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Silver(I) and Copper(I) Cocatalyzed Tandem Reaction of 2-Alkynylbenzaldoximes with Aldehydes or Alcohols: Approach to 4-Carboxylated Isoquinolines

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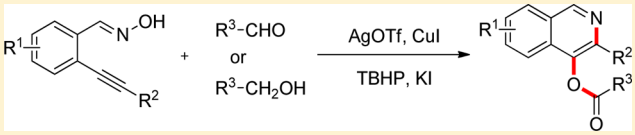
Supporting Information

ABSTRACT: A novel and efficient route for the preparation of 4-carboxylated isoquinolines via a Ag(I) and Cu(I) cocatalyzed tandem reaction of 2-alkynylbenzaldoximes with aldehydes or alcohols in moderate to good yields is described. The reaction proceeds smoothly to produce C−N and C−O bonds in a one-pot procedure with structural complexity and molecular diversity.



INTRODUCTION

It is generally accepted that the construction of a natural-product-like library with structural complexity and molecular diversity is of great importance in the hunt for lead compounds in medicinal chemistry.[1] Among the privileged structures, the isoquinoline core has been the object of in-depth investigation both in the development of synthetic methodologies and in further biological screening, due to its remarkable biological and physical properties.[2,3] Recently, a significant advance has been made in the synthesis of isoquinolines.[4] However, for combinatorial chemistry and its library construction, the development of efficient catalytic methods for the preparation of diverse isoquinolines is still in great demand.

On the other hand, the ester functionality is prevalent in a wide range of important natural and synthetic molecules.[5] Conventionally, ester synthesis involves esterification of a stoichiometric amount of "activated carboxylates" with the appropriate nucleophiles. In the past decade, direct oxidative esterification of aldehydes with alcohols, boronic acids, and reactive halides provided an attractive possibility to readily access esters,[6] whereas direct and efficient catalytic transformation via C−H bond activation to 4-carboxylated isoquinoline has rarely been exploited.[7]

Inspired by what was mentioned above, we envisioned that an intermediate isoquinoline *N*-oxide derived in situ from 2-alkynylbenzaldoxime[8] via 6-*endo* cyclization would be employed as a partner in [3 + 2] cycloaddition,[9] and carboxylated isoquinolines could be synthesized through C−H functionalization of isoquinoline *N*-oxides with aldehydes.[10]

Herein we report the 4-carboxylative reactions of isoquinolines via a Ag(I) and Cu(I) cocatalyzed tandem reaction of 2-alkynylbenzaldoximes with aldehydes or alcohols in the presence of *tert*-butyl hydroperoxide (TBHP) as the ideal oxidant.

RESULTS AND DISCUSSION

Initially, reaction of 2-alkynylbenzaldoxime **1a** with *p*-methylbenzaldehyde **2a** was performed in the presence of AgOTf (10 mol %), CuI (10 mol %), and TBHP (3.0 equiv), as shown in Scheme 1. Interestingly, the distinctive 4-carboxylated isoquinoline **3a** via oxidative esterification at 40 °C was detected in 35% yield and confirmed by an X-ray ORTEP illustration (see the Supporting Information, Figure 1).

Next, we explored the optimal conditions for this transformation (see the Supporting Information, Table 4). Various oxidants, solvents, copper salts, and additives were screened; the yield was improved to 55% when TBHP was used as the oxidant in the presence of AgOTf and CuI as cocatalysts and KI as an additive in DCM at 40 °C. Further screening of solvents revealed that a cosolvent (DCM/DCE) was the best choice, which could afford the corresponding product **3a** in 60% yield. Increasing the temperature to 55 °C made the reaction more efficient, and the desired product **3a** could be generated in 74% yield.

With the optimized reaction conditions (AgOTf (10 mol %), CuI (10 mol %), KI (20 mol %), TBHP (3.0 equiv), DCM/DCE (v/v) 3/2, 55 °C) in hand, the scope of the reaction of 2-alkynylbenzaldoxime **1a** with aldehyde **2** was then investigated, and the results are summarized in Table 1. At the outset, a range of aldehydes were explored, and to our delight, the reaction proceeded smoothly to afford the corresponding 4-carboxylated isoquinoline **3** in moderate to good yields (Table 1). As expected, both electron-donating and electron-withdrawing aryl aldehydes are suitable substrates in this process (**3a**−**g**). For instance, 4-methoxybenzaldehyde reacted with 2-alkynylbenzaldoxime effectively, leading to the product **3b** in

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Scheme 1. Reaction of 2-Alkynylbenzaldoxime 1a with Aldehyde 2a for the Synthesis of Carboxylated Isoquinolines

