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**COMMUNICATION**

# Cobalt(II)-catalyzed asymmetric hydrosilylation of simple ketones using dipyridylphosphine ligands in air†

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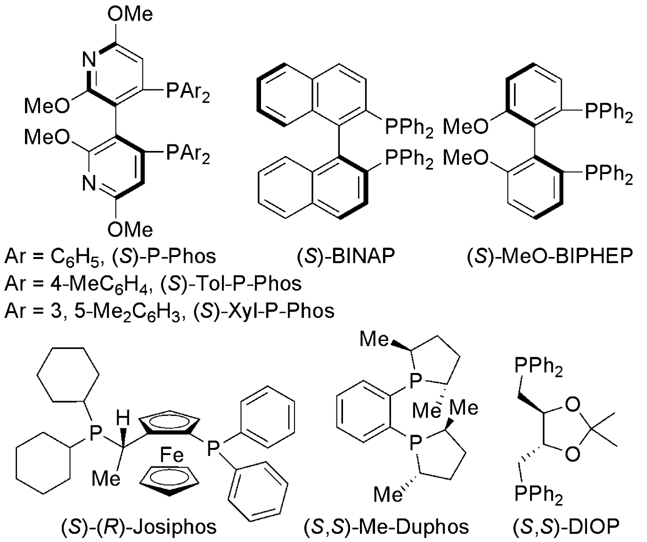
**In the presence of $PhSiH_3$ as the hydride donor, catalytic amounts of non-racemic dipyridylphosphine and an easy-to-handle cobalt salt $Co(OAc)_2{\cdot}4H_2O$ formed *in situ* an effective catalyst system for the asymmetric reduction of a diverse range of aryl alkyl ketones with moderate-to-excellent enantioselectivities (up to 96% ee). This approach tolerated the handling of both catalyst and reactants under air without special precautions.**

Optically active alcohols are valuable intermediates for the manufacture of structurally interesting and biologically active compounds.[1] Non-precious metal-catalyzed asymmetric hydrosilylation of ketones toward enantiomerically enriched alcohols as a desirable alternative to hydrogenation methods has attracted growing interest due to the economic benefits, smooth reaction conditions and the operational simplicity.[2] In the past two decades, a variety of transition metal catalysts, especially those based on titanium,[3] zinc,[4] tin,[5] copper[6,7] and iron[8,9] have been broadly exploited and applied in the relevant hydrosilylation reactions with moderate to excellent enantioselectivities. In contrast, the asymmetric hydrosilylation of ketones mediated by cobalt, an inexpensive and environmentally friendly metal, has received relatively scant attention. The pioneering work in this area was reported in 1991 by Brunner and Amberger, who developed a Co(I)/pyridinyloxazoline/$Ph_2SiH_2$ system for the reduction of acetophenone with 56% ee.[10] A breakthrough came in 2010 when Nishiyama and co-workers disclosed an efficient chiral Co(II) catalyst derived from $Co(OAc)_2$ and bis(oxazolinylphenyl)amine ligands (Bopa) along with $(EtO)_2MeSiH$, which allowed for the highly enantioselective hydrosilylation of a series of simple ketones with up to 98% ee.[11]

P-Phos[12a] and its analogues (Scheme 1, Tol-P-Phos, Xyl-P-Phos) are a family of versatile atropisomeric bipyridyldiphosphine ligands effective for an array of transition metal-catalyzed asymmetric reactions including hydrogenation and C–C bond formation with good to excellent reactivities and absolute stereocontrol.[12b] An attractive attribute of P-Phos ligands is their good air-stability, which makes the catalysts' preparation and handling easy in most cases.[12b] Based on the aforementioned features of P-Phos ligands, a remarkably efficient catalyst system, $CuF_2$/dipyridylphosphine (P-Phos or Xyl-P-Phos)/$PhSiH_3$, has been developed by us, which rendered competitive levels of enantioinduction (up to 98% ee) and activity (S $L^{-1}$ up to 100 000) for the reduction of aryl alkyl,[13a] diaryl[13a] and hetero-aromatic ketones[13b] under normal atmosphere. Hence, we became interested in investigating P-Phos family ligands in the cobalt-catalyzed asymmetric hydrosilylation of ketones in air.



