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# Applications of Asymmetric Hydrosilylations Mediated by Catalytic (DTBM-SEGPHOS)CuH

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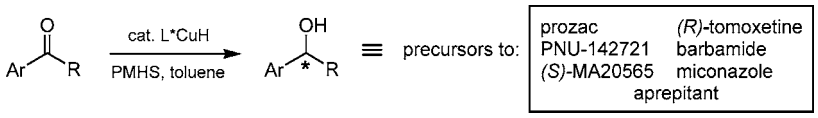
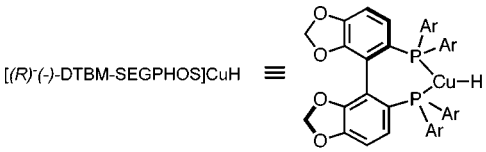
## ABSTRACT




**Several aryl ketone precursors useful in the synthesis of known physiologically active compounds have been reduced to the corresponding nonracemic alcohols. The previously reported combination of a catalytic quantity of (*R*)-(–)-DTBM-SEGPHOS-ligated CuH and stoichiometric PMHS is shown to be very effective in these asymmetric hydrosilylations.**

Nonracemically ligated, in situ generated CuH has been shown to be a powerful reagent for effecting asymmetric hydrosilylations of several substrate types.[1] Ligands that have shown great promise in this regard include Solvias' PPF-P(*t*-Bu)$_2$[2] (for 1,4-additions to acyclic enones and enoates), Roche's 3,5-Xyl-MeO-BIPHEP[3] (for 1,2-additions to aryl ketones), and in particular Takasago's DTBM-SEGPHOS[4] (for 1,4-additions to enoates and cyclic enones and 1,2-additions to imines and aryl ketones). The preformed species (*R*)-(−)-DTBM-(SEGPHOS)CuH, in the presence of excess silane PMHS (polymethylhydrosiloxane), is remarkably stable at room temperature when protected from the atmosphere and was introduced last year as a storable "CuH in a Bottle".[5] Turnover numbers in the thousands to hundreds of




[Ar = 3,5-*di*-*t*-Bu-4-MeO-phenyl]

thousands to one are observed in several substrate types. To showcase this reagent combination, several targets of interest mainly in the pharma arena have been selected wherein a secondary benzylic or benzylic-like alcohol serves as a synthetic intermediate. Thus, in this letter, we describe several applications of our recently developed hydrosilylation technology.

First on our list of educts was keto ester **1** (Table 1, entry a), as this compound serves as an important precursor to derivative **2**, used in the synthesis of Lilly's antidepressant fluoxetine (prozac, **A**; Figure 1). The reported route by Sepracor relies on a CBS reduction using 10% catalyst, leading to a good yield (95%) of the desired product in high

(1) Aryl ketones: (a) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8779. (b) Lipshutz, B. H.; Lower, A.; Noson, K. *Org. Lett.* **2002**, *4*, 4045. (c) Lipshutz, B. H.; Noson, K.; Chrisman, W. *J. Am. Chem. Soc.* **2001**, *123*, 12917. Imines: (d) Lipshutz, B. H.; Shimizu, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 2228. 1,4-Reductions: (e) Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keith, J. M. *Tetrahedron* **2000**, *56*, 2779. (f) Lipshutz, B. H.; Servesko, J. M.; Petersen, T. B.; Papa, P. P.; Lover, A. A. *Org. Lett.* **2004**, *6*, 1273. (g) Lipshutz, B. H.; Servesko, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4789.

(2) (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.

(3) (a) 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. (b) Schmid, R.; Foricher, J.; Cereghetti, M.; Schonholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370.

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

(5) Lipshutz, B. H.; Frieman, B. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6345.

