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Squaramide-Catalyzed Michael Addition as a Key Step for the Direct Synthesis of GABAergic Drugs

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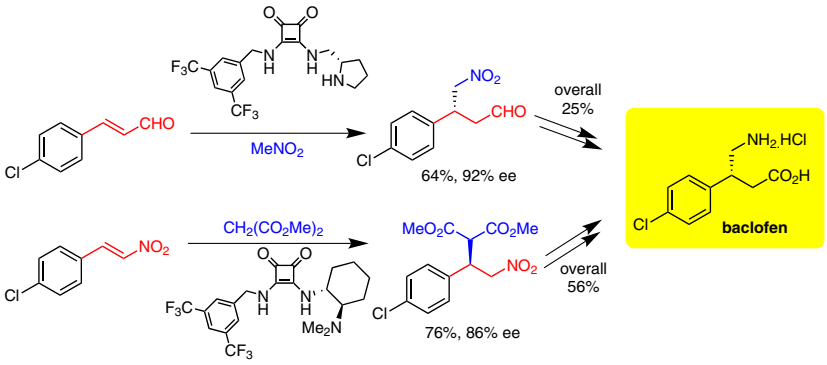

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Abstract Enantioselective organocatalytic Michael additions serve as the key step in syntheses of chiral drugs based on γ-aminobutyric acid. The applicability of various squaramide catalysts for these Michael-type reactions has been assessed. Very good results in terms both activity and enantioselectivity were obtained in the Michael addition of dimethyl malonate to β-nitrostyrenes. On the other hand, a complementary approach, the addition of nitromethane to cinnamaldehydes, worked well with a squaramide catalyst possessing an adjacent pyrrolidine moiety. The corresponding Michael adducts obtained in the best conditions are suitable chiral intermediates for the synthesis of therapeutically useful GABA derivatives. Polymer-immobilized squaramides afforded the Michael adduct in high enantiomeric purity, but yield deterioration was observed between runs. Two different formal total syntheses of baclofen have also been accomplished.

Key words asymmetric catalysis, organocatalysis, Michael addition, squaramides, baclofen

3-Substituted derivatives of γ-aminobutyric acid (GABA) are already certified or potentially centrally acting skeletal muscle relaxants, and some of them are active ingredients in drugs.[1] Baclofen (Lioresal® and Baclon®) is used to treat spasticity caused by spinal cord injury or various neurological disorders.[2] Another related GABA-mimetic psychotropic drug phenibut has anxiolytic effects.[3] Because only one enantiomer of both of these compounds exhibits the required activity, it is important to develop enantioselective strategies for their preparation.

Asymmetric organocatalysis has proved useful in the synthesis of many biologically relevant compounds.[4–7] Key intermediates in the enantioselective synthesis of GABAergic drugs are products of asymmetric Michael additions. From among various activation modes, hydrogen-bonding catalysts have proved useful for this kind of Michael addition.[8–11] Chiral thioureas[12–16] and squaramides[17–19] became typical structural motives in this catalysis. The key step in the organocatalyzed synthesis of GABA derivatives such as baclofen involves Michael addition of enolizable carbonyl compounds to nitroalkenes with thioureas as catalysts.[20,21] Interestingly, squaramides often function in a complementary manner to thiourea catalysts. Therefore, many useful Michael additions[22–27] and related domino reactions[28–30] have also been catalyzed by squaramides. Recently, our group has reported an efficient enantioselective Michael addition of 1,3-dicarbonyl compounds to an aliphatic nitroalkene catalyzed by various squaramides. The Michael adduct, obtained by a reaction of Meldrum's acid and (*E*)-4-methyl-1-nitropent-1-ene with an enantiomeric purity of 97:3 e.r., was successfully used as a key intermediate in the total synthesis of pregabalin. Song and Bae recently described highly enantioselective Michael additions in the syntheses of rolipram and pregabalin using squaramide catalysis on water.[31] The synthesis of baclofen based on a conjugate addition of nitromethane to α,β-unsaturated carbonyl compounds catalyzed by chiral pyrrolidines was performed by Zu and co-workers.[32] However, the use of chiral squaramides in Michael additions of nitromethane has only been described a few times.[33,34]

In this context, we decided to investigate both alternative Michael additions of malonate to aromatic nitroalkenes as well as the conjugate addition of nitromethane to the corresponding α,β-unsaturated aldehyde with the aim to prepare the chiral intermediates for the synthesis baclofen and phenibut.

As shown in Figure 1, we prepared various squaramide catalysts including polymer-supported systems. The squaramide organocatalysts **C1**,[35] **C2**,[36] **C3**,[37] **C4**,[22] **C5**,[33] **C6**,[21] and **C7**[38,39] were synthesized according to literature procedures. The preparation of squaramides **C8** and **C9** and polymer-supported catalysts **C10**–**12** is described in the experimental section.

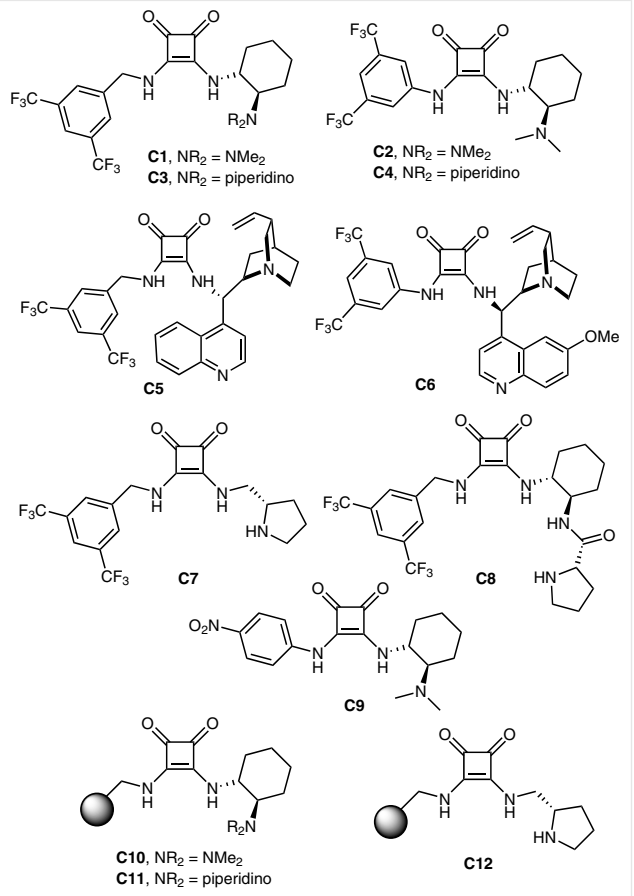
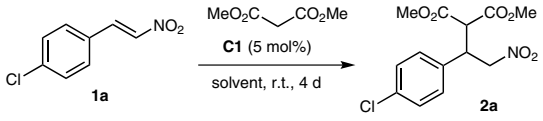


