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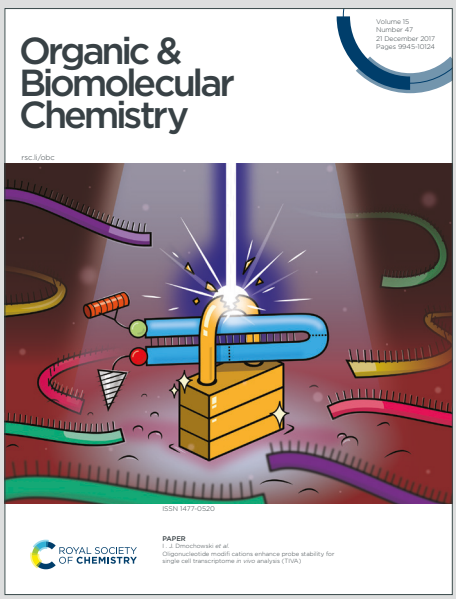

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ARTICLE

Lewis acid-promoted site-selective cyanation of phenols

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An efficient Lewis acid-promoted site-selective electrophilic cyanation of 3-substituted and 3,4-disubstituted phenols has been developed. The cyanation reactions using MeSCN as the cyanating reagent proceeded efficiently to afford a wide range of 2-hydroxybenzonitriles with high efficiency and excellent regioselectivity. This protocol could provide a practical tool for the synthesis and modification of biologically active molecules.

Introduction

Phenols as abundant feedstocks are key structural scaffolds in natural products, pharmaceuticals, agrochemicals, materials, and catalysts, and often employed as useful synthetic intermediates for their preparation (Fig. 1a).[1] As a result, many efforts from chemists and pharmaceutical scientists were devoted to the modification of phenols at their *ortho*-, *meta*-, and *para*- positions, and significant advances have been achieved, with the direct C–H functionalization being the most popular because of its high efficiency in synthesis of complex organic molecules from readily available starting materials.[1c,2] However, to the best of our knowledge, the examples of cyanation of phenols are very rare,[3,4] despite that aromatic nitriles are versatile building blocks in organic and fine chemical synthesis, especially in the drug synthesis.[5] For example, phenol derivatives bearing cyano functional group with excellent biological activities are numerous, such as epanolol as a selective β_1-blocker in the treatment of angina pectoris and mild hypertension,[5b] febuxostat as an antihyperuricemic agent used to treat gout,[5c] and azoxystrobin as a broad spectrum pesticide used in cultivation (Fig. 1b).[5d]

Aromatic nitriles can be readily converted to a variety of valuable synthons, such as amines, ketones, aldehydes, amides, and carboxylic acids, which made them the important role in synthetic chemistry.[6] Conventionally, the preparation of aromatic nitriles mainly relies on transition-metal catalyzed electrophilic cyanation of aromatic compounds[7] or the coupling of aryl halides with nucleophilic cyanating reagents (NaCN, CuCN, $Zn(CN)_2$, TMSCN, etc),[8] and the coupling of aryl organometallic reagents ($ArB(OR)_2$, ArMgBr, ArLi, etc) with electrophilic cyanating reagents (BrCN, ClCN, BtCN, etc).[9] However, these methods may suffer from toxic cyanating reagents, expensive catalysts, poor functional group tolerance, and/or harsh reaction conditions. Thus, it is still of great interest and high desirability to develop efficient and practical cyanation methods. Given the abundance and significance of phenols and diverse transformations of nitriles, we believe that the cyanation of phenols could play an important role in the synthesis and modification of phenol-containing biologically active molecules, especially pharmaceuticals.

