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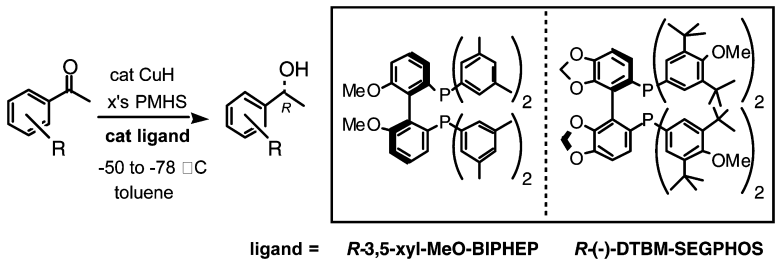

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Asymmetric Hydrosilylation of Aryl Ketones Catalyzed by Copper Hydride Complexed by Nonracemic Biphenyl Bis-phosphine Ligands

Bruce H. Lipshutz,* Kevin Noson, Will Chrisman, and Asher Lower

Contribution from the Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106

Received December 2, 2002; E-mail: lipshutz@chem.ucsb.edu

Abstract: When complexed by selected ligands in either the BIPHEP or the SEGPHOS series, CuH is an extremely reactive catalyst capable of effecting asymmetric hydrosilylations of aromatic ketones at temperatures between −50 and −78 °C. Inexpensive silanes serve as stoichiometric sources of hydride. Substrate-to-ligand ratios exceeding 100,000:1 have been documented. The level of induction is usually in the >90% ee category. The nature of the reagent has been investigated using spectroscopic and chemical means, although its composition remains unclear.

Introduction

Asymmetric hydrosilylation of prochiral aromatic ketones has a rich history in organic synthesis as a valued means of producing nonracemic secondary alcohols.[1] Dating from early work of Ojima, Nagai, Corriu, and Kagan based on a phosphine-modified Rh(I) catalyst in the presence of a silane,[2] many alternative complexes of rhodium bearing new and more effective ligands have appeared, several of which can be expected to afford products with enantiomeric excesses (ee's) above 90%. Among the most stereodifferentiating are Nishiyama's pybox complex of $RhCl_3/AgBF_4$,[3] as well as Ito's TRAP,[4] Saigo's Phos-oxazole,[5] and Fu's planar-chiral P,N ligand[6] derivatives of $[Rh(COD)Cl]_2$ (Figure 1). Recent work based on ligated ruthenium also shows promise.[7] Hydrosilylations employing less expensive metals have been reported, such as the case of the dimethylzinc(ebpe) species **1** (Figure 2),[8] which benefits from the active yet inexpensive nature of polymethylhydrosiloxane (PMHS)[9] as the stoichiometric source of hydride.

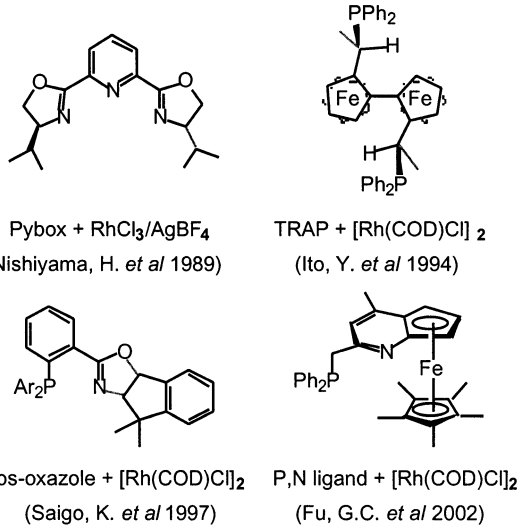

Figure 1. Ligands for use in rhodium-based asymmetric hydrosilylations; S/C ranges from ca. 100−300.

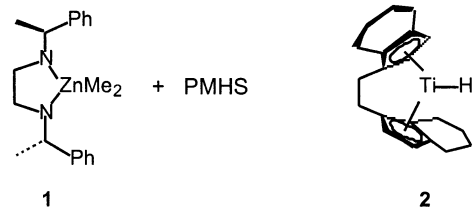

Figure 2. Nonracemic catalysts **1** and **2** used in asymmetric hydrosilylations.

This silane has also served well in reductions catalyzed by nonracemic Brintzinger-ligand-complexed titanium hydride **2**.[10]

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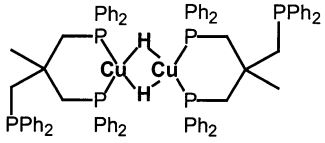
The first use of CuH in asymmetric hydrosilylation, to our knowledge, was described by Brunner in 1984,[11] wherein catalytic amounts of copper hydride were complexed mainly by DIOP, using acetophenone as educt and Ph_2SiH_2 as hydride donor. Although a substrate to catalyst (S/C) ratio as high as 2500 was found to be effective, the ee's obtained for α-phenylethanol were below 39%. More recently, Riant has shown that a BINAP-modified $CuF_2/PhSiH_3$ combination,[12] unexpectedly enhanced by the presence of air, affords product alcohols in good ee's after acidic hydrolytic workup. By far, most of these systems operate at S/C ratios on the order of 100−300:1,[1] which is considerably lower than those characteristic of asymmetric hydrogenations[13] routinely run in the thousands and tens of thousands to one S/C category.

Background

As the structural organometallic chemistry of copper hydride has evolved over the past few decades, with major insights provided by Churchill,[14] Caulton,[15] and others,[16] so has the synthetic chemistry of this thermally labile solid. In its triphenylphosphine-stabilized form (i.e., $[(PPh_3)CuH]_6$; "Stryker's reagent"),[17] this hexameric species was introduced[18] as an attractive reagent for carrying out conjugate reductions of enones, enals, and enoates, initially in a stoichiometric fashion and eventually under catalytic conditions.[19] Several groups have made related contributions involving CuH-based 1,4-additions, including asymmetric variations on this theme.[20] However, the propensity of CuH to add in a 1,2-sense to nonconjugated carbonyls, a relatively rare mode of reaction for a Cu(I) species, had gone unappreciated in the literature when we began our studies in this area. We found that $(PPh_3)CuH$ is not chemospecific toward 1,4-reduction of an enone in the presence of an aldehyde,[21] the outgrowth of an effort to effect a net three-component coupling (i.e., 1,4-addition of hydride followed by a Mukaiyama aldol reaction). Rather, competing reduction of the aldehyde took place. This led to development of a one-pot process for converting an isolated aldehyde to its corresponding silyl-protected primary alcohol in virtually quantitative yield, using a silane (rather than a silyl halide or equivalent) as both the source of hydride and the protecting group (eq 1).[22] With ketones the hydrosilylation was markedly slower, and in fact aldehydes could be selectively reduced in the presence of dialkyl ketones. We therefore took special note of Stryker's studies[23a] on the impact of phosphines[15b] on the ability of CuH to hydrogenate ketones. The tripod ligand was utilized in a bidentate capacity,[23b] suggesting that two coordination sites in this copper(I) complex **3** are available for occupancy, although this reagent was studied mainly in the solid state. It was pleasing to see, therefore, that hydrosilylation of a cyclic dialkyl ketone (e.g., 4-*t*-butylcyclohexanone) could be effected rapidly at room temperature by the simple addition of catalytic DPPF or racemic BINAP to a mixture of catalytic $(Ph_3P)CuH$ plus PMHS.[22] This observation opened the door for our switch to CuH ligated by nonracemic bidentate phosphines/PMHS as a potentially potent combination for asymmetric hydrosilylations of aromatic ketones. We certainly had no basis on which to anticipate the unprecedented reactivities about to be uncovered when CuH is chelated by selected biaryl bis-phosphines. In this report, which expands significantly on our initial study on asymmetric hydrosilylations of aromatic ketones,[24] we describe remarkably kinetically active catalyst systems which allow for substrate-to-ligand ratios that are orders of magnitude greater than those reported to date[1] and which are comparable to levels commonly seen in related ruthenium-based asymmetric *hydrogenations*.[13]

$$\mathrm{RCHO} \xrightarrow[\mathrm{R'_3SiH,\ PhMe,\ rt}]{\mathrm{cat\ (PH_3P)CuH}} \mathrm{RCH_2OSiR'_3} \qquad (1)$$

$$\left[\mathrm{R'_3SiH = PMHS,\ TMDS,\ PhMe_2SiH,\ Ph_2MeSiH,\ Ph_2(\mathit{t}\text{-}Bu)SiH}\right]$$



3 $[(tripod)CuH]_2$

Results and Discussion

Substrate:Ligand (S/L) Ratios. In preliminary studies,[24] the combination of either Stryker's reagent or in situ-generated CuH, together with Roche's 3,5-xyl-MeO-BIPHEP[25] (**4A**; Chart 1), afforded an especially reactive catalyst capable of effecting asymmetric hydrosilylations of aryl alkyl ketones in toluene at low temperatures (Scheme 1). Using excess PMHS as the stoichiometric source of hydride, we isolated high yields and ee's of product alcohols following a basic hydrolytic workup of the polymeric silyl ethers initially formed. The sense of induction, where the *R*-isomer **4A (**as well as the *R*-(−)-isomer of **14B**, vide infra) leads to the *R*-product alcohol, appears to be general on the basis of optical rotations measured and compared with known data and applies to both aromatic as well

