LETTER

doi:10.1038/nature17191

Copper-catalysed enantioselective stereodivergent synthesis of amino alcohols

Shi-Liang Shi[1], Zackary L. Wong[1] & Stephen L. Buchwald[1]

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[1,2]. 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[3]. Here, we report a stereodivergent copper-based approach for the expeditious 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[1,2]. 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[1,2].

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[3]. 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[3]. Aside from classical techniques in asymmetric catalysis—such as using additives[4,5], modifying catalyst structure[6–10], and varying substrate-protecting groups[11,12]—multicatalytic approaches[13–16] have been advanced to access the full complement of stereoisomers for certain classes of compounds. For example, MacMillan and colleagues[13,14] 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[15,16] 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 (Fig. 1b)[17]. These compounds are also building blocks for catalysts and auxiliaries in asymmetric synthesis. We speculated that our recently disclosed catalytic systems[18–23] for enantioselective hydroamination[24,25] based on copper hydride (CuH) intermediates[26]

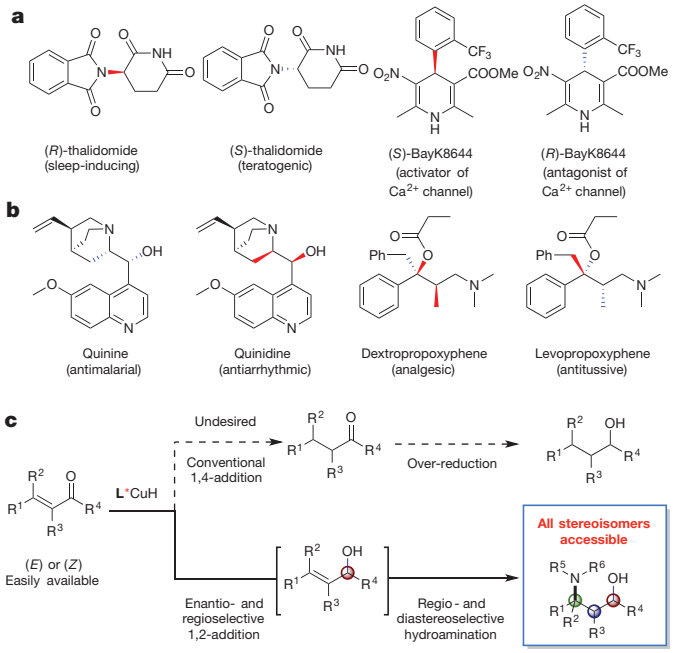

Figure 1 | Varying biological activity of some different stereoisomers, and our strategy for constructing all stereoisomers of amino alcohols. **a**, Different enantiomers give distinct activities in biological systems. **b**, Stereoisomeric amino alcohols (esters) and their biological activities. **c**, 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.

[1]Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA.

