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Nickel or Phenanthroline Mediated Intramolecular Arylation of sp³ C–H Bonds Using Aryl Halides

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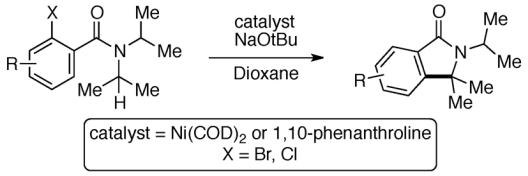
Abstract



The development of an intramolecular arylation of sp^3 C–H bonds adjacent to nitrogen using aryl halides is described. Arylation was accomplished using either $Ni(COD)_2$ or 1,10-phenanthroline in sub-stoichiometric amounts and the reaction conditions were applied to a variety of electronically differentiated benzamide substrates. Preliminary studies suggest a mechanism involving aryl and alkyl radical intermediates.

The direct functionalization of C–H bonds is a powerful method for the introduction of aryl groups into organic molecules. The majority of known methods for the arylation of sp^3 C–H bonds utilize precious metal (e.g. Pd, Ru, Rh) catalysts and/or expensive phosphine ligands.[1,2] In recent years a number of reports on Cu-[3] and Fe-[4] catalyzed sp^3 C–H bond arylation using heteroarenes[5] or transmetallating reagents[6] have been described. Additionally, an example of Ni-catalyzed intermolecular oxidative arylation of C–H bonds adjacent to ether oxygen or amine nitrogen atoms has been published.[7] Although these reports represent important advances toward general systems for alkyl C–H arylations using inexpensive catalysts, most of these protocols require the use of potentially hazardous oxidants (e.g., TBHP, DDQ) at high temperatures. This drawback could be addressed by replacing transmetallating reagents with aryl halides, which can serve as both the aryl source and the oxidant. To the best of our knowledge, no examples of *alkyl* C–H arylations using *aryl halides* and sub-stoichiometric amounts of first row transition metals have been disclosed.[1]

Herein, we describe a method for the intramolecular coupling of aryl halides (halide = Br, Cl) with alkyl C–H bonds adjacent to nitrogen in benzamide substrates using sub-stoichiometric $Ni(COD)_2$. During the course of these investigations we discovered that the same transformation could often be effected using sub-stoichiometric 1,10-phenanthroline in place of $Ni(COD)_2$. These latter results are the first demonstration of the use of transition metal-free catalysts for the arylation of *alkyl* C–H bonds adjacent to heteroatoms using aryl halides.[8,9,10,11]

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Our studies commenced with the investigation of reaction parameters for the intramolecular arylation of amide **1-Br** using the $Ni(COD)_2/PCy_3$ catalyst system (Table 1). Although the use of carbonate and phosphate bases provided only trace cyclization product (entries 1–4), higher conversion was obtained with NaOtBu in xylene or dioxane (entries 5 and 6). Strikingly, in contrast to the previously reported Pd-catalyzed reactions (which afford **1a**),[12] isoindolinone **1b** was formed as the major product via arylation of the cyclohexyl C–H bond.

Control experiments revealed that the yield of **1b** could be improved to 45% in the absence of PCy_3 (entry 7). However, diminished product yields were obtained when $Ni(COD)_2$ was excluded (entry 8). The preferential arylation of the more substituted C–H bond (cyclohexyl versus methyl) using the $Ni(COD)_2$/NaOtBu system suggested the possible involvement of alkyl radicals in these reactions. As would be expected, in this scenario the use of radical scavengers such as TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl) and galvinoxyl led to lower yields of **1b** (entries 9 and 10).

The potential involvement of radicals and the requirement for strong bases is reminiscent of the recently reported 1,10-phenanthroline catalyzed arylation of sp^2 C–H bonds using aryl halides.[8,9] As shown in Scheme 1, 1,10-phenanthroline could be used in place of $Ni(COD)_2$ to afford **1b** in comparable yield (38%) albeit with higher catalyst loadings (20 mol %). Although complete conversion of **1-Br** is observed using either $Ni(COD)_2$ or 1,10-phenanthroline, the modest yield of **1b** is in part due to significant demethylation of the protodebrominated substrate (producing a 2° amide). The observation of this product suggested that 1° C–H bonds are not amenable to the desired arylation.

