

A New Enantioselective Synthesis of Milnacipran and an Analogue by Catalytic Asymmetric Cyclopropanation

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Abstract: Milnacipran and analogues are conveniently prepared by a short sequence of steps from phenylacetic acid, the key step being highly enantio-

selective catalytic asymmetric cyclopropanation.

Keywords: NMDA receptor antagonist; asymmetric catalysis; cyclopropanation; chiral rhodium carboxamides.

Introduction

The cyclopropane-NMDA (*N*-methyl-D-aspartic acid) receptor antagonist milnacipran (**1**) is a clinically efficient antidepressant^[1] that is administered for the treatment of major depressive disorder.^[2] The preparation of the racemic compound commonly requires the synthesis of cyclopropane-fused lactone **2** to which there are several multistep pathways (Figure 1).^[3,4] An asymmetric synthesis of **2** from chiral epichlorohydrin (Scheme 1) has recently been reported.^[5]

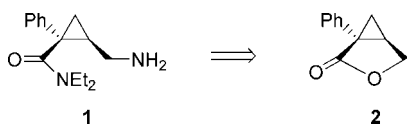
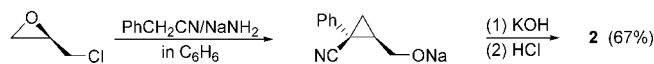


Figure 1.



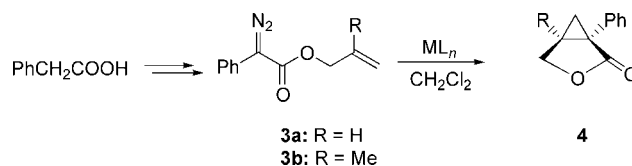
Scheme 1.

We wish to report an alternative strategy for the synthesis of **2** and some of its analogues through the use of phenyldiazoacetates and chiral dirhodium(II) carboxamidate catalysts.^[6–8]

Results and Discussion

Intermolecular cyclopropanation from allyl phenyldiazoacetate and its analogues provides a direct route to the key synthetic intermediate **2** and its substituted

derivatives from readily available reactants.^[8] When these reactions are performed in the presence of a chiral catalyst, non-racemic **4** are the anticipated products (Scheme 2). Dirhodium(II) carboxamidates with chiral pyrrolidinone ligands are reported to be unreactive towards diazo decomposition of phenyldiazoacetates,^[9] but those with azetidine ligands (**5**) exhibit exceptional reactivity with these diazo compounds.^[8] The phenyldiazoacetates were conveniently prepared from phenylacetic acid.



Scheme 2.

Results from catalytic diazo decomposition of **3** (R = H and R = Me) are given in Table 1, where comparison is made between **5** (Figure 2), a chiral dirhodium(II) carboxylate, Rh₂(S-TBPRO)₄,^[10] and a chiral copper(I) catalyst derived from Cu(MeCN)₄PF₆ and chiral bis-oxazoline **6** (Figure 3).^[11] As is evident from the data, the chiral dirhodium(II) azetidinone catalysts **5** are the most selective, and among this set of catalysts **5a** provided the highest % ee values.

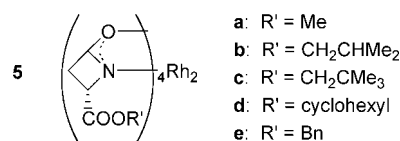


Figure 2.

Attempts were made to optimize these results, and the outcome was unexpected. With **3b** (R = Me) we have found that increasing the rate of addition re-

Table 1. Catalytic diazo decomposition of **3** under standard reaction conditions.^[a]

