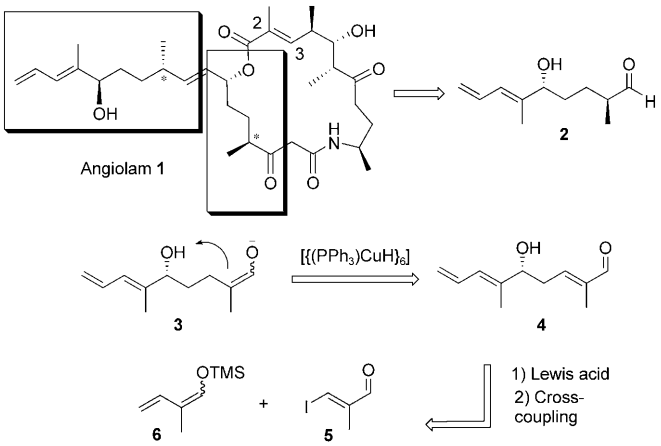
Stereoselective Protonation

DOI: 10.1002/anie.201004619

Intramolecular Stereoselective Protonation of Aldehyde-Derived Enolates

*Anastasie Kena Diba, Claudia Noll, Michael Richter, Marc Timo Gieseler, and Markus Kalesse**

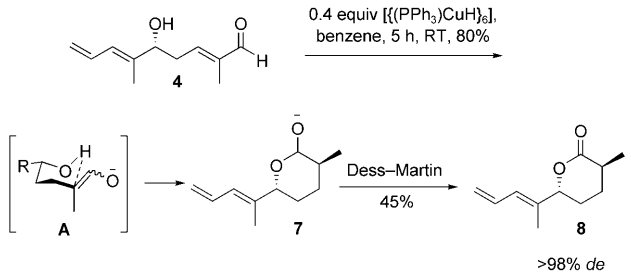
The stereoselective protonation of enolates derived from aldehydes remains a challenging transformation and only a limited number of examples for the enantioselective protonation are reported.[1] Nevertheless, it has the potential to significantly optimize total synthesis by avoiding extensive protecting and functional group manipulations or changes in oxidation states.[2] In the course of our synthetic endeavors towards the natural product angiolam[3] we envisioned establishing α-chiral centers by an intramolecular protonation (Scheme 1). Enolate **3** required for this transformation should



Scheme 1. Retrosynthetic analysis of angiolam. TMS = trimethylsilyl.

be generated by the addition of Stryker's reagent ([{(PPh$_3$)CuH}$_6$])[4] to unsaturated aldehyde **4**. We proposed that using a 1,4-addition to generate the enolate in combination with internal protonation would circumvent the problems known for aldehyde-derived enolates such as homoaldol couplings. Additionally, the α,β-unsaturated aldehyde can be obtained conveniently by a vinylogous Mukaiyama aldol reaction[5,6] and therefore both transformations provide an efficient strategy for the assembly of polyketide segments. In the case of angiolam this asymmetric protonation can be utilized twice for the construction of the southern hemisphere as depicted in Scheme 1. At the outset of our synthesis we investigated the stereochemical outcome of the copper hydride addition to **4**, the side-chain segment of angiolam (Scheme 1).

Unsaturated aldehyde **4** was obtained by Lewis acid catalyzed addition of **6** to **5**. Subsequent cross-coupling and addition of CuH led to reduction of the activated double bond and generation of the corresponding enolate. This enolate was then internally quenched through the secondary alcohol. The observed selectivity is consistent with protonation via transition-state **A** in which the sterically demanding substituents adopt the equatorial positions. The so-generated alkoxide then forms hemiacetal **7** which prevents the chiral aldehyde from epimerization and thus enhances the overall selectivity observed for this transformation. For the determination of the relative configuration Dess–Martin oxidation led to lactone **8** (Scheme 2). At this stage the stereochemistry was assigned by comparison with known compounds[7] and through nOe experiments. Careful examination of the NMR data indicated that only one isomer was generated with selectivity higher than 98% *de*.



Scheme 2. Intramolecular protonation and oxidation.

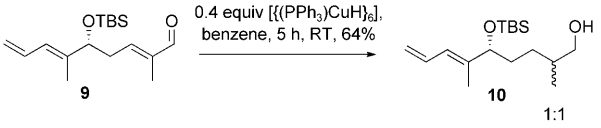
Analysis of the selectivity was performed using alcohol **10** which was obtained from nonselective conjugate reduction of aldehyde **9** (1:1 mixture of both diastereomers; Scheme 3).

Consequently, lactol **11** derived from the selective protonation protocol was transformed into the TBS-protected alcohol **12** (Scheme 4). With both isomers in our hands we were able to determine the selectivity of the intramolecular protonation through comparison of the NMR spectra of the mixed samples using different ratios of **10** and **12** (see the Supporting Information).

