DOI: 10.1002/adsc.201900813

Advanced Synthesis & Catalysis

Lewis Acid-Mediated Cyanation of Phenols Using *N*-Cyano-*N*-phenyl-*p*-toluenesulfonamide

Wu Zhang,[a] Tao Li,[a] Qingli Wang,[a,*] and Wanxiang Zhao[a,*]

[a] State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha, Hunan 410082, People's Republic of China
E-mail: zhaowanxiang@hnu.edu.cn; qingliwang@hnu.edu.cn

Manuscript received: July 3, 2019; Revised manuscript received: August 27, 2019;
Version of record online: ■■, ■■

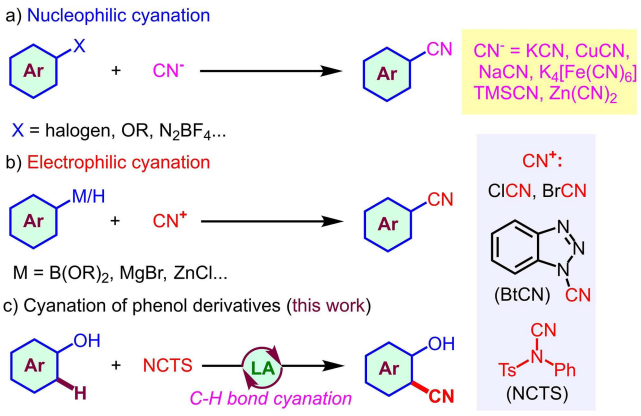
Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.201900813

Abstract: Lewis acid-mediated cyanation of phenol derivatives with *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) has been developed. The reaction proceeded efficiently with high regioselectivity to produce aromatic nitriles in moderate to excellent yields, which provides a direct and practical access to valuable products.

Keywords: Cyanation; Lewis acid; Phenols; *N*-Cyano-*N*-phenyl-*p*-toluenesulfonamide

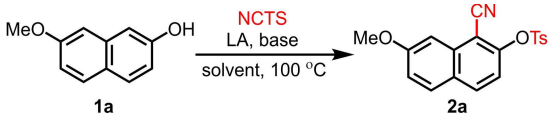
Aromatic nitriles are wildly present in a variety of natural products, pharmaceuticals, dyes, agrochemicals, materials and cosmetics.[1] In addition, nitriles are crucial building blocks in synthetic chemistry as they can be efficiently converted into amine, ketone, aldehyde, amide and carboxylic acid.[2] To date, numerous methods for the synthesis of aromatic nitriles have been developed, and they can be divided into three categories according to cyanating reagent: nucleophilic-,[3] electrophilic-[1a,4] and radical-cyanation.[5] The cyanides used in nucleophilic cyanation include KCN,[3d] CuCN,[3e] NaCN,[3f] $K_4[Fe(CN)_6]$,[3g] etc (Scheme 1a), which have the risk of generating hazardous HCN and leading to environmental pollution. On the other hand, the cyanating reagents employed in electrophilic cyanation (Scheme 1b), such as 1-cyanobenzotriazole (BtCN)[4a–b] and PhOCN,[4c] are usually prepared from ClCN or BrCN that possess safety issue. The examples of radical cyanation are rare. Therefore, the use of safe, user- and eco-friendly reagents for cyanation is highly desirable. Recently, *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS)[4d–g] has received much attention in cyanation reactions due to its low toxicity, stability and ready availability. For instance, Wang developed an elegant method for cyanation of indoles and pyrroles using NCTS in 2011.[4d] In addition, Rh-catalyzed C–H bond cyanation has also been well developed in the presence of NCTS.[4g] As part of our interest in C–O bond cleavage of 2-cyanophenols,[6] we envisioned whether it is possible to produce 2-cyanophenols via direct C–H bond cyanation of phenols using NCTS as the cyanating reagent.

Traditionally, 2-cyanophenol derivatives are synthesized via dehydration of 2-hydroxy aromatic aldehydes,[7a–b] oximes[7c] and amides.[7d] Transition-metal-catalyzed cyanation of 2-halo phenol derivatives[8] is also an efficient method access to 2-cyanophenols. In 1990, Sugasawa disclosed an approach to covert phenols into 2-cyanophenols using a toxic and stinking cyanation reagent CH_3SCN in the presence of stoichiometric amount of BCl_3 and $AlCl_3$.[9] Therefore, it is still highly desirable to develop a green, safe, eco-friendly and efficient cyanation under mild reaction conditions. Herein, we describe a Lewis acid-mediated cyanation of phenols using low toxic, stable, eco-friendly and readily available NCTS as the cyanating reagent, which produces a range of *o*-



Scheme 1. Aromatic nitrile synthesis.

