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Copper-Catalyzed Enantioselective Hydroamination of Alkenes

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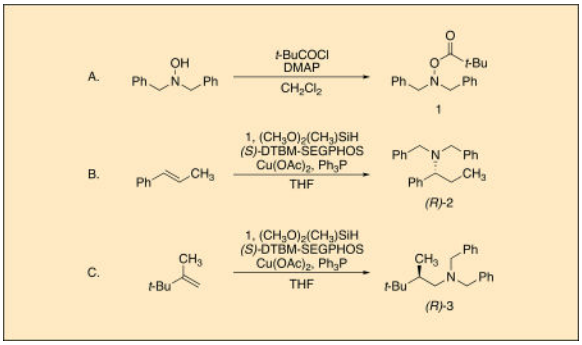
Graphical abstract



Procedure (Note 1)

A. N,N-Dibenzyl-O-pivaloylhydroxylamine (1)

A 500-mL, single-necked, round-bottomed flask (Note 2) is equipped with a 4-cm, Teflon-coated magnetic stir bar and a rubber septum, through which a needle connected to a manifold under a positive pressure of dry nitrogen is inserted. The septum is removed and the flask is charged sequentially with *N*,*N*-dibenzylhydroxylamine (21.3 g, 100 mmol, 1 equiv), 4-dimethyl-aminopyridine (12.8 g, 105 mmol, 1.05 equiv), and dichloromethane (250 mL) (Figure 1) (Note 3). The flask is resealed with the septum and is flushed with nitrogen. The suspension is stirred for 5 min and then cooled to 0 °C in an ice-water bath for 20 min.

Pivaloyl chloride (12.9 mL, 105 mmol, 1.05 equiv) is added dropwise over 5 min using a plastic 30-mL syringe (Figure 2) (Note 4). The reaction mixture is allowed to warm to room temperature (23 °C) and then stirred for an additional 6 h (Note 5). The septum is removed and saturated aqueous ammonium chloride (50 mL) is added. The mixture is transferred to a 1-L separatory funnel using dichloromethane (50 mL) and the organic phase is collected. The aqueous phase is extracted with dichloromethane (2 × 50 mL), and the combined organic layers are washed with deionized water (200 mL) and then concentrated with the aid of a rotary evaporator (30 °C, 80 mmHg) to afford a crude, colorless, heterogeneous

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mixture. This material is dissolved in dichloromethane (50 mL) and eluted through a pad of alumina (Note 6) to yield **1** as a white solid (27.5–28.0 g, 93–94%) (Figure 3) (Note 7).

B. (R)-N,N-Dibenzyl-1-phenylpropan-1-amine (2)

A 250-mL, two-necked, round-bottomed flask (Note 2) is equipped with a 1-cm, Teflon-coated magnetic stir bar and rubber septa, through one of which a needle connected to a manifold under a positive pressure of dry nitrogen is inserted. One septum is removed and the flask is charged sequentially with *N*,*N*-dibenzyl-*O*-pivaloylhydroxylamine (**1**, 7.55 g, 25.4 mmol, 1.2 equiv), copper(II) acetate (38 mg, 0.21 mmol, 0.010 equiv), *(S)*-DTBM-SEGPHOS (274 mg, 0.23 mmol, 0.011 equiv), triphenylphosphine (61 mg, 0.46 mmol, 0.011 equiv), and *trans*-β-methylstyrene (2.50 g, 2.75 mL, 21.1 mmol, 1 equiv) under nitrogen flow (Figure 4)(Note 8).

The septum is reattached to the flask, and THF (21 mL) (Note 9) is added by syringe. The flask is submerged in a room-temperature (23 °C) water bath such that the solvent level is barely below the water surface. Once the mixture has become homogeneous, using a 6-mL plastic syringe, dimethoxy(methyl)silane (5.22 mL, 4.49 g, 42.3 mmol, 2 equiv) (Note 10) is added dropwise over 10 min, during which time the color of the solution gradually changes from blue to green to bright yellow to orange (Figure 5).

At this time, the reaction flask is removed from the water bath and allowed to stir for an additional 12 h (Note 11). The septum is removed and saturated aqueous sodium bicarbonate (50 mL) is slowly added, followed by the addition of ethyl acetate (50 mL). After transferring the mixture to a 250-mL separatory funnel, the organic layer is separated and retained, and the aqueous layer is extracted with additional ethyl acetate (2 × 50 mL). The combined organic layers are concentrated with the aid of a rotary evaporator (35 °C water bath temperature, 50 mmHg) to afford a heterogeneous yellow-green mixture. This material is purified by flash column chromatography (Note 12) to yield **2** as a colorless, viscous oil (5.72 g, 86%) in 98% enantiomeric excess (Figure 6) (Note 13).

