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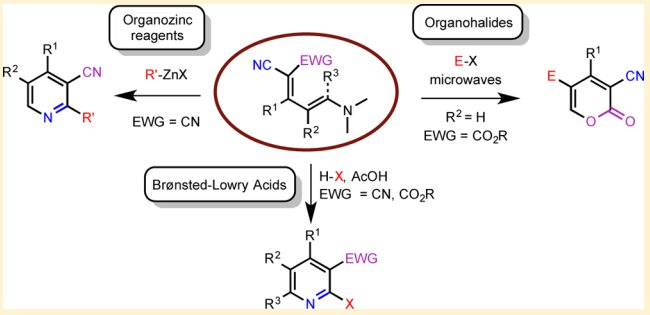
Synthesis and Reactivity Profile of Ylidenemalononitrile Enamines and Their Ester Analogs Towards Electrophiles and Nucleophiles

Ashley R. Longstreet,[†] Daniel Rivalti,[†] and D. Tyler McQuade*

Department of Chemistry and Biochemistry, Florida State University, 95 Chieftan Way, Tallahassee, Florida 32306, United States

Supporting Information

ABSTRACT: Herein, we describe the synthesis and reactivity of enamines derived from ylidenemalononitriles and ylidenecyanoacetates. The enamine scope was expanded by (1) increasing yields of aldehyde-derived ylidenemalononitriles, (2) incorporating silyl functionalities, and (3) using other amide acetals to expand the substitution patterns of pyridines resulting from enamine cyclization. In addition, methods to produce α-pyrones and polysubstituted pyridines from both ylidenemalononitriles and ylidenecyanoacetates are described.



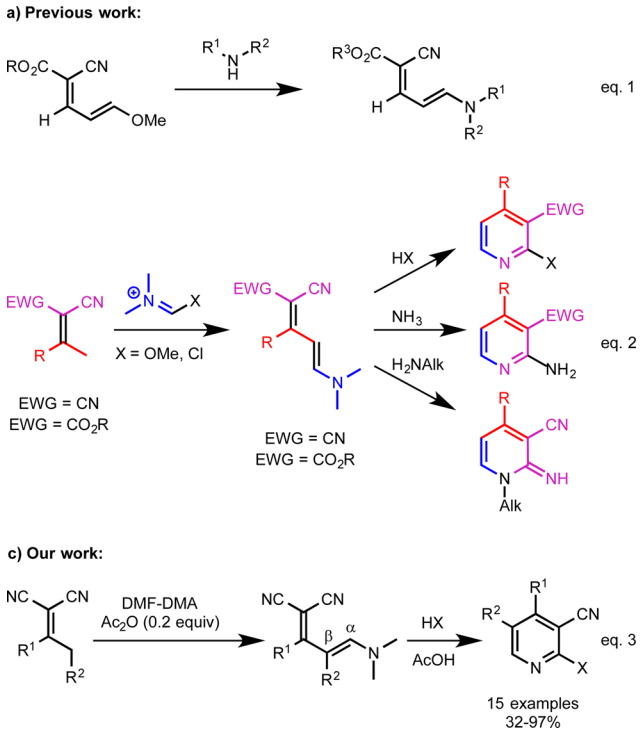
INTRODUCTION

Enamines are intermediates in classic chemical transformations such as Stork enamine synthesis and Mannich-type reactions due to their unique nucleophilic and electrophilic properties. The synthesis and applications of push−pull enamines, unlike classic enamines, have a more modest history. Early reports described reactions of enol ethers with secondary amines to yield push−pull enamines (Scheme 1, eq 1).[1] Entry into this class of enamine was later simplified by producing them directly from alkylidenemalononitriles and cyanoacetates by reaction with a C_1 source, typically Vilsmeier reagent or *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) (Scheme 1, eq 2).[2] Aside from the Pinner and amine-initiated cyclizations to polysubstituted azaheterocycles as shown in Scheme 1 (eq 2),[1,3a,2,3b−h] the reactivity of push−pull enamines toward electrophiles and nucleophiles is largely unexplored. The use of these push−pull enamines to produce substituted pyridines was highlighted in the synthesis of the natural products amphimedine[4,3b] and ascididemin[5] as well as biological probes[1,3f] and analogs to biologically active compounds.[3d]

