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Potassium *tert*-Butoxide Promoted Intramolecular Arylation via a Radical Pathway

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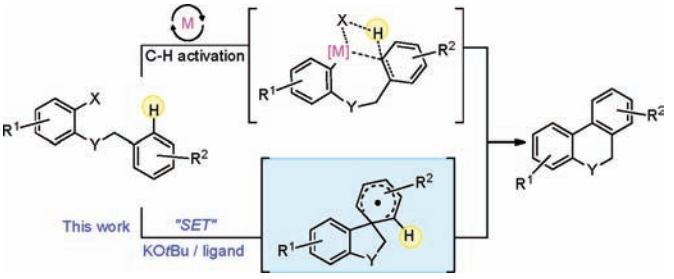
ABSTRACT



Potassium *tert*-butoxide mediated intramolecular cyclization of aryl ethers, amines, and amides was efficiently performed under microwave irradiation to provide the corresponding products in high regioisomeric ratios. The reaction proceeds via single-electron transfer to initiate the formation of an aryl radical, followed by a kinetically favored 5-*exo*-*trig* and subsequent ring expansion.

Direct C−H functionalization processes have recently emerged as an alternative strategy to classic cross-coupling chemistry in biaryl synthesis.[1] The employment of the highly versatile yet expensive noble metals such as Pd,[2] Rh,[3] and Ru[4] in catalytic direct arylations has become well established. Furthermore, the less privileged transition metals (such as Cu, Fe, Ni) are capable of performing the same task under appropriate conditions.[5] More specifically, given its low toxicity and cost, Fe has rapidly made a leading appearance and substantiated its promising status in the realm of modern synthetic chemistry.[6] Among other seminal contributions to this field, our group also disclosed an Fe-catalyzed direct arylation of unactivated arenes through aryl radical transfer.[6e] In a short period of time, however, the renowned dexterity of these transition metals became rather overshadowed, once several pioneering reports revealed that the presence of such metal catalysts is not entirely necessary to promote biaryl coupling.[7]

Itami and co-workers first described an unprecedented account on KO-*t*-Bu-mediated biaryl coupling of aryl halides and electron-deficient heterocycles in the absence of a transition metal catalyst.[7a] Subsequently, this discovery

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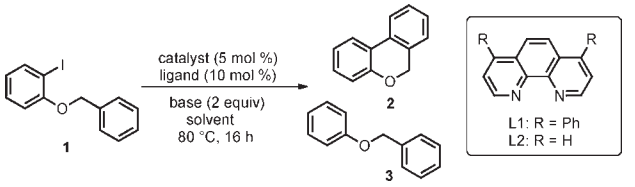
was revisited when others observed similar phenomena. The notable feature of these reaction systems is the combination of an inorganic base and a catalytic amount of diamine ligand.[7] These pairs presumably initiate single electron transfer (SET) to a carbon−halide bond at elevated temperatures, initially providing a radical anion that gives rise to a radical species for further propagation.[8] The preliminary experimental data from those reports strongly suggests the involvement of radical intermediates, as their propagation chains were essentially terminated by the addition of common radical scavengers and the kinetic isotope effect was found to be approximately 1.[7] Additionally, substituted aryl halides exclusively afforded single regioisomers;[9] therefore, it rules out the presence of a benzyne intermediate. While attempting to expand the scope of the Fe-catalyzed direct arylation to an intramolecular system, we also observed that KO-*t*-Bu can solely promote C−C bond formation. Herein, we describe intramolecular cyclizations of aryl ether, aniline, and amide derivatives using KO-*t*-Bu as the sole coupling promoter in pyridine and present our mechanistic insights.

We chose iodo arene **1** as our model substrate for the optimization (Table 1). Using our previously reported conditions,[6e,10] we observed 45% yield of the desired benzopyran **2**, along with small quantities of reduced iodo arene **3** (entry 1).[11] Employing phenanthroline L2 as ligand lowered the conversion (entry 2). Employing DMEDA or ETA greatly diminished the conversion (entries 3 and 4). Our breakthrough came when we switched to pyridine as the reaction solvent (entry 5). The reaction underwent >99% conversion and provided **2** in 80% yield. To our surprise, we observed similar yields in the absence of the iron catalyst (entry 6). Microwave conditions (entries 7−10) enabled us to shorten the reaction time to 10 min at 160 °C and use inexpensive L2. The transformation occurs even in the absence of the ligand (entry 8). Moreover, an extensive base screening revealed that weaker bases (NaO-*t*-Bu, LiO-*t*-Bu, and K_2CO_3)[12] were completely ineffective, whereas HMDS-derived bases provided mostly dehalogenation (entry 10).