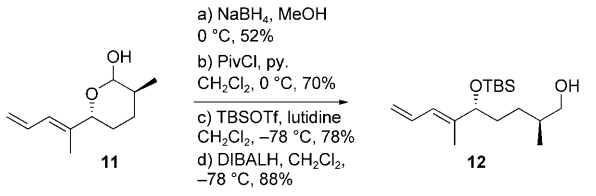
To show the scope of the substrates that can be transformed under these reaction conditions compounds **13**–**19**, derived from saturated, unsaturated, and aromatic aldehydes,

[*] A. Kena Diba, C. Noll, M. Richter, M. T. Gieseler, Prof. Dr. M. Kalesse
Centre for Biomolecular Drug Research (BMWZ)
Leibniz Universität Hannover
Schneiderberg 1B, 30167 Hannover (Germany)
Fax: (+49) 511-7623011
E-mail: Markus.Kalesse@oci.uni-hannover.de
Prof. Dr. M. Kalesse
Leiter Medizinische Chemie
Helmholtz Zentrum für Infektionsforschung
Inhoffenstraße 7, 38124 Braunschweig (Germany)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201004619.



Scheme 3. Nonselective protonation.



Scheme 4. Alcohol **12** used for the determination of the enantioselectivity. DIBALH = diisobutylaluminum hydride, Piv = pivaloyl, TBS = *tert*-butyldimethylsilyl.

were generated using 1 equivalent of Stryker's reagent (Figure 1). It can be seen that the best selectivity was observed for unsaturated and aromatic aldehydes.

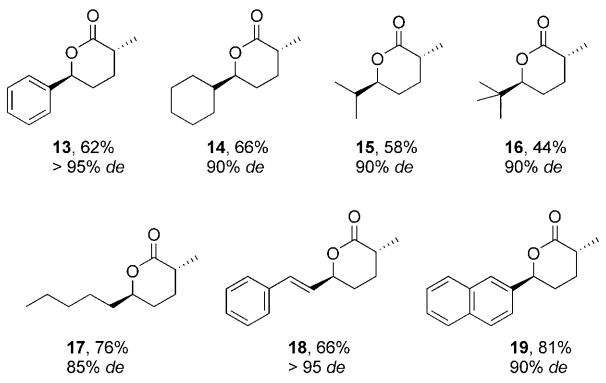
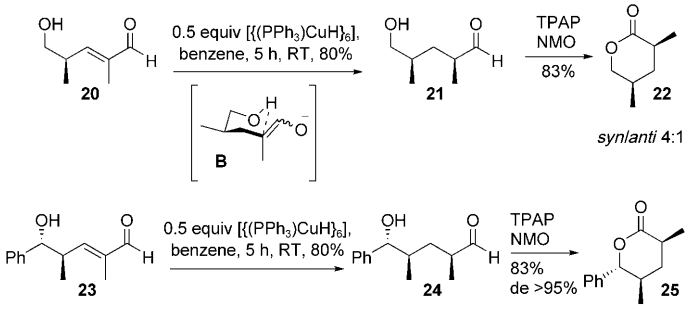


Figure 1. Lactones generated by intramolecular protonation and subsequent oxidation.

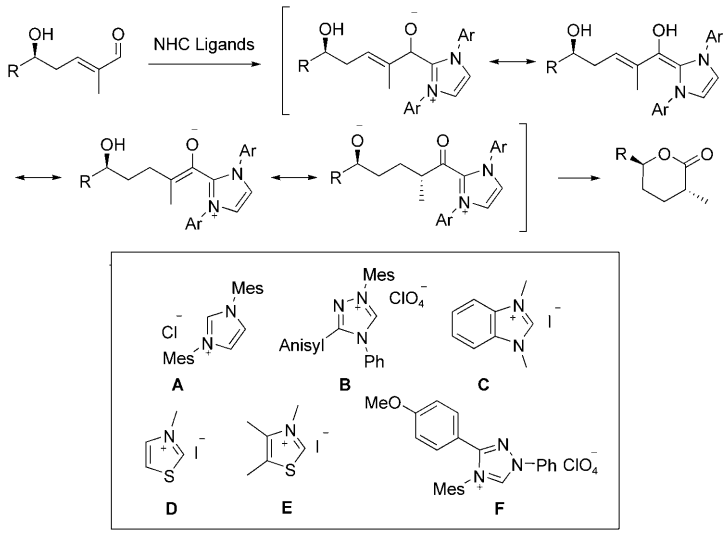
To evaluate the directing effects of methyl groups that are in a 1,3-relationship with respect to each other, compound **20** was subjected to intramolecular protonation conditions (Scheme 5). The obtained *syn* product is consistent with the cyclic transition-state **B** in which the methyl group adopts an equatorial position. However, the directing effect of 1,3-relationship is less pronounced. In contrast, with two chiral centers, as in the case of the matched *anti*-aldehyde **23**, only one isomer (**25**) was observed (Scheme 5).



