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Regioselective Decarboxylative Cross-Coupling of Carboxy Isoquinoline *N*-Oxides

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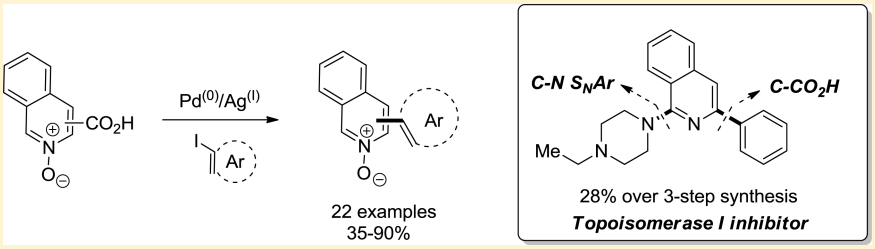
Supporting Information



ABSTRACT: A straightforward method for direct decarboxylative arylation of 1- and 3-carboxy isoquinaldic acid *N*-oxides with aryl iodides is reported. The reaction proceeded selectively at the carboxy function site to exclusively give the corresponding $C\text{-}_1$ or $C\text{-}_3$ arylated product. This methodology tolerates various aryl iodides substituted by electronically different groups. Combined with subsequent Reissert-Henze chlorination and S_NAr amination, the decarboxylative arylation provides an efficient access to 1,3-functionalized isoquinoline-based antitumor agent.

Arylated isoquinoline is a naturally occurring heterocycle found in several alkaloids and in pharmaceuticals with a broad array of biological activities, e.g., antitumor, analgesic, antihistaminic, antimalarial, anti-inflammatory, and antifertility activities (Figure 1).[1] They are also found in a wide variety of

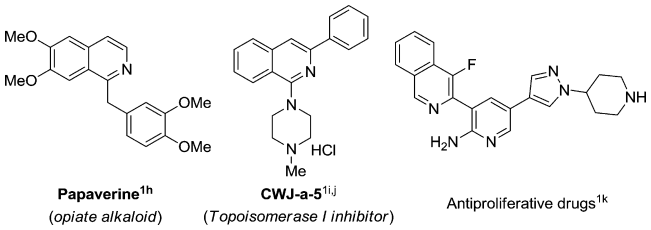


Figure 1. Isoquinoline-containing pharmaceuticals and natural products.

synthetically and functionally valuable compounds in particular as chiral ligands for transition metal catalysts,[2] phosphorescent materials[3] and fluorosensors.[4] Due to their widespread applications, several attractive methodologies have been developed, almost all relying on prearylation before the cyclization.[5−12]

In the current context where cross-coupling process remained a synthetic challenge due the instability of the organometallic species at the $C\text{-}_1$ or $C\text{-}_3$ positions of the isoquinoline core,[13] several direct C_1−H arylation methodologies has been actively developed, mainly from the *N*-oxide derivatives through (i) the direct C−H arylation under palladium catalysis with (pseudo)halides[14] or with carboxyarenes (Scheme 1, eq 1),[15] (ii) the oxidative C−H/C−H cross-coupling devoid of prefunctionalization steps (Scheme 1, eq 2),[14e,16] and (iii) the S_NH-type reaction by the generation of aryl radicals from arylboronic acids (Scheme 1, eq 3).[14e,17] In the context where only the (hetero)arylation at the $C\text{-}_1$ position of the isoquinoline ring has been developed, the substitutive cross-coupling of prefunctionalized isoquinolines appeared as a reliable and appropriate method to fully control the selectivity at the $C\text{-}_1$ and $C\text{-}_3$ positions. Therefore, $C\text{-}_1$ and $C\text{-}_3$ carboxy isoquinolines have been selected as suitable substrates for regioselective catalytic cross-coupling reaction via the selective *in situ* generation of organometallic species by the transition metal-mediated extrusion of CO_2.[18] Since the past decade, the decarboxylative cross-coupling reaction has received remarkable attention since carboxylic acid derivatives are stable, easy to handle and to store, readily available and nontoxic. Since the first example reported by Nilsson,[19] several groups such as Gooßen,[20] Liu,[21] Larossa[22] and Myers[23] have achieved some exciting breakthroughs toward the Pd-catalyzed arylation with aromatic and electron-rich heteroaromatic carboxylic acids.[24−28] However, a very limited number of examples were reported to use π-deficient heteroaryl carboxylic acids.[29]

Recently, our group reported the first decarboxylative cross-coupling of substituted 2-carboxyazine *N*-oxides involving a bimetallic $Pd^{(0)}/Cu^{(I)}$ or $Pd^{(0)}/Ag^{(I)}$ catalysis.[29c] On the basis of our previous results, we report here the selective $C\text{-}_3$ or $C\text{-}_1$ Pd-catalyzed decarboxylative arylation of carboxyisoquinoline *N*-oxides, leading access indifferently to $C\text{-}_1$ or $C\text{-}_3$ arylated

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Scheme 1. Various Isoquinoline *N*-Oxides Coupling

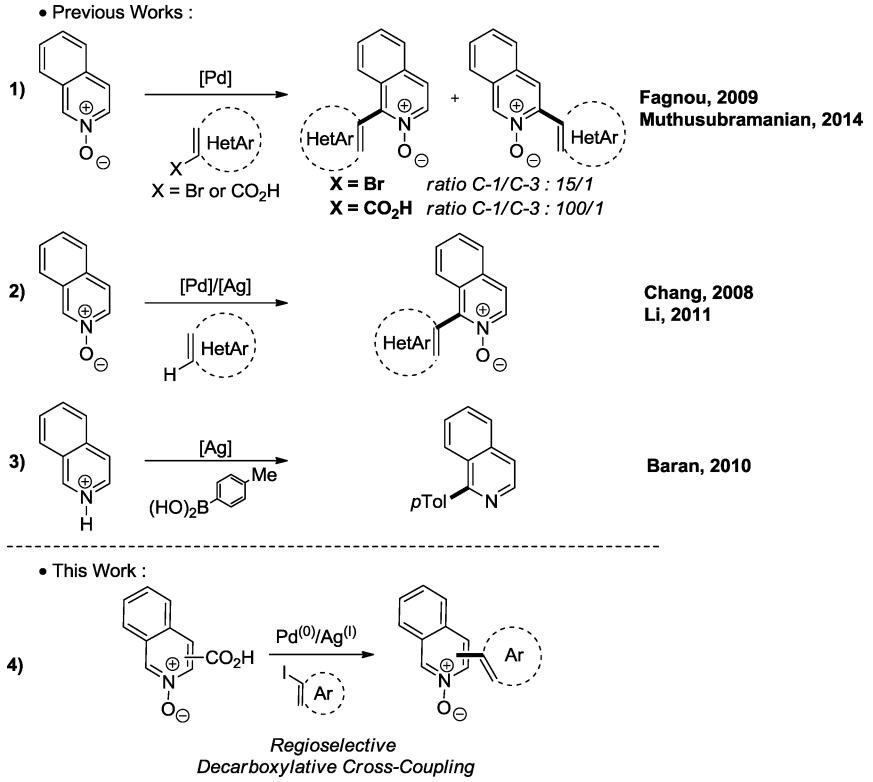
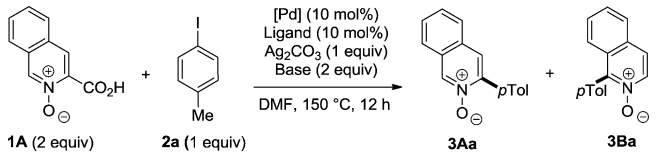


