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Asymmetric Catalysis

Catalytic Michael/Ring-Closure Reaction of α,β-Unsaturated Pyrazoleamides with Amidomalonates: Asymmetric Synthesis of (−)-Paroxetine

Yu Zhang, Yuting Liao, Xiaohua Liu,* Qian Yao, Yuhang Zhou, Lili Lin, and Xiaoming Feng*[a]

Abstract: A highly enantioselective tandem Michael/ring-closure reaction of α,β-unsaturated pyrazoleamides and amidomalonates has been accomplished in the presence of a chiral *N*,*N*′-dioxide–Yb(OTf)$_3$ complex (Tf: trifluoromethanesulfonyl) to give various substituted chiral glutarimides with high yields and diastereo- and enantioselectivities. Moreover, this methodology could be used for gram-scale manipulation and was successfully applied to the synthesis of (−)-paroxetine. Further nonlinear and HRMS studies revealed that the real catalytically active species was a monomeric L-**PMe$_2$**–Yb^{3+} complex. A plausible transition state was proposed to explain the origin of the asymmetric induction.

Introduction

Substituted piperidines are endowed with properties that make them of interest for biological and medicinal applications.[1] For instance, the *trans*-3,4-disubstituted piperidine (−)-paroxetine (Paxil R) has emerged as a selective serotonin re-uptake inhibitor for the treatment of depression, anxiety, and panic disorders (Figure 1).[2] The asymmetric synthesis of this heterocyclic scaffold has attracted significant interest for a long time.[3] Several catalytic enantioselective synthetic methods have been developed, such as allylic alkylation,[4] hydrogenation,[5] and Michael addition.[6] Among them, Michael addition is an efficient and straightforward technique with the advantage of accessible starting materials and convenient operation (Scheme 1). Although Michael additions of malonates with α,β-unsaturated aldehydes[6b,c] or nitroalkenes[6d] have been well reported, a reductive amination cyclization step was required to construct the lactam structure enantioselectively. Subsequently, Rios and co-workers used amidomalonate as an alternative nucleophile that could undergo an intramolecular hemiaminal formation to form the heterocycle.[6e,f] However, good results were given in the presence of the unusual solvent trifluoroethanol, which restricted the reaction's execution for scaled-up production. Therefore, the development of a concise synthetic methodology to form substituted piperidines was in high demand.

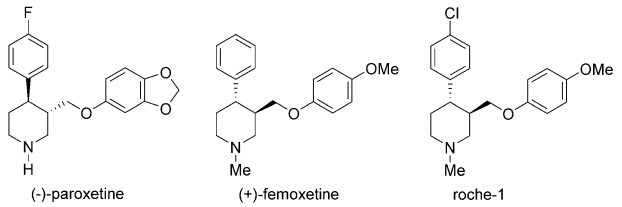
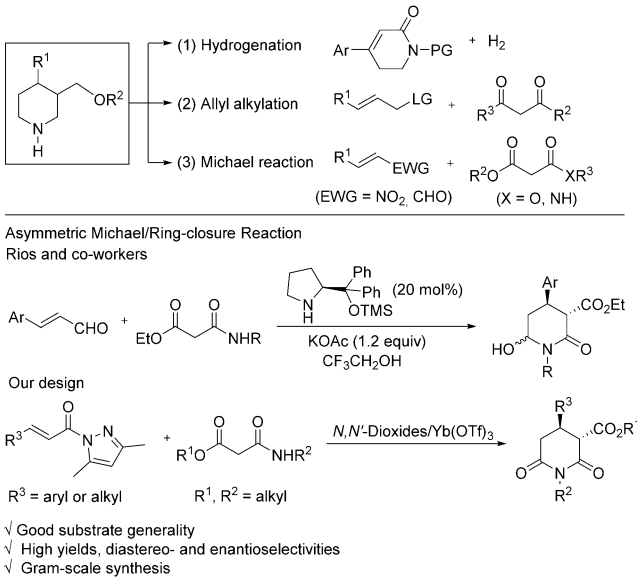


Figure 1. Selected biologically active compounds containing piperidines.



Scheme 1. Catalytic asymmetric reactions for the synthesis of (−)-paroxetine. PG: protecting group; LG: leaving group; EWG: electron-withdrawing group; TMS: trimethylsilyl; Tf: trifluoromethanesulfonyl.

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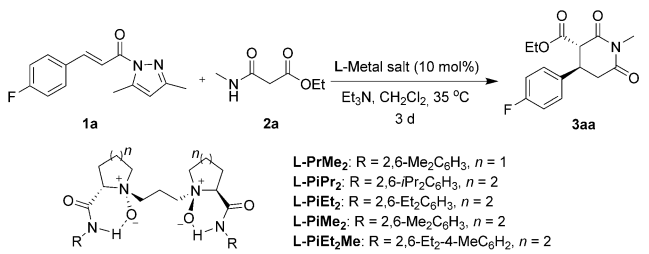
α,β-Unsaturated pyrazoleamides are useful Michael acceptors, in which the pyrazole unit could act as both a good directing group and a leaving group.[7] In the light of the advance of in situ cyclization of α,β-unsaturated amides,[8] we reasoned that the catalytic asymmetric reaction between α,β-unsaturated pyrazoleamides and amidomalonates would provide a straightforward access to the piperidine-2,6-dione backbone, a key intermediate for (−)-paroxetine and its analogues (+)-femoxetine and roche-1 as well. Here, we report a diastereo- and enantioselective Michael/ring-closure reaction of α,β-unsaturated pyrazoleamides with amidomalonates. The reaction performed well in the presence of a chiral *N*,*N*′-dioxide–Yb(OTf)$_3$ complex (Tf: trifluoromethanesulfonyl)[9] to furnish a wide range of chiral glutarimides in high yields and diastereo- and enantioselectivities (up to 99% yield, >95:5 d.r., 98% *ee*). (−)-Paroxetine could be obtained in 66% overall yield and 98% *ee* through a four-step transformation.

