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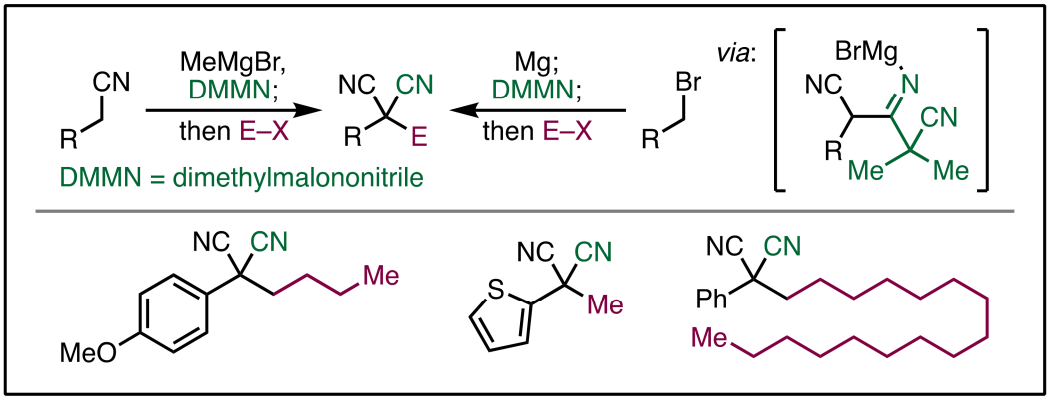

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A one-pot electrophilic cyanation–functionalization strategy for the synthesis of disubstituted malononitriles

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ABSTRACT

Malononitriles are valuable synthetic intermediates for many applications, including the synthesis of herbicides and other biologically active molecules, and the synthesis of chiral ligands for asymmetric catalysis. This article describes the development of a procedure for the conversion of primary nitriles to malononitriles using dimethylmalononitrile, a commercial, non-toxic, carbon-bound source of electrophilic cyanide. This procedure avoids the use of toxic cyanide or malononitrile as a starting material. This protocol is further applied to the dicyanation of benzyl Grignard reagents, generated from benzyl bromides, yielding fully functionalized malononitriles from a nitrile-free precursor.

1. Introduction

Malononitriles are important reaction partners and synthetic building blocks for a variety of applications.[1] Arylmalononitriles are key intermediates in the synthesis of oxopyrazoline herbicides such as pinoxaden.[2] Arylmalononitriles have been used as intermediates in the synthesis of the 2-amino-pyrazolo[1,5-a]pyrimidine class of molecules, which are inhibitors for JAK2,[3] and in the synthesis of a series of ERα and ERβ ligands.[4] Disubstituted malononitriles have been used as antiparasitic agents in mammals.[5] They are also presursors to bisoxazoline (BOX) ligands, a popular class of chiral ligands for asymmetric catalysis.[6] Substituted malononitriles can be quickly accessed in one or two steps from malononitrile,[7,8] which is commercially available and inexpensive. However, malononitrile is toxic[9] and has a low melting point of 30–32 ºC, making it a less than ideal reagent. Further, the synthesis of aryl-substituted malononitrile derivatives can sometimes require forcing conditions[10,2b] or reactive reagents.[11,12]

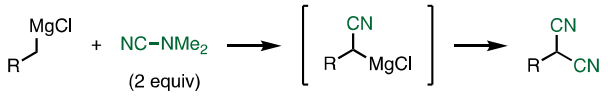
One approach towards the synthesis of substituted malononitriles which avoids the use of toxic malononitrile is the electrophilic cyanation of primary nitriles (Scheme 1a). Electrophilic cyanation is a well-established strategy to access myriad nitrile-containing compounds,[13,14] including malononitriles.[15] For example, one industrial route for the preparation of malononitrile includes electrophilic cyanation of acetonitrile using cyanogen chloride at high temperature (Scheme 1a, top arrow).[16] The generation of substituted malononitriles via electrophilic cyanation has also been known since 1927 (Scheme 1a, middle arrow).[17] Vuylsteke and coworkers observed that Grignard reagents could be converted to malononitriles in the presence of two equivalents of *N*,*N*-dimethylcyanamide, via two transnitrilation events. Since then, much work has gone into the design of mild and safe electrophilic cyanating reagents for the synthesis of malononitriles from primary nitriles (Scheme 1a, bottom arrow), including cyanamides,[18] cyanates,[19] thiocyanates,[20] and 1-cyanobenzotriazole.[21,22]

In 2015, Reeves and coworkers reported that dimethylmalononitrile (DMMN) could be used as a reagent for the electrophilic cyanation of aryllithium and aryl Grignard reagents.[14,23] DMMN is a commercially available bench-stable solid, which has a health rating of 2 in HMIS and NFPA rating systems. The electrophilic nitrile is carbon-bound, imparting stability compared to some of the previously used heteroatom-bound electrophilic cyanating reagents. Its reactivity as an efficient transnitrilation reagent has been known since work reported by Erickson in 1935.[24] Reeves and coworkers have also reported that other derivatives, such as dibenzylmalononitrile (DBMN), are competent electrophilic cyanation reagents.[23]

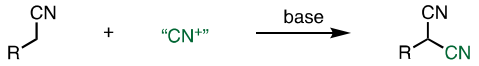
a) Preparation of Malononitriles Using Electrophilic Cyanide

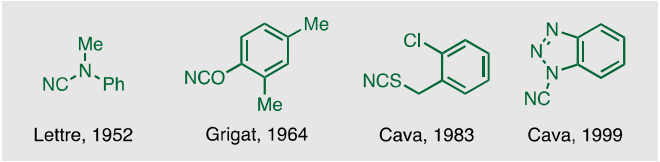
Industrial preparation of malononitrile

Dicyanation of Grignard reagents (Vuylsteke, 1927)

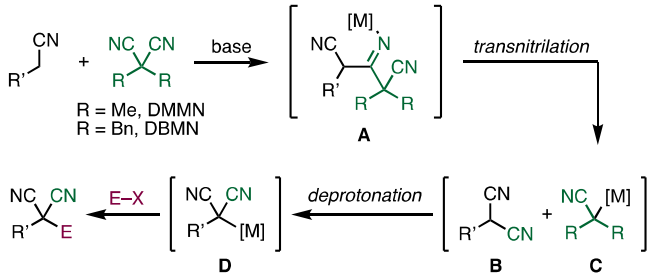


Reaction of nitriles with "CN+" reagents





b) Reaction Design: One-Pot Transnitrilation–Functionalization



Scheme 1. (a) Examples of electrophilic cyanation for accessing malononitriles; (b) Reaction design: Tandem electrophilic cyanation–functionalization with DMMN or DBMN to synthesize disubstituted malononitriles. DMMN = dimethylmalononitrile; DBMN = dibenzylmalononitrile.

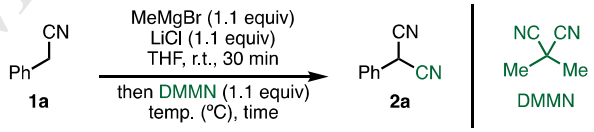
Inspired by this work on the electrophilic cyanation of C(sp^2) centers, we were interested in probing the use of DMMN and DBMN as safe reagents for the cyanation of primary nitriles, which would generate malononitriles via transnitrilation (Scheme 1b). Thus, upon deprotonation with base, a primary nitrile could undergo addition to DMMN to form metal imine intermediate **A**. This intermediate would undergo retro-Thorpe fragmentation[25] to generate the desired transnitrilated malononitrile (**B**) and the corresponding nitrile α-anion (**C**). At this stage, due to the low pK_a of newly formed malononitrile **B**, α-anion **C** would deprotonate **B** to form the more stable α-anion **D**. Conveniently, this α-anion is primed for functionalization, and can be trapped with an appropriate electrophile (E–X) to yield the disubstituted malononitrile.[26] Alternately, rather than using an electrophile, the monosubstituted malononitrile could be obtained via acidic quench of the reaction. Since cyanide salts are never present in the reaction mixture, the generation of HCN gas is not a concern. This strategy represents a facile method for accessing malononitriles from primary nitriles without the use of highly toxic cyanating reagents or malononitrile. Herein, we describe the development of a one-pot protocol for the formation of disubstituted malononitriles from primary nitriles using the electrophilic cyanating reagent DMMN, as well as the application of this strategy to the dicyanation of benzyl bromide.

