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Rh(I)-Catalyzed Asymmetric Synthesis of 3-Substituted Isoindolinones through CO Gas-Free Aminocarbonylation

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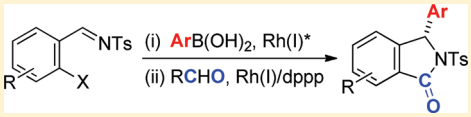
Supporting Information

ABSTRACT: A highly efficient and accessible synthesis of chiral 3-substituted isoindolinone frameworks is described. The synthesis involved the Rh(I)-catalyzed asymmetric arylation of boronic acids to 2-halobenzaldimines and the subsequent Rh(I)-catalyzed intramolecular aminocarbonylation of the resulting 2-halobenzylamines using an aldehyde as the carbonyl source. The method tolerates a variety of functional groups, yielding isoindolinone derivatives in moderate to high yields with high ee-values. In addition, two Rh(I)-catalyzed transformations could be efficiently accomplished in a one-pot sequence to give chiral isoindolinones by the simple addition of a ligand and an aldehyde after the Rh(I)-catalyzed asymmetric arylation.



INTRODUCTION

Chiral 3-substituted isoindolinone frameworks are frequently found in bioactive molecules. Examples include the anxiolytic drug candidate pagoclone (**1**),[1] a sedative-hypnotic drug candidate JM-1232 (**2**),[2] a dopamine D4 receptor antagonist PD-172938 (**3**),[3] and a NK_2 antagonist ZD7944 (**4**)[4] (Figure 1). In addition, the chiral 3-methyl analogues **5a** or **b**, which contain a dienophile[5a] or diene,[5b,c] have been used as a chiral auxiliary in asymmetric Diels–Alder reactions. Because of this, interest has focused on the development of an efficient synthetic method for the synthesis of such a framework.[6]

The rhodium(I)-catalyzed reaction of 2-(*N*-tosylimino)-benzoates with arylboronic acids has been reported to be an effective approach for the construction of a chiral 3-substituted isoindolinone framework.[7] The reaction involves the asymmetric arylation of the imino group and the subsequent, spontaneous ester-amide exchange, leading to the complete formation of isoindolinones, accompanied by the production of a new chiral center at the 3-position. This method has a major disadvantage, in that the substrates, 2-(*N*-tosylimino)benzoates, and their synthetic materials, 2-formylbenzoates, are not readily available.

On the other hand, the palladium-catalyzed aminocarbonylation of aryl halides that contains a nitrogen-nucleophile at the *ortho*-position also represents a convenient synthesis of isoindolinones.[8] However, the method suffers from the need for the use of toxic, gaseous carbon monoxide. In constrast, we recently reported on a concise synthesis of isoindolinones by the rhodium(I)-catalyzed intramolecular aminocarbonylation of aryl halides having a nitrogen-nucleophile at the *ortho*-position, using aldehydes as a carbonyl source (Scheme 1).[9] The method can be operationally simply substituted for the original aminocarbonylation using carbon monoxide. Thus, two rhodium-catalyzed processes, namely, the abstraction of a carbonyl moiety from an aldehyde by the rhodium catalyst (decarbonylation) and the introduction of the abstracted carbonyl moiety into 2-bromobenzylamine (amino-carbonylation), function cooperatively, resulting in a simple, straightforward aminocarbonylation procedure.

If the method is to be applied to the asymmetric synthesis of 3-chiral isoindolinones, chiral 2-halobenzylamines, which can be prepared by the rhodium(I)-catalyzed asymmetric addition of boronic acids to 2-haloarylaldimines, are required.[10] We describe herein a new concise synthesis of chiral 3-substituted isoindolinones based on the above rhodium(I)-catalyzed aminocarbonylation, which can be carried out in conjunction with the rhodium(I)-catalyzed asymmetric addition of arylboronic acids to 2-haloarylaldimines, and on the one-pot sequence of these rhodium(I)-catalyzed reactions (Scheme 2). In the one-pot synthesis, the loaded rhodium complex plays three sequential catalytic roles, asymmetric arylation/decarbonylation/aminocarbonylation. The present method reported here affords a more accessible route for the synthesis of chiral 3-substituted isoindolinones compared with the conventional methods from the following aspects: (i) the ready availability of the substrates, *N*-tosyl-2-bromoarylaldimines, and their synthetic precursors, 2-bromoarylaldehydes, and (ii) no need for the use of carbon monoxide.

RESULTS AND DISCUSSION

We first examined the rhodium(I)-catalyzed aminocarbonylation reaction of an enantioenriched 2-halobenzylamine with an aldehyde. Enantioenriched *N*-tosyl-2-bromobenzylamine (**7a**), prepared in 99% ee (*S*) from 2-bromobenzaldimine (**6a**) using the method described by Hayashi, was used as the substrate (Scheme 3i).[11] When (*S*)-**7a** was treated with 5 equiv of pentafluorobenzaldehyde in the presence of 5 mol % of $[RhCl(cod)]_2$, 10 mol % of dppp, and 2 equiv of K_2CO_3 in xylene at 130 °C,[8] the aminocarbonylation proceeded to give the desired 3-phenylisoindolinone (**8a**) in 89% isolated yield, along with 10% of the hydrogenated starting material (**9a**) in 10% yield (Scheme 3i-b). Although it is known that the deprotonation of isoindolinone at the C-3 position can lead to epimerization under strongly basic

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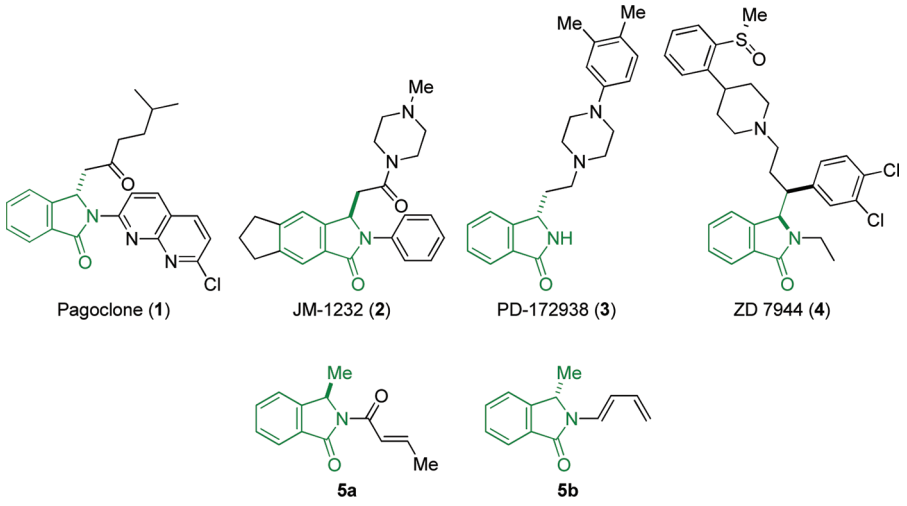
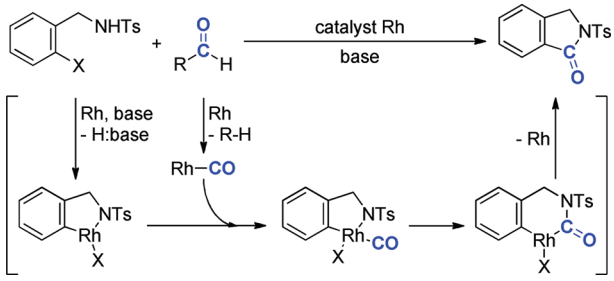
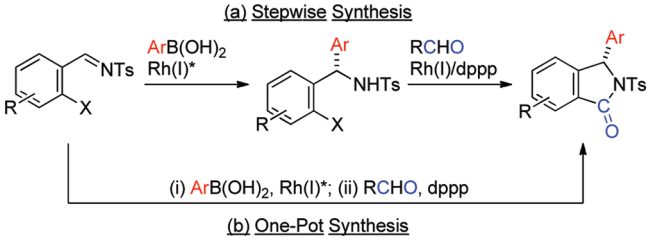


Figure 1. Representative chiral 3-substituted isoindolinone.

Scheme 1. Rh(I)-Catalyzed Isoindolinone Synthesis from 2-Halobenzylamines with Aldehydes through CO Gas-Free Aminocarbonylation



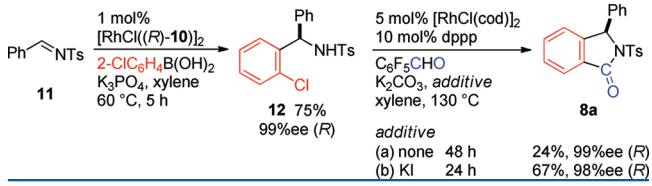
Scheme 2. A New Strategy for the Convenient Synthesis of Chiral 3-Substituted Isoindolinones



conditions,[6d,12] the enantiomeric excess and the absolute configuration of **8a** (99% ee (*S*)) were not diminished under the present basic conditions, compared with those of **7a**. When **7a** was reacted with 1 atm of carbon monoxide, instead of C_6F_5CHO, under otherwise identical conditions, **7a** was completely consumed within 8 h to give **8a** in a lower yield (77% with 98% ee (*S*)). In the case of this transformation, paraformaldehyde, a low-cost C1 feedstock, could also be used as the carbonyl source.[9,13,14] The use of paraformaldehyde (10 equiv) in the transformation resulted in the production of the carbonylated product **8a** in 68% yield; however, the yield of the unfavorable product **9a** was increased to 30% (Scheme 3ii-b).

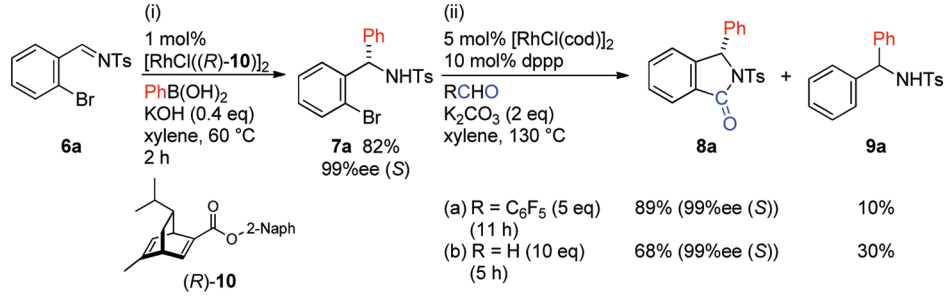
The reverse enantiomer, (*R*)-**8a**, was synthesized via the rhodium(I)-catalyzed aminocarbonylation of the (*R*)-enantiomer of *N*-tosyl-2-chlorobenzylamine (**12**), which can be readily prepared by the asymmetric addition of 2-chlorophenylboronic acid to *N*-tosylbenzaldimine (**11**) using the same rhodium catalyst ($[RhCl((R)\text{-}\mathbf{10})]_2$) with Scheme 3i.[15] When (*R*)-**12** (99% ee) was reacted with pentafluorobenzaldehyde in the presence of the rhodium catalyst, the desired isoindolinone, (*R*)-**8a**, was obtained with 99% ee, although in low yield (24%) (Scheme 4). The use of KI (1 equiv) as an additive increased the chemical yield to 67% with the ee maintained.

Scheme 4. Synthesis of Reverse Enantiomer, (*R*)-8a



We next explored the scope of the reaction with respect to the substituents on the aromatic ring of the arylboronic acids. Reactions using pentafluorobenzaldehyde as a carbonyl source

Scheme 3. Rh(I)-Catalyzed Aminocarbonylation of Chiral Benzylamine (*S*)-7a with Aldehydes



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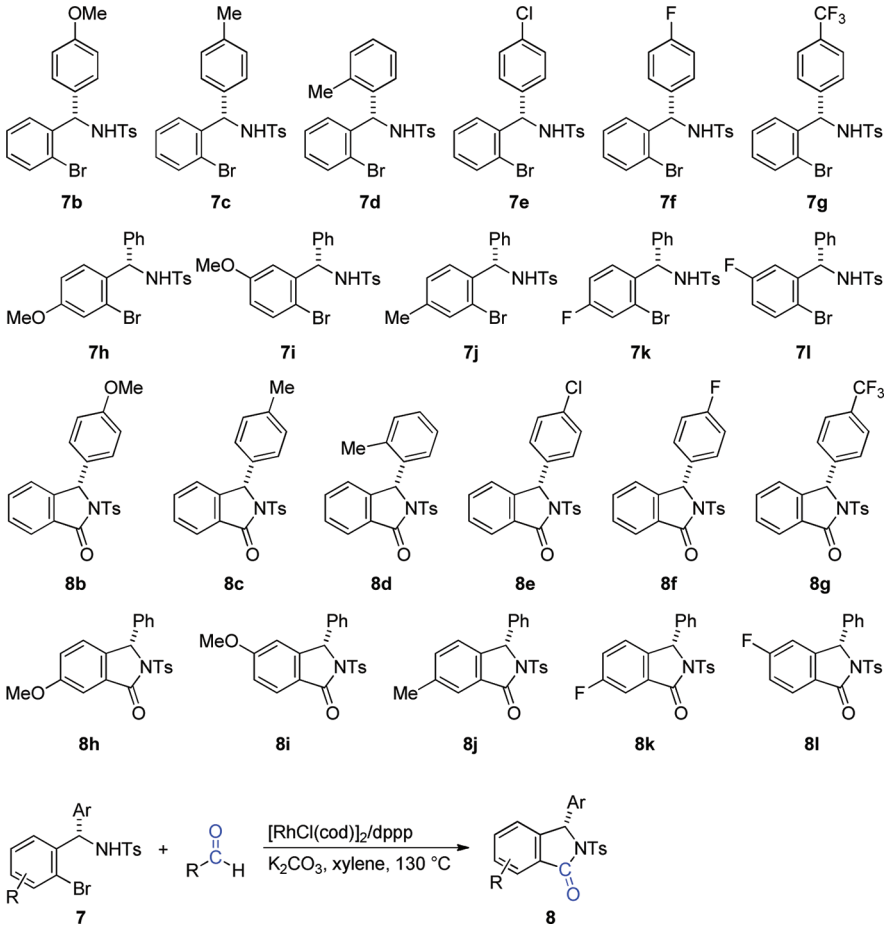
are general and high-yielding and usually do not involve the degradation of the optical purity of the substrates. The results are summarized in Table 1. Substrates containing an electron-donating group such as methoxy and methyl groups reacted

Table 1. Rh(I)-Catalyzed Aminocarbonylative Cyclization of Various Chiral Bromobenzylamines[a]



entry	substrate	aldehyde (R)[b]	time (h)	product	yield (%)[c]	ee (%) (config)[d]
1	**7b** (99% ee (*S*))	C_6F_5	7	**8b**	84	99 (*S*)
2		H	7		73	99 (*S*)
3	**7c** (99% ee (*S*))	C_6F_5	8	**8c**	93	98 (*S*)
4		H	6		71	99 (*S*)
5	**7d** (99% ee (*S*))	C_6F_5	8	**8d**	88	95 (*S*)
6		H	6		64	99 (*S*)
7	**7e** (99% ee (*S*))	C_6F_5	10	**8e**	86	99 (*S*)
8		H	8		54	99 (*S*)
9	**7f** (99% ee (*S*))	C_6F_5	5	**8f**	80	99 (*S*)
10		H	5		58	99 (*S*)
11	**7g** (99% ee (*S*))	C_6F_5	5	**8g**	81	99 (*S*)
12		H	5		53	99 (*S*)
13	**7h** (99% ee (*S*))	C_6F_5	48	**8h**	87	99 (*S*)
14		H	18		73	99 (*S*)
15	**7i** (99% ee (*S*))	C_6F_5	60	**8i**	75	98 (*S*)
16		H	18		51	96 (*S*)
17	**7j** (99% ee (*S*))	C_6F_5	20	**8j**	90	99 (*S*)
18		H	15		68	99 (*S*)
19	**7k** (99% ee (*S*))	C_6F_5	16	**8k**	84	99 (*S*)
20		H	15		53	97 (*S*)
21	**7l** (99% ee (*S*))	C_6F_5	17	**8l**	91	99 (*S*)
22		H	16		55	97 (*S*)

[a]Reaction conditions: *N*-tosyl-2-bromobenzylamine (0.25 mmol), aldehyde, $[RhCl(cod)]_2$ (0.0125 mmol), dppp (0.025 mmol), K_2CO_3 (0.5 mmol), and xylene (2 mL) at 130 °C. [b]C_6F_5: C_6F_5CHO (1.25 mmol); H: paraformaldehyde (2.5 mmol). [c]Isolated yield. [d]Products' ee-values were measured by HPLC analysis. Their absolute configurations were determined from specific optical rotation measurement or X-ray crystallographic analysis. See the Supporting Information.