3 (R =)	Catalyst	Yield (%) of isolated product ^[b]	% ee ^[c]
H	5a : Rh ₂ (4S-MEAZ) ₄	80	68
H	5b : Rh ₂ (4S-IBAZ) ₄	83	64
H	5c : Rh ₂ (4S-NEPAZ) ₄	72	54
H	5d : Rh ₂ (4S-CHAZ) ₄	69	44
H	Rh ₂ (S-TBPRO) ₄	92	28
H	CuPF ₆ /6	36	20
Me	5a : Rh ₂ (4S-MEAZ) ₄	82	84
Me	5b : Rh ₂ (4S-IBAZ) ₄	80	68
Me	5c : Rh ₂ (4S-NEPAZ) ₄	84	5
Me	5d : Rh ₂ (4S-CHAZ) ₄	82	33
Me	5e : Rh ₂ (4S-BNAZ) ₄	80	85
Me	Rh ₂ (S-TBPRO) ₄	77	29
Me	CuPF ₆ /6	85	1

^[a] Reactions were performed in refluxing CH₂Cl₂ by 2 h addition of the diazo compound (0.4 mmol in 2.0 mL) to 1.0 mol % of catalyst in 4.0 mL of solvent.

^[b] Weight yield of product after chromatographic separation of catalyst.

^[c] Product configuration was (1*R*, 5*S*) in each case.

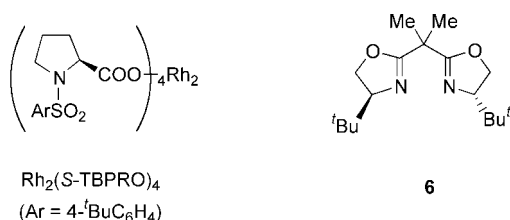


Figure 3.

Table 2. Optimization of enantiocontrol for the conversion of **3** (R = Me) to **4** (R = Me) using **5a**.^[a]

Addition time	Total reaction time ^[b]	Temperature (°C)	S/C ^[c]	% ee ^[d]
2.0 h	2.0 h	40	100	84
0.5 h	0.5 h	40	100	91
1.0 h	1.0 h	40	200	90
< 1 min	0.5 h	40	200	95
< 1 min	48 h	0	200	58
< 1 min	2 h	40	2 000	94
< 1 min	4 h	40	10 000	95 ^[e]

^[a] Reactions were carried out to 100% conversion in CH₂Cl₂ at reflux or at 0 °C. Complete conversion was determined by GC (SPB-5 column).

^[b] Total time from start of addition.

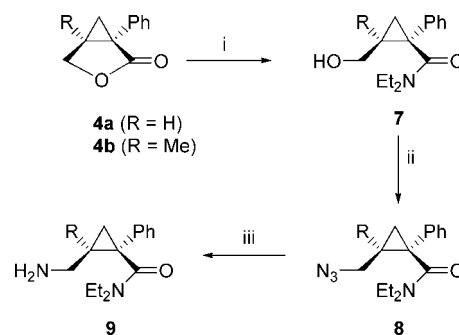
^[c] Diazo substrate to catalyst **5a** molar ratio.

^[d] Determined by GC on a 30-m Chiraldex B-DM column.

^[e] Conversion at 4 h was 52%.

sulted in dramatic increases in enantiocontrol. Furthermore, enantioselectivity further increased with decreased catalyst loading. These results are outlined in Table 2. They demonstrate that optimum results are obtained when the diazo compound is added all-at-once to a minimal amount of catalyst in refluxing CH₂Cl₂. Decreasing the reaction temperature was detrimental to selectivity. The probability that these results signify a non-linear effect in catalyst operations is evident, but similar experiments to those reported in Table 2 performed on **3a** (R = H) had no effect on enantioselectivity.

Conversion of **4** to milnacipran (R = H) and an analogue (R = Me) was accomplished by the sequence of synthetic steps that is outlined in Scheme 3. These steps followed closely the procedure reported in the literature for the synthesis of **9a**.^[4]



Reagents: (i) LiNEt₂/THF, -78 °C, 2 h (**7a**, 82% yield; **7b**, 84% yield); (ii) NaN₃, Ph₃P, CBr₄/DMF, rt, 24 h (**8a**, 80% yield; **8b**, 99% yield); (iii) H₂, 10% Pd/C in MeOH (**9a** = **1**, 98% yield; **9b** 82% yield).

