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Nucleophilic Substitution Reaction at the Nitrogen of Arylsulfonamides with Phosphide Anion

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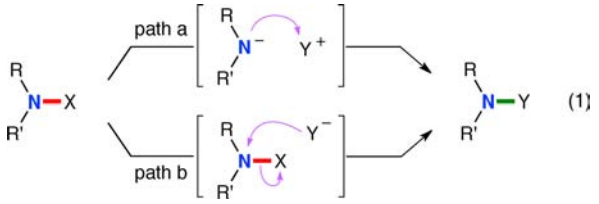
Supporting Information

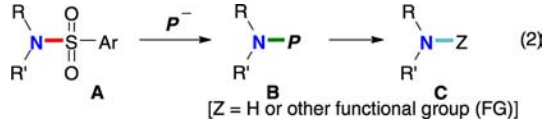
ABSTRACT: A novel nucleophilic substitution reaction at the nitrogen of arylsulfonamides by means of phosphide anions has been described. This reaction allows for the efficient transformation of arylsulfonamides into synthetically valuable phosphamides, amines, and a variety of protected amines.

The importance of nitrogen-containing organic compounds across a wide range of scientific and technological fields is undisputed. Therefore, the development of more efficient and flexible synthetic methods for manipulating nitrogen functionalities is an important subject in organic synthesis. In particular, the synthesis and transformation of amines and their derivatives are the most fundamental and critical issues in this field of chemistry.[1] To accomplish this, bond formation at nitrogen using its nucleophilic nature is the most reasonable, efficient, and often utilized approach (eq 1, path a).[2] In contrast, the



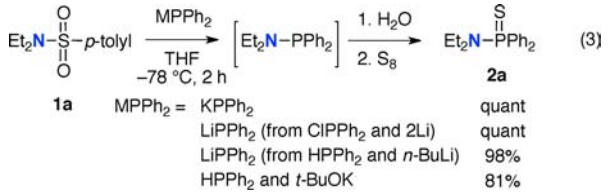
opposite approach, i.e., nucleophilic substitution at nitrogen (eq 1, path b), is fairly undeveloped and limited to the reaction of highly activated nitrogen compounds such as haloamine and hydroxylamine derivatives.[3]

To successfully execute this difficult approach, we have focused on the sulfonamide motif, because the sulfonyl group increases the electrophilicity of the attached nitrogen as a result of its electron-withdrawing ability and it can also act as a leaving group.[4] As a result of this study, we found that a variety of arylsulfonamides **A** undergo this type of reaction with a properly selected azaphilic nucleophile, phosphide anion (P^-), that provides the corresponding phosphamides **B**, which are readily converted to protic amines and their derivatives **C** (eq 2).[5] This approach is valuable, not only as a rare example of



nucleophilic substitution at nitrogen but also as an efficient transformation method for sulfonamides, which are widely utilized in organic synthesis. The details of the study are provided below.

We first examined the reaction of *N*,*N*-diethyl-*p*-toluenesulfonamide (**1a**) with several nucleophiles as a model reaction to survey the probability of the nucleophilic substitution reaction. After several attempts, we found that the reaction with commercially available $KPPh_2$ (1.3 equiv) in THF proceeded smoothly at −78 °C, consuming **1a** and quantitatively providing an unstable polar product along with *p*-tolyl-SO_2H. This result suggested that the desired Et_2NPPh_2 would be generated in the reaction; however, it was then readily oxidized to $Et_2NP(O)Ph_2$ by air during the workup and/or purification process. In order to avoid air oxidation and obtain a manageable product, we performed the same reaction and subsequently treated the product with an excess amount of sulfur.[6] As a result, the expected phosphamide **2a** was obtained quantitatively, which showed that the nucleophilic substitution reaction at the nitrogen of **1a** with the liberation of the *p*-toluenesulfonyl moiety was successfully performed with phosphide anion (eq 3).[7−10] Similar results were obtained in



the reaction with $LiPPh_2$ prepared from $ClPPh_2$ or $HPPh_2$.[11] Furthermore, the reaction with a mixture of $HPPh_2$ and *t*-BuOK at rt, followed by the addition of sulfur, also provided **2a** in good yield (81%); this would be a convenient procedure in practice.[12] In addition, the rather unique reactivity observed seems to be specific to phosphide anions. Similar reactions with other nucleophiles such as LiSPh, LiS(*n*-$C_{12}H_{25}$), LiI, and *n*-Bu_2NLi failed to provide the corresponding substitution reaction products.