**Scheme 1** Chiral diphosphine ligands tested in this study.

In the preliminary study, a series of Co(II) catalyst precursors were examined in the reduction of 4′-nitroacetophenone (**1a**) in toluene at 40 °C in air employing 2 mol% (*S*)-P-Phos ligand and 1.2 equivalents of $PhSiH_3$ as a hydride donor (Table 1). When utilizing 6 mol% anhydrous $CoF_2$, the reaction was worked up after 40 h and the desired alcohol (*S*)-**2a** was furnished in 74% yield and 90% ee (entry 1), while 94% yield and 93% ee were achieved in the case of anhydrous $Co(OAc)_2$ as a cobalt source (entry 2). In consideration of the practical applications, $Co(OAc)_2{\cdot}4H_2O$, which is easy-to-handle and substantially less expensive than anhydrous $Co(OAc)_2$ or $CoF_2$, was tested. Disappointedly, the yield of (*S*)-**2a** dropped sharply to 23% although the ee was consistently high (entry 3).

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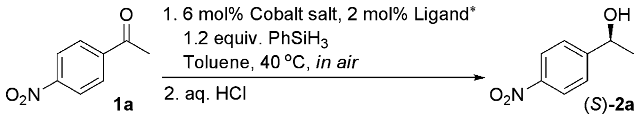
† Electronic Supplementary Information (ESI) available.

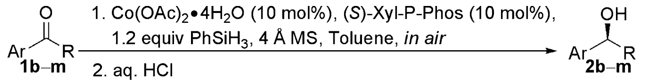
**Table 1** Cobalt(II)-catalyzed asymmetric hydrosilylation of 4′-nitroacetophenone **1a** in air[a]



| Entry | Ligand | [Co]/Additive[b] | Time (h) | Yield (%) | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | (*S*)-P-Phos | $CoF_2$ | 40 | 74 | 90 |
| 2 | (*S*)-P-Phos | $Co(OAc)_2$ | 40 | 94 | 93 |
| 3 | (*S*)-P-Phos | $Co(OAc)_2·4H_2O$ | 40 | 23 | 92 |
| 4[d] | (*S*)-P-Phos | $Co(OAc)_2·4H_2O$/4 Å MS | 38 | 82 | 93 |
| 5 | (*S*)-P-Phos | $Co(OAc)_2·4H_2O$/4 Å MS | 40 | 99 | 93 |
| 6[e] | (*S*)-P-Phos | $Co(OAc)_2·4H_2O$/4 Å MS | 40 | 93 | 93 |
| 7[f] | (*S*)-P-Phos | $Co(OAc)_2·4H_2O$/4 Å MS | 40 | 50 | 92 |
| 8 | (*S*)-BINAP | $Co(OAc)_2·4H_2O$/4 Å MS | 40 | 99 | 91 |
| 9 | (*S*)-MeO-BIPHEP | $Co(OAc)_2·4H_2O$/4 Å MS | 40 | 85 | 89 |
| 10 | (*S*)-P-Phos | $Co(OAc)_2·4H_2O$/4 Å MS | 24 | 74 | 93 |
| 11 | (*S*)-Tol-P-Phos | $Co(OAc)_2·4H_2O$/4 Å MS | 24 | 99 | 94 |
| 12 | (*S*)-BINAP | $Co(OAc)_2·4H_2O$/4 Å MS | 24 | 70 | 92 |
| 13[g] | (*S*)-Xyl-P-Phos | $Co(OAc)_2·4H_2O$/4 Å MS | 24 | 99 | 95 |
| 14[h] | (*S*)-Xyl-P-Phos | $Co(OAc)_2·4H_2O$/4 Å MS | 6 | 99 | 95 |
| 15[g,i] | (*S*)-Xyl-P-Phos | $Co(OAc)_2·4H_2O$/4 Å MS | 32 | 98 | 96 |