Results and Discussion

We selected the addition reaction of α,β-unsaturated pyrazoleamide **1a** and ethyl-*N*-methylmalonamide **2a** as a model reaction to optimize the reaction conditions, as summarized in Table 1. A preliminary study showed that lanthanide metal salts in combination with the chiral *N*,*N*′-dioxide L-**PiEt$_2$Me** were effective to promote the transformation to generate the desired *trans*-3,4-disubstituted glutarimide **3aa** (Table 1, entries 1 and 2). Yb(OTf)$_3$ gave a result of 96% *ee* and 94:6 d.r., albeit with a lower yield (Table 1, entry 2). The yield was slightly improved when the amount of Et$_3$N was increased (Table 1, entry 3). Next, a detailed screening of chiral *N*,*N*′-dioxide ligands revealed that L-**PiMe$_2$** could provide a comparable outcome of 22% yield and 97% *ee* (Table 1, entries 4–7). In order to improve the reaction yield, the modulation of other reaction parameters, including by fixing the ratio of metal/L-**PiMe$_2$**, by adding 3 Å molecular sieves, by raising the temperature, and by increasing the concentration, clearly improved the reactivity without erosion of the diastereo- and enantioselectivity (Table 1, entries 8 and 9). Finally, product **3aa** was isolated in 90% yield, 96:4 d.r., and 98% *ee*. Moreover, a change of the solvent to ClCH$_2$CH$_2$Cl had no obvious effect on the result (Table 1, entry 10). We therefore chose these reaction conditions (Table 1, entry 9) for further studies.

We next explored the scope of amidomalonates that could participate in this transformation (Table 2). *N*-Benzyl-substituted ones also afforded the corresponding glutarimides in excellent yields (89–93%) and enantioselectivities (94–98% *ee*).

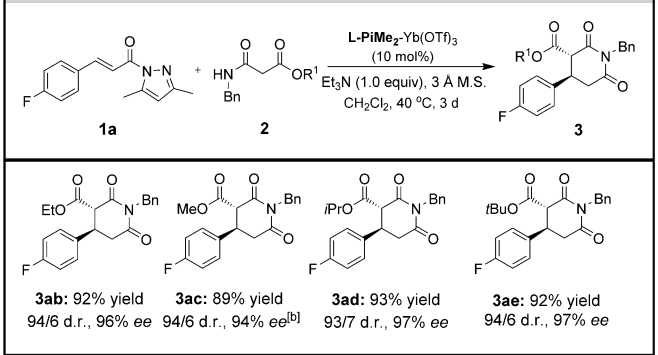
Table 1. Optimization of the reaction conditions.[a]



Entry	Ligand	Metal salt	Yield [%][b]	d.r.[c]	*ee* [%][d]
1[e]	L-**PiEt$_2$Me**	La(OTf)$_3$	24	94/6	89
2[e]	L-**PiEt$_2$Me**	Yb(OTf)$_3$	10	94/6	96
3	L-**PiEt$_2$Me**	Yb(OTf)$_3$	21	95/5	96
4	L-**PiPr$_2$**	Yb(OTf)$_3$	27	95/5	80
5	L-**PiEt$_2$**	Yb(OTf)$_3$	22	92/8	94
6	L-**PiMe$_2$**	Yb(OTf)$_3$	22	95/5	97
7	L-**PrMe$_2$**	Yb(OTf)$_3$	10	93/7	89
8[f]	L-**PiMe$_2$**	Yb(OTf)$_3$	36	95/5	97
9[f,g]	L-**PiMe$_2$**	Yb(OTf)$_3$	90	96/4	98
10[f,h]	L-**PiMe$_2$**	Yb(OTf)$_3$	90	96/4	97

[a] Unless otherwise noted, the reactions were carried out with **1a** (0.2 mmol), **2a** (0.3 mmol), **L**/metal salt (1:1.2, 10 mol%), and Et$_3$N (1.0 equiv) in CH$_2$Cl$_2$ (1.0 mL) at 35 °C for 3 d. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by chiral HPLC analysis after flash column chromatography purification. [e] Et$_3$N (0.2 equiv). [f] At 40 °C. [g] **L**/metal salt (1:1, 10 mol%), 3 Å molecular sieves (40 mg) in CH$_2$Cl$_2$ (0.4 mL). [h] **L**/metal salt (1:1, 10 mol%), 3 Å molecular sieves (40 mg) in ClCH$_2$CH$_2$Cl (0.4 mL).

