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AIBN as an Electrophilic Reagent for Cyano Group Transfer

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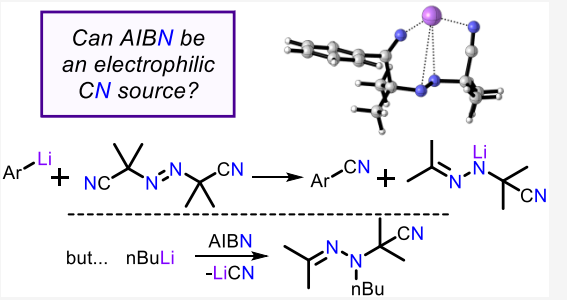
ABSTRACT: AIBN is a convenient electrophilic cyanation reagent for transforming ArLi into ArCN under mild conditions. The addition/fragmentation cascade is controlled by Li···N chelation in which AIBN nitrogens assist in the nearly barrierless fragmentation into the desired ArCN product. Acidic C−H bonds in the fragmented byproduct partially consume ArLi by protonation. Density functional theory calculations and isotopic labeling probe the mechanism and explain the switch to substituted hydrazones in reactions with BuLi.



The nitrile group is a ubiquitous functionality that can be converted into a range of other organic functional groups.[1−5] Alkyl nitriles are readily synthesized by using anionic cyanides as nucleophiles toward either an alkyl halide/pseudohalide or a carbonyl.[5,6] Because nucleophilic substitution on an sp^2 carbon is more difficult,[7] installation of a nitrile onto arenes is less trivial. Commonly, benzonitriles are made via reactions of stoichiometric amounts of CuCN and either diazonium salt[8] or an aryl halide[9,10] at increased temperatures.

An alternative strategy that avoids transition metals by utilizing nitrile as an electrophile goes back to Victor Grignard, who demonstrated that cyanogen chloride and bromide can transform aryl Grignard reagents into benzonitriles (Scheme 1a).[11] However, the toxic nature and instability of cyano halides prompted the development of alternative heteroatom-based electrophilic cyanation reagents (ECRs).

In addition to cyanogen chloride,[15] Grignard reagents also form benzonitriles (typically in yields ranging from 40% to >95%) with a variety of electrophilic CN sources such as cyanates,[12,13] tosyl cyanides,[14] 1-cyanobenzimidazole,[16] and *N*-cyano sulfonamides[17,18] (Scheme 1a). Additionally, aryl lithiums have been converted to benzonitriles via 1-cyanobenzotriazoles (in 16−83% yields).[19] Unfortunately, many of these reagents are either expensive, are not commercially available, or have to be prepared from toxic reagents such as NCCN, ClCN, or BrCN.

To address some of these problems, nontoxic and readily available ECRs have been developed (Scheme 1a). In particular, dimethyl malononitrile (commercially available) has been shown to convert Grignard reagents into benzonitriles.[20] Alternatively, reactions with aryl bromides in the presence of catalytic Ni, stoichiometric Zn, and 2-methyl-2-phenyl malononitrile (prepared in two steps) produce ArCN.[21]

Interestingly, azobis(isobutyronitrile) (AIBN), a common reagent for radical reactions, was reported as a radical CN source for C−H cyanation of 2-phenylpyridines in the presence of catalytic copper(II) (Scheme 1b).[22,23]

Herein, we will report a serendipitous discovery that AIBN can also be used as a readily available source of an electrophilic CN moiety. When exploring the scope of recently developed C−H amination reactions that proceed via coupling of N anions and C radicals,[24,25] we tested the behavior of AIBN in the presence of strong bases and/or nucleophiles and found that, although AIBN was unreactive toward aryl, as well as alkyne, vinyl, and alkyl Grignard reagents, CN group transfer from AIBN was possible toward more nucleophilic ArLi species (Scheme 1c). Considering that this fast reaction occurs under mild conditions, does not require transition metals, and expands the range of C anion leaving groups applicable for ECR (Scheme 1d), we decided to explore this process in more detail.

PhLi was generated *in situ* prior to the addition of AIBN. The reaction with AIBN at room temperature afforded the desired product in 27% yield (Table 1, entry 1). Cooling the AIBN solution to 0 °C noticeably improved the yield (entry 5, 52% yield). Longer reaction times had no effect (entries 2 and 6). However, the yields decreased when the temperature was decreased to −20 or −41 °C (entries 12 and 13). Increasing reaction temperatures or using 1 equiv of AIBN decreased the yield (entries 3, 4, and 7). Adding >2 equiv of AIBN did not increase the yield (entries 8 and 9). Altering the concentration of the AIBN solution had a minimal effect (entries 10 and 11).

