Copper-Catalyzed Enantioselective Stereodivergent Synthesis of Amino Alcohols

By

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B.S. Chemistry
University of California, Irvine, 2013

Submitted to the Department of Chemistry in Partial Fulfillment of the Requirement for the Degree of

Master of Science in Chemistry

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ABSTRACT

Different stereoisomers of bioactive molecules can have distinct activities in biological systems. For this reason, it is routine procedure in the drug discovery and development process to prepare the full matrix of possible stereoisomers of drug candidates for biological evaluation and to determine the stereochemical purity of these molecules. Despite many recent advances in asymmetric synthesis, the development of general and practical strategies that are fully divergent and give rise to all stereoisomers of products bearing multiple contiguous stereocenters remains a significant challenge.

Herein we report a stereodivergent copper-based approach for the expeditious construction of amino alcohols with high levels of chemo-, regio-, diastero- and enantioselectivity. Specifically, these amino alcohol products were synthesized using the sequential copper hydride-catalyzed hydrosilylation and hydroamination of readily available enals and enones. This strategy provides a route to all possible stereoisomers of these amino alcohol products, which contain up to three contiguous stereocenters. Catalyst control and stereospecificity were simultaneously leveraged to attain exceptional control of the product stereochemistry. Beyond the utility of this protocol, the strategy demonstrated here should inspire the development of methods providing complete sets of stereoisomers for other valuable synthetic targets.

Thesis Supervisor: Stephen L. Buchwald

Title: Camille Dreyfus Professor of Chemistry
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Preface

The thesis has been adapted from the below article co-written by the author:


Respective Contributions

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1. Introduction

Different stereoisomers of drugs can have distinct therapeutic properties or adverse effects due to the chiral environments of enzymes and receptors in biological systems. The most well-known example is thalidomide, the R-enantiomer of which was an effective sedative, while the S-enantiomer caused severe teratogenic side effects and resulted in tragic birth defects during the 1950s. Stereoisomers of drugs can also have contrasting indications as in the case of quinine and quinidine or even opposing biological activities. For these reasons, regulatory agencies require the evaluation of the bioactivity of all stereoisomers of pharmaceutical candidates during the drug discovery and development process\textsuperscript{1,2}. Furthermore, manufacturers must develop assays to determine stereochemical purity to ensure drug safety. Consequently, all stereoisomers of a molecule must be prepared for use in biological testing or as standard samples. Thus, the construction of complete stereoisomeric sets represents a practically important synthetic problem as well as a fundamentally significant research topic\textsuperscript{1,2}.

In the past few decades, asymmetric synthesis has witnessed tremendous progress, providing numerous chiral bioactive compounds with high levels of selectivity\textsuperscript{3}. Although asymmetric catalysis has allowed enantiomers of a chiral molecule to be obtained with equal ease, relatively few methods are capable of providing a unified route leading to all possible stereoisomers of products containing multiple contiguous stereocenters. Thus, full control of absolute and relative stereochemical configuration remains an unmet synthetic challenge\textsuperscript{3}. Aside from classical techniques in asymmetric catalysis, such as the use of additives\textsuperscript{4,5}, modification of catalyst structure\textsuperscript{6-10}, and variation of substrate protecting group\textsuperscript{11,12}, multi-catalytic approaches\textsuperscript{14-16} have been advanced to access the full complement of stereoisomers for certain classes of compounds. MacMillan has previously described the novel concept of cycle-specific amino-
catalysis in which two chiral catalysts sequentially perform an iminium/enamine catalysis cascade to selectively functionalize enals. Carreira recently demonstrated an elegant dual catalyst system to independently control the two stereocenters for the \(\alpha\)-allylation of branched aldehydes. Despite these important developments, a rapid and predictable approach to access complete stereoisomeric sets of important products bearing multiple stereocenters (e.g. three contiguous stereocenters) from readily available precursors based on a single catalyst system would be highly desirable but remains underdeveloped.

Optically pure amino alcohols are important structural elements frequently found in pharmaceutical agents and bioactive natural products. Moreover, these compounds also serve as important building blocks for catalysts and auxiliaries in asymmetric synthesis. We speculated that our recently disclosed catalytic systems for enantioselective hydroamination based on copper hydride (CuH) intermediates and electrophilic aminating reagents could be applied to the synthesis of this class of compounds.
We hypothesized that enals and enones, which are readily available as geometrically pure isomers, could serve as ideal precursors to amino alcohols. In particular, we anticipated that a CuH-based catalyst could reduce enals and enones chemoselectively to the corresponding allylic alcohols, which would undergo regio- and stereoselective hydroamination to afford amino alcohol products bearing multiple contiguous stereocenters in one synthetic operation. As a consequence of the synfacial nature of the hydroamination process, we reasoned that this two-step sequence would be stereospecific with respect to olefin geometry. Thus, effective catalyst-control would allow the generation of all diastereomeric possibilities through the appropriate choice of substrate geometry (E or Z) and ligand enantiomer (R or S). Although the asymmetric hydrosilylation of ketones using a copper catalyst is a well-known process, we were aware that 1,2-reduction of α, β-unsaturated carbonyl compounds by CuH is less favorable than 1,4-reduction due to the inherent preference of Cu to coordinate to the olefin via soft–soft interactions. Pioneering work by...
Stryker\textsuperscript{29} and Lipshutz\textsuperscript{30} suggested that control of the regioselectivity in the CuH reduction of Michael acceptors was sensitive to subtle variation in steric and electronic properties of the ligand and the substituents of substrates. On the other hand, the control of regio- and stereoselectivity of hydroamination step is also non-trivial\textsuperscript{25}, due to the steric and electronic bias of the allylic silyl ether intermediates and potential matched/mismatched effects between substrates and chiral catalysts. Here, we report a copper-based catalyst system for the execution of this strategy that provides access to all possible amino alcohol stereoisomers in high chemo-, regio-, diastereo- and enantioselectivity starting from readily available enals and enones.

2. Results and Discussion

In initial efforts to implement this proposed hydrosilylation/hydroamination sequence, we first treated (E)-2-methyl-cinnamaldehyde (1a) with an excess of dimethoxymethylsilane in the presence of 5 mol \% of copper acetate and (S)-DTBM-SEGPHOS (L1) at room temperature for 15 minutes. Neither the conventional 1,4-reduction product nor the over-reduced saturated alcohol was observed and the desired 1,2-adduct was obtained in nearly quantitative yield. Further treatment of the reaction mixture with aminating reagent 2a at 55 °C effectively provided the amino alcohol 3a in 95\% yield and with complete diastereo- and enantioselectivity (>20/1 d.r., >99\% e.e.).

A thorough evaluation of the electrophilic amine source indicated that 2a was the optimal aminating reagent (Table 1). We attributed the high efficiency of 2a to the electron-rich para-diethylaminobenzoyl group. This group resulted in slower reductive decomposition of 2a and presumably faster regeneration of the CuH catalyst through $\sigma$-bond metathesis between the
corresponding copper benzoate species and hydrosilane species. L1 was the best ligand among the phosphines screened both in terms of reactivity and selectivity (Table 2).

Table 1: Evaluation of aminating agents.
Table 2: Evaluation of phosphine ligands.

With these optimized reaction conditions, we investigated the substrate scope of this one-pot transformation. We found that an array of β-aryl substituted (E)-enals could be efficiently transformed to the corresponding chiral amino alcohols in a highly regio-, diastereo- and enantioselective manner (Table 3, 3a-3n).
Table 3: Enal substrate scope.

<table>
<thead>
<tr>
<th>R'</th>
<th>R''</th>
<th>N</th>
<th>N</th>
<th>R''</th>
<th>R'</th>
</tr>
</thead>
</table>

A diverse range of hydroxylamine esters and enals with a variety of functional groups were suitable coupling partners for this sequential transformation, including phenols (3g, 3h), an aryl chloride (3k), an ester (3h), an acetal (3d), a trifluoromethoxyl (3e), cis-olefins (3f, 3i) and a trimethylsilyl group (from the reaction of a vinyl silane) (3l). In addition to acyclic substrates, both a cyclic enal and cyclic aminating reagents were compatible, providing the products with high levels of stereocontrol (3d, 3i, 3k). Furthermore, substrates bearing a broad range of pharmaceutically important heteroaromatic components—including an indole (3g), a thiophene (3f), a pyridine (3h), a pyrrole (3j), a pyrimidylpiperidine (3i), and a chromene (3k)—could be
readily converted to the desired products in excellent enantioselectivity. Additionally, an enal substrate bearing a ketone functional group smoothly underwent double hydrosilylation and hydroamination sequence under these conditions, furnishing amino diol (3m) bearing three stereocenters as a single stereoisomer. Lastly, a reaction conducted on a 5 mmol scale with decreased catalyst loading (1 mol%) efficiently provided the desired product (3a) in undiminished yield and stereoselectivity, demonstrating the robustness and practicality of this process.

As previously described, we were particularly interested in applying this approach to selectively access all of the possible stereoisomers, with high diasterero- and enantiocontrol for a given substrate. We felt that the use of the (Z)-enal substrate would lead to the formation of the complementary pair of diastereomers as that realized from the (E)-enal substrate. Accordingly, (Z)-2-amyl-cinnamaldehyde (1b) was subjected to the current reaction conditions, and produced the desired diastereomeric syn-amino alcohol in high chemical yield with complete diastereo- and enantioselectivity. Thus, by using the proper combinations of the enantiomer of ligand for the CuH catalyst and the olefin geometry of the enal substrate, all four stereoisomers of the corresponding amino alcohol could be readily prepared with full control of absolute and relative stereochemistry (Table 4a).
Table 4: a. Synthesis of all stereoisomers of 1,3-aminoalcohols containing two stereocenters. b. Synthesis of 1,3-aminoalcohols with chiral aminating agents.

