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# L-Prolinamide derivatives as efficient organocatalysts for aldol reactions on water

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ABSTRACT

A series of L-prolinamide derivatives have been evaluated as potential organocatalysts for aldol reactions. To synthesize these catalysts, a novel and simple route has been developed using proline *N*-carboxyanhydride (proline-NCA). A new catalyst with a trifluoromethyl-sulfonamide group has been found exhibiting excellent diastereoselectivity (*anti*/*syn*: 97/3) and enantioselectivity (99% ee) with 10 mol % loading and being easily recyclable in water.



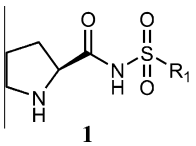
In recent years organocatalysis with proline, its derivatives and with proline analogs has experienced an impressive development.[1,2] Furthermore, the use of water as solvent for organocatalysis,[3] especially in enantioselective aldol reactions,[4] has found a lot of interest. Despite promising results, however, the design of new effective catalysts for aldol reaction in or on water is still a challenge.[3]

Two factors seem to be crucial for an efficient organocatalyst in an aqueous environment: its hydrophobic/hydrophilic properties and its acidity. Imid structures derived from proline like *N*-sulfonyl-L-prolin-amide (**1**) and *N*-carboxyl-L-prolinamide (**2**) provide potential in both directions. A recent paper features the relationship between amide acidity and catalytic activity of proline derivatives in aldol reactions in DMSO on theoretical calculations, which in most cases correlate well with experimental results.[5] Amazingly the most acidic compound, *N*-(trifluoromethyl)sulfonyl-L-proline amide (**1c**), which was predicted to give the highest selectivity, has not been prepared so far.

Strongly acidic amide derivatives of proline have been found to be good catalysts for direct aldol and Mannich reactions. In 2005, first Berkessel[6] reported a sulfonamide derivative of proline as a catalyst for aldol reactions. Later on, Kokotos,[7] Ley,[8] Wang, [9] and Liu[10] published similar derivatives for aldol reactions and Mannich reactions affording good results. Later, Carter[11] used sulfonamide derivatives with long hydrophobic chains as efficient catalysts for aldol reactions with high enantio- and diastereoselectivities.

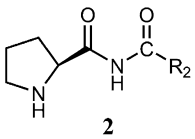
Most of the reported sulfonamide derivatives contain hydrophobic groups in order to have good liposolubility.[6,9,11] But this leads inevitably to increasing difficulties in the separation of product and organocatalyst. Perfluorinated residues have a specific hydrophobic character and a strong electron withdrawing ability. Recently the trifluoromethyl group has been noted as an interesting functional group for organocatalysts[12] and *N*-(trifluoroacetyl) pyrrolidine-2-carboxamide (**2a**) has been tested as an organocatalyst in the aldol reaction (Fig. 1).[13]

All the known L-proline amide derivatives have been prepared by acylation of *N*-protected proline. But when we tried to synthesize a series of imide products from *N*-Boc-prolinamide with different acylating reagents by this procedure, we got no satisfying results. Therefore we developed a novel route starting with



**1**

**1a** $R_1 = C_6H_5CH_3$
**1b** $R_1 = CH_3$
**1c** $R_1 = CF_3$



**2**

**2a** $R_2 = CF_3$
**2b** $R_2 = CCl_3$
**2c** $R_2 = C(CH_3)_3$
**2d** $R_2 = C_6H_5$

**Figure 1.** Structures of organocatalysts.

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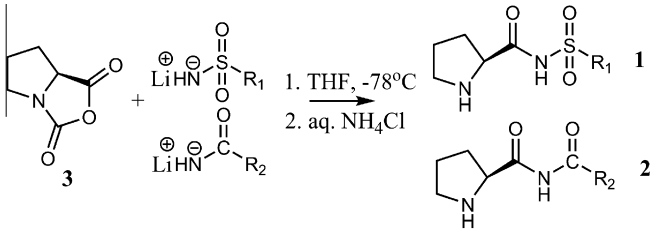
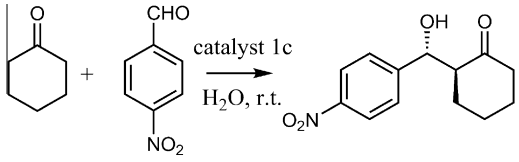



**Scheme 1.** $R_1$ = $C_6H_5CH_3$, $CH_3$, $CF_3$, $R_2$ = $CF_3$, $CCl_3$, $C(CH_3)_3$, $C_6H_5$.

proline-*N*-carboxyanhydride (proline-NCA) (**3**), which can be easily prepared in solution according to a published procedure from proline.[14] Reaction with the corresponding deprotonated amides leads to the imide series of compounds in an easy and general way (Scheme 1).[15] In comparison to the old three step procedure by which the yields of **1a** and **1b** are 25% and 44%,[9] our route of reacting proline-NCA with the corresponding deprotonated amides has only two steps starting from proline and gives better yields (46% and 42%). Following this route we could even synthesize trifluorosulfonyl derivative (**1c**) for the first time.

