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PALLADIUM-CATALYZED ASYMMETRIC HALOIMINOLACTONIZATION OF α-ALLYLMALONAMIDES

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Abstract – A catalyst composed of 10 mol% of $Pd(OAc)_2$ and (*R*,*R*)-PhBox was proven to be effective in the asymmetric haloiminolactonization of α-allylmalonamides with *N*-halosuccinimides, giving the dihalogenated cyclic products with good diastereomeric ratio (up to 89/11) and enantiomeric excess (up to 72% ee).

INTRODUCTION

Halolactonization has been known as a powerful synthetic method, which realizes the efficient functionalization of unsaturated carbon-carbon bonds.[1] The resulting halolactones are useful building blocks in organic synthesis and medicinal chemistry.[2] Recently, asymmetric halolactonization reactions with organocatalysts have gained much attention because of their remarkable regio- and stereo-selectivities.[3,4] On the other hand, a chiral copper-catalyzed asymmetric iodoiminolactonization has been developed as a promising process,[5] while transition metal-catalyzed enantioselective halolactonization has been pursued with cobalt, nickel, zinc, palladium, and gold catalysts.[6] However, no metal-catalyzed method with successful control of both enantio- and diastereo-selectivities has been reported. Herein, we will describe a palladium-catalyzed asymmetric haloiminolactonization of α-allylmalonamides to afford precursors for optically active γ-butyrolactone derivatives.

RESULTS AND DISCUSSION

The asymmetric bromoiminolactonization reactions of α-allylmalonamide **1a** using a series of transition metals with (*R*,*R*)-PhBox (i.e. (*R*,*R*)-2,2'-isopropylidenebis(4-phenyl-2-oxazoline))[7,8] in the presence of *N*-bromosuccinimide (NBS) were examined in toluene at room temperature (Table 1). The chiral catalysts generated from Cu(II), Co(II), and Pt(II) with (*R*,*R*)-PhBox promoted the reaction to give the cyclized products **2a** and **2a'** with high yields and high diastereoselectivities, but quite low enantioselectivities

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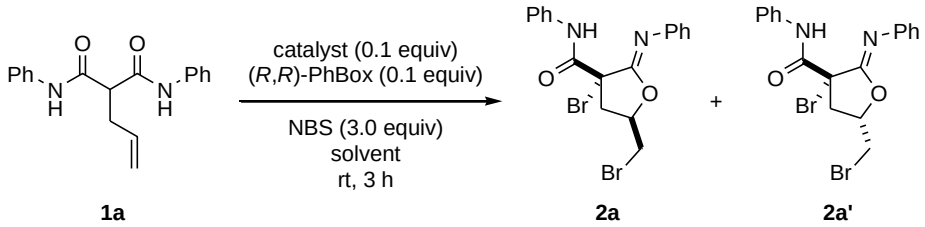
Dedicated with respect to Dr. Kiyoshi Tomioka on the occasion of his 70th birthday

were observed (entries 1-3). While $PdCl_2$ led to 14% ee in **2a** and 0% ee in **2a'** (entry 4), the reactions using $Pd(OAc)_2$ and $Pd(OCOCF_3)_2$ gave **2a** with 49% ee and 46% ee, respectively (entries 5 and 6). In a control experiment, the absence of chiral transition-metal catalysts decreased a yield dramatically and **1a** was obtained in a good recovery efficiency (entry 7), which suggested that metal catalysts might promote this transformation as Lewis acids. Investigation into the influence of solvents proved that aromatic solvents gave the excellent results in terms of yields, and diethyl ether increased enantioselectivities leading to 64% ee in **2a** and 60% ee in **2a'** (entries 8-15). Therefore, we examined the effect caused by combinations of solvents. The bromoiminolactonization with use of a mixture of toluene/Et_2O (1/1) proceeded almost quantitatively with 72% ee for **2a** (entry 16). When NBS (1 equiv) was applied to this reaction, **2a** was obtained in 40% yield with 60% ee, in which **1a** was recovered in 51% yield. Then, considerable reduction in yields and selectivities was observed at 0 ºC, giving **2a** in only 9% yield.

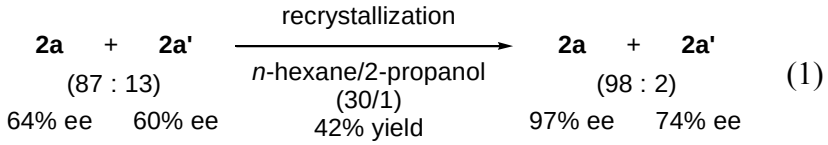
Table 1. Asymmetric bromoiminolactonization using NBS under various reaction conditions [a]