C. (R)-N,N-Dibenzyl-2,3,3-trimethylbutan-1-amine (3)

A 250-mL, two-necked, round-bottomed flask (Note 2) is equipped with a 1-cm, Teflon-coated magnetic stir bar and two rubber septa, through one of which a needle connected to a manifold under dry nitrogen is inserted. One septum is removed and the flask is charged sequentially with *N*,*N*-dibenzyl-*O*-pivaloylhydroxylamine (**1**, 9.09 g, 30.6 mmol, 1.2 equiv), copper(II) acetate (46 mg, 0.25 mmol, 0.010 equiv), *(S)*-DTBM-SEGPHOS (330 mg, 0.28 mmol, 0.011 equiv), triphenylphosphine (74 mg, 0.28 mmol, 0.011 equiv), and 2,3,3-trimethyl-1-butene (2.50 g, 3.55 mL, 25.5 mmol, 1 equiv) (Notes 8 and 14) under nitrogen flow. The flask is resealed with the septum, THF (25 mL) (Note 9) is added by syringe, and the flask is partially submerged in an oil bath heated to 40 °C (Note 9). Once the mixture has become homogeneous, using a 6-mL plastic syringe, dimethoxy(methyl)silane (6.27 mL, 5.41 g, 50.9 mmol, 2 equiv) (Note 10) is added dropwise over 10 min, during which the color of the solution gradually changes from blue to green to bright yellow to orange. The reaction mixture is allowed to stir for additional 12 h at 40 °C. The reaction is cooled to room temperature (23 °C), the septum is removed and saturated aqueous sodium carbonate

(50 mL) is slowly added, followed by the addition of ethyl acetate (50 mL). After transferring the mixture to a 250-mL separatory funnel, the organic layer is separated and retained, and the aqueous layer is extracted with additional ethyl acetate (2 × 50 mL). The combined organic layers are concentrated with the aid of a rotary evaporator (35 °C water bath temperature, 50 mmHg) and purified by flash column chromatography (Note 15) to yield **3** as a colorless, viscous oil (6.54 g, 87%) in 90% enantiomeric excess (Figure 7) (Note 16).

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of “Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical). See also “Identifying and Evaluating Hazards in Research Laboratories” (American Chemical Society, 2015) which is available via the associated website “Hazard Assessment in Research Laboratories” at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with *N*,*N*-dibenzylhydroxylamine, 4-dimethylaminopyridine, dichloromethane, pivaloyl chloride, ammonium chloride, copper(II) acetate, *(S)*-DTBM-SEGPHOS, triphenylphosphine, *trans*-β-methylstyrene, dimethoxy(methyl)silane, sodium bicarbonate, ethyl acetate, 2,3,3-trimethyl-1-butene, tetrahydrofuran, sodium carbonate, silica gel, aluminum oxide, and hexanes. The reactions described in steps B and C are highly exothermic and can potentially generate a significant amount of flammable hydrogen gas. It is advisable to conduct these experiments in a large flask, adequately vented to a standard inert gas manifold or bubbler into a fume hood. In addition, the apparatus should be placed behind a weighted blast shield and inside a fume hood away from heat sources or flammable solvents.

2. All glassware and stir bars were dried in a conventional oven (140 °C) for at least 12 h and filled with dry nitrogen while hot. Unless otherwise stated, reactions were performed under a positive pressure of nitrogen by connection to a gas manifold.

3. *N*,*N*-Dibenzylhydroxylamine (>98.0%) was purchased from TCI America and used as received, except that a few colored or darker crystals, which were present in trace amounts, were discarded using standard tweezers. 4-Dimethylaminopyridine (>99%) was purchased from Sigma-Aldrich and used as

received. Dichloromethane was purchased from J.T. Baker in CYCLE-TAINER® solvent delivery kegs and purified by passage under argon pressure through two packed columns of neutral alumina and copper(II) oxide.

4. Pivaloyl chloride (>98%) was purchased from Alfa Aesar and used as received.

5. The reaction was monitored by TLC analysis using glass-backed 60 Å silica gel plates purchased from SiliCycle with dichloromethane as the mobile phase. UV light (254 nm) was used as the visualization method. *N,N*-Dibenzylhydroxylamine: R_f = 0.42; **1**: R_f = 0.71.

6. Aluminum oxide (neutral, powder, reagent-grade) was purchased from J.T. Baker. The crude reaction mixture is suspended in dichloromethane (50 mL) and is loaded onto a column, with interior diameter of roughly 2 inches, packed with alumina (100 g) and wetted with hexanes. Dichloromethane is used as the eluent, and fractions are collected in Erlenmeyer flasks (50 mL each). The desired product typically elutes in fractions 2 through 25. The fractions that contain **1** are combined and the solvent is removed with the aid of a rotary evaporator (30 °C, 80 mmHg) to afford a cloudy white, viscous oil, which slowly solidifies on standing under vacuum (10 mmHg).

7. The desired product **1** has the following properties. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.92 (s, 9H), 4.06 (s, 4H), 7.23 – 7.34 (m, 6H), 7.40 (d, J = 7.1 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 27.1, 38.4, 62.4, 127.7, 128.3, 129.6, 136.2, 176.3. IR (neat film, NaCl) ν: 3064, 3031, 2973, 2932, 2906, 2872, 1751, 1496, 1479, 1456, 1273, 1116, 1029, 738, 698 cm^{-1}. HRMS (ESI-TOF): calculated $[M+H]^+$ *m/z* 298.1802, found 298.1794. mp (capillary, uncorrected): 56–57 °C. Quantitative NMR using 1,1,2,2-tetrachloroethane (>98%, purchased from Alfa Aesar) in $CDCl_3$ indicates 99% purity. The compound is stable in a dry, dark environment.

8. Copper(II) acetate (anhydrous, 97%) was purchased from Strem and used as received. *(S)*-DTBM-SEGPHOS (>94%) was obtained from Takasago and used as received. Triphenylphosphine (99%) was purchased from Sigma-Aldrich and used as received. *trans*-β-Methylstyrene (97%, stabilized) was purchased from Combi-Blocks or Acros and used as received.

