LETTERS

Proline-catalysed Mannich reactions of acetaldehyde

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Small organic molecules recently emerged as a third class of broadly useful asymmetric catalysts that direct reactions to yield predominantly one chiral product, complementing enzymes and metal complexes[1]. For instance, the amino acid proline and its derivatives are useful for the catalytic activation of carbonyl compounds via nucleophilic enamine intermediates. Several important carbon–carbon bond-forming reactions, including the Mannich reaction, have been developed using this approach[2], all of which are useful for making chiral, biologically relevant compounds. Remarkably, despite attempts[3,4], the simplest of all nucleophiles, acetaldehyde, could not be used in this way. Here we show that acetaldehyde is a powerful nucleophile in asymmetric, proline-catalysed Mannich reactions with *N*-*tert*-butoxycarbonyl (*N*-Boc)-imines, yielding β-amino aldehydes with extremely high enantioselectivities—desirable products as drug intermediates and in the synthesis of other biologically active molecules. Although acetaldehyde has been used as a nucleophile in reactions with biological catalysts such as aldolases[5] and thiamine-dependent enzymes[6], and has also been employed indirectly[7–9], its use as an inexpensive and versatile two-carbon nucleophile in asymmetric, small-molecule catalysis will find many practical applications.

Discovered in 2000 (ref. 10), the proline-catalysed Mannich reaction has evolved into a broadly useful transformation that has been applied to the synthesis of natural products, pharmaceuticals, and several classes of chiral amino acids[2]. Very recently, *N*-Boc-imines have been introduced to the proline-catalysed Mannich reaction[11,12], significantly widening the already large substrate scope and utility of this process. We found that several α-unbranched aldehydes react with aromatic *N*-Boc-imines to furnish crystalline α,β-branched β-amino aldehydes in excellent *syn*-diastereoselectivities and enantioselectivities[12]. However, acetaldehyde, which would be a particularly useful nucleophile in this reaction, could not be used under our original conditions. The resulting amino aldehyde products of such reactions are highly attractive precursors of chiral β^3-amino acids, recently pioneered by Gellman *et al.*[13] and Seebach *et al.*[14] in investigations of β-peptides and pharmaceuticals.

There are several problems associated with the potential use of acetaldehyde in proline-catalysed Mannich reactions (and in enamine catalysis in general). First, acetaldehyde rapidly reacts with itself via aldol condensation, forming coloured oligomers and polymers if treated with proline. Additionally, hypothetical acetaldehyde Mannich products, themselves α-unbranched aldehydes, may undergo further reaction with an additional imine equivalent or eliminate to form the corresponding unsaturated aldehydes.

We have now found that these potential side reactions can be suppressed if a higher excess of acetaldehyde (5–10 equivalents) is used. Treating a variety of *N*-Boc-imines with acetaldehyde in the presence of (*S*)-proline (20 mol.%) in acetonitrile at 0 °C gave the desired β-amino aldehydes in extremely high enantioselectivities and reasonable yields (Fig. 1).

The reactions of acetaldehyde with aromatic imines give products **3a** to **3e** in 40–58% yield and in a minimum of 98:2 enantiomeric ratio. Fural-derived imine **1f** provided the Mannich product in moderate yield but maintained excellent enantioselectivity. Most remarkably, we found that even imines derived from aliphatic aldehydes, which so far had not found use in any cross-Mannich reaction of aldehydes, could be utilised. Isovaleraldehyde *N*-Boc-imine **1g** reacted with acetaldehyde to give the corresponding product **3g** in good yield (55%) and essentially perfect enantioselectivity (>99:1 enantiomeric ratio). Moreover, the highly reactive and unstable imine derived from propionaldehyde **1h** could be used. Again, extremely high enantioselectivity was achieved although the yield is only

