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## Copper-catalyzed enantioselective stereodivergent synthesis of amino alcohols

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### Abstract

The chirality, or ‘handedness’, of a biologically active molecule can alter its physiological properties. For this reason, it is routine procedure in the drug discovery and development process to prepare and fully characterize all possible stereoisomers of a drug candidate for biological evaluation<sup>1,2</sup>. Despite many recent advances in asymmetric synthesis, the development of general and practical strategies to obtain all possible stereoisomers of an organic compound bearing multiple contiguous stereocenters remains a significant challenge<sup>3</sup>. In this manuscript, we report a stereodivergent copper-based approach for the expeditious construction of amino alcohols with high levels of chemo-, regio-, diastereo- 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 the 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.

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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 (Fig. 1a and 1b). For these reasons, regulatory agencies require the evaluation of the bioactivity of all stereoisomers of pharmaceutical candidates during the drug discovery and development

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**Supplementary Information** is available in the online version of the paper.

**Author contributions** S.-L.S. and S.L.B. conceived the idea and designed the research. S.-L.S. and Z.W. performed the experiments. S.-L.S. and S.L.B. wrote the manuscript. All authors commented on the final draft of the manuscript and contributed to the analysis and interpretation of the data.

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process<sup>1,2</sup>. 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<sup>1,2</sup>.

In the past few decades, asymmetric synthesis has witnessed tremendous progress, providing numerous chiral bioactive compounds with high levels of selectivity<sup>3</sup>. 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<sup>3</sup>. Aside from classical techniques in asymmetric catalysis, such as the use of additives<sup>4,5</sup>, modification of catalyst structure<sup>6-10</sup>, and variation of substrate protecting group<sup>11,12</sup>, multi-catalytic approaches<sup>13-16</sup> 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<sup>13,14</sup>. Carreira recently demonstrated an elegant dual catalyst system to independently control the two stereocenters for the  $\alpha$ -allylation of branched aldehydes<sup>15,16</sup>. 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 (Fig. 1b)<sup>17</sup>. Moreover, these compounds also serve as important building blocks for catalysts and auxiliaries in asymmetric synthesis. We speculated that our recently disclosed catalytic systems<sup>18,23</sup> for enantioselective hydroamination<sup>24,25</sup> based on copper hydride (CuH) intermediates<sup>26</sup> and electrophilic aminating reagents<sup>27</sup> 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 (Fig. 1c). 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<sup>28</sup>, we were aware that 1,2-reduction of  $\alpha$ ,  $\beta$ -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<sup>26</sup>. Pioneering work by Stryker<sup>29</sup> and Lipshutz<sup>30</sup> 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<sup>25</sup>, 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.

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. 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<sup>22,23</sup>. **L1** was the best ligand among the phosphines screened both in terms of reactivity and selectivity (See Supplementary Information for details).

With these optimized reaction conditions, we investigated the substrate scope of this one-pot transformation. We found that an array of  $\beta$ -aryl substituted (*E*)-enals could be efficiently transformed to the corresponding chiral amino alcohols in a highly regio-, diastereo- and enantioselective manner (Fig. 2, **3a–3n**). 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**, **3l**) 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 diastereo- 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 (Fig. 3a).

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  $\alpha$ -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 (Fig. 3b).

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<sup>30</sup>, we found that readily accessible enone **4a** could be effectively converted to the corresponding chiral allylic alcohol in quantitative yield and 92 % e.e. at  $-60$  °C in the presence of 5 mol % of Cu(OAc)<sub>2</sub>-**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  $\alpha$ -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.

Subsequently, we wondered whether these conditions could be adapted to the stereodivergent construction of all eight stereoisomers of **5a**. Above (Fig. 4), 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 enantiomeric 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) (Fig. 5a). Upon isolation and chromatographic, all isomers were obtained in >20/1 d.r., as confirmed by the HPLC traces displayed in Fig. 5b. These results indicate that the enantioselective hydroamination steps proceeded through excellent catalyst-control in all eight cases.

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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

