Aziridine Synthesis

DOI: 10.1002/anie.201200966

New Catalysts for the Transition-Metal-Catalyzed Synthesis of Aziridines

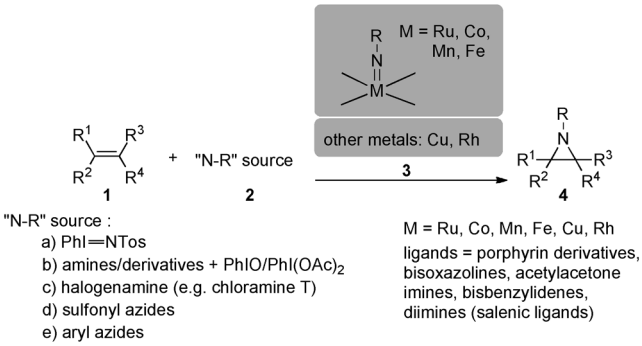
*Nicole Jung and Stefan Bräse**

azides · aziridine synthesis · homogeneous catalysis · porphyrinoids · transition metals

Aziridines are especially in demand because of their natural occurrence in diverse biologically active compounds and their manifold transformations in chemical reactions. The ring constraint renders them very reactive substances. In the presence of nucleophiles (N, O, S, C nucleophiles, and halides) they undergo ring-opening, they are used for [3+2] cycloadditions and [3+3] annulations, and they undergo ring extension in reactions with isocyanates and nitriles. Furthermore, aziridines can undergo rearrangements or they can be allylated, alkylated, or arylated through palladium catalysis, to mention only a few possible reactions.[1] Traditionally, aziridines are synthesized by the cyclization of amino alcohols (Wenker synthesis),[2] and by the reaction of imines with diazo-containing compounds (aza-Darzens reaction)[3] or sulfur ylides (Corey–Chaykovsky aziridination).[4,5]

As an alternative to these protocols more and more procedures have been presented over the past years for the (C_2+N_1) synthesis of aziridines through the reaction of alkenes with nitrenes (or their precursors). The possible variations of this nitrogen-transfer reaction differ in the choice of the nitrene source and the catalyst.[6] The transformation of alkenes with phenyl imino iodinanes as the nitrogen-transfer reagents under manganese and iron catalysis (Mn^{III} and Fe^{III} porphyrins) has been known for roughly 30 years and gives—depending on the catalyst—modest to very good yields.[7] Fundamental progress has been achieved through the use of copper catalysts by Evans et al.[8] and rhodium catalysts by Müller et al.[9] Beyond the imino iodinanes, halogen amines (more seldom) and sulfonyl azides or aryl azides can be used as the nitrogen source. Through the appropriate choice of the catalytic system, the 1,3-dipolar cycloaddition of azides can be suppressed and aziridines can be obtained in good to excellent yields according to Scheme 1.

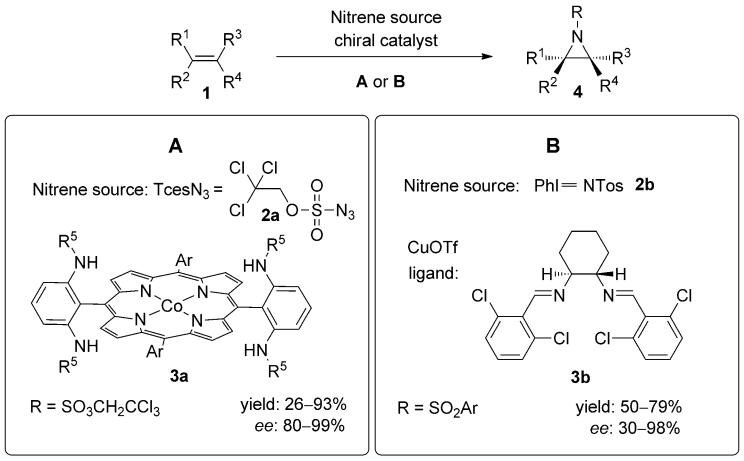
The use of azides instead of the often chosen imino iodinanes as the nitrene source has several advantages, especially because application of the latter is limited owing to the more laborious preparation, the formation of side products, and poor solubility. One disadvantage of using azides is that their activation often requires high temperatures or irradiation. To facilitate the elimination of nitrogen and the transfer of the nitrene under mild conditions, different catalysts for azide-mediated aziridine syntheses on the basis of iron, cobalt, manganese, copper, and ruthenium have been developed.[1a,5a,6a] Of these, outstanding Co^{II} and Cu^{I} catalysts (Scheme 2) have been used successfully to develop asymmetric syntheses of aziridines with good to excellent enantioselectivities.[10]