Despite the advances described above, synthetic routes into enamines containing the malononitrile fragment remain low yielding, and this lack of convenient synthetic access might explain the paucity of literature despite the number of potential nucleophilic and electrophilic sites present. Recently, we added another chapter to this area by developing a new method that enables the formation of ylidenemalononitrile enamines in high yields (Scheme 1, eq 3). The key aspect of our new method was the observation that substoichiometric addition of acetic anhydride significantly improved the yield of the desired enamine, in turn enabling access to a wide range of 4-substituted and 4,5-disubstituted 2-halonicotinonitrile scaffolds in good to excellent yield.[6]

Herein, we report a more thorough study of the synthesis and reactivity of enamines derived from ylidenemalononitriles and ylidenecyanoacetates. We begin by describing a physical organic study that provides a more detailed understanding of the role of acetic anhydride in the formation of these types of

Scheme 1. Strategies for the Synthesis of Enamines and of Pyridines



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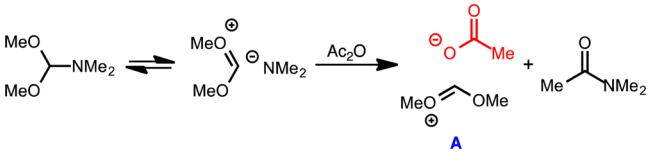
push−pull enamines. We then expand the scope of the method to increase the substitution pattern at the α-position of the enamine and include a new approach to introduce silyl-functionalities in both the enamines and the pyridine products after cyclization under Pinner conditions. Lastly, we explore the reactivity of the enamines toward both electrophiles and nucleophiles by showcasing how these molecules can be used as entry points to both highly substituted pyridines and α-pyrones, via a cyclization with organozinc halides and organohalides, respectively.

RESULTS AND DISCUSSION

Mechanistic Considerations. *Anhydrides as Additives for Enamine Formation.* In 2013, we reported an improved synthesis of 4-substituted and 4,5-disubstituted-2-halonicotinonitriles from alkylidenemalononitriles by improving the yield of the enamine (Scheme 1, eq 3) through the addition of substoichiometric quantities of acetic anhydride.[6a] The synthesis of **2a** (see Table 1) established by Baldwin, Raab, and Ponticello was originally hindered by competing dimerization of the ylidenemalononitriles.[7,2a] Acetic anhydride was chosen as a methanol scavenger because removing methanol would either slow the rate of dimerization or increase the concentration of the reactive iminium species.[6a] However, monitoring the reaction by ^{1}H NMR spectroscopy revealed the reaction between acetic anhydride and methanol to be slow thus contradicting the methanol scavenging hypothesis.[6a] The ^{1}H NMR experiment did indicate the formation of byproducts *N*,*N*-dimethylacetamide (DMA), methyl formate, and trimethyl orthoformate (TMOF) at the very start of the reaction.[6a] In addition, acetic anhydride was also shown to increase the rate of the desired reaction.[6a] Combined with the knowledge obtained in the last communication and new experiments, a more informed model for the role of acetic anhydride in the reaction is described below.