Figure 1 Squaramide catalysts used in this study

Table 1 Optimization of the Reaction Conditions for Michael Addition of Dimethyl Malonate to Alkene **1a**[a]



Entry	Solvent	Conversion[b] (%)	Yield (%)	e.r.[c]
1	CH_2Cl_2	56[d]	52	90:10
2	CH_2Cl_2	91	84	93:7
3	THF	100	96	63:37
4	toluene	83	80	83:17
5	MeCN	65	46	85:15
6	brine	–[e]	67	90:10

[a] Reaction conditions: *trans*-4-chloro-β-nitrostyrene (0.55 mmol), dimethyl malonate (0.5 mmol), **C1** (5 mol%, unless otherwise stated), solvent (1 mL), r.t., 4 d.
[b] Determined by ^{1}H NMR of the crude reaction mixture.
[c] Determined by chiral HPLC on the purified product.
[d] 1 mol% of catalyst.
[e] Not determined.

With organocatalysts in hand, we started screening the reaction conditions for the Michael addition of dimethyl malonate to selected aromatic nitroalkenes.

Firstly, the reaction between dimethyl malonate and *trans*-4-chloro-β-nitrostyrene (**1a**) in the presence of squaramide **C1** was examined. The results are collected in Table 1. We selected the substrate **1a** because the corresponding chiral adduct **2a** can be further processed to afford baclofen.

As follows from Table 1, the use of 1 mol% of the catalyst leads to low conversion of reactants, and, therefore, we increased catalyst loading to 5 mol% (Table 1, entry 1 vs. 2). The effect of solvent was also investigated, and it can be concluded that dichloromethane appeared to be the best solvent to obtain high ee values, other solvents provided poorer results (Table 1, entry 2 vs. 3–5). Interestingly, also brine can be used with good effect, but the yield was somewhat lower than in dichloromethane (Table 1, entry 6).

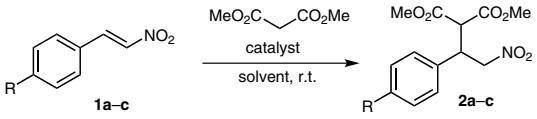
Next, the effect of squaramide catalysts **C2**–**9** on the course of the reaction was tested (Table 2). The catalysts **C2**–**6**, which worked well in our previous study on the Michael addition to an aliphatic nitroalkene,[37] afforded lower yields and moderate enantioselectivities in comparison with catalyst **C1** (Table 1, entry 2 vs. Table 2, entries 1–6). The catalysts **C7** and **C8**, which possess an additional pyrrolidine unit, gave very little or no chiral product **2a** even if catalyst loading was increased and the reaction time was prolonged (Table 2, entries 7–9). Poor results were also obtained with catalyst **C9** (Table 2, entries 10 and 11).

Hence, we selected the optimal reaction conditions as follows: dichloromethane as solvent, 96 hours reaction time, **C1** at 5 mol% catalyst loading. Under these conditions, the Michael product **2a** was obtained in 84% yield and enantiomeric purity 86% ee also on a synthetically useful scale.

We expanded the optimized protocol to *trans*-β-nitrostyrene because phenibut has a similar structure to baclofen (only without chlorine atom in the *para*-position of the phenyl group. The chiral phenibut intermediate **2b** was prepared in comparable yield and enantioselectivity to adduct **2a** (Table 2, entry 12). The substrate bearing an aromatic ring with an electron-donating substituent, a methoxy group, **1c** participated equally well in the reaction (Table 2, entry 13).

In a view of potentially more efficient chemical production, the design and preparation of immobilized, easily recoverable, and reusable catalysts appears as one of the most promising strategies. Some pyrrolidine derivatives supported on polystyrene resins display high catalytic activity and enantioselectivity in various Michael additions.[40] Several squaramide catalysts have been immobilized by various strategies.[41–44] Polymer-immobilized squaramide catalysts

Table 2 Screening of Squaramide Catalysts for the Michael Reaction Dimethyl Malonate to β-Nitrostyrenes[a]

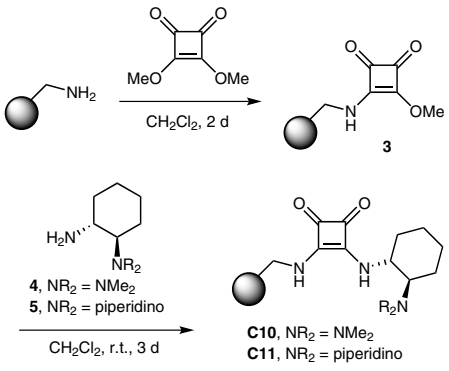


Entry	Alkene, R	Catalyst (mol%)	Time (d)	Yield (%) (conversion, %)[b]	e.r.[c]
1	**1a**, Cl	**C2** (5)	4	25 (39)	85:15
2	**1a**, Cl	**C3** (5)	4	59 (65)	98:2
3	**1a**, Cl	**C3** (5)	4	50 (–)[d]	97:3
4	**1a**, Cl	**C4** (5)	4	25 (35)	77:23
5	**1a**, Cl	**C5** (5)	4	52 (55)	95:5
6	**1a**, Cl	**C6** (5)	4	8 (26)	–
7	**1a**, Cl	**C7** (5)	4	5 (58)	–
8	**1a**, Cl	**C7** (10)	14	6 (64)	–
9	**1a**, Cl	**C8** (5)	10	0 (64)	–
10	**1a**, Cl	**C9** (5)	4	17 (34)	82:18
11	**1a**, Cl	**C9** (10)	14	9 (63)	85:15
12	**1b**, H	**C1** (5)	4	82 (95)	91:9
13	**1c**, OMe	**C1** (5)	4	70 (83)	95:5

[a] Reaction conditions: **1** (0.55 mmol), dimethyl malonate (0.5 mmol), catalyst **C1**–**9** (5 mol%), CH_2Cl_2 (1 mL), r.t.
[b] Determined by ^{1}H NMR of the crude reaction mixture.
[c] Determined by chiral HPLC on the purified product.
[d] Not determined.

have not been used in this transformation. Therefore, we prepared immobilized catalyst **C10** and **C11** with the best effective squaramide units **C1** (yield) and **C2** (enantioselectivity).

