Reduction

Deutsche Ausgabe: DOI: 10.1002/ange.201604025
Internationale Ausgabe: DOI: 10.1002/anie.201604025

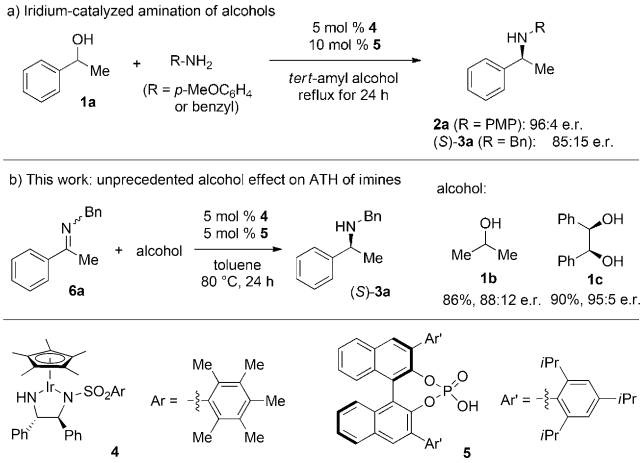
Asymmetric Transfer Hydrogenation of Imines using Alcohol: Efficiency and Selectivity are Influenced by the Hydrogen Donor

Hui-Jie Pan, Yao Zhang, Chunhui Shan, Zhaoyuan Yu, Yu Lan, and Yu Zhao**

Abstract: *The influence of the alcohol, as the hydrogen donor, on the efficiency and selectivity of the asymmetric transfer hydrogenation (ATH) of imines is reported for the first time. This discovery not only leads to a highly enantioselective access to N-aryl and N-alkyl amines, but also provides new insight into the mechanism of the ATH of imines. Both experimental and computational studies provide support for the reaction pathway involving an iridium alkoxide as the reducing species.*

Development of efficient methods for the preparation of chiral amines in high enantiopurity has long been an important goal in organic synthesis because of their wide use in fine-chemicals and pharmaceutical industries.[1] One of the most explored reactions for this purpose is the asymmetric reduction of imines using either molecular hydrogen [asymmetric hydrogenation (AH)][2] or other reducing agents including formic acid, silanes, alcohols, the Hantzsch ester, etc. [asymmetric transfer hydrogenation (ATH)].[3] Among these agents, alcohol is highly preferred as a convenient, economical, and environmentally benign choice, with 2-propanol used almost exclusively. Despite the great success with ATH of ketones using alcohol,[4] the related ATH of imines using alcohol proved to be extremely challenging. Highly enantioselective variants remained elusive until recent reports from the groups of Beller, Morris, and Yus.[5] We report herein our recent discovery that the efficiency and enantioselectivity of iridium-catalyzed ATH of imines can be easily tuned by the use of different alcohols as the hydrogen donor. Such a simple yet unprecedented modification not only enabled a highly enantioselective ATH of *N*-aryl as well as *N*-benzyl imines, but also provided important insights into the mechanism of ATH of imines using alcohol.

Recently our group reported the first example of asymmetric amination of alcohols using the borrowing-hydrogen methodology catalyzed by the iridium complex **4** and chiral phosphoric acid **5** (Scheme 1 a).[6,7] While it represents an attractive redox-neutral synthesis of *N*-aryl amines in high enantioselectivity (e.g. **2a**), for the synthetically more flexible benzyl amine only moderate enantioselectivity could be achieved [85:15 e.r. for (*S*)-**3a**]. In an effort to better understand this reaction and to overcome this limitation, we decided to examine ATH of the preformed N-benzyl imine **6a** using alcohol as the hydrogen donor. After extensive optimization using 2-propanol (**1b**), however, the selectivity remained unsatisfactory (88:12 e.r.; Scheme 1 b).



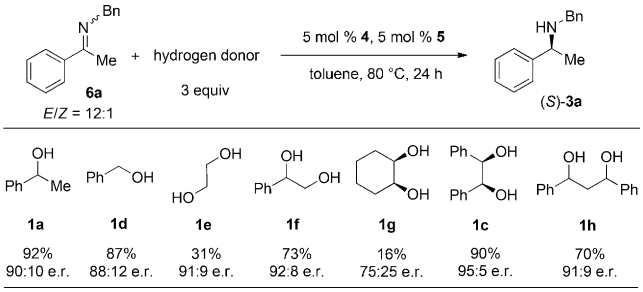
Scheme 1. Identification of the alcohol effect in ATH. PMP = *para*-methoxyphenyl.