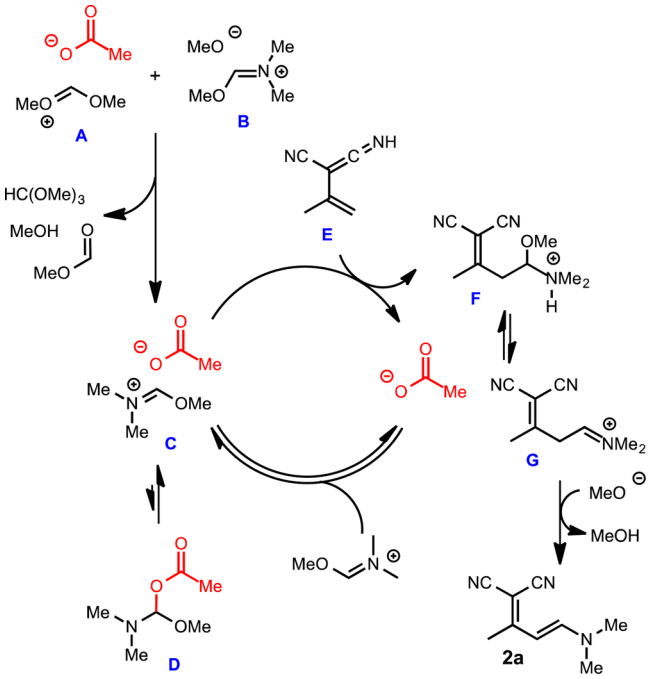
The formation of byproducts DMA, methyl formate, and TMOF suggests an aminolysis between DMF-DMA and acetic anhydride yielding an oxocarbenium acetate salt (**A**) and DMA (Scheme 2). From this model, we propose the following catalytic cycle that uses the acetate anion generated in the process shown in Scheme 2 to catalyze the reaction (Scheme 3).

Scheme 2. Aminolysis of Acetic Anhydride with DMF-DMA



After the formation of the oxocarbenium salt (**A**, Scheme 3), an anion exchange occurs between **A** and iminium salt of DMF-DMA (**B**) to produce the iminium acetate salt (**C**). The methoxide anion is paired with the oxonium cation to produce TMOF or methyl formate if adventitious water is present. The iminium acetate salt **C** is now in equilibrium with the covalently bound species **D**. Because the equilibrium between **D** and **C** should favor **C** due to the stability of the acetate over methoxide, rate enhancement would occur as we have originally observed in the previous communication.[6a] Although no acetate-methoxide exchange has been reported, formation of iminium salts similar to **C** from carboxylic acids[8] or equilibria

Scheme 3. Proposed Catalytic Cycle for Acetate-Catalyzed Rate Enhancement of the Enamine Formation



between alcohols[9] or amines[10] with their amine acetals are known. After the formation of hemiaminal **F** occurs by iminium salt **C** reacting with the alkylidenemalononitrile tautomer, **E**, the free acetate is regenerated and exchanged with methoxide in another molecule of **B**. The methoxide in this previous exchange then facilitates the formation of product **2a** from iminium intermediate **G**. This catalytic cycle is favorable because the increased rate is achieved by altering the reactivity of DMF-DMA, not the alkylidene malononitrile. Increasing the rate of the alkylidene malononitrile tautomerization to **D** will also increase the rate of both the desired reaction and the undesired dimerization. Attempts to identify reactive intermediates **C** or **D** by ^{1}H NMR spectroscopy by combining DMF-DMA and acetic anhydride in DCM-d_2 (0.2 M) were not successful. Without the alkylidenemalononitrile present, we hypothesized that **C** decomposes by hydrolysis to form DMF or a known demethylation between the methoxy and acetate occurs to form DMF and methyl acetate (as both are observed).[8]

With the acetate identified as the potential cause for the observed rate enhancement, other acetate sources were investigated in hopes of further improving the formation of **2a** (Table 1). The addition of acetic acid alone provided the same yield as using no additive (43%, entries 1 and 2) suggesting that acetate is critical, not acetic acid. To test the "acetate not acetic acid" hypothesis, the enamine yield in the presence of a series of acetate sources was measured. As shown in Table 1, 1:1 triethylamine-acetic acid (TEA-AcOH) at varying concentrations provided an improvement in yield compared to acetic acid (entries 3−5). The increase in yield was still not as dramatic as when acetic anhydride was used. A control experiment also indicated the slight increase in yield was not due to TEA alone (entry 6). The data may indicate that the nature of the acetate ion is important and that counterions play a significant role. Tetrabutylammonium-acetate (TBA-OAc) exhibited even lower yields at 34% (entry 7) further

