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Redox-Neutral α-Arylation of Alkylnitriles With Aryl Sulfoxides: A Rapid Electrophilic Rearrangement

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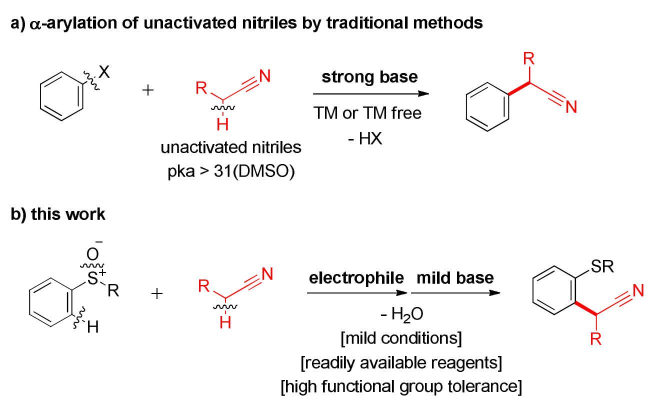
ABSTRACT: A facile α-arylation of nitriles has been developed by simply introducing Tf_2O and DABCO to the mixture of nitriles and aryl sulfoxides. The transformation consists of two sequential steps: (i) Tf_2O-initiated electrophilic assembling; and (ii) DABCO-triggered rearrangement. Each step can be tuned independently by temperature and/or base change. This adjustability renders the method to accommodate a wide range of substrates. Notable features of this new protocol include remarkable efficiency (20 min, -30 ℃), exclusive regioselectivity and high functional group compatibility, which can be challenging issues faced by traditional approaches. NMR studies not only identified a unique, highly unstable sulfonium imine complex but also demonstrated the importance of temperature in the formation and manipulation of this key intermediate. Further DFT calculations suggested that an electrophilic assembling, followed by removal of HOTf (by base) and finally, [3,3]-sigmatropic rearrangement are three key stages in the reaction. The versatile transformability of the products and easy scalability of this reaction are also exhibited here.

■ INTRODUCTION

α-Aryl nitriles are desired building blocks with their biological activities[1] and appealing synthetic diversities[2]. They can be readily converted into other valuable functionalities such as α-aryl carboxylic acids and amides by hydrolysis[2a], α-aryl aldehydes and β-aryl amines by reduction[2b,2c], and α-aryl ketones by nucleophilic addition[2d]. They are also crucial precursors for the synthesis of N-heterocycles[3]. Therefore, methods of constructing α-aryl nitriles have received great attention from synthetic community. Commonly used methods for preparing α-aryl nitriles include cyanation of benzylic halides or alcohols[4], Friedel-Crafts reactions[5], and dehydration of amides[6]. However, the use of toxic cyanide, limited functional group tolerance, and challenges in the synthesis of substrates have restricted these strategies.

Based on the nature of substrates, other well studied protocols accessing α-aryl nitriles can be mainly condensed into two reaction modes: (i) reactions of nucleophilic nitrile anions with aryl electrophiles[7] and (ii) reactions between electrophilic nitriles and aryl nucleophiles[8]. Among them, the cross coupling of unactivated nitriles with aryl halides appears to be a superior and more practical strategy due to the easy accessible substrates and broad substrate scope[7a-d] (Scheme 1a). However, strong bases required in the reaction for generating nitrile anions from weakly acidic nitriles, frequently result in the issue of functional group tolerance (Scheme 1a). To avoid the use of strong bases, Hartwig[7g], Liu[9a], Kwong[9b] turned their attentions to activated nitrile sources such as α-silyl nitriles, α-zinc nitriles, or cyanoacetate salts. However, the extra preparation of nitrile substrates decreases the step efficiency of the reaction. Although significant progress has been made in this area, direct α-arylation of unactivated nitriles presenting high functional group tolerance is still a great deal of challenge. Here we present the development of a facile α-arylation of unactivated nitirles with aryl sulfoxides by using an electrophile and a mild base as promoters, in which excellent chemo- and regi oselectivities are exhibited (Scheme 1b).[10-12]

Scheme 1. a) Traditional α-arylation of unactivated nitriles. b) This work: electrophile/mild base promoted α-arylation of unactivated nitriles



Scheme 2. Unexpected α-arylation of acetonitirle

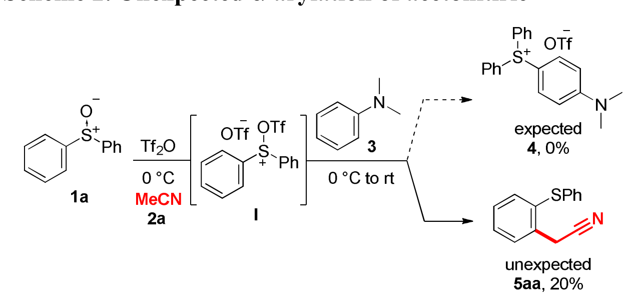
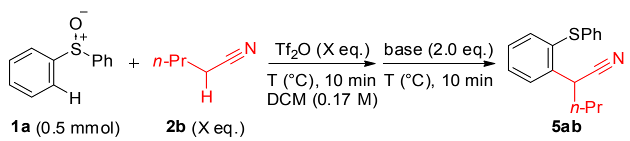


