VIP Homogeneous Catalysis

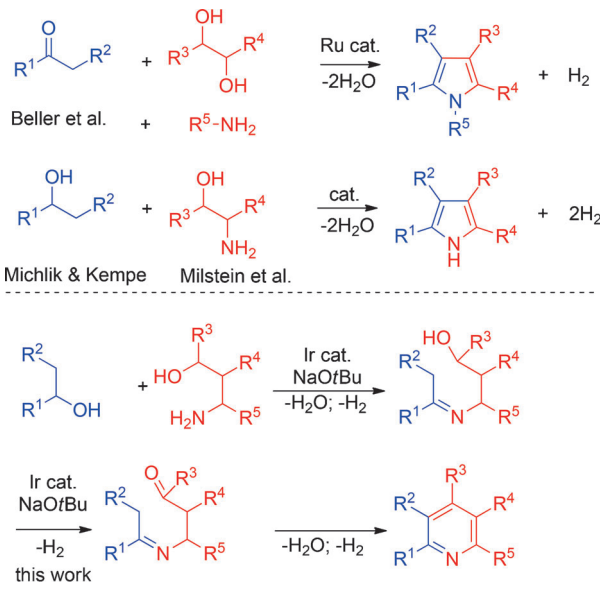
DOI: 10.1002/anie.201301919

Regioselectively Functionalized Pyridines from Sustainable Resources**

*Stefan Michlik and Rhett Kempe**

Pyridines play an important role in the life sciences.[1] For instance, many herbicides and fungicides as well as many thousands of drugs contain the pyridine motif.[1c,2] Furthermore, polymers based on pyridines have diverse applications in the chemical industry.[3,4] Considering the importance of the pyridine moiety and the required substitution of petroleum/coal-based chemistry, a pyridine synthesis from renewable resources would be an attractive goal. Such a synthesis would find significantly faster acceptance if it provides access to diversely functionalized pyridines that are difficult to prepare by existing methods. Recently, the Beller group,[5a] the Milstein group,[6a] and our group[6b] have developed sustainable catalytic syntheses of pyrroles based on dehydrogenative condensation reactions (Scheme 1, top).

These syntheses are based on observations made by the research groups of Ishii and Crabtree.[7] Ishii and co-workers reacted 2-aminoethanol or 2-(methylamino)ethanol with an excess of propiophenone in the presence of a catalyst and a base and observed the formation of two pyrrole derivatives.[7a] Propiophenone serves as both the substrate and as an H_2 acceptor. Considering our pyrrole synthesis (Scheme 1, middle) and using 1,3-amino alcohols (instead of 1,2-amino alcohols), we propose a new [2+4] pyridine synthesis which we present here. A primary or secondary alcohol can act as a C_2 building block that reacts in the initial step with a 1,3-amino alcohol in an iridium-catalyzed dehydrogenative Schiff-base reaction (Scheme 1, bottom).[8] Mechanistic studies indicate that the oxidation of the amino alcohols is significantly slower and this enables the selective formation of the imine (Figures 1 and 2 in the Supporting Information). Subsequently, the remaining hydroxyalkyl group is dehydrogenated and the olefin forms through intramolecular ring closure and elimination of water.[9] Finally, aromatization by liberation of H_2 takes place (Figures 3 and 4 in the Supporting Information). In the course of the reaction, two equivalents of water and three equivalents of hydrogen gas are eliminated (Scheme 1). The choice of the alcohol substrate determines the substituents in positions 2 and 3 of the pyridine ring; positions 4–6 are determined by the substitution pattern of the amino alcohol. In this way diversely substituted pyridine derivatives are accessible regioselectively.



Scheme 1. Known relevant catalytic pyrrole syntheses and the pyridine synthesis presented here.

