

Published in final edited form as:

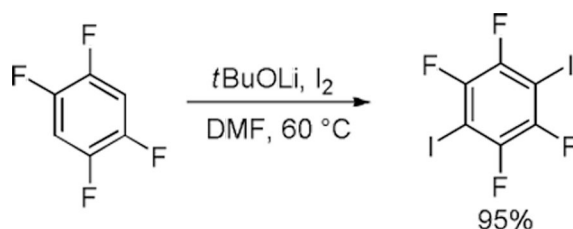
Org Lett. 2009 January 15; 11(2): 421–423. doi:10.1021/ol802411f.

A Simple Base-Mediated Halogenation of Acidic sp^2 C-H Bonds under Non-Cryogenic Conditions

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Abstract



A new method has been developed for *in situ* halogenation of acidic sp^2 carbon-hydrogen bonds in heterocycles and electron-deficient arenes. Either selective monohalogenation or one-step exhaustive polyhalogenation is possible for substrates possessing several C-H bonds that are flanked by electron-withdrawing groups. For the most acidic arenes, such as pentafluorobenzene, K_3PO_4 base can be employed instead of BuLi for metalation/halogenation sequences.

We have recently developed a method for copper-catalyzed arylation of sp^2 C-H bonds possessing DMSO pKa's below 35.¹ The reaction was shown to proceed via an aryllithium or arylpotassium intermediate that is formed *in situ* by the reaction of the arene with either K_3PO_4 or *t*BuOLi metalating agent (Scheme 1A). It occurred to us that halogenation of arenes that are reactive under the copper-catalyzed arylation conditions should be possible under mild nucleophilic conditions by employing relatively weak bases such as K_3PO_4 or *t*BuOLi (Scheme 1B). Current methods for halogenation of electron-deficient arenes such as polyfluoro- or polychlorobenzenes involve either harsh electrophilic conditions or the use of strong alkylolithium bases and cryogenic conditions.² If the positive halogen source would form an active halogenating agent in the reaction with base, an *in situ* trapping of the arylmetal species should be possible. Martin has reported use of a strong LiTMP base for *in situ* deprotonation/silylation of aromatic nitriles, esters, and pyridine derivatives.³ Other relevant examples include trifluorobenzene metalation by *t*BuLi in the presence of TMSCl first reported by Gilman and reinvestigated by Schlosser as well as Kondo's report on functionalizing electron-rich and electron-deficient arenes by employing *t*-Bu-P4 base/electrophile combinations.⁴ Several other groups have described similar methodologies with either silyl or boryl-derived electrophiles.⁵ It appears, however, that *in situ* trapping has not been widely applied to arene halogenation.^{3d,e} Furthermore, potassium phosphate and *t*BuOLi have not been employed as metalating agents for such reactions. We report here a simple method for *in situ* halogenation of sp^2 C-H bonds in heterocycles as well as electron-deficient arenes under non-cryogenic conditions.

Minor modifications of the copper-catalyzed arylation conditions allowed the development of an efficient process for *in situ* sp^2 C-H bond halogenation. The scope of the halogenation reaction is presented in Table 1. Electron-rich heterocycles such as benzothiazole, butylimidazole, and phenyloxazole can be chlorinated and brominated (entries 1–4). The halogenating reagent must be optimized for each case. Either carbon tetrahalides (entries 1–3) or dibromotetrafluoroethylene (entry 4) may be employed for electron-rich heterocycle halogenation.

Electron-deficient heterocycles such as pyridine *N*-oxide and 2-phenylpyridine *N*-oxide are brominated by employing a mixture of *t*BuOLi base and carbon tetrabromide (entries 5 and 6). For pyridine *N*-oxide, dihalogenation/reduction to the dibromopyridine product is obtained in a moderate yield (entry 6). Selective monohalogenation of pyridine *N*-oxide was not achieved under a variety of conditions. In contrast with the copper-catalyzed arylation process, halogenation is unsuccessful for pyridazine and pyrimidine, presumably due to their insufficient acidity.⁶ Consequently, higher acidity is required for the halogenation reaction if it is compared to arylation.⁷

Electron-deficient arenes can also be efficiently halogenated (entries 7–14). Pentachlorobenzene is iodinated in excellent yield by using a combination of iodine(I) chloride and *t*BuOLi in DMF (entry 7). Nitro and cyano groups are tolerated as shown in bromination of 3-nitrofluorobenzene (entry 8) and one-step tribromination of 3,5-difluorobenzonitrile (entry 9). For the latter substrate, selective monohalogenation could not be achieved. If acidic pentafluorobenzene is halogenated, even the weak K_3PO_4 base can be employed (entry 10), affording iodopentafluorobenzene in excellent yield. Previously, butyllithium has been used for pentafluorobenzene deprotonation-reaction with electrophiles sequences.⁸ Monoiodination of methoxytetrafluorobenzene and one-step diiodination of 1,2,4,5-tetrafluorobenzene affords the corresponding halides in excellent yields (entries 11 and 12). 1,3,5-Trifluorobenzene can be either monoiodinated or triiodinated in acceptable yields depending on the ratio of arene to iodine(I) chloride (entries 13 and 14). 1,3-Dihalobenzenes are insufficiently acidic and are unreactive under these conditions. Attempted bromination of 1,3-dinitrobenzene resulted in about 10% conversion to the product. 1,3,5-Trinitrobenzene decomposes under the reaction conditions.

