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Copper-catalyzed direct acyloxylation of C(sp^2)–H bonds with Benzoic acids

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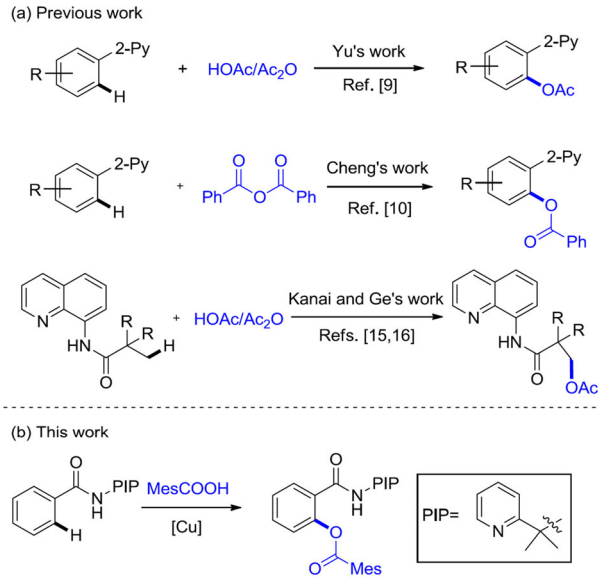
A copper-catalyzed acyloxylation of C(sp_2)–H bond with sterically bulky benzoic acids was achieved. This protocol is compatible with a broad range of functional groups and could proceed in gram scale, providing an efficient and practical protocol for the synthesis of aryl esters.

copper, C–H activation, acyloxylation, ester, bidentate

1 Introduction

Over the past decades, transition metal catalyzed C–H functionalization has received great interest for the expeditious synthesis of organic molecules [1–6]. Within this reaction category, the use of first-row transition metals would be beneficial compared with relatively expensive second- and third-row transition metals [7]. In particular, the direct oxygenation of C–H bonds mediated by first-row transition metals, such as copper, has been extensively investigated (Scheme 1) [8]. In 2006, Yu *et al*. [9] reported a copper(II)-catalyzed acetoxylation and hydroxylation of 2-arylpyridine using O_2 as terminal oxidant. Subsequently, Cheng *et al*. [10] developed the copper-catalyzed acyloxylation of 2-arylpyridine with anhydride. Lei *et al*. [11,12] has also shown that copper-catalyzed oxidation of electron-deficient arenes is possible. Recently, Daugulis *et al*. [13] and Song *et al*. [14] developed the copper-catalyzed etherification of arenes with alcohols using different bidentate directing groups. More recently, our group developed a copper mediated C–H hydroxylation of arenes using our newly developed PIP auxiliary [15]. Besides, Kanai [16] and Ge [17] groups have reported copper-catalyzed C(sp^3)–H acetoxylation by using a combination of stoichiometric amounts of copper and silver salts. Despite of these significant advancements, copper-catalyzed acyloxylation of unactivated C–H bonds with benzoic acids has never been achieved.



Scheme 1 Copper-catalyzed C–H acyloxylation.

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Esters play an important role in bioactive natural products, pharmaceuticals and organic synthesis. In addition, esters are of great importance either as protecting groups of carboxylic acids and alcohols or building blocks for further transformation. Traditional strategies towards esters depend on the reactions between the corresponding alcohols and carboxylic acid derivates such as carboxylic halides and anhydrides. Recently, transition-metal catalyzed esterifications, such as oxidative esterification of aldehydes, oxidative esterification of alcohols with alkanes, esterification of alcohols through oxidative carbonylation, and acyloxylation of C–H bonds, have emerged as efficient and viable synthetic alternatives to the traditional way [18]. To continue our interest in direct functionalization of unactivated C–H bonds, we herein reported a copper-catalyzed acyloxylation of aryl C(sp^2)–H with benzoic acids by employing our newly developed PIP directing group [19,20].

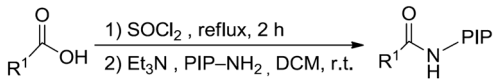
2 Experimental

2.1 General experimental section

N,*N*-dimethylformamide was dried by CaH_2, distilled under reduced pressure and stored under nitrogen. The other materials and solvents were purchased from Adamas-beta and other commercial suppliers and used without additional purification. NMR spectra were recorded on a Bruke Avance (Germany) operating for ^{1}H NMR at 400 MHz, and ^{13}C NMR at 100 MHz using TMS as internal standard. Chemical shifts were given relative to $CDCl_3$ (7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR). The following abbreviations (or combinations thereof) were used to explain multiplicities: s=singlet, d=doublet, t=triplet, m=multiplet, br= broad. Mass spectroscopy data of the products were collected on an HRMS-TOF.

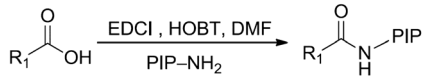
2.2 General procedures for the preparation of starting materials

Method A:



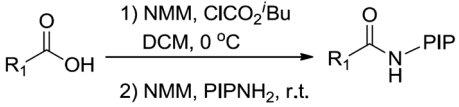
A solution of acid (5 mmol) in $SOCl_2$ (5 mL) was refluxed for 2 h and cooled to r.t.. The excess of $SOCl_2$ was removed under vacuum to give the corresponding acid chloride. The acid chloride was then re-dissolved in 5 mL anhydrous CH_2Cl_2 and added dropwise to a 20 mL anhydrous CH_2Cl_2 solution containing PIP-NH_2 (5 mmol) and Et_3N (10 mmol) at 0 °C. After stirring for 6 h at r.t., the resulting mixture was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give the desired product.