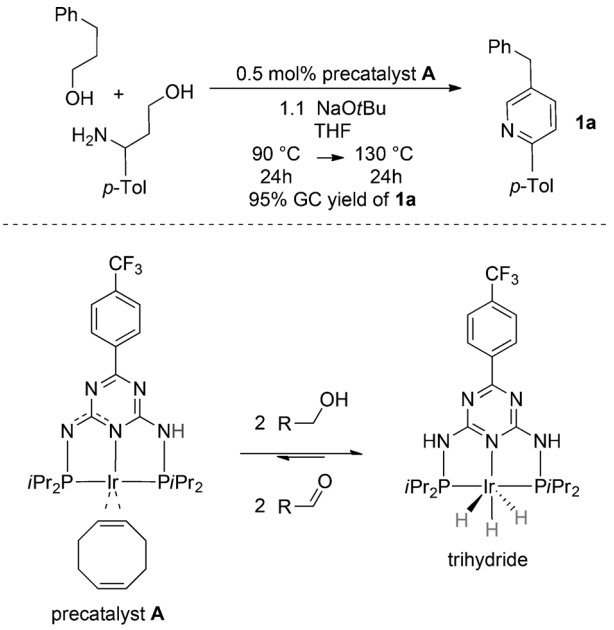
The reaction of 3-phenylpropanol with 3-amino-3-*p*-tolylpropan-1-ol was investigated (Scheme 2, top) to find suitable conditions for the new pyridine synthesis. In studies toward catalyst optimization we started with iridium complexes stabilized by P,N ligands that can use aliphatic amino alcohols as alkylating agents without alkylating the N atom.[6b,10] This type of selectivity is a prerequisite for the catalyst in our pyridine synthesis since amino alcohols are substrates. Precatalyst **A** gave the highest GC yield in the screening reaction (Scheme 2, top). Details of the syntheses of the ligand and complex are given in the Supporting Information.

After optimizing the reaction conditions (solvent, base, and temperature, for details see the Supporting Information) we observed 95 % yield of **1a** (Scheme 2, top) in the reaction with 0.5 mol % of precatalyst **A**. The yields obtained after a reaction time of 24 h at 90 °C can be improved further by subjecting the reaction mixture to further 24 h at 130 °C. Besides full conversion of the amino alcohol and formation of a considerable amount of the desired pyridine, a substantial amount of a noncyclized imino/ketone intermediate (Scheme 1, bottom left) is present after the first 24 h. The catalyst resting state was found to be an iridium(III) trihydride complex (Scheme 2, bottom right). It can be made by reacting precatalyst **A** with, for instance, alcohols at temperatures above 70 °C or with H_2 (Scheme 2, bottom).

[*] S. Michlik, Prof. Dr. R. Kempe
Lehrstuhl Anorganische Chemie II
Universität Bayreuth
95440 Bayreuth (Germany)
E-mail: kempe@uni-bayreuth.de

[**] This project was supported by the Deutsche Forschungsgemeinschaft (DFG KE 756/23-1).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201301919.

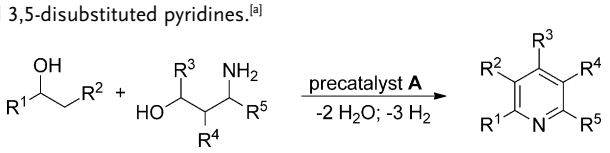


Scheme 2. Optimized reaction conditions (top) and formation of the catalyst resting state (trihydride, bottom right).

