Tetrahedron: *Asymmetry* 23 (2012) 1657–1662

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Catalytic enantioselective synthesis of atropisomeric 2-aryl-4-quinolinone derivatives with an N–C chiral axis

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ARTICLE INFO

Article history:
Received 26 September 2012
Accepted 6 November 2012

ABSTRACT

In the presence of an (*R*)-MOP-$Pd_2(dba)_3$ catalyst, the reaction of *ortho*-*tert*-butylaniline with 2-bromophenyl arylethynyl ketone proceeded via a tandem amination (1,4-addition of aniline to an ynone and subsequent intramolecular Buchwald–Hartwig amination) to afford axially chiral *N*-(2-*tert*-butylphenyl)-2-aryl-4-quinolinone derivatives with moderate enantioselectivity (up to 72% ee).

1. Introduction

Atropisomeric compounds with an N–C chiral axis have received much attention as novel chiral molecules.[1] Noteworthy recent topics in this field include the catalytic asymmetric synthesis of N–C axially chiral compounds.[2] In 2005, we reported the highly enantioselective synthesis of axially chiral *ortho*-*tert*-butylanilides **I** and *N*-(*ortho*-*tert*-butylphenyl)-3,4-dihydroquinolin-2-one **II** (Fig. 1) via chiral Pd-catalyzed inter- and intramolecular *N*-arylation of achiral NH-anilides.[3] These reactions provided the first practical catalytic asymmetric synthesis of N–C axially chiral compounds. After publication of this work,[3a] the catalytic asymmetric synthesis of similar N–C axially chiral compounds was also reported by many other groups.[2c–n] We also succeeded in achieving the catalytic enantioselective synthesis of N–C axially chiral indoles **III** (Fig. 1) through the chiral Pd-catalyzed 5-*endo*-hydroaminocyclization of *ortho*-alkynylanilines.[4]

Herein we report the catalytic enantioselective synthesis of atropisomeric *N*-(2-*tert*-butylphenyl)-2-aryl-4-quinolinone derivatives **1**, which are new N–C axially chiral compounds.

2. Results and discussion

Recently, Xu et al. reported a Pd-catalyzed tandem amination reaction for the synthesis of 1,2-diaryl-4-quinolinones.[5] This reaction, which involves aniline and 2-bromophenyl arylethynyl ketone substrates in the presence of Ph_3P-$Pd_2(dba)_3$ catalyst, proceeds smoothly via 1,4-addition of an aniline to an ynone and subsequent intramolecular Buchwald–Hartwig amination.[6] This reaction is not only applicable to simple aniline, but also to 1-aminonaphthalene and *ortho*-substituted anilines such as *ortho*-toluidine and *ortho*-anisidine, although there is no mention of any axial chirality of the 4-quinolinone products obtained by the reaction with these aryl amines.

On the basis of these results, we thought that the catalytic enantioselective synthesis of N–C axially chiral 4-quinolinones **1** could be achieved by using *ortho*-*tert*-butylaniline **3** (R = *t*-Bu) in the presence of a chiral Pd-catalyst (Scheme 1). In the present reaction, the chiral axis of **1** should be constructed during the reductive elimination step of the amide–Pd intermediate, and this step might proceed in a highly enantioselective manner because the N–C bond forming reaction occurs near a chiral ligand (L*).

It was expected that the N–C chiral axis of *N*-(*ortho*-*tert*-butylphenyl)-4-quinolinone products **1** would have a high rotational barrier because of the rigid aromatic structure of the 4-quinolinone.[7] In the presence of a $Pd_2(dba)_3$ catalyst and various chiral phosphine ligands, the reaction of *ortho*-*tert*-butylaniline **3a** with 2-bromophenyl phenylethynyl ketone **2a** was investigated in refluxing 1,4-dioxane (K_2CO_3 was used as the base, Table 1). When bidentate chiral phosphine ligands such as (*R*)-BINAP, (*R*)-SEGPHOS, (*R*)-DIFLUOROPHOS, (*R*)-SYNPHOS, (*R*)-TUNEPHOS, and (*S*,*S*)-Trost ligand were used, the 4-quinolinone product **1a** was obtained with poor chemical yields (4–21%) and low enantioselectivity (2–22% ee, entries 1–7). The use of a monodentate phosphine ligand such as (+)-MENPHOS led to an increase in the chemical yield (46%), but the enantioselectivity remained poor (9% ee, entry 8). Using (*R*)-MOP[8] gave the best results for both in terms of chemical yield and enantioselectivity. In this case, the product **1a** was obtained in 51% yield and 53% ee (entry 9).

Although other solvents (toluene and diglyme), bases (Cs_2CO_3, Na_2CO_3, and NaH), and Pd-catalyst [$Pd(OAc)_2$] were also investigated, no better results than those obtained in entry 9 were obtained. Subsequently, a survey of arylamines was performed. The reaction with *ortho*-*iso*-propylaniline **3b** gave product **1b** in good yield (63%), but the enantioselectivity was lower than that

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http://dx.doi.org/10.1016/j.tetasy.2012.11.004

