

Asymmetric Catalysis

Deutsche Ausgabe: DOI: 10.1002/ange.201601025
Internationale Ausgabe: DOI: 10.1002/anie.201601025Direct Asymmetric Reductive Amination for the Synthesis of Chiral β -Arylamines

Haizhou Huang, Xiaoyan Liu, Le Zhou,* Mingxin Chang,* and Xumu Zhang

Abstract: The highly efficient and direct asymmetric reductive amination of arylacetones catalyzed by an iridium complex for the preparation of enantiomerically pure β -arylamines is described. The monodentate phosphoramidite ligand exhibits superb reactivity (TONs of up to 20 000) and enantioselectivity (up to 99% *ee*). Additives played important roles in this reductive coupling reaction.

Enantiomerically pure β -arylamines are ubiquitous structural motifs and key pharmacophores of many active pharmaceutical ingredients (Figure 1),^[1] for example, dextroam-

compounds^[8] are two highly efficient approaches, especially the latter, because its concise synthetic route and high atom economy represent a greener and more promising method.

For the preparation of unfunctionalized chiral β -arylamines by asymmetric reductive amination reactions, there has been some progress in the areas of biocatalysis (mainly using ω -transaminases)^[9] and organocatalysis (using chiral phosphoric acids)^[10] in recent years. In contrast, the transition-metal-catalyzed counterpart to prepare such compounds lags behind. To the best of our knowledge, the only related research was reported in 2010 for the asymmetric reductive amination of 2-tetralone in 47% *ee*.^[11] At the same time, a number of transition-metal complexes succeeded in the preparation of chiral α -arylamines by asymmetric reductive coupling reactions.^[8,12] The structure of the corresponding acetophenone is rigid (π - π conjugation), while phenylacetone is floppy (σ -bond rotations) and thus results in difficulties regarding enantiocontrol. Other factors, such as the inhibitory effect of amines on the catalyst and ketone reduction as a side-reaction, also stand as obstacles to advances in this research area.^[1,8]

Herein, we report a highly efficient direct asymmetric reductive amination of arylacetones using diphenylmethylamine as the nitrogen source [Eq. (1); M.S. = 4 Å molecular

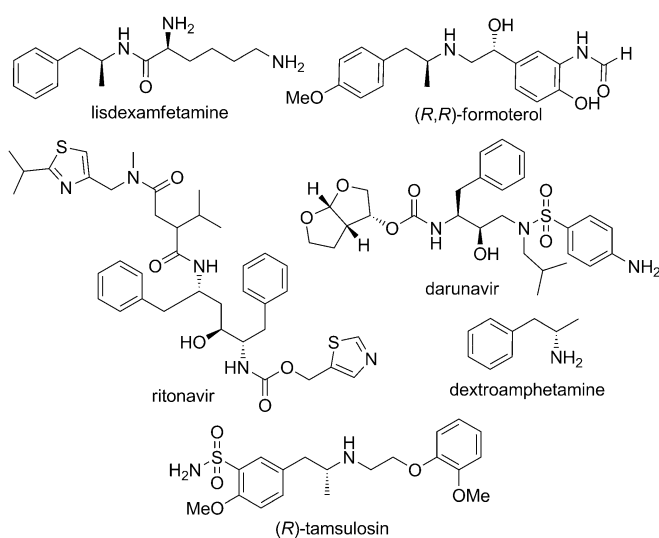
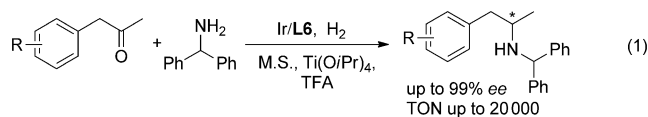
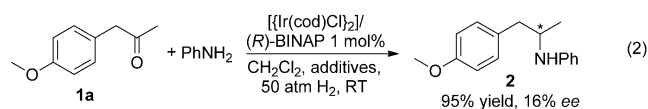


Figure 1. Chiral β -aryamine pharmaceuticals.