Scheme 5. Intramolecular protonation and oxidation. NMO = *N*- methylmorpholine-*N*-oxide, TPAP = tetrapropylammonium perruthenate.

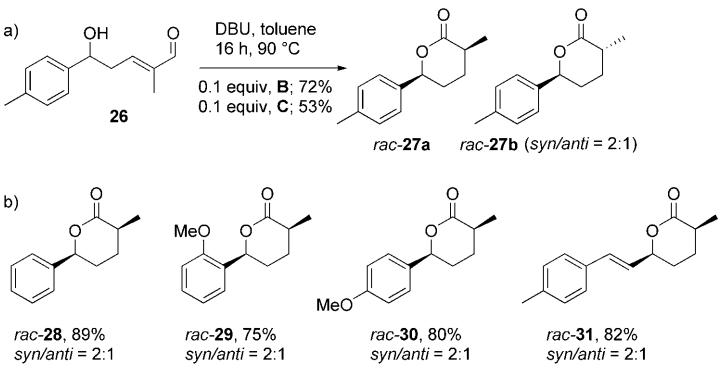
The 1,4- and 1,3-relationships of chiral centers are prominent features of polyketide natural products, as well as lactones. We sought to extend this strategy and to perform the lactonization subsequent to the protonation step. For this we took advantage of the redox lactonization protocol using N-heterocyclic carbene (NHC) ligands[8] (Scheme 6).[9] This umpolung strategy should provide the enolate required for protonation and additionally lead to the corresponding lactones as shown for other substrates by Zeitler et al.[10]

This strategy exhibited an additional challenge since NHC ligands are known to react only sluggishly with unsaturated aldehydes that exhibit an alpha substituent which result in unfavorable steric interactions. During the course of our investigations we screened a variety of different ligands (Scheme 6) and reaction conditions, thereby identifying immidazolium ligands of the type **B** and **C** to be the most effective catalyst. Highest yields were observed when triazole catalyst **B** and benzimidazole catalyst **C** were used in toluene at 90 °C using DBU as the base (Scheme 7 a). Surprisingly, for other substrates subjected to these reaction conditions only diastereomeric mixtures of both the *syn* and *anti* isomers were observed (Scheme 7 b). In the cases where the reaction time was prolonged the *syn* isomer became the prominent product. We rationalize this observation by suggesting that an epimerization occurs at such high temperatures in the presence of a base. The slight preference for the *syn* product can be explained by small differences in kinetic acidity for the H in the axial versus the equatorial position.



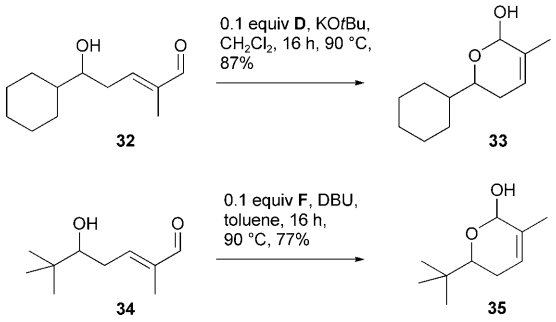
Scheme 6. Synthesis of lactones by intramolecular protonation and redox cyclization. Mes = 1,3,5-trimethylphenyl.

Remarkably, the use of **D** and **F** provided only the isomerized products in good yields, which is consistent with the observations made by Bode and co-workers and



Scheme 7. Lactones derived by redox cyclization. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene.

Scheidt and co-workers,[9c,d] who reported on the different protonation states in connection with the nature of the base employed for the carbene formation (Scheme 8).



Scheme 8. Isomerized lactols.

In summary, we have developed a protocol that allows the selective protonation of aldehyde-derived enolates. The major advantage is the fact that subsequent transformations such as olefinations can proceed without the need for additional functional group manipulations. In cases where the enolate was generated using Stryker's reagent excellent selectivity for the *anti* isomer was observed. The advantage of using NHC ligands was the direct access to lactones exhibiting the opposite diastereoisomer, albeit with modest selectivity. Furthermore, optimizations of the NHC-catalyzed reactions and applications in total syntheses will be reported in due course.

