Asymmetric Catalysis

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# Bifunctional Brønsted Base Catalyzes Direct Asymmetric Aldol Reaction of α-Keto Amides

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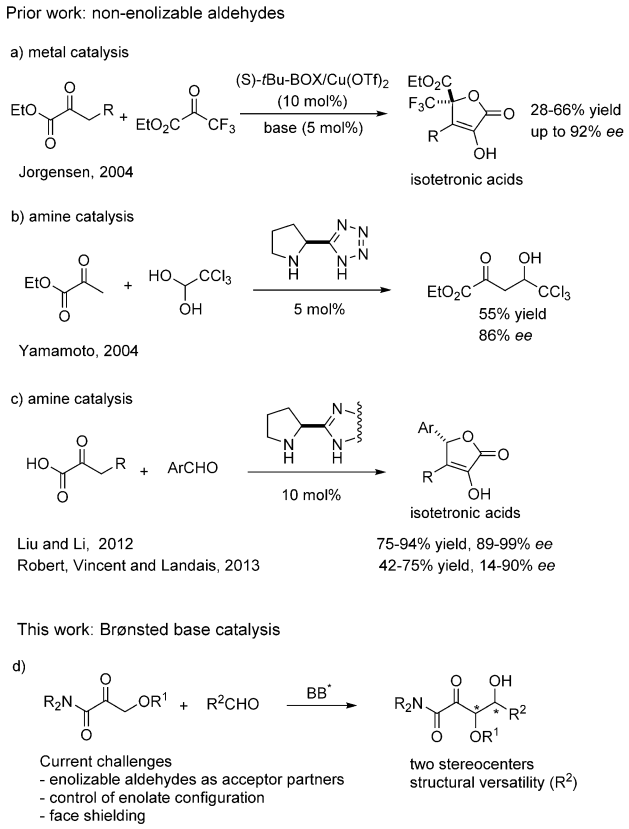
***Abstract:*** *The first enantioselective direct cross-aldol reaction of α-keto amides with aldehydes, mediated by a bifunctional ureidopeptide-based Brønsted base catalyst, is described. The appropriate combination of a tertiary amine base and an aminal, and urea hydrogen-bond donor groups in the catalyst structure promoted the exclusive generation of the α-keto amide enolate which reacted with either non-enolizable or enolizable aldehydes to produce highly enantioenriched poly-oxygenated aldol adducts without side-products resulting from dehydration, α-keto amide self-condensation, aldehyde enolization, and isotetronic acid formation.*

**1,2-D**icarbonyl compounds, such as pyruvic acid and phosphoenolpyruvate, are employed as $C_3$-donor units in the aldolase-promoted biosynthesis of ulosonic acids and sialic acids.[1] Despite the synthetic interest, however, the utilization of pyruvates in the realm of chemical synthesis has been mainly limited to their use as electrophilic counterparts because of the inherently high reactivity of the α,β-dicarbonyl in nucleophilic 1,2-additions.[2] The asymmetric homoaldol reaction of ethyl pyruvate was first described by Jørgensen and co-workers wherein a chiral copper/bisoxazoline complex was used.[3] A few years later, Dondoni and co-workers described the homoaldol reaction of ethyl pyruvate using secondary amine catalysis[4] to produce the more stable isotetronic acids. For pyruvate cross-aldol reactions to be effective highly reactive acceptor carbonyl compounds are usually required (Scheme 1a and 1b),[5] however, the aldol adducts also tend to lactonize, which is an important limitation when substituted pyruvates are employed because the cyclization implies loss of a stereogenic center. This limitation also exists for enamine-based cross-aldol reactions between α-ketoacids and either aromatic aldehydes[6] or substituted pyridine carbaldehydes[7] which also give isotetronic acids (Scheme 1c). In contrast, a masked pyruvate equivalent, such as pyruvic aldehyde dimethyl acetal, has been employed under amine catalysis in the reaction with aromatic aldehydes, to prevent lactonization.[8] Clearly, this enamine aldol technology would be nicely complemented in terms of product scope and reaction mechanism if a Brønsted base catalyzed approach addressing this problem would be available. Mlynarski and co-workers,[9] based upon the observation that esters of bulky phenols prevent pyruvate self-condensation and lactonization,[10] reported a diastereoselective aldol reaction of 2,6-di-*tert*-butyl-4-methoxyphenyl pyruvate with chiral nonracemic α-oxy aldehydes using this approach. Later on Liu, Li, and co-workers[11] documented the reaction of ethyl pyruvate with isatins, a highly electrophilic class of ketones. In this case, however, lactonization occured and, again, isotetronic acids were formed with the loss of a stereogenic center. Despite these advances, Brønsted base catalyzed cross-aldol couplings of α-substituted pyruvates with enolizable aldehydes have not yet been realized. Probably, the major reason that justifies this notable deficiency is the difficulty associated with the α-deprotonation of 1,2-dicarbonyl compounds resulting from the relatively low acidity of the α-carbon atom in this class of pronucleophiles.[12] Not surprisingly, α-substituted pyruvates and related 1,2-dicarbonyl compounds have been employed in Brønsted base mediated reactions involving, as far as we know, only highly reactive acceptors.[11,13] Given their bidentate charac-




