

# Copper-Catalyzed Asymmetric Hydrogenation of Aryl and Heteroaryl Ketones

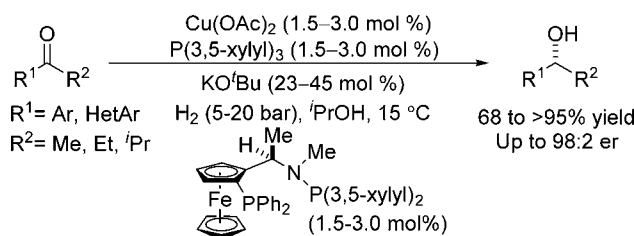
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Received July 26, 2013

## ABSTRACT



High throughput screening enabled the development of a Cu-based catalyst system for the asymmetric hydrogenation of prochiral aryl and heteroaryl ketones that operates at H<sub>2</sub> pressures as low as 5 bar. A ligand combination of (*R,S*)-*N*-Me-3,5-xylyl-BoPhoz and tris(3,5-xylyl)phosphine provided benzylic alcohols in good yields and enantioselectivities. The electronic and steric characteristics of the ancillary triarylphosphine were important in determining both reactivity and selectivity.

Asymmetric hydrogenation of simple, unactivated prochiral ketones is an important process that provides access to synthetically useful chiral secondary alcohol building blocks from inexpensive starting materials. Transition metals (Ru, Rh, Pd, Ir)<sup>1</sup> are generally the catalysts of choice for these reductions because they provide highly active and selective catalysts. The high cost, limited supply, and sometimes significant toxicity of transition metals have sparked interest in the use of more environmentally friendly base metals such as iron<sup>2</sup> and copper. The purpose of this communication is to report a new copper-based

catalyst system for the enantioselective hydrogenation of prochiral ketones.

Racemic reduction using copper hydride complexes has been known for several decades. Pioneering work by Stryker and co-workers provided the hexameric copper hydride species, [ $\{\text{CuH}(\text{PPh}_3)\}_6$ ], which was particularly useful in the reduction of  $\alpha,\beta$ -unsaturated carbonyl compounds.<sup>3</sup> Phosphine steric modifications and tethering provided particularly regioselective catalyst systems.<sup>4</sup>

With respect to asymmetric reduction, the use of copper hydride complexes and silanes as the stoichiometric reductant has been reported, with a variety of chiral ligands providing exceptional reactivity and selectivity.<sup>5,6</sup> Most of these systems require the use of cryogenic temperatures for optimal selectivity, and the reactions generate superstoichiometric silane byproducts that detract from the overall mass efficiency. A greener and more scalable alternative would utilize hydrogen, but significantly less work has been reported in this area.

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Shimizu and co-workers reported the first asymmetric copper-catalyzed ketone hydrogenation utilizing the chiral ligand BDPP, but only ortho-substituted aryl and heteroaryl ketones provided good enantioselectivities.<sup>7</sup> Beller and co-workers reported a more general catalyst system using copper acetate and monodentate binaphthophosphine ligands, but enantioselectivities generally did not exceed 75%.<sup>8</sup> In addition to the moderate enantioselectivities, both methodologies required hydrogen pressures (50 bar) generally outside the desired range for process applications.

We sought to employ high throughput screening of commercially available chiral phosphine ligands to develop a catalyst system which would provide usable enantioselectivities and operate at lower pressures. By virtue of the design of our screening procedure (all reagents were mixed without a catalyst precomplexation time and run at 20 bar of H<sub>2</sub> pressure),<sup>9</sup> only those ligands that perform well under our desired conditions were identified. Screening of ~60 chiral phosphine ligands under conditions similar to those of Shimizu and Beller for hydrogenation of acetophenone led to the identification of several active and selective complexes (Figure 1).

Given the precedent for asymmetric ketone reduction with BIPHEP- and SEGPHOS-ligated copper hydride species, their activity, and that of closely related ligands, under the current conditions is not surprising.<sup>5d</sup> Unfortunately, commercially available variants provided little