10.1021/ol060854+ CCC: $33.50 
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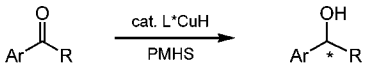
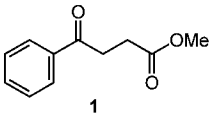
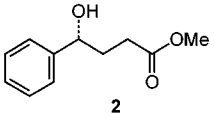
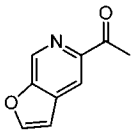
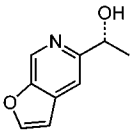
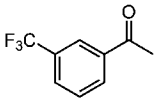
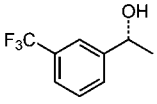
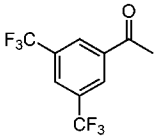
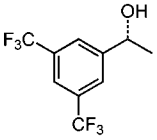
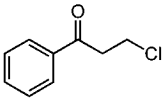
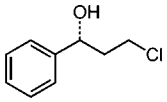
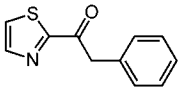
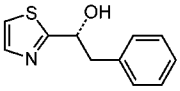
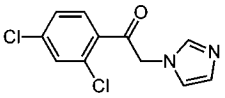
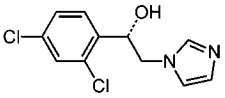
**Table 1.** Asymmetric Hydrosilylations of Aryl Ketones Related to Physiologically Active Targets

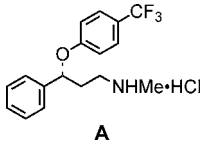



| entry | aryl ketone | conditions | product[a] | yield(%)[b] | ee(%)[c] |
|---|---|---|---|---|---|
| a |  **1** | 1% CuCl / NaO-*t*-Bu, 0.05% (*R*)-(-)-DTBM-SEGPHOS, 1 equiv *t*-BuOH / PMHS, 1:1 THF/Tol, -78 °C, 2 h |  **2** | 92 | 99.4 |
| b |  **3** | 2% CuCl / NaO-*t*-Bu, 0.25% (*R*)-(-)-DTBM-SEGPHOS, 1 equiv *t*-BuOH / PMHS 4:1 THF / Tol, -78 °C, 1 h |  **4** | 88 | 97.1 |
| c |  **5** | 2% CuCl / NaO-*t*-Bu, 0.25% (*R*)-Xyl-MeO-BIPHEP 1 equiv *t*-BuOH / PMHS, Tol, -78 °C, 10 h |  **6** | 95<br>89 | 95.3<br>93.4[d] |
| d |  **7** | 2% $Cu(OAc)_2$, 0.25% (*R*)-(-)-DTBM-SEGPHOS, 1 equiv *t*-BuOH / PMHS. 2:1 THF / Tol, -78 °C, 18 h |  **8** | 90<br>98 | 95.0<br>91.7[e] |
| e |  **9** | 1% CuCl/NaO-*t*-Bu, 0.05% (*R*)-(-)-DTBM-SEGPHOS, 1 equiv *t*-BuOH / PMHS. 4:1 Tol / THF, -78 °C, 8 h |  **10** | 98 | 92.0 |
| f |  **11** | 1% CuCl / NaO-*t*-Bu, 0.25% (*R*)-(-)-DTBM-SEGPHOS, 1 equiv *t*-BuOH / PMHS. 2:1 THF / Tol, -78 °C, 3 h |  **12** | quant | 89.3 |
| g |  **13** | 2% $Cu(OAc)_2$, 0.25% (*R*)-(-)-DTBM-SEGPHOS, 1 equiv *t*-BuOH / PMHS. 2:1 THF / Tol, -78 °C, 18 h |  **14** | 90 | 86.1 |

[a] Fully characterized by IR, NMR, MS, and HRMS data. [b] Isolated, chromatographically purified material. [c] Determined by chiral GC analyses. [d] Run under the following conditions: 2% CuCl/2% NaO$^t$Bu, 0.25% (*R*)-(−)-DTBM-SEGPHOS, 1 equiv of *t*-BuOH/PMHS. Toluene, −78 °C, 16 h. [e] Run under the following conditions: 2% CuCl/2% NaO$^t$Bu, 0.10% (*R*)-Xyl-MeO-BIPHEP, 1 equiv of *t*-BuOH/PMHS. Toluene, −78 °C, 8 h.

ee (96%).[6] Using our copper hydride chemistry,[1a] with a convenient substrate (keto ester **1**)-to-ligand (S/L) ratio of 2000:1 (i.e., 0.5 mol % of DTBM-SEGPHOS) and in the presence of *t*-BuOH (1 equiv), we could isolate alcohol **2** in 92% yield and an ee of 99.4%. As shown previously, enantioselectivities in these hydrosilylations are temperature sensitive; hence, the highest ee's, in general, were obtained when reactions were run at low temperatures independent of catalyst loading. Thus, −78 °C was preferred, although the temperature is usually determined by the solubility profile of each substrate.