Table 1. Optimization of reaction conditions



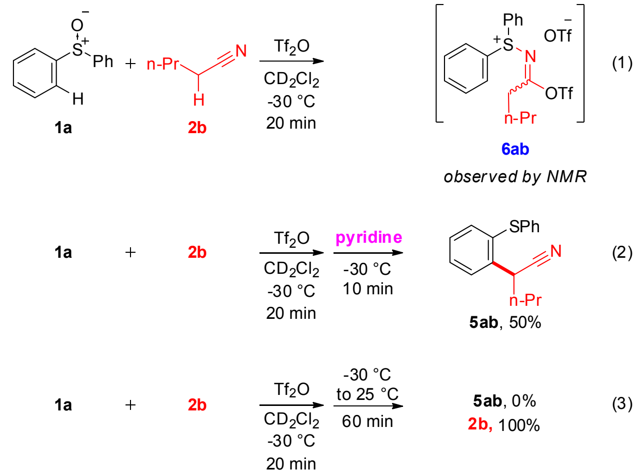
entry	base	T (℃)	X (equiv)	yield (%)[a]
1	*N*,*N*-dimethylaniline	0	1.0	30
2	*N*,*N*-dimethylaniline	-30	1.0	62
3[b,c]	none	-30 to 25	1.0	0
4[c]	DBU	-30	1.0	28
5	pyridine	-30	1.0	54
6[c]	2-bromopyridine	-30	1.0	0
7	2,6-dimethylpyridine	-30	1.0	54
8[c]	DMAP	-30	1.0	0
9[c]	K_2CO_3	-30	1.0	0
10	4-methylmorpholine	-30	1.0	64
11	iPr$_2$EtN	-30	1.0	62
12	DABCO	-30	1.0	70
13[c]	DABCO	-60	1.0	< 5
14	DABCO	-40	1.0	48
15[c]	DABCO	0	1.0	22
16	DABCO	-30	1.5	94(84)
17[d,e]	DABCO	-20	1.5	0

[a]NMR yield with mesitylene as internal standard and isolated yield in parentheses. [b]After addition of Tf_2O, the reaction was warmed to 25 ℃ for 12 h. [c]**1a** deteriorated after the reaction. [d]TFAA (2.0 equiv) was used instead of Tf_2O. [e]95% of **1a** was recovered after the reaction.

■ RESULTS AND DISCUSSION

Discovery and Optimization. Our research began with the attempted synthesis of triphenyl sulfonium **4** (Scheme 2). According to the reported procedures[13], we assumed that triflyloxy sulfonium **I** generated in situ by treating diphenyl sulfoxide **1a** with Tf_2O would interact with nucleophilic *N,N*-dimethylaniline delivering **4** as the expected product. To our surprise, in lieu of triphenyl sulfonium **4**, α-arylated acetonitrile **5aa** was isolated in 20% yield. Interestingly, acetonitrile (solvent) was introduced to the *ortho* position of aryl sulfoxde **1a**.[14] Inspired by this result, we decided to explore this α-arylation reaction further.

First, we optimized the reaction conditions using diphenyl sulfoxide **1a** and pentanenitrile **2b** as model substrates (Table 1). Selected conditions are shown in the Table and more optimization details are provided in the supporting information. Since acetonitrile was used as solvent in our initial finding, we were interested to examine if the amount of nitrile could be reduced to stoichiometric levels. Excitingly, employing 1.0 equiv of **2b** still afforded a reasonable yield of desired α-aryl nitrile **5ab** (entry 1). When the reaction temperature was low



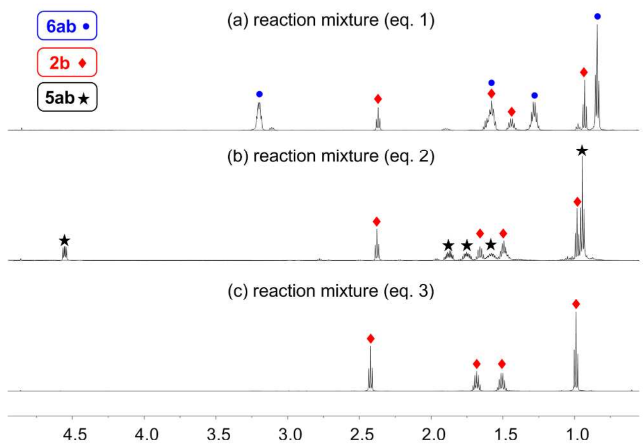


Figure 1. Crude ^{1}H-NMR spectra (a), (b) and (c) related to the reaction mixtures shown in eq. 1, eq. 2 and eq. 3, respectively.

ered to -30 ℃, the efficiency of the reaction was significantly improved as the NMR yield increased from 30% to 62% (entry 2). This result demonstrated that the reaction temperature was a key parameter for this transformation. Next, the necessity of *N,N*-dimethylanline was examined (entry 3), and no desired product was detected in its absence.[15] We suspected that *N,N*-dimethylanline probably served as a critical base in the reaction, thus prompted us to screen a number of bases (entries 4-12). It was found that DBU furnished a lower yield than that of *N,N*-dimethylanline (entry 4). Pyridines bearing different substituents displayed dramatically different reactivities in the reaction (entries 5-8). Both pyridine and 2,6-dimethylpyridine afforded identical NMR yields of **5ab** (54%). In sharp contrast, no expected product could be detected when 2-bromopyridine or 4-dimethylamino-pyridine (DMAP) were introduced in the reaction. Further studies showed that inorganic base, K_2CO_3 was ineffective in promoting the reaction (entry 9). Remarkably, the yields were increased slightly by using tertiary amine bases (entries 10-12), and among them, DABCO yielded the best result (entry 12). Again the influence of the reaction temperature was witnessed when either decreasing or increasing the reaction temperature, in the presence of DABCO as base, dramatically reduced the chemical yields of **5ab** (entries 13-15). Further optimization revealed that using slight excess of nitrile **2b** (1.5 equiv) and Tf_2O (1.5 equiv) could achieve the best yield (94% NMR yield) (entry 16). When TFAA was used instead of Tf_2O (entry 17), this weaker electrophile