We also found that amino alcohols bearing three stereogenic centers could be generated in excellent catalyst-controlled diastereoselectivity when chiral hydroxylamine esters were used. The existing α-stereocenter on chiral aminating reagents did not interfere with the stereoselectivity when applied to the current catalyst system. Thus, all eight stereoisomers of the amino alcohol 3n were easily constructed in good yield and excellent diastereoselectivity in one step by selecting the appropriate enantiomer of the chiral aminating reagent and geometric isomer of the enal substrate as starting materials and employing either enantiomer of the chiral catalyst (Table 4b).

We then sought to examine the possibility of using enones as substrates for the rapid synthesis of chiral amino alcohols with three contiguous stereocenters. Based on Lipshutz’s exceptional work on the asymmetric CuH-catalyzed 1,2-reduction of enones, we found that readily accessible enone 4a could be effectively converted to the corresponding chiral allylic alcohol in quantitative yield and 92 % ee at −60 °C in the presence of 5 mol % of Cu(OAc)₂-L₁.
complex. Upon addition of the aminating reagent to the reaction mixture while heated at 55 °C, 5a was furnished in 76% chemical yield with complete diastereo- and enantioselectivity (>20/1 d.r., >99% e.e.). Under these reaction conditions, a variety of enones were transformed successfully to the respective amino alcohol products (Fig. 4, 5a-5f) with excellent absolute and relative stereoselectivity (>20/1 d.r., >99% e.e.). In addition, a cyclic enone was converted into indanyl amino alcohol 5g in high diastereoselectivity (10/1 d.r.) and outstanding enantioselectivity (>99% e.e.) for both diastereomers. Lastly, we found that α-substitution on the enone was not crucial for selective 1,2-reduction. For instance, less substituted product 5h could be obtained in high enantioselectivity and synthetically useful diastereomeric ratio from benzylidenacetone (Table 6).

**Table 5**: Enone substrate scope.

<table>
<thead>
<tr>
<th>Enone Substrate</th>
<th>Amino Alcohol</th>
<th>Yield</th>
<th>Diastereomeric Ratio</th>
<th>Enantiomeric Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a†, 76% yield, &gt;20/1 d.r., &gt;99% e.e.</td>
<td>5b, 70% yield, &gt;20/1 d.r., &gt;99% e.e.</td>
<td>5c, 72% yield, &gt;20/1 d.r., &gt;99% e.e.</td>
<td>5d, 68% yield, &gt;20/1 d.r., &gt;99% e.e.</td>
<td>5e, 71% yield, &gt;20/1 d.r., &gt;99% e.e.</td>
</tr>
</tbody>
</table>

Subsequently, we wondered whether these conditions could be adapted to the stereodivergent construction of all eight stereoisomers of 5a. We prepared (S,S,R)-5a from (E)-4a in a one-pot sequence by employing (S)-L1 as the ligand. To prepare (S,R,S)-5a, we developed a modified protocol involving a ligand switch in which (E)-4a was first hydrosilylated using (S)-L1.
as the ligand, and the resulting chiral allylic alcohol was isolated and subjected to hydroamination conditions using copper catalyst based on (R)-L1. Use of antipodal ligands for the one-pot and ligand switch protocols yielded (R,R,S)- and (R,S,R)-5a, respectively, allowing four of the possible stereoisomers of 5a to be prepared from (E)-4a. We sought to prepare the four remaining stereoisomers of 5a from (Z)-4a by employing a similar strategy. The same ligand-switch protocol applied to (Z)-4a furnished (R,S,S)-5a and (S,R,R)-5a. Initial attempts to prepare (S,S,S)-5a and (R,R,R)-5a were unsuccessful, presumably due to the unfavorable steric interactions between the intermediate chiral (Z)-allylic alcohol and L1-based catalyst. Accordingly, a less bulky ligand, DM-SEGPHOS (L2), was selected for the hydroamination step to obtain these products. Ultimately, all eight stereoisomers of 5a were prepared expediently in one to two steps in useful isolated yields (33 to 76%), with complete enantioselectivity (>99% e.e.) and good to excellent diastereoselectivity (7:1 - >20:1 produced in the reaction mixture prior to purification) (Table 6a).
Table 6: a. Synthesis of all stereoisomers of 1, 3-aminoalcohols containing three stereocenters. b. HPLC traces separation of stereoisomers.

Upon isolation and chromatographic, all isomers were obtained in >20/1 d.r., as confirmed by the HPLC traces displayed (Table 6b). These results indicate that the enantioselective hydroamination steps proceeded through excellent catalyst-control in all eight cases.
The absolute and relative configuration of 5a (Prepared from \((E)\)-3-methyl-4-phenylbut-3-en-2-one using (S)-L1 was determined to be \((S,S,R)\) by X-ray diffraction after debenzylation and hydrobromide salt formation. The stereochemistries of the remaining amino alcohols were tentatively assigned by analogy.

3. Conclusion

In conclusion, we have developed a unified and stereodivergent strategy for the rapid and predictable construction of amino alcohols amenable to the synthesis of all possible stereoisomers of a given product. This practical protocol assembles two or three contiguous stereocenters utilizing enal and enone substrates in a highly selective copper catalyzed hydrosilylation/hydroamination sequence. The application of a stereospecific process to readily obtained pure geometric isomers of alkenes and highly effective catalyst control were critical aspects of our approach and may prove to be generally applicable to the development of other enantio- and diastereodivergent hydrofunctionalization reactions.
4. Experimental

**General: Reagent Information.** All the reactions were set up on the benchtop and conducted under an argon atmosphere. Flash column chromatography was performed using Silicycle SiliaFlash P60 (230–400 mesh) silica gel. Reaction solvents anhydrous tetrahydrofuran (THF) was purified by passing through two packed columns of neutral alumina and copper (II) oxide under a positive pressure of argon. Cu(OAc)$_2$ was purchased from Aldrich Chemical Co. and used as received. DTBM-SEGPHOS was purchased from Takasago International Co. and used as received. HSiMe(OMe)$_2$ (moisture-sensitive) was purchased from TCI and was stored under nitrogen at -20 °C. α-Methyl-trans-cinnamaldehyde and (E)-4-phenylbut-3-en-2-one were purchased from Aldrich Chemical Co. and used as received. Cis and trans α-Amylcinnamaldehyde were purchased from TCI and used as received. Other enal and enone substrates were prepared following literature procedures as indicated in each case. Hydroxyamine esters were prepared following literature procedures.$^{21}$ All reported yields of the copper-catalyzed hydrosilylation/hydroamination reactions stated are isolated yields and the average of at least two experiments unless otherwise stated.

**General: Analytical Information.** All new compounds were characterized by NMR spectroscopy, IR spectroscopy, high-resolution mass spectroscopy (or elemental analysis), and melting point (if solids). NMR spectra were recorded on a Bruker AMX 400 spectrometer and were calibrated using residual solvent as an internal reference (CDCl$_3$: 7.26 ppm for $^1$H NMR and 77.16 ppm for $^{13}$C NMR). All IR spectra were taken on a Thermo Scientific Nicolet iS5 spectrometer (iD5 ATR, diamond). Elemental analyses were performed by Atlantic Microlabs Inc.,
Norcross, GA. HRMS spectra were recorded on a Bruker Daltonics APEX IV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS). Melting points (M.P.) were obtained on a Mel-Temp capillary melting point apparatus. GC analyses were performed on an Agilent 6890 gas chromatograph with an FID detector using a J & W DB-1 column (10 m, 0.1 mm I.D.). The enantiomeric excesses (ee) of the products were determined by high-performance liquid chromatography (HPLC) analysis performed on Agilent 1200 Series chromatographs using a chiral column (25 cm) as noted for each compound. Optical rotations were measured on a Jasco P-1010 polarimeter with [α]D values reported in degrees; concentration (c) is in g/100 mL.

General Procedure A: An oven-dried screw-cap reaction tube equipped with a magnetic stir bar was charged with Cu(OAc)₂ (4.5 mg, 0.025 mmol, 5 mol %) and (S)-DTBM-SEGPHOS (33.2 mg, 0.0275 mmol, 5.5 mol %). The reaction tube was sealed with a screw-cap septum, then evacuated and backfilled with argon (this process was repeated a total of two times). Anhydrous THF (0.5 mL) and (MeO)₂MeSiH (0.25 mL, 2.0 mmol, 4.0 equiv) were added sequentially via syringe. The resulting mixture was stirred at room temperature (rt) for 15 min until the color changed from blue to orange. A second oven-dried screw-cap reaction tube equipped with a stir bar was charged with enal substrate I (0.5 mmol, 1.0 equiv). The reaction tube was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of two times). The catalyst solution from the first reaction tube was added slowly at rt via syringe. After stirring at rt
for an additional 15 min, hydroxylamine ester 2 (1.0 mmol, 1.0 equiv) was then added quickly to the reaction mixture under positive pressure of argon. The reaction tube was sealed with a screw-cap septum, then evacuated and backfilled with argon (this process was repeated a total of two times). The reaction mixture was stirred at 55 °C for 36 h. After completion, solvent was removed in vacuo with the aid of a rotary evaporator. The crude reaction mixture was stirred in a saturated solution of NH₄F in MeOH (3 mL) at rt for 10 min and then followed by addition of a saturated aqueous solution of Na₂CO₃ (10 mL) and EtOAc (20 mL). The phases were separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with a saturated aqueous solution of Na₂CO₃ (2 x 10 mL) and then concentrated in vacuo. At this stage, the diastereomeric ratio of 3 was determined by ¹H-NMR analysis to be >20/1 in all cases. The crude products were purified by flash column chromatography. The enantiomeric excesses of the products were determined by HPLC analysis using chiral stationary phases as indicated for each substrate.

