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Cu^{II}-Catalyzed Asymmetric Hydrosilylation of Diaryl- and Aryl Heteroaryl Ketones: Application in the Enantioselective Synthesis of Orphenadrine and Neobenodine

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Abstract: With certain amounts of sodium *tert*-butoxide and *tert*-butanol as additives, catalytic amounts of an inexpensive and easy-to-handle copper source $Cu(OAc)_2 \cdot H_2O$, a commercially available and air-stable non-racemic dipyridylphosphine ligand, as well as the stoichiometric desirable hydride donor polymethylhydrosiloxane (PMHS), formed a versatile in situ catalyst system for the enantioselective reduction of a broad spectrum of prochiral diaryl and aryl heteroarylketones in air, in high yields and with good to excellent enantioselectivities (up to 96%). In particular, the practical viability of this process was evinced by its successful applications in the asymmetric synthesis of optically enriched potent antihistaminic drugs orphenadrine and neobenodine.

Keywords: alcohols · asymmetric catalysis · copper · enantioselectivity · hydrosilylation

Introduction

Optically active diaryl- and aryl heteroarylmethanols are not only crucial structural elements in many physiologically or/and biologically active molecules,[1] such as in antihistamines (*R*)-orphenadrine (**1**) and (*S*)-neobenodine (**2**)[1a,b] and the medically useful histamine H_1-antagonist (*S*)-carbinoxamine (**3**; Figure 1),[2] but they are also the precursors to some potentially interesting ligand scaffolds (e.g., tetraarylethanes).[3] Thus, the development of efficient systems for the catalytic enantioselective synthesis of diaryl- and aryl heteroaryl alcohols is of substantial interest to both the academic community and the industrial sector.

Typically, catalytic asymmetric approaches towards enantiomerically enriched diarylmethanols can be divided into three broad categories: 1) the enzyme-catalyzed enantioselective reduction of diaryl ketones,[4] 2) the 1,2-addition of aryl organometallic nucleophiles to aromatic aldehydes,[5] and 3) the catalytic reduction of prochiral ketones.[5c,6] Intensive study in this area has focused on the stereoselective arylation of aromatic aldehydes and good-to-excellent enantioselectivities have been realized by using a variety of arylmetallic reagents.[5,7–10] From both scientific and commercial points of view, the asymmetric reduction of unsymmetrical diaryl ketones as a direct route to single enantiomers of alcohols is potentially attractive. Accordingly, several strategies, including reduction with lithium aluminum hydride chiral amino alcohol complexes,[11] hydroboration catalyzed by chiral oxazaborolidines,[5c,6a,12] and hydrogenation mediated by chiral diphosphine/diamine Ru complexes,[5c,6b,c,13] have been developed. Nevertheless, reports on the asymmetric hydrosilylation of diaryl ketones to benzhydrol derivatives are relatively scarce. The first example was reported by

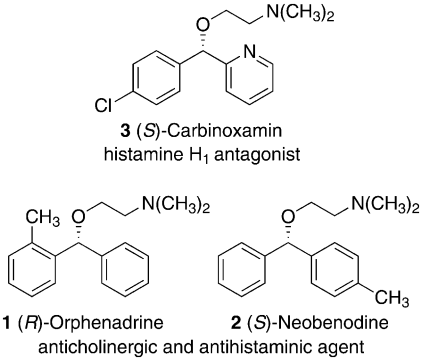

Figure 1. Representative examples of biologically active compounds that are derived from diaryl- or aryl heteroarylmethanols.

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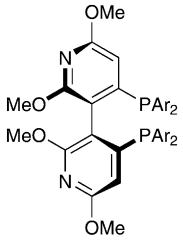
Kagan and co-workers in 1980,[14] who employed a Rh^I-DIOP[15] catalyst for the hydrosilylation of *p*-methylbenzophenone in 26% *ee*. Brunner and Kuerzinger reported a related reaction in 1988[16] that used rhodium complexes to afford the product in 37% *ee*.