2. Results and Discussion

We imagined a two-step, one-pot process for the cyanation and functionalization of primary nitriles: 1) transnitrilation in order to generate intermediate **D**, and 2) electrophilic functionalization of **D**. Thus, we set out to optimize each step independently with the goal of later merging them into a one-pot transformation.

For the optimization of the first step of the reaction, we used methylmagnesium bromide as a base, knowing that magnesium(II) anions are competent for transnitrilation chemistry.[23] Thus, a solution of benzyl cyanide (**1a**) in THF was stirred in the presence of methylmagnesium bromide for 30 min to afford the deprotonated α-anion, which was then treated with 1.1 equiv of DMMN (Table 1). Lithium chloride (1.1 equiv) was included to improve the solubility of the organomagnesium species in THF. After 1 h at room temperature, 43% yield of desired 2-phenylmalononitrile (**2a**) was observed (Table 1, Entry 1). By heating the reaction mixture at 80 ºC for 1 h, the yield could be increased to 91% (Entry 2). Stirring at 80 ºC for 6 h gave an optimal yield of 99% (Entry 3). The viability of *n*-butyllithium in this reaction was probed as well. By using *n*-butyllithium as a base, 89% of **2a** could be obtained after stirring at 80 ºC for 1 h (Entry 4). If the reaction was stirred for longer (6 h), slightly greater conversion of **1a** was observed (Entry 5). However, the yield of **2a** varied in these trials, and we often observed the product of nucleophilic addition of α-anion **C** to **2a** in varying amounts, which affected the reproducibility of the transformation using *n*-BuLi.

Table 1. Optimization of the transnitrilation step[a]



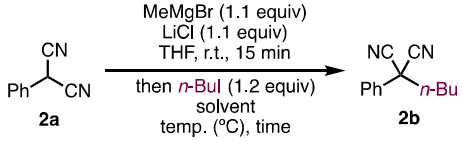
Entry	Temp. (ºC)	Time (h)	Yield **2a** (%)[b]
1	r.t.	1	43
2	80	1	91
3	80	6	99
4[c]	80	1	89
5[c]	80	6	30–99[d]

[a]Reaction conditions: **1a** (46 µL, 0.40 mmol, 1.0 equiv), MeMgBr (1.1 equiv), LiCl (1.1 equiv), THF (0.40 mL, 1.0 M), DMMN (1.1 equiv). DMMN = dimethylmalononitrile.
[b]GC-MS yield based on *n*-dodecane as internal standard.
[c]Using *n*-BuLi (1.1 equiv) instead of MeMgBr and LiCl.
[d]The major observed side-product was the imine resulting from nucleophilic addition of α-anion intermediate **C** to **2a.**

Next, we probed the electrophilic functionalization step of our one-pot process (Table 2). 2-Phenylmalononitrile (**2a**) was used as a malononitrile α-anion precursor. Deprotonation of **2a** using methylmagnesium bromide generates intermediate **D**, which was then treated with iodobutane in various solvents. When THF was used as the solvent, product **2b** was not observed after 1 h at room temperature (Entry 1). The alkylation reaction was observed when a polar co-solvent (DMF) was used (1:1 THF/DMF mixture, Entry 2). If the reaction was stirred at 80 ºC

for 1 h, 30% of **2b** was observed (Entry 3). Finally, when the reaction was left for 16 h, high conversion to **2b** was achieved (Entry 4). *n*-Butyllithium was found to be viable for the functionalization step as well, delivering **2b** in 24% and 93% yields at r.t. and 80 ºC, respectively, after only 1 h (Entries 5 and 6). However, due to the inconsistent formation of side-products when lithium α-anions are generated in the first step of our desired transformation (Table 1, Entry 5), methylmagnesium bromide was chosen as the optimal base for the combined one-pot protocol.

Table 2. Optimization of the electrophilic functionalization step[a]

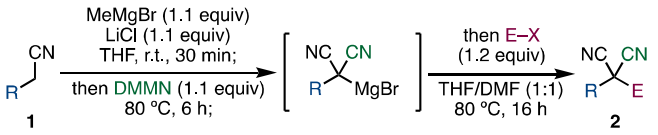


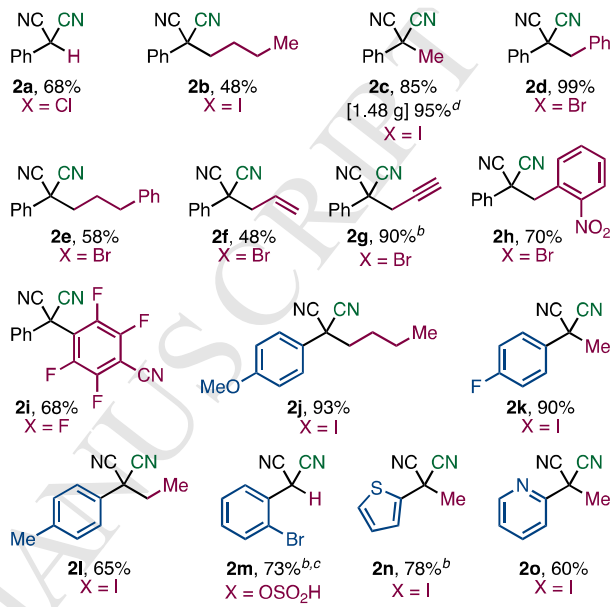
Entry	Solvent	Temp. (ºC)	Time (h)	Yield **2b** (%)[b]
1	THF	r.t.	1	0
2	THF/DMF (1:1)	r.t.	1	6
3	THF/DMF (1:1)	80	1	30
4	THF/DMF (1:1)	80	16	87
5[c]	THF/DMF (1:1)	r.t.	1	24
6[c]	THF/DMF (1:1)	80	1	93

[a]Reaction conditions: **2a** (46 µL, 0.40 mmol, 1.0 equiv), MeMgBr (1.1 equiv), LiCl (1.1 equiv), solvent (0.80 mL, 0.50 M), *n*-BuI (1.2 equiv).
[b]GC-MS yield based on *n*-dodecane as internal standard.
[c]Using *n*-BuLi (1.1 equiv) instead of MeMgBr and LiCl.

Having determined optimal conditions for each individual step of this process, we next combined them into a one-pot protocol by adding DMF after transnitrilation to bring the reaction solvent to a 1:1 THF/DMF mixture. As designed, this protocol was viable for a variety of substrates (Table 3). Thus, primary nitriles (**1**) could be deprotonated using methylmagnesium bromide (1.1 equiv) in the presence of lithium chloride (1.1 equiv) in THF over 30 min. Transnitrilation was achieved in the presence of DMMN (1.1 equiv) by stirring at 80 ºC for 6 h, generating the malononitrile α-anion intermediate. Then, the desired electrophile (1.2 equiv) could be added with DMF to obtain disubstituted malononitriles (**2**) in moderate to excellent yields. A variety of primary alkyl halides (**2b**, **2c**, and **2e**) were viable electrophiles, as well as benzyl, allyl, and propargyl bromides (**2d**, **2f**–**2h**). Alternately, the monosubstituted malononitrile **2a** could be isolated if HCl was used to quench the reaction. Arylation could be achieved using aryl fluorides that were sufficiently activated (**2i**). Finally, a variety of primary benzylic nitriles could be used as starting materials, including electron-rich (**2j**), electron-deficient (**2k**), electron-neutral (**2l**), and heterocyclic derivatives (**2n**, **2o**). The formation of *ortho*-pyridine derivative **2o** is noteworthy since the Lewis basic nitrogen in the pyridine ring does not appear to significantly retard transnitrilation via formation of a magnesium chelate, as has been previously observed in related transnitrilation processes.[14] A sterically hindered substrate (**2m**) was also obtained, although slightly longer transnitrilation times (24 h) were required in this case. The procedure also translated well to a larger scale reaction, delivering 1.48 g of **2c** (95%) on 10-mmol scale.

