New Chiral Hypervalent Iodine Compounds in Asymmetric Synthesis

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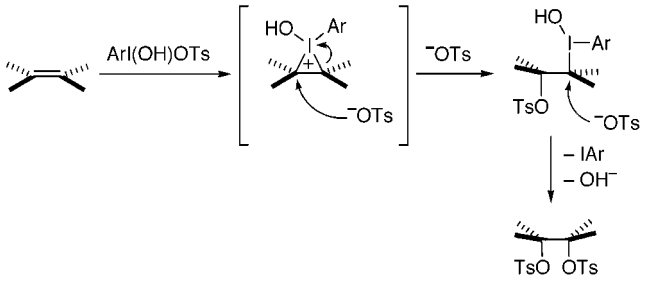
The synthesis of new chiral hypervalent iodine compounds **3** and their use in asymmetric oxidative functionalizations are described. The substituents in the chiral moiety and the stereoelectronic properties of the reagents **3**, as well as the reaction conditions, have been optimized. Chiral hypervalent iodine compounds **3** have been investigated in the asymmetric dioxytosylation of styrene and in the α-oxytosylation of propiophenone as test reactions. X-ray structural analysis of some reagents shows an interaction between the chiral moiety and the iodine resulting in stereoselectivities up to 53% ee in the products.

Introduction

Hypervalent iodine compounds have been known for more than a century, but only recently they were found to be versatile and mild reagents for various oxidation and oxygenation reactions. They can substitute for various toxic and heavy metal containing reagents, which have been used frequently for oxidative transformations in former times. The class of hypervalent iodine compounds has found broad application in various natural product synthesis and for the preparation of complex target molecules, because of the mild reaction conditions and the high selectivities obtained with these reagents.[1]

Beside the oxidation of alcohols with the Dess−Martin periodinane to the corresponding carbonyl compounds also other hypervalent iodine compounds such as diacetoxyiodobenzene,[2] iodosobenzene, or hydroxy(tosyloxy)-iodobenzene [PhI(OH)OTs, Koser's reagent] and its analogues have found many applications in organic synthesis. Hypervalent iodine compounds can be used not only as oxidants but also as electrophilic reagents to functionalize C=C bonds. Subsequent reactions such as iodolactonizations,[3] dioxytosylations,[4] or α-oxytosylations of ketones[5] are yielding versatile building blocks for further synthesis. Recently it was shown that iodonium salts can be used for C−C bond formations as well.[1b,6] In some of these reactions new stereogenic centers are created. The reactions of electrophilic iodine species with double bonds have been shown to proceed via a S_N2 type mechanism (Scheme 1).[7]

Scheme 1



Chiral hypervalent iodine compounds should therefore be promising reagents for asymmetric variants of these reactions. Until now only few chiral hypervalent iodine compounds have been synthesized.[8] Most of them are compounds of type **1** bearing a chiral substituent on the iodine. They have only been used in asymmetric oxidations to convert sulfides into sulfoxides.[9] Chiral hypervalent iodine compounds of type **2** and **3**, in which the chiral moiety is fixed in the *ortho*-position to the iodine, were recently described by us[10] and others[11] (Chart 1).

Compounds of type **3** with a protected alcohol as chiral moiety beside the iodine atom are readily accessible. The oxygen has a strong interaction with the iodine which was shown by X-ray structural analysis. We described for the first time that hypervalent iodine compounds **3** can be employed in asymmetric functionalizations of alkenes and ketones.[10]

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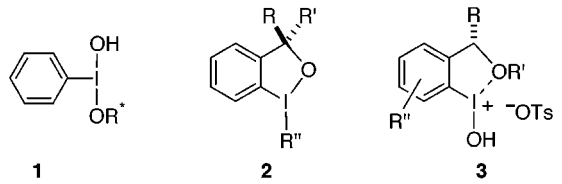
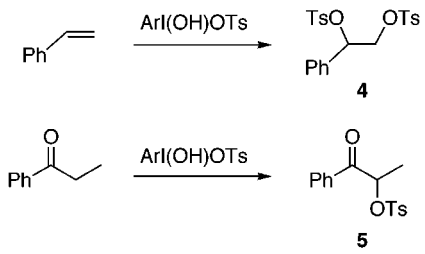
Chart 1



Scheme 2



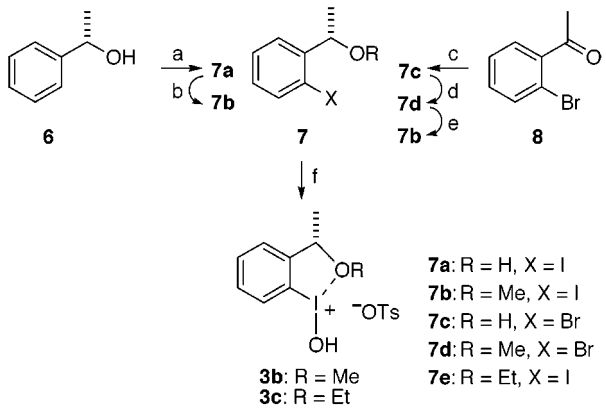
Results and Discussion

Hypervalent iodine compounds are electrophilic species and can attack double bonds as shown in Scheme 1. We confirmed this mechanism by converting either (*E*)- or (*Z*)-2-pentene with the hypervalent iodine compounds **3** into *syn*- or *anti*-2,3-bis(tosyloxy)pentane selectively. A clean S_N2 type mechanism is the prerequisite for the development of asymmetric reactions with chiral hypervalent iodine compounds. For these investigations we chose the dioxytosylation of styrene and the α-oxytosylation of propiophenone as test reactions (Scheme 2). In these reactions new stereocenters are created and the products of these reactions, 1,2-bis(tosyloxy)phenylethane (**4**) and α-(tosyloxy)propiophenone (**5**), are compounds containing asymmetric carbon atoms.

Employing chiral hypervalent iodine compounds of type **3** as electrophilic reagents, we observe a facial selectivity upon reaction with alkenes and ketones and enantiomerically enriched products **4** and **5** are generated. With compound **3a** (R = Et, R′ = Me, R″ = H) we reported asymmetric reactions yielding **4** and **5** with 21% ee and 15% ee, respectively.[10] Because of the low stereoselectivities we tried to optimize the chiral hypervalent iodine compounds of type **3**. First we focused our interest on the substituents R and R′ in the chiral moiety of **3**. In a second step we then varied the substituent R″ to understand its influence on the electronic properties of the reagent. A further target was the optimization of the reaction conditions to obtain better yields and stereoselectivities.