These catalysts were prepared by a route shown in Scheme 1. Aminomethylpolystyrene was treated with dimethyl squarate to provide functionalized resin **3**. Both catalysts **C10** and **C11** were prepared from the resin **3** through functionalization with diamines **4** and **5**, respectively.

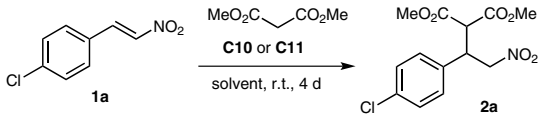


Scheme 1 Synthesis of immobilized catalysts **C10** and **C11**

First, the resin **C10** was tested as a catalyst for the Michael addition of dimethyl malonate to 4-chloro-β-nitrostyrene (**1a**). The reaction was carried out in dichloromethane. A very good result was achieved in the first run. The product **2a** was obtained in a synthetically valuable yield (83%) with high enantiomeric purity (96% ee) (Table 3, entry 1). The high enantiomeric purity of product **2a** remained unchanged in following cycles, but the yield decreased dramatically especially in the third cycle (Table 3, entries 2 and 3). The catalyst **C11** was equally as enantioselective as **C10**, but it was less active in terms of the yield (Table 2, entries 5–7).

In an attempt to improve the yield of the product **2a**, we tried to use toluene as the solvent (Table 3, entries 7–9). We observed that the yield increased markedly in the second run (Table 3, entry 8). This fact is probably caused by adsorption of the product onto aminopolystyrene in the first run while the saturated resin does not allow this adsorption in the second cycle. The activity of the catalyst unfortunately again decreased in the subsequent third run (Table 3, entry 9). We tried to improve the recycling of our immobilized catalysts by using ultrasound technique, but without visible progress.

Table 3 Addition of Dimethyl Malonate to *trans*-4-Chloro-β-nitrostyrene (**1a**) Using Resins **C10** and **C11**[a]



Entry	Catalyst	Solvent	Cycle	Yield (%) (conversion, %)[b]	e.r.[c]
1	**C10**	CH_2Cl_2	1	83 (100)	98:2
2	**C10**	CH_2Cl_2	2	61 (73)	98:2
3	**C10**	CH_2Cl_2	3	11 (24)	98:2
4	**C11**	CH_2Cl_2	1	55 (100)	95:5
5	**C11**	CH_2Cl_2	2	48 (69)	97:3
6	**C11**	CH_2Cl_2	3	15 (19)	98:2
7	**C11**	toluene	1	59 (100)	94:6
8	**C11**	toluene	2	82 (94)	95:5
9	**C11**	toluene	3	41 (46)	96:3

[a] Reaction conditions: **1a** (0.55 mmol), dimethyl malonate (0.5 mmol), **C10**,**11** (100 mg), solvent (0.5 mL), 4 d.
[b] Determined by ^{1}H NMR of the crude reaction mixture.
[c] Determined by chiral HPLC on the purified product.

In the second part of our study, we examined a reversed Michael addition, that is the addition of nitromethane to α,β-unsaturated aldehydes. We envisaged that bifunctional catalysts **C7** and **C8** could prove useful here. These catalysts showed very small or no activity in the above described reaction of β-nitrostyrene with dimethyl malonate. We presumed that the pyrrolidine unit in compounds **C7** and **C8**

could activate the aldehyde via iminium salt formation. On the other hand, the squaramide moiety can activate nitromethane via hydrogen bonding. Another reason for the choice of this reaction was again that its products could be used in the syntheses of baclofen or phenibut.

At first, we tested the addition of nitromethane to cinnamaldehyde (**6a**) with a higher amount of catalyst **C7** (20 mol%). As follows from Table 4, we achieved very poor results when dichloromethane or methanol was used as a solvent (entries 1 and 2).

Based on experiences with the Michael addition of nitromethane to cinnamaldehyde (**6a**) reported by many groups, an acidic or basic additives are necessary for a successful reaction. We decided to perform the reaction similar conditions as published by Hayashi and co-workers using benzoic acid (20 mol%) as an acidic additive and methanol as the solvent.[45] The catalyst **C7** afforded the product **7a** in medium yield and catalyst **C8** even displayed markedly lower activity (Table 4, entries 3 and 4). Therefore we tried to use a basic additive, and the reaction was realized according to a protocol reported by Lombardo et al., using 20 mol% of catalyst and 30 mol% of sodium acetate in a mixture of dichloromethane/methanol (9:1).[46] Pleasingly, a significant increase in the yield of up to 81% was achieved with the catalyst **C7**. The product **7a** was isolated in high enantiomeric purity (90% ee) (Table 4, entry 5). Decreasing the catalyst loading from 20 mol% to 5 mol% did not have a negative effect in terms of the yield and enantioselectivity (Table 4, entry 6). Catalyst **C8** afforded the product **7a** in lower yield and poor enantiomeric purity in comparison to catalyst **C7** (Table 4, entry 7).

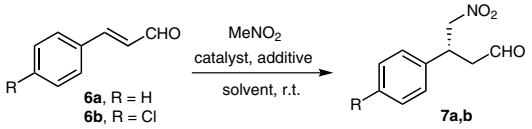
Surprisingly, the application of catalyst **C1** or racemic proline afforded the product in much lower yields (Table 4, entries 8 and 9). These results suggest that combination of squaramide and pyrrolidine unit (**C7**) is very useful for conjugated Michael addition of nitromethane to cinnamaldehyde.

As an extension of the present protocol to the preparation of baclofen, we applied catalyst **C7** in the reaction of *p*-chlorocinnamaldehyde (**6b**) with nitromethane. The chiral intermediate **7b** was obtained in high enantiomeric purity (92% ee) and in preparatively significant yield (91%) (Table 4, entry 10).

Lastly, we prepared immobilized catalyst **C12** with the active part similar to that of catalyst **C7** (Scheme 2). The synthesis of this polystyrene supported catalyst consisted of functionalization of the resin **3** with amine **8**, followed by removal of the Boc group from the amine.