For testing L-proline imide derivatives **1**and **2**, we used the standard model aldol reaction with 4-nitrobenzaldehyde and cyclohexanone in DMSO (Table 1). As in the known examples the main product is the anti isomer with 2*R*, 1′*S*-configuration.[6] The results obviously show that the catalysts with sulfonamide structure gave much better yield and selectivity than the catalysts with carboxyl imide structure (Table 1). With **2a**, we also observed the aldol condensation product as Wang[13] reported, but as the main product we isolated the unsaturated condensation product. In the other cases water elimination did not occur under the described conditions at room temperature. In accordance with our expectation the most acidic prolinamide **1c** proved to be the best catalyst in the model reaction in DMSO, but unexpectedly gave even better results in dichloromethane (DCM) and water (entries 10 and 11, Table 1). Whereas in DCM the reaction phase is still homogeneous, in pure water a two phase system is observed, but this has no significant effect on the reactivity and selectivity. With **1c** the *anti*/*syn* ratio of 96/4 in both solvents was the highest of all tested catalysts and with 92% ee in DCM and 93% ee on water the best enantioselectivity was detected (entries 10 and 11, Table 1). With these promising results for trifluoromethylsulfonamide derivative **1c** of proline as an effective catalyst for the aldol reaction on water, the influence of catalyst loading, the water volume, the amount of ketone, and the reaction time were studied. We tested 30, 20, 10, and 5 mol % catalyst loading in water under the standard conditions in the model reaction. As expected the reaction rate is obviously affected by the loading amount (Table 2), the medial rate was

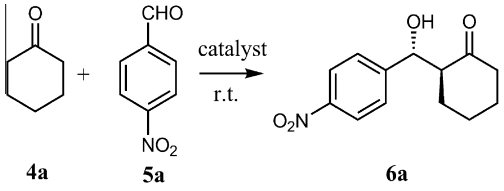
**Table 2**
Screening of conditions for the aldol reaction[a]




| Entry | Catalyst [mol %] | Time [h] | Yield [%][b] | anti/syn[c] | ee [%] (major)[d] |
|---|---|---|---|---|---|
| 1 | 30 | 24 | 64 | 96/4 | 93 |
| 2 | 20 | 48 | 63 | 91/9 | 94 |
| 3 | 10 | 72 | 60 | 96/4 | 99 |
| 4 | 5 | 72 | 48 | 90/10 | 96 |
| 5[e] | 10 | 72 | 77 | 95/5 | 97 |
| 6[f] | 10 | 72 | 67 | 97/3 | 98 |
| 7[g] | 10 | 72 | 64 | 97/3 | 99 |

[a] The reaction was performed with **1c**, **4a** (0.51 mL, 5.0 mmol) and **5a** (76 mg, 0.5 mmol), water (1 mL), and at room temperature.
[b] Combined yields of isolated diastereomers.
[c] Determined by $^1$H NMR of the crude product.
[d] Determined by chiral-phase HPLC analysis of the major product.
[e] Reaction in 0.5 mL water.
[f] Reaction in 0.5 mL water with 2.5 mmol cyclohexanone.
[g] Reaction in 0.5 mL water with 1 mmol cyclohexanone.

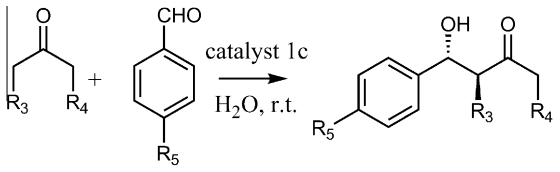
**Table 1**
Screening of organocatalysts for the aldol reaction[a]




| Entry | Catalyst | Solvent | Catalyst [mol %] | Time [h] | Yield [%][b] | *anti*/*syn*[c] | ee [%] (major)[d] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | DMSO | 30 | 24 | 58 | 88/12 | 82 |
| 2 | **1b** | DMSO | 30 | 24 | 54 | 73/37 | 61 |
| 3 | **1c** | DMSO | 30 | 24 | 64 | 94/6 | 85 |
| 4 | **2a** | DMSO | 30 | 24 | 33 | 58/42 | 20 |
| 5 | **2b** | DMSO | 30 | 24 | 22 | 56/44 | 13 |
| 6 | **2c** | DMSO | 30 | 24 | Trace | ND | ND |
| 7 | **2d** | DMSO | 30 | 24 | Trace | ND | ND |
| 8[e] | **2c** | DMSO | 30 | 24 | 14 | 55/45 | 4 |
| 9[e] | **2d** | DMSO | 30 | 24 | 12 | 56/44 | 5 |
| 10[f] | **1c** | DCM | 30 | 24 | 58 | 96/4 | 92 |
| 11[g] | **1c** | $H_2O$ | 30 | 24 | 64 | 96/4 | 93 |

