Catalytic Activation of Silylated Nucleophiles Using *t*Bu-P4 as a Base

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Trialkylsilyl groups play an important role as effective protecting groups in organic synthesis. Various O, N, and C nucleophilic sites can be protected by trialkylsilyl groups to control the selectivity of reactions. The nucleophilic attack of a fluoride anion on a silyl group is recognized as one of the most useful methods for desilylation. The activation of the nucleophile–silicon bond is important not only for desilylation but also for the generation of a reactive nucleophilic anion to achieve a new bond formation. The phosphazene bases developed by Schwesinger are known to be strong non-metallic organic bases. Among them, the *t*Bu-P4 base has been used for various selective deprotonative transformations, although the ability of *t*Bu-P4 base to activate silylated nucleophiles has not yet been shown. A novel catalytic activation of various O, N, and C nucleophile–silicon bonds using *t*Bu-P4 base was investigated to perform nucleophilic reactions with various electrophiles.

Trialkylsilyl groups play a very important role as effective protecting groups in organic synthesis.[1] Various O, N, and C nucleophilic sites can be protected by trialkylsilyl groups to control the selectivity of reactions. Various methods for desilylation have been investigated, and the nucleophilic attack of fluoride anion on a silyl group is recognized as one of the most useful.[2] The activation of nucleophile–silicon bonds is important not only for desilylation but also for the generation of reactive nucleophilic anion to achieve new bond formation. During the course of our recent studies on base-promoted transformations,[3] we became interested in the selective functionalization of silylated nucleophiles using catalytic *t*Bu-P4 base as a promoter.[4] A novel catalytic activation of various O, N, and C nucleophile–silicon bonds using *t*Bu-P4 base was investigated to perform nucleophilic reactions with various electrophiles (Figure 1).

The phosphazene bases developed by Schwesinger are known to be strong non-metallic organic bases.[5] Among them, *t*Bu-P4 base shows extremely high basicity (pK_{BH^+} = 42.1 in MeCN) and has been used for various selective deprotonative transformations.[6] The strong affinity of *t*Bu-P4 base for a proton is regarded as being synthetically useful, however the ability of *t*Bu-P4 base to activate silylated nucleophiles has not been shown.[7] Therefore, various catalytic reactions using silylated nucleophiles as precursors of highly nucleophilic anions promoted by *t*Bu-P4 base were investigated, as shown in Figure 1. Initially, the activation of *O*-silylated phenols in the presence of catalytic *t*Bu-P4 base to generate a phenoxy anion was investigated and the nucleophilic displacement of aryl fluoride was examined. Recently, many important aryloxylations of aryl halides have been reported using transition metal and other heavy metal-catalyzed reactions;[8] however, a transition-metal-free nucleophilic substitution reaction promoted by an organic base[9] is also considered to be an attractive process. The reaction of TMS-OPh with 2-fluoronitrobenzene was carried out in the presence of 10 mol-% *t*Bu-P4 base and the reaction proceeded smoothly at room temperature to give the biaryl ether in quantitative yield (Table 1, entry 2). When phenol was treated with 2-fluoronitrobenzene (**1**, Scheme 1) under the same reaction conditions, the yield of the biaryl ether (**2a**) was only 1.6% and unreacted 2-fluoronitrobenzene (**1**) remained in the reaction (Table 1, entry 1). TBDMS ethers are more stable toward nucleophilic cleavage than TMS ethers and can be handled as stable synthetic blocks. To our surprise, TBDMS-OPh also showed high reactivity in spite of the steric hindrance of the TBDMS group, and the desired biaryl **2a** was obtained in 96% yield (Table 1, entry 3).

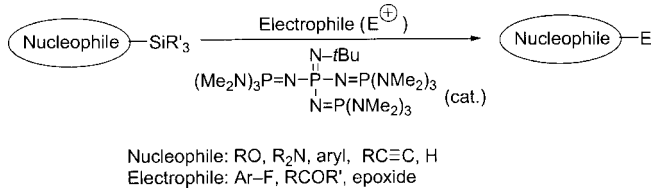

Figure 1. Catalytic activation of silylated nucleophiles using *t*Bu-P4 base.