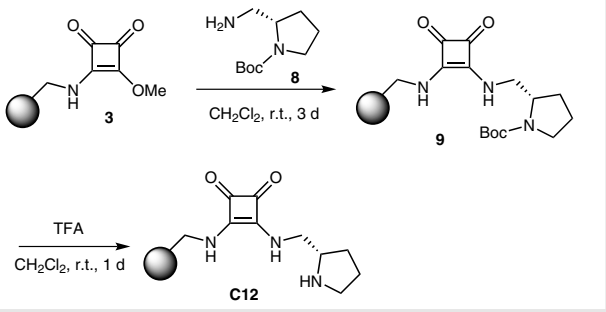
As follows from Table 5, the application of catalyst **C12** led to high yields of product **7b** especially in the second and third cycle but the enantioselectivity was lower in comparison with a nonsupported counterpart **C7**. In this view, the catalyst **C7** is preferable to **C12** in the total synthesis of baclofen via the addition of nitromethane to α,β-unsaturated aldehyde **6b**.

Table 4 Optimization of Conjugate Addition of Nitromethane to *trans*-Cinnamaldehydes **6a**,**b**[a]



Entry	Catalyst (mol%)	Solvent, additive	Time (d)	Yield (%)	e.r.[b]
1	**C7** (20)	CH_2Cl_2	4	0	–
2	**C7** (20)	MeOH	4	17 (**7a**)	–
3	**C7** (20)	MeOH, $PhCO_2H$[c]	4	43 (**7a**)	–
4	**C8** (20)	MeOH, $PhCO_2H$[c]	4	16 (**7a**)	–
5	**C7** (20)	CH_2Cl_2, MeOH, NaOAc[d]	2	81 (**7a**)	95:5
6	**C7** (5)	CH_2Cl_2, MeOH, NaOAc[d]	2	78 (**7a**)	97:3
7	**C8** (5)	CH_2Cl_2, MeOH, NaOAc[d]	2	67 (**7a**)	55:45
8	**C1** (5)	CH_2Cl_2, MeOH, NaOAc[d]	2	16 (**7a**)	–
9	D,L-proline (20)	CH_2Cl_2, MeOH, NaOAc[d]	2	5 (**7a**)	rac
10	**C7** (5)	CH_2Cl_2, MeOH, NaOAc[d]	1	91 (**7b**)	96:4

[a] Reaction conditions: **6a**,**b** (0.3 mmol), $MeNO_2$ (0.9 mmol), catalyst (0.015 or 0.06 mmol), solvent (0.5 mL).
[b] Determined by chiral HPLC of the purified product.
[c] 20 mol% of $PhCO_2H$ was used.
[d] 30 mol% of NaOAc was used.

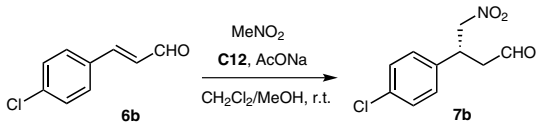


Scheme 2 Synthesis of immobilized catalyst **C12**

To compare the synthetic versatility of both adducts **2a** and **7b**, we demonstrate here two different total syntheses of (*R*)-baclofen. As there are several baclofen syntheses described in the literature, we chose those that utilize chiral intermediates obtained by the above-mentioned Michael additions.

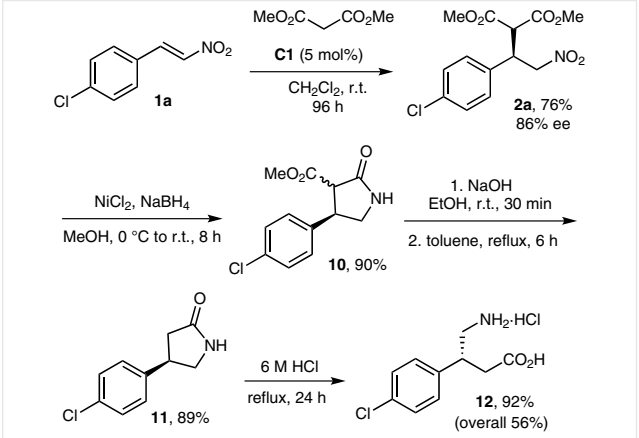
We started the synthesis by performing the Michael addition of dimethyl malonate to nitroalkene **1a** on a 5-mmol scale. The adduct **2a** allowed the synthesis of baclofen hydrochloride (**12**) via a three-step sequence described by Takemoto and co-workers in 56% overall yield (Scheme 3, route A).[47]

Table 5 Conjugate Addition of Nitromethane to *trans*-*p*-Chlorocinnamaldehyde (**6b**) Using Resin **C12**[a]



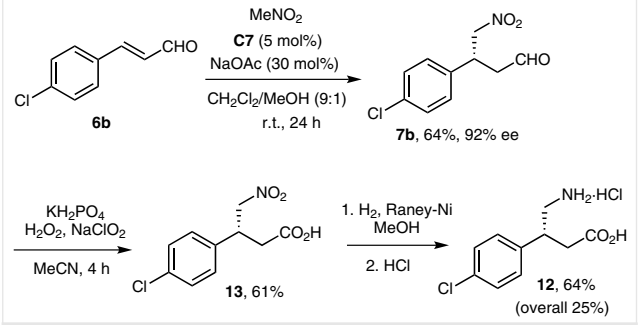
Cycle	Conversion (%)	Yield (%)	e.r.[b]
1	100	71	85:15
2	100	94	82:18
3	100	92	83:17

[a] Reaction conditions: **6b** (0.3 mmol), $MeNO_2$ (0.9 mmol), **C12** (100 mg), NaOAc (0.09 mmol), CH_2Cl_2/MeOH (9:1, 0.5 mL), r.t., 24 h.
[b] Determined by chiral HPLC on the purified product.



Scheme 3 Synthesis of baclofen hydrochloride (**10**); route A

Alternative Michael addition of nitromethane to enal **6b** was performed on a 6-mmol scale. Starting from compound **7b**, baclofen hydrochloride (**12**) was prepared in only two steps, an oxidation according to protocol by Zu et al.[32] and a reduction published by Camps et al. in 25% overall yield (Scheme 4, route B).[48]



Scheme 4 Synthesis of baclofen hydrochloride (**10**); route B

In terms of the total yield of baclofen, route A seems preferable to route B, probably for higher stability of adduct **2a** in comparison to compound **7b**. On the other hand, route B appears preferable judging by enantioselectivity of the Michael addition.