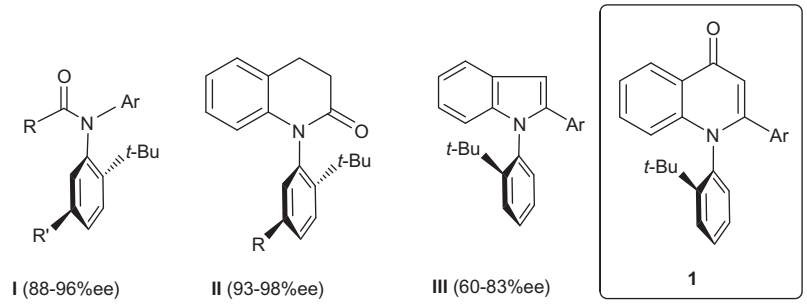
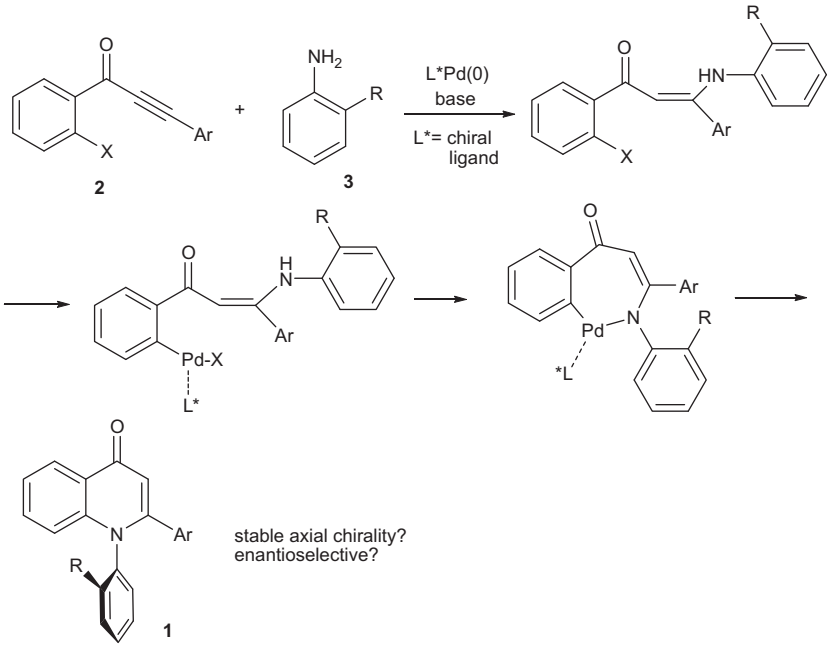


Figure 1. Several N–C axially chiral compounds prepared by catalytic asymmetric reactions.



Scheme 1. Synthetic scheme for preparing axially chiral 1,2-diaryl-4-quinolinones via chiral Pd-catalyzed tandem amination.

of *ortho*-*tert*-butylaniline **3a** (30% ee, entries 9 and 10). With 2,5-di-*tert*-butylaniline **3c**, decreases in both yield and enantioselectivity were observed (27%, 21% ee, entries 9 and 11).

The reactions of *ortho*-*tert*-butylaniline **3a** with various 2-bromophenyl arylethynyl ketones **2d**–**h** were investigated further under the optimized conditions (Table 2). The reaction with 4-methoxyphenyl and 4-methylphenyl derivatives **2d** and **2e** gave products **1d** and **1e** with yield and enantioselectivities similar to those of phenyl derivative **2a** (**1d**: 46%, 52% ee, **1e**: 48%, 54% ee, entries 2 and 3). While, in the reaction with 4-chlorophenyl and 4-nitrophenyl derivatives **2f** and **2g** with an electron-withdrawing group at the *para*-position, a decrease in yield was observed (**1f**: 31%, **1g**: 34%), and the enantioselectivity was increased in comparison with the phenyl derivative **2a** (**1f**: 66% ee, **1g**: 72% ee, entries 4 and 5). The reaction with *ortho*-methoxyphenyl derivative **2h** led to a slight increase in the enantioselectivity relative to that of the *para*-methoxyphenyl derivative **2d** (entry 6).

In addition to the arylethynyl ketones **2a**,**d**–**h** shown in Table 2, the reaction with 2-bromophenyl cyclohexylethynyl ketone and 2-bromophenyl 1-hexynyl ketone was also investigated under the same conditions. However, in the ethynyl ketones with a non-aromatic substituent, the formation of 4-quinolinone products did not occur.

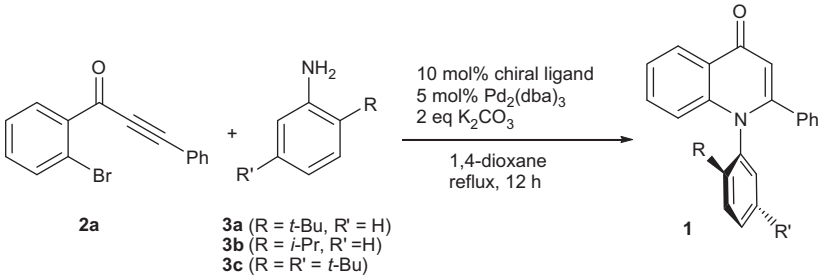
The axially chiral 4-quinolinone products **1** were also found to have a high rotational barrier. When **1g** (71.6% ee) was heated for 18 h in refluxing 1,4-dioxane, the enantiomeric excess of **1g** was almost unchanged (70.4% ee). This result may indicate that in the reaction of Table 2, any decrease in the ee due to the partial thermal racemization of products **1** is excluded.

The absolute configuration of the chiral axis in **1** was determined in accordance with Scheme 2. Compound **1g** (72% ee) was converted into almost enantiomerically pure form (>99% ee) through self-disproportionation of the enantiomers (SDE) by MPLC using an achiral silica gel column,[3d,9] that is, the MPLC chart of **1g** (72% ee, 38 mg) showed two distinct peaks and looked like a regular chart observed for a mixture of two chemically different compounds, and the ee of **1g** in the less polar and more polar fractions were >99% ee (13 mg) and 54% ee (20 mg), respectively. The reduction of the nitro group in **1g** (>99% ee) obtained from the less polar fraction followed by condensation with (*S*)-2-acetoxypropionyl chloride gave compound **4g**. The X-ray crystal structure of **4g** indicates that the absolute stereochemistry of the major enantiomer in **1g** is an (*S*)-configuration (Scheme 2).[10]

3. Conclusion

We have explored the catalytic asymmetric synthesis of axially chiral *N*-(*ortho*-*tert*-butylphenyl)-2-aryl-4-quinolinone derivatives through the chiral Pd-catalyzed tandem amination with *ortho*-

Table 1
Optimization of the conditions for the catalytic asymmetric tandem amination of **2a** and **3**[a]