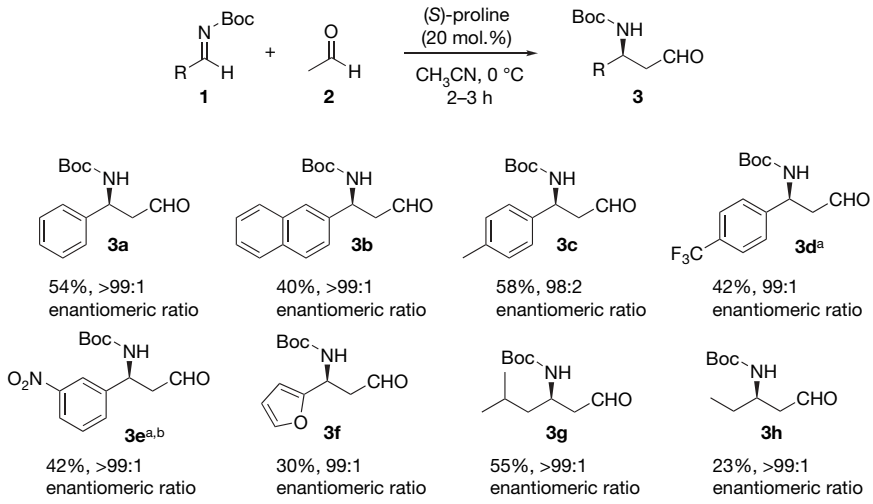

Figure 1 | Highly enantioselective proline-catalysed Mannich reactions of acetaldehyde with *N*-Boc-imines. Superscript 'a' refers to the reaction being conducted at room temperature. Superscript 'b' refers to *in situ* reduction ($NaBH_4$, MeOH) to the corresponding alcohol. Yield (in %) and enantiomeric ratio were then determined.

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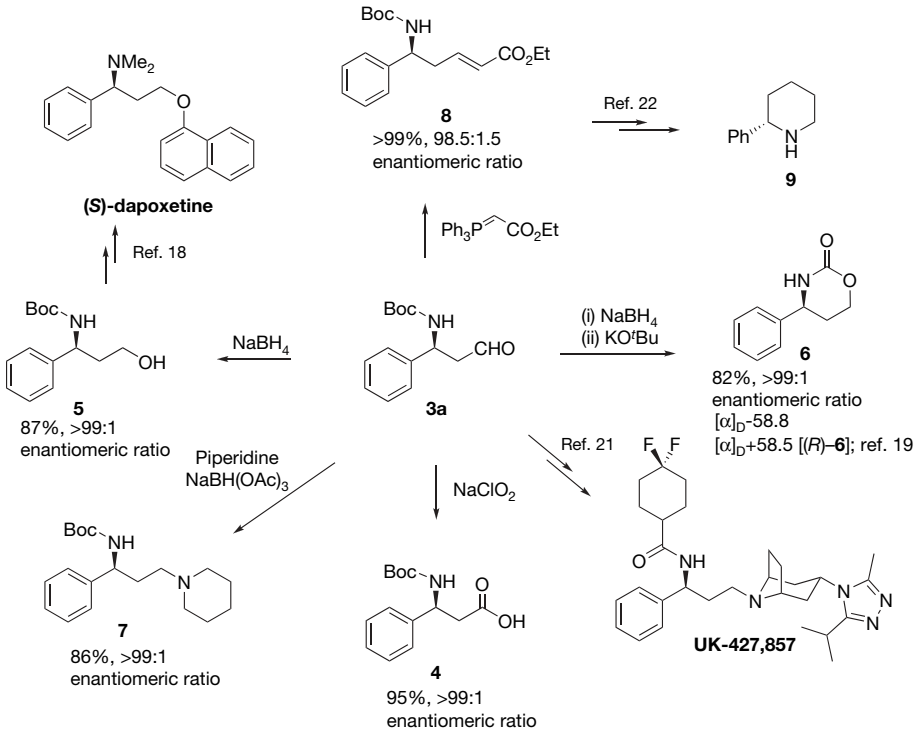

Figure 2 | Utility of Mannich product 3a in the highly enantioselective synthesis of natural products, pharmaceuticals, β[3]-amino acids, and other building blocks. KO^t-Bu, potassium *tert*-butoxide.

moderate in this challenging case. These are the first examples (to our knowledge) of proline-catalysed cross-Mannich reactions with aliphatic unbranched imine acceptors.

