

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

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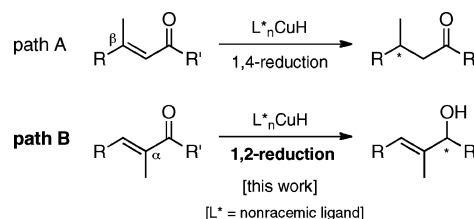
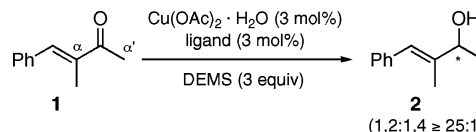
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Asymmetric copper hydride chemistry has become an especially powerful tool for controlling chirality in a variety of substrate types.¹ Most notably, nonracemically ligated CuH can be used to direct remarkably selective hydride delivery to the β -site 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 diaryl³ 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 $d-\pi^*$ 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 SEGPHOS⁸ and BIPHEP⁹ series give similar levels of induction; (4) diethoxymethylsilane (DEMS) as the stoichiometric source of hydride¹⁰ gives the best ee's; (5) Et₂O 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**)CuH¹¹ produces the *S*-allylic alcohol while (**L3b**)CuH leads to the enantiomeric product.

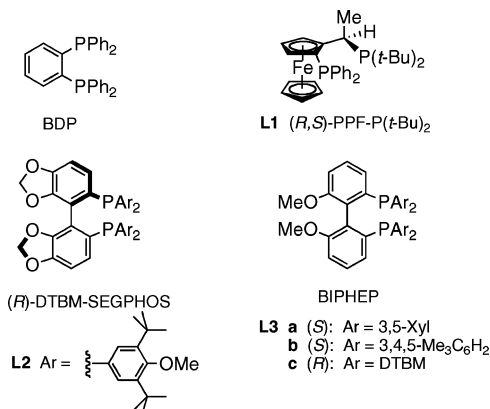
Several additional examples of acyclic and cyclic enones can be found in Table 2. α' -Substitution with an alkyl group other than methyl in **1** led to the desired product **3** in high ee using **L3b**, while α -substitution with residues including ethyl and *n*-pentyl (**4** and **5**) gave consistently 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

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	<i>T</i> (°C)	yield of 2 (%) ^b	ee of 2 (%) ^c
1	L1	THF	rt	90	50 (<i>S</i>)
2	L2	THF	rt	78	75 (<i>S</i>)
3	L2	THF	-25°C	87	86 (<i>S</i>)
4	L2	Et ₂ O	-25°C	83 (98) ^d	91 (<i>S</i>)
5 ^e	L2	Et ₂ O	-35°C	n.d.	n.d.
6	L3a	Et ₂ O	-25°C	96	89 (<i>R</i>)
7	L3b	Et ₂ O	-25°C	95	91 (<i>R</i>)
8	L3c	Et ₂ O	-25°C	99	90 (<i>S</i>)
9 ^f	BDP	THF	rt	—	—

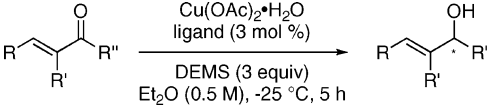
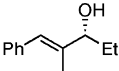
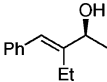
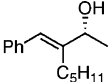
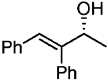
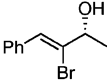
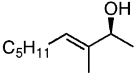
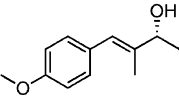
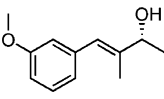
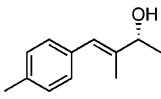
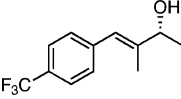
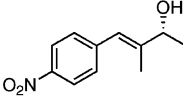
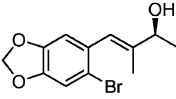
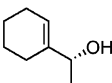
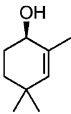
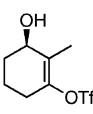
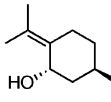
^a Performed on a 0.1 mmol scale in 0.3 mL of solvent. See the Supporting Information for full details. ^b ¹H NMR yield using Ph₃CH as internal standard. ^c Determined by chiral HPLC analysis. The absolute stereochemistry was determined by comparing the optical rotation to that of the known compound. ^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.



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

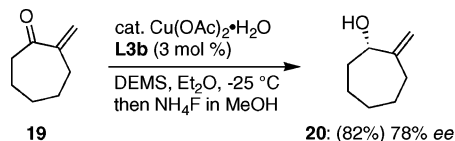
Table 2. CuH-Catalyzed Asymmetric 1,2-Reductions of α -Substituted Enones^a

			
 3:^b L3b , (96%) 93% ee	 4: L2 , (94%) 93% ee	 5: L3b , (92%) 90% ee	
 6: L3b , (85%) 76% ee	 7: L3b , (91%) 77% ee	 8: L2 , (82%) 90% ee	
 9:^b L3b , (98%) 89% ee	 10: L3b , (97%) 92% ee	 11: L3b , (98%) 90% ee	
 12: L3b , (96%) 93% ee	 13: L3b , (88%) 95% ee	 14: L2 , (99%) 62% ee	
 15:^b L2 , (86%) 83% ee	 16:^b L2 , (90%) 95% ee	 17: L2 , (90%) 86% ee	 18:^c ent-L2 , (88%) 4:1 dr

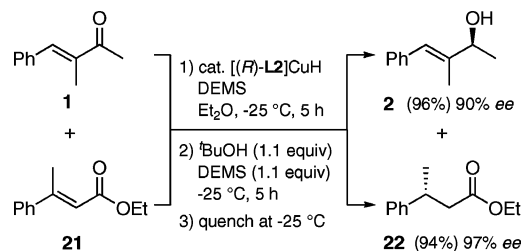
^a Reactions were carried out on a 0.25 mmol scale in 0.5 mL of Et₂O. Isolated yields after column chromatography are given in parentheses. The reported ee's were determined by chiral HPLC or GC analyses. The stereochemistry shown was determined by analogy to **2** (see Table 1). ^b Absolute stereochemistry 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 -Unsubstituted 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 nonracemically 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.

Acknowledgment. Support of this work by the NIH is gratefully acknowledged. We are indebted to Takasago and Roche for supplying the SEGPHOS and BIPHEP ligands, respectively.

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>.

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