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# Boron Lewis Acid Catalysis Enables the Direct Cyanation of Benzyl Alcohols by Means of Isonitrile as Cyanide Source

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**Abstract:** The development of an efficient and straightforward method for cyanation of alcohols is of great value. However, the cyanation of alcohols always requires toxic cyanide sources. Herein, an unprecedented synthetic application of an isonitrile as a safer cyanide source in $B(C_6F_5)_3$-catalyzed direct cyanation of alcohols is reported. With this approach, a wide range of valuable α-aryl nitriles was synthesized in good to excellent yields (up to 98%). The reaction can be scaled up and the practicability of this approach is further manifested in the synthesis of an anti-inflammatory drug, naproxen. Moreover, experimental studies were performed to illustrate the reaction mechanism.

**Keywords:** boron Lewis acid; α-aryl nitrile; cyanation; isonitrile; green chemistry

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## 1. Introduction

The need for the development of new reactions that are based on applying the atom-economy concept [1] and avoiding the use of toxic reagents has become a consensus. Alcohols are highly attractive starting materials for synthesis because they are stable, have low toxicity, and are available. Direct nucleophilic substitution of an alcohol is attractive since water is, in principle, the only by-product [2–5]. However, this reaction is difficult because hydroxide is such a poor leaving group and therefore alcohols are classically derivatized to halides or pseudohalides prior to substitution, which results in the formation of vast amounts of waste. Thus, the development of new catalytic methodologies for dehydrative substitutions of alcohols was considered a central issue, as demonstrated by the inclusion of the "direct substitution of alcohols" in the ACS Green Chemistry Institute® Pharmaceutical Roundtable's 2018 update on key green chemistry research areas [6]. In this context, the deoxygenative cyanation of readily available benzyl alcohols represent one of the most powerful methods for preparing α-aryl nitriles [7–20], an important class of core structures found in bioactive moleculars [21] and functional materials [22], and precursors that have applications in the synthesis of well-known drugs such as verapamil [23], naproxen [24], and cytenamide [25] as shown in Figure 1.

As early as 1967, the one-pot method for the conversion of alcohols into cyanides based on the concept of the Mitsunobu reaction using NaCN as the cyanide source has been described [26]. Subsequently, there are a few reports on one-pot transformations of alcohols to α-aryl nitrile using $Me_3SiCl$/NaI/NaCN [27], $PPh_3$/$n$$Bu_4NCN$/DDQ [28], *N*-(*p*-toluenesulfonyl)imidazole (TsIm)/NaCN [29], and $PPh_3$/DEAD/acetone cyanohydrin [30].

However, these methods suffer from major disadvantages such as the presence of hazardous and toxic cyanide sources and the use of stoichiometric activating reagents.

Recently, catalytic synthesis of α-aryl nitrile from benzyl alcohols was successfully developed. Ding's group performed pioneering work on the direct cyanation of α-aryl alcohols with trimethylsilyl cyanide (TMSCN) by indium halide catalysis [31]. Later, other Lewis acids, such as $FeCl_3 \cdot 6H_2O$ [32], $Zn(OTf)_2$ [33], Brønsted acid montmorillonite

catalysts [34], and others [35] were also used to catalyze this transformation. Besides these, ruthenium-catalyzed cyanation of benzyl alcohol with cuprous cyanide (CuCN) was also reported [36]. Again, these methods are typically plagued by notorious toxic cyanide source issues. To solve the severe safety issues associated with the handling of traditional cyanide sources, such as metal cyanides, ketone cyanohydrins [37–39], or TMSCN, several safer alternatives have been introduced, including: DMF [40], DMSO/ammonium ion [41], azobisisobutyronitrile (AIBN) [42], TsN(Ph)CN [43], isocyanides [44–51], and so on [52,53]. However, no direct cyanation of alcohols has been described so far for the synthesis of α-aryl nitriles from these safer organic CN surrogates (Scheme 1A).

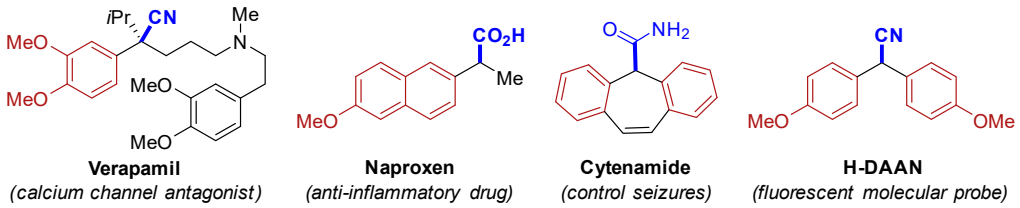
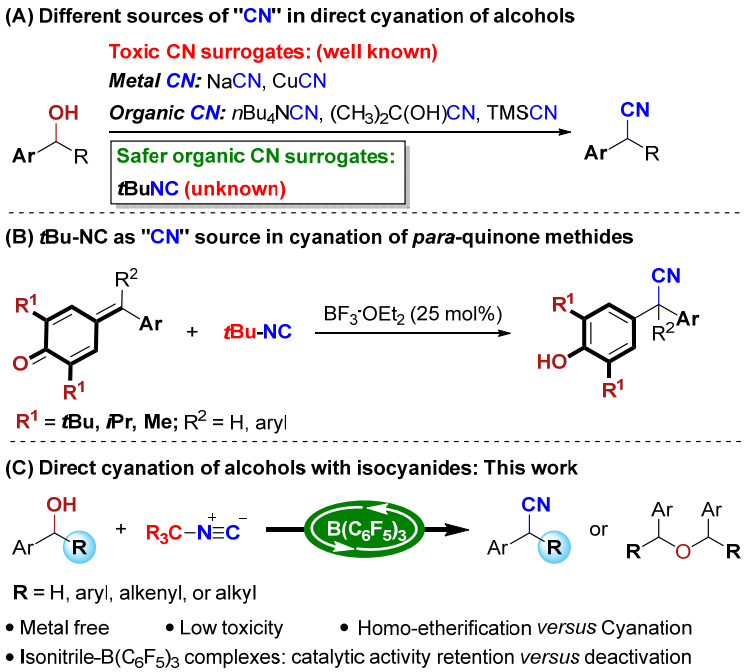



