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CuH-Catalyzed Enantioselective 1,2-Reductions of α,β-Unsaturated Ketones

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Asymmetric copper hydride chemistry has become an especially powerful tool for controlling chirality in a variety of substrate types.[1] Most notably, nonracemically ligated CuH can be used to direct remarkably selective hydride delivery to the β-site in a variety of Michael acceptors (Scheme 1, path A). In the absence of extended conjugation, asymmetric 1,2-additions of CuH are now known for aromatic ketones,[2] diaryl[3] and heteroaromatic ketones,[4] and imines.[5] Redirecting the natural tendency of copper complexes away from additions in a 1,4-sense can be challenging. The potential to alter, in the achiral manifold, such regioselectivity toward the 1,2-mode by a "subtle interplay of steric and electronic factors" of the phosphine ligand on copper was recognized years ago by Stryker.[6] Overcoming the inherent mechanistic preference for initial d−π* complexation associated with, for example, Cu(I)−olefin soft−soft interactions in α,β-unsaturated ketones remains an unsolved problem, notwithstanding the synthetic potential of the resulting nonracemic allylic alcohols (Scheme 1, path B). While isolated examples of copper-catalyzed enantioselective 1,2-reductions of enones exist,[7] any semblance of a general asymmetric protocol resulting from the correlation of substrate substitution pattern with ligand biases and/or tuning of reaction conditions for this important transformation is still lacking. Herein, we describe a new methodology for the enantioselective CuH-catalyzed 1,2-reduction of α-substituted unsaturated ketones leading to secondary allylic alcohols (Scheme 1).

As illustrated in Table 1, optimization studies using enone **1** revealed that (1) 1,2-addition to arrive at cinnamyl alcohol derivative **2** is strongly favored over conjugate addition; (2) enantiomeric excesses (ee's) on the order of 90% could be achieved; (3) ligands in both the SEGPHOS[8] and BIPHEP[9] series give similar levels of induction; (4) diethoxymethylsilane (DEMS) as the stoichiometric source of hydride[10] gives the best ee's; (5) Et_2O is the solvent of choice; (6) reactions should be run at −25 °C for optimal conversion and enantioselectivity; and (7) the sense of induction is such that (**L2**)CuH[11] produces the *S*-allylic alcohol while (**L3b**)CuH leads to the enantiomeric product.

Several additional examples of acyclic and cyclic enones can be found in Table 2. α′-Substitution with an alkyl group other than methyl in **1** led to the desired product **3** in high ee using **L3b**, while α-substitution with residues including ethyl and *n*-pentyl (**4** and **5**) gave consistently high yields and ee's of 1,2-addition products with one or both ligand systems.[12] Modified educts with either α-phenyl (**6**) or α-bromo (**7**) likewise led to 1,2-adducts, albeit in somewhat lower ee's. Replacing the β-phenyl group in **1** with an alkyl moiety (as in **8**) did not alter the outcome of the reaction.

The impact of varying the substituents on a β-aryl ring in an educt was also investigated. Electron-donating as well as electron-withdrawing groups were tolerated and gave secondary allylic alcohols **9**−**14** in high yields and good ee's. Surprisingly, a strong electron-withdrawing group (e.g., a nitro group) led to a significant amount of the corresponding 1,4-reduced product when **L2** was used (see the Supporting Information), whereas **L3b** gave the desired alcohol **13** with excellent regio- and stereocontrol.[12]

Various cyclic arrays (**15**−**17**) fit into the anticipated pattern of regio- and enantiocontrol using (DTBM-SEGPHOS)CuH. The mild

Scheme 1. Pathways for Addition of CuH to Unsaturated Ketones

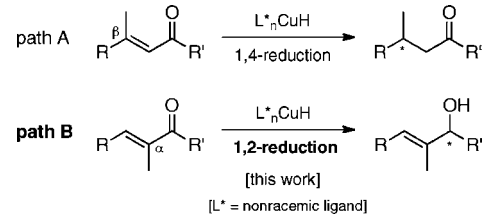
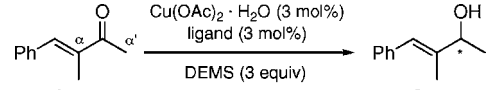


Table 1. Selected Optimization Conditions for Regio- and Stereocontrolled 1,2-Reductions[a]



entry	ligand	solvent	*T* (°C)	yield of **2** (%)[b]	ee of **2** (%)[c]
1	**L1**	THF	rt	90	50 (*S*)
2	**L2**	THF	rt	78	75 (*S*)
3	**L2**	THF	−25	87	86 (*S*)
4	**L2**	Et_2O	−25	83 (98)[d]	91 (*S*)
5[e]	**L2**	Et_2O	−35	n.d.	n.d.
6	**L3a**	Et_2O	−25	96	89 (*R*)
7	**L3b**	Et_2O	−25	95	91 (*R*)
8	**L3c**	Et_2O	−25	99	90 (*S*)
9[f]	BDP	THF	rt	−	−