entry	catalyst	solvent	yield (%) of **2a**+**2a'**	dr **2a**/**2a'**	ee (%) **2a**/**2a'**
1	$Cu(OTf)_2$	toluene	97	82/18	5/0
2	$CoCl_2$	toluene	96	87/13	13/6
3	$PtCl_2$	toluene	80	88/12	0/0
4	$PdCl_2$	toluene	96	85/15	14/0
5	$Pd(OAc)_2$	toluene	94	89/11	49/52
6	$Pd(OCOCF_3)_2$	toluene	96	87/13	46/44
7	none	toluene	35	80/20	0/0
8	$Pd(OAc)_2$	benzene	98	85/15	49/37
9	$Pd(OAc)_2$	xylene	90	84/16	31/26
10	$Pd(OAc)_2$	chlorobenzene	91	83/17	20/7
11	$Pd(OAc)_2$	CH_2Cl_2	87	73/27	2/20
12	$Pd(OAc)_2$	Et_2O	75	87/13	64/60
13	$Pd(OAc)_2$	THF	52	77/23	10/27
14	$Pd(OAc)_2$	AcOEt	46	79/21	17/39
15	$Pd(OAc)_2$	MeCN	32	80/20	0/43
16	$Pd(OAc)_2$	toluene/Et_2O (1/1)	98	89/11	72/44

[a] Reaction conditions: **1a** (0.3 mmol), catalyst (0.03 mmol), (*R*,*R*)-PhBox (0.03 mmol), NBS (0.9 mmol), solvent (5 mL), rt.

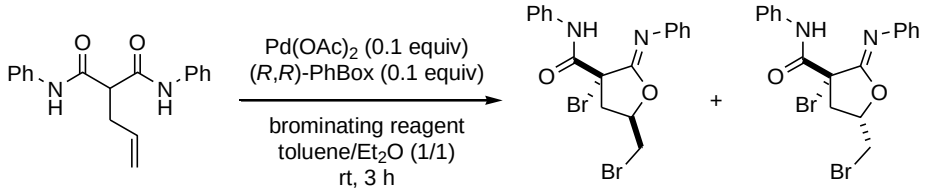
While the enantioselectivity of **2a** was up to 72% ee, improvement for optical purity of **2a** was accomplished by recrystallization of optically active **2a** (64% ee) from a mixture of *n*-hexane and 2-propanol (30/1) (Eq. 1).

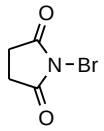
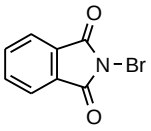
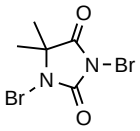


(1)

The influence of varying brominating reagents in the asymmetric bromoiminolactonization under the optimized reaction conditions was investigated (Table 2). All brominating reagents except bromine promoted reactions efficiently with good diastereoselectivities, but *N*-bromophthalimide and 1,3-dibromo-5,5-dimethylhydantoin showed moderate enantioselectivities (entries 1-3). Bromine was too reactive and gave a complex mixture (entry 4). On the other hand, *N*-chlorosuccinimide (NCS) did not promote the chloroiminolactonization and *N*-iodosuccinimide (NIS) afforded a complex mixture.

Table 2. Influence of brominating reagents in asymmetric bromoiminolactonization [a]

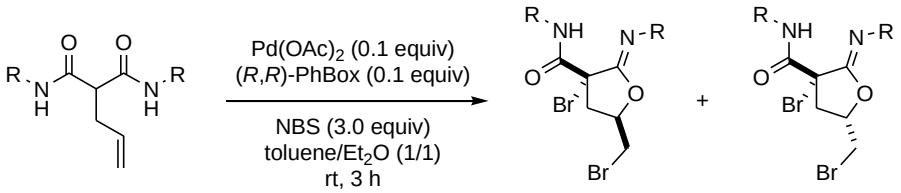


entry	brominating reagent	yield (%) of **2a**+**2a'**	dr **2a**/**2a'**	ee (%) **2a**/**2a'**
1		98	89/11	72/44
2[b]		82	87/13	46/30
3		90	84/16	42/42
4	Br_2	complex mixture	-	-

[a] Reaction conditions: **1a** (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), (*R*,*R*)-PhBox (0.03 mmol), brominating reagent (0.9 mmol), toluene/Et_2O (2.5 mL/2.5 mL), rt, 3 h. [b] The reaction was carried out for 12 h.

Effects of *N*-substituents of α-allylmalonamides on the asymmetric bromoiminolactonization were also investigated (Table 3). The α-allylmalonamides substituted with aryl groups bearing electron-donating and electron-withdrawing groups on nitrogen atoms (**1b** and **1c**) led to high yields and diastereomeric ratios but gave 61% ee and 63% ee in **2b** and **2c**, respectively (entries 2 and 3). While the reaction using the substrate with benzyl group on nitrogen atoms afforded lower diastereoselectivities and moderate enantioselectivities, the substrate with *n*-octyl groups on nitrogen atoms gave the diastereomeric ratio of 95/5 but only 30% ee in **2e** (entries 4 and 5).

