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## COMMUNICATION

## Cobalt-Catalyzed Asymmetric Hydroboration of Aryl Ketones with Pinacolborane

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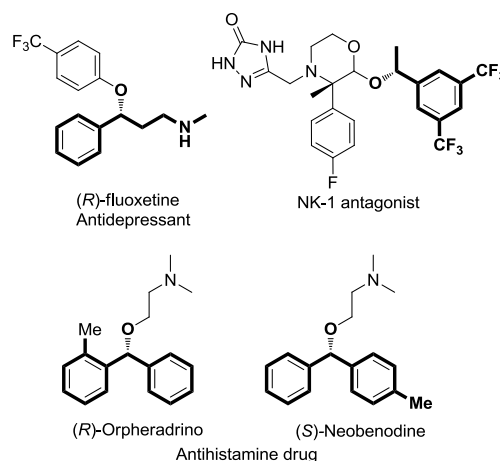
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**Highly enantioselective cobalt-catalyzed hydroboration of aryl ketones with HBpin was developed using iminopyridine oxazoline ligands. Halides, amines, ethers, sulfides, esters and amides are well tolerated under the mild reaction conditions, demonstrating its synthetic advantage. Substituted diaryl ketones could also be hydroborated with high enantioselectivity.**

Optically active secondary alcohols are extremely useful precursors for bioactive molecules<sup>1</sup> (Fig. 1), as well as valuable synthetic intermediates. One of the most fundamental methods for synthesis of these compounds is enantioselective reduction of prochiral ketones, for example, asymmetric hydrogenation<sup>2</sup> and hydrosilylation.<sup>3</sup> Asymmetric hydroboration of ketones is also an efficient strategy to achieve optically active alcohols.<sup>4</sup> Since Itsuno<sup>5</sup> and Corey<sup>6</sup> disclosed the first oxazaborolane-catalyzed asymmetric reduction of ketones with borane reagents, enormous progress has been made in borane reduction. Pinacolborane (HBpin) is a synthetic useful borane reagent,<sup>7</sup> and could potentially tolerate a variety of different functional groups. To the best of our knowledge, it has not been successfully applied in asymmetric hydroboration of ketones.<sup>8</sup>

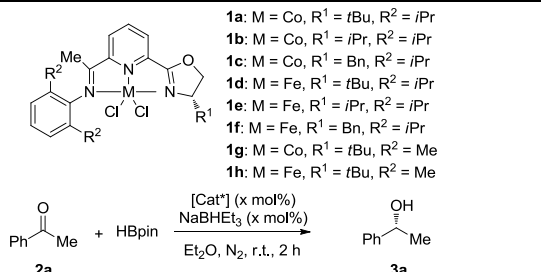
Due to the lower costs and toxicity, as well as the excellent tolerance to various functional groups, cobalt catalysts have received growing attention during the last two decades.<sup>9</sup> Enantioselective cobalt catalysis has also contributed to the development of various asymmetric transformations.<sup>10</sup> Cobalt-catalyzed asymmetric hydroboration of ketones was firstly reported by Mukaiyama in 1995<sup>11</sup> and developed by Yamada<sup>12</sup>. The modified borohydride solution has to be prepared by mixing of over stoichiometric amount of NaBH<sub>4</sub>, CHCl<sub>3</sub>, ethanol and tetrahydrofurfuryl alcohol at 0 °C under nitrogen or argon atmosphere and stirred for 3 h, additionally, the reactions were usually carried out at low temperature (-40-0 °C). Although aryl ketones and steric bulky aliphatic ketones were successfully reduced to afford the corresponding alcohols in 61-99% ee, the chiral ligands are still limited in semicorrin structure. Recently, the Huang group<sup>13</sup> and our group<sup>14</sup> independently developed cobalt-catalyzed asymmetric hydroboration of styrenes



**Fig. 1** Bioactive compounds derivatized from chiral secondary alcohols.

with pinacolborane (HBpin)<sup>15</sup> using iminopyridine oxazoline ligands. We also disclosed that a chiral iron catalyst could promote the highly enantioselective hydroboration of 1,1-disubstituted styrenes.<sup>16</sup> Herein, we demonstrate iminopyridine oxazoline metal complex-catalyzed highly enantioselective hydroboration of aryl ketones with HBpin under the mild conditions.

