Nucleophilic aromatic substitution using Et_3SiH/cat. *t*-Bu-P4 as a system for nucleophile activation†

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A novel type of deprotonative arylation of nucleophiles was conducted using Et_3SiH/cat. *t*-Bu-P4 and the powerful S_NAr reactions of aryl fluorides were accomplished using alcohols and malonates as nucleophiles.

The nucleophilic aromatic substitution (S_NAr) reaction is one of the most fundamental transformations in synthetic organic chemistry.[1] Various nucleophiles, such as alcohols, phenols, amines, and 1,3-dicarbonyl compounds, have been employed for the reaction. Traditionally, highly reactive bases such as NaH, *t*-BuOK *etc.* have been utilized to deprotonate nucleophiles and so generate reactive anions. The stoichiometric use of bases has been regarded as essential for completion of the substitution reaction. However, catalytic use of strong bases is desirable from the viewpoint of selectivity, safety and environmental benignity. Recently we have focused our interest on selective molecular transformations using organic superbases.[2] Here we report effective S_NAr reactions *via in situ* generation of activated nucleophiles using triethylsilane (Et_3SiH) and catalytic *t*-Bu-P4 (Fig. 1).

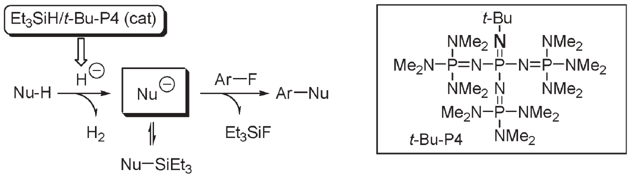
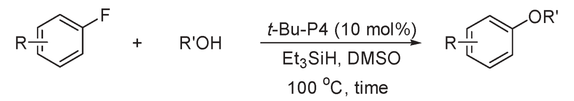


Fig. 1

The *t*-Bu-P4 base was developed as an extremely strong non-metallic organic base by Schwesinger *et al.*[3] and various of its deprotonative transformations have been investigated.[4] We recently reported that *t*-Bu-P4 base can catalyze the coupling reaction of aryl fluorides with silyl ethers.[2c] Moreover, Urgaonkar and Verkade have also reported a similar reaction using a proazaphosphatrane base as catalyst.[5] The use of silyl ether was required for these reactions, and direct arylation of unsilylated alcohols using superbase-catalyzed coupling reaction has been a challenge. However, the generation of hydride from Et_3SiH using catalytic *t*-Bu-P4 has been demonstrated in the reduction of ketones.[2c] Therefore, the combination of Et_3SiH and catalytic *t*-Bu-P4 is considered to represent an attractive hydride generating system with which to carry out sequential deprotonation and S_NAr reaction. We started our investigation with the arylation of various alcohols using 2-fluoronitrobenzene. The reaction of 2-fluoronitrobenzene with *n*-hexanol was carried out in the presence of Et_3SiH and 10 mol% of *t*-Bu-P4 at 100 °C for 2 h. The arylation reaction proceeded to give the ether quantitatively (Table 1, entry 1). The reaction with *n*-butanol also proceeded smoothly (Table 1, entry 2). Secondary alcohols, such as 2-phenylethylalcohol and 2-butanol were arylated under the same reaction conditions to give ethers in excellent yields (Table 1, entries 3 and 4). Aryl fluorides with weaker electron withdrawing groups were then examined. 4-Fluorobenzonitrile and 4-fluorobenzotrifluoride were employed and found to be good substrates. Accordingly, reaction with *n*-butanol proceeded under the same conditions to give the corresponding ethers (Table 1, entries 5 and 6).

Table 1



Entry	R	R′OH	*t*/h	Yield (%)
1	*o*-NO_2	*n*-Hexanol	2	100
2	*o*-NO_2	*n*-BuOH	2	97
3	*o*-NO_2	PhMeCHOH	2	92
4	*o*-NO_2	EtMeCHOH	18	71
5	*p*-CN	*n*-BuOH	13	98
6	*p*-CF_3	*n*-BuOH	13	58

When alcohols were reacted with Et_3SiH and catalytic *t*-Bu-P4 in the absence of aryl fluorides at room temperature, the silylation of alcohols proceeded smoothly. This result indicates that the deprotonation of alcohol occurs rapidly in this catalytic system, and that the *in situ* formation of silyl ethers may be considered a very fast process.

As shown in Table 2, silylations of various alcohols were examined.[6] The reaction of 8-nonen-1-ol with triethylsilane proceeded smoothly at room temperature in the presence of cat. *t*-Bu-P4 and the corresponding silyl ether was obtained in 98% yield (Table 2, entry 1). Benzyl alcohol was then reacted with Et_3SiH to give the silyl ether in 95% yield (Table 2, entry 2). α-Phenylethylalcohol was also reacted with Et_3SiH at room

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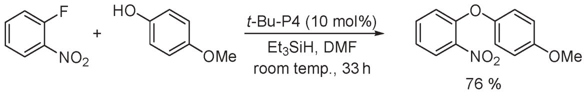
temperature and the silyl ether was obtained in 97% yield (Table 2, entry 3). Silylation of 4-dodecanol was examined using Et_3SiH to give the corresponding silyl ether in 98% yield (Table 2, entry 4). The silylation of sterically hindered tertiary alcohols also proceeded smoothly at room temperature and the silyl ether was obtained in excellent yields (Table 2, entries 5 and 6). Clearly, this reaction proceeds under mild conditions without forming stoichiometric amounts of ammonium salt, which is the fundamental drawback associated with the conventional method that uses R_3SiCl and amines.