Table 3. Influence of substituents on nitrogen atoms in substrates **1a-e** [a]

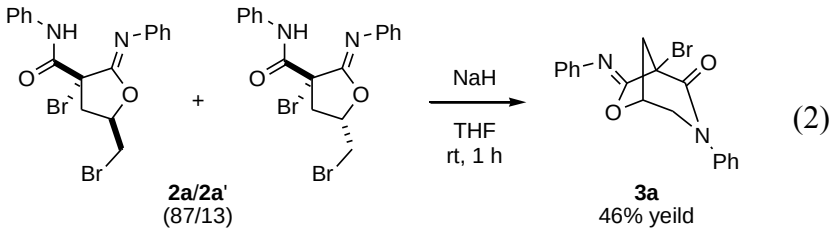


1a-e **2a-e** **2a'-e'**

entry	R	yield (%) of **2**+**2'**	dr **2**/**2'**	ee (%) **2**/**2'**
1	Ph (**1a**)	98	89/11	72/44
2	*p*-tolyl (**1b**)	96	86/14	61/41
3	*p*-Cl-Ph **(1c**)	93	90/10	63/46
4	benzyl (**1d**)	88	76/24	45/53
5	*n*-octyl (**1e**)	86	95/5	30/41

[a] Reaction conditions: **1a-e** (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), (*R*,*R*)-PhBox (0.03 mmol), NBS (0.9 mmol), toluene/Et_2O (2.5 mL/2.5 mL), rt, 3 h.

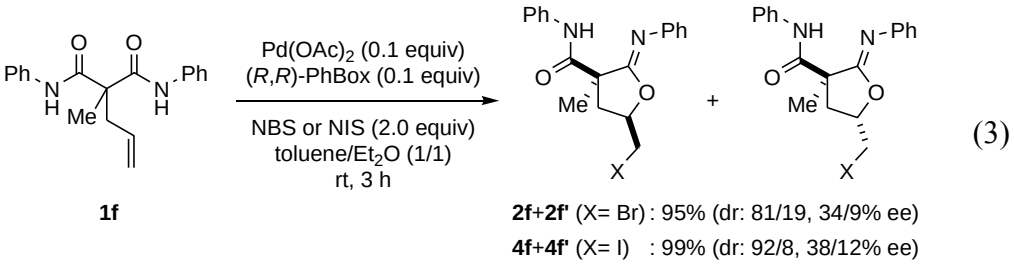
The mixture of **2a** and **2a'** was then treated with sodium hydride in THF at room temperature, giving the bicyclo[3.2.1] compound **3a** with 46% yield (Eq. 2). Thus, it was revealed that the major diastereomer **2a** has *cis*-configuration between 3-*N*-phenylcarbamoyl and 5-bromomethyl groups.



2a/**2a'** (87/13) **3a** 46% yeild (2)

The haloiminolactonization was applicable to α-allyl-α-methylmalonamide **1f** to afford cyclized products **2f** and **4f** under the similar reaction conditions in high diastereoselectivities with moderate enantio-selectivities (Eq. 3). After purification with recrystallization of a mixture of **4f** and **4f'** to obtain the

optically pure sample of **4f**, the absolute stereoconfiguration of **4f** was determined by X-ray analysis (Figure 1).[9,10]



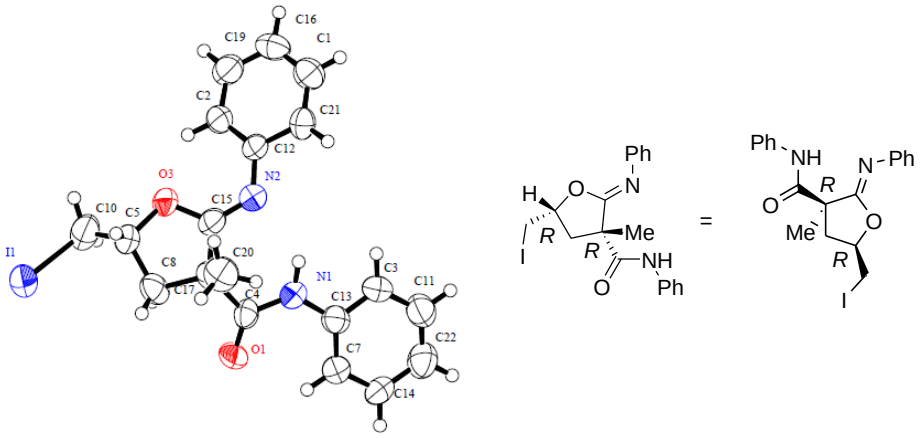


Figure 1. ORTEP drawing of **4f**

In summary, we found that the (*R*,*R*)-PhBox-Pd(II) complex catalyzed the asymmetric haloimino-lactonization of α-allylmalonamides to give the cyclized products with good enantio- and diastereo-selectivities in excellent yields. Further efforts are focused on mechanistic investigation and synthetic application to biologically active agents in our laboratory.