The developed reaction would be synthetically valuable, not only as an efficient approach for phosphamides, which is especially important in the field of ligand synthesis,[13] but also as a versatile transformation method for sulfonamides in combination with further reactions. For example, cleavage of the N−P bond of phosphamides could occur under acidic

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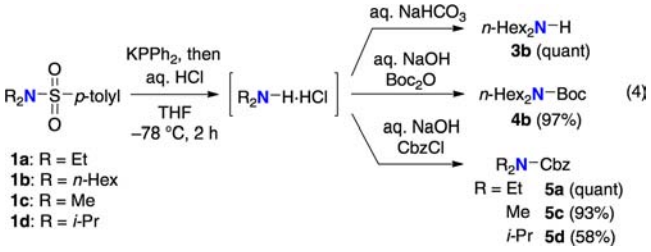
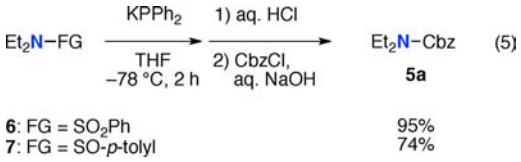
conditions.[14] The treatment of *N*,*N*-dihexyl-*p*-toluenesulfonamide **1b** with $KPPh_2$, followed by the addition of 1 M aqueous hydrochloric acid and successive neutralization of the reaction mixture with a saturated aqueous sodium bicarbonate solution, quantitatively afforded the corresponding amine **3b** (eq 4).[15] In



place of aqueous sodium bicarbonate, the addition of 1 M aqueous sodium hydroxide and di-*tert*-butyl dicarbonate furnished Boc-protected amine **4b** in a one-pot procedure with an excellent yield (97%). In a similar manner, Cbz-protected amines **5a** and **5c** were successfully prepared upon treatment with CbzCl in excellent yields (**5a**: quant, **5c**: 93%). Even the reaction of sterically hindered **1d** provided the corresponding Cbz-amide **5d** in moderate yield (58%).

Furthermore, we found that the reaction with a phosphide anion was versatile and that there was significant selectivity in terms of the functional group on the nitrogen of the amides. The reaction of benzenesulfonamide **6** with $KPPh_2$ (1.3 equiv) in THF at −78 °C followed by CbzCl treatment provided **5a** in 95% yield (eq 5). A similar reaction of sulfinamide **7** also

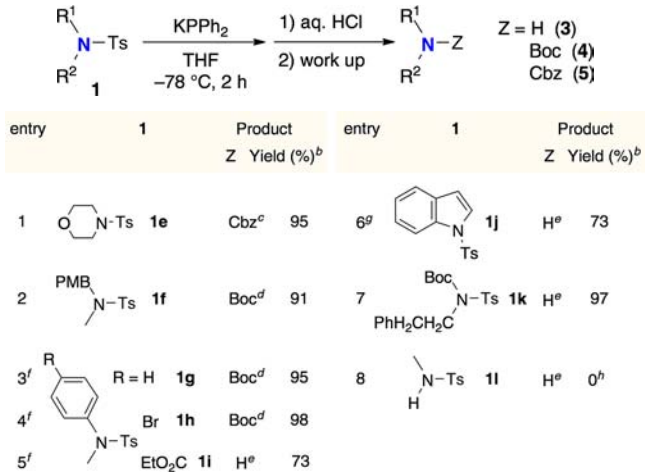


furnished Cbz-amide **5a** in good yield (74%). In sharp contrast, the methanesulfonamide, Cbz-amide, Boc-amide, and *p*-methoxybenzyl (PMB)-amine derived from Et_2NH were inert under these conditions, and the starting materials were recovered quantitatively. On the other hand, nosylamide was not tolerated under the reaction conditions and provided a complex mixture of products.[16] These results clearly suggest that the phosphide anion reaction can be utilized as a group-selective transformation of arylsulfonamide in multinitrogen-functionalized compounds (*vide infra*).