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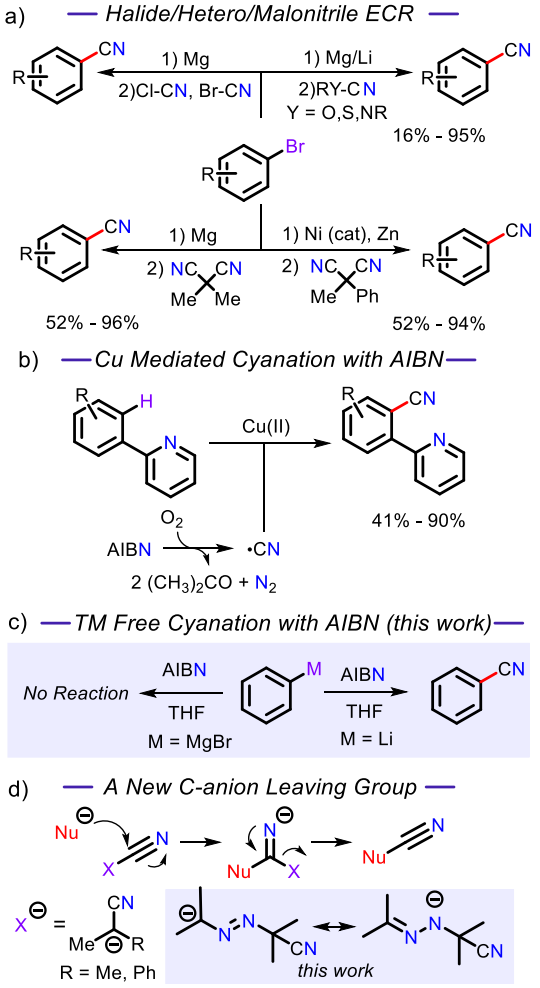
Scheme 1. (a) Literature Examples for Transforming Aryl Bromides into Benzonitriles Using Electrophilic Cyanation Reagents (ECRs), (b) Cu-Mediated C−H Cyanation with AIBN as a Source of CN Radicals, (c) Transition Metal (TM)-Free Cyanation of ArLi with AIBN as an ECR (this work), and (d) Expanding the Range of Carbanion Leaving Groups in ECR



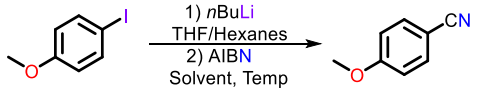
Altering the solvent for AIBN delivery did not provide notable improvements (entries 14−19). Ultimately, we chose the conditions in entry 5 as they provided the best compromise between the yield and convenience.

We explored the scope of this reaction by preparing a range of benzonitriles from heterocyclic, polyaromatic, and electron-rich arenes (Scheme 2). Utilizing AIBN as an ECR provided the desired nitriles in moderate (30−52%) yields with an exception of **8** (16%). The main side product observed in all reactions was the proto-dehalogenated arene.

On the contrary, the reaction of *n*-BuLi with AIBN did not result in the formation of valeronitrile. Instead, it produced substituted hydrazone **12** in a 38% yield via nucleophilic addition to the N═N bond (Scheme 3). Analogously, the reaction with ABCN led to the formation of cyclohexyl-substituted hydrazone **13** in 39% yield.

DFT calculations provide insights into the mechanism of this transformation and suggest potential reasons for both the moderate yield and the switch in chemoselectivity (Figure 1). AIBN has two electrophilic sites, i.e., the N═N and C≡N moieties. Addition of phenyl lithium to the azo bond forms the

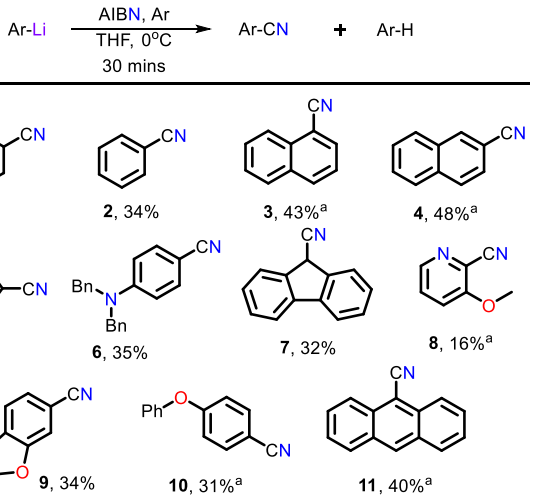
Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	temp (°C)	AIBN (equiv)	yield (%)
1	THF	r.t.	2	27
2[b]	THF	r.t.	2	29
3	THF	35	2	39
4	THF	50	2	15
5	THF	0	2	52
6[b]	THF	0	2	46
7	THF	0	1	22
8	THF	0	3	47
9	THF	0	4	48
10[c]	THF	0	2	46
11[d]	THF	0	2	51
12	THF	−20	2	18
13	THF	−41	2	10
14	toluene	0	2	53
15	MeCN	0	2	<5
16	DMF	0	2	<5
17	DCM	0	2	<5
18	benzene	0	2	36
19	ethyl ether	0	2	42

[a]A 0.34 M solution of ArLi (0.3 mmol) in THF/hexanes was added dropwise to a 0.5 M solution of AIBN in THF. The reaction proceeded for 30 min. The yield was determined by NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]Reaction proceeded for 2 h. [c]In a 0.25 M solution of AIBN in THF. [d]In a 0.1 M solution of AIBN in THF.