EXPERIMENTAL

General. All melting points are not corrected. IR spectra were expressed in cm^{-1}. ^1H NMR spectra were measured at 300 and 400 MHz, and ^{13}C NMR spectra were taken at 100 MHz. Chemical shift values are expressed in ppm relative to internal or external TMS. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded using electron ionization (EI) mass spectrometry or fast atom bombardment (FAB) mass spectrometry. The products were isolated by silica gel column chromatography. All reagents and solvents were used as received without further purification.

Typical Synthetic Procedure of α-Allylmalonamides (1a-f)

The mixture of diethyl malonate (9.61 g, 60 mmol) and aniline (11.18 g, 120 mmol) was stirred at 200 °C for 9 h to give a white precipitate, and it was filtered and washed with CH_2Cl_2 to give *N*,*N'*-diphenyl-malonamide as a white solid with 50% yield (7.63 g).

N,*N'*-Diphenylmalonamide (7.63 g, 30 mmol) and sodium hydroxide (4.8 g, 120 mmol) in the mixture of 100 mL of THF and 100 mL of water were stirred at room temperature for 30 min, and then, allyl bromide (10.89 g, 90 mmol) in 50 mL of THF was added over 1 h and stirred for 6 h. The resulting mixture was filtered to remove remaining *N*,*N'*-diphenylmalonamide. The filtrate was evaporated to remove THF and extracted with AcOEt. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was recrystallized from $CHCl_3$ to give *N*,*N'*-diphenyl-α-allylmalonamide (**1a**) in 24% yield (2.12 g).

***N*,*N'*-Diphenyl-α-allylmalonamide (1a).** White solids of mp 190-193 °C. IR (neat): 3281, 3138, 2924, 1674, 1618, 1545, 1498, 1442, 1354, 1313, 1257, 1244, 1175, 1078, 970, 918, 906, 750, 690, 642 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.83 (t, *J* = 7.5 Hz, 2H), 3,41 (t, *J* = 7.5 Hz, 1H), 5.12 (d, *J* = 8.4 Hz, 1H), 5.22 (d, *J* = 16.5 Hz, 1H), 5.81-5.91 (m, 1H), 7.15 (t, *J* = 8.2 Hz, 2H), 7.34 (t, *J* = 8.2 Hz, 4H), 7.55 (d, *J* = 8.2 Hz, 4H), 8.74 (brs, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 37.4, 56.2, 118.7, 120.4, 124.9, 129.0, 133.4, 137.2, 168.7. HRMS (FAB): *m/z* calcd for $C_{18}H_{19}N_2O_2$ $[M+H]^+$ 295.1446, found 295.1421.

***N*,*N'*-Di(4-methylphenyl)-α-allylmalonamide (1b).** White solids of mp 192-195 °C. IR (neat): 3285, 3202, 3130, 3076, 2920, 1896, 1672, 1607, 1534, 1512, 1449, 1406, 1354, 1311, 1296, 1244, 1171, 1122, 1038, 1018, 991, 920, 816, 746, 640 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.32 (s, 6H), 2.80 (t, *J* = 7.2 Hz, 2H), 3.37 (t, *J* = 7.2 Hz, 1H), 5.11 (d, *J* = 10.2 Hz, 1H), 5.20 (d, *J* = 18.6 Hz, 1H), 5.78-5.88 (m, 1H), 7.13 (d, *J* = 8.4 Hz, 4H), 7.42 (d, *J* = 8.4 Hz, 4H), 8.76 (br s, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.9, 37.4, 56.1, 118.5, 120.3, 129.5, 133.5, 134.5, 134.7, 168.6. HRMS (FAB): *m/z* calcd for $C_{20}H_{23}N_2O_2$ $[M+H]^+$ 323.1759, found 323.1755.

***N*,*N'*-Di(4-chlorophenyl)-α-allylmalonamide (1c).** White solids of mp 165-168 °C. IR (neat): 3285, 3200, 3077, 2361, 1680, 1609, 1537, 1493, 1447, 1400, 1302, 1290, 1244, 1175, 1092, 1011, 968, 922, 825 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.81 (t, *J* = 7.2 Hz, 2H), 3.31 (t, *J* = 7.2 Hz, 1H), 5.16 (d, *J* = 10.5 Hz, 1H), 5.23 (d, *J* = 15.6 Hz, 1H), 5.76-5.88 (m, 1H), 7.31 (d, *J* = 8.7 Hz, 4H), 7.48 (d, *J* = 8.7 Hz, 4H), 8.52 (br s, 2H). ^{13}C-NMR (100 MHz, THF-d_8) δ: 37.1, 57.1, 117.7, 121.8, 129.4, 135.4, 138.5, 168.8. HRMS (FAB): *m/z* calcd for $C_{18}H_{17}{}^{35}Cl_2N_2O_2$ $[M+H]^+$ 363.0667, found 363.0648.

