J|A|C|S COMMUNICATIONS

Published on Web 04/29/2009

Metal−Brønsted Acid Cooperative Catalysis for Asymmetric Reductive Amination

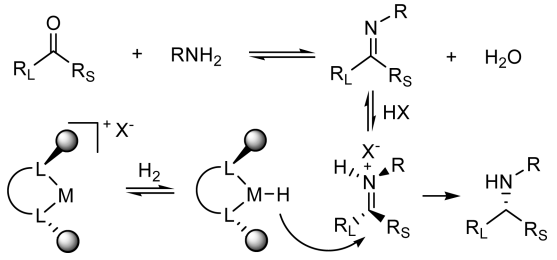
Chaoqun Li, Barbara Villa-Marcos, and Jianliang Xiao*

Liverpool Centre for Materials and Catalysis, Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, U.K.

Received March 19, 2009; E-mail: j.xiao@liv.ac.uk

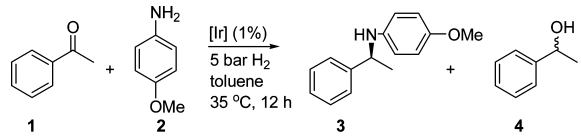
Chiral amines are one of the ubiquitous functional groups in fine chemical, agrochemical, and pharmaceutical products.[1] They can be accessed by asymmetric hydrogenation of imines.[1,2] A shortfall of this powerful method is the need for isolated imines as substrates, which are not always easy to synthesize due to their limited stability. The most convenient, economical, and eco-benign synthetic pathway to chiral amines is direct asymmetric reductive amination (DARA) of prochiral ketones in a one-pot fashion.[1a,3] It is surprising, however, that "few laboratory methods are known for enantioselective reductive amination"[4] and DARA remains a *key green chemistry research area*.[5] Indeed, there are thus far only a few efficient homogeneous metal catalysts reported for DARA, displaying varying enantioselectivities for a limited range of ketones and amines.[6] A major progress has recently been made with organocatalysts by the groups of List, MacMillan, and Antilla, who showed that DARA with Hantzsch esters can be catalyzed by chiral phosphoric acids, which activate the imines via protonation and induce chirality via ion pairing between the resulting phosphate anion and iminium cation.[4,7] Inspired by this and our recent work on imine asymmetric hydrogenation,[8] we envisioned that efficient DARA might be effected by cooperative catalysis of a metal catalyst and a chiral Brønsted acid HX, with the former reducing an in situ generated iminium cation via ionic hydrogenation[9] and the latter aiding enantioselective hydride transfer via ion pairing of its conjugate base X^- with the iminium ion (Scheme 1).[10] Our preliminary results are herein described.

Scheme 1



We recently found that the half-sandwich Cp*M(III)-diamine (M = Rh, Ir) catalysts enables highly enantioselective hydrogenation of both cyclic and acyclic imines.[8,11] In particular, the complex **5b**, which bears a chiral phosphate counteranion derived from the phosphoric acid *R*-**7**,[12] showed superior performance in the hydrogenation of acyclic imines, key intermediates in DARA.[8b] With these results in hand, we set out to examine the feasibility of **5** in DARA of a model ketone **1** with *p*-anisidine **2** in toluene. As can be seen from Table 1, no reduction was observed when using **5a** or its SbF_6^- derivative at 5 bar of H_2 and 35 °C (entries 1 and 2). Switching to the phosphate catalyst **5b**, a 5% conversion of **2** into the chiral amine **3** was observed. However, under the same conditions but with no ketone present, the reduction of ketimines was much faster, affording a 94% conversion and 97% ee when using the ketimine isolated from the condensation of **1** with **2**. Speculating that formation of the ketimine might be rate-limiting in the DARA[13] and a Brønsted acid might assist both this step and the subsequent hydrogenation[9] (Scheme 1), we examined the effect of **7** on the DARA. Delightfully, introduction of increasing quantities of **7** into the reaction indeed afforded a higher conversion and a higher ee (entries 3−7). Thus, when 10% of **7** was added, an 81% conversion and an excellent ee of 97% were recorded (entry 7). Further studies revealed that the DARA went still faster in the presence of 4 Å molecular sieves (entries 8−10), affording a nearly full conversion at a 5% loading of **7** in 15 h (entry 11). The molecular sieves are expected to facilitate the ketimine formation; however, they were less effective when added alone (entry 8). The effect of **7** on both the DARA rate and enantioselectivity is graphically illustrated in Figure 1, demonstrating that the DARA is cocatalyzed by the hydrogen-activating **5b** and the Brønsted acid **7**. Note various amounts of alcohol **4** were also produced and, importantly, its formation can be significantly suppressed by **7** (entries 3 and 4 vs 4−7 and 8−10).