Method B:



A mixture of amine (5 mmol), acid (5 mmol), 3-(ethyliminomethyleneamino)-*N*,*N*-dimethyl-propan-1-amine (EDCI, 5.5 mmol) and HOBT (5.5 mmol) in anhydrous *N*,*N*-dimethylformamide (DMF, 20 mL) was stirred at room temperature overnight. Water was added and the mixture was extracted with diethyl ether. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give the desired product.

Method C:



To a round bottom flask was added the acid (5 mmol) and anhydrous CH_2Cl_2 (20 mL). Then the flask was submerged in an ice bath, *N*-methylmorpholine (6 mmol) was added via syringe and the solution stirred for 15 min. Isobutylchloroformate (5.5 mmol) was added dropwise over 20 min. After that, 20 mL anhydrous CH_2Cl_2 solution containing PIP–NH_2 (5 mmol) and *N*-methylmorpholine (NMM, 5 mmol) was added to the solution. After stirring for 6 h at ambient temperature, the resulting mixture was washed with sat. Na_2CO_3, and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give the desired product.

2.2.1 *N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (**1a**)

The title compound **1a** was prepared according to the general procedure (Method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.56 (ddd, *J*=4.8, 1.6, 0.8 Hz, 1H), 7.92–7.90 (m, 2H), 7.75 (td, *J*=8.0, 2.0 Hz, 1H), 7.50–7.43 (m, 4H), 7.23 (ddd, *J*=7.6, 4.8, 0.8 Hz, 1H), 1.88 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.35, 164.83, 147.70, 137.35, 136.15, 131.17, 128.55, 127.11, 122.06, 119.67, 56.76, 27.63. HRMS (EI-TOF) calcd for $C_{15}H_{16}N_2O$ (M^+): 240.1263, found: 240.1259.

2.2.2 2-Fluoro-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (**1b**)

The title compound **1b** was prepared according to the general procedure (Method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J*=11.0 Hz, 1H), 8.56 (d, *J*=4.4 Hz, 1H), 8.06 (td, *J*=8.0, 1.6 Hz, 1H), 7.73 (td, *J*=7.6, 1.6 Hz, 1H), 7.49–7.40 (m, 2H), 7.25–7.17 (m, 2H), 7.14 (dd, *J*=11.6, 8.0 Hz, 1H), 1.88 (s, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ 164.63, 162.38 (d, $J_{C–F}$=3.1 Hz), 160.77 (d, $J_{C–F}$=247.1 Hz), 148.01, 137.14, 132.88 (d, $J_{C–F}$=9.1 Hz), 131.86, 124.66 (d, $J_{C–F}$=3.3 Hz), 122.88 (d, $J_{C–F}$=12.2 Hz), 121.96, 119.55, 116.14 (d, $J_{C–F}$=24.7 Hz), 57.66, 27.80. HRMS (EI-TOF) calcd for $C_{15}H_{15}FN_2O$ (M^+): 258.1168, found: 258.1165.

2.2.3 2-Chloro-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (**1c**)

The title compound **1c** was prepared according to the general procedure (Method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J*=4.2 Hz, 1H), 8.36 (s, 1H), 7.73 (td, *J*=7.8, 1.8 Hz, 1H), 7.63 (dd, *J*=7.2, 2.0 Hz, 1H), 7.47 (d, *J*=8.0 Hz, 1H), 7.41 (dd, *J*=7.6, 1.6 Hz, 1H), 7.36–7.28 (m, 2H), 7.19 (ddd, *J*=7.4, 4.8, 0.8 Hz, 1H), 1.90 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.94, 164.34, 147.75, 137.15, 130.89, 130.24, 129.75, 127.02, 122.04, 119.58, 57.63, 27.64.

2.2.4 *N*-(2-(pyridin-2-yl)propan-2-yl)-2-(trifluoromethyl) benzamide (**1d**)

The title compound **1d** was prepared according to the general procedure (Method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44–8.42 (m, 1H), 8.30 (s, 1H), 7.75–7.68 (m, 2H), 7.60–7.58 (m, 2H), 7.51 (t, *J*=6.8 Hz, 1H), 7.45 (dd, *J*=8.0, 0.8 Hz, 1H), 7.20–7.16 (m, 1H), 1.88 (d, *J*=2.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.97, 164.15, 147.57, 137.46 (q, J_{C-F}=2.0 Hz), 137.33, 132.03, 129.41, 128.67, 127.67 (q, J_{C-F}=31.7 Hz), 126.41 (q, J_{C-F}=5.0 Hz), 123.91 (q, J_{C-F}=272.1 Hz), 122.09, 119.56, 57.42, 27.21; HRMS (EI-TOF) calcd for $C_{16}H_{15}F_3N_2O$ (M^+): 308.1136, found: 308.1133.

2.2.5 3-Methoxy-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (**1e**)

The title compound **1e** was prepared according to the general procedure (Method B).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.56 (dd, *J*=4.8, 0.4 Hz, 1H), 7.75 (td, *J*=7.6, 1.6 Hz, 1H), 7.50–7.42 (m, 3H), 7.35 (t, *J*=8.0 Hz, 1H), 7.23 (ddd, *J*=7.6, 4.8, 0.8 Hz, 1H), 7.04–7.02 (m, 1H), 3.86 (s, 3H), 1.88 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.15, 164.61, 159.82, 147.60, 137.43, 137.36, 129.41, 122.01, 119.62, 118.92, 117.47, 112.30, 56.71, 55.41, 27.55; HRMS (EI-TOF) calcd for $C_{16}H_{18}N_2O_2$ (M^+): 270.1368, found: 270.1371.

