Organocatalysis

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# Highly Diastereo- and Enantioselective Mannich Reactions of Synthetically Flexible Ketimines with Secondary Amine Organocatalysts**

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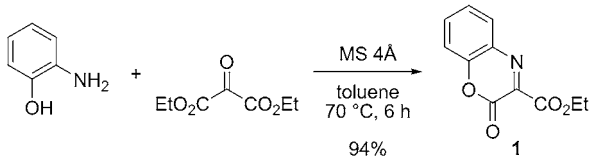
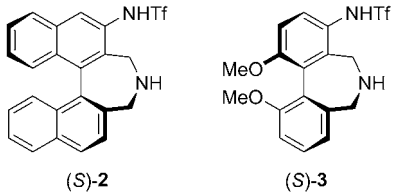
Asymmetric Mannich reactions provide a powerful method for synthesizing optically active β-aminocarbonyl units, which are useful chiral building blocks for a number of biologically active and pharmaceutically important compounds.[1] Among these reactions, catalytic asymmetric Mannich reactions of ketimines that afford tetrasubstituted chiral carbon centers are rare,[2,3] and, with few exceptions, only aromatic ketimines are used as acceptors.[2c–e] The use of non-aromatic ketimines[4] has distinct advantages in terms of broadening the range of substrates that can be used and their high synthetic utility for asymmetric Mannich reactions. As the catalytic asymmetric synthesis of tetrasubstituted carbon atoms remains a significant challenge in organic synthesis[5] and examples of asymmetric Mannich reactions with non-aromatic ketimines are scarce, we are interested in the development of organocatalytic Mannich reactions between non-aromatic ketimines and aldehydes.[6] To overcome the low reactivity of ketimines, we chose ketimine **1** (Scheme 1),[7]




***Scheme 1.*** Synthesis of ketimine **1**. MS = molecular sieves.

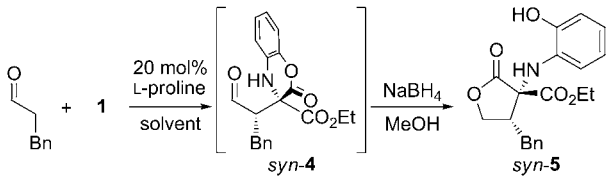
which is sterically less congested and strongly activated by two different ester groups, as an ideal electrophile. Ketimine **1** is readily prepared from commercially available 2-aminophenol and diethyl ketomalonate. As **1** is substituted with versatile ester functional groups and a removable N-protecting group, the Mannich reaction with this ketimine would be synthetically useful. Herein, we report a highly diastereo- and enantioselective Mannich reaction of **1** with aldehydes catalyzed by either proline or an axially chiral aminosulfonamide of type (*S*)-**3** (Scheme 2).




***Scheme 2.*** Structures of catalysts (*S*)-**2** and (*S*)-**3**. Tf = trifluoromethanesulfonyl.

We examined the reaction between 3-phenylpropanal and **1** in the presence of 20 mol% L-proline in various solvents at room temperature (Table 1). Although the desired Mannich product **4** was formed in moderate to good yield in all of the solvents that were tested (Table 1, entries 1–5), only a trace amount of **4** was isolated after chromatography on a silica gel column as a result of the low stability of **4**. Therefore, **4** was treated with $NaBH_4$ in situ and converted into the corresponding γ-lactone **5**. Among the solvents examined,

***Table 1:*** *syn*-Selective Mannich reactions between ketimine **1** and 3-phenylpropanal catalyzed by L-proline.[a]




| Entry | Solvent | Temp [°C] | Time [h] | Yield [%][b] | *syn*/*anti*[c] | *ee* [%][d] |
|---|---|---|---|---|---|---|
| 1 | THF | RT | 1 | 53 (31) | >20:1 | 99 |
| 2 | toluene | RT | 1 | 83 (53) | >20:1 | 99 |
| 3 | $CH_2Cl_2$ | RT | 1 | 83 (56) | >20:1 | 99 |
| 4 | DMF | RT | 1 | 70 (51) | >20:1 | 99 |
| 5 | MeCN | RT | 1 | 83 (63) | >20:1 | 98 |
| 6 | MeCN | 0 | 6 | 87 (64) | >20:1 | 99 |
| 7[e] | MeCN | 0 | 5 | 90 (72) | >20:1 | 99 |

