Pure Appl. Chem., Vol. 82, No. 7, pp. 1529–1536, 2010.
doi:10.1351/PAC-CON-09-09-23

Combined coinage metal catalysis for the synthesis of bioactive molecules*

Norbert Krause‡, Özge Aksin-Artok, Viola Breker, Carl Deutsch, Birgit Gockel, Manojkumar Poonoth, Yoshinari Sawama, Yuka Sawama, Tao Sun, and Christian Winter

Department of Organic Chemistry, Dortmund University of Technology, Otto-Hahn-Strasse 6, D-44227 Dortmund, Germany

Abstract: The use of the coinage metals copper, silver, and gold enables an efficient and stereoselective assembly of bioactive heterocycles via allenic intermediates. The synthesis of functionalized allenes by S_N2'-substitution or S_N2'-reduction is mediated or catalyzed by copper, whereas silver and gold are the catalysts of choice for subsequent 5- or 6-*endo*-cyclizations. Overall, this sequence proceeds with efficient *center-to-axis-to-center chirality transfer.*

Keywords: allenes; copper catalysis; gold catalysis; heterocycles; silver catalysis.

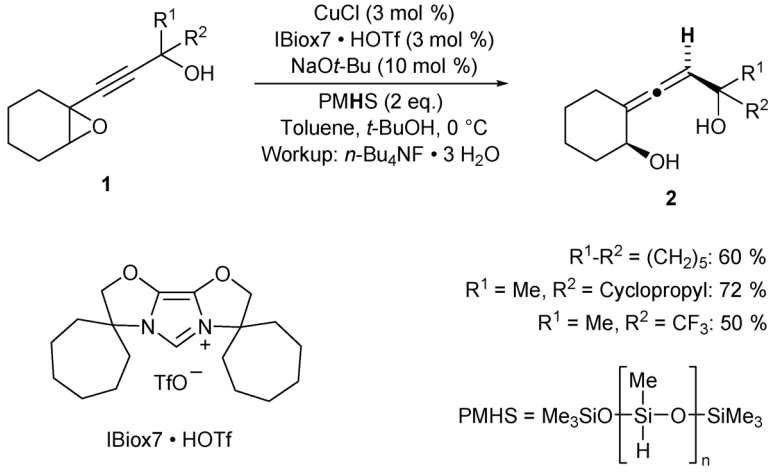
The *coinage metals* copper, silver, and gold belong to the seven metals of alchemy. They have been known to mankind for thousands of years, and gold may have been the first metal ever used by humans [1]. Whereas copper enjoys a rich history in organometallic chemistry and organic synthesis, starting with contributions by Kharasch and Gilman in the 1940s and 1950s [1,2], the usage of silver and gold in transition-metal catalysis commenced much more recently. In our research program, we find it particularly interesting to combine the (quite different) reactivities of the coinage metals in the stereoselective synthesis of bioactive target molecules [3]. Functionalized allenes are ideal substrates for these transformations since they are not only very reactive [4], but also inherently chiral [5].

Copper is the transition element of choice for the synthesis of functionalized allenes by S_N2'-substitution of propargyl electrophiles. Whereas various carbon nucleophiles can be introduced by this method, either using stoichiometric cuprates or copper catalysis together with Grignard reagents [6], the smallest nucleophile—the hydride ion—has so far only played a minor role in this chemistry. Recently, we have established a copper-catalyzed S_N2'-reduction of propargyl oxiranes **1** which provides an efficient route to α-hydroxyallenes of the type **2** (Scheme 1) [7]. Key to success is the stabilization of the catalytically active copper hydride species (formed in situ from CuCl and the stoichiometric hydride source polymethylhydridosiloxane [PMHS]) by an *N*-heterocyclic carbene (e.g., IBiox7). This transformation proceeds with high *anti*-stereoselectivity by *center-to-axis chirality transfer* and is compatible with various functional groups (alcohols, esters, ethers, etc.). Extension to propargyl carbonates [8] has broadened the range of allenes available by the method and offers advantages with respect to stereoselectivity and substrate reactivity.

---

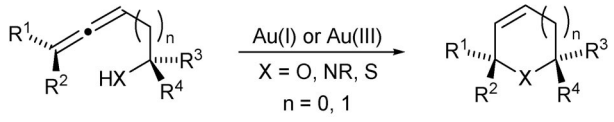
*Paper based on a presentation at the 15th International Conference on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-15), 26–31 July 2009, Glasgow, UK. Other presentations are published in this issue, pp. 1353–1568.