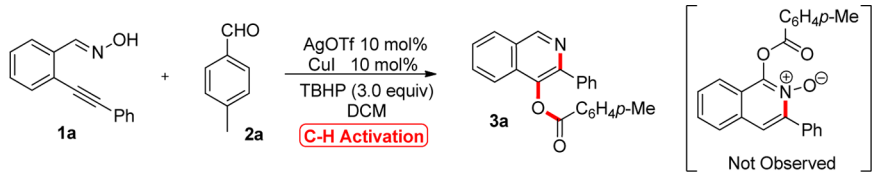
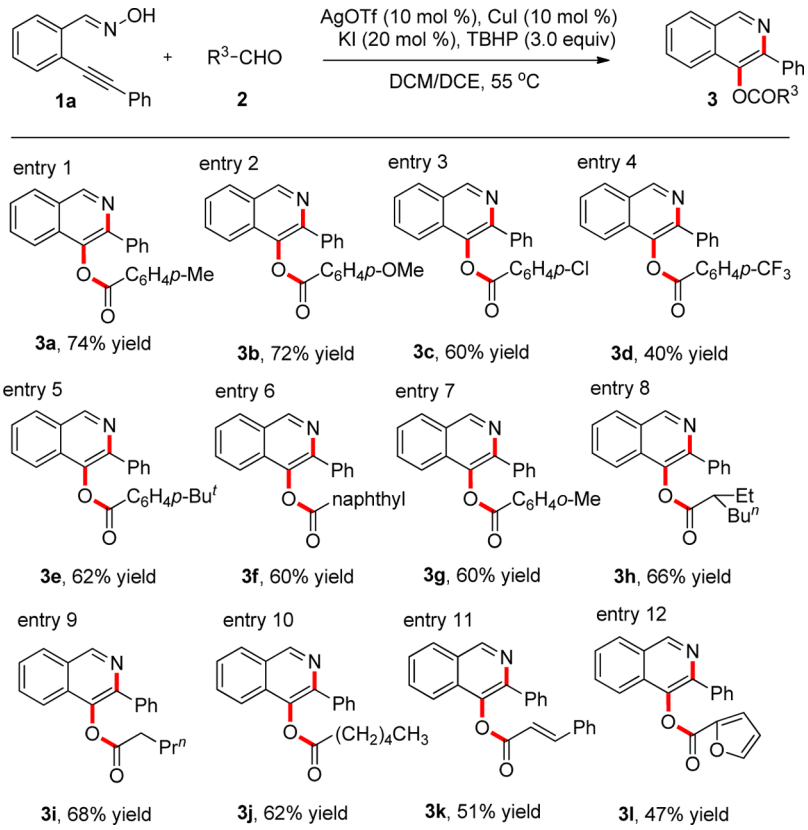


Table 1. AgOTf and CuI Cocatalyzed Reaction of 2-Alkynylbenzaldoxime 1a with Aldehydes 2[a]



[a]Isolated yield based on 2-alkynylbenzaldoxime **1a**.

72% yield (Table 1, entry 2). A lower yield was obtained when an ortho-substituted aryl aldehyde was employed (Table 1, entry 7) instead of a para-substituted aryl aldehyde (Table 1, entry 1), possibly due to steric hindrance. Furthermore, it was found that aliphatic aldehyde and unsaturated aldehyde were also suitable for the transformations (Table 1, entries 8−11). In addition, a heterocyclic aldehyde such as furan-2-carbaldehyde was also tolerated, resulting in the corresponding product **3l** in 47% yield (Table 1, entry 12).

Encouraged by the above results, reactions of a series of substituted 2-alkynylbenzaldoximes **1** were also examined. As shown in Table 2, 2-alkynylbenzaldoximes **1** with electron-donating groups or electron-withdrawing groups attached to the aromatic ring and different substituents attached to the triple bond were explored under the standard conditions. The reactions worked well and afforded the desired 4-carboxylated isoquinolines **3** in moderate to good yields (**3m−v**). For examples, the methyl-substituted 7-methyl-3-phenylisoquinolin-4-yl 4-methoxybenzoate **3m** was isolated in 76% yield (Table 2, entry 1), and the methoxy-substituted product **3r** was furnished in 73% yield (Table 2, entry 5). Furthermore, functional groups such as fluorine and chlorine also could be tolerated in the transformation, which may allow high diversity of 4-carboxylated isoquinolines (Table 2, entries 2−4, 7, and 8). However, only a trace amount of product was detected when a cyclopropyl group at the triple-bond position of 2-alkynylbenzaldoximes **1** was utilized (Table 2, entry 11).

To enlarge the scope of our method, we hypothesized that alcohols instead of aldehydes could also be good reaction participants for the synthesis of 4-carboxyl isoquinolines **3**. In the process, alcohols were oxidized in situ to aldehydes in the presence of oxidants.[11] To our delight, the AgOTf and CuI cocatalyzed reaction of 2-alkynylbenzaldoxime **1a** with *p*-tolylmethanol **4a** proceeded smoothly in the presence of TBHP in DCE, giving rise to the corresponding 4-carboxylated isoquinoline **3a** in 45% yields. Then, we further explored the optimal conditions for this transformation. Different oxidants, solvents, and temperatures were examined (see the Supporting Information, Table 5). The reaction worked most efficiently when TBHP was employed as the oxidant. Interestingly, the yield was increased to 67% when 1,4-dioxane was used as the solvent in the reaction, and no better results were obtained when other solvents were used. Further temperature evaluation showed that 40 °C was the best choice for this reaction, affording the desired product **3a** in 70% yield.