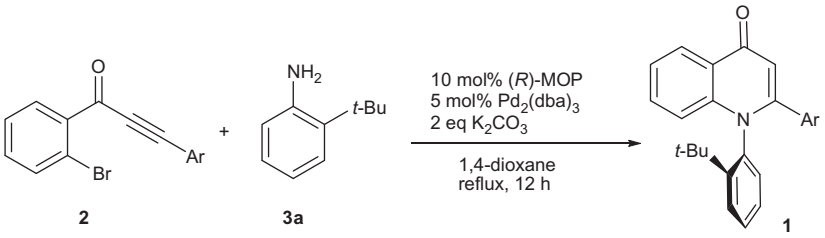


2a **3a** (R = *t*-Bu, R' = H)
3b (R = *i*-Pr, R' =H)
3c (R = R' = *t*-Bu)

Entry	3a	Chiral ligand	1a	Yield[b] (%)	ee[c] (%)
1	**3a**	(*R*)-BINAP	**1a**	4	16
2	**3a**	(*R*)-SEGPHOS	**1a**	7	18
3	**3a**	(*R*)-DTBM-SEGPHOS	**1a**	21	2
4	**3a**	(*R*)-DIFLUOROPHOS	**1a**	4	17
5	**3a**	(*R*)-SYNPHOS	**1a**	9	7
6	**3a**	(*R*)-C3-TUNEPHOS	**1a**	14	22
7	**3a**	(*S,S*)-Trost ligand	**1a**	5	20
8	**3a**	(+)-MENPHOS	**1a**	46	9
9	**3a**	(*R*)-MOP	**1a**	51	53
10	**3b**	(*R*)-MOP	**1b**	63	30
11	**3c**	(*R*)-MOP	**1c**	27	21

[a] Reaction conditions: **2a** (0.3 mmol), **3** (0.6 mmol), ligand (0.03 mmol), Pd (0.015 mmol), K_2CO_3 (0.6 mmol), dioxane (3 mL), reflux 12 h.
[b] Isolated yield.
[c] The ee was determined by HPLC using a chiral column.

Table 2
Catalytic asymmetric tandem amination with various arylethynyl ketone substrates **2a**[a]



2 **3a**

Entry	2a	Ar	1a	Yield[b] (%)	ee[c] (%)
1	**2a**	Ph	**1a**	51	53
2	**2d**	4-$MeOC_6H_4$	**1d**	46	52
3	**2e**	4-MeC_6H_4	**1e**	48	54
4	**2f**	4-ClC_6H_4	**1f**	31	66
5	**2g**	4-$NO_2C_6H_4$	**1g**	34	72
6	**2h**	2-$MeOC_6H_4$	**1h**	45	60

[a] Reaction conditions: **2** (0.3 mmol), **3a** (0.6 mmol), (*R*)-MOP (0.03 mmol), Pd (0.015 mmol), K_2CO_3 (0.6 mmol), dioxane (3 mL), reflux 12 h.
[b] Isolated yield.
[c] The ee was determined by HPLC using a chiral column.

tert-butylaniline and 2-bromophenyl arylethynyl ketones. This reaction proceeded with moderate yields and enantioselectivity through the 1,4-addition of aniline to ynones and subsequent intramolecular Buchwald–Hartwig amination in the presence of the (*R*)-MOP-$Pd_2(dba)_3$ catalyst. The absolute configuration of the major enantiomer in the N–C axially chiral 4-quinolinone product was determined on the basis of X-ray crystal structural analysis.

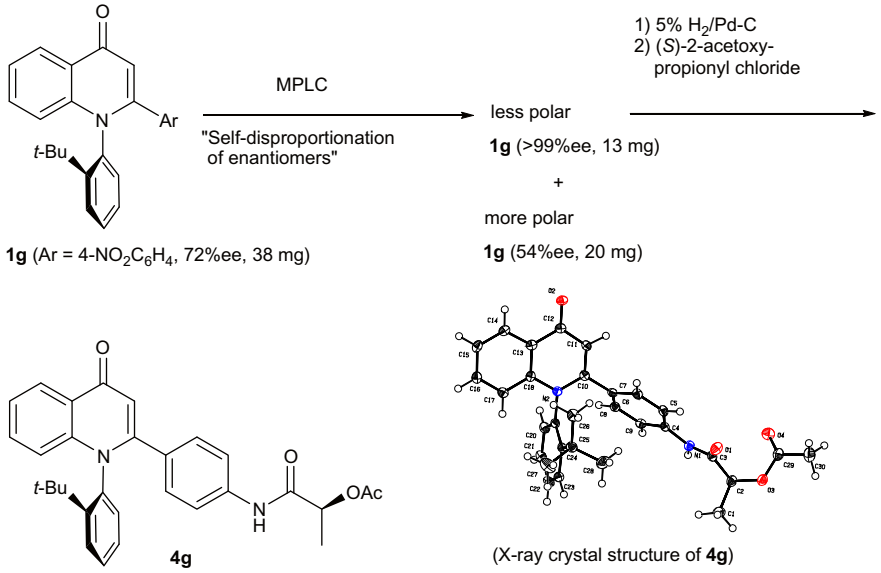
4. Experimental

4.1. General techniques

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. In ^1H and ^{13}C NMR spectra, chemical shifts are expressed in δ (ppm) downfield from $CHCl_3$ (7.26 ppm) and $CDCl_3$ (77.0 ppm), respectively. Mass spectra were recorded by electrospray ionization. Column chromatography was performed on silica gel (75–150 mm). Medium-pressure liquid chromatography (MPLC) was performed on a 25×4 cm i.d. prepacked column (silica gel, 10 μm) with a UV detector. High-performance liquid chromatography (HPLC) was performed on a 25×0.4 cm i.d. chiral column with a UV detector.

4.2. Synthesis of 2-bromophenyl arylethynyl ketones 2

Ketones **2a**,**d**,**f** are known compounds and were prepared in accordance with the literature.[5] Ketones **2e**,**g**,**h** were prepared in accordance with the following procedures.