[a] The reaction of **1** (0.1 mmol) with 3-phenylpropanal (0.5 mmol) was performed in the presence of L-proline (0.02 mmol) in a solvent (50 μL). [b] Determined by $^1$H NMR spectroscopy by using an internal standard technique. The numbers in parentheses are isolated yield of **5**. [c] Determined by $^1$H NMR spectroscopy. [d] The *ee* value of *syn*-**5** was determined by HPLC on a chiral stationary phase. [e] Benzoic acid (0.01 mmol) was used as an additive. Bn = benzyl.

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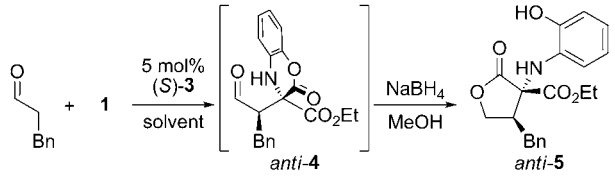
acetonitrile was found to be the best in terms of yield (Table 1, entry 5). When the reaction was performed in acetonitrile at 0 °C in the presence of benzoic acid as co-catalyst, γ-lactone **5** was obtained in good yield with virtually complete *syn* selectivity and enantioselectivity (Table 1, entry 7).

We have previously developed the axially chiral aminosulfonamide catalyst (*S*)-**2** (Scheme 2).[8] The direct asymmetric Mannich reaction of aldimines catalyzed by (*S*)-**2** give mainly *anti* products,[9] whereas proline and the related catalysts have the opposite *syn* selectivity.[11] We anticipated that the development of an *anti*-selective Mannich reaction with the sterically more hindered ketimine would be more difficult because of the moderate nucleophilicity of (*S*)-**2**. Fortunately, (*S*)-**2** promotes the reaction of **1** with 3-phenylpropanal in THF at room temperature to give optically pure *anti*-**5** exclusively, albeit in low yield (Table 2, entry 1). At

***Table 2:*** *anti*-Selective Mannich reactions between ketimine **1** and 3-phenylpropanal catalyzed by (*S*)-**2** or (*S*)-**3**.[a]



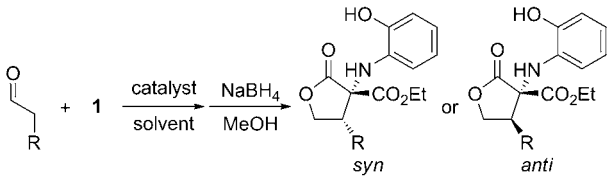

| Entry | Solvent | Temp [°C] | Time [h] | Yield [%][b] | *syn*/*anti*[c] | *ee* [%][d] |
|---|---|---|---|---|---|---|
| 1[e] | THF | RT | 4 | 25 (22) | 1:>20 | 99 |
| 2[e] | THF | 45 | 4 | 35 (32) | 1:>20 | 99 |
| 3 | THF | 45 | 4 | 40 (34) | 1:>20 | 99 |
| 4 | toluene | 45 | 4 | 27 (27) | 1:>20 | 99 |
| 5 | MeCN | 45 | 4 | 42 (36) | 1:>20 | 95 |
| 6 | DMF | 45 | 4 | 47 (39) | 1:>20 | 99 |
| 7 | DMAc | 45 | 4 | 55 (51) | 1:>20 | 99 |
| 8 | DMAc | 45 | 12 | 70 (59) | 1:>20 | 99 |

[a] Unless otherwise noted, the reaction of **1** (0.1 mmol) with 3-phenylpropanal (0.3 mmol) was performed in the presence of (*S*)-**3** (0.005 mmol) in a solvent (50 μL). [b] Determined by $^1$H NMR spectroscopy by using an internal standard technique. The numbers in parentheses are yield of isolated **5**. [c] Determined by $^1$H NMR spectroscopy. [d] The *ee* value of *anti*-**5** was determined by HPLC on a chiral stationary phase. [e] (*S*)-**2** (0.005 mmol) was used instead of (*S*)-**3**. Bn = benzyl.

