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Selective Synthesis of β-Ketonitriles via Catalytic Carbopalladation of Dinitriles

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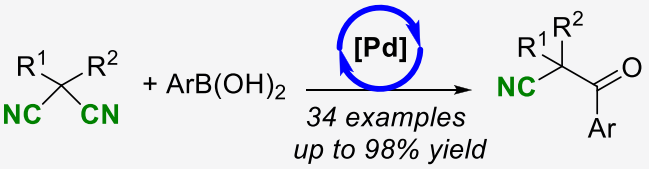
ABSTRACT: A practical, convenient, and highly selective method of synthesizing β-ketonitriles from the Pd-catalyzed addition of organoboron reagents to dinitriles has been developed. This method provides excellent functional-group tolerance, a broad scope of substrates, and the convenience of using commercially available substrates. The method is expected to show further utility in future synthetic procedures.



INTRODUCTION

β-Ketonitriles are important materials that could serve as key precursors for the synthesis of numerous heterocycles[1−5] and structural fragments of biologically active molecules.[6] Thus, over the years, a series of protocols to construct β-ketonitriles have been developed. The most direct approach relies on the nucleophilic substitution between carbonyl species with cyanide or metalated nitriles (Figure 1a, left).[7] Nevertheless, the well-established method has been limited by the lack of general applicability to various electrophilic functionalities. To overcome this issue, metal-catalyzed carbonylative coupling has attracted attention as an alternative approach because of its high functional-group tolerance (Figure 1a, right).[8] The Liu group reported a green and convenient copper-catalyzed cascade coupling of aromatic alcohols and acetonitrile to β-ketonitriles.[8a] Lee and co-workers developed a one-pot, three-component reaction to produce β-ketonitriles by Pd-catalyzed carbonylation of aryl iodides, trimethylsilylacetonitrile, and carbonic oxide (or $Mo(CO)_6$).[8b,c] Beller and co-workers described a carbonylative α-arylation process of aryl iodides and alkyl nitriles yielding α,α-disubstituted products.[8f]

2,2-Disubstituted malononitriles are safe, bench-stable, efficient, and commercially available cyanating agents that have found use in the synthesis of aryl nitriles with aryl boronic acids by Rh catalysis.[9a] Moreover, in a similar catalytic system (Rh-catalyzed), these reagents display diverse application prospects as synthetic precursors in the construction of β-ketonitriles with aryl boronic acids (Figure 1b).[10] When compared with other methods to produce β-ketonitriles, this process offers the convenience of commercially available starting materials and proceeds under milder reaction conditions. However, the imperfection of this protocol is that only substituted malononitriles have been explored. Furthermore, the process of Rh-catalyzed addition of aryl boronic acids to dinitriles needs bases as additives. The synthesis of β-ketonitriles under acid-promoted conditions has not been reported. Herein, we report the development of the Pd-catalyzed addition of organoboron reagents to malononitrile under acidic conditions as an efficient means of preparing β-ketonitriles (Figure 1c).

RESULTS AND DISCUSSION

We initiated our studies by attempting the conversion of malononitrile to the β-ketonitrile using $Pd(CF_3CO_2)_2$ as the catalyst, 2,2′-bipyridine (L1) as the ligand, and 4-methylbenzenesulfonic acid (TsOH) as the acidic additive. When the reaction was conducted at 80 °C in air (Table 1, entry 1), we were surprised to find that the desired product **3a** was obtained in 85% yield and only a trace amount of diaddition product (1,3-diphenylpropane-1,3-dione) was detected (Table 1, entry 1). Next, commercially available Pd catalysts were screened. We found that Pd(II) and Pd(0) could catalyze the present reaction and $Pd(acac)_2$ was the most efficient catalyst (entries 2−7). Encouraged by this result, a series of bidentate nitrogen ligands were examined (entries 8−13). The reaction showed excellent yield, and 4,4′-dimethyl-2,2′-bipyridine (L3) proved the best to give **3a** in 98% yield (entry 9). After the determination of the preferred ligand, the effect of the reaction solvent was studied (entries 14−19). The yield was strongly affected by the reaction medium. Solvents such as toluene, tetrahydrofuran, dimethyl sulfoxide, and methanol gave relatively lower yields, while toluene/H_2O as a mixed solvent was optimal. The screening of reaction time demonstrated that

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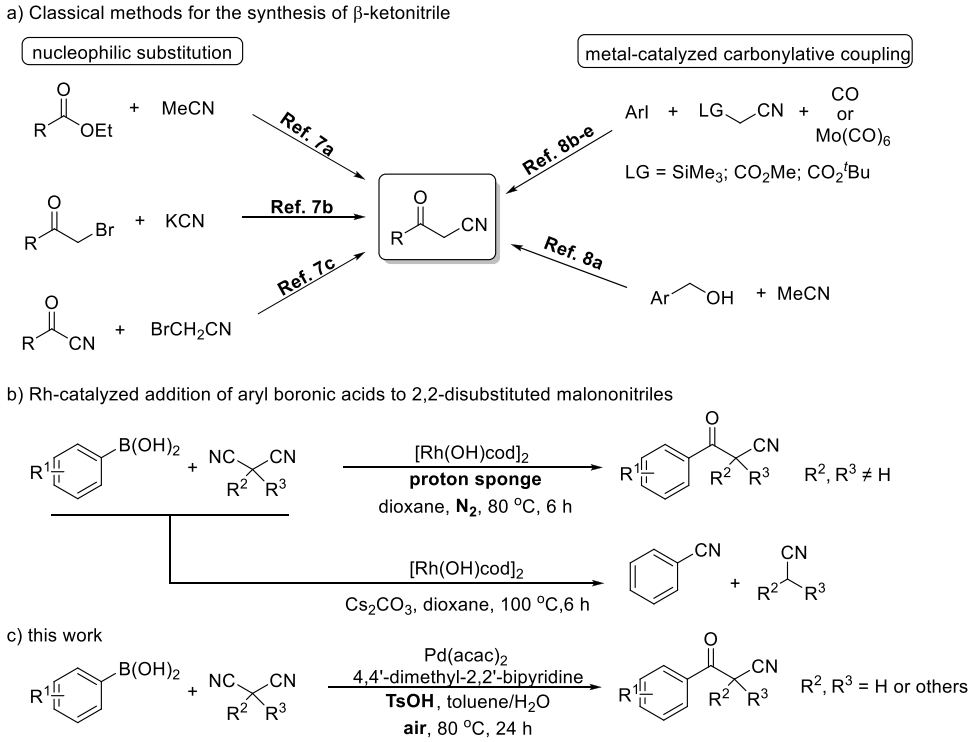
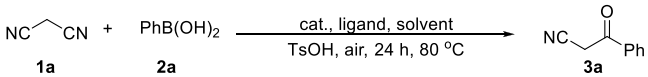
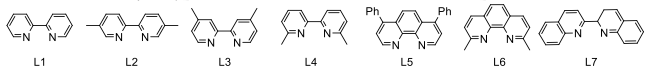


Figure 1. Synthetic methods of *β*-ketonitriles.