Scheme 2. Stereochemical assignment of the chiral axis in **1g**.

4.2.1. 1-(2-Bromophenyl)-3-(*p*-tolyl)prop-2-yn-1-one 2e

Under an N_2 atmosphere, to $(Ph_3P)_2PdCl_2$ (43 mg, 0.06 mmol) and CuI (23 mg, 0.12 mmol) in THF (3 mL) were added 2-bromobenzoyl chloride (658 mg, 3.0 mmol) in THF (1.5 mL) and 4-methylphenylacetylene (348 mg, 3.0 mmol) in Et_3N (1.5 mL). After stirring for 3 h at rt, the mixture was poured into NH_4Cl aq and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 50) gave **2e** (747 mg, 83%). **2e**: pale yellow solid; mp 90–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 8.06 (1H, dd, J = 1.4, 7.3 Hz), 7.70 (1H, dd, J = 0.9, 7.8 Hz), 7.54 (2H, d, J = 7.9 Hz), 7.45 (1H, dt, J = 0.9, 7.3 Hz), 7.37 (1H, dt, J = 1.8, 7.9 Hz), 7.22 (2H, d, J = 7.9 Hz), 2.40 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ = 177.6, 141.8, 137.7, 134.9, 133.2, 133.1, 132.6, 129.5, 127.3, 121.1, 116.9, 95.0, 87.9, 21.8; IR (CH_2Cl_2) 2192, 1644 cm^{-1}; MS (ESI, m/z) 301, 299 (MH^+); Anal. Calcd for $C_{16}H_{11}BrO$: C, 64.24; H, 3.71. Found: C, 64.27; H, 3.93.

4.2.2. 1-(2-Bromophenyl)-3-(4-nitrophenyl)prop-2-yn-1-one 2g

Compound **2g** was prepared from 2-bromobenzoyl chloride (342 mg, 1.56 mmol) and 4-nitrophenylacetylene (294 mg, 1.56 mmol) in accordance with the procedure for the synthesis of **2e**. Purification of the residue by column chromatography (hexane/AcOEt = 30) gave **2g** (110 mg, 21%). **2g**: pale yellow solid; mp 149–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 8.28 (2H, td, J = 1.8, 9.2 Hz), 8.05 (1H, dd, J = 1.8, 7.3 Hz), 7.80 (2H, td, J = 1.8, 9.2 Hz), 7.73 (1H, dd, J = 1.4, 7.8 Hz), 7.48 (1H, dt, J = 1.4, 7.3 Hz), 7.42 (1H, dt, J = 1.8, 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ = 176.8, 148.6, 136.9, 135.1, 133.8, 133.6, 132.8, 127.5, 126.6, 123.8, 121.5, 90.6, 90.2; IR (CH_2Cl_2) 2205, 1650 cm^{-1}; MS (ESI, m/z) 330, 332 (MH^+); Anal. Calcd for $C_{15}H_8BrNO_3$: C, 54.57; H, 2.44; N, 4.24. Found: C, 54.79; H, 2.51; N, 4.02.

4.2.3. 1-(2-Bromophenyl)-3-(2-methoxyphenyl)prop-2-yn-1-one 2h

Compound **2h** was prepared from 2-bromobenzoyl chloride (1.097 g, 5.0 mmol) and 2-methoxyphenylacetylene (661 mg, 5.0 mmol) in accordance with the procedure for the synthesis of **2h**. Purification of the residue by column chromatography (hexane/AcOEt = 30) gave **2h** (1.167 g, 74%). **2h**: pale brown solid; mp 45–46 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 8.25 (1H, dd, J = 1.8, 7.8 Hz), 7.68 (1H, dd, J = 1.4, 7.8 Hz), 7.57 (1H, dd, J = 1.4, 7.3 Hz), 7.41–7.47 (2H, m), 7.36 (1H, dt, J = 1.8, 7.8 Hz), 6.96 (1H, dt, J = 0.9, 7.3 Hz), 6.92 (1H, d, J = 8.2 Hz), 3.91 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ = 177.2, 161.8, 137.2, 134.9, 133.5, 133.2, 132.7, 127.2, 121.2, 120.6, 110.9, 109.2, 92.0, 91.3, 55.8; IR (CH_2Cl_2) 2189, 1645 cm^{-1}; MS (ESI, m/z) 315, 317 (MH^+); Anal. Calcd for $C_{16}H_{11}BrO_2$: C, 60.98; H, 3.52. Found: C, 60.95; H, 3.65.

4.3. General procedure for the synthesis of axially chiral 4-quionolinone derivatives 1

Under an N_2 atmosphere, to (*R*)-MOP (15 mg, 0.03 mmol) in 1, 4-dioxane (1.0 mL) was added $Pd_2(dba)_2$ (14 mg, 0.015 mmol), and the mixture was stirred for 10 min. Next K_2CO_3 (83 mg, 0.6 mmol), and then **2a** (86 mg, 0.3 mmol) and *ortho*-*tert*-butylaniline **3a** (90 mg, 0.6 mmol) in 1,4-dioxane (2.0 mL) were added to the mixture. After being stirred for 12 h in refluxing 1,4-dioxane, the reaction mixture was poured into a saturated $NaHCO_3$ solution and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over Na_2SO_4, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 1) gave **1a** (54 mg, 51%). The ee (53% ee) of **1a** was determined by HPLC analysis using a CHIRALPACK OD-3 column [25 × 0.46 cm i.d.; 10% *i*-PrOH in hexane; flow rate, 1.5 mL/min; (−)-**1a** (major); t_R = 11.1 min, (+)-**1a** (minor); t_R = 19.7 min].