(2S,3R)-3-(dibenzylamino)-2-methyl-3-phenylpropan-1-ol (3a).

Following General Procedure A, using (E)-2-methyl-cinnamaldehyde (73 mg, 0.5 mmol, 1.0 equiv), (MeO)₂MeSiH (0.25 mL, 2.0 mmol, 4.0 equiv), and 4-(((dibenzylamino)oxy)carbonyl)-N,N-diethylaniline (233 mg, 0.6 mmol, 1.2 equiv) in THF (0.5 mL), the reaction mixture was stirred at 55 °C for 36 h. The crude product was purified by flash column chromatography (0-8% EtOAc in hexanes) to provide the title compound as a pale yellow liquid in 95% yield (164 mg).

IR (thin film, cm⁻¹) 3027, 2926, 1452, 908, 729, 697; ¹H NMR (400 MHz, CDCl₃) δ: 7.53 − 7.26
(m, 15H), 6.09 – 5.73 (br s, 1H), 4.11 (d, J = 13.2 Hz, 2H), 3.91 (dd, J = 10.8, 3.9 Hz, 1H), 3.79 – 3.59 (m, 2H), 3.04 (d, J = 13.2 Hz, 2H), 2.69 – 2.80 (m, 1H), 0.56 (d, J = 6.6 Hz, 3H); 13C NMR (101 MHz, CDCl3) δ: 138.37, 134.15, 129.92, 129.09, 128.53, 127.93, 127.44, 127.21, 69.30, 68.92, 53.95, 33.85, 15.27. [ET] = 141.9 (c = 1.0, CHCl3). HPLC analysis (IC, 2% IPA in hexanes, 1 mL/min, 220 nm) indicated >99% ee: tR (minor) = 11.8 min, tR (major) = 16.5 min. HRMS (DART-TOF) calculated for C24H27NO [M+H]+ m/z 346.2165, found 346.2147. For a 5 mmol-scale reaction: Following General Procedure A, using Cu(OAc)2 (9.0 mg, 0.05 mmol, 1 mol %), (S)-DTBM-SEGPHOS (66.4 mg, 0.055 mmol, 1.1 mol %), (E)-2-methyl-cinnamaldehyde (731 mg, 5 mmol, 1.0 equiv), (MeO)2MeSiH (1.85 mL, 15.0 mmol, 3.0 equiv), and 4-(((dibenzylamino)oxy)carbonyl)-N,N-diethylaniline (2.33 g, 6.0 mmol, 1.2 equiv) in THF (5 mL), the reaction mixture was stirred at 55 °C for 60 h. The crude product was purified by flash column chromatography (0-8% EtOAc in hexanes) to provide the title compound as a pale yellow liquid in 96% yield (1.66 g) and >99% ee.

\[(S,Z)-2-((R)-(benzyl(thiophen-2-ylmethyl)amino)(phenyl)methyl)dec-7-en-1-ol\] (3f).

Following General Procedure A, using \((2E,7Z)-2\)-benzylidenedec-7-enal (121 mg, 0.5 mmol, 1.0 equiv), (MeO)2MeSiH (0.25 mL, 2.0 mmol, 4.0 equiv), and 4-(((benzyl(thiophen-2-ylmethyl)amino)oxy)carbonyl)-N,N-diethylaniline (296 mg, 0.75 mmol, 1.5 equiv) in THF (0.5 mL), the reaction mixture was stirred at 55 °C for 60 h. The crude product was purified by flash
column chromatography (0-20% EtOAc in hexanes) to provide the title compound as a colorless liquid in 78% yield (174 mg). IR (thin film, cm\(^{-1}\)) 2929, 1453, 1072, 1039, 698; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.35 – 7.32 (m, 4H), 7.26 (t, \(J = 7.7\) Hz, 3H), 7.20 – 7.09 (m, 4H), 6.91 – 6.81 (m, 2H), 5.26 – 5.14 (m, 1H), 5.14 – 4.99 (m, 1H), 4.61 (br s, 1H), 4.09 – 3.86 (m, 3H), 3.63 (d, \(J = 11.3\) Hz, 1H), 3.48 (dd, \(J = 11.3, 6.8\) Hz, 1H), 3.18 (d, \(J = 13.9\) Hz, 1H), 2.89 (d, \(J = 13.5\) Hz, 1H), 2.30 (m, 1H), 1.83 (m, 2H), 1.74 (q, \(J = 7.1\) Hz, 2H), 1.19 – 0.93 (m, 4H), 0.83 – 0.70 (m, 5H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\): 142.40, 138.61, 134.35, 131.66, 130.06, 129.02, 128.95, 128.79, 128.19, 127.65, 127.45, 126.83, 126.74, 125.24, 67.12, 65.50, 53.97, 48.95, 39.42, 29.70, 28.76, 26.85, 26.65, 20.50, 14.44. \([\alpha]\)\textsubscript{D}\(^{23}\) = 115.9 (c = 2.0, CHCl\(_3\)). HPLC analysis (OD-H, 2% IPA in hexanes, 1 mL/min, 220 nm) indicated >99% ee: \(t_R\) (major) = 11.0 min, \(t_R\) (minor) = 13.0 min. HRMS (DART-TOF) calculated for C\(_{29}\)H\(_{37}\)NOS [M+H]\(^+\) m/z 448.2669, found 448.2670.

(2\text{R,3S})-3-(benzyl(2-(cyclohex-1-en-1-yl)ethyl)amino)-2-methyl-3-(trimethylsilyl)propan-1-ol (3l).

Following General Procedure A, using (E)-2-methyl-3-(trimethylsilyl)prop-2-en-1-ol\(^{31}\) (72 mg, 0.5 mmol, 1.0 equiv), (MeO)\(_2\)MeSiH (0.25 mL, 2.0 mmol, 4.0 equiv), and 4-(((benzyl(2-(cyclohex-1-en-1-yl)ethyl)amino)oxy)carbonyl)-N,N-diethylaniline (305 mg, 0.75 mmol, 1.5 equiv) in THF (0.5 mL), the reaction mixture was stirred at 55 °C for 60 h. The crude product was purified by flash column chromatography (0-70% CH\(_2\)Cl\(_2\) in hexanes) to provide the title
compound as a colorless liquid in 77% yield (138 mg). IR (thin film, cm\textsuperscript{-1}) 2926, 1251, 1103, 752, 699; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\): 7.39 – 7.23 (m, 5H), 5.46 – 5.30 (m, 1H), 5.07 (br s, 1H), 3.98 (d, \(J = 12.7\) Hz, 1H), 3.75 – 3.50 (m, 2H), 3.36 (dd, \(J = 10.6, 8.1\) Hz, 1H), 2.87 – 2.80 (m, 1H), 2.71 – 2.64 (m, 1H), 2.32 (m, 1H), 2.25 – 2.09 (m, 2H), 2.09 – 1.77 (m, 5H), 1.55 (m, 4H), 0.79 (d, \(J = 6.8\) Hz, 3H), 0.23 (s, 9H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\): 139.14, 135.52, 129.61, 128.54, 127.37, 122.33, 72.25, 60.15, 57.67, 51.51, 37.63, 34.75, 28.59, 25.31, 22.99, 22.46, 16.76, 2.27. \([\alpha]\textsubscript{D}\textsuperscript{23} = 43.3 (c = 2.0, CHCl\textsubscript{3}).\) HPLC analysis (AD-H, 1% IPA in hexanes, 1 mL/min, 220 nm) indicated >99% ee: \(t_R\) (minor) = 8.5 min, \(t_R\) (major) = 11.6 min. HRMS (DART-TOF) calculated for C\textsubscript{22}H\textsubscript{37}NOSi \([M+H]^+\) \(m/z\) 360.2717, found 360.2724.

(2S,3R)-3-(dibenzylamino)-3-(4-((S)-1-hydroxyethyl)phenyl)-2-methylpropan-1-ol (3m).

Following General Procedure A, using (E)-3-(4-acetylphenyl)-2-methylacrylaldehyde (94 mg, 0.5 mmol, 1.0 equiv), (MeO)\textsubscript{2}MeSiH (0.31 mL, 2.5 mmol, 5.0 equiv), and 4-(((dibenzylamino)oxy)carbonyl)-N,N-diethylaniline (291 mg, 0.6 mmol, 1.5 equiv) in THF (0.5 mL), the reaction mixture was stirred at 55 °C for 60 h. The crude product was purified by flash column chromatography (0-33% EtOAc in hexanes) to provide the title compound as a white foam in 76% yield (148 mg). IR (thin film, cm\textsuperscript{-1}) 3340, 2967, 1453, 1028, 733, 698; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\): 7.49 – 7.13 (m, 14H), 4.93 (q, \(J = 6.4\) Hz, 1H), 3.99 (d, \(J = 13.2\) Hz, 2H), 3.82 – 3.72 (m, 1H), 3.60 (d, \(J = 11.0\) Hz, 1H), 3.49 (dd, \(J = 10.9, 8.4\) Hz, 1H), 2.93 (d, \(J = 13.2\) Hz, 2H), 2.67 – 2.61 (m, 1H), 1.55 (d, \(J = 6.5\) Hz, 3H), 0.44 (d, \(J = 6.6\) Hz, 3H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3})
δ: 145.29, 138.42, 133.19, 130.11, 129.25, 128.68, 127.36, 125.18, 69.82, 69.59, 68.99, 54.10, 33.86, 25.31, 15.38. [α]D23 = 186.8 (c = 0.25, CHCl3). HPLC analysis (AD-H, 10% IPA in hexanes, 1 mL/min, 220 nm) indicated >99% ee: tr (minor) = 12.0 min, tr (major) = 14.4 min. HRMS (DART-TOF) calculated for C26H31NO2 [M+H]+ m/z 390.2428, found 390.2433.