[a] Reaction conditions: 24.8 mg substrate, substrate concentration = 0.15–0.4 M in toluene. [b] 30 mg of 4 Å MS was added unless otherwise noted. [c] The ee values were determined by chiral GC analysis. The absolute configuration was determined by comparing the retention times with the known data. [d] 15 mg of 4 Å MS was added. [e] 124 mg substrate was used. [f] Dioxane was used as the solvent. [g] 2 mol% $Co(OAc)_2·4H_2O$ was used. [h] 10 mol% Co(II) salt and 10 mol% ligand were used. [i] The reaction was carried out under room temperature

**Table 2** Cobalt(II)-catalyzed asymmetric hydrosilylation of ketones using (*S*)-Xyl-P-Phos in air[a]



**b** Ar = $C_6H_5$, R = $CH_3$
**c** Ar = 4-$CH_3C_6H_4$, R = $CH_3$
**d** Ar = 3-$NO_2C_6H_4$, R = $CH_3$
**e** Ar = 2-$NO_2C_6H_4$, R = $CH_3$
**f** Ar = 3-$CF_3C_6H_4$, R = $CH_3$
**g** Ar = 4-$CF_3C_6H_4$, R = $CH_3$
**h** Ar = 3,5-$(CF_3)_2C_6H_3$ , R = $CH_3$
**i** Ar = 4-$CNC_6H_4$, R = $CH_3$
**j** Ar = 3-$NO_2C_6H_4$, R = $CH_3CH_2$
**k** Ar = 3,5-$(CF_3)_2C_6H_3$ , R = $CH_3CH_2$
**l** Ar = $C_6F_5$, R = $CH_3$
**m** Ar = 2,4,5-$F_3C_6H_2$, R = $CH_3$

| Entry | Ketone | *T*/°C | Time (h) | Yield (%) | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | **1b** | 45 | 48 | < 5 | — |
| 2 | **1c** | 55 | 60 | < 5 | — |
| 3 | **1d** | 40 | 24 | 99 | 94 |
| 4 | **1d** | 55 | 12 | 90 | 89 |
| 5 | **1e** | 55 | 20 | 6 | 51 |
| 6 | **1f** | 40 | 60 | 31 | 85 |
| 7 | **1f** | 55 | 36 | 75 | 75 |
| 8 | **1g** | 40 | 60 | 92 | 85 |
| 9 | **1h** | 40 | 36 | 92 | 79 |
| 10 | **1i** | 40 | 42 | 99 | 90 |
| 11 | **1j** | 40 | 36 | 99 | 85 |
| 12 | **1k** | 40 | 36 | 95 | 87 |
| 13 | **1l** | 40 | 36 | 97 | 85 |
| 14 | **1m** | 40 | 40 | 98 | 80 |

[a] Reaction conditions: 20.1–40.5 mg substrate, substrate concentration = 0.10–0.15 M in toluene. [b] The ee values were determined by chiral HPLC or GC analysis. The absolute configuration was determined by comparing the retention times with the known data.

Interestingly, under otherwise identical reaction conditions, the addition of certain amounts of 4 Å MS facilitated dramatic enhancements in yields with no diminution of enantioselectivities (entries 4–6 *vs.* entry 3). Lower activities and selectivities were observed by applying $Co(acac)_2$, $Co(NO_3)_2·6H_2O$, or other cobalt halides as catalyst precursors (see the ESI†).

