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In Situ Generation and Trapping of Aryllithium and Arylpotassium Species by Halogen, Sulfur, and Carbon Electrophiles

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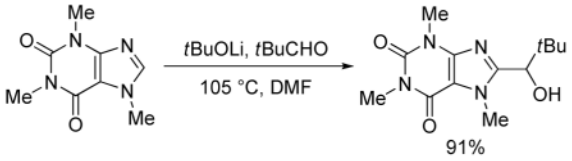
Abstract

A general method has been developed for in situ trapping of arylmetal intermediates by halogen, sulfur, ketone, and aldehyde electrophiles affording the functionalization of the most acidic position in arene. Pentafluorobenzene, benzothiazole, and benzoxazole can be functionalized by using K_3PO_4 base. For less acidic arenes, *t*BuOLi base is required. Arenes with DMSO pKa's of 35 or less are reactive.



1. Introduction

Arene deprotonation followed by quench with electrophiles is a powerful method for introducing functionality in organic molecules (Scheme 1A). Typically, such reactions require cryogenic conditions and limited functional group tolerance is observed due to the possibility of aryl(alkyl)lithium reaction with electrophilic groups in arene molecule. Alternatively, in situ trapping techniques allow simultaneous presence of base and electrophile in the reaction mixture (Scheme 1B).[1] This concept was developed by Martin for arene deprotonation/silylation sequences.[1a,b] LiTMP/TMSCl mixtures were employed for functionalization of aromatic nitriles, esters, and pyridines. Low concentrations of intermediate aryllithium species result in increased functional group tolerance. Other examples of in situ trapping sequences include trifluorobenzene metalation by *t*BuLi in the presence of TMSCl that has been described by Gilman and reinvestigated by Schlosser[1c,d] as well as nitrofluorobenzene, N-Boc-indole, and substituted bromobenzene lithiation/silylation.[1e,f,g] Exhaustive bromination of cyclopentadiene by a mixture of KOH/KOBr was reported in 1930.[1h] Bunnett has shown that tribromobenzene can be brominated by treatment with a mixture of *t*BuOK and *t*BuOBr.[1i] Several groups have demonstrated that in situ metalation/boronation sequences are successful for protected indoles, neopentyl benzoates, benzonitriles, halobenzenes, and pyridylamides.[1f,2] Metalation of pentafluorobenzene by KOH/liquid NH_3 in the presence of methyl iodide results in the formation of pentafluorotoluene.[3] Organic bases have also been used for in situ generation/trapping of aryl anions. 2-Acylimidazoles have been prepared by the reaction of imidazoles and benzimidazoles with acid chlorides in the presence of triethylamine base.[4] Presumably, N-acylation is followed by deprotonation of the acidic C-2 proton and subsequent

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

acyl migration affords the final product. Silylations under similar conditions have also been successful.[5] Finally, Kondo has shown that electron-rich and electron-deficient arenes can be functionalized by employing *t*Bu-P4 base/non-enolizable ketone and aldehyde mixtures.[6]

We have recently developed a method for copper-catalyzed arylation of sp^2 C-H bonds possessing DMSO pKa's below 35.[7a] The reaction was shown to proceed via an aryllithium or arylpotassium intermediate formed *in situ* by the reaction of the arene with either K_3PO_4 or *t*BuOLi metalating agent (Scheme 2A). It occurred to us that electrophilic trapping of arylmetals formed under the copper-catalyzed arylation conditions may result in a convenient method for functionalization of acidic arenes (Scheme 2B). Preliminary results describing arene in situ halogenation were recently disclosed.[7b] We report here a method for arylmetal in situ trapping with halogen, sulfur, and carbonyl electrophiles.

2. Results and Discussion

2.1 Halogenation

Minor modifications of the copper-catalyzed arylation conditions[7b] allowed the development of an efficient process for *in situ* sp^2 C-H bond halogenation. The reactions are carried out in DMF or mixed DMF/xylenes solvent at 50–130 °C (Table 1). Halogen electrophile needs to be optimized for each reaction. Carbon tetrachloride and tetrabromide (entries 1, 2, 6, 7, 9, 10) as well as dibromotetrafluoroethane (entries 3–5), iodine (entries 11–12, 15), and ICl (entries 8, 13, 14) can be employed. Electron rich heterocycles such as benzothiazole (entries 1, 2), *N*-phenyltriazole (entry 3), caffeine (entry 4), and 5-phenyloxazole (entry 5) are halogenated in the most acidic positions.[8] Electron-poor pyridine oxides are also halogenated under the optimized conditions (entries 6 and 7). For pyridine oxide reaction with carbon tetrabromide, dibromination-deoxygenation product is obtained in 30% yield.

Halogenation of electron-poor arenes is also successful. Typically, such reactions require either harsh electrophilic conditions or use of strong alkylithium bases and cryogenic conditions.[9] By employing in situ trapping conditions, either *t*BuOLi or weak K_3PO_4 bases can be used under relatively mild temperatures (50–130 °C). Polychloro- and polyfluoroarenes can be halogenated in moderate to high yields (entries 8, 11–15). Cyano- (entry 10) and nitro (entry 9) groups are tolerated. Selective mono (entry 13) or polyhalogenation (entries 10, 12, 14) is possible by changing the reaction stoichiometry. The following substrates were not efficiently halogenated: 1,3-dinitrobenzene, 1,3,5-trinitrobenzene, 1,3-difluorobenzene, pyrimidine, and pyridazine. Either low conversions (<10%) or substrate decomposition was observed.

2.2 Reactions with Sulfur Electrophiles

We also show that sulfur electrophiles can be employed for in situ trapping of arylmetals (Table 2). One can employ either elemental sulfur or diphenyldisulfide as the trapping agent. The reaction scope is somewhat limited compared with the halogenation reaction. Electron-rich heterocycles such as benzoxazole and *N*-phenyl-1,2,4-triazole react with sulfur in the presence of *t*BuOLi base to afford the respective thiones (entries 1, 2). Phenylsulfenylation can be effected by the reaction with diphenyl disulfide (entries 3–7). Benzothiazole, *N*-phenylbenzimidazole, *N*-methyl-1,2,4-triazole, and *N*-phenylpyrazole can be converted to the corresponding *S*-phenyl derivatives. The reaction of 2-chlorothiophene with PhSSPh afforded 2,5-bis(phenylthio)thiophene. Less acidic pyrazole derivative requires the use of a stronger *t*BuOK base for high conversion to the product. The limitations of the reaction are as follows. Dibutyl disulfide reacts with benzothiazole to form the benzothiazolethione by butylsulfenylation/dealkylation. Alkyl aryl ether containing substrates such as tetrafluoroanisole are dealkylated by RS^- that is formed in the reaction mixture.

Polyfluoroarenes such as 1,3,5-trifluorobenzene undergo nucleophilic substitution of fluorides in addition to the desired reaction.

2.3. Reactions with Carbonyl Electrophiles

An impressive advance in aryl anion in situ trapping by nonenolizable ketones and aldehydes has been demonstrated previously by Kondo.[6] However, expensive phosphazene bases were employed and only benzophenone and pivalaldehyde electrophiles were employed. A thermal reaction of *N*-alkylimidazoles with aldehydes affording addition products at the 2-position has been reported by Roe.[10] A similar iridium-catalyzed reaction between imidazoles, aldehydes, and dimethylethylsilane producing 2-substituted imidazoles was published by Murai.[11] Hlasta has shown that imidazoles, thiazoles, and triazoles can react with aldehydes in the presence of acid chlorides and triethylamine to give 2-substituted azoles.[12] A more general method that would allow functionalization of a variety of substrates by employing cheaper reagents would be useful.

The results of in situ trapping with aldehydes and ketones are presented in Table 3. Electron-rich heterocycles such as 2-chlorothiophene, benzothiazole, *N*-phenyltriazole, caffeine, and benzoxazole are reactive (entries 1–4, 8). In situ trapping can be extended to electron-deficient arenes such as substituted tetrafluorobenzenes (entries 5–7). Both ketones and aldehydes can be employed as the carbonyl component. For the most acidic substrates such as benzoxazole, the reaction with enolizable cyclohexanecarbaldehyde is successful producing the addition product in acceptable yield (entry 8). Reactions fail with primary enolizable aldehydes due to aldol condensation. It is known that base-catalyzed self-condensation of secondary aldehydes is reversible, in contrast to acetaldehyde self-aldol that has been described as “sufficiently irreversible” reaction.[13]

3. Conclusions

We have developed a method for in situ trapping of aryllithium and potassium species with halogen, sulfur, ketone, and aldehyde electrophiles. For halogen and carbonyl electrophiles, both five-membered ring heterocycles and electron-deficient arenes are reactive. Heterocycle anion trapping is successful also with sulfur electrophiles. In the case of most acidic arenes such as pentafluorobenzene, benzothiazole, and benzoxazole, K_3PO_4 base can be employed instead of the currently used alkyllithiums for metalation/functionalization sequences.

Experimental Section

General procedure for halogenation—Outside the glovebox a 1-dram or 2-dram vial equipped with a magnetic stir bar was charged with substrate (1.0 or 2.0 mmol) and halogenating reagent (1.0–3.0 equiv). The vial was flushed with argon, capped and placed inside a glovebox. To this mixture anhydrous DMF or a mixture (1/1) of DMF and xylenes (1.0 mL) was added, followed by base (K_3PO_4 or *t*BuOLi, 2.0–4.0 equiv). The sealed vial was taken out of the glovebox and placed in a preheated oil bath (50–130 °C) for the indicated time. The reaction mixture was allowed to cool to room temperature and subjected to flash chromatography on silica gel. After concentrating the fractions containing the product, the residue was dried under reduced pressure to yield pure halogenation product.

8-Bromo-3,7-dihydro-1,3,7-trimethyl-*1H*-purine-2,6-dione (Entry 4, Table 1)—Caffeine (194 mg, 1.0 mmol), dibromotetrafluoroethane (780 mg, 3.0 mmol), *t*BuOLi (320 mg, 4.0 mmol), and DMF (2.0 mL), 100 °C, 13 hours. After column chromatography (gradient 10%–15% AcOEt in CH_2Cl_2) 176 mg (65%) of a white solid was obtained. R_f=0.25 (SiO_2, hexanes/AcOEt 1/1). This compound is known.[14] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.56 (s, 3H), 3.97 (s, 3H).

General procedure for reaction with sulfur electrophiles—Outside the glovebox a 1-dram or 2-dram vial equipped with a magnetic stir bar was charged with substrate (1.0–2.0 mmol) and sulfur electrofile (1.5–8.0 equiv). The vial was flushed with argon, capped and placed inside a glovebox. To this mixture anhydrous DMF or DMPU (1.0–2.0 mL) was added, followed by base (K_3PO_4, *t*BuOK or *t*BuOLi, 1.5–3.0 equiv). The sealed vial was taken out of the glovebox and placed in a preheated oil bath (80–130 °C) for the indicated time. The reaction mixture was allowed to cool to room temperature, quenched with 15% aqueous citric acid, extracted with AcOEt, washed with brine, dried over anhydrous $MgSO_4$, filtered and subjected to flash chromatography on silica gel or preparative TLC. After concentrating the fractions containing the product, the residue was dried under reduced pressure to yield pure product.