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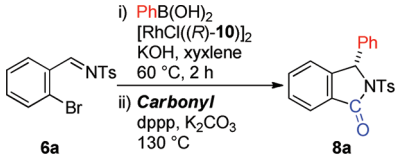
smoothly with pentafluorobenzalehyde to afford **8b** and **8c** in 84 and 93%, respectively (Table 1, entries 1 and 3). **7d**, containing a 2-methyl phenyl group also reacted readily, despite the steric hindrance close to the reaction site (Table 1, entry 5). The reaction of **7e** gave the corresponding **8e** without the loss of the Cl group (Table 1, entry 7). Compounds **7f** and **7g**, which contain electron-withdrawing groups, such as F and CF_3, also reacted smoothly to yield **8f** and **8g** in 80 and 81%, respectively (Table 1, entries 9 and 11). The use of paraformaldehyde instead of pentafluorobenzaldehyde as a carbonyl source also afforded the corresponding isoindolinones with their ee-values maintained, but the yields were lower than when pentafluorobenzaldehyde was used (Table 1, entries 2, 4, 6, 8, 10, and 12). We further examined the effect of various substituents on the aromatic ring of 2-bromoarylaldimines on the carbonylation reaction. Irrespective of the electronic nature of the substituent introduced, the reaction proceeded slightly more slowly than that of the substrates of entries 1−12 (Table 1), but the corresponding isoindolinones were obtained in good to high yields with 96−99% ee (Table 1, entries 13−22).

The fact that the synthesis of **7a**, as well as the above aminocarbonylation of **7a**, can be catalyzed by a rhodium(I) complex encouraged us to further investigate the rhodium(I)-catalyzed one-pot arylation−aminocarbonylation sequence from aldimine **6a** to isoindolinone **8a**. The asymmetric arylation of aldimines catalyzed by a rhodium(I)-chiral diene complex was chosen as the first step, the in situ formation of enantiomerically enriched 2-bromobenzylamines, because it is well-known that the use of chiral diene ligands leads to a more smooth reaction with higher enantioselectivity than chiral phosphine ligands in the rhodium(I)-catalyzed arylation of aldimines.[16] Aldimine **6a** was first reacted with 1.1 equiv of $PhB(OH)_2$ in the presence of 5 mol % $[RhCl((R)\text{-}\mathbf{10})]_2$ and 0.4 equiv of KOH as a base in xylene at 60 °C for 2 h. After completion of this reaction, **5** equiv of pentafluorobenzaldehyde, 10 mol % of dppp, and 2 equiv of K_2CO_3 were added to the reaction mixture, and the resulting mixture was stirred at 130 °C until the intermediate **7a** had been completely consumed (7 h). The desired isoindolinone **8a** was obtained in 82% yield with 97% ee (*S*) (Scheme 5a). This result shows that the one-step sequence is more efficient than the two-step one, which yields the same product **8a** in 73% combined yield as shown in Scheme 3. Paraformaldehyde could also work well to give **8a** in 68% yield with 99% ee (*S*) (Scheme 5b). As for the aminocarbonylation of **7a** mentioned above, these aldehydes were superior to carbon monoxide as a carbonyl source in this sequential catalysis. Thus, the use of atmospheric carbon monoxide instead of pentafluorobenzaldehyde in the second step resulted in a longer reaction time for the complete consumption of the synthetic intermediate **7a** (13 h) and a lower chemical yield of **8a** (58%) with 98% ee (*S*). Unfortunately, a one-pot procedure in which all the reagents are introduced simultaneously afforded no phenylation product **7a**, and no carbonylated product **8a**.[17]

Scheme 5. One-Pot Procedure for Synthesis of Chiral Isoindolinone 8a from Aldimine 6a



(a) C_6F_5CHO (7 h) 82% (97%ee (*S*)) (73% for 2 steps)
(b) $(CH_2O)_n$ (8 h) 68% (99%ee (*S*))
(c) CO (1 atm) (13 h) 58% (98%ee (*S*))

The results for the one-pot reactions using various arylboronic acids and aldimines are listed in Table 2. Reactions of **6a** with various arylboronic acids containing electron-donating or -withdrawing groups on the aromatic ring proceeded smoothly to give the corresponding 3-arylisoindolinones **8b−g** in high yields and ee-values. The introduction of substituents into the aromatic ring of aldimines had only negligible effects, and one-pot asymmetric synthesis of 3-arylisoindolinones **8h−l** also proceeded smoothly.

The synthesis of the reverse enantiomer (*R*)-**8a** was examined under the developed one-pot conditions. The rhodium(I)-catalyzed reaction of *N*-tosylbenzaldimine (**11**) with 2-chlorophenylboronic acid, followed by reaction with pentafluorobenzaldehyde, afforded (*R*)-**8a** in 56% isolated yield with 98% ee. Compared to that of Scheme 4, this is slightly more efficient (Scheme 6).

Finally, we applied the one-pot procedure to the construction of a chiral 3-arylphthalide framework, which is also found in a variety of bioactive molecules.[18] When 2-bromobenzaldehyde (**13**) was exposed to conditions similar to those described in Table 2, except for the base used (K_3PO_4), the reaction led to the formation of the desired phthalide **14** in 73% yield with 62% ee (*S*) (Scheme 7). As in the other cases described above, no decrease in chemical yield and enantiomeric excess was detected for the one-pot operation because, in the case of two-step synthesis of phthalide **14**, the first step gave the primary product **15** in 93% with 62% ee (*S*) and the second step resulted in the production of **14** in 75% yield. Although some optimization will still be required for higher yield and higher enantioselectivity, it was found that the present one-pot method appears to be a convenient synthetic tool for producing enantioenriched 3-substituted phthalides.

CONCLUSION

We report on a new protocol for the synthesis of chiral 3-substituted isoindolinones through Rh(I)-catalyzed asymmetric arylation and the subsequent aminocarbonylative cyclization using an aldehyde as the carbonyl source. Enantioenriched 3-substituted isoindolinones containing a wide range of substituents on the aromatic ring could be obtained from readily available substrates in moderate to high yields with high ee-values. The two Rh(I)-catalyzed processes can be carried out efficiently in a one-pot operation without any detectable loss of enantioselectivity. Furthermore, the present one-pot protocol is applicable to the asymmetric arylation-alkoxycarbonylation sequence of 2-bromobenzaldehyde leading to the synthesis of enantioenriched 3-arylphthalides.

EXPERIMENTAL SECTION

General Considerations. Nuclear magnetic resonance spectra were recorded on a 500 MHz spectrometer. Chemical shifts of ^1H NMR spectra are given in ppm using the solvent signal as the internal standard ($CDCl_3$, δ = 7.26 ppm). Data are reported as follows: multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constant in Hz, and integration. ^{13}C NMR chemical shifts are given in ppm using deuteriochloroform (77.0 ppm) as the internal standard. Infrared absorption peaks are reported in reciprocal centimeters with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra were obtained with ionization voltages of 70 eV. High performance liquid chromatography was

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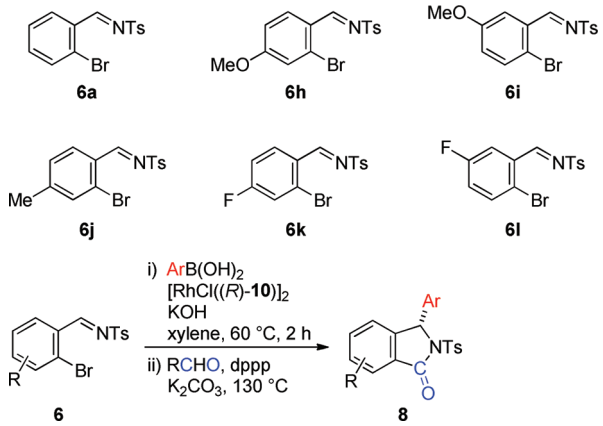
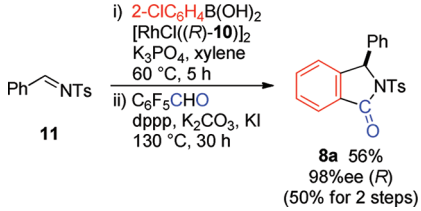
Table 2. One-Pot Synthesis of Various Chiral Isoindolinone from Aldimines[a]



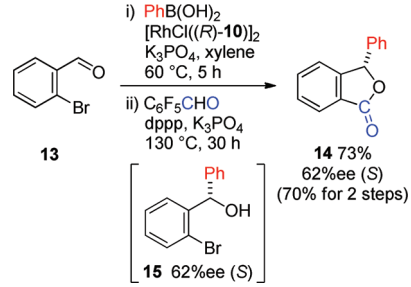
entry	aldimine	Ar	aldehyde (R)[b]	time (h)	product	yield (%)[c]	ee (%) (config)[d]
1	**6a**	4-OMeC_6H_4	C_6F_5	17	**8b**	79	99 (*S*)
2			H	10		66	99 (*S*)
3	**6a**	4-MeC_6H_4	C_6F_5	14	**8c**	85	97 (*S*)
4			H	10		59	97 (*S*)
5	**6a**	2-MeC_6H_4	C_6F_5	14	**8d**	82	96 (*S*)
6			H	12		56	97 (*S*)
7	**6a**	4-ClC_6H_4	C_6F_5	7	**8e**	74	99 (*S*)
8			H	6		51	99 (*S*)
9	**6a**	4-FC_6H_4	C_6F_5	9	**8f**	24	99 (*S*)
10			H	8		38	97 (*S*)
11	**6a**	4-$CF_3C_6H_4$	C_6F_5	7	**8g**	79	99 (*S*)
12			H	11		55	95 (*S*)
13	**6h**	Ph	C_6F_5	14	**8h**	87	90 (*S*)
14			H	12		70	94 (*S*)
15	**6i**	Ph	C_6F_5	16	**8i**	85	99 (*S*)
16			H	10		71	99 (*S*)
17	**6j**	Ph	C_6F_5	17	**8j**	89	94 (*S*)
18			H	16		65	99 (*S*)
19	**6k**	Ph	C_6F_5	26	**8k**	78	95 (*S*)
20			H	11		50	85 (*S*)
21[e]	**6l**	Ph	C_6F_5	16	**8l**	79	95 (*S*)
22[e]			H	12		51	96 (*S*)

[a]Reaction conditions: aldimine 6 (0.50 mmol), arylboronic acid (0.55 mmol), [RhCl((*R*)-10)]$_2$ (0.025 mmol), KOH (0.20 mmol), and xylene (2 mL) at 60 °C for 2 h; then, aldehyde, dppp (0.050 mmol), and K_2CO_3 (1.0 mmol) at 130 °C. [b]C_6F_5: C_6F_5CHO (2.5 mmol); H: paraformaldehyde (5 mmol). [c]Isolated yield. [d]Products' ee-values were measured by HPLC analysis. Their absolute configurations were determined from specific optical rotation measurement or X-ray crystallographic analysis. See the Supporting Information. [e]In step (i), K_2CO_3 was used as a base instead of KOH.

Scheme 6. One-Pot Synthesis of (*R*)-3-Phenylisoindolinone (8a)



Scheme 7. Application for the Synthesis of (*S*)-3-Phenylphthalide (14)



conducted using an ultraviolet detector. Optical rotations were measured on a digital polarimeter. Chrystal of suitable for X-ray structural determination was mounted on a glass fiber. The structure was solved by direct methods and refined on *F* by full-matrix least-squares using all unique data. Hydrogen atoms have been included in calculated positions (riding model) for the structure.

Materials. All commercial reagents were used as supplied or purified by standard techniques where necessary. [RhCl(cod)]$_2$,[19] chiral diene (*R*)-**10**,[11] and [RhCl((*R*)-**10**)]$_2$[20] were prepared using reported methods, respectively. *N*-Tosyl-benzaldimines, **6a–l** and **11** were prepared from the corresponding benzaldehydes and *p*-toluenesulfonamide using the reported procedure.[21] Racemic and chiral benzylamines **7** and **12** were prepared using the reported procedure[11] with [RhCl(cod)]$_2$ and [RhCl((*R*)-**10**)]$_2$, respectively, with minor modifications.

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Determination of Absolute Configuration. The absolute configurations of **7b–k** were determined from specific optical rotation data of the known compounds **9b–k**, which were prepared by the hydrogenation of **7b–k** using a Pd-catalyst.[22] The absolute configurations of **7l** and **8c–l** were determined from X-ray crystallographic analysis.[23]

Substrates for Schemes 3 and 4 and Table 1: *N*-Tosylbenzylamines 7 and 12. *N-[(2S)-(2-Bromophenyl)-phenylmethyl]-4-methylbenzenesulfonamide (**7a**).*[24] White solid: mp 173.5–174.6 °C; R_f 0.22 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 5.28 (d, J = 6.7 Hz, 1H), 5.90 (d, J = 6.7 Hz, 1H), 7.05–7.09 (m, 3H), 7.17 (d, J = 8.6 Hz, 2H), 7.19–7.23 (m, 4H), 7.36 (dd, J = 7.6, 1.5 Hz, 1H), 7.43 (dd, J = 7.6, 1.5 Hz, 1H), 7.63 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 60.4, 123.0, 127.2, 127.4, 127.5, 127.8, 128.6, 128.9, 129.3, 129.4, 133.0, 136.8, 139.0, 139.2, 143.3; IR (KBr) 3291 m, 3237 m, 1597 w, 1494 w, 1467 m, 1439 m, 1321 s, 1305 m, 1152 s, 1093 s, 1045 w, 1022 m, 941 m, 906 w, 830 w, 813 m, 755 s, 697 s, 680 m, 663 m, 606 w, 574 s, 547 s, 504 w; MS m/z (relative intensity, %) 263 (11), 262 (85), 261 (16), 260 (M^+ – Ts, 100), 207 (24), 182 (11), 180 (29), 166 (20), 165 (29), 155 (24), 104 (18), 92 (12), 91 (68), 77 (29), 65 (15), 51 (12); exact mass-ESI calcd for $C_{20}H_{18}BrNNaO_2S$ 438.0139 [M + Na]$^+$, found 438.0140; $[\alpha]^{17}_D$ = +24.5° (c 0.77, $CHCl_3$) for 99% ee (S); HPLC (Chiralpak AD-H, n-hexane/2-propanol = 90/10, flow = 0.7 mL/min, detection at 254 nm) R_t = 27.1 min (S), R_t = 29.9 min (R). The absolute configuration was assigned as S from the comparison with the reported HPLC retention time and specific optical rotation (lit. $[\alpha]^{20}_D$ = +14.5° (c 0.77, $CHCl_3$) for 84% ee (S)).

*N-[(2S)-(2-Bromophenyl)(4-methoxyphenyl)methyl]-4-methylbenzenesulfonamide (**7b**).* White solid: mp 144.7–145.9 °C; R_f 0.19 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.72 (s, 3H), 5.77 (d, J = 6.7 Hz, 1H), 5.88 (d, J = 6.7 Hz, 1H), 6.72 (d, J = 8.6 Hz, 2H), 6.97 (d, J = 8.6 Hz, 2H), 7.04 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 7.9 Hz, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.61 (d, J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4, 55.1, 59.9, 113.8, 122.9, 127.1, 127.5, 128.7, 128.8, 129.1, 129.3, 131.2, 132.9, 136.8, 139.3, 143.2, 158.9; IR (KBr) 3251 m, 1609 m, 1512 s, 1439 m, 1332 m, 1307 m, 1255 s, 1156 s, 1093 m, 1068 m, 1024 m, 945 w, 922 w, 842 w, 816 m, 782 w, 752 w, 728 w, 680 m, 663 m, 572 m, 546 m; MS m/z (relative intensity, %) 293 (12), 292 (79), 291 (41), 290 (M^+ – Ts, 100), 289 (33), 288 (18), 260 (16), 258 (16), 211 (11), 210 (63), 196 (14), 195 (18), 181 (10), 167 (12), 165 (12), 155 (14), 153 (12), 152 (16), 134 (31), 109 (10), 92 (13), 91 (71), 77 (18), 65 (23); exact mass-ESI calcd for $C_{21}H_{20}BrNNaO_3S$ 468.0245 [M + Na]$^+$, found 468.0246; $[\alpha]^{17}_D$ = +41.3° (c 1.00, $CHCl_3$) for 99% ee (S); HPLC (Chiralpak AD-H, n-hexane/2-propanol = 90/10, flow = 0.7 mL/min, detection at 254 nm) R_t = 40.1 min (R), R_t = 44.8 min (S). The absolute configuration of **7b** was determined from specific optical rotation of the known compound **9b**,[25] which was prepared by the hydrogenation of **7b** using a Pd-catalyst.