Over the last decade, the application of copper hydride complexes that were ligated by enantiomerically pure ligands in asymmetric hydrosilylation reactions has gained a considerable amount of attention owing to the advantages of using inexpensive metals and mild reaction conditions.[17] Thus, a variety of copper-based catalytic hydrosilylation systems have been exploited for effecting the stereoselective reduction of a wide range of simple ketones,[18–22] imines,[23] as well as the 1,4-reduction of various α,β-unsaturated Michael acceptors,[24] with moderate to excellent enantioselectivities. With respect to the prochiral diaryl ketonic substrates, in 2005, we reported a CuF_2/dipyridylphosphine (Figure 2, P-Phos **4a** or Xyl-P-Phos **4b**)[25]/$PhSiH_3$ system



(*S*)-**4a** (*S*)-P-Phos Ar = C_6H_5
(*S*)-**4b** (*S*)-Xylyl-P-Phos Ar = 3,5-$Me_2C_6H_3$
(*S*)-**4c** (*S*)-Tol-P-Phos Ar = 4-MeC_6H_4

Figure 2. Dipyridylphosphine ligands.

which, to the best of our knowledge, allowed the first highly asymmetric hydrosilylation of *ortho*-substituted benzophenones with good to excellent enantioselectivity (up to 98%).[26] In 2008, Lee and Lipshutz[27] demonstrated that CuH complexed with DTBM-SEGPHOS or DM-SEGPHOS[28] were efficient catalysts for the asymmetric hydrosilylation of a broad range of *ortho*-substituted benzophenone derivatives and selected aromatic-heteroaromatic ketones in good to excellent yields and enantioselectivities. In a similar manner to other reduction methods,[6a,b,13] *meta*- and *para*-substituted benzophenones were converted into their corresponding alcohols with low or moderate *ee* values[26,27] because of the lack of asymmetric bias in the transition state. In addition, upon exposure to the copper-catalyzed hydrosilylation conditions, diaryl ketone substrates often showed inferior reactivity to aryl alkyl ketones under otherwise identical conditions.

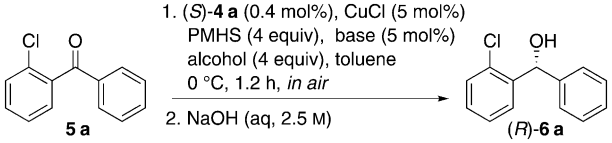
Very recently, we established a new set of reaction conditions to facilitate the copper-catalyzed enantioselective 1,4-reduction of β-(acylamino)acrylates.[29] In the presence of stoichiometric polymethylhydrosiloxane (PMHS), a low-cost and air-stable hydride donor, with *t*BuONa and *t*BuOH as additives, the formation of a range of β-alkyl-β-amino acid derivatives with high levels of enantiopurity (up to 99%) was realized in air by using a copper(II)-dipyridylphosphine (**4a** or **4b**) catalyst. This catalyst system also exhibited high efficiency and remarkable practical potential in the stereoselective hydrosilylation of a wide range of aryl alkyl and heteroaromatic ketones in good to excellent *ee* values (up to 97%) with a substrate-to-ligand (S/L) molar ratio of up to 50000.[30] Herein, we report the extension of this catalyst system to the hydrosilylation of diaryl and aryl heteroaryl ketones. Copper-catalyzed reactions proceeded smoothly in air and gave access to structurally diverse alcohols in up to 96% *ee*. Furthermore, this process was applied to the asymmetric synthesis of optically enriched orphenadrine (**1**) and neobenodine (**2**), which possess potent anticholinergic and antihistaminic activities.[1a,b]