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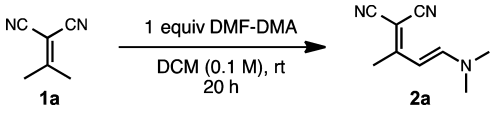
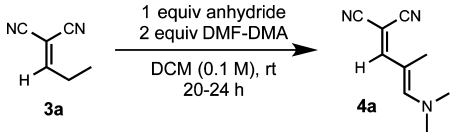
Table 1. Addition of Varying Acetate Sources[a]



entry	additive	addition (mol %)	yield (%)[a]
1	none	–	43
2	AcOH	2.5	43
3	TEA-AcOH	2.5	54
4	TEA-AcOH	5	54
5	TEA-AcOH	10	56
6	TEA	10	45
7	TBA-OAc	2.5	34
8	Ac_2O	10	83
9	Ac_2O	5	80

[a]Calibrated yields determined by gas chromatography using dodecane (10 mol %) as an internal standard.

Table 2. Anhydride Screen for the Enamine Formation[a]



entry	anhydride	yield (%)[a]
1	none	<10
2	acetic	53
3	isobutyric	37
4	trimethylacetic	17
5	benzoic	57
6	succinic	58
7	phthalic	64
8	trifluoroacetic	59

[a]Calibrated yields determined by GC analysis using dodecane (10 mol %) as an internal standard.

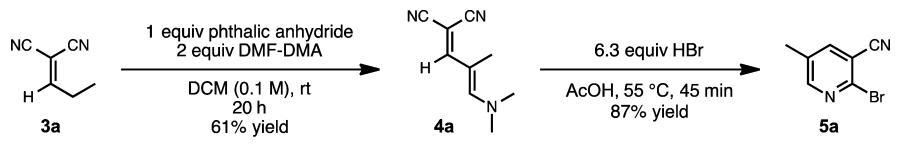
demonstrating the impact that the counterion plays. When anion exchange occurs between DMF-DMA and TEA-AcOH or TBA-OAc, triethylamine or methoxide is produced, respectively. The base formation can negatively effect the reaction for two reasons: (1) the formation of base during the exchange increases the rate of dimer formation because this process is base catalyzed or (2) if the anion exchange is reversible, the presence of acid or base negatively effects the equilibrium so less of the iminium acetate salt (**C**, Scheme 3) is produced. Acetic anhydride is unique because the only base present after the anion exchange is the acetate, the critical component of the reaction. While the data are consistent with our mechanistic model, we recognize that this study is merely the beginning. One test of a good model is whether or not the model provides new insight. As we demonstrate below, our improved understanding of the system has enabled us to increase the yields associated with aldehyde substrates by leveraging our new mechanistic model.

As we demonstrated in our initial communication, the use of aldehyde-based alkylidene malononitriles as substrates yielded the desired enamines but with lower yields compared to ketone-based alkylidenes.[6a] In our mechanistic study described above, we demonstrated that the sources of the acetate anion were important, and we speculated that changing the acetate ion source might improve the yield when aldehyde-based substrates were used in the enamine synthesis. To test this hypothesis, anhydrides with varying steric and electronic factors were tested with propylidenemalononitrile **3a** (Table 2). When compared to acetic anhydride (Table 2, entry 2), bulkier anhydrides (entries 3 and 4) provided progressively lower yields as the bulk of the anhydride increased. Modest yield increases began to emerge when benzoic and succinic anhydrides (entry 5 and 6) were used. Phthalic anhydride (entry 7) demonstrated a further increase in yield to 64%, and no further improvement was seen with trifluoroacetic anhydride (59%, entry 8). Based on the observed trends, the electronics of the carboxylate play a role in the outcome of the reaction. While the increase in yield appears modest, we observed an improvement in the scale-up and purification of the reaction. When phthalic anhydride is used as an additive to synthesize 2-bromo-5-methylnicotinonitrile (**5a**) from **3a**, the overall yield of these two steps is 53% (Scheme 4). This is an improvement over using acetic anhydride, which provided an overall yield of 36% for **5a**.[6a]

