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Asymmetric Hydrogenation of Aryl Ketones Mediated by a Copper Catalyst

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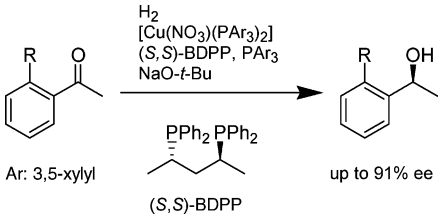
ABSTRACT



A novel asymmetric hydrogenation protocol using a copper catalyst is reported. A Cu(I) complex in the presence of nonracemic BDPP hydrogenates aryl ketones with moderate to high enantioselectivity.

There is no doubt that homogeneous asymmetric hydrogenation plays an especially important role in asymmetric syntheses, providing an effective route to optically active compounds.[1] A majority of these reactions are catalyzed by transition metal complexes such as Rh and Ru catalysts, some of which have been successfully applied to industrial production.[2]

We envisioned that if the reaction could be catalyzed by a less-expensive base metal, it would be more industrially attractive in terms of cost. Copper catalysts have shown exceptional enantioselectivity in asymmetric reductions such as hydrosilylation,[3] hydroboration,[4] and transfer hydrogenation.[5] On the other hand, it is known that copper is a useful catalyst for heterogeneous hydrogenation.[6] In addition, a landmark study by Stryker showed that a copper hydride ($[CuH(PPh_3)]_6$) has the ability to catalyze homogeneous hydrogenation.[7] These studies encouraged us to develop a new system for homogeneous asymmetric hydrogenation mediated by a copper catalyst. Reported herein is a novel copper-based system that hydrogenates aryl ketones in moderate to high enantioselectivity, and with high catalytic activity.[8]

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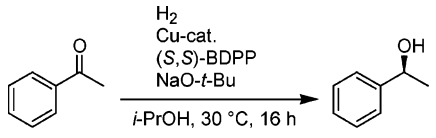
Table 1. Asymmetric Hydrogenation of Acetophenone[a]



entry	Cu catalyst	S/C[b]	conversion (%)[c]	ee (%)[c,d]
1[e]	CuCl	300	21	40
2[e]	CuCl[f]	300	>99	48
3	$[CuH(PPh_3)]_6$[g,h]	500[i]	>99	47
4	$[Cu(NO_3)(PPh_3)_2]$	1000	>99	47
5[j]	$[Cu(NO_3)(PPh_3)_2]$[f]	3000	97 (94[k])	48
6	$[Cu(NO_3)(P(3,5\text{-xylyl})_3)_2]$	500	>99	56

[a] All reactions were carried out with (*S*,*S*)-BDPP (1 equiv to Cu) and NaO-*t*-Bu (10 equiv to Cu) under an initial hydrogen pressure of 5.0 MPa unless otherwise noted. [b]Substrate to catalyst molar ratio. [c]Conversions and ee's were determined by GC analysis using a Chirasil DEX-CB column. [d]All absolute configurations were determined as *S*. [e]NaO-*t*-Bu (6 equiv to Cu) was used. [f]PPh_3 (3 equiv to Cu) was added. [g]PPh_3 (1 equiv to Cu) was added. [h]Without NaO-*t*-Bu. [i]S/C was calculated on the basis of the Cu atom. [j]Reaction time was 96 h. [k]Isolated yield after distillation.

Our initial screening using acetophenone as substrate is described in Table 1. Use of a catalyst system consisting of CuCl, BDPP,[9] and NaO-*t*-Bu (at a substrate to catalyst molar ratio (S/C) = 500) afforded the reduced product in moderate enantioselectivity (40% ee), although with limited catalytic activity (entry 1). As was reported by Stryker,[7b] addition of PPh_3 in the system increased catalytic activity, completing the reaction with slight improvement in enantioselectivity (entry 2). In these reactions, NaO-*t*-Bu presumably played a role to generate a CuO-*t*-Bu species that should mediate heterolytic hydrogen activation.[10] Use of $[CuH(PPh_3)]_6$ led to completion of the reaction even without NaO-*t*-Bu (entry 3). We settled on a catalyst precursor $[Cu(NO_3)(PPh_3)_2]$[11] that gave higher catalytic activity, up to a turnover number of 1000 (entry 4). Further reduced catalyst loading (S/C = 3000) led to near completion of the reaction with additional PPh_3 and an extended reaction time (entry 5). Later, we found that use of $[Cu(NO_3)(P(3,5\text{-xylyl})_3)_2]$[12] enhanced the enantioselectivity to 56% ee (entry 6).

