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Co-catalyzed reductive cyclization of azido and cyano substituted α,β-unsaturated esters with $NaBH_4$: enantioselective synthesis of (*R*)-baclofen and (*R*)-rolipram

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Abstract—Sodium borohydride in combination with a catalytic amount of $CoCl_2$ has been found to be an excellent catalytic system in reductive cyclizations of suitably substituted azido and cyano groups of α,β-unsaturated esters to afford γ and δ-lactams in high yields. The process has been demonstrated for the enantioselective synthesis of (*R*)-baclofen, (*R*)-rolipram, and (*R*)-4-fluorophenylpiperidinone, a key intermediate for (−)-paroxetine.
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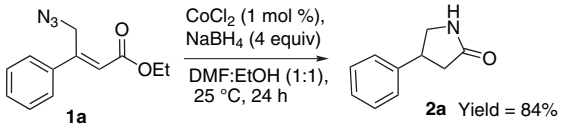
1. Introduction

Metal hydrides, particularly sodium borohydride and lithium aluminum hydride have emerged as prominent reducing agents capable of reducing most functional groups.[1] Moreover, by attaching organic ligands at the B or Al centers, or changing the metal counterion, one can modulate the scope, regio, and stereoselectivity of such reductions.[2] Quite recently, transition metal salts have been used as catalysts or additives in conjunction with $NaBH_4$ or $LiAlH_4$ in order to enhance the reducing power of these reagents.[3] In particular, the cobalt–sodium borohydride system[3d] is a well-known reducing system, capable of selectively reducing a variety of functional groups including C=C, N_3, CN, etc. when present alone. In this paper we disclose a single step, new synthetic procedure for the reductive cyclization of azido and cyano substituted α,β-unsaturated esters with $NaBH_4$ catalyzed by cobalt chloride, leading to synthesis of γ and δ-lactams in high yields.

2. Results and discussion

In continuation with our studies[4a] on simultaneous reduction of multifunctional moieties, we were interested in subjecting γ-azido olefinic ester **1a** to reduction with the $NaBH_4$–$CoCl_2$ system in order to obtain the corresponding γ-amino esters. To our surprise, γ-lactam **2a** was obtained in 84% yield, presumably due to the simultaneous reduction of both the azido group and C–C double bond followed by its cyclization, all occurring concurrently in a single step (Scheme 1). In the absence of $CoCl_2$, no reaction took place; also, other metal salts such as $PdCl_2$, $CuCl_2$, $NiCl_2$, etc. were not effective in achieving the transformation of γ-azido ester **1a** to the corresponding γ-lactam **2a**.



Scheme 1. Co-catalyzed reductive cyclization of γ-azido ester with $NaBH_4$.

For systematic evaluation of this study, the required starting γ-azido esters **1a**–**g** were prepared in three steps as presented in Table 1: (i) Pd-catalyzed arylation of ethyl crotonate with the respective aryl boronic acids **3a**–**g** producing α,β-unsaturated esters **4a**–**g**; (ii) allylic bromination of the methyl group in **4** with NBS yielding the bromo derivatives **5a**–**g**; and (iii) nucleophilic displacement of bromide with azide giving γ-azido esters **1a**–**g**. Alternatively, alkyl and aryl α,β-unsaturated esters **4** were also obtained in high yields, although in two steps, by the Reformatsky reaction of the corresponding ketones (see Scheme 4 in Section 4 for their preparation) with ethyl bromoacetate, followed by dehydration of the resulting alcohols with *p*-TSA.[4a]

It was of interest to develop the asymmetric version of this reductive cyclization process. As a model compound,

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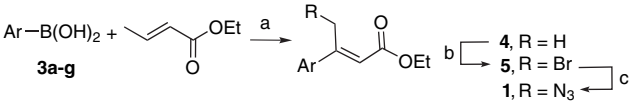
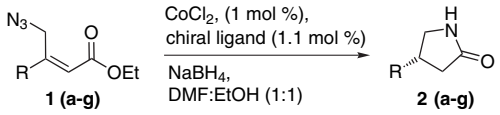
Table 1. Preparation of starting γ-azido olefinic esters **1a–g**: Pd-catalyzed arylation,[a] allylic bromination[b] followed by bromide displacement with azide[c]



Entry	Ar	Yield (%)[a]		
		4 (R=H)[b]	**5** (R=Br)[c]	**1** (R=N_3)[d]
a	Ph	86	72	86
b	4-ClPh	82	88	77
c	4-FPh	80	84	80
d	2-MeOPh	91	80	90
e	4-MeOPh	93	86	95
f	3-CpO-4-MeOPh[e]	92	90	99
g	*t*-C_4H_9	82[f]	76	91

[a] Isolated yield after chromatographic purification.
[b] Ethyl crotonate (2 mmol), boronic acid **3** (1 mmol), cat. $Pd(OAc)_2$ (1 mol %), Na_2CO_3 (1.5 mmol), O_2 (1 atm), DMF, 50 °C, 12 h, 80–93%.
[c] Olefinic ester **4** (1 mmol), NBS (1.2 mmol), AIBN (1 mol %), CCl_4, 80 °C, 24 h, 72–90%.
[d] Bromo ester **5** (1 mmol), NaN_3 (3 mmol), EtOH/H_2O (1:1), 50 °C, 12 h, 86–99%.
[e] Cp=cyclopentyl.
[f] Prepared by Reformatsky route.

Table 2. $CoCl_2$-catalyzed reductive cyclization of γ-azido-α,β-unsaturated esters with $NaBH_4$[a] in the presence of chiral ligands



Entry	R	Chiral ligand	Yield of **2** (%)[b]	% ee[c] (Configuration)
a	Ph	**6**	86	51 (*R*)
b	4-ClPh	**6**	82	89 (*R*)
	4-ClPh	**7**	86	05
	4-ClPh	**8**	80	12
	4-ClPh	**9**	73	05
c	4-FPh	**6**	80	[d]
d	2-MeOPh	**6**	91	[d]
e	4-MeOPh	**6**	93	98 (*R*)
f	3-CpO-4-MeOPh[e]	**6**	92	92 (*R*)
g	*t*-C_4H_9	**6**	77	[d]

[a] Conditions: azido ester (1 mmol), $CoCl_2$ (1 mol %), chiral ligands **6–9** (1.1 mol %), $NaBH_4$ (4 mmol), DMF/EtOH (1:1), 25 °C, 24 h, 77–93%.
[b] Isolated yield after chromatographic purification.
[c] Determined by comparison of $[\alpha]_D$ with the reported values as well as by chiral HPLC analysis.
[d] % ee not determined.
[e] Cp=cyclopentyl.

4-chlorophenyl-γ-azido olefinic ester **1b** was chosen and subjected to reduction with $CoCl_2$ (1 mol %), $NaBH_4$ (4 equiv) in the presence of ligands **6–9** (1.1 mol %) (Fig. 1), at 25 °C and obtained the corresponding chiral γ-lactam **2b** in high yields with good enantioselectivity (Table 2).

In order to systematically explore the utility of this catalytic system for the synthesis of various 4-substituted pyrrolidin-2-ones, a variety of γ-azido olefinic esters **1a–g** were successfully screened to afford the corresponding 4-substituted pyrrolidin-2-ones **2a–g** in excellent yields. Table 2 shows the results of several such azido esters, which underwent reductive cyclization smoothly under the reaction conditions. The methodology also works well in the case of an aliphatic system (entry *g*). As can be seen from Table 2, only (4*S*)-(+)-phenyl-α-[(4*S*)-phenyloxazolidin-2-ylidine]-2-oxazoline-2-acetonitrile **6** gave high optical induction in the product (up to 98% ee) (Fig. 1).

These γ-lactams **2(a–g)** are the precursors to γ-aminobutyric acid (GABA) analogues, which are of great interest due to their importance in various nervous system functions (Fig. 1).[5] For instance, the strongly lipophilic β-substituted analogue, 4-amino-3-(4-chlorophenyl)butyric acid (**10**, baclofen) is until now the only available selective agonist of the $GABA_B$ receptor.[6] Also the cyclic GABA analogue, 4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-one (**2f**, rolipram) is known for its potent inhibitor activity of the cardiac cyclic AMP phosphodiesterase, found in brain tissue.[7] Research has shown that for both the compounds, the pharmacological activity resides in the (*R*)-enantiomers only.[8] The 4-arylpiperidine moiety (**11**) is also an important structural element in many biologically active compounds, possibly due to its similarity to the aryl alkylamine pharmacophore common to neurotransmitters such as serotonin or dopamine. Notably, (−)-paroxetine (**11**) possessing a 4-arylpiperidine moiety, is used in the treatment of depression, obsessive–compulsive disorder, and panic disorder.[9] Several stereoselective syntheses of (*R*)-baclofen (**10**),[4] (*R*)-rolipram (**2f**),[10] and (−)-paroxetine (**11**)[11] have already been reported (Fig. 2).