Table 3. Scope of the one-pot transnitrilation–functionalization reaction for primary nitriles[a]



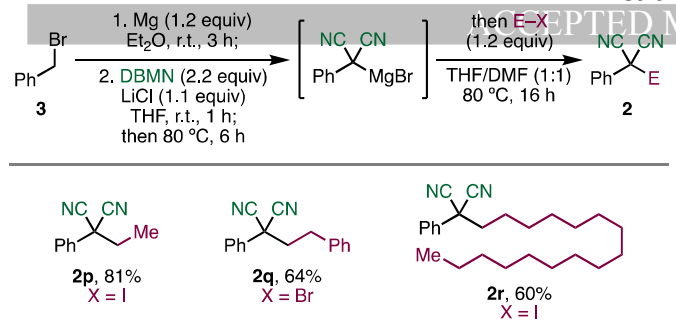


[a]Reaction conditions: Nitrile (0.40 mmol, 1.0 equiv), methylmagnesium bromide (1.1 equiv), lithium chloride (1.1 equiv), THF (1.0 M); then DMMN (1.1 equiv) or DBMN (1.1 equiv), THF (0.5 M); then electrophile (1.2 equiv), THF/DMF (1:1, 0.25 M). Yields are isolated. DMMN = dimethylmalononitrile; DBMN = dibenzylmalononitrile.
[b]Using DBMN (1.1 equiv) instead of DMMN.
[c]Transnitrilation was performed at 80 ºC for 24 h instead of 6 h.

Primary alkyl nitriles are often prepared via nucleophilic cyanation of alkyl halides with toxic cyanide salts such as NaCN or KCN.[27] We therefore wondered if benzyl bromides could be directly converted to malononitriles via formation of a Grignard reagent and a double transnitrilation strategy (Table 4). This protocol represents a rapid and convenient way to access disubstituted malononitriles from a nitrile-free precursor, generating three new C−C bonds in the process.

As demonstrated in Table 4, benzyl bromide (**3**) was converted to benzylmagnesium bromide, which was then treated with DBMN (2.2 equiv)[28] for 1 h at r.t. to allow the first transnitrilation even to take place. Conversion to the malononitrile was achieved by then stirring the reaction mixture at 80 ºC for 6 h. The resulting α-magnesiated malononitrile could then be functionalized with a variety of electrophiles in a 1:1 THF/DMF solvent mixture, affording malononitriles **2p**–**2r** in good yields over two steps.

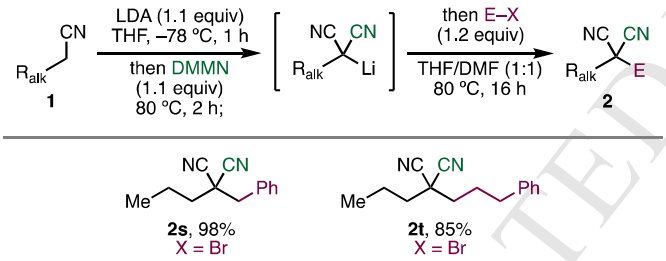
Table 4. Scope of the cyanation–functionalization reaction using benzylmagnesium bromide[a]



[a]Reaction conditions: 1. Benzyl bromide (20 mmol), Mg(0) turnings (1.2 equiv), Et_2O (1.0 M). 2. Benzylmagnesium bromide (0.40 mmol of a solution in Et_2O), lithium chloride (1.1 equiv), DBMN (2.2 equiv), THF (0.50 M); then electrophile (1.2 equiv), THF/DMF (1:1, 0.25 M). Yields are isolated and represent the combined yield over two steps. DBMN = dibenzylmalononitrile.

The transnitrilation–functionalization strategy could be applied to primary alkyl nitriles as well, but with a slight modification. When alkylnitriles were employed in the optimized conditions using methylmagnesium bromide as a base, unselective deprotonation of the α position was observed, which resulted in a mixture of products. This selectivity issue could be circumvented if lithium diisopropylamide (LDA) was used as the base and if the deprotonation was performed at −78 °C instead of r.t. (Table 5). Thus, the transnitrilation–functionalization procedure was used to generate dialkyl-substituted malononitriles **2s** and **2t** in good yield.

Table 5. Cyanation–functionalization of alkyl nitriles using LDA[a]



[a]Reaction conditions: Alkyl nitrile (0.40 mmol, 1.0 equiv), diisopropylamine (1.2 equiv), *n*-BuLi (1.1 equiv), THF (1.0 M); then DMMN (1.1 equiv), THF (0.5 M); then electrophile (1.2 equiv), THF/DMF (1:1, 0.25 M). Yields are isolated. DMMN = dimethylmalononitrile.

3. Conclusion

In conclusion, we have developed a transnitrilation strategy for the synthesis of disubstituted malononitriles from primary nitriles using transnitrilation reagents DMMN and DBMN. This protocol avoids the use of toxic malononitrile or other toxic cyanating reagents. Additionally, this strategy can be applied to the dicyanation of benzylmagnesium bromide to rapidly form disubstituted malononitriles. Further work on transnitrilation chemistry is ongoing in our laboratory.

4. Experimental Section

4.1 General Information

Unless otherwise noted, all reactions were set up on the benchtop and run under an atmosphere of Ar or N_2 using flame-dried glassware and anhydrous solvents. THF, Et_2O, and MeCN were purchased as HPLC-grade (inhibitor-free) from Caledon or Sigma–Aldrich, were dried using a PureSolv MD 5 solvent purification system, and were used without further manipulation. DMF was purchased from Acros as Extra Dry over molecular sieves and was used as received. Methylmagnesium bromide and *n*-butyllithium solutions were purchased from Sigma–Aldrich and were titrated with I_2 on a weekly basis.[29] All other commercial reagents and starting materials were used as received. Compounds were purified by flash column chromatography using SiliCycle SilicaFlash P60 silica gel.

^1H and ^{13}C NMR spectra were recorded on Varian MercuryPlus 400 MHz, Agilent DD2 500 MHz, or Bruker AvanceIII 400 MHz spectrometers. TLC samples were run on EMD Millipore TLC Silica gel 60 F_{254} plates and were visualized by UV or by staining with standard $KMnO_4$, phosphomolybdic acid (PMA), or *p*-anisaldehyde stains. IR spectra were obtained on a Perkin-Elmer Spectrum 100 instrument equipped with a single-bounce diamond/ZnSe ATR accessory as solids or thin films. Melting points were obtained on a Fisher-Johns Melting Point Apparatus. High-resolution mass spectra (HRMS) were recorded on a JEOL AccuTOF JMS-T1000LV mass spectrometer equipped with a Direct Analysis in Real Time (DART) ion source.

4.2 Experimental Procedures and Product Characterization

4.2.1 2,2-Dimethylmalononitrile (DMMN): To a flame-dried 250-mL round-bottom flask with stir bar was added MeCN (100 mL, 0.5 M), malononitrile (4.0 g, 50 mmol, 1.0 equiv), iodomethane (6.8 mL, 110 mmol, 2.2 equiv), and potassium carbonate (17 g, 125 mmol, 2.5 equiv). The reaction was stirred at r.t. for 16 h under N_2. The reaction was opened to air, diluted with DCM (100 mL), filtered using a fritted funnel, and the filtrate was concentrated. The concentrate was purified by flash column chromatography (gradient of 0–40% EtOAc/hexanes) to yield DMMN as a white solid (2.4 g, 26 mmol, 52%). ^1H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 1.82 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ_c 116.9, 26.5, 26.4 ppm; R_f (8:2 hexanes/EtOAc; $KMnO_4$): 0.43.

