Ligand-Accelerated, Copper-Catalyzed Asymmetric Hydrosilylations of Aryl Ketones

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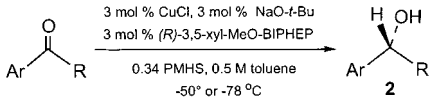
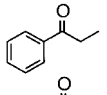
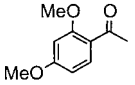
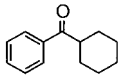
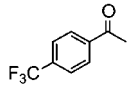
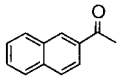
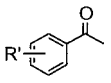
Received June 25, 2001

Within the field of catalytic asymmetric synthesis,[1] hydrosilylations of carbon−carbon and carbon−heteroatom double bonds are viewed as a valued alternative to asymmetric hydrogenation.[2] Since the first reports appeared about three decades ago, research continues to focus on ketones and related systems (e.g., imines),[3] with most of the methods relying on ligated rhodium hydride catalysts.[4] Impressive chemical yields and enantioselectivities of product alcohols have also been documented from reactions involving nonracemic titanium hydrides,[5a−c] and alternatives which promote complexes of ruthenium can also effect such transformations.[6] No single procedure appears to be ideal, each having its virtues as well as limitations. Issues such as costs can be associated with (1) the metal (e.g., Ru or Rh) or (2) the ligand (e.g., nonracemic Brintzinger titanocenes),[7] or both; (3) their recovery and reuse, and potentially (4) the stoichiometric source of hydride (e.g., $PhSiH_3$). Finally, ratios in the 50−500:1 range[2a] of substrate to either catalyst or ligand rarely approach those associated with related hydrogenations.[8] We now describe asymmetric hydrosilylations of aryl ketones mediated by catalytic quantities of bidentate phosphine-ligated copper hydride[9] which are efficient, occur under very mild conditions, afford competitive levels of enantioselectivity, and can be performed with very high ratios of substrate to ligand (S/L).

Our recent observation[10] that bidentate ligands (e.g., DPPF and racemic BINAP) significantly enhance the rate of 1,2-reduction of 4-*tert*-butylcyclohexanone by catalytic amounts of Stryker's reagent[11a] (hexameric $(Ph_3P)CuH$) led to trials involving nonracemic BINAP and various aryl ketones. Under a given set of conditions (3 mol % $(Ph_3P)CuH$, 3% BINAP, 0.34 equiv of PMHS,[12] toluene, −78 °C), acetophenone, propiophenone, and α-tetralone gave good levels of enantioselectivity (75, 86, and 80% ee, respectively). A series of other ligands were screened, including bidentate phosphines (e.g., BINAPFu,[13a] phanephos,[13b] a hexafluoro-BINAP analog[13c]), P,N ligands (e.g., MAP),[13d] and nonracemic diamines (e.g., PINDY),[13e] which in all cases led to no observed reaction. Complete hydrosilylation was observed employing JOSIPHOS,[13f] Trost's ligand,[13g] DIOP,[13h] Et-ferroTANE,[13i] and Me-DuPHOS,[13j] although the enantioselectivity in each case was low (<45% ee). On the basis of these results, we returned to a bidentate diaryl-substituted phosphine as part of a biaryl array (analogous to BINAP) which appeared to be critical for selective stereoinduction.

Table 1. Asymmetric Hydrosilylations Using Catalytic CuH and Roche BIPHEP Ligand **1**



Entry	Aryl ketone	Time (h)	Yield (%)[a]	ee (%)[b]
1		7.5	95	95[e]
		48	87	97[c]
2		5	98	94[c]
3		6.5	99	92[e]
4		50	89	94[d]
5		10	94	88[e]
6		1	85	95[e]
7		48	95	95[c]
8		1.5	98	67[e,f]
		5	99	93[c,g]
		5.5	97	78[c,h]

[a] Isolated. See ref 5d. [b] ee values were determined by conversion of each product to its acetate and analysis by chiral capillary GC. [c] Reaction was run at -78 °C. [d] Reaction was given 10 h at −50 °C and then warmed to room temperature. [e] Reaction was run at −50 °C. [f] R′ = *o*-Br. [g] R′ = *m*-Br. [h] R′ = *o*-Cl.

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(12) PMHS = poly(methylhydrosiloxane; a 29mer, with one hydride per monomeric unit; MW 1900); CAS Registry No. 9004-73-3, available from Lancaster Chemicals and used as received. Thus, 0.34 equiv of a 29mer is (0.34 equiv × 29) or ca. 9−10 equiv of hydride per substrate.

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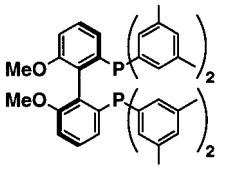
10.1021/ja011529e CCC: $20.00
Published on Web 12/19/2001