1-Phenyl-2-(phenylthio)-*1H*-benzimidazole (Entry 4, Table 2)—1-Phenylbenzimidazole (388 mg, 2.0 mmol), diphenyl disulfide (873 mg, 4.0 mmol), *t*BuOLi (320 mg, 4.0 mmol), and DMF (2.0 mL), 130 °C, 12 hours. After column chromatography (30% CH_2Cl_2 in hexanes, CH_2Cl_2, then 30% AcOEt in CH_2Cl_2) 512 mg (84%) of a light tan solid was obtained. R_f=0.52 (SiO_2, hexane/AcOEt 3/1). Analytical sample was recrystallized from hexanes/AcOEt, mp 92–94 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09–7.15 (m, 1H), 7.17–7.54 (m, 12H), 7.56–7.80 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.2, 119.7, 122.9, 123.5, 127.6, 128.4, 129.1, 129.4, 129.7, 131.1, 132.4, 135.7, 137.5, 143.4, 149.5. FT-IR (neat, cm^{-1}) υ 1497, 1424, 1343, 1260, 1220. Anal calcd for $C_{19}H_{14}N_2S$ (302.39 g/mol): C, 75.47; H, 4.67; N, 9.26; Found. C, 75.41; H, 4.60; N, 9.21.

General procedure for reaction with carbon electrophiles—Outside the glovebox a 1-dram or 2-dram vial equipped with a magnetic stir bar was charged with substrate (1.0–2.0 mmol) and aldehyde or ketone (3.0 equiv). The vial was flushed with argon, capped and placed inside a glovebox. To this mixture anhydrous DMF (1.0–2.0 mL) was added, followed by base (K_3PO_4 or *t*BuOLi, 1.5–3.0 equiv). The sealed vial was taken out of the glovebox and was placed in a preheated oil bath (60–105 °C) or stirred at RT for the indicated time. The reaction mixture was allowed to cool to room temperature, quenched with 15% aqueous citric acid, extracted with AcOEt, washed with brine, dried over anhydrous $MgSO_4$, filtered and subjected to flash chromatography on silica gel or preparative TLC. After concentrating the fractions containing the product, the residue was dried under reduced pressure to yield pure product.

(4-Chlorophenyl)(2,3,5,6-tetrafluoro-4-methoxyphenyl)methanol (Entry 6, Table 3)—2,3,5,6-Tetrafluoroanisole (180 mg, 1.0 mmol), 4-chlorobenzaldehyde (422 mg, 3.0 mmol), t-BuOLi (120 mg, 1.5 mmol), and DMF (1.0 mL), RT, 2 hours. After column chromatography (gradient 30%–60% CH_2Cl_2 in hexanes) 300 mg (93%) of a colorless oil was obtained. R_f=0.45 (SiO_2, hexanes/CH_2Cl_2 1/4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.64 (dt, *J*=7.5 Hz, 1.1 Hz, 1H), 4.08 (t, *J*=1.4 Hz, 3H), 6.18 (d, *J*=7.5 Hz, 1H), 7.33 (s, 4H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −160.6– −160.4 (m, 2F), −148.2 – −148.0 (m, 2F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.6 (t, $J_{C\text{-}F}$=3.6 Hz), 67.4 (quintet, $J_{C\text{-}F}$=2.4 Hz), 114.5–115.4 (m), 127.4, 129.3, 134.4, 138.3–140.0 (m), 140.1, 142.8–143.9 (m), 146.6–147.3 (m). FT-IR (neat, cm^{-1}) υ 3387, 1651, 1491, 1438, 1416, 1196, 1132, 1092. Anal calcd for $C_{14}H_9ClF_4O_2$ (320.67 g/mol): C, 52.44; H, 2.83; Found. C, 52.40; H, 2.88. At elevated temperatures, base-catalyzed formation of p-chlorobenzyl p-chlorobenzoate is observed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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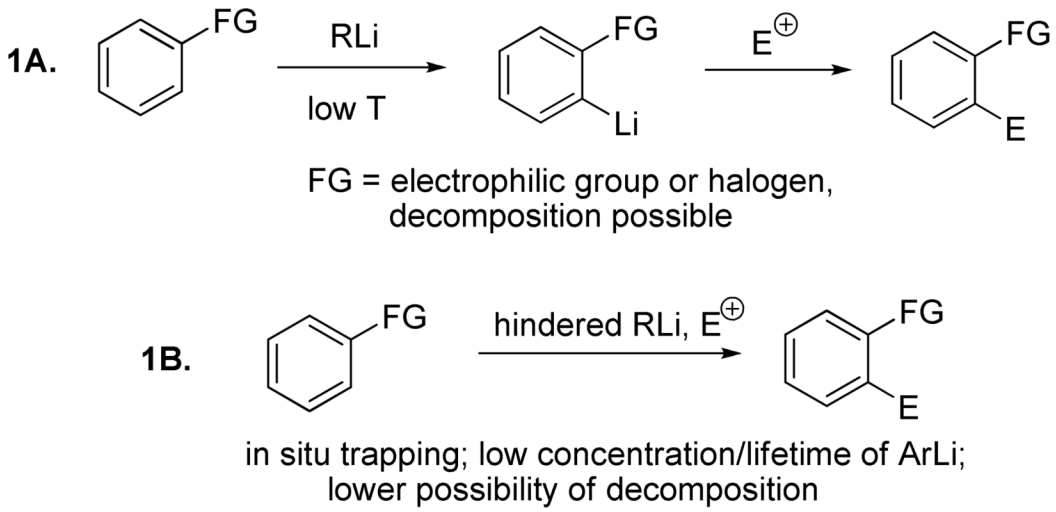
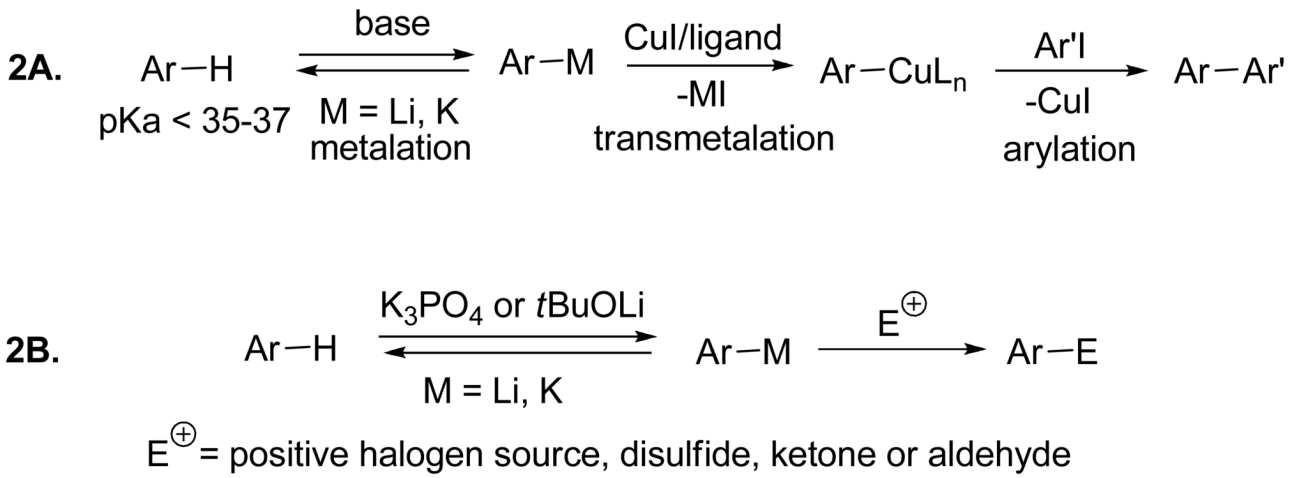


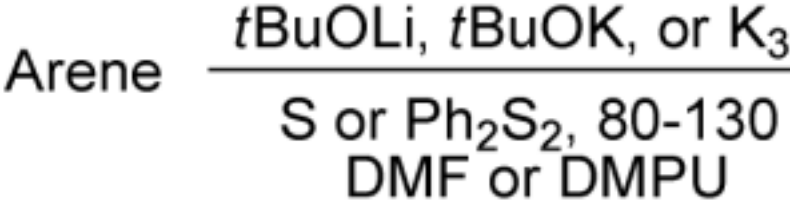
Scheme 1.
Arene Deprotonation/Electrophilic Quench



Scheme 2.
Deprotonative Functionalization of Arene Carbon-Hydrogen Bonds

Table 1

In Situ Halogenation



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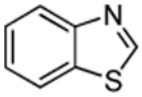
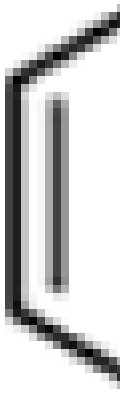
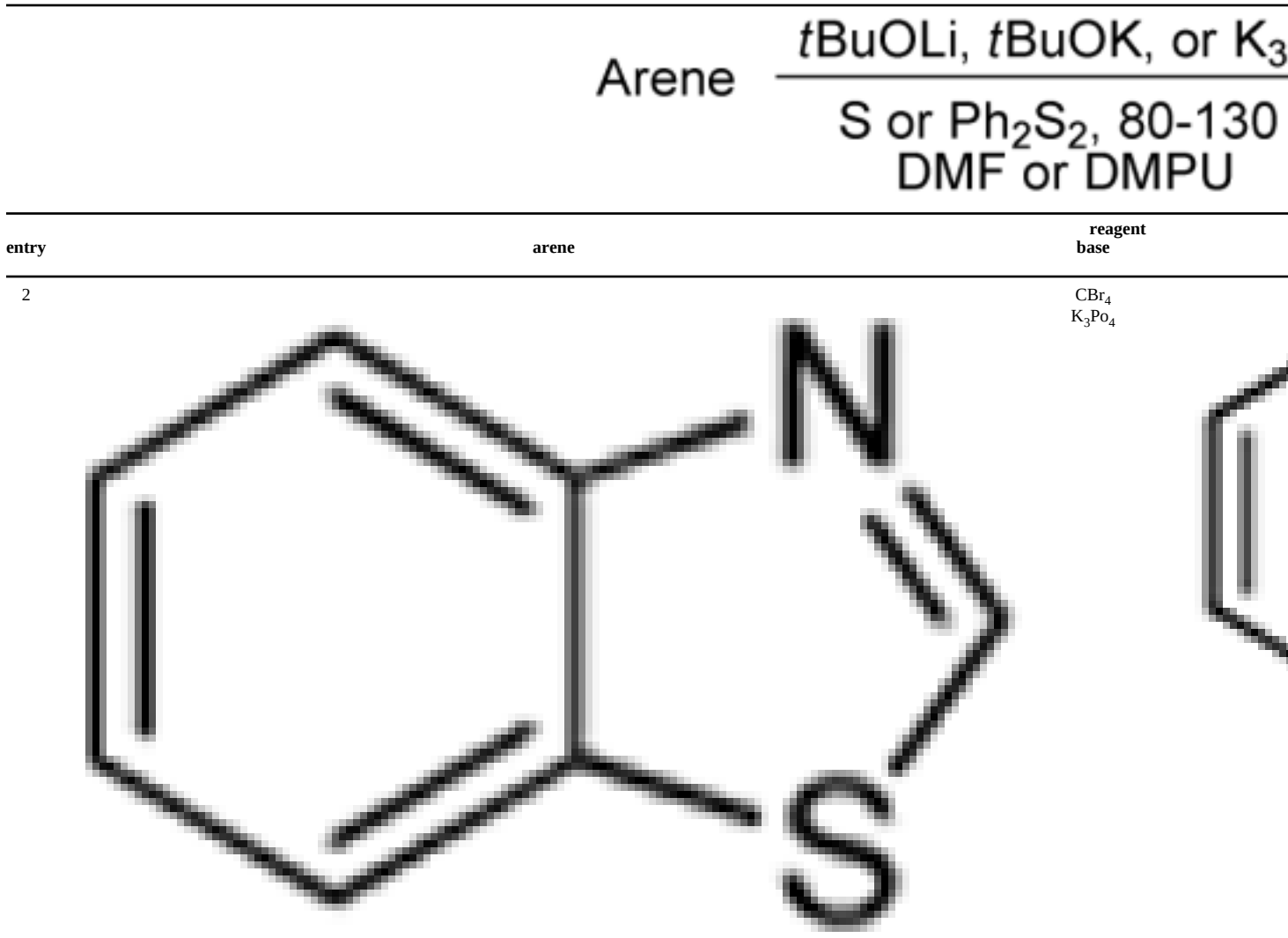
1		CCl_4 *t*BuOLi