An intriguing discovery was made during an attempted combination of the ATH of **6a** with the desymmetrization of a *meso* diol. By using **1c** instead of **1b** under otherwise identical reaction conditions, the amine (*S*)-**3a** was obtained with a much higher e.r. value of 95:5. The identity of the hydrogen donor had a dramatic influence on the selectivity of the transfer hydrogenation. This result is in contrast to the well-established bifunctional catalysis mechanism of asymmetric transfer hydrogenation, pioneered by the groups of Noyori and Ikariya, in which the metal hydride served as the reductant and the identity of the hydrogen donor (formic acid or alcohol) should play no role in the enantio-determining step.[8,9]

Following this discovery, we decided to examine a wide range of primary and secondary alcohols, as well as diols to further evaluate this interesting hydrogen-donor effect. As shown in Scheme 2, both efficiency and enantioselectivity of the ATH of **6a** were clearly affected by the alcohol used.[10] While there is no clear trend on the influence of enantioselectivity by different alcohols, benzylic alcohols in general provided higher efficiency, and **1c** remained the optimal choice.

This catalytic system using **1c** as the hydrogen donor could be applied to the ATH of a wide range of N-benzyl

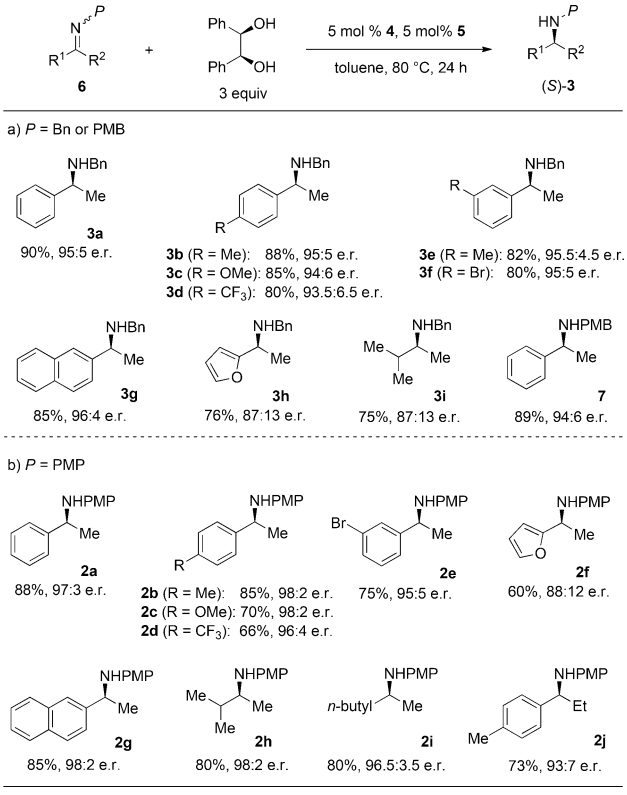
[*] H.-J. Pan, Y. Zhang, Prof. Y. Zhao
Department of Chemistry, National University of Singapore
3 Science Drive 3, Singapore 117543 (Singapore)
E-mail: zhaoyu@nus.edu.sg
Homepage: http://zhaoyu.science.nus.edu.sg
C. Shan, Z. Yu, Prof. Y. Lan
School of Chemistry and Chemical Engineering, Chongqing University, Chongqing, 400030 (P.R. China)
E-mail: lanyu@cqu.edu.cn
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201604025.



Scheme 2. Screening of hydrogen donors for ATH. The reactions were carried out under an N_2 atmosphere. The yield of (*S*)-**3a** was determined by GC using an internal standard. The e.r. value was determined by HPLC. See the Supporting Information for details.

imines, the type of substrate which has proven to be highly challenging (Scheme 3a). The substrates were directly used as a mixture of geometrical isomers. For the aryl, methyl-containing substrates, various substituents on the aryl ring could be well-tolerated to yield **3a–h** in high efficiencies and good to excellent selectivities. For dialkyl-substituted chiral amines such as **3i**, the enantioselectivity dropped slightly to 87:13. In addition to N-benzyl substrates, the *para*-methoxybenzyl (PMB)-protected amine could be obtained in similar yield and selectivity (**7**).

