## **Direct Catalytic Asymmetric Reductive Amination of Simple Aromatic Ketones**

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## ABSTRACT



A green method for chiral amine synthesis, the direct catalytic asymmetric reductive amination, was developed. Phenylhydrazide is an ideal nitrogen source for reductive amination. Molecular sieves play dual roles in this reaction. They help to remove H<sub>2</sub>O to form imine, as well as promote an imine reduction. f-Binaphane minimizes the inhibition effect from amines and helps the coordination of sterically demanding imines to the iridium center, thus leading to a smooth reaction.

The synthesis of chiral amines is one of the major tasks in organic chemistry.<sup>1</sup> Chiral amines play important roles in pharmaceutical and agrochemical industry. For instance, 45 out of 200 top brand name drugs by US retail sales in 2010 contain one or more chiral amine centers.<sup>2</sup> Some examples are cinacalcet<sup>3</sup> and rivastigmine<sup>4</sup> (Figure 1). Among those various methods for chiral amine synthesis, hydrogenation is one efficient route.<sup>5</sup> In hydrogenation previously research focused on reduction of imine and enamine substrates. For asymmetric hydrogenation of imines, the instability of certain substrates and reduced enantios-electivities resulting from the E/Z isomers limit its application.<sup>1</sup> And hydrogenation of enamines requires additional steps for preparation and deprotection. At the same time, a more efficient and operationally simpler method, direct

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Figure 1. Structure of cinacalcet, rivastigmine, arylhydrazide, and pyrazolidine.

catalytic asymmetric reductive amination, was rarely studied.<sup>6</sup> Successful asymmetric reductive amination systems are sparse, and the substrate scope is very limited.<sup>7</sup> Several major problems stand as obstacles to the advance in this research area: (1) the starting ketone can be reduced before reductive amination takes place; (2) the E/Z isomers

<sup>(1)</sup> Chiral Amine Synthesis; Nugent, T. C., Ed.; Wiley-VCH: Weinheim, 2010.

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resulting from the acyclic imine intermediates make stereoselective reduction difficult; (3) the amine used as a nitrogen source inhibits the reactivity of the transition metal.<sup>1,7b</sup>



Figure 2. Structures of chiral phosphine ligands.

In 1999, Blaser et al. explored the first asymmetric reductive amination in the synthesis of (S)-metolachlor.<sup>7c</sup> Then Kadyrov reported highly enantioselective hydrogen transfer reductive amination using ammonium formate. But this system created a large amount of side products.<sup>7d</sup> Ammonium salts were proven to be good nitrogen sources for the synthesis of  $\beta$ -amino ester and  $\beta$ -amino amide.<sup>7e-g</sup> Chiral 1-methyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline was synthesized by Wills and co-worker via intramolecular reductive amination.<sup>7h</sup> Our group contributed efficient reductive amination of simple aryl ketones using aniline in the presence of titanium(IV) isopropoxide and iodine with excellent enantioselectivities in high yields.<sup>7i</sup> Since then, several papers were published using anilines as nitrogen sources.<sup>7j–1</sup> Although in some systems<sup>7i,k,1</sup> anilines offered excellent enantioselectivities, the removal of anilines as protecting groups is not easy.<sup>8</sup> So it is still a challenge to find out suitable nitrogen sources that can be used and removed for asymmetric reductive amination of simple ketones. Herein, we report highly efficient direct

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asymmetric reductive amination of simple ketones using phenylhydrazide as the nitrogen source. To our knowledge, this is the first time phenylhydrazide was used for the reductive amination of ketones. With the help of several additives, excellent reactivity (up to 1000 TONs) and enantioselectivities (up to 99% ee) were achieved in this iridium–f-Binaphane (Figure 2) catalyzed reaction.

The chiral hydrazide products were made in high enantioselectivities by Burk and Feaster in 1992 from the asymmetric hydrogenation of N-benzovlhydrazone.<sup>9a</sup> However, direct reductive amination was not realized in this system.<sup>9b</sup> Phenylhydrazide is a desired nitrogen source due to its carbonyl group acting as a chelation group, formation of an E-imine structure in Burk's system to ensure high enantioselectivities, and ease in cleaving the N-N or N-C(O) bond to form chiral hydrazine and chiral amine.9b Chiral hydrazines, arylhydrazide, and its derivatives, pyrazolidines, are of great importance in biological and medicinal chemistry, as well as important synthetic intermediates (Figure 1).<sup>10–13</sup>In our experiment, we explored phenylhydrazide as a nitrogen source for reductive amination using acetophenone as a standard ketone, and results are summarized in Table 1. We selected an iridium-f-Binaphane complex as the catalyst because it does not promote ketone reduction, and it exhibited excellent performance in the asymmetric hydrogenation of imines and reductive amination.14

Additives are key to the success of this reaction. Without any additive, there was no reaction (Table 1, entry 1). With the addition of 10 mol % *p*-toluenesulfonic acid, the major product was *N*-benzoylhydrazone intermediate **4** and some alcohol product **5**. After using iodine along with *p*toluenesulfonic acid, some product **3a** started to appear. And when molecular sieves (4 Å), *p*-toluenesulfonic acid, and iodine were added at the same time, the desired product **3a** was obtained as the major product with 88% ee, and the alcohol side product **5** disappeared (Table 1,

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Table 1. Direct Asymmetric Reductive Amination of Acetophenone with Phenylhydrazide Using Iridium-f-Binaphane<sup>a</sup>