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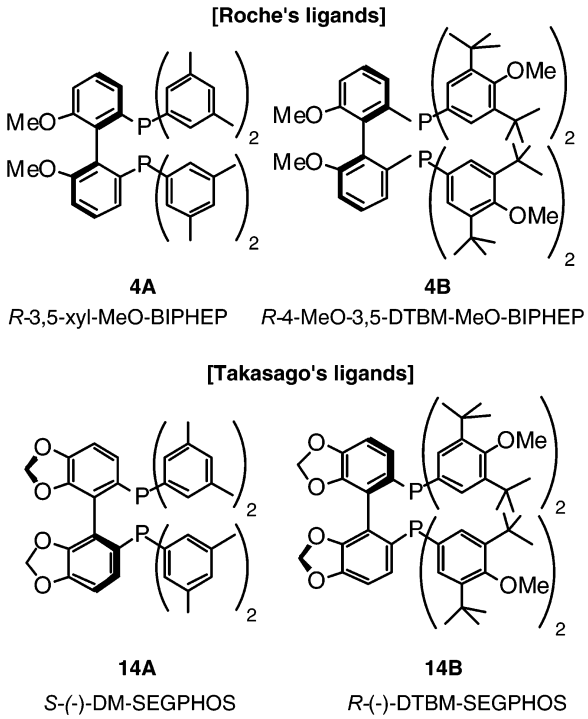
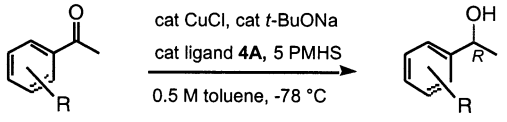
Chart 1. Structures for the BIPHEP and SEGPHOS Ligands Used in This Study



Scheme 1. Asymmetric Hydrosilylations of Aryl Ketones Using Ligand **4**

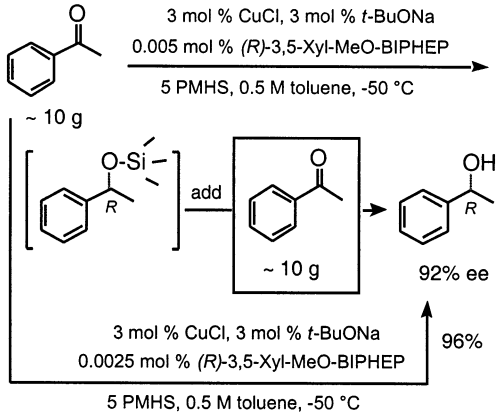


representative substrates	*ee(%)*	*yield(%)*
acetophenone	94	98
propiophenone	97	87
α-tetralone	92	99
4-CF_3-acetophenone	95	85
2,4-dimethoxyacetophenone	94	89

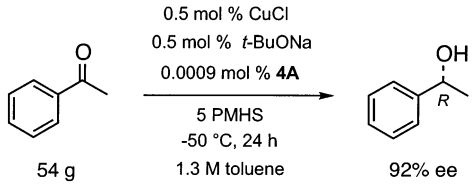
as heteroaromatic ketones.[26] Reactions run in pure toluene, pure THF, or mixtures of these two solvents did not impact the ee's observed, observations which curiously do not hold for heteroaromatic substrates.[26] Ratios of substrate to ligand (S/L) as high as 20 000:1 could be used, and, following distillation of the product alcohol, the ligand could be recoverd by trituration with Et_2O and reused in three cycles without loss of chirality or chemical efficacy.[24] Although such levels of S/L are unprecedented in asymmetric hydrosilylation chemistry, in general,[1] just what the limits of activity might be using this copper hydride technology still remained to be established.

One approach used to evaluate catalyst activity involved reintroduction of fresh substrate into a reaction mixture upon complete consumption of educt. Hydrosilylation of acetophenone on a 10 g scale at −50° for a (arbitrarily set) period of 24 h using ligand **4A** (3.2 mg; 0.005 mol %; 20,000:1 S/L) was followed by recharging the reaction mixture with a second 10 g sample (Scheme 2). After a second 24 h period, the reaction was worked up to cleanly afford the (*R*)-benzylic alcohol bearing the expected ee (92%). No acetophenone remained unreacted.

Scheme 2. Consecutive Reductions at 20 000:1 S/L and Direct Hydrosilylation at 40 000:1 S/L



Scheme 3. Reduction of Acetophenone Using ≥100 000:1 S/L



This experiment suggested not only that (*R*)-3,5-xyl-MeO-BIPHEP·CuH (**5**) could be used at the 40,000:1 S/L ratio, but that **5** is still active and stable under these conditions. Thus, the corresponding experiment using one-half of the amount of ligand (i.e., 0.0025 mol %) at the start of this 24 h period led to the same net outcome (i.e., 92% ee, with an isolated yield of 96%), thereby doubling the best S/L ratio we had seen to date. In cutting the amount of ligand **4A** further to 0.0012 mol %, thereby exceeding a 62,000:1 ratio, and realizing the same outcome, we decided to attempt an experiment at the S/L ratio of ≥100,000:1. This entailed 54 g of acetophenone and only 2.9 mg (0.0009 mol %) of ligand **4A** (Scheme 3). The reaction was uneventful, with virtually no difference in outcome from all of the others run at lower S/L ratios. Handling of larger amounts of PMHS during workup, however, required care in the hydrolysis step to avoid excessive frothing.[27] Nonetheless, the product alcohol obtained was of equal quality (92% ee).

Variations in the Silane. Although PMHS serves well as an inexpensive source of hydride,[9] other nonoligomeric silanes were investigated, some of which would be expected to afford isolable silyl ether products, thus avoiding a hydrolytic workup.[22] As illustrated in Table 1, those that participate in the (presumed) transmetalation step include diphenylmethylsilane and tetramethyldisiloxane (TMDS). Each is a suitable replacement for PMHS, at least as determined in the case of acetophenone under our standard reaction conditions (−78 °C, 12−24 h). In terms of reaction rates, however, neither is as reactive as PMHS. The sense of induction appears to be independent of silane, as were the levels of ee's observed. The monomeric-like form of PMHS, 1,1,1,3,5,5,5-heptamethyltrisiloxane (HMTS),[28] was surprisingly inert. Other common silanes, such as Et_3SiH, are also not amenable to transmetalation of copper alkoxides at reduced temperatures. Although the observations above in the composite

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(27) As a result of extensive and unexpected frothing, a considerable amount of the reaction mixture was lost, accounting for an isolated yield of only 48%. The TLC of the reaction mixture, as usual, was 'spot-to-spot'.

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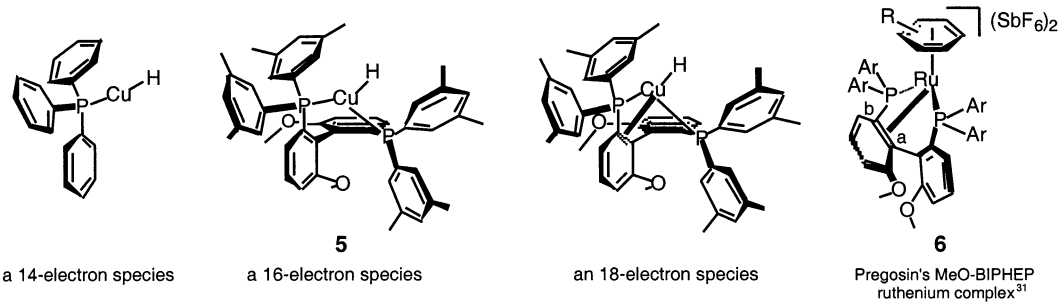

Figure 3. Possible modes of complexation for CuH.

Table 1. Study of Monomeric Silanes as Alternatives to PMHS

silane	comments
Ph_2MeSiH	takes longer than PMHS (12 h); leads to silyl ether product in **95% ee** at -78°; **90% yield**
$Me_2Si(H)-O-Si(H)Me_2$ (TMDS)	takes longer than PMHS (11 h); leads to silyl ether product in **94% ee** at -78°; **98% yield**
TMSO-Si(H)(Me)-OTMS (HMTS)	inactive; no hydrosilylation at -78 °C after 5 h
Et_3Si-H	at 0°, get at most 3% product in the presence of 5 equiv of this silane.
$PhSiH_3$	inactive (toward propiophenone); no hydrosilylation at -78 to 0 °C

do not suggest any obvious trends, as more data on these hydrosilylations gradually became available, the role and importance of the silane began to shift from that of an innocent "bystander" in the stereodifferentiating step to a key reaction ingredient (vide infra).

