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A Facile Access to Fluorinated Pyrrolidines via Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides with Methyl α-Fluoroacrylate

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Asymmetric 1,3-dipolar cycloaddition of methyl α-fluoroacrylate with azomethine ylides for the construction of optically active fluorinated pyrrolidines bearing one unique fluorinated quaternary and two tertiary stereogenic centers has been achieved with $Cu(CH_3CN)_4BF_4$/TF-BiphamPhos complexes for the first time. This catalytic system performs well over a broad scope of substrates, providing the synthetically useful adducts in good yields and excellent diastereoselectivities and good to high enantioselectivities.

Keywords asymmetric catalysis, 1,3-dipolar cycloaddition, azomethine ylide, methyl α-fluoroacrylate, pyrrolidine

Introduction

Organofluorine compounds are of ever increasing importance and the chemistry of organofluorine compounds is a rapidly developing area of research due to their wide range of applications in a number of important fields such as pharmaceuticals, agrochemicals, and functional materials.[1] Amongst organofluorine molecules, chiral fluorinated compounds containing a fluorine atom bonded directly to a stereogenic center play a unique and significant role in agricultural and medicinal chemistry, as it often imparts enhanced biological activity, metabolic stability, binding interaction, or other desirable changes in physical properties to drug molecules.[2] One such example is (3*S*,4*S*)-F-DADMe-ImmH[3] (Figure 1), the potent immucillin purine nucleoside phosphorylase (PNP) inhibitor, which was obtained through 1,3-dipolar cycloaddition followed by enzymatic resolution. The fluorinated quaternary stereogenic carbon center on the pyrrolidine ring plays a great role in the structure-activity relationship.

Recent decades have witnessed the great importance of 1,3-dipolar cycloaddition in organic chemistry.[4] Especially, the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides to electron-deficient alkenes[5] by using either chiral metal-based catalysts or organocatalysts[6] has offered a robust method to access structural motifs of chiral pyrrolidines, which presents frequently in natural alkaloids and artificial molecules with vital bioactivities. It is noteworthy that although various

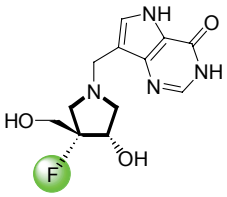

Figure 1 Potent immucillin purine nucleoside phosphorylase (PNP) inhibitor F-DADMe-ImmH.

highly functionalized pyrrolidine derivatives have been achieved, chiral fluorinated pyrrolidines have seldom been realized via catalytic asymmetric 1,3-dipolar cycloaddition. To the best of our knowledge, only one example of such compounds has been reported using chiral-auxiliary-induced 1,3-dipolar cycloaddition reaction with synthetic challenging α-fluoroacrylate as the dipolarophile.[7] Most surprisingly, commercially available methyl α-fluoroacrylate, which is expected to be a possible dipolarophile, has seldom been employed in the 1,3-dipolar cycloaddition of azomethine ylides, and only limited racemic examples have been reported so far.[8] An enantioselective version of this transformation may not only diversify the existing asymmetric 1,3-dipolar cycloaddition of azomethine ylides but also be uniquely valuable in the efficient construction of fluorinated pyrrolidines. In continuation of our interest in the field of asymmetric construction of enantiomeric enriched pyrrolidine derivatives,[9] herein we reported the first catalytic asymmetric 1,3-dipolar cycloaddition of azome-

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thine ylides to methyl α-fluoroacrylate affording the fluorinated pyrrolidines in good yields with excellent diastereoselectivity and high enantioselectivity. Moreover, another key feature of the present method is that one unique fluorinated quaternary stereogenic center[10,11] was generated along with the other two tertiary stereogenic centers in the pyrrolidine moiety.

Experimental

Melting points were obtained with a Yanagimoto micro melting point apparatus and uncorrected. Optical rotations were determined in solution of $CHCl_3$ at 25 ℃ by using a Perkin-Elmer-241 MC polarimeter; $[\alpha]_D$-Values are given in units of 10^{-1} (°)•cm^2•g^{-1}. Infrared spectra were measured on a Thermo Fisher Scientific Nicolet iS10 spectrometer. ^{1}H NMR spectra were recorded on a VARIAN Mercury 300 MHz or a Bruker 400 MHz spectrometer in $CDCl_3$ with TMS as an internal standard. ^{13}C NMR spectra were recorded on a VARIAN Mercury 75 MHz or a Bruker 100 MHz spectrometer in $CDCl_3$. Chemical shifts are reported in ppm with the internal chloroform signal at δ 77.0 as a standard. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with silica gel-coated plates. Diastereomeric ratios were determined from crude ^{1}H NMR or HPLC analysis. Enantiomeric excesses were determined by HPLC, using a chiralpak AD-H column or a chiralpak AS-H column with hexane and *i*-PrOH as solvents. The racemic adducts were attained by using AgOAc/PPh_3 as the catalyst. The absolute configuration of (2*R*,4*S*,5*R*)-**4a** was determined unequivocally according to the X-ray diffraction analysis, and those of other adducts were deduced on the basis of these results.

General procedure for the synthesis of racemic cycloadduct fluorinated pyrrolidine

Under argon atmosphere, PPh_3 (6.6 mg, 0.0253 mmol) and AgOAc (3.8 mg, 0.023 mmol) were dissolved in 2 mL of DCM, and stirred at room temperature for about 0.5 h. Then, imine substrate (0.35 mmol), Et_3N (0.03 mmol) and methyl α-fluoroacrylate (0.23 mmol) were added sequentially. Once starting material was consumed (monitored by TLC), the organic solvent was removed and the residue was purified by column chromatography to give the cycloadduct (60%—90% yield), which was used as the racemic sample for HPLC analysis.