‡Corresponding author



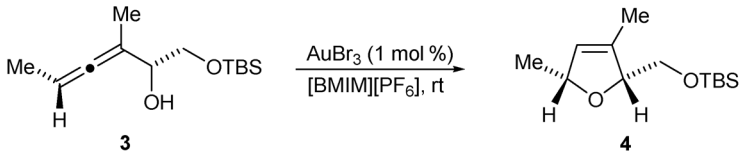
Scheme 1 Copper-catalyzed S_N2'-reduction of propargyl oxiranes **1**.

α-Hydroxyallenes can be easily converted into the corresponding amino- or thioallenes by Mitsunobu reaction [3]. When exposed to silver [9] or gold salts [3,10], these functionalized allenes (as well as the corresponding substrates bearing a nucleophilic group in β-position) undergo a highly regio- and stereoselective *endo*-cycloisomerization to afford chiral five- or six-membered heterocycles (Scheme 2). In most cases, gold catalysts are more reactive than their silver counterparts; hence, stoichiometric or substoichiometric amounts of the latter are often necessary in order to achieve full conversion. Whereas alkyl-substituted allenes react with complete *axis-to-center chirality transfer* [3,10,11], substrates bearing phenyl or electron-rich aryl groups are prone to epimerization when treated with gold(I) or gold(III) salts. This undesired process probably occurs via zwitterionic intermediates and can be prevented by modulating the Lewis acidity of the gold catalyst [3,11].

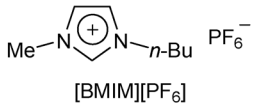


Scheme 2 Gold-catalyzed *endo*-cycloisomerization of functionalized allenes.

An important task for the future development of preparative chemistry is the improvement of sustainability. In transition-metal catalysis, this involves decrease of the catalyst loading, recycling of the catalyst, and use of environmentally friendly reaction media. We have recently shown that gold-catalyzed *endo*-cycloisomerizations of functionalized allenes can be performed in water [12] as well as in ionic liquids [13]. In the latter case, $AuBr_3$ in the imidazolium-derived medium [BMIM][PF_6] gives the best results (Scheme 3). This catalyst system is not only stable to water and air, but can also be recycled easily without loss of efficiency. For example, the yield of 2,5-dihydrofuran **4** formed by cyclization of α-hydroxyallene **3** remains unchanged after five runs. Interestingly, the reactivity of the catalyst decreases after the first run, but is constant after that. Over these five runs, only 0.03 % of the original catalyst loading is lost during extraction of the product. This almost negligible leaching makes the method attractive for the synthesis of pharmacologically active target molecules and indicates that the solution of $AuBr_3$ in [BMIM][PF_6] is potentially recyclable several thousand times.



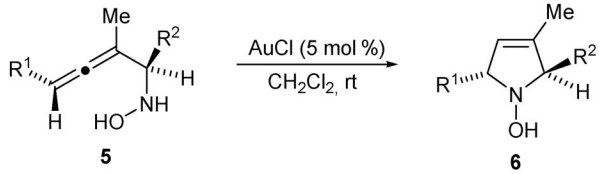
Run	Time	Yield (%)
1	10 min	84
2	3 h	74
3	3 h	81
4	3 h	84
5	3 h	84



[BMIM][PF_6]

Scheme 3 Gold-catalyzed cyclization of α-hydroxyallene **3** in the ionic liquid [BMIM][PF_6].

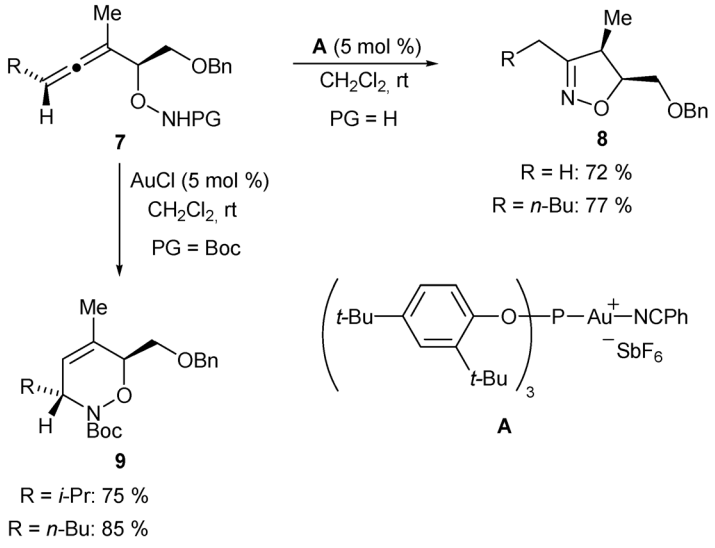
In order to broaden the scope of the gold-catalyzed allene cyclization, we have recently applied the method to substrates containing two adjacent allenic systems or heteroatoms. Allenic hydroxylamine derivatives proved to be particularly interesting substrates since three different chiral heterocycles can be obtained with high regio- and stereoselectivity, depending on the starting material, the gold precatalyst, and the protecting group at nitrogen [14]. In all cases, the nitrogen atom acts as the nucleophile and attacks the allene in a 5- or 6-*endo*-cyclization. Thus, *N*-hydroxy-α-aminoallenes **5** afford *N*-hydroxypyrrolines **6** with complete *axis-to-center chirality transfer* in the presence of 5 mol % AuCl (Scheme 4).



