Synthesis of β-Alkyl Cyclopentanones in High Enantiomeric Excess via Copper-Catalyzed Asymmetric Conjugate Reduction

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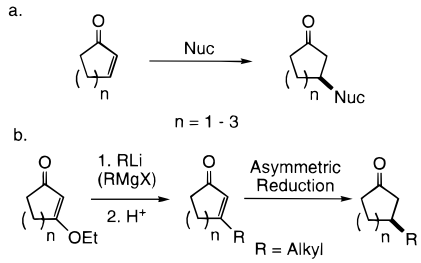
Most synthetic routes to chiral β-substituted cyclic ketones are based on the conjugate addition of nucleophiles to cyclic α,β-unsaturated ketones (Scheme 1a).[1] Recently, excellent catalysts for the asymmetric conjugate addition of nucleophiles to cyclic enones that contain a 6- or 7-membered ring have been discovered.[2] Highly enantioselective catalysts for conjugate addition of aryl, vinyl,[3] or enolate[4] nucleophiles to cyclopentenone are also known. However, catalysts for the asymmetric conjugate addition of nucleophilic alkyl groups to cyclopentenone typically afford products with enantiomeric excesses (ee's) lower than 90%.[2] Currently, the most enantioselective catalytic method to produce β-alkylcyclopentanones utilizes Rh(Me-DUPHOS) and Rh(BINAP) complexes to catalyze the asymmetric intramolecular hydroacylation of 4-substituted pent-4-enals.[5] We felt that a procedure based on asymmetric reduction of β-substituted enones, which can be readily synthesized via the Stork−Danheiser procedure,[6] could also provide a useful synthetic route to enantiomerically enriched β-substituted cyclic ketones (Scheme 1b).

Recently, we described a new copper catalyst for the asymmetric conjugate reduction of α,β-unsaturated esters.[7] This catalyst employs polymethylhydrosiloxane (PMHS), a safe and inexpensive polymer, as the stoichiometric reductant. Other catalysts for asymmetric conjugate reduction are based on chiral cobalt complexes and utilize stoichiometric amounts of borohydrides, such as $NaBH_4$.[8] Although the cobalt catalysts are very effective for the asymmetric conjugate reduction of α,β-unsaturated esters and amides, the same catalysts cannot be used for the asymmetric conjugate reduction of enones because reduction by the borohydride is rapid and nonselective. The pioneering work of Stryker, Lipshutz, and Hiyama demonstrated that achiral phosphine−copper hydrides, such as $[(Ph_3P)CuH]_6$, preferentially reduce enones via 1,4-reduction.[9] We now report that chiral (bisphosphine)Cu catalysts can reduce β-substituted enones to afford chiral ketones with very high ee's. These catalysts are especially effective for the asymmetric reduction of β-substituted cyclopentenones.

Scheme 1



In practice, efficient catalysts were generated in situ by first combining a chiral bis-phosphine ((*S*)-*p*-tol-BINAP, (*S*)-BINAP, or (*S*)-BIPHEMP),[10] CuCl, and NaO*t*-Bu in toluene, followed by the addition of PMHS. As shown in Table 1, cyclopentanones were obtained in high yields and excellent ee's. For most of the β-substituted cyclopentenones, conjugate reductions were complete in 24 h with 5 mol % catalyst and 1 equiv, relative to the substrate, of PMHS. Lower catalyst loadings (1 mol %) could be used without any effect on the ee of the product, but the reactions took a longer time to go to completion. Previously, we reported that 4 equiv of PMHS were necessary for the (*S*)-*p*-tol-BINAP-derived catalyst to reduce α,β-unsaturated esters.[7] However, for the reduction of α,β-unsaturated ketones it was important to limit the amount of PMHS such that 1 equiv of Si−H was present relative to substrate.[11] If extra PMHS was used, then overreduction to the saturated alcohol was observed.

Cyclopentenones designed to test the tolerance of the catalyst to functional groups and steric hindrance were subjected to the reduction conditions. A cyclopentenone that contained an isolated olefin was successfully reduced in high ee (entry 5). Substrates with either a benzyl ether (entry 6) or an ester (entry 7) were also reduced with high enantioselectivity. Examination of the tolerance of the catalyst to steric hindrance on the substrate revealed that longer reaction times were necessary as the steric bulk of the substituent on the β-carbon increased. For instance, the reduction of 3-isopropylcyclopentenone (entry 8) proceeded to 90% completion after 3 days to afford 3-isopropylcyclopentanone in 88% yield and 94% ee.[13,14] To date, attempted reductions

(1) For reviews of conjugate addition, see: Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. Tomioka, K.; Nagaoka, Y. Conjugate Addition of Organometallic Reagents. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, Chapter 31.1, pp 1105−1120. For recent examples of chiral additives for asymmetric conjugate addition, see: Kanai, M.; Nakagawa, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 3831. Chong, J. M.; Shen, L.; Taylor, N. J. *J. Am. Chem. Soc.* **2000**, **122**, 1822. For a recent example of a chiral auxiliary for asymmetric conjugate addition, see: Funk, R. L.; Yang, G. *Tetrahedron Lett.* **1999**, *40*, 1073.

