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

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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 due to 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 where carbon-hydrogen bond is used as a functional group.² 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 heterocycle and electron-deficient arene arylation results in the functionalization of the most acidic sp^2 C-H bonds.⁴ Several recent reports describe arene and electron-deficient heterocycle arylation by aryl halides that presumably proceed by radical-type mechanisms without transition metal involvement.⁵ The latter methods avoid heavy metal contamination of the products simplifying purification for pharmaceutical applications.⁶ Additionally, these methods are among the simplest synthetic routes to biaryls. However, arylation of simple arenes such as anisole afford isomer mixtures and the arene coupling component is often employed in large excess (up to 100 equivalents) 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 arene coupling component and does not require large excess of any 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 6H-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 aryl anion⁸ 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

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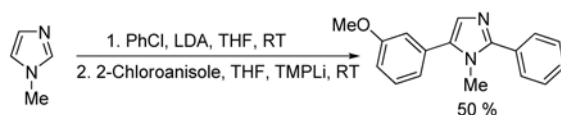
SUPPORTING INFORMATION AVAILABE: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

aryl chloride benzyne sources. Use of hindered 2,2,6,6-tetramethylpiperidides (TMP) should retard the reaction of benzyne with base.¹⁰ Relative reactivity of the base and aryl anion with benzyne can be modulated by employing a solvent where amide base is sparingly soluble. A brief optimization of reaction conditions showed that best results were obtained by employing a mixed pentane/THF solvent system. In pentane, the arylations are slow due to low base solubility. Competitive addition of TMPLi to benzyne decreases arylation yields in THF.

Arylation scope with respect to aryl halides is presented in Table 1. Benzothiophene is arylated by aryl halides in the most acidic position. Arylation by 2-chloroanisole and 2-chlorobenzotrifluoride (entries 1 and 2) affords the *meta*-substituted products in good yields. If benzothiophene is arylated by either 2- or 3-chloro-*N,N*-dimethylaniline, the *m*-substitution product is obtained (entries 3 and 4). This regioselectivity pattern may be advantageous if *o*-chloroarene is more available than the corresponding *m*-isomer. Substitutions by a benzyne mechanism often produce the same isomer if 2- and 3-haloarene starting materials are used.¹¹ Regioselectivity is explained by energy required to distort aryne into two possible transition states and by ground-state polarization of aryne by electron-withdrawing substituents.^{11c} 3,5-Dimethoxychlorobenzene is reactive and 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). If 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, 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, TMPLi base affords slightly higher yields than either lithium dicyclohexylamide or diisopropylamide (entries 1, 2, 3, 4, 6). Fluorobenzene can be used instead of chlorobenzene and nearly identical yields were 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 derivatives afford the arylation products in excellent yields (entries 6, 7, 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 sequential, one-pot diarylation of *N*-methylimidazole. The heterocycle mixture with chlorobenzene was treated with LDA in THF at RT, followed by quench with MeOH and evaporation. Following addition of 2-chloroanisole and TMPLi in THF, a single isomer of diarylation product was obtained in 50% yield (eq 1).



(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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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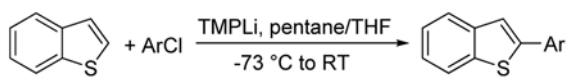
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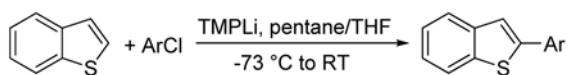
Table 1

