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Palladium-Catalyzed Carbonylative α-Arylation of *tert*-Butyl Cyanoacetate with (Hetero)aryl Bromides

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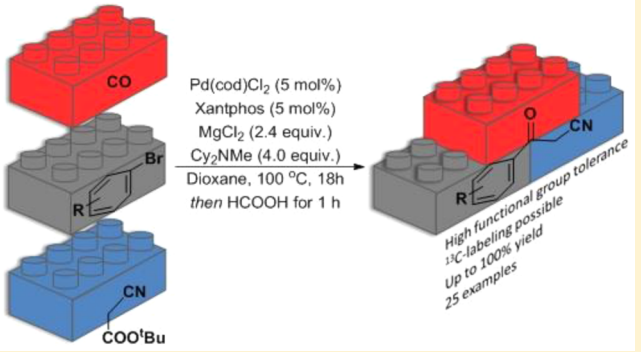
Supporting Information

ABSTRACT: A three-component coupling protocol has been developed for the generation of 3-oxo-3-(hetero)-arylpropanenitriles via a carbonylative palladium-catalyzed α-arylation of *tert*-butyl 2-cyanoacetates with (hetero)aryl bromides followed by an acid-mediated decarboxylation step. Through the combination of only a stoichiometric loading of carbon monoxide and mild basic reaction conditions such as $MgCl_2$ and dicyclohexylmethylamine for the deprotonation step, an excellent functional group tolerance was ensured for the methodology. Through the use of ^{13}C-labeled carbon monoxide generated from ^{13}COgen, the corresponding ^{13}C-isotopically labeled β-ketonitriles were obtained, and these products could subsequently be converted into cyanoalkynes and 3-cyanobenzofurans with site specific ^{13}C-isotope labeling.



INTRODUCTION

3-Oxo-3-(hetero)arylpropanenitriles, more commonly referred to as β-ketonitriles, are key precursors applied for the synthesis of imidazo[1,2-*a*]pyridines,[1] 2-pyridones,[2] furans,[3] amino-pyrazoles,[4] thiophenes,[5] and others (Scheme 1). Furthermore, they have been employed for the synthesis of biological active targets against HIV,[6] toward NHE-1 inhibitors,[7] or toward antidepressants (e.g., Prozac).[8] One of the earliest examples of β-ketonitrile preparation was reported by Obrégia in 1891 by the direct displacement of an α-bromide with potassium cyanide.[9] This classical halogen displacement is still applied today, most often with sodium cyanide as the cyanide donor (Scheme 1).[10] Alternatively, nucleophilic displacement of ethyl esters with α-substituted acetonitriles,[11] copper-catalyzed oxidation of alcohols in the presence of acetonitrile,[12] etc.[13a−e] all provide β-ketonitriles (Scheme 1). Nevertheless, for accessing 3-oxo-3-(hetero)arylpropanenitriles, these approaches require advanced (hetero)aryl intermediates.

On the other hand, in 2012, Lee et al. reported the first carbonylative coupling approach to β-ketonitriles from aryl iodides with (trimethylsilyl)acetonitrile promoted by a Pd catalyst.[14] One year later, Beller and Skrydstrup reported β-ketonitrile formation via Pd-catalyzed carbonylation of aryl iodides with α,α-disubstituted acetonitrile derivatives (Scheme 1).[15] Although both protocols proved effective for accessing the target β-ketonitriles, they are confined to the use of aryl iodides, and the former approach requires two additional metal additives, namely ZnF_2 and $CuBr_2$, whereas the latter relies on the addition of strong base, NaHMDS, to activate the nucleophile. We therefore set out to expand the usefulness of the carbonylative α-arylation route to β-ketonitriles by identifying reaction conditions that can also include (hetero)-aryl bromides as viable substrates for this three-component coupling strategy, as well as the adaptation of mild basic conditions for the deprotonation step.

In this paper, we demonstrate the usefulness of *tert*-butyl 2-cyanoacetate as an appropriate nucleophile for the carbonylative α-arylation of (hetero)aryl bromides with a trialkylamine base for accessing the desired 3-oxo-3-(hetero)-arylpropanenitriles after a simple acid-mediated decarboxylation reaction. Importantly, our approach relies on the use of only stoichiometric amounts of carbon monoxide generated from COgen for effective coupling, which also allow us to easily adapt the developed protocol for ^{13}C-isotope labeling.

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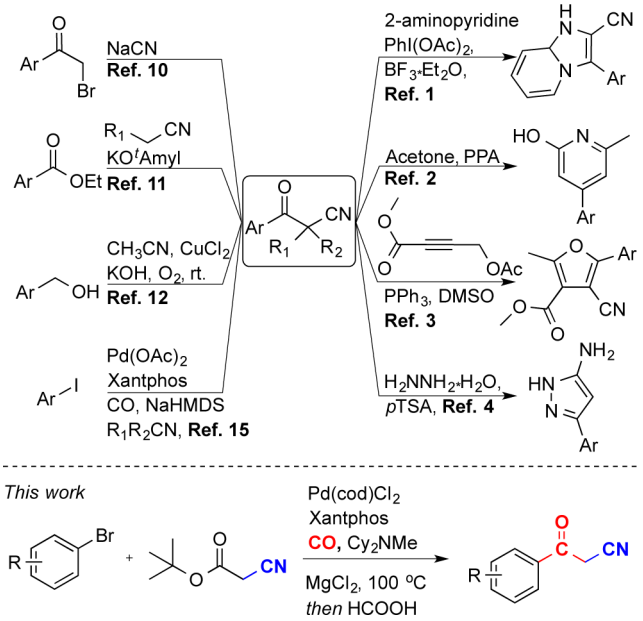
Scheme 1. Representative Methods for the Generation and Synthetic Utility of β-Ketonitriles



RESULTS AND DISCUSSION

We have previously reported on the development of intermolecular Pd-catalyzed carbonylative α-arylations with iodo- and bromoarenes to 1,3-diketones,[16] β-ketoesters,[17a] and -amides,[17b] and (heteroaryl)methyl ketones.[18] These methods rely on 1,3-dicarbonyl-derived nucleophiles (or analogues thereof), such as acetyl acetone, potassium acetoacetates, acetoacetamides, and 2-heteroarylacetones, thereby increasing the acidity toward mild α-deprotonation in the activation step of the nucleophile. Subsequent to the carbonylative transformation, the additional acyl functionality was selectively removed upon acidic treatment. To investigate the carbonylative transformations to 3-oxo-3-(hetero)-arylpropanenitriles, a model system based on our previous reports[16−18] utilizing a palladium/Xantphos catalytic system combined with a mixture of anhydrous magnesium chloride ($MgCl_2$, 1.2 equiv) and *N*,*N*-dicyclohexyl-*N*-methylamine (Cy_2NMe, 4.0 equiv) was initially tested. As the nucleophile, potassium 2-cyanoacetate (1.1 equiv) was chosen in combination with bromoanisole as the electrophile. A slight excess of carbon monoxide (1.5 equiv) was delivered by applying the two-chamber technique previously developed in our laboratories. Following an acidic treatment with formic acid this provided a low NMR conversion of 14% to the desired β-ketonitrile **1** (result not shown). Substituting the nucleophile with *tert*-butyl 2-cyanoacetate (1.1 equiv), however, afforded the desired β-ketonitrile **1** in a 69% NMR conversion after acidic treatment. Speculating that the lack of a 1,3-dicarbonyl moiety in *tert*-butyl 2-cyanoacetate could account for a reduced efficiency of the added Lewis acid, we doubled the loading of $MgCl_2$ from 1.2 to 2.4 equiv. To our delight, this simple alteration increased the NMR conversion of **1** to a good 78% (70% yield) after treatment of the intermediately formed *tert*-butyl 2-cyano-3-oxo-3-phenylpropanotate with formic acid at 100 °C. Performing the reaction without the addition of $MgCl_2$ provided **1** in less than 10% yield.

With these conditions in hand, the scope of this simple transformation was undertaken, the results of which are depicted in Scheme 2. In general, all *meta*- and *para*-substituted aryl bromides afforded the desired β-ketonitriles in yields ranging from 63−89% (compounds **1**−**3**, **4**−**13**). Electron-withdrawing groups did not affect the reactivity and provided yields of up to 89% (**6**−**9**, **12**, **13**). Similar reactivity was observed when aryl bromides were applied with electron-donating functionalities (compounds **2**, **3**, **10**, **14**, and **15**). Even a free aniline successfully afforded the β-ketonitrile **17**, although in a lowered yield of 50%. β-Ketonitrile **4** could be isolated in a near-quantitative yield using bromobenzene as the electrophile. Unfortunately, *ortho*-substitution of the aryl bromides resulted in a complete shut down of reactivity. Next, a few alternative electrophiles were tested including phenyl triflate, two 2-bromovinylbenzenes, and benzyl chloride, all affording the target compounds in 95%, 54%, 66%, and 93% yields (compounds **4** and **18**−**20**, respectively). Finally, the application of heteoaryl bromides as electrophiles was investigated. 2-Bromothiophene, 2-bromo- and 6-bromobenzothiophene, 5-bromobenzofuran, and *N*-Boc-5-bromoindole were tested and in all cases provided the β-ketonitriles in yields ranging from 40 to 68% (compounds **21**−**25**). Not surprisingly, in the case of *N*-Boc-5-bromoindole, the carbamate protection group was removed during the acid-promoted decarboxylative step. Performing the reaction on a larger scale (2.5 or 3.0 mmol) allowed for a reduction of the catalyst loading from 5 to 2 mol% without affecting the yields (compounds **2**, **4**, **12**, and **15**). Finally, by substituting CO for its ^{13}C-isotopically labeled counterpart, compounds **4*** and **15*** were successfully obtained in yields of 96% and 74%, respectively, carrying a ^{13}C-labeled carbonyl moiety in the β-ketonitrile structure.

