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Axially Chiral C_2-Symmetric *N*-Heterocyclic Carbene (NHC) Palladium Complex-Catalyzed Asymmetric Fluorination and Amination of Oxindoles†

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Chiral C_2-symmetric *N*-heterocyclic carbene (NHC) palladium diaquo complex **5b** prepared from (*S*)-BINAM was found to be a fairly effective catalyst for the enantioselective asymmetric fluorination of oxindoles to give the corresponding products in moderate enantioselectivities along with good to excellent yields.

Keywords chiral C_2-symmetric *N*-heterocyclic carbene (NHC) palladium diaquo complex, (*S*)-BINAM, asymmetric fluorination of oxindoles, *N*-fluorobenzenesulfonimide (NFSI), 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (selectfluor)

Introduction

The stereoselective introduction of the C—F bond into organic compounds has attracted much attention because fluorine containing chiral organic molecules are very fascinating in the field of medicinal chemistry.[1-12] After the first work on catalytic enatioselective fluorination reported by Togni *et al*. in 2000,[13] catalytic asymmetric fluorination has witnessed great progress in the past eleven years.[14,15] Several chiral metal complexes and phase transfer catalysts have been developed for the fluorination of carbonyl compounds such as *β*-keto esters, imides, and aldehydes.[16-46] However, stereoselective construction of fluorinated quaternary carbon centers via introduction of fluorine atoms is still a big challenge.[47,48]

Previously, we reported that axially chiral C_2-symmetric *N*-heterocyclic carbene (NHC) palladium complexes **5a** — **5e** were highly effective catalysts in 1,4-addition of *α*,*β*-unsaturated ketones, 1,2-addition of aldehydes, and oxidative kinetic resolution of secondary alcohols.[49-61] As a part of our ongoing research project on the application of these chiral NHC-Pd complexes in asymmetric catalysis, we attempted to utilize these complexes in the fluorination reaction of 3-substituted oxindoles, since these optically active fluorinated derivatives could have significant applications in the field of medicinal chemistry.[62] In this context, we wish to report that axially chiral C_2-symmetric *N*-heterocyclic carbene (NHC) palladium complex **5b** is a fairly effective catalyst in the asymmetric fluorination of 3-substituted oxindoles to give the corresponding fluorinated products in moderate enantioselectivities along with good to excellent yields.

Experimental

General methods

m.p. was obtained with a Yanagimoto micro melting point apparatus and is uncorrected. Optical rotations were determined in a solution of $CHCl_3$, CH_2Cl_2, or acetone at 20 ℃ by using a Perkin-Elmer-241 MC polarimeter; $[\alpha]_D$-Values are given in units of 10^{-1} (°)•cm^2•g^{-1}. Infra-red spectra were measured on a spectrometer. ^{1}H NMR spectra were recorded for solution in $CDCl_3$ with tetramethylsilane (TMS) as internal standard; ^{31}P NMR spectra were recorded at 121 MHz for a solution in $CDCl_3$ with 85% H_3PO_4 as the external reference. *J* values are in Hz. Mass spectra were recorded with an HP-5989 instrument and HRMS was measured by a Finnigan MA＋ mass spectrometer. Organic solvents used were dried by standard methods when necessary. Commercially obtained reagents were used without further purification. All reactions were moni-

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† Dedicated to Professor Jun Zhou on the occasion of his 80th birthday.

tored by TLC with Huanghai $60F_{254}$ silica gel coated plates. Flash column chromatography was carried out using 300—400 mesh silica gel at increased pressure. All asymmetric addition reactions were performed under argon using standard Schlenk techniques. The optical purities of adducts were determined by HPLC analysis using a chiral stationary phase column (column, Daicel Co. Chiralcel AD and OD) and the absolute configuration of the major enantiomer was assigned according to the sign of the specific rotation with those of the reported literature compounds (see experimental section).

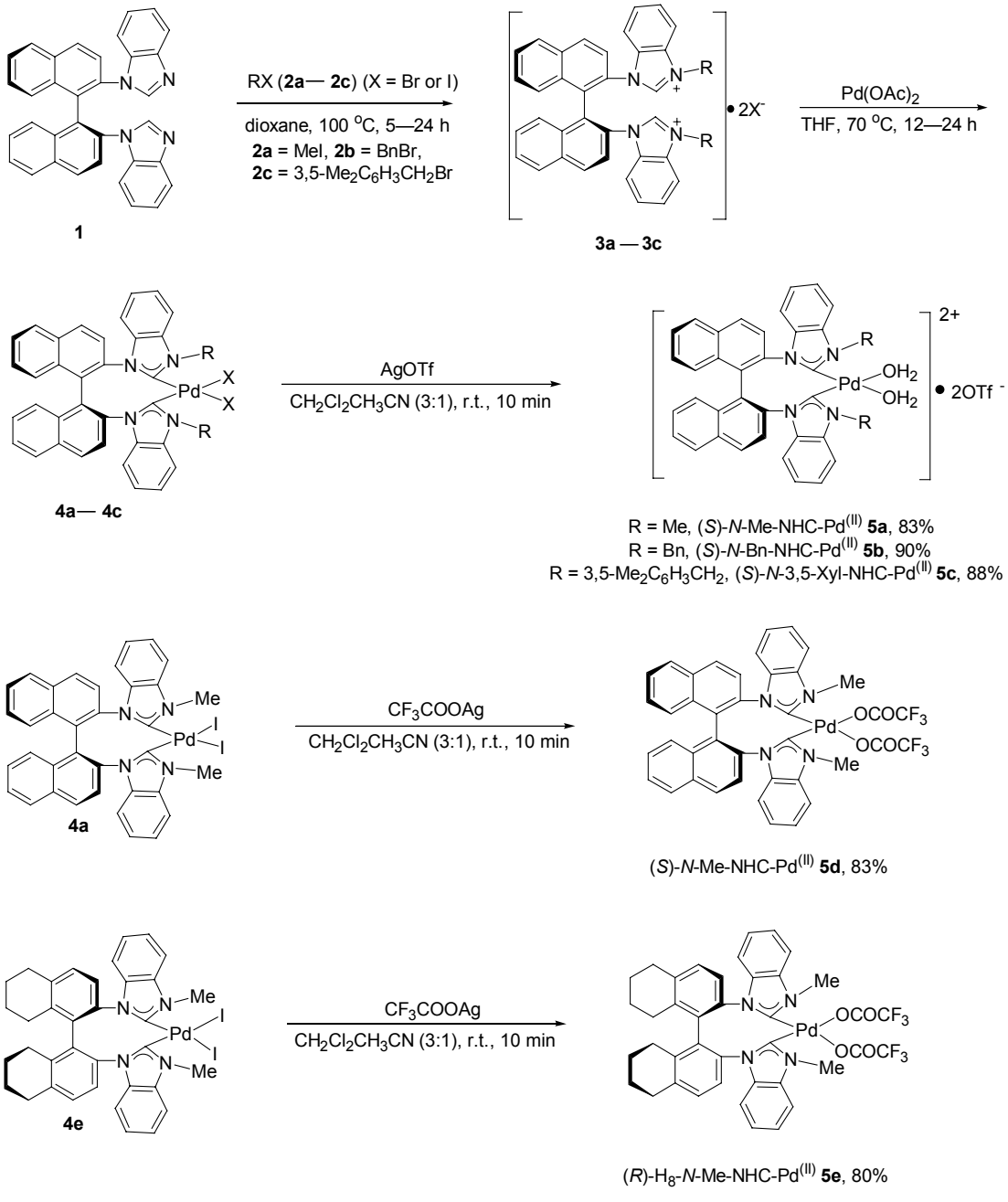
General procedure for the synthesis of NHC-Pd(II) complexes 5a—5e

Chiral C_2-symmetric *N*-heterocyclic carbene (NHC) palladium diaquo complexes **5a**—**5c** as well as chiral C_2-symmetric NHC-palladium complexes **5d** and **5e** were synthesized from (*S*)-BINAM or (*R*)-H_8-BINAM, respectively according to our previous literature (Scheme 1).[57]

General procedure for the synthesis of imidazolium salts 3a—3c

Compound **1** (485 mg, 0.4 mmol) and **2a**—**2c** (0.5

Scheme 1 General procedure for the synthesis of NHC-Pd(II) complexes **5a**—**5e**



CHINESE JOURNAL OF CHEMISTRY

mmol) (RX, X＝Br or I) in dioxane (10 mL) were stirred under reflux for 5—24 h. After cooling down to room temperature, volatiles were removed under reduced pressure and the obtained solid compounds **3a—3c** were used for the next reaction without any further purification.

