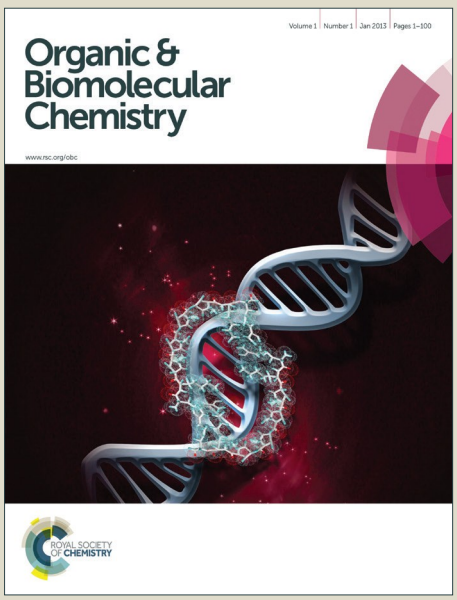
Organic & Biomolecular Chemistry

Accepted Manuscript



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Organocatalytic Enantioselective Michael Addition of Cyclic Hemiacetals to Nitroolefins: A Facile Access to Chiral Substituted 5- and 6-Membered Cyclic Ethers

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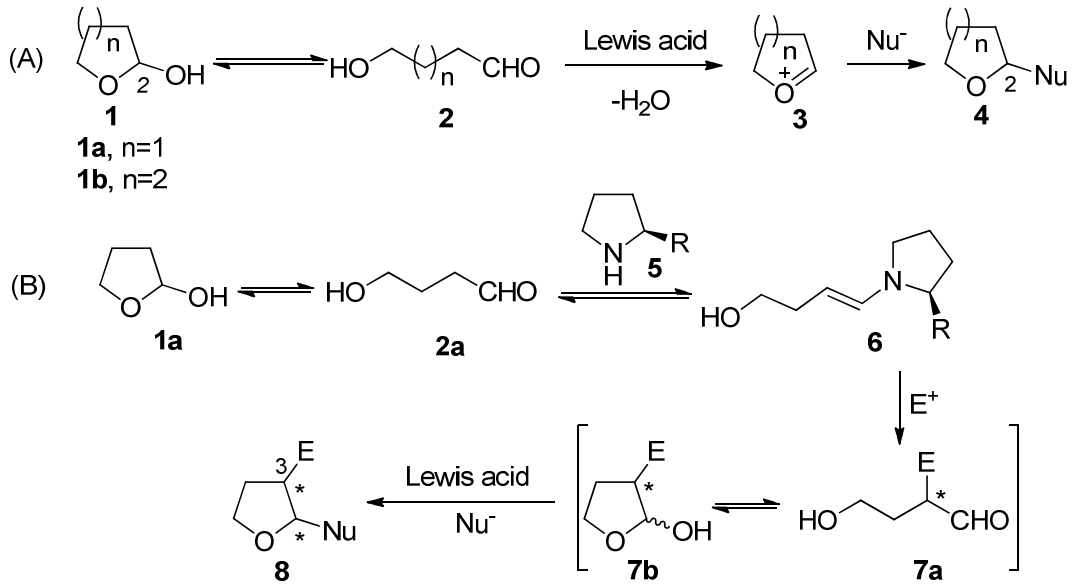
[†] Electronic supplementary information (ESI) available.

Introduction

Cyclic ethers, tetrahydrofurans (THFs) and tetrahydropyrans (THPs), are broadly featured in numerous natural products and biologically active molecules, including macrolides,[1] macrodiolides,[2] lignans,[3] ionophores,[4] acetogenins[5] and nucleosides.[6] Consequently, there has been a long-standing interest in the development of catalytic enantioselective methods for their preparation.[1-8] However, most of these reported methods have focused on the preparations of 2- substituted THFs and THPs.[7] In contrast, only a handful of examples have been described for the synthesis of 3-substituted analogues.[8]

One appealing protocol to synthesize cyclic ethers is the employment of readily available cyclic hemiacetals as starting materials.[9,10] It has been well established that a highly active electrophilic oxonium ion **3** produced from a hemiacetal **1** or **2** in the presence of Lewis acid reacts with a nucleophile to install the substituents at position 2 of cyclic ether **4**[9.10] (Scheme 1A). Accordingly, on the basis of these established techniques, a new asymmetric method of preparing 3-substituted hemiacetal **7b** would lead to a convenient access to chiral 3-substituted THFs **8** (Scheme 1B).



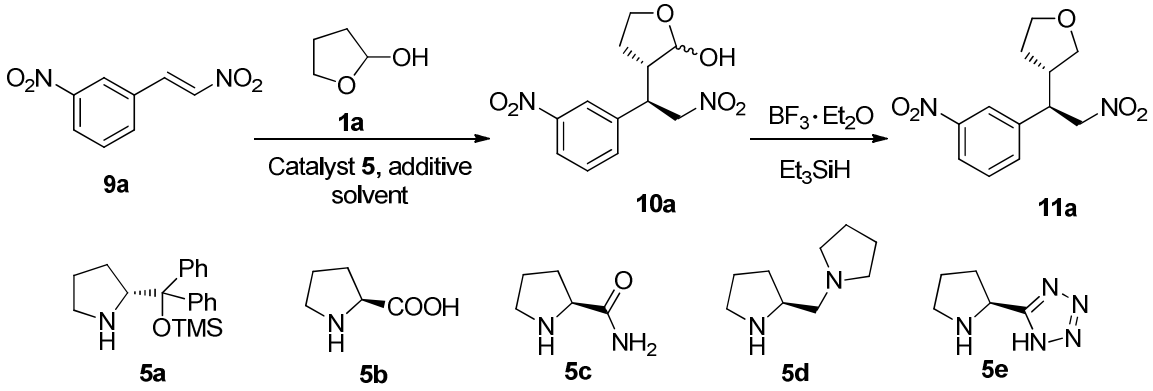
Scheme 1. The reactions of hemiacetals.

