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Organocatalytic asymmetric 5-hydroxypyrrolidine synthesis: a highly enantioselective route to 3-substituted proline derivatives

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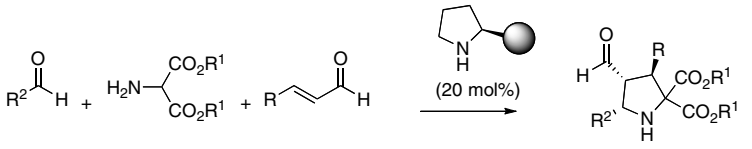
Abstract—The highly enantioselective organocatalytic tandem reaction between 2-acylaminomalonates and α,β-unsaturated aldehydes is presented. The reaction is a direct entry to 5-hydroxypyrrolidines and 3-substituted proline derivatives, which are furnished in high yields and 90–99% ee.

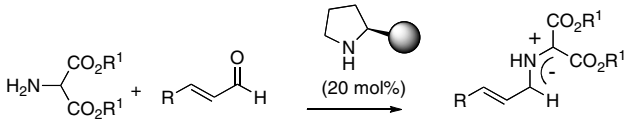
Substituted chiral proline derivatives are constituents of natural products and pharmaceutically active compounds such as protease inhibitors and antiviral compounds.[1] Moreover, proline derivatives are important metal-free catalysts for asymmetric transformations.[2] Proline derivatives are also used to induce conformational constraints into peptides.[3] Thus, catalytic asymmetric methods, which rely on 1,3-dipolar additions, have been developed for their preparation.[4]

Racemic 5-hydroxypyrrolidine derivatives are important building blocks for the synthesis of optically active proline derivatives.[5] For example, they are obtained by resolution.[5d] However, there is only one report, from Merck, of a catalytic enantioselective synthesis of 5-hydroxyproline derivatives that gives the compounds in up to 62% ee.[6]

In the research field of organocatalysis, amine-catalyzed domino, cascade and tandem reactions were recently developed.[2e,7–9] Moreover, chiral amines catalyze the asymmetric synthesis of chiral pyrrolidine derivatives.[10] In this context, we recently found that chiral pyrrolidines catalyze the formation of chiral pyrrolidine derivatives via an asymmetric multicomponent [C + NC + CC] reaction between aldehydes, 2-aminomalonates, and enals (Eq. 1).[10b] The reaction between 2-aminomalonate and the enal without the aldehyde component gave exclusively the corresponding ylide (Eq. 2).



(1)



(2)

However, previous work[6,9] and retrosynthetic analysis suggested a possibility to completely change the reaction pathway and obtain optically active 5-hydroxypyrrolidines by acylation of 2-aminomalonates (Scheme 1).