It is well recognized that sulfonamides, as typified by *p*-toluenesulfonamide, represent the most important and commonly utilized nitrogen functionality as robustly protected amine derivatives, in addition to being suitable substrates for N−C bond formation in the Mitsunobu reaction with alcohols and alkylation with alkyl halides.[16a,17,18] However, the requirement of harsh conditions for the deprotection of sulfonamides, i.e., the transformation to amines, is their major drawback, which can often be problematic in the synthesis of nitrogen-containing compounds.[16,19,20] The presently proposed method, which is the sequential reaction with phosphide and acidic hydrolysis, will be an efficient solution to this problem.

To demonstrate the generality of this procedure, we next examined a similar transformation with a variety of *p*-toluenesulfonamides, as shown in Table 1. The reaction of tosylmorpholine (**1e**) with $KPPh_2$ and subsequent Cbz protection also afforded the corresponding amide **5e** in

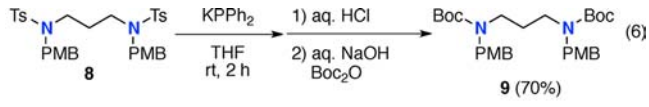
Table 1. Deprotection and Transformation of Various Tosylamides[a]

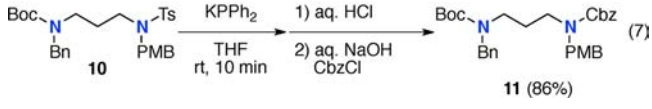


[a]Conditions: $KPPh_2$ (1.3 equiv), THF, −78 °C. [b]Isolated yields. [c]Workup with CbzCl and aq. NaOH. [d]Workup with Boc_2O and aq. NaOH. [e]Workup with aq. $NaHCO_3$. [f]$KPPh_2$ (1.6 equiv) was used. [g]$KPPh_2$ (3.0 equiv) was used. [h]Starting material (**1l**) was recovered quantitatively.

excellent yield (entry 1). The tosyl moiety of **1f** can also be efficiently converted to Boc without damage to the PMB moiety (entry 2). In the case of aniline derivatives **1g**−**i**, the conversion to Boc or the deprotection was successful and gave good to excellent yields, leaving the other functional groups untouched (entries 3−5). It is worth noting that the reaction of 4-bromoanilide **1h** proceeded without reduction of the bromo group (entry 4), which was reduced in the conventional deprotection by lithium naphthalenide.[17,21] Notably, the ethoxycarbonyl moiety was tolerated under the reaction conditions (entry 5), unlike the reaction with Red-Al,[17,22,23] which reduced only the ester moiety. The deprotection of tosylindole (**1j**) was also successful, although excess amounts of phosphide anion were required (entry 6). Furthermore, the reaction of imide **1k** resulted in selective and efficient deprotection of the tosyl moiety (entry 7). Yet, *N*-methyltosylamide (**1l**) was recovered under these conditions (entry 8).

Toward synthesis of complex polyamine such as various spider toxins, the selective deprotection of arylsulfonamides by means of phosphide anions should serve as a novel methodology comparable to Fukuyama's nosyl strategy.[16a,b] We thus examined the protective group transformations of diamine derivatives as models of protected polyamines (eqs 6,7). The





double nucleophilic substitution reactions of diamide **8** proceeded smoothly to afford Boc-protected amide **9** in good yield at room temperature (eq 6). Moreover, the selective removal of the tosyl group of diamide **10** resulted in good yield, leaving the benzyl, Boc, and PMB protecting groups intact (eq

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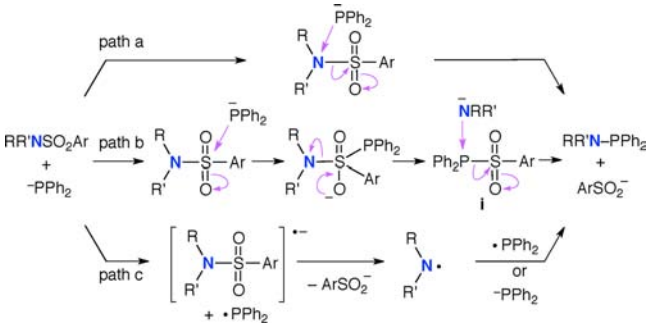
7). Thus, the developed selective deprotection enhanced the utility of the arylsulfonyl group as an amine protecting group.