45 °C, the yield of the reaction improved without the loss of stereoselectivity (Table 2, entry 2). The reaction with the more nucleophilic (*S*)-**3** gave a better yield (Table 2, entry 3),[10,11] and the best solvent for the reaction was dimethylacetamide (DMAc, Table 2, entry 7). A longer reaction time resulted in a slight increase in the yield of the reaction (Table 2, entry 8).

The diastereo- and enantioselective direct Mannich reaction of **1** with several other donor aldehydes was examined under the optimal reaction conditions (Table 3). All of the reactions with sterically less congested aldehydes proceeded to give either *syn*- or *anti*-γ-lactones with almost perfect diastereo- and enantioselectivity, respectively. However, the reactions with bulky aldehydes, such as 3-methylbutanal, gave only a trace amount of the desired products.

***Table 3:*** Mannich reactions between ketimine **1** and various aldehydes catalyzed by L-proline or (*S*)-**3**.[a]

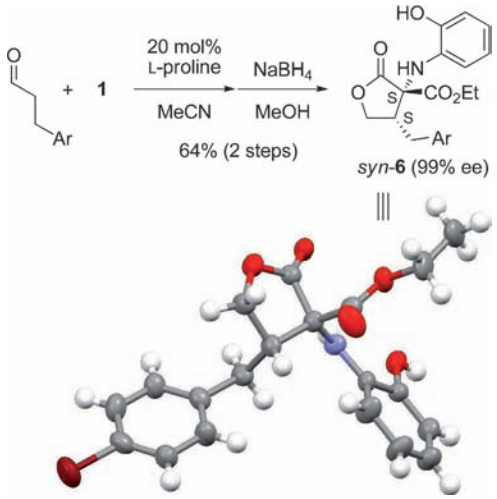



| Entry | R | Conditions[a] | Yield [%][b] | *syn*/*anti*[c] | *ee* [%][d] |
|---|---|---|---|---|---|
| 1[e] | Et | A | 62 | >20:1 | 99 |
| 2[e] | Bu | A | 72 | >20:1 | 99 |
| 3 | Hex | A | 62 | >20:1 | 99 |
| 4 | Bn | A | 72 | >20:1 | 99 |
| 5 | $CH_2Cy$ | A | 71 | >20:1 | 99 |
| 6 | Et | B | 60 | 1:>20 | 99 |
| 7 | Bu | B | 60 | 1:>20 | 99 |
| 8 | Hex | B | 79 | 1:>20 | 99 |
| 9 | Bn | B | 59 | 1:>20 | 99 |
| 10 | $CH_2Cy$ | B | 60 | 1:>20 | 99 |

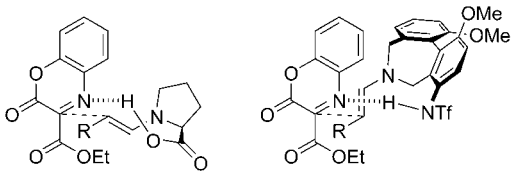
[a] Conditions A: The reaction of the aldehyde (0.5 mmol) with **1** (0.1 mmol) was performed in the presence of L-proline (0.02 mmol) and benzoic acid (0.01 mmol) in MeCN (50 μL) for 5 h at 0 °C; Conditions B: The reaction of the aldehyde (0.3 mmol) with **1** (0.1 mmol) was performed in the presence of (*S*)-**3** (0.005 mmol) in DMAc (50 μL) for 5 h at 45 °C. [b] Yield of isolated product. [c] Determined by $^1$H NMR spectroscopy. [d] The *ee* value of the major isomer was determined by HPLC on a chiral stationary phase. [e] The reaction was performed for 12 h.

