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Note

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

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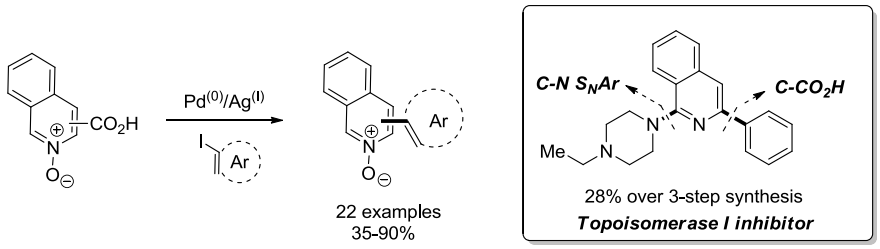


ABSTRACT: A straightforward method for direct decarboxylative arylation of 1- and 3-carboxy isoquinaldic acid *N*-oxides with aryl iodides is reported. The reaction proceeded selectively at the carboxy function site to exclusively give the corresponding $C\text{-}_1$ or $C\text{-}_3$ arylated product. 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.[1] They are also found in a wide variety of 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 pre-arylation before the cyclisation.[5-12]

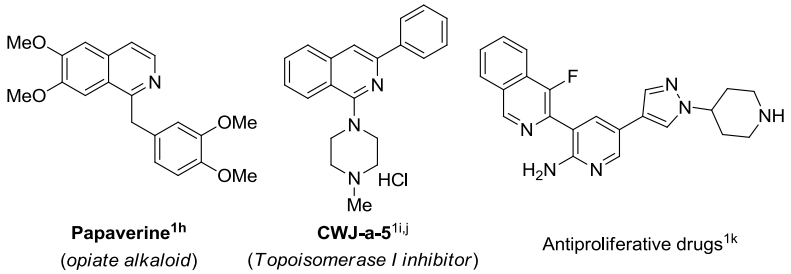
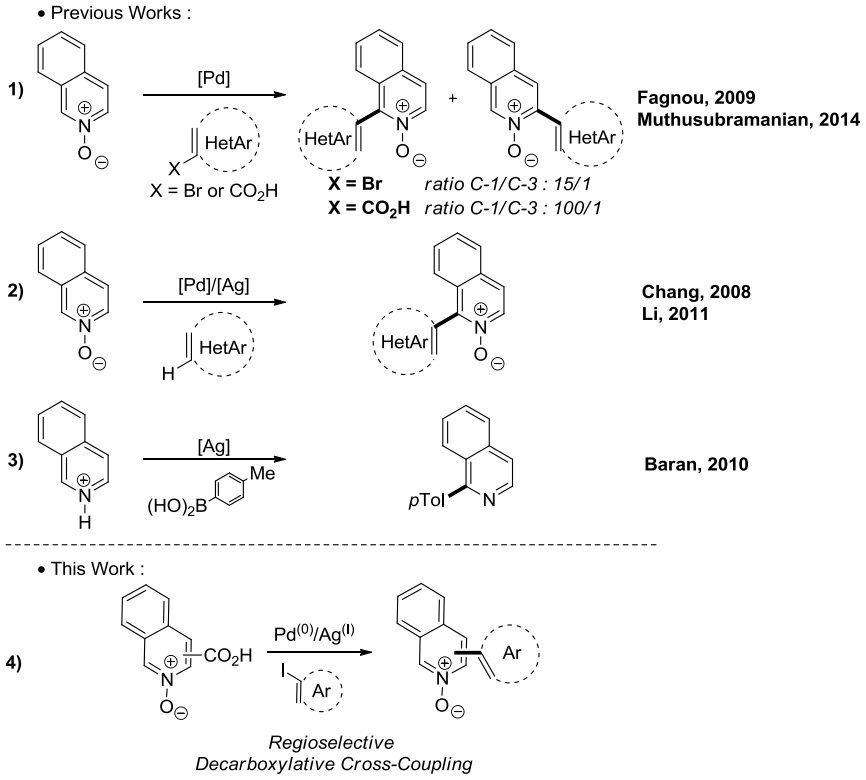