4.2.2 2,2-Dibenzylmalononitrile (DBMN): To a flame-dried 500-mL round-bottom flask with stir bar was added MeCN (200 mL, 0.5 M), malononitrile (6.6 g, 100 mmol, 1.0 equiv), benzyl bromide (26 mL, 220 mmol, 2.2 equiv), and potassium carbonate (35 g, 250 mmol, 2.5 equiv). The reaction was stirred at r.t. for 16 h under N_2. The reaction was opened to air, diluted with EtOAc (200 mL), filtered using a fritted funnel, and the filtrate was concentrated. The concentrate was purified by recrystallization (DCM/pentane) to yield DBMN as a white solid (19 g, 77 mmol, 77%). ^1H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.48–7.30 (m, 10H), 3.25 (s, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ_C 132.0, 130.3, 129.0, 128.9, 114.9, 43.5, 41.2 ppm; R_f (9:1 hexanes/EtOAc; $KMnO_4$): 0.33.

4.2.3 General Procedure A: Synthesis of malononitriles from primary nitriles using MeMgBr: Step 1: To an 8-mL culture tube with stir bar was added lithium chloride (1.1 equiv) and the flask was flame-dried under vacuum and cooled under an atmosphere of N_2. THF (1.0 M) was added, followed by the appropriate nitrile (1.0 equiv). While stirring, methylmagnesium bromide (1.1 equiv of a solution in Et_2O) was added dropwise at r.t., and the solution was stirred at r.t. for 30 min under an atmosphere of N_2. A 1.1 M stock solution of dimethylmanononitrile (DMMN) or dibenzylmalononitrile (DBMN) in THF was prepared and added at r.t. (1.1 equiv of a 1.1 M solution in THF, reaction volume = 0.50 M with respect to nitrile starting material). The reaction was stirred at 80 °C for 6 h under an atmosphere of N_2. Step 2: The reaction was cooled to r.t. and DMF was added to

bring the reaction solvent to a 1:1 THF/DMF ratio (0.25 M of a 1:1 THF/DMF mixture with respect to nitrile starting material). The desired electrophile (1.2 equiv) was added in a single portion. If the electrophile was a solid, it was added with the DMF as a 0.60 M stock solution. The reaction was stirred at 80 ºC for 16 h, or until complete conversion was achieved as judged by TLC. The reaction was cooled to r.t., opened to air, quenched with 1 M aq. HCl, and extracted with EtOAc (×3). The organic fractions were combined, dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography to yield the desired malononitrile.

*4.2.4 2-Phenylmalononitrile (**2a**):* According to General Procedure A, **2a** was prepared using the following amounts of reagent: lithium chloride (19 mg, 0.44 mmol, 1.1 equiv), THF (0.40 mL), benzyl cyanide (46 µL, 0.40 mmol, 1.0 equiv), methylmagnesium bromide (0.21 mL of a 2.1 M solution in Et_2O, 0.44 mmol, 1.1 equiv), and dimethylmalononitrile (0.40 mL of a 1.1 M solution in THF, 0.44 mmol, 1.1 equiv) (total reaction volume = 0.80 mL of THF, 0.50 M). After transnitrilation, the reaction was cooled to r.t., quenched with 1 M aq. HCl, and worked up as outlined in the general procedure. The crude residue was purified by flash column chromatography (gradient of 0–30% EtOAc/hexanes) to yield **2a** as a white solid (39 mg, 0.27 mmol, 68%). Analytical data:[20] ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.62–7.42 (m, 5H), 5.07 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ_C 130.4, 130.2, 127.2, 126.2, 111.7, 28.1 ppm; R_f (9:1 hexanes/EtOAc; $KMnO_4$/PMA): 0.16.

*4.2.5 2-Butyl-2-phenylmalononitrile (**2b**):* According to General Procedure A, **2b** was prepared using the following amounts of reagent: Step 1: lithium chloride (19 mg, 0.44 mmol, 1.1 equiv), THF (0.40 mL), benzyl cyanide (46 µL, 0.40 mmol, 1.0 equiv), methylmagnesium bromide (0.21 mL of a 2.1 M solution in Et_2O, 0.44 mmol, 1.1 equiv), and dimethylmalononitrile (0.40 mL of a 1.1 M solution in THF, 0.44 mmol, 1.1 equiv). Step 2: DMF (0.80 mL; total reaction solvent = 1.6 mL of a 1:1 DMF/THF mixture, 0.25 M) and iodobutane (55 µL, 0.48 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (gradient of 0–10% EtOAc/hexanes) to yield **2b** as a colourless oil (37 mg, 0.19 mmol, 48%). Analytical data:[12] ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.64–7.45 (m, 5H), 2.30–2.20 (m, 2H), 1.71–1.58 (m, 2H), 1.43 (h, J = 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ_C 132.3, 129.8, 129.7, 125.7, 115.1, 42.5, 42.4, 27.6, 21.9, 13.6 ppm; R_f (9:1 hexanes/EtOAc; UV/$KMnO_4$): 0.61.

*4.2.6 2-Methyl-2-phenylmalononitrile (**2c**):* According to General Procedure A, **2c** was prepared using the following amounts of reagent: Step 1: lithium chloride (19 mg, 0.44 mmol, 1.1 equiv), THF (0.40 mL), benzyl cyanide (46 µL, 0.40 mmol, 1.0 equiv), methylmagnesium bromide (0.21 mL of a 2.1 M solution in Et_2O, 0.44 mmol, 1.1 equiv), and dimethylmalononitrile (0.40 mL of a 1.1 M solution in THF, 0.44 mmol, 1.1 equiv). Step 2: DMF (0.80 mL; total reaction solvent = 1.6 mL of a 1:1 DMF/THF mixture, 0.25 M) and iodomethane (30 µL, 0.48 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (gradient of 0–30% EtOAc/hexanes) to yield **2c** as a colourless oil (53 mg, 0.34 mmol, 85%). Analytical data:[30] ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.64–7.42 (m, 5H), 2.13 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ_C 131.1, 130.0, 129.8, 129.3, 115.7, 36.4, 29.5 ppm; R_f (9:1 hexanes/EtOAc; UV): 0.39.

*4.2.7 2-Benzyl-2-phenylmalononitrile (**2d**):* According to General Procedure A, **2d** was prepared using the following amounts of reagent: Step 1: lithium chloride (19 mg, 0.44 mmol, 1.1 equiv), THF (0.40 mL), benzyl cyanide (46 µL, 0.40 mmol, 1.0 equiv), methylmagnesium bromide (0.21 mL of a 2.1 M solution in Et_2O, 0.44 mmol, 1.1 equiv), and dimethylmalononitrile (0.40 mL of a 1.1 M solution in THF, 0.44 mmol, 1.1 equiv). Step 2: DMF (0.80 mL; total reaction solvent = 1.6 mL of a 1:1 DMF/THF mixture, 0.25 M) and benzyl bromide (57 µL, 0.48 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (gradient of 0–15% EtOAc/hexanes) to yield **2d** as a white solid (93 mg, 0.40 mmol, 99%). Analytical data:[12] ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.52–7.43 (m, 5H), 7.39–7.26 (m, 3H), 7.17–7.10 (m, 2H), 3.46 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ_C 131.7, 131.6, 130.6, 130.1, 129.7, 129.0, 128.8, 126.3, 114.8, 48.7, 44.2 ppm; R_f (9:1 hexanes/EtOAc): 0.41.