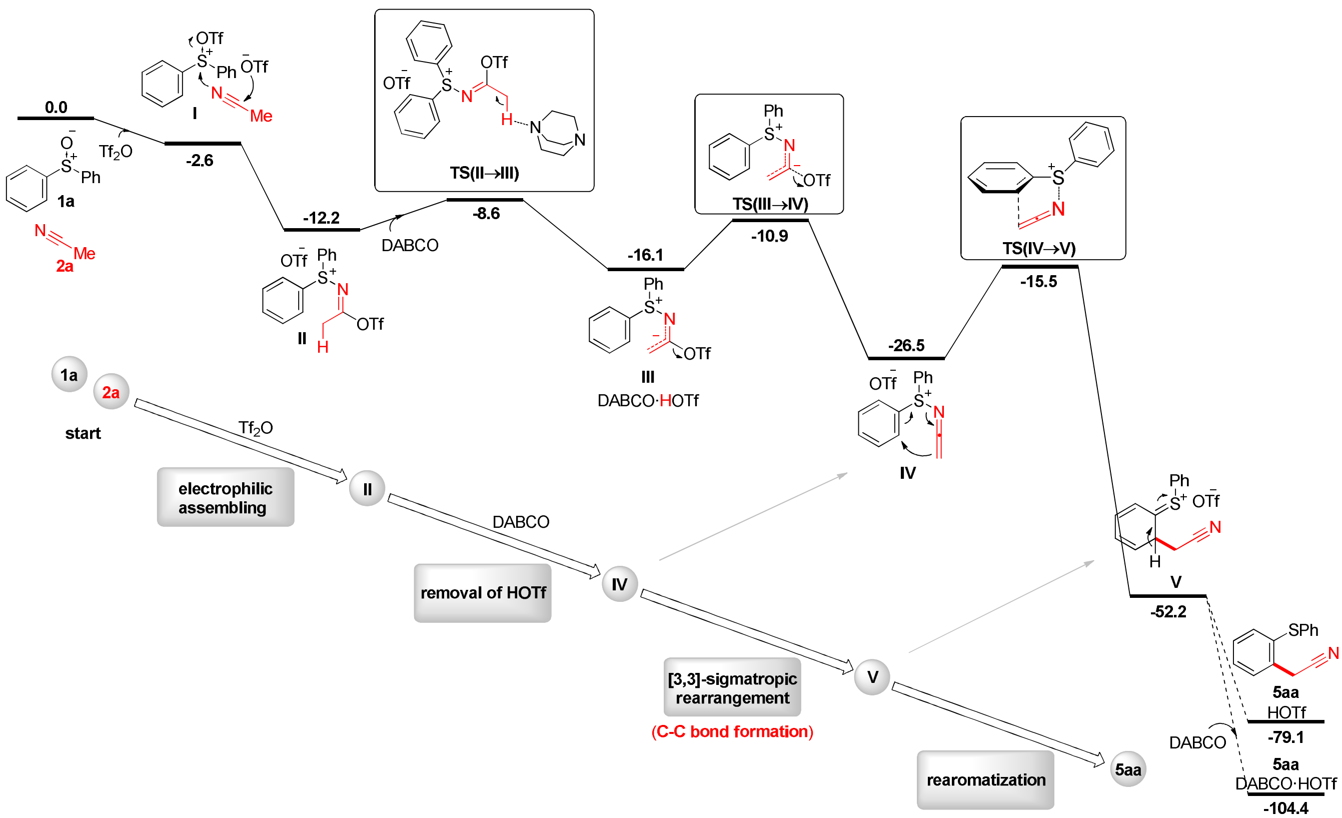


Figure 2. Relative free energies (in kcal/mol) of intermediates and transition states computed at the WB97XD/6-311++G(d,p) level. Energies reported are in kcal/mol.

proved to be completely ineffective in activating the sulfoxide **1a** and 95% of **1a** was recovered after the reaction.

NMR Investigation. The sensitivity of the reaction to temperature and base prompted us to further investigate the identity of the intermediate generated prior to the addition of base. Thus, an in situ NMR study on the reaction of diphenyl sulfoxide **1a** and pentanenitrile **2b** was performed (eq. 1-3), and their corresponding ^{1}H NMR spectra are provided in Figure 1. Interestingly a sulfonium imine intermediate **6ab** that closely resembled an analogue of Ritter type intermediate[16], was observed (eq. 1 and spectrum a). As predicted, further treating **6ab** with pyridine base afforded the desired product **5ab** (eq. 2 and spectrum b).[17] Notably, the intermediate **6ab** was not stable in the reaction mixture. When the temperature was raised to 25 ℃, **6ab** completely decomposed to release free pentaneitrile **2b** and other unknown by-products (eq. 3 and spectrum c).[18]

Density Functional Theory (DFT) Calculations: Although the key intermediate **6ab** was identified in our NMR studies, the process of its formation and further conversion to final product still remains obscure. In order to gain more insight into the mechanism, we carried out DFT calculations on the reaction.

Diphenyl sulfoxide **1a** and acetonitrile **2a** were chosen as model substrates. All geometry optimizations and frequency calculations were performed in Gaussian 09 with the WB97XD functional and 6-311++g(d,p) basis set.[19] The calculated results of vibrational frequencies ascertain the structure is stable (no imaginary frequencies). The statistical thermodynamic and vibrational analyses were carried out. The Gibbs free energies of all compounds were obtained at 243.15 K. For the solvent effects on the solutes in dichloromethane solution, the SMD solvation model proposed by Truhlar *et al*. has been used.[20] The transition states were obtained by STQN method.

Solvation free energy (G_s) is that the calculated single-point energy in the solvent model minus the calculated value in the gas phase. Moreover, the Gibbs energy change (0.69 kcal/mol) caused by the phase change from an atmospheric gas molecule to a 0.17 M solution has also been considered. And the free energy of the solute in dichloromethane solution at 243.15K is equal to sum of electronic and thermal Free Energies (G_F) subtracted by solvation free energy.