Scheme 2. Exploring the Scope of ArLi Reagents[b]



[a]Yield determined by NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]A 0.34 M solution of ArLi in THF/hexanes (2.5 mmol) was added dropwise to a solution of AIBN (0.5 M in THF) at 0 °C.

C−N bond in adduct **14** ($\Delta G^{\ddagger}$ = 18.2 kcal/mol, and ΔG = −25.6 kcal/mol). Addition to the nitrile bond forms a C−C bond in imine intermediate **15** ($\Delta G^{\ddagger}$ = 10.4 kcal/mol, and ΔG = −25.0 kcal/mol). Although formation of both **14** and **15** is equally favorable from a thermodynamic point of view, addition to the C≡N moiety is kinetically preferred (~8 kcal/mol lower activation barrier).

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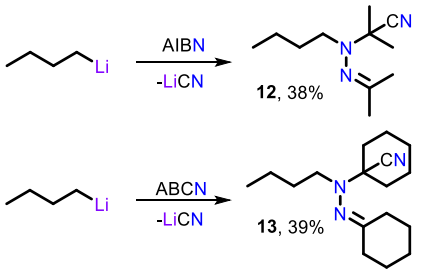
Scheme 3. Formation of Hydrazones in a Reaction between *n*-BuLi and AIBN/ABCN



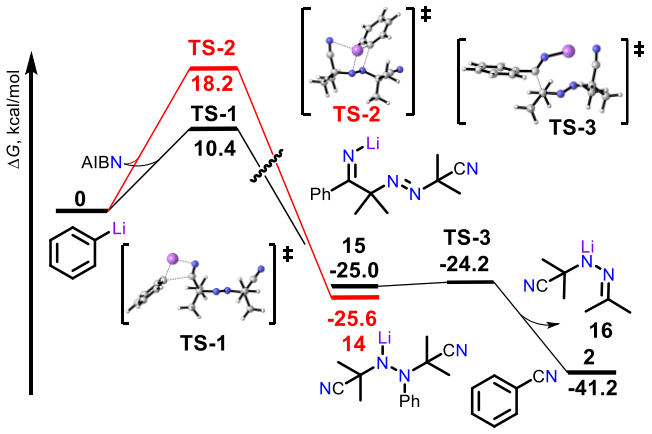
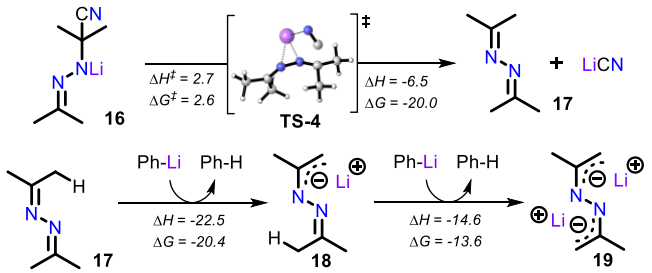


Figure 1. Potential energy diagram for the preferred reaction pathway between PhLi and AIBN. Energies are given in kilocalories per mole at the B3LYP(D3)/6-31+G(d,p) Int=UF, SMD=THF level.

The initial addition to AIBN is the rate-limiting step of this reaction cascade. The process is continued by a nearly barrierless fragmentation of lithiated imine intermediate **15**. This step produces final product **2** along with N-lithiated fragment **16** ($\Delta G^{\ddagger}$ = 0.8 kcal/mol, and ΔG = −16.2 kcal/mol). The latter can quickly and irreversibly eliminate LiCN to produce ketazine **17** (Scheme 4; $\Delta G^{\ddagger}$ = 2.6 kcal/mol, and ΔG

Scheme 4. Reaction Energies for Proton Transfer from 17 and 18 to PhLi[a]



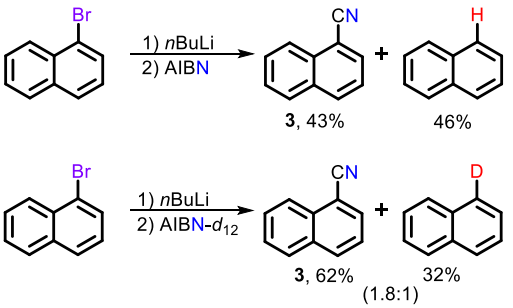
[a]Energies are given in kilocalories per mole at the B3LYP(D3)/6-31+G(d,p) Int=UF, SMD=THF level.

= −20.0 kcal/mol). Importantly, C−H bonds in the ketazine are sufficiently acidic to protonate the remaining unreacted PhLi, as indicated by the highly favorable computed free energies for this process (for **18**, ΔG = −20.4 kcal/mol; for **19**, ΔG = −13.6 kcal/mol).