Increasing the Scope of Push–Pull Enamine Synthesis. *Incorporation of Silicon.* In addition to understanding the role of acetic anhydride, we also wanted to expand the scope of the method to prepare enamines. Examples of enamines (such those in Scheme 5) bearing heteroatoms (N or O) at the R^1 position are known[11] and are produced via (1) reaction of malononitrile with a trialkylorthoacetate or (2) dimethyl acetate dimethylacetal (DMA-DMA) to generate the alkoxy-substituted[12] or dialkylamine-substituted ylidenemalononitriles,[11c,13] respectively. These heteroatom-substituted enamines are entry points to heterocyclic scaffolds such as azafluorenones[12e] and polysubstituted pyridines[12c] and to bioactive molecules such as gimeracil.[12b]

We hypothesized that R^1 could also be silicon and that our general approach leading to enamines might enable incorporation of a C–Si bond. Enamines where R^1 is an alkylsilyl substituent could yield pyridines featuring C–Si bonds (vide infra) in the 4-position. We tested our hypothesis using three ylidenemalononitrile derived from acylsilanes of varying substitution with respect to the silicon functionality as well as the R^2 position (Table 3). Commercially available acetyltrimethylsilane was converted to the corresponding silylalkylidene malononitrile via a Knoevenagel condensation according to previously reported procedure (entry 1).[14] The acylsilane **6b** was synthesized via a previously reported dithiane route using hydrocinnamaldehyde,[15] whereas acylsilane **6c** was obtained

Scheme 4. Synthesis of 2-Bromo-5-methylnicotinotrile via Acyclic Enamine Derived from Propionaldehyde[a]



[a]Yields reported are of isolated product.

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Scheme 5. Formation of Granik-Type Enamines (R^1 = OMe) and Mittelbach-Type Enamines (R^1 = NMe_2)

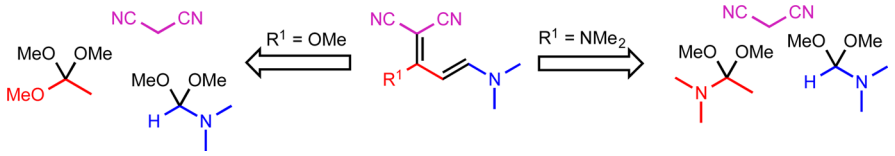
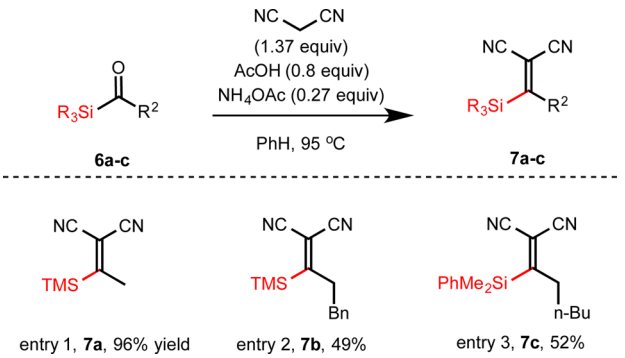
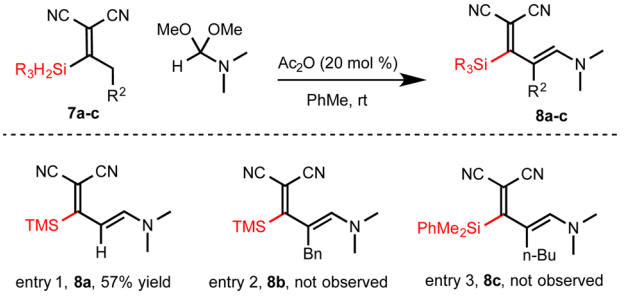


Table 3. Synthesis of Silylalkylidene Malononitriles



from its corresponding morpholine amide precursor, via the method developed by Scheidt.[16] The Knoevenagel condensation products **7b** and **7c** were obtained without much difficulty (entry 2 and 3). Data shown in Table 4 indicate that the

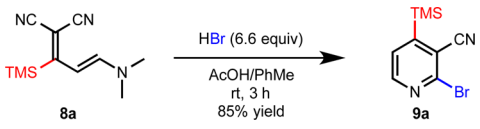
Table 4. Formation of Silicon-Substituted Enamines



incorporation of a C−Si substituent into the enamine backbone using our DMF-DMA and acetic anhydride method is possible, but only when the R^2 substituent is small.