R^1 = *n*-Bu, R^2 = CH_2OBn: 80 %
R^1 = Ph, R^2 = CH_2OBn: 73 %
R^1 = *n*-Bu, R^2 = CH_2OH: 67 %

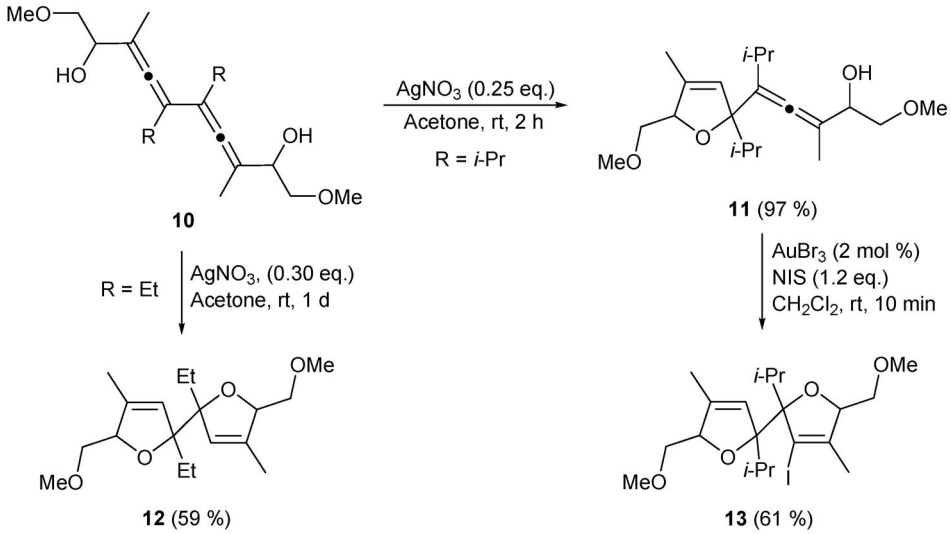
Scheme 4 Gold-catalyzed cycloisomerization of *N*-hydroxy-α-aminoallenes **5** to *N*-hydroxypyrrolines **6**.

Under these conditions, the allenic hydroxylamine ethers **7** with exchanged positions of the heteroatoms afford mixtures of 4,5-dihydroisoxazoles and 3,6-dihydro-1,2-oxazines. The regioselectivity can be shifted in favor of the isoxazoles **8** by using the cationic gold(I) complexes Ph_3PAuBF_4 or **A** (Scheme 5) [14]. In contrast to this, a selective 6-*endo*-cyclization to the oxazines **9** is possible by treatment of the *N*-Boc-protected hydroxylamine ethers with gold(I) chloride. Overall, this method is particularly versatile because the precursors **5** and **7** of the three heterocycles **6**, **8**, and **9** are all obtained in a stereoselective manner by Mitsunobu reaction from the same α-hydroxyallenes.