4.3.1. 1-(2-(*tert*-Butyl)phenyl)-2-phenylquinolin-4(1*H*)-one 1a

Compound **1a** (57% ee): white solid; $[\alpha]_D^{25} = -36.1$ (c 0.41, $CHCl_3$); mp 221–223 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 8.51 (1H, dd, J = 1.8, 8.2 Hz), 7.46–7.51 (2H, m), 7.33–7.40 (2H, m), 7.16–7.25 (6H, m), 7.12 (1H, dd, J = 1.8, 8.2 Hz), 6.77 (1H, d, J = 8.7 Hz), 6,47 (1H, s), 0.98 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ = 178.1, 154.2, 147.5, 143.7, 135.5, 135.2, 133.0, 131.9, 131.3, 129.9, 129.5, 128.8, 127.7, 126.6, 126.2, 125.9, 123.6, 118.7, 113.1, 36.3, 31.5; IR (neat) 1624 cm^{-1}; MS (ESI, m/z) 354 (MH^+); Anal. Calcd for $C_{25}H_{23}NO$: C, 84.95; H, 6.56; N, 3.96. Found: C, 84.70; H, 6.38; N, 3.83.

4.3.2. 1-(2-(*iso*-Propyl)phenyl)-2-phenylquinolin-4(1*H*)-one 1b

Compound **1b** was prepared from **2a** (86 mg, 0.3 mmol) and *ortho*-*iso*-propylaniline **3b** (86 mg, 0.6 mmol) in accordance with the general procedure for the synthesis of **1**. Purification of the res-

idue by column chromatography (hexane/AcOEt = 1) gave **1b** (64 mg, 63%). The ee (30% ee) of **1b** was determined by HPLC analysis using a CHIRALPACK OD-3 column [25 × 0.46 cm i.d.; 10% *i*-PrOH in hexane; flow rate, 1.5 mL/min; (−)-**1b** (major); t_R = 9.8 min, (+)-**1b** (minor); t_R = 19.3 min]. Compound **1b** (30% ee): white solid; $[\alpha]_D^{25} = -29.9$ (*c* 0.40, $CHCl_3$); mp 228–230 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 8.52 (1H, dd, *J* = 1.4, 7.8 Hz), 7.46 (1H, ddd, *J* = 1.8, 6.9, 8.7 Hz), 7.28–7.39 (4H, m), 7.16–7.25 (6H, m), 6.79 (1H, d, *J* = 8.7 Hz), 6,50 (1H, s), 2.46 (1H, sept, *J* = 6.9 Hz), 0.84 (3H, d, *J* = 6.9 Hz), 0.78 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ = 178.0, 154.1, 146.8, 142.7, 136.2, 135.1, 131.7, 130.8, 130.1, 129.5, 128.8, 127.65, 127.56, 126.3, 126.2, 126.1, 123.8, 118.3, 112.6, 27.7, 24.9, 22.0; IR (neat) 1625 cm^{-1}; MS (ESI, *m*/*z*) 340 (MH^+); Anal. Calcd for $C_{24}H_{21}NO$: C, 84.92; H, 6.24; N, 4.13. Found: C, 84.93; H, 6.31; N, 4.03.

4.3.3. 1-(2,5-(Di-*tert*-butyl)phenyl)-2-phenylquinolin-4(1*H*)-one 1c

Compound **1c** was prepared from **2a** (86 mg, 0.3 mmol) and 2, 5-di-*tert*-butylaniline **3c** (74 mg, 0.36 mmol) in accordance with the general procedure for the synthesis of **1**. Purification of the residue by column chromatography (hexane/AcOEt = 1) gave **1c** (33 mg, 27%). The ee (21% ee) of **1c** was determined by HPLC analysis using a CHIRALPACK OD-3 column [25 × 0.46 cm i.d.; 10% *i*-PrOH in hexane; flow rate, 1.0 mL/min; (+)-**1c** (minor); t_R = 6.8 min, (−)-**1c** (major); t_R = 9.1 min]. Compound **1c** (21% ee): white solid; $[\alpha]_D^{25} = -14.9$ (*c* 0.40, $CHCl_3$); mp 216–218 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 8.52 (1H, dd, *J* = 1.4, 7.8 Hz), 7.50 (1H, ddd, *J* = 1.4, 7.3, 8.7 Hz), 7.36–7.40 (2H, m), 7.32 (1H, dd, *J* = 1.8, 8.7 Hz), 7.14–7.23 (5H, m), 7.03 (1H, d, *J* = 1.8 Hz), 6.82 (1H, d, *J* = 8.7 Hz), 6,49 (1H, s), 1.25 (9H, m), 0.98 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ = 178.1, 154.4, 149.8, 144.2, 143.7, 135.6, 134.7, 131.9, 130.8, 129.9, 129.8, 128.7, 127.6, 126.4, 126.3, 125.9, 123.6, 118.8, 113.0, 35.8, 34.1, 31.5, 30,9; IR (neat) 1623 cm^{-1}; MS (ESI, *m*/*z*) 410 (MH^+); HRMS (ESI). Calcd for $C_{29}H_{32}NO$ (MH^+) 410.2484. Found: 410.2481.

4.3.4. 1-(2-(*tert*-Butyl)phenyl)-2-(4-methoxyphenyl)quinolin-4(1*H*)-one 1d

Compound **1d** was prepared from **2d** (95 mg, 0.3 mmol) and *ortho*-*tert*-butylaniline **3a** (90 mg, 0.6 mmol) in accordance with the general procedure for the synthesis of **1**. Purification of the residue by column chromatography (hexane/AcOEt = 1) gave **1d** (53 mg, 46%). The ee (52% ee) of **1d** was determined by HPLC analysis using a CHIRALPACK OD-3 column [25 × 0.46 cm i.d.; 10% *i*-PrOH in hexane; flow rate, 1.5 mL/min; (−)-**1d** (major); t_R = 16.0 min, (+)-**1d** (minor); t_R = 26.3 min]. **1d** (52% ee): white solid; $[\alpha]_D^{25} = -42.3$ (*c* 0.41, $CHCl_3$); mp 173–176 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 8.50 (1H, dd, *J* = 1.4, 7.8 Hz), 7.45–7.51 (2H, m), 7.33–7.40 (2H, m), 7.25 (1H, dt, *J* = 1.4, 7.9 Hz), 7.10–7.16 (3H, m), 6.75 (1H, d, *J* = 8.7 Hz), 6.70 (2H, dt, *J* = 2.7, 9.2 Hz), 6,46 (1H, s), 3.74 (3H, s), 0.96 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ = 178.1, 159.7, 154.1, 147.5, 143.7, 135.4, 133.0, 131.8, 131.4, 131.3, 129.5, 127.8, 126.6, 126.2, 125.9, 123.5, 118.7, 113.1, 55.2, 36.3, 31.5; IR (neat) 1620 cm^{-1}; MS (ESI, *m*/*z*) 384 (MH^+); HRMS (ESI). Calcd for $C_{26}H_{26}NO_2$ (MH^+) 384.1964. Found: 384.1963.