Analysis of the structure of *syn*-**6** by X-ray crystallography provided clear proof that the Mannich reactions of **1** catalyzed by L-proline gave *syn*-γ-lactones with 3*S*,4*S* configuration (Scheme 3). On the other hand, the absolute configuration of *anti*-**6**, which was obtained in the reaction catalyzed by (*S*)-**3**, was determined to be 3*S*,4*R* by treating *anti*-**6** with NaOEt to convert it into *syn*-**6**, and by comparison of the HPLC retention times.

Based on the stereochemistry of the products, the transition-state models shown in Scheme 4 account for the



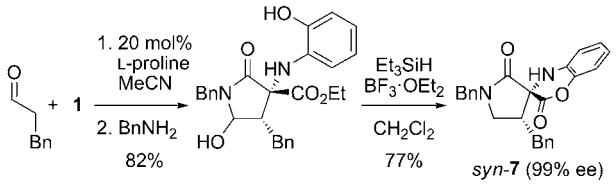

***Scheme 3.*** Synthesis of *syn*-**6** (top) and the X-ray crystal structure of *syn*-**6** with ellipsoids set at 50% probability (bottom). Ar = 4-Br-$C_6H_4$.




***Scheme 4.*** Transition-state models for the asymmetric Mannich reaction catalyzed by L-proline (left) and (*S*)-**3** (right). Tf = trifluoromethanesulfonyl.

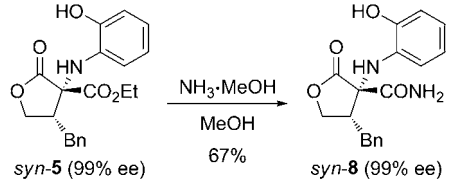
selectivity of the reaction. In the case of the reaction catalyzed by L-proline, the *Re* face of **1** approaches the *Re* face of the dominant *s-trans*-enamine (TS1, Scheme 4). Whereas both the *s-trans*-enamine and the *s-cis*-enamine may be formed in the reaction catalyzed by (*S*)-**3**, only the *s-cis*-enamine can react with activated **1**, which gives the 3*S*,4*R* isomer predominantly (TS2, Scheme 4).

The Mannich product **4** and γ-lactones **5** are versatile intermediates in organic synthesis and can be readily converted into important chiral building blocks. For example, treatment of *syn*-**4** with benzylamine in situ and subsequent reduction with $Et_3SiH$ in the presence of $BF_3{\cdot}OEt_2$ gave γ-lactam *syn*-**7** without the loss of optical purity (Scheme 5).[12] γ-Lactone *syn*-**5** was converted into the corresponding amide




***Scheme 5.*** Synthesis of γ-lactam *syn*-**7**. Bn = benzyl.

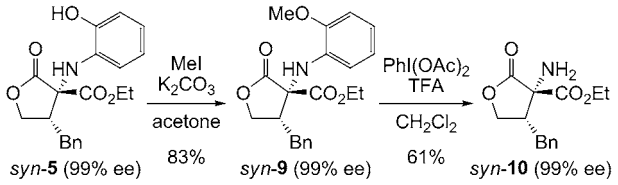
*syn*-**8** by a chemoselective amidation with methanolic ammonia (Scheme 6). These transformations represent the functional differentiation of two ester groups in **4**. Furthermore,




***Scheme 6.*** Chemoselective amidation of *syn*-**5**. Bn = benzyl.

the *N*-substituent of *syn*-**5** can be removed as shown in Scheme 7. Thus, methylation of the phenolic hydroxy group and deprotection with $PhI(OAc)_2$ in the presence of trifluoroacetic acid (TFA) gave the α-amino ester *syn*-**10**.[13]

In summary, we have developed a highly diastereoselective and enantioselective direct Mannich reaction of ketimine **1** with aldehydes catalyzed by proline or the axially chiral aminosulfonamide (*S*)-**3**. This organocatalytic process is a




***Scheme 7.*** Deprotection of *syn*-**5**. Bn = benzyl.

rare example of a Mannich reaction of a non-aromatic ketimine. Further application of the present Mannich reaction and Mannich reactions with other ketimines are under investigation.

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