Enantiomerically enriched GABAergic drugs can be synthesized by asymmetric organocatalytic Michael additions using chiral squaramide organocatalysts. We have tested a range of structurally diverse squaramide derivatives and found that squaramide **C1** was the most useful for catalyzing the Michael addition of dimethyl malonate to *trans*-β-nitrostyrenes. Under optimized reaction conditions, the products **2a**–**c** were obtained in synthetically important yields with very good enantiomeric purities. Based on this strategy, the product **2a** can be transformed into the highly enantioenriched baclofen in 56% overall yield.

On the other hand, the squaramide organocatalyst possessing additional pyrrolidine unit **C7** worked very well in the complementary conjugated addition of nitromethane to cinnamaldehydes. Under basic reaction conditions, the corresponding adduct **7b** was prepared in high yield with an enantiomeric purity of 92% ee. Using this methodology as a key step, a short synthesis of baclofen can be realized in 25% overall yield. Both approaches can be used in the synthesis of baclofen. The former route gives higher overall yield, but the latter is more enantioselective. Polymer-immobilized squaramides **C10** and **C11** catalyzed the Michael addition highly enantioselectively, but yields decreased between runs.

Chiral squaramides appear as viable alternatives to thioureas in catalysis of Michael additions, which are key steps in the syntheses of chiral GABA derivatives.

The solvents were purified by standard methods.[49] NMR spectra were recorded on Varian NMR System 300 or 600 instrument (300 MHz for ^1H, 151 MHz for ^{13}C) relative to TMS. Specific optical rotations were measured on Jasco P-2000 instrument and are given in deg cm^3 g^{-1} dm^{-1}. Column chromatography was performed on Merck silica gel 60. TLC was performed on Merck TLC-plates silica gel 60, F-254. Enantiomeric excesses were determined by HPLC using Chiralpak AD-H, AS-H, or OD-H (Daicel Chemical Industries) columns using *n*-hexane/*i*-PrOH as a mobile phase and detected by UV at 254 nm and 210 nm. The squaramide organocatalysts **C1**,[35] **C2**,[36] **C3**,[37] **C4**,[22] **C5**,[33] **C6**,[21] and **C7**[38,39] were synthesized according to literature procedures.

(*S*)-*N*-{(1*R*,2*R*)-2-[(2-{[3,5-Bis(trifluoromethyl)benzyl]amino}-3,4-dioxocyclobut-1-en-1-yl)amino]cyclohexyl}pyrrolidine-2-carboxamide (C8)

A solution of (*S*)-Boc-proline (215 mg, 1.0 mmol) and Et_3N (100 mg, 1.0 mmol) in THF (4 mL) was stirred for 1 h at 0 °C. Then ethyl chloroformate (88 μL, 1.0 mmol) was added and the mixture was stirred for 30 min at 0 °C. After this time, 3-{[3,5-bis(trifluoromethyl)benzyl]}amino-4-{[(*R*,*R*)-2-aminocyclohexyl]amino}cyclobut-3-ene-1,2-dione[23] (400 mg, 0.9 mmol) was added, the solution was allowed to reach r.t. and stirred for a further 12 h. The resulting solid Boc-protected **C8** was obtained by filtration. Deprotection was performed

with CH_2Cl_2/TFA (4:1; 12.5 mL) for 2 h at r.t. After concentration, the oil residue was triturated with MeOH saturated with NH_3 (10 mL). Catalyst **C8** was obtained as a colorless solid; yield: 350 mg (86%); mp 232 °C (decomp.); $[\alpha]_D^{25}$ +4.1 (*c* 0.5, MeOH).

IR: 3195, 3051, 2930, 1647, 1563, 1470, 1435, 1381, 1339, 1274, 1172, 1124, 840, 801, 724, 703, 682 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 7.98 (s, 2 H), 7.88 (s, 1 H), 4.94 (s, 2 H), 3.89–3.81 (m, 2 H), 3.74–3.66 (m, 1 H), 3.12–3.07 (m, 2 H), 2.26–2.15 (m, 1 H), 2.12–2.04 (m, 1 H), 1.97–1.92 (m, 1 H), 1.83–1.71 (m, 4 H), 1.50–1.34 (m, 5 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 182.5, 182.1, 170.9, 168.0, 161.8 (q, *J* = 34.5 Hz), 141.8, 131.6 (q, *J* = 33.0 Hz), 128.2, 124.2 (q, *J* = 272 Hz), 121.1, 117.8 (q, *J* = 293 Hz), 59.8, 57.3, 53.3, 46.3, 46.1, 33.0, 31.3, 30.0, 24.3, 24.1.

HRMS (HESI): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{27}F_6N_4O_3$: 533.1982; found: 533.1992.

UV-VIS: λ_{max} = 292 nm.

3-{[(1*R*,2*R*)-2-(Dimethylamino)cyclohexyl]amino}-4-[(4-nitrophenyl)amino]cyclobut-3-ene-1,2-dione (C9)

To a solution of (*R*,*R*)-1,2-diaminocyclohexane (220 mg, 1.92 mmol) in CH_2Cl_2 (8 mL) was added 3-methoxy-4-[(4-nitrophenyl)amino]cyclobut-3-ene-1,2-dione[50] (477 mg, 1.92 mmol). The mixture was stirred for 24 h at r.t. After this time, the resulting mixture was diluted with H_2O (50 mL) and the generated precipitate was collected by filtration. Then, to the precipitate was added aq HCHO (37%, 2 mL) and HCO_2H (80%, 2 mL) and the mixture was stirred at 65 °C for 24 h. The mixture was filtered with the aid of HCO_2H (2 mL). The filtrate was basified by 6 M aq NaOH to pH 12 and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and then concentrated. Recrystallization (MeOH) gave **C9** as an orange solid; yield: 110 mg (30%); mp 238 °C (decomp.); $[\alpha]_D^{25}$ –98.4 (*c* 0.20, MeOH).

IR: 3194, 3144, 2934, 2856, 2780, 1798, 1666, 1620, 1602, 1576, 1558, 1509, 1433, 1417, 1335, 1270, 1190, 1110, 848, 748 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.20 (d, *J* = 9.3 Hz, 2 H), 7.56 (d, *J* = 9.3 Hz, 2 H), 4.00 (m, 1 H), 2.54–2.47 (m, 1 H), 2.32 (s, 6 H), 2.26–2.21 (m, 1 H), 1.99–1.76 (m, 3 H), 1.49–1.26 (m, 4 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 186.1, 181.9, 171.5, 164.3, 146.6, 143.9, 126.9, 126.5, 119.1, 111.5, 68.5, 56.6, 40.6, 40.4, 36.1, 26.0, 25.8, 22.9.