Consistent with this proposal, the dimethyl substrate **2-Br** provided the desired product only in trace amounts under both sets of conditions (Table 2, entry 1). Gratifyingly, substrates bearing only 3° C–H bonds adjacent to nitrogen led to higher yields of products than those bearing 1° or 2° C–H bonds (entries 1–4).[13]

Under the Ni-mediated conditions (Conditions A), the isoindolinone products are formed in good yields from electronically varied substrates. Although good yield of **8a** is obtained from **8-Br**, competitive substitution of the F and Br groups by $^tBuO^-$ ion was observed with this substrate. In contrast to the Ni-mediated transformations, the efficiency of the corresponding phenanthroline-mediated reactions (Conditions B) is significantly influenced by the substrate electronics. While substrates bearing electron neutral aryl rings were transformed to the desired products in excellent yields (entries 3–5), those bearing substituents that are electron withdrawing with respect to the *ipso* C–Br position afforded only trace cyclization products (**7-Br** and **8-Br**, entries 6 and 7). The observed poor reaction efficiencies of these substrates is partly due to a faster rate of nucleophilic aromatic substitution by $^tBuO^-$ than the desired C–C bond formation, as this S_NAr product is detected at the end of the reaction.

We next explored the efficiency of the analogous transformations of aryl chlorides. As shown in Table 3, the use of $Ni(COD)_2$ generally led to significantly higher yields than the phenanthroline conditions for aryl chlorides. Overall the functional group tolerance and electronic effects were similar to those observed with aryl bromides.

The reaction of substrates bearing a substituent *meta* to the amide moiety was next examined (Table 4). The reaction of *meta*-Me, -OMe and -F substituted benzamides revealed that C–C bond formation does not take place exclusively at the *ipso* (C_{Ar}–X) position. Instead a mixture of isomeric products was formed, exhibiting a slight preference for C–C bond

formation at the more sterically hindered position on the aryl ring (i.e., *ortho* to the preexisting aryl substituent, entries 1–3, 5, and 6).

This selectivity trend was upheld for both substrates **11-Br** and **12-Br**, which differ in the nature of the alkyl groups on the amide. Interestingly however, the reaction of dimethoxy substrate **13-Br** displayed modest selectivity for alkylation at the less sterically hindered *ortho* position, *para* to one of the OMe groups (entry 4). The site-selectivity of the phenanthroline-mediated transformations was comparable to that of the Ni-mediated process described above (entries 1–3, 6). Consistent with the poor reactivity of substrates **7-Br** and **8-Br** under phenanthroline conditions (Table 2), substrates **13-Br** and **14-Br** led to trace product with phenanthroline, while displaying good reactivity with $Ni(COD)_2$ (Table 4, entries 4–5).

A plausible mechanism for the Ni-mediated intramolecular arylation involves (i) an initiation step via single electron transfer from Ni^0 to the substrate to generate radical anion **B**, (ii) loss of Br^- to form the aryl radical **C**, (iii) intramolecular H-atom abstraction to provide the stabilized alkyl radical **D**, (iv) radical addition into the arene to generate isomeric aryl radical intermediates **E** and **F**, and finally (v) re-aromatization to afford the cyclized product with concomitant regeneration of the radical anion **B** (Scheme 2). Alternatively, under phenanthroline conditions, the 1 e^- transfer steps (*i* and *v*) are mediated by a phenanthroline/*t*BuO^- adduct analogous to that previously documented in sp^2 C–H arylations.[8,9,14]

This mechanism is consistent with several observations described above. First, radical scavengers such as TEMPO and galvinoxyl inhibit the Ni-mediated transformation (Table 1, entries 9 and 10). Second, the efficiency of the arylation increases with more substituted alkyl C–H bonds, which is in accord with a mechanism involving alkyl radical intermediates like **D**. Third, *meta*-substituted amides lead to mixtures of isomeric products. This latter result is expected for a mechanism involving the proposed step *iv* (Scheme 2). Finally, the diminished efficiencies of the reactions of aryl chloride substrates (versus the analogous aryl bromides) under phenanthroline conditions parallels the trend in reduction potentials of aryl halides (Ar–Br>Ar–Cl).[14,15]