In view of its biological importance, chiral γ-lactam **2b** thus prepared by the present protocol, was subjected to

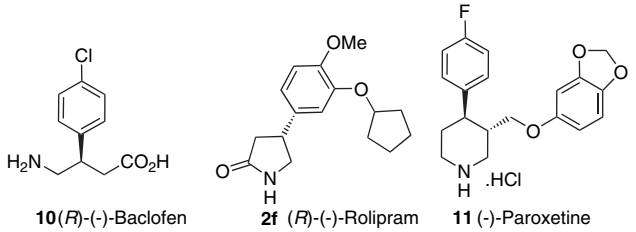


Figure 2.

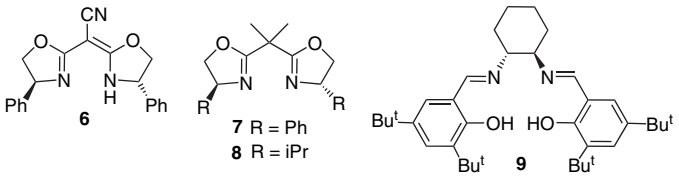
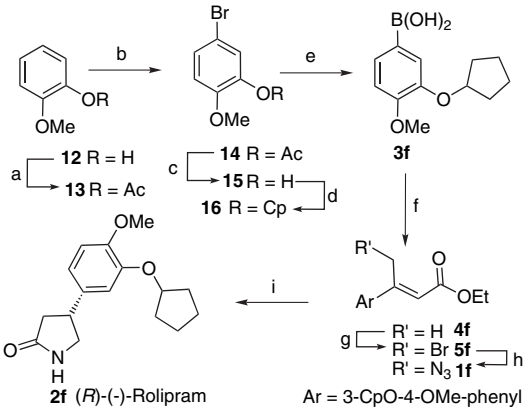


Figure 1.

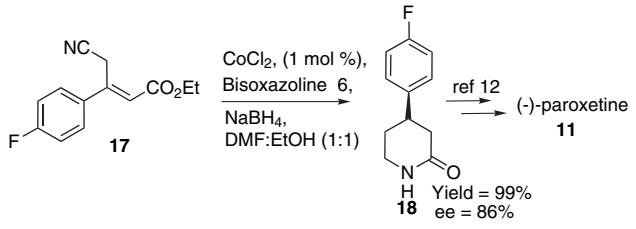
hydrolysis with 6 M HCl to give the optically active (*R*)-baclofen (**10**) as its hydrochloride salt in 73% yield and 88% ee.

Aryl boronic acid **3f** utilized in (*R*)-rolipram synthesis was prepared in five steps from guaiacol **14** as shown in Scheme 2. Acetyl protection of the guaiacolic hydroxy group has facilitated the selective bromination occurring at the *p*-position to the methoxy group. The boronic acid **3f** was then used for arylation of ethyl crotonate using Pd catalysis to obtain α,β-unsaturated esters **4f**, which were further transformed to azido intermediate **1f**. Finally, γ-azido ester **1f** when subjected to Co-catalyzed reduction with $NaBH_4$ yielded (*R*)-rolipram in 92% yield and 92% ee.



Scheme 2. Synthesis of (*R*)-rolipram from guaiacol. Conditions: (a) Ac_2O, concd H_2SO_4, 100 °C, 7 h, 97%; (b) NBS, CH_3CN, 50 °C, 4 h, 99%; (c) aq 10% $NaHCO_3$, MeOH, reflux, 6 h, 95%; (d) cyclopentyl bromide, K_2CO_3, DMF, 60 °C, 12 h, 89%; (e) BuLi, $B(OMe)_3$, −78 °C, 3 h; aq HCl (10%), reflux, 6 h, 15%; (f) ethyl crotonate, boronic acid **3f**, cat. $Pd(OAc)_2$, Na_2CO_3, O_2 (1 atm), DMF, 50 °C, 12 h, 92%; (g) olefinic ester **4f**, NBS, AIBN, CCl_4, 80 °C, 24 h, 90%; (h) bromoester **5f**, NaN_3, EtOH/H_2O (1:1), 50 °C, 12 h, 99%; (i) azido ester **1f** (1 mmol), $CoCl_2$ (1 mol %), ligand **6** (1.1 mol %), $NaBH_4$ (4 mmol), DMF/EtOH (1:1), 25 °C, 24 h, 92%, 92% ee.

Further, when cyano ester **17**, was subjected to Co-catalyzed asymmetric reduction with $NaBH_4$-bisoxazoline **6** at 25 °C, the corresponding chiral δ-lactam **18**, an important intermediate for (−)-paroxetine,[12] was obtained in 99% yield and 86% ee (Scheme 3). The cyano ester **17** was in turn prepared from the corresponding bromoester **5c** by displacement with cyanide using NaCN in dry DMF at 25 °C in 81% yield.



Scheme 3. Synthesis of intermediate **18** for (−)-paroxetine.

3. Conclusion

In conclusion, we have developed a new one-step procedure in which suitably substituted azido and cyano functions of α,β-unsaturated esters undergo reductive cyclization with $NaBH_4$ in the presence of a catalytic amount of $CoCl_2$ affording γ and δ-lactams in high yields. The methodology has been successfully applied to an efficient, enantioselective synthesis of (*R*)-baclofen, (*R*)-rolipram, and (*R*)-4-fluorophenylpiperidinone, a key intermediate for (−)-paroxetine.

4. Experimental

4.1. General information

Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60–80 °C was used. Melting points are uncorrected. HPLC analyses were performed on a chiral column (Chiralpak®). Optical rotations were measured on a Jasco DIP 181 digital polarimeter. Infrared spectra were recorded on a Shimadzu FTIR-8400 spectrometer. ^1H NMR and ^{13}C NMR were recorded on Bruker AC-200 and MSL-300 NMR spectrometers, respectively. Mass spectra were obtained with a Finnigan MAT-1020 B-70 eV mass spectrometer. Elemental analysis was carried on a Carlo Erba CHNS-O analyzer.

4.2. General experimental procedure for the synthesis of α,β-unsaturated esters from aryl boronic acids (arylation route)

A 25 ml flask with reflux condenser attached was charged with boronic acid **3** (1 mmol), ethyl crotonate (0.228 g, 0.25 ml, 2 mmol), Na_2CO_3 (0.159 g, 1.5 mmol), catalytic amount of $Pd(OAc)_2$ (0.022 g, 0.1 mmol), and DMF (5 ml) under oxygen (1 atm). The flask was heated at 50 °C for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool to 25 °C. The organic layer was separated and the aqueous layer was extracted with EtOAc (2×10 ml). The combined organic extracts were washed with water (5 ml) followed by brine (10 ml) and concentrated under reduced pressure to give the crude product. This was then purified by column chromatography eluting with 10% ethyl acetate in petroleum ether to get the olefinic esters **4**.

4.3. General experimental procedure for the synthesis of α,β-unsaturated esters from ketones (Reformatsky route)

A 100 ml two-necked RB flask was charged with activated zinc (3.40 g, 44 mmol), and kept under an N_2 atmosphere. Dry benzene (30 ml) was introduced and the reaction mixture was heated to 80 °C (oil bath temp). A solution of ethyl bromoacetate (7.25 g, 44 mmol) and ketone (40 mmol) in dry benzene (20 ml) was added dropwise to the reaction mixture. After completion of the addition, the resulting reaction mixture was refluxed for 6 h, cooled to 25 °C, and quenched by adding ice-cold 4 M H_2SO_4 (30 ml). The crude hydroxyester was extracted with diethyl ether, evaporated under reduced pressure, and then was subjected to dehydration using Dean–Stark apparatus with *p*-toluenesulphonic acid (0.7 g, 3.68 mmol) in toluene at reflux. Water generated during the dehydration was separated azeotropically and

then toluene was distilled off. The crude olefinic ester **4** was purified by column chromatography packed with silica gel, eluting with EtOAc/petroleum ether (1:10) to give **4**.