**Figure 1.** Verapamil, H-DAAN, and some derivatives of α-aryl nitriles.




**Scheme 1.** Our catalytic strategy to access α-aryl nitriles and its scientific context.

Isocyanides, which are isoelectronic with carbon monoxide, have emerged as powerful C1 building blocks in organic synthesis [54–60]. The distinctive reactivity of isocyanides makes them well-known in Passerini and Ugi multicomponent reactions and others [61]. In 1982, Saegusa and co-workers performed seminal work on the conjugate hydrocyanation and 1,2-addition reactions with *tert*-butyl isocyanide in the presence of stoichiometric Lewis acids [44]. Subsequently, commercially available *tert*-butyl isocyanide as a safer cyanide alternative in C-H cyanation [45–48], noble-metal-catalyzed cyanation of aryl iodides [49], and cyanothiolation of alkynes [50] has been reported, which further broadened the application of isocyanides in organic synthesis. To date, the catalytic method to obtain valuable α-aryl nitriles relied upon the usage of isocyanides as a cyanide source; however, these are rarely known. As a rare example, Muthukrishnan and co-workers reported a $BF_3{\cdot}OEt_2$-catalyzed 1,6-conjugate addition reaction of *p*-quinone methides (*p*-QMs) with *tert*-butyl isocyanide for synthesis of α-diaryl and α-triaryl nitriles (Scheme 1B) [51]. Nonetheless, the substrates of the reaction are limited to *p*-QMs that feature bulky *tert*-butyl substituents

at the 2- and 6-positions. Therefore, the development of new reactions with isocyanides for synthesis of α-aryl nitriles is highly desirable.

In recent years, $B(C_6F_5)_3$ as a non-metallic Lewis acid has received widespread attention because of its strong Lewis acidity, commercial availability, and environmental friendliness [62–68]. Although still limited in its success, it mainly involves the $B(C_6F_5)_3$-catalyzed activation of hydroxyl groups, as reported by Meng, Zhao and Chan [69,70], Marek [71], Tang [72], Maji [73], Gevorgyan [74], and Moran [75]. Inspired by these reports and building on our ongoing interest in the developing atom-economic reactions [76–79], we questioned if the direct cyanation of alcohols with isocyanides in the presence of $B(C_6F_5)_3$ could be realized to meet the requirements of atom economy and green chemistry (Scheme 1C). However, this hypothesis may face considerable challenges, such as the following: (a) the catalyst should be stable in wet and Lewis basic conditions, and (b) *tert*-butylisocyanide/$B(C_6F_5)_3$ and nitrile/$B(C_6F_5)_3$ adducts can be easily formed, as reported by Berke and Erker and co-workers [80]. It is unknown whether $B(C_6F_5)_3$ can maintain its catalytic activity during the current cyanation reaction, and (c) the catalyst should be able to dissociate from nitrile products. Finally, (d) another challenge is to suppress the $B(C_6F_5)_3$-catalyzed homo-etherification of alcohols reported by Chan and co-workers [70].

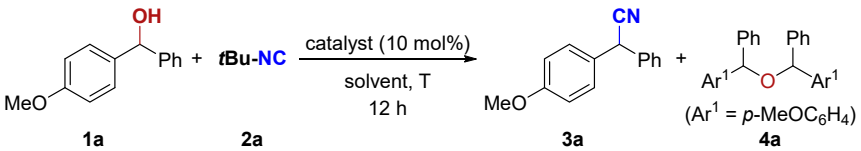
## 2. Results

We initiated our investigation with the optimization of the reaction of benzhydryl alcohol (**1a**) and *tert*-butyl isocyanide (**2a**). Initially, **1a** and 1.5 equivalents of **2a** were subjected to a solution of $FeCl_3$ (10 mol%) in toluene at 100 °C (Table 1, entry 1). However, $FeCl_3$ showed almost no catalytic activity. Other commonly used Lewis acids, including $AlCl_3$, $Cu(OTf)_2$, $AgClO_4$, and $BF_3{\cdot}(OEt)_2$ were also tested, but led to low yield (see entries 2–5 in Table 1). Of note, using $AlCl_3$, $BF_3{\cdot}(OEt)_2$, or $TsOH{\cdot}H_2O$ as a catalyst, a mixture of **3a** and some homo-etherification side product **4a** was obtained (entries 2, 5 and 7). With the use of Brønsted acid $Tf_2NH$, the cyanation provided the desired **3a** in 72% NMR yield. Interestingly, the reaction favors the formation of etherification product **4a** rather than **3a** when using diphenyl phosphate as the catalyst (entry 8 versus 9). Gratifyingly, we found that $B(C_6F_5)_3$ affords the desired α-aryl nitrile **3a** in >99% NMR yield at 100 °C (entry 6). No reaction occurred when $B(C_6F_5)_3$ was used as the catalyst at 50 °C (entry 11). Increasing the temperature to 80 °C improved both the yield of **3a** (20%) and ether **4a** (30%). Different solvents such as 1,2-dichloroethane (DCE), THF, and hexafluoroisopropanol (HFIP) (entries 12–15) were also tested, and the results revealed that toluene was superior to other solvents.

With the optimized conditions identified, we then proceeded to explore the scope of isocyanides (Scheme 2). Besides *t*Bu-NC (**2a**), other tertiary amine-derived isocyanides, such as **2b** and **2c**, can also be used as a novel cyano source in the current direct cyanation of α-aryl alcohols. In contrast, when secondary amine- and aniline-derived isocyanides were used as substrates, only the corresponding ether products were obtained (not shown). Of note, treatment of **1a** and **2c** with the standard conditions afforded **3a** in 81% NMR yield together with internal alkene **5** in 53% NMR yield and terminal alkene **6** in 38% NMR yield (Scheme 2b), indicating a tertiary carbon cation might be an intermediate.

Next, we turned to explore the generality of this cyanidation reaction with a variety of alcohols with *t*Bu-NC (**2a**). As shown in Scheme 3, a wide range of benzylic alcohols can smoothly react with **2a** under the optimized conditions, giving the corresponding α-aryl nitriles in good to excellent yields. Diarylsubstituted alcohols ($R^2$ = aryl) underwent reaction with *t*Bu-NC to furnish the corresponding products (**3a**–**3k**) in 19−98% yields.