We chose acetophenone **2a** as the model substrate to conduct the hydroboration reaction with HBpin in the presence of earth abundant transition metal complexes (2.5 mol%) and NaHBET<sub>3</sub> under a nitrogen atmosphere using diethyl ether as the solvent at room temperature (Table 1). Using **1a** as a catalyst and NaHBET<sub>3</sub> as a reductive reagent, which is the best catalytic system for asymmetric hydroboration of alkenes, the hydroboration of **2a** is quite efficient to afford the (R)-1-phenylethanol in an excellent yield with 83% ee. After screening a variety of metal catalysts, we found that cobalt catalyst **1g** gave a high yield and best enantioselectivity, and the reaction could be easily reproduced (entry 7). Using iron complex (**1h**) instead of **1g**, the enantioselectivity was decreased (entry 8).<sup>17</sup>

**Table 1** Optimization studies for asymmetric hydroboration of ketones with HBpin<sup>a</sup>


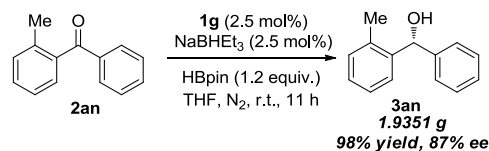
1a: M = Co, R<sup>1</sup> = *t*Bu, R<sup>2</sup> = *i*Pr  
 1b: M = Co, R<sup>1</sup> = *i*Pr, R<sup>2</sup> = *i*Pr  
 1c: M = Co, R<sup>1</sup> = Bn, R<sup>2</sup> = *i*Pr  
 1d: M = Fe, R<sup>1</sup> = *t*Bu, R<sup>2</sup> = *i*Pr  
 1e: M = Fe, R<sup>1</sup> = *i*Pr, R<sup>2</sup> = *i*Pr  
 1f: M = Fe, R<sup>1</sup> = Bn, R<sup>2</sup> = *i*Pr  
 1g: M = Co, R<sup>1</sup> = *t*Bu, R<sup>2</sup> = Me  
 1h: M = Fe, R<sup>1</sup> = *t*Bu, R<sup>2</sup> = Me

Reaction scheme: Ketone **2a** + HBpin  $\xrightarrow[\text{Et}_2\text{O, N}_2, \text{r.t., 2 h}]{\text{[Cat*] (x mol\%), NaBHET}_3 \text{ (x mol\%)}}$  Alcohol **3a**

Entry	Cat. (mol%)	Yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	<b>1a</b> (2.5)	99	83
2	<b>1b</b> (2.5)	99	89
3	<b>1c</b> (2.5)	96	45
4	<b>1d</b> (2.5)	97	81
5	<b>1e</b> (2.5)	99	78
6	<b>1f</b> (2.5)	89	66
7	<b>1g</b> (2.5)	98	98
8	<b>1h</b> (2.5)	98	67
9	<b>1g</b> (1.0)	98	95
10	<b>1g</b> (0.5)	83	92
11 <sup>d</sup>	<b>1g</b> (2.5)	99	97
12 <sup>e</sup>	<b>1g</b> (2.5)	97	97
13 <sup>f</sup>	<b>1g</b> (2.5)	92	84

<sup>a</sup> The reactions were conducted using **2a** (1.0 mmol), HBpin (1.2 mmol) in a solution of ether (1 mL) at room temperature under the atmosphere of N<sub>2</sub> for 2 h. <sup>b</sup> Yields were determined by <sup>1</sup>H NMR using trimethylsilylbenzene as an internal standard. <sup>c</sup> Ee values were determined by HPLC. <sup>d</sup> At 0 °C. <sup>e</sup> Using 1.0 mmol of HBpin. <sup>f</sup> 0.1 mmol of water was added.