4.3.1. (*E*)-Ethyl 3-phenylbut-2-enoate (4a). Yield: 80%; gum; IR ($CHCl_3$, cm^{-1}): 428, 694, 756, 871, 950, 1000, 1026, 1045, 1076, 1170, 1215, 1242, 1272, 1344, 1365, 1377, 1448, 1492, 1575, 1600, 1627, 1656, 1710, 1959, 2360, 2979, 3031, 3058, 3028, 3303, 3398; ^1H NMR (500 MHz, $CDCl_3$): δ 1.31 (t, J=7.4 Hz, 3H), 2.58 (s, 3H), 4.20 (q, J=7.4 Hz, 2H), 6.11 (s, 1H), 7.33–7.54 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.10, 18.47, 59.29, 116.99, 121.71, 125.96, 127.96, 128.18, 132.05, 154.92, 166.14; MS *m*/*z* (% rel intensity): 190 (70), 175 (5), 161 (50), 145 (100), 131 (5), 115 (90), 102 (10), 91 (40), 77 (20), 57 (20), 51 (30); Analysis: $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42; found C, 75.70; H, 7.36%.

4.3.2. (*E*)-Ethyl 3-(4-chlorophenyl)but-2-enoate (4b). Yield: 82%; viscous liquid; IR ($CHCl_3$, cm^{-1}): 840, 887, 1056, 1109, 1182, 1288, 1493, 1578, 1594, 1641, 1725, 1915, 2116, 3001; ^1H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, J=7.0 Hz, 3H), 2.54 (s, 3H), 4.19 (q, J=8.0 Hz, 2H), 6.08 (s, 1H), 7.29 (d, J=8.7 Hz, 2H), 7.37 (d, J=9.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.29, 17.60, 59.58, 117.62, 127.47, 128.61, 134.93, 140.55, 153.57, 165.95; MS *m*/*z* (% rel intensity): 224 (M^+, 96), 209 (8), 195 (55), 179 (100), 152 (32), 115 (92); Analysis: $C_{12}H_{13}ClO_2$ requires C, 64.15; H, 5.83; found C, 64.12; H, 5.80%.

4.3.3. (*E*)-Ethyl 3-(4-fluorophenyl)but-2-enoate (4c). Yield: 90%; yellow viscous liquid; IR ($CHCl_3$, cm^{-1}): 696, 770, 878, 1045, 1175, 1280, 1345, 1366, 1445, 1577, 1620, 1710, 2988, 3062; ^1H NMR (200 MHz, $CDCl_3$): δ 1.33 (t, J=7.0 Hz, 3H), 2.56 (s, 3H), 4.22 (q, J=7.0 Hz, 2H), 6.09 (s, 1H), 7.05 (d, J=8.6 Hz, 2H), 7.45 (d, J=9.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.25, 17.56, 59.52, 116.21, 118.13, 127.73, 130.66, 138.52, 153.47, 162.43, 165.78; Analysis: $C_{12}H_{13}FO_2$ requires C, 69.22; H, 6.29; found C, 69.12; H, 6.21%.

4.3.4. (*E*)-Ethyl 3-(2-methoxyphenyl)but-2-enoate (4d). Yield: 80%; gum; IR ($CHCl_3$, cm^{-1}): 754, 806, 883, 1026, 1112, 1163, 1228, 1247, 1274, 1369, 1434, 1461, 1490, 1579, 1598, 1639, 1712, 1726, 2837, 2937, 2977, 3072, 3452; ^1H NMR (500 MHz, $CDCl_3$): δ 1.21 (t, J=7.7 Hz, 3H), 2.39 (s, 3H), 3.72 (s, 3H), 4.10 (q, J=7.7 Hz, 2H), 5.77 (s, 1H), 6.77 (d, J=8.3 Hz, 1H), 6.81 (t, J=7.3 Hz, 1H), 7.02 (d, J=7.8 Hz, 1H), 7.16 (d, J=7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.90, 19.38, 54.90, 59.16, 110.73, 118.88, 120.19, 128.35, 129.09, 132.73, 156.02, 166.14; Analysis: $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32; found C, 70.80; H, 7.30%.

4.3.5. (*E*)-Ethyl 3-(4-methoxyphenyl)but-2-enoate (4e). Yield: 93%; gum; IR ($CHCl_3$, cm^{-1}): 589, 668, 701, 759, 840, 928, 978, 1018, 1040, 1083, 1123, 1184, 1215, 1272, 1411, 1509, 1572, 1606, 1672, 1695, 1736, 2400, 3019, 3617; ^1H NMR (500 MHz, $CDCl_3$): δ 1.22 (t, J=7.0 Hz, 3H), 2.47 (s, 3H), 3.72 (s, 3H), 4.11 (q, J=7.0 Hz, 2H), 6.02 (s, 1H), 6.79 (d, J=8.7 Hz, 2H), 7.35 (d, J=8.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.13, 17.34, 54.99, 59.40, 113.65, 115.13, 127.41, 134.08, 154.52, 160.31, 166.73; MS *m*/*z* (% rel intensity): 220 (90), 205 (3), 191 (10), 175 (100), 161 (5), 148 (90), 131 (15), 115 (20), 103 (15), 91 (25), 77 (20), 63 (10), 51 (12); Analysis: $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32; found C, 70.72; H, 7.26%.

4.3.6. (*E*)-Ethyl 3-(3-(cyclopentyloxy)-4-methoxyphenyl)but-2-enoate (4f). Yield: 88%; colorless liquid; ^1H NMR (200 MHz, $CDCl_3$): δ 1.32 (t, J=7.1 Hz, 3H), 1.61–1.64 (m, 2H), 1.85–1.92 (m, 6H), 2.55 (s, 3H), 3.84 (s, 3H), 4.18 (q, J=6.0 Hz, 2H), 4.79–4.80 (m, 1H), 6.02 (s, 1H), 6.78 (d, J=10.0 Hz, 1H), 6.96 (s, 1H), 7.00 (d, J=3.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.27, 17.67, 23.93, 32.74, 55.94, 59.60, 80.63, 111.51, 113.31, 115.37, 119.22, 134.59, 147.36, 151.13, 155.04, 166.93; Analysis: $C_{18}H_{24}O_4$ requires C, 71.03; H, 7.95; found C, 71.00; H, 7.90%.

4.3.7. (*E*)-Ethyl 3,4,4-trimethylpent-2-enoate (4g). Yield: 82%; colorless liquid; IR ($CHCl_3$, cm^{-1}): 740, 870, 965, 1035, 1163, 1200, 1272, 1340, 1465, 1635, 1732, 2907; ^1H NMR (200 MHz, $CDCl_3$): δ 1.10 (s, 9H), 1.26 (t, J=7.0 Hz, 3H), 2.14 (s, 3H), 4.10 (q, J=7.0 Hz, 2H), 5.68 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.92, 28.08, 37.34, 58.66, 115.66, 166.10; Analysis: $C_{10}H_{18}O_2$ requires C, 70.55; H, 10.66; found C, 70.52; H, 10.52%.

4.4. General experimental procedure for the synthesis of γ-bromo-α,β-unsaturated esters (5a–g) (allylic bromination)

A solution of α,β-unsaturated ester **4** (15.62 mmol), NBS (2.81 g, 17.2 mmol), and AIBN (0.102 g, 0.62 mmol) in dry CCl_4 (35 ml) was refluxed under nitrogen atmosphere for 10 h. The resulting reaction mixture was cooled to room temperature and then filtered through a sintered funnel to separate succinimide formed during the reaction. The filtrate was concentrated under reduced pressure to obtain bromoester **5**. It was then purified by column chromatography packed with silica gel to give pure bromoester **5**, as a pale yellow gum.

4.4.1. (*Z*)-Ethyl 4-bromo-3-phenylbut-2-enoate (5a). Yield: 72%; gum; IR ($CHCl_3$, cm^{-1}): 447, 460, 696, 767, 881, 960, 1020, 1047, 1095, 1176, 1218, 1286, 1344, 1367, 1448, 1492, 1577, 1596, 1623, 1710, 1766, 1890, 1955, 2345, 2935, 2979, 3058, 3537; ^1H NMR (500 MHz, $CDCl_3$): δ 1.33 (t, J=7.4 Hz, 3H), 4.25 (q, J=7.4 Hz, 2H), 4.95 (s, 2H), 6.18 (s, 1H), 7.38–7.53 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.04, 26.34, 60.24, 119.55, 126.36, 128.53, 129.47, 138.19, 152.90, 165.18; Analysis: $C_{12}H_{13}BrO_2$ requires C, 53.55; H, 4.87; found C, 53.63; H, 4.81%.