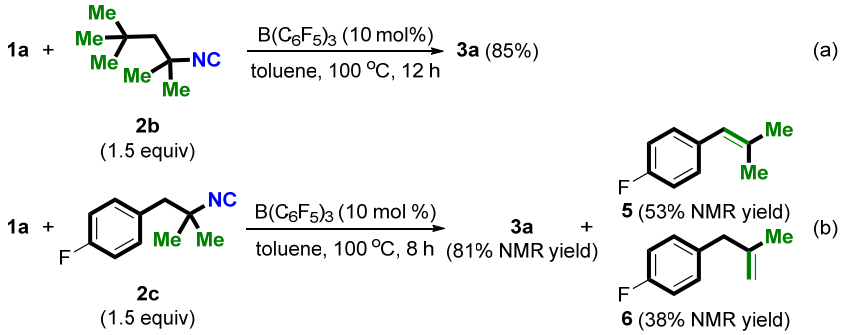
**Table 1.** Optimization of reaction conditions [a].




1a 2a 3a 4a

| Entry | Catalyst | Solvent | T [°C] | Conv. (%) | 3a [%] [b] | 4a [%] [b] |
|---|---|---|---|---|---|---|
| 1 | $FeCl_3$ | toluene | 100 | 10 | 0 | 0 |
| 2 | $AlCl_3$ | toluene | 100 | 86 | 16 | 28 |
| 3 | $Cu(OTf)_2$ | toluene | 100 | 100 | 57 | 0 |
| 4 | $AgClO_4$ | toluene | 100 | 21 | 7 | 0 |
| 5 | $BF_3{\cdot}Et_2O$ | toluene | 100 | 48 | 24 | 11 |
| 6 | $B(C_6F_5)_3$ | toluene | 100 | 100 | >99(98) | 0 |
| 7 | $TsOH{\cdot}H_2O$ | toluene | 100 | 84 | 32 | 29 |
| 8 | $Tf_2NH$ | toluene | 100 | 100 | 72 | 0 |
| 9 | $(PhO)_2P(=O)OH$ | toluene | 100 | 100 | 0 | 45 |
| 10 | $B(C_6F_5)_3$ | toluene | 80 | 70 | 20 | 30 |
| 11 | $B(C_6F_5)_3$ | toluene | 50 | 0 | 0 | 0 |
| 12 | $B(C_6F_5)_3$ | DCE | reflux | 100 | 93 | 0 |
| 13 | $B(C_6F_5)_3$ | THF | reflux | 100 | 82 | 0 |
| 15 | $B(C_6F_5)_3$ | HFIP | reflux | 50 | 20 | 0 |

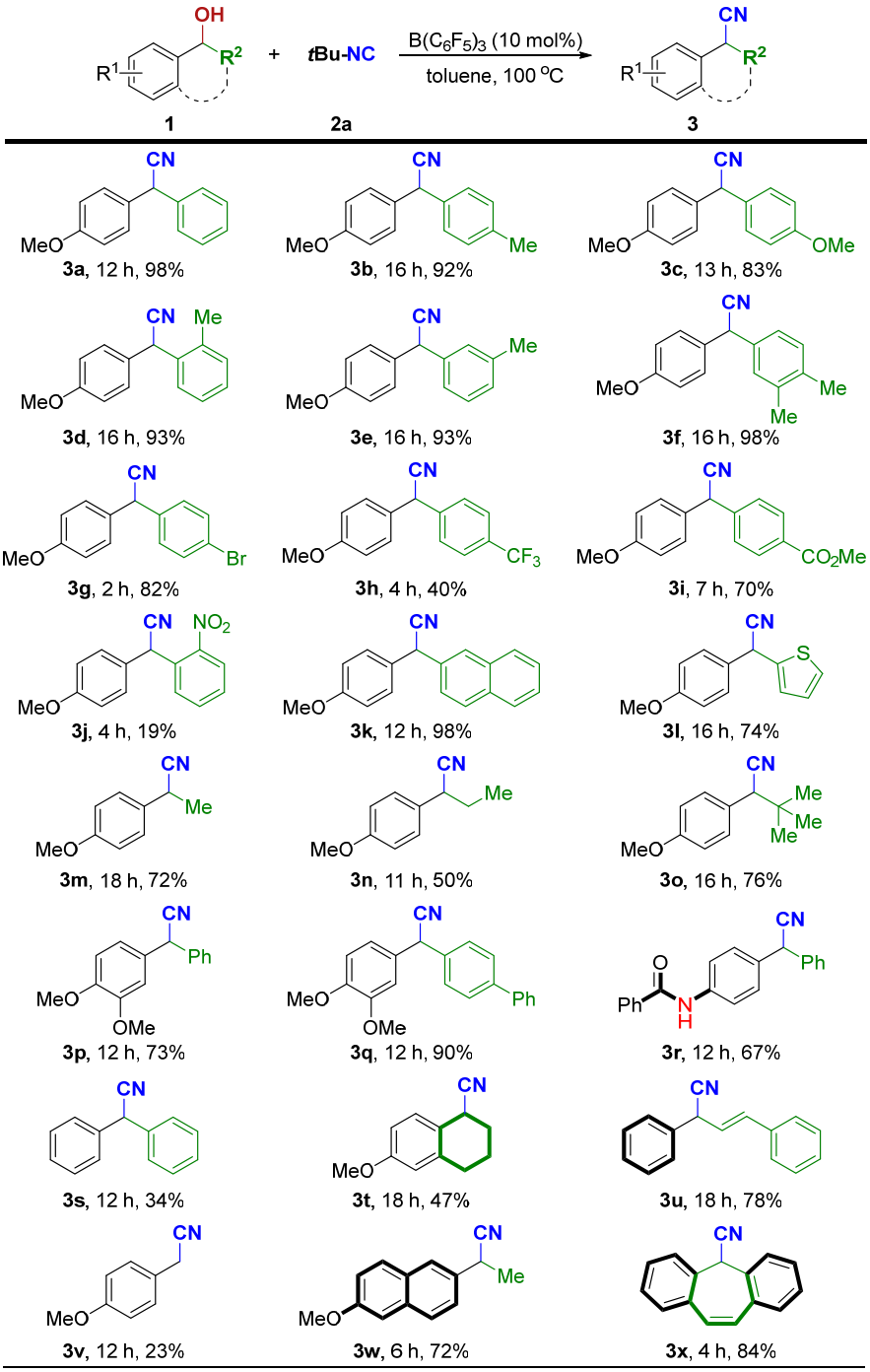
[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.30 mmol, 1.5 equiv), catalyst (10 mol%), solvent (2 mL), T °C, under $N_2$ for 12 h. [b] The yields were determined by $^1H$ NMR spectroscopy using $CH_2Br_2$ as the internal standard. The number in the parentheses is the isolated yield of **3a**.




