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Highly enantioselective organocatalytic synthesis of piperidines. Formal synthesis of (−)-Paroxetine

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ABSTRACT

A highly enantioselective organocatalytic synthesis of piperidines is reported. The reaction is catalyzed by simple and commercially available secondary amines, affording the corresponding adducts with high yields and enantioselectivities. Moreover, this reaction is used for the formal synthesis of (−)-Paroxetine, a blockbuster drug, in only three steps.

The discovery of new reactions that allow us to build complex molecular scaffolds in an efficient way from readily available starting materials remains a challenging goal in chemical synthesis. However, a limited number of catalytic enantioselective cascade reactions,[1] which enable the facile construction of complex scaffolds, have been developed thus far.

Due to the widespread occurrence of the piperidine ring in biologically active compounds,[2] the development of efficient methods for its diastereoselective or enantioselective synthesis is a subject of considerable practical importance. It is widely accepted that the biological properties of piperidines are highly dependent on the type and location of substituents in the heterocycle. Accordingly, great attention has been paid to the construction of functionalized piperidines. It is well documented that piperidin-2-ones are common synthetic precursors for biologically important polycyclic alkaloids, such as indolo[2,3-α]quinolizidines and benzo[α]quinolizidines. In the literature, we can find several methodologies that allow us to obtain this privileged structure. In 2005, Takasu et al. reported a synthesis of racemic piperidines from α,β-unsaturated amides by an intermolecular aza-double Michael addition.[3] In the realm of organocatalysis,[4] Jorgensen and coworkers reported a Michael addition[5] of malonates to α,β-unsaturated aldehydes that could be used to obtain piperidines in only three steps in excellent yields and enantioselectivities.[6,7] In 2007, Rios and Córdova[8] reported a synthesis of pyrrolidines from 2-amidomalonates and α,β-unsaturated aldehydes, catalyzed by simple secondary amines with excellent enantioselectivities and yields. In this Letter, the authors developed a malonate addition to α,β-unsaturated aldehydes followed by a hemiacetal formation to furnish the pyrrolidine moiety. The same authors have shown in their synthesis of 5-hydroxyisoxazolidines[9] that the intramolecular formation of hemiacetals or hemiaminals could push the organocatalytic reaction and exert an important positive effect in terms of conversion and enantioselectivity.

With these ideas in mind, we envisioned an easy and direct entry to piperidines by coupling of imidomalonates **1** and α,β-unsaturated aldehydes **2**, as shown in Scheme 1, which could be used for the facile synthesis of valuable compounds such as (−)-Paroxetine[5,7] and (+)-Femoxetine[5] in a highly enantioselective fashion.

In our initial experiments (Table 1), we selected the TMS-protected diphenylprolinol **I** as the catalyst, and we screened different solvents and additives in order to achieve high enantioselectivities and yields in the addition of imidomalonate **1a** to 4-nitrocinnamaldehyde (**2a**).

To our delight, when polar protic solvents such as MeOH and EtOH (entries 6 and 8) were used, the reaction performed well but with moderate enantioselectivities. Interestingly, when non-polar or non-protic solvents (entries 2, 3, 9 and 10) were used, no reaction was observed. The reaction is simply catalyzed by secondary amines, but requires an additional base such as KOAc to afford high yields. Surprisingly when 2,2,2-trifluoroethanol, a more acidic solvent (entry 11), was used as a solvent we achieved very high enantioselectivities and yields.[10]

Once we determined the optimal conditions to perform the reaction, we screened several secondary amines as catalysts. As is shown in Table 2, catalyst **I** gave us the best enantioselectivities, while proline (**II**) or catalyst **III** or **IV** afforded worse enantioselectivities and yields.

Next, we screened different α,β-unsaturated aldehydes in order to study the scope of the process (Table 3). In all the examples screened, the reaction furnished the desired piperidines in moderate to excellent yields and excellent enantioselectivities (90–99%).