We chose to synthesize the most simple compound **3b** with R = R′ = Me and R″ = H. The synthesis of this compound starts with an *ortho*-deprotonation of (*S*)-1-phenylethanol (**6**) with *n*-BuLi followed by introduction of iodine yielding compound **7a**. The hydroxy group was methylated, and the precursor **7b** was oxidized with sodium perborate in glacial acetic acid.[12] Subsequent treatment with *p*-toluenesulfonic acid monohydrate leads to the hypervalent iodine compound **3b**. An alternative way to obtain **3b** is chiral reduction[13] of 2-bromoacetophenone (**8**) followed by methylation. After the bromine−iodine exchange compound **7b** can be oxidized as described above. Because of the inefficent *ortho*-deprotonation of **6**, the second route leads to a higher overall yield of **3b** (43%) (Scheme 3).

Scheme 3[a]



[a] Key: (a) *N*,*N*,*N*′,*N*′-TMEDA, *n*-BuLi, I_2, 22%; (b) NaH, MeI, 72%; (c) (−)-Ipc_2BCl, 92%; (d) NaH, MeI, 92%; (e) *t*-BuLi, I_2, 74%; (f) (i) $NaBO_3 \cdot 4H_2O$, AcOH, 73%, (ii) *p*-TsOH·H_2O, 95%.

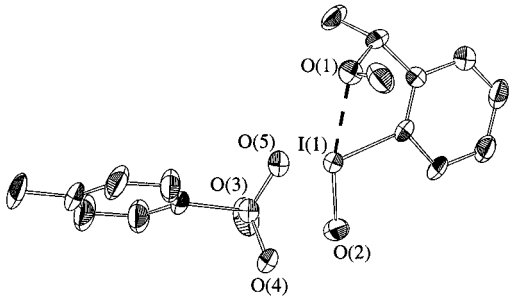


Figure 1. X-ray structure of **3b**.

The hypervalent iodine compound **3b** can be purified only by recrystallization. The X-ray structural analysis shows a strong interaction between the oxygen of the methoxy group and the iodine (Figure 1). The distance between these two atoms (2.47 Å) is much less than the distance from the iodine to the oxygen of the tosyloxy group (2.82 Å). Because the hydroxy group is tightly bound to the iodine (1.94 Å), we prefer writing the structures of these hypervalent iodine compounds as salts of *p*-toluenesulfonic acid.

Compound **3b** shows a similar T-shaped structure like the Koser reagent.[14] Interestingly, the oxygen of the methoxy group is now replacing the tosylate leading to an oxygen−iodine−oxygen angle of 166° (Koser reagent: 179°).[14] Compared with the X-ray structural analysis of **3a**, the hypervalent iodine compound **3b** shows a very similar geometry at the iodine atom. With **3b** the products **4** and **5** were obtained with 33% ee and 15% ee, respectively.

Compared to **3a**, the smaller substituent R = Me in **3b** shows a higher enantiomeric excess in the product **4**. If R′ is changed into a larger substituent in **3c** (R = Me, R′ = Et), the product **4** is obtained with only 21% ee.

With the optimized chiral moiety in **3b** (R = R′ = Me), we started to synthesize derivatives with methoxy groups (R″ = OMe) in the *ortho*-, *meta*-, and *para*-positions with respect to iodine.

Two synthetic routes to the chiral hypervalent iodine compound **3d** with an *ortho*-methoxy substituent have

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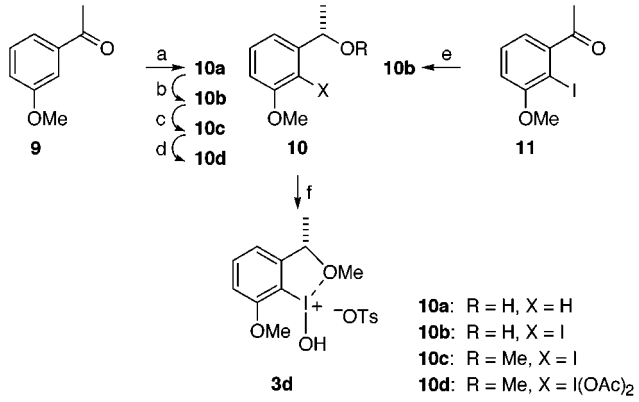
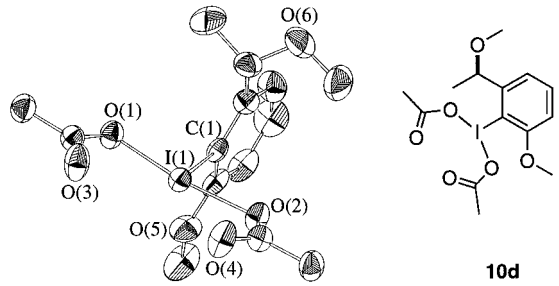
Scheme 4[a]



[a] Key: (a) (−)-Ipc$_2$BCl, 80%; (b) *N*,*N*,*N*′,*N*′-TMEDA, *n*-BuLi, I_2, 22%; (c) NaH, MeI, 80%; (d) $NaBO_3 \cdot 4H_2O$, AcOH, 87%; (e) (−)-Ipc$_2$BCl, 91%; (f) *p*-TsOH·H_2O, 95%.



10d

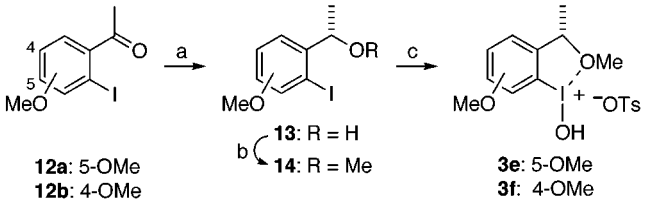
Figure 2. X-ray structure of **10d**.

been worked out. Reduction of 3-methoxyacetophenone (**9**) with (−)-*B*-chlorodiisopinocampheylborane leads to the chiral alcohol **10a** (96% ee).[15] Iodine is introduced by *ortho*-lithiation,[16] and after methylation **10c** is obtained. Oxidation of the iodine generates the diacetoxyiodo derivative **10d**, which is then transformed into the hypervalent iodine compound **3d**. A better synthetic access can be achieved by the use of **11** as easily accessible precursor.[17] After chiral reduction (96% ee) and methylation the iodine is oxidized and **3d** is obtained in 60% overall yield (Scheme 4).

The diacetoxyiodo derivative **10d** was purified by recrystallization from hexane. The X-ray structural analysis shows the same shape around the iodine as it is found in diacetoxyiodobenzene (Figure 2).[18] It is interesting that the oxygen of the chiral side chain does not interact with the iodine. The coordination sphere around the iodine is pentagonal planar like in diacetoxyiodobenzene. The reagent **3d** prepared from **10d** is an amorphous solid, and no crystals suitable for an X-ray structural analysis could be obtained.