In summary, this paper describes the development of intramolecular arylation of sp^3 C–H bonds adjacent to an amide nitrogen using Ar–X (X = Br, Cl) using sub-stoichiometric $Ni(COD)_2$ or 1,10-phenanthroline. Preliminary studies suggest the involvement of aryl and alkyl radical intermediates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Supporting Information Available: Experimental details and spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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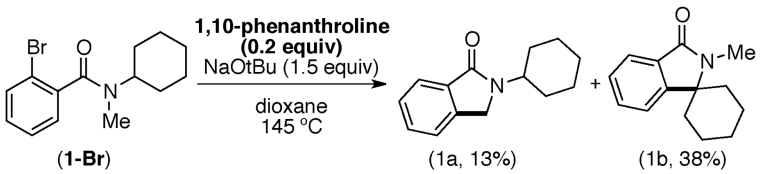
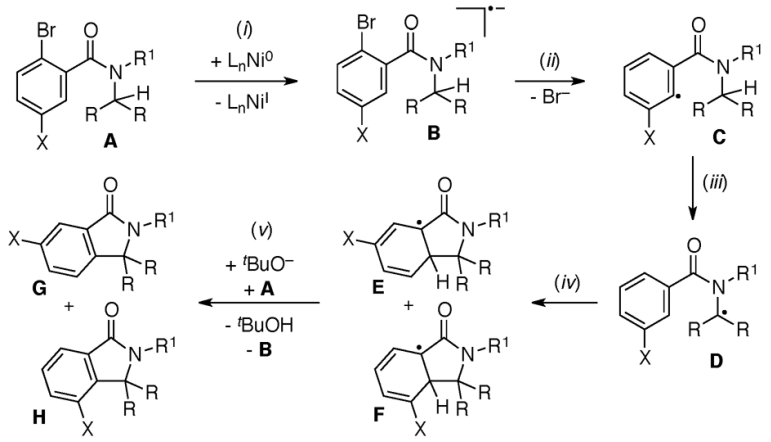
15. The mechanism in Scheme 2 is just one proposal. The regeneration of Ni^0 in step (v) cannot be excluded amongst other possibilities.



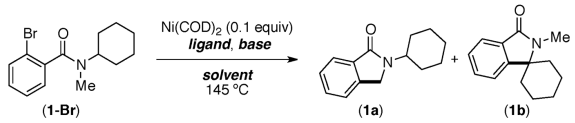
Scheme 1.
Arylation Using 1,10-Phenanthroline



Scheme 2.
Plausible Mechanism

Table 1

Optimization of the Intramolecular Arylation of 1-Br[a]



entry	ligand	base	solvent	1a (% yield)[b]	1b (% yield)[b]	conversion(%)[c]
1	PCy_3HBF_4	Cs_2CO_3	xylene	0	0	33
2	PCy_3HBF_4	Rb_2CO_3	xylene	0	0	31
3	PCy_3HBF_4	K_2CO_3	xylene	0	2	5
4	PCy_3HBF_4	K_3PO_4	xylene	0	2	34
5	PCy_3HBF_4	NaOtBu	xylene	8	30	88
6	PCy_3HBF_4	NaOtBu	dioxane	8	30	83
7	none	NaOtBu	dioxane	9	45	100
8[d]	none	NaOtBu	dioxane	2	11	52
9[e]	none	NaOtBu	dioxane	0	24	69
10[f]	none	NaOtBu	dioxane	0	11	56

[a] General conditions: $Ni(COD)_2$ (0.1 equiv), PCy_3HBF_4 (0 or 0.2 equiv), base (1.5 equiv), solvent, 145 °C, 15 h.

[b] Calibrated GC yields against hexadecane as the internal standard.

[c] Calibrated yield of remaining **1-Br** determined by gas chromatographic analysis of the crude reaction mixtures.