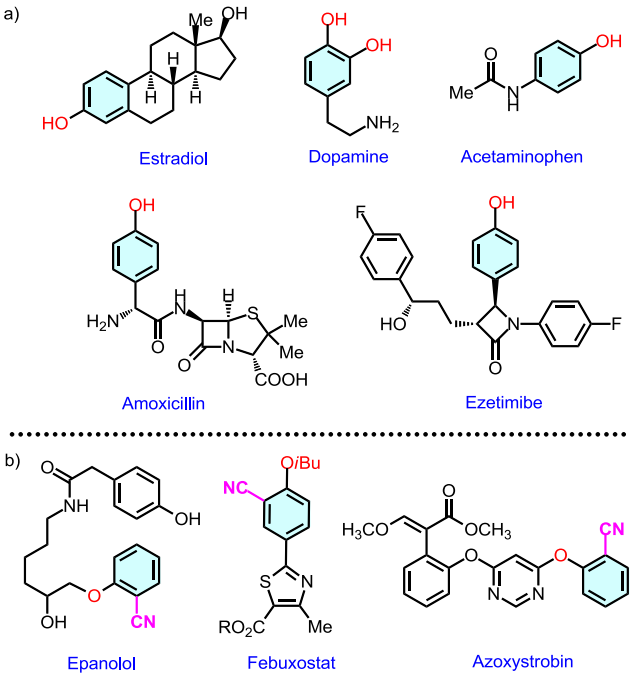

Fig. 1 Representative natural products and pharmaceuticals.

Despite many methods for aromatic nitriles have been reported,[7-10] the C–H cyanation of phenols still remains underdeveloped.[3] Sugasawa described a BCl_3-promoted *ortho* cyanation of phenols with MeSCN (Scheme 1a).[3a] In the seminal work, preliminary investigation with just a few substrate examples was disclosed, and the regioselectivity-control in the cyanation process was not completed. Very recently, we reported a Lewis-mediated α-cyanation of 2-naphthols using NCTS as the cyanating reagent (Scheme 1b).[3c] Although regioselective α-cyanation process was achieved for special substrates (2-naphthols), the regioselectivity-control with general 3,4-disubstituted phenols is a significant and

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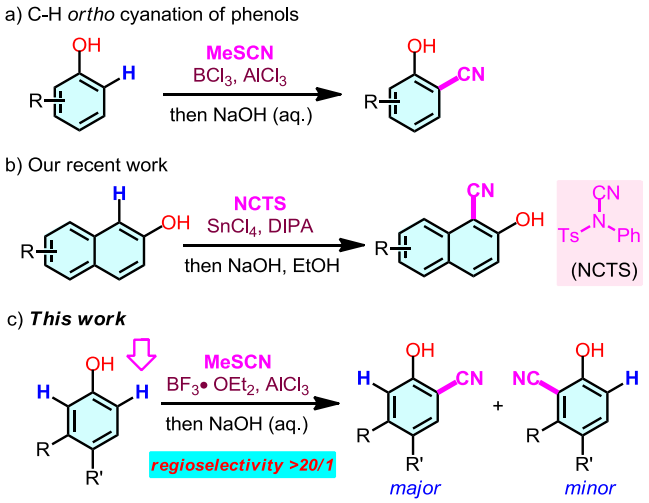
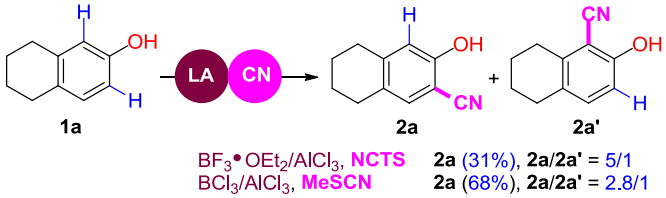
challenging work and remains unsolved. For our persistent interest in the synthesis and application of 2-hydroxy aromatic nitriles,[3c,11] herein, we would like to develop an efficient and practical Lewis acid-promoted site-selective C–H *ortho* cyanation of 3-substituted and 3,4-disubstituted phenols bearing two different *meta*-positions, complementing the established approaches (Scheme 1c).



Scheme 1 Direct C-H *ortho* cyanation of phenols.

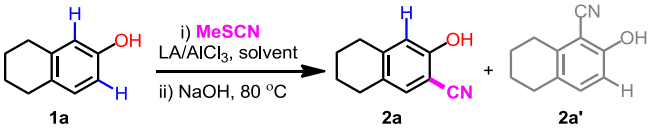
Initially, we used 5,6,7,8-tetrahydronaphthalen-2-ol **1a** as a model and treated it with the optimal reaction conditions previously reported by us and Sugasawa. As shown in Scheme 2, in the present of $BF_3 \bullet OEt_2/AlCl_3$, the cyanation with NCTS provided **2a** in low yield with good regioselectivity (31%, **2a**/**2a´**= 5/1). When **1a** was subjected to Sugasawa's conditions, the desired cyanated product of **2a** was produced in 68% yield but with poor regioselectivity (**2a**/**2a´**= 2.8/1).