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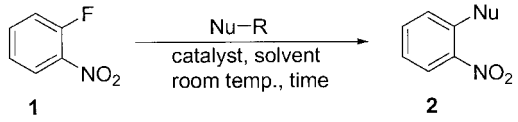
Table 1. Activation of trialkyl-silylated nucleophiles and nucleophilic aromatic substitution.

Entry	Nu	R	Catalyst (mol-%)	Solvent	Time (h)	2	Yield (%)
1	PhO	H	*t*Bu-P4 base (10)	DMF	1	**a**	1.6
2	PhO	TMS	*t*Bu-P4 base (10)	DMF	6	**a**	quant.
3	PhO	TBDMS	*t*Bu-P4 base (10)	DMF	1	**a**	96
4	PhO	TBDMS	*t*Bu-P4 base (10)	DMSO	1	**a**	96
5	2-*t*Bu-C_6H_4O	TBDMS	*t*Bu-P4 base (10)	DMSO	1	**b**	99
6	2-Br-C_6H_4O	TBDMS	*t*Bu-P4 base (10)	DMSO	6	**c**	95
7	2-I-C_6H_4O	TBDMS	*t*Bu-P4 base (10)	DMSO	8	**d**	87
8	4-$MeOC_6H_4O$	TBDMS	*t*Bu-P4 base (10)	DMSO	1	**e**	98
9	PhO	TBDMS	TBAF[c] (10)	DMF	1	**a**	trace
10	*n*HexO	TBDMS	*t*Bu-P4 base (10)	DMSO	24	**f**	72[a]
11	morpholino	TMS	*t*Bu-P4 base (10)	DMSO	12	**g**	92
12	N_3	TMS	*t*Bu-P4 base (10)	DMSO	29	**h**	95
13	PhCC	TMS	*t*Bu-P4 base (20)	DMF	12	**i**	41[b]
14	PhCC	TMS	TBAF[c] (20)	DMF	12	**i**	6[b]

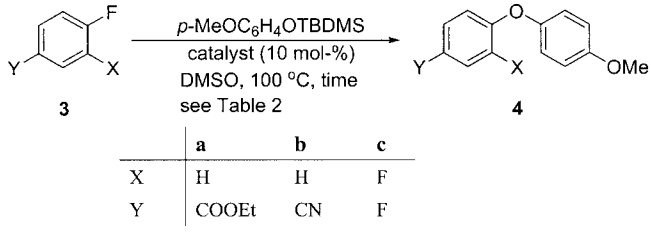
[a] Reaction was carried out at 100 °C. [b] Reaction was carried out at –78 °C followed by gradual warming to 10 °C. [c] Commercially available TBAF in THF solution (trihydrate) was used.



Scheme 1.

DMSO and DMF were found to be promising solvents for the reaction and the dryness of the solvent was critical for obtaining the products in high yields. TBDMS ethers of other phenol derivatives were tested as substrates, and the 2-*tert*-butyl, 2-bromo, and 2-iodo derivatives gave excellent results in spite of the steric bulkiness of the nucleophile. (Table 1, entries 5, 6, and 7). The tolerance of a bromo or iodo group is very attractive for the subsequent transformation as conventional metal-catalyzed reactions do not allow this kind of selectivity. When TBAF was employed as a catalyst the reaction was very sluggish, and only a trace amount of product was obtained (Table 1, entry 9). The reaction of *O*-silylated aliphatic alcohols was found to be slow, but when the reaction was conducted at 100 °C, 72% yield of the product **2f** was obtained (Table 1, entry 10). As a silylated N-nucleophile, *N*-TMS morpholine was reacted to give the arylamine **2g** in high yield (Table 1, entry 11). The reaction with TMS-N_3 also proceeded smoothly to give the aryl azide **2h** (Table 1, entry 12). As a *C*-silylated nucleophile, TMS phenylacetylene was employed to give the phenylethynylated product **2i** in 41% yield, although some unreacted starting material still remained (Table 1, entry 13). Further improvement of the reaction conditions is underway. Examples of the introduction of an alkyne moiety onto an aromatic ring by nucleophilic substitution in the absence of a transition metal catalyst are quite limited.[10]