Results and Discussion

Optimization of the copper-catalyzed reaction conditions: In an initial study, 2-chlorobenzophenone (**5a**) was used as a model substrate (Table 1). When compound **5a** was mixed with ligand (*S*)-**4a** (0.4 mol%), CuCl (5 mol%), and PMHS (4 equiv) as the reductant in toluene at 0°C in air, only 57% conversion into (*R*)-**6a** (82% *ee*) was observed after 1.2 h. Consistent with previous reports,[24d,e,k,31] the rate of reaction was increased by adding certain amounts of sterically demanding alcohol *t*BuOH to the reaction mixture (Table 1, cf. entries 2 and 1). Comparison studies showed that the further introduction of *t*BuONa (5 mol%) into the catalyst system allowed for the complete transformation of diarylketone **5a** into the desired alcohol with no diminution of the *ee* either in air or under a N_2 atmosphere (Table 1, entries 3 and 4 versus entry 2).[27,29,30] Moreover, less than 40% conversion was obtained only if *t*BuONa was added in the absence of alcohol, although the *ee* value remained unchanged (Table 1, entries 5 and 3).

The roles of the alcohol and the base in the increased reaction rate remain unclear at present. It appeared that, in the initial step of the catalytic cycle, upon combining (*S*)-P-

Table 1. Effects of additives on the copper-catalyzed hydrosilylation of 2-chlorobenzophenone (**5a**).[a]



5a (*R*)-**6a**

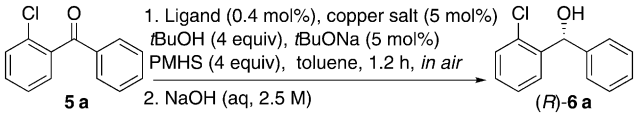
Entry	Alcohol	Base	Conv. [%][b]	*ee* [%][c]
1	–	–	57	82
2	*t*BuOH	–	66	78
3	*t*BuOH	*t*BuONa	99	81
4[d]	*t*BuOH	*t*BuONa	99	81
5	–	*t*BuONa	34	82

[a] Reaction conditions: substrate (35 mg, 0.33 M in toluene). [b] Conversion was determined by NMR spectroscopy and GC. [c] The *ee* values were determined by chiral HPLC analysis; the absolute configuration was determined by comparison of the retention times with literature data (see the Supporting Information). [d] Performed under a N_2 atmosphere.

Phos with CuCl and *t*BuONa, chiral Cu^{I} complex [(*t*BuO)-CuL*] (**A**, L* = (*S*)-P-Phos) was likely formed. Also, in the final step, the copper alkoxide intermediate [{(^{1}Ar)-(^{2}Ar)HCO}CuL*] (**B**) may have been protonated by the alcohol additive *t*BuOH to give the desired chiral diaryl alcohol product and copper complex **A**. Complex **A** may have been capable of undergoing σ-bond metathesis with PMHS more-rapidly than either CuCl or copper alkoxide intermediate **B** to generate active copper hydride species [CuHL*] (**C**), which is conjectured to be the rate-limiting step.[17f,24d,30,31a]

Next, we examined the effects of various Cu^{I} and Cu^{II} precursors on the enantioselective reduction of compound **5a** under a given set of conditions (Table 2, entries 1–6).

Table 2. Effects of the copper salt and the ligand on the copper-catalyzed asymmetric hydrosilylation of compound **5a** in air.[a]