2.2.6 3-Methyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (**1g**)

The title compound **1g** was prepared according to the general procedure (Method A).^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 1H), 8.57 (d, *J*=4.8 Hz, 1H), 7.77–7.72 (m, 2H), 7.68 (d, *J*=7.2 Hz, 1H), 7.47 (d, *J*=8.0 Hz,1H), 7.35–7.29 (m, 2H), 7.22 (dd, *J*=7.2, 4.8 Hz, 1H) 2.42 (s, 3H), 1.88 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.61, 164.88,147.33, 138.29, 137.32, 136.06, 131.86, 128.38, 127.89, 124.04, 122.00, 119.66, 56.77, 27.65, 21.49; HRMS (EI-TOF) calcd for $C_{16}H_{18}N_2O$ (M^+): 254.1419, found: 254.1418.

2.2.7 Methyl 4-((2-(pyridin-2-yl)propan-2-yl)carbamoyl) benzoate (**1h**)

The title compound **1h** was prepared according to the general procedure (Method C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.56 (dd, *J*=4.1, 0.8 Hz, 1H), 8.12 (d, *J*=8.4 Hz, 2H), 7.96 (d, *J*=8.4 Hz, 2H), 7.77 (td, *J*=8.0, 1.6 Hz, 1H), 7.47 (d, *J*=8.0 Hz, 1H), 7.26–7.20 (m, 1H), 3.95 (s, 3H), 1.89 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.65, 165.43, 164.57, 147.70, 140.17, 137.50, 132.45, 129.90, 127.19, 122.21, 119.68, 56.92, 52.43, 27.53. HRMS (EI-TOF) calcd for $C_{17}H_{18}N_2O_3$ (M^+): 298.1317, found: 298.1320.

2.2.8 4-Methyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (**1i**)

The title compound **1i** was prepared according to the general procedure (Method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.56 (d, *J*=4.4 Hz, 1H), 7.80 (d, *J*=8.0 Hz, 2H), 7.75 (td, *J*=8.0, 1.6 Hz, 1H), 7.46 (d, *J*=8.0 Hz, 1H), 7.26–7.22 (m, 3H), 2.40 (s, 3H), 1.88 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.37, 164.99, 147.74, 141.44, 137.31, 133.37, 129.22, 127.12, 122.02, 119.68, 56.74, 27.70, 21.55. HRMS (EI-TOF) calcd for $C_{16}H_{18}N_2O$ (M^+): 254.1419, found: 254.1421.

2.3 General procedure for copper-catalyzed C(sp^2)–H esterification

To a 50 mL sealed tube was added **1** (0.15 mmol), acid (0.45 mmol), CuOAc (7.4 mg, 0.06 mmol), $AgNO_3$ (101.9 mg, 0.6 mmol), Li_2CO_3 (33.3 mg, 0.45 mmol) and DMF (3 mL). The mixture was purged with N_2 and stirred at 120 °C for 24 h. The reaction mixture was then cooled to room temperature, diluted with dichloromethane and quenched with saturated sodium sulfide. The aqueous phase was extracted with dichloromethane (3×10 mL). The combined organic phase was dried with anhydrous magnesium sulfate. After concentration, the resulting residue was purified by flash chromatography to afford the product.

2.3.1 2-((2-(Pyridin-2-yl)propan-2-yl)carbamoyl)phenyl 2, 4,6-trimethylbenzoate (**2a**)

The title compound **2a** was prepared according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (brs, 1H), 8.04 (dd, *J*=7.6, 1.6 Hz, 1H), 7.93 (d, *J*=4.8 Hz, 1H), 7.60 (td, *J*=8.0, 1.6 Hz, 1H), 7.52 (td, *J*=8.0, 2.0 Hz, 1H), 7.38–7.29 (m, 3H), 7.00 (ddd, *J*=7.2, 5.2, 0.8 Hz, 1H), 6.82 (s, 2H), 2.40 (s, 6H), 2.28 (s, 3H), 1.75 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.68, 164.27, 164.03, 148.30, 147.58, 140.29, 136.89, 136.63, 131.60, 130.98, 129.31, 129.07, 128.92, 126.28, 123.19, 121.55, 119.13, 57.43, 27.51, 21.28, 20.56; HRMS (EI-TOF) calcd for $C_{25}H_{26}N_2O_3$ (M^+): 402.1943, found: 402.1950.

2.3.2 2-((2-(Pyridin-2-yl)propan-2-yl)carbamoyl)-1,3-phenylene bis(2,4,6-trimethylbenzoate) (**2a′**)

The title compound **2a′** was prepared according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J*=4.0 Hz, 1H), 7.85 (brs, 1H), 7.52 (t, *J*=8.0 Hz, 1H), 7.36–7.22 (m, 4H), 7.04–7.00 (m, 1H), 6.84 (s, 4H), 2.37 (s, 12H), 2.28 (s, 6H), 1.56 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.69, 163.86, 162.17, 148.51, 147.68, 140.44, 137.04, 136.80, 129.86, 129.00, 128.80, 121.74, 120.35, 119.26, 57.68, 27.45, 21.31, 20.71; HRMS (ESI-TOF) calcd for $C_{35}H_{36}N_2O_5H^+$ (M^+): 565.2697, found: 565.2700.