What is the Active Catalyst? Considering that $(Ph_3P)CuH$ is unreactive under the conditions of these hydrosilylations, this is a notable example of ligand-accelerated catalysis.[29] Because the silane (PMHS) is presumably responsible for regenerating CuH (assumed to occur via a four-centered Negishi-like transmetalation;[30] vide infra), it appeared to be acting after the stereodefining 1,2-addition step by **5**. Unlike Stryker's reagent, which is readily observed by ^{1}H NMR at ambient temperatures (δ 3.52, m, H−Cu),[22] all attempts to locate the hydride in **5** between −100 and 25 °C met with failure. Moreover, the ^{31}P NMR spectrum of **5** was complex and uninterpretable, with multiple signals by no means suggestive of a single discrete entity. Portionwise addition of ligand **4A** to readily observed $(Ph_3P)CuH$ did indeed cause the gradual decrease and eventual loss of signal at 3.52 ppm; however, no new discernible hydride peak appeared in its absence that could be assigned to that in hydride **5**.

The possibility that **5**, a 16-electron species (shown as a monomer in Figure 3), derives additional electron density at copper by virtue of electron donation from a π-bond in the biaryl ligand was also considered. This mode of bonding, thereby formally converting **5** into an 18-electron species, is not unreasonable in light of extensive literature precedent in related ruthenium complexes. Pregosin has shown unequivocally via X-ray analyses that such bonding patterns exist for BIPHEP ligands (as in **6**).[31] In these cases, spectroscopic analyses using ^{13}C NMR further support the structure, with carbons labeled "a" and "b" in **6** appearing at 85 and 91 ppm, respectively. A similar ^{13}C NMR experiment unfortunately revealed no new signals in the ^{13}C NMR spectrum for the corresponding two biaryl carbon atoms in complex **5**.

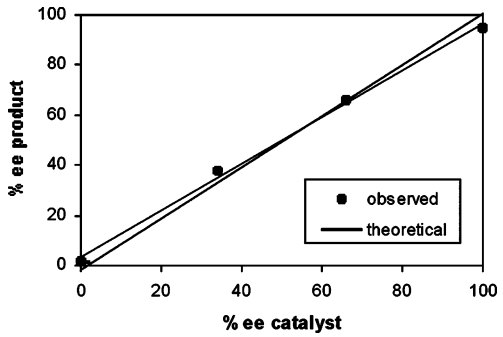

Figure 4. Plot of observed ee of product alcohol as a function of optical purity of **5**.

Additional insight regarding the aggregation state of the reactive reagent(s) under these hydrosilylation conditions was anticipated from experiments in which the ee of the ligand was varied. As illustrated in Figure 4, an essentially 1:1 correspondence between ligand and product ee was found using acetophenone as a test case under our original conditions (i.e., 3% $(Ph_3P)CuH$, 3% **4A**, PMHS, −50 °C, 0.5 M in substrate), indicative of the absence of nonlinear effects[32] in these reductions. Thus, it is likely that one (or more) species of a monomeric nature is involved, notwithstanding the tendency of copper hydride to aggregate.[14,15,23]

CuH·L$_n$*: Ligand Variations. Although CuH ligated in an as yet unknown fashion by bis-phosphine **4A** possesses an extraordinary reactivity profile relative to that seen in its complexation by Ph_3P or BINAP, other bidentate ligands were also screened. At issue were questions regarding stereoelectronic effects on both the biaryl as well as the substituents on phosphorus and the relationship, if any, between the dihedral angle associated with the biaryl array and product ee. The nature of the aromatic ring itself needed to be addressed as well, as

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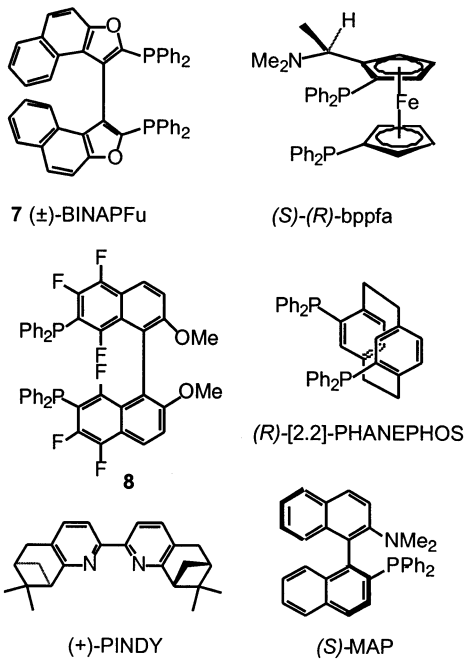


Figure 5. Biaryl ligands which showed no activity in the presence of CuH.

bidentate phosphines composed of a heteroaromatic biaryl core are well known to function as ligands in asymmetric catalysis.[1] Several ligands (Figure 5), therefore, were individually tested in the presence of CuH/PMHS on acetophenone; all were ineffective in their ability to activate CuH. These results provided interesting clues as to the chelation requirements of CuH for successful hydrosilylations. While both PINDY[33] and MAP[34] highlight the importance of bis-phosphines, the total inactivity of CuH in the presence of PHANEPHOS[35] or bppfa suggested that a biaryl nucleus may be essential. The latter result based on this ferrocenyl derivative was surprising given the activity of CuH complexed by dppf (vide supra).[22] The lack of efficacy displayed by CuH in the presence of BINAPFu (**7**)[36] or Yudin's hexafluorobiaryl **8**,[37] both ligands being relatively electron-deficient at phosphorus, was yet another hint that stereoelectronic factors were equally as influential as were gross structural considerations.

Given the success with reagent **5** based on the BIPHEP motif, the subtleties associated with this class of biaryl ligand were manifested in attempted reactions of CuH complexed by bis-phosphines **9**−**11** (Figure 6). Curiously, replacement of the aryl moieties on phosphorus by alkyl groups (cf. **9** and **10**), thereby increasing electron density at the site of chelation, rendered these resulting species inactive. Likewise, substitution of the aryl rings by a heteroaromatic in **11** leading to decreased Lewis basicity at phosphorus had the same net effect.

Although the data above might lead to the conclusion that catalyst activity required a biaryl bis-phosphine array bearing

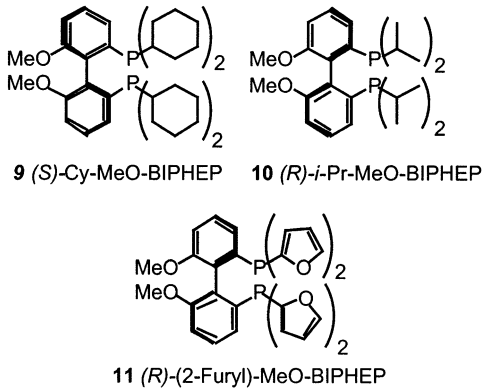


Figure 6. BIPHEP ligands which led to no reaction in the presence of CuH.

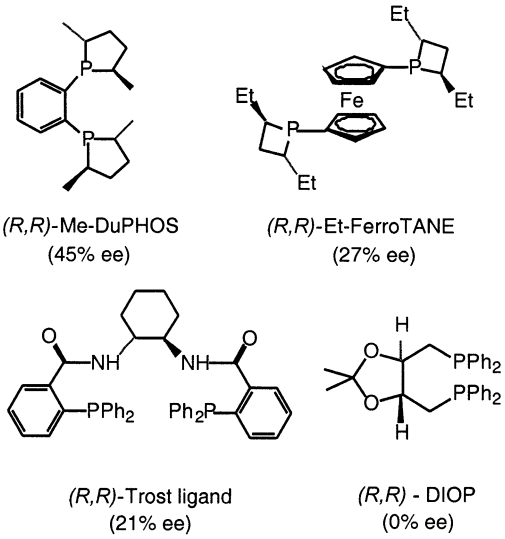


Figure 7. Representative biaryl ligands screened for effectiveness.

residues on phosphorus of a particular electron density, such a ligand design was found not to be essential for hydrosilylation to take place, even at −50°. A number of structurally unrelated ligands (Figure 7), as their presumed CuH complexes, did in fact effect clean reduction of acetophenone, although the level of ee in each case was not useful. Other ligands, such as JOSIPHOS and related ferrocenyl derivatives provided in "kit" form from Solvias (Figure 8),[38] were all active under our standard (low temperature) conditions. These latter species showed no apparent trends, although the highest ee (a respectable 88%) was achieved by CuH complexed by the most electron-rich ligand in this series.