9. Tetrahydrofuran (THF) was purchased from J.T. Baker in CYCLE-TAINER® solvent delivery kegs and purified by passage under argon pressure through two packed columns of neutral alumina and copper(II) oxide.

10. Dimethoxy(methyl)silane (>97%) was purchased from TCI America, stored in a freezer at −20 °C, and used without further purification.

11. The reaction was monitored by TLC analysis using glass-backed 60 Å silica gel plates purchased from SiliCycle with 2% ethyl acetate in hexanes as the mobile phase. UV light (254 nm) was used as the visualization method. Styrene reactant: R_f = 0.64; **2**: R_f = 0.36.

12. The crude reaction mixture is dissolved in a minimal quantity of benzene or toluene and is loaded onto a column, with interior diameter of roughly 2 inches, packed with silica (200 g, SiliCycle, F60/230–400 mesh) and equilibrated with hexanes. The column is eluted under air pressure with hexanes (500 mL), then 1% ethyl acetate in hexanes (1 L), then 2% ethyl acetate in hexanes (1 L). During elution, fractions are collected in test tubes (roughly 28 mL each), and the desired product **2** typically elutes around fractions 18 through 66. The fractions that contain **2** are combined and the solvent is removed with the aid of a rotary evaporator (30 °C, 80 mmHg) to afford pure **2**.

13. A second run of this experiment on 11.0 mmol scale yielded 3.04 g, (88%) of the identical product **2**, which has the following properties. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.01 (t, *J* = 7.3 Hz, 3H), 1.89 (ddq, *J* = 14.2, 7.2, 7.1 Hz, 1H), 2.17 (ddq, *J* = 14.1, 7.2, 7.1 Hz, 1H), 3.24 (d, *J* = 13.9 Hz, 2H), 3.68 (t, *J* = 7.5 Hz, 1H), 3.91 (d, *J* = 13.8 Hz, 2H), 7.50–7.28 (m, 15H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 11.9, 24.4, 53.8, 63.8, 126.8, 127.0, 128.0, 128.3, 128.9, 129.1, 139.1, 140.6. IR (neat film, NaCl) ν: 3083, 3061, 3027, 2962, 2932, 2873, 2802, 1948, 1872, 1809, 1602, 1493, 1453, 761, 742 cm^{-1}. HRMS (ESI-TOF): calculated $[M+H]^+$ *m/z* 316.2060, found 316.2049. Enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H column), eluting with 4% isopropanol in hexanes at 0.6 mL/min: 10.9 min (minor), 13.4 min (major), 98% ee for the first run and 99% ee for the second run. Specific rotation: $[\alpha]_D$ = +108 (c = 1.0, chloroform). Quantitative NMR using ferrocene (98%, purchased from Sigma-Aldrich, recrystallized from pentane) in $CDCl_3$ indicates 99% purity. The compound is stable in a dry environment at room temperature.

14. 2,3,3-Trimethyl-1-butene (98%) was purchased from Sigma-Aldrich and used as received.

15. Silica (30 g) is added to the crude reaction mixture and the solvent removed in *vacuo*. This mixture is loaded onto a column, with interior diameter of roughly 2 inches, packed with silica (200 g, SiliCycle, F60/230–400 mesh) and equilibrated with hexanes. The column is eluted under air pressure with 1% ethyl acetate in hexanes (2500 mL). During elution, fractions are collected in test tubes (roughly 28 mL each), and the desired product **3** typically elutes around fractions 13 through 72 (**3**: R_f = 0.34). The fractions that contain **3** are combined and the solvent is removed with the aid or a rotary evaporator (30 °C, 80 mmHg) to afford pure **3**.

16. A second run of this experiment on the same scale (25.5 mmol) yielded 6.01 g, 80% of the identical product **3**, which has the following properties. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.81 (s, 9H), 0.90 (d, *J* = 6.7 Hz, 3H), 1.49 (dq, *J* = 7.1, 3.4 Hz, 1H), 2.13 (dd, *J* = 12.3, 10.5 Hz, 1H), 2.39 (dd, *J* = 12.2, 2.8 Hz, 1H), 3.21 (d, *J* = 13.7 Hz, 2H), 3.83 (d, *J* = 13.7 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 4H), 7.37 (d, *J* = 7.5 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 13.9, 27.6, 32.4, 41.0, 56.6, 59.1, 126.8, 128.2, 129.0, 140.2. IR (neat) ν 3063, 3027, 2964, 2870, 2791, 1602, 1494, 1453, 1365, 1244, 1121, 1069, 1028, 974, 745,

698 cm^{-1}. HRMS (ESI-TOF): calculated $[M+H]^+$ *m/z* 296.2373, found 296.2375. Enantiomeric excess was determined by SFC (Daicel Chiralpak AD-H column, heated to 40 °C), eluting with a linear gradient over 6 min from 5% to 10% isopropanol in supercritical CO_2 at 2.5 mL/min.: 2.57 min (major), 2.98 min (minor), 90% ee for both runs. Specific rotation: $[\alpha]_D = -114$ (c = 1.0, chloroform). Quantitative NMR using ferrocene (98%, purchased from Sigma-Aldrich, recrystallized from pentane) in $CDCl_3$ indicates 97% purity. The compound is stable in a dry environment at room temperature.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red “Caution Notes” within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

Many methods have been developed for the synthesis of chiral aliphatic amines, primarily due to the prevalence of these fragments in organic building blocks, natural products, and synthetic compounds of biological interest. The most popular strategies include reductive amination, stereospecific substitution, asymmetric hydrogenation, the use of chiral auxiliaries, and biocatalysis.[2] Hydroamination, formally the insertion of an olefin into an N-H bond, represents an alternative approach that has been the subject of considerable academic interest.[3] The attractiveness of this approach originates from the availability and versatility of alkenes and alkynes, and the opportunity for catalyst control over chemo-, regio-, and stereoselectivity in the transformation.

