Angewandte Highlights

Sustainable Chemistry

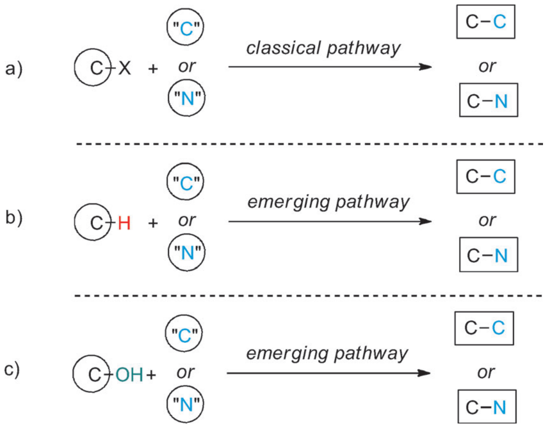
DOI: 10.1002/anie.201303015

More Sustainable Formation of C–N and C–C Bonds for the Synthesis of N-Heterocycles**

Johannes Schranck, Anis Tlili, and Matthias Beller*

C–C bonds · C–N bonds · heterocycles ·
homogeneous catalysis · sustainable chemistry

Combining the selective and efficient construction of carbon–carbon and carbon–nitrogen bonds is of significant interest to organic synthesis. The resulting nitrogen-containing products find a plethora of applications in life and material sciences. The classical concept to construct such bonds is based on nucleophilic substitutions or transition-metal-catalyzed reactions of suitably activated substrates. Thus, in general a leaving group is required and often halides or pseudo-halides are used in this context. Without doubt, these reactions have proved their efficiency in numerous syntheses; however, they suffer from several shortcomings. In particular, the generation of considerable amounts of waste and the required multistep prefunctionalization of the starting materials are drawbacks (Scheme 1 a).[1]

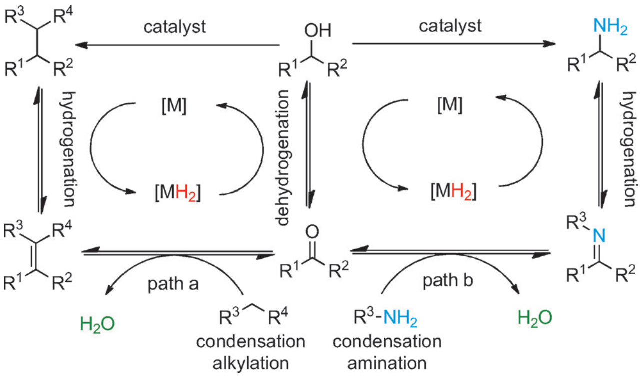


Scheme 1. Concepts for the construction of C–C or C–N bonds.

To avoid these disadvantages, the selective functionalization of inert C–H bonds has become a "hot topic" in catalysis (Scheme 1 b).[2] Even though significant progress has been made in this field, challenging problems remain to be solved such as the activation of less acidic C–H bonds, the dependency on directing groups, and the need for more efficient catalysts in terms of catalyst turnover number (TON) and turnover frequency (TOF).

Apart from the activation of C–X compounds (X = halide or H), the use of hydroxy groups in alcohols to form new C–C or C–N bonds offers more benign opportunities (Scheme 1 c). With respect to sustainability, alcohols and polyols represent attractive renewable resources, since a number of them constitute major natural products or can easily be derived from biomass.[3] A classic example of using alcohols for C–C bond formation is the Guerbet reaction in which primary alcohols are dehydrogenated at higher temperature and the resulting aldehydes undergo subsequent aldol condensation and hydrogenation to give the β-alkylated alcohol.[4] Although modern variants of this transformation exist, such reactions typically have to be performed under drastic conditions with low functional group tolerance. Complementary to the Guerbet reaction, the amination and the alkylation of alcohols can be realized by transition-metal catalysis with the so-called "borrowing hydrogen" methodology also known as "hydrogen auto-transfer" (Scheme 2, paths a and b).[5]

While in recent years elegant investigations have focused on the development of improved catalysts for the synthesis of aliphatic amines, most recently, interest has risen in using such methodologies to build up structurally more complex heterocycles. Currently, numerous heterocyclic compounds are available from fine chemical suppliers and their production on the ton scale contributes significantly to the waste generated by this industry. In this respect, the development



Scheme 2. Amination and alkylation of alcohols.