*(2R)-N-[(4-Methoxyphenyl)phenylmethyl]-4-methylbenzenesulfonamide (**9b**).*[25] White solid: mp 125.7–127.0 °C; R_f 0.28 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.74 (s, 3H), 5.33 (d, J = 7.3 Hz, 1H), 5.52 (d, J = 7.3 Hz, 1H), 6.72 (d, J = 8.6 Hz, 2H), 7.00 (d, J = 8.6 Hz, 2H), 7.10–7.13 (m, 4H), 7.18–7.20 (m, 3H), 7.55 (d, J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4, 55.2, 60.7, 113.8, 127.1, 127.2, 127.4, 128.4, 128.5, 129.3, 132.7, 137.3, 140.7, 143.0, 158.9; IR (KBr) 3239 s, 3007 m, 2952 s, 2833 m, 1885 w, 1609 s, 1510 s, 1494 s, 1433 s, 1378 w, 1322 s, 1252 s, 1159 s, 1114 s, 1092 s, 1033 s, 932 m, 905 m, 873 m, 843 s, 804 s, 776 m, 745 s, 728 s, 703 s, 672 s, 632 m, 581 s, 559 s, 540 s, 488 m; MS m/z (relative intensity, %) 213 (15), 212 (M^+ – Ts, 100), 211 (44), 210 (56), 197 (31), 181 (11), 180 (55), 165 (11), 155 (10), 153 (11), 134 (19), 104 (15), 91 (50), 77 (17), 65 (14); exact mass-ESI calcd for $C_{21}H_{21}NNaO_3S$ 390.11398 [M + Na]$^+$, found 390.11400; $[\alpha]^{23}_D$ = +20.8° (c 1.20, $CHCl_3$) for 98% ee (R) (lit. $[\alpha]^{20}_D$ = +13.6° (c 0.58, $CHCl_3$) for 93% ee (R)); HPLC (Chiralpak OD-H, n-hexane/2-propanol = 70/30, flow = 0.7 mL/min, detection at 254 nm) R_t = 11.9 min (S), R_t = 16.6 min (R).

*N-[(2S)-(2-Bromophenyl)(4-methylphenyl)methyl]-4-methylbenzenesulfonamide (**7c**).* White solid: mp 151.7–153.1 °C; R_f 0.23 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.39 (s, 3H), 5.17 (d, J = 6.7 Hz, 1H), 5.85 (d, J = 6.7 Hz, 1H), 6.92 (d, J = 7.9 Hz, 2H), 7.03 (d, J = 7.9 Hz, 2H), 7.07 (td, J = 7.6, 1.5 Hz, 1H), 7.18 (d, J = 7.9 Hz, 2H), 7.20 (td, J = 7.6, 1.5 Hz, 1H), 7.38 (dd, J = 7.6, 1.5 Hz, 1H), 7.42 (dd, J = 7.6, 1.5 Hz, 1H), 7.63 (d, J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.9, 21.4, 60.0, 122.9, 127.1, 127.2, 127.5, 128.7, 129.1, 129.2, 129.3, 132.8, 136.2, 136.8, 137.3, 139.3, 143.1; IR (KBr) 3292 m, 3247 m, 2923 w, 1597 w, 1511 w, 1494 w, 1440 m, 1321 s, 1152 s, 1123 m, 1094 s, 1076 m, 1022 m, 950 m, 931 m, 873 w, 837 w, 814 m, 782 w, 752 m, 719 m, 705 w, 681 m, 662 s, 576 s, 547 m, 487 w; MS m/z (relative intensity, %) 277 (13), 276 (84), 275 (16), 274 (M^+ – Ts, 100), 207 (11), 194 (31), 180 (13), 179 (10), 165 (25), 155 (15), 118 (18), 92 (11), 91 (75), 77 (11), 65 (23); exact mass-ESI calcd for $C_{21}H_{20}BrNNaO_2S$ 452.0296 [M + Na]$^+$, found 452.0295; $[\alpha]^{17}_D$ = +31.5° (c 1.00, $CHCl_3$) for 99% ee (S); HPLC (Chiralpak OD-H, n-hexane/2-propanol = 90/10, flow = 1.0 mL/min, detection at 254 nm) R_t = 9.3 min (R), R_t = 13.3 min (S). The absolute configurations of **7c** was determined from specific optical rotation of the known compound **9c**,[25] which was prepared by the hydrogenation of **7c** using a Pd-catalyst.

*(2R)-N-[(4-Methylphenyl)phenylmethyl]-4-methylbenzenesulfonamide (**9c**).*[25] White solid: mp 112.6–114.1 °C; R_f 0.30 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.38 (s, 3H), 5.36 (d, J = 7.3 Hz, 1H), 5.52 (d, J = 7.3 Hz, 1H), 6.98 (d, J = 8.6 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 7.10–7.13 (m, 4H), 7.18–7.21 (m, 3H), 7.56 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.4, 61.0, 127.1, 127.2, 127.3, 127.4, 128.4, 129.1, 129.3, 137.2, 137.3, 137.6, 140.6, 143.1; IR (KBr) 3853 w, 3734 w, 3649 w, 3261 w, 2922 w, 2360 w, 1599 w, 1558 w, 1541 w, 1508 w, 1491 w, 1434 m, 1321 m, 1163 s, 1093 m, 1043 m, 932 w, 843 w, 811 m, 777 w, 722 m, 701 m, 678 m, 561 m, 543 m; MS m/z (relative intensity, %) 197 (15), 196 (M^+ – Ts, 100), 194 (17), 181 (16), 180 (28), 165 (11), 118 (10), 104 (12), 91 (41), 77 (10), 65 (11); exact mass-ESI calcd for $C_{21}H_{21}NNaO_2S$ 374.11907 [M + Na]$^+$, found 374.11909; $[\alpha]^{26}_D$ = +12.5° (c 0.70, $CHCl_3$) for 99% ee (R) (lit. $[\alpha]^{20}_D$ = +11.0° (c 0.7, $CHCl_3$) for 94% ee (R)); HPLC (Chiralpak OD-H, n-hexane/2-propanol = 95/5, flow = 1.0 mL/min, detection at 254 nm) R_t = 17.5 min (S), R_t = 25.7 min (R).

*N-[(2S)-(2-Bromophenyl)(2-methylphenyl)methyl]-4-methylbenzenesulfonamide (**7d**).* White solid: mp 187.4–188.2 °C; R_f 0.23 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H), 2.38 (s, 3H), 4.85 (d, J = 6.1 Hz, 1H), 6.09 (d, J = 6.1 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 7.01 (br s, 1H), 7.08 (t, J = 7.9 Hz, 1H), 7.14–7.18 (m, 5H), 7.31 (d, J = 7.9 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.61 (d, J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 19.0, 21.5, 57.6, 123.4, 126.1, 127.1, 127.3, 127.6, 128.1, 128.9, 129.4, 129.5, 130.8, 133.0, 136.8, 136.9, 137.1, 138.7, 143.4; IR (KBr) 3288 m, 3062 w, 1597 w, 1494 w, 1435 m, 1346 m, 1327 m, 1304 w, 1185 w, 1157 s, 1092 m, 1054 m, 1018 m, 947 w, 904 w, 881 m, 837 w, 810 m, 791 w, 756 s, 723 m, 682 m, 665 m, 617 w, 578 m, 546 m, 499 w, 453 w; MS m/z (relative intensity, %) 276 (17), 274 (M^+ – Ts, 23), 260 (13), 258 (13), 194 (14), 180 (20), 179 (100), 178 (18), 165 (15), 155 (16), 91 (55), 65 (20); exact mass-ESI calcd for $C_{21}H_{20}BrNNaO_2S$ 452.02958 [M + Na]$^+$, found 452.02959; $[\alpha]^{17}_D$ = +83.4° (c 1.00, $CHCl_3$) for 99% ee (S); HPLC (Chiralpak OD-H, n-hexane/2-propanol = 95/5, flow = 0.6 mL/min, detection at 254 nm) R_t = 23.7 min (S), R_t = 25.8 min (R). The absolute configuration of **7d** was assigned as S from the specific optical rotation of **9d**,[25] which was prepared by the hydrogenation of **7d** using a Pd-catalyst.

*(2R)-N-[(2-Methylphenyl)phenylmethyl]-4-methylbenzenesulfonamide (**9d**).*[25] White solid: mp 166.0–167.5 °C; R_f 0.30 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H), 2.37 (s, 3H), 5.38 (d, J = 7.3 Hz, 1H), 5.80 (d, J = 7.3 Hz, 1H), 7.03–7.07 (m, 4H), 7.09–7.14 (m, 4H), 7.17–7.20 (m, 3H), 7.54 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 19.3, 21.4, 58.0, 126.1, 127.0, 127.2, 127.3, 127.4, 127.5, 128.5, 129.2, 130.5, 135.4, 137.4, 138.2, 139.9, 143.1; IR (KBr) 3734 w, 3649 w, 3292 m, 3236 m, 2922 w, 1653 w, 1597 w, 1541 w, 1494 m, 1436 m, 1316 s, 1151 s, 1119 m, 1095 s, 1064 m, 940 m, 908 m, 838 m, 815 m, 788 w, 758 m, 723 m, 699 s, 668 s, 640 m, 608 w,

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572 s, 548 s; MS m/z (relative intensity, %) 197 (16), 196 (M^+ − Ts, 100), 194 (40), 181 (20), 180 (49), 179 (29), 178 (11), 166 (13), 165 (19), 155 (19), 118 (13), 104 (12), 91 (65), 77 (15), 65 (17); exact mass-ESI calcd for $C_{21}H_{21}NNaO_2S$ 374.11907 $[M + Na]^+$, found 374.11907; $[\alpha]^{27}_D$ = −8.8° (c 0.98, $CHCl_3$) for 99% ee (R) (lit. $[\alpha]^{20}_D$ = −10.0° (c 0.98, $CHCl_3$) for 95% ee (R)); HPLC (Chiralpak OD-H, n-hexane/2-propanol = 80/20, flow = 0.5 mL/min, detection at 254 nm) R_t = 13.9 min (R), R_t = 16.7 min (S).

*N-[(2S)-(2-Bromophenyl)(4-chlorophenyl)methyl]-4-methylbenzenesulfonamide (**7e**).* White solid: mp 109.0−110.7 °C; R_f 0.24 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 5.94 (d, J = 7.9 Hz, 1H), 6.31 (d, J = 7.9 Hz, 1H), 7.01−7.06 (m, 3H), 7.11 (d, J = 7.9 Hz, 2H), 7.13−7.15 (m, 3H), 7.33 (d, J = 7.9 Hz, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3, 59.6, 122.8, 127.0, 127.6, 128.5, 128.7, 129.0, 129.1, 129.3, 132.9, 133.4, 136.7, 137.8, 138.7, 143.3; IR (KBr) 3268 s, 3063 m, 1912 w, 1597 m, 1570 w, 1490 s, 1470 s, 1434 s, 1409 s, 1336 s, 1265 m, 1185 m, 1157 s, 1090 s, 1058 s, 1018 s, 945 m, 910 s, 873 m, 822 s, 809 s, 755 s, 714 s, 685 s, 664 s, 621 m, 572 s, 546 s, 495 m, 455 m, 428 w; MS m/z (relative intensity, %) 298 (24), 297 (16), 296 (100), 295 (13), 294 (M^+ − Ts, 82), 214 (19), 165 (38), 155 (21), 138 (16), 111 (11), 92 (12), 91 (77), 77 (13), 75 (12), 65 (23); exact mass-ESI calcd for $C_{20}H_{17}BrClNNaO_2S$ 471.9750 $[M + Na]^+$, found 471.9749; $[\alpha]^{17}_D$ = +20.7° (c 1.00, $CHCl_3$) for 99% ee (S); HPLC (Chiralpak OD-H, n-hexane/2-propanol = 90/10, flow = 1.0 mL/min, detection at 254 nm) R_t = 10.5 min (R), R_t = 17.2 min (S). The absolute configuration of **7e** was assigned as S from the specific optical rotation of **9e**,[26] which was prepared by the hydrogenation of **7e** using a Pd-catalyst.

*(2R)-N-[(4-Chlorophenyl)phenylmethyl]-4-methylbenzenesulfonamide (**9e**).*[26] White solid: mp 116.3−118.1 °C; R_f 0.36 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H), 5.09 (d, J = 6.7 Hz, 1H), 5.53 (d, J = 6.7 Hz, 1H), 7.03−7.07 (m, 4H), 7.14−7.18 (m, 4H), 7.20−7.23 (m, 3H), 7.55 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 60.7, 127.2, 127.3, 127.9, 128.6, 128.7, 128.8, 129.4, 133.5, 137.1, 138.9, 140.0, 143.5; IR (KBr) 3239 s, 3057 w, 3036 w, 2919 w, 2865 w, 1598 m, 1490 m, 1448 m, 1433 s, 1412 w, 1379 m, 1321 s, 1293 m, 1276 w, 1249 w, 1189 w, 1161 s, 1092 s, 1048 s, 1030 m, 1014 m, 935 m, 904 m, 872 m, 837 s, 804 m, 745 m, 721 m, 701 s, 669 s, 650 w, 629 w, 573 s, 558 s, 539 m; MS m/z (relative intensity, %) 218 (32), 217 (15), 216 (M^+ − Ts, 100), 214 (10), 201 (10), 180 (20), 166 (13), 165 (19), 155 (12), 138 (11), 104 (14), 91 (45), 77 (15), 65 (12); exact mass-ESI calcd for $C_{20}H_{18}ClNNaO_2S$ 394.06445 $[M + Na]^+$, found 394.06445; $[\alpha]^{20}_D$ = +5.8° (c 0.85, $CHCl_3$) for 92% ee (R) (lit. $[\alpha]^{27}_D$ = +6.3° (c 0.85, $CHCl_3$) for 94% ee (R)); HPLC (Chiralpak OD-H, n-hexane/2-propanol = 70/30, flow = 0.7 mL/min, detection at 254 nm) R_t = 8.7 min (S), R_t = 10.6 min (R).

*N-[(2S)-(2-Bromophenyl)(4-fluorophenyl)methyl]-4-methylbenzenesulfonamide (**7f**).* White solid: mp 109.0−110.7 °C; R_f 0.24 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 5.61 (d, J = 7.3 Hz, 1H), 5.89 (d, J = 7.3 Hz, 1H), 6.90 (t, J = 8.6 Hz, 2H), 7.02−7.09 (m, 3H), 7.15 (d, J = 7.9 Hz, 2H), 7.18 (td, J = 7.6, 1.5 Hz, 1H), 7.31 (dd, J = 7.6, 1.5 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.60 (d, J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 59.9, 115.5 (d, $^2J_{C-F}$ = 21.1 Hz), 123.0, 127.2, 127.6, 129.1, 129.2, 129.3 (d, $^3J_{C-F}$ = 12.5 Hz), 129.4, 133.2, 135.0 (d, $^4J_{C-F}$ = 2.9 Hz), 136.8, 138.8, 143.5, 162.1 (d, $^1J_{C-F}$ = 247.6 Hz); IR (KBr) 3283 s, 3238 s, 3070 m, 2876 m, 1919 w, 1604 s, 1670 w, 1509 s, 1467 m, 1440 s, 1317 s, 1234 s, 1184 m, 1148 s, 1125 s, 1095 s, 1078 s, 1019 s, 947 s, 928 s, 871 m, 829 m, 814 s, 797 s, 753 s, 722 m, 705 m, 681 s, 661 s, 574 s, 547 s, 488 m, 420 w; MS m/z (relative intensity, %) 281 (14), 280 (88), 279 (17), 278 (M^+ − Ts, 100), 198 (29), 184 (28), 183 (33), 182 (10), 155 (23), 122 (21), 95 (13), 92 (11), 91 (72), 77 (11), 75 (10), 65 (21); exact mass-ESI calcd for $C_{20}H_{17}BrFNNaO_2S$ 456.00451 $[M + Na]^+$, found 456.00450; $[\alpha]^{17}_D$ = +23.8° (c 1.00, $CHCl_3$) for 99% ee (S); HPLC (Chiralpak OD-H, n-hexane/2-propanol = 90/10, flow = 1.0 mL/min, detection at 254 nm) R_t = 10.1 min (R), R_t = 14.9 min (S). The absolute configuration of **7f** was assigned as S from the specific optical rotation of **9f**,[25] which was prepared by the hydrogenation of **7f** using a Pd-catalyst.