**Scheme 2.** Survey of the scope of isocyanides (**a**,**b**).

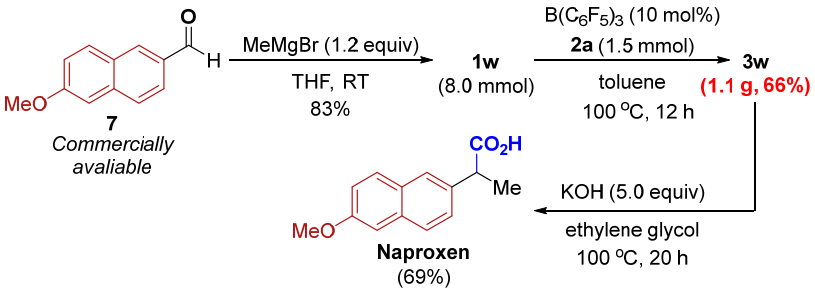
Diarylsubstituted alcohols bearing electron-donating (methoxy, alkyl) groups at the *para*-, *ortho*- or *meta*-positions of the benzene rings reacted smoothly (**1a**–**1f**). A variety of electron-withdrawing functional groups at the *para*-positions of the benzene rings such as -Br, $-CF_3$, and $-CO_2Me$ were tolerated, affording the desired products in moderate to good yields (**1g**–**1i**). However, a low yield of **3j** was isolated from **1j** having an *ortho*-nitro group on the aromatic substituent. The naphthyl-containing alcohol **1k** and heteroaryl-containing alcohol **1l** also afforded the corresponding products in good to excellent yields. In addition, alkyl-substituted alcohols ($R^2$ = methyl, ethyl, and *tert*-butyl) were also well-tolerated to afford the desired products **3m**–**3o**. Of note, a competitive side reaction encountered in the reaction with **1m** or **1n** is the formation of styrene derivatives via the dehydration reactions of alcohols. Besides $R^1$ = methoxy (**1p**–**1q**), the substituent $R^1$ can be benzamide (**1r**). Benzhydrol **1s** was tested but afforded the corresponding product **3s** in low yield together with (oxybis(methanetriyl))tetrabenzene in 64% NMR yield. However, 1,2,3,4-tetrahydronaphthalen-1-ol (**1t**) and allylic alcohol (**1u**) underwent smooth cyanation. It is worth noting that the reported indium halide-catalyzed protocol with TMSCN as the cyanide source is not amenable to primary alcohol **1v** for cyanation reaction [31]. Our system, however, gives reasonable yield for the same substrate. To our delight, the

precursors for naproxen and cytenamide, respectively, can also be efficiently obtained in high yields by this protocol (**3w** and **3x**).



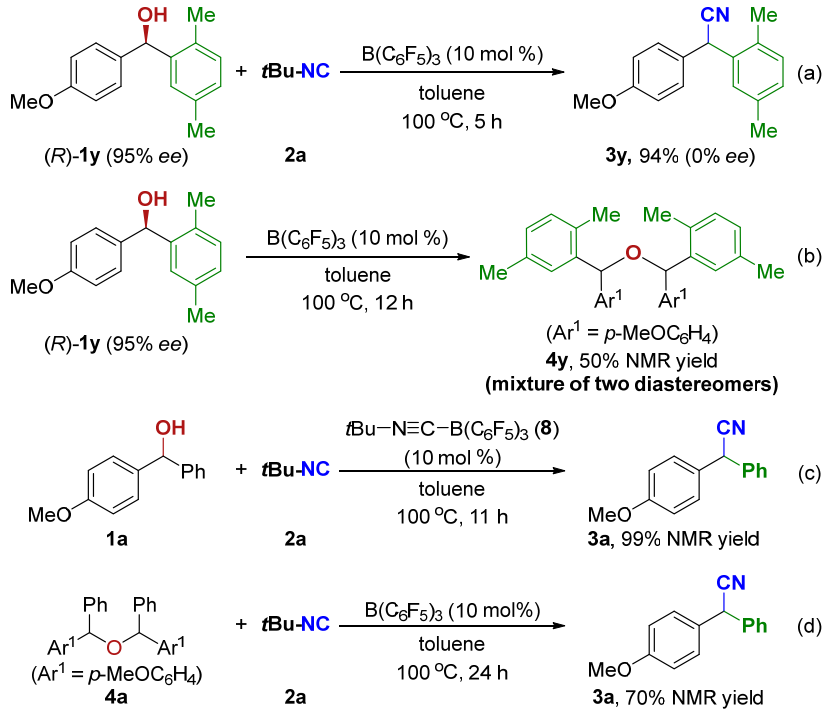

**Scheme 3.** Survey of the scope of α-aryl alcohols [a,b]. [a] Standard conditions: **1** (0.20 mmol), **2a** (0.30 mmol, 1.5 equiv), $B(C_6F_5)_3$ (10 mol%), toluene (2 mL), at 100 °C for 2–18 h. [b] Isolated yield of **3**.

To disclose the synthetic practicability of the developed method, we studied a gram-scale reaction, and 66% yield of **3w** was obtained, which might provide potential value in synthetic chemistry. Having established a protocol for the efficient synthesis of α-aryl nitrile **3w**, (±)-naproxen, a nonsteroidal anti-inflammatory drug [24], was prepared in three steps from commercially available materials (Scheme 4).