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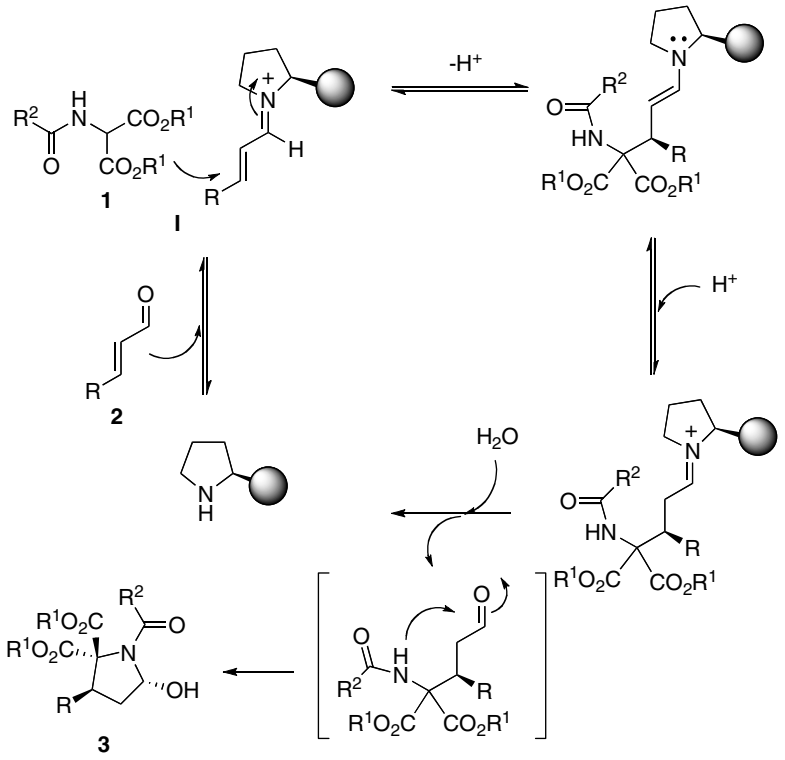
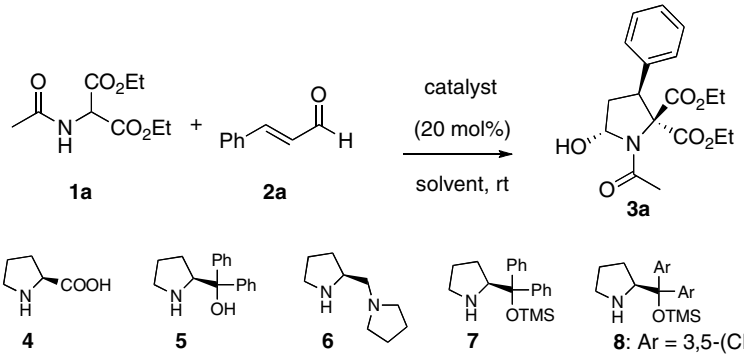


Scheme 1. A plausible reaction pathway for a chiral amine-catalyzed enantioselective formation of 5-hydroxyproline derivatives.

Table 1. Catalyst screen for the reaction between **1a** and **2a**

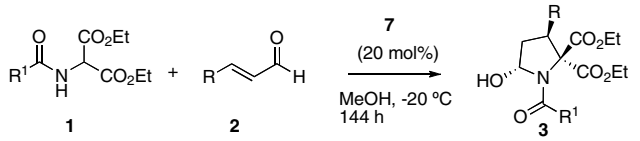


Entry	Catalyst	Solvent	Time (h)	Conv.[a] (%)	α/β[a]	ee[b] (%)
1	**4**	MeOH	14	0	—	—
2	**5**	MeOH	14	0	—	—
3	**6**	MeOH	14	75	5:1	5
4	**7**	MeOH	14	100	5:1	46
5	**8**	$CHCl_3$	72	<5	n.d.	n.d.
6	**7**	$CHCl_3$	48	100[c]	5:1[c]	30[c]
7	**7**	DMF	14	0	—	—
8	**7**	*i*-PrOH	44	100	5:1	20
9	**7**	EtOH	14	100	5:1	37
10	**7**	MeOH	72	100[d]	5:1[d]	65[d]
11	**7**	MeOH	144	100[e]	5:1[e]	97[e]

[a] Determined by NMR analysis.
[b] Determined by chiral-phase HPLC analyses.
[c] 1 equiv TEA was used as an additive.
[d] Reaction run at 4 °C.
[e] Reaction run at −20 °C.

Thus, we envisioned that the chiral amine-catalyzed tandem reaction between 2-acylaminomalonates and enals would be a simple asymmetric entry to 5-hydroxypyrrolidines where the subsequent intramolecular

Table 2. Scope of the organocatalytic tandem reaction



1 2 3

Entry	R^1	R	Prod.	Yield[a] (%)	α/β[b]	ee[c] (%)
1	Me	Ph	**3a**	74	5:1	97
2	Me	4-BrC_6H_4	**3b**	67	5:1	95
3	Me	4-$O_2NC_6H_4$	**3c**	72	6:1	99
4	Me	4-NCC_6H_4	**3d**	77	5:1	96
5	Me	2-Naphth	**3e**	76	5:1	90
6	Ph	Ph	**3f**	71	>10:1	99
7	Ph	4-$O_2NC_6H_4$	**3g**	70	>10:1	99

