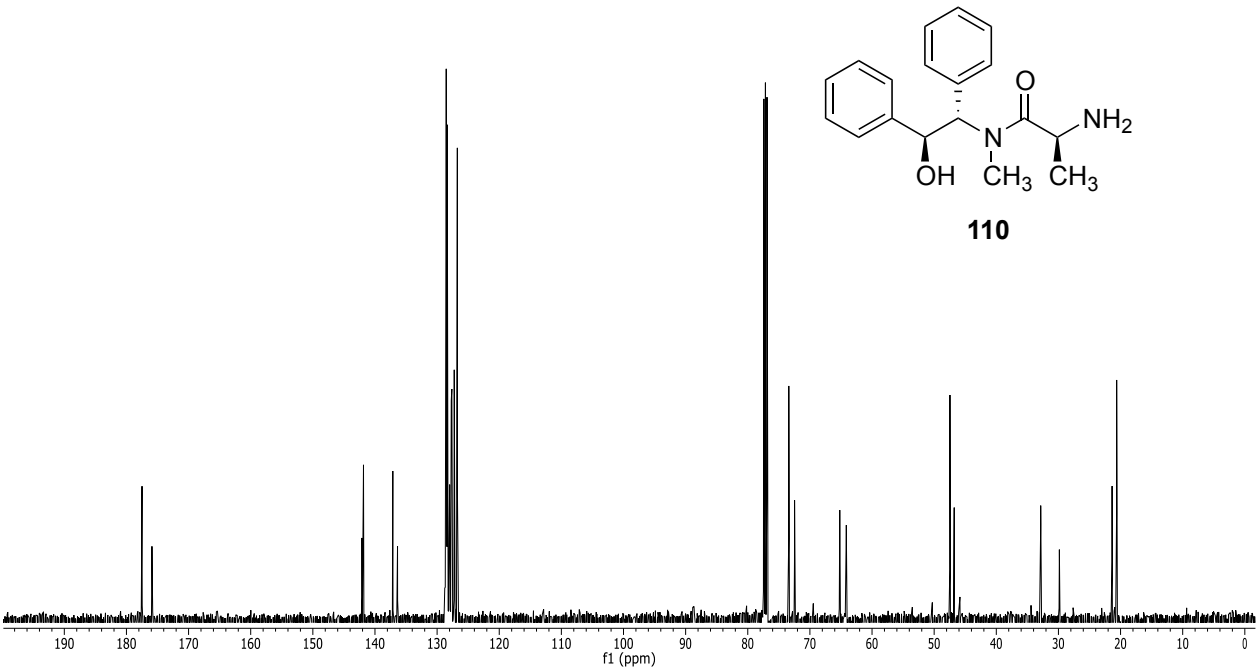

O
NHBoc
N
OH
CH3
CH3

109

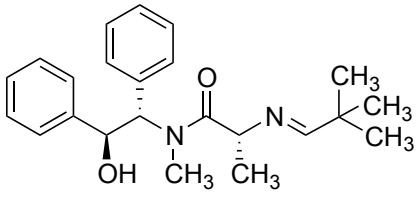
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
NH2
N
OH
CH3
CH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

110

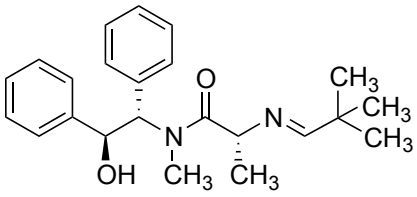

O
NH2
N
OH
CH3
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

110


O
N
CH3
CH3
CH3
N
OH
CH3
CH3

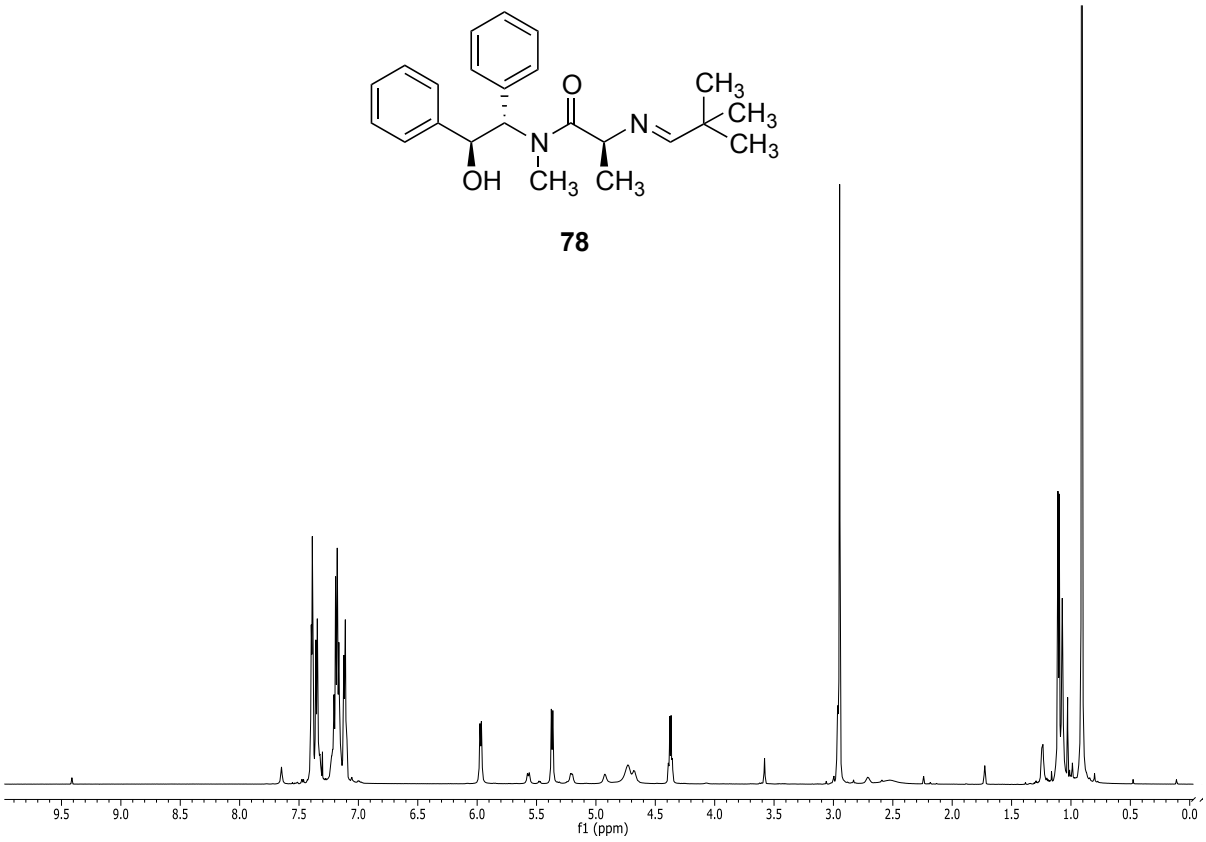
71

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

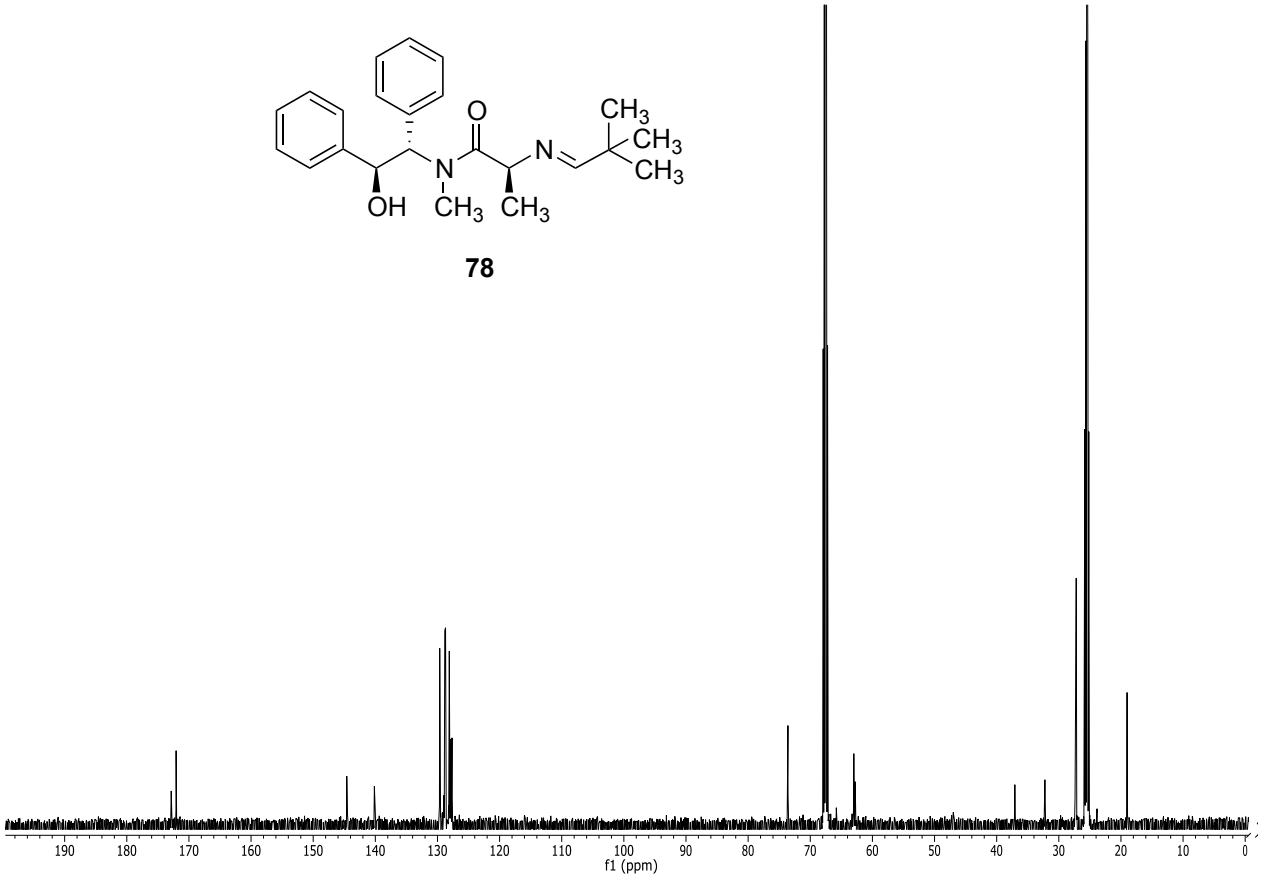

O
N
CH3
CH3
CH3
N
OH
CH3
CH3

71

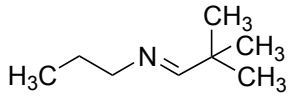
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
CH3
CH3
CH3
N
N
OH
CH3
CH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

78

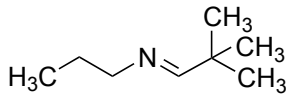

O
CH3
CH3
CH3
N
N
OH
CH3
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

78


CH3
CH3
CH3
N
H3C

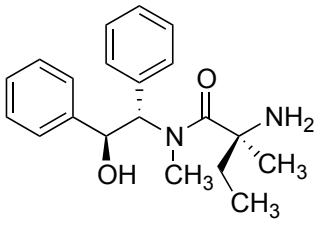
112

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


CH3
CH3
CH3
N
H3C

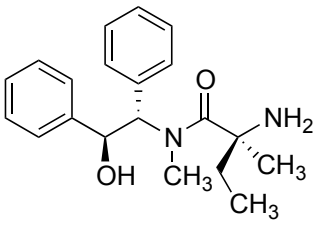
112

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
NH2
N
OH
CH3
CH3
CH3

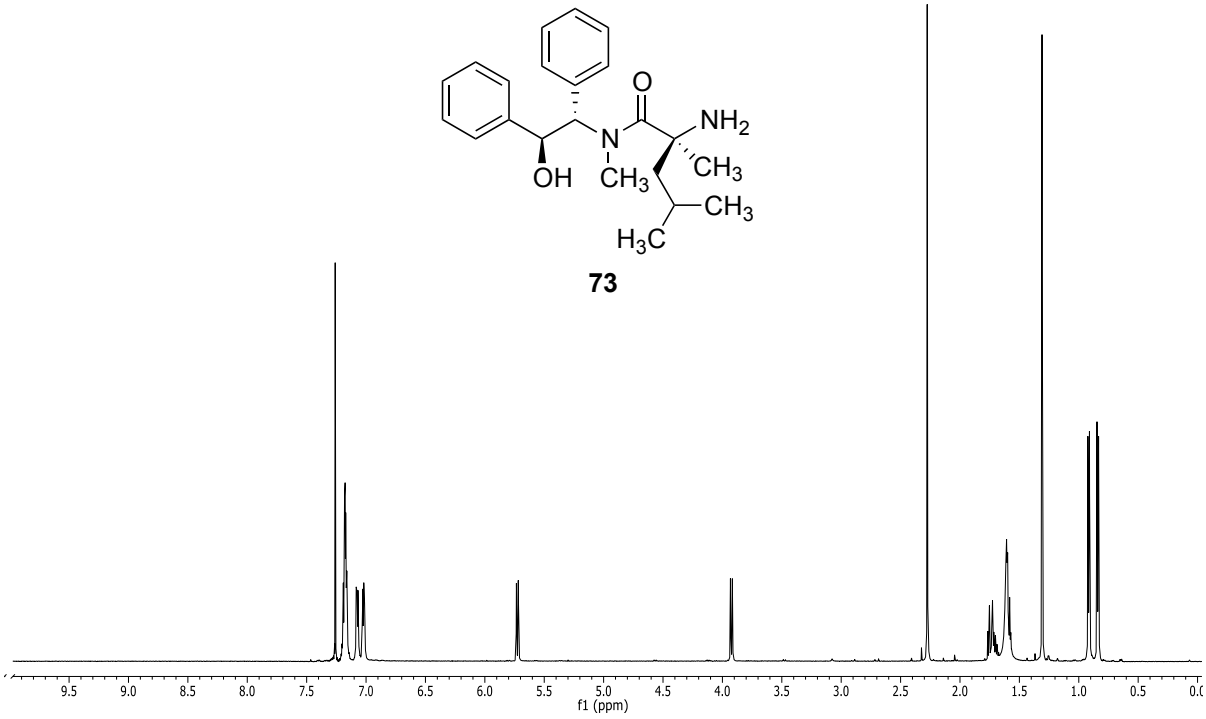
72

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

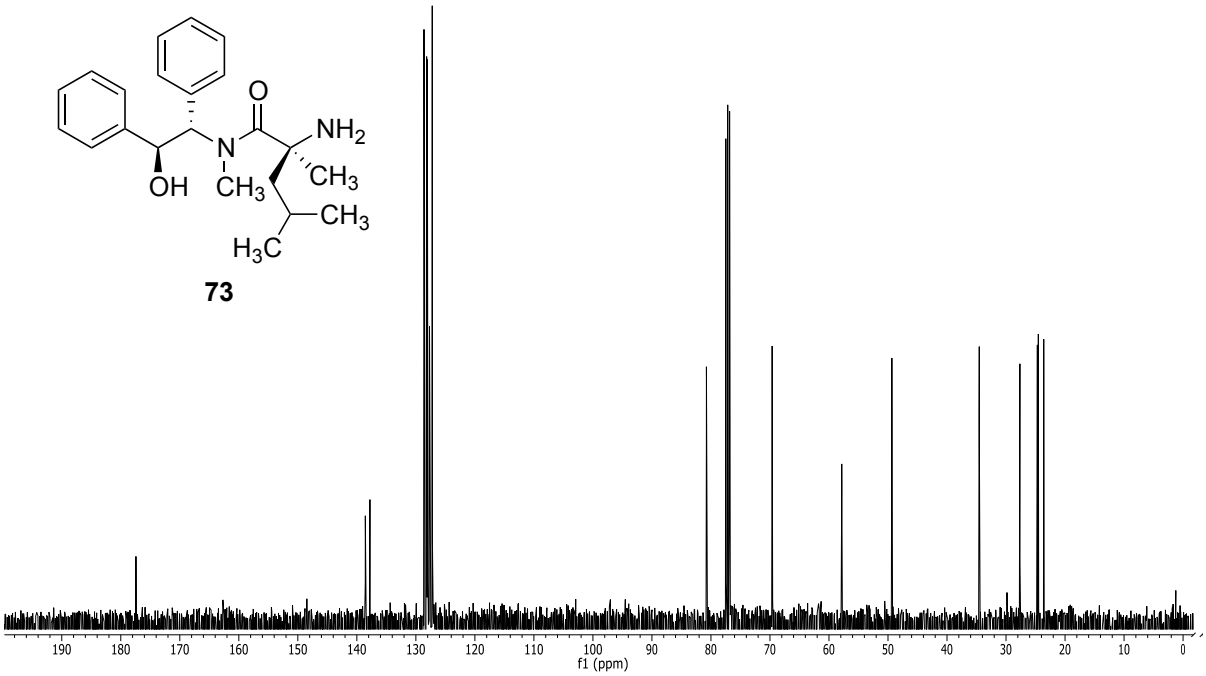

O
NH2
N
OH
CH3
CH3
CH3

72

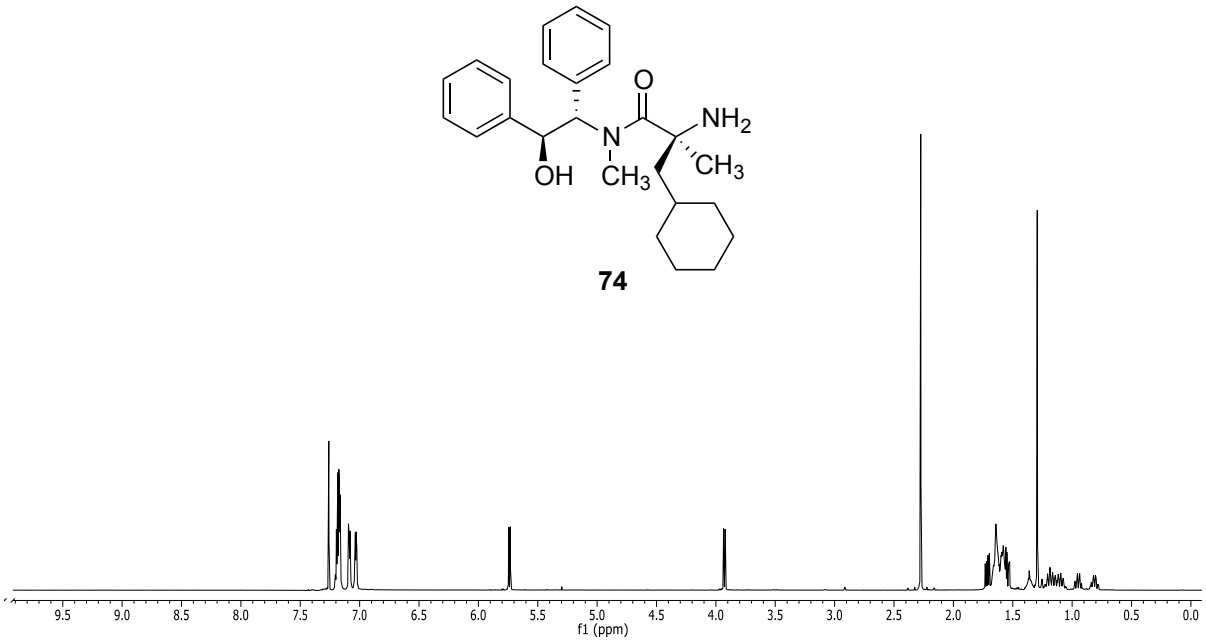
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



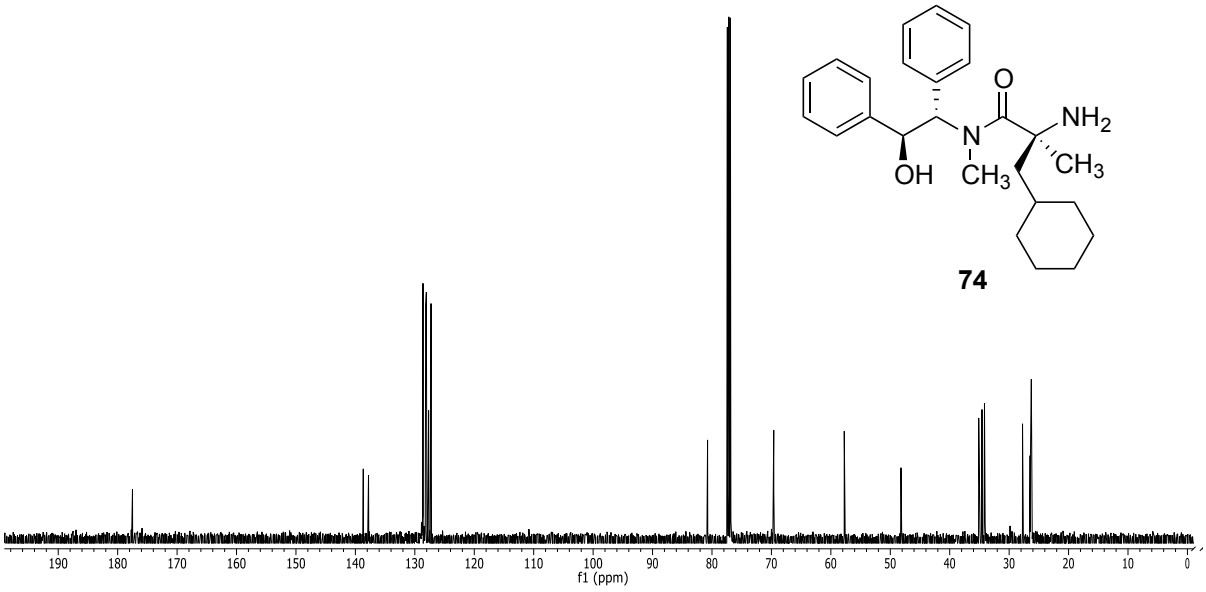
73



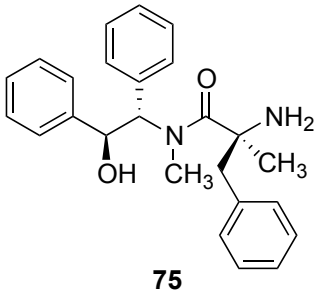
73


O
NH2
N
CH3
OH
CH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

74

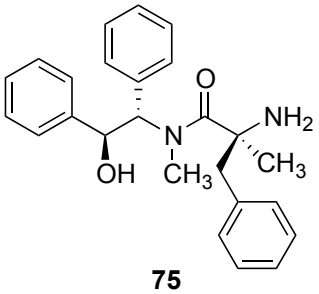

O
NH2
N
CH3
OH
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

74


O
NH2
N
CH3
OH
CH3

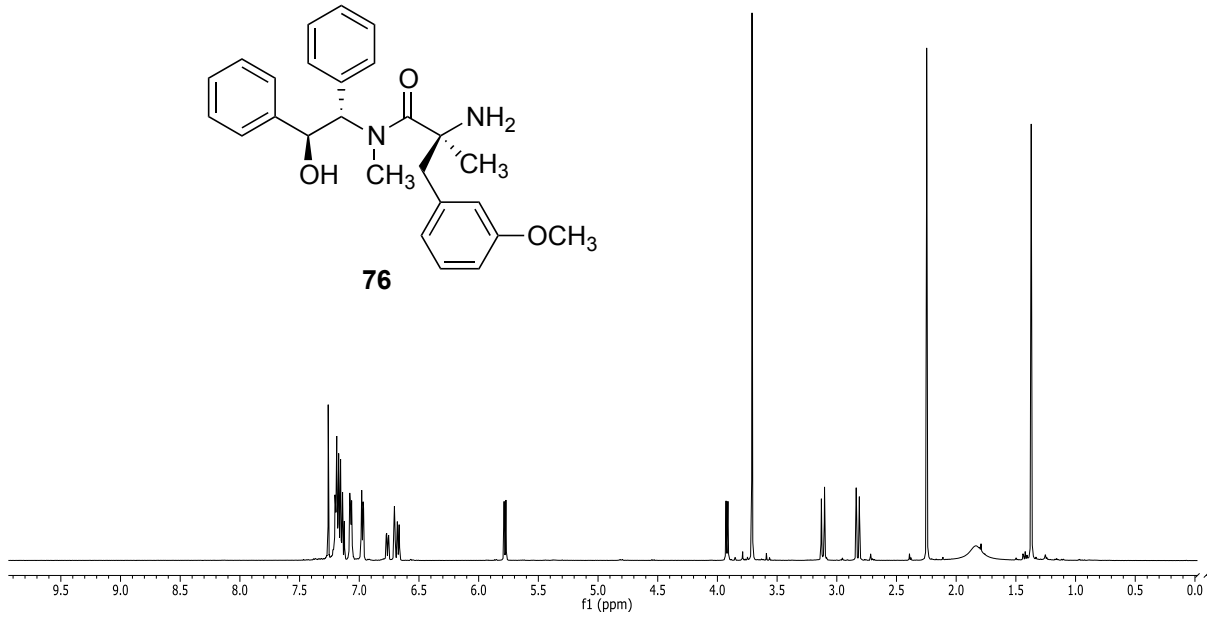
75

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

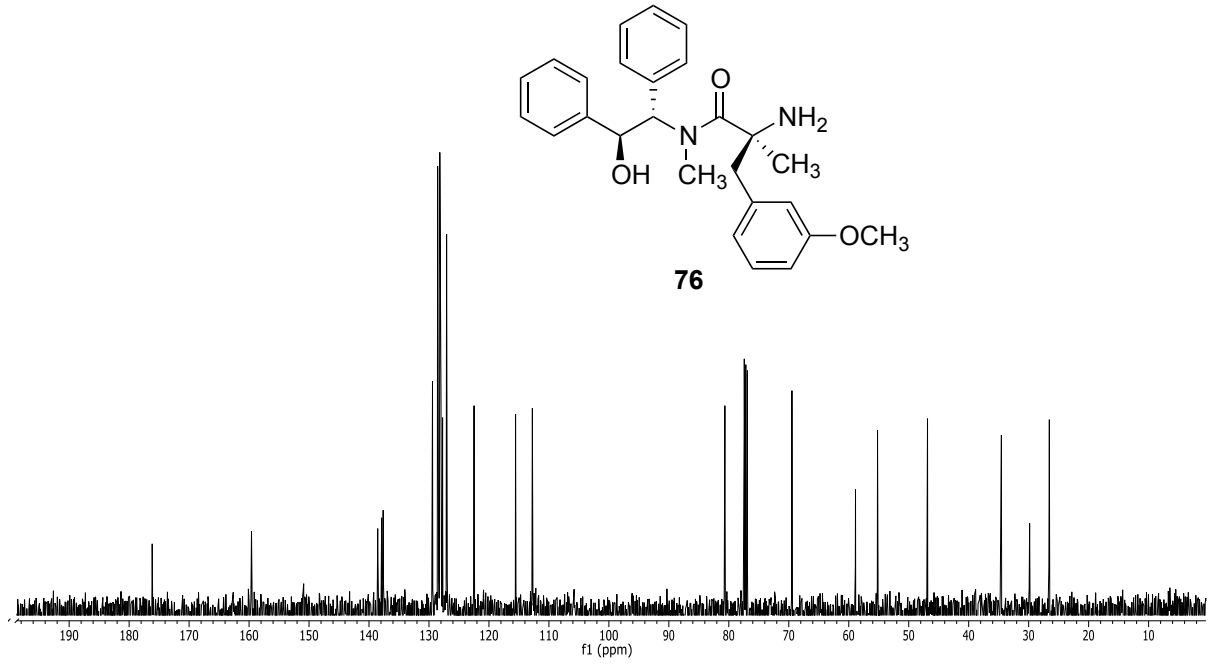

O
NH2
N
CH3
OH
CH3

75

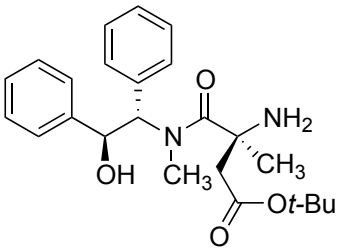
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


