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P(*i*-BuNCH$_2$CH$_2$)$_3$N: an efficient promoter for the microwave synthesis of diaryl ethers

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Abstract

With the title proazaphosphatrane as a promoter, the coupling of aryl fluorides with aryl TBDMS ethers under microwave conditions gave moderate to high yields of the desired products at low catalyst loadings and in short times. In this methodology, electron deficient aryl fluorides possessing substituents, such as nitro, cyano, and ester, were coupled with sterically demanding aryl TBDMS ethers as well as with aryl TBDMS ethers bearing a variety of functionalities such as methoxy, halo, and cyano groups.

Keywords: Proazaphosphatrane; Microwave; Diaryl ethers; TBDMS aryl ethers

The synthesis of diaryl ethers has been intensely studied owing primarily to the presence of diaryl ether moieties in many biologically active natural products such as Piperazinomycin, Bouvardin, Vancomycin, Ristocetin A, and the anti-HIV agent Chloropeptin I.[1] Three general methods developed for the synthesis of diaryl ethers are (1) S_NAr reactions between aryl halides (order of reactivity F > Cl > Br > I)[2] and phenols,[3] (2) copper-catalyzed Ullmann reactions between aryl halides and phenols,[4] and (3) palladium-catalyzed reactions of aryl halides with phenols.[5]

Disadvantages of the Ullmann coupling are its requirements for harsh reaction conditions and environmentally unfriendly copper. Palladium-mediated syntheses suffer from the expense of the metal. Because of these issues, investigators have focused on seeking superior S_NAr routes owing to their generally milder reaction conditions. Ways have also been sought to employ the nucleophilic phenolic coupling partner more efficiently by, for example, deprotection of a trimethylsilyl- (TMS)-protected or a *tert*-butyldimethylsilyl- (TBDMS)-protected phenol in the presence of a strong base. Thus, Kondo and co-workers found that by using the phosphazene base P4-*t*-Bu, diaryl ethers could be synthesized in a highly polar solvent such as DMSO or DMF using electron deficient aryl fluorides and electron rich TBDMS-protected phenols.[6]

About the time Kondo's work was published, our group reported that proazaphosphatrane **3** in Figure 1 also efficiently promoted such diaryl ether syntheses;[7] a finding that was based on our earlier report of the first observation of the efficient deprotection of TBDMS-protected alcohols and phenols with **1**.[8] Proazaphosphatranes are strong nonionic bases (pK_a 32–34[9]), although these are much weaker than P4-*t*-Bu (pK_a 41.4[10]). However, the former may be more nucleophilic, perhaps in part because of the possible transannulation of the basal nitrogen to the phosphorus during the reaction.

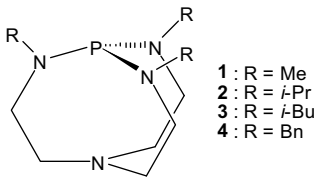

Fig. 1. Proazaphosphatranes.

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To obtain diaryl ethers in high yields using our reported thermal protocol with **3**, high mole percentages of this base were needed (10–50 mol %) even with highly electron deficient aryl fluorides.[7] To avoid using large molar percentages of promoters for a variety of S_NAr reactions, several groups have resorted to microwave techniques.[11] For example, Wang and co-workers used a microwave for the S_NAr reaction involving 2 equiv of K_2CO_3 in the highly polar solvent DMSO in the absence of catalyst.[12]

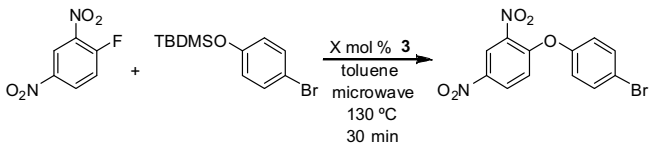
In this report, we describe the utility of **3** at low loading in the synthesis of diaryl ethers under microwave conditions. Since we previously reported using **3** under thermal conditions for such syntheses,[7] we began our study by determining the lowest loading of **3** which can be usefully employed for this reaction under microwave conditions to achieve high product yields. Using the same model reaction given in our previous report, we found that only 1 mol % of **3** was necessary to obtain a 99% isolated yield of the desired product under microwave conditions in the nonpolar solvent toluene (Table 1).