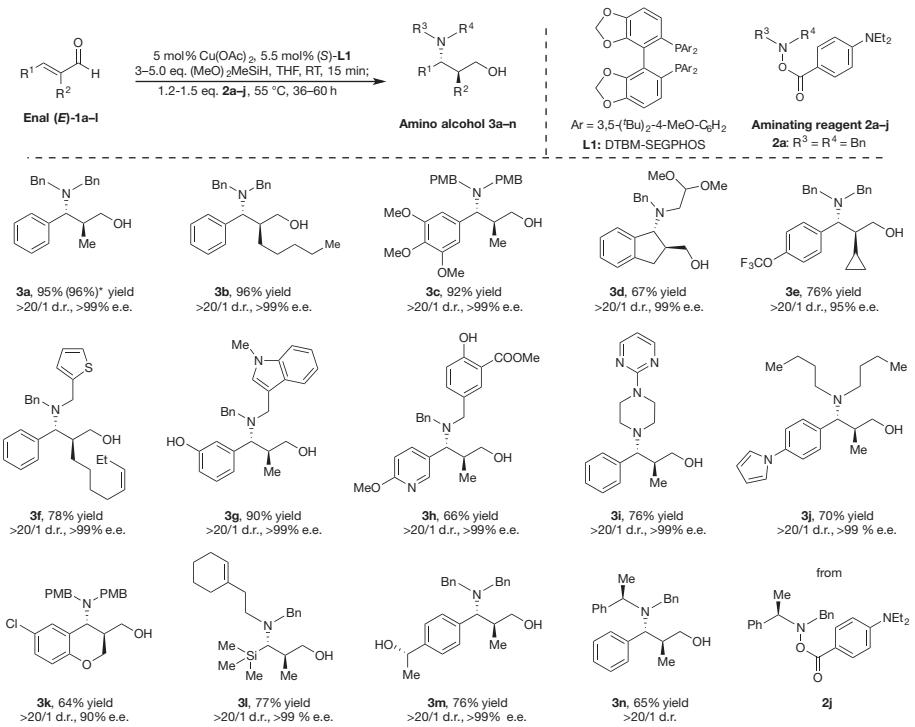

Figure 2 | Asymmetric hydrosilylation/hydroamination of enals. Top row, the reaction studied here; bottom rows, substrate scope. Isolated yields are reported (average of two runs on 0.5 mmol scale). Diastereomeric ratios (d.r.) were determined by gas-chromatography (GC) and nuclear magnetic resonance (NMR) analysis. Enantiomeric excesses (e.e.) were determined by high-performance liquid-chomatography (HPLC) analysis using chiral stationary phases. *Reaction was conducted on 5 mmol scale. See Supplementary Information for details. Bn, benzyl; PMB, *p*-methoxylbenzyl; RT, room temperature; THF, tetrahydrofuran.

and electrophilic aminating reagents[27] 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 hydroamination to afford amino-alcohol products bearing multiple contiguous stereocentres (Fig. 1c). Because 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 all diastereomeric possibilities to be generated 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[28], we were aware that 1,2-reduction of α,β-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[26]. 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 hydroamination step is also non-trivial[25], because of the steric and electronic bias of the allylic silyl ether 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 dimethoxymethylsilane in the presence of 5 mol% of copper acetate and (*S*)-DTBM-SEGPHOS ((*S*)-(+)-5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl) phosphino]-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 σ-bond metathesis between the corresponding copper benzoate 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 β-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 trimethylsilanyl 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 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 with excellent enantioselectivity. Additionally, an enal substrate bearing a ketone functional group smoothly underwent

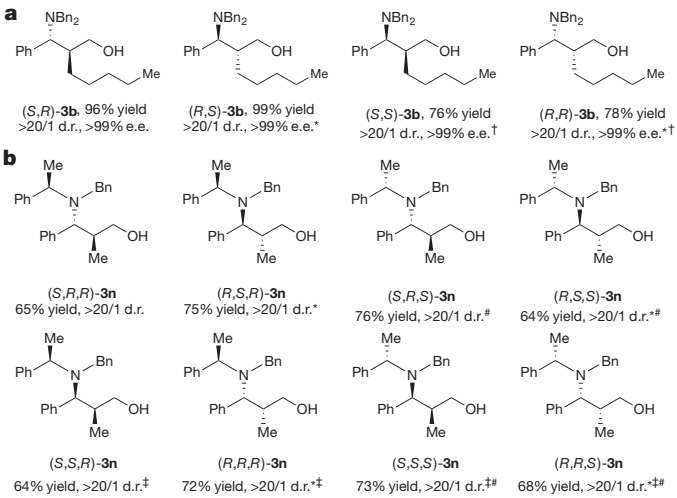

Figure 3 | All stereoisomers of amino alcohols from enals. a, Reaction using (*S*)-**L1** and (*E*)-2-amyl-cinnamaldehyde (**1b**) under the standard conditions. Asterisks denote reactions using (*R*)-**L1** instead of (*S*)-**L1**. The dagger denotes a reaction using (*Z*)-**1b** instead of (*E*)-**1b**. **b**, Reaction using (*S*)-**L1**, (*E*)-2-methyl-cinnamaldehyde (**1a**) and **2j** under the standard conditions. Asterisk denotes the use of (*R*)-**L1** instead of (*S*)-**L1**. The double dagger denotes the use of (*Z*)-**1a** instead of (*E*)-**1a**. The hash symbol indicates reactions using *ent*-**2j** instead of **2j**.