4.4.2. (*Z*)-Ethyl 4-bromo-3-(4-chlorophenyl)but-2-enoate (5b). Yield: 88%; yellow colored liquid; IR ($CHCl_3$, cm^{-1}): 649, 734, 908, 1012, 1095, 1182, 1288, 1340, 1369, 1490, 1625, 1710, 2982, 3060; ^1H NMR (200 MHz, $CDCl_3$): δ 1.34 (t, J=7.0 Hz, 3H), 4.26 (q, J=8.0 Hz, 2H), 4.94 (s, 2H), 6.19 (s, 1H), 7.36 (d, J=9.0 Hz, 2H), 7.47 (d, J=9.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.14,

26.13, 60.57, 120.01, 127.87, 128.94, 135.74, 136.77, 151.80, 165.22; MS *m/z* (% rel intensity): 304 (M^+, 5), 289 (5), 224 (8), 179 (10), 152 (100), 137 (55), 115 (92), 101 (48), 91 (22), 75 (15); Analysis: $C_{12}H_{12}BrClO_2$ requires C, 47.48; H, 3.98; found C, 47.50; H, 3.83%.

4.4.3. (*Z*)-Ethyl 4-bromo-3-(4-fluorophenyl)but-2-enoate (5c). Yield: 84%; gum; IR ($CHCl_3$, cm^{-1}): 742, 912, 1214, 1090, 1185, 1283, 1332, 1363, 1495, 1622, 1715, 2980, 3055; ^1H NMR (200 MHz, $CDCl_3$): δ 1.32 (t, J=7.0 Hz, 3H), 4.25 (q, J=7.0 Hz, 2H), 4.94 (s, 2H), 6.14 (s, 1H), 7.0 (d, J=8.6 Hz, 2H), 7.52 (d, J=9.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.86, 25.97, 60.03, 115.24, 119.36, 128.30, 130.41, 134.19, 151.56, 164.62; Analysis: $C_{12}H_{12}BrFO_2$ requires C, 50.20; H, 4.21; found C, 50.16; H, 4.20%.

4.4.4. (*Z*)-Ethyl 4-bromo-3-(2-methoxyphenyl)but-2-enoate (5d). Yield: 80%; gum; IR ($CHCl_3$, cm^{-1}): 682, 754, 806, 883, 933, 950, 1022, 1041, 1112, 1176, 1240, 1269, 1298, 1340, 1367, 1434, 1461, 1488, 1579, 1598, 1631, 1710, 2042, 2837, 2937, 2977, 3060; ^1H NMR (200 MHz, $CDCl_3$): δ 1.33 (t, J=7.4 Hz, 3H), 3.84 (s, 3H), 4.26 (q, J=7.0 Hz, 2H), 5.03 (s, 2H), 5.95 (s, 1H), 6.92 (d, J=8.2 Hz, 1H), 6.99 (t, J=7.4 Hz, 1H), 7.21–7.27 (m, 1H), 7.33–7.41 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.89, 28.26, 55.09, 59.98, 110.52, 120.34, 121.66, 128.09, 130.08, 130.30, 153.82, 156.03, 164.96; Analysis: $C_{13}H_{15}BrO_3$ requires C, 52.19; H, 5.05; found C, 52.20; H, 5.10%.

4.4.5. (*Z*)-Ethyl 4-bromo-3-(4-methoxyphenyl)but-2-enoate (5e). Yield: 86%; gum; IR ($CHCl_3$, cm^{-1}): 412, 428, 667, 757, 810, 833, 879, 950, 1024, 1031, 1047, 1095, 1174, 1217, 1253, 1288, 1342, 1369, 1438, 1461, 1514, 1573, 1604, 1708, 1890, 2057, 2430, 2549, 2839, 2904, 2937, 2981, 3014, 3398, 3568; ^1H NMR (500 MHz, $CDCl_3$): δ 1.23 (t, J=7.2 Hz, 3H), 3.73 (s, 3H), 4.14 (q, J=7.0 Hz, 2H), 4.86 (s, 2H), 6.05 (s, 1H), 6.80 (d, J=8.9 Hz, 2H), 7.40 (d, J=8.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.93, 26.07, 54.98, 59.97, 113.86, 117.25, 127.67, 152.16, 160.67, 165.28; MS *m/z* (% rel intensity): 300 (10), 298 (10), 254 (60), 252 (60), 239 (3), 228 (5), 219 (40), 191 (60), 174 (8), 163 (10), 145 (100), 131 (15), 115 (12), 103 (60), 91 (10), 77 (70), 63 (30), 40 (80); Analysis: $C_{13}H_{15}BrO_3$ requires C, 52.19; H, 5.05; found C, 52.13; H, 5.11%.

4.4.6. (*Z*)-Ethyl 4-bromo-3-(3-(cyclopentyloxy)-4-methoxyphenyl)but-2-enoate (5f). Yield: 90%; crystalline solid; mp: 167–169 °C (recrystallized from petroleum ether); IR ($CHCl_3$, cm^{-1}): 666, 756, 808, 858, 990, 1024, 1095, 1164, 1218, 1256, 1299, 1348, 1367, 1440, 1513, 1578, 1597, 1619, 1708, 2038, 2572, 2872, 2961, 3331; ^1H NMR (200 MHz, $CDCl_3$): δ 1.37 (t, J=8.0 Hz, 3H), 1.66 (m, 2H), 1.89–1.95 (m, 6H), 3.89 (s, 3H), 4.27 (q, J=6.0 Hz, 2H), 4.84 (s, 1H), 4.96 (s, 2H), 6.15 (s, 1H), 6.86 (d, J=3.0 Hz, 1H), 7.11 (s, 1H), 7.13 (d, J=4.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.34, 24.14, 26.33, 32.86, 55.86, 60.27, 80.53, 111.59, 113.27, 117.72, 119.48, 130.83, 147.68, 151.67, 152.86, 165.53; Analysis: $C_{18}H_{23}BrO_4$ requires C, 56.41; H, 6.05; found C, 56.33; H, 6.00%.

4.4.7. (*Z*)-Ethyl 3-(bromomethyl)-4,4-dimethylpent-2-enoate (5g). Yield: 76%; IR ($CHCl_3$, cm^{-1}): 412, 430, 460, 688, 707, 730, 745, 877, 962, 1033, 1095, 1155, 1193, 1267, 1338, 1371, 1469, 1631, 1720, 1755, 2358, 2873, 2908, 2968, 3417; ^1H NMR (200 MHz, $CDCl_3$): δ 1.19 (s, 9H), 1.28 (t, J=7.0 Hz, 3H), 4.15 (q, J=7.0 Hz, 2H), 4.53 (s, 2H), 5.87 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.96, 24.18, 28.96, 37.60, 59.83, 117.73, 163.56; MS (*m/z*, % rel intensity): 248 (5), 235 (3), 205 (10), 189 (3), 169 (5), 155 (50), 141 (10), 127 (30), 123 (20), 109 (15), 95 (45), 79 (20), 57 (50), 41 (100); Analysis: $C_{10}H_{17}BrO_2$ requires C, 48.21; H, 6.88; found C, 48.13; H, 6.73%.

4.5. General experimental procedure for the synthesis of γ-azido-α,β-unsaturated esters (1a–g) (azidation)

A solution of bromoester **5** (6.1 mmol) and sodium azide (0.594 g, 9.14 mmol) in ethanol/water (80:20, 15 ml) mixture was taken in 50 ml RB and refluxed for 8 h. The resulting yellow solution was concentrated under reduced pressure to yield crude azido ester **1**, which was purified by column chromatography packed with silica gel to give pure azido ester **1** as colorless viscous liquid.

4.5.1. (*Z*)-Ethyl 4-azido-3-phenylbut-2-enoate (1a). Yield: 86%; gum; IR ($CHCl_3$, cm^{-1}): 443, 669, 698, 757, 1035, 1182, 1215, 1371, 1448, 1710, 1845, 2104, 2343, 2360, 3018, 3421; ^1H NMR (500 MHz, $CDCl_3$): δ 1.25 (t, J=7.4 Hz, 3H), 4.17 (q, J=7.4 Hz, 2H), 4.69 (s, 2H), 6.25 (s, 1H), 7.33–7.43 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.73, 47.79, 60.12, 120.40, 126.29, 128.39, 129.28, 138.28, 150.16, 165.23; Analysis: $C_{12}H_{13}N_3O_2$ requires C, 62.33; H, 5.67; N, 18.17; found C, 62.28; H, 5.65; N, 18.09%.

4.5.2. (*Z*)-Ethyl 4-azido-3-(4-chlorophenyl)but-2-enoate (1b). Yield: 77%; colorless liquid; IR ($CHCl_3$, cm^{-1}): 415, 427, 435, 457, 478, 1179, 1350, 1591, 1713, 2101, 2982; ^1H NMR (200 MHz, $CDCl_3$): δ 1.32 (t, J=7.0 Hz, 3H), 4.24 (q, J=8.0 Hz, 2H), 4.74 (s, 2H), 6.30 (s, 1H), 7.34 (d, J=8.0 Hz, 2H), 7.43 (d, J=8.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.96, 48.03, 60.53, 121.04, 127.87, 128.87, 135.67, 136.95, 149.19, 165.33; Analysis: $C_{12}H_{12}ClN_3O_2$ requires C, 54.25; H, 4.55; N, 15.82; found C, 54.12; H, 4.48; N, 15.80%.