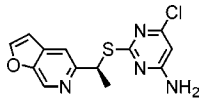
The HIV-1 non-nucleoside reverse transcriptase inhibitor, PNU-142721 (**B**; Figure 2), has been synthesized in nonracemic form, proceeding via the racemic form of alcohol **4** (Table 1, entry b) followed by eventual resolution.[7] Acetyl




**A**

**Figure 1.** Structure of fluoxetine (prozac).

(6) Hilborn, J. W.; Lu, Z.; Jurgens, A. R.; Fang, Q. K.; Byers, P.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **2001**, *42*, 8919.

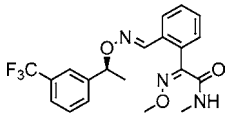


**B**

**Figure 2.** Structure of PNU-142721.

derivative **3** is susceptible to asymmetric hydrosilylation with (DTBM-SEGPHOS)CuH to give product **4** in good yield and with 97.1% ee.

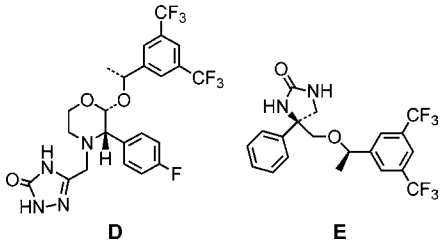
(*S*)-MA20565, a Mitsubishi compound that contains a new pharmacophore, has shown promise as a potent agricultural fungicide (**C**; Figure 3).[8] The asymmetric synthesis of subunit



**C**

**Figure 3.** Structure of Mitsubishi's (*S*)-MA20565.

benzylic alcohol **6** (Table 1, entry c) calls for a Noyori transfer hydrogenation using formic acid as the source of hydrogen in a reaction at 50 °C with ketone **5** leading to **6** in 91% ee (96% yield).[9] CuH-based technology, in this case best effected using the Roche BIPHEP ligand to complex CuH,[3] could be employed on this substrate as well, giving rise to the desired alcohol in both high yield (95%) and ee (95.3%).



**D** **E**

**Figure 4.** Representative NK-1 antagonists.

Merck's route to aprepitant (**D**, Figure 4), an NK-1 receptor antagonist, relies on access to the key chiral intermediate **8** (Table 1, entry c).[10] This benzylic alcohol is also common to several related targets, including Schering−Plough's analogue, **E**. Large-scale production of alcohol **8** calls for asymmetric transfer hydrogenation of **7** using 0.5 mol % of a *cis*-aminoindanol−ruthenium complex, run at 0.5 M in IPA (2-propanol), affording the product in a reported 91% ee. Similar results could be obtained with DTBM-SEGPHOS-complexed CuH employing a S/L = 1000:1, although far higher ratios might be anticipated on the basis of earlier observations.[1a]

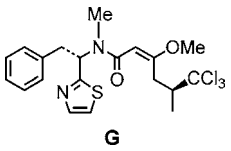
(*R*)-Tomoxetine, **F** (Figure 5), akin to fluoxetine (prozac) and nisoxetine, is also widely used to treat psychological

**F**

**Figure 5.** Structure of (*R*)-tomoxetine.

disorders, as well as certain metabolic concerns such as bulimia and obesity.[11] $\beta$-Chloropropiophenone **9** (Table 1, entry e) has been used successfully on the way toward this target, the asymmetric reduction of which relies on a CBS-like reduction. The route calls for 5% of a norbornane-derived amino alcohol to generate a chiral oxazaborolidine catalyst.[12] Alcohol **10** is thereby formed in 82% ee (89% yield). Treatment of this ketone with in situ generated (DTBM-SEGPHOS)CuH, at a S/L ratio of 2000:1, efficiently consumed educt to form product **10** in 98% yield (92.0% ee).