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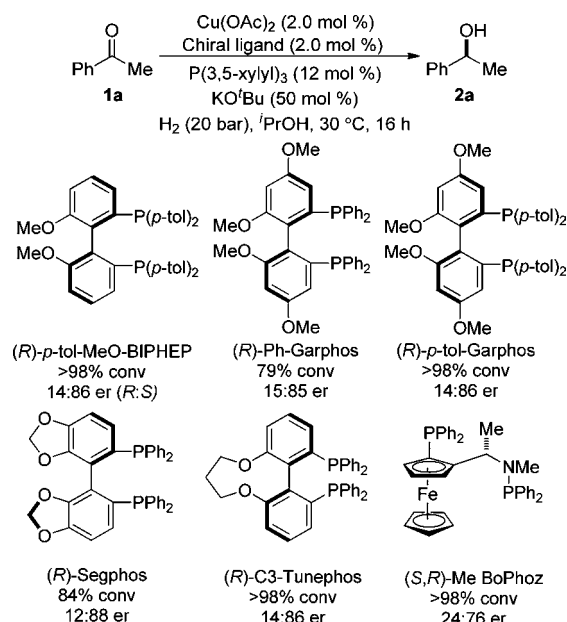
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**Figure 1.** Ligands identified by parallel screening.

increase in selectivity. Despite the lower selectivity observed, Me-BoPhoz emerged as an attractive candidate for development due to its modular synthesis, relatively high reactivity even at lower base loadings, and excellent stability.<sup>10</sup> Attempts to increase selectivity using the parent ligand through variation of additives and conditions were unsuccessful.<sup>9</sup> Of 33 phosphines tested, tris(3,5-xylyl)phosphine

**Table 1.** BoPhoz Ligand Screening

**1a** **2a**

**(R,S)-BoPhoz, 3**

entry	R	Ar		conv (%) <sup>a</sup>	er (R:S) <sup>b</sup>
1	Me	Ph	<b>3a</b>	100	79:21
2	Et	Ph	<b>3b</b>	98	72:28
3	H	Ph	<b>3c</b>	16	67:33
4	Me	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<b>3d</b>	52	75:25
5	Me	4-F-C <sub>6</sub> H <sub>4</sub>	<b>3e</b>	76	67:33
6	Me	3,5-diCF <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	<b>3f</b>	0	—
7	Me	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<b>3g</b>	100	79:21
8	Et	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<b>3h</b>	100	74:26
9	Me	4-OMe-C <sub>6</sub> H <sub>4</sub>	<b>3i</b>	100	68:32
10	Me	3,5-diMe-C <sub>6</sub> H <sub>3</sub>	<b>3j</b>	100	91:9
11	H	3,5-diMe-C <sub>6</sub> H <sub>3</sub>	<b>3k</b>	53	57:43
12	Et	3,5-diMe-C <sub>6</sub> H <sub>3</sub>	<b>3l</b>	76	80:20
13	Me	3,5-diMe-4-OMe-C <sub>6</sub> H <sub>2</sub>	<b>3m</b>	100	67:33
14	Me	3,5-tBu-4-OMe-C <sub>6</sub> H <sub>2</sub>	<b>3n</b>	43	89:11

<sup>a</sup> Determined by comparison of relative integration by HPLC of alcohol to ketone. <sup>b</sup> Determined by HPLC analysis.

**Table 2.** Ancillary Phosphine Screening

$  \begin{array}{c}  \text{O} \\  \parallel \\  \text{Ph}-\text{C}-\text{Me} \\  \mathbf{1a}  \end{array}  \xrightarrow[\text{H}_2 \text{ (20 bar), } ^i\text{PrOH, 30 }^\circ\text{C, 16 h}]{\begin{array}{c} \text{Cu(OAc)}_2 \text{ (2.0 mol \%)} \\ \mathbf{3j} \text{ (2.0 mol \%)} \\ \text{P(R)}_3 \text{ (2.0 mol \%)} \\ \text{KO}^t\text{Bu (30 mol \%)} \end{array}}  \begin{array}{c}  \text{OH} \\    \\  \text{Ph}-\text{C}-\text{Me} \\  \mathbf{2a}  \end{array}  $				
entry	R		conv (%) <sup>a</sup>	er (R:S) <sup>b</sup>
1	3,5-CF <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	<b>4b</b>	10	31:69
2 <sup>c</sup>	3,5-CF <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	<b>4b</b>	78	8:92
3	3,5-F-C <sub>6</sub> H <sub>3</sub>	<b>4c</b>	37	42:58
4	4-F-C <sub>6</sub> H <sub>4</sub>	<b>4d</b>	>99	41:59
5	3-F-C <sub>6</sub> H <sub>4</sub>	<b>4e</b>	>99	47:53
6	no ancillary		17	53:47
7	Ph	<b>4f</b>	>99	51:49
8	c-hexyl	<b>4g</b>	24	52:48
9	4-Me-C <sub>6</sub> H <sub>4</sub>	<b>4h</b>	>99	52:48
10	2-Me-C <sub>6</sub> H <sub>4</sub>	<b>4i</b>	17	53:47
11	3-Me-C <sub>6</sub> H <sub>4</sub>	<b>4j</b>	>99	75:25
12	3-Et-C <sub>6</sub> H <sub>4</sub>	<b>4k</b>	>99	66:34
13	3,5-Me-C <sub>6</sub> H <sub>3</sub>	<b>4a</b>	>99	91:9
14	3,5-Et-C <sub>6</sub> H <sub>3</sub>	<b>4l</b>	90	87:13
15	3,5-Me-4-OMe-C <sub>6</sub> H <sub>2</sub>	<b>4m</b>	>99	89:11

