

# SYNLETT Spotlight 454

## Acetaldehyde: Use in Organocatalysis

Compiled by Sun Min Kim



This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

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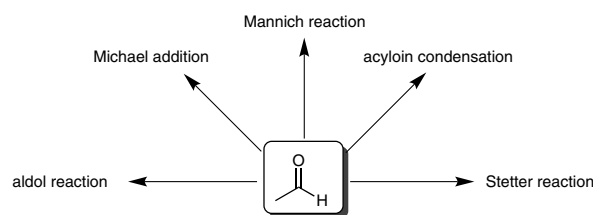
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### Introduction

Acetaldehyde is a small organic molecule and the simplest enolizable aldehyde. It is an important synthon for the construction of  $\beta$ -amino acid derivatives,  $\alpha$ -hydroxy ketones, and so forth, if suitable reagents are employed. Despite this versatility, the use of acetaldehyde can be complicated due to its tendency to oligomerize or polymerize.

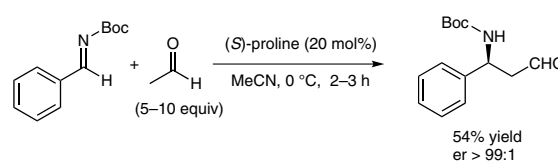
Recently, several research groups reported the multifarious utility of acetaldehyde in many diverse asymmetric organocatalytic transformations by controlling the reactivity of acetaldehyde.<sup>1</sup> The reactions furnished the corre-

sponding products in high yields with stereoselectivities. An overview of typical applications of acetaldehyde is shown in Scheme 1.

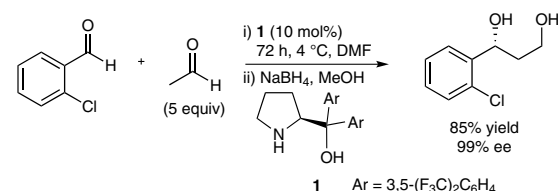


**Scheme 1** Versatile use of acetaldehyde in asymmetric organocatalysis

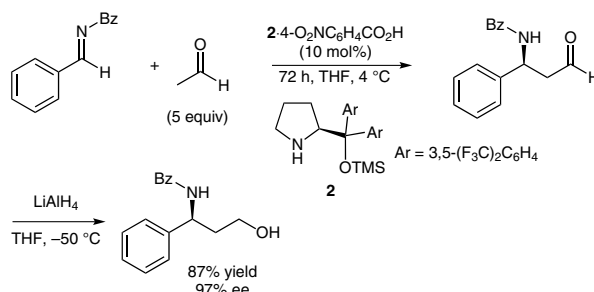
(A) List and co-worker reported the first proline-catalyzed enantioselective Mannich reaction of *N*-Boc imines with acetaldehyde.<sup>2</sup> This method is one of the simplest ways to synthesize enantiopure  $\beta^3$ -amino acid derivatives. It is noteworthy that unwanted side reactions were successfully suppressed by using an excess of acetaldehyde (5–10 equiv).



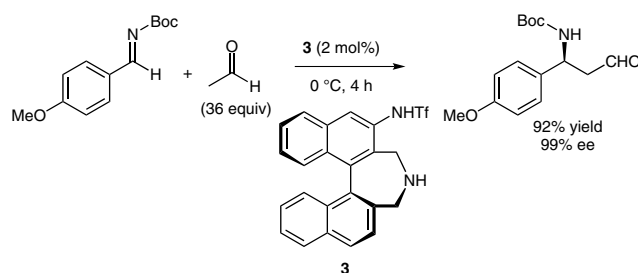
(B) The direct asymmetric crossed-aldol reaction of acetaldehyde was reported by the group of Hayashi.<sup>3</sup> In particular, trifluoromethyl-substituted diarylprolinol **1** was found to be an effective organocatalyst and gave excellent enantioselectivities. Due to its instability, the aldehyde intermediate was transformed into the corresponding alcohol using  $\text{NaBH}_4$  in methanol.



