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Cooperative Catalysis: Combining an Achiral Metal Catalyst with a Chiral Brønsted Acid Enables Highly Enantioselective Hydrogenation of Imines

Weijun Tang, Steven Johnston, Chaoqun Li, Jonathan A. Iggo, John Bacsa, and Jianliang Xiao*[a]

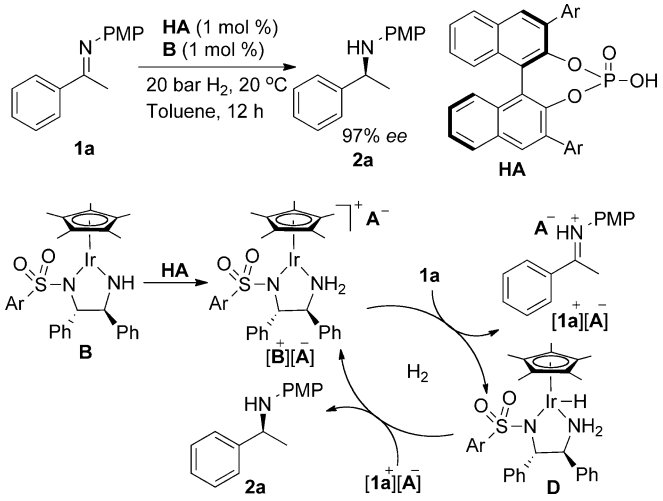
Abstract: Asymmetric hydrogenation of imines leads directly to chiral amines, one of the most important structural units in chemical products, from pharmaceuticals to materials. However, highly effective catalysts are rare. This article reveals that combining an achiral pentamethylcyclopentadienyl (Cp*)–iridium complex with a chiral phosphoric acid affords a catalyst that allows for highly enantioselective hydrogenation of imines derived from aryl ketones, as well as those derived from aliphatic ones, with *ee* values varying from 81 to 98%. A range of achiral iridium complexes containing diamine ligands were examined, for which the ligands were shown to have a profound effect on the reaction rate, enantioselectivity and catalyst deactivation. The chiral phosphoric acid is no less important, inducing enantioselection in the hydrogenation. The induction occurs, however, at the expense of the reaction rate.

Keywords: asymmetric hydrogenation · Brønsted acid · cooperative catalysis · imines · iridium

Introduction

Over the past few decades, a great deal of effort has been focussed on the asymmetric reduction of imines to access optically active amines,[1–5] ubiquitous functionalities in fine chemical, agrochemical and pharmaceutical products.[6] Among the approaches reported so far, asymmetric hydrogenation with cheap, clean hydrogen gas offers a totally atom-economical and very convenient route. However, in contrast to the great success in asymmetric hydrogenation of prochiral olefins and ketones,[7] the highly enantioselective hydrogenation of imines is still challenging. In particular, apart from isolated examples,[8,9] few catalysts are known that can deliver enantioselectivity higher than 80% *ee* in the hydrogenation of imines derived from aliphatic ketones.[2a,c,f,g,k] Herein, we report that by exploiting achiral–chiral metal–organo cooperative catalysis, acyclic imines, including aliphatic ones, can be readily hydrogenated with enantioselectivities of up to 98% *ee*.

The combination of metal catalysts with organocatalysts has recently become one of the most active and exciting topics in catalysis, allowing reactivity and selectivity patterns that are inaccessible within the fields of either homogeneous or organo-catalysis alone.[10] We reported in 2008 that the chiral [Cp*Ir(diamine)] (Cp* = pentamethylcyclopentadienyl) complex [$\mathbf{B}^+$][$\mathbf{A}^-$], generated from the protonation of the chiral complex **B** with the chiral phosphoric acid **HA**, activates H_2 and catalyses the asymmetric hydrogenation of acyclic imines[9a] and the reductive amination of ketones[9b–c] with excellent enantioselectivities (Scheme 1). The reduction was thought to proceed through an ionic pathway involving metal–organo cooperative catalysis,[11] in which the phosphate anion pairs with the iminium cation,[12] thereby influencing the face-selective addition of hydride **D** to the imino C=N bond and thus influencing the enantioselectivity. In line with this hypothesis, dramatic changes in enantioselectivity and reversal of amine configuration were observed on altering the steric bulk of (*R*)-**HA**, or on replacing the (*S*,*S*)-diamine with an (*R*,*R*)-diamine ligand in **B**.[9a] These results



Scheme 1. Hydrogenation of imines with a cooperative catalytic system resulting from **B** and **HA** (Ar = 2,4,6-triisopropylphenyl; PMP = *para*-methoxyphenyl).