Scheme 2 Initial results.

Next, we turned our attention to further optimize various reaction parameters, and the results are summarized in Table 1. A variety of Lewis acid were tested (Table 1, entries 1–5), and $BF_3 \bullet OEt_2$ was found to be the best Lewis acid which promoted the cyanation reaction smoothly to afford product **2a** in 75% yield with high regioselectivity (**2a**/**2a´**= 16/1, entry 5). Encouraged by this fascinating serendipity, we then shifted our efforts to examine solvents, and found 1,2-dichloroethane (DCE) was superior to other solvents (Table 1, entries 6–9). Pleasingly, the yield was improved to 86% with a slightly higher ratio (**2a**/**2a´**= 17/1) when the reaction time was prolonged to 24 h (Table 1, entry 10). In addition, both the yield and the product ratio were decreased at either higher or lower reaction temperature (Table 1, entries 11–12). The concentration was also screened, but no better result was obtained (Table 1, entries 13–14). Finally, the amounts of $BF_3 \bullet OEt_2$, $AlCl_3$, and MeSCN were investigated. As illustrated, the yield or/and regioselectivity declined with the decrease of the amount of $BF_3 \bullet OEt_2$ or $AlCl_3$ (Table 1, entries 15–20). In contrast, both the yield and regioselectivity were improved when the amount of MeSCN was increased from 1.2 equivalents to 2.0 equivalents (Table 1, entries 21–23). Notably, the sole use of $AlCl_3$ or $BF_3 \bullet OEt_2$ all gave poor results (Table 1, entries 24–25). The results indicate that the cyanation reaction requires working together of $BF_3 \bullet OEt_2$ and $AlCl_3$ to ensure high efficiency and excellent regioselectivity.

Table 1 Optimization of the reaction conditions[a]



Entry	MeSCN (equiv.)	LA (equiv.)	solvent	t (h)	yield (%)[b] (**2a**/**2a'**)
1	1.5	$MgCl_2$ (1.2)	DCE	12	6 (1/2)
2	1.5	$TiCl_4$ (1.2)	DCE	12	7 (1/1)
3	1.5	$ZnCl_2$ (1.2)	DCE	12	20 (1/2)
4	1.2	BCl_3 (1.2)	DCE	3	68 (2.8/1)
5	1.5	$BF_3 \bullet OEt_2$ (2.0)	DCE	12	75 (16/1)
6	1.5	$BF_3 \bullet OEt_2$ (2.0)	MeCN	12	54 (8/1)
7	1.5	$BF_3 \bullet OEt_2$ (2.0)	dioxane	12	30 (5/1)
8	1.5	$BF_3 \bullet OEt_2$ (2.0)	THF	12	--
9	1.5	$BF_3 \bullet OEt_2$ (2.0)	toluene	12	59 (10/1)
10	1.5	$BF_3 \bullet OEt_2$ (2.0)	DCE	24	86 (17/1)
11[c]	1.5	$BF_3 \bullet OEt_2$ (2.0)	DCE	24	63 (10/1)
12[d]	1.5	$BF_3 \bullet OEt_2$ (2.0)	DCE	24	46 (3/1)
13[e]	1.5	$BF_3 \bullet OEt_2$ (2.0)	DCE	24	85 (16/1)
14[f]	1.5	$BF_3 \bullet OEt_2$ (2.0)	DCE	24	76 (15/1)
15	1.5	$BF_3 \bullet OEt_2$ (1.5)	DCE	24	85 (16/1)
16	1.5	$BF_3 \bullet OEt_2$ (1.0)	DCE	24	83 (16/1)
17	1.5	$BF_3 \bullet OEt_2$ (0.5)	DCE	24	76 (15/1)
18	1.5	$BF_3 \bullet OEt_2$ (0.2)	DCE	24	52 (4/1)
19[g]	1.5	$BF_3 \bullet OEt_2$ (2.0)	DCE	24	70 (15/1)
20[h]	1.5	$BF_3 \bullet OEt_2$ (2.0)	DCE	24	54 (10/1)
21	1.2	$BF_3 \bullet OEt_2$ (2.0)	DCE	24	64 (15/1)
22	1.8	$BF_3 \bullet OEt_2$ (2.0)	DCE	24	88 (18/1)
23	2.0	$BF_3 \bullet OEt_2$ (2.0)	DCE	24	91 (21/1)
24	1.5	--	DCE	24	5 (1/1.8)
25[i]	1.5	$BF_3 \bullet OEt_2$ (2.0)	DCE	24	24 (2.5/1)