[a] Performed on a 0.1 mmol scale in 0.3 mL of solvent. See the Supporting Information for full details. [b] ^1H NMR yield using Ph_3CH as internal standard. [c] Determined by chiral HPLC analysis. The absolute stereochemistry was determined by comparing the optical rotation to that of the known compound. [d] Isolated yield (0.25 mmol scale). [e] Low conversion after prolonged reaction time. [f] A 1,2/1,4 ratio of 1:7 and a 60% isolated yield of the 1,4-reduced enone were obtained.

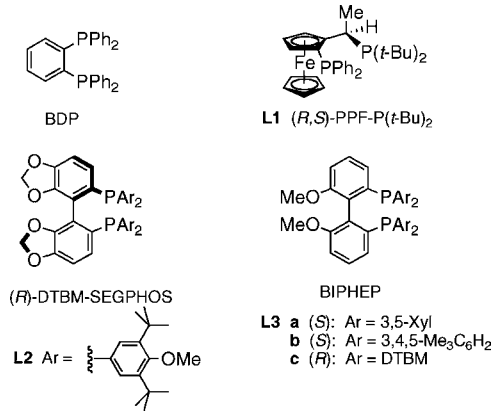


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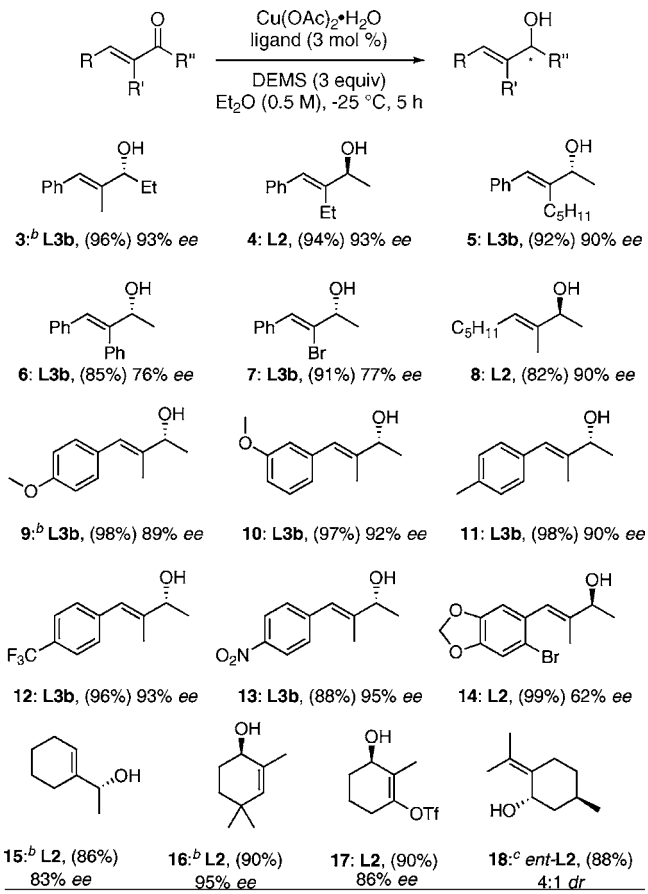
Table 2. CuH-Catalyzed Asymmetric 1,2-Reductions of α-Substituted Enones[a]

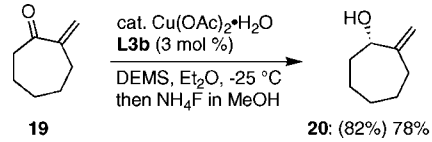


[a] Reactions were carried out on a 0.25 mmol scale in 0.5 mL of Et_2O. Isolated yields after column chromatography are given in parentheses. The reported ee's were determined by chiral HPLC or GC analyses. The stereochemistry shown was determined by analogy to **2** (see Table 1). [b] Absolute stereochemistry determined by comparing the optical rotation with that of the known compound. [c] See text. [d] See the Supporting Information.

conditions involved allowed for isolation of a nonracemic cyclohexenol **17** bearing a cross-coupling partner, vinyl triflate, without losses due to ring fragmentation observed with harsher reducing agents.[13] While treatment of (*R*)-pulegone with catalytic [(*R*)-**L2**]CuH gave the highly favored anticipated cis product (93%; 99:1 dr), CuH complexed by *ent*-**L2** led predominantly to the less common trans isomer **18** (88%; 4:1 dr).[14]