Table 1. Optimization of the Reaction Conditions[a]



entry	[Pd]	base	[Ag]	ligand	yield [%][b] (ratio **3Aa**:**3Ba**)
1[c]	$PdBr_2$	Cs_2CO_3	Ag_2CO_3	$PCy_3{\cdot}HBF_4$	32 (4/1)
2	$PdBr_2$	Cs_2CO_3	Ag_2CO_3	$PCy_3{\cdot}HBF_4$	25 (>99/1)
3	**$PdBr_2$**	**K_2CO_3**	**Ag_2CO_3**	**$PCy_3{\cdot}HBF_4$**	**90 (>99/1)**[d]
4	$PdBr_2$	KOAc	Ag_2CO_3	$PCy_3{\cdot}HBF_4$	8 (1:4)
5	$PdBr_2$	K_2CO_3	AgOAc	$PCy_3{\cdot}HBF_4$	6 (1:4)
6	$PdBr_2$	K_2CO_3	Ag_2O	$PCy_3{\cdot}HBF_4$	61 (>99:1)
7[e]	$PdBr_2$	K_2CO_3	Ag_2CO_3	$PCy_3{\cdot}HBF_4$	44 (>99:1)
8[f]	$PdBr_2$	K_2CO_3	Ag_2CO_3	$PCy_3{\cdot}HBF_4$	54 (>99:1)
9	$Pd(OAc)_2$	K_2CO_3	Ag_2CO_3	$PCy_3{\cdot}HBF_4$	62 (>99:1)
10	$Pd(acac)_2$	K_2CO_3	Ag_2CO_3	$PCy_3{\cdot}HBF_4$	19 (>99:1)
11	$PdBr_2$	K_2CO_3	Ag_2CO_3	PPh_3	66 (>99:1)
12	$PdBr_2$	K_2CO_3	Ag_2CO_3	CyJohnPhos	82 (>99:1)
13[g]	$PdBr_2$	K_2CO_3	Ag_2CO_3	$PCy_3{\cdot}HBF_4$	Trace

[a]Reaction conditions: **1A** (2 equiv), **2a** (0.2 mmol), [Pd] (10 mol %), ligand (10 mol %), Ag_2CO_3 (1 equiv), base (2 equiv), anhydrous DMF, (0.2 M), 150 °C. [b]Yield based on isolated product after flash chromatography. [c]1,4-Dioxane instead of DMF as solvent. [d]With a ratio $PdBr_2/PCy_3{\cdot}HBF_4$ 1:2 the yield was similar. [e]0.5 equiv of Ag_2CO_3 was used. [f]1 equiv of **1A** was used. [g]4-Bromotoluene was used instead of 4-iodotoluene.

isoquinolines, respectively (Scheme 1, eq 4). This unprecedented C-$_3$ arylated protocol was also judiciously combined with a S_NAr process at the C-$_1$ position for a rapid elaboration of highly valuable 1,3-functionalized isoquinoline which has considerable interest as potent anticancer agent.

We initiated our investigations with the 3-carboxyisoquinoline *N*-oxide **1A** as substrate model and *p*-tolyl iodide **2a** as coupling partner. Within initial attempt using our previously designed procedure for quinaldic- and picolinic *N*-oxides series,[29c] the reaction was carried out under bimetallic $PdBr_2$ (10 mol%)/Ag_2CO_3 (1 equiv) catalysis in 1,4-dioxane using Cs_2CO_3 base and $PCy_3{\cdot}HBF_4$ as ligand. The expected 3-arylisoquinoline *N*-oxide **3Aa** was formed as the major product (Table 1, entry 1) of a mixture of isomers, **3Aa** and the 1-aryl isoquinoline *N*-oxide **3Ba** arising from the protodecarboxylative[30−32]/direct C−H arylation side sequence.[33] Interestingly, we found that the reaction is fully selective at the C-$_3$ position using DMF as solvent (Table 1, entry 2) which was further

