Organocatalysis

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Organocatalytic Reactions with Acetaldehyde**

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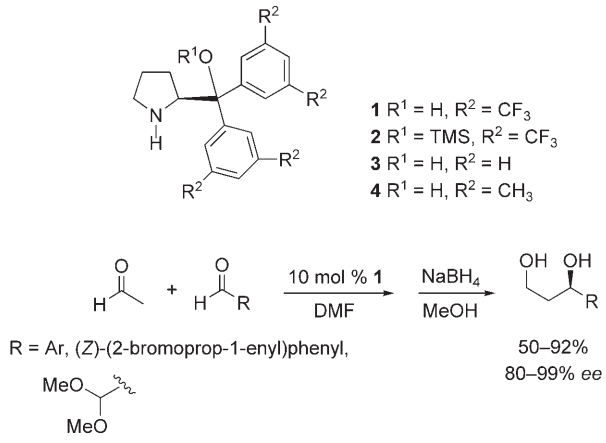
acetaldehyde · asymmetric synthesis · C–C coupling · natural products · synthetic methods

One of the rapidly growing research areas in the field of asymmetric synthesis is that of catalytic transformations by using small organic molecules called organocatalysts. Organocatalysis has received much attention in organic chemistry because of the obvious advantages over its metal-mediated counterpart.[1] Given the current fascination with asymmetric organocatalysis, we should ponder how this change in fortune for simple organic molecules, where an inorganic element is not part of the active principle, has come about. Although Wiechert and co-workers and Hajos et al. independently reported the first highly enantioselective organocatalytic reaction in the early 1970's, an intramolecular proline-catalyzed process,[2] organocatalysis was not viewed as a viable alternative to the two main classes of established asymmetric catalysts (transition-metal complexes and enzymes). A report appeared in the year 2000 that completely changed this perception and highlighted the fascinating attributes of small organic molecules as asymmetric catalysts,[3] marking the explosive growth of low-molecular-weight enamine/iminium-ion organocatalysis.[4] The reasons for the delay in the development of this new field may be complex.

At this advanced stage of modern organocatalysis the controlled stereoselective cross-aldol reaction of acetaldehyde,[5] which is considered the simplest of enolizable carbonyls,[6] has found no general solution.[7] The problems associated with the above mentioned reaction include: 1) polyaldolization, which results from secondary additions to the acetaldehyde-derived aldol product, which is unsubstituted at the α position and may react as both a nucleophile and an electrophile, 2) dehydration of the product, which enables Michael-type additions, 3) Tishchenko-type processes, and 4) oligomerization of the product. In 2005 Denmark et al. documented the Lewis base catalyzed enantioselective aldol addition of acetaldehyde-derived silyl enol ethers to aldehydes with a chiral phosphoramide.[8] Nevertheless, stoichiometric amounts of an adjunct reagent (such as a silylating agent to form the enol silyl ether) is required and decreases the atom efficiency of the process. Therefore, efforts should be devoted to the development of the direct catalytic enantioselective cross-aldol reaction of acetaldehyde without the need for additional activation of the starting materials. On the basis of the good results obtained with the L-proline-promoted direct enantioselective aldol condensation between acetone and various aldehydes, Hayashi et al. was interested in examining the capacity of proline to catalyze the asymmetric cross-aldol reaction of acetaldehyde.[9] However, hardly any cross-aldol adduct was obtained; the major component of the reaction mixture was crotonaldehyde, which was formed by a self-aldol reaction with concomitant dehydration. Inspired by the recent emergence of diarylprolinol ethers as potential general enamine organocatalysts,[10] the reaction was tested by using the diarylprolinol-based catalysts (**1**–**4**).[9] When trifluoromethyl-substituted diarylprolinol **1** was used as an organocatalyst the acetaldehyde cross-aldol adducts were obtained in reasonable yields with high enantioselectivities as determined after a reduction step (Scheme 1). In contrast, the diarylprolinol-based silyl ether **2** was not effective, and the aldol reaction catalyzed by proline derivatives **3** and **4** resulted in low yields albeit with high enantioselectivities. The stereochemical course of the



Scheme 1. An organocatalytic aldol reaction using acetaldehyde as a nucleophile.

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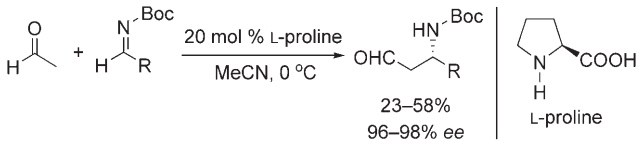
reaction is explained by the generally accepted reaction pathway.[11] The diol, which is obtained from the sodium borohydride reduction of the adduct from the cross-aldol reaction of benzaldehyde and acetaldehyde, is a key intermediate in the synthesis of fluoxetine (Prozac). A drawback of this cross-aldol reaction of acetaldehyde is the narrow scope of acceptor aldehydes employed; the transformation is mainly restricted to aromatic aldehydes. Additionally, the method is limited because of the instability of the aldol products, which must be reduced in situ to the corresponding 1,3-diols.