O
NH2
N
CH3
OH
CH3
OCH3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

76

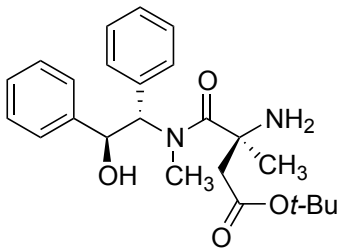

O
NH2
N
CH3
OH
CH3
OCH3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

76


O
NH2
N
CH3
OH
CH3
Ot-Bu
O

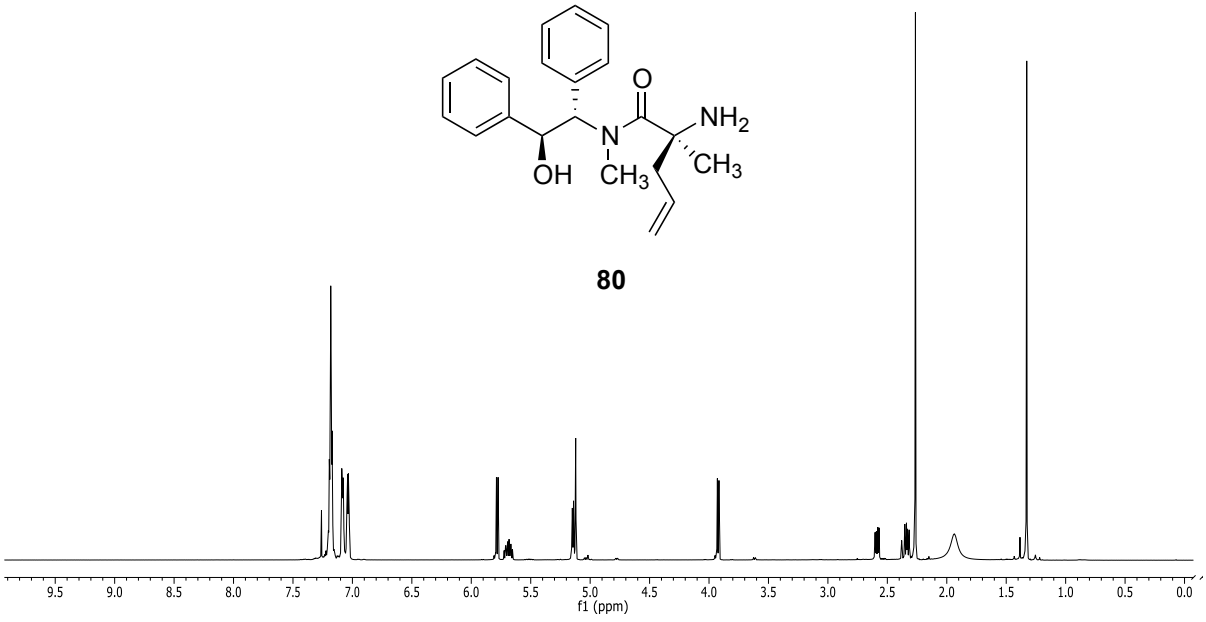
77

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

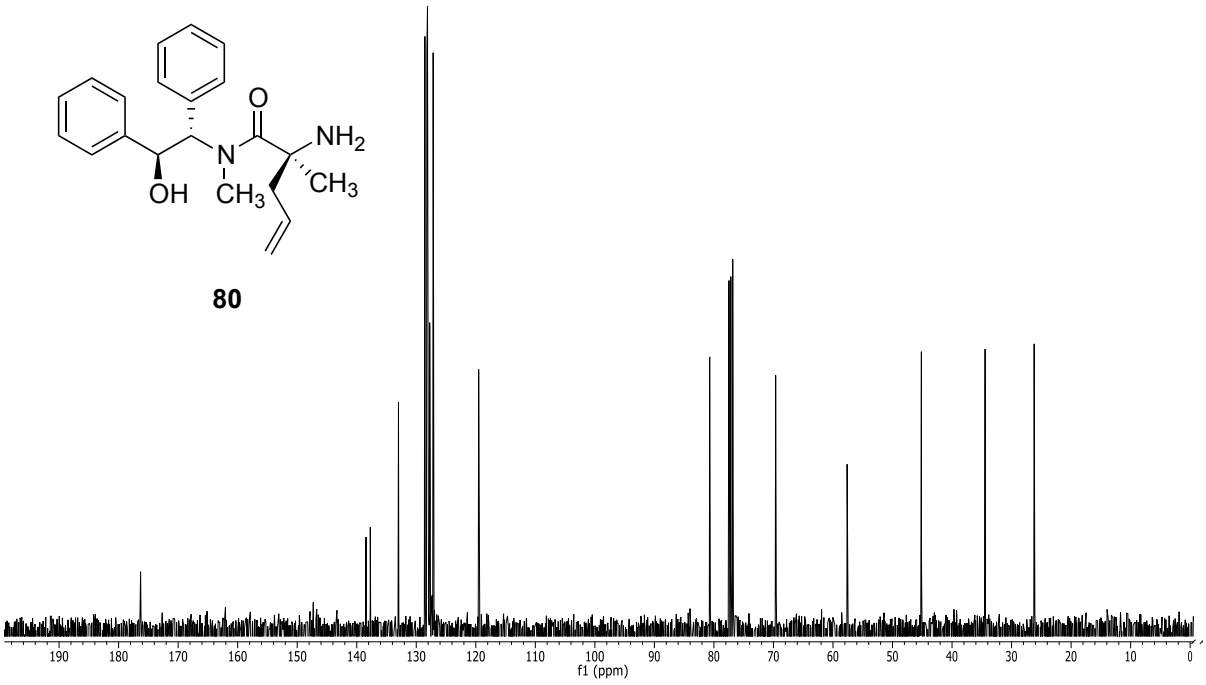

O
NH2
N
CH3
OH
CH3
Ot-Bu
O

77

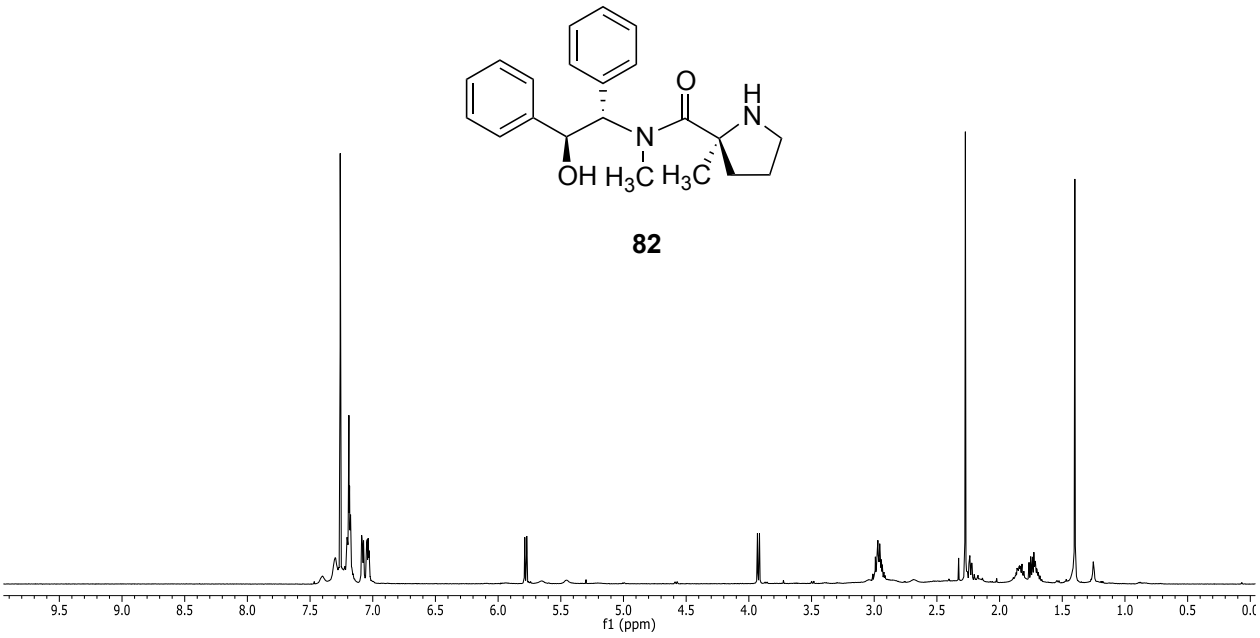
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
NH2
N
OH
CH3
CH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

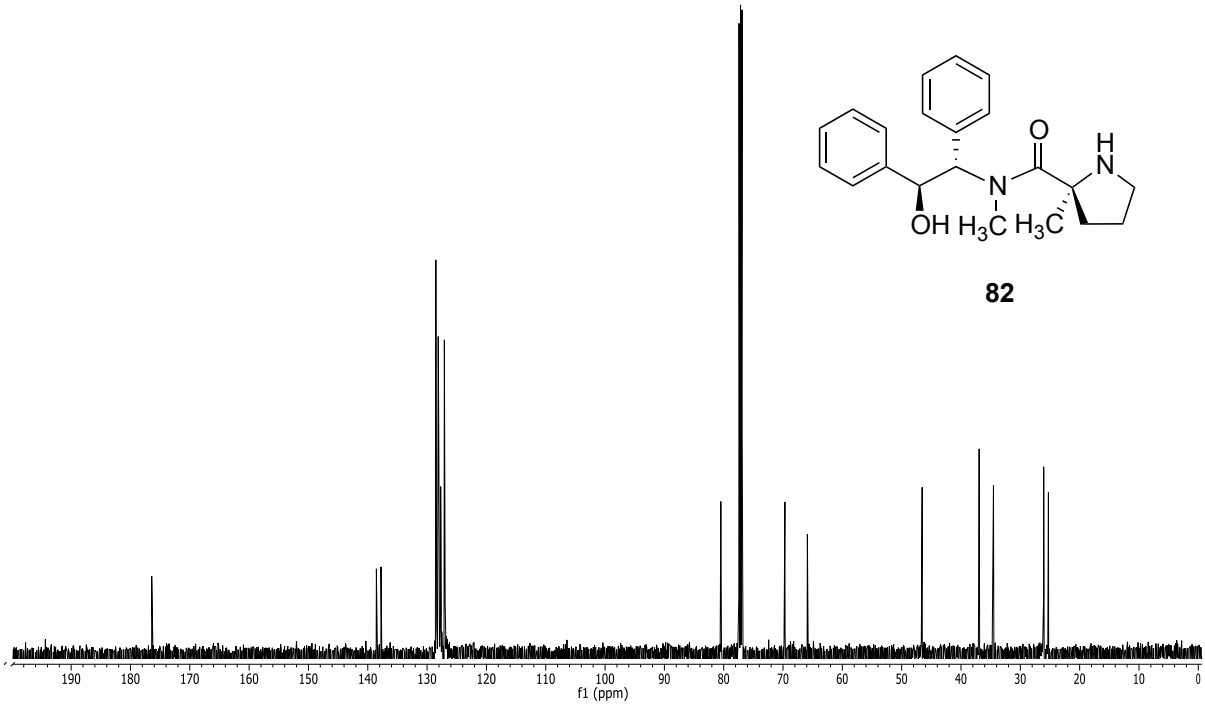
80


O
NH2
N
OH
CH3
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

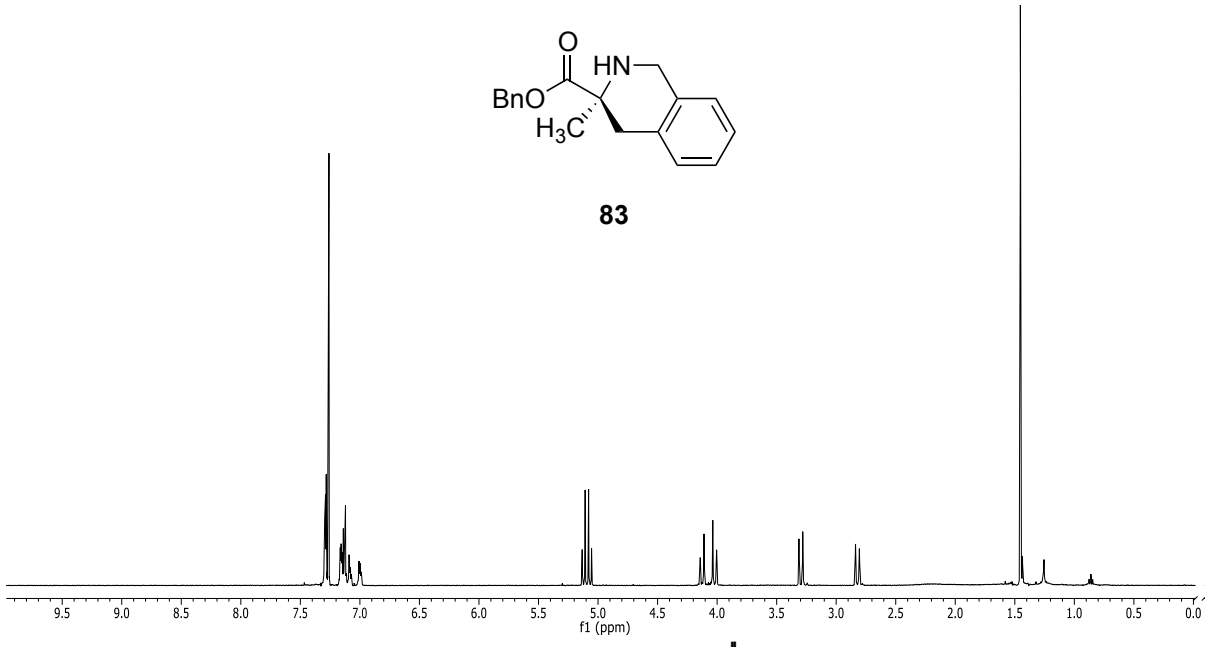
80


O
H
N
N
OH H3C H3C
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

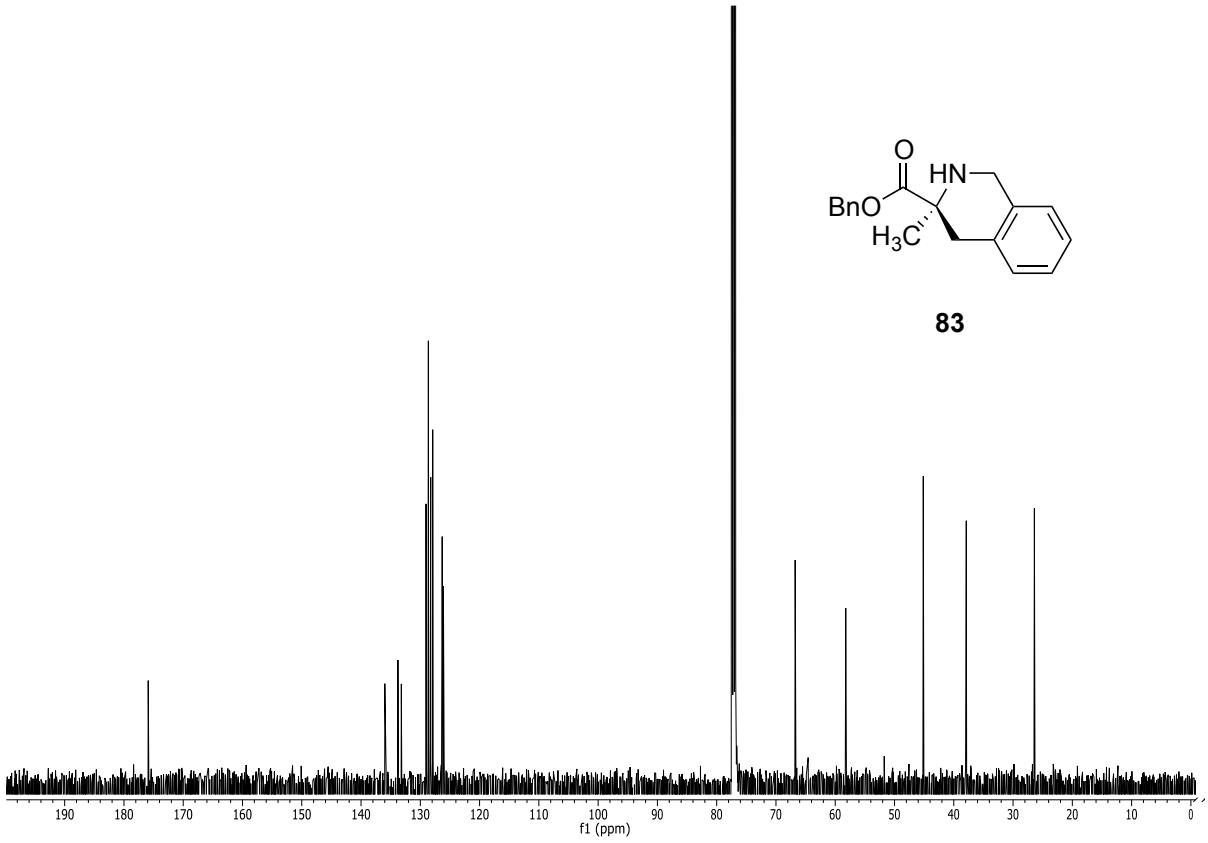
82


O
H
N
N
OH H3C H3C
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

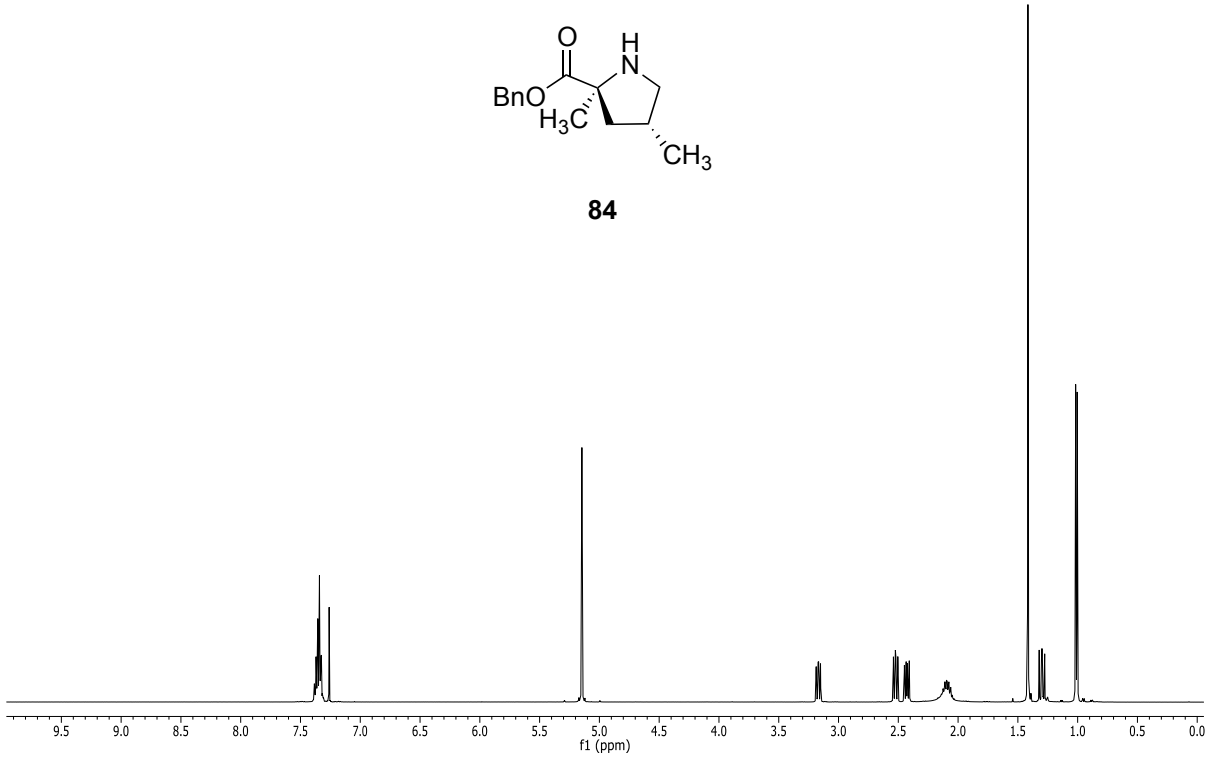
82


O
HN
BnO
H3C
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

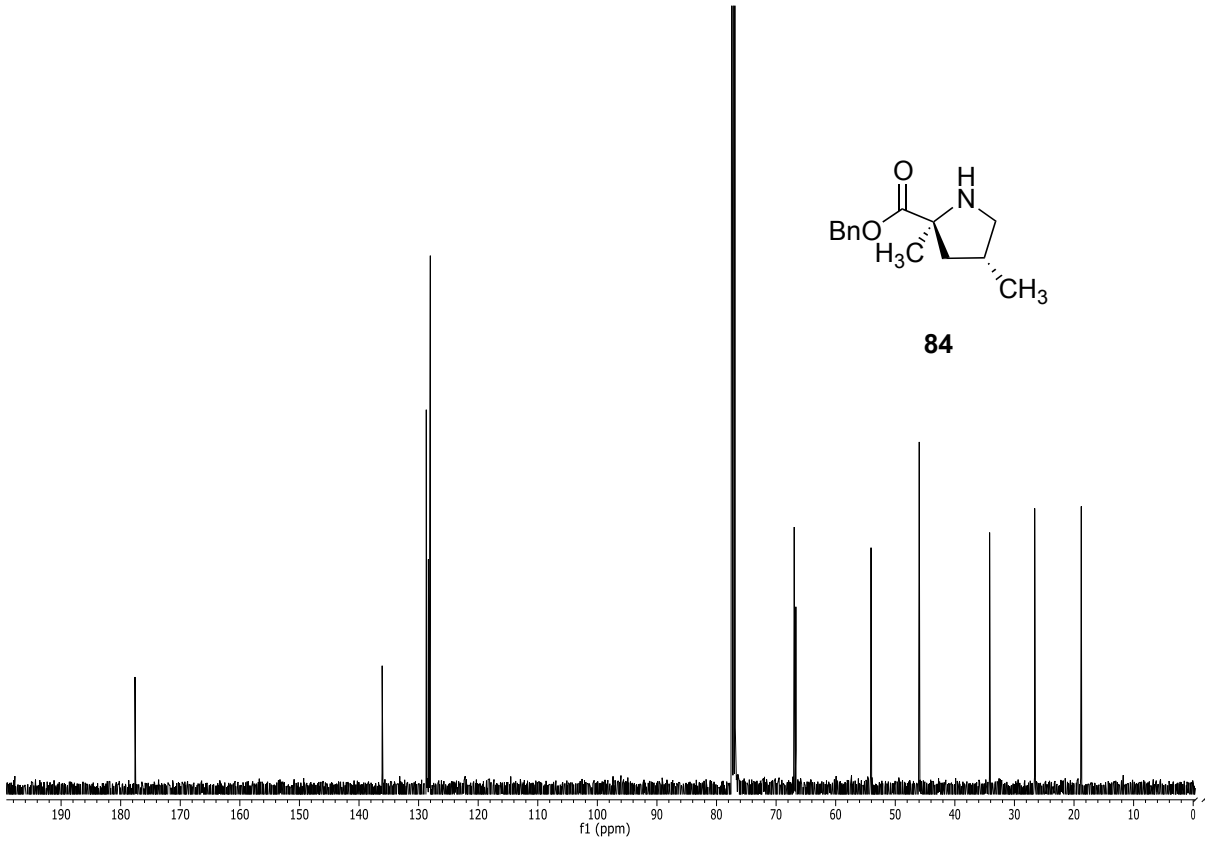
83


O
HN
BnO
H3C
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

83


O
H
N
BnO
H3C
CH3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

84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H
N
BnO
H3C
CH3
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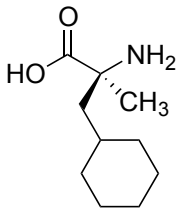
f1 (ppm)