2.3.3 3-Fluoro-2-((2-(pyridin-2-yl)propan-2-yl)carbamoyl)-phenyl 2,4,6-trimethylbenzoate (**2b**)

The title compound **2b** was prepared according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (d, *J*=4.0 Hz, 1H), 8.18 (brs, 1H), 7.61 (t, *J*=7.6 Hz), 7.46 – 7.36 (m , 2H), 7.15–7.10 (m, 2H), 7.06 (t, *J*=8.0 Hz), 6.85 (s, 2H), 2.39 (s, 6H), 2.28 (s, 3H), 1.78 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.76, 163.97, 159.94 ($J_{C–F}$=247.5 Hz), 158.70, 148.91 ($J_{C–F}$=6.3 Hz), 147.68, 140.38, 137.11, 136.87, 130.54 ($J_{C–F}$=9.5 Hz), 128.94, 128.87, 121.94, 121.19 ($J_{C–F}$=20.9 Hz), 119.41, 118.88 ($J_{C–F}$=3.4 Hz), 113.59 ($J_{C–F}$=22.0 Hz), 57.74, 27.60, 21.28, 20.59; HRMS (EI-TOF) calcd for $C_{25}H_{25}FN_2O_3$ (M^+): 420.1849, found: 420.1846.

2.3.4 3-Chloro-2-((2-(pyridin-2-yl)propan-2-yl)carbamoyl)-phenyl 2,4,6-trimethylbenzoate (**2c**)

The title compound **2c** was prepared according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, *J*=4.0 Hz, 1H), 8.01 (brs, 1H), 7.56 (t, *J*=8.0 Hz, 1H), 7.41–7.32 (m, 3H), 7.27 (d, *J*=8.0 Hz, 1H), 7.12 (dd, *J*=7.2, 4.8 Hz, 1H), 6.83 (s, 2H), 2.35 (s, 6H), 2.27 (s, 3H), 1.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.79, 163.94, 162.76, 148.45, 147.64, 140.45, 137.08, 136.91, 132.36, 131.76, 130.06, 128.96, 128.77, 127.25, 121.94, 121.48, 119.43, 57.75, 27.48, 21.29, 20.60; HRMS (EI-TOF) calcd for $C_{25}H_{25}ClN_2O_3$ (M^+): 436.1554, found: 436.1554.

2.3.5 2-((2-(Pyridin-2-yl)propan-2-yl)carbamoyl)-3-(trifluoromethyl)phenyl 2,4,6-trimethylbenzoate (**2d**)

The title compound **2d** was prepared according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, *J*=4.4 Hz, 1H), 8.18 (brs, 1H), 7.63–7.56 (m, 3H), 7.53 (td, *J*=8.0, 1.2 Hz, 1H), 7.33 (d, *J*=8.0 Hz, 1H), 7.10 (dd, *J*=7.2, 5.2 Hz, 1H), 6.83 (s, 2H), 2.34 (s, 6H), 2.27 (s, 3H), 1.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.67, 163.82, 162.53, 148.42, 147.49, 140.55, 137.09, 137.03, 130.48, 129.76, 129.17, 129.00, 128.85, 128.49, 126.82, 123.69 (q, $J_{C–F}$=4.8 Hz), 123.45 (q, $J_{C–F}$=272.5 Hz), 121.93, 119.38, 57.62, 27.04, 21.28, 20.59; HRMS (EI-TOF) calcd for $C_{26}H_{25}F_3N_2O_3$ (M^+): 470.1817, found: 470.1821.

2.3.6 2-Methoxy-6-((2-(pyridin-2-yl)propan-2-yl)carbamoyl)phenyl 2,4,6-trimethylbenzoate (**2e**)

The title compound **2e** was prepared according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (s, 1H), 7.96 (d, *J*=4.8 Hz, 1H), 7.61–7.55 (m, 2H), 7.33–7.28 (m, 2H), 7.12 (d, *J*=8.0 Hz, 1H), 6.99 (dd, *J*=6.4, 5.2 Hz, 1H), 6.82 (s, 2H), 3.89 (s, 3H), 2.45 (s, 6H), 2.27 (s, 3H), 1.74 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.42, 164.28, 164.12, 151.73, 147.61, 140.27, 137.85, 136.83, 130.71, 129.07, 128.89, 126.63, 121.97, 121.54, 119.11, 114.52, 57.49, 56.20, 27.55, 21.27, 20.95; HRMS (EI-TOF) calcd for $C_{26}H_{28}N_2O_4$ (M^+): 432.2049, found: 432.2049.

2.3.7 4-Methoxy-2-((2-(pyridin-2-yl)propan-2-yl)carbamoyl)phenyl 2,4,6-trimethylbenzoate (**2f**)

The title compound **2f** was prepared according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (s, 1H), 7.85 (d, *J*=4.0 Hz, 1H), 7.63–7.57 (m, 2H), 7.31 (d, *J*=8.0 Hz, 1H), 7.24 (d, *J*=9.2 Hz, 1H), 7.05 (dd, *J*=8.8, 2.8 Hz, 1H), 6.98 (dd, *J*=6.4, 4.8 Hz, 1H), 6.81 (s, 2H), 3.86 (s, 3H), 2.37 (s, 6H), 2.28 (s, 3H), 1.73 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.04, 164.25, 163.61, 157.47, 147.62, 141.85, 140.25, 136.85, 136.57, 129.44, 129.29, 128.91, 124.22, 121.52, 119.07, 118.40, 114.54, 57.53, 55.95, 27.50, 21.28, 20.56; HRMS (EI-TOF) calcd for $C_{26}H_{28}N_2O_4$ (M^+): 432.2049, found: 432.2048.