Figure 1. Isoquinoline-containing in pharmaceuticals and natural products

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

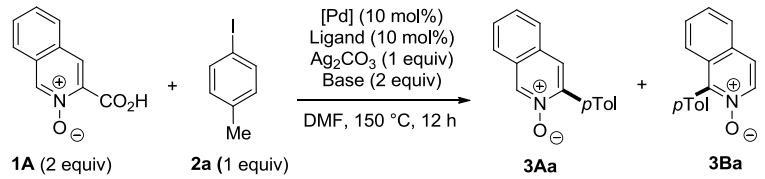
direct C_1–H arylation methodologies has been actively developed, mainly from the *N*-oxide derivatives through i) the direct C–H arylation under palladium catalysis with (pseudo)halides[14] or with carboxyarenes (Scheme 1, eq 1),[15] ii) the oxidative C–H/C–H cross-coupling devoid of prefunctionalization 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_{-1} position of the isoquinoline ring has been developed, the substitutive cross-coupling of pre-functionalized isoquinolines appeared as a reliable and appropriate method to fully control the selectivity at the C_{-1} and C_{-3} positions. Therefore, C_{-1} and C_{-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 Gooβen,[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]

Scheme 1. Various isoquinoline *N*-oxides coupling



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] Based on our previous results, we report here the selective $C\text{-}_3$ or $C\text{-}_1$ Pd-catalyzed decarboxylative arylation of carboxyisoquinoline *N*-oxides respectively leading access indifferently to $C\text{-}_1$ or $C\text{-}_3$ arylated isoquinolines (Scheme 1, eq 4). This unprecedented $C\text{-}_3$ arylated protocol was also judiciously combined with a S_NAr process at the $C\text{-}_1$ position for a rapid elaboration of highly valuable 1,3-functionalized isoquinoline which has considerable interest as potent anticancer agent.

Table 1. Optimization of the reaction conditions[a]



