Stereoselective Synthesis

DOI: 10.1002/anie.200903773

Creating Aldols Differently: How to Build up Aldol Products with Quaternary Stereocenters Starting from Alkynes**

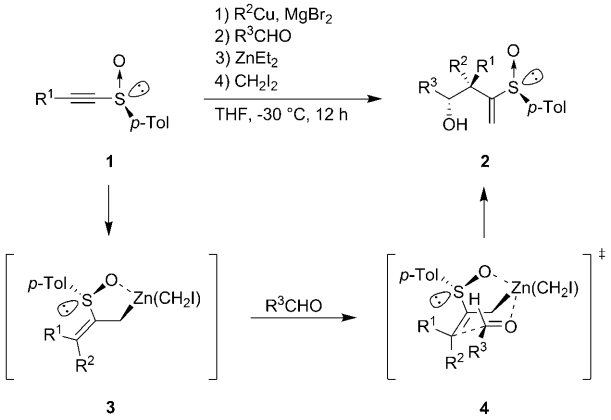
*Dennis C. Koester and Daniel B. Werz**

aldol reaction · carbenoids · enantioselectivity · quaternary stereocenters · synthetic methods

Among the numerous challenges presented by stereoselective synthesis there is one that especially stands out, namely the selective construction of quaternary stereocenters. In this category the ultimate challenge consists of the asymmetric synthesis of all-carbon quaternary stereocenters. In recent years interesting methods which deal with chiral auxiliaries have been developed.[1] Today various catalytic methods are available for the synthesis of all-carbon quaternary stereocenters.[2] Among these are Diels–Alder reactions,[3] which use chiral Lewis acids, as well as copper-[4] and zinc-mediated[5] cyclopropanations. Further catalytic methods for the construction of quaternary stereocenters make use of the Michael reaction[6] or the intramolecular Heck reaction;[7] in this, for the most part ligands such as BINAP guarantee good to excellent enantioselectivities[8] and allow for the application of these reactions in the construction of many natural products.[9]

It is particularly difficult to construct all-carbon quaternary stereocenters in acyclic systems, which in contrast to cyclic systems have higher degrees of freedom and are therefore harder to fix conformationally. Here, especially aldol products with quaternary steoreocenters in the α position of the carbonyl moiety have been the focus. It is practically impossible to generate this structural motif using conventional methods owing to the difficulty in selectively synthesizing the (*E*)- or the (*Z*)-enolate starting from the α,α′-disubstituted carbonyl compound.[10]

Marek and co-workers have recently reported the successful enantioselective construction of this structural element.[11] The group's early work dealt with a new retrosynthetic approach to generate homoallyl alcohols[12] and homoallyl amines[13] by starting from alkynes. By using a sequential multicomponent reaction they succeeded in constructing a homoallyl alcohol **2** with a quaternary stereocenter adjacent to the hydroxy moiety. In this, alkynyl sulfoxide **1** served as the starting material, which was consecutively treated with an alkyl copper species, an aldehyde, diethyl zinc, and diiodomethane to yield the desired product in high diastereoselectivity (Scheme 1).[12]

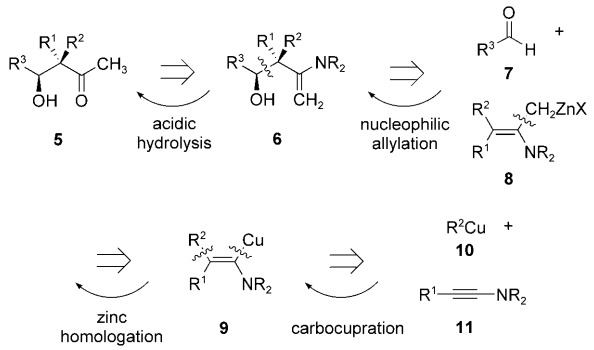


Scheme 1. Sequential four-component reaction to generate homoallyl alcohols **2** with quaternary stereocenters using alkynyl sulfoxides **1** as the starting material (R^1, R^2 = alkyl, R^3 = aryl).