The Mannich reaction of acetaldehyde, which is used as a nucleophile, facilitated by chiral nonracemic organic molecules is a new and challenging dimension to this powerful method of forming C–C bonds. In this respect, List an coworkers have identified L-proline as an organocatalyst for the direct enantioselective Mannich reaction of acetaldehyde and a variety of *N*-*tert*-butoxycarbonyl imines.[12] The recognition of acetaldehyde as a powerful nucleophile in these transformations is not a trivial issue because, in addition to the autocondensation problems, Mannich adducts may undergo additional reactions because of the presence of additional imine. These side reactions were avoided by using an excess of acetaldehyde. Thus, the treatment of both aromatic and aliphatic N-Boc imines with acetaldehyde (5–10 equivalents) under L-proline catalysis afforded the corresponding β-amino aldehydes in moderate yields and excellent enantioselectivities (Scheme 2). This result constitutes the first example of

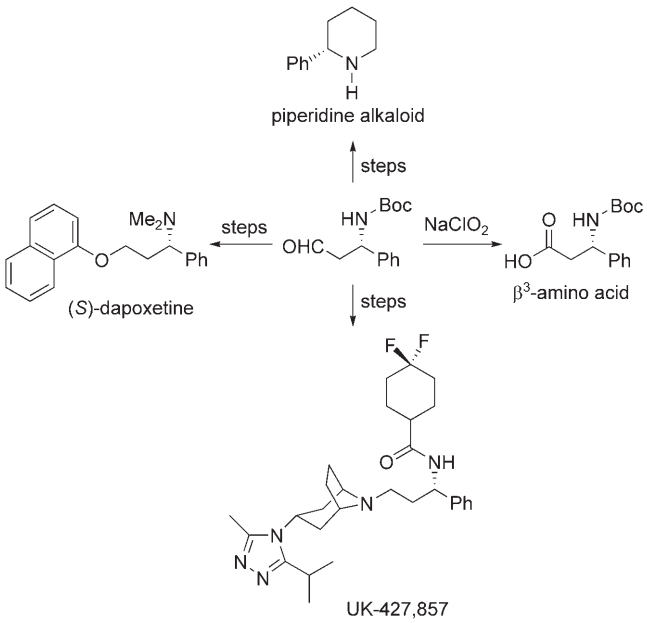


Scheme 2. An organocatalytic Mannich reaction using acetaldehyde as a nucleophile.

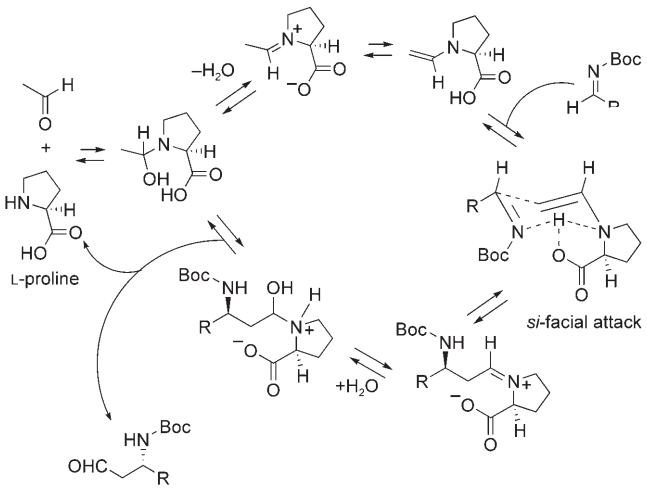
aliphatic aldehyde-derived imines being used in cross-Mannich reactions of aldehydes. The β-amino aldehyde obtained from *tert*-butyl benzylidenecarbamate and acetaldehyde in the cross-Mannich reaction was shown to be a versatile building block for the preparation of β^3-amino acids, piperidines, UK-427,857 (a CCR5 inhibitor for the treatment of AIDS), as well as for the serotonin reuptake inhibitor (*S*)-dapoxetine (Scheme 3).

The resulting absolute configurations of the acetaldehyde-derived Mannich products were in good agreement with the previously proposed models on the proline-catalyzed Mannich reactions (Scheme 4).[13] According to this proposal proline functions as a microaldolase, in which the secondary amine group acts as a nucleophilic enamine catalyst and the carboxylic acid moiety acts as a general Brønsted co-catalyst. The observed stereochemistry can be explained by invoking a metal-free Zimmermann–Traxler-like transition state. A hydrogen bond involving the carboxylate, the enamine, and the imine serves to organize the transition state.[14]