Table 1. Optimization of Reaction Conditions[a]



entry	Catalyst	ligand	solvent[b]	yield (%)[c]
1	$Pd(CF_3CO_2)_2$	L1	toluene/H_2O	85
2	$Pd(OAc)_2$	L1	toluene/H_2O	92
3	$PdCl_2$	L1	toluene/H_2O	trace
4	$Pd(acac)_2$	L1	toluene/H_2O	95
5	$Pd(PPh_3)_2$	L1	toluene/H_2O	ND
6	$Pd(CH_3CN)_2Cl_2$	L1	toluene/H_2O	trace
7	$Pd_2(dba)_3$	L1	toluene/H_2O	40
8	$Pd(acac)_2$	L2	toluene/H_2O	96
9	$Pd(acac)_2$	L3	toluene/H_2O	98
10	$Pd(acac)_2$	L4	toluene/H_2O	27
11	$Pd(acac)_2$	L5	toluene/H_2O	77
12	$Pd(acac)_2$	L6	toluene/H_2O	55
13	$Pd(acac)_2$	L7	toluene/H_2O	84
14	$Pd(acac)_2$	L3	toluene	42
15	$Pd(acac)_2$	L3	THF	27
16	$Pd(acac)_2$	L3	DMSO	16
17	$Pd(acac)_2$	L3	MeOH	12
18	$Pd(acac)_2$	L3	acetone	trace
19	$Pd(acac)_2$	L3	1,4-dioxane	ND
20	$Pd(acac)_2$	L3	toluene/H_2O	65[d]
21	$Pd(acac)_2$	L3	toluene/H_2O	94[e]



[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), Pd source (10 mol %), ligand (20 mol %), solvent (3.0 mL), TsOH (2 equiv), air, 80 °C, 24 h. [b]Toluene/H_2O (2.5 mL/0.5 mL). [c]Isolated yield. [d]Reaction time: 12 h. [e]Reaction time: 36 h.

neither a shorter nor a longer reaction time increases the reaction yield (entries 20−21). After in-depth screening, the optimal reaction conditions were determined to comprise $Pd(acac)_2$ as the catalyst, 4,4′-dimethyl-2,2′-bipyridine as the ligand, TsOH as an acidic additive, toluene/H_2O as the cosolvent, and an 80 °C reaction temperature under an air atmosphere.

With the optimal conditions established, we proceeded to examine the substrate scope of this transformation, with respect to different substituted phenylboronic acids. As shown in Scheme 1, a wide range of substituted phenylboronic acids were suitable substrates under the acidic conditions and furnished the corresponding *β*-ketonitriles in good to excellent yields. For instance, a variety of alkyl or aryl substituents on the phenyl ring of boronic acids, including methyl (**2b−2d**), tertiary butyl (**2e**), isopropyl (**2f**), and phenyl (**2g**), allowed the reaction to proceed smoothly, affording products **3b−3g** with yields in the range of 77−94%. Substrates that contained fused rings such as 1-naphthyl and 2-naphthyl were also transformed smoothly (Scheme 1, **3h−3i**), while phenylboronic acids bearing halogen groups, such as −F, −Cl, −Br, and −I, were also valid substrates and provided expected products **3j−3q**. Furthermore, electron-donating substituents (−OMe, −OPh, and $-OCF_3$) and electron-withdrawing substituents ($-COCH_3$, −COOEt, and $-CF_3$) on the phenyl rings of the boronic acids were compatible with the reaction (**3r−3w**). Notably, the treatment of thiophen-2-ylboronic acid and benzo[*b*]thiophen-2-ylboronic acid was also successful (**3x−3y**).

2,2-Dimethylmalononitrile is a novel carbon-bound cyanating reagent that undergoes a retro-Thorpe-type reaction with aryl boronic acid or an aryl organometallic reagent to give the aryl nitrile product.[9] Recently, the Reeves group reported the Rh-catalyzed addition of arylboronic acids to 2,2-disubstituted malononitriles to synthesize *α*,*α*-disubstituted *β*-ketonitriles.[10]

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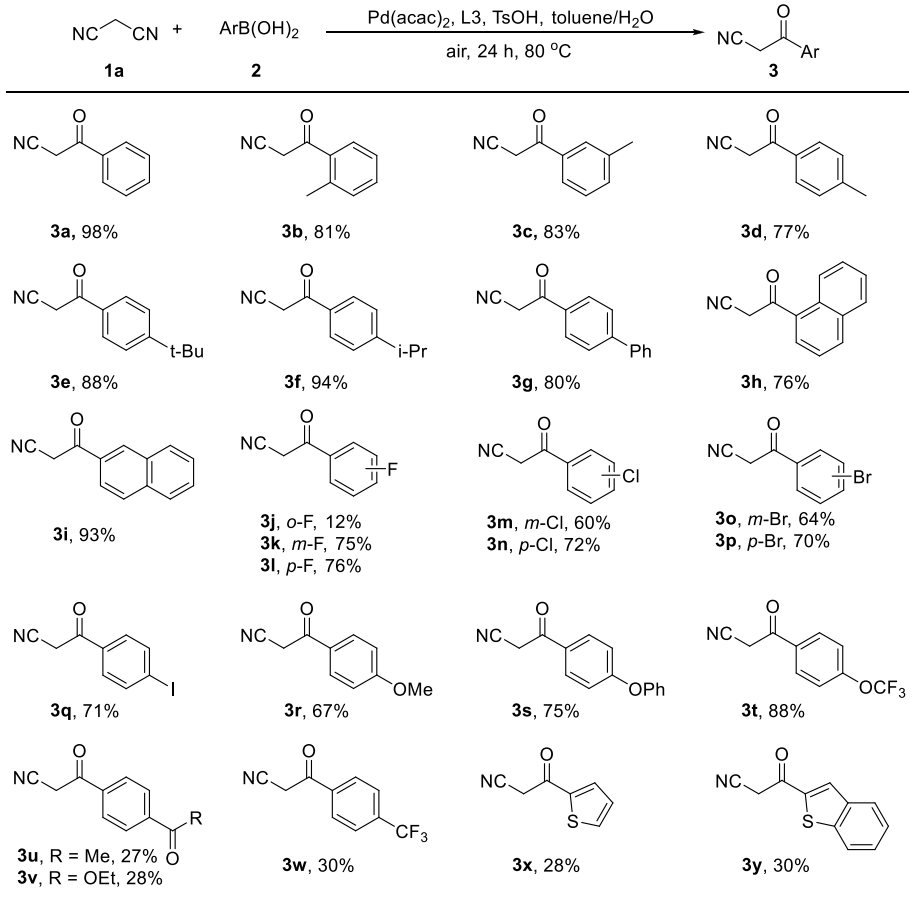
Scheme 1. Synthesis of β-Ketonitrile from Malononitrile[a]



[a]Reaction conditions: **1a** (0.4 mmol), **2** (0.2 mmol), $Pd(acac)_2$ (10 mol %), L3 (20 mol %), toluene/H_2O (2.5 mL/0.5 mL), TsOH (2 equiv), air, 80 °C, 24 h, isolated yield.