Even with 0.5 mol% of catalyst loading, high ee value (92%) could still be achieved (entry 10). Decreasing the temperature to 0 °C, no further improvement was observed (entry 11). The reaction with 1

**Scheme 1** Gram-Scale Reaction.

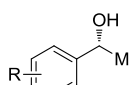
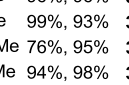
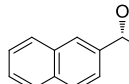
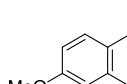
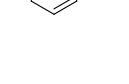
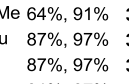
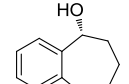
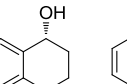

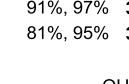
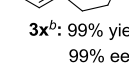
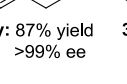
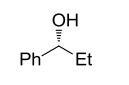
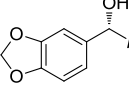
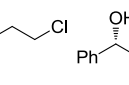
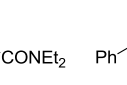
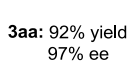
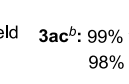
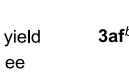
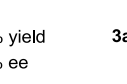
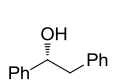
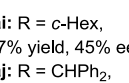
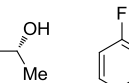
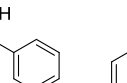
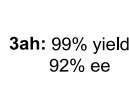
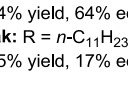

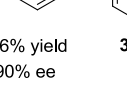
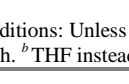
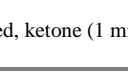
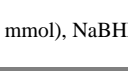
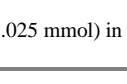
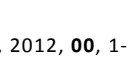

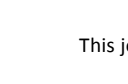
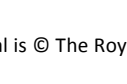




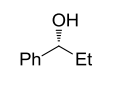
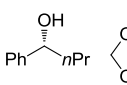
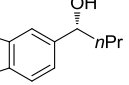
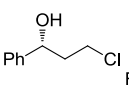
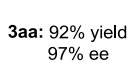
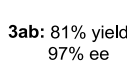
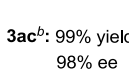
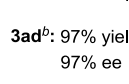
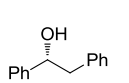
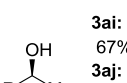
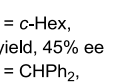
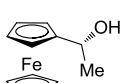
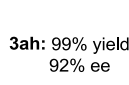
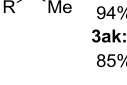
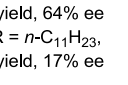
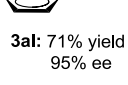
equiv of HBpin gave a similar result (entry 12). Although a additional water still gave a high yield, it did diminish the enantioselectivity (entry 13).

With the best complex **1g** in hands, studies exploring the scope of this process are summarized in Table 2. 1) A variety of acetophenones with both electron-rich and electron-deficient groups at the *para*-, *meta*- or *ortho*- positions on the phenyl ring are capable of being reduced to afford chiral 1-arylethan-1-ols in good yields with excellent enantioselectivities; 2) Halides, amines, ethers, sulfides, esters and amides are well tolerated, demonstrating the synthetic advantage; 3) Long alkyl chains or functionalized alkyl chains have been shown to be suitable partners for aryl ketones, leading to the desired products with high enantioselectivities; 4) Five-, six- and seven-membered cyclic aryl ketones also reacted to afford cyclic alcohols in excellent yields with  $\geq 99\%$  ee; 5) 2-Acetonaphthone and acetylferrocene provide chiral alcohols with  $\geq 95\%$  ee, but 2-acetylbenzylfuran gives a slightly lower enantioselectivity; 6) Dialiphatic ketones also participate in this reaction to afford the alcohols in 67-94% yield with 17-64% ee; 7) Gratifyingly, diaryl ketones (**2an** and **2ano**) with *ortho*-substitution could be hydroborated in 90% ee and 87% ee, respectively.