[a] Isolated yield of the pure product **3** after silica gel chromatography.
[b] Determined by NMR analysis of the crude reaction mixture.
[c] Determined by chiral-phase HPLC analyses.

hemiaminal formation would be an important driving force for product formation (Scheme 1). Moreover, our recent work on the tandem synthesis of 5-hydroxyisoxazolidines indicated that this strategy could be possible.[11]

Herein, we present a highly enantioselective catalytic route to the synthesis of 5-hydroxyproline derivatives (67–77% yield, 90–99% ee) that are readily converted into the corresponding 3-substituted proline derivatives (up to >25:1 dr).

In an initial catalyst screen for the reaction between 2-acetylaminomalonate **1a** (0.25 mmol) and cinnamaldehyde **2a** (0.50 mmol), we found that simple chiral pyrrolidines such as **6** and **7** catalyzed the enantioselective formation of 5-hydroxypyrrolidine **3a** (Table 1). However, amines **4**, **5**, and **8** did not catalyze the formation of **3a** under our reaction conditions. The protected chiral diamine **6** and prolinol **7**[12] catalyzed the formation of **3a** with poor and moderate enantioselectivity, respectively (entries 3 and 4). Thus, the reaction was further investigated using chiral amine **7** as the catalyst.

We found that the reaction was the fastest in polar protic solvents such as MeOH, *i*-PrOH, and EtOH. The reaction rate decreased at lower temperature. However, to our delight, excellent enantioselectivity was achieved (entry 11). Thus, we decided to investigate the scope of the catalytic asymmetric tandem reaction at −20 °C using MeOH as the solvent (Table 2).[13]

The organocatalytic enantioselective tandem reactions were highly enantioselective at −20 °C and the corresponding 5-hydroxypyrrolidines **3** were isolated in 67–77% yield with 90–99% ee. Notably, the reactions with 2-benzoylaminomalonate **1b** led to increased enantioselectivity of the reaction and gave the corresponding products **3** in high yields with 99% ee (entries 6 and 7). Moreover, the larger phenyl group increased the α/β ratio of hemiaminals **3**. The relative stereochemistry of 5-hydroxypyrrolidines was determined by 1D NOE experiments on compound **3g** (Fig. 1).

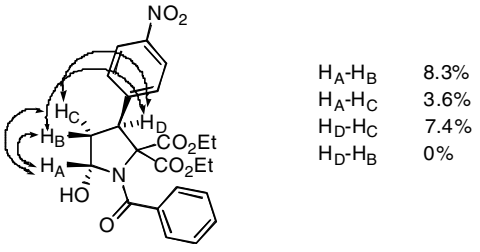
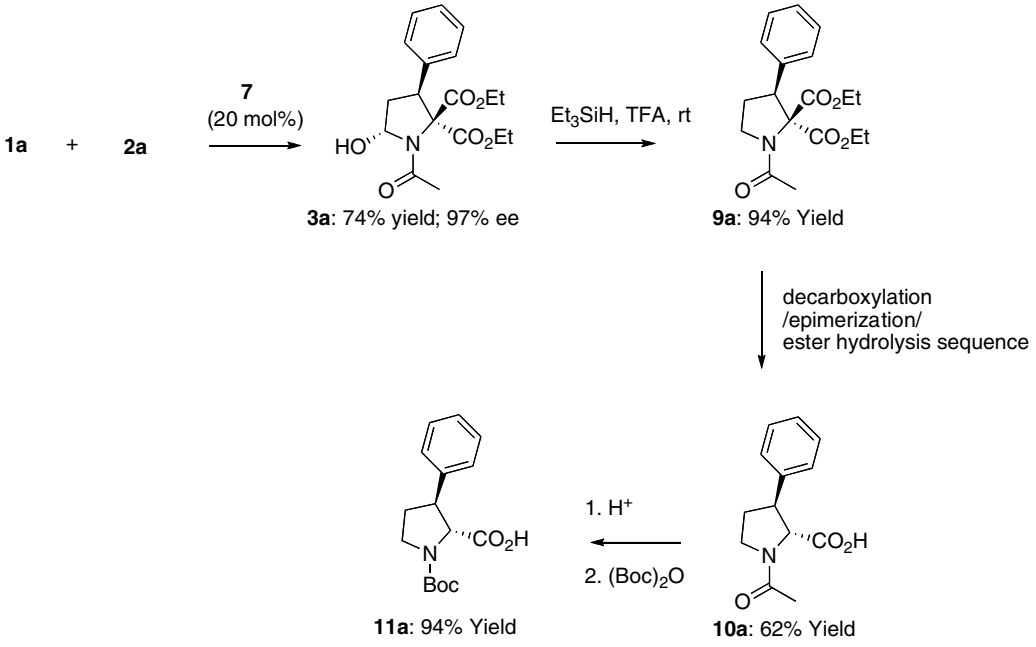