[a] Dr. W. Tang, S. Johnston, Dr. C. Li, Dr. J. A. Iggo, Dr. J. Bacsa, Prof. J. Xiao
Liverpool Centre for Materials & Catalysis
Department of Chemistry, University of Liverpool
Liverpool, L69 7ZD (UK)
E-mail: jxiao@liv.ac.uk

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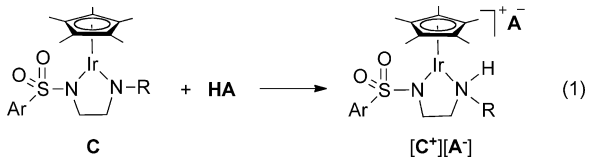
suggested to us that it might be possible to combine a chiral **HA** with an achiral analogue of **B** to effect the same asymmetric hydrogenation, with the former inducing chirality at the latter.[13–15] This was not very far-fetched, since chiral phosphoric acids had been demonstrated to be able to direct highly enantioselective hydride transfer from achiral organo-hydride donors to imines.[4,16] In fact, while our search for the optimal chiral–achiral "couple" was in progress,[14] Rueping and co-workers reported, in 2011, that chiral *N*-trifylphosphoramide can induce chirality at an achiral analogue of **B**, although the enantioselectivity was low (32% *ee*) in the hydrogenation of quinoline.[17] More recently, Beller and co-workers developed a highly effective catalytic system that combines an achiral iron complex with a chiral phosphoric acid,[2c] affording excellent *ee* values (up to 97%) for aryl ketone-derived imines, but lower values (up to 83%) for the analogous aliphatic imines.

Described below are our results on the asymmetric hydrogenation of acyclic imines obtained by using an easily accessible achiral [Cp*Ir(diamine)] catalyst coupled with a chiral phosphoric acid. The use of a chiral organocatalyst to induce chirality at an achiral metal complex, or vice versa, is interesting, not only because of "economy" in chirality but also because it gives an increased number of potential catalysts. In a very recent communication built on the study of a model hydrogenation, we provided detailed mechanistic insight into how the chiral acid and achiral metal catalyst act cooperatively to effect the highly enantioselective hydrogenation.[13]

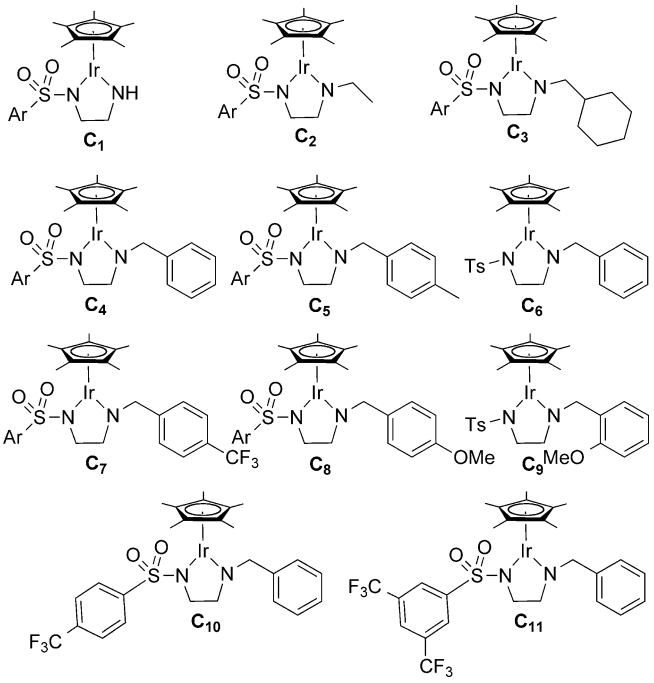
Results and Discussion

Identification of catalysts: Following on from our initial search for a viable chiral–achiral combination catalyst,[14] we synthesised a series of neutral 16e$^-$ complexes, exemplified by $\mathbf{C_1}$–$\mathbf{C_{11}}$, from cheaply available ethylene diamine and its derivatives (Scheme 2).[18] Mixing the phosphoric acid **HA** with **C** leads to its protonation at the amido nitrogen atom, forming an analogue of $\mathbf{B^+}$, that is, the active catalyst $[\mathbf{C^+}][\mathbf{A^-}]$ [Eq. (1)].[9,13,19]



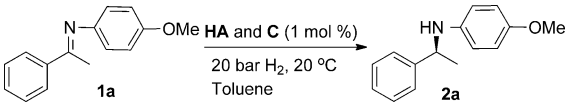
(1)

With these complexes in hand, the asymmetric hydrogenation of a model imine, **1a**, was examined under the same conditions as reported previously, that is, 20 bar of H_2 in a non-polar solvent, toluene, at room temperature, with the catalyst $[\mathbf{C^+}][\mathbf{A^-}]$ formed in situ by combining **C** with **HA**.[9a] The results are shown in Table 1. Compared with those obtained with the chiral combination $[\mathbf{B^+}][\mathbf{A^-}]$ (Scheme 1), the conversion and enantioselectivity were both decreased considerably when using the achiral complex $\mathbf{C_1}$ in the presence of **HA** (Table 1, entry 1). Replacing the hydrogen atom with an ethyl group on the nitrogen atom in $\mathbf{C_1}$ did not lead to a better catalyst ($\mathbf{C_2}$; Table 1, entry 2). Some-



Scheme 2. Achiral metal catalysts synthesised and studied for cooperative hydrogenation (Ar = 2,4,6-triisopropylphenyl; Ts = *para*-toluenesulfonyl).