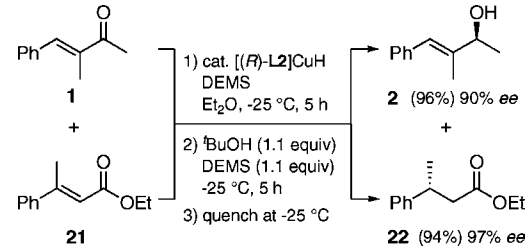
The influence exerted by an α-substituent is further highlighted by the case of exocyclic olefin-containing enone **19**. Notwithstanding full accessibility of CuH to the *β*-site, delivery of hydride took place in a 1,2-fashion, giving allylic alcohol **20** in 78% ee (Scheme 2).

Scheme 2. (**L3b**)CuH-Catalyzed 1,2-Addition to a *β*,*β*-*Un*substituted Enone



The potential for a ligated CuH complex to induce asymmetry in two distinct functional groups *within the same pot* is illustrated in Scheme 3. Simultaneous exposure of enone **1** and enoate **21**

Scheme 3. One Reagent, Two Reactions: One-Pot Asymmetric 1,2-Reduction of an Enone and 1,4-Reduction of an Enoate



(1:1 ratio) to conditions first favoring enone 1,2-reduction gave **2**, with <5% conjugate reduction of **1** being observed. Without isolation, addition of *t*-BuOH (1.1 equiv), as originally reported by Stryker,[6,15] was used to enhance the rate of catalyst regeneration. The presence of this additive along with added silane (1.1 equiv) led to the asymmetric 1,4-reduction of **21** to ester **22**. Both processes gave high isolated yields and excellent ee's.

In summary, regioselectivity in reactions of nonracemicaly ligated, in situ-generated CuH can be dramatically shifted to favor asymmetric 1,2-reductions over the normally observed 1,4-reductions of α,*β*-unsaturated ketones. This powerful methodology affords high yields and ee's of the resulting allylic alcohols having defined olefin geometries and central chirality.

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Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Review: Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916. (b) Yun, J.; Kim, D.; Lee, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 2785. (c) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352. (d) Buchwald, S. L.; Aye, Y.; Rainka, M. P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5821. (e) Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4793.
(2) Lipshutz, B. H.; Noson, K.; Chrisman, W. *J. Am. Chem. Soc.* **2001**, *123*, 12917.
(3) Lee, C.-T.; Lipshutz, B. H. *Org. Lett.* **2008**, *10*, 4187.
(4) Lipshutz, B. H.; Lower, A.; Noson, K. *Org. Lett.* **2002**, *4*, 4045.
(5) Lipshutz, B. H.; Shimizu, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 2228.
(6) Chen, J.-X.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2153.
(7) Chemoselective Cu-catalyzed hydrogenation of enals: (a) Shimizu, H.; Sayo, N.; Saito, T. *Synlett* **2009**, 1295. Chemoselective Cu-catalyzed asymmetric hydrogenation of cyclic and acyclic enones: (b) Shimizu, H.; Nagano, T.; Sayo, N.; Saito, T.; Ohshima, T.; Mashima, K. *Synlett* **2009**, 3143. Chemoselective Cu-catalyzed reduction of α,*β*-unsaturated amino ketones: (c) Pelss, A.; Kumpulainen, E. T. T.; Koskinen, A. M. P. *J. Org. Chem.* **2009**, *74*, 7598. Chemo- and enantioselective hydrosilylation of enones using monodentate binaphthophosphepine ligands: (d) Junge, K.; Wendt, B.; Addis, D.; Zhou, S.; Das, S.; Beller, M. *Chem. Eur. J.* **2010**, *16*, 68.
(8) Saito, T.; Yokozawa, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.
(9) (a) Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Mueller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.* **1996**, *68*, 131. (b) Schmid, R.; Foricher, J.; Cereghetti, M.; Schonholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370.
(10) Nishiyama, H.; Shiomi, T.; Tsuchiya, Y.; Matsuda, I. *J. Am. Chem. Soc.* **2005**, *127*, 6972.
(11) Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405.
(12) For results obtained using ligands other than the ones shown in Table 2, see the Supporting Information.
(13) (a) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775. (b) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2006**, *128*, 6499.
(14) Ohkuma, T.; Ikehira, H.; Ikariya, T.; Noyori, R. *Synlett* **1997**, 467.
(15) (a) Stryker, J. M.; Mahoney, W. S.; Daeuble, J. F.; Brestensky, D. M. In *Catalysis of Organic Reactions*; Pascoe, W. E., Ed.; Chemical Industries *47*; Marcel Dekker: New York, 1992; pp 29−44. (b) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253.

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