*(2R)-N-[(4-Fluorophenyl)phenylmethyl]-4-methylbenzenesulfonamide (**9f**).*[25] White solid: mp 108.3−110.2 °C; R_f 0.31 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H), 5.01 (d, J = 7.3 Hz, 1H), 5.55 (d, J = 7.3 Hz, 1H), 6.90 (td, J = 8.9, 2.2 Hz, 2H), 7.05−7.10 (m, 4H), 7.16 (d, J = 7.9 Hz, 2H), 7.21−7.23 (m, 3H), 7.56 (d, J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4, 60.6, 115.3 (d, $^2J_{C-F}$ = 22.1 Hz), 127.2 (d, $^3J_{C-F}$ = 12.5 Hz), 127.7, 128.6, 129.0, 129.1, 129.3, 136.3 (d, $^4J_{C-F}$ = 2.9 Hz), 137.2, 140.3, 143.3, 162.0 (d, $^1J_{C-F}$ = 246.6 Hz); IR (KBr) 3853 w, 3735 w, 3649 w, 3274 s, 2925 w, 2363 w, 1603 m, 1158 w, 1506 s, 1456 m, 1322 s, 1225 m, 1155 s, 1092 s, 1064 m, 1016 m, 930 m, 859 m, 814 m, 797 m, 747 m, 701 s, 669 s, 565 s; MS m/z (relative intensity, %) 201 (14), 200 (M^+ − Ts, 100), 198 (21), 185 (13), 122 (13), 91 (35), 77 (11), 65 (10); exact mass-ESI calcd for $C_{20}H_{18}FNNaO_2S$ 378.09400 $[M + Na]^+$, found 378.09399; $[\alpha]^{20}_D$ = −3.9° (c 1.02, $CHCl_3$) for 97% ee (R) (lit. $[\alpha]^{20}_D$ = −4.1° (c 1.02, $CHCl_3$) for 93% ee (R)); HPLC (Chiralpak OD-H, n-hexane/2-propanol = 80/20, flow = 0.8 mL/min, detection at 254 nm) R_t = 9.0 min (S), R_t = 10.7 min (R).

*N-[(2S)-(2-Bromophenyl)(4-trifluoromethylphenyl)methyl]-4-methylbenzenesulfonamide (**7g**).* White solid: mp 126.5−128.1 °C; R_f 0.24 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 5.32 (d, J = 7.3 Hz, 1H), 5.97 (d, J = 7.3 Hz, 1H), 7.11 (td, J = 7.6, 1.5 Hz, 1H), 7.16 (d, J = 7.9 Hz, 2H), 7.21 (td, J = 7.6, 1.5 Hz, 1H), 7.22−7.25 (m, 3H), 7.45 (dd, J = 7.6, 1.5 Hz, 1H), 7.48 (d, J = 8.6 Hz, 2H), 7.60 (d, J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4, 60.1, 123.0, 123.9 (d, $^2J_{C-F}$ = 272.5 Hz), 125.5 (q, $^1J_{C-F}$ = 3.5 Hz), 127.1, 127.7, 127.8, 129.4, 129.4, 129.5, 129.9 (d, $^3J_{C-F}$ = 32.6 Hz), 133.3, 136.7, 138.3, 143.2 (d, $^4J_{C-F}$ = 2.9 Hz), 143.6; IR (KBr) 3260 m, 2361 w, 1619 w, 1596 w, 1473 w, 1432 m, 1413 w, 1327 s, 1164 s, 1135 s, 1092 w, 1069 s, 1016 m, 926 w, 850 w, 839 w, 809 w, 752 w, 730 w, 704 w, 684 m, 664 m, 568 m, 541 w, 453 w; MS(EI) m/z (relative intensity) 331 (14), 330 (84), 329 (15), 328 (M^+ − Ts, 87), 248 (13), 234 (11), 207 (11), 182 (10), 172 (13), 165 (26), 157 (10), 155 (36), 145 (13), 92 (18), 91 (100), 77 (13), 65 (27); exact mass-ESI calcd for $C_{21}H_{17}BrF_3NNaO_2S$ 506.00132 $[M + Na]^+$, found 506.00129; $[\alpha]^{17}_D$ = +4.9° (c 1.00, $CHCl_3$) for 99% ee (S); HPLC (Chiralpak AD-H, n-hexane/2-propanol = 95/5, flow = 0.8 mL/min, detection at 254 nm) R_t = 30.3 min (R), R_t = 33.1 min (S). The absolute configuration of **7g** was assigned as S from the specific optical rotation of **9g**,[27] which was prepared by the hydrogenation of **7g** using a Pd-catalyst.

*(2R)-N-[(4-Trifluoromethylphenyl)phenylmethyl]-4-methylbenzenesulfonamide (**9g**).*[27] White solid: mp 122.6−124.2 °C; R_f 0.33 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 5.57 (d, J = 7.3 Hz, 1H), 5.60 (d, J = 7.3 Hz, 1H), 7.05 (br s, 2H), 7.10 (d, J = 7.9 Hz, 2H), 7.20−7.27 (m, 5H), 7.42 (d, J = 7.3 Hz, 2H), 7.52 (d, J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4, 61.0, 123.9 (d, $^2J_{C-F}$ = 271.6 Hz), 125.4 (q, $^1J_{C-F}$ = 3.5 Hz), 127.1, 127.3, 127.7, 128.1, 128.9, 129.4, 129.7 (d, $^3J_{C-F}$ = 32.6 Hz), 137.0, 139.7, 143.5, 144.2; IR (KBr) 3853 w, 3735 w, 3649 w, 3246 m, 3031 w, 2925 m, 2853 w, 2361 w, 1618 w, 1598 w, 1558 w, 1541 w, 1496 m, 1438 m, 1327 s, 1155 s, 1136 s, 1119 s, 1092 m, 1068 s, 1053 m, 1015 m, 927 m, 903 w, 873 m, 847 w, 813 m, 748 m, 696 m, 678 s, 658 m, 633 m, 602 m, 569 m, 543 s; MS m/z (relative intensity, %) 251 (16), 250 (M^+ − Ts, 100), 155 (11), 91 (37), 77 (11); exact mass-ESI calcd for $C_{21}H_{18}F_3NNaO_2S$ 428.09080 $[M + Na]^+$, found 428.09076; $[\alpha]^{23}_D$ = −9.5° (c 1.00, $CHCl_3$) for 94% ee (R) (lit. $[\alpha]^{20}_D$ = −10.1° (c 1.00, $CHCl_3$) for 76% ee (R)); HPLC (Chiralpak OD-H, n-hexane/2-propanol = 80/20, flow = 0.5 mL/min, detection at 254 nm) R_t = 14.6 min (S), R_t = 21.1 min (R).

*N-[(2S)-(2-Bromo-4-methoxyphenyl)phenylmethyl]-4-methylbenzenesulfonamide (**7h**).* White solid: mp 178.0−179.2 °C; R_f 0.19 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 3.74 (s, 3H), 5.46 (d, J = 7.3 Hz, 1H), 5.86 (d, J = 7.3 Hz, 1H), 6.72 (dd, J = 8.6, 2.4 Hz, 1H), 6.96 (d, J = 2.4 Hz, 1H), 7.09 (dd, J = 7.0, 1.5 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 7.20−7.22 (m, 4H), 7.62 (d, J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 55.5, 60.1, 113.6, 118.2, 123.3, 127.2, 127.3, 127.7, 128.6, 129.4, 130.1, 131.1, 136.9, 139.6, 143.3, 159.3; IR (KBr) 3256 s, 3066 m, 2982 m, 2941 m, 1732 w, 1597 s, 1569 m, 1480 s, 1452 m, 1429 s, 1338 s, 1303 m, 1283 s, 1223 s, 1168 s, 1110 m, 1092 m, 1067 s, 1021 s, 938 m, 902 m, 868 m, 844 m, 820 s, 758 m, 698 s, 667 s, 580 s, 541 s; MS m/z (relative intensity, %) 293 (14), 292 (81),

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291 (22), 290 (M^+ − Ts, 100), 289 (10), 288 (15), 287 (10), 275 (11), 260 (10), 212 (11), 210 (35), 196 (20), 195 (19), 167 (11), 165 (10), 155 (22), 152 (13), 104 (18), 91 (73), 77 (23), 65 (17); exact mass-ESI calcd for $C_{21}H_{20}BrNNaO_3S$ 468.0245 [M + Na]$^+$, found 468.0246; $[\alpha]^{23}_D$ = −2.5° (*c* 1.00, $CHCl_3$) for 99% ee (*S*); HPLC (Chiralpak OD-H, *n*-hexane/2-propanol = 95/5, flow = 0.8 mL/min, detection at 254 nm) R_t = 35.7 min (*S*), R_t = 40.2 min (*R*). The absolute configuration of **7h** was assigned as *S* from the specific optical rotation of **9h**[26] (the enantiomer of **9b**), which was prepared by the hydrogenation of **7h** using a Pd-catalyst; $[\alpha]^{14}_D$ = −20.3° (*c* 0.93, $CHCl_3$) for 99% ee (*S*) (lit. $[\alpha]^{28}_D$ = −19.6° (*c* 0.93, $CHCl_3$) for 95% ee (*S*)).

*(2S)-N-[(4-Methoxyphenyl)phenylmethyl]-4-methylbenzenesulfonamide (**9h**) (Enantiomer of **9b**).* ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 3.74 (s, 3H), 5.28 (d, *J* = 7.3 Hz, 1H), 5.51 (d, *J* = 7.3 Hz, 1H), 6.72 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 7.10−7.14 (m, 4H), 7.18−7.20 (m, 3H), 7.55 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4, 55.2, 60.8, 113.8, 127.1, 127.2, 127.4, 128.4, 128.6, 129.3, 132.7, 137.3, 140.7, 143.1, 158.9.

*N-[(2S)-(2-Bromo-5-methoxyphenyl)phenylmethyl]-4-methylbenzenesulfonamide (**7i**).* White solid: mp 150.5−152.1 °C; R_f 0.20 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 3.66 (s, 3H), 5.85 (d, *J* = 7.9 Hz, 1H), 5.91 (d, *J* = 7.9 Hz, 1H), 6.60 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.86 (d, *J* = 2.7 Hz, 1H), 7.11−7.14 (m, 4H), 7.20−7.22 (m, 3H), 7.28 (d, *J* = 8.9 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4, 55.3, 60.4, 113.3, 114.5, 115.1, 127.1, 127.3, 127.7, 128.5, 129.3, 133.5, 136.8, 139.1, 139.8, 143.3, 158.9; IR (KBr) 3275 m, 3244 m, 2959 w, 2359 w, 1734 w, 1593 m, 1573 w, 1463 s, 1320 s, 1291 m, 1240 m, 1150 s, 1093 s, 1050 m, 1016 m, 940 m, 907 w, 876 w, 865 m, 836 w, 810 m, 754 w, 699 m, 670 s, 652 m, 592 m, 540 s; MS *m*/*z* (relative intensity, %) 447 (14), 445 (M^+, 13), 366 (22), 293 (10), 292 (71). 291 (19), 290 (M^+ − Ts, 82), 260 (17), 213 (13), 211 (14), 210 (71), 196 (20), 195 (16), 181 (17), 167 (15), 155 (35), 153 (11), 152 (15), 104 (21), 92 (12), 91 (100), 77 (28), 65 (22); exact mass-ESI calcd for $C_{21}H_{20}BrNNaO_3S$ 468.0245 [M + Na]$^+$, found 468.0246; $[\alpha]^{23}_D$ = +30.2° (*c* 1.00, $CHCl_3$) for 99% ee (*S*); HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90/10, flow = 0.5 mL/min, detection at 254 nm) R_t = 51.6 min (*S*), R_t = 53.7 min (*R*). The absolute configuration of **7i** was assigned as *S* from the specific optical rotation of **9i**,[25] which was prepared by the hydrogenation of **7i** using a Pd-catalyst.

*(2S)-N-[(3-Methoxyphenyl)phenylmethyl]-4-methylbenzenesulfonamide (**9i**).*[25] White solid: mp 150.3−151.9 °C; R_f 0.28 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.67 (s, 3H), 5.45 (d, *J* = 7.3 Hz, 1H), 5.53 (d, *J* = 7.3 Hz, 1H), 6.62 (s, 1H), 6.68 (d, *J* = 7.3 Hz, 1H), 6.72 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.09−7.13 (m, 5H), 7.18−7.21 (m, 3H), 7.56 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4, 55.0, 61.2, 112.8, 113.0, 119.6, 127.1, 127.2, 127.5, 128.5, 129.3, 129.5, 137.3, 140.4, 142.0, 143.1, 159.6; IR (KBr) 3853 w, 3735 w, 3649 w, 3283 m, 2930 w, 2360 w, 1654 w, 1596 m, 1558 w, 1541 w, 1491 m, 1457 m, 1411 m, 1324 s, 1268 m, 1161 s, 1092 m, 1041 m, 915 w, 865 w, 818 m, 782 m, 731 m, 705 m, 672 s, 569 m, 553 m, 420 w; MS *m*/*z* (relative intensity, %) 213 (17), 212 (M^+ − Ts, 100), 211 (10), 210 (18), 180 (35), 155 (12), 104 (13), 91 (44), 77 (14), 65 (10); exact mass-EI calcd for $C_{21}H_{21}NO_3S$ 367.1242 [M]$^+$, found 367.1240; $[\alpha]^{18}_D$ = −2.5° (*c* 1.10, $CHCl_3$) for 99% ee (*R*) (lit. $[\alpha]^{20}_D$ = −2.4° (*c* 1.10, $CHCl_3$) for 91% (*R*)); HPLC (Chiralpak OD-H, *n*-hexane/2-propanol = 95/5, flow = 0.8 mL/min, detection at 254 nm) R_t = 34.4 min (*R*), R_t = 39.0 min (*S*).

*N-[(2S)-(2-Bromo-4-methylphenyl)phenylmethyl]-4-methylbenzenesulfonamide (**7j**).* White solid: mp 181.2−182.1 °C; R_f 0.20 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3H), 2.39 (s, 3H), 5.24 (d, *J* = 6.7 Hz, 1H), 5.85 (d, *J* = 6.7 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 7.05−7.07 (m, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.20−7.24 (m, 5H), 7.62 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (CDC_{l3}) δ 20.5, 21.4, 60.0, 122.7, 127.1, 127.2, 127.5, 128.3, 128.4, 129.1, 129.2, 133.2, 136.0, 136.8, 139.1, 139.4, 143.1; IR (KBr) 3363 m, 3303 s, 2923 m, 2361 w, 1742 w, 1598 m, 1493 m, 1448 m, 1335 s, 1164 s, 1093 m, 1072 m, 1030 m, 932 m, 901 m, 849 m, 809 m, 753 w, 738 m, 719 w, 696 m, 669 s, 629 w, 580 s, 548 s, 465 m; MS *m*/*z* (relative intensity, %) 277 (15), 276 (91), 275 (18), 274 (M^+ − Ts, 100), 270 (11), 194 (27), 180 (17), 179 (17), 165 (26), 155 (21), 91 (73), 89 (11), 77 (22), 65 (18); exact mass-ESI calcd for $C_{21}H_{20}BrNNaO_2S$ 452.02958 [M + Na]$^+$, found 452.02961; $[\alpha]^{23}_D$ = +7.2° (*c* 1.00 $CHCl_3$) for 99% ee (*S*); HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 95/5, flow = 0.4 mL/min, detection at 254 nm) R_t = 78.9 min (*S*), R_t = 82.2 min (*R*). The absolute configuration of **7j** was assigned as *S* from the specific optical rotation of **9j**[26] (the enantiomer of **9c**), which was prepared by the hydrogenation of **7j** using a Pd-catalyst; $[\alpha]^{15}_D$ = −12.1° (*c* 0.97, $CHCl_3$) for 99% ee (*S*) (lit. $[\alpha]^{27}_D$ = −11.9° (*c* 0.97, $CHCl_3$) for 91% ee (*S*)).