[a] Conditions: i) **1a** (1.0 mmol, 1.0 equiv.), MeSCN, $AlCl_3$ (1.0 equiv.), LA, solvent (1.0 mL). ii) NaOH (4 M aq. 3.3 mL), 80 °C for 0.5 h. LA = Lewis acid. $TiCl_4$ (1.0 M in dichloromethane). BCl_3 (1.0 M in dichloromethane). [b] Yields and ratios were determined by ^1H NMR using CH_2Br_2 as internal standard. Numbers in parentheses are the ratio of **2a**/**2a´**. [c] 60 °C. [d] 100 °C. [e] DCE (0.5 mL). [f] DCE (2.0 mL). [g] $AlCl_3$ (0.5 equiv.). [h] $AlCl_3$ (0.2 equiv.). [i] Without $AlCl_3$.

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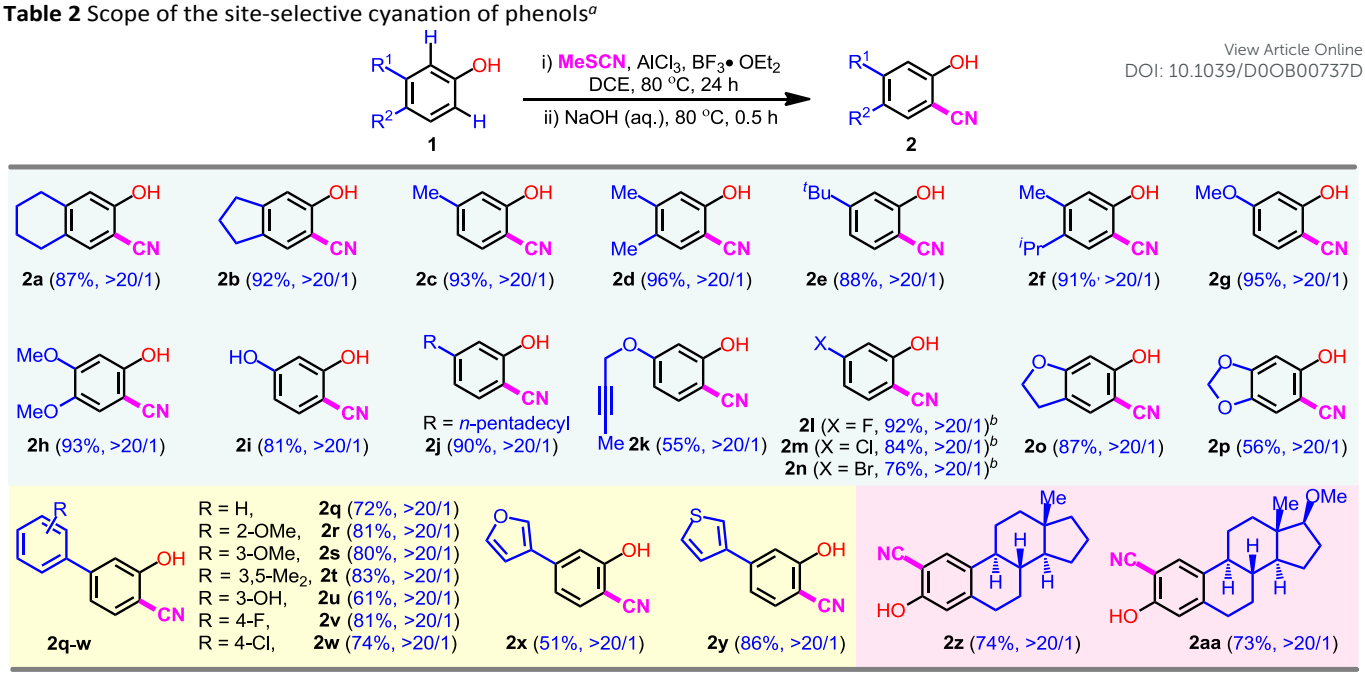
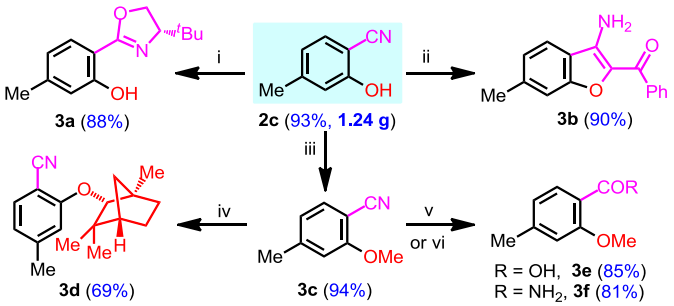
Table 2 Scope of the site-selective cyanation of phenols[a]