(S)-2-((R)-(dibenzylamino)(phenyl)methyl)heptan-1-ol ((S,R)-3b).

Following General Procedure A, using Cu(OAc)2 (4.5 mg, 0.025 mmol, 5 mol %), (S)-DTBM-SEGPHOS (33.2 mg, 0.0275 mmol, 5.5 mol %), (E)-2-benzylideneheptanal (101 mg, 0.5 mmol, 1.0 equiv), (MeO)2MeSiH (0.25 mL, 2.0 mmol, 4.0 equiv), and 4-(((dibenzylamino)oxy)carbonyl)-N,N-diethylaniline (291 mg, 0.75 mmol, 1.5 equiv) in THF (0.5 mL), the reaction mixture was stirred at 55 °C for 48 h. The crude product was purified by flash column chromatography (0-10% Et2O in hexanes) to provide the title compound as a colorless liquid in 96% yield (193 mg). IR (thin film, cm⁻¹) 2927, 1494, 1453, 1028, 699; 1H NMR (400 MHz, CDCl3) δ: 7.46 – 7.17 (m, 15H), 5.59 (s, 1H), 4.00 (d, J = 12.9 Hz, 3H), 3.68 (d, J = 11.3 Hz, 1H), 3.48 (dd, J = 11.1, 7.7 Hz, 1H), 2.93 (d, J = 13.2 Hz, 2H), 2.54 – 2.34 (m, 1H), 1.25 – 0.70 (m, 11H); 13C NMR (101 MHz, CDCl3) δ: 138.59, 134.27, 130.22, 129.32, 128.74, 128.08, 127.61, 127.42, 68.03, 66.57, 54.24, 39.07, 31.87, 28.95, 26.75, 22.43, 13.99. [α]D23 = 121.3 (c = 2.0, CHCl3). HPLC analysis (OD-H, 2% IPA in hexanes, 1 mL/min, 220 nm) indicated >99% ee: tr (minor) = 7.1 min, tr (major) = 12.4 min. HRMS (DART-TOF) calculated for C28H35NO [M+H]+ m/z 402.2791, found 402.2788.
(S)-2-((S)-(dibenzylamino)(phenyl)methyl)heptan-1-ol ((S,S)-3b).

Following General Procedure A, using Cu(OAc)$_2$ (4.5 mg, 0.025 mmol, 5 mol %), (S)-DTBMS-SEGPHOS (33.2 mg, 0.0275 mmol, 5.5 mol %), (Z)-2-benzylideneheptanal (101 mg, 0.5 mmol, 1.0 equiv), (MeO)$_2$MeSiH (0.25 mL, 2.0 mmol, 4.0 equiv), and 4-(((dibenzylamino)oxy)carbonyl)-N,N-diethylaniline (291 mg, 0.75 mmol, 1.5 equiv) in THF (0.5 mL), the reaction mixture was stirred at 55 °C for 60 h. The crude product was purified by flash column chromatography (0-10% Et$_2$O in hexanes) to provide the title compound as a colorless liquid in 76% yield (153 mg). IR (thin film, cm$^{-1}$) 2925, 1494, 1453, 1028, 698; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.43 – 7.35 (m, 6H), 7.31 (t, $J$ = 7.5 Hz, 5H), 7.25 – 7.15 (m, 3H), 3.90 (d, $J$ = 13.8 Hz, 2H), 3.62 (d, $J$ = 10.5 Hz, 1H), 3.42 (dd, $J$ = 11.3, 4.1 Hz, 1H), 3.22 (dd, $J$ = 11.3, 4.4 Hz, 1H), 3.15 – 2.95 (m, 2H), 2.35 – 2.27 (m, 1H), 2.19 – 1.99 (m, 1H), 1.52 – 1.23 (m, 8H), 1.00 – 0.89 (m, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$: 139.80, 136.43, 129.71, 128.97, 128.38, 128.19, 127.40, 126.96, 64.11, 62.82, 53.78, 40.78, 32.68, 27.56, 26.49, 22.93, 14.33. [$\alpha$]$^2$$_{D}$ = 65.8 (c = 2.0, CHCl$_3$). HPLC analysis (IC, 2% IPA in hexanes, 1 mL/min, 220 nm) indicated >99% ee: $t_R$ (major) = 7.4 min, $t_R$ (minor) = 11.6 min. HRMS (DART-TOF) calculated for C$_{28}$H$_{35}$NO [M+H]$^+$ $m/z$ 402.2791, found 402.2798.
Following General Procedure A, using Cu(OAc)₂ (4.5 mg, 0.025 mmol, 5 mol %), (S)-DTBM-SEGPHOS (33.2 mg, 0.0275 mmol, 5.5 mol %), (E)-2-methyl-cinnamaldehyde (73 mg, 0.5 mmol, 1.0 equiv), (MeO)₂MeSiH (0.25 mL, 2.0 mmol, 4.0 equiv), and (R)-4-(((benzyl(1-phenylethyl)amino)oxy)carbonyl)-N,N-diethylaniline (242 mg, 0.6 mmol, 1.2 equiv) in THF (0.5 mL), the reaction mixture was stirred at 55 °C for 36 h. The crude product was purified by flash column chromatography (0-10% EtOAc in hexanes) to provide the title compound as a colorless liquid in 65% yield (117 mg) and >20/1 dr. IR (thin film, cm⁻¹) 1493, 1451, 1216, 752, 576; ¹H NMR (400 MHz, CDCl₃) δ: 7.51 – 7.18 (m, 15H), 4.41 (d, J = 15.3 Hz, 1H), 3.90 – 3.64 (m, 5H), 3.36 (d, J = 15.4 Hz, 1H), 2.44 – 2.37 (m, 1H), 1.10 (d, J = 6.9 Hz, 3H), 0.51 (d, J = 6.7 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ: 146.05, 142.40, 136.73, 130.11, 128.86, 128.51, 127.99, 127.62, 127.35, 127.18, 126.63, 68.99, 67.83, 62.45, 52.91, 36.15, 24.03, 15.61. [α]D²³ = 59.2 (c = 2.0, CHCl₃). HRMS (DART-TOF) calculated for C₂₅H₂₉NO [M+H]⁺ m/z 360.2322, found 360.2304.

Following General Procedure A, using Cu(OAc)₂ (4.5 mg, 0.025 mmol, 5 mol %), (R)-DTBM-SEGPHOS (33.2 mg, 0.0275 mmol, 5.5 mol %), (E)-2-methyl-cinnamaldehyde (73 mg, 0.5 mmol, 1.0 equiv), (MeO)₂MeSiH (0.25 mL, 2.0 mmol, 4.0 equiv), and (R)-4-(((benzyl(1-phenylethyl)amino)oxy)carbonyl)-N,N-diethylaniline (242 mg, 0.6 mmol, 1.2 equiv) in THF (0.5 mL), the reaction mixture was stirred at 55 °C for 36 h. The crude product was purified by flash column chromatography (0-10% EtOAc in hexanes) to provide the title compound as a colorless liquid in 65% yield (117 mg) and >20/1 dr. IR (thin film, cm⁻¹) 1493, 1451, 1216, 752, 576; ¹H NMR (400 MHz, CDCl₃) δ: 7.51 – 7.18 (m, 15H), 4.41 (d, J = 15.3 Hz, 1H), 3.90 – 3.64 (m, 5H), 3.36 (d, J = 15.4 Hz, 1H), 2.44 – 2.37 (m, 1H), 1.10 (d, J = 6.9 Hz, 3H), 0.51 (d, J = 6.7 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ: 146.05, 142.40, 136.73, 130.11, 128.86, 128.51, 127.99, 127.62, 127.35, 127.18, 126.63, 68.99, 67.83, 62.45, 52.91, 36.15, 24.03, 15.61. [α]D²³ = 59.2 (c = 2.0, CHCl₃). HRMS (DART-TOF) calculated for C₂₅H₂₉NO [M+H]⁺ m/z 360.2322, found 360.2304.
mL), the reaction mixture was stirred at 55 °C for 36 h. The crude product was purified by flash column chromatography (0-10% EtOAc in hexanes) to provide the title compound as a colorless liquid in 75% yield (135 mg) and >20/1 dr. IR (thin film, cm⁻¹) 1486, 1457, 1209, 752 571; ¹H NMR (400 MHz, CDCl₃) δ: 7.48 – 7.18 (m, 12H), 4.35 – 4.01 (m, 3H), 3.68 – 3.60 (m, 3H), 3.25 (dd, J = 10.9, 7.1 Hz, 1H), 2.50 – 2.40 (m, 1H), 0.93 (d, J = 7.0 Hz, 3H), 0.43 (d, J = 6.7 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ: 143.66, (d, J = 1.8 Hz), 129.73, 139.34, 129.43, 128.77, 128.49, 128.33, 128.16, 127.41, 127.34, 127.20, 68.41, 66.65, 55.99, 51.48, 35.81, 15.43, 13.65. [α]D²³ = −54.3 (c = 2.0, CHCl₃). HRMS (DART-TOF) calculated for C₂₅H₂₉NO [M+H]⁺ m/z 360.2322, found 360.2304.

(2S,3S)-3-(benzyl((R)-1-phenylethyl)amino)-2-methyl-3-phenylpropan-1-ol ((S,S,R)-3n).