The heteroaromatic biaryl bis-phosphines **12** and **13** (Figure 9), prepared and studied by Sannicolo,[39] were screened using acetophenone as educt both to examine the potential influence of sulfur on the activity of the derived CuH complex and to compare BITIANP with closely related BINAPFu (**7**).[36] While BITIOP (**12**) led to no 1,2-reduction of acetophenone, BITIANP reacted at −50° in 8 h and afforded the expected alcohol product in 89% ee. Although it is tempting to invoke reduced elec-

(33) (a) Malkov, A. V.; Baxendale, I. R.; Bella, M.; Langer, V.; Fawcett, J.; Russell, D.; Mansfield, D. J.; Valko, M.; Kocovsky, P. *Organometallics* **2001**, *20*, 673. (b) Malkov, A. V.; Bella, M.; Langer, V.; Kocovsky, P. *Org. Lett.* **2000**, *2*, 3047.
(34) Vyskocil, S.; Smrcina, M.; Hanus, V.; Polasek, M.; Kocovsky, P. *J. Org. Chem.* **1998**, *63*, 7738.
(35) (a) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207. (b) Rossen, K.; Pye, P. J.; Maliakal, A.; Volante, R. P. *J. Org. Chem.* **1997**, *62*, 6462.
(36) Anderson, N. G.; Parvez, M.; Keay, B. A. *Org. Lett.* **2000**, *2*, 2817.
(37) Generously provided by Prof. A. Yudin, University of Toronto.
(38) (a) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062. (b) Blaser, H.-U.; Brieden, W.; Pugin, B.; Spindler, F.; Studer, M.; Togni, A. *Top. Catal.* **2002**, *19*, 3.
(39) (a) Benincori, T.; Cesarotti, E.; Piccolo, O.; Sannicolo, F. *J. Org. Chem.* **2000**, *65*, 2043. (b) Benincori, T.; Brenna, E.; Sannicolo, F.; Trimarco, L.; Antognazza, P.; Cesarotti, E.; Demartin, F.; Pilati, T. *J. Org. Chem.* **1996**, *61*, 6244.

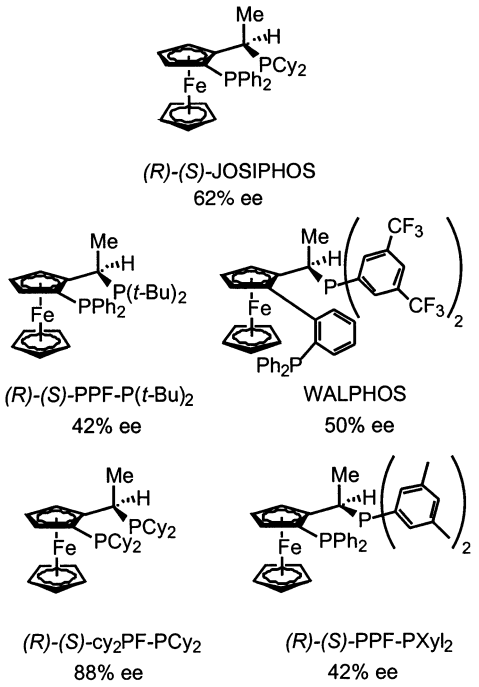


Figure 8. Results using JOSIPHOS-type ligands with CuH.

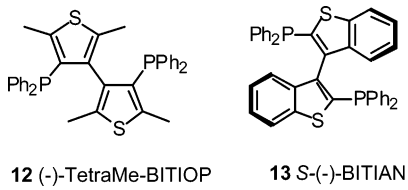


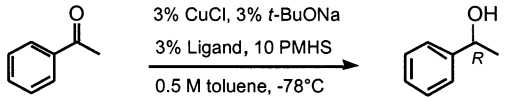
Figure 9. Representative heterobiaryl ligands.

tronegativity of sulfur in **13** relative to oxygen in **7** as the key factor accounting for the activity in the CuH-derived complex from **13**, clearly more results with other bis-benzthiazole ligands in this group are needed before any meaningful analysis should be offerred.

On the basis of a recent report by Saito and co-workers,[40] selected examples of Takasago's new SEGPHOS series of biaryl ligands were examined, as these seemingly fulfilled the criteria for both activity and high chiral induction displayed by Roche ligands **4A** and **4B** (Chart 1). Indeed, the two related bis-benzodioxole biaryl ligands, *S*-(−)-DM-SEGPHOS **14A** and *R*-(−)-DTBM-SEGPHOS **14B**, were found to possess exceptional catalytic properties for this CuH-based hydrosilylation chemistry. While initially the reagent combination of DM-SEGPHOS·CuH (**15**) plus PMHS reduced acetophenone to the silylated alcohol with 95% ee at −78° within 6 h (at 0.5 M in toluene), a rate and ee which are roughly comparable to those seen using **5** (Table 2), the 3,5-di-*tert*-butyl-4-methoxy analogue (DTBM-SEGPHOS·CuH; **16**) afforded the product alcohol in 96% ee under identical conditions in *minutes*. This trend was maintained in the form of a second comparison example using cyclohexyl phenyl ketone **17**, from which the ee of alcohol **10** was raised from 88[24] to 93% (Scheme 4). Additional results using biaryl ligand **14B** at a S/L ratio of 2000:1 on three other aryl ketones are illustrated in Table 3.

(40) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

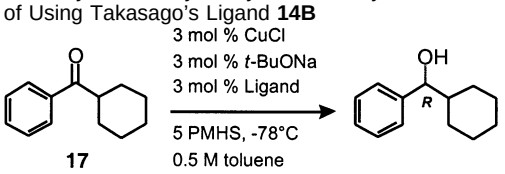
Table 2. Hydrosilylations of Acetophenone: Comparison of BIPHEP- and SEGPHOS-Ligated CuH



ligand	% ee	time (h)
(*R*)-3,5-Xyl-MeO-BIPHEP	94	5
(*R*)-4-MeO-3,5-DTB-MeO-BIPHEP	90	*a*
(−)-DM-SEGPHOS	95	6
(−)-DTBM-SEGPHOS	96	≤1

[a] 1 h: 50% conversion.

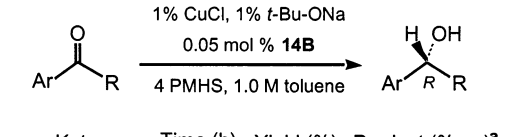
Scheme 4. Asymmetric Hydrosilylations of Aryl Ketone **17**: The Impact of Using Takasago's Ligand **14B**

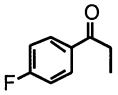
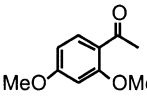


(R)-3,5-Xyl-MeO-BIPHEP 88% ee 10 h

(-)-DTBM-SEGPHOS 93% ee ≤ 1 h

Table 3. Hydrosilylation of Aromatic Ketones Using *R*-(−)-DTBM-SEGPHOS at −50 °C



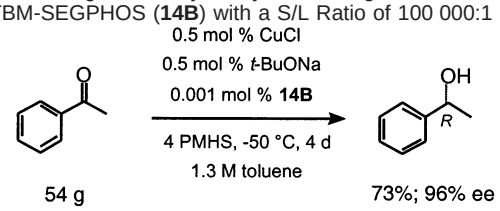
Ketone	Time (h)	Yield (%)	Product (% ee)[a]
	4	93	95[b]
	3	91	82
	8	98	98

[a] ee values were determined by conversion of each product to its acetate and analysis by chiral capillary GC. [b] Observed, $[\alpha]_D = +36°$ ($c = 2.5$ $CHCl_3$); (*R*)-enantiomer lit., $[\alpha]_D = +51°$ ($c = 2.5$ $CHCl_3$).

That DTBM-SEGPHOS is also active at the ≥100,000:1 S/L level was documented employing the identical large-scale experiment on acetophenone as was performed previously using catalyst **5** in the presence of excess PMHS. After an extended period of time (4 d), the reaction was complete and afforded the desired product in 96% ee (Scheme 5). Although the reaction was essentially "spot-to-spot", workup proved to be difficult for this one-time experiment due to formation of siloxanes which occluded material and led to the moderate yield of distilled product obtained (73%).

Reagent Stability. Considering that very high S/L ratios can be used in these hydrosilylations, the CuH presumed to be generated in situ is virtually all in nonligated (i.e., unstabilized) form. Thus, it might be viewed as remarkable that hydrosilylations requiring several hours can be carried out without significant loss of CuH. This observation, however, notwith-

Scheme 5. Large-Scale Hydrosilylation Using (−)-DTBM-SEGPHOS (**14B**) with a S/L Ratio of 100 000:1



standing the thermal instability of CuH,[41] is a result of the low-temperature conditions being used. Upon warming a reaction toward 0°, considerable decomposition can be observed by the gradual formation of black particulates, assumed to be copper(II) oxide formed via oxidation by trace amounts of dissolved oxygen in the reaction medium. These reagents (i.e., **5**, **15**, and **16**) can be utilized over time at temperatures in the −20 to 0 °C range, however, by simply including an equivalent of Ph_3P relative to CuH. Thus, for reactions to be run at higher temperatures, either the in situ preparation of CuH in the presence of an equivalent of Ph_3P or the use of preformed Stryker's reagent helps to maintain the lifetime of CuH. Trace amounts of a BIPHEP or SEGPHOS ligand, which presumably divert equal quantities of CuH into a highly reactive, ligated form, together carry out the intended hydrosilylation, while the majority of CuH remains available for the released biaryl ligand once 1,2-reduction/transmetalation has occurred. This "trick" of storing CuH by inclusion of Ph_3P derives from the fact that (Ph_3P)CuH itself cannot compete with the ligand-accelerated catalysis manifested by catalysts **5**, **15**, and **16**.

