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Nickel-Mediated Synthesis of Isoindolinones at Room Temperature

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Abstract

This communication describes a method for the Ni(cod) ₂-mediated intramolecular arylation of alkyl C–H bonds adjacent to the nitrogen atom in benzamide substrates. The transformation proceeds at room temperature and exhibits selectivity for functionalization of more substituted C–H bonds. The yields of the desired isoindolinone products are higher with benzamide substrates containing tertiary alkyl groups on the nitrogen atom than with those bearing primary or secondary alkyls. The results described herein suggest a mechanism involving radical intermediates for these reactions.

Keywords

amides; arylation; intramolecular; nickel; halides

Palladium-catalyzed direct arylation of both sp² and sp³ C–H bonds has emerged as a powerful strategy for the construction of C–C bonds.^{1,2} Recently, however, there has been an increasing demand to replace precious-metal catalysts with earth-abundant metals.³ The development of nickel-catalyzed C–H arylations, analogous to known Pd-catalyzed transformations, has the potential to significantly enhance the economic viability and synthetic applicability of C–H arylation protocols. In light of this advantage, a number of research groups have described the nickel-catalyzed arylation of C(sp²)–H bonds.^{3,4} In contrast, examples of nickel-catalyzed arylation of alkyl C–H bonds are rare: Liu et al. achieved the nickel-catalyzed oxidative arylation of alkyl C–H bonds by using arylboronic acids (Scheme 1, a) ⁵ and the groups of Chatani and You have reported the intermolecular ligand-directed arylation of sp³ C–H bonds using aryl halides (halide = I, Br) (Scheme 1, b).⁶

Recently, we published an example of nickel-mediated synthesis of isoindolinones through intramolecular coupling of an aryl halide with a C(sp³)–H bond (Scheme 2, a) .^{7,8} Despite the efficiency of these arylations mediated by bis(1,5-cyclooctadiene) nickel(0) [Ni(cod) ₂], their synthetic applicability is limited by the requirement for high temperatures (145°C) . Since our initial report, we have made efforts to address this drawback and have identified

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conditions that allow the analogous nickel-mediated synthesis of isoindolinones to take place at room temperature. Herein, we detail the scope and limitations of these transformations (Scheme 2, b). To our knowledge, these reactions represent the first example of nickel-mediated arylation of sp^3 C–H bonds using aryl halides at ambient temperatures.

Our investigations toward establishing more moderate conditions for nickel-mediated isoindolinone synthesis began with a detailed screen of solvents, bases, and nickel sources for the reaction of benzamide **1-Br** at room temperature (Table 1). As shown in Table 1, the use of $\text{Ni}(\text{cod})_2$ in conjunction with sodium *tert*-butoxide afforded **1a** in a number of solvents at room temperature, albeit in low yields (entries 1–5). Interestingly, however, simple replacement of sodium *tert*-butoxide with potassium *tert*-butoxide enabled excellent yields of **1a** to be obtained after the same period of time (entry 6). Similar cation effects have been observed for C(aryl)–H coupling with aryl halides.⁹ Dioxane and tetrahydrofuran performed equally well as solvents for the arylation using potassium *tert*-butoxide as the base (entries 6 and 7). Importantly, no reaction was observed in the absence of a nickel source. However, a number of nickel(II) salts also induced formation of **1a**, albeit in low yields (entries 9–12). The addition of triphenylphosphine as a potential reductant for nickel(II) did not significantly affect the observed yield of **1a** under these conditions (cf. entries 9, 12 with 13 and 14). As such, conditions employing $\text{Ni}(\text{cod})_2$ in conjunction with potassium *tert*-butoxide in tetrahydrofuran were identified as optimal for the formation of the desired iso-indolinone.

We next investigated the generality of this reaction with respect to electronically varied benzamide substrates. As shown in Table 2, the chloride (**1-Cl**) and iodide (**1-I**) analogues of **1-Br** could also be used to form **1a** in excellent yields (entry 1). Additionally, aryl rings bearing electron-donating (entry 2) or electron-withdrawing substituents (entry 4) underwent the desired transformation to provide isoindolinone products in modest to excellent yields. The moderate yield of product **4a** is partly attributed to a competing $\text{S}_{\text{N}}\text{Ar}$ reaction to yield products (detected by GC/MS analysis of the crude reaction mixtures) in which F is substituted by the *tert*-butoxide anion.

Table 3 depicts the site-selectivities observed for the intra-molecular arylation reaction using substrates that can lead to isomeric products. The site-selectivity for the reaction of **6-Br**, **6-I**, and **7-Br** exemplifies the preference for arylation of more substituted sp^3 C–H bonds. The reaction is more efficient with substrates containing tertiary alkyls on the N atom than those bearing primary or secondary alkyls (entries 1–3 versus 4–7). Interestingly, this selectivity is orthogonal to that documented for palladium-catalyzed arylations.¹⁰ For example, whereas the nickel-mediated reaction of **6-Br** affords **6a** as the major product, isomer **6b** is the observed product under palladium catalysis. Furthermore, benzamides containing two different tertiary *N*-alkyl groups (**8-Br** and **9-Br**) afforded an approximately 1:1 mixture of isomeric isoindolinones (entries 4 and 5). Finally, use of *meta*-substituted amide substrates **10-Cl** and **11-Br** led to a ca. 1:1.5 mixture of isomeric products (entries 6 and 7).