These results explain why the reaction yields did not exceed 50%. Formation of **17**, made possible by two fast and efficient eliminations, acidifies the methyl C−H bonds, so they become capable of protonating PhLi. For every mole of benzonitrile produced, 1−2 mol of phenyl lithium is potentially wasted via protonation.

Our experimental data are consistent with this mechanistic picture. For example, 1-bromonaphthalene forms 1-cyanonaphthalene **3** and naphthalene in 43% and 46% yields, respectively (Scheme 5). The use of AIBN-d_{12} in place of

Scheme 5. Under the Standard Conditions, 1-Bromonaphthalene Forms 3 and Naphthalene in 43% and 46% Yields, Respectively[a]



[a]Using AIBN-d_{12} in place of AIBN yields **3** and naphthalene-D in 62% and 32% yields, respectively.

AIBN increased the yield of the desired nitrile **3** at the expense of the protonated byproduct (the ratio of nitrile **3** to naphthalene-D improved to 1.8). Deuterium incorporation supports the idea that the aryl lithium can be quenched by **17** and/or **18**.

We have further expanded computational analysis to explore the reaction of *n*-BuLi and AIBN (Figure 2). For this

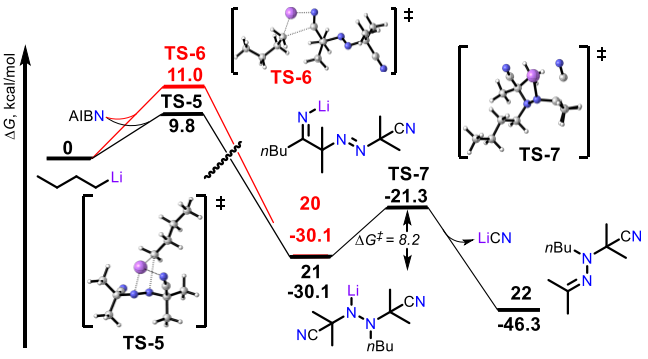


Figure 2. Potential energy diagram for the preferred reaction pathway between *n*-BuLi and AIBN. Energies are given in kilocalories per mole at the B3LYP(D3)/6-31+G(d,p) Int=UF, SMD=THF level.

nucleophile, addition to the nitrile ($\Delta G^{\ddagger}$ = 11.0 kcal/mol, and ΔG = −30.1 kcal/mol) is kinetically disfavored over addition to the azo bond ($\Delta G^{\ddagger}$ = 9.8 kcal/mol, and ΔG = −30.1 kcal/mol). Elimination of LiCN from adduct **21** is predicted to quickly ($\Delta G^{\ddagger}$ = 8.2 kcal/mol, and ΔG = −16.8 kcal/mol) produce observed product **22**.

Intermediates and transition state geometries for the two diverging mechanistic paths are summarized in Scheme 6. In all transition states, the nucleophilic attack is preceded by coordination of Li^+ to the nitrogen adjacent to the attack site.

The Li^+ ion in intermediate **15** (and similarly **20**) is bound to the imine anion (1.8 Å), and it also coordinates with the other three AIBN nitrogen atoms. In this species, lithium

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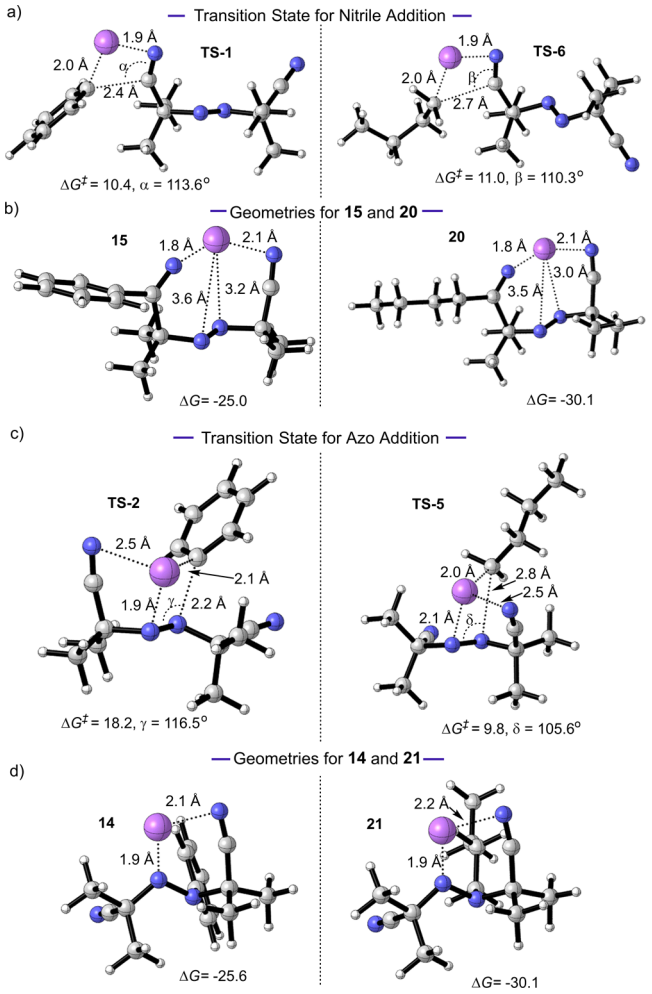
Scheme 6. Intermediate and Transition State Geometries for Nucleophilic Addition to AIBN[a]