[a] The reaction was performed with **1** or **2** (0.15 mmol), **4a** (0.51 mL, 5.0 mmol) and **5a** (76 mg, 0.5 mmol), DMSO (1 mL), and at room temperature.
[b] Combined yields of isolated diastereomers.
[c] Determined by $^1$H NMR of the crude product.
[d] Determined by chiral-phase HPLC analysis of the major product.
[e] With 10 mol % TFA.
[f] The reaction was performed with 1 mL DCM as solvent.
[g] The reaction was performed with 1 mL $H_2O$ as solvent

**Table 3**
Direct aldol reaction of substituted benzaldehydes with ketones catalyzed by catalyst **1c**[a]




4 5 6

| Entry | $R_3$ | $R_4$ | $R_5$ | Product | Yield [%][b] | *anti*/*syn*[c] | ee [%] (major)[d] |
|---|---|---|---|---|---|---|---|
| 1 | $-(CH_2)_3-$ | | $NO_2$ | **4a** | 64 | 97/3 | 99 |
| 2 | $-(CH_2)_2-$ | | $NO_2$ | **4b** | 54 | 97/3 | 94 |
| 3 | H | H | $NO_2$ | **4c** | 55 | | 86 |
| 4 | $-(CH_2)_3-$ | | Cl | **4d** | 43 | 99/1 | 97 |
| 5 | $-(CH_2)_3-$ | | $OCH_3$ | **4e** | 42 | 97//3 | 91 |
| 6[e] | $-(CH_2)_3-$ | | $NO_2$ | **4a** | 58 | 98/2 | 98 |
| 7[f] | $-(CH_2)_3-$ | | $NO_2$ | **4a** | 61 | 97/3 | 98 |

[a] The reaction was performed with **1c** (10 mol %), **4** (0.1 mL, 1.0 mmol) and **5** (0.5 mmol), water (0.5 mL), and at room temperature for 72 h.
[b] Combined yields of isolated diastereomers.
[c] Determined by $^1$H NMR of the crude product.
[d] Determined by chiral-phase HPLC analysis of the major product.
[e] The reaction was performed with **1c** (10 mol %) recycled after use in entry 1, **4**, **5**, and water with the same moleratio with entry 1.
[f] The reaction was performed with **1c** (10 mol %) recycled after use in entry 7, **4**, **5**, and water with the same moleratio with entry 1.

observed with 30 mol % of catalyst leading after 24 h to a high yield of 64% (entry 1, Table 2), whereas the reaction with 10 mol % loading gave a 77% yield compared to 48% with 5 mol % loading after 72 h (entries 2 and 3, Table 2), showing that higher catalyst loading or longer reaction time will raise the yield. The reaction with 5 mol % catalyst resulted only in a little lower enantioselectivity (96%) than with 10 mol % (entry 4, Table 2). After this, we tested the dependence of the reaction from water volume, and found that the result is similar between 110 and 55 equiv water. Decreasing the excess of ketone had only little influence on selectivity. With 10 mol % catalyst, the highest enantiomeric excess (99%) was reached with 10 equiv as well as with 2 equiv of ketone (entries 3 and 7, Table 2). Therefore it should be pointed out that a decrease in the catalyst loading had no significant impact on the enantioselectivity and large excess of ketone is not necessary for high yield and selectivity.

Getting the highest enantioselectivity in the reaction on water with 10 mol % loading, we further studied the aldol reaction with different ketones and aldehydes under these conditions. We found out that the enantioselectivities for cyclopentanone and acetone are also high but lower than those for cyclohexanone (Table 3). For different aromatic aldehydes, the *p*-chloro and -methoxy substitution reduced the aldehyde activity—as expected—giving lower yield, the selectivity, however, was not affected.

Finally, we elaborated a procedure for catalyst recycling utilizing another advantage of the trifluoromethyl group. After reaction, diethyl ether (10 mL) and water (5 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with ether ($2 \times 10$ mL). Then, the aqueous layers were collected, and water was removed by lyophilization. The remaining is the pure catalyst as revealed by NMR analysis. The recycling rate can easily reach over 90%, higher than other catalysts.[16] The activity of recycled **1c** exhibited almost no change in the test (entries 6 and 7, Table 3).

In conclusion, a simple way has been developed to synthesize proline imide and sulfonamide derivatives from L-proline-NCA. By this route we have prepared a novel proline trifluoromethylsulfonamide derivative, which turned out to be an efficient organocatalyst for asymmetric aldol reaction on water. Compared with other prolinamide-based catalysts, better yields (77%) and higher enantioselectivities (up to 99% ee) were obtained by using 10 mol % of the catalyst in water. Besides this, a simple recycling procedure of this catalyst could be established with a recovering rate higher than 90%. As has been found for other prolinamide-based catalysts this catalyst can be expected to be well suited for other organocatalytic reactions like Mannich reactions, Michael reactions, etc.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.009.

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