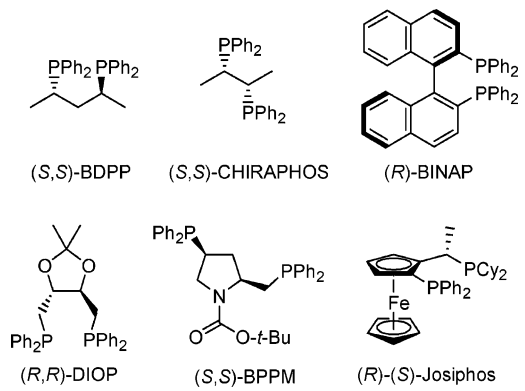
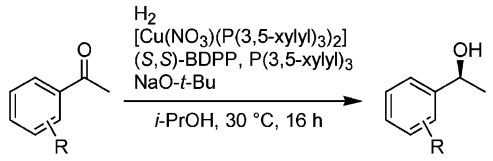
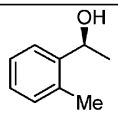
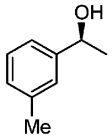
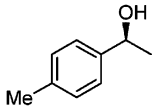
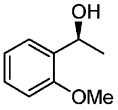
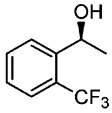
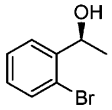
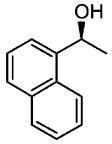


Figure 1. Ligands tested.

Table 2. Asymmetric Hydrogenation of Aryl Ketones[a]



entry	product	conversion (%)[b]	yield (%)[c]	ee (%)[b,d]
1		99	98	86
2		>99	92	64
3		>99	92	62
4		>99	92	91
5[e,f]		95	80	90
6[e]		98	82	81
7		>99	88	63

[a] All reactions were carried out with $[Cu(NO_3)(P(3,5\text{-xylyl})_3)_2]$ (S/C = 500), (*S*,*S*)-BDPP (1 equiv to Cu), $P(3,5\text{-xylyl})_3$ (6 equiv to Cu), and NaO-*t*-Bu (10 equiv to Cu) under an initial hydrogen pressure of 5.0 MPa unless otherwise noted. [b]Conversions and ee's were determined by GC analysis using a Chirasil DEX-CB column. [c]Isolated yield. [d]All absolute configurations were determined as *S*. [e]NaO-*t*-Bu (30 equiv to Cu) was used. [f]S/C = 400.

Screening of ligands using $[Cu(NO_3)(PPh_3)_2]$ revealed that conversions and enantioselectivities were greatly influenced by choice of a chiral ligand. Surprisingly, CHIRAPHOS,[13] a ligand structurally similar to BDPP, resulted in almost no reaction. Biaryl ligands such as BINAP[14] led to a lower conversion and ee (17% and 24% ee, respectively). Of the ligands tested, diphosphine ligands with comparatively flexible C3−C4 linkers, such as DIOP,[15] BPPM,[16] and

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Josiphos,[17] gave complete conversion albeit without enhanced enantioselectivity relative to BDPP (12% ee, 27% ee, and 45% ee, respectively). Investigation of the scope of the reaction was expanded to various aryl ketones. Table 2 shows cases tested, beginning with 2′-, 3′-, and 4′-methyl acetophenones in the presense of additional $P(3,5\text{-xylyl})_3$. Of the three, 2′-methylacetophenone was reduced in high enantioselectivity (86% ee), whereas 3′- and 4′-counterparts resulted in moderate ee's (entries 1−3). In general, the reaction hydrogenates various 2′-substituted acetophenone-type substrates in high enantioselectivity (81−91% ee; entries 4−6). In the case of 1-acetonaphthone, the enantioselectivity dropped to 63% ee (entry 7).

In summary, a homogeneous copper-catalyzed asymmetric hydrogenation has been discovered. The system afforded moderate to high enantioselectivity in asymmetric hydrogenation of acetophenone-type substrates. Although catalytic activity and enantioselectivity is still modest relative to Noyori's Ru system,[18] Cu catalysis may in time offer a more economical and effective protocol. Expansion of the scope to heteroaryl ketones and alkyl ketones, as well as mechanistic details, will be disclosed in due course.

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

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