Gram-scale reaction took place smoothly to give the corresponding chiral alcohol **3ao** in 98% yield. (Scheme 1).

In summary, we have developed a cobalt-catalyzed highly enantioselective hydroboration of aryl ketones with pinacolborane. Halides, amines, ethers, sulfides, esters and amides are well tolerated under the mild conditions, demonstrating its synthetic advantage. Substituted diaryl ketones could also be reduced with high

**Table 2** Products of the Cobalt-Catalyzed Asymmetric Hydroboration of Aryl Ketones with HBpin<sup>a</sup>

	3b <sup>b</sup> : R = 4-Me 93%, 99%		3i: R = 4-Cl 83%, 96%		3v: 95% yield >99% ee		3w: 84% yield 96% ee
	3c: R = 3-Me 96%, 96%		3m: R = 3-Cl 89%, 98%		3x <sup>b</sup> : 99% yield 99% ee		3y: 87% yield >99% ee
	3d: R = 2-Me 99%, 93%		3n: R = 4-Br 84%, 96%		3z <sup>b</sup> : 92% yield 99% ee		3a: 81% yield 95% ee
	3e: R = 4-OMe 76%, 95%		3o: R = 4-CF <sub>3</sub> 92%, 96%		3b: 94% yield 98% ee		3c: 64% yield 91% ee
	3f: R = 3-OMe 94%, 98%		3p: R = 3-CF <sub>3</sub> 88%, 92%		3d: 64% yield 91% ee		3e: 64% yield 91% ee
	3g: R = 2-OMe 64%, 91%		3q: R = 3,5-diCF <sub>3</sub> 90%, 93%		3e: 87% yield 97% ee		3f: 81% yield 90% ee
	3h: R = 4- <i>t</i> Bu 87%, 97%		3r: R = 4-SMe 95%, 97%		3f: 81% yield 90% ee		3g: 88% yield 98% ee
	3i <sup>b</sup> : R = 4-F 87%, 97%		3s: R = 4-NMe <sub>2</sub> 98%, 96%		3g: 81% yield 97% ee		3h: 88% yield 98% ee
	3j <sup>b</sup> : R = 3-F 91%, 97%		3t: R = 4-CO <sub>2</sub> Me 88%, 96%		3h: 99% yield 92% ee		3i: 85% yield 17% ee
	3k: R = 2-F 81%, 95%		3u: R = 3-Br-4-OMe 72%, 96%		3i: 67% yield 45% ee		3j: 94% yield 64% ee
	3aa: 92% yield 97% ee		3ab: 81% yield 97% ee		3ac <sup>b</sup> : 99% yield 98% ee		3ad <sup>b</sup> : 97% yield 97% ee
	3ae <sup>b</sup> : 87% yield 98% ee		3af <sup>b</sup> : 81% yield 90% ee		3ag <sup>b</sup> : 88% yield 98% ee		3ah: 99% yield 92% ee
	3aj: R = CHPh <sub>2</sub> , 94% yield, 64% ee		3al: 71% yield 95% ee		3am <sup>b</sup> : 90% yield 63% ee		3an <sup>b</sup> : 96% yield 90% ee
	3ak: R = <i>n</i> -C <sub>11</sub> H <sub>23</sub> , 85% yield, 17% ee		3ao: 99% yield 87% ee		3ap <sup>b</sup> : 96% yield 90% ee		3aq <sup>b</sup> : 99% yield 87% ee

<sup>a</sup> Standard conditions: Unless otherwise noted, ketone (1 mmol), HBpin (1.2 mmol), **1g** (0.025 mmol), NaBHET<sub>3</sub> (0.025 mmol) in 1 mL of Et<sub>2</sub>O at rt under nitrogen for 2 h. <sup>b</sup> THF instead of Et<sub>2</sub>O

enantioselectivity by differentiating steric effect. Current efforts in our laboratory are underway to understand the mechanistic intricacies of this process and develop new asymmetric reactions based on non-noble transition metals.

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## Notes and references

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