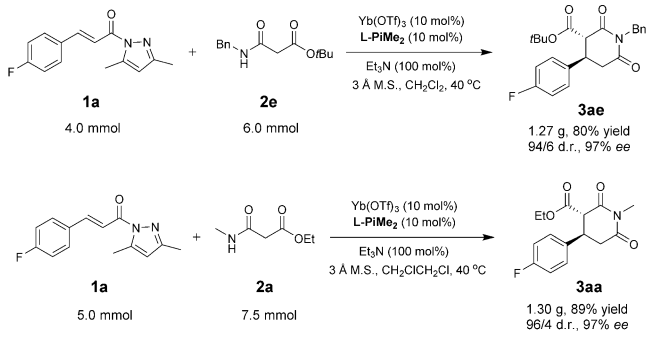
Table 2. Substrate scope of the amidomalonates **2**.[a]



[a] Reaction conditions: The same as in Table 1, entry 9. [b] Determined after derivation (see the Supporting Information).

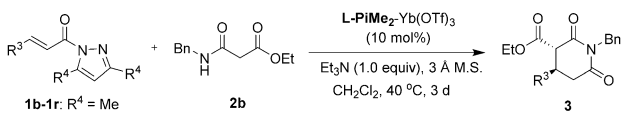
Variation in the size of the ester group did not affect the outcome. Notably, product **3ae**, which could be further transformed into (−)-paroxetine, was generated with good results under the optimal reaction conditions. The reaction was also tolerable on a gram scale, and 80% yield, 94:6 d.r., and 97% *ee* were obtained. With consideration of the ease for industrial manipulation, this gram-scale transformation also proceeded smoothly if ClCH$_2$CH$_2$Cl was used instead of CH$_2$Cl$_2$, to provide the corresponding product **3aa** in 90% yield, 96:4 d.r., and 97% *ee* (Scheme 2).

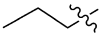
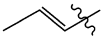
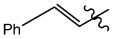
The generality of the α,β-unsaturated pyrazoleamides was then tested (Table 3). A β-aryl group bearing electron-withdrawing or -donating substituents at various positions could be tolerated in the reaction, and the related products were isolated in 87–99% yields with 93–97% *ee* (Table 3, entries 1–11). The diastereoselectivity dropped a little when substrates bearing a 2-substituted aryl group were used (Table 3, entries 7 and 8). Moreover, if α,β-unsaturated pyrazoleamides containing fused ring, heteroaromatic, or alkyl groups at the β position were employed in the transformation, the catalyst could pro-



Scheme 2. Experimental procedure for the scale-up reactions.

Table 3. Substrate scope for the α,β-unsaturated pyrazoleamides **1**.[a]

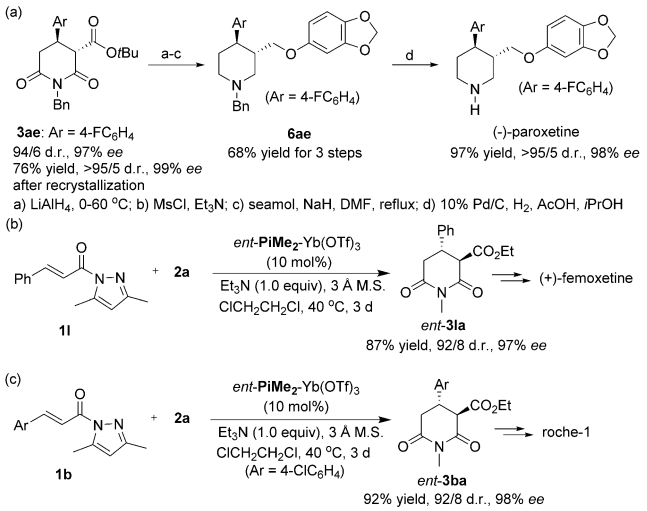


Entry	R^3	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	4-ClC_6H_4	99 (**3bb**)	>95/5	97
2	4-BrC_6H_4	99 (**3cb**)	>95/5	97
3	4-$F_3CC_6H_4$	96 (**3db**)	95/5	95
4	4-NCC_6H_4	98 (**3eb**)	>95/5	96
5	4-MeC_6H_4	97 (**3fb**)	95/5	97
6	4-$MeOC_6H_4$	90 (**3gb**)	>95/5	96
7	2-BrC_6H_4	87 (**3hb**)	85/15	94
8	2-$MeOC_6H_4$	96 (**3ib**)	85/15	95
9	3-MeC_6H_4	97 (**3jb**)	91/9	94
10	3,4-$Cl_2C_6H_3$	97 (**3kb**)	92/8	93
11	Ph	97 (**3lb**)	91/9	96
12	2-naphthyl	94 (**3mb**)	91/9	90
13	2-thienyl	58 (**3nb**)	92/8	85
14	2-furyl	75 (**3ob**)	89/11	91[e]
15		78 (**3pb**)	77/23	89
16		67 (**3qb**)	88/12	92
17		51 (**3rb**)	89/11	86
18[f]	4-BrC_6H_4	99 (**3cb**)	95/5	88

[a] Reaction conditions: The same as Table 1, entry 9. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by chiral HPLC analysis after flash column chromatography purification. [e] Determined from a derivative of **3ob** (see the Supporting Information). [f] **1s** was used as the starting material.