HRMS (HESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{23}N_4O_4$: 359.1714; found: 359.1716.

UV-VIS: λ_{max} = 388 nm.

Immobilized Squaramide 3

Aminomethylpolystyrene (AM-NH_2, f_o = 1.4 mmol/g; 1.051 g) was added to a solution of dimethyl squarate (1.007 g, 7.09 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred for 2 d at r.t. The suspension was filtered, and the resin **3** was sequentially washed with Et_2O (50 mL), EtOAc (2 × 50 mL), and MeOH (2 × 50 mL). The resin was dried at r.t. for 1 d to give **3** (1.321 g); content squaramide unit 1.527 mmol g^{-1}. The content of squaramide unit was calculated on the basic weight of unreacted dimethyl squarate that was recovered from combined washings after concentration (0.779 g, 5.48 mmol).

Immobilized Catalyst C10

The resin **3** (0.42 g, 0.64 mmol of squaramide unit) was added to a solution of diamine **4**[51] (273 mg, 1.92 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 3 d at r.t. The suspension was filtered, and the solid was sequentially washed with Et_2O (50 mL), EtOAc (2 × 50 mL), and MeOH (2 × 50 mL). The resin was dried at r.t. for 1 d to give the immobilized catalyst **C10** (0.445 g); Anal. C, 79.73; H, 8.04; N, 4.52. The final functionalization (1.46 mmol g^{-1}) was calculated from the difference between reacted and unreacted diamine that was recovered from combined washings after concentration (0.180 g, 1.27 mmol, ca. 2 equiv).

Immobilized Catalyst C11

The resin **3** (663 mg, 1.01 mmol of the squaramide unit) was added to a solution of diamine **5**[37] (445 mg, 2.44 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 3 d at r.t. The suspension was filtered, and the solid was sequentially washed with Et_2O (50 mL), EtOAc (2 × 50 mL), and MeOH (2 × 50 mL). The filtrate was evaporated, and weight of unreacted diamine was 297 mg (1.63 mmol). The resin was dried at r.t. for 1 d to give the immobilized catalyst **C11** (781 mg); Anal. C, 81.99; H, 8.09; N, 4.27. The final functionalization (1.04 mmol g^{-1}) was calculated from the difference between reacted and unreacted diamine that was recovered from combined washings after concentration (0.297 g, 1.63 mmol).

Immobilized Catalyst C12

The resin **3** (0.42 g, 0.64 mmol of squaramide unit) was added to solution of amine **8**[39] (0.32 g, 1.6 mmol) in CH_2Cl_2 (2.5 mL). The mixture was stirred for 3 d at r.t. Resin **9** was separated by filtration and washed with CH_2Cl_2 (2 × 20 mL) (the filtrate was evaporated, and weight of unreacted diamine was 192 mg, 0.96 mmol, 1.5 equiv). The deprotection was performed with a mixture of TFA (2 mL) in CH_2Cl_2 (10 mL) for 1 d at r.t. Deprotected resin **C12** was removed by filtration and then suspended in 1% $NaHCO_3$ solution (50 mL). After 1 h, the resin was again filtered and washed with water (2 × 50 mL) and MeOH (2 × 50 mL). The resin was dried in air at r.t. for 1 d to give **C12** (419 mg); Anal. C, 75.51; H, 7.04; N, 3.88. The final functionalization (1.53 mmol g^{-1}) was calculated from the difference between reacted and unreacted diamine that was recovered from combined washings after concentration (192 mg, 0.96 mmol).

Enantioselective Michael Addition of Dimethyl Malonate to Substituted *trans*-β-Nitrostyrenes; General Procedure

To a solution of *trans*-β-nitrostyrene **1a**–**c** (0.55 mmol) and dimethyl malonate (66 mg, 0.50 mmol) in CH_2Cl_2 (0.5 mL), catalyst **C1**–**9** (0.025 mmol) was added. The mixture was stirred at r.t. for 96 h. Then, the mixture was diluted with CH_2Cl_2 (15 mL), washed with 1 M HCl (10 mL), and dried (Na_2SO_4). After evaporation of solvent, the residue was purified by column chromatography (silica gel, EtOAc/hexanes 1:5) to afford desired product **2a**–**c**. Yields and enantiomeric excesses are summarized in Tables 1 and 2.

Polymer-Supported Michael Addition of Dimethyl Malonate to *trans*-4-Chloro-β-nitrostyrene (1a)

To a solution of *trans*-β-nitrostyrene **1a** (0.55 mmol) and dimethyl malonate (66 mg, 0.5 mmol) in CH_2Cl_2 (0.5 mL), catalyst **C10** (100 mg, 0.025 mmol) or **C11** (100 mg, 0.025 mmol) was added. The mixture was stirred at r.t. for 96 h. Then, the mixture was diluted with CH_2Cl_2 (15 mL) and the catalyst was directly filtered off. The solid resin was washed with Et_2O (15 mL) followed by EtOAc (15 mL) and reused in the next cycle after drying in air at r.t. for 1 d. The combined filtrates

were concentrated and the residue was purified by column chromatography (silica gel, EtOAc/hexanes 1:5) to afford desired product **2a**. Yield and enantiomeric excess data for **2a** are summarized in Table 3.

Dimethyl 2-[1-(4-Chlorophenyl)-2-nitroethyl]malonate (2a)

Colorless solid; yield: 132 mg (84%); 86% ee; mp 93 °C (Lit.[52] 93.1–94.7 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 8.4 Hz, 2 H), 7.18 (d, *J* = 8.4 Hz, 2 H), 4.94–4.83 (m, 2 H), 4.26–4.18 (m, 1 H), 3.83 (d, *J* = 9 Hz, 1 H), 3.76 (s, 3 H), 3.59 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.6, 167.0, 134.6, 134.4, 129.27, 129.26, 77.2, 54.5, 53.1, 53.0, 42.3.

Spectral data are consistent with those in the literature.[53] Enantiomeric purity was determined by HPLC [Daicel Chiralpac OD-H, hexanes/*i*-PrOH (70:30), flow rate 1.0 mL/min, λ = 220 nm]: t_R = 9.96 (minor), 12.42 min (major).

