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Base-Mediated Intermolecular sp^2 C−H Bond Arylation via Benzyne Intermediates

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Supporting Information

ABSTRACT: A transition-metal-free method for arylation of heterocycle and arene carbon−hydrogen bonds by aryl chlorides and fluorides has been developed. The reactions proceed via aryne intermediates and are highly regioselective with respect to the C−H bond coupling component.

Regioselective formation of aryl−aryl bonds has attracted substantial interest because of the prevalence of sp^2−sp^2 bonds in pharmaceuticals, natural products, and dyes.[1] In recent years, classical methods for creating aryl−aryl bonds have been supplanted by direct arylation methodology in which the carbon−hydrogen bond is used as a functional group.[2] A majority of the C−H bond arylation examples include palladium-, rhodium-, or ruthenium-catalyzed functionalization of five-membered-ring heterocycles and directing-group-containing arenes.[3] Copper-catalyzed deprotonative arylation of heterocycles and electron-deficient arenes results in the functionalization of the most acidic sp^2 C−H bonds.[4] Several recent reports have described the arylation of arenes and electron-deficient heterocycles by aryl halides, which presumably proceed by radical-type mechanisms without transition metal involvement.[5] The latter methods avoid heavy-metal contamination of the products, simplifying the purification for pharmaceutical applications.[6] Additionally, these methods are among the simplest synthetic routes to biaryls. However, arylations of simple arenes such as anisole afford isomer mixtures, and the arene coupling component is often employed in large excess (up to 100 equiv) as a solvent. We report here a method for transition-metal-free intermolecular sp^2 C−H bond arylation via benzyne intermediates that is highly regioselective with respect to the arene coupling component and does not require a large excess of any of the coupling components.

We have recently reported a transition-metal-free, base-mediated intramolecular C-arylation of phenols with aryl halides. In the presence of *t*-BuOK in dioxane at 140 °C, the cyclization of 3-(2-halobenzyloxy)phenols affords 6*H*-benzo[*c*]chromenes in high yields.[7a] The reaction proceeds by an initial formation of a benzyne intermediate followed by an aromatic sp^2 C−H functionalization to form the carbon−carbon bond. To expand the synthetic utility of the reaction, we decided to investigate intermolecular carbon−carbon bond formation proceeding via benzyne intermediates. The reaction would occur by a simultaneous generation of benzyne and the aryl anion[8] followed by biaryl formation.[9] Early examples of chloroarene phenylation by phenyllithium were reported by Huisgen more than 50 years ago.[9a] More recent examples of aryne arylations have been described by Hart, Schlosser, Meyers, Aubert, and Mamane.[9] Benzyne can be generated from silyl aryl triflates under mild conditions.[7b] However, these starting materials are quite expensive, and only a few of them are commercially available. Consequently, we decided to use readily accessible and cheap aryl chloride benzyne sources. Use of hindered 2,2,6,6-tetramethylpiperidides (TMPs) should retard the reaction of benzyne with base.[10] The relative reactivity of the base and aryl anion with benzyne can be modulated by employing a solvent in which the amide base is sparingly soluble. A brief optimization of the reaction conditions showed that the best results were obtained by employing a mixed pentane/THF solvent system. In pentane, the arylations are slow because of low base solubility. Competitive addition of TMPLi to benzyne decreases the arylation yields in THF.

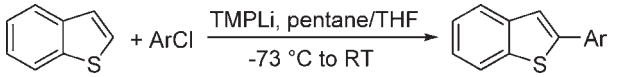
The arylation scope with respect to aryl halides is presented in Table 1. Benzothiophene is arylated by aryl halides at the most acidic position. Arylation by 2-chloroanisole and 2-chlorobenzotrifluoride (entries 1 and 2) affords the meta-substituted products in good yields. When benzothiophene is arylated using either 2- or 3-chloro-*N*,*N*-dimethylaniline, the meta-substituted product is obtained (entries 3 and 4). This regioselectivity pattern may be advantageous if *o*-chloroarene is more available than the corresponding meta isomer. Substitutions by a benzyne mechanism often produce the same isomer when 2- and 3-haloarene starting materials are used.[11] The regioselectivity is explained in terms of the energy required to distort the aryne into two possible transition states and ground-state polarization of the aryne by electron-withdrawing substituents.[11c] 3,5-Dimethoxychlorobenzene is reactive, and the arylation product is obtained in good yield (entry 5). 2,3,4,5-Tetrasubstituted chloroarenes can be employed, and benzothiophene is arylated by 9-chlorophenanthrene (entry 6). When 3-chloro-4-methoxytoluene is used, the arylation occurs meta to the methoxy substituent (entry 7). Fluoroarene starting materials can be employed, and the reaction tolerates an ester group (entry 8). If 4-substituted chloroarenes are used, a nearly 1/1 isomer mixture is obtained, as expected (entry 9).[11]