Arylation scope with respect to aryl halides^a

entry	aryl halide	product	yield, %
1			78
2			61
3			77
4			81



entry	aryl halide	product	yield, %
5			62
6			75
7			73



entry	aryl halide	product	yield, %
8			60 50 ^b
9			85 ^c

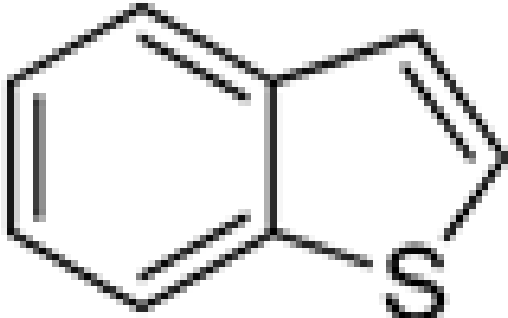
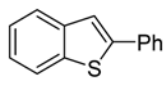
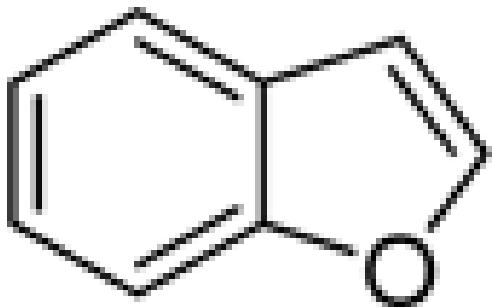
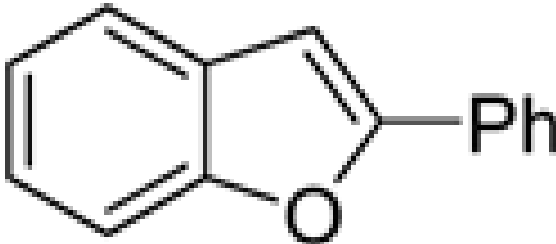
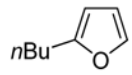
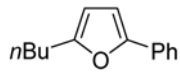
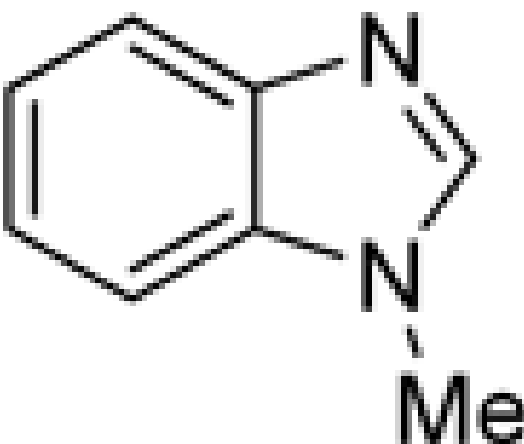
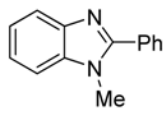
^a Aryl halide (1.6–2.5 equiv), benzothiophene (1 equiv), 0.5 mmol scale. Yields are isolated yields. See Supporting Information for details.

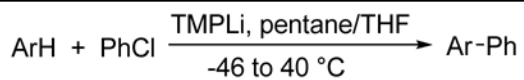
^b *tert*-Butyl-3-bromobenzoate used.

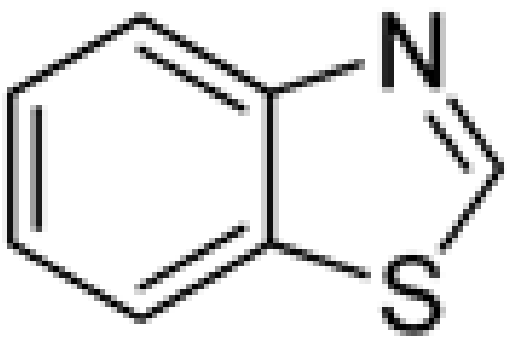
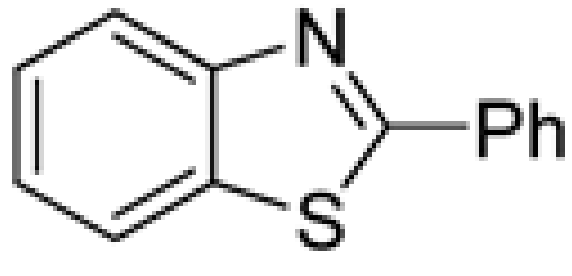
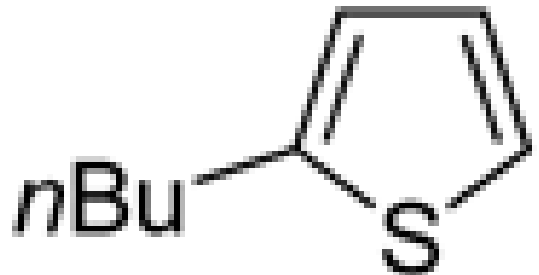