General procedure for the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with methyl α-fluoroacrylate

Under argon atmosphere, (*S*)-TF-BiphamPhos **1e** (6.1 mg, 0.0076 mmol) and $Cu(CH_3CN)_4BF_4$ (2.2 mg, 0.0069 mmol) were dissolved in 2 mL of DCM, and stirred at room temperature for about 0.5 h. Then, imine substrate (0.35 mmol), Et_3N (0.03 mmol) and methyl α-fluoroacrylate (0.23 mmol) were added sequentially. Once starting material was consumed (monitored by TLC), the mixture was filtered through celite and the filtrate was concentrated to dryness. The product was purified by column chromatography to give the corresponding cycloadduct, which was then directly analyzed by HPLC on a chiralpak AD-H or a chiralpak AS-H column to determine the enantiomeric excess.

(2*R*,4*S*,5*R*)-Dimethyl 5-(4-chlorophenyl)-4-fluoropyrrolidine-2,4-dicarboxylate (**4a**): White solid, yield 85%; m.p. 75—77 ℃; $[\alpha]_D^{25}$ 7.6 (*c* 0.78, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.35—7.27 (m, 4H), 4.59 (d, *J*=26.4 Hz, 1H), 4.22 (dd, *J*=6.9, 9.9 Hz, 1H), 3.83 (s, 3H), 3.35 (s, 3H), 2.76—2.54 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 172.6, 168.4 (d, J_{CF}=27.8 Hz), 135.8, 133.9, 128.3, 128.2, 103.1 (d, J_{CF}=195.6 Hz), 70.8 (d, J_{CF}=28.2 Hz), 57.9, 52.3, 52.1, 39.0 (d, J_{CF}=22.4 Hz); IR (film) *v*: 3019, 1753, 1438, 1215, 755, 666 cm^{-1}; HRMS calcd for $C_{14}H_{15}ClFNO_4$ 315.0674, found 315.0669. The product was analyzed by HPLC to determine the enantiomeric excess: 94% *ee* (chiralpak AD-H, *i*-propanol/hexane, *V*∶*V*=15∶85, flow rate 1.0 mL/min, λ=220 nm); t_r=17.16 and 20.31 min.

(2*R*,4*S*,5*R*)-Dimethyl 5-(3-chlorophenyl)-4-fluoropyrrolidine-2,4-dicarboxylate (**4b**): Colorless oil, 82% yield; $[\alpha]_D^{25}$ 23.5 (*c* 1.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.42 (s, 1H), 7.27—7.25 (m, 3H), 4.59 (d, *J*=26.4 Hz, 1H), 4.22 (dd, *J*=6.6, 9.6 Hz, 1H), 3.84 (s, 3H), 3.37 (s, 3H), 2.67—2.54 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.6, 168.4 (d, J_{CF}=28.1 Hz), 139.4, 134.2, 129.5, 128.3, 127.0, 125.0, 103.1 (d, J_{CF}=192.5 Hz), 70.8 (d, J_{CF}=28.3 Hz), 58.0, 52.4, 52.2, 38.9 (d, J_{CF}=23.1 Hz); IR (film) *v*: 3019, 1746, 1524, 1438, 1215, 928, 756, 666 cm^{-1}; HRMS calcd for $C_{14}H_{15}ClFNO_4$ 315.0674, found 315.0677. The product was analyzed by HPLC to determine the enantiomeric excess: 85% *ee* (chiralpak AS-H, *i*-propanol/hexane, *V*∶*V*=15∶85, flow rate 1.0 mL/min, λ=220 nm); t_r=11.48 and 12.94 min.

(2*R*,4*S*,5*R*)-Dimethyl 5-(2-chlorophenyl)-4-fluoropyrrolidine-2,4-dicarboxylate (**4c**): Colorless oil, 65% yield; $[\alpha]_D^{25}$ −7.5 (*c* 1.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.75—7.73 (m, 1H), 7.33—7.21 (m, 3H), 5.22 (d, *J*=27.0 Hz, 1H), 4.26 (dd, *J*=6.0, 10.2 Hz, 1H), 3.83 (s, 3H), 3.38 (s, 3H), 2.80—2.52 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.8, 168.1 (d, J_{CF}=26.9 Hz), 135.9, 133.4, 129.4, 129.1, 129.0, 126.8, 103.2 (d, J_{CF}=196.7 Hz), 67.4 (d, J_{CF}=29.6 Hz), 57.9, 52.3, 52.3, 38.9 (d, J_{CF}=22.0 Hz); IR (film) *v*: 3019, 1746, 1522, 1424, 1219, 1018, 928, 849, 771, 668 cm^{-1}; HRMS calcd for $C_{14}H_{15}ClFNO_4$ 315.0674, found 315.0672. The product was analyzed by HPLC to determine the enantiomeric excess: 87% *ee* (chiralpak AS-H, *i*-propanol/hexane, *V*∶*V*=15∶85, flow rate 1.0 mL/min, λ=220 nm); t_r=10.18 and 11.99 min.

(2*R*,4*S*,5*R*)-Dimethyl 5-(4-bromophenyl)-4-fluoropyrrolidine-2,4-dicarboxylate (**4d**): White solid, 78% yield; m.p. 80—82 ℃; $[\alpha]_D^{25}$ 0.1 (*c* 1.42, $CHCl_3$); ^{1}H

NMR ($CDCl_3$, 300 MHz) δ: 7.46—7.44 (m, 2H), 7.28—7.25 (m, 2H), 4.56 (d, J=26.0 Hz, 1H), 4.21 (dd, J=7.5, 9.6 Hz, 1H), 3.82 (s, 3H), 3.34 (s, 3H), 2.80—2.48 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.7, 168.5 (d, J_{CF}=28 Hz), 136.2, 131.3, 128.5, 122.1, 103.1 (d, J_{CF}=195.5 Hz), 70.9 (d, J_{CF}=28 Hz), 58.0, 52.4, 52.2, 39.1 (d, J_{CF}=22.4 Hz); IR (film) v: 3020, 1750, 1523, 1438, 1219, 1011, 929, 771, 666 cm^{-1}; HRMS calcd for $C_{14}H_{15}BrFNO_4$ 315.0618, found 315.0617. The product was analyzed by HPLC to determine the enantiomeric excess: 84% *ee* (chiralpak AD-H, *i*-propanol/hexane, V∶V=15∶85, flow rate 1.0 mL/min, λ=220 nm); t_r= 14.41 and 17.49 min.