(2) (a) Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988. (b) Hu, X.; Chen, H.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3518. (c) Yan, M.; Chan, A. S. C. *Tetrahedron Lett.* **1999**, *40*, 6645. (d) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865. (e) Escher, I. H.; Pfaltz, A. *Tetrahedron* **2000**, *56*, 2879. (f) Krause, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 283 and references sited within.

(3) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1999**, *40*, 6957.

(4) (a) Kobayashi, S.; Suda, S.; Yamada, M.; Mukaiyama, T. *Chem. Lett.* **1994**, 97. (b) Arai, T.; Sasai, H.; Aoe, K.-I.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed., Engl.* **1996**, *35*, 104.

(5) (a) Bardhart, R. W.; McMorran, D. A.; Bosnich, B. *Chem. Commun.* **1997**, 589. (b) Fujio, M.; Tanaka, M.; Wu, X.-M.; Funakoshi, K.; Sakai, K.; Suemune, H. *Chem. Lett.* **1998**, 881.

(6) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.

(7) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473.

(8) (a) Leutenegger, U.; Madin, A.; Pfaltz, A. *Angew. Chem., Int. Ed., Engl.* **1989**, *28*, 60. (b) Misun, M.; Pfaltz, A. *Helv. Chim. Acta* **1996**, *79*, 961. (c) Yamada, T.; Ohtsuka, Y.; Ikeno, T. *Chem. Lett.* **1998**, 1129.

(9) (a) Mahoney, W. S.; Stryker, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 8818. (b) Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627. (c) Mori, A.; Fujita, A.; Kajiro, H.; Nishihara, Y.; Hiyama, T. *Tetrahedron* **1999**, *55*, 4573.

(10) *p*-tol-BINAP = 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl, BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, BIPHEMP = 2,2′-bis(diphenylphosphino)-6,6′-dimethyl-1,1′-biphenyl.

(11) PMHS from Aldrich has an average molecular weight between 3200 and 17 000, and a density of 1.006 g/mL. From these values, 0.06 mL of PMHS/mmol of Si−H was calculated and this value was used to determine the volume of PMHS to add to the reaction so that there was only 1 equiv of Si−H relative to substrate.

(12) We are in the process of developing reaction conditions that do not require a drybox by trying to replace CuCl with a copper salt that is less sensitive to air.

(13) Isolation of the volatile product in high yield could only be accomplished by Kugelrohr distillation to remove toluene followed by chromatography with ether/pentane (a high vacuum pump could not be used to remove solvents without losing substantial amounts of the product).

(14) Cyclopentenones with substituents larger than an isopropyl group on the β-carbon did not react with the catalyst; for instance, 3-*tert*-butylcyclopentenone could not be reduced. Additionally, at present we are unable to reduce 2,3-disubstituted cyclopentenones.

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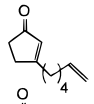
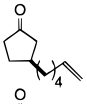
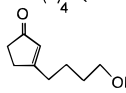
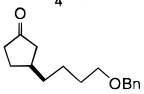
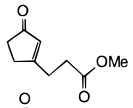
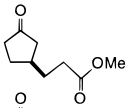
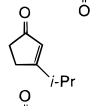
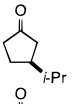
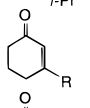
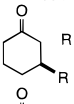
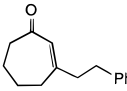
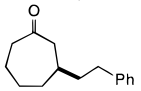
Table 1. Asymmetric Conjugate Reductions with (*S*)-*p*-tol-BINAP, CuCl, NaO*t*-Bu, and PMHS[a]

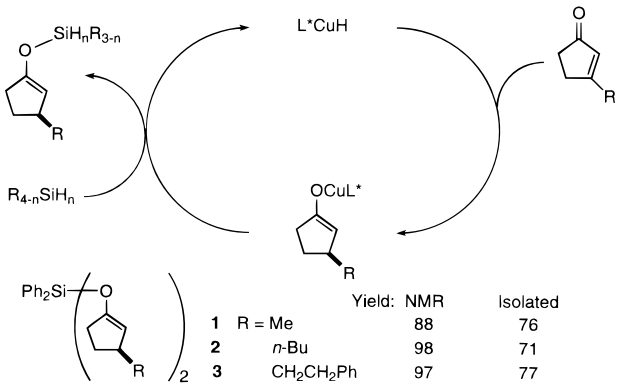
Entry	Substrate[b]	Product		Temp. (°C)	Yield[c] (%)	ee[d] (%)
1			R = Me	-78	42[e]	94
2			*n*-Bu	0	84[f]	98
3			CH_2Ph	0	78	96
4			CH_2CH_2Ph	0	86	94
5				15	87	96[g]
6				0	91	94
7				0	86	92
8				0	88[h]	94
9			R = Me	-78	61[i]	92[j]
10			*n*-Bu	0	82[k]	87[j]
11				0	82[l]	96[g]