A pressure measurement experiment was conducted during the synthesis of **4** by adaptation of a manometer to the COware setup (Figure 1). CO is released within the first few minutes causing the internal pressure to reach a plateau of 3 bar.

The pressure profile then shows a continuous drop in pressure over the next 18 h with the majority of the reaction already completed within the first 6 hours.

Instead of treatment with warm formic acid, the direct coupling product could also be easily isolated as exemplified with compound **26** shown in Scheme 3. Ethyl 2-cyanoacetate also coupled well with isolation of product **27** in an excellent 97% yield. Finally, the similar nitro derivative *tert*-butyl 2-nitroacetate was tested as a nucleophile affording compound **28** in a 61% yield after acidic decarboxylation (Scheme 3).

In 1990, Leclercq et al. reported on the conversion of β-ketosulfonamides into sulfonamide-substituted alkynes upon treatment with triethylamine in combination with Mukaiyama's reagent followed by the addition of aqueous sodium hydroxide.[19] In a similar manner, we found that the β-ketonitriles **4** and **15** could be transformed into the corresponding cyanoalkynes in good yields under the same mild conditions (Scheme 4A, compounds **29** and **30**). Starting with **4*** and **15***, this afforded the equivalent specifically monolabeled ^{13}C-cyanoalkynes in practically identical yields of 71% and 74% (compounds **29*** and **30***, respectively).[20]

In 2012, Zhou et al. reported a one-pot two-step procedure for the preparation of 3-cyanobenzofurans through a C−H activation step starting from cyanoalkynes.[23] This same method was applied to the preparation of the 3-cyanobenzofurans from β-ketonitriles **29** and **30**.

In this manner, compounds **31** and **32** could be secured by column chromatography in 30% and 42% yields for the two

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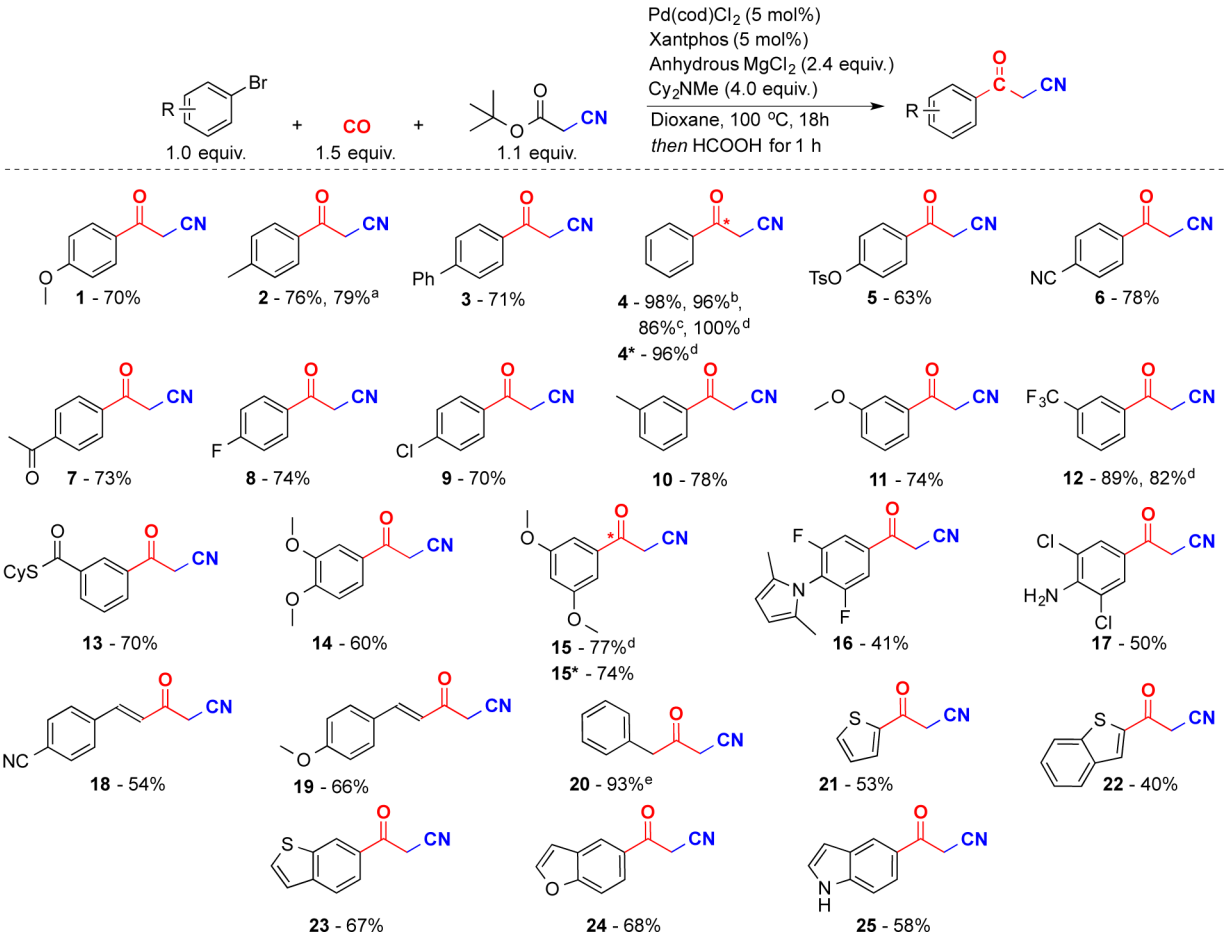
Scheme 2. Scope of Aryl Bromides toward β-Ketonitriles[a]



[a]Full experimental details are described in the Experimental Procedures. Key: (a) $Pd(cod)Cl_2$ (2 mol%), Xantphos (2 mol%), anhydrous $MgCl_2$ (2.4 equiv), *tert*-butyl 2-cyanoacetate (1.1 equiv), aryl bromide (3.0 mmol), dioxane (15 mL) and Cy_2NMe (4.0 equiv); (b) starting from phenyl trifluoromethanesulfonate; (c) starting from compound **26** (Scheme 3) with HCOOH in dioxane at 100 °C; (d) $Pd(cod)Cl_2$ (2 mol%), Xantphos (2 mol%), anhydrous $MgCl_2$ (2.4 equiv), *tert*-butyl 2-cyanoacetate (1.1 equiv), aryl bromide (2.50 mmol), dioxane (15 mL) and Cy_2NMe (4.0 equiv); (e) starting from BnCl. * = ^{13}C-labeled.

sequential steps (Scheme 4B).[23] As before, applying the ^{13}C-isotopically labeled cyanoalkynes **29*** and **30***, it was possible to incorporate the ^{13}C-carbon label directly into the furan core obtaining compounds **31*** and **32*** in 37% and 38% yields, respectively.

In conclusion, a mild method has been developed for accessing 3-oxo-3-(hetero)arylpropanenitriles from the Pd-catalyzed carbonylative α-arylation of *tert*-butyl 2-cyanoacetates with aryl bromides and stoichiometric carbon monoxide. Various β-ketonitriles were prepared in good to excellent yields including their ^{13}C-isotopically labeled versions as well. The protocol displayed excellent functional group tolerance and operated well when starting from hetereoaromatic bromides. Selected β-ketonitriles were transformed into the corresponding cyanoalkynes that could subsequently be applied to the synthesis of 3-cyanobenzofurans. Two ^{13}C-carbon-labeled β-ketonitriles could also be adapted to this synthetic route, in turn leading to the isolation of two functionalized and ^{13}C-carbon labeled 3-cyanobenzofurans.

EXPERIMENTAL PROCEDURES

General Procedures. Standard procedures were applied for drying solvents. Column chromatography was performed on silica gel 60 (230−400 mesh), unless otherwise stated. Fine silica refers to silica gel 60 (0.015−0.040 mm). NMR was conducted at 400, 100, and 376 MHz for ^1H NMR, $^{13}C\{^1H\}$ NMR, and $^{19}F\{^1H\}$ NMR, respectively, on a 400 MHz NMR apparatus. The NMR chemical shifts were reported in parts per million (ppm) compared to the solvent residual signal.[21] Signals in NMR are reported as s = singlet, d = doublet, t = triplet, q = quartet, and b = broad. In some cases, it was not possible to fully separate the title compounds and a side product of 3-oxo-3-phenylpropanenitrile **4** probably arising from aryl scrambling.[22] The yields in these examples are therefore corrected for the low amount of **4** and marked as (corrected) (compounds **8**, **10**, and **11**). Melting points were obtained on a melting point apparatus. HRMS spectra were recorded on an LC-TOF (ES) apparatus. Pressure curves were measured on a digital manometer with electronic data collection. With the exception of $MgCl_2$, all purchased chemicals were used without any further purification. Anhydrous $MgCl_2$ was prepared by drying the commercial $MgCl_2$ under high vacuum at 165 °C for a minimum of 5 days and thereafter storage in an argon filled glovebox at rt.