Several years ago, our group[4] and the Miura group[5] contemporaneously developed an *umpolung* strategy for hydroamination of olefins, employing hydrosilanes as hydride sources and *O*-acylhydroxylamines as electrophilic amine equivalents. This approach is based on the catalytic generation of a phosphine-ligated copper–hydride intermediate, which can insert a C–C π-bond to form an alkylcopper species (Scheme 1). After trapping with the amine electrophile, σ-bond metathesis with the hydrosilane closes the catalytic cycle by regenerating the initial hydride complex.

Despite diminished atom economy relative to traditional hydroamination with nucleophilic amine reagents, this new method features several practical advantages. Most importantly, the mildness of the reaction conditions preserves compatibility with useful functional groups such as alcohols, esters, amides, sulfonamides, aryl or alkyl halides, and heterocycles. Furthermore, using the same earth-abundant metal catalyst, many classes of alkenes are transformed efficiently and with excellent stereoselectivity.

Generally, the hydroamination of olefins bearing an activating substituent such as aryl, silyl, or boryl results in the regioisomer with the amine introduced adjacent to this substituent (Table 1). Using non-racemic DTBM-SEGPHOS as the supporting ligand, the Markovnikov-selective hydroamination of styrenes can be effected with high enantioselectivity, thus constructing a common α-chiral amine substructure.[4] Likewise, α-aminosilanes[6] and α-aminoboranes,[7] which are also useful fragments in organic synthesis, can be assembled using this strategy from simple olefins. Furthermore, all of the above hydroamination reactions are known to proceed with exclusive *syn*-diastereoselectivity relative to the olefin.

In comparison, the hydroamination of unactivated olefins such as terminal aliphatic alkenes[4] strongly favors the formation of the anti-Markovnikov isomer (Table 2). In the case of 1,1-disubstituted or trisubstituted substrates, highly enantioselective construction of the β-stereocenter can be achieved with a chiral ligand.[8] Recent advances have made the use of internal olefins possible, despite their relative inertness and poor binding ability toward metal centers.[9] For instance, from 2-butene, amine products bearing otherwise synthetically challenging methyl-ethyl stereocenters can be produced efficiently. Useful regioisomeric control can also be imparted, either using steric effects of the substrate, or using a directing group that electronically biases the π-bond.[10]

To date, several classes of bond constructions remain challenging for this type of catalytic process. Highly hindered olefins and *cis*-disubstituted olefins are not efficiently converted. Moreover, very electron-deficient alkenes generally produce hydroamination products with low levels of enantioselectivity. While the design of more robust electrophilic amine reagents has allowed for the synthesis of secondary amines,[11] corresponding reagents for the synthesis of primary or aryl amines have not yet been reported. Additional limitations of copper–hydride-catalyzed hydroamination, along with many more successful examples, are described in a recent mini-review.[12]

Beyond addressing deficiencies in terms of scope, current research has also been aimed at devising synthetically valuable combinations of this hydroamination strategy with other

copper-catalyzed processes,[13] or at extending this reactivity to other useful organic electrophiles, such as ketones and imines.[14]

References

1. Richard Y. Liu and Dr. Stephen L. Buchwald, Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Ave., Cambridge, MA 02139. Email: Richard Liu: ryl@mit.edu, Stephen Buchwald: sbuchwal@mit.edu. The submitters acknowledge the National Institutes of Health for financial support under award no. GM58160. The submitters further acknowledge Dr. Mycah Uehling and Dr. Christine Nguyen for assistance in the preparation of this manuscript.
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Appendix

Chemical Abstracts Nomenclature (Registry Number)

Pivaloyl chloride: Propanoyl chloride, 2,2-dimethyl-; (3282-30-2)

4-Dimethylaminopyridine: 4-Pyridinamine, *N,N*-dimethyl-; (1122-58-3)

Copper(II) acetate: Acetic acid, copper(2+) salt (2:1) (142-71-2)

(S)-DTBM-SEGPHOS: Phosphine, 1,1'-(4S)-[4,4'-bi-1,3-benzodioxole]-5,5'-diylbis[1,1-bis[3,5-bis(1,1-dimethylethyl)-4-methoxyphenyl]-; (210169-40-7)

Dimethoxy(methyl)silane: Silane, dimethoxymethyl- (16881-77-9)

N,N-Dibenzyl-*O*-pivaloylhydroxylamine (**1**)

(R)-*N,N*-Dibenzyl-1-phenylpropan-1-amine (**2**)

(R)-*N,N*-Dibenzyl-2,3,3-trimethylbutan-1-amine (**3**)

Biographies

Richard Y. Liu grew up in Toronto, Canada, and obtained his undergraduate degree in chemistry and physics from Harvard, with mentorship from Professors Eric Jacobsen and Theodore Betley. In 2016, he joined the Buchwald research group at MIT, where he is currently a Ph. D. candidate.