4.5.3. (*Z*)-Ethyl 4-azido-3-(4-fluorophenyl)but-2-enoate (1c). Yield: 80%; gum; IR ($CHCl_3$, cm^{-1}): 730, 830, 910, 1014, 1090, 1185, 1250, 1372, 1453, 1495, 1590, 1630, 1710, 2104, 2991; ^1H NMR (200 MHz, $CDCl_3$): δ 1.33 (t, J=7.0 Hz, 3H), 4.22 (q, J=7.0 Hz, 2H), 4.72 (s, 2H), 6.29 (s, 1H), 7.09 (d, J=8.8 Hz, 2H), 7.54 (d, J=8.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.13, 47.86, 61.13, 115.31, 119.42, 128.27, 131.63, 134.21, 151.54, 164.75; Analysis: $C_{12}H_{12}FN_3O_2$ requires C, 57.83; H, 4.85; N, 16.86; found C, 57.82; H, 4.88; N, 16.80%.

4.5.4. (*Z*)-Ethyl 4-azido-3-(2-methoxyphenyl)but-2-enoate (1d). Yield: 90%; gum; IR ($CHCl_3$, cm^{-1}): 650, 755, 821, 836, 887, 941, 1030, 1094, 1120, 1177, 1250, 1293, 1371, 1425, 1478, 1515, 1581, 1611, 1703, 1888, 2100, 2548, 2830, 2900, 2930, 2984, 3337; ^1H NMR (200 MHz, $CDCl_3$): δ 1.32 (t, J=7.0 Hz, 3H), 3.85 (s, 3H),

4.22 (q, J=7.0 Hz, 2H), 4.79 (s, 2H), 6.00 (s, 1H), 6.86–6.99 (m, 2H), 7.17–7.38 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.03, 49.98, 55.24, 60.28, 110.56, 120.74, 121.88, 128.53, 129.67, 130.34, 152.83, 156.40, 165.55; Analysis: $C_{13}H_{15}N_3O_3$ requires C, 59.76; H, 5.79; N, 16.08; found C, 59.75; H, 5.80; N, 16.10%.

4.5.5. (*Z*)-Ethyl 4-azido-3-(4-methoxyphenyl)but-2-enoate (1e). Yield: 95%; gum; IR ($CHCl_3$, cm^{-1}): 666, 758, 810, 834, 885, 937, 1029, 1096, 1115, 1174, 1254, 1291, 1369, 1421, 1462, 1513, 1574, 1604, 1712, 1891, 2101, 2550, 2831, 2906, 2937, 2981, 3332; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (t, J=7.2 Hz, 3H), 3.83 (s, 3H), 4.24 (q, J=7.2 Hz, 2H), 4.77 (s, 2H), 6.31 (s, 1H), 6.93 (d, J=8.6 Hz, 2H), 7.49 (d, J=8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.96, 47.56, 55.06, 60.20, 113.98, 118.39, 127.87, 130.34, 149.63, 160.77, 165.77; MS *m*/*z* (% rel intensity): 261 (10), 253 (10), 225 (5), 219 (100), 204 (5), 191 (70), 173 (5), 163 (80), 145 (30), 131 (35), 115 (15), 103 (40), 83 (30), 77 (35), 55 (40), 40 (55); Analysis: $C_{13}H_{15}N_3O_3$ requires C, 59.76; H, 5.79; N, 16.08; found C, 59.63; H, 5.72; N, 16.10%.

4.5.6. (*Z*)-Ethyl 4-azido-3-(3-(cyclopentyloxy)-4-methoxyphenyl)but-2-enoate (1f). Yield: 99%; light yellow liquid; IR ($CHCl_3$, cm^{-1}): 667, 756, 1045, 1166, 1216, 1253, 1373, 1442, 1514, 1598, 1734, 2104, 2966, 3019, 3403; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.23 (t, J=6.0 Hz, 3H), 1.52 (m, 2H), 1.72–1.85 (m, 6H), 3.76 (s, 3H), 4.14 (q, J=6.0 Hz, 2H), 4.65 (s, 2H), 4.72 (s, 1H), 6.18 (s, 1H), 6.76 (d, J=3.0 Hz, 1H), 6.96 (s, 1H), 7.00 (d, J=4.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.72, 23.59, 32.34, 47.48, 55.40, 59.95, 80.25, 111.37, 113.07, 118.21, 119.36, 130.47, 147.30, 149.70, 151.42, 165.43; Analysis: $C_{18}H_{23}N_3O_4$ requires C, 62.59; H, 6.71; N, 12.17; found C, 62.63; H, 6.54; N, 12.10%.

4.5.7. (*Z*)-Ethyl 3-(azidomethyl)-4,4-dimethylpent-2-enoate (1g). Yield: 91%; colorless gum; IR ($CHCl_3$, cm^{-1}): 680, 710, 734, 875, 971, 1034, 1100, 1160, 1269, 1340, 1376, 1630, 1735, 2109, 2968; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.14 (s, 9H), 1.29 (t, J=7.0 Hz, 3H), 4.17 (q, J=7.0 Hz, 2H), 4.27 (s, 2H), 6.00 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.95, 24.12, 29.00, 36.55, 59.75, 117.52, 163.00; Analysis: $C_{10}H_{17}N_3O_2$ requires C, 56.85; H, 8.11; N, 19.89; found C, 56.73; H, 8.10; N, 19.90%.

4.5.8. Preparation of (*E*)-ethyl 4-cyano-3-(4-fluorophenyl)but-2-enoate (17) (cyanation). In a 25 ml flask were added γ-bromoester **5c** (2.87 g, 10 mmol), NaCN (0.735 g, 15 mmol), and dry DMF (20 ml) under an argon atmosphere. The reaction mixture was heated at 50 °C for 6 h (monitored by TLC). After completion of the reaction it was diluted with water (5 ml) and extracted with EtOAc (4×15 ml); the combined organic extracts were washed with brine (10 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product. This was further purified by column chromatography on silica gel using EtOAc/petroleum ether (2:8) as eluent to afford cyano ester **17** (1.88 g, 81%).

Yield: 81%; yellow colored liquid; IR ($CHCl_3$, cm^{-1}): 827, 1027, 1103, 1164, 1240, 1317, 1369, 1427, 1512, 1602, 1735, 2216, 2360, 2983, 3066; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20 (t, J=8.0 Hz, 3H), 3.88 (s, 2H), 4.14 (q, J=8.0 Hz, 2H), 5.77 (s, 1H), 7.41 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.14, 39.32, 61.38, 99.20, 116.48, 126.11, 128.98, 130.41, 137.04, 155.63, 168.27; MS *m*/*z* (% rel intensity): 233 (M^+, 25), 218 (5), 205 (8), 188 (10), 174 (7), 161 (100), 133 (55), 121 (8), 96 (40), 75 (20), 57 (15); Analysis: $C_{13}H_{12}FNO_2$ requires C, 66.94; H, 5.19; N, 6.01; found C, 67.00; H, 5.20; N, 6.00%.

4.6. General experimental procedure for enantioselective synthesis of 4-substituted pyrrolidin-2-ones (2a–g) (asymmetric reduction)

To azido ester **1** (10 mmol) in a 25 ml RB flask was added a solution of $CoCl_2\cdot 6H_2O$ (0.021 g, 0.1 mmol) in ethanol (2 ml), followed by a solution of (4*S*)-(+)-phenyl-α-[(4*S*)-phenyloxazolidin-2-ylidine]-2-oxazoline-2-acetonitrile **6** (0.039 g, 0.12 mmol) in EtOH (1 ml) under nitrogen atmosphere. After dilution with DMF (1 ml), the clear, dark blue solution was degassed by three freeze–thaw cycles. To this mixture, which was kept under nitrogen, was added sodium borohydride solution (1.514 g, 40 mmol) in DMF (1 ml), which resulted in an instantaneous color change to yellow. The slightly foaming solution was immediately degassed by three freeze–thaw cycles. The evacuated flask containing the yellow, slightly turbid solution was stirred at 25 °C. In the beginning, slow H_2-evolution was observed, which gradually ceased after 1 h. Toward the end of the reaction, solid precipitate along with a brown-yellow foam began to form. After completion of the reaction (monitored by TLC), the reaction mixture was transferred to a separatory funnel containing 50 ml of EtOAc and 75 ml of water, and extracted with EtOAc. The organic layer was washed three times with brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuum. Column chromatographic purification (EtOAc/petroleum ether 4:1) afforded pyrrolidin-2-one **2** as solid.

