Enantioselective Arylation of 2-Methylacetoacetates Catalyzed by CuI/*trans*-4-Hydroxy-L-Proline at Low Reaction Temperatures

Xiaoan Xie¹, Yu Chen¹ and Dawei Ma^{2*}

¹Department of Chemistry, Fudan University, Shanghai 200433, China. ²State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

Supporting Information

Table CuI-catalyzed coupling reaction of 2-iodotrifluoroacetanilide with ethyl 2-methylacetoacetate^a

entry		solvent	Time (h)	Yield (%)	[α] _D
1	1 mL DMSO	without water 5 μL water (1.1 eq to substrate)	24	75	110° (ee. 44%)
2	1 mL DMF	without water 5 μL water	24 3	87 46 80	106° (ee. 44%) 108° (ee. 44%) 105° (ee. 44%)
3		1 mL dioxane + 5 μL water	24	58	26°
4	1 mL THF	without water 5 μL water	24 20	18 82	/ 36°
5	1 mL CH ₂ Cl ₂	without water 5 μL water	24 26	trace 60	/ 11°
6	1 mL toluene	without water 5 μL water	24 26	trace 19	/ 5°
7		1 mL acetone + 5 μL water	24	78	48°
8	1 mL DMF	1 μL water (0.2 eq to substrate)	3	81	107°

9	1 mL DMF	10 μ L water (2.2 eq to substrate)	3	80	104°
10	1 mL DMF	20 μ L water (4.4 eq to substrate)	3	71	92°
11	1 mL DMF	50 μ L water (11 eq to substrate)	5	complex	/
12	5 mL DMF	25 μ L water	5	47	/
13	5 mL DMF	5 μ L water	3	82	106°
14	1 mL DMF	23 μ L <i>t</i> -BuOH (1eq to substrate)	3	83	104°

^aReaction conditions: 0.25 mmol iodide, 1.5 eq keto ester, 4 eq base, 0.2 eq CuI, 0.4 eq *L*-Hyp-OH, room temperature, NaOH as the base for entries 3-14, Cs₂CO₃ as the base in entries 1 and 2.

Experimental

General methods. ¹H NMR or ¹³C NMR spectra were recorded on JEOL ECA-400, Bruker DPX-300, Bruker DMX-500. Proton chemical shifts were given in relative to tetramethylsilane (δ 0.00 ppm) in CDCl₃. Carbon chemical shifts were internally referenced to the deuterated solvent signals in CDCl₃ (δ 77.00 ppm). Mass spectra were recorded on a HP 5989A mass spectrometer. High resolution mass spectra were recorded on a Finnigan MAT mass spectrometer. Optical rotations were measured on a RUDOLPH AP IV-589 polarimeter. Enantiomeric excesses

were determined by HPLC using a Daicel Chiralpak AD, AD-H, AS or OD column (wavelength = 214, 220 or 230 nm) with hexane/*i*-PrOH as the eluent.

Material. All solvents and CuI were purified according to *Purification of Laboratory Chemicals (4th edition)*. Others were used as received. Silica gel plate GF254 were used for thin layer chromatography (TLC) and silica gel H were used for flash column chromatography.

General procedure for CuI catalyzed coupling reaction. A Schlenk tube was charged with aryl iodide (0.5 mmol), CuI (19 mg, 0.2 mmol), *trans*-4-hydroxy-L-proline (26 mg, 0.4 mmol), and NaOH (80 mg, 2 mmol), evacuated and backfilled with argon. After H₂O (5 μ L) and DMF (1 mL) were injected, the tube was immersed in a cooling bath and β -keto ester was then injected. The reaction mixture was stirred at the indicated temperatures until the conversion was completed monitored by TLC. The mixture was partitioned between ethyl acetate and saturated NH₄Cl, the organic layer was washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with PE/EA = 50:1 to 20:1) to provide the desired product. The enantiomeric excess was determined by HPLC.