**Scheme 4.** Scale-up synthesis and synthetic transformations.

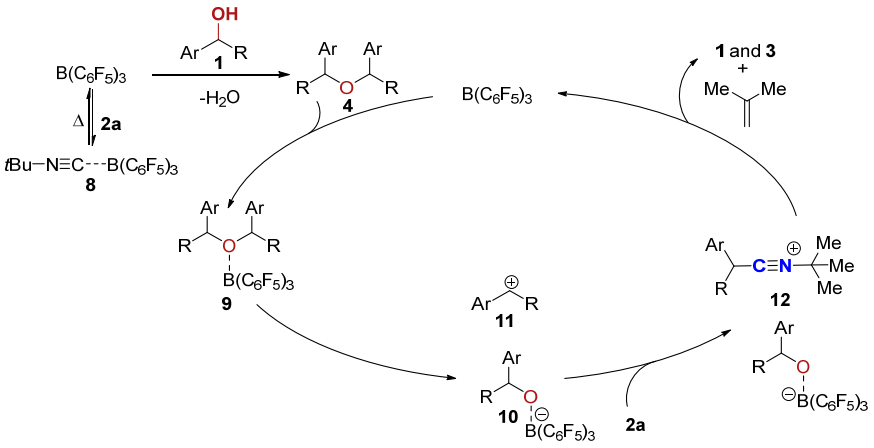
To gain insight into the reaction mechanism, several control experiments were conducted. When an enantiomerically pure sample of (*R*)-**1y** was subjected to standard conditions, the resulting nitrile **3y** was obtained in racemic form (Scheme 5a). Moreover, (*R*)-**1y** was also employed to perform the etherification reaction under the standard condition. The $^1$H NMR spectrum showed the ether **4y** was obtained in 50% NMR yield with a 48/52 ratio of the two diastereomers (Scheme 5b). These control experiments support an $S_N1$ pathway and rule out a concerted $S_N2$ mechanism. The *tert*-Butylisocyanide-B($C_6F_5$)$_3$ adduct (**8**) was easily prepared [80] and used as a catalyst in the current reaction, affording the corresponding product **3a** in 99% NMR yield (Scheme 5c). As shown in Table 1, entry 10, the reaction did form **3a** in 20% NMR yield along with ether **4a** in 30% NMR yield at 80 °C. Treatment of **4a** with the standard setup then gave the desired **3a** in 70% NMR yield (Scheme 5d).




**Scheme 5.** Control experiments (**a**–**d**).

Based on the results above, a plausible mechanism is proposed in Scheme 6. First, *tert*-butylisocyanide **2a** forms a reversibly Lewis adduct **8** with B($C_6F_5$)$_3$ [80]. The homo-etherification of alcohol in the presence of the B($C_6F_5$)$_3$ quickly delivers the ether **4** [70], which could furnish an adduct **9** with B($C_6F_5$)$_3$ through the oxygen center. Subsequently, the adduct **9** could break into an intermediate **10** and carbocation **11**. However, an alternative reaction path for the formation of the carbocation **11** directly from alcohol in the presence of the in situ-generated strong Brønsted acid B($C_6F_5$)$_3$·n$H_2O$ or boron Lewis acid B($C_6F_5$)$_3$

(not shown, see Supporting Information for details) cannot be ruled out [69,70]. The carbocation **11** could then be intercepted instantaneously by the *t*Bu-NC (**2a**) to afford an intermediate **12** with a borate anion **10** as the counteranion. The stability of the tertiary carbon cation is the driving force to break the C-N bond in **12**, leading to the α-aryl nitrile **3** and 2-methylpropene by proton elimination via a *tert*-butyl carbon cation intermediate (supported by Scheme 2b) [81]. The borate anion **10**, on the other hand, transforms into alcohol **1** with the regeneration of the $B(C_6F_5)_3$ catalyst.




**Scheme 6.** Proposed mechanism.

## 3. Materials and Methods

### *3.1. General Information*

All reactions were performed in flame-dried glassware using conventional Schlenk techniques under a static pressure of nitrogen unless otherwise stated. Liquids and solutions were transferred with syringes. The known alcohols **1** [31,35] and *t*Bu-NC-$B(C_5F_5)_3$ adduct **8** [80] were prepared according to reported procedures. (*R*)-**1y** was prepared in 80% yield according to the known procedure [82] (95% *ee* of (*R*)-**1y** was determined by HPLC: OJ-H Column, 5/95 iPrOH/hexane, 0.5 mL/min, 254 nm, 35 °C; retention time = 75.36 min (minor), 81.66 min (major)). Tris(pentafluorophenyl)borane ($B(C_5F_5)_3$, 98%, *Energy Chemical*) and *tert*-butyl isocyanate (97%, *Energy Chemical*) were purchased from commercial suppliers and used as received. Other commercially available reagents were purchased from *Sigma-Adrich*, *Leyan* and *Bide* Chemical Company. All solvents (tetrahydrofuran, toluene, and 1,2-dichloroethane etc.) were dried and purified following standard procedures. Technical grade solvents for extraction or chromatography (petroleum ether, $CH_2Cl_2$, and ethyl acetate) were distilled prior to use. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 glass plates by *Merck*. Flash column chromatography was performed on silica gel 60 (40–63 μm, 230–400 mesh, ASTM) by *Grace* using the indicated solvents. $^1H$, $^{13}C$ NMR spectra (Supplementary Materials) were recorded in $CDCl_3$ on Bruker AV400 instruments. Chemical shifts are reported in parts per million (ppm) and are referenced to the residual solvent resonance as the internal standard ($CHCl_3$: δ = 7.26 ppm for $^1H$ NMR and $CDCl_3$: δ = 77.0 ppm for $^{13}C$ NMR). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplett, q = quartet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were recorded on a THERMO FINNIGAN LTQ-XL. The MS inlet capillary temp was always maintained at 275 °C and capillary voltage at 5 kV. No other source gases were used when digestion was performed in microdroplets. The samples were dissolved in 1:1 methanol:water.

### *3.2. Typical Procedure for Direct Cyanation of Alcohols*

In a glove box, alcohol **1** (0.2 mmol), isocyanide **2** (0.3 mmol, 1.5 equiv), $B(C_6F_5)_3$ (10.2 mg, 20 μmol, 10 mol%), and toluene (2.0 mL) were added to an oven-dried 10 mL pressure vial. The vial was sealed and removed from the glove box. The reaction mixture

was stirred at 100 °C (oil bath) for 2–18 h. After the reaction was completed, the reaction mixture was purified by silica gel column chromatography by using petroleum ether/ethyl acetate mixture to obtain the desired nitrile **3**.