However, the unsubstituted malononitrile was not described in Reeves' report. To examine the difference between our methodology and Reeves' approach, we observed that the Rh-catalyzed addition of phenylboronic acids to malononitriles to synthesize 3-oxo-3-phenylpropanenitrile proceeded in 34% less yield than that achieved with $Pd(acac)_2$ (Figure 2, 34% yield vs 98% yield).

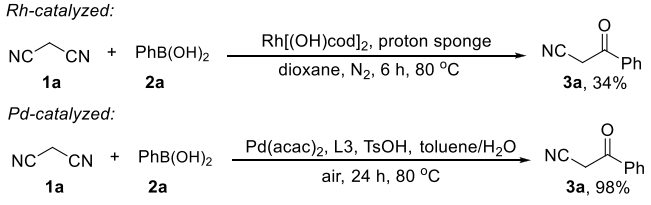
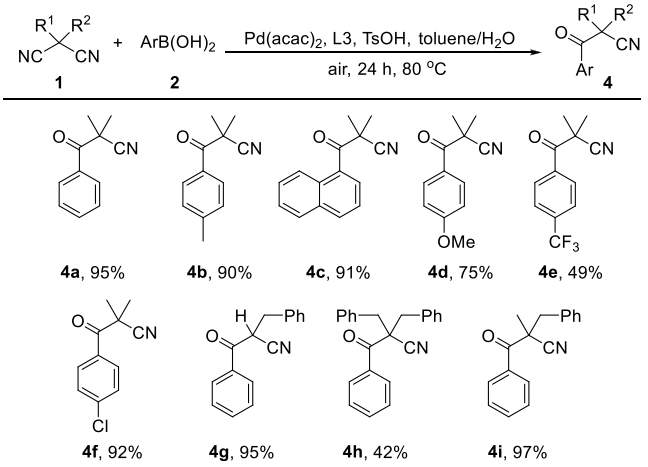


Figure 2. Rh-catalyzed vs Pd-catalyzed reaction in the addition of arylboronic acids to malononitrile.

In a further comparison, we also screened various organoboronic acids with substituted malononitrile (Scheme 2). Generally, our methodology was applicable to 2,2-dimethylmalononitrile with excellent functional-group tolerance, producing the corresponding β-ketonitriles in medium to high yields as per the Reeves strategy. Phenylboronic acids bearing electron-donating groups or electron-withdrawing groups were all afforded the corresponding products in yields

Scheme 2. Synthesis of β-Ketonitrile from Substituted Malononitriles[a]



[a]Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), $Pd(acac)_2$ (10 mol %), L3 (20 mol %), toluene/H_2O (2.5 mL/0.5 mL), TsOH (2 equiv), air, 80 °C, 24 h, isolated yield.

of 49−95% (Scheme 2, **4a**−**4f**). Monosubstituted malononitrile bearing an acidic α-proton or bulky malononitrile also gave β-ketonitriles (Scheme 2, **4g**−**4i**). The reaction was sensitive to steric hindrance of malononitrile given that a

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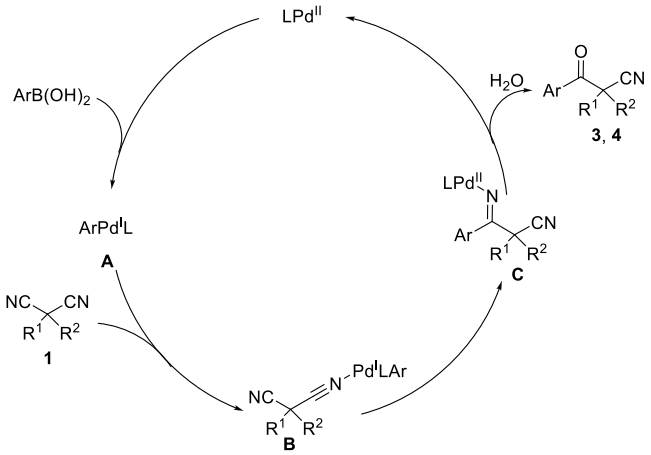
reduced yield was obtained with 2,2-dibenzylmalononitrile relative to 2,2-dibenzylmalononitrile and 2-benzyl-2-methylmalononitrile (**4h**, 42% vs **4g**, 95% and **4i**, 97%, respectively).

Based on previous reports,[11] the proposed catalytic cycle of this Pd-catalyzed β-ketonitrile formation is shown in Scheme 3.

Scheme 3. Proposed Mechanism



The transmetallation of the arylboronic acid with the Pd catalyst would generate arylpalladium species A. Then, the cyano group would coordinate with Pd, leading to intermediate B. Subsequently, carbopalladation of the malononitrile would give Pd-ketimine C. Hydrolysis of the imine Pd complex C would generate the corresponding β-ketonitrile under acidic conditions as well as the active Pd species.

CONCLUSIONS

In summary, we developed a practical, convenient, and highly selective method of synthesizing β-ketonitriles by Pd-catalyzed addition of organoboron reagents to dinitriles under acid conditions. This method provides excellent functional-group tolerance and a broad scope of substrates and uses commercially available substrates. Compared with the similar Rh-catalyzed process, our methodology showed a similarly efficient catalytic effect, which is even better in some cases, using cheaper Pd(acac)$_2$ as the catalyst and TsOH as the acidic additive in an air atmosphere. A plausible mechanism described here is expected to be helpful in identifying or tuning other substrates and catalysts, thereby helping to develop more efficient catalytic processes.

EXPERIMENTAL SECTION

General Methods. Chemicals were received from commercial sources without further purification or prepared by literature methods. Melting points are uncorrected and recorded on a digital melting point apparatus WRS-1B. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 500 or 400 MHz spectrometer using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as the internal standard at room temperature. Chemical shifts are given in δ relative to TMS, and the coupling constants J are given in Hz. High-resolution mass spectrometry (HRMS) was performed with a TOF MS instrument with an EI or ESI source.