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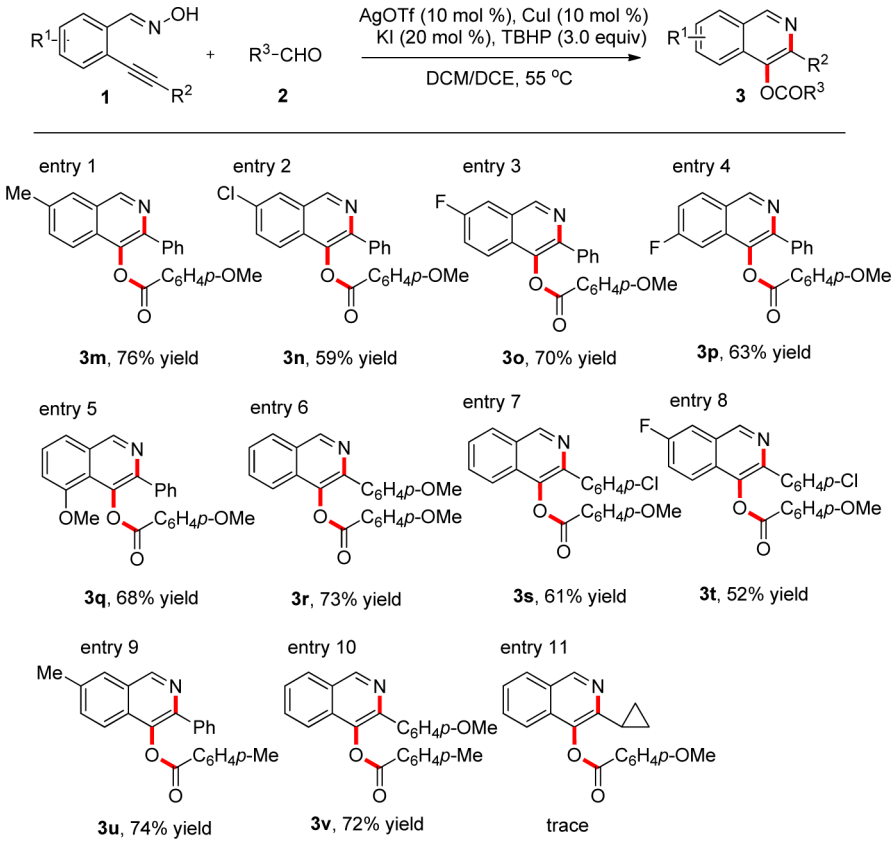
Table 2. AgOTf and CuI Cocatalyzed Reaction of 2-Alkynylbenzaldoxime 1 with Aldehydes 2[a]



[a]Isolated yield based on 2-alkynylbenzaldoxime **1**.

The generality of this AgOTf and CuI cocatalyzed tandem reaction of 2-alkynylbenzaldoximes **1** with alcohols **2** was then explored under the optimized conditions (AgOTf (10 mol %), CuI (10 mol %), KI (20 mol %), TBHP (6.0 equiv), 1,4-dioxane, 40 °C). The results are summarized in Table 3. Benzyl alcohols were demonstrated to be good partners in the transformation, giving rise to the corresponding product **3** in moderate to good yields. For instance, (4-methoxyphenyl)-methanol reacted with 2-(phenylethynyl)benzaldehyde oxime **1a**, leading to the corresponding 4-carboxylated isoquinoline **3b** in 68% yield (Table 3, entry 2). Unfortunately, only trace amounts of products were detected when other aliphatic alcohols were utilized, due to their low reactivities (Table 3, entries 11 and 12). A series of substituted 2-alkynylbenzaldoximes **1** with electron-donating groups or electron-withdrawing groups were explored under the optimized conditions. A slightly lower yield was obtained when substituted 2-alkynylbenzaldoximes **1** with electron-withdrawing groups were employed instead of 2-alkynylbenzaldoximes **1** with electron-donating groups. However, the reaction was complicated and only a trace amount of product was generated when 2-alkynylbenzaldoximes **1** with an alkyl group attached to the triple bond were used, which might be due to the lower reactivity of these substrates (Table 3, entry 10).

To clarify the reaction mechanism, a control experiment was carried out (Scheme 2). When the reaction of 2-(phenylethynyl)benzaldehyde oxime **1a** with 4-methylbenzaldehyde **2a** was carried out under standard condition in the presence of 2,2,6,6-tetramethyl-1-piperidin-1-oxyl (TEMPO) as an additive, no desired product **3a** was detected. This result indicated a plausible radical mechanism (Scheme 3). It is proposed that alcohol **4a** was oxidized to aldehyde **2a** by TBHP, which would then react with intermediate **A** via [3 + 2] cyclization to afford compound **B**. The N−O bond of intermediate **B** is unstable and would undergo cleavage to produce radical **C**. Subsequent intramolecular radical rearrangement and aromatization would occur to furnish the unexpected product **3a**.

CONCLUSION

In conclusion, we have developed a highly efficient, novel, and straightforward synthetic protocol for the construction of 4-carboxylated isoquinolines through a Ag(I) and Cu(I) cocatalyzed one-pot reaction of 2-alkynylbenzaldoxime and aldehyde or alcohol in the presence of KI and TBHP under mild conditions starting from easily available materials. The reaction enriches the tool box for the preparation of esters which could be applied in materials science and medicinal chemistry.

EXPERIMENTAL SECTION

General Information. ^{1}H NMR spectra were recorded at 25 °C on a 400 MHz spectrometer. Chemical shifts are reported on the scale relative to tetramethylsilane (0 ppm). ^{13}C NMR spectra were recorded at 25 °C on a 100 MHz spectrometer. Chemical shifts are reported on the scale relative to $CDCl_3$ (77.1 MHz) as an internal reference. HRMS was measured on a micrOTOF II instrument. Melting points were tested with a SGW X-4 microscopic melting point meter, which was made by Shanghai Precision Scientific Instrument Co., Ltd. All reactions were carried out under a nitrogen atmosphere. The progress of all reactions was monitored by TLC on precoated silica gel plates.