[a]Geometries for PhLi as a nucleophile (left) and geometries for *n*-BuLi as a nucleophile (right). Energies are given in kilocalories per mole at the B3LYP(D3)/6-31+G(d,p) Int=UF, SMD=THF level.

positions itself directly above the azo moiety (3.2 and 3.6 Å) and adjacent to the nitrile bond (2.1 Å), so the lithium is "cradled" by the four nitrogens. This chelation assists with the fragmentation that releases the nitrile product and forms **16** as a byproduct.

DFT calculations show that nucleophilic addition to the N═N bond can provide two different patterns for Li···N coordination. In **TS-2**, Li^+ first coordinates to nitrogen in the azo bond and the adjacent C≡N group (Scheme 6). As the bulky phenyl group attacks the N═N bond (2.2 Å), it pushes away one of the C≡N groups and incorporates the N···Li···N moiety in a strained "five-membered ring". Conversely, as *n*-BuLi moves to attack the N═N bond (2.8 Å) in **TS-5**, Li^+ incorporates the N···Li···N contact within a six-membered ring with nitrogen in the azo bond and the furthest C≡N bond. Note that the kinetically favored transition state can be reached via an earlier transition geometry with a less bulky nucleophile. The lowest-energy geometry observed for intermediates **14** and **21** has Li^+ coordinated within a "six-membered ring". For additional information about the energies of the orbital interactions between the lone pairs of nitrogen and Li, see the Supporting Information.

In summary, AIBN can serve as a readily available and inexpensive ECR that transforms ArLi into benzonitriles in moderate yields. After the initial addition of phenyl lithium to the nitrile bond of AIBN, the intermediate "cradles" lithium between several nitrogen atoms. The transfer of lithium from one nitrogen to another allows for a near barrierless fragmentation that produces the desired nitrile product and a lithiated nitrogen-rich byproduct. Calculations suggest that, to increase the yield of cyanoarenes, one would need to slow this fragmentation because the N-rich side product can undergo a second LiCN elimination to form acetone bis-hydrazone. The latter has relatively acidic C−H bonds that are capable of protonating the still unreacted ArLi. Kinetic isotope studies with AIBN-d_{12} in place of AIBN increased the yield of the desired product. Interestingly, *n*-BuLi prefers addition to the azo bond with the subsequent formation of a highly substituted hydrazone.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all ^{1}H NMR experiments were performed on BRUKER AV 400 MHz, BRUKER AV 500 MHz, and BRUKER AV 600 MHz spectrometers at 298 K. Proton chemical shifts are given relative to the residual proton signal of $CDCl_3$ (7.26 ppm). Carbon chemical shifts were internally referenced to $CDCl_3$ (77.23 ppm). Data are reported as follows: chemical shifts in parts per million (δ), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constants (hertz), and integration. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. High-resolution mass spectra (HRMS) were recorded on an Agilent 6200 Series TOF instrument. Acetonitrile, benzene, diethyl ether, dichloromethane, DMF, toluene, and tetrahydrofuran (THF) were obtained from a model SPS-4 solvent purification system. Hexanes for column chromatography and preparatory thin layer chromatography were distilled prior to use. All other solvents were used as purchased. Unless otherwise specified, all reagents were used as is from suppliers without further purification. Column chromatography was performed using silica gel (60 Å), and preparatory thin layer chromatography was performed using a 1000 μm glass-backed plate containing UV dye. All TLC analysis was visualized by UV light (254 nm). Structural drawings were produced with CYLView version 1.0.1.[26]

General Procedure. All solvents were purged with argon and, if needed, dried under 4 Å molecular sieves. All round-bottom flasks were charged with a stir bar and flame-dried three times. The dry flask was charged with an aryl halide and backfilled three times with argon.