[a] Reactions were performed at 0.5 M [enone], with 1.05 equiv of PMHS, 5 mol % CuCl, 5 mol % NaO*t*-Bu, 5 mol % (*S*)-*p*-tol-BINAP, for 24 h, at the temperature specified. Note: The reactions were set up with the aid of a nitrogen filled drybox.[12] [b] See Supporting Information for details on substrate preparation. [c] Yields are the average of two isolated yields of >95% purity as determined by GC and ^{1}H NMR. [d] The average ee for two reactions is reported for each entry. The absolute stereochemistry of the products in entries 1, 2, 8, 9, and 10 was assigned by comparing the sign of their optical rotations to published values (see Supporting Information for details). The absolute stereochemistry of all other products was assigned by analogy. [e] Low isolated yield due to volatility of the product, GC yield was 86%. [f] Reaction time was 12 h. [g] (*S*)-BINAP was the ligand. [h] Reaction time was 3 days. In addition to the desired product,10% starting material was recovered. [i] Low isolated yield due to volatility of the product, GC yield was 85%. [j] (S)-BIPHEMP was the ligand. [k] The reaction time was 2 days. In addition to the desired product, 6% of 3-butylcyclohexanol was isolated. [l] The reaction time was 4 days. In addition to the desired product, 9% of 3-phenethylcycloheptenol was isolated.

of cyclopentenones with vinyl or alkynyl groups conjugated to the enone gave mixtures of products resulting from competing 1,4- and 1,6-reductions.

The conjugate reductions of β-substituted cyclohexenones and cycloheptenones produced the desired products in high ee. For cyclohexenones, the BIPHEMP-derived catalyst produced products in higher ee than the catalysts derived from the other two ligands. In some cases, minor amounts of overreduced products were isolated. For instance, the reduction of 3-methylcyclohexenone (entry 9) produced the product cleanly (92% ee), but the reduction of 3-butylcyclohexenone (entry 10) afforded the desired product (87% ee) along with 3-butylcyclohexanol (6%). Similar problems with competing overreduction were observed with the catalysts derived from *p*-tol-BINAP and BINAP. For 3-phenethylcycloheptenone, BINAP was the ligand of choice, and the desired product was obtained in 96% ee (entry 11). Competing

Scheme 2



1,2-reduction of the substrate was a problem in this reduction; in addition to the desired product, 3-phenethylcycloheptenol (9%) was also isolated. The *p*-tol-BINAP and BIPHEMP derived catalysts produced the same mixture of the desired product and the product of 1,2-reduction.

Our current view is that a (bis-phosphine)CuH complex is the key intermediate in the catalytic cycle of the reduction. Conjugate reduction of cyclopentenones by such a complex should result in formation of a copper enolate that subsequently undergoes metathesis with a silane[15] to form a silyl enol ether (Scheme 2). Circumstantial evidence supporting this mechanism was obtained when the silyl bis-(enol ethers) **1**−**3** were isolated from the catalytic reduction of the corresponding cyclopentenones with 0.53 equiv of diphenylsilane. Treatment of **1**−**3** with TBAF afforded the 3-alkylcyclopentanone with the same ee as the catalytic reduction with PMHS.

In conclusion, the combination of catalytic amounts of CuCl, NaO*t*-Bu, and a chiral bis-phosphine with PMHS generates a highly enantioselective catalyst for the asymmetric conjugate reduction of α,β-unsaturated ketones. The catalysts examined in this study produce β-substituted cyclopentanones with ee's that have not been obtained via asymmetric conjugate addition. These catalysts react with cyclopentenones exclusively via 1,4-reduction. The reductions of cyclohexenones and cycloheptenones also give the products of 1,4-reduction in high ee's; however, in these reactions competing 1,2-reduction occurs to a minor extent. Stryker and co-workers have reported that the reactivity of copper hydride complexes is highly dependent on the nature of the phosphine ligand.[16] We are currently exploring copper hydride complexes with new ligands to access catalysts with increased selectivity for asymmetric conjugate reduction of a wide variety of substrates.

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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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(15) Lorenz, C.; Schubert, U. *Chem. Ber.* **1995**, *128*, 1267.
(16) Chen, J.-X.; Daeuble, J. F.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2789.