Following General Procedure A, using Cu(OAc)₂ (4.5 mg, 0.025 mmol, 5 mol %), (S)-DTBM-SEGPHOS (33.2 mg, 0.0275 mmol, 5.5 mol %), (Z)-2-methyl-cinnamaldehyde³²,³³,³⁴ (73 mg, 0.5 mmol, 1.0 equiv), (MeO)₂MeSiH (0.25 mL, 2.0 mmol, 4.0 equiv), and (R)-4-(((benzyl(1-phenylethyl)amino)oxy)carbonyl)-N,N-diethylaniline (242 mg, 0.6 mmol, 1.2 equiv) in THF (0.5 mL), the reaction mixture was stirred at 55 °C for 36 h. The crude product was purified by flash column chromatography (0-10% EtOAc in hexanes) to provide the title compound as a colorless liquid in 64% yield (115 mg) and >20/1 dr. IR (thin film, cm⁻¹) 2967, 1493, 1450, 1027, 699; ¹H NMR (400 MHz, CDCl₃) δ: 7.51 – 7.14 (m, 15H), 4.34 (d, J = 15.8 Hz, 1H), 3.82 (q, J = 6.9 Hz, 1H), 3.56 (d, J = 9.7 Hz, 1H), 3.43 (d, J = 15.8 Hz, 1H), 3.29 (dd, J = 10.9, 3.8 Hz, 1H), 2.97 (dd,
$J = 10.9, 6.4 \text{ Hz}, 1H), 2.33 - 2.23 \text{ (m, } 1H), 1.23 \text{ (d, } J = 6.6 \text{ Hz, } 3H), 1.07 \text{ (d, } J = 6.9 \text{ Hz, } 3H); ^{13}\text{C NMR (101 MHz, CDCl}_3) \delta: 145.82, 143.66, 138.04, 129.53, 128.40, 128.21, 128.05, 127.93, 127.51, 127.27, 126.79, 126.23, 67.99, 66.26, 61.63, 51.77, 37.85, 23.35, 15.99. [\alpha]_D^{23} = 25.1 \text{ (c = 2.0, CHCl}_3). \text{ HRMS (DART-TOF) calculated for C}_{25}H_{29}NO [M+H]^+ m/z 360.2322, found 360.2320.\]

(2\text{R,3R})-3-(benzyl((R)-1-phenylethyl)amino)-2-methyl-3-phenylpropan-1-ol ((R,R,R)-3n).

Following General Procedure A, using Cu(OAc)$_2$ (4.5 mg, 0.025 mmol, 5 mol %), (R)-DTBM-SEGPHOS (33.2 mg, 0.0275 mmol, 5.5 mol %), (Z)-2-methyl-cinnamaldehyde (73 mg, 0.5 mmol, 1.0 equiv), (MeO)$_2$MeSiH (0.25 mL, 2.0 mmol, 4.0 equiv), and (R)-4-(((benzyl(1-phenylethyl)amino)oxy)carbonyl)-N,N-diethylaniline (242 mg, 0.6 mmol, 1.2 equiv) in THF (0.5 mL), the reaction mixture was stirred at 55 °C for 36 h. The crude product was purified by flash column chromatography (0-10% EtOAc in hexanes) to provide the title compound as a colorless liquid in 72% yield (130 mg) and >20/1 dr. IR (thin film, cm$^{-1}$) 2967, 1493, 1451, 1027, 698; $^1\text{H NMR (400 MHz, CDCl}_3) \delta$: 7.45 - 7.19 (m, 15H), 4.22 (q, $J = 6.9$ Hz, 1H), 4.06 (d, $J = 14.2$ Hz, 1H), 3.62 (d, $J = 14.2$ Hz, 1H), 3.50 (d, $J = 9.2$ Hz, 1H), 3.31 (dd, $J = 10.9, 3.9$ Hz, 1H), 2.94 (dd, $J = 10.9, 6.5$ Hz, 1H), 2.38 - 2.27 (m, 1H), 1.00 (d, $J = 6.6$ Hz, 3H), 0.97 (d, $J = 6.9$ Hz, 3H). $^{13}\text{C NMR (101 MHz, CDCl}_3) \delta$: 144.39, 140.97, 140.22, 129.22, 128.86, 128.36, 128.30, 128.12, 128.10, 127.22, 126.87, 126.66, 66.13, 65.94, 55.45, 51.34, 37.55, 15.91, 13.49. [\alpha]_D^{23} = -23.6 \text{ (c} = \text{2.0, CHCl}_3).
HRMS (DART-TOF) calculated for C$_{31}$H$_{30}$N$_2$O$_2$S [M+H]$^+$ m/z 360.2322, found 360.2313.

General Procedure B (one-pot procedure): An oven-dried screw-cap reaction tube equipped with a magnetic stir bar was charged with Cu(OAc)$_2$ (9.0 mg, 0.05 mmol, 5 mol %) and (S)-DTBM-SEGPHOS (66.4 mg, 0.055 mmol, 5.5 mol %). The reaction tube was sealed with a screw-cap septum, then evacuated and backfilled with argon (this process was repeated a total of two times). Anhydrous THF (0.3 mL) and (MeO)$_2$MeSiH (0.25 mL, 2.0 mmol, 2.0 equiv) were added sequentially via syringe. The resulting mixture was stirred at rt for 15 min until the color changed from blue to orange. A second oven-dried screw-cap reaction tube equipped with a stir bar was charged with enone substrate 4 (1.0 mmol, 1.0 equiv). The reaction tube was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of two times). Anhydrous THF (0.7 mL) and (MeO)$_2$MeSiH (0.37 mL, 3.0 mmol, 3.0 equiv) were added sequentially via syringe at rt. The catalyst solution from the first reaction tube was added slowly to the stirred mixture at –60 °C via syringe. After stirring at –60 °C for an additional 15 h, the reaction mixture was allowed to warm to rt and hydroxylamine ester 2a (1.5 mmol, 1.5 equiv) was then added. The reaction tube was sealed with a screw-cap septum, then evacuated and backfilled with argon (this process was repeated a total of two times). The reaction mixture was stirred at 55 °C for 70 h. After completion, solvent was removed in vacuo with the aid of a rotary evaporator. The crude reaction mixture was stirred in a saturated solution of NH$_4$F in MeOH (5 mL) at rt for
10 min and then followed by addition of a saturated aqueous solution of Na$_2$CO$_3$ (10 mL) and EtOAc (20 mL). The phases were separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic phases were washed with a saturated aqueous solution of Na$_2$CO$_3$ (2 x 15 mL) and then concentrated in vacuo. The diastereomeric ratio of 5 was determined at this stage by $^1$H-NMR analysis. The crude products were purified by flash column chromatography. The enantiomeric excesses of the products were determined by HPLC analysis using chiral stationary phases as indicated for each substrate.

(2S,3S,4R)-4-(3-chlorophenyl)-4-(dibenzylamino)-3-methylbutan-2-ol (5b).

Following General Procedure B, using (E)-4-(3-chlorophenyl)-3-methylbut-3-en-2-one$^{35}$ (195 mg, 1.0 mmol, 1.0 equiv), (MeO)$_2$MeSiH (0.62 mL, 5.0 mmol, 5.0 equiv), and 4-(((dibenzylamino)oxy)carbonyl)-N,N-diethylaniline (583 mg, 1.5 mmol, 1.5 equiv) in THF (1.0 mL), the reaction mixture was stirred at 55 °C for 70 h. The crude product was purified by flash column chromatography (0-10% Et$_2$O in hexanes) to provide the title compound as a yellow liquid in 70% yield (276 mg). IR (thin film, cm$^{-1}$) 2972, 1453, 907, 733, 698; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.42 - 7.23 (m, 13H), 7.15 (dt, $J = 7.0, 1.7$ Hz, 1H), 4.56 - 4.30 (m, 1H), 3.93 (d, $J = 13.1$ Hz, 2H), 3.78 (d, $J = 5.8$ Hz, 1H), 3.61 (d, $J = 11.3$ Hz, 1H), 2.50 - 2.41 (m, 1H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.48 (d, $J = 6.7$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ: 138.85, 137.32, 134.30, 130.18, 129.42, 129.40, 128.84, 128.42, 127.76, 127.64, 68.34, 64.49, 53.92, 37.70, 18.68, 12.83. [α]$_D^{23}$ = 144.1 (c = 1.0, CHCl$_3$). HPLC analysis (IC, 1% IPA in hexanes, 1 mL/min, 220 nm) indicated
>99% ee: $t_R$ (minor) = 7.9 min, $t_R$ (major) = 11.5 min. HRMS (DART-TOF) calculated for C$_{25}$H$_{28}$ClNO [M+H]$^+$ $m/z$ 394.1932, found 394.1935.

(2S,3R)-3-(benzyl((R)-1-phenylethyl)amino)-2-methyl-3-phenylpropan-1-ol (5c).

Following General Procedure B, using (E)-3-methyl-4-(4-(trifluoromethyl)phenyl)but-3-en-2-one$^{35}$ (228 mg, 1.0 mmol, 1.0 equiv), (MeO)$_2$MeSiH (0.62 mL, 5.0 mmol, 5.0 equiv), and 4-(((dibenzylamino)oxy)carbonyl)-N,N-diethylaniline (583 mg, 1.5 mmol, 1.5 equiv) in THF (1.0 mL), the reaction mixture was stirred at 55 °C for 70 h. The crude product was purified by flash column chromatography (0-10% Et$_2$O in hexanes) to provide the title compound as a white solid liquid in 72% yield (306 mg). M.P. 140 – 141°C; IR (thin film, cm$^{-1}$) 1325, 1119, 1103, 1067, 750; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.63 (d, $J$ = 8.0 Hz, 2H), 7.33 – 7.15 (m, 12H), 4.50 – 4.29 (m, 1H), 3.87 (d, $J$ = 13.1 Hz, 2H), 3.69 – 3.51 (m, 2H), 2.84 (d, $J$ = 13.1 Hz, 2H), 2.45 – 2.37 (m, 1H), 0.92 (d, $J$ = 6.6 Hz, 3H), 0.39 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ: 139.28 (d, $J$ = 1.5 Hz), 138.80, 130.48, 129.79 (q, $J$ = 30.3 Hz), 128.88, 127.70, 125.12 (q, $J$ = 3.7 Hz), 124.32 (q, $J$ = 272.7 Hz), 68.18, 64.47, 53.94, 37.72, 18.79, 12.66. [$\alpha$]$_D^{23}$ = 143.3 (c = 1.0, CHCl$_3$).