(2*R*,4*S*,5*R*)-Dimethyl 4-fluoro-5-(4-fluorophenyl)-pyrrolidine-2,4-dicarboxylate (**4e**): Colorless oil, 68% yield; $[\alpha]_D^{25}$ −0.2 (*c* 1.04, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.39—7.34 (m, 2H), 7.05—6.99 (m, 2H), 4.59 (d, J=27.0 Hz, 1H), 4.21 (dd, J=6.9, 9.3 Hz, 1H), 3.83 (s, 3H), 3.34 (s, 3H), 2.81—2.53 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.7, 168.6, (d, J_{CF}=28 Hz), 162.5 (d, J_{CF}=245.3 Hz), 132.9, 128.6 (d, J_{CF}= 8.1 Hz), 115.1 (d, J_{CF}=21.4 Hz), 103.2 (d, J_{CF}=195.8 Hz), 70.9 (d, J_{CF}=28 Hz), 58.0, 52.4, 52.2, 39.0 (d, J_{CF}=22.4 Hz); IR (film) v: 3020, 1746, 1605, 1512, 1438, 1216, 928, 771, 668 cm^{-1}; HRMS calcd for $C_{14}H_{15}F_2NO_4$ 299.0969, found 299.0967. The product was analyzed by HPLC to determine the enantiomeric excess: 86% *ee* (chiralpak AD-H, *i*-propanol/hexane, V∶V=15∶85, flow rate 1.0 mL/min, λ=220 nm); t_r= 11.12 and 12.51 min.

(2*R*,4*S*,5*R*)-Dimethyl 4-fluoro-5-(4-(trifluoromethyl)-phenyl)pyrrolidine-2,4-dicarboxylate (**4f**): Colorless oil, 63% yield; $[\alpha]_D^{25}$ −1.6 (*c* 0.48, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.65—7.52 (m, 4H), 4.67 (d, J= 26.0 Hz, 1H), 4.25 (dd, J=6.3, 9.3 Hz, 1H), 3.84 (s, 3H), 3.30 (s, 3H), 2.82—2.51 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.6, 168.4 (d, J_{CF}=28.1 Hz), 141.4, 130.4 (q, J_{CF}=32.2 Hz), 127.3, 125.1 (q, J_{CF}= 3.6 Hz), 123.9 (q, J_{CF}=270.3 Hz), 103.1 (d, J_{CF}=196 Hz), 71.0 (d, J_{CF}=28.1 Hz), 58.1, 52.5, 52.2, 39.1 (d, J_{CF}=22.3 Hz); IR (film) v: 3019, 1747, 1523, 1423, 1325, 1211, 928, 787, 751, 668 cm^{-1}. The product was analyzed by HPLC to determine the enantiomeric excess: 84% *ee* (chiralpak AD-H, *i*-propanol/hexane= 15/85, flow rate 1.0 mL/min, λ=220 nm); t_r=9.26 and 11.69 min.

(2*R*,4*S*,5*R*)-Dimethyl 4-fluoro-5-phenylpyrrolidine-2,4-dicarboxylate (**4g**): White solid, 79% yield; m.p. 70—72 ℃; $[\alpha]_D^{25}$ 9.1 (*c* 0.93, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.36—7.26 (m, 5H), 4.61 (d, J= 26.0 Hz, 1H), 4.26—4.20 (m, 1H), 3.84 (s, 3H), 3.29 (s, 3H), 2.77—2.55 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.9, 168.7 (d, J_{CF}=28.2 Hz), 137.0, 136.9, 128.2, 126.7, 103.4 (d, J_{CF}=195.1 Hz), 71.6 (d, J_{CF}=27.6 Hz), 58.1, 52.4, 52.1, 39.4 (d, J_{CF}=22.5 Hz); IR (film) v: 3019, 1746, 1602, 1521, 1425, 1218, 1019, 928, 767, 699 cm^{-1}; HRMS calcd for $C_{14}H_{16}FNO_4$ 281.1063, found 281.1059. The product was analyzed by HPLC to determine the enantiomeric excess: 93% *ee* (chiralpak AS-H, *i*-propanol/hexane, V∶V=15∶85, flow rate 1.0 mL/min, λ=220 nm); t_r=9.31 and 10.80 min.

(2*R*,4*S*,5*R*)-Dimethyl 4-fluoro-5-(*p*-tolyl)pyrrolidine-2,4-dicarboxylate (**4h**): Colorless oil, 82% yield; $[\alpha]_D^{25}$ 9.1 (*c* 0.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.26—7.11 (m, 4H), 4.56 (d, J=26.0 Hz, 1H), 4.21—4.17 (m, 1H), 3.83 (s, 3H), 3.32 (s, 3H), 2.81—2.53 (m, 3H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.7, 168.6, 137.9, 133.8, 128.9, 126.6, 103.5 (d, J_{CF}=191.1 Hz), 71.6 (d, J_{CF}=27.6 Hz), 58.2, 52.4, 52.2, 39.6 (d, J_{CF}=22.6 Hz), 21.1; IR (film) v: 3019, 1746, 1552, 1424, 1219, 1018, 928, 849, 771, 668 cm^{-1}; HRMS calcd for $C_{15}H_{18}FNO_4$ 295.1220, found 295.1218. The product was analyzed by HPLC to determine the enantiomeric excess: 87% *ee* (chiralpak AS-H, *i*-propanol/hexane, V∶V=15∶85, flow rate 1.0 mL/min, λ=220 nm); t_r=8.75 and 10.60 min.