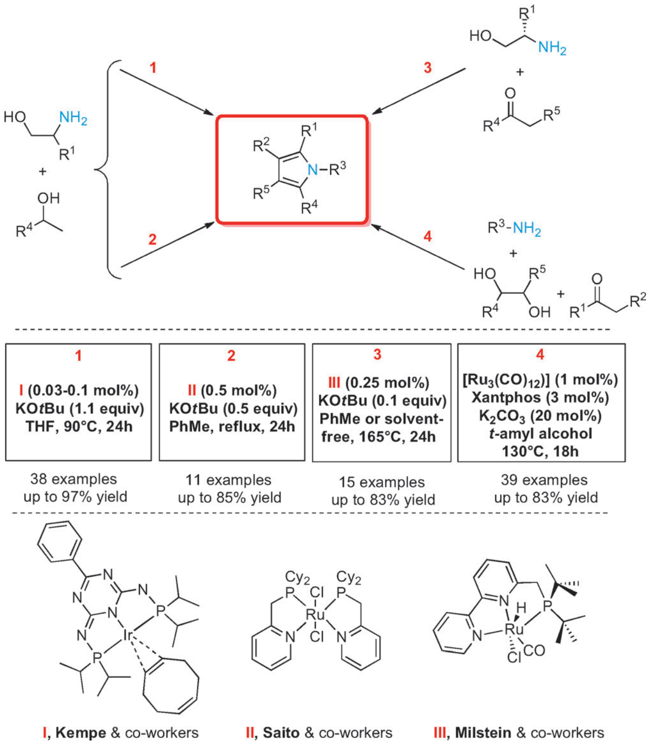
---

[*] J. Schranck, Dr. A. Tlili, Prof. Dr. M. Beller
Leibniz-Institut für Katalyse an der Universität Rostock
Albert-Einstein-Strasse 29a, 18059 Rostock (Germany)
E-mail: Matthias.Beller@catalysis.de
Homepage: http://www.catalysis.de

[**] We thank the State of Mecklenburg-Vorpommern and the Bundesministerium für Bildung und Forschung (BMBF) for financial support.

of efficient syntheses of biologically interesting pyrroles starting from 1,2-amino alcohols and alcohols or carbonyl compounds by the groups of Kempe, Milstein, and Saito are remarkable and are highlighted herein.

Notably, Kempe and Michlik first published well-defined PNP-type iridium-based complexes for an efficient synthesis of pyrroles through consecutive C-N and C−C bonds formation (Scheme 3, path 1).[6] Key to the success of this procedure are the selective iridium-catalyzed dehydrogenation and condensation of 1,2-amino alcohols and secondary alcohols in the presence of a slight excess of base (KO*t*Bu) under comparably mild reaction conditions. It is worth noting that remarkably low catalyst loadings are necessary (as low as 0.03 mol %) to obtain the desired products in good yields. In addition, the authors demonstrated that their procedure is also suitable for the synthesis of dipyrroles or amino pyrroles.



Scheme 3. More benign approaches for the synthesis of pyrroles and derivatives.