The energy profile is depicted in Figure 2. DFT studies suggest that each step of the reaction is exothermic. The overall free energy of reaction is ca. -79.1 kcal/mol (or -104.4 with DABCO assisted rearomatization), indicating that there is a large thermodynamic driving force for this transformation. The barriers of three essential transition states, **TS(II→III)**, **TS(III→IV)**[21] and **TS(IV→V)** are relatively small so that the reaction can proceed smoothly at low temperature (-30 ℃). The transformation can be divided into four key steps: (1) **Electrophilic assembling**: Diphenyl sulfoxide is activated by Tf_2O to form diphenylsulfonium **I**.[11h,22] This highly electrophilic species would proceed to trap the mildly Leiwis basic acetonitrile to generate a sulfonium imine **II**. Its analogue, **6ab** has been observed in our NMR investigation. (2) **Removal of HOTf**: The treatment of the sulfonium imine **II** with DABCO produces a zwitterionic intermediate **III**. A small barrier (3.6 kcal/mol) of **TS(II→III)** indicates that this deprotonation process might take place readily. The breaking of C1-H (1.37 Å) bond and the forming of H-N1 (1.33 Å) bond are the features of **TS(II→III)** (Figure 3). Intermediate **III** facilely releases

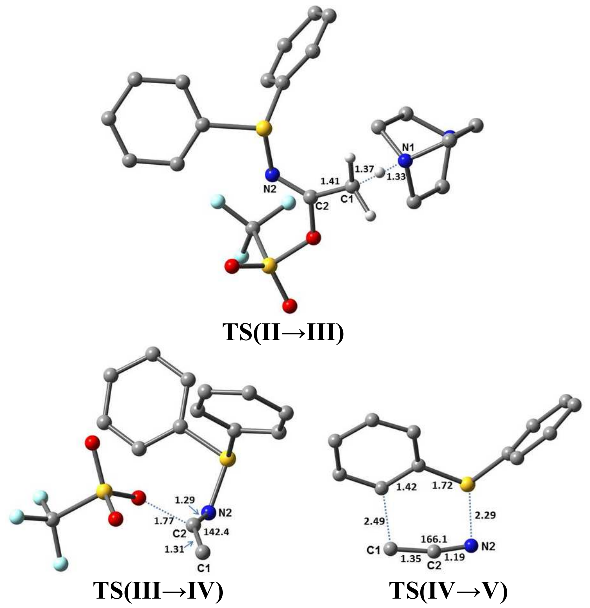
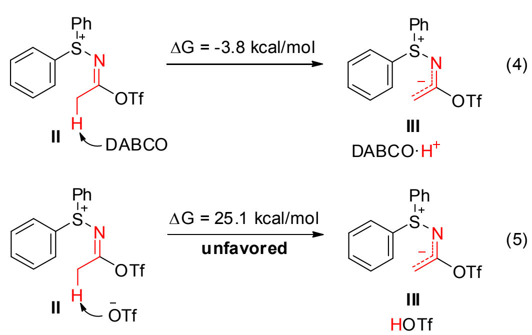


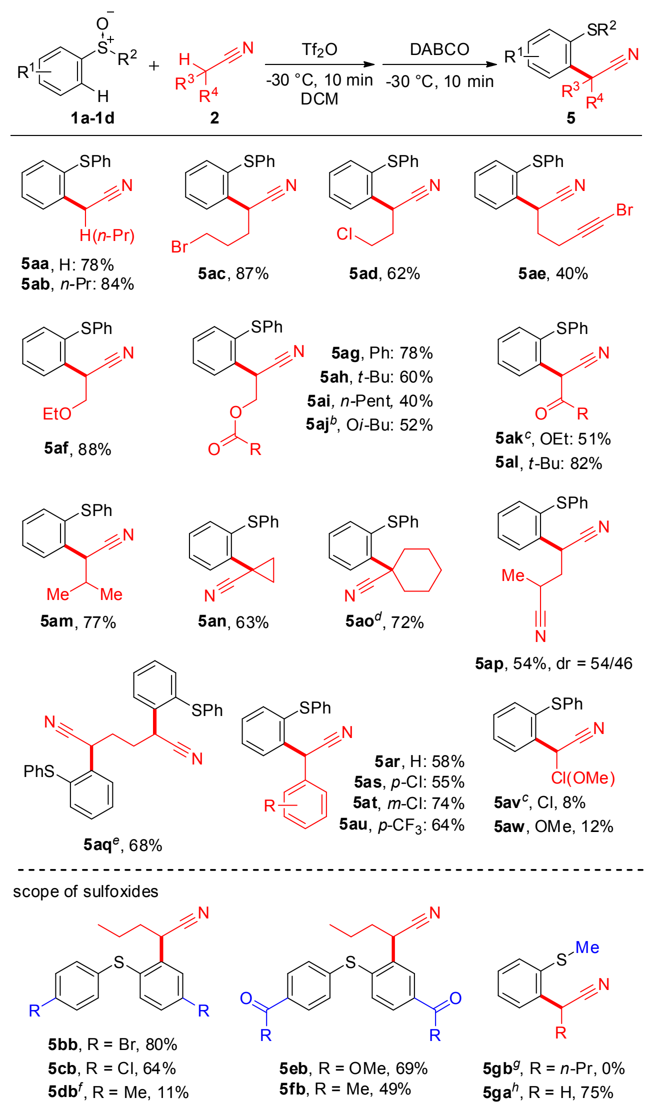
Figure 3. Optimized geometries of the transition states for the conversions **II→III**, **III→IV** and **IV→V**. Noncritical hydrogen atoms omitted for clarity. Relevant bond distances (Å) and angles (°) are given.



the OTf anion to provide a sulfonium ketenimine **IV**. Interestingly, the bond angle of C1-C2-N changes dramatically from 134.8º (**III**) to 176.2º (**IV**). The seemly unfavorable ketenimine **IV** is achieved by overcoming a relative small energy barrier (5.2 kcal/mol). (3) **[3,3]-Sigmatropic Rearrangement**: The sulfonium ketenimine **IV** undergoes a [3,3]-sigmatropic rearrangement to afford a dearomative sulfonium **V** by conquering the highest free energy barrier (11.0 kcal/mol) in the reaction. To the best of our knowledge, [3,3]-sigmatropic rearrangement of this type promoted by the labile "S-N" bond is unprecedented. (4) **Rearomatization**: The final rearomatization of **V** by loss of a proton is speculated to be assisted either by OTf anion or DABCO. Both deprotonation processes proceed readily with large free energy driven forces (26.9 kcal/mol and 52.2 kcal/mol, respectively).