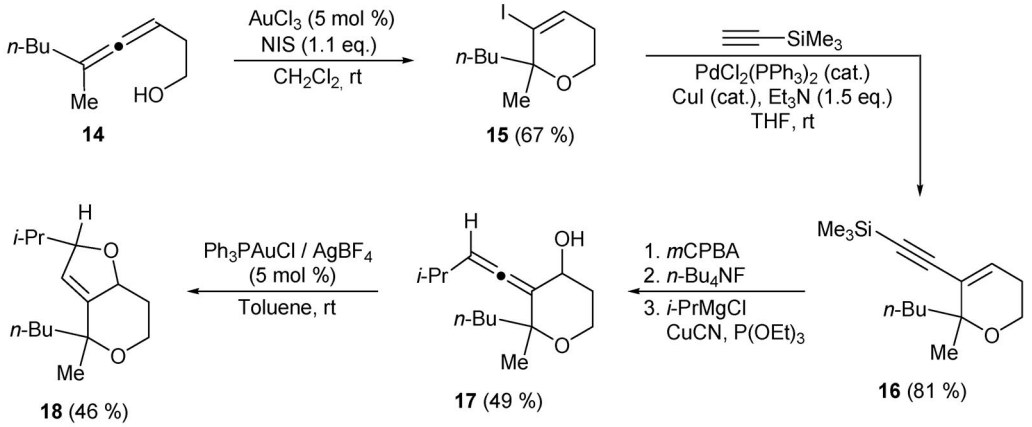
Scheme 5 Gold-catalyzed cycloisomerization of allenic hydroxylamine ethers **7**.

Conjugated bis(α-hydroxyallenes) **10** represent another intriguing substrate class for coinage metal catalysis. Like their "simple" counterparts (e.g., **3**), they are accessible by copper-mediated S_N2'-substitution of bis(propargyloxiranes) [15]. Interestingly, silver turned out to be superior with regard to gold for the cycloisomerization of the bisallenes. Depending on the steric demand of the substituent R, either mono-cyclization products **11** or bis(2,5-dihydrofurans) **12** were obtained in the presence of 0.25–0.3 equiv of silver nitrate in acetone (Scheme 6). In contrast to this, no conversion whatsoever (or decomposition of the starting material) was observed with gold(I) or gold(III) salts alone. In the presence of stoichiometric amounts of *N*-iodosuccinimide (NIS), however, a very fast gold-catalyzed cyclization of **11** to the iodinated bis(2,5-dihydrofuran) **13** took place [15].



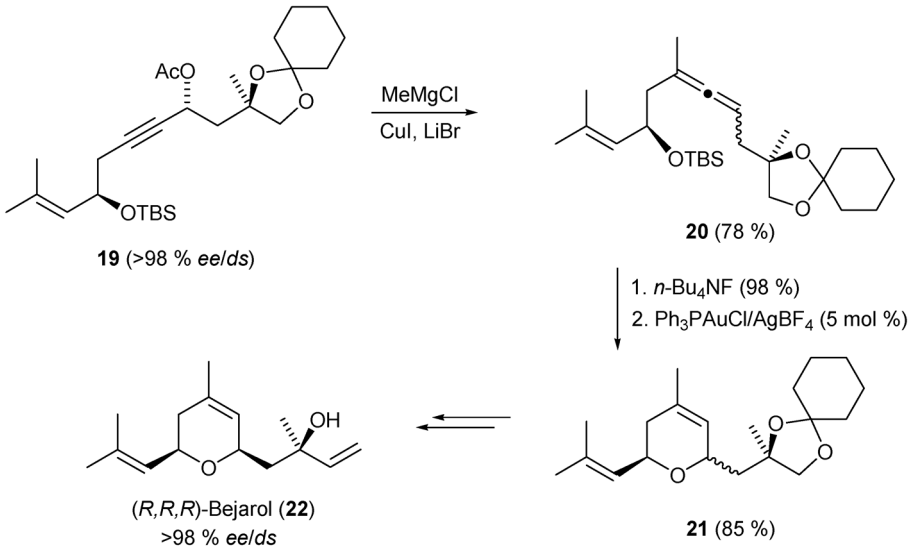
Scheme 6 Silver- and gold-catalyzed cyclization of conjugated bis(α-hydroxyallenes) **10**.

We are not only interested in the accelerating effect of NIS on gold-catalyzed cyclizations, but also in the utilization of the iodinated products for further transformations. This was demonstrated by conversion of the α-hydroxyallene **14** into the furopyran **18** via a gold/palladium/gold-catalyzed cyclization/cross-coupling sequence (Scheme 7) [16]. In the first of three transition-metal-catalyzed steps, the gold-catalyzed cyclization of **14** in the presence of NIS was utilized for the rapid formation of iodinated dihydropyran **15**, which was converted into the enyne **16** by palladium-catalyzed Sonogashira coupling. After allene formation by epoxidation and copper-mediated S_N2'-substitution, a second gold-catalyzed cyclization of **17** afforded the desired furopyran **18**. Even though this sequence needs further optimization with regard to yield and stereoselectivity, it opens an easy access to bicyclic ethers, which occur in a variety of natural products and biologically active compounds [16].