Shortly after, Milstein and co-workers published another pyrrole synthesis based on amino alcohols and secondary alcohols.[7] Their procedure makes use of discrete PNN-type ruthenium pincer complexes (0.5 mol %), which enable the use of substoichiometric (0.5 equiv) amounts of base to give the five-membered heterocycles in good to excellent yields (Scheme 3, path 3). Most recently, another well-defined PNNP-type ruthenium complex was reported by Saito and co-workers for related syntheses.[8] In the latter case pyrroles could be synthesized from 1,2-amino alcohols and ketones in moderate to very good yields at higher temperature (165 °C). In some cases, only a low amount (10 mol %) of base (KO*t*Bu) was necessary to achieve efficient dehydrogenation and condensation reactions (Scheme 3, path 2). In order to obtain more information concerning the possible reaction pathway, control experiments were carried out starting from a tertiary 1,2-amino alcohol in the presence of propiophenone. In doing so the α,β-unsaturated ketone was obtained as a major product. Thus, the authors suggested that the C−C bond formation takes place first followed by subsequent C−N bond formation and aromatization. For comparison it should also be noted that a related Ru-catalyzed three-component coupling protocol applying ketones, 1,2-diols, and amines was reported at the beginning of this year (Scheme 3, path 4).[9] Advantageously, all the procedures recently discovered for the synthesis of pyrroles produce only water and hydrogen as side products. In this regard, they represent excellent examples for atom-efficient and benign synthesis. Moreover, they allow for an easy and straightforward construction of multiple substituted heterocycles. For example, tetra- and pentasubstituted pyrroles can be assembled in one step from commercially available substrates. Notably, most of the products synthesized by the group of Kempe were new, demonstrating the synthetic usefulness of these methodologies. Furthermore, it is important to note that the concept of the above presented work is not limited to the preparation of pyrroles. In fact, most recently, Kempe as well as Milstein and their co-workers also succeeded in synthesizing a variety of pyridines and quinolines in the presence of their Ir or Ru complexes.[10] Here, the 1,2-amino alcohol substrate has to be simply replaced by a 1,3-amino alcohol. In summary, the novel procedures represent attractive alternatives to well-established methodologies for heterocycle synthesis and will remain an attractive field of research in the near future.

Received: April 11, 2013

---

[1] a) E.-i. Negishi, *Angew. Chem.* **2011**, *123*, 6870; *Angew. Chem. Int. Ed.* **2011**, *50*, 6738; b) A. Suzuki, *Angew. Chem.* **2011**, *123*, 6854; *Angew. Chem. Int. Ed.* **2011**, *50*, 6722; c) X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem.* **2010**, *122*, 9231; *Angew. Chem. Int. Ed.* **2010**, *49*, 9047; d) *Metal-Catalyzed Cross-Coupling Reactions*, *2nd ed.* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**.

[2] For selected recent general reviews on C−H activation see: a) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740; b) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; d) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315; e) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; f) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654; g) F. Collet, C. Lescot, P. Daubon, *Chem. Soc. Rev.* **2011**, *40*, 1926.

[3] a) A. Corma, S. Iborra, A. Velty, *Chem. Rev.* **2007**, *107*, 2411; b) J. Zakzeski, P. C. A. Bruijnincx, A. L. Jongerius, B. M. Weckhuysen, *Chem. Rev.* **2010**, *110*, 3552.

[4] a) O. Kose, S. Saito, *Org. Biomol. Chem.* **2010**, *8*, 896; b) P. Anbarasan, Z. C. Baer, S. Sreekumar, E. Gross, J. B. Binder, H. W. Blanch, D. S. Clark, F. D. Toste, *Nature* **2012**, *491*, 235.

[5] For reviews on "borrowing hydrogen" methodology, see: a) R. H. Crabtree, *Organometallics* **2011**, *30*, 17; b) G. E. Dober-

einer, R. H. Crabtree, *Chem. Rev.* **2010**, *110*, 681; c) T. D. Nixon, M. K. Whittlesey, J. M. J. Williams, *Dalton Trans.* **2009**, 753; d) G. W. Lamb, J. M. J. Williams, *Chim. Oggi* **2008**, *26*, 17; e) M. H. S. A. Hamid, P. A. Slatford, J. M. J. Williams, *Adv. Synth. Catal.* **2007**, *349*, 1555.

[6] S. Michlik, R. Kempe, *Nat. Chem.* **2013**, *5*, 140.

[7] D. Srimani, Y. B. David, D. Milstein, *Angew. Chem.* **2013**, *125*, 4104; *Angew. Chem. Int. Ed.* **2013**, *52*, 4012.

[8] K. Lida, T. Miura, J. Ando, S. Saito, *Org. Lett.* **2013**, *15*, 1463.

[9] M. Zhang, H. Neumann, M. Beller, *Angew. Chem.* **2013**, *125*, 625; *Angew. Chem. Int. Ed.* **2013**, *52*, 597.

[10] a) S. Michlik, R. Kempe, *Angew. Chem.* **2013**, *125*, 6450; *Angew. Chem. Int. Ed.* **2013**, *52*, 6326; b) D. Milstein, D. Srimani, Y. Ben-David, *Chem. Commun.* **2013**, DOI: 10.1039/C3CC43227K.