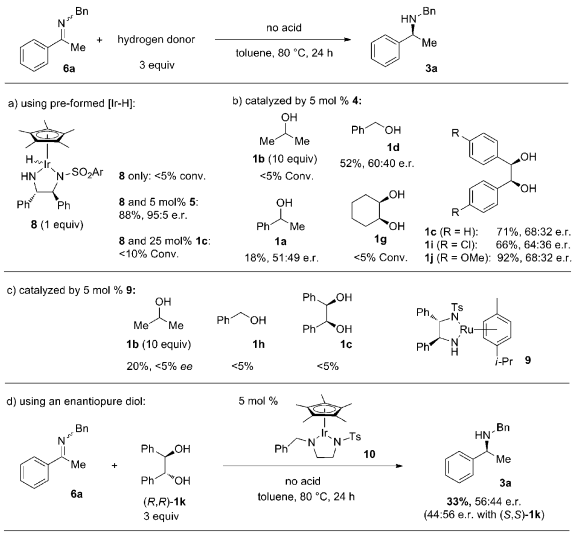
Interestingly, a similar trend with alcohols as the hydrogen donor was observed for the ATH of *N*-aryl imines as well (see the Supporting Information for details). Under the optimal



Scheme 3. Scope of ATH of *N*-benzyl and *N*-aryl imines. See footnote of Scheme 2. Yields are those of isolated products. PMB = *para*-methoxybenzyl.

reaction conditions, the *N*-PMP amine **2a** was obtained in a high yield of 88% with an excellent 97:3 e.r. (Scheme 3b). This set of reaction conditions again proved general to produce a range of aryl,methyl-substituted chiral amines (**2a–g**) with excellent selectivity (up to 98:2 e.r.). More significantly, the dialkyl-substituted amines **2h** and **2i** could also be accessed with excellent e.r. values. This method is not limited to chiral amines bearing a methyl substituent. The chiral amine **2j** was obtained with a high e.r. value of 93:7. Overall, this simple and general procedure represents a rare example of highly enantioselective transfer hydrogenation of *N*-aryl and *N*-alkyl imines using alcohol.

Efforts were then directed towards a better understanding of the reaction mechanism of this catalytic system. For the ATH of ketones using alcohol and the Noyori–Ikariya-type complexes, the concerted bifunctional catalysis mechanism was widely accepted,[8a–d] but recent studies also point to the alternative stepwise ion-pair mechanism for ruthenium catalysis, especially by taking into consideration the protic solvent effect.[8e–g] For the corresponding ATH of imines, in contrast, an alternative anionic mechanism was proposed and involves activation of the imine by an external acid cocatalyst.[9] The original ATH of imines catalyzed by a Ru/TsDPEN complex (e.g., **9** in Scheme 4) utilizes formic acid/Et_3N as the terminal



Scheme 4. Mechanistic studies for ATH of imines. See footnote of Scheme 2. Ts = 4-toluenesulfonyl.

reductant, while isopropyl alcohol was reported to be unsuitable for this purpose.[3c] For the reduction of an imine using the [Ru-H] complex related to **9**, an acid cocatalyst was also reported to be necessary.[9c] To provide direct evidence for the reaction mechanism, we synthesized the iridium hydride **8** (~2.4:1 d.r.), by using the procedure reported by the group of Rauchfuss,[11] and subjected it to the stoichiometric reduction of **6a** (Scheme 4a). Similar to the case of Ru-H,[9c] **8** alone could not reduce **6a** at all. Only by adding the chiral phosphoric acid cocatalyst, a highly efficient ATH of **6a** was achieved.

For the intriguing hydrogen-donor effect in our iridium-catalyzed process, we hypothesized the following two possible scenarios:[12] 1) the diol functionality may activate the imine as a general acid (because of its elevated acidity relative to simple alcohol); 2) an alternative reducing agent may be operative instead of the iridium hydride. The corresponding iridium alkoxide species may reduce the imine directly through a Meerwein–Ponndorf–Verley (MPV) reduction pathway. Such a possibility has been suggested for transfer hydrogenation of ketones using iridium-based catalysts.[13] We then turned our attention to the differentiation of the two possibilities.