4.6.1. (*R*)-4-Phenylpyrrolidin-2-one (2a). Yield: 86%; colorless solid; mp: 112 °C; $[\alpha]_D^{25}$ −18.90 (*c* 0.91, $CHCl_3$); HPLC: 92% ee, Chiralpak®, λ=210 nm, 10% EtOH/hexane, 1 ml/min, retention time: (*R*) 9.5 min; IR ($CHCl_3$, cm^{-1}): 665, 703, 756, 1092, 1218, 1373, 1490, 1697, 2100, 3211, 3422; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.35–2.47 (dd, J=16.0, 8.0 Hz, 1H), 2.65–2.77 (dd, J=16.0, 8.0 Hz, 1H), 3.32–3.41 (m, 1H), 3.60–3.82 (m, 2H), 7.25–7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 38.22, 39.51, 49.43, 126.28, 128.40, 132.00, 136.65, 175.53; Analysis: $C_{10}H_{11}NO$ requires C, 64.60; H, 6.19; N, 10.76; found C, 64.53; H, 6.11; N, 10.69%.

4.6.2. (*R*)-4-(4-Chlorophenyl)pyrrolidin-2-one (2b). Yield: 84%; colorless solid; mp: 115–117 °C; $[\alpha]_D^{25}$: –34.82 (*c* 1.0, EtOH), 89% ee, {Lit.[4,12] $[\alpha]_D^{25}$: −39 (*c* 1.0, EtOH)}; HPLC: 92% ee, Chiralpak®, λ=210 nm, 10% EtOH/hexane, 1 ml/min, retention time: (*R*) 9.8 min; IR ($CHCl_3$, cm^{-1}): 486, 550, 625, 676, 829, 1015,1106, 1168, 1273, 1297, 1410, 1460, 1488, 1666, 1763, 1911, 2228, 2840, 2898, 2952, 3106, 3197, 3443; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.39–2.51 (dd, J=16.9, 8.4 Hz, 1H), 2.68–2.81 (dd, J=16.9, 8.7 Hz, 1H), 3.35–3.43 (m, 1H), 3.62–3.84

(m, 2H), 7.18 (d, J=9.1 Hz, 2H), 7.31 (d, J=9.1 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 38.22, 39.51, 49.43, 128.02, 128.83, 132.72, 140.59, 178.01; MS m/z (% rel intensity): 195 (M^+, 15), 140 (24), 138 (100), 75 (5); Analysis: $C_{10}H_{10}ClNO$, requires C, 61.39; H, 5.15; N, 7.16; found: C, 61.30; H, 5.10; N, 7.19%.

4.6.3. 4-(4-Fluorophenyl)pyrrolidin-2-one (2c). Yield: 80%; colorless solid; mp: 98–99 °C; $[\alpha]_D^{25}$: −27.54 (c 1.12, MeOH); IR ($CHCl_3$, cm^{-1}): 669, 704, 760, 1095, 1210, 1375, 1493, 1695, 2105, 3209, 3417; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.53–2.69 (m, 2H), 3.37–3.46 (m, 1H), 3.61–3.82 (m, 2H), 7.06 (d, J=8.6 Hz, 2H), 7.51 (d, J=9.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 38.12, 39.68, 49.51, 115.31, 128.74, 134.14, 151.22, 178.00; Analysis: $C_{10}H_{10}FNO$, requires C, 67.03; H, 5.62; N, 7.82; found: C, 67.00; H, 5.58; N, 7.79%.

4.6.4. 4-(2-Methoxyphenyl)pyrrolidin-2-one (2d). Yield: 91%; colorless solid; mp: 118 °C; $[\alpha]_D^{25}$: −27.62 (c 1.10, MeOH); IR ($CHCl_3$, cm^{-1}): 664, 673, 685, 731, 1046, 1250, 1441, 1542, 1694, 2405, 2977; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.56–2.60 (d, J=8.0 Hz, 2H), 3.40–3.46 (m, 1H), 3.69–3.77 (m, 2H), 6.84–6.95 (m, 2H), 7.17–7.25 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 35.17, 48.22, 55.17, 110.49, 117.84, 120.67, 127.36, 128.06, 129.89, 157.21, 175.00; Analysis: $C_{11}H_{13}NO_2$ requires C, 69.09; H, 6.85; N, 7.32; found C, 69.10; H, 6.80; N, 7.20%.

4.6.5. (*R*)-4-(4-Methoxyphenyl)pyrrolidin-2-one (2e). Yield: 93%; colorless solid; mp: 121–123 °C; $[\alpha]_D^{25}$: −21.00 (c 1.00, MeOH); HPLC: 92% ee, Chiralpak®, λ=210 nm, 10% EtOH/hexane, 1 ml/min; IR ($CHCl_3$, cm^{-1}): 495, 516, 546, 564, 604, 641, 685, 772, 829, 884, 926, 1030, 1059, 1080, 1112, 1161, 1184, 1247, 1298, 1316, 1352, 1413, 1458, 1516, 1558, 1611, 1680, 1889, 1957, 2021, 2051, 2430, 2515, 2840, 2905, 2959, 3090, 3200; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 (s, 1H), 2.41–2.54 (d, J=7.2 Hz, 1H), 2.67–2.79 (d, J=8.6 Hz, 1H), 3.37–3.45 (m, 1H), 3.63–3.80 (m, 2H), 3.83, (s, 3H), 6.88 (d, J=8.6 Hz, 2H), 7.19 (d, J=8.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 38.44, 39.43, 49.80, 54.95, 113.98, 127.54, 134.05, 158.38, 178.19; Analysis: $C_{11}H_{13}NO_2$ requires C, 69.09; H, 6.85; N, 7.32; found C, 69.00; H, 6.72; N, 7.30%.

4.6.6. (*R*)-4-(3-(Cyclopentyloxy)-4-methoxyphenyl)pyrrolidin-2-one: (*R*)-(−)-rolipram (2f). Yield: 92%; colorless solid; mp: 133–134 °C (recrystallized from $CHCl_3$); $[\alpha]_D^{25}$ –27.80 (c 1.01, MeOH), 92% ee, {Lit.[12] $[\alpha]_D^{25}$: −30.2 (c 1.0, MeOH)}; HPLC: 92% ee, Chiralpak®, λ=210 nm, 10% EtOH/hexane, 1 ml/min, Retention time: (*R*) 10.3 min; IR ($CHCl_3$, cm^{-1}): 508, 601, 619, 641, 686, 772, 816, 877, 973, 1002, 1025, 1060, 1145, 1164, 1236, 1250, 1272, 1310, 1438, 1513, 1592, 1686, 1701, 1868, 2042, 2575, 2942, 3098, 3200; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.62 (m, 2H), 1.82–1.93 (m, 6H), 2.50 (d, J=8.7 Hz, 1H), 2.74 (d, J=8.7 Hz, 1H), 3.40 (t, J=8.0 Hz, 1H), 3.62 (q, J=8.7 Hz, 1H), 3.77 (t, J=9.0 Hz, 1H), 3.83 (s, 3H), 4.77 (m, 1H), 6.76 (s, 2H), 6.82 (s, 1H), 7.05 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.95, 23.95, 32.74, 38.20, 39.77, 49.97, 56.07, 80.54, 112.18, 113.77, 118.73, 134.34, 147.84, 149.13, 175.42, 178.61; MS (m/z, % rel intensity): 275 (10), 208 (5), 207 (80), 196 (5), 168 (5), 151 (10), 150 (100), 135 (15), 125 (20), 93 (15), 77 (10), 65 (15); Analysis: $C_{16}H_{21}NO_3$ requires C, 69.79; H, 7.69; N, 5.09; found C, 69.63; H, 7.67; N, 5.03%.

4.6.7. 4-*tert*-Butylpyrrolidin-2-one (2g). Yield: 77%; colorless solid; mp: 81 °C; $[\alpha]_D^{25}$: −6.17 (c 0.74, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.01 (s, 9H), 1.98–2.32 (m, 1H), 2.22–2.59 (m, 2H), 3.31–3.56 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.82, 33.46, 35.20, 41.18, 41.63, 176.30; Analysis: $C_8H_{15}NO$ requires C, 68.04; H, 10.71; N, 9.92; found C, 68.00; H, 10.72; N, 9.78%.

4.6.8. (*R*)-(−)-Baclofen hydrochloride (10). Lactam **2b** (0.170 g, 0.9 mmol) in 6 M HCl (4 ml) was heated at 100 °C for 16 h. The excess of water in the reaction mixture was removed under reduced pressure to obtain solid residue, which was triturated in isopropanol affording (*R*)-baclofen hydrochloride (**10**) as a colorless solid (0.164 g).