Table 1. Optimization of the reaction conditions.[a]



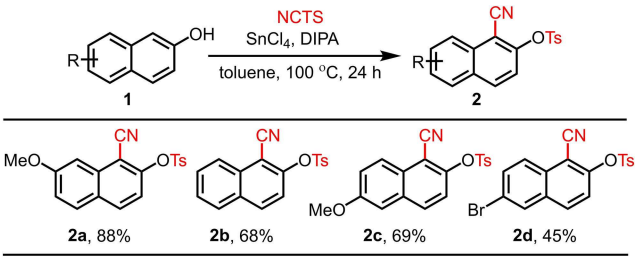
1a 2a

Entry	LA (equiv.)	NCTS (equiv.)	Base	Solvent	Yield (%)[b]
1	$In(OTf)_3$ (0.1)	1.5	Et_3N	toluene	26
2	$Sn(OTf)_2$ (0.1)	1.5	Et_3N	toluene	28
3	$SnCl_4$ (0.5)	1.5	Et_3N	toluene	58
4	–	1.5	Et_3N	toluene	0
5	$SnCl_4$ (0.5)	1.5	Et_3N	DCE	15
6	$SnCl_4$ (0.5)	1.5	Et_3N	dioxane	10
7	$SnCl_4$ (0.5)	1.5	Et_3N	MeCN	0
8	$SnCl_4$ (0.5)	1.5	Me_3N	toluene	34
9	$SnCl_4$ (0.5)	1.5	$BnNMe_2$	toluene	18
10	$SnCl_4$ (0.5)	1.5	DIPA	toluene	63
11	$SnCl_4$ (0.5)	1.5	–	toluene	0
12[c]	$SnCl_4$ (0.5)	2.0	DIPA	toluene	76
13[c]	$SnCl_4$ (0.5)	2.5	DIPA	toluene	96
14[c]	$SnCl_4$ (0.5)	3.0	DIPA	toluene	98 (88)[d]

[a] Reaction conditions: **1a** (0.2 mmol), NCTS, base (4.0 equiv.), solvent (2 mL), 16 h, 100 °C. $SnCl_4$ (1.0 M in dichloromethane). Me_3N (2.0 M in THF). LA = Lewis acid. DCE = 1.2-dichloroethane. DIPA = diisopropylamine.
[b] ^1H NMR yield using CH_2Br_2 as the internal standard.
[c] Reaction time was 24 h.
[d] Isolated yield.

cyanophenols with high efficiency and regioselectivity (Scheme 1c).

We began our investigation with the evaluation of Lewis acid using 7-methoxynaphthalen-2-ol **1a** as the model substrate in the presence of NCTS (Table 1). We observed that $SnCl_4$ promoted the C–H bond cyanation of **1a** to afford 1-cyano-7-methoxynaphthalen-2-yl 4-methylbenzenesulfonate **2a** with OH being protected by Ts in moderate yield, although $Sn(OTf)_2$ and $In(OTf)_3$ can also be used as a promoter (Table 1, entries 1–3). It is worth noting that no desired product was observed in the absence of Lewis acid (Table 1, entry 4). Other solvents were also examined, but all resulted in either low or no conversion (Table 1, entries 5–7). We then paid attention to the base. As shown, diisopropylamine gave the best yield among the bases examined (Table 1, entries 8–10). Notably, no product **2a** was formed in the absence of base (Table 1, entry 11), indicating the important role of the base in this cyanation. Pleasingly, we found the yield was improved to 76% with prolonged reaction time (Table 1, entry 12), and the highest yield was obtained when 3 equivalents of NCTS was employed (Table 1, entry 14).