(*S*)-2,2'-Di(1*H*-benzo[*d*]imidazol-1-yl)-1,1'-binaphthyl (1)

This is a known compound,[57] a white solid; m.p. 294.5—294.8 ℃; $[\alpha]_D$ −516.7 (*c* 0.97, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS) *δ*: 8.06 (d, *J*＝8.8 Hz, 4H), 7.67—7.63 (m, 2H), 7.55—7.48 (m, 6H), 7.43 (d, *J*＝8.8 Hz, 2H), 6.99 (s, 2H), 6.95 (d, *J*＝8.0 Hz, 2H), 6.50 (t, *J*＝7.6 Hz, 2H), 6.11 (d, *J*＝8.0 Hz, 2H).

General procedure for the synthesis of NHC-Pd(II) complexes 4a—4c

Compounds **3a—3c** (0.2 mmol) and $Pd(OAc)_2$ (44.8 mg, 0.2 mmol) were refluxed in THF (10 mL) for 16—30 h. The volatiles were then removed under reduced pressure and the residue was purified by a silica gel flash column chromatography (eluent: petroleum ether/EtOAc, 2/1 to 0/1) to give **4a—4c** as yellow solids.

(*S*)-NHC-Pd(II) complex 4a This is a known compound,[57] a yellow solid; m.p. ＞300 ℃ (dec.); $[a]_D^{20}$ −270.0 (*c* 0.086, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS) *δ*: 8.10—8.03 (m, 4H), 7.72 (d, *J*＝8.4 Hz, 2H), 7.25—7.19 (m, 2H), 6.94—6.87 (m, 4H), 6.85—6.82 (m, 2H), 6.78—6.74 (m, 4H), 6.68 (d, *J*＝8.7 Hz, 2H), 3.82 (s, 6H).

(*S*)-NHC-Pd(II) complex 4b This is a known compound,[57] a pale-yellow solid; m.p. ＞300 ℃ (dec.); $[a]_D^{20}$ −45.0 (*c* 0.245, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS) *δ*: 7.84 (d, *J*＝8.4 Hz, 2H), 7.79 (d, *J*＝8.4 Hz, 2H), 7.63 (d, *J*＝8.7 Hz, 2H), 7.33 (d, *J*＝8.4 Hz, 2H), 7.30—7.27 (m, 6H), 6.94—6.85 (m, 10H), 6.77—6.71 (m, 8H), 5.39 (d, *J*＝15.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) *δ*: 170.9, 136.3, 135.3, 134.6, 133.0, 132.7, 132.1, 131.4, 130.5, 128.5, 128.1, 128.0, 127.8, 127.7, 127.4, 126.7, 124.5, 123.6, 123.1, 112.3, 111.5, 55.6.

(*S*)-NHC-Pd(II) complex 4c This is a known compound,[57] a pale-yellow solid; m.p. ＞300 ℃ (dec.); $[a]_D^{20}$ −132.0 (*c* 0.195, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS) *δ*: 7.62 (d, *J*＝8.1 Hz, 2H), 7.48 (d, *J*＝8.4 Hz, 2H), 7.27—7.21 (m, 8H), 7.05—6.85 (m, 10H), 6.73 (d, *J*＝8.7 Hz, 2H), 6.60 (d, *J*＝8.1 Hz, 2H), 6.55 (d, *J*＝15.6 Hz, 2H), 5.29 (d, *J*＝14.4 Hz, 2H), 2.38 (s, 12H).

General procedure for the synthesis of cationic NHC-Pd(II) diaquo complexes 5a—5c

Complexes **4a—4c** (0.20 mmol) were suspended in a mixture of CH_2Cl_2 (15 mL) and CH_3CN (5 mL). AgOTf (108 mg, 0.42 mmol) was added and the mixture was stirred at room temperature for 10 min. The resulting suspension was filtered from the precipitated AgX (X＝Br or I) through the celite and the solvent was removed under reduced pressure to give **5a—5c** as a white powder.

(*S*)-Cationic NHC-Pd(II) diaquo complex 5a This is a known compound,[57] a white solid; m.p. 289 ℃ (Dec.); $[a]_D^{20}$ −43.0 (*c* 0.315, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS) *δ*: 8.14 (s, 4H), 7.76 (d, *J*＝8.1 Hz, 2H), 7.30—7.27 (m, 2H), 7.05—6.91 (m, 8H), 6.84—6.77 (m, 4H), 3.93 (s, 6H), 2.16 (brs, 4H); ^{19}F NMR (282 MHz, $CDCl_3$, CF_3CO_2H) *δ*: −83.8 (s).

(*S*)-Cationic NHC-Pd(II) diaquo complex 5b This is a known compound,[57] a white solid; m.p. 259 ℃ (Dec.); $[a]_D^{20}$ −66.0 (*c* 0.22, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS) *δ*: 8.03 (d, *J*＝8.4 Hz, 2H), 7.93 (d, *J*＝8.4 Hz, 2H), 7.83 (d, *J*＝8.1 Hz, 2H), 7.35—7.32 (m, 8H), 7.03—6.89 (m, 6H), 6.84—6.72 (m, 10H), 5.84 (d, *J*＝16.2 Hz, 2H), 5.65 (d, *J*＝15.9 Hz, 2H), 4.13 (brs, ＞4H); ^{19}F NMR (282 MHz, $CDCl_3$, CF_3CO_2H) *δ*: −83.6 (s).

(*S*)-Cationic NHC-Pd (II) diaquo complex 5c This is a known compound,[57] a white solid; m.p. ＞250 ℃ (Dec.); $[a]_D^{20}$ −95.0 (*c* 0.22, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS) *δ*: 7.78 (d, *J*＝7.8 Hz, 2H), 7.44—7.34 (m, 4H), 6.97—6.73 (m, 18H), 6.66—6.63 (m, 4H), 5.72 (d, *J*＝9.9 Hz, 2H), 5.37 (brs, 4H), 2.27 (s, 12H); ^{19}F NMR (282 MHz, $CDCl_3$, CF_3CO_2H) *δ*: −83.6 (s).

General procedure for the synthesis of NHC-Pd(II) complex 5d

NHC-Pd(II) complex **5d** was prepared by the similar procedure using (*S*)-2,2'-di(1*H*-benzo[*d*]imidazol-1-yl)-1,1'-binaphthyl as the starting materials.

(*S*)-NHC-Pd(II) complex 5d This is a known compound,[57] a white solid; m.p. ＞250 ℃ (Dec.); $[a]_D^{20}$ −33.0 (*c* 0.395, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS) *δ*: 8.09 (s, 4H), 7.73 (d, *J*＝8.4 Hz, 2H), 7.27—7.23 (m, 3H), 6.97—6.75 (m, 11H), 3.88 (s, 6H).

General procedure for the synthesis of NHC-Pd(II) complex 5e

NHC-Pd(II) complex **5e** was prepared by the similar procedure using (*R*)-1,1'-(4a,5,5',6,6',7,7',8,8a,8'-decahydro-1,1'-binaphthyl-2,2'-diyl)bis(1*H*-benzo[*d*]imidazole) as the starting materials.

(*R*)-NHC-Pd (II) complex 4e This is a known compound,[57] a pale-yellow solid; m.p. ＞300 ℃ (dec.); $[a]_D^{20}$ ＋53 (*c* 0.24, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS) *δ*: 7.60 (d, *J*＝8.1 Hz, 2H), 7.24—7.22 (m, 3H), 7.20—7.18 (m, 1H), 7.15—7.11 (m, 4H), 6.89 (d, *J*＝8.1 Hz, 2H), 3.92 (s, 6H), 2.66—2.56 (m, 2H), 2.31—2.20 (m, 2H), 1.91—1.81 (m, 2H), 1.64—1.55 (m, 4H), 1.41—1.17 (m, 6H).

(*R*)-NHC-Pd (II) complex 5e This is a known compound,[57] a pale-yellow solid. ^1H NMR (400 MHz, $CDCl_3$, TMS) *δ*: 7.68 (d, *J*＝8.0 Hz, 2H), 7.30—7.24 (m, 4H), 7.20—7.13 (m, 4H), 6.90 (d, *J*＝8.0 Hz, 2H), 3.96 (s, 6H), 2.65—2.60 (m, 2H), 2.32—2.26 (m, 2H), 2.01—1.93 (m, 2H), 1.77—1.72 (m, 2H), 1.44—1.40

(m, 2H), 1.29—1.22 (m, 4H), 0.44—0.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 166.7, 161.7 (q, J= 35.3 Hz), 139.9, 137.6, 135.4, 134.5, 133.8, 133.7, 129.7, 124.9, 124.1, 123.8, 116.0 (q, J=289.6 Hz), 112.6, 109.8, 34.9, 29.2, 27.2, 21.9, 21.5; ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −74.6 (s).