Yield: 73%; colorless solid; mp: 196–197 °C; $[\alpha]_D^{25}$: –1.76 (c 0.5, H_2O) 88% ee {Lit.[4b] $[\alpha]_D^{25}$: −2.00 (c 0.6, H_2O)}; IR ($CHCl_3$, cm^{-1}): 698, 704, 758, 1090, 1490, 1550, 1620, 2955, 2092, 3200; ^{1}H NMR (200 MHz, DMSO-d_6+$CDCl_3$): 2.51–2.71 (m, 2H), 3.42–3.65 (m, 2H), 4.15–4.21 (m, 1H), 7.01–7.21 (m, 4H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 37.57, 38.88, 43.00, 128.27, 129.62, 131.57, 138.95, 171.95; MS m/z (% rel intensity): 195 (10), 140 (61), 138 (100), 125 (6), 115 (10), 103 (45), 89 (9), 77 (29); Analysis: $C_{10}H_{13}Cl_2NO_2$ requires C, 48.02; H, 5.24; N, 5.60; found C, 48.24; H, 5.15; N, 5.49%.

4.6.9. Preparation of (*R*)-4-(4-fluorophenyl)piperidin-2-one (18). To a 1.01 g (4.33 mmol) of cyano ester **17** in a 15 ml RB flask was added a solution of $CoCl_2\cdot 6H_2O$ (0.009 g, 0.04 mmol) in ethanol (4 ml), followed by a solution of (4*S*)-(+)-phenyl-α-[(4*S*)-phenyloxazolidin-2-ylidine]-2-oxazoline-2-acetonitrile (**6**) (0.016 g, 0.048 mmol) in ethanol (2 ml) under a nitrogen balloon. After dilution with DMF (2 ml), the clear, dark blue solution was degassed by three freeze–thaw cycles. The solution, which was kept under nitrogen, was then added to sodium borohydride solution (0.64, 17 mmol) in DMF (2 ml) resulted in an instantaneous color change to yellow. The slightly foaming solution was immediately degassed by three freeze–thaw cycles. The evacuated flask containing the yellow, slightly turbid solution was stirred at room temperature. In the beginning, slow H_2-evolution was observed, which gradually ceased after 1 h. Toward the end of the reaction, solid precipitated and brown-yellow foam began to form. After completion of reaction (as monitored by TLC), the reaction mixture was transferred to a separatory funnel with 50 ml of EtOAc and 50 ml of water, diluted with 25 ml of ice water, and extracted with EtOAc. The organic layer was washed three times with brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuum. Column chromatographic purification (EtOAc/petroleum ether 4:1) afforded 0.828 g (99%) of piperidin-2-one **18** in 86% ee as a colorless solid.

Yield: 99%; crystalline solid; mp: 158 °C (recrystallized from $CHCl_3$); $[\alpha]_D^{25}$ +16.63 (c 1.00, $CHCl_3$), 86% ee, {Lit.[11] $[\alpha]_D^{25}$: +19.0 (c 1.02, $CHCl_3$)}; IR ($CHCl_3$, cm^{-1}):

627, 675, 832, 1013, 1102, 1159, 1275, 1300, 1414, 1458, 1476, 1685, 1756, 1910, 2231, 2842, 2895, 2950, 3100, 3201, 3440; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.78–1.95 (m, 1H), 2.02–2.10 (m, 1H), 2.40 (dd, J=17.6, 10.7 Hz, 1H), 2.64 (dd, J=17.6, 5.3 Hz, 1H), 3.00–3.31 (m, 1H), 3.37–3.43 (m, 2H), 7.11 (d, J=8.5 Hz, 3H), 7.27 (d, J=8.5 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.48, 37.90, 38.70, 41.20, 127.88, 128.91, 132.64, 141.98, 171.76; Analysis: $C_{11}H_{12}FNO$ requires C, 68.38; H, 6.26; N, 7.25; found C, 68.33; H, 6.20; N, 7.23%.

4.6.10. Preparation of 2-methoxyphenyl acetate (13). To a mixture of guaiacol **12** (2.48 g, 20 mmol) and acetic anhydride (40 ml) was added three drops of concd H_2SO_4 with vigorous stirring. The reaction mixture was heated at 100 °C for 6 h and then allowed to cool to 25 °C and stirring continued for 3 h (monitored by TLC). The organic layer was separated and the aqueous layer was extracted with ether (2×15 ml). The combined ethereal extracts were washed with water (15 ml) followed by brine (15 ml) and concentrated under reduced pressure to give crude product, which was further purified by column chromatography on silica gel using petroleum ether/EtOAc (9:1) as eluent to afford acetate **13** (3.22 g).

Yield: 97%; colorless liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.27 (s, 3H), 3.78 (s, 3H), 6.89–7.14 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.28, 55.57, 112.32, 120.52, 122.62, 126.62, 151.03, 168.64; MS (*m*/*z*, % rel intensity): (M^+ 166, 5), 124 (100), 109 (90), 95 (8), 91 (4), 81 (60), 77 (18), 64 (15); Analysis: $C_9H_{10}O_3$ requires C, 65.05; H, 6.07; found C, 64.93; H, 6.11%.

4.6.11. Preparation of 5-bromo-2-methoxyphenyl acetate (14). A solution of guiacolic ester **13** (2.59 g, 15.62 mmol) and NBS (2.81 g, 17.2 mmol) in dry CH_3CN (35 ml) was heated at 60 °C under a nitrogen atmosphere for 10 h. The resulting reaction mixture was cooled to room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc (2×15 ml). The combined organic extracts were washed with a saturated solution of sodium sulfite (15 ml), water (15 ml) followed by brine (15 ml), and concentrated under reduced pressure to give crude product, which was further purified by column chromatography on silica gel using petroleum ether/EtOAc (9:1) as eluent to afford pure 3.75 g of pale yellow color gum, bromoester **14**.

Yield: 99%; pale yellow color gum; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.27 (s, 3H), 3.75 (s, 3H), 6.77 (d, J=10.0 Hz, 1H), 7.18 (d, J=3.0 Hz, 1H), 7.24–7.29 (d, J=10.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.21, 55.79, 111.66, 113.54, 125.78, 129.34, 140.19, 150.41, 168.23; MS (*m*/*z*, % rel intensity): (M^+ 244, 10), 204 (100), 187 (60), 173 (3), 161 (10), 143 (4), 123 (5), 108 (5), 94 (7), 79 (20), 71 (3), 63 (8); Analysis: $C_9H_9BrO_3$ requires C, 44.11; H, 3.70; found C, 44.00; H, 3.65%.

4.6.12. Preparation of 5-bromo-2-methoxyphenol (15). A 25 ml flask was charged with ester **14** (3.66 g, 15 mmol), 10% $NaHCO_3$ (2.5 g, 22 mmol), and MeOH (15 ml) under nitrogen atmosphere. The solution was allowed to reflux for 3 h. Then EtOAc (25 ml) was added to reaction mixture. The organic layer was separated and the aqueous layer was extracted with EtOAc (2×15 ml). The combined organic extracts were washed with water (15 ml) followed by brine (15 ml) and concentrated under reduced pressure to give crude product, which was further purified by column chromatography on silica gel using petroleum ether/EtOAc (3:1) as eluent to phenol **15** (2.85 g).

Yield: 95%; yellow solid; mp: 102–105 °C (recrystallized from EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.77 (s, 3H), 6.58 (d, J=10.0 Hz, 1H), 6.83–6.89 (d, J=10.0 Hz, 1H), 6.97 (d, J=2.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.05, 111.88, 113.39, 117.95, 122.76, 145.88, 146.58, 159.74; MS (*m*/*z*, % rel intensity): (M^+ 204, 20), 202 (20), 189 (20), 160 (20), 131 (5), 116 (3), 107 (7), 91 (5), 79 (900), 62 (100); Analysis: $C_7H_7BrO_2$ requires C, 41.41; H, 3.48; found C, 41.38; H, 3.52%.