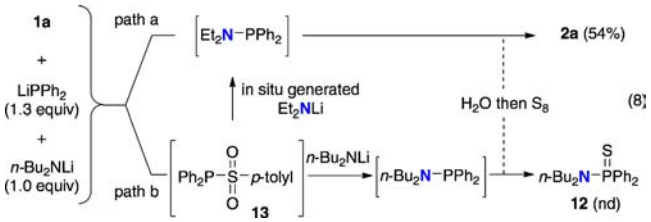
Our attention was next directed toward the detailed mechanism of the phosphide anion reaction. For this reaction, we considered not only the initially envisioned "direct N−P bond formation pathway" (Scheme 1, path a) but also the

Scheme 1. Possible Mechanisms for the Substitution Reaction



"stepwise pathway," which consists of (1) a nucleophilic attack of P^- on the sulfur atom to form sulfonphosphide **i** and an amide anion and (2) N−P bond formation by the nucleophilic substitution reaction of **i** and the amide anion (Scheme 1, path b). Alternatively, a single electron transfer (SET)-mediated "radical pathway" is also conceivable (Scheme 1, path c).

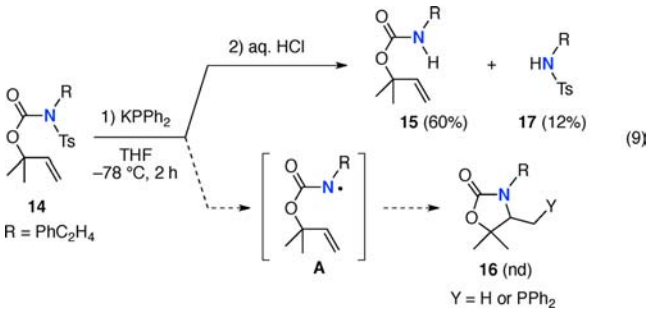
To gain insight into the probability of path b, we performed the reaction of *p*-toluenesulfonamide **1a** and $LiPPh_2$ in the presence of *n*-Bu_2NLi in THF at −78 °C to determine whether crossover product **12** was obtained via possible intermediate **13** (≡ **i**, Ar = *p*-tolyl) (eq 8). As a result, normal phosphamide **2a**



was obtained exclusively, and no trace of **12** was observed in the ^1H NMR analysis. This result supports the conclusion that the path a mechanism is more appropriate than the path b mechanism.

Furthermore, in order to know whether the radical mechanism (Scheme 1, path c) is involved, we performed a similar reaction of *δ*,*ε*-unsaturated *p*-toluenesulfonamide **14**, which should provide cyclization product **16** if the amidyl radical intermediate **A** is generated (eq 9).[24,25] These results suggest that the SET process is not likely to be a major pathway, although SET participation cannot be rigorously excluded.

Theoretical calculations also support the path a mechanism. We conducted a computational analysis of the reaction of a simplified sulfonamide and lithium phosphide using the density functional theory (DFT) B3LYP/6-311G(d,p) method.[26] The transition state structure **TS** obtained for the substitution reaction at the nitrogen (Figure 1) indicated that the coordination of lithium at nitrogen and oxygen would enhance the elimination of sulfinate, and the calculated activation energy ($\Delta E^{\ddagger}$ = 12.7 kcal/mol)[27] was in good agreement with the



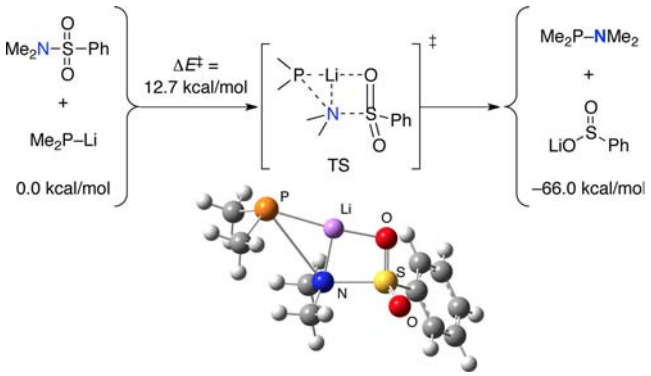


Figure 1. DFT calculation for the putative transition state .

experimental results. The calculation revealed that the nucleophilic substitution reaction of the sulfonamide with the phosphide anion at nitrogen can proceed with a low activation barrier.