***N*,*N'*-Dibenzyl-α-allylmalonamide (1d).** White solids of mp 142-145 °C. IR (neat): 3289, 3065, 2924, 2361, 1663, 1552, 1496, 1454, 1437, 1364, 1259, 1238, 1199, 1126, 1080, 1043, 1030, 991, 918, 736, 694 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.66 (t, *J* = 7.2 Hz, 2H), 3.09 (t, *J* = 7.2 Hz, 1H), 4.38-4.48 (m, 4H), 5.06 (d, *J* = 11.4 Hz, 1H), 5.12 (d, *J* = 16.5 Hz, 1H), 5.67-5.80 (m, 1H), 6.92 (brs, 2H), 7.22- 7.35 (m,

10H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 36.5, 43.5, 54.7, 118.0, 127.5, 128.6, 133.9, 137.7, 170.0. HRMS (FAB): *m/z* calcd for $C_{20}H_{22}N_2O_2$ $[M]^+$ 322.1699, found 322.1679.

***N,N'*-Di(*n*-octyl)-α-allylmalonamide (1e).** White solids of mp 53-55 °C. IR (neat): 3289, 3079, 3003, 2957, 2924, 2872, 2361, 1668, 1653, 1645, 1556, 1527, 1468, 1435, 1377, 1354, 1304, 1289, 1209, 1157, 1070, 993, 972, 914, 723, 644 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, *J* = 6.9 Hz, 6H), 1.27 (s, 20H), 1.48 (t, *J* = 6.9 Hz, 4H), 2.59 (t, *J* = 6.9 Hz, 2H), 2.97 (t, *J* = 6.9 Hz, 1H), 3.19-3.25 (m, 4H), 5.06 (d, *J* = 10.2 Hz, 1H), 5.11 (d, *J* = 18.7 Hz, 1H), 5.66-5.82 (m, 1H), 6.62 (brs, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.6, 26.8, 29.1, 29.2, 29.3, 31.8, 36.7, 39.6, 54.7, 117.6, 134.2, 170.3. HRMS (FAB): *m/z* calcd for $C_{22}H_{43}N_2O_2$ $[M+H]^+$ 367.3324, found 367.3326.

***N,N'*-Diphenyl-α-allyl-α-methylmalonamide (1f).** White solid of mp 167-169 °C. IR (KBr): 3355, 3271, 1678, 1653, 1597, 1534, 1447, 1321, 1258 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.64 (s, 3H), 2.83 (d, *J* = 7.3 Hz, 2H), 5.10-5.30 (m, 2H), 5.75-5.85 (m, 1H), 7.14 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 4H), 7.51 (d, *J* = 7.3 Hz, 4H), 8.67 (brs, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.0, 43.4, 54.2, 119.8, 120.4, 124.9, 124.9, 129.0, 132.9, 137.2, 170.7. HRMS (FAB): *m/z* calcd for $C_{19}H_{21}N_2O_2$ $[M+H]^+$ 309.1603, found 309.1606.

General Procedure of Asymmetric Bromoiminolactonization of α-Allylmalonamides

A round-bottom flask was charged with *N,N'*-diphenyl-α-allylmalonamide (**1a**) (88.3 mg, 0.3 mmol), $Pd(OAc)_2$ (6.73 mg, 0.03 mmol), and (*R,R*)-PhBox (10.0 mg, 0.03 mmol), and then 5 mL of toluene/Et_2O (1/1) was added and stirred at room temperature for 30 min. *N*-Bromosuccinimide (NBS) (160.0 mg, 0.9 mmol) was added, and the mixture was stirred at room temperature for 3 h. To the reaction mixture, 5 mL of saturated sodium thiosulfate solution was added. After extraction with AcOEt, the combined organic layers were washed with saturated sodium bicarbonate solution and successively brine, and then dried over $MgSO_4$. Concentration and purification through silica gel column chromatography (hexane/AcOEt = 3/1) gave the product **2a** and **2a'**.

3-Bromo-5-(bromomethyl)-3-(*N*-phenylcarbamoyl)-2-(*N*-phenylimino)tetrahydrofuran (2a). Pale yellow solids of mp 92-95 °C. $[\alpha]_D^{22.0}$ +49.6 (*c* 0.45, $CHCl_3$, the mixture of **2a**/**2a'** = 89/11). IR (neat): 3194, 3154, 3067, 2926, 1696, 1601, 1559, 1499, 1489, 1449, 1366, 1335, 1265, 1235, 1196, 1078, 1007, 908, 853, 771, 756, 733, 692 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.76 (dd, *J* = 9.9, 15.3 Hz, 1H), 3.02 (dd, *J* = 4.8, 15.3 Hz, 1H), 3.58-3.71 (m, 2H), 4.94-5.01 (m, 1H), 7.09-7.65 (m, 10H), 11.06 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 31.6, 42.1, 69.5, 77.9, 119.8, 123.8, 124.8, 126.0, 128.9, 129.1, 158.4, 163.2. 72% ee (**2a**), 44% ee (**2a'**), HPLC: Daicel Chiralcel OD-H column, hexane/isopropanol = 20/1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 16.2 min, 28.1 min for **2a**, 18.1 min, 22.3 min for **2a'**. HRMS (EI): *m/z* calcd for $C_{18}H_{16}{}^{79}Br^{81}BrN_2O_2$ $[M]^+$ 451.9558, found 451.9568.

