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Asymmetric 1,4-Reductions of Hindered β-Substituted Cycloalkenones Using Catalytic SEGPHOS–Ligated CuH

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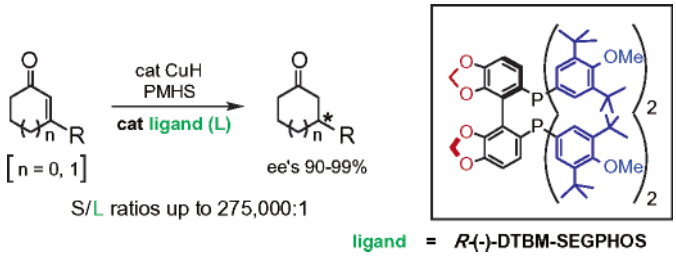
ABSTRACT



The reagent combination of catalytic amounts of copper hydride ligated by a nonracemic SEGPHOS ligand leads in situ to an extremely reactive species capable of effecting asymmetric hydrosilylations of conjugated cyclic enones in very high ees. An unprecedented substrate-to-ligand ratio as high as 275 000:1 for this transformation has been documented.

Control of asymmetry β- to the carbonyl group in a cyclic ketone is usually reserved for one of several powerful methods relying on conjugate addition from metals such as Cu[1] and Rh[2] or via use of nonracemic Lewis acid catalysts.[3] An alternative strategy is based on conjugate reduction of a β-substituted system and offers considerable flexibility in synthesis.[4] Recently, we described the remarkable accelerating effect imparted by nonracemic biaryl ligands such a Takasago's DTBM-SEGPHOS (**1**)[5] and Roche's xyl-MeO-BIPHEP (**2**)[6] on CuH toward aryl ketones,[7a] resulting in a highly effective Cu(I)-catalyzed method for asymmetric hydrosilylation. Although such reactions of ketones are likely to be mechanistically distinct from those of either cyclic or acyclic[7b] α,β-unsaturated ketones, the same reagent combination might offer greater reactivity along with higher levels of enantioselectivity than currently available.[8] Substrate-to-ligand (S/L) ratios might be greatly increased and ees enhanced as well. It was also conceivable that far more hindered educts not amenable to existing procedures would participate. We now disclose that, indeed, asymmetric hydrosilylations of cyclic enones take place using SEGPHOS **1**-ligated CuH at unprecedented S/L levels with high enantioselectivities even in very sterically demanding cases.

Using preformed $(Ph_3P)CuH$[9] or generating CuH in situ in the usual fashion from 1% CuCl, 1% NaO-*t*-Bu,[10] and

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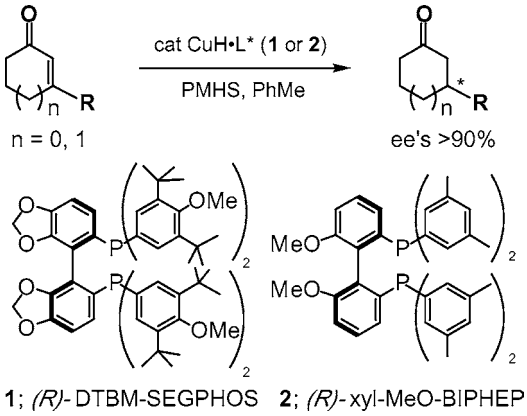
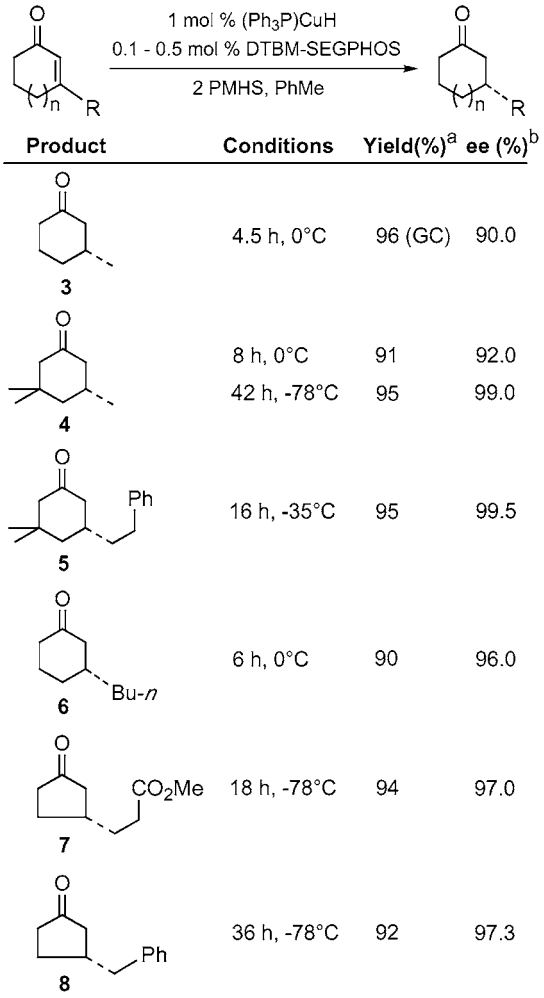