Aldehydes perhaps are the most widely used substrates in aminocatalysis[11] while cyclic hemiacetals, considering a special type of aldehydes, and often utilized as electrophiles, have seldom been explored as nucleophiles, especially in the field of organocatalysis. To our knowledge, so far only two examples have been reported by Goeke and McQuade.[12] Furthermore, cyclic five- and six-membered hemiacetals are dominant forms in the *equilibrium*. It is expected that it is more difficult to perform enamine catalytic reactions with these hemiacetals than the free aldehydes. Herein, we wish to disclose the first example of an organocatalytic highly enantioselective Michael addition of 2-hydroxytetrahydrofuran (2-HTHF, **1a**) and 2-hydroxytetrahydropyran (2-HTHP, **1b**) to nitroolefins.[13]

Results and discussion

The initial investigation was conducted between **1a**[14] (5.0 equiv) and nitrostyrene **9a** (1.0 equiv) in the presence of catalyst **5a** (0.4 equiv) at rt (Table 1). To our delight, the reactions proceeded smoothly in all of the solvents probed (Table 1, entries 1-6). The best results came from $CHCl_3$ (87% yield, 99% *ee* and 6:1 *dr*) (entry 6), while others, such as toluene, MeOH, DMF, THF and EtOAc, were inferior (31-68% yields, 79-93% *ee* and 2:1-4:1 *dr*) (entries 1-5). The effects of additives on the reaction were then examined. It was found that acetic acid could accelerate the process dramatically albeit with slightly decreased *ee* and *dr* values (entry 7). Next, we tried to reduce the loading of **1a** from 5.0 to 2.5 and 2.0 equiv (entries 8 and 9). The use of 2.5 equiv of **1a** gave the best choice, providing an excellent yield (98%) and *ee* (98%) as well as an improved *dr* (from 4:1 to 6:1, entry 7 *vs* entry 8). An attempt to reduce the catalyst loading from 0.4 to 0.3 equiv did not achieve the benefit even after a longer reaction time (entry 10 *vs* entry 7). Furthermore, other pyrrolidine based catalysts **5b-e** were also screened, but gave disappointing results (entries 11-14).

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



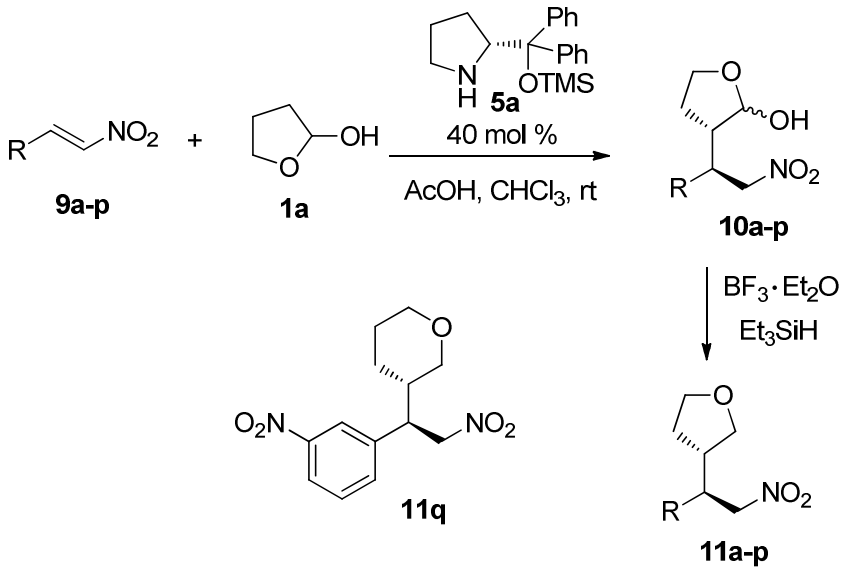
Entry	Cat.	Solvent	Time (h)	Yield (%)[c]	Ee (%)[d]	Dr[e]
1	**5a**	toluene	15	64	93	4:1
2	**5a**	MeOH	15	50	84	2:1
3	**5a**	DMF	12	68	83	2:1
4	**5a**	THF	20	31	85	3:1
5	**5a**	EtOAc	18	39	79	4:1
6	**5a**	$CHCl_3$	9	87	99	6:1
7[f]	**5a**	$CHCl_3$	6	96	97	4:1
8[f,g]	**5a**	$CHCl_3$	12	98	98	6:1
9[f,h]	**5a**	$CHCl_3$	20	87	98	6:1
10[f,g,i]	**5a**	$CHCl_3$	20	76	98	5:1
11[f,g]	**5b**	$CHCl_3$	24	<5	-	-
12[f,g]	**5c**	$CHCl_3$	18	70	-78	3:1
13[f,g]	**5d**	$CHCl_3$	29	50	-24	3:1
14[f,g]	**5e**	$CHCl_3$	40	44	-77	4:1

[a] Reaction conditions unless otherwise specified: A mixture of **9a** (1.0 mmol), **1a** (5.0 mmol), and catalyst **5** (0.40 mmol) in solvent (3.0 mL) was stirred at rt for a specified time. After workup, the crude product **10a** was reduced into **11a** by $Et_3SiH/BF_3{\cdot}Et_2O$ for HPLC analysis. [b] The absolute configurations of compound **11a** were determined by analogy with comound **11k** (see supporting information). [c] Isolated yields for two steps. [d] Determined by chiral HPLC analysis of **11a**. [e] Determined by ^1H NMR analysis of the crude reaction mixture of **11a**. [f] AcOH (1.0 mmol) was used as additive. [g] 2.5 mmol of **1a** was used. [h] 2.0 mmol of **1a** was used. [i] 0.3 mmol of **5a** was used.

With the optimal reaction conditions in hand, we then probed the scope of the Michael addition of 2-HTHF **1a** to a wide range of nitroolefins. As shown in Table 2, a number of nitrostyrenes bearing electron-withdrawing, -neutral and -donating substituents on the benzene ring were successfully applied in the Michael addition reactions. 3-Substituted THFs **11a-l** were isolated with high enantioselectivities (91-99% *ee*) and in moderate to

excellent yields (55-98%) (entries 1-12). It seems that the steric hindrance had a pronounced effect on the process; lower yields and diastereoselectivities were observed for the *ortho* substituted substrates (entries 2 and 4). Fused naphthyl substituted nitroolefin also gave an excellent *ee* value (98%) and high *dr* (9:1), albeit a moderate yield (49%) (entry 13). Moreover, heterocyclic 2-furyl substituted nitroolefin **9n** was proven to be a suitable substrate, affording the desired product with high efficiency (entry 14). A similar trend was observed with aliphatic nitroolefins **9o** and **9p** employed by achieving high *ee* and good *dr* (entries 15 and 16). Eventually, six-membered cyclic hemiacetal 2-HTHP **1b** was tested for the process under the same reaction conditions and provided 3-substituted tetrahydropyran **11q** in a high yield and with a comparable enantioselectivity and diastereoselectivity to 2-HTHF (Table 2, entry 17 *vs* entry 1). The absolute configuration of product **11k** was determined by using single crystal X-ray diffraction (see supporting information).[15]