General Procedure for the Synthesis of β-Ketonitriles. Dinitriles **1** (0.4 mmol), arylboronic acid (0.2 mmol), Pd(acac)$_2$ (10 mmol %), 4,4′-dimethyl-2,2′-bipyridine (20 mmol %), TsOH (2 equiv), toluene (2.5 mL), and H_2O (0.5 mL) were successively added to a 25 mL Schlenk reaction tube. The reaction mixture was stirred vigorously at 80 °C for 24 h in a heating mantle. After that, the reaction mixture was cooled to room temperature, washed with saturated $NaHCO_3$, and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography with petroleum ether (PE)/ethyl acetate to afford the desired product.

Procedure for the Synthesis of 2-Benzylmalononitrile and 2,2-Dibenzylmalononitrile.[12] At room temperature, NaH 400 mg (10 mmol) was dissolved in 40 mL of tetrahydrofuran (THF) and 4 mL of dimethylformamide solution, and then, a solution of malononitrile (1.32 g, 20 mmol, in 5 mL of THF) was added dropwise. Two hours later, a solution of benzyl bromide (10 mmol) in THF (10 mL) was added slowly. The mixture was subjected to continuous stirring at room temperature for 10 h, washed with saturated NH_4Cl, and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography with PE/ethyl acetate to afford desired products **1c** in 23% yield and **1d** in 38% yield.

Procedure for the Synthesis of 2-Benzyl-2-methylmalononitrile.[12] 2-Benzylmalononitrile (1 mmol) was dissolved in acetone (5 mL). Then, methyl iodide (2 mmol) and K_2CO_3 (2.5 mmol) were added. The mixture was stirred overnight at room temperature. After filtration and concentration, the residue was purified by flash chromatography to yield desired product **1e** in 98% yield.

*3-Oxo-3-phenylpropanenitrile (**3a**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3a**. Pale-yellow solid (28.5 mg, 98%), mp 80−81 °C. Lit.[13] 68−70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93−7.90 (m, 2H), 7.68−7.65 (m, 1H), 7.54−7.51 (m, 2H), 4.10 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 187.0, 134.7, 134.3, 129.2, 128.5, 113.7, 29.3.

*3-Oxo-3-(o-tolyl)propanenitrile (**3b**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3b**. White solid (25.8 mg, 81%), mp 69−71 °C. Lit.[13] 68−70 °C.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 7.6 Hz, 1H), 7.49−7.45 (m, 1H), 7.34−7.30 (m, 2H), 4.07 (s, 2H), 2.56 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 189.4, 140.3, 133.9, 133.2, 132.7, 129.2, 126.1, 114.0, 31.4, 21.7.

*3-Oxo-3-(m-tolyl)propanenitrile (**3c**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3c**. White solid (26.4 mg, 83%), mp 71−72 °C. Lit.[13] 65−67 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73−7.66 (m, 2H), 7.46 (d, J = 7.6 Hz, 1H), 7.41−7.37 (m, 1H), 4.09 (s, 2H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 187.3, 139.1, 135.4, 134.3, 128.9, 128.8, 125.6, 113.9, 29.3, 21.2.

*3-Oxo-3-(p-tolyl)propanenitrile (**3d**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3d**. White solid (24.5 mg, 77%), mp 95−96 °C. Lit.[13] 94−96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 4.07 (s, 2H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 186.7, 145.9, 131.8, 129.8, 128.5, 113.9, 29.2, 21.7.

*3-(4-(tert-Butyl)phenyl)-3-oxopropanenitrile (**3e**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3e**. White solid (35.4 mg, 88%), mp 75−77 °C. Lit.[14] 71−75 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 4.10 (s, 2H), 1.32 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 186.8, 158.7, 131.7, 128.4, 126.0, 114.0, 35.2, 30.8, 29.2.

*3-(4-Isopropylphenyl)-3-oxopropanenitrile (**3f**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3f**. White solid (35.2 mg, 94%), mp 94−96 °C. Lit.[15] 92−94 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 4.08 (s, 2H), 2.97 (m, 1H), 1.25 (d, J = 6.9 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 186.7, 156.5, 132.1, 128.7, 127.1, 114.0, 34.3, 29.2, 23.4.

*3-([1,1′-Biphenyl]-4-yl)-3-oxopropanenitrile (**3g**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3g**. White solid (35.4 mg, 80%), mp 112−113 °C. Lit.[8e] 112.1−113.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02−7.95 (m, 2H), 7.76−7.71 (m, 2H), 7.66−7.60 (m, 2H), 7.51−7.48 (m, 2H), 7.45−7.42 (m,

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1H), 4.12 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ. 186.6, 147.5, 139.2, 133.0, 129.1, 128.7, 127.7, 127.3, 113.8, 29.3.

*3-(Naphthalen-1-yl)-3-oxopropanenitrile (**3h**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3h**. White solid (29.6 mg, 76%), mp 96−97 °C. Lit.[15] 98−100 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.82 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.88−7.92 (m, 2H), 7.68−7.65 (m, 1H), 7.61−7.52 (m, 2H), 4.21 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 189.5, 135.2, 134.1, 131.6, 130.4, 129.5, 129.2, 128.7, 127.1, 125.6, 124.2, 114.0, 31.8.

*3-(Naphthalen-2-yl)-3-oxopropanenitrile (**3i**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3i**. White solid (36.3 mg, 93%), mp 107−108 °C. Lit.[15] 97−101 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.00−7.90 (m, 4H), 7.69−7.66 (m, 1H), 7.63−7.60 (m, 1H), 4.22 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 186.9, 136.2, 132.3, 131.7, 130.7, 129.7, 129.5, 129.2, 127.9, 127.4, 123.4, 113.8, 29.4.

*3-(2-Fluorophenyl)-3-oxopropanenitrile (**3j**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3j**. White solid (3.9 mg, 12%), mp 54−56 °C. Lit.[18] 60−61 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.00−7.95 (m, 1H), 7.65−7.63 (m, 1H), 7.33−7.29 (m, 1H), 7.23−7.18 (m, 1H), 4.10 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 185.0 (C−F, $^4J_{C-F}$ = 3.8 Hz), 162.2 (C−F, $^1J_{C-F}$ = 252.5 Hz), 136.6 (C−F, $^3J_{C-F}$ = 8.8 Hz), 131.2 (C−F, $^4J_{C-F}$ = 2.5 Hz), 125.2 (C−F, $^4J_{C-F}$ = 2.5 Hz), 122.7 (C−F, $^3J_{C-F}$ = 12.5 Hz), 116.9 (C−F, $^2J_{C-F}$ = 22.5 Hz), 113.4 (C−F, $^4J_{C-F}$ = 5.0 Hz), 33.7 (C−F, $^3J_{C-F}$ = 12.5 Hz).

