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Nonracemic Diarylmethanols From CuH-Catalyzed Hydrosilylation of Diaryl Ketones

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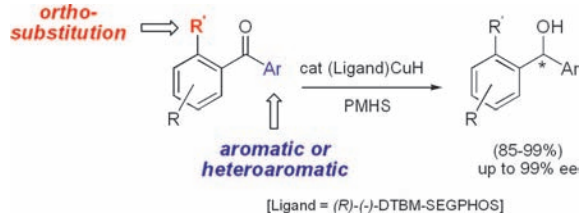
ABSTRACT



An efficient method for the synthesis of nonracemic diarylmethanols has been developed. The use of (*R*)-(−)-(DTBM-SEGPHOS)CuH effects highly enantioselective 1,2-hydrosilylation of prochiral diaryl ketones.

The diarylmethyl moiety, ArAr'CH−, is a common subunit present in a variety of physiologically active compounds, such as (*R*)-neobenodine,[1a] CDP-840,[1b] and tolterodine[1c] (DetrolLA; Figure 1). It can also be found in precursors to new ligand scaffolds[1d] (e.g., tetraarylethanes). Asymmetric inroads to such targets follow several lines, although most fall within the three broader categories of (1) biocatalytic reductions,[2] (2) diaryl ketone reductions,[3] or (3) 1,2-additions of aryl organometallics to aryl aldehydes[4] (Scheme 1). An extensive review[5] by Bolm and co-workers recently highlighted the role played by catalysis en route to this functional group array.

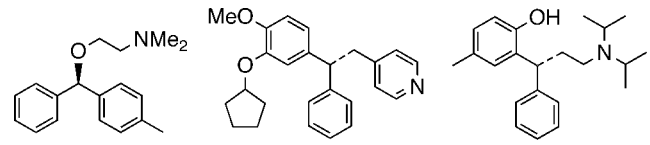


Figure 1. Representative bioactive diarylmethanes.

Notably, relatively few reports were quoted involving transfer hydrogenation beyond the Noyori[6] study of 2000 on substituted benzophenones, which occurs under mild temperatures (23−35 °C) and pressures (8 atm). Even fewer studies have appeared utilizing an alternative

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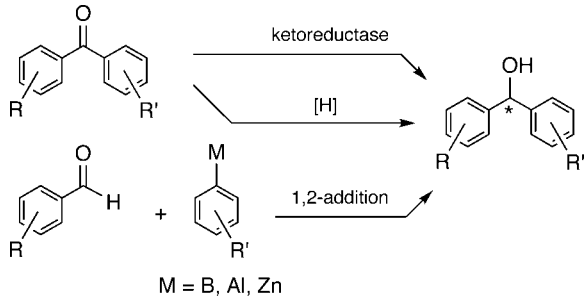
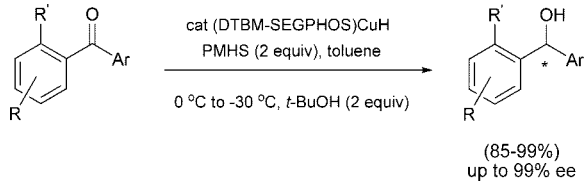
Scheme 1. Three Traditional Routes to Diarylmethanes



asymmetric hydrosilylation.[7] In this Letter, we describe a study on the use of nonracemically ligated CuH as a catalyst to effect asymmetric hydrosilylation of an assortment of aromatic and heteroaromatic ketones (Scheme 2).

Scheme 2. CuH-Catalyzed Asymmetric Hydrosilylation

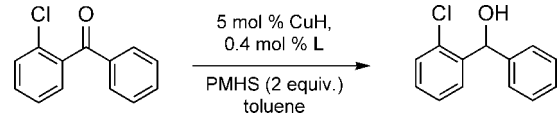


CuH was prepared in situ by mixing 5% CuCl, 5% NaO-*t*-Bu, and 0.4% ligand relative to substrate in the presence of excess PMHS (polymethylhydrosiloxane).[8] Several nonracemic ligands from Takasago and Solvias were screened using *ortho*-chlorobenzophenone (Table 1). Levels of enantioselectivity above 90% ee and full conversion of starting materials were obtained for all but two ligands (**L4** and **L6**), using substrate-to-ligand (S/L) ratios of 250:1. Higher S/L ratios (up to 1250:1) have been used, although prolonged reaction times are needed. Noteworthy is the option for arriving at either enantiomeric product in good ee, an option not characteristic of enzymatic processes.[2]

Hydrosilylation of benzophenones bearing substituents at varying positions revealed a requirement for *ortho*-substitution (Scheme 3). Although in all cases the reactions proceeded in less than two hours (~1 M) with high efficiency (>95% isolated yields) at 0 °C, ee's for all *meta*- and *para*-substituted examples were nil.