The chlorinated metabolite from Curacao cyanobacterium *Lyngbya majuscula*, barbamide (**G**), possesses molluscidal activity (Figure 6).[13] A potential precursor to this natural



**G**

**Figure 6.** Sponge-based dysidenin barbamide.

product, alcohol **12** (Table 1, entry f), might be anticipated from asymmetric reduction of acylated thiazole **11**. In the event, hydrosilylation of **11** upon exposure to nonracemically ligated copper hydride gave alcohol **12** quantitatively (89.3% ee).

(7) Matsugi, M.; Itoh, K.; Nojima, M.; Hagimoto, Y.; Kita, Y. *Tetrahedron Lett.* **2003**, *44*, 3355.

(8) Tanaka, K.; Katsurada, M.; Ohno, F.; Shiga, Y.; Oda, M.; Miyagi, M.; Takehara, J.; Okano, K. *J. Org. Chem.* **2000**, *65*, 432.

(9) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931.

(10) (a) Brands, K. M. J.; Payack, J. F.; Rosen, J. D.; Nelson, T. D.; Candelario, A. *J. Am. Chem. Soc.* **2003**, *125*, 2129. (b) Nelson, T. D.; Rosen, J. D.; Brands, K. M. J.; Craig, B.; Huffman, M. A.; McNamara, J. M. *Tetrahedron Lett.* **2004**, *45*, 8917.

(11) Pandey, R. K.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2002**, *43*, 4425.

(12) Lapis, A. A. M.; Fatima, A.; Martins, J. E. D.; Costa, V. E. U.; Pilli, R. A. *Tetrahedron Lett.* **2005**, *46*, 495.

(13) Gerwick, W. H.; Leslie, P.; Long, G. C.; Marquez, B. L.; Willis, C. L. *Tetrahedron Lett.* **2003**, *44*, 285.

Miconazole (**H**) is one of several examples within the azole class of antifungal agents (Figure 7).[14] Other types of drugs

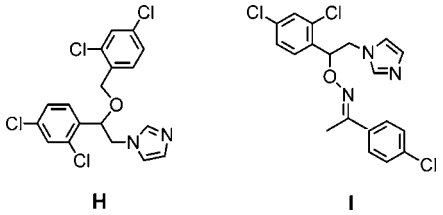
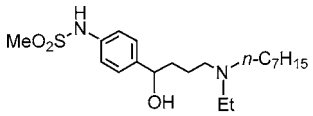


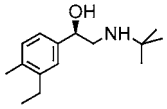

**Figure 7.** Structure of antifungal miconazole (**H**) and an analogue (**I**).

that may be used topically or systemically for clinical treatment of fungal infections include polyenes, thiocarbamates, allylamines, hexapeptide echinocandins, and fluoropyridines. Analogue oxime ethers such as **I** are also of interest, the (racemic) syntheses of which, likewise, pass through an intermediate alcohol, racemic **14** (Table 1, entry g). Asymmetric reduction of aryl ketone **13** was found to take place using CuH in a bottle to afford the corresponding (*S*)-benzylic alcohol **14** in 86.1% ee (90% isolated yield).

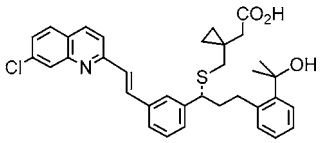
In summary, several examples of functionalized aryl ketones have been converted using copper hydride catalysis to their corresponding chiral benzylic alcohol derivatives. Either CuCl/NaO-*t*-Bu or $Cu(OAc)_2$ (1−2%, conveniently chosen for the scale of reactions studied)[15] can be used as a precursor to in situ generated CuH with similar outcomes. Each case represents a useful intermediate en route to a known physiologically active compound. High yields, ee's, and turnover numbers that are competitive with existing procedures are demonstrated. Opportunities for further applications to several additional drugs, including as examples the antiarrhythmia compound ibutilide, as well as both albuterol and singulair (for bronchial asthma), may now exist using methods based on inexpensive organocopper chemistry.




Ibutilide




Albuterol (*R*-salbutamol)




Singulair

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**Supporting Information Available:** Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060854+

(14) Rossello, A.; Bertini, S.; Lapucci, A.; Macchia, M., Martinelli, S. R.; Herreros, E.; Maccia, B. *J. Med. Chem.* **2002**, *45*, 4903.

(15) These copper salts are best stored in a dry argon atmosphere but can be weighed in air immediately prior to use.