(2*R*,4*S*,5*R*)-Dimethyl 4-fluoro-5-(*m*-tolyl)pyrrolidine-2,4-dicarboxylate (**4i**): Colorless oil, 77% yield; $[\alpha]_D^{25}$ 8.2 (*c* 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.26—7.08 (m, 4H), 4.56 (d, J=26.0 Hz, 1H), 4.21 (dd, J=7.2, 9.3 Hz, 1H), 3.83 (s, 3H), 3.31 (s, 3H), 2.80—2.49 (m, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.8, 168.9 (d, J_{CF}=28.2 Hz), 137.9, 136.7, 128.9, 128.2, 127.4, 123.7, 103.5 (d, J_{CF}=195.3 Hz), 71.7 (d, J_{CF}=27.5 Hz), 58.2, 52.4, 52.1, 39.6 (d, J_{CF}=22.5 Hz), 21.4; IR (film) v: 2919, 1752, 1735, 1216, 770, 665 cm^{-1}; HRMS calcd for $C_{15}H_{18}FNO_4$ 295.1220, found 295.1221. The product was analyzed by HPLC to determine the enantiomeric excess: 84% *ee* (chiralpak AS-H, *i*-propanol/hexane, V∶V=15∶85, flow rate 1.0 mL/min, λ=220 nm); t_r=7.95 and 9.77 min.

(2*R*,4*S*,5*R*)-Dimethyl 4-fluoro-5-(*o*-tolyl)pyrrolidine-2,4-dicarboxylate (**4j**): Colorless oil, 75% yield; $[\alpha]_D^{25}$ 5.0 (*c* 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.26—7.22 (m, 2H), 7.14—7.11 (m, 2H), 4.57 (d, J= 26.4 Hz, 1H), 4.24—4.18 (m, 1H), 3.83 (s, 3H), 3.32 (s, 3H), 2.81—2.46 (m, 3H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.9, 168.9 (d, J_{CF}=30.8 Hz), 137.9, 133.8, 133.8, 129.0, 126.6, 103.5 (d, J_{CF}=195.1 Hz), 71.6 (d, J_{CF}=27.7 Hz), 58.2, 52.4, 52.2, 39.6 (d, J_{CF}=22.5 Hz), 21.1; IR (film) v: 3019, 1757, 1512, 1425, 1215, 1028, 928, 757, 668 cm^{-1}; HRMS calcd for $C_{15}H_{18}FNO_4$ 295.1220, found 295.1223. The product was analyzed by HPLC to determine the enantiomeric excess: 90% *ee* (chiralpak AS-H, *i*-propanol/hexane, V∶V=15∶85, flow rate 1.0 mL/min, λ=220 nm); t_r= 8.74 and 10.53 min.

(2*R*,4*S*,5*R*)-Dimethyl 4-fluoro-5-(naphthalen-1-yl)-pyrrolidine-2,4-dicarboxylate (**4k**): Colorless oil, 78% yield; $[\alpha]_D^{25}$ −97.7 (*c* 0.7 2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.12—8.09 (m, 1H), 7.91—7.77 (m, 3H), 7.54—7.46 (m, 3H), 5.52 (d, J=27.0 Hz, 1H), 4.33 (dd, J=6.6, 11.1 Hz, 1H), 3.86 (s, 3H), 2.90—2.59 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.8, 168.5 (d, J_{CF}= 27.4 Hz), 133.4, 131.0, 128.6, 128.5, 126.1, 125.6,

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125.2, 124.9, 123.1, 123.0, 103.6 (d, J_{CF}=195.3 Hz), 67.1 (d, J_{CF}=28.1 Hz), 58.0, 52.4, 51.8, 39.4 (d, J_{CF}=22.3 Hz); IR (film) v: 3019, 1745, 1522, 1425, 1217, 1018, 849, 771, 669 cm^{-1}; HRMS calcd for $C_{18}H_{18}FNO_4$ 331.1220, found 331.1218. The product was analyzed by HPLC to determine the enantiomeric excess: 90% *ee* (chiralpak AS-H, *i*-propanol/hexane, V∶V=15∶85, flow rate 1.0 mL/min, λ=220 nm); t_r=11.57 and 15.78 min.

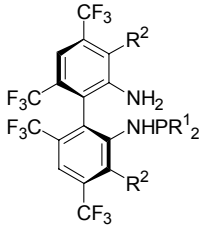
(2*R*,4*S*,5*R*)-Dimethyl 4-fluoro-5-(furan-2-yl)pyrrolidine-2,4-dicarboxylate (**4l**): Colorless oil, 68% yield; $[\alpha]_D^{25}$ 15.65 (*c* 1.34, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36—7.27 (m, 1H), 6.37—6.33 (m, 2H), 4.63 (d, J=22.0 Hz, 1H), 4.19—4.15 (m, 1H), 3.82 (s, 3H), 3.57 (s, 3H), 2.79—2.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.9, 168.3 (d, J_{CF}=27.3 Hz), 150.2, 142.6, 110.5, 108.4, 102.5 (d, J_{CF}=195.4 Hz), 66.0 (d, J_{CF}=29.7 Hz), 58.3, 52.7, 52.5, 39.1 (d, J_{CF}=22.1 Hz); IR (film) v: 3012, 1740, 1500, 1430, 1055, 875, 788, 680 cm^{-1}; HRMS calcd for $C_{12}H_{14}FNO_5$ 271.0856, found 271.0861. The product was analyzed by HPLC to determine the enantiomeric excess: 71% *ee* (chiralpak AD-H, *i*-propanol/hexane, V∶V=15∶85, flow rate 1.0 mL/min, λ=254 nm); t_r=9.72 and 10.73 min.

Absolute configuration determination of cycloadduct (2*R*,4*S*,5*R*)-4a

Crystal data for (2*R*,4*S*,5*R*)-**4a**: $C_{14}H_{15}ClFNO_4$, M_r=315.72, T=293 K, monoclinic, space group $P2(1)$, a=8.0809(15) Å, b=7.9705(14) Å, c=23.140(4) Å, V=1477.4(5) Å^3, Z=4, 4818 unique reflections, final R_1=0.0364 and wR_2=0.0887 for 4239 observed [I>2σ(I)] reflections, Flack χ=0.0106(11). CCDC 893074 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Results and Discussion

Initially, we examined the reaction of commercially available methyl α-fluoroacrylate (**2**) and *N*-(4-chlorobenzylidene)-glycine methyl ester (**3a**) in the presence of chiral TF-BiphamPhos (Figure 2) and metal salts to establish the optimal reaction condition.