In determining the best proazaphosphatrane for diaryl ether synthesis using the present protocol, we standardized on employing 1 mol % each of **1**–**4** (Table 2). As shown in entry 1 of this table, 90% of the desired product was achieved using **1**. Earlier we showed that proazaphosphatrane basicity rises with the steric bulk of the substituent on its P–N nitrogens.[9] Herein, a parallel trend is seen for the product yield in Table 2. Because **4** is apparently less basic than **3**,[13] it was surprising to observe that proazaphosphatrane **4** (as well as **3**) gave a quantitative yield of the desired product (Table 2, entry 4).

It was previously shown by our group that the reaction in Table 1 fails under thermal conditions in the absence of a proazaphosphatrane.[8] However, in the same experiment carried out under microwave conditions, 45% of desired product was obtained (Table 2, entry 5). When the same model compounds were used with no catalyst in DMF at 180 °C for 5 h, the yields of the desired products did not increase.

With these results in hand, the scope of our microwave approach was explored with a variety of aryl fluorides and

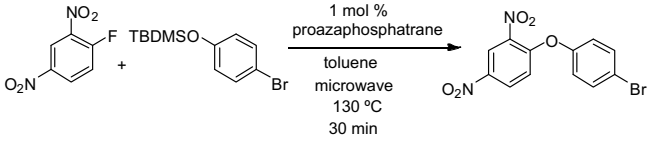
Table 1
Optimization study on amount of proazaphoshpatrane



Entry	mol % **3**	Yield[a] (%)
1	10	99[b]
2	5	99
3	1	99
4	0.5	76

[a] Average of two runs.
[b] Thermal reaction required 1 h (Ref. 7).

Table 2
Optimization study for proazaphosphatranes using **1** mol % catalyst



Entry	Proazaphosphatrane	Yield[a,b] (%)
1	**1**	90 (98)
2	**2**	91 (98)
3	**3**	99 (98)
4	**4**	99
5	None	45 (0)

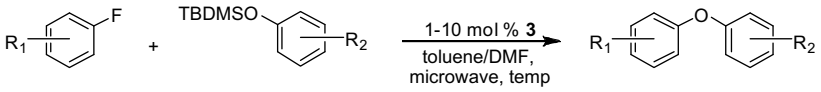
[a] Average of two runs.
[b] Yields in parentheses are under thermal conditions with 10 mol % **3** (Ref. 7).

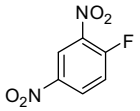
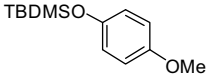
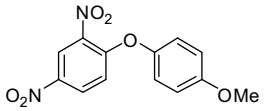
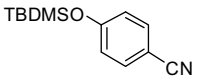
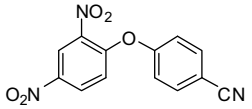
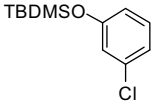
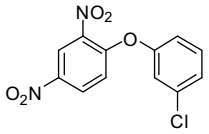
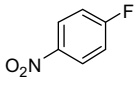
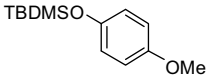
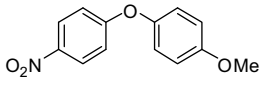
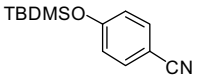
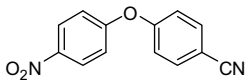
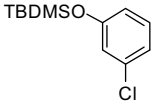
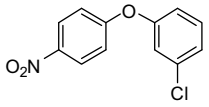
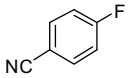
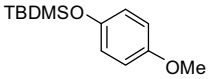
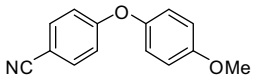
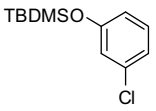
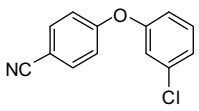
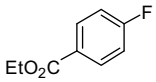
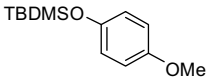
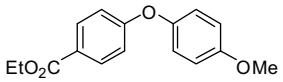
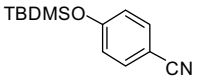
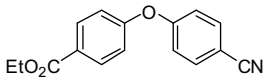
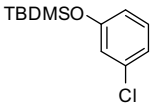
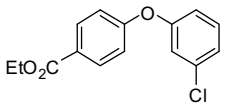
TBDMS aryl ethers (Table 3) using **3** because of its ease of handling and its commercial availability. Two solvents (toluene and DMF) were used for the S_NAr reactions in this table. Nitro-substituted aryl fluorides functioned better in the relatively non-polar solvent toluene, while other aryl fluorides required highly polar DMF, apparently to stabilize the Meisenheimer complex.[14] Thus, the coupling of highly activated 2,4-dinitrofluorobenzene with 4-methoxyphenyl and 3-chlorophenyl TBDMS ethers proceeded well with only 1 mol % of **3** in toluene (Table 3, entries 1 and 3). S_NAr reactions have been observed to proceed smoothly with electron rich phenols but are sluggish with electron deficient analogues.[7] Even coupling between 2,4-dinitrofluorobenzene and electron deficient 4-cyanophenyl TBDMS ether proceeded in 45 min with a 93% isolated yield in the presence of 1 mol % **3** in toluene (Table 3, entry 2).