Table 2. Scope of the Michael addition of 2-HTHF **1a** to nitroolefins.[a,b]



Entry	R	**11**	Time	Yield (%)[c]	Ee (%)[d]	Dr[e]
1	3-$NO_2C_6H_4$	**11a**	12 h	98	98	6:1
2	2-$NO_2C_6H_4$	**11b**	18 h	55	97	3:1
3	4-$NO_2C_6H_4$	**11c**	12 h	80	98	6:1

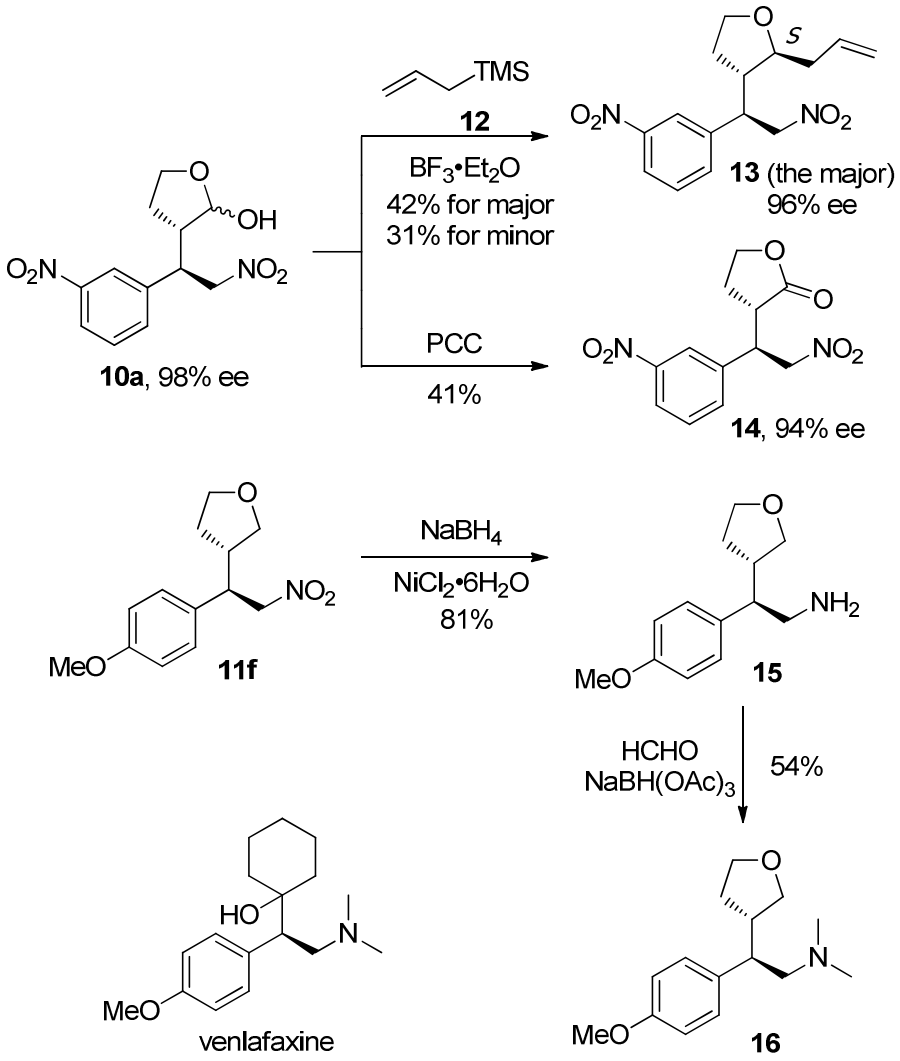
4	2-$MeOC_6H_4$	**11d**	24 h	63	98	4:1
5	3-$MeOC_6H_4$	**11e**	18 h	64	99	11:1
6	4-$MeOC_6H_4$	**11f**	24 h	70	90	9:1
7	4-CNC_6H_4	**11g**	12 h	91	94	8:1
8	C_6H_5	**11h**	12 h	95	98	7:1
9	2-BrC_6H_4	**11i**	16 h	75	97	5:1
10	3-FC_6H_4	**11j**	12 h	87	98	5:1
11	4-BrC_6H_4	**11k**	12 h	85	92	6:1
12	4-ClC_6H_4	**11l**	12 h	91	99	8:1
13	1-naphthyl	**11m**	18 h	49	98	9:1
14	2-furyl	**11n**	24 h	59	84	4:1
15	Et	**11o**	15 h	49	96	6:1
16	*i*-Pr	**11p**	15 h	56	96	4:1
17[f]	3-$NO_2C_6H_4$	**11q**	15 h	94	92	5:1

[a] Reaction conditions unless otherwise specified: A mixture of **9** (1.0 mmol), **1a** (2.5 mmol), AcOH (1.0 mmol) and catalyst **5a** (0.40 mmol) in $CHCl_3$ (3.0 mL) was stirred at rt for a specified time. After workup, crude product **10** was reduced into **11** by $Et_3SiH/BF_3{\cdot}Et_2O$ for HPLC analysis. [b] The absolute configurations of compound **11** were determined by analogy with comound **11k** (see supporting information). [c] Isolated yields for two steps. [d] Determined by chiral HPLC analysis of **11**. [e] Determined by ^1H NMR analysis of the crude reaction mixture of **11**. [f] 2-hydroxytetrahydropyran (2-HTHP, **1b**) was used as the nucleophile.

To demonstrate the synthetic utility of the Michael adducts, we explored their organic transformations (Scheme 2). For example, in the presence of $BF_3{\cdot}Et_2O$, the reaction between hemiacetal **10a** and allyltrimethylsilane **12** led to 2,3-disubstituted THF. One pure major diastereoisomer **13** was obtained in 42% yield, and the minor one mixing with **13** and other byproducts was difficult to be isolated in a pure form (combined about 31% yield) by chromatography method. It is noted that minimal *ee* erosion was observed

in these conversions. The configuration of newly created chiral center was determined to be *S* by NOESY analysis (see supporting information).