General Method A. *3-(4-Chlorophenyl)-3-oxopropanenitrile (9): General Procedure for the Carbonylation of Aryl Bromides toward β-Ketonitriles. Chamber 2.* In a glovebox under argon, to chamber 2 of the two-chamber system (20 mL) were added $Pd(cod)Cl_2$ (2.0 mg, 0.008 mmol), $HBF_4{\cdot}P(^tBu)_3$ (2.2 mg, 0.015 mmol), COgen (9-methylfluorene-9-carbonyl chloride) (182 mg, 0.75 mmol), and dioxane (3 mL) in that order. Chamber 1: In a glovebox under argon, to chamber 1 of the two-chamber system (20 mL) were added

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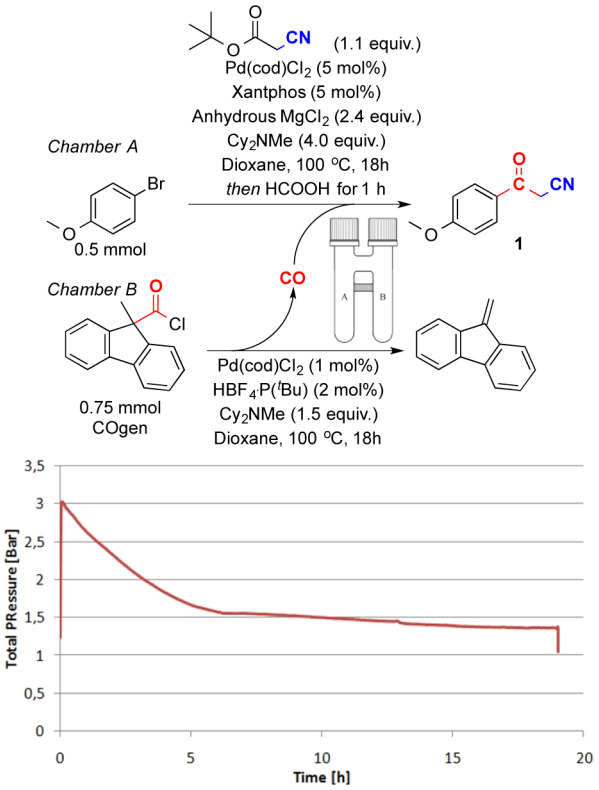
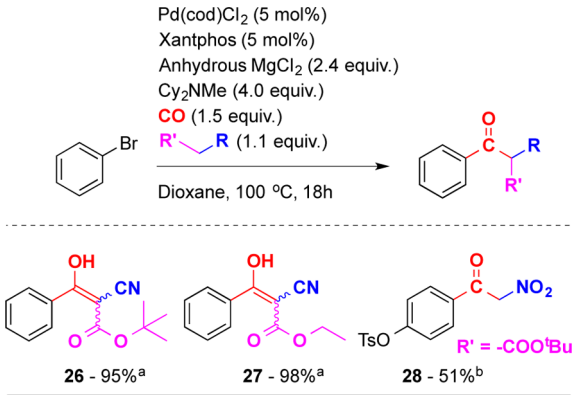


Figure 1. Pressure measurement in the preparation of β-ketonitrile **4**.

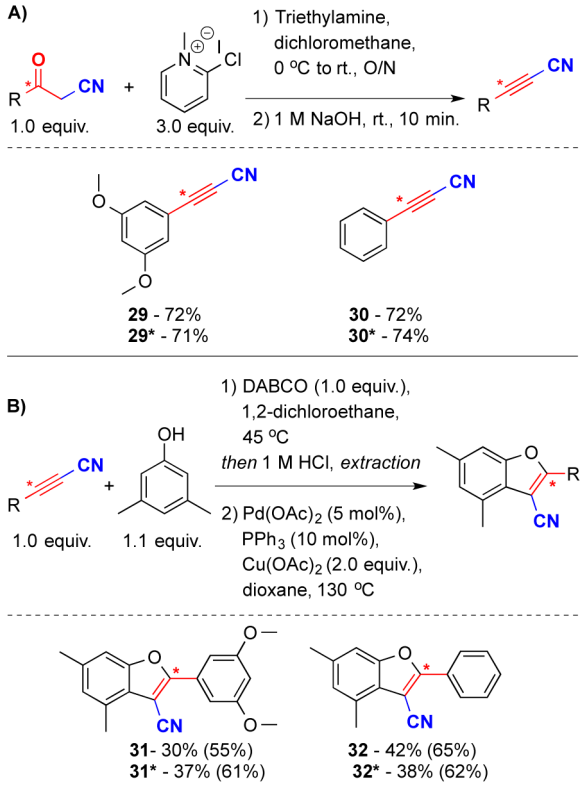
Scheme 3. Isolation of Reaction Intermediate and Coupling with Alternative Nucleophiles



[a]*E*/*Z* ratio not determined. [b]Treated with HCOOH for 1 h at 100 °C.

Pd(cod)Cl_2 (7.1 mg, 0.025 mmol), Xantphos (14.5 mg, 0.050 mmol), anhydrous $MgCl_2$ (115 mg, 1.20 mmol), *tert*-butyl 2-cyanoacetate (78.6 μL, 0.55 mmol), 1-bromo-4-chlorobenzene (96.0 mg, 0.50 mmol), dioxane (3 mL), and Cy_2NMe (426 μL, 2.0 mmol) in that order. To chamber 2 was added Cy_2NMe (320 μL, 1.5 mmol), and both chambers were sealed with a screwcap fitted with a PTFE/silicon seal. The loaded two-chamber system was removed from the glovebox and heated to 100 °C for 18 h. The lid was removed, and HCOOH (1.0 mL) was added and stirring continued for 1 h before cooling to rt and concentration under reduced pressure. Purification was performed by column chromatography (pentane/Et_2O/HCOOH 34/6/1−14/6/1) to yield the title compound as a yellow solid (63.0 mg, 0.35 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ H ppm 7.86 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 4.07 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 186.2, 141.6, 132.7, 130.0 (2C), 129.7 (2C), 113.7, 29.6. HRMS C_9ClH_6ONNa [M + Na^+]: calcd 202.0030, found 202.0030. Mp (uncorrected): 110.8−113.6 °C.[13a]

Scheme 4. Synthetic Applications of β-Ketonitriles[a]



[a]Yield in parentheses indicate average yields for first and second step. * = ^{13}C-labeled.

General Method B. *3-Oxo-3-phenylpropanenitrile (4). General Procedure for Scale-Up Carbonylation of Aryl Bromides to β-Ketonitriles. Chamber 2.* In a glovebox under argon, to chamber 2 of the two-chamber system (100 mL) were added Pd(cod)Cl_2 (10 mg, 0.04 mmol), $HBF_4{\cdot}P(^tBu)_3$ (11.0 mg, 0.075 mmol), COgen (9-methylfluorene-9-carbonyl chloride) (910 mg, 3.75 mmol), and dioxane (15 mL) in that order. Chamber 1: In a glovebox under argon, to chamber 1 of the two-chamber system (100 mL) were added Pd(cod)Cl_2 (14.2 mg, 0.05 mmol), Xantphos (29 mg, 0.05 mmol), anhydrous $MgCl_2$ (575 mg, 6.0 mmol), *tert*-butyl 2-cyanoacetate (393 μL, 2.75 mmol), bromobenzene (393 mg, 2.50 mmol), dioxane (15 mL), and Cy_2NMe (2.13 mL, 10.0 mmol) in that order. To chamber 2 was added Cy_2NMe (1.60 mL, 7.5 mmol), and both chambers were sealed with a screwcap fitted with a PTFE/silicone seal. The loaded two-chamber system was removed from the glovebox and heated to 100 °C for 18 h. The lid was removed, HCOOH (5.0 mL) was added, and stirring was continued for 1 h before cooling to rt and concentration under reduced pressure. Purification was performed by column chromatography (pentane/Et_2O/HCOOH 34/6/1−14/6/1) to yield the title compound as a yellow solid (361 mg, 2.50 mmol, quant). ^{1}H NMR (400 MHz, $CDCl_3$): δ H ppm 7.92 (d, J = 7.3 Hz, 2H), 7.68 (t, J = 7.3 Hz, 1H), 7.52 (m, 2H), 4.10 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 187.3, 134.9, 134.4, 129.3 (2C), 128.6 (2C), 114.0, 29.5. HRMS C_9H_8ON [M + H^+]: calcd 146.0600, found 146.0596. Mp (uncorrected): 79.5−80.8 °C.[13a]