Stephen L. Buchwald is the Camille Dreyfus Professor and Associate Head of the Department of Chemistry at the Massachusetts Institute of Technology (MIT). He obtained his Sc.B. from Brown University in 1977 and his Ph. D. in 1982, studying with Jeremy Knowles at Harvard. After a postdoctoral period at Caltech with Robert Grubbs, he was joined the faculty at MIT in 1984. Professor Buchwald is best known for the development of ligands and transition metal catalysts for cross-coupling reactions. He is the recipient of numerous awards and honors, including the Arthur C. Cope Award, the Linus Pauling Medal and the BBVA Frontiers of Knowledge Award in Basic Sciences.

Aurapat (Fa) Ngamnithiporn was born in Thailand before she moved to the US and received her Bachelor’s degree in chemistry from Carleton College in 2015. She is currently a doctoral student under the supervision of Professor Brian M. Stoltz at the California Institute of Technology, working on transition-metal catalyzed asymmetric catalysis.

Dr. Gerit Pototschnig obtained her undergraduate and Masters degrees in Chemical Engineering from the Technical University of Graz, Austria. Then she moved to Vienna University of Technology, Austria where she conducted her PhD in under the supervision of Prof. Marko D. Mihovilovic. After a research stay at the Max-Planck-Institut für Kohlenforschung (Mülheim, Germany) with Prof. Alois Fuerstner she is currently working as postdoctoral researcher with Professor Brian M. Stoltz at the California Institute of Technology.

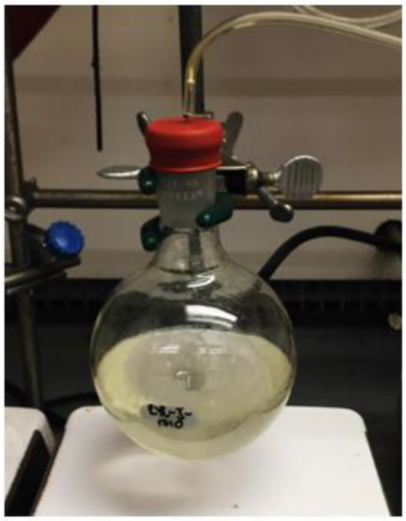


Figure 1.
Hydroxylamine, DMAP, and their mixture in dichloromethane

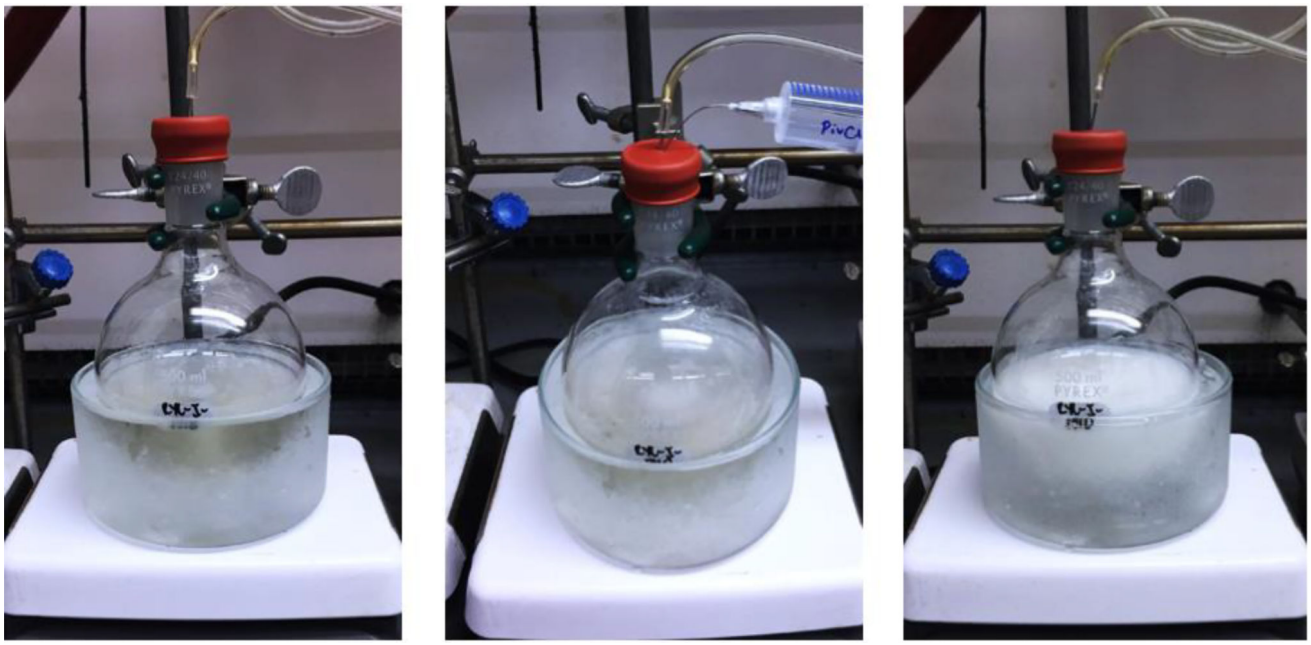


Figure 2.
Reaction mixture before, during, and after addition of pivaloyl chloride