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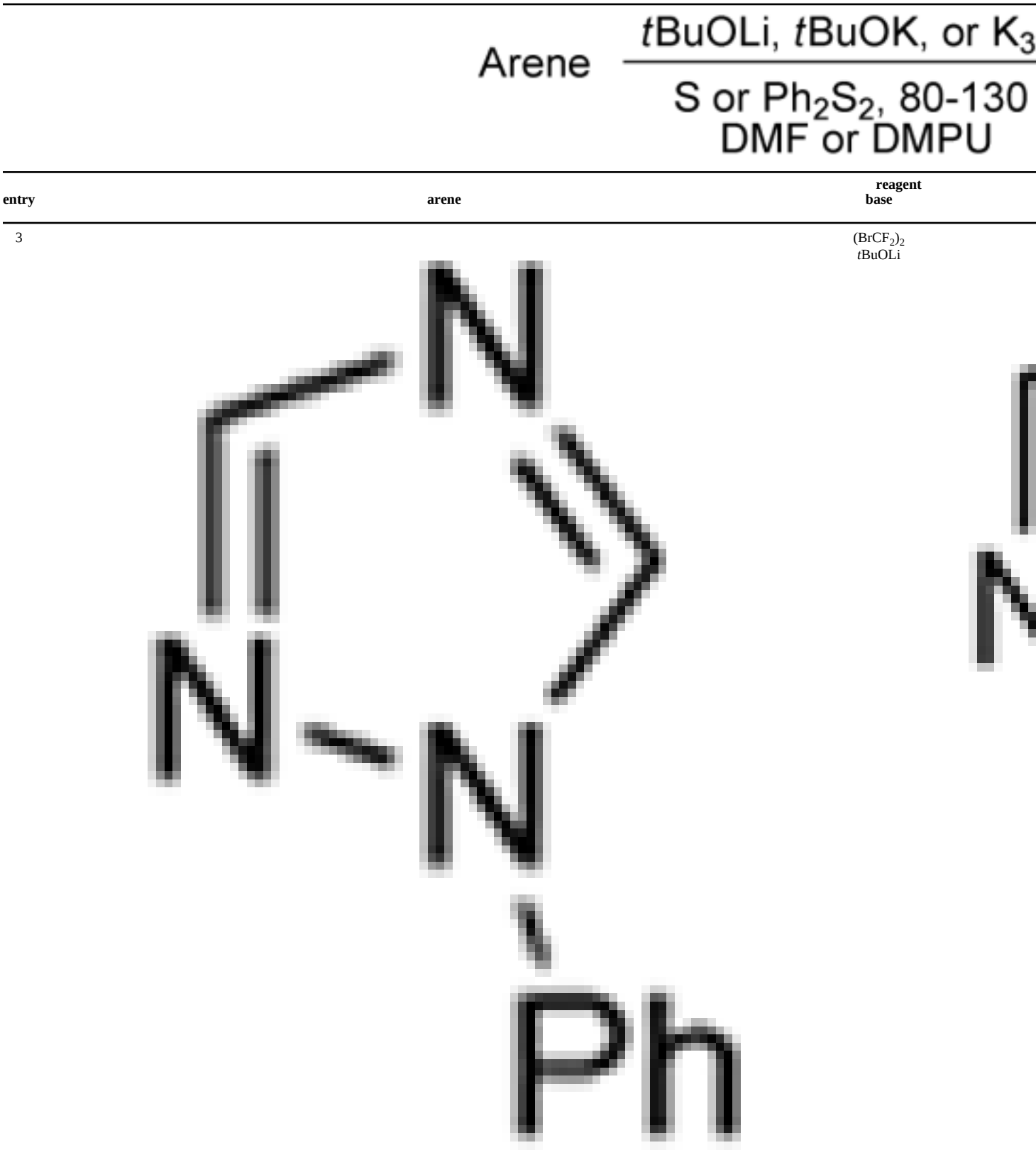
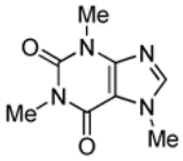
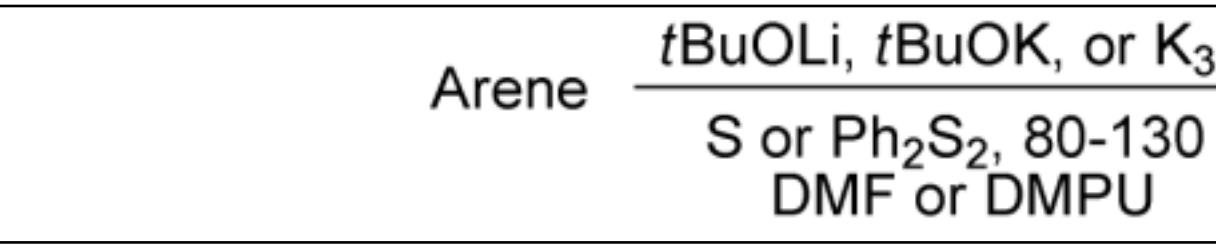


entry	arene	reagent base
3		$(BrCF_2)_2$ *t*BuOLi

Arene —(*t*BuOLi, *t*BuOK, or K_3 / S or Ph_2S_2, 80-130 / DMF or DMPU)→

entry	arene	reagent base
4		$(BrCF_2)_2$ *t*BuOLi



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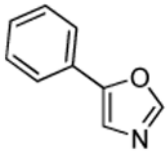
5		$(BrCF_2)_2$ *t*BuOLi

Arene —(*t*BuOLi, *t*BuOK, or K_3 / S or Ph_2S_2, 80-130 / DMF or DMPU)→

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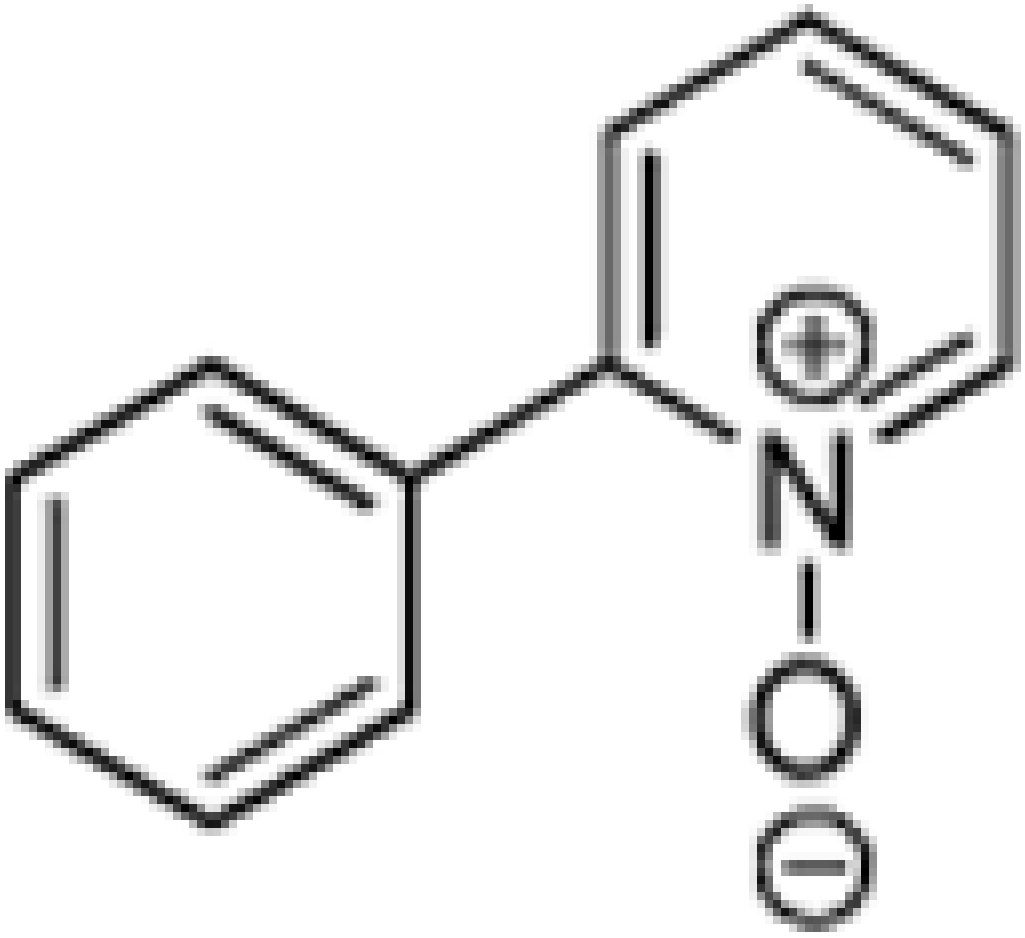
6		CBr_4 *t*BuOLi

