

Nucleophilic aromatic substitution using Et₃SiH/cat. *t*-Bu-P4 as a system for nucleophile activation†

Masahiro Ueno,^a Misato Yonemoto,^a Masahiro Hashimoto,^a Andrew E. H. Wheatley,^{‡b} Hiroshi Naka^a and Yoshinori Kondo^{*a}

Received (in Cambridge, UK) 5th January 2007, Accepted 5th February 2007

First published as an Advance Article on the web 28th February 2007

DOI: 10.1039/b700140a

A novel type of deprotonative arylation of nucleophiles was conducted using Et₃SiH/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 (Et₃SiH) and catalytic *t*-Bu-P4 (Fig. 1).

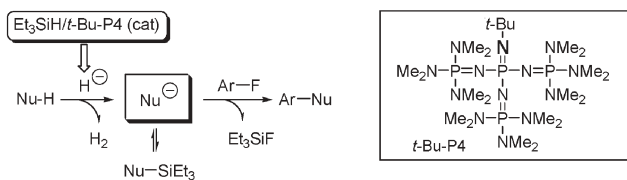


Fig. 1

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, Urganokar and Verkade have also reported a similar reaction using a proazaphosphatranne 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 Et₃SiH using catalytic *t*-Bu-P4 has been demonstrated in the reduction of ketones.^{2c} Therefore, the combination of Et₃SiH 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 Et₃SiH 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	<i>o</i> -NO ₂	<i>n</i> -Hexanol	2	100
2	<i>o</i> -NO ₂	<i>n</i> -BuOH	2	97
3	<i>o</i> -NO ₂	PhMeCHOH	2	92
4	<i>o</i> -NO ₂	EtMeCHOH	18	71
5	<i>p</i> -CN	<i>n</i> -BuOH	13	98
6	<i>p</i> -CF ₃	<i>n</i> -BuOH	13	58

When alcohols were reacted with Et₃SiH 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 Et₃SiH to give the silyl ether in 95% yield (Table 2, entry 2). α -Phenylethylalcohol was also reacted with Et₃SiH at room

^aGraduate School of Pharmaceutical Sciences, Tohoku University, Aramaki Aza Aoba 6-3, Aoba-ku, Sendai, 980-8578, Japan. E-mail: ykondo@mail.pharm.tohoku.ac.jp; Fax: 81-22-795-6804; Tel: 81-22-795-6804

^bDepartment Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EH. E-mail: aehw2@cam.ac.uk; Fax: 44-1223-336362; Tel: 44-1223-763122

† Electronic supplementary information (ESI) available: Experimental procedures and spectral data for synthesized compounds. See DOI: 10.1039/b700140a

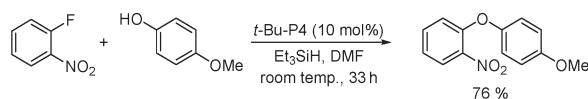
‡ JSPS Fellow 19th January 2006–19th April 2006.

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

Entry	R	t/h	Yield (%)
1	$\text{CH}_2=\text{CH}(\text{CH}_2)_7$	1	98
2	PhCH_2	1	95
3	PhMeCH	2	97
4	<i>n</i> -Hex(<i>n</i> -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 $\text{S}_{\text{N}}\text{Ar}$ reaction using $\text{Et}_3\text{SiH}/\text{cat. } t\text{-Bu-P4}$ was examined. The reaction of 2-fluoronitrobenzene proceeded at room temperature to give the diaryl ether in 76% yield (Scheme 1).



