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Direct Catalytic Asymmetric Reductive Amination of Aliphatic Ketones Utilizing Diphenylmethanamine as Coupling Partner

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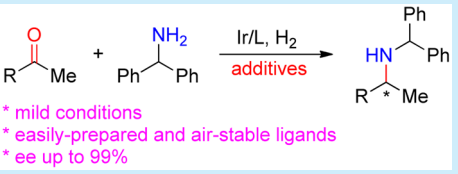
Supporting Information

ABSTRACT: The highly efficient direct catalytic reductive amination of ketones with diphenylmethanamine catalyzed by iridium−phosphoramidite complexes is described. As an effective coupling partner, diphenylmethanamine is suitable for a wide range of ketones to provide chiral amines in high yields and enantioselectivity. The chiral monodentate phosphoramidite ligands are tunable and competent to accommodate substrates with different structures.

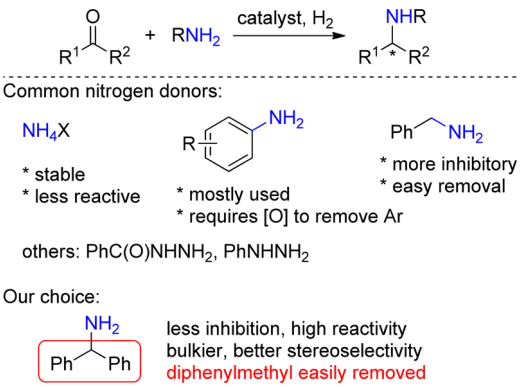


The reductive amination reaction is one of the most widely utilized transformations in both biological systems and synthetic organic chemistry.[1] It chemoselectively couples ketones and amines to form diverse C−N bonds. It is a privileged in vivo tool for nature to enantioselectively generate essential biomonomers. A renowned example is the formation of the naturally occurring amino acids.[1a,2] In synthetic chemistry, some progress has been made for the synthesis of chiral amines via transition-metal-catalyzed asymmetric reductive amination[3] since the first example was reported by Blaser and co-workers in 1999 for the production of the herbicide Metolachlor.[4a] A number of catalysts have been examined on reductively coupling various ketones and amines. However, successful transition-metal-catalytic systems are very limited. One major obstacle is the inhibitory effect of coupling partner amines on the catalysts, resulting in their low reactivity. At the same time, the detailed mechanism of transition-metal-catalyzed asymmetric reductive amination remains to be elucidated.

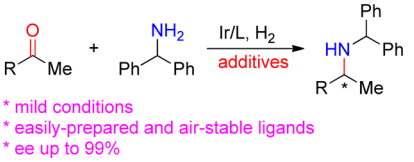
For the transition-metal-catalyzed asymmetric reductive amination, anilines are the most utilized ketone coupling partners due to their less restrictive impact on catalysts compared with alkyl amines.[4] Other nitrogen donors include inorganic ammonium salts,[5] benzylamine,[6] hydrazines,[7] and hydrazides[4g,8] (Scheme 1). Simple benzylamine is more nucleophilic compared with anilines and thus exerts more inhibitory effect on the transition-metal center. We propose that diphenylmethanamine, with another phenyl group on the benzylic carbon of the simple benzylamine, would be less likely to restrain the catalyst reactivity. Herein, we report the application of diphenylmethanamine as a reductive amination partner of a variety of ketones catalyzed by iridium−monodentate phosphoramidite complexes (Scheme 2).

Chiral aliphatic amines are present in many active pharmaceutical ingredients, and certain unfunctionalized ones are difficult to synthesize by asymmetric catalytic methods.[9] Especially for the primary amines with linear aliphatic chain and lower molecular weight, their large-scale production depends on classic resolution.[10] The BINOL-based phosphoramidite MonoPhos was initiated by Pringle and

Scheme 1. Comparison of Different Nitrogen Donors for Asymmetric Ketone Reductive Amination



Scheme 2. Diphenylmethanamine-Involved Reductive Amination



Feringa in 2000.[11] This series of ligands found success in numerous catalytic research areas, largely due to their ease of preparation at low cost and their bench stability.[12] We started our research on the asymmetric reductive amination of the simple 2-pentanone with diphenylmethanamine **2** to synthesize the corresponding chiral amines catalyzed by 1 mol % iridium−phosphoramidite complexes. **L1a** worked perfectly for the reductive coupling of phenylacetone with **2**.[13] As for 2-pentanone, the reaction proceeded smoothly to give exclusively the desired product, but only rendered 61% ee. We then continued to develop a series of phosphoramidite

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chiral ligands based on BINOL and H8-BINOL backbones (Figure 1) and utilized them in the reductive amination of 2-pentanone. The results are summarized in Table 1. The ee values resulting from phosphoramidite ligands bearing simple 6-membered or 5-membered *N*-monocyclic rings were all less than 65% (entries 2−7). In addition, the H8-BINOL-based ligands furnished lower enantiomeric excesses than the BINOL-based ones (entries 1−4 versus 5−7). When the *N*-tricyclic ligand **L2e** was applied, ee was enhanced to 86% and could be further improved to 87% (entries 8 and 9). When 0.1 mol % of iridium−**L2e** was utilized, the reaction proceeded completely (entry 10). When the H_2 pressure was decreased to 40 atm, the reaction yield and ee remained the same. Further lowering the pressure to 30 atm, the yield for the reaction slightly dropped but the enantioselectivity was not affected (entries 11 and 12). In comparison, we utilized aniline and benzylamine as coupling partners (eq 1). As expected, neither of them provided satisfactory results.