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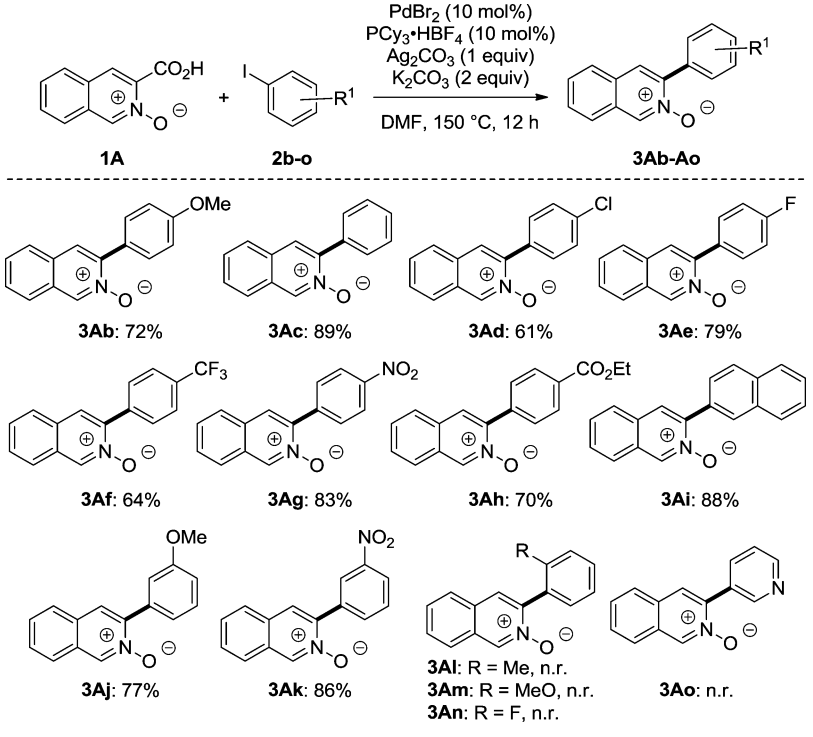
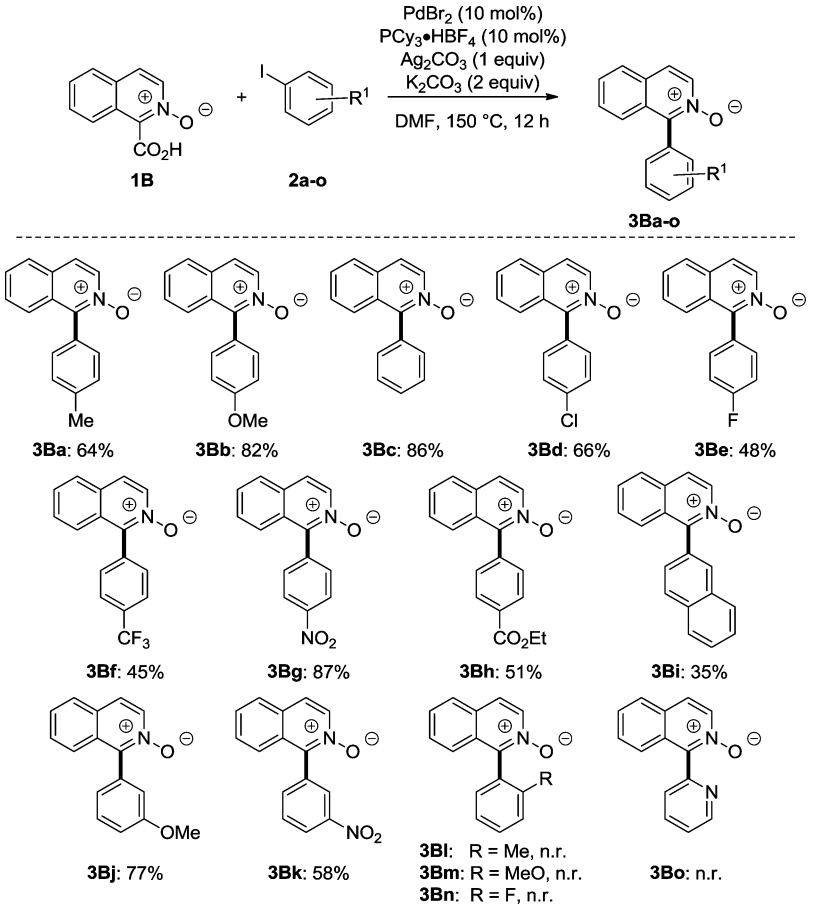
Scheme 2. Scope of the Decarboxylative Cross-Coupling Reaction with Various Iodoarenes 2b−o and 3-Carboxyisoquinoline *N*-Oxide 1A



Scheme 3. Scope of the Decarboxylative Cross-Coupling Reaction with Various Iodoarenes 2b−o and 1-Carboxyisoquinoline *N*-Oxide 1B



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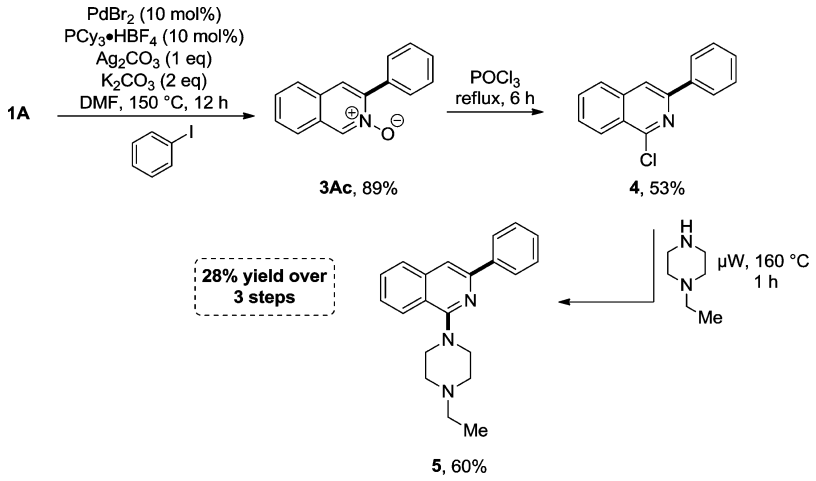
Scheme 4. Synthesis of 1,3-Functionalized Isoquinoline 5, a Potent Antitumor Agent



selected to optimize the performance of the decarboxylative cross-coupling. The yield of **3Aa** was then immediately improved by switching the Cs_2CO_3 to K_2CO_3 as base, whereas KOAc proved to be ineffective (Table 1, entries 3 and 4). Under this K_2CO_3-assistance, the 3-arylated isoquinoline **3Aa** was selectively produced in 90% yield without the formation of the other isomer **3Ba**. We next evaluated other Pd- and Ag-catalyst sources, as well as electronically and bulky different phosphines. Selected results are depicted in Table 1 (entries 5−12). Regarding the source of Pd- and Ag-catalyst, $PdBr_2$ and Ag_2CO_3 were the most powerful pair of catalyst/base. On the other hand, reducing the amount of Ag-catalyst from 1 to 0.5 equiv, along with amount of acid **1A** from 2 to 1.0 equiv, affects the efficiency of the $Pd^{(0)}/Cu^{(I)}$-catalyzed decarboxylative process (Table 1, entries 7 and 8).

The scope of the optimized protocol was then examined (Scheme 2). All envisaged decarboxylative arylations of **1A** were successfully performed with both electron-rich and electron-deficient iodoarenes in high selectivity for the $C\text{-}_3$ position, affording the expected 3-arylated isoquinolines **3Ab**−**3Ak** in fair to excellent yields. Notably, the presence of various substituents such as ester, nitro, methoxy, trifluoromethyl, and halides at the meta or para positions of the iodoarenes are tolerated. On the other hands, the decarboxylative cross-coupling of **1A** with (hetero)aryl as well as the ortho-substituted aryl iodides gave no success.

