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Organocatalytic asymmetric aldol reactions mediated by a cysteine-derived prolinamide

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ABSTRACT

In this Letter, a cysteine-derived prolinamide is described to act as a robust and effective organocatalyst for enantioselective aldol reactions.

The search for new catalysts that display high activity and exquisite selectivity is a major focus of current research in the field of asymmetric synthesis. In this context, the use of chiral small organic molecules as catalysts has recently experienced a renaissance and the field of asymmetric organocatalysis has become a highly active area of research with many opportunities for discovery of new reactions and their application in asymmetric synthesis.[1]

In this context, the amino acid proline occupies a central role, since it is described to catalyze more than 10 different enantioselective C–C and C-heteroatom bond-forming reactions, which would render to it the status of a privileged catalyst.[2] However, despite the ability of proline to successfully catalyze many asymmetric transformations, some drawbacks still need to be overcome, for example, its low solubility in most organic solvents, usually high catalyst loadings and difficult tuning of its reactivity through structural modifications. Therefore, several derivatives, based in the proline framework that might exhibit improved reactivity and selectivity have been synthesized and their catalytic properties have been evaluated. In particular, secondary amides derived from the condensation of proline and a chiral amino alcohol have found to provide higher yields and ee's than proline itself, in the asymmetric aldol reaction of acetone with several aldehydes.[3,4] Additionally, chiral sulfur ligands and catalysts have been successfully employed in a number of transition metal-catalyzed asymmetric transformations, particularly with soft metals.[5,6] On the other hand, the incorporation of a sulfur in organocatalysts is still rare, and only a few examples are described in the literature.[7] For example, sulfur-containing organocatalysts have been used in asymmetric aldol,[8] Mannich,[9] and Michael additions.[10] To the best of our knowledge, no catalyst with selenium has been described thus far.[11]

In the context of our continuing interest in the development of chiral organochalcogen compounds and their application as ligands and catalysts in asymmetric synthesis, we describe herein the preparation of a series of chiral cysteine-derived prolinamides and their application in the organocatalytic asymmetric aldol reaction. Additionally, for the first time, a selenium-containing chiral molecule was evaluated in organic catalysis.

The organocatalysts **3** were synthesized in a short, high yielding sequence, starting from *N*-Boc-L-proline, which reacted with the appropriate *S*-alkyl-L-cysteine methyl ester to afford amide **1**. Double Grignard addition to the ester group or reduction with sodium borohydride, followed by removal of the Boc group delivered the desired organocatalysts **3** in good overall yields (Scheme 1).[12]

First, organocatalyst **3a** was chosen for optimization studies and several parameters such as temperature, solvent, and catalyst loading were screened in the aldol reaction between acetone and benzaldehyde and the results are depicted in Table 1. Performing the reaction in the presence 10 mol % of **3a**, at room temperature and using acetone as the solvent, the aldol product was obtained in only 40% ee. A decrease in the temperature resulted in an increase

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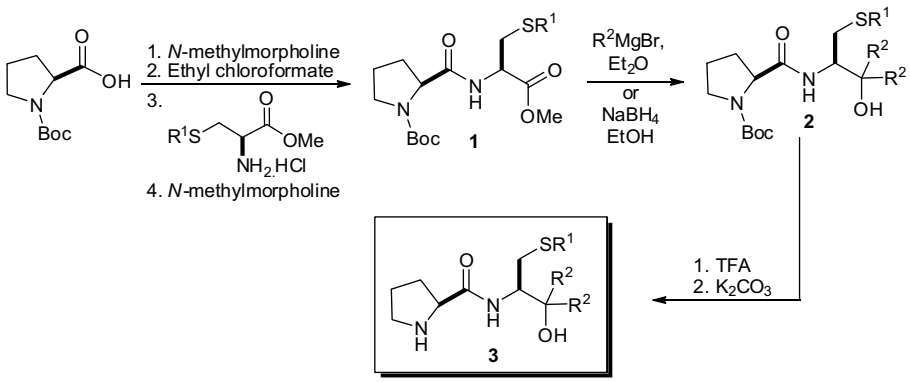
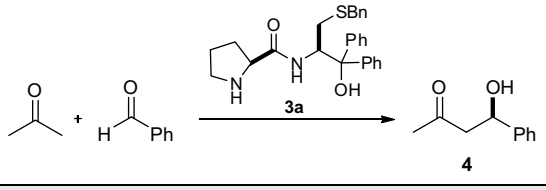


Scheme 1. Synthesis of organocatalysts.