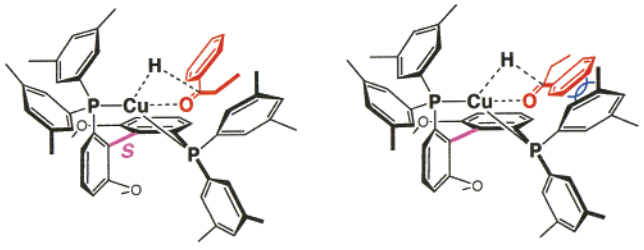
The extensive series of nonracemic biphenyl ligands originally developed by Schmid, Scalone, and co-workers at Roche[14a] led us to examine the parent species MeO-BIPHEP.[14b] The result initially obtained with propiophenone (85% ee) paralleled that with nonracemic BINAP. In switching to the dimethylphenyl analogue, 3,5-xyl-MeO-BIPHEP (**1**), significant improvements in enantioselectivity were observed, with ee values in most cases exceeding 90%. Several illustrative examples of aryl ketones reduced to their corresponding secondary alcohols **2** with 3 mol % each of CuCl/NaO-*t*-Bu and this ligand (and thus, in the absence of PPh_3), along with PMHS as the hydride donor, is shown in Table 1. Most hydrosilylations proceed at −50 °C in 12 h or less, while those at −78 °C can take up to ca. 2 days. Chemical yields in all cases are high.[5d] Both electron-rich (entry 4) and electron-poor (entry 6) substrates react with comparable selectivity, although in the latter case the reaction required less time to reach completion. A few anomalous cases were noted, including *ortho*-halo-substituted acetophenones (entry 8) and 1-acetylnaphthalene (not shown).[15] Replacement of toluene by THF as solvent afforded similar results.[16] That the role of the silane involves regeneration of CuH *subsequent* to the stereo-defining 1,2-addition seems likely since no impact on rate or ee was observed upon switching from PMHS to Ph_2MeSiH.



1, *R*-3,5-xyl-MeO-BIPHEP

The stereochemical outcome, where either *(R)*-**2** induces *(R)*-alcohol **3** or *(S)*-**2** induces the corresponding *(S)*-alcohol, can be rationalized as shown in Figure 1. Steric interactions between the conjugated aryl ring in the educt and a disubstituted aryl moiety in the phosphine strongly disfavor transition state **4** relative to **3**.

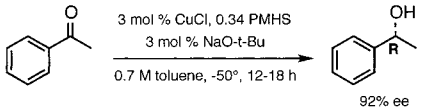
Having invested up to 3 mol % of ligand **1** in the above reactions, it seemed worthwhile to consider prospects for its recovery and reuse. Upon completion of the hydrosilylation of acetophenone, and after reaction workup, it was found that following distillation of the product alcohol the residue could be triturated with Et_2O leading to isolation of ca. 75% of **1** initially present. Reuse of recovered **1** (along with fresh CuCl and NaO-*t*-Bu) in two additional cycles afforded from each the desired product in the same chemical (>90%) and optical yields (92% ee).



3 (favored) **4** (disfavored)

Figure 1. Rationale for induction observed in CuH·3,5-xyl-MeO-BIPHEP-catalyzed hydrosilylations.

Table 2. Level of Roche Ligand **1** that Effects CuH-Catalyzed Hydrosilylations



92% ee

mol % (R)-3,5-xyl-MeO-BIPHEP	ratio of substrate / ligand	ratio of copper(I) / ligand
3.00	33	1
0.50	200	6
0.05	2000	60
0.02	5000	150
0.005	**20,000**	600

With substrate-to-catalyst ratios in these hydrosilylations at ca. 33:1, we questioned the need for a 1:1 stoichiometry between CuH and ligand **1**. It was not obvious that any significant downward variation in the quantity of **1** would be tolerated, since uncomplexed CuH is notoriously unstable.[17] However, use at low temperatures might extend its lifetime and allow for a decrease in ligand stoichiometry. Toward this end, with acetophenone as substrate, the amount of Cu(I) was held constant at 3 mol % as the mol % of ligand **1** was lowered. As indicated in Table 2, virtually identical results were obtained with levels of **1** as low as 0.005 mol %, which corresponds to a substrate-to-ligand ratio of 20,000:1. The amount of copper(I) could also be decreased from 3.0 to 0.5 mol %, as could the number of equivalents of PMHS from 0.34 to 0.14, while the net conversion was maintained (>98.5% in 20 h). Identical treatment of propiophenone, which led to results akin to those listed in Table 1 (i.e., 87−95% chemical yields, 95−97% ee), suggests an element of generality, which demonstrates S/L ratios normally reserved for asymmetric hydrogenations.[8]

In summary, a reagent prepared in situ from catalytic quantities of CuH and a nonracemic Roche ligand *(R)*- or *(S)*-3,5-xyl-MeO-BIPHEP[14] has been found to possess remarkable reactivity in asymmetric hydrosilylations of aromatic ketones. Chemical yields of isolated alcohol products are excellent, as are their optical purities. These reductions take place in the presence of excess PMHS as a source of hydride, and occur under especially mild conditions within reasonable time frames. Given the combination of a very inexpensive polymeric silane,[12,18] along with <1 mol % of a trivial copper(I) salt and exceedingly low levels of a known, readily prepared nonracemic ligand,[14] this technology would appear to offer some unique and practical, as well as economic, benefits relative to existing methods.[2] Applications to several other substrate types which may involve similar ligand-accelerated catalysis are being pursued, results from which will be reported in due course.

Acknowledgment. We warmly acknowledge the NSF for financial support. We are indebted to Drs. Rudolf Schmid and Michelangelo Scalone (Hoffmann-La Roche, Basel) for a most generous supply of BIPHEP ligands, as well as the senior authors in refs 13a−d for providing some of the ligands used in this study.

Supporting Information Available: Representative procedure and data for asymmetric hydrosilylations associated with Table 1, along with procedures for hydrosilylation with (PPh_3)CuH/PMHS and BINAP·CuH/PMHS (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA011529E

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(15) The corresponding alcohol was isolated in 99% yield, but with only 31% ee.

(16) With other toluene/THF mixtures (e.g., 80/20 toluene/THF, and 90/10 toluene/THF) complete hydrosilylation of propiophenone was observed. The yields and ee values of 2-phenylethanol were 95% and 97%, respectively, for each of the above solvent combinations.

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