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Copper(I) Hydride-Catalyzed Asymmetric Hydrosilylation of Heteroaromatic Ketones

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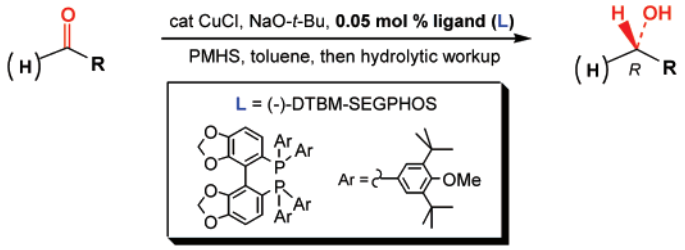
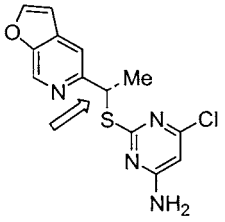
ABSTRACT

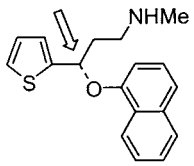


In situ generation of CuH ligated by Takasago's new nonracemic ligand, DTBM-SEGPHOS, leads to an especially reactive reagent capable of effecting asymmetric hydrosilylation of heteroaromatic (H) ketones under very mild conditions. PMHS serves as an inexpensive source of hydride. Substrate-to-ligand ratios on the order of 2000:1 are employed.

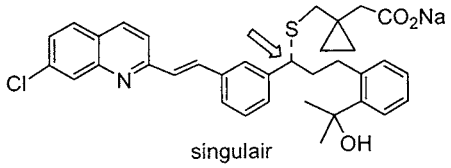
Asymmetric reduction of heteroaromatic ketones offers an especially attractive entry to chiral nonracemic alcohols that serve as valuable intermediates en route to a variety of target structures. Representative examples of physiologically active compounds of interest include the anti-HIV compound PNU-142721,[1] an inhibitor of serotonin and norepinephrine uptake carriers (*S*)-duloxetine,[2] and Singulair for treatment of chronic asthma.[3] Recently disclosed methods of accomplishing such transformations are very impressive; indeed, a number are among the portfolios of Nobel prize-winning synthetic groups.[4]



PNU-142721



(*S*)-duloxetine



singulair

Surprisingly, as an alternative to asymmetric hydrogenation, the corresponding process of hydrosilylation of heteroaromatic ketones has received scant attention. As is often the case in this area, catalysis is based mainly on expensive rhodium complexes.[5] Moreover, the levels of enantiomeric excess obtained to date have not exceeded 63%.[6] In this

(1) Wishka, D. G.; Graber, D. R.; Seest, E. P.; Dolak, F. H.; Watt, W.; Morris, J. *J. Org. Chem.* **1998**, *63*, 7851.
(2) Deeter, J.; Frazier, J.; Staten, G.; Staszak, M.; Weigel, L. *Tetrahedron Lett.* **1990**, *31*, 7101.
(3) Labelle, M.; Belley, M.; Gareau, Y.; Gauthier, J. Y.; Guay, D.; Gordon, R.; Grossman, S. G.; Jones, T. R.; Leblanc, Y.; McAuliffe, M.; McFarlane, C.; Masson, P.; Metters, K. M.; Ouimet, N.; Patrick, D. H.; Piechuta, H.; Rochette, C.; Sawyer, N.; Xiang, Y. B.; Pickett, C. B.; Ford-Hutchinson, A. W.; Zamboni, R. J.; Young, R. N. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 283.
(4) (a) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

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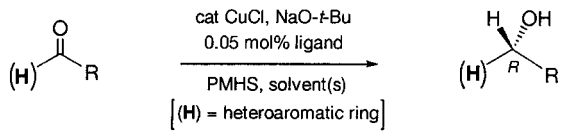
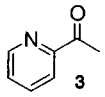
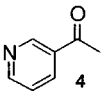
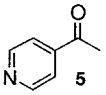
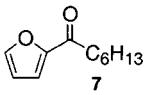
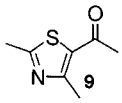
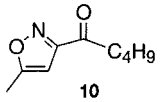
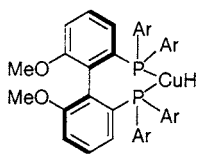
Table 1. Representative Hydrosilylations of Heteroaromatic (H) Ketones



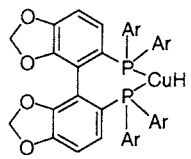
entry	ketone	ligand	temp (°C)	time (h)	yield (%)	product ee (%)[a]
1	 3	**2a**	-50	2	97	90[b,c,d]
		1b	-78	*e*	*e*	70[f,g,h]
		1a	-78	*e*	*e*	51[f,g,h]
2	 4	**2a**	-35	8	92	75[b,c,d]
3	 5	**2a**	-78	6.5	97	84[g,i,j]
4	 6	**2a**	-50	5	85	92[b,d,f]
		1b	-78	*e*	*e*	90[d,f,h]
		1a	-78	*e*	*e*	78[d,f,h]
5	 7	**2a**	-50	12	98	81[b,d,f]
		1b	-78	*e*	*e*	70[c,d,h]
		1a	-78	*e*	*e*	77[c,d,h]
6	 8	**2a**	-50	4	97	90[b,d,f]
		1b	-78	*e*	*e*	79[c,d,h]
7	 9	**2a**	-50	4	94	99[d,f,h]
8	 10	**2a**	-50	10	68[k]	83[b,c,d]

