Asymmetric Conjugate Reduction of α,β-Unsaturated Esters Using a Chiral Phosphine−Copper Catalyst

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Currently, there are few catalysts that can reduce carbon−carbon double bonds to generate products with stereocenters β to carbonyls and with high enantiomeric excess (ee). In this area, asymmetric conjugate additions of nucleophiles to α,β-unsaturated ketones have been intensely investigated (Scheme 1); the best catalysts for these reactions work well for a limited number of substrates and nucleophiles.[1] In some cases, asymmetric hydrogenation catalysts also provide access to products with stereocenters β to carbonyls.[2] Asymmetric conjugate reduction of an α,β-unsaturated carbonyl portion of a molecule can also generate a stereocenter β to a carbonyl.[3] Despite the numerous catalysts available for conjugate reduction,[4] only Pfaltz's chiral semicorrin cobalt system is a highly effective catalyst for asymmetric conjugate reductions. In this system, sodium borohydride is used as the stoichiometric reducing agent.[5,6]

We have begun to investigate whether a copper hydride, with a chiral phosphine ligand, can be used as a catalyst for asymmetric conjugate reduction using a silane reagent as the stoichiometric reductant. Achiral phosphine−copper hydride complexes, such as $[(Ph_3P)CuH]_6$, have been shown to act as catalysts for conjugate reductions of α,β-unsaturated carbonyl compounds in combination with phenylsilane or phenyldimethylsilane.[7,8] We now report that a catalyst formed from *p*-tol-BINAP,[9] CuCl, and NaO*t*-Bu affects the asymmetric conjugate reduction of α,β-unsaturated esters in the presence of 4 equiv of polymethylhydrosiloxane (PMHS) relative to the substrate. We felt that using PMHS, a safe and inexpensive polymer that has been previously employed as a stoichiometric reductant in metal-catalyzed reductions of ketones[10] and imines,[11] would greatly enhance the utility of any process that we would develop.

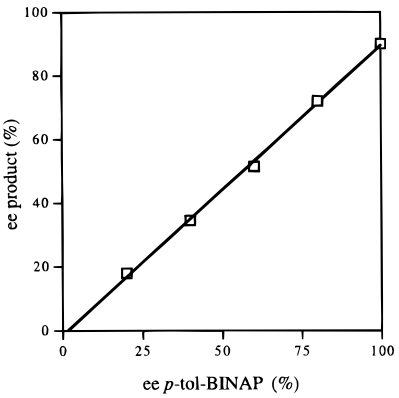
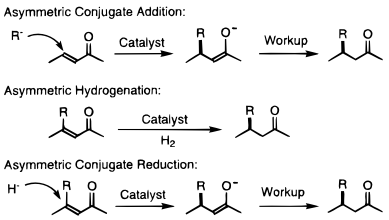


Figure 1. Conjugate reduction of ethyl *trans*-β-methylcinnamate using *p*-tol-BINAP of varying ee. Each data point is the average of two reactions; the line corresponds to a least-squares linear regression of the data with slope = 0.909, intercept = 1.450, and $r^2 = 0.998$.

Scheme 1



In practice, we were able to generate an efficient catalyst in situ by first combining (*S*)-*p*-tol-BINAP, CuCl, and NaO*t*-Bu in toluene, followed by addition of PMHS. For a series of α,β-unsaturated esters, conjugate reductions usually took 24 h at room temperature with 5 mol % catalyst and 4 equiv of PMHS. As shown in Table 1, products were obtained with good ee's and in excellent yields. When the amount of catalyst was lowered to 1 mol %, a longer reaction time was necessary for the reaction to go to completion, but the ee of the product was unchanged. The reaction worked best when carried out under air-free conditions, presumably due to the sensitivity of copper hydrides to oxygen.

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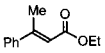
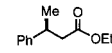
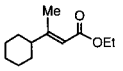
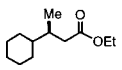
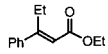
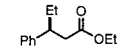
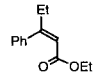
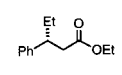
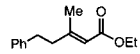
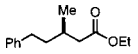
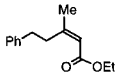
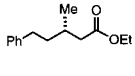
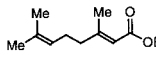
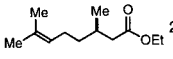
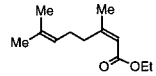
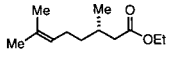
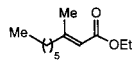
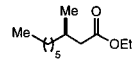
Table 1. Asymmetric Conjugate Reductions with (*S*)-*p*-tol-BINAP, CuCl, NaO*t*-Bu, and PMHS[a]