General procedure for the asymmetric fluorination of oxindoles

NHC-Pd(II) catalyst **5b** (3 mol%, 7.5 μmol), oxindole **6** (0.25 mmol) and 20 mg activated 4 Å molecule sieves were dissolved in acetone (1.0 mL) in a flame-dried Schlenk tube equipped with a septum and stirring bar and the mixture was stirred under argon at −20 ℃ for 10 min. After that, the selectfluor **7c** (0.375 mmol) was added into the mixture and stirred for 24 h. And then the mixture was concentrated under reduced pressure, and purified by flash chromatography on silica gel (eluent: EtOAc/petroleum ether=1/8) to yield the corresponding pure product **8**.

(*S*)-*tert*-Butyl 3-fluoro-2-oxo-3-phenylindoline-1-carboxylate (8a) A known compound,[24,62] a colorless solid, 81.3 mg, 99% yield. $[a]_D^{20}$ +71.0 (*c* 0.785, $CHCl_3$), 56% *ee* [HPLC conditions: Chiracel OD-H column, hexane/2-propanol=100∶2, flow rate=0.3 mL/min, wavelength=254 nm, t_{minor}=17.52 min and t_{major}=19.13 min]; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 8.01 (d, J=8.4 Hz, 1H), 7.51 (t, J=8.0 Hz, 1H), 7.49—7.34 (m, 6H), 7.29—7.25 (m, 1H), 1.62 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −145.4 (s).

(*S*)-*tert*-Butyl 3-fluoro-5-methyl-2-oxo-3-phenylindoline-1-carboxylate (8b) A colorless oil, 82.0 mg, 96% yield. $[a]_D^{20}$ +90.8 (*c* 0.91, $CHCl_3$), 47% *ee* [HPLC conditions: Chiracel OD-H column, hexane/2-propanol=100∶2, flow rate=0.3 mL/min, wavelength=254 nm, t_{minor}=14.89 min and t_{major}=16.09 min]; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 7.88 (d, J=8.8 Hz, 1H), 7.40—7.34 (m, 5H), 7.30 (d, J=8.4 Hz, 1H), 7.17 (s, 1H), 6.16 (s, 1H), 2.36 (s, 3H), 1.61 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −145.6 (s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 170.3 (d, J= 24.9 Hz), 148.9, 138.5 (d, J=5.5 Hz), 135.6 (d, J=9.5 Hz), 135.2 (d, J=2.7 Hz), 132.3 (d, J=3.4 Hz), 129.4 (d, J=1.4 Hz), 128.6, 126.6, 126.2 (d, J=6.4 Hz), 125.5 (d, J=17.6 Hz), 115.4, 92.8 (d, J=186.7 Hz), 84.8, 28.0, 20.9; IR (CH_2Cl_2) ν: 3360, 3195, 2923, 2852, 2358, 2324, 1786, 1736, 1153, 822, 719, 698 cm^{-1}; MS (ESI) *m/z*: 705.3 ($2M^+$+Na, 100). HRMS (ESI) calcd for $C_{40}H_{40}N_2O_6F_2Na$ 705.2752, found 705.2752.

(*S*)-*tert*-Butyl 3-fluoro-5-methoxy-2-oxo-3-phenylindoline-1-carboxylate (8c) A known compound,[24] a colorless oil, 86.6 mg, 97% yield. $[a]_D^{20}$ +13.9 (*c* 0.50, $CHCl_3$), 44% *ee* [HPLC conditions: Chiracel AD-H column, hexane/2-propanol = 100∶2, flow rate=0.7 mL/min, wavelength=254 nm, t_{minor}=12.24 min and t_{major}=12.81 min]; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 7.93 (dd, J=0.8, 8.8 Hz, 1H), 7.40—7.34 (m, 5H), 7.03 (dt, J=2.4, 8.8 Hz, 1H), 6.90—6.89 (m, 1H), 3.79 (s, 3H), 1.61 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −146.2 (s).

(+)-*tert*-Butyl 3,5-difluoro-2-oxo-3-phenylindoline-1-carboxylate (8d) A colorless oil, 84.6 mg, 98% yield. $[a]_D^{20}$ +47.8 (*c* 0.73, $CHCl_3$), 59% *ee* [HPLC conditions: Chiracel OD-H column, hexane/2-propanol =100∶2, flow rate=0.5 mL/min, wavelength=254 nm, t_{minor}=12.17 min and t_{major}=16.31 min]; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 8.04—8.00 (m, 1H), 7.42—7.33 (m, 5H), 7.21 (tt, J=2.4, 9.2 Hz, 1H), 7.10—7.07 (m, 1H), 1.60 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −115.9 (d), −146.5 (s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 169.7 (d, J=24.8 Hz), 160.1 (dd, J=3.9, 245.1 Hz), 148.8, 136.9 (dd, J=2.9, 5.1 Hz), 135.0 (d, J=26.7 Hz), 129.7 (d, J=1.5 Hz), 128.7, 127.2 (dd, J=7.9, 17.8 Hz), 126.0 (d, J=5.7 Hz), 118.6 (dd, J=3.0, 22.4 Hz), 117.3 (d, J=7.2 Hz), 113.5 (d, J=24.9 Hz), 92.4 (d, J=188.3 Hz), 85.3, 28.0; IR (CH_2Cl_2) ν: 2925, 2847, 2357, 2345, 1784, 1732, 1340, 1294, 1268, 1251, 822, 719, 648 cm^{-1}; MS (ESI) *m/z*: 713.2 ($2M^+$ + Na, 100). HRMS (ESI) calcd for $C_{38}H_{34}N_2O_6F_4Na$ 713.2251, found 713.2271.

(+)-*tert*-Butyl 3-fluoro-3-(naphthalen-2-yl)-2-oxoindoline-1-carboxylate (8e) A colorless oil, 89.6 mg, 95% yield. $[a]_D^{20}$ +17.1 (*c* 0.66, $CHCl_3$), 42% *ee* [HPLC conditions: Chiracel AD-H column, hexane/2-propanol=95∶5, flow rate=0.5 mL/min, wavelength=254 nm, t_{minor}=10.78 min and t_{major}=12.08 min]; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 8.05 (d, J=8.4 Hz, 1H), 7.89—7.79 (m, 3H), 7.73 (s, 1H), 7.57—7.49 (m, 4H), 7.42 (d, J=7.6 Hz, 1H), 7.30 (t, J=7.6 Hz, 1H), 1.61 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −145.2 (s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 170.1 (d, J=25.1 Hz), 148.9, 141.0 (d, J=5.1 Hz), 133.6 (d, J=1.6 Hz), 132.9 (d, J=27.9 Hz), 132.6, 132.0 (d, J=3.0 Hz), 128.7, 128.4, 127.7, 127.0, 126.6, 126.3, 126.0 (d, J=5.3 Hz), 125.6, 125.4 (d, J= 2.9 Hz), 123.3 (d, J=5.0 Hz), 115.7, 92.9 (d, J=187.2 Hz), 85.1, 28.0; IR (CH_2Cl_2) ν: 3133, 2917, 2851, 2361, 2324, 1782, 1736, 1342, 1278, 1250, 1149, 1099, 750 cm^{-1}; MS (ESI) *m/z* (%): 777.3 ($2M^+$+Na, 100). HRMS (ESI) calcd for $C_{46}H_{40}N_2O_6F_2Na$ 777.2752, found 777.2742.

(+)-*tert*-Butyl 3-fluoro-3-(3-fluorophenyl)-2-oxoindoline-1-carboxylate (8f) A colorless oil, 79.4 mg, 92% yield. $[a]_D^{20}$ +1.5 (*c* 0.75 $CHCl_3$), 48% *ee* [HPLC conditions: Chiracel OD-H column, hexane/2-propanol=99∶1, flow rate=0.5 mL/min, wavelength=254 nm, t_{minor}=20.72 min and t_{major}=24.95 min]; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 8.02 (d, J=8.4 Hz, 1H), 7.55—7.50 (m, 1H), 7.37—7.33 (m, 2H), 7.31—7.26 (m, 1H), 7.14—7.06 (m, 3H), 1.62 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −111.5——111.6 (m), −145.4 (s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 169.6 (d, J=24.6 Hz), 162.7 (d, J=246.0 Hz), 148.7, 141.0 (d, J=5.2 Hz), 138.0 (dd, J=7.2, 27.7 Hz), 132.1 (d, J=2.7 Hz), 130.3 (d, J=8.1 Hz), 126.1, 125.5 (d, J=2.5 Hz), 125.0 (d, J=17.9 Hz),

CHINESE JOURNAL OF CHEMISTRY

121.9 (dd, J=3.1, 5.9 Hz), 116.6 (d, J=21.4 Hz), 115.8 (d, J=1.6 Hz), 113.7 (dd, J=6.6, 23.4 Hz), 92.1 (dd, J=2.1, 187.8 Hz), 85.2, 28.0; IR (CH_2Cl_2) v: 3319, 2959, 2926, 2854, 1785, 1735, 1591, 1445, 1161, 1149, 788 cm^{-1}; MS (ESI) m/z (%): 713.2 ($2M^+$+Na, 100). HRMS (ESI) calcd for $C_{38}H_{34}N_2O_6F_4Na$ 713.2251, found 713.2256.