To illustrate the value of our highly enantioselective acetaldehyde Mannich reaction, several useful transformations of product **3a** have been devised (Fig. 2). For example, oxidation of the aminoaldehyde with sodium chlorite provided the corresponding *N*-Boc-amino acid **4** in high yield (95%) without loss of enantiopurity[15]. β[3]-Amino acids such as **4** are commonly used in the preparation of β-peptides and our methodology complements Gellman's elegant organocatalytic approach to the isomeric β[2]-amino acids[16]. Reduction of aldehyde **3a** to the corresponding alcohol (**5**) was also achieved. Alcohol **5** is a known intermediate in the synthesis of the selective serotonin reuptake inhibitor (*S*)-dapoxetine (created by Ely Lilly)[17,18]. *In situ* cyclisation of alcohol **5** to the corresponding oxazinone **6** was accomplished in high yield and the absolute configuration was determined to be (*S*) by comparison with the optical rotation ($[\alpha]_D$) of the known (*R*)-enantiomer[19]. Reductive amination of aldehyde **3a** to piperidine derivative **7** is also facile. A similar reductive amination of aldehyde **3a** was used in the synthesis of UK-427,857 (developed and marketed as Selzentry by Pfizer), a recently approved CCR5 inhibitor for the treatment of AIDS[20,21]. Wittig reaction of compound **3a** gave δ-amino-α,β-unsaturated ester **8**, an intermediate in the synthesis of 2-phenylpiperidine (**9**) (ref. 22). 2-Substituted piperidine alkaloids are found extensively throughout nature and demonstrate a wide range of biological activities[23].

Thus we have developed a proline-catalysed Mannich reaction of acetaldehyde with *N*-Boc-imines. The reaction is exceptionally enantioselective and the products are of high value for multiple synthetic applications. We are continuing to explore the enormous potential of acetaldehyde as a nucleophile in organic synthesis, including applications in organocatalytic Michael and aldol reactions. The results of these investigations will be reported elsewhere.

METHODS SUMMARY

Mannich reaction of acetaldehyde with aryl *N*-Boc-imines. A 0.74 M stock solution of acetaldehyde (9.5 ml, 7 mmol), prepared by adding 0.63 ml of redistilled acetaldehyde to 14.37 ml of CH_3CN, was transferred via syringe into a vial containing the aryl *N*-Boc-imine (1.4 mmol) at 0 °C. (*S*)-Proline (32.2 mg, 0.28 mmol) was added to the solution and the resulting mixture was stirred for 2–3 h at 0 °C. The reaction was quenched with water and the mixture was extracted with diethylether (50 ml × 3). The organic layer was washed with brine, dried over Na_2SO_4, filtered and the solvent was removed under vacuum. The pure product was isolated by silica gel column chromatography (10–20% ethyl acetate in hexane).

Mannich reaction of acetaldehyde with alkyl *N*-Boc-imines. A solution of the freshly prepared alkyl *N*-Boc-imine (derived from 0.5 mmol of the corresponding phenylsulphonyl alkylamine precursor)[24] was immediately dissolved in CH_3CN (4 ml) and cooled to −10 °C. Redistilled acetaldehyde (300 µl, 5.3 mmol) was added and the mixture was transferred to an addition funnel equipped with a cooling system set at −10 °C. In a separate round-bottomed flask a solution of (*S*)-proline (11.5 mg, 0.1 mmol) in CH_3CN (4 ml) was cooled to 0 °C. The above mixture was added to the catalyst solution over 2 h (the addition funnel was rinsed with 1 ml CH_3CN into the reaction flask) and stirred an additional 30 min at 0 °C after complete addition. The reaction was poured into a separation funnel containing H_2O (30 ml) and extracted with CH_2Cl_2 (25 ml × 3). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent was removed under vacuum. Purification by silica gel column chromatography (10% ethyl acetate in hexane) gave the corresponding product.

Received 9 November 2007; accepted 22 January 2008.
Published online 20 February 2008.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

Acknowledgements We acknowledge support by the Max-Planck-Society, the DFG (Priority Program *Organocatalysis*), Novartis (Young Investigator Award to B.L.), Astra Zeneca (Research Award in Organic Chemistry), and by the Fonds der Chemischen Industrie. We also thank J. Rosentreter and S. Ruthe for gas chromatographic measurements, and A. Deege and H. Hinrichs for HPLC measurements.

Author Contributions J.W.Y. and M.S. planned, conducted and analysed experiments for the aromatic Mannich products. C.C. planned, conducted and analysed experiments for the aliphatic Mannich products. J.W.Y., C.C. and D.K. planned and conducted experiments and analysed the data for the compounds to demonstrate the utility of the Mannich products. B.L. designed and directed the project and wrote the manuscript with contributions by J.W.Y., C.C. and D.K. J.W.Y., C.C. and D.K. compiled most of the Supplementary Information. All authors contributed to discussions.

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