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Practical one-pot conversion of aryl bromides and β-bromostyrenes into aromatic nitriles and cinnamonitriles

Genki Ishii, Ryo Harigae, Katsuhiko Moriyama, Hideo Togo *

Graduate School of Science, Chiba University, Yayoi-cho 1-33, Inage-ku, Chiba 263-8522, Japan

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ABSTRACT

Various aryl bromides were efficiently converted into the corresponding aromatic nitriles in good yields by the treatment with Mg turnings and subsequently DMF, followed by treatment with molecular iodine and aq NH_3. The same treatment of aryl bromides, which are weakly reactive to Mg turnings, with ^{i}PrMgCl·LiCl and subsequently DMF, followed by the treatment with molecular iodine and aq NH_3 also afforded the corresponding aromatic nitriles in good yields. On the other hand, when *N*-formylpiperidine was used instead of DMF, *p*-substituted β-bromostyrenes were converted into the corresponding *p*-substituted cinnamonitriles, i.e., α,β-unsaturated nitriles, in good to moderate yields by the same procedure. The reactions were carried out by means of a simple experimental procedure and did not require any toxic metal cyanides or expensive rare metals. Therefore, the present reactions are practical and environmentally benign one-pot methods for the preparation of aromatic nitriles, cinnamonitriles, and aliphatic nitriles from aryl bromides, β-bromostyrenes, and alkyl bromides, respectively, through the formation of Grignard reagents and their DMF or *N*-formylpiperidine adducts.

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1. Introduction

Nitriles are one of the most important compounds for organic synthesis[1,2a–d] because they can be easily converted into esters, amides, carboxylic acids, amines, amidines, aldehydes, ketones, and nitrogen-containing heterocycles,[2e–o] such as tetrazoles, imidazoles, oxazoles, thiazoles, and selenazoles, and are used as pharmaceuticals, liquid crystals, and synthetic intermediates for agrochemicals, pharmaceuticals, and functional materials. For example, aromatic nitriles, such as Citalopram hydrobromide® (treatment of alcohol dependency), Periciazine® (anti-psychotic drug), Fadrozole® (oncolytic drug), Letrozole® (breast cancer therapy), Bicalutamide (prostate cancer and breast cancer therapy), and Etravirine (anti-HIV), are pharmaceutically important,[2] and 4-cyano-4′-pentylbiphenyl is one of the typical liquid crystal materials. One of the most conventional methods for the preparation of aromatic nitriles and aliphatic nitriles is the dehydration of primary aromatic amides and aliphatic amides, respectively, with $SOCl_2$, TsCl/Py, P_2O_5, $POCl_3$, $COCl_2$, or Ph_3P/CCl_4.[3] In addition, the most typical method for the preparation of aliphatic nitriles is the reaction of alkyl bromides with toxic metal cyanides through one-carbon (C_1) increase.[3] On the other hand, the conventional method for the preparation of aromatic nitriles is the Sandmeyer reaction, which uses aromatic diazonium halides and toxic CuCN.[3,4] Recently, the direct conversion of aromatic bromides into the corresponding aromatic nitriles (Rosenmund–von Braun reaction)[5] and its related reactions have been actively studied. Hitherto the reported conversion conditions include CuCN at DMF refluxing temperature,[5,6a] $Pd(OAc)_2·K_4[Fe(CN)_6]$ at 120 °C,[6b] Pd·(binaphthyl) $P(^{t}Bu)_2·Zn(CN)_2·Zn$ at 80–95 °C,[6c] $Pd_2(dba)_3·Zn(CN)_2·DPPF$ at 80–120 °C,[6d] $Pd(tmhd)_2·K_4[Fe(CN)_6]$ at 80 °C,[6e] $Zn(CN)_2·Pd_2(dba)_3$ at 100 °C,[6f] $Pd/C·CuI·K_4[Fe(CN)_6]·3H_2O$ at 130–140 °C,[6g] CuI-·alkylimidazole·Pd/C·CuI·$K_4[Fe(CN)_6]$ at 140–180 °C,[6h] $Zn(CN)_2·Pd_2(dba)_3·dppf·Zn·ZnBr_2$ at 95 °C,[6i] $CuO·Pd·K_4[Fe(CN)_6]$ at 120 °C,[6j] $Pd(OAc)_2·Cu(OAc)_2·K_4[Fe(CN)_6]$ at 130 °C,[6k] $CuI·K_4[Fe(CN)_6]$ at 175 °C,[6l] $Pd(dba)_2·K_4[Fe(CN)_6]$ at 50 °C,[6m] $P[(NC_5H_{10})(C_6H_{11})_2PdCl_2·K_4[Fe(CN)_6]$ at 140 °C,[6n] $Pd(Ph_3P)_4·DBU·K_4[Fe(CN)_6]$ at 85 °C,[6o] $Pd\{C_6H_4[CH_2N(CH_2Ph)_2](\mu\text{-}Br)_2\}·K_4[Fe(CN)_6]$ at 130 °C,[6p] and $\{[P[(NC_5H_{10})(C_6H_{11})_2]_2PdCl_2]·K_4[Fe(CN)_6]$ at 140 °C.[6q] However, those reactions require toxic metal cyanides and/or expensive rare metals, such as Pd, at high temperature. As metal-cyanide-free methods, the reaction of aryl bromide with $Cu(OAc)_2·DMF·TMEDA$ at 150 °C,[6r] the reaction of 3-iodoindoles, which are formed from indoles and NH_4I, with $Cu(CF_3CO_2)_2·DMF$ at 130 °C,[6s] and the reaction of aryl bromides with $Cu(OAc)_2·Ag_2O·Ph_3PO·CH_3CN$ at

* Corresponding author. E-mail address: togo@faculty.chiba-u.jp (H. Togo).