*4.2.8 2-Phenyl-2-(3-phenylpropyl)malononitrile (**2e**):* According to General Procedure A, **2e** was prepared using the following amounts of reagent: Step 1: lithium chloride (19 mg, 0.44 mmol, 1.1 equiv), THF (0.40 mL), benzyl cyanide (46 µL, 0.40 mmol, 1.0 equiv), methylmagnesium bromide (0.23 mL of a 1.9 M solution in Et_2O, 0.44 mmol, 1.1 equiv), and dimethylmalononitrile (0.40 mL of a 1.1 M solution in THF, 0.44 mmol, 1.1 equiv). Step 2: DMF (0.80 mL; total reaction solvent = 1.6 mL of a 1:1 DMF/THF mixture, 0.25 M) and 1-bromo-3-phenylpropane (73 µL, 0.48 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (gradient of 0–10% EtOAc/hexanes) to yield **2e** as a white solid (59 mg, 0.23 mmol, 58%). 7.56–7.42 (m, 5H), 7.33–7.25 (m, 2H), 7.25–7.18 (m, 1H), 7.17–7.10 (m, 2H), 2.70 (t, *J* = 7.4 Hz, 2H), 2.28–2.18 (m, 2H), 2.02–1.91 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ_C 140.0, 132.0, 129.9, 129.7, 128.6, 128.3, 126.4, 125.7, 115.0, 42.2, 41.9, 34.5, 26.9 ppm; HRMS *m/z* (DART): calcd for $C_{18}H_{17}N_2$ (M+H) 261.1392; found 261.1398; IR (neat): 3028, 2943, 2931, 2863, 2180, 2169, 2030, 1979, 1884, 1601, 1493, 1453, 1339, 1203, 1156, 1101, 1084, 1029, 1002, 982, 755, 695 cm^{-1}; R_f (9:1 hexanes/EtOAc; UV/$KMnO_4$): 0.58.

*4.2.9 2-Allyl-2-phenylmalononitrile (**2f**):* According to General Procedure A, **2f** was prepared using the following amounts of reagent: Step 1: lithium chloride (19 mg, 0.44 mmol, 1.1 equiv), THF (0.40 mL), benzyl cyanide (46 µL, 0.40 mmol, 1.0 equiv), methylmagnesium bromide (0.23 mL of a 1.9 M solution in Et_2O, 0.44 mmol, 1.1 equiv), and dimethylmalononitrile (0.40 mL of a 1.1 M stock solution in THF, 0.44 mmol, 1.1 equiv). Step 2: DMF (0.80 mL; total reaction solvent = 1.6 mL of a 1:1 DMF/THF mixture, 0.25 M) and allyl bromide (42 µL, 0.48 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (gradient of 0–15% EtOAc/hexanes) to yield **2f** as a colourless oil (35 mg, 0.19 mmol, 48%). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.60–7.54 (m, 2H), 7.53–7.44 (m, 3H), 5.88–5.74 (m, 1H), 5.44–5.31 (m, 2H), 2.97–2.90 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ_C 131.7, 130.1, 129.8, 128.5, 126.0, 123.8, 114.7, 46.7, 42.6 ppm; IR (neat): 3091, 3085, 3070, 2990, 2928, 2357, 2254, 1881, 1645, 1600, 1495, 1452, 1441, 1418, 1027, 990, 934, 759, 715, 694, 655 cm^{-1}; R_f (9:1 hexanes/EtOAc; UV/$KMnO_4$): 0.44.

*4.2.10 2-Phenyl-2-(prop-2-yn-1-yl)malononitrile (**2g**):* According to General Procedure A, **2g** was prepared using the following amounts of reagent: Step 1: lithium chloride (19 mg, 0.44 mmol, 1.1 equiv), THF (0.40 mL), benzyl cyanide (46 µL, 0.40 mmol, 1.0 equiv), methylmagnesium bromide (0.23 mL of a 1.9 M solution in Et_2O, 0.44 mmol, 1.1 equiv), and dibenzylmalononitrile (0.40 mL of a 1.1 M solution in THF, 0.44 mmol, 1.1 equiv). Step 2: DMF (0.80 mL; total reaction solvent = 1.6 mL of a 1:1 DMF/THF mixture, 0.25 M) and propargyl bromide (53 µL of a 80% w/w solution in PhMe, 0.48 mmol, 1.2 equiv). The crude residue was purified by flash column

chromatography (gradient of 0–20% EtOAc/hexanes) to yield **2g** as a colourless oil (64 mg, 0.36 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.66–7.58 (m, 2H), 7.55–7.48 (m, 3H), 3.15 (d, *J* = 2.6 Hz, 2H), 2.37 (t, *J* = 2.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ_C 130.8, 130.6, 129.9, 126.1, 114.1, 75.7, 74.7, 42.1, 33.7 ppm; HRMS *m/z* (DART) calcd for $C_{12}H_9N_2$ (M+H) 181.0766; found 181.0763; IR (neat): 3293 (br), 3069, 3040, 2966, 2935, 2255, 2249, 2132, 1960, 1600, 1494, 1452, 1428, 1338, 1257, 1192, 1069, 1028, 1003, 757, 694, 666, 650 cm^{-1}; R_f (9:1 hexanes/EtOAc; UV/$KMnO_4$): 0.26.

*4.2.11 2-(Nitrobenzyl)-2-phenylmalononitrile (**2h**):* According to General Procedure A, **2h** was prepared using the following amounts of reagent: Step 1: lithium chloride (19 mg, 0.44 mmol, 1.1 equiv), THF (0.40 mL), benzyl cyanide (46 µL, 0.40 mmol, 1.0 equiv), methylmagnesium bromide (0.23 mL of a 1.9 M solution in Et_2O, 0.44 mmol, 1.1 equiv), and dimethylmalononitrile (0.40 mL of a 1.1 M stock solution in THF, 0.44 mmol, 1.1 equiv). Step 2: 2-nitrobenzyl bromide (0.10 g in 0.80 mL of DMF, 0.48 mmol, 1.2 equiv) (total reaction solvent = 1.6 mL of a 1:1 DMF/THF mixture, 0.25 M). The crude residue was purified by flash column chromatography (gradient of 10–40% EtOAc/hexanes) to yield **2h** as a yellow solid (77 mg, 0.28 mmol, 70%). Analytical data:[12] ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 8.15–8.03 (m, 1H), 7.74–7.64 (m, 1H), 7.64–7.42 (m, 6H), 7.35–7.20 (m, 1H), 4.06 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ_C 149.3, 133.9, 133.6, 131.2, 130.43, 130.36, 130.0, 127.1, 126.12, 126.07, 114.4, 43.9, 43.5 ppm; R_f (9:1 hexanes/EtOAc; UV/$KMnO_4$): 0.13.

*4.2.12 2-(4-Cyano-2,3,5,6-tetrafluorophenyl)-2-phenylmalononitrile (**2i**):* According to General Procedure A, **2i** was prepared using the following amounts of reagent: Step 1: lithium chloride (19 mg, 0.44 mmol, 1.1 equiv), THF (0.40 mL), benzyl cyanide (46 µL, 0.40 mmol, 1.0 equiv), methylmagnesium bromide (0.23 mL of a 1.9 M solution in Et_2O, 0.44 mmol, 1.1 equiv), and dimethylmalononitrile (0.40 mL of a 1.1 M stock solution in THF, 0.44 mmol, 1.1 equiv). Step 2: DMF (0.80 mL; total reaction solvent = 1.6 mL of a 1:1 DMF/THF mixture, 0.25 M) and 2,3,4,5,6-pentafluorobenzonitrile (60 µL, 0.48 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (gradient of 0–20% hexanes/EtOAc) to yield **2i** as a red oil (86 mg, 0.27 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.67–7.59 (m, 2H), 7.59–7.40 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): 149.4–142.2 (m), 131.4, 130.6, 130.1, 126.8, 126.0 (t, *J* = 1.2 Hz), 118.9 (t, *J* = 10.6), 111.2, 106.2 (t, *J* = 3.7 Hz), 38.9 ppm; ^{19}F NMR (376 MHz, $CDCl_3$, 298 K): −128.4, −133.3 ppm; IR (neat): 2924, 2854, 2250, 1653, 1490, 1453, 1307, 1260, 1002, 978, 919, 813, 784, 751, 709, 693, 673, 637 cm^{-1}; R_f (9:1 hexanes/EtOAc; UV): 0.28.