[a] Determined by conversion of each alcohol (following hydrolytic workup) to its acetate and analysis by chiral capillary GC; HP Chiral 10β column, 1.0 mL/min flow rate, 80 °C isotherm was typical. [b] CuCl/NaO-*t*-Bu (1 mol %). [c] Toluene (0.50 M). [d] PMHS (4 equiv). [e] Reaction was quenched before completion. [f] Toluene (1.0 M). [g] PMHS (5 equiv). [h] CuCl/NaO-*t*-Bu (3 mol %). [i] THF/toluene (12.5%). [j] CuCl/NaO-*t*-Bu (2 mol %). [k] Single experiment.

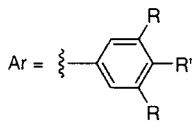
contribution, we describe an alternative technology based on catalytic copper(I) chemistry, using CuH ligated to a nonracemic biaryl bisphosphine (i.e., reagents **1** and **2**).



1; *(R)*-BIPHEP•CuH



2; SEGPHOS•CuH



(a) R = *t*-Bu, R' = OMe

(b) R = Me, R' = H

Previously, we have shown that simple aromatic ketones could be reduced in excellent ees under the influence of catalytic copper hydride,[7] where polymethylhydrosiloxane (PMHS)[8] served as the otherwise innocuous stoichiometric source of hydride. Remarkable levels of substrate to ligand (S/L) could be realized employing Roche's 3,5-xyl-MeO-BIPHEP ligand to form (presumed) reagent **1b**.[9] The impact of heteroatoms, within either the aromatic ring or the side-

(5) Nishiyama, H.; Itoh, K. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 1990; pp 111−143.
(6) Lukevics, É.; Iovel', I.; Rubina, K.; Popelis, Y.; Gaukhman, A. *Chem. Heterocycl. Compd. (NY)* **1996**, *32*, 294.
(7) Lipshutz, B. H.; Noson, K.; Chrisman, W. *J. Am. Chem. Soc.* **2001**, *123*, 12917.
(8) Lawrence, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 3381.
(9) Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Muller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.* **1996**, *68*, 131.

chain, had yet to be determined. Although the Cu(I) participating in these reductions must be ligated at some point by one or both phosphorus atoms in **1** or **2**, both sulfur and/or nitrogen (as part of a heteroaromatic array) also form strong bonds to copper(I) and could sequester the metal, thereby terminating the catalytic cycle.

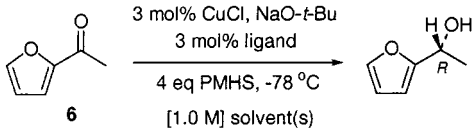
The study began with three acetylpyridines **3**−**5**, as summarized in Table 1 (entries 1−3). In all cases, 0.05 mol % nonracemic biaryl bisphosphine ligand was chosen as a representative of the high substrate to ligand (S/L) ratios possible (thus, in these examples, S/L = 2000:1). Neither 2- nor 3-acetylpyridine could be run in the preferred solvent toluene at −78 °C (0.5 M) due to limited solubility at this temperature. The former reacted completely at −50 °C using the Takasago SEGPHOS ligand-based system **2a** [(−)-DTBM-SEGPHOS][10] to afford the (*R*)-product alcohol[11] in high yield and with an ee of 90%. By way of comparison, although reactions of **3** under the influence of the corresponding reagents **1a** and **1b** proceeded to a limited extent at −78 °C, the ees in each case were actually lower than that realized with reagent **2a** at the higher reaction temperature. Likewise, **4** required warming to −35 °C to reach completion after 8 h. Use of THF as a cosolvent with 4-acetylpyridine **5** allowed for complete reaction at −78 °C (entry 3), although some erosion in ee was observed. This pattern due to solvent (vide infra) was unexpected on the basis of prior observations involving aromatic ketones,[7] where reactions run solely in THF afforded ees essentially identical to those obtained in 100% toluene.

Two examples in the furan series were examined (Table 1, entries 4 and 5). Again, SEGPHOS-ligated CuH was the reagent of choice. Although methyl ketone **6** reacted at −50 °C to give a product of 92% ee, substrate **7** bearing a larger side-chain led to less steric discrimination by **2a** in the presumed four-centered transition state for hydride delivery.[7] A brief survey of solvent and ligand effects on the ees of the furanyl alcohol derived from **6** is illustrated in Table 2. Clearly, although at −78 °C these reactions did not go to completion, the percentage of THF present can significantly alter the extent of stereoinduction. Moreover, under otherwise identical conditions, while reagents **1b** and **2a** led to products of essentially the same ee in pure toluene (entries 1 vs 2), **1a** was considerably less effective in this medium (entry 5).