Scheme 1. Variations of the transition-metal-catalyzed synthesis of aziridines.

The hitherto known procedures can be applied to a broad spectrum of alkenes and—although the mechanism and the structure of the active species are not fully understood—excellent selectivities and yields of the desired aziridines have been achieved with a variety of studied catalysts. While the transition-metal-catalyzed syntheses of aziridines via sulfonyl azides (and their derivatives) as the N_1 sources are universally applied in many fields,[11] transformations of aryl azides have not been frequently described despite their many advantages.[12] The azides, which are used as starting materials, can be synthesized very easily and inexpensively and they allow for a wide diversity of substrates.[13] Through the direct introduction of the desired aryl residue (in comparison to sulfonyl azides) the more complex two-step variant of removal of the sulfonyl residue and introduction of necessary substituents can be circumvented. This advantage is of special interest when one considers the low stability of tosyl aziridines and the

[*] Prof. Dr. S. Bräse
Institut für Organische Chemie, KIT-Campus Süd
Fritz-Haber-Weg 6, 76131 Karlsruhe (Germany)
E-mail: braese@kit.edu
Dr. N. Jung
Institut für Toxikologie und Genetik (ITG)
ComPlat, KIT-Campus Nord
Hermann-von-Helmholtz Platz 1
76344 Eggenstein-Leopoldshafen (Germany)

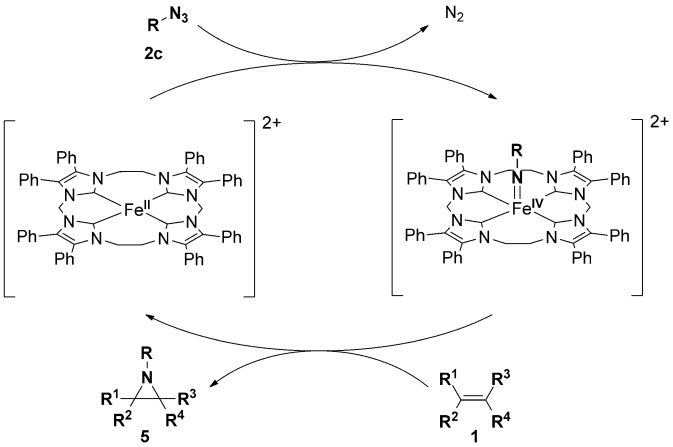


Scheme 2. Transition-metal-catalyzed, enantioselective synthesis of aziridines.