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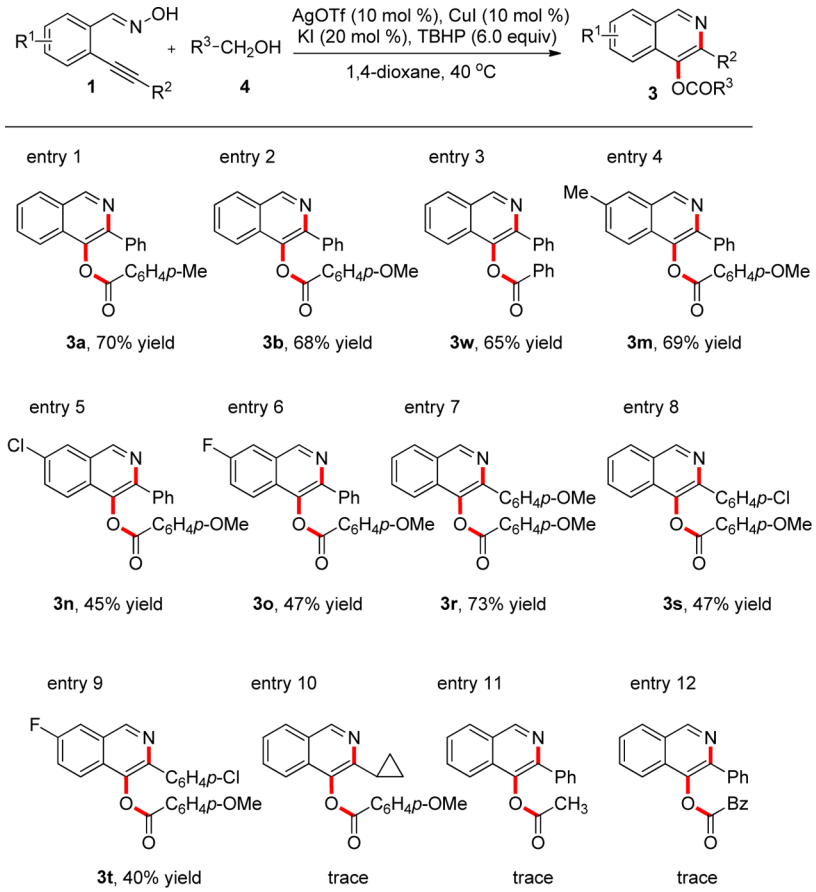
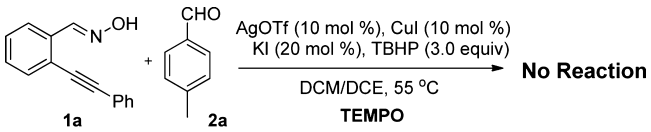
Table 3. AgOTf and CuI Cocatalyzed Reaction of 2-Alkynylbenzaldoxime 1 with Alcohols 4[a]

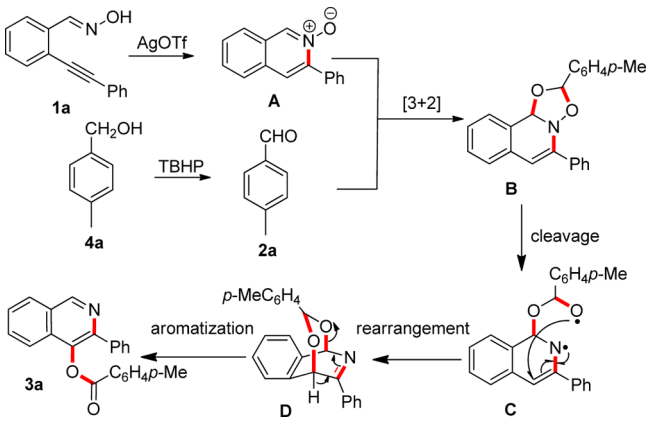


[a]Isolated yield based on 2-alkynylbenzaldoxime **1**.

Scheme 2. Control Experiment



Scheme 3. Plausible Mechanism



Column chromatography was performed using silica gel (60 Å pore size, 32−63 μm, standard grade) with ethyl acetate and petroleum ether as eluent, unless otherwise indicated. Solvents and reagents were obtained from commercial sources. Solvents were anhydrous unless otherwise noted.

General Procedure for Synthesis of Compounds 3 from the Reaction of 2-Alkynylbenzaldoximes 1 with Aldehydes 2. 2-Alkynylbenzaldoxime **1** (0.2 mmol) was added to a solution of silver triflate (10 mol %) in DCE (1.0 mL). After this mixture was stirred at room temperature for 2 h, aldehyde **2** (1.0 mmol), TBHP (0.6 mmol), CuI (10 mol %), KI (20 mol %), and DCM (1.5 mL) were added. Then the mixture was stirred at 55 °C. After completion of the reaction as indicated by TLC, the solvent was evaporated and purified by column chromatography on silica gel to provide the product **3**.

General Procedure for Synthesis of Compounds 3 from the Reaction of 2-Alkynylbenzaldoximes 1 with Alcohols 4. 2-Alkynylbenzaldoxime **1** (0.2 mmol) was added to a solution of silver triflate (10 mol %) in 1,4-dioxane (1.0 mL). After this mixture was stirred at room temperature for 2 h, alcohol **4** (1.0 mmol), TBHP (1.2 mmol), CuI (10 mol %), KI (20 mol %), and 1,4-dioxane (1.0 mL) were added and then the mixture was stirred at 40 °C. After completion of reaction as indicated by TLC, the solvent was evaporated and purified by column chromatography on silica gel to provide the product **3**.

