JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

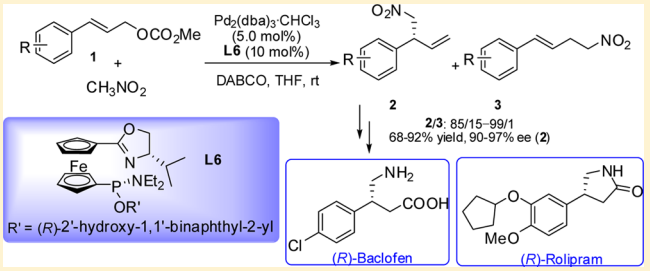
Regio- and Enantioselective Palladium-Catalyzed Allylic Alkylation of Nitromethane with Monosubstituted Allyl Substrates: Synthesis of (*R*)-Rolipram and (*R*)-Baclofen

Xiao-Fei Yang,[†] Chang-Hua Ding,[†] Xiao-Hui Li,[†] Jian-Qiang Huang,[†] Xue-Long Hou,*[,†,‡] Li-Xin Dai,[†] and Pin-Jie Wang[†]

[†]State Key Laboratory of Organometallic Chemistry and [‡]Shanghai-Hong Kong Joint Laboratory in Chemical Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, People's Republic of China

Supporting Information

ABSTRACT: The Pd-catalyzed asymmetric allylic alkylation (AAA) reaction of nitromethane with monosubstituted allyl substrates was realized for the first time to provide corresponding products in high yields with excellent regio- and enantioselectivities. The protocol was applied to the enantioselective synthesis of (*R*)-baclofen and (*R*)-rolipram.



INTRODUCTION

The palladium-catalyzed AAA reaction has become one of the most powerful tools in organic synthesis to build chiral centers through carbon−carbon bond-forming reactions.[1] Nitro compounds are valuable intermediates in organic synthesis, as they are conveniently transformed into a wide variety of synthetically important compounds such as amines, carboxylic acids, aldehydes, and nitriles.[2] The employment of nitroalkanes as nucleophiles in Pd-catalyzed asymmetric allylic alkylation has been reported for more than 15 years. Helmchen reported the first intermolecular Pd-catalyzed asymmetric allylic alkylation of nitromethane with 1,3-symmetrically disubstituted allyl substrates in 1995.[3] Since then, many reports have appeared for Pd-catalyzed allylic alkylation reactions using nitroalkanes, providing corresponding products in high enatioselectivities.[4,5] However, the electrophiles used in these reactions are always limited to those symmetrically 1,3-disubstituted allylic substrates. The use of monosubstituted allyl substrates remains unexplored and daunting. Recently, we have developed a series of ferrocene-based chiral ligands, SIOCPhox, and their superior ability to control regio- and enantioselectivities in Pd-catalyzed AAA of monosubstituted allyl substrates has been demonstrated.[6] On the basis of these successes, we envisioned that the regio- and enantioselectivities of Pd-catalyzed AAA of nitromethanes with monosubstituted allyl substrates should be controlled if SIOCPhox is used as a ligand so that the optically active branched products could be provided. Herein we report our preliminary results in the Pd-catalyzed AAA reaction of nitromethane with monosubstituted allyl substrates and apply the protocol to the enantioselective synthesis of (*R*)-rolipram and (*R*)-baclofen.

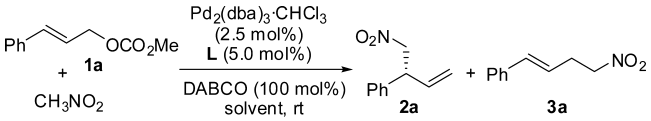
RESULTS AND DISCUSSION

Our initial investigations on the reaction of nitromethane with cinnamyl methyl carbonate (**1a**) was carried out using DABCO as base under the effect of 2.5 mol % of $Pd_2(dba)_3CHCl_3$ and 5.0 mol % of (S_c,R_{phos},S_a)-SIOCPhox (**L1**) in dichloromethane or toluene. However, both experiments failed to afford an allylated product (entries 1 and 2, Table 1). When DMSO was applied as solvent, the desired branched product **2a** was acquired in 72% yield with 78% ee (entry 3, Table 1). With these promising results, other chiral SIOCPhox ligands shown in Figure 1 were tested. The two SIOCPhox ligands (R_{phos},S_a)-**L2** and (S_{phos},S_a)-**L3**, having no chiral center on the oxazoline, gave the product **2a** with opposite configuration, which suggested the central chirality on the phosphorus atom controls the configuration of the product (entries 4 and 5, Table 1). The use of (S_c,S_{phos},S_a)-**L4** and (S_c,S_{phos},R_a)-**L5** led to lower regio- and enantioselectivities in comparison with those for (S_c,R_{phos},S_a)-**L1**, indicating the chiralities in the two ligands are mismatched (entries 6 and 7 vs entry 3, Table 1). An increase in enantioselectivity to 84% was observed using (S_c,R_{phos},R_a)-**L6** as ligand, although the regioselectivity was reduced to 80/20 (entries 8 vs 3, Table 1). On the basis of the above trials and especially the ee value, (S_c,R_{phos},R_a)-**L6** was chosen as the ligand for further investigation of the reaction.