The observation that this reaction requires base disserves some comment. Because, a seemingly related α-arylation of carbonyl compounds reported by Maulide and coworkers could proceed under base free conditions.[11i,11j] To shed light on this difference, we carried out DFT studies both on the base-free and DABCO-mediated deprotonation of **II** (eq. 4 and eq. 5). Apparently, without the assistance of an extra base, the deprotonation of **II** by OTf anion towards **III** is unfavorable. Because it proceeds with a much higher free energy (25.1 kcal/mol) than the DABCO involved process (-3.8 kal/mol).

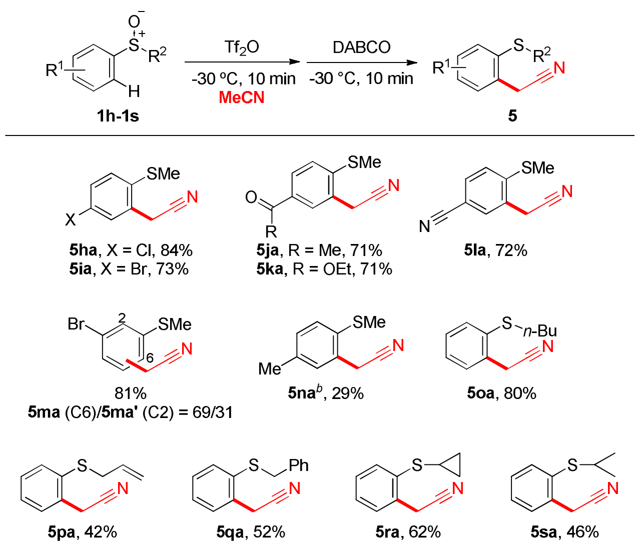
Table 2. Reaction scope[a]



[a]Unless otherwise noted, the reaction was performed under optimized conditions. [b]i-Pr_2EtN (2.0 equiv) used as base. [c]The mixture was stirred under -40 ℃ for 12 h before the addition of DABCO. [d]4-Methylpyridine (2.0 equiv) used as base while no desired product was determined with DABCO as base. [e]1.0 equiv of nitrile **2q** was used and 8% of mono-arylated nitrile **5aq'** was obtained. [f]10.0 equiv of **2b** used. [g]Sulfoxide **1e** deteriorated after the reaction. [h]Acetonitrile (0.17 M) used as solvent.

Reaction Scope: With the optimized conditions in hand, we investigated the substrate scope of the reaction. As depicted in Table 2, a wide range of alkylnitriles were found to be compatible in these reactions. Acetonitrile smoothly underwent this transformation affording α-aryl nitrile **5aa** in good yields (78%). Remarkably, various functionalities including alkyl halides (**5ac** and **5ad**), alkynyl bromide (**5ae**), ether (**5af**), esters (**5ag-5ai** and **5ak**), carbonate (**5aj**), ketone (**5al**), nitrile (**5ap**) were well tolerated under these conditions to afford α-aryl nitriles in modest to very good yields. Notably, these functionalities would provide a platform for later manipula tions. Excitingly, α-arylation of cyclopropyl nitrile **2n** which potentially poses a synthetic challenge[23] was accomplished to produce aryl cyclopropane **5an** in synthetically useful yields. Notably 4-methylpyridine was found to be a more suitable

Table 3. Scope of aryl sulfoxides in the cyanomethylation[a]

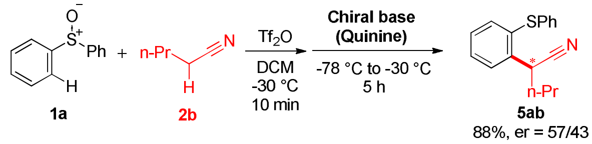


[a]The reaction was performed with aryl sulfoxide **1** (0.5 mmol), nitrile **2** (3 mL), Tf_2O (1.5 equiv) and DABCO (2.0 equiv). [b]The mixture was stirred under -40 ℃ for 12 h before the addition of DABCO.

base for hindered alkylnitrile (**2o**) which afforded **5ao** in good yield (72%). The reaction of **2p** exclusively produced **5ap**, in which α-arylation preferentially occurred on the less hindered nitrile group. Apart from unactivated alkylnitriles, more acidic nitrileacetates (**2k**, **2l**) and α-aryl nitriles (**2r**-**2u**) were also suitable substrates for the reaction. The α-chloro nitrile **2v** and α-methoxy nitrile **2w** were, however, problematic and **5av** and **5aw** could only be furnished in very low yields of (8% and 12%, respectively).

We then examined the reaction with other aryl sulfoxides **1b**-**1g** (bottom of Table 2). Substrates **1b**, **1c**, **1e** and **1f** bearing electron withdrawing groups (-Br, -Cl, -COOMe, -COMe) exhibited much better reactivity than **1d** with electron donating group (Me). Remarkably, the ester and enolizable ketone groups on aryl sulfoxides **1e** and **1f**, respectively, survived the highly electrophilic reagent (Tf_2O), thus producing α-aryl nitriles **5eb** (69%) and **5fb** (49%).[24] To our disappointment, however, extending to the aryl alkyl sulfoxide **1g** with pentanonitrile **2b** was unsuccessful at the moment. This can be ascribed to two reasons: (1) phenyl methyl sulfonium intermediate **V**[25] possessing weaker electrophilicity (compared with diphenyl sulfonium **I**) was not capable of trapping nitrile **2b**; (2) the methyl group of **V** could readily undergo the undesired nucleophilic attack or deprotonation.[26] However, employing acetonitrile as both reactant and solvent somehow overcame these challenging issues, accomplishing desired **5ea** in good yield (75%).