(*S*)-*tert*-Butyl 3-fluoro-2-oxo-3-*p*-tolylindoline-1-carboxylate (8g) A known compound,[24] a colorless oil, 83.6 mg, 98% yield. $[a]_D^{20}$ +13.1 (c 1.10, $CHCl_3$), 34% *ee* [HPLC conditions: Chiracel AD-H column, hexane/2-propanol=299∶1, flow rate=0.8 mL/min, wavelength=254 nm, t_{minor}=12.90 min and t_{major}=15.29 min]; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 8.00 (d, J=8.0 Hz, 1H), 7.53—7.48 (m, 1H), 7.38—7.36 (m, 1H), 7.29—7.24 (m, 3H), 7.20—7.18 (m, 2H), 2.35 (s, 3H), 1.61 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −144.6 (s).

(+)-*tert*-Butyl 3-fluoro-3-(4-fluorophenyl)-2-oxoindoline-1-carboxylate (8h) A known compound,[24] a white solid, 82.0 mg, 95% yield. $[a]_D^{20}$ +16.0 (c 0.94, $CHCl_3$), 22% *ee* [HPLC conditions: Chiracel OD-H column, hexane/2-propanol=100∶2, flow rate=0.5 mL/min, wavelength=254 nm, t_{minor}=9.37 min and t_{major}=10.97 min]; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 8.01 (d, J=8.4 Hz, 1H), 7.53 (t, J=8.0 Hz, 1H), 7.38—7.34 (m, 3H), 7.31—7.27 (m, 1H), 7.08 (t, J=8.4 Hz, 2H), 1.62 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −111.5 (d), −142.9 (d).

(*S*)-*tert*-Butyl 3-fluoro-5-methyl-2-oxo-3-*p*-tolylindoline-1-carboxylate (8i) A known compound,[24] a colorless oil, 80.1 mg, 90% yield. $[a]_D^{20}$ +68.5 (c 0.91, $CHCl_3$), 45% *ee* [HPLC conditions: Chiracel OD-H column, hexane/2-propanol=100∶2, flow rate=0.3 mL/min, wavelength=254 nm, t_{minor}=15.62 min and t_{major}=18.60 min]; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 7.86 (d, J=8.4 Hz, 1H), 7.30—7.17 (m, 6H), 2.36 (s, 6H), 1.60 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −144.9 (s).

(+)-*tert*-Butyl 3-fluoro-3-(4-fluorophenyl)-5-methyl-2-oxoindoline-1-carboxylate (8j) A colorless oil, 85.3 mg, 95% yield. IR (CH_2Cl_2) v: 3133, 2361, 1785, 1736, 1655, 1630, 1400 cm^{-1}. $[a]_D^{20}$ +35.0 (c 1.45, $CHCl_3$), 28% *ee* [HPLC conditions: Chiracel OD-H column, hexane/2-propanol=299∶1, flow rate=0.8 mL/min, wavelength=254 nm, t_{minor}=13.61 min and t_{major}=21.24 min]; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 7.88 (d, J=8.4 Hz, 1H), 7.37—7.31 (m, 3H), 7.17 (s, 1H), 7.08 (t, J=8.4 Hz, 2H), 2.37 (s, 3H), 1.61 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −111.7 (d), 143.2 (d); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 170.1 (d, J=24.0 Hz), 163.5 (dd, J=1.9, 247.7 Hz), 148.9, 138.5 (d, J=5.6 Hz), 135.3 (d, J=3.1 Hz), 132.6 (d, J=2.6 Hz), 131.5 (dd, J=2.7, 28.6 Hz), 128.5 (dd, J=5.3, 8.0 Hz), 126.5, 125.0 (d, J=17.4 Hz), 115.7, 115.6 (d, J=21.5 Hz), 92.3 (d, J=185.5 Hz), 85.0, 28.0, 21.0; MS (ESI) m/z (%): 741 ($2M^+$+Na, 100). HRMS (ESI) calcd for $C_{40}H_{38}N_2O_6F_4Na$ 741.2564, found 741.2575.

(*S*)-*tert*-Butyl 3-fluoro-5-methoxy-2-oxo-3-*p*-tolylindoline-1-carboxylate (8k) A known compound,[24] a colorless oil, 91.0 mg, 98% yield. $[a]_D^{20}$ +59.2 (c 1.15, $CHCl_3$), 49% *ee* [HPLC conditions: Chiracel OD-H column, hexane/2-propanol=100∶2, flow rate=0.3 mL/min, wavelength=254 nm, t_{minor}=18.48 min and t_{major}=19.26 min]; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 7.92 (dd, J=1.2, 8.8 Hz, 1H), 7.27—7.24 (m, 2H), 7.20—7.18 (m, 2H), 7.04—7.00 (m, 1H), 6.90 (t, J=2.4 Hz, 1H), 3.79 (s, 3H), 2.36 (s, 3H), 1.60 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −145.3 (s).

(*S*)-*tert*-Butyl-3-fluoro-3-(4-fluorophenyl)-5-methoxy-2-oxoindoline-1-carboxylate (8l) A known compound,[24] a colorless oil, 88.2 mg, 94% yield. $[a]_D^{20}$ +14.1 (c 0.24, $CHCl_3$), 38% *ee* [HPLC conditions: Chiracel OD-H column, hexane/2-propanol=299∶1, flow rate=0.8 mL/min, wavelength=254 nm, t_{minor}=14.88 min and t_{major}=33.56 min]; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 7.93 (dd, J=0.8, 8.8 Hz, 1H), 7.36 (dd, J=5.2, 8.4 Hz, 2H), 7.10—7.02 (m, 3H), 6.90 (t, J=2.0 Hz, 1H), 3.81 (s, 3H), 1.61 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −111.50 — −111.58 (m), −143.8 (s).

(+)-*tert*-Butyl 3,5-difluoro-2-oxo-3-*p*-tolylindoline-1-carboxylate (8m) A colorless oil, 85.3 mg, 95% yield. $[a]_D^{20}$ +31.5 (c 0.79, $CHCl_3$), 40% *ee* [HPLC conditions: Chiracel AD-H column, hexane/2-propanol=100∶2, flow rate=0.5 mL/min, wavelength=254 nm, t_{major}=10.61 min and t_{minor}=11.27 min]; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 8.03—7.99 (m, 1H), 7.25—7.18 (m, 5H), 7.11—7.08 (m, 1H), 2.36 (s, 3H), 1.60 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −116.1 (s), −145.6 (s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 169.9 (d, J=25.9 Hz), 160.1 (d, J=244.3 Hz), 148.9, 139.9 (d, J=2.7 Hz), 136.8 (dd, J=1.8, 4.9 Hz,), 132.1 (d (J=27.6 Hz), 129.4, 127.2 (dd, J=8.1, 17.8 Hz), 126.1 (d, J=6.2 Hz), 118.5 (dd, J=3.3, 22.8 Hz), 113.5 (d, J=24.8 Hz), 113.4, 92.3 (d, J=188.3 Hz), 85.2, 28.0, 21.2; IR (CH_2Cl_2) v: 3358, 2924, 2852, 2369, 2341, 1785, 1731, 1488, 1384, 1295, 1155, 764, 750 cm^{-1}; MS (ESI) m/z (%): 741.3 ($2M^+$+Na, 100). HRMS (ESI) calcd for $C_{40}H_{38}N_2O_6F_4Na$ 741.2564, found 741.2571.