4.3.5. 1-(2-(*tert*-Butyl)phenyl)-2-(4-methylphenyl)quinolin-4(1*H*)-one 1e

Compound **1e** was prepared from **2e** (90 mg, 0.3 mmol) and *ortho*-*tert*-butylaniline **3a** (90 mg, 0.6 mmol) in accordance with the general procedure for the synthesis of **1**. Purification of the residue by column chromatography (hexane/AcOEt = 1) gave **1e** (53 mg, 48%). The ee (54% ee) of **1e** was determined by HPLC analysis using a CHIRALPACK OD-3 column [25 × 0.46 cm i.d.; 10% *i*-PrOH in hexane; flow rate, 1.5 mL/min; (−)-**1e** (major); t_R = 9.2 min, (+)-**1e** (minor); t_R = 15.7 min]. Compound **1e** (55% ee): white solid; $[\alpha]_D^{25} = -35.1$ (*c* 0.42, $CHCl_3$); mp 174–177 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 8.51 (1H, dd, *J* = 1.4, 7.8 Hz), 7.45–7.50 (2H, m), 7.35–7.39 (2H, m), 7.24 (1H, dt, *J* = 1.8, 8.2 Hz), 7.09–7.13 (3H, m), 6.98 (2H, d, *J* = 8.2 Hz), 6.75 (1H, d, *J* = 8.2 Hz), 6,46 (1H, s), 2.26 (3H, s), 0.97 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ = 178.1, 154.4, 147.5, 143.7, 138.8, 135.4, 133.0, 132.6, 131.8, 131.3, 129.8, 129.5, 128.4, 126.6, 126.2, 125.9, 123.6, 118.7, 113.1, 36.3, 31.5, 21.1; IR (neat) 1621 cm^{-1}; MS (ESI, *m*/*z*) 368 (MH^+); HRMS (ESI). Calcd for $C_{26}H_{26}NO$ (MH^+) 368.2014. Found: 368.2006.

4.3.6. 1-(2-(*tert*-Butyl)phenyl)-2-(4-chlorophenyl)quinolin-4(1*H*)-one 1f

Compound **1f** was prepared from **2f** (96 mg, 0.3 mmol) and *ortho*-*tert*-butylaniline **3a** (90 mg, 0.6 mmol) in accordance with the general procedure for the synthesis of **1**. Purification of the residue by column chromatography (hexane/AcOEt = 1) gave **1f** (36 mg, 31%). The ee (66% ee) of **1f** was determined by HPLC analysis using a CHIRALPACK OD-3 column [25 × 0.46 cm i.d.; 10% *i*-PrOH in hexane; flow rate, 1.5 mL/min; (−)-**1f** (major); t_R = 9.8 min, (+)-**1f** (minor); t_R = 26.2 min]. Compound **1f** (66% ee): white solid; $[\alpha]_D^{25} = -38.3$ (*c* 0.41, $CHCl_3$); mp 196–198 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 8.49 (1H, dd, *J* = 1.4, 7.8 Hz), 7.46–7.52 (2H, m), 7.34–7.40 (2H, m), 7.25 (1H, dt, *J* = 2.7, 7.8 Hz), 7.16–7.17 (4H, m), 7.10 (1H, dd, *J* = 1.4, 7.8 Hz), 6.75 (1H, d, *J* = 8.7 Hz), 6,41 (1H, s), 0.97 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ = 178.0, 152.9, 147.6, 143.6, 135.1, 135.0, 134.0, 132.9, 132.0, 131.5, 131.2, 129.8, 128.0, 126.8, 126.3, 126.0, 123.8, 118.7, 113.2, 36.3, 31.6; IR (neat) 1622 cm^{-1}; MS (ESI, *m*/*z*) 388 (MH^+); HRMS (ESI). Calcd for $C_{25}H_{23}ClNO$ (MH^+) 388.1468. Found: 388.1458.

4.3.7. (*S*)-1-(2-(*tert*-Butyl)phenyl)-2-(4-nitrophenyl)quinolin-4(1*H*)-one 1g

Compound **1g** was prepared from **2g** (70 mg, 0.3 mmol) and *ortho*-*tert*-butylaniline **3a** (90 mg, 0.6 mmol) in accordance with the general procedure for the synthesis of **1**. Purification of the residue by column chromatography (hexane/AcOEt = 1) gave **1g** (41 mg, 34%). The ee (72% ee) of **1g** was determined by HPLC analysis using a CHIRALPACK OD-3 column [25 × 0.46 cm i.d.; 50% *i*-PrOH in hexane; flow rate, 1.0 mL/min; (−)-**1g** (major); t_R = 8.8 min, (+)-**1g** (minor); t_R = 17.1 min]. Compound **1g** (72% ee): white solid; $[\alpha]_D = -49.1$ (*c* 0.40, $CHCl_3$); mp 261–264 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 8.50 (1H, dd, *J* = 1.4, 8.2 Hz), 8.07 (2H, td, *J* = 2.2, 8.7 Hz), 7.50–7.55 (2H, m), 7.37–7.46 (4H, m), 7.26 (1H, dt, *J* = 1.4, 7.8 Hz), 7.13 (1H, dd, *J* = 1.4, 7.8 Hz), 6.78 (1H, d, *J* = 8.2 Hz), 6,42 (1H, s), 1.01 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ = 177.8, 151.6, 147.7, 147.6, 143.6, 141.7, 134.7, 132.8, 132.4, 131.6, 130.9, 130.1, 127.0, 126.4, 126.1, 124.1, 122.9, 118.7, 113.2, 36.3, 31.7; IR (neat) 1625 cm^{-1}; MS (ESI, *m*/*z*) 399 (MH^+); HRMS (ESI). Calcd for $C_{25}H_{23}N_2O_3$ (MH^+) 399.1709. Found: 399.1697.