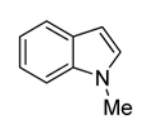
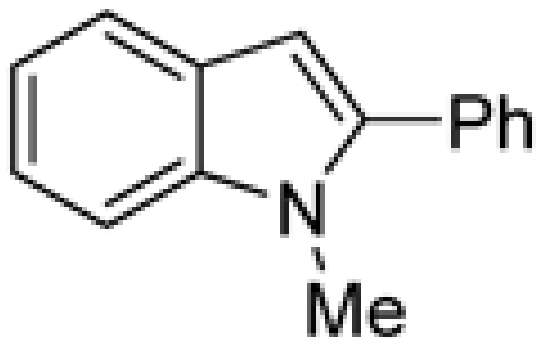
^c Isomer mixture; *m/p* ratio 1/1.2.

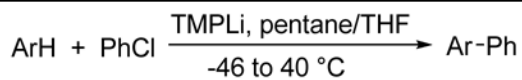
Table 2

Arylation scope with respect to heterocycles and arenes^a

		$\text{ArH} + \text{PhCl} \xrightarrow[-46 \text{ to } 40 \text{ }^\circ\text{C}]{\text{TMPLi, pentane/THF}} \text{Ar-Ph}$			
entry	arene	product		yield, %	
1				86	
				72 ^b	
				85 ^c	
2				81	
				75 ^d	
3				80	
				68 ^b	
4				91	
				81 ^b	

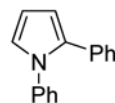


entry	arene	product	yield, %
5			72
6			80 74 ^b
7			90



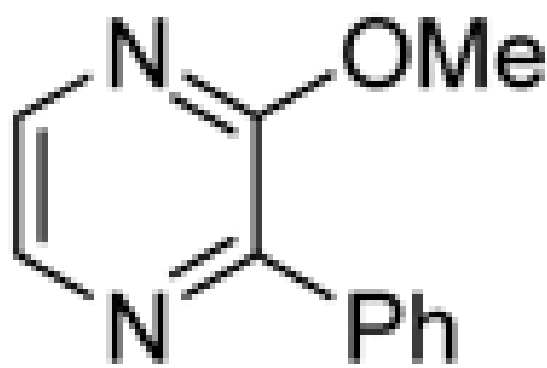
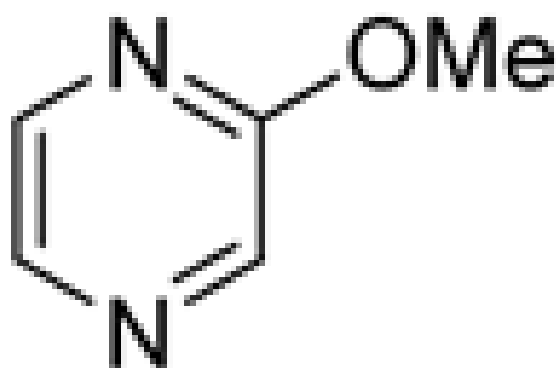
entry	arene	product	yield, %
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8^e