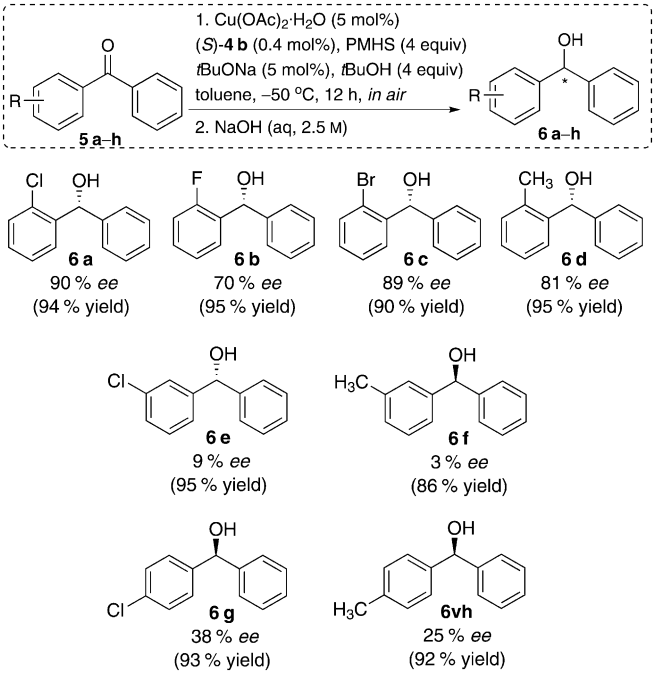


Entry	Copper salt	Ligand	*T* [°C]	Conv. [%][b]	*ee* [%][c]
1	CuF_2	(*S*)-**4a**	0	94	78
2	$CuCl_2$	(*S*)-**4a**	0	84	82
3	$CuCl_2{\cdot}2H_2O$	(*S*)-**4a**	0	80	82
4	$CuBr_2$	(*S*)-**4a**	0	12	82
5	[Cu(acac)$_2$]	(*S*)-**4a**	0	81	81
6	$Cu(OAc)_2{\cdot}H_2O$	(*S*)-**4a**	0	93	81
7[d]	$Cu(OAc)_2{\cdot}H_2O$	(*S*)-**4a**	−30	>99	87
8[d]	$Cu(OAc)_2{\cdot}H_2O$	(*S*)-**4b**	−30	>99	88
9[d]	$Cu(OAc)_2{\cdot}H_2O$	(*S*)-**4c**	−30	>99	88

[a] Reaction conditions: substrate (65 mg, 0.33 M in toluene). [b] Conversions were determined by NMR spectroscopy and GC analysis. [c] The *ee* values were determined by chiral HPLC analysis; the absolute configuration was determined by comparison of the retention times with literature data (see the Supporting Information). [d] Reaction time 3 h.

The counterion of the copper salts didn't have any obvious influence on the reaction. With the exception of $CuBr_2$ (Table 2, entry 4), the product, (*R*)-**6a**, was afforded in above 80% conversion and 78–82% *ee* after 1.2 h (Table 2, entries 1–3, 5, and 6) in most cases. In terms of both activity and enantioselectivity, $Cu(OAc)_2{\cdot}H_2O$, an easy-to-handle and inexpensive copper resource appeared to be the best choice (Table 2, entry 6). Further investigation demonstrated that lowering the reaction temperature was beneficial for enhancing the enantioselectivity whilst a longer reaction time was required for complete conversion (Table 2, cf. entries 7 and 6). In addition, sterically more-demanding ligands (*S*)-**4b** and (*S*)-**4c** possessed similar efficacies compared to parent ligand (*S*)-**4a** (Table 2, entries 8 and 9 versus entry 7).

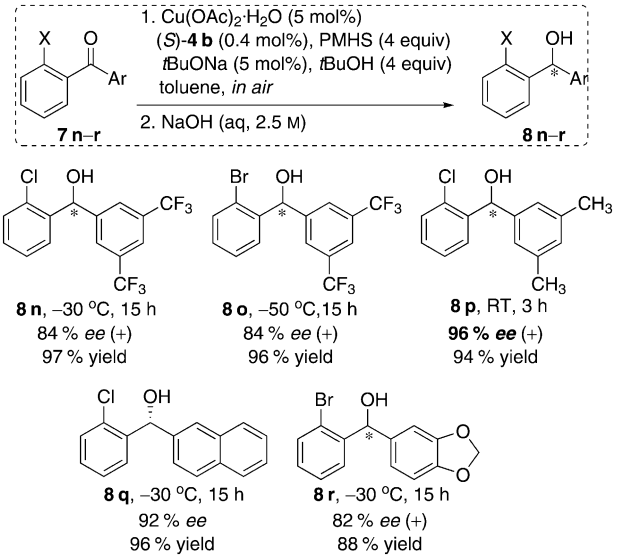
Asymmetric hydrosilylation of aryl phenyl ketones: With the aforementioned optimized conditions in hand, we turned to establishing the general utility of this Cu-catalyzed procedure for the asymmetric hydrosilylation of a selection of mono-substituted benzophenones (**5a–5h**) in air. As shown in Scheme 1, the complete reduction of most of the substrates into their corresponding substituted benzhydrols



Scheme 1. Effect of the substituent on the copper-catalyzed asymmetric hydrosilylation of aryl phenyl ketones (**5**) in air.