*3-(3-Fluorophenyl)-3-oxopropanenitrile (**3k**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3k**. White solid (24.2 mg, 75%), mp 69−71 °C. Lit.[18] 71−72 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.70−7.68 (m, 1H), 7.63−7.60 (m, 1H), 7.55−7.50 (m, 1H), 7.39−7.35 (m, 1H), 4.10 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 186.1, 162.9 (C−F, $^1J_{C-F}$ = 248.8 Hz), 136.2 (C−F, $^3J_{C-F}$ = 6.3 Hz), 130.9 (C−F, $^3J_{C-F}$ = 7.5 Hz), 124.2 (C−F, $^4J_{C-F}$ = 3.8 Hz), 121.9 (C−F, $^2J_{C-F}$ = 21.3 Hz), 115.2 (C−F, $^2J_{C-F}$ = 22.5 Hz), 113.4, 29.6.

*3-(4-Fluorophenyl)-3-oxopropanenitrile (**3l**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3l**. White solid (22.8 mg, 76%), mp 72−74 °C. Lit.[13] 75−77 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.99−7.95 (m, 2H), 7.23−7.19 (m, 2H), 4.06 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 185.6, 166.6 (C−F, $^1J_{C-F}$ = 256.3 Hz), 131.3 (C−F, $^3J_{C-F}$ = 10.0 Hz), 130.8 (C−F, $^4J_{C-F}$ = 3.0 Hz), 116.4(C−F, $^2J_{C-F}$ = 22.5 Hz), 113.6, 29.3.

*3-(3-Chlorophenyl)-3-oxopropanenitrile (**3m**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3m**. White solid (21.4 mg, 60%), mp 80−81 °C. Lit.[13] 72−73 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.50−7.46 (m, 1H), 4.07 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 186.0, 135.7, 135.6, 134.7, 130.5, 128.5, 126.5, 113.3, 29.5.

*3-(4-Chlorophenyl)-3-oxopropanenitrile (**3n**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3n**. White solid (25.8 mg, 72%), mp 123−125 °C. Lit.[13] 121−123 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 4.09 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 186.0, 141.4, 132.6, 129.8, 129.5, 113.5, 29.4.

*3-(3-Bromophenyl)-3-oxopropanenitrile (**3o**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3o**. Yellow solid (28.3 mg, 64%), mp 91−93 °C. Lit.[19] 92−94 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.81 (dd, ^1J = 21.6, ^2J = 7.2 Hz, 2H), 7.43−7.39 (m, 1H), 4.08 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 186.0, 137.5, 135.8, 131.4, 130.7, 126.9, 123.4, 113.3, 29.5.

*3-(4-Bromophenyl)-3-oxopropanenitrile (**3p**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3p**. White solid (30.9 mg, 70%), mp 153−155 °C. Lit.[13] 156−157 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 4.06 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 186.2, 133.0, 132.6, 130.3, 129.9, 113.4, 29.3.

*3-(4-Iodophenyl)-3-oxopropanenitrile (**3q**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3q**. White solid (38.5 mg, 71%), mp 173−174 °C. Lit.[13] 173−175 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 4.03 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 186.5, 138.6, 133.6, 129.6, 113.3, 103.2, 29.3.

*3-(4-Methoxyphenyl)-3-oxopropanenitrile (**3r**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3r**. White solid (23.5 mg, 67%), mp 126−127 °C. Lit.[8e] 129.2−131.1 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 4.03 (s, 2H), 3.88 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 185.4, 164.7, 130.9, 127.3, 114.3, 114.1, 55.6, 29.0.

*3-Oxo-3-(4-phenoxyphenyl)propanenitrile (**3s**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3s**. White solid (35.5 mg, 75%). mp 98−100 °C. Lit.[8a] ^1H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.5 Hz, 2H), 7.43−7.40 (m, 2H), 7.25−7.22 (m, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 4.04 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 185.6, 163.4, 154.8, 130.9, 130.2, 128.7, 125.1, 120.4, 117.4, 113.9, 29.1.

*3-Oxo-3-(4-(trifluoromethoxy)phenyl)propanenitrile (**3t**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3t**. White solid (40.3 mg, 88%), mp 88−89 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.01−7.98 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.08 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 185.6, 153.8, 132.3, 130.7, 120.2 (C−F, $^1J_{C-F}$ = 257.5 Hz), 120.7, 113.3, 29.4. HRMS (ESI): calcd for $C_{10}H_6F_3NO_2$ $[M + Na]^+$, 252.0249; found, 252.0239.

*3-(4-Acetylphenyl)-3-oxopropanenitrile (**3u**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3u**. Yellow solid (6.4 mg, 17%), mp 121−123 °C. Lit.[8e] 121.7−122.8 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.0 Hz, 2H), 8.01 (d, *J* = 8.4 Hz, 2H), 4.13 (s, 2H), 2.66 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 196.9, 186.7, 141.4, 137.2, 128.9, 128.7, 113.3, 29.7, 26.9.

*Ethyl 4-(2-Cyanoacetyl)benzoate (**3v**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3v**. Orange oil (6.4 mg, 17%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.4 Hz, 2H), 7.98 (d, *J* = 8.4 Hz, 2H), 4.42 (q, *J* = 7.2 Hz, 2H), 4.11 (s, 2H), 1.42 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 186.7, 165.2, 137.2, 135.8 130.2, 128.4, 113.3, 61.8, 29.7, 14.2. HRMS (ESI): calcd for $C_{12}H_{11}NO_3$ $[M + Na]^+$, 240.0637; found, 240.0638.

*3-Oxo-3-(4-(trifluoromethyl)phenyl)propanenitrile (**3w**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3w**. Yellow solid (6.4 mg, 17%), mp 141−143 °C. Lit.[18] 143−144 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H), 4.12 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 186.3, 135.9 (C−F, $^2J_{C-F}$ = 32.5 Hz), 128.8, 126.3 (C−F, $^4J_{C-F}$ = 3.8 Hz), 123.2 (C−F, $^1J_{C-F}$ = 271.3 Hz), 113.2, 29.7.

*3-Oxo-3-(thiophen-2-yl)propanenitrile (**3x**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3x**. Yellow solid (8.9 mg, 30%), mp 137−138 °C. Lit.[8e] 136.3−138.3 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.80−7.78 (m, 2H), 7.21−7.19 (m, 1H), 4.01 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 179.5, 140.9, 133.7, 128.7, 113.4, 29.6.