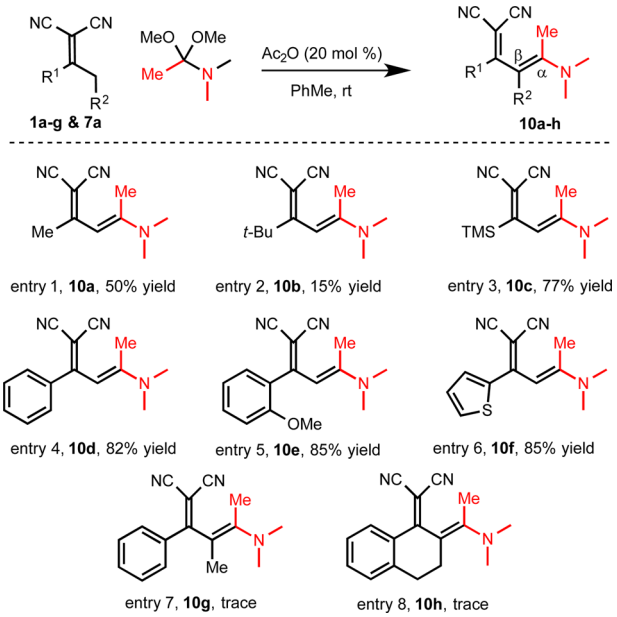
Next, we wanted to demonstrate whether simple silyl-functionalized enamines such as **8a** could be viable substrates for the Pinner cyclization. The cyclization was carried out at room temperature with TMS-substituted enamine **8a** using an HBr (33 wt % in acetic acid). While we postulated that the strongly acidic conditions necessary for the cyclization might cleave the C−Si bond, product **9a** was isolated in 85% yield (Scheme 6). No cleavage of the C−Si bond was observed by crude ^{1}H NMR, further demonstrating that these push−pull enamines featuring a silyl group support formation of 4-silyl-substituted pyridines.

Scheme 6. Formation of 2-Bromo-4-trimethylsilyl Nicotinonitrile from Enamine 8a



Use of DMA-DMA. The enamine formation followed by Pinner cyclization is unique in enabling access to 4-substituted and 4,5-disubstituted-2-halonicotinonitriles. However, the scope might offer the potential to increase substitution to include the 6-position. Functionalizing this position would require amide acetals other than DMF-DMA. While more elaborate amide acetals are known,[17] we found limited evidence of their application to form enamines of the class shown in Table 5. We tested our hypothesis by reacting *N,N*-

Table 5. Substrate Scope for α-Methyl-Substituted Enamines



dimethylacetamide-dimethyl acetal (DMA-DMA) with various ylidenemalononitriles (Table 5). The reaction between the alkylidenemalononitrile **1a** with DMA-DMA furnished the desired enamine in 50% yield (entry 1). We determined that the outcome of the reaction of ylidenemalononitriles (**1**) and DMA-DMA was dependent on the size of the R^2 substituent. As the R^2 substituent size increases, the yield of the enamine decreases (entries 2, 7, and 8). Aryl- and heteroaryl-derived ylidenemalononitriles afforded the expected enamines **10d−f** with yields in the 82−85% range (entries 4−6). In addition, the TMS-derived ylidenemalononitrile **7a** could be used to give a high yield of the corresponding product **10c** (entry 3) further illustrating the use of the silyl-substituted enamines.