(S)-Ethyl 2-methyl-3-oxo-2-(2-(2,2,2-trifluoroacetamido)phenyl)butanoate (3):

^1H NMR (400 MHz, CDCl_3) δ 10.27 (br s, 1H), 7.71-7.34 (m, 4H), 4.32-4.20 (m, 2H), 1.95 (s, 3H), 1.88 (s, 3H), 1.31 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.2, 173.0, 155.8, 134.2, 131.8, 129.6, 127.5, 127.0, 114.5, 63.9, 63.1, 24.5, 20.3, 13.9; ESI-MS m/z 354 ($\text{M} + \text{Na}$) $^+$; HRMS calcd for $\text{C}_{15}\text{H}_{16}\text{NO}_4\text{F}_3\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 354.0924, found 354.0920; HPLC Chiralpak AD (hexane/*i*-PrOH = 95:5, 0.7 mL/min) τ_{major} = 10.2 min, τ_{minor} = 9.7 min. $[\alpha]_{\text{D}}^{20}$ +191 (c 1.0, CHCl_3 , 71% ee).

(*S*)-iso-Propyl 2-methyl-3-oxo-2-(2-(2,2,2-trifluoroacetamido)phenyl)butanoate (4):

^1H NMR (400 MHz, CDCl_3) δ 10.27 (br s, 1H), 7.72-7.32 (m, 4H), 5.13-5.07 (m, 1H), 1.94 (s, 3H), 1.85 (s, 3H), 1.31 (d, J = 3.0 Hz, 3H), 1.25 (d, J = 3.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 206.0, 172.3, 156.1, 141.0, 134.2, 131.8, 129.4, 127.4, 126.9, 114.5, 71.1, 63.8, 24.4, 21.5, 21.4, 20.3; ESI-MS m/z 363 ($\text{M} + \text{NH}_4$) $^+$; HRMS calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_4\text{F}_3\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 368.1080, found 368.1091; HPLC Chiralpak AD (hexane/*i*-PrOH = 95:5, 0.7 mL/min) τ_{major} = 11.7 min, τ_{minor} = 12.1 min. $[\alpha]_{\text{D}}^{20}$ +204 (c 1.0, CHCl_3 , 74% ee).

(S)-tert-butyl 2-methyl-3-oxo-2-(2-(2,2,2-trifluoroacetamido)phenyl)butanoate (5a):

¹H NMR (400 MHz, CDCl₃) δ 10.23 (br s, 1H), 7.72-7.32 (m, 4H), 1.92 (s, 3H), 1.81 (s, 3H), 1.49 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 206.3, 172.0, 156.1, 134.2, 132.1, 129.4, 127.5, 127.4, 126.8, 114.5, 84.5, 64.5, 27.8, 24.6, 20.6; ESI-MS *m/z* 382 (M + Na)⁺; HRMS calcd for C₁₇H₂₀NO₄F₃Na (M + Na)⁺ 382.1237, found 382.1244; HPLC Chiralpak AD (hexane/*i*-PrOH = 98:2, 0.7 mL/min) τ_{major} = 10.4 min, τ_{minor} = 9.5 min. [α]_D²⁰ +224 (c 1.0, CHCl₃, 89% ee).

(S)-tert-Butyl 2-methyl-2-(5-methyl-2-(2,2,2-trifluoroacetamido)phenyl)-3-oxobutanoate (5b):

¹H NMR (400 MHz, CDCl₃) δ 10.03 (br s, 1H), 7.58-7.23 (m, 3H), 2.40 (s, 3H), 1.92 (s, 3H), 1.79 (s, 3H), 1.49 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 206.2, 171.9, 155.2, 137.2, 131.8, 131.5, 129.8, 128.0, 126.7, 114.9, 84.3, 64.4, 27.8, 24.5, 21.3, 20.6; ESI-MS *m/z* 391 (M + NH₄)⁺; HRMS calcd for C₁₈H₂₂NO₄F₃Na (M + Na)⁺ 396.1393, found 396.1413; HPLC Chiralpak AD-H (hexane/*i*-PrOH = 98:2, 0.8 mL/min) τ_{major} = 6.9 min, τ_{minor} = 8.1 min. [α]_D²⁰ +229 (c 1.0, CHCl₃, 93% ee).

(S)-tert-Butyl 2-(5-(hydroxymethyl)-2-(2,2,2-trifluoroacetamido)phenyl)-2-methyl-3-oxobutanoate (5c):

¹H NMR (400 MHz, CDCl₃) δ 10.18 (br s, 1H), 7.70-7.41 (m, 3H), 4.76 (s, 2H), 1.93 (s, 3H), 1.83 (s, 3H), 1.49 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 206.1, 171.9, 155.7, 140.0, 133.4, 132.3, 127.6, 126.9, 125.9, 114.4, 84.5, 64.7, 64.5, 27.8, 24.6, 20.6; ESI-MS *m/z* 407 (M + NH₄)⁺; HRMS calcd for C₁₈H₂₂NO₅F₃Na (M + Na)⁺ 412.1348, found 412.1350; HPLC Chiralpak AS (hexane/*i*-PrOH = 95:5, 0.7 mL/min) τ_{major} = 20.5 min, τ_{minor} = 19.2 min. [α]_D²⁰ +221 (c 1.0, CHCl₃, 91% ee).

