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P(i-BuNCH$_2$CH$_2$)$_3$N: An Efficient Promoter for the Nucleophilic Aromatic Substitution Reaction of Aryl Fluorides with Aryl TBDMS (or TMS) Ethers

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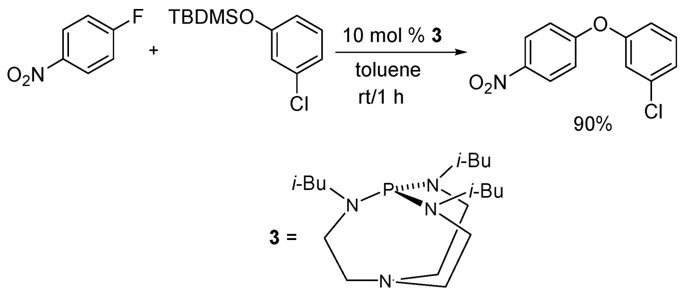
ABSTRACT



The nucleophilic aromatic substitution reaction between electron-deficient aryl fluorides and aryl TBDMS (or TMS) ethers has been shown to be efficiently promoted by proazaphosphatranes such as P(i-BuNCH$_2$CH$_2$)$_3$N (3). Excellent yields of diaryl ether products were obtained under unusually mild conditions.

The synthesis of diaryl ethers has attracted significant interest because of the frequent occurrence of these structural units in biologically active natural products such as vancomycin, riccardin C, ristocetin aglycon, and chloropeptin I.[1] Furthermore, poly(aryl ethers) find applications as engineering thermoplastic materials.[2] Three general routes to diaryl ethers are (1) nucleophilic aromatic substitution (S$_N$Ar) reactions between activated aryl halides (of general reactivity order F > Cl > Br > I) and phenols,[3] (2) classical copper-catalyzed Ullmann reactions of aryl halides with phenols,[4] and (3) more recently developed palladium-catalyzed arylations of phenols.[5]

Of these three methods, the S$_N$Ar reaction is relatively milder and more environmentally benign. In addition to identifying suitable reaction conditions for the standard S$_N$Ar reaction, research in this field has also focused on modifying the nucleophilic phenol coupling partner. For example, in 1988, Saunders found that activated aryl fluorides react directly with TBDMS (*tert*-butyl dimethyl silyl) aryl ethers in the presence of tetrabutylammonium fluoride in THF to give diaryl ethers.[6] However, this novel method was

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(1) (a) Nicolaou, K. C.; Boddy, C. N. C. *J. Am. Chem. Soc.* **2002**, *124*, 10451. (b) Zhu, J. *Synlett* **1997**, 133. (c) Boger, D. L.; Patane, M. A.; Zhou, J. *J. Am. Chem. Soc.* **1994**, *116*, 8544. (d) Gottsegen, A.; Vermes, B.; Kajtarperedy, M.; Bihatsikarasai, E.; Nogradi, M. *Tetrahedron Lett.* **1988**, *29*, 5039. (e) Crowley, B. M.; Mori, Y.; McComas, C. C.; Tang, D.; Boger, D. L. *J. Am. Chem. Soc.* **2004**, *126*, 4310. (f) Deng, H.; Jung, J.-K.; Liu, T.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 9032.

(2) Cotter, R. J. *Engineering Plastics: A Handbook of Polyarylethers*; Gordon and Breach: Langhorne, PA, 1995.

(3) (a) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273. (b) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1. (c) Sawyer, J. S. *Tetrahedron* **2000**, *56*, 5045. (d) Sawyer, J. S.; Schmittling, E. A.; Palkowitz, J. A.; Smith, W. J., III *J. Org. Chem.* **1998**, *63*, 6338.

(4) (a) Ullmann, F. *Chem. Ber.* **1904**, *37*, 853. (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433. (c) Thomas, A. W.; Ley, S. V. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

(5) (a) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369. (b) Mann, G.; Hartwig, J. F. *Tetrahedron Lett.* **1997**, *38*, 8005.

(6) Saunders, D. G. *Synthesis* **1988**, 377.