duce the corresponding products with moderate to good yields and stereoselectivities (Table 3, entries 12–15). The catalyst was also suitable for α,β,γ,δ-unsaturated pyrazoleamides **1q** and **1r**, bearing a conjugated alkene substituent, and generated only the 1,4-addition/cyclization products in moderate yields with good diastereo- and enantioselectivities (Table 3, entries 16 and 17). The pyrazole substituent obviously affected the enantioselectivity, and the *ee* value decreased to 88% if an unsubstituted pyrazole group was introduced into the substrate (Table 3, entry 18). The absolute configuration of the major isomer of the product **3aa** was unambiguously established as 3*S*,4*R*, in accordance with the previous report.[10]

To show the synthetic utility of current catalyst system, the synthesis of (−)-paroxetine was performed from the piperidine-2,6-dione product **3ae**, in accordance with to a previous report.[3b] Initially, the reduction of **3ae** with $LiAlH_4$ followed by methanesulfonylation provided the intermediate mesylate. Installation of the seamol fragment gave the *N*-Bn product **6ae** in 68% overall yield. Finally, the target compound was obtained in nearly quantitative yield after removal of the benzyl group by hydrogenation. Thus, (−)-paroxetine could be efficiently attained in 66% total yield with >95/5 d.r. and 98% *ee* in four steps (Scheme 3a). (+)-Femoxetine and roche-1 possess



Scheme 3. The application of the catalytic asymmetric reaction for the synthesis of (−)-paroxetine, (+)-femoxetine, and roche-1. Ms: methanesulfonyl.

the opposite enantiomeric configuration to (−)-paroxetine and also exhibit very important pharmaceutical activities.[11] For instance, (+)-femoxetine is used in the treatment of depression, obsessive-compulsive disorder, and panic attacks. The synthesis of the corresponding *trans*-piperidine core structures was carried out by the use of the chiral *N*,*N*′-dioxide ***ent*-PiMe$_2$**, prepared from D-pipecolic acid. The reactions of α,β-unsaturated pyrazoleamide **1l** and **1b** with ethyl-*N*-methylmalonamide **2a** were successful and afforded the related glutarimides ***ent*-3la** and ***ent*-3ba** in good yields and excellent diastereo- and enantioselectivities (97 and 98% *ee*, respectively; Scheme 3b and 3c). The intermediates could undergo similar transformations to those described for (−)-paroxetine to synthesize (+)-femoxetine and roche-1.

For further understanding of the reaction process, the relationship between the *ee* values of ligand L-**PiMe$_2$** and product **3aa** was explored.[12] A nonlinear effect was not observed, which suggests that **L-PiMe$_2$** coordinated with the Yb^{3+} ions in a 1:1 ratio (Figure 2). Additionally, this could be verified through HRMS experiments, in which ESI-MS species assigned to [L-**PiPr$_2$**+Yb^{3+}+$^-$OTf]$^{2+}$ (*m*/*z* 429.6121) were detected from the mixture of the catalyst system (see the Supporting Information). Operand IR experiments were also carried out. As the peaks at $\tilde{\nu}$ = 1381 and 1728 cm^{-1}, which are related to the sub-

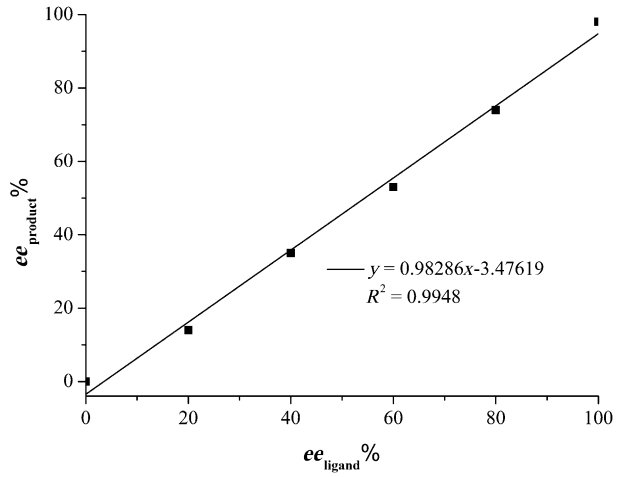


Figure 2. Exploration of the nonlinear effect on the catalytic asymmetric tandem Michael/ring-closure reaction of **1a** with **2a**.

strates, gradually decreased in intensity, the peak of the Michael/ring-closure product **3ba** at $\tilde{\nu} = 1678\ cm^{-1}$ increased (Figure 3). No additional peaks related to Michael addition intermediates were detected, which indicated that the rate of the ring-closure step was faster than that of the Michael addition step. This result implied that the Michael addition step might be the rate-determining step.

Based on our previous work and the absolute configuration of the product **3aa**, a transition state was proposed to rationalize the stereoinduction (Figure 4). In the proposed model, both the *N*,*N*′-dioxide and amide oxygen atoms of L-**PiMe$_2$** coordinate to the Yb^{3+} ion in a tetradentate manner to form two six-membered chelate rings. Pyrazoleamide **1a** then coordinates to the Yb^{3+} ion in a bidentate manner. Malonamide **2a** attacks the *Re* face of pyrazoleamide **1a** because the *Si* face is shielded by the neighboring 2,6-dimethylphenyl group on ligand L-**PiMe$_2$**. Thereby, (3*S*,4*R*)-**3aa** is obtained with simultaneous liberation of the catalyst.