The synthetic strategy of the chiral hypervalent iodine compounds with methoxy substituents in the *meta*- and *para*-positions to the iodine is different from the synthesis of **3d**. The *ortho*-deprotonation of the corresponding alcohols could not be achieved. Therefore the methoxy-substituted 2-iodoacetophenones **12a** (5-OMe)[19] and **12b** (4-OMe)[20] were used to prepare the chiral alcohols **13a** (92% ee) and **13b** (91% ee) by reduction with (−)-*B*-chlorodiisopinocampheylborane.[21] After methylation the compounds **14a**,**b** were oxidized to **3e**,**f**, respectively (Scheme 5).

Scheme 5[a]



[a] Key: (a) (−)-Ipc$_2$BCl, **13a**, 92%, and **13b**, 89%; (b) NaH, MeI, **14a**, 90%, and **14b**, 93%; (c) (i) $NaBO_3 \cdot 4H_2O$, (ii) *p*-TsOH·H_2O, **3e**, 83%, and **3f**, 37%.

Table 1. Dioxytosylation of Styrene with Chiral Hypervalent Iodine Compounds 3

entry	reagent	R	R′	R″	temp (°C)	ee of **4** (%)[24]
1	**3a**	Et	Me	H	25	21
2	**3b**	Me	Me	H	25	26
3	**3b**	Me	Me	H	−30	33
4	**3c**	Me	Et	H	25	21
5	**3d**	Me	Me	6-OMe	−30	53
6	**3e**	Me	Me	5-OMe	−30	37
7	**3f**	Me	Me	4-OMe	−30	42

Table 2. α-Oxytosylation of Propiophenone with Chiral Hypervalent Iodine Compounds 3 at 0 °C

entry	reagent	R	R′	R″	ee of **5** (%)[25]
1	**3a**	Et	Me	H	10
2	**3b**	Me	Me	H	15
3	**3d**	Me	Me	6-OMe	28
4	**3e**	Me	Me	5-OMe	26
5	**3f**	Me	Me	4-OMe	15

The methoxy-substituted chiral hypervalent iodine compounds **3d**−**f** have subsequently been employed in the reactions mentioned above. The stereoselectivities obtained with these reagents are in all cases higher than with compounds **3b** having no further substituents. The electronic properties in the reagents **3d**−**f** are not negligible and do indeed have an influence on the stereoselectivity. As it can be seen from Tables 1 and 2, the dioxytosylation of styrene as well as the α-oxytosylation of propiophenone proceeds with the highest stereoselectivities using the chiral hypervalent iodine compound **3d**. The compounds **4** and **5** were obtained with 53% ee and 28% ee, respectively. The results indicate that the methoxy group has additional steric effects on the reaction course, which seems to play an important role. The influence of the methoxy group in the *ortho*- and *para*-positions to the iodine is larger than in the *meta*-position. The ^{1}H NMR of **3d** shows broad and shifted signals for the methoxy group in position 3 which might indicate an interaction between the oxygen of the methoxy group and the iodine.

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(20) Compound **12b** was synthesized from 2-amino-5-methoxyacetophenone: (a) Fürstner, A.; Jumbam, D. N.; Seidel, G. *Chem. Ber.* **1994**, *127*, 1125−1130. For spectroscopic data see: (b) Buchwald, S. L.; Watson, B. T.; Lum, R. T.; Nugent, W. A. *J. Am. Chem. Soc.* **1987**, *109*, 7137−7141.
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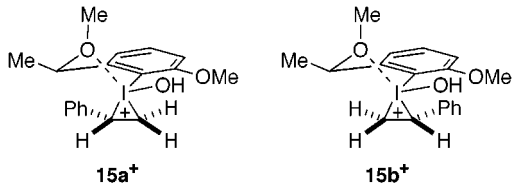
Chart 2



The reaction of (*S*)-configured compounds **3** with styrene yields the dioxytosylate **4** with (*R*)-configuration.[22] This corresponds to a *re* attack of styrene as shown in the intermediate **15a**$^+$ (Chart 2). The diastereomeric intermediate **15b**$^+$ can also gain from π-stacking but is assumed to be higher in energy as we calculated it for the corresponding seleniranium ions.[23]

The dioxytosylation of styrene with hypervalent iodine compounds of type **3** is very efficient. Full conversion of the hypervalent iodine compound is usually observed, and 1,1-ditosyloxy-2-phenylethane is the only (known) byproduct isolated in small amounts.[4] Following purification of the crude reaction mixture on silica gel we isolated **4** in 75% yield.

The α-oxytosylation of propiophenone is less efficient than the dioxytosylation of styrene. Up to 28% ee is obtained, and the product **5** is isolated in about 35% yield. It was already shown that compound **5** has the (*R*)-configuration.[10] It is known that some ketones show low conversions in the reaction with the Koser reagent.[5] The enantiomeric excess depends on the hypervalent iodine compound **3**. Probably steric effects do not play an important role because of the almost same results using the hypervalent iodine compounds **3d**,**e** (Table 2, entries 3 and 4).

During our work using the Koser reagent and its analogues in oxidative functionalizations we observed a dramatic increase of the reaction rate after the addition of a little amount of *p*-toluenesulfonic acid monohydrate to the reaction mixture of the hypervalent iodine compound and the alkene. The reactions at room temperature are finished after approximately 4 h and can now be performed even at −30 °C. Only a small amount of the additional *p*-toluenesulfonic acid is dissolved. We suspect that also the Koser reagent and its analogues are dissociated only partially in the dichloromethane solution and that the additional *p*-toluenesulfonic acid is used to attack the activated double bonds.

The nature of the solvent seems to play also an important role. We screened a variety of solvents as shown in Table 3 using the chiral hypervalent iodine compound **3b**. The solvent of choice is dichloromethane which was employed in all the reactions mentioned above.

Conclusion

New chiral hypervalent iodine compounds have been developed, and their use in asymmetric oxygenation reactions has been described. With sterically and electronically modified reagents of type **3**, the reaction products were obtained with up to 53% ee. The investigation of other asymmetric reactions as well as modified chiral hypervalent iodine compounds are in progress.

Table 3. Solvent Variation in the Dioxytosylation of Styrene at 25 °C

solvent	ee of **4** (%)	solvent	ee of **4** (%)
dichloromethane	26	trichloroethene	20
1,2-dichloroethane	16	a,a,a-trifluorotoluene	23
1,2-dimethoxyethane	7	ethyl acetate	16

[a] No reaction took place with the solvents chloroform, carbon tetrachloride, acetonitrile, ethylene glycol, dimethyl sulfoxide, and dimethyl formamide.