3-(4-Methoxyphenyl)-3-oxopropanenitrile (1). Reaction with 1-bromo-4-methoxybenzene (62.6 μL, 0.50 mmol) using general method A was followed by workup by addition to satd $NaHCO_{3(aq)}$ (30 mL) and extraction with dichloromethane (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtrated and concentrated under reduced pressure. Purification was performed by column chromatography (Pentane/Et_2O/HCOOH 14/6/1) resulting in the title compound as a yellow solid (61.4 mg, 0.35 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ H ppm 7.92−7.89 (m, 2H), 7.00−6.96

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(m, 2H), 4.01 (s, 2H), 3.90 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 185.5, 164.9, 131.1 (2C), 127.4, 114.5 (2C), 114.2, 55.8, 29.2. HRMS $C_{10}H_9NNaO_2$ [M + Na^+]: calculated 198.0525, found 198.0527. Mp (uncorrected): 129.2−131.1 °C.[13a]

*3-Oxo-3-(p-tolyl)propanenitrile (**2**).* Reaction with 1-bromo-4-methylbenzene (85.5 mg, 0.50 mmol) using general method A was followed by workup by addition to satd $NaHCO_{3(aq)}$ (30 mL) and extraction with dichloromethane (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification was performed by column chromatography (pentane/Et_2O/HCOOH 16/4/1−15/5/1) resulting in the title compound as a yellow solid (69.2 mg, 0.43 mmol, 76%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 7.81 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 4.04 (s, 2H), 2.44 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 186.7, 146.1, 132.0, 130.0 (2C), 128.8 (2C), 114.0, 29.4, 22.0. HRMS $C_{10}H_9NONa$ [M + Na^+]: calcd 182.0576, found 182.0576. Mp (uncorrected): 100.5−102.4 °C.[13a]

*3-Oxo-3-(p-tolyl)propanenitrile (**2**).* Reaction with 1-bromo-4-methylbenzene (513 mg, 3.0 mmol) using general method B was followed by workup by addition to satd $NaHCO_{3(aq)}$ (30 mL) and extraction with dichloromethane (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification was performed by column chromatography (pentane/EtOAc 1/10−3/10) resulting in the title compound as a yellow solid (376 mg, 2.4 mmol, 79%). The physical and spectroscopic data were in accordance with those reported for the same compound using method A.

*3-([1,1′-Biphenyl]-4-yl)-3-oxopropanenitrile (**3**).* Reaction with 4-bromo-1,1′-biphenyl (117 mg, 0.50 mmol) using general method A was followed by workup by addition to satd $NaHCO_{3(aq)}$ (30 mL) and extraction with dichloromethane (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification was performed by column chromatography (pentane/Et_2O/HCOOH 18/2/1−14/6/1). A second column using fine silica (pentane/acetone 10/1) resulted in the title compound as a yellow solid (78.5 mg, 0.36 mmol, 71%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 8.00 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 1H), 4.11 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 186.7, 147.5, 139.4, 133.1, 129.2 (4C), 128.9 (2C), 127.9 (2C), 127.5, 113.9, 29.5. HRMS $C_{15}H_{12}NO$ [M + H^+]: calcd 222.0913, found 222.0915. Mp (uncorrected): 112.1−113.3 °C.[25]

*3-Oxo-3-phenylpropanenitrile (**4**).* Reaction with bromobenzene (52.5 μL, 0.50 mmol) using general method A was followed by workup by addition to satd $NaHCO_{3(aq)}$ (30 mL) and extraction with dichloromethane (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification was performed by column chromatography (pentane/Et_2O/HCOOH 15/4/1) resulting in the title compound as a yellow solid (71.0 mg, 0.49 mmol, 98%). The physical and spectroscopic data were in accordance with that reported for the same compound under method B.

*3-Oxo-3-phenylpropanenitrile (**4**).* Reaction with phenyl trifluoromethanesulfonate (113 mg, 0.50 mmol) using general method A followed by column chromatography (pentane/Et_2O/HCOOH 34/6/1−14/6/1) resulted in the title compound as a yellow solid (69.8 mg, 0.48 mmol, 96%). The physical and spectroscopic data were in accordance with that reported for the same compound under method B.

*3-Oxo-3-phenylpropanenitrile (**4**).* To *tert*-butyl (*E*/Z)-2-cyano-3-hydroxy-3-phenyl acrylate (**26**) (116 mg, 0.47 mmol) in anhydrous dioxane (3.0 mL) was added HCOOH (1.0 mL) and the reaction heated to 100 °C for 1 h. Purification by column chromatography (pentane/Et_2O/HCOOH 34/6/1−14/6/1) resulted in the title compound as a yellow solid (58.7 mg, 0.40 mmol, 86%). The physical and spectroscopic data were in accordance with those reported for the same compound under method B.

*[3-^{13}C]-3-Oxo-3-phenylpropanenitrile (**4***).* Reaction with bromobenzene (393 mg, 2.50 mmol) using general method B (with ^{13}COgen, 914 mg, 3.50 mmol) followed by column chromatography (pentane/Et_2O/HCOOH 34/6/1−14/6/1) resulted in the title compound as a yellow solid (351 mg, 2.40 mmol, 96%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 7.94−7.84 (m, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 2H), 4.12 (d, *J* = 6.2 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 187.5 (^{13}C enriched), 134.7, 134.3 (d, *J* = 57.8 Hz), 129.1 (d, *J* = 4.3 Hz, 2C), 128.5 (d, *J* = 2.9 Hz, 2C), 114.1 (d, *J* = 3.5 Hz), 29.5 (d, *J* = 40.1 Hz). HRMS $C_8{}^{13}CH_8NO$ [M + H^+]: calcd 147.0634, found 147.0635. Mp (uncorrected): 82.1−84.0 °C.

*4-(2-Cyanoacetyl)phenyl 4-methylbenzenesulfonate (**5**).* Reaction with 4-bromophenyl 4-methylbenzenesulfonate (164 mg, 0.50 mmol) using general method A was followed by workup by addition to satd $NaHCO_{3(aq)}$ (30 mL) and extraction with dichloromethane (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification was performed by column chromatography (pentane/Et_2O/HCOOH 12/8/1) resulting in the title compound as a yellow solid (99.2 mg, 0.31 mmol, 63%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 7.87 (d, *J* = 8.8, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.8 Hz, 2H), 4.05 (s, 2H), 2.46 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 186.0, 154.2, 146.2, 132.9, 132.0, 130.5 (2C), 130.2 (2C), 128.6 (2C), 123.2 (2C), 113.5, 29.6, 21.9. HRMS $C_{16}H_{13}NO_4SNa$ [M + Na^+]: calcd 338.0457, found 338.0457. Mp (uncorrected): 125.3−126.4 °C.

*4-(2-Cyanoacetyl)benzonitrile (**6**).* Reaction with 4-bromobenzonitrile (91.0 mg, 0.50 mmol) using general method A was followed by workup by addition to satd $NaHCO_{3(aq)}$ (30 mL) and extraction with dichloromethane (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification was performed by column chromatography (pentane/Et_2O/HCOOH 14/6/1) resulting in the title compound as a yellow solid (66.4 mg, 0.39 mmol, 78%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 8.03 (d, *J* = 8.5 Hz, 2H), 7.84 (d, *J* = 8.5 Hz, 2H), 4.12 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 186.3, 137.2, 133.1 (2C), 129.0 (2C), 118.1, 117.5, 113.1, 29.9. HRMS $C_{10}H_7N_2O$ [M + H^+]: 171.0553, found 171.0549. Mp (uncorrected): 128.4−130.2 °C.[14]

*3-(4-Acetylphenyl)-3-oxopropanenitrile (**7**).* Reaction with 1-(4-bromophenyl)ethan-1-one (99.5 mg, 0.50 mmol) using general method A was followed by workup by addition to satd $NaHCO_{3(aq)}$ (30 mL) and extraction with dichloromethane (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification was performed by column chromatography (pentane/Et_2O/HCOOH12/8/1−8/12/1) resulting in the title compound as a yellow solid (68.5 mg, 0.36 mmol, 73%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 8.08 (d, *J* = 8.3 Hz, 2H) 8.01 (d, *J* = 8.3 Hz, 2H), 4.12 (s, 2H), 2.66 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 197.1, 186.8, 141.5, 137.3, 129.0 (2C), 128.9 (2C), 113.4, 29.9, 27.1. HRMS $C_{11}H_9NNaO_2$ [M + Na^+]: calcd 210.0525, found 210.0524. Mp (uncorrected): 121.7−122.8 °C.[14]