***Scheme 1.*** Cross-aldol reactions of 1,2-dicarbonyl compounds. BB = Brønsted base, Tf = trifluoromethanesulfonyl.

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ter, we questioned whether substrate activation through multiple hydrogen-bonding interactions might facilitate deprotonation by a mild Brønsted base to give an α-keto enolate with a specific configuration. Recently, we introduced ureidopeptide-based Brønsted bases as a new subfamily of organic catalysts bearing several hydrogen-bond donors.[14] Herein we report the utility of these newly developed Brønsted bases by documenting the first direct catalytic enantioselective cross-aldol reaction of α-keto amides with either enolizable or non-enolizable aldehydes.[15]

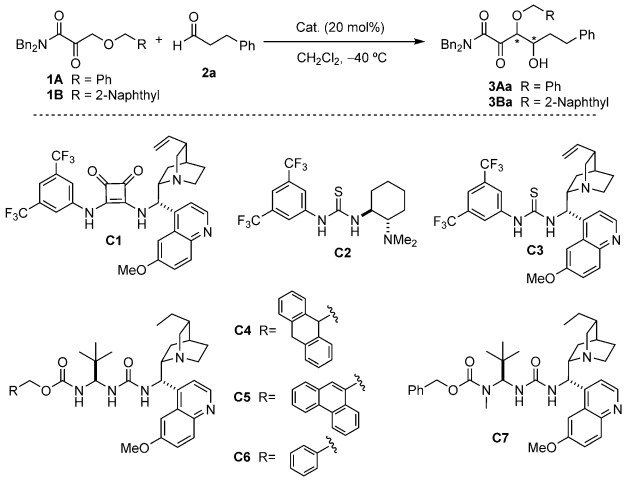
In contrast to the progress achieved in enamine based aldol reactions, cross-aldol couplings mediated by Brønsted bases appear to be more challenging to establish.[16] Probably, the most effective systems to date involve highly electrophilic carbonyl acceptors such as 1,2-dicarbonyl compounds.[17] We initiated this work by evaluating several known Brønsted bases for the reaction of the α-keto amide **1A** and hydrocinnamaldehyde (**2a**; Table 1). The experiments soon revealed that, indeed, the Brønsted base was the key for success. For example, when using quinine, quinidine, and $(DHQ)_2PYR$, no aldol product (**3Aa**) was observed after 24 hours, either at −40 °C or 0 °C. While the squaramide **C1** was also ineffective in terms of reactivity and selectivity (entry 1), the bifunctional thiourea-tertiary amine catalysts **C2** and **C3** provided **3Aa** with good diastereomeric ratios and *ee* values, but the transformations required prolonged reaction times (entries 2–5). We were gratified to observe that ureidopeptide-based Brønsted bases, which might display up to three hydrogen-bonding interactions,[18] promoted this cross-aldol addition most effectively.

As the results in Table 1 show, the catalysts **C4** and **C5** promoted complete conversion into **3Aa** within 48 hours (entries 6 and 7), whereas the catalyst **C6** achieved a somewhat higher level of stereocontrol in a relatively shorter reaction time (entry 8). Importantly, under these reaction conditions self-condensation of either **1A** or **2a** were not detected. Also, neither dehydrated nor lactonized aldol products were observed. Further experiments revealed an improvement in diastereoselectivity by increasing the aromatic character of the substituent in the α-keto amide. The adduct **3Ba** was produced, with increased diastereoselectivity (90:10 d.r.), whilst maintaining the enantioselectivity (92% *ee*), from the α-keto amide **1B** (entry 9). In addition, the N-methylated catalyst **C7** behaved similarly to both **C2** and **C3**, and provided the aldol **3Aa** in 30% conversion (d.r.75:25, 86% *ee*) after 48 hours.