Cyclic hemiacetal is also known as a common precursor for the synthesis of lactone.[10b-c] Thus, treatment of **10a** with PCC (pyridinium chlorochromate) afforded lactone **14** in an acceptable yield and with a slightly decreased *ee* value. This strategy provides a new route of access to chiral α-substituted lactones.



Scheme 2. The synthetic elaboration of the Michael adducts.

Finally, the synthetic value of the Michael adducts was further demonstrated by preparing analogues of the antidepressant drug venlafaxine. A two-step procedure was developed. The reduction of the nitro group with $NaBH_4/NiCl_2 \cdot 6H_2O$ was followed by

the reductive amination with HCHO/$NaBH(OAc)_3$ providing **16** readily. Moreover, a series of venlafaxine analogues were synthesized using this synthetic strategy. The bioactivity studies of these analogues are currently ongoing in our laboratory.

Conclusion

In summary, we have developed an efficient organocatalytic enantioselective Michael addition reaction of cyclic hemiacetals to nitroolefins in moderate to excellent yields and with good to excellent enantioselectivity. Notably, hemiacetals with relatively low reactivities are used as nucleophiles in aminocatalysis for the first time. The process serves as a powerful approach to the synthetically valued THFs and THPs. The Michael adducts are versatile building blocks for the preparation of chiral 3-substituted and 2,3-disubstituted cyclic ethers or α-substituted lactones. This strategy can also be explored for the rapid synthesis of new venlafaxine analogues in drug discovery. Further applications of cyclic hemiacetals in organocatalysis are underway and will be reported in due course.

Experimental section

General methods

Chemicals and reagents were purchased from commercial suppliers and used without special instructions. TLC was performed on silica $HSGF_{254}$ plates. ^1H and ^{13}C NMR spectra were obtained from a solution in $CDCl_3$ with TMS as internal standard using a 400/101 MHz ($^1H/^{13}C$) or 300/75 MHz ($^1H/^{13}C$) spectrometer. Chemical shifts (δ) are given in ppm and *J* in Hz. Analytical high performance liquid chromatography (HPLC) was performed using a UV detector on an Agilent 1100 LC with HPLC-grade isopropanol, THF and hexanes as the eluting solvents. Optical rotation values are measured on a polarimeter.

General Procedure

To a solution of nitroolefin **9** (1.0 mmol) and 2-hydroxytetrahydrofuran **1a** (2.5 mmol, 2.5 equiv.) in $CHCl_3$ (3.0 mL) was added catalyst **5a** (0.40 mmol, 0.4 equiv.) and AcOH (1.0 mmol, 1.0 equiv.). The reaction was stirred at rt for a specified time until TLC

showed the complete conversion of nitroolefins **9**. CH_2Cl_2 (15 mL) was added to the reaction mixture and the organic layer was washed successively with 1M HCl (5 mL), 5% aqueous $NaHCO_3$ (5 mL) and brine (5 mL), and then dried over Na_2SO_4. The solvent was removed in vacuum and the crude product was dissolved in CH_2Cl_2 (4.0 mL). Et_3SiH (3.0 mmol, 3.0 equiv.) was added, followed by the addition of $BF_3{\cdot}Et_2O$ (3.0 mmol, 3.0 equiv.) within 5 min under argon. The reaction was stirred at rt for 2 h before the solvent was removed in vacuum. The crude product was purified by column chromatography on silica gel to afford the desired product **11**.

The corresponding racemic **11** was prepared using racemic **5a** as catalyst in the same procedure described above.

(*S*)-3-((*R*)-2-Nitro-1-(3-nitrophenyl)ethyl)tetrahydrofuran (11a, Table 2, entry 1)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (m, 1H), 8.13 (s, 1H), 7.57-7.55 (m, 2H), 4.73-4.59 (m, 2H), 4.03 (t, J = 7.2 Hz, 1H), 3.87-3.83 (m, 1H), 3.76-3.71 (m,1H), 3.61 (t, J = 8.1 Hz,1H), 3.54-3.49 (m, 1H), 2.62-2.58 (m, 1H), 1.78-1.74 (m, 1H), 1.48-1.43 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.55, 139.91, 133.14, 129.13, 122.11, 121.41, 78.17, 70.09 , 66.71, 46.40, 41.31, 30.27; HR-MS (ESI): *m/z* = 267.0975, calcd. for $C_{12}H_{15}N_2O_5$ $[M + H]^+$: 267.0981; HPLC (Daicel Chiralpak AS-H, *i*-PrOH:hexane = 10:90, flow rate = 1.0 mL/min, λ = 254 nm): t_{major} = 36.73 min, t_{minor} = 30.91min, *ee* = 98%; $[\alpha]_D^{25}$ -27.7º (c = 0.12 in $CHCl_3$).

(*S*)-3-((*R*)-2-Nitro-1-(2-nitrophenyl)ethyl)tetrahydrofuran (11b, Table 2, entry 2)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.2 Hz, 1H), 7.66-7.63 (m, 1H), 7.49-7.44 (m, 2H), 4.81-4.68 (m, 2H), 4.06 (t, J = 8.4 Hz, 2H), 3.91-3.84 (m, 1H), 3.78-3.72 (m, 1H), 3.60 (t, J = 9.9 Hz, 1H), 2.76-2.72 (m, 1H), 1.82-1.74 (m, 1H), 1.60-1.53 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.41, 133.23, 128.74, 125.02, 79.02, 71.26, 67.73, 41.94, 31.02; HR-MS (ESI): *m/z* = 267.0970, calcd. for $C_{12}H_{15}N_2O_5$ $[M + H]^+$: 267.0981; HPLC (Daicel Chiralpak OD-H, *i*-PrOH:hexane = 10:90, flow rate = 1.0 mL/min, λ = 254 nm): t_{major} = 80.06 min, t_{minor} = 93.43 min, *ee* = 97%; $[\alpha]_D^{25}$ -45.1º (c = 0.18 in $CHCl_3$).