3-Bromo-5-(bromomethyl)-3-(*N*-*p*-tolylcarbamoyl)-2-(*N*-*p*-tolylimino)tetrahydrofuran (2b). Brown solids of mp 54-57 °C. $[\alpha]_D^{22.0}$ +38.7 (*c* 0.65, $CHCl_3$, the mixture of **2b**/**2b'** = 86/14). IR (neat): 3121, 3028, 2921, 1696, 1611, 1551, 1508, 1408, 1333, 1319, 1263, 1190, 1007, 910, 858, 823, 814, 733 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.34 (s, 3H), 2.37 (s, 3H), 2.73 (dd, *J* = 9.0, 16.2 Hz, 1H), 3.03 (dd, *J* = 4.8, 16.2 Hz, 1H), 3.64-3.69 (m, 2H), 4.96-5.03 (m, 1H), 7.15-7.54 (m, 8H), 11.03 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.9, 21.1, 31.7, 42.2, 54.6, 77.8, 119.8, 123.9, 129.5, 134.4, 134.9, 135.9, 140.6, 157.8, 163.0. 61% ee (**2b**), 41% ee (**2b'**), HPLC: Daicel Chiralcel OD-H column, hexane/isopropanol = 30/1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 13.4 min, 24.8 min for **2b**, 15.9 min, 22.5 min for **2b'**. HRMS (FAB): *m/z* calcd for $C_{20}H_{21}{}^{79}Br^{81}BrN_2O_2$ $[M+H]^+$ 480.9949, found 480.9940.

3-Bromo-5-(bromomethyl)-3-(*N*-*p*-chlorophenylcarbamoyl)-2-(*N*-*p*-chlorophenylimino)tetrahydrofuran (2c). Yellow solids of mp 55-58 °C. $[\alpha]_D^{22.0}$ +42.6 (*c* 1.5, $CHCl_3$, the mixture of **2c**/**2c'** = 90/10). IR (neat): 3184, 3109, 1769, 1694, 1597, 1545, 1491, 1402, 1335, 1314, 1289, 1260, 1194, 1092, 1011, 910, 829, 730 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.77 (dd, *J* = 9.9, 15.0 Hz, 1H), 3.02 (dd, *J* = 5.1, 15.0 Hz, 1H), 3.60-3.77 (m, 2H), 4.98-5.06 (m, 1H), 7.26-7.59 (m, 8H), 10.91 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 31.4, 41.9, 54.1, 120.8, 120.9, 125.1, 129.0, 125.1, 129.0, 129.1, 129.8, 131.4, 135.8, 141.5, 158.8, 162.9. 63% ee (**2c**), 46% ee (**2c'**), HPLC: Daicel Chiralcel OD-H column, hexane/isopropanol = 20/1, wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 38.4 min, 40.4 min for **2c**, 36.3 min, 51.3 min for **2c'**. HRMS (FAB): *m/z* calcd for $C_{18}H_{15}{}^{79}Br^{81}Br^{35}ClN_2O_2$ $[M+H]^+$ 520.8857, found 520.8820.

3-Bromo-5-(bromomethyl)-3-(*N*-benzylcarbamoyl)-2-(*N*-benzylimino)tetrahydrofuran (2d). White solids of mp 70-72 °C. $[\alpha]_D^{22.0}$ +20.0 (*c* 1.0, $CHCl_3$, the mixture of **2d**/**2d'** = 76/24). IR (neat): 3241, 3080, 3063, 3030, 2926, 1950, 1871, 1705, 1682, 1547, 1497, 1454, 1497, 1454, 1431, 1360, 1333, 1304, 1265, 1238, 1188, 1080, 1059, 1030, 1007, 955, 907, 825, 735, 698, 660 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.61 (dd, *J* = 10.2, 15.3 Hz, 1H), 2.95 (dd, *J* = 4.8, 15.3 Hz, 1H), 3.62 (d, *J* = 4.8 Hz, 2H), 4.44-4.55 (m, 4H), 4.83-4.96 (m, 1H), 7.16-7.28 (m, 10H), 9.24 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 31.8, 42.9, 43.8, 51.2, 53.3, 126.7, 127.4, 127.6, 128.4, 128.7, 137.3, 139.1, 159.8, 165.7. 45% ee (**2d**), 53% ee (**2d'**), HPLC: Daicel Chiralcel OD-H column, hexane/isopropanol = 20/1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 13.8 min, 22.2 min for **2d**, 15.3min, 18.1min for **2d'**. HRMS (FAB): *m/z* calcd for $C_{20}H_{21}{}^{79}Br^{81}BrN_2O_2$ $[M+H]^+$ 480.9949, found 480.9976.

