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Efficient assembly of α-aryl and α-vinyl nitriles via iron-catalyzed ether bond activation

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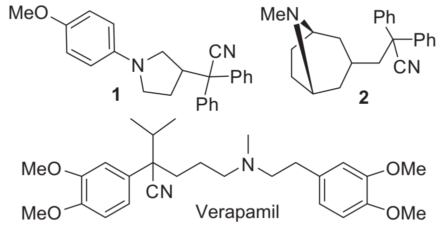
ABSTRACT

A novel and practical method for the synthesis of diverse α-aryl and α-vinyl nitriles was developed via an iron-catalyzed sp^3 C–O ether bond cleavage with C–C bond formation in the reaction of π-activated ethers with TMSCN.

α-Aryl nitriles are an attractive family of organic compounds, which are found as core structures in a number of naturally occurring molecules and pharmaceutically useful compounds (Fig. 1).[1] They also serve as useful synthetic intermediates for heterocycles, aldehydes, ketones, amides, carboxylic acids, and amines,[2] as well as biologically active compounds such as indoprofen, cicloprofen, and naproxen.[3] Usually, α-aryl nitriles are synthesized by dehydration of α-substituted amides,[4] cyanation of benzyl halides or triflates,[5] and hydrocyanation of olefins.[6] In addition, several other useful strategies also can be applied for the synthesis of these compounds.[7] Recently, two facile accesses to α-aryl nitriles, i.e. transition metal-catalyzed α-arylation of nitriles with aryl halides[8] and Lewis acid-mediated direct cyanation of benzylic alcohols by TMSCN have drawn much attention.[9,10] In 2008, Ding and co-workers reported an attractive method for the synthesis of α-aryl nitriles by direct cyanation of alcohols with TMSCN under the catalysis of $InBr_3$.[9] After that, other Lewis acids such as $B(C_6F_5)_3$ and $Zn(OTf)_2$, have also been developed to this transformation by Kim and Lalitha groups, respectively.[9b,c] Despite these methodologies providing fascinating routes to α-aryl nitriles, however, there remain some drawbacks to these reported protocols, such as using air-sensitive and expensive Lewis acids as catalysts, performing the reaction at high temperature and complicated workup procedures. Therefore, further exploration of mild, economical, and environmentally friendly synthetic methods for nitriles would be valuable.



1: 2-[(3S)-1-(4-methoxyphenyl)pyrrolidin-3-yl]-2,2-diphenyl-ethanenitrile
2: 3-(8-methyl-8-azabicyclo-[3.2.1]octan-3-yl)-2,2-diphenylpropanenitrile

Figure 1. Selected examples of biologically active α-aryl nitriles.

In continuation of our previous work in the synthesis of *N*-alkylation compounds via an iron-catalyzed sp^3 C–O ether bond cleavage protocol,[11] we were attracted to extend this strategy for preparing α-aryl nitriles. To our knowledge, approach to nitriles that combination of ecologically benign Lewis acid $FeCl_3$ with readily available ethers has not been reported previously. Ethers are environmentally friendly compounds that have been extensively explored over the past decade as novel electrophiles in transition metal-catalyzed cross-coupling reactions,[12] such as using aryl or benzyl ethers instead of halides in Suzuki and Kumada couplings.[12c,e,h,i] In contrast with transition metal-catalyzed reactions, relatively few examples exist on the Lewis acids catalytic activation of C–O ether bonds for construction of C–C bonds.[13] As part

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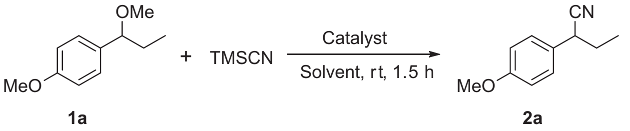
Table 1

Optimization of reaction conditions[a]