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successful only with highly active 2,4-dinitrofluorobenzene. In a related process, Oriyama and co-workers described the direct conversion of TBDMS aryl ethers to aryl alkyl ethers by their reaction with an alkyl halide in DMF using CsF as the source of silyl group activation.[7]

Very recently, Kondo and co-workers coupled aryl fluorides with aryl TBDMS or TMS (trimethylsilyl) ethers using the phosphazene base P4-*t*-Bu.[8] In that study, it was interesting to note that weaker bases such as DBU and BEMP were totally ineffective.[8] This significantly improved method does, however, require a highly polar aprotic solvent (DMF or DMSO) even with active fluoronitrobenzenes. Because the TBDMS group is a common protecting group for OH groups in organic synthesis, the aforementioned direct coupling by in situ activation of the silyl group not only eliminates the unmasking step of a TBDMS-protected OH group but it also opens new avenues for synthetic chemists to exploit. Related to this intriguing chemistry is the report from our group of a few years ago in which the first observation of the desilylation of TBDMS ethers by a nonionic base, namely, proazaphosphatrane **1**, was described (Figure 1).[9] This reaction takes place efficiently in DMSO at 80 °C under catalytic conditions. These findings prompted us to determine whether proazaphosphatranes, which we have demonstrated to activate silyl groups, can also be used for coupling aryl fluorides with TBDMS ethers in a synthesis of diaryl ethers. In the present report, we illustrate the usefulness of proazaphosphatranes as an activator for such couplings and further expand the method developed by Saunders.

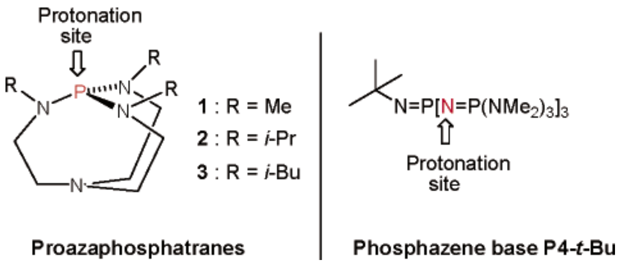
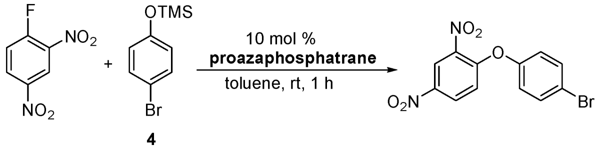


Figure 1. Nonnucleophilic superbases.

Proazaphosphatranes are powerful nonionic bases with pK_a values in the range of 32−34[10] in CH_3CN. However, their basicities are 7−9 pK_a units less basic than the phosphazene base P4-*t*-Bu (pK_a: 41.4 in CH_3CN[11]). The nucleophilicity and basicity of proazaphosphatranes stem in part from transannular bond formation between the bridgehead phosphorus and nitrogen atoms. It is also interesting to note that, unlike P4-*t*-Bu, proazaphosphatranes can become protonated on the phosphorus atom whereas the imino nitrogen is the basic site in P4-*t*-Bu (Figure 1).

We began our study by screening the proazaphosphatrane catalysts **1**−**3** owing to their commercial availability[12] and the demonstrated ability of **1** and **2** to activate the silyl group.[9,10] The S_NAr reaction of 2,4-dinitrofluorobenzene with TMS aryl ether **4** was chosen as a representative reaction. Pleasingly, almost quantitative yields of the corresponding diaryl ether were obtained in the presence of 10 mol % of **1**, **2**, or **3** in toluene within 1 h at room temperature (Table 1, entries 1−3). In a control experiment, no reaction was observed in the absence of a proazaphosphatrane even after 16 h at room temperature (Table 1, entry 4). The S_NAr reaction is usually performed in a highly polar aprotic solvent such as DMF or DMSO in order to stabilize the charged intermediate Meisenheimer complex formed during the reaction.[13] Thus, it is remarkable that in the presence of proazaphosphatranes, the reaction proceeded smoothly even in the apolar solvent toluene.

Table 1. Optimization Study



entry	proazaphosphatrane	yield (%)[a]
1	**1**	98
2	**2**	98
3	**3**	>98
4	none	no reaction[b]

[a] Isolated yields (average of two runs). [b] Reaction time: 16 h.