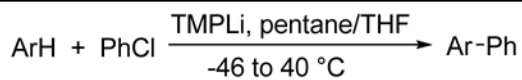


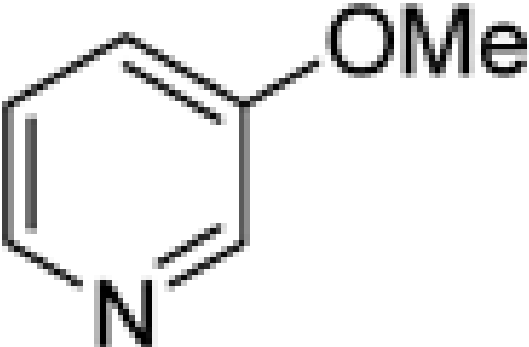
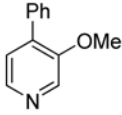
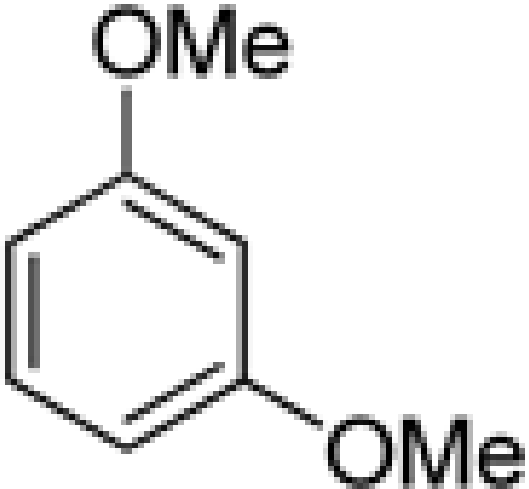
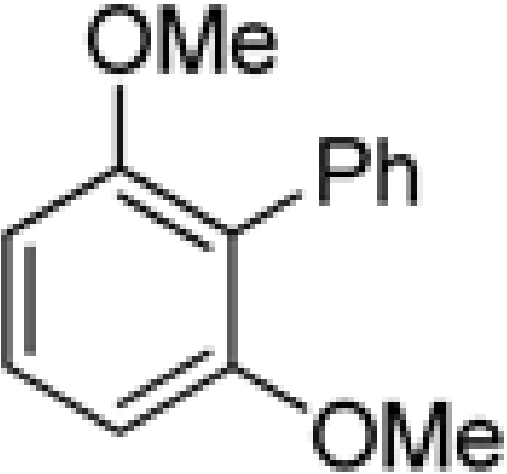
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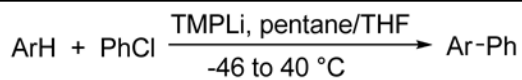
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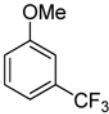
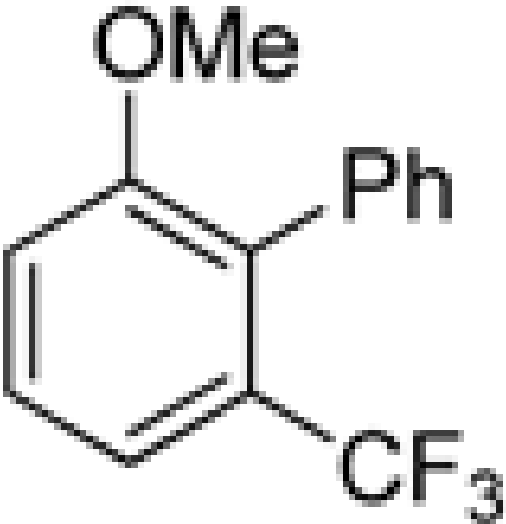


55



entry	arene	product	yield, %
10			71
11			95



entry	arene	product	yield, %
12			81

^aChlorobenzene (1.3–2 equiv), arene or heterocycle (1 equiv), 0.5 mmol scale. Yields are isolated yields. See Supporting Information for details.

^bLithium dicyclohexylamide base.

^cPhF used instead of PhCl.

^dLiNiPr₂ base.

^ePhenylpyrrole (2 equiv), PhCl (1 equiv).