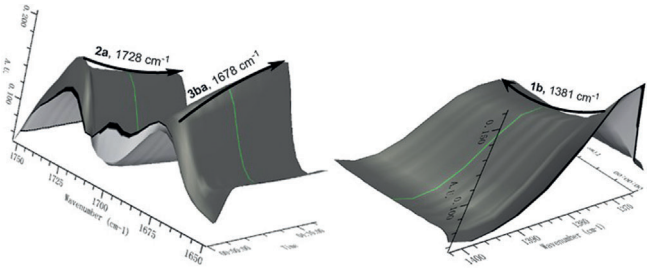


Figure 3. Operando IR experiments.

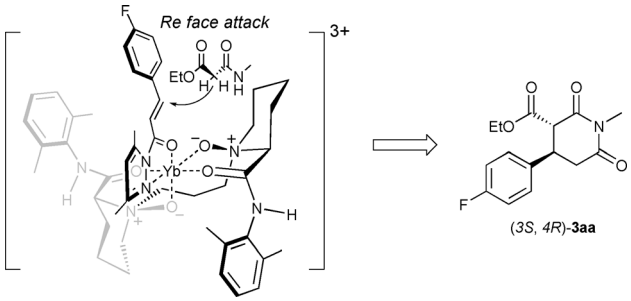


Figure 4. Plausible transition state for the reaction.

Conclusions

In summary, we have described a highly enantioselective Michael addition with one-step ring closure of α,β-unsaturated pyrazoleamides and amidomalonates catalyzed by a chiral *N*,*N*′-dioxide–$Yb(OTf)_3$ complex. The desired glutarimides with C3 and C4 chiral centers were afforded with high enantioselectivities and reactivity (up to 98% *ee* and 99% yield). This new procedure has been successfully applied to the enantioselective synthesis of the antidepressant drug (−)-paroxetine. The application of the *N*,*N*′-dioxide/metal catalyst system in the synthesis of other pharmaceuticals was also explored.

Experimental Section

General procedure for the preparation α,β-unsaturated pyrazoleamides

All of the α,β-unsaturated pyrazoleamides were prepared by similar procedures to those in the literature.[7]

General procedure for the preparation of amidomalonates

A mixture of amine (25 mmol) and 4 Å molecular sieves (2.00 g) was dropwise added to a solution of dialkylmalonate (50 mmol) in toluene (30 mL) at room temperature. After the reaction mixture had been heated to reflux for 5 h, the resultant suspension was filtered and concentrated in vacuo. The crude product was purified by flash column chromatography to afford the desired product.

General procedure for the catalytic asymmetric reactions

$Yb(OTf)_3$ (12.4 mg, 0.02 mmol), L-**PiMe$_2$** (10.7 mg, 0.02 mmol), 3 Å molecular sieves (40.0 mg), α,β-unsaturated pyrazoleamide (0.20 mmol), and CH_2Cl_2 (0.4 mL) were added to an oven-dried reaction tube under a nitrogen atmosphere. After the mixture had been stirred for 30 min at 35 °C, amidomalonates (0.30 mmol) and Et_3N (28.0 μL, 0.2 mmol) were subsequently added. The reaction mixture was stirred at 40 °C for 72 h and directly purified by flash column chromatography (ethyl acetate/petroleum ether, 1:6–1:2) to afford the desired product.

Typical characterization of **3aa**: White solid; m.p. 112–115 °C; 90% yield; 96:4 d.r. by ^1H NMR spectroscopy; 98% *ee*; $[\alpha]_D^{14} = -55.7$ (c = 0.56 in CH_2Cl_2); HPLC: DAICEL CHIRALCEL ADH column, *n*-hexane/2-propanol = 80/20, flow rate = 1.0 mL min^{-1}, λ = 210 nm, t_R (major) = 11.77 min, t_R (minor) = 18.90 min; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.16 (m, 2H), 7.09–7.00 (m, 2H), 4.19–4.02 (m, 2H), 3.83–3.74 (m,1H), 3.73–3.62 (m, 1H), 3.21 (s, 3H), 3.06–2.96 (m, 1H), 2.87–2.76 (m, 1H), 1.11 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.4, 168.6, 167.6, 162.3 (d, J = 248.2 Hz), 134.5 (d, J = 3.2 Hz), 128.6 (d, J = 8.3 Hz), 116.2 (d, J = 21.6 Hz), 61.9, 56.4, 38.9, 37.7, 27.0, 13.9 ppm; HRMS (ESI-TOF): m/z calcd for $C_{15}H_{16}FNO_4Na^+$ [M+Na^+]: 316.0956; found: 316.0965.

Synthesis of (−)-paroxetine

See ref. [3c] for a previous synthesis of (−)-paroxetine in the literature.