Table 1. Optimization of Conditions for the DARA of **1**[a]



entry	catalyst	additive	conv. (%)[b]	**3**/**4**[c]	ee (%)[d]
1	**5a**	none	NR	−	−
2	**5a**	$AgSbF_6$ (2%)	NR	−	−
3	**5b**	none	5	1/3	−
4	**5b**	**7** (1%)	10	1/2	86
5	**5b**	**7** (3%)	44	3/1	92
6	**5b**	**7** (5%)	62	3/1	97
7	**5b**	**7** (10%)	81	4/1	97
8	**5b**	4 Å Ms	10	1/2	90
9	**5b**	**7** (1%), 4 Å MS	58	3/1	97
10	**5b**	**7** (5%), 4 Å MS	92	10/1	97
11[e]	**5b**	**7** (5%), 4 Å MS	>99	10/1	97

[a] Conditions: 0.6 mmol of **1**, 0.5 mmol of **2**, 1 mol % of **5**, 2 mL of toluene, 5 bar of H_2, 200 mg of molecular sieves (MS) when added, 35 °C, 12 h. [b] Conversion of **2**, determined by ^{1}H NMR analysis of crude product. [c] Molar ratio of **3**/**4**. [d] *S*-**3**, determined by HPLC; configuration assigned by comparison with the literature [see the Supporting Information (SI)]. [e] 15 h.

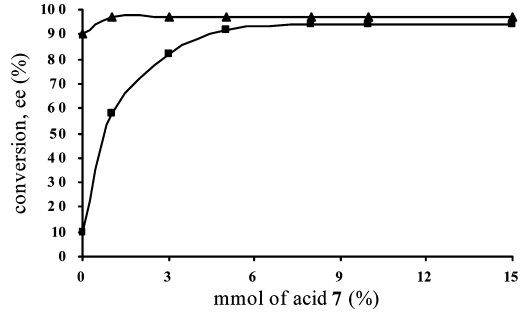
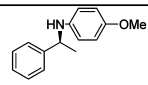
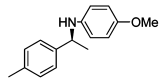
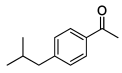
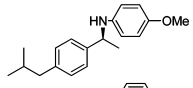
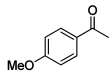
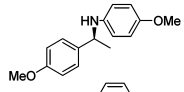
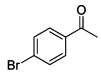
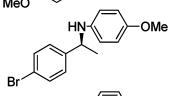
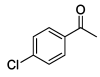
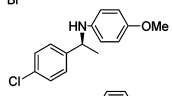
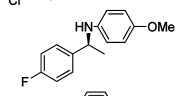
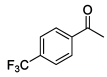
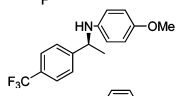
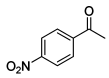
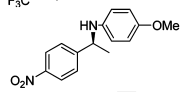
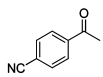
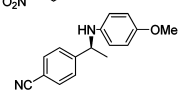
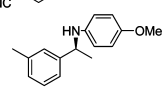
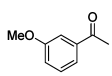
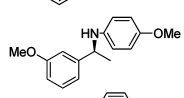
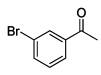
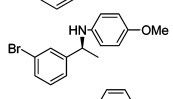
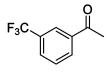
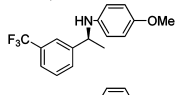
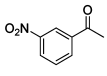
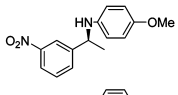
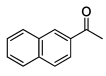
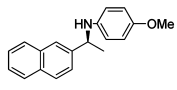
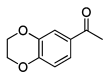
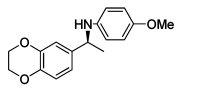
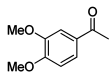
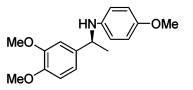