Encouraged by the optimization results, we started examining other classes of substrates (Table 2). Both the iodide and bromide analogues **1** and **1a** underwent the cyclization to afford **2** in good yields. Incorporating a nitrogen atom in the tether allowed us to obtain >99% conversion without the presence of phenanthroline. Amine protecting groups such as methyl and benzyl (entries 2 and 3) both provided the corresponding products **5a** and **5b** in good yields.[13] Substitution on the aniline moiety is applicable, albeit in moderate to low yields (entries 4 and 5). The carbon variants of either the iodide or bromide **6a** and **6a′** were excellent substrates, affording the cyclized product in 89% and 71% yields respectively.

Exploring substitution on the benzyl moiety of the aryl system (Table 3), we observed a mixture of regioisomeric products in most cases,[14] whereas the metal-catalyzed direct C−H arylation pathway would only give one product.[1,15] *p-tert*-Butyl-substituted aryl ether **1b** participated in the cyclization effectively, giving an 88% yield of a mixture of two regioisomers (5:1, entry 1). An analogous *N*-methyl-protected aniline derivative **4e** exhibited the same trend with an even greater regioisomeric preference (>10:1, entry 2). Similarly, *p*-methoxy- and *p*-methyl-substituted anilines were very well tolerated, providing **5f** and **5g** with remarkable regioselectivity (entries 3 and 4). In the case of *m*-methoxyaniline derivative **4h**, product **5h** was isolated in 67% yield, along with a trace amount of a minor isomer (entry 5). 3,5-Dimethoxy-substituted aniline **4i** also yielded a mixture of products (entry 6). The cyclization of *o*-methyl-substituted **4j** afforded only 25% yield of product **5j**, presumably due to increased steric congestion by the methyl group (entry 7). Furthermore, *p*-methyl-substituted carbon analogue **6b** smoothly underwent the cyclization to give a mixture of products, favoring the opposite isomer **7b′** as major (entry 8).

Table 1. Optimization of Intramolecular Arylation



entry	catalyst	ligand	base/solvent	conv[b] (%)	yield[a] (%) 2	3
1	$Fe(OAc)_2$	L1	KO-*t*-Bu/PhH	66	45	2
2	$Fe(OAc)_2$	L2	KO-*t*-Bu/PhH	39	35	2
3	$Fe(OAc)_2$	ETA[d]	KO-*t*-Bu/PhH	44	27	4
4	$Fe(OAc)_2$	DMEDA[e]	KO-*t*-Bu/PhH	15	6	0
5	$Fe(OAc)_2$	L1	KO-*t*-Bu/py	>99	80	9
6		L1	KO-*t*-Bu/py	88	79	4
7[c]		L2	KO-*t*-Bu/py	>99	77	4
8[c]			KO-*t*-Bu/py	80	50	18
9[c]			NaO-*t*-Bu/py	0	0	0
10[c]			KHMDS/py	>99	25	60

[a] ^{1}H NMR yield using trimethoxybenzene as internal standard. [b] Based on recovered starting material by ^{1}H NMR using trimethoxybenzene as internal standard. No coupling product with PhH or py was observed. [c] Reaction was run in the microwave for 10 min at 160 °C. [d] ETA = ethanolamine. [e] DMEDA = dimethylethylenediamine.

(8) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413.

(9) Hayashi observed byproduct formation via aryne intermediate when KO-*t*-Bu was used instead of NaO-*t*-Bu. See ref 7e.

(10) KO-*t*-Bu was freshly sublimed prior to use. ICP-AES analysis indicated no significant amount of transition-metal impurities in KO-*t*-Bu. See the Supporting Information.

(11) Benzopyran **2** can be accesed in 18% yield through standard Sn-mediated radical conditions. See: Harrowven, D. C.; Nunn, M. I. T.; Newman, N. A.; Fenwick, D. R. *Tetrahedron Lett.* **2001**, *42*, 961.