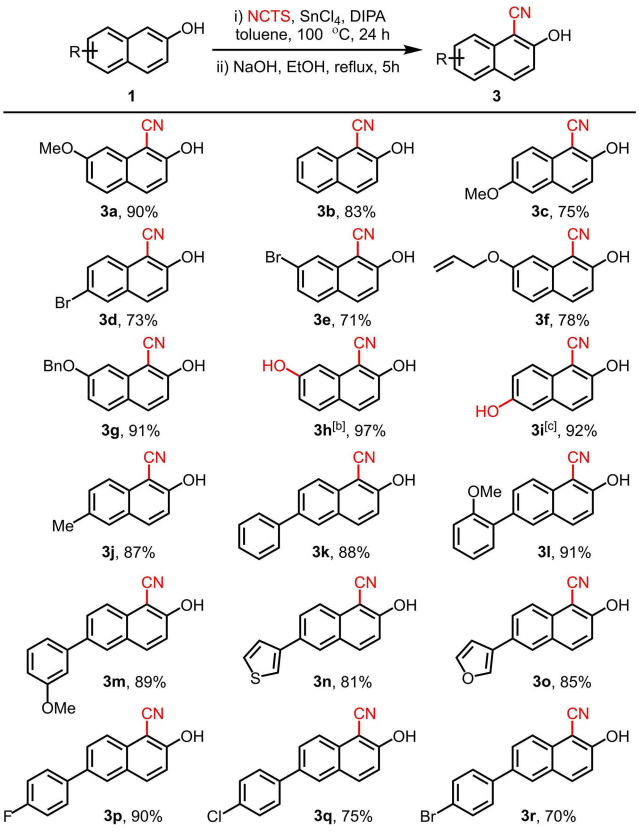
Reaction conditions: 1 (0.2 mmol), NCTS (3.0 equiv.), SnCl4 (0.5 equiv.), DIPA (4.0 equiv.), toluene (2 mL), 24 h, 100 °C.v

Scheme 2. $SnCl_4$-mediated cyanation of 2-naphthol derivatives.

With the optimized conditions in hand, we then examined the scope of 2-naphthols. As illustrated in Scheme 2, the reaction of 2-naphthols with NCTS proceeded smoothly to furnish the corresponding products in moderate to good yields (Scheme 2, **2a–d**). Both electron-donating and electron withdrawing groups were tolerated. However, we found that the purification of products **2** is problematic. For ease of isolation and characterization, the crude products **2** were then treated with NaOH and EtOH, which led to the desulfonylation products **3** in high efficiency.

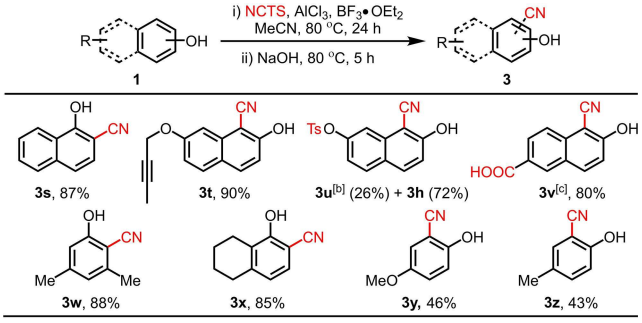
As shown in Scheme 3, a variety of 2-naphthols reacted with NCTS efficiently to give the 1-naphthonitriles. Various functional groups were tolerated, such as MeO, BnO and alkene. It is worth to mention that TBS-protected naphthalene-2, 6-diol and naphthalene-2, 7-diol all successfully participated in this cyanation reaction to afford the corresponding desilylated naphthonitriles (**3h** and **3i**) in 97% and 92% yield, respectively. The substrates with halogens, including F, Cl and Br, are applicable in this transformation (**3d–e**, **3p–r**). Noticeably, hetero-aromatic rings, such as thiophene and furan, were also compatible.

Although the cyanation of 2-naphthols provided a range of 2-hydroxy naphthonitriles in the presence of $SnCl_4$, NCTS and base, low yield was obtained when 1-naphthol was employed as the substrate. Pleasantly, we found that the combination of $AlCl_3$ and $BF_3 \cdot OEt_2$[10] was efficient for the cyanation of 1-naphthol, and afforded the 1-hydroxy-2-naphthonitrile in 87% yield. It is notable that the substrates resulting in low yields (**1t** and **1u**) or no reaction (**1v**) when $SnCl_4$ was employed, all worked well when $AlCl_3$ and $BF_3 \cdot OEt_2$ employed to produce the naphthonitriles in good yields (Scheme 4, **3t–3v**). It is worth noting that the tosylated product **3u** was isolated in 26% when naphthalene-2,7-diol was used as the substrate, which was generated via Ts transfer from the NCTS to the **3h** in the presence of NaOH.[11] Furthermore, phenol derivatives also reacted smoothly with NCTS to provide the corresponding benzonitriles in moderate to good yields (Scheme 4, **3w–3z**), although the $SnCl_4$ can not catalyze the cyanation of these substrates.