Scheme 3

Conclusion

Overall, the sequence involving intramolecular cyclopropanation beginning with phenylacetic acid represents the most efficient and most highly selective procedure for the synthesis of milnacipran and its analogues. Particularly noteworthy is the synthesis of **9b** whose hydrochloride salt is conveniently prepared and may have enhanced pharmacological value.

Experimental Section

Allyl Phenyl diazoacetate (**3a**)

A solution of allyl alcohol (20 mL) and Et₃N (3.03 g, 30 mmol) was cooled (0 °C) before the dropwise addition of phenylacetyl chloride (5.09 g, 20 mmol) over 1 h. The reaction mixture was then warmed to room temperature over 2 h, then concentrated *in vacuo*. The residue was dissolved in ethyl ace-

tate (200 mL) and washed with water (2×50 mL) then brine (50 mL). The organic layer was then dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum to yield the intermediate allyl phenylacetate as a colorless oil, which was used without further purification in the subsequent diazo transfer reaction; ^1H NMR (250 MHz, CDCl_3): δ = 7.38–7.20 (comp, 5H), 5.89 (ddt, J = 17.2 Hz, 10.6 Hz, 5.7 Hz, 1H), 5.25 (dq, J = 17.2 Hz, 1.3 Hz, 1H), 5.19 (dq, J = 10.6 Hz, 1.3 Hz, 1H), 4.59 (dt, J = 5.7 Hz, 1.5 Hz, 2H), 3.64 (s, 2H); ^{13}C NMR (67.5 MHz, CDCl_3): δ = 171.1, 133.9, 132.0, 129.2, 128.5, 127.1, 118.1, 65.4, 61.3.

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (1.82 g, 12 mmol) in THF (10 mL) was added to a solution of allyl phenylacetate (2.0 g, 11.4 mmol) and *p*-acetamidobenzene-sulfonyl azide (ABSA) (2.9 g, 12.0 mmol) in anhydrous THF (20 mL) over 1 h at room temperature. The reaction mixture was stirred for an additional 12 hours, then quenched by addition of saturated aqueous ammonium chloride (30 mL). The aqueous layer was extracted with ethyl acetate (2×50 mL). The combined organic layer was washed with water (2×50 mL) and brine (50 mL), then dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel, eluting with hexanes:ethyl acetate = 10:1, to furnish the desired allyl phenyldiazoacetate **3a** (yield: 1.7 g, 74%) as a yellow oil; ^1H NMR (500 MHz, CDCl_3): δ = 7.49 (d, J = 8.5 Hz, 2H), 7.39 (dd, J = 8.5 Hz, 7.4 Hz, 2H), 7.18 (t, J = 7.4 Hz, 1H), 5.98 (ddt, J = 17.2 Hz, 10.4 Hz, 5.7 Hz, 1H), 5.36 (dq, J = 17.2 Hz, 1.5 Hz, 1H), 5.27 (dq, J = 10.4 Hz, 1.5 Hz, 1H), 4.77 (dt, J = 5.7 Hz, 1.5 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ = 164.8, 132.1, 128.9, 125.4, 124.0, 65.4; IR (CHCl_3): ν = 2089 ($\text{C}=\text{N}_2$), 1699 cm^{-1} ($\text{C}=\text{O}$); MS (FAB^+): m/z = 203.1 (M^+ + 1).

2-Methyl-2-propen-1-yl Phenyldiazoacetate (**3b**)

Treatment of 2-methyl-2-propen-1-ol (1.17 g, 16.2 mmol) in CH_2Cl_2 (5 mL) with Et_3N (1.52 g, 15 mmol) and phenylacetyl chloride (1.16 g, 7.5 mmol) furnished the intermediate 2-methyl-2-propen-1-ol phenylacetate (yield: 1.2 g, 85%) as a colorless oil; ^1H NMR (500 MHz, CDCl_3): δ = 7.35–7.24 (comp, 5H), 4.91 (s, 1H), 4.89 (s, 1H), 4.51 (s, 2H), 3.60 (s, 2H), 1.70 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ = 171.2, 139.7, 133.9, 129.2, 128.5, 127.1, 112.8, 70.0, 41.4, 19.4.