3-Bromo-5-(bromomethyl)-3-(*N*-*n*-octylcarbamoyl)-2-(*N*-*n*-octylimino)tetrahydrofuran (2e). White solids of mp 50-52 °C. $[\alpha]_D^{22.0}$ +11.0 (*c* 1.0, $CHCl_3$, the mixture of **2e**/**2e'** = 95/5). IR (neat): 3237, 3073, 2924, 2870, 1711, 1682, 1557, 1466, 1439, 1377, 1364, 1333, 1302, 1269, 1194, 1080, 1007, 899, 723, 657 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.881 (t, *J* = 6.0 Hz, 6H), 1.18-1.30 (m, 10H), 1.50-1.56 (m,

4H), 2.50 (dd, *J* = 9.9, 15.0 Hz, 1H), 2.89 (dd, *J* = 4.5, 15.0 Hz, 1H), 3.23-3.43 (m, 4H), 3.59 (d, *J* = 4.5 Hz, 2H), 4.77-4.85 (m, 1H), 8.99 (t, *J* = 4.2 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.6, 26.9, 27.4, 29.0, 29.2, 29.3, 30.1, 31.2, 32.1, 39.7, 42.9, 47.4, 53.3, 76.5, 158.9, 165.8. 30% ee (**2e**), 41% ee (**2e'**), HPLC: Daicel Chiralcel OD-H column x2, hexane/isopropanol = 20/1, wavelength: 210 nm, flow rate: 1.0 mL/min, retention time: 11.7 min, 12.9 min for **2e**, 16.9 min, 18.3 min for **2e'**. HRMS (FAB): *m/z* calcd for $C_{22}H_{41}{}^{79}Br^{81}BrN_2O_2$ $[M+H]^+$ 525.1514, found 525.1515.

5-(Bromomethyl)-3-methyl-3-(*N*-phenylcarbamoyl)-2-(*N*-phenylimino)tetrahydrofuran (2f), (2f'). Data of **2f**: Pale yellow solids of mp 98-101 °C. $[\alpha]_D^{27.0}$ +8.4 (*c* 0.60, $CHCl_3$). IR (neat): 3337, 2932, 1755, 1682, 1601, 1541, 1499, 1445, 1320, 1250, 1200, 1080, 1022, 754, 693 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.69 (s, 3H), 2.35 (dd, *J* = 6.3, 13.6 Hz, 1H), 4.64 (dd, *J* = 8.8, 13.6 Hz, 1H), 3.42 (d, *J* = 5.4 Hz, 2H), 4.55-7.70 (m, 1H), 6.90-7.10 (m, 2H), 7.10-7.32 (m, 6H), 7.45-7.58 (m, 2H), 10.69 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 27.1, 33.2, 37.6, 52.0, 77.8, 119.5, 123.4, 124.2, 125.0, 128.9, 129.0, 137.9, 144.4, 163.6, 169.3. 34% ee (major diastereomer), HPLC: Daicel Chiralpak AD column, hexane/isopropanol = 10/1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 9.3 min, 12.4 min. HRMS (EI): *m/z* calcd for $C_{19}H_{19}{}^{81}BrN_2O_2$ $[M]^+$ 388.0609, found 388.0623.

Data of **2f'**: Pale yellow oil. $[\alpha]_D^{27.0}$ +9.3 (*c* 0.70, $CHCl_3$). IR (neat): 2924, 1696, 1601, 1557, 1464, 1456, 1260, 1098, 1024, 804, 752, 693 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.79 (s, 3H), 1.99 (dd, *J* = 8.8, 13.2 Hz, 1H), 3.42 (dd, *J* = 6.3, 13.2 Hz, 1H), 3.55 (dd, *J* = 3.9, 11.2 Hz, 1H), 3.65 (dd, *J* = 4.9, 11.2 Hz, 1H), 4.57-4.67 (m, 1H), 7.08-7.20 (m, 2H), 7.20-7.30 (m, 2H), 7.30-7.45 (m, 4H), 7.52-7.62 (m, 2H), 9.50 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 26.6, 34.0, 36.9, 53.6, 78.4, 119.4, 123.2, 124.4, 124.8, 128.8, 129.1, 137.7, 145.1, 164.2, 168.2. 9% ee (minor diastereomer), HPLC: Daicel Chiralcel OD column, hexane/isopropanol = 50/1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 17.0 min, 25.4 min. HRMS (EI): *m/z* calcd for $C_{19}H_{19}{}^{81}BrN_2O_2$ $[M]^+$ 388.0609, found 388.0623.