The substituted aryl fluorides **3a**–**e** react with TBDMS-OC_6H_4OMe-*p* in the presence of 10 mol-% *t*Bu-P4 base (Scheme 2). Ethyl *p*-fluorobenzoate (**3a**) reacts at 80 °C to give the biaryl ether **4a** in 91% yield (Table 2, entry 1). Other bases such as BEMP or DBU were found to be almost inactive (Table 2, entries 2 and 3). *p*-Fluorobenzonitrile (**3b**) reacts at 100 °C to give the desired product **4b** in 92% yield (Table 2, entry 4). *p*-Fluoro(trifluoromethyl)ben-



	a	b	c
X	H	H	F
Y	COOEt	CN	F

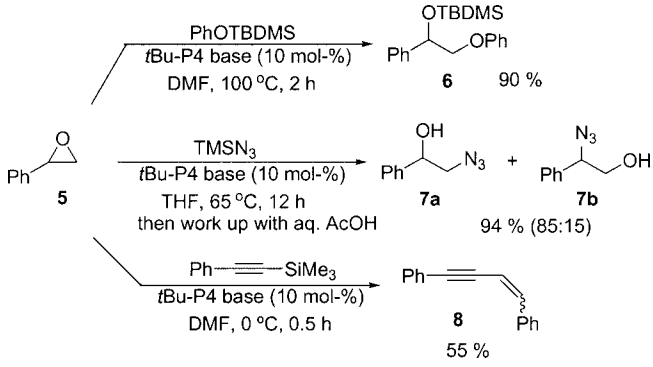
Scheme 2.

Table 2. Reaction of substituted aryl fluorides with TBDMS-OC_6H_4OMe-*p*.

Entry	3	X	Y	Catalyst	Solvent	Temp. (°C)	Time (h)	4	Yield (%)
1	**a**	H	COOEt	*t*Bu-P4 base	DMSO	80	2	**a**	92
2	**a**	H	COOEt	BEMP	DMSO	80	2	**a**	1
3	**a**	H	COOEt	DBU	DMSO	80	2	**a**	0
4	**b**	H	CN	*t*Bu-P4 base	DMSO	100	4	**b**	92
5	**c**	H	CF_3	*t*Bu-P4 base	DMSO	100	10	**c**	93
6	**d**	Br	H	*t*Bu-P4 base	DMF	100	48	**d**	85
7	**e**	I	H	*t*Bu-P4 base	DMF	100	48	**e**	43

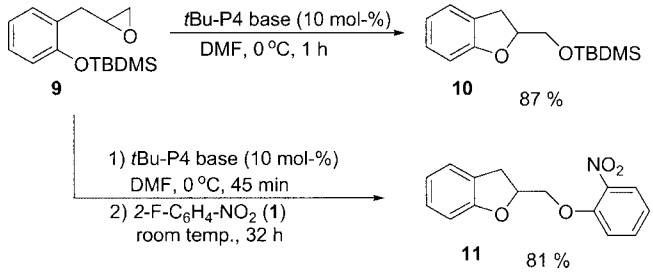
zene (**3c**) also reacts at 100 °C to give the desired product **4c** in 93% yield. Interestingly, when the reaction of *o*-fluorobromobenzene (**3d**) was carried out at 100 °C in DMF, the substitution occurred only at the fluorine-substituted position to give the bromo biaryl ether **4d** exclusively in 85% yield (Table 2, entry 6). The reaction of *o*-iodofluorobenzene (**3e**) was also examined and the iodo biaryl ether **4e** was obtained in 43% yield (Table 2, entry 7). The reverse and complimentary regioselectivity to transition-metal-catalyzed reactions is attractive for the selective functionalization of aromatic compounds.

The reaction of styrene oxide (**5**) with TBDMS-OPh in the presence of 10 mol-% *t*Bu-P4 base at 100 °C gave the ring-opening adduct **6**. The reaction of TMS-N_3 with **5** in the presence of 10 mol-% *t*Bu-P4 base at 65 °C in THF gave ring-opened adducts (**7a** and **7b**) in 94% yield. The reaction of alkynylsilane with **5** gave the enyne derivative **8**; the intermediary ring-opening adduct was not isolated (Scheme 3).



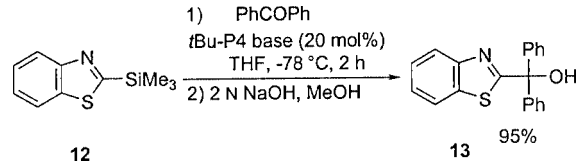
Scheme 3.