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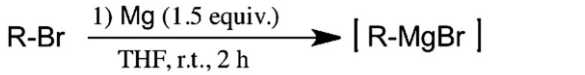
125 °C[6t] were reported. On the other hand, the reactions of aryl Grignard reagents with organic cyanation reagents, such as *N*-cyanobenzimidazole[7a] and *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide,[7b] which are not commercially available compounds, and *p*-toluenesulfonyl cyanide,[7c] which is commercially available, but very expensive, were reported. Given the above situation for the preparation of aromatic nitriles and aliphatic nitriles, simple, practical, less toxic, and conventional methods for the preparation of aromatic nitriles, cinnamonitriles, and aliphatic nitriles from aryl bromides, β-bromostyrenes, and alkyl bromides, respectively, using low-cost and safe reagents are of urgent demand. On the other hand, molecular iodine is one of the simplest oxidants currently available. It is highly affordable and has very low toxicity. From the standpoint of environmentally benign organic synthesis, molecular iodine has been used in various organic reactions, including the oxidation of alcohols or aldehydes to esters, the introduction of protecting groups, the deprotection of protecting groups, iodocyclization, carbon–carbon bond formation, and the formation of heterocycles.[8] Recently, we reported a direct, efficient, practical, and low-toxicity method for the oxidative conversion of benzylic alcohols and benzylic halides into their corresponding aromatic nitriles using molecular iodine and aq NH_3.[9b,c,9g–i,l] The same treatment of aliphatic alcohols and alkyl halides with molecular iodine and aq NH_3 also generated the corresponding aliphatic nitriles in good yields, although a long reaction time was required.[9b,c,g–i,l] In those reactions, aromatic aldehydes could be also smoothly converted into the corresponding aromatic nitriles with molecular iodine and aq NH_3.[9b,g,10] Esters and amides were also directly converted into the corresponding nitriles using DIBAL-H (di-*iso*-butylaluminium hydride) or SDBBA-H (DIBAL-H·^{t}BuONa: sodium di(*iso*-butyl)-*tert*-butoxy-aluminum hydride), followed by the treatment with molecular iodine and aq NH_3, via the formation of hemiacetal intermediates and hemiaminal intermediates, respectively.[9o,q] More recently, we reported the reaction of aryl bromides with *n*-BuLi and subsequently DMF, followed by the reaction with molecular iodine and aq NH_3 to generate the corresponding aromatic nitriles in good yields.[11] This reaction is very useful as it can be carried out at room temperature using less toxic commercially available reagents. However, this reaction is limited to the preparation of aromatic nitriles that do not bear nucleophile-sensitive functional groups, such as an ester and a nitrile. In view of industrial utilization, safer and more easily available reagent instead of *n*-BuLi is desired. The use of aryl bromides and alkyl bromides with Mg[12] for the preparation of aromatic nitriles and aliphatic nitriles, respectively, is very attractive and their scale-up reaction can be easily carried out. As part of our studies on the use of molecular iodine for organic synthesis,[9] we would like to report herein a simple, practical, less toxic, low-cost, and conventional method for the preparation of aromatic nitriles, cinnamonitriles, and aliphatic nitriles from aryl bromides, β-bromostyrenes, and alkyl bromides, respectively, in detail.[13]

2. Results and discussion

Mg turnings were added to a solution of 1-bromo-4-methylbenzene in THF at room temperature. After 2 h, DMF was added and the obtained mixture was stirred for 2 h at 0 °C. Then, aq NH_3 (28–30%) and I_2 were added and the obtained mixture was further stirred for 2 h at room temperature to provide 4-methyl-1-benzonitrile in 82% yield, as shown in Table 1 (entry 1). After removal of ether from the ether extract of the reaction mixture, the purity of 4-methyl-1-benzonitrile was estimated to be over 85%. The same treatment of 1-bromo-3-methylbenzene, 1-bromo-2-methylbenzene, 1-bromo-2,4-dimethylbenzene, 1-bromo-3,4-dimethyl-benzene, 1-bromo-2,5-dimethylbenzene, 1-bromo-2,4,6-tri

Table 1
Transformation of aryl and alkyl bromides into aromatic and aliphatic nitriles



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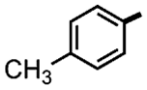
1		82
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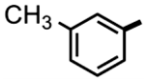
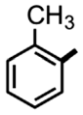
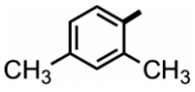
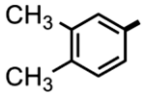
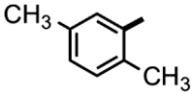
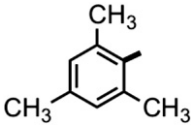
3		73
4		67
5		62
6		74
7		80
8		79
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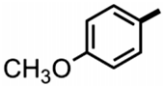
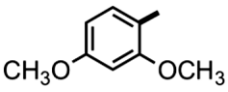
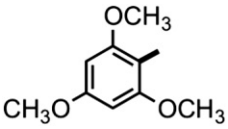
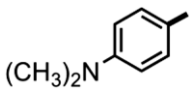
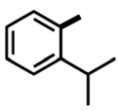
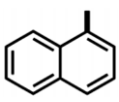
10		84
11		77
12		64
13		62
14		68
15		62

(*continued on next page*)

Table 1 (*continued*)

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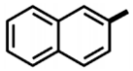
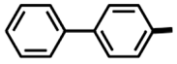
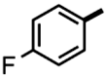
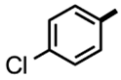
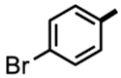
16		65
17		64
18		69
19		61
20		63
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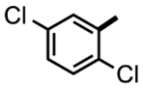
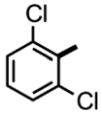
22		72
23		72
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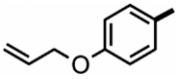
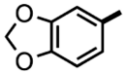
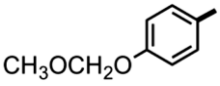
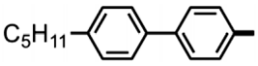
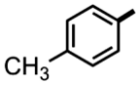
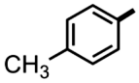
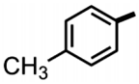
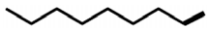
25		71
26		62
27		83
28[c]		80
29[d]		80
30[e]		0
31[f]		75
32		60

