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Aryl(sulfonyl)amino Group: A Convenient and Stable Yet Activated Modification of Amino Group for Its Intramolecular Displacement

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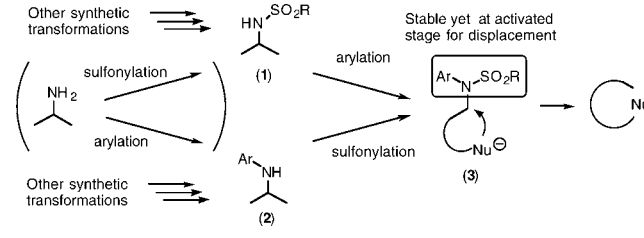
ABSTRACT

Aryl(sulfonyl)amino groups, readily derived from sulfonyl- or arylamines by standard methods as well as the recently introduced methods of sulfonylation and arylation, proved to be good leaving groups in intramolecular substitution reactions by various nitrogen, oxygen, and carbon nucleophiles.

Substitution of an amino group or its protected group at an ordinary sp^3 carbon with a nucleophile, leading to other functional groups, has not been thoroughly considered in organic synthesis.[1] This obviously comes from not only their intrinsically low leaving ability but also the fact that amino groups themselves are primarily prepared by displacement of other functional groups, and thus, the reversed transformation would be pointless.[1] However, recent rapid expansion of organic synthesis to the area of biomolecules, which ubiquitously possess amino groups, should cause the above transformation to gain more importance.[2] In addition, as asymmetric reactions often inevitably produce (protected) amines in order to attain high ee values,[3] their subsequent conversion to other functional groups appears to be in more demand. In this paper, we report a dependable method for the intramolecular substitution of (protected) amino groups, via their conversion to aryl(sulfonyl) derivatives **3** (Scheme 1). These aryl(sulfonyl)amino groups are readily prepared from sulfonyl- or arylamines (**1** or **2**), which are, when necessary, derived from parent amino groups by a variety of standard[4,5] and recently introduced[6] methods of sulfonylation and arylation as shown in Scheme 1.

Scheme 1. Formulation of Synthetic Utility



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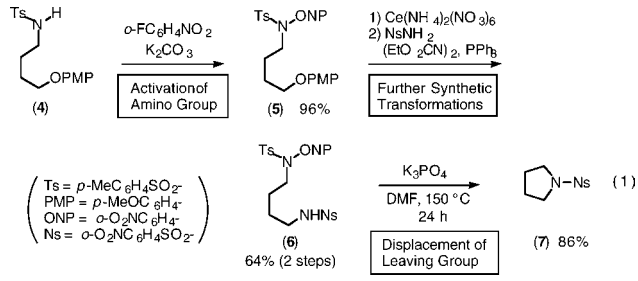
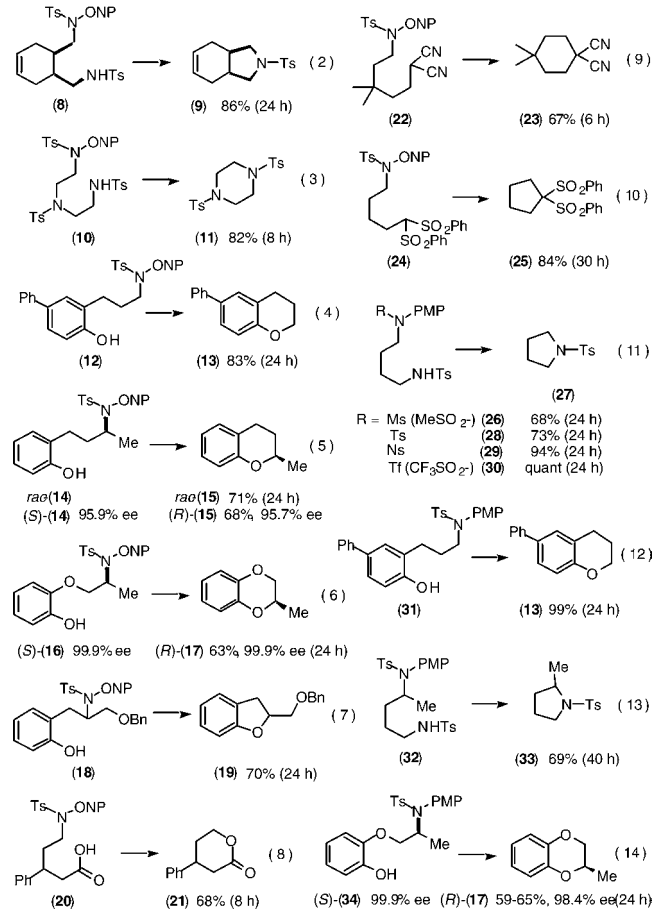
Equation 1 illustrates the above strategy.[7] The Ts-protected amino moiety in **4** was first converted to an ONP(Ts)N-group by *o*-nitrophenylation to attain the activation of the amino group (to **5**).[5] This amino-derived leaving group was still stable enough[8] to allow the modification of the other side of molecule **5** to afford **6**. However, once its displacement became necessary, simple heating effected the ring closure to give pyrrolidine derivative **7**.