2.3.8 4-Methoxy-2-((2-(pyridin-2-yl)propan-2-yl)carbamoyl)-1,3-phenylene bis(2,4,6-trimethylbenzoate) (**2f′**)

The title compound **2f′** was prepared according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J*=4.0 Hz, 1H), 7.82 (s, 1H), 7.32–7.22 (m, 3H), 7.08 (d, *J*=8.8 Hz, 1H), 7.00 (t, *J*=5.2 Hz, 1H), 6.84 (s, 2H), 6.83 (s, 2H), 3.89 (s, 3H), 2.41 (s, 6H), 2.36 (s, 6H), 2.27 (s, 3H), 1.58 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.13, 166.57, 163.86, 162.05, 149.56, 147.71, 140.86, 140.43, 140.27, 138.13, 137.39, 136.96, 136.73, 129.15, 129.01, 128.95, 128.31, 127.36, 121.69, 120.66, 119.23, 112.70, 57.71, 56.41, 27.53, 21.29, 21.00, 20.68; HRMS (EI-TOF) calcd for $C_{36}H_{38}N_2O_6$ (M^+): 594.2730, found: 594.2734.

2.3.9 4-Methyl-2-((2-(pyridin-2-yl)propan-2-yl)carbamoyl) phenyl 2,4,6-trimethylbenzoate (**2g**)

The title compound **2g** was prepared according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1H), 7.91 (d, *J*=4.4 Hz, 1H), 7.85 (s, 1H), 7.60 (td, *J*=8.0, 1.6 Hz, 1H), 7.32 (d, *J*=8.0 Hz, 2H), 7.21 (d, *J*=8.0 Hz, 1H), 6.99 (dd, *J*=6.4, 4.8 Hz, 1H), 6.81 (s, 2H), 2.40 (s, 3H), 2.38 (s,6H), 2.28 (s, 3H), 1.73 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.88, 164.33, 164.14, 147.61, 146.06, 140.20, 136.83, 136.57, 136.08, 132.20, 131.34, 129.45, 128.88, 128.44, 122.92, 121.51, 119.12, 57.44, 27.51, 21.27, 20.96, 20.54; HRMS (EI-TOF) calcd for $C_{26}H_{28}N_2O_3$ (M^+): 416.2100, found: 416.2102.

2.3.10 4-Methoxy-2-((2-(pyridin-2-yl)propan-2-yl)carbamoyl)-1,3-phenylene bis(2,4,6-trimethylbenzoate) (**2g′**)

The title compound **2g′** was prepared according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, *J*=4.4 Hz, 1H), 7.75 (s, 1H), 7.36 (d, *J*=7.6 Hz, 1H), 7.26–7.19 (m, 3H), 6.99 (t, 5.6 Hz), 6.88 (s, 3H), 6.83 (s, 3H), 5.30 (s, 3H), 2.47 (s, 6H), 2.35 (s, 6H), 2.29 (s, 6H), 2.28 (s, 3H), 1.51 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.82, 166.66, 163.93, 162.74, 147.75, 146.87, 146.32, 141.09, 140.29, 139.17, 136.97, 136.65, 131.50, 129.81, 129.20, 128.95, 127.31, 126.51, 121.64, 120.45, 119.25, 57.68, 27.44, 22.07, 21.29, 20.64, 17.25; HRMS (EI-TOF) calcd for $C_{36}H_{38}N_2O_5$ (M^+): 578.2781, found: 578.2780.

2.3.11 5-(Methoxycarbonyl)-2-((2-(pyridin-2-yl)propan-2-yl)carbamoyl)phenyl 2,4,6-trimethylbenzoate (**2h**)

The title compound **2h** was prepared according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (s, 1H), 8.08 (d, *J*=8.0 Hz, 1H), 8.01 (d, *J*=8.4 Hz, 1H), 7.97 (s, 1H), 7.94 (d, *J*=4.0 Hz, 1H), 7.62 (t, *J*=7.6 Hz, 1H), 7.33 (d, *J*=8.0 Hz, 1H), 7.02 (dd, *J*=6.4, 5.2 Hz, 1H), 6.83 (s, 2H), 3.96 (s, 3H), 2.41 (s, 6H), 2.29 (s, 3H), 1.75 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.43, 165.84, 164.03, 163.32, 148.14, 147.55, 140.54, 137.02, 136.92, 133.32, 133.14, 131.01, 129.02, 128.87, 127.22, 124.57, 121.70, 119.15, 57.56, 52.66, 27.43, 21.30, 20.72; HRMS (EI-TOF) calcd for $C_{27}H_{28}N_2O_5$ (M^+): 460.1998, found: 460.2007.

2.3.12 5-(Methoxycarbonyl)-2-((2-(pyridin-2-yl)propan-2-yl)carbamoyl)-1,3-phenylene bis(2,4,6-trimethylbenzoate) (**2h′**)

The title compound **2h′** was prepared according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J*=4.0 Hz, 1H), 8.04 (s, 1H), 1.95 (s, 2H), 7.40 (td, *J*=8.0, 1.6 Hz, 1H), 7.23 (d, *J*=8.0 Hz, 1H), 7.05 (dd, *J*=6.4, 4.8 Hz, 1H), 6.84 (s, 4H), 3.97 (s, 3H), 2.38 (s, 12H), 2.27 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.39, 165.25, 163.62, 161.44, 148.46, 147.63, 140.66, 137.22, 136.91, 132.02, 130.02, 129.07, 128.36, 121.86, 121.66, 119.20, 57.73, 52.83, 27.35, 21.31, 20.79; HRMS (EI-TOF) calcd for $C_{37}H_{38}N_2O_7$ (M^+): 622.2679, found: 622.2653.