Scheme 1

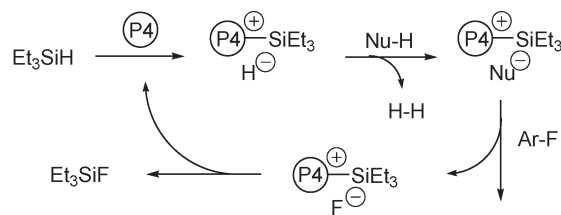
Our interest was next focused on using the $\text{Et}_3\text{SiH}/\text{cat. } t\text{-Bu-P4}$ system to effect the $\text{S}_{\text{N}}\text{Ar}$ reaction of C-nucleophiles. Introduction of O-nucleophiles to aromatics has been well investigated for $\text{S}_{\text{N}}\text{Ar}$ reactions, but there are limited numbers of successful examples for the arylation of carbanions by $\text{S}_{\text{N}}\text{Ar}$ reaction.⁸ Highly activated aryl fluorides, such as fluoronitroarenes have been the only successful substrates for the $\text{S}_{\text{N}}\text{Ar}$ 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 malonitrile 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 $\text{S}_{\text{N}}\text{Ar}$ reaction with these C-nucleophiles, and the present method provides a new and highly effective $\text{S}_{\text{N}}\text{Ar}$ 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	<i>n</i> -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 phosphazanium nucleophile anion. This anion would be highly nucleophilic and would promote the $\text{S}_{\text{N}}\text{Ar}$ reaction, which gives the product and Et_3SiF , regenerating *t*-Bu-P4 catalyst.



Scheme 2



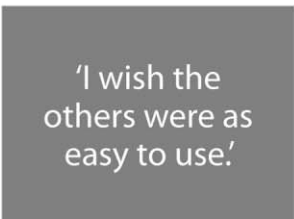
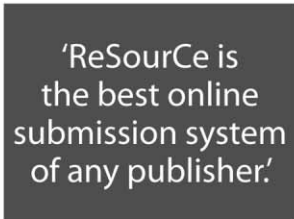



In summary, a novel type of deprotonative arylation of nucleophiles was achieved using $\text{Et}_3\text{SiH}/\text{cat. } t\text{-Bu-P4}$. The method provides a more powerful $\text{S}_{\text{N}}\text{Ar}$ reaction when compared to the conventional method using stoichiometric NaH . Further investigations on the scope and limitations of this reaction and mechanistic studies on the catalytic system are underway.

This work was partly supported by the Grant-in Aid for Scientific Research (No. 16659002, No. 18659001) from the Ministry of Education, Science, Sports and Culture, Japan and grants from the Sumitomo Foundation and Yamada Science Foundation and also by a Visiting Fellowship from The Japan Society for the Promotion of Science.

Notes and references

- (a) M. B. Smith and J. March, *Advanced Organic Chemistry*, Wiley-Interscience, New York, 2001, 5th edn, ch. 13, p. 850; (b) C. Paradisi, *Comprehensive Organic Synthesis*, Pergamon Press, Oxford, 1991, vol. 4, pp. 423–450; (c) E. Buncl, J. M. Dust and F. Terrier, *Chem. Rev.*, 1995, **95**, 2261; (d) J. A. Zoltewics, *Top. Curr. Chem.*, 1975, **59**, 33.