A representative selection of aldehydes was subjected to the optimized reaction conditions to produce the aldol adducts **3B** for which diastereomeric ratios and enantiomeric excesses were determined (Table 2). To avoid α-epimerization during purification,[19] each crude reaction mixture of the products **3B** was submitted to reduction with L-selectride. The reduction proceeded cleanly at −78 °C and with essentially complete stereoselectivity to give the corresponding *syn,syn* 1,2,3-triols **4B** in 60–72% yields upon isolation after two steps. As the data in Table 2 show, results were consistently good. Short alkyl chain aldehydes (e.g., propanal), longer chain aldehydes (e.g., hexanal and heptanal), β-branched isovaleraldehyde, and even aldehydes bearing side chains with functional groups (e.g., alkene, ester, carbamate, and ether) participate satisfactorily, thus giving enantiomeric excesses of up to 96%. In contrast, diastereomeric ratios seemed to decrease as the length of the alkyl chain in the aldehyde increased (compare **4Bb**, **4Bc**, and **4Bd**), and with the presence of α-substitution (**4Bj** and **4Bk**) while maintaining high enantiomeric excesses. In addition, 3 mmol scale reactions proceeded without any detrimental effect in the reaction outcome (**4Ba** and **4Bf**).

The relative and absolute configurations of the major *syn,syn* enantiomer were determined by X-ray crystallographic analysis of **4Bd** (Scheme 2a) and a uniform reaction mechanism for the aldol reaction was assumed.[20] Taking into account the diastereo- and enantioselectivity observed, the capacity of the ureidopeptide-based catalysts to mainly produce *syn*-configured adducts might be consistent with the generation, as a result of electrostatic and hydrogen-bonding interactions, of a more stabilized *Z* enolate which preferentially approaches the *Si* face of the aldehyde (Scheme 2b). Although we still have no evidence of the actual mode of substrate–catalyst interaction,[21] the fact that reactions with common Brønsted base catalysts, as well as with **C7**, were significantly less efficient supports the beneficial effect of multiple hydrogen-bonding interactions to boost reactivity.

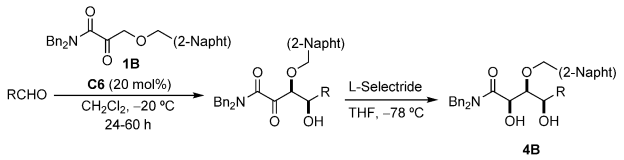
***Table 1:*** Catalyst screening for the aldol reaction between **1A** and **2a**.[a]

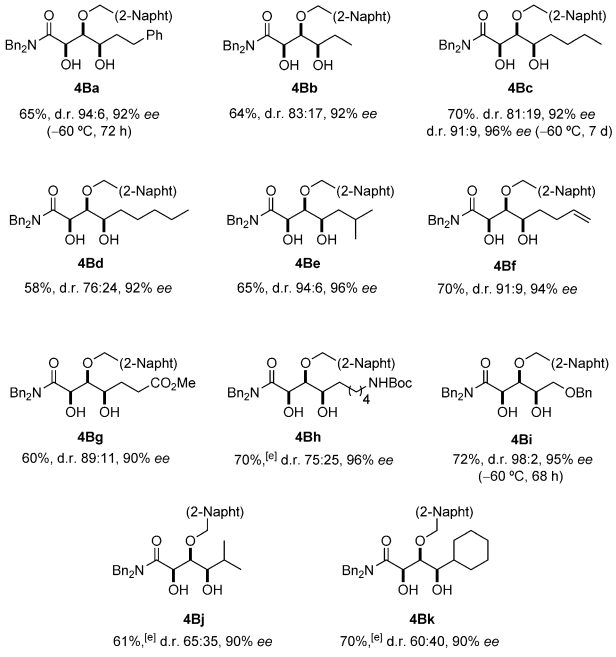



| Entry | 1 | Cat. | *t* [h] | Conv. [%][b] | d.r.[c] | *ee* [%][d] |
|---|---|---|---|---|---|---|
| 1 | **1A** | **C1** | 48 | 30[e] | 44:56 | 64 |
| 2 | **1A** | **C2** | 48 | 40 | 83:17 | 90 |
| 3 | **1A** | **C2** | 96 | 60 | 85:15 | 92 |
| 4 | **1A** | **C3** | 48 | 60 | 96:4 | 94 |
| 5 | **1A** | **C3** | 96 | 80 | 96:4 | 94 |
| 6 | **1A** | **C4** | 48 | >95 | 75:25 | 92 |
| 7 | **1A** | **C5** | 48 | >95 | 79:21 | 90 |
| 8 | **1A** | **C6** | 36 | >95 | 86:14 | 92 |
| 9 | **1B** | **C6** | 36 | >95 | 90:10 | 92 |
| 10 | **1A** | **C7** | 48 | >30 | 75:25 | 86 |