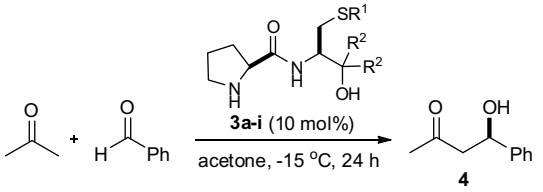
Table 1
Optimization studies: effects of temperature, solvent, and catalyst loading in the aldol reaction of acetone with benzaldehyde



#	**3a** (mol %)	Solvent	Temp. (°C)	Yield[a] (%)	ee[b] (%)
1	**3a** (10)	Acetone	25	65	40
2	**3a** (10)	Acetone	0	58	70
3	**3a** (10)	Acetone	−15	83	94
4	**3a** (10)	Acetone	−70	35	97
5	**3a** (10)	Acetonitrile	−15	40	93
6	**3a** (10)	Chloroform	−15	37	84
7	**3a** (10)	CH_2Cl_2	−15	08	81
8	**3a** (10)	DMSO	−15	24	93
9	**3a** (10)	THF	−15	46	93
10	**3a** (10)	1,4-Dioxane	−15	10	73
11	**3a** (10)	DMF	−15	62	97
12	**3a** (10)	Toluene	−15	58	90
13	**3a** (5)	Acetone	−15	55	90

[a] Isolated yield.
[b] Enantioselectivities were determined by HPLC analysis and absolute configurations were determined by comparison with the literature data.[4]

Table 2
Influence of the structure of the catalyst in the organocatalytic asymmetric aldol reaction



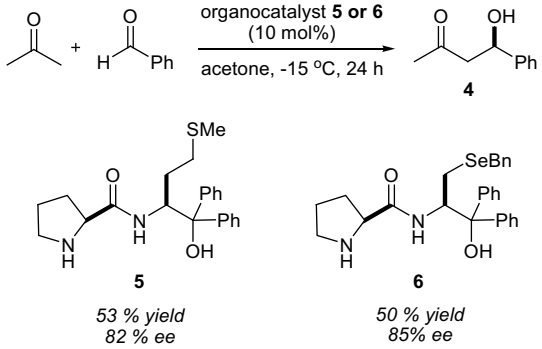
Entry	Catalyst	R^1	R^2	Yield[a] (%)	ee[b] (%)
1	**3a**	Bn	Ph	83	94
2	**3b**	Bn	Me	41	67
3	**3c**	Bn	Et	39	71
4	**3d**	Bn	Decyl	40	60
5	**3e**	Bn	Bn	35	74
6	**3f**	Bn	H	34	67
7	**3g**	Me	Ph	60	82
8	**3h**	Et	Ph	55	79

[a] Isolated yield.
[b] Enantioselectivities were determined by HPLC analysis and absolute configurations were determined by comparison with the literature data.[4]

in the enantioselectivity of the reaction and the aldol product **4** was obtained in 94% ee, when the reaction was performed at −15 °C. It is important to mention that the yield also increased by carrying out the reaction at this temperature, mainly due to suppression of side reactions such as the elimination of water from the aldol product. Further decrease in the temperature to −70 °C led to a slight increase in the ee (94% vs 97%; compare entries 3 and 4), but the yield dropped from 83% to only 35%. Next, the effect of the solvent was examined. Performing the reaction in several polar solvents such as acetonitrile, chloroform, dichloromethane, DMSO, THF, and 1,4-dioxane always resulted in diminished yields and ee's, compared to the result obtained with acetone as the solvent (entries 5–10). A further improvement in the enantioselectivity was achieved using DMF as solvent, and the aldol adduct was obtained in 97% ee, although in a lower yield of 62% (entry 11). When the solvent was changed to the apolar toluene, the product **4** was obtained with moderate yield and in ee of 90% (entry 12). The amount of catalyst was also examined, and we observed a decrease, in both yield and enantioselectivity, when the loading of **3a** was reduced to 5 mol %.