Moreover, similarly to Nishiyama's finding,[11] the reaction activities largely relied on the choice of silane. For example, excluding $PhSiH_3$, only trace reaction was detected in utilizing $(EtO)_3SiH$, $(EtO)_2MeSiH$ or PMHS (polymethylhydrosiloxane) as the stoichiometric reductant. The present catalyst system was also strongly solvent-dependent and toluene served as the best choice. When selecting THF, $CHCl_3$ or $CH_3CN$ as the solvent, almost no reduction took place. Whereas, 50% yield and 92% ee were reached when the hydrosilylation was conducted in dioxane (entry 7).

In addition, among the different chiral diphosphine ligands screened (Scheme 1), promising results were also attained by employing (*S*)-BINAP or (*S*)-MeO-BIPHEP (Table 1, entries 8 and 9). However, (*S*)-(*R*)-Josiphos, (*S*,*S*)-Me-Duphos or (*S*,*S*)-DIOP exhibited poor activities (see the ESI†). Further studies demonstrated that the more sterically encumbered Xyl-P-Phos was beneficial for a higher optical yield and reaction rate (entry 13 *vs.* entries 10–12). For instance, in the presence of 2 mol% (*S*)-Xyl-P-Phos and $Co(OAc)_2·4H_2O$ with 30 mg of 4 Å MS, the reduction of 0.15 mmol **1a** proceeded smoothly in air and afforded (*S*)-**2a** neatly bearing 95% of enantiopurity within 24 h (entry 13). Upon improving the catalyst loading to 10 mol%, the reaction completed after only 6 h at 40 °C (entry 14). Finally, full conversion and 96% ee were realized under room temperature simply by prolonging the reaction time (entry 15).

Having established the preferred conditions, the general applicability of the present catalyst system in the reduction of a wide spectrum of aryl alkyl ketones **1b–1m** was evaluated under an air atmosphere and the representative results are listed in Table 2. It is worth noting that the reaction activities are dependent on the electronic nature of the substituents on the arene ring of the substrates. For example, under a given set of conditions, only a trace of reaction occurred for acetophenone **1b** or 4′-methylacetophenone **1c** (entries 1 and 2). Nonetheless, the aryl alkyl ketones embodying electron-withdrawing substituents on the phenyl group were apparently more conducive to both faster reaction rates and higher ee values (entries 3–14 *vs.* entries 1 and 2). Another observation was that the positioning of the substituents on the phenyl ring of the ketones had a dramatic effect on the reaction outcomes. Acetophenone with an $NO_2$ group substituted on either the *para*- (**1a**, Table 1, entries 12–14) or *meta*- (**1d**, Table 2, entry 3) position resulted in a quantitative yield and high ee, whilst the sterically hindered *ortho*-substituted substrate (**1e**, Table 2, entry 5) led to a low yield and moderate ee (51%), even if the reaction was performed at 55 °C for 20 h. Elevating the reaction temperature increased the reaction rate albeit at the expense of the enantioselectivity (entry 4 *vs.* entry 3). Other electron-deficient prochiral ketones possessing substituents such as $CF_3$ and CN, **1f–1k**, were also reduced in moderate to good yields (75–99%) and ee values (75–90%, entries 6–12). Additionally, multi-fluoro substituted ketones were selected as well and pentafluoro-substituted acetophenone **1l** gave a superior ee to that obtainable from trifluoro-substituted ketone **1m** (entry 13 *vs.* entry 14).

In conclusion, catalytic amounts of $Co(OAc)_2 \cdot 4H_2O$ and chiral (*S*)-Xyl-P-Phos, which is commercially available and air-stable, along with stoichiometric $PhSiH_3$ generated *in situ* the first effective cobalt(II)–diphosphine-catalyzed hydrosilylation system. With the addition of appropriate amounts of 4 Å MS, high yields and moderate to excellent ee values (up to 96%) were achieved for a variety of aryl alkyl ketones. Noticeably, this approach can tolerate the handling of both catalyst and reactants under air without special precautions and therefore shows good potential for practical applications. Studies aimed at expanding the present catalyst system and understanding the reaction mechanism are underway in our laboratory.

## Acknowledgements

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