(3*S*,4*R*)-[1-Benzyl-4-(4-fluorophenyl)piperidin-3-yl]-methanol (4 ae): Lithium aluminum hydride (228 mg, 6.0 mmol) was added to a mixture of tetrahydrofuran (6.0 mL) at 0 °C and stirred for 15 min. A solution of **3 ae** (397 mg, 1.0 mmol) in tetrahydrofuran (3.0 mL) was added slowly with a syringe, over 5 min. The mixture was warmed up to 60 °C and continuously stirred for 4 h. After reaction completion, the resulting solution was cooled to 0 °C, quenched with EtOAc (20 mL) and H_2O (0.52 mL), and stirred for a further 20 min. The resulting colorless suspension was filtered through Celite® and washed with CH_2Cl_2 (40 mL). The organic portions were dried with Na_2SO_4 and concentrated in vacuo to afford the alcohol as a colorless oil. This material was directly used in the next stage without further purification.

(−)-*N*-Benzylparoxetine (6 ae): Et_3N (0.21 mL, 1.5 mmol) and MsCl (0.11 mL, 1.5 mmol) were added sequentially, with a syringe, to an ice-cooled (0 °C) solution of the crude alcohol in anhydrous CH_2Cl_2 (4.0 mL), which resulted in the immediate formation of a colorless precipitate. The mixture was stirred at room temperature for 20 min, diluted with water (30 mL) and saturated aqueous $NaHCO_3$ (50 mL), and extracted with CH_2Cl_2 (3×40 mL). The combined organic portions were dried with Na_2SO_4 and concentrated in vacuo to afford the mesylate as a yellow solid. NaH (60% dispersion in mineral oil, 80 mg, 2.0 mmol) was added to a solution of seamol (277 mg, 2.0 mmol) in anhydrous DMF (4.0 mL), and the resulting mixture was stirred at room temperature for 20 min. The mesylate in DMF (6.0 mL) was then added, and the mixture was heated at 90 °C for 15 h. The mixture was then cooled to room temperature, diluted with EtOAc (100 mL), and washed sequentially with water (50 mL), aqueous 1 M NaOH (2×50 mL), and brine (50 mL). The organic portion was dried (Na_2SO_4) and concentrated in vacuo to afford a residue (d.r. = 90/10 and the isomers were separable), which was purified by flash column chromatography (ethyl acetate/petroleum ether, 1:6) to separate the major isomer *N*-benzylparoxetine (**6 ae**; 286 mg, 68% yield for 3 steps) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.18 (m, 4H), 7.16–7.11 (m, 1H), 7.06–2.99 (m, 2H), 6.88–6.76 (m, 2H), 6.48 (d, J = 8.4 Hz, 1H), 6.21 (d, J = 2.4 Hz, 1H), 5.98 (dd, J = 8.4, 2.4 Hz, 1H), 5.70 (s, 2H), 3.52 (d, J = 13.2 Hz, 1H), 3.46–3.36 (m, 2H), 3.35–3.27 (m, 1H), 3.18–3.08 (m, 1H), 2.91–2.81 (m, 1H), 2.45–2.26 (m, 1H), 2.16–2.03 (m, 1H), 2.02–1.89 (m, 2H), 1.80–1.60 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.6 (d, J = 245.0 Hz), 154.4, 148.2, 141.6, 139.9 (d, J = 3.1 Hz), 138.3, 129.3, 128.9 (d, J = 7.7 Hz), 128.3, 127.1, 115.4 (d, J = 21.1 Hz), 107.9, 105.6, 101.1, 98.0, 69.6, 63.4, 57.6, 53.8, 44.1, 42.2, 34.4 ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{26}H_{26}FNO_3Na^+$ [M+Na^+]: 442.1789; found: 442.1789.

(−)-Paroxetine: A suspension of 10% Pd/C (50 mg) and *N*-benzylparoxetine (**6 ae**; 150 mg, 0.36 mmol) in AcOH (1.4 mL) and *i*PrOH (3.5 mL) was sealed inside a hydrogenation bomb. The vessel was purged with hydrogen (6 purge cycles at 6 bar) and heated at 50 °C for 15 h. The mixture was cooled to room temperature and then depressurized, filtered through Celite®, washed with AcOH (20 mL), MeOH (20 mL), and CH_2Cl_2 (20 mL), and concentrated in vacuo to afford a colorless oil. It was dissolved in saturated aqueous Na_2CO_3 solution (20 mL) and extracted with CH_2Cl_2 (3×25 mL). The organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford the free amine (115 mg, 97% yield) as a colorless oil; >95:5 d.r. by ^{1}H NMR spectroscopy; 98% *ee*; $[\alpha]_D^{23} = -77.5$ (c = 1.1 in CH_3OH); UPC[2]: Phenomenex CHIRALCEL Lux 5u Cellulose-3 column, CO_2/CH_3OH = 85/15, flow rate = 1.0 mL min^{-1}, λ = 254 nm, t_R (minor) = 8.05 min, t_R (major) = 8.97 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.09 (m, 2H), 7.00–6.91 (m, 2H), 6.60 (d, J = 8.4 Hz, 1H), 6.32 (d, J = 2.0 Hz, 1H), 6.10 (dd, J = 8.4, 2.0 Hz, 1H), 5.84 (s, 2H), 3.54 (dd, J = 9.2, 2.0 Hz, 1H), 3.48–3.32 (m, 2H), 3.18–3.10 (m, 1H), 2.83–2.49 (m, 3H), 2.09–1.98 (m, 1H), 1.83–1.75 (m, 1H), 1.74–1.65 (m, 1H), 1.64–1.49 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.4 (d, J = 245.2 Hz), 154.4, 148.1, 141.5, 140.0 (d, J = 3.2 Hz), 128.8 (d, J = 7.8 Hz), 115.4 (d, J = 21.1 Hz), 107.8, 105.5, 101.0, 97.9, 69.5, 50.4, 47.1, 44.6, 43.0, 35.4 ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{20}FNO_3Na^+$ [M Na^+]: 352.1319; found: 352.1319.