2.3.13 5-Methyl-2-((2-(pyridin-2-yl)propan-2-yl)carbamoyl)phenyl 2,4,6-trimethylbenzoate (**2i**)

The title compound **2i** was prepared according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1H), 7.95 (d, *J*=8.0 Hz, 1H), 7.89 (d, *J*=4.4 Hz, 1H), 7.59 (t, *J*=7.6 Hz, 1H), 7.31 (d, *J*=8.0 Hz, 1H), 7.16 (d, *J*=8.0 Hz, 1H), 7.12 (s, 1H), 6.99 (dd, *J*=6.0, 4.8 Hz, 1H), 6.82 (s, 2H), 2.43 (s, 3H), 2.40 (s, 6H), 2.28 (s, 3H), 1.73 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.68, 164.44, 164.02, 148.26, 147.62, 142.44, 140.27, 136.81, 136.69, 131.04, 129.40, 128.94, 127.16, 126.04, 123.55, 121.48, 119.11, 57.41, 27.56, 21.45, 21.28, 20.62; HRMS (EI-TOF) calcd for $C_{26}H_{28}N_2O_3$ (M^+): 416.2100, found: 416.2102.

2.3.14 2-((2-(Pyridin-2-yl)propan-2-yl)carbamoyl)phenyl 2,6-dimethylbenzoate (**3**)

The title compound **3** was prepared according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (brs, 1H), 8.03 (dd, *J*=8.0, 1.6 Hz, 1H), 7.90 (d, *J*=4.4 Hz, 1H), 7.60 (td, *J*=8.0, 1.6 Hz, 1H), 7.53 (td, *J*=8.0, 1.6 Hz, 1H), 7.40–7.31 (m, 3H), 7.20 (t, *J*=7.6 Hz, 1H), 7.04–6.98 (m, 3H), 2.43 (s, 6H), 1.75 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.63, 164.22, 164.04, 148.22, 147.58, 136.95, 136.27, 132.41, 131.60, 130.96, 130.18, 129.13, 128.05, 126.37, 123.15, 121.70, 119.16, 57.43, 27.51, 20.43; HRMS (EI-TOF) calcd for $C_{24}H_{24}N_2O_3$ (M^+): 388.1787, found: 388.1785.

2.3.15 2-((2-(Pyridin-2-yl)propan-2-yl)carbamoyl)-1,3-phenylene bis(2,6-dimethylbenzoate) (**3′**)

The title compound **3′** was prepared according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J*=4.4 Hz, 1H), 7.93 (brs, 1H), 7.54 (t, *J*=8.4 Hz, 1H), 7.39–7.33 (m, 3H), 7.26–7.17 (m, 3H), 7.06–7.00 (m, 5H), 2.40 (s, 12H), 1.56 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.54, 163.81, 162.04, 148.43, 147.63, 136.87, 136.50, 131.96, 130.22, 129.85, 128.04, 125.83, 121.80, 120.30, 119.23, 57.65, 27.36, 20.49; HRMS (ESI-TOF) calcd for $C_{33}H_{32}N_2O_5H^+$ (M^+): 537.2384, found: 537.2382.

2.3.16 2-((2-(Pyridin-2-yl)propan-2-yl)carbamoyl)phenyl 2,4,6-triisopropylbenzoate (**4**)

The title compound **4** was prepared according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.30 (s, 1H), 8.13 (dd, *J*=8.0, 1.6 Hz, 1H), 7.60–7.51 (m, 3H), 7.43 (d, *J*=8.0 Hz, 1H), 7.39–7.30 (m, 2H), 7.03 (s, 2H), 6.93 (dd, *J*=6.4, 4.8 Hz, 1H), 3.18–3.08 (m, 2H), 2.98–2.89 (m, 1H), 1.77 (s, 6H), 1.29 (d, *J*=7.2 Hz, 6H), 1.20 (d, *J*=6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.19, 164.23, 163.78, 151.10, 148.49, 147.28, 146.27, 136.88, 131.57, 131.33, 129.25, 128.54, 126.05, 122.71, 121.48, 121.17, 119.21, 57.46, 34.67, 31.50, 27.58, 24.34, 24.13; HRMS (ESI-TOF) calcd for $C_{31}H_{38}N_2O_3H^+$ (M^+): 487.2955, found: 487.2957.

2.3.17 2-((2-(Pyridin-2-yl)propan-2-yl)carbamoyl)-1,3-phenylene bis(2,4,6-triisopropylbenzoate) (**4′**)

The title compound **4′** was prepared according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J*=4.0 Hz, 1H), 7.82 (s, 1H), 7.53 (dd, *J*=9.2, 7.2 Hz, 1H), 7.47–7.43 (m, 2H), 7.25–7.22 (m, 1H), 7.14 (td, *J*=7.2, 1.6 Hz, 1H), 7.03–6.95 (m, 5H), 3.12–3.03 (m, 4H), 2.93–2.84 (m, 2H), 1.55 (s, 6H), 1.24 (d, *J*=7.2 Hz, 12H), 1.19 (d, *J*=6.8 Hz, 24H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.25, 163.95, 162.03, 151.03, 148.68, 147.62, 146.06, 136.79, 129.71, 128.93, 125.42, 121.56, 121.11, 119.42, 119.26, 57.81, 34.59, 31.53, 27.68, 24.41, 24.04; HRMS (ESI-TOF) calcd for $C_{47}H_{60}N_2O_5H^+$ (M^+): 733.4575, found: 733.4578.