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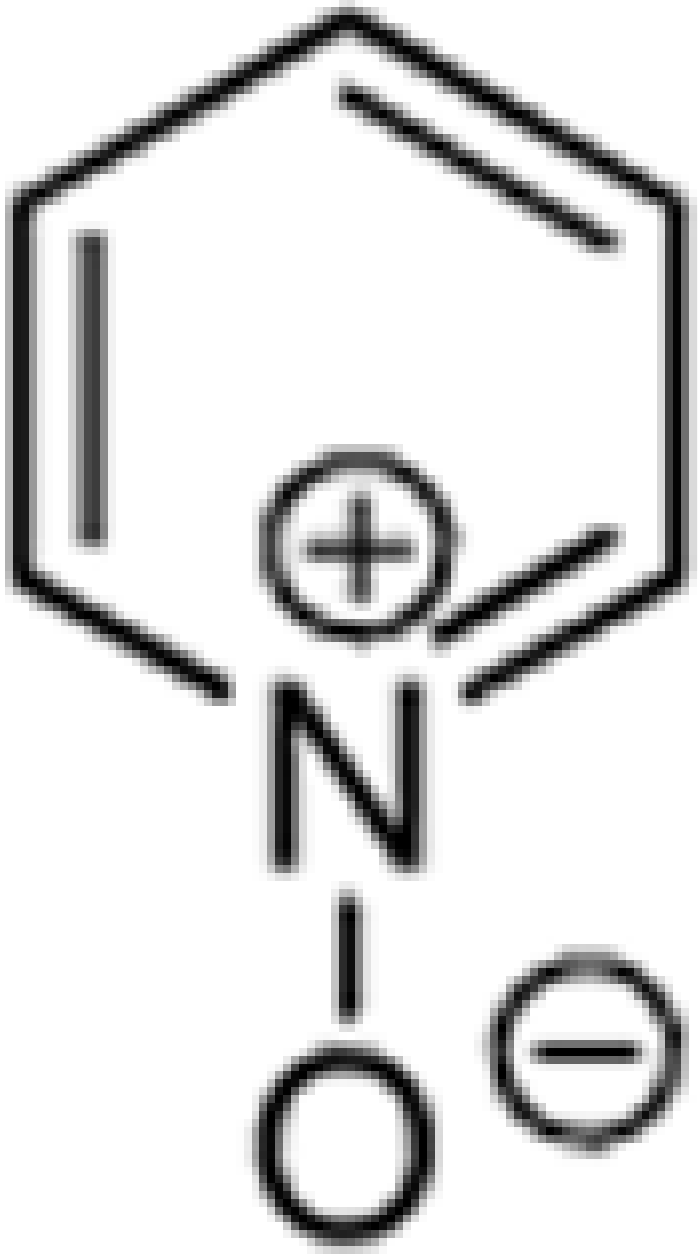
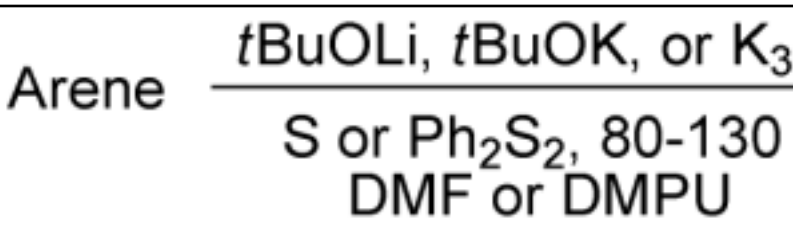
7[b]		CBr_4 *t*BuOLi



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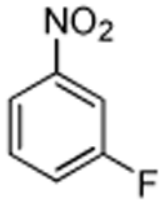
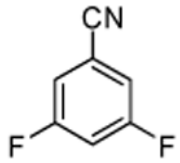
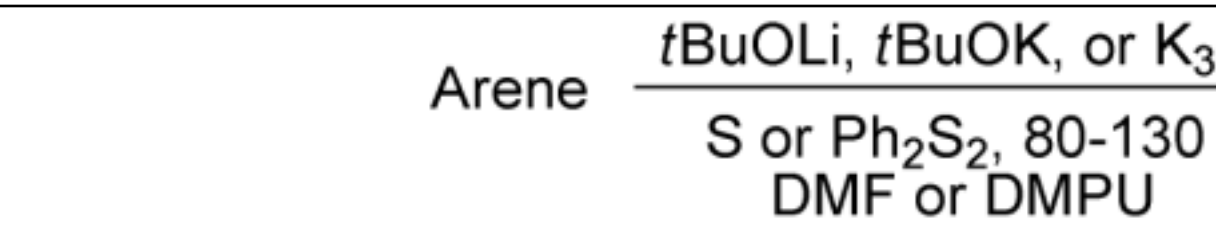
9		CBr_4 *t*BuOLi
10		CBr_4 *t*BuOLi



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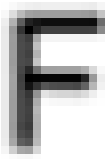
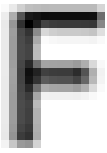
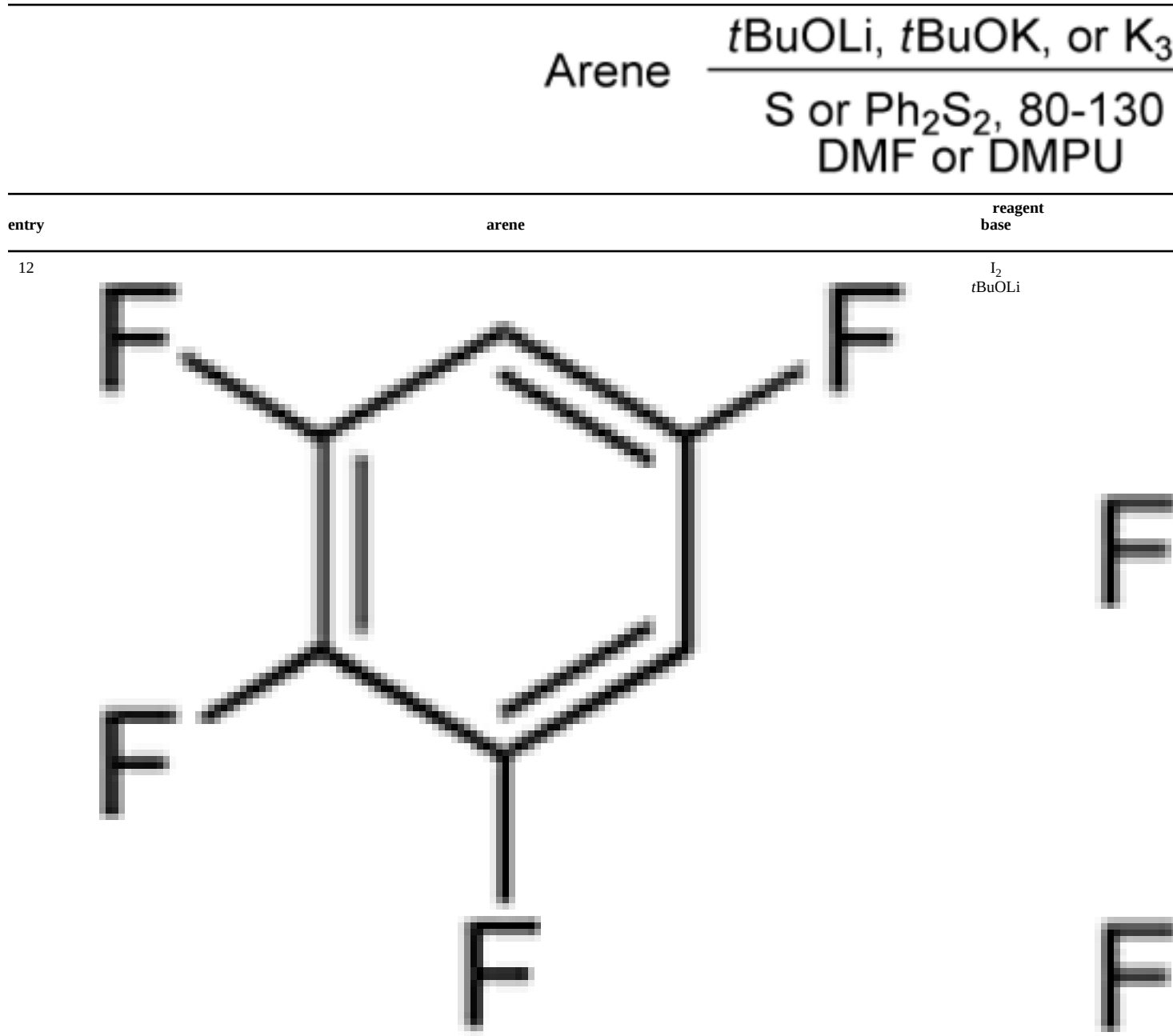
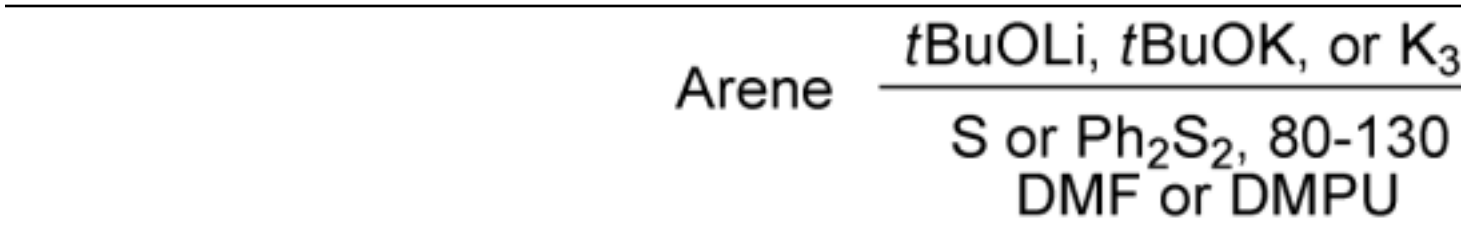
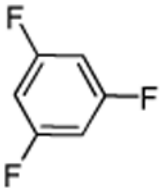