The evaluation of the role of the solvents showed that the mixed solvents of DMSO and THF could significantly increase the regioselectivity (entries 9−11, Table 1), while THF proved to be the solvent of choice, affording the allylated product **2a** in 81% yield, the **2a**/**3a** ratio being 92/8 and ee being 95% for **2a**

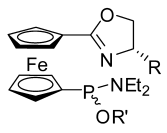
Received: July 17, 2012
Published: September 19, 2012

Table 1. Impact of Reaction Parameters on the Pd-Catalyzed Reaction of Cinnamyl Methyl Carbonate (1a) with Nitromethane[a]



entry	ligand	solvent[b]	2a/3a[c]	yield (%)[d]	ee (%)[e]
1	**L1**	CH_2Cl_2			
2	**L1**	toluene			
3	**L1**	DMSO	89/11	72	78
4	**L2**	DMSO	89/11	62	66
5	**L3**	DMSO	82/18	45	−62[f]
6	**L4**	DMSO	60/40	14	−54[f]
7	**L5**	DMSO	77/23	18	−76[f]
8	**L6**	DMSO	80/20	69	84
9	**L6**	THF/DMSO (1/1)	85/15	60	88
10	**L6**	THF/DMSO (10/1)	90/10	73	94
11	**L6**	THF	92/8	81	97
12	**L7**	THF	88/12	10	
13	**L8**	THF	95/5	58	96
14	**L9**	THF	87/13		

[a]Conditions: molar ratio **1a**/DABCO/$Pd_2(dba)_3CHCl_3$/**L** = 100/100/2.5/5.0, 0.5 mL of CH_3NO_2, 2.0 mL of THF. [b]Reaction time: entries 3−8, 1 h; entries 9−15, 12 h. [c]Determined by chiral GC. [d]Isolated yield of product **2a**. [e]Determined by chiral GC. [f]A minus sign means that the product has the opposite configuration.



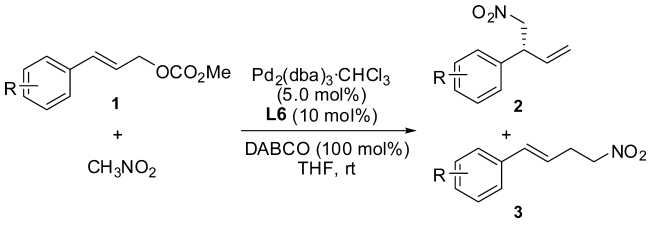
R = ^{i}Pr: (S_c,R_{phos},S_a)-**L1**
R = H: (R_{phos},S_a)-**L2**
R = H: (S_{phos},S_a)-**L3**
R = ^{i}Pr: (S_c,S_{phos},S_a)-**L4**
R = ^{i}Pr: (S_c,S_{phos},R_a)-**L5**
R = ^{i}Pr: (S_c,R_{phos},R_a)-**L6**
R = Ph: (S_c,R_{phos},R_a)-**L7**
R = Bn: (S_c,R_{phos},R_a)-**L8**
R = ^{t}Bu: (S_c,R_{phos},R_a)-**L9**

Figure 1. *P,N*-Ferrocene-based SIOCPhox ligands.

(entry 12, Table 1), though it needed more time (entries 12 vs 8, Table 1). The effect of base on the reaction with the ligand (S,R_{phos},R)-**L6** uncovered that DABCO is the best among the bases we screened such as DIPEA, TEA, Cs_2CO_3, and DMAP (see the Supporting Information). The influence of substituent on the oxazoline ring in ligands (S,R_{phos},R)-**L7**−**9** was also studied. The Pd catalysts derived from them showed lower catalytic activity in the reaction (entries 13−15 vs entry 12, Table 1).

The substrate generality of this Pd-catalyzed AAA reaction with nitromethane was examined under the optimized reaction conditions, and the results are compiled in Table 2. In general, the reaction proceeded smoothly to afford branched allylated products in high regio- and enantioselectivities with high yields. Both electron-donating and -withdrawing groups in the para position of the aryl ring exerted little influence on enantioselectivity (entries 2−5, Table 2). However, a strongly electron withdrawing group, such as a *p*-NO_2 group, resulted in a complex reaction (not shown in the table). The reaction also occurred with excellent enantioselectivity for allyl reagents **1** with meta substituents and an *o*-bromo group on the aryl ring (entries 6−9, Table 2). The allyl **1** with 1-naphthyl also gave excellent yields with high regio- and enantioselectivities (entry 10, Table 2). The employment of allyl **1** containing *p*-methoxy

Table 2. Substrate Scope for Pd-Catalyzed Reaction of Allyl Methyl Carbonate 1 with Nitromethane[a]



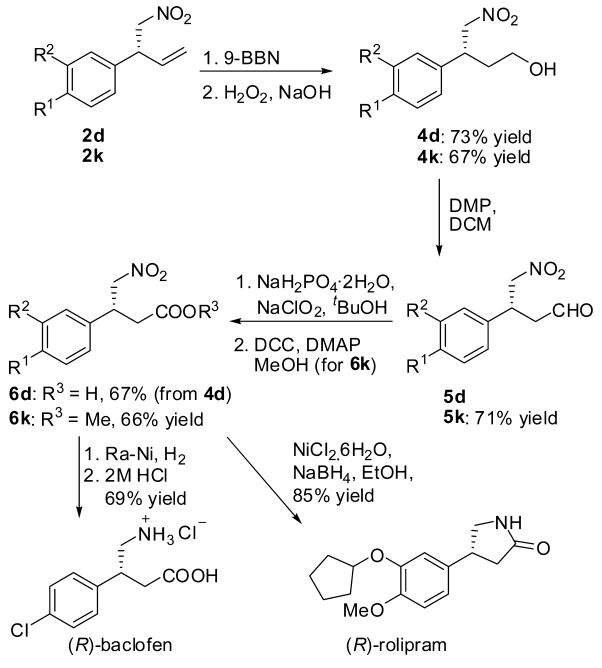
entry	R	2/3[b]	2, yield (%)[c]	ee (%)[d]
1	H	92/8	**2a**, 81	97
2	*p*-CH_3	95/5	**2b**, 88	97
3	*p*-OCH_3	97/3	**2c**, 68	98
4	*p*-Cl	87/13	**2d**, 83	96
5	*p*-F	94/6	**2e**, 88	96
6	*m*-Cl	85/15	**2f**, 80	95
7	*m*-OCH_3	96/4	**2g**, 92	96
8	*m*-OCH_2O-*p*	95/5	**2h**, 80	97
9	*o*-Br	96/4	**2i**, 89	90
10	1-naphthyl	99/1	**2j**, 91	93
11	*p*-OCH_3, *m*-^{c}C_5H_9O	94/6	**2k**, 87	97

[a]Conditions: molar ratio **1**/DABCO/$Pd_2(dba)_3CHCl_3$/**L6** = 100/100/5/10, 0.5 mL of CH_3NO_2, 2.0 mL of THF. [b]Determined by GC. [c]Isolated yield of product **2**. [d]Determined by chiral GC or HPLC.