The trihydride is present during the entire reaction as verified by NMR spectroscopy and no noticeable decomposition was observed. For the pyridine syntheses precatalyst **A** was used since the trihydride is extremely air sensitive and much more difficult to handle. The trihydride is quantitatively formed from precatalyst **A** in less than 30 min under catalytic conditions. After optimization of the reaction conditions we explored the synthetic scope of the reaction. By using different 1,3-amino alcohols as well as primary or the secondary alcohols, products with diverse functional groups can prepared. Various substituted 1,3-amino alcohols were reacted with 3-phenylpropanol, and aryl- as well as alkyl-substituted pyridines (**1a–f**, Table 1) could be obtained in mainly very good yields. Subsequently, we used diverse primary alcohols. These products (**1g–o**, Table 1) carry a tolyl substituent in position 2 of the pyridine ring which was brought in by the amino alcohol. Nine different primary alcohols were used, of which seven gave rise to new pyridine derivatives (shown in gray in Table 1). The low yield for products **1j**,**k** (Table 1) can be explained by the formation of *p*-tolyl-(6-*p*-tolylpyridin-3-yl)methanamine (**1o**, Table 1) as a by-product arising from self-condensation of two molecules of the amino alcohol. This side reaction can be "favored" (35% yield) when no other alcohol is added, leading to 5-(aminomethyl)pyridines (**1o**, Table 1).

We could show that the new pyridine synthesis works well with primary alcohols. Thus, an efficient route to 2,5-disubstituted pyridines was achieved. If one uses 1-substituted ethanols, 2,6-disubstituted pyridines can be prepared, and two examples were synthesized (**1q**,**r** Table 1). However, lower yields of isolated product were observed since the corresponding cyclic imines or tetrahydropyridines were formed in a side reaction. Since positions 3–5 of the pyridine ring are unprotected, the C–C bond formed by ring closure undergoes facile hydrogenation and hydrogen is not liberated. Furthermore, 2,4-disubstituted pyridines (**1p**, Table 1) are accessible. If the appropriately substituted 1,3-amino alcohols were used, also 3,5-disubstituted pyridines, which are accessible usually only under extreme reaction conditions by using electrophilic substitution reactions, could be synthesized easily (**1s**, Table 1). Since this synthesis tolerates many functional groups such as chlorides, amines, ethers, olefins, heteroarenes, and organometallic moieties, broad application is expected. The methodology is especially efficient regarding the forma-

Table 1: Synthesized 2,4-, 2,5-, 2,6-, and 3,5-disubstituted pyridines.[a]