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Keywords: asymmetric synthesis · heterocycles · Michael reactions · paroxetine · ring-closure reactions

[1] a) S. E. De Laszlo, B. L. Bush, J. J. Doyle, W. J. Greenlee, D. G. Hangauer, T. A. Halgren, R. J. Lynch, T. W. Schorn, P. K. S. Siegl, *J. Med. Chem.* **1992**, *35*, 833–846; b) P. Wei, G. W. Kaatz, R. J. Kerns, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3093–3097.

[2] N. S. Gunasekara, S. Noble, P. Benfield, *Drugs* **1998**, *55*, 85–120.

[3] For a review on the synthesis of paroxetine: a) C. De Risi, G. Fanton, G. P. Pollini, C. Trapella, F. Valente, V. Zanirato, *Tetrahedron: Asymmetry* **2008**, *19*, 131–155; for recent examples, see: b) M. Ito, A. Sakaguchi, C. Kobayashi, T. Ikariya, *J. Am. Chem. Soc.* **2007**, *129*, 290–291; c) J. F. Bower, T. Riis-Johannessen, P. Szeto, A. J. Whitehead, T. Gallagher, *Chem. Commun.* **2007**, 728–730; d) M.-h. Kim, Y. Park, B.-S. Jeong, H.-g. Park, S.-s. Jew, *Org. Lett.* **2010**, *12*, 2826–2829; e) N. R. Chaubey, S. K. Ghosh, *Tetrahedron: Asymmetry* **2012**, *23*, 1206–1212; f) K. L. Jensen, P. H. Poulsen, B. S. Donslund, F. Morana, K. A. Jørgensen, *Org. Lett.* **2012**, *14*, 1516–1519; g) D. A. Devalankar, P. U. Karabal, A. Sudalai, *Org. Biomol. Chem.* **2013**, *11*, 1280–1285; h) C. F. Despiau, A. P. Dominey, D. C. Harrowven, B. Linclau, *Eur. J. Org. Chem.* **2014**, 4335–4341; i) H. Y. Bae, C. E. Song, *ACS Catal.* **2015**, *5*, 3613–3619; j) Y.-M. Wang, N. C. Bruno, Á. L. Placeres, S. Zhu, S. L. Buchwald, *J. Am. Chem. Soc.* **2015**, *137*, 10524–10527; k) K. Kubota, Y. Watanabe, K. Hayama, H. Ito, *J. Am. Chem. Soc.* **2016**, *138*, 4338–4341; l) T. Yasukawa, Y. Saito, H. Miyamura, S. Kobayashi, *Angew. Chem. Int. Ed.* **2016**, *55*, 8058–8061; *Angew. Chem.* **2016**, *128*, 8190–8193.

[4] T. Nemoto, T. Sakamoto, T. Fukuyama, Y. Hamada, *Tetrahedron Lett.* **2007**, *48*, 4977–4981.

[5] G. Hughes, M. Kimura, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11253–11258.

[6] a) Z.-T. He, Y.-B. Wei, H.-J. Yu, C.-Y. Sun, C.-G. Feng, P. Tian, G.-Q. Lin, *Tetrahedron* **2012**, *68*, 9186–9191; b) S. Brandau, A. Landa, J. Franzén, M. Marigo, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2006**, *45*, 4305–4309; *Angew. Chem.* **2006**, *118*, 4411–4415; c) A. Ma, S. Zhu, D. Ma, *Tetrahedron Lett.* **2008**, *49*, 3075–3077; d) P. S. Hynes, P. A. Stupple, D. J. Dixon, *Org. Lett.* **2008**, *10*, 1389–1391; e) G. Valero, J. Schimer, I. Cisarova, J. Vesely, A. Moyano, R. Rios, *Tetrahedron Lett.* **2009**, *50*, 1943–1946; f) S. Číhalová, G. Valero, J. Schimer, M. Humpl, M. Dračínský, A. Moyano, R. Rios, J. Vesely, *Tetrahedron* **2011**, *67*, 8942–8950.

[7] a) K. Ishihara, M. Fushimi, *Org. Lett.* **2006**, *8*, 1921–1924; b) M. P. Sibi, K. Itoh, *J. Am. Chem. Soc.* **2007**, *129*, 8064–8065; c) X.-Q. Dong, X. Fang, H.-Y. Tao, X. Zhou, C.-J. Wang, *Chem. Commun.* **2012**, *48*, 7238–7240; d) J. Zhang, X. Liu, R. Wang, *Chem. Eur. J.* **2014**, *20*, 4911–4915; e) Q. Yao, Z. Wang, Y. H. Zhang, X. H. Liu, L. L. Lin, X. M. Feng, *J. Org. Chem.* **2015**, *80*, 5704–5712; f) Y. Zheng, Y. Yao, L. Ye, Z. Shi, X. Li, Z. Zhao, *Tetrahedron* **2016**, *72*, 973–978.