Unreactive Aromatic Ketones. Despite the reactivity profile of CuH when associated with either a BIPHEP or a SEGPHOS ligand, there were a number of aryl ketones which did not undergo hydrosilylation. Included among this group are compounds **18**−**20** (Figure 10). Although it could be argued that **18** is akin to a doubly vinylogous amide and thus is deactivated, the trifluoromethyl residue should aid considerably by increasing the electrophilicity of this substrate toward hydride addition. Both **19** and **20**, where the conjugated nitrile might inductively activate the ketone, showed the opposite effect. While neither substituent (Me_2N− or −CN) is likely to exert any steric impediment given their para- and meta-orientations, respectively, it is also unlikely that complexation of Cu(I) (a poor Lewis acid) by the conjugated amine is operative. In **19** or **20**, a transient η^2 dπ* association between Cu(I) and the nitrile residue is unknown,[42] leaving a linear dπ* interaction from copper to nitrogen as a possibility to account for reagent inactivity. Nonconjugated nitriles (e.g., 5-cyano-2-pentanone) are known to show the same inhibitory effect.[23a] Nonetheless, just what the overriding factors are that negate hydrosilylation even at ambient temperatures remains clouded at this time.

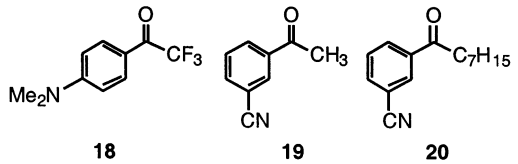
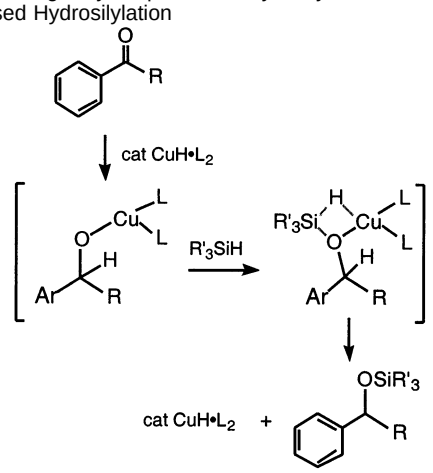


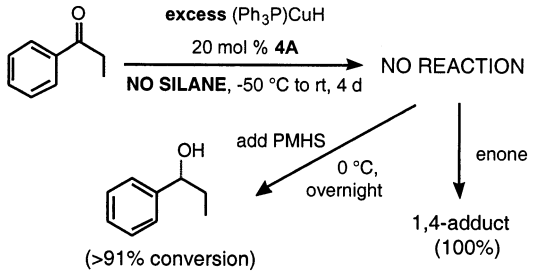
Figure 10. Aryl ketones which did not undergo hydrosilylation.

(41) Whitesides, G. M.; Stredronsky, E. R.; Casey, C. P.; San Filippo, J. *J. Am. Chem. Soc.* **1970**, *92*, 1426.

Scheme 6. Originally Proposed Catalytic Cycle for CuH/Silane-Based Hydrosilylation



Scheme 7. Impact of the Silane on an Aryl Ketone Reduction with CuH

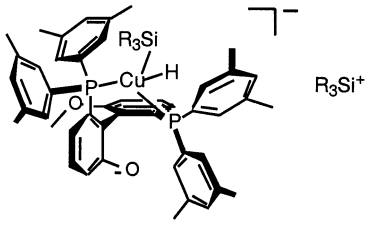


Role of the Silane. It has been proposed by us[22] and others[30] that a Negishi four-centered transition state may be the mechanism by which an initially formed copper alkoxide undergoes transmetalation to the product silyl ether with concomitant regeneration of CuH (Scheme 6). An alternative mechanism which relies on an oxidative addition of silane to a Cu(I) *ate* complex (in DMI) has also been advanced.[30a] In our ongoing studies aimed at better understanding this combination of reagents (i.e., CuH + ligand + silane), the experiment was conducted where a *stoichiometric* amount of CuH was introduced to propiophenone, along with 20 mol % BIPHEP **4A** *in the absence of a silane* (Scheme 7). Considering that hydrosilyation of this ketone can be effected at −78 °C with less than 1 mol % CuH and 10^{-3} mol % **4A** (in the presence of excess silane), hydrosilylation would be expected to occur extremely rapidly at temperatures between −50 and −78 °C. It was, therefore, unexpected to find that *none* of the ketone was consumed, independent of temperature (up to room temperature). Maintenance of catalyst integrity was confirmed by addition of 4,4-dimethylcyclohexenone at 0 °C, which led to complete conjugate reduction. Moreover, subsequent addition of PMHS to the reaction mixture at 0 °C overnight induced the expected hydrosilylation, leading to nearly complete consumption of ketone.

From these preliminary results, we conclude that the silane is an integral part of catalyst makeup, that these asymmetric hydrosilylation-silyl ether forming reactions could alternatively

(42) Such bonding schemes are well-established, however, for various complexes of Mn,[42a] Rh,[42b] and Mo.[42c] (a) Aspinall, H. C.; Deeming, A. J.; Donovan-Mtunzi, S. *J. Chem. Soc., Dalton Trans.* **1983**, 2669. (b) Deraniyagala, S. P.; Grundy, K. R. *Inorg. Chim. Acta* **1984**, *84*, 205. (c) Curtis, M. D.; Klinger, R. J. *J. Organomet. Chem.* **1978**, *161*, 23. Curtis, M. D.; Han, K. R.; Butler, W. M. *Inorg. Chem.* **1980**, *19*, 2096.

be viewed as potentially involving a nonracemic silyl hydrido cuprate (e.g., **21**), rather than discrete CuH ligated by bidentate phosphines as originally thought. Sensitivity of these reductions to the nature of the silane (cf. Table 1) thus appears to be in line with similar findings in related rhodium-,[2,6] zinc-,[8] and titanium-based[10] systems. More experimental work is warranted to sort out the events which occur upon mixing various silanes with ligated CuH.[43]



21

Dihedral Angle versus ee. Last, it is interesting to note the correlation between the calculated dihedral angles associated with various biaryl bis-phosphines (Figure 11),[40] complexed to ruthenium, and the ee's obtained from these CuH-mediated hydrosilylations. That is, the levels of chiral induction appear to increase as the angle narrows (e.g., using acetophenone: BINAP, 75% ee; BIPHEP **5**, 94% ee; SEGPHOS **16**, 96% ee). As proposed by Saito and co-workers,[40] the enhanced selectivity may reflect increasing steric interactions as the bulky aryl residues on phosphorus are brought in closer proximity to the conjugated aryl ketone portion of the educt.[44]

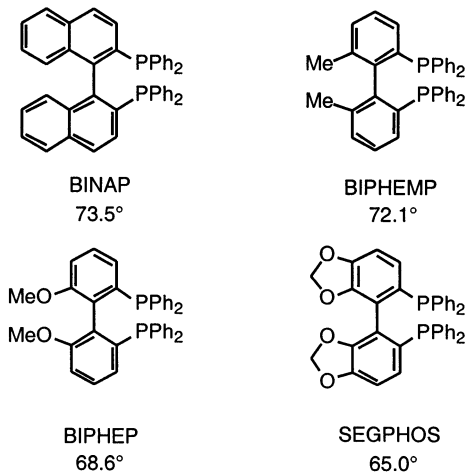


Figure 11. Dihedral angles for Ru complexes of various bis-phosphine ligands (CAChe MM2).

Summary and Conclusions

Asymmetric hydrosilylations of aromatic ketones have for years been dominated by the chemistry of rhodium, and to a lesser extent that of ruthenium and titanium. As compared to asymmetric hydrogenations which routinely take place at substrate-to-catalyst ratios in the (tens of) thousands or higher, hydrosilylations have not been competitive in this regard. Two ligand systems have now been identified, which via their CuH complexes give rise to extremely reactive reagents capable of effecting asymmetric hydrosilylations not only in high yields and ee's, but at temperatures on the order of 100 °C lower than those typically used which rely on other metal hydrides. Of course, the need for temperatures in the −50 to −78 °C range to maximize ee's may well be viewed as a negative feature, because this reaction parameter can be costly for large-scale reactions. The catalysts formed from CuH/PMHS and either Roche's 3,5-xyl-MeO-BIPHEP or Takasago's DTBM-SEGPHOS are unique insofar as the ligands examined thus far are concerned in their abilities to transfer chirality to prochiral aryl ketones in an efficient and predictable way. The survey of ligands conducted is suggestive of certain structural and stereoelectronic features which impart both reactivity and chirality via association with an as yet undetermined CuH/silane complex prior to the 1,2-reduction of an aryl ketone. These key features include (1) a biaryl bis-phosphine skeleton, preferrably a biphenyl array; (2) aryl (but not heteroaryl), rather than alkyl, substitution on phosphorus; and (3) a minimized dihedral angle in the biaryl bis-phosphine-complexed copper hydride. Nonetheless, although some understanding of the factors that have led to an effective method for asymmetric hydrosilylations of aryl ketones is in hand, attempts to identify the active species involved have been unsuccessful to date. While no conclusions can as yet be drawn from spectroscopic data, mechanistic studies, theoretical work, and possibly new ligand designs may help to better understand this intriguing combination of reagents.