Figure 1. The results from the NOE experiments on **3g**.



Scheme 2. Enantioselective synthesis of 3-substituted proline derivatives **10a** and **11a**.

The organocatalytic reaction was readily scaled up and gave access to a variety of proline derivatives. For example, optically active 3-substituted proline derivatives such as **9a** were accessible using the chiral amine **7**-catalyzed reaction (Scheme 2).

Thus, reductive deoxygenation of 5-hydroxypyrrolidine **3a** gave the corresponding N-protected 3-phenylpyrrolidine **9a** in 94% yield.[14] Moreover, a highly diastereoselective decarboxylation/epimerization/ester hydrolysis sequence on **9a** gave proline **10a** in 62% yield as a single diastereoisomer (>25:1 dr). It should be mentioned that the *cis*-proline derivative of **10a** was also readily available by decarboxylation of **9a**.[5d] Thus, both diastereoisomers of the 3-substituted proline derivatives are available. Changing the protective group from an acetyl group to a Boc group gave the known proline **11a** in 94% yield ready to be used in peptide synthesis. Comparison with the literature revealed that the absolute configuration of **11a** at C3 was *S* and C2 was *R* ($[\alpha]_D^{25}$ −34.7 (*c* 0.5, $CHCl_3$)), lit. ($[\alpha]_D^{25}$ −35.9 (*c* 1.0, $CHCl_3$)[15]).[16] Thus, efficient shielding of the *Re*-face of the chiral iminium intermediate by the bulky aryl groups of **7** leads to stereoselective *Si*-facial nucleophilic conjugate attack on the β-carbon of **1** (Scheme 1). This is in accordance with other amine-catalyzed reactions between malonates and enals.[9] Next, the released N-protected aminoaldehyde intermediate undergoes favored hemiaminal formation to give 5-hydroxypyrrolidine **3**.

In summary, we have reported a highly enantioselective organocatalytic synthesis of 5-hydroxypyrrolidines, which are formed in high yields with 90–99% ee. Moreover, the organocatalytic tandem reaction represents a versatile asymmetric entry to different proline derivatives. Mechanistic studies, synthetic applications of this transformation, and the development of other enantioselective tandem reactions are ongoing in our laboratory.