We next investigated the efficiency of our optimized procedure with the formation of 1-arylated isoquinoline *N*-oxides from the 1-carboxyisoquinoline *N*-oxide (**1B**) (Scheme 3). As first assay, the decarboxylative cross-coupling of **1B** was carried out with the iodotoluene under the optimized protocol. We were pleased to obtain the expected 1-arylated isoquinoline *N*-oxide **3Ba** in 64% yield without trace of the 3-arylated isomer **3Aa**. Overall, the coupling with various iodo arenes was also successfully achieved in fair to good yields whatever the electronic effect of substituted group on aryl iodides. However, only substituents at the meta and para positions are tolerated revealing that steric hindrance has a strong influence on the efficiency of the reaction. Moreover, the full selectivity observed at $C\text{-}_1$ position allows us to discount the decarboxylative cross-coupling/direct C−H arylation sequence since a mixture of $C\text{-}_1$ and $C\text{-}_3$ arylated isoquinoline in a 4:1 ratio was obtained when simple isoquinoline *N*-oxide as substrate was used under our reaction conditions with-4-iodotoluene.[34]

As application herein, the selective direct C_3-CO_2H bonds arylation methodology was here applied to the design of innovative, modular and short synthetic route toward 1,3-functionnalized isoquinolines. Notably, the 3-arylisoquinolines have attracted considerable interest as potent antitumor agent against several types of human tumor cells.[35,36] We focused thus on the neat synthesis of the anticancer chemotherapeutic agent **5** from 3-carboxyisoquinoline *N*-oxide **1A**.[36d] Its preparation was successfully achieved through a three-step sequential combination of decarboxylative arylation at the 3-position with iodobenzene followed by Reissert-Henze reaction[37] and finally S_NAr reaction with *N*-ethylpiperazine (Scheme 4). This innovative sequence provided the expected antitumor agent **5** in 28% overall yield.

In summary, we disclosed the first Pd-catalyzed decarboxylative arylations of 1- and 3-carboxyisoquinoline *N*-oxides with silver as cocatalyst. This innovative method is functional-group tolerant, site-selective and proceeds in moderate to good yields. Moreover, the reported methodology constitutes the *first intermolecular approach enabled to arylate the C-3 position* which has never been reached selectively by Pd-catalyzed direct C−H arylation or by using alternative methods that require organometallic intermediates. As application, a modular and flexible approach has been developed for the synthesis of the highly functionalized 1,3-substituted isoquinoline **5**, an antitumor agent, employing Pd-catalyzed decarboxylative cross-coupling and S_NAr process.

EXPERIMENTAL SECTION

General Comments. Commercially available reagents were used throughout without further purification. Reactions were routinely carried out under an N_2 atmosphere using oven or flame-dried glassware. Melting points were determined on a hot stage melting point apparatus and are uncorrected. ^1H, ^{19}F and ^{13}C NMR spectra were recorded using a 300 spectrometer operating at 300 MHz (^1H frequency, corresponding ^{13}C and ^{19}F frequencies are 75 and 282 MHz). The chemical shifts are calibrated to residual proton and carbon resonance of $CDCl_3$ (^1H 7.26 and ^{13}C 77.16 ppm) or DMSO (^1H 2.52 and ^{13}C 39.5 ppm). In the ^{13}C NMR spectra, signals corresponding to C, CH, CH_2, or CH_3 groups are assigned from DEPT. The obtained signal multiplicities were distinguished with the common abbreviations s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet), hep (heptet), sex (sextet) and the combinations thereof. IR spectra were recorded on a FT-IR intrument. Low resolution mass spectra analyses were performed with spectrometer in chemical ionization. High Resolution Mass spectra (HRMS) were

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performed under ESI conditions with a micro Q-TOF detector. All reactions were monitored by thin-layer chromatography with silica gel 60 F_{254} precoated aluminum plates (0.25 mm). Flash chromatography was performed with the indicated solvents using silica gel 60 (35−70 μm mesh).

General Procedure A. Substrates **1A**−**B** were synthesized according to the literature procedure.[29c] Carboxyisoquinolines (1.0 equiv) and UHP (2.0 equiv) were dissolved in anhydrous CH_2Cl_2 (0.3 M). The mixture was cooled to 0 °C, and trifluoroacetic anhydride (2 equiv) was added dropwise. After 30 min at 0 °C, the mixture was allowed to warm to room temperature and stir for 12 h. A saturated $Na_2S_2O_8$ aqueous solution was added. The aqueous layer was extracted with CH_2Cl_2 (3 times). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. Isoquinoline carboxylic acid *N*-oxides were obtained after trituration with Et_2O followed by filtration and drying under high vacuum.

General Procedure B. A flame-dried tube filled with argon was charged with aryl iodides (1 equiv), carboxyisoquinoline *N*-oxide (2.0 equiv), $PCy_3{\cdot}HBF_4$ (10 mol %), $PdBr_2$ (10 mol %), Ag_2CO_3 (1 equiv), K_2CO_3 (2 equiv), and anhydrous DMF (0.2 M). The tube was sealed and heated to 150 °C for 12 h. The reaction mixture was filtered through a plug of Celite (washed with dichloromethane and MeOH), and the solvents were removed under reduced pressure. The crude product was then purified by flash column chromatography.

Synthesis of Carboxyisoquinoline *N*-Oxides. *3-Carboxyisoquinoline N-Oxide **1A**.* Compound **1A** was prepared from isoquinoline-3-carboxylic acid (500 mg, 2.89 mmol) according to the general procedure A. The desired product was obtained as a colorless solid (455 mg, 2.40 mmol, 83%) after trituration in Et_2O and filtration. The compound exhibited spectra data identical to previous reports.[29c] Mp =226−228 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.96 (s, 2H), 8.08−8.05 (m, 1H), 7.98−7.95 (m, 1H), 7.90−7.86 (m, 2H).

*1-Carboxyisoquinoline N-Oxide **1B**.* Compound **1B** was prepared from isoquinoline-1-carboxylic acid (1.00 g, 5.77 mmol) according to the general procedure A. The desired product was obtained as a colorless solid (0.888 g, 4.67 mmol 81%) after trituration in Et_2O and filtration. The compound exhibited spectra data identical to previous reports.[29c] Mp =150−152 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 9.78 (d, 1H, J = 8.5 Hz), 8.27 (d, 1H, J = 7.1 Hz), 7.98 (d, 1H, J = 7.1 Hz), 7.90−7.78 (m, 3H).

Decarboxylative Cross-Coupling at the C-3 Position. *3-(p-Tolyl)isoquinoline N-Oxide **3Aa**.* The compound **3Aa** was prepared [from 4-iodotoluene (1 equiv, 44 mg, 0.2 mmol), isoquinoline 3-carboxylic acid *N*-oxide **1A** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1.0 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (gradient from EtOAc/PE 8:2 to EtOAc) to afford 3-(*p*-tolyl)isoquinoline *N*-oxide **3Aa** (42 mg, 0.179 mmol) in 90% yield as a yellow solid. The compound exhibited spectra data identical to previous reports.[29c] Mp =135 °C (Et_2O). ^1H NMR (300 MHz, acetone) δ 8.89 (s), 7.98 (s, 1H), 7.94 (d, J = 7.9 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.78 (d, J = 8.2 Hz, 2H), 7.66−7.55 (m, 2H), 7.27 (d, J = 7.9 Hz, 2H), 2.38 (s, 3H).