Table 1. Screening of achiral metal catalysts for the asymmetric hydrogenation of imine **1a**.[a]



Entry	C	HA [%]	*t* [h]	Conv. [%][b]	*ee* [%][c]
1	$\mathbf{C_1}$	2	5	10	50
2	$\mathbf{C_2}$	2	5	15	48
3	$\mathbf{C_3}$	2	5	2	–
4	$\mathbf{C_4}$	2	5	100	97
5	$\mathbf{C_5}$	2	5	100	94
6	$\mathbf{C_6}$	2	5	100	95
7	$\mathbf{C_7}$	2	5	100	83
8	$\mathbf{C_8}$	2	5	100	97
9	$\mathbf{C_9}$	2	5	90	94
10	$\mathbf{C_{10}}$	2	5	50	93
11	$\mathbf{C_{11}}$	2	5	11	–
12	$\mathbf{C_4}$	1	5	82	97
13	$\mathbf{C_4}$	1	12	100	97
14[d]	$\mathbf{C_4}$	1	12	87	98
15[e]	$\mathbf{C_4}$	1	12	43	97

[a] The reaction was carried out with **1a** (0.15 mmol) in toluene (0.7 mL). [b] The conversion was determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis; configuration was assigned by comparison with the literature (see the Supporting Information). [d] The temperature was 10 °C. [e] 5 bar of H_2 was used.

what surprisingly, when a cyclohexylmethyl group was installed ($\mathbf{C_3}$), little hydrogenation was observed (Table 1, entry 3), highlighting the critical effect of the diamine structure on the catalysis.[20] A further search led to the discovery of $\mathbf{C_4}$, in which the NH hydrogen is replaced with a benzyl group, and when $\mathbf{C_4}$ was combined with **HA**, an excellent enantioselectivity of 97% *ee* was observed along with complete conversion of **1a** (Table 1, entry 4).

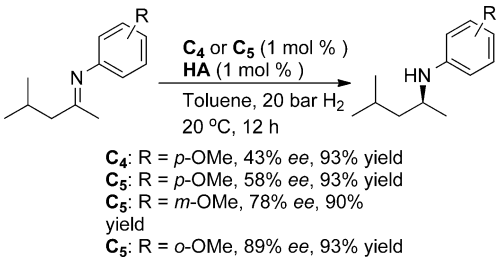
Aiming to further improve the enantioselectivity, $\mathbf{C_4}$ was altered and the resulting complexes were tested. Although none of the complexes ($\mathbf{C_5}$–$\mathbf{C_{11}}$) gave better results when combined with **HA**, we made some interesting observations. Introducing an electron-withdrawing group on either the benzyl or sulfonyl unit resulted in a lower *ee* (Table 1, compare entries 4, 5 and 8 with 7 and 10), and in the case of the latter, the reaction was significantly slower (Table 1, compare entry 6 with 10 and 11). The bulky Ar group in $\mathbf{C_4}$ is beneficial; replacing it with *para*-tolyl ($\mathbf{C_6}$) led to a slight decrease in the *ee* (Table 1, entry 4 vs. 6), but increasing the bulk of the benzyl unit has an adverse effect on both the *ee* and reaction rate (Table 1, entry 6 vs. 9). The effect of these substituents on the hydrogenation may originate from their effect on the ternary transition state in the hydride-transfer step.[13]

With $\mathbf{C_4}$, the loading of the phosphoric acid **HA** can be reduced without compromising the *ee* value but the hydrogenation became slower (Table 1, entry 12). Full conversion was, however, reached after a longer reaction time (12 h; Table 1, entry 13). As may be expected, a lower temperature improved the enantioselectivity slightly but reduced the reaction rate (Table 1, entry 14). Additionally, the pressure of hydrogen impacts the hydrogenation rate, with lower pressures leading to lower conversion (Table 1, entry 15).

Asymmetric hydrogenation of acyclic aromatic imines: Having established a highly enantioselective achiral–chiral combination of catalysts for the hydrogenation of imine **1a**, we turned our attention to examining the scope of the $\mathbf{C_4}$–**HA**-couple-catalysed asymmetric hydrogenation of substituted acyclic aromatic imines **1b**–**p**. The results are shown in Table 2. In general, all substrates examined were reduced smoothly in excellent enantioselectivities and yields, with *ee* values ranging from 92 to 98%. Notably, this catalytic system tolerates not only functional groups with diverse electronic properties, for example, -MeO, -CN, -Br and -NO_2, but also substituents at different positions (Table 2, entries 2–4). Imine substrates bearing *ortho*-substituents on the phenyl ring necessitated harsher conditions for the reaction to proceed with a reasonable rate; however, the enantioselectivity remained high (Table 2, entries 2, 4 and 11). The low reactivity of these imines likely stems from the *ortho*-substitution, which increases the steric bulk of the imine, impeding its approach to the Ir–H hydride.[13] Replacing the anisidine in **1** with other aryl groups, such as aniline or *para*-bromoaniline, does not appear to impact the hydrogenation, with excellent enantioselectivities and high yields again observed (Table 2, entries 14–15). Finally, α-substituted *N*-aryl ketimine could be reduced with high enantioselectivity (Table 2, entry 16).

For most of the reactions in Table 2, the enantioselectivities obtained with the achiral–chiral couple $\mathbf{C_4}$–**HA** are comparable to those from the reaction in the presence of the chiral–chiral **B**–**HA** catalyst.[9a] However, $\mathbf{C_4}$–**HA** led to significantly higher *ee* values in the case of the -CN- and -NO_2-substituted imines **1h**, **1i** and **1l**. For example, for **1l**, 92% *ee* was observed with $\mathbf{C_4}$–**HA** (Table 2, entry 12) in comparison with 84% *ee* with **B**–**HA**.[9a] Why this is the case is not immediately clear to us.