Figure 3.
Crude mixture after extraction and final, purified product

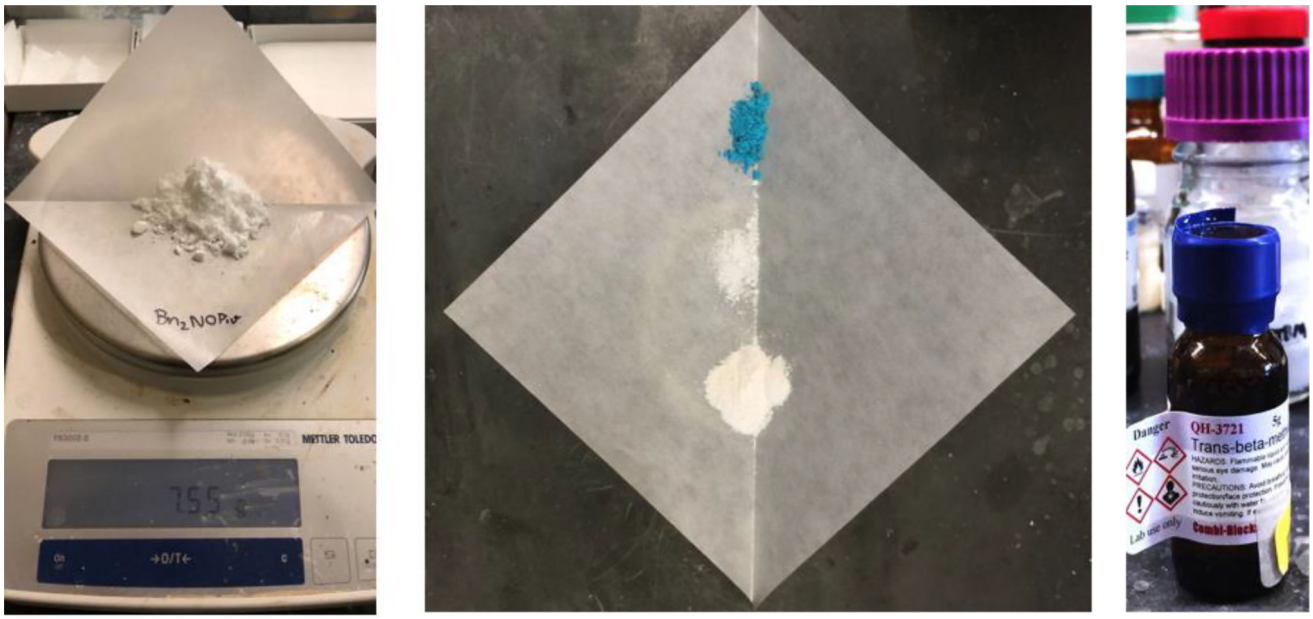


Figure 4.
Compound 1, catalyst components, and substrate

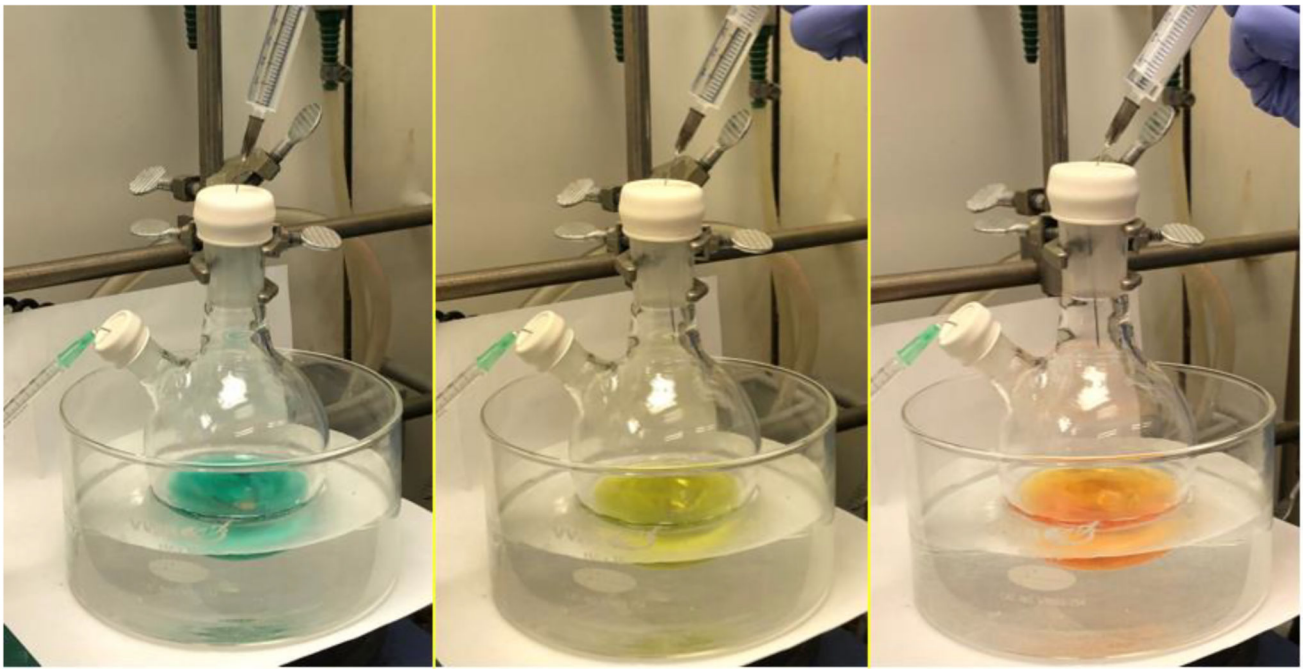
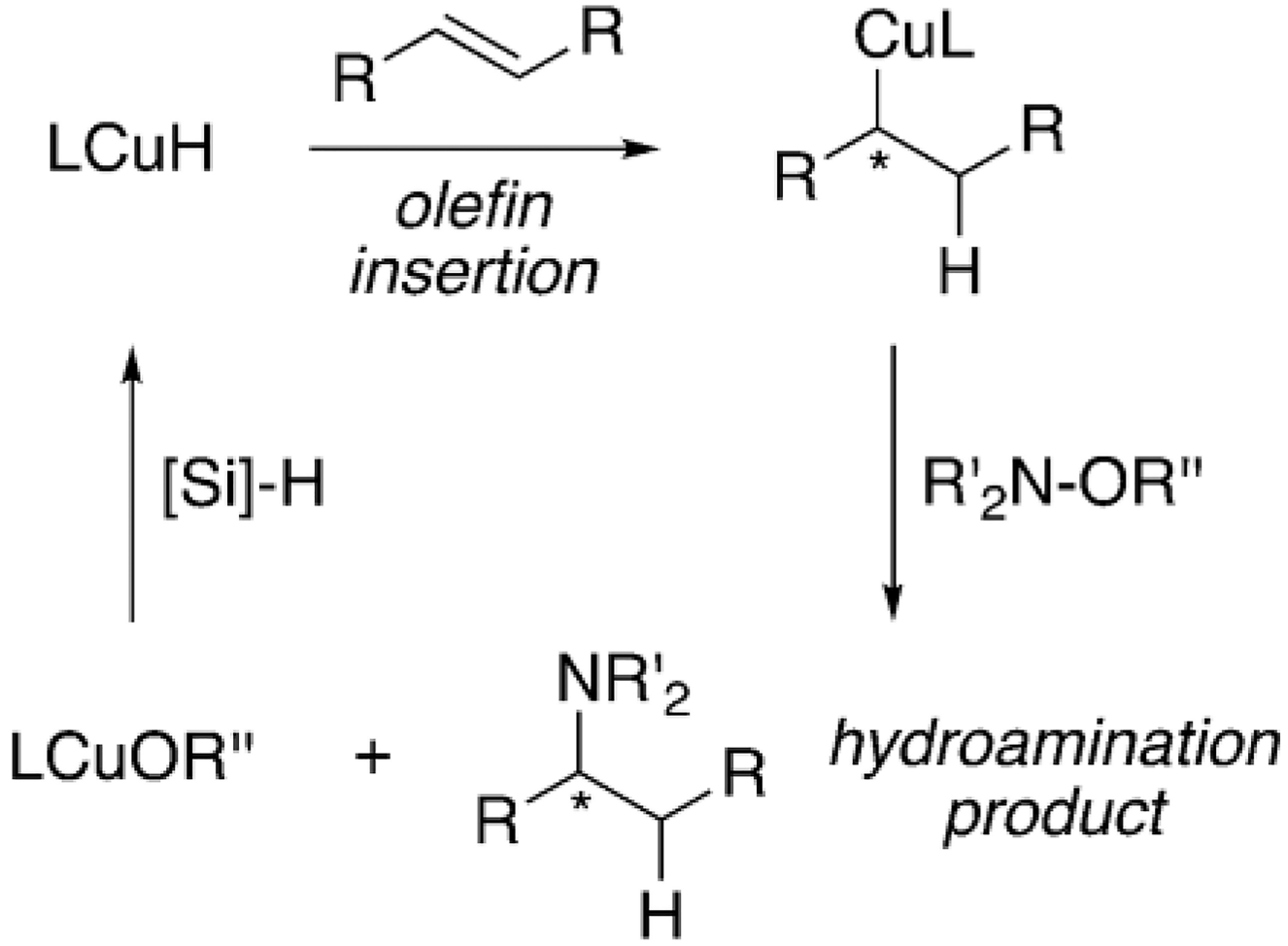


Figure 5.
Progression of color changes upon addition of hydrosilane

Figure 6.
Reaction mixture after quenching, concentrated crude mixture, and purified product

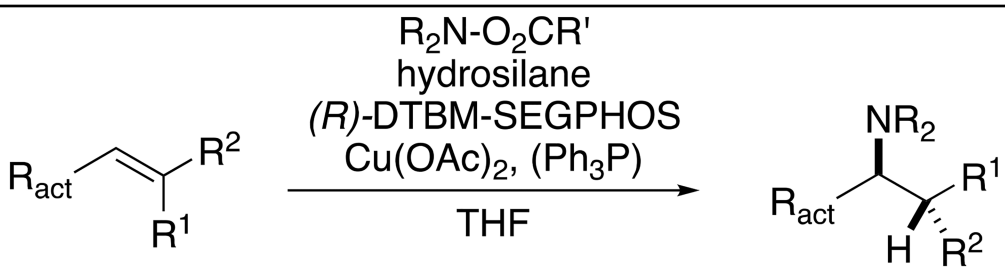
Figure 7.
Reaction after 12 h, concentrated crude mixture, and purified product