### *3.3. Procedure for the Preparation of Naproxen*

To a solution of 6-methoxy-2-naphthaldehyde (1.86 g, 10.0 mmol, 1.0 equiv) in THF (20 mL, 0.5 M), methylmagnesium bromide (4.0 mL, 12 mmol, 3.0 M, 1.2 equiv) was added. When the reaction was judged to have reached completion (as determined by TLC), sat. $NH_4Cl$ was added slowly at 0 °C, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and purified by column chromatography on silica gel to obtain **1w** (1.60 g, 80% yield).

To an oven-dried 200 mL Schlenk flask containing a magnetic stir bar under an atmosphere of nitrogen, alcohol **1w** (1.62 g, 8.0 mmol), isocyanide **2a** (1.0 g, 12 mmol, 1.5 equiv), $B(C_6F_5)_3$ (0.41 g, 0.8 mmol, 10 mol%), and toluene (80 mL) were added. The reaction mixture was stirred at 100 °C (oil bath) for 12 h. After the reaction was completed, the reaction mixture was purified by silica gel column chromatography by using petroleum ether/ethyl acetate mixture to obtain the desired nitrile **3w** (1.12 g, 66% yield).

To a suspension of **3w** (42.3 mg, 0.2 mmol, 1.0 equiv) in ethylene glycol (0.6 mL), KOH (0.1 mL, 10 M solution in $H_2O$, 5.0 equiv) was added. The reaction vessel was sealed with a rubber septum and submerged in an oil bath at 100 °C for 20 h. We then added 1M HCl (2.5 mL) dropwise, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to obtain Naproxen (31.8 mg, 69% yield).

### *3.4. Characterization Data of the Products*

**2-(4-methoxyphenyl)-2-phenylacetonitrile** (**3a**) [83]. White solid (43.8 mg, 98% yield); mp 130–132 °C; $R_f$ = 0.50 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.39–7.29 (m, 5H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.09 (s, 1H), 3.79 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.4, 136.2, 129.1, 128.9, 128.1, 127.9, 127.6, 119.9, 114.5, 55.3, 41.8 ppm.

**2-(4-methoxyphenyl)-2-(*p*-tolyl)acetonitrile** (**3b**) [83]. White solid (43.9 mg, 92% yield); mp 85–87 °C; $R_f$ = 0.50 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.25–7.15 (m, 6H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.05 (s, 1H), 3.79 (s, 3H), 2.33 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.3, 137.9, 133.2, 129.8, 128.8, 128.2, 127.5, 120.0, 114.4, 55.3, 41.4, 21.0 ppm.

**2,2-bis(4-methoxyphenyl)acetonitrile** (**3c**) [83]. White solid (41.9 mg, 83% yield); mp 156–158 °C; $R_f$ = 0.50 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.4 Hz, 4H), 6.88 (d, *J* = 8.8 Hz, 4H), 5.04 (s, 1H), 3.79 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.3, 128.7, 128.2, 120.1, 114.4, 55.3, 41.0 ppm.

**2-(4-methoxyphenyl)-2-(*o*-tolyl)acetonitrile** (**3d**) [83]. Colorless oil (44.4 mg, 93% yield); $R_f$ = 0.50 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.40–7.38 (m, 1H), 7.25 (t, *J* = 4.8 Hz, 2H), 7.20–7.17 (m, 3H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.23 (s, 1H), 3.78 (s, 3H), 2.26 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.3, 135.8, 133.8, 131.2, 128.9, 128.5, 128.4, 126.8, 126.7, 119.8, 114.4, 55.3, 39.1, 19.4 ppm. MS (ESI) *m*/*z*: $[M+H]^+$ calcd. for $C_{16}H_{16}NO$: 238.12; found: 238.18.

**2-(4-methoxyphenyl)-2-(*m*-tolyl)acetonitrile** (**3e**) [83]. Colorless oil (44.4 mg, 93% yield); $R_f$ = 0.50 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.25–7.22 (m, 3H), 7.14–7.10 (m, 3H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.04 (s, 1H), 3.78 (s, 3H), 2.33 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.3, 139.0, 136.1, 128.9, 128.84, 128.81, 128.2, 128.0, 124.6, 120.0, 114.4, 55.3, 41.7, 21.3 ppm. MS (ESI) *m*/*z*: $[M+H]^+$ calcd. for $C_{16}H_{16}NO$: 238.12; found: 238.82.

**2-(3,4-dimethylphenyl)-2-(4-methoxyphenyl)acetonitrile** (**3f**) [83]. Colorless oil (55.1 mg, 98% yield); $R_f$ = 0.50 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz,

$CDCl_3$): δ 7.24 (d, *J* = 6.8 Hz, 2H), 7.12–7.03 (m, 3H), 6.87 (d, *J* = 6.4 Hz, 2H), 5.02 (s, 1H), 3.78 (s, 3H), 2.24 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.3, 137.5, 136.6, 133.6, 130.2, 128.8, 128.7, 128.3, 124.9, 120.1, 114.4, 55.3, 41.4, 19.8, 19.4 ppm. MS (ESI) *m*/*z*: $[M+H]^+$ calcd. for $C_{17}H_{18}NO$: 252.14; found: 252.18.

**2-(4-bromophenyl)-2-(4-methoxyphenyl)acetonitrile** (**3g**) [83]. Colorless oil (49.4 mg, 82% yield); $R_f$ = 0.50 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.20 (t, *J* = 7.5 Hz, 4H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.04 (s, 1H), 3.79 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.6, 135.3, 132.2, 129.2, 128.8, 127.2, 122.2, 119.3, 114.6, 55.3, 41.2 ppm. MS (ESI) *m*/*z*: $[M+H]^+$ calcd. for $C_{15}H_{13}BrNO$: 302.02; found: 302.36.