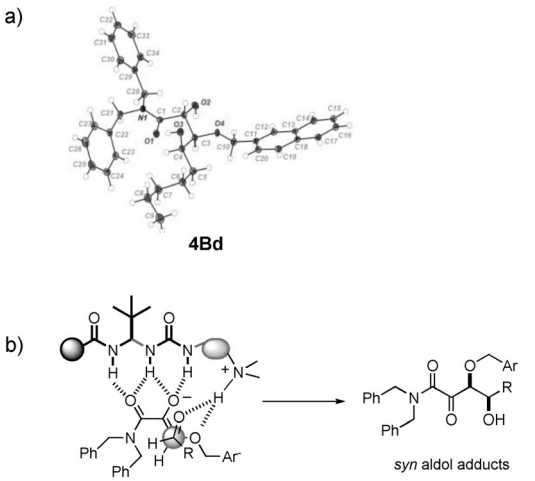
[a] Reactions conducted on a 0.2 mmol scale in 0.5 mL of $CH_2Cl_2$ (mol ratio of **1A**/**2a**, 1: 1.2). [b] Determined by $^1$H NMR spectroscopy. [c] Determined by $^1$H NMR spectroscopy and corroborated by HPLC. [d] The *ee* value of the major diastereomer determined by chiral-phase HPLC. [e] 50% conversion after 96 h.

***Table 2:*** Scope of the catalytic aldol reaction of enolizable aldehydes.[a–e]



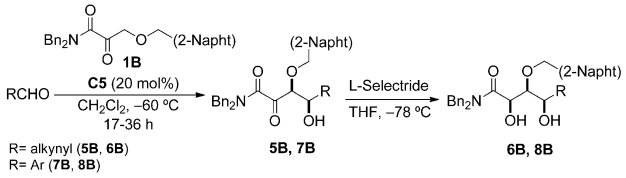



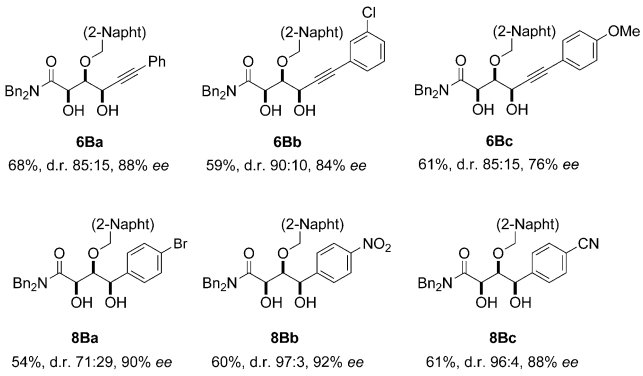

[a] Reactions conducted on a 0.6 mmol scale in 1.5 mL of $CH_2Cl_2$ (mol ratio of **1B**/aldehyde, 1: 3. For the aldehydes **2g** and **2h**: mol ratio of **1B**/aldehyde = 1: 1.5). [b] Yield of the isolated *syn,syn* adduct **4B** after aldol reaction and stereoselective reduction. [c] The *syn/anti* ratio determined by $^1$H NMR spectroscopy and corroborated by HPLC for the aldol adducts **3B** before stereoselective reduction. [d] The *ee* value of the major diastereomer (*syn* aldol adduct), before reduction, was determined by chiral-phase HPLC. [e] Combined yield of the *syn,syn* and *syn,anti* products. Boc = *tert*-butoxycarbonyl, THF = tetrahydrofuran.




***Scheme 2.*** a) ORTEP representation for **4Bd**. Thermal ellipsoids shown at 50% probability. b) Proposed model that might account for the observed preference of *syn*- over *anti*-aldol product formation.