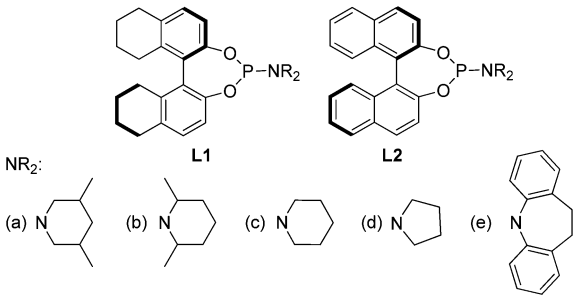
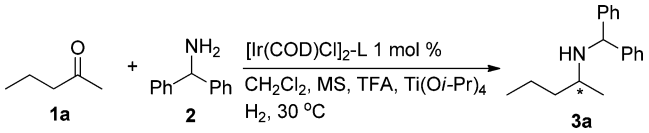


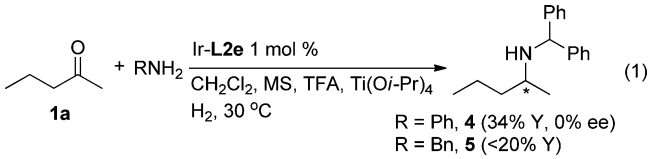
Figure 1. Structures of phosphoramidite ligands.

Table 1. Screening of Phosphoramidite Chiral Ligands[a]



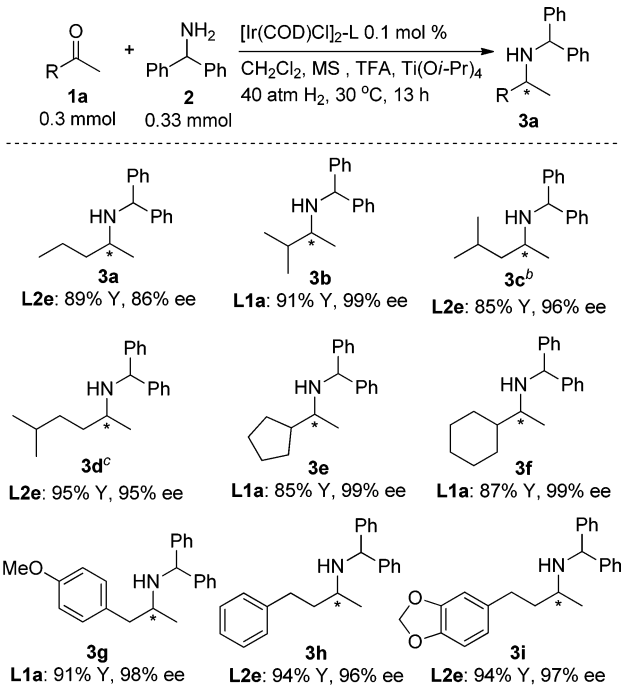
entry	cat. (mol %)	H_2 (atm)	ligand[b]	ee[c] (%)
1	**1**	60	**L1a**	62
2	**1**	60	**L1b**	6
3	**1**	60	**L1c**	52
4	**1**	60	**L1d**	38
5	**1**	60	**L2a**	64
6	**1**	60	**L2c**	63
7	**1**	60	**L2d**	45
8	**1**	60	**L2e**	86
9[d]	**1**	60	**L2e**	87
10	**0.1**	60	**L2e**	86
11	**0.1**	40	**L2e**	86
12[e]	**0.1**	30	**L2e**	86

[a]Reaction conditions: [Ir]/L/**1a**/**2** = 1:2:100:110, **1a** 0.2 mmol, CH_2Cl_2 2 mL, 60 atm of H_2, 13 h; COD = 1,5-cyclooctadiene; MS = 4 Å molecular sieves, 0.1 g; TFA = CF_3COOH, 0.3 equiv; $Ti(Oi\text{-}Pr)_4$ 0.3 equiv. [b]When ligand **L2e** was used, the TFA amount was 0.5 equiv. [c]Enantiomeric excesses were determined by chiral HPLC. [d]Ir-$(COD)_2$Barf metal precursor was used instead of $[Ir(COD)Cl]_2$, Barf = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate. [e]Reaction yield dropped 5%.