Entry	TMSCN (equiv)	Catalyst (mol %)	Solvent	Yield[b] (%)
1	1.5	$FeCl_3$ (5)	DCM	86
2	1.5	$FeCl_3$ (10)	DCM	97
3	1.2	$FeCl_3$ (10)	DCM	90
4	1.5	$FeCl_3$ (10)	DCE	80
5	1.5	$FeCl_3$ (10)	Dioxane	0
6	1.5	$FeCl_3$ (10)	CH_3NO_2	Trace
7	1.5	$FeCl_3$ (10)	Toluene	Trace
8	1.5	$FeCl_3$ $6H_2O$ (10)	DCM	91
9	1.5	$FeBr_3$ (10)	DCM	78
10	1.5	BF_3 Et_2O (10)	DCM	49
11	1.5	$TiCl_4$ (10)	DCM	71
12	1.5	$ZnCl_2$ (10)	DCM	0
13	1.5	$AlCl_3$ (10)	DCM	85
14	1.5	$FeCl_2$ (10)	DCM	0
15	1.5	None	DCM	0
16	1.5	TfOH (10)	DCM	76

[a] Reaction conditions: benzylic ether (0.35 mmol), TMSCN (0.525 or 0.42 mmol), solvent (3 mL), room temperature, in air.

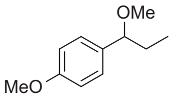
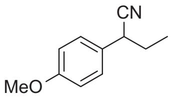
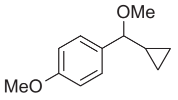
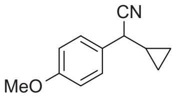
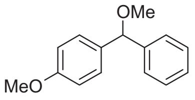
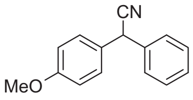
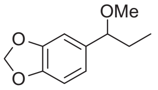
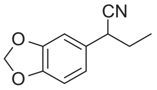
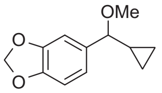
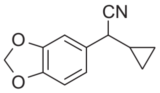
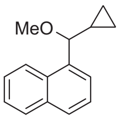
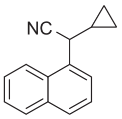
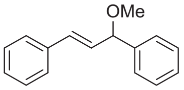
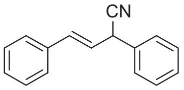
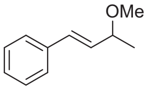
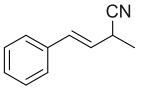
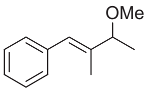
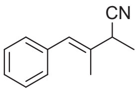
[b] Isolated yield.

of our ongoing program examining the utility of ethers in organic synthesis, we report herein a practical and efficient method for the synthesis of α-aryl and α-vinyl nitriles in the reaction of π-activated ethers with TMSCN under the catalysis of $FeCl_3$.

At the outset of our studies, we focused our attention on the reaction of 1-(4-methoxyphenyl)-1-methoxypropane **1a** with TMSCN under the catalysis of $FeCl_3$ in a range of solvents to establish the reaction conditions (Table 1). To our delight, the reaction proceeded very well with 10 mol % catalytic amount of $FeCl_3$ in dichloromethane (DCM) at room temperature within 1.5 h (Table 1, entry 2). Further investigation of the solvent effect indicates that the nature of the reaction media significantly affects the reaction (Table 1, entries 4–7), DCM was found to be the most suitable solvent. With respect to the substrate loading, 1:1.5 ratio of **1a** with TMSCN gave the best result (Table 1, entries 2 and 3). Under this optimized reaction conditions, the desired cyanation product **2a** could be isolated in 97% yield (Table 1, entry 2). Replacing $FeCl_3$ with $FeCl_3{\cdot}6H_2O$, the reaction proceeded in a slightly lower yield (91%, Table 1, entry 8). Other Lewis acids such as $FeBr_3$, $BF_3{\cdot}Et_2O$, $TiCl_4$, $ZnCl_2$, $AlCl_3$, and $FeCl_2$ were proved to be less effective or ineffective to promote this transformation (Table 1, entries 9–14). Control experiment indicated that $FeCl_3$ is essential for this reaction (Table 1, entry 15). Furthermore, among the examined Brønsted acids (e.g., TfOH and HCl), only triflic acid exhibited catalytic activity and a relatively lower yield of **2a** was obtained