The aryl halide (2.5 mmol) was dissolved in 5 mL of dry THF and cooled to −78 °C. Once cooled, 2.5 M *n*-BuLi (2.2 mL, 5.5 mmol, 2.2 equiv) was added dropwise and left to stir for 30 min. Unless otherwise noted, the reaction mixture was then warmed to room temperature. A separate 0.5 M solution of AIBN (5 mmol, 2 equiv) in THF was cooled to 0 °C, and the phenyl lithium solution was added dropwise via cannula. The reaction mixture was left to stir for 30 min at 0 °C, and the reaction quenched with deionized (DI) water. The organic and aqueous layers were separated, and the aqueous layer was washed twice with diethyl ether. The organic layers were collected, dried, and concentrated. The crude mixture was then washed with methyl *tert*-butyl ether and cooled, causing AIBN to crystallize out. The AIBN was collected and purified via recrystallization for future batches. The solute was concentrated and purified via column chromatography using hexanes and methyl *tert*-butyl ether. NMR yields were determined using 1,3,5-trimethoxybenzene as an internal standard.

Synthesis of AIBN-d_{12}. To a two-neck flask charged with a stir bar were added acetone-d_6 (10 g, 156 mmol), 34 mL of DI water, and then sodium cyanide (6.4 g, 130 mmol). Once everything was dissolved, the reaction flask was cooled in an ice bath to 0 °C and a 30% (v/v) solution of H_2SO_4 (41 mL) was added dropwise over 1 h.

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After the addition was complete, the reaction mixture was allowed to warm to room temperature and stir for 18 h. The reaction mixture was washed with Et_2O (3 × 30 mL), and the organic layers were collected, washed with brine (20 mL), and dried over Na_2SO_4. After the organic layer was concentrated, the crude product was purified via distillation to give the desired cyanohydrin as a colorless oil in 65% yield (9.2 g, 101 mmol).

To a round-bottom flask charged with a stir bar were added the cyanohydrin (8.74 g, 95.9 mmol) and 40 mL of DI water. Hydrazine monohydrate [85% (w/w), 2.1 mL, 43.2 mmol] was added, and the reaction mixture was stirred vigorously for 24 h at room temperature. A colorless crystal was formed and collected via filtration to give the desired AIBN-H-d_{12} in 40% yield (6.8 g, 38 mmol).

To a two-neck round-bottom flask charged with a stir bar were added KBr (4.5 g, 38 mmol) and DI water (100 mL). After the KBr was dissolved, AIBN-H-d_{12} (6.8 g, 38 mmol) was added, and the reaction mixture was cooled to 0 °C. A solution of Oxone (23.2 g, 152 mmol) dissolved in 121 mL of DI water was then added via cannula, and the reaction mixture was stirred for 45 min. The reaction was quenched with a solution of sodium thiosulfate, and the solid product was obtained via filtration. The crude product was purified via recrystallization with methanol, and the desired AIBN-d_{12} was obtained as a colorless crystal in 77% yield (5.2 g, 29.3 mmol): ^{1}H NMR (500 MHz, chloroform-*d*) δ 1.65 (s); ^{2}H NMR (92 MHz, chloroform-*d*) δ 1.82−1.71 (m); $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 119.10, 67.99 (d, J = 6.1 Hz), 25.69−22.90 (m); HRMS (ESI-TOF) m/z [M + H$^+$] calcd for $(C_8D_{12}N_4)$+H$^+$ 177.1888, found 177.1900.

4-Methoxybenzonitrile (**1**). Following the general procedure with 4-iodoanisole provided the desired product as a colorless solid in 52% yield as determined by NMR: ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.58 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.9 Hz, 2H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 162.86, 134.01, 119.26, 114.77, 103.99, 55.57. Spectra matched those previously reported.[21]

Benzonitriles (**2**). Following the general procedure with 1-bromobenzene provided the desired product as a colorless oil in 34% yield (238 mg, 2.31 mmol): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.67 (d, J = 7.1 Hz, 1H), 7.61 (d, J = 7.5 Hz, 0H), 7.49 (t, J = 7.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*) δ 132.80, 132.14, 129.14, 118.86, 112.43.[27]

1-Naphthonitrile (**3**). Following the general procedure with 1-bromonaphthalene provided the desired product as a colorless powder in 43% yield, and naphthalene was isolated in 46% yield (163 mg, 1.08 mmol): ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.27 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 8.3 Hz, 1H), 8.00−7.92 (m, 2H), 7.78−7.69 (m, 1H), 7.69−7.62 (m, 1H), 7.55 (dd, J = 8.3, 7.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*) δ 133.29, 132.94, 132.64, 132.38, 128.67, 128.62, 127.57, 125.18, 124.94, 117.83, 110.23. Spectra matched those previously reported.[28]

2-Naphthonitrile (**4**). Following the general procedure with 2-bromonaphthalene provided the desired product as a colorless powder in 48% yield as determined by NMR: ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.27 (d, J = 1.5 Hz, 1H), 8.09−7.84 (m, 3H), 7.68 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.64 (ddt, J = 7.9, 3.6, 1.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 134.68, 134.20, 132.28, 129.23, 129.07, 128.45, 128.09, 127.69, 126.39, 119.30, 109.41. Spectra matched those previously reported.[21]

1-Methyl-1H-indole-2-carbonitrile (**5**). 1-Methyl-1*H*-indole (328 mg, 2.5 mmol) dissolved in dry THF (5 mL) was cooled to 0 °C, and *n*-BuLi (2.2 mL, 2.5 M in hexanes) was added dropwise. After the addition, the reaction mixture was warmed to 0 °C, added via cannula to a solution of AIBN (821 mg, 5 mmol) in dry THF (0.5 M), and allowed to stir for 30 min. The reaction was quenched with DI water. The organic and aqueous layers were separated, and the aqueous layer was washed twice with diethyl ether. The organic layers were collected, dried, and concentrated. The crude mixture was then washed with methyl *tert*-butyl ether and cooled, causing AIBN to crystallize out.