1A (2 equiv) **2a** (1 equiv) **3Aa** **3Ba**

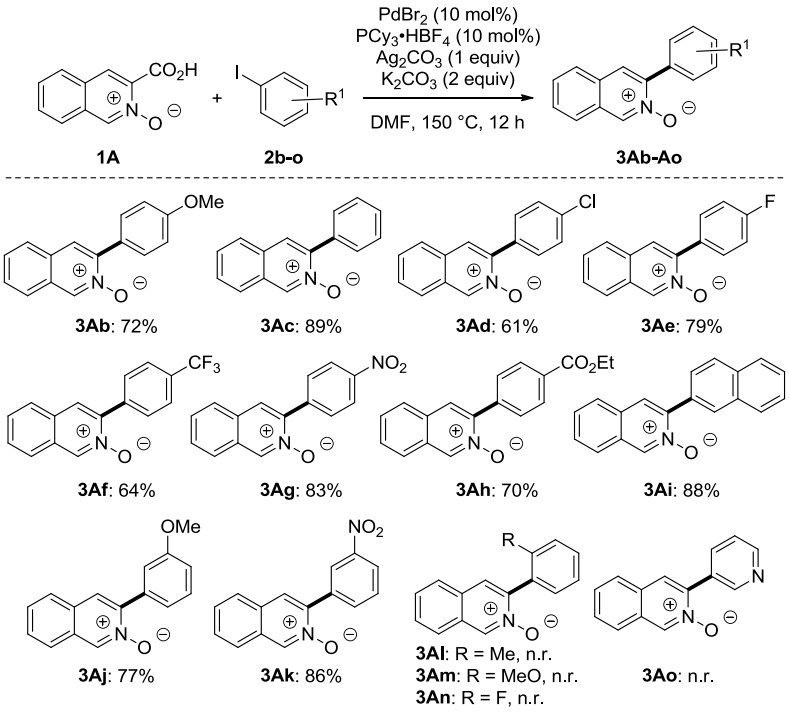
Entry	[Pd]	Base	[Ag]	Ligand	Yield [%][b] (ratio **3Aa**:**3Ba**)
1[c]	$PdBr_2$	Cs_2CO_3	Ag_2CO_3	$PCy_3{\bullet}HBF_4$	32 (4/1)
2	$PdBr_2$	Cs_2CO_3	Ag_2CO_3	$PCy_3{\bullet}HBF_4$	25 (>99/1)
3	**$PdBr_2$**	**K_2CO_3**	**Ag_2CO_3**	**$PCy_3{\bullet}HBF_4$**	**90 (>99/1)[d]**
4	$PdBr_2$	KOAc	Ag_2CO_3	$PCy_3{\bullet}HBF_4$	8 (1:4)
5	$PdBr_2$	K_2CO_3	AgOAc	$PCy_3{\bullet}HBF_4$	6 (1:4)
6	$PdBr_2$	K_2CO_3	Ag_2O	$PCy_3{\bullet}HBF_4$	61 (>99:1)
7[e]	$PdBr_2$	K_2CO_3	Ag_2CO_3	$PCy_3{\bullet}HBF_4$	44 (>99:1)
8[f]	$PdBr_2$	K_2CO_3	Ag_2CO_3	$PCy_3{\bullet}HBF_4$	54 (>99:1)
9	$Pd(OAc)_2$	K_2CO_3	Ag_2CO_3	$PCy_3{\bullet}HBF_4$	62 (>99:1)
10	$Pd(acac)_2$	K_2CO_3	Ag_2CO_3	$PCy_3{\bullet}HBF_4$	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	$PCy_3{\bullet}HBF_4$	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 $PdBr_2/PCy_3{\bullet}HBF_4$ 1:2 the yield was similar. [e]0.5 equivalent of Ag_2CO_3 was used.[f] 1 equivalent of **1A** was used. [g]4-bromotoluene was used instead of 4-iodotoluene.

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 $PCy_3{\bullet}HBF_4$ 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, entries 2) which was further 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 3-4). 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 equivalent, along with amount of acid **1A** from 2 to 1.0 equivalents, affect the efficiency of the $Pd^{(0)}/Cu^{(I)}$-catalyzed decarboxylative process (Table 1, entries 7-8).

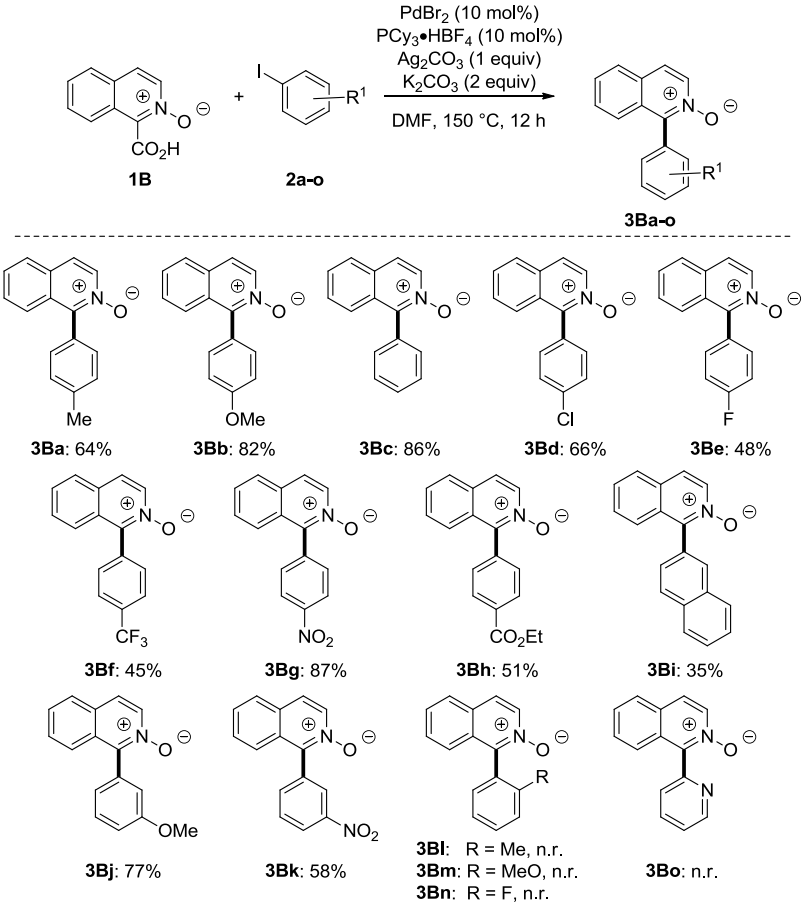
Scheme 2. Scope of the decarboxylative cross-coupling reaction with various iodoarenes 2b-o and 3-carboxyisoquinoline *N*-oxide 1A