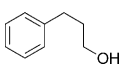
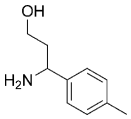
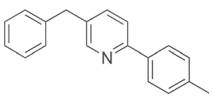
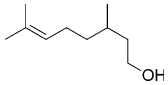
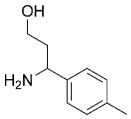
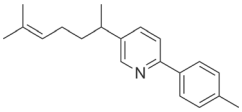
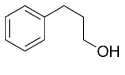
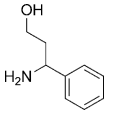
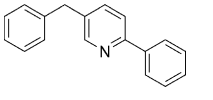
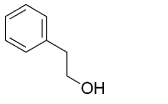
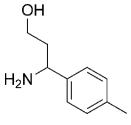
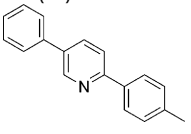
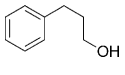
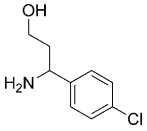
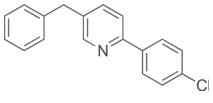
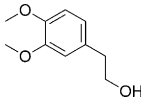
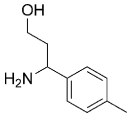
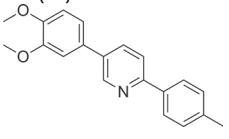
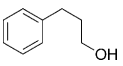
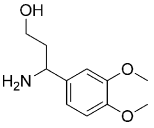
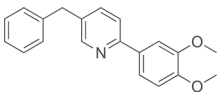
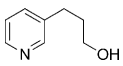
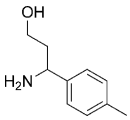
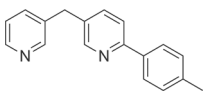
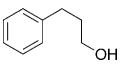
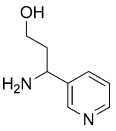
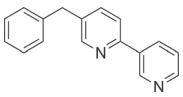
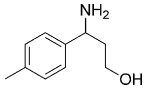
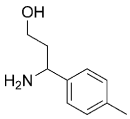
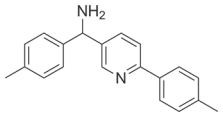
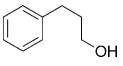
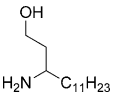
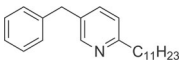
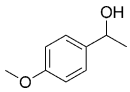
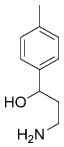
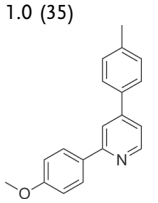
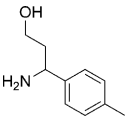
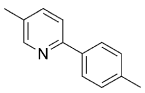
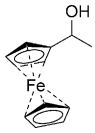
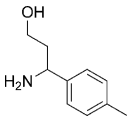
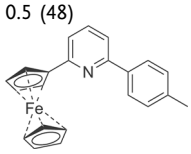
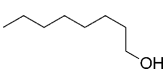
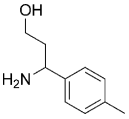
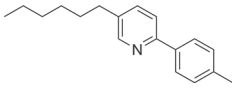
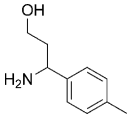
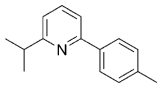
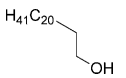
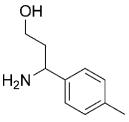
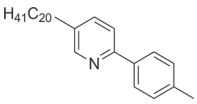
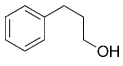
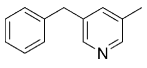
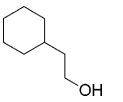
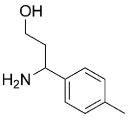
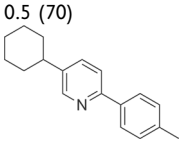
Prod.	Alcohol	Amino alcohol	Product[b] precat. **A** [mol%] (yield [%])	Prod.	Alcohol	Amino alcohol	Product[b] precat. **A** [mol%] (yield [%])
1a			 0.5 (90)	**1k**			 0.5 (63)
1b			 0.5 (86)	**1l**			 0.3 (70)
1c				**1m**			

Table 1: (Continued)

Prod.	Alcohol	Amino alcohol	Product[b] precat. **A** [mol%] (yield [%])	Prod.	Alcohol	Amino alcohol	Product[b] precat. **A** [mol%] (yield [%])
1d			1.5 (86) 	**1n**			1.5 (93) 
1e			0.5 (92) 	**1o**			1.5 (94) 
1f			1.5 (61) 	**1p**			1.0 (35) 
1g			0.5 (92) 	**1q**			0.5 (48) 
1h			1.0 (85) 	**1r**			0.05 (54[c]) 
1i			0.5 (94) 	**1s**			0.5 (57[c]) 
1j			0.5 (70) 				1.5 (61)
			1.0 (45)				

[a] Reaction conditions: 12.0 mmol alcohol, 3.0 mmol amino alcohol, 3.3 mmol NaO*t*Bu, 10.0 mL THF, precatalyst **A**, 24 h/90 °C→24 h/130 °C; the pyridine products in gray were previously unknown. [b] Yield of isolated product. [c] 24 h/90 °C.

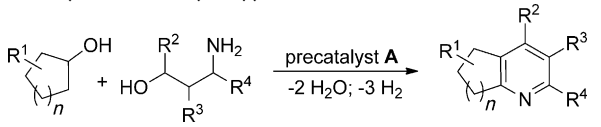
tion of unsymmetrically substituted pyridines. Furthermore, the fact that many of these pyridines were prepared here for the first time (compounds in gray in Table 1) indicates that our method significantly extends the scope of existing pyridine syntheses.