The solute was concentrated and purified via column chromatography using hexanes and methyl *tert*-butyl ether. The desired product was formed as a yellow solid in 45% yield as determined by NMR: ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.72 (dt, J = 8.1, 1.1 Hz, 1H), 7.46 (dt, J = 8.6, 1.1 Hz, 1H), 7.42 (ddd, J = 8.4, 6.7, 1.2 Hz, 1H), 7.23 (d, J = 0.9 Hz, 1H), 7.19 (ddd, J = 8.0, 6.7, 1.2 Hz, 1H), 4.10 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 140.37, 136.55, 125.95, 125.69, 123.00, 120.75, 113.93, 110.28, 31.84. Spectra matched those previously reported.[29]

4-(Dibenzylamino) Benzonitrile (**6**). Following the general procedure with *N*,*N*-dibenzyl-4-bromoaniline provided the desired product as a yellow-brown crystal in 35% yield as determined by NMR: ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.42 (d, J = 8.9 Hz, 2H), 7.36 (t, J = 7.5 Hz, 4H), 7.30 (t, J = 7.3 Hz, 2H), 7.21 (d, J = 7.5 Hz, 4H), 6.72 (d, J = 8.9 Hz, 2H), 4.72 (s, 4H); $^{13}C\{^1H\}$ NMR (151 MHz, chloroform-*d*) δ 151.86, 136.82, 133.68, 128.99, 127.47, 126.34, 120.40, 112.12, 98.57, 54.16. Spectra matched those previously reported.[21]

9H-Fluorene-9-carbonitrile (**7**). 9*H*-Fluorene (333 mg, 2.0 mmol) dissolved in dry THF (4 mL) was cooled to 0 °C, and *n*-BuLi (2.2 mL, 2.5 M in hexanes) was added dropwise. After the addition, the reaction mixture was warmed to 0 °C, added via cannula to a solution of AIBN (655 mg, 4 mmol) in dry THF (0.5 M), and allowed to stir for 30 min. The reaction was quenched with DI water. The organic and aqueous layers were separated, and the aqueous layer was washed twice with diethyl ether. The organic layers were collected, dried, and concentrated. The crude mixture was then washed with methyl *tert*-butyl ether and cooled, causing AIBN to crystallize out.

The solute was concentrated and purified via column chromatography using hexanes and methyl *tert*-butyl ether. The desired product was formed as yellow crystals in 32% yield (123 mg, 0.64 mmol): ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.78 (d, J = 7.6 Hz, 2H), 7.72 (d, J = 7.5 Hz, 2H), 7.50 (t, J = 7.5 Hz, 2H), 7.46−7.38 (m, 2H), 4.90 (s, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 140.87, 137.85, 129.31, 128.22, 125.11, 120.63, 118.27, 37.04. Spectra matched those previously reported.[30]

3-Methoxypicolinonitrile (**8**). Following the general procedure with 2-bromo-3-methoxypyridine provided the desired product as a light tan solid in 16% yield as determined by NMR: ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.31 (dd, J = 4.6, 1.3 Hz, 1H), 7.51 (dd, J = 8.7, 4.6 Hz, 1H), 7.38 (dd, J = 8.7, 1.3 Hz, 1H), 4.00 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 158.63, 142.71, 127.88, 123.72, 119.11, 115.10, 56.17. Spectra matched those previously reported.[31]

Benzo[d][1,3]dioxole-5-carbonitrile (**9**). Following the general procedure with 5-bromobenzo[*d*][1,3]dioxole provided the desired product as a faint yellow crystal in 34% yield (123 mg, 0.84 mmol): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.23 (dd, J = 8.1, 1.7 Hz, 1H), 7.05 (d, J = 1.7 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 6.09 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*) δ 151.54, 148.04, 128.23, 118.90, 111.42, 109.14, 104.97, 102.22. Spectra matched those previously reported.[27]

4-Phenoxybenzonitrile (**10**). Following the general procedure with 1-bromo-4-phenoxybenzne provided the desired product as a white-yellow solid in 31% yield as determined by NMR: ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.61 (d, J = 8.6 Hz, 2H), 7.43 (t, J = 7.8 Hz, 2H), 7.25 (t, J = 7.4 Hz, 1H), 7.10 (d, 2H), 7.02 (d, J = 8.7 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*) δ 161.66, 154.83, 134.13, 130.25, 125.15, 120.40, 118.83, 117.93, 105.84. Spectra matched those previously reported.[32]