(+)-*tert*-Butyl 3,5-difluoro-3-(4-fluorophenyl)-2-oxoindoline-1-carboxylate (8n) A colorless oil, 86.3 mg, 95% yield. $[a]_D^{20}$ +14.1 (c 1.88, $CHCl_3$), 20% *ee* [HPLC conditions: Chiracel AD-H column, hexane/2-propanol=100∶2, flow rate=0.5 mL/min, wavelength=254 nm, t_{major}=11.58 min and t_{minor}=13.57 min]; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 8.03 (dd, J=4.0, 8.8 Hz, 1H), 7.37—7.33 (m, 2H), 7.23—7.21 (m, 1H), 7.12—7.08 (m, 3H), 1.61 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −111.0 (s), −115.7 (s), −144.1 (s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 169.6 (d, J=25.1 Hz), 163.6 (dd, J=1.9, 248.3 Hz), 160.1 (dd, J=3.3, 244.9 Hz), 148.8, 136.9 (dd, J=2.3, 5.2 Hz), 130.8 (dd, J=3.2, 28.8 Hz), 128.4 (dd, J=5.9, 8.3 Hz), 126.7 (dd, J=8.0, 17.6 Hz), 118.8 (dd, J=2.8,

23.1 Hz), 117.4 (d, J=6.6 Hz), 115.8 (d, J=21.9 Hz), 113.5 (d, J=24.6 Hz), 91.9 (d, J=189.7 Hz), 85.4, 27.9; IR (CH_2Cl_2) v: 3585, 2918, 2852, 2366, 2337, 1784, 1738, 1511, 1488, 1150, 811, 732 cm^{-1}; MS (ESI) *m/z* (%): 749.2 ($2M^+$+Na, 100). HRMS (ESI) calcd for $C_{38}H_{32}N_2O_6F_6Na$ 749.2062, found 749.2068.

(−)-*tert*-Butyl 3-fluoro-2-oxo-3-*o*-tolylindoline-1-carboxylate (8o) A colorless oil, 75.1 mg, 88% yield. $[a]_D^{20}$ −2.0 (*c* 1.85, $CHCl_3$), 21% *ee* [HPLC conditions: Chiracel OD-H column, hexane/2-propanol=299∶1, flow rate=0.5 mL/min, wavelength=254 nm, t_{minor}=23.00 min and t_{major}=27.12 min]; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 7.97 (d, J=8.8 Hz, 1H), 7.59—7.57 (m, 1H), 7.49—7.46 (m, 1H), 7.29—7.27 (m, 2H), 7.19—7.12 (m, 3H), 2.01 (s, 3H), 1.64 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −143.1 (s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 169.8 (d, J=23.2 Hz), 148.9, 141.0 (d, J=5.8 Hz), 134.9 (d, J=4.0 Hz), 133.9 (d, J=25.7 Hz), 131.85 (d, J=4.9 Hz), 131.78 (d, J=2.1 Hz), 129.2, 126.2, 126.1, 125.9 (d, J=2.0 Hz), 125.8 (d, J=1.9 Hz), 125.3 (d, J=3.3 Hz), 115.5 (d, J=2.3 Hz), 93.4 (d, J=182.4 Hz), 85.1, 28.0, 19.9 (d, J=2.0 Hz); IR (CH_2Cl_2) v: 2979, 2928, 2363, 2354, 1786, 1737, 1149, 750 cm^{-1}; MS (ESI) *m/z* (%): 705 ($2M^+$ + Na, 100). HRMS (ESI) calcd for $C_{40}H_{40}N_2O_6F_2Na$ 705.2752, found 705.2770.

(+)-*tert*-Butyl 3-fluoro-2-oxo-3-*m*-tolylindoline-1-carboxylate (8p) A colorless oil, 82.0 mg, 96% yield. $[a]_D^{20}$ +24.5 (*c* 0.24, $CHCl_3$), 44% *ee* [HPLC conditions: Chiracel OD-H column, hexane/2-propanol=100∶2, flow rate=0.5 mL/min, wavelength=254 nm, t_{minor}=9.30 min and t_{major}=10.32 min]; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 8.00 (d, J=8.0 Hz, 1H), 7.50 (t, J=8.0 Hz, 1H), 7.37—7.35 (m, 1H), 7.28—7.18 (m, 4H), 7.10 (d, J=8.0 Hz, 1H), 2.35 (s, 3H), 1.62 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −145.4 (s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 170.2 (d, J=25.2 Hz), 148.9, 140.9 (d, J=4.9 Hz.), 138.5, 135.6 (d, J=26.4 Hz), 131.8 (d, J=3.8 Hz), 130.3 (d, J=1.3 Hz), 128.5, 126.7 (d, J=5.9 Hz), 126.2, 125.7 (d, J=17.8 Hz), 125.3 (d, J=2.5 Hz), 123.3 (d, J=6.0 Hz), 115.6, 92.7 (d, J=186.7 Hz), 85.0, 28.0, 21.4; IR (CH_2Cl_2) v: 3320, 2919, 2361, 2345, 1784, 1736, 1344, 1269, 1251, 1150, 776, 727 cm^{-1}; MS (ESI) *m/z* (%): 364 (M^++Na, 37). HRMS (ESI) calcd for $C_{20}H_{20}NO_3FNa$ 364.1325, found 364.1327.

(+)-*tert*-Butyl 3-(3,5-dimethylphenyl)-3-fluoro-2-oxoindoline-1-carboxylate (8q) A colorless oil, 85.3 mg, 96% yield. $[a]_D^{20}$ +24.5 (*c* 0.24, $CHCl_3$), 35% *ee* [HPLC conditions: Chiracel OD-H column, hexane/2-propanol=299∶1, flow rate=0.5 mL/min, wavelength=254 nm, t_{minor}=19.36 min and t_{major}=23.96 min]; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 8.01 (d, J=8.4 Hz, 1H), 7.50 (t, J=8.0 Hz, 1H), 7.36—7.35 (m, 1H), 7.28—7.25 (m, 1H), 7.02 (s, 1H), 6.94 (s, 2H), 2.29 (s, 6H), 1.62 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −145.8 (s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 170.3 (d, J=24.7 Hz), 149.0, 140.9 (d, J=4.9 Hz), 138.3, 135.5 (d, J=27.1 Hz), 131.7 (d, J=4.0 Hz), 131.2 (d, J=1.6 Hz), 129.7, 128.4, 126.2, 125.9 (d, J=18.6 Hz), 125.3 (d, J=3.2 Hz), 123.8 (d, J=5.9 Hz), 115.6, 92.8 (d, J=185.6 Hz), 85.0, 53.4, 28.0, 21.3; IR (CH_2Cl_2) v: 3312, 2924, 2847, 2353, 2324, 1784, 1736, 1607, 1481, 1150, 843, 772, 725 cm^{-1}; MS (ESI) *m/z* (%): 733 ($2M^+$+Na, 100). HRMS (ESI) calcd for $C_{42}H_{44}N_2O_6F_2Na$ 733.3065, found 733.3073.

(+)-*tert*-Butyl 3-benzyl-3-fluoro-2-oxoindoline-1-carboxylate (8r) A known compound,[48] a colorless oil, 68.3 mg 80% yield. $[a]_D^{20}$ +7.8 (*c* 0.50, $CHCl_3$), 6% *ee* [HPLC conditions: Chiracel Oj-H column, hexane/2-propanol=99∶1, flow rate=0.7 mL/min, wavelength=254 nm, t_{minor}=17.87 min and t_{major}=27.50 min]; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 7.74 (d, J=8.4 Hz, 1H), 7.35 (t, J=8.0 Hz, 1H), 7.23—7.17 (m, 3H), 7.12 (t, J=8.0 Hz, 1H), 7.04—7.00 (m, 3H), 3.57 (dd, J=9.6, 13.2 Hz, 1H), 3.24 (dd, J=13.6, 22.4 Hz, 1H), 1.60 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −150.3 (s).

(−)-1-Benzyl-3-fluoro-3-phenylindolin-2-one (8s) A colorless oil, 68.2 mg, 86% yield. $[a]_D^{20}$ −57.0 (*c* 0.30, $CHCl_3$), 23% *ee* [HPLC conditions: Chiracel OD-H column, hexane/2-propanol = 299∶1, flow rate=1.0 mL/min, wavelength=254 nm, t_{minor}=12.94 min and t_{major}=15.89 min]; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 7.42—7.38 (m, 5H), 7.34—7.27 (m, 7H), 7.10 (t, J=8.0 Hz, 1H), 6.79 (d, J=7.6 Hz, 1H), 4.97 (d, J=15.6 Hz, 1H), 4.85 (d, J=15.2 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −152.9 (s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 172.5 (d, J=24.0 Hz), 143.7 (d, J=4.8 Hz), 135.9 (d, J=26.8 Hz), 135.0, 131.4 (d, J=2.7 Hz), 129.2 (d, J=1.8 Hz), 128.8, 128.6, 127.8, 126.9 (d, J=17.1 Hz), 126.1, 125.8 (d, J=5.2 Hz), 123.5 (d, J=2.6 Hz), 109.9, 93.2 (d, J=186.6 Hz), 43.9; IR (CH_2Cl_2) v: 3648, 2925, 2855, 2360 2341, 1716, 1540, 1506, 1472, 750 cm^{-1}; MS (ESI) *m/z* (%): 318.1 (M^+, 100). HRMS (ESI) calcd for $C_{21}H_{17}NOF$ 318.1294, found 318.1293.