Treatment of 2-methyl-2-propen-1-yl phenylacetate (1.76 g, 10.0 mmol) with ABSA (2.90 g, 12.0 mmol), and DBU (1.82 g, 12.0 mmol) in CH_3CN (50 mL) at room temperature overnight furnished diazoacetate **3b** (yield: 1.55 g, 77%) as a brown oil, after purification by chromatography on silica gel, eluting with hexanes; ^1H NMR (250 MHz, CDCl_3): δ = 7.49 (d, J = 7.5 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.17 (t, J = 7.5 Hz, 1H), 5.01 (s, 1H), 4.96 (s, 1H), 4.69 (s, 2H), 1.79 (s, 3H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 164.7, 139.7, 128.9, 125.8, 125.4, 123.9, 123.0, 67.9, 19.4; IR (neat): ν = 2088 ($\text{C}=\text{N}_2$), 1692 cm^{-1} ($\text{C}=\text{O}$); HRMS: calcd for $\text{C}_{12}\text{H}_{13}\text{O}_2\text{N}_2$: 217.0977; found: 217.0977.

General Procedure for Diazo Decomposition of Phenyldiazoacetates **3**

A solution of phenyldiazoacetate **3** (0.4 mmol) in dichloromethane (2 mL) was added via a syringe pump (1.0 mL/h) over 2 h to a refluxing solution of catalyst (1.0 mol %) in

CH_2Cl_2 (4 mL). The mixture was cooled to room temperature, then passed through a short plug of silica gel, which was subsequently washed with 10 mL of CH_2Cl_2 . The crude product was purified by flash column chromatography on silica gel, eluting with hexanes:ethyl acetate (10:1), to furnish the desired cyclopropane **4**.

(1*R*,5*S*)-1-phenyl-5-oxabicyclo[3.1.0]hexan-2-one (4a): ^1H NMR (250 MHz, CDCl_3): δ = 7.48–7.20 (comp, 5H), 4.30 (dd, J = 9.2 Hz, 4.6 Hz, 1H), 4.25 (d, J = 9.2 Hz, 1H), 2.54 (dt, J = 7.7 Hz, 4.6 Hz, 1H), 1.62 (dd, J = 7.7 Hz, 4.6 Hz, 1H), 1.33 (t, J = 4.6 Hz, 1H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 175.9, 134.0, 128.4, 128.2, 127.5, 67.9, 31.5, 24.9, 19.9; IR (CHCl_3): ν = 1765 ($\text{C}=\text{O}$) cm^{-1} ; HRMS (FAB^+) calcd for $\text{C}_{11}\text{H}_{11}\text{O}_2$: 175.0759; found: 175.0752; GC on a 30-m SPB-5 column, t_R 15.16 min (flow rate: 1 mL/min, oven temperature: 100 °C for 2 min, then 10 °C/min to 275 °C); GC on a 30-m ChiralDEX B-DM column: t_R for (1*S*,5*R*)-**4a** 70.9 min, t_R for (1*R*,5*S*)-**4a** 72.0 min (flow rate: 1 mL/min, oven temperature: 100 °C for 5 min, then 1 °C/min to 160 °C); $[\alpha]_D^{30}$: +36.2 (*c* 0.85, MeOH) for 44% ee catalyzed by $\text{Rh}_2(4\text{S-CHAZ})_4$; [(1*S*,5*R*)-**4a**: $[\alpha]_D^{30}$: −78.5 (*c* 1.42, MeOH) for 96% ee].^[4]