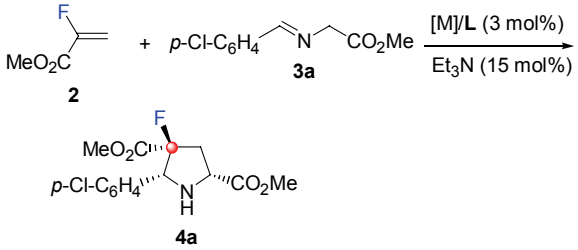


(*S*)-TF-BiphamPhos

1a: R^1 = Ph, R^2 = H;
1b: R^1 = 3,5-bis(methyl)phenyl, R^2 = H;
1c: R^1 = 3,5-bis(trifluoromethyl)phenyl, R^2 = H;
1d: R^1 = Cy, R^2 = H;
1e: R^1 = Ph, R^2 = Br

Figure 2 Structure of chiral ligand TF-BiphamPhos.

Table 1 Screening studies of the asymmetric 1,3-dipolar cycloaddition of imino ester **3a** with methyl α-fluoroacrylate **2**



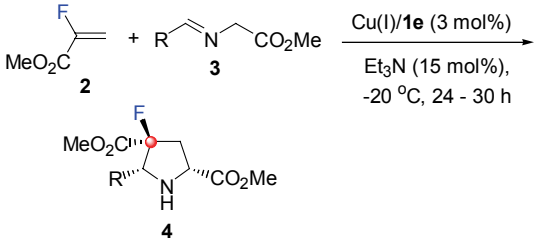
Entry	L	[M]	Solvent	T/℃	t/min	Yield[b]/%	ee[c]/%
1	**1a**	AgOAc	DCM	r.t.	12	80	33
2	**1a**	$Cu(CH_3CN)_4BF_4$	DCM	r.t.	12	81	84
3	**1b**	$Cu(CH_3CN)_4BF_4$	DCM	r.t.	12	70	65
4	**1c**	$Cu(CH_3CN)_4BF_4$	DCM	r.t.	12	79	28
5	**1d**	$Cu(CH_3CN)_4BF_4$	DCM	r.t.	12	81	45
6	**1e**	$Cu(CH_3CN)_4BF_4$	DCM	r.t.	12	83	87
7	**1e**	$Cu(CH_3CN)_4BF_4$	THF	r.t.	12	81	75
8	**1e**	$Cu(CH_3CN)_4BF_4$	Ether	r.t.	12	63	65
9	**1e**	$Cu(CH_3CN)_4BF_4$	EtOAc	r.t.	12	68	71
10	**1e**	$Cu(CH_3CN)_4BF_4$	PhMe	r.t.	12	81	73
11	**1e**	$Cu(CH_3CN)_4BF_4$	DCM	−20	24	85	94

[a] All reactions were carried out with 0.23 mmol of **2** and 0.35 mmol of **3a** in 2 mL of solvent. [b] Isolated yield. [c] Determined by HPLC analysis.

To our delight, the reaction was finished smoothly in less than 12 h with AgOAc/(*S*)-TF-BiphamPhos (**L**) as the catalyst and Et_3N as base in dichloromethane at room temperature, yielding the expected fluorinated pyrrolidine **4a** in 80% yield with excellent diastereoselectivity (dr>98∶2) and 33% *ee* (Table 1, Entry 1), which indicated that methyl α-substituted fluoroacrylate could be applied in our catalytic system as dipolarophiles for the efficient construction of fluorinated pyrrolidines bearing a unique fluorinated quaternary stereogenic center. Switching the metal precursor from AgOAc into $Cu(CH_3CN)_4BF_4$ witnessed the great enhancement of the enantiomeric excess from 33% to 84% (Table 1, Entry 2). Encouraged by these promising results, $Cu(CH_3CN)_4BF_4$ was chosen as the metal precursor for further ligand and solvent screening and the representative results are tabulated in Table 1. Inferior asymmetric inductions were observed when the phenyl group on the phosphorus atom of TF-BiphamPhos (**1a**) was replaced by bulkier xylyl group (**1b**) or cyclohexyl group (**1d**) although the diastereoselectivities were still kept at the similar level (Table 1, Entries 3 and 5). Much lower enantioselectivity was delivered by chiral ligand TF-BiphamPhos (**1c**) bearing the electron-withdrawing 3,5-bis(trifluoromethyl)phenyl groups on the phosphorus atom (Table 1, Entry 4). Further ligand tuning revealed that TF-BiphamPhos (**1e**) with two bromine at the 3,3'-position of TF-BIPHAM backbone[12] was the most effective chiral ligand and provided **4a** in

83% yield with excellent diastereoselectivity (>98∶2) and 87% *ee* (Table 1, Entry 6). A study of reaction with $Cu(CH_3CN)_4BF_4$/(*S*)-**1e** in various solvents identified CH_2Cl_2 was the best solvent in terms of the yield and enantioselectivity (Table 1, Entries 7—10). Examination of various organic and inorganic bases such as DBU, TMG, DMAP, and K_2CO_3 disclosed that Et_3N was the optimal base. Reducing the temperature to −20 ℃ in DCM led to full conversion with exclusive diastereoselectivity and 94% *ee* within 24 h (Table 1, Entry 11), but further lowering the temperature could not improve the enantioselectivity.