Table 1 (*continued*)

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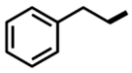
33		62

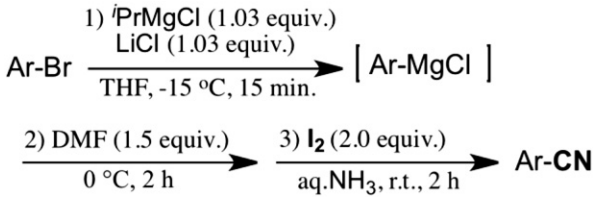
[a] Yield was calculated based on aryl or alkyl halide, and isolated yield of nitrile was shown.
[b] *N*-Formylpiperidine (1.5 equiv) instead of DMF was used.
[c] I_2 (0.05 g) was added and the mixture was heated to 70 °C at first step reaction.
[d] *p*-Iodotoluene was used instead of *p*-bromotoluene.
[e] *p*-Chlorotoluene was used and LiBr (1.2 equiv) was added at first step reaction.
[f] *p*-Bromotoluene (30 mmol) was used.

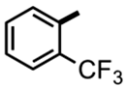
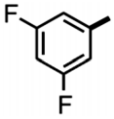
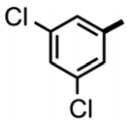
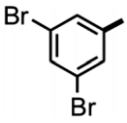
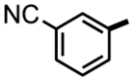
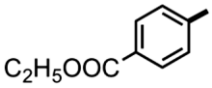
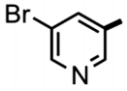
methylbenzene, 1-bromo-4-methoxy-benzene, 1-bromo-2,4-dimethoxybenzene, 1-bromo-2,4,6-trimethoxybenzene, 1-bromo-4-(*N*,*N*-dimethylamino)-benzene, and 1-bromo-2-isopropylbenzene gave the corresponding aromatic nitriles, respectively, in good yields (Table 1, entries 3–8, 10–14). Using the same procedure, 1-bromonaphthalene, 2-bromonaphthalene, and 4-bromobiphenyl also provided the corresponding aromatic nitriles in good yields (Table 1, entries 15–17). In addition, the same treatment of aromatic halides, such as 1-bromo-4-fluorobenzene, 1-bromo-4-chlorobenzene, 1,4-dibromobenzene, 1-bromo-2,5-dichlorobenzene, and 1-bromo-2,6-dichlorobenzene, generated 4-fluoro-1-benzonitrile, 4-chloro-1-benzonitrile, 4-bromo-1-benzonitrile, 2,5-dichloro-1-benzonitrile, and 2,6-dichloro-1-benzonitrile, respectively, in good yields (entries 18–20, 22, 23). When *N*-formylpiperidine instead of DMF was used under the same conditions, the corresponding aromatic nitriles were obtained in similar yields to that with DMF (entries 2, 9, 21). The same treatment of bromoarenes bearing an allyl group and an acetal group afforded the corresponding aromatic cyanides in good yields without affect to those functional groups (entries 25–27). Moreover, treatment of 1-bromo-4′-pentylbiphenyl with Mg turnings and then DMF, followed by the reaction with molecular iodine and aq NH_3 under the same conditions, generated 4′-pentyl-1-cyanobiphenyl, which is one of the typical liquid crystal materials, in 80% yield (entry 28). 4-Methyl-1-iodobenzene reacted smoothly with Mg turnings and then DMF, and treatment of the adduct with molecular iodine and aq NH_3 furnished 4-methyl-1-benzonitrile in 80% yield (entry 29). Meanwhile, the same treatment of 1-chloro-4-methylbenzene did not generate 4-methyl-1-benzonitrile at all because no Grignard reagent was formed under the present reaction conditions (entry 30). The large-scale treatment of 1-bromo-4-methylbenzene (30 mmol) with Mg turnings and then DMF, followed by the reaction with molecular iodine and aq NH_3 could be also accomplished to generate 4-methyl-1-benzonitrile in good yield (entry 31). The same treatment of aliphatic nitriles, such as 1-bromooctane and 1-bromo-2-phenylethane, provided the corresponding aliphatic nitriles in 60% and 62% (entries 32, 33), respectively.

Those aliphatic nitriles are the same as those produced in the S_N2 reaction of 1-bromooctane and 1-bromo-2-phenylethane with NaCN. However, the present reaction does not require toxic NaCN.

Electron-deficient aromatic bromides, such as 1-bromo-3-cyanobenzene, and ethyl 4-bromo-1-benzoate did not react with Mg turnings or Mg turnings with LiCl. Therefore, to extend the applicability of the present reaction, an aromatic bromide-^{i}PrMgCl·LiCl exchange reaction to generate the corresponding Grignard reagents was used based on the literature method.[14] Bromo-2-trifluoromethylbenzene, 1-bromo-3,5-difluorobenzene, 1-bromo-3,5-dichlorobenzene, 1,3,5-tribromobenzene, 1-bromo-3-cyanobenzene, ethyl 4-iodo-1-benzoate, 3-bromopyridine, and 3,5-dibromopyridine were treated with ^{i}PrMgCl·LiCl in THF at −15 °C and then DMF at 0 °C, followed by the reaction with molecular iodine and aq NH_3 to provide the corresponding aromatic nitriles in good to moderate yields, as shown in Table 2.