The yield and site-selectivities of the room-temperature arylation shown in Tables 2 and 3 are comparable to those that we previously reported using the $\text{Ni}(\text{cod})_2$ /sodium *tert*-

butoxide conditions at 145°C.⁷ A plausible mechanism consistent with the observed reactivity and selectivity of this system is depicted in Scheme 3. It involves: (i) single electron transfer from a Ni(0) complex to the substrate **A** to generate the radical anion **B**,¹¹ (ii) loss of Br[−] to afford aryl radical **C**, (iii) intramolecular H-atom abstraction to give **D**, (iv) radical addition to the arene to afford isomeric intermediates **E** and **F**, and, finally (v) rearomatization to release the product and regenerate **B**. Importantly, this mechanism is similar to those proposed for potassium *tert*-butoxide mediated coupling of aromatic C–H bonds with aryl halides.^{12–15}

The pathway depicted in Scheme 3 is consistent with a number of observations. First, the diminished yield of the desired products in the presence of a radical scavenger (Scheme 4) implicates the possible involvement of radical intermediates. Second, the preferential functionalization of more substituted tertiary C–H bonds is in agreement with the proposed intermediacy of alkyl radical species such as **D** (Scheme 3). Finally, the negligible site-selectivity observed with *meta*-substituted benzamide substrates is consistent with a fast, unselective radical reaction as depicted in step (iv).

This communication describes a method for the nickel-mediated room-temperature intramolecular arylation of sp³ C–H bonds adjacent to amide nitrogen atoms by using aryl halides (halide = Cl, Br, I). These arylation reactions afford electronically and sterically diverse isoindolinone products in good to excellent yields. In general, the yields of the desired arylated products are higher with substrates bearing electron-rich and electron-neutral aryl rings, and the reactions display selectivity for the functionalization of tertiary over primary and secondary alkyl C–H bonds.

The comparable selectivities of these room-temperature arylations to those obtained in the previously reported Ni(cod)₂/sodium *tert*-butoxide system at 145°C suggest similar mechanistic pathways for the two transformations.

NMR spectra were obtained with a Bruker 400 (399.96 MHz for ¹H; 100.57 MHz for ¹³C) spectrometer. ¹H NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as internal reference. Multiplicities are reported as: singlet (s), doublet (d), doublet of doublets (dd), triplet of doublets (td), triplet (t), multiplet (m), or septet (sept). IR spectra were obtained with a Thermo scientific Nicolet iS5 iD5 ATR spectrophotometer. Melting points were obtained with a Thomas Hoover melting point apparatus.

Anhydrous *t*-BuONa, *t*-BuOK, 2-chlorobenzoyl chloride, anhydrous diisopropylamine, dicyclohexylamine, diisopropylethyl amine, *N*-ethyl-*N*-isopropyl amine, galvinoxyl free radical, thionyl chloride (SOCl₂), and anhydrous Et₃N were obtained from Aldrich and used as received. Ni(cod)₂ was obtained from Strem chemicals and used as received. 2-Bromo-4-fluorobenzoyl chloride and 2-bromo-5-trifluoromethylbenzoic acid were obtained from Matrix Scientific and used as received. 2-Bromobenzoyl chloride was obtained from TCI America and used as received. Substrates **1-Br**,⁷ **1-Cl**,⁷ **1-I**,¹⁴ **2-Br**,⁷ **2-Cl**,⁷ **3-Br**,⁷ **4-Br**,⁷ **4-Cl**,⁷ **5-Br**,⁷ **6-Br**,⁷ **6-I**,¹⁶ and **10-Cl**,⁷ were prepared by following reported procedures. Anhydrous xylene and anhydrous dioxane was obtained from Aldrich and used as received.

Anhydrous CH₂Cl₂, anhydrous THF, and anhydrous Et₂O were purified by using a Glass Contour solvent purification system column composed of neutral alumina. Toluene was purified by using a Glass Contour solvent purification system column composed of neutral alumina and a copper catalyst. DMF was purified with a Glass Contour solvent purification system by passing through a column packed with molecular sieves. Other solvents were obtained from Fisher Chemical or VWR Chemical and used without further purification. Flash chromatography was performed on EM Science silica gel 60 (0.040–0.063mm particle size, 230–400 mesh) and thin-layer chromatography was performed with An-altech TLC plates pre-coated with silica gel 60 F₂₅₄.

2-Bromo-*N*-ethyl-*N*-isopropylbenzamide (7-Br)

To a 100 mL Schlenk flask containing a solution of *N*-ethyl-*N*-iso-propylamine (0.597 g, 6.85 mmol, 1.50 equiv), in anhydrous Et₂O (22 mL) was added diisopropylethylamine (DIPEA; 0.89 g, 6.85 mmol, 1.50 equiv) under a N₂ atmosphere. The reaction mixture was cooled to 0°C using an ice bath and 2-bromobenzoyl chloride (1.00 g, 4.56 mmol, 1.00 equiv) was added dropwise. The resulting mixture was stirred at r.t. for 1 h, then transferred to a separatory funnel using EtOAc (20 mL) and washed with sat. aq NaCl (3×30 mL). The organic layer was dried over MgSO₄, concentrated, and purified by chromatography on a silica gel column (hexanes–EtOAc, 70:30) to afford product **7-Br**.

Yield: 595 mg (48% yield); white solid; mp 96–97°C; *R*_f = 0.40 (hexanes–EtOAc, 70:30).

IR (neat film): 2972, 1622, 1587, 1444, 1420, 1341, 1316, 1216, 1103, 1023, 775, 753, 615cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ (mixture of rotamers) = 7.55 (t, *J* = 7.0Hz, 1H), 7.35–7.31 (m, 1H), 7.27–7.19 (m, 2H), 4.77 (sept, *J* = 6.8Hz, 0.3H), 3.69–3.53 (m, 1.4H), 3.35–3.27 (m, 0.7H), 3.18–3.02 (m, 0.6H), 1.32 (t, *J* = 7.1Hz, 2H), 1.30 (d, *J* = 6.9Hz, 2H), 1.24 (d, *J* = 6.7Hz, 2H), 1.06 (d, *J* = 6.7Hz, 2H), 1.00 (t, *J* = 7.2Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ (mixture of rotamers) = 168.9, 168.2, 139.3, 139.2, 132.8, 132.7, 129.7, 127.7, 127.5, 127.4, 119.1, 50.3, 46.0, 39.0, 35.3, 21.2, 21.1, 20.6, 20.1, 16.2, 14.4.

HRMS: *m/z* [M + Na]⁺ calcd for C₁₂H₁₆BrNO: 292.0307; found: 292.0302.