4.3.8. 1-(2-(*tert*-Butyl)phenyl)-2-(2-methoxyphenyl)quinolin-4(1*H*)-one 1h

Compound **1h** was prepared from **2h** (95 mg, 0.3 mmol) and *ortho*-*tert*-butylaniline **3a** (90 mg, 0.6 mmol) in accordance with the general procedure for the synthesis of **1**. Purification of the residue by column chromatography (hexane/AcOEt = 1) gave **1h** (51 mg, 45%). The ee (60% ee) of **1h** was determined by HPLC analysis using a CHIRALPACK AD column [25 × 0.46 cm i.d.; 10% *i*-PrOH in hexane; flow rate, 2.0 mL/min; (+)-**1h** (minor); t_R = 12.5 min, (−)-**1h** (major); t_R = 16.1 min]. Compound **1h** (60% ee): white solid; $[\alpha]_D^{25} = +19.4$ (*c* 0.40, $CHCl_3$); mp 236–238 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 8.51 (1H, dd, *J* = 1.8, 8.2 Hz), 7.47 (1H, ddd,

J = 1,8, 7.3, 8.7 Hz), 7.42 (1H, d, J = 8.2 Hz), 7.36 (1H, dt, J = 0.9, 7,8 Hz), 7.23–7.30 (3H, m), 7.20 (1H, dt, J = 1.4, 8.7 Hz), 7.10 (1H, m), 6.84 (1H, m), 6.71 (1H, d, J = 8.2 Hz), 6.67 (1H, d, J = 7.8 Hz), 6,37 (1H, s), 3.70 (3H, s), 1.06 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ = 178.2, 155.8, 151.9, 146.9, 144.0, 135.4, 131.7, 131.1, 130.8, 130.6, 129.9, 129.4, 126.3, 125.9, 125.8, 124.8, 123.3, 119.7, 118.4, 113.2, 110.4, 54.8, 36.3, 31.7; IR (neat) 1623 cm^{-1}; MS (ESI, m/z) 384 (MH^+); HRMS (ESI). Calcd for $C_{26}H_{26}NO_2$ (MH^+) 384.1964. Found: 384.1957.

Acknowledgments

This work was partly supported by a Grant-in-Aid (C22590015) for Scientific Research and the Ministry of Education, Science, Sports and Culture of Japan.