*3-Phenylisoquinolin-4-yl 4-methylbenzoate (**3a**):* 50.2 mg, 74% (Table 1); 47.5 mg, 70% (Table 3); yellow crystalline solid; mp 137.2−137.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.28−7.34 (m, 3H), 7.38 (t, J = 7.2 Hz, 2H), 7.61 (t, J = 7.1 Hz, 1H), 7.69 (t, J = 7.3 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 7.3 Hz, 2H), 8.05 (d, J = 8.1 Hz, 1H), 8.10 (d, J = 8.2 Hz, 2H), 9.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 121.1, 126.0, 127.6, 127.7, 128.1, 128.3, 128.4, 128.5, 128.9, 129.1, 129.4, 129.5, 130.2, 130.4, 131.1, 145.0, 150.2, 164.7; HRMS (ESI) calcd for $C_{23}H_{17}NO_2$ 339.1259 (M), found 339.1258.

*3-Phenylisoquinolin-4-yl 4-methoxybenzoate (**3b**):* 51.1 mg, 72% (Table 1); 48.3 mg, 68% (Table 3); yellow crystalline solid; mp 129.8−130.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 6.98 (d,

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J = 8.9 Hz, 2H), 7.30 (t, J = 7.3 Hz, 1H), 7.38 (t, J = 7.2 Hz, 2H), 7.61 (t, J = 8.0 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.85−7.90 (m, 3H), 8.05 (d, J = 8.1 Hz, 1H), 8.16 (d, J = 8.8 Hz, 2H), 9.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 114.0, 121.0, 121.1, 127.5, 127.6, 128.3, 129.0, 131.0, 131.2, 132.1, 132.5, 137.3, 139.9, 144.5, 150.1, 164.2; HRMS (ESI) calcd for $C_{23}H_{17}NO_3$ 356.1281 (M + H^+), found 356.1298.

*3-Phenylisoquinolin-4-yl 4-chlorobenzoate (**3c**):* 43.1 mg, 60%; yellow crystalline solid; mp 130.2−131.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, J = 7.2 Hz, 1H), 7.38 (t, J = 7.1 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 7.64 (t, J = 7.1 Hz, 1H), 7.72 (t, J = 7.0 Hz, 1H), 7.82−7.87 (m, 3H), 8.07 (d, J = 8.2 Hz, 1H), 8.14 (d, J = 8.6 Hz, 2H), 9.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.8, 127.1, 127.7, 128.4, 128.5, 129.0, 129.1, 129.2, 130.9, 131.2, 131.7, 137.2, 139.6, 140.6, 144.5, 150.4, 163.8; HRMS (ESI) calcd for $C_{22}H_{14}ClNO_2$ 360.0786 (M + H^+), found 360.0803.

*3-Phenylisoquinolin-4-yl 4-(trifluoromethyl)benzoate (**3d**):* 31.4 mg, 40%; yellow crystalline solid; mp 75.8−76.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, J = 7.3 Hz, 1H), 7.39 (t, J = 7.1 Hz, 2H), 7.66 (t, J = 7.1 Hz, 1H), 7.74 (t, J = 6.8 Hz, 1H), 7.81 (t, J = 6.4 Hz, 3H), 7.85 (d, J = 7.3 Hz, 2H), 8.09 (d, J = 8.1 Hz, 1H), 8.32 (d, J = 8.1 Hz, 2H), 9.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.7, 125.8, 125.9, 127.8, 128.4, 128.5, 128.6, 128.8, 128.9, 129.0, 129.0 (q, $^1J_{CF}$ = 272.8 Hz), 129.1, 130.7, 131.3, 132.0, 137.1,144.6, 150.6, 163.4; HRMS (ESI) calcd for $C_{23}H_{14}F_3NO_2$ 394.1049 (M + H^+), found 394.1068.

*3-Phenylisoquinolin-4-yl 4-tert-butylbenzoate (**3e**):* 47.3 mg, 62%; yellow crystalline solid; mp 107.8−108.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 9H), 7.31 (t, J = 7.3 Hz, 1H), 7.39 (t, J = 7.2 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 7.62 (t, J = 8.0 Hz, 1H), 7.69 (t, J = 7.9 Hz, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.90 (d, J = 8.4 Hz, 2H), 8.06 (d, J = 8.1 Hz, 1H), 8.15 (d, J = 8.5 Hz, 2H), 9.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.1, 35.2, 121.1, 125.8, 125.9, 127.5, 127.6, 128.3, 128.4, 129.1, 130.3, 131.1, 137.3, 140.1, 144.5, 150.2, 157.4, 164.6; HRMS (ESI) calcd for $C_{26}H_{23}NO_2$ 382.1802 (M + H^+), found 382.1809.

*3-Phenylisoquinolin-4-yl 2-naphthoate (**3f**):* 45.0 mg, 60%; yellow crystalline solid; mp 112.6−113.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, J = 7.3 Hz, 1H), 7.39 (t, J = 7.2 Hz, 2H), 7.53−7.56 (m, 2H), 7.64 (t, J = 7.3 Hz, 1H), 7.72 (t, J = 7.1 Hz, 1H), 7.89−7.92 (m, 3H), 7.96 (d, J = 8.3 Hz, 1H), 8.07−8.12 (m, 2H), 8.53 (d, J = 87.2 Hz, 1H), 8.77−8.79 (m, 1H), 9.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.0, 124.6, 125.6, 126.6, 127.6, 127.7, 128.4, 128.5, 128.7, 129.1, 129.2, 131.2, 131.3, 131.8, 133.9, 134.7, 137.5, 144.9, 150.3, 165.0; HRMS (ESI) calcd for $C_{26}H_{17}NO_2$ 376.1332 (M + H^+), found 376.1339.