*3-(4-Methoxyphenyl)isoquinoline N-Oxide **3Ab**.* The compound **3Ab** was prepared [from 1-iodo-4-methoxybenzene (1 equiv, 47 mg, 0.2 mmol), isoquinoline 3-carboxylic acid *N*-oxide **1A** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone 7:3) to afford 3-(4-methoxyphenyl)isoquinoline *N*-oxide **3Ab** (36 mg, 0.143 mmol) in 72% yield as a yellow solid. The compound exhibited spectra data identical to previous reports.[14b] Mp =148 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.78 (m, 4H), 7.73−7.68 (m, 1H), 7.60−7.51 (m, 2H), 7.02 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H).

*3-phenylisoquinoline N-Oxide **3Ac**.* The compound **3Ac** was prepared [from iodobenzene (1 equiv, 41 mg, 22 μL, 0.2 mmol), isoquinoline 3-carboxylic acid *N*-oxide **1A** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone 7:3) to afford 3-phenylisoquinoline *N*-oxide **3Ac** (39 mg, 0.177 mmol) in 89% yield as a yellow solid. The compound exhibited spectra data identical to previous reports.[14b] Mp =149−151 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.83−7.79 (m, 4H), 7.75−7.72 (m, 1H), 7.61−7.58 (m, 2H), 7.52−7.47 (m, 3H).

*3-(4-Chlorophenyl)isoquinoline N-Oxide **3Ad**.* The compound **3Ad** was prepared [from 1-chloro-4-iodobenzene (1 equiv, 48 mg, 0.2 mmol), isoquinoline 3-carboxylic acid *N*-oxide **1A** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone: 7:3) to afford 3-(4-chlorophenyl)-isoquinoline *N*-oxide **3Ad** (31 mg, 0.121 mmol) in 61% yield as a yellow solid. The compound exhibited spectra data identical to previous reports.[38] Mp =193−195 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.82−7.70 (m, 5H), 7.67−7.54 (m, 2H), 7.47 (d, J = 8.2 Hz, 2H).

*3-(4-Fluorophenyl)isoquinoline N-Oxide **3Ae**.* The compound **3Ae** was prepared [from 1-fluoro-4-iodobenzene (1 equiv, 44 mg, 23 μL, 0.2 mmol), isoquinoline 3-carboxylic acid *N*-oxide **1A** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone 7:3) to afford 3-(4-fluorophenyl)-isoquinoline *N*-oxide **3Ae** (38 mg, 0.158 mmol) in 79% yield as a yellow solid. The compound exhibited spectra data identical to previous reports.[39] Mp =190−192 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.86−7.75 (m, 4H), 7.73−7.71 (m, 1H), 7.63−7.55 (m, 2H), 7.18 (t, J = 8.7 Hz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −111.30 (tt, J = 8.6, 5.3 Hz).

*3-(4-(Trifluoromethyl)phenyl)isoquinoline N-Oxide **3Af**.* The compound **3Af** was prepared [from 1-iodo-4-(trifluoromethyl)benzene (1 equiv, 54 mg, 29 μL, 0.2 mmol), isoquinoline 3-carboxylic acid *N*-oxide **1A** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone 7:3) to afford 3-(4-trifluoromethylphenyl)isoquinoline *N*-oxide **3Af** (37 mg, 0.128 mmol) in 64% yield as a yellow solid. Mp =207−209 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.95 (d, J = 8.1 Hz, 2H), 7.83−7.81 (m, 2H), 7.77−7.74 (m, 3H), 7.63−7.58 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.82 (s). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 145.8 (C), 137.3 (CH), 136.5 (C), 131.4 (C, J = 33 Hz), 130.3 (2xCH), 129.7 (CH), 129.4 (C), 129.3 (C), 129.1 (C), 126.9 (CH), 125.4 (CH), 125.3 (CH) 125.2 (CH), 124.7 (CH), 124.1 (C, J = 270 Hz). IR (neat) ν_{max}: 3048, 2962, 1718, 1633, 1599, 1488, 1439, 1407, 1313, 1261, 1237, 1201, 1178, 1162, 1108, 1064, 1017, 959, 919, 897, 875 cm^{-1}. HMRS (ESI-TOF): calcd for $C_{16}H_{11}F_3NO$ 290.0793; found 290.0790.

*3-(4-Nitrophenyl)isoquinoline N-Oxide **3Ag**.* The compound **3Ag** was prepared [from 1-iodo-4-nitrobenzene (1 equiv, 50 mg, 0.2 mmol), isoquinoline 3-carboxylic acid *N*-oxide **1A** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone 7:3) to afford 3-(4-nitrophenyl)-isoquinoline *N*-oxide **3Ag** (44 mg, 0.165 mmol) in 83% yield as a yellow solid. Mp =238−240 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.34 (d, J = 8.9 Hz, 2H), 8.03 (d, J = 8.9 Hz, 2H), 7.85−7.82 (m, 2H), 7.78−7.75 (m, 1H), 7.69−7.60 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 148.3 (C), 144.8 (C), 139.2 (C), 137.4 (CH), 130.9 (2xCH), 130.1 (CH), 129.6 (C), 129.5 (CH), 129.0 (C),

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127.0 (CH), 125.5 (CH), 124.7 (CH), 123.5 (2xCH). IR (neat) ν_{max}: 3018, 1599, 1510, 1438, 1344, 1309, 1260, 1238, 1204, 1173, 1124, 1017, 957, 934, 918, 853 cm^{-1}. HMRS (ESI-TOF): calcd for $C_{15}H_{11}N_2O_3$ 267.0770; found 267.0768.

3-(4-(Ethoxycarbonyl)phenyl)isoquinoline N-Oxide ***3Ah***. The compound **3Ah** was prepared [from ethyl 4-iodobenzoate (1 equiv, 55 mg, 34 μL, 0.2 mmol), isoquinoline 3-carboxylic acid *N*-oxide **1A** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone 7:3) to afford 3-(4-(ethoxycarbonyl)phenyl)isoquinoline *N*-oxide **3Ah** (41 mg, 0.140 mmol) in 70% yield as a yellow solid. The compound exhibited spectra data identical to previous reports.[14b] Mp =205−207 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.16 (d, J = 8.3 Hz, 2H), 7.90 (d, J = 8.3 Hz, 2H), 7.81−7.79 (m, 2H), 7.75−7.72 (m, 1H), 7.64−7.56 (m, 2H), 4.41 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H).