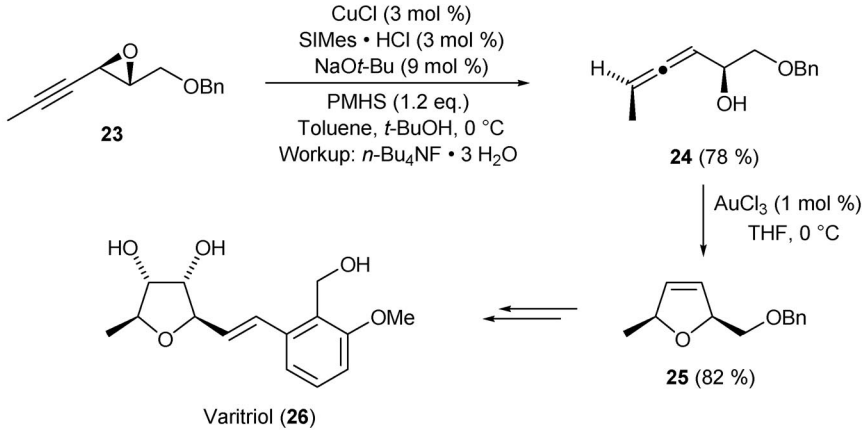
Scheme 7 Synthesis of furopyrans **18** by a gold/palladium/gold-catalyzed cyclization/cross-coupling sequence.

Further examples for the prolific use of the coinage metals in the synthesis of bioactive target molecules via functionalized allenes were recently established by our group [17–20] and others [10g,h]. These include the β-carboline alkaloids isocyclocapitelline and isochrysotricine [17], the fragrance compound linalool oxide [17b], as well as boivinianin B [18], bejarol [19], and varitriol [20]. In the first total synthesis of the naturally occurring sesquiterpenoid (*R*,*R*,*R*)-bejarol (**22**) and its (3*R*,5*S*,9*R*)-isomer, the propargyl acetate **19** was subjected to an S_N2'-substitution with a methylmagnesium cuprate, which afforded the desired allene **20** as a mixture of diastereomers with regard to the allenic chirality axis (Scheme 8). Deprotection of the silyl ether set the stage for the gold-catalyzed cycloisomerization to the dihydropyran **21**, which could be converted easily into the target molecule **22** [19].



Scheme 8 Synthesis of (*R*,*R*,*R*)-bejarol (**22**).

In the stereoselective synthesis of the cytostatic natural product varitriol (**26**) and several analogs [20], the propargyl oxirane **23** served as substrate for a copper-catalyzed S_N2'-reduction using the protocol established by our group [7] (Scheme 9). The α-hydroxyallene **24** thus obtained was converted into the 2,5-dihydrofuran **25** by treatment with 1 mol % of gold(III) chloride in THF. The subsequent transformation of **25** into the target molecule **26** was accomplished by Sharpless dihydroxylation of the double bond and coupling with the aromatic side chain via WHWE olefination [20].



Scheme 9 Copper- and gold-catalyzed synthesis of varitriol (**26**).

In conclusion, we have demonstrated that the coinage metals copper, silver, and gold are ideal tools for the synthesis of bioactive molecules via allenic intermediates. Whereas copper is indispensable for the synthesis of functionalized allenes from propargyl electrophiles by C–C or C–H bond formation, silver and gold are the catalysts of choice for subsequent cyclizations to afford chiral five- or six-membered heterocycles. Overall, this sequence enables an efficient *center-to-axis-to-center chiral-*

ity transfer. We are continuing to expand the repertoire of coinage metal catalysis and to apply these methods to target-oriented synthesis.

ACKNOWLEDGMENTS

Continuous support of our work by the Deutsche Forschungsgemeinschaft and the European Community is gratefully acknowledged.