Scheme 2 shows the generality of this substitution reaction. In addition to nitrogen nucleophiles (eqs 2 and 3), oxygen (eqs 4−8) and carbon nucleophiles (eqs 9 and 10) entered the reaction, producing azacycles, cyclic ethers or a lactone, and carbocyclic compounds. Gratifyingly, when a few optically active substrates were submitted to the reaction (eqs 5, 6, and 14), each product maintained virtually the same ee value as that of the original compound with inversion of configuration. While oxygen-

Scheme 2. Substitution of Aryl(sulfonyl)amino Groups[a]



[a] The reactions were performed with K_3PO_4 in DMF at 150 °C, except for eq 14 where Cs_2CO_3 was used instead of K_3PO_4. The isolated yield and reaction period (in parentheses) are indicated for each product.

ated or polyamine substrates are frequently encountered in the manipulation of biomolecules, the nucleophilic displacement in these systems is known to be retarded.[9] However, the present method did not suffer from any apparent decrease in the product yields, as evidenced by the reactions in eqs 3, 6, and 7. An efficient amino-based leaving group is not limited to ONP-plus-Ts derivatization. Even the electron-rich PMP group, which has been used as an amino-protecting group,[10] worked well as a leaving group as demonstrated in eq 11, where the effect of the sulfonyl group is also shown. Thus, the PMP group,

(1) Textbooks of organic chemistry allot many pages to substitution reactions *by* amino and related groups, but little is described on the reversed transformation, substitution *of* amino and related groups. For example, see: (a) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 5th ed.; Springer: New York, 2007; Part A, pp 389−472; Part B, pp 215−242. (b) McMurry, J. *Organic Chemistry*, 5th ed.; Brooks/Cole: Belmont, CA, 2000; pp 976−1029. (c) Morrison, R. T.; Boyd, R. N. *Organic Chemistry*, 6th ed.; Prentice Hall: Upper Saddle River, NJ, 1997; pp 821−888. (d) Malpass, J. R. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Sutherland, I. O., Eds.; Pergamon Press: Oxford, 1979; Vol. 2, pp 3−59. In practice, substitution of amino group at ordinary sp^3 carbon, apart from activated carbon centers such as those at the allylic, benzylic, or acetal position, is usually carried out by its diazotization and quaternarization prior to the substitution. For example, see: (e) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 6th ed.; Wiley: Hoboken, NJ, 2007; pp 498−500. (f) Solomons, T. W. G.; Fryhle, C. B. *Organic Chemistry*, 8th ed.; Wiley: Hoboken, NJ, 2004; pp 963−964. For substitution via quaternarization of amines to pyridinium salts, see: (g) Katritzky, A. R.; Musumarra, G. *Chem. Soc. Rev.* **1984**, *13*, 47–68. (h) Katritzky, A. R. *Tetrahedron* **1980**, *36*, 679–699. For a broad survey of methods for C−N bond cleavage, see: (i) Harrison, I. T.; Harrison, S.; Hegedus, L. S.; Wade, L. G., Jr.; Smith, M. B. *Compendium of Organic Synthetic Methods*; Wiley: New York, 1971−1992; Vols. 1−7.

(2) (a) Hughes, A. B., Ed. *Amino Acids, Peptides and Proteins in Organic Chemistry*; Wiley-VCH: Weinheim, 2009; Vols. *1* and *2*. (b) Dewick, P. M. *Medicinal Natural Products*, 3rd ed.; Wiley: Chichester, 2009. (c) Trauner, D. *Chem. Rev.* **2008**, *108*, 1499–1796. (d) Gladysz, J. A. *Chem. Rev.* **2005**, *105*, 4235–4812. (e) Walsh, C. T.; Wright, G. D. *Chem. Rev.* **2005**, *105*, 391–774.

(3) (a) Nugent, T. C., Ed. *Chiral Amine Synthesis*; Wiley-VCH: Weinheim, 2010. (b) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541–2569. (c) List, B. *Chem. Rev.* **2007**, *107*, 5413–5883. (d) Weinreb, S. M.; Orr, R. K. *Synthesis* **2005**, 1205–1227.

(4) For sulfonylation of amines and anilines, see: (a) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; Wiley: Hoboken, NJ, 2007; pp 851−868. (b) Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: Stuttgart, 1994; pp 212−216.

(5) For *o*-nitrophenylation of amines or sulfonamides, see: (a) Kulagowski, J. J.; Rees, C. W. *Synthesis* **1980**, 215. (b) Burke, P. O.; Spillane, W. J. *Synthesis* **1985**, 935–937. (c) Newington, I.; Perez-Arlandis, J. M.; Welton, T. *Org. Lett.* **2007**, *9*, 5247–5250. An actual procedure adopted in our laboratory is simpler; see the Supporting Information.