3-(Naphthalen-2-yl)isoquinoline N-Oxide ***3Ai***. The compound **3Ai** was prepared [from 2-iodonaphthalene (1 equiv, 41 mg, 0.16 mmol), isoquinoline 3-carboxylic acid *N*-oxide **1A** (2 equiv, 61 mg, 0.32 mmol), $PdBr_2$ (10 mol %, 4 mg, 0.016 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 6 mg, 0.016 mmol), Ag_2CO_3 (1 equiv, 44 mg, 0.16 mmol), K_2CO_3 (2 equiv, 44 mg, 0.32 mmol), DMF (0.8 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone 7:3) to afford 3-(naphthalen-2-yl)isoquinoline *N*-oxide **3Ai** (38 mg, 0.140 mmol) in 88% yield as a yellow solid. Mp =111−113 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.21 (s, 1H), 7.97−7.85 (m, 5H), 7.79−7.68 (m, 2H), 7.59−7.48 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1 (C), 137.0 (CH), 133.6 (C), 133.1 (C), 130.6 (C), 129.4 (CH), 129.3 (C), 129.1 (CH), 129.0 (C), 128.9 (CH), 128.5 (CH), 127.7 (CH), 127.5 (CH), 126.9 (CH), 126.9 (CH), 126.7 (CH), 126.3 (CH), 125.1 (CH), 124.4 (CH). IR (neat) ν_{max}: 3673, 2986, 2904, 1394, 1249, 1066, 892, 743 cm^{-1}. HMRS (ESI-TOF): calcd for $C_{19}H_{14}NO$ 272.1075; found 272.1072.

3-(3-methoxyphenyl)isoquinoline N-Oxide ***3Aj***. The compound **3Aj** was prepared [from 1-iodo-3-methoxybenzene (1 equiv, 47 mg, 24 μL, 0.2 mmol), isoquinoline 3-carboxylic acid *N*-oxide **1A** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone 7:3) to afford 3-(3-methoxyphenyl)isoquinoline *N*-oxide **3Aj** (38 mg, 0.151 mmol) in 77% yield as a yellow solid. Mp =122−124 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.80−7.77 (m, 2H), 7.74−7.70 (m, 1H), 7.61−7.56 (m, 2H), 7.43−7.32 (m, 3H), 7.03−6.99 (m, 1H), 3.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ^{13}C NMR (75 MHz, CDCl3) δ 159.4 (C), 146.9 (C), 137.4 (CH), 134.1 (C), 129.5 (C), 129.4 (CH), 129.3 (CH), 129.2 (CH), 129.0 (C), 126.8 (CH), 125.1 (CH), 124.7 (CH), 122.2 (CH), 115.6 (CH), 115.1 (CH), 55.5 (CH_3). IR (neat) ν_{max}: 3351, 2929, 1597, 1578, 1489, 1468, 1423, 1313, 1281, 1247, 1212, 1144, 1123, 1087, 1046. 922, 876 cm^{-1}. HMRS (ESI-TOF): calcd for $C_{16}H_{14}NO_2$ 252.1025; found 252.1023.

3-(3-Nitrophenyl)isoquinoline N-Oxide ***3Ak***. The compound **3Ak** was prepared [from 1-iodo-3-nitrobenzene (1 equiv, 50 mg, 0.2 mmol), isoquinoline 3-carboxylic acid *N*-oxide **1A** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone 7:3) to afford 3-(3-nitrophenyl)-isoquinoline *N*-oxide **3Ak** (46 mg, 0.173 mmol) in 86% yield as a yellow solid. Mp =232−234 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.67 (t, J = 1.8 Hz, 1H), 8.34 (dd, J = 8.2 and 1.3 Hz, 1H), 8.26 (d, J = 7.9 Hz, 1H), 7.88−7.83 (m, 2H), 7.79−7.76 (m, 1H), 7.71−7.61 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2 (C), 144.6 (C), 137.3 (C), 136.1 (CH), 134.4 (C), 130.0 (CH), 129.6 (CH), 129.5 (CH), 129.3 (CH), 129.2 (C), 127.0 (CH), 125.4 (CH), 125.0 (CH), 124.8 (CH), 124.4 (CH). IR (neat) ν_{max}: 3100, 3066, 3020, 2924, 1600, 1521, 1463, 1443, 1342, 1317, 1265, 1238, 1169, 1126, 1025, 989, 960, 923, 871, 837, 805 cm^{-1}. HMRS (ESI-TOF): calcd for $C_{15}H_{11}N_2O_3$ 267.0770; found 267.0767.

Decarboxylative Cross-Coupling at the C-1 Position. *1-(p-Tolyl)isoquinoline N-Oxide* ***3Ba***. The compound **3Ba** was prepared [from 4-iodotoluene (1 equiv, 44 mg, 0.2 mmol), isoquinoline 1-carboxylic acid *N*-oxide **1B** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (gradient from EtOAc/PE 8:2 to EtOAc) to afford 1-(*p*-tolyl)isoquinoline *N*-oxide **3Ba** (30 mg, 0.128 mmol) in 64% yield as a yellow solid. The compound exhibited spectra data identical to previous reports.[14b] Mp =129−131 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, J = 7.2 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.59−7.46 (m, 3H), 7.45−7.35 (m, 4H), 2.47 (s, 3H).

1-(4-Methoxyphenyl)isoquinoline N-Oxide ***3Bb***. The compound **3Bb** was prepared [from 1-iodo-4-methoxybenzene (1 equiv, 47 mg, 0.2 mmol), isoquinoline 1-carboxylic acid *N*-oxide **1B** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone 7:3) to afford 1-(4-methoxyphenyl)isoquinoline *N*-oxide **3Bb** (41 mg, 0.163 mmol) in 82% yield as a yellow solid. The compound exhibited spectra data identical to previous reports.[13b] Mp =178−180 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J = 7.2 Hz, 1H), 7.80−7.77 (m, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.65−7.63 (m, 5H), 7.11 (d, J = 8.7 Hz, 2H), 3.90 (s, 3H).

1-Phenylisoquinoline N-Oxide ***3Bc***. The compound **3Bc** was prepared [from iodobenzene (1 equiv, 41 mg, 22 μL, 0.2 mmol), isoquinoline 1-carboxylic acid *N*-oxide **1B** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone 7:3) to afford 1-phenylisoquinoline *N*-oxide **3Bc** (38 mg, 0.172 mmol) in 86% yield as a yellow solid. The compound exhibited spectra data identical to previous reports.[16a,40] Mp =141−143 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, J = 7.2 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.59−7.45 (m, 8H).