Encouraged by these initial successes, we next focused on expanding the scope of the methodology using the most basic of the three proazaphosphatranes,[10] namely, **3**, as the promoter. Table 2 contains the results of S_NAr reactions of various nitro-substituted aryl fluorides. The coupling of the more active 2,4-dinitrofluorobenzene with 3-chlorophenyl TBDMS ether and 2-methoxy-4-methylphenyl TBDMS ether occurred in excellent yields (Table 2, entries 1 and 3). It should be noted that S_NAr reactions of aryl fluorides generally proceed readily with electron-rich phenols and sluggishly with electron-poor phenols. However, in the presence of **3**, even a TBDMS aryl ether bearing an electron-withdrawing group served as an efficient coupling partner,

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(7) Oriyama, T.; Noda, K.; Yatabe, K. *Synlett* **1997**, 701.

(8) Ueno, M.; Hori, C.; Suzawa, K.; Ebisawa, M.; Kondo, Y. *Eur. J. Org. Chem.* **2005**, 1965.

(9) Yu, Z.; Verkade, J. G. *J. Org. Chem.* **2000**, *65*, 2065.

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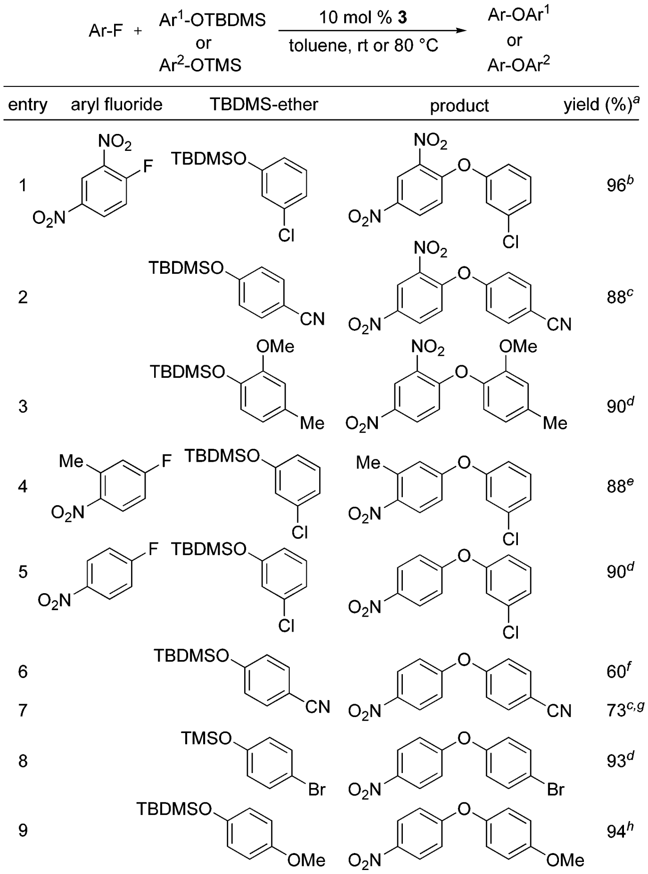
(11) Schwesinger, R.; Schlemper, H.; Hasenfratz, C.; Willaredt, J.; Dambacher, T.; Breuer, T.; Ottaway, C.; Fletschinger, M.; Boele, J.; Fritz, H.; Putzas, D.; Rotter, H. W.; Bordwell, F. G.; Satish, A. V.; Ji, G.-Z.; Peters, E.-M.; Peters, K.; von Schnering, H. G.; Walz, L. *Liebigs Ann.* **1996**, 1055.

(12) Proazaphosphatranes **1**, **2**, and **3** are commercially available from Aldrich, and **1** and **2** can also be obtained from Strem Chemicals.

(13) (a) Acevedo, O.; Jorgensen, W. L. *Org. Lett.* **2004**, *6*, 2881. (b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 4th ed.; Plenum Publishing: New York, 2001.