(S)-tert-Butyl 2-(5-methoxy-2-(2,2,2-trifluoroacetamido)phenyl)-2-methyl-3-oxobutanoate (5d):

¹H NMR (400 MHz, CDCl₃) δ 10.33 (br s, 1H), 7.36-6.85 (m, 3H), 3.84 (s, 3H), 1.91 (s, 3H), 1.78 (s, 3H), 1.49 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 206.5, 172.3, 159.9, 135.2, 128.2, 123.7, 116.9, 114.4, 113.3, 111.7, 84.3, 63.9, 55.5, 27.7, 24.4, 20.6; ESI-MS *m/z* 407 (M + NH₄)⁺;

HRMS calcd for $C_{18}H_{22}NO_5F_3Na$ ($M + Na$)⁺ 412.1342, found 412.1351; HPLC Chiralpak AD (hexane/*i*-PrOH = 98:2, 0.7 mL/min) $\tau_{major} = 9.9$ min, $\tau_{minor} = 8.5$ min. $[\alpha]_D^{20} +221$ (c 1.0, CHCl₃, 87% ee).

(*S*)-*tert*-Butyl 2-methyl-2-(5-(2-methyl-1,3-dioxolan-2-yl)-2-(2,2,2-trifluoroacetamido)phenyl)-3-oxobutanoate (5e):

¹H NMR (400 MHz, CDCl₃) δ 10.15 (br s, 1H), 7.69-7.56 (m, 3H), 4.08-4.06 (m, 2H), 3.81-3.79 (m, 2H), 1.93 (s, 3H), 1.83 (s, 3H), 1.66 (s, 3H), 1.50 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 206.0, 172.0, 156.0, 142.7, 133.7, 131.9, 126.6, 126.4, 124.3, 113.0, 108.5, 84.5, 64.6, 27.8, 27.7, 24.6, 20.7; ESI-MS m/z 463 ($M + NH_4$)⁺; HRMS calcd for $C_{21}H_{26}NO_6F_3Na$ ($M + Na$)⁺ 468.1610, found 468.1604; HPLC Chiralpak OD (hexane/*i*-PrOH = 100:1, 0.6 mL/min) $\tau_{major} = 18.9$ min, $\tau_{minor} = 17.7$ min. $[\alpha]_D^{20} +214$ (c 1.0, CHCl₃, 86% ee).

(*S*)-*tert*-Butyl 2-(5-fluoro-2-(2,2,2-trifluoroacetamido)phenyl)-2-methyl-3-oxobutanoate (5f):

¹H NMR (400 MHz, CDCl₃) δ 10.06 (br s, 1H), 7.69-7.10 (m, 3H), 1.94 (s, 3H), 1.79 (s, 3H), 1.50 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 205.2, 171.4, 159.8, 155.8, 134.5, 130.2, 128.6, 116.1, 115.9, 115.0, 84.8, 64.4, 27.8, 24.6, 20.5; ESI-MS *m/z* 395 (M + NH₄)⁺; HRMS calcd for C₁₇H₁₉NO₄F₄Na (M + Na)⁺ 400.1148, found 400.1158; HPLC Chiralpak AD-H (hexane/*i*-PrOH = 98:2, 0.8 mL/min) τ_{major} = 8.3 min, τ_{minor} = 10.1 min. [α]_D²⁰ +200 (c 1.0, CHCl₃, 83% ee).

(*S*)-*tert*-Butyl 2-(5-iodo-2-(2,2,2-trifluoroacetamido)phenyl)-2-methyl-3-oxobutanoate (5g).