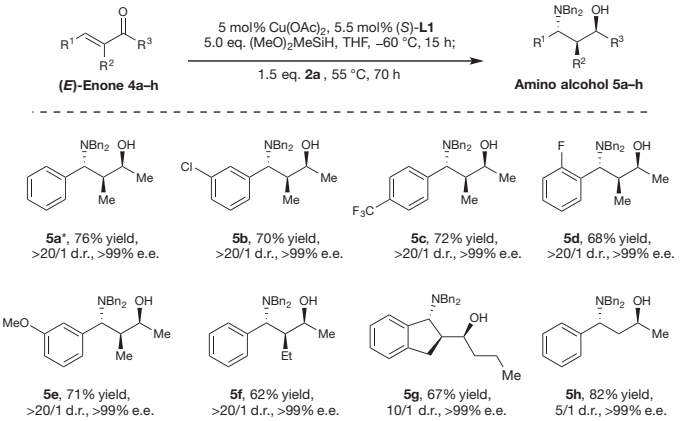

Figure 4 | Asymmetric hydrosilylation/hydroamination of enones. Top row, the reaction studied here; bottom rows, substrate scope. Isolated yields are reported (average of two runs on 1.0 mmol scale). Diastereomeric ratios (d.r.) were determined by GC and NMR analysis. Enantiomeric excesses (e.e.) were determined by HPLC analysis. The 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.

the double hydrosilylation and hydroamination sequence under these conditions, furnishing amino diol (**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 diasterero- 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 diastereo- 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 corresponding amino alcohol with full control of absolute and relative stereochemistry (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 α-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[30] 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 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 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-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole; **L2**), for the hydroamination step to obtain these products. Ultimately, all eight stereoisomers of **5a** were prepared expediently 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). Upon isolation and chromatography, all isomers were obtained at >20/1 d.r., as confirmed by the high-performance liquid-chromatography traces in Fig. 5b. Thus, the enantioselective hydroamination steps proceeded through excellent catalyst control in all eight cases.

We have developed a unified and stereodivergent strategy for rapidly and predictably constructing amino alcohols that allows all possible stereoisomers of a given product to be synthesized. This protocol assembles two or three contiguous stereocentres, using enal and enone substrates, in a highly selective, copper-catalysed hydrosilylation/hydroamination sequence. Essential to our approach were highly effective catalyst control and the application of a stereospecific process