Experimental Section

General Methods. All reactions were performed under argon with anhydrous solvents. The ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ using TMS as an internal standard at 300 and 75 MHz, respectively. Melting points are uncorrected.

All starting materials are commercially available and used without further purification. Compounds **11**[17] and **13**[19] were synthesized according to literature procedures.

General Procedures. GP1. Chiral reductions of acetophenone derivatives with (−)-*B*-chlorodiisopinocampheylborane were carried out as described.[21] To a solution of 1.1 equiv of (−)-*B*-chlorodiisopinocampheylborane in THF (1.0 M) at −25 °C the acetophenone derivative dissolved in THF was added. After the reaction (15−25 h) the solution was allowed to warm to room temperature and the solvent was removed. The residue was dissolved in diethyl ether, and 2.2 equiv of diethanolamine was added. After 2 h of stirring at room temperature, the mixture was filtered through Celite and concentrated in vacuo. The products were purified by flash-chromatography on silica gel.

GP2. Sodium hydride (4 equiv) (55−65% in oil) was washed with pentane (4×). *N*,*N*-Dimethylformamide was added to obtain a 0.8 M solution. To this mixture 1 equiv of the alcohol was added at 0 °C. After 1 h of stirring at room temperature, the mixture was cooled to 0 °C and methyl iodide (4.2 equiv) was added. After an additional 3−5 h at room temperature, water was added carefully. The solution was extracted with *tert*-butyl methyl ether (3×), the combined organic phases were washed with brine (3×) and dried with $MgSO_4$.

GP3.[12] A 0.1 M solution of an aryliodine in glacial acetic acid was heated to 50−65 °C. To this solution 10 equiv of sodium perborate tetrahydrate was added slowly. The reaction mixture was stirred for 3−4 h. The conversion was monitored by TLC. After completion of the reaction, the reaction mixture was extracted quickly with a small amount of methylene chloride (2×) and dried with $MgSO_4$. The solvent was removed in vacuo. The diacetoxyiodo derivatives can be either purified by washing with pentane or by dissolving the crude product in acetonitrile and washing with pentane.

GP4. The diacetoxyiodobenzene derivative was dissolved in acetonitrile (∼0.9 M). To this solution exactly 1 equiv of *p*-toluenesulfonic acid monohydrate in acetonitrile (0.4 M) was added. After the solution was stirred for 1 h the solvent was removed in vacuo. Some of the products were found to be instable and therefore characterized only by NMR spectroscopy.

GP5. The alcohol was dissolved in pentane (0.55 M), and 2 equiv of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine was added. At 0 °C 2 equiv of *n*-butyllithium (1.6 M in hexane) was added. The first 1 equiv was added slowly while the second was added quickly. The mixture was refluxed for 12 h, and then THF was added to dissolve the precipitate. After the solution was cooled to 0 °C, 1.2 equiv of iodine in THF (1 M) was added. After additional stirring for 3 h the reaction mixture was diluted with aqueous sodium thiosulfate and extracted with *tert*-butyl methyl ether (3×). The product was purified by flash chromatography on silica gel.

(22) The absolute configuration was determined by comparison with (*S*)-**4**, which was synthesized from (*S*)-mandelic acid by reduction and tosylation: Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1970**, *35*, 4002−4003.

(23) Wirth, T.; Fragale, G.; Spichty, M. *J. Am. Chem. Soc.* **1998**, *120*, 3376−3381.

Dioxytosylation and α-Oxytosylation. The chiral hypervalent iodine compound **3** (0.5 mmol) and *p*-toluenesulfonic acid monohydrate (0.6 mmol, 115 mg) were dissolved in CH_2Cl_2 (3 mL). For the dioxytosylation styrene (0.6 mmol, 62 mg) and for the α-oxytosylation propiophenone (1.2 mmol, 160 mg) was added at the temperature indicated in Tables 1 and 2. The solution was stirred at this temperature for 4−24 h. After filtration over silica gel the solvent was removed in vacuo and the residue purified by flash chromatography on silica gel.

***(S)*-Hydroxy(4-methylbenzenesulfonato-*κO*)[2-(1-methoxyethyl)phenyl]iodine (3b).** GP4: yield 95% (1.12 g); recrystallized from acetonitrile; colorless crystals; mp 124−126 °C; $[\alpha]_D^{25} = 16.3$ ($c = 1.045$, $CHCl_3$); ^{1}H NMR δ 1.49 (d, 3H, $J = 6.6$ Hz), 2.36 (s, 3H), 3.68 (s, 3H), 4.75 (q, 1H, $J = 6.4$ Hz), 7.1 (d, 2H, $J = 7.8$ Hz), 7.29 (d, 1H, $J = 1.5$ Hz, $J = 7.5$ Hz), 7.4−7.6 (m, 2H), 7.74 (d, 2H, $J = 8.1$ Hz), 7.83 (d, 1H, $J = 7.8$ Hz); ^{13}C NMR δ 20.6, 21.3, 59.3, 82.1, 113.3, 126.1, 127.5, 127.9, 128.8, 130.9, 131.1, 140.1, 140.2, 141.6; IR ($CHCl_3$) ν 3374, 2934, 1178, 1135, 1008 cm^{-1}. Anal. Calcd for $C_{13}H_{17}IO_5$: C, 42.68; H, 4.25; O, 17.77. Found: C, 42.74; H, 4.25; O, 17.72.

***(S)*-Hydroxy(4-methylbenzenesulfonato-*κO*)[2-(1-ethoxyethyl)phenyl]iodine (3c).** GP4: yield 92% (162 mg); yellow oil; ^{1}H NMR δ 1.37 (t, 3H, $J = 6.9$ Hz) 1.49 (d, 3H, $J = 6.5$ Hz), 2.34 (s, 3H), 3.85 (m, 2H), 4.86 (q, 1H, $J = 6.5$ Hz), 7.14 (d, 2H, $J = 7.7$ Hz), 7.29 (d, 1H, $J = 1.0$ Hz, $J = 7.7$ Hz), 7.47 (t, 1H, $J = 7.0$ Hz), 7.55 (t, 1H, $J = 7.7$ Hz), 7.76 (d, 2H, $J = 8.2$ Hz), 7.87 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR δ 15.1, 21.3, 21.4, 64.2, 68.9, 80.1, 112.4, 126.2, 127.2, 127.9, 128.8, 131.0, 131.2, 140.6, 140.7; IR ($CHCl_3$) ν 3306, 2981, 1717, 1435, 1115, 1009 cm^{-1}.