84


O
HO
NH2
CH3

85

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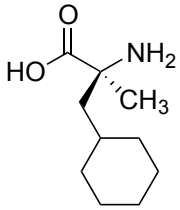
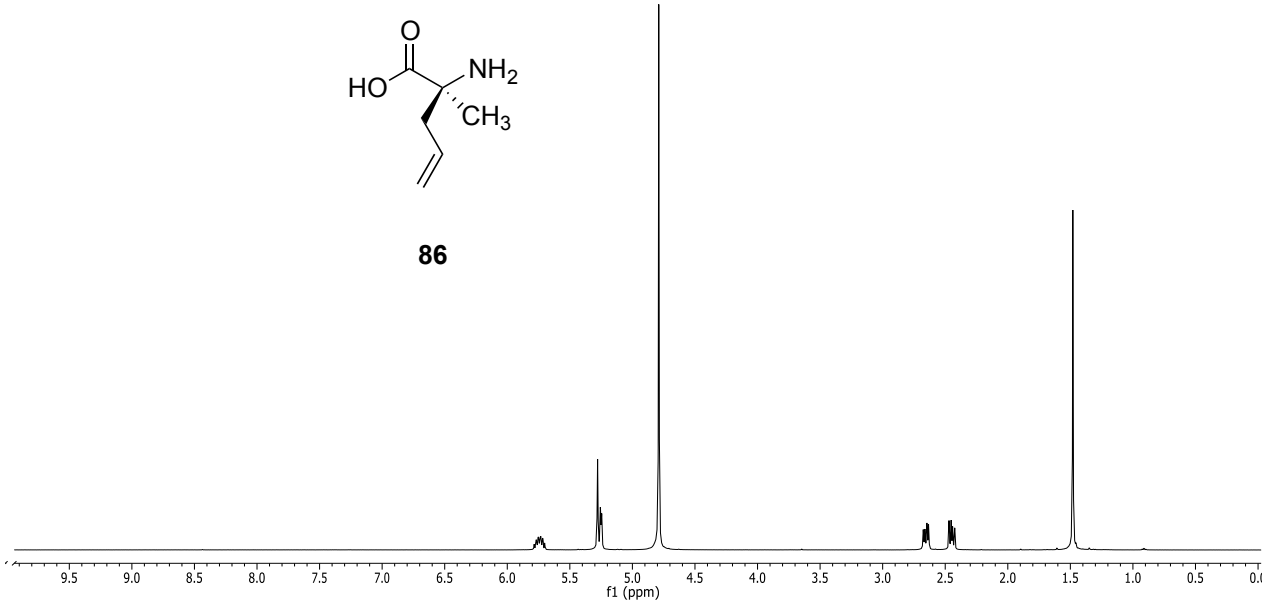
f1 (ppm)

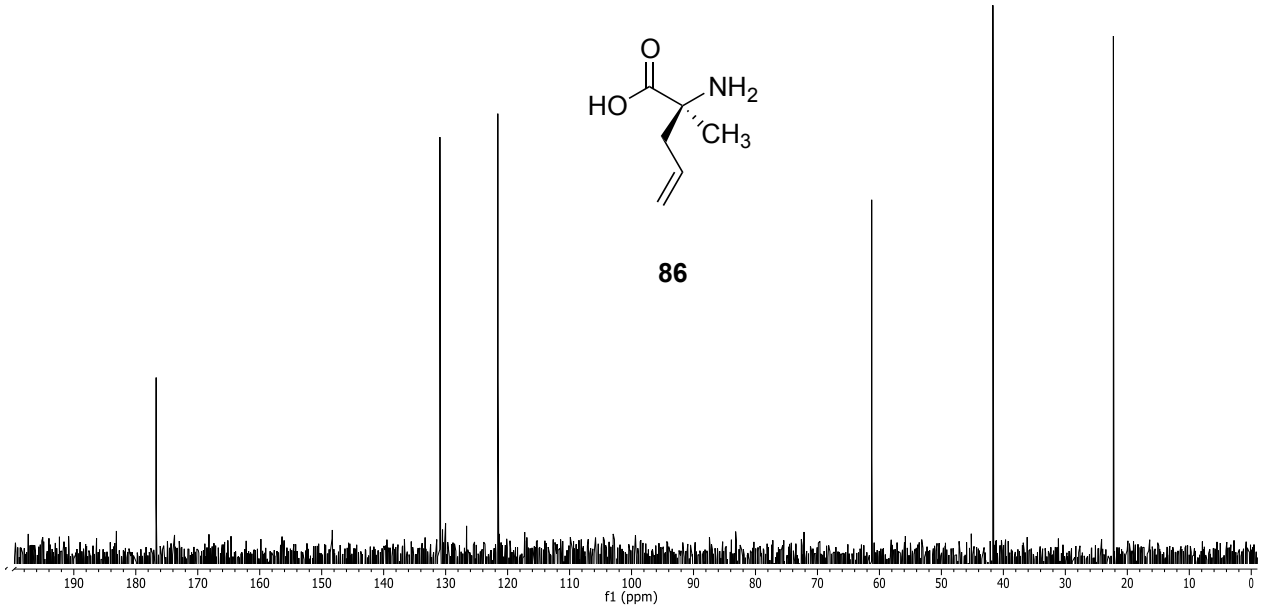

O
HO
NH2
CH3

85

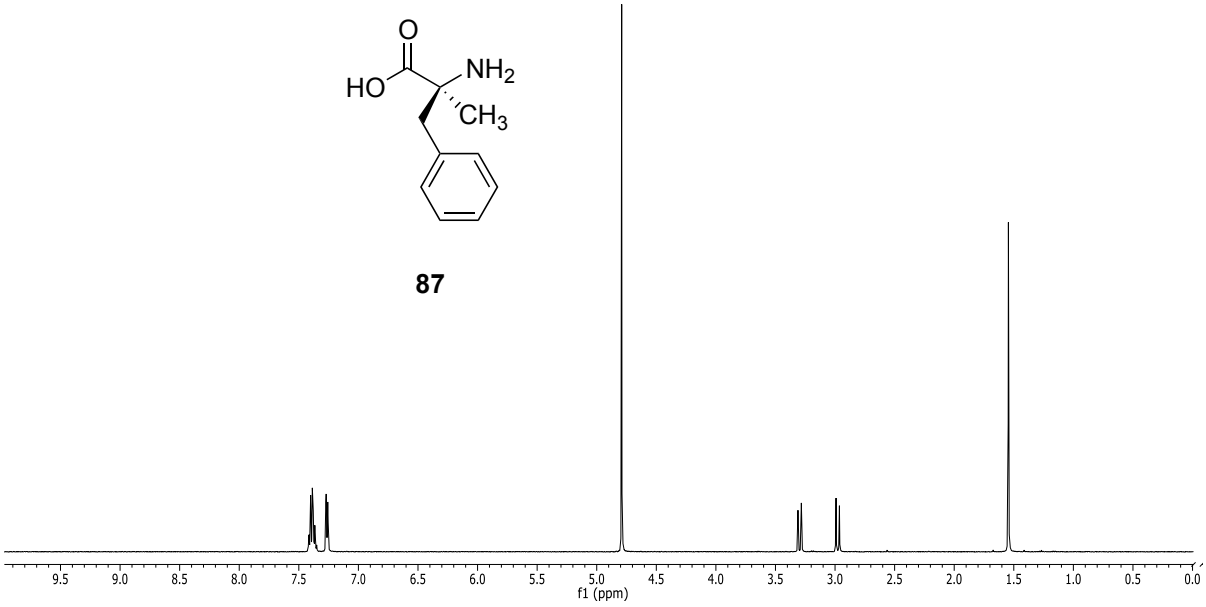
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


O
HO
NH2
CH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

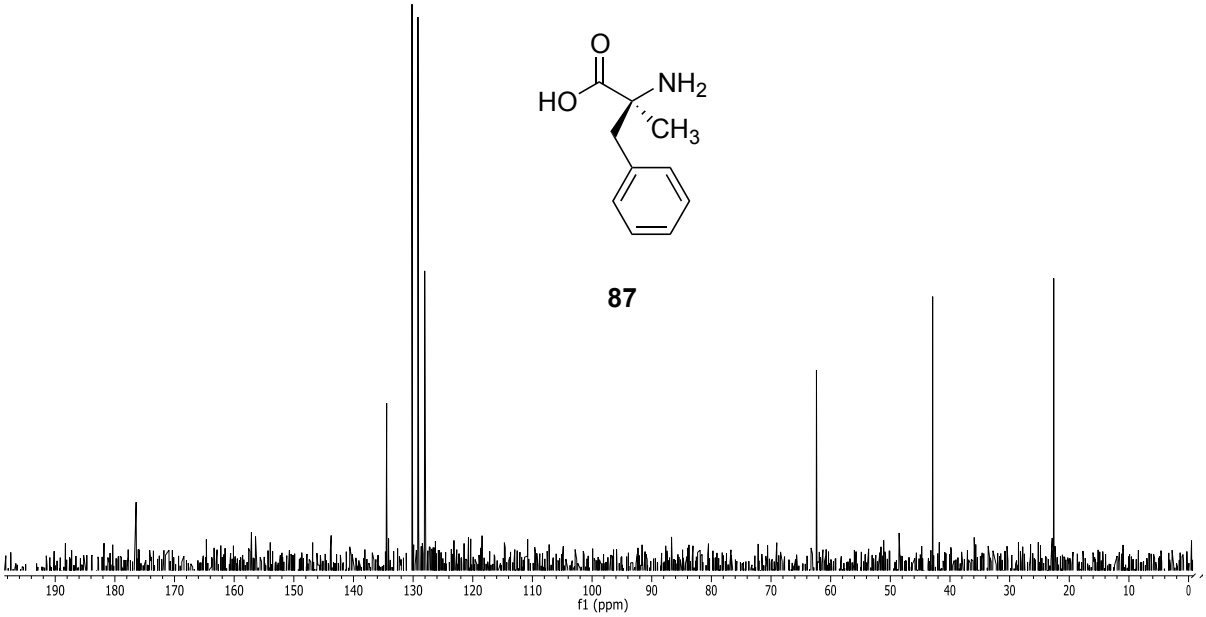
86


O
HO
NH2
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

86


O
HO
NH2
CH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

87


O
HO
NH2
CH3
190
180
170
160
150
140
130
120
110
100
90
80
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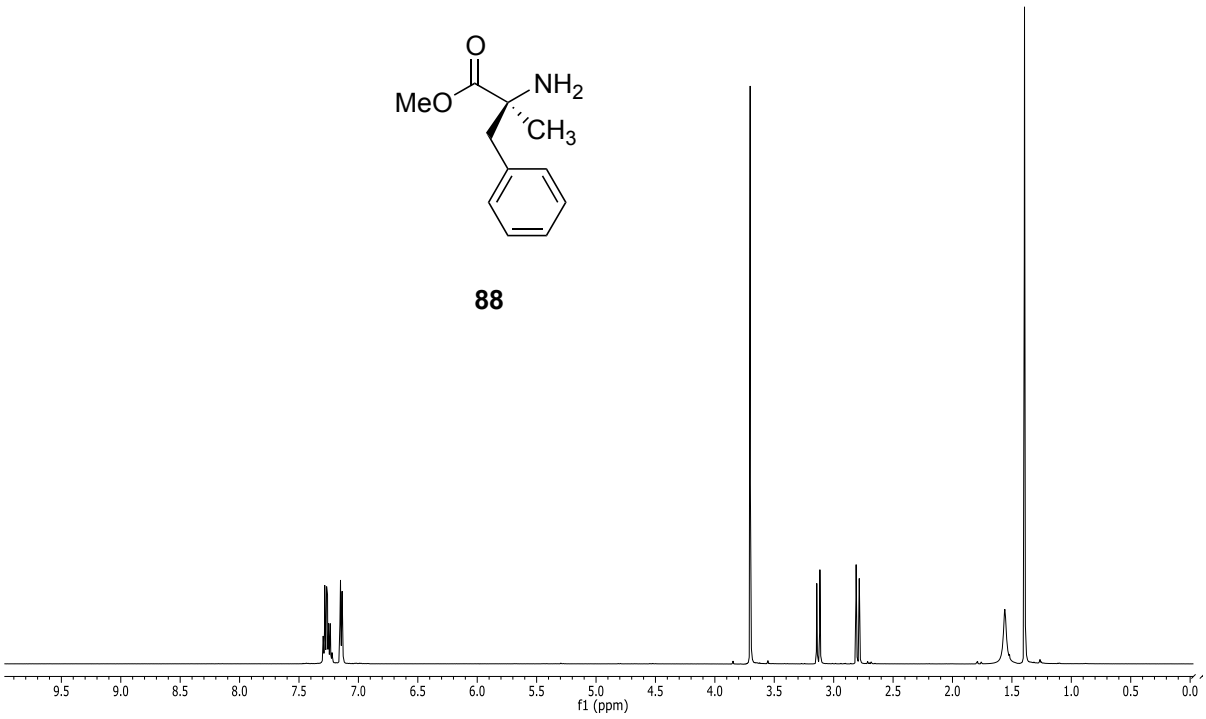
60
50
40
30
20
10
0
f1 (ppm)

87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MeO
NH2
CH3
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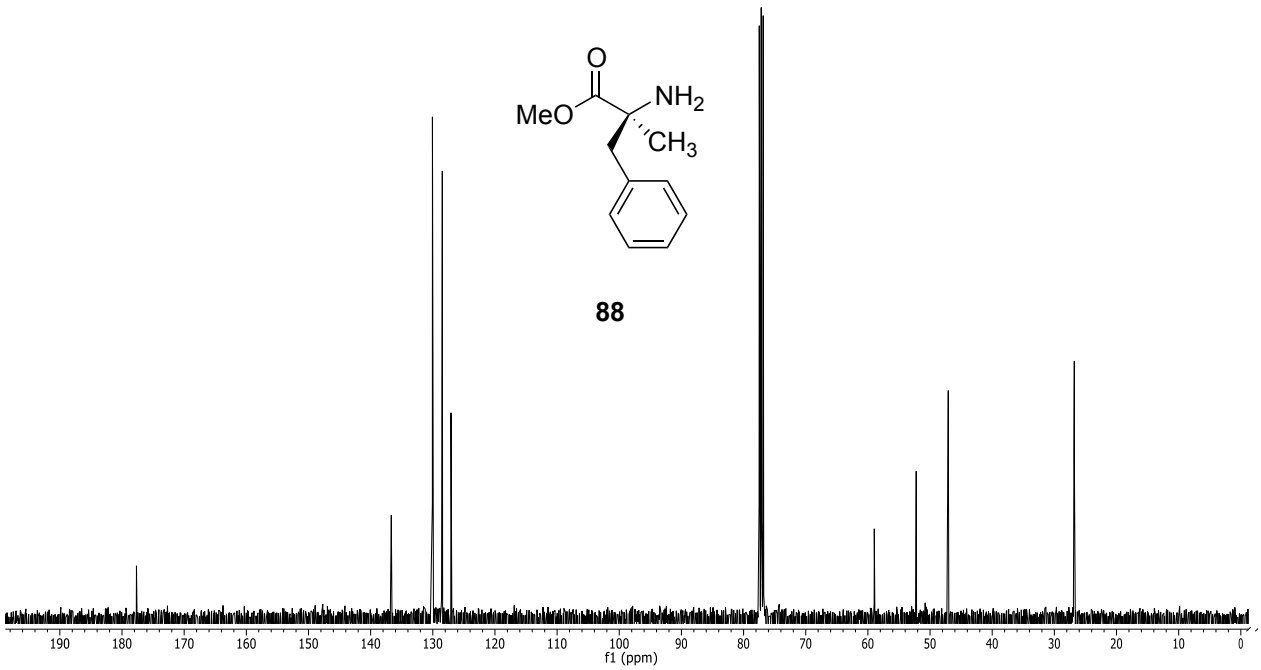
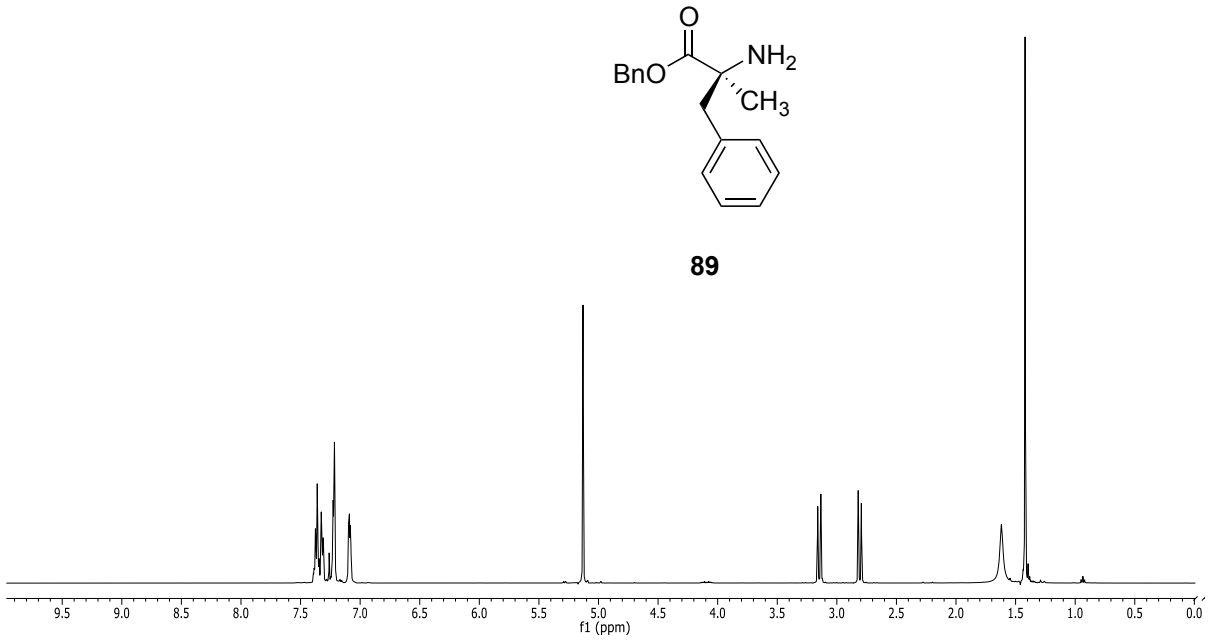
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