HPLC analysis (IC, 1% IPA in hexanes, 1 mL/min, 220 nm) indicated >99% ee: $t_R$ (minor) = 6.7 min, $t_R$ (minor) = 10.4 min. Anal. Calcd. for C$_{26}$H$_{28}$FNO: C, 73.05; H, 6.60. Found: C, 73.09; H, 6.62.
(2S,3S,4R)-4-(dibenzylamino)-4-(2-fluorophenyl)-3-methylbutan-2-ol (5d).

Following General Procedure B, using (E)-4-(2-fluorophenyl)-3-methylbut-3-en-2-one (178 mg, 1.0 mmol, 1.0 equiv), (MeO)\(_2\)MeSiH (0.62 mL, 5.0 mmol, 5.0 equiv), and 4-(((dibenzylamino)oxy)carbonyl)-N,N-diethylaniline (583 mg, 1.5 mmol, 1.5 equiv) in THF (1.0 mL), the reaction mixture was stirred at 55 °C for 70 h. The crude product was purified by flash column chromatography (0-10% Et\(_2\)O in hexanes) to provide the title compound as a yellow liquid in 66% yield (249 mg). IR (thin film, cm\(^{-1}\)) 2972, 1486, 1452, 750, 699; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.49 – 7.26 (m, 14H), 4.45 (dt, \(J = 6.5, 3.3\) Hz, 1H), 4.19 – 4.04 (m, 4H), 3.08 (dd, \(J = 13.1, 1.7\) Hz, 2H), 2.71 (br s, 1H), 1.00 (d, \(J = 6.6\) Hz, 3H), 0.60 (d, \(J = 6.8\) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\): 163.22, 160.79, 139.12, 129.65, 129.27 (d, \(J = 8.6\) Hz), 128.65, 127.54, 123.72 (d, \(J = 3.3\) Hz), 122.53 (d, \(J = 16.0\) Hz), 116.14 (d, \(J = 25.3\) Hz), 69.10, 54.20, 37.47, 18.32, 13.06. \([\alpha]_D^{23} = 145.2\) (c = 2.0, CHCl\(_3\)). HPLC analysis (IC, 1% IPA in hexanes, 1 mL/min, 220 nm) indicated >99% ee: \(t_R\) (minor) = 12.6 min, \(t_R\) (major) = 26.2 min. HRMS (DART-TOF) calculated for C\(_{25}\)H\(_{28}\)FNO [M+\(\text{H}\)]\(^+\) \(m/z\) 378.2228, found 378.2218.

(2S,3S,4R)-4-(dibenzylamino)-4-(3-methoxyphenyl)-3-methylbutan-2-ol (5e).

Following General Procedure B, using (E)-4-(3-methoxyphenyl)-3-methylbut-3-en-2-one\(^{35}\) (190 mg, 1.0 mmol, 1.0 equiv), (MeO)\(_2\)MeSiH (0.62 mL, 5.0 mmol, 5.0 equiv), and 4-(((dibenzylamino)oxy)carbonyl)-N,N-diethylaniline (583 mg, 1.5 mmol, 1.5 equiv) in THF (1.0
mL), the reaction mixture was stirred at 55 °C for 70 h. The crude product was purified by flash column chromatography (0-10% Et₂O in hexanes) to provide the title compound as a yellow liquid in 71% yield (276 mg). IR (thin film, cm⁻¹) 2970, 1492, 1258, 910, 576; ¹H NMR (400 MHz, CDCl₃) δ: 7.50 – 7.25 (m, 11H), 7.01 – 6.80 (m, 3H), 4.43 (s, 1H), 4.23 (s, 1H), 3.97 (d, J = 13.2 Hz, 2H), 3.90 (s, 3H), 3.65 (d, J = 11.3 Hz, 1H), 3.06 (d, J = 13.2 Hz, 2H), 2.58 – 2.49 (m, 1H), 0.98 (d, J = 6.5 Hz, 3H), 0.53 (d, J = 6.7 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ: 159.42, 139.11, 136.63, 129.47, 128.97, 128.72, 127.49, 122.76, 116.78, 112.12, 68.79, 64.76, 55.31, 53.96, 37.59, 18.48, 13.10. [α]D²³ = 132.8 (c = 2.0, CHCl₃). HPLC analysis (IC, 1% IPA in hexanes, 1 mL/min, 220 nm) indicated >99% ee: tᵣ (minor) = 12.6 min, tᵣ (major) = 26.2 min. HRMS (DART-TOF) calculated for C₂₆H₃₁NO₂ [M+H]^+ m/z 390.2428, found 390.2408.

(2S,3S)-3-((R)-(dibenzylamino)(phenyl)methyl)pentan-2-ol (5f).

Following General Procedure B, using (E)-3-benzylidenepentan-2-one³⁵ (174 mg, 1.0 mmol, 1.0 equiv), (MeO)₂MeSiH (0.62 mL, 5.0 mmol, 5.0 equiv), and 4-(((dibenzylamino)oxy)carbonyl)-N,N-diethylaniline (583 mg, 1.5 mmol, 1.5 equiv) in THF (1.0 mL), the reaction mixture was stirred at 55 °C for 70 h. The crude product was purified by flash column chromatography (0-10% Et₂O in hexanes) to provide the title compound as a yellow liquid in 62% yield (232 mg). IR (thin film, cm⁻¹) 2967, 1493, 1453, 733, 698; ¹H NMR (400 MHz, CDCl₃) δ: 7.53 – 7.21 (m, 15H), 6.17 (d, J = 7.6 Hz, 1H), 4.41 – 4.22 (m, 1H), 34.03 – 3.87 (m, 3H), 2.95 (d, J = 13.0 Hz, 2H), 2.55 – 2.48 (m, 1H), 0.98 – 0.67 (m, 8H); ¹³C NMR (101 MHz, CDCl₃) δ: 138.43, 133.93, 130.50, 129.78, 128.59, 128.01, 127.57, 127.46, 68.44, 64.25, 53.80, 42.61, 22.01, 17.24, 12.37. [α]D²³ = 120.9 (c
HPLC analysis (IC, 1% IPA in hexanes, 0.5 mL/min, 220 nm) indicated >99% ee: 
$t_R$ (major) = 20.0 min, $t_R$ (minor) = 24.0 min. HRMS (DART-TOF) calculated for C$_{26}$H$_{31}$NO 
[M+H]$^+$ $m/z$ 374.2478, found 374.2469.

Following General Procedure B, using 1-(1H-inden-2-yl)butan-1-one (186 mg, 1.0 mmol, 1.0 
equiv), (MeO)$_2$MeSiH (0.62 mL, 5.0 mmol, 5.0 equiv), and 4-(((dibenzylamino)oxy)carbonyl)-
$N,N$-diethylaniline (583 mg, 1.5 mmol, 1.5 equiv) in THF (1.0 mL), the reaction mixture was 
stirred at 55 ºC for 70 h. The crude product was purified by flash column chromatography (0-10% 
CH$_2$Cl$_2$ in hexanes) to provide the title compound as a yellow liquid in 67% yield (258 mg) with 
10/1 dr. IR (thin film, cm$^{-1}$) 2927, 1453, 1126, 909, 732, 697; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.54 
– 7.13 (m, 14H), 4.41 (d, $J$ = 7.4 Hz, 1H), 3.97 – 3.47 (m, 5H), 2.87 – 2.72 (m, 2H), 2.63 – 2.57 
(m, 1H), 1.85 – 1.58 (m, 1H), 1.53 – 1.39 (m, 1H), 1.39 – 1.12 (m, 3H), 0.90 (t, $J$ = 6.9 Hz, 3H); $^{13}$C 
NMR (101 MHz, CDCl$_3$) $\delta$: 143.20, 143.07, 140.17, 129.34, 129.00, 128.40, 127.40, 127.12, 
126.18, 125.07, 72.04, 65.18, 54.86, 47.03, 37.09, 30.72, 19.61, 14.14. [$\alpha$]$_D^{23}$ = $-$128.2 (c = 3.0, 
CHCl$_3$). HPLC analysis (IA, 20% IPA in hexanes, 0.5 mL/min, 220 nm) indicated >99% ee: 
$t_R$ (major) = 8.9 min, $t_R$ (minor) = 11.8 min. HRMS (DART-TOF) calculated for C$_{27}$H$_{31}$NO 
[M+H]$^+$ $m/z$ 386.2478, found 386.2451.
Following General Procedure B, using Cu(OAc)$_2$ (9.0 mg, 0.05 mmol, 5 mol %), (S)-DTBM-SEGPHOS (66.4 mg, 0.055 mmol, 5.5 mol %), (E)-3-methyl-4-phenylbut-3-en-2-one $^{35}$ (160 mg, 1.0 mmol, 1.0 equiv), (MeO)$_2$MeSiH (0.62 mL, 5.0 mmol, 5.0 equiv), and 4-(((dibenzylamino)oxy)carbonyl)-N,N-diethylaniline (583 mg, 1.5 mmol, 1.5 equiv) in THF (1.0 mL), the reaction mixture was stirred at 55 °C for 70 h. The crude product was purified by flash column chromatography (0-10% Et$_2$O in hexanes) to provide the title compound as white foam in 76% yield (273 mg). IR (thin film, cm$^{-1}$) 2972, 1452, 907, 731, 698; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.44 – 7.04 (m, 15H), 4.44 – 4.01 (m, 2H), 3.87 (d, $J = 13.2$ Hz, 2H), 3.59 (d, $J = 11.3$ Hz, 1H), 2.91 (d, $J = 13.2$ Hz, 2H), 2.50 – 2.43 (m, 1H), 0.87 (d, $J = 6.5$ Hz, 3H), 0.40 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$: 139.09, 134.95, 130.40, 129.54, 128.75, 128.12, 127.57, 127.53, 69.00, 64.80, 53.94, 37.52, 18.43, 13.31. [α]$_D^{23} = 125.0$ (c = 3.0, CHCl$_3$). HPLC analysis (IC, 1% IPA in hexanes, 0.5 mL/min, 220 nm) indicated >99% ee: $t_R$ (minor) = 21.0 min, $t_R$ (major) = 30.7 min. HRMS (DART-TOF) calculated for C$_{25}$H$_{29}$NO [M+H]$^+$ $m/z$ 360.2322, found 360.2321.