2-Bromo-*N*-cyclohexyl-*N*-isopropylbenzamide (8-Br)

To a 100 mL Schlenk flask containing a solution of *N*-cyclohexyl-*N*-isopropylamine (0.97 g, 6.85 mmol, 1.50 equiv), in anhydrous Et₂O (22 mL) was added DIPEA (0.885 g, 6.85 mmol, 1.50 equiv) under a N₂ atmosphere. The reaction mixture was cooled to 0°C using an ice bath and 2-bromobenzoyl chloride (1.00 g, 4.56 mmol, 1.00 equiv) was added dropwise. The resulting mixture was stirred at r.t. for 1 h, then transferred to a separatory funnel using EtOAc (20 mL) and washed with sat. aq NaCl solution (3×30 mL). The organic layer was dried over MgSO₄, concentrated, and purified by chromatography on a silica gel column (hexanes–EtOAc, 80:20) to afford **8-Br**.

Yield: 1.44 g (97%) ; white solid; mp 74–76°C; R_f = 0.34 (hexanes–EtOAc, 80:20) .

IR (neat) : 2924, 1624, 1589, 1451, 1436, 1370, 1346, 1325, 992, 764, 749, 737, 693, 647cm⁻¹.

¹H NMR (400 MHz, CDCl₃) : δ (mixture of rotamers) = 7.55 (d, J = 8.0Hz, 1H) , 7.33–7.29 (m, 1H) , 7.21–7.14 (m, 2H) , 3.65–3.50 (m, 1H) , 3.11–2.99 (m, 1H) , 2.76–2.62 (m, 1H) , 2.01–0.90 (m, 15H) .

¹³C NMR (100 MHz, CDCl₃) : δ (mixture of rotamers) = 168.4, 168.2, 140.3, 140.1, 132.82, 132.76, 129.4, 129.3, 127.5, 127.4, 126.50, 126.46, 118.9, 60.0, 54.9, 51.2, 47.2, 31.2, 31.0, 29.9, 29.4, 26.7, 26.5, 25.7, 25.6, 25.3, 25.1, 20.8, 20.6, 20.1.

HRMS: m/z [M + Na]⁺ calcd for C₁₆H₂₂BrNO: 346.0777; found: 346.0787.

2-Bromo-*N*-cyclohexyl-4-fluoro-*N*-isopropylbenzamide (9-Br)

To a 100 mL Schlenk flask containing a solution of *N*-cyclohexyl-*N*-isopropylamine (0.44 g, 3.12 mmol, 1.49 equiv) , in anhydrous Et₂O (11 mL) was added DIPEA (0.41 g, 3.17 mmol, 1.51 equiv) under a N₂ atmosphere. The reaction mixture was cooled to 0°C using an ice bath and 2-bromo-4-fluorobenzoyl chloride (0.5 g, 2.10 mmol, 1.0 equiv) was added dropwise. The resulting mixture was stirred at r.t. for 1 h, then transferred to a separatory funnel using EtOAc (20 mL) and extracted with sat. aq NaCl solution (3×30 mL) . The organic layer was dried over MgSO₄, concentrated, and purified by chromatography on a silica gel column (hexanes–EtOAc, 80:20) to afford product 9-Br.

Yield: 562 mg (78%) ; light-yellow solid; mp 90–91°C; R_f = 0.43 (hexanes–EtOAc, 80:20)
IR (neat) : 2915, 1622, 1595, 1441, 1371, 1355, 1345, 1326, 1260, 1193, 1127, 892, 879, 869, 815, 584cm⁻¹.

¹H NMR (400 MHz, CDCl₃) : δ = 7.30 (dd, J = 8.3, 2.3Hz, 0.5H) , 7.29 (dd, J = 8.3, 2.3Hz, 0.5H) , 7.143 (dd, J = 8.8, 5.8Hz, 0.5H) , 7.136 (dd, J = 8.5, 5.5Hz, 0.5H) , 7.03 (td, J = 8.3, 2.5Hz, 1H) , 3.62–3.49 (m, 1H) , 3.08–2.97 (m, 1H) , 2.70–2.59 (m, 1H) , 1.98–0.91 (m, 15H) .

¹³C NMR (100 MHz, CDCl₃) : δ = 167.6, 167.5, 161.7 (J_{C-F} = 250Hz) , 136.6, 136.5, 127.6 (J_{C-F} = 8.6Hz) , 120.14 (J_{C-F} = 23Hz) , 119.3 (J_{C-F} = 9.5Hz) , 114.9 (J_{C-F} = 21Hz) , 114.8 (J_{C-F} = 21Hz) , 60.1, 55.0, 51.3, 47.2, 31.2, 31.0, 29.9, 29.4, 26.6, 26.5, 25.63, 25.58, 25.2, 25.1, 20.8, 20.6, 20.5, 20.1.

HRMS: m/z [M + Na]⁺ calcd for C₁₆H₂₁BrNO: 364.0683; found: 364.0680.

2-Bromo-*N,N*-diisopropyl-5-(trifluoromethyl) benzamide (11-Br)

To a 20 mL scintillation vial containing a magnetic stirbar and a solution of 2-bromo-5-trifluoromethyl benzoic acid (613 mg, 2.28 mmol, 1.00 equiv) in anhydrous toluene (8.0 mL) were added anhydrous DMF (2 drops) and SOCl₂ (0.33 g, 2.77 mmol, 1.22 equiv) . The vial was sealed with a Teflon-lined cap and the reaction mixture was stirred at 80°C for 2.5 h

and then cooled to r.t. to afford a solution of the intermediate 2-bromo-5-trifluoromethylbenzoyl chloride. Two such reactions were conducted and the solution of the 2-bromo-5-trifluoromethylbenzoyl chloride obtained from each reaction was combined for the next step.