***(S)*-Hydroxy(4-methylbenzenesulfonato-*κO*)[2-(1-methoxyethyl)-6-methoxyphenyl]iodine (3d).** GP4: yield 95% (150 mg); amorphous yellow solid; ^{1}H NMR δ 1.4 (b, 3H), 2.35 (s, 3H), 3.08 (b, 3H), 4.15 (b, 3H), 4.65 (b, 1H), 6.2 (b, 1H), 7.1 (m, 1H), 7.15 (d, 2H, $J = 8.0$ Hz), 7.23 (m, 1H), 7.57 (d, 2H, $J = 8.2$ Hz), 7.64 (m, 1H).

***(S)*-Hydroxy(4-methylbenzenesulfonato-*κO*)[2-(1-methoxyethyl)-5-methoxyphenyl]iodine (3e).** GP4: yield 93% (100 mg); amorphous yellow solid; ^{1}H NMR δ 1.46 (d, 3H, $J = 6.4$ Hz), 2.34 (s, 3H), 3.70 (s, 3H), 3.80 (s, 3H), 4.74 (q, 1H, $J = 6.3$ Hz), 6.95 (m, 1H), 7.13 (m, 2H), 7.3 (m, 2H), 7.72 (d, 2H, $J = 8.2$ Hz); IR ($CHCl_3$) ν 3300, 3034, 1597, 1488, 1136, 1035 cm^{-1}.

***(S)*-Hydroxy(4-methylbenzenesulfonato-*κO*)[2-(1-methoxyethyl)-4-methoxyphenyl]iodine (3f).** GP4: yield 93% (30 mg); amorphous yellow solid; ^{1}H NMR δ 1.48 (d, 3H, $J = 6.5$ Hz), 2.32 (s, 3H), 3.62 (s, 3H), 3.85, (s, 3H), 4.70 (q, 1H, $J = 6.3$ Hz), 6.85 (s, 1H), 7.01 (d, 1H, $J = 8.1$ Hz), 7.12 (d, 2H, $J = 8.5$ Hz) 8.7 (d, 3H, $J = 8.5$ Hz); 8.9 (s, 1H).

***(S)*-1-(2-Iodophenyl)ethanol (7a).** GP5: purification by flash chromatography on silica gel (1:5 *tert*-butyl methyl ether/pentane); yield 22% (935 mg); colorless crystals; $[\alpha]_D^{25} = 46.1$ ($c = 1.26$, $CHCl_3$), mp 63−65 °C; ^{1}H NMR δ 1.39 (d, 3H, $J = 6.3$ Hz), 2.7 (b, 1H), 4.99 (q, 1H, $J = 6.1$ Hz), 6.92 (dt, 1H, $J = 1.7$ Hz, $J = 7.6$ Hz), 7.33 (dt, 1H, $J = 1.1$ Hz, $J = 7.5$ Hz), 7.49 (dd, 1H, $J = 1.5$ Hz, $J = 7.9$ Hz), 7.74 (dd, 1H, $J = 1.0$ Hz, $J = 7.8$ Hz); ^{13}C NMR δ 23.7, 73.5, 97.1, 126.3, 128.6, 129.0, 139.1, 147.4; MS (EI) *m/z* (relative intensity) 248 (54), 234 (15), 233 (100), 231 (15), 127 (9), 105 (31), 103 (10), 91 (13), 78 (75), 77 (49), 76 (20); HRMS M$^+$ *m/e* 247.9702, calcd for C_8H_9IO *m/e* 247.9698; IR ($CHCl_3$) ν 3604, 2966, 1464, 1437, 1087 cm^{-1}.

***(S)*-1-Iodo-2-(1-methoxyethyl)benzene (7b).** A 4.77 g (22.2 mmol) amount of **7a** was dissolved in 100 mL of THF under argon at −78 °C. A solution of 25 mL (40 mmol) *tert*-butyllithium (1.6 M in pentane) was added slowly. The solution was stirred for 10 min at this temperature and allowed to warm at 0 °C. After additional 30 min at −78 °C, 10.2 g (40 mmol) of iodine in 60 mL of THF was added. The reaction mixture was allowed to warm slowly to room temperature. After 12 h the mixture was diluted with aqueous sodium thiosulfate and extracted with *tert*-butyl methyl ether (3×). After drying with $MgSO_4$ the crude product was purified by flash chromatography on silica gel (1:50 *tert*-butyl methyl ether/pentane): yield 74% (4.31 g). GP2: deprotonation, 1 h; methylation, 4 h; 72% (189 mg) yield; purification by flash chromatography on silica gel (1:10 *tert*-butyl methyl ether/pentane); $[\alpha]_D^{25} = -42.0$ ($c = 1.04$, $CHCl_3$); ^{1}H NMR δ 1.37 (d, 3H, $J = 6.4$ Hz), 3.24 (s, 3H), 4.53 (q, 1H, $J = 6.3$ Hz), 6.95 (m, 1H), 7.36 (dt, 1H, $J = 1.0$ Hz, $J = 7.4$ Hz), 7.42 (dd, 1H, $J = 2.0$ Hz, $J = 7.8$ Hz), 7.79 (dd, 1H, $J = 1.1$ Hz, $J = 7.9$ Hz); ^{13}C NMR δ 22.6, 56.7, 82.8, 98.1, 126.5, 128.7, 129.0, 139.3, 145.4; MS (EI) *m/z* (relative intensity) 262 (19), 247 (100), 231 (9), 105 (6), 104 (12), 91 (6), 77 (11); HRMS M$^+$ *m/e* 261.9859, calcd for $C_9H_{11}IO$ *m/e* 261.9855; IR ($CHCl_3$) ν 2981, 2931, 1564, 1464, 1454, 1435, 1372, 1110 cm^{-1}.

***(S)*-1-(2-Bromophenyl)ethanol (7c).** GP1: reaction time, 15 h at −25 °C; 92% (9.25 g) yield; 95% ee.[26] Purification by flash-chromatography (silica gel, 1:5 *tert*-butyl methyl ether/pentane). Spectroscopic data: lit.[13]

***(S)*-2-Bromo-1-(1-methoxyethyl)benzene (7d).** GP2: deprotonation, 1 h; methylation 4 h; 92% (4.94 g) yield without further purification; colorless oil; $[\alpha]_D^{25} = -71.2$ ($c = 0.75$, $CHCl_3$); ^{1}H NMR δ 1.39 (d, 3H, $J = 6.4$ Hz), 3.24 (s, 3H), 4.7 (q, 1H, $J = 6.4$ Hz), 7.1 (dt, 1H, $J = 1.8$ Hz, $J = 7.6$ Hz), 7.32 (dt, 1H, $J = 0.9$ Hz, $J = 7.5$ Hz), 7.46 (dd, 1H, $J = 1.8$ Hz, $J = 7.9$ Hz), 7.50 (dd, 1H, $J = 1.2$ Hz, $J = 8.0$ Hz); ^{13}C NMR δ 22.4, 56.6, 78.2, 122.6, 126.9, 127.8, 128.6, 132.6, 142.6; MS (EI) *m/z* (relative intensity) 216 (8), 214 (8), 201 (98), 199 (100), 185 (16), 183 (16), 104 (24), 91 (16), 77 (29), 59 (13), 51 (13), 45 (16); HRMS M$^+$ *m/e* 214.0000, calcd for $C_9H_{11}BrO$ *m/e* 213.9993; IR ($CHCl_3$) ν 2983, 2932, 1470, 1442, 1372, 1111 cm^{-1}.