Different alcohols were examined for the ATH of **6a** under acid-free conditions where **8** was shown to be unreactive (Scheme 4b). When **1b** was used (even with a higher loading), no conversion into (*S*)-**3a** was observed at all. In contrast, benzylic alcohols such as **1a** and **1d** provided the desired product in noticeable to moderate yields. The diol **1g** again was ineffective, while the diols **1c**, **1i**, and **1j**, which are electronically modified, yielded (*S*)-**3a** in good to excellent efficiency, with the more electron-rich reagent providing the highest reactivity. Clearly the trend of reactivity (e.g., **1c** versus **1i**, **1j**) does not correlate with the acidity of the alcohols utilized. In addition, as shown in Scheme 4a, by adding **1c** as an additive, the ATH of the imine **8** also failed to produce the amine product in good efficiency. All these observations seemed to support the iridium alkoxide pathway.

It is also noteworthy that the hydrogen-donor effect does not operate for ATH of an imine catalyzed by the Noyori catalyst **9**, thus emphasizing the difference of the reactivity of ruthenium- and iridium-based catalysts (Scheme 4c).

To provide further evidence to the iridium alkoxide pathway, the use of the enantiopure diol (*R*,*R*)-**1k** for ATH of **6a** was carried out in the absence of acid (Scheme 4d). An achiral iridium complex **10** was used in this instance, so that the diol (*R*,*R*)-**1k** was the only source of chirality.[14] As it turned out, a low but meaningful e.r. value of 56:44 was observed for (*S*)-**3a**. This chirality transfer lent further support for an iridium alkoxide mechanism.

The density functional theory (DFT) method M06-2X,[15] based on the B3LYP optimized geometries of stationary points, was also carried out to study the ATH of imines. The optimization was carried out in the presence of toluene with C-PCM solvation model,[8e–g,16] and the calculated Gibbs free energies based on the structures optimized in toluene are discussed below. As depicted in Figure 1a, the iridium alkoxide **A** (derived from **4** via **TS-A**) may reduce the activated substrate **11** via **TS-B** to form **12** and **13** with the regeneration of **4**. Alternatively the Ir-H **B** which is formed from **4** (via **TS-C**) may reduce the activated imine (Figure 1b; Ir-H pathway).[17] The free-energy profiles for these processes in toluene were calculated (in the units of kcal mol^{-1}). Among the iridium complexes, **4** was set to a relative value of zero.

As the data shows, **A** could be formed from **4** and **1a** with ease (**TS-A**; 12.3 kcal mol^{-1}). The hydride transfer from **A** to **11** (activated by **5**) could take place via the transition-state **TS-B** with 26.6 kcal mol^{-1} overall activation free energy in toluene, and results in the formation of acetophenone (**12**) and chiral amine phosphate **13**, together with the regeneration of **4** exothermally. In **TS-B**, the lengths for the forming C–H bond and breaking C–H bond were 1.53 Å and 1.31 Å, respectively. The distance between the hydrogen atom in the reacting imine and oxygen atom in phosphoric acid moiety