3-Fluoro-1-methyl-3-phenylindolin-2-one (8t) A colorless oil, 48.3 mg, 80% yield. $[a]_D^{20}$ 0 (*c* 0.73, $CHCl_3$), 0% *ee* [HPLC conditions: Chiracel OD-H column, hexane/2-propanol=299∶1, flow rate=1.0 mL/min, wavelength=254 nm, t_{minor}=14.20 min and t_{major}=24.27 min]; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 7.40—7.27 (m, 7H), 7.09 (td, J=0.8, 7.6 Hz, 1H), 6.91 (d, J=8.0 Hz, 1H), 3.25 (s, 3H), 1.60 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$, CF_3CO_2H) δ: −152.9 (s). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 172.3 (d, J=24.1 Hz), 144.6 (d, J=5.5 Hz), 135.8 (d, J=26.9 Hz), 131.5 (d, J=3.8 Hz), 129.1 (d, J=1.4 Hz), 128.5, 126.7 (d, J=17.0 Hz), 126.0, 125.8 (d, J=6.9 Hz), 123.5 (d, J=2.5 Hz), 108.8, 93.1 (d, J=187.2 Hz), 26.4; IR (CH_2Cl_2) v: 3058, 2932, 1716, 1612, 1495, 1448, 1419, 1344, 811, 751, 697 cm^{-1}; MS (ESI) *m/z* (%): 280.1 (M^++K, 100). HRMS (ESI) calcd for $C_{15}H_{12}NOFK$ 280.0540, found 280.0539.

CHINESE JOURNAL OF CHEMISTRY

General procedure for the asymmetric *α*-amination reaction of oxindole (6a)

NHC-Pd (II) catalyst **5b** (3 mol%, 7.5 μmol), oxindole **6a** (0.25 mmol) and 20 mg activated 4 Å molecule sieves were dissolved in THF (1.0 mL) in a flame-dried Schlenk tube equipped with a septum and stirring bar and the mixture was stirred under argon at −20 ℃ for 10 min. After that, the (*E*)-di-*tert*-butyl diazene-1,2-dicarboxylate **9** (0.375 mmol) was added into the mixture and the resulting solution was stirred for 24 h. Then the reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (eluent: EtOAc/petroleum ether＝1/4) to yield the corresponding pure product **10**.

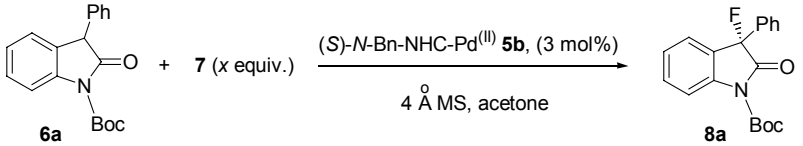
(−)-Di-*tert*-butyl 1-(1-(*tert*-butoxycarbonyl)-2-oxo-3-phenylindolin-3-yl)hydrazine-1,2-dicarboxylate (10) A colorless oil, 117.4 mg, 87% yield. $[a]_D^{20}$ −19.5 (*c* 0.73, $CHCl_3$), 30% *ee* [HPLC conditions: Chiracel AD-H column, hexane/2-propanol＝90∶10, flow rate＝1.0 mL/min, wavelength＝254 nm, t_{minor}＝12.55 min and t_{major}＝17.81 min]; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) *δ*: 8.25 (d, *J*＝7.6 Hz, 1H), 7.90 (d, *J*＝8.4 Hz, 1H), 7.55—7.54 (m, 2H), 7.37—7.30 (m, 5H), 6.30 (brs, 1H), 1.60 (s, 9H), 1.30 (s, 9H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) *δ*: 174.1, 154.8, 153.1, 149.1, 138.8, 132.9, 129.7, 129.3, 128.81, 128.77, 128.2, 126.4, 124.4, 114.8, 84.2, 83.1, 80.9, 72.5, 28.1, 27.8, 27.7; IR (CH_2Cl_2) *ν*: 3295, 2978, 2930, 1788, 1748, 1729, 1707, 1504, 1480, 1603, 1394, 1370, 1322, 1307, 1251, 1151, 1061, 753, 730 cm^{-1}; MS *m/z* (%): 439.2 ([M−Boc＋H]$^+$ 0.2), 253.1 (12), 209.1 (100), 180.1 (57), 57.1 (15). HRMS (EI) calcd for $C_{24}H_{29}N_3O_5$ 439.2107, found 439.2110.

Results and Discussion

Initial examinations using *N*-Boc-protected-3-phenyloxindole **6a** (0.25 mmol) as the substrate for enantioselective fluorination in the presence of chiral C_2-symmetric *N*-heterocyclic carbene (NHC) palladium diaquo complex **5b** (3 mol%, 0.0075 mmol) and 4 Å MS (20 mg) in the presence of various fluorination reagents **7** (0.375 mmol) in acetone were aimed at determining the optimal conditions and the results of these experiments are summarized in Table 1. The electrophilic *N*-fluorobenzenesulfonimide (NFSI) **7a** and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (selectfluor) **7c** could afford the desired product **8a** in good yields in the presence of NHC-Pd-complex **5b** (Table 1, Entries 2 and 4). Using NSFI as the fluorination reagent could also afford **8a** in 99% yield with no *ee* value in the absence of catalyst **5b** and even in the presence of catalyst **5b**, **8a** was obtained in 99% yield with no *ee* value (Table 1, Entries 1 and 2). Notably, the nucleophilic diethylaminosulfur trifluoride (DAST) **7b** did not give the desired product **8a** (Table 1, Entry 3). Using selectfluor as fluorination reagent afforded **8a** in ＞99% yield and 40% *ee* in the presence of NHC-Pd-complex **5b** (Table 1, Entry 4). Increasing or decreasing the employed amounts of selectfluor did not improve reaction outcomes (Table 1, Entries 4—7). When selectfluor was added in three portions, the desired product **8a** was formed in ＞99% yield and 39% *ee* (Table 1, Entry 8).

With these tentatively optimized reaction conditions in hand, we next attempted to examine the catalyst, solvent and temperature effects under identical conditions as shown in Table 2. Catalyst **5a** (3 mol%) had the

Table 1 Optimization of the reaction conditions in the asymmetric fluorination of oxindoles[a]



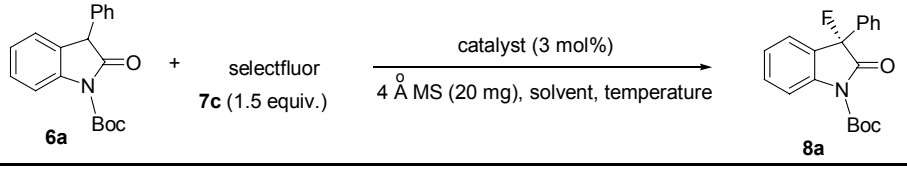
Entry	7	*x*	Time/h	Yield[b]/%	*ee*[c]/%
1[d]	**7a**, NFSI	1.5	24	99	0
2	**7a**, NFSI	1.5	24	99	0
3[e]	**7b**, DAST	1.5	24	n.r.	n.d.
4	**7c**, Selectfluor	1.5	24	＞99	40 (*S*)
5	**7c**, Selectfluor	1.0	24	＞99	30 (*S*)
6	**7c**, Selectfluor	2.0	24	＞99	28 (*S*)
7	**7c**, Selectfluor	0.5	24	48	39 (*S*)
8[f]	**7c**, Selectfluor	1.5	24	＞99	39 (*S*)

[a] Reaction conditions: oxindole **6a** (0.25 mmol), **7** (0.375 mmol), NHC-Pd(II) **5b** (3 mol%, 0.0075 mmol), 4 Å MS (20 mg), acetone (1.0 mL), and the reaction was carried out at 20 ℃. [b] Isolated yields. [c] The *ee* value was determined by HPLC using a Chiralcel OD-H column (see the Supporting Information). The absolute configuration of the products was assigned by comparison of the sign of optical rotation with those of the literature compounds. [d] Oxindole **6a** (0.25 mmol), **7a** (0.375 mmol), 4 Å MS (20 mg), acetone (1.0 mL), and the reaction was carried out at 20 ℃ in the absence of catalyst. [e] No reaction. [f] Oxindole **6a** (0.25 mmol), **7c** (0.375 mmol) added in to three portions, NHC-Pd(II) **5b** (3 mol%, 0.0075 mmol), 4 Å MS (20 mg), acetone (1.0 mL), and the reaction was carried out at 20 ℃.

similar catalytic ability as that of **5d** (3 mol%), giving the desired product **8a** in excellent yield (>99%) and 35% *ee* after 24 h (Table 2, Entries 1 and 3). Other NHC-Pd complex **5c** and complex **5e**, which has an axially chiral H_8-binaphthyl scaffold, were as effective as catalyst **5a** in above reaction (Table 2, Entries 2 and 4). Furthermore, using chiral NHC-Pd catalyst **5b**, we also examined the solvent effects in this asymmetric reaction in 1,2-dichloroethane (DCE), CH_3CN, tetrahydrofuran (THF), 1,4-dioxane, isopropanol (IPA), ethyl acetate (EA), toluene, dichloromethane and chlorobenzene. We found that no improvement could be observed in these solvents (Table 2, Entries 5—13). Using NHC-Pd complex **5b** as the catalyst, we found that lowering the reaction temperature could improve the reaction outcome, affording desired product **8a** in >99% yield and 56% *ee* at −20 ℃ (Table 2, Entries 14—18).