2.3.18 2-((2-(Pyridin-2-yl)propan-2-yl)carbamoyl)phenyl 4-bromo-2,6-dimethylbenzoate (**5**)

The title compound **5** was prepared according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (brs, 1H), 8.02 (dd, *J*=7.6, 1.2 Hz, 1H), 7.94 (d, *J*=4.4 Hz, 1H), 7.65 (td, *J*=7.6, 1.6 Hz, 1H), 7.53 (td, *J*=8.0, 1.6 Hz, 1H), 7.41–7.29 (m, 3H), 7.16 (s, 2H), 7.07 (dd, *J*=7.2, 5.2 Hz, 1H), 2.40 (s, 6H), 1.78 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.91, 164.19, 164.04, 148.02, 147.41, 138.49, 137.10, 131.62, 131.40, 130.89, 129.34, 126.56, 124.28, 123.09, 121.85, 119.19, 57.43, 27.46, 20.28. HRMS (EI-TOF) calcd for $C_{24}H_{23}BrN_2O_3$ (M^+): 466.0892, found: 466.0888.

2.2.19 2-((2-(Pyridin-2-yl)propan-2-yl)carbamoyl)-1,3-phenylene bis(4-bromo-2,6-dimethylbenzoate) (**5′**)

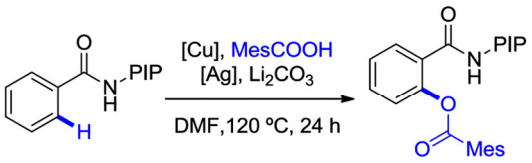
The title compound **5′** was prepared according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J*=4.0 Hz, 1H), 8.06 (brs, 1H), 7.56–7.46 (m, 2H), 7.32 (d, *J*=8.4 Hz, 2H), 7.28–7.24 (m, 1H), 7.19 (s, 4H), 7.08 (ddd, *J*=7.2, 4.8, 0.8 Hz, 1H), 2.37 (s, 12H), 1.57 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.78, 163.69, 161.88, 148.26, 147.55, 138.78, 137.04, 130.99, 130.84, 129.97, 125.80, 124.47, 122.00, 120.42, 119.28, 57.55, 27.34, 20.37. HRMS (EI-TOF) calcd for $C_{33}H_{30}Br_2N_2O_5$ (M^+): 692.0521, found: 692.0516.

3 Results and discussion

3.1 Optimization of reaction conditions

We started our study by investigating the optimal conditions for copper-catalyzed C(sp^2)–H esterification. PIP-NH_2 was employed as directing group and MesCOOH was chosen as coupling partner. Our initial condition using CuOAc (10 mol%) as catalyst, Li_2CO_3 (3.0 equiv.) as base, $AgNO_3$ (4.0 equiv.) as oxidant in DMF at 120 °C for 24 h afforded the desired product in 51% overall yield (Table 1, Entry 1, mono:di=3.3:1). The overall yield was improved to 63% when 20 mol% CuOAc was used (Entry 2). Subsequent screening of several copper salts revealed that CuOAc and $Cu(OAc)_2$ gave identical efficiency (Entries 3–8). Li_2CO_3 was crucial for this transformation since no product was observed in the absence of Li_2CO_3 (Entry 9). To our delight, the yield could be increased by simply lowering the concentration of the reaction and enhancing the amount of copper salts (entry 10, 70% yield, mono:di=1.3:1).

Table 1 Optimization of reaction condictions



1a **2a**

Entry	[Cu] (equiv.)	[Ag] (equiv.)	MesCOOH (equiv.)	Li_2CO_3 (equiv.)	DMF (mL)	Yield (%) [a]
1	CuOAc (0.1)	$AgNO_3$ (4.0)	3.0	3.0	1.5	51 (3.3:1)
2	CuOAc (0.2)	$AgNO_3$ (4.0)	3.0	3.0	1.5	63 (2.7:1)
3	$Cu_2(OH)_2CO_3$ (0.2)	$AgNO_3$ (4.0)	3.0	3.0	1.5	44 (7.8:1)
4	$Cu(OAc)_2$ (0.2)	$AgNO_3$ (4.0)	3.0	3.0	1.5	61 (3.7:1)
5	$CuBr_2$ (0.2)	$AgNO_3$ (4.0)	3.0	3.0	1.5	51 (2.6:1)
6	CuO (0.2)	$AgNO_3$ (4.0)	3.0	3.0	1.5	N.D.
7	CuCN (0.2)	$AgNO_3$ (4.0)	3.0	3.0	1.5	44 (3.9:1)
8	CuI (0.2)	$AgNO_3$ (4.0)	3.0	3.0	1.5	57 (3.4:1)
9	CuOAc (0.2)	$AgNO_3$ (4.0)	3.0	–	1.5	N.D.
10 [b]	**CuOAc (0.4)**	**$AgNO_3$ (4.0)**	**3.0**	**3.0**	**3.0**	**70 (1.3:1)**

a) ^{1}H NMR yield using CH_2Br_2 as the internal standard; b) isolated yield.