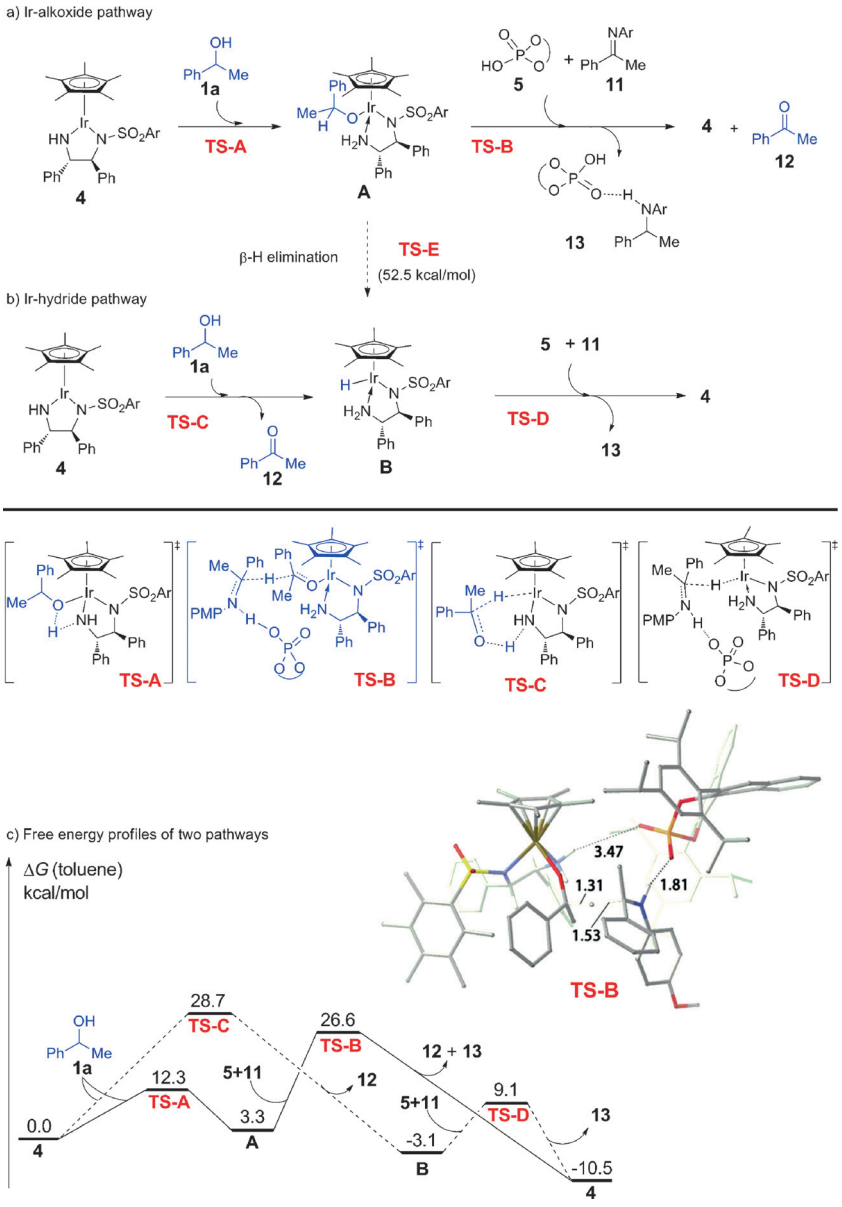


Figure 1. Free-energy profiles for the hydride transfer. TS = transition state.

was 1.81 Å, thus indicating a regular hydrogen bond. However, the distance between the hydrogen atom in the coordinated ethanediamine ligand and the oxygen atom in phosphoric acid moiety was as long as 3.47 Å. Therefore, the hydrogen bond between the phosphoric acid moiety and the coordinated ethanediamine ligand could not be observed, and could be attributed to the repulsion between phosphoric acid and the coordinated diamine.

Alternatively, **B** could be formed from **4** and **1a** with the release of **12** via the transition-state **TS-C** with an activation free energy of 28.7 kcal mol^{-1} (higher than that of **TS-B**). In our system, the possible intermediates/TSs for the stepwise mechanism of the formation of **B**[8e–g] could not be allocated. The use of an iridium-based catalyst and aprotic solvent of toluene is believed to be the key factors. Once formed, **B** can reduce the activated imine with a very low barrier of 12.2 kcal mol^{-1} (**TS-D**) to form **13** and regenerate **4**. In **TS-D** hydrogen-bond interaction between the acid to the imine could be located, but similar to **TS-B**, the hydrogen-bond interaction between the oxygen atom in the phosphoric acid and the ethanediamine ligand on iridium could not be located. Overall, Ir-H is more effective for the reduction, but the formation of Ir-H requires a higher activation barrier. The direct hydride transfer from the iridium alkoxide to the activated imine is thus believed to be operative in this iridium-catalyzed ATH of imines. As to the stereoselectivity of this ATH system, it is possible that hydrogen-bond interactions between the optimal diol **1c** and the catalyst and substrate may partially contribute to the enhanced selectivity. More detailed computations on the comparison of alcohols/diols (with or without the acid co-catalyst) are ongoing to gain more insight into the origin of the stereoselectivity.

In conclusion, we have developed a highly selective ATH of *N*-aryl and *N*-alkyl ketimines, using alcohol as the hydrogen donor, catalyzed by a chiral iridium complex in cooperation with a chiral phosphoric acid. The discovery of the hydrogen-donor effect on the reactivity and enantioselectivity was key to the success of this system. Based on the experimental evidence and DFT calculations, a mechanism involving an iridium alkoxide as the reducing agent is proposed.

Acknowledgments

We are grateful for the generous financial support from Singapore National Research Foundation (R-143-000-477-281) and the Ministry of Education of Singapore (R-143-000-613-112). The computation part was supported by the National Science Foundation of China (Grant No. 21372266).