1-(4-Chlorophenyl)isoquinoline N-Oxide ***3Bd***. The compound **3Bd** was prepared [from 1-chloro-4-iodobenzene (1 equiv, 48 mg, 0.2 mmol), isoquinoline 1-carboxylic acid *N*-oxide **1B** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone 7:3) to afford 1-(4-chlorophenyl)-isoquinoline *N*-oxide **3Bd** (34 mg, 0.133 mmol) in 66% yield as a yellow solid. The compound exhibited spectra data identical to previous reports.[14b] Mp =191−193 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 7.2 Hz, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.68 (d, J = 7.1 Hz, 1H), 7.58−7.55 (m, 3H), 7.50−7.43 (m, 4H).

1-(4-Fluorophenyl)isoquinoline N-Oxide ***3Be***. The compound **3Be** was prepared [from 1-fluoro-4-iodobenzene (1 equiv, 44 mg, 23 μL, 0.2 mmol), isoquinoline 1-carboxylic acid *N*-oxide **1B** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone 7:3) to afford 1-(4-fluorophenyl)-isoquinoline *N*-oxide **3Be** (23 mg, 0.096 mmol) in 48% yield as a yellow solid. Mp =201−203 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J = 7.2 Hz, 1H), 7.82 (d, J = 7.4 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.59−7.45 (m, 5H), 7.31−7.25 (m, 3H). ^{19}F NMR (282

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MHz, $CDCl_3$) δ −111.1 (tt, J = 8.6 and 5.3 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.9 (C, J = 255 Hz), 145.3(C), 137.5 (CH), 132.5 (2xCH, J = 8 Hz), 129.7 (C), 129.4 (CH), 129.3 (C), 128.5 (CH), 127.1 (CH), 126.8 (C, J = 8 Hz), 125.6 (CH), 123.6 (CH), 116.1 (2xCH, J = 23 Hz). IR (neat) ν_{max}: 2986, 1599, 1514, 1493, 1425, 1394, 1318, 1220, 1154, 1140, 1091, 960, 824 cm^{-1}. HMRS (ESI-TOF): calcd for $C_{15}H_{11}FNO$ 240.0825; found 240.0823.

1-(4-(Trifluoromethyl)phenyl)isoquinoline N-Oxide ***3Bf.*** The compound **3Bf** was prepared [from 1-iodo-4-(trifluoromethyl)benzene (1 equiv, 54 mg, 29 μL, 0.2 mmol), isoquinoline 1-carboxylic acid *N*-oxide **1B** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone 7:3) to afford 1-(4-(trifluoromethyl)phenyl)isoquinoline *N*-oxide **3Bf** (26 mg, 0.090 mmol) in 64% yield as a yellow solid. Mp =204−206 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, J = 7.2 Hz, 1H), 7.85 (m, 3H), 7.74−7.67 (m, 3H), 7.56 (dtd, J = 16.6, 7.0, and 1.2 Hz, 2H), 7.40 (d, J = 8.2 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.83 (s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6 (C), 137.5 (CH), 134.8 (C), 131.5 (C, J = 32 Hz), 130.9 (2xCH), 129.6 (CH), 129.3 (C), 129.2 (C) 128.6 (CH), 127.2 (CH), 125.9 (CH), 125.9 (CH), 125.1 (CH), 124.0 (C, J = 270 Hz), 124.0 (CH). IR (neat) ν_{max}: 3422, 2922, 2854, 1620, 1562, 1495, 1456, 1398, 1321, 1222, 1161, 1107, 1065, 1019 962, 825 cm^{-1}. HMRS (ESI-TOF): calc.dfor $C_{16}H_{11}F_3NO$ 290.0793; found 290.0790.

1-(4-Nitrophenyl)isoquinoline N-Oxide ***3Bg.*** The compound **3Bg** was prepared [from 1-iodo-4-nitrobenzene (1 equiv, 50 mg, 0.2 mmol), isoquinoline 1-carboxylic acid *N*-oxide **1B** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone 7:3) to afford 1-(4-nitrophenyl)-isoquinoline *N*-oxide **3Bg** (46 mg, 0.173 mmol) in 87% yield as a yellow solid. Mp =212−214 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, J = 8.7 Hz, 2H), 8.29 (d, J = 7.2 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.77−7.74 (m, 3H), 7.64−7.52 (m, 2H), 7.37 (d, J = 8.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5 (C), 143.8 (C), 137.7 (C), 137.5 (CH), 131.9 (2xCH), 129.9 (CH), 129.2 (C), 129.1 (C), 128.8 (CH), 127.4 (CH), 124.7 (CH), 124.4 (CH), 124.1 (2xCH). IR (neat) ν_{max}: 1508, 1440, 1397, 1344, 1280, 1222, 1149, 1104, 1059, 987, 958, 853 cm^{-1}.HMRS (ESI-TOF): calcd for $C_{15}H_{10}N_2O_3$ 266.0691; found 266.0690.

1-(4-(Ethoxycarbonyl)phenyl)isoquinoline N-Oxide ***3Bh.*** The compound **3Bh** was prepared [from ethyl 4-iodobenzoate (1 equiv, 55 mg, 34 μL, 0.2 mmol), isoquinoline 1-carboxylic acid *N*-oxide **1B** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone 7:3) to afford 1-(4-(ethoxycarbonyl)phenyl)isoquinoline *N*-oxide **3Bh** (30 mg, 0.102 mmol) in 51% yield as a yellow solid. The compound exhibited spectra data identical to previous reports.[14b] mp =198−200 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.30−8.26 (m, 3H), 7.83 (d, J = 7.6 Hz, 1H), 7.71 (d, J = 7.1 Hz, 1H), 7.64−7.62 (m, 2H), 7.58−7.48 (m, 2H), 7.40 (d, J = 8.1 Hz, 1H), 4.44 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H).

1-(Naphthalen-2-yl)isoquinoline N-Oxide ***3 Bi.*** The compound **3 Bi** was prepared [from 2-iodonaphthalene (1 equiv, 51 mg, 0.2 mmol), isoquinoline 1-carboxylic acid *N*-oxide **1B** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone 7:3) to afford 1-(naphthalen-2-yl)isoquinoline *N*-oxide **3 Bi** (19 mg, 0.070 mmol) in 35% yield as a yellow solid. Mp =135−137 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, J = 7.2 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.99 (s, 1H), 7.94−7.88 (m, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.70−7.64 (m, 2H), 7.60−7.44 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1 (C), 137.4 (CH), 133.6 (C), 133.2 (C), 130.1 (CH), 129.7 (C), 129.2 (C), 129.2 (CH), 128.5 (CH), 128.4 (CH), 128.4 (C), 128.3 (CH), 127.9 (CH), 127.2 (CH), 127.1 (CH), 126.9 (CH), 126.4 (CH), 125.8 (CH), 123.5 (CH). IR (neat) ν_{max}: 2980, 1750, 1605, 1517, 1495, 1450, 1354, 1303, 1245, 1204, 1131, 1072, 1017, 963, 927 cm^{-1}. HMRS (ESI-TOF): calcd for $C_{19}H_{14}NO$ 272.1075; found 272.1071.