[8] S. Somaiah, S. Sashikanth, V. Raju, K. V. Reddy, *Tetrahedron: Asymmetry* **2011**, *22*, 1–3.

[9] For selected asymmetric examples based on chiral *N,N'*-dioxides, see: a) X. H. Liu, L. L. Lin, X. M. Feng, *Acc. Chem. Res.* **2011**, *44*, 574 – 587; b) X. H. Liu, L. L. Lin, X. M. Feng, *Org. Chem. Front.* **2014**, *1*, 298 – 302; c) K. Shen, X. H. Liu, W. T. Wang, G. Wang, W. D. Cao, W. Li, X. L. Hu, L. L. Lin, X. M. Feng, *Chem. Sci.* **2010**, *1*, 590 – 595; d) H. F. Zheng, X. H. Liu, C. R. Xu, Y. Xia, L. L. Lin, X. M. Feng, *Angew. Chem. Int. Ed.* **2015**, *54*, 10958 – 10962; *Angew. Chem.* **2015**, *127*, 11108 – 11112; e) Y. Xia, X. H. Liu, H. F. Zheng, L. L. Lin, X. M. Feng, *Angew. Chem. Int. Ed.* **2015**, *54*, 227 – 230; *Angew. Chem.* **2015**, *127*, 229 – 232; f) X. H. Zhao, X. H. Liu, Q. Xiong, H. J. Mei, B. W. Ma, L. L. Lin, X. M. Feng, *Chem. Commun.* **2015**, *51*, 16076 – 16079; g) Y. T. Liao, X. H. Liu, Y. Zhang, Y. L. Xu, Y. Xia, L. L. Lin, X. M. Feng, *Chem. Sci.* **2016**, *7*, 3775 – 3779; h) Q. Yao, Y. T. Liao, L. L. Lin, X. B. Lin, J. Ji, X. H. Liu, X. M. Feng, *Angew. Chem. Int. Ed.* **2016**, *55*, 1859 – 1863; *Angew. Chem.* **2016**, *128*, 1891 – 1895; i) T. F. Kang, S. L. Ge, L. L. Lin, Y. Lu, X. H. Liu, X. M. Feng, *Angew. Chem. Int. Ed.* **2016**, *55*, 5541 – 5544; *Angew. Chem.* **2016**, *128*, 5631 – 5634.

[10] Z. Bao, B. Su, Y. Yang, Q. Ren, *J. Liq. Chromatogr. Rel. Technol.* **2008**, *31*, 1147 – 1161.

[11] a) G. M. Shutske, *Expert Opin. Ther. Pat.* **1994**, *4*, 335; b) M. G. Bursavich, C. W. West, D. H. Rich, *Org. Lett.* **2001**, *3*, 2317 – 2320; c) M. G. Bursavich, D. H. Rich, *J. Med. Chem.* **2002**, *45*, 541 – 558.

[12] a) D. Guillaneux, S.-H. Zhao, O. Samuel, D. Rainford, H. B. Kagan, *J. Am. Chem. Soc.* **1994**, *116*, 9430 – 9439; b) C. Girard, H. B. Kagan, *Angew. Chem. Int. Ed.* **1998**, *37*, 2922 – 2959; *Angew. Chem.* **1998**, *110*, 3088 – 3127; c) T. Satyanarayana, S. Abraham, H. B. Kagan, *Angew. Chem. Int. Ed.* **2009**, *48*, 456 – 494; *Angew. Chem.* **2009**, *121*, 464 – 503.

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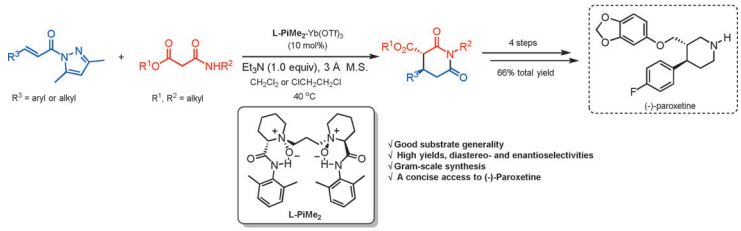

Tandem heterocycle formation: A tandem Michael/ring-closure reaction of α,β-unsaturated pyrazoleamides and amidomalonates has been accomplished in the presence of a chiral *N*,*N*′-dioxide–$Yb(OTf)_3$ complex to give the chiral glutarimides with high yields and diastereo- and enantioselectivities (see scheme: Tf = trifluoromethanesulfonyl; M.S. = molecular sieves). The methodology was successfully applied to the synthesis of (−)-paroxetine.

Asymmetric Catalysis

Y. Zhang, Y. Liao, X. Liu, Q. Yao, Y. Zhou, L. Lin, X. Feng**

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Catalytic Michael/Ring-Closure Reaction of α,β-Unsaturated Pyrazoleamides with Amidomalonates: Asymmetric Synthesis of (−)-Paroxetine