*(2S)-N-[(4-Methylphenyl)phenylmethyl]-4-methylbenzenesulfonamide (**9j**) (Enantiomer of **9c**).* ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.38 (s, 3H), 5.06 (d, *J* = 6.7 Hz, 1H), 5.52 (d, *J* = 6.7 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 2H), 7.02 (d, *J* = 7.9 Hz, 2H), 7.10−7.15 (m, 4H), 7.19−7.21 (m, 3H), 7.56 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.5, 61.1, 127.1, 127.2, 127.3, 127.5, 128.5, 129.2, 129.3, 137.2, 137.3, 137.6, 140.6, 143.1.

*N-[(2S)-(2-Bromo-4-fluorophenyl)phenylmethyl]-4-methylbenzenesulfonamide (**7k**).* White solid: mp 135.1−136.9 °C; R_f 0.22 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 5.57 (br s, 1H), 5.88 (d, *J* = 6.7 Hz, 1H), 6.92 (td, *J* = 8.2, 2.2 Hz, 1H), 7.04 (dd, *J* = 6.4, 2.7 Hz, 2H), 7.17−7.22 (m, 6H), 7.37 (dd, *J* = 8.2, 5.8 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 59.9, 114.7 (d, $^2J_{C-F}$ = 21.1 Hz), 120.1 (dd, $^2J_{C-F}$ = 24.5, 3.4 Hz), 123.0 (d, $^3J_{C-F}$ = 9.6 Hz), 127.2, 127.3, 128.0, 128.7, 129.5, 130.4 (d, $^3J_{C-F}$ = 8.6 Hz), 135.2 (d, $^4J_{C-F}$ = 3.8 Hz), 136.7, 139.0, 143.6, 161.5 (d, $^1J_{C-F}$ = 251.4 Hz); IR (KBr) 3367 m, 3254 s, 3071 m, 1599 s, 1482 s, 1454 s, 1419 s, 1337 s, 1305 s, 1266 m, 1226 s, 1160 s, 1093 s, 1028 s, 937 s, 904 m, 865 s, 850 m, 828 m, 816 s, 797 m, 753 m, 697 s, 667 s, 628 m, 580 s, 547 s, 474 m, 445 m; MS *m*/*z* (relative intensity, %) 281 (13), 280 (90), 279 (15), 278 (M^+ − Ts, 100), 198 (22), 184 (23), 183 (32), 155 (22), 104 (13), 92 (11), 91 (69), 77 (23), 65 (19), 51 (10); exact mass-ESI calcd for $C_{20}H_{17}BrFNNaO_2S$ 456.00451 [M + Na]$^+$, found 456.00446; $[\alpha]^{23}_D$ = +27.3° (*c* 1.00, $CHCl_3$) for 99% ee (*S*); HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90/10, flow = 1.0 mL/min, detection at 254 nm) R_t = 14.5 min (*S*), R_t = 22.9 min (*R*). The absolute configuration of **7k** was assigned as *S* from the specific optical rotation of **9k**[24] (the enantiomer of **9f**), which was prepared by the hydrogenation of **7k** using a Pd-catalyst; $[\alpha]^{22}_D$ = +3.7° (*c* 0.91, $CHCl_3$) for 99% ee (*S*) (lit. $[\alpha]^{20}_D$ = +3.8° (*c* 0.91, $CHCl_3$) for 94% (*S*)).

*(2S)-N-[(4-Fluorophenyl)phenylmethyl]-4-methylbenzenesulfonamide (**9k**) (Enantiomer of **9f**).* ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H), 5.06 (d, *J* = 7.3 Hz, 1H), 5.55 (d, *J* = 7.3 Hz, 1H), 6.90 (td, *J* = 8.6, 0.6 Hz, 2H), 7.02−7.12 (m, 4H), 7.15 (d, *J* = 7.9 Hz, 2H), 7.21−7.22 (m, 3H), 7.55 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 60.7, 115.4 (d, $^2J_{C-F}$ = 21.1 Hz), 127.2 (d, $^3J_{C-F}$ = 8.6 Hz), 127.8, 128.7, 129.0, 129.1, 129.4, 136.2 (d, $^4J_{C-F}$ = 2.9 Hz), 137.2, 140.2, 143.4, 162.1 (d, $^1J_{C-F}$ = 246.6 Hz).

*N-[(2S)-(2-Bromo-5-fluorophenyl)phenylmethyl]-4-methylbenzenesulfonamide (**7l**).* White solid: mp 167.4−168.5 °C; R_f 0.23 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H), 5.55 (d, *J* = 6.7 Hz, 1H), 5.86 (d, *J* = 6.7 Hz, 1H), 6.80 (td, *J* = 8.2, 3.1 Hz, 1H), 7.03 (dd, *J* = 6.4, 3.4 Hz, 2H), 7.15 (dd, *J* = 9.8, 3.1 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.22−7.23 (m, 3H), 7.39 (dd, *J* = 8.2, 5.2 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4, 60.4, 116.2 (d, $^2J_{C-F}$ = 22.1 Hz), 116.5 (d, $^2J_{C-F}$ = 25.0 Hz), 117.0 (d, $^4J_{C-F}$ = 3.8 Hz), 127.2, 127.4, 128.1, 128.8, 129.5, 134.2 (d, $^3J_{C-F}$ = 7.7 Hz), 136.6, 138.4, 141.3 (d, $^3J_{C-F}$ = 6.7 Hz), 143.6, 161.9 (d, $^1J_{C-F}$ = 247.6 Hz); IR (KBr) 3248 s, 1583 m, 1495 m, 1467 s, 1434 s, 1328 s, 1265 s, 1220 m, 1149 s, 1093 s, 1027 s, 938 m, 904 m, 879 s, 840 m, 812 s, 747 m, 697 s, 669 s, 647 m, 617 m, 593 s, 577 s, 538 s, 479 m, 438 m; MS *m*/*z* (relative intensity, %) 281 (15), 280 (95), 279 (15), 278 (M^+ − Ts, 100), 198 (27), 184 (21), 183 (30), 155 (25), 104 (14), 92 (13), 91 (78), 77 (25), 65 (21), 51 (10); exact mass-ESI calcd for $C_{20}H_{17}BrFNNaO_2S$ 456.00451 [M + Na]$^+$, found 456.00450; $[\alpha]^{23}_D$ = +36.4° (*c* 1.00, $CHCl_3$) for 99% ee (*S*); HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 95/5, flow = 0.8 mL/min, detection at 254 nm) R_t = 34.2 min (*S*), R_t = 37.4 min (*R*). The absolute configuration was assigned as the (*S*)-configuration by X-ray crystallographic analysis.[23]

*N-[(2R)-(2-Chlorophenyl)phenylmethyl]-4-methylbenzenesulfonamide (**12**).* White solid: mp 171.1−172.5 °C; R_f 0.23 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 5.54 (d, J = 7.3 Hz, 1H), 5.93 (d, J = 7.3 Hz, 1H), 7.07−7.22 (m, 10H), 7.36 (br s, 1H), 7.61 (d, J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4, 58.5, 126.9, 127.1, 127.2, 127.7, 128.6, 128.7, 129.2, 129.3, 129.8, 132.7, 136.8, 137.4, 139.2, 143.3; IR (KBr) 3853 w, 3735 w, 3649 w, 3287 m, 3236 m, 1699 w, 1653 w, 1597 w, 1558 w, 1541 w, 1507 w, 1495 w, 1442 m, 1320 s, 1151 s, 1094 s, 1038 m, 941 m, 906 w, 831 w, 813 m, 755 s, 697 s, 666 s, 607 w, 574 s, 546 s, 419 w; MS m/z (relative intensity, %) 218 (31), 217 (14), 216 (M^+ − Ts, 100), 180 (11), 166 (10), 165 (16), 155 (16), 138 (13), 104 (10), 91 (45), 77 (15), 65 (11); exact mass-ESI calcd for $C_{20}H_{18}ClNNaO_2S$ 394.0644 [M + Na]$^+$, found 394.0645; $[\alpha]^{19}_D$ = −16.5° (c 1.00, $CHCl_3$) for 99% ee (*S*); HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90/10, flow 0.7 mL/min, detection at 254 nm) R_t = 25.5 min (*S*), R_t = 29.3 min (*R*). The absolute configuration was assigned as *S* from the comparison with the repoted HPLC retention time and specific optical rotation data (lit.[25] $[\alpha]^{20}_D$ = −16.5° (c 0.49, $CHCl_3$) for 95% ee (*S*)).

Typical Procedure for Rhodium-Catalyzed Aminocarbonylative Cyclization Using Pentafluorobenzaldehyde (Schemes 3 and 4 and Table 1). In a 5 mL two-necked flask equipped with reflux condenser were placed $[RhCl(cod)]_2$ (6.2 mg, 0.0125 mmol), dppp (10.3 mg, 0.025 mmol), and xylene (0.5 mL), and the solution was stirred at room temperature for 15 min, whereupon a light yellow suspension occurred. At this point, benzylamine **7a** (104.2 mg, 0.25 mmol, 99% ee), pentafluorobenzaldehyde (245.1 mg, 1.25 mmol), K_2CO_3 (69.1 mg, 0.50 mmol) (in addition, KI (83.0 mg, 0.50 mmol) for the reaction of **12**), and xylene (1.5 mL) were added. The mixture was degassed through three freeze−pump−thaw cycles and stirred at 130 °C under N_2 until the substrate was completely consumed. The reaction mixture was filtered, and the filtrate was concentrated in vacuo to give a residue that was purified by column chromatography on silica gel (eluent: hexane/AcOEt = 4/1) to give (3*S*)-2,3-dihydro-3-(4-methoxyphenyl)-2-[(4-methylphenyl)sulfonyl]-1*H*-isoindol-1-one (**8a**) (81.0 mg, 0.223 mmol) in 89% yield as a white solid, along with the hydrogenated starting material (**9a**) in 10% yield as white solid.

*(3S)-2,3-Dihydro-2-[(4-methylphenyl)sulfonyl]-3-phenyl-1H-isoindol-1-one ((S)-**8a**).*[7a] White solid: mp 207.8−209.4 °C; R_f 0.20 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 6.22 (s, 1H), 7.08 (d, J = 7.3 Hz, 2H), 7.13 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 7.9 Hz, 1H), 7.26 (t, J = 7.3 Hz, 2H), 7.32 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 7.51 (d, J = 8.6 Hz, 2H), 7.56 (t, J = 7.9 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 65.5, 123.7, 124.6, 128.0, 128.1, 128.6, 128.7, 128.8, 128.9, 129.1, 134.3, 135.7, 136.8, 144.7, 146.3, 166.4; IR (KBr) 1723 s, 1595 w, 1494 w, 1455 w, 1372 m, 1350 m, 1292 m, 1189 m, 1169 s, 1091 m, 815 w, 736 w, 701 w, 687 w, 676 w, 664 m, 605 w, 577 m, 546 w; MS m/z (relative intensity, %) 300 (22), 299 (M^+ − SO_2, 100), 298 (70), 222 (20), 208 (M^+ − Ts, 55), 168 (15), 165 (19), 152 (10), 130 (28), 105 (17), 91 (63), 77 (38),76 (13), 65 (24), 51 (15); exact mass-ESI calcd for $C_{21}H_{17}NNaO_3S$ 386.08268 [M + Na]$^+$, found 386.08265; $[\alpha]^{27}_D$ = +82.5° (c 0.95, $CHCl_3$) for 99% ee (*S*); HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90/10, flow = 0.4 mL/min, detection at 254 nm) R_t = 66.6 min (*S*), R_t = 69.3 min (*R*).

*N-(Diphenylmethyl)-4-methylbenzenesulfonamide (**9a**).*[28] White solid: mp 207.8−209.4 °C; R_f 0.29 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 5.57 (d, J = 7.3 Hz, 1H), 5.61 (d, J = 7.3 Hz, 1H), 7.10−7.12 (m, 6H), 7.19−7.20 (m, 6H), 7.56 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4, 61.2, 127.1, 127.3, 127.4, 128.4, 129.2, 137.2, 140.5, 143.0; IR (KBr) 3247 m, 1599 w, 1495 w, 1452 m, 1315 s, 1161 s, 1096 m, 1058 w, 1028 w, 940 w, 834 w, 811 w, 734 w, 700 s, 675 m, 571 s; MS m/z (relative intensity, %) 183 (15), 182 (M^+ − Ts, 100), 180 (23), 167 (15), 165 (12), 155 (13), 104 (21), 91 (35), 77 (19); exact mass-ESI calcd for $C_{20}H_{19}NNaO_2S$ 360.10342 [M + Na]$^+$, found 360.10342.

*(3R)-2,3-Dihydro-2-[(4-methylphenyl)sulfonyl]-3-phenyl-1H-isoindol-1-one ((R)-**8a**).* White solid: ^{1}H NMR ($CDCl_3$) δ ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 6.22 (s, 1H), 7.07 (d, J = 7.3 Hz, 2H), 7.13 (d, J = 7.9 Hz, 2H), 7.16 (d, J = 7.9 Hz, 1H), 7.26 (t, J = 7.3 Hz, 2H), 7.32 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 7.50 (d, J = 7.9 Hz, 2H), 7.56 (t, J = 7.9 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 65.6, 123.7, 124.7, 128.0, 128.1, 128.6, 128.7, 128.8, 129.0, 129.1, 134.3, 135.8, 136.8, 144.7, 146.4, 166.4; $[\alpha]^{27}_D$ = −80.8° (c 0.95, $CHCl_3$) for 99% ee (*R*) (lit.[7a] $[\alpha]^{20}_D$ = +86.8° (c 0.95, $CHCl_3$) for 99% ee (*S*)); HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90/10, flow = 0.4 mL/min, detection at 254 nm) R_t = 66.7 min (*S*), R_t = 69.6 min (*R*).

*(3S)-2,3-Dihydro-3-(4-methoxyphenyl)-2-[(4-methylphenyl)-sulfonyl]-1H-isoindol-1-one (**8b**).*[7a] White solid: mp 97.5−98.9 °C; R_f 0.18 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 3.80 (s, 3H), 6.19 (s, 1H), 6.77 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 8.6 Hz, 2H), 7.13 (d, J = 8.6 Hz, 2H), 7.15 (d, J = 7.6 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.51 (d, J = 8.6 Hz, 2H), 7.55 (t, J = 7.6 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 55.3, 65.2, 113.9, 123.7, 124.5, 127.9, 128.6, 128.8, 128.9, 129.1, 129.4, 134.2, 135.9, 144.6, 146.5, 159.7, 166.3; IR (KBr) 2934 m, 2836 m, 1731 s, 1611 m, 1513 s, 1468 m, 1359 s, 1289 s, 1268 m, 1247 s, 1215 m, 1173 s, 1092 s, 1035 s, 903 w, 880 w, 847 s, 812 s, 777 m, 738 s, 724 s, 705 m, 686 m, 666 s, 631 w, 619 m, 576 s, 546 s, 416 w; MS m/z (relative intensity, %) 393 (M^+, 10), 329 (M^+ − SO_2, 28), 328 (10), 239 (16), 238 (M^+ − Ts, 100), 195 (14), 130 (28), 91 (28), 77 (12), 65 (11); exact mass-ESI calcd for $C_{22}H_{19}NNaO_4S$ 416.0932 [M + Na]$^+$, found 416.0933; $[\alpha]^{17}_D$ = +42.7° (c 1.00, $CHCl_3$) for 99% ee (*S*) (lit. $[\alpha]^{20}_D$ = +50.0° (c 1.01, $CHCl_3$) for 99% ee (*S*)); HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 80/20, flow = 0.7 mL/min, detection at 254 nm) R_t = 25.1 min (*S*), R_t = 31.5 min (*R*).