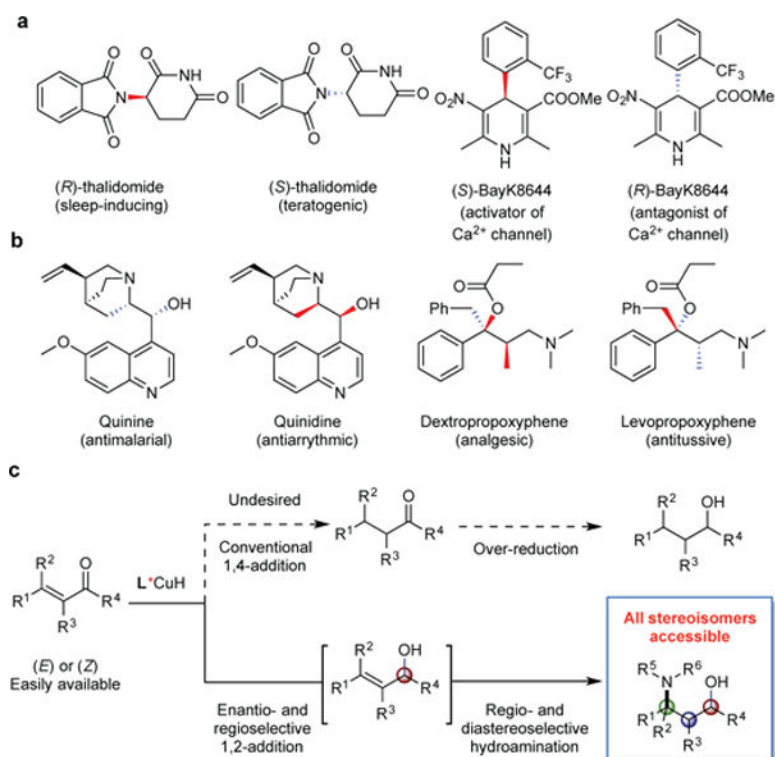
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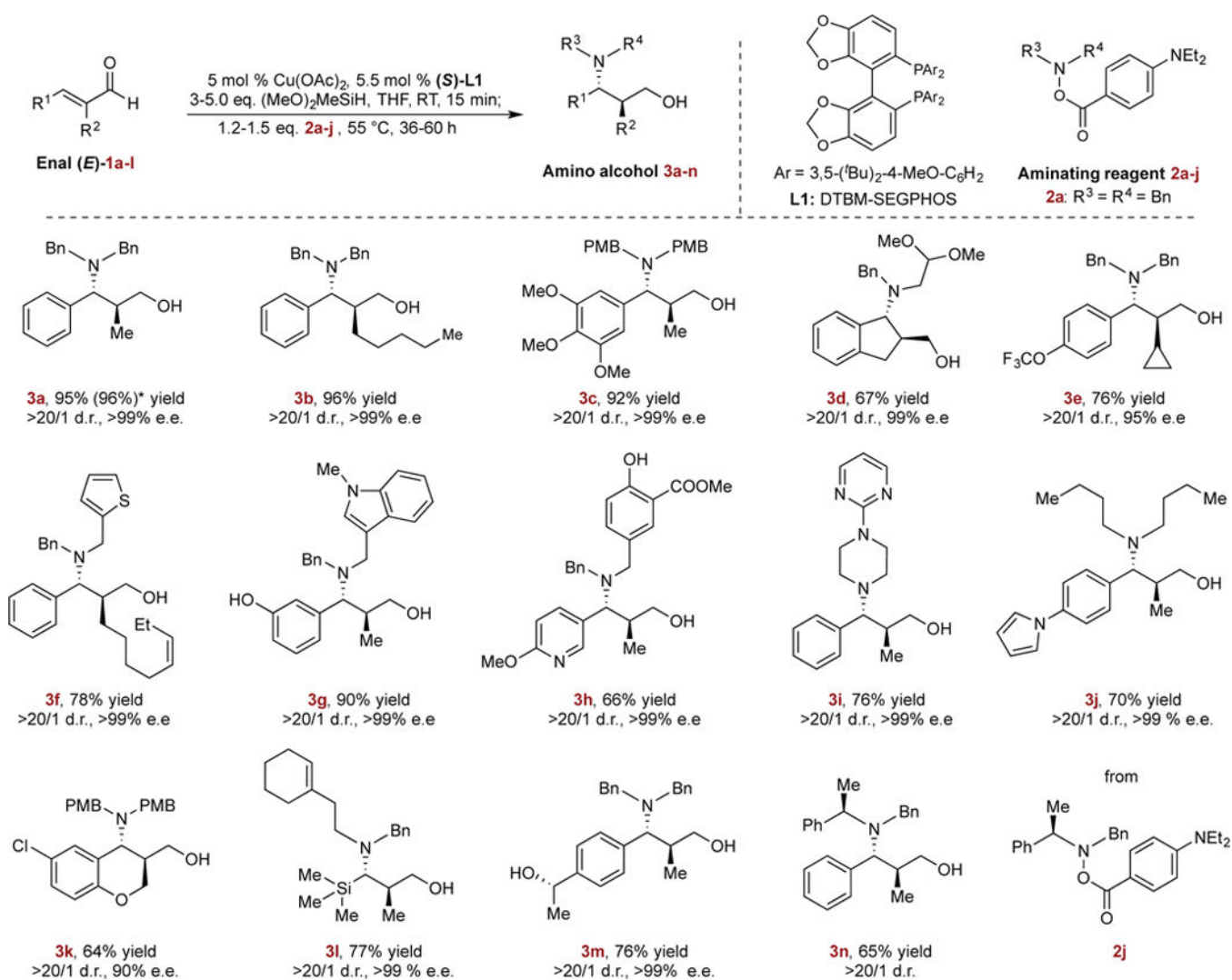
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**Figure 1. Bioactive stereoisomers and strategies for construction of all stereoisomers of amino alcohols**

