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Direct Transition-Metal-Free Intramolecular Arylation of Phenols

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Abstract

Direct transition-metal-free, base-mediated intramolecular arylation of phenols with aryl halides has been developed. In the presence of 2.5 equivalents of *t*-BuOK in dioxane at 140 °C, the intramolecular cyclization of 3-(2-halobenzyloxy)phenols affords 6*H*-benzo[*c*]chromenes in high yields. This reaction proceeds by an initial formation of a benzyne intermediate followed by an aromatic sp^2 C–H functionalization (a formal C–H activation) to form the carbon-carbon bond.

Arylation of aromatic C–H bonds has become a topic of intense interest in recent years.¹ The methodology has potential advantages over the well-known cross-coupling reactions because the arylmetal coupling partner can be replaced by a simple arene.² Recently, palladium catalysis has appeared as a general tool for the synthesis of biaryls by C–H bond functionalization methodology.³ We are interested in developing simple and efficient protocols for direct arylation of sp^2 C–H bonds.⁴ We have previously reported copper-catalyzed intermolecular arylation of C–H bonds of heteroaromatics and polyfluorobenzenes with aryl halides.⁵ Minor amounts of arylation products were detected in the reaction mixtures even in the absence of copper catalyst if *t*-BuOK base was used. By using deuterium labelling, it was determined that these reactions proceed via benzyne intermediates. We reasoned that generation of a benzyne with a tethered aryl nucleophile should result in an efficient aryl-aryl bond formation in the absence of a transition-metal catalyst (Scheme 1). Several catalytic systems that accomplish such transformations by using either transition-metal catalysis or radical chemistry have been reported. In pioneering work, Rawal and co-workers have developed a method for anion-accelerated palladium-catalyzed intramolecular coupling of phenols with aryl halides under mild conditions.⁶ Subsequently, Fagnou and co-workers developed related palladium-based catalytic systems that are more general.⁷ Tributyltin hydride reagent has also been utilized to effect oxidative radical cyclizations of similar substrates.⁸ Herein, we report that direct intramolecular arylation of 3-(2-halobenzyloxy)phenols can be achieved in the presence of *t*-BuOK base at 140 °C without a transition-metal catalyst (Scheme 1).

In 1950s, Bunnett⁹ and Huisgen¹⁰ developed the intramolecular addition reactions of aryne-tethered nucleophiles.¹¹ This strategy was successfully employed in the synthesis of benzo-fused heterocycles such as indolines,¹² indoles,¹³ phenothiazines,¹³ benzoxazoles,^{13,14} xanthenes,¹⁵ and benzothiazoles^{13,16} by using tethered nitrogen, oxygen or sulfur nucleophiles. However, tethered carbanions have rarely been used in the benzyne cyclization reactions. For this purpose either a stabilized carbanion¹⁷ or an atom capable of supporting a

negative charge must be employed.¹⁸ Benzyne coupling with a tethered aryllithium followed by quenching with an external electrophile has been described.¹⁹

The initial experiments were carried out in the presence of a copper(I) catalyst. Upon treatment of 3-(2-bromobenzyloxy)phenol (**1**) with 10 mol % CuI and 3 equivalents of *t*-BuOK in DMF at 140 °C, 1-hydroxy-6*H*-benzo[*c*]chromene (**2**) and 3-hydroxy-6*H*-benzo[*c*]chromene (**3**) were isolated in 25% and 28% yields, respectively. Interestingly, the reaction performed without addition of CuI proceeds with an improved regioselectivity (Table 1, entry 1). Other alkali metal bases such as *t*-BuONa and *t*-BuOLi are less effective (entries 2 and 3). Weaker bases such as K₂CO₃ and Cs₂CO₃ are ineffective and starting material was recovered quantitatively (entries 4 and 5). These results rule out the involvement of a nucleophilic substitution-type mechanism. Reaction proceeds in a range of solvents and dioxane was the solvent of choice affording **2** and **3** in a 78% combined yield (entries 6–12). Decreasing the amount of *t*-BuOK to 2.5 equivalents improves the yield (entry 13). Employing 2 equivalents of *t*-BuOK is almost as effective (entry 14). The best results for the cyclization of **1** were obtained by using 2.5 equivalents of *t*-BuOK in dioxane at 0.3 M concentration at 140 °C (entry 15). The reaction proceeds at lower temperature of 100 °C; however, several days are required for achieving complete conversion (entry 16).

The scope of the intramolecular arylation is presented in Table 2. Under optimized reaction conditions, bromide **1**, iodide **4**, and chloride **5** underwent smooth cyclization (entries 1–3). Bromine-substituted reactant displayed superior reactivity compared to iodine and chlorine containing compounds. Methoxy and methyl substituents in 5-position are well tolerated yielding corresponding chromenes in excellent yields (entries 4 and 5). Substrate **12** bearing methyl group at 2-position produced only **13** in a 64% yield (entry 6). Compound **14**, in which 4-position is blocked with a *tert*-butyl group, was cyclized producing **15** in excellent yield (entry 7). Substrates possessing an electron withdrawing trifluoromethyl group or an electron donating methoxy substituent at aryl halide moiety smoothly underwent cyclization affording corresponding products in high yields (entries 8 and 9). Proof for the intermediacy of benzyne was obtained by employing substrate **22** that produced **23** in 56% yield (entry 10). The cyclization of 3-((2-bromophenoxy)-methyl)phenol (**24**) regioselectively produced **25** in a good yield (entry 11). In all cases arylation *ortho* to the phenolate is the major reaction pathway.