*3-Phenylisoquinolin-4-yl 2-methylbenzoate (**3g**):* 40.7 mg, 60%; yellow crystalline solid; mp 91.2−92.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 7.29 (d, J = 7.6 Hz, 1H), 7.33−7.36 (m, 2H), 7.40 (t, J = 7.1 Hz, 2H), 7.49 (t, J = 6.4 Hz, 1H), 7.64 (t, J = 7.5 Hz, 1H), 7.73 (t, J = 8.1 Hz, 1H), 7.86 (d, J = 7.1 Hz, 2H), 7.90 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.2 Hz, 1H), 8.23 (d, J = 7.8 Hz, 1H), 9.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 121.0, 126.1, 127.6, 127.7, 127.9, 128.4, 128.8, 129.1, 131.1, 131.2, 132.0, 133.0, 137.4, 139.8, 141.7, 144.8, 150.1, 165.0; HRMS (ESI) calcd for $C_{23}H_{17}NO_2$ 340.1332 (M + H^+), found 340.1341.

*3-Phenylisoquinolin-4-yl 2-ethylhexanoate (**3h**):* 45.8 mg, 66%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.4 Hz, 6H), 1.15−1.21 (m, 2H), 1.47−1.73 (m, 6H), 2.53−2.57 (m, 1H), 7.38 (t, J = 7.1 Hz, 1H), 7.45 (t, J = 7.1 Hz, 2H), 7.63 (t, J = 7.0 Hz, 1H), 7.73−7.78 (m, 3H), 7.83 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.2 Hz, 1H), 9.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 13.9, 22.7, 24.7, 29.4, 30.9, 31.7, 47.0, 120.8, 127.7, 128.3, 128.4, 129.1, 129.4, 131.0, 131.1, 137.4, 145.2,149.9, 173.9, 164.2; HRMS (ESI) calcd for $C_{23}H_{25}NO_2$: 348.1958 (M + H^+), found 348.1974.

*3-Phenylisoquinolin-4-yl butyrate (**3i**):* 39.7 mg, 68%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 2.5 Hz, 3H), 1.63−1.72 (m, 2H), 2.56 (t, J = 7.4 Hz, 2H), 7.41 (d, J = 7.3 Hz, 1H), 7.47 (t, J = 7.2 Hz, 2H), 7.64 (t, J = 7.0 Hz, 1H), 7.73−7.77 (m, 1H), 7.81 (t, J = 7.6 Hz, 3H), 8.05 (d, J = 8.2 Hz, 1H), 9.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 19.5, 36.1, 120.8, 127.5, 127.6, 128.3, 128.8, 129.1, 130.4, 131.0, 150.1, 174.0; HRMS (ESI) calcd for $C_{19}H_{17}NO_2$ 292.1332 (M + H^+), found 292.1336.

*3-Phenylisoquinolin-4-yl hexanoate (**3j**):* 39.6 mg, 62%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 6.7 Hz, 3H), 1.29−1.31 (m, 4H), 1.45−1.48 (m, 2H), 2.57 (t, J = 7.5 Hz, 2H), 7.38−7.42 (m, 1H), 7.47 (d, J = 7.1 Hz, 2H), 7.64 (t, J = 8.1 Hz, 1H), 7.73−7.83 (m, 4H), 8.05 (d, J = 8.2 Hz, 1H), 9.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 22.3, 24.4, 31.2, 34.2, 120.8, 127.6, 127.7, 128.3, 128.4, 129.1, 131.1, 150.0, 171.6; HRMS (ESI) calcd for $C_{21}H_{21}NO_2$ 320.1645 (M + H^+), found 320.1658.

*3-Phenylisoquinolin-4-yl cinnamate (**3k**):* 35.8 mg, 51%; yellow crystalline solid; mp 100.3−100.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (d, J = 16.0 Hz, 1H), 7.36 (t, J = 7.4 Hz, 1H), 7.43−7.47 (m, 5H), 7.59−7.61 (m, 2H), 7.64 (t, J = 8.0 Hz, 1H), 7.75 (t, J = 7.0 Hz, 1H), 7.86−7.91 (m, 4H), 8.06 (d, J = 8.2 Hz, 1H), 9.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.2, 121.1, 127.5, 127.6, 128.4, 128.5, 129.0, 129.1, 131.0, 131.1, 133.9, 137.3, 139.7, 144.4, 147.7, 150.2, 164.9; HRMS (ESI) calcd for $C_{24}H_{17}NO_2$ 390.0891 (M + K^+), found 390.0899.

*3-Phenylisoquinolin-4-yl furan-2-carboxylate (**3l**):* 29.6 mg, 47%; yellow crystalline solid; mp 169.8−170.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61−6.62 (m, 1H), 7.34 (t, J = 7.3 Hz, 1H), 7.39−7.45 (m, 3H), 7.65 (t, J = 7.2 Hz, 1H), 7.72 (s, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.89 (d, J = 7.4 Hz, 3H), 8.07 (d, J = 8.1 Hz, 1H), 9.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.3, 120.1, 120.9, 127.6, 127.7, 128.4, 128.5, 129.1, 131.0, 131.2, 137.1, 144.5, 147.6, 150.5, 156.2; HRMS (ESI) calcd for $C_{20}H_{13}NO_3$ 316.0968 (M + H^+), found 316.0980.