Under the optimized reaction conditions, we next examined the substrate scope with various oxindoles and the results are summarized in Table 3. As can be seen from Table 3, all reactions proceeded smoothly to give the corresponding products **8** in good yields and moderate *ee* values under the optimal conditions (Table 3). Whether R^1 is an electron-donating or -withdrawing group, the reactions proceeded smoothly to give the corresponding products **8b**—**8f** in excellent yields and 42%—59% *ee* values (Table 3, Entries 1—5). However, when R^2 are electron-rich or -deficient aromatic rings, the corresponding products **8g**—**8n** were obtained in excellent yields along with lower *ee* values (20%—49% *ee*), perhaps due to the combined electronic properties of R^1 and R^2 groups (Table 3, Entries 6—13). When R^2 is *o*-MeC_6H_4, *m*-MeC_6H_4, or *m,m*-dimethylC_6H_3, the corresponding products **8o**, **8p** and **8q** were obtained in good yields also along with lower *ee* values (21%—44% *ee*), presumably due to the steric effect (Table 3, Entries 14—16). When R^2 is an aliphatic group (R^2= Bn), the reaction also proceeded efficiently to afford the corresponding product **8r** in 80% yield but along with 6% *ee* (Table 3, Entry 17). Changing the *N*-Boc-protecting group to *N*-Bn or *N*-Me protecting group provided the corresponding products **8s** and **8t** in 86% yield along with 23% *ee* and 80% yield with no chiral induction, respectively, suggesting that the carbonyl group in the *N*-Boc-protecting group plays a significant role in this reaction (Table 3, Entries 18 and 19). Furthermore, NHC-Pd catalyst **5b** was also used in the asymmetric*α*-amination reaction of oxindole **6a** with (*E*)-di-*tert*-butyl diazene-1,2-dicarboxylate (**9**). It was found that the corresponding product **10** was obtained in good

Table 2 Optimization of the reaction conditions in the enantioselective fluorination of oxindoles[a]

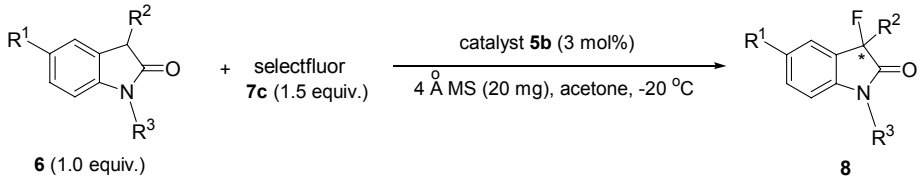


Entry	Catalyst	Solvent	Temp/℃	Time/h	Yield[b]/%	*ee*[c]/%
1	**5a**	Acetone	20	24	>99	35 (*S*)
2	**5c**	Acetone	20	24	96	25 (*S*)
3	**5d**	Acetone	20	36	>99	35 (*S*)
4	**5e**	Acetone	20	24	80	30 (*S*)
5	**5b**	DCE	20	24	85	20 (*S*)
6	**5b**	CH_3CN	20	24	>99	0
7	**5b**	DCM	20	24	75	30 (*S*)
8	**5b**	THF	20	24	20	13 (*S*)
9	**5b**	1,4-Dioxane	20	24	70	0
10	**5b**	IPA	20	24	20	15 (*S*)
11	**5b**	EA	20	24	>99	41 (S)
12	**5b**	Toluene	20	36	80	11 (*S*)
13	**5b**	Chlorobenzene	20	24	trace	n.d.
14	**5b**	Acetone	0	24	>99	40 (*S*)
15	**5b**	Acetone	−20	24	>99	56 (*S*)
16	**5b**	Acetone	−25	24	>99	46 (*S*)
17	**5b**	Acetone	−30	48	>99	50 (*S*)
18	**5b**	Acetone	−35	48	>99	43 (*S*)

[a] Reaction conditions: oxindole **6a** (0.25 mmol), selectfluor **7c** (0.375 mmol), NHC-Pd(II) **5** (3 mol%, 0.0075 mmol), 4 Å MS (20 mg), and solvent (1.0 mL). [b] Isolated yields. [c] The *ee* value was determined by HPLC using a Chiralcel OD-H column (see the Supporting Information). The absolute configuration of the products was assigned by comparison of the sign of optical rotation with those of the literature compounds.

CHINESE JOURNAL OF CHEMISTRY

Table 3 Enantioselective fluorination of oxindoles under the optimal conditions[a]



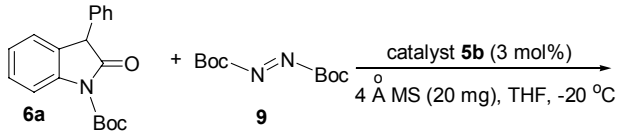
Entry	Oxindoles **6** ($R^1/R^2/R^3$)	Time/h	Yield[b]/%	*ee*[c]/%
1	**6b** (Me/C_6H_5/Boc)	24	96	**8b**, 47 (*S*)
2	**6c** (OMe/C_6H_5/Boc)	24	97	**8c**, 44 (*S*)
3	**6d** (F/C_6H_5/Boc)	24	98	**8d**, 59 (+)
4	**6e** (H/*β*-naphthyl/Boc)	24	95	**8e**, 42 (+)
5	**6f** (H/*m*-FC_6H_4/Boc)	24	92	**8f**, 48 (+)
6	**6g** (H/*p*-MeC_6H_4/Boc)	24	98	**8g**, 34 (+)
7	**6h** (H/*p*-FC_6H_4/Boc)	24	95	**8h**, 22 (+)
8	**6i** (Me/*p*-MeC_6H_4/Boc)	24	90	**8i**, 45 (*S*)
9	**6j** (Me/*p*-FC_6H_4/Boc)	24	95	**8j**, 28 (+)
10	**6k** (OMe/*p*-MeC_6H_4/Boc)	24	98	**8k**, 49 (*S*)
11	**6l** (OMe/*p*-FC_6H_4/Boc)	24	94	**8l**, 38 (*S*)
12	**6m** (F/*p*-MeC_6H_4/Boc)	24	95	**8m**, 40 (+)
13	**6n** (F/*p*-FC_6H_4/Boc)	24	95	**8n**, 20 (+)
14	**6o** (H/*o*-MeC_6H_4/Boc)	48	88	**8o**, 21 (−)
15	**6p** (H/*m*-MeC_6H_4/Boc)	24	96	**8p**, 44 (+)
16	**6q** (H/*m*,*m*-dimethylC_6H_3/Boc)	24	96	**8q**, 35 (+)
17	**6r** (H/Bn/Boc)	48	80	**8r**, 6 (+)
18	**6s** (H/Ph/Bn)	48	86	**8s**, 23 (−)
19	**6t** (H/Ph/Me)	48	80	**8t**, 0

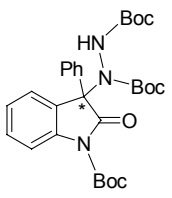
[a] Reaction conditions: oxindoles **6** (0.25 mmol), selcetfluor **7c** (0.375 mmol), NHC-Pd(II) **5b** (3 mol%, 0.0075 mmol) and 4 Å MS (20 mg). [b] Isolated yields. [c] The *ee* value was determined by HPLC using a Chiralcel column (see the Supporting Information). The absolute configuration of the products was assigned by comparison of the sign of optical rotation with those of the literature compounds.

yield but with 30% *ee* value under the standard conditions (Scheme 2).