phetamine and lisdexamfetamine for ADHD,^[2] (*R,R*)-formoterol for asthma and COPD,^[3] (*R*)-tamsulosin for BPH,^[4] and ritonavir and darunavir for HIV.^[5,6] Among those various methods to synthesize chiral amines, catalytic asymmetric imine reductions^[7] and reductive aminations of carbonyl



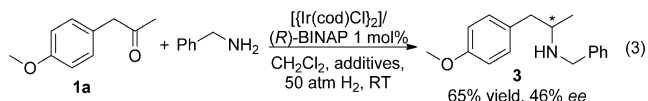
sieves, TFA = trifluoroacetic acid]. The monodentate phosphoramidite chiral ligand **L6** (see Figure 2) along with an iridium precursor demonstrated excellent reactivity (TONs up to 20 000) and enantioselectivity (up to 99% *ee*). In our initial studies, the commonly used ketone coupling partners aniline^[8] and benzylamine^[11,13] were probed for the reductive amination of 1-(4-methoxyphenyl)-propan-2-one (**1a**). Molecular sieves (M.S.; 4 Å), tetraisopropoxytitanium [Ti(OiPr)₄], and trifluoroacetic acid (TFA) were introduced as additives based on our previous studies.^[12a,f] Aniline led to a good yield but poor enantioselectivity [Eq. (2); BINAP = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl, cod = 1,5-cyclooctadiene], and benzylamine furnished 65% yield and a moderate *ee* value [Eq. (3)]. As benzyl is a universal



[*] H. Huang, X. Liu, Prof. Dr. L. Zhou, Prof. Dr. M. Chang
Department of Chemistry and Chemical Engineering
Northwest A&F University
22 Xinong Road, Yangling, Shaanxi 712100 (PR China)
E-mail: zhoulechem@nwsuaf.edu.cn
mxchang@nwsuaf.edu.cn

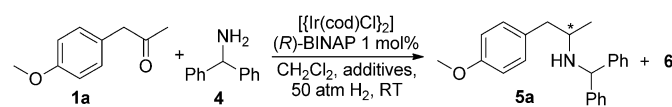
Prof. Dr. X. Zhang
Department of Chemistry and Chemical Biology
Rutgers, The State University of New Jersey
Piscataway, NJ 08854 (USA)

Supporting information for this article can be found under:
<http://dx.doi.org/10.1002/anie.201601025>.



protecting group of amines,^[14] we decided to continue with benzylamine and envisioned a less-electron-rich, but bulkier amine would be of service to both reactivity and enantioselectivity. So we explored diphenylmethylamine (**4**) as the ketone coupling partner. To our great delight, it provided much better result (Table 1, entry 1). The two phenyl rings in **4** greatly limit the inhibitory effect on the catalyst and exert positive influence during the enantioinducing process as compared to that of the single phenyl ring of benzylamine.

Table 1: Studies on additives.^[a]



Entry	Additives ^[b]	1 a/5 a/6 ^[c]	ee [%] ^[c]
1	M.S., Ti(OiPr) ₄ , TFA	2:98:0	62
2	–	12:0:88	–
3	M.S.	31:36:33	57
4	Ti(OiPr) ₄	29:0:71	–
5	TFA	19:27:54	61
6	M.S., Ti(OiPr) ₄	10:5:85	–
7	M.S., TFA	16:36:48	59
8	Ti(OiPr) ₄ , TFA	9:43:48	61
9	M.S., Ti(OiPr) ₄ , HOAc	9:46:45	53

[a] Reaction conditions: [Ir]/(R)-BINAP/1 a/4 = 1:1:100:110, **1 a** 0.2 mmol, 50 atm of H₂, 13 h. [b] Amounts used: M.S. (0.1 grams); TFA (30 mol %); Ti(OiPr)₄ (30 mol %); HOAc (30 mol %). [c] Ratios and enantiomeric excesses were determined by chiral-phase HPLC. cod = 1,5-cyclooctadiene, RT = room temperature, TFA = CF₃COOH.

As for the additive effects (Table 1), the desired product was not formed in the absence of additives (entry 2). With the addition of only either molecular sieves, TFA, or Ti(OiPr)₄, a large portion of ketone remained along with the formation of the by-product **6** (entries 3–5), which decomposed on the column during purification. The combination of Ti(OiPr)₄ and TFA enhanced the product yield to 43 %. TFA is crucial to this reaction. It greatly improved the enantioselectivity as well as the reactivity (entry 1 versus 6). By replacing TFA with acetic acid, the reaction afforded less than 50 % of the desired product.