*3-(Benzo[b]thiophen-2-yl)-3-oxopropanenitrile (**3y**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 6/1, v/v) to afford **3y**. Yellow solid (14.3 mg, 36%), mp 136−137 °C. Lit.[8e] 118.4−125.6 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.91 (dd, J_1 = 23.5 Hz, J_2 = 8.0 Hz, 2H), 7.55−7.52 (m, 1H), 7.47−7.44 (m, 1H), 4.11 (s, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 181.1, 143.1, 140.1, 138.6, 131.1, 128.5, 126.4, 125.6, 123.0, 113.3, 29.5.

*2,2-Dimethyl-3-oxo-3-phenylpropanenitrile (**4a**).*[16] Flash column chromatography on silica gel (eluent: PE/EtOAc = 16/1, v/v) to afford **4a**. Pale-yellow oil (32.9 mg, 95%). Lit.[16] ^1H NMR (500 MHz, $CDCl_3$): δ 8.17−8.15 (m, 2H), 7.63−7.60 (m, 1H), 7.52−7.49 (m, 2H), 1.72 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 193.9, 133.7, 133.6, 129.3, 128.7, 122.6, 40.8, 25.6.

*2,2-Dimethyl-3-oxo-3-(p-tolyl)propanenitrile (**4b**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 16/1, v/v) to

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afford **4b**. White solid (33.7 mg, 90%), mp 43−45 °C. Lit.[9] 44−46 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 2.42 (s, 3H), 1.71 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 193.3, 144.7, 130.9, 129.5, 129.3, 122.7, 40.6, 25.5, 21.5.

*2,2-Dimethyl-3-(naphthalen-1-yl)-3-oxopropanenitrile (**4c**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 16/1, v/v) to afford **4c**. Colorless oil (40.8 mg, 91%). Lit.[9] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98−7.90 (m, 4H), 7.57−7.54 (m, 3H), 1.75 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 199.1, 134.0, 133.7, 132.0, 129.9, 128.6, 127.8, 126.6, 125.5, 124.8, 123.9, 121.9, 44.0, 25.2.

*2,2-Dimethyl-3-oxo-3-(p-tolyl)propanenitrile (**4d**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 16/1, v/v) to afford **4d**. Colorless oil (30.5 mg, 75%). Lit.[9] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (d, J = 8.9 Hz, 2H), 6.96 (d, J = 8.9 Hz, 2H), 3.88 (s, 3H), 1.70 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 192.0, 164.0, 131.9, 126.2, 123.0, 113.9, 55.5, 40.3, 25.7.

*2,2-Dimethyl-3-oxo-3-(4-(trifluoromethyl)phenyl)propanenitrile (**4e**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 16/1, v/v) to afford **4e**. White solid (23.4 mg, 49%), mp 95−97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 1.73 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 193.4, 136.6, 135.0 (q, $^2J_{C-F}$ = 32.5 Hz, 3C), 129.6, 125.8 (q, $^4J_{C-F}$ = 3.7 Hz, 3C), 123.3 (q, $^1J_{C-F}$ = 271.3 Hz, 3C), 122.0, 41.1, 25.4. HRMS (ESI) calcd for $C_{12}H_{10}F_3NO$ $[M + Na]^+$, 264.0612; found, 264.0604.

*3-(4-Chlorophenyl)-2,2-dimethyl-3-oxopropanenitrile (**4f**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 16/1, v/v) to afford **4f**. White solid (38.4 mg, 92%). mp 74−75 °C. Lit.[9] 74−76 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, J = 9.0 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 1.69 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 192.7, 140.3, 131.8, 130.7, 129.0, 122.3, 40.7, 25.4.

*2-Benzyl-3-oxo-3-phenylpropanenitrile (**4g**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 12/1, v/v) to afford **4g**. White solid (44.5 mg, 95%). mp 85−86 °C. Lit.[9] 80−83 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 8.0 Hz, 2H), 7.66−7.63 (m, 1H), 7.53−7.50 (m, 2H), 7.35−7.27 (m, 5H), 4.58−4.55 (m, 1H), 3.36 (dd, J_1 = 14.0, J_2 = 6.0 Hz, 1H), 3.24 (dd, J_1 = 14.0, J_2 = 8.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 190.0, 135.9, 134.5, 134.1, 129.1, 129.0, 128.9, 128.8, 127.6, 116.9, 41.8, 35.5.

*2,2-Dibenzyl-3-oxo-3-phenylpropanenitrile (**4h**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 12/1, v/v) to afford **4h**. Light-yellow oil (26.8 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38−7.35 (m, 1H), 7.33−7.27 (m, 10H), 7.20−7.13 (m, 4H), 3.58 (d, J = 13.5 Hz, 2H), 3.21 (d, J = 13.5 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 197.7, 137.0, 134.3, 132.5, 130.5, 128.6, 128.0, 127.82, 127.80, 120.9, 56.3, 44.7. HRMS (ESI): calcd for $C_{23}H_{19}NO$ $[M + Na]^+$, 348.1359; found, 348.1356.

*2-Benzyl-2-methyl-3-oxo-3-phenylpropanenitrile (**4i**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 12/1, v/v) to afford **4i**. Light-yellow oil (48.5 mg, 97%). Lit.[9] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00−7.97 (m, 2H), 7.60−7.56 (m, 1H), 7.48−7.44 (m, 2H), 7.34−7.289 (m, 5H), 3.50 (d, J = 13.6 Hz, 1H), 3.11 (d, J = 13.6 Hz, 1H), 1.69 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 194.8, 134.7, 134.3, 133.5, 130.4, 129.1, 128.50, 128.48, 127.7, 121.6, 47.5, 43.8, 24.0.

*2-Benzylmalononitrile (**1c**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 16/1, v/v) to afford **1c**. White solid (589.9 mg, 38%), mp 90−91 °C. Lit.[17] 84−86 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43−7.39 (m, 3H), 7.33 (d, J = 7.0 Hz, 2H), 3.92 (t, J = 7.0 Hz, 1H), 3.27 (d, J = 7.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 132.9, 129.2, 129.1, 128.7, 112.2, 36.5, 24.9.

*2,2-Dibenzylmalononitrile (**1d**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 16/1, v/v) to afford **1d**. White solid (277.0 mg, 23%), mp 125−127 °C. Lit.[17] 128−130 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42−7.41 (m, 10H), 3.25 (s, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 132.0, 130.3, 129.0, 128.8, 114.9, 43.5, 41.2.

*2-Benzyl-2-methylmalononitrile (**1e**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 16/1, v/v) to afford **1e**. White solid (166.4 mg, 98%), mp 94−95 °C, Lit.[12] 94.3−95.3 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42−7.39 (m, 3H), 7.38−7.36 (m, 2H), 3.21 (s, 2H), 1.81 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 131.9, 130.2, 129.0,128.9, 115.9, 44.5, 33.1, 24.4.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02388.