*(3S)-2,3-Dihydro-3-(4-methylphenyl)-2-[(4-methylphenyl)-sulfonyl]-1H-isoindol-1-one (**8c**).* White solid: mp 147.5−149.1 °C; R_f 0.21 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 2.37 (s, 3H), 6.19 (s, 1H), 6.97 (d, J = 7.9 Hz, 2H), 7.07 (d, J = 7.9 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 7.16 (d, J = 7.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 7.9 Hz, 2H), 7.55 (t, J = 7.6 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.1, 21.6, 65.4, 123.6, 124.6, 127.9, 128.1, 128.8, 128.9, 129.1, 129.3, 133.9, 134.2, 135.9, 138.5, 144.6, 146.5, 166.4; IR (KBr) 3276 w, 2922 w, 2360 w, 1732 s, 1596 w, 1513 w, 1469 w, 1353 s, 1288 m, 1171 s, 1102 s, 851 m, 814 m, 741 m, 718 w, 703 m, 687 m, 666 s, 619 w, 575 s, 542 m; MS m/z (relative intensity, %) 314 (23), 313 (M^+ − SO_2, 99), 312 (57), 223 (17), 222 (M^+ − Ts, 100), 206 (10), 182 (10), 165 (14), 130 (38), 105 (17), 102 (10), 91 (70), 77 (17), 76 (11), 65 (34); exact mass-ESI calcd for $C_{22}H_{19}NNaO_3S$ 400.09833 [M + Na]$^+$, found 400.09825; $[\alpha]^{17}_D$ = +61.6° (c 1.00, $CHCl_3$) for 98% ee (*S*); HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90/10, flow = 1.0 mL/min, detection at 254 nm) R_t = 24.3 min (*S*), R_t = 28.4 min (*R*). The absolute configuration was assigned as the (*S*)-configuration by X-ray crystallographic analysis.[23]

*(3S)-2,3-Dihydro-3-(2-methylphenyl)-2-[(4-methylphenyl)-sulfonyl]-1H-isoindol-1-one (**8d**).* White solid: mp 175.9−177.3 °C; R_f 0.21 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 2.78 (s, 3H), 6.29 (d, J = 7.3 Hz, 1H), 6.60 (s, 1H), 6.81 (t, J = 7.3 Hz, 1H), 7.11−7.15 (m, 3H), 7.17 (d, J = 7.9 Hz, 1H), 7.30 (d, J = 7.3 Hz, 1H), 7.44−7.55 (m, 5H), 7.86 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.7, 21.6, 61.0, 123.3, 124.8, 126.3, 126.4, 127.8, 128.1, 128.2, 128.8, 129.1, 130.9, 134.3, 135.0, 135.7, 136.5, 144.7, 146.9, 166.7; IR (KBr) 2925 w, 2359 w, 1717 s, 1597 w, 1468 w, 1363 m, 1343 w, 1292 m, 1209 w, 1189 m, 1172 s, 1112 m, 1090 m, 829 w, 813 w, 757 w, 744 m, 724 m, 693 m, 666 m, 610 w, 571 s, 546 m, 452 w; MS m/z (relative intensity, %) 314 (12), 313 (M^+ − SO_2, 45), 223 (17), 222 (M^+ − Ts, 100), 179 (15), 178 (12), 130 (24), 91 (52), 77 (11), 65 (24); exact mass-ESI calcd for $C_{22}H_{20}NO_3S$ 378.11639 [M + H]$^+$, found 378.11641; $[\alpha]^{17}_D$ = +128.3° (c 1.00, $CHCl_3$) for 95% ee (*S*); HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 95/5, flow = 0.4 mL/min, detection at 254 nm) R_t = 78.8 min (*S*), R_t = 82.4 min (*R*). The absolute configuration was assigned as the (*S*)-configuration by X-ray crystallographic analysis.[23]

*(3S)-3-(4-Chlorophenyl)-2,3-dihydro-2-[(4-methylphenyl)-sulfonyl]-1H-isoindol-1-one (**8e**).* White solid: mp 180.3−181.0 °C; R_f 0.22 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 6.18 (s, 1H), 7.02 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 7.3 Hz, 1H), 7.17 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H), 7.48 (t, J = 7.3 Hz, 1H), 7.54−7.59 (m, 3H), 7.85 (d, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6,

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64.8, 123.6, 124.8, 128.0, 128.8, 128.9, 129.2, 129.3, 129.4, 134.4, 134.6, 135.6, 135.8, 145.0, 145.8, 166.2; IR (KBr) 3062 m, 2927 w, 2361 w, 1738 s, 1596 m, 1493 m, 1465 m, 1416 m, 1371 s, 1288 s, 1215 m, 1189 m, 1171 s, 1090 s, 1015 m, 903 w, 850 s, 815 m, 746 s, 717 m, 704 s, 671 s, 662 m, 615 m, 573 s, 549 s, 539 s, 499 m; MS *m*/*z* (relative intensity, %) 335 (32), 334 (40), 333 ($M^+ - SO_2$, 100), 332 (61), 244 (19), 242 ($M^+ - Ts$, 62), 222 (17), 207 (22), 202 (17), 165 (11), 152 (11), 130 (30), 111 (10), 105 (20), 102 (11), 92 (11), 91 (81), 77 (23), 76 (18), 75 (12), 65 (34), 51 (13); exact mass-ESI calcd for $C_{21}H_{17}ClNO_3S$ 398.06177 $[M + H]^+$, found 398.06177; $[\alpha]^{17}_D$ = +59.5° (*c* 1.00, $CHCl_3$) for 99% ee (*S*); HPLC (Chiralpak OJ-H, *n*-hexane/2-propanol = 80/20, flow = 1.0 mL/min, detection at 254 nm) R_t = 23.8 min (*R*), R_t = 28.9 min (*S*). The absolute configuration was assigned as the (*S*)-configuration by X-ray crystallographic analysis.[23]

(3S)-2,3-Dihydro-3-(4-fluorophenyl)-2-[(4-methylphenyl)-sulfonyl]-1H-isoindol-1-one (**8f**). White solid: mp 165.6−166.9 °C; R_f 0.22 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 6.21 (s, 1H), 6.95 (t, *J* = 8.6 Hz, 2H), 7.06 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.14−7.17 (m, 3H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.57 (td, *J* = 7.6, 1.2 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 64.7, 115.6 (d, $^2J_{C-F}$ = 21.1 Hz), 123.6, 124.7, 127.9, 128.7, 129.1, 129.2, 129.8 (d, $^3J_{C-F}$ = 8.6 Hz), 132.7 (d, $^4J_{C-F}$ = 2.9 Hz), 134.4, 135.8, 144.8, 146.1, 162.7 (d, $^1J_{C-F}$ = 247.6 Hz), 166.2; IR (KBr) 3086 m, 3064 m, 2927 m, 2359 w, 1810 w, 1736 s, 1604 s, 1511 s, 1496 m, 1465 s, 1424 m, 1399 m, 1371 s, 1331 m, 1289 s, 1226 s, 1189 s, 1171 s, 1092 s, 1014 m, 954 w, 939 w, 904 m, 851 s, 816 s, 790 s, 738 s, 718 s, 705 m, 687 s, 676 s, 662 s, 617 m, 572 s, 555 s, 539 s, 511 m, 496 m, 471 w, 412 w; MS *m*/*z* (relative intensity, %) 317 ($M^+ - SO_2$, 100), 316 (72), 227 (10), 226 ($M^+ - Ts$, 58), 222 (15), 186 (20), 183 (20), 130 (25), 105 (17), 91 (62), 77 (19), 76 (13), 65 (29); exact mass-ESI calcd for $C_{21}H_{17}FNO_3S$ 382.0913 $[M + H]^+$, found 382.0914; $[\alpha]^{17}_D$ = +89.3° (*c* 1.00, $CHCl_3$) for 99% ee (*S*); HPLC (Chiralpak OJ-H, *n*-hexane/2-propanol = 70/30, flow = 1.0 mL/min, detection at 254 nm) R_t = 18.6 min (*R*), R_t = 23.5 min (*S*). The absolute configuration was assigned as the (*S*)-configuration by X-ray crystallographic analysis.[23]

(3S)-2,3-Dihydro-2-[(4-methylphenyl)sulfonyl]-3-[4-(trifluoromethyl)phenyl]-1H-isoindol-1-one (**8g**). White solid: mp 139.3−141.1 °C; R_f 0.21 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 6.25 (s, 1H), 7.14−7.16 (m, 3H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.49−7.53 (m, 3H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.58 (t, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 64.8, 123.6, 123.7 (d, $^2J_{C-F}$ = 272.5 Hz), 125.0, 125.7 (q, $^1J_{C-F}$ = 3.8 Hz), 127.9, 128.3, 128.8, 129.3, 129.4, 130.9 (d, $^3J_{C-F}$ = 32.6 Hz), 134.5, 135.7, 141.0, 145.1, 145.4, 166.1; IR (KBr) 3439 w, 3068 w, 2956 w, 2361 w, 1925 w, 1727 s, 1597 m, 1494 m, 1468 m, 1423 m, 1372 s, 1328 s, 1290 s, 1212 s, 1170 s, 1109 s, 1067 s, 1018 s, 904 w, 861 s, 813 s, 799 m, 771 m, 748 s, 736 s, 705 m, 695 s, 665 s, 649 s, 622 m, 594 s, 572 s, 542 s, 490 m, 414 w; MS *m*/*z* (relative intensity, %) 368 (24), 367 ($M^+ - SO_2$, 100), 366 (73), 276 ($M^+ - Ts$, 31), 236 (21), 222 (31), 105 (15), 92 (10), 91 (85), 77 (21), 76 (14), 65 (37); exact mass-ESI calcd for $C_{22}H_{16}F_3NNaO_3S$ 454.0701 $[M + Na]^+$, found 454.0700; $[\alpha]^{17}_D$ = +88.8° (*c* 1.00, $CHCl_3$) for 99% ee (*S*); HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 95/5, flow = 0.8 mL/min, detection at 254 nm) R_t = 43.3 min (*S*), R_t = 46.4 min (*R*). The absolute configuration was assigned as the (*S*)-configuration by X-ray crystallographic analysis.[23]

(3S)-2,3-Dihydro-6-methoxy-2-[(4-methylphenyl)sulfonyl]-3-phenyl-1H-isoindol-1-one (**8h**). White solid: mp 208.9−210.4 °C; R_f 0.18 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 3.83 (s, 3H), 6.15 (s, 1H), 7.04 (d, *J* = 9.2 Hz, 1H), 7.06 (d, *J* = 7.3 Hz, 2H), 7.10−7.14 (m, 3H), 7.25 (t, *J* = 7.3 Hz, 2H), 7.28 (d, *J* = 1.8 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.6, 55.7, 65.2, 106.4, 123.1, 124.6, 127.9, 128.0, 128.5, 128.6, 129.1, 130.0, 135.8, 137.0, 138.9, 144.6, 160.4, 166.5; IR (KBr) 3853 w, 3735 w, 3649 w, 2954 w, 1719 s, 1619 w, 1595 w, 1558 w, 1493 s, 1471 m, 1455 m, 1369 s, 1336 m, 1310 m, 1278 m, 1174 s, 1092 s, 1072 s, 1019 m, 948 m, 913 w, 861 w, 847 m, 814 s, 776 w, 763 m, 722 w, 702 m, 691 m, 664 s, 625 m, 600 m, 568 s, 545 s; MS *m*/*z* (relative intensity, %) 330 (19), 329 ($M^+ - SO_2$, 78), 328 (38), 252 (11), 239 (21), 238 ($M^+ - Ts$, 100), 207 (36), 195 (18), 160(12), 155(10), 135 (31), 92 (12), 91 (74), 77 (27), 65 (18), 60 (10); exact mass-ESI calcd for $C_{22}H_{19}NNaO_4S$ 416.0932 $[M + Na]^+$, found 416.0933; $[\alpha]^{17}_D$ = +137.3° (*c* 1.00, $CHCl_3$) for 99% ee (*S*); HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90/10, flow = 1.0 mL/min, detection at 254 nm) R_t = 28.0 min (*R*), R_t = 32.0 min (*S*). The absolute configuration was assigned as the (*S*)-configuration by X-ray crystallographic analysis.[23]

(3S)-2,3-Dihydro-5-methoxy-2-[(4-methylphenyl)sulfonyl]-3-phenyl-1H-isoindol-1-one (**8i**). White solid: mp 208.9−210.2 °C; R_f 0.18 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 3H), 3.66 (s, 3H), 6.05 (s, 1H), 6.48 (d, *J* = 1.8 Hz, 1H), 6.88 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.00 (d, *J* = 7.3 Hz, 2H), 7.03 (d, *J* = 7.9 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 2H), 7.67 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 55.7, 65.2, 107.4, 116.4, 121.0, 126.2, 127.8, 127.9, 128.5, 128.6, 129.0, 135.9, 136.9, 144.4, 148.9, 164.7, 166.0; IR (KBr) 3853 w, 3735 w, 3649 w, 2942 w, 2362 w, 1731 s, 1608 s, 1558 w, 1541 w, 1491 m, 1456 m, 1399 w, 1364 s, 1296 m, 1277 m, 1246 s, 1187 m, 1172 s, 1081 s, 1019 m, 943 m, 869 w, 843 m, 812 m, 765 m, 721 m, 703 m, 678 m, 660 m, 608 w, 575 s, 547 m, 516 m, 465 w, 441 w; MS *m*/*z* (relative intensity, %) 330 (23), 329 ($M^+ - SO_2$, 100), 328 (73), 252 (17), 238 ($M^+ - Ts$, 52), 195 (10), 168 (12), 160 (13), 135 (14), 106 (10), 91 (59), 77 (24), 65 (20), 63 (10); exact mass-ESI calcd for $C_{22}H_{19}NNaO_4S$ 416.0932 $[M + Na]^+$, found 416.0933; $[\alpha]^{20}_D$ = −8.2° (*c* 0.85, $CHCl_3$) for 99% ee (*S*); HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 80/20, flow = 1.0 mL/min, detection at 254 nm) R_t = 21.5 min (*S*), R_t = 25.2 min (*R*). The absolute configuration was assigned as the (*S*)-configuration by X-ray crystallographic analysis.[23]

(3S)-2,3-Dihydro-6-methyl-2-[(4-methylphenyl)sulfonyl]-3-phenyl-1H-isoindol-1-one (**8j**). White solid: mp 186.5−188.1 °C; R_f 0.23 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 2.40 (s, 3H), 6.17 (s, 1H), 7.04 (d, *J* = 7.9 Hz, 1H), 7.06 (d, *J* = 7.3 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 2H), 7.64 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.2, 21.6, 65.4, 123.3, 124.5, 127.9, 128.0, 128.5, 128.6, 128.8, 129.1, 135.5, 135.8, 137.0, 139.2, 143.7, 144.6, 166.5; IR (KBr) 3252 m, 3064 w, 2361 w, 1717 s, 1594 m, 1507 m, 1492 s, 1455 m, 1442 m, 1375 s, 1352 s, 1308 s, 1266 s, 1232 m, 1189 s, 1166 s, 1112 s, 1091 s, 1069 s, 955 m, 923 m, 881 m, 854 m, 814 s, 783 m, 764 s, 731 m, 702 s, 673 s, 661 s, 619 m, 593 s, 565 s, 545 s, 421 w; MS *m*/*z* (relative intensity, %) 314 (23), 313 ($M^+ - SO_2$, 100), 312 (64), 298 (14), 236 (21), 223 (12), 222 ($M^+ - Ts$, 70), 207 (15), 168 (10), 165 (14), 144 (19), 119 (28), 91 (87), 90 (12), 89 (18), 77 (22), 65 (29), 51 (10); exact mass-ESI calcd for $C_{22}H_{19}NNaO_3S$ 400.09833 $[M + Na]^+$, found 400.09830; $[\alpha]^{23}_D$ = +67.9° (*c* 1.00, $CHCl_3$) for 99% ee (*S*); HPLC (Chiralpak OD-H, *n*-hexane/2-propanol = 90/10, flow = 1.0 mL/min, detection at 254 nm) R_t = 14.6 min (*R*), R_t = 17.1 min (*S*). The absolute configuration was assigned as the (*S*)-configuration by X-ray crystallographic analysis.[23]