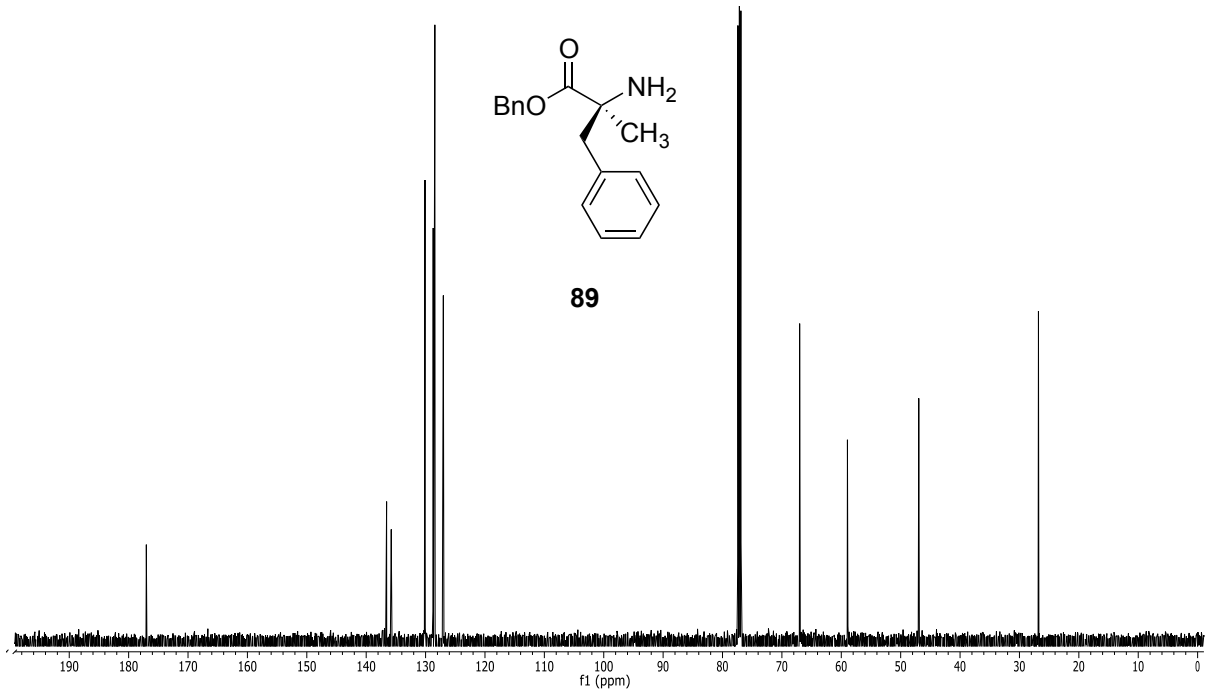
88


O
MeO
NH2
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

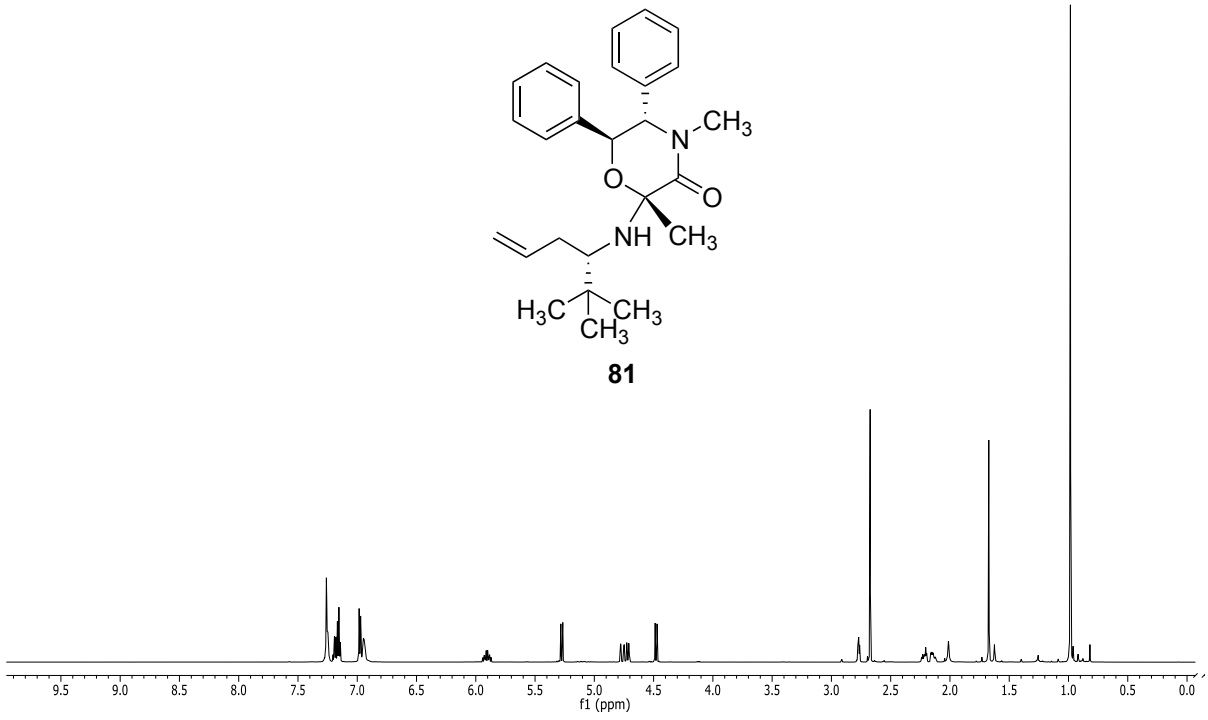
88


O
BnO
NH2
CH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

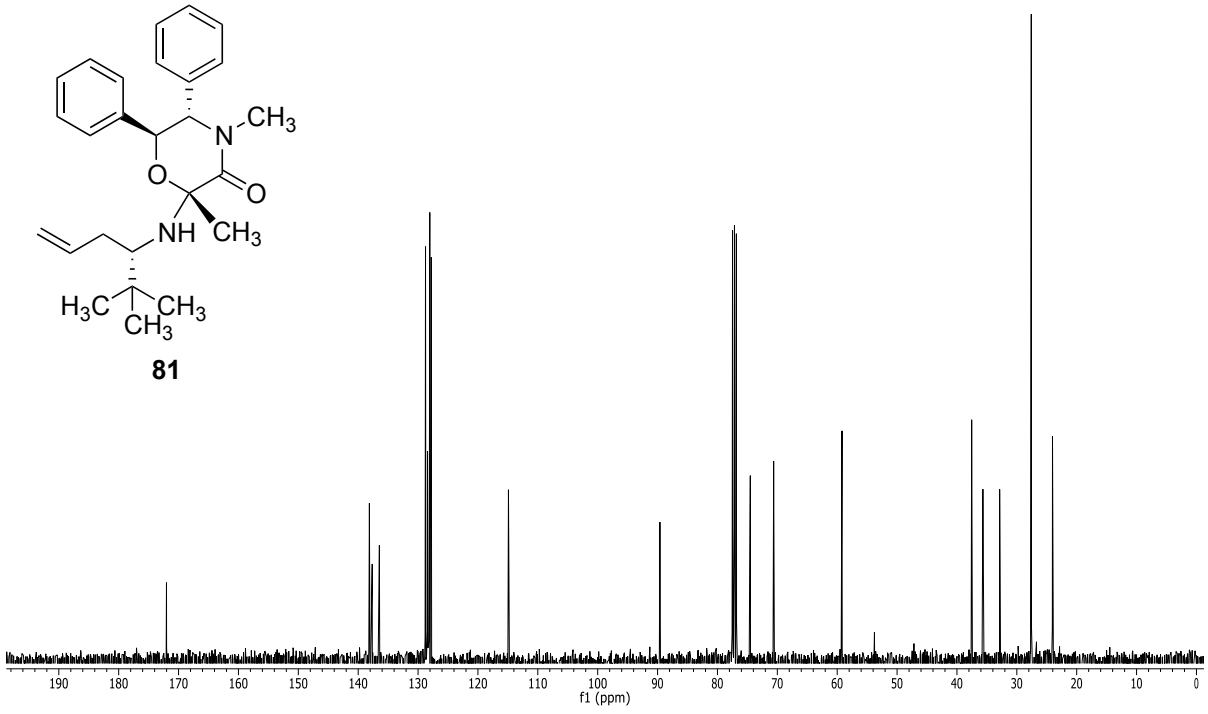
89


O
BnO
NH2
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

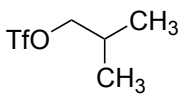
89


N
CH3
O
O
NH
CH3
H3C
CH3
CH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

81

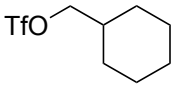

N
CH3
O
O
NH
CH3
H3C
CH3
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

81

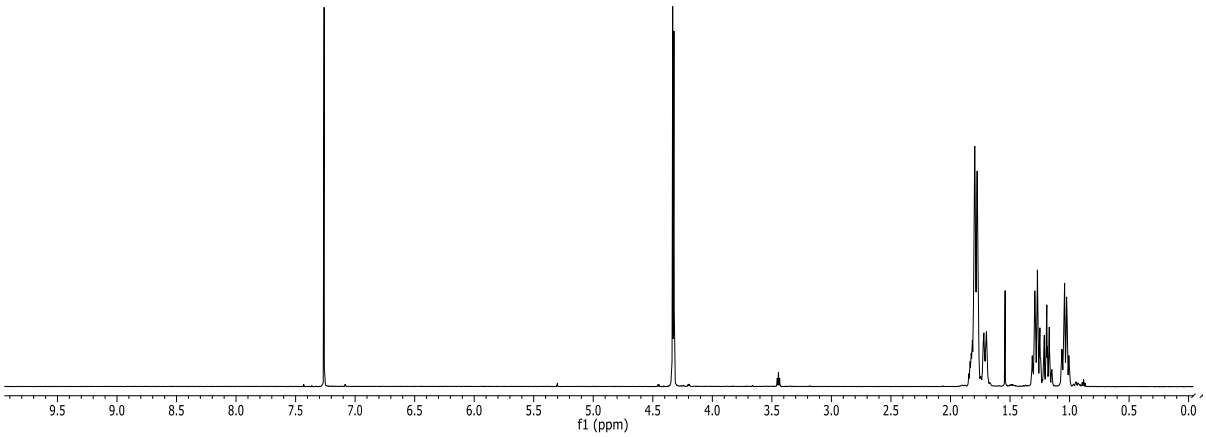

TfO
CH3
CH3

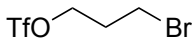
114

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

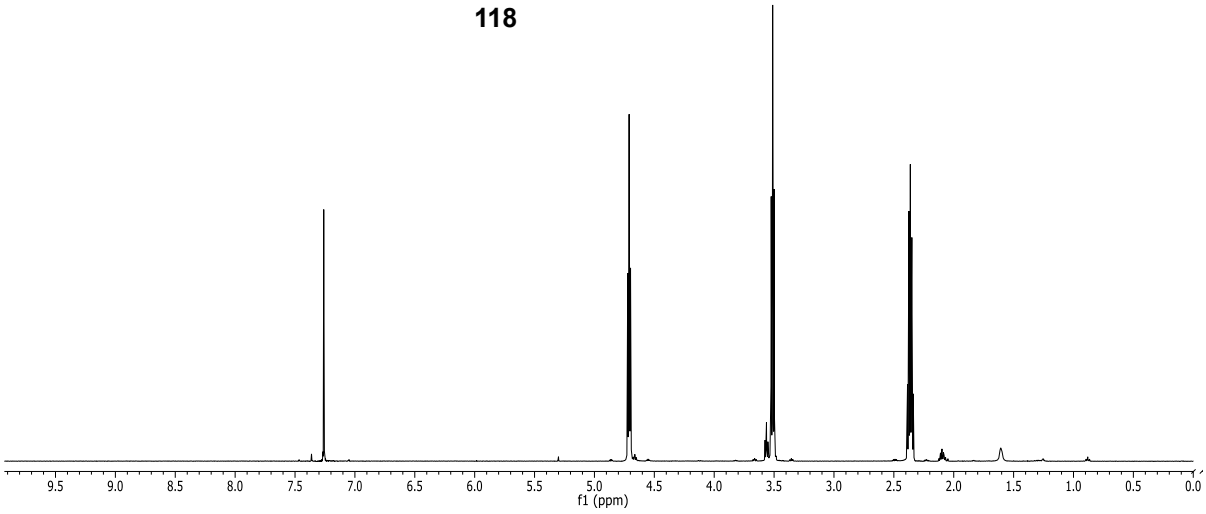

TfO

116


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


TfO
Br

118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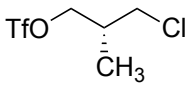
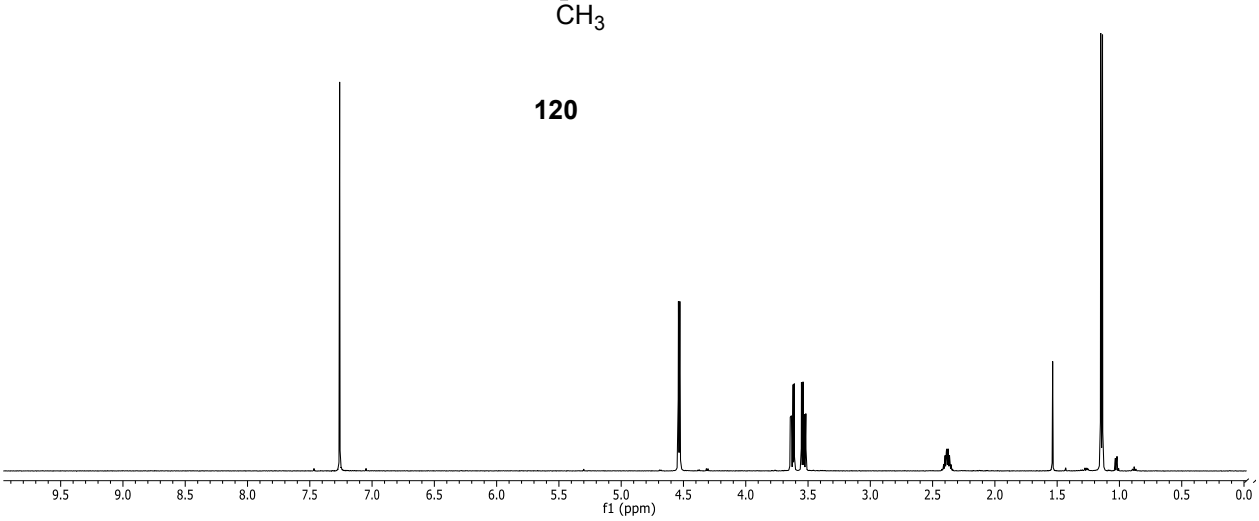
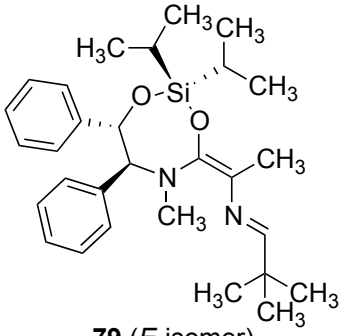
f1 (ppm)

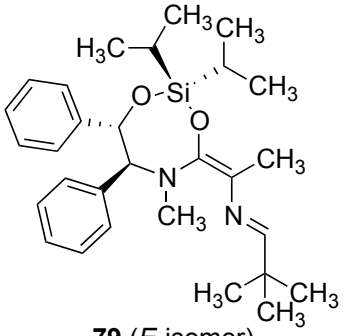

TfO
Cl
CH3

120


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



79 (*E*-isomer)



79 (*E*-isomer)

Chapter 4

On a Simple, Scalable Synthesis of (+)- and (–)-Pseudoephenamine

Introduction

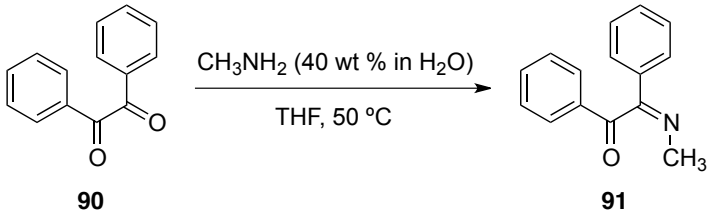
The two previous chapters have demonstrated the burgeoning utility of pseudoephenamine in asymmetric synthesis, and Chapter 2 outlined an effective route for the preparation of this chiral auxiliary. However, continued use of pseudoephenamine has created demand for the auxiliary that cannot be met by the first-generation synthesis in an economical manner. Specifically, synthesis of both enantiomers of pseudoephenamine using the prior synthetic route required the purchase of two relatively expensive amino alcohol starting materials, and the conversion of these amino alcohols to the two optically pure enantiomers of pseudoephenamine required four chemical transformations and one recrystallization per enantiomer, for a total of 10 chemical manipulations. Additionally, the first route was hampered by an epimerization step that was poorly scalable due to the required heating of large amounts of water to reflux. The following chapter details a second-generation synthesis of both (+)- and (–)-pseudoephenamine from the inexpensive starting material benzil that provides access to large amounts of both enantiomers of the auxiliary in 6 total chemical manipulations.

Synthesis of Methylimino Benzil

As a precursor to pseudoephenamine, methylimino benzil (**91**, Scheme 4.1) is nearly ideal, as it contains every carbon atom and heteroatom present in the final auxiliary. Fortunately, Wheatley and co-workers previously described the preparation of **91** by the condensation of methylamine and benzil (**90**) in methanol–water at 50 ºC, reporting a yield of 84%.[90] In practice, this reaction proved to be highly scalable, though it was critical to use a fresh (commercial) 40 wt % solution of methylamine in water (such that the titer of the volatile methylamine reactant was accurate) and crystalline benzil as co-reactants in order to obtain a good yield of the desired

[90] Wheatley, W. B.; Fitzgibbon, W. E.; Cheney, L. C. *J. Org. Chem.* **1953**, *18*, 1564–1571.

product. In the reaction, the heterogeneous mixture of starting materials was warmed in an oil bath while stirring until an internal temperature of 50 ºC was achieved and all solids were dissolved. Heating was immediately discontinued at this point, as further reaction lead to the formation of bis-methylimino benzil as a by-product. Upon cooling, the mono-imine crystallized from the reaction mixture, and the product was isolated in pure form by simple filtration (≥88% yield, 100–600-g scale, Table 1). The crystalline methylimino benzil obtained was confirmed to have (*Z*)-geometry by NOE and HMBC NMR correlations as well as by X-ray crystallography (see Experimental Information).



90 **91**

Scale	Yield
100 g	88%
300 g	92%
600 g	91%

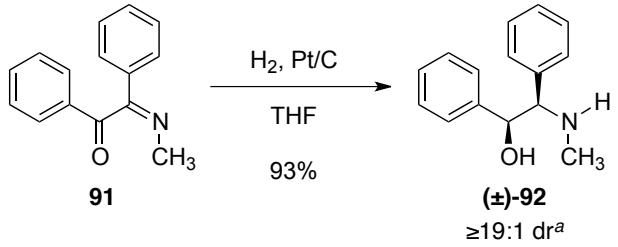
Scheme 4.1 Synthesis of methylimino benzil (**91**) from the inexpensive starting material benzil (**90**).

Reduction of Methylimino Benzil to (±)-Pseudoephenamine

The reduction of methylimino benzil to pseudoephenamine was unprecedented. Two prior studies of the reduction of **91** explored the use of Raney nickel[88] and sodium borohydride[91] as reductants, and in each case ephenamine (**92**) was reported to be the major or exclusive product. Initially, an enantio- as well as diastereoselective reduction of mono-imine **91** was explored with

[91] Hahn, W. E.; Bartnik, R.; Mloston, G. *Acta Poloniae Pharmaceutica*. **1979**, *36*, 619–620.

various chiral reductants,[92] but in each instance only racemic ephenamine was obtained. Although reduction of **91** to form racemic ephenamine was not an objective, Scheme 4.2 depicts a convenient method by which this transformation was achieved with ≥19:1 dr.[93,94]



91 **(±)-92** ≥19:1 dr[a]

Scheme 4.2 Synthesis of (±)-ephenamine (**92**) from methylimino benzil (**91**). [a] dr refers to the ratio of **(±)-92** to **(±)-25** as determined by ^{1}H NMR analysis of the crude reaction mixture.

Based upon the promising report of the reduction in the desired sense of achiral *N*-aryl and *N*-benzyl benzil mono-imines using lithium aluminum hydride (LAH),[95] the use of this reagent was investigated in the reduction of methylimino benzil.[96] In an initial experiment, reduction of methylimino benzil with LAH in THF at –78 ºC afforded a 4:1 mixture of diastereomeric amino alcohols favoring pseudoephenamine. Further investigations revealed that the diastereoselectivity of the reduction varied as a function of the rate of addition of LAH to the reaction mixture, and it

---

[92] See, for example: (a) Prasad, K. R. K.; Joshi, N. N. *J. Org. Chem.* **1996**, 61, 3888–3889. (b) Murata, K.; Okano, K.; Miyagi, M.; Iwane, H.; Noyori, R.; Ikariya, T. *Org. Lett.* **1999**, *1*, 1119–1121. (c) Touge, T.; Hakamata, T.; Nara, H.; Kobayashi, T.; Sayo, N.; Saito, T.; Kayaki, Y.; Ikariya, T. *J. Am. Chem. Soc.* **2011**, *133*, 14960–14963.

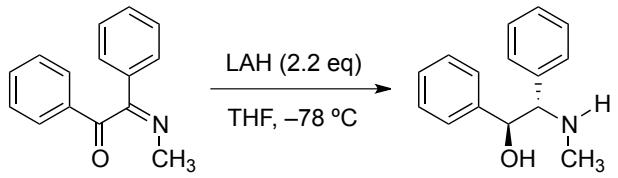
[93] Reductive amination of benzil in the presence of methylamine and a platinum catalyst has been reported to form ephenamine: Skita, A.; Keil, F. Manufacture of Aminoalcohols. U.K. Patent 313,217, July 24, 1930.

[94] While the importance of ephenamine in asymmetric synthesis was recognized, no attempt to resolve the racemic substance was made. For a resolution of racemic ephenamine with penicillin, see reference 5.

[95] Alcaide, B.; López-Mardomingo, C.; Pérez-Ossorio, R.; Plumet, J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1649–1653.

[96] For the use of LAH in the reduction of chiral benzil mono-imines, see: (a) Haro-Ramos, R.; Jimenez-Tebar, A.; Pérez-Ossario, R.; Plumet, J. *Tetrahedron Lett.* **1979**, *20*, 1355–1356. (b) Alcaide, B.; Fernández de la Pradilla, R.; López-Mardomingo, C.; Pérez-Ossorio, R.; Plumet, J. *J. Org. Chem.* **1981**, *46*, 3234–3238. (c) Alcaide, B.; Dominguez, G.; López-Mardomingo, C.; Pérez-Ossorio, R.; Plumet, J. *J. Chem. Soc., Perkin Trans. 2* **1986**, 99–103.

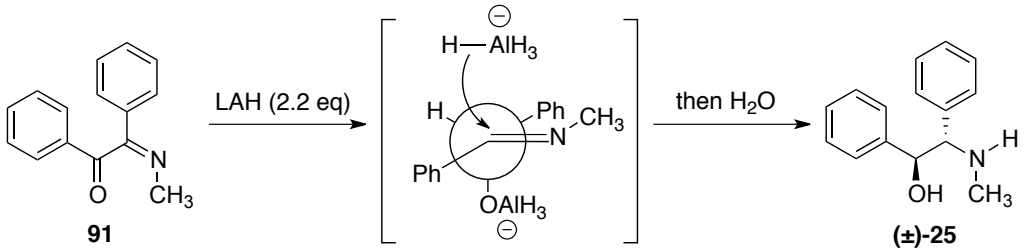
was noted that addition of powdered LAH too quickly led to delayed exotherms. Controlled addition of LAH with a powder addition funnel prevented these exotherms and allowed an internal temperature of –70 ºC to be maintained. It is useful to note that the exotherms more commonly occurred early in the course of the reaction; thus, the rate of LAH addition was increased as the reaction progressed. Efficient mechanical stirring of the reaction was also very important, especially on large scale, so as to prevent the aggregation of powdered LAH on the surface of the reaction mixture. In this manner, racemic pseudoephenamine of 4.7–5.4:1 dr was routinely prepared on 75–570 g scales in reproducibly high yield (>85%, see Scheme 4.3). As noted by Alcaide et al. in their study of the reduction of *N*-aryl and *N*-benzyl benzil mono-imines, the observed diastereoselectivity of the reduction is consistent with the Felkin-Ahn model (Figure 4.1).[95]



91 **(±)-25**

Scale	Yield	dr[a]
75 g	86%	5.4:1
290 g	92%	5:1
570 g	98%	4.7:1

Scheme 4.3 Synthesis of (±)-pseudoephenamine by reduction of methylimino benzil with LAH. [a] dr refers to the ratio of **(±)-25** to **(±)-92** as determined by ^{1}H NMR analysis of the crude reaction mixture.



91 **(±)-25**

Figure 4.1 The reduction of methylimino benzil to form pseudoephenamine is consistent with the Felkin-Ahn model for addition of nucleophiles to carbonyl systems, as noted by Alcaide and co-workers.[95]

Resolution of (±)-Pseudoephenamine

While the reduction of methylimino benzil to pseudoephenamine resulted in a mixture of four stereoisomers of the amino alcohol, direct resolution of either enantiomer of pseudoephenamine from the mixture of diastereomers in methanol was achieved with mandelic acid. Serendipitously, it was found that *(R,R)*-pseudoephenamine preferentially formed a highly crystalline salt with *(R)*-mandelic acid but not with *(S)*-mandelic acid under the resolution conditions, while neither diastereomeric ephenamine mandelate salt crystallized in the experiments.[97,98] Two procedures for the direct resolution of the LAH reduction products were developed, including one protocol with stirring and one without stirring. Both methods produced highly diastereoenriched mandelate crystals (≥19:1 dr by ^{1}H NMR, with no trace of either ephenamine mandelate salt) with good recovery (defined as the percent of the theoretical amount of the targeted enantiomer of pseudoephenamine). Seed crystals were typically unnecessary for these resolutions, though they effectively initiated resolution if crystal formation was sluggish. It is worthwhile to note that ^{1}H NMR analysis of the mandelate salts of pseudoephenamine is a convenient method to assay the enantiomeric purity of a sample of the auxiliary. Specifically, mixing a sample of pseudoephenamine (10 mg, 1 equiv) with (*S*)-mandelic acid (6.7 mg, 1 equiv) in $CDCl_3$ followed by ^{1}H NMR analysis (500 MHz) will reveal well-resolved resonances for the diastereomeric salts present in the solution, allowing simple assessment of the

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[97] For a comprehensive guide to the optical resolution of racemic compounds via formation of diastereomeric salts, see: *CRC Handbook of Optical Resolutions via Diastereomeric Salt Formation*; Kozma, D., Ed; CRC Press: Boca Raton, 2002.

[98] For selected resolutions of structurally similar amino alcohols, see: (a) Erlenmeyer E.; Arnold A. *Justus Liebigs Ann. Chem.* **1904**, *337*, 307–328. (b) Manske, R. H. F.; Johnson, T. B. *J. Am. Chem. Soc.* **1929**, *51*, 1906–1909. (c) Weijlard J.; Pfister III K.; Swanezy E. F.; Robinson C. A.; Tishler M. *J. Am. Chem. Soc.* **1951**, *73*, 1216–1218. (d) Saigo, K.; Sugiura, I.; Shida, I.; Tachibana, K.; Hasegawa, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2915–2916.

enantiopurity of the sample of pseudoephenamine (see Experimental Information for representative ^{1}H NMR spectra).

In the first resolution method, a solution of pseudoephenamine mandelate in methanol was allowed to stand at –20 ºC for several days without stirring, producing orthorhombic crystals. A representative set of experiments demonstrating this protocol is illustrated in Scheme 4.4. In the optimized procedure, pseudoephenamine (10 g, 5.4:1 dr, racemic) was mixed with (*S*)-mandelic acid (1 equivalent) in methanol (2.2 M in pseudoephenamine and ephenamine combined), and the mixture was warmed to 50 ºC in a 100-mL round-bottom flask to effect dissolution of the solid materials.[99] After cooling to room temperature and removing the stir bar, the base of the flask was carefully scratched with a spatula, and the vessel was transferred to a –20 ºC freezer to promote crystallization. After standing for several days (incubation times ranging from 2–10 days were typical), crystalline (*S*,*S*,*S*)-**93** of ≥19:1 dr was obtained by filtration using a Büchner funnel. The mother liquor was concentrated, and, after formation of the free base, resolution with the opposite enantiomer of mandelic acid was conducted. The pseudoephenamine mandelate salts obtained by this process will serve as suitable seed crystals for later resolutions, if necessary. Pseudoephenamine was conveniently isolated as its free base following treatment with aqueous sodium hydroxide solution, and, after recrystallization from hot absolute ethanol, optically pure auxiliary was obtained (81% recovery, ≥99% ee, see Scheme 4.5).[100] The mandelic acid was also easily recovered and recycled (see Experimental Information).