For 4-nitrofluorobenzene in toluene, the catalyst loading required for **3** for timely completion of the reaction was 2 mol % and the temperature needs to be increased to 180 °C for complete conversion of the starting material. Under these conditions, 4-nitrofluorobenzene reacted readily with 4-methoxyphenyl and 3-chlorophenyl TBDMS ethers affording product yields of 97% and 95%, respectively (Table 3, entries 4 and 6). With this increased catalyst loading, 4-cyanophenyl TBDMS ether as a coupling partner provided an excellent product yield of 96% (Table 3, entry 5). Under thermal conditions, we obtained only a moderate yield of this product (73%) using 20 mol % of **3**.[7] Although Wang and co-workers reported a 95% yield of the same product in 5 min using microwave conditions, 2 equiv of K_2CO_3 in DMSO was required.[12]

We then screened aryl fluorides bearing a nitrile or an ester functional group (Table 3, entries 7–12). These substrates required DMF as a solvent to avoid the sluggishness we observed for their reactions in toluene. Although longer reaction times were needed, the reactions in Table 3, entries 7–12 were amenable to lower loadings of **3** than we had reported under thermal conditions,[7] particularly for the reaction of 4-cyanofluorobenzene with 3-chlorophenyl

Table 3
S_NAr reactions of aryl fluoride with TBDMS ethers



Entry	Aryl fluoride	TBDMS ether	mol % time	Product	Yield[a,b] (%)
1			1/30 min		97 (88)[c,d]
2			1/45 min		93 (88)[c,e]
3			1/30 min		95 (96)[c,e]
4			2/1 h		97 (92)[f,g]
5			2/3 h		96 (95)[f,h]
6			2/90 min		95 (90)[e,f]
7			1/3 h		94 (85)[f,i]
8			1/5 h		90 (95)[e,f]
9			2/5 h		92 (92)[f,j]
10			10/5 h		61 (84)[f,k]
11			5/5 h		73 (96)[e,f]

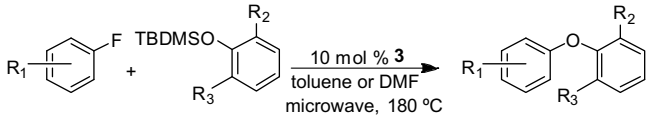
[a] Isolated yields (average of two runs).
[b] Yields in parentheses are literature values.
[c] Reaction temperature is 130 °C.
[d] See Ref. 16.
[e] See Ref. 7.
[f] Reaction temperature is 180 °C.
[g] See Ref. 17.
[h] See Ref. 12.
[i] See Ref. 11c.
[j] See Ref. 6.
[k] See Ref. 18.