Reaction optimization of β-ketonitrile and ^{1}H and ^{13}C NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Klahn, P.; Kirsch, S. F. IBX-Mediated Dehydrogenation of Substituted β-Oxonitriles. *Eur. J. Org. Chem.* **2014**, 3149.

(2) (a) Sirichaiwat, C.; Intaraudom, C.; Kamchonwongpaisan, S.; Vanichtanankul, J.; Thebtaranonth, Y.; Yuthavong, Y. Target Guided Synthesis of 5-Benzyl-2,4-diamonopyrimidines: Their Antimalarial Activities and Binding Affinities to Wild Type and Mutant Dihydrofolate Reductases from Plasmodium falciparum. *J. Med. Chem.* **2004**, *47*, 345. (b) Zhu, X.; Zhang, M.; Liu, J.; Ge, J.; Yang,

G. Ametoctradin is a Potent Q_o Site Inhibitor of the Mitochondrial Respiration Complex III. *J. Agric. Food Chem.* **2015**, *63*, 3377.
(3) Velcicky, J.; Miltz, W.; Oberhauser, B.; Orain, D.; Vaupel, A.; Weigand, K.; Dawson King, J.; Littlewood-Evans, A.; Nash, M.; Feifel, R.; Loetscher, P. Development of Selective, Orally Active GPR4 Antagonists with Modulatory Effffects on Nociception, Inflflammation, and Angiogenesi. *J. Med. Chem.* **2017**, *60*, 3672.
(4) Krasavin, M.; Korsakov, M.; Zvonaryova, Z.; Semyonychev, E.; Tuccinardi, T.; Kalinin, S.; Tanç, M.; Supuran, C. T. Human carbonic anhydrase inhibitory profile of mono- and bis-sulfonamides synthesized via a direct sulfochlorination of 3- and 4-(hetero)-arylisoxazol-5-amine scaffolds. *Bioorg. Med. Chem.* **2017**, *25*, 1914.
(5) Marković, R.; Baranac, M.; Dzambaski, Z.; Stojanovic, M.; Steel, P. J. High regioselectivity in the heterocyclization of b-oxonitriles to 4-oxothiazolidines: X-ray structure proof. *Tetrahedron* **2003**, *59*, 7803.
(6) (a) Lee, S.; Kim, T.; Lee, B. H.; Yoo, S.-e.; Lee, K.; Yi, K. Y. 3-Substituted-(5-arylfuran-2-ylcarbonyl)guanidines as NHE-1 inhibitors. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1291. (b) Farghaly, T. A.; Abdel Hafez, N. A.; Ragab, E. A.; Awad, H. M.; Abdalla, M. M. Synthesis, anti-HCV, antioxidant, and peroxynitrite inhibitory activity of fused benzosuberone derivatives. *Eur. J. Med. Chem.* **2010**, *45*, 492. (c) Hughes, T. V.; Emanuel, S. L.; Beck, A. K.; Wetter, S. K.; Connolly, P. J.; Karnachi, P.; Reuman, M.; Seraj, J.; Fuentes-Pesquera, A. R.; Gruninger, R. H.; Middleton, S. A.; Lin, R.; Davis, J. M.; Moffat, D. F. C. 4-Aryl-5-cyano-2-aminopyrimidines as VEGF-R2 inhibitors: Synthesis and biological evaluation. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3266.
(7) (a) Ji, Y.; Trenkle, W. C.; Vowles, J. V. A High-Yielding Preparation of β-Ketonitriles. *Org. Lett.* **2006**, *8*, 1161. (b) Sureshbabu, V.; Nagendra, G.; Sureshbabu, V. V. Synthesis of N-Urethane Protected α-Aminoalkyl-α'-cyanomethyl Ketones; Application to the Synthesis of 3-Substituted 5-Amino-1H-pyrazole Tethered Peptidomimetics. *Synlett* **2012**, *23*, 1913. (c) Yoo, B. W.; Hwang, S. K.; Kim, D. Y.; Choi, J. W.; Ko, J. J.; Choi, K. I.; Kim, J. H. Indium-mediated coupling of bromoacetonitriles with aromatic acyl cyanides: convenient synthesis of aromatic α-cyano ketones. *Tetrahedron Lett.* **2002**, *43*, 4813. (d) Sim, M. M.; Lee, C. L.; Ganesan, A. Solid-phase C-acylation of active methylene compounds. *Tetrahedron Lett.* **1998**, *39*, 2195.
(8) (a) Shen, J.; Yang, D.; Liu, Y.; Qin, S.; Zhang, J.; Sun, J.; Liu, C.; Liu, C.; Zhao, X.; Chu, C.; Liu, R. Copper-Catalyzed Aerobic Oxidative Coupling of Aromatic Alcohols and Acetonitrile to β-Ketonitriles. *Org. Lett.* **2014**, *16*, 350. (b) Park, A.; Lee, S. Palladium-Catalyzed Carbonylative α-Arylation of tert-Butyl Cyanoacetate with (Hetero)aryl Bromides. *J. Org. Chem.* **2016**, *81*, 1358. (c) Lee, S.; Pyo, A.; Park, A.; Jung, H. M. Palladium-Catalyzed Carbonylation with $Mo(CO)_6$ for the Synthesis of Benzoylacetonitriles. *Synthesis* **2012**, *44*, 2885. (d) Lee, S.; Kim, H.-S.; Min, H.; Pyo, A. One-pot synthesis of benzoylacetonitriles through sequential Pd-catalyzed carbonylation and decarboxylation. *Tetrahedron Lett.* **2016**, *57*, 239. (e) Jensen, M. T.; Juhl, M.; Nielsen, D. U.; Jacobsen, M. F.; Lindhardt, A. T.; Skrydstrup, T. Palladium-Catalyzed Carbonylative α-Arylation of tert-Butyl Cyanoacetate with (Hetero)aryl Bromides. *J. Org. Chem.* **2016**, *81*, 1358. (f) Schranck, J.; Burhardt, M.; Bornschein, C.; Neumann, H.; Skrydstrup, T.; Beller, M. Palladium-Catalyzed Carbonylative α-Arylation to β-Ketonitriles. *Chem.—Eur. J.* **2014**, *20*, 9534. (g) Kiyokawa, K.; Minakata, S.; Nagata, T. Recent Advances in the Synthesis of β-Ketonitriles. *Synthesis* **2018**, *50*, 485.