To a 100 mL Schlenk flask containing a solution of *N,N*-diisopropylamine (693 mg, 6.85 mmol, 1.50 equiv), in anhydrous CH₂Cl₂ (23 mL) was added Et₃N (1.39 g, 13.7 mmol, 3.00 equiv) under a N₂ atmosphere. The reaction mixture was cooled to 0°C using an ice bath and the solution of the 2-bromo-5-trifluoromethylbenzoyl chloride obtained in the first step was added dropwise. The resulting mixture was stirred at r.t. for 16 h, then transferred to a separatory funnel and extracted with H₂O (3×30 mL). The organic layer was dried over MgSO₄, concentrated, and purified by chromatography on a silica gel column (hexanes–tOAc, 80:20) to afford product **11-Br**.

Yield: 582 mg (36%); white solid; mp 114–116°C; *R*_f = 0.58 (hexanes–EtOAc, 80:20).

IR (neat): 2977, 1631, 1372, 1344, 1313, 1257, 1172, 1126, 1107, 1076, 1043, 1025, 904, 845, 795, 612 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.70 (d, *J* = 8.3 Hz, 1H), 7.45 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.42 (d, *J* = 2.2 Hz, 1H), 3.55 (sept, *J* = 6.9 Hz, 1H), 3.53 (sept, *J* = 6.7 Hz, 1H), 1.58 (d, *J* = 6.8 Hz, 3H), 1.57 (d, *J* = 6.8 Hz, 3H), 1.25 (d, *J* = 6.6 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 166.7, 140.8, 133.6, 130.2 (*J*_{C–F} = 33 Hz), 126.2 (*J*_{C–F} = 3.6 Hz), 123.45 (*J*_{C–F} = 271 Hz), 123.5 (*J*_{C–F} = 3.6 Hz), 123.0, 51.4, 46.2, 20.7, 20.64, 20.56, 20.0.

HRMS: *m/z* [M + H]⁺ calcd for C₁₄H₁₇BrF₃NO: 352.0518; found: 352.0523.

C–H Arylation; General Procedure

To an oven-dried 20 mL scintillation vial containing a magnetic stir bar and substrate, was added Ni(cod)₂, *t*-BuOK, and anhydrous THF in a glove box. The vial was sealed with a Teflon-lined cap, taken out of the glove box, and the reaction mixture was stirred at r.t. for the indicated time. The reaction mixture was filtered through a 3.8 cm plug of silica gel, eluting with EtOAc (100 mL). The filtrate was concentrated and purified by chromatography on a silica gel column to afford the product.

2-Isopropyl-3,3-dimethylisoindolin-1-one (1a)

From 1-Br

Following the general procedure, **1-Br** (142 mg, 0.500 mmol, 1.00 equiv), Ni(cod)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), *t*-BuOK (84.2 mg, 0.750 mmol, 1.50 equiv), and anhydrous THF (2.00 mL) were combined in a 20 mL scintillation vial. The reaction mixture was stirred at r.t. for 13 h. Chromatography on a silica gel column (hexanes–EtOAc, 70:30) gave **1a**.

Yield: 97.8 mg (96%) ; white solid.

^1H NMR (400 MHz, CDCl_3) : δ = 7.72 (d, J = 7.5 Hz, 1H) , 7.45 (td, J = 7.5, 1.2 Hz, 1H) , 7.34 (td, J = 7.5, 1.0 Hz, 1H) , 7.29 (d, J = 7.6 Hz, 1H) , 3.60 (sept, J = 6.8 Hz, 1H) , 1.51 (d, J = 6.8 Hz, 6H) , 1.42 (s, 6H) . The spectroscopic data is consistent with the literature.⁷

From 1-Cl

Following the general procedure, **1-Cl** (120 mg, 0.500 mmol, 1.00 equiv) , $\text{Ni}(\text{cod})_2$ (13.8 mg, 0.05 mmol, 0.10 equiv) , *t*-BuOK (84.2 mg, 0.750 mmol, 1.50 equiv) and anhydrous THF (2.00 mL) were combined in a 20 mL scintillation vial. The reaction mixture was stirred at r.t. for 21 h. Chromatography on a silica gel column (hexanes–EtOAc, 70:30) gave **1a** (95.5 mg, 94%) as a white solid. The spectroscopic data was identical to the product isolated from the reaction of **1-Br**.

From 1-I

Following the general procedure, **1-I** (166 mg, 0.500 mmol, 1.00 equiv) , $\text{Ni}(\text{cod})_2$ (13.8 mg, 0.05 mmol, 0.10 equiv) , *t*-BuOK (84.2 mg, 0.750 mmol, 1.50 equiv) , and anhydrous THF (2.00 mL) were combined in a 20 mL scintillation vial. The reaction mixture was stirred at r.t. for 21 h. Chromatography on a silica gel column (hexanes–EtOAc, 80:20) gave **1a** (98.0 mg, 96%) as a white solid. The spectroscopic data was identical to the product isolated from the reaction of **1-Br**.

2-Isopropyl-5-methoxy-3,3-dimethylisoindolin-1-one (2a)

From 2-Br

Following the general procedure, **2-Br** (157 mg, 0.500 mmol, 1.00 equiv) , $\text{Ni}(\text{cod})_2$ (13.8 mg, 0.05 mmol, 0.10 equiv) , *t*-BuOK (84.2 mg, 0.750 mmol, 1.50 equiv) , and anhydrous THF (2.00 mL) were combined in a 20 mL scintillation vial. The reaction mixture was stirred at r.t. for 18.5 h. Chromatography on a silica gel column (hexanes–EtOAc, 75:25) gave **2a**.

Yield: 106.9 mg (92%) ; white solid.