**2-(4-methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)acetonitrile** (**3h**). Colorless oil (23.2 mg, 40% yield); $R_f$ = 0.40 (petroleum ether/EtOAc = 10/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 5.14 (s, 1H), 3.80 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.8, 140.1, 130.6 (q, *J* = 32.8 Hz), 128.9, 128.0, 126.9, 126.1 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 270.5 Hz, 1H), 119.1, 114.8, 55.3, 41.6 ppm. $^{19}$F NMR (376 MHz, $CDCl_3$) δ −62.75 (s) ppm. HRMS (MALDI-TOF/TOF) for $C_{16}H_{13}F_3NO$ $[M+H]^+$: calculated 292.0944, found 292.0947.

**Methyl 4-(cyano(4-methoxyphenyl)methyl)benzoate** (**3i**). Yellow oil (39.4 mg, 70% yield); $R_f$ = 0.50 (petroleum ether/EtOAc = 5/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.14 (s, 1H), 3.91 (s, 3H), 3.79 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 166.3, 159.6, 141.0, 130.4, 130.1, 128.9, 127.6, 127.1, 119.2, 114.7, 55.3, 52.2, 41.7 ppm. HRMS (ESI) for $C_{17}H_{16}NO_3$ $[M+H]^+$: calculated 282.1125, found 282.1126.

**2-(4-methoxyphenyl)-2-(2-nitrophenyl)acetonitrile** (**3j**) [84]. Yellow oil (10.1 mg, 19% yield); $R_f$ = 0.40 (petroleum ether/EtOAc = 10/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.69 (t, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.11 (s, 1H), 3.79 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.8, 147.7, 134.0, 130.9, 130.7, 129.5, 129.1, 126.0, 125.7, 118.8, 114.7, 55.3, 37.6 ppm.

**2-(4-methoxyphenyl)-2-(naphthalen-2-yl)acetonitrile** (**3k**) [85]. Colorless oil (53.5 mg, 98% yield). $R_f$ = 0.50 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.87–7.81 (m, 4H), 7.53–7.48 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.25 (s, 1H), 3.79 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.5, 133.4, 133.2, 132.7, 129.2, 129.0, 128.0, 127.8, 127.7, 126.7, 126.6, 126.5, 125.2, 119.8, 114.5, 55.3, 42.0 ppm.

**2-(4-methoxyphenyl)-2-(thiophen-2-yl)acetonitrile** (**3l**). Colorless oil (33.8 mg, 74% yield); $R_f$ = 0.50 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 5.2 Hz, 1H), 7.06 (d, *J* = 3.2 Hz, 1H), 6.97–6.95 (m, 1H), 6.91 (d, *J* = 8.4 Hz, 2H), 5.30 (s, 1H), 3.80 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.7, 139.1, 128.7, 127.5, 127.0, 126.5, 126.3, 119.0, 114.5, 55.3, 37.2 ppm. HRMS (MALDI-TOF/TOF) for $C_{13}H_{12}NOS$ $[M+H]^+$: calculated 230.0634, found 230.0631.

**2-(4-methoxyphenyl)propanenitrile** (**3m**) [48]. Colorless oil (23.3 mg, 72% yield); $R_f$ = 0.70 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 3.85 (q, *J* = 7.6 Hz, 1H), 3.81 (s, 3H), 1.61 (d, *J* = 7.3 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.2, 129.0, 127.8, 121.8, 114.4, 55.3, 30.4, 21.5 ppm.

**2-(4-methoxyphenyl)butanenitrile** (**3n**) [86]. Colorless oil (17.5 mg, 50% yield); $R_f$ = 0.50 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 3.81 (s, 3H), 3.68 (t, *J* = 7.2 Hz, 1H), 1.95–1.86 (m, 2H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.3, 128.4, 127.7, 121.0, 114.3, 55.3, 38.1, 29.2, 11.4 ppm.

**2-(4-methoxyphenyl)-3,3-dimethylbutanenitrile** (**3o**) [87]. White solid (31.1 mg, 76% yield); mp 50–52 °C; $R_f$ = 0.70 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, *J* = 6.8 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 3.82 (s, 3H), 3.51 (s, 1H), 1.04 (s, 9H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.3, 130.4, 125.4, 120.6, 113.6, 55.3, 48.9, 35.1, 27.3 ppm.

**2-(3,4-dimethoxyphenyl)-2-phenylacetonitrile** (**3p**) [88]. Colorless oil (37.0 mg, 73% yield); $R_f$ = 0.50 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.38–7.31 (m, 5H), 6.90–6.80 (m, 3H), 5.10 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 149.4, 148.9, 136.0, 129.1, 128.13, 128.12, 127.5, 120.1, 119.8, 111.3, 110.7, 55.89, 55.88, 42.1 ppm.

**2-([1,1′-biphenyl]-4-yl)-2-(3,4-dimethoxyphenyl)acetonitrile** (**3q**) [48]. Colorless oil (59.3 mg, 90% yield); $R_f$ = 0.50 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.60–7.55 (m, 4H), 7.45–7.39 (m, 4H), 7.37–7.33 (m, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 7.2 Hz, 2H), 5.13 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 149.5, 149.0, 141.1, 140.1, 135.0, 128.8, 128.1, 128.0, 127.8, 127.6, 127.0, 120.2, 119.8, 111.4, 110.7, 56.0, 55.9, 41.8 ppm. HRMS (MALDI-TOF/TOF) for $C_{22}H_{20}NO_2$ $[M+H]^+$: calculated 330.1489, found 330.1386.

***N*-(4-(cyano(phenyl)methyl)phenyl)benzamide** (**3r**). White solid (41.6 mg, 67% yield); mp 196–198 °C; $R_f$ = 0.50 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz, DMSO-d6): δ 10.35 (s, 1H), 7.98 (d, *J* = 7.6 Hz, 2H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.65–7.61 (m, 1H), 7.58–7.55 (m, 2H), 7.48–7.39 (m, 7H), 5.81 (s, 1H) ppm. $^{13}$C NMR (100 MHz, DMSO-d6): δ 166.5, 139.8, 137.7, 135.6, 132.5, 130.1, 129.3, 128.8, 128.7, 128.5, 128.3, 121.8, 121.3, 41.2 ppm. HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd. for $C_{21}H_{17}N_2O$: 313.1336; found: 313.1334.