**General Procedure C (for 1,2-reduction):** An oven-dried screw-cap reaction tube equipped with a magnetic stir bar was charged with Cu(OAc)$_2$ (9.0 mg, 0.05 mmol, 5 mol %) and (S)-DTBM-SEGPHOS (66.4 mg, 0.055 mmol, 5.5 mol %). The reaction tube was sealed with a screw-cap septum, then evacuated and backfilled with argon (this process was repeated a total of two times). Anhydrous THF (0.3 mL) and (MeO)$_2$MeSiH (0.37 mL, 3.0 mmol, 3.0 equiv) were added.
sequentially via syringe. The resulting mixture was stirred at rt for 15 min until the color changed from blue to orange. A second oven-dried screw-cap reaction tube equipped with a stir bar was charged with enone substrate 4 (1.0 mmol, 1.0 equiv). The reaction tube was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of two times). Anhydrous THF (0.7 mL) were added via syringe at rt. The catalyst solution from the first reaction tube was then added slowly to the stirred mixture at \(-60^\circ\text{C}\) via syringe. After stirring at \(-60^\circ\text{C}\) for an additional 15 h, the reaction mixture was quenched at \(-60^\circ\text{C}\) by addition of a saturated aqueous solution of Na\(_2\)CO\(_3\) (10 mL). After completion, solvent was removed \textit{in vacuo} with the aid of a rotary evaporator. The crude reaction mixture was stirred in a saturated solution of NH\(_4\)F in MeOH (3 mL) at rt for 10 min and then followed by addition of a saturated aqueous solution of Na\(_2\)CO\(_3\) (10 mL) and EtOAc (20 mL). The phases were separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with a saturated aqueous solution of Na\(_2\)CO\(_3\) (2 x 10 mL) and then concentrated in vacuo. The crude allylic alcohols were purified by flash column chromatography. The enantiomeric excesses of the products were determined by HPLC analysis using chiral stationary phases as indicated for each substrate.

**General Procedure D (for hydroamination):** An oven-dried screw-cap reaction tube equipped with a magnetic stir bar was charged with Cu(OAc)\(_2\) (4.5 mg, 0.025 mmol, 5 mol %) and (R)-DTBM-SEGPHOS (33.2 mg, 0.0275 mmol, 5.5 mol %). The reaction tube was sealed with a screw-cap septum, then evacuated and backfilled with argon (this process was repeated a total of two times). Anhydrous THF (0.5 mL) and (MeO)\(_2\)MeSiH (0.31 mL, 2.5 mmol, 5.0 equiv) were added sequentially via syringe. The resulting mixture was stirred at rt for 15 min until the color
changed from blue to orange. A second oven-dried screw-cap reaction tube equipped with a stir bar was charged with allylic alcohol intermediate (0.5 mmol, 1.0 equiv) and hydroxylamine ester 2a (1.0 mmol, 2.0 equiv). The reaction tube was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of two times). The catalyst solution from the first reaction tube was then added slowly to the stirred mixture at rt via syringe. After stirring at rt for 15 min, the reaction mixture was then stirred at 55 °C for 70 h. After completion, solvent was removed in vacuo with the aid of a rotary evaporator. The crude reaction mixture was stirred in a saturated solution of NH₄F in MeOH (3 mL) at rt for 10 min and then followed by addition of a saturated aqueous solution of Na₂CO₃ (10 mL) and EtOAc (20 mL). The phases were separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with a saturated aqueous solution of Na₂CO₃ (2 x 10 mL) and then concentrated in vacuo. The crude products were purified by flash column chromatography. The enantiomeric excesses of the products were determined by HPLC analysis using chiral stationary phases as indicated for each substrate.

\[
\begin{align*}
\text{N} & \text{Bn} \\
\text{Me} & \text{Me} \\
\text{H} & \\
\end{align*}
\]

(2R,3S,4R)-4-(dibenzylamino)-3-methyl-4-phenylbutan-2-ol ((R,S,R)-5a).

Following General Procedure C (for 1,2-reduction), using Cu(OAc)₂ (18.0 mg, 0.1 mmol, 5 mol %) and (R)-DTBM-SEGPHOS (133.0 mg, 0.11 mmol, 5.5 mol %), (E)-3-methyl-4-phenylbut-3-en-2-one (320 mg, 2.0 mmol, 1.0 equiv), (MeO)₂MeSiH (0.74 mL, 6.0 mmol, 3.0 equiv), the reaction mixture was stirred at −60 °C for 15 h. The crude product was purified by flash column chromatography (0-15% EtOAc in hexanes) to provide (R,E)-3-methyl-4-phenylbut-3-en-2-ol as
a colorless liquid in 99% yield (321 mg). \([\alpha]_D^{23} = 13.5 \ (c = 2.0, \text{CHCl}_3)\). HPLC analysis (IC, 5% IPA in hexanes, 1 mL/min, 220 nm) indicated 92% ee: \(t_R\) (minor) = 7.2 min, \(t_R\) (major) = 8.5 min.

Following General Procedure D (for hydroamination), using Cu(OAc)\(_2\) (4.5 mg, 0.025 mmol, 5 mol %) and (S)-DTBM-SEGPHOS (33.2 mg, 0.0275 mmol, 5.5 mol %), (R,E)-3-methyl-4-phenylbut-3-en-2-ol (81 mg, 0.5 mmol, 1.0 equiv), (MeO)\(_2\)MeSiH (0.31 mL, 2.5 mmol, 5.0 equiv), the reaction mixture was stirred at 55 °C for 70 h. The diastereomeric ratio was determined to 13/1 via \(^1\)H NMR analysis of the crude sample. The crude product was purified by flash column chromatography (0-10% Et\(_2\)O in hexanes) to provide the title compound as white foam in 61% yield (110 mg). IR (thin film, cm\(^{-1}\)) 2971, 1494, 1452, 1125, 697; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.93 (br s, 1H), 7.51 – 7.15 (m, 15H), 4.05 (d, \(J = 13.2\) Hz, 2H), 3.69 (d, \(J = 11.1\) Hz, 1H), 3.62 – 3.55 (m, 1H), 2.93 (d, \(J = 13.2\) Hz, 2H), 2.39 – 2.20 (m, 1H), 1.23 (d, \(J = 6.1\) Hz, 3H), 0.43 (d, \(J = 6.6\) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\): 138.11, 134.12, 130.29, 129.41, 129.75, 128.13, 127.62, 127.43, 74.14, 69.99, 54.32, 39.03, 21.91, 15.22. \([\alpha]_D^{23} = 123.6 \ (c = 3.0, \text{CHCl}_3)\). HPLC analysis (IC, 1% IPA in hexanes, 0.5 mL/min, 220 nm) indicated >99% ee: \(t_R\) (major) = 26.5 min, \(t_R\) (minor) = 28.3 min. HRMS (DART-TOF) calculated for C\(_{25}\)H\(_{29}\)NO [M+H]\(^+\) \(m/z\) 360.2322, found 360.2323.

General Procedure E for the Preparation of Enals

![Chemical Reaction Diagram](image)
To a vigorously stirring suspension of benzyltriethylammonium chloride (1.0 mmol) and potassium hydroxide (1.50 mmol) in toluene (15.0 mL) was added aryl aldehyde (10.0 mmol) and aliphatic aldehyde (12.0 mmol). The mixture was stirred at room temperature and monitored by thin-layer chromatography. The reaction mixture was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (ethyl acetate/hexanes) or recrystallization to afford the enal.\textsuperscript{37}

\[(E)-2\text{-methyl-3-(3,4,5-trimethoxyphenyl)acrylaldehyde.}\]

The title compound was prepared by following General Procedure E as an off-white solid. M.P. 86 – 87 °C; IR (thin film, cm\textsuperscript{-1}) 1662, 1575, 1330, 1244, 1123; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta: 9.55 (s, 1H), 7.18 (d, \textit{J} = 1.9 Hz, 1H), 6.77 (s, 2H), 3.90 (d, \textit{J} = 2.6 Hz, 9H), 2.10 (d, \textit{J} = 1.3 Hz, 3H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \delta: 195.44, 153.33, 150.04, 139.61, 137.65, 130.73, 107.70, 61.11, 56.34, 11.13. HRMS (DART-TOF) calculated for C\textsubscript{13}H\textsubscript{16}O\textsubscript{4} [M+H]\textsuperscript{+} \textit{m/z} 237.1121, found 237.1115.

\[(E)-2\text{-cyclopropyl-3-(4-(trifluoromethoxy)phenyl)acrylaldehyde.}\]
The title compound was prepared by following General Procedure E as a bright yellow liquid. IR (thin film, cm\(^{-1}\)) 1688, 1252, 1217, 1205, 1159; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 9.65 – 9.42 (m, 1H), 7.69 (d, \(J = 8.7\) Hz, 1H), 7.34 – 7.20 (m, 3H), 1.74 – 1.61 (m, 1H), 0.98 – 0.84 (m, 2H), 0.78 – 0.64 (m, 2H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\): 195.12, 149.88, 149.15, 142.80, 133.36, 131.89, 121.82, 120.72, 119.26, 8.71, 7.57. HRMS (DART-TOF) calculated for C\(_{13}\)H\(_{11}\)F\(_3\)O\(_2\) [M+H]\(^+\) \(m/z\) 257.0784, found 257.0778.