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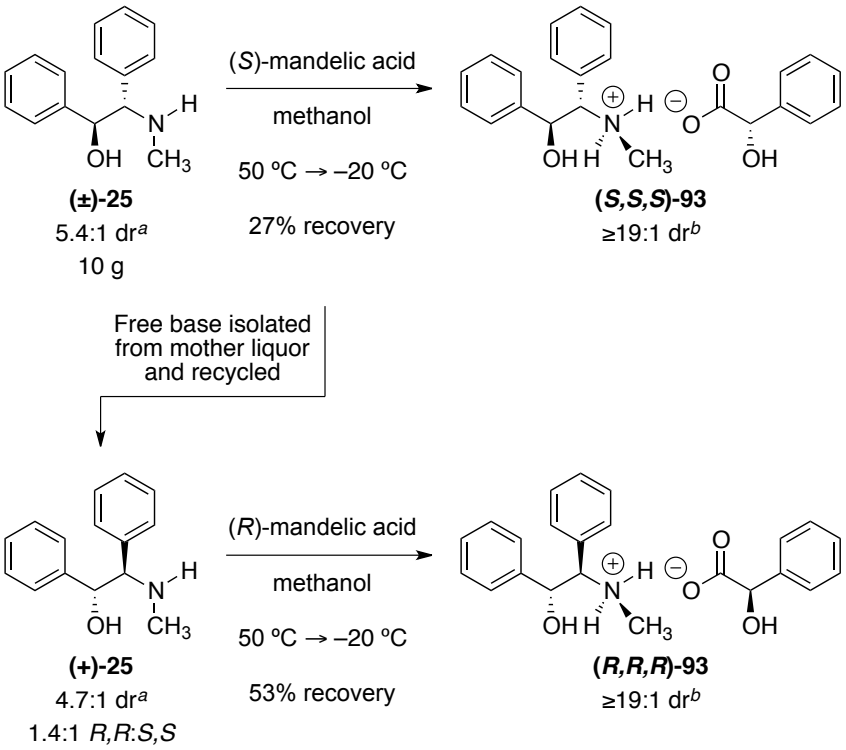
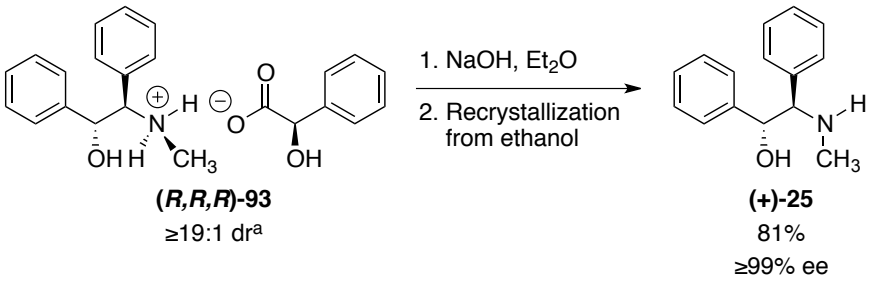
[99] It is recommended the solution be filtered through a fritted funnel while warm if insoluble impurities are observed in the flask.

[100] Crystallization of pseudoephenamine is an exothermic process, and concentrated solutions of the auxiliary in volatile solvents such as ethyl ether (employed in the workup of these reactions) can produce pressure buildup in a sealed vessel if spontaneous crystallization occurs.



Scheme 4.4 Resolution of (±)-pseudoephenamine with mandelic acid at –20 ºC without stirring. [a] dr refers to the ratio **of (+)-** and **(–)-25** to **(±)-92**. [b] dr refers to the ratio of **(*S*,*S*,*S*)-** or **(*R*,*R*,*R*)-93** to **(*R*,*R*,*S*)-** or **(*S*,*S*,*R*)-93**, respectively.

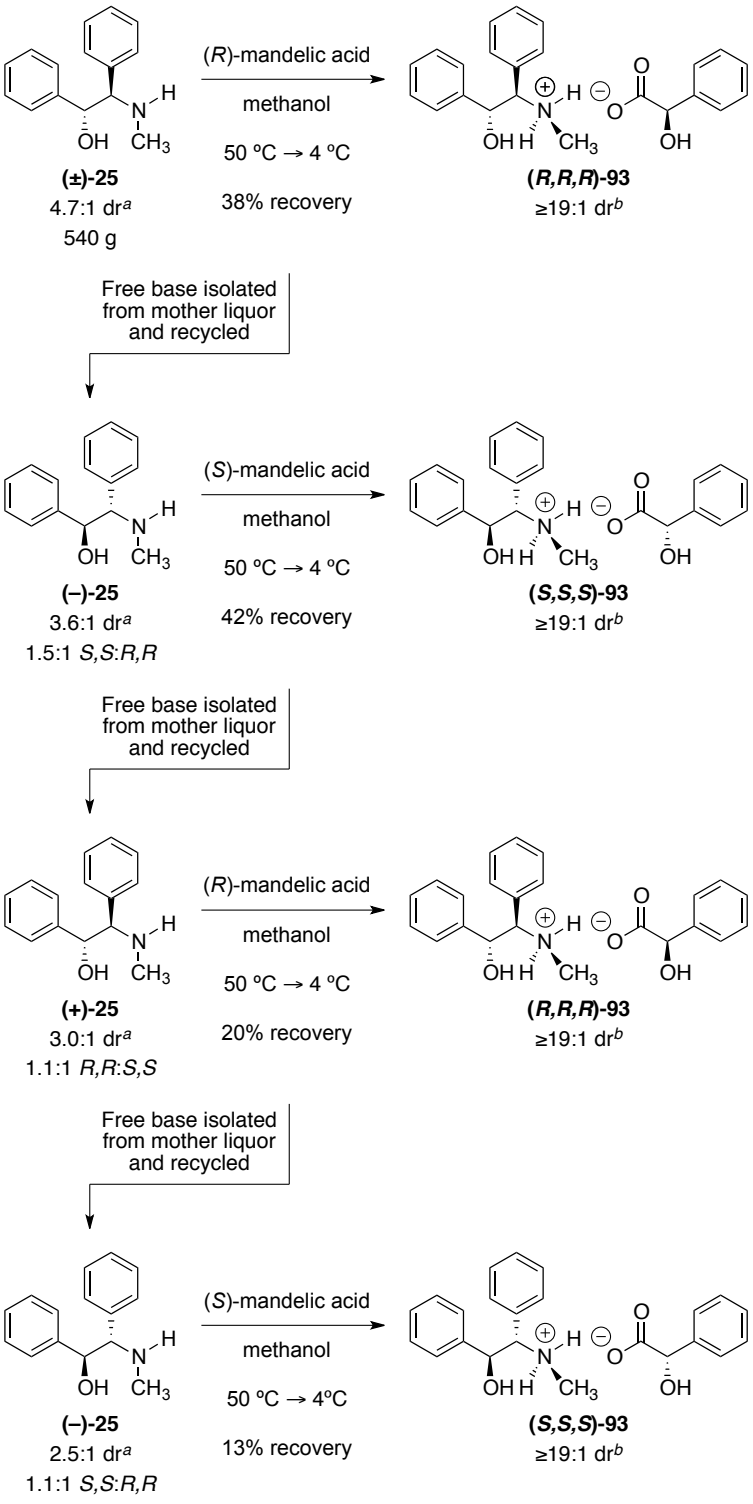


Scheme 4.5 Isolation of (+)-pseudoephenamine. [a] dr refers to the ratio of **(*R*,*R*,*R*)-93** to **(*S*,*S*,*R*)-93**.

Conducting resolutions of pseudoephenamine on a larger scale (>300 g) required the development of a second protocol involving gentle stirring of the cooled solution of pseudoephenamine mandelate in methanol at 4 ºC.[101] Resolutions employing this method

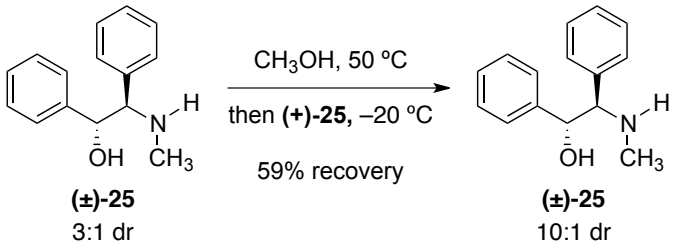
[101] See chapter 3 of reference 95 for a discussion of the effect of stirring on the resolution of diastereomeric salts.

produced fine, powdery crystals and progressed much more rapidly than resolutions performed using the earlier protocol, with typical resolution times ranging from 2–12 hours. A series of iterative resolutions conducted on a single batch of 570 g of pseudoephenamine (4.7:1 dr, racemic) demonstrated the ability of the stirring protocol to produce highly enriched mandelate crystals (≥19:1 dr by ^{1}H NMR, see Scheme 4.6) and provided approximately 100 g of each enantiomer of pseudoephenamine (≥92% ee). Recrystallization of the auxiliary from absolute ethanol gave more than 80 g of each enantiomer (≥99% ee). This protocol was the most convenient method of resolving pseudoephenamine and was routinely performed on large amounts of material (>300 g), though it also worked well on much smaller scales (<50 g).



Scheme 4.6 Resolution of (±)-pseudoephenamine with mandelic acid at 4 ºC with stirring. *Total pseudoephenamine recovery after isolation of the free auxiliary and recrystallization from ethanol:* 91.12 g **(+)-25** (≥99% ee) and 89.54 g **(–)-25** (≥99% ee). [a] dr refers to the ratio of **(+)-** and **(–)-25** to **(±)-92**. [b] dr refers to the ratio of **(*R*,*R*,*R*)-** or **(*S*,*S*,*S*)-93** to **(*S*,*S*,*R*)-** or **(*R*,*R*,*S*)-93**, respectively.

As seen in Scheme 4.6, recoveries upon resolution with mandelic acid were low when pseudoephenamine was appreciably contaminated with ephenamine (<2.5:1 dr). To circumvent this problem, amino alcohol mixtures of low dr were diastereomerically enriched by recrystallization from methanol in the presence of a seed crystal of optically pure pseudoephenamine (Scheme 4.7). The diastereomerically-enriched pseudoephenamine obtained was then subjected to mandelic acid resolution as in Scheme 4.6.

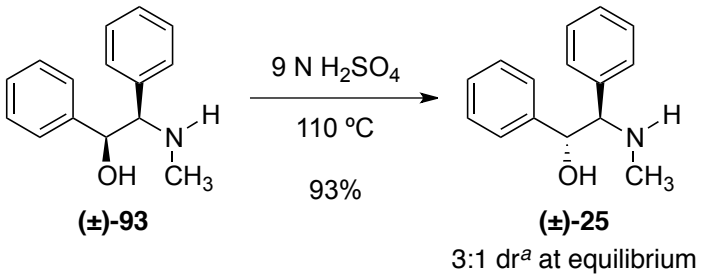


Scheme 4.7 Diastereoenrichment of (±)-pseudoephenamine. [a] dr refers to the ratio of **(±)-25** to **(±)-92**.

Lastly, it was recognized that the LAH reduction of methylimino benzil produces a significant amount of ephenamine by-product in the reaction, to the point that large-scale reductions generate more than 100 g of the undesired diastereomer of the amino alcohol. To prevent this material from going to waste, conditions were developed to convert ephenamine to pseudoephenamine directly. Specifically, ephenamine was slowly converted to pseudoephenamine upon heating (110 °C) in 9 N H_2SO_4 (Scheme 4.8),[102] producing a mixture of amino alcohols favoring the pseudoephenamine diastereomer (~3:1 dr at equilibrium). Recrystallization of this material from methanol as in Scheme 4.7 provided diastereomerically-enriched pseudoephenamine suitable for mandelic acid resolution. Leveraging this epimerization

[102] A similar process has been reported to transform ephedrine to pseudoephedrine: Chou, T. Q. *J. Biol. Chem.* **1926**, *70*, 109–114.

reaction, it was possible to convert the majority of the amino alcohols obtained in the reduction of methylimino benzil to optically pure pseudoephenamine.



(±)-93 **(±)-25**

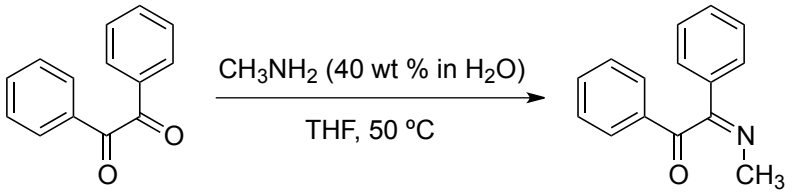
3:1 dr[a] at equilibrium

Scheme 4.8 Isomerization of ephenamine to pseudoephenamine. [a] dr refers to the ratio of **(±)-25** to **(±)-93**.

Experimental Information

General experimental procedures, materials, and instrumentation: Reactions were conducted without precautions to exclude moisture or air, unless otherwise noted. Organic solutions were concentrated by rotary evaporation (ca. 40 Torr) at 35 ºC, unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60 Å pore size, 230–400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and then were stained by submersion in aqueous potassium permanganate solution followed by brief heating on a hot plate. Commercial reagents were used as received. Tetrahydrofuran (anhydrous), methanol, and ethanol (absolute) were used as received without further purification. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 500 MHz at 23 ºC. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, m = multiplet and/or multiple resonances), integration, coupling constant (*J*) in Hertz. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 125 MHz at 23 ºC. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, δ 77.0). Infrared (IR) spectral data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak). Melting points were determined using a Thomas Scientific capillary melting point apparatus. High-resolution mass spectra were obtained at the Harvard University Mass Spectrometry Facility.

Synthesis of (±)-pseudoephenamine:

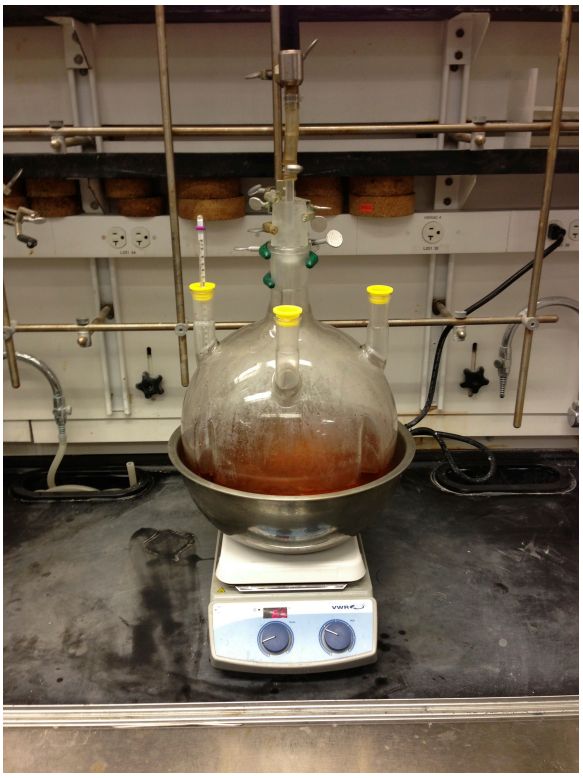


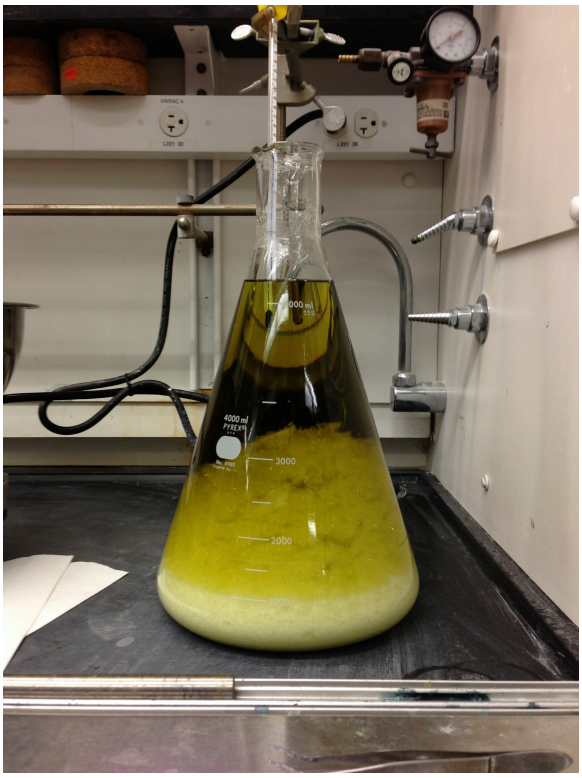
90 **91**

(*Z*)-2-(methylimino)-1,2-diphenylethanone (91)

A 12-L four-neck round-bottom flask was charged with benzil (600 g, 2.85 mol, 1.00 equiv) and methanol (2.85 L) and the reaction vessel was immersed in an oil bath at 23 °C. One neck of the flask was equipped with a mechanical stirrer, while the remaining necks of the flask were equipped with a thermometer, a wide-mouth funnel, and a loose-fitting polyethylene cap, respectively. The mechanical stirrer was set to stir at 180 rpm, producing a bright yellow slurry. Methylamine solution (40 wt% in water, 741 mL, 8.56 mol, 3.00 equiv) was added to the slurry, which became dark orange in color. The funnel was then replaced with a loose-fitting polyethylene cap, and the mixture was warmed to 50 °C. Prior to reaching the desired temperature, all of the solid material dissolved to give a clear, orange solution. Once the internal temperature of the solution reached 50 °C, the flask was removed from the oil bath, and the reaction solution was transferred to a 4-L Erlenmeyer flask to cool. As the solution cooled, the product began to crystallize. Once the temperature of the mother liquor dropped below 30 °C, the crystalline product was collected in a large Büchner funnel. The collected off-white crystals were then washed twice with water. Additional crystalline product formed in the filtrate, and these crystals were collected separately and washed with water. Formation of crystalline product in the filtrate was once again noted, and the filtration process was repeated thrice more until no additional crystalline product was observed in the filtrate. The solids were dried via suction for three hours before being transferred to three round bottom flasks (3-L and two 1-L flasks) and

further dried under reduced pressure (<1 torr, 72 h) to remove any remaining water. The crystalline imine **91** (582 g, 91%, mp = 75–77 ºC) thus obtained was used in subsequent reactions without further purification. TLC (20% ethyl acetate–hexanes): R_f = 0.54 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.95 – 7.88 (m, 2H), 7.73–7.66 (m, 2H), 7.67–7.57 (m, 1H), 7.53–7.44 (m, 2H), 7.46–7.31 (m, 3H), 3.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 198.96, 198.96, 168.08, 168.08, 135.16, 135.16, 134.62, 134.62, 134.51, 134.51, 130.77, 130.77, 129.25, 129.25, 129.08, 129.08, 128.59, 128.59, 127.04, 127.04, 41.01, 41.01. FTIR (neat), cm^{-1}: 3061 (w), 1670 (s), 1629 (m), 1446 (m), 1223 (s). HRMS (ESI): Calcd for (C15H13NO + Na)+: 246.0889. Found: 246.0886.





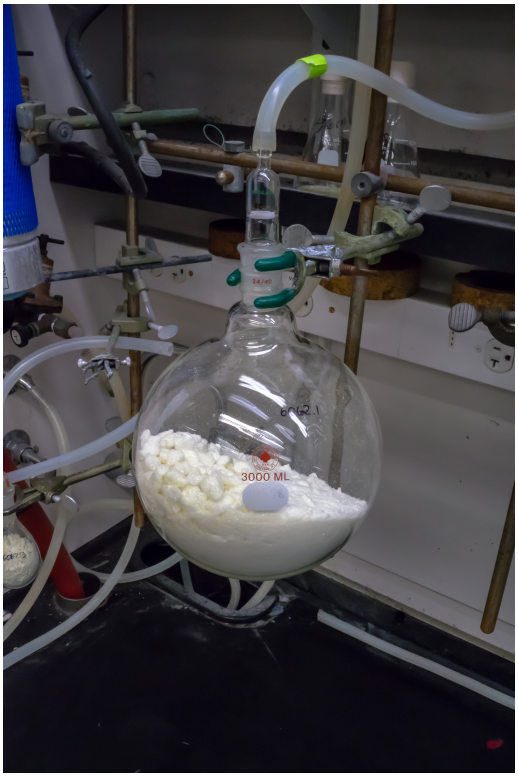
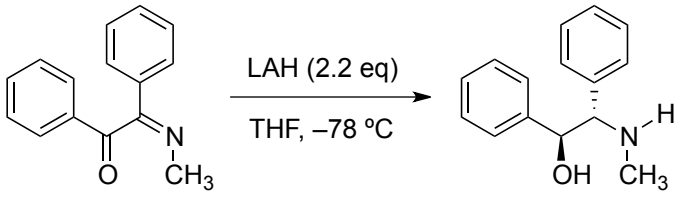


Image 4.1: Clockwise from top left: 1) Synthesis of methylimino benzil in a 12-L flask equipped with a mechanical stirrer. 2) Crystallization of methylimino benzil upon cooling. 3) A portion of isolated methylimino benzil in a 3-L flask after filtration.



91 **(±)-25**

(±)-pseudoephenamine ((±)-25)

A 12-L 4-neck round bottom flask was charged with methylimino benzil (572.54 g, 2.56 mol, 1.00 equiv) and THF (6.41 L). The flask was equipped with a mechanical stirrer, and the remaining three necks of the flask were equipped with a low-temperature thermometer, a loose-fitting polyethylene cap, and a powder addition funnel equipped with an argon inlet, respectively. The mechanical stirrer was set to stir at 300 rpm, and the solid imine dissolved to give a bright yellow solution. The reaction vessel was immersed in a –78 °C dry ice–acetone bath. Once the internal temperature of the solution reached –75 °C, the powder addition funnel was charged with lithium aluminum hydride (LAH, 225 g, 5.64 mol, 2.20 equiv), and the addition of LAH commenced at a rate such that the internal temperature of the reaction solution did not rise above –70 °C (CAUTION: exotherms are common in the early stages of the addition, so the LAH must be added at a slower rate at the beginning of the reaction). The addition of LAH was complete after 2.5 h, and the starting material was consumed after stirring for an additional 1 h (3.5 h total reaction time). Upon complete reaction, the polyethylene cap in one neck of the reaction flask was replaced with a 250 ml liquid addition funnel which was used to introduce sequentially the quenching liquids water (230 mL), 2 N aqueous sodium hydroxide solution (460 mL), and water (690 mL).[61] Caution should be exercised during the addition of the quenching liquids, as this is an exothermic process proceeding with gas evolution and precipitation of solids. The internal temperature did not rise above –30 °C during the quenching process. After the quench was complete, the reaction vessel was removed from the cooling bath and allowed to warm to room

temperature with continued stirring. The salt by-products were separated from the reaction solution by filtration through a fritted funnel, and the solids were washed with 4x1 L of ethyl ether. The filtrate and washes were combined and the combined liquid was concentrated to remove the organic solvents. The resulting concentrate was then partitioned between ethyl ether (4 L) and water (500 mL) in a 12-L separatory funnel. The layers were separated, and the organic phase was washed sequentially with water (500 mL) and saturated aqueous sodium chloride solution (500 mL). The organic solution was then dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated to give **(±)-25** (569.72 g, 98%, mp = 84–86 ºC) as an off-white/pale yellow solid. The dr of the crude material was determined to be 4.7:1 by ^{1}H NMR analysis. TLC (10% methanol–dichloromethane): R_f = 0.21, streak (UV, $KmnO_4$). ^{1}H NMR (4.7:1 dr, asterisk denotes minor diastereomer peaks, 500 MHz, $CDCl_3$), δ: 7.29 – 7.12 (m, 6H), 7.11–7.07 (m, 2H), 7.05–7.00 (m, 2H), 4.82* (d, 1H, *J* = 5.9 Hz), 4.57 (d, 1H, *J* = 8.5 Hz), 3.77* (d, 1H, *J* = 5.9 Hz), 3.49 (d, 1H, *J* = 8.5 Hz), 2.32 (s, 3H), 2.29* (s, 3H). ^{13}C NMR (4.7:1 dr, asterisk denotes minor diastereomer peaks, 125 MHz, $CDCl_3$), δ: 141.40, 140.78*, 139.39, 138.98*, 128.30*, 128.12, 128.07*, 127.97*, 127.88, 127.78, 127.55*, 127.47*, 127.31, 127.30, 126.81, 126.78*, 77.64, 76.46*, 72.27, 70.90*, 34.19*, 34.10. FTIR (neat), cm^{-1}: 3062 (w), 3030 (w), 2797 (w), 1492 (w), 1454 (m). HRMS (ESI): Calcd for (C15H17NO + Na)+: 250.1202. Found: 250.1201.