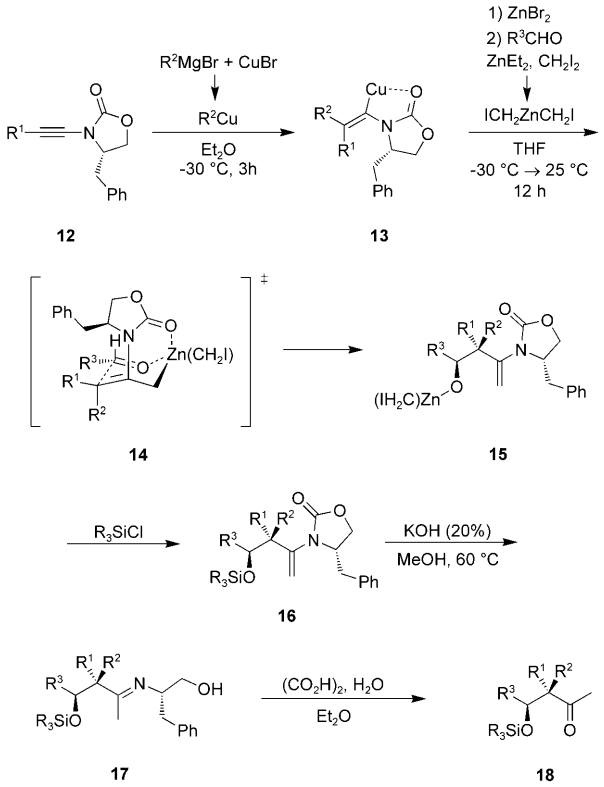
In the now published work,[11] Marek and co-workers were able to show that aldol products **5**, which have quaternary stereocenters, could also be afforded by using a sequential one-pot procedure. Instead of alkynyl sulfoxides **1**, alkynyl oxazolidinones were used to yield the desired aldol products. The retrosynthetic approach dispenses with—and this is the simple yet brilliant aspect of this strategy—using an enolate as a nucleophilic agent to react with the aldehyde to form an aldol product. Rather, as in the stereoselective synthesis of the homoallyl alcohols, the nucleophilicity of an allyl zinc **8** was exploited (Scheme 2). Later their double-bond substitution patterns permit an easy transformation into the desired aldol product. In contrast to the difficulties involved in the diastereoselective construction of disubstituted enolates, the highly diastereoselective creation of the tetrasubstituted

[*] Dipl.-Chem. D. C. Koester, Dr. D. B. Werz
Institut für Organische und Biomolekulare Chemie
Georg-August Universität Göttingen
Tammannstrasse 2, 37077 Göttingen (Germany)
Fax: (+49) 551-399-476
E-mail: dwerz@gwdg.de
Homepage: http://www.werz.chemie.uni-goettingen.de

[**] We thank the Deutsche Forschungsgemeinschaft (Emmy Noether Fellowship to D.B.W.) and the Fonds der Chemischen Industrie (FCI). Furthermore, we are grateful to Prof. Lutz F. Tietze for generous support of our work.



Scheme 2. Retrosynthetic approach for the construction of an aldol product **5** with an all-carbon quaternary stereocenter starting from nitrogen-substituted alkyne **11** (R^1, R^2 = alkyl, R^3 = aryl).



Scheme 3. Synthesis of an aldol product **18** with an all-carbon quaternary stereocenter starting from ynamide **12** (R^1 = alkyl; R^2 = alkyl, aryl; R^3 = aryl, cycloalkyl; R_3 = Me_3, $PhMe_2$).

double bond in **8** from the allyl zinc compound is a relatively simple process. The starting point is a nitrogen-substituted alkyne **11**, which undergoes a carbometalation with the organocopper species **10**, which in turn is easily accessible from copper and alkyl halide. The carbometalation proceeds both regio- and diastereoselectively to the β,β-disubstituted copper enamine **9**. This intermediate already contains three out of four substituents of the later quaternary stereocenter. A zinc homologation of the copper species **9** with the zinc carbenoid [$Zn(CH_2I)_2$] leads to the allyl zinc compound **8**.

In this process a metallotropic equilibrium producing inverse stereochemistry at the all-carbon quaternary stereocenter must be avoided, since this would reduce or destroy the diastereoselectivity of the complete reaction. For the case of homoallyl alcohol synthesis this problem has been solved by making use of the chelating features of the sulfoxide group. For the creation of aldol products the solution to this problem consists of using oxazolidinones as nitrogen substituents at the triple bond (Scheme 3). This approach leads to a coordination of the metal towards the carbonyl moiety of the oxazolidinone. In this way the *E*/*Z* isomerization of the double bond is effectively avoided. An elegant method involves using the Evans auxiliary,[14] because then the absolute stereochemistry of the product can also be controlled.