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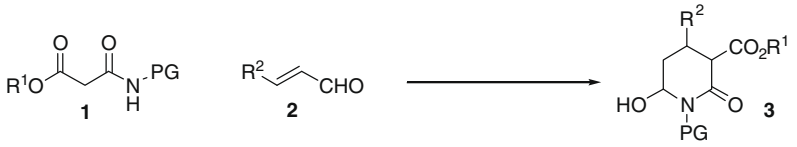
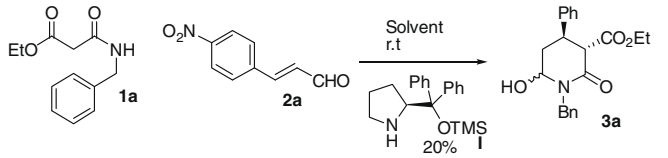


Scheme 1. Amidomalonate addition.

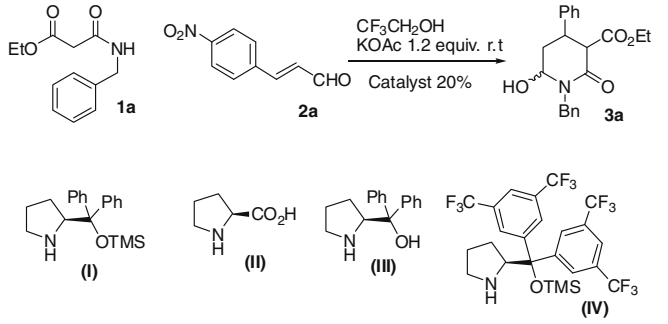
Table 1
Conditions screening[a]



Entry	Solvent	Additive	Yield[b] (%)	dr[c]	ee[d] (%)
1	$CHCl_3$	—	0	—	—
2	$CHCl_3$	Et_3N	0	—	—
3	$CHCl_3$	KOAc	Traces	—	—
4	MeOH	—	0	—	—
5	MeOH	Et_3N	67	5:1	57
6	MeOH	KOAc	86	5:1	74
7	MeOH[e]	KOAc	72	5:1	96
8	EtOH	KOAc	75	5:1	62
9	AcOEt	Et_3N	0	—	—
10	Toluene	Et_3N	0	—	
11	CF_3CH_2OH	KOAc	92	5:1	95

[a] The experimental conditions: A mixture of **1a** (0.30 mmol), catalyst **I** (20%, 0.05 mmol), **2a** (0.25 mmol) and additive (0.30 mmol) in solvent (1 mL) was stirred at rt overnight. Crude product **3a** was purified by column chromatography.
[b] Isolated yield.
[c] Determined by NMR analysis of crude reaction.
[d] Determined by chiral HPLC analysis.
[e] Reaction run at 0 °C.

Table 2
Catalyst screening[a]

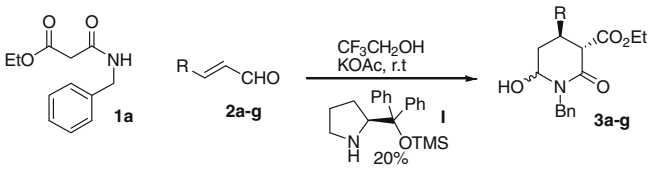


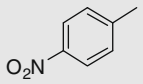
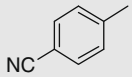
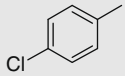
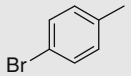
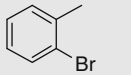
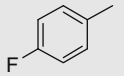
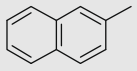
Entry	Catalyst	Yield[b] (%)	dr[c]	ee[d] (%)
1	**I**	92	5:1	95
2	**II**	76	5:1	22
3	**III**	0	—	—
4	**IV**	56	5:1	58

[a] The experimental conditions: A mixture of **1a** (0.30 mmol), catalyst (20%, 0.05 mmol), **2a** (0.25 mmol) and KOAc (0.30 mmol) in CF_3CH_2OH (1 mL) was stirred at rt overnight. Crude product **3a** was purified by column chromatography.
[b–d] Same as in Table 1.