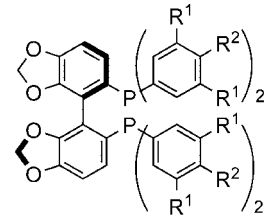
As illustrated in Scheme 4, a wide range of *ortho*-substituted benzophenone derivatives were successfully reduced to their corresponding alcohols with good to excellent ee's and in high isolated yields. A variety of

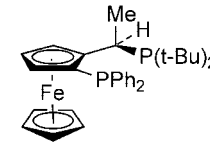
Table 1. Ligands Screened



ligand	time (h)	temp (°C)	ee (%)[a]
L1	1	0	82(*S*)
	13	−30	92(*S*)
	24	−30	90(*S*)[b]
L2	1	0	81(*S*)
L3	1	0	84(*R*)
	13	−30	90(*R*)
L4	1	0	14(*R*)
L5[c]	1	0	83(*R*)
	13	−30	91(*R*)
L6	1	0	57(*S*)[d]

[a] By chiral HPLC. [b] 0.008% **L1**. [c] (*S*)-BINAP. [d] Incomplete.





L6 = (*R*,*S*)-PPF-P(*t*-Bu)$_2$

L1 = (*R*)-DTBM-SEGPHOS, R^1= *t*-Bu, R^2= OMe
L2 = (*R*)-SEGPHOS, R^1= R^2 = H
L3 = (*S*)-DM-SEGPHOS, R^1= Me, R^2 = H
L4 = (*S*)-*i*-Pr-SEGPHOS, R^1= *i*-Pr, R^2 = H

functional groups (e.g., halogen, ether, thioether, naphthalene, and acetal) and heteroaromatic systems (e.g., furan, pyrrole, and thiophene) are readily tolerated. On the other hand, *ortho*-methylated substrates such as **10** and **11** led to modest ee's for both product alcohols (Figure 2). Relative to alkyl aryl ketones and dialkyl ketones,[9] these substrates possess lower reactivity toward hydrosilylation by ligated CuH. Hence, a higher temperature (**2** in Scheme 4, 0 °C to rt) and the presence of *t*-BuOH[10] (**2** and **9** in Scheme 4) are crucial to complete the reduction. Absolute stereochemical assignments follow from both an X-ray determination for alcohol **2** and comparison of optical rotation for product **9** with known data[6] (see Supporting Information).

An evaluation of the protocol for asymmetric hydrosilylation applied to aryl pyridyl and aryl imidazolyl ketones was also made (Figure 3), given the limited number of