Cyclization of Substituted Enamines Yielding 6-Substituted Nicotinonitriles. As we previously demonstrated, these push−pull enamines cyclize to form nicotinonitriles under Pinner conditions.[6] We expected that enamines with greater substitution would also cyclize to yield nicotinonitriles. We tested this premise by treating a range of enamines containing methyl groups in the α-position (Table 6). As is evident from the uniformly strong yields, methyl substitution at the α-position does not impede the cyclization. This method is a

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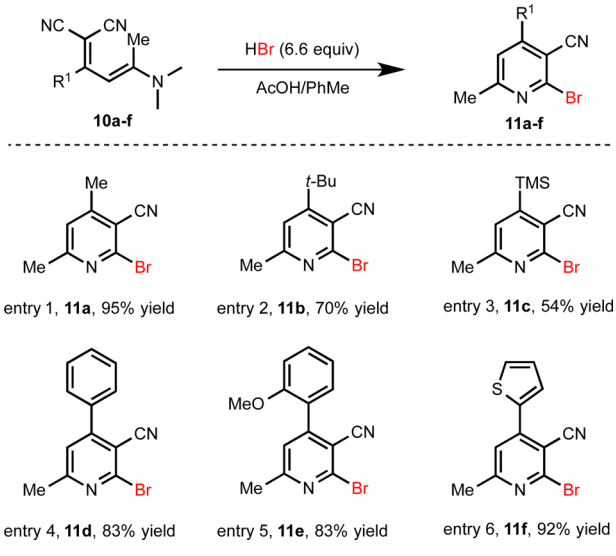
Table 6. Synthesis of 2-Bromonicotinonitriles from Various Alkylidene Malononitriles

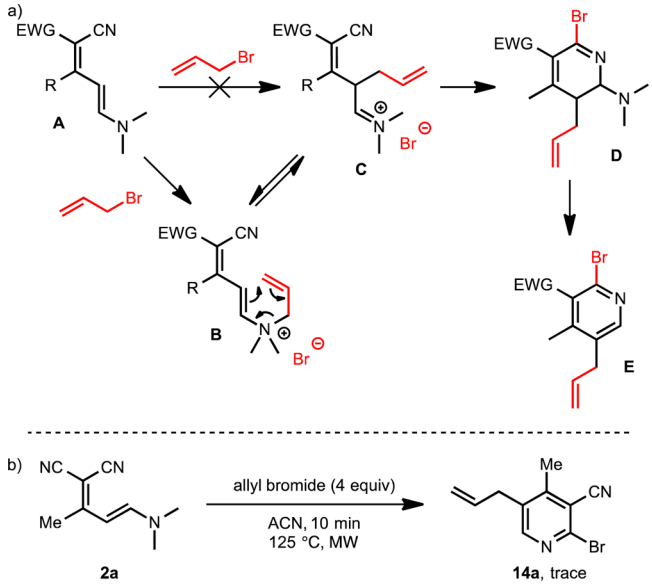


convenient strategy to install a wide variety of groups in the 4- and 6-positions of nicotinonitriles including a *t*-butyl **11b** (entry 2), trimethylsilane **11c** (entry 3), and various aromatic and heteroaromatic substrates **11d**, **11e** and **11f** (entries 4–6).

Reactivity of Push–Pull Enamines Toward Electrophiles and Nucleophiles. *Cyclization with Organohalides.* Until now, cyclizations between ylidenemalononitrile enamines and electrophiles only include Pinner cyclizations with hydrogen halides to afford polysubstituted nicotinonitriles. While a notional Pinner cyclization mechanism is suggested,[1a,3c] few mechanistic studies provide evidence to support these widely presented arrow-pushing mechanisms. Our hypothesis of the mechanism illustrated in Scheme 7 (eq 1) involves the addition of a proton at the enamine *β*-carbon. To test this, the cyclization of enamine **12** was performed with DCl in AcOD (Scheme 7, eq 2). The cyclization resulted in a high ratio of the deuterium-labeled product at 5-position of the corresponding nicotinonitrile (**13a** and **13b**) supporting our proposed mechanism. This enamine protonation model suggests that enamine alkylation, silylation, or electrophilic halogenation should also promote the reaction.