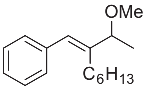
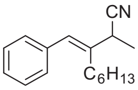
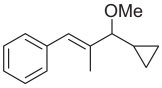
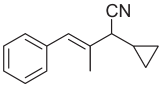
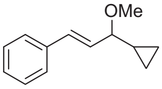
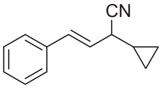
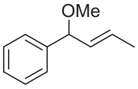
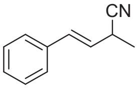
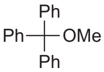
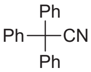
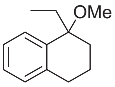
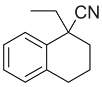
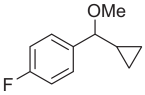
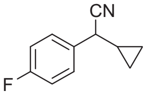
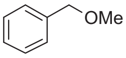
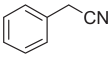
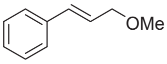
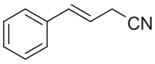
Table 2

$FeCl_3$-catalyzed direct cyanation of ethers with TMSCN[a]

Entry	Ether	Product	*t* (h)	Yield[b] (%)
1	 **1a**	 **2a**	1.5	97
2	 **1b**	 **2b**	1.5	90
3	 **1c**	 **2c**	1.5	99
4	 **1d**	 **2d**	1.5	99
5	 **1e**	 **2e**	1.0	85
6	 **1f**	 **2f**	0.5	91
7	 **1g**	 **2g**	0.5	87
8	 **1h**	 **2h**	1.5	89
9	 **1i**	 **2i**	0.5	89

(*continued on next page*)

Table 2 (*continued*)

Entry	Ether	Product	*t* (h)	Yield[b] (%)
10	 **1j**	 **2j**	3.5	81
11	 **1k**	 **2k**	1.5	99
12	 **1l**	 **2l**	1.5	67
13	 **1m**	 **2h**	1.5	65
14	 $\mathrm{Ph_3C{-}OMe}$ **1n**	 $\mathrm{Ph_3C{-}CN}$ **2n**	3.5	82
15	 **1o**	 **2o**	1.5	86
16	 **1p**	 **2p**	1.5	36
17	 **1q**	 **2q**	1.5	n.r.
18	 **1r**	 **2r**	1.5	n.r.

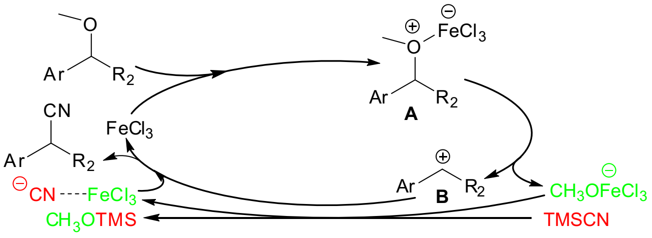
[a] Reaction conditions: benzylic ether (0.35 mmol), TMSCN (0.525 mmol), DCM (3 mL), $FeCl_3$ (10 mol %), room temperature, in air.

[b] Isolated yield.

(Table 1, entry 16), which suggests that the present reaction is catalyzed by Fe(III) species. It is worth noting that $FeCl_3$ has been demonstrated to be an incompetent catalyst for direct cyanation of benzylic alcohols,[9a,c] however, it showed excellent catalytic ability in our reaction.