Table 2 Substrate scope of Cu(I)/**1e**-catalyzed asymmetric 1,3-dipolar cycloaddition of imino esters **3** with methyl *α*-fluoroacrylate **2**



Entry	R	Product	Yield[b]/%	*ee*[c]/%
1	*p*-Cl-C_6H_4 (**3a**)	**4a**	85	94
2	*m*-Cl-C_6H_4 (**3b**)	**4b**	82	85
3	*o*-Cl-C_6H_4 (**3c**)	**4c**	65	87
4	*p*-Br-C_6H_4 (**3d**)	**4d**	78	84
5	*p*-F-C_6H_4 (**3e**)	**4e**	68	86
6	*p*-CF_3-C_6H_4 (**3f**)	**4f**	63	84
7	Ph (**3g**)	**4g**	79	93
8	*p*-Me-C_6H_4 (**3h**)	**4h**	82	88
9	*m*-Me-C_6H_4 (**3i**)	**4i**	77	84
10	*o*-Me-C_6H_4 (**3j**)	**4j**	75	90
11	1-Naphthyl (**3k**)	**4k**	78	90
12	2-Furyl (**3l**)	**4l**	68	71

[a]All reactions were carried out with 0.23 mmol of **2** and 0.35 mmol of **3** in 2 mL of DCM. [b] Isolated yield. [c] Determined by HPLC analysis.

In the presence of 3 mol% of $Cu(CH_3CN)_4BF_4$/**1e**, and 15 mol% Et_3N in CH_2Cl_2, 1,3-dipolar cycloaddition of a series of representative imino esters **3** derived from glycinate with methyl *α*-fluoroacrylate **2** was investigated to test the generality of the reaction. As shown in Table 2, imino esters bearing electron deficient (Table 2, Entries 1—6), electron-neutral (Table 2, Entries 7 and 11), and electron-rich groups (Table 2, Entries 8—10) on the aryl rings reacted with methyl *α*-fluoroacrylate **2** smoothly affording the corresponding cycloadducts (**4a**—**4k**) exclusively in good yields (63%—85%) and good enantioselectivities (84%—94%). The substitution pattern and electronic property of the phenyl ring have little effect on the enantioselectivity. The consistently excellent diastereo-/enantioselectivity obtained with the sterically hindered *ortho*-chloro-substituted imino ester **3c**, *ortho*-methyl-substituted imino ester **3j** and 1-naphthylaldehyde derived imino ester **3k** is noteworthy (Table 2, Entries 3, 10 and 11). Additionally, the heteroaryl substituted imino ester **3l** derived from 2-furylaldehyde also works in this transformation leading to 68% yield and 71% *ee* (Table 2, Entry 12). However, no cycloaddition was observed when alkyl substituted imino ester was tested under the same reaction conditions. The absolute configuration of **4a** achieved by $Cu(CH_3CN)_4BF_4$/(*S*)-TF-BiphamPhos **1e** was unequivocally determined as (2*R*,4*S*,5*R*) by X-ray diffraction analysis (Figure 3). Those of other adducts were deduced on the basis of these results.

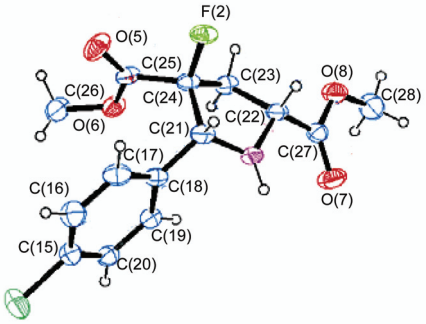


Figure 3 X-ray crystallographic structure of (2*R*,4*S*,5*R*)-**4a**.

This asymmetric 1,3-dipolar cycloaddition reaction can be explained through the proposed transition state as illustrated in Figure 4. The *in situ*-formed azomethine ylide is coordinated to the metallic center and oriented preferentially to form a tetracoordinated transition state,[13] followed by cycloaddition with methyl *α*-fluoroacrylate from *Si* face (C=N) of the azomethine ylide to give the adduct in (2*R*,4*S*,5*R*)-configuration, which is compatible with the experimental results. The carbonyl group of methyl *α*-fluoroacrylate could coordinate with the Cu(I) center, which can stabilize the negatively charged oxygen atom in the proposed transition state.[14] It could not rule out the possible hydrogen bonds interaction between the carbonyl group and the NH_2 group of the chiral ligand, which also facilitate stabilizing the proposed transition state.[15] Nevertheless, the real catalytic mechanism still needs further investigation.

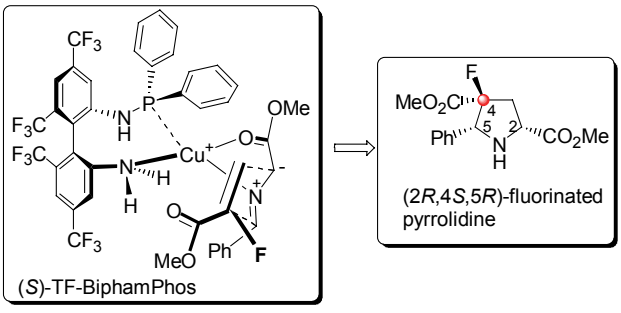


Figure 4 Proposed transition state.

Conclusions

In summary, we have successfully developed the first example of facile access to the enantiomerically enriched fluorinated pyrrolidine derivatives via catalytic asymmetric 1,3-dipolar cycloaddition of azomthine ylides to methyl α-fluoroacrylate under mild condition. The highly efficient $Cu(CH_3CN)_4BF_4$/TF-BiphamPhos catalytic system exhibited excellent performance, providing pyrrolidine derivatives containing one unique fluorinated quaternary and two tertiary stereogenic center in good yields, excellent diastereoselectivity (＞98∶2) and good to high enantioselectivity (71%—94% *ee*). The ready availability of the starting materials and the great importance of the enantiomerically enriched fluorinated compounds make the current methodology particularly interesting in synthetic chemistry. Efforts are currently underway to elucidate the mechanistic details and the scope and limitations of this reaction, and the results will be reported in due course.

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References

[1] (a) *Fluorine in Medicinal Chemistry and Chemical Biology*, Ed.: Ojima, I., Wiley-Blackwell, New York, **2009**; (b) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*, John Wiley & Sons, Inc., New York, **2008**; (c) Tressaud, A.; Haufe, G. *Fluorine and Health-Molecular Imaging*, *Biomedical Materials and Pharmaceuticals*, Elsevier, Amsterdam, **2008**; (d) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15; (e) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881; (f) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305; (g) Qing, F. *Chin. J. Org. Chem.* **2012**, *32*, 815 (in Chinese).