stoichiometric polymethylhydrosiloxane (PMHS),[11] the presence of 0.1−0.5 mol % **1** (or S/L = 200:1 to 1000:1) in toluene at 0 °C was sufficient to provide a reagent capable of delivering hydride in a 1,4-sense with excellent levels of stereoinduction. Table 1 illustrates the cases studied. Noteworthy is the observation that highly hindered examples such as isophorone (**4**) and related substrates (e.g., **5**)[12] led to good ees from reactions run at 0 °C, while those carried out at lower temperatures afforded especially selective reductions.[13] Comparisons with literature examples (**3** and **6**−**8**)[8] that do not include any cases analogous to 5,5-disubstituted cyclohexenones reflect the far greater pace at which DTBM-SEGPHOS accelerates these asymmetric reductions relative to other bis-phosphines used previously (*p*-tol-BINAP, BIPHEMP).[8] Isophorone itself, for example, reacts with modest selectivity and to a limited extent under the influence of CuH·BIPHEMP/PMHS (14% in 10 h at 0 °C; 47% ee). Moreover, unlike prior art,[8] there is no sensitivity to excess silane and, hence, no over-reduction in the presence of 2 equiv of PMHS.

Solvents other than toluene were also screened, with results being illustrated in Scheme 1. While the level of induction dropped somewhat in CH_2Cl_2, both THF and especially THF/dioxane mixtures (2:1) led to appreciably greater ees than in toluene, notwithstanding higher reaction temperatures. These data suggest that considerable latitude exists in choosing a medium and temperature for these reductions.

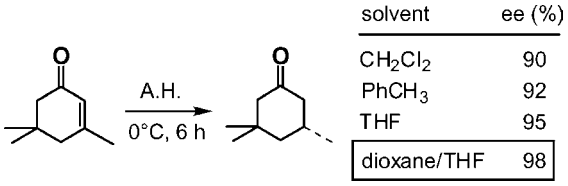
Table 1. 1,4-Reductions of Hindered Cyclic Enones



Product	Conditions	Yield(%)[a]	ee (%)[b]
3	4.5 h, 0°C	96 (GC)	90.0
4	8 h, 0°C	91	92.0
	42 h, -78°C	95	99.0
5	16 h, -35°C	95	99.5
6	6 h, 0°C	90	96.0
7	18 h, -78°C	94	97.0
8	36 h, -78°C	92	97.3

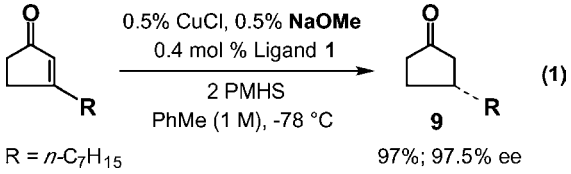
[a] Isolated, chromatographically pure material. [b] Determined by chiral GC analyses.

Scheme 1



solvent	ee (%)
CH_2Cl_2	90
$PhCH_3$	92
THF	95
dioxane/THF	98

Although the standard protocol for preparing CuH calls for the 1:1 ratio of CuCl/NaO-*t*-Bu so as to initially generate CuO-*t*-Bu, we recently found that the trivial base NaOMe can serve in the same capacity.[14] Use of this inexpensive alternative en route to ligated CuH affords, in the case of a cyclopentenone, a similar level of selectivity as indicated by product **9** (eq 1; compare with Table 1, products **7** and **8**).



A S/L ratio of 250:1 was routinely used in the examples above, a ratio chosen solely on the basis of accuracy in measuring the milligram quantities of phosphine ligand required per reaction. To test the limits of catalysis, an

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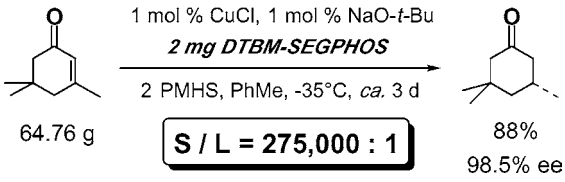
(12) Use of ligand **2** required 96 h to obtain an ee of 97%, whereas ligand **1** led to **5** at −35 °C in 99.5% ee after 16 h.

(13) Using ligand **1**, absolute stereochemistry was confirmed by comparisons of rotation data with known products. **3** (R): comparison with commercial material. **4**: (R) (Allinger, N. L.; Riew, C. K. *J. Org. Chem.* **1975**, *40*, 1316). **6**: (R). **7**: (S). **8**: (S) (cf. ref 8).

experiment was conducted on 64.76 g of isophorone in the presence of only 2 mg of DTBM-SEGPHOS (Scheme 2).