Under the standard conditions used for the cyclization of **1**, methyl ether analogue **26** produced substitution products **27** (70%) and **28** (19%) (eq 1). This result clearly indicates that if tethered arene is less nucleophilic, benzyne intermediate is trapped by an external nucleophile.

(1)

The reaction mechanism was investigated (Scheme 2). The cyclization of **1** was carried out in the presence of *t*-BuOK in dioxane with added 2.5 equivalents of *t*-BuOD (Scheme 2A). After completion, the reaction mixture was quenched with 2 N HCl followed by usual work up and purification. Products **2-d** and **3-d** were obtained with deuterium incorporated both at C-10 and methylene group. Similar level of deuterium incorporation was observed when the reaction

was performed employing *t*-BuOK and *t*-BuOD in dioxane-*d*₈ followed by quenching with 2 N DCl in D₂O (Scheme 2B). Furthermore, heating potassium 3-(2-bromobenzyloxy)phenolate (**29**) in the presence of *t*-BuOK (1.5 equiv) and *t*-BuOD (2.5 equiv) in dioxane afforded **2-d** and **3-d** with increased deuterium incorporation (Scheme 2C). These observations point to *t*-butanol being a source of protonation at C-10.

We speculate that this reaction proceeds by an initial formation of a benzyne intermediate followed by an aromatic sp² C–H functionalization. The benzyne intermediate generated in the presence of a strong base, undergoes cyclization via *ortho* (and/or *para*)-arylation (Scheme 3). Subsequent protonation by *t*-butanol and aromatization leads to the final products. Catalysis by trace amounts of palladium is unlikely since aryl chloride **5** affords the cyclized products in a good yield.²⁰

In conclusion, we have developed a method for direct transition-metal-free, base-mediated intramolecular arylation of phenols with aryl halides. The sp² C–H bond functionalization occurs via a benzyne intermediate. At this point, a phenolate activating group is essential for the arylation. Further scope elaboration is under progress in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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20. It has been shown that ppb to ppm level palladium contaminants in commercial bases allows cross-coupling reactions to proceed without adding transition-metal catalysts. However, (1) aryl chlorides should not be reactive under such conditions (Table 2, Entry 3), (2) deuterium incorporation in 10-position of the product would not be observed if the reactions proceed by conventional cross-coupling pathways (Scheme 2), and (3) the cyclization is less regioselective compared with Rawal's Pd-catalyzed method (ref. 6). Arvela RK, Leadbeater NE, Sangi MS, Williams VA, Granados P, Singer RD. *J Org Chem* 2005;70:161. [PubMed: 15624918]

Scheme 1.

Direct Transition-Metal-Free Intramolecular Arylation of Phenols

Scheme 2.
Deuteration Experiments

Scheme 3.
Mechanistic Considerations

Table 1

Optimization of the Reaction Conditions.^a

entry	base (equiv)	solvent	2, yield (%)	3, yield (%)
1	<i>t</i> -BuOK (3)	DMF	44 ^b	20 ^b
2	<i>t</i> -BuONa (3)	DMF	26	30
3	<i>t</i> -BuOLi (3)	DMF	trace	trace
4	K ₂ CO ₃ (3)	DMF	0	0
5	Cs ₂ CO ₃ (3)	DMF	trace	trace
6	<i>t</i> -BuOK (3)	DMA	30	36
7	<i>t</i> -BuOK (3)	DMPU	38	36
8	<i>t</i> -BuOK (3)	NMP	28	35
9	<i>t</i> -BuOK (3)	toluene	20	22
10	<i>t</i> -BuOK (3)	DMSO	16	41
11	<i>t</i> -BuOK (3)	<i>m</i> -xylene	12	22
12	<i>t</i> -BuOK (3)	dioxane	60	18
13	<i>t</i> -BuOK (2.5)	dioxane	68	20
14	<i>t</i> -BuOK (2)	dioxane	60	22
15 ^c	<i>t</i>-BuOK (2.5)	dioxane	73^b	23^b
16 ^{c,d}	<i>t</i> -BuOK (2.5)	dioxane	62	17

^a Substrate (1 equiv, 0.5 mmol), base (2-3 equiv), solvent (1 mL), 16 h at 140 °C. Yields are calculated by ¹H NMR integration of crude reaction mixtures employing CH₃NO₂ internal standard.

^b Isolated yield.

^c Concentration 0.3 M.

^d Reaction run at 100 °C for 3 days.

Table 2Scope of Base-Mediated Direct Intramolecular Arylation of Phenols.^a

entry	substrate	products	yield%(ratio) ^b
1	 1, X = Br 4, X = I 5, X = Cl	 2	96 (3.2:1)
2			77 (1.4:1)
3 ^c			69 (3.6:1)
4	 6	 7	97 (5.5:1)
		 8	
5	 9	 10	96 (1.1:1)
		 11	
6	 12	 13	64
7	 14	 15	93
8	 16	 17	85 (1.2:1)
		 18	
9	 19	 20	80 (2.8:1)
		 21	
10	 22	 23	56
11	 24	 25	80

^a Substrate (1 equiv, 0.5 mmol), *t*-BuOK (2.5 equiv), dioxane (1.5 mL), 16 h at 140 °C.^b Isolated yields. See the Supporting Information for details.

^c Reaction time 48 h.