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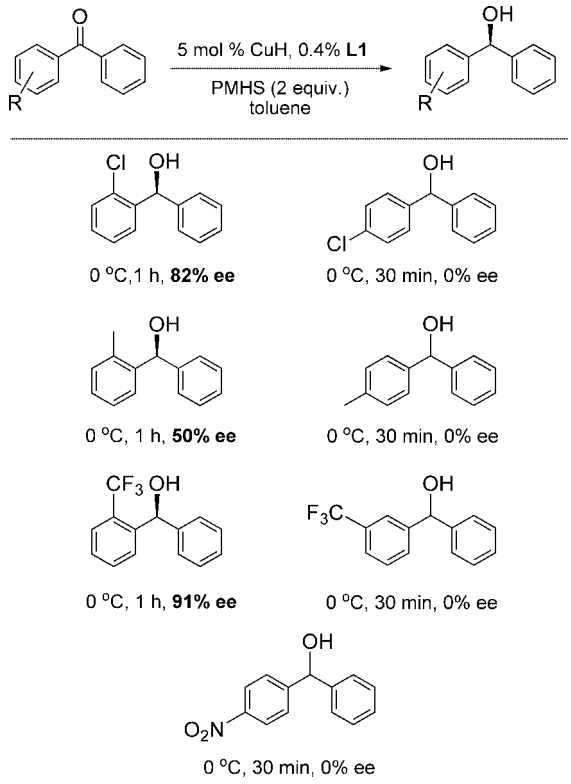
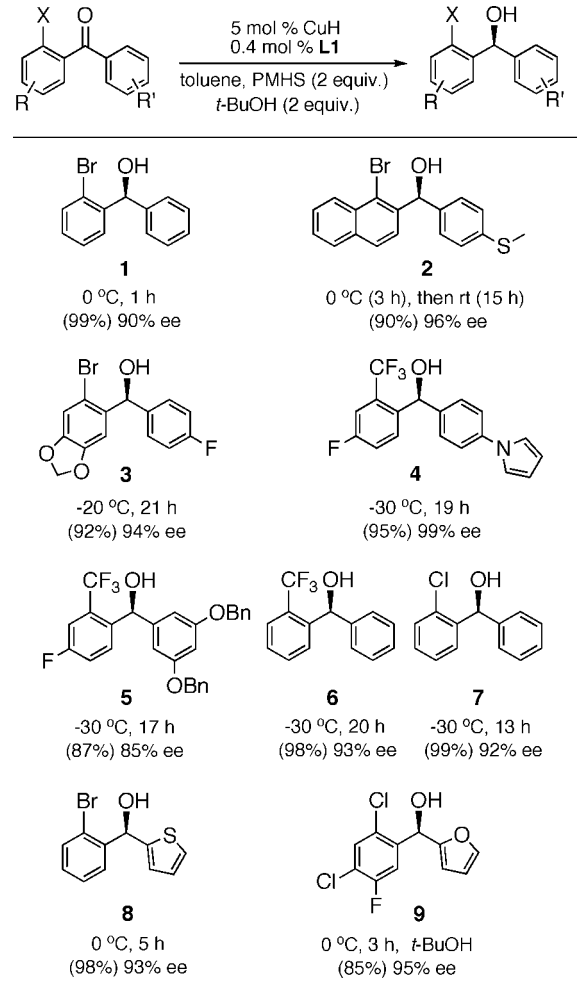
Scheme 3. Impact of Aryl Substitution on CuH-Catalyzed Asymmetric Hydrosilylation



Scheme 4. Representative Examples of Asymmetric Hydrosilylation[a]



[a]All yields in parentheses refer to isolated materials.

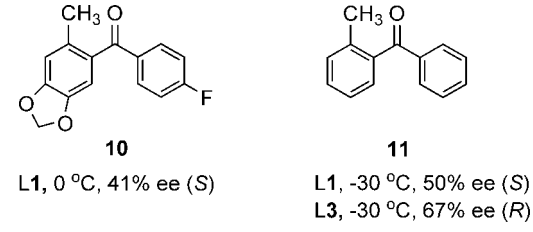


Figure 2. *ortho*-Methyl aryl ketones: modest ee's from CuH-catalyzed hydrosilylation.

reports[11] on asymmetric syntheses of the corresponding derived nonracemic alcohols. Similar to results described by Chen,[11b] reductions of 2-benzopyridines (**12** and **13**) gave the product alcohols in modest ee's (67%, 56%, respectively), while the parent ketone **14** led to racemic material. On the other hand, *meta*-substituted pyridyl ketone (3-benzopyridine, **15**) gave the product alcohol in far higher ee (86%). Hydrosilylation of 2-benzo-1-methyl-1*H*- imidazole (**16**) also afforded the derived alcohol in low ee, suggesting that internal coordination by a heteroaromatic nitrogen to the catalyst erodes stereoselectivity.

Surprisingly, while a bulky *ortho*-TMS group (**17**, Table 2) slows hydrosilylation, it does not necessarily improve enantioselectivity. Under optimized conditions, using (*R*)-DTBM-SEGPHOS (**L1**), (*R*)-SEGPHOS (**L2**), or (*S*)-BINAP (**L5**), limited conversion of educt **17** was noted. With ligation of CuH by (*R*)-Xyl-MeO-BIPHEP (**L7**), the reaction took place at room temperature to the extent of 60% conversion and 41% ee. Notably, (*S*)-DM-SEGPHOS (**L3**) was the most effective of the ligands examined (74% ee), although this reaction was also sluggish, even in the presence of *t*-BuOH. A cyano group (**18** in Table 2) appears to impart considerable substrate activity, leading to nearly full conversion (87% yield) albeit with modest enantioselectivity (78% ee).

The high ee's realized with *ortho*-brominated substrates (see products **1**−**3** in Scheme 4) offer several possibilities for further manipulation. For example, while reaction of *ortho*-vinylbenzophenone (**19**) afforded carbinol **20** in moderate ee (72%; Scheme 5), the same product **20** (with 94% ee) can be easily made from **3** (94% ee) by Stille coupling without erosion in enantiomeric excess.

