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

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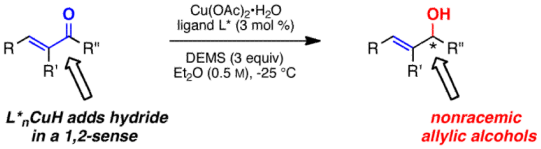
Abstract



The first study describing a general technology for arriving at valued nonracemic allylic alcohols using asymmetric ligand-accelerated catalysis by copper hydride is described.

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 for 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, e.g., with 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 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 **2** is strongly favored over conjugate addition; (2) *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; (7) the sense of

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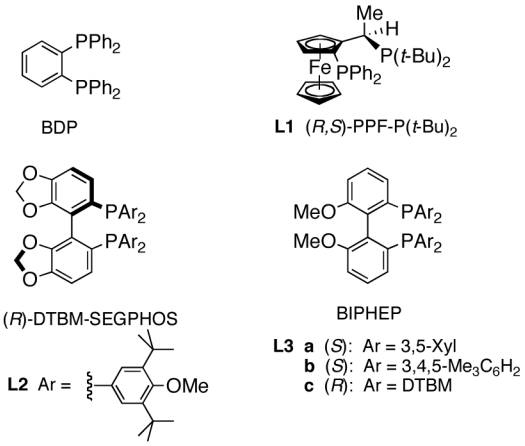
Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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** leads to the desired product **3** in high *ee* using **L3b**, while α-substitution with residues including ethyl and *n*-pentyl (**4** and **5**) gives 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, lead 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 variation in 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 significant amounts of the corresponding 1,4-reduced product when **L2** was used (see SI), 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 enantio-control using (DTBM-SEGPHOS)CuH. The mild conditions involved allow 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 takes place in a 1,2-fashion, giving allylic alcohol **20** in 78% *ee* (Scheme 2).

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** (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 asymmetric 1,4-reduction of **21** to ester **22**, both processes taking place in high isolated yields and excellent *ee*'s.

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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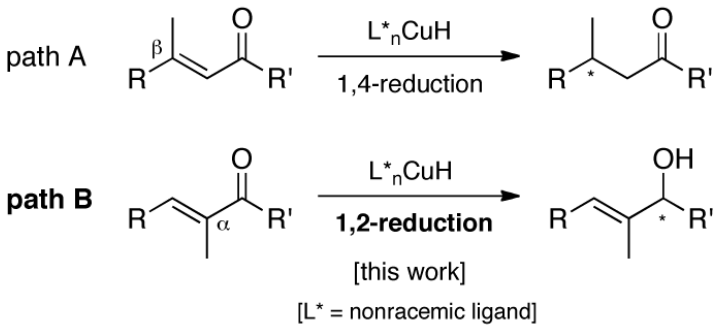
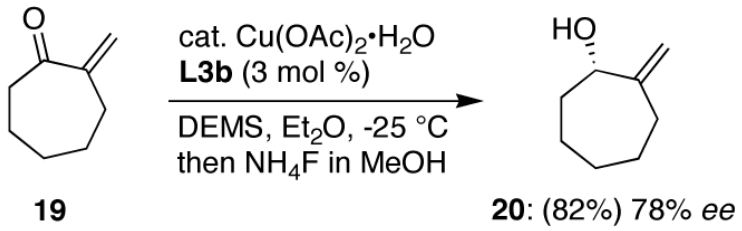
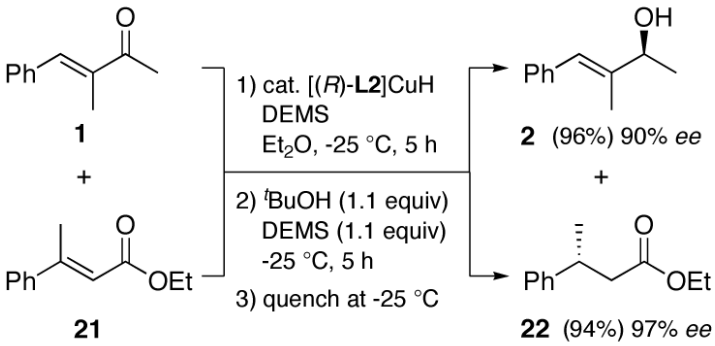


Scheme 1.
Pathways for addition of CuH to unsaturated ketones



Scheme 2.
(**L3b**)CuH catalyzed 1,2-addition to a β,β-*un*substituted enone

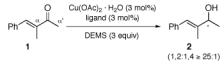


Scheme 3.

One reagent, two reactions: 1-pot asymmetric 1,2-reduction of an enone and 1,4-reduction of an enoate

Table 1

Selected optimization conditions for regio- and stereo-controlled 1,2-reductions (see SI for full details)[a]



Entry	Ligand	Solv.	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 solvent.

[b] By ^1H NMR using Ph_3CH as internal standard.

[c] By chiral HPLC. Absolute stereochemistry was determined by comparing optical rotation to that of the known compound.

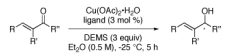
[d] Isolated yield (0.25 mmol scale).

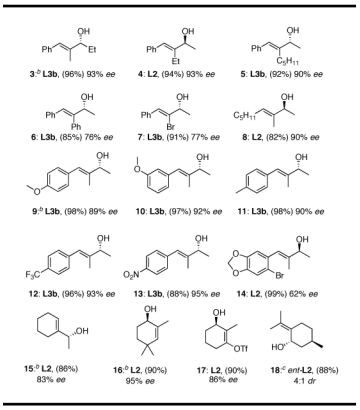
[e] Low conversion after prolonged reaction time.

[f] 1,2-/1,4-ratio = 1:7, 60% isolated yield of 1,4-reduced enone.

Table 2

CuH cat. asymmetric 1,2-reductions of α-substituted enones[a]





[a] Reactions were carried out on 0.25 mmol scale in 0.5 mL Et_2O. Isolated yields after column chromatography are given in parentheses. *Ee*'s were determined by chiral HPLC or GC analyses. Stereochemistry shown was determined by analogy to **2** (see Table 1).

[b] Absolute stereochemistry determined by comparing optical rotations with known compounds.

[c] See text.

[d] See SI.