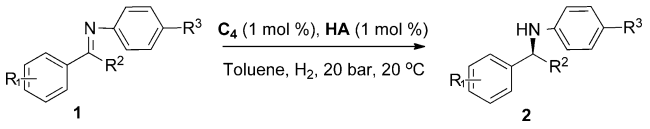
Asymmetric hydrogenation of aliphatic ketone-derived imines: In contrast to aromatic imines, successful examples of asymmetric hydrogenation of imines derived from aliphatic ketones are rare.[2a,c,f,g] Subsequent to the study above, we explored the use of the same catalytic system for asymmetric hydrogenation of the more challenging aliphatic *N*-aryl imines. We started our investigation by using 4-methoxy-*N*-(4-methylpentan-2-ylidene)aniline as a model substrate (Scheme 3, R = *p*-OMe), which afforded a high enantioselectivity of 92% *ee* under the catalysis by a chiral–chiral couple analogous to **B**–**HA**.[9a] However, combining the achiral catalyst $\mathbf{C_4}$ with **HA** resulted in a much lower enantioselectivity of 43% *ee*. A moderate increase in *ee* was observed when $\mathbf{C_4}$ was replaced with $\mathbf{C_5}$. Since increasing the steric bulk of imines may render their C=N faces easier to discriminate,[2a,g] we went on to study the hydrogenation of imines with different substitution patterns. As can be seen from Scheme 3, the enantioselectivity increased progressively as the imine became sterically more demanding, that is, as the substitution position at the *N*-aryl ring changed from *para* to *meta* to *ortho*, reaching a remarkable value of 89% *ee*. This observation may not be surprising, considering that the interaction between the phosphate $\mathbf{A^-}$ and the iminium cation is non-covalent and weak; therefore, the enantioselectivity is expected to be sensitive to the steric bulk of the imine.[12,13]

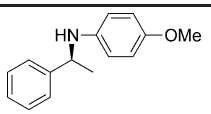
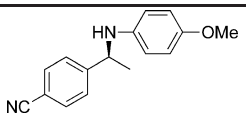
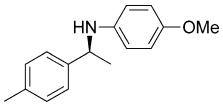
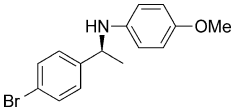
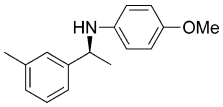
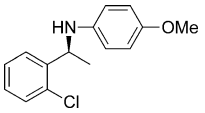
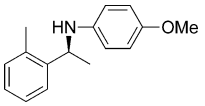
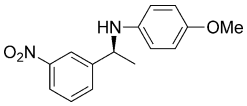
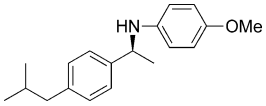
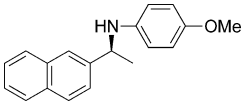
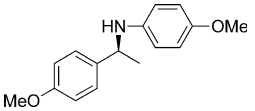
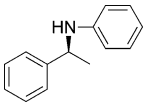
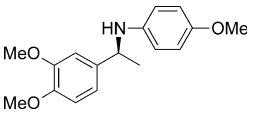
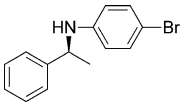
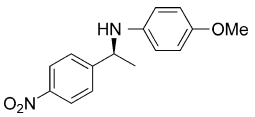
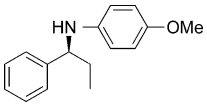


Scheme 3. Effect of substrate size on enantioselectivity.

To probe the generality of the $\mathbf{C_5}$–**HA** combination for aliphatic ketone-derived imines, a series of *ortho*-substituted *N*-aryl aliphatic imines were subjected to the hydrogenation. As can be seen from Table 3, all of the substrates examined were hydrogenated in high yields and enantioselectivities. In general, higher enantioselectivities were observed for imines with bulkier *ortho*-substituents on the phenyl ring. For in-

Table 2. Asymmetric hydrogenation of acyclic aromatic imines.[a]



Entry	Sub.	Product	Yield [%][b]	*ee* [%][c]	Entry	Sub.	Product	Yield [%][b]	*ee* [%][c]
1	**1a**		95	97	9	**1i**		93	96
2	**1b**		94	97	10	**1j**		92	98
3	**1c**		95	98	11[d,e]	**1k**		93	94
4[d,e]	**1d**		93	97	12	**1l**		93	92
5	**1e**		93	98	13	**1m**		95	98
6	**1f**		97	97	14	**1n**		96	98
7	**1g**		92	98	15	**1o**		95	97
8	**1h**		95	96	16[d]	**1p**		93	92

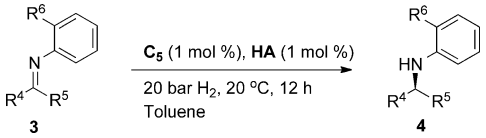
[a] All reactions were carried out with the substrate (0.15 mmol), toluene (0.7 mL), and H_2 (20 bar), at 20 °C for 12 h. [b] Yields of the isolated product. [c] The enantioselectivities were determined by HPLC; *S* configuration, assigned by comparison with the literature (see the Supporting Information). [d] The reactions were carried out in 20 h with 2% of the phosphoric acid **HA**. [e] The pressure was 30 bar.