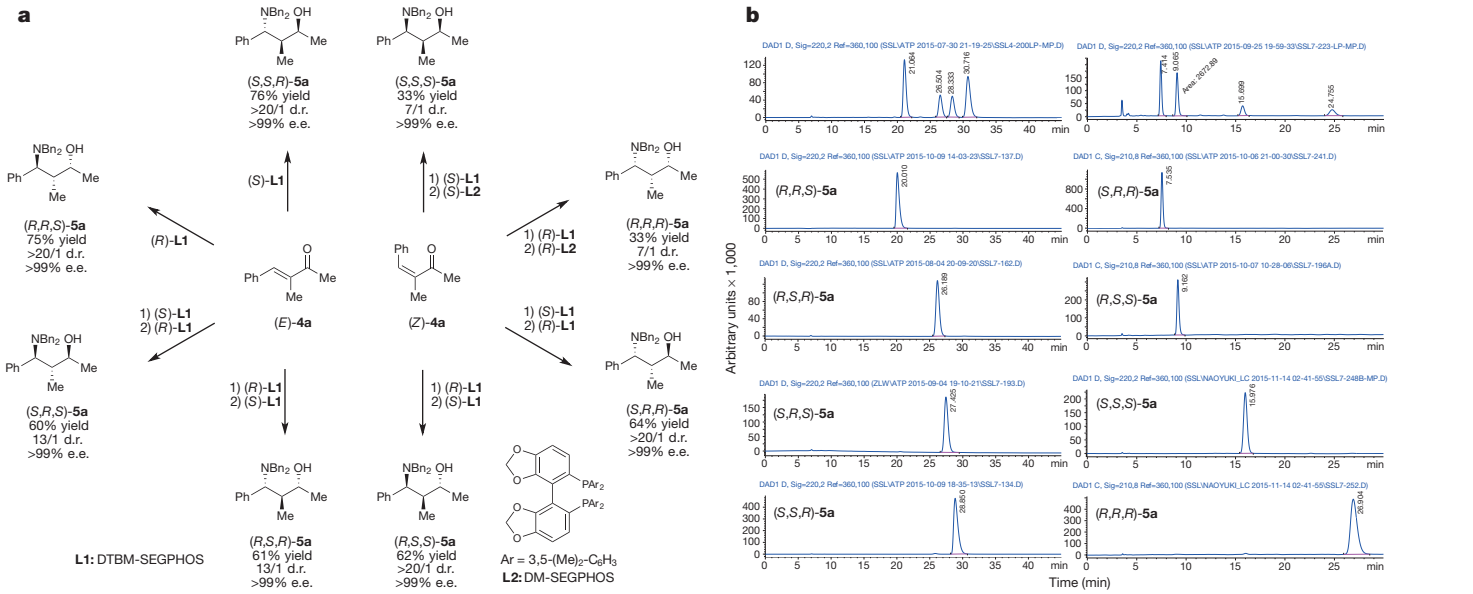

Figure 5 | All eight stereoisomers of amino alcohols synthesized from enones. a, Access to all stereoisomers via a reaction using (*E*)- or (*Z*)-**4a**, showing the catalyst permutations in each step. Isolated yields are reported. Diastereomeric ratios (d.r.) were determined by NMR analysis using a crude reaction mixture. **b**, HPLC traces of all stereoisomeric amino-alcohol samples. See Supplementary Information for details.

to readily obtained pure geometric alkene isomers—factors that might be generally applicable to the development of other enantio- and diastereodivergent hydrofunctionalization reactions.

Received 24 November 2015; accepted 27 January 2016.
Published online 28 March 2016.