(**6a–6h**) within 12 h was observed in the presence of ligand (*S*)-**4d** at −50 °C (86–95% yield). The position of the substituent on the phenyl ring of benzophenone had a significant effect on the stereoselectivity. Substrates that contained either electron-withdrawing or electron-donating *ortho*-substituents (**5a–5d**) afforded the desired alcohols (**6a–6d**, respectively) with moderate to good *ee* values (70–90%). However, the presence of a *meta*- or *para*-substituent (**5e–5h**) resulted in a substantial drop in enantioselectivity (3–38% *ee*). Moreover, the introduction of a more-electron-withdrawing *o*-chloro or *o*-bromo unit was conductive to higher *ee* values (compounds **6a** and **6c** versus compounds **6b** and **6d**),[8i,8m,13a,13b,13e,27] which may have been because the extent of the coplanarity of the benzene rings with C=O in the transition state largely relied on the asymmetric bias that was generated from the two aryl groups that were connected to the C=O functional group.

Asymmetric hydrosilylation of *ortho*-substituted unsymmetrical diaryl ketones: Having envisaged that the presence of an *o*-Br or *o*-Cl substituent on one of the aryl groups in unsymmetrical diaryl ketones could be favorable for the hydrosilylation reactions with higher degrees of enantioselection, we designed a broad range of structurally diverse *ortho*-substituted unsymmetrical diaryl ketones (**7a–7r**; Table 3 and Scheme 2) that could be conveniently prepared by the nucleophilic addition of appropriate aryl magnesium bromides

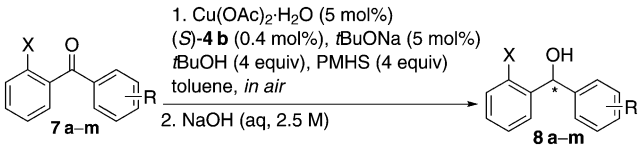


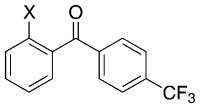
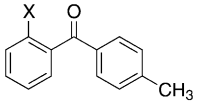
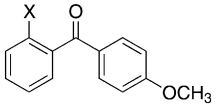
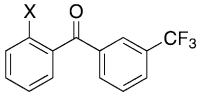
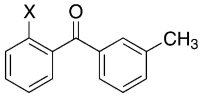
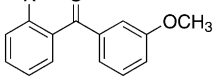
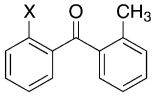
Scheme 2. Cu^{II}-catalyzed asymmetric hydrosilylation of *ortho*-substituted unsymmetric diaryl ketones **7n**–**7r** in air.

to 2-bromobenzaldehyde or 2-chlorobenzaldehyde, followed by oxidation of the resultant alcohol with pyridinium chlorochromate (PCC; see the Supporting Information).[32] We chose these substrates based on two considerations: 1) the *ortho*-substituted bromine- or chlorine atom could act as an enantiodirecting functional group in the Cu-catalyzed hydrosilylation step; 2) the halogen groups could be readily removed from the alcohol products, if needed.