*3-(4-Fluorophenyl)-3-oxopropanenitrile (**8**).* Reaction with 1-bromo-4-fluorobenzene (88.0 mg, 0.50 mmol) using general method A was followed by column chromatography (pentane/Et_2O/HCOOH 34/6/1−14/6/1). A second column using fine silica (pentane/Et_2O/HCOOH 34/6/1−14/6/1) resulted in the title compound as a yellow solid (60.4 mg, 0.37 mmol, 74% (corrected)). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 8−00−7−93 (m, 2H), 7.23−7.15 (m, 2H), 4.08 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 185.8, 166.7 (d, *J* = 258 Hz), 131.4 (d, *J* = 9.7 Hz, 2C), 130.9 (d, *J* = 3.0 Hz), 116.6 (d, *J* = 22.2 Hz, 2C), 113.8, 29.5. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ F ppm −101.6. HRMS C_9H_6FNNaO [M + Na^+]: calcd 186.0326, found 186.0329. Mp (uncorrected): 88.5−92.0 °C.[13a]

*3-Oxo-3-(m-tolyl)propanenitrile (**10**).* Reaction with 1-bromo-3-methylbenzene (86.0 mg, 0.50 mmol) using general method A was followed by column chromatography (pentane/Et_2O/HCOOH 34/6/1). A second column using fine silica (pentane/Et_2O/HCOOH 34/6/1−14/6/1) resulted in the title compound as a yellow solid (62.1 mg, 0.39 mmol, 78% (corrected). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 7.73 (s, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 4.07 (s, 2H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 187.4, 139.3, 135.7, 134.5, 129.1, 129.1, 125.8,

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114.0, 29.5, 21.4. HRMS $C_{10}H_{10}NO$ [M + H^+]: calcd 160.0757, found 160.0754. Mp (uncorrected): 73.4−75.0 °C.[13a]

*3-(3-Methoxyphenyl)-3-oxopropanenitrile (**11**).* Reaction with 1-bromo-3-methoxybenzene (94.0 mg, 0.50 mmol) using general method A was followed by column chromatography (pentane/Et_2O/HCOOH 34/6/1 to 14/6/1). A second column using fine silica (pentane/Et_2O/HCOOH 34/6/1−14/6/1) resulted in the title compound as a yellow solid (64.8 mg, 0.37 mmol, 74% (corrected)). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 7.47−7.38 (m, 3H), 7.20−7.16 (m, 1H), 4.09 (s, 2H), 3.85 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 187.2, 160.2, 135.6, 130.2, 121.3, 121.1, 114.0, 112.8, 55.7, 29.6. HRMS $C_{10}H_9NNaO_2$ [M + Na^+]: calcd 198.0525, found 198.0527. Mp (uncorrected): 80.9−83.3 °C.[14]

*3-Oxo-3-(3-(trifluoromethyl)phenyl)propanenitrile (**12**).* Reaction with 1-bromo-3-(trifluoromethyl)benzene (69.7 μL, 0.50 mmol) using general method A was followed by workup by addition to satd $NaHCO_{3(aq)}$ (30 mL) and extraction with dichloromethane (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification was performed by column chromatography (pentane/Et_2O/HCOOH 15/5/1) resulting in the title compound as a yellow solid (95.3 mg, 0.45 mmol, 89%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 8.17 (s, 1H), 8.12 (d, J = 7.9 Hz, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.70 (t, J = 7.9 Hz, 1H), 4.13 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 186.0, 134.8, 131.9 (q, J = 33.4 Hz), 132.6−131.4 (m), 131.4 (q, J = 3.51 Hz), 130.0, 125.3 (q, J = 3.80 Hz), 123.3 (q, J = 272 Hz), 113.1, 29.6. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ F ppm −63.0. HRMS $C_{10}H_6F_3NNaO$ [M + Na^+]: calcd 236.0294, found 236.0296. Mp (uncorrected): 56.8−58.0 °C.[26]

*3-Oxo-3-(3-(trifluoromethyl)phenyl)propanenitrile (**12**).* Reaction with 1-bromo-3-(trifluoromethyl)benzene (563 mg, 2.50 mmol) using general method B followed by column chromatography (pentane/Et_2O/HCOOH 34/6/1−14/6/1) resulted in the title compound as a yellow solid (436 mg, 2.05 mmol, 82%). The physical and spectroscopic data were in accordance with that reported for the same compound using method A.

*S-Cyclohexyl 3-(2-Cyanoacetyl)benzothioate (**13**).* Reaction with *S*-cyclohexyl 3-bromobenzothioate (150 mg, 0.50 mmol) using general method A followed by column chromatography (pentane/Et_2O/HCOOH 34/6/1−14/6/1) resulted in the title compound as a yellow solid (100 mg, 0.35 mmol, 70%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 8.41 (s, 1H), 8.22 (d, J = 7.7 Hz, 1H), 8.13 (d, J = 7.7 Hz, 1H), 7.62 (t, J = 7.7 Hz, 1H), 4.14 (s, 2H), 3.82−3.71 (m, 1H), 2.09−1.96 (m, 2H), 1.82−1.71 (m, 2H), 1.69−1.59 (m, 1H), 1.58−1.45 (m, 4H), 1.40−1.26 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 190.8, 186.5, 138.5, 134.7, 133.1, 132.6, 129.8, 127.0, 113.5, 43.3, 33.2 (2C), 29.7, 26.1 (2C), 25.7. HRMS $C_{16}H_{18}NO_2S$ [M + H^+]: calcd 288.1053, found 288.1055. Mp (uncorrected): 81.7−84.3 °C.

*3-(3,4-Dimethoxyphenyl)-3-oxopropanenitrile (**14**).* Reaction with 4-bromo-1,2-dimethoxybenzene (72.2 μL, 0.50 mmol) using general method A was followed by workup by addition to satd $NaHCO_{3(aq)}$ (30 mL) and extraction with dichloromethane (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification was performed by column chromatography (pentane/Et_2O/HCOOH 12/8/1) resulting in the title compound as a yellow solid (61.6 mg, 0.30 mmol, 60%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 7.52−7.48 (m, 2H), 6.92 (d, J = 8.8 Hz, 1H), 4.03 (s, 2H), 3.97 (s, 3H), 3.94 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 185.6, 154.8, 149.7, 127.6, 123.6, 114.2, 110.5, 110.4, 56.4, 56.3, 29.1. HRMS $C_{11}H_{11}NNaO_3$ [M + Na^+]: calcd 228.0631, found 228.0634. Mp (uncorrected): 134.4−135.7 °C.[27]

*3-(3,5-Dimethoxyphenyl)-3-oxopropanenitrile (**15**).* Reaction with 1-bromo-3,5-dimethoxybenzene (542 mg, 2.50 mmol) using general method B followed by column chromatography (pentane/Et_2O/HCOOH 34/6/1−14/6/1) resulted in the title compound as a yellow solid (395 mg, 1.93 mmol, 77%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 7.01 (d, J = 2.2 Hz, 2H), 6.71 (t, J = 2.2 Hz, 1H), 4.04 (s, 2H), 3.84 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 187.0, 161.3 (2C), 136.2, 113.8, 106.8, 106.4 (2C), 55.9, 29.6 (2C). HRMS $C_{11}H_{12}NO_3$ [M + H^+]: 206.0814, found 206.0817. Mp (uncorrected): 123.2−124.4 °C.

*[3-^{13}C]-3-(3,5-Dimethoxyphenyl)-3-oxopropanenitrile (**15***).* Reaction with 1-bromo-3,5-dimethoxybenzene (108 mg, 0.50 mmol) using general method A (with ^{13}COgen, 184 mg, 0.75 mmol) followed by column chromatography (pentane/Et_2O/HCOOH 34/6/1−14/6/1) resulted in the title compound as a yellow solid (76.0 mg, 0.37 mmol, 74%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 7.00 (dd, J = 4.4 Hz, J = 2.2 Hz, 2H), 6.72−6.69 (m, 1H), 4.05 (d, J = 6.3 Hz, 2H), 3.83 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 187.0 (^{13}C enriched), 169.3 (Unkwon ^{13}C impurity), 161.3 (d, J = 6.2 Hz, 2C), 136.2 (d, J = 57.5 Hz), 113.9 (d, J = 3.5 Hz), 106.8, 106.4 (d, J = 3.2 Hz, 2C), 55.8, 29.6 (d, J = 40.5 Hz, 2C). HRMS $C_{10}{}^{13}CH_{12}NO_3$ [M + H^+]: calcd 207.0846, found 207.0845. Mp (uncorrected): 122.4−123.6 °C.

*3-(4-(2,5-Dimethyl-1H-pyrrol-1-yl)-3,5-difluorophenyl)-3-oxopropanenitrile (**16**).* Reaction with 1-(4-bromo-2,6-difluorophenyl)-2,5-dimethyl-1*H*-pyrrole (143 mg, 0.50 mmol) using general method A followed by column chromatography (pentane/Et_2O/HCOOH 68/3/1−34/6/1−14/6/1) resulted in the title compound as a yellow solid (56.8 mg, 0.21 mmol, 41%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 7.65 (d, J = 7.0 Hz, 2H), 5.99 (s, 2H), 4.10 (s, 2H), 2.02 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 184.5, 159.5 (dd, J = 256 Hz, J = 3.8 Hz, 2C), 135.1 (t, J = 7.6 Hz), 129.4 (2C), 122.4 (t, J = 16.8 Hz), 112.9, 112.6−112.3 (m, 2C), 107.9 (s, 2C), 29.7, 12.2 (2C). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ F ppm −113.7. HRMS $C_{15}H_{13}F_2N_2O$ [M + H^+]: calcd 275.0990, found 275.0991. Mp (uncorrected): 113.7−117.0 °C.