[a]Reaction conditions: i) 1 (0.2 mmol), NCTS (3.0 equiv.), SnCl4 (0.5 equiv.), DIPA (4.0 equiv.), toluene (2 mL) at 100 °C for 24 h. ii) NaOH (12 equiv.), EtOH (10 mL), 5 h, 80 °C.
[b] The substrate is 7-tert-butyldimethylsiloxy-2-naphthol.
[c] The substrate is 6-tert-butyldimethylsiloxy-2-naphthol.

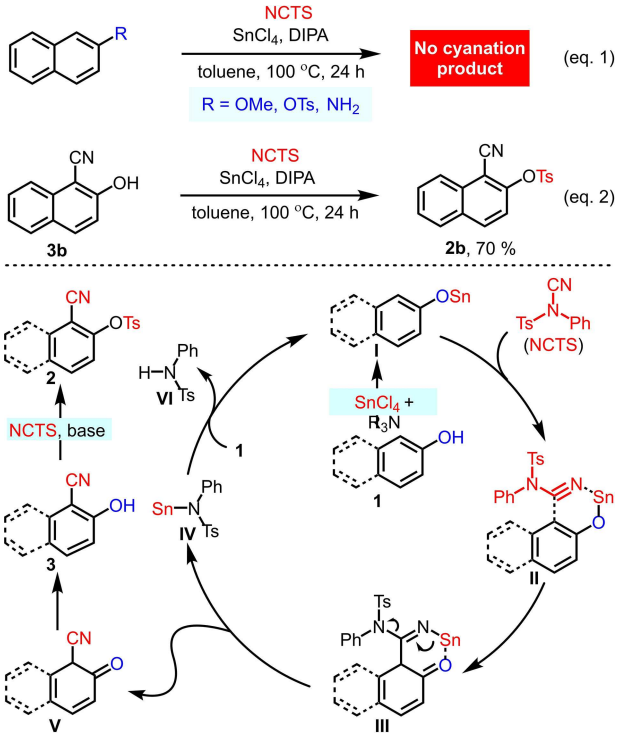
Scheme 3. $SnCl_4$-mediated cyanation for the synthesis of 2-hydroxy naphthonitriles.



[a] Reaction conditions: i) 1 (0.5 mmol), NCTS (2.5 equiv.), AlCl3 (1.0 equiv.), BF3·OEt2 (2.0 equiv.), MeCN (1.0 mL) at 80 °C for 24 h. ii) NaOH (4.0 M, 1.7 mL), 5 h, 80 °C.
[b] The substrate is naphthalene-2,7-diol.
[c] The substrate is 6-hydroxy-2-naphthonitrile.

Scheme 4. $BF_3 \cdot OEt_2$-mediated cyanation of phenol derivatives.

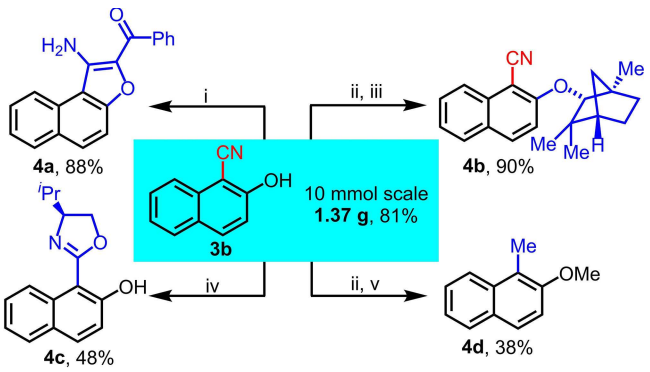
To get more mechanistic information, we carried out a series of control experiments. First, we treated the sulfonyl-protected naphthol, 2-methoxynaphthalene, and 2-naphthylamine with the standard reaction conditions, and no cyanation product was observed



Scheme 5. Proposed mechanism.