Keywords: amines · cooperative effects · enantioselectivity · hydrogenation · iridium

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 9615–9619
Angew. Chem. **2016**, *128*, 9767–9771

[1] For selected recent reviews, see: a) *Chiral Amine Synthesis: Methods, Developments and Applications* (Ed.: T. C. Nugent), Wiley-VCH, Weinheim, **2010**; b) T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, *352*, 753–819; c) C. Wang, B. Villa-Marcos, J. Xiao, *Chem. Commun.* **2011**, *47*, 9773–9785.

[2] For selected reviews, see: a) N. Fleury-Brégeot, V. de la Fuente, S. Castillón, C. Claver, *ChemCatChem* **2010**, *2*, 1346–1371; b) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713–1760; For selected recent examples, see: c) C. Moessner, C. Bolm, *Angew. Chem. Int. Ed.* **2005**, *44*, 7564–7567; *Angew. Chem.* **2005**, *117*, 7736–7739; d) S.-F. Zhu, J.-B. Xie, Y.-Z. Zhang, S. Li, Q.-L. Zhou, *J. Am. Chem. Soc.* **2006**, *128*, 12886–12891; e) Q. Yang, G. Shang, W. Gao, J. Deng, X. Zhang, *Angew. Chem. Int. Ed.* **2006**, *45*, 3832–3835; *Angew. Chem.* **2006**, *118*, 3916–3919; f) M. T. Reetz, O. Bondarev, *Angew. Chem. Int. Ed.* **2007**, *46*, 4523–4526; *Angew. Chem.* **2007**, *119*, 4607–4610; g) C. Li, C. Wang, B. Villa-Marcos, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 14450–14451; h) C. Li, B. Villa-Marcos, J. Xiao, *J. Am. Chem. Soc.* **2009**, *131*, 6967–6969; i) Z. Han, Z. Wang, X. Zhang, K. Ding, *Angew. Chem. Int. Ed.* **2009**, *48*, 5345–5349; *Angew. Chem.* **2009**, *121*, 5449–5453; j) N. Mrsić, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *J. Am. Chem. Soc.* **2009**, *131*, 8358–8359; k) G. Hou, F. Gosselin, W. Li, J. C. McWilliams, Y. Sun, M. Weisel, P. D. Shea, C.-Y. Chen, I. W. Davies, X. Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 9882–9883; l) G. Hou, R. Tao, Y. Sun, X. Zhang, F. Gosselin, *J. Am. Chem. Soc.* **2010**, *132*, 2124–2125; m) D. S. Wang, Q. A. Chen, W. Li, C. B. Yu, Y. G. Zhou, X. M. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 8909–8911; n) Q. A. Chen, D. S. Wang, Y. G. Zhou, Y. Duan, H. J. Fan, Y. Yang, Z. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 6126–6129; o) Q.-A. Chen, M.-W. Chen, C.-B. Yu, L. Shi, D.-S. Wang, Y. Yang, Y.-G. Zhou, *J. Am. Chem. Soc.* **2011**, *133*, 16432–16435; p) M. Rueping, R. M. Koenigs, *Chem. Commun.* **2011**, *47*, 304–306; q) S. Zhou, S. Fleischer, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2011**, *50*, 5120–5124; *Angew. Chem.* **2011**, *123*, 5226–5230; r) Z.-Y. Ding, F. Chen, J. Qin, Y.-M. He, Q.-H. Fan, *Angew. Chem. Int. Ed.* **2012**, *51*, 5706–5710; *Angew. Chem.* **2012**, *124*, 5804–5808.