*3-(4-Amino-3,5-dichlorophenyl)-3-oxopropanenitrile (**17**).* Reaction with 4-bromo-2,6-dichloroaniline (120 mg, 0.50 mmol) using general method A followed by column chromatography (pentane/Et_2O/HCOOH 34/6/1−14/6/1) resulted in the title compound as a yellow solid (57.2 mg, 0.25 mmol, 50%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 7.78 (s, 2H), 5.14 (bs, 2H), 3.95 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 183.5, 145.7, 128.9 (2C), 124.4, 119.2 (2C), 113.8, 28.9. HRMS $C_9H_7Cl_2N_2O$ [M + H^+]: calcd 228.9930, found 228.9930. Mp (uncorrected): 125.8−129.7 °C.

*(E)-4-(4-Cyano-3-oxobut-1-en-1-yl)benzonitrile (**18**).* Reaction with (*E*)-4-(2-bromovinyl)benzonitrile (104 mg, 0.50 mmol) using general method A was followed by column chromatography (pentane/Et_2O/HCOOH 34/6/1−14/6/1). A second column using fine silica (pentane/Et_2O/HCOOH 34/6/1−14/6/1) resulted in the title compound as a yellow solid (53.2 mg, 0.27 mmol, 54%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 7.76−7.63 (m, 5H), 6.95 (d, J = 16.0 Hz, 1H), 3.72 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 186.0, 144.0, 137.7, 133.0 (2C), 129.2 (2C), 125.1, 118.2, 114.8, 113.7, 31.4. HRMS $C_{12}H_9N_2O$ [M + H^+]: calcd 197.0709, found 197.0713. Mp (uncorrected): 143.9−145.9 °C.

*(E)-5-(4-Methoxyphenyl)-3-oxopent-4-enenitrile (**19**).* Reaction with (*E*)-1-(2-bromovinyl)-4-methoxybenzene (107 mg, 0.50 mmol) using general method A was followed by column chromatography (pentane/Et_2O/HCOOH 14/6/1−14/14/1). A second column using fine silica (pentane/Et_2O/HCOOH 34/6/1−14/6/1) resulted in the title compound as a yellow solid (66.4 mg, 0.33 mmol, 66%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 7.64 (d, J = 15.9 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 6.74 (d, J = 15.9 Hz, 1H), 3.86 (s, 3H), 3.68 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 186.3, 162.7, 146.5, 131.0 (2C), 126.2, 121.1, 114.8 (2C), 114.4, 55.6, 30.8. HRMS $C_{12}H_{12}NO_2$ [M + H^+]: calcd 202.0863, found 202.0865. Mp (uncorrected): 132.9−134.0 °C.

*3-Oxo-4-phenylbutanenitrile (**20**).* Reaction with benzyl chloride (63.0 mg, 0.50 mmol) using general method A followed by column chromatography (pentane/Et_2O/HCOOH 38/3/1−34/6/1−14/6/1) resulted in the title compound as a yellow oil (74.2 mg, 0.47 mmol, 93%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 7.41−7.28 (m, 3H), 7.21 (d, J = 6.7 Hz, 2H), 3.84 (s, 2H), 3.46 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 195.5, 132.1, 129.5 (2C), 129.3 (2C), 128.0, 113.8, 49.2, 31.3. HRMS $C_{10}H_{10}NO$ [M + H^+]: calcd 160.0757, found 160.0756.[25]

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*3-Oxo-3-(thiophene-2-yl)propanenitrile (**21**).* Reaction with 2-bromothiophene (82.0 mg, 0.50 mmol) using general method A was followed by column chromatography (pentane/Et_2O/HCOOH 14/6/1). A second column using fine silica (pentane/Et_2O/HCOOH 34/6/1−14/6/1) resulted in the title compound as a yellow solid (40.1 mg, 0.27 mmol, 53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ H ppm 7.82−7.76 (m, 2H), 7.23−7.16 (m, 1H), 3.99 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 179.6, 141.1, 136.4, 133.8, 128.9, 113.5, 29.7. HRMS C_7H_5NNaOS [M + Na^+]: calcd 173.9984, found 173.9983. Mp (uncorrected): 136.3−138.3 °C.[25]

*3-(Benzo[b]thiophene-2-yl)-3-oxopropanenitrile (**22**).* Reaction with 2-bromobenzo[*b*]thiophene (107 mg, 0.50 mmol) using general method A followed by column chromatography with fine silica (pentane/Et_2O/HCOOH 34/6/1) resulted in the title compound as a yellow solid (40.6 mg, 0.20 mmol, 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ H ppm 8.05 (s, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.2 Hz, 1H), 4.11 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 181.2, 143.1, 140.3, 138.8, 131.3, 128.7, 126.6, 125.8, 123.2, 114.1, 29.7. HRMS $C_{11}H_8NOS$ [M + H^+]: calcd 202.0321, found 202.0326. Mp (uncorrected): 118.4−125.6 °C.

*3-(Benzo[b]thiophene-6-yl)-3-oxopropanenitrile (**23**).* Reaction with 6-bromobenzo[*b*]thiophene (107 mg, 0.50 mmol) using general method A was followed by workup by addition to satd $NaHCO_{3(aq)}$ (30 mL) and extraction with dichloromethane (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification was performed by column chromatography (pentane/EtOAc 10/2) resulting in the title compound as a yellow solid (67.3 mg, 0.33 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ H ppm 8.49 (s, 1H), 7.95−7.88 (m, 2H), 7.77 (d, J = 5.4 Hz, 1H), 7.44 (d, J = 5.4 Hz, 1H), 4.16 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 186.7, 144.2, 140.1, 132.6, 130.4, 124.3, 124.1, 124.1, 123.9, 114.0, 29.7. HRMS $C_{11}H_7NNaOS$ [M + Na^+]: calcd 224.0141, found 224.0140. Mp (uncorrected): 111.2−112.8 °C.

*3-(Benzofuran-5-yl)-3-oxopropanenitrile (**24**).* Reaction with 5-bromobenzofuran (99.0 mg, 0.50 mmol) using general method A followed by column chromatography (pentane/Et_2O/HCOOH 34/6/1) resulted in the title compound as a yellow solid (63.2 mg, 0.34 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ H ppm 8.22 (d, J = 1.5 Hz, 1H), 7.91 (dd, J = 8.7 Hz, J = 2.0 Hz, 1H), 7.74 (d, J = 2.0 Hz, 1H), 7.60 (d, J = 8.7 Hz, 1H), 6.89 (d, J = 1.5 Hz, 1H), 4.16 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 186.8, 158.3, 148.3, 129.9, 128.2, 125.2, 123.1, 114.1, 112.3, 107.4, 29.6. HRMS $C_{11}H_8NO_2$ [M + H^+]: calcd 186.0550, found 186.0550. Mp (uncorrected): 129.0−130.1 °C.

*3-(1H-Indol-5-yl)-3-oxopropanenitrile (**25**).* Reaction with *tert*-butyl 5-bromoindole-1-carboxylate (123 mg, 0.43 mmol) using general method A followed by column chromatography (pentane/Et_2O/HCOOH 34/6/1−14/6/1−14/14/1−0/29/1) resulted in the title compound as a yellow solid (45.9 mg, 0.24 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ H ppm 8.49 (bs, 1H), 8.26 (s, 1H), 7.83 (dd, J = 8.6 Hz, J = 1.6 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.34 (m, 1H), 6.71 (s, 1H), 4.15 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 186.9, 139.3, 127.8, 127.2, 126.5, 123.5, 122.5, 114.6, 111.8., 104.8, 29.4. HRMS $C_{11}H_9N_2O$ [M + H^+]: calcd 185.0709, found 185.0711. Mp (uncorrected): 95.9−96.2 °C.

*tert-Butyl (E/Z)-2-Cyano-3-hydroxy-3-phenylacrylate (**26**).* Reaction with bromobenzene (79.0 mg, 0.50 mmol) using general method A (without treatment with HCOOH at 100 °C) followed by column chromatography (pentane/Et_2O/HCOOH 68/3/1−34/6/1) resulted in the title compound as a yellow solid (116 mg, 0.47 mmol, 95%). Leaving the title compound on the column or in solution after column for an extended time period result in degradation into 3-oxo-3-phenylpropanenitrile (**1**). ^{1}H NMR (400 MHz, $CDCl_3$): δ H ppm 14.43 (s, 1H), 8.04−7.93 (m, 2H), 7.62−7.54 (m, 1H), 7.54−7.44 (m, 2H), 1.61 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 183.0, 171.1, 133.2, 132.0, 128.8 (2C), 128.7 (2C), 116.3, 85.6, 80.2, 28.2 (3C). HRMS $C_{14}H_{16}NO_3$ [M + H^+]: calcd 246.1125, found 246.1130. Mp (uncorrected): 103.5−105.5 °C.