and *m*-cyclopentyloxy substituents resulted in product **2k** with a slightly reduced regioselectivity but excellent enantioselectivity (entry 11, Table 2). The absolute configuration of the product **2a** was determined to be *R* by comparison of retention time of its HPLC with that in the literature.[5]

To showcase the utility of our methodology, syntheses of (*R*)-rolipram and (*R*)-baclofen were undertaken from the common scaffold **2** (Scheme 1). Rolipram is used as an anti-inflammatory agent and antidepressant, while baclofen is widely employed as an antispasmodic agent. The synthesis of optically

Scheme 1. Synthesis of (*R*)-Baclofen and (*R*)-Rolipram using Allylic Alkylated Products 2



dx.doi.org/10.1021/jo301506p | *J. Org. Chem.* 2012, 77, 8980−8985

active rolipram[7] and baclofen[7f−h,j,k,8] on the basis of asymmetric catalysis has been accomplished by many groups. Among them, Michael addition reactions using chiral organometallic or organocatalytic catalysts are the most common approaches to constructing the stereocenter of these two drugs. Feng and Lin approached (*R*)-baclofen and (*R*)-rolipram by a two-step elaboration of products derived from a rhodium/diene-catalyzed asymmetric addition of arylboronic acids to *α,β*-unsaturated *γ*-lactams.[7j] Wang completed a three-step synthesis of chiral baclofen via an enantioselective conjugate addition reaction of nitromethane with *α,β*-unsaturated aldehydes.[8e]

We began the synthesis of (*R*)-baclofen and (*R*)-rolipram by treatment of the alkylated products **2d,k** with 9-BBN followed by oxidation with H_2O_2/NaOH to afford the alcohols **4** (Scheme 1). Dess−Martin oxidation of alcohols **4** gave the corresponding aldehydes **5**. The aldehyde **5d** was subjected to a Pinnick oxidation to provide the acid **6d** in 84% yield, which was facilely converted to (*R*)-baclofen according to the reported procedure in 69% yield.[9] The aldehyde **5k** was subjected to an one-pot Pinnick oxidation and ester formation to furnish ester **6k** in 66% overall yield. Further elaboration of the ester **6k** with $NaBH_4/C_2H_5OH$ successfully gave the desired (*R*)-rolipram in 85% yield. These results also demonstrate the *R* configuration of the allylate product **2k**.

■ CONCLUSION

We have successfully realized the Pd-catalyzed AAA reaction of monosubstituted allyl substrates with nitromethane, which can provide the corresponding products in high yields with excellent regio- and enantioselectivities. The usefulness of the protocol was demonstrated. Further studies on the extension of the protocol to other nucleophiles and applications in organic synthesis are in progress.

■ EXPERIMENTAL SECTION

General Methods. The reactions were carried out in flame-dried glassware under a dry argon atmosphere. All solvents were purified and dried by using standard methods prior to use. Commercially available reagents were used without further purification. ^{1}H NMR spectra were recorded on a NMR instrument operated at 400 MHz. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet or unresolved), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on a NMR instrument operated at 100 MHz with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.1 ppm). Infrared spectra were recorded from thin films of pure samples. Mass and HRMS spectra were measured in EI or ESI mode, and the mass analyzer of the HRMS was TOF. Thin-layer chromatography was performed on precoated glass-backed plates and visualized with UV light at 254 nm. Flash column chromatography was performed on silica gel. Enantiomer ratios were determined by chiral HPLC analysis in comparison with authentic racemic materials.

General Experimental Procedure for Table 2. In a flame-dried Schlenk tube were added $Pd_2(dba)_3{\cdot}CHCl_3$ (5.2 mg, 0.005 mmol), ligand (S_c,R_{phos},R_a)-**L6** (6.84 mg, 0.010 mmol), and freshly distilled anhydrous THF (2.0 mL). The resulting mixture was stirred for 30 min. The methyl carbonate **1** (0.1 mmol) and DABCO (0.1 mmol) were added subsequently, and then 0.5 mL of nitromethane was added. The resulting reaction mixture was stirred at room temperature overnight (TLC control). After the ratio of compounds **2** and **3** was determined by GC, the volatiles were removed in vacuo. The resulting residue was purified by flash chromatography (FC) on silica gel with petroleum ether and EtOAc as eluent to give product **2** (the products **2** and **3** could be separated by flash chromatography).

*(R)-(1-Nitrobut-3-en-2-yl)benzene (**2a**):*[5] colorless oil; 81% yield; 97% ee. $[\alpha]_D^{20}$ = −6.1° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (q, *J* = 8 Hz, 1H), 4.61−4.72 (m, 2H), 5.18 (d, *J* = 17.2 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 5.99 (ddd, *J* = 7.2, 10.2, 17.2 Hz, 1H), 7.21−7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.7, 79.4, 117.8, 127.5, 127.8, 129.1, 135.7, 138.0; IR (film) 701, 1018, 1087, 1260, 1553, 2963 cm^{-1}; MS (EI) 77 (18), 91 (53), 116 (20), 128 (19), 130 (100), 177 (M^+, 0.8); HRMS calcd for $C_{10}H_{11}NO_2$ 177.0790, found 177.0792; chiral GC (CHIRALDEX B-DM column, 30 m × 0.25 mm × 0.12 *μ*m, carrier gas nitrogen; injector temperature 250 °C, split ratio 30, constant column flow 1.0 mL/min, column temperature 120 °C (5 min), 120−170 °C (1.5 °C/min, 30 min), FID detector temperature 250 °C) t_R = 28.4 min (major), 28.9 min (minor), chiral HPLC (Chiralcel OD-H, 0.46 cm × 250 mm, *n*-hexane/2-propanol = 90/10, flow rate 0.5 mL/min, UV 214 nm) t_R = 19.8 min (major), 29.7 min (minor).