(eq. 1). Additionally, we found that the Ts group can transfer from the NCTS to **3b**, resulting in the formation of **2b** (eq. 2).[11] Based on these results, a proposed mechanism for this cyanation is demonstrated in Scheme 5.[12] Initially, the intermediate **I** generated from $SnCl_4$, base and phenol derivative reacts with NCTS via a six-membered transition state **II** to give the intermediate **III**, which then undergoes the elimination of PhNSnTs (**IV**) to give the product **V**. The subsequent tautomerization leads to the formation of desired cyanation product, which could further react with NCTS in the presence of base to generate product **2**. In addition, the tin exchange between the intermediate **IV** and phenol derivative regenerates the intermediate **I** and completes the catalytic cycle.

To demonstrate the utility of this cyanation reaction, 2-hydroxy naphthonitrile synthesized from a gram scale reaction of 2-naphthol with NCTS was employed as a platform for synthesis of various useful building blocks (Scheme 6). First, an antibacterial compound **4a** was prepared in 88% yield from **3b** and 2-bromoacetophenone via intermolecular cyclization.[13] Besides, the chiral alcohol, (+)-Fenchol, can be incorporated into naphthalene via our reported alcohol exchange reaction.[6] We then investigated the synthesis of chiral oxazoline ligand from **3b** and chiral amino alcohol, and found the desired product was formed in the presence of $ZnCl_2$ albeit with 48% yield.[14] Finally, the Ni-catalyzed coupling of 2-methoxy-1-naphthonitrile with methylmagnesium bromide was carried out,



Reaction conditions: i) 2-bromoacetophenone, acetone, reflux, 8 h; ii) CH3I, DMF, rt, 30 min; iii) (+)-Fenchol, KOtBu, dioxane, rt, overnight; iv) (S)-(+)-2-amino-3-methyl-1-butanol, ZnCl2, PhCl, 131 °C, 72 h; v) NiCl2(PCy3)2, LiOtBu, CH3MgBr, THF, 60 °C, 15 h.

Scheme 6. Gram-scale synthesis of **3 b** and its synthetic transformations.

in which the methylation product was formed in 38% yield.[15]

In conclusion, we have developed a mild Lewis acid-mediated cyanation of phenol derivatives using a readily available cyanating reagent (NCTS). This protocol tolerated well with various functional groups due to its mild reaction conditions. In addition, the utility of method was demonstrated by a gram-scale reaction and a diverse set of transformations of the product. Efforts to address the regioselectivity issue of this transformation are currently underway.

Experimental Section

General procedure for the synthesis of 1-cyano-naphthalen-2-yl 4-methylbenzenesulfonates 2 and 2-hydroxy-naphthonitriles 3 a–3 r: To a solution of 2-naphthol derivative (0.2 mmol, 1 equiv.) and NCTS (3.0 equiv.) in toluene (2 mL) was added $SnCl_4$ (1.0 M in dichloromethane, 0.1 mL, 0.1 mmol). The mixture was stirred for 5 min at room temperature, and then DIPA (0.1 mL, 4.0 equiv.) was added. The resulting reaction mixture was stirred at 100 °C for 24 h. After cooled to room temperature, the reaction mixture was filtered through a short pad of celite and washed with ethyl acetate. The crude mixture was concentrated under *vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether-ethyl acetate as eluent) to give the corresponding 1-cyano-naphthalen-2-yl 4-methylbenzenesulfonates **2 a–2 d**. When the reaction mixture were treated with NaOH (2.4 mmol, 12.0 equiv.) and EtOH (10 mL), then refluxed for 5 h. After completed, the reaction mixture was acidified with 6.0 M HCl, and extracted with EtOAc for 3 times. The combined organic layer was washed with water and brine, then dried over Na_2SO_4, filtered, and concentrated under *vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether-ethyl acetate as eluent) to give the corresponding 2-hydroxy-naphthonitriles **3 a–3 r**.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (Grant No. 21702056, 21971059 and 21605070), the National Program for Thousand Young Talents of China and the Fundamental Research Funds for the Central Universities.

References

[1] a) Y. Ping, Q. Ding, Y. Peng, *ACS Catal.* **2016**, *6*, 5989–6005 and references cited therein; b) H. S. Kim, G. Huseynova, Y.-Y. Noh, D.-H. Hwang, *Macromolecules* **2017**, *50*, 7550–7558; c) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. J. Shook, *J. Med. Chem.* **2010**, *53*, 7902–7917; d) U. Mayerhöffer, B. Fimmel, F. Wrthner, *Angew. Chem. Int. Ed.* **2012**, *51*, 164–167; e) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336–345.