***(S)*-1-(1-Ethoxyethyl)-2-iodobenzene (7e).** GP2: ethyl iodide is used instead of methyl iodide; deprotonation, 45 min; ethylation, 3 h; yield 91% (203 mg) as colorless oil; $[\alpha]_D^{25} = 22.1$ ($c = 0.480$, $CHCl_3$); ^{1}H NMR δ 1.19 (t, 3H, $J = 7.0$ Hz), 1.37 (d, 3H, $J = 6.4$ Hz), 3.35 (m, 2H), 4.62 (q, 1H, $J = 6.4$ Hz), 6.94 (dt, 1H, $J = 1.8$ Hz, $J = 7.5$ Hz), 7.36 (dt, 1H, $J = 1.1$ Hz, $J = 7.5$ Hz), 7.46 (dd, 1H, $J = 1.8$ Hz, $J = 7.8$ Hz), 7.78 (dd, 1H, $J = 1.2$ Hz, $J = 7.9$ Hz); ^{13}C NMR δ 15.4, 22.9, 64.1, 80.8, 98.0, 126.6, 128.6, 128.9, 139.2, 146.1; MS (EI) *m/z* (relative intensity) 276 (23), 262 (18), 261 (100), 233 (59), 231 (26), 104 (34), 78 (44), 77 (34); HRMS M$^+$ *m/e* 276.0015, calcd for $C_{10}H_{13}IO$ *m/e* 276.0011; IR ($CHCl_3$) ν 2978, 1464, 1435, 1372, 1114, 1010 cm^{-1}.

***(S)*-1-(3-Methoxyphenyl)ethanol (10a).** GP1: reaction time, 21 h at −25 °C; 80% (2.02 g) yield, 96% ee;[27] purification by flash-chromatography (silica gel, 1:5 *tert*-butyl methyl ether/pentane); $[\alpha]_D^{25} = -32.0$ ($c = 1.135$, MeOH); ^{1}H NMR δ 1.45 (d, 3H, $J = 6.5$ Hz), 2.4 (d, 1H, $J = 2.4$ Hz), 3.78 (s, 3H), 4.8 (dq, 1H, $J = 1.6$ Hz, $J = 6.4$ Hz), 6.78 (ddd, 1H, $J = 1.0$ Hz, $J = 2.5$ Hz, $J = 8.2$ Hz), 6.9 (m, 2H), 7.23 (t, 1H, $J = 8.1$ Hz); ^{13}C NMR δ 25.1, 55.1, 70.1, 110.8, 112.7, 117.6, 129.4, 147.6, 159.6; MS (EI) *m/z* (relative intensity) 278 (100), 263 (92), 247 (6), 220 (7), 136 (62), 108 (70), 92 (18), 91 (17), 77 (27), 65 (19), 63 (20); IR ($CHCl_3$) ν 3431, 2975, 1602, 1487, 1456, 1157, 1045 cm^{-1}.

***(S)*-1-(2-Iodo-3-methoxyphenyl)ethanol (10b).** GP1: reaction time, 18 h at −25 °C; purification by flash chromatography (1:10 ethyl acetate/pentane); yield 91% (580 mg); colorless crystals. GP5: purification by flash chromatography (1:2 *tert*-butyl methyl ether/pentane); yield 13% (214 mg); mp 68−70 °C; $[\alpha]_D^{25} = -41.5$ ($c = 0.71$, $CHCl_3$); 96% ee; ^{1}H NMR δ 1.46 (d, 3H, $J = 6.4$ Hz), 2.0 (d, 1H, $J = 2.4$ Hz), 3.89 (s, 3H), 5.19 (dq, 1H, $J = 2.2$ Hz, $J = 6.2$ Hz), 6.74 (dd, 1H, $J = 1.4$ Hz, $J = 8.0$ Hz), 7.19 (dd, 1H, $J = 1.4$ Hz, $J = 7.8$ Hz), 7.32 (t, 1H, $J = 7.9$ Hz); ^{13}C NMR δ 23.5, 56.5, 73.7, 89.6, 109.7, 118.6, 129.4, 149.6, 157.8; MS (EI) *m/z* (relative intensity) 279 (15), 278 (100), 264 (12), 263 (93), 220 (6), 218 (5), 136 (63), 135

(24) The enantiomeric excess was determined by HPLC: Chiralcel OD; 9:1 hexane/2-propanol; 0.5 mL/min; 254 nm.

(25) The enantiomeric excess was determined by HPLC: Chiralcel OB; 4:1 hexane/2-propanol, 0.5 mL/min; 240 nm.

(26) The enantiomeric excess was determined by GC: Chrompack, β-CD-permethylated; 25 m, 80 → 140 °C; 5 °C/min.

(27) The enantiomeric excess was determined by HPLC: Chiralcel OD; 9:1 hexane/2-propanol, 0.5 mL/min; 220 nm.

(37), 134 (9), 109 (12), 108 (75), 107 (12), 103 (10), 92 (19), 91 (19), 79 (9), 77 (33); HRMS M^+ *m/e* 277.9814, calcd for $C_9H_{11}IO_2$ *m/e* 277.9804; IR ($CHCl_3$) ν 3604, 2967, 1567, 1466, 1427, 1059 cm^{-1}.