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_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]

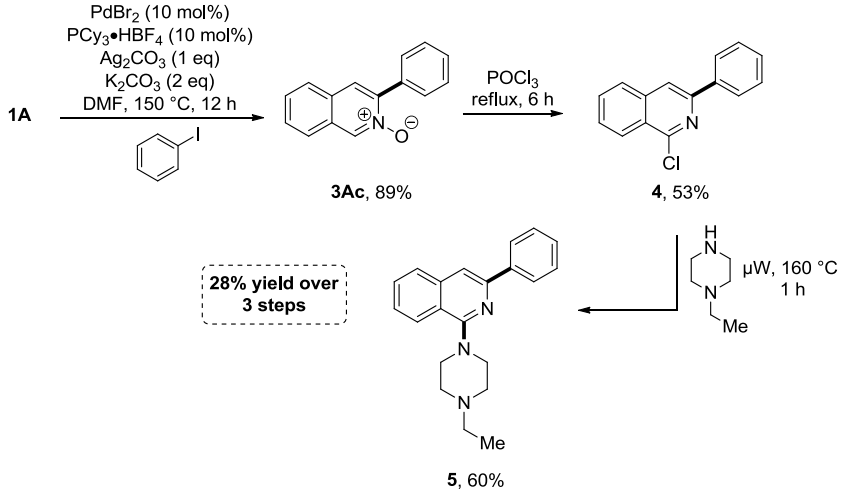
Scheme 3. Scope of the decarboxylative cross-coupling reaction with various iodoarenes 2b-o and 1-carboxyisoquinoline *N*-oxide 1B



As application herein, the selective direct $C_3\text{-}CO_2H$ bonds arylation methodology was here applied to the design of innovative, modular and short synthetic route towards 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.

Scheme 4. Synthesis of 1,3-functionalized isoquinoline 5, a potent antitumor agent



In summary, we disclosed the first Pd-catalyzed decarboxylative arylations of 1- and 3-carboxyisoquinoline *N*-oxides with silver as co-catalyst. 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 enable 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 (^{1}H 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 $CDCl_3$ (^{1}H 7.26 and ^{13}C 77.16 ppm) or DMSO (^{1}H 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 ionisation. High Resolution Mass spectra (HRMS) were performed under ESI conditions with a micro Q-TOF detector. All reactions were monitored by thin-layer chromatography with silica gel 60 F_{254} pre-coated aluminium plates (0.25 mm). Flash chromatography was performed with the indicated solvents using silica gel 60 (35-70 µm mesh).

General procedure A:

Substrate **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 stirred for 12 hour. 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 vaccum.