o-Cl- or *o*-Br-phenyl aryl ketones that contained *para*- or *meta*-substituted electron-deficient (Table 3, entries 1, 2, 7, and 8) and electron-rich aryl groups (Table 3, entries 3–6 and 9–12) all underwent facile hydrosilylation under the optimized conditions to afford the desired alcohols in good to excellent enantiopurity (up to 95% *ee*) and high yield. With the exception of substrates **7e** (Table 3, entry 5) and **7i** (Table 3, entry 9), the reduction of *o*-Br-substituted diaryl ketones afforded higher enantioselectivities than those of related *o*-Cl-substituted substrates under otherwise identical conditions (Table 3, for example, cf. entries 1 and 2, and entries 3 and 4). As expected, *ortho*-chlorophenyl *ortho*-methylphenyl ketone (**7m**) was reduced in quantitative yield in only 69% *ee* (Table 3, entry 14), presumably owing to the

Table 3. Cu^{II}-catalyzed asymmetric hydrosilylation of *ortho*-substituted unsymmetrical diaryl ketones **7a**–**7m** in air.[a]



Entry	Substrate	X	*T* [°C]	*t* [h]	Yield [%]	*ee* [%][b]
1		X = Br, **7a**	–50	36	95	95 (+)
2		X = Cl, **7b**	–50	36	96	92 (+)
3		X = Br, **7c**	–30	15	94	92 (*R*)
4		X = Cl, **7d**	–30	15	95	91 (*R*)
5		X = Br, **7e**	–50	36	92	77 (*R*)
6		X = Cl, **7f**	–50	36	96	91 (*R*)
7		X = Br, **7g**	–50	36	96	94 (+)
8		X = Cl, **7h**	–50	36	96	90 (+)
9		X = Br, **7i**	–30	15	96	81 (+)
10		X = Cl, **7j**	–30	15	95	87 (*R*)
11		X = Br, **7k**	–50	36	95	88 (*R*)
12		X = Cl, **7l**	–30	15	96	83 (*R*)
13		X = H, **5d**	–50	36	95	81 (*S*)
14		X = Cl, **7m**	–30	15	94	69 (*R*)

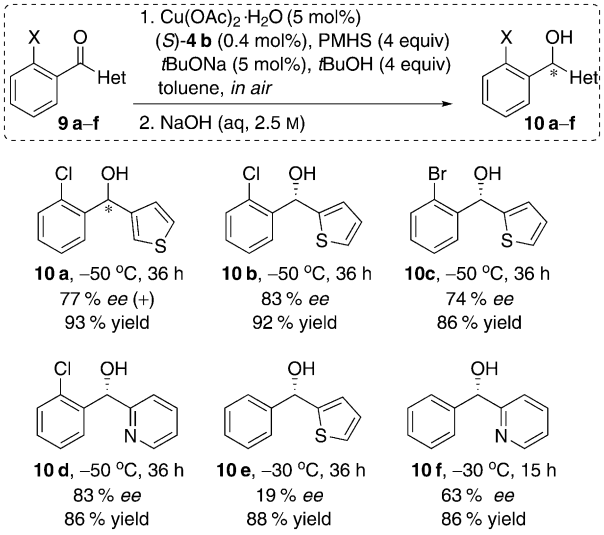
[a] Reaction conditions: substrate (0.5 mmol, 0.3 M in toluene); full conversion was observed for all of the reactions. [b] The *ee* values were determined by chiral HPLC analysis. The absolute configurations were determined by comparison of the retention times or optical rotations with literature data (see the Supporting Information).

lack of sufficient steric dissymmetry derived from the substrates.