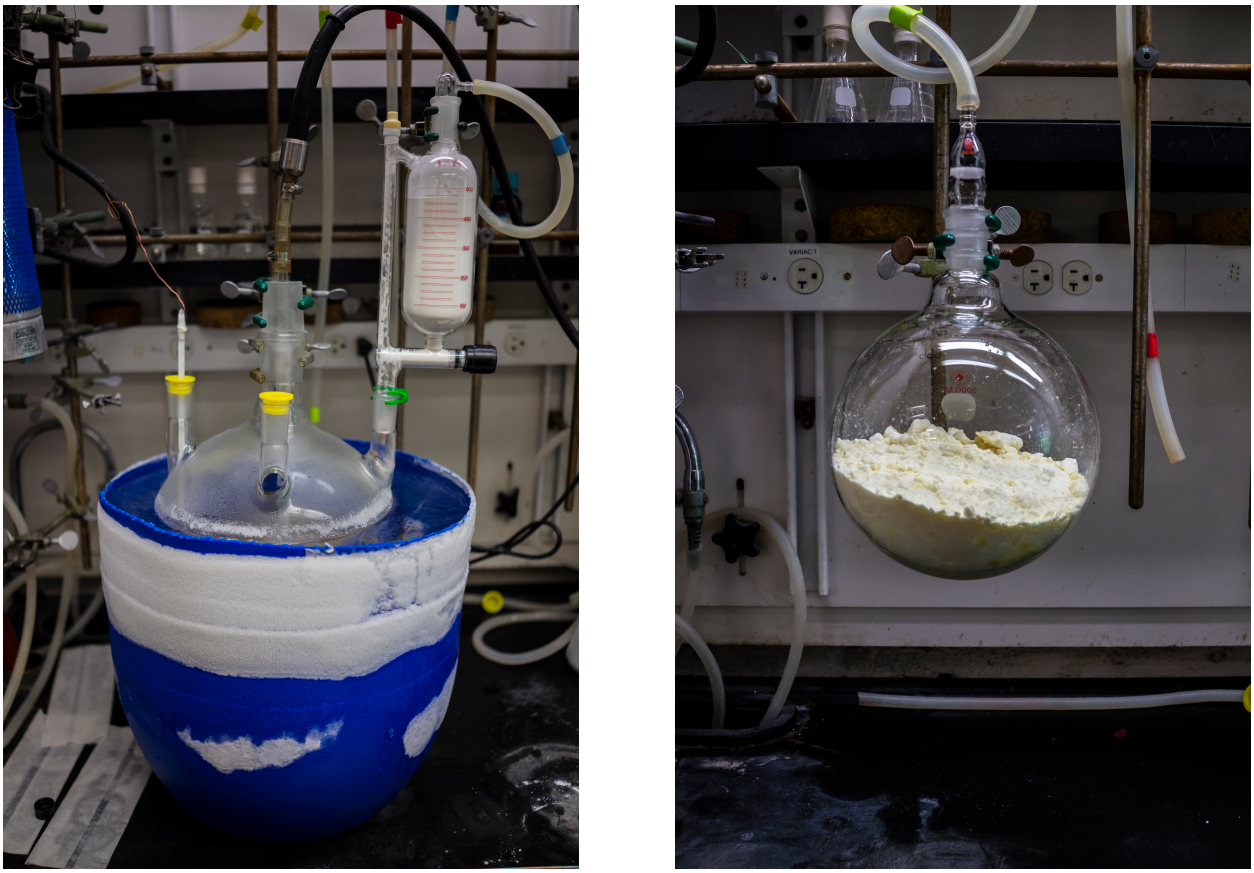
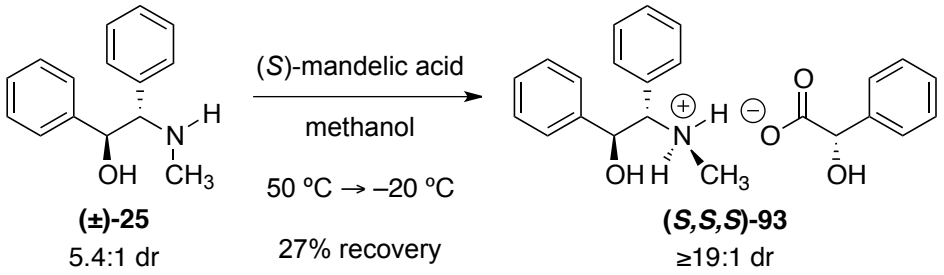


Image 4.2: From left: 1) Reduction of methylimino benzil in a 12-L flask equipped with a mechanical stirrer and a powder addition funnel charged with LAH. 2) Crude pseudoephenamine in a 3-L flask after workup and concentration.

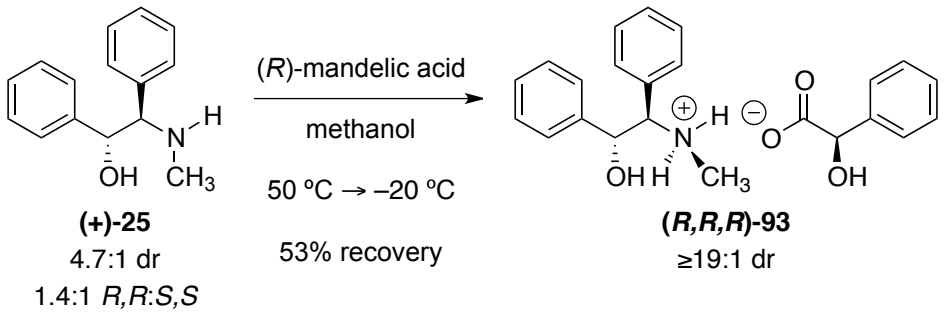
Resolution at –20 ºC without stirring:



(*S*,*S*,*S*)-pseudoephenamine mandelate ((*S*,*S*,*S*)-93)

A 100-mL round-bottom flask was charged with (±)-pseudoephenamine (5.4:1 dr, 10.0 g, 44.0 mmol, 1.00 equiv), (*S*)-mandelic acid (6.69 g, 44.0 mmol, 1.00 equiv), methanol (20.0 mL), and a Teflon-coated magnetic stirring bar. The flask was immersed in an oil bath preheated to 50 ºC, and the mixture was stirred until all solid materials dissolved, producing a golden yellow solution. The stir bar was then removed from the flask, and the solution was allowed to cool to room temperature. Once cool, the base of the flask was carefully scratched with spatula, and the flask was sealed with aluminum foil and placed into a –20 ºC freezer to promote crystallization. Crystal formation occurred slowly, and, after 2 d, the flask was removed from the freezer. The mother liquor was decanted from the flask, and the crystals were rinsed with methanol before drying under reduced pressure. Crystalline **(*S*,*S*,*S*)-93** (1.90 g, 27% of theory) was determined to be >19:1 dr by ^{1}H NMR, and these crystals were kept to use as seed crystals in further resolutions. The mother liquor was concentrated to a thick oil that was partitioned between dichloromethane (10 mL) and aqueous 1 *N* sodium hydroxide solution (10 mL). The layers were separated, and the organic material was extracted from the aqueous phase with dichloromethane (2x10 mL). The combined organic extracts were dried over potassium carbonate. The dried solution was filtered, and the filtrate was concentrated to give **(+)-25** (7.96 g, 4.7:1 dr, pseudoephenamine 1.4:1 er) as an off-white/pale yellow solid that was used in a later resolution.

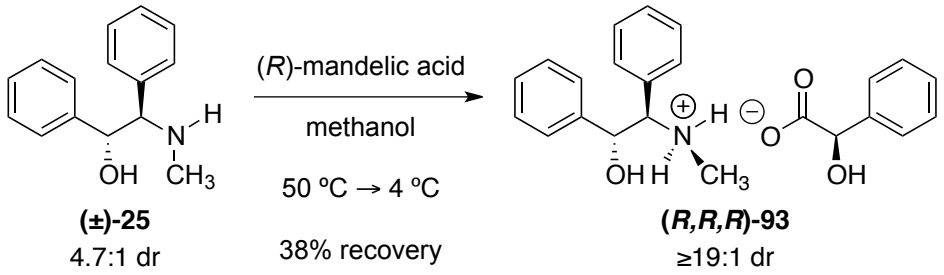
Characterization data for **(*S*,*S*,*S*)-93**: ^{1}H NMR (≥19:1 dr, asterisk denotes minor diastereomer peaks, 500 MHz, $CDCl_3$), δ: 7.63–7.57 (m, 2H), 7.37–7.29 (m, 2H), 7.31–7.09 (m, 7H), 7.00–6.91 (m, 4H), 5.11 (s, 1H), 5.00* (d, *J* = 10.1 Hz , 1H), 4.84 (d, *J* = 10.1 Hz, 1H), 3.84 (d, *J* = 10.1 Hz, 1H), 3.70* (d, *J* = 10.1 Hz, 1H) 2.18 (s, 3H), 2.08* (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 179.74, 142.18, 139.47, 131.57, 129.19, 129.01, 128.67, 128.19, 128.11, 127.91, 127.28, 126.86, 126.66, 75.71, 74.63, 70.31, 30.73. FTIR (neat), cm^{-1}: 3032 (w), 1593 (m), 1360 (m), 613 (s), 646 (s).



(*R*,*R*,*R*)-pseudoephenamine mandelate ((*R*,*R*,*R*)-93)

A 100-mL round-bottom flask was charged with (+)-pseudoephenamine (4.7:1 dr, pseudoephenamine 1.4:1 er, 7.96 g, 35.0 mmol, 1.00 equiv), (*R*)-mandelic acid (5.44g, 35.0 mmol, 1.00 equiv), methanol (15.9 mL), and a Teflon-coated magnetic stirring bar. The flask was immersed in an oil bath preheated to 50 ºC, and the mixture was stirred until all solid materials dissolved, producing a golden yellow solution. The stir bar was then removed from the flask, and the solution was allowed to cool to room temperature. Once cool, the base of the flask was carefully scratched with spatula, and the flask was sealed with aluminum foil and placed into a –20 ºC freezer to promote crystallization. Crystal formation occurred slowly, and, after 10 d, the flask was removed from the freezer. The mother liquor was decanted from the flask, and the crystals were rinsed with methanol before drying under reduced pressure. Crystalline **(*R*,*R*,*R*)-93** (3.40 g, 53% of theory) was determined to be ≥19:1 dr by ^{1}H NMR, and these crystals were kept to use as seed crystals in further resolutions. The mother liquor was concentrated to a thick oil that was partitioned between dichloromethane (10 mL) and aqueous 1 *N* sodium hydroxide solution (10 mL). The layers were separated, and the organic material was extracted from the aqueous phase with dichloromethane (2x10 mL). The combined organic extracts were dried over potassium carbonate. The dried solution was filtered, and the filtrate was concentrated to give **(–)-25** (5.80 g, 3:1 dr, pseudoephenamine 1.6:1 er) as an off-white/pale yellow solid that was used in a later resolution. Characterization data for **(*R*,*R*,*R*)-93** were identical to those reported above for **(*S*,*S*,*S*)-93** above.

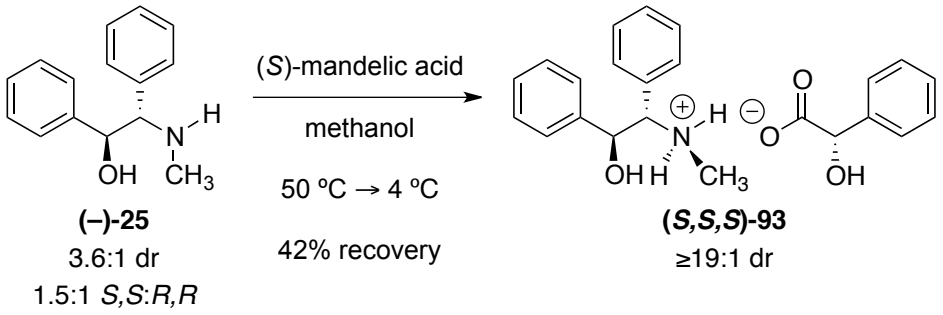
Resolution at 4 ºC with stirring:



(*R*,*R*,*R*)-pseudoephenamine mandelate ((*R*,*R*,*R*)-93)

A 5-L three-necked flask was charged with (±)-pseudoephenamine (4.7:1 dr, 541.04 g, 2.38 mol, 1.00 equiv), (*R*)-mandelic acid (370 g, 2.38 mol, 1.00 equiv), and methanol (1.08 L). The flask was then equipped with a mechanical stirrer and immersed in an oil bath preheated to 50 ºC. The mechanical stirrer was set to stir at 120 rpm, and the mixture was stirred until all solids dissolved, producing a yellow-orange solution. The solution was filtered while warm through a fritted glass funnel to remove insoluble impurities. The filtered solution was then transferred to a 6-L Erlenmeyer flask containing a large, flat, Teflon-coated magnetic stirring bar, and the solution was allowed to cool to room temperature. Once cool, the flask was sealed with aluminum foil and placed on a stir plate in a cold room at 4 ºC, and the solution was set to gently stir for 12 h. The large amount of powdery solid that formed during this time was then filtered through a Büchner funnel while cold. The collected solid was not washed, as the off-white powdery solid was found to be appreciably soluble in cold methanol. The solid cake was dried via suction for 2 h before it was broken apart and further dried under reduced pressure (<1 Torr). The crystalline **(*R*,*R*,*R*)-93** (141.85 g, 38% of theory) was determined to be ≥19:1 dr by ^{1}H NMR. Characterization data for **(*R*,*R*,*R*)-93** were identical to those reported above for **(*S*,*S*,*S*)-93** above. The mother liquor was concentrated to a thick, orange oil that was partitioned between diethyl ether (1 L) and aqueous 1 *N* sodium hydroxide solution (2.5 L). The layers were

separated, and the organic material was extraction from the aqueous phase with ethyl ether (2x1 L). The combined organic extracts were dried over potassium carbonate. The dried solution was filtered, and the filtrate was concentrated to give **(–)-25** (446.93 g, 3.6:1 dr, pseudoephenamine 1.5:1 er) as a pale yellow solid that was used in a later resolution. The aqueous sodium hydroxide solution was adjusted to pH 1 by addition of 6 *N* hydrochloric acid solution (420 mL), and the mandelic acid was extracted from this aqueous solution using ethyl ether (3x2 L). The combined organic extracts were concentrated to provide an off-white solid. The recovered (*R*)-mandelic acid (301.74 g, 81% recovery) was recrystallized from hot water (661 mL) to give pure (*R*)-mandelic acid (175 g) suitable for use in later resolutions. Recrystallization of the (*R*)-mandelic acid recovered from the aqueous mother liquor provided an additional 63 g of the acid.



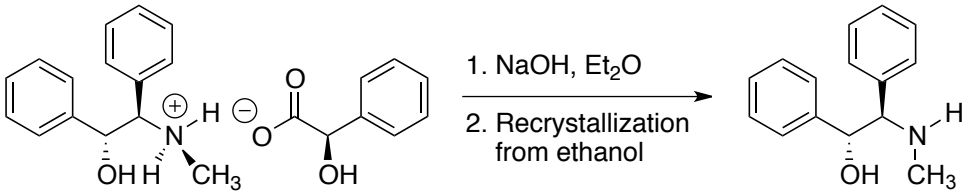
(*S*,*S*,*S*)-pseudoephenamine mandelate ((*S*,*S*,*S*)-93)

A 5-L three-necked flask was charged with (–)-pseudoephenamine (4.6:1 dr, pseudoephedrine 1.5:1 er, 446.93 g, 1.97 mol, 1.00 equiv), (*S*)-mandelic acid (302 g, 1.97 mol, 1.00 equiv), and methanol (894 mL). The flask was then equipped with a mechanical stirrer and immersed in an oil bath preheated to 50 °C. The mechanical stirrer was set to stir at 120 rpm, and the mixture was stirred until all solids dissolved, producing a yellow-orange solution. The solution was filtered while warm through a fritted glass funnel to remove insoluble impurities. The filtered solution was then transferred to a 6-L Erlenmeyer flask containing a large, flat, Teflon-coated magnetic stirring bar, and the solution was allowed to cool to room temperature. Once cool, the flask was sealed and placed on a stir plate in a cold room at 4 °C, and the solution was set to gently stir for 12 h. The large amount of powdery solid that formed during this time was then filtered through a Büchner funnel while cold. The collected solid was not washed, as the off-white powdery solid was found to be appreciably soluble in cold methanol. The solid cake was dried via suction for 2 h before it was broken apart and dried further under reduced pressure (<1 Torr). The crystalline **(*S*,*S*,*S*)-93** (148 g, 42% of theory) was determined to be ≥19:1 dr by ^{1}H NMR. Characterization data for **(*S*,*S*,*S*)-93** were identical to those reported above for **(*S*,*S*,*S*)-93** above. The mother liquor was concentrated to a thick, orange oil that was partitioned between ethyl ether (1 L) and aqueous 1 *N* sodium hydroxide solution (2 L). The layers were separated, and the organic material was extraction from the aqueous phase with ethyl ether (2x1 L). The

combined organic extracts were dried over potassium carbonate. The dried solution was filtered, and the filtrate was concentrated to give **(+)-25** (350.87 g, 3:1 dr, pseudoephenamine 1.1:1 er) as a pale yellow solid that was used in a later resolution. The aqueous sodium hydroxide solution was adjusted to pH 1 by addition of 6 *N* hydrochloric acid solution (333 mL), and the mandelic acid was extracted from this aqueous solution using ethyl ether (3x2 L). The combined organic extracts were concentrated to provide an off-white solid. The recovered (*S*)-mandelic acid (238.76 g, 79% recovery) was recrystallized from hot water (523 mL) to give pure (*S*)-mandelic acid (123.5 g) suitable for use in later resolutions. Recrystallization of the (*S*)-mandelic acid recovered from the aqueous mother liquor provided an additional 72 g of the acid.

Image 4.3: Resolution of pseudoephenamine by stirring at 4 ºC in a cold room.

Isolation of optically pure pseudoephenamine



(*R,R,R*)-93
≥19:1 dr

(+)-25
81%
≥99% ee

(+)-pseudoephenamine ((+)-25)

A 4-L Erlenmeyer flask was charged with pseudoephenamine mandelate **(*R,R,R*)-93** (≥19:1 dr, 187.37 g, 494 mmol, 1.00 equiv), ethyl ether (1.5 L), 1 *N* aqueous sodium hydroxide solution (500 ml), and a Teflon-coated magnetic stirring bar. The resulting slurry was stirred until all of the solid material dissolved. The biphasic mixture was then transferred to a 4-L separatory funnel. The layers were separated, and **(+)-25** was extracted from the basic aqueous phase with ethyl ether (2x1 L). The combined organic extracts were dried over potassium carbonate. The dried solution was filtered, and the filtrate was concentrated to give (+)-pseudoephenamine (111.9 g, 100%) as an off-white solid. The basic aqueous solution was then adjusted to pH 1 by addition of 6 *N* aqueous hydrochloric acid solution (90 mL). (*R*)-mandelic acid was then extracted from the acidic aqueous solution with ethyl ether (3x600 mL). The combined organic extracts were concentrated to give pure (*R*)-mandelic acid (74.12 g, 99%) as a white solid. The crude pseudoephenamine was determined to be 92% ee by ^{1}H NMR analysis of its (*S*)-mandelic acid salt. Recrystallization of the solid product from absolute ethanol (213 mL, 80 ºC) gave optically pure (+)-pseudoephenamine (69.22 g, 62%) as large, colorless, orthorhombic crystals. Recrystallization of the concentrated mother liquor twice more gave an additional 21.9 g of

auxiliary, for a total yield of 91.12 g (81%) of optically pure **(+)-25**. The characterization data for **(+)-25** were in agreement with those previously reported.[103]

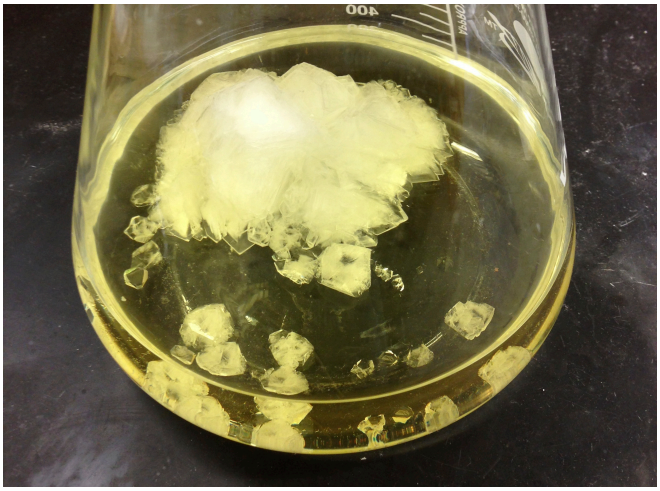
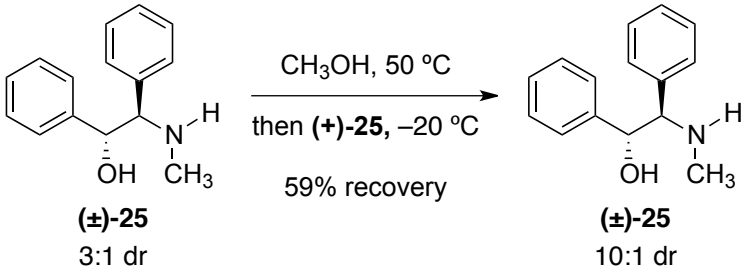


Image 4.4: Pseudoephenamine after recrystallization from ethanol.

[103] Morales, M.R.; Mellem, K.T.; Myers, A.G. *Angew. Chem. Int. Ed.* **2012**, *51,* 4568–4571.

Recrystallization to enrich pseudoephenamine of low dr:



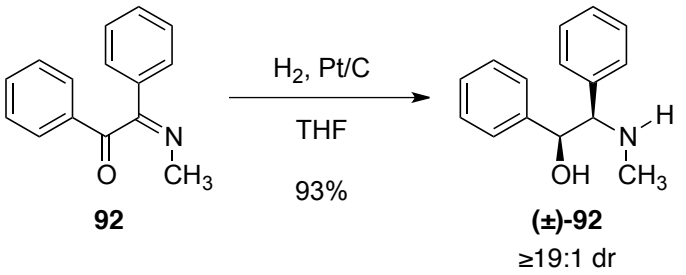
(±)-25
3:1 dr

(±)-25
10:1 dr

(±)-pseudoephenamine ((±)-25)

A 50-mL round-bottom flask was charged with (±)-pseudoephenamine (3:1 dr, 9.23 g, 40.9 mmol), a Teflon-coated magnetic stirring bar, and methanol (18.6 mL). The flask was then immersed in an oil bath preheated to 50 ºC, and the mixture was stirred to effect dissolution of all solid material, producing a yellow-orange solution. This solution was then transferred to a 50-mL Erlenmeyer flask and allowed to cool to room temperature. Once cool, a single crystal of **(+)-25** was added to the solution, and the flask was sealed with aluminum foil and placed into a –20 ºC freezer. After standing in the freezer for 12 h, an off-white to pale yellow solid was present in the flask. This solid was collected by filtration through a Büchner funnel and dried via suction for 1 h before it was further dried under reduced pressure (<1 torr). The (±)-pseudoephenamine so obtained (4.56 g, 59% of theory) was determined to be 10:1 dr by ^{1}H NMR analysis. This material was subjected to mandelic acid resolution as outlined above. The mother liquor from the recrystallization was concentrated and dried under reduced pressure to give (±)-pseudoephenamine (4.33 g) that was determined to be 1.3:1 dr by ^{1}H NMR. The characterization data for the isolated compounds were identical to those reported above for **(±)-25**.

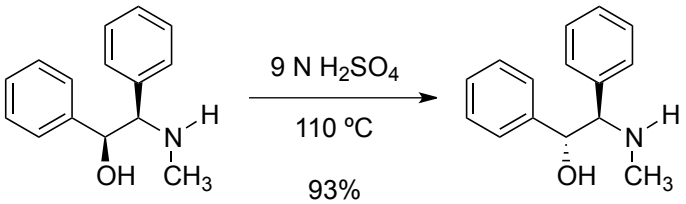
Synthesis of (±)-ephenamine:



(±)-ephenamine ((±)-92)

A 1-L round-bottom flask was charged with methylimino benzil (15.64 g, 70.0 mmol, 1.00 equiv), THF (350 mL), and a Teflon-coated magnetic stirring bar. Platinum on carbon (5 wt%, 4.69 g) was added to the resulting yellow solution, producing a black slurry. The flask was equipped with a hydrogen balloon attached to a stainless steel needle. The atmosphere of the flask was purged by bubbling hydrogen through the reaction mixture for 20 min, after which the needle was removed from the reaction mixture and left above the surface of the mixture. The slurry was left to stir under the hydrogen atmosphere. After 23 h, the hydrogen atmosphere of the flask was purged with argon. The reaction mixture was then filtered through a pad of Celite to give a pale yellow solution. This solution was concentrated to give **(±)-92** (14.8 g, 93%, mp = 127–129 ºC) as a fluffy white solid. TLC (10% methanol–dichloromethane): R_f = 0.3, streak (UV, $KmnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.32 – 7.22 (m, 6H), 7.18–7.11 (m, 4H), 4.84 (d, 1H, *J* = 5.9 Hz), 3.78 (d, 1H, *J* = 5.9 Hz), 2.29 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 140.70, 139.01, 128.27, 128.06, 127.95, 127.54, 127.45, 126.75, 76.48, 70.92, 34.22. FTIR (neat), cm^{-1}: 2252 (w), 1454 (w), 906 (s), 729 (s), 698 (s). HRMS (ESI): Calcd for (C15H17NO + Na)+: 250.1202. Found: 250.1206.