*7-Methyl-3-phenylisoquinolin-4-yl 4-methoxybenzoate (**3m**):* 56.1 mg, 76% (Table 2); 50.9 mg, 69% (Table 3); yellow crystalline solid; mp 126.4−127.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (s, 3H), 3.88 (s, 3H), 6.98 (d, J = 8.8 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 7.37 (t, J = 7.8 Hz, 2H), 7.52 (d, J = 8.6 Hz, 1H), 7.74 (t, J = 8.6 Hz, 1H), 7.81 (s, 1H), 7.88 (d, J = 7.2 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H), 9.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 55.6, 114.0, 114.2, 121.0, 121.1, 126.4, 128.2, 128.3, 128.6, 129.0, 129.4, 130.4, 132.5, 133.3, 137.4, 137.7, 143.7, 149.5, 164.2; HRMS (ESI) calcd for $C_{24}H_{19}NO_3$ 370.1438 (M + H^+), found 370.1452.

*7-Chloro-3-phenylisoquinolin-4-yl 4-methoxybenzoate (**3n**):* 45.9 mg, 59% (Table 2); 35.0 mg, 45% (Table 3); yellow crystalline solid; mp 161.1−161.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 6.99 (d, J = 8.9 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 7.38 (t, J = 7.1 Hz, 2H), 7.62 (dd, J = 9.0 Hz, 1.9 Hz, 1H), 7.80 (t, J = 9.0 Hz, 1H), 7.88 (d, J = 7.2 Hz, 2H), 8.03 (d, J = 1.8 Hz, 1H), 8.15 (d, J = 8.9 Hz, 2H), 9.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 114.1, 120.7, 123.1, 126.2, 128.4, 128.5, 129.0, 129.5, 129.6, 132.0, 133.4, 136.9, 139.8, 144.9, 149.0, 164.3; HRMS (ESI) calcd for $C_{23}H_{16}ClNO_3$ 390.0891 (M + H^+), found 390.0902.

*7-Fluoro-3-phenylisoquinolin-4-yl 4-methoxybenzoate (**3o**):* 52.2 mg, 70% (Table 2); 35.1 mg, 47% (Table 3); yellow crystalline solid; mp 133.3−133.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 6.88 (d, J = 8.6 Hz, 1H), 7.00 (d, J = 8.9 Hz, 2H), 7.28−7.33 (m, 1H), 7.38 (t, J = 7.1 Hz, 2H), 7.46−7.51 (m, 1H), 7.67 (dd, J = 8.6 Hz, 2.4 Hz, 1H), 7.87 (d, J = 7.2 Hz, 2H), 8.16 (d, J = 8.9 Hz, 2H), 9.25 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 114.0 (d, $^2J_{CF}$ = 25.2 Hz), 120.8, 121.6 (d, $^2J_{CF}$ = 25.6 Hz), 124.2, 124.3, 128.4, 129.0, 129.8, 132.6, 137.0, 149.2, 161.2 (d, $^1J_{CF}$ = 249.1 Hz), 164.3; HRMS (ESI) calcd for $C_{23}H_{16}FNO_3$ 374.1187 (M + H^+), found 374.1197.

*6-Fluoro-3-phenylisoquinolin-4-yl 4-methoxybenzoate (**3p**):* 47.0 mg, 63%. yellow crystalline solid; mp 131.4−132.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 7.00 (d, J = 8.9 Hz, 2H), 7.32 (t, J = 7.2 Hz, 1H), 7.38 (t, J = 6.9 Hz, 3H), 7.43−7.46 (m, 1H), 7.88 (d, J = 7.2 Hz, 2H), 8.06−8.10 (m, 1H), 8.15 (d, J = 8.9 Hz, 2H), 9.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 105.3 (d, $^2J_{CF}$ = 23.1 Hz), 114.1, 118.2 (d, $^2J_{CF}$ = 25.7 Hz), 120.7, 126.3, 128.4, 128.6, 129.0, 130.8 (d, $^3J_{CF}$ = 9.8 Hz), 132.2, 132.6, 137.0, 145.4, 149.6, 163.9 (d, $^1J_{CF}$ = 252.5 Hz), 164.4; HRMS (ESI) calcd for $C_{23}H_{16}FNO_3$ 374.1187 (M + H^+), found 374.1197.

*5-Methoxy-3-phenylisoquinolin-4-yl 4-methoxybenzoate (**3q**):* 52.4 mg, 68%. yellow crystalline solid; mp 140.1−140.8 °C; ^{1}H

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NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 3.88 (s, 3H), 6.93 (d, J = 8.9 Hz, 1H), 6.99 (t, J = 6.4 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.38 (t, J = 7.2 Hz, 2H), 7.51 (t, J = 7.9 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.84 (d, J = 7.2 Hz, 1H), 8.01 (d, J = 8.9 Hz, 1H), 8.12 (d, J = 8.9 Hz, 2H), 9.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 55.8, 110.0, 113.7, 113.8, 119.9, 122.2, 122.8, 123.1, 128.0, 128.1, 129.4, 132.3, 137.4, 145.4, 149.8, 154.8, 163.7, 163.9, 165.2; HRMS (ESI) calcd for $C_{24}H_{19}NO_4$ 386.1387 (M + H^+), found 386.1420.