*(R)-1-Methyl-4-(1-nitrobut-3-en-2-yl)benzene (**2b**):* colorless oil; 88% yield; 97% ee; $[\alpha]_D^{20}$ = −4.7° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 4.16 (q, *J* = 8 Hz, 1H), 4.57−4.69 (m, 2H), 5.16 (dd, *J* = 0.8, 18 Hz, 1H), 5.20 (dd, *J* = 0.8, 10.8 Hz, 1H), 5.97 (ddd, *J* = 7.2, 10.2, 18 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 47.4, 79.5, 117.6, 127.4, 129.7, 135.0, 136.0, 137.5; IR (film) 814, 925, 1262, 1376, 1513, 1551, 1727, 2924 cm^{-1}; MS (EI) 65 (6), 77 (8), 91 (19), 115 (29), 129 (100), 144 (87), 191 (M^+, 2); HRMS calcd for $C_{11}H_{13}NO_2$ 191.0946, found 191.0941; chiral GC (CHIRALDEX B-DM column, 30 m × 0.25 mm × 0.12 *μ*m, carrier gas nitrogen; injector temperature 250 °C, split ratio 30, constant column flow 1.0 mL/min, column temperature 120 °C (5 min), 120−170 °C (1.0 °C/min, 30 min), FID detector temperature 250 °C) t_R = 40.3 min (major), 41.1 min (minor).

*(R)-1-Methoxy-4-(1-nitrobut-3-en-2-yl)benzene (**2c**):* colorless oil; 68% yield, 98% ee; $[\alpha]_D^{20}$ = +6.1° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 4.12−4.17 (m, 1H), 4.56−4.68 (m, 2H), 5.15 (dd, *J* = 0.8, 18 Hz, 1H), 5.20 (d, *J* = 10.4 Hz, 1H), 5.95 (ddd, *J* = 7.2, 10.2, 18 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.0, 55.3, 79.6, 114.4, 117.4, 128.6, 129.9, 136.1, 159.1; IR (film) 798, 1030, 1258, 1377, 1512, 1551, 2960 cm^{-1}; MS (EI) 65 (9), 77 (18), 91 (42), 115 (28), 129 (30), 147 (32), 160 (100), 207 (M^+, 18); HRMS calcd for $C_{11}H_{13}NO_3$ 207.0895, found 207.0898; chiral GC (CHIRALDEX B-DM column, 30 m × 0.25 mm × 0.12 *μ*m, carrier gas nitrogen; injector temperature 250 °C, split ratio 30, constant column flow 1.0 mL/min, column temperature 120 °C (5 min), 120−170 °C (1.0 °C/min, 30 min), FID detector temperature 250 °C): t_R = 55.7 min (major), 56.6 min (minor).

*(R)-1-Chloro-4-(1-nitrobut-3-en-2-yl)benzene (**2d**):* colorless oil; 83% yield, 96% ee; $[\alpha]_D^{20}$ = −6.5° (*c* = 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (q, *J* = 8 Hz, 1H), 4.58−4.70 (m, 2H), 5.17 (dd, *J* = 0.8, 17.2 Hz, 1H), 5.25 (d, *J* = 10.4 Hz, 1H), 5.94 (ddd, *J* = 7.2, 10.2, 17.2 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.0, 79.1, 118.1, 129.0, 129.2, 133.7, 135.3, 136.5; IR (film) 797, 1015, 1092, 1260, 1492, 1553, 2962 cm^{-1}; MS (EI) 77 (6), 103 (5), 115 (19), 129 (100), 164 (20), 211 (M^+, 1); HRMS calcd for $C_{10}H_{10}NO_2Cl$ 211.0400, found 211.0399; chiral GC (CHIRALDEX B-DM column, 30 m × 0.25 mm × 0.12 *μ*m, carrier gas nitrogen; injector temperature 250 °C, split ratio 30, constant column flow 1.0 mL/min, column temperature 120 °C (5 min), 120−140 °C (1.0 °C/min, 5 min), 140−165 °C (0.8 °C/min, 5 min), 165−170 °C (1.0 °C/min, 20 min)): t_R =60.3 min (major), 61.6 min (minor).

*(R)-1-Fluoro-4-(1-nitrobut-3-en-2-yl)benzene (**2e**):* colorless oil; 88% yield, 96% ee; $[\alpha]_D^{20}$ = +6.0° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (m, 1H), 4.57−4.70 (m, 2H), 5.17 (dd, *J* = 0.8, 17.2 Hz, 1H), 5.23 (dd, *J* = 0.8, 10.4 Hz, 1H), 5.96 (ddd, *J* = 7.2, 10.2, 17.2 Hz, 1H), 7.02−7.06 (m, 2H), 7.18−7.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.9, 79.3, 116.0 (d, *J* = 20 Hz), 117.8, 129.2 (d, *J* = 9 Hz), 133.7, 135.6 (d, *J* = 3 Hz), 161.5 (d, *J* = 251.5 Hz); ^{19}F

dx.doi.org/10.1021/jo301506p | J. Org. Chem. 2012, 77, 8980−8985

NMR (376 MHz) −114.4 (m); IR (film) 775, 806, 928, 1159, 1224, 1508, 1550, 2925 cm^{-1}; MS (EI) 75 (7), 109 (52), 129 (12), 133 (38), 148 (100), 195 (M^+, 1); HRMS calcd for $C_{10}H_{10}NO_2F$ 195.0696, found 195.0694; chiral GC (CHIRALDEX B-DM column, 30 m × 0.25 mm × 0.12 μm, carrier gas nitrogen; injector temperature 250 °C, split ratio 30, constant column flow 1.0 mL/min, column temperature 120 °C (5 min), 120−140 °C (1.0 °C/min, 5 min), 140−165 °C (0.8 °C/min, 5 min), 165−170 °C (1.0 °C/min, 20 min)): t_R = 37.1 min (major), 38.2 min (minor).