(9) (a) Malapit, C. A.; Reeves, J. T.; Busacca, C. A.; Howell, A. R.; Senanayake, C. H. Rhodium-Catalyzed Transnitrilation of Aryl Boronic Acids with Dimethylmalononitrile. *Angew. Chem., Int. Ed.* **2016**, *55*, 326. (b) Reeves, J. T.; Malapit, C. A.; Buono, F. G.; Sidhu, K. P.; Marsini, M. A.; Sader, C. A.; Fandrick, K. R.; Busacca, C. A.; Senanayake, C. H. Transnitrilation from Dimethylmalononitrile to Aryl Grignard and Lithium Reagents: A Practical Method for Aryl Nitrile Synthesis. *J. Am. Chem. Soc.* **2015**, *137*, 9481. (c) Mills, L. R.; Graham, J. M.; Patel, P.; Rousseaux, S. A. L. Ni-catalyzed reductive cyanation of aryl halides and phenol derivatives via transnitrilation. *J. Am. Chem. Soc.* **2019**, *141*, 19257. (d) Malapit, C. A.; Luvaga, I. K.; Reeves, J. T.; Volchkov, I.; Busacca, C. A.; Howell, A. R.; Senanayake, C. H. 1,4-Dicarbofunctionalization of 4-Fluoroaryl Grignard and Lithium Reagents with Disubstituted Malononitriles. *J. Org. Chem.* **2017**, *82*, 4993.
(10) Malapit, C. A.; Caldwell, D. R.; Luvaga, I. K.; Reeves, J. T.; Volchkov, I.; Gonnella, N. C.; Han, Z. S.; Busacca, C. A.; Howell, A. R.; Senanayake, C. H. Rhodium-Catalyzed Addition of Aryl Boronic Acids to 2,2-Disubstituted Malononitriles. *Angew. Chem., Int. Ed.* **2017**, *56*, 6999.
(11) (a) Chen, L.; Gong, J.; Zhang, Y.; Shao, Y.; Chen, Z.; Li, R.; Chen, J. Palladium-catalyzed tandem C−C activation/cyclization induced by carbopalladation of functionalized nitriles: synthesis of benzo dipyrromethenes. *Org. Lett.* **2020**, *22*, 6943. (b) Dai, L.; Yu, S.; Xiong, W.; Chen, Z.; Xu, T.; Shao, Y.; Chen, J. Divergent palladium-catalyzed tandem reaction of cyanomethyl benzoates with arylboronic acids: synthesis of oxazoles and isocoumarins. *Adv. Synth. Catal.* **2020**, *362*, 1893. (c) Xiong, W.; Hu, K.; Lei, Y.; Zhen, Q.; Zhao, Z.; Shao, Y.; Li, R.; Zhang, Y.; Chen, J. Palladium-catalyzed cascade reactions of 2-(cyanomethoxy)chalcones with arylboronic acids: selective synthesis of emissive benzofuro[2,3-c]pyridines. *Org. Lett.* **2020**, *22*, 1239. (d) Qi, L.; Li, R.; Yao, X.; Zhen, Q.; Ye, P.; Shao, Y.; Chen, J. Syntheses of pyrroles, pyridines, and ketonitriles via catalytic carbopalladation of dinitriles. *J. Org. Chem.* **2020**, *85*, 1097. (e) Zhen, Q.; Li, R.; Qi, L.; Hu, K.; Yao, X.; Shao, Y.; Chen, J. Nickel(II)-catalyzed C−C, N−C cascade coupling of ketonitriles into substituted pyrroles and pyridines. *Org. Chem. Front.* **2020**, *7*, 286. (f) Xiong, W.; Chen, Z.; Shao, Y.; Li, R.; Hu, K.; Chen, J. The synthesis of fluorescent benzofuro[2,3-c]pyridines via palladium-catalyzed heteroaromatic C−H addition and sequential tandem cyclization. *Org. Chem. Front.* **2020**, *7*, 756. (g) Rakshit, A.; Kumar, P.; Alam, T.; Dhara, H.; Patel, B. K. Visible-Light-Accelerated Pd-Catalyzed Cascade Addition/Cyclization of Arylboronic Acids to γ- and β-Ketodinitriles for the Construction of 3-Cyanopyridines and 3-Cyanopyrrole Analogues. *J. Org. Chem.* **2020**, *85*, 12482. (h) Ye, X.; Xu, B.; Sun, J.; Dai, L.; Shao, Y.; Zhang, Y.; Chen, J. Pd-Catalyzed Approach for Assembling 9-Arylacridines via a Cascade Tandem Reaction of 2-(Arylamino)benzonitrile with Arylboronic Acids in Water. *J. Org. Chem.* **2020**, *85*, 13004.
(12) Wu, Z.-L.; Li, Z.-Y. Practical Synthesis of Optically Active α,α-Disubstituted Malonamic Acids through Asymmetric Hydrolysis of Malonamide Derivatives with Rhodococcus sp. CGMCC 0497. *J. Org. Chem.* **2003**, *68*, 2479.
(13) Shen, H.; Li, J.; Liu, Q.; Pan, J.; Huang, R.; Xiong, Y. Umpolung Strategy for Synthesis of β-Ketonitriles through Hypervalent Iodine-Promoted Cyanation of Silyl Enol Ethers. *J. Org. Chem.* **2015**, *80*, 7212.
(14) Havel, S.; Khirsariya, P.; Akavaram, N.; Paruch, K.; Carbain, B. Preparation of 3,4-Substituted-5-Aminopyrazoles and 4-Substituted-2-Aminothiazoles. *J. Org. Chem.* **2018**, *83*, 15380.
(15) Yang, Z.; Son, K.-I.; Li, S.; Zhou, B.; Xu, J. Specific 1,2-Hydride Shift in the Boron Trifluoride Catalyzed Reactions of Aromatic Aldehydes with Diazoacetonitrile: Simple Synthesis of β-Ketonitriles. *Eur. J. Org. Chem.* **2014**, 6380.
(16) Schranck, J.; Burhardt, M.; Bornschein, C.; Neumann, H.; Skrydstrup, T.; Beller, M. Palladium-Catalyzed Carbonylative α-Arylation to β-Ketonitriles. *Chem.—Eur. J.* **2014**, *20*, 9534.
(17) Doni, E.; Murphy, J. A. Reductive decyanation of malononitriles and cyanoacetates using photoactivated neutral organic super-electron-donors. *Org. Chem. Front.* **2014**, *1*, 1072.
(18) Xu, K.; Liu, H.; Hou, Y.; Shen, J.; Liu, D.; Zhang, W. A Pd-catalyzed asymmetric allylic substitution cascadeviaan asymmetric desymmetrization for the synthesis of bicyclic dihydrofurans. *Chem. Commun.* **2019**, *55*, 13295.
(19) Lee, S.; Pyo, A.; Park, A.; Jung, H. M. Palladium-Catalyzed Carbonylation with $Mo(CO)_6$ for the Synthesis of Benzoylacetonitriles. *Synthesis* **2012**, *44*, 2885.

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