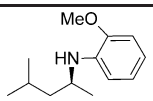
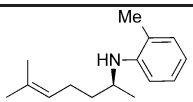
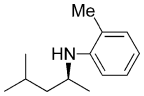
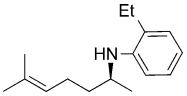
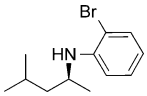
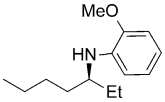
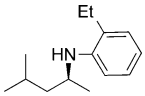
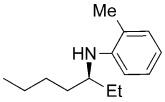
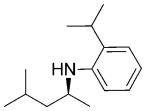
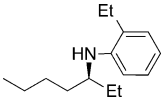
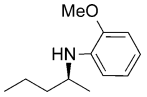
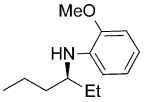
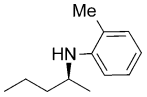
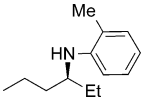
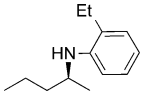
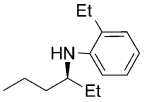
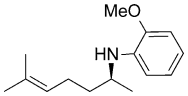
stance, the ethyl-substituted imines always afford higher *ee* values than their methyl analogues (Table 3, entries 4, 8, 11, 14 and 17 vs. 2, 7, 10, 13 and 16.).

It is worth noting that the catalytic system tolerates the presence of reducible C=C double bonds, affording excellent enantioselectivities for imines **3i–k**. More remarkably, this **C_5–HA** catalyst is capable of discriminating, highly effectively, an ethyl group from a butyl group (Table 3, entries 12–14) or from a propyl (Table 3, entries 15–17) group, giving *ee* values of up to 94%. To the best of our knowledge, these *ee* values represent some of the highest enantioselectivities ever reported for aliphatic *N*-aryl imines. Only a few scattered examples are known for which higher *ee* values have been observed.[2g,8]

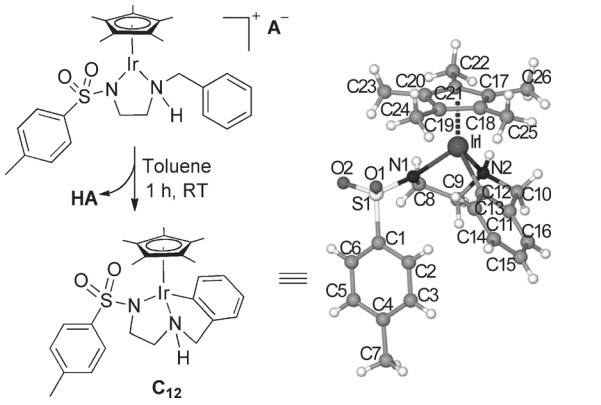
Catalyst deactivation: Although the catalysts **C_4–HA** and **C_5–HA** are highly effective for the reaction in question, their preparation or method of use can impact the catalytic activity. We noted that when **C_4** or **C_5** was mixed with **HA** in the absence of **1a** or was not used immediately upon mixing, the resulting species $[\mathbf{C}^+][\mathbf{A}^-]$ was much less effective in catalysing the hydrogenation. Further study showed that under such conditions, the benzyl group in the cation undergoes cyclometallation with the iridium atom, forming a catalytically inactive complex. This was verified by X-ray diffraction analysis in the case of **C_6**, which formed a yellow precipitate when protonated with **HA** in toluene at ambient temperature (Scheme 4). The X-ray analysis revealed the formation of a stable cyclometallated complex **C_{12}**. This complex does not catalyse the hydrogenation of **1a**. However, its formation is suppressed in the presence of an imine, presumably due to coordination of the imine to the cationic $16e^-$ iridium centre. Thus, in the absence of a coordinating substrate, $[\mathbf{C}^+][\mathbf{A}^-]$ deactivates through cyclometallation.

Table 3. Asymmetric hydrogenation of aliphatic ketone derived imines with $\mathbf{C_5}$–**HA**.[a]



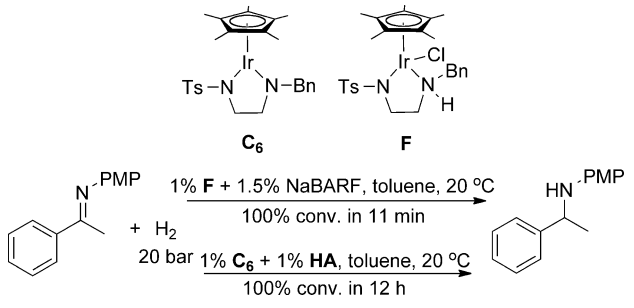
Entry	Sub.	Product	Yield [%][b]	*ee* [%][c]	Entry	Sub.	Product	Yield [%][b]	*ee* [%][c]
1	**3a**		93	89	10	**3j**		95	89
2	**3b**		91	94	11	**3k**		95	92
3	**3c**		93	94	12	**3l**		94	85
4	**3d**		95	97	13	**3m**		95	94
5	**3e**		96	94	14	**3n**		95	94
6	**3f**		94	84	15	**3o**		93	81
7	**3g**		93	85	16	**3p**		94	89
8	**3h**		95	91	17	**3q**		90	91
9	**3i**		96	92					

[a] All reactions were carried out with the substrate (0.15 mmol), toluene (0.7 mL), and H_2 (20 bar), at 20 °C for 12 h. [b] Yields of the isolated product. [c] Enantioselectivities determined by HPLC, with configuration assigned by analogy with the literature (see the Supporting Information).