Entry	Substrate[b]	Product	Time (hr)	Yield[c] (%)	ee[d] (%)
1			24	84	90[e]
2			22	89	92
3			25	98	91
4			27	98	83
5			20	95	84
6			18	96	83
7			25	90	85[f]
8			23	93	80
9			24	94	81

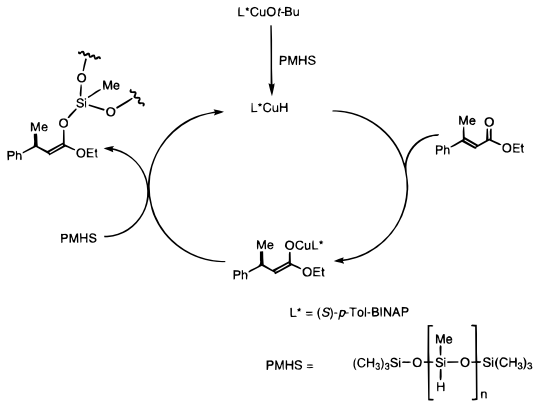
[a] Reactions were run at 0.25 M [olefin] with 4 equiv of PMHS, 5 mol % CuCl, 5 mol % NaO*t*-Bu, and 10 mol % (*S*)-*p*-tol-BINAP at room temperature. [b] All substrates were either >99:1 (*E*) or >99:1 (*Z*). [c] Yields are the average of two isolated yields of >95% purity as determined by GC, ^{1}H NMR, and, for new compounds, elemental analysis. [d] The average ee for two reactions is reported for each entry. [e] Stereochemistry of the product was assigned by hydrolysis to the acid and comparison to commercially available (*S*)-3-phenylbutyric acid. [f] Stereochemistry of the product was assigned by comparison to ethyl (*R*)-citronellate that was prepared from commercially available (*R*)-citronellic acid.

The asymmetric reductions of (*E*)- and (*Z*)-isomers of several substrates were examined. As shown in entries 3−8, (*E*)- and (*Z*)-isomers react to give products with nearly the same ee, with the opposite enantiomer predominating.

The use of 2 equiv of (*S*)-*p*-tol-BINAP relative to CuCl provided products with ee's that were slightly higher than when the ratio was 1:1. This result indicated that, in the catalytic complex, a ratio greater than 1:1 of *p*-tol-BINAP:copper might be present. To probe this question, the reduction of ethyl *trans*-*β*-methylcinnamate (Table 1, entry 1) was performed using *p*-tol-BINAP of varying ee. As shown in Figure 1, a linear correlation between the ee of the ligand and that of the product was observed, indicating that a 1:1 ratio of ligand to metal is present in the catalytic complex.[12]

We propose that (*p*-tol-BINAP)CuH is the key intermediate in the catalytic cycle of the reaction that is responsible for discriminating between the enantiotopic faces of the alkene (Scheme 2). Upon combining *p*-tol-BINAP, CuCl, and NaO*t*-Bu,

Scheme 2



formation of (*p*-tol-BINAP)CuO*t*-Bu most likely occurs.[13] Addition of PMHS then results in a *σ*-bond metathesis between (*p*-tol-BINAP)CuO*t*-Bu and PMHS,[14] to generate (*p*-tol-BINAP)-CuH. Asymmetric conjugate reduction then occurs, resulting in formation of a copper enolate intermediate[15] that subsequently undergoes *σ*-bond metathesis with PMHS to make a silylketene acetal and regenerate the copper hydride. While we have no clear rationale for the enantioselectivity of the reduction at the present time, the catalyst seems to discriminate between enantiotopic faces of the alkene primarily on the basis of the orientation of the ester, since (*E*)- and (*Z*)-isomers give products of almost the same ee but enriched in opposite enantiomers.

In conclusion, the combination of catalytic CuCl, NaO*t*-Bu, and (*S*)-*p*-Tol-BINAP with PMHS generates a highly enantioselective catalyst system for the asymmetric conjugate reduction of α,*β*-unsaturated esters. The advantages of this catalyst system are the commercial availability of the ligand and the safety and low cost of PHMS. Complexes of BINAP and copper have previously found application in asymmetric aldol and related reactions[16] and kinetic resolutions of chiral esters.[17] The results of this study indicate that similar complexes will be useful for asymmetric reductions.[18] Further work to examine the scope and mechanism of this catalyst system is in progress.

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Supporting Information Available: Preparation and characterization of all substrates and products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Yoshizumi, T.; Takaya, H. *Tetrahedron: Asymmetry* **1995**, *6*, 1253.

(18) In preliminary results, we found that, under the same conditions where α,*β*-unsaturated esters were reduced to saturated esters, α,*β*-unsaturated ketones were typically overreduced to give saturated alcohols, and an α,*β*-unsaturated amide was not reduced.