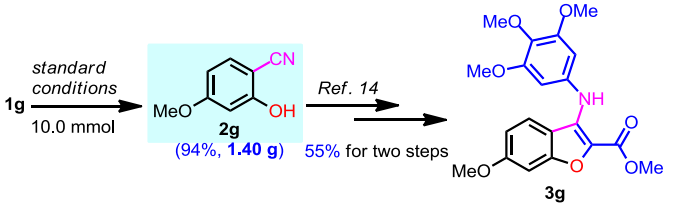
[a] Reaction conditions: i) **1** (1.0 mmol), MeSCN (2.0 mmol), $AlCl_3$ (1.0 mmol), BF_3•OEt_2 (2.0 mmol), DCE (1 mL), 80 °C for 24 h. ii) NaOH (4 M aq, 3.3 mL), 80 °C for 0.5 h. [b] BCl_3.

With the optimized conditions in hand, we next explored the substrate scope of the site selective cyanation reaction (Table 2). A wide range of 3-substituted or 3,4-disubstituted phenols **1** were examined, generally furnishing the desired 2-hydroxybenzonitriles **2** in good to excellent yields. It is noteworthy that excellent regioselectivities (**2**/**2'**>20/1) were observed in all cases, which were determined by ^{1}H NMR analysis of the crude reaction mixtures. Alkyl, alkoxy, hydroxyl, and aryl groups (**1a**–**k**, **1o**–**w**) are all viable substituents. However, *m*-halophenols **1l**–**n** were found to be less efficient under the standard conditions, probably because the halogen substituents reduce the electron richness of phenol ring. Fortunately, with slight modification of the conditions (BCl_3 instead of BF_3•OEt_2), the desired cyanated products **2l**–**2n** were successfully obtained in good to high yields (76-92%). Heterocycles, such as furane and thiophene, could be incorporated into the products (**2x**–**y**) with good efficiency. Notably, this method is also suitable for the cyanation of phenol-containing complex molecules. For example, the installation of a cyano group into estrone- and estradiol-derived substrates (**1z**, **1aa**) was achieved with good efficiency (74% and 73% yield, respectively). It shows that our method can be applied to the modification of natural products and pharmaceuticals.

To further demonstrate the utility of this protocol, we carried out the gram-scale synthesis and product derivatizations (Schemes 3 and 4). First, the gram-scale preparation of **2c** was performed well with no erosion in the yield (93%). Second, based on facile transformations of cyano and hydroxyl groups, product **2c** was efficiently converted into diverse useful building blocks. For example, in the presence of $ZnCl_2$, **2c** reacted smoothly with (*S*)-2-amino-3,3-dimethyl-butan-1-ol to afford chiral oxazoline ligand **3a** in 88% yield.[12] The construction of benzofuran ring (**3b**) was achieved with high efficiency via intermolecular cyclization of **2c** with *α*-bromoacetophenone.[13] Methyl ether **3c** was obtained in 94% yield after methylation with methyl iodide. By our previously reported method, the transetherification of **3c** with (+)-fenchol led to chiral ether **3d** in a good yield.[11] The hydrolysis of **3c** under different reaction conditions efficiently provided the corresponding acid **3e** and amide **3f**, respectively.[11,14] Moreover, according to the known procedure,[15] an antitumor agent **3g** was efficiently synthesized in two simple steps, using 2-hydroxybenzonitrile **2g** as the starting material, which can be readily prepared on gram-scale from 3-methoxyphenol **1g** by this cyanation method.