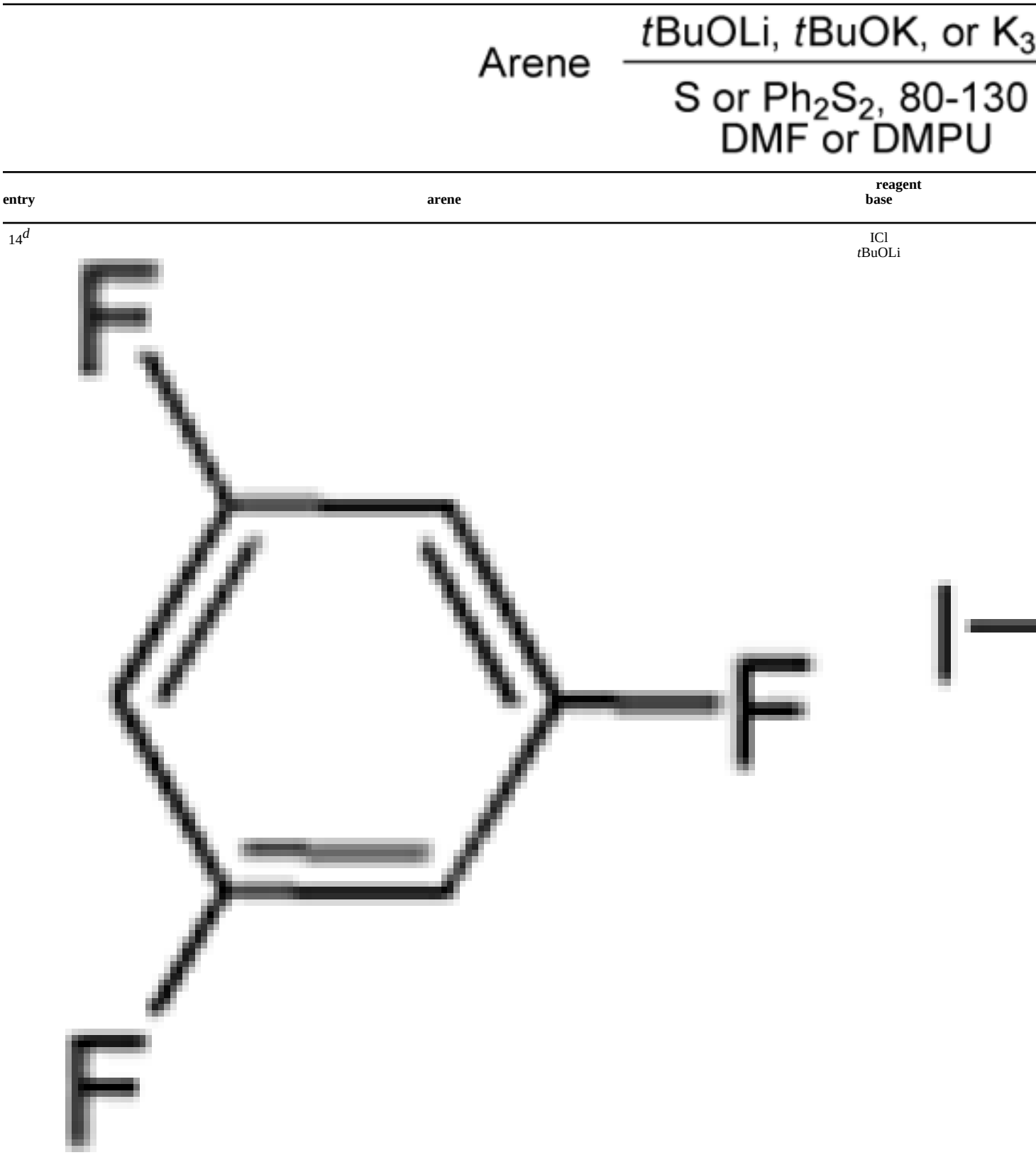




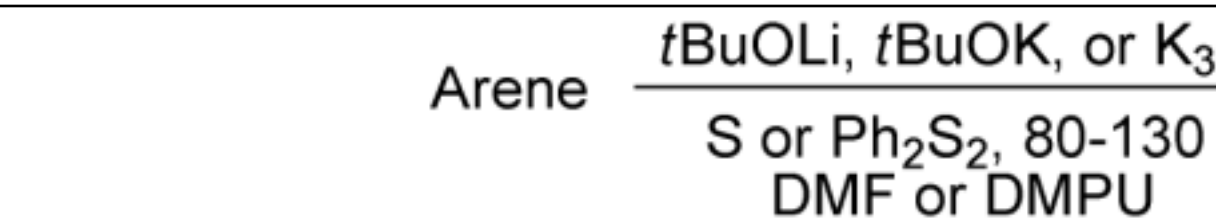
entry	arene	reagent base
12		I_2 *t*BuOLi

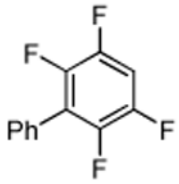


entry	arene	reagent base
13[c]		ICl *t*BuOLi



entry	arene	reagent base
14[d]		ICl *t*BuOLi



entry	arene	reagent base
15		I_2 *t*BuOLi

[a] Substrate (1 equiv), base (2.0–4.0 equiv), halogenating reagent (1.0–3.0 equiv). Yields are isolated yields. See the Supporting Information for details.

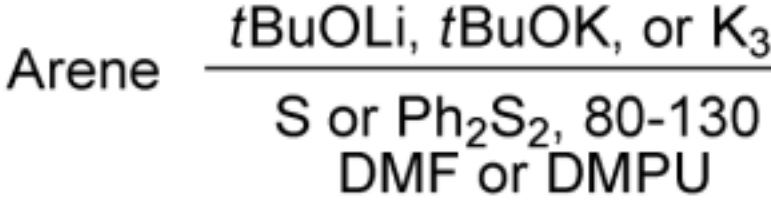
[b] *m*-Xylene solvent.

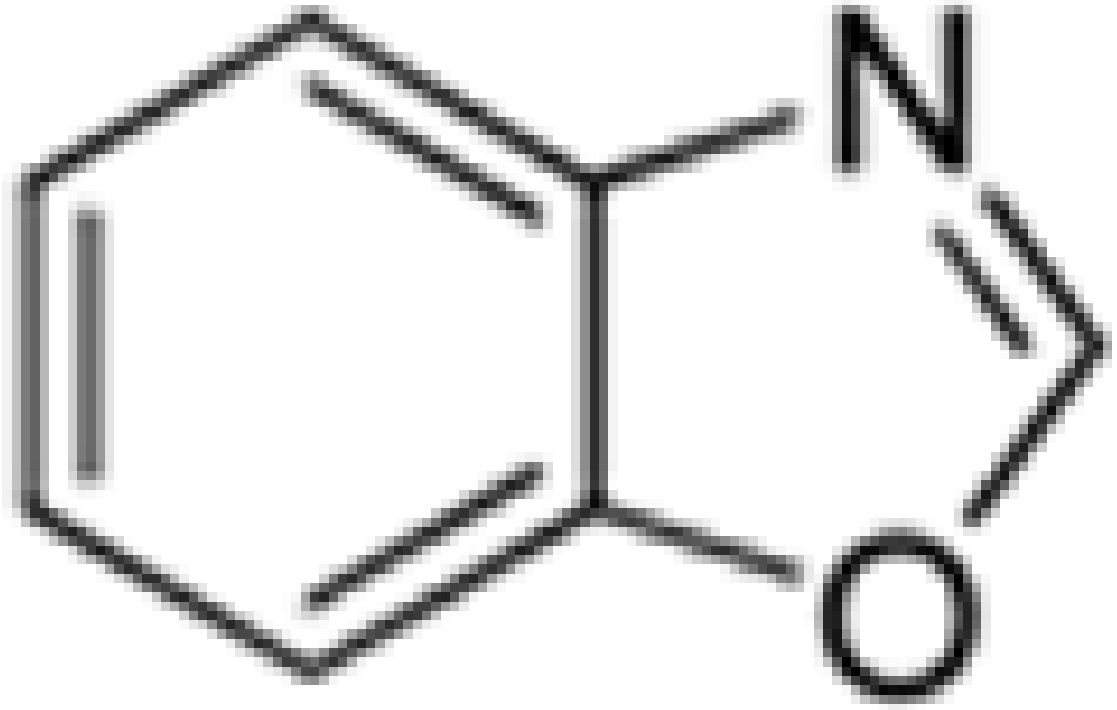
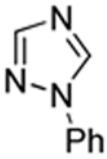
[c] 1,3,5-Trifluorobenzene (3 equiv), ICl (1 equiv).

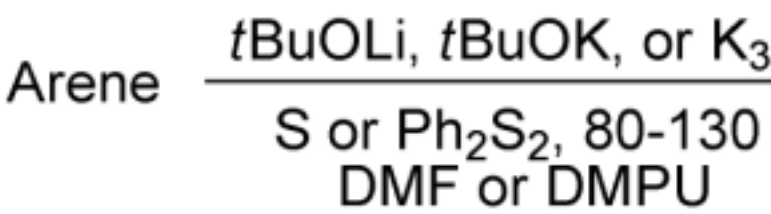
[d] 1,3,5-Trifluorobenzene (1 equiv), ICl (3 equiv).

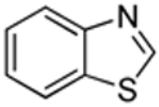
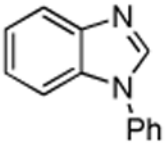
Table 2

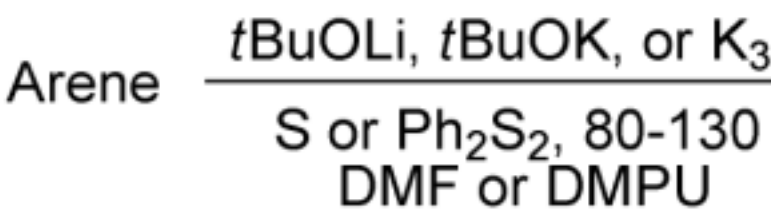
Reactions with Sulfur Electrophiles[a]

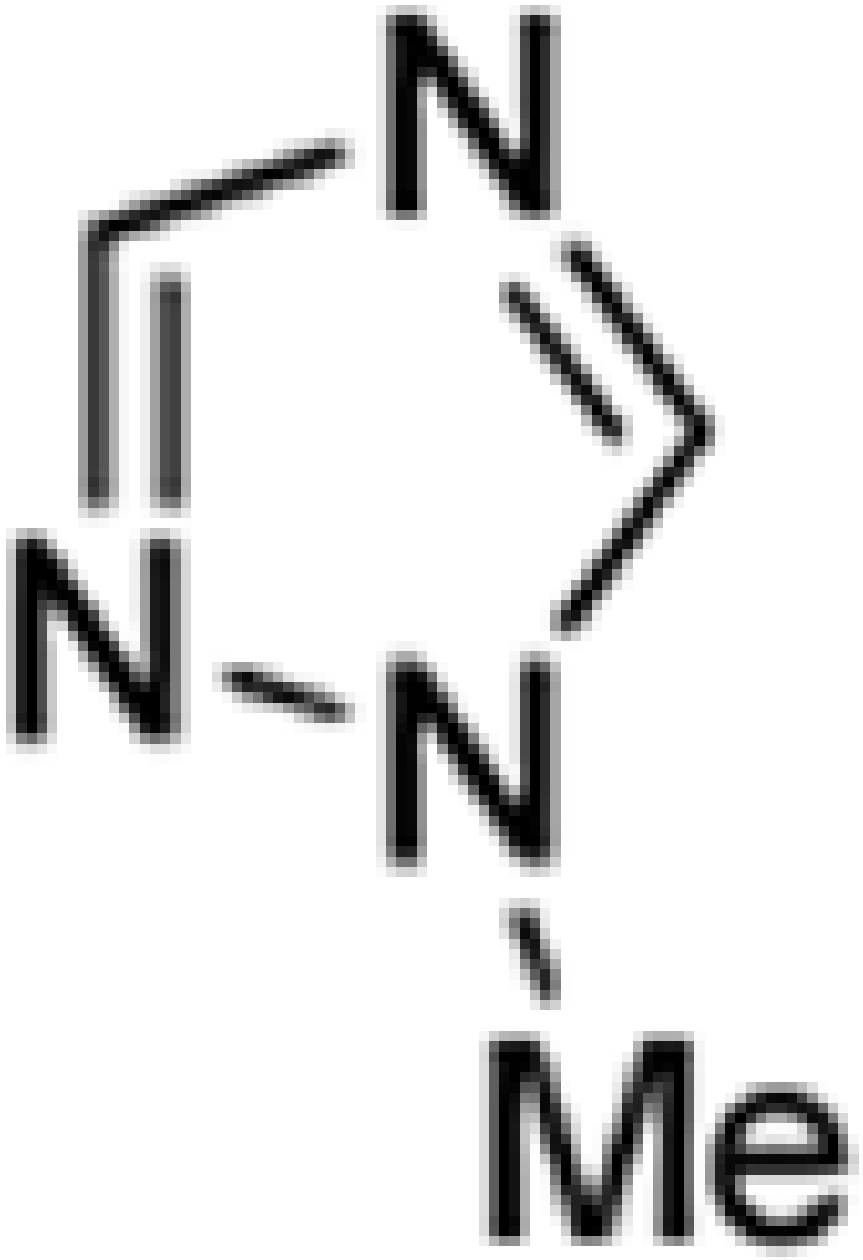


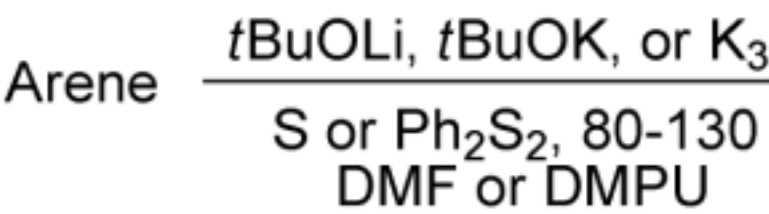
entry	arene	reagent base
1		S *t*BuOLi
2		S *t*BuOLi