Anthracene-9-carbonitrile (**11**). Following the general procedure with 9-bromoanthracene provided the desired product as a yellow solid in 40% yield as determined by NMR: ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.69 (s, 1H), 8.44 (d, J = 8.7 Hz, 2H), 8.10 (d, J = 8.5 Hz, 2H), 7.74 (ddd, J = 8.4, 6.7, 1.3 Hz, 2H), 7.61 (ddd, J = 8.0, 6.6, 1.1 Hz, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, chloroform-*d*) δ 133.35, 132.77, 130.66, 128.98 (d, J = 1.4 Hz), 126.38, 125.33, 117.29, 105.47. Spectra matched those previously reported.[27]

2-[1-Butyl-2-(propan-2-ylidene)hydrazineyl]-2-methylpropanenitrile (**12**). *n*-BuLi (3.1 mL, 7.8 mmol, 2.5 M in hexanes) was added to dry THF (19 mL), cooled to 0 °C, added via cannula to a solution

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of AIBN (2.57 g, 15.6 mmol) in dry THF (0.5 M), and allowed to stir for 30 min. The reaction was quenched with DI water. The organic and aqueous layers were separated, and the aqueous layer was washed twice with diethyl ether. The organic layers were collected, dried, and concentrated. The crude mixture was then washed with methyl *tert*-butyl ether and cooled, causing AIBN to crystallize out.

The solute was concentrated and purified via column chromatography using hexanes and methyl *tert*-butyl ether. The desired product was formed as a yellow oil in 38% yield (581 mg, 3.0 mmol): ^{1}H NMR (500 MHz, chloroform-*d*) δ 2.63 (dd, J = 8.4, 6.5 Hz, 2H), 1.94 (s, 3H), 1.89 (s, 3H), 1.29 (s, 6H), 1.25−1.18 (m, 2H), 1.17−1.09 (m, 2H), 0.79 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 173.17, 57.36, 52.36, 30.04, 25.84, 24.56, 20.46, 19.90, 13.99; HRMS (ESI-TOF) m/z [M + H$^+$] calcd for ($C_{11}H_{21}N_3$)+H$^+$ 196.1735, found 196.1804.[33]

*1-(1-Butyl-2-cyclohexylidenehydrazineyl) Cyclohexane-1-carbonitrile (**13**).* *n*-BuLi (2 mmol, 2.5 M in hexanes) was added to dry THF (4 mL), cooled to 0 °C, added via cannula to a solution of AIBN (655 mg, 4 mmol) in dry THF (0.5 M), and allowed to stir for 30 min. The reaction was quenched with DI water. The organic and aqueous layers were separated, and the aqueous layer was washed twice with diethyl ether. The organic layers were collected, dried, and concentrated. The crude mixture was then washed with methyl *tert*-butyl ether and cooled, causing AIBN to crystallize out.

The solute was concentrated and purified via column chromatography using hexanes and methyl *tert*-butyl ether. The desired product was formed as a colorless oil in 39% yield as determined by NMR: ^{1}H NMR (500 MHz, chloroform-*d*) δ 2.76 (t, J = 7.3 Hz, 2H), 2.57 (t, J = 6.1 Hz, 2H), 2.38 (t, J = 6.3 Hz, 2H), 2.06 (d, J = 13.1 Hz, 2H), 1.74 (td, J = 7.9, 6.4, 2.9 Hz, 4H), 1.63 (dddd, J = 16.9, 12.8, 7.5, 4.0 Hz, 6H), 1.42−1.14 (m, 7H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 178.10, 120.61, 63.05, 51.34, 35.81, 34.45, 30.37, 30.19, 27.63, 26.58, 26.04, 25.06, 22.54, 20.62, 14.12; HRMS (ESI-TOF) m/z [M + H$^+$] for ($C_{17}H_{29}N_3$)+H$^+$ 276.2361, found 276.2428.

Naphthalene-1-d. Following the general procedure with 1-bromonaphthalene (580 mg, 2.8 mmol) and AIBN-d_{12} (987 mg, 5.6 mmol) in place of AIBN provided the desired product as a colorless powder in 34% yield (114 mg, 0.9 mmol): ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.96 (dd, J = 6.0, 3.5 Hz, 3H), 7.70−7.44 (m, 4H); ^{2}H NMR (92 MHz, chloroform-*d*) δ 7.83 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 133.57, 133.51, 128.01, 127.97, 125.95, 125.83. Spectra matched those previously reported.[34]

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c02859.

Full experimental details, ^{1}H and ^{13}C NMR spectra for all of the prepared compounds, and computational details for all calculated structures (PDF)

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Notes

The authors declare no competing financial interest.

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