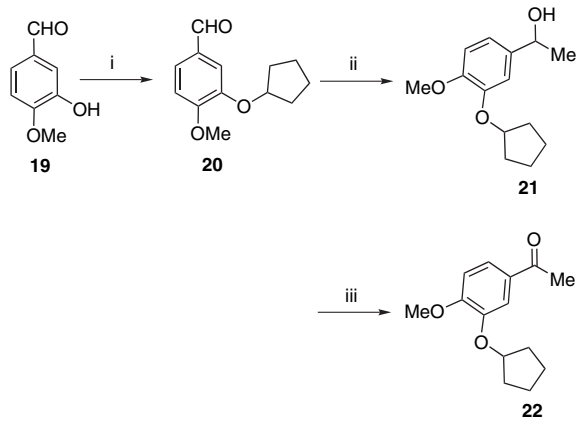
4.6.13. Preparation of 4-bromo-2-(cyclopentyloxy)-1-methoxybenzene (16). To a mixture of bromo phenol **15** (2.04 g, 10 mmol) and K_2CO_3 (1.2 g, 20 mmol) in DMF (40 ml) was added cyclopentyl bromide through a syringe at 50 °C with vigorous stirring. After completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool to room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc (2×15 ml). The combined organic extracts were washed with water (15 ml) followed by brine (15 ml) and concentrated under reduced pressure to give crude product, which was further purified by column chromatography on silica gel using petroleum ether/EtOAc (9:1) as eluent to afford bromo ether **16** (2.42 g).

Yield: 89%; yellowish liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.59–1.87 (m, 8H), 3.79 (s, 3H), 4.71 (m, 1H), 6.67 (d, J=10.0 Hz, 1H), 6.96–7.00 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.55, 32.27, 55.53, 80.20, 112.14, 112.91, 117.54, 122.80, 148.13, 148.97; MS (*m*/*z*, % rel intensity): (M^+ 272, 10), 270 (10), 202 (100), 187 (60), 173 (5), 159 (10), 142 (5), 123 (7), 108 (7), 94 (20), 79 (70), 63 (40); Analysis: $C_{12}H_{15}BrO_2$ requires C, 53.15; H, 5.58; found C, 53.10; H, 5.50%.

4.6.14. Preparation of 3-(cyclopentyloxy)-4-methoxyphenylboronic acid (3f). To a mixture of bromo ether **16** (4.56 g, 20 mmol) in diethyl ether (40 ml) was added dropwise through a syringe, 1 M *n*-BuLi solution in hexane (15 ml) at −78 °C with vigorous stirring. The reaction mixture was stirred for 1 h and then $B(OMe)_3$ (2 ml) was added. After stirring for 1 h, the reaction mixture was quenched with satd NH_4Cl solution (10 ml) and organic layer was separated and the aqueous layer was extracted with ether (2×15 ml). The combined ethereal extracts were washed with water (15 ml) followed by brine (15 ml) and concentrated under reduced pressure to give crude boronic acid **3f** (0.236 g), which was used, as it was for further reactions.

Yield: 15%; gray color solid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.82 (m, 8H), 2.53 (br s, 2H), 3.73 (m, 1H), 3.95 (s, 3H), 7.02 (d, J=8.0 Hz, 1H), 7.71 (s, 1H), 7.81 (d, J=8.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.25, 33.01, 55.94, 80.59, 121.34, 129.66, 147.21, 153.90; Analysis: $C_{12}H_{17}BO_4$ requires C, 61.05; H, 7.26; found C, 61.10; H, 7.20%.

4.6.15. Synthetic strategy for preparation of 1-(3-(cyclopentyloxy)-4-methoxyphenyl)ethanone (22).



(i) Cyclopentyl bromide (1.5 equiv), K_2CO_3 (1.2 equiv), DMF, 60 °C, 12 h, 85%; (ii) MeMgBr (1.3 equiv), Et_2O, 0–25 °C, 1 h, 76%; (iii) $H_2Cr_2O_7$, Et_2O, 0–25 °C, 4 h, 75%.

4.6.16. Preparation of 3-(cyclopentyloxy)-4-methoxybenzaldehyde (20). To a mixture of isovaniline **19** (3.04 g, 20 mmol) and K_2CO_3 (1.76 g, 20 mmol) in DMF (40 ml) was added cyclopentyl bromide (3.73 g, 25 mmol) through a syringe at 50 °C with vigorous stirring. After completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool to room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc (2×15 ml). The combined organic extracts were washed with water (15 ml) followed by brine (15 ml) and concentrated under reduced pressure to give crude product, which was further purified by column chromatography on silica gel using petroleum ether/EtOAc (9:1) as eluent to afford ether **20** (3.74 g).

Yield: 85%; yellow solid; mp: 107–110 °C (recrystallized from EtOAc); IR ($CHCl_3$, cm^{-1}): 426, 446, 452, 590, 742, 868, 902, 936, 968, 1022, 1238, 1362, 2038, 2360, 2606, 2720, 3078, 3354, 3624; ^1H NMR (200 MHz, $CDCl_3$): δ 1.63–2.00 (m, 8H), 3.93 (s, 3H), 4.86 (m, 1H), 6.65 (d, J=8.0 Hz, 1H), 7.41–7.45 (m, 2H), 9.84 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.66, 32.30, 55.64, 80.01, 110.45, 111.74, 125.85, 129.60, 147.80, 155.04, 190.47; MS (*m*/*z*, % rel intensity): (M^+ 220, 10), 177 (5), 151 (100), 137 (10), 122 (12), 108 (15), 95 (8), 79 (20), 65 (20); Analysis: $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32; found C, 70.63; H, 7.25%.

4.6.17. Preparation of 1-(3-(cyclopentyloxy)-4-methoxyphenyl)ethanol (21). A dry, argon flushed 100 ml round-bottom flask, equipped with a magnetic stirring (bar, reflux water condenser, and dropping funnel, was charged with 2–3 crystals of iodine, and magnesium turnings (0.675 g, 28 mmol) in dry diethyl ether (20 ml) at 25 °C. Then methyl iodide (3.8 g, 2.12 ml, 28 mmol) was added dropwise at 25 °C in diethyl ether. After stirring for 3–4 h, the dropping funnel was replaced by a rubber septum. The reaction flask was cooled in ice water, followed by slow addition of aldehyde **20** (5.0 g, 23 mol) in ether over a period of 10 min. Then it was allowed to stir over night. The reaction mixture was quenched with a saturated solution of NH_4Cl, poured into water (50 ml), and extracted with ether (3×50 ml). The combined organic fractions were washed with brine, then dried over Na_2SO_4, and concentrated under reduced pressure to afford crude alcohol **21**. The crude alcohol was purified by column chromatography packed with silica gel, eluting with petroleum ether/EtOAc (5:1) gave 4.12 g of **21**.

Yield: 76%; gray solid; mp: 123–125 °C (recrystallized from EtOAc+petroleum ether); ^1H NMR (200 MHz, $CDCl_3$): δ 1.43 (d, J=6.0 Hz, 3H), 1.86–1.99 (m, 8H), 3.81 (s, 3H), 4.75–4.84 (m, 2H), 6.76–6.92 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.93, 23.85, 24.51, 24.91, 32.74, 56.23, 69.98, 74.10, 74.43, 80.49, 112.47, 113.46, 117.65, 118.57, 118.72, 137.28, 138.83, 147.98, 149.38; MS (*m*/*z*, % rel intensity): (M^+ 236, 20), 218 (5), 196 (5), 168 (40), 153 (100), 135 (10), 125 (40), 107 (5), 93 (17), 77 (10), 65 (12); Analysis: $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53; found C, 71.13; H, 8.51%.

4.6.18. Preparation of 1-(3-(cyclopentyloxy)-4-methoxyphenyl)ethanone (22). To a mixture of alcohol **21** (3.54 g, 15 mmol) in diethyl ether (40 ml) was added dropwise through an addition funnel freshly prepared chromic acid solution (15 ml) under ice-cold condition with vigorous stirring. The reaction mixture was allowed to warm to room temperature and stirring continued for 3 h (monitored by TLC). The organic layer was separated and the aqueous layer was extracted with ether (3×15 ml). The combined ethereal extracts were washed with water (15 ml) followed by brine (15 ml) and concentrated under reduced pressure to give the crude product, which was further purified by column chromatography on silica gel using petroleum ether/EtOAc (9:1) as eluent to afford cyclopentyl acetophenone **22** (2.63 g).

Yield: 75%; brown colored solid; mp: 127–129 °C (crystallized from EtOAc); IR ($CHCl_3$, cm^{-1}): 408, 430, 442, 456, 466, 472, 588, 642, 668, 776, 808, 878, 898, 1076, 1132, 1178, 1216, 1356, 1584, 1676, 2360, 2870, 2960; ^1H NMR (200 MHz, $CDCl_3$): δ 1.72–1.91 (m, 8H), 2.56 (s, 3H), 3.91 (s, 3H), 4.81–4.90 (m, 1H), 6.85 (d, J=10.0 Hz, 1H), 7.53–7.57 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.92, 26.05, 32.63, 55.94, 80.42, 110.38, 113.54, 122.84, 130.30, 147.54, 154.23, 196.68; Analysis: $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74; found C, 71.75; H, 7.68%.

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