(*S*)-3-((*R*)-2-Nitro-1-(4-nitrophenyl)ethyl)tetrahydrofuran (11c, Table 2, entry 3)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.6 Hz, 2H), 4.74-4.59 (m, 2H), 4.03 (t, *J* = 8.1 Hz, 1H), 3.90-3.83 (m, 1H), 3.77-3.69 (m, 1H), 3.61 (t, *J* = 8.1 Hz, 1H), 3.55-3.48 (m, 1H), 2.63-2.55 (m, 1H), 1.78-1.73 (m, 1H), 1.50-1.43 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.51, 146.31, 128.79 , 124.24, 79.07, 71.09, 67.70, 47.47, 42.26, 31.18; HR-MS (ESI): *m/z* = 267.0988, calcd. for $C_{12}H_{15}N_2O_5$ $[M + H]^+$: 267.0981; HPLC (Daicel Chiralpak AS-H, *i*-PrOH:hexane = 20:80, flow rate = 1.0 mL/min, λ = 254 nm): t_{major} = 81.31 min, t_{minor} = 70.13 min, *ee* = 98%; $[\alpha]_D^{25}$ +25.6º (c = 0.14 in $CHCl_3$).

(*S*)-3-((*R*)-1-(2-Methoxyphenyl)-2-nitroethyl)tetrahydrofuran (11d, Table 2, entry 4)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (t, *J* = 6.6 Hz, 1H), 7.11 (d, *J* = 7.2 Hz 1H), 6.94-6.88 (m, 2H), 4.84 (dd, *J* = 7.5, 10.8 Hz, 1H), 4.53 (dd, *J* = 7.2, 11.1 Hz, 1H), 4.00 (t, *J* = 7.5 Hz, 1H), 3.85 (s, 3H), 3.83-3.78 (m, 1H), 3.74-3.64 (m, 2H), 3.53 (t, *J* = 8.0 Hz, 1H), 2.81-2.78 (m, 1H), 1.76-1.72 (m, 1H), 1.49-1.44 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.24, 129.66, 128.90, 126.47, 120.82, 111.06, 78.44, 71.64, 67.75, 55.39, 43.67, 40.98, 31.20; HR-MS (ESI): *m/z* = 252.1219, calcd. for $C_{13}H_{18}NO_4$ $[M + H]^+$: 252.1236; HPLC (Daicel Chiralpak AS-H, *i*-PrOH:hexane = 10:90, flow rate = 1.0 mL:min, λ = 254 nm): t_{major} = 17.42 min, t_{minor} = 16.45 min, *ee* = 98%; $[\alpha]_D^{25}$ +44.7º (c = 0.15 in $CHCl_3$).

(*S*)-3-((*R*)-1-(3-Methoxyphenyl)-2-nitroethyl)tetrahydrofuran (11e, Table 2, entry 5)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.9 Hz, 1H), 6.83-6.78 (m, 2H), 6.73 (s, 1H), 4.67-4.50 (m, 2H), 4.00 (t, *J* = 7.8 Hz, 1H), 3.88-3.82 (m, 1H), 3.81 (s, 3H), 3.75-3.67 (m, 1H), 3.55 (t, *J* = 8.1 Hz, 1H), 3.38-3.30 (m, 1H), 2.59-2.50 (m, 1H), 1.81-1.75 (m, 1H), 1.55-1.48 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.86, 140.28, 130.03, 119.85, 113.99, 112.63, 79.79, 71.21, 67.74, 55.21, 47.73, 42.65, 31.29; HR-MS (ESI): *m/z* = 252.1229, calcd. for $C_{13}H_{18}NO_4$ $[M + H]^+$: 252.1236; HPLC (Daicel Chiralpak AS-H, *i*-PrOH:hexane = 10:90, flow rate = 1.0 mL/min, λ = 254 nm): t_{major} = 43.10 min, t_{minor} = 30.87 min, *ee* = 99%; $[\alpha]_D^{25}$ +5.8º (c = 0.18 in $CHCl_3$).

(*S*)-3-((*R*)-1-(4-Methoxyphenyl)-2-nitroethyl)tetrahydrofuran (11f , Table 2, entry 6)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.64-4.52 (m, 2H), 4.00 (t, *J* = 7.8 Hz, 1H), 3.88-3.83 (m, 1H), 3.81 (s, 3H), 3.76-3.68 (m, 1H),

3.56 (t, J = 8.1 Hz, 1H), 3.38-3.29 (m, 1H), 2.59-2.50 (m, 1H), 1.81-1.77 (m, 1H), 1.54-1.44 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.05, 130.55, 128.68, 114.31, 80.07, 71.26, 67.75, 55.22, 47.04, 42.75, 31.30; HR-MS (ESI): m/z = 252.1225, calcd. for $C_{13}H_{18}NO_4$ $[M + H]^+$: 252.1236; HPLC (Daicel Chiralpak OD-H, i-PrOH:hexane = 10:90, flow rate = 1.0 mL/min, λ = 254 nm): t_{major} = 39.58 min, t_{minor} = 45.89 min, ee = 90%; $[\alpha]_D^{25}$ +80.3º (c = 0.10 in $CHCl_3$).

4-((*R*)-2-nitro-1-((*S*)-Tetrahydrofuran-3-yl)ethyl)benzonitrile (11g, Table 2, entry 7)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.6 Hz, 2H), 7.37 (d, J = 7.6 Hz, 2H), 4.69-4.56 (m, 2H), 4.11 (t, J = 7.8 Hz, 1H), 3.96-3.92 (m, 1H), 3.82-3.76 (m, 1H), 3.66 (t, J = 10.4 Hz, 1H), 3.49-3.43 (m, 1H), 2.66-2.59 (m, 1H), 1.80-1.76 (m, 1H), 1.54-1.48 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.23, 132.84, 128.62, 118.33, 111.96, 79.09 , 71.09, 67.70, 47.70, 42.22, 31.20; HR-MS (ESI): m/z = 247.1088, calcd. for $C_{13}H_{15}N_2O_3$ $[M + H]^+$: 247.1083; HPLC (Daicel Chiralpak AS-H, i-PrOH:hexane = 20:80, flow rate = 1.0 mL/min, λ = 280 nm): t_{major} = 23.63 min, t_{minor} = 22.27 min, ee = 94%; $[\alpha]_D^{25}$ +72.9º (c = 0.18 in $CHCl_3$).