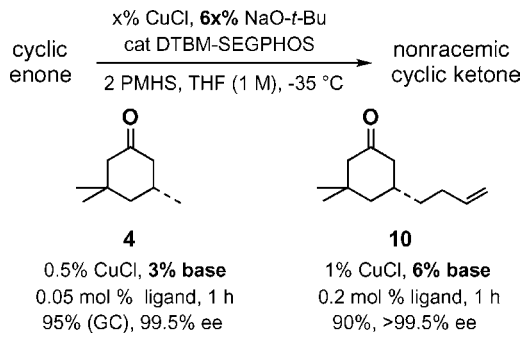
Scheme 2



At this unprecedented S/L ratio of 275,000:1,[14] which also involved only 2 equiv of PMHS, conjugate reduction and the associated hydrolytic workup proceeded uneventfully to afford the expected product in 88% (distilled) yield and with an ee of 98.5%.

Interestingly, the rates of these hydrosilylations could be dramatically increased when the ratio of base to CuCl was raised to an optimized 6:1 level.[15] As illustrated in Scheme 3, isophorone reacted completely at −35 °C within 1 h while

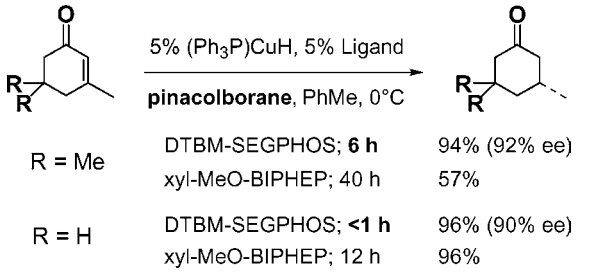
Scheme 3



maintaining high S/L levels. At the more typical 1:1 ratio, 8 h were needed for 100% conversion at 0 °C (cf. Table 1). Likewise, product **10** was obtained in essentially enantiomerically pure form in good isolated yield in the same time frame.

Last, we note that the initial outcome to these asymmetric reductions is a silyl enol ether derivative of PMHS, which requires subsequent hydrolytic workup to arrive at product ketones. To obviate this step, we have found that pinocolborane (in place of PMHS) can function as the stoichiometric source of hydride without impact on the levels of stereoinduction (Scheme 4). The presumed labile boron enolate is lost upon workup to directly afford the desired ketones. DTBM-SEGPHOS (**1**) was found to enhance the rates of these asymmetric reductions relative to xyl-MeO-BIPHEP (**2**) as well in both of the β,β-disubstituted enones examined.

Scheme 4



In summary, an especially effective case of ligand-accelerated catalysis has been uncovered for carrying out conjugate reductions of (hindered) β-substituted cyclic enones based on either an in situ-generated SEGPHOS-chelated CuH or a SEGPHOS-modified form of Stryker's reagent.[9] High catalyst turnovers have been realized, very mild conditions prevail, and both yields and enantioselectivities are the highest reported to date for these substrates.

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Supporting Information Available: Procedures and spectral data for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) **Representative Procedure: Large-Scale Hydrosilylation of Isophorone (275,000:1 S/L).** To a 500 mL round-bottomed flask, flame-dried and purged with argon, were added CuCl (426 mg, 4.30 mmol), NaO-*t*-Bu (412 mg, 4.29 mmol), and (*R*)-DTBM-SEGPHOS (2.0 mg, 0.0017 mmol), Dry, distilled toluene (215 mL) was added and the solution stirred at rt for 20 min, during which time the mixture changed from clear white to pale yellow. The mixture was cooled to −35 °C (Cryocool refrigeration), and isophorone (distilled, neat, 64.76 g, 70.30 mL, 469.27 mmol) was added dropwise, during which time the mixture turned dark black. PMHS (distilled, 56 mL, 938 mmol) was introduced via cannula. The mixture was stirred at −35 °C for 5 h and analyzed by GC, which indicated 60% conversion. The reaction was allowed to continue and was analyzed at various times: 18 h (72% conversion), 30 h (80%), 48 h (87%), 72 h (92%), 80 h (99%), after which time it was warmed to 0 °C and then quenched by pouring into cold, saturated bicarbonate and Et_2O (without stirring). The mixture slowly evolved gas over 6 h and was then stirred vigourously for 6 h. The aqueous layer was extracted three times with Et_2O, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation with caution due to slight volatility. The residue was purified by fractional distillation to afford 58.14 g (88.5%) of the title compound. Analysis by chiral GC (Chiraldex B-DM 75) indicated an ee of 98.5%.

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