Letter

Direct Transition-Metal-Free Intramolecular Arylation of Phenols

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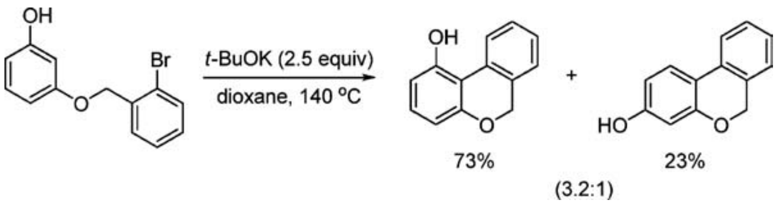

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Direct Transition-Metal-Free Intramolecular Arylation of Phenols

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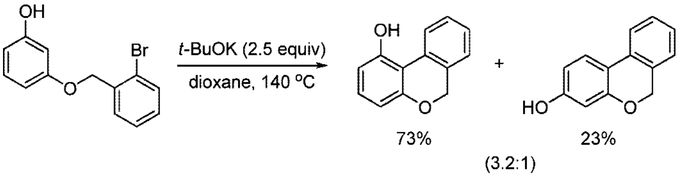
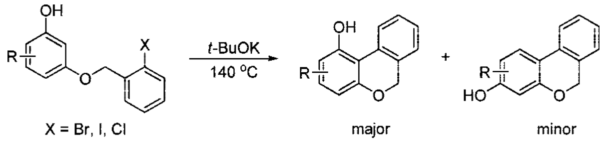
ABSTRACT



Direct transition-metal-free, base-mediated intramolecular arylation of phenols with aryl halides has been developed. In the presence of 2.5 equiv 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 labeling, 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

Scheme 1. Direct Transition-Metal-Free Intramolecular Arylation of Phenols



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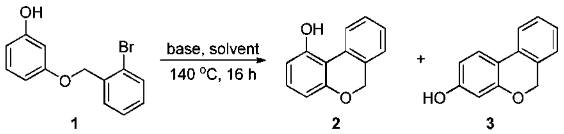
co-workers developed related palladium-based catalytic systems that are more general.[7] Tributyltin hydride reagent has also been utilized to effect oxidative radical cyclizations of similar substrates.[8] Herein, we report that direct intramolecular arylation of 3-(2-halobenzyloxy)phenols can be achieved in the presence of *t*-BuOK base at 140 °C without a transition-metal catalyst (Scheme 1).

In the 1950s, Bunnett[9] and Huisgen[10] 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 carbanion[17] 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 % of CuI and 3 equiv 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 K_2CO_3 and Cs_2CO_3 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 equiv of *t*-BuOK is almost as effective (entry 14). The best results for the cyclization of **1** were obtained by using 2.5 equiv 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).

Table 1. Optimization of the Reaction Conditions[a]



entry	base (equiv)	solvent	**2**, yield (%)	**3**, yield (%)
1	*t*-BuOK (3)	DMF	44[b]	20[b]
2	*t*-BuONa (3)	DMF	26	30
3	*t*-BuOLi (3)	DMF	trace	trace
4	K_2CO_3 (3)	DMF	0	0
5	Cs_2CO_3 (3)	DMF	trace	trace
6	*t*-BuOK (3)	DMA	30	36
7	*t*-BuOK (3)	DMPU	38	36
8	*t*-BuOK (3)	NMP	28	35
9	*t*-BuOK (3)	toluene	20	22
10	*t*-BuOK (3)	DMSO	16	41
11	*t*-BuOK (3)	*m*-xylene	12	22
12	*t*-BuOK (3)	dioxane	60	18
13	*t*-BuOK (2.5)	dioxane	68	20
14	*t*-BuOK (2)	dioxane	60	22
15[c]	***t*-BuOK (2.5)**	**dioxane**	**73**[b]	**23**[b]
16[c,d]	*t*-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 CH_3NO_2 internal standard. [b] Isolated yield. [c] Concentration 0.3 M. [d] Reaction run at 100 °C for 3 days.

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 the 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 the 4-position is blocked with a *tert*-butyl group, was cyclized producing **15** in excellent yield (entry 7). Substrates possessing an electron-withdrawing trifluromethyl group or an electron-donating methoxy substituent at the aryl halide moiety smoothly underwent cyclization to afford 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-bromophenyloxy)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