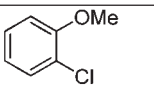
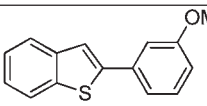
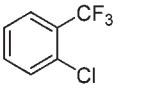
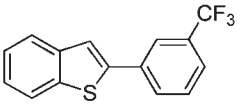
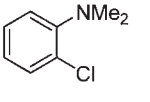
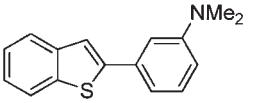
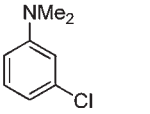
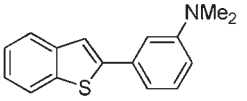
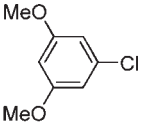
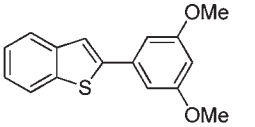
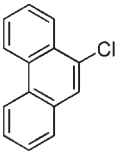
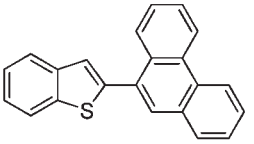
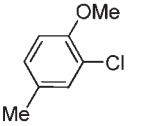
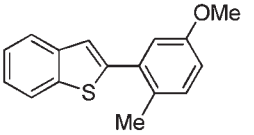
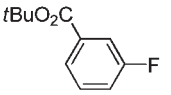
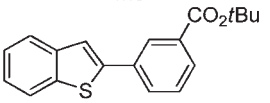
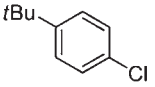
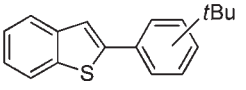
The arylation scope with respect to heterocycles and arenes is shown in Table 2. In most cases, use of TMPLi as the base affords slightly higher yields than either lithium dicyclohexylamide or diisopropylamide (entries 1−4 and 6). When fluorobenzene is used instead of chlorobenzene, nearly identical yields are obtained in the reactions with benzothiophene (entry 1). Furan derivatives, such as benzofuran and 2-butylfuran, are arylated in good yields (entries 2 and 3). *N*-Methylbenzimidazole and benzothiazole are reactive (entries 4 and 5). Thiophene, indole, and pyrrole

Received: January 7, 2011
Published: March 08, 2011

dx.doi.org/10.1021/ja200184b | *J. Am. Chem. Soc.* 2011, 133, 4243–4245

Table 1. Arylation Scope with Respect to Aryl Halides[a]

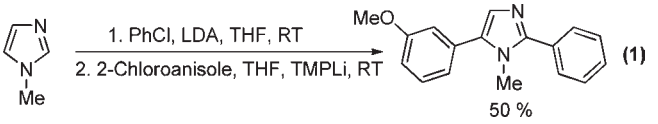


entry	aryl halide	product	yield, %
1			78
2			61
3			77
4			81
5			62
6			75
7			73
8			60 50[b]
9			85[c]

[a] Conditions: aryl halide (1.6−2.5 equiv), benzothiophene (1 equiv), 0.5 mmol scale. Yields are isolated yields. See the Supporting Information for details. [b] *tert*-Butyl-3-bromobenzoate was used. [c] Isomer mixture; meta/para ratio = 1/1.2.

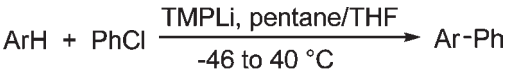
derivatives afford the arylation products in excellent yields (entries 6−8). The arylation is not limited to five-membered-ring heterocycles. Pyridine and pyridazine derivatives are arylated in reasonable yields (entries 9 and 10). Arenes such as 1,3-dimethoxybenzene and 3-methoxybenzotrifluoride are reactive (entries 11 and 12).

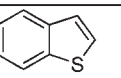
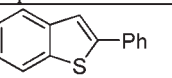
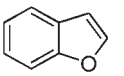
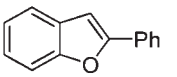
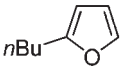
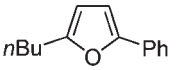
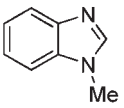
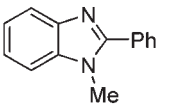
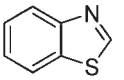
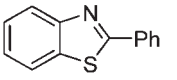
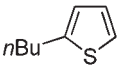
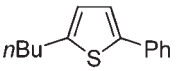
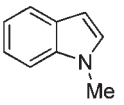
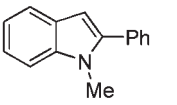
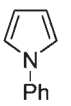
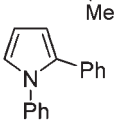
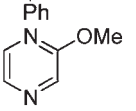
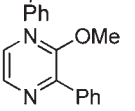
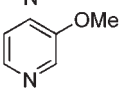
We performed a sequential one-pot diarylation of *N*-methylimidazole. The heterocycle mixture with chlorobenzene was treated with LDA in THF at room temperature, and this was



(1)

Table 2. Arylation Scope with Respect to Heterocycles and Arenes[a]



entry	arene	product	yield, %
1			86 72[b] 85[c]
2			81 75[d]
3			80 68[b]
4			91 81[b]
5			72
6			80 74[b]
7			90
8[e]			78
9			55
10			71
11			95
12			81

[a] Conditions: chlorobenzene (1.3−2 equiv), arene or heterocycle (1 equiv), 0.5 mmol scale. Yields are isolated yields. See the Supporting Information for details. [b] Lithium dicyclohexylamide was used as the base. [c] PhF was used instead of PhCl. [d] $LiN(iPr)_2$ was used as the base. [e] Phenylpyrrole (2 equiv) and PhCl (1 equiv) were used.

followed by quenching with MeOH and evaporation. Following the addition of 2-chloroanisole and TMPLi in THF, a single isomer of the diarylation product was obtained in 50% yield (eq 1).

In conclusion, we have developed a transition-metal-free method for base-promoted arylation of heterocycles and arenes by aryl chlorides and fluorides. The reactions proceed via aryne intermediates at mild temperatures and allow for highly regioselective arylation of the arene and heterocycle C−H bonds. Functionalization occurs at the most acidic carbon−hydrogen bond.

dx.doi.org/10.1021/ja200184b |*J. Am. Chem. Soc.* 2011, 133, 4243–4245

■ ASSOCIATED CONTENT

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

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■ ACKNOWLEDGMENT

We thank the Welch Foundation (Grant E-1571), the National Institute of General Medical Sciences (Grant R01GM077635), the Alfred P. Sloan Foundation, and the Camille and Henry Dreyfus Foundation for supporting this research.

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