Experimental Section

General. Reactions were performed using standard Schlenk techniques involving flame-dried glassware, oven-dried Teflon coated stir bars, and double septa tops under an argon atmosphere. Toluene and THF were freshly distilled from sodium benzophenone ketyl under argon before use. CH_2Cl_2 and triethylamine were freshly distilled from CaH_2 under argon. CuCl was prepared from $CuCl_2$ following a literature procedure.[46] NaO-*t*-Bu was purchased from Aldrich and used as received. Ac_2O and all commercially available ketones were distilled prior to use. Melting points were measured on a Fisher-Johns apparatus and are uncorrected. Products were purified by chromatography on 200−425 mesh Fisher brand silica gel. TLC analyses were performed on commercial Kieselgel 60 F_{254} silica gel plates. NMR spectra were obtained on Varian Inova systems using $CDCl_3$ with proton and carbon resonances at 400 and 100 MHz, respectively; the δ scale was referenced to $CDCl_3$ (δ 7.27) or TMS (additive, δ 0.00) residual lines. FTIR spectra were obtained on an ATI Mattson Infinity Series spectrometer neat on NaCl plates or as KBr pellets and are reported in cm^{-1}. Mass spectral data were acquired on a VF Autospec or an analytical VG-70-250 HF instrument.

Representative Procedure for Asymmetric Reduction of Aryl Ketones.[24] A flame-dried 10 mL round-bottomed flask (RBF) was equipped with a magnetic stir bar and purged with argon. CuCl (6.2 mg, 0.063 mmol, 3 mol %), NaO-*t*-Bu (6.7 mg, 0.070 mmol, 3.5 mol %), and (*R*)-3,5-Xyl-MeO-BIPHEP (44.2 mg, 0.064 mmol, 3 mol %) were added as solids and then stirred in toluene (2 mL) at room temperature for 20 min to give a colorless solution. A flame-dried 5 mL pear bottomed flask (PBF) was cooled under argon and charged with toluene (2 mL), and then propiophenone (0.27 mL, 2.03 mmol) was added at room temperature. The RBF was then charged

(43) Significant insight in this regard can be gleaned from the work of Schubert and co-workers who studied reactions between CuH and various silanes and stannanes.[45] Preliminary experiments from mixing catalyst **5** with PMHS do suggest that H_2 is evolved. Full details will be reported in due course.

(44) This trend argues against an 18 electron species (cf. Figure 3), as complexation of CuH by a π-bond of the biaryl ligand requires significant twisting, which *increases* the dihedral angle.

(45) Schubert, U.; Mayer, B.; Ruzz, C. *Chem. Ber.* **1994**, *127*, 2189.

(46) Keller, R. N.; Wycoff, H. D. In *Inorganic Syntheses*; Fernelius, W. C., Ed.; McGraw-Hill: New York, 1946; pp 1−4.

with polymethylhydrosiloxane (PMHS) (1.32 mL, 20.3 mmol, 10.0 equiv) at room temperature to give a colorless solution which was then cooled to −78 °C. The contents of the PBF were then added to the RBF via cannula, and the reaction was monitored by TLC (10% ether: hexanes). Upon completion, the reaction was poured into 2.5 M aqueous NaOH (20 mL). The rate of stirring of the mixture was gradually increased after which it was stirred vigorously for ≥3 h (CAUTION: premature stirring will result in excessive PHMS frothing!). The biphasic mixture was extracted with ether (5 × 20 mL), and the organic layer was concentrated to an oil before being redissolved in ether (25 mL) and dried over anhydrous Na_2SO_4. Filtration followed by column chromatography (25% ether:hexanes) provided the desired alcohol (216.4 mg, 87%) as a yellow oil. $R_f = 0.27$. IR (thin film): 3358, 2964, 2929, 2877, 1496, 1453, 1010. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 5H), 4.51 (t, $J = 6.8$, 6.4 Hz, 1H), 2.37 (bs, 1H), 1.73 (m, 2H), 0.87 (t, $J = 7.6$, 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8, 128.5, 127.5, 126.1, 76.0, 32.0, 10.3. GCMS calcd for $C_9H_{12}O$ (M^+) 136.09, found 136.0.

General Procedure for Derivatization of Chiral Alcohols and Determination of Enantiomeric Excess (ee). The purified alcohol product was dissolved in dichloromethane (0.2 M) and cooled to 0 °C. Ac_2O (2.0 mL, 21.2 mmol, 10 equiv) followed by Et_3N (2.8 mL, 20.1 mmol, 10 equiv) were added via syringe, and the reaction was monitored by TLC. Upon completion, the reaction was poured into brine (10 mL) and extracted with dichloromethane (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Filtration through a plug of silica and subsequent chrial GC analysis (Chiraldex G-TA or Chiraldex B-DM column, isothermal) led to an indicated ee.

Consecutive Hydrosilylations at 20,000:1 Substrate to Ligand (S/L). To a flame-dried 500 mL RBF equipped with a magnetic stir bar were added CuCl (258.4 mg, 2.61 mmol, 3 mol %), NaO-*t*-Bu (251.4 mg, 2.62 mmol, 3 mol %), and (*R*)-3,5-Xyl-MeO-BIPHEP (3.2 mg, 0.00461 mmol, 0.005 mol %) as solids in a glovebox. In a separate flame-dried and argon purged 100 mL PBF were added toluene (50 mL) and then acetophenone (10.1 mL, 87 mmol). The RBF was then charged with toluene (125 mL) and cooled to −50 °C. This solution was warmed to ca. 0 °C and then immediately returned to −50 °C, this sequence being repeated three times until all solids dissolved to form a clear solution. The RBF was then charged with PMHS (28 mL, 435 mmol, 5.0 equiv) at −50 °C followed by introduction of the ketone by cannulation. Note: white precipitates may form (some ketone freezing). The reaction was monitored by TLC (10% ether:hexanes). After 28 h, a flame-dried 50 mL PBF was charged with toluene (10 mL) and then acetophenone (10 mL, 87 mmol). This solution was then transferred via cannula to the existing reaction mixture which was still maintained at −50 °C. The reaction was monitored by TLC and quenched after an additional 34.5 h; the total reaction time was 62.5 h. The reaction mixture was slowly transferred into aqueous NaOH (100 mL, 2.5 M) and stirred for ≥3 h (CAUTION: premature stirring will result in excessive PMHS frothing!). The aqueous layer was extracted with diethyl ether (5 × 100 mL), and the organic layer was concentrated in vacuo to an oil and then redissolved in diethyl ether and dried over anhydrous Na_2SO_4. The product was converted to the corresponding acetate derivative followed by chiral GC analysis (Chiraldex G-TA column, 80 °C), which indicated a 92% ee favoring the (*R*)-enantiomer.

Asymmetric Hydrosilylation Using (*R*)-3,5-Xyl-MeO-BIPHEP at 100,000:1 S/L. To a flame-dried 700 mL cylindrical flask equipped with a magnetic stir bar were added CuCl (220.1 mg, 2.22 mmol, 0.5 mol %), NaO-*t*-Bu (214.9 mg, 2.24 mmol, 0.5 mol %), and (*R*)-3,5-Xyl-MeO-BIPHEP (2.9 mg, 0.00417 mmol, 0.001 mol %) as solids in a glovebox. In a separate flame-dried and argon purged 100 mL PBF were added toluene (44 mL) and then acetophenone (54 mL, 463 mmol). The cylindrical vessel was then charged with toluene (306 mL) and cooled to −50 °C. This solution was warmed to ca. 0 °C and then immediately returned to −50 °C three times until a solution resulted. The cylindrical vessel was then charged with PMHS (146 mL, 2.235 mol, 5.0 equiv) at −50 °C, followed by introduction of the ketone. Note: white precipitates may form (some ketone freezing). The reaction was monitored by TLC (10% ether:hexanes). Upon complete consumption of ketone (26 h), the reaction was poured into 2.5 M aqueous NaOH (500 mL) and stirred >3 h (CAUTION: premature stirring will result in excessive PMHS frothing!). The aqueous layer was extracted with diethyl ether (5 × 500 mL), and the organic layer was concentrated in vacuo to an oil which was redissolved in diethyl ether (100 mL) and then dried over anhydrous Na_2SO_4. Concentration in vacuo followed by distillation (bp = 113 °C at 11 mmHg) yielded the desired product alcohol (27.2 g, 48%, see CAUTION above) as a clear liquid. Conversion to the corresponding acetate derivative and chiral GC analysis (Chiraldex G-TA column, 60 °C) indicated that the (*R*)-enantiomer had been formed in 93% ee.