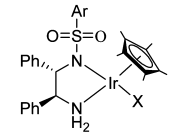
Figure 1. Effect of added **7** (mmol %) on the **5b**-catalyzed conversion (■) of **2** into and the enantioselectivity (▲) of **3** in the DARA of **1** in toluene in the presence of 4 Å MS at 35 °C (1 mol % of **5b**, 200 mg of MS).

Table 2. DARA of Aromatic Ketones with **2**[a]

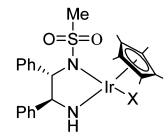
entry	ketone	product	yield (%)[b]	ee (%)[c]
1			94	97
2			93	97
3			93	95
4			93	95
5			94	94
6			94	95
7			93	95
8[d]			91	91
9[d]			92	88
10[d]			92	86
11			93	94
12			93	94
13			93	94
14[d]			94	93
15[d]			88	81
16			91	96
17			92	95
18			90	93

[a] Conditions: 0.6 mmol of ketone, 0.5 mmol of **2**, 1 mol % of **5b**, 5 mmol % of **7**, 2 mL of toluene, 200 mg of 4 Å MS, 5 bar of H_2, 35 °C, 15−24 h. [b] Isolated yields. [c] Determined by HPLC; configuration assigned by comparison with the literature (see the SI). [d] 0.7 mmol of ketone, 8 mmol % of **7**. With 5 mmol % of **7**, the ee was ca. 3% lower.

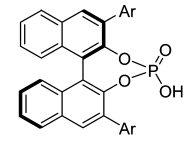
Using the conditions established above, i.e., 1 mol % **5b** in the presence of 5 mol % **7** and molecular sieves, a wide range of *para*- and *meta*-substituted aromatic ketones were readily aminated with **2** under 5 bar of H_2 at 35 °C (Table 2). As can be seen, the amines **3** were obtained with excellent yields and ee's in almost all the cases. Notably, the catalyst tolerates functional groups of diverse electronic properties on the ketones (−OMe, −Br, −Cl, −CN, $-NO_2$, $-CF_3$, −F), but the enantioselectivities suffered with the strongly electron-withdrawing $-NO_2$ and −CN groups ($\sigma_p = 0.78, 0.70$, respectively). In comparison with our recent results on ketimine hydrogenation using **5b** at 20 °C,[8b] the DARA afforded the amines with slightly decreased enantioselectivities, but with the advantage of not isolating problematic imines.



(*S*,*S*)-**5**
Ar = 2,4,6-(2-C_3H_7)$_3C_6H_2$
a: X = Cl; **b**: X = **7**-H
c: Ar = 4-$CH_3C_6H_4$, X = **7**-H
d: Ar = 2,3,4,5,6-$(CH_3)_5C_6$, X = **7**-H



(*S*,*S*)-**6**
X = **7**-H

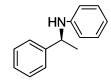


R-**7**
Ar = 2,4,6-(2-C_3H_7)$_3C_6H_2$

We next investigated the DARA of aniline and its electron-deficient analogues. As shown in Table 3, a range of amines **3** were obtained in good yields and decent ee's. Comparing the results in Tables 2 (entry 1) and 3, it is clear that electron deficiency on the anilines reduces both the DARA yield and enantioselectivity. This is reminiscent of the observations above and, to some degree, those in organocatalysis.[4,7a]

We encountered problems when attempting the DARA of sterically more demanding ketones. Thus, using **5b** as above, the reaction of 2′-methylacetophenone with **2** led to only a 49% ee. However, much improved enantioselectivities became accessible when less bulky metal catalysts were selected. Thus, ee's of 69%, 85%, and 91% were observed with the catalysts **5c**, **5d**, and **6**, respectively. Table 4 summarizes the results obtained with a series of ketones. Clearly, by replacing **5b** with