Scheme 4. Formation of a catalytically inactive cyclometallated complex from protonated $\mathbf{C_6}$. For the structural details of $\mathbf{C_{12}}$, see the Supporting Information.

The pros and cons of the chiral acid: The cooperative asymmetric hydrogenation by **C**–**HA** proceeds via a ternary complex comprised of an iridium hydride, an iminium ion and [$\mathbf{A}^-$], mainly bound together through hydrogen bonding.[13] Although the phosphate is highly effective in chirality relay, its bulk retards the hydride transfer and hence reduces the reaction rate. This can be clearly seen in the comparison shown in Scheme 5, in which the hydrogenation was complete in 12 h with the catalyst generated from $\mathbf{C_6}$ and **HA** but a mere 11 min was required with the catalyst derived from the complex **F** and NaBARF (BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate). The non-hydrogen-bonding BARF anion means that the hydride transfer from the iridium to the "naked" iminium ion (Scheme 1) is much faster, but proceeds with no enantioselectivity.



Scheme 5. Comparison of the hydrogenation of **1a** with a catalyst derived from **F** and NaBARF and one derived from $\mathbf{C_6}$ and **HA**.

We have followed these reactions by use of in situ ^{1}H high-pressure (HP) NMR spectroscopy at a constant H_2 pressure of 20 bar at 25 °C. Figure 1 gives the conversion–time profiles obtained for these reactions. Examination of the profiles reveals that the initial rate of the hydrogenation with **F**–NaBARF is 22 times faster than that with $\mathbf{C_6}$–**HA**. More interestingly, the former proceeds at an approximately constant rate whereas the latter becomes much slower after the first few hours (see the Supporting Information for more details), suggesting that the counteranion alters the reaction mechanism. The linear dependence of the conversion on time in the case of **F**–NaBARF is consistent with fast, non-turnover-limiting hydride transfer to the iminium ion over the entire course of the reaction (Scheme 1), whereas with $\mathbf{C_6}$–**HA** the catalytic turnover is likely to be controlled by the hydride transfer to the iminium ion. The rate of the former is most likely limited by the hydride-formation step. These observations, together with those mentioned previously,[13] support the view that the increased bulk of the chiral acid inhibits the reduction of the imine and yet, paradoxically, the reduction occurs enantioselectively only as a result of the phosphate intervention by hydrogen bonding with both the metal catalyst and the substrate.

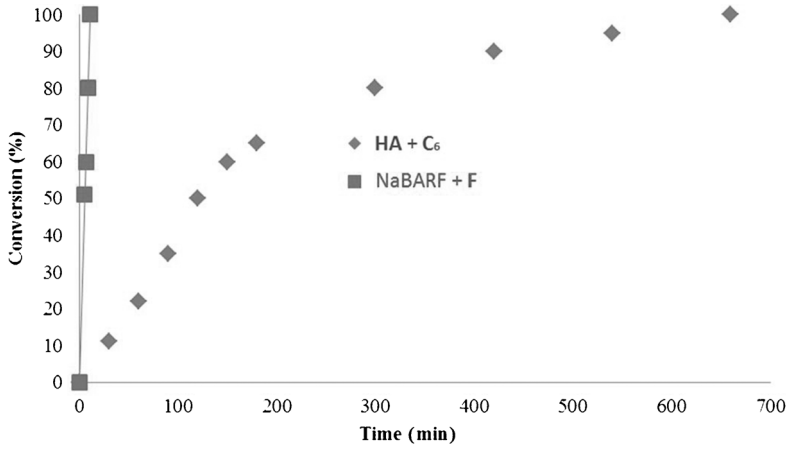


Figure 1. Time profiles for the hydrogenation of **1a** with catalysts derived from **F** and NaBARF (■) and $\mathbf{C_6}$ and **HA** (◆) monitored by in situ ^{1}H HP NMR spectroscopy. Reactions were carried out with 0.09 mmol substrate in [D_8]toluene (0.5 mL), at 20 bar H_2 pressure and 25 °C.

Conclusion

We have developed a new cooperative metal–organo catalytic system, in which a chiral Brønsted acid induces chirality in an achiral-metal-catalysed hydrogenation reaction. The catalyst is highly efficient, affording excellent enantioselectivities and high yields in the hydrogenation of imines derived from either aryl or aliphatic ketones, thus opening a new avenue for accessing chiral amines. However, the enantioselectivity is attained at the expense of the reaction rate, due to the steric hindrance created by the chiral acid.

