Copper-catalysed enantioselective stereodivergent synthesis of amino alcohols

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The chirality, or 'handedness', of a biologically active molecule can alter its physiological properties. Thus 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. Despite many advances in asymmetric synthesis, developing general and practical strategies for obtaining all possible stereoisomers of an organic compound that has multiple contiguous stereocentres remains a challenge. Here, we report a stereodivergent copper-based approach for the expedient construction of amino alcohols with high levels of chemo-, regio-, diastereo- and enantioselectivity. Specifically, we synthesized these amino-alcohol products using sequential, copper-hydride-catalysed 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 stereocentres. We leveraged catalyst control and stereospecificity simultaneously to attain exceptional control of the product stereochemistry. Beyond the immediate utility of this protocol, our strategy could inspire the development of methods that provide complete sets of stereoisomers for other valuable synthetic targets.

Different stereoisomers of drugs can have distinct therapeutic properties or adverse effects, because of the chiral environments provided by 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 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, b). For these reasons, regulatory agencies require the bioactivity of all stereoisomers of pharmaceutical candidates to be evaluated during the drug discovery and development process. Furthermore, manufacturers must develop assays by which 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 important research topic.

In the past few decades, there has been tremendous progress in the field of asymmetric synthesis, providing numerous chiral biologically active compounds with high levels of selectivity. However, although asymmetric catalysis has allowed enantiomers of a chiral molecule to be obtained with equal ease, relatively few methods can provide a unified route that leads to all possible stereoisomers of products containing multiple contiguous stereocentres. Thus, full control of absolute and relative stereochemical configuration remains an unmet synthetic challenge. Aside from classical techniques in asymmetric catalysis—such as using additives, modifying catalyst structure, and varying substrate-protecting groups—multicatalytic approaches have been advanced to access the full complement of stereoisomers for certain classes of compounds. For example, MacMillan and colleagues described the novel concept of cycle-specific amino-catalysis, in which two chiral catalysts sequentially perform an iminium/enamine catalysis cascade to functionalize enals selectively. More recently, Carreira and colleagues demonstrated an elegant dual catalyst system for independently controlling the two stereocentres during the α-allylation of branched aldehydes. Nonetheless, a rapid and predictable way to access complete stereoisomeric sets of products bearing multiple stereocentres (for example, three contiguous stereocentres), using readily available precursors and based on a single catalyst system, remains underdeveloped but is highly desirable.

Optically pure amino alcohols are important structural elements that are frequently found in pharmaceutical agents and biologically active natural products. These compounds are also 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.

Figure 1 | Varying biological activity of some different stereoisomers, and our strategy for constructing all stereoisomers of amino alcohols.

a. Different enantiomers give distinct activities in biological systems.

b. Stereoisomeric amino alcohols (esters) and their biological activities.

c. Bottom, our proposed one-pot synthesis protocol for forming all stereoisomers of amino alcohols via selective hydrosilylation/hydroamination reactions. The start point is an (E)- or (Z)-enal or enone, which is chemoselectively reduced by a CuH-based catalyst to yield corresponding allylic alcohols, which then undergo regio- and stereoselective hydroamination to afford amino-alcohol products bearing multiple contiguous stereocentres. Further details are in Fig. 2. Top, undesired potential side reactions. ‘L’ denotes ‘ligand’. Red bonds highlight different stereocentres.
Isolated yields are reported (average of two runs on 0.5 mmol scale). Top row, the reaction studied here; bottom rows, substrate scope.

Asymmetric hydrosilylation/hydroamination of enals.

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 be ideal precursors to amino alcohols. In particular, we anticipated that, in one synthetic operation, a CuH-based catalyst could reduce enals and enones chemoselectively to the corresponding allylic alcohols, which would then undergo regio- and stereoselective hydrosilylation to afford amino-alcohol products bearing multiple contiguous stereocentres (Fig. 1c). Because of the synergetic nature of the hydrosilylation process, we reasoned that this two-step sequence would be stereospecific with respect to olefin geometry. Thus, effective catalyst control would allow all diastereomeric possibilities to be generated through the appropriate choice of substrate geometry (E or Z) and ligand enantiomer (R or S).

While the asymmetric hydrosilylation of ketones using a copper catalyst is a well-known process, we were aware that 1,2-reduction of \( \alpha,\beta\)-unsaturated carbonyl compounds by CuH is less favourable than 1,4-reduction, owing to the inherent preference of copper to coordinate to the olefin via soft-soft interactions\(^{28}\). Previous work\(^{29,30}\) suggested that control of the regioselectivity in the CuH reduction of Michael acceptors was sensitive to subtle variations in the steric and electronic properties of the ligand and of the substituents of substrates. On the other hand, controlling the regio- and stereoselectivity of the hydrosilylation step is also non-trivial\(^{25}\), because of the steric and electronic bias of the allylic silylether intermediates and potential matched/mismatched effects between substrates and chiral catalysts. The copper-based catalyst system described here alleviates these problems, providing 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 (Fig. 2; compound 1a) with an excess of dimethoxyethylsilane in the presence of 5 mol% of copper acetate and (S)-DTBM-SEGPHOS ((S)-(++)-5,5'-bis(di3,5-di-tert-butyl-4-methoxyphenyl)phenyl]-4,4’-bi-1,3-benzodioxole; (S)-L1) at room temperature for 15 minutes. We observed neither the conventional 1,4-reduction product nor the over-reduced saturated alcohol, 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 with a 95% yield and with complete diastereo- and enantioselectivity (diastereometric ratio (d.r) > 20/1; enantiomeric excess (e.e.)) > 99%). 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 presence of its 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 benzoxa species and hydrosilane species\(^{22,23}\). L1 was the best ligand among the phosphines screened in terms of both 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 \( \alpha,\beta\)-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, 3i) and a trimethylsilyl group (from the reaction of a vinyl silane) (3l). In addition to acyclic substrates, a cyclic enal and cyclic aminating reagents were both compatible, providing the products with high levels of stereocontrol (3d, 3i, 3k).