3.2 Substrate scope

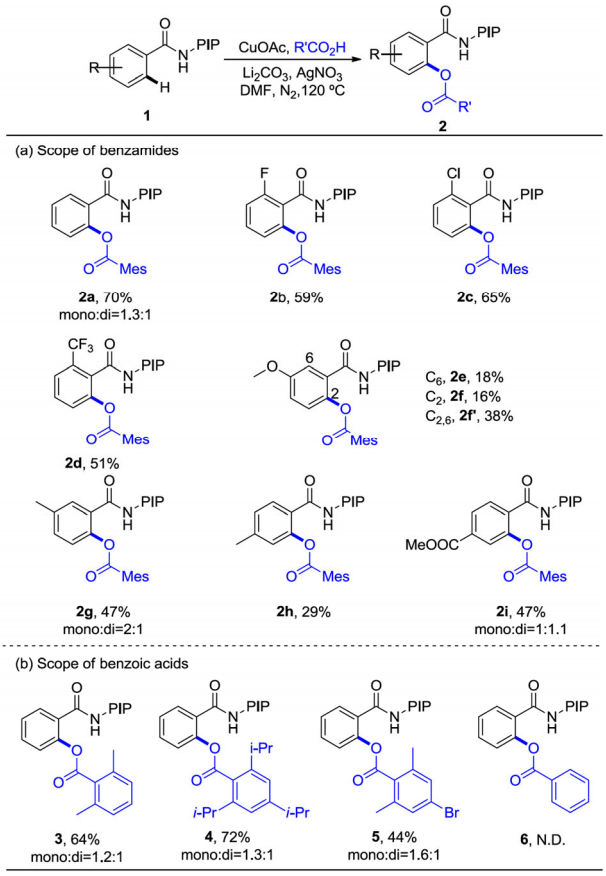
With the optimized reaction conditions in hand, we then explored the amide substrate scope under the optimized conditions. As shown in Scheme 2, a variety of functional groups were well tolerated, such as fluoro (**2b**), chloro (**2c**), trifluoromethyl (**2d**), methoxy (**2e** and **2f**), and methoxycarbonyl (**2i**). Notably, when *meta*-methylbenzamide **1g** was employed, the esterification occured predominantly at the sterically more accessible site to avoid the steric congestion. Interestingly, *meta*-methoxybenzamide **1e** gave a mixture of esterification at both of C6 and C2-position (**2e** and **2f**), probably due to the coordination effect of the methoxy substitutent in stabilizing the aryl copper intermediate. Subsequently, we further explored the scope of benzoic acids. Generally, sterically bulky benzoic acids with 2,6-disubstituents showed good reaction efficiency, thus affording the desired esterification products in moderate to good yields (**3–5**). However, simple benzoic acid did not provide the desired product.

3.3 Gram scale synthesis

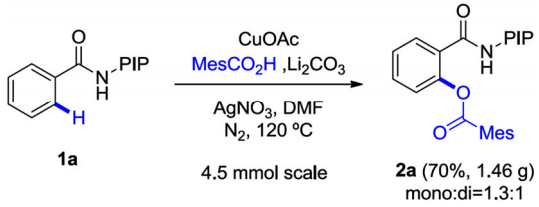
To demonstrate the synthetic utility of this reaction, we performed this reaction on gram scale (4.5 mmol) and the desired product was obtained in 70% overall yield (Scheme 3, 1.46 g, mono:di=1.3:1).

3.4 Plausible reaction mechanism

On the basis of the experiments above and previous work on copper-catalyzed C–H functionalized [21–25], the reaction mechanism was tentatively proposed as shown in Scheme 4. The reaction starts with Cu(II)-catalyzed C–H activation to generate C,N,N-Cu(II) intermediate **A**, which undergoes



Scheme 2 Copper-catalyzed acyloxylation of C(sp^2)–H bonds. Reaction conditions: benzamides **1** (0.15 mmol), CuOAc (0.06 mmol), acid (0.45 mmol), Li_2CO_3 (0.45 mmol), $AgNO_3$ (0.6 mmol), DMF (3.0 mL), 120 °C, N_2.

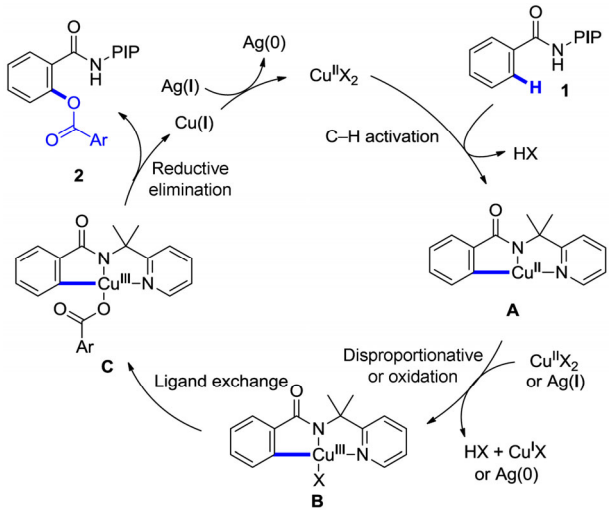


Scheme 3 Gram scale synthesis of **2a**.

disproportion or oxidation to afford the C,N,N-Cu(III) species **B**. Finally, ligand exchange and reductive elimination from intermediate **C** delivered the desired product **2** with Cu(I). Notably, when CuOAc was used as catalyst, the catalytic cycle is both initiated and closed by the reoxidation of Cu(I) to Cu(II) by silver salt.

4 Conclusions

In conclusion, we have developed a copper-catalyzed esterification of C(sp^2)–H bonds with sterically bulky benzoic acids. The presence of Li_2CO_3 is crucial for this process.



Scheme 4 Proposed reaction mechanism.

The reaction could tolerate various functional groups and proceed in good yield even in gram scale, providing an efficient and practical protocol for the synthesis of aryl esters.

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