Table 3. DARA with other Aniline Derivatives[a]

product	yield (%)	ee (%)	product	yield (%)	ee (%)
	92	93		92	91
	86	87		92	91
	85	85		75	83

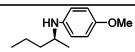
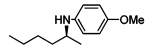
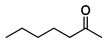
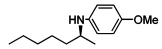
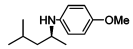
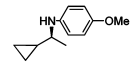
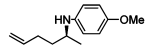
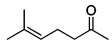
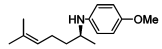
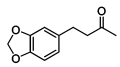
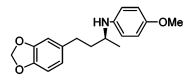
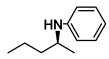
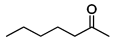
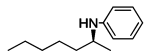
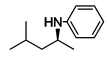
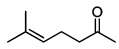
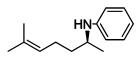
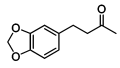
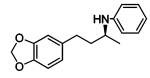
[a] Reaction conditions were the same as those in Table 2 except with 0.7 mmol of ketones and 24 h reaction time.

Table 4. DARA of Bulkier Aromatic Ketones with **2**[a]

catal.	product	yield ee (%)	catal.	product	yield ee (%)
5d		93 92	**6**		92 91 (49)[b]
5d		91 92 93	**6**		93 86 (49)[b]
5d		91 (81)[b]	**5c**		92 96 (85)[b]
6		90 87 (46)[b]	**6**		92 83 (23)[b]

[a] Same conditions as those in Table 2 except for 20−24 h. [b] Ee%, **5b** as catalyst.

Table 5. DARA of Aliphatic Ketones[a]

entry	ketone	product	yield (%)	ee (%)[b]
1			88	90
2			82	93
3			79	91
4			91	87
5			90	93
6			80	92
7			89	95
8			85	93
9			92	94
10			83	92
11			80	88
12			91	92
13			91	91
14			95	91

[a] Conditions: 0.55 mmol of ketone, 0.5 mmol of **2**, 1 mol % of **5d**, 2 mL of toluene, 150 mg of 4 Å MS, 5 bar of H_2, 35 °C, 12−20 h. [b] Determined by HPLC; configuration assigned by comparison with the literature (see the SI).

the analogous **5c**, **5d**, or **6** while keeping **7**, α and *ortho* substituted ketones can be aminated, affording amines in excellent enantioselectivities. We note that few metal catalysts are capable of DARA of these substrates. The results highlight one advantage of the current method; i.e., the metal and Brønsted acid catalysts can be *independently* varied to tackle a particular set of substrates.

With the success in aromatic ketones, we were eager to extend the catalysis into aliphatic ketones, bearing in mind in particular that there appear to be no metal catalysts capable of DARA of both aryl and aliphatic ketones. A quick screening established that **5d** outperformed **5b** in both enantioselectivity and conversion, and in the presence of molecular sieves, the effect of **7** on the DARA was, surprisingly somehow, less significant than in the case of aromatic ketones (see Table S1 in the SI). Unlike aromatic ketones, aliphatic ketones were not reduced under the DARA conditions and so are less likely to compete with DARA. This may have partly contributed to the diminished role of **7**. However, the phosphate counteranion remains *critical*.[14] Aiming to reduce the chiral acid loading, we chose to use **5d** with no extra **7** added. As shown in Table 5, various aliphatic ketones were aminated with **2** and aniline, furnishing good amine yields with enantioselectivities up to 95%. Notably, the catalyst system tolerates other reducible groups in the ketone substrates (entries 5−7, 12, 13). The easy access to these chiral amines via DARA is particularly pleasing, as the corresponding ketimines are prone to decomposition and so are difficult to isolate.

In conclusion, we have developed a new catalytic system for DARA. Hinging on the cooperative catalysis of a hydrogen-activating metal cation and a Brønsted acid, this mild and operationally easy amination has been successfully demonstrated with a wide spectrum of ketones. Remarkable features of the catalytic system include (a) clean, economic H_2 as a reductant; (b) a wide substrate scope with high yield and enantioselectivity; and (c) independent tunability of catalyst components to meet substrates of diverse properties. Further mechanistic studies and extension into other carbonyl compounds are underway.