[2] (a) *Fluorine Containing Amino Acids——Synthesis and Properties*, Eds.: Kukhar, V. P.; Soloshonok, V. A., Wiley, Chichester, **1995**; (b) *Biomedical Frontiers of Fluorine Chemsitry*, Eds.: Ojima, I.; McCarthy, J. R.; Welch, J. T., ACS Symposium Series 639, American Chemical Society, Washington, DC, **1996**; (c) Hiyama, T. *Organofluorine Compounds*: *Chemistry and Applications*, Springer, Berlin, **2000**; (d) Kirsch, P. *Morden Fluoroorganic Chemistry*: *Synthesis*, *Reactivity*, *Applications*, Wiley-VCH, Weiheim, Germany, **2004**; (e) Uneyama, K. In *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*, Ed.: Soloshonok, V. A., Wiley, Chichester, **1999**, Chapter 12; (f) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320; (g) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1; (h) Smits, R.; Cadicamo, C. D.; Burger, K.; Koksch, B. *Chem. Soc. Rev.* **2008**, *37*, 1727; (i) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2010**, *111*, 455; (j) Georgii, G. F. In *Advances in Heterocyclic Chemistry*, Vol. 86, Ed.: Katritzky, A. R., Elsevier, Amsterdam, **2004**, pp. 129—224; for recent special issues on organofluorine chemistry, see: (k) *Adv. Synth. Catal.* **2010**, *352*, 2677.

[3] Mason, J. M.; Murkin, A. S.; Li, L.; Schramm, V. L.; Gainsford, G. J.; Skelton, B. W. *J. Med. Chem.* **2008**, *51*, 5880.

[4] Padwa, A.; Pearson, W. H. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*, John Wiley & Sons, Inc., New York, **2002**.

[5] For recent reviews about 1,3-dipolar cycloaddition reactions of azomethine ylides, see: (a) Engels, B.; Christl, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7968; (b) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887; (c) Alvarez-Corral, M.; Munoz-Dorado, M.; Rodrıguez-Garcıa, I. *Chem. Rev.* **2008**, *108*, 3174; (d) Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, *108*, 3132; (e) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247; (f) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6874.

[6] For the first catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides to activated alkenes, see: (a) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400; (b) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 423; for the early report on the stoichiometric amount of chiral catalyst, see: (c) Grigg, R. *Tetrahedron*: *Asymmetry* **1995**, *6*, 2475; (d) Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817; for the very recent examples, see: (e) Kim, H. Y.; Li, J.-Y.; Kim, S.; Oh, K. *J. Am. Chem. Soc.* **2011**, *133*, 20750; (f) He, L.; Chen, X.-H.; Wang, D.-N.; Luo, S.-W.; Zhang, W.-Q.; Yu, J.; Ren, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2011**, *133*, 13504; (g) Bai, J.-F.; Wang, L.-L.; Peng, L.; Guo, Y.-L.; Ming, J.-N.; Wang, F.-Y.; Xu, X.-Y.; Wang, L.-X. *Eur. J. Org. Chem.* **2011**, 4472; (h) Cheng, M.-N.; Wang, H.; Gong, L.-Z. *Org. Lett.* **2011**, *13*, 2418; (i) Robles-Machin, R.; Alonso, I.; Adrio, J.; Carretero, J. C. *Chem.-Eur. J.* **2011**, *17*, 13118; (j) Shi, F.; Luo, S.-W.; Tao, Z.-L.; He, L.; Yu, J.; Tu, S.-J.; Gong, L.-Z. *Org. Lett.* **2011**, *13*, 4680; (k) Wu, H.; Wang, B.; Liu, H.; Wang, L. *Tetrahedron* **2011**, *67*, 1210; (l) Oura, I.; Shimizu, K.; Ogata, K.; Fukuzawa, S.-I. *Org. Lett.* **2010**, *12*, 1752; (m) Robles-Machín, R.; Alonso, I.; Adrio, J.; Carretero, J. C. *Chem.-Eur. J.* **2010**, *16*, 5286; (n) Yu, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 4050; (o) Arai, T.; Mishiro, A.; Yokoyama, N.; Suzuli, K.; Sato, H. *J. Am. Chem. Soc.* **2010**, *132*, 5338; (p) Arai, T.; Yokoyama, N.; Mishiro, A.; Sato, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 7895; (q) Reboredo, S.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; Cózar, A.; Cossío, F. P. *Chem.-Eur. J.* **2012**, *18*, 7179; (r) Han, M.-L.; Wang, D.-Y.; Zeng, P.-W.; Zheng, Z.; Hu, X.-P. *Tetrahedron*: *Asymmetry* **2012**, *23*, 306; (s) Awata, A.; Arai, T. *Chem.-Eur. J.* **2012**, *18*, 8278; (t) Li, X.; Yi, R.; Liu, B.; Li, Z.; Yu, X.; Yi, P. *Chin. J. Org. Chem.* **2012**, *32*, DOI: 10.6023/cjoc201207027.

[7] Bonini, B. F.; Boschi, F.; Franchini, M. C.; Fochi, M.; Fini, F.; Mazzanti, A.; Ricci, A. *Synlett* **2006**, 543.

[8] (a) Qiu, Y.-L.; Ying, L.; Or, Y. S.; Wang, C.; Long, J. *US 20090004140 A1*, **2009** [*Chem. Abstr.* **2009**, *150*, 98139]; (b) Rogel, O.; Rondeau, J.-M.; Rueeger, H.; Simic, O.; Sirockin, F.; Tintelnot-Blombey, M. *WO 2007140980 A1*, **2007** [*Chem. Abstr.* **2007**, *147*, 323011]; (c) Yarmolchuk, V. S.; Mykhailiuk, P. K.; Komarov, I. V. *Tetrahedron Lett.* **2011**, *52*, 1330.