*4.2.13 2-Butyl-2-(4-methoxyphenyl)malononitrile (**2j**):* According to General Following General Procedure A, **2j** was prepared using the following amounts of reagent: Step 1: lithium chloride (19 mg, 0.44 mmol, 1.1 equiv), THF (0.40 mL), 4-methoxyphenylacetonitrile (54 µL, 0.40 mmol, 1.0 equiv), methylmagnesium bromide (0.16 mL of a 2.7 M solution in Et_2O, 0.44 mmol, 1.1 equiv), and dimethylmalononitrile (0.40 mL of a 1.1 M solution in THF, 0.44 mmol, 1.1 equiv). Step 2: DMF (0.80 mL; total reaction solvent = 1.6 mL of a 1:1 DMF/THF mixture, 0.25 M) and iodobutane (55 µL, 0.48 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (gradient of 0–15% EtOAc/hexanes) to yield **2j** as a colourless oil (84 mg, 0.37 mmol, 93%). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ_H 7.49–7.44 (m, 2H), 7.01–6.95 (m, 2H), 3.84 (s, 3H), 2.21–2.15 (m, 2H), 1.63–1.56 (m, 2H), 1.44–1.34 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ_C 160.5, 127.1, 124.0, 115.3, 114.9, 55.5, 42.4, 41.7, 27.5, 21.8, 13.6 ppm; HRMS *m/z* (DART): calcd for $C_{14}H_{17}N_2O_1$ (M+H) 229.1341; found 229.1345; IR (neat): 3006, 2962, 2935, 2876, 2867, 2841, 2251, 2055, 1609, 1585, 1512, 1463, 1444, 1423, 1306, 1256, 1184, 1120, 1031, 829, 813, 798, 733, 662, 634, 604 cm^{-1}; R_f (9:1 hexanes/EtOAc; UV/$KMnO_4$): 0.47.

*4.2.14 2-(4-Fluorophenyl)-2-methylmalononitrile (**2k**):* Following General Procedure A, **2k** was prepared using the following amounts of reagent: Step 1: lithium chloride (19 mg, 0.44 mmol, 1.1 equiv), THF (0.40 mL), 4-fluorobenzyl cyanide (48 µL, 0.40 mmol, 1.0 equiv), methylmagnesium bromide (0.21 mL of a 2.1 M solution in Et_2O, 0.44 mmol, 1.1 equiv), and dimethylmalononitrile (0.40 mL of a 1.1 M solution in THF, 0.44 mmol, 1.1 equiv). Step 2: DMF (0.80 mL; total reaction solvent = 1.6 mL of a 1:1 DMF/THF mixture, 0.25 M) and iodomethane (30 µL, 0.48 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (gradient of 0–15% EtOAc/hexanes) to yield **2k** as a colourless oil (62 mg, 0.36 mmol, 90%). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ_H 7.63–7.54 (m, 2H), 7.24–7.15 (m, 2H), 2.11 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ_C 163.5 (d, *J* = 250.0 Hz), 129.1 (d, *J* = 3.5 Hz), 127.6 (d, *J* = 8.7 Hz), 117.1 (d, *J* = 22.4 Hz), 115.6, 36.0, 29.6 ppm; ^{19}F NMR (376 MHz, $CDCl_3$, 298 K): −110.3 ppm; HRMS *m/z* (DART): calcd for $C_{10}H_8F_1N_2$ (M+H) 175.0672; found 175.0665; IR (neat): 3083, 3008, 2252, 1898, 1603, 1509, 1454, 1415, 1385, 1309, 1238, 1167, 1107, 1096, 1015, 879, 834, 813, 719, 632 cm^{-1}; R_f (9:1 hexanes/EtOAc): 0.42.

*4.2.15 2-Ethyl-2-(p-tolyl)malononitrile (**2l**):* According to General Procedure A, **2l** was prepared using the following amounts of reagent: Step 1: lithium chloride (19 mg, 0.44 mmol, 1.1 equiv), THF (0.40 mL), 4-methylbenzyl cyanide (53 µL, 0.40 mmol, 1.0 equiv), methylmagnesium bromide (0.21 mL of a 2.1 M solution in Et_2O, 0.44 mmol, 1.1 equiv), and dimethylmalononitrile (0.40 mL of a 1.1 M solution in THF, 0.44 mmol, 1.1 equiv). Step 2: DMF (0.80 mL; total reaction solvent = 1.6 mL of a 1:1 DMF/THF mixture, 0.25 M) and iodoethane (39 µL, 0.48 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (gradient of 0–15% EtOAc/hexanes) to yield **2l** as a colourless oil (47 mg, 0.26 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.46–7.41 (m, 2H), 7.31–7.26 (m, 2H), 2.39 (s, 3H), 2.27 (q, *J* = 7.4 Hz, 2H), 1.22 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ_C 140.2, 130.4, 129.1, 125.8, 115.2, 43.0, 36.6, 21.2, 10.1 ppm; HRMS *m/z* (DART): calcd for $C_{12}H_{13}N_2$ (M+H) 185.1079; found 185.1084; IR (neat): 3303, 2981, 2942, 2928, 2883, 2252, 1908, 1615, 1513, 1459, 1414, 1387, 1192, 1128, 1097, 1044, 1021, 937, 905, 811, 714 cm^{-1}; R_f (9:1 hexanes/EtOAc; UV/$KMnO_4$) 0.55.

*4.2.16 2-(2-Bromophenyl)malononitrile (**2m**):* According to General Procedure A, **2m** was prepared using the following amounts of reagent: Step 1: lithium chloride (19 mg, 0.44 mmol, 1.1 equiv), THF (0.40 mL), 2-bromophenylacetonitrile (52 µL, 0.40 mmol, 1.0 equiv), methylmagnesium bromide (0.16 mL of a 2.7 M solution in Et_2O, 0.44 mmol, 1.1 equiv), and dibenzylmalononitrile (0.40 mL of a 1.1 M stock solution in THF, 0.44 mmol, 1.1 equiv). The reaction mixture was stirred at 80 ºC for 24 h for the transnitrilation step. After transnitrilation, the reaction was cooled to r.t. and quenched with 10% aq. H_2SO_4 and worked up following the procedure outlined in General Procedure A. The crude residue was purified by flash column chromatography (gradient of 0–20% EtOAc/hexanes) to yield **2m** as a white solid (64 mg, 0.29 mmol, 73%), which contained some remaining dibenzylmalononitrile (10 mg, 0.041 mmol).

Analytical data:[31] ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.78–7.66 (m, 2H), 7.55–7.46 (m, 1H), 7.44–7.35 (m, 1H), 5.39 (s, 2H) ppm; 134.1, 132.3, 129.6, 129.2, 126.5, 123.2, 111.1, 29.2 ppm; R_f (9:1 hexanes/EtOAc; UV/$KMnO_4$): 0.13.

*4.2.17 2-Methyl-2-(thiophen-2-yl)malononitrile (**2n**):* According to General Procedure A, **2n** was prepared using the following amounts of reagent: Step 1: lithium chloride (19 mg, 0.44 mmol, 1.1 equiv), THF (0.40 mL), 2-thiopheneacetonitrile (43 µL, 0.40 mmol, 1.0 equiv), methylmagnesium bromide (0.16 mL of a 2.7 M solution in Et_2O, 0.44 mmol, 1.1 equiv), and dibenzylmalononitrile (0.40 mL of a 1.1 M stock solution in THF, 0.44 mmol, 1.1 equiv). Step 2: DMF (0.80 mL; total reaction solvent = 1.6 mL of a 1:1 DMF/THF mixture, 0.25 M) and iodomethane (30 µL, 0.48 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (gradient of 0–20% EtOAc/hexanes) to yield **2n** as an orange oil (51 mg, 0.21 mmol, 78%). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ_H 7.44 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.34 (dd, *J* = 3.6, 1.3 Hz, 1H), 7.06 (dd, *J* = 5.2, 3.6 Hz, 1H), 2.23 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ_C 135.2, 127.9, 127.6, 127.5, 115.0, 32.4, 29.0 ppm; HRMS *m/z* (DART): calcd for $C_8H_7N_2S$ (M+H) 163.0330; found 163.0334; IR (neat): 3115, 3005, 2945, 2253, 2099, 1498, 1452, 1430, 1383, 1355, 1345, 1209, 1165, 1089, 1074, 1044, 927, 858, 831, 704, 653, 617 cm^{-1}; R_f (9:1 hexanes/EtOAc; UV/$KMnO_4$/*p*-anisaldehyde): 0.25.