(1*R*,5*S*)-5-Methyl-1-phenyl-5-oxabicyclo[3.1.0]hexan-2-one (4b): ^1H NMR (500 MHz, CDCl_3): δ = 7.39–7.23 (comp, 5H), 4.34 (d, J = 9.0 Hz, 1H), 4.17 (d, J = 9.0 Hz, 1H), 1.60 (d, J = 4.5 Hz, 1H), 1.37 (d, J = 4.5 Hz, 1H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ = 177.1, 132.0, 130.1, 128.6, 127.9, 73.0, 36.8, 31.1, 22.6, 15.1; IR (CHCl_3): ν = 1764 ($\text{C}=\text{O}$) cm^{-1} ; HRMS (FAB^+): calcd for $\text{C}_{12}\text{H}_{13}\text{O}_2$: 189.0916; found: 189.0913; GC on a 30-m SPB-5 column: t_R 15.22 min (flow rate: 1 mL/min, oven temperature: 100 °C for 2 min, then 10 °C/min to 275 °C); GC on a 30-m ChiralDEX B-DM column: t_R for (1*S*,5*R*)-**4b** 67.7 min, t_R for (1*R*,5*S*)-**4b** 69.4 min (flow rate: 1 mL/min, oven temperature: 100 °C for 5 min, then 1 °C/min to 170 °C).

One-Pot Diazo Decomposition of **3b** using a 0.02 mol % Catalyst

To a refluxing dichloromethane (133 mL) solution of phenyldiazoacetate **3b** (8.6 g, 40 mmol) was added $\text{Rh}_2(4\text{S-MEAZ})_4$ (2.9 mg, 0.004 mmol). After 4 h at reflux, another portion of catalyst $\text{Rh}_2(4\text{S-MEAZ})_4$ (2.9 mg, 0.004 mmol) was added and the reaction mixture was refluxed overnight. Solvent was evaporated and the residue was recrystallized from 10% ethyl acetate in hexanes (150 mL) to give colorless crystalline **4b** (yield: 6.4 g, 84% yield); mp: 92.5–93 °C; $[\alpha]_D^{19}$: +84.0 (*c* 0.64, CH_2Cl_2) for >99% ee.

(1*R*,2*S*)-1-Phenyl-2-(hydroxymethyl)-*N,N*-diethylcyclopropanecarboxamide (7a):^[4] ^1H NMR (250 MHz, CDCl_3): δ = 7.32–7.11 (comp, 5H), 4.85 (br s, 1H), 4.10–3.90 (comp, 1H), 3.60–3.25 (comp, 4H), 3.25–3.17 (comp, 1H), 1.68–1.52 (comp, 2H), 1.15–1.10 (comp, 1H), 1.11 (t, J = 7.1 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 171.0, 140.1, 128.5, 126.4, 125.5, 64.6, 41.8, 39.3, 34.2, 31.5, 16.7, 12.9, 12.1.

(1*R*,2*S*)-1-Phenyl-2-methyl-2-(hydroxymethyl)-*N,N*-diethylcyclopropanecarboxamide (7b): Prepared using the same procedure as that described in literature.^[4] To a THF (30 mL) solution of **4b** (1.98 g, 10 mmol) was added LiNEt_2 (1.20 g, 15 mmol) in THF (10 mL) at −78 °C during

1 h via a syringe pump. The reaction mixture was stirred at -78°C for additional 2 h. The reaction was quenched with saturated NH_4Cl (30 mL) and the resulting mixture was extracted with ethyl acetate (3×50 mL). The combined organic layer was dried over anhydrous MgSO_4 . Solvent was evaporated, and the resulting solid was recrystallized from hexanes:ethyl acetate (90:10) to give a white crystalline **7b** (yield: 2.2 g, 84%); $[\alpha]_{\text{D}}^{30}$: -128.7 (c 1.2, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3): δ = 7.46–7.20 (comp, 5H), 4.95 (dd, J = 11.5 Hz, 2.5 Hz, 1H), 3.81 (t, J = 11.5 Hz, 1H), 3.55–3.46 (comp, 2H), 3.38 (dq, J = 14.0 Hz, 2.0 Hz, 1H), 3.22–3.14 (comp, 2H), 1.45 (d, J = 5.5 Hz, 1H), 1.06 (d, J = 5.5 Hz, 1H), 1.05 (t, J = 7.0 Hz, 3H), 0.85 (s, 3H), 0.83 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ = 172.0, 157.0, 128.6, 128.4, 126.9, 70.1, 41.7, 39.8, 39.6, 30.3, 20.7, 17.8, 13.2, 12.5; IR (CHCl_3): ν = 3401 (OH), 1610 cm^{-1} (C=O); HRMS: calcd. for $\text{C}_{16}\text{H}_{24}\text{NO}_2$: 262.1807; found: 262.1809.