In summary, a novel nucleophilic substitution reaction at the nitrogen of arylsulfonamides by means of phosphide anions has been described. This reaction allows for the efficient transformation of arylsulfonamides into synthetically valuable phosphamides, amines, and a variety of protected amines. These transformations should greatly expand the utility of the arylsulfonyl moiety as a protecting group for amines. Further nucleophilic substitution reactions of sulfonamides will allow us to access various nitrogen-containing compounds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(6) For protection of P(III) by sulfur, see: Clarke, M. L.; Williams, J. M. J. The synthesis and applications of phosphines. In *Organophosphorus Reagents*; Murphy, P. J., Ed.; Oxford University Press: Oxford, 2004; p 26.
(7) It has been reported that the reaction of benzaldehyde tosylhydrazone and sodium phosphite affords the *N*-benzylidenehydrazide of phosphoric acid diethyl ester; see: Marek, T.; Janusz, R. *Zeitschrift für Chemie* **1990**, *30*, 246. Marek and Janusz proposed a Bamford–Stevens-type mechanism for this reaction instead of a nucleophilic substitution mechanism. Also, we have examined a reaction of **1a** with diethyl phosphite in the presence of sodium hydride; however, the corresponding substitution product was not obtained.
(8) After the reaction of **1a** and $LiPPh_2$ followed by extraction of **2a** with ethyl acetate, sulfinic acid was obtained quantitatively from the water layer after it was acidified with 1 M hydrochloric acid.
(9) It has been reported that the phosphide anion acts as an electron donor to alkyl halides and causes a radical-mediated substitution reaction; see: Ashby, E. C.; Gurumurthy, R.; Ridlehuber, R. W. *J. Org. Chem.* **1993**, *58*, 5832 and references cited therein. Accordingly, we considered the possibility of a similar radical mechanism for the present reaction and performed mechanistic studies (*vide infra*).
(10) Rossi and colleagues have reported a photostimulated reaction of R_2NTs and the phosphide anion in liquid ammonia, which provides the substitution product in good to moderate yields. They concluded that the reaction proceeded through a radical mechanism; see: (a) Foray, G. S.; Peñéñory, A. B.; Rossi, R. A. *J. Phys. Org. Chem.* **1995**, *8*, 356. (b) Foray, G. S.; Peñéñory, A. B.; Rossi, R. A. *Can. J. Chem.* **1999**, *77*, 676. In contrast, our reaction does not require photostimulation. Indeed, the substitution reaction of Et_2NTs and $KPPh_2$ proceeds smoothly in THF under light-shielded conditions.
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(12) It is reasonable to consider that $KPPh_2$ was generated in situ, based on the pK_a value of $HPPh_2$. The reported pK_a value of $HPPh_2$ is 23.8 in THF; see: Abdur-Rashid, K.; Fong, T. P.; Greaves, B.; Gusev, D. G.; Hinman, J. G.; Landau, S. E.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 9155.
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(20) Deprotection of tosylamides with silyllithium was reported by I. Fleming, et al., although they suggested that the reaction involved a nucleophilic attack to sulfur; see: Fleming, I.; Frackenpohl, J.; Ila, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1229.
(21) The reaction of **1h** and lithium naphthalenide afforded a mixture of desired *p*-bromo-*N*-methylaniline (50%) and *N*-methylaniline (35%).
(22) Ishizaki and Hoshino reported that the reaction of tosylamides and Red-Al in hot toluene afforded the corresponding amines. Although the reaction mechanism was not described in the literature, the reaction might proceed via a nucleophilic substitution reaction at nitrogen; see: Ishizaki, M.; Hoshino, O. *J. Org. Chem.* **1992**, *57*, 7285.
(23) The reaction of **1i** and Red-Al afforded 4′-hydroxymethyl-*N*-methyl-4-toluenesulfonanilide in 74% yield.
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(25) To confirm the possibility of the radical cyclization of **A**, we examined the copper(I) promoted reaction of the corresponding chloroamide according to Göttlich's procedure (ref 24c). As a result, 5-*exo*-trigonal cyclization product **16** (Y = Cl) was obtained in 57% yield along with **15** (11%). This result supports our proposed mechanism; see Supporting Information for details.
(26) This calculation was performed at the B3LYP/6-311G(d,p) level of theory with Gaussian 03.
(27) The zero-point energy difference between the reactant complex and the transition state.