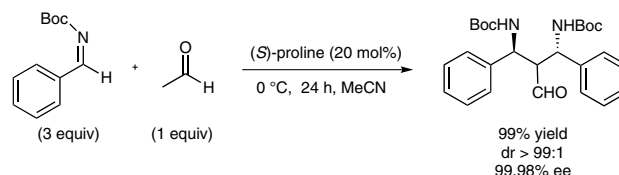
(C) Hayashi, Uchamaru, and co-workers reported that diarylprolinol silyl ether **2** catalyzed the asymmetric Mannich reaction between *N*-protected imines and acetaldehyde (5 equiv).<sup>4</sup> A wide range of aromatic *N*-benzoyl, *N*-Boc, and *N*-Ts imines were investigated. The reaction proceeded smoothly to afford  $\beta^3$ -aminoaldehydes with high enantioselectivity. The aldehydes were reduced to the corresponding alcohols using  $\text{LiAlH}_4$ .



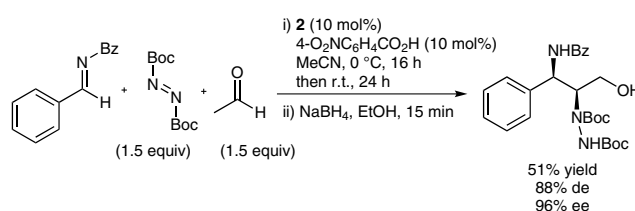
(D) Maruoka and co-workers designed a new catalyst motif – axially chiral bifunctional amino sulfonamide catalyst **3** – and performed asymmetric Mannich reactions of *N*-Boc imines with acetaldehyde (36 equiv).<sup>5</sup> As a result, the desired products were obtained in good yields and excellent enantioselectivities (up to 99% ee) in most cases. Undesired side reactions were suppressed with this less nucleophilic chiral amino sulfonamide.



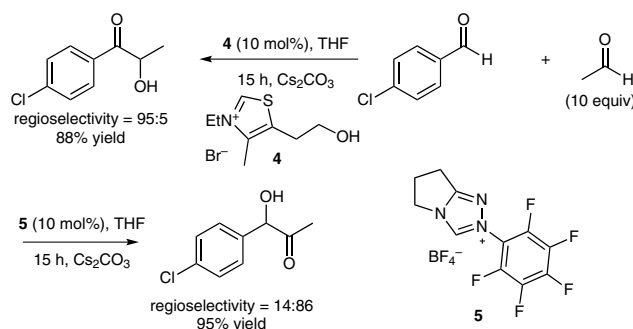
(E) List and co-workers reported the proline-catalyzed double Mannich reaction of *N*-Boc imines with acetaldehyde.<sup>6</sup> This method provided pseudo-*C*<sub>2</sub>-symmetric β,β'-diaminoaldehydes with extremely high diastereo- and enantioselectivities (dr > 99:1, er > 300:1) by reacting one equivalent of acetaldehyde with three equivalents of both aromatic and aliphatic *N*-Boc imines via stepwise enamine catalytic activation.



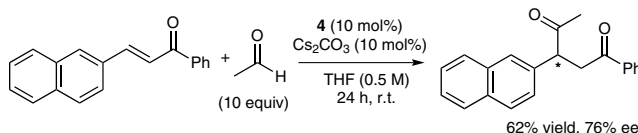
(F) Greck et al. investigated the one-pot, organocatalytic α,α-bifunctionalization of acetaldehyde with two different electrophiles (*N*-benzoyl imine and di-*tert*-butylazodicarboxylate) using diarylprolinol silyl ether catalyst **2**.<sup>7</sup> This reaction consists of a tandem Mannich reaction–electrophilic amination. *syn*-Selective 2,3-diaminoalcohols were obtained with moderate yields and high diastereo- and enantioselectivities (dr up to 96:4, up to 98% ee).



(G) In *N*-heterocyclic carbene (NHC) catalysis, the chemoselective intermolecular cross-acyloin condensation reaction of two different aldehydes is one of the biggest challenges. Yang and co-workers established an efficient chemoselective catalytic system using acetaldehyde as the acyl anion source.<sup>8</sup> The most striking feature is the switch of chemoselectivity by changing the scaffold of the NHC catalyst.



(H) Yang and co-workers reported the intermolecular Stetter reaction of various Michael acceptors, including *trans*-chalcone derivatives, with acetaldehyde as a biomimetic acyl anion source.<sup>9</sup> The authors also extended their work to the enantioselective Stetter reaction which resulted in moderate to good enantioselectivities (up to 76% ee) for the corresponding products.



## References

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