Experimental Section

A mixture of the imine (0.15 mmol) and phosphoric acid **HA** (1 mol%) in toluene (0.5 mL) was stirred at room temperature for 5 min. Thereafter, a solution of $\mathbf{C_4}$ or $\mathbf{C_5}$ (1 mol%) in toluene (0.2 mL) was added and the mixture was transferred to a stainless steel autoclave. The hydrogenation was performed under H_2 (20 bar) whilst the mixture was stirred at 20 °C for 12 h. After carefully releasing the hydrogen gas in a fume hood, the solvent was removed and HCl (1 M, 1 mL) was added. After stirring for 10 min, saturated aqueous sodium bicarbonate was added slowly and the mixture was extracted with ethyl acetate (3×1 mL). The combined solution of ethyl acetate was dried with Na_2SO_4 and the solvent was removed. The residue was purified by passing it through a silica gel column eluted with hexane/CH_2Cl_2 (1:1–0:1) to give the pure amine product. The enantiomeric excess was determined by HPLC on a chromatograph equipped with a chiral column (OB-H or OD-H). The configuration of amines **2a**–**2p** was determined to be *S* by comparison of their HPLC behaviour with that of authentic samples.[16b] For amines **4a**–**4q**, the configuration was assumed to be *S* by analogy with the reported literature.[9]

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[1] For recent reviews of the asymmetric hydrogenation of imines, see: a) T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, *352*, 753–819; b) J. H. Xie, S. F. Zhu, Q. L. Zhou, *Chem. Rev.* **2011**, *111*, 1713–1760; for a significant industrial application, see: c) H.-U. Blaser, *Adv. Synth. Catal.* **2002**, *344*, 17–31.

[2] For recent examples of the asymmetric hydrogenation of imines, see: a) N. Mršić, A. J. Minnaard, B. L. Feringa, J. G. De Vries, *J. Am. Chem. Soc.* **2009**, *131*, 8358–8359; b) S. Shirai, H. Nara, Y. Kayaki, T. Ikariya, *Organometallics* **2009**, *28*, 802–809; c) S. L. Zhou, S. Fleischer, K. Junge, M. Beller, *Angew. Chem.* **2011**, *123*,

5226–5230; *Angew. Chem. Int. Ed.* **2011**, *50*, 5120–5124; d) F. Chen, T. L. Wang, Y. M. He, Z. Y. Ding, Z. W. Li, L. J. Xu, Q. H. Fan, *Chem. Eur. J.* **2011**, *17*, 1109–1113; e) X. Y. Zhou, M. Bao, Y. G. Zhou, *Adv. Synth. Catal.* **2011**, *353*, 84–88; f) F. Chen, Z. Y. Ding, Y. M. He, J. Qin, T. L. Wang, Q. H. Fan, *Tetrahedron* **2012**, *68*, 5248–5257; g) C. J. Hou, Y. H. Wang, Z. Zheng, J. Xu, X. P. Hu, *Org. Lett.* **2012**, *14*, 3554–3557; h) N. Arai, N. Utsumi, Y. Matsumoto, K. Murata, K. Tsutsumi, T. Ohkuma, *Adv. Synth. Catal.* **2012**, *354*, 2089–2095; i) S. Werkmeister, S. Fleischer, K. Junge, M. Beller, *Chem. Asian J.* **2012**, *7*, 2562–2568; j) K. Gao, B. Wu, C. B. Yu, Q. A. Chen, Z. S. Ye, Y. G. Zhou, *Org. Lett.* **2012**, *14*, 3890–3893; k) Y. Schramm, F. Barrios-Landeros, A. Pfaltz, *Chem. Sci.* **2013**, *4*, 2760–2766.

[3] For selected examples of the metal-catalysed transfer hydrogenation of imines, see: a) H. Matsunaga, K. Nakanishi, M. Nakajima, T. Kunieda, T. Ishizuka, *Heterocycles* **2009**, *78*, 617–622; b) D. Guijarro, O. Pablo, M. Yus, *Tetrahedron Lett.* **2009**, *50*, 5386–5388; c) D. Guijarro, O. Pablo, M. Yus, *J. Org. Chem.* **2010**, *75*, 5265–5270; d) S. H. Kwak, S. A. Lee, K. I. Lee, *Tetrahedron: Asymmetry* **2010**, *21*, 800–804; e) A. A. Mikhailine, M. I. Maishan, R. H. Morris, *Org. Lett.* **2012**, *14*, 4638–4641; f) P. Šot, M. Kuzma, J. Václarík, J. Pencháček, J. Přech, J. Januščák, P. Kačer, *Organometallics* **2012**, *31*, 6496–6499.

[4] For recent reviews of the organocatalytic transfer hydrogenation of imines, see: a) D. Kampen, C. M. Reisinger, B. J. List, *Top. Curr. Chem.* **2009**, *291*, 395–456; b) Z. Wang, Z. Jiang, *Asian J. Chem.* **2010**, *22*, 4141–4149; c) M. Rueping, E. Sugiono, F. R. Schoepke, *Synlett* **2010**, 852–865; d) C. Zheng, S. L. You, *Chem. Soc. Rev.* **2012**, *41*, 2498–2518; e) J. G. De Vries, N. Mršić, *Catal. Sci. Technol.* **2011**, *1*, 727–735.

[5] For a recent review of the asymmetric hydrosilylation of imines, see: S. Jones, C. J. A. Warner, *Org. Biomol. Chem.* **2012**, *10*, 2189–2200.

[6] a) F. Spinder, H.-U. Blaser in *Handbook of Homogeneous Hydrogenation* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**, p. 1193; b) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keßeler, R. Stuürmer, T. Zelinski, *Angew. Chem.* **2004**, *116*, 806–843; *Angew. Chem. Int. Ed.* **2004**, *43*, 788–824.