Next, a few other commercially available chiral ligands (Figure 2) were screened (Table 2, entries 1–5). Even though the BINOL-based MonoPhos **L5a** did not provide an outstanding result, given the ease of its preparation and vast applications in asymmetric hydrogenation,^[15] we synthesized a series of this type of ligand (Figure 2; **L5b–g** and **L6**) and tested them in our reaction (Table 2, entries 6–10). **L5b** afforded much better enantioselectivity than MonoPhos. Encouragingly **L5f** further improved the enantiomeric purity to 89 %, so we focused on the 3,5-dimethylpiperidine motif and prepared **L6** by partially hydrogenating the

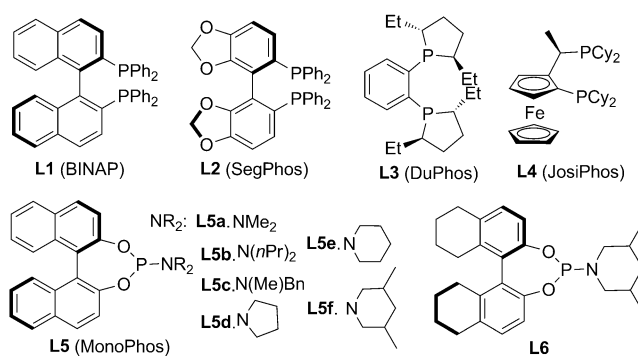
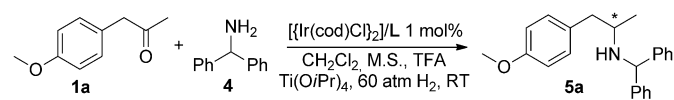


Figure 2. Structures of chiral ligands.

Table 2: Studies on chiral ligands.^[a]

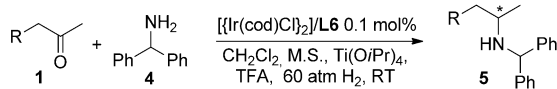


Entry	Ligand	Yield [%] ^[b]	ee [%] ^[c]
1	L1	99	62
2	L2	98	70
3	L3	98	3
4	L4	83	43
5	L5a	98	51
6	L5b	90	82
7	L5c	24	69
8	L5d	97	59
9	L5e	98	86
10	L5f	98	89
11	L6	98	98
12 ^[d]	L6	98	98
13 ^[e]	L6	97	98
14 ^[f]	L6	90	98

[a] Reaction conditions: [Ir]/L/1 a/4 = 1:1:100:110, **1 a** (0.2 mmol), 60 atm of H₂, 13 h, M.S. (0.1 grams), TFA (30 mol %), Ti(OiPr)₄ (30 mol %). [b] Yields were calculated from the ¹H NMR spectra. [c] Enantiomeric excesses were determined by chiral-phase HPLC. [d] Catalyst loading was 0.1 mol %. [e] Catalyst loading was 0.01 mol %; TFA was 1 equiv. [f] Catalyst loading was 0.005 mol %; H₂ was 80 atm; TFA was 1 equiv.

binaphthalene of BINOL. **L6** exhibited the best performance, thus rendering 98 % ee (entry 11). When the Ir/**L6** complex loading was reduced to 0.1 mol % or even to 0.01 mol %, the reaction still ran smoothly without compromising enantioselectivity (entries 12 and 13). The catalyst loading was further decreased to 0.005 mol %, and a slightly lower conversion was obtained (entry 14). To the best of our knowledge, this result represents the highest reactivity (TON) in a direct asymmetric reductive amination using chiral iridium catalysts.^[16]