*4.2.18 2-Methyl-2-(pyridin-2-yl)malononitrile (**2o**):* Following General Procedure A, **2o** was prepared using the following amounts of reagent: Step 1: lithium chloride (19 mg, 0.44 mmol, 1.1 equiv), THF (0.40 mL), 2-pyridylacetonitrile (45 µL, 0.40 mmol, 1.0 equiv), methylmagnesium bromide (0.21 mL of a 2.1 M solution in Et_2O, 0.44 mmol, 1.1 equiv), and dimethylmalononitrile (0.40 mL of a 1.1 M solution in THF, 0.44 mmol, 1.1 equiv). Step 2: DMF (0.80 mL; total reaction solvent = 1.6 mL of a 1:1 DMF/THF mixture, 0.25 M) and iodomethane (30 µL, 0.48 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (gradient of 10–50% EtOAc/hexanes) to yield **2o** as a yellow oil (38 mg, 0.24 mmol, 60%). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 8.74–8.66 (m, 1H), 7.91–7.82 (m, 1H), 7.75–7.67 (m, 1H), 7.46–7.38 (m, 1H), 2.19 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ_C 151.6, 150.5, 138.3, 124.7, 120.2, 115.3, 38.5, 27.3 ppm; HRMS *m/z* (DART) calcd for $C_9H_8N_3$ (M+H) 158.0718; found 158.0718; IR (neat): 3081, 3060, 3004, 2256, 2196, 1588, 1577, 1468, 1435, 1379, 1303, 1182, 1113, 1097, 1050, 994, 781, 747, 622, 615 cm^{-1}; R_f (9:1 hexanes/EtOAc; UV/$KMnO_4$): 0.13.

4.2.19 Benzylmagnesium bromide: To a 25-mL pear-shaped flask with stir bar were added magnesium(0) turnings (0.58 g, 24 mmol, 1.2 equiv). The flask was sealed and was flame-dried and cooled under vacuum. The flask was backfilled with N_2 and Et_2O (20 mL, 1.0 M) was added. The magnesium(0) turnings were activated with 1,2-dibromoethane (ca. 0.050 mmol, 0.58 mmol, 0.029 equiv) and benzyl bromide (**3**) (2.4 mL, 20 mmol, 1.0 equiv) was added portionwise over 2 h at r.t. The reaction was stirred for an additional 1 h at r.t. then was allowed to stand for 1 h at r.t. to yield benzylmagnesium bromide as a grey solution. The solution was titrated with I_2 and was found to have a concentration of 0.85 M (17 mmol, 85%).

4.2.20 General Procedure B: Synthesis of malononitriles from benzylmagnesium bromide: Step 1: To an 8-mL culture tube with stir bar was added lithium chloride (1.1 equiv) and the flask was flame-dried under vacuum and cooled under an atmosphere of N_2. THF (1.0 M) was added, followed by benzylmagnesium bromide (0.47 mL of a 0.85 M solution in Et_2O, 0.40 mmol, 1.0 equiv). A 2.2 M stock solution of dibenzylmalononitrile (DBMN) in THF was prepared and was added at r.t. (2.2 equiv of a 2.2 M solution in THF; reaction volume = 0.50 M with respect to benzylmagnesium bromide). The reaction was stirred under an atmosphere of N_2 at r.t. for 1 h, then was moved to a pre-heated 80 ºC oil bath and was stirred for an additional 6 h. Step 2: The reaction was cooled to r.t. and DMF was added to bring the reaction solvent to a 1:1 THF/DMF ratio (0.25 M of a 1:1 THF/DMF mixture with respect to benzylmagnesium bromide starting material). The desired electrophile (1.2 equiv) was added in a single portion. If the electrophile was a solid, it was added with the DMF as a 0.60 M stock solution. The reaction was stirred at 80 ºC for 16 h, or until complete conversion was achieved as judged by TLC. The reaction was cooled to r.t., opened to air, quenched with 1 M aq. HCl, and extracted with EtOAc (×3). The organic fractions were combined, dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography to yield the desired malononitrile.

*4.2.21 2-Ethyl-2-phenylmalononitrile (**2p**):* According to General Procedure B, **2p** was prepared using the following amounts of reagent: Step 1: lithium chloride (19 mg, 0.44 mmol, 1.1 equiv), benzylmagnesium bromide (**3**) (0.47 mL of a 0.85 M solution in Et_2O, 0.40 mmol, 1.0 equiv), and DBMN (0.80 mL of a 1.1 M stock solution in THF, 0.88 mmol, 2.2 equiv). Step 2: DMF (0.80 mL; total reaction solvent = 1.6 mL of a 1:1 DMF/THF mixture, 0.25 M) and iodoethane (39 µL, 0.48 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (gradient of 0–10% EtOAc/hexanes) to yield **2p** as a colourless oil (65 mg, 0.38 mmol, 95%; 81% from benzyl bromide). Analytical data:[12] ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.59–7.54 (m, 2H), 7.53–7.43 (m, 3H), 2.29 (q, J = 7.4 Hz, 2H), 1.24 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ_C 132.1, 130.0, 129.8, 125.9, 115.1, 43.4, 36.7, 10.1 ppm; R_f (9:1 hexanes/EtOAc; UV/$KMnO_4$): 0.41.

*4.2.22 2-Phenethyl-2-phenylmalononitrile (**2q**):* According to General Procedure B, **2q** was prepared using the following amounts of reagent: Step 1: lithium chloride (19 mg, 0.44 mmol, 1.1 equiv), benzylmagnesium bromide (**3**) (0.47 mL of a 0.85 M solution in Et_2O, 0.40 mmol, 1.0 equiv), and DBMN (0.80 mL of a 1.1 M stock solution in THF, 0.88 mmol, 2.2 equiv). Step 2: DMF (0.80 mL; total reaction solvent = 1.6 mL of a 1:1 DMF/THF mixture, 0.25 M) and (2-bromoethyl)benzene (68 µL, 0.48 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (gradient of 0–10% EtOAc/hexanes) to yield **2q** as a colourless oil (73 mg, 0.30 mmol, 75%; 64% from benzyl bromide). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.64–7.58 (m, 2H), 7.55–7.46 (m, 2H), 7.36–7.20 (m, 4H), 7.20–7.14 (m, 2H), 2.99–2.89 (m, 2H), 2.54–2.44 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ_C 138.3, 132.1, 130.2, 130.0, 129.0, 128.5, 127.1, 125.9, 115.0, 44.5, 32.1 ppm; HRMS *m/z* (DART): calcd for $C_{17}H_{15}N_2$ (M+H) 247.1235; found 247.1237; IR (neat): 3088, 3066, 3030, 2933, 2250, 2158, 1978, 1969, 1604, 1589, 1495, 1452, 1340, 1281, 1216, 1160, 1068, 1030, 1005, 915, 867, 762, 749, 694, 638 cm^{-1}; R_f (9:1 hexanes/EtOAc; UV/$KMnO_4$): 0.47.

*4.2.23 2-Hexadecyl-2-phenylmalononitrile (**2r**):* According to General Procedure B, **2r** was prepared using the following amounts of reagent: Step 1: lithium chloride (19 mg, 0.44 mmol, 1.1 equiv), benzylmagnesium bromide (**3**) (0.47 mL of a 0.85 M solution in Et_2O, 0.40 mmol, 1.0 equiv), and DBMN (0.80 mL of a 1.1 M stock solution in THF, 0.88 mmol, 2.2 equiv). Step 2: iodohexadecane (0.80 mL of a 0.60 M stock solution in DMF, 0.48 mmol, 1.2 equiv; total reaction solvent = 1.6 mL of a 1:1 DMF/THF mixture, 0.25 M). The crude residue was purified by flash column chromatography (gradient of 0–5%

EtOAc/hexanes) to yield **2r** as a colourless oil (0.10 g, 0.27 mmol, 70%; 60% from benzyl bromide). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.60–7.53 (m, 2H), 7.52–7.42 (m, 3H), 2.26–2.13 (m, 2H), 1.69–1.55 (m, 2H), 1.47–1.07 (m, 26H), 0.94–0.73 (m, 3H) ppm; HRMS *m/z* (DART): calcd for $C_{25}H_{42}N_3$ (M+NH_4) 384.3379; found 384.3376; IR (neat): 2955, 2923, 2853, 2370, 2251, 1602, 1495, 1467, 1452, 1378, 1034, 1004, 917, 758, 695 cm^{-1}; R_f (9:1 hexanes/EtOAc; UV/$KMnO_4$): 0.66.