To explore the substrate scope of this Ir−phosphoramidite catalytic system, a range of ketones was studied. The results are summarized in Scheme 3. For different substrates, the suitable ligand varied; e.g., for substrate **1b**, **L1a** worked much better than the sterically hindered **L2e**. This is because for different sized substrates, according ligands are required to accommodate their spatial demand. From the experiments, we can see **L1a** functioned well for substrates **1b** and **1e−h**. Increasing the substrates size by changing the alkyl substituents from linear to branched has a positive influence on stereocontrol. Compared with the 86% ee value of **3a**, the ee's for **3b** and **3c** were improved to 99% and 95%, respectively. The best results were obtained for cyclic alkyl group substituted ketones **1e** and **1f**. The catalytic system also worked quite well for aliphatic and aromatic hybrid ketones **1h** and **1i**, providing **3h** and **3i** in 96% and 97% ee, respectively, and perfect yields.

Scheme 3. Asymmetric Reductive Amination of Aliphatic Ketones[a]



[a]Reaction conditions: [Ir]/L/**1a**/**2** = 1:2:1000:1100, CH_2Cl_2 2 mL, 40 atm of H_2, 13 h; MS 0.1 g; TFA 0.5 equiv; $Ti(Oi\text{-}Pr)_4$ 0.3 equiv. Yields are isolated yields. Enantiomeric excesses were determined by chiral HPLC. [b]Catalyst loading was 0.4 mol %. [c]Catalyst loading was 0.3 mol %.

To further demonstrate the practical application of this protocol, the asymmetric reductive amination of **1h** was performed on large scale. Product **3h** was obtained with 93% isolated yield and 96% ee. The facile removal of the diphenylmethyl group was carried out with Pd/C and H_2. The product was then derived with acetic anhydride to give **4**

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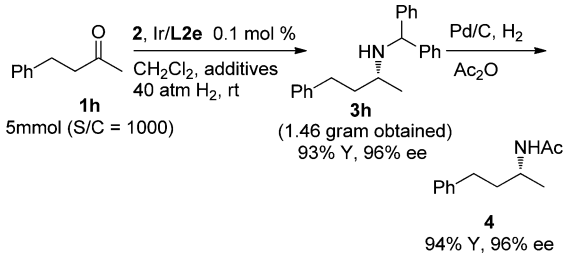
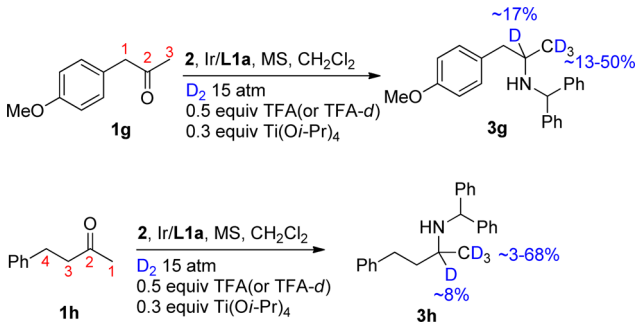
in 94% yield without any erosion of the enantioselectivity (Scheme 4).

Scheme 4. Large-Scale Reductive Amination of 1g and Facile Deprotection



To gain insight into the reaction pathways, we conducted isotopic-labeling experiments for the reductive amination of ketones **1g** and **1h** with diphenylmethanamine using deuterium gas (Scheme 5). From the ^{1}H NMR integration,

Scheme 5. Deuterium Incorporation Study



for **3g**, only 17% deuterium was incorporated on chiral center C2; for **3h**, deuterium on chiral center C2 was also only 8%. We repeated the isotopic-labeling experiments using deuterated trifluoroacetic acid (TFA-*d*). Similar results were obtained. The above results indicated these asymmetric reductive amination reactions proceeded other than the common inner-sphere imine intermediate reduction.[14] There was an interesting observation that protons on C1, C2, and C3 of **3g** and **3h** were partially substituted by deuteriums. The deuterium abundance on those positions increased with elongated reaction time. We proposed that those deuteriums underwent D/H exchange with the environmental molecular hydrogen.[15] For the roles of the additives, TFA activates the ketone substrates and lessens the inhibitory effect of nitrogen-containing compounds on the catalyst; MS, TFA and Ti(O-*i*-Pr)$_4$ together facilitate the formation of the imine intermediates.

In summary, diphenylmethanamine reductively coupled with various ketones catalyzed by the iridium−phosphoramidite complexes under mild conditions. As an excellent nitrogen source, diphenylmethanamine minimizes the inhibitory effect on catalyst; its suitable size enables better stereocontrol. The chiral monodentate phosphoramidite ligands are cost-efficient, air-stable, and tunable to accommodate different types of substrates. By this protocol, a range of corresponding amine products could be prepared in high enantioselectivity. We are currently investigating the mechanistic aspects of the reaction in a more thorough manner, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00212.

Experimental materials and procedures, NMR of products, and HPLC for racemic and chiral products (PDF)

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Notes

The authors declare no competing financial interest.

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