(*S*)-2-Iodo-3-methoxy-(1-methoxyethyl)benzene (10c). GP2: deprotonation, 30 min; methylation 4 h; purification by flash-chromatography (silica gel, 1:10 *tert*-butyl methyl ether/pentane); 80% (145 mg) yield; colorless oil; $[\alpha]_D^{25} = -79.8$ (c = 1.615, $CHCl_3$); ^1H NMR δ 1.37 (d, 3H, J = 6.4 Hz), 3.24 (s, 3H), 3.88 (s, 3H), 4.68 (q, 1H, J = 6.4 Hz), 6.73 (dd, 1H, J = 1.4 Hz, J = 8.0 Hz), 7.07 (dd, 1H, J = 1.4 Hz, J = 7.7 Hz), 7.30 (t, 1H, J = 8.0 Hz); ^{13}C NMR δ 22.5, 56.5, 56.7, 83.0, 90.7, 109.7, 118.8, 129.5, 147.5, 157.6; MS (EI) *m/z* (relative intensity) 292 (50), 277 (100), 262 (20), 134 (19), 91 (14), 77 (13); HRMS M^+ *m/e* 291.9957, calcd for $C_{10}H_{13}IO_2$ *m/e* 291.9960; IR ($CHCl_3$) ν 2981, 1567, 1465, 1136, 1109 cm^{-1}.

(*S*)-Bis(acetato-*O*)[2-(1-methoxyethyl)-6-methoxyphenyl]iodine (10d). GP3: reaction conditions, 65 °C, 4 h; recrystallization from hexane, 87% (100 mg) as colorless crystals; mp 94−97 °C; $[\alpha]_D^{25} = -75.2$ (c = 0.94 $CHCl_3$); ^1H NMR δ 1.47 (d, 3H, J = 6.4 Hz), 1.95 (s, 3H), 1.96 (s, 3H), 3.23 (s, 3H), 3.99 (s, 3H), 4.71 (q, 1H, J = 6.5 Hz), 7.07 (dd, 1H, J = 1.2 Hz, J = 8.2 Hz), 7.27 (dd, 1H, J = 1.3 Hz, J = 7.9 Hz), 7.60 (t, 1H, J = 8.0 Hz); ^{13}C NMR δ 20.2, 23.7, 56.8, 57.1, 82.4, 110.9, 117.4, 119.4, 134.6, 146.9, 155.9, 176.7, 176.9; IR ($CHCl_3$) ν 2934, 1646, 1586, 1469, 1366, 1274, 1053 cm^{-1}. Anal. Calcd for $C_{14}H_{19}IO_6$ (410.21): C, 40.99; H, 4.67. Found: C, 41.00; H, 4.68.

2-Iodo-5-methoxyacetophenone (12b). A 484 mg amount of sodium nitrite was dissolved in 2.5 mL of water and stirred at 0 °C for 15 min. To this solution 1.055 g of **15a** was added slowly followed by 4 mL of concentrated HCl in 4 g of ice. After 20 min at 0 °C 10.6 g of potassium iodide in 12 mL of water was added and the solution was stirred for additional 5 h at room temperature. After extraction with *tert*-butyl methyl ether (3×) the product was isolated. Yield: 75% (1.32 g). Spectroscopic data: lit.[20b]

(*S*)-1-(2-Iodo-4-methoxyphenyl)ethanol (13a). GP1: reaction time, 18 h at −25 °C; 92% (920 mg) yield; 92% ee;[28] purification by flash-chromatography (silica gel, 1:5 *tert*-butyl methyl ether/pentane); $[\alpha]_D^{25} = -37.4$ (c = 0.760, $CHCl_3$); ^1H NMR δ 1.4 (d, 3H, J = 6.4 Hz), 2.3 (s, 1H), 3.77 (s, 3H), 5.0 (q, 1H, J = 6.3 Hz), 6.9 (dd, 1H, J = 2.6 Hz, J = 8.6 Hz), 7.3 (d, 1H, J = 2.3 Hz), 7.4 (d, 1H, J = 8.5 Hz); ^{13}C NMR δ 23.8, 55.5, 73.1, 97.2, 114.7, 124.2, 126.6, 139.6, 159.0; MS (EI) *m/z* (relative intensity) 278 (44), 264 (16), 263 (100), 136 (5), 135 (20), 134 (7), 108 (38), 92 (6), 77 (12), 63 (11); HRMS M^+ *m/e* 277.9794, calcd for $C_9H_{11}IO_2$ *m/e* 277.9804; IR ($CHCl_3$) ν 3424, 2974, 1598, 1488, 1283, 1037 cm^{-1}. Anal. Calcd for $C_9H_{11}IO_2$ (278.09): C, 38.87; H, 3.99; O, 11.51. Found: C, 38.88; H, 4.07; O, 11.61.

(*S*)-1-(2-Iodo-5-methoxyphenyl)ethanol (13b). GP1: reaction time, 19 h at −25 °C; 89% (895 mg) yield; 96% ee;[29] purification by flash-chromatography (silica gel, 1:20 ethyl acetate/pentane). $[\alpha]_D^{25} = -41.9$ (c = 0.675, $CHCl_3$); ^1H NMR δ 1.42 (d, 3H, J = 6.4 Hz), 2.3 (br, 1H), 3.79 (s, 3H), 4.99 (q, 1H, J = 6.3 Hz), 6.56 (dd, 1H, J = 3.0 Hz, J = 8.7 Hz), 7.14 (d, 1H, J = 3.0 Hz), 7.63 (d, 1H, J = 8.7 Hz); ^{13}C NMR δ 23.7, 55.4, 73.5, 85.3, 111.9, 115.4, 139.7, 148.6, 160.3; MS (EI) *m/z* (relative intensity) 278 (100), 263 (68), 136 (53), 135 (31), 109 (10), 108 (74), 107 (11), 92 (14), 91 (12), 77 (24); HRMS M^+ *m/e* 277.9806, calcd for $C_9H_{11}IO_2$ *m/e* 277.9804; IR ($CHCl_3$) ν 3424, 2976, 1591, 1567, 1467, 1288, 1006 cm^{-1}.

(*S*)-2-Iodo-4-methoxy-(1-methoxyethyl)benzene (14a). GP2: deprotonation, 30 min; methylation 3 h; purification by flash-chromatography (silica gel, 1:20 *tert*-butyl methyl ether/pentane); 90% (135 mg) yield; colorless oil; $[\alpha]_D^{25} = -70.6$ (c = 1.075, $CHCl_3$); ^1H NMR δ 1.35 (d, 3H, J = 6.3 Hz), 3.22 (s, 3H), 3.78 (s, 3H), 4.49 (q, 1H, J = 6.3 Hz), 6.95 (dd, 1H, J = 2.6 Hz, J = 8.6 Hz), 7.30 (d, 1H, J = 8.6 Hz), 7.33 (d, 1H, J = 2.6 Hz); ^{13}C NMR δ 22.7, 55.4, 56.4, 82.1, 98.1, 115.0, 124.0, 126.8, 137.4, 159.0; MS (EI) *m/z* (relative intensity) 292 (28), 278 (19), 277 (100), 261 (21), 149 (7), 134 (17), 121 (7), 119 (6), 91 (10), 77 (8), 63 (8); HRMS M^+ *m/e* 291.9954, calcd for $C_{10}H_{13}IO_2$ *m/e* 291.9960; IR ($CHCl_3$) ν 2978, 1597, 1562, 1488, 1284, 1110, 1037 cm^{-1}.