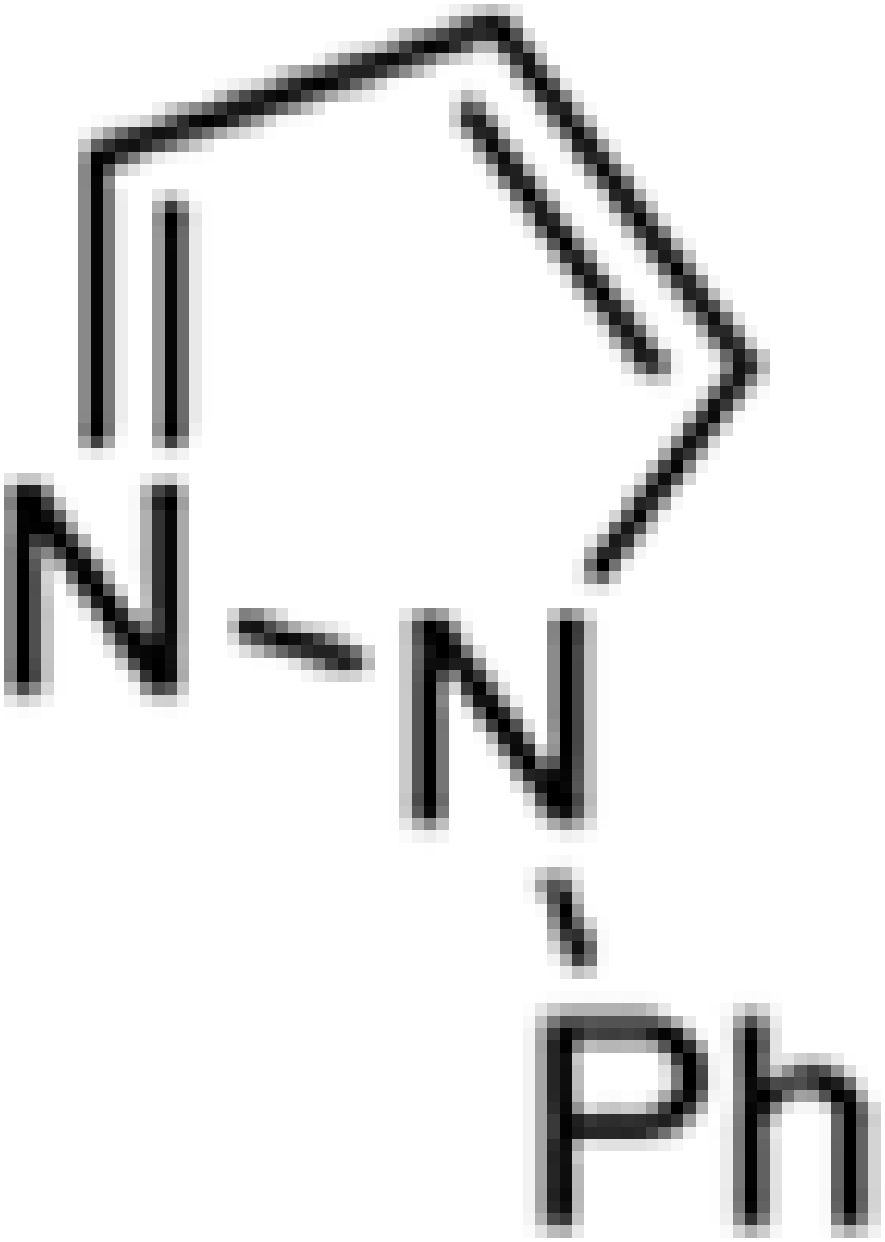


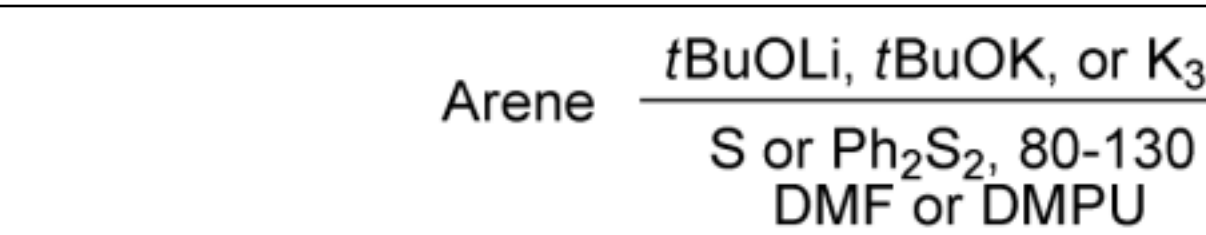
entry	arene	reagent base
3		PhSSPh K_3PO_4
4		PhSSPh *t*BuOLi

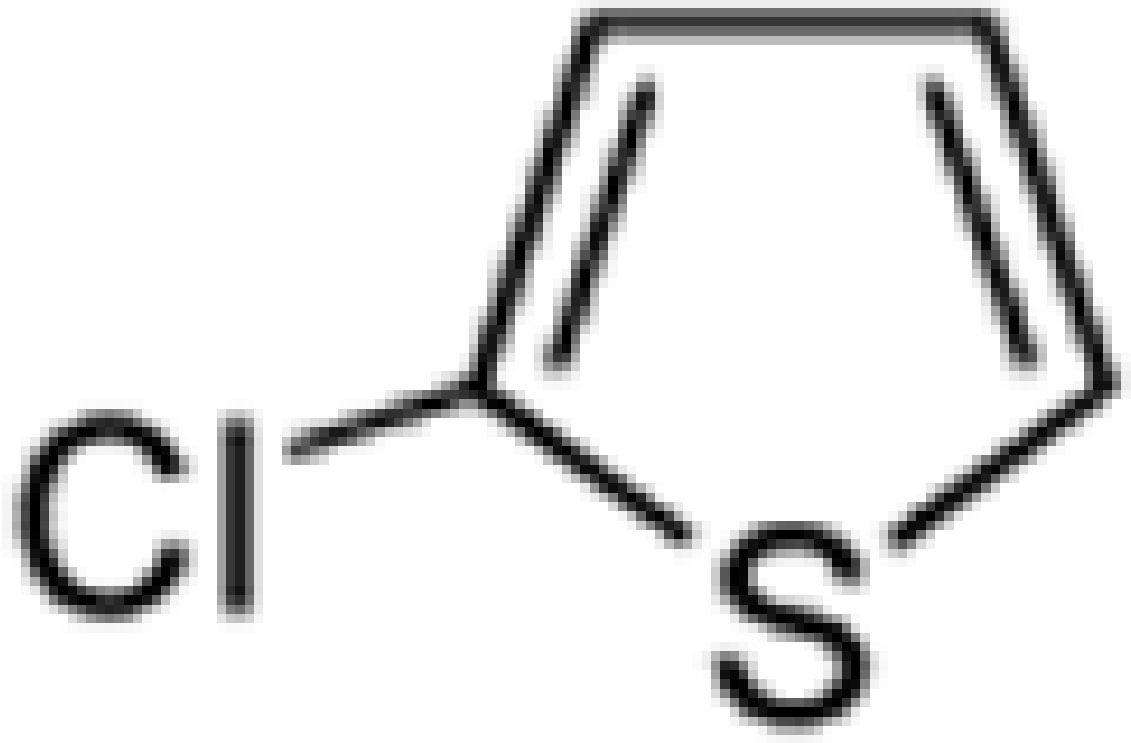


entry	arene	reagent base
5		PhSSPh *t*BuOLi



entry	arene	reagent base
6		PhSSPh *t*BuOK

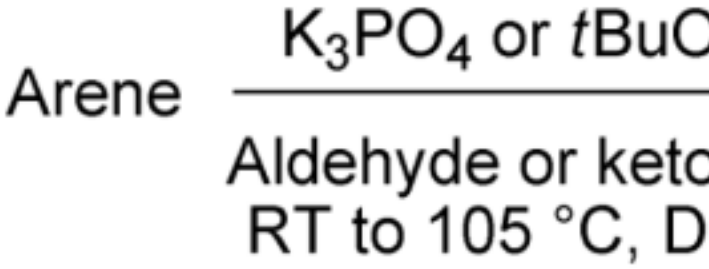


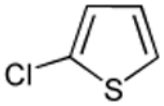
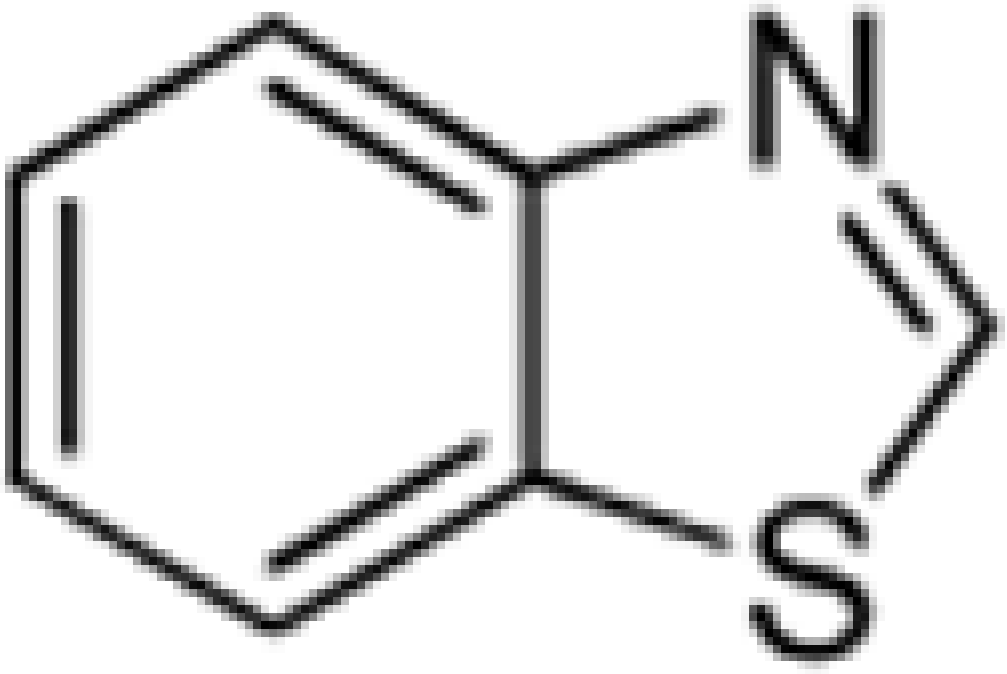
entry	arene	reagent base
7		PhSSPh *t*BuOLi

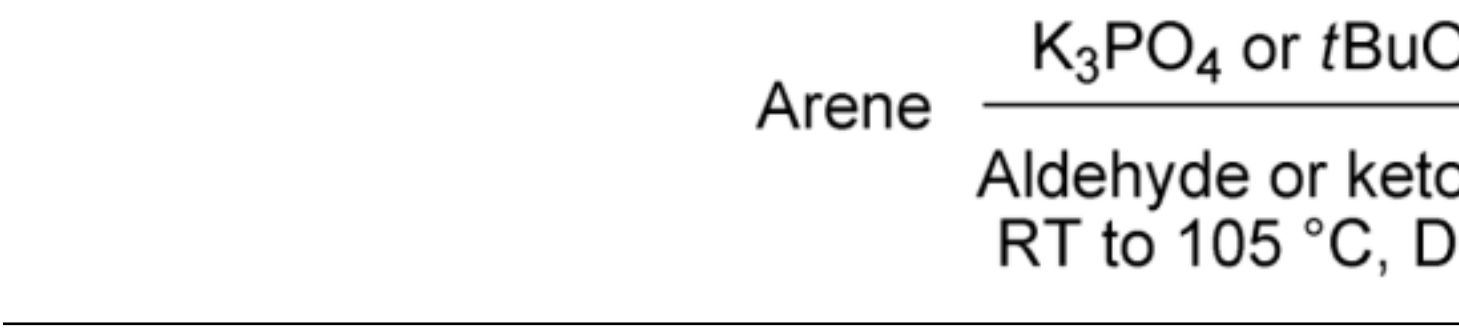
[a]Substrate (1 equiv), base (1.5–3.0 equiv), sulfur (8 equiv) or PhSSPh (1.5–2.0 equiv). Yields are isolated yields. See the Supporting Information for details.