^1H NMR (400 MHz, CDCl_3) : δ = 7.68 (d, J = 8.3 Hz, 1H) , 6.92 (dd, J = 8.3, 2.2 Hz, 1H) , 6.80 (d, J = 2.2 Hz, 1H) , 3.87 (s, 3H) , 3.62 (sept, J = 6.8 Hz, 1H) , 1.54 (d, J = 6.8 Hz, 6H) , 1.45 (s, 6H) . The spectroscopic data is consistent with the literature.⁷

From 2-Cl

Following the general procedure, **2-Cl** (135 mg, 0.500 mmol, 1.00 equiv) , $\text{Ni}(\text{cod})_2$ (13.8 mg, 0.05 mmol, 0.10 equiv) , *t*-BuOK (84.2 mg, 0.750 mmol, 1.50 equiv) , and anhydrous THF (2.00 mL) were combined in a 20 mL scintillation vial. The reaction mixture was stirred at r.t. for 12 h. Chromatography on a silica gel column (hexanes–EtOAc, 80:20 to 70:30) gave **2a** (97.4 mg, 83%) as a white solid. The spectroscopic data was identical to the product isolated from the reaction of **2-Br**.

2-Isopropyl-3,3,5-trimethylisoindolin-1-one (3a)

Following the general procedure, **3-Br** (149 mg, 0.500 mmol, 1.00 equiv), Ni(cod)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), *t*-BuOK (84.2 mg, 0.750 mmol, 1.50 equiv), and anhydrous THF (2.00 mL) were combined in a 20 mL scintillation vial. The reaction mixture was stirred at r.t. for 16 h. Chromatography on a silica gel column (hexanes–EtOAc, 75:25) gave **3a**.

Yield: 107.7 mg (99%); white solid.

¹H NMR (400 MHz, CDCl₃): δ = 7.61 (d, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 7.10 (s, 1H), 3.59 (sept, *J* = 6.9 Hz, 1H), 2.40 (s, 3H), 1.51 (d, *J* = 6.9 Hz, 6H), 1.42 (s, 6H). The spectroscopic data is consistent with the literature.⁷

5-Fluoro-2-isopropyl-3,3-dimethylisoindolin-1-one (4a)

From 4-Br

Following the general procedure, **4-Br** (151 mg, 0.500 mmol, 1.00 equiv), Ni(cod)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), *t*-BuOK (84.2 mg, 0.750 mmol, 1.50 equiv), and anhydrous THF (2.00 mL) were combined in a 20 mL scintillation vial. The reaction mixture was stirred at r.t. for 16 h. Chromatography on a silica gel column (hexanes–EtOAc, 80:20) gave **4a**.

Yield: 56.6 mg (51%); white solid.

¹H NMR (400 MHz, CDCl₃): δ = 7.72 (dd, *J* = 8.3, 5.1 Hz, 1H), 7.07 (td, *J* = 8.4, 2.1 Hz, 1H), 7.00 (dd, *J* = 8.2, 2.2 Hz, 1H), 3.61 (sept, *J* = 6.9 Hz, 1H), 1.53 (d, *J* = 6.8 Hz, 6H), 1.46 (s, 6H). The spectroscopic data is consistent with the literature.⁷

From 4-Cl

Following the general procedure, **4-Cl** (129 mg, 0.500 mmol, 1.00 equiv), Ni(cod)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), *t*-BuOK (84.2 mg, 0.750 mmol, 1.50 equiv), and anhydrous THF (2.00 mL) were combined in a 20 mL scintillation vial. The reaction mixture was stirred at r.t. for 15 h. Chromatography on a silica gel column (hexanes–EtOAc, 80:20) gave **4a** (82.4 mg, 74%) as a white solid. The spectroscopic data was identical to the product isolated from the reaction of **4-Br**.

2'-Cyclohexylspiro(cyclohexane-1,1'-isoindolin)-3'-one (5a)

Following the general procedure, **5-Br** (182 mg, 0.500 mmol, 1.00 equiv), Ni(cod)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), *t*-BuOK (84.2 mg, 0.750 mmol, 1.50 equiv), and anhydrous THF (2.00 mL) were combined in a 20 mL scintillation vial. The reaction mixture was stirred at r.t. for 20 h. Chromatography on a silica gel column (hexanes–EtOAc, 80:20) gave **5a**.

Yield: 136.4 mg (96%); white solid.

^1H NMR (400 MHz, CDCl_3) : δ = 7.76 (d, J = 7.0 Hz, 1H) , 7.71 (d, J = 7.1 Hz, 1H) , 7.43–7.34 (m, 2H) , 3.12–3.04 (m, 1H) , 2.64–2.51 (m, 2H) , 1.94–1.21 (m, 18H) . The spectroscopic data is consistent with the literature.⁷

2'-Methylspiro[cyclohexane-1,1'-isoindolin]-3'-one (6a)

From 6-Br

Following the general procedure, **6-Br** (148 mg, 0.500 mmol, 1.00 equiv) , $\text{Ni}(\text{cod})_2$ (27.5 mg, 0.10 mmol, 0.20 equiv) , *t*-BuOK (84.2 mg, 0.750 mmol, 1.50 equiv) , and anhydrous THF (2.00 mL) were combined in a 20 mL scintillation vial. The reaction mixture was stirred at r.t. for 21 h. Chromatography on a silica gel column (hexanes–EtOAc, 70:30) gave **6a**.

Yield: 48.2 mg (45%) ; white solid.

^1H NMR (400 MHz, CDCl_3) : δ = 7.85 (d, J = 7.0 Hz, 1H) , 7.76 (d, J = 7.4 Hz, 1H) , 7.47 (td, J = 7.4, 1.5 Hz, 1H) , 7.42 (td, J = 7.4, 1.2 Hz, 1H) , 3.01 (s, 3H) , 2.01–1.82 (m, 7H) , 1.45–1.30 (m, 3H) . The spectroscopic data is consistent with the literature.⁷

From 6-I

Following the general procedure, **6-I** (172 mg, 0.500 mmol, 1.00 equiv) , $\text{Ni}(\text{cod})_2$ (27.5 mg, 0.10 mmol, 0.20 equiv) , *t*-BuOK (84.2 mg, 0.750 mmol, 1.50 equiv) , and anhydrous THF (2.00 mL) were combined in a 20 mL scintillation vial. The reaction mixture was stirred at r.t. for 21 h. Chromatography on a silica gel column (hexanes–EtOAc, 70:30) gave **6a** (56.1 mg, 52%) as a white solid. The spectroscopic data was identical to the product isolated from the reaction of **6-Br**.