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•HBF_4 (10 mol%), $PdBr_2$ (10 mol%), Ag_2CO_3 (1 equiv) and K_2CO_3 (2 equiv) and anhydrous DMF (0.2 M). The tube was sealed and heated to 150 °C for 12 hours. 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. 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. 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•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. 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•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. 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•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. Exhibited spectra data identical to previous reports.[14b] mp = 149 – 151 °C (Et_2O). ^{1}H 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•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. Exhibited spectra data identical to previous reports.[38] mp = 193 – 195 °C (Et_2O). ^{1}H 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•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 genral 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. Exhibited spectra data identical to previous reports.[39] mp = 190 – 192 °C (Et_2O). ^{1}H 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•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). ^{1}H 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): calc. 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•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). ^{1}H 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), 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): calc. 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•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. Exhibited spectra data identical to previous reports.[14b] mp = 205 – 207 °C (Et_2O). ^{1}H 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), $PCy_3 \bullet HBF_4$ (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). ^{1}H 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): calc. 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), $PCy_3 \bullet HBF_4$ (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). ^{1}H 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 13C 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): calc. 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), $PCy_3 \bullet HBF_4$ (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). ^{1}H 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): calc. 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•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. Exhibited spectra data identical to previous reports.[14b] mp = 129 – 131 °C (Et_2O). ^{1}H 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•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. Exhibited spectra data identical to previous reports.[13b] mp = 178 – 180 °C (Et_2O). ^{1}H 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•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. Exhibited spectra data identical to previous reports.[16a,40] mp = 141 – 143 °C (Et_2O). ^{1}H 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•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. Exhibited spectra data identical to previous reports.[14b] mp = 191 – 193 °C (Et_2O). ^{1}H 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•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). ^{1}H 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 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): calc. 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•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-trifluoromethylphenyl)isoquinoline *N*-oxide **3Bf** (26 mg, 0.090 mmol) in 64% yield as a yellow solid. mp = 204 – 206 °C (Et_2O). ^{1}H 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. for $C_{16}H_{11}F_3NO$: 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•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). ^{1}H 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): calc. 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•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. Exhibited spectra data identical to previous reports.[14b] mp = 198 – 200 °C (Et_2O). ^{1}H 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 **3Bi**

The compound **3Bi** 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•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 **3Bi** (19 mg, 0.070 mmol) in 35% yield as a yellow solid. mp = 135 – 137 °C (Et_2O). ^{1}H 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): calc. 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•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. Exhibited spectra data identical to previous reports.[40] mp = 103 – 105 °C (Et_2O). ^{1}H 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•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). ^{1}H 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): calc. 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, 0.2M) was added dropwise to 3-phenylisoquinoline *N*-oxyde **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. Exhibited spectra data match to previous reports.[41] ^{1}H 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 hour. 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-phenylisoquinoline **5** (48 mg, 0.15 mmol, 60%) as a pale yellow oil. ^{1}H 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 – 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): calc. for $C_{21}H_{24}N_3$: 318.1970; found: 318.1967.

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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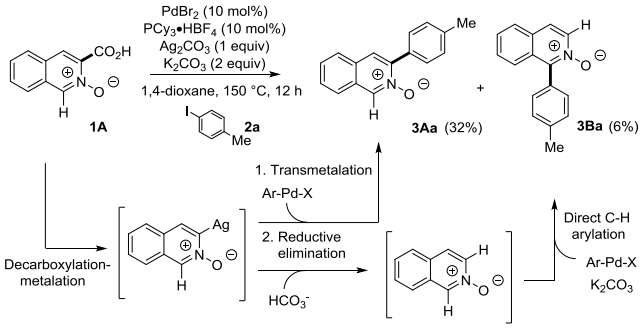
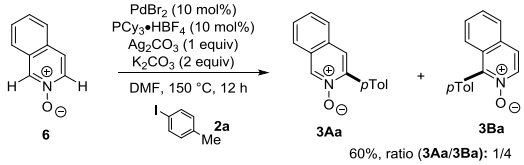


(34)



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