[9] (a) Wang, C.-J.; Liang, G.; Xue, Z.-Y.; Gao, F. *J. Am. Chem. Soc.* **2008**, *130*, 17250; (b) Wang, C.-J.; Xue, Z.-Y.; Liang, G.; Lu, Z. *Chem. Commun.* **2009**, 2905; (c) Liang, G.; Tong, M.-C.; Wang, C.-J. *Adv. Synth. Catal.* **2009**, *351*, 3101; (d) Xue, Z.-Y.; Liu, T.-L; Lu, Z.; Huang, H.; Tao, H.-Y.; Wang, C.-J. *Chem. Commun.* **2010**, *46*, 1727; (e) Liang, G.; Tong, M.-C.; Tao, H.-Y.; Wang, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 1851; (f) Liu, T.-L.; Xue, Z.-Y.; Tao, H.-Y.; Wang, C.-J. *Org. Biomol. Chem.* **2011**, *9*, 1980; (g) Xue, Z.-Y.;

Fang, X.; Wang, C.-J. *Org*. *Biomol*. *Chem*. **2011**, *9*, 3622; (h) Liu, T.-L.; He, Z.-L.; Tao, H.-Y.; Cai, Y.-P.; Wang, C.-J. *Chem*. *Commun*. **2011**, *47*, 2616; (i) Li, Q.-H.; Tong, M.-C.; Li, J.; Tao, H.-Y.; Wang, C.-J. *Chem*. *Commun*. **2011**, *47*, 11110; (j) Liu, T.-L.; He, Z.-L.; Wang, C.-J. *Chem*. *Commun*. **2011**, *47*, 9600; (k) Teng, H.-L.; Huang, H.; Tao, H.-Y.; Wang, C.-J. *Chem*. *Commun*. **2011**, *47*, 5494; (l) Liu, T.-L.; He, Z.-L.; Li, Q.-H.; Tao, H.-Y.; Wang, C.-J. *Adv*. *Synth*. *Catal*. **2011**, *353*, 1713; (m) Teng, H.-L.; Luo, F.-L.; Tao, H.-Y.; Wang, C.-J. *Org*. *Lett*. **2011**, *13*, 5600; (n) Li, Q.-H.; Xue, Z.-Y.; Tao, H.-Y.; Wang, C.-J. *Tetrahedron Lett*. **2012**, *53*, 3650; (o) Liu, T.-L.; He, Z.-L.; Tao, H.-Y.; Wang, C.-J. *Chem*.-*Eur*. *J*. **2012**, *18*, 8042.

[10] (a) Corey, E. J.; Guzman-Perez, A. *Angew*. *Chem*., *Int*. *Ed*. **1998**, *37*, 388; (b) Christoffers, J.; Mann, A. *Angew*. *Chem*., *Int*. *Ed*. **2001**, *40*, 4591; (c) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105; (d) Christoffers, J.; Baro, A. *Adv*. *Synth*. *Catal*. **2005**, *347*, 1473; (e) Riant, O.; Hannedouche, J. *Org*. *Biomol*. *Chem*. **2007**, *5*, 873; (f) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur*. *J*. *Org*. *Chem*. **2007**, 5969.

[11] (a) Hintermann, L.; Togni, A. *Angew*. *Chem*., *Int*. *Ed*. **2000**, *39*, 4359; (b) Hamashima, Y.; Yagi, K.; Takano, H.; Tamas, L.; Sodeoka, M. *J*. *Am*. *Chem*. *Soc*. **2002**, *124*, 14530; (c) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J*. *Am*. *Chem*. *Soc*. **2005**, *127*, 10164; (d) Shibata, N.; Kohno, J.; Takai, K.; Ishimaru, T.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew*. *Chem*., *Int*. *Ed*. **2005**, *44*, 4204; (e) Reddy, D. S.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew*. *Chem*., *Int*. *Ed*. **2008**, *47*, 164; (f) Nakamura, M.; Hajra, A.; Endo, K.; Nakamura, E. *Angew*. *Chem*., *Int*. *Ed*. **2005**, *44*, 7248; (g) Han, X.; Luo, J.; Liua, C.; Lu, Y. *Chem*. *Commun*. **2009**, 2044; (h) Liu, W.-B.; Zheng, S.-C.; He, H.; Zhao, X.-M.; You, S.-L. *Chem*. *Commun*. **2009**, 6604.

[12] Wang, C.-J.; Gao, F.; Liang, G. *Org*. *Lett*. **2008**, *10*, 4711.

[13] (a) Cabrera, S.; Arrayás, R. G.; Martín-Matute, B. F.; Cossío, P.; Carretero, J. C. *Tetrahedron* **2007**, *63*, 6587; (b) Zeng, W.; Chen, G.-Y.; Zhou, Y.-G.; Li, Y.-X. *J*. *Am*. *Chem*. *Soc*. **2007**, *129*, 750; (c) Kim, H. Y.; Shih, H.-J.; Knabe, W. E.; Oh, K. *Angew*. *Chem*., *Int*. *Ed*. **2009**, *48*, 7420; (d) Nájera, C.; Retamosa, M. D. G.; Sansano, J. M.; Cózar, A.; Cossío, F. P. *Tetrahedron*: *Asymmetry* **2008**, *19*, 2913.

[14] Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew*. *Chem*., *Int*. *Ed*. **2006**, *45*, 1979.

[15] (a) Xue, Z.-Y.; Li, Q.-H.; Tao, H.-Y.; Wang, C.-J. *J*. *Am*. *Chem*. *Soc*. **2011**, *133*, 11757; (b) Tong, M.-C.; Li, J.; Tao, H.-Y.; Li, Y.-X.; Wang, C.-J. *Chem*.-*Eur*. *J*. **2011**, *17*, 12922; (c) Wang, M.; Wang, C.-J.; Lin, Z. *Organometallic* **2012**, *31*, doi: 10.1021/om300435s, for recent studies of directing effect of hydrogen bonds in transition metal-catalyzed reactions, see: (d) Fackler, P.; Berthold, C.; Voss, F.; Bach, T. *J*. *Am*. *Chem*. *Soc*. **2010**, *132*, 15911.

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