[2] a) R. C. Larock, *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, Weinheim, **1999**; b) P. Anbarasan, T. Schareina, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 5049–5067.

[3] a) T. Sandmeyer, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1633–1635; b) K. W. Rosenmund, E. Struck, *Ber. Dtsch. Chem. Ges.* **1919**, *2*, 1749–1756; c) Y. Gan, G. Wang, X. Xie, Y. Liu, *J. Org. Chem.* **2018**, *83*, 14036–14048; d) C. Yang, J. M. Williams, *Org. Lett.* **2004**, *6*, 2837–2840; e) F. Chen, F. Zhu, M. Zhang, R. Liu, W. Yu, B. Han, *Org. Lett.* **2017**, *19*, 3255–3258. f) J. Zanon, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 2890–2891; g) P. Y. Yeung, C. M. So, C. P. Lau, F. Y. Kwong, *Angew. Chem. Int. Ed.* **2010**, *49*, 8918–8922; h) W. Xu, Q. H. Xu, Z. F. Zhang, J. Z. Li, *Asian J. Org. Chem.* **2014**, *3*, 1062–1065.

[4] a) O. V. Denisko, G. Nikonov, *e-Encyclopedia of Reagents for Organic Synthesis*, Wiley: **2003**; b) P. Anbarasan, H. Neumann, M. Beller, *Chem. Eur. J.* **2010**, *16*, 4725–4728; c) F. F. Fleming, V. Gudipati, O. W. Steward, *Tetrahedron* **2003**, *59*, 5585–5593; d) Y. Yang, Y. Zhang, J. Wang, *Org. Lett.* **2011**, *13*, 5608–5611; e) K. Kiyokawa, T. Nagata, S. Minakata, *Angew. Chem. Int. Ed.* **2016**, *55*, 10458–10462; f) P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2011**, *50*, 519–522; g) T.-J. Gong, B. Xiao, W.-M. Cheng, W. Su, J. Xu, Z.-J. Liu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 10630–13633. h) P. Anbarasan, H. Neumann, M. Beller, *Chem. Eur. J.* **2011**, *17*, 4217–4222; i) J. Cui, J. Song, Q. Liu, H. Liu, Y. Dong, *Chem. Asian J.* **2018**, *13*, 482–495; j) . F. Kurzer, *J. Chem. Soc.* **1949**, 1034–1038; k) . F. Kurzer, *J. Chem. Soc.* **1949**, 3029–3033.

[5] a) F.-D. Lu, D. Liu, L. Zhu, L.-Q. Lu, Q. Yang, Q.-Q. Zhou, Y. Wei, Y. Lan, W.-J. Xiao, *J. Am. Chem. Soc.* **2019**, *141*, 6167–6172; b) W. Hu, F. Teng, H. Peng, J. Yu, S. Sun, J. Cheng, Y. Shao, *Tetrahedron Lett.* **2015**, *56*, 7056–7058; c) S. Kamijo, T. Hoshikawa, M. Inoue, *Org. Lett.* **2011**, *13*, 5928–5931; d) C. H. Cho, J. Y. Lee, Su. Kim, *Synlett.* **2009**, 81–84; e) S. Kim, H.-J. Song,

Synlett. **2002**, 2110–2112; f) J. Martin, L. M. Jaramillo G, P. G. Wang, *Tetrahedron Lett.* **1998**, *39*, 5927–5930.

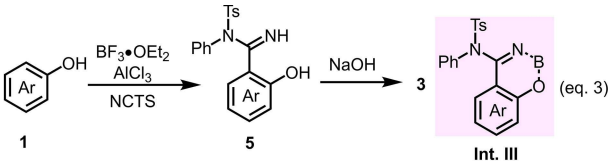
[6] X. Wang, C. Li, X. Wang, Q. Wang, X.-Q. Dong, A. Duan, W. Zhao, *Org. Lett.* **2018**, *20*, 4267–4272.