Table 2. S_NAr of Nitro-Substituted Aryl Fluorides with Aryl TBDMS (or TMS) Ethers

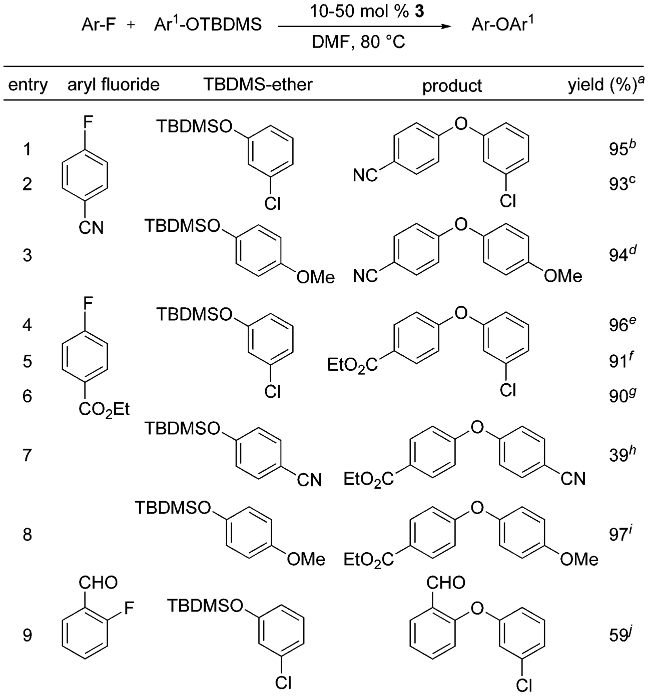


[a] Isolated yields (average of two runs). [b] Conditions: rt, 45 min. [c] Conditions: 80 °C, 3 h. [d] Conditions: rt, 1 h. [e] Conditions: rt, 75 min. [f] Conditions: 80 °C, 105 min. [g] Conditions: 20 mol % **3**. [h] Conditions: rt, 5 h.

although a higher temperature was required (Table 2, entry 2). 4-Fluoronitrobenzene also reacted efficiently with electronically diverse TBDMS as well as TMS aryl ethers. Since TMS groups are more labile than TBDMS moieties, only one aryl TMS ether was employed in this study in order to demonstrate the versatility of our method. Again most striking is the electronically disfavored reaction of 4-fluoronitrobenzene with 4-cyanophenyl TBDMS ether (Table 2, entries 6 and 7). The yield obtained in the traditional S_NAr reaction of 4-fluoronitrobenzene with 4-cyanophenol using KOH/DMSO/55 °C[14] was significantly higher (98% isolated yield) compared with ours (73% isolated yield, entry 7 in Table 2). On the other hand, the isolated yield (93%) we obtained for the reaction detailed in entry 8 demonstrates the somewhat greater efficacy of the proazaphosphatrane catalyst **3** than the similar reaction performed with 4-methoxyphenol in the presence of $KF-Al_2O_3$/Aliquat 336 ($MeOct_3N^+Cl^-$)[15] in a microwave oven (92%).

The scope of this novel S_NAr reaction was also explored with respect to the aryl fluorides containing functional groups other than nitro such as ester, nitrile, and aldehyde (Table 3). Thus, for 4-fluorobenzonitrile, ethyl-4-fluorobenzoate, and 2-fluorobenzaldehyde, DMF was the solvent of choice owing to the sluggishness of these reactions in toluene. While longer reaction times, a higher temperature (80 °C), and an increased loading of **3** (20−50 mol %) were necessary for these reactions, it is noteworthy that reasonable to excellent yields of the desired diaryl ethers were obtained (Table 3, entries 1−9). Not surprisingly, the electronically favored reaction of ethyl-4-fluorobenzoate with 4-methoxyphenyl TBDMS ether afforded a 97% isolated yield of the corresponding diaryl ether (Table 3, entry 8), and the electronically disfavored reaction of ethyl-4-fluorobenzoate with 4-cyanophenyl TBDMS ether gave a significantly lower yield (39%, Table 3, entry 7). An aldehyde functional group on an aryl fluoride was also compatible under these conditions, although a slightly lower yield was obtained in the reaction of 2-fluorobenzaldehyde with 3-chlorophenyl TBDMS ether (59%, Table 3, entry 9).

Table 3. S_NAr of Cyano-, Ester-, and Aldehyde-Substituted Aryl Fluorides with Aryl TBDMS Ethers



[a] Isolated yields (average of two runs). [b] Conditions: 50 mol % **3**, 4 h. [c] Conditions: 20 mol % **3**, 9 h. [d] Conditions: 10 mol % **3**, 3 h. [e] Conditions: 50 mol % **3**, 12 h. [f] Conditions: 20 mol % **3**, 17 h. [g] Conditions: 20 mol % **1**, 17 h. [h] Conditions: 20 mol % **3**, 8 h. [i] Conditions: 10 mol % **3**, 2 h. [j] Conditions: 20 mol % **3**, 10 h.