*(R)-1-Chloro-3-(1-nitrobut-3-en-2-yl)benzene (**2f**):* colorless oil; 80% yield, 95% ee; $[\alpha]_D^{20}$ = −2.3° (*c* = 0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.21 (q, *J* = 8 Hz, 1H), 4.59−4.71 (m, 2H), 5.20 (d, *J* = 17.2 Hz, 1H), 5.26 (d, *J* = 10.4 Hz, 1H), 5.95 (ddd, *J* = 7.2, 10.2, 17.2 Hz, 1H), 7.11−7.12 (m, 1H), 7.22−7.31 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.3, 79.0, 118.4, 125.8, 127.8, 128.1, 130.3, 134.9, 135.0, 140.0; IR (film) 703, 785, 929, 1376, 1550, 2923 cm^{-1}; MS (EI) 77 (5), 89 (4), 115 (16), 125 (13), 129 (100), 164 (15), 211 (M^+, 0.4); HRMS calcd for $C_{10}H_{10}NO_2Cl$ 211.0400, found 211.0399; chiral GC (CHIRALDEX B-DM column, 30 m × 0.25 mm × 0.12 μm, carrier gas nitrogen; injector temperature 250 °C, split ratio 30, constant column flow 1.0 mL/min, column temperature 120 °C (5 min), 120−140 °C (1.0 °C/min, 5 min), 140−165 °C (0.8 °C/min, 5 min), 165−170 °C (1.0 °C/min, 20 min)): t_R = 54.0 min (major), 55.7 min (minor).

*(R)-1-Methoxy-3-(1-nitrobut-3-en-2-yl)benzene (**2g**):* colorless oil; 92% yield, 96% ee; $[\alpha]_D^{20}$ = −2.7° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 4.18 (q, *J* = 8 Hz, 1H), 4.60−4.70 (m, 2H), 5.19 (dd, *J* = 0.8, 18 Hz, 1H), 5.22 (dd, *J* = 0.8, 10 Hz, 1H), 5.98 (ddd, *J* = 7.2, 10.2, 18 Hz, 1H), 6.76 (m, 1H), 6.81−6.84 (m, 2H), 7.26−7.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.7, 55.2, 79.4, 112.8, 113.6, 117.8, 119.7, 130.1, 135.6, 139.6, 160.0; IR (film) 699, 781, 1039, 1261, 1552, 2838, 2923 cm^{-1}; MS (EI) 65 (9), 77 (15), 91 (40), 115 (36), 129 (60), 145 (35), 160 (100), 207(M^+, 55); HRMS calcd for $C_{11}H_{13}NO_3$ 207.0895, found 207.0900; chiral GC (CHIRALDEX B-DM column, 30 m × 0.25 mm × 0.12 μm, carrier gas nitrogen; injector temperature 250 °C, split ratio 30, constant column flow 1.0 mL/min, column temperature 120 °C (5 min), 120−170 °C (1.0 °C/min, 30 min), FID detector temperature 250 °C): t_R = 51.9 min (major), 52.5 min (minor).

*(R)-5-(1-Nitrobut-3-en-2-yl)benzo[d][1,3]dioxole (**2h**):* colorless oil; 80% yield, 97% ee; $[\alpha]_D^{20}$ = +12.8° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.13 (q, *J* = 8 Hz, 1H), 4.54−4.67 (m, 2H), 5.16 (dd, *J* = 0.8, 17.2 Hz, 1H), 5.21 (dd, *J* = 0.8, 10 Hz, 1H), 5.89−5.98 (m, 3H), 6.66−6.70 (m, 2H), 6.76−6.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.3, 79.5, 101.2, 107.8, 108.6, 117.4, 120.6, 131.7, 135.8, 147.0, 148.1; IR (film) 809, 927, 1035, 1235, 1487, 1548, 2898, 3670 cm^{-1}; MS (EI) 79 (46), 91 (53), 103 (44), 115 (90), 129 (74), 144 (51), 174 (100), 221 (M^+, 49); HRMS calcd for $C_{11}H_{11}NO_4$ 221.0688, found 221.0685; chiral GC (CHIRALDEX B-DM column, 30 m × 0.25 mm × 0.12 μm, carrier gas nitrogen; injector temperature 250 °C, split ratio 30, constant column flow 1.0 mL/min, column temperature 120 °C (5 min), 120−170 °C (1.0 °C/min, 30 min), FID detector temperature 250 °C): t_R = 70.0 min (major), 71.7 min (minor).

*(R)-1-Bromo-2-(1-nitrobut-3-en-2-yl)benzene (**2i**):* colorless oil; 89% yield, 90% ee; $[\alpha]_D^{20}$ = +13.8° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.62−4.72 (m, 2H), 4.75−4.79 (m, 1H), 5.24 (dd, *J* = 0.8, 17.2 Hz, 1H), 5.30 (dd, *J* = 0.8, 11.6 Hz, 1H), 5.99 (ddd, *J* = 7.2, 11.6, 17.2 Hz, 1H), 7.14−7.18 (m, 1H), 7.22−7.26 (m, 1H), 7.30−7.34 (m, 1H), 7.60−7.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.1, 77.7, 118.7, 124.5, 128.0, 128.5, 129.2, 133.7, 134.3, 137.1; IR (film) 794, 1017, 1082, 1259, 1553, 2961 cm^{-1}; MS (EI) 51 (5), 77 (7), 115 (21), 129 (100), 169 (5), 208 (7), 255 (M^+, 2); HRMS calcd for $C_{10}H_{10}BrNO_2$: 254.9895, found 254.9896; chiral GC (CHIRALDEX B-DM column, 30 m × 0.25 mm × 0.12 μm, carrier gas nitrogen; injector temperature 250 °C, split ratio 30, constant column flow 1.0 mL/min, column temperature 120 °C (5 min), 120−170 °C (1.0 °C/min, 30 min), FID detector temperature 250 °C): t_R = 51.7 min (minor), 52.1 min (major).