Acknowledgment. We gratefully acknowledge the Research Councils UK for a Dorothy Hodgkin Postgraduate Award (C.L.) and AstraZeneca for a studentship (B.V.-M.). We also thank EPSRC and Pfizer for financial support.

Supporting Information Available: Experimental details and spectroscopy data (^{1}H and ^{13}C NMR, MS, HPLC). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Blaser, H.-U.; Spinder, F. In *Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.: Wiley-VCH, Weinheim, 2007; p 1193. (b) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keβeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788.
(2) Recent examples of asymmetric ketimine hydrogenation: (a) Nolin, K. A.; Ahn, R. W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 12462. (b) Moessner, C.; Bolm, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 7564. (c) Yang, Q.; Shang, G.; Gao, W.; Deng, J.; Zhang, X. *Angew. Chem., Int. Ed.* **2006**, *45*, 3832. (d) Zhu, S.; Xie, J.; Zhang, Y.; Li, S.; Zhou, Q. *J. Am. Chem. Soc.* **2006**, *128*, 12886. (e) Reetz, M. T.; Bondarev, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 4523.
(3) (a) Tararov, V. I.; Börner, A. *Synlett* **2005**, 203. (b) Tripathi, R. P.; Verma, S. S.; Pandey, J.; Tiwari, V. K. *Curr. Org. Chem.* **2008**, *12*, 1093.
(4) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84.
(5) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L., Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.
(6) DARA of aliphatic ketones: (a) Blaser, H.-U.; Buser, H.-P.; Jalett, H.-P.; Pugin, B.; Spindler, F. *Synlett* **1999**, 867. (b) Rubio-Pérez, L.; Pérez-Flores, F. J.; Sharma, P.; Velasco, L.; Cabrera, A. *Org. Lett.* **2009**, *11*, 265. DARA of aromatic ketones: (c) Kadyrov, R.; Riermeier, T. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5472. (d) Chi, Y.; Zhou, Y.; Zhang, X. *J. Org. Chem.* **2003**, *68*, 4120. DARA of ketone acids: (e) Kadyrov, R.; Riermeier, T. H.; Dingerdissen, U.; Tararov, V.; Börner, A. *J. Org. Chem.* **2003**, *68*, 4067. Intramolecular DARA: (f) Williams, G. D.; Pike, R. A.; Wade, C. E.; Wills, M. *Org. Lett.* **2003**, *5*, 4227.
(7) (a) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424. (b) Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074. (c) Li, G.; Liang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 5830. Organocatalytic reductive amination via hydrosilylation: (d) Malkov, A. V.; Stončius, S.; Kočovský, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 3722.
(8) (a) Li, C.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 13208. (b) Li, C.; Wang, C.; Villa-Marcos, B.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 14450.
(9) Guan, H.; Iimura, M.; Magee, M. P.; Norton, J. R.; Zhu, G. *J. Am. Chem. Soc.* **2005**, *127*, 7805.
(10) Anion effects in catalysis: (a) Macchioni, A. *Chem. Rev.* **2005**, *105*, 2039. (b) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336. (c) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496.
(11) For a pioneering contribution, see: (a) Ohkuma, T.; Utsumi, N.; Tsutsumi, K.; Murata, K.; Sandoval, C.; Noyori, R. *J. Am. Chem. Soc.* **2006**, *128*, 8724. More recent work: (b) Zhou, H.; Li, Z.; Wang, Z.; Wang, T.; Xu, L.; He, Y.; Fan, Q.; Pan, J.; Gu, L.; Chan, A. S. C. *Angew. Chem., Int. Ed* **2008**, *47*, 8464. (c) Shirai, S.; Nara, H.; Kayaki, Y.; Ikariya, T. *Organometallics* **2009**, *28*, 802.
(12) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.
(13) Menche, D.; Hassfeld, J.; Li, J.; Menche, G.; Ritter, A.; Rudolph, S. *Org. Lett.* **2006**, *8*, 741.
(14) Replacing **7**-H with SbF_6 in **5d** led to a 42% conversion and 15% ee in the DARA shown in entry 4, Table 5, in 17 h.

JA9021683