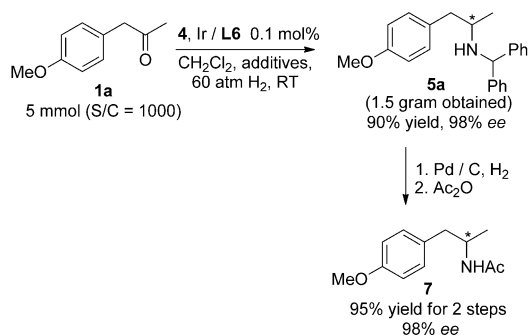
To explore the scope and limitations of this Ir/**L6** catalytic system, a range of aryl/alkyl acetones were studied under the optimized reaction conditions. The results are summarized in Table 3. For all chosen arylacetones, the chiral products **5a–m** were obtained in excellent selectivity (94 % to 99 % ee) and good yields. For *ortho*-substituted arylacetones, the electronic properties of the substituents did not exert any noticeable effect on either the selectivity or reactivity (entries 1 and 3–5).

Table 3: Asymmetric reductive amination of aryl-acetones.^[a]


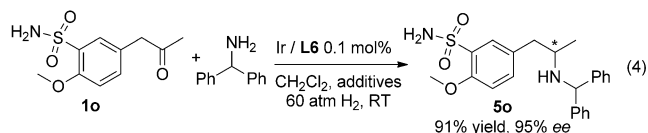
Entry	R	Product	Yield [%] ^[b]	ee [%] ^[c]
1	4-MeOC ₆ H ₄	5a	91	98
2	Ph	5b	92	97
3	4-MeC ₆ H ₄	5c	98	97
4	4-BrC ₆ H ₄	5d	97	94
5	4- <i>t</i> BuC ₆ H ₄	5e	88	97
6	3-MeOC ₆ H ₄	5f	93	98
7	3-MeC ₆ H ₄	5g	90	98
8 ^[d]	3-ClC ₆ H ₄	5h	87	94
9	2-MeOC ₆ H ₄	5i	89	98
10	2-ClC ₆ H ₄	5j	89	99
11	3,5-(MeO) ₂ C ₆ H ₃	5k	92	> 99
12	3,5-F ₂ C ₆ H ₃	5l	84	97
13	2-naphthyl	5m	91	98
14	<i>i</i> Pr	5n	92	86
15 ^[e]	Ph	5b	91	97
16 ^[f]	4-MeOC ₆ H ₄	5a	91	98

[a] Reaction conditions: [Ir]/**L6**/**1a**/**4** = 1:1:1000:1100, **1a** (0.2 mmol), 60 atm of H₂, 13 h, M.S. (0.1 grams), TFA (30 mol%), Ti(OiPr)₄ (30 mol%). [b] Yield of isolated product. [c] Enantiomeric excesses were determined by chiral-phase HPLC. [d] Catalyst loading was 0.1 mol%; TFA was 0.8 equiv. [e] Catalyst loading was 0.1 mol%; **4** was 0.95 equiv; TFA was 1 equiv [f] Reaction operations were conducted open to air; H₂ pressure was 30 atm.

As for the *meta* position, the electron-withdrawing 3-chloro substrate (**1h**) required more acidic conditions to achieve better conversion. The catalytic system worked well for the sterically hindered *ortho*-substituted substrates **1i** and **1j**, and multisubstituted substrates **1k** and **1l** (entries 9–12). The enantioselectivity in these cases were similarly high as those obtained for substrates with aryl groups bearing substituents in either the *meta*- or *para*- positions. This protocol also worked for the alkylacetone **5n** (entry 14). To further examine the reactivity of the catalytic system, 0.005 mol % of Ir/**L6** was used for the reaction of **5b** with **4**, and an excellent result was achieved (entry 15). To take advantage of the bench-stability of the newly developed **L6**, the asymmetric reductive coupling of **1a** and **4** was operated under an air atmosphere and H₂ pressure was decreased to 30 atm, and the same result was obtained (entry 16).