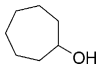
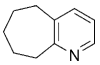
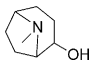
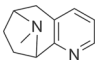
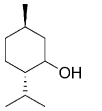
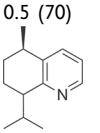
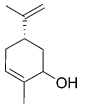
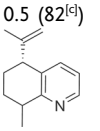
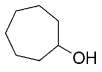
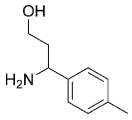
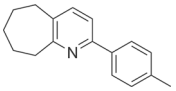
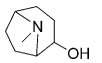
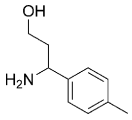
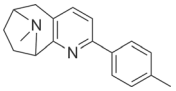
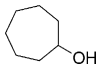
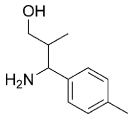
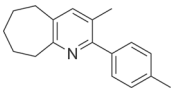
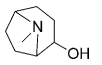
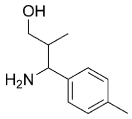
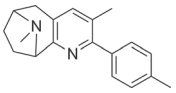
Finally, we became interested in the formation of bicyclic pyridines starting from cyclic alcohols. The optimization of the reaction conditions was carried out on the model system 3-aminopropan-1-ol/cycloheptanol. By using the optimized conditions, bicyclic pyridines were synthesized, including highly substituted examples (**2g**,**h**; Table 2).

Furthermore, bicyclic pyridines that bear chiral substituents are accessible starting from inexpensive chiral natural products (**2c**,**d**; Table 2). The pyridine synthesis introduced here is sustainable. The hydrogen gas formed is not just nontoxic but is a very useful by-product. Furthermore, the two substrates, the alcohols and the 1,3-amino alcohols, can be obtained from renewable resources or waste feedstock. Lignocellulosic materials are available in huge amounts,[11] and they are indigestible and can be (partially) processed to alcohols or polyoles.[12] The 1,3-amino alcohols can be made from 1,3-diols and ammonia using the borrowing-hydrogen or hydrogen-autotransfer methodology;[13,14] alternatively, they are also accessible from malonic acid, alcohols/aldehydes, and ammonia.[15]

In summary, we have described a new catalytic pyridine synthesis. It provides access to a variety of regioselectively substituted pyridines, including challenging unsymmetrically

Table 2: Synthesis of bicyclic pyridines.[a]



Prod.	Alcohol	Amino alcohol	Product[b] precat. **A** [mol%] (yield [%])
2a			 0.5 (91)
2b			 0.5 (70)
2c			 0.5 (82[c])
2d			 1.0 (76[c])
2e			 0.5 (96)
2f			 0.5 (84)
2g			 1.0 (80)
2h			 1.0 (84)

[a] Reaction conditions: 12.0 mmol cyclic alcohol, 3.0 mmol amino alcohol, 3.3 mmol NaO*t*Bu, 10.0 mL THF, precatalyst **A**, 24 h/90 °C; the pyridine products in gray were previously unknown. [b] Yield of isolated product. [c] 12.0 mmol cyclic alcohol.

substituted pyridines. A broad spectrum of functional groups is tolerated. In the dehydrogenative condensation steps three equivalents of H_2 are liberated per formed pyridine. The required starting materials can be obtained from renewable resources with ammonia serving as the nitrogen source. This synthesis method is part of what can be called "new (catalytic) chemistry", which provides access to virtually any important organic compound from renewable resources. The broad scope of our pyridine synthesis could lead to the rapid advance of this reaction and thus accelerate the acceptance of the "new chemistry".