The best conditions determined for catalyst **3a** were then extended to catalysts **3b**–**h**, in order to determine which structural features of the sulfurated amide moiety would be responsible for the high levels of asymmetric induction. By examining the results depicted in Table 2, we can conclude that the presence of a *gem*-diphenyl group is crucial for a high enantioselectivity. When the *gem*-diphenyl was replaced by a *gem*-dialkyl group, dramatic decrease in ee could be observed (94% vs 60-74%; compare entries 1 and 2–5). The best result for the *gem*-dialkyl series was achieved when R^2 = Bn, which resulted in a 74% ee of the product (entry 5). When R^2 was H, the result was similar to those obtained with catalysts with alkyl groups in the β-position and **4** was formed in only 34% yield and a moderate 67% ee (entry 6). Additionally, the substitution pattern at the sulfur atom also plays a role in the enantioselectivity. The replacement of the *S*-Bn group by either an *S*-Me or *S*-Et group led to a diminished level of enantioselection and a decrease in the yield.

Further modifications in the structure of the organocatalyst were made, by changing the chalcogen moiety (Scheme 2). First, we prepared a catalyst derived from L-methionine in order to increase the tether length between the sulfur atom and the pyrrolidine ring. Thus, organocatalyst **5** was prepared according to the same strategy depicted in Scheme 1, only changing the L-cysteine derivative by the appropriate protected L-methionine. Evaluation of the behavior of the catalyst in the asymmetric addition of acetone to benzaldehyde, under our optimized conditions, delivered the aldol product in 53% yield and an ee of 82%. This result is



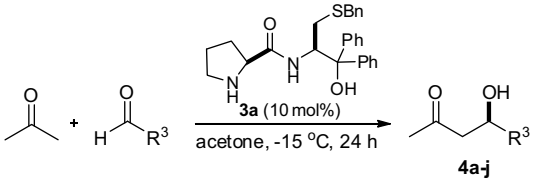
Scheme 2. Asymmetric aldol reaction organocatalyzed by **5** or **6**. Yields and ee's refer to product **4**.

inferior to that obtained with organocatalyst **3a** (83% yield, 94% ee) and is comparable to that obtained with **3g** (R^1 = Me, R^2 = Ph; 60% yield, 82% ee). These results indicate that the distance between the sulfur atom and the pyrrolidine nucleus does not play a significant role in the reaction outcome. Another change that was made, aiming to refine the catalytic properties of our system, was the replacement of L-cysteine by their selenium analog, L-selenocysteine.[13] In this way, organocatalyst **6** was prepared and its catalytic behavior was tested toward our standard reaction, and the aldol product was isolated in 50% yield and 85% ee. Direct comparison of the results achieved using this selenium-derived prolinamide with **3a** shows that the selenium atom does not improve the efficiency of the catalyst.

The optimal conditions were employed for the organocatalytic asymmetric aldol reaction of acetone with a broad scope of aldehydes and the results of this study are summarized in Table 3. In general, high enantioselectivities (82–94% ee) were obtained with aldehydes substituted in the 4 position, with the exception of the *para*-nitrobenzaldehyde, which furnished the corresponding aldol adduct in a moderate 64% ee. The catalytic system displays some sensitivity toward steric effects, and *ortho*-substituted benzaldehydes resulted in slightly decreased levels of ee's.

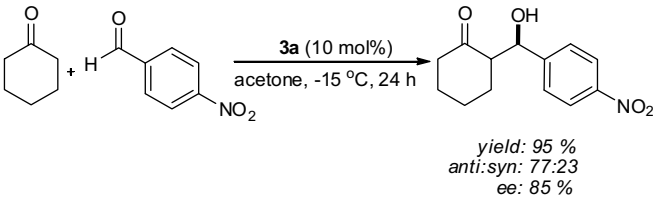
The aldol reaction between the 2-cyclohexan-1-one and 4-nitro benzaldehyde also proceeded smoothly under the standard conditions, affording the corresponding product in 95% yield and 77:23 of diastereomeric ratio, favoring the *anti* diastereomer with high level of enantioselectivity (Scheme 3).

Table 3
Organocatalytic asymmetric aldol reaction of acetone with several aromatic aldehydes



Entry	Product	R^3	Yield[a] (%)	ee[b] (%)
1	**4a**	Ph	83	94
2	**4b**	4-NO_2Ph	40	64
3	**4c**	2-NO_2Ph	53	61
4	**4d**	4-ClPh	57	87
5	**4e**	4-MePh	56	85
6	**4f**	2-MePh	56	81
7	**4g**	4-OMePh	35	82
8	**4h**	2-OMePh	36	72

[a] Isolated yield.
[b] Enantioselectivities were determined by HPLC analysis and absolute configurations were determined by comparison with the literature data.[4]



Scheme 3. Organocatalytic asymmetric aldol reaction with cyclohexanone.