2-Ethyl-3,3-dimethylisoindolin-1-one (7a)

Following the general procedure, **7-Br** (135 mg, 0.500 mmol, 1.00 equiv) , $\text{Ni}(\text{cod})_2$ (27.5 mg, 0.10 mmol, 0.20 equiv) , *t*-BuOK (84.2 mg, 0.750 mmol, 1.50 equiv) , and anhydrous THF (2.00 mL) were combined in a 20 mL scintillation vial. The reaction mixture was stirred at r.t. for 21 h. Chromatography on a silica gel column (hexanes–acetone– CH_2Cl_2 , 80:5:15) gave **7a**.

Yield: 57.1 mg (60%) ; white solid; mp 90–91°C; R_f = 0.13 (hexanes–acetone– CH_2Cl_2 , 80:5:15) .

IR (neat) : 2972, 1671, 1397, 1371, 1351, 1320, 767, 699, 689, 565 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) : δ = 7.78 (d, J = 7.5 Hz, 1H) , 7.49 (td, J = 7.4, 0.7 Hz, 1H) , 7.40–7.34 (m, 2H) , 3.49 (q, J = 7.2 Hz, 2H) , 1.46 (s, 6H) , 1.28 (t, J = 7.2 Hz, 3H) .

^{13}C NMR (100 MHz, CDCl_3) : δ = 167.2, 151.5, 131.3, 131.0, 127.8, 123.3, 120.5, 62.6, 33.9, 25.9, 14.6.

HRMS: m/z [$\text{M} + \text{Na}$]⁺ calcd for $\text{C}_{12}\text{H}_{15}\text{NO}$: 212.1046; found: 212.1047.

2'-Isopropylspiro(cyclohexane-1,1'-isoindolin)-3'-one and 2-Cyclohexyl-3,3-dimethylisoindolin-1-one (**8a** and **8b**)

Following the general procedure, **8-Br** (162 mg, 0.500 mmol, 1.00 equiv), Ni(cod)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), *t*-BuOK (84.2 mg, 0.750 mmol, 1.50 equiv), and anhydrous THF (2.00 mL) were combined in a 20 mL scintillation vial. The reaction mixture was stirred at r.t. for 21 h. Chromatography on a silica gel column (hexanes–acetone–CH₂Cl₂, 85:5:10) gave a mixture of products **8a** and **8b** (102.1 mg, 84%) as a white solid. Note: Although the total yield is reported for the mixture of **8a** and **8b**, small amounts of pure **8a** and **8b** were isolated to obtain the following spectroscopic and HRMS data.

Isomer **8a**

R_f = 0.14 (hexanes–acetone–CH₂Cl₂, 85:5:10); mp 119–120°C.

IR (neat): 2926, 1676, 1468, 1411, 1377, 1331, 1326, 765, 700, 561 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.82–7.80 (m, 1H), 7.75 (d, *J* = 6.8 Hz, 1H), 7.47–7.40 (m, 2H), 3.64 (sept, *J* = 6.8 Hz, 1H), 1.97–1.84 (m, 7H), 1.55 (d, *J* = 6.8 Hz, 6H), 1.49–1.45 (m, 2H), 1.40–1.24 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 167.2, 150.1, 132.6, 130.3, 127.6, 123.2, 123.1, 65.8, 44.4, 33.0, 24.6, 22.5, 20.4.

HRMS: *m/z* [M + Na]⁺ calcd for C₁₆H₂₁NO: 266.1515; found: 266.1513.

Isomer **8b**

R_f = 0.18 (hexanes–acetone–CH₂Cl₂, 85:5:10); mp 141–142°C.

IR (neat): 2953, 2932, 2857, 1672, 1614, 1469, 1451, 1414, 1364, 1325, 764, 699 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.76 (d, *J* = 7.5 Hz, 1H), 7.49 (td, *J* = 7.4, 0.8 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 3.18–3.10 (m, 1H), 2.60–2.50 (m, 2H), 1.87–1.80 (m, 2H), 1.70–1.60 (m, 3H), 1.47 (s, 6H), 1.36–1.25 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 167.0, 151.1, 132.0, 131.1, 127.8, 123.2, 120.5, 63.3, 53.1, 30.1, 26.5, 25.5, 25.2.

HRMS: *m/z* [M + Na]⁺ calcd for C₁₆H₂₁NO: 266.1515; found: 266.1512.

6'-Fluoro-2'-isopropylspiro(cyclohexane-1,1'-isoindolin)-3'-one and 2-Cyclohexyl-5-fluoro-3,3-dimethylisoindolin-1-one (**9a** and **9b**)

Following the general procedure, **9-Br** (171 mg, 0.50 mmol, 1.00 equiv), Ni(cod)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), *t*-BuOK (84.2 mg, 0.75 mmol, 1.50 equiv), and anhydrous THF (2.00 mL) were combined in a 20 mL scintillation vial. The reaction mixture was stirred at r.t. for 21 h. Chromatography on a silica gel column (hexanes–acetone–CH₂Cl₂,

80:5:15) gave a mixture of products **9a** and **9b** (119 mg, 91%) as a white solid. Note: Although the total yield is reported for the mixture of **9a** and **9b**, small amounts of pure **9a** and **9b** were isolated to obtain the following spectroscopic and HRMS data.

Isomer 9a

R_f = 0.33 (hexanes–acetone–CH₂Cl₂, 80:5:15) ; mp 122–124°C.

IR (neat) : 2940, 1676, 1413, 1364, 1330, 1169, 961, 896, 884, 834, 785, 755, 695, 654 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) : δ = 7.77 (dd, J = 8.3, 5.4 Hz, 1H) , 7.43 (dd, J = 9.3, 2.1 Hz, 1H) , 7.12 (td, J = 8.7, 2.2 Hz, 1H) , 3.62 (sept, J = 6.8 Hz, 1H) , 1.96–1.24 (m, 10H) , 1.54 (d, J = 6.8 Hz, 6H) .