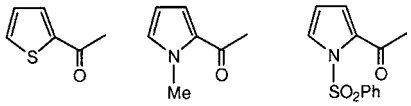
2-Acetylthiazole **8** could be smoothly reduced at −50 °C in toluene with **2a** (Table 1, entry 6). In keeping with the apparent trend noted above, the BIPHEP-ligated CuH **1b**, even at −78 °C, produced the desired alcohol in lower ee. The fully substituted 5-acetylthiazole **9** reacted readily at the same temperature to afford essentially a single enantiomeric alcohol. Acylated isoxazole **10**, sterically akin to furan **7** (entry 5), led to a similar rate and level of stereoinduction (entry 8).

Unfortunately, not all of the heteroaromatics investigated underwent this copper hydride-catalyzed asymmetric hydrosilylation. Acetylated thiophene and pyrrole nuclei, represented by potential educts **11**−**13**, were completely inert. Remarkably, even upon warming of these three reactions to ambient temperatures, and independent of ligand, no reduction took place. Addition of acetophenone to these reaction mixtures at room-temperature did not result in any 1,2-addition of hydride to this aryl ketone. Why there would be special opportunities for sequestering copper by sulfur and nitrogen (assuming this accounts for the lack of reactivity observed) in these 2-acylated five-membered ring arrays, when related chelation is possible in heteroaromatics **3**, **8**, **9**, and **10**, remains unclear at this time. Attempts to alter the substrate and/or reagent by introduction of a Lewis acid (e.g., $BF_3{\cdot}OEt_2$, $(EtO)_3B$)[12] or alternative source of sulfur(II) (e.g., dimethyl sulfide; 2 equiv)[13] did not have an impact on reagent activity.

Table 2. Effect of THF as a Solvent on Product ee



entry	reagent	solvent(s)	product ee (%)
1	**2a**	100% toluene	91
2	**1b**	100% toluene	90
3	**1b**	12.5% THF/tol	88
4	**1b**	100% THF	70
5	**1a**	100% toluene	78
6	**1a**	12.5% THF/tol	74
7	**1a**	100% THF	67



11 **12** **13**

In summary, an effective method[14] has been developed for the asymmetric 1,2-reduction of heteroaromatic ketones

(10) Saito, T.; Yokoawa, T.; Ishizakik, T.; Moroi, T. Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264. The absolute stereochemistry of (−)-DTBM-SEGPHOS has yet to be established.

(11) Product alcohol from **4** using reagent **2a**: (*R*)-1-(3-pyridinyl)ethanol, $[\alpha]_D$ +28.2 (*c* 1.06, MeOH) (lit. $[\alpha]_D$ +28.15 (*c* 1.06, MeOH)); *Dictionary of Organic Compounds*, 6th ed.; Chapman & Hall: London, 1996; p 5525.

(12) Noyori, R.; Ohkuma, T.; Koizumi, M.; Yoshida, M. *Org. Lett.* **2000**, *2*, 1749.

(13) Lipshutz, B. H.; Ung, C.; Sengupta, S. *Synlett* **1989**, *1*, 64.

(14) **Representative Procedure for DTBM-SEGPHOS·CuH-Catalyzed Asymmetric Hydrosilylations of Heteroaromatic Ketones (Table 1, Entry 1).** To a flame-dried 25 mL round-bottom flask (RBF) equipped with a magnetic stir bar and purged with argon in a glovebox were added commercial Cu(I)Cl (4.5 mg, 0.045 mmol, 1 mol %) and NaO-*t*-Bu (4.4 mg, 0.045 mmol, 1 mol %), (−)-DTBM-SEGPHOS (2.7 mg, 2.25×10^{-3} mmol, 0.05 mol %), and 6.0 mL of toluene at room temperature. The mixture was stirred for 30 min before being cooled to −50 °C. PMHS (1.10 mL, 18.0 mmol, 4 equiv of hydride) was added to the RBF and stirred for 15 min. In a separate 10 mL pear-bottomed flask (PBF) were combined 2-acetylpyridine (0.51 mL, 4.50 mmol) and 3.0 mL of toluene under argon, and the mixture was cooled to −50 °C. The contents of the PBF were transferred via cannula to the RBF, and the reaction was monitored by TLC. Upon completion (2 h), the reaction was quenched with 2.5 M aqueous NaOH (15 mL) and THF (15 mL) and stirred for 3 h. The biphasic mixture was salted out with NaCl and extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to yield 530 mg (97%) of a colorless oil.[12,15]

based on a highly activated form of CuH generated by the presence of a bidentate SEGPHOS ligand.[10] These hydrosilylations can be conducted at substrate-to-ligand ratios on the order of 2000:1, which significantly exceed those commonly used in related reactions of aryl ketones.[5] Their reliance on catalytic amounts of copper, rather than on more expensive metals, adds to the attractive economic features of this process. Several additional methods and applications of (asymmetrically) bisphosphine-ligated copper hydride will be reported in due course.

(15) On this scale, the ligand is lost upon workup. Lower ratios involving more ligand are likely to require chromatographic separation of the product.

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

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