- 2 (a) T. Imahori and Y. Kondo, *J. Am. Chem. Soc.*, 2003, **125**, 8082; (b) T. Imahori, C. Hori and Y. Kondo, *Adv. Synth. Catal.*, 2004, **346**, 1090; (c) M. Ueno, C. Hori, K. Suzawa, M. Ebisawa and Y. Kondo, *Eur. J. Org. Chem.*, 2005, 1965; (d) K. Kobayashi, M. Ueno and Y. Kondo, *Chem. Commun.*, 2006, 3128; (e) M. Ueno, A. E. H. Wheatley and Y. Kondo, *Chem. Commun.*, 2006, 3549; (f) K. Suzawa, M. Ueno, A. E. H. Wheatley and Y. Kondo, *Chem. Commun.*, 2006, 4850; (g) Y. Kondo and M. Ueno, *Jpn. Pat.*, JP 2006265157 A2 20061005, 2006; Y. Kondo and M. Ueno, *Chem. Abstr.*, 2006, **145**, 396791.
- 3 (a) R. Schwesinger and H. Schlemper, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 1167; (b) R. Schwesinger, H. Schlemper, C. Hasenfratz, J. Willaredt, T. Dambacher, T. Breuer, C. Ottaway, M. Fletschinger, J. Boele, H. Fritz, D. Putzas, H. D. Rotter, F. G. Bordwell, A. V. Satish, G.-Z. Ji, E.-M. Peters, K. Peters, H. G. von Schnering and L. Walz, *Liebigs Ann.*, 1996, 1055.
- 4 (a) G. A. Kraus, N. Zhang, J. G. Verkade, M. Nagarajan and P. B. Kisanga, *Org. Lett.*, 2000, **2**, 2409; (b) T. Pietzonka and D. Seebach, *Chem. Ber.*, 1991, **124**, 1837; (c) T. Pietzonka and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 716; (d) L. Leito, T. Rodima, I. A. Koppel, R. Schwesinger and V. M. Vlasov, *J. Org. Chem.*, 1997, **62**, 8479.
- 5 S. Urgaonkar and J. G. Verkade, *Org. Lett.*, 2005, **7**, 3319.
- 6 For recent silylation of alcohol with Et_3SiH : (a) H. Ito, K. Takagi, T. Miyahara and M. Sawamura, *Org. Lett.*, 2005, **7**, 3001; (b) H. Ito, A. Watanabe and M. Sawamura, *Org. Lett.*, 2005, **7**, 1869.
- 7 (a) K. C. Nicolaou and C. N. C. Boddy, *J. Am. Chem. Soc.*, 2002, **124**, 10451; (b) D. L. Boger, M. A. Patane and J. Zhou, *J. Am. Chem. Soc.*, 1994, **116**, 8544; (c) B. M. Crowley, Y. Mori, C. C. McComas, D. Tang and D. L. Boger, *J. Am. Chem. Soc.*, 2004, **126**, 4310; (d) H. Deng, J.-K. Jung, T. Liu, K. W. Kuntz, M. L. Snapper and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2003, **125**, 9032.
- 8 (a) N. Selvakumar, B. Yadi Reddy, G. Sunil Kumar and J. Iqbal, *Tetrahedron Lett.*, 2001, **42**, 8395; (b) R. J. Snow, T. Butz, A. Hammach, S. Kapadia, T. M. Morwick, A. S. Prokopowicz, III, H. Takahashi, J. D. Tan, M. A. Tschantz and X.-J. Wang, *Tetrahedron Lett.*, 2002, **43**, 7553; (c) N. Selvakumar, J. Yadi Reddy, A. Malar Azhagan, M. Mumar Khera, J. Moses Babu and J. Iqbal, *Tetrahedron Lett.*, 2003, **44**, 7065; (d) N. J. Lawrence, C. J. Davies and M. Gray, *Org. Lett.*, 2004, **6**, 4957; (e) M. Bella, S. Kobbelgaard and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 3670; (f) S. Kobbelgaard, M. Bella and K. A. Jørgensen, *J. Org. Chem.*, 2006, **71**, 4980.
- 9 (a) G. J. Quallich and P. M. Morrissey, *Synthesis*, 1993, 51; (b) L. Sun, N. Tran, F. Tang, H. App, P. Hirth, G. McMahon and C. Tang, *J. Med. Chem.*, 1998, **41**, 2588; (c) L. Sun, N. Tran, C. Liang, F. Tang, A. Rice, R. Schreck, K. Waltz, L. K. Shawver, G. Mchanon and C. Tang, *J. Med. Chem.*, 1999, **42**, 5120.

	Comments received from just a few of the thousands of satisfied RSC authors and referees who have used ReSource - the online portal helping you through every step of the publication process.
	authors benefit from a user-friendly electronic submission process, manuscript tracking facilities, online proof collection, free pdf reprints, and can review all aspects of their publishing history
	referees can download articles, submit reports, monitor the outcome of reviewed manuscripts, and check and update their personal profile
	NEW!! We have added a number of enhancements to ReSource, to improve your publishing experience even further.
	New features include:
	<ul style="list-style-type: none"> ● the facility for authors to save manuscript submissions at key stages in the process (handy for those juggling a hectic research schedule) ● checklists and support notes (with useful hints, tips and reminders) ● and a fresh new look (so that you can more easily see what you have done and need to do next)
	Go online today and find out more.

08030628

Registered Charity No. 207890

RSC Publishing

www.rsc.org/resource