The halogenation of electron-deficient arenes most likely proceeds by an initial generation of equilibrium concentration of the aryl anion followed by reaction with an electrophile.^{3d,e} The lifetime of aryllithium and arylpotassium species must be short since significant amounts of benzyne-derived products are not formed.

At this point we are unsure about the exact structure of the electrophilic halogenating agent. It is conceivable that the reaction of *t*BuOLi with the halogen electrophile may produce a *t*-butyl hypohalide.⁹ However, it is known that, at least for iododerivative, the structure of the hypohalide varies with the method of preparation.¹⁰

In conclusion, we have developed a new method for *in situ* halogenation of acidic sp^2 carbon-hydrogen bonds in heterocycles and electron-deficient arenes. Either monohalogenation or one-step polyhalogenation is possible for substrates possessing several C-H bonds that are flanked by electron-withdrawing groups. For the most acidic substrates, such as pentafluorobenzene, K_3PO_4 base can be employed instead of the currently used BuLi for metalation/functionalization sequences.

Supplementary Material

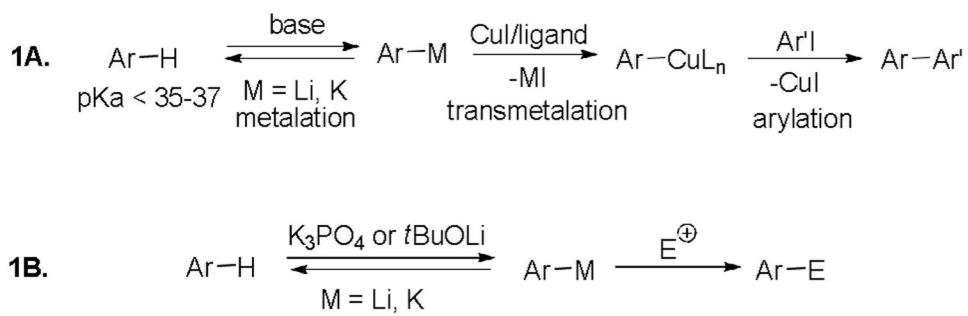
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Acknowledgment

We thank the Welch Foundation (Grant No. E-1571), the NIGMS (Grant No. R01GM077635), A. P. Sloan Foundation, and Camille and Henry Dreyfus Foundation for supporting this research. We also thank Prof. Hans J. Reich (University of Wisconsin-Madison) for helpful comments.

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
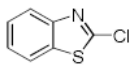

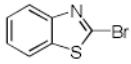


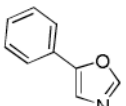
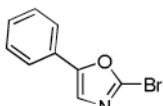
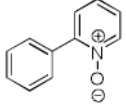
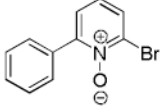
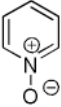
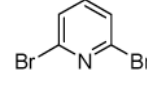
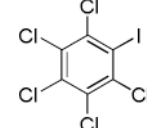


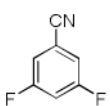
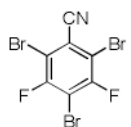
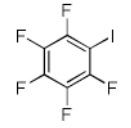
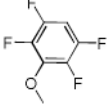
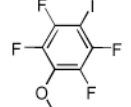
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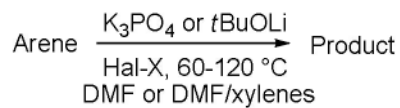


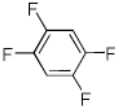
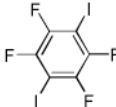
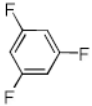
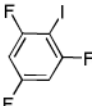
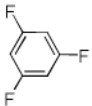
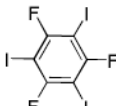
Scheme 1.
Functionalization of Acidic sp^2 C-H Bonds.

Table 1

Halogenation scope.^a

$\text{Arene} \xrightarrow[\text{DMF or DMF/xylenes}]{\text{K}_3\text{PO}_4 \text{ or } t\text{BuOLi, Hal-X, 60-120 } ^\circ\text{C}} \text{Product}$				
entry	arene	reagent base	product	yield
1		CCl ₄ <i>t</i> BuOLi		80%
2		CBr ₄ K ₃ PO ₄		82%
3		CBr ₄ <i>t</i> BuOLi		91%
4		(BrCF ₂) ₂ <i>t</i> BuOLi		80%
5		CBr ₄ <i>t</i> BuOLi		56%
6 ^b		CBr ₄ <i>t</i> BuOLi		30%
7	C ₆ Cl ₅ H	ICI <i>t</i> BuOLi		90%
8		CBr ₄ <i>t</i> BuOLi		55%
9		CBr ₄ <i>t</i> BuOLi		40%
10	C ₆ F ₅ H	I ₂ K ₃ PO ₄		85%
11		I ₂ <i>t</i> BuOLi		98%



entry	arene	reagent base	product	yield
12		I ₂ <i>t</i> BuOLi		95%
13 ^c		ICl <i>t</i> BuOLi		58%
14 ^d		ICl <i>t</i> BuOLi		39%

^aSubstrate (1 equiv), base (2–4 equiv), halogenating reagent (1.5–4 equiv). Yields are isolated yields. See the Supporting Information for details.

^b*m*-Xylene solvent.

^c1,3,5-Trifluorobenzene (3 equiv), ICl (1 equiv).

^d1,3,5-Trifluorobenzene (1 equiv), ICl (4 equiv).