Dimethyl 2-[1-(4-Methoxyphenyl)-2-nitroethyl]malonate (2c)

Colorless oil; yield: 109 mg (70%); 90% ee.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 8.7 Hz, 2 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 4.90–4.81 (m, 2 H), 4.23–4.15 (m, 1 H), 3.83 (d, *J* = 9.3 Hz, 1 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 3.57 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$,): δ = 170.4, 169.9, 161.8, 131.3, 130.4, 116.0, 79.8, 56.8, 56.5, 57.1, 53.8, 44.9.

Spectral data are consistent with those in literature.[53] Enantiomeric purity was determined by HPLC [Daicel Chiralpac OD-H, hexane/*i*-PrOH (70:30), flow rate 1.0 mL/min, λ = 254 nm]: t_R = 12.38 (minor), 14.24 min (major).

Dimethyl 2-(2-Nitro-1-phenylethyl)malonate (2b)

Colorless solid; yield: 115 mg (82%); 82% ee; mp 63 °C (Lit.[54] 63 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 3 H), 7.24–7.21 (m, 2 H), 4.94–4.86 (m, 2 H), 4.28–4.21 (m, 1 H), 3.86 (d, *J* = 9 Hz, 1 H), 3.76 (s, 3 H), 3.56 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$,): δ = 168.1, 167.8, 136.3, 129.2, 128.6, 128.1, 77.4, 55.0, 53.3, 53.0, 43.1.

Spectral data are consistent with those in the literature.[25] Enantiomeric purity was determined by HPLC [Daicel Chiralpac OD-H, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL/min, λ = 220 nm]: t_R = 11.32 (minor), 19.71 min (major).

Enantioselective Conjugate Addition of Nitromethane to *trans*-Cinnamaldehydes; General Procedure

To a solution of cinnamaldehyde **6a**,**b** (0.3 mmol) in CH_2Cl_2/MeOH (9:1, 0.5 mL) catalyst **C7** or **C8** (0.015 mmol), $MeNO_2$ (91 mg, 0.9 mmol), and NaOAc·3H_2O (12.2 mg, 0.09 mmol) were added. The resulting mixture was stirred at r.t. for the stated time. The mixture was then diluted with CH_2Cl_2 (15 mL), washed with 1 M HCl (10 mL), and dried (Na_2SO_4). After concentration, the residue was purified by column chromatography (silica gel, EtOAc/hexanes 1:5) to afford desired product **7a**,**b**. Yields and enantiomeric excesses are summarized in Table 4.

Polymer-Supported Conjugate Addition of Nitromethane to *trans*-*p*-Chlorocinnamaldehyde (6b)

To a solution of cinnamaldehyde **6b** (50 mg, 0.3 mmol) in CH_2Cl_2/MeOH (9:1, 0.5 mL), catalyst **C12** (100 mg), $MeNO_2$ (91 mg, 0.9 mmol), and NaOAc·3H_2O (12.2 mg, 0.09 mmol) were added. The resulting mixture was stirred at r.t. for 24 h. The mixture was then diluted CH_2Cl_2 (15 mL) and the resin was directly filtered off. The solid resin was washed with Et_2O (15 mL) followed by EtOAc (15 mL) and reused in another cycle after drying in air at r.t. for 1 d. The combined filtrates were washed with 1 M HCl (10 mL) and dried (Na_2SO_4). After concentration, the residue was purified by column chromatography (silica gel, EtOAc/hexanes 1:5) to afford the desired product **7b**. Yields and enantiomeric excesses are summarized in Table 5.

4-Nitro-3-phenylbutanal (7a)

Colorless oil; yield: 45 mg (78%); 94% ee.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.71 (s, 1 H), 7.35–7.22 (m, 5 H), 4.70–4.58 (m, 2 H), 4.11–4.06 (m, 1 H), 2.96 (d, *J* = 7.2 Hz, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$,): δ = 198.9, 133.6, 130.1, 128.5, 127.4, 79.4, 46.4, 37.9.

Spectral data are consistent with those in the literature.[46] Enantiomeric purity was determined by HPLC [Daicel Chiralpac OD-H, hexane/*i*-PrOH (70:30), flow rate 0.70 mL/min, λ = 210 nm]: t_R = 34.2 (minor), 38.3 min (major).

3-(4-Chlorophenyl)-4-nitrobutanal (7b)

Colorless oil; yield: 62 mg (91%); 92% ee.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.70 (s, 1 H), 7.33 (d, *J* = 8.7 Hz, 2 H), 7.18 (d, *J* = 8.7 Hz, 2 H), 4.71–4.55 (m, 2 H), 4.15–4.01 (m, 1 H), 2.94 (d, *J* = 7.2 Hz, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$,): δ = 198.2, 136.7, 129.4, 128.8, 124.3, 79.1, 46.3, 37.3.

Spectral data are consistent with those in the literature.[46] Enantiomeric purity was determined by HPLC [Daicel Chiralpac OD-H, hexane/*i*-PrOH (70:30), flow rate 0.70 mL/min, λ = 210 nm]: t_R = 26.0 (minor), 31.9 min (major).

Baclofen; Synthesis by Route A

Large-Scale Preparation of 2a

To a solution of *trans*-β-nitrostyrene **1a** (1.068 g, 5.82 mmol) and dimethyl malonate (700 mg, 5.30 mmol) in CH_2Cl_2 (6 mL), catalyst **C1** (122 mg, 0.265 mmol) was added. The mixture was stirred at room temperature for 96 h. Then, the reaction mixture was diluted by CH_2Cl_2 (50 mL) washed with 1 M HCl (2 × 50 mL) and dried (Na_2SO_4). After evaporation of solvent, the residue was purified by column chromatography (SiO_2, EtOAc/hexanes 1:5) to afford desired product **2a** (1.27 g, 76%).