**Scheme 1.** Large-scale reductive amination of **1a** and deprotection of **5a**.

To further demonstrate the practical utility of the newly developed method, the asymmetric reductive amination of **1a** was performed on a 5 mmol scale. The desired product **5a** was obtained in 90 % yield upon isolation in 98 % *ee*. The facile removal of the diphenylmethyl group proceeded with palladium on carbon and H₂. The product was then acylated to give **7** in 95 % yield without any erosion of the enantioselectivity (Scheme 1). We also examined the substrate **1o** and the same result was obtained [Eq. (4)]. The product **5o** could be utilized as the key intermediate for the synthesis of (*R*)-Tamsulosin.^[17]



In summary, we have developed a highly efficient and direct asymmetric reductive amination of arylacetones, catalyzed by an iridium complex, for the preparation of enantiomerically pure β -arylamines. The use of diphenylmethanamine as an amine source reduces the inhibitory effect on the catalyst and assures the stereoselectivity. TFA as an additive significantly improved the reaction rate and enantioselectivity. The iridium-phosphoramidite complex displayed excellent reactivity and stereoselectivity. Together with the ease of removal of the diphenylmethyl group and the bench stability of the catalyst, this protocol is a promising method for the synthesis of related β -arylamine pharmaceuticals. Further applications of these chiral phosphoramidite complexes for the asymmetric reductive amination of other ketones are under investigation within our laboratories, and the results will be reported in due course.

Experimental Section

General procedure for asymmetric reductive amination: In a nitrogen-filled glovebox, [Ir(cod)Cl]₂ (0.1 μ mol) and **L6** (0.2 μ mol) were dissolved in anhydrous CH₂Cl₂ (1.0 mL), stirred for 20 min, and equally divided into 10 vials charged with α -arylacetonones (0.2 mmol) and diphenylmethanamine (0.22 mmol) in anhydrous CH₂Cl₂ solution (1.0 mL). Then 4 Å molecular sieves (0.1 gram), Ti(OiPr)₄ (0.3 equiv), and trifluoroacetic acid (0.3 equiv) were added and brought to a total volume of 2.0 mL for each vial. The resulting vials were transferred to an autoclave, which was charged with 60 atm of H₂, and stirred at room temperature for 13 h. The solution was neutralized with aqueous sodium bicarbonate solution. The organic phase was concentrated and passed through a short column of silica gel to remove the metal complex to give the chiral β -arylamine products, which were then analyzed by chiral-phase HPLC to determine the enantiomeric excesses.

Acknowledgements

We thank the National Natural Science Foundation of China (No. 21402155) and Northwest A&F University for financial support. Hongli Zhang is thanked for NMR analysis.

Keywords: asymmetric catalysis · enantioselectivity · iridium · ligand design · reductions

How to cite: *Angew. Chem. Int. Ed.* **2016**, 55, 5309–5312
Angew. Chem. **2016**, 128, 5395–5398