Furthermore, substrates bearing a broad range of pharmacetically 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 with excellent enantioselectivity. Additionally, an enal substrate bearing a ketone functional group smoothly underwent
the double hydroisilylation and hydroamination sequence under these conditions, furnishing amino alcohol (3m) bearing three stereocentres 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 described above, we were particularly interested in applying this approach to access all of the possible stereoisomers selectively, with high diastereroselective and enantiocontrol for a given substrate. We felt that using the (Z)-enal substrate would produce the pair of diastereomers that is complementary to the pair realized from the (E)-enal substrate. Accordingly, we subjected (Z)-2-amyl-cinnamaldehyde (1b) to the reaction conditions described above, and produced the desired diastereomeric syn-amino alcohol in high chemical yield with complete diastereoselectivity and enantioselectivity. Thus, by correctly combining the appropriate enantiomer of the CuH catalyst’s ligand with the olefin geometry of the enal substrate, we could readily prepare all four stereoisomers of the amino alcohol (Fig. 3a).

We also found that amino alcohols bearing three stereogenic centres could be generated with excellent catalyst-controlled diastereoselectivity when we used chiral hydroxylamine esters. The existing ω-stereocentre on chiral aminating reagents did not interfere with the stereoselectivity when applied to our catalyst system. Thus, all eight stereoisomers of the amino alcohol (3n) were easily constructed with 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 using 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 stereocentres. Basing our protocol on Lipshutz and colleagues’ work on the asymmetric CuH-catalysed 1,2-reduction of enones, we found that the 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)2-L1 complex. We added the aminating reagent to the reaction mixture while heating the mixture at 55 °C, furnishing compound (5a) at 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) with 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, the less-substituted product (5h) could be obtained with high enantioselectivity and a synthetically useful diastereomeric ratio from benzylideneacetone.

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 using (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 then the resulting chiral allylic alcohol was isolated and subjected to hydroamination conditions using a copper catalyst based on (R)-L1. Use of enantiomeric ligands for the one-pot and ligand-switch protocols yielded (R,R,S)-5a 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 using 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 owing to the unfavourable steric interactions between the intermediate chiral (Z)-allylic alcohol and the L1-based catalyst. Accordingly, we selected a less bulky ligand, DM-SEGPHOS [5,5′-bis(di(3,5-xylene)phosphino)-4,4′-bi-1,1,3-benzodioxole; L2], for the hydrosilylation step to obtain these products. Ultimately, all eight stereoisomers of 5a were prepared expeditiously in one to two steps with useful isolated yields (33% to 76%), with complete enantioselectivity (>99% e.e.) and good to excellent diastereoselectivity (7/1 to >20/1 produced in the reaction mixture before purification) (Fig. 5a).

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 asterisk indicates where 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.

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We also found that amino alcohols bearing three stereogenic centres could be generated with excellent catalyst-controlled diastereoselectivity when we used chiral hydroxylamine esters. The existing ω-stereocentre on chiral aminating reagents did not interfere with the stereoselectivity when applied to our catalyst system. Thus, all eight stereoisomers of the amino alcohol (3n) were easily constructed with 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 using either enantiomer of the chiral catalyst (Fig. 3b).
reported. Diastereomeric ratios (d.r.) were determined by NMR analysis using a crude reaction mixture. b, HPLC traces of all stereoisomic amino-alcohol samples. See Supplementary Information for details.

Received 24 November 2015; accepted 27 January 2016.

Published online 28 March 2016.

Figure 5 | All eight stereoisomers of amino alcohols synthesized from enones. a, Access to all stereoisomers via a reaction using (E)- or (Z)-4a, showing the catalyst permutations in each step. Isolated yields are to readily obtained pure geometric alkene isomers—factors that might be generally applicable to the development of other enantio- and diastereodivergent hydrofunctionalization reactions.

Acknowledgements We thank the National Institutes of Health (grant GM-58503 to S.L.B.). The content of this paper is solely our responsibility and does not necessarily represent the official views of the National Institutes of Health. We thank Y.-M. Wang and M. T. Pirmot for help preparing the manuscript. The departmental X-ray diffraction instrumentation was purchased with the help of funding from the National Science Foundation (CHE-0946721). We thank P. Müller for Kray crystallographic analysis of compound 5a.

Author Contributions S.-L.S. and S.L.B. conceived the idea and designed the research. S.-L.S. and Z.L.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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Addendum: Copper–catalysed enantioselective stereodivergent synthesis of amino alcohols
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Addendum to: Nature https://doi.org/10.1038/nature17191, published online 28 March 2016.

In the Supplementary Information of this Letter, we described the use of dimethoxymethylsilane (DMMS), which is used in excess in the reported reaction. This compound is categorized by several vendors as an H318, category 1 (causing serious eye damage) and by other vendors as an H319, category II (an eye irritant). We have now found a more practical and safer modified method, which requires a small change in the workup procedure. Rather than evaporation of volatiles before workup, the excess DMMS is quenched with ammonium fluoride. This method has been experimentally verified and does not affect the results or conclusions of the original Letter. The Supplementary Information of this Addendum is the modified Supplementary Information, containing the revised workup procedure (pages S7, S23, S29 and S30) but otherwise unchanged.

Supplementary information is available in the online version of this Addendum.