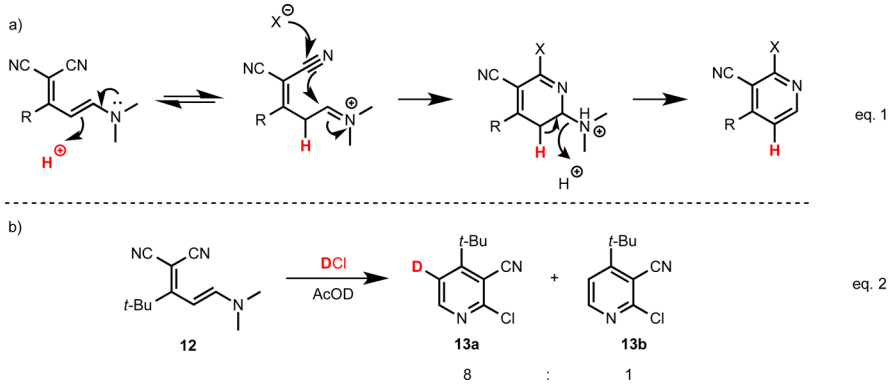
With evidence of electrophilic addition at the *β*-carbon, enamine **2a** was subjected to a variety of electrophiles: bromine, acetyl chloride and bromide, and trimethylsilyl chloride, bromide, and iodide. Despite many changes in the reaction conditions, no evidence for the cyclization event was observed. Instead, the silylation of the nitrogen, a Pinner cyclization with HCl/HBr impurities, or no reaction was the observed outcome. We then speculated that use of allyl bromide might enable cyclization via an alternative mechanism whereby N-alkylation is followed by a [3,3]-sigmatropic shift (aza-Claisen) (Scheme 8a).[18] Although attempts using conventional heating failed,

Scheme 8. (a) Hypothesized Mechanism to Produce 5-Allyl Substituted Pyridines from Allyl Bromide via N-Alkylation Followed by an aza-Claisen Rearrangement and (b) Cyclization with Ylidenemalononitrile Enamine with Allyl Bromide



reactions performed under microwave irradiation provided promising results. Microwave-based heating at 125 °C for 10 min in acetonitrile enabled the conversion of **2a** to product (**14a**, Scheme 8b). While the NMR data provided evidence of the predicted cyclization, only trace quantities were isolated. Longer reaction times only led to product decomposition. The low reactivity of the enamine is most likely due to the low nucleophilicity of the nitrogen. By replacing the malononitrile fragment for the less electron-withdrawing cyanoacetate group, we hypothesized the enamine would be more nucleophilic and the product stability would increase. Enamine substrates **15a–d**

Scheme 7. (a) Proposed Mechanism for Pinner Cyclization and (b) Deuterium Incorporation Studies



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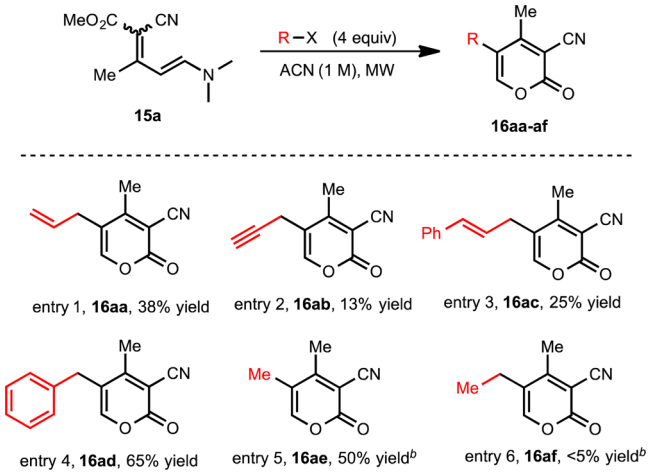
were synthesized using our previously developed procedure for malononitrile substrates. The formation of the enamines with the ethylcyanoacetate moiety was lower yielding than with the malononitrile fragment potentially due to the slower rates of reaction between DMF-DMA and the ylidenecyanoacetates compared to ylidenemalononitriles.

When **15a** was treated with allyl bromide at 125 °C for 6 h (Table 7, entry 1), the starting material was consumed, and less

Table 7. Cyclization of 15a with Various Organohalides To Produce α-Pyrones[a]