Methyl (*R*)-4-(4-Chlorophenyl)-2-oxopyrrolidine-3-carboxylate (10)[47]

To a solution of **2a** (196 mg, 0.62 mmol) in MeOH (3 mL) was added $NiCl_2$·6H_2O (146 mg, 0.62 mmol) and then $NaBH_4$ (258 mg, 7.44 mmol) at 0 °C. The resulting mixture was stirred for 8 h at r.t. Then sat. NH_4Cl solution was added and the product was extracted with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and concentrated. Column chromatography (silica gel, $CHCl_3$/MeOH 20:1) afforded **10** (142 mg, 90%) as a colorless solid; mp 162–163 °C (Lit.[47] 161–162 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8.7 Hz, 2 H), 7.20 (d, *J* = 8.7 Hz, 2 H), 6.42 (br s, 1 H), 4.15–4.06 (q, *J* = 9 Hz, 1 H), 3.84–3.79 (m, 3 H), 3.52 (d, *J* = 9.6 Hz, 1 H), 3.40 (t, *J* = 9 Hz, 1 H).

^{1}H NMR data agree with those in the literature.

(*R*)-4-(4-Chlorophenyl)pyrrolidin-2-one (11)[47]

To a solution of **10** (142 mg, 0.53 mmol) in EtOH (3 mL), 1 M aq NaOH (1 mL) was added and the resulting mixture was stirred for 30 min at r.t. EtOH was evaporated in vacuo; the residue was neutralized with 1 M HCl and extracted with $CHCl_3$ (4 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Solid residue was dissolved in boiling toluene (8 mL) and this solution was refluxed for 6 h. Distillation of the solvent afforded compound **11** (98 mg, 89%) as a colorless solid; mp 108–111 °C (Lit.[47] 111–112 °C). $[\alpha]_D^{30}$ –40.0 (*c* 1.0, $CHCl_3$) {Lit.[47] $[\alpha]_D^{30}$ –39.0 (*c* 1.0, $CHCl_3$)}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8.4 Hz, 2 H), 7.19 (d, *J* = 8.4 Hz, 2 H), 6.32 (br s, 1 H), 3.78 (t, *J* = 8.7 Hz, 1 H), 3.68 (m, 1 H), 3.38 (q, *J* = 8.7, 7.2 Hz, 1 H), 2.74 (dd, *J* = 16.8, 8.7 Hz, 1 H), 2.46 (dd, *J* = 17.1, 8.4 Hz, 1 H).

^{1}H NMR data agree with those in the literature.

(*R*)-4-Amino-3-(4-chlorophenyl)butanoic Acid Hydrochloride (12)[47]

A solution of **11** (80 mg, 0.40 mmol) in 6 M HCl (2.5 mL) was refluxed for 24 h. Careful evaporation and subsequent drying afforded **12** (94 mg, 92%) as a colorless solid; mp 198–200 °C (Lit.[55] 198–199 °C); $[\alpha]_D^{25}$ –1.97 (*c* 0.6, H_2O) {Lit.[47] $[\alpha]_D^{25}$ –2.17 (*c* 0.6, H_2O)}.

^{1}H NMR (300 MHz, D_2O): δ = 7.49–7.36 (m, 4 H), 3.50–3.24 (m, 3 H), 2.94–2.74 (m, 2 H).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.20 (br s, 1 H), 7.97 (s, 3 H), 7.34–7.25 (m, 4 H), 3.06–3.00 (m, 1 H), 2.92–2.85 (m, 1 H), 2.75 (dd, *J* = 5.4, 16.5 Hz, 1 H), 2.50 (dd, *J* = 9.3, 16.2 Hz, 1 H).

^{13}C NMR (75 MHz, D_2O): δ = 175.3, 137.0, 133.3, 129.4, 129.2, 43.6, 39.4, 38.3.

NMR data agree with those in the literature.

Baclofen; Synthesis by Route B

Large-Scale Preparation of 7b

To a solution of cinnamaldehyde **6b** (906 mg, 5.46 mmol) in CH_2Cl_2/MeOH (9:1, 6 mL) catalyst **C7** (115 mg, 0.273 mmol), $MeNO_2$ (1.048 g, 16.4 mmol) and NaOAc·3H_2O (223 mg, 1.63 mmol) were added. The resulting mixture was stirred at room temperature for 24 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) washed with 1 M HCl (2 × 50 mL) and dried (Na_2SO_4). After concentration, the residue was purified by column chromatography (SiO_2, EtOAc/hexanes 1:5) to afford desired product **7b** (793 mg, 64%).

3-(4-Chlorophenyl)-4-nitrobutanoic Acid (13)[32]

To a solution of **7b** (738 mg, 2.21 mmol) in MeCN (17 mL), a solution of KH_2PO_4 (332 mg, 2.44 mmol) in H_2O (8 mL) and 30% H_2O_2 (480 mg, 4.24 mmol) were added at 0 °C. Then a solution of $NaClO_2$ (830 mg, 9.17 mmol, technical grade 80%) in H_2O (16 mL) was added and the resulting mixture was stirred for 4 h at r.t The reaction was stopped by the addition of sat. aq $Na_2S_2O_3$ solution and then acidified with sat. $KHSO_4$ solution. The crude product was extracted with CH_2Cl_2 (5 × 50 mL) and the combined extracts were dried ($MgSO_4$). Evaporation of solvents afforded carboxylic acid **13** (480 mg, 61%) as colorless oil, in acceptable purity for the next reaction step; $[\alpha]_D^{25}$ +21.7 (*c* 0.5, $CHCl_3$) {Lit.[32] $[\alpha]_D^{20}$ +10.4 (*c* 1.0, $CHCl_3$)}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.31 (m, 2 H), 7.18–7.16 (m, 2 H), 4.74–4.56 (m, 2 H), 3.98–3.82 (m, 1 H), 2.82–2.78 (m, 2 H).

^{1}H NMR data agree with those in the literature.

(*R*)-4-Amino-3-(4-chlorophenyl)butanoic Acid Hydrochloride (12)[48]

To a solution of acid **13** (200 mg, 1.65 mmol) in MeOH (30 mL), Raney nickel (500 mg, 50% in H_2O) was added. The resulting mixture was stirred for 24 h at r.t. under an atmosphere of H_2 (5 atm). The reaction was quenched with 0.1 M aq NaOH (15 mL) and the mixture was filtered through a pad of Celite. The filtrate was concentrated and then dissolved in 2 M HCl (10 mL). This solution was then washed with EtOAc (2 × 20 mL). Aqueous phase was concentrated and the residue dissolved in MeOH (10 mL) and filtered. The solvent was then distilled off and the solid residue was refluxed in 6 M HCl (5 mL) for 2 h. The solvent was then again distilled off and the residue dried under reduced pressure to give **12** (127 mg, 64%).

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Supporting Information

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