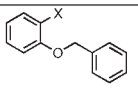
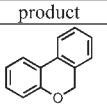
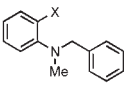
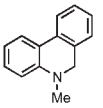
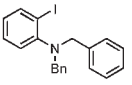
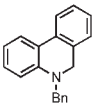
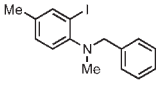
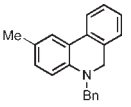
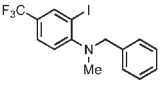
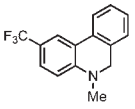
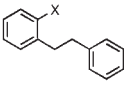
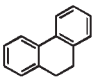
(12) See the Supporting Information for complete optimization.

(13) When the aniline was substituted by protecting groups such as Ms and Cbz the cyclization failed. See the Supporting Information.

(14) The structures were determined by 1D NOE experiments. Details in the Supporting Information.

(15) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *128*, 581 and references therein.

Table 2. Intramolecular Cyclization of Aryl Halides[a]

entry	arene	product	yield (%)[b]
1	 1/1a	 2	1: X = I 79[c] 1a: X = Br 75[c]
2	 4a/4a'	 5a	4a: X = I 82 4a': X = Br 64[c]
3	 4b	 5b	65
4	 4c	 5c	64
5	 4d	 5d	31
6	 6a/6a'	 7a	6a: X = I 89 6a': X = Br 71[c]

[a] Reaction conditions: aryl halide (1 equiv), KO-*t*-Bu (2 equiv), py (0.13 M), 160 °C, 10 min, microwave. [b] In certain cases, < 3% reduced arene was isolated along with product. See the Supporting Information for details. [c] 10 mol % of L2 was added to the reaction.

Electron-deficient anilines turned out to be poor substrates,[16] which suggests that the initially formed radical species exhibits an intrinsic electrophilicity, as opposed to the generally known nucleophilic properties of phenyl radicals,[17] which implies that SOMO/HOMO interactions are predominant in the bond-forming process.[18]

The corresponding phenanthridone **9** can be accessed in good yields from the dihydrophenanthridine analogue by oxidation with $BaMnO_4$ (Scheme 1). Alternatively, the direct cyclization of amide derivative **8** is also possible, but with slightly diminished yields.

Daugulis and Bajracharya[19] proposed a benzyne intermediate in their KO-*t*-Bu-mediated intramolecular arylation of phenols. However, when our regioisomeric ratios are compared to the ones they obtained, the benzyne pathway is unlikely due to strikingly large discrepancies. Additionally, in their control experiment on a methyl ether that resembles **4h** structurally, they observed products resulting from S_NAr trapping of benzyne by *tert*-butoxide. Experiments performed in the presence of known radical

(16) See the Supporting Information.

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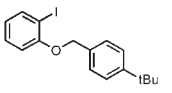
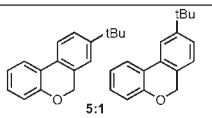
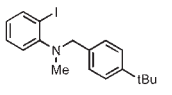
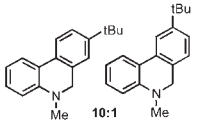
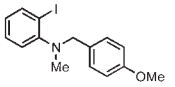
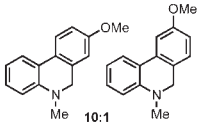
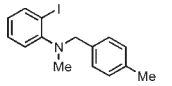
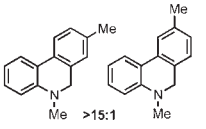
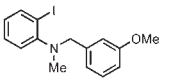
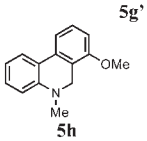
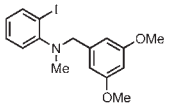
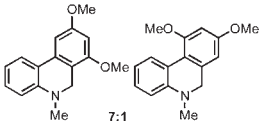
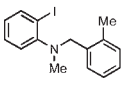
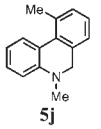
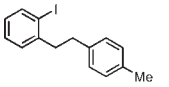
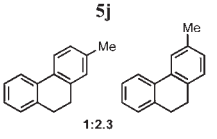
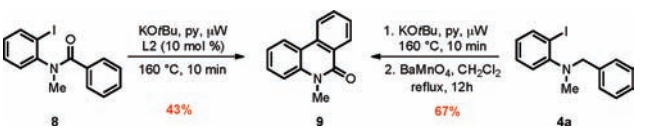
(19) Bajracharya, G. B.; Daugulis, O. *Org. Lett.* **2008**, *10*, 4625.