[7] For reviews, see: a) *Comprehensive Asymmetric Catalysis, Vols. I–III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto,), Springer, Berlin, **1999**; b) *Modern Reduction Methods* (Eds.: P. G. Andersson, I. J. Munslow), Wiley-VCH, Weinheim, **2008**.

[8] L. Rubio-Pérez, F. J. Perez-Flores, P. Sharma, L. Velaso, A. Cabrera, *Org. Lett.* **2009**, *11*, 265–268.

[9] a) C. Q. Li, C. Wang, B. Villa-Marcos, J. L. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 14450–14451; b) C. Q. Li, B. Villa-Marcos, J. L. Xiao, *J. Am. Chem. Soc.* **2009**, *131*, 6967–6969; c) B. Villa-Marcos, C. Q. Li, K. R. Mulholland, P. J. Hogan, J. L. Xiao, *Molecules* **2010**, *15*, 2453–2472.

[10] For reviews, see: a) Z. H. Shao, H. B. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745–2755; b) C. Zhong, X. Shi, *Eur. J. Org. Chem.* **2010**, 2999–3025; c) M. Rueping, R. M. Koenigs, J. Atodiresei, *Chem. Eur. J.* **2010**, *16*, 9350–9365; d) A. E. Allen, D. W. C. MacMillan, *Chem. Sci.* **2012**, *3*, 633–658; e) L. Stegbauer, F. Sladojevich, D. J. Dixon, *Chem. Sci.* **2012**, *3*, 942–958; f) Z. K. Yu, W. W. Jin, Q. B. Jiang, *Angew. Chem.* **2012**, *124*, 6164–6177; *Angew. Chem. Int. Ed.* **2012**, *51*, 6060–6072; g) Z. Du, Z. Shao, *Chem. Soc. Rev.* **2013**, *42*, 1337–1378.

[11] For the ionic hydrogenation mechanism, see: a) R. M. Bullock, *Chem. Eur. J.* **2004**, *10*, 2366–2374; b) H. R. Guan, M. Limura, M. P. Magee, J. R. Norton, G. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 7805–7814.

[12] M. Fleischmann, D. Drettwan, E. Sugiono, M. Reuping, R. M. Gschwind, *Angew. Chem.* **2011**, *123*, 6488–6493; *Angew. Chem. Int. Ed.* **2011**, *50*, 6364–6369.

[13] For mechanistic details, see: W. J. Tang, S. Johnston, J. Iggo, N. G. Berry, M. Phelan, L. Lian, J. Basca, J. L. Xiao, *Angew. Chem.* **2013**, *125*, 1712–1716; *Angew. Chem. Int. Ed.* **2013**, *52*, 1668–1672.

[14] C. Q. Li, Ph.D. Thesis, University of Liverpool (UK), **2009**.

[15] M. Klussmann, *Angew. Chem.* **2009**, *121*, 7260–7261; *Angew. Chem. Int. Ed.* **2009**, *48*, 7124–7125.

[16] For the organocatalytic reductive amination of ketones, see: a) S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem.* **2005**, *117*, 7590–7593; *Angew. Chem. Int. Ed.* **2005**, *44*, 7424–7427; b) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84–86; c) V. N. Wakchaure, M. Nicoletti, L. Ratjen, B. J. List, *Synlett* **2010**, 2708–2710; d) V. N. Wakchaure, J. Zhou, S. Hoffmann, B. J. List, *Angew. Chem.* **2010**, *122*, 4716–4718; *Angew. Chem. Int. Ed.* **2010**, *49*, 4612–4614; e) K. Saito, T. Akiyama, *Chem. Commun.* **2012**, *48*, 4573–4575.

[17] M. Rueping, R. M. Koenigs, *Chem. Commun.* **2011**, *47*, 304–306.

[18] a) K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem.* **1997**, *109*, 297–300; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 285–299; b) Z. M. Heiden, B. J. Gorecki, T. B. Rauchfuss, *J. Am. Chem. Soc.* **2006**, *128*, 13048–13049.

[19] a) T. Ohkuma, N. Utsumi, K. Tsutsumi, K. Murata, C. Sandoval, R. Noyori, *J. Am. Chem. Soc.* **2006**, *128*, 8724–8725; b) T. Ohkuma, N. Utsumi, M. Watanabe, K. Tsutsumi, N. Arai, K. Murata, *Org. Lett.* **2007**, *9*, 2565–2567; c) Z. M. Heiden, B. J. Gorecki, T. B. Rauchfuss, *J. Am. Chem. Soc.* **2009**, *131*, 3593–3600.

[20] For examples of catalysts containing substituted ethylene diamine ligands, see: a) D. S. Matharu, D. J. Morris, A. M. Kawamoto, G. J. Clarkson, M. Wills, *Org. Lett.* **2005**, *7*, 5489–5491; b) D. S. Matharu, D. J. Morris, G. J. Clarkson, M. Wills, *Chem. Commun.* **2006**, 3232–3234; c) D. S. Matharu, J. E. D. Martins, M. Wills, *Chem. Asian J.* **2008**, *3*, 1374–1383; d) J. E. D. Martins, G. J. Clarkson, M. Wills, *Org. Lett.* **2009**, *11*, 847–850.

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