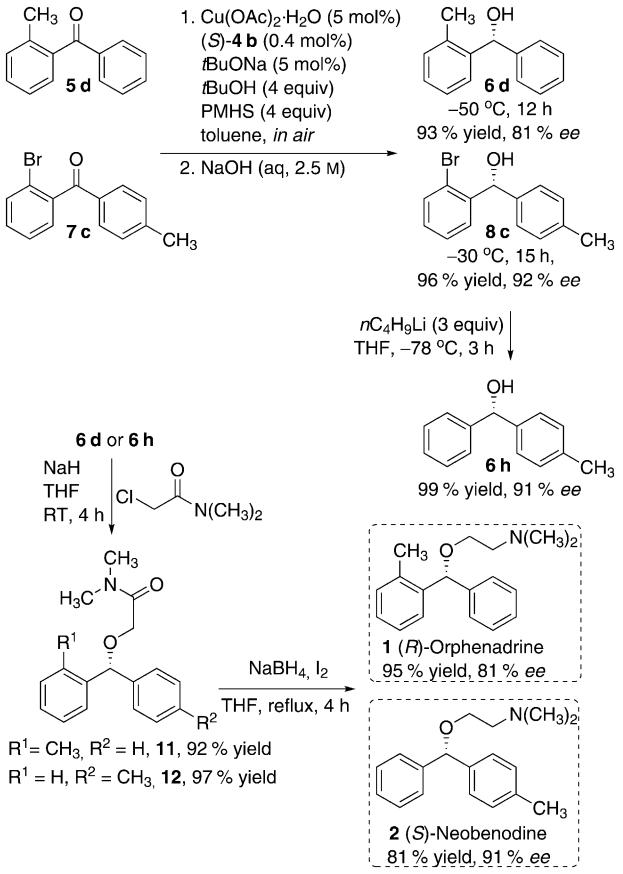
Furthermore, as shown in Scheme 2, several other *ortho*-substituted unsymmetrical diaryl ketones (**7n**–**7r**) that contained disubstituted aryl- or naphthyl groups also underwent efficient and selective reaction to afford the desired alcohol products in quantitative yield and with *ee* values of 82–96%. In particular, the transformation of (2-chlorophenyl)(3,5-dimethylphenyl)methanone (**7p**) neatly afforded the corresponding alcohol (**8p**) in up to 96% *ee*, even at ambient temperature.

Asymmetric hydrosilylation of aryl heteroaryl ketones: Although enantioenriched aryl heteroaryl alcohols are regarded as important intermediates and structural motifs in medicinal chemistry, there are few reports of their catalytic asymmetric synthesis.[4,8m–o,13c,e,27] Given the good performance of our catalyst system in the hydrosilylation of diaryl ketones, we were therefore interested in the extension of our system to the stereoselective reduction of aryl heteroaryl ketones (Scheme 3). Similar to the results from the hydrosilylation of diaryl ketones, the introduction of Cl- or Br substituents at the *ortho* position of the phenyl ring in the aromatic-heteroaromatic ketones was beneficial for the production of their corresponding alcohols (**10a**–**10d**) with modest to good *ee* values (74–83%). However, the absence of an *ortho*-substituent on the phenyl ring resulted in a substantial erosion of the enantioselectivity (**10e** versus **10b** and **10c**, and **10f** versus **10d**).

Enantioselective synthesis of orphenadrine and neobenodine: With an efficient catalyst system for the enantioselective hydrosilylation of diaryl ketones in hand, we sought to apply this procedure to the asymmetric synthesis of antihistaminic agents (*R*)-orphenadrine (**1**) and (*S*)-neobenodine (**2**).[33] Thus, the asymmetric hydrosilylation of ketones **5d** and **7c** under similar conditions to those given in Table 3 proceeded smoothly in air to furnish non-racemic alcohols **6d** and **8c** in 81% and 92% *ee*, respectively (Scheme 4). The *ortho*-substituted bromine group of compound **8c** was readily removed by lithiation with nC_4H_9Li (3 equiv) in THF at −78°C for 3 h, followed by hydrolysis, to give compound **6h** in quantitative yield and 91% *ee*. In contrast, compound **6h** was obtained in only 25% *ee* through the direct reduction of its corresponding ketone (**5h**; Scheme 1). Next, a mixture of the enantioenriched alcohol product and 2-chloro-*N*,*N*-dimethyl-acetamide in THF was treated with sodium hydride at room temperature for 4 h to cleanly afford amide intermediate **11** or **12**. Finally, 1.2 equiv I_2 was added at 0°C to the solution of $NaBH_4$ (2.3 equiv) and amide **11** or **12** in THF over 0.5 h and the mixture was heated at reflux for 4 h followed by work-up with 10% aqueous HCl to provide the target chiral product (*R*)-orphenadrine (95% yield) or (*S*)-neobenodine (81% yield).