Table 2
Transformation of aryl bromides into aromatic nitriles



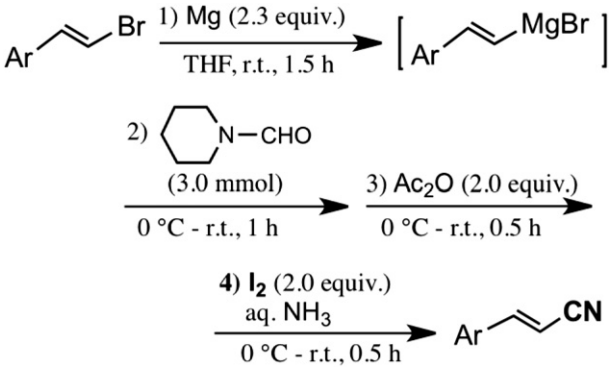
Entry	R	Yield[a] (%)
1		63
2		82
3		72
4		75
5		71
6[b]		95
7		52
8		68

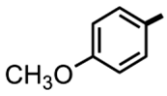
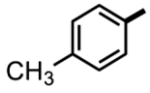
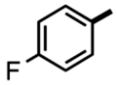
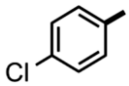
[a] Yield was calculated based on aryl halide, and isolated yield of nitrile was shown.
[b] Ethyl *p*-iodobenzoate was used instead of ethyl *p*-bromobenzoate.

The same treatment of ethyl 4-bromo-1-benzoate did not generate ethyl 4-cyanobenzoate at all because the aromatic bromide-^{i}PrMgCl·LiCl exchange reaction did not occur at the present reaction conditions. Thus, the present reaction can be used for the preparation of electron-deficient aromatic nitriles bearing chloro, bromo, trifluoromethyl, cyano, and ester groups.

Moreover, β-bromostyrene in THF was treated with Mg turnings at room temperature to generate the corresponding Grignard reagent. Then, DMF was added and the formed adduct was treated with molecular iodine and aq NH_3 to generate cinnamonitrile, i.e., α,β-unsaturated nitrile, in only 3% yield, as shown in Table 3 (entry 1). This is due to the Michael-type addition of dimethylamine to the formed cinnamonitrile, in the reaction with molecular iodine and aq NH_3. Based on studies aimed at optimizing the reaction conditions, it was found that *N*-formylpiperidine was a better reagent than DMF (entries 2, 3), and the secondary amines formed from

Table 3
Transformation of α-alkenyl bromides into α,β-unsaturated nitriles

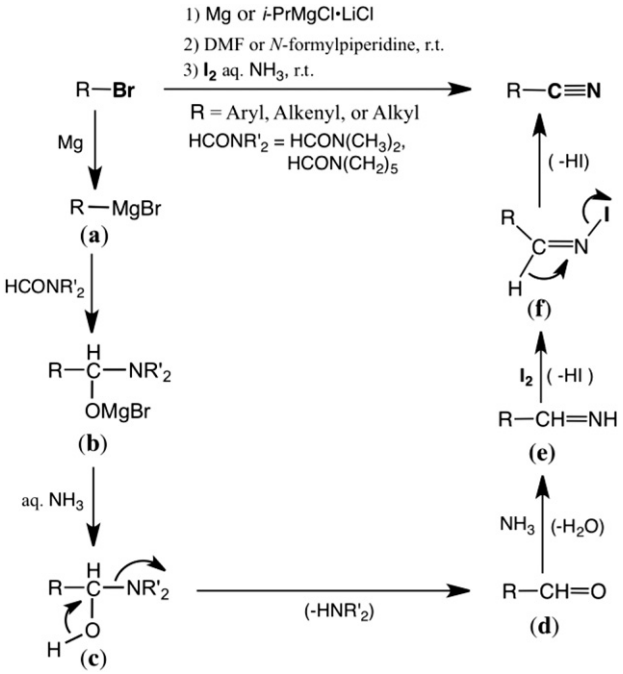


Entry	Ar	Yield[a] (%)
1[b]		3
2[c]		69
3		83
4		81
5[d]		75
6[e]		54
7		60

[a] Yield was calculated based on DMF or *N*-formylpiperidine, and isolated yield of nitrile was shown.
[b] Without addition of Ac_2O at the third step.
[c] DMF (3.0 mmol) instead of *N*-formylpiperidine was used.
[d] Reaction was carried out under the dark conditions at the third-step and fourth-step reactions.
[e] LiCl (2.3 equiv) was added at the first-step reaction.

DMF or *N*-formylpiperidine should be trapped by Ac_2O to form the corresponding acetamides prior to the addition of molecular iodine and aq NH_3 (the third step), providing cinnamonitirile in good yield. With the optimal conditions in hand, *p*-methoxy, *p*-methyl, *p*-fluoro, and *p*-chloro substituted β-bromostyrenes were treated with Mg turnings and then *N*-formylpiperidine. This was followed by the reaction with molecular iodine and aq NH_3 to give the corresponding *p*-substituted cinnamonitriles, i.e., α,β-unsaturated nitriles, in good to moderate yields (entries 4–7).

A plausible reaction mechanism is shown in Scheme 1. The initial step is the formation of Grignard reagent (**a**) by the reaction of aromatic bromide, β-bromostyrene, or aliphatic bromide with Mg turnings. Then, the Grignard reagent (**a**) reacts with DMF or *N*-formylpiperidine to generate adduct (**b**). The addition of molecular iodine and aq NH_3 induces the formation of dimethylamine or piperidine, and imine (**e**), which further reacts with molecular iodine to form *N*-iodo imine (**f**), through the formations of hemiaminal (**c**) and aldehyde (**d**). Once *N*-iodo imine (**f**) is formed, HI elimination smoothly occurs by the reaction with NH_3 to generate an aromatic nitrile, a cinnamonitrile, or an aliphatic nitrile.



Scheme 1. Possible reaction pathway for nitrile.

3. Conclusion

Various aromatic bromides, such as bromotoluenes, bromodimethylbenzenes, bromotrimethylbenzene, bromomethoxybenz ene, bromodimethoxybenzene, bromotrimethoxybenzene, bromo(*N*,*N*-dimethylamino)-benzene, bromonaphthalenes, bromobiphenyl, bromobenzenes bearing fluoro, chloro, bromo, allyl, and acetal groups, and bromopyridine, could be smoothly converted into the corresponding aromatic nitriles in good yields by treatment with Mg turnings and subsequently DMF or *N*-formylpiperidine, followed by treatment with molecular iodine and aq NH_3. Aliphatic bromides could be also converted into the corresponding aliphatic nitriles in good yields by the same procedure. Moreover, electron-deficient aromatic bromides, such as 1-bromo-2-trifluoromethylbenzene, 1-bromo-3-cyanobenzene, ethyl 4-iodo-1-benzoate, 3-bromopyridine, and 3,5-dibromopyridine, were treated with ^{i}PrMgCl·LiCl and then DMF, followed by the reaction with molecular iodine and aq NH_3 to provide the corresponding aromatic nitriles in good to moderate yields. In addition, the same treatment of *p*-substituted β-bromostyrenes with Mg turnings and then *N*-formylpiperidine, followed by the reaction with Ac_2O and then with molecular iodine and aq NH_3 gave the corresponding *p*-substituted cinnamonitriles, i.e., α,β-unsaturated nitriles, in good to moderate yields. The scale-up preparation of aromatic nitrile from aromatic bromide with the present method was easily achieved. Therefore, the present reactions are practical and environmentally benign one-pot methods for the preparation of aromatic nitriles, cinnamonitriles, and aliphatic nitriles from aryl bromides, β-bromostyrenes, and alkyl bromides, respectively, through the formation of Grignard reagents and their DMF or *N*-formylpiperidine adducts.

4. Experimental section

4.1. General

^{1}H NMR spectra were recorded with JEOL-JNM-ECX400, JEOL-JNM-ECS400, and JEOL-JNM-ECA500 spectrometers. Chemical shifts are expressed in parts per million downfield from TMS in δ units. Mass spectra were recorded on JMS-T100GCV, JMS-HX110, and Thermo LTQ Orbitrap XL spectrometers. IR spectra were measured with a JASCO FT-IR4100 spectrometer. Melting points were determined on an YAMATO Melting Point electrothermal apparatus MP-21 in open capillary tubes and are uncorrected. Kieselgel 60 F_{254} (Merck) was used for TLC and Silica gel 60 (Kanto Kagaku Co.) was used for column chromatography.

4.2. Typical experimental procedure for conversion of aromatic bromides into aromatic nitriles with Mg, DMF, I_2, and aq NH_3

To a flask containing Mg turnings (0.29 g, 12 mmol) was added 1-bromo-4-methylbenzene (1.37 g, 8.0 mmol) in THF (8 mL) at room temperature. After being stirred for 2 h, DMF (1.3 mL, 12 mmol) was added to the reaction mixture. The obtained mixture was stirred for 2 h at 0 °C. Then, aq NH_3 (7 mL, 28–30%) and I_2 (4.06 g, 16 mmol) were added to the reaction mixture. After being stirred for 2 h at room temperature, the reaction mixture was poured into satd aq Na_2SO_3 solution and was extracted with $CHCl_3$ (3×30 mL). The organic layer was dried over Na_2SO_4 and filtered. After removal of the solvent, the residue was purified by short column chromatography on silica gel (eluent: hexane/ethyl acetate=9:1, v/v) to provide pure 4-methyl-1-benzonitrile (0.77 g) in 82% yield.

4.3. Typical experimental procedure for conversion of aromatic bromides into aromatic nitriles with ^{i}PrMgCl, DMF, I_2, and aq NH_3

To a flask containing dried LiCl (0.35 g, 8.24 mmol) was added ^{i}PrMgCl (2 M in THF, 4.1 mL) and THF (5 mL) at −15 °C. After being stirred for 15 min, 3-bromo-1-benzonitrile (1.46 g, 8.03 mmol) in THF (1 mL) was added to the reaction mixture and the obtained mixture was stirred for 15 min. Then, DMF (1.3 mL, 12 mmol) was added at 0 °C and the mixture was stirred for 2 h. Then, aq NH_3 (7 mL, 28–30%) and I_2 (4.06 g, 16 mmol) were added to the reaction mixture. After being stirred for 2 h at room temperature, the reaction mixture was poured into satd aq Na_2SO_3 solution and was extracted with $CHCl_3$ (3×30 mL). The organic layer was dried over Na_2SO_4 and filtered. After removal of the solvent, the residue was purified by short column chromatography on silica gel (eluent: hexane/ethyl acetate=9:1, v/v) to provide pure 1,3-dicyanobenzene (0.73 g) in 71% yield.

Most nitriles mentioned in this work are commercially available and were identified by comparison with the authentic samples.

4.3.1. 4-Methyl-1-benzonitrile. Mp 26–28 °C (commercial, mp 26–28 °C); IR (Nüjol): 2227 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.52 (d, *J*=8.1 Hz, 2H), 7.26 (d, *J*=8.1 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=143.6, 131.9, 129.7, 119.1, 109.2, 21.7.

4.3.2. 3-Methyl-1-benzonitrile. Colorless oil (commercial); IR (neat): 2229 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.47–7.32 (m, 4H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=139.0, 133.4, 132.2, 129.0, 128.8, 118.8, 111.9, 20.8.

4.3.3. 2-Methyl-1-benzonitrile. Colorless oil (commercial); IR (neat): 2225 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.58 (d, *J*=7.6 Hz, 1H), 7.48 (t, *J*=7.6 Hz, 1H), 7.31 (d, *J*=7.6 Hz, 1H), 7.26 (t, *J*=7.6 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=141.5, 132.3, 132.1, 130.0, 126.0, 117.8, 112.3, 20.0.

4.3.4. 2,4-Dimethyl-1-benzonitrile. Mp 23–24 °C (commercial, mp 23–25 °C); IR (neat): 2221 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.43

(d, J=8.0 Hz, 1H), 7.10 (s, 1H), 7.05 (d, J=8.0 Hz, 1H), 2.47 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=143.4, 141.6, 132.2, 130.9, 126.9, 118.3, 109.5, 21.6, 20.2.

4.3.5. 3,4-Dimethyl-1-benzonitrile. Mp 63–64 °C (commercial, mp 64–67 °C); IR (Nüjol): 2224 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.41 (s, 1H), 7.39 (d, J=7.8 Hz, 1H), 7.21 (d, J=7.8 Hz, 1H), 2.32 (s, 3H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=142.4, 137.8, 132.8, 130.2, 129.6, 119.3, 109.4, 20.1, 19.5.

4.3.6. 2,5-Dimethyl-1-benzonitrile. Colorless oil (commercial); IR (neat): 2227 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.36 (s, 1H), 7.27 (d, J=7.9 Hz, 1H), 7.18 (d, J=7.9 Hz, 1H), 2.48 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=138.4, 135.8, 133.3, 132.3, 129.8, 118.0, 112.2, 20.3, 19.6.

4.3.7. 2,4,6-Trimethyl-1-benzonitrile. Mp 50–51 °C (commercial, mp 54–55 °C); IR (Nüjol): 2218 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=6.93 (s, 2H), 2.48 (s, 6H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=142.7, 141.9, 128.1, 117.6, 110.2, 21.5, 20.6.

4.3.8. 4-Methoxy-1-benzonitrile. Mp 54–55 °C (commercial, mp 57–59 °C); IR (Nüjol): 2216 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.59 (d, J=8.9 Hz, 2H), 6.95 (d, J=8.9 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=55.5, 103.8, 114.7, 119.2, 133.9, 162.8.

4.3.9. 2,4-Dimethoxy-1-benzonitrile. Mp 93–94 °C (commercial, mp 93–94 °C); IR (Nüjol): 2219 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.48 (d, J=8.5 Hz, 1H), 6.51 (d, J=8.5 Hz, 1H), 6.46 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=164.6, 162.8, 134.8, 116.9, 105.7, 98.4, 93.8, 55.9, 55.6.

4.3.10. 2,4,6-Trimethoxy-1-benzonitrile. Mp 139–140 °C (commercial, mp 143–145 °C); IR (Nüjol): 2212 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=6.09 (s, 2H), 3.88 (s, 6H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=165.3, 163.8, 114.6, 90.3, 84.0, 56.0, 55.6.

4.3.11. 4-(N,N-Dimethylamino)-1-benzonitrile. Mp 74–75 °C (commercial, mp 75 °C); IR (Nüjol): 2210 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.47 (d, J=9.1 Hz, 2H), 6.64 (d, J=9.1 Hz, 2H), 3.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=152.4, 133.3, 120.7, 111.3, 97.2, 39.9.

4.3.12. 2-Isopropyl-1-benzonitrile. Colorless oil (lit.[15]); IR (neat): 2222 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.60 (dd, J=7.6, 1.2 Hz, 1H), 7.54 (td, J=7.6, 1.2 Hz, 1H), 7.39 (d, J=7.5 Hz, 1H), 7.27 (td, J=7.6, 1.2 Hz, 1H), 3.39 (sep, J=6.9 Hz, 1H), 1.32 (d, J=9.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=152.4, 133.0, 132.8, 126.7, 125.9, 118.1, 111.6, 32.4, 23.2; HRMS (APCI) Calcd for $C_{10}H_{12}N$ 146.0970. Found 146.0967.

4.3.13. 1-Naphthonitrile. Mp 35–36 °C (commercial, mp 36–38 °C); IR (Nüjol): 2219 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=8.22 (d, J=8.2 Hz, 1H), 8.05 (d, J=8.2 Hz, 1H), 7.91 (d, J=7.9 Hz, 1H), 7.89 (d, J=7.9 Hz, 1H), 7.67 (t, J=8.2 Hz, 1H), 7.59 (t, J=8.2 Hz, 1H), 7.49 (t, J=7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=133.2, 132.8, 132.5, 132.2, 128.5, 128.4, 127.4, 124.9, 124.8, 117.7, 110.0.

4.3.14. 2-Naphthonitrile. Mp 68–70 °C (commercial, mp 66–70 °C); IR (Nüjol): 2225 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=8.24 (s, 1H), 7.93–7.88 (m, 3H), 7.68–7.58 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=134.6, 134.1, 132.2, 129.2, 129.0, 128.4, 128.0, 127.6, 126.3, 119.2, 109.3.

4.3.15. 4-Cyanobiphenyl. Mp 85–88 °C (commercial, mp 85–87 °C); IR (Nüjol): 2225 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.73 (d, J=8.8 Hz, 2H), 7.69 (d, J=8.8 Hz, 2H), 7.59 (d, J=7.3 Hz, 2H), 7.49 (t, J=7.3 Hz, 2H), 7.44 (t, J=7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=145.6, 139.0, 132.5, 129.0, 128.6, 127.6, 127.1, 118.9, 110.8.

4.3.16. 4-Fluoro-1-benzonitrile. Colorless oil (commercial); IR (neat): 2232 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.70 (dd, J_{H-F}=5.2 Hz, J_{H-H}=9.0 Hz, 2H), 7.20 (tt, J_{H-F}=8.6 Hz, J_{H-H}=9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=165.0 (J_{C-F}=130 Hz), 134.7 (J_{C-F}=10.0 Hz), 118.0, 116.8 (J_{C-F}=2.2 Hz), 108.6.

4.3.17. 4-Chloro-1-benzonitrile. Mp 92–95 °C (commercial, mp 90–93 °C); IR (Nüjol): 2226 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.61 (d, J=8.8 Hz, 2H), 7.48 (d, J=8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=139.5, 133.3, 129.6, 117.9, 110.7.

4.3.18. 4-Bromo-1-benzonitrile. Mp 106–107 °C (commercial, mp 113 °C); IR (Nüjol): 2224 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.64 (dt, J=8.6, 2.1 Hz, 2H), 7.53 (dt, J=8.9, 2.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=133.4, 132.6, 128.0, 118.0, 111.2.

4.3.19. 2,5-Dichloro-1-benzonitrile. Mp 122–125 °C (commercial, mp 128–132 °C); IR (Nüjol): 2230 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.66 (d, J=2.6 Hz, 1H), 7.52 (dd, J=10.0, 2.6 Hz, 1H), 7.46 (d, J=10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=135.3, 134.1, 133.5, 133.3, 131.2, 114.7 (2C).

4.3.20. 2,6-Dichloro-1-benzonitrile. Mp 142–145 °C (commercial, mp 143–146 °C); IR (Nüjol): 2231 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.50–7.42 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=138.5, 133.8, 128.1, 114.5, 113.3.

4.3.21. 2-Cyanothiophene. Colorless oil (commercial); IR (neat): 2222 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.65 (d, J=3.8 Hz, 1H), 7.62 (d, J=5.0 Hz, 1H), 7.75 (dd, J=5.0, 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=137.3, 132.5, 127.6, 114.2, 109.8.

4.3.22. 4-Allyloxy-1-benzonitrile. Mp 42–44 °C (lit.,[16] mp 43–44 °C); IR (Nüjol): 2214 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz); δ=7.58 (dt, J=9.0, 2.4 Hz, 2H), 6.96 (dt, J=8.8, 2.4 Hz, 2H), 6.00–6.10 (m, 1H), 5.42 (dq, J=17.2, 1.5 Hz, 1H), 5.34 (dq, J=10.4, 1.3 Hz, 1H), 4.59 (dt, J=5.5, 1.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=161.8, 113.9, 132.0, 119.7, 118.5, 115.4, 104.0, 69.0; HRMS (APCI) Calcd for $C_{10}H_{10}NO$ (M + H) 169.0762. Found 169.0757.

4.3.23. Piperonylonitrile. Mp 89–92 °C (commercial, mp 93–95 °C); IR (Nüjol): 2222 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.21 (dd, J=8.0, 1.7 Hz, 1H), 7.04 (d, J=1.7 Hz, 1H), 6.87 (d, J=8.0, 1H), 6.07 (s, 2H): ^{13}C NMR ($CDCl_3$, 125 MHz); δ=151.5, 148.0, 128.2, 188.8, 111.4, 109.1, 104.9, 102.2.

4.3.24. 4-(Methoxymethoxy)-1-benzonitrile. Colorless oil (lit.[17]); IR (neat): 2225 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.59 (dt, J=8.4, 2.0 Hz, 2H), 7.10 (dt, J=8.4, 2.3 Hz, 2H), 5.22 (s, 2H), 3.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=160.5, 133.9, 119.0, 116.7, 105.0, 94.1, 56.3; HRMS (APCI) Calcd for $C_9H_{10}NO_2$ (M + H) 164.0712. Found 164.0706.

4.3.25. 4-Cyano-4′-pentylbiphenyl. Colorless oil (commercial, mp 23 °C); IR (neat): 2226 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.69 (q, J=8.0 Hz, 4H) 7.51 (d, J=8.4 Hz, 2H) 7.29 (d, J=8.4 Hz, 2H), 2.68 (t, J=7.7 Hz, 2H), 1.65 (quint, J=7.5 Hz, 2H), 1.40–1.31 (m, 4H), 0.90 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=145.6, 143.8, 136.4, 132.5, 129.2, 127.4, 127.0, 119.0, 110.5, 35.6, 31.5, 31.1, 22.5, 14.0.

4.3.26. Nonanecarbonitrile. Colorless oil (commercial); IR (neat): 2247 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.40 (t, J=7.3 Hz, 2H), 1.60 (quint, J=7.3 Hz, 2H), 1.50 (quint, J=7.3 Hz, 2H), 1.2–1.4 (m, 8H), 0.90

(t, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=119.6, 31.7, 29.4, 28.8, 28.6, 25.1, 22.5, 16.9, 13.9.

4.3.27. 3-Phenylpropanenitrile. Colorless oil (commercial); IR (neat): 2212 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.49–7.20 (m, 5H), 2.94 (t, J=7.4 Hz, 2H), 2.61 (t, J=7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=133.5, 128.8, 128.2, 127.2, 118.1, 31.6, 19.3.

4.3.28. 2-(Trifluoromethyl)-1-benzonitrile. Colorless oil (commercial); IR (neat): 2235 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.86 (dt, J=7.4, 0.6 Hz, 1H), 7.82 (dt, J=8.0, 0.7 Hz, 1H), 7.75 (td, J=7.8, 0.6 Hz, 1H), 7.70 (td, J=7.6, 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=134.7, 132.9 (d, J=6.7 Hz), 132.2, 126.7 (t, J=12.0 Hz), 123.7, 121.0, 115.4, 110.1.

4.3.29. 3,5-Difluoro-1-benzonitrile. Mp 83–85 °C (commercial, mp 85–89 °C); IR (Nüjol): 2234 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz); δ=7.22 (dt, J=6.9, 2.4 Hz, 2H), 7.11 (tt, J=8.6, 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=162.8 (dd, J=253.7, 12.4 Hz), 116.5, 115.6 (m), 114.5, 109.4 (t, J=24.8 Hz).

4.3.30. 3,5-Dichloro-1-benzonitrile. Mp 65–67 °C (commercial, mp 66–69 °C); IR (Nüjol): 2236 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.62 (t, J=1.9 Hz, 1H), 7.55 (d, J=0.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=136.2, 133.4, 130.2, 116.2, 114.9.

4.3.31. 3,5-Dibromo-1-benzonitrile. Mp 95–96 °C (commercial, mp 98 °C); IR (Nüjol): 2234 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.92 (t, J=1.8 Hz, 1H), 7.74 (d, J=1.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=138.8, 133.4, 123.6, 115.9, 115.4.

4.3.32. Isophthalonitrile. Mp 160–161 °C (commercial, mp 162 °C); IR (Nüjol): 2240 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.97 (t, J=0.8 Hz, 1H), 7.91 (dd, J=8.1, 1.8 Hz, 2H), 7.66 (t, J=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=136.0, 135.4, 130.3, 116.6, 114.2.

4.3.33. Ethyl 4-cyano-1-benzoate. Mp 50–52 °C (commercial, mp 52–54 °C); IR (Nüjol): 2227, 1718 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=8.14 (d, J=6.8 Hz, 2H), 7.72 (d, J=6.1 Hz, 2H), 4.42 (q, J=7.2 Hz, 2H), 1.41 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=164.8, 134.2, 132.1, 130.0, 117.9, 116.2, 61.7, 14.1.

4.3.34. 3-Cyanopyridine. Mp 49–52 °C (commercial, mp 48–53 °C); IR (Nüjol): 2228 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=8.91 (t, J=2.0 Hz, 1H), 8.83 (d, J=4.3 Hz, 1H), 8.00–7.96 (m, 1H), 7.48–7.43 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=153.0, 152.5, 139.2, 123.6, 116.5, 110.1.

4.3.35. 3-Bromo-5-cyanopyridine. Mp 100–101 °C (commercial, mp 104–105 °C); IR (Nüjol): 2234 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=8.90 (d, J=2.1 Hz, 1H), 8.81 (d, J=1.6 Hz, 1H), 8.11 (t, J=2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=154.5, 150.3, 141.3, 120.6, 115.0, 111.2.

4.4. Typical experimental procedure for conversion of β-bromostyrenes to cinnamonitriles with Mg, *N*-formylpiperidine, I_2, and aq NH_3

β-Bromostyrene (1.10 g, 6.0 mmol) in THF (7.5 mL) was added to a flask containing Mg turnings (0.17 g, 6.9 mmol) at room temperature. After being stirred for 1.5 h, *N*-formylpiperidine (0.34 g, 3.0 mmol) in THF (2 mL) was added to the reaction mixture at 0 °C and the obtained mixture was stirred for 1 h at room temperature. Then, acetic anhydride (0.6 mL, 6.0 mmol) was added to the reaction mixture at 0 °C and the mixture was stirred for 0.5 h at room temperature. Then, aq NH_3 (6 mL, 28–30%) and I_2 (1.53 g, 6.0 mmol) were added to the reaction mixture at 0 °C and the obtained mixture was stirred for 0.5 h at room temperature. Then, the reaction mixture was quenched with satd aq Na_2SO_3 and was extracted with $CHCl_3$ (3×20 mL). The organic layer was dried over Na_2SO_4 and filtered. After removal of the solvent, the residue was purified by short column chromatography on silica gel (eluent: hexane/ethyl acetate=9:1, v/v) to provide pure cinnamonitrile (0.32 g) in 83% yield.

4.4.1. (E)-4-Methoxycinnamonitrile. Mp 59–61 °C (lit.,[18] mp 58–60 °C); IR (ATR): 2213 cm^{-1}; ^{1}H NMR ($CDCl_3$: 500 MHz) δ=7.40 (d, 2H, J=6.9 Hz), 7.33 (d, J=16.6 Hz, 1H), 6.91 (d, J=6.9 Hz, 2H), 5.72 (d, J=16.6 Hz, 1H), 3.85 (s, 3H),; ^{13}C NMR (125 MHz, $CDCl_3$) δ=162.2, 150.0, 129.1, 126.4, 118.7, 114.5, 93.4, 55.4.

4.4.2. (E)-4-Methylcinnamonitrile. Mp 70–72 °C (lit.,[19] mp 71–72 °C); IR (ATR): 2213 cm^{-1}; ^{1}H NMR ($CDCl_3$: 500 MHz) δ=7.34–7.38 (m, 3H), 7.21 (d, J=8.0 Hz, 2H), 5.82 (d, J=16.6 Hz, 1H), 2.39 (s, 3H),; ^{13}C NMR (125 MHz, $CDCl_3$); δ=150.5, 141.8, 130.9, 129.8, 127.3, 118.4, 95.0, 21.5.

4.4.3. (E)-Cinnamonitrile. Colorless oil (commercial); IR (ATR): 2217 cm^{-1}; ^{1}H NMR ($CDCl_3$: 500 MHz) δ=7.37–7.46 (m, 6H), 5.87 (d, J=16.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=150.5, 133.4, 131.1, 129.1, 127.3, 118.1, 96.2.

4.4.4. (E)-4-Chlorocinnamonitrile. Mp 81–82 °C (lit.,[20] mp 85–86 °C); IR (ATR): 2217 cm^{-1}; ^{1}H NMR ($CDCl_3$: 500 MHz) δ=7.39 (br s, 4H), 7.36 (d, J=16.6 Hz, 1H), 5.87 (d, J=16.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=149.1, 137.3, 132.0, 129.4, 128.5, 117.8, 97.0.

4.4.5. (E)-4-Fluorocinnamonitrile. Mp 66–68 °C (lit.,[21] mp 67–68 °C); IR (ATR): 2211 cm^{-1}; ^{1}H NMR ($CDCl_3$: 500 MHz) δ=7.43–7.47 (m, 2H), 7.37 (d, J=16.6 Hz, 1H), 7.08–7.13 (m, 2H), 5.81 (d, J=16.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=164.5 (d, J=253.1 Hz), 149.2, 129.8 (d, J=3.6 Hz), 129.4 (d, J=8.4 Hz), 117.9, 116.4 (d, J=22.8 Hz), 96.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ=−107.6.

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