Asymmetric Catalysis

DOI: 10.1002/anie.200903765

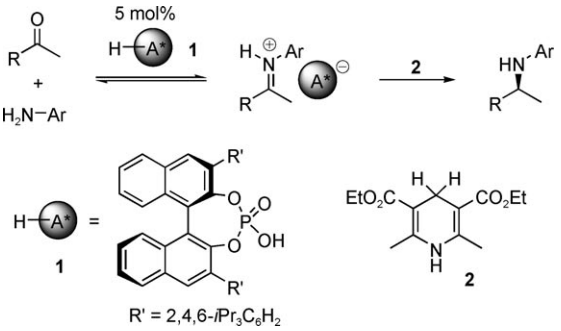
# Asymmetric Reductive Amination by Combined Brønsted Acid and Transition-Metal Catalysis

*Martin Klussmann**

amination · asymmetric catalysis · hydrogenation · organocatalysis · transition metals

Chiral amines are important building blocks for pharmaceutical and agrochemical applications, and considerable research effort has been put into the development of efficient methods for their synthesis. One method for the asymmetric synthesis of amines is the catalytic reduction of ketimines. Even more attractive though is the direct reductive amination as it combines two steps in one: the formation of intermediate imines from simple starting materials (ketones and amines) and their subsequent hydrogenation.[1] In comparison to other methods like the addition of organometallic compounds to imines, it is also potentially more atom economical and easier to perform. Despite continued interest in this field, only relatively few successful methods for either the asymmetric reduction of preformed imines or the direct asymmetric reductive amination have been developed until recently.

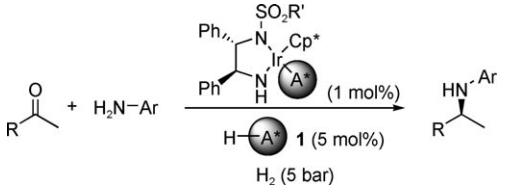
Organocatalytic approaches have emerged as powerful methods for the asymmetric transfer hydrogenation of imines with the Hantzsch ester dihydropyridine **2** as the hydrogen source.[2–4] The imines, either preformed or made in situ[3,4] from ketones and aromatic amines, are protonated by a Brønsted acid like **1** and then reduced by hydrogen transfer from the Hantzsch ester (Scheme 1). Stereoselectivity is induced by using chiral Brønsted acids, which serve as chiral counteranions to the protonated imine.[5] High yields and enantioselectivities were achieved for a series of α-branched arylalkyl- and dialkylmethylamines with catalyst loadings as low as 1 mol%. A disadvantage of these transfer-hydrogenation reactions in comparison with transition-metal-catalyzed reductions using hydrogen is the poorer atom economy.




***Scheme 1.*** Organocatalytic Brønsted acid catalyzed asymmetric reductive amination using Hantzsch ester **2** as the hydrogen source.

Transition-metal complexes can be used to hydrogenate with perfect atom economy using elemental hydrogen, but imines have been much less developed than ketones and olefins as substrates. Some progress has been made in the field recently by the development of chiral Ir catalysts for the asymmetric reduction of preformed cyclic and acyclic imines.[6] Acyclic arylalkyl or dialkyl imines were hydrogenated with high yields and stereoselectivities with Ir catalysts featuring a chiral chelating ligand as well as a chiral phosphate counteranion, both of which are required for achieving high stereoselectivity.[6b] Additionally, a catalytic amount of the corresponding chiral phosphoric acid was added to improve the yield. A disadvantage of these reactions is the additional synthetic step needed to preform the imines, but the direct asymmetric reductive amination of ketones using transition-metal catalysis also still suffers from limited substrate scope and performance.[7]

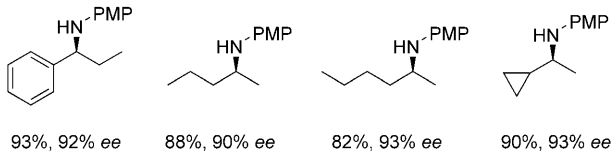
J. Xiao et al. have now reported a combination of these catalysis concepts. They used a transition-metal complex together with the Brønsted acid organocatalyst **1** to facilitate the direct reductive amination of ketones with anilines using hydrogen (Scheme 2).[8] The concept borrows two features from each field: a chiral phosphate counteranion and a chiral ligand on the metal to achieve high stereoselectivity, a chiral Brønsted acid **1** to mediate the in situ formation of protonated imines from ketones and primary amines, and a transition metal for the activation of $H_2$.