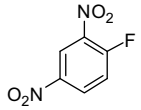
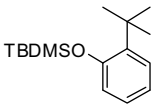
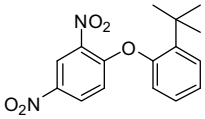
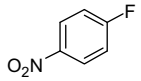
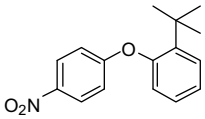
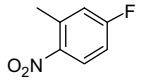
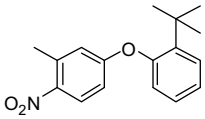
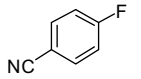
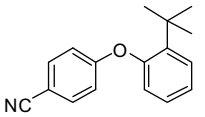
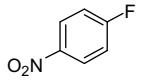
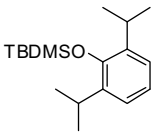
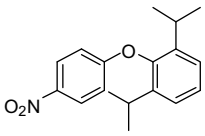
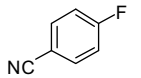
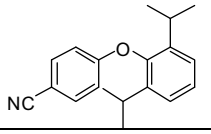
TBDMS ether (Table 3, entry 8). The 90% product yield for this reaction was obtained with only 1 mol % of **3**, in contrast to the 50 mol % of this catalyst that was necessary to obtain a 95% product yield thermally.[7] For the fluoroaryl ester (Table 3, entries 8–11) higher loadings of **3** were required to obtain reasonable to high product yields. Although the reaction between ethyl-4-fluorobenzoate and 4-cyanophenyl TBDMS ether required 10 mol % of **3** to obtain a 61% product yield, 20 mol % of this catalyst was required to obtain only a 39% product yield thermally.[7]

Finally, we examined two sterically hindered aryl TBDMS ethers in our protocol (Table 4). Under the thermal conditions used in our previous work,[7] 50 mol % of **3** was needed to obtain high yields, whereas under microwave conditions, the same products were made in excellent yields by employing only 10 mol % of **3** (Table 4, entries 1–6). However, the new compound made from 2-nitro-4-fluorotoluene generated only a moderate product yield of 56% (Table 4, entry 3). With 4-fluorobenzonitrile, the reaction failed in toluene, but when DMF was used as the solvent, a 95% yield of the desired product was achieved (Table 4, entry 4). Surprisingly, 4-nitrofluorobenzene also reacted with the sterically demanding 2,6-di-isopropylphenyl TBDMS ether to give a 92% product yield using 10 mol % of **3** (Table 4, entry 5). A previous method for making this compound involved the use of a 4-nitrophenoxide anion and 1,4-dinitrobenzene in DMSO to obtain a 76% product yield.[15] 4-Fluorobenzonitrile reacted with 2,6-di-isopropylphenyl TBDMS ether to afford a 98% yield of the new compound in Table 4, entry 6.

In summary, we have demonstrated the utility of proazaphosphatrane **3** under the microwave conditions for synthesizing diaryl ethers from electron poor aryl fluorides and a variety of TBDMS-protected phenols, including sterically hindered ones. As in our previous work under the thermal conditions,[7] the reaction of 2,4-dinitrofluorobenzene with 4-methoxyphenol also failed in our microwave

Table 4
S_NAr reactions of aryl fluoride with sterically hindered TBDMS ethers



Entry	Aryl fluoride	TBDMS ether	mol % time	Product	Yield[a,b] (%)
1			10/3 h		92
2			10/3 h		95 (90)[c]
3			10/3 h		56
4			10/3 h		95 (77)[d]
5			10/3 h		92 (76)[e]
6			10/3 h		98

[a] Isolated yields (average of two runs).
[b] Yields in parentheses are literature values.
[c] See Ref. 17.
[d] See Ref. 11c.
[e] See Ref. 15.

protocol. This result is consistent with our earlier finding that the phosphorus of **3** can activate the silicon atom by weakening the Si–O bond.[8] Thermal[7] as well as microwave conditions require the use of an electron deficient aryl fluoride with a TBDMS aryl ether. Thus, the reaction of 4-fluoroanisole with 3-chlorophenyl TBDMS ether failed in both protocols.

General procedure: To a 10 mL microwave tube was charged 1.2 mmol of aryl TBDMS ether to which was added 1 mmol of aryl fluoride. Proazaphosphatrane **3** (from a stock solution prepared in the appropriate solvent) was then added to the tube under inert atmosphere. The tube was capped and placed in the microwave for the times given in Tables 1–3 and in entries 1–3 in Table 4, after which the solvent was removed in vacuo to produce the crude product that was purified by column chromatography (0–10% EtOAc/hexanes).

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Supplementary data

Supplementary data (complete experimental procedures and characterizational data for all compounds.) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.089.

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