*3-(4-Methoxyphenyl)isoquinolin-4-yl 4-methoxybenzoate (**3r**):* 56.2 mg, 73% (Table 2); 56.2 mg, 73% (Table 3); yellow crystalline solid; mp 141.7−142.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.91 (s, 3H), 6.91 (d, J = 8.9 Hz, 2H), 7.01 (d, J = 8.9 Hz, 2H), 7.60 (t, J = 7.1 Hz, 1H), 7.68 (t, J = 7.1 Hz, 1H), 7.82−7.88 (m, 3H), 8.04 (d, J = 8.1 Hz, 1H), 8.19 (d, J = 8.9 Hz, 2H), 9.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 55.6, 113.8, 114.1, 120.9, 121.1, 127.2, 127.6, 128.8, 129.8, 130.3, 130.9, 131.2, 132.5, 139.4, 144.1, 150.0, 159.7, 164.2; HRMS (ESI) calcd for $C_{24}H_{19}NO_4$ 386.1387 (M + H^+), found 386.1384.

*3-(4-Chlorophenyl)isoquinolin-4-yl 4-methoxybenzoate (**3s**):* 47.5 mg, 61% (Table 2); 36.6 mg, 47% (Table 3); yellow crystalline solid; mp 134.4−135.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 7.01 (d, J = 8.9 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 7.64 (t, J = 7.2 Hz, 1H), 7.71 (t, J = 7.0 Hz, 1H), 7.85 (d, J = 8.5 Hz, 3H), 8.06 (d, J = 8.1 Hz, 1H), 8.17 (d, J = 8.9 Hz, 2H), 9.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 114.2, 120.8, 121.1, 127.6, 127.8, 128.6, 130.4, 131.2, 132.6, 134.4, 135.9, 140.0, 143.3, 150.2, 164.4; HRMS (ESI) calcd for $C_{23}H_{16}ClNO_3$ 390.0891 (M + H^+), found 390.0909.

*3-(4-Chlorophenyl)-7-fluoroisoquinolin-4-yl 4-methoxybenzoate (**3t**):* 42.3 mg, 52% (Table 2); 32.6 mg, 40% (Table 3); yellow crystalline solid; mp 193.5−194.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.01 (d, J = 8.9 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 7.46−7.51 (m, 1H), 7.66 (dd, J = 8.0 Hz, 2.4 Hz, 1H), 7.84 (t, J = 8.6 Hz, 2H), 7.86−7.90 (m, 1H), 8.16 (d, J = 8.9 Hz, 2H), 9.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 110.7 (d, $^2J_{CF}$ = 20.9 Hz), 120.5, 121.7 (d, $^2J_{CF}$ = 25.5 Hz), 124.2, 124.3, 128.3, 128.6, 130.3, 132.6, 134.5, 135.5, 143.0, 149.2, 149.3, 161.3 (d, $^1J_{CF}$ = 249.4 Hz), 164.5; HRMS (ESI) calcd for $C_{23}H_{15}ClFNO_3$ 408.0797 (M + H^+), found 408.0818.

*7-Methyl-3-phenylisoquinolin-4-yl 4-methylbenzoate (**3u**):* 52.2 mg, 74%; yellow crystalline solid; mp 77.4−78.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H), 2.58 (s, 3H), 7.34 (t, J = 7.9 Hz, 3H), 7.41 (t, J = 7.3 Hz, 2H), 7.56 (d, J = 8.6 Hz, 1H), 7.78 (d, J = 8.6 Hz, 1H), 7.85 (s, 1H), 7.93 (d, J = 7.4 Hz, 2H), 8.14 (d, J = 8.1 Hz, 2H), 9.25 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 21.8, 120.9, 126.1, 126.3, 128.2, 128.3, 128.7, 129.0, 129.3, 129.5, 130.4, 133.3, 137.4, 137.8, 140.0, 143.6, 144.9, 149.6, 164.7; HRMS (ESI) calcd for $C_{24}H_{19}NO_2$ 354.1489 (M + H^+), found 354.1495.

*3-(4-Methoxyphenyl)isoquinolin-4-yl 4-methylbenzoate (**3v**):* 53.1 mg, 72%; yellow crystalline solid; mp 149.3−149.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3H), 3.82 (s, 3H), 6.94 (d, J = 8.9 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.63 (t, J = 8.1 Hz, 1H), 7.71 (t, J = 8.1 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 9.2 Hz, 2H), 8.07 (d, J = 8.1 Hz, 1H), 8.16 (d, J = 8.2 Hz, 2H), 9.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 55.2, 113.9, 120.9, 126.1, 127.3, 127.6, 128.8, 129.5, 129.8, 130.3, 130.5, 131.0, 131.2, 139.4, 144.2, 144.9, 150.1, 159.7, 164.6; HRMS (ESI) calcd for $C_{24}H_{19}NO_3$ 370.1438 (M + H^+), found 370.1446.

*3-Phenylisoquinolin-4-yl benzoate (**3w**):* 42.3 mg, 65%; yellow crystalline solid; mp 87.8−88.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 7.3 Hz, 1H), 7.36−7.39 (m, 2H), 7.53 (t, J = 7.9 Hz, 2H), 7.63−7.69 (m, 2H), 7.73 (t, J = 7.0 Hz, 1H), 7.88 (t, J = 7.3 Hz, 3H), 8.08 (d, J = 8.1 Hz, 1H), 8.22 (d, J = 8.4 Hz, 2H), 9.32 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.0, 127.0, 127.6, 127.7, 128.4, 128.6, 128.8, 129.0, 130.4, 131.1, 131.2, 134.0, 150.3, 164.7; HRMS (ESI) calcd for $C_{22}H_{15}NO_2$ 326.1176 (M + H^+), found 326.1178.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Tables 4 and 5 giving details of reaction conditions optimization, a table and a CIF file giving X-ray crystal data for compound **3a**, and figures giving ^{1}H and ^{13}C NMR spectra of compounds **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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