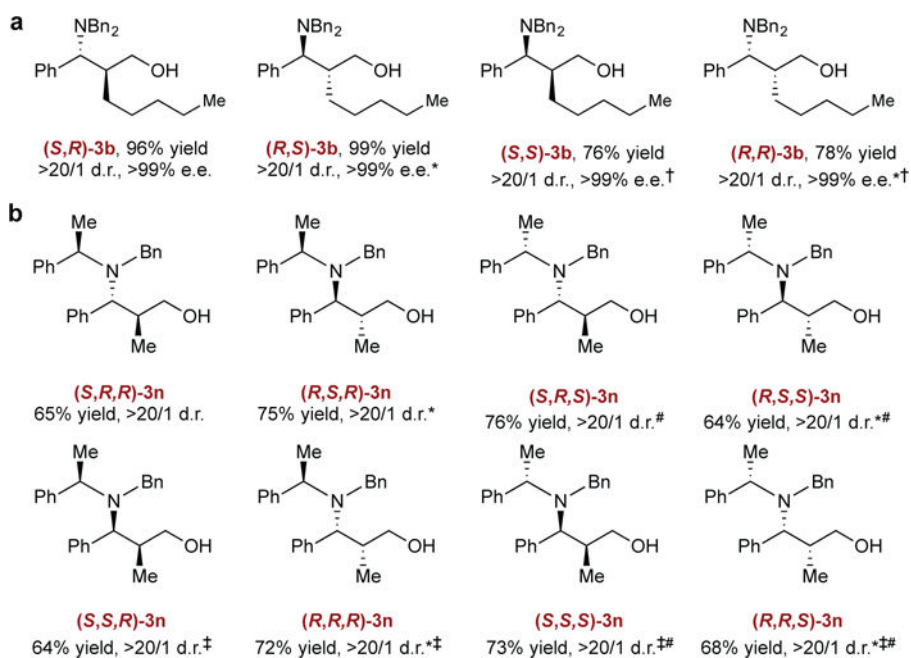
**a** Different enantiomers give distinct activities in biological systems. **b.** Stereoisomeric amino alcohols (esters) and their biological activities. **c.** Top, potential side reactions; Bottom (this work), forming all stereoisomers of amino alcohols via selective hydrosilylation/hydroamination reactions.



**Figure 2. Asymmetric hydrosilylation/hydroamination of enals**

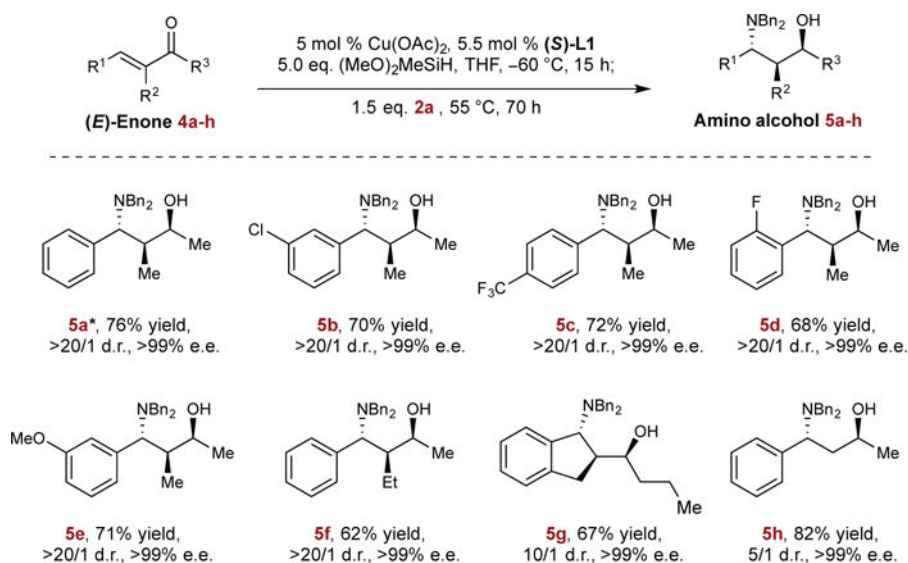
Top row, reaction studied; Bottom rows, substrate scope. Isolated yields are reported (average of two runs on 0.5 mmol scale). Diastereomeric ratios (d.r.) were determined by GC and NMR analysis. Enantiomeric excesses (e.e.) were determined by HPLC analysis using chiral stationary phases. \*Reaction was conducted in 5 mmol scale. See Supplementary Information for details. Bn, benzyl; PMB, *p*-methoxybenzyl; RT, room temperature.