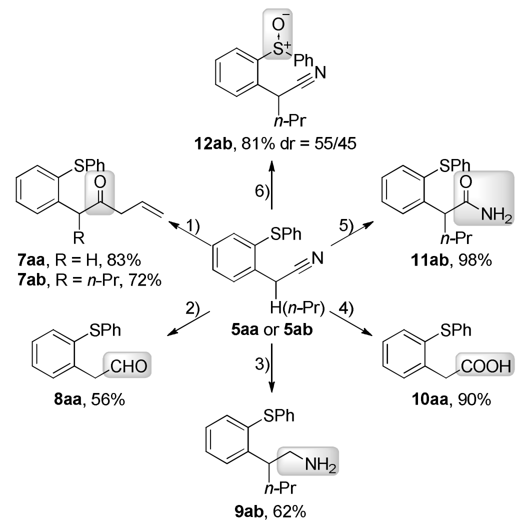
The importance of cyanomethylation of arenes[27] prompted us to further investigate the scope of the aryl sulfoxides with acetonitrile (Table 3). To our delight, a broad range of aryl alkyl sulfoxides **1h**-**1s** was found suitable for the reaction. In line with our previous findings, electron poor aryl sulfoxides (**1h**-**1m**) surpassed the electron rich sulfoxide **1n** in reactivity. Allyl sulfoxide **1p** and benzyl sulfoxide **1q** normally considered as problematic substrates were also well tolerated in the reaction albeit leading to modest yields of **5pa** and **5qa**, respectively. Moreover, bulkier aryl sulfoxides (**1r** and **1s**) also proved to be suitable substrates. It is anticipated that this cyanomethylation protocol could well complement existing methods.[27]



(6)

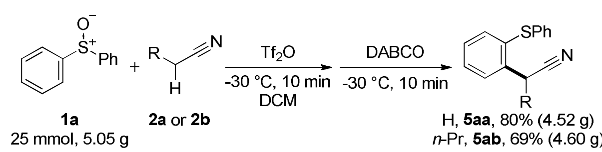
Encouraged by the established broad substrate scope, we speculated that the use of chiral base in the reaction might induce a stereoselective formation of C-C bond (eq. 6). To verify this hypothesis, we tested a readily available chiral base, Quinine. Surprisingly, the free hydroxyl group of Quinine was well tolerated in the reaction as the desired **5ab** was afforded in a very good chemical yield (88%). More excitingly, the use of chiral base indeed influenced on the stereoseletivity of reaction, albeit giving a low enantiomeric ratio of **5ab** (er = 57/43). This result confirmed a feasibility of developing T_2O/chiral base mediated asymmetric α-arylation of alkyl nitriles.[28]

Scheme 3. Elaboration of products 5aa and 5ab.



1) $Zn/AlCl_3$, allyl bromide, THF; 2) DIBAL-H, Et_2O; 3) $LiAlH_4$, DCM; 4) KOH, $EtOH/H_2O$; 5) K_2CO_3/H_2O_2, DMSO; 6) *m*-CPBA, DCM

Scheme 4. Gram scale synthesis and application for the synthesis of crucial precursor of Zaltoprofen



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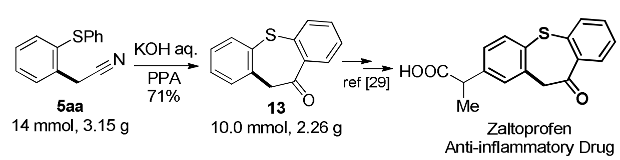

(8)

Applications and Practicability Evaluation: To demonstrate the synthetic utility of this transformation, we further elaborated the products **5aa** and **5ab** (Scheme 3). The nitrile group could be easily reduced or hydrolyzed producing α-arylated ketones **7aa** and **7ab**, aldehyde **8aa**, carboxylic acid **10aa**, amide **11ab** as well as β-arylated amine **9ab** in modest to excellent yields. In addition, sulfur ether could be oxidized to aryl sulfoxide **12ab** in good yield which provides opportunities for its further functionalization. Finally, we examined the reaction in gram scale to evaluate the practicability of the reaction. More than five grams of diphenyl sulfoxide **1a** with acetonitrile **2a** or pentanenitrile **2b** were subjected to the reaction conditions (Scheme 4). These two scale-up reactions proceeded smoothly to afford the respective desired products in synthetically useful yields. The product **5aa** could then be simply converted into tricyclic compound **13** by a sequential hydrolysis and Friedel-Crafts cyclization. **13** is a key precursor for the synthesis of a commercial available anti-inflammatory drug namely Zaltoprofen.[29]

■ CONCLUSIONS

In summary, we have developed a metal free α-arylation of alkylnitirles by sequentially introducing Tf_2O and a mild base to the mixture of alkylnitriles and aryl sulfoxides. A variety of α-arylated nitriles bearing a wide range of functional groups have been chemo- and regioselectively prepared under mild conditions. NMR studies have identified an unprecedented formation of the sulfonium imine **6ab** and demonstrated the importance of temperature on the formation and manipulation of this highly unstable specie. Computational investigations suggested that the reaction is likely to proceed through electrophilic assembling, and subsequent removal of HOTf, followed by [3,3]-sigmatropic rearrangement. We believe that the advent of this arylation reaction will promote the development of other "S-N" bond breaking induced [3,3]-sigmatropic rearrangements which are currently under investigation in our lab. More efforts to the development of the chiral base induced asymmetric α-arylation and the practical syntheses of high value bioactive compounds are also underway.

ASSOCIATED CONTENT

Supporting Information

Full experimental details, characterization datas, NMR and DFT studies, NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interests.

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REFERENCES

(1) (a) Baker, D.; Burce, M.; Cahn, A.; Thomas, M. Patent WO2010097114, A1 20100902, **2010**; (b) Kuwata, K.; Kimura, T.; Muto, J. Pantent WO2010131717, A1 20101118, **2010**; (c) Tyagi, O. D.; Ray, P. C.; Chauhan, Y. K.; Rao, K. B.; Reddy, N. M.; Reddy, D. S. P. Patent WO2009125430, A2 20091015, **2009**.