(1R,2S)-1-Phenyl-2-(azidomethyl)-N,N-diethylcyclopropanecarboxamide (8a):^[4] ^1H NMR (250 MHz, CDCl_3): δ = 7.55–7.14 (comp, 5H), 3.62–3.41 (comp, 2H), 3.37 (d, J = 7.2 Hz, 2H), 3.29–3.05 (comp, 2H), 1.97 (dtd, J = 9.0 Hz, 7.2 Hz, 6.2 Hz, 1H), 1.57 (dd, J = 6.2 Hz, 5.0 Hz, 1H), 1.21 (dd, J = 9.0 Hz, 5.0 Hz, 1H), 1.15 (t, J = 7.0 Hz, 3H), 0.66 (t, J = 7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 169.0, 140.1, 128.6, 126.6, 126.2, 51.9, 41.7, 39.4, 34.7, 23.6, 19.6, 12.3, 12.2.

(1R,2S)-1-Phenyl-2-methyl-2-(azidomethyl)-N,N-diethylcyclopropanecarboxamide (8b): Prepared using the same procedure as that described in literature.^[4] To a DMF (5 mL) solution of **7b** (104 mg, 0.4 mmol) was added NaN_3 (0.52 g, 8.0 mmol), Ph_3P (0.63 g, 2.4 mmol), and CBr_4 (0.40 g, 1.2 mmol) at 0°C . The resulting reaction mixture was allowed to warm to room temperature and stirred for 3 h. Water (10 mL) was added and the resulting mixture was extracted with ethyl acetate (3×10 mL). The organic solution was washed with H_2O (10 mL) and brine (10 mL), then dried over anhydrous MgSO_4 . The residue was purified by column chromatography on silica gel (hexanes:ethyl acetate = 5:1) to give **8b** as a colorless oil (yield: 113 mg, 99%); $[\alpha]_{\text{D}}^{26}$: -110.9 (c 3.0, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3): δ = 7.41 (d, J = 7.5 Hz, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.25 (d, J = 7.5 Hz, 1H), 3.69 (d, J = 13.0 Hz, 1H), 3.49 (dq, J = 14.0 Hz, 7.0 Hz, 1H), 3.43 (dq, J = 14.0 Hz, 7.0 Hz, 1H), 3.34 (dq, J = 14.0 Hz, 7.0 Hz, 1H), 3.25 (d, J = 13.0 Hz, 1H), 3.18 (dq, J = 14.0 Hz, 7.0 Hz, 1H), 1.48 (d, J = 5.5 Hz, 1H), 1.27 (d, J = 5.5 Hz, 1H), 1.03 (t, J = 7.0 Hz, 3H), 0.86 (s, 3H), 0.80 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ = 169.7, 136.9, 128.8, 128.4, 127.0, 59.3, 41.5, 39.3, 21.9, 18.3, 13.3, 12.5; IR (CHCl_3): ν = 2101 (N_3), 1624 (C=O) cm^{-1} ; HRMS: calcd for $\text{C}_{16}\text{H}_{22}\text{N}_4\text{O}$: 287.1872; found: 287.1861.