The epoxide opening reaction was then utilized for heterocyclic synthesis. The TBDMS aryl ether **9**, which possesses an epoxide moiety, was subjected to the cyclization reaction in the presence of 10 mol-% *t*Bu-P4 base; the dihydrobenzofuran derivative **10** was obtained in 87% yield in the TBDMS ether form. Subsequent reaction of the cyclized TBDMS ether with 2-fluoronitrobenzene (**1**) was achieved in one flask without isolating the TBDMS ether to give the aryl ether **11** in 81% yield (Scheme 4).



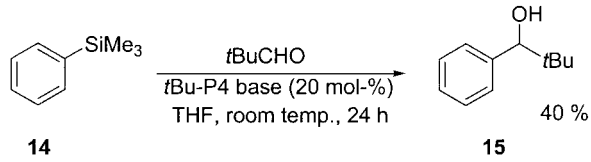
Scheme 4.

Other silylated C-nucleophiles can be similarly activated by using *t*Bu-P4 base, and the reaction of 2-TMS-benzothiazole (**12**)[11] with benzophenone gave the alcohol **13** in 95% yield (Scheme 5).



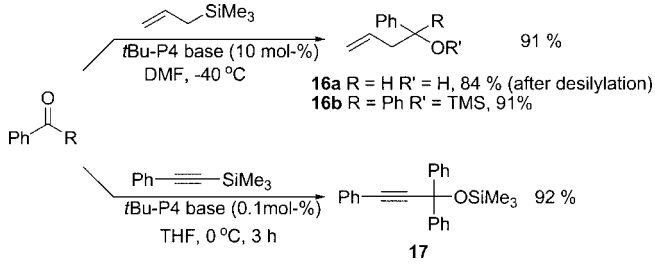
Scheme 5.

Phenyltrimethylsilane (**14**) also reacted with pivalaldehyde in the presence of *t*Bu-P4 base to give the desired alcohol **15** in 40% yield (Scheme 6). The reaction conditions should be further optimized, but it is known that the conventional fluoride anion cannot activate phenyltrimethylsilane to generate a phenyl nucleophile.[12]



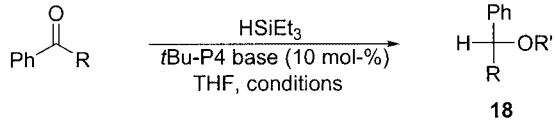
Scheme 6.

The reaction of allyltrimethylsilane[13] or alkynylsilane[14] with carbonyl compounds gave the 1,2 adducts in excellent yields (Scheme 7).



Scheme 7.

Triethylsilane can also be activated by treatment with *t*Bu-P4 base and the reactions with benzaldehyde, acetophenone, and benzophenone were examined. As for the reaction of benzaldehyde, the TES ether of the reduction product was treated with aq. AcOH to cleave the silyl ether to give the alcohol **18a** in 89% yield. In the reaction of acetophenone and benzophenone with triethylsilane, the silyl ethers **18b** and **18c** were obtained in 62% and 72% yields, respectively (Scheme 8, Table 3).[15]



Scheme 8.

In summary, a unique method for activating various nucleophile–silicon bonds using *t*Bu-P4 base has been developed and catalytic bond-forming reactions of silylated nucleophiles accomplished. As for the reaction mechanism, analysis of the interaction between *t*Bu-P4 base and silyl

Table 3. Reaction of carbonyl compounds with triethylsilane.

Entry	R	Conditions	Desilylation	18	R'	Yield (%)
1	H	0 °C, 0.5 h	aq. AcOH	**a**	H	89
2	Me	room temp., 23 h	-	**b**	$SiEt_3$	62
3	Ph	room temp., 23 h	-	**c**	$SiEt_3$	72

group is likely to be important. Further detailed experiments are necessary to identify the exact mode of the nucleophile–silicon bond activation.[16] Extensive investigations of the scope and limitation of the catalytic reaction and mechanistic studies of the activation are underway.

Supporting Information Available: Experimental details and spectroscopic data of the products (see also the footnote on the first page of this article).

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[16] In order to remove any traces of water, *t*Bu-P4 base was treated with ethyl bromide (ref. [5b]). The "dried P4 base" also showed catalytic reactivity for the activation of alkynylsilanes. However, further careful spectroscopic experiments are necessary to clarify the exact mode of activation; NMR studies are currently underway.

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