***Scheme 2.*** Combined transition metal and Brønsted acid catalyzed asymmetric reductive amination utilizing hydrogen. Cp* = 1,2,3,4,5-pentamethyl cyclopentadienyl.

[*] Dr. M. Klussmann
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr (Germany)
Fax: (+49) 208-306-2980
E-mail: klusi@mpi-muelheim.mpg.de
Homepage: http://www.kofo.mpg.de/klussmann/

The scope, yield, and stereoselectivity of the method are greatly improved over existing metal-catalyzed reductive aminations. Not only aryl methyl ketones but also more challenging substrates like aryl ethyl and dialkyl ketones can be used successfully (Scheme 3). For the latter substrates, a modification of the sulfonyl group of the diamine ligand was necessary to maintain high stereoselectivities. Yields of these




93%, 92% *ee* 88%, 90% *ee* 82%, 93% *ee* 90%, 93% *ee*

***Scheme 3.*** List of selected products along with their yields and enantioselectivities. PMP = *para*-methoxyphenyl.

reactions are consistently high with enantioselectivities ranging from 81 to 97%. Interestingly, in the case of dialkyl ketones, no additional Brønsted acid catalyst was required.

It will be interesting to see whether future developments of this strategy will expand the substrate scope to other synthetically interesting compounds like diaryl ketones or keto esters or to amination components like *N*-benzyl amines or ammonia.

Some interesting questions regarding the mechanism remain to be addressed. The phosphoric acid is suggested to fulfill three roles: as a Brønsted acid it catalyzes the formation of the imine, and it also serves as a chiral counteranion to the iridium catalyst and to the iminium ion. The results reported by Xiao and co-workers show that the interplay of the chiral diamine ligand and the phosphate counteranion in the iridium complex is crucial for achieving high stereoselectivities.[6b,8] But the reports on organocatalytic reductive aminations and imine reductions show that one chiral counteranion as a single source of chirality is sufficient to achieve high *ee* values in the product.[2–4] It seems therefore possible to design a combined transition metal/Brønsted acid catalyst containing one chiral and one achiral entity that would be even simpler and cheaper to use. On the other hand, the combination of two chiral catalysts in the system of Xiao et al. might actually be responsible for the consistently high *ee* values achieved with a broad substrate scope.

The report by Xiao et al. gives another example of how developments in metal and organocatalysis can be combined to make progress in the field of catalysis in general.[9] Such developments show that the field of organocatalysis has matured in just a few years to a point where it no longer appears exotic but has earned its place in the general repertoire of asymmetric catalysis. The future will certainly see more such combinations that cross the borders between two disciplines.

Received: July 9, 2009
Published online: August 28, 2009

[1] a) V. I. Tararov, A. Börner, *Synlett* **2005**, 203–211; b) R. P. Tripathi, S. S. Verma, J. Pandey, V. K. Tiwari, *Curr. Org. Chem.* **2008**, *12*, 1093–1115.
[2] M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781–3783.
[3] S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem.* **2005**, *117*, 7590–7593; *Angew. Chem. Int. Ed.* **2005**, *44*, 7424–7427.
[4] R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84–86.
[5] For asymmetric Brønsted acid catalysis and counteranion effects in organo- and metal catalysis, see for example: a) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758; b) S. Mayer, B. List, *Angew. Chem.* **2006**, *118*, 4299–4301; *Angew. Chem. Int. Ed.* **2006**, *45*, 4193–4195; c) G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496–499; d) S. Mukherjee, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 11336–11337, and references therein.
[6] For recent examples, see: a) C. Li, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 13208–13209; b) C. Li, C. Wang, B. Villa-Marcos, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 14450–14451; c) G. Hou, F. Gosselin, W. Li, J. C. McWilliams, Y. Sun, M. Weisel, P. D. O'Shea, C.-y. Chen, I. W. Davies, X. Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 9882–9883, and references therein.
[7] For a recent example, see: L. Rubio-Pérez, F. J. Pérez-Flores, P. Sharma, L. Velasco, A. Cabrera, *Org. Lett.* **2009**, *11*, 265–268, and references therein.
[8] C. Li, B. Villa-Marcos, J. Xiao, *J. Am. Chem. Soc.* **2009**, *131*, 6967–6969.
[9] Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745–2755.