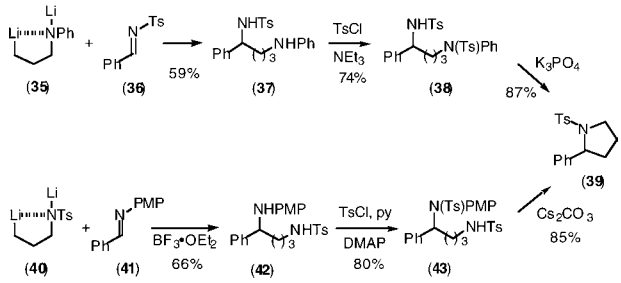
(6) For reviews on recent progress in transition-metal-catalyzed *N*-arylation of both amines and sulfonamides, see: (a) Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041–2075. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449. (c) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428–2439. (d) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3096–3099. (e) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450–1460. (f) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534–1544. For arylation of sulfonamides, see: (g) Deng, W.; Liu, L.; Zhang, C.; Liu, M.; Guo, Q.-X. *Tetrahedron Lett.* **2005**, *46*, 7295–7298. (h) Steinhuebel, D.; Palucki, M.; Askin, D.; Dolling, U. *Tetrahedron Lett.* **2004**, *45*, 3305–3307. (i) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101–1104.

(7) Some fundamental results of cyclization are shown in the Supporting Information.

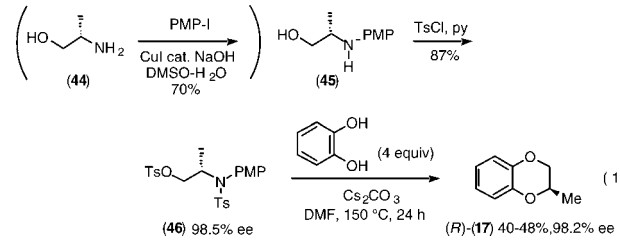
combined with a more electron-withdrawing sulfonyl group (Ms (**26**) < Ts (**28**) < Ns (**29**) < Tf (**30**)), increased the leaving capacity of the modified amino group. Other examples for PMP-amino substrates are shown in eqs 12−14.

In addition to eq 1, a couple of applications of this method are shown in Scheme 3 and eq 15. The addition of lithium reagent **35** to imine **36** produced diamine **37**, but its further synthetic elaboration appears to be hampered. However, selective activation of a PhNH group in **37** to the leaving group and the subsequent cyclization of the resultant **38** gave heterocycle **39**. On the other hand, the reaction between **40** and **41** afforded **42**, whose similar treatment as above afforded the same heterocycle **39**. It should be noted that the nitrogen atom in **39** comes from *electrophile* **36** in the upper equation, but from *nucleophile* **40** in the lower one, and that these reactions are solely taking advantage of amino groups.

Scheme 3. Synthetic Manipulation Solely Based on Amino Groups



Equation 15 shows a direct conversion of amino alcohol **45**, which represents frequently encountered synthetic intermediates or can be derived from parent amine **44**,[6,11] to a conjunctive reagent **46**. Upon reaction with catechol, this reagent underwent double substitution to afford benzodioxane (*R*)-**17**. Thus, (protected) 1,2-amino alcohols could be converted to bis-electrophilic units by the present method.



In conclusion, we reported a convenient method for the displacement of an amino group with inversion of configuration. Further extension of this reaction and its synthetic applications are now under investigation.

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Supporting Information Available: Some fundamental data of cyclization, experimental procedures, and physical properties of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Although disulfonylamine (sulfonimide) has been known to work as a leaving group since the late 1960s, its synthetic utility has not been well explored. To the best of our knowledge, intramolecular cyclization with this group has not been reported. This most likely comes from the fact that the requisite disulfonylamine is difficult to prepare in the presence of an (incipient) nucleophile, as this functional group is rather labile and behaves, at the same time, as a sulfonylating agent. For selected initial studies, see: (a) DeChristopher, P. J.; Adamek, J. P.; Lyon, G. D.; Galante, J. J.; Haffner, H. E.; Boggio, R. J.; Baumgarten, R. J. *J. Am. Chem. Soc.* **1969**, *91*, 2384–2385. (b) Müller, P.; Phuong, N. T. M. *Tetrahedron Lett.* **1978**, 4727–4730, and references cited therein. For recent reports, see: (c) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520–7521. (d) Toulgoat, F.; Langlois, B. R.; Médebielle, M.; Sanchez, J.-Y. *J. Org. Chem.* **2008**, *73*, 5613–5616. (e) Said, S. A.; Fiksdahl, A. *Tetrahedron: Asymmetry* **2001**, *12*, 893–896. (f) Lescop, C.; Mévellec, L.; Huet, F. *J. Org. Chem.* **2001**, *66*, 4187–4193. For sulfonylation with disulfonylamines, see: (g) Hendrickson, J. B.; Sternbach, D. D.; Bair, K. W. *Acc. Chem. Res.* **1977**, *10*, 306–312. (h) Zeller, W. E. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, 1995; Vol. 6, pp 4096−4097.

(9) Kotsuki, H.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1990**, *55*, 4417–4422, and references cited therein.

(10) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; Wiley: Hoboken, NJ, 2007; pp 813−814.

(11) For chemoselective *N*-arylation of amino alcohols, see: (a) Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3703–3706. (b) Shafir, A.; Lichtor, P. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3490–3491. (c) Willis, M. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3402–3404.