[3] For selected reviews, see: a) S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226–236; b) M. Rueping, E. Sugiono, F. R. Schoepke, *Synlett* **2010**, 852–865; For selected examples using formic acid, see: c) N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 4916–4917; d) J. Mao, D. C. Baker, *Org. Lett.* **1999**, *1*, 841–843; e) R. Kadyrov, T. H. Riermeier, *Angew. Chem. Int. Ed.* **2003**, *42*, 5472–5474; *Angew. Chem.* **2003**, *115*, 5630–5632; for selected examples using hydrosilane: f) X. Verdaguer, U. E. W. Lange, S. L. Buchwald, *Angew. Chem. Int. Ed.* **1998**, *37*, 1103–1107; *Angew. Chem.* **1998**, *110*, 1174–1178; g) B. H. Lipshutz, H. Shimizu, *Angew. Chem. Int. Ed.* **2004**, *43*, 2228–2230; *Angew. Chem.* **2004**, *116*, 2278–2280; h) K. A. Nolin, R. W. Ahn, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 12462–12463; i) A. V. Malkov, A. Mariani, K. N. MacDougall, P. Kocovsky, *Org. Lett.* **2004**, *6*, 2253–2256; for selected examples using Hantzch ester: j) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781–3783; k) S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem. Int. Ed.* **2005**, *44*, 7424–7427; *Angew. Chem.* **2005**, *117*, 7590–7593; l) M. Rueping, A. P. Antonchik, T. Theissmann, *Angew. Chem. Int. Ed.* **2006**, *45*, 3683–3686; *Angew. Chem.* **2006**, *118*, 3765–3768; m) M. Rueping, A. P. Antonchik, T. Theissmann, *Angew. Chem. Int. Ed.* **2006**, *45*, 6751–6755; *Angew. Chem.* **2006**, *118*, 6903–6907; n) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84–86; o) S. Hoffmann, M. Nicoletti, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13074–13075; p) G. Li, Y. Liang, J. C. Antilla, *J. Am. Chem. Soc.* **2007**, *129*, 5830–5831.

[4] R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97–102.

[5] a) S. Zhou, S. Fleischer, K. Junge, S. Das, D. Addis, M. Beller, *Angew. Chem. Int. Ed.* **2010**, *49*, 8121 – 8125; *Angew. Chem.* **2010**, *122*, 8298 – 8302; b) A. A. Mikhailine, M. I. Maishan, R. H. Morris, *Org. Lett.* **2012**, *14*, 4638 – 4641; c) W. Zuo, A. J. Lough, Y. F. Li, R. H. Morris, *Science* **2013**, *342*, 1080 – 1083; d) O. Pablo, D. Guijarro, G. Kovács, A. Lledós, G. Ujaque, M. Yus, *Chem. Eur. J.* **2012**, *18*, 1969 – 1983.

[6] a) Y. Zhang, C.-S. Lim, D. S. B. Sim, H.-J. Pan, Y. Zhao, *Angew. Chem. Int. Ed.* **2014**, *53*, 1399 – 1403; *Angew. Chem.* **2014**, *126*, 1423 – 1427; b) Z.-Q. Rong, Y. Zhang, H. B. R. Chua, H.-J. Pan, Y. Zhao, *J. Am. Chem. Soc.* **2015**, *137*, 4944 – 4947; for more recent diastereo- or enantioselective amination of alcohols, see: c) N. J. Oldenhuis, V. M. Dong, Z. Guan, *J. Am. Chem. Soc.* **2014**, *136*, 12548 – 12551; d) M. Peña-López, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2016**, *55*, 7826 – 7830; *Angew. Chem.* **2016**, *128*, 7957 – 7961.

[7] For selected reviews on the borrowing-hydrogen methodology, see: a) M. H. S. A. Hamid, P. A. Slatford, J. M. J. Williams, *Adv. Synth. Catal.* **2007**, *349*, 1555 – 1575; b) T. D. Dixon, M. K. Whittlesey, J. M. J. Williams, *Dalton Trans.* **2009**, 753 – 762; c) G. E. Dobereiner, R. H. Crabtree, *Chem. Rev.* **2010**, *110*, 681 – 703; d) G. Guillena, D. J. Ramón, M. Yus, *Chem. Rev.* **2010**, *110*, 1611 – 1641; e) A. J. A. Watson, J. M. J. Williams, *Science* **2010**, *329*, 635 – 636; f) S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann, M. Beller, *ChemCatChem* **2011**, *3*, 1853 – 1864; g) S. Pan, T. Shibata, *ACS Catal.* **2013**, *3*, 704 – 712. The Krische group has developed highly enantioselective catalytic C–C coupling involving transfer hydrogenation: h) J. F. Bower, M. J. Krische, *Top. Organomet. Chem.* **2011**, *34*, 107 – 138; i) J. Moran, M. J. Krische, *Pure Appl. Chem.* **2012**, *84*, 1729 – 1739.