(*S*)-3-((*R*)-2-Nitro-1-phenylethyl)tetrahydrofuran (11h, Table 2, entry 8)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 3H), 7.20 (d, J = 6.6 Hz, 2H), 4.66-4.52 (m, 2H), 4.00 (t, J = 7.8 Hz, 1H), 3.84-3.80 (m, 1H), 3.73-3.69 (m, 1H), 3.55 (t, J = 8.0 Hz, 1H), 3.39-3.34 (m, 1H), 2.59-2.54 (m, 1H), 1.76-1.73 (m, 1H), 1.52-1.47 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.67, 129.00, 127.89, 127.68, 79.86, 71.24, 67.75, 47.75 , 42.68, 31.32; HR-MS (ESI): m/z = 222.1133, calcd. for $C_{12}H_{16}NO_3$ $[M + H]^+$: 222.1130; HPLC (Daicel Chiralpak AS-H, i-PrOH:hexane = 10:90, flow rate = 1.0 mL/min, λ = 254 nm): t_{major} = 18.11 min, t_{minor} = 15.89 min, ee = 98%; $[\alpha]_D^{25}$ +30.7º (c = 0.13 in $CHCl_3$).

(*S*)-3-((*R*)-1-(2-Bromophenyl)-2-nitroethyl)tetrahydrofuran (11i, Table 2, entry 9)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.0 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.25 (d, J = 7.2 Hz, 1H), 7.15 (t, J = 7.2 Hz, 1H), 4.70-4.68 (m, 1H), 4.59 (dd, J = 7.2, 14.0 Hz, 1H), 4.06-3.98 (m, 2H), 3.89-3.84 (m, 1H), 3.73 (t, J = 8.0 Hz, 1H), 3.60 (t, J = 7.6 Hz, 1H), 2.72-2.66 (m, 1H), 1.81-1.74 (m, 1H), 1.60-1.56 (m, 1H); ^{13}C NMR (101 MHz,

$CDCl_3$) δ 137.95, 133.65, 129.22, 128.07, 78.56, 71.11, 67.76, 45.24, 42.33, 30.79; HR-MS (ESI): *m/z* = 300.0219, calcd. for $C_{12}H_{15}BrNO_3$ $[M + H]^+$: 300.0235; HPLC (Daicel Chiralpak IC, *i*-PrOH:hexane = 10:90, flow rate = 1.0 mL/min, λ = 254 nm): t_{major} = 28.34 min, t_{minor} = 43.82 min, *ee* = 97%; $[\alpha]_D^{25}$ +46.9º (c = 0.16 in $CHCl_3$).

(*S*)-3-((*R*)-1-(3-Fluorophenyl)-2-nitroethyl)tetrahydrofuran (11j, Table 2, entry 10)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (m, 1H), 7.01-6.97 (m, 2H), 6.93 (d, *J* = 9.5 Hz, 1H), 4.65-4.52 (m, 2H), 3.99 (t, *J* = 8.0 Hz, 1H), 3.86-3.81 (m, 1H), 3.74-3.68 (m, 1H), 3.56 (t, *J* = 8 Hz, 1H), 3.38-3.36 (m, 1H), 2.56-2.52 (m, 1H), 1.78-1.75 (m, 1H), 1.52-1.47 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.58 , 161.31 , 141.27, 141.18, 130.68, 130.57, 123.48, 123.45, 115.10, 114.82, 114.50, 79.54, 71.14, 67.72, 47.45, 42.52, 31.25; HR-MS (ESI): *m/z* = 240.1043, calcd. for $C_{12}H_{15}FNO_3$ $[M + H]^+$: 240.1036; HPLC (Daicel Chiralpak AS-H, *i*-PrOH:hexane = 10:90, flow rate = 1.0 mL/min, λ = 220 nm): t_{major} = 27.78 min, t_{minor} = 23.37 min, *ee* = 98%; $[\alpha]_D^{25}$ +45.1º (c = 0.20 in $CHCl_3$).

(*S*)-3-((*R*)-1-(4-Bromophenyl)-2-nitroethyl)tetrahydrofuran (11k, Table 2, entry 11)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.9 Hz, 2H), 7.09 (d, *J* = 7.8 Hz, 2H), 4.62-4.51 (m, 2H), 3.98 (t, *J* = 8.0 Hz, 1H), 3.83-3.80 (m, 1H), 3.71-3.69 (m, 1H), 3.54 (t, *J*= 8.0 Hz, 1H), 3.34-3.32 (m, 1H), 2.56-2.46 (m, 1H), 1.80-1.68 (m, 1H), 1.50-1.41 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.76, 132.21, 129.40, 121.87, 79.55, 71.18, 67.73, 47.25, 42.50 , 31.29; HR-MS (ESI): *m/z* = 300.0231, calcd. for $C_{12}H_{15}BrNO_3$ $[M + H]^+$: 300.0235; HPLC (Daicel Chiralpak AS-H, *i*-PrOH:hexane = 10:90, flow rate = 1.0 mL/min, λ = 254 nm): t_{major} = 18.73 min, t_{minor} = 16.32 min, *ee* = 92%.

(*S*)-3-((*R*)-1-(4-Chlorophenyl)-2-nitroethyl)tetrahydrofuran (11l, Table 2, entry 12)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 4.65-4.54 (m, 2H), 4.01 (t, *J* = 8.1 Hz, 1H), 3.87-3.81 (m, 1H), 3.76-3.68 (m, 1H), 3.57 (t, *J* = 8.0 Hz, 1H), 3.41-3.33 (m, 1H), 2.58-2.49 (m, 1H), 1.80-1.74 (m, 1H), 1.49-1.44 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.17, 133.75, 129.23, 129.02, 79.61, 71.17, 67.72, 47.18, 42.52, 31.27; HR-MS (ESI): *m/z* = 256.0742, calcd. for $C_{12}H_{15}ClNO_3$ $[M + H]^+$: 256.0740; HPLC (Daicel Chiralpak IC, *i*-PrOH:hexane = 10:90, flow rate = 1.0 mL/min,

λ = 254 nm): t_{major} = 54.31min, t_{minor} = 71.07min, *ee* = 99%; $[\alpha]_D^{25}$ +36.9º (c = 0.17 in $CHCl_3$).