(*S*)-2-Iodo-5-methoxy-(1-methoxyethyl)benzene (14b). GP2: deprotonation, 30 min; methylation, 4 h; purification by flash-chromatography (silica gel, 1:50 *tert*-butyl methyl ether/pentane); 93% (146 mg) yield; colorless oil; $[\alpha]_D^{25} = -75.9$ (c = 0.70, $CHCl_3$); ^1H NMR δ 1.36 (d, 3H, J = 6.5 Hz), 3.25 (s, 3H), 3.80 (s, 3H), 4.47 (q, 1H, J = 6.4 Hz), 6.58 (dd, 1H, J = 3.1 Hz, J = 8.7 Hz), 7.01 (d, 1H, J = 3.2 Hz), 7.65 (d, 1H, J = 8.7 Hz); ^{13}C NMR δ 22.6, 55.3, 56.7, 82.7, 86.3, 111.856, 115.6, 139.7, 146.6, 160.5; MS (EI) *m/z* (relative intensity) 293 (10), 292 (61), 278 (18), 277 (100), 262 (29), 261 (13), 135 (21), 134 (26), 91 (17), 77 (13); HRMS M^+ *m/e* 291.9956 calcd for $C_{10}H_{13}IO_2$ *m/e* 291.9960; IR ($CHCl_3$) ν 2932, 1590, 1467, 1285, 1111, 1006 cm^{-1}.

(*S*)-Bis(acetato-*O*)[2-(1-methoxyethyl)phenyl]iodine. GP3: reaction conditions, 50 °C, 3 h; yield 73% (1.58 g); white powder, mp 104−106 °C; $[\alpha]_D^{25} = -61.1$ (c = 0.94, $CHCl_3$); ^1H NMR δ 1.5 (d, 3H, J = 6.3 Hz), 1.97 (s, 6H), 3.24 (s, 3H), 4.67 (q, 1H, J = 6.3 Hz), 7.37 (m, 1H), 7.71 (m, 2H), 8.20 (dd, 1H, J = 1.2 Hz, J = 8.0 Hz); ^{13}C NMR δ 20.2, 23.8, 56.8, 82.0, 124.9, 127.4, 130.3, 133.1, 137.4, 144.6, 176.3; IR ($CHCl_3$) ν 2933, 1714, 1648, 1365, 1110 cm^{-1}.

(*S*)-Bis(acetato-*O*)[2-(1-methoxyethyl)-5-methoxyphenyl]iodine. GP3: reaction conditions, 60 °C, 3 h; yield 89% (73 mg); white solid, mp 93−96 °C; $[\alpha]_D^{25} = -45.2$ (c = 0.98, $CHCl_3$); ^1H NMR δ 1.47 (d, 3H, J = 6.4 Hz), 1.98 (s, 6H), 3.21 (s, 3H), 3.87 (s, 3H), 4.6 (q, 1H, J = 6.4 Hz), 7.21 (dd, 1H, J = 2.5 Hz, J = 8.7 Hz), 7.62 (dd, 1H, J = 0.9 Hz, J = 8.7 Hz), 7.72 (d, 1H, J = 2.6 Hz); ^{13}C NMR δ 20.3, 23.9, 55.8, 56.6, 81.1, 119.6, 121.9, 124.7, 128.1, 136.0, 159.8, 176.3; IR ($CHCl_3$) ν 2980, 1730, 1597, 1488, 1284, 1110, 1020 cm^{-1}.

(*S*)-Bis(acetato-*O*)[2-[1-methoxyethyl]-4-methoxyphenyl]iodine. GP3: reaction conditions, 60 °C, 3 h; yield 40% (55 mg); white powder, mp 91−94 °C; $[\alpha]_D^{25} = -68.6$ (c = 0.55, $CHCl_3$); ^1H NMR δ 1.49 (d, 3H, J = 6.4 Hz), 1.95 (s, 6H), 3.26 (s, 3H), 3.89 (s, 3H), 4.62 (q, 1H, J = 6.4 Hz), 6.87 (dd, 1H, J = 3.1 Hz, J = 8.8 Hz), 7.17 (d, 1H, J = 3.1 Hz), 8.11 (d, 1H, J = 8.8 Hz); ^{13}C NMR δ 20.3, 23.9, 55.7, 57.0, 82.0, 112.7, 114.9, 139.3, 147.2, 163.4, 176.4; IR ($CHCl_3$) ν 2936, 1645, 1588, 1470, 1365, 1295, 1111 cm^{-1}.

(*S*)-Bis(acetato-*O*)[2-(1-ethoxyethyl)phenyl]iodine. GP3: reaction conditions, 50 °C, 4 h; yield 61% (165 mg); ^1H NMR δ 1.19 (t, 3H, J = 7.0 Hz), 1.50 (d, 3H, J = 6.5 Hz), 1.96 (s, 6H), 3.38 (m, 2H), 4.77 (q, 1H, J = 6.4 Hz), 7.36 (tm, 1H, J = 7.6 Hz), 7.67 (t, 1H, J = 7.5 Hz), 7.75 (d, 1H, J = 7.7 Hz), 8.20 (d, 1H, J = 7.9 Hz); ^{13}C NMR δ 15.2, 20.15, 24.0, 64.3, 80.0, 124.7, 127.8, 130.1, 133.0, 137.3, 145.2, 176.2; IR ($CHCl_3$) ν 2979, 1650, 1435, 1371, 1275, 1098, 1009 cm^{-1}.

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Supporting Information Available: ^1H NMR spectra of compounds **3d**, **7a**,**b**,**d**,**e**, **10b**−**d**, **13a**,**b**, and **14a**,**b** and X-ray diagrams and crystallographic data tables for compounds **3b** and **10d** (27 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(28) The configuration is determined by reduction of **13a** with $LiAlH_4$ to (*S*)-1-(4-methoxyphenyl)ethanol and comparison of the optical rotation with the literature: Brown, S. M.; Davies, S. G.; Sousa, J. A. A. *Tetrahedron: Asymmetry* **1993,** *4*, 813−822.

(29) The configuration is determined by reduction of **13b** with $LiAlH_4$ to (*S*)-1-(3-methoxyphenyl)ethanol and comparison of the optical rotation with the literature: Chen, C. P.; Prasad, K.; Repic, O. *Tetrahedron Lett.* **1991**, *32*, 7175−7178.