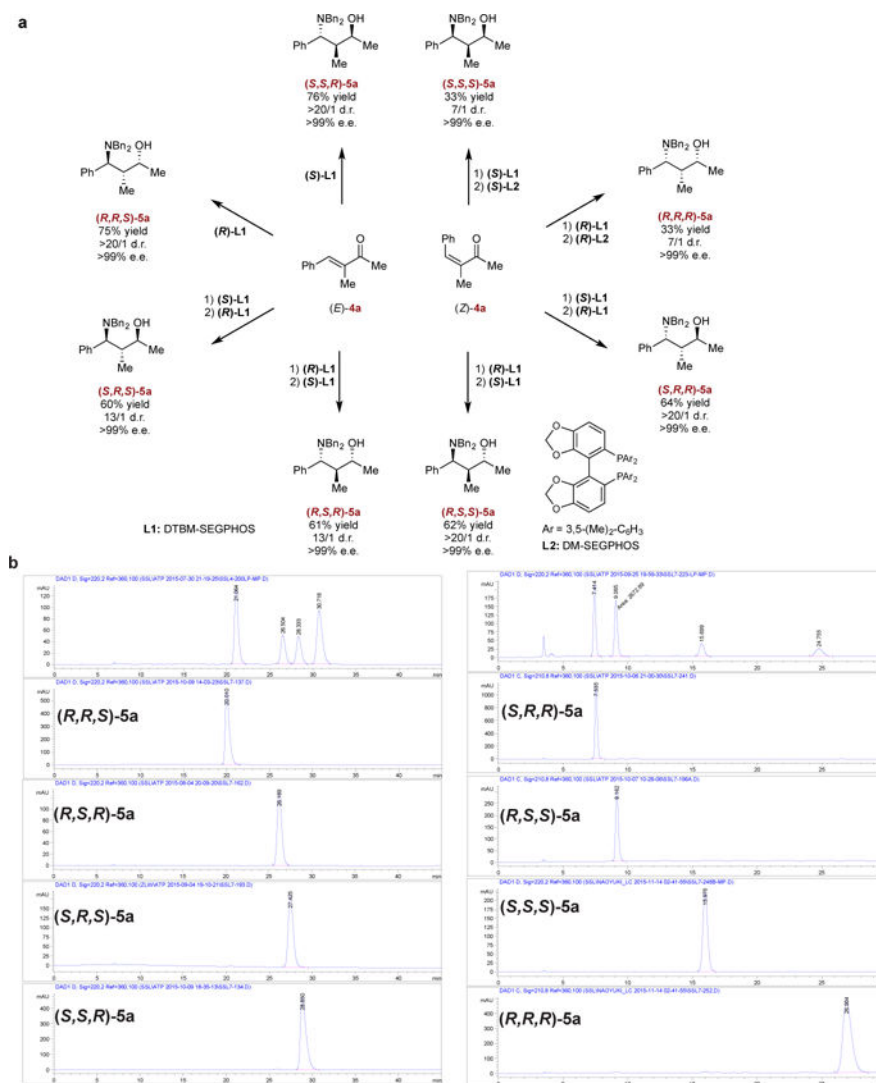
**Figure 3. All stereoisomers of amino alcohols from enals**

**a** Reaction using (*S*)-**L1** and (*E*)-2-amyl-cinnamaldehyde (**1b**) under the standard conditions; \*using (*R*)-**L1** instead of (*S*)-**L1**; †using (*Z*)-**1b** instead of (*E*)-**1b**. **b** Reaction using (*S*)-**L1**, (*E*)-2-methyl-cinnamaldehyde (**1a**) and **2j** under the standard conditions; \* using (*R*)-**L1** instead of (*S*)-**L1**; ‡using (*Z*)-**1a** instead of (*E*)-**1a**; #using *ent*-**2j** instead of **2j**.



**Figure 4. Asymmetric hydrosilylation/hydroamination of enones**

Top row, reaction studied; Bottom rows, substrate scope. Isolated yields are reported (average of two runs on 1.0 mmol scale). Diastereomeric ratios (d.r.) were determined by GC and NMR analysis. Enantiomeric excesses (e.e.) were determined by HPLC analysis. \* The absolute and relative stereochemistry of **5a** was determined to be (*S,S,R*) by single crystal X-ray diffraction. See Supplementary Information for details.



**Figure 5. All eight stereoisomers of amino alcohols from enones**

**a** Access to all stereoisomers via reaction using (*E*)- or (*Z*)-**4a** with catalyst permutation in each step. Isolated yields are reported. Diastereomeric ratios (d.r.) were determined by NMR analysis using a crude reaction mixture. **b** HPLC traces of all stereoisomeric amino alcohol samples. See Supplementary Information for details.