¹³C NMR (100 MHz, CDCl₃) : δ = 166.3, 164.1 (J_{C-F} = 248 Hz) , 152.1 (J_{C-F} = 9.0 Hz) , 128.6, 125.0 (J_{C-F} = 9.7 Hz) , 115.1 (J_{C-F} = 23 Hz) , 110.9 (J_{C-F} = 25 Hz) , 65.5, 44.5, 32.9, 24.5, 22.4, 20.4.

HRMS: m/z [M + Na]⁺ calcd for C₁₆H₂₀FNO: 284.1421; found: 284.1425.

Isomer 9b

R_f = 0.40 (hexanes–acetone–CH₂Cl₂, 80:5:15) ; mp 167–168°C.

IR (neat) : 2926, 1674, 1624, 1485, 1410, 1362, 1325, 1214, 1179, 901, 890, 829, 778, 704, 693, 610 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) : δ = 7.73 (dd, J = 8.3, 5.0 Hz, 1H) , 7.08 (td, J = 8.8, 2.3 Hz, 1H) , 7.00 (dd, J = 8.3, 2.2 Hz, 1H) , 3.17–3.09 (m, 1H) , 2.57–2.47 (m, 2H) , 1.90–1.82 (m, 2H) , 1.66–1.60 (m, 3H) , 1.46 (s, 6H) , 1.31–1.25 (m, 3H) .

¹³C NMR (100 MHz, CDCl₃) : δ = 166.1, 165.0 (J_{C-F} = 249 Hz) , 153.5 (J_{C-F} = 8.9 Hz) , 127.9, 125.3 (J_{C-F} = 9.8 Hz) , 115.5 (J_{C-F} = 23 Hz) , 108.0 (J_{C-F} = 24 Hz) , 63.0, 53.2, 30.1, 26.5, 25.4, 25.1.

HRMS: m/z [M + Na]⁺ calcd for C₁₆H₂₀FNO: 284.1421; found: 284.1423.

2-Isopropyl-3,3,6-trimethylisoindolin-1-one and 2-Isopropyl-3,3,4-trimethylisoindolin-1-one (10a and 10b)

Following the general procedure, **10-Cl** (127 mg, 0.500 mmol, 1.00 equiv) , Ni(cod)₂ (13.8 mg, 0.05 mmol, 0.10 equiv) , *t*-BuOK (84.2 mg, 0.750 mmol, 1.50 equiv) , and anhydrous THF (2.00 mL) were combined in a 20 mL scintillation vial. The reaction mixture was stirred at r.t. for 21 h. Chromatography on a silica gel column (hexanes–EtOAc–CH₂Cl₂, 80:10:10) gave a mixture of products **10a** and **10b** (**10a/10b** = 1.1:1) . Yield: 99.5 mg (92%) ; clear oil.

^1H NMR (400 MHz, CDCl_3) : δ (**10a**) = 7.56 (s, 1H) , 7.30 (d, J = 7.7Hz, 1H) , 7.21 (d, J = 7.7Hz, 1H) , 3.62 (sept, J = 6.8Hz, 1H) , 2.41 (s, 3H) , 1.54 (d, J = 6.9Hz, 6H) , 1.44 (s, 6H) . The spectroscopic data is consistent with the literature.⁷

^1H NMR (400 MHz, CDCl_3) : δ (**10b**) = 7.62 (d, J = 7.2Hz, 1H) , 7.31–7.24 (m, 2H) , 3.63 (sept, J = 6.8Hz, 1H) , 2.47 (s, 3H) , 1.56 (d, J = 6.9Hz, 6H) , 1.53 (s, 6H) . The spectroscopic data is consistent with the literature.⁷

2-Isopropyl-3,3-dimethyl-6-(trifluoromethyl) isoindolin-1-one and 2-Isopropyl-3,3-dimethyl-4-(trifluoromethyl) isoindolin-1-one (**11a** and **11b**)

Following the general procedure, **11-Br** (176 mg, 0.500 mmol, 1.00 equiv) , $\text{Ni}(\text{cod})_2$ (27.5 mg, 0.10 mmol, 0.20 equiv) , $t\text{-BuOK}$ (84.2 mg, 0.750 mmol, 1.50 equiv) , and anhydrous THF (2.00 mL) were combined in a 20 mL scintillation vial. The reaction mixture was stirred at r.t. for 21 h. Chromatography on a silica gel column (hexanes–EtOAc– CH_2Cl_2 , 80:10:10) gave **11a** and **11b** (71.3 mg, 53%) as a white solid. Note: Although the total yield is reported for the mixture of **11a** and **11b**, small amounts of pure **11a** and **11b** were isolated to obtain the following spectroscopic and HRMS data.

Isomer **11a**

R_f = 0.33 (hexanes–EtOAc, 85:15) ; mp 133–135°C. IR (neat) : 2976, 1678, 1322, 1279, 1159, 1113, 1077, 1049, 907, 852, 794, 655, 631 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) : δ = 8.04 (s, 1H) , 7.77 (d, J = 7.9Hz, 1H) , 7.47 (d, J = 7.9Hz, 1H) , 3.66 (sept, J = 6.8Hz, 1H) , 1.56 (d, J = 6.8Hz, 6H) , 1.51 (s, 6H) .

^{13}C NMR (100 MHz, CDCl_3) : δ = 165.7, 154.4, 132.8, 130.7 ($J_{\text{C-F}}$ = 33Hz) , 128.1 ($J_{\text{C-F}}$ = 3.6Hz) , 123.9 ($J_{\text{C-F}}$ = 271Hz) , 121.3, 120.7 ($J_{\text{C-F}}$ = 3.9Hz) , 63.5, 44.8, 25.2, 20.4.

HRMS: m/z [$\text{M} + \text{Na}$]⁺ calcd for $\text{C}_{14}\text{H}_{16}\text{F}_3\text{NO}$: 294.1076; found: 294.1073.