(3S)-2,3-Dihydro-6-fluoro-2-[(4-methylphenyl)sulfonyl]-3-phenyl-1H-isoindol-1-one (**8k**). White solid: mp 170.0−172.3 °C; R_f 0.21 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 6.19 (s, 1H), 7.06 (d, *J* = 7.3 Hz, 2H), 7.12−7.15 (m, 3H), 7.23−7.28 (m, 3H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 2H), 7.50 (dd, *J* = 7.3, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 65.2, 110.9 (d, $^2J_{C-F}$ = 24.0 Hz), 122.2 (d, $^2J_{C-F}$ = 24.0 Hz), 125.6 (d, $^3J_{C-F}$ = 7.7 Hz), 127.9, 128.0, 128.7, 128.8, 129.2, 130.8 (d, $^3J_{C-F}$ = 8.6 Hz), 135.5, 136.3, 141.9 (d, $^4J_{C-F}$ = 1.9 Hz), 144.9, 162.9 (d, $^1J_{C-F}$ = 250.5 Hz), 165.3 (d, $^4J_{C-F}$ = 3.8 Hz); IR (KBr) 3853 w, 3735 w, 3649 w, 3067 w, 1909 w, 1747 s, 1596 m, 1558 w, 1541 w, 1488 s, 1456 m, 1441 m, 1400 w, 1364 s, 1290 s, 1260 s, 1231 m, 1189 m, 1170 s, 1090 s, 1069 s, 954 m, 922 w, 880 m, 852 m, 829 m, 813 m, 780 m, 765 s, 734 w, 698 m, 670 s, 618 m, 594 m, 563 s, 546 s, 526 m, 420 w, 406 w; MS *m*/*z* (relative intensity, %) 318 (21), 317 ($M^+ - SO_2$, 100), 316 (57), 240 (19), 227 (10), 226 ($M^+ - Ts$, 63), 183 (16), 168 (14), 148 (24), 123 (18), 95 (10), 92 (10), 91 (73), 77 (26), 65 (30), 51 (12); exact mass-ESI calcd for $C_{21}H_{16}FNNaO_3S$ 404.0733 $[M + Na]^+$, found 404.0732; $[\alpha]^{23}_D$ = +78.3° (*c* 1.00, $CHCl_3$) for 99% ee (*S*); HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90/10, flow = 1.0 mL/min, detection at 254 nm)

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R_t = 19.5 min (*R*), R_t = 21.8 min (*S*). The absolute configuration was assigned as the (*S*)-configuration by X-ray crystallographic analysis.[23]

*(3S)-2,3-Dihydro-5-fluoro-2-[(4-methylphenyl)sulfonyl]-3-phenyl-1H-isoindol-1-one (**8l**).* White solid: mp 173.4−173.5 °C; R_f 0.18 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 6.18 (s, 1H), 6.84 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.07 (d, *J* = 7.3 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 7.16 (td, *J* = 7.9, 1.8 Hz, 1H), 7.28 (t, *J* = 7.3 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 2H), 7.86 (dd, *J* = 7.9, 4.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 65.1 (d, $^4J_{C-F}$ = 1.9 Hz), 111.0 (d, $^2J_{C-F}$ = 24.0 Hz), 117.3 (d, $^2J_{C-F}$ = 24.0 Hz), 124.9 (d, $^4J_{C-F}$ = 1.9 Hz), 127.1 (d, $^3J_{C-F}$ = 9.6 Hz), 127.9, 128.0, 128.8, 128.9, 129.1, 135.6, 136.2, 144.8, 148.9 (d, $^3J_{C-F}$ = 9.6 Hz), 165.2, 166.5 (d, $^1J_{C-F}$ = 256.2 Hz); IR (KBr) 3735 w, 3649 w, 3067 w, 2920 w, 1724 s, 1620 m, 1604 m, 1484 m, 1456 m, 1366 s, 1337 m, 1306 s, 1264 m, 1236 m, 1189 m, 1171 s, 1134 m, 1090 s, 951 m, 918 w, 869 m, 841 m, 814 m, 782 w, 762 m, 721 m, 699 m, 686 s, 669 s, 654 m, 607 w, 577 s, 552 m, 514 m, 469 w, 431 w; MS *m*/*z* (relative intensity, %) 318 (21), 317 (M^+ − SO_2, 100), 316 (70), 240 (18), 226 (M^+ − Ts, 52), 183 (14), 168 (17), 148 (22), 123 (13), 91 (68), 77 (28), 65 (31), 51 (12); exact mass-ESI calcd for $C_{21}H_{16}FNNaO_3S$ 404.07326 $[M + Na]^+$, found 404.07328; $[\alpha]^{23}_D$ = +86.6° (*c* 1.00, $CHCl_3$) for 99% ee (*S*); HPLC (Chiralpak AD-H, *n*-hexane/2-propanol = 90/10, flow = 1.0 mL/min, detection at 254 nm) R_t = 23.2 min (*S*), R_t = 26.7 min (*R*). The absolute configuration was assigned as the (*S*)-configuration by X-ray crystallographic analysis.[23]

Substrates for Schemes 3−6 and Table 2: *N*-Tosylbenzaldimines 6 and 11. *N-[(2-Bromophenyl)methylene]-4-methylbenzenesulfonamide (**6a**).*[29] White solid: mp 144.3−146.3 °C; R_f 0.36 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 7.36−7.39 (m, 3H), 7.43 (td, *J* = 7.9, 1.8 Hz, 1H), 7.66 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.90 (d, *J* = 7.9 Hz, 2H), 8.15 (dd, *J* = 7.9, 1.8 Hz, 1H), 9.43 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 127.9, 128.1, 128.8, 129.8, 130.4, 130.9, 133.7, 134.4, 135.7, 144.8, 169.0; IR (KBr) 1597 s, 1556 m, 1430 m, 1359 w, 1319 s, 1290 m, 1273 m, 1214 m, 1156 s, 1086 s, 1026 m, 861 m, 807 s, 786 s, 760 s, 705 m, 688 s, 658 m, 613 m, 546 s, 498 m, 449 m, 422 w; MS *m*/*z* (relative intensity, %) 258 (M^+ − Br, 39), 155 (40), 92 (12), 91 (100), 65 (22); exact mass-EI calcd for $C_{14}H_{12}BrNO_2S$ 336.9772, found 336.9773.

*N-[(2-Bromo-4-methoxyphenyl)methylene]-4-methylbenzenesulfonamide (**6h**).* White solid: mp 122.1−123.6 °C; R_f 0.37 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 3.85 (s, 3H), 6.87 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.87 (d, *J* = 7.9 Hz, 2H), 8.09 (d, *J* = 8.6 Hz, 1H), 9.30 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 55.9, 114.5, 118.4, 123.6, 127.9, 129.7, 130.6, 132.0, 135.1, 144.4, 165.1, 168.3; IR (KBr) 3853 w, 3735 w, 3648 w, 3006 w, 2359 w, 1924 w, 1699 w, 1684 w, 1653 w, 1584 s, 1559 s, 1538 s, 1653 w, 1584 s, 1559 s, 1538 s, 1491s, 1456 m, 1435 m, 1403 m, 1325 s, 1292 m, 1260 s, 1221 m, 1184 m, 1159 s, 1126 m, 1086 s, 1029 m, 1018 m, 884 m, 849 m, 827 s, 813 s, 801 s, 776 s, 705 w, 671 s, 602 m, 555 m, 542 s, 526 s, 454 m, 424 w; MS *m*/*z* (relative intensity) 288 (M^+ − Br, 21), 214 (27), 212 (M^+ − Ts, 30), 207 (16), 155 (17), 92 (20), 91 (100), 77 (10), 65 (25), 63 (15); exact mass-ESI calcd for $C_{15}H_{14}BrNNaO_3S$ 389.9776 $[M + Na]^+$, found 389.9777.

*N-[(2-Bromo-5-methoxyphenyl)methylene]-4-methylbenzenesulfonamide (**6i**).* White solid: mp 144.1−146.1 °C; R_f 0.38 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 3.78 (s, 3H), 6.99 (dd, *J* = 8.6, 3.1 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 1H), 7.59 (d, *J* = 3.1 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 2H), 9.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 55.7, 113.2, 119.7, 123.6, 128.2, 129.8, 131.4, 134.3, 134.4, 144.8, 159.0, 169.1; IR (KBr) 3087 s, 2939 s, 1749 w, 1588 s, 1491 m, 1462 s, 1417 s, 1357 m, 1324 s, 1292 s, 1231 s, 1186 s, 1156 s, 1089 s, 1052 s, 1014 s, 995 m, 945 s, 876 s, 817 s, 749 s, 704 m, 692 m, 673 s, 624 s, 598 s, 566 m, 545 s, 455 s; MS *m*/*z* (relative intensity) 289 (11), 288 (M^+ − Br, 58), 155 (16), 139 (18), 92 (11), 91 (100), 65 (19), 63 (12); exact mass-ESI calcd for $C_{15}H_{14}BrNNaO_3S$ 389.9776 $[M + Na]^+$, found 389.9775.

*N-[(2-Bromo-4-methylphenyl)methylene]-4-methylbenzenesulfonamide (**6j**).* White solid: mp 143.6−146.2 °C; R_f 0.39 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 2.42 (s, 3H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.45 (s, 1H), 7.88 (d, *J* = 7.9 Hz, 2H), 8.00 (d, *J* = 7.9 Hz, 1H), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 21.6, 128.0, 128.1, 128.3, 128.9, 129.7, 130.3, 134.1, 134.7, 144.6, 147.6, 168.9; IR (KBr) 3735 m, 3649 m, 2361 w, 1749 w, 1647 w, 1582 s, 1456 w, 1395 w, 1355 w, 1323 s, 1293 m, 1277 m, 1227 m, 1183 m, 1155 s, 1088 s, 1041 m, 878 w, 832 s, 810 m, 774 s, 706 w, 666 s, 589 s, 559 m, 545 m, 531 m, 514 m, 478 w, 448 m; MS *m*/*z* (relative intensity, %) 272 (M^+ − Br, 41), 207 (20), 155 (25), 92 (15), 91 (100), 90 (11), 65 (22); exact mass-ESI calcd for $C_{15}H_{14}BrNNaO_2S$ 373.9826 $[M + Na]^+$, found 373.9830.

*N-[(2-Bromo-4-fluorophenyl)methylene]-4-methylbenzenesulfonamide (**6k**).* White solid: mp 143.6−146.9 °C; R_f 0.41 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 7.09 (td, *J* = 8.2, 2.0 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.37 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 2H), 8.17 (dd, *J* = 8.2, 5.5 Hz, 1H), 9.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 115.8 (d, $^2J_{C-F}$ = 22.1 Hz), 121.1 (d, $^2J_{C-F}$ = 25.0 Hz), 127.6 (d, $^4J_{C-F}$ = 2.9 Hz), 128.2, 129.7 (d, $^3J_{C-F}$ = 10.6 Hz), 129.8, 132.5 (d, $^3J_{C-F}$ = 9.6 Hz), 134.4, 144.9, 165.9 (d, $^1J_{C-F}$ = 263.0 Hz), 167.6; IR (KBr) 3084 m, 1699 w, 1670 w, 1590 s, 1481 s, 1394 m, 1362 m, 1328 s, 1246 s, 1187 m, 1158 s, 1119 m, 1087 s, 1032 m, 973 w, 894 m, 864 s, 833 m, 812 s, 711 s, 704 m, 666 s, 588 s, 553 s, 537 m, 513 s, 478 m, 460 m, 450 m; MS *m*/*z* (relative intensity, %) 276 (M^+ − Br, 21), 155 (45), 92 (11). 91 (100), 65 (24); exact mass-ESI calcd for $C_{14}H_{11}BrFNNaO_2S$ 377.9576 $[M + Na]^+$, found 377.9575.

*N-[(2-Bromo-5-fluorophenyl)methylene]-4-methylbenzenesulfonamide (**6l**).* White solid: mp 114.1−116.8 °C; R_f 0.43 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.41 (d, *J* = 3.7 Hz, 3H), 7.14 (tt, *J* = 8.5, 2.5 Hz, 1H), 7.34 (dd, *J* = 8.2, 2.1 Hz, 2H), 7.58 (dd, *J* = 8.5, 5.0 Hz, 1H), 7.75 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.86 (dd, *J* = 8.2, 2.1 Hz, 2H), 9.30 (dd, *J* = 4.3, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 116.6 (dd, $^2J_{C-F}$ = 24.5, 3.4 Hz), 122.7 (d, $^4J_{C-F}$ = 2.9 Hz), 123.0 (d, $^2J_{C-F}$ = 23.0 Hz), 128.1, 129.8, 132.4 (dd, $^3J_{C-F}$ = 7.7, 2.9 Hz), 133.9, 135.1 (d, $^3J_{C-F}$ = 7.7 Hz), 145.0, 161.5 (dd, $^1J_{C-F}$ = 249.5, 1.9 Hz), 167.7 (t, $^4J_{C-F}$ = 1.9 Hz); IR (KBr) 3735 m, 3649 m, 3096 m, 2362 w, 1914 w, 1748 w, 1699 w, 1591 s, 1573 s, 1507 w, 1469 s, 1451 m, 1409 s, 1360 m, 1331 s, 1294 m, 1265 s, 1225 m, 1185 m, 1163 s, 1105 m, 1089 s, 1034 m, 1018 w, 995 w, 980 m, 875 m, 824 s, 806 s, 752 s, 695 m, 672 s, 621 s, 599 m, 579 m, 552 s, 539 s, 521 m, 481 w, 452 m; MS *m*/*z* (relative intensity, %) 276 (M^+ − Br, 31), 155 (39), 92 (10), 91 (100), 65 (23); exact mass-ESI calcd for $C_{14}H_{11}BrFNNaO_2S$ 377.95756 $[M + Na]^+$, found 377.95758.

*N-(Phenylmethylene)benzenesulfonamide (**11**).*[29] White solid: mp 91.0−92.6 °C; R_f 0.35 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.49 (t, *J* = 7.9 Hz, 2H), 7.62 (t, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 2H), 7.93 (d, *J* = 7.9 Hz, 2H), 9.03 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 127.9, 129.0, 129.7, 131.1, 132.1 134.8, 134.9, 144.5, 170.0; IR (KBr) 3070 w, 1652 w, 1598 s, 1574 s, 1496 w, 1450 s, 1403 w, 1364 m, 1319 s, 1224 m, 1187 m, 1157 s, 1088 s, 1020 w, 999 m, 924 w, 867 s, 783 s, 756 s, 704 w, 689 m, 674 s, 618 s, 554 s, 540 s, 490 m, 473 s; MS *m*/*z* (relative intensity, %) 259 (M^+, 12), 155 (44), 104 (M^+ − Ts, 12), 92 (11) 91 (100), 77 (12), 65 (22), 51 (12); exact mass-EI calcd for $C_{14}H_{13}NO_2S$ 259.06670, found 259.06670.

Typical Procedure for the One-Pot Synthesis (Schemes 5 and 6 and Table 2). In a 5 mL two-necked flask equipped with a reflux condenser were placed *N*-tosyl-2-bromobenzaldimine (**6a**) (169.1 mg, 0.50 mmol), phenylboronic acid (67.1 mg, 0.55 mmol), $[RhCl((R)\text{-}\mathbf{10})]_2$ (23.5 mg, 0.025 mmol), KOH (11.2 mg, 0.20 mmol), and xylene (2 mL). The reaction mixture was then degassed through three freeze−pump−thaw cycles and stirred at 60 °C for 2 h. Pentafluorobenzaldehyde (490.2 mg, 2.50 mmol), dppp (11.2 mg, 0.050 mmol) (in addition, KI (83.0 mg, 0.50 mmol) for the reaction of **11**), and K_2CO_3 (138.2 mg, 1.0 mmol) were then added, and the mixture was degassed again and stirred at 130 °C until the substrate had been completely consumed. After filtering the reaction mixture, the filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (eluent: hexane/AcOEt = 4/1) to give (3S)-2,3-dihydro-2-[(4-methylphenyl)sulfonyl]-3-phenyl-1*H*-isoindol-1-one (**8a**) (148.9 mg, 0.410 mmol) in 82% yield as a white solid.