(1R,2S)-1-Phenyl-2-(aminomethyl)-N,N-diethylcyclopropanecarboxamide (9a):^[4] ^1H NMR (500 MHz, CDCl_3): δ = 7.31–7.16 (comp, 5H), 3.55 (dq, J = 14.0 Hz, 7.0 Hz, 1H), 3.48 (dq, J = 14.0 Hz, 7.0 Hz, 1H), 3.25 (dq, J = 14.0 Hz, 7.0 Hz, 1H), 3.19 (dq, J = 14.0 Hz, 7.0 Hz, 1H), 2.80 (dd, J = 13.0 Hz, 7.5 Hz, 1H), 2.70 (dd, J = 13.0 Hz, 7.0 Hz, 1H), 2.18 (br s, 2H), 1.75 (dddd, J = 8.5 Hz, 7.5 Hz, 7.0 Hz, 6.5 Hz, 1H), 1.33 (dd, J = 6.5 Hz, 5.0 Hz, 1H), 1.20 (dd, J = 8.5 Hz, 5.0 Hz, 1H), 1.11 (t, J = 7.0 Hz, 3H), 0.69 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ = 170.0, 140.9, 128.5, 126.0, 125.8, 43.5, 41.5, 39.1, 34.7, 29.4, 19.2, 12.6, 12.2.

(1R,2S)-1-Phenyl-2-methyl-2-(aminomethyl)-N,N-diethylcyclopropanecarboxamide (9b): Prepared using the same procedure as described in literature.^[4] A mixture of **8b** (100 mg, 0.35 mmol) and 10% Pd/C (10 mg) in MeOH (10 mL) was stirred under 2 atm of hydrogen pressure for 1 h. The catalyst was filtered through a plug of celite. The filtrate was evaporated and the residue was purified by column chromatography on silica gel (CHCl_3 :MeOH:28% NH_4OH = 90:20:0.5) to give free amine **9b** (yield: 75 mg, 82%); ^1H NMR (500 MHz, CDCl_3): δ = 7.45–7.39 (comp, 2H), 7.33–7.26 (comp, 2H), 7.24–7.21 (comp, 1H), 3.56 (dq, J = 14.0 Hz, 7.0 Hz, 1H), 3.47 (dq, J = 14.0 Hz, 7.0 Hz, 1H), 3.36 (dq, J = 14.0 Hz, 7.0 Hz, 1H), 3.15 (dq, J = 14.0 Hz, 7.0 Hz, 1H), 2.89 (d, J = 13.0 Hz, 1H), 2.54 (d, J = 13.0 Hz, 1H), 2.20 (br s, 2H), 1.39 (d, J = 5.0 Hz, 1H), 1.04 (d, J = 5.0 Hz, 1H), 1.03 (t, J = 7.0 Hz, 3H), 0.86 (s, 3H), 0.80 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ = 170.9, 137.6, 128.8, 128.1, 126.5, 50.6, 41.5, 39.2, 21.5, 18.0, 13.3, 12.3.

The hydrochloride salt of **9b** was obtained by addition of HCl (1 M solution in ether): mp: 151 – 153°C ; $[\alpha]_{\text{D}}^{26}$: -167.1 (c 0.12, MeOH); ^1H NMR (300 MHz, CD_3OD): δ = 7.43–7.20 (comp, 5H), 4.78 (br s, 3H), 3.55–3.11 (comp, 5H), 2.62 (d, J = 13.5 Hz, 1H), 1.70 (d, J = 6.0 Hz, 1H), 1.29 (d, J = 6.0 Hz, 1H), 0.95 (t, J = 6.9 Hz, 3H), 0.75 (s, 3H), 0.71 (t, J = 6.9 Hz, 3H); ^{13}C NMR (62.5 MHz, CD_3OD): δ = 172.9, 137.1, 129.9, 128.8, 49.1, 43.3, 41.8, 40.9, 26.3, 23.4, 18.2, 13.3, 12.5; HRMS: calcd for $\text{C}_{16}\text{H}_{25}\text{N}_2\text{O}$: 261.1967; found: 261.1968.

Acknowledgements

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