5-(Iodomethyl)-3-methyl-3-(*N*-phenylcarbamoyl)-2-(*N*-phenylimino)tetrahydrofuran (4f), (4f'). Data of **4f**: Pale yellow solids of mp 131-132 °C. $[\alpha]_D^{19.1}$ +20.3 (*c* 1.0, $CHCl_3$). IR (neat): 3249, 3063, 1698, 1601, 1557, 1498, 1447, 1320, 1252, 1202, 1105, 1005, 774, 756, 693 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.77 (s, 3H), 2.52 (dd, *J* = 6.3, 13.7 Hz, 1H), 2.61 (dd, *J* = 8.8, 13.7 Hz, 1H), 3.31 (dd, *J* = 7.3, 10.7 Hz, 1H), 3.37 (dd, *J* = 4.9, 10.7 Hz, 1H), 4.54-4.60 (m, 1H), 7.11 (t, *J* = 7.3 Hz, 1H), 7.11 (t, *J* = 7.3 Hz, 1H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.27-7.39 (m, 6H), 7.61 (d, *J* = 8.3 Hz, 1H), 10.80 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 6.5, 27.0, 39.4, 25.3, 78.3, 119.5, 123.4, 124.2, 125.0, 128.8, 129.0, 137.9, 144.3, 163.6, 169.3. 38% ee (major diastereomer), HPLC: Daicel Chilalcel OD-H column, hexane/isopropanol = 10/1, wavelength: 254 m, flow rate: 1.0 mL/min, retention time: 8.2 min, 14.0 min. HRMS (FAB) *m/z* calcd for $C_{19}H_{20}IN_2O_2$ $[M+H]^+$: 435.0569. Found: 435.0582.

Data of **4f'**: Colorlessoil. $[\alpha]_D^{19.1}$ −21.0 (*c* 0.5, $CHCl_3$). IR (neat): 3324, 2926, 1694, 1601, 1549, 1489, 1445, 1250, 1096, 1003, 754, 695 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.78 (s, 3H), 1.84 (dd, *J* = 9.3, 13.2 Hz, 1H), 3.38-3.49 (m, 3H), 4.27-4.33 (m, 1H), 7.11-7.17 (m, 2H), 7.25-7.27 (m, 2H), 7.33-7.38 (m, 4H), 7.56 (d, *J* = 8.3 Hz, 2H), 9.47 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 8.2, 26.5, 39.0, 53.9, 78.6, 119.4, 123.2, 124.4, 124.8, 128.8, 129.1, 137.7, 145.1, 164.2, 168.2. 12% ee (minor diastereomer), HPLC: Daicel Chilalcel OD-H column, hexane/isopropanol = 30/1, wavelength: 254 m, flow rate: 1.0 mL/min, retention time: 11.3 min, 14.6 min. HRMS (FAB) *m/z* calcd for $C_{19}H_{20}IN_2O_2$ $[M+H]^+$: 435.0569. Found: 435.0571.

Synthesis of 3-aza-1-bromo-6-oxa-3-phenyl-7-phenylimino-bicyclo[3.2.1]octan-2-one (3a). To the mixture of **2a** and **2a'** (**2a**/**2a'** = 87/13, 46% ee in **2a**, 44% ee in **2a'**) (0.1 mmol) in THF (3 mL) was added NaH (0.5 mmol), and the reaction mixture was stirred at room temperature for 1 h. To the reaction flask was added brine (3 mL), and THF was removed under reduced pressure. The residue was extracted with AcOEt, and then the combined organic layers were washed with brine and dried over $MgSO_4$. Concentration and purification through silica gel column chromatography (hexane/AcOEt = 3/1) gave the product **3a** with 46% yield. White solids of mp 175-178 °C. $[\alpha]_D^{22.0}$ +57.2 (*c* 0.2, $CHCl_3$). IR (neat) 3059, 2350, 1705, 1680, 15931491, 1414, 1308, 1265, 1242, 1194, 1154, 1067, 963, 754, 690 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.09 (s, 1H), 3.14 (d, *J* = 6.0 Hz, 1H), 3.89 (s, 1H), 3.91 (d, *J* = 2.4 Hz, 1H), 4.98-5.00 (m, 1H), 7.11-7.42 (m, 10H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 41.7, 56.8, 58.8, 74.3, 122.7, 124.8, 126.0, 127.8, 128.6, 129.5, 140.7, 145.3. HRMS (FAB): *m/z* calcd for $C_{18}H_{16}{}^{79}BrN_2O_2$ $[M+H]^+$ 371.0395, found 371.0385.

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9. The absolute stereoconfiguration of the major enantiomer in **2a** could be deduced to be (3*S*,5*R*) on the basis of the absolute stereoconfiguration of **4f**.
10. Crystallographic data for **4f**: CCDC 885370 contains the supplementary crystallographic data. The data can be obtained free of charge from The Cambridge Crystallographic Data Center. Formula: $C_{19}H_{19}IN_2O_2$. M_r: 434.28. Crystal system: orthorhombic. Space group: $P2_12_12_1$. *a*: 5.7165(2) Å. *b*: 17.1142(8) Å. *c*: 18.5235(7) Å. $\alpha = \beta = \gamma$: 90 °. *V*: 1812.22(13) Å^3. *Z*: 4. μ: 13.986 (mm^{-1}). R_1 (I>2σ(I)): 0.0634. R (I>0.5σ(I)): 0.0844. wR_2 (I>0.5σ(I)): 0.2026. *D*: 1.592 (g/cm^3). *S*: 0.598.