*(R)-1-(1-Nitrobut-3-en-2-yl)naphthalene (**2j**):* colorless oil; 91% yield, 93% ee; $[\alpha]_D^{20}$ = +29.6° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.76−4.78 (m, 2H), 5.13 (q, *J* = 8 Hz, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 5.30 (d, *J* = 10.4 Hz, 1H), 6.15 (ddd, *J* = 7.2, 10.2, 17.4 Hz, 1H), 7.37−39 (m, 1H), 7.45−7.49 (m, 1H), 7.53−7.55 (m, 1H), 7.59−7.63 (m, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.5, 78.6, 118.1, 122.3, 124.4, 125.2, 125.9, 126.7,128.3, 129.1, 130.8, 133.8, 134.0, 135.4; IR (film) 775, 799, 926, 1375, 1549, 2917, 3047 cm^{-1}; MS (EI) 82 (10), 115 (15), 152 (22), 165 (100), 181 (29), 227 (M^+, 35); HRMS calcd for $C_{14}H_{13}NO_2$ 227.0946, found 227.0948; chiral HPLC (Chiralcel OJ, 0.46 cm × 250 mm, *n*-hexane/2-propanol 70/30, flow rate 0.5 mL/min, UV 214 nm): t_R = 27.3 min (minor), 29.9 min (major).

*(R)-2-(Cyclopentyloxy)-1-methoxy-4-(1-nitrobut-3-en-2-yl)-benzene (**2k**):* white solid; mp 56−57 °C; 87% yield, 97% ee; $[\alpha]_D^{20}$ = +12.8° (*c* = 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.60−1.63 (m, 2H), 1.83−1.94 (m, 6H), 3.82 (s, 3H), 4.13 (q, *J* = 8 Hz, 1H), 4.56−4.68 (m, 2H), 4.75−4.77 (m, 1H), 5.16 (d, *J* = 17.2 Hz, 1H), 5.21 (d, *J* = 10.4 Hz, 1H), 5.96 (ddd, *J* = 7.2, 10.2, 17.4 Hz, 1H), 6.72−6.75 (m, 2H), 6.82−6.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 32.72, 32.75, 47.2, 56.0, 79.6, 80.5, 112.2, 114.5, 117.4, 119.5, 130.2, 136.0, 147.9, 149.6; IR (film) 939, 980, 1017, 1138, 1231, 1259, 1516, 1548, 1589, 2940 cm^{-1}; MS (EI) 41 (21), 91 (14), 103 (17), 117 (32), 144 (36), 161 (24), 176 (100), 223 (11), 291(M^+, 18); HRMS calcd for $C_{16}H_{21}NO_4$ 291.1471, found 291.1468; chiral HPLC (Chiralcel OJ-H, 0.46 cm × 250 mm, hexane/2-propanol 95/5, flow rate 0.5 mL/min, UV 214 nm): t_R = 49.2 min (major), 54.0 min (minor).

(*R*)-3-(4-Chlorophenyl)-4-nitrobutan-1-ol (4d).[10] To a solution of **2d** (21.1 mg, 0.1 mmol) in THF (1 mL) at room temperature was added 9-borabicyclo[3.3.1]nonane (9-BBN; 0.5 M solution in toluene, 0.4 mmol). The resulting reaction mixture was stirred for 20 h. EtOH (182 μL) was added to quench the excess 9-BBN, and then 6 N NaOH (62 μL) and 30% H_2O_2 (122 μL) was added dropwise. The resulting mixture was warmed to 50 °C and stirred for another 1 h. Then 5 mL of water was added. After being extracted with EtOAc, the organic phase was washed sequentially with H_2O, saturated aqueous Na_2SO_3, and brine. The organic phase was then dried with $MgSO_4$ and concentrated in vacuo. Purification of the residual oil by chromatography gave **4d** (colorless oil; 17.1 mg, 73%): ^1H NMR (400 MHz, $CDCl_3$) δ 1.65 (br, 1H), 1.85−1.89 (m, 1H), 1.91−1.96 (m, 1H), 3.44−3.47 (m, 1H), 3.60−3.65 (m, 1H), 3.69−3.73 (m, 1H), 4.55−4.69 (m, 2H), 7.16 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.5, 40.4, 59.6, 80.3, 128.9, 129.2, 133.6, 137.4; IR (film) 822, 1013, 1042, 1091, 1260, 1378, 1492, 1547, 1901, 2925 cm^{-1}; MS (ESI) 228 (M − H); HRMS (ESI) calcd for $C_{10}H_{11}ClNO_3$ (M − H) 228.0433, found 228.0435.

(*R*)-3-(3-(Cyclopentyloxy)-4-methoxyphenyl)-4-nitrobutan-1-ol (4k). The experimental procedure was same as that for product **4d**: white solid; mp 72−73 °C; 25 mg, 67% yield; ^1H NMR (400 M Hz, $CDCl_3$) δ 1.56−1.65 (m, 2H), 1.78−1.96 (m, 8H), 3.49−3.54 (m, 1H), 3.60−3.65 (m, 1H), 3.82 (s, 3H), 4.55−4.63 (m, 2H), 4.75−4.77 (m, 1H), 6.71−6.75 (m, 2H), 6.81−6.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 32.7, 35.6, 40.7, 56.0, 59.9, 80.5, 80.3, 112.3, 114.5, 119.5, 131.0, 147.8, 149.5; IR (film) 649, 807, 1047, 1137, 1256, 1511, 1590, 2854, 2926, 3542 cm^{-1}; MS (ESI) 309 (M^+); HRMS calcd for $C_{16}H_{23}NO_5$ 309.1576, found 309.1579.

(*R*)-3-(3-(Cyclopentyloxy)-4-methoxyphenyl)-4-nitrobutanal (5k). To a solution of **4k** (43.2 mg, 0.14 mmol) in dichloromethane (3 mL) at room temperature was added Dess−Martin periodinane (66.1 mg, 0.16 mmol). The resulting mixture was stirred for 0.5 h before the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (0.5 mL) and $NaHCO_3$ (0.5 mL). The aqueous phase was extracted with Et_2O. The combined organic phase was dried with $MgSO_4$ and concentrated in vacuo to afford **5k** as a liquid (30.5 mg, 71%): ^1H NMR (400 MHz, $CDCl_3$) δ 1.59−1.64 (m, 2H), 1.81−1.94 (m, 6H), 2.91 (d, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 3.97−4.01 (q, *J* = 8 Hz, 1H), 4.55−4.67 (m, 2H), 4.74−4.77 (m, 1H), 6.73−6.75 (m, 2H), 6.80−6.82 (m, 1H), 9.69 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 32.69, 32.72, 46.5, 56.0,

dx.doi.org/10.1021/jo301506p | J. Org. Chem. 2012, 77, 8980−8985

79.6, 80.6, 112.3, 114.5, 119.2, 130.3, 147.9, 149.8, 199.0; IR (film) 1014, 1139, 1236, 1257, 1514, 1550, 1732, 2927 cm^{-1}; MS (EI) 55 (12), 97 (13), 114 (100), 164 (10), 192 (8), 239 (3), 307 (M^+, 3); HRMS calcd for $C_{16}H_{21}NO_5$ 307.1420, found 307.1417.