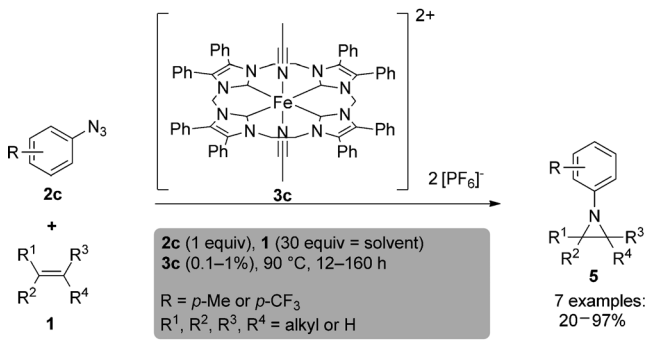
involved possibility of side-product formation. Some isolated protocols for the removal of the tosyl group under mild conditions have been reported in the past, but competing reactions (ring opening),[14] hampered the isolation of the products in acceptable yields. In the hitherto known conversions with aryl azides, nearly exclusively ruthenium porphyrin complexes have been used. These catalysts promote the reaction of selected alkenes under optimized conditions in excellent yields,[15] nevertheless the dependency on the alkene concentration and the inactivation of the catalyst through formation of triazoline side products limits their general application.[16]

A fundamental improvement in the transition-metal-catalyzed synthesis of aziridines has been reported recently by Jenkins and Cramer with their synthesis of a new octahedral iron(II) complex (**3c**; Scheme 3).[17] In the recently published work the advantages of the use of aryl azides are combined with a new, effective catalyst, whereby very good yields of aziridines can be achieved at low catalyst loadings (0.1–1 mol%). Problems that were mentioned in previous studies—caused by inactivation of the catalyst—seem to be solved by the new generation of catalysts: Jenkins and Cramer proved that the catalyst retained activity even after multiple applications.

For the synthesis of the new iron tetracarbene complex, the macrocyclic tetraimidazole was generated (($^{Me,Et}TC^{Ph}$)($I)_4$) in situ by deprotonation with lithium diisopropylamide and subsequent carbene ligation to the Fe^{II} salt in the presence of $TlPF_6$ in acetonitrile. The structure of the new catalyst was verified by X-ray analysis and allows, on the basis of comparable, known aziridine syntheses, the postulation of the mechanism shown in Scheme 4.



Scheme 4. Postulated mechanism for the Fe^{II}-catalyzed formation of aziridines.



Scheme 3. Aziridination of alkenes by azides through Fe^{II} catalysis.

The report by Jenkins and Cramer underlines new possibilities for the transition-metal-catalyzed synthesis of aziridines through the application of aryl azides in combination with new catalyst systems. This and related investigations in the recent past[18] give important mechanistic insights and evince the potential of the transition-metal catalysis for the synthesis of the synthetically and biologically important aziridines.