**2,2-diphenylacetonitrile** (**3s**) [83]. White solid (13.1 mg, 34% yield); mp 70–72 °C; $R_f$ = 0.50 (petroleum ether/EtOAc = 15/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.39–7.30 (m, 10H), 5.14 (s, 1H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 135.9, 129.2, 128.2, 127.7, 119.6, 42.6 ppm.

**6-methoxy-1,2,3,4-tetrahydronaphthalene-1-carbonitrile** (**3t**) [48]. Colorless oil (17.5 mg, 47% yield); $R_f$ = 0.50 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.8 Hz, 1H), 6.78–6.75 (m, 1H), 6.64 (s, 1H), 3.92 (t, *J* = 6.4 Hz, 1H), 3.78 (s, 3H), 2.87–2.71 (m, 2H), 2.13–2.09 (m, 2H), 2.07–1.96 (m, 1H), 1.87–1.77 (m, 1H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.1, 137.7, 129.9, 121.9, 114.2, 112.8, 55.2, 30.1, 28.7, 27.5, 20.7 ppm.

**(*E*)-2,4-diphenylbut-3-enenitrile** (**3u**) [89]. Colorless oil (34.0 mg, 78% yield); $R_f$ = 0.50 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.42–7.26 (m, 10H), 6.81 (d, *J* = 15.6 Hz, 1H), 6.19 (dd, *J* = 16.0, 6.4 Hz, 1H), 4.69 (d, *J* = 6.4 Hz, 1H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 135.4, 134.5, 133.2, 129.2, 128.7, 128.4, 127.5, 126.7, 123.2, 118.8, 40.0 ppm.

**2-(4-methoxyphenyl)acetonitrile** (**3v**) [90]. Colorless oil (17.0 mg, 23% yield, 0.5 mmol scale); $R_f$ = 0.50 (petroleum ether/EtOAc = 15/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 3.80 (s, 3H), 3.68 (s, 2H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.3, 129.0, 121.8, 118.1, 114.5, 55.3, 22.8 ppm.

**2-(6-methoxynaphthalen-2-yl)propanenitrile** (**3w**) [91]. White solid (42.3 mg, 72% yield); mp 72–74 °C; $R_f$ = 0.70 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.76–7.72 (m, 3H), 7.38 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.18 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 4.02 (q, *J* = 7.2 Hz, 1H), 3.92 (s, 3H), 1.71 (d, *J* = 7.2 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 158.1, 134.0, 132.0, 129.3, 128.8, 127.9, 125.4, 124.9, 121.7, 119.6, 105.7, 55.3, 31.2, 21.4 ppm.

**5*H*-dibenzo[*a*,*d*][7]annulene-5-carbonitrile** (**3x**) [25]. Colorless oil (36.6 mg, 84% yield); $R_f$ = 0.50 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.35–7.28 (m, 4H), 7.11 (s, 2H), 4.72 (s, 1H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 133.9, 132.3, 131.3, 129.2, 128.6, 127.8, 125.3, 118.3, 41.1 ppm.

**2-(2,5-dimethylphenyl)-2-(4-methoxyphenyl)acetonitrile** (**3y**) [92]. Colorless oil (47.2 mg, 94% yield); $R_f$ = 0.50 (petroleum ether/EtOAc = 20/1). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.22–7.17 (m, 3H), 7.07 (s, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.20 (s, 1H), 3.79 (s, 3H), 2.33 (s, 3H), 2.21 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.3, 136.4, 133.6, 132.6, 131.1, 129.2, 129.1, 128.9, 127.1, 120.0, 114.4, 55.3, 39.1, 21.0, 18.9 ppm.

**2,2′-(oxybis((4-methoxyphenyl)methylene))bis(1,4-dimethylbenzene)** (**4y**). Colorless oil (17.9 mg, 38% yield); $R_f$ = 0.50 (petroleum ether/EtOAc = 15/1). $^1$H NMR (400

MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.39 (s, 1H), 7.20–7.18 (m, 4H), 6.98 (d, *J* = 10.8 Hz, 4H), 6.82 (t, *J* = 6.4 Hz, 4H), 5.46 (s, 1H), 5.45 (s, 1H), 3.77 (s, 6H), 2.33 (s, 3H), 2.31 (s, 3H), 1.96 (s, 6H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 158.8, 158.6, 139.9, 139.6, 135.3, 134.0, 133.8, 133.0, 132.3, 130.4, 130.2, 129.1, 128.7, 128.3, 128.0, 127.8, 127.5, 113.6, 113.5, 76.9, 76.5, 55.2, 21.2, 21.2, 18.9, 18.8 ppm. HRMS (ESI) for $C_{32}H_{34}O_3Na$ $[M+Na]^+$: calculated 489.2400, found 489.2414.

**2-(6-methoxynaphthalen-2-yl)propanoic acid (Naproxen)** [24]. White solid (31.8 mg, 69% yield); mp 156–158 °C; $R_f$ = 0.50 (petroleum ether/EtOAc/MeOH = 5/2/1). $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.70–7.67 (m, 3H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.14–7.10 (m, 2H), 3.90–3.85 (m, 4H), 1.58 (d, *J* = 6.8 Hz, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 179.9, 157.7, 135.1, 133.8, 129.3, 128.9, 127.2, 126.2, 126.1, 118.9, 105.7, 55.3, 45.3, 18.2 ppm.

## 4. Conclusions

In conclusion, by taking advantage of isonitriles as low-toxic CN surrogates in the metal-free cyanation of alcohols, an efficient and green method for the direct catalytic synthesis of α-aryl nitriles was developed (up to 98% yield). To the best of our knowledge, this is the first $B(C_6F_5)_3$-catalyzed transformation of isonitriles. Control experiments support an $S_N1$ pathway and rule out a concerted $S_N2$ mechanism. The in situ-generated ether **4** can be converted to the desired α-aryl nitriles under the current catalytic system via cleavage of the C-O bond. The use of readily available starting materials, low catalyst loading, a broad substrate scope, ease of scale-up, and application in the synthesis of the precursors for naproxen and cytenamide make this approach very practical and attractive. With these advantages, we expect that this method will find wide applications in organic synthesis.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules28052174/s1, $^1H$, $^{13}C$, $^{19}F$ and HPLC spectra.

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**Sample Availability:** Samples of the compounds **3** are available from the authors.

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