(*R*)-3-(4-Chlorophenyl)-4-nitrobutanoic Acid (6d).[11] To the crude product **5d** (34.9 mg, 0.15 mmol), which was obtained from compound **4d** by the same procedure as that for product **5k**, was added successively $NaH_2PO_4{\cdot}2H_2O$ (46.8 mg, 0.3 mmol), 2-methyl-2-butene (0.4 mL), *t*-BuOH (1.2 mL), and H_2O (0.4 mL). To the resulting mixture was added $NaClO_2$ (40.5 mg, 0.45 mmol) at 0 °C. After the reaction mixture was stirred for 2 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl (0.5 mL) and the resulting mixture was stirred for another 10 min. After the solution was diluted with EtOAc (2 mL), the aqueous phase was extracted with EtOAc (2 mL). The combined organic phase was dried with anhydrous magnesium sulfate. The organic layer was filtered through Celite and concentrated in vacuo. The residue was purified by silica gel to afford **6d** (31.7 mg) in 67% yield (for two steps starting from compound **4d**): ^1H NMR (400 MHz, $CDCl_3$) δ 2.73−2.85 (m, 2H), 3.93−3.99 (m, 1H), 4.66 (dd, J = 8.4, 12 Hz, 2H), 6.05−6.27 (br, 1H), 7.17 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.1, 39.2, 79.0, 128.7, 129.3, 134.0, 136.4, 175.6; MS (ESI) 242 $(M - H)^-$; HRMS (ESI) calcd for $C_{10}H_9ClNO_4$ 242.0226, found 242.0224.

(*R*)-Methyl 3-(3-(Cyclopentyloxy)-4-methoxyphenyl)-4-nitrobutanoate (6k). Compound **5k** (0.1 mmol) was oxidized to the corresponding acid by the same procedure as that for compound **5d**. The resulting crude acid was dissolved in MeOH (3 mL), to which was added 4-dimethylaminopyridine (cat.) and dicyclohexylcarbodiimide (24.7 mg) at 0 °C. The resulting reaction mixture was stirred at room temperature until the disappearance of acid (TLC control). The reaction mixture was concentrated in vacuo. The residue was purified by silica gel to afford **6k** (21.6 mg, 66%): white solid; mp 103−104 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.67−1.71 (m, 2H), 1.84−1.92 (m, 6H), 2.74 (d, J = 7.2 Hz, 2H), 3.64 (s, 3H), 3.82 (s, 3H), 3.89−3.92 (m, 1H), 4.58−4.63 (m, 1H), 4.67−4.76 (m, 2H), 6.72−6.82 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 32.71, 32.74, 37.7, 39.8, 51.9, 55.9, 79.6, 80.5, 112.2, 114.3, 119.1, 130.5, 147.8, 149.7, 171.1; IR (film) 646, 808, 1140, 1165, 1257, 1514, 1538, 1693, 1730, 2852, 2927 cm^{-1}; MS (EI) 41 (17), 131 (20), 164 (17), 191 (12), 222 (17), 238 (5), 269 (3), 337 (10); HRMS calcd for $C_{17}H_{23}NO_6$ 337.1525, found 337.1522.

(*R*)-Baclofen Hydrochloride.[9] A mixture of **6d** (40 mg, 0.16 mmol), MeOH (5 mL), and Ra−Ni (50% water content, 111 mg) was hydrogenated at 5 atm at room temperature for 24 h. The catalyst was filtered off in vacuo through Celite. The filtrate was made basic with 1 M NaOH (0.5 mL, 0.5 mmol), and the resulting aqueous phase was washed with EtOAc (1 mL). The residue was taken up in 2 M HCl (0.5 mL) and evaporated at reduced pressure. The resulting solid was taken up in MeOH (3 mL) and filtered. The filtrate was evaporated under reduced pressure to give (*R*)-baclofen hydrochloride (28 mg, 69%): ^1H NMR (400 MHz, D_2O) δ 2.76 (dd, J = 8.8, 16 Hz, 1H), 2.88 (dd, J = 5.6, 16 Hz, 1H), 3.27 (t, J = 12.4 Hz, 1H), 3.39−45 (m, 2H), 7.36−7.47 (m, 4H); ^{13}C NMR (100 MHz, D_2O) δ 38.1, 39.3, 43.6, 129.2, 129.4, 133.3, 136.9, 175.1; ESI-MS (m/z): 214.0 $[M^+]$, 215.0 $[M + H]^+$, 216.0 $[M + 2]^+$; $[\alpha]_D^{20} = -1.8°$ (c = 0.28, H_2O).