In summary, the results from this investigation demonstrate that the cysteine-derived prolinamide is a robust and effective catalyst for enantioselective aldol reaction. Expanding the scope of this organocatalyst in asymmetric transformations is underway in this laboratory.[14]

Acknowledgments

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12. *General procedure for the synthesis of compound* **3a**: Under an argon atmosphere, *N*-methylmorpholine (1.01 g, 10 mmol) was added to a solution of *N*-(*tert*-butoxycarbonyl)-L-proline (2.15 g, 10 mmol) in $CHCl_3$ (100 mL) at 0 °C. After stirring for 15 min at this temperature, ethyl chloroformate (1.08 g, 10 mmol) was added dropwise and stirring was prolonged for additional 30 min at 0 °C. After this time a $CHCl_3$ (10 mL) solution of the *S*-Bn-L-cysteine methyl ester (2.61 g, 10 mmol) was added dropwise, followed by 1 equiv of *N*-methylmorpholine and the resulting solution was stirred at 0 °C for additional 1 h and then at room temperature for 24 h. After this time the solution was diluted with 30 mL of $CHCl_3$, and washed with 1 M NaOH (2 × 20 mL), 1 M HCl

(2 × 20 mL), and brine (20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The resulting product was used without further purification. PhMgBr (15 mmol) in Et_2O (15 mL, 1 M solution) was added to a Et_2O (10 mL) solution of **1** (5 mmol) at 0 °C, and the mixture was stirred for additional 24 h at room temperature. After this time, the reaction mixture was quenched with aqueous saturated NH_4Cl (10 mL) and extracted with AcOEt (3 × 15 mL). The combined organic phases were dried with $MgSO_4$, filtered, and the solvent removed under vacuum. The crude product was purified by flash chromatography, first eluting with hexanes and then with a mixture of hexanes/ethyl acetate (70:30), furnishing the desired product in 60% yield. The Boc protecting group was removed by treatment with trifluoroacetic acid (3.66 mL), which was slowly added to *N*-(*tert*-butoxycarbonyl)-L-prolinamide **2a** (1 g, 1.83 mmol) at 0 °C, and the resulting solution was stirred for 4 h at room temperature. Excess of trifluoroacetic acid was carefully neutralized by adding solid potassium carbonate, the whole mixture was filtered and the solvent was removed to obtain the pure product. Analytical data for **3a**: Yield: 90%; $[\alpha]_D^{20}$ −115.7 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, 1H, *J* = 4.2 Hz), 7.47 (m, 4H), 7.17 (m, 11H), 5.97 (br, 1H), 4.59 (t, 1H, *J* = 10.6 Hz), 3.58 (s, 2H), 3.47 (m, 1H), 2.93 (m, 1H), 2.78 (m, 1H), 2.62 (m, 2H), 1.85 (m, 1H), 1.44 (m, 2H), 1.27 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0, 146.1, 144.7, 138.3, 128.7, 128.4, 128.2, 127.9, 126.8, 126.7, 126.6, 125.7, 125.5, 80.6, 60.4, 57.8, 46.9, 36.7, 31.9, 30.4, 25.4. HRMS-ESI: *m/z* calcd for $C_{27}H_{30}N_2O_2S$ + H+: 447.2101; found: $C_{27}H_{30}N_2O_2S$ + H+: 447.2098.

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14. *General procedure for the enantioselective direct aldol reaction:* A solution of a catalyst **3a** (0.1 mmol) in dry acetone (1 mL) was stirred at the temperature indicated in the tables, for 30 min. Aldehyde (1 mmol) was then added and the resulting mixture was stirred at the same temperature for 24 h. After completion of the reaction, as indicated by TLC, the reaction mixture was treated with saturated aqueous ammonium chloride solution and the whole mixture was extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with brine, dried with $MgSO_4$, and the solvent was removed under vacuum. The crude mixture was purified by column chromatography on silica gel eluting with hexane–ethyl acetate (8:2) and the ee's were determined by HPLC analysis using Chiralcel OD-H or Chiralpak AD-H columns.