With the optimized reaction conditions in hand (Table 1, entry 2), the substrate scope and limitations of this reaction were then investigated on a series of primary, secondary, and tertiary benzylic and allylic methyl ethers (Table 2). It was found that the present reaction conditions showed good substrate compatibility with a wide variety of secondary and tertiary ethers, providing the corresponding nitriles in good to excellent yields within a short period of reaction time at room temperature (Table 2, entries 1–15). Primary benzylic and allylic methyl ethers, such as **1q** and **1r**, could not undergo this transformation even under harsh reaction conditions (Table 2, entries 17–18),[14] presumably because of the lower stability of the primary carbocation intermediates derived from **1q** and **1r**. Functional groups, e.g., aromatic fluoro, or methoxy groups, C=C double bond, cyclopropyl, and acetal, tolerate the reaction conditions very well (Table 2, entries 2, 4, 5, 7, and 16). Overall, the reaction is facilitated with electron-rich benzylic methyl ethers and gives the corresponding cyanation products in high yield (Table 2, entries 1, 4, and 6). In contrast, the use of electron-poor benzylic ether **1p**, which bear a fluorine atom at the *para*-position of the phenyl ring, resulted in a quite lower yield of product **2p** (36%, Table 2, entry 16). With respect to the steric properties of the ethers, no obvious influence on the reaction was observed, tertiary benzylic ethers also served as efficient electrophiles in this transformation (Table 2, entries 14–15). For example, the higher sterically hindered triphenylmethyl methyl ether **1n** reacted smoothly with TMSCN at room temperature to give the desired tertiary nitrile **2n** in high yield (Table 2, entry 14). Note that the allylic secondary ether **1m** ((*E*)-1-methoxy-1-phenylbut-2-ene) led cleanly to the thermodynamically favored regioisomeric cyanation product **2h** ((*E*)-2-methyl-4-phenyl-3-butenenitrile, Table 2, entry 13), suggesting that the reaction most likely proceeds via a carbocation pathway. In order to verify this proposal, enantioenriched (*R*)-**1a** (63% ee) was subjected to this reaction. After 1.5 h, the racemic cyanation product **2a** was obtained in 95% yield. This result is consistent with our previously mechanistic study in iron-catalyzed *N*-alkylation.[11] Moreover, benzylic ethyl ether such as 1-(1-ethoxypropyl)-4-methoxybenzene was also tested to this reaction. However, only trace amount of cyanation product **2a** was obtained,[15] which might be attributed to the difficulty in the formation of a carbocation intermediate from benzylic ethyl ether.

Based on the above experimental results and previously reported studies by us and Ding group,[9a,11] a tentative reaction pathway was proposed in Scheme 1. We speculate that the reaction might involve activation of the C–O bond through coordination of $FeCl_3$ with the methoxy group in ethers. This delivers the Fe(III)-coordinated species **A**, which then undergoes an iron-catalyzed sp^3 C–O ether bond cleavage to give the benzylic cation



Scheme 1. Proposed mechanism.

intermediate **B** and $Fe^{-}Cl_3(OCH_3)$. Subsequently, disassociation of TMSCN by $Fe^{-}Cl_3(OCH_3)$ followed by a simultaneous addition of the in situ formed cyanide ion to benzylic cation intermediate **B** would give rise to the cyanation product and regenerate the catalyst $FeCl_3$.

In summary, a practical and efficient route to α-aryl and α-vinyl nitriles that combination of the readily available ethers and TMSCN with a catalytic amount of environmentally benign Lewis acid FeCl3 has been achieved. This method can be used for a structurally diverse set of secondary and tertiary benzylic and allylic methyl ethers and gives the corresponding nitriles in good to excellent yields at room temperature. Further exploration of ethers as electrophiles in organic synthesis via Lewis acid-catalyzed C–O bond activation is in progress in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.083.

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14. These substrates kept almost intact under high reaction temperature and prolonged reaction time.
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