Epimerization of ephenamine to pseudoephenamine:



(±)-92 **(±)-25**

(±)-pseudoephenamine ((±)-25)

A 100-mL round bottom flask was charged with (±)-ephenamine (10.0 g, 44.0 mmol) and 9 N aqueous sulfuric acid solution (44 mL). The flask was equipped with a reflux condenser and immersed in an oil bath preheated to 110 ºC. Upon warming, the solid material slowly dissolved to give a clear, orange solution. The reaction mixture was left to stir, and the progress of the reaction was monitored by the removal of small aliquots of the reaction solution. These aliquots were adjusted to pH 14 by addition of 5 N NaOH, and the amino alcohol mixture was extracted into dichloromethane. After concentration of the organic solution, the isolated solid was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) to determine the dr of the material. After 9 days, equilibrium had been achieved (3:1 dr favoring pseudoephenamine – this was verified independently in a separate experiment using pseudoephenamine as starting material). The flask was removed from the oil bath, and the solution was diluted with 44 ml of water. This dilute aqueous solution was cooled to 0 ºC, and the pH of the solution was adjusted to 14 by slow addition of 5 M aqueous sodium hydroxide solution (100 mL) and 50% aqueous sodium hydroxide solution (5 mL), sequentially. The crude pseudoephenamine was extracted from the aqueous solution with ethyl ether (3x100 mL). The organic solution was dried over potassium carbonate. The dried solution was filtered, and the filtrate was concentrated to give **(±)-25** as a tan solid (9.3 g, 93% yield) that was determined to be 3:1 dr by ^{1}H NMR analysis. The characterization data for **(±)-25** were in agreement with those reported above. The pseudoephenamine obtained in this reaction could be

recrystallized from methanol (18.6 mL) as outlined above to give (±)-pseudoephenamine (4.56 g, 59% recovery) of 10:1 dr as determined by ^{1}H NMR analysis. This diastereomerically enriched pseudoephenamine was subjected to mandelic acid resolution as described above.

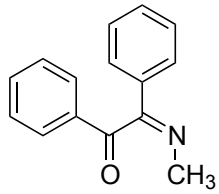
X-ray Data:

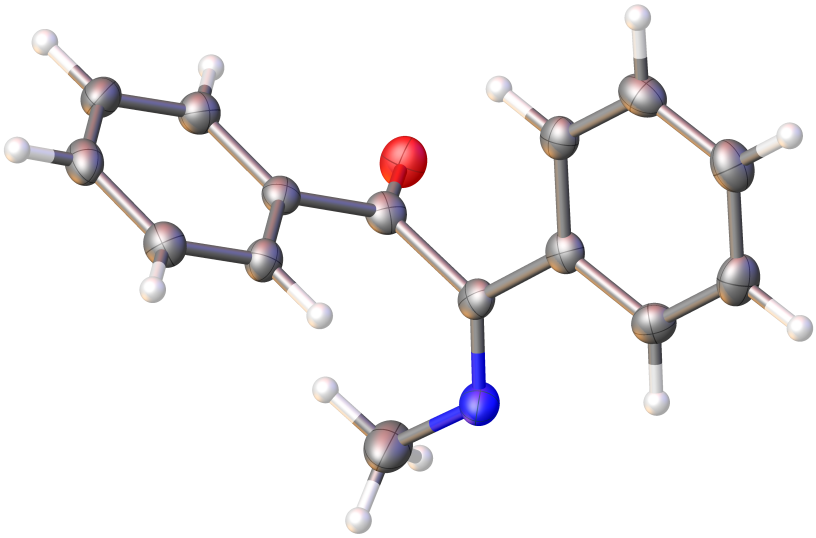
X-ray Crystallographic Laboratory

Harvard University

Structure Report

Shao-Liang Zheng





CCDC Deposition Number: CCDC 960508

X-Ray Crystallography: A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II CCD diffractometer ($Mo_{K\alpha}$ radiation, λ=0.71073 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 0.5° scans in ω at 28° in 2θ. Data integration down to 0.84 Å resolution was carried out using SAINT V8.30 A (Bruker diffractometer, 2013) with reflection spot size optimization. Absorption corrections were made with the program SADABS (Bruker diffractometer, 2013). The structure was solved by the direct methods procedure and refined by least-squares methods again F^2 using SHELXS-2013 and SHELXL-2013 (Sheldrick, 2008) with OLEX 2 interface (Dolomanov, et al., 2009). Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table 1, and geometric parameters are shown in Table 2. The Ortep plots produced with SHELXL-2013 program, and the other drawings were produced with Accelrys DS Visualizer 2.0 (Accelrys, 2007).

Table 4.1: Experimental details

	KTM-MIB
Crystal data	
Chemical formula	$C_{15}H_{13}NO$
M_r	223.26
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	100
a, b, c (Å)	8.0114 (19), 12.186 (3), 12.003 (3)
β (°)	90.951 (4)
V (Å^3)	1171.6 (5)
Z	4
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.08
Crystal size (mm)	0.28 × 0.20 × 0.14
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector diffractometer

Table 4.1 (continued)

Absorption correction	Multi-scan *SADABS*
T_{min}, T_{max}	0.676, 0.745
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	9227, 2085, 1760
R_{int}	0.040
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.597
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.065, 0.181, 1.03
No. of reflections	2085
No. of parameters	156
No. of restraints	0
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.28, -0.23

Computer programs: *APEX2* v2013.4.1 (Bruker-AXS, 2013), *SAINT* 8.30A (Bruker-AXS, 2012), *SHELXS2013* (Sheldrick, 2013), *SHELXL2013* (Sheldrick, 2013), Bruker *SHELXTL* (Sheldrick, 2013).

Table 4.2: Geometric parameters (Å, º)

C1—C2	1.377 (5)	C9—C14	1.391 (5)
C1—C6	1.398 (5)	C9—C10	1.393 (5)
C1—H1	0.9500	C10—C11	1.389 (5)
C2—C3	1.387 (5)	C10—H10	0.9500
C2—H2	0.9500	C11—C12	1.388 (6)
C3—C4	1.392 (5)	C11—H11	0.9500
C3—H3	0.9500	C12—C13	1.385 (6)
C4—C5	1.391 (5)	C12—H12	0.9500
C4—H4	0.9500	C13—C14	1.388 (5)
C5—C6	1.390 (5)	C13—H13	0.9500
C5—H5	0.9500	C14—H14	0.9500
C6—C7	1.481 (5)	C15—N1	1.471 (5)
C7—O1	1.224 (4)	C15—H15A	0.9800
C7—C8	1.527 (5)	C15—H15B	0.9800
C8—N1	1.266 (5)	C15—H15C	0.9800

Table 4.2 (continued)

C8—C9	1.494 (5)		
C2—C1—C6	120.2 (3)	C14—C9—C8	120.6 (3)
C2—C1—H1	119.9	C10—C9—C8	120.0 (3)
C6—C1—H1	119.9	C11—C10—C9	120.4 (3)
C1—C2—C3	120.0 (3)	C11—C10—H10	119.8
C1—C2—H2	120.0	C9—C10—H10	119.8
C3—C2—H2	120.0	C12—C11—C10	119.8 (4)
C2—C3—C4	120.6 (3)	C12—C11—H11	120.1
C2—C3—H3	119.7	C10—C11—H11	120.1
C4—C3—H3	119.7	C13—C12—C11	120.0 (4)
C5—C4—C3	119.1 (3)	C13—C12—H12	120.0
C5—C4—H4	120.4	C11—C12—H12	120.0
C3—C4—H4	120.4	C12—C13—C14	120.3 (4)
C6—C5—C4	120.5 (3)	C12—C13—H13	119.9
C6—C5—H5	119.7	C14—C13—H13	119.9
C4—C5—H5	119.7	C13—C14—C9	120.1 (3)
C5—C6—C1	119.5 (3)	C13—C14—H14	120.0
C5—C6—C7	120.5 (3)	C9—C14—H14	120.0
C1—C6—C7	120.0 (3)	N1—C15—H15A	109.5
O1—C7—C6	123.3 (3)	N1—C15—H15B	109.5
O1—C7—C8	118.2 (3)	H15A—C15—H15B	109.5
C6—C7—C8	118.5 (3)	N1—C15—H15C	109.5
N1—C8—C9	121.0 (3)	H15A—C15—H15C	109.5
N1—C8—C7	122.9 (3)	H15B—C15—H15C	109.5
C9—C8—C7	116.0 (3)	C8—N1—C15	118.9 (3)
C14—C9—C10	119.4 (3)		
C6—C1—C2—C3	1.0 (5)	C6—C7—C8—C9	-86.8 (4)
C1—C2—C3—C4	-1.1 (6)	N1—C8—C9—C14	-178.4 (3)
C2—C3—C4—C5	0.9 (5)	C7—C8—C9—C14	3.1 (5)
C3—C4—C5—C6	-0.7 (5)	N1—C8—C9—C10	1.1 (5)
C4—C5—C6—C1	0.6 (5)	C7—C8—C9—C10	-177.4 (3)
C4—C5—C6—C7	-179.4 (3)	C14—C9—C10—C11	-2.0 (5)
C2—C1—C6—C5	-0.8 (5)	C8—C9—C10—C11	178.4 (3)
C2—C1—C6—C7	179.2 (3)	C9—C10—C11—C12	1.9 (6)

Table 4.2 (continued)

C5—C6—C7—O1	176.8 (3)	C10—C11—C12—C13	-0.2 (6)
C1—C6—C7—O1	-3.2 (5)	C11—C12—C13—C14	-1.3 (6)
C5—C6—C7—C8	-3.1 (5)	C12—C13—C14—C9	1.1 (5)
C1—C6—C7—C8	176.8 (3)	C10—C9—C14—C13	0.5 (5)
O1—C7—C8—N1	-85.2 (4)	C8—C9—C14—C13	-179.9 (3)
C6—C7—C8—N1	94.7 (4)	C9—C8—N1—C15	178.2 (3)
O1—C7—C8—C9	93.2 (4)	C7—C8—N1—C15	-3.4 (5)

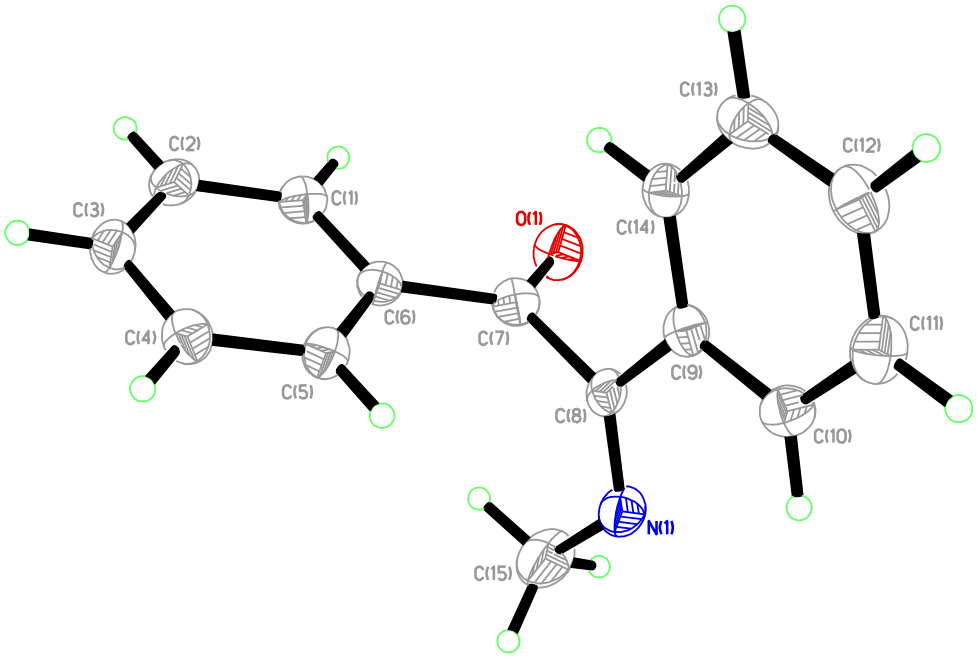


Figure 4.2: Perspective views showing 50% probability displacement.

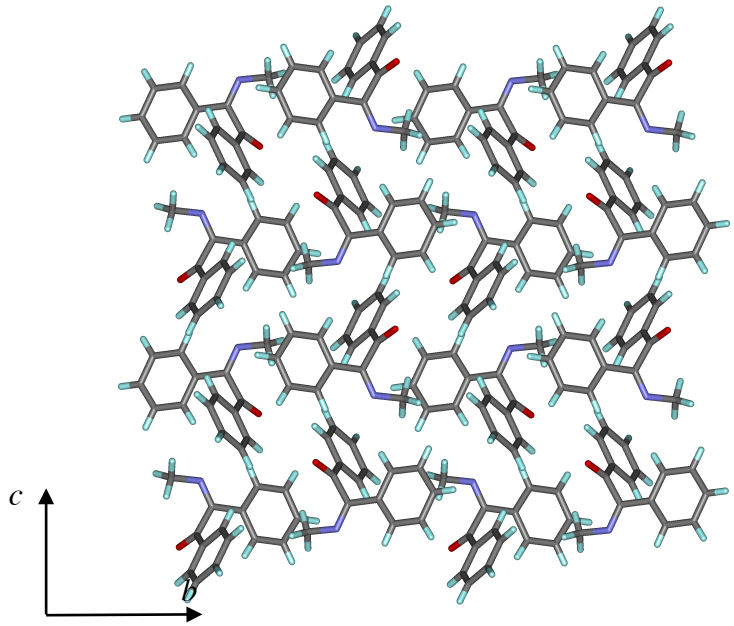
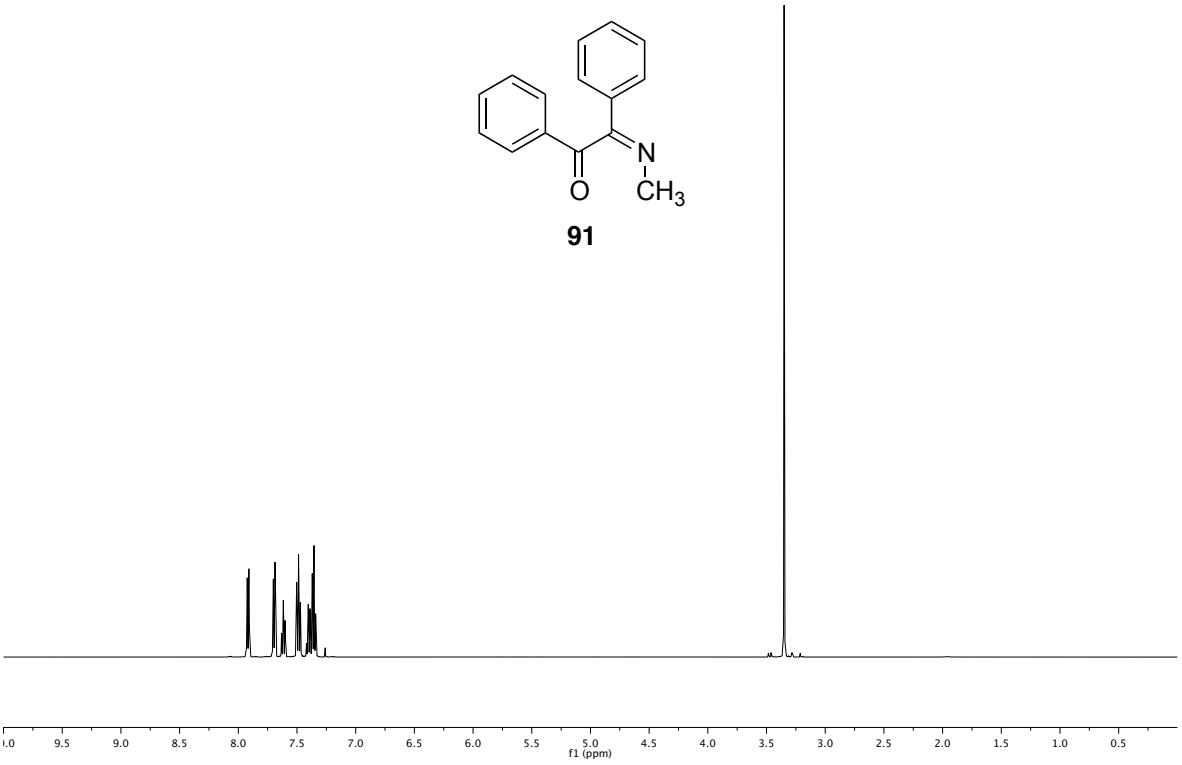
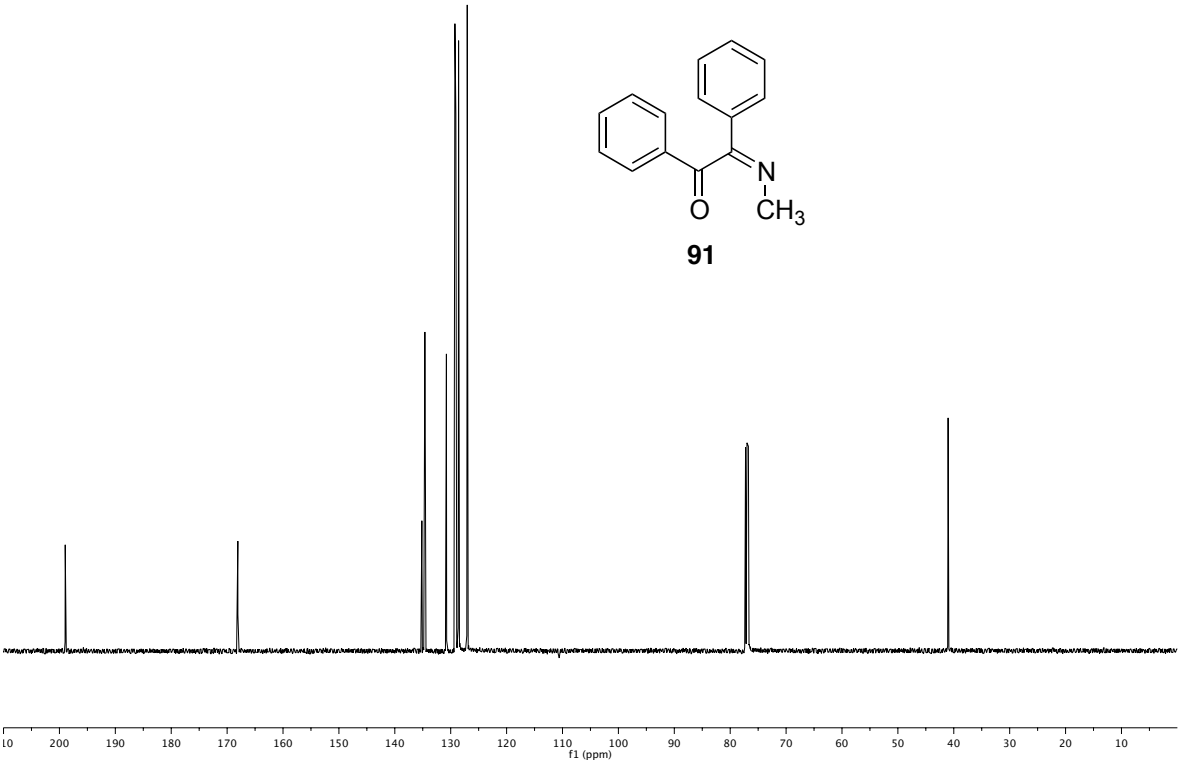
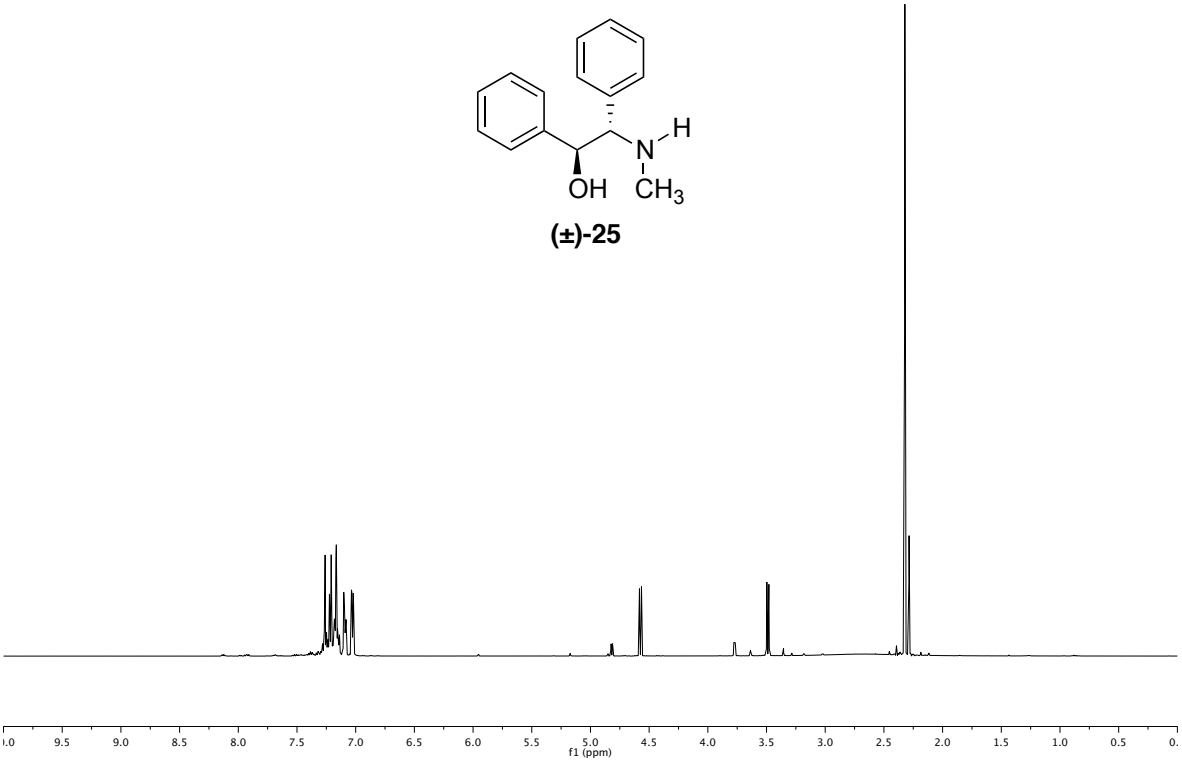


Figure 4.3: Three-dimensional supramolecular architecture viewed along the *a*-axis direction.