1-(3-Methoxyphenyl)isoquinoline N-Oxide ***3Bj.*** The compound **3Bj** was prepared [from 1-iodo-3-methoxybenzene (1 equiv, 47 mg, 24 μL, 0.2 mmol), isoquinoline 1-carboxylic acid *N*-oxide **1B** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone 7:3) to afford 1-(3-methoxyphenyl)isoquinoline *N*-oxide **3Bj** (45 mg, 0.179 mmol) in 90% yield as a yellow solid. The compound exhibited spectra data identical to previous reports.[40] Mp =103−105 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, J = 7.3 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.58−7.48 (m, 4H), 7.09−7.06 (m, 3H), 3.85 (s, 3H).

1-(3-Nitrophenyl)isoquinoline N-Oxide ***3Bk.*** The compound **3Bk** was prepared [from 1-iodo-3-nitrobenzene (1 equiv, 50 mg, 0.2 mmol), isoquinoline 1-carboxylic acid *N*-oxide **1B** (2 equiv, 76 mg, 0.4 mmol), $PdBr_2$ (10 mol %, 5 mg, 0.02 mmol), $PCy_3{\cdot}HBF_4$ (10 mol %, 7 mg, 0.02 mmol), Ag_2CO_3 (1 equiv, 55 mg, 0.2 mmol), K_2CO_3 (2 equiv, 55 mg, 0.4 mmol), DMF (1 mL)] according to the general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/acetone 7:3) to afford 1-(3-nitrophenyl)-isoquinoline *N*-oxide **3Bk** (31 mg, 0.116 mmol) in 58% yield as a yellow solid. Mp =243−245 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.45−8.41 (m, 2H), 8.30 (d, J = 7.2 Hz, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.82−7.75 (m, 2H), 7.64−7.53 (m, 2H), 7.40 (d, J = 8.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6 (C), 143.5 (C), 137.3 (CH), 136.89 (CH), 132.6 (C), 130.0 (CH), 129.9 (CH), 129.2 (C), 129.2 (C), 128.9 (CH), 127.4 (CH), 125.9 (CH), 124.7 (CH), 124.5 (CH), 124.4 (CH). IR (neat) ν_{max}: 3039, 2920, 2853, 1623, 1526, 1502, 1393, 1349, 1321, 1292, 1224, 1141, 1132, 1082, 976, 894 cm^{-1}. HMRS (ESI-TOF): calcd for $C_{15}H_{11}N_2O_3$ 267.0770; found 267.0768.

Synthesis of 1-(4-Ethylpiperazin-1-yl)-3-phenylisoquinoline. *1-Chloro-3-phenylisoquinoline* ***4.*** Phosphoryl chloride (4.6 mL, 0.2 M) was added dropwise to 3-phenylisoquinoline *N*-oxide **3Ac** (200 mg, 0.92 mmol, 1.0 equiv) under N_2 atmosphere. The mixture was refluxed for 6 h, then cooled to room temperature and poured onto ice. A saturated solution of Na_2CO_3 was added dropwise until the solution was basic. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). Combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (PE/AcOEt, 80:20) to afford 1-chloro-3-phenylisoquinoline **4** (117 mg, 0.488 mmol, 53%) as a yellow oil. The compound exhibited spectra data match to previous reports.[41] ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 8.3 Hz, 1H), 8.14−8.11 (m, 2H), 8.00 (s, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.73 (t, J = 7.1 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.53−7.48 (m, 2H), 7.45−7.40 (m, 1H).

1-(4-Ethylpiperazin-1-yl)-3-phenylisoquinoline ***5.*** The compound **5** was prepared following the reported procedure.[42] 1-Chloro-3-phenylisoquinoline **4** (60 mg, 0.25 mmol) and *N*-ethyl piperazine (2.5 mL, 0.1 M) were added to a microwave tube and heated at 160 °C for 1 h. The resulting mixture was diluted with water and extracted with EtOAc. Drying over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc) to afford 1-(4-ethylpiperazin-1-yl)-3-phenyl-isoquinoline **5** (48 mg, 0.15 mmol, 60%) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 7.4 Hz, 2H), 8.08 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.71 (s, 1H), 7.59 (t, J = 7.3 Hz, 1H), 7.51−7.44 (m, 3H), 7.40−7.36 (m, 1H), 3.65−3.62 (m, 4H), 2.82−

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2.79 (m, 4H), 2.60 (q, J = 7.2 Hz, 1H), 1.20 (t, J = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6 (C), 148.3 (C), 139.8 (C), 139.2 (C), 129.8 (CH), 128.7 (2xCH), 128.4 (CH), 127.8 (CH), 126.7 (2xCH), 125.9 (CH), 125.6 (CH), 120.7 (C), 111.3 (CH), 52.9 (2x CH_2), 52.6 (CH_2), 51.0 (2xCH_2), 11.98 (CH_3) IR (neat) ν_{max}: 3056, 2966, 2924, 2808, 1618, 1560, 1498, 1410.3, 1395, 1368, 1264, 1168, 1015, 950, 874 cm^{-1}. HMRS (ESI-TOF): calcd for $C_{21}H_{24}N_3$ 318.1970; found: 318.1967.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00475.

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Notes

The authors declare no competing financial interest.

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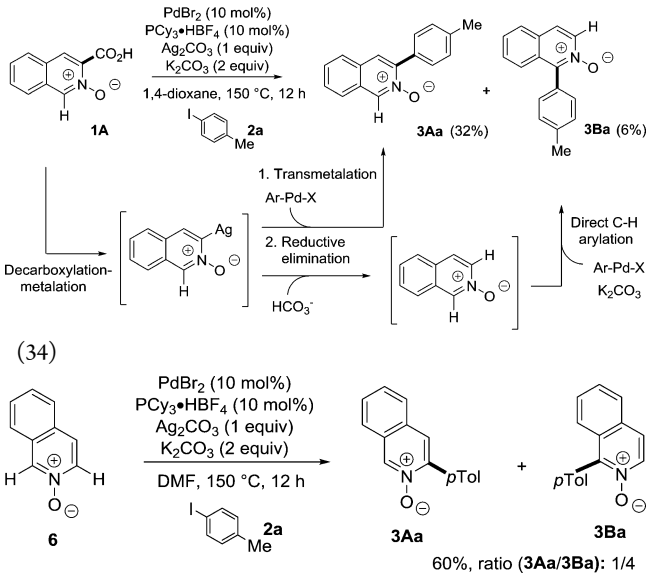

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60%, ratio (**3Aa/3Ba**): 1/4

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