(*S*)-3-((*R*)-1-(Naphthalen-1-yl)-2-nitroethyl)tetrahydrofuran (11m, Table 2, entry 13)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J*= 8.1 Hz, 1H), 7.89 (d, *J*= 8.1 Hz, 1H), 7.81 (d, *J*= 8.0 Hz, 1H), 7.59 (t, *J*= 7.6 Hz, 1H), 7.57-7.47 (m, 2H), 7.43 (d, *J*= 6.8 Hz, 1H), 4.79-4.70 (m, 1H), 4.45-4.43 (m, 1H), 4.04 (t, *J* = 8 Hz, 1H), 3.82 (m, 1H), 3.72-3.65 (m, 2H), 2.79 (m, 1H), 1.81-1.79 (m, 1H), 1.48-1.45 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.14, 133.01, 128.17, 127.29, 125.77, 124.95, 124.33, 122.75, 121.25, 78.64, 70.19, 66.71, 42.54, 39.55, 30.10; HR-MS (ESI): *m/z* = 272.1281, calcd. for $C_{16}H_{18}NO_3$ $[M + H]^+$: 272.1287; HPLC (Daicel Chiralpak AS-H, *i*-PrOH:hexane = 10:90, flow rate = 1.0 mL/min, λ = 254 nm): t_{major} = 20.89min, t_{minor} = 19.96min, *ee* = 98%; $[\alpha]_D^{25}$ +12.7º (c = 0.11 in $CHCl_3$).

2-((*S*)-2-nitro-1-((*S*)-Tetrahydrofuran-3-yl)ethyl)furan (11n, Table 2, entry 14)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 0.9 Hz, 1H), 6.31 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.18 (d, *J* = 3.1 Hz, 1H), 4.69-4.65 (m, 1H), 4.52 (dd, *J* = 12.6, 5.4 Hz,1H), 3.92 (t, *J* = 8.4 Hz, 1H), 3.82-3.68 (m, 2H), 3.62-3.52 (m, 2H), 2.63-2.55 (m, 1H), 1.96-1.90 (m, 1H), 1.68-1.61 (m, 1H). ^{13}C NMR (75 MHz, DMSO) δ 145.50, 136.71, 104.54, 102.40, 71.55, 65.04, 62.04, 34.96, 34.84, 24.37; HR-MS (ESI): *m/z* = 212.0911, calcd. for $C_{10}H_{14}NO_4$ $[M + H]^+$: 212.0923; HPLC (Daicel Chiralpak IC, *i*-PrOH:hexane = 10:90, flow rate = 1.0 mL/min, λ = 220 nm): t_{major} = 44.92 min, t_{minor} = 63.42 min, *ee* = 84%; $[\alpha]_D^{25}$ +104.7º (c = 0.20 in $CHCl_3$).

(*S*)-3-((*S*)-1-Nitrobutan-2-yl)tetrahydrofuran (11o, Table 2, entry 15)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42-4.33 (m, 2H), 3.95-3.88 (m, 2H), 3.77-3.71 (m, 1H), 3.45 (t, *J* = 8.1 Hz, 1H), 2.29-2.24 (m, 1H), 2.15-2.06 (m, 2H), 1.65-1.62 (m, 1H), 1.61-1.54 (m, 1H), 1.49-1.42 (m, 1H), 0.97 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 76.55, 69.91, 67.10, 41.10, 39.43, 29.13 , 21.75, 9.31; HR-MS (ESI): *m/z* = 174.1134, calcd. for $C_8H_{16}NO_3$ $[M + H]^+$: 174.1130; HPLC (Daicel Chiralpak IC, *i*-PrOH:hexane =

10:90, flow rate = 1.0 mL/min, λ = 220 nm): t_{major} = 25.53 min, t_{minor} = 39.43 min, *ee* = 96%; $[\alpha]_D^{25}$ +23.1º (c = 0.15 in $CHCl_3$).

(*S*)-3-((*R*)-3-Methyl-1-nitrobutan-2-yl)tetrahydrofuran (11p, Table 2, entry 16)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.38 (dd, *J* = 12.9, 6.3 Hz,1H), 4.21 (dd, *J* = 13.2, 5.7 Hz,1H), 3.90-3.84 (m, 2H), 3.75-3.67 (m, 1H), 3.34 (t, *J* = 8.4 Hz, 1H), 2.40-2.19 (m, 2H), 2.10-2.08 (m, 1H), 1.96-1.92 (m, 1H), 1.69-1.59 (m, 1H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.04, 69.72, 66.72, 45.15, 39.69, 30.32, 28.45, 19.08, 16.59; HR-MS (ESI): *m/z* = 188.1297, calcd. for $C_9H_{18}NO_3$ $[M + H]^+$: 188.1287; HPLC (Daicel Chiralpak IC, *i*-PrOH:hexane = 10:90, flow rate = 1.0 mL/min, λ = 220 nm): t_{major} = 21.79 min, t_{minor} = 33.29 min, *ee* = 96%; $[\alpha]_D^{25}$ +9.2º (c = 0.12 in $CHCl_3$).

(*S*)-3-((*R*)-2-Nitro-1-(3-nitrophenyl)ethyl)tetrahydro-2*H*-pyran (11q, Table 2, entry 17)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14-8.12 (m, 1H), 8.05 (s, 1H), 7.53-7,51 (m, 2H), 4.79-4.64 (m, 2H), 3.96 (d, *J* = 11.1 Hz, 1H), 3.80 (d, *J* = 11.4 Hz, 1H), 3.51-4.49 (m, 1H), 3.48-3.26 (m, 2H), 2.02-1.90 (m, 1H), 1.56-1.47 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.46, 140.10, 134.42, 129.97, 122.94, 122.86, 76.69, 70.66, 68.29 , 45.78, 38.36, 27.40, 24.88; HR-MS (ESI): *m/z* = 281.1129, calcd. for $C_{13}H_{17}N_2O_5$ $[M + H]^+$: 281.1137; HPLC (Daicel Chiralpak OD-H, *i*-PrOH:hexane = 10:90, flow rate = 1.0 mL/min, λ = 254 nm): t_{major} = 61.54 min, t_{minor} = 49.03 min, *ee* = 92%; $[\alpha]_D^{25}$ +2.9º (c = 0.16 in $CHCl_3$).