Table 2

$$\text{R-OH} \xrightarrow[\text{DMF, room temp., time}]{\text{Et}_3\text{SiH (1.2 eq.)} \quad t\text{-Bu-P4 (1 mol\%)}} \text{R-OSiEt}_3$$

Entry	R	*t*/h	Yield (%)
1	$CH_2{=}CH(CH_2)_7$	1	98
2	$PhCH_2$	1	95
3	PhMeCH	2	97
4	*n*-Hex(*n*-Pr)CH	2	98
5	$PhMe_2C$	3	95
6	Ph_3C	6	87

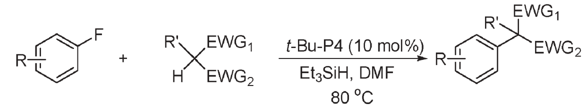
The diaryl ether structural unit has been found in a number of biologically important natural products, such as vancomycin, and many synthetic studies for diaryl ethers have been carried out.[7] *p*-Methoxyphenol was used as a representative phenol substrate and the S_NAr reaction using Et_3SiH/cat. *t*-Bu-P4 was examined. The reaction of 2-fluoronitrobenzene proceeded at room temperature to give the diaryl ether in 76% yield (Scheme 1).



Scheme 1

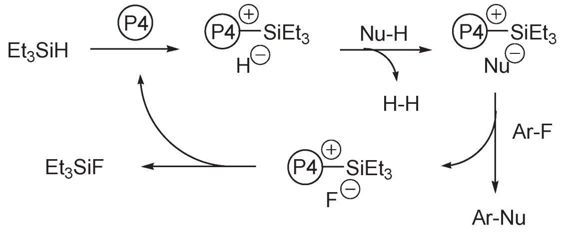
Our interest was next focused on using the Et_3SiH/cat. *t*-Bu-P4 system to effect the S_NAr reaction of C-nucleophiles. Introduction of O-nucleophiles to aromatics has been well investigated for S_NAr reactions, but there are limited numbers of successful examples for the arylation of carbanions by S_NAr reaction.[8] Highly activated aryl fluorides, such as fluoronitroarenes have been the only successful substrates for the S_NAr reactions using malonates as nucleophiles. To begin with, diethyl methylmalonate was reacted with 2-fluoronitrobenzene at 80 °C for 1 h, and the arylation was found to proceed smoothly to give the arylmalonate in 99% yield (Table 3, entry 1). The reaction with diethyl malonate was found to be slower and the arylmalonate was obtained in 56% yield after reacting for 22 h (Table 3, entry 2). Other α-substituted malonates also reacted with 2-fluoronitrobenzene to give arylmalonates (Table 3, entries 3 and 4). These 2-nitrophenylmalonates are expected to be important precursors for the synthesis of oxyindole derivatives.[9] α-Substituted cyanoacetate and α-substituted malononitrile were also found to be excellent C-nucleophiles, with arylation smoothly (Table 3, entries 5 and 6). 4-Fluoronitrobenzene reacted with methylmalonate to give the arylmalonate in 97% yield (Table 3, entry 7). The less reactive 2-fluoro- and 4-fluorobenzonitrile also reacted with methylmalonate to give the corresponding arylmalonates in 46 and 66% yield, respectively (Table 3, entries 8 and 9). Conventionally aryl fluorides with weak electron withdrawing groups have not been used for S_NAr reaction with these C-nucleophiles, and the present method provides a new and highly effective S_NAr reaction protocol.

Table 3



Entry	R	R′	EWG_1	EWG_2	*t*/h	Yield (%)
1	2-NO_2	Me	COOEt	COOEt	1	99
2	2-NO_2	H	COOEt	COOEt	22	56
3	2-NO_2	*n*-Hexyl	COOEt	COOEt	24	76
4	2-NO_2	Allyl	COOEt	COOEt	2	95
5	2-NO_2	Allyl	COOEt	CN	3	89
6	2-NO_2	Allyl	CN	CN	3	89
7	4-NO_2	Me	COOEt	COOEt	2	97
8	2-CN	Me	COOEt	COOEt	24	46
9	4-CN	Me	COOEt	COOEt	24	66

A plausible mechanism for the transformations reported here is shown in Scheme 2. The combination of Et_3SiH and cat. *t*-Bu-P4 is considered to generate a reactive hydride species, which deprotonates a nucleophile to form a phosphazenium nucleophile anion. This anion would be highly nucleophilic and would promote the S_NAr reaction, which gives the product and Et_3SiF, regenerating *t*-Bu-P4 catalyst.



Scheme 2

In summary, a novel type of deprotonative arylation of nucleophiles was achieved using Et_3SiH/cat. *t*-Bu-P4. The method provides a more powerful S_NAr reaction when compared to the conventional method using stoichiometric NaH. Further investigations on the scope and limitations of this reaction and mechanistic studies on the catalytic system are underway.

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