[7] a) J. Q. Dylan, J. H. Graham, M.-L. Gustavo, *Tetrahedron Lett.* **2016**, *57*, 3844–3847; b) Y. Nakai, K. Moriyama, H. Togo, *Eur. J. Org. Chem.* **2014**, 6077–6083; c) E. Whiting, M. E. Lanning, J. A. Scheenstra, S. Fletcher, *J. Org. Chem.* **2015**, *80*, 1229–1234; d) S. I. Maffioli, E. Marzorati, A. M. Marazzi, *Org. Lett.* **2005**, *7*, 5237–5239.

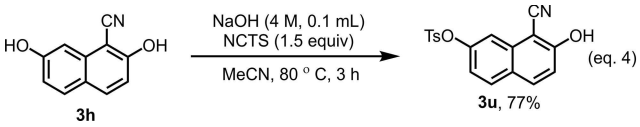
[8] a) M. Shevlin, *Tetrahedron Lett.* **2010**, *51*, 4833–4836; b) D. Ganapathy, S. S. Kotha, G. Sekar, *Tetrahedron Lett.* **2015**, *56*, 175–178.

[9] M. Adachi, T. Sugasawa, *Synth. Commun.* **1990**, *20*, 71–84.

[10] In the $BF_3 \cdot OEt_2/AlCl_3$-mediated cyanation, the reaction produced compound **5** first in the presence of Lewis acid, which then underwent elimination in the presence of NaOH to give the cyanation product **3** (eq. 3). The compound **5** can react with $BF_3 \cdot OEt_2$ to form the **Int. III** or its analogs and inhibit the regeneration of BF_3. Therefore, excessive $BF_3 \cdot OEt_2$ is required. The $AlCl_3$ can activate the $BF_3 \cdot OEt_2$ and increase the Lewis acidity of $BF_3 \cdot OEt_2$. The activation of borane by Lewis acid was reported, see reference: R. Johnsson, R. Cukalevski, F. Dragén, D. Ivanisevic, I. Johansson, L. Petersson, E. E. Wettergren, K. B. Yam, B. Yang, U. Ellervik, *Carbohydr. Res.* **2008**, *343*, 2997–3000.



[11] For *N*- to *O*-sulfonyl transfer, see: a) J. N. Ayres, M. W. Ashford, Y. Stöckl, V. Prudhomme, K. B. Ling, J. A. Platts, L. C. Morrill, *Org. Lett.* **2017**, *19*, 3835–3838; b) J. N. Ayres, M. T. J. Williams, G. J. Tizzard, S. J. Coles, K. B. Ling, L. C. Morrill, *Org. Lett.* **2018**, *20*, 5282–5285. The product **3u** was generated in 77% yield when the **3h** was treated with the NCTS and NaOH (eq. 4).



[12] G. Casiraghi, G. Casnati, G. Puglia, G. Sartori, G. Terenghi, *J. Chem. Soc. Perkin Trans. 1*, **1980**, 1862–1865.

[13] a) M. Z. A. Badr, A. M. Kamal El-Dean, O. S. Moustafa, R. M. Zaki, *J. Chem. Res.* **2006**, 748–752; b) M. N. Kumaraswamy, D. A. Prathima Mathias, C. Chandrashekhar, V. P. Vaidya, *Indian J. Pharm. Sci.* **2006**, *68*, 731–735.

[14] H. C. Aspinall, O. Beckingham, M. D. Farrar, N. Greeves, C. D. Thomas, *Tetrahedron Lett.* **2011**, *52*, 5120–5123.

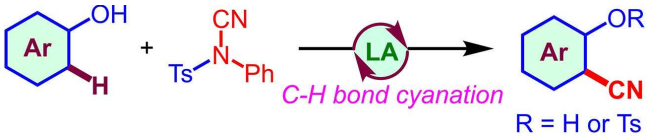
[15] a) J. A. Miller, *Tetrahedron Lett.* **2001**, *42*, 6991–6993; b) Q. Wen, P. Lu, Y. Wang, *RSC Adv.* **2014**, *4*, 47806–47826.

COMMUNICATIONS

Lewis Acid-Mediated Cyanation of Phenols Using *N*-Cyano-*N*-phenyl-*p*-toluenesulfonamide

Adv. Synth. Catal. **2019**, *361*, 1 – 6

W. Zhang, T. Li, Q. Wang*, W. Zhao*



- Safe and readily available cyanation reagent
- High regioselectivity
- Mild reaction conditions, gram-scale synthesis
- 26 examples, 43-97% yield