- [1] a) *Chiral Amine Synthesis: Methods, Developments and Applications* (Ed.: T. C. Nugent), Wiley-VCH, Weinheim, **2010**; b) "Stereoselective Formation of Amines": *Topics in Current Chemistry, Vol. 343* (Eds.: W. Li, X. Zhang), Springer, Heidelberg, **2014**.
- [2] D. J. Heal, S. L. Smith, J. Gosden, D. J. Nutt, *J. Psychopharmacol.* **2013**, 27, 479.
- [3] K. Murase, T. Mase, H. Ida, K. Takahashi, M. Murakami, *Chem. Pharm. Bull.* **1978**, 26, 1123.
- [4] P. Abrams, M. Speakman, M. Stott, D. Arkell, R. Pocock, *Br. J. Urol.* **1997**, 80, 587.
- [5] D. J. Kempf, K. C. Marsh, J. F. Denissen, E. McDonald, S. Vasvanonda, C. A. Flentge, B. E. Green, L. Fino, C. H. Park, X. P. Kong, N. E. Wideburg, A. Saldivar, L. Ruitz, W. M. Kati, H. L. Sham, T. Robins, K. D. Stewart, A. Hsu, J. J. Plattner, J. M. Leonard, D. W. Norbeck, *Proc. Natl. Acad. Sci. USA* **1995**, 92, 2484.
- [6] A. K. Ghosh, Z. L. Dawson, H. Mitsuya, *Bioorg. Med. Chem.* **2007**, 15, 7576.
- [7] For reviews on asymmetric reduction of imines, see: a) W. Tang, X. Zhang, *Chem. Rev.* **2003**, 103, 3029; b) *Handbook of Homogeneous Hydrogenation* (Ed.: I. Ojima), Wiley-VCH, Hoboken, **2010**; c) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, 111, 1713; d) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, 112, 2557.
- [8] For reviews on asymmetric reductive amination, see: a) T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, 352, 753; b) C. Wang, J. Xiao, *Top. Curr. Chem.* **2014**, 343, 261.
- [9] Selected examples of biocatalytic asymmetric reductive aminations for the preparation of unfunctionalized chiral β -arylamines: a) D. Koszelewski, I. Lavandera, D. Clay, G. M. Guebitz, D. Rozzell, W. Kroutil, *Angew. Chem. Int. Ed.* **2008**, 47, 9337; *Angew. Chem.* **2008**, 120, 9477; b) A. K. Holzer, K. Hiebler, F. G. Mutti, R. C. Simon, L. Lauterbach, O. Lenz, W. Kroutil, *Org. Lett.* **2015**, 17, 2431; c) L. J. Ye, H. H. Toh, Y. Yang, J. P. Adams, R. Snajdrova, Z. Li, *ACS Catal.* **2015**, 5, 1119.
- [10] Selected examples of organocatalytic asymmetric reductive aminations for the preparation of unfunctionalized chiral β -arylamines: a) D. Enders, J. X. Liebich, G. Raabe, *Chem. Eur. J.* **2010**, 16, 9763; b) K.-H. Kim, C.-Y. Lee, C.-H. Cheon, *J. Org. Chem.* **2015**, 80, 6367.
- [11] O. Bondarev, C. Bruneau, *Tetrahedron: Asymmetry* **2010**, 21, 1350.
- [12] Selected examples of transition-metal-catalyzed asymmetric reductive aminations for the preparation of unfunctionalized chiral α -arylamines: a) Y. Chi, Y.-G. Zhou, X. Zhang, *J. Org. Chem.* **2003**, 68, 4120; b) R. Kadyrov, T. H. Riermeier, *Angew. Chem. Int. Ed.* **2003**, 42, 5472; *Angew. Chem.* **2003**, 115, 5630; c) G. D. Williams, R. A. Pike, C. E. Wade, M. Wills, *Org. Lett.* **2003**, 5, 4227; d) C. Li, B. Villa-Marcos, J. Xiao, *J. Am. Chem. Soc.* **2009**, 131, 6967; e) B. Villa-Marcos, C. Li, K. R. Mulholland, P. J. Hogan, J. Xiao, *Molecules* **2010**, 15, 2453; f) M. Chang, S. Liu, X. Zhang, *Org. Lett.* **2013**, 15, 4354; g) S. Zhou, S. Fleischer, H. Jiao, K. Junge, M. Beller, *Adv. Synth. Catal.* **2014**, 356, 3451; h) Z.-P. Chen, S.-B. Hu, J. Zhou, Y.-G. Zhou, *ACS Catal.* **2015**, 5, 6086.
- [13] Benzylamine as nitrogen source: a) R. Kadyrov, T. H. Riermeier, U. Dingerdissen, V. Tararov, A. Borner, *J. Org. Chem.* **2003**, 68, 4067; b) V. N. Wakchaure, M. Nicoletti, L. Ratjen, B. List, *Synlett* **2010**, 2708.
- [14] T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, **1999**.
- [15] a) C. Claver, E. Fernandez, A. Gillon, K. Heslop, D. J. Hyett, A. Martorell, A. G. Orpen, P. G. Pringle, *Chem. Commun.* **2000**, 961; b) M. van den Berg, A. J. Minnaard, E. P. Schudde, J. V. Esch, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc.* **2000**, 122, 11539; c) L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, *Org. Lett.* **2004**, 6, 1733; d) A. J. Minnaard, B. L. Feringa, L. Lefort, J. G. de Vries, *Acc. Chem. Res.* **2007**, 40, 1267.
- [16] Blaser et al. achieved 10 000 TON, see: H.-U. Blaser, H.-P. Buser, H.-P. Jalett, B. Pugina, F. Spindler, *Synlett* **1999**, 867.
- [17] K. Niigata, T. Fujikura, U.S. Patent 4,731,478, March 15, **1988**.

Received: January 29, 2016

Published online: March 16, 2016