¹H NMR (400 MHz, CDCl₃) δ 10.19 (br s, 1H), 7.77-7.46 (m, 3H), 1.94 (s, 3H), 1.79 (s, 3H), 1.50 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 205.3, 171.5, 155.6, 138.3, 136.6, 134.1, 134.1, 128.3, 114.6, 92.0, 84.9, 64.1, 27.9, 24.6, 20.6; ESI-MS *m/z* 503 (M + NH₄)⁺; HRMS calcd for C₁₇H₁₉INO₄F₃Na (M + Na)⁺ 508.0209, found 508.0214; HPLC Chiralpak AD-H (hexane/*i*-PrOH = 95:5, 0.8 mL/min) τ_{major} = 6.9 min, τ_{minor} = 7.9 min. [α]_D²⁰ +201 (c 1.0, CHCl₃, 81% ee).

(*S*)-Methyl 3-(1-*tert*-butoxy-2-methyl-1,3-dioxobutan-2-yl)-4-(2,2,2-trifluoroacetamido)benzoate (5h):

^1H NMR (400 MHz, CDCl_3) δ 10.51 (br s, 1H), 8.18-7.86 (m, 3H), 3.95 (s, 3H), 1.94 (s, 3H), 1.88 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 205.7, 171.9, 166.1, 155.6, 138.5, 131.9, 130.5, 129.1, 128.7, 126.3, 114.3, 84.9, 64.5, 52.4, 27.7, 24.6, 20.5; ESI-MS m/z 435 ($\text{M} + \text{NH}_4$) $^+$; HRMS calcd for $\text{C}_{19}\text{H}_{22}\text{NO}_6\text{F}_3\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 440.1297, found 440.1304; HPLC Chiralpak AD-H (hexane/*i*-PrOH = 98:2, 0.8 mL/min) τ_{major} = 9.4 min, τ_{minor} = 10.9 min. $[\alpha]_{\text{D}}^{20}$ +167 (*c* 1.0, CHCl_3 , 60% ee).

(S)-tert-Butyl 2-(5-iodo-4-methyl-2-(2,2,2-trifluoroacetamido)phenyl)-2-methyl-3-oxobutanoate (6).

^1H NMR (400 MHz, CDCl_3) δ 10.13 (br s, 1H), 7.60 (s, 1H), 7.82 (s, 1H), 7.60 (s, 1H), 2.46 (s, 3H), 1.93 (s, 3H), 1.78 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 205.6, 171.7, 155.0, 143.2, 137.7, 134.2, 131.1, 127.5, 116.1, 99.0, 84.7, 63.7, 27.9, 24.6, 22.7, 20.5; ESI-MS m/z 517 ($\text{M} + \text{NH}_4$) $^+$; HRMS calcd for $\text{C}_{18}\text{H}_{21}\text{INO}_4\text{F}_3\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 522.0365, found 522.0376; HPLC Chiralpak AD-H (hexane/*i*-PrOH = 95:5, 0.8 mL/min) τ_{major} = 5.6 min, τ_{minor} = 6.5 min. $[\alpha]_{\text{D}}^{20}$ +206 (*c* 1.0, CHCl_3 , 82% ee).

(*R*)-*tert*-Butyl 2-acetoxy-2-(2-(2,2,2-trifluoroacetamido)phenyl)propanoate (7):

^1H NMR (400 MHz, CDCl_3) δ 10.27 (br s, 1H), 8.13 (d, $J = 3.4$ Hz, 1H), 7.46–7.21 (m, 3H), 2.14 (s, 3H), 2.03 (s, 3H), 1.41 (s, 9H); ESI-MS m/z 393 ($\text{M} + \text{NH}_4$) $^+$; HRMS calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_5\text{F}_3\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 398.1191, found 398.1199.

(*R*)-3-Hydroxy-3-methylindolin-2-one (8):

^1H NMR (400 MHz, DMSO-d_6) δ 10.16 (br s, 1H), 7.24 (d, $J = 3.7$ Hz, 1H), 7.15 (dt, $J = 3.6, 1.4$ Hz, 1H), 6.92 (t, $J = 3.7$ Hz, 1H), 6.76 (d, $J = 3.9$ Hz, 1H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 180.8, 139.8, 131.9, 129.6, 123.9, 123.3, 110.4, 74.0, 24.8; ESI-MS m/z 181 ($\text{M} + \text{NH}_4$) $^+$; HRMS calcd for $\text{C}_9\text{H}_9\text{NO}_2\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 186.0531, found 186.0535; $[\alpha]_D^{27} +46$ (c 0.63, MeOH, 89% ee).

631

6-86-1

6-38.2

6-18-5

6-56-2