Scheme 3 Gram-scale synthesis of **2c** and its synthetic transformations. Reaction conditions: i) (*S*)-2-Amino-3,3-dimethylbutan-1-ol, $ZnCl_2$, PhCl, 131 °C, 72 h; ii) α-Bromoacetophenone, K_2CO_3, acetone, reflux, 8 h; iii) MeI, K_2CO_3, DMF, 60 °C, 5 h; iv) (+)-Fenchol, KO^{t}Bu, dioxane, rt, overnight; v) 34% aq. KOH, EtOH, 80°C, overnight, for **3e**; vi) KOH(s), ^{t}BuOH, 60 °C, overnight, for **3f**.



Scheme 4 Synthesis of anticancer drug **3g**.

To gain more mechanistic information, control experiments were carried out. Firstly, 1-methoxy-3-methylbenzene was subjected to the standard condition, and no cyanation product was detected (eq. 1). It indicates that the free hydroxyl group is crucial to this process.

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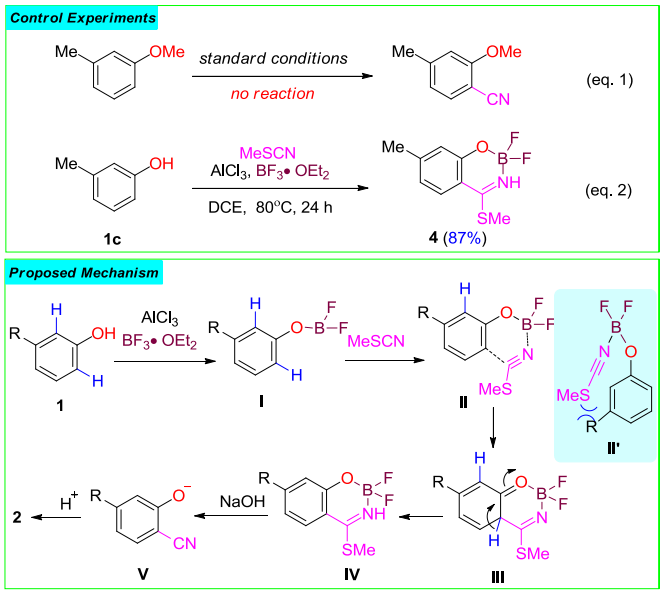
Additionally, the first step product **4** from **1c** was obtained in 87% isolated yield, and its structure was confirmed by NMR and HRMS. Based on the observed results and previous study,[3a,c] we proposed a similar plausible mechanism for this cyanation (Scheme 5). First, the intermediate **I** is generated from phenol **1c** and BF_3•OEt_2 with the help of $AlCl_3$. The role of $AlCl_3$ is to activate BF_3•OEt_2 and improve its Lewis acidity.[16] Then it reacts with MeSCN though a six-membered ring transition state **II** to form the intermediate **III**, which undergoes tautomerization to give the key intermediate **IV**, which was demonstrated by us. Due to the steric hindrance of substituent at the *meta*-position, the formation of the transition state **II'** is unfavored, which accounts for excellent regioselectivity. Finally, the treatment of **IV** with NaOH aqueous solution followed by protonation leads to the desired cyanation product **2**.



Scheme 5 Control experiments and proposed reaction mechanism.

Conclusions

In conclusion, we have developed an efficient Lewis acid-promoted site-selective direct cyanation of 3-substituted and 3,4-disubstituted phenols using commercially available cyanating reagent MeSCN. The cyanation reactions proceeded smoothly to afford a wide range of 2-hydroxybenzonitriles with moderate to excellent yields and excellent regioselectivities. Moreover, the practicality of this method was demonstrated by the gram-scale preparation and various product transformations. This process features broad substrate scope, excellent regioselectivity, good functional group tolerance, and easy gram-scale preparation. This protocol, as a new example of electrophilic cyanation, may provide a practical tool to find applications in the synthesis of key building blocks and the late-stage modifications of biologically active complex molecules, especially pharmaceuticals.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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An efficient Lewis acid-promoted site-selective C–H *ortho* cyanation of 3-substituted and 3,4-disubstituted phenols with MeSCN has been developed.