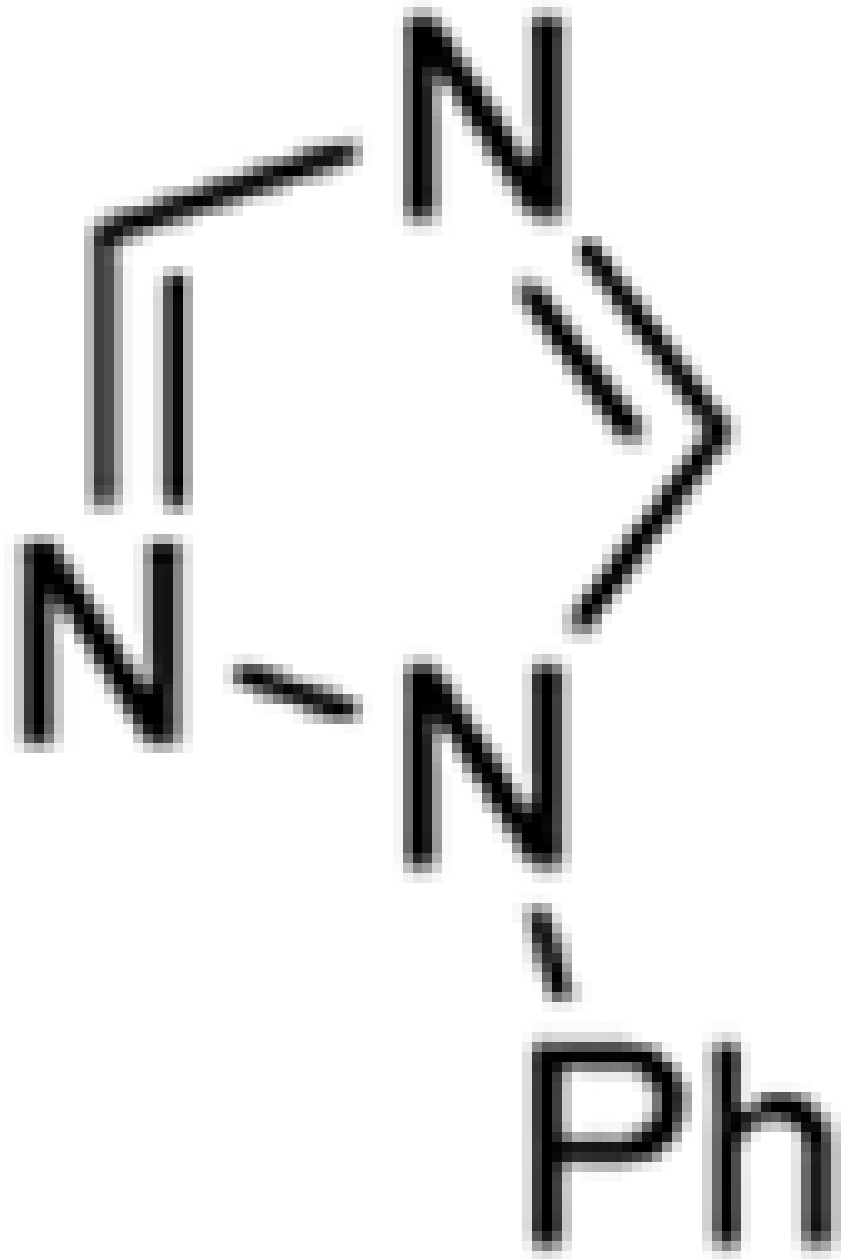
Table 3

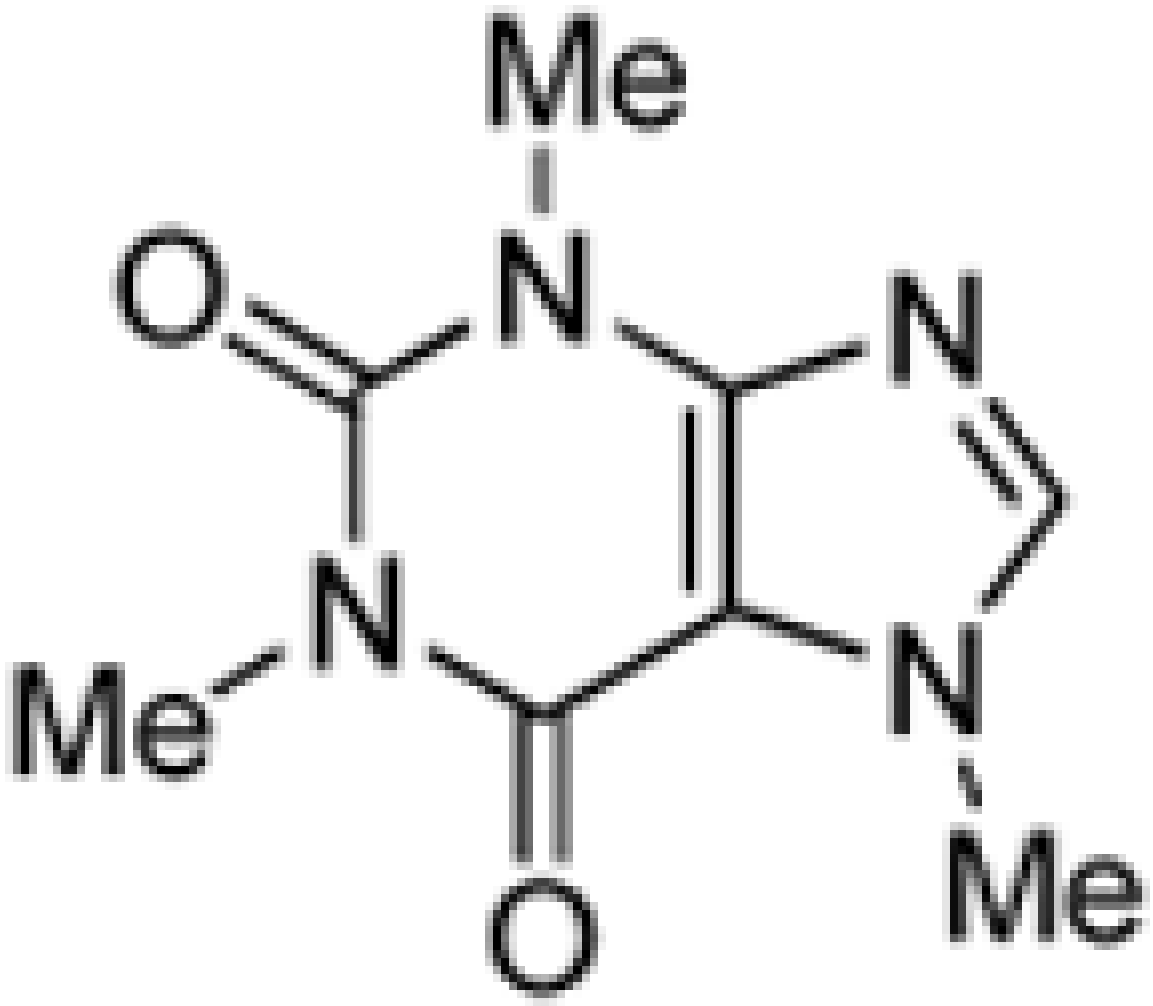
In Situ Trapping with Aldehydes and Ketones[a]

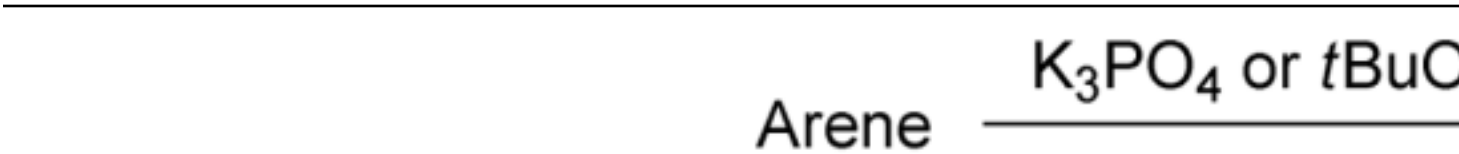


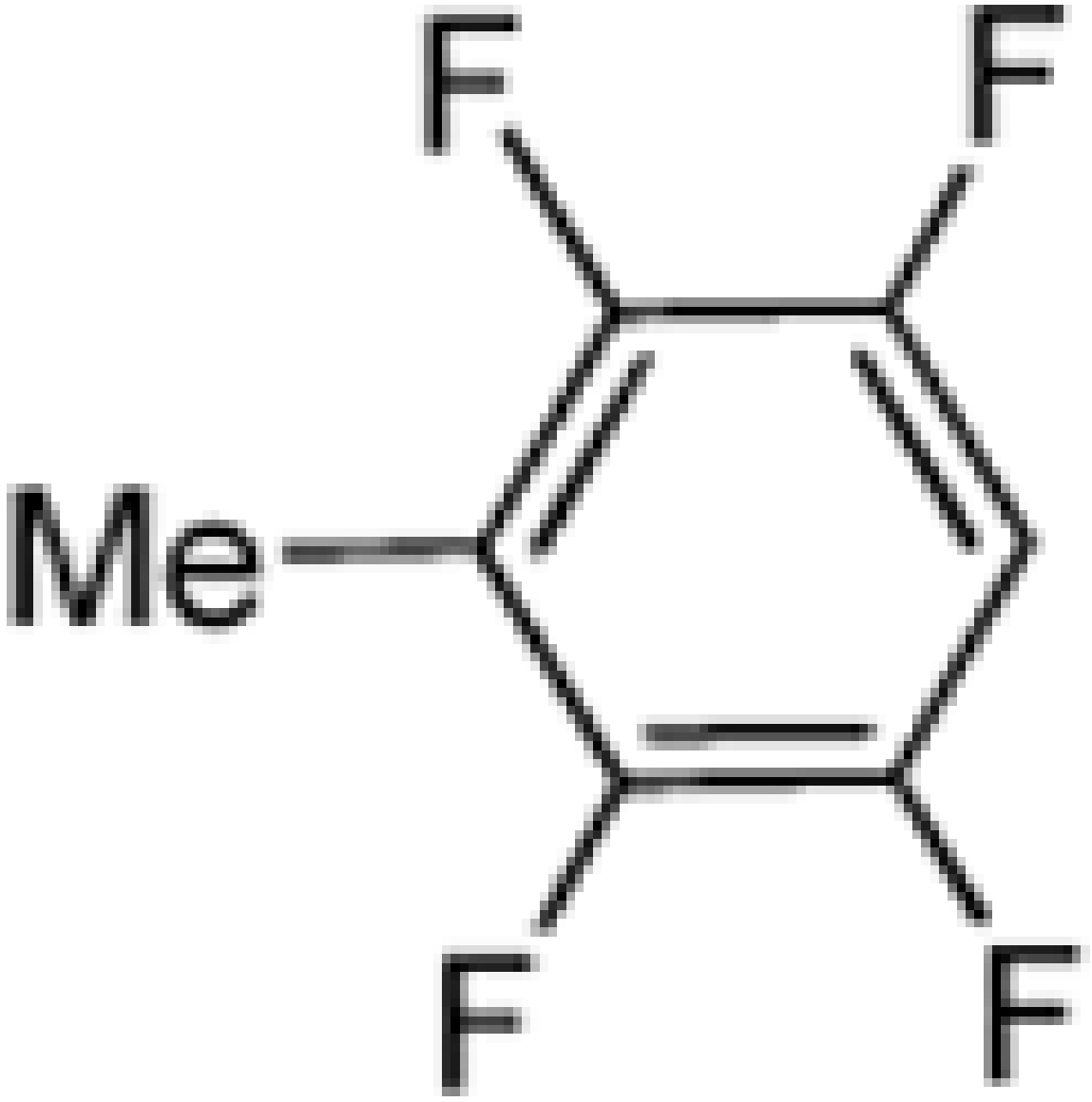
entry	arene	reagent base
1		Ph_2CO *t*BuOLi
2		Ph_2CO *t*BuOLi