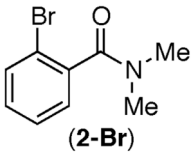
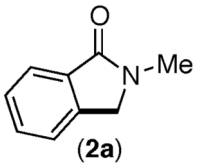
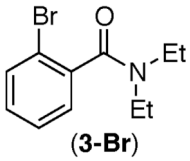
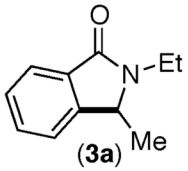
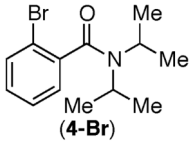
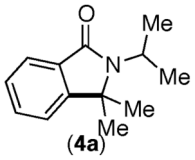
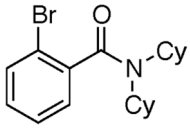
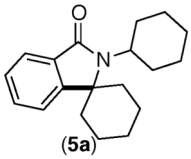
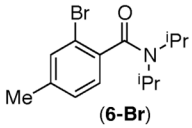
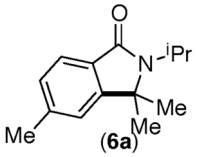
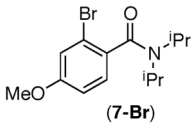
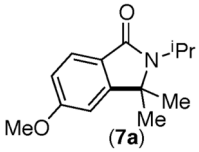
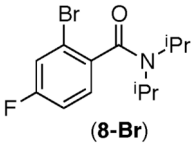
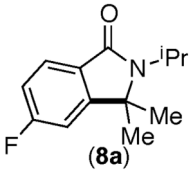
[d] General conditions, but with no $Ni(COD)_2$.

[e] In the presence of TEMPO (0.5 equiv).

[f] In the presence of galvinoxyl (0.5 equiv).

Table 2

Scope of Arylation Using Bromide Substrates

entry	substrate	product	*Conditions A* yield[a],[b]	*Conditions B* yield[c],[d]
1	 (**2-Br**)	 (**2a**)	<10%	<10%
2	 (**3-Br**)	 (**3a**)	53%	47%
3	 (**4-Br**)	 (**4a**)	76%	89%
4	 (**5-Br**)	 (**5a**)	92%	95%
5	 (**6-Br**)	 (**6a**)	83%	90%
6	 (**7-Br**)	 (**7a**)	80%[d]	trace
7	 (**8-Br**)	 (**8a**)	60%[d]	13%[b]

[a]Conditions A: $Ni(COD)_2$ (0.1 equiv), NaO*t*Bu (1.5 equiv), dioxane, 145 °C.

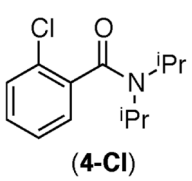
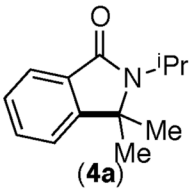
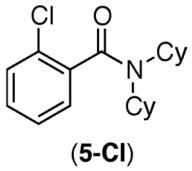
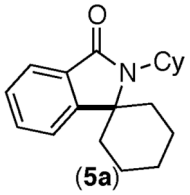
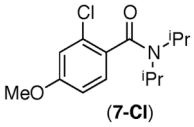
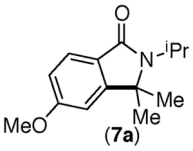
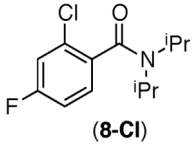
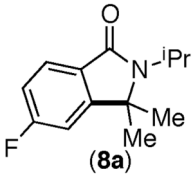
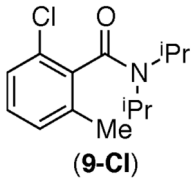
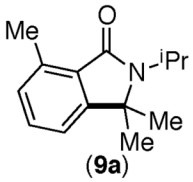
[b] ^{1}H NMR yields against 1,4-dinitrobenzene as the internal standard.

[c] Conditions B: 1,10-phenanthroline (0.2 equiv), NaO*t*Bu (1.5 equiv), dioxane, 145 °C.

[d] Isolated yields (isolated yields were generally within 5% of the crude ^{1}H NMR yields).

Table 3

Scope of Arylation Using Chloride Substrates

entry	substrate	product	*Conditions A* yield[a],[b]	*Conditions B* yield[c],[d]
1	 (**4-Cl**)	 (**4a**)	86%	45%
2	 (**5-Cl**)	 (**5a**)	81%	68%
3	 (**7-Cl**)	 (**7a**)	66%	trace
4	 (**8-Cl**)	 (**8a**)	65%	trace
5	 (**9-Cl**)	 (**9a**)	67%	46%

[a] Conditions A: $Ni(COD)_2$ (0.1 equiv), NaO*t*Bu (1.5 equiv), dioxane, 145 °C.