1. Jozwiak, K., Lough, W. J. & Wainer, I. W. *Drug Stereochemistry: Analytical Methods and Pharmacology* 3rd edn (Informa, 2012).
2. Wermuth, C. G. *The Practice of Medicinal Chemistry* 3rd edn (Elsevier, 2008).
3. Jacobsen, E. N., Pfaltz, A. & Yamamoto, H. (eds) *Comprehensive Asymmetric Catalysis* Vol. I–III, Suppl. I–II (Springer, 1999).
4. Tian, X. *et al.* Diastereodivergent asymmetric sulfa-Michael additions of α-branched enones using a single chiral organic catalyst. *J. Am. Chem. Soc.* **133,** 17934–17941 (2011).
5. McInturff, E. L., Yamaguchi, E. & Krische, M. J. Chiral-anion-dependent inversion of diastereo- and enantioselectivity in carbonyl crotylation via ruthenium-catalyzed butadiene hydrohydroxyalkylation. *J. Am. Chem. Soc.* **134,** 20628–20631 (2012).
6. Wang, B., Wu, F., Wang, Y., Liu, X. & Deng, L. Control of diastereoselectivity in tandem asymmetric reactions generating nonadjacent stereocenters with bifunctional catalysis by cinchona alkaloids. *J. Am. Chem. Soc.* **129,** 768–769 (2007).
7. Yan, X.-X. *et al.* Highly diastereoselective switchable enantioselective Mannich reaction of glycine derivatives with imines. *J. Am. Chem. Soc.* **130,** 14362–14363 (2008).
8. Luparia, M. *et al.* Catalytic asymmetric diastereodivergent deracemization. *Angew. Chem. Int. Edn* **50,** 12631–12635 (2011).
9. Lu, G., Yoshino, T., Morimoto, H., Matsunaga, S. & Shibasaki, M. Stereodivergent direct catalytic asymmetric mannich-type reactions of α-isothiocyanato ester with ketimines. *Angew. Chem. Int. Edn* **50,** 4382–4385 (2011).
10. Mechler, M. & Peters, R. Diastereodivergent asymmetric 1,4-addition of oxindoles to nitroolefins by using polyfunctional nickel-hydrogen-bond-azolium catalysts. *Angew. Chem. Int. Edn* **54,** 10303–10307 (2015).
11. Lee, E. C., Hodous, B. L., Bergin, E., Shih, C. & Fu, G. C. Catalytic asymmetric Staudinger reactions to form β-lactams: an unanticipated dependence of diastereoselectivity on the choice of the nitrogen substituent. *J. Am. Chem. Soc.* **127,** 11586–11587 (2005).
12. Huber, J. D. & Leighton, J. L. Highly enantioselective imine cinnamylation with a remarkable diastereochemical switch. *J. Am. Chem. Soc.* **129,** 14552–14553 (2007).
13. Huang, Y., Walji, A. M., Larsen, C. H. & MacMillan, D. W. C. Enantioselective organo-cascade catalysis. *J. Am. Chem. Soc.* **127,** 15051–15053 (2005).
14. Simmons, B., Walji, A. M. & MacMillan, D. W. C. Cycle-specific organocascade catalysis: application to olefin hydroamination, hydro-oxidation, and amino-oxidation, and to natural product synthesis. *Angew. Chem. Int. Edn* **48,** 4349–4353 (2009).
15. Krautwald, S., Sarlah, D., Schafroth, M. A. & Carreira, E. M. Enantio- and diastereodivergent dual catalysis: α-allylation of branched aldehydes. *Science* **340,** 1065–1068 (2013).
16. Schindler, C. S. & Jacobsen, E. N. A new twist on cooperative catalysis. *Science* **340,** 1052–1053 (2013).
17. Nugent, T. C. *Chiral Amine Synthesis: Methods, Developments and Applications* (Wiley VCH, 2010).
18. Zhu, S., Niljianskul, N. & Buchwald, S. L. Enantio- and regioselective CuH-catalyzed hydroamination of alkenes. *J. Am. Chem. Soc.* **135,** 15746–15749 (2013).
19. Shi, S.-L. & Buchwald, S. L. Copper-catalyzed selective hydroamination reactions of alkynes. *Nature Chem.* **7,** 38–44 (2015).
20. Zhu, S. & Buchwald, S. L. Enantioselective CuH-catalyzed anti-Markovnikov hydroamination of 1, 1-disubstituted alkenes. *J. Am. Chem. Soc.* **136,** 15913–15916 (2014).
21. Yang, Y., Shi, S.-L., Niu, D., Liu, P. & Buchwald, S. L. Catalytic asymmetric hydroamination of unactivated internal olefins to aliphatic amines. *Science* **349,** 62–66 (2015).
22. Niu, D. & Buchwald, S. L. Design of modified amine transfer reagents allows the synthesis of α-chiral secondary amines via CuH-catalyzed hydroamination. *J. Am. Chem. Soc.* **137,** 9716–9721 (2015).
23. Bandar, J. S., Pirnot, M. T. & Buchwald, S. L. Mechanistic studies lead to dramatically improved reaction conditions for the Cu-catalyzed asymmetric hydroamination of olefins. *J. Am. Chem. Soc.* **137,** 14812–14818 (2015).
24. Miki, Y., Hirano, K., Satoh, T. & Miura, M. Copper-catalyzed intermolecular regioselective hydroamination of styrenes with polymethylhydrosiloxane and hydroxylamines. *Angew. Chem. Int. Edn* **52,** 10830–10834 (2013).
25. Hannedouche, J. & Schulz, E. Asymmetric hydroamination: a survey of the most recent developments. *Chemistry* **19,** 4972–4985 (2013).
26. Deutsch, C., Krause, N. & Lipshutz, B. H. CuH-catalyzed reactions. *Chem. Rev.* **108,** 2916–2927 (2008).
27. Barker, T. J. & Jarvo, E. R. Developments in transition-metal-catalyzed reactions using electrophilic nitrogen sources. *Synthesis* **24,** 3954–3964 (2011).
28. Lipshutz, B. H., Noson, K., Chrisman, W. & Lower, A. Asymmetric hydrosilylation of aryl ketones catalyzed by copper hydride complexed by nonracemic biphenyl bis-phosphine ligands. *J. Am. Chem. Soc.* **125,** 8779–8789 (2003).
29. Chen, J.-X. *et al.* Highly chemoselective catalytic hydrogenation of unsaturated ketones and aldehydes to unsaturated alcohols using phosphine-stabilized copper(I) hydride complexes. *Tetrahedron* **56,** 2153–2166 (2000).
30. Moser, R., Boskovic, Z. V., Crowe, C. S. & Lipshutz, B. H. CuH-catalyzed enantioselective 1,2-reductions of α,β-unsaturated ketones. *J. Am. Chem. Soc.* **132,** 7852–7853 (2010).

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

Acknowledgements We thank the National Institutes of Health (grant GM-58160 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. Pirnot 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 X-ray 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.

Author Information Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to S.L.B. (sbuchwal@mit.edu).