Procedure for the synthesis of compounds 13-16

(2*R*,3*R*)-2-Allyl-3-((*R*)-2-nitro-1-(3-nitrophenyl)ethyl)tetrahydrofuran (13)

A solution of **10a** (166 mg, 0.59 mmol) and allyltrimethylsilane **12** (202 mg, 1.77 mmol, 3 eq) in MeCN (4 mL) was stirred at -45 ºC for 10 min before a solution of $BF_3{\cdot}Et_2O$ (251 mg, 1.77 mmol, 3 eq) in MeCN (1 mL) was added within 10 min. The reaction was allowed to warm to rt over a period of 2 h. The solvent was removed under vacuum and the crude product was purified by column chromatography on silica gel to afford the desired product **13** (76 mg, 42% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18-8.14 (m, 1H),

8.08 (s, 1H), 7.59-7.53 (m, 2H), 5.88-5.79 (m, 1H), 5.19 (d, J = 6.2 Hz, 1H), 4.74-4.62 (m, 2H), 3.86-3.69 (m, 3H), 3.65-3.57 (m, 1H), 2.37-2.25 (m, 3H), 1.89-1.82 (m, 1H), 1.54-1.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.52, 140.38, 134.57, 133.89, 130.06, 123.10, 122.69, 118.29, 81.20 , 78.97, 66.52 , 46.63, 45.71, 39.66, 30.56; HR-MS (ESI): *m/z* = 307.1303, calcd. for $C_{15}H_{19}N_2O_5$ $[M + H]^+$: 307.1294; HPLC (Daicel Chiralpak AS-H, *i*-PrOH:hexane = 10:90, flow rate = 1.0 mL/min, λ = 254 nm): t_{major} = 36.70 min, t_{minor} = 25.26 min, *ee* = 96%; $[\alpha]_D^{25}$ +40.0º (c = 0.18 in $CHCl_3$).

(*R*)-3-((*R*)-2-Nitro-1-(3-nitrophenyl)ethyl)dihydrofuran-2(3*H*)-one (14)

To a solution of **10a** (96 mg, 0.34 mmol) in CH_2Cl_2 (5 mL) was added silica gel (0.8 g) and pyridinium chlorochromate (146 mg, 0.68 mmol, 2 eq). The reaction mixture was stirred at rt for 5 h and then filtered and washed with CH_2Cl_2 (10 mL). The solvent was removed under vacuum and the crude product was purified by column chromatography on silica gel to afford the desired product **14** (39 mg, 41% yield).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J = 7.2 Hz, 1H), 8.15 (s, 1H), 7.66 -7.58 (m, 2H), 5.56 (dd, J = 13.2, 4.8 Hz,1H), 4.88 (dd, J = 13.5, 10.2 Hz,1H), 4.40-4.33 (m, 1H), 4.27-4.20 (m, 1H), 3.97-3.92 (m, 1H), 3.04-2.97 (m, 1H), 2.16-2.07 (m, 1H), 1.98-1.91 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.99, 148.63, 139.04, 134.52, 130.44, 123.58, 122.50, 66.32, 44.01 , 41.07 , 27.86; HR-MS (ESI): *m/z* = 281.0772, calcd. for $C_{12}H_{13}N_2O_6$ $[M + H]^+$: 281.0774; HPLC (Daicel Chiralpak IC, THF:hexane =20:80, flow rate = 1.0 mL/min, λ = 254 nm): t_{major} = 23.17 min, t_{minor} = 27.51 min, *ee* = 95%.

2-(4-Methoxyphenyl)-2-(tetrahydrofuran-3-yl)ethanamine (15)

To a solution of **11f** (120 mg, 0.48 mmol) in MeOH (5 mL) was added $NiCl_2 \cdot 6H_2O$ (228 mg, 0.96 mmol, 2 eq). The mixture was stirred at rt for 5 min before $NaBH_4$ (182 mg, 4.8 mmol, 10 eq) was added in some portions within 15 min. The reaction was then stirred at rt for another 30 min, water (5 mL) was added to quench the reaction. The mixture was added CH_2Cl_2 (2 mL), filtered through celite and the filtrate was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and the crude product was purified by column chromatography on silica gel to afford the desired product **15** (86 mg, 81% yield). ^{1}H NMR (400 MHz,

CDCl3) δ 7.09 (d, *J* = 8.1 Hz, 2H), 6.85 (d, *J* = 7.7 Hz, 2H), 4.02 (t, *J* = 7.1 Hz, 1H), 3.82-3.72 (m, 4H), 3.67-3.61 (m, 1H), 3.53-3.46 (m, 1H), 2.82 (s, 2H), 2.41-2.36 (m, 2H), 1.67-1.62 (m, 1H), 1.41-1.36 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.33, 134.14, 129.04, 114.03, 77.51, 77.09, 76.66, 72.16, 67.78, 55.21, 52.64, 46.94, 43.45, 31.65.

2-(4-Methoxyphenyl)-*N*,*N*-dimethyl-2-(tetrahydrofuran-3-yl)ethanamine (16)

To a solution of **15** (106 mg, 0.48 mmol) in THF (5 mL) was added 37% aqueous HCHO (195 mg, 2.4 mmol, 5 eq). The solution was stirred at rt for 10 min and $NaBH(OAc)_3$ (305 mg, 1.44 mmol, 3 eq) was added. After 2 h, TLC monitored the complete conversion of **15**, and water (10 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3×10 mL), the combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and the crude product was purified by column chromatography on silica gel to afford the desired product **16** (65 mg, 54% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 4.00 (t, *J* = 7.9 Hz, 1H), 3.72 (s, 3H), 3.70-3.67 (m, 1H), 3.59-3.53 (m, 1H), 3.43 (t, *J* = 8.5 Hz, 1H), 2.60-2.46 (m, 2H), 2.36-2.20 (m, 2H), 2.08 (s, 6H), 1.56-1.50 (m, 1H), 1.39-1.31 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.03, 135.50, 128.55, 113.86, 72.33, 67.58, 65.41, 55.13, 47.04, 45.92, 45.05, 31.63; HR-MS (ESI): *m/z* = 250.1792, calcd. for $C_{15}H_{24}NO_2$ $[M + H]^+$: 250.1807.

Acknowledgements

The work was supported by National Natural Science Foundation of China (Grant No.21202112), Ph.D. Programs Foundation of Ministry of Education of China (20123201120019) and PAPD (A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions).

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