(2) (a) Kukushkin, V. Y.; Pombeiro, A. J. L. *Inorg. Chim. Acta* **2005**, *358*, 1; (b) Xi, F.; Kamal, F.; Schenerman, M. A. *Tetrahedron Lett.* **2002**, *43*, 1395; (c) Trivedi, B. K.; Holmes, A.; Stoeber, T. L.; Blankey, C. J.; Roark, W. H.; Picard, J. A.; Shaw, M. K.; Essenburg, A. D.; Stanfield, R. L.; Krause, B. R. *J. Med. Chem.* **1993**, *36*, 3300; (d) Wong, Y.-C.; Parthasarathy, K.; Cheng, C.-H. *Org. Lett.* **2010**, *12*, 1736.

(3) Friedrich, K.; Wallenfels, K. *The Chemistry of the Cyano Group*; Wiley-Interscience: New York, **1970**, pp. 341-421.

(4) (a) Chen, G.; Wang, Z.; Wu, J.; Ding, K. *Org. Lett.* **2008**, *10*, 4573; (b) Soli, E. D.; Manoso, A. S.; Patterson, M. C.; Deshong, P.; Favor, D. A.; Hirschmann, R.; Smith, A. B. *J. Org. Chem.* **1999**, *64*, 3171.

(5) Kurz, M. E.; Lapin, S. C.; Mariam, A.; Hagen, T. J.; Qian, X. Q. *J. Org. Chem.* **1984**, *49*, 2728.

(6) Enthaler, S.; Inoue, S. *Chem. Asian J.* **2012**, *7*, 169.

(7) For α-arylation of unactivated alkylnitriles, see: (a) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330; (b) You, J.; Verkade, J. G. *Angew. Chem. Int. Ed.* **2003**, *42*, 5051; (c) Klapars, A.; Waldman, J. H.; Campos, K. R.; Jensen, M. S.; Mclaughlin, M.; Chung, J. Y. L.; Cvetovich, R. J.; Chen, C. *J. Org. Chem.* **2005**, *70*, 10186; (d) Caron, S.; Vazquez, E.; Wojcik, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 712; for α-arylation of activated alkylnitriles, see: (e) Stauffer, S. R.; Beare, N. A.; Stambuli, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4641; (f) Xie, S. W.; Qin, P.; Li, M.; Zhang, X. J.; Jiang, Y.; Ma, D. *Tetrahedron Lett.* **2013**, *54*, 3889; (g) Wu, L. Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824.

(8) (a) Nambo, M.; Yar, M.; Smith, J. D.; Crudden, C. M. *Org. Lett.* **2015**, *17*, 50; (b) Choi, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 9102.

(9) (a) Shang, R.; Ji, D. S.; Chu, L.; Fu, Y.; Liu, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 4470; (b) Yeung, P. Y.; Chung, K. H.; Kwong, F. Y. *Org. Lett.* **2011**, *13*, 2912.

(10) (a) Lýpez, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 13170; (b) Nerush, N.; Vogt, M.; Gellrich, U.; Leitus, G.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **2016**, *138*, 6985.

(11) For recent reviews, see: (a) Pulis, A. P.; Procter, D. J. *Angew. Chem. Int. Ed.* **2016**, *55*, 9842; (b) Shafir, A. *Tetrahedron Lett.* **2016**, *57*, 2673; (c) Huang, X.; Klimczyk, S.; Maulide, N. *Synthesis* **2012**, *44*, 175; for reactions of aryl sulfoniums with nucleophiles, see: (d) Akai, S.; Kawashita, N.; Satoh, H.; Wada, Y.; Kakiguchi, K.; Kuriwaki, I.; Kita, Y. *Org. Lett.* **2004**, *6*, 3793; (e) Akai, S.; Morita, N.; Iio, K.; Nakamura, Y.; Kita, Y. *Org. Lett.* **2000**, *2*, 2279; (f) Akai, S.; Kawashita, N.; Morita, N.; Nakamura, Y;. Iio, K.; Kita, Y. *Heterocycles* **2002**, *58*, 75; (g) Akai, S.; Kawashita, N.; Satoh, H.; Wada, Y.; Kakiguchi, K.; Kuriwaki, I.; Kita, Y. *Org. Lett.* **2004**, *6*, 3793; (h) Padwa, A.; Nara, S.; Wang, Q. *Tetrahedron. Lett.* **2006**, *29*, 595; (i) Huang, X.; Maulide, N. *J. Am. Chem. Soc.* **2011**, *133*, 8510; (j) Huang, X.; Patil, N.; Farès, C.; Thiel, W.; Maulide, N. *J. Am. Chem. Soc.* **2013**, *135*, 7312; (k) Eberhart, A. J.; Procter, D. J. *Angew. Chem. Int. Ed.* **2013**, *52*, 4008; (l) Eberhart, A; Cicoira, C.; Procter, D. J. *Org. Lett.* **2013**, *15*, 3994; (m) Eberhart, A. J.; Shrives, H. J.; Ýlvarez, A.; Carrër, A.; Zhang, Y. T.; Procter, D. J. *Chem. Eur. J.* **2015**, *21*, 7428; (n) Eberhart, A. J.; Imbriglio, J. E.; Procter, D. J. *Org. Lett.* **2011**, *13*, 5882; (o) Eberhart, A. J.; Shrives, H.; Zhang, Y. T.; Carrër, A.; Parry, A. V. S.; Tate, D. J.; Turner, M. L.; Procter, D. J. *Chem. Sci.* **2016**, *7*, 1281; (p) Fernández-Salas, J.; Pulis, A. P.; Procter, D. J. *Chem. Commun.* **2016**, *52*, 12364; for other elegant examples of sulfonium salts reacting with nucleophiles, see: (q) Yoshida, S.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2009**, *11*, 2185; (r) Kobatake, T.; Fujino, D.; Yoshida, S.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2010**, *132*, 11838; (s) Ookubo, Y.; Wakamiya, A.; Yorimitsu, H.; Osuka, A. *Chem. Eur. J.* **2012**, *18*, 12690; (t) Murakami, K.; Yorimitsu, H.; Osuka, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 7510; (u) Hu, G.; Xu, J.; Li, P. *Org. Lett.* **2014**, *16*, 6036.