Table 3. Substitution Effect on Regioselectivity[a]

entry	arene	products/ratio	yield (%)[b]
1	 1b	 5:1 2b 2b'	88[c]
2	 4e	 10:1 5e 5e'	86
3	 4f	 10:1 5f 5f'	83
4	 4g	 >15:1 5g 5g'	82
5	 4h	 5h	67
6	 4i	 7:1 5i 5i'	62
7	 4j	 5j	25
8	 6b	 1:2.3 7b 7b'	92

[a] Reaction conditions: aryl halide (1 equiv), KO-*t*-Bu (2 equiv), py (0.13 M), 160 °C, 10 min, microwave. [b] In certain cases, < 3% reduced arene was isolated along with product. See the Supporting Information for details. [c] 10 mol % of L2 was added to the reaction.

Scheme 1. Access to Phenanthridones via Two Pathways



inhibitors such as TEMPO or galvinoxyl shut down the reaction.[20] KO-*t*-Bu is generally known to function as both

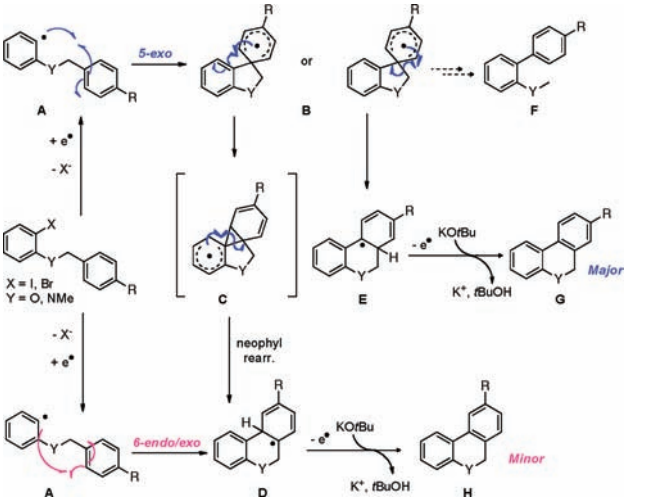
(20) See the Supporting Information.

single- and two-electron donor to certain functional groups.[21] However, the exact mechanism of electron transfer to the aryl−X bond in pyridine appears to be far from straightforward, especially in the absence of a SET mediator such as Phen[22] in our reaction system.

A representative example of our proposed mechanism is shown in Scheme 2. Upon generation of radical **A**, kinetically favored 5-*exo*-*trig ipso* attack results in the formation of spirocyclohexadienyl radical **B**,[23] which can undergo a concerted ring expansion[24] to furnish the thermodynamically more stable radical **E**. This ultimately yields the observed major product **G** after rearomatization. Alternatively, aryl radical **B** can form the fused-cyclic system **C** via a 3-*exo* closure, followed by the successive neophyl rearrangement[25] to give the regioisomeric product **H**. The formation of the minor product can also be accounted through an initial 6-*endo*/*exo*-*trig* cyclization, which gives rise to the same aryl radical intermediate **D**. β-Scission of **B** to give a biaryl **F** is also equally viable and well documented[11,26] under conventional Sn-mediated radical reactions, especially when incipient radicals become stable by delocalizing electrons onto heteroatoms. However, such a competing path may be much slower in our case since we never isolated any biaryl isomers. Indeed, 5-*exo* cyclization followed by concerted ring enlargement via **B** appears to consistently be the major path for *p*-, *m*- and *o*-substituted derivatives.[27] In the formation of **7b** and **7b′**, the selectivity is reversed, suggesting the direct involvement of the heteroatom lone pair in the stabilization of the **B** to **E** ring expansion.

In summary, we developed a highly regioselective KO-*t*-Bu-mediated intramolecular cyclization of aryl ether, aniline, and amide derivatives in the absence of a transition metal catalyst. The product distribution led us to propose a radical pathway for the reaction. Studies are underway to further investigate the synergistic effect of the pyridine and KO-*t*-Bu in the SET process and will be reported in due course.

Scheme 2. Proposed Reaction Mechanism



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Note Added after ASAP Publication. Due to a production error Tables 2 and 3 were incomplete in the version of this paper that published ASAP May 13, 2011; the correct version reposted May 17, 2011.

Supporting Information Available. Experimental procedures, sample spectra, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org

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(27) Detailed mechanisms for these are shown in the Supporting Information.