Finally, we probed the S_NAr reaction of aryl fluorides with a sterically hindered TBDMS aryl ether. Sterically encumbered nucleophiles such as 2-*tert*-butylphenol, have been quite problematic as coupling partners in S_NAr reactions.[3d] As illustrated in Table 4, 4-cyanofluorobenzene (entry 1) with **3** (50 mol %) as the promoter was efficiently coupled with the sterically hindered TBDMS aryl ether **5** in DMF at

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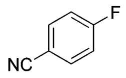
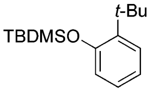
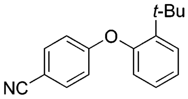
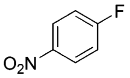
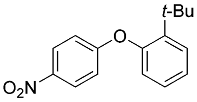
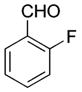
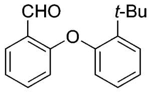
[14] Wilcox, C. S. *Tetrahedron Lett.* **1985**, *26*, 5749.

[15] Lee, J. C.; Choi, J.-H.; Lee, J. S. *Bull. Korean Chem. Soc.* **2004**, *25*, 1117.

Table 4. S_NAr of Aryl Fluorides with a Sterically Hindered Aryl TBDMS Ether

$$\text{Ar-F} + \text{Ar}^1\text{-OTBDMS} \xrightarrow[\text{DMF, 80 °C}]{\text{50 mol \% } \mathbf{3}} \text{Ar-OAr}^1$$

entry	aryl fluoride	TBDMS-ether	product	yield (%)[a]
1		 **5**		98[b]
2				99[c]
3				70[d]

[a] Isolated yields (average of two runs). [b] Reaction time: 5 h. [c] Toluene was used as the solvent, 9 h. [d] Conditions: 40 mol % **3**, 10 h.

80 °C to provide the corresponding diaryl ether product in excellent yield. Although fluoronitrobenzenes react efficiently with silyl ethers in toluene at room temperature, we were disappointed to observe that the S_NAr reaction of 4-fluoronitrobenzene with **5** proceeded slowly at room temperature. To our delight, however, efficient coupling occurred in toluene at 80 °C, affording the diaryl ether product in almost quantitative yield (entry 2). Steric hindrance on an aryl fluoride was also well accommodated. Thus, the reaction of ortho-substituted aryl fluoride (2-fluorobenzaldehyde) with **5** produced the corresponding diaryl product in 70% isolated yield (entry 3). It is worth noting that the conventional S_NAr reactions of 4-fluorobenzonitrile and 4-fluoronitrobenzene with 2-*tert*-butylphenol, promoted by $KF-Al_2O_3$/18-crown-6, required 120 and 84 h, respectively, to proceed to completion in refluxing CH_3CN, and the corresponding coupling products were obtained in 83 and 98% yields, respectively.[3d] However, under more forcing conditions ($KF-Al_2O_3$/Aliquat 336, microwave, no solvent), the S_NAr coupling of 4-fluoronitrobenzene with 2-*tert*-butylphenol provided the diaryl ether product in 90% yield in 10 min.[15] It is important to emphasize, however, that the S_NAr method using microwave conditions was limited to nitroaryl fluorides.

In summary, we have successfully demonstrated the scope and generality of a novel nucleophilic aromatic substitution reaction of electron-poor aryl fluorides with TBDMS (or TMS) aryl silyl ethers. Proazaphosphatrane **3** was shown to be a highly efficient promoter for this reaction, and excellent yields of diaryl ethers were obtained under particularly mild conditions. Most significantly, it was observed that S_NAr reactions of fluoronitrobenzenes can be efficiently performed even in an apolar solvent (toluene), thus circumventing the need of the more tedious workup procedure required when employing DMF or DMSO. Further studies are underway to elucidate mechanistic details of our protocol. In this context, it is worth mentioning the following observations: (a) a silyl (TBDMS or TMS)-protected phenol is required since the reaction of 4-fluoronitrobenzene with 3-chlorophenol failed, and (b) the presence of an electron-poor aryl fluoride is also important, because no reaction occurred between 4-chloronitrobenzene and 4-methoxyphenyl TBDMS ether (both reactions performed in the presence of **3** under typical conditions).

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

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