References

1. Typical examples of atropisomeric compounds with an N–C chiral axis: (a) Bock, L. H.; Adams, R. *J. Am. Chem. Soc.* **1931**, *53*, 374; (b) Kashima, C.; Katoh, A. *J. Chem. Soc., Perkin Trans.* **1980**, 1599; (c) Mannschreck, A.; Koller, H.; Stühler, G.; Davis, M. A.; Traber, J. *Eur. J. Med. Chem.: Chim. Ther.* **1984**, *19*, 381; (d) Roussel, C.; Adjimi, M.; Chemlal, A.; Djafri, A. *J. Org. Chem.* **1988**, *53*, 5076; (e) Mintas, M.; Mihaljevic, V.; Koller, H.; Schuster, D.; Mannschreck, A. *J. Chem. Soc., Perkin Trans. 2* **1990**, 619; (f) Kawamoto, T.; Tomishima, M.; Yoneda, F.; Hayami, J. *Tetrahedron Lett.* **1992**, *33*, 3169; (g) Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 3131; (h) Dai, X.; Wong, A.; Virgil, S. C. *J. Org. Chem.* **1998**, *63*, 2597; (i) Kitagawa, O.; Izawa, H.; Sato, K.; Dobashi, A.; Taguchi, T.; Shiro, M. *J. Org. Chem.* **1998**, *63*, 2634; (j) Hughes, A. D.; Price, D. A.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1295; (k) Hata, T.; Koide, H.; Taniguchi, N.; Uemura, M. *Org. Lett.* **2000**, *2*, 1907; (l) Kondo, K.; Iida, T.; Fujita, H.; Suzuki, T.; Yamaguchi, K.; Murakami, Y. *Tetrahedron* **2000**, *56*, 8883; (m) Shimizu, K. D.; Freyer, H. O.; Adams, R. D. *Tetrahedron Lett.* **2000**, *41*, 5431; (n) Sakamoto, M.; Utsumi, N.; Ando, M.; Seki, M.; Mino, T.; Fujita, T.; Katoh, A.; Nishino, T.; Kashima, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 4360; (o)Tetrahedron symposium-in-print on axially chiral amides (atropisomerism): Clayden, J., Ed.*Tetrahedron* **2004**, *60*, 4325–4558; (p) Tokitoh, T.; Kobayashi, T.; Nakada, E.; Inoue, T.; Yokoshima, S.; Takahashi, H.; Natsugari, H. *Heterocycles* **2006**, *70*, 93; (q) Kamikawa, K.; Kinoshita, S.; Furusyo, M.; Takemoto, S.; Matsuzaka, H.; Uemura, M. *J. Org. Chem.* **2007**, *72*, 3394; (r) Yilmaz, E. M.; Dogan, I. *Tetrahedron: Asymmetry* **2008**, *19*, 2184; (s) Kawabata, T.; Jiang, C.; Hayashi, K.; Tsubaki, K.; Yoshimura, T.; Majumdar, S.; Sasamori, T.; Tokitoh, N. *J. Am. Chem. Soc.* **2009**, *131*, 54.
2. (a) Kitagawa, O.; Kohriyama, M.; Taguchi, T. *J. Org. Chem.* **2002**, *67*, 8682; (b) Terauchi, J.; Curran, D. P. *Tetrahedron: Asymmetry* **2003**, *14*, 587; (c) Brandes, S.; Bella, M.; Kjoersgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1147; (d) Tanaka, K.; Takeishi, K.; Noguchi, K. *J. Am. Chem. Soc.* **2006**, *128*, 4586; (e) Brandes, S.; Niess, B.; Bella, M.; Prieto, A.; Overgaard, J.; Jorgensen, K. A. *Chem. Eur. J.* **2006**, *12*, 6039; (f) Duan, W.; Imazaki, Y.; Shintani, R.; Hayashi, T. *Tetrahedron* **2007**, *63*, 8529; (g) Oppenheimer, J.; Hsung, R. P.; Figueroa, R.; Johnson, W. L. *Org. Lett.* **2007**, *9*, 3969; (h) Tanaka, K.; Takeishi, K. *Synthesis* **2007**, 2920; (i) Tanaka, K.; Takahashi, Y.; Suda, T.; Hirano, M. *Synlett* **2008**, 1724; (j) Clayden, J.; Turner, H. *Tetrahedron Lett.* **2009**, *50*, 3216; (k) Oppenheimer, J.; Johnson, W. L.; Figueroa, R.; Hayashi, R.; Hsung, R. P. *Tetrahedron* **2009**, *65*, 5001; (l) Lin, S.; Leow, D.; Huang, K.-W.; Tan, C-H. *Chem. Asian J.* **2009**, *4*, 1741; (m) Onodera, G.; Suto, M.; Takeuchi, R. *J. Org. Chem.* **2012**, *77*, 908; (n) Shirakawa, S.; Liu, K.; Maruoka, K. *J. Am. Chem. Soc.* **2012**, *134*, 916.
3. (a) Kitagawa, O.; Takahashi, M.; Yoshikawa, M.; Taguchi, T. *J. Am. Chem. Soc.* **2005**, *127*, 3676; (b) Kitagawa, O.; Yoshikawa, M.; Tanabe, H.; Morita, T.; Takahashi, M.; Dobashi, Y.; Taguchi, T. *J. Am. Chem. Soc.* **2006**, *128*, 12923; (c) Kitagawa, O.; Kurihara, D.; Tanabe, H.; Shibuya, T.; Taguchi, T. *Tetrahedron Lett.* **2008**, *49*, 471; (d) Takahashi, M.; Tanabe, H.; Nakamura, T.; Kuribara, D.; Yamazaki, T.; Kitagawa, O. *Tetrahedron* **2010**, *66*, 288; For a review: (e) Takahashi, M.; Kitagawa, O. *Yuki Gosei Kagaku Kyokaishi* **2011**, *69*, 985.
4. Ototake, N.; Morimoto, Y.; Mokuya, A.; Fukaya, H.; Shida, Y.; Kitagawa, O. *Chem. Eur. J.* **2010**, *16*, 6752.
5. Zhao, T.; Xu, B. *Org. Lett.* **2010**, *12*, 212.
6. (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348; (b) Hartwig, J. F.; Loue, J. *Tetrahedron Lett.* **1995**, *36*, 3609; (c) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043; (d) Shen, Q.; Shashank, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371.
7. Recently we found that the rotational barrier of *N*-(*ortho*-*tert*-butylphenyl)-2-quinolinone is higher than 10 kcal/mol in comparison to that of *N*-(*ortho*-*tert*-butylphenyl)-3,4-dihydro-2-quinolinone. The high rotational barrier of *N*-(*ortho*-*tert*-butylphenyl)-2-quinolinone was disclosed to be due to the rigid aromatic structure: Suzumura, N.; Kageyama, M.; Kamimura, D.; Inagaki, T.; Dobashi, Y.; Hasegawa, H.; Fukaya, H.; Kitagawa, O. *Tetrahedron Lett.* **2012**, *53*, 4332.
8. (a) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887; (b) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354.
9. Typical examples of SED through achiral chromatography: (a) Cundy, K. C.; Crooks, P. A. *J. Chromatogr.* **1983**, *281*, 17; (b) Charles, R.; Gil-Av, E. *J. Chromatogr.* **1984**, *298*, 516; (c) Dobashi, A.; Motoyama, Y.; Kinoshita, K.; Hara, S.; Fukasaku, N. *Anal. Chem.* **1987**, *59*, 2209; (d) Matusch, R.; Coors, C. *Angew. Chem., Int. Ed. Engl.* **1989**, *101*, 624; (e) Diter, P.; Taudien, S.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1994**, *59*, 370; (f) Kosugi, H.; Abe, M.; Hatsuda, R.; Uda, H.; Kato, M. *Chem. Commun.* **1997**, *1857*; (g) Tanaka, K.; Osuga, H.; Suzuki, H.; Shogase, Y.; Kitahara, Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 935; (h) Ernholt, B. V.; Thomsen, I. B.; Lohse, A.; Plesner, I. W.; Jensen, K. B.; Hazell, R. G.; Liang, X.; Jacobsen, A.; Bols, M. *Chem. Eur. J.* **2000**, *6*, 278; (i) Suchy, M.; Kutschy, P.; Monde, K.; Goto, H.; Harada, N.; Takasugi, M.; Dzurilla, M.; Balentova, E. *J. Org. Chem.* **2001**, *66*, 3940; (j) Ogawa, S.; Nishimine, T.; Tokunaga, E.; Nakamura, S.; Shibata, N. *J. Fluorine Chem.* **2010**, *131*, 521; For reviews: (k) Takahata, H. *Yuki Gosei Kagaku Kyokaishi* **1996**, *54*, 708; (l) Soloshonok, V.; Roussel, C.; Kitagawa, O.; Sorochinsky, A. *Chem. Soc. Rev.* **2012**, *41*, 4180.
10. CCDC-901836 **4g** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.com.ac.uk/data_request/cif.