<sup>a</sup> Determined by comparison of relative HPLC integration of alcohol to ketone. <sup>b</sup> Determined by HPLC analysis. <sup>c</sup> <sup>t</sup>BuOH instead of <sup>i</sup>PrOH.

**Table 3.** Temperature and Pressure Optimization

$  \begin{array}{c}  \text{O} \\  \parallel \\  \text{Ph}-\text{C}-\text{Me} \\  \mathbf{1a}  \end{array}  \xrightarrow[\text{H}_2, ^i\text{PrOH}]{\begin{array}{c} \text{Cu(OAc)}_2 \text{ (1.5 mol \%)} \\ \mathbf{3j} \text{ (1.5 mol \%)} \\ \mathbf{4a} \text{ (1.5 mol \%)} \\ \text{KO}^t\text{Bu (23 mol \%)} \end{array}}  \begin{array}{c}  \text{OH} \\    \\  \text{Ph}-\text{C}-\text{Me} \\  \mathbf{2a}  \end{array}  $				
entry <sup>a</sup>	temp (°C)	pressure (bar)	t (h)	er (R:S) <sup>b</sup>
1	30	20	16	89.5:10.5
2	25	20	24	90.5:9.5
3	20	20	24	90.7:9.3
4	15	20	24	92.1:7.9
5	10	20	24	92.3:7.7
6	25	5	28	90.6:9.4

<sup>a</sup> All reactions proceeded to >97% conversion in the specified time period. <sup>b</sup> Determined by HPLC analysis.

was identified as the optimal ancillary ligand. Based on these unsuccessful attempts to increase selectivity, structural modification of the BoPhoz ligand was pursued (Table 1).

Variation of the alkyl-amino group from methyl to ethyl resulted in diminished reactivity and selectivity (entry 2). Further decreased reactivity and selectivity was observed when the free amino group was used (entry 3). Systematic variation of the aryl substituents on the nonferrocenyl phosphorus was easily achieved from a single precursor and a variety of diaryl phosphorus chlorides. Decreased electron density on this phosphorus resulted in less reactive systems (entries 4–6). Electron releasing para-substituents

showed little to no increase in selectivity (entries 7–9). Gratifyingly, 3,5-dimethyl-substitution resulted in an increase in selectivity while maintaining reactivity (entry 10). Increasing the steric demand at the 3 and 5 positions from Me to <sup>t</sup>Bu resulted in a similarly selective catalyst albeit with diminished reactivity (entry 14).

**Table 4.** Substrate Scope

$  \begin{array}{ccc}  \text{Cu(OAc)}_2 \text{ (1.5 mol \%)} & & \text{OH} \\  \mathbf{3j} \text{ (1.5 mol \%)} & \xrightarrow{\hspace{1cm}} & \text{R}^1\text{---}\text{C}^*\text{---}\text{R}^2 \\  \mathbf{4a} \text{ (1.5 mol \%)} & & \mathbf{2} \\  \text{KO}^t\text{Bu (23 mol \%)} & & \\  \text{H}_2 \text{ (20 bar), } ^i\text{PrOH, 15 }^\circ\text{C} & &   \end{array}  $					
entry	product		<i>t</i> (h) <sup>a</sup>	yield (%) <sup>b</sup>	er ( <i>R</i> : <i>S</i> ) <sup>c</sup>
1 <sup>d</sup>	H	<b>2a</b>	16	68	93:7
2 <sup>d,c</sup>	H	<b>ent-2a</b>	16	68	12:88
3	H	<b>2a</b>	24	93	92:8
4 <sup>f</sup>	4-OMe	<b>2b</b>	24	>95	93:7
5	4-F	<b>2c</b>	24	92	92:8
6	4-CF <sub>3</sub>	<b>2d</b>	12	79	93:7
7	3-Me	<b>2e</b>	38	92	95:5
8	3-Br	<b>2f</b>	24	86	92:8
9	3-CF <sub>3</sub>	<b>2g</b>	10	77	90:10
10 <sup>f</sup>	2-Me	<b>2h</b>	30	>95	88:12
11	2-Br	<b>2i</b>	30	75	86:14
12		<b>2j</b>	33	>95	93:7
13 <sup>g</sup>		<b>2k</b>	24	>95	95:5
14		<b>2l</b>	18	93	97:3
15		<b>2m</b>	16	>95	75:25
16 <sup>f</sup>		<b>2n</b>	24	>95	84:16
17		<b>2o</b>	14	70	83:17
18		<b>2p</b>	24	90	85:15
19 <sup>f</sup>		<b>2q</b>	24	>95	98:2
20 <sup>f</sup>		<b>2r</b>	27	91	97:3
21 <sup>f</sup>		<b>2s</b>	45	>95	92:8