Isomer **11b**

R_f = 0.28 (hexanes–EtOAc, 58:15) ; mp 55–57°C.

IR (neat) : 2977, 1686, 1422, 1380, 1370, 1352, 1307, 1234, 1159, 1121, 1081, 1066, 829, 769, 709, 615, 561 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) : δ = 8.01 (d, J = 7.5Hz, 1H) , 7.80 (d, J = 7.8Hz, 1H) , 7.55 (t, J = 7.7Hz, 1H) , 3.66 (sept, J = 6.8Hz, 1H) , 1.573 (s, 6H) , 1.571 (d, J = 6.8Hz, 6H) .

^{13}C NMR (100 MHz, CDCl_3) : δ = 165.0, 147.4, 134.8, 129.5 ($J_{\text{C-F}}$ = 5.7Hz) , 128.4, 127.2, 124.7 ($J_{\text{C-F}}$ = 33Hz) , 123.9 ($J_{\text{C-F}}$ = 271Hz) , 65.5, 44.6, 23.7, 20.3.

HRMS: m/z [$\text{M} + \text{Na}$]⁺ calcd for $\text{C}_{14}\text{H}_{16}\text{F}_3\text{NO}$: 294.1076; found: 294.1072.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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14. The mechanism in Scheme 3 is just one proposal. The regeneration of Ni⁰ in step (v) cannot be excluded amongst other possibilities.
15. We have explored the use of phenanthroline in place of Ni(cod)₂ for the room temperature arylations described in this paper. Specifically, the reaction of 1-Br or 1-Cl using phenanthroline in place of Ni(cod)₂ under otherwise identical conditions showed no product in the GC/MS trace of the crude reaction mixture. Interestingly, the arylation of 1-I using phenanthroline (0.2 equiv) , *t*-BuOK (1.5 equiv) , and THF did proceed at room temperature to afford 1a in 80% yield, as determined by GC/MS analysis of the crude reaction mixture against hexadecane as the internal standard. These results suggest that Ni(cod)₂ is a more effective initiator for the arylations of bromide and chloride substrates. However, either Ni(cod)₂ or phenanthroline could serve as initiator for the reaction of iodide substrates.
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Scheme 1.

Previous reports of nickel-catalyzed sp³ C–H bond arylation

Scheme 2.

Our previous results and proposed work

Scheme 3.
Proposed mechanism

Scheme 4.
Effect of radical scavengers

Table 1Optimization of Room-Temperature Arylations^a

Entry	[Ni]	Base	Solvent	Yield of 1a (%) ^b
1	Ni(cod) ₂	<i>t</i> -BuONa	dioxane	20
2	Ni(cod) ₂	<i>t</i> -BuONa	THF	5
3	Ni(cod) ₂	<i>t</i> -BuONa	xylene	8
4	Ni(cod) ₂	<i>t</i> -BuONa	DMF	27
5	Ni(cod) ₂	<i>t</i> -BuONa	NMP	33
6	Ni(cod) ₂	<i>t</i> -BuOK	dioxane	99 ^c
7	Ni(cod) ₂	<i>t</i> -BuOK	THF	100
8	none	<i>t</i> -BuOK	THF	0
9	Ni(OAc) ₂	<i>t</i> -BuOK	THF	24
10	NiCl ₂ (PCy ₃) ₂	<i>t</i> -BuOK	THF	22
11	Ni(acac) ₂	<i>t</i> -BuOK	THF	25
12	NiBr ₂ ·DME ^d	<i>t</i> -BuOK	THF	24
13 ^e	Ni(OAc) ₂	<i>t</i> -BuOK	THF	27 ^c
14 ^e	NiBr ₂ ·DME ^d	<i>t</i> -BuOK	THF	29 ^c

^aReaction conditions: Ni(cod)₂ (0.1 equiv), base (1.5 equiv), solvent, r.t., 21 h.^b¹H NMR yields against 1,4-dinitrobenzene as the internal standard unless otherwise noted.^cCalibrated GC yields against hexadecane as the internal standard.^dDME = 1,2-Dimethoxyethane^eGeneral conditions, but with Ph₃P (0.2 equiv).

Table 2

Scope of Intramolecular Arylations

Entry	Substrate	Product	Yield ^{a,b}
1	1-Br X = Br 1-Cl X = Cl 1-I X = I	1a	X = Br, 96% X = Cl, 94% X = I, 96%
2	2-Br X = Br 2-Cl X = Cl	2a	X = Br, 92% X = Cl, 83%
3	3-Br	3a	99%
4	4-Br X = Br 4-Cl X = Cl	4a	X = Br, 51% X = Cl, 74%
5	5-Br	5a	96%

^a Reaction conditions: Ni(cod) 2 (0.1 equiv), *t*-BuOK (1.5 equiv), THF, r.t.

^b Isolated yield.

Table 3

Site-Selectivity of Intramolecular Arylation Reactions^a

Entry	Substrate	Product	Yield (%) ^b	
1 ^d				45 (1:0) ^c
	6-Br	6a	6b	
2 ^d				52 (1:0) ^c
	6-I	6a	6b	
3 ^d				60 ^e (4:1) ^f
	7-Br	7a	7b	
4				84 (1.1:1) ^c
	8-Br	8a	8b	
5				91 (1.2:1) ^c
	9-Br	9a	9b	
6				92 (1:1.6) ^c
	10-Cl	10a	10b	

Entry	Substrate	Product	Yield (%) ^b
7 ^d	11-Br	11a 11b	53 (1:1.5) ^c

^aReaction conditions: Ni(cod) 2 (0.1 equiv) , *t*-BuOK (1.5 equiv) , THF, r.t.

^bIsolated yield.

^cSelectivity determined by ¹H NMR spectroscopic analysis of the crude reaction mixture.

^dGeneral conditions but with Ni(cod) 2 (0.2 equiv) .

^eReported yield of the major isomer only.

^fSelectivity determined by GC/MS analysis of the crude reaction mixture.