Acknowledgments

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13. *Typical experimental procedure for the organocatalytic synthesis of chiral pyrrolidines*: To a stirred solution of aldehyde (0.5 mmol, 2.0 equiv) in MeOH at −20 °C, catalyst **7** (0.05 mmol, 0.2 equiv) and diethyl (*N*-acetylamino)malonate (0.25 mmol, 1.0 equiv) were added. The reaction mixture was stirred at −20 °C for 144 h. Next, the crude reaction mixture was directly loaded on and purified by silica gel chromatography (EtOAc/pentane mixtures) to afford the corresponding pyrrolidine derivative **3**. Compound **3a**: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.35–7.18$ (m, 5H), 5.74 (d, $J = 4.4$ Hz, 1H), 4.38–4.30 (m, 2H), 4.14 (dd, $J = 12.8$ Hz, $J = 8$ Hz, 1H), 3.90–3.82 (m, 1H), 3.70–2.64 (m, 1H), 2.76 (td, $J = 12.8$ Hz, $J = 4.8$ Hz, 1H), 2.30 (s, 3H), 2.30–2.24 (m, 1H), 1.33 (t, $J = 7.2$ Hz, 3H), 0.85 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 170.2, 169.3, 163.6, 134.9, 129.1, 128.6, 128.1, 128.0, 82.3, 75.3, 62.3, 61.5, 49.9, 38.5, 21.6, 13.9, 13.4. $[\alpha]_D$ −45.0 (*c* 1.0, $CHCl_3$). HRMS (ESI): calcd for $[M+Na]^+$ ($C_{18}H_{23}NO_6$) requires *m*/*z* 372.1418, found 372.1421. The enantiomeric excess was determined by HPLC with an ODH column. (*n*-hexane/*i*-PrOH = 90:10, $\lambda = 230$ nm), 1.0 mL/min; t_R = major enantiomer 16.2 min, minor enantiomer 30.8 min. Compound **3d**: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.61$ (d, $J = 8.4$ Hz, 2H), 7.38 (d, $J = 8.4$ Hz, 2H), 5.78 (d, $J = 4.8$ Hz, 1H), 4.36–4.31 (m, 2H), 4.17–4.12 (m, 1H), 3.93–3.86 (m, 1H), 3.77–3.71 (m, 1H), 2.76–2.67 (m, 1H), 2.30 (s, 3H), 2.31–2.26 (m, 1H), 1.32 (t, $J = 7.2$ Hz, 3H), 0.90 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 170.1, 169.3, 165.6, 141.0, 132.2, 130.0, 127.0, 118.6, 82.5, 75.3, 63.0, 62.0, 49.8, 38.7, 22.0, 14.2, 13.8. $[\alpha]_D$ −14.1 (*c* 1.0, $CHCl_3$). HRMS (ESI): calcd for $[M+Na]^+$ ($C_{19}H_{22}NO_6$) requires *m*/*z* 397.1370, found 397.1370. The enantiomeric excess was determined by HPLC with an ODH column. (*n*-hexane/*i*-PrOH = 90:10, $\lambda = 230$ nm), 1.0 mL/min; t_R = major enantiomer 36.5 min, minor enantiomer 58.6 min. Compound **3g**: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.17$ (d, $J = 8.8$ Hz, 2H), 7.68 (d, $J = 7.6$ Hz, 2H),7.56 (d, $J = 8.8$ Hz, 2H), 7.52–7.40 (m, 3H), 5.59 (d, $J = 4.4$ Hz, 1H), 4.48–4.30 (m, 3H), 3.94–3.82 (m, 2H), 2.75 (td, $J = 13.2$ Hz, $J = 4.8$ Hz, 1H), 2.20 (dd, $J = 12.4$ Hz, $J = 6.4$ Hz, 1H), 1.35 (t, $J = 7.2$ Hz, 3H), 0.98 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 169.1, 165.5, 147.8, 143.0, 135.5, 131.0, 130.4, 128.9, 127.3, 123.4, 83.0, 75.3, 63.0, 62.1, 49.2, 38.7, 14.3, 13.9. $[\alpha]_D$ +116.9 (*c* 1.0, $CHCl_3$). HRMS (ESI): calcd for $[M+Na]^+$ ($C_{23}H_{24}N_2O_8$) requires *m*/*z* 479.1425, found 479.1440. The enantiomeric excess was determined by HPLC with an AD column. (*n*-hexane/*i*-PrOH = 85:15, $\lambda = 230$ nm), 1.0 mL/min; t_R = major enantiomer 19.5 min, minor enantiomer 16.5 min.