*Ethyl (E/Z)-2-Cyano-3-hydroxy-3-phenylacrylate (**27**).* Reaction with bromobenzene (79.0 mg, 0.50 mmol) using general method A (without treatment with HCOOH at 100 °C) followed by column chromatography (pentane/Et_2O/HCOOH 68/3/1−34/6/1−14/6/1) resulted in the title compound as a yellow solid (107 mg, 0.49 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ H ppm 14.25 (s, 1H), 8.04−7.95 (m, 2H), 7.65−7.53 (m, 1H), 7.53−7.44 (m, 2H), 4.41 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 183.1, 171.5, 133.4, 131.6, 128.8 (2C), 128.7 (2C), 116.0, 79.0, 63.0, 14.2. HRMS $C_{12}H_{12}NO_3$ [M + H^+]: calcd 218.0812, found 218.0814. Mp (uncorrected): 40.4−40.8 °C.[28]

*4-(2-Nitroacetyl)phenyl 4-Methylbenzenesulfonate (**28**).* Reaction with 4-bromophenyl 4-methylbenzenesulfonate (79.0 mg, 0.50 mmol) using general method A followed by column chromatography (pentane/Et_2O/HCOOH 34/6/1−14/6/1) resulted in the title compound as a yellow solid (102.3 mg, 0.31 mmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ H ppm 13.74 (s, 0.13H, enol (minor isomer)), 7.83 (d, J = 8.7 Hz, 2H), 7.71 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 5.84 (s, 1.61H, ketone (major isomer)), 2.46 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 184.6, 154.5, 146.3, 132.0, 132.0, 130.3 (2C), 130.2 (2C), 128.6 (2C), 123.4 (2C), 81.2, 21.9. HRMS $C_{15}H_{14}NO_6S$ [M + H^+]: calcd 336.0536, found 336.0540. Mp (uncorrected): 128.4−130.2 °C.[29]

*3-(3,5-Dimethoxyphenyl)propiolonitrile (**29**).* 3-(3,5-Dimethoxyphenyl)-3-oxopropanenitrile (**15**) (65.4 mg, 0.32 mmol), 2-chloro-1-methylpyridin-1-ium iodide (246 mg, 0.95 mmol), anhydrous dichloromethane (3 mL), and triethylamine (1.58 mL, 11 mmol) was added to a 8 mL vial in that order at 0 °C under an argon atmosphere. The mixture was vigorously stirred for 30 min before stirring at rt overnight. NaOH (1 M, 3 mL) was added, and the mixture was stirred for an additional 10 min before dilution with dichloromethane and water. The reaction was extracted with dichloromethane (3 × 30 mL), and the combined organic phases were washed with 1 × 1 M NaOH (30 mL) and 1 × 1 M HCl (30 mL) and concentrated under reduced pressure. The crude product was purified by column chromatography (pentane/Et_2O/HCOOH 7/3/0−7/3/1) resulting in the title compound as a clear solid (43.0 mg, 0.23 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ H ppm 6.72 (d, J = 2.1 Hz, 2H), 6.61 (t, J = 2.1 Hz, 1H), 3.79 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 160.9, 118.7, 111.2 (2C), 105.5, 105.5 (2C), 83.1, 62.5, 55.7 (2C). HRMS $C_{11}H_{10}NO_2$ [M + H^+]: calcd 188.0706, found 188.0706. Mp (uncorrected): 110.7−112.3 °C.

*[3-^{13}C]-3-(3,5-Dimethoxyphenyl)propiolonitrile (**29***).* [3-^{13}C]-3-(3,5-Dimethoxyphenyl)-3-oxopropanenitrile (**15***) (64.2 mg, 0.31 mmol)), 2-chloro-1-methylpyridin-1-ium iodide (244 mg, 0.93 mmol), anhydrous dichloromethane (3 mL), and triethylamine (1.43 mL, 10 mmol) were added to a 8 mL vial in that order at 0 °C under an argon atmosphere. The mixture was vigorously stirred for 30 min before being stirred at rt overnight. NaOH (1 M, 3 mL) was added, and the mixture was stirred for an additional 10 min before dilution with dichloromethane and water. The reaction was extracted with dichloromethane (3 × 30 mL), and the combined organic phases were washed with 1 × 1 M NaOH (30 mL) and 1 × 1 M HCl (30 mL) and concentrated under reduced pressure. The crude product was purified by column chromatography (pentane/Et_2O/HCOOH 7/3/0−7/3/1) resulting in the title compound as a clear solid (41.5 mg, 0.22 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ H ppm 6.73 (dd, J = 6.0 Hz, J = 2.2 Hz, 2H), 6.63−6.60 (m, 1H), 3.80 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 160.9 (d, J = 8.1 Hz), 118.8 (d, J = 89.8 Hz), 111.2 (d, J = 2.1 Hz, 2C), 105.7, 105.5 (2C), 83.1 (^{13}C enriched), 63.5, 55.7 (2C). HRMS $C_{10}{}^{13}CH_{10}NO_2$ [M + H^+]: calcd 189.0740, found 189.0739. Mp (uncorrected): 110.8−112.5 °C.

*3-Phenylpropiolonitrile (**30**).* 3-Oxo-3-phenylpropanenitrile (**1**) (182 mg, 1.25 mmol), 2-chloro-1-methylpyridin-1-ium iodide (958 mg, 3.75 mmol), anhydrous dichloromethane (11 mL), and triethylamine (5.6 mL, 40 mmol) were added to a round-bottom bottle in that order at 0 °C under an argon atmosphere. The mixture was vigorously stirred for 30 min before stirring at rt overnight. NaOH (1 M, 11 mL) was added, and the mixture was stirred for an additional 10 min before dilution with dichloromethane and water. The reaction

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J. Org. Chem. 2016, 81, 1358−1366

was extracted with dichloromethane (3 × 30 mL), and the combined organic phases were washed with 1 × 1 M NaOH (30 mL) and 1 × 1 M HCl (30 mL) and concentrated under reduced pressure (the title compound was found to be volatile and the pressure during concentration was therefore never lower than 600 mbar at 30 °C). The crude product was purified by column chromatography (pentane/Et_2O 1/0−40/1) resulting in the title compound as a clear solid (115 mg, 0.90 mmol, 72%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 7.66−7.58 (m, 2H), 7.57−7.50 (m, 1H), 7.42 (t, J = 7.6 Hz, 2H), 5.29 (Dichloromethane impurity). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 133.6 (2C), 132.0, 129.0 (2C), 117.6, 105.6, 83.1, 63.2. HRMS C_9H_6N [M + H^+]: calcd 128.0495, found 128.0495. Mp (uncorrected): 37.8−38.4 °C.[30]

*[3-^{13}C]-3-Phenylpropiolonitrile (**30***).* [3-^{13}C]-3-Oxo-3-phenylpropanenitrile (**1***) (146 mg, 1.00 mmol), 2-chloro-1-methylpyridin-1-ium iodide (764 mg, 3.00 mmol), anhydrous dichloromethane (8.7 mL), and triethylamine (4.5 mL, 32 mmol) were added to a round-bottom bottle in that order at 0 °C under an argon atmosphere. The mixture was vigorously stirred for 30 min before stirring at rt overnight. NaOH (1 M, 8.7 mL) was added, and the mixture was stirred for an additional 10 min before dilution with dichloromethane and water. The reaction was extracted with dichloromethane (3 × 30 mL), and the combined organic phases were washed with 1 × 1 M NaOH (30 mL) and 1 × 1 M HCl (30 mL) and concentrated under reduced pressure (the title compound was found to be volatile and the pressure during concentration therefore never lower than 600 mbar at 30 °C). The crude product was purified by column chromatography (pentane/Et_2O 1/0−40/1) resulted in the title compound as a pale yellow solid (94.8 mg, 0.74 mmol, 74%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 7.65−7.58 (m, 2H), 7.54 (t, J = 7.1 Hz, 1H), 7.42 (t, J = 7.7 Hz, 2H), 5.29 (dichloromethane impurity). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 133.6 (d, J = 1.8 Hz, 2C), 132.0 (d, J = 1.7 Hz), 129.0 (d, J = 5.7 Hz, 2C), 117.6 (d, J = 89.8 Hz), 105.6 (d, J = 20.1 Hz), 83.1 (s, ^{13}C enriched), 63.2 (d, J = 203 Hz). HRMS $C_8{}^{13}CH_6N$ [M + H^+]: calcd 129.0528, found 129.0523. Mp (uncorrected): 37.7−39.5 °C.