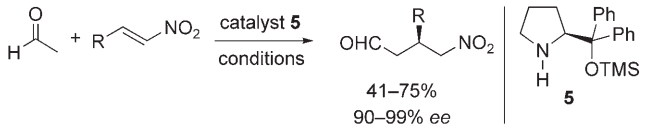
The good levels of reaction efficiency observed in the proline-catalyzed asymmetric Mannich reaction of acetaldehyde, prompted List's group to evaluate pyrrolidine-based compounds to promote the enantioselective Michael reaction of acetaldehyde, an elusive transformation. The fundamental challenge is to suppress the formation of undesirable aldol byproducts. When proline and prolinol **3** were used as catalysts considerable amounts of self-aldolization adducts were formed; but happily, it was found that the homodimerization reaction can be suppressed by slow addition of an acetaldehyde solution to the Michael acceptor. Diarylprolinol silyl ether **5** was selected as the catalyst of choice, and acetaldehyde reacted with aromatic as well as aliphatic nitroalkenes under chiral amine catalysis to form Michael adducts in reasonable yields and good enantioselectivities (Scheme 5).[15] Scheme 6 illustrates the utility of the acetaldehyde-derived Michael adducts in the formal syntheses of



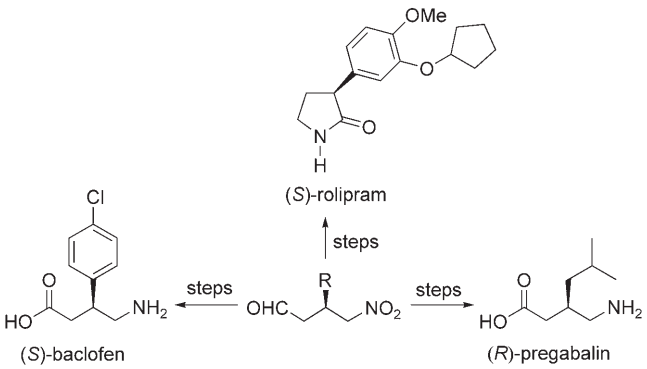
Scheme 3. Utility of the cross-Mannich adduct derived from acetaldehyde and *tert*-butyl benzylidenecarbamate.



Scheme 4. Rationalization for the L-proline-catalyzed Mannich reaction of acetaldehyde.



Scheme 5. Organocatalytic Michael reaction of acetaldehyde. Conditions: a) 20 mol% **5**, MeCN, 0°C; b) 20 mol% **5**, DMF, *i*PrOH, RT; c) 10 mol% **5**, 1,4-dioxane, RT. TMS = trimethylsilyl.



Scheme 6. Synthetic applications of Michael adducts derived from acetaldehyde.

three pharmaceuticals, namely, baclofen (a $GABA_B$ receptor antagonist), pregabalin (an anticonvulsant drug), and rolipram (an antidepressant). A drawback to both the proline-catalyzed Mannich reaction of acetaldehyde and the diarylprolinol-based silyl ether-catalyzed Michael reaction of acetaldehyde was the large quantity of catalyst required (20 mol%). However, Hayashi et al. independently demonstrated that the catalyst loading could be reduced to 10 mol% of diphenylprolinol **5** by using 1,4-dioxane as the solvent (Scheme 5).[16]

In summary, the asymmetric organocatalyzed reactions in which acetaldehyde is used as a nucleophile is a powerful, metal-free method for the synthesis of 1,3-diols, β-amino aldehydes, and β-substituted-γ-nitroaldehydes. These adducts have been shown to be versatile building blocks for the preparation of products of chemical and biological relevance. However, there are unsolved problems in the area of the formation of acetaldehyde-derived aliphatic cross-aldol products, and also in expanding the number and type of electrophiles that may be used. The direct use of acetaldehyde, which permits great flexibility in selection of different electrophiles, coupled with the versatility of the reactions are significant advantages that should facilitate the synthesis of many useful molecules. The search for small metal-free organic molecules that are more broadly applicable and more selective catalysts should reveal more information on the use of acetaldehyde as a nucleophile in organic synthesis.

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[5] Curiously, long before the explosion of organocatalysis, acetaldehyde itself may be considered one of the first compounds used as an organocatalyst: J. von Liebig, *Justus Liebigs Ann. Chem.* **1860**, *113*, 246.

[6] For the employment of acetaldehyde as a nucleophile in aldolase-catalyzed reactions, see: a) S. M. Dean, W. A. Greenberg, C.-H. Wong, *Adv. Synth. Catal.* **2007**, *349*, 1308; b) T. D. Machajewski, C.-H. Wong, *Angew. Chem.* **2000**, *112*, 1406; *Angew. Chem. Int. Ed.* **2000**, *39*, 1352. For the employment of acetaldehyde as a nucleophile in thiamine-catalyzed reactions, see: c) G. Goetz, P. Iwan, B. Hauer, M. Breuer, M. Pohl, *Biotechnol. Bioeng.* **2001**, *74*, 317.

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[10] For a review, see: C. Palomo, A. Mielgo, *Angew. Chem.* **2006**, *118*, 8042; *Angew. Chem. Int. Ed.* **2006**, *45*, 7876.

[11] The configuration of the product is imposed by the bulkiness of the substituent α to the pyrrolidine nitrogen atom, forcing the attack of the electrophile to the lower face of the enamine. Thus, the configuration of the final adducts is opposite to that for the L-proline-catalyzed reactions.

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[14] It should be mentioned that the enantioselectivity of the L-proline catalyzed Mannich reaction is opposite to that of the sterochemistry observed for the corresponding L-proline catalyzed aldol reaction.

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