Received: July 27, 2010
Published online: September 28, 2010

Keywords: asymmetric catalysis · organocatalysis · protonation · natural products · reduction

[1] a) J. T. Mohr, A. Y. Hong, B. M. Stoltz, *Nat. Chem.* **2009**, *1*, 359 – 369; b) M. Kalesse, *Sci. Synth.* **2007**, *Chapter 25.1.6*, 147 – 150; c) H. E. Zimmerman, J. Cheng, *J. Org. Chem.* **2006**, *71*, 873 – 882; d) N. T. Reynolds, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 16406 – 16407; e) H. E. Zimmerman, J. Cheng, *Org. Lett.* **2005**, *7*, 2595 – 2597; f) L. Duhamel, P. Duhamel, J. C. Plaquevent, *Tetrahedron: Asymmetry* **2004**, *15*, 3653 – 3691; g) R. Henze, L. Duhamel, M.-C. Lasne, *Tetrahedron: Asymmetry* **1997**, *8*, 3363 – 3365; h) L. Duhamel, J. C. Plaquevent, *Tetrahedron Lett.* **1977**, *18*, 2285 – 2288.

[2] N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem.* **2009**, *121*, 2896 – 2910; *Angew. Chem. Int. Ed.* **2009**, *48*, 2854 – 2867.

[3] W. Kohl, B. Witte, B. Kunze, V. Wray, D. Schomburg, H. Reichenbach, G. Höfle, *Liebigs Ann. Chem.* **1985**, 2088 – 2097. Careful analysis of the published X-ray structure of angioloam identified the C2–C3 double bond to be *E* configured.

[4] a) W. S. Mahoney, D. M. Brestensky, J. M. Stryker, *J. Am. Chem. Soc.* **1988**, *110*, 291 – 293; for a practical synthesis of Stryker's reagent see b) P. Chiu, Z. Li, K. C. M. Fung, *Tetrahedron Lett.* **2003**, *44*, 455 – 457.

[5] Reviews and recent total syntheses involving the vinylogous Mukaiyama aldol reaction are: a) I. Paterson, J. D. Smith, R. A. Ward, *Tetrahedron* **1995**, *51*, 9413 – 9436; b) M. Christmann, M. Kalesse, *Tetrahedron Lett.* **2001**, *42*, 1269 – 1271; c) J. Hassfeld, M. Christmann, M. Kalesse, *Org. Lett.* **2001**, *3*, 3561 – 3564; d) M. Kalesse, *Top. Curr. Chem.* **2005**, *244*, 43 – 76; e) J. Hassfeld, M. Kalesse, *Tetrahedron Lett.* **2002**, *43*, 5093 – 5095; f) S. Simsek. M. Horzella, M. Kalesse, *Org. Lett.* **2007**, *9*, 5637 – 5639; g) S. Simsek, M. Kalesse, *Tetrahedron Lett.* **2009**, *50*, 3485 – 3488.

[6] Preparation of the trimethylsilyl enol ether: K. Krohn, K. Tolkiehn, V. Lehne, H. W. Schmalle, H.-F. Grützmacher, *Liebigs Ann. Chem.* **1985**, 1311 – 1328.

[7] a) Y.-D. Zhang, W.-W. Ren, Y. Lan, Q. Xiao, K. Wang, J. Xu, J.-H. Chen, Z. Yang, *Org. Lett.* **2008**, *10*, 665 – 668.

[8] a) Catalyst **B:** D. Enders, K. Breuer, U. Kallfass, T. Balensiefer, *Synthesis* **2003**, *8*, 1292 – 1295; b) Catalyst **C:** B. Bostai, Z. Novák, At. C. Bényei, A. Kotschy, *Org. Lett.* **2007**, *9*, 3437 – 3439; c) Ed.: F. Glorius, *Top. Organomet. Chem.* **2007**, 21; d) Catalysts **D** and **E:** Y.-T. Chen, F. Jordan, *J. Org. Chem.* **1991**, *56*, 5029 – 5038; e) Catalysis **F:** M. S. Kerr, J. Read deAlaniz, T. Rovis et al., *J. Org. Chem.* **2005**, *70*, 5725 – 5728.

[9] a) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370 – 14371; b) C. Burstein, F. Glorius, *Angew. Chem.* **2004**, *116*, 6331 – 6334; *Angew. Chem. Int. Ed.* **2004**, *43*, 6205 – 6208; c) S. S. Sohn, S. S.; J. W. Bode, *Org. Lett.* **2005**, *7*, 3873 – 3876; J. W. Bode, *Org. Lett.* **2005**, *7*, 3873 – 3876; d) A. Chan, K. A. Scheidt, *Org. Lett.* **2005**, *7*, 905 – 908; e) K. Zeitler, *Org. Lett.* **2006**, *8*, 637 – 640.

[10] a) K. Zeitler, C. A. Rose, *J. Org. Chem.* **2009**, *74*, 1759 – 1762; b) K. Zeitler, I. Mager, *Adv. Synth. Catal.* **2007**, *349*, 1851 – 1857.