When electron-withdrawing substituents were used in the aromatic ring, the yields and enantioselectivities were excellent (Table 3, entries 1 and 2) and the reaction times were shorter. The reaction works also fine with halogen substituents in the aromatic ring such as chloro, bromo or fluoro in 4-position (Table 3, entries 3, 5 and 7) or in 2-position (Table 3, entry 6).

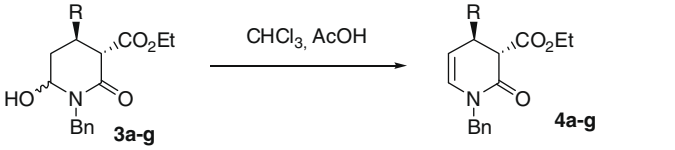
Table 3
Aldehyde screening[a]



Entry	Compound	R	Product	Yield[b] (%)	dr[c]	ee[d] (%)
1	**2a**		**3a**	92	5:1	95
2	**2b**		**3b**	94	5:1	94[e]
3	**2c**		**3c**	84	4:1	90[e]
4	**2d**		**3d**	90	3:1	98
5	**2e**		**3e**	93	5:1	94[e]
6	**2f**		**3f**	71	5:1	96
7	**2g**		**3g**	84	5:1	90[e]
8	**2h**		**3h**	86	3:1	99

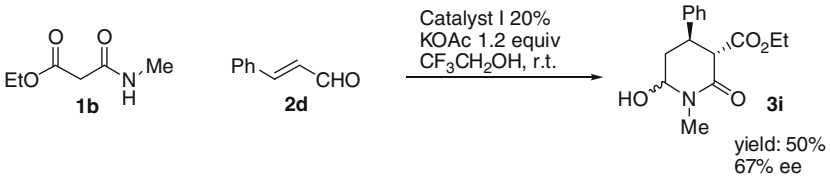
[a–d] Same as Table 1.
[e] ee of dehydrated product.

In all the examples, we obtained a mixture of diastereomers with 3:1 to 5:1 ratio. This diastereoselectivity corresponds to the equatorial or axial position of the hemiaminal hydroxyl of the piperidine. This can be easily confirmed by elimination of the



quantitative yield, 1 diastereomer

Scheme 2. Dehydration of compounds **3**.



Scheme 3. Reaction with imidomalonate **1b**.

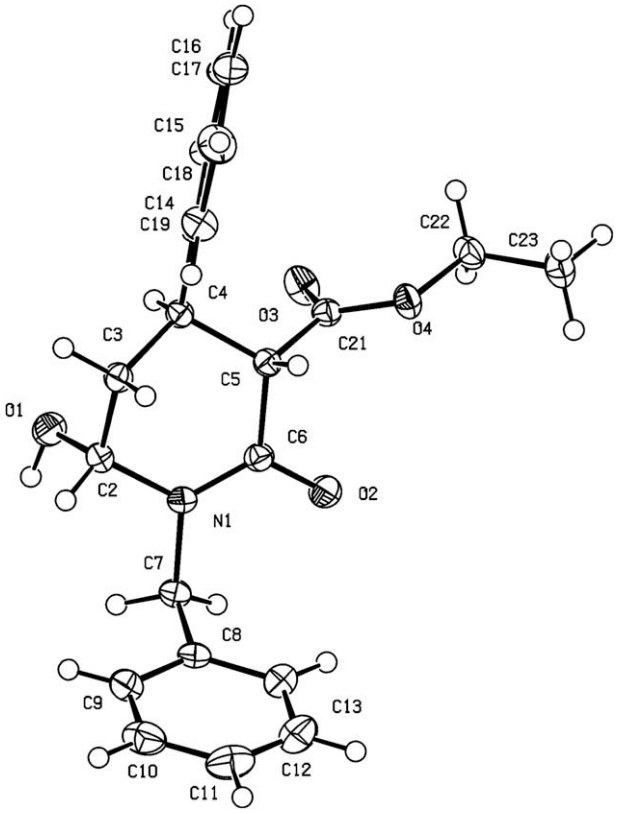


Figure 1. X-ray structure of **3d**.[13]