REFERENCES

1. B. H. Lipshutz, Y. Yamamoto (Eds.). Special issue on "Coinage Metals in Organic Synthesis": *Chem. Rev.* **108**, 2793–3442 (2008).
2. N. Krause (Ed.). *Modern Organocopper Chemistry*, Wiley-VCH, Weinheim (2002).
3. N. Krause, V. Belting, C. Deutsch, J. Erdsack, H.-T. Fan, B. Gockel, A. Hoffmann-Röder, N. Morita, F. Volz. *Pure Appl. Chem.* **80**, 1063 (2008).
4. Enthalpy of formation for $H_2C{=}C{=}CH_2$: ca. 190 kJ mol^{-1}. See: J. D. Cox, G. Pilcher. *Thermochemistry of Organic and Organometallic Compounds*, pp. 140–141, Academic Press, London (1970).
5. N. Krause, A. S. K. Hashmi (Eds.). *Modern Allene Chemistry*, Wiley-VCH, Weinheim (2004).
6. (a) A. Alexakis. *Pure Appl. Chem.* **64**, 387 (1992); (b) N. Krause, A. Hoffmann-Röder. *Tetrahedron* **60**, 11671 (2004); (c) X. Tang, S. Woodward, N. Krause. *Eur. J. Org. Chem.* 2836 (2009).
7. (a) C. Deutsch, B. H. Lipshutz, N. Krause. *Angew. Chem.* **119**, 1677 (2007); (b) C. Deutsch, B. H. Lipshutz, N. Krause. *Angew. Chem., Int. Ed.* **46**, 1650 (2007); (c) C. Deutsch, N. Krause, B. H. Lipshutz. *Chem. Rev.* **108**, 2916 (2008).
8. C. Deutsch, B. H. Lipshutz, N. Krause. *Org. Lett.* **11**, 5010 (2009).
9. (a) J.-M. Weibel, A. Blanc, P. Pale. *Chem. Rev.* **108**, 3149 (2008); (b) M. Alvarez-Corral, M. Munoz-Dorado, I. Rodriguez-Garcia. *Chem. Rev.* **108**, 3174 (2008).
10. Review: (a) H. C. Shen. *Tetrahedron* **64**, 3885 (2008); recent examples: (b) C. T. Hyland, L. S. Hegedus. *J. Org. Chem.* **71**, 8658 (2006); (c) M. Brasholz, H.-U. Reissig. *Synlett* 1294 (2007); (d) S. Kim, P. H. Lee. *Adv. Synth. Catal.* **350**, 547 (2008); (e) J. Park, S. H. Kim, P. H. Lee. *Org. Lett.* **10**, 5067 (2008); (f) B. Alcaide, P. Almendros, T. Martinez del Campo. *Chem.—Eur. J.* **14**, 7756 (2008); (g) Z. Gao, Y. Li, J. P. Cooksey, T. N. Snaddon, S. Schunk, E. M. E. Viseux, S. M. McAteer, P. J. Kocienski. *Angew. Chem.* **121**, 5122 (2009); (h) Z. Gao, Y. Li, J. P. Cooksey, T. N. Snaddon, S. Schunk, E. M. E.Viseux, S. M. McAteer, P. J. Kocienski. *Angew. Chem., Int. Ed.* **48**, 5022 (2009).
11. (a) N. Bongers, N. Krause. *Angew. Chem.* **120**, 2208 (2008); (b) N. Bongers, N. Krause. *Angew. Chem., Int. Ed.* **47**, 2178 (2008); (c) V. Gandon, G. Lemiere, A. Hours, L. Fensterbank, M. Malacria. *Angew. Chem.* **120**, 7644 (2008); (d) V. Gandon, G. Lemiere, A. Hours, L. Fensterbank, M. Malacria. *Angew. Chem., Int. Ed.* **47**, 7534 (2008).
12. C. Winter, N. Krause. *Green Chem.* **11**, 1309 (2009).
13. Ö. Aksin, N. Krause. *Adv. Synth. Catal.* **350**, 1106 (2008).
14. (a) C. Winter, N. Krause. *Angew. Chem.* **121**, 6457 (2009); (b) C. Winter, N. Krause. *Angew. Chem., Int. Ed.* **48**, 6339 (2009).
15. M. Poonoth, N. Krause. *Adv. Synth. Catal.* **351**, 117 (2009).
16. B. Gockel, N. Krause. *Eur. J. Org. Chem.* 311 (2010).
17. (a) F. Volz, N. Krause. *Org. Biomol. Chem.* **5**, 1519 (2007); (b) F. Volz, S. H. Wadman, A. Hoffmann-Röder, N. Krause. *Tetrahedron* **65**, 1902 (2009).
18. T. Miura, M. Shimada, P. De Mendoza, C. Deutsch, N. Krause, M. Murakami. *J. Org. Chem.* **74**, 6050 (2009).

19. Y. Sawama, Y. Sawama, N. Krause. *Org. Biomol. Chem.* **6**, 3573 (2008).
20. T. Sun, N. Krause. To be published.