<sup>*a*</sup> Reaction conditions: [Ir]/ligand/ketone/phenylhydrazide = 1:1:110:100, ligand/metal 1:1, 50 atm of H<sub>2</sub>, 60 °C, 24 h. <sup>*b*</sup> TsOH = *p*-toluenesulfonic acid, 10 mol %; MS = 4 Å molecular sieves, 0.2 g; I<sub>2</sub> = iodine, 10 mol %. <sup>*c*</sup> Conversions, product ratios, and enantiomeric excesses were determined by chiral HPLC. <sup>*d*</sup> Reaction temperature was room temperature. <sup>*e*</sup> Catalyst loading was 0.1 mol %.

entries 2–5). From the data in Table 1 the addition of molecular sieves and *p*-toluenesulfonic acid facilitated the formation of intermediate imine **4**, and  $I_2$  benefited the yield of the desired product **3a**. From solvent screening, the highest enantioselectivity and reactivity were achieved from the combination of methanol and dichloromethane (Table 1, entry 8). When the catalyst loading was 0.1 mol %, full conversion was still achieved (Table 1, entry 10). Under the same reaction conditions, other chiral diphosphine ligands were tested (Figure 2). DuanPhos, JosiPhos, Et-DuPhos, and BINAP yielded predominately hydrozone intermediate **4**.

Table 2. Asymmetric Hydrogenation of N-Benzoylhydrazone 4<sup>4</sup>



entry	$\operatorname{additives}^{b}$	yield $(\%)^c$	ee (%) of <b>3</b> <sup>c</sup>
1	$I_2$	18	92
2	$I_2$ , TsOH	12	92
3	$I_2$ , MS	>99	94
4	$I_2$ , MS, TsOH	>99	94

<sup>*a*</sup> Reaction conditions: [Ir]/ligand/**4** = 1:1:110:100, ligand/metal 1:1, 50 atm of H<sub>2</sub>, room temperature, 24 h. <sup>*b*</sup> TsOH = *p*-toluene-sulfonic acid, 10 mol %; MS = 4 Å molecular sieves, 0.2 g; I<sub>2</sub> = iodine, 10 mol %. <sup>*c*</sup> Yields and enantiomeric excesses were determined by chiral HPLC.

To gain a better understanding of the functions of additives, asymmetric hydrogenation of corresponding

imine 4 was carried out (Table 2). Surprisingly, 4 Å molecular sieves facilitated this reaction. This result is interesting since molecular sieves were commonly believed to only promote imine formation in reductive amination.<sup>15</sup>

After establishing the optimized reaction conditions, a range of commercial available aromatic ketones were reductively animated using this Ir-f-Binaphane catalyst.

For all chosen *para*- (1a-1f) and *meta*-substituted (1g-1i) aromatic ketones, the chiral hydrazide products 3 were obtained in excellent yields and ee's (ee ranged from 94% to 99%, Scheme 1), regardless of their electronic properties. For *ortho*-substituted aromatic ketone (1j), the reactivity and enantioselectivity decreased slightly, maybe due to its sterical hindrance. This catalytic system also worked quite well for heteroaromatic ketone (1l) and 2-naphthalene ketone (1k). To evaluate the practical utility of our method, acetophenone and 4-methoxylacetophenone were reductively aminated on half-gram scale, and excellent ee's and yields were obtained for both ketones (Scheme 2).

In summary, we have demonstrated the highly enantioselective direct reductive amination of aromatic ketones. With phenylhydrazide as the nitrogen source, various chiral hydrazides were synthesized in excellent enantioselectivities and yields. The success of this reaction results from several factors: (a)  $H^+$  facilitated the formation of imine intermediates; (b) 4 Å molecular sieves not only helped to remove H<sub>2</sub>O to form imines but also promoted

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**Scheme 1.** Direct Asymmetric Reductive Amination of Simple Aromatic Ketones Using Iridium–f-Binaphane.<sup>*a*</sup>



<sup>*a*</sup> Reaction conditions: [Ir]/ligand/TsOH/I<sub>2</sub>/ketone/phenylhydrazide = 1:1:10:10:110:100, ligand/metal 1:1, 50 atm of H<sub>2</sub>, rt, 24 h. TsOH = *p*-toluenesulfonic acid, MS = 4 Å molecular sieves 0.2 g, I<sub>2</sub> = iodine. Yields are isolated yields. Enantiomeric excesses were determined by chiral HPLC. The absolute configuration of product is assigned by comparison of rotation sign with literature data. <sup>9b</sup> Reaction temperature was 60 °C.

the reduction of imines; (c) with the addition of  $I_2$ , Ir(III)- $I_2$ Cl(f-Binaphane) was formed, <sup>14a</sup> which is an effective

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Scheme 2. Scale-up Reductive Amination of Acetophenone and 4-Methoxylacetophenone



catalytic precursor for the hydrogenation of imines; (d) phenylhydrazide and the amine products have weak coordination ability to Ir, so the catalytic reaction can proceed smoothly; (e) f-Binaphane is a unique electron-donating ligand with a big bite angle  $(P^*-Ir-P^*)$ .<sup>16</sup> f-Binaphane minimizes the inhibition effect from amines and helps iridium to accommodate sterically demanding imines, thus leading to a smooth reaction. The superb performance of the methodology offers an attractive route for chiral amine and chiral hydrazine derived heterocyclic compounds synthesis. We are currently examining the extension of this methodology to other substrates.

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**Supporting Information Available.** Spectral data for all new compounds (<sup>1</sup>H NMR, <sup>13</sup>C NMR, and HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.