hydroxyl to furnish compounds **4** in acid media. In all the cases, we obtained only one product in quantitative yield and without loss of enantioselectivity, as shown in Scheme 2.

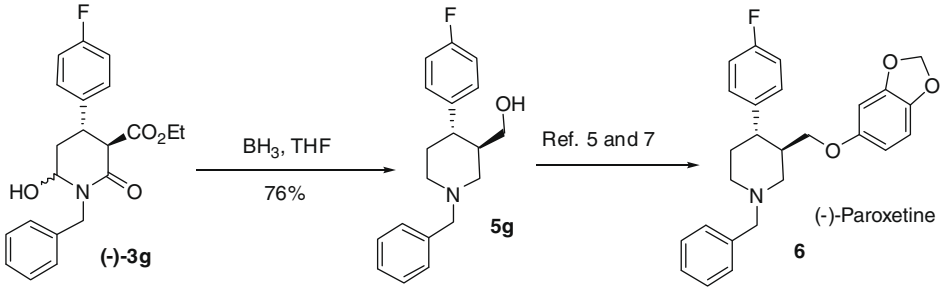
The use of amidomalonates other than **1a** was briefly investigated. For example, when ethyl 3-(methylamino)-3-oxopropanoate **1b** was used instead of ethyl 3-(benzylamino)-3-oxopropanoate **1a**, the reaction furnished the corresponding piperidine derivative **3i** with lower yields and enantioselectivities (50% yield, 67% ee) (Scheme 3).

In order to elucidate the structure of the major diastereomer of compound **3d,** we performed an X-ray diffraction analysis as shown in Figure 1.

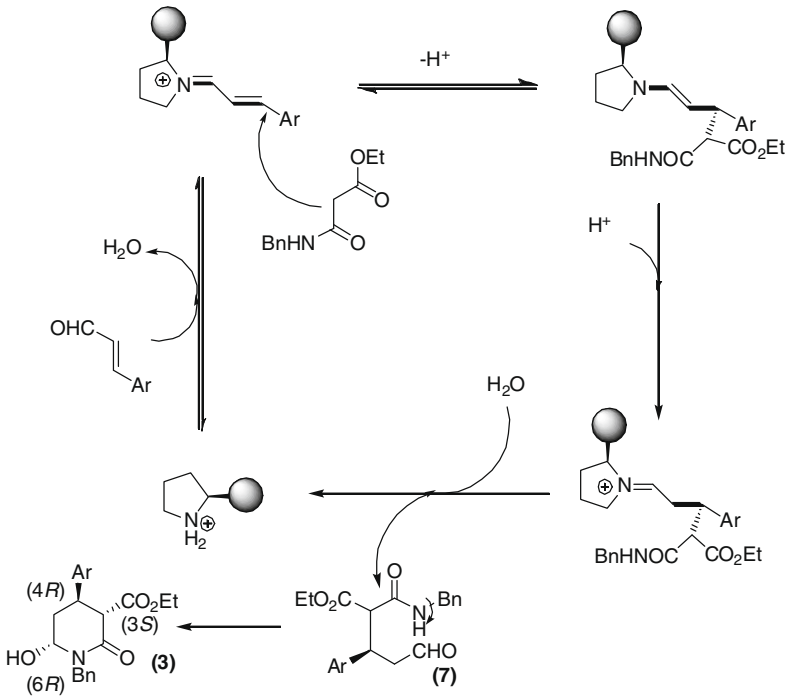
On the other hand, the absolute configuration of the adducts was ascertained by chemical correlation. Thus, reduction of compound (−)-**3g** (obtained by using **ent-I** as the catalyst) gave the corresponding piperidine **5g** as shown in Scheme 4. Comparison with the literature data revealed that the absolute configuration of compound **5g** is (3*R*,4*S*) ($[\alpha]_D^{25}$ −23.4 (*c* 1.2, $CHCl_3$), lit. (Ref. 5) ($[\alpha]_D^{25}$ −21.2 (*c* 0.5, $CHCl_3$). This compound is described as a chiral intermediate in the synthesis of (−)-Paroxetine, a blockbuster antidepressive drug.[5,7,11]