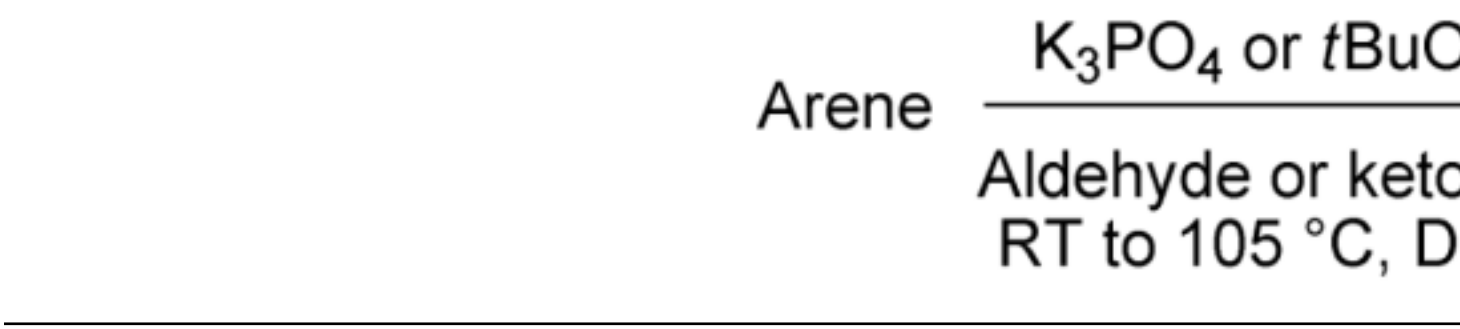


entry	arene	reagent base
3		*t*BuCHO *t*BuOLi

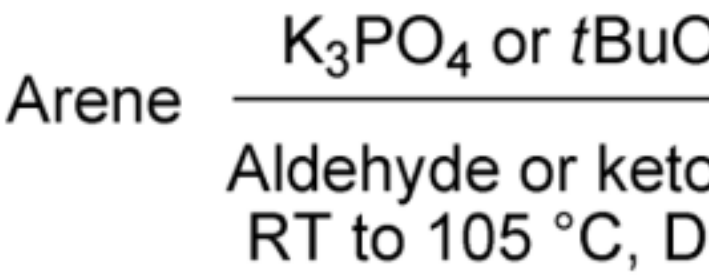
entry	arene	reagent base
4		*t*BuCHO *t*BuOLi

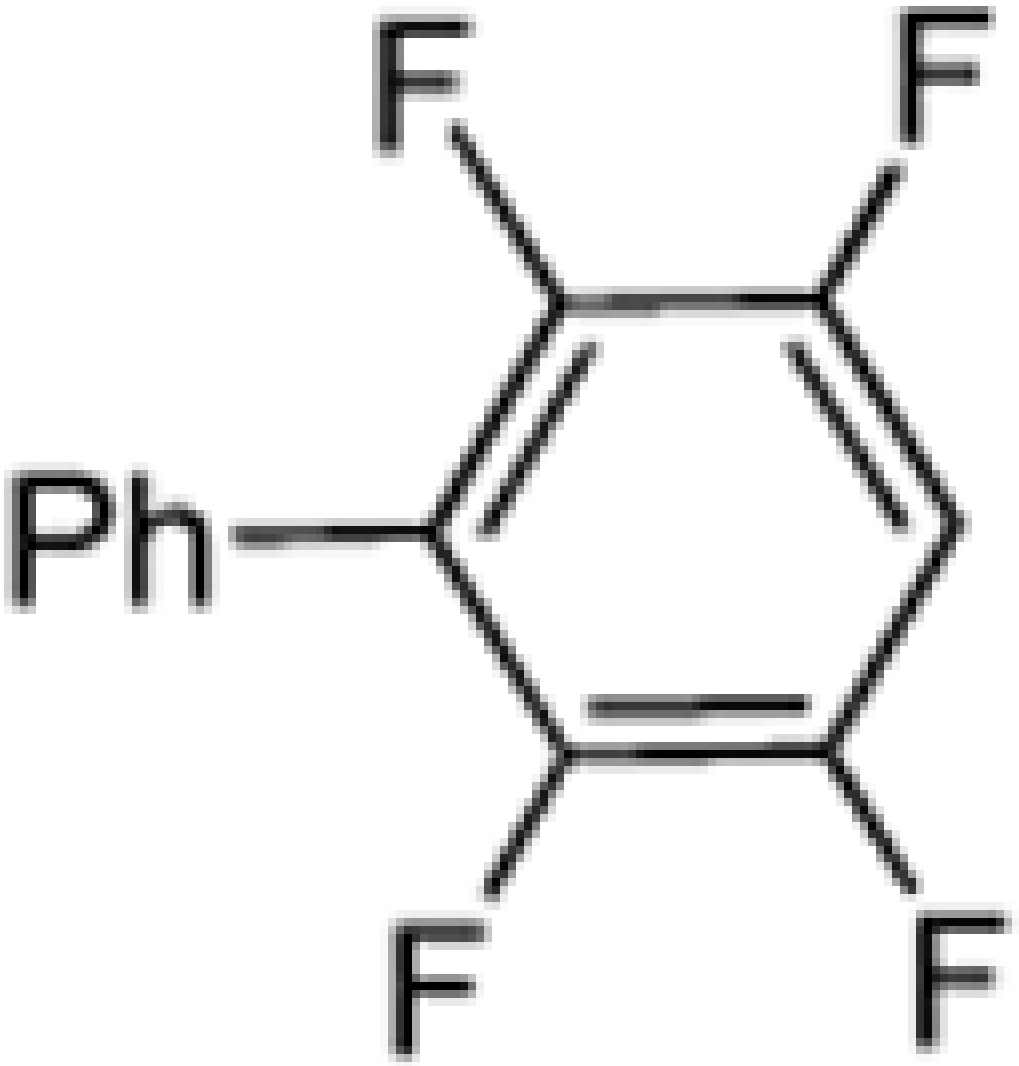


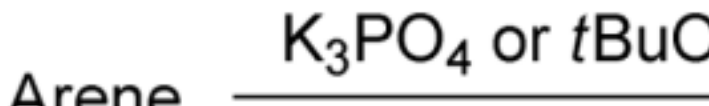
entry	arene	reagent base
5		*t*BuCHO *t*BuOLi

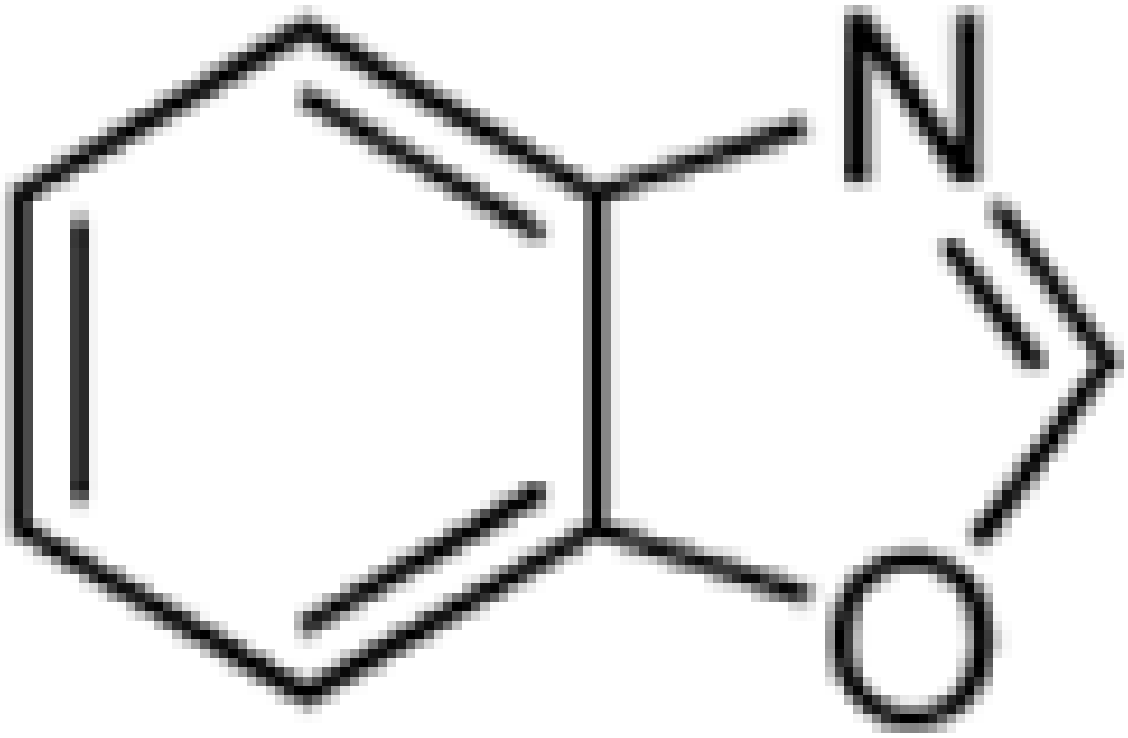


entry	arene	reagent base
6		p-Chloro-benzaldehyde *t*BuOLi



entry	arene	reagent base
7		p-Chloro-benzaldehyde *t*BuOLi



entry	arene	reagent base
8		$C_6H_{11}CHO$ K_3PO_4

[a] Substrate (1 equiv), base (1.5–3.0 equiv), ketone or aldehyde (3.0 equiv). Yields are isolated yields. See the Supporting Information for details.