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Procedure for the One-Pot Synthesis of (3*S*)-3-Phenyl-1(3*H*)-isobenzofuranone (14) (Scheme 7). In a 5 mL two-necked flask equipped with a reflux condenser were placed 2-bromobenzaldehyde (**13**) (53.1 mg, 0.50 mmol), phenylboronic acid (67.1 mg, 0.55 mmol), $[RhCl((R)\text{-}\mathbf{10})]_2$ (23.5 mg, 0.025 mmol), K_3PO_4 (21.2 mg, 1.0 mmol), and xylene (2 mL), and the reaction mixture was degassed through three freeze−pump−thaw cycles and stirred at 60 °C for 5 h. Pentafluorobenzaldehyde (490.2 mg, 2.50 mmol), dppp (20.6 mg, 0.050 mmol), and K_3PO_4 (21.2 mg, 1.0 mmol) were then added, and the mixture was degassed again and stirred at 130 °C until **13** was had been completely consumed. The reaction mixture was filtered, the filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (eluent: hexane/AcOEt = 4/1) to give (3*S*)-3-phenyl-1(3*H*)-isobenzofuranone (**14**)[30] (76.7 mg, 0.365 mmol) in 73% yield as a white solid. White solid: mp 113.2−115.3 °C; R_f 0.49 (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$) δ 6.41 (s, 1H), 7.28 (dd, J = 6.1, 3.1 Hz, 2H), 7.34 (d, J = 7.6 Hz, 1H), 7.36−7.40 (m, 3H), 7.56 (t, J = 7.6 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 82.7, 122.8, 125.5, 125.6, 126.9, 128.9, 129.2, 129.3, 134.3, 136.4, 149.6, 170.5; IR (KBr) 3483 m, 3064 m, 3033 m, 2950 m, 2545 w, 2253 w, 2135 w, 2037 w, 1955 w, 1744 s, 1611 s, 1599 s, 1494 s, 1474 m, 1456 s, 1335 s, 1286 s, 1210 s, 1184 s, 1157 m, 1099 s, 1067 s, 1012 s, 966 s, 920 s, 894 s, 841 m, 790 m, 763 s, 742 s, 698 s, 621 s, 569 m, 537 s; MS m/z (relative intensity, %) 210 (M^+, 49), 209 (12), 181 (10), 165 (19), 133 (12), 105 (100), 104 (29), 77 (37), 76 (17), 51 (18), 50 (10); exact mass-ESI calcd for $C_{14}H_{10}Na_1O_2$ 233.0578 $[M + Na]^+$, found 233.0579; $[\alpha]^{28}_D$ = +29.0° (c 0.80, $CHCl_3$) for 62% ee (*S*) (lit. $[\alpha]^{20}_D$ = +40.5° (c 0.80, $CHCl_3$) for 93% ee); HPLC (Chiralpak OD-H, *n*-hexane/2-propanol = 85/15, flow = 1.0 mL/min, detection at 225 nm) R_t = 8.0 min (*S*), R_t = 9.8 min (*R*).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all compounds; HPLC charts by which enantiomeric excesses of benzylamines **7** and **12**, their hydrogenated derivatives **9**, and carbonylated products **8** and **14** were measured; and X-ray crystallographic data and ORTEP drawings of **7l** and **8c−l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Stuk, T. L.; Assink, B. K.; Bates, R. C.; Erdman, D. T.; Fedij, V.; Jennings, S. M.; Lassig, J. A.; Smith, R. J.; Smith, T. L. *Org. Process Res. Dev.* **2003**, *7*, 851−855. (b) Atack, J. R. *Expert Opin. Invest. Drugs* **2005**, *14*, 601−618.

(2) (a) Kanamitsu, N.; Osaki, T.; Itsuji, Y.; Yoshimura, M.; Tsujimoto, H.; Soga, M. *Chem. Pharm. Bull.* **2007**, *55*, 1682−1688. (b) Shirasaka, T.; Kunitake, T.; Tsuneyoshi, I. *Brain Res.* **2009**, *1300*, 105−113.

(3) (a) Belliotti, T. R.; Brink, W. A.; Kesten, S. R.; Rubin, J. R.; Wustrow, D. J.; Zoski, K. T.; Whetzel, S. Z.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1499−1502. (b) Sanner, M. A. *Expert Opin. Ther. Pat.* **1998**, *8*, 383−393. (c) Steiner, G.; Bach, A.; Bialojan, S.; Greger, G.; Hege, H.-G.; Höger, T.; Jochims, K.; Munschauer, R.; Neumann, B.; Teschendorf, H.-J.; Traut, M.; Unger, L.; Gross, G. *Drugs Future* **1998**, *23*, 191−204. (d) Kulkarni, S. K.; Ninan, I. *Fundam. Clin. Pharmacol.* **2000**, *14*, 529−539.

(4) Bernstein, P. R.; Aharony, D.; Albert, J. S.; Andisik, D.; Barthlow, H. G.; Bialecki, R.; Davenport, T.; Dedinas, R. F.; Dembofsky, B. T.; Koether, G.; Kosmider, B. J.; Kirkland, K.; Ohnmacht, C. J.; Potts, W.; Rumsey, W. L.; Shen, L.; Shenvi, A.; Sherwood, S.; Stollman, D.; Russell, K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2769−2773.

(5) (a) Oppolzer, W.; Wills, M.; Kelly, M. J.; Signer, M.; Blagg, J. *Tetrahedron Lett.* **1990**, *31*, 5015−5018. (b) Murphy, J. P.; Nieuwenhuyzen, M.; Reynolds, K.; Sarma, P. K. S.; Stevenson, P. J. *Tetrahedron Lett.* **1995**, *36*, 9533−9536. (c) McAlonan, H.; Murphy, J. P.; Nieuwenhuyzen, M.; Reynolds, K.; Sarma, P. K. S.; Stevenson, P. J.; Thompson, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 69−79.

(6) (a) Hunter, R.; Richards, P. *Org. Biomol. Chem.* **2003**, *1*, 2348−2356. (b) Stájer, G.; Csende, F. *Curr. Org. Chem.* **2005**, *9*, 1277−1286. (c) Chen, M.-D.; He, M.-Z.; Zhou, X.; Huang, L.-Q.; Ruan, Y.-P.; Huang, P.-Q. *Tetrahedron* **2005**, *61*, 1335−1344. (d) Lamblin, M.; Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron: Asymmetry* **2008**, *19*, 111−123. (e) Deniau, E.; Couture, A.; Grandclaudon, P. *Tetrahedron: Asymmetry* **2008**, *19*, 2735−2740. (f) Yu, X.; Lu, A.; Wang, Y.; Wu, G.; Song, H.; Zhou, Z.; Tang, C. *Eur. J. Org. Chem.* **2011**, 892−897.

(7) (a) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336−5337. (b) Kurihara, K.; Yamamoto, Y.; Miyaura, N. *Adv. Synth. Catal.* **2009**, *351*, 260−270. (c) Wang, L.; Wang, Z.-Q.; Xu, M.-H.; Lin, G.-Q. *Synthesis* **2010**, 3263−3267. (d) Guo, S.; Xie, Y.; Hu, X.; Xia, C.; Huang, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 2728−2731.

(8) For reports on an intramolecular aminocarbonylation reaction using carbon monoxide for the constructing of the isoindolinone framework, see: (a) Mori, M.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1978**, *43*, 1684−1687. (b) Grigg, R.; Sridharan, V.; Suganthan, S.; Bridge, A. W. *Tetrahedron* **1995**, *51*, 295−306. (c) Ryu, I.; Matsu, K.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **1998**, *120*, 5838−5839. (d) Bocelli, G.; Catellani, M.; Cugini, F.; Ferraccioli, R. *Tetrahedron Lett.* **1999**, *40*, 2623−2624. (e) Anderson, J. C.; Flaherty, A.; Swarbrick, M. E. *J. Org. Chem.* **2000**, *65*, 9152−9156. (f) Grigg, R.; MacLachlan, W. S.; MacPherson, D. T.; Sridharan, V.; Suganthan, S.; Thornton-Pett, M.; Zhang, J. *Tetrahedron* **2000**, *56*, 6585−6594. (g) Grigg, R.; Zhang, L.; Collard, S.; Keep, A. *Tetrahedron Lett.* **2003**, *44*, 6979−6982. (h) Gai, X.; Grigg, R.; Khamnaen, T.; Rajviroongit, S.; Sridharan, V.; Zhang, L.; Collard, S.; Keep, A. *Tetrahedron Lett.* **2003**, *44*, 7441−7443. (i) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342−14343. (j) Grigg, R.; Zhang, L.; Collard, S.; Ellis, P.; Keep, A. *J. Organomet. Chem.* **2004**, *689*, 170−173. (k) Grigg, R.; Gai, X.; Khamnaen, T.; Rajviroongit, S.; Sridharan, V.; Zhang, L.; Collard, S.; Keep, A. *Can. J. Chem.* **2005**, *83*, 990−1005. (l) Orito, K.; Miyazawa, M.; Nakamura, T.; Horibata, A.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Yamazaki, T.; Tokuda, M. *J. Org. Chem.* **2006**, *71*, 5951−5958. (m) Cao, H.; McNamee, L.; Alper, H. *Org. Lett.* **2008**, *10*, 5281−5284. (n) Grigg, R.; Sridharan, V.; Shah, M.; Mutton, S.; Kilner, C.; MacPherson, D.; Milner, P. *J. Org. Chem.* **2008**, *73*, 8352−8356. (o) Onozaki, Y.; Kurono, N.; Senboku, H.; Tokuda, M.; Orito, K. *J. Org. Chem.* **2009**, *74*, 5486−5495. (p) Kallan, N. C.; Spencer, K. L.; Blake, J. F.; Xu, R.; Heizer, J.; Bencsik, J. R.; Mitchell, I. S.; Gloor, S. L.; Martinson, M.; Risom, T.; Gross, S. D.; Morales, T. H.; Wu, W.-I; Vigers, G. P. A; Brandhuber, B. J.; Skelton, N. J. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2410−2414. (q) Marosvölgyi-Haskó, D.; Takács, A.; Riedl, Z.; Kollár, L. *Tetrahedron* **2011**, *67*, 1036−1040.

(9) (a) Morimoto, T.; Fujioka, M.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K. *Chem. Lett.* **2003**, *32*, 154−155. (b) Morimoto, T.; Fujioka, M.;

Fuji, K.; Tsutsumi, K.; Kakiuchi, K. *J. Organomet. Chem.* **2007**, *692*, 625−634. (c) Morimoto, T.; Fujioka, M.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K. *Pure Appl. Chem.* **2008**, *80*, 1079−1087.
(10) (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169−196. (b) Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315−1392. (c) Schmidt, F.; Stemmler, R.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454−470. (d) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541−2569. (e) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482−4502. (f) Shintani, R.; Hayashi, T. *Aldrichimica Acta* **2009**, *42*, 31−38. (g) Marques, C. S.; Burke, A. J. *ChemCatChem* **2011**, *3*, 635−645.
(11) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Chem. Commun.* **2009**, 4815−4817.
(12) (a) Enders, D.; Braig, V.; Raabe, G. *Can. J. Chem.* **2001**, *79*, 1528−1535. (b) Clayden, J.; Menet, C. J. *Tetrahedron Lett.* **2003**, *44*, 3059−3062. (c) Lamblin, M.; Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **2006**, *62*, 2917−2921.
(13) For reports on the use of formaldehyde as a carbonyl source in carbonylation reactions, see: (a) Fuji, K.; Morimoto, T.; Tsutsumi, K.; Kakiuchi, K. *Angew. Chem. Int., Ed.* **2003**, *42*, 2409−2411 (Pauson−Khand Reaction). (b) Fuji, K.; Morimoto, T.; Tsutsumi, K.; Kakiuchi, K. *Chem. Commun.* **2005**, 3295−3297 (cyclohydrocarbonylation of alkynes). (c) Matsuda, T.; Tsuboi, T.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12596−12597 (carbonylation of spiropentanes). (d) Morimoto, T.; Yamasaki, K.; Hirano, A.; Tsutsumi, K.; Kagawa, N.; Kakiuchi, K.; Harada, Y.; Fukumoto, Y.; Chatani, N.; Nishioka, T. *Org. Lett.* **2009**, *11*, 1777−1780 (carbonylation of alkynes with 2-bromophenylboronic acid).
(14) For hydroformylation using paraformaldehyde as a substitute for synthesis gas (CO/H_2), see: (a) Okano, T.; Kobayashi, T.; Konishi, H.; Kiji, J. *Tetrahedron Lett.* **1982**, *23*, 4967−4968. (b) Kondo, T.; Akazome, M.; Tsuji, Y.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 1286−1291. (c) Ahn, H. S.; Han, S. H.; Uhm, S. J.; Seok, W. K.; Lee, H. N.; Korneeva, G. A. *J. Mol. Catal. A: Chem.* **1999**, *144*, 295−306. (d) Rosales, M.; González, A.; González, B.; Moratinos, C.; Pérez, H.; Urdaneta, J.; Sánchez-Delgado, R. A. *J. Organomet. Chem.* **2005**, *690*, 3095−3098. (e) Rosales, M.; Arrieta, F.; Baricelli, P.; González, A.; González, B.; Guerrero, Y.; Moratinos, C.; Pacheco, I.; Pérez, H.; Urdaneta, J. *Catal. Lett.* **2008**, *126*, 367−370. (f) Makado, G.; Morimoto, T.; Sugimoto, Y.; Tsutsumi, K.; Kagawa, N.; Kakiuchi, K. *Adv. Synth. Catal.* **2010**, *352*, 299−304.
(15) The rhodium(I)-catalyzed addition reaction of 2-bromophenylbronic acid with *N*-tosylbenzaldimine (**11**) failed to yield the desired benzylamine (*R*)-**7a**.
(16) (a) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584−13585. (b) Otomaru, Y.; Tokunaga, N.; Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 307−310.
(17) In this procedure, the hydrolysis of **6a** proceeded mainly to give 2-bromobenzaldehyde (**13**), and a small fraction of **13** was phenylated with phenylboronic acid to produce the 1,2-adduct **15**.
(18) For selected papers, see: (a) Hirai, G.; Ohkubo, M.; Tamura, Y.; Sodeoka, M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3587−3590 (PKCα activator). (b) Liu, J.; Li, F.; Kim, E. L.; Li, J. L.; Hong, J.; Bae, K. S.; Chung, H. Y.; Kim, H. S.; Jung, J. H. *J. Nat. Prod.* **2011**, *74*, 1826−1829 (antibacterial activity). (c) Wang, H.; Wang, Y.; Wang, W.; Fu, P.; Liu, P.; Zhu, W. *J. Nat. Prod.* **2011**, *74*, 2014−2018 (purpuresters A). (d) Bava, A.; Dallavalle, S.; Fronza, G.; Nasini, G.; Vajna de Pava, O. *J. Nat. Prod.* **2006**, *69*, 1793−1795 (sporotricale). (e) Chatterjee, P.; Franklin, M. R. *Drug Metab. Dispos.* **2003**, *31*, 1391−1397 (hydrastine). (f) Palermo, J. A.; Brasco, M. F. R.; Spagnuolo, C.; Seldes, A. M. *J. Org. Chem.* **2000**, *65*, 4482−4486 (alcyopterosin E). (g) Höller, U.; Gloer, J. B.; Wicklow, D. T. *J. Nat. Prod.* **2002**, *65*, 876−882 (herbaric acid).
(19) Giordano, G.; Crabtree, R. H. *Inorg. Synth.* **1979**, *19*, 218−220.
(20) Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588−13589.
(21) Love, B. E.; Raje, P. S.; Williams, T. C. II *Synlett* **1994**, 493−494.
(22) Monguchi, Y.; Kume, A.; Hattori, K.; Maegawa, T.; Sajiki, H. *Tetrahedron* **2006**, *62*, 7926−7933.
(23) See the Supporting Information.
(24) Ma, G.; Zhang, T.; Shi, M. *Org. Lett.* **2009**, *11*, 875−878.
(25) Duan, H.; Jia, Y.; Wang, L.; Zhou, Q. *Org. Lett.* **2006**, *8*, 2567−2569.
(26) Shao, C.; Yu, H.; Wu, N.; Feng, C.; Lin, G. *Org. Lett.* **2010**, *12*, 3820−3823.
(27) Hayashi, T.; Kawai, M.; Tokunaga, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6125−6128.
(28) Wang, Z.; Zhang, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2008**, *10*, 1863−1866.
(29) Ruano, J. L. G.; Alemán, J.; Cid, M. B.; Parra, A. *Org. Lett.* **2005**, *7*, 179−182.
(30) Phan, D. H. T.; Kim, B.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 15608−15609.