(12) For reactions of aryl sulfoxides with electrophilic species, see: (a) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160; (b) Lu, B.; Li, Y.; Wang, Y.; Aue, D. H.; Luo, Y.; Zhang, L. *J. Am. Chem. Soc.* **2013**, *135*, 8512; (c) Lau, V. M.; Gorin, C. F.; Kanan, M. W.

Chem. Sci. **2014**, *5*, 4975; (d) Peng, B.; Geerdink, D.; Farès, C.; Maulide, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 5462; (e) Peng, B.; Huang, X.; Xie, L. -G.; Maulide, N. *Angew. Chem. Int. Ed.* **2014**, *53*, 8718; (f) Kaiser, D.; Veiros, L. F.; Maulide, N. *Chem. Eur. J.* **2016**, *22*, 4727; (g) Kaldre, D.; Maryasin, B.; Kaiser, D.; Gajsek, O.; González, L. Maulide, N. *Angew. Chem. Int. Ed.* **2017**, *56*, 2212.

(13) (a) Liu, G.; Mori, S.; Wang, X.; Noritake, S.; Tokunaga, E.; Shibata, N. *New J. Chem.* **2012**, *36*, 1769; (b) Prakash, G. K. S.; Ledneczki, L.; Chacko, S.; Olah, G. A. *Org. Lett.* **2008**, *10*, 557; (c) Yoo, J. B.; Park, S-W.; Kang, H. N.; Mondkar, H. S.; Sohn, K.; Kim, H-M.; Kim, K-B.; Lee, H. *Polymer* **2014**, *55*, 3599.

(14) Procter developed a Tf_2O induced *ortho*-propargylation of aryl sulfoxides using acetonitrile as solvent. Nevertheless, **5aa** was not observed in their studies, see: ref 11h, 11j and 11l.

(15) Magnier disclosed perfluoroalkyl sulfoxides mediated α-arylation of nitriles under base free conditions. However in our case the base free reaction of **1a** and **2b** merely resulted in a deterioration of **1a** (Table 1, entry 3). a) Macé, Y.; Urban, C.; Pradet, C.; Blazejewski, J-C.; Magnier, E. *Eur. J. Org. Chem.* **2009**, 5313 ; b) Pégot, B.; Urban, C.; Diter, P.; Magnier, E. *Eur. J. Org. Chem.* **2013**, 7800. For more details, see the supporting information.

(16) Guérinot, A.; Reymond, S.; Cossy, J. *Eur. J. Org. Chem.* **2012**, 19.

(17) Because DABCO as a solid base was difficult to be transferred into an NMR tube, pyridine was used as base herein.

(18) During this research Proctor group reported an elegant metal free CH-CH cross coupling of aryl sulfoxides with internal alkynes, where they observed a similar intermediate. For details, see: Fernández-Salas, J. A.; Eberhart, A. J.; Procter, D. J. *J. Am. Chem. Soc.* **2016**, *138*, 790.

(19) Frisch, M. J., et al. *Gaussian 09*; Gaussian, Inc.: Wallingford, CT, 2013.

(20) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* 2009, *113*, 6378.

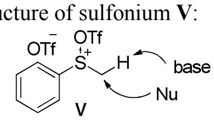
(21) Besides the proposed pathway of **III**→**IV**→**V**, the direct conversion of **III** to **V** is also possible and cannot be excluded currently.

(22) Fascione, M. A.; Adshead, S. J.; Mandal, P. K.; Kilner, C. A.; Leach, A. G.; Turnbull, W. B. *Chem. Eur. J.* **2012**, *18*, 2987.

(23) (a) Dune, J. M. M.; Kuethe, J. T.; Orr, R. K.; Tudge, M.; Campeam, L-C. *Org. Lett.* **2014**, *16*, 6314; (b) Caron, S.; Vazquez, E. Wojcik, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 712.

(24) For a comprehensive review covering reactions of Tf_2O with carbonyl compounds, see: Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S. *Tetrahedron* **2000**, 56, 3077.

(25) The putative structure of sulfonium **V**:



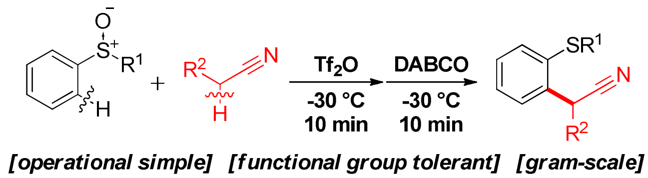
V

(26) (a) Smith, L. H. S.; Coote, S. C.; Sneddon, H. F.; Procter, D. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 5832; (b) Akai, S.; Kita, Y. *Top. Curr. Chem.* **2007**, *274*, 35.

(27) The cyanomethylation of arenes is heavily relied on the use of modified nitriles derivatives as nitrile sources. For examples, see: (a) Velcicky, J.; Soicke, A.; Steiner, R.; Schmalz, H-G. *J. Am. Chem. Soc.* **2011**, *133*, 6948; (b) Kosugi, M.; Ishiguro, M.; Negishi, Y.; Sano, H.; Migita, T. *Chem. Lett.* **1984**, 1511; (c) Frejd, T.; Klingstedt, T. *Synthesis* **1987**, 40; (d) ref. 7g and 9a. Acetonitrile is rarely used for the cyanomethylation of arenes, for examples, see: e) Yoshida, H.; Fujimura, Y.; Yuzawa, H.; Kumagai, J.; Yoshida, T. *Chem. Commun.* **2013**, *49*, 3793; (f) Kamila, S.; Koh, B.; Biehl, E. R. *Synth. Commun.* **2006**, *36*, 3493.

(28) For a recent example of palladium catalyzed asymmetric α-arylation of alkylnitriles, see: Jiao, Z; Chee, K.; Zhou, J. *J. Am. Chem. Soc.* **2016**, *138*, 16240. To the best of our knowledge, metal free asymmetric α-arylation of alkylnitriles has not yet been reported.

(29) Tendo, A. Patent WO2013161842, A1 20131031, **2013**.


Tf2O
-30 °C
10 min
DABCO
-30 °C
10 min
[operational simple] [functional group tolerant] [gram-scale]