Asymmetric Hydrosilylation Using *R*-(−)-DTBM-SEGPHOS at 100,000:1 S/L. To a flame-dried 500 mL cylindrical flask equipped with a magnetic stir bar were added CuCl (219.7 mg, 2.22 mmol, 0.5 mol %), NaO-*t*-Bu (215.0 mg, 2.24 mmol, 0.5 mol %), and *R*-(−)-DTBM-SEGPHOS (5.2 mg, 0.00441 mmol, 0.001 mol %) as solids in a glovebox. In a separate flame-dried and argon purged 100 mL PRB were added toluene (50 mL) and then acetophenone (54 mL, 463 mmol). The cylindrical vessel was then charged with 300 mL of freshly distilled, dry toluene, and the contents were cooled to −50 °C. The resulting mixture was warmed to ca. 0 °C and then immediately returned to −50 °C three times until a homogeneous reaction mixture resulted. The cylindrical vessel was then charged with PMHS (120 mL, 1852 mmol, 4.0 equiv) at −50 °C, followed by introduction of the ketone via cannula. Note: white precipitates may form (some ketone freezing). The reaction was monitored by TLC (10% ether:hexanes). Upon complete consumption of ketone (4 d), the reaction was poured into 2.5 M aqueous NaOH (500 mL) and stirred ≥3 h (CAUTION: premature stirring will result in excessive PMHS frothing!). The aqueous layer was extracted with diethyl ether (5 × 500 mL), and the organic layer was concentrated to an oil which was then redissolved in diethyl ether and dried over anhydrous Na_2SO_4. Concentration in vacuo followed by distillation (bp = 113 at 11 mmHg) yielded the product alcohol (41.3 g, 73%) as a clear liquid. Conversion to the acetate derivative and chiral GC analysis (Chiraldex G-TA column, 60 °C) indicated that the (*R*)-enantiomer had been formed in 96% ee.

Hydrosilylation Using Ph_2MeSiH (Table 1, Entry 1). A flame-dried 10 mL RBF was equipped with a magnetic stir bar and purged with argon. Cu(I)Cl (7.2 mg, 0.073 mmol, 4 mol %), *t*-BuONa (7.1 mg, 0.074 mmol, 4 mol %), and (*R*)-3,5-Xyl-MeO-BIPHEP (50.2 mg, 0.072 mmol, 3 mol %) were added as solids and then dissolved in toluene (2 mL) at room temperature for 20 min. A flame-dried 5 mL PBF was cooled to room temperature under argon and charged with toluene (2 mL) to which was added acetophenone (0.24 mL, 2.05 mmol) at room temperature. The RBF was then charged with diphenylmethylsilane (1.60 mL, 8.2 mmol, 4.0 equiv) at room temperature and cooled to −78 °C. The PBF was then added to the RBF via cannula, and the reaction was monitored by TLC (10% ether:hexanes). Upon completion, the reaction was filtered through a pad of Celite/charcoal with copious EtOAc washings, and the solvents were subsequently removed under vacuum via rotary evaporation. Column chromatography (hexanes) provided the corresponding silyl ether (590.7 mg, 90%) as a yellow oil. Treatment of silyl ether with TBAF (2.42 mL, 2.70 mmol, 1.3 equiv) in THF (9.2 mL, 0.2 M) followed by Ac_2O (1.9 mL, 0.20 mmol, 10 equiv) and NEt_3 (2.86 mL, 0.2 mmol, 10 equiv) in CH_2Cl_2 (10 mL, 0.2 M) afforded the corresponding acetate derivative, and chiral GC analysis (Chiraldex G-TA column) indicated an ee of 95%.

Asymmetric Hydrosilylation of Acetophenone Using TMDS (Table 1, Entry 2). To a flame-dried 10 mL RBF equipped with a magnetic stir bar were added CuCl (4.4 mg, 0.0444 mmol, 2 mol %), NaO-*t*-Bu (4.7 mg, 0.0468 mmol, 2 mol %), and (*R*)-3,5-Xyl-MeO-BIPHEP (14.5 mg, 0.0206 mmol, 1 mol %) as solids in a glovebox. The flask was then charged with toluene (2 mL) and stirred at room

temperature for 20 min. To a flame-dried 5 mL PBF were added toluene (2 mL) and then acetophenone (0.23 mL, 2.0 mmol). The RBF was then charged with TMDS (0.88 mL, 10 mmol, 5.0 equiv) and immediately cooled to −78 °C followed by addition of ketone via cannula. The reaction was monitored by TLC (10% ether:hexanes). Upon completion (11 h), the reaction was filtered through a pad of Celite/charcoal and rinsed with EtOAc (ca. 50 mL). The solvents were concentrated in vacuo, and the silyl ether was dissolved in THF (3 mL) to which was added TBAF (0.7 mL, 1.0 M in THF). The corresponding alcohol was isolated (239.6 mg, 98%) after flash chromatography (20% ether:hexanes). Treatment of the alcohol (1.45 mmol) with Ac_2O (1.4 mL, 15 mmol, 10 equiv) and NEt_3 (2 mL, 15 mmol, 10 equiv) in CH_2Cl_2 (7 mL, 0.2 M) afforded the corresponding acetate which was determined to be 94% ee by chiral capillary GC.

Asymmetric Hydrosilylations Using other Ligands; (*R*,*R*)-Me-DuPHOS. We followed the general procedure above using CuCl (3.5 mg, 0.0354 mmol, 3 mol %), NaO-*t*-Bu (3.5 mg, 0.0364 mmol, 3 mol %), (*R*,*R*)-Me-DuPHOS (10 mg, 0.0326 mmol, 3 mol %), PMHS (0.16 mL, 2.5 mmol, 2.5 equiv), toluene (2 mL, 0.5 M), and propiophenone (0.13 mL, 1.0 mmol). The reaction was run at 0 °C for 4 h. Conversion of the alcohol product to its acetate derivative and chiral GC analysis (Chiraldex G-TA column) indicated an ee of 45%.

(*R*,*R*)-Et-FerroTANE. We followed the general procedure above using (PPh_3)CuH (12.2 mg, 0.00625 mmol, 3.75 mol %), (*R*,*R*)-Et-FerroTANE (16.1 mmol, 0.0342 mmol, 3.5 mol %), PMHS (0.16 mL, 2.5 mmol, 2.5 equiv), toluene (2.0 mL, 0.5 M), and propiophenone (0.13 mL, 1.0 mmol). The reaction was run at 0 °C for 18 h. Conversion of the alcohol product to its acetate derivative and chiral GC analysis (Chiraldex G-TA column) indicated an ee of 27%.

(*R*,*R*)-Trost Ligand. We followed the general procedure above using (PPh_3)CuH (11.3 mg, 0.00583 mmol, 3.5 mol %), (*R*,*R*)-Trost ligand (20.9 mmol, 0.0303 mmol, 3 mol %), PMHS (0.16 mL, 2.5 mmol, 2.5 equiv), toluene (2.0 mL, 0.5 M), and propiophenone (0.13 mL, 1.0 mmol). The reaction was run at 0 °C for 9 h and then warmed to room temperature and stirred for 2 d. Conversion of the alcohol product to its acetate derivative and chiral GC analysis (Chiraldex G-TA column) indicated an ee of 21%.

(*R*,*R*)-DIOP. We followed the general procedure above using (PPh_3)-CuH (11.3 mg, 0.00583 mmol CuH, 3.5 mol %), (*R*,*R*)-DIOP (20.2 mmol, 0.0405 mmol, 4 mol %), PMHS (0.16 mL, 2.5 mmol, 2.5 equiv), toluene (2.0 mL, 0.5 M), and acetophenone (0.12 mL, 1.0 mmol). The reaction was run at 0 °C for 1 h. Conversion of the alcohol product to its acetate derivative and chiral GC analysis (Chiraldex G-TA column) indicated an ee of 0%.

(*R*)-(*S*)-JOSIPHOS. We followed the general procedure above using CuCl (4.2 mg, 0.0424 mmol, 4 mol %), NaO-*t*-Bu (3.3 mg, 0.0343 mmol, 3 mol %), (*R*)-(*S*)-JOSIPHOS (18.8 mg, 0.0316 mmol, 3 mol %), PMHS (0.65 mL, 10 mmol, 10 equiv), toluene (2 mL, 0.5 M), and acetophenone (0.12 mL, 1.0 mmol). The reaction was run at −78 °C for 20 h. Conversion of the alcohol product to its acetate derivative and chiral GC analysis (Chiraldex G-TA column, 60 °C) indicated an ee of 62%.