Received: March 19, 2012
Published online: May 8, 2012

[1] a) W. H. Pearson, B. W. Lian, S. C. Bergmeier in *Comprehensive Heterocyclic Chemistry II*, *Vol. 1A*, Elsevier, Amsterdam, **1996**, pp. 1 – 60; b) C. Schneider, *Angew. Chem.* **2009**, *121*, 2116 – 2118; *Angew. Chem. Int. Ed.* **2009**, *48*, 2082 – 2084.
[2] X. Y. Li, N. Chen, J. X. Xu, *Synthesis* **2010**, 3423 – 3428.
[3] S. E. Larson, G. L. Li, G. B. Rowland, D. Junge, R. C. Huang, H. L. Woodcock, J. C. Antilla, *Org. Lett.* **2011**, *13*, 2188 – 2191.
[4] J. J. Li, *Name Reactions in Heterocyclic Chemistry*, Wiley, Hoboken **2005**, pp. 2 – 14.
[5] a) A. Padwa, S. S. Murphree, *ARKIVOC* **2006**, 6 – 33; b) *Aziridines and Epoxides in Organic Synthesis* (Ed.: A. Yudin), Wiley-VCH, Weinheim, **2006**.
[6] a) M. M. Abu-Omar, *Dalton Trans.* **2011**, *40*, 3435 – 3444; b) J. W. W. Chang, T. M. U. Ton, P. W. H. Chan, *Chem. Rec.* **2011**, *11*, 331 – 357.
[7] D. Mansuy, J. P. Mahy, A. Dureault, G. Bedi, P. Battioni, *J. Chem. Soc. Chem. Commun.* **1984**, 1161 – 1163.
[8] D. A. Evans, M. M. Faul, M. T. Bilodeau, *J. Org. Chem.* **1991**, *56*, 6744 – 6746.
[9] P. Müller, C. Baud, Y. Jacquier, *Tetrahedron* **1996**, *52*, 1543 – 1548.
[10] a) V. Subbarayan, J. V. Ruppel, S. Zhu, J. A. Perman, X. P. Zhang, *Chem. Commun.* **2009**, 4266 – 4268; b) Z. Li, K. R. Conser, E. N. Jacobsen, *J. Am. Chem. Soc.* **1993**, *115*, 5326 – 5327.
[11] a) L. Liang, H. Lv, Y. Yu, P. Wang, J.-L. Zhang, *Dalton Trans.* **2012**, *41*, 1457 – 1460; b) Y. Li, J. Y. He, V. Khankhoje, E. Herdtweck, K. Kohler, O. Storcheva, M. Cokoja, F. E. Kuhn, *Dalton Trans.* **2011**, *40*, 5746 – 5754; c) J. V. Ruppel, J. E. Jones, C. A. Huff, R. M. Kamble, Y. Chen, X. P. Zhang, *Org. Lett.* **2008**, *10*, 1995 – 1998; d) J. E. Jones, J. V. Ruppel, G. Y. Gao, T. M. Moore, X. P. Zhang, *J. Org. Chem.* **2008**, *73*, 7260 – 7265; e) A. I. Olivos Suarez, H. Jiang, X. P. Zhang, B. B. de Bruin, *Dalton Trans.* **2011**, *40*, 5697 – 5705.
[12] S. Cenini, S. Tollari, A. Penoni, C. Cereda, *J. Mol. Catal. A* **1999**, *137*, 135 – 146.
[13] S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem.* **2005**, *117*, 5320 – 5374; *Angew. Chem. Int. Ed.* **2005**, *44*, 5188 – 5240.
[14] a) H. Senboku, K. Nakahara, T. Fukuhara, S. Hara, *Tetrahedron Lett.* **2010**, *51*, 435 – 438; b) E. Vedejs, S. Lin, *J. Org. Chem.* **1994**, *59*, 1602 – 1603.
[15] S. Fantauzzi, E. Gallo, A. Caselli, C. Piangiolino, F. Ragaini, S. Cenini, *Eur. J. Org. Chem.* **2007**, 6053 – 6059.
[16] S. Fantauzzi, E. Gallo, A. Caselli, F. Ragaini, P. Macchi, N. Casati, S. Cenini, *Organometallics* **2005**, *24*, 4710 – 4713.
[17] S. A. Cramer, D. M. Jenkins, *J. Am. Chem. Soc.* **2011**, *133*, 19342 – 19345.
[18] a) K. H. Hopmann, A. Ghosh, *ACS Catal.* **2011**, *1*, 597 – 600; b) R. Lorpitthaya, Z.-Z. Xie, K. B. Sophy, J.-L. Kuo, X.-W. Liu, *Chem. Eur. J.* **2010**, *16*, 588 – 594, S588/581-S588/525; c) P. Comba, C. Lang, d. L. C. Lopez, A. Muruganantham, G. Rajaraman, H. Wadepohl, M. Zajaczkowski, *Chem. Eur. J.* **2008**, *14*, 5313 – 5328; d) M. J. Zdilla, M. M. Abu-Omar, *J. Am. Chem. Soc.* **2006**, *128*, 16971 – 16979; e) G.-Y. Gao, J. E. Jones, R. Vyas, J. D. Harden, X. P. Zhang, *J. Org. Chem.* **2006**, *71*, 6655 – 6658; f) P. Comba, C. Haaf, A. Lienke, A. Muruganantham, H. Wadepohl, *Chem. Eur. J.* **2009**, *15*, 10880 – 10887.

Vacancy