Received: March 7, 2013
Published online: April 29, 2013

Keywords: alcohols · dehydrogenation · iridium · pyridine · sustainable resources

[1] a) M. D. Hill, *Chem. Eur. J.* **2010**, *16*, 12052 – 12062; b) G. Jones, *Comprehensive Heterocyclic Chemistry II*, *Vol. 5* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven, A. McKillop), Pergamon, Oxford, **1996**, pp. 167 – 243; c) G. D. Henry, *Tetrahedron* **2004**, *60*, 6043 – 6060; d) J. A. Joule, K. Mills, *Heterocyclic Chemistry*, *4th ed.*, Blackwell Science, Cambridge, **2000**, p. 63 – 120; e) J. P. Michael, *Nat. Prod. Rep.* **2005**, *22*, 627 – 646; f) *Pharmaceutical Chemistry*, *Drug Synthesis*, *Vol. 1* (Eds.: H. J. Roth, A. Kleemann), Prentice Hall Europe, London, **1988**.

[2] MDL Drug Data Registry (MDDR), by MDL Informations Systems, Inc; San Leandro, California, USA.

[3] A. Kirschning, H. Monenschein, R. Wittenberg, *Angew. Chem.* **2001**, *113*, 670 – 701; *Angew. Chem. Int. Ed.* **2001**, *40*, 650 – 679.

[4] J. M. J. Fréchet, M. V. de Meftahi, *Br. Polym. J.* **1984**, *16*, 193 – 198.

[5] a) M. Zhang, H. Neumann, M. Beller, *Angew. Chem.* **2013**, *125*, 625 – 629; *Angew. Chem. Int. Ed.* **2013**, *52*, 597 – 601; b) after submission of our study: K. Iida, T. Miura, J. Ando, S. Saito, *Org. Lett.* **2013**, *15*, 1436 – 1439.

[6] a) D. Srimani, Y. Ben-David, D. Milstein, *Angew. Chem.* **2013**, *125*, 4104 – 4107; *Angew. Chem. Int. Ed.* **2013**, *52*, 4012 – 4015; b) S. Michlik, R. Kempe, *Nat. Chem.* **2013**, *5*, 140 – 144.

[7] a) K. Taguchi, S. Sakaguchi, Y. Ishii, *Tetrahedron Lett.* **2005**, *46*, 4539 – 4542; b) N. Schley, G. Dobereiner, R. H. Crabtree, *Organometallics*, **2011**, *30*, 4174 – 4179.

[8] B. Gnanaprakasam, J. Zhang, D. Milstein, *Angew. Chem.* **2010**, *122*, 1510 – 1513; *Angew. Chem. Int. Ed.* **2010**, *49*, 1468 – 1471.

[9] B. Blank, R. Kempe, *J. Am. Chem. Soc.* **2010**, *132*, 924 – 925.

[10] a) B. Blank, S. Michlik, R. Kempe, *Adv. Synth. Catal.* **2009**, *351*, 2903 – 2911; b) S. Michlik, T. Hille, R. Kempe, *Adv. Synth. Catal.* **2012**, *354*, 847 – 862.

[11] C. O. Tuck, E. Pérez, I. T. Horváth, R. A. Sheldon, M. Poliakoff, *Science* **2012**, *337*, 695 – 699.

[12] T. P. Vispute, H. Zhang, A. Sanna, R. Xiao, G. W. Huber, *Science* **2010**, *330*, 1222 – 1227.

[13] G. Walther, J. Deutsch, A. Martin, F.-E. Baumann, D. Fridag, R. Franke, A. Köckritz, *ChemSusChem* **2011**, *4*, 1052 – 1054.

[14] S. Imm, S. Bähn, M. Zhang, L. Neubert, H. Neumann, F. Klasovsky, J. Pfeffer, T. Haas, M. Beller, *Angew. Chem.* **2011**, *123*, 7741 – 7745; *Angew. Chem. Int. Ed.* **2011**, *50*, 7599 – 7603.

[15] C. Y. K. Tan, D. F. Weaver, *Tetrahedron* **2002**, *58*, 7449 – 7461.