The stereochemical outcome could be rationalized by the mechanistic proposal outlined in Scheme 5. Thus, efficient shielding of the *Re*-face of the chiral iminium intermediate by the bulky aryl groups of **I** leads to stereoselective *Si*-facial nucleophilic conjugate attack on the β-carbon of **2**. This is in accordance with other amine-catalyzed reactions between malonates and enals. Next, intermediate **7** cyclizes spontaneously to afford the hemiacetal **3**. It should be noticed that epimerization of the stereochemically labile stereocentre at C3 will establish the thermodynamically more stable (3*S*,4*R*) trans-configuration.

In summary, we have reported an organocatalytic, highly enantioselective conjugate addition of amidomalonates to α,β-unsaturated aldehydes, that furnishes chiral piperidines after hemiaminal formation in excellent yields and enantioselectivities. Furthermore, we have developed a simple synthesis of (−)-Paroxetine in only three steps from commercially starting materials in high yields and enantioselectivities. This new synthesis improves the reported procedures by the reduced number of steps and the high levels of enantioselectivity achieved.[11] Mechanistic studies, synthetic applications and the discovery of new reactions based on this concept are ongoing in our laboratory.[12]



Scheme 4. Formal synthesis of (−)-Paroxetine.



Scheme 5. Mechanism of the reaction.

Acknowledgements

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10. *Typical experimental procedure for the synthesis of compound* **3d**: To a stirred solution of catalyst **I** (16 mg, 0.05 mmol, 20 mol %) in CF_3CH_2OH (1.0 mL) were added 4-nitrocinnamaldehyde **2a** (33 mg, 0.25 mmol, 1 equiv), KOAc (30 mg, 0.3 mmol, 1.2 equiv) and amidomalonate **1a** (64 mg, 0.3 mmol, 1.2 equiv). The reaction was vigorously stirred at rt overnight. Next, the crude product was purified by silica gel chromatography (hexane/EtOAc mixtures) to give the corresponding piperidine derivative **3a**. *Compound* **3d**: ^{1}H NMR (400 MHz. $CDCl_3$, TMS_{int}): δ (ppm) = 8.26 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 7.44–7.37 (m, 5H), 5.30–5.12 (m, 2H), 4.43 (d, J = 15.0 Hz, 1H), 4.30–4.10 (m, 3.72–3.66 (m, 2H), 2.30–2.12 (m, 2H), 1.19 (t, 3H, J = 7.1 Hz). ^{13}C NMR (100 MHz. $CDCl_3$): δ (ppm) = 169.6, 165.5, 148.1, 136.6, 129.0, 128.8, 128.3, 128.2, 128.1, 127.8, 124.3, 78.0, 61.8, 56.7, 48.0, 37.1, 37.0, 14.2. HRMS: Calculated for $[C_{21}H_{22}N_2O_6Na]^+$: 421.1370; found: 421.1372. $([\alpha]_D^{25}$ +5.3 (95% ee). HPLC: Chiralpak® IA hexane/IPA 90:10 1 mL/min. Time: 19.3 min and 35.4 min.
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