Scheme 3. Cu^{II}-catalyzed asymmetric hydrosilylation of aryl heteroaryl ketones **9a**–**9f** in air.



Scheme 4. Asymmetric synthesis of (*R*)-orphenadrine **1** and (*S*)-neobenodine **2**.

Conclusion

We have developed a versatile and practical copper-catalyzed hydrosilylation method for the formation of a diverse range of diaryl- and aryl heteroarylmethanols with good to

excellent *ee* values (up to 96%). Our catalyst system was generated in situ by the combination of an inexpensive and easy-to-handle copper source, $Cu(OAc)_2 \cdot H_2O$, a commercially available and air-stable chiral ligand, (*S*)-Xyl-P-Phos, and a stoichiometric hydride donor, PMHS, in air with certain amounts of *t*BuONa and *t*BuOH as additives. In particular, the synthetic utility of the chiral products was highlighted by the efficient transformation of enantiomerically enriched diaryl alcohols into the anticholinergic and antihistaminic agents (*R*)-orphenadrine and (*S*)-neobenodine.

Experimental Section

Typical procedure for the asymmetric hydrosilylation of diaryl ketones in air: $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol), *t*BuONa (1.5 mg, 0.015 mmol), and (*S*)-Xyl-P-Phos (1.0 mg, 0.0012 mmol) were weighted in air and placed in a 25 mL round-bottomed flask that was equipped with a magnetic stirrer bar. Toluene (0.2 mL) was added and the mixture was stirred at RT for 15 min. To the mixture was added a solution of PMHS (80 μL, 4 equiv) in toluene (0.1 mL) and the mixture was cooled to −50 °C. A solution of 2-chlorobenzophenone **5a** (65 mg, 0.3 mmol) in toluene (0.3 mL) and *t*BuOH (60 μL, 4 equiv) was added under vigorous stirring and the flask was stoppered. The reaction was monitored by TLC. Upon completion, the reaction was quenched with 2.5 M NaOH (2.0 mL) and Et_2O (2.0 mL) and the mixture was stirred vigorously for 1 h. The aqueous layer was extracted with Et_2O (3×1 mL) and the combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered through a plug of silica gel, and concentrated under vacuum to provide the crude product. The conversion and enantiomeric excess of the product (**6a**) were determined by NMR spectroscopy, GC (J & W Scientific INNOWAX; 30 m×0.25 mm, carrier gas: N_2), and chiral HPLC (Daicel Chiralcel OD−H column, 25 cm×4.6 mm) to be 97% and 90%, respectively. The pure product was isolated by column chromatography on silica gel (EtOAc/petroleum ether, 1:10; 65 mg, 94% yield).

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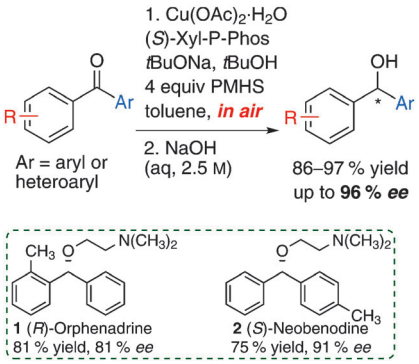
Asymmetric Catalysis

*Y.-Z. Sui, X.-C. Zhang, J.-W. Wu, S. Li, J.-N. Zhou, M. Li, W. Fang, A. S. C. Chan, J. Wu** ..... ■■■■–■■■■

Cu^{II}-Catalyzed Asymmetric Hydrosilylation of Diaryl- and Aryl Heteroaryl Ketones: Application in the Enantioselective Synthesis of Orphenadrine and Neobenodine



Could do with a copper: The Cu-catalyzed conversion of diaryl- and aryl heteroaryl ketones into their corresponding alcohols proceeded in high yields and with good to excellent *ee* values. This process was used in the asymmetric synthesis of two antihistamines.