(2E,7Z)-2-benzylidenedec-7-enal.

The title compound was prepared by following General Procedure E as a pale yellow liquid. IR (thin film, cm\(^{-1}\)) 2931, 2858, 1660, 1623, 755; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 9.55 (s, 1H), 7.52 – 7.39 (m, 5H), 7.22 (s, 1H), 5.42 – 5.24 (m, 2H), 2.61 – 2.48 (m, 2H), 2.03 (m, 4H), 1.56 – 1.41 (m, 3H), 0.94 (t, \(J = 7.5\) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\): 195.83, 150.00, 143.34, 135.08, 132.01, 129.73, 128.93, 30.09, 28.04, 26.93, 24.82, 20.66, 14.49. HRMS (DART-TOF) calculated for C\(_{17}\)H\(_{22}\)O [M–H]\(^+\) \(m/z\) 241.1598, found 259.1700.

(E)-3-(3-hydroxyphenyl)-2-methylacrylaldehyde.

The title compound was prepared by following General Procedure E as a white solid. M.P. 119 – 120 °C; IR (thin film, cm\(^{-1}\)) 3228, 1650, 1575, 1281, 1194; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 9.57
(s, 5H), 7.33 (t, J = 7.9 Hz, 5H), 7.23 (s, 1H), 7.15 – 7.07 (m, 5H), 7.04 (d, J = 2.2 Hz, 4H), 6.91 (ddd, J = 8.2, 2.6, 0.9 Hz, 5H), 5.56 (s, 5H), 2.08 (d, J = 1.4 Hz, 15H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ: 196.14, 155.99, 150.12, 138.69, 136.70, 130.09, 122.88, 116.96, 116.74, 11.14. HRMS (DART-TOF) calculated for C$_{10}$H$_{10}$O$_2$ [M+H]$^+$ m/z 163.0754, found 163.0750.

(E)-3-(6-methoxypyridin-3-yl)-2-methylacrylaldehyde.

The title compound was prepared by following General Procedure E as a light brown solid. M.P. 105 – 106 °C; IR (thin film, cm$^{-1}$) 1669, 1597, 1493, 1293, 1007; $^1$H NMR (400 MHz, CDCl$_3$) δ: 9.56 (s, 1H), 8.37 (d, J = 2.4 Hz, 1H), 7.80 (dd, J = 8.7, 2.5 Hz, 1H), 7.16 (d, J = 1.6 Hz, 1H), 6.82 (d, J = 8.7 Hz, 1H), 3.98 (s, 3H), 2.07 (d, J = 1.4 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ: 195.02, 164.65, 149.58, 146.26, 139.46, 137.71, 124.77, 111.31, 53.95, 11.10. HRMS (DART-TOF) calculated for C$_{10}$H$_{11}$NO$_2$ [M+H]$^+$ m/z 178.0863, found 178.0857.

(E)-3-(4-(1H-pyrrol-1-yl)phenyl)-2-methylacrylaldehyde.

The title compound was prepared by following General Procedure E as a bright yellow solid. M.P. 102 – 104 °C; IR (thin film, cm$^{-1}$) 1667, 1600, 1518, 1326, 700; $^1$H NMR (400 MHz, CDCl$_3$) δ: 9.60 (s, 1H), 7.62 (d, J = 8.6 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 7.26 – 7.23 (m, 1H), 7.16 (t, J = 2.2 Hz, 2H), 6.39 (t, J = 2.2 Hz, 2H), 2.12 (d, J = 1.3 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ:
HRMS (DART-TOF) calculated for C_{14}H_{13}NO [M+H]^+ m/z 212.1070, found 212.1066.

\[ \text{(E)-3-(4-acetylphenyl)-2-methylacrylaldehyde.} \]

A solution of 4'-bromoacetophenone (13.2 mmol, 2.63 g, 1.0 equiv), acrolein (6.0 mmol, 0.39 mL, 0.45 equiv), palladium acetate (0.66 mmol, 0.148 g, 0.05 equiv), triethylamine (39.6 mmol, 5.5 mL, 3.0 equiv) and benzyltriethylammonium chloride (13.2 mmol, 3.05 g, 1.0 equiv) in dimethylformamide (40 mL) was stirred and heated to 70 °C. After 3 hours, additional acrolein (6.0 mmol, 0.393 mL, 0.45 equiv) and palladium acetate (0.66 mmol, 0.148 g, 0.05 equiv) was added. After 17 hours, the reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic layer was washed with water and dried over sodium sulfate. Solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (20% EtOAc in hexanes) to give the title compound as a light orange solid (50% yield, 2.26 g).³⁸

M.P. 73 – 74 °C; IR (thin film, cm⁻¹) 1674, 1264, 1183, 1010, 591; \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \): 9.59 (s, 1H), 8.00 (d, \( J = 8.4 \) Hz, 2H), 7.58 (d, \( J = 8.3 \) Hz, 2H), 7.31 – 7.27 (m, 1H), 2.60 (s, 3H), 2.05 (d, \( J = 1.5 \) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl₃) \( \delta \): 197.39, 195.18, 147.93, 140.18, 139.55, 137.26, 130.05, 128.62, 26.74, 11.11. HRMS (DART-TOF) calculated for C_{12}H_{12}O_{2} [M+H]^+ m/z 189.0910, found 189.0906.
1-(1H-inden-2-yl)butan-1-one\(^{39}\).

A solution of 2-bromobenzaldehyde (3.0 mmol), hex-1-en-3-ol (3.6 mmol), tetrabutylammonium chloride (6.0 mmol), sodium acetate (7.5 mmol), lithium chloride (6.0 mmol), and palladium acetate (0.15 mmol) in dimethylformamide (30 mL) under an argon atmosphere was heated at 110 °C and stirred for 4 h. The reaction mixture was cooled to room temperature and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography (hexane/ethyl acetate, 5:1) to yield the product as a yellow solid (60% yield). M.P. 75 - 76 °C; IR (thin film, cm\(^{-1}\)) 2957, 1647, 1556, 1174, 752; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.53 (q, \(J=1.6\) Hz, 1H), 7.48 - 7.35 (m, 2H), 7.27 - 7.18 (m, 2H), 3.67 - 3.45 (m, 2H), 2.71 (t, \(J=7.4\) Hz, 2H), 1.65 (h, \(J=7.4\) Hz, 2H), 0.90 (t, \(J=7.4\) Hz, 3H); \(^1^3\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\): 198.32, 146.25, 145.02, 143.04, 140.17, 128.10, 127.04, 124.61, 123.83, 40.97, 37.66, 18.44, 14.09. HRMS (DART-TOF) calculated for C\(_{13}\)H\(_{14}\)O [M+H]\(^+\) \(m/z\) 187.1117, found 187.1107.

(S)-4-(((benzyl(1-phenylethyl)amino)oxy)carbonyl)-N,N-diethylaniline

The title compound was prepared by following the reported procedure as a yellow solid.\(^1\) M.P. 93 - 94 °C; IR (thin film, cm\(^{-1}\)) 1722, 1601, 1256, 1179, 696; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.76 (d, \(J=8.9\) Hz, 2H), 7.58 - 7.46 (m, 2H), 7.44 - 7.14 (m, 7H), 6.57 (d, \(J=9.0\) Hz, 2H), 4.20 (q, \(J\)}
= 6.7 Hz, 1H), 4.09 (d, J = 14.0 Hz, 1H), 3.92 (d, J = 14.0 Hz, 1H), 3.39 (q, J = 7.1 Hz, 4H), 1.53 (d, J = 6.6 Hz, 3H), 1.18 (t, J = 7.1 Hz, 6H); 13C NMR (101 MHz, CDCl3) δ: 165.57, 150.87, 136.71, 131.38, 129.35, 128.49, 127.95, 127.51, 127.17, 114.98, 110.12, 65.76, 59.70, 44.45, 19.85, 12.50. [α]D²3 = 19.3 (c = 1.0, CHCl₃). HRMS (DART-TOF) calculated for C₂₆H₃₀N₂O₂ [M+H]⁺ m/z 403.2380, found 403.2390.

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The image contains a chemical structure and spectral data. The structure is labeled with various chemical groups and elements. The spectral data includes a series of chemical shifts (δ) in ppm, listed as follows:

- 138.85
- 137.32
- 134.30
- 130.18
- 130.42
- 129.84
- 128.84
- 128.42
- 127.76

The chemical shifts are associated with different environments, indicated by "CDCl3" annotations. The spectral data likely pertains to a 1H NMR spectrum, given the context of the structure and the nature of the shifts.
dr = 91: 9
dr = 91:9