The possible transition state of this asymmetric fluorination of 3-substituted oxindole can be explained as the approach of selectfluor toward the tetracoordinated Pd(II) complex and 3-substituted oxindole as illustrated in Scheme 3. According to the previous work reported

Scheme 2 Asymmetric *α*-amination reaction of oxindole **6a**

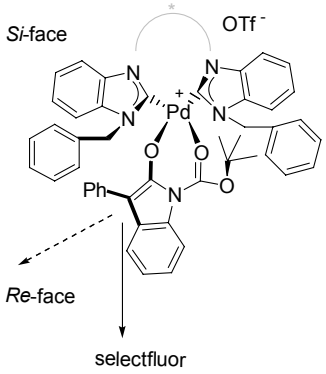




10

yield = 87%, *ee* = 30%

Scheme 3 A plausible transition state for the enantioselectivity



by Sodeoka using NHC-Pd(II)$(OTFA)_2$ complex as the catalyst,[48] the *Si*-face of the putative Pd enolate would be blocked by one of the aryl groups of the ligand and *t*-Bu group of Boc protecting group might locate at the *Si*-face to avoid the steric repulsion with the aryl groups of the ligand. As a result, the enolized 3-substituted oxindoles could react with selectfluor from the *Re* face to form the (*S*)-products in accordance with the experimental results. A more detailed investigation on the reaction mechanism using DFT calculation is undergoing

(Scheme 3).

Conclusions

In conclusion, chiral C_2-symmetric *N*-heterocyclic carbene (NHC) palladium diaquo complex **5b** was found to be a fairly effective catalyst for the enantioselective fluorination of oxindoles to give the corresponding adducts in moderate enantioselectivities along with good to excellent yields. Efforts are underway to elucidate the mechanistic details of this asymmetric addition reaction in the presence of chiral NHC-Pd(II) catalyst and to disclose the exact structure of the active species in this catalytic system.

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References

[1] Kirsch, P. *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, **2004**.
[2] Filler, R.; Kobayashi, Y. In *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, Ed.: Yagupolskii, L. M., Elsevier, Amsterdam, **1993**.
[3] Uneyama, K. *Organofluorine Chemistry*, Blackwell, Oxford, **2006**.
[4] Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15.
[5] Chambers, R. D. *Fluorine in Organic Chemistry*, Blackwell, Oxford, **2004**.
[6] Hiyama, T.; Kanie, K.; Kusumoto, T.; Morizawa, Y.; Shimizu, M. In *Organofluorine Compounds*: *Chemistry and Applications*, Springer-Verlag, Berlin, **2000**.
[7] Kirk, K. L. *J. Fluorine Chem*. **2006**, *127*, 1013.
[8] Isanbor, C.; O'Hagan, D. *J. Fluorine Chem*. **2006**, *127*, 303.
[9] Ma, J.; Cahard, D. *Chem. Rev.* **2004**, *104,* 6119.
[10] Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.
[11] Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.
[12] Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev*. **2008**, *37*, 320.
[13] Hintermann, L.; Togni, A. *Angew. Chem.*, *Int. Ed*. **2000**, *39*, 4359.
[14] Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147.
[15] Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal*. **2010** *352*, 2708.
[16] Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc*. **2000**, *122*, 10728.
[17] Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001.
[18] Shibata, N.; Ishimaru, T.; Suzuki, E.; Kirk, K. L. *J. Org. Chem*. **2003**, *68*, 2494.
[19] Shibata, N.; Ishimaru, T.; Nakamura, M.; Toru, T. *Synlett* **2004**, 2509.
[20] Shibata, N.; Ishimaru, T.; Nagai, T.; Kohno, J.; Toru, T. *Synlett* **2004**, 1703.
[21] Fukuzumi, T.; Shibata, N.; Sugiura, M.; Nakamura, S.; Toru, T. *J. Fluorine Chem*. **2006**, *127*, 548.
[22] Shibata, N.; Yasui, H.; Nakamura, S.; Toru, T. *Synlett* **2007**, 1153.
[23] Reddy, D. S.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew. Chem.*, *Int. Ed*. **2008**, *47*, 164.
[24] Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem.*, *Int. Ed*. **2008**, *47*, 4157.
[25] Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc*. **2002**, *124*, 14530.
[26] Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A. *Org. Lett*. **2003**, *5*, 1709.
[27] Hamashima, Y.; Takano, H.; Hotta, D.; Sodeoka, M. *Org. Lett.* **2003**, *5*, 3225.
[28] Toullec, P. Y.; Bonaccorsi, C.; Mezztti, A.; Togni, A. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5810.
[29] Ma, J.-A.; Cahard, D. *Tetrahedron*: *Asymmetry* **2004**, *15*, 1007.
[30] Kim, H. R.; Kim, D. Y. *Tetrahedron Lett*. **2005**, *46*, 3115.
[31] Bernardi, L.; Jøgensen, K. A. *Chem. Commun*. **2005**, 1324.
[32] Perseghini, M.; Massaccesi, M.; Liu, Y.; Togni, A. *Tetrahedron* **2006**, *62*, 7180.
[33] Bonaccorsi, C.; Althaus, M.; Becker, C.; Togni, A.; Mezzetti, A. *Pure Appl. Chem.* **2006**, *78*, 391.
[34] Kim, S. M.; Kang, Y. K.; Lee, K. S.; Mang, J. Y.; Kim, D. Y. *Bull. Korean Chem. Soc*. **2006**, *27*, 423.
[35] Suzuki, S.; Furuno, H.; Yokoyama, Y.; Inanaga, J. *Tetrahedron*: *Asymmetry* **2006**, *17*, 504.
[36] Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Tsuchiya, Y.; Moriya, K.; Goto, T.; Sodeoka, M. *Tetrahedron* **2006**, *62*, 7168.
[37] Althaus, M.; Becker, C.; Togni, A.; Mezzetti, A. *Organometallics* **2007**, *26*, 5902.
[38] Suzuki, T.; Goto, T.; Hamashima, Y.; Sodeoka, M. *J. Org. Chem*. **2007**, *72*, 246.
[39] Shibatomi, K.; Tsuzuki, Y.; Nakata, S.; Sumikawa, Y.; Iwasa, S. *Synlett* **2007**, 551.
[40] Kang, K.; Cho, M. J.; Kim, S. M.; Kim, D. Y. *Synlett* **2007**, 1135.
[41] Moriya, K.; Hamashima, Y.; Sodeoka, M. *Synlett* **2007**, 1139.
[42] Enders, D.; Hüttl, M. R. M. *Synlett* **2005**, 991.
[43] Marigo, M.; Fielenbach, D.; Braunton, A.; Kjæsgaard, A.; Jøgensen, K. A. *Angew. Chem.*, *Int. Ed*. **2005**, *44*, 3703.
[44] Steiner, D. D.; Mase, N.; Barbas III, C. F. *Angew. Chem.*, *Int. Ed*. **2005**, *44*, 3706.
[45] Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2005**, *127*, 8826.
[46] Shibatomi, K.; Yamamoto, H. *Angew. Chem.*, *Int. Ed*. **2008**, *47*, 5796.
[47] Brandes, S.; Niess, B.; Bella, M.; Prieto, A.; Overgaard, J.; Jøgensen, K. A. *Chem. Eur. J*. **2006**, *12*, 6039.
[48] Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc*. **2005**, *127*, 10164.
[49] Xu, Q.; Duan, W. L.; Lei, Z. Y.; Zhu, Z. B.; Shi, M. *Tetrahedron* **2005**, *61*, 11225.
[50] Chen, T.; Jiang, J. J.; Xu, Q.; Shi, M. *Org. Lett.* **2007**, *9*, 865.
[51] Zhang, T.; Shi, M. *Chem. Eur. J*. **2008**, *14*, 3759.
[52] Ma, G. N.; Zhang, T.; Shi, M. *Org. Lett*. **2009**, *11*, 875.
[53] Wang, W. F.; Zhang, T.; Shi, M. *Organometallics* **2009**, *28*, 2640.
[54] Liu, Z.; Shi, M. *Tetrahedron* **2010**, *66*, 2619.
[55] Liu, Z.; Shi, M. *Organometallics* **2010**, *29*, 2831.
[56] Xu, Q.; Zhang, R.; Zhang, T.; Shi, M. *J. Org. Chem*. **2010**, *75*, 3935.
[57] Zhang, R.; Xu, Q.; Zhang, X.; Zhang, T.; Shi, M. *Tetrahedron*: *Asymmetry* **2010**, *21*, 1928.
[58] Wang, W.; Zhang, T.; Wang, F.; Shi, M. *Tetrahedron* **2011**, *67*, 1523.
[59] Liu, Z.; Gu, P.; Shi, M. *Org. Lett*. **2011**, *13*, 2314.
[60] Liu, Z.; Gu, P.; Shi, M. *Chem. Eur. J.* **2011**, *17*, 5796.
[61] Wang, W.; Yang, J.; Wang, F.; Shi, M. *Organometallics* **2011**, *30*, 3859.
[62] Shibata, N.; Kohno, J.; Takai, K.; Ishimaru, T.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew. Chem.*, *Int. Ed.* **2005**, *44*, 4204.

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