*2-(3,5-Dimethoxyphenyl)-4,6-dimethylbenzofuran-3-carbonitrile (**31**).*[23] To an 8 mL vial were added 3-(3,5-dimethoxyphenyl)-propiolonitrile-3 (**29**) (93.5 mg, 0.50 mmol), 3,5-dimethylphenol (67.2 mg, 0.55 mmol), DABCO (56.1 mg, 0.50 mmol), and 1,2-dichloroethane (1.0 mL). The vial was sealed with a lid, heated to 45 °C, and stirred overnight before addition of 1 M HCl (1 mL) and extraction with 1,2-dichloroethane (3 × 1.0 mL). The organic phases were transferred to a 10 mL vial and concentrated under reduced pressure. The vial was transferred to an argon-filled glovebox, and $Pd(OAc)_2$ (5.61 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.050 mmol), $Cu(OAc)_2$ (182 mg, 1.00 mmol), and dioxane (1.0 mL) were added in the order listed. The vial was sealed and removed from the glovebox before heating to 130 °C and stirred for 24 h. The mixture was cooled to rt and filtered over a small plug of silica (EtOAc). Purification by column chromatography (pentane/Et_2O 40/1−30/1−20/1) resulted in the title compound as a clear solid (46.6 mg, 0.15 mmol, 30%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 7.31 (d, J = 2.1 Hz, 2H), 7.17 (s, 1H), 6.92 (s, 1H), 6.61−6.55 (m, 1H), 3.88 (s, 6H), 2.69 (s, 3H), 2.44 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 161.3 (2C), 161.2, 153.9, 137.1, 131.4, 129.8, 127.3, 123.1, 116.1, 110.3, 104.2 (2C), 103.7, 87.9, 55.7 (2C), 21.8, 18.0. HRMS $C_{19}H_{18}NO_3$ [M + H^+]: calcd 308.1281, found 308.1284. Mp (uncorrected): 172.4−173.7 °C.

*[2-^{13}C]-2-(3,5-Dimethoxyphenyl)-4,6-dimethylbenzofuran-3-carbonitrile (**31***).*[23] To an 8 mL vial were added [3-^{13}C]-3-(3,5-dimethoxyphenyl)propiolonitrile (**29***) (79.4 mg, 0.42 mmol), 3,5-dimethyl phenol (56.4 mg, 0.46 mmol), DABCO (47.1 mg, 0.42 mmol), and 1,2-dichloroethane (0.84 mL). The vial was sealed with a lid, heated to 45 °C, and stirred overnight before addition of 1 M HCl (0.84 mL) and extraction with 1,2-dichloroethane (3 × 1.0 mL). The organic phases were transferred to a 10 mL vial and concentrated under reduced pressure. The vial was transferred to an argon-filled glovebox, and $Pd(OAc)_2$ (4.7 mg, 0.021 mmol), PPh_3 (11.0 mg, 0.042 mmol), $Cu(OAc)_2$ (153 mg, 0.84 mmol), and dioxane (0.84 mL) were added in the order listed. The vial was sealed and removed from the glovebox before heating to 130 °C and stirred for 24 h. The mixture was cooled to rt and filtered over a small plug of silica (EtOAc). Purification by column chromatography using general method F followed by column chromatography (pentane/Et_2O 40/1−30/1−20/1) resulted in the title compound as a clear solid (47.8 mg, 0.16 mmol, 37%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 7.31 (dd, J = 4.8 Hz, J = 2.2 Hz, 2H), 7.18 (s, 1H), 6.92 (s, 1H), 6.61−6.54 (m, 1H), 3.88 (s, 6H), 2.70 (s, 3H), 2.44 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 161.3 (2C), 161.2 (^{13}C enriched), 153.9 (d, J = 2.2 Hz), 137.1, 131.4 (d, J = 4.1 Hz), 129.8 (d, J = 69.6 Hz), 127.4, 123.1, 116.1 (d, J = 6.7 Hz), 109.5 (d, J = 2.8 Hz), 104.3 (d, J = 2.4 Hz, 2C), 103.7, 87.9 (d, J = 82.2 Hz), 55.7 (2C), 21.8, 18.0. HRMS $C_{18}{}^{13}CH_{18}NO_3$ [M + H^+]: calcd 309.1315, found 309.1316. Mp (uncorrected): 174.7−175.8 °C.

*4,6-Dimethyl-2-phenylbenzofuran-3-carbonitrile (**32**).*[23] To an 8 mL vial were added 3-phenylpropiolonitrile-3 (**30**) (63.6 mg, 0.50 mmol), 3,5-dimethylphenol (67.2 mg, 0.55 mmol), DABCO (56.1 mg, 0.50 mmol), and 1,2-dichloroethane (1.0 mL). The vial was sealed with a lid, heated to 45 °C, and stirred overnight before addition of 1 M HCl (1 mL) and extraction with 1,2-dichloroethane (3 × 1.0 mL). The organic phases were transferred to a 10 mL vial and concentrated under reduced pressure. The vial was transferred to an argon-filled glovebox, and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.050 mmol), $Cu(OAc)_2$ (182 mg, 1.00 mmol), and dioxane (1.0 mL) were added in the order listed. The vial was sealed and removed from the glovebox before heating to 130 °C and stirred for 24 h. The mixture was cooled to rt and filtered over a small plug of silica (EtOAc). Purification by column chromatography (pentane/Et_2O 40/1) resulted in the title compound as a clear solid (51.7 mg, 0.21 mmol, 42%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 8.17 (d, J = 6.7 Hz, 2H), 7.58−7.46 (m, 3H), 7.19 (s, 1H), 6.94 (s, 1H), 2.71 (s, 3H), 2.45 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 161.4, 154.0, 137.0, 131.4, 130.9, 129.2 (2C), 128.4, 127.4, 126.5 (2C), 123.2, 116.2, 109.5, 87.6, 21.8, 18.0. HRMS $C_{17}H_{14}NO$ [M + H^+]: calcd 248.1070, found 248.1072. Mp (uncorrected): 110.5−111.8 °C.[23]

*[2-^{13}C]-4,6-Dimethyl-2-phenylbenzofuran-3-carbonitrile (**32***).*[23] To a 8 mL vial were added [3-^{13}C]-3-phenylpropiolonitrile (**30***) (51.8 mg, 0.40 mmol), 3,5-dimethylphenol (53.8 mg, 0.44 mmol), DABCO (44.9 mg, 0.40 mmol), and 1,2-dichloroethane (0.80 mL). The vial was sealed with a lid, heated to 45 °C, and stirred overnight before addition of 1 M HCl (0.80 mL) and extraction with 1,2-dichloroethane (3 × 0.80 mL). The organic phases were transferred to a 10 mL vial and concentrated under reduced pressure. The vial was transferred to an argon-filled glovebox, and $Pd(OAc)_2$ (4.5 mg, 0.020 mmol), PPh_3 (10.5 mg, 0.040 mmol), $Cu(OAc)_2$ (146 mg, 0.80 mmol), and dioxane (0.80 mL) were added in the order listed. The vial was sealed and removed from the glovebox before heating to 130 °C and stirred for 24 h. The mixture was cooled to rt and filtered over a small plug of silica (EtOAc). Purification by column chromatography (pentane/Et_2O 40/1) resulted in the title compound as a clear solid (37.5 mg, 0.15 mmol, 38%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 8.22−8.12 (m, 2H), 7.57−7.45 (m, 3H), 7.19 (s, 1H), 6.93 (s, 1H), 2.71 (s, 3H), 2.44 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 161.4 (^{13}C enriched), 154.0 (d, J = 2.2 Hz), 137.0, 131.4 (d, J = 4.1 Hz), 130.9 (d, J = 1.4 Hz), 129.2 (d, J = 4.8 Hz, 2C), 128.3 (d, J = 69.5 Hz), 127.3, 126.5 (d, J = 2.1 Hz, 2C), 123.2, 116.2 (d, J = 6.7 Hz), 109.5 (d, J = 2.8 Hz), 87.5 (d, J = 82.0 Hz), 21.8, 18.0. HRMS $C_{16}{}^{13}CH_{14}NO$ [M + H^+]: calcd 249.1103, found 249.1105. Mp (uncorrected): 118.6−121.2 °C.

tert-Butyl 2-Nitroacetate.[24] Nitrite supported on a polymer (Fluka, 4 mmol/g resin, Amberlyst A26, batch 72580, 10 g) was dried on a vacuum line overnight. The polymer−nitrite (5 g (wet weight), approximately 20 mmol) was added to anhydrous acetonitrile (50 mL) at −15 °C and stirred under an argon atmosphere for 30 min before addition of *tert*-butyl 2-bromoacetate (1.95 g, 10 mmol). The reaction was followed by GC analysis and quenched upon completion (18 h) by filtration. The polymer was washed with 5× dichloromethane, and the combined organic phases concentrated under reduced pressure. The resulting oil was purified by column chromatography (pentane/

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J. Org. Chem. 2016, 81, 1358−1366

Et_2O 97/3) resulting in the title compound as a clear oil (676 mg, 4.20 mmol, 42%). ^1H NMR (400 MHz, $CDCl_3$): δ H ppm 5.07 (s, 2H), 1.51 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ C ppm 160.8, 85.4, 28.0 (3C). HRMS $C_6H_{11}NNaO_4$ [M + Na^+]: 184.0580, found 184.0582.[24]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02897.

^1H, $^{13}C\{^1H\}$, and $^{19}F\{^1H\}$ NMR spectra for all produced compounds (PDF)

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Notes

The authors declare the following competing financial interest: Anders T. Lindhardt and Troels Skrydstrup are co-owners of SyTracks Aps, which commercializes the two-chamber technology.

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