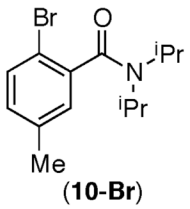
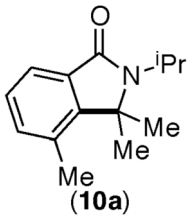
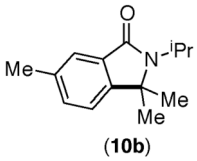
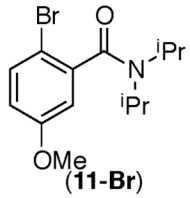
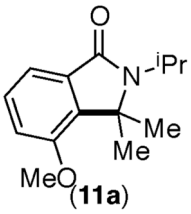
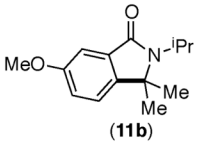
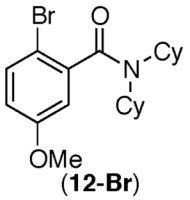
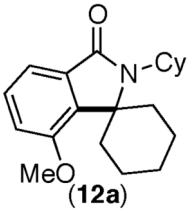
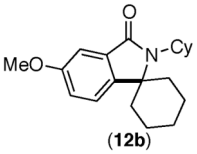
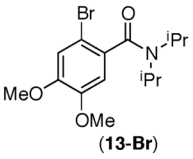
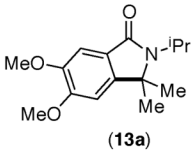
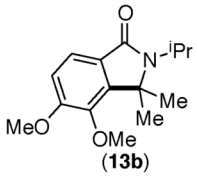
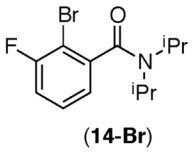
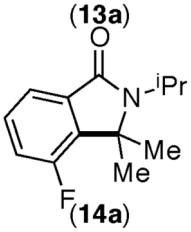
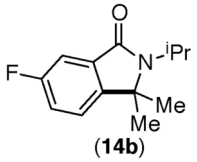
[b] Isolated yields, (isolated yields were generally within 5% of the crude NMR yields).

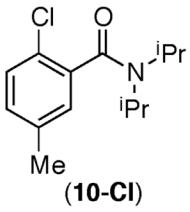
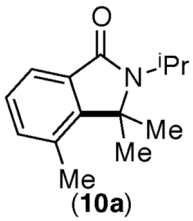
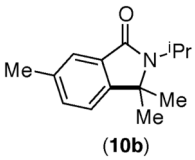
[c] Conditions B: 1,10-phenanthroline (0.2 equiv), NaO*t*Bu (1.5 equiv), dioxane, 145 °C.

[d] ^{1}H NMR yields against 1,4-dinitrobenzene as the internal standard.

Table 4

Site-Selectivity of C-C Bond Formation

entry	substrate	major product	minor product	yield (selectivity) *Conditions* A[a]	yield (selectivity) *Conditions* B[b],[c]
1	 (**10-Br**)	 (**10a**)	 (**10b**)	84% (1.1:1)[d],[e]	93% (1.3:1)[e]
2	 (**11-Br**)	 (**11a**)	 (**11b**)	71% (2.0:1)[d],[e]	94% (1.7:1)[e]
3	 (**12-Br**)	 (**12a**)	 (**12b**)	83% (1.3:1)[d],[e]	94% (1.3:1)[e]
4	 (**13-Br**)	 (**13a**)	 (**13b**)	79% (2.2:1)[c],[e]	trace
5	 (**14-Br**)	(**13a**)  (**14a**)	 (**14b**)	80% (2.7:1)[c],[e]	trace

entry	substrate	major product	minor product	yield (selectivity) *Conditions* A[a]	yield (selectivity) *Conditions* B[b],[c]
6	 (**10-Cl**)	 (**10a**)	 (**10b**)	67% (1.2:1)[d],[e]	82% (1.4:1)[c],[e]

[a] Reaction conditions: $Ni(COD)_2$ (0.1 equiv), NaO*t*Bu (1.5 equiv), dioxane, 145 °C.

[b] Reaction conditions: 1,10-phenanthroline (0.2 equiv), NaO*t*Bu (1.5 equiv), dioxane, 145 °C.

[c] Isolated yields (all isolated yields were within 5% of the crude NMR yields).

[d] ^{1}H NMR yields against 1,4-dinitrobenzene as the internal standard.

[e] Selectivities determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures.