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Oxidative Cyclization of 2-Aryl-3-arylamino-2-alkenenitriles to *N*-Arylindole-3-carbonitriles Mediated by NXS/$Zn(OAc)_2$

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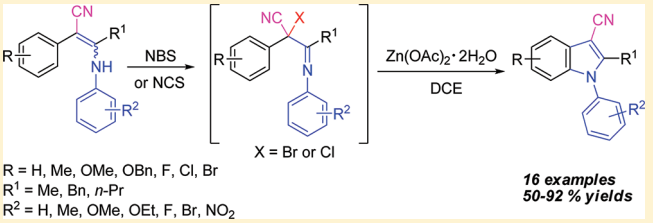
Supporting Information

ABSTRACT: A variety of 2-aryl-3-arylamino-2-alkenenitriles were converted to *N*-arylindole-3-carbonitriles in a one-pot manner through NBS- or NCS-mediated halogenation followed by $Zn(OAc)_2$-catalyzed intramolecular cyclization. It is postulated that the process involves the formation of arylnitrenium ion intermediates, which undergo the electrophilic aromatic substitution to give the cyclized *N*-arylindole product.



INTRODUCTION

The *N*-arylindole skeleton is an important heterocyclic motif due to its presence in many synthetically challenging[1] and pharmaceutically active compounds.[2] Although a great many methods have been developed for the synthesis of various substituted indoles, the strategic approaches to the N-arylated pattern of indole compounds are limited. Generally, these methodologies can be categorized into the following types: (1) Fischer cyclization of *N*,*N*-diarylhydrazones (path a, Figure 1);[3] (2) connecting an indole compound to a functionalized arene under various coupling conditions, which is considered as the predominant strategy of the *N*-arylindole synthesis (path b, Figure 1);[4] (3) tandem amination and cyclization approach using *o*-alkynylhaloarenes or *o*-alkenylhaloarenes and substituted anilines as the starting materials (path c and d, Figure 1);[5] (4) joining the N-atom on the side chain in an enamine substrate to the benzene ring via palladium-mediated cyclization (W = I)[6] or direct oxidative annulation (W = H) (path e, Figure 1);[7] (5) reduction of indolin-2-ones or desulfurization of indoline-2-thiones (path f, Figure 1).[8] In addition, the synthesis of *N*-arylindole may also be achieved by the reaction of a diarylamine with triethanolamine mediated by a ruthenium catalyst.[9] Herein we report an alternative one-pot route to *N*-arylindole-3-carbonitriles via halogenation of 2-aryl-3-arylamino-2-alkenenitriles followed by $Zn(OAc)_2$-mediated intramolecular cyclization.

RESULTS AND DISCUSSION

We began our work by assuming that the treatment of enamine substrate **1a** with NBS would afford the reactive *N*-bromo intermediate **2a**′,[10] which could be taken as a nitrenium ion[11] intermediate and undergo Lewis acid mediated intramolecular cyclization to give the cyclized indole product **3a**. However, we found the reaction of substrate **1a** with NBS in dichloromethane (DCM) nearly quantitatively led to the benzylic bromination product **2a**, a theoretically more reasonable

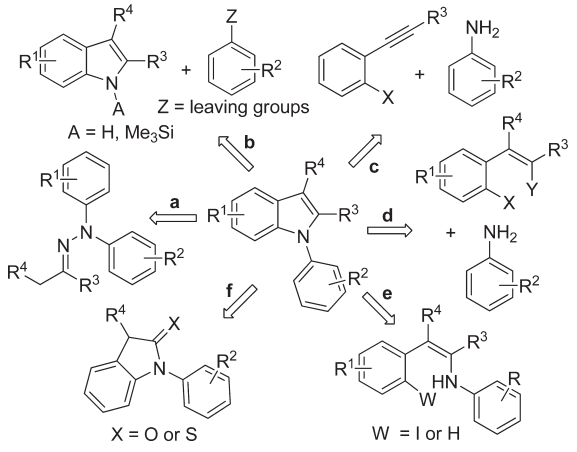


Figure 1. General strategies for the construction of the *N*-arylindole skeleton.

structure than **2a**′. The structure of compound **2a** was determined by the NMR spectroscopic data of the crude reaction mixture (see the Supporting Information). An attempt to isolate the pure **2a** through silica gel column chromatography was not successful since the rearranged enamine **4a** was isolated in 95% yield instead during this purification process. Fortunately, both the benzylic brominated intermediate **2a** and allylic brominated intermediate **4a**, upon treatment with $Zn(OAc)_2$ in DCE,[12] can efficiently provide the desired indole **3a** (Scheme 1).

Considering that both compound **2a** and **4a** were unstable intermediates, a one-pot procedure of adding $Zn(OAc)_2$ directly to the crude reaction mixture to promote the intramolecular cyclization was investigated. The screening of the reaction conditions using 2-phenyl-3-(phenylamino)-2-butenenitrile **1a**

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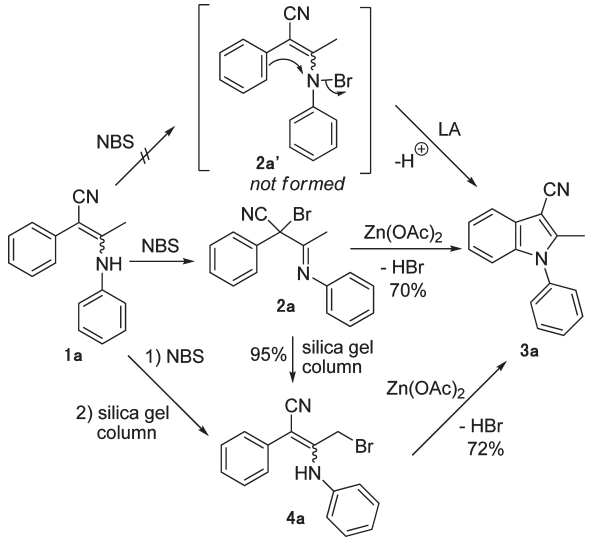
Scheme 1. Unexpected Formation of *N*-Phenylindole-3-carbonitrile 3a via Bromination of 1a Followed by Lewis Acid Mediated Intramolecular Cyclization

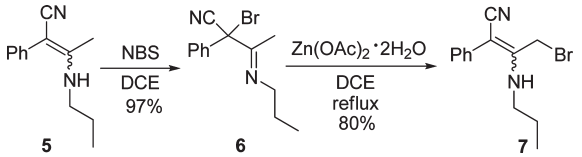


as a model substrate showed that the best result could be achieved when **1a** was treated with 1.2 equiv of NBS in DCE, with the subsequent introduction of 0.8 equiv of $Zn(OAc)_2$ while keeping the reaction mixture at reflux for 1 h (see the Supporting Information for details).

With optimal conditions in hand, the scope and limitations of this one-pot methodology have been investigated. As shown in Table 1, when R is H and R_2 is H, an electron-withdrawing bromo group or electron-donating methoxy group, the reaction can give the desired *N*-arylindole product in 72%, 69%, and 62% yields, respectively (Table 1, entries 1−3). A range of varying aryl groups on the enamine with the *N*-substituents being phenyl or *p*-tolyl groups, as shown in entries 4−7, tolerate both electron-deficient as well as electron-rich groups and give the corresponding indoles in good to excellent yields. It is worth noting that for substrates with R being a methoxy group, the reaction with NBS under standard conditions gave a complex mixture. We assume that bromination processes on the electron-rich aromatic rings occurred as competitive side reactions. The replacement of NBS with NCS led to clean formation of the corresponding chlorinated intermediate.[14] Subsequent treatment of the less reactive chloroimino nitriles with $Zn(OAc)_2$ under similar conditions facilitated the intramolecular cyclization at slightly lower temperature to afford the desired products (Table 1, entries 4−6).

More interestingly, when the aryl groups are more complicated aromatic or heteroaromatic rings, the desired indole-3-carbonitriles were also successfully prepared in good yields (entries 8 and 9). A number of additional examples have also demonstrated to be efficient when a series of electron-rich and electron-deficient aryl groups were employed. The *meta*-substituted enamine **3j** afforded a 3:1 mixture of 5- and 7-substituted indoles as inseparable regioisomers, determined by ^1H NMR of the crude reaction mixture. However, for entries 5 and 6, only single products **3e** and **3f** were observed, respectively, in each case. Finally, diversity studies focused on the R_1 groups have proved that the substrates bearing primary alkyl group can be successfully converted into 2-alkyl-substituted indoles in moderate to good yields (Table 1, entries 14−16).

Scheme 2. Study of *N*-Alkylenamine 5 under Identical Conditions



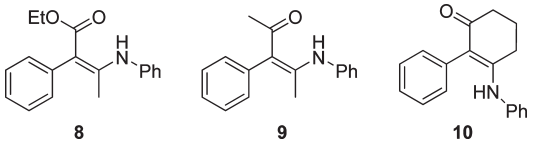


Figure 2. Other models that failed to afford the desired *N*-arylindoles.

In addition, we were disappointed to find that this approach was not successful for the synthesis of the corresponding *N*-alkylindole-3-carbonitriles. Subjecting 2-phenyl-3-(propylamino)-2-butenenitrile **5** to NBS at room temperature in DCE afforded benzylic brominated imine **6**, which is stable enough for column chromatography and was isolated in excellent yield of 97%. However, the subsequent treatment of imine **6** with $Zn(OAc)_2$ under identical conditions only led to the rearranged enamine **7**, which is a stable compound even at reflux temperature in the presence of $Zn(OAc)_2$ (Scheme 2). This result clearly indicates that *N*-aryl substituents are essential for the Lewis acid assisted cyclization process.

Disappointingly, similar substrates **8**−**10** (Figure 2), differing from **1a** with only the benzylic cyano group being replaced by an ethoxycarbonyl (ester) or acyl group, yielded none of the expected cyclized product via this one-pot procedure in each case. This intriguing result implies that the benzylic cyano group plays some important role in the course of this reaction.

A plausible mechanism for the above halogenation−cyclization process, taking substrate **1a** as an example, is shown in Scheme 3.[13] Initially, the reaction of enamine **1a** with NBS provides the brominated imine **2a**. In view of the fact that imine **2a** converts to enamine **4a** in the presence of silica gel and both **2a** and **4a** can undergo $Zn(OAc)_2$-mediated cyclization to give indole product **3a**, we propose that compound **2a** adopts a rearrangement to give enamine **A**, imine **B** and then tautomerize into **4a** before the intramolecular cyclization mediated by $Zn(OAc)_2$ occurs. Assisted by the Lewis acid, the bromide anion will be eliminated from **B** to give the nitrenium ion intermediate **C**, which can be stabilized to a great extent by an aromatic ring.[15] The electrophilic attack on the nitrenium ion by the benzene ring will give the cyclized intermediate **D**. With the loss of a proton, the Wheland intermediate **D** will be converted to **E**, which can undergo tautomerization and aromatization to furnish the title *N*-arylindole-3-carbonitrile **3**. We tentatively propose that the unsuccessful cyclization of *N*-alkylenamine **5** could be attributed to the failure of the formation of the nitrenium ion[11] similar to **C** since an alkyl substituent on the N-atom cannot stabilize this highly reactive species.

Previously, we described an alternative synthesis route for the indole compounds from the reactions of the same enamine substrates with phenyliodine bis(trifluoroacetate) (PIFA) via intramolecular cyclization.[7] With that method, substrates other than the *N*-arylenamine ones as described herein, such as **5** and **8**, can also undergo oxidative annulation to give the corresponding

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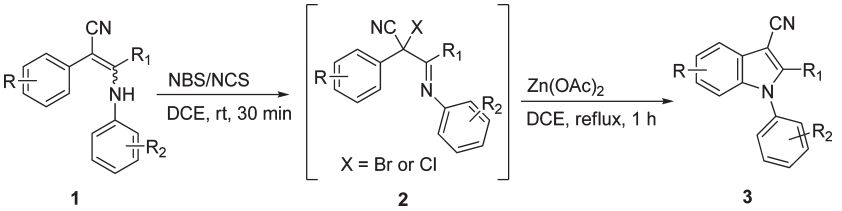
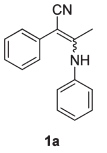
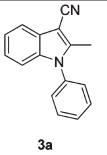
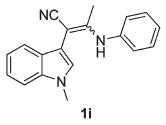
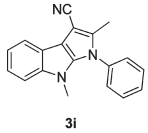
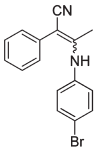
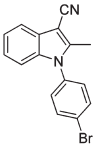
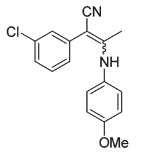
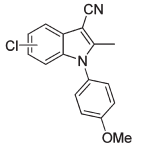
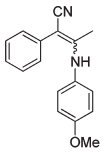
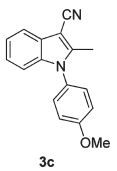
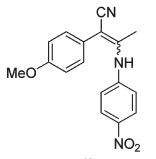
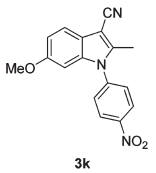
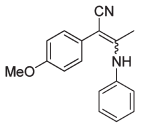
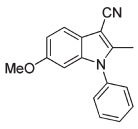
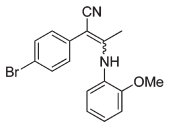
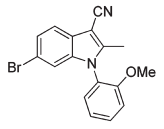
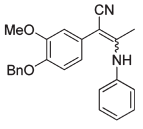
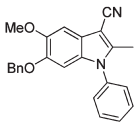
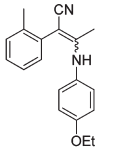
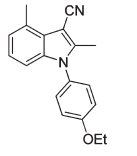
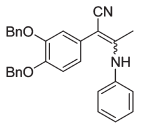
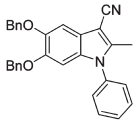
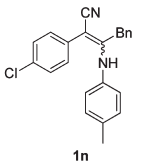
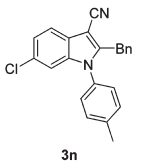
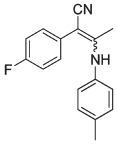
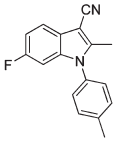
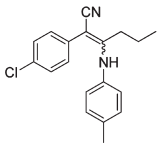
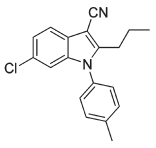
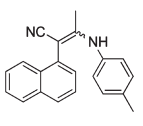
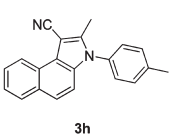
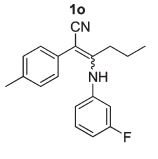
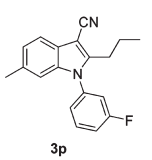
Table 1. Synthesis of *N*-Arylindole-3-carbonitriles via Halogenation Followed by $Zn(OAc)_2$-Mediated Intramolecular Cyclization[a]



1 **2** **3**

entry	substrate **1**	product **3**	yield (%)[e]	entry	substrate **1**	product **3**	yield (%)[e]
1	 **1a**	 **3a**	72	9	 **1i**	 **3i**	67
2	 **1b**	 **3b**	69	10[b]	 **1j**	 **3j**	50[d]
3	 **1c**	 **3c**	62	11[b,c]	 **1k**	 **3k**	90
4[b,c]	 **1d**	 **3d**	73	12[b]	 **1l**	 **3l**	66
5[b,c]	 **1e**	 **3e**	92	13	 **1m**	 **3m**	78
6[b,c]	 **1f**	 **3f**	77	14	 **1n**	 **3n**	64
7	 **1g**	 **3g**	92	15	 **1o**	 **3o**	91
8[b]	 **1h**	 **3h**	90	16	 **1p**	 **3p**	74

[a] Reaction conditions: (1) substrate **1** (2.0 mmol), NBS (1.2 equiv), DCE (15 mL); (2) $Zn(OAc)_2$ (0.8 equiv), reflux, unless otherwise noted. [b] The reaction was operated at 50 °C after the addition of $Zn(OAc)_2$. [c] NCS (1.5 equiv) instead of NBS was used. [d] Overall yield of the two isomers. [e] Yields after silica gel chromatography.

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N-substituted indole products. Disappointingly, the substrate scope in our current study is confined to only *N*-aryl-2-aryl-3-amino-2-alkenenitrile substrates. However, we have found that by avoiding applying stoichiometric amout of PIFA, the combination of the inexpensive halogenation reagent (NXS) and the readily available $Zn(OAc)_2$ also give the corresponding *N*-arylindole-3-carbonitriles with equally good yields via a unique ring-closure process.[13,15]

CONCLUSION

In summary, we have demonstrated herein an alternative method for the formation of *N*-arylindole-3-nitriles, the process of which involves an unprecedented halogenation of 2-aryl-3-arylamino-2-alkenenitriles followed by a Lewis acid mediated cyclization. This route features simple procedures, inexpensive reagents, and good to excellent yields, which can be utilized for the synthesis of a variety of substituted *N*-arylindole-3-nitriles. Further mechanistic studies are currently in progress within the research group.

EXPERIMENTAL SECTION

General Information. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer at 25 °C. Chemical shifts values are given in ppm and referred as the internal standard to TMS: 0.00 ppm. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; sxt, sextuplet; m, multiplet and dd, doublet of doublets. The coupling constants *J* are reported in hertz (Hz). Low-resolution mass spectrometry (ESI) was performed on an ion-trap spectrometer. High-resolution mass spectra (HRMS) were obtained on a Q-TOF micro spectrometer. Melting points were determined with a national micro-melting point apparatus without corrections. TLC plates were visualized by exposure to ultraviolet light. THF, DCE, and toluene were dried by CaH_2 before use. Other reagents and solvents were purchased from commercial suppliers as reagent grade and were used without further purification. Flash column chromatography was performed over silica gel 200−300 mesh, and the eluent was a mixture of petroleum ether (PE) and ethyl acetate (EtOAc). R_f values of 2-aryl-3-arylamino-2-alkenenitrile are given for the major isomer.

Preparation of Substrates. *1. General Procedure for the Synthesis of 2-Aryl-3-substituted-2-alkenenitriles* ***1***, ***5***, *and* ***8*****−*****10***[7]. The desired substrate **1** was prepared following the general procedure described in the previous paper.[7] The ratio of the *trans* and *cis* isomers of 2-aryl-3-substituted-2-alkenenitrile **1** was determined from the ^{1}H NMR spectral data. Compounds **1a**, **1h**, **1i**, **1l**, and **1o** have been prepared and characterized in our previous paper;[7] the new compounds thus obtained were characterized as follows:

3-[(4-Bromophenyl)amino]-2-phenyl-2-butenenitrile, 1b. White solid. Yield: 80% (*cis*/*trans* = 1:4.5). Mp: 115−117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): major isomer (*trans*) δ 7.40−7.24 (m, 7H), 6.85 (d, *J* = 8.0 Hz, 2H), 6.65 (s, 1H), 2.29 (s, 3H); minor isomer (*cis*) δ 7.47 (d, *J* = 8.0 Hz, 2H), 7.42−7.24 (m, 5H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.94 (s, 1H), 2.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): major isomer (*trans*) δ 153.1, 137.9, 132.8, 132.4, 129.6, 129.0, 127.9, 125.8, 121.5, 118.6, 85.7, 18.7; minor isomer (*cis*) δ 155.1, 137.9, 133.7, 132.4, 129.6, 128.7, 127.1, 126.2, 120.1, 118.8, 85.7, 17.0. HRMS (ESI): *m*/*z* calcd for $C_{16}H_{13}{}^{79}BrN_2Na^+$ [M + Na^+] 335.0154, found 335.0157.

3-[(4-Methoxyphenyl)amino]-2-phenyl-2-butenenitrile, ***1c***. White solid. Yield: 65% (*cis*/*trans* = 1:4.5). Mp: 117−119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): major isomer (*trans*) δ 7.46−7.20 (m, 5H), 6.95 (dd, *J* = 8.5, 2.0 Hz, 2H), 6.84 (dd, *J* = 8.5, 2.0 Hz, 2H), 6.68 (s, 1H), 3.79 (s, 3H), 2.20 (s, 3H); minor isomer (*cis*) δ 7.46−7.20 (m, 5H), 7.07 (dd, *J* = 8.5, 2.0 Hz, 2H), 6.89 (dd, *J* = 8.5, 2.0 Hz, 3H), 3.81 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): major isomer (*trans*) δ 158.0, 155.0, 133.3, 131.4, 129.5, 128.6, 127.5, 127.2, 122.2, 114.5, 82.6, 55.5, 18.5; minor isomer (*cis*) δ 158.1, 157.1, 134.3, 131.4, 129.6, 128.6, 127.5, 126.6, 122.2, 114.5, 82.6, 55.5, 16.7. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{16}N_2NaO^+$ [M + Na^+] 287.1155, found 287.1156.

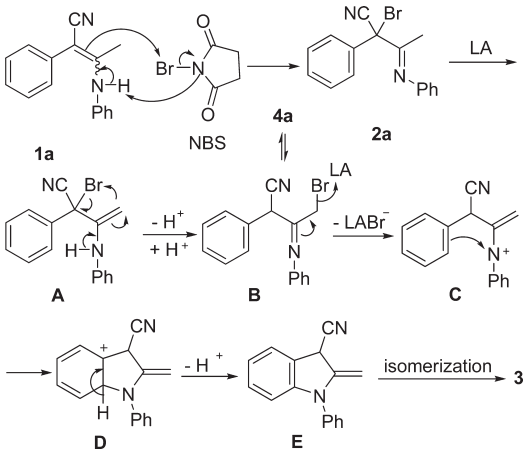
2-(4-Methoxyphenyl)-3-(phenylamino)-2-butenenitrile, ***1d***. Yellow solid. Yield: 82% (*cis*/*trans* = 1:5.9). Mp: 117−119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): major isomer (*trans*) δ 7.37−7.29 (m, 4H), 7.24−7.14 (m, 1H), 6.98−6.92 (m, 4H), 6.59 (s, 1H), 3.81 (s, 3H), 2.30 (s, 3H); minor isomer (*cis*) δ 7.37−7.29 (m, 2H), 7.24−7.14 (m, 3H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.59 (s, 1H), 3.81 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): major isomer (*trans*) δ 159.0, 153.3, 138.9, 130.4, 129.3, 125.3, 124.9, 124.6, 124.2, 114.9, 84.2, 55.3, 18.4; minor isomer (*cis*) δ 159.0, 153.3, 138.9, 130.9, 129.3, 125.4, 124.9, 124.6, 121.9, 114.0, 84.2, 55.3, 16.8. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{16}N_2NaO^+$ [M + Na^+] 287.1155, found 287.1159.

2-[4-(Benzyloxy)-3-methoxyphenyl]-3-(phenylamino)-2-butenenitrile, ***1e***. White solid. Yield: 89% (*cis*/*trans* = 1:12.5). Mp: 190−192 °C. ^{1}H NMR (400 MHz, $CDCl_3$): major isomer (*trans*) δ 7.44−7.28 (m, 7H), 7.21−7.08 (m, 1H), 6.97−6.85 (m, 5H), 6.70 (s, 1H), 5.15 (s, 2H), 3.87 (s, 3H), 2.28 (s, 3H); minor isomer (*cis*) δ 7.44−7.28 (m, 5H), 7.21−7.08 (m, 3H), 6.97−6.85 (m, 3H), 6.77 (d, *J* = 8.0 Hz, 2H), 6.70 (s, 1H), 5.15 (s, 2H), 3.89 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): major isomer (*trans*) δ 153.5, 150.4, 147.7, 138.9, 136.8, 129.2, 128.6, 127.9, 127.2, 125.8, 125.4, 124.7, 124.3, 121.4, 114.5, 112.8, 84.2, 71.0, 56.1, 18.4. The ^{13}C NMR data of the *cis* isomer was not collected due to its low concentration. HRMS (ESI): *m*/*z* calcd for $C_{24}H_{22}N_2NaO_2^+$ [M + Na^+] 393.1573, found 393.1577.

2-[3,4-Bis(benzyloxy)phenyl]-3-(phenylamino)-2-butenenitrile, ***1f***. White solid. Yield: 90% (*cis*/*trans* = 1:14.3). Mp: 116−118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): major isomer (*trans*) δ 7.45−7.34 (m, 6H), 7.31−7.27 (m, 3H), 7.19−7.14 (m, 4H), 6.98−6.80 (m, 5H), 6.51 (s, 1H), 5.16 (d, *J* = 8.0 Hz, 4H), 2.23 (s, 3H); minor isomer (*cis*) δ 7.45−7.34 (m, 10H), 7.31−7.27 (m, 1H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.98−6.80 (m, 5H), 6.51 (s, 1H), 5.16 (d, *J* = 4.0 Hz, 4H), 1.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): major isomer (*trans*) δ 153.4, 149.3, 148.4, 138.8, 137.0, 136.9, 129.2, 128.6, 128.5, 127.9, 127.8, 127.2, 126.0, 125.4, 124.6, 124.5, 122.3, 121.8, 115.8, 115.7, 84.0, 71.3, 71.3, 18.5. The ^{13}C NMR data of the *cis* isomer was not collected due to its low concentration. HRMS (ESI): *m*/*z* calcd for $C_{30}H_{26}N_2NaO^{2+}$ [M + Na^+] 469.1887, found 469.1891.

2-(4-Fluorophenyl)-3-(p-tolylamino)-2-butenenitrile, ***1g***. White solid. Yield: 76% (*cis*/*trans* = 1:4). Mp: 122−124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): major isomer (*trans*) δ 7.42 (dd, *J* = 8.5, 5.0 Hz, 2H), 7.18−7.00 (m, 4H), 6.92−6.88 (m, 2H), 6.52 (s, 1H), 2.33 (s, 3H), 2.25 (s, 3H); minor isomer (*cis*) δ 7.18−7.00 (m, 7H), 6.92−6.88

Scheme 3. Proposed Mechanism



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(m, 1H), 6.52 (s, 1H), 2.35 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): major isomer (*trans*) δ 161.9 (d, J_{C-F} = 246.0 Hz), 154.6, 135.9 (d, J_{C-F} = 4.0 Hz), 131.4 (d, J_{C-F} = 8.0 Hz), 131.0 (d, J_{C-F} = 8.0 Hz), 129.9, 125.3, 124.9, 116.5 (d, J_{C-F} = 21.5 Hz), 115.5 (d, J_{C-F} = 21.5 Hz), 82.5, 20.9, 18.5. The ^{13}C NMR data of the *cis* isomer was not collected due to its low concentration. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{15}FN_2Na^+$ [M + Na^+] 289.1111, found 289.1117.

2-(3-Chlorophenyl)-3-[(4-methoxyphenyl)amino]-2-butenenitrile, ***1j***. White solid. Yield: 91% (*cis*/*trans* = 1:3.5). Mp: 106−108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): major isomer (*trans*) δ 7.44 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.29−7.17 (m, 1H), 6.97 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 6.69 (s, 1H), 3.80 (s, 3H), 2.19 (s, 3H); minor isomer (*cis*) δ 7.29−7.17 (m, 4H), 7.08 (d, *J* = 9.0 Hz, 2H), 6.98−6.95 (m, 1H), 6.90 (d, *J* = 9.0 Hz, 2H), 3.82 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): major isomer (*trans*) δ 158.2, 155.7, 135.2, 131.0, 130.6, 129.0, 127.5, 127.3, 127.1, 121.8, 121.7, 114.5, 81.3, 55.5, 18.6; minor isomer (*cis*) δ 158.3, 157.8, 136.2, 134.2, 129.7, 129.4, 127.6, 127.7, 127.6, 126.6, 120.2, 120.2, 114.9, 79.8, 16.7. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{15}{}^{35}ClN_2NaO^+$ [M + Na^+] 321.0765, found 321.0768.

2-(4-Methoxyphenyl)-3-[(4-nitrophenyl)amino]-2-butenenitrile, ***1k***. Yellow solid. Yield: 91% (*cis*/*trans* = 1:3.3). Mp: 171−173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): major isomer (*trans*) δ 8.15 (d, *J* = 9.0 Hz, 2H), 7.33−7.25 (m, 2H), 6.96−6.93 (m, 4H), 6.70 (s, 1H), 3.82 (s, 3H), 2.49 (s, 3H); minor isomer (*cis*) δ 8.22 (d, *J* = 9.0 Hz, 2H), 7.33−7.25 (m, 2H), 7.14−7.08 (m, 2H), 6.96−6.93 (m, 2H), 6.71 (s, 1H), 3.84 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): major isomer (*trans*) δ 149.7, 145.3, 130.8, 130.3, 125.5, 125.4, 123.9, 120.4, 120.1, 115.1, 114.3, 55.4, 19.2. The ^{13}C NMR data of the *cis* isomer was not collected due to its low concentration. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{15}N_3NaO_3^+$ [M + Na^+] 332.1006, found 332.1011.

3-[(4-Ethoxyphenyl)amino]-2-o-tolyl-2-butenenitrile, ***1m***. White solid. Yield: 68% (*cis*/*trans* = 1:7.7). Mp: 92−94 °C. ^{1}H NMR (400 MHz, $CDCl_3$): major isomer (*trans*) δ 7.33−7.17 (m, 4H), 6.92−6.80 (m, 4H), 5.98 (s, 1H), 4.05−3.97 (m, 2H), 2.39 (s, 3H), 2.21 (s, 3H), 1.40 (t, *J* = 7.0 Hz, 3H); minor isomer (*cis*) δ 7.33−7.17 (m, 4H), 7.06 (d, *J* = 9.0 Hz, 2H), 6.92−6.80 (m, 3H), 4.05−3.97 (m, 2H), 2.35 (s, 3H), 1.69 (s, 3H), 1.40 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): major isomer (*trans*) δ 157.3, 155.5, 138.4, 131.9, 131.2, 131.1, 130.4, 128.7, 127.3, 126.9, 121.6, 114.9, 81.1, 63.7, 19.7, 17.7, 14.8; minor isomer (*cis*) δ 157.3, 155.5, 138.4, 131.9, 131.4, 131.3, 130.4, 128.0, 127.4, 126.1, 121.6, 115, 81.1, 63.7, 19.7, 17.7, 14.8. HRMS (ESI): *m*/*z* calcd for $C_{19}H_{20}N_2NaO^+$ [M + Na^+] 315.1468, found 315.1470.

2-(4-Chlorophenyl)-4-phenyl-3-(p-tolylamino)-2-butenenitrile, ***1n***. White solid. Yield: 79% (*cis*/*trans* = 1:8.3). Mp: 107−109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): major isomer (*trans*) δ 7.37−7.18 (m, 7H), 7.10 (d, *J* = 7.0 Hz, 2H), 7.02−6.91 (m, 2H), 6.68 (d, *J* = 9.0 Hz, 2H), 6.41 (s, 1H), 4.01 (s, 2H), 2.28 (s, 3H); minor isomer (*cis*) δ 7.37−7.18 (m, 6H), 7.02−6.91 (m, 5H), 6.82 (m, 3H), 3.72 (s, 2H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): major isomer (*trans*) δ 156.4, 136.3, 135.9, 135.8, 133.3, 131.7, 130.3, 129.6, 129.4, 128.9, 128.6, 128.4, 127.0, 125.0, 84.6, 37.6, 20.9; minor isomer (*cis*) δ 156.4, 136.5, 135.9, 135.8, 133.3, 131.7, 130.8, 129.7, 129.5, 128.9, 128.7, 128.0, 126.8, 125.3, 84.6, 36.7, 34.2. HRMS (ESI): *m*/*z* calcd for $C_{23}H_{19}{}^{35}ClN_2Na^+$ [M + Na^+] 381.1129, found 381.1133.

3-[(3-Fluorophenyl)amino]-2-p-tolyl-2-hexenenitrile, ***1p***. White solid. Yield: 83% (*cis*/*trans* = 1:11.1). Mp: 101−104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): major isomer (*trans*) δ 7.33−7.29 (m, 2H), 7.23−7.16 (m, 3H), 6.89−6.79 (m, 3H), 6.40 (s, 1H), 2.73 (t, *J* = 8.0 Hz, 2H), 2.33 (s, 3H), 1.63−1.54 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H); minor isomer (*cis*) δ 7.33−7.25 (m, 2H), 7.23−7.16 (m, 3H), 6.89−6.79 (m, 3H), 6.40 (s, 1H), 2.43 (t, *J* = 8.0 Hz, 2H), 2.36 (s, 3H), 1.33−1.25 (m, 2H), 0.70 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): major isomer (*trans*) δ 163.0 (d, J_{C-F} = 245.5 Hz), 156.5, 141.0 (d, J_{C-F} = 10.5 Hz), 137.8, 130.3 (d, J_{C-F} = 9.5 Hz), 130.1, 129.7, 128.7, 121.2, 118.9 (d, J_{C-F} = 3.0 Hz), 111.7 (d, J_{C-F} = 21.0 Hz), 110.6 (d, J_{C-F} = 23.5 Hz), 87.7, 33.2, 21.6, 21.2, 13.5. The ^{13}C NMR data of the *cis* isomer was not collected due to its low concentration. HRMS (ESI): *m*/*z* calcd for $C_{19}H_{19}FN_2Na^+$ [M + Na^+] 317.1424, found 317.1425.

2-Phenyl-3-(propylamino)-2-butenenitrile, ***5***. Yellow liquid. Yield: 87% (*cis*/*trans* = 1:5). ^{1}H NMR (400 MHz, $CDCl_3$): major isomer (*trans*) δ 7.39−7.30 (m, 4H), 7.23−7.16 (m, 1H), 5.14 (s, 1H), 3.11−3.06 (m, 2H), 2.26 (s, 3H), 1.51−1.42 (m, 2H), 0.88 (t, *J* = 7.5 Hz, 3H); minor isomer (*cis*) δ 7.39−7.30 (m, 2H), 7.23−7.16 (m, 3H), 5.14 (s, 1H), 3.25−3.21 (m, 2H), 1.99 (s, 3H), 1.63−1.58 (m, 2H), 0.98 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): major isomer (*trans*) δ 156.7, 133.8, 129.3, 128.9, 126.9, 123.1, 78.6, 45.4, 23.7, 17.5, 11.1; minor isomer (*cis*) δ 158.7, 134.9, 129.6, 128.4, 126.1, 121.4, 78.6, 45.5, 23.7, 15.6, 11.2. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{16}N_2Na^+$ [M + Na^+] 223.1206, found 223.1206.

Ethyl 2-Phenyl-3-(propylamino)-2-butenoate, ***8***. Light yellow liquid. Yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.32 (s, 1H), 7.36−7.13 (m, 10H), 4.16−4.13 (m, 2H), 1.82 (d, *J* = 3.0 Hz, 3H), 1.18−1.15 (m, 3H). ESI-MS: *m*/*z* 584.4.

2. General Procedure for the Synthesis of 9. *3-Phenyl-4-(propylamino)-3-penten-2-one,* ***9***. To a solution of 3-phenylpentane-2,4-dione (1.0 mmol) in toluene (10 mL) was added aniline (1.5 mmol). The reaction mixture was stirred at reflux until TLC indicated the total consumption of 3-arylpentane-2,4-dione. The mixture was evaporated to partially remove the solvent. EtOAc (15 mL × 3) was used to extract the mixture, and the combined organic phase, after being dried with anhydrous Na_2SO_4, was evaporated to remove the solvent. White solid. Yield: 87%. Mp: 105−107 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.58 (s, 1H), 7.39−7.27 (m, 5H), 7.23−7.18 (m, 3H), 7.14 (d, *J* = 7.5 Hz, 2H), 1.90 (s, 3H), 1.74 (s, 3H). ESI-MS: *m*/*z* 274.0.

3. General Procedure for the Synthesis of 10. *2-Phenyl-3-(phenylamino)-2-cyclohexenone,* ***10***. 2-Phenylcyclohexane-1,3-dione (3 mmol) was dissolved in neat aniline (5 mL). The solution was stirred at 140 °C until TLC indicated the completion of the reaction. White solid. Yield: 67%. Mp: 127−130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (t, *J* = 8.0 Hz, 2H), 7.33−7.26 (m, 5H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.52 (s, 1H), 2.60 (t, *J* = 8.0 Hz, 2H), 2.54 (t, *J* = 8.0 Hz, 2H), 2.06−2.00 (m, 2H). ESI-MS: *m*/*z* 549.2.

General Procedure for the Synthesis of Imine 2 and 6. To a solution of substrate **1** (4.0 mmol) in dried dichloromethane (20 mL) was added NBS (4.8 mmol) or NCS (6 mmol) (when R was methoxy or benzyloxy) in one portion with stirring at room temperature, and the process of the reaction was monitored by TLC analysis. After the consumption of substrate **1**, the mixture was evaporated to dryness. The selected crude compounds thus obtained were characterized as follows:

(E)-2-Bromo-2-phenyl-3-(phenylimino)butanenitrile, ***2a***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.0 Hz, 2H), 7.49−7.41 (m, 3H), 7.34 (t, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 7.0 Hz, 1H), 6.77 (d, *J* = 7.5 Hz, 2H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 148.8, 133.9, 130.1, 129.3, 129.1, 127.5, 124.6, 118.7, 117.3, 56.0, 15.5. HRMS (ESI): *m*/*z* calcd for $C_{16}H_{13}BrN_2Na^+$ [M + Na^+] 335.0154, found 335.0155.

(E)-2-Chloro-2-(4-methoxyphenyl)-3-(phenylimino)butanenitrile, ***2d***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 9.0 Hz, 2H), 6.78 (d, *J* = 7.5 Hz, 2H), 3.84 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 164.1, 160.8, 148.7, 129.1, 128.0, 124.6, 118.8, 117.0, 114.6, 66.6, 55.5, 14.7. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{15}{}^{35}ClN_2NaO^+$ [M + Na^+] 321.0765, found 321.0767.

(E)-2-Bromo-2-(4-bromophenyl)-3-[(2-methoxyphenyl)imino]-butanenitrile, ***2l***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 9.0 Hz, 2H), 7.10 (t, *J* = 7.0 Hz, 1H), 6.98−6.90 (m, 2H), 6.79 (d, *J* = 7.0 Hz, 1H), 3.78 (s, 3H), 1.83 (s, 3H). HRMS (ESI): *m*/*z* calcd for $C_{17}H_{14}{}^{79}Br_2N_2NaO^+$ [M + Na^+] 442.9365, found 442.9369.

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(E)-2-Bromo-2-(4-chlorophenyl)-3-(p-tolylimino)hexanenitrile, ***2o***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 6.66 (d, J = 8.0 Hz, 2H), 2.39−2.32 (m, 5H), 1.30−1.02 (m, 2H), 0.60 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 146.0, 136.2, 133.8, 132.9, 129.6, 129.2, 129.1, 118.0, 117.3, 54.6, 32.1, 21.0, 20.8, 14.2. HRMS (ESI): m/z calcd for $C_{19}H_{18}{}^{79}BrClN_2Na^+$ [M + Na^+] 411.0234, found 411.0237.

(E)-2-Bromo-2-phenyl-3-(propylimino)butanenitrile, ***6***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 7.5 Hz, 2H), 7.56−7.48 (m, 3H), 3.37 (q, J = 7.0 Hz, 2H), 1.88 (s, 3H), 1.67 (sxt, J = 7.0 Hz, 2H), 0.95 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2, 134.5, 130.4, 129.8, 127.7, 118.2, 57.5, 53.5, 23.4, 14.3, 12.2. HRMS (ESI): m/z calcd for $C_{13}H_{15}{}^{79}BrN_2Na^+$ [M + Na^+] 301.0311, found 301.0317.

Conversion of Substrate Imine 2 to Enamine 4. Compound **2** was passed through silica gel (100 g) chromatography for purification, enanitriles **4** were fully characterized, and the corresponding analytical data are described in a later section.

4-Bromo-2-phenyl-3-(phenylamino)-2-butenenitrile, ***4a***. White solid (*cis*/*trans* = 1:4). ^{1}H NMR (400 MHz, $CDCl_3$): major isomer (*trans*) δ 7.51−7.27 (m, 8H), 7.08 (d, J = 8.0 Hz, 2H), 6.52 (s, 1H), 4.39 (s, 2H); minor isomer (*cis*) δ 7.51−7.27 (m, 5H), 7.24−7.17 (m, 5H), 6.66 (s, 1H), 4.07 (s, 2H). HRMS (ESI): m/z calcd for $C_{16}H_{13}{}^{79}BrN_2Na^+$ [M + Na^+] 335.0154, found 335.0159.

4-Bromo-2-(4-bromophenyl)-3-[(2-methoxyphenyl)amino]-2-butenenitrile, ***4l***. White solid (*cis*/*trans* = 1:4). Mp: 25−26 °C. ^{1}H NMR (400 MHz, $CDCl_3$): major isomer (*trans*) δ 7.53−7.30 (m, 4H), 7.16−7.09 (m, 2H), 6.86 (t, J = 8.0 Hz, 2H), 6.52 (s, 1H), 4.35 (s, 2H), 3.83 (s, 3H); minor isomer (*cis*) δ 7.53−7.30 (m, 5H), 7.16−7.09 (m, 1H), 7.02−6.94 (m, 2H), 6.68 (s, 1H), 4.02 (s, 2H), 3.88 (s, 3H). HRMS (ESI): m/z calcd for $C_{17}H_{14}{}^{79}Br_2N_2NaO^+$ [M + Na^+], 442.9365; Found 442.9369.

4-Bromo-2-(4-chlorophenyl)-3-(p-tolylamino)-2-hexenenitrile, ***4o***. Light yellow solid (*cis*/*trans* = 1:2.2). Mp: 28−30 °C. ^{1}H NMR (400 MHz, $CDCl_3$): major isomer (*trans*) δ 7.73 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 7.5 Hz, 2H), 6.65 (d, J = 7.5 Hz, 2H), 6.38 (s, 1H), 2.37−2.29 (m, 5H), 1.15 (t, J = 7.0 Hz, 1H), 0.60 (t, J = 7.0 Hz, 3H); minor isomer (*cis*) δ 7.42 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 7.5 Hz, 1H), 7.01−6.94 (m, 3H), 6.77 (d, J = 8.0 Hz, 2H), 6.50 (d, J = 8.0 Hz, 1H), 6.38 (s, 1H), 2.37−2.29 (m, 1H), 2.26−2.19 (m, 2H), 2.15 (s, 3H), 0.87 (t, J = 7.0 Hz, 3H). HRMS (ESI): m/z calcd for $C_{19}H_{18}{}^{79}Br^{35}ClN_2Na^+$ [M + Na^+] 411.0234, found 411.0237.

Procedure for the Conversion of Compound 6 to 7. To a solution of substrate **6** (4.0 mmol) in dried DCE (20 mL) was added $Zn(OAc)_2 \cdot 2H_2O$ (3.2 mmol) in one portion, and then the mixture was stirred at reflux temperature. The process of the reaction was monitored by TLC analysis. After the total consumption of compound **6**, the reaction mixture was evaporated in vacuum to remove the solvent. The residue was purified by silica gel chromatography using a mixture of PE and EA as eluent to give the product **7**.

4-Bromo-2-phenyl-3-(propylamino)-2-butenenitrile, ***7***. Yellow solid. Yield: 80% (*cis*/*trans* = 1:2.5). Mp: 74−75 °C. ^{1}H NMR (400 MHz, $CDCl_3$): major isomer (*trans*) δ 7.42−7.35 (m, 5H), 4.96 (s, 1H), 4.33 (s, 2H), 3.20 (q, J = 7.0 Hz, 2H), 1.54 (sxt, J = 7.0 Hz, 2H), 0.91 (t, J = 7.5 Hz, 3H); minor isomer (*cis*) δ 7.42−7.35 (m, 2H), 7.29−7.26 (m, 3H), 4.96 (s, 1H), 3.97 (s, 2H), 3.37 (q, J = 7.0 Hz, 2H), 1.68 (sxt, J = 7.0 Hz, 2H), 1.03 (t, J = 7.5 Hz, 3H). HRMS (ESI): m/z calcd for $C_{13}H_{15}{}^{79}BrN_2Na^+$ [M + Na^+] 301.0311, found 301.0312.

General One-Pot Procedure for the Synthesis of *N*-Aryl-indole-3-carbonitrile Derivatives 3. To a solution of 2-phenyl-3-(phenylamino)but-2-enenitrile **1a** (4 mmol) in DCE (20 mL) was added NBS in one portion. The reaction was stirred at room temperature until the total consumption of **1a**. Then $Zn(OAc)_2 \cdot 2H_2O$ (3.2 mmol) was added in one potion. The reaction temperature was gradually raised to reflux (when R was methoxyl or benzyloxyl, the temperature was reduced to 50 °C). After completion of the reaction, the reaction mixture was evaporated in vacuum to remove the solvent. The residue was purified by silica gel chromatography using a mixture of PE and EA as eluent to give the desired products.

2-Methyl-1-phenyl-1H-indole-3-carbonitrile, ***3a***. White solid. Yield: 72%. Mp: 105−106 °C. This compound was consistent with the one we have synthesized in our previous work.[7]

1-(4-Bromophenyl)-2-methyl-1H-indole-3-carbonitrile, ***3b***. White solid. Yield: 69%. Mp: 191−192 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.29−7.20 (m, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7, 137.1, 135.0, 133.3, 129.4, 126.9, 123.8, 123.3, 122.7, 119.1, 116.0, 110.8, 87.0, 12.6. HRMS (ESI): m/z calcd for $C_{16}H_{11}{}^{79}BrN_2Na^+$ [M + Na^+] 332.9998, found 333.0002.

1-(4-Methoxyphenyl)-2-methyl-1H-indole-3-carbonitrile, ***3c***. White solid. Yield: 62%. Mp; 144−145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 7.5 Hz, 1H), 7.27−7.17 (m, 4H), 7.06 (t, J = 9.0 Hz, 3H), 3.90 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 146.4, 137.6, 128.9, 128.5, 126.8, 123.3, 122.3, 118.9, 116.4, 115.1, 111.1, 86.0, 55.7, 12.6. HRMS (ESI): m/z calcd for $C_{17}H_{14}N_2NaO^+$ [M + Na^+] 285.0998, found 285.1004.

6-Methoxy-2-methyl-1-phenyl-1H-indole-3-carbonitrile, ***3d***. White solid. Yield: 74%. Mp: 159−156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62−7.53 (m, 4H), 7.33 (d, J = 8.0 Hz, 2H), 6.92 (dd, J = 8.5, 2.0 Hz, 1H), 6.53 (d, J = 2.0 Hz, 1H), 3.74 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 145.2, 138.1, 136.1, 130.0, 129.2, 127.7, 120.7, 119.5, 116.4, 111.7, 94.9, 86.2, 55.7, 12.6. HRMS (ESI): m/z calcd for $C_{17}H_{14}N_2NaO^+$ [M + Na^+] 285.0998, found 285.1002.

6-(Benzyloxy)-5-methoxy-2-methyl-1-phenyl-1H-indole-3-carbonitrile, ***3e***. White solid. Yield: 92%. Mp: 200−201 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60−7.53 (m, 3H), 7.39−7.28 (m, 5H), 7.24 (dd, J = 8.0, 2.0 Hz, 2H), 7.17 (s, 1H), 6.61 (s, 1H), 5.05 (s, 2H), 3.98 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 146.6, 144.1, 136.9, 136.2, 131.2, 129.9, 129.0, 128.5, 127.9, 127.6, 127.5, 120.5, 116.6, 100.9, 98.1, 86.1, 71.8, 56.5, 12.6. HRMS (ESI): m/z calcd for $C_{24}H_{20}N_2NaO_2^+$ [M + Na^+] 391.1417, found 391.1418.

5,6-Bis(benzyloxy)-2-methyl-1-phenyl-1H-indole-3-carbonitrile, ***3f***. White solid. Yield: 77%. Mp: 147−148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59−7.53 (m, 3H), 7.50 (d, J = 8.0 Hz, 2H), 7.39−7.28 (m, 8H), 7.25−7.23 (m, 3H), 6.62 (s, 1H), 5.20 (s, 2H), 5.02 (s, 2H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4, 147.0, 144.4, 137.1, 137.0, 136.1, 131.8, 129.9, 129.0, 128.4, 128.3, 127.84, 127.82, 127.6, 127.5, 127.4, 120.7, 116.5, 104.1, 98.9, 86.1, 72.2, 71.9, 12.6. HRMS (ESI): m/z calcd for $C_{30}H_{24}N_2NaO^+$ [M + Na^+] 467.1730, found 467.1737.

6-Fluoro-2-methyl-1-(p-tolyl)-1H-indole-3-carbonitrile, ***3g***. White solid. Yield: 92%. Mp: 134−136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (dd, J = 8.5, 5.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 7.5 Hz, 2H), 7.01 (t, J = 9.0 Hz, 1H), 6.75 (dd, J = 9.0, 1.5 Hz, 1H), 2.48 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4 (d, J_{C-F} = 239.5 Hz), 146.7 (d, J_{C-F} = 2.0 Hz), 139.7, 137.5 (d, J_{C-F} = 12.0 Hz), 132.9, 130.7, 127.3, 123.0, 119.7 (d, J_{C-F} = 10.0 Hz), 116.0, 110.9 (d, J_{C-F} = 24.0 Hz), 97.9 (d, J_{C-F} = 27.0 Hz), 86.2, 21.2, 12.6. HRMS (ESI): m/z calcd for $C_{17}H_{13}FN_2Na^+$ [M + Na^+] 287.0955, found 287.0956.