In summary, CuH complexed with Takasago's nonracemic ligands DM-SEGPHOS or DTBM-SEGPHOS are efficient catalysts for asymmetric hydrosilylation of selected diaryl and aromatic-heteroaromatic ketones in good to excellent ee's and isolated yields.[12] This technol-

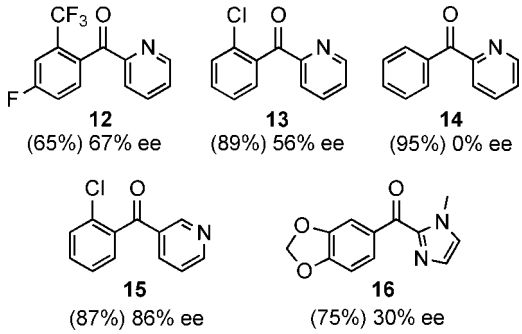
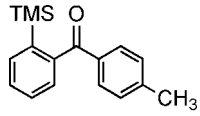


Figure 3. Reductions using **L1**: impact of the location of nitrogen within the aryl ring.

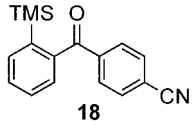
ogy offers an attractive alternative to traditional carbon-based organometallic nucleophiles (zinc/boron reagents) and hydrogenations, as well as to the recently reported enzymatic reductions that do not rely on *ortho*-substitution on one of the aromatic rings. CuH-catalyzed additions involve very mild conditions, atmospheric pressures, and an economically appealing transition metal.

Table 2. Hydrosilylations of *ortho*-TMS-Substituted Aryl Ketones



17

ligand	time (h)	temp (°C)	ee (%)
L1	24 h	rt	-
L2	24 h	rt	-
L3	24 h	rt	77 (30% conversion; *R*)
	24 h[a]	0	74 (85% conversion; *R*)
L5	24 h	rt	-
L7[b]	24 h	rt	41 (60% conversion; *S*)

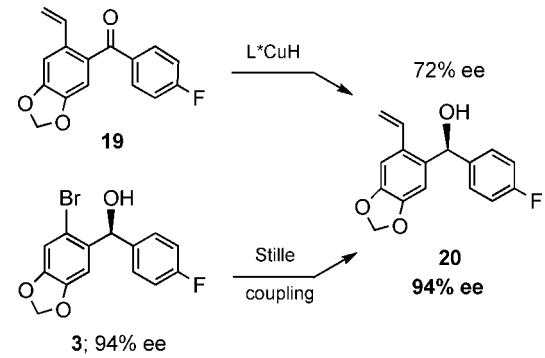


18

L3	2 h[a]	rt	75 (*R*)
	24 h	-30	78 (87% yield; *R*)

[a] With *t*-BuOH. [b] (*R*)-Xyl-MeO-BIPHEP

Scheme 5. Two Alternative Routes to *ortho*-Substituted Diarylcarbinols, e.g., **20**



Acknowledgment. Financial support provided by the NSF (CHE 0550232) is warmly acknowledged. We thank Tagasako and Solvias for a generous supply of the ligands used in this study.

Supporting Information Available: Procedures, characterization data of products, and X-ray crystal structure of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) General procedure for the asymmetric CuH hydrosilylation of diaryl ketones. To an oven-dried, argon-purged round bottomed flask (10 mL) was added CuCl (2.5 mg, 0.025 mmol), NaO-*t*-Bu (2.5 mg, 0.025 mmol), (*R*)-DTBM-SEGPHOS (2.5 mg, 0.002 mmol), and 0.5 mL of toluene. The mixture was cooled to 0 °C and stirred for 15 min before PMHS (65 μL, 1 mmol) was added, and the solution was cooled to the temperature shown in Table 3. A solution of diaryl ketone (1 mmol) in 0.5 mL of toluene and *t*-BuOH (0.095 mL, 1 mmol; if indicated) was added to the CuH solution via cannula. The reaction was monitored by TLC and quenched with 2 mL of NaOH (30% aq.) and 2 mL of EtOAc. An hour of vigorous stirring was needed to quench the initially formed silyl ether and excess PHMS. The aqueous layer was extracted with three portions of EtOAc, and the combined organic layers were dried over anhydrous $MgSO_4$ and then concentrated via rotary evaporation. Flash chromatography on silica gel with hexane and EtOAc provided the desired diarylmethanol.