(*R*)-Rolipram.[7i] To a stirred solution of **6k** (20.2 mg, 0.06 mmol) and $NiCl_2{\cdot}6H_2O$ (23.7 mg, 0.1 mmol) in EtOH (2 mL) was added $NaBH_4$ (37.8 mg, 1 mmol) at 0 °C. The reaction mixture was stirred for 2 h before being quenched with saturated aqueous NH_4Cl (0.5 mL). The reaction mixture was diluted with $CHCl_3$ (2 mL), and the aqueous layer was extracted with $CHCl_3$ (2 mL). The combined organic layer was dried with anhydrous magnesium sulfate and filtered through Celite. The volatiles were removed in vacuo, and the residue was purified by silica gel to afford (*R*)-rolipram (14.4 mg, 85%): ^1H NMR (400 MHz, $CDCl_3$) δ 1.58−1.65 (m, 2H), 1.82−1.91 (m, 6H), 2.48 (dd, J = 8.8, 16.8 Hz, 1H), 2.72 (dd, J = 8.8, 16.8 Hz, 1H), 3.36−3.40 (m, 1H), 3.61−3.65 (m, 1H), 3.73−3.78 (m, 1H), 3.83 (s, 3H), 4.75−4.79 (m, 1H), 6.03 (br, 1H), 6.76−6.79 (m, 2H), 6.82−6.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 32.8, 37.9, 39.9, 49.7, 56.1, 80.6, 112.2, 113.8, 118.8, 134.5, 147.9, 149.2, 177.6; MS (EI) 41 (42), 75 (27), 114 (94), 150 (100), 207 (56), 222 (6), 275 (M^+, 20); HRMS calcd for $C_{16}H_{21}NO_3$ 275.1521, found 275.1520; $[\alpha]_D^{20} = -24.6°$ (c = 0.8, MeOH).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Tables giving additional reaction details and figures giving spectral data of compounds **2a−k**, **4−6**, (*R*)-baclofen hydrochloride, and (*R*)-rolipram. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xlhou@sioc.ac.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the Major Basic Research Development Program (2010CB833300), National Natural Science Foundation of China (21121062, 21002113, 21032007), the External Cooperation Program of Chinese Academy of Sciences (GJHZ200816), the Technology Commission of Shanghai Municipality, and the Croucher Foundation of Hong Kong.

■ REFERENCES

(1) For reviews, see: (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (b) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258.

(2) (a) Barrett, A. G. M.; Grabowski, G. G. *Chem. Rev.* **1986**, *86*, 751. (b) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: Weinheim, New York, 2001. (c) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, *12*, 1877.

(3) For intramolecular examples, see: (a) Genêt, J. P.; Grisoni, S. *Tetrahedron Lett.* **1988**, *36*, 4543. (b) Rieck, H.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2687.

(4) (a) Trost, B. M.; Surivet, J.-P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3122. (b) Trost, B. M.; Surivet, J.-P. *J. Am. Chem. Soc.* **2000**, *122*, 6291. (c) Nemoto, T.; Jin, L.; Nakamura, H.; Hamada, Y. *Tetrahedron Lett.* **2006**, *47*, 6577. (d) Uozumi, Y.; Suzuka, T. *J. Org. Chem.* **2006**, *71*, 8644. (e) Maki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 4250. (f) Nemoto, T.; Hamada, Y. *J.Synth. Org. Chem. Jpn.* **2011**, *69*, 763.

(5) For iridium-catalyzed asymmetric allylic alkylation of nitro compounds, see: Dahnz, A.; Helmchen, G. *Synlett* **2006**, 697.

(6) (a) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471. (b) Sun, N.; Hou, X.-L. *Org. Lett.* **2004**, *6*, 4399. (c) Zheng, W.-H.; Sun, N.; Hou, X.-L. *Org. Lett.* **2005**, *7*, 5151. (d) Zheng, W.-H.; Zheng, B.-H.; Zhang, Y.; Hou, X.-L. *J. Am. Chem. Soc.* **2007**, *129*, 7718. (e) Zhang, K.; Peng, Q.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1741. (f) Liu, W.; Chen, D.; Zhu, X.-Z.; Wan, X.-L.; Hou, X.-L. *J. Am. Chem. Soc.* **2009**, *131*, 8734. (g) Lei, B.-L.; Ding, C.-H.; Yang, X.-F.; Wan, X.-L.; Hou, X.-L. *J. Am. Chem. Soc.* **2009**, *131*, 18250. (h) Chen, J.-P.; Ding, C.-H.; Liu, W.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2010**, *132*, 15493. (i) Fang, P.; Ding, C.-H.; Hou, X.-L.; Dai, L.-X. *Tetrahedron: Asymmetry* **2010**, *21*, 1176. (j) Zheng, B.-H.; Ding, C.-H.; Hou, X.-L. *Synlett* **2011**, 2262.

(7) For some examples regarding the synthesis of Rolipram: (a) Anada, M.; Mita, O.; Watanabe, H.; Kitagaki, S.; Hashimoto, S. *Synlett* **1999**, 1775. (b) Barluenga, J.; Fernández-Rodríguez Lic., M. A.; Aguilar, E.; Fernández-Marí, F.; Salinas, A.; Olano, B. *Chem. Eur. J.* **2001**, *7*, 3533. (c) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394. (d) Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.;

Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097. (e) Yoon, C. H.; Nagle, A.; Chen, C.; Gandhi, D.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2259. (f) Becht, J. M.; Meyer, O.; Helmchen, G. *Synthesis* **2003**, 2805. (g) Paraskar, A. S.; Sudalai, A. *Tetrahedron* **2006**, *62*, 4907. (h) Deng, J.; Duan, Z.-C.; Huang, J.-D.; Hu, X.-P.; Wang, D.-Y.; Yu, S.-B.; Xu, X.-F.; Zheng, Z. *Org. Lett.* **2007**, *23*, 4825. (i) Hynes, P. S.; Stupple, P. A.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 1389. (j) Shao, C.; Yu, H.-J.; Wu, N.-Y.; Tian, P.; Wang, R.; Feng, C.-G.; Lin, G.-Q. *Org. Lett.* **2011**, *13*, 788. (k) Han, F.; Chen, J.; Zhang, X.; Liu, J.; Cun, L.; Zhu, J.; Deng, J.; Liao, J. *Tetrahedron Lett.* **2011**, *52*, 830.

(8) For some examples regarding the synthesis of Baclofen: (a) Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **1998**, *39*, 79. (b) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, *2*, 4257. (c) Belda, O.; Lundgren, S.; Moberg, C. *Org. Lett.* **2003**, *5*, 2275. (d) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (e) Zu, L.-S.; Xie, H.-X.; Li, H.; Wang, J.; Wang, W. *Adv. Synth. Catal.* **2007**, *347*, 2660.

(9) Camps, P.; Muňoz-Torrero, D.; Sánchez, L. *Tetrahedron: Asymmetry* **2004**, *15*, 2039.

(10) Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1151.

(11) Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5307.