In the transmetalation step the immediate presence of an electrophilic scavenger agent is called for, as further unwanted reactions with the present zinc carbenoid would otherwise occur. During a diastereoselective reaction with the aldehyde **7** (R^3CHO), whose main product can be explained by the well-established Zimmerman–Traxler model,[15] the last of the three C–C bonds in this sequence is formed. The benzyl substituent of the oxazolidinone makes possible a facial differentiation, thus leading to **15** by way of proceeding through transition state **14** (Scheme 3). In the presence of a chlorosilane the newly created hydroxy group is protected. Without the latter reagent the Evans auxiliary would be destroyed in the creation of a six-membered enamide. After basic hydrolysis, which generated first the imine **17** and acidic workup, Marek and co-workers obtained the silyl-protected aldol product **18** in excellent diastereo- and enantiomeric excess of up to 98%.

For most advanced students of organic chemistry the finer points of the aldol reaction, consisting of the typical steps of the thermodynamic or kinetic enolate formation, capture of the enolate under the influence of various Lewis acids, and diverse chiral auxiliaries or catalysts, make up a considerable part of their studies. This new retrosynthetic approach, which starting from the simplest functionality known to organic chemists—namely the C–C triple bond—from which one of the most complicated structural motifs in organic chemistry is made accessible in a one-pot procedure, is even more impressive. This most elegant approach to aldols with all-carbon quaternary stereocenters is therefore not only highly interesting in of itself, but brings with it the obligation for all organic chemists to rethink established ways of generating well-known functionalities.

Received: July 9, 2009
Published online: September 4, 2009

[1] Reviews: a) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473–1482; b) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402–415; *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401.
[2] Review: B. M. Trost, C. Jiang, *Synthesis* **2006**, 369–396.
[3] V. Alezra, G. Berardinelli, C. Corminboeuf, U. Frey, E. P. Kündig, A. E. Merbach, C. M. Saudan, F. Viton, J. Weber, *J. Am. Chem. Soc.* **2004**, *126*, 4843–4853.
[4] T. G. Gant, M. C. Noe, E. J. Corey, *Tetrahedron Lett.* **1995**, *36*, 8745.

[5] S. E. Denmark, S. P. O'Connor, *J. Org. Chem.* **1997**, *62*, 584–594.
[6] A. Bhattacharya, U.-H. Dolling, E. J. J. Grabowski, S. Karady, K. M. Ryan, L. M. Weinstock, *Angew. Chem.* **1986**, *98*, 442–443; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 476–477.
[7] K. Ohrai, K. Kondo, M. Sodeoka, M. Shibasaki, *J. Am. Chem. Soc.* **1994**, *116*, 11737–11748.
[8] A. B. Dounay, K. Hatanaka, J. J. Kodanko, M. Oestreich, L. E. Overman, L. A. Pfeifer, M. M. Weiss, *J. Am. Chem. Soc.* **2003**, *125*, 6261–6271.
[9] a) A. Ashimori, T. Matsuura, L. E. Overman, D. J. Poon, *J. Org. Chem.* **1993**, *58*, 6949–6951; b) T. Matsuura, L. E. Overman, D. J. Poon, *J. Am. Chem. Soc.* **1998**, *120*, 6500–6503.
[10] S. Yamago, D. Machii, E. Nakamura, *J. Org. Chem.* **1991**, *56*, 2098–2106.
[11] J. P. Das, H. Chechik, I. Marek, *Nat. Chem.* **2009**, *1*, 128–132.
[12] a) G. Sklute, I. Marek, *J. Am. Chem. Soc.* **2006**, *128*, 4642–4649; b) I. Marek, *Chem. Eur. J.* **2008**, *14*, 7460–7468.
[13] G. Kolodney, G. Sklute, S. Perrone, P. Knochel, I. Marek, *Angew. Chem.* **2007**, *119*, 9451–9454; *Angew. Chem. Int. Ed.* **2007**, *46*, 9291–9294.
[14] D. A. Evans, J. V. Nelson, T. R. Taber, *Top. Stereochem.* **1982**, *13*, 1–115.
[15] H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.