14. To a solution of proline derivative **3a** (44 mg, 0.125 mmol) and triethylsilane (0.03 mL, 0.186 mmol) in 0.5 mL of $CHCl_3$ was added slowly trifluoroacetic acid (0.1 mL, 125 mmol) over 10 min with a syringe while stirring. After stirring for 2.5 h at room temperature, the solution was concentrated under reduced pressure, and then an EtOAc solution of the residue was washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated to afford 0.040 mg of a colorless oil. The NMR data matched with the literature in Ref. 5d. Compound **9a**: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.35–7.25$ (m, 3H), 7.25–7.15 (m, 2H), 4.28 (q, $J = 7.5$ Hz, 2H), 3.96–3.84 (m, 3H), 3.80–3.70 (m, 2H), 2.65–2.55 (m, 1H), 2.30–2.22 (m, 1H), 2.15 (s, 3H), 1.30 (t, $J = 7.2$ Hz, 3H), 0.86 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 169.3, 168.4, 166.3, 135.9, 128.3, 128.0, 127.7, 75.1, 61.8, 61.3, 53.2, 47.5, 29.1, 22.1, 14.0, 13.4. $[\alpha]_D^{25}$ +3.3 (*c* 1.0, MeOH).
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16. Crude diester **9a** (36 mg, 0.108 mmol) was suspended in 1 mL of 0.5 N NaOH and stirred at room temperature for 21 h. Next, the solution was extracted once with EtOAc and then acidified to pH 2 with 3 N HCl. The precipitate was dissolved in $CHCl_3$ and the aqueous phase was extracted twice with $CHCl_3$. The combined $CHCl_3$ fractions were concentrated to a solid residue, which was heated for 1 h at 75 °C in 1 mL of toluene. After evaporation of the solvent, the residue was heated at reflux for 2 h with 1 mL of 1 M NaOEt in EtOH, which contained 30 μL of ethyl trifluoroacetate as an H_2O scavenger. After cooling, water (1 mL) was added, the solution was stirred for 2.5 h at room temperature, and then acidic and neutral compounds were separated by extractive techniques. The crude acid was dissolved in 0.4 mL of AcOH and 1.2 mL of 8 N HCl and heated at reflux for 18 h. The mixture was concentrated to dryness, the residue was taken up in H_2O and extracted once with an equal volume of AcOEt, and the aqueous phase was again concentrated to dryness. The residue was dissolved in 1 mL of 1:1 H_2O/dioxane and treated with Et_3N (48 mL, 35 mg, 0.35 mmol) and Boc_2O (75 mg, 0.345 mmol). After stirring for 4 h, additional Et_3N was added to ca. pH 9, then stirring was continued for an additional 18 h. Extractive isolation of the acidic component afforded 32 mg of a tan foam. Chromatography over silica gel (1:1 AcOEt/hexanes containing 1% AcOH) afforded 18 mg (58%) of the final compound. Compound **11a**[14]: colorless powder. Melting point: 158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$) (two rotamers): $\delta = 7.40–7.20$ (m, 5H), 4.42 (d, $J = 4.4$ Hz, 0.55H), 4.27 (d, $J = 6.4$ Hz, 0.45H), 3.84–3.43 (m, 3H), 2.36–2.26 (m, 1H), 2.10–2.02 (m, 1H), 1.52 (s, 5H), 1.43 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): 177.7, 174.0, 156.3, 153.6, 140.9, 140.4, 128.9, 128.8, 127.4, 127.2, 127.0, 81.9, 80.7, 65.5, 65.3, 49.9, 46.8, 46.3, 45.9, 32.6, 32.4, 28.4, 28.3. $[\alpha]_D$ −34.7 (*c* 0.5, $CHCl_3$).