***Table 3:*** Scope of the catalytic aldol reaction of propargylic and aromatic aldehydes.[a–d]



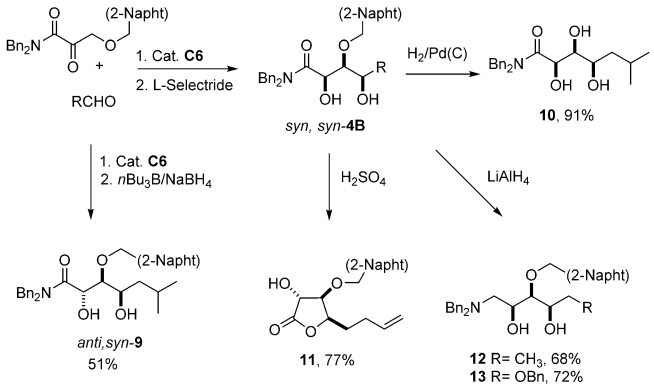




[a] Reactions conducted on a 0.2 mmol scale in 0.5 mL of $CH_2Cl_2$ (mol ratio of **1B**/aldehyde, 1:1.2). [b] Yield of the isolated *syn,syn* adduct after aldol reaction and stereoselective reduction. [c] The *syn/anti* ratio determined by $^1$H NMR spectroscopy and corroborated by HPLC for the aldol adducts **5B** and **7B** before respective stereoselective reduction. [d] The *ee* value of the major diastereomer (*syn* aldol adduct), before reduction, was determined by chiral-phase HPLC.

Considering the shortage of effective direct Brønsted base catalyzed asymmetric cross-aldol reactions, we explored the ability of aromatic, as well as propargylic aldehydes, to participate in the reaction with α-keto amides (Table 3). Once again, ureidopeptide-based catalysts performed well in comparison with other bifunctional thiourea-tertiary amine catalysts,[22] and the highest stereoselectivity was induced by the phenanthrenyl-derived catalyst **C5**. In particular, electronically diverse, substituted ynals produced, after stereoselective reduction of the resulting aldol adducts **5B**, the corresponding *syn,syn* propargylic alcohols **6B**, which are attractive compounds for further chemical transformations resulting from the rich chemistry of the triple bond.[23]

The aldol adducts obtained in the cross-aldol reaction of α-keto amides are valuable precursors of several structural motifs with more than two stereocenters (Scheme 3). In this respect, the stereochemical outcome of the stereoselective reduction of the aldol adducts, promoted by L-Selectride, to give *syn,syn*-**4B** could be inverted to efficiently produce, under treatment with $nBu_3B/NaBH_4$, a 70:30 mixture of *anti,syn*/*syn,syn* diastereomers from which the major *anti,syn* adduct **9** was isolated in reasonable yield. Trivial manipulations such as the cleavage of the 2-naphthyl auxiliary by catalytic hydrogenation and acidic treatment of the *syn,syn* adducts **4B**, produced either the corresponding free triol **10** or lactone **11**. Significantly, this aldol reaction provides, through simple reduction of the amide function with $LiAlH_4$, a quick entry for construction of stereodefined aminotriol units such




***Scheme 3.*** Selected products synthesized from aldol adducts.

as **12** and **13**, which are interesting building blocks for hydroxylated pyrrolidine-containing iminosugars and related products.[24]

In summary, we have developed the first direct catalytic asymmetric cross-aldol reaction of α-keto amides and it expands the realm of aldol additions promoted by Brønsted bases. Given the occurrence of di- and trihydroxylated fragments in bioactive molecules and their frequent use as intermediates in synthesis, this reaction provides a new tool for their rapid construction. The catalysts employed are distinguished from the known bifunctional Brønsted bases (BBs) in that they comprise three consecutive moieties, an aminal, an urea, and a tertiary amine base, which facilitates direct carbon–carbon bond-forming reactions under proton-transfer conditions. We believe these catalysts to be of great utility for broadening the domain of reactions for catalytic asymmetric BB methodologies.

## Experimental Section

To a solution of α-ketoamide **1B** (0.6 mmol, 0.254 g) and the ureidopetide-based catalyst **C6** (0.02 equiv, 0.12 mmol, 0.071 g) in $CH_2Cl_2$ (1.5 mL) was added the corresponding aldehyde (3 equiv for enolizable aldehydes) at the indicated temperature. The resulting solution was stirred until complete disappearance of **1B**. The reaction mixture was quenched with HCl 0.1 M (5 mL), the organic layer was washed with HCl 0.1 M (3 × 5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the corresponding crude reaction mixture containing the aldol adduct, which was subjected to reduction. To a solution of the corresponding crude reaction mixture containing the aldol adduct in THF (6 mL) was added L-Selectride (1 M THF, 2 equiv 1.2 mmol, 1.2 mL) at −78 °C. After stirring for 1.5 hours, water (0.4 mL) and EtOH (0.8 mL) were successively added followed by $H_2O_2$ (30 %, 0.8 mL) 5 min later. The reaction temperature rose to room temperature and the mixture was stirred for an additional 10 min. Then, it was diluted with AcOEt (5 mL) and water (5 mL). The aqueous phase was extracted with AcOEt (3 × 5 mL), the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude reaction mixture was purified by flash column chromatography (Hex/AcOEt) to afford the pure compounds **4B**.

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