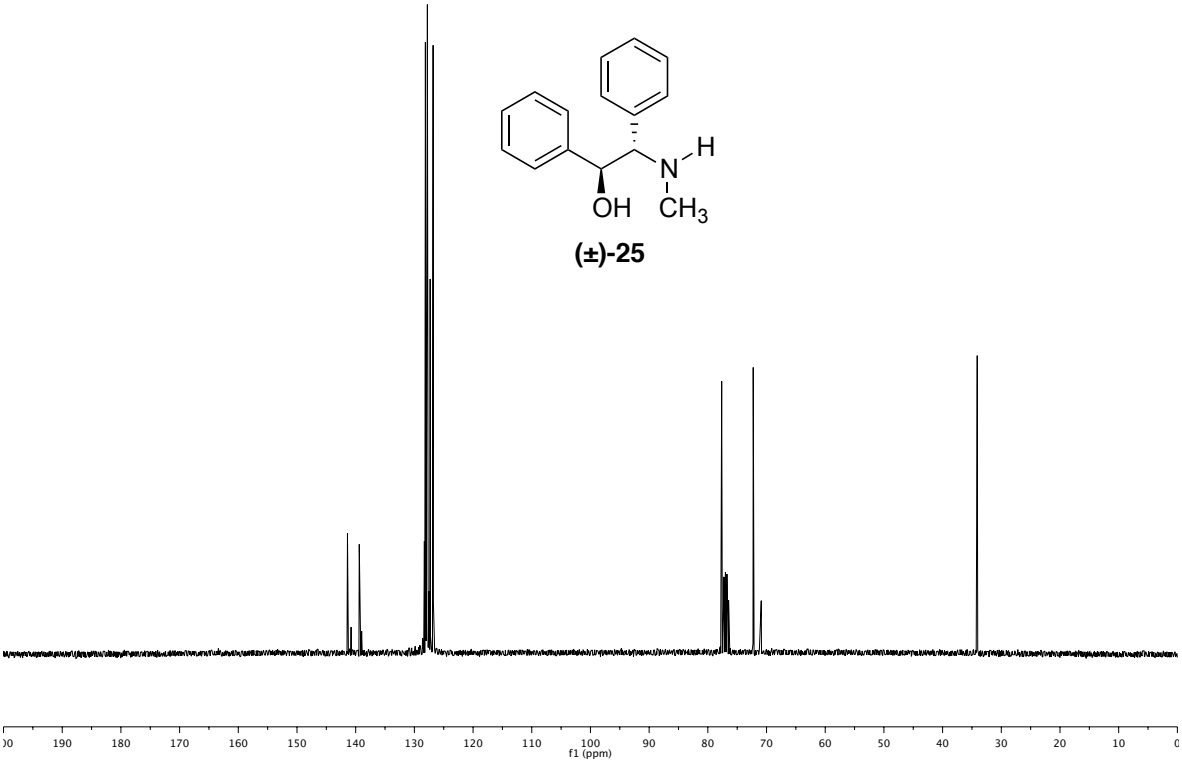
[1]H and [13]C NMR Spectra:



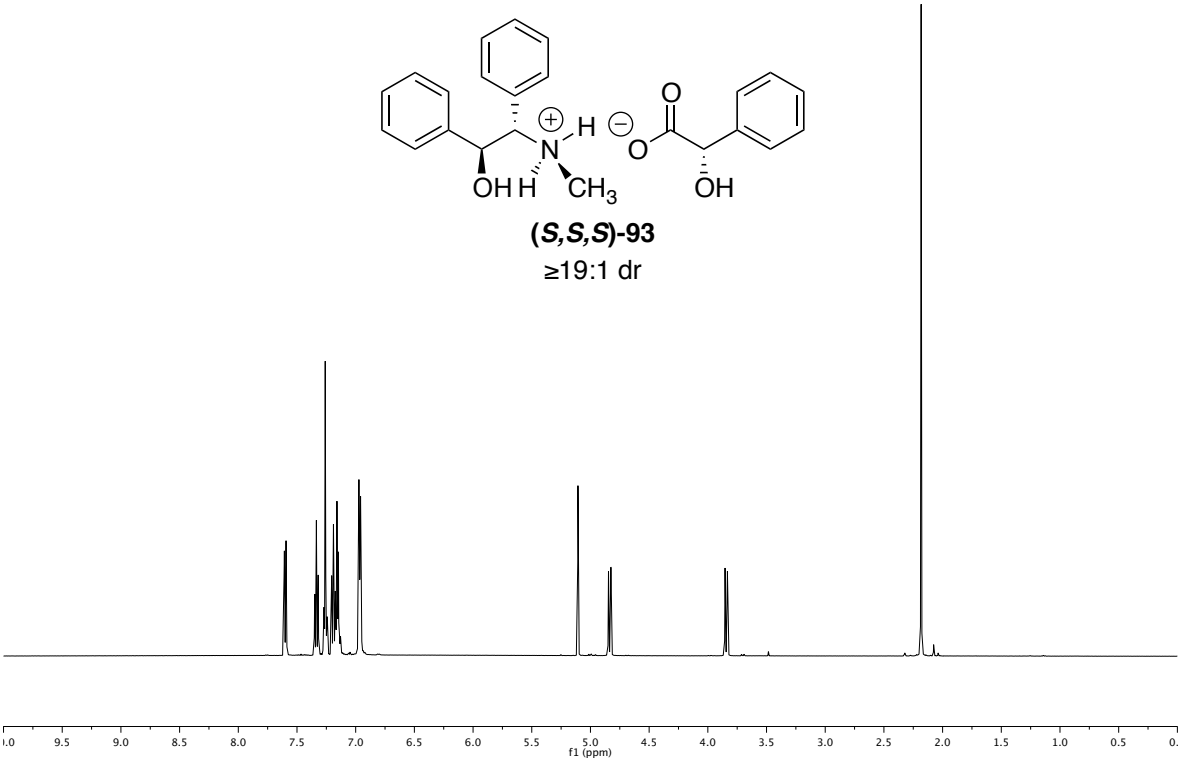




(±)-25

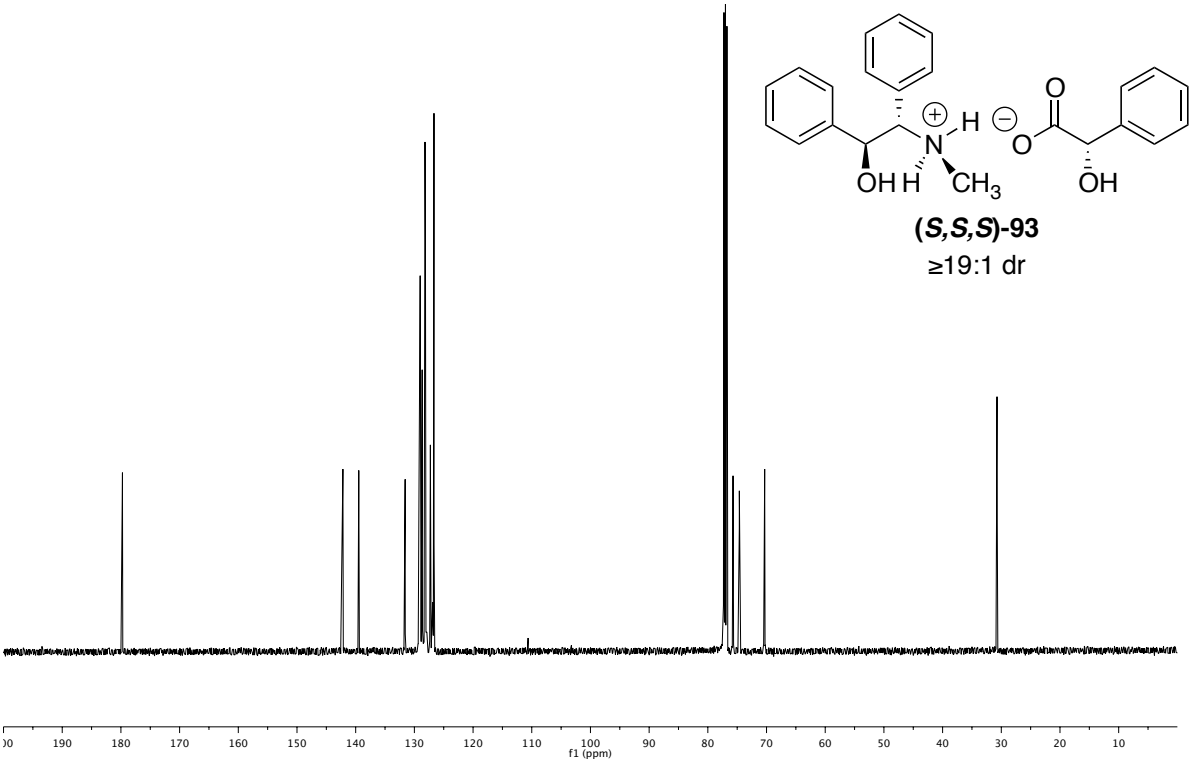


(±)-25



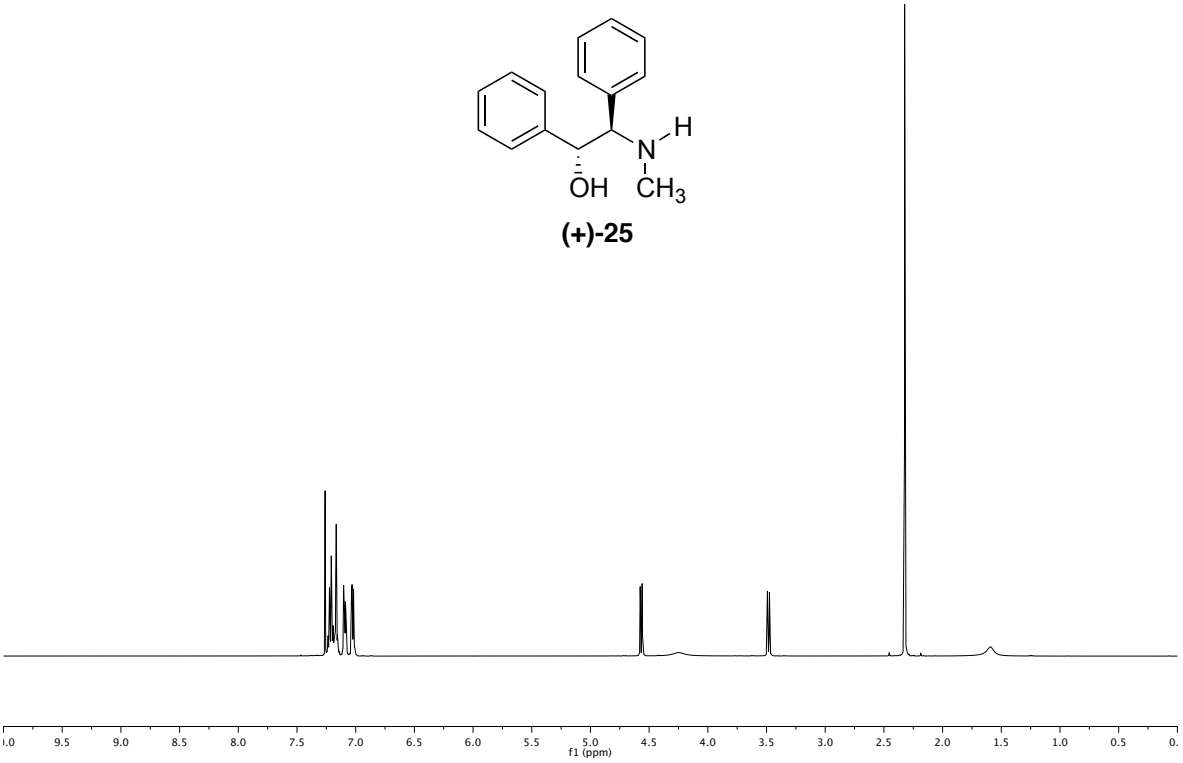
(*S,S,S*)-93

≥19:1 dr

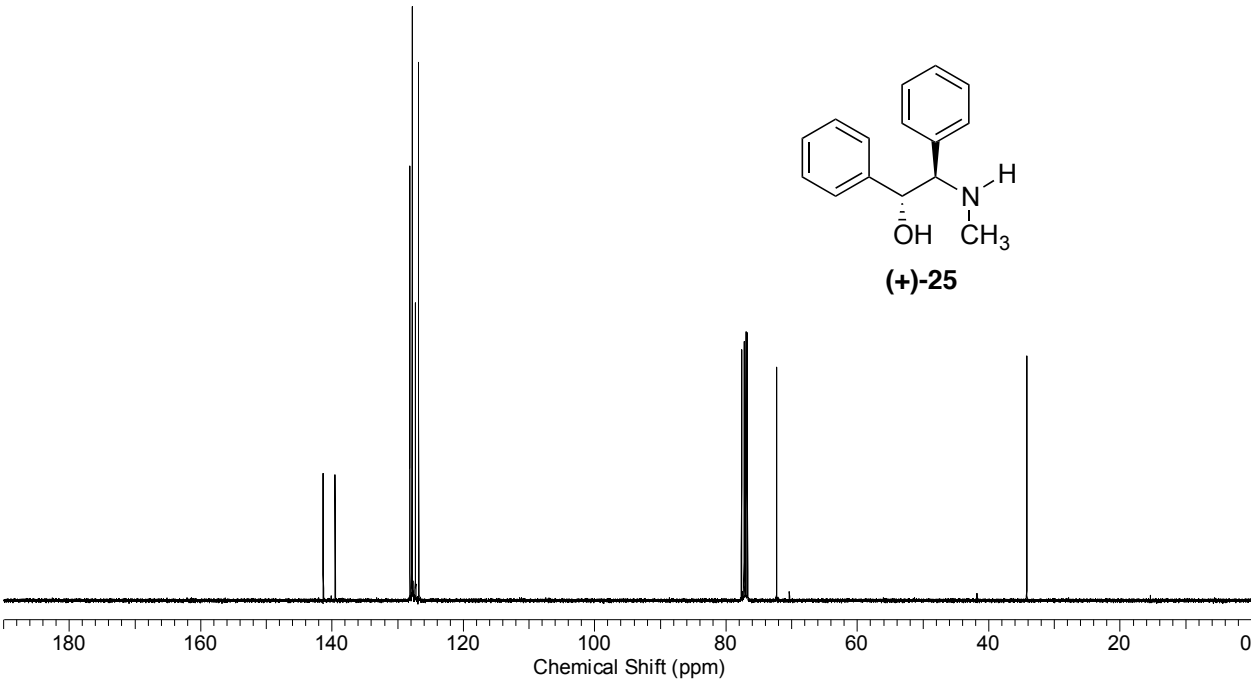


(*S,S,S*)-93

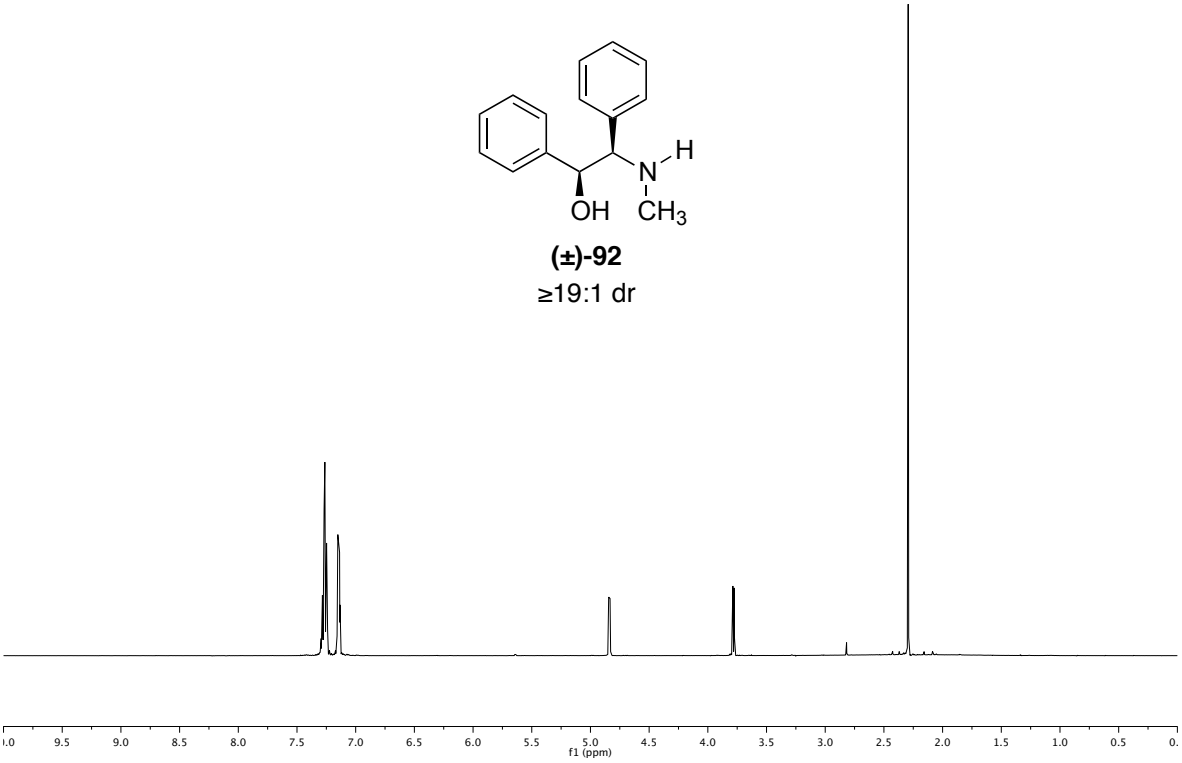
≥19:1 dr


H
N
OH
CH3
f1 (ppm)

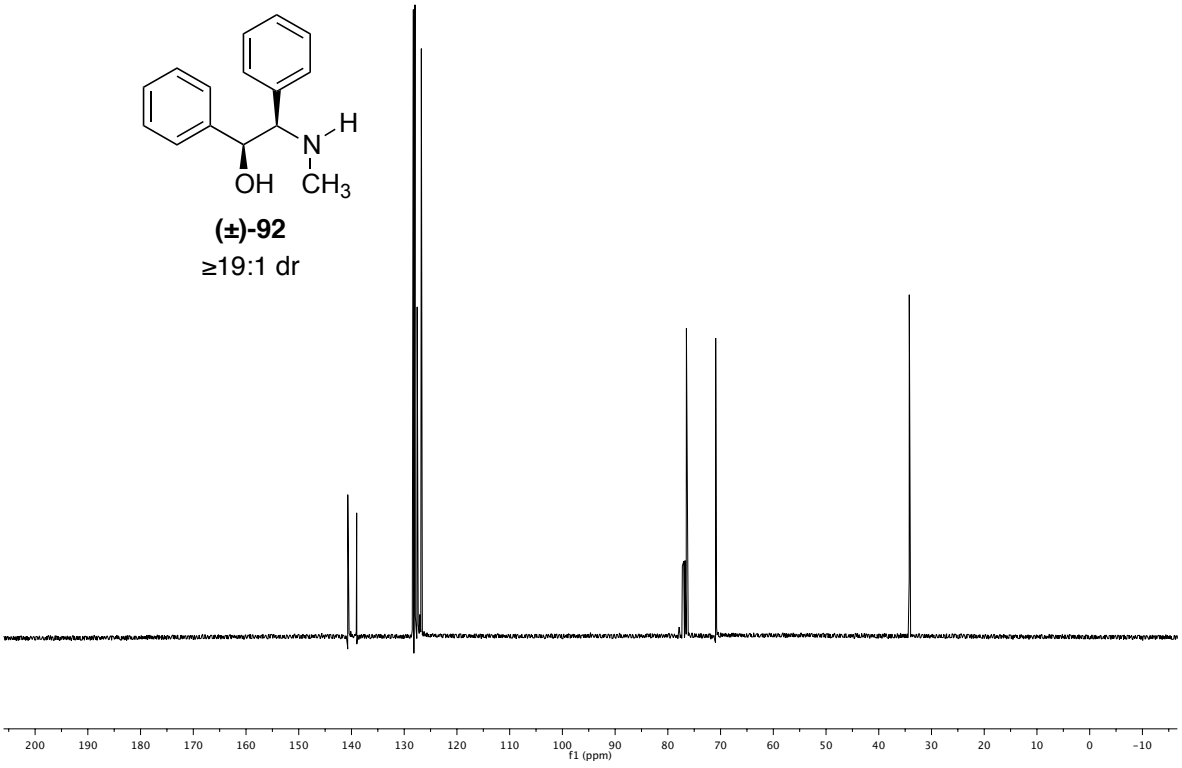
(+)-25


H
N
OH
CH3
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

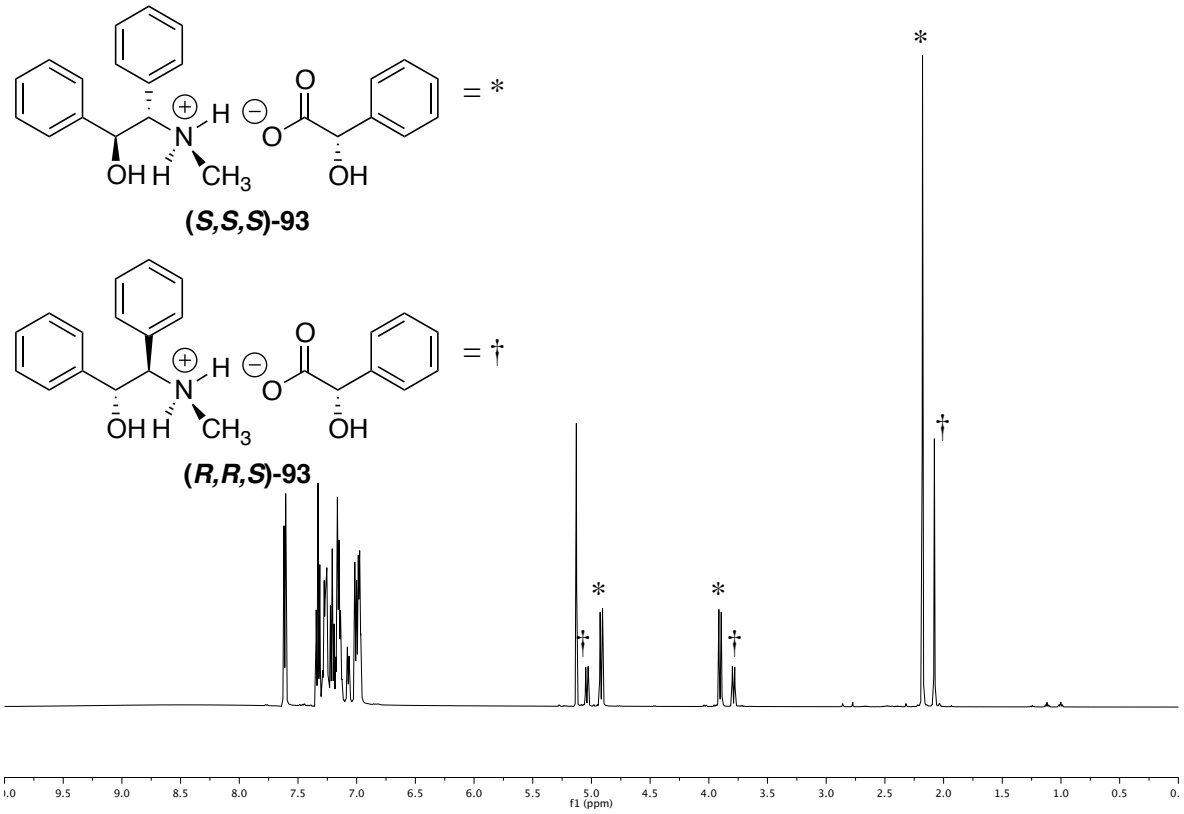
(+)-25

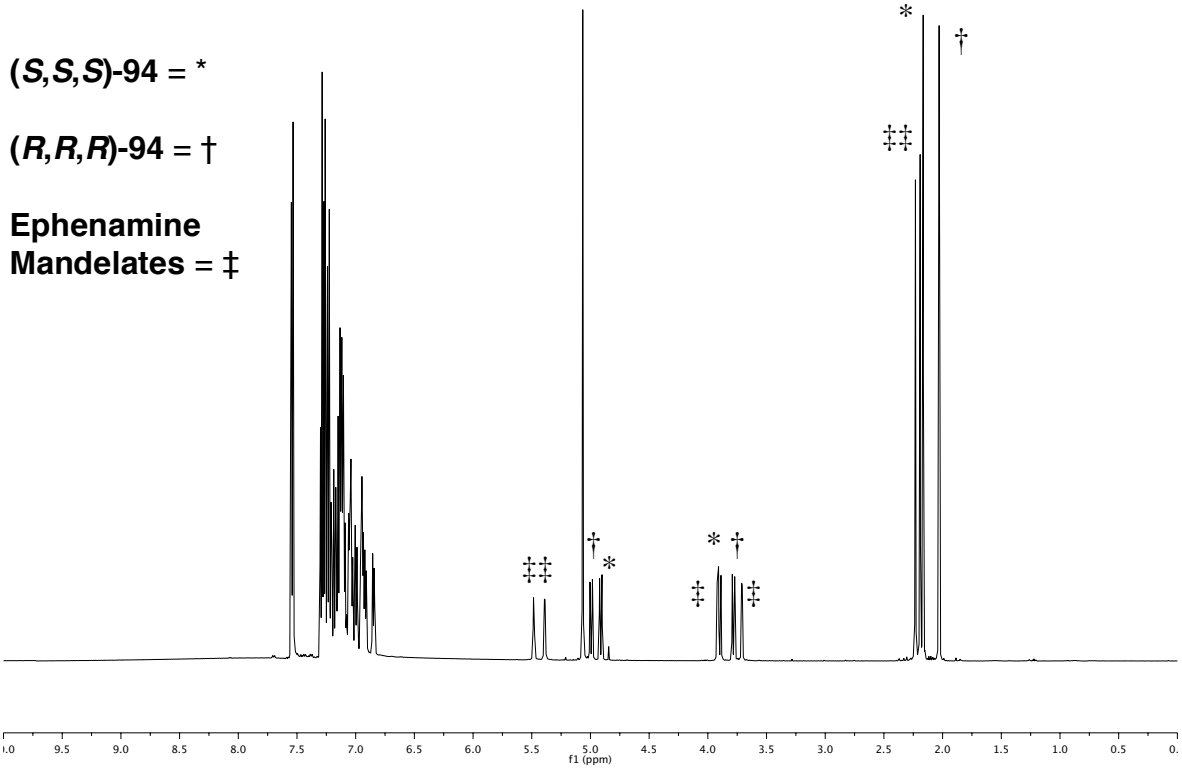


(±)-92
≥19:1 dr



(±)-92
≥19:1 dr


= *
(S,S,S)-93
= †
(R,R,S)-93
f1 (ppm)


(S,S,S)-94 = *
(R,R,R)-94 = †
Ephenamine Mandelates = ‡
f1 (ppm)