[8] For selected reports, see: a) M. Yamakawa, H. Ito, R. Noyori, *J. Am. Chem. Soc.* **2000**, *122*, 1466 – 1478; b) D. A. Alonso, P. Brandt, S. J. M. Nordin, P. G. Andersson, *J. Am. Chem. Soc.* **1999**, *121*, 9580 – 9588; c) T. Ikariya, K. Murata, R. Noyori, *Org. Biomol. Chem.* **2006**, *4*, 393 – 406; d) T. Ikariya, A. J. Blacker, *Acc. Chem. Res.* **2007**, *40*, 1300 – 1308; e) P. A. Dub, T. Ikariya, *J. Am. Chem. Soc.* **2013**, *135*, 2604 – 2619; f) P. A. Dub, N. J. Henson, R. L. Martin, J. C. Gordon, *J. Am. Chem. Soc.* **2014**, *136*, 3505 – 3521; g) P. A. Dub, J. C. Gordon, *Dalton Trans.* **2016**, *45*, 6756 – 6781.

[9] For selected reviews and examples, see: a) S. E. Clapham, A. Hadzovic, R. H. Morris, *Coord. Chem. Rev.* **2004**, *248*, 2201 – 2237; b) J. S. M. Samec, J.-E. Bäckvall, P. G. Andersson, P. Brandt, *Chem. Soc. Rev.* **2006**, *35*, 237 – 248; c) J. B. Åberg, J. S. M. Samec, J.-E. Bäckvall, *Chem. Commun.* **2006**, 2771 – 2773; d) D. G. Blackmond, M. Ropic, M. Stefinvic, *Org. Process Res. Dev.* **2006**, *10*, 457 – 463; e) J. E. D. Martins, G. J. Clarkson, M. Wills, *Org. Lett.* **2009**, *11*, 847 – 850; f) R. Soni, F. K. Cheung, G. C. Clarkson, J. E. D. Martins, M. A. Graham, M. Wills, *Org. Biomol. Chem.* **2011**, *9*, 3290 – 3294; g) J. S. M. Samec, A. H. Ell, J. B. Åberg, T. Primalov, L. Eriksson, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2006**, *128*, 14293 – 14305; h) C. P. Casey, T. B. Clark, I. A. Guzei, *J. Am. Chem. Soc.* **2007**, *129*, 11821 – 11827; i) S. – *y.* Shirai, H. Nara, Y. Kayaki, T. Ikariya, *Organometallics* **2009**, 28, 802 – 809.

[10] The reactions were complicated by a small amount of amine side product, which was formed by transfer of the amino group in **6** to the ketones generated from the alcohol **1** followed by reduction.

[11] C. S. Letko, Z. M. Heiden, T. B. Rauchfuss, S. R. Wilson, *Inorg. Chem.* **2011**, *50*, 5558 – 5566.

[12] A third possibility could be operative: the use of different alcohols may lead to the formation of [Ir-H] with a different d.r. value, which in turn results in the difference in *ee* value of the chiral amine product. By following the stoichiometric reactions, using NMR spectroscopy, of **4** and either **1b** or **1c** in the absence of imine, however, we observed the [Ir-H] formation in a small amount and with the similar d.r. value of 2.1:1 and 2.3:1 (see the Supporting Information). This observation ruled out this possibility for the alcohol effect.

[13] J.-W. Handgraaf, J. N. H. Reek, E. J. Meijer, *Organometallics* **2003**, *22*, 3150 – 3157.

[14] The iridium complex **10** was reported by the group of Xiao group to be an effective AH catalyst. See: W. Tang, S. Johnston, J. A. Iggo, N. G. Berry, M. Phelan, L. Lian, J. Bacsa, J. Xiao, *Angew. Chem. Int. Ed.* **2013**, *52*, 1668 – 1672; *Angew. Chem.* **2013**, *125*, 1712 – 1716. While **1k** could in principle lead to an enantioselective generation of [Ir-H] (chiral at iridium) from **10**, such a hydride species was reported to be inactive without acid activation of the imine substrate.

[15] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215 – 241.

[16] a) A. Pavlova, E. J. Meijer, *ChemPhysChem* **2012**, *13*, 3492 – 3496; b) M. C. Carrión, M. R. Castañeda, G. Espino, C. Aliende, L. Santos, A. M. Rodríguez, B. R. Manzano, F. A. Jalón, A. Lledós, *ACS Catal.* **2014**, *4*, 1040 – 1053.

[17] The Ir-H **B** could also be formed from the iridium alkoxide **A** by β-hydride elimination. However this **TS-E** was shown to be prohibitively high in energy (52.5 kcal mol^{-1}).

Received: April 26, 2016
Revised: June 14, 2016
Published online: July 4, 2016