<sup>a</sup> Time when hydrogen uptake ceased. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC analysis. <sup>d</sup> <sup>t</sup>BuOH instead of <sup>i</sup>PrOH. <sup>e</sup> **4b** instead of **4a**, 30 °C. <sup>f</sup> 3.0 mol % Cu(OAc)<sub>2</sub>, 3.0 mol % **3j**, 3.0 mol % **4a**, 45 mol % KO<sup>t</sup>Bu. <sup>g</sup> 25 °C.

Having identified BoPhoz ligand **3j** as the most selective of those examined, we revisited the impact of the ancillary triarylphosphine (Table 2). As previously observed with commercial (*S,R*)-*N*-Me-BoPhoz, the electronic and steric characteristics of the aryl substituents played a key role in determining reactivity and selectivity. In the absence of added triarylphosphine, poor reactivity and selectivity were observed (entry 6). Relatively electron deficient phosphines favored the formation of the (*S*)-alcohol (entries 1–5), while electron rich phosphines favored formation of the (*R*)-alcohol (entries 7–15). Remarkably, complete reversal of enantioselectivity could be achieved by switching from phosphine **4b** to **4a** (entries 2 and 13).<sup>11</sup> Unfortunately, ancillary phosphine **4b** was only effective when <sup>t</sup>BuOH was used as the solvent (entry 1 vs 2). Lower isolated yields of the chiral alcohols were obtained with <sup>t</sup>BuOH; therefore, <sup>i</sup>PrOH was selected for further study.

We next turned our attention to the effects of both temperature and pressure on selectivity (Table 3). Lowering the temperature provided a modest increase in selectivity without greatly increasing the reaction time (entries 1–5). Gratifyingly, in contrast to the Cu-catalyzed hydrogenations previously reported, the current system still operates efficiently at pressures as low as 5 bar, giving the same selectivity with only a slight increase in reaction time (entry 6).

With standard conditions realized, we examined the substrate scope of this hydrogenation (Table 4). A variety

of 4- and 3-substituted acetophenones, both electron-rich and -deficient, were effectively reduced under the standard conditions with good enantioselectivities (entries 3–9). 2-Substituted acetophenones were also reduced, albeit in slightly decreased enantioselectivities (entries 10–11). Increasing steric demand by variation of the ketone  $\alpha$ -substitution was well tolerated (entries 13–14). Although the selectivity remains modest, 4-phenyl-2-butanone was reduced with higher enantioselectivity than previously reported with Cu-catalyzed hydrogenation (entry 15). Several heteroaryl substituted ketones were also viable substrates (entries 16–20), with some giving the best enantioselectivities observed with this methodology. The reduction of acetylferrocene, the first step in the synthesis of BoPhoz ligands, can also be performed with this catalyst system providing **2s** in excellent yield and good enantioselectivity (entry 21).

In summary, high throughput screening enabled the identification of commercially available (*S,R*)-*N*-Me-BoPhoz as a lead ligand in the Cu-catalyzed asymmetric reduction of prochiral ketones. Systematic structural variation of both the chiral BoPhoz ligand and the ancillary triarylphosphine provided a catalyst system which operates at moderate H<sub>2</sub> pressures and provides good enantioselectivities for a variety of aryl and heteroaryl ketones. Investigation into the use of this catalyst system in the reduction of other unsaturated systems is currently underway.

**Supporting Information Available.** Hydrogenation screening procedures and additional data not included in manuscript tables; chiral ligand sources or synthesis; selectivity determination methods. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.