2-Methyl-3-(p-tolyl)-3H-benzo[e]indole-1-carbonitrile, ***3h***. White solid. Yield: 90%. Mp: 204−206 °C. This compound was consistent with the one we have synthesized in our previous work.[7]

2,8-Dimethyl-1-phenyl-1,8-dihydropyrrolo[2,3-b]indole-3-carbonitrile, ***3i***. Light yellow solid. Yield: 67%. Mp: 164−166 °C. This compound was consistent with the one we have synthesized in our previous work.[7]

5-Chloro- and 7-Chloro-1-(4-methoxyphenyl)-2-methyl-1H-indole-3-carbonitrile, ***3j***. White solid. Yield: 50% (5-Cl/7-Cl = 3:1). Mp: 150−151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): major isomer (5-Cl) δ 7.63

(d, J = 2.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.13 (dd, J = 8.0, 2.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 8.0 Hz, 1H), 3.91 (s, 3H), 2.42 (s, 3H); minor isomer (7-Cl) δ 7.74 (s, 1H), 7.28 (d, J = 8.5 Hz, 2H), 7.23−7.18 (m, 2H), 7.12−7.07 (m, 1H), 7.00 (dd, J = 8.5, 6.0 Hz, 1H), 3.92 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): major isomer (5-Cl) δ 160.2, 147.5, 136.0, 128.8, 128.2, 128.0, 127.7, 123.7, 118.3, 115.8, 115.2, 112.1, 85.6, 55.6, 12.6; minor isomer (*cis*) δ 160.4, 148.3, 136.6, 130.0, 128.7, 128.3, 127.4, 125.7, 119.6, 115.6, 115.4, 114.3, 85.7, 55.7, 12.7. HRMS (ESI): m/z calcd for $C_{17}H_{13}{}^{35}ClN_2NaO^+$ [M + Na^+] 319.0609, found 319.0612.

6-Methoxy-2-methyl-1-(4-nitrophenyl)-1H-indole-3-carbonitrile, ***3k***. Yellow solid. Yield: 90%. Mp: 144−145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 3H), 6.95 (dd, J = 9.0, 2.0 Hz, 1H), 6.56 (d, J = 1.5 Hz, 1H), 3.76 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 147.7, 144.0, 141.8, 137.6, 128.6, 125.5, 120.8, 120.0, 115.6, 112.3, 94.7, 88.3, 55.8, 12.8. HRMS (ESI): m/z calcd for $C_{17}H_{13}N_3NaO_3^+$ [M + Na^+] 330.0849, found 330.0854.

6-Bromo-1-(2-methoxyphenyl)-2-methyl-1H-indole-3-carbonitrile, ***3l***. Light yellow solid. Yield: 66%. Mp: 165−166 °C. This compound was consistent with the one we have synthesized in our previous work.[7]

1-(4-Ethoxyphenyl)-2,4-dimethyl-1H-indole-3-carbonitrile, ***3m***. White solid. Yield: 78%. Mp: 164−166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, J = 9.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 7.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 4.11 (q, J = 6.8 Hz, 2H), 2.78 (s, 3H), 2.42 (s, 3H), 1.48 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 146.7, 137.6, 130.1, 128.9, 128.5, 125.2, 123.3, 123.2, 118.1, 115.5, 108.9, 85.2, 63.9, 18.5, 14.8, 12.4. HRMS (ESI): m/z calcd for $C_{19}H_{18}N_2NaO^+$ [M + Na^+] 313.1311, found 313.1313.

2-Benzyl-6-chloro-1-(p-tolyl)-1H-indole-3-carbonitrile, ***3n***. White solid. Yield: 64%. Mp: 141−142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 9.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.22 (dd, J = 8.5 1.5 Hz, 1H), 7.18−7.12 (m, 3H), 7.15 (s, 1H), 6.98−6.94 (m, 3H), 6.88 (dd, J = 7.0, 3.5 Hz, 2H), 4.14 (s, 2H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1, 139.9, 138.2, 136.3, 132.6, 130.5, 129.8, 128.6, 128.5, 127.9, 126.9, 125.3, 123.2, 120.1, 115.8, 111.4, 87.0, 32.4, 21.3. HRMS (ESI): m/z calcd for $C_{23}H_{17}{}^{35}ClN_2Na^+$ [M + Na^+] 379.0972, found 379.0975.

6-Chloro-2-propyl-1-(p-tolyl)-1H-indole-3-carbonitrile, ***3o***. White solid. Yield: 91%. Mp: 106−107 °C. This compound was consistent with the one we have synthesized in our previous work.[7]

1-(3-Fluorophenyl)-6-methyl-2-propyl-1H-indole-3-carbonitrile, ***3p***. Light yellow liquid. Yield: 74%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61−7.55 (m, 2H), 7.30−7.24 (m, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.11−7.06 (m, 2H), 6.83 (s, 1H), 2.80 (t, J = 8.0 Hz, 2H), 2.39 (s, 3H), 1.61−1.51 (m, 2H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2 (d, J_{C-F} = 249.0 Hz), 149.2, 137.6 (d, J_{C-F} = 3.0 Hz), 137.5 (d, J_{C-F} = 9.0 Hz), 133.9, 131.3 (d, J_{C-F} = 9.0 Hz), 124.7, 124.3, 124.0 (d, J_{C-F} = 2.0 Hz), 118.7, 116.5 (d, J_{C-F} = 21.0 Hz), 116.3, 115.7 (d, J_{C-F} = 23.0 Hz), 110.8, 86.5, 28.2, 22.3, 21.7, 13.6. HRMS (ESI): m/z calcd for $C_{19}H_{17}FN_2Na^+$ [M + Na^+] 315.1268, found 315.1270.

■ ASSOCIATED CONTENT

Supporting Information. Spectral data for all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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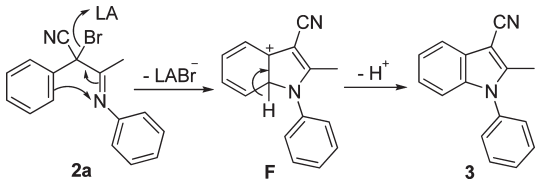
(12) (a) Some other Lewis acids were also tested but were not as efficient as $Zn(OAc)_2 \cdot 2H_2O$: (1) $AlCl_3$ (1 equiv), DCE, reflux, 0.5 h, 10%; (2) $FeCl_3$ (1 equiv), DCE, reflux, 0.5 h, 5%; (3) $ZnCl_2$ (1.0 equiv), DCE, reflux, 0.5 h, 20%; (4) $BF_3 \cdot Et_2O$ (1 equiv), DCE, reflux, 0.5 h, 8%. (b) Anhydrous $Zn(OAc)_2$ did not give a better result than $Zn(OAc)_2 \cdot 2H_2O$.

(13) We thank one of the reviewers for putting forward an alternative mechanistic pathway, which includes the following: (i) formation of a C−N bond via intramolecular electrophilic aromatic substitution of **2a**; (ii) formation of the title *N*-arylindole-3-carbonitrile **3** from the

intermediate arenium ion **F** via rearomatization through the loss of a proton.



(14) Imine **2d** also rearranged to enamine compound after silica gel column chromatography.

(15) For a similar indole synthesis describing the formation of nitrenium ion intermediate that is stablized by a methoxy group, see: Creary, X.; Burtch, E. A.; Jiang, Z. *J. Org. Chem.* **2003**, *68*, 1117.

dx.doi.org/10.1021/jo2012187 |*J. Org. Chem.* 2011, 76, 8690–8697