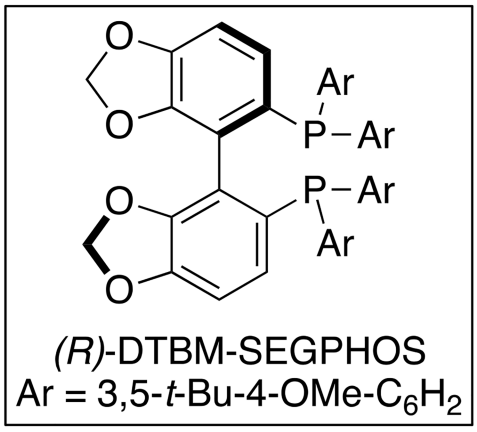


Scheme 1.
Catalytic Mechanism for CuH-Catalyzed Hydroamination

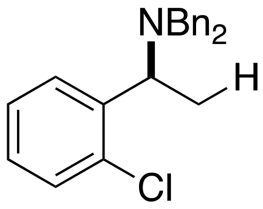
Table 1

Enantioselective, Markovnikov Hydroamination of Alkenes

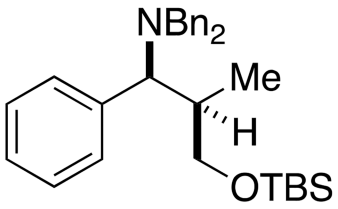




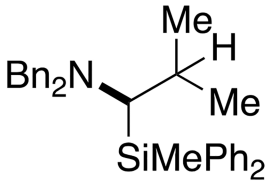
(*R*)-DTBM-SEGPHOS
Ar = 3,5-*t*-Bu-4-OMe-C_6H_2



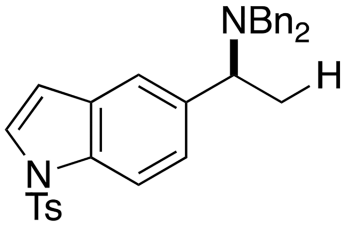
86% yield
92% ee



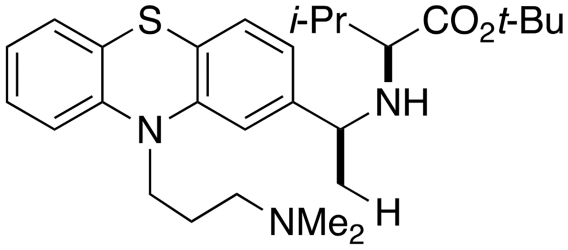
83% yield
>99% ee



74% yield
99% ee



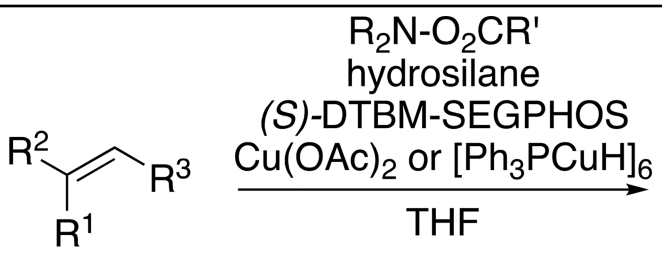
80% yield
98% ee

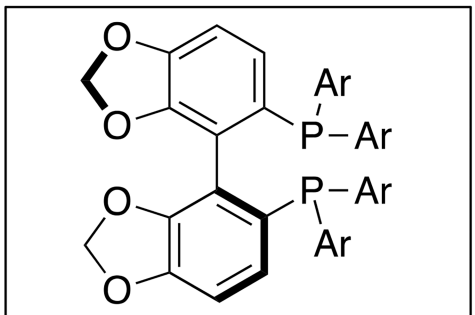


82% yield
>20:1 dr

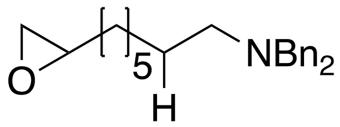
Table 2

Enantioselective, Anti-Markovnikov Hydroamination of Alkenes

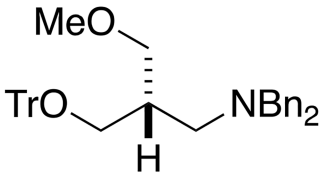




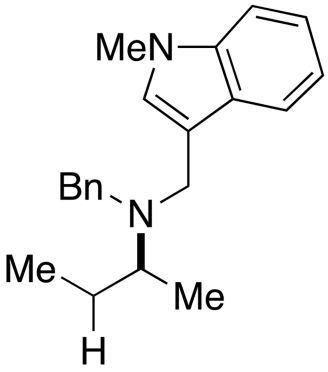
(*S*)-DTBM-SEGPHOS
Ar = 3,5-*t*-Bu-4-OMe-C_6H_2



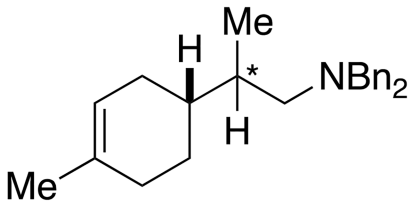
90% yield



91% yield
80% ee

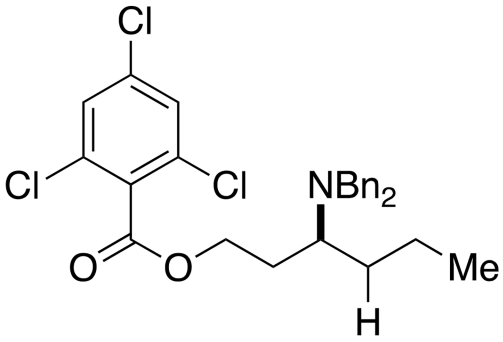


76% yield
97% ee



(*R*)-ligand
85% yield
20:1 dr

(*S*)-ligand
86% yield
1:14 dr



9:1 rr
84% yield
97% ee