4.2.24 General Procedure C: Synthesis of malononitriles from alkyl nitriles using LDA: Step 1: To a flame-dried 8-mL culture tube with stir bar was added THF (0.40 mL) and diisopropylamine (67 μL, 0.48 mmol, 1.2 equiv). The solution was cooled to 0 ºC and *n*-BuLi (0.28 mL of a 1.6 M solution in hexanes, 0.44 mmol, 1.1 equiv) was added, dropwise, and the reaction was stirred at 0 ºC for 10 min. The solution was cooled to −78 ºC and the desired alkyl nitrile was added neat, dropwise (0.40 mmol, 1.0 equiv), and the reaction was stirred at −78 ºC for 1 h. The reaction was warmed to r.t. and a stock solution of dimethylmalononitrile (DMMN) in THF was added (1.1 equiv of a 1.1 M solution in THF; reaction volume = 0.50 M with respect to alkyl nitrile). The reaction was stirred at 80 ºC for 6 h under an atmosphere of N_2. Step 2: The reaction was cooled to r.t. and DMF was added to bring the reaction solvent to a 1:1 THF/DMF ratio (0.25 M of a 1:1 THF/DMF mixture with respect to alkyl nitrile). The desired electrophile (1.2 equiv) was added in a single portion. If the electrophile was a solid, it was added with the DMF as a 0.60 M stock solution. The reaction was stirred at 80 ºC for 16 h, or until complete conversion was achieved as judged by TLC. The reaction was cooled to r.t., opened to air, quenched with 1 M aq. HCl, and extracted with EtOAc (×3). The organic fractions were combined, dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography to yield the desired malononitrile.

*4.2.25 2-Benzyl-2-propylmalononitrile (**2s**):* According to General Procedure C, malononitrile **2s** was prepared using the following amounts of reagent: Step 1: THF (0.40 mL), diisopropylamine (67 μL, 0.48 mmol, 1.2 equiv), *n*-butyllithium (0.28 mL of a 1.6 M solution in hexanes, 0.44 mmol, 1.1 equiv), valeronitrile (42 μL, 0.40 mmol, 1.0 equiv), and DMMN (0.40 mL of a 1.1 M stock solution in THF, 0.44 mmol, 1.1 equiv). Step 2: benzyl bromide (57 μL, 0.48 mmol, 1.2 equiv) and DMF (0.80 mL; total reaction solvent = 1.6 mL of a 1:1 THF/DMF mixture, 0.25 M with respect to the alkyl nitrile). The crude residue was purified by flash column chromatography (gradient of 0–20% hexanes/EtOAc) to yield **2s** as a white solid (78 mg, 0.39 mmol, 98%). 7.45–7.32 (m, 5H), 3.21 (s, 2H), 1.97–1.86 (m, 2H), 1.83–1.69 (m, 2H), 1.05 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ_C 132.1, 130.2, 129.0, 128.8, 115.4, 43.4, 39.4, 39.3, 19.2, 13.4 ppm; HRMS *m/z* (DART): calcd for $C_{13}H_{18}N_3$ (M+NH_4) 216.1501; found 216.1505; IR (neat): 3070, 3037, 2990, 2966, 2951, 2937, 2924, 2870, 2881, 2249, 1606, 1498, 1469, 1458, 1450, 1274, 1141, 1011, 760, 702, 666 cm^{-1}; TLC R_f (9:1 hexanes/EtOAc; UV/$KMnO_4$): 0.39.

*4.2.26 2-(3-phenylpropyl)-2-propylmalononitrile (**2t**):* According to General Procedure C, **2t** was prepared using the following amounts of reagent: Step 1: THF (0.40 mL), diisopropylamine (67 μL, 0.48 mmol, 1.2 equiv), *n*-butyllithium (0.28 mL of a 1.6 M solution in hexanes, 0.44 mmol, 1.1 equiv), valeronitrile (42 μL, 0.40 mmol, 1.0 equiv), and DMMN (0.40 mL of a 1.1 M stock solution in THF, 0.44 mmol, 1.1 equiv). Step 2: 1-bromo-3-phenylpropane (73 μL, 0.48 mmol, 1.2 equiv) and DMF (0.80 mL; total reaction solvent = 1.6 mL of a 1:1 THF/DMF mixture, 0.25 M with respect to the alkyl nitrile). The crude residue was purified by flash column chromatography (gradient of 0–20% hexanes/EtOAc) to yield **2t** as a colourless oil (76 mg, 0.34 mmol, 85%). 7.36–7.13 (m, 5H), 2.74 (t, *J* = 7.0 Hz, 2H), 2.08–1.97 (m, 2H), 1.96–1.82 (m, 4H), 1.75–1.62 (m, 2H), 1.03 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ_C 140.2, 128.7, 128.3, 126.4, 115.7, 39.7, 37.6, 37.2, 34.8, 27.0, 19.1, 13.4 ppm; HRMS *m/z* (DART): calcd for $C_{15}H_{19}N_2$ (M+H) 227.1548; found 227.1549; IR (neat): 3063, 3029, 2966, 2936, 2877, 2870, 2249, 1736, 1605, 1497, 1461, 1455, 1384, 1244, 1032, 750, 745, 700 cm^{-1}; TLC R_f (9:1 hexanes/EtOAc; UV/$KMnO_4$): 0.30.

*4.2.27 Gram-scale preparation of 2-methyl-2-phenylmalononitrile (**2c**):* According to General Procedure A, 2c was prepared using the following amounts of reagent: Step 1: benzyl cyanide (1.2 mL, 10 mmol, 1.0 equiv), lithium chloride (0.46 g, 11 mmol, 1.1 equiv), THF (10 mL), methylmagnesium bromide (4.1 mL of a 2.7 M solution in Et_2O, 11 mmol, 1.1 equiv), and DMMN (10 mL of a 1.1 M stock solution in THF, 11 mmol, 1.1 equiv); Step 2: iodomethane (0.75 mL, 12 mmol, 1.2 equiv) and DMF (20 mL). The crude residue was purified by flash column chromatography (gradient of 0–20% EtOAc/hexanes) to yield **2c** (1.48 g, 9.5 mmol, 95%). The analytical data matched that of **2c** prepared on 0.40-mmol scale.

*4.2.28 Large-scale preparation of 2-phenylmalononitrile (**2a**):*[32] To a flame-dried 500-mL flask was added copper(I) iodide (1.9 g, 10 mmol, 20 mol %), L-proline (1.2 g, 10 mmol, 20 mol %), potassium carbonate (28 g, 200 mmol, 4 equiv), and malononitrile (9.9 g, 150 mmol, 3.0 equiv). The flask was sealed, evacuated and backfilled with N_2 (×3), and DMSO was added (250 mL, 0.20 M). Iodobenzene (5.6 mL, 50 mmol, 1.0 equiv) was added and the reaction was stirred at 90 ºC for 18 h under N_2. The flask was cooled to 0 ºC, opened to air, and 1 M HCl was added to bring the solution to pH 2–3. The solution was extracted with EtOAc (×3) and the organic fractions were combined, washed with brine (×3), dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (gradient of 10–20% EtOAc/hexanes) to yield **2a** as an off-white solid (6.2 g, 44 mmol, 88%). The characterization data matched that of **2a** prepared using General Procedure A.

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