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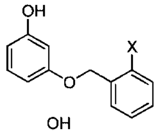
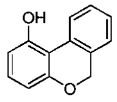
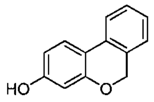
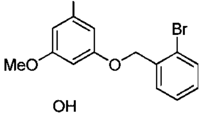
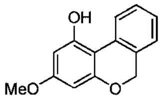
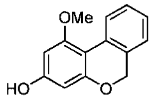
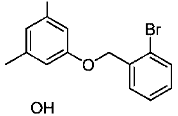
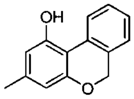
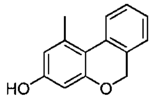
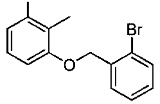
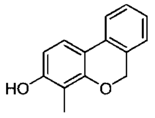
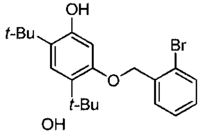
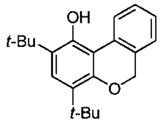
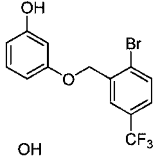
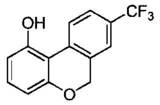
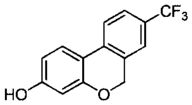
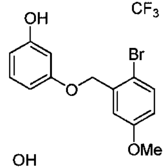
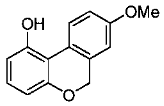
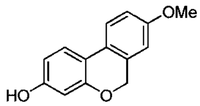
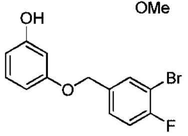
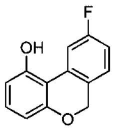
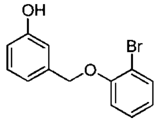
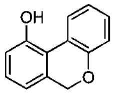
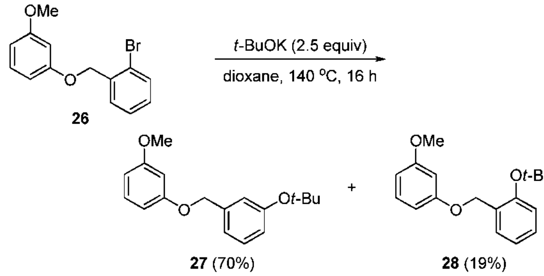
Table 2. Scope of Base-Mediated Direct Intramolecular Arylation of Phenols[a]

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

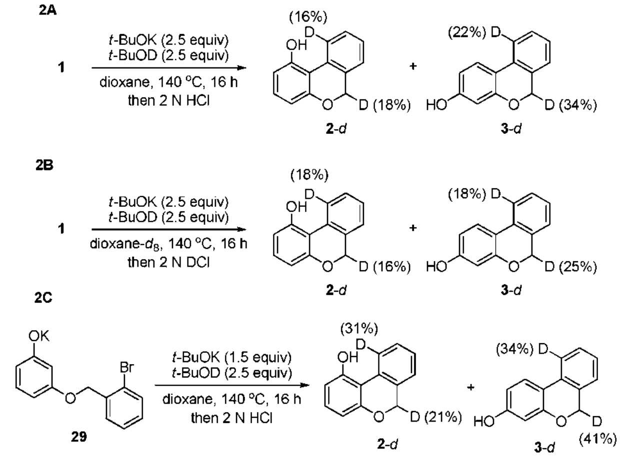
[a] Substrate (1 equiv, 0.5 mmol), *t*-BuOK (2.5 equiv), dioxane (1.5 mL), 16 h at 140 °C. [b] Isolated yields. See the Supporting Information for details. [c] Reaction time 48 h.

that if tethered arene is less nucleophilic, benzyne intermediate is trapped by an external nucleophile.



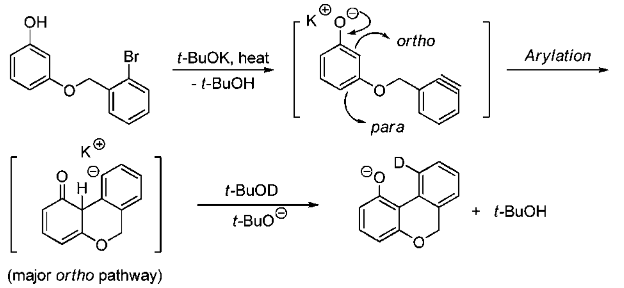
(1)

The reaction mechanism was investigated (Scheme 2). The cyclization of **1** was carried out in the presence of *t*-BuOK in dioxane with 2.5 equiv of *t*-BuOD (Scheme 2A). After completion, the reaction mixture was quenched with 2 N HCl followed by usual workup and purification. Products **2**-*d* and **3**-*d* were obtained with deuterium incorporated both at C-10 and the methylene group. A 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 D_2O (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 *tert*-butyl alcohol being a source of protonation at C-10.



Scheme 2. Deuteration Experiments

We speculate that this reaction proceeds by an initial formation of a benzyne intermediate followed by an aromatic sp^2 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 *tert*-butyl alcohol and aromatization leads to the final products. Catalysis by trace amounts of palladium is unlikely since aryl cloride **5** affords the cyclized products in a good yield.[20]



Scheme 3. Mechanistic Considerations

In conclusion, we have developed a method for direct transition-metal-free, base-mediated intramolecular arylation of phenols with aryl halides. The sp^2 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.

Acknowledgment. G.B.B. is the recipient of the 2008−2009 Eby Nell McElrath Postdoctoral Fellowship. We thank the Welch Foundation (Grant No. E-1571), NIGMS (Grant No. R01GM077635), A. P. Sloan Foundation, and Camille and Henry Dreyfus Foundation for supporting this research.

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

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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, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. D. *J. Org. Chem.* **2005**, *70*, 161.