(*R*)-(*S*)-PPF-P(*t*-Bu)$_2$. We followed the general procedure above using CuCl (3.3 mg, 0.0333 mmol, 3 mol %), NaO-*t*-Bu (3.6 mg, 0.0375 mmol, 3 mol %), (*R*)-(*S*)-PPF-P(*t*-Bu)$_2$ (34 mg, 0.0627 mmol, 6 mol %), PMHS (0.65 mL, 10 mmol, 10 equiv), toluene (2 mL, 0.5 M), and acetophenone (0.12 mL, 1.0 mmol). The reaction was run at −78 °C for 20 h. Conversion of the alcohol product to its acetate derivative and chiral GC analysis (Chiraldex G-TA column, 60 °C) indicated an ee of 42%.

(*S*)-(*S*)-WALPHOS. We followed the general procedure above using CuCl (3.7 mg, 0.0374 mmol, 3.5 mol %), NaO-*t*-Bu (4.0 mg, 0.0416 mmol, 4 mol %), WALPHOS (31.5 mg, 0.0339 mmol, 3 mol %), PMHS (0.65 mL, 10 mmol, 10 equiv), toluene (2 mL, 0.5 M), and acetophenone (0.12 mL, 1.0 mmol). The reaction was run at −78 °C for 2 h. Conversion of the alcohol product to its acetate derivative and chiral GC analysis (Chiraldex G-TA column, 60 °C) indicated an ee of 50%.

(*R*)-(*S*)-cy$_2$PF-PCy$_2$. We followed the general procedure above using CuCl (3.6 mg, 0.0364 mmol, 3.5 mol %), NaO-*t*-Bu (3.6 mg, 0.0375 mmol, 4 mol %), (*R*)-(*S*)-cy$_2$PF-PCy$_2$ (19.1 mg, 0.0315 mmol, 3 mol %), PMHS (0.65 mL, 10 mmol, 10 equiv), toluene (2 mL, 0.5 M), and acetophenone (0.12 mL, 1.0 mmol). The reaction was run at −78 °C for 2 h. Conversion of the alcohol product to its acetate derivative and chiral GC analysis (Chiraldex G-TA column, 60 °C) indicated an ee of 88%.

(*R*)-(*S*)-PPF-P(Xyl)$_2$. We followed the general procedure above using CuCl (3.3 mg, 0.0333 mmol, 3.5 mol %), NaO-*t*-Bu (3.7 mg, 0.0385 mmol, 3 mol %), (*R*)-(*S*)-PPF-PXyl$_2$ (20.8 mg, 0.0326 mmol, 3 mol %), PMHS (0.65 mL, 10 mmol, 10 equiv), toluene (2 mL, 0.5 M), and acetophenone (0.12 mL, 1.0 mmol). The reaction was run at −78 °C for 20 h. Conversion of the alcohol product to its acetate derivative and chiral GC analysis (Chiraldex G-TA column, 60 °C) indicated an ee of 42%.

(−)-BITIANP. We followed the general procedure above using CuCl (6.4 mg, 0.0646 mmol, 3 mol %), NaO-*t*-Bu (6.2 mg, 0.0645 mmol, 3 mol %), (−)-BITIANP (39.3 mg, 0.0619 mmol, 3 mol %), PMHS (1.34 mL, 20.5 mmol, 10 equiv), toluene (4 mL, 0.5 M), and acetophenone (0.24 mL, 2.05 mmol). The reaction was run at −50 °C for 8 h. Conversion of the alcohol product to its acetate derivative and chiral GC analysis (Chiraldex G-TA column, 80 °C) indicated an ee of 84%.

Asymmetric Hydrosilylation of Cyclohexyl Phenyl Ketone (Scheme 4).[47] We followed the general procedure above using cyclohexyl phenyl ketone (800 mg, 4.25 mmol), CuCl (4.2 mg, 0.043 mmol), NaO-*t*-Bu (4.1 mg, 0.043 mmol), *R*-(−)-DTBM-SEGPHOS (2.5 mg, 2.13×10^{-3} mmol), PMHS (1.11 mL, 17.0 mmol), and toluene (4.25 mL). Conversion of the alcohol product to its acetate derivative and chiral GC analysis (Chiraldex B-DM column 90 °C) indicated an ee of 93%.

Asymmetric Hydrosilylation of Acetophenone; Comparison of Substituted BIPHEP versus SEGPHOS Ligands: (*R*)-4-MeO-3,5-DTB-MeO-BIPHEP. We followed the general procedure above using CuCl (3.5 mg, 0.0355 mmol, 3.5 mol %), NaO-*t*-Bu (3.7 mg, 0.0385 mmol, 3 mol %), (*R*)-4-MeO-3,5-DTB-MeO-BIPHEP (34.7 mg, 0.0301 mmol, 3 mol %), PMHS (0.65 mL, 10 mmol, 10 equiv), toluene (2 mL, 0.5 M), and acetophenone (0.12 mL, 1.0 mmol). Conversion of the alcohol product to its acetate derivative and chiral GC analysis (Chiraldex G-TA column, 60 °C) indicated an ee of 90%.

***R*-(+)-DM-SEGPHOS.** We followed the general procedure above using CuCl (6.3 mg, 0.0636 mmol, 3 mol %), NaO-*t*-Bu (6.1 mg, 0.0635 mmol, 3 mol %), *R*-(+)-DM-SEGPHOS (45.1 mg, 0.0624 mmol, 3 mol %), PMHS (1.34 mL, 20.5 mmol, 10 equiv), toluene (4 mL, 0.5 M), and acetophenone (0.24 mL, 2.05 mmol). Conversion of the alcohol product to its acetate derivative and chiral GC analysis (Chiraldex G-TA column, 80 °C) indicated an ee of 95%.

***R*-(−)-DTBM-SEGPHOS.** We followed the general procedure above using CuCl (7.3 mg, 0.0737 mmol, 3.5 mol %), NaO-*t*-Bu (6.1 mg, 0.0635 mmol, 3 mol %), *R*-(−)-DTBM-SEGPHOS (72.7 mg, 0.0616 mmol, 3 mol %), PMHS (1.34 mL, 20.5 mmol, 10 equiv), toluene (4 mL, 0.5 M), and acetophenone (0.24 mL, 2.05 mmol). Conversion of the alcohol product to its acetate derivative and chiral GC analysis (Chiraldex G-TA column, 80 °C) indicated an ee of 96%.

Asymmetric Hydrosilylation of 4-Fluoropropiophenone.[48] We followed the general procedure above using CuCl (2.3 mg, 0.023 mmol), NaO-*t*-Bu (2.2 mg, 0.023 mmol), *R*-(−)-DTBM-SEGPHOS (1.4 mg, 1.15×10^{-3} mmol), PMHS (0.60 mL, 9.20 mmol), toluene (2.30 mL), and 4-fluoropropiophenone (0.32 mL, 2.30 mmol). Isolation afforded 330 mg (93%) of the corresponding alcohol product. Comparison of spectral data with known literature values[48] confirmed the identity of

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the product. Conversion of the alcohol product to its acetate derivative and chiral GC analysis (Chiraldex B-DM column, 80 °C) indicated an ee of 95%.

Asymmetric Hydrosilylation of 2-Bromoacetophenone.[47] We followed the general procedure above using CuCl (1.1 mg, 0.011 mmol), NaO-*t*-Bu (1.1 mg, 0.011 mmol), *R*-(−)-DTBM-SEGPHOS (3.24 mg, 2.75×10^{-3} mmol), PMHS (0.28 mL, 4.40 mmol), toluene (1.10 mL), and 2-bromoacetophenone (0.145 mL, 1.10 mmol). Isolation afforded 200 mg (91%) of the corresponding alcohol product. Comparison of spectral data with known literature values[47] confirmed the identity of the product. Conversion of the alcohol product to its acetate derivative and chiral GC analysis (Chiraldex B-DM column, 90 °C) indicated an ee of 82%.

Asymmetric Hydrosilylation of 2,4-Dimethoxyacetophenone.[47] We followed the general procedure above using CuCl (3.5 mg, 0.035 mmol), NaO-*t*-Bu (3.4 mg, 0.035 mmol), (*R*)-(−)-DTBM-SEGPHOS (2.1 mg, 1.75×10^{-3} mmol), PMHS (0.90 mL, 14.0 mmol), toluene (3.50 mL), and 2,4-dimethoxyacetophenone (630 mg, 3.50 mmol). Isolation afforded 625 mg (98%) of the corresponding alcohol product. Comparison of spectral data with known literature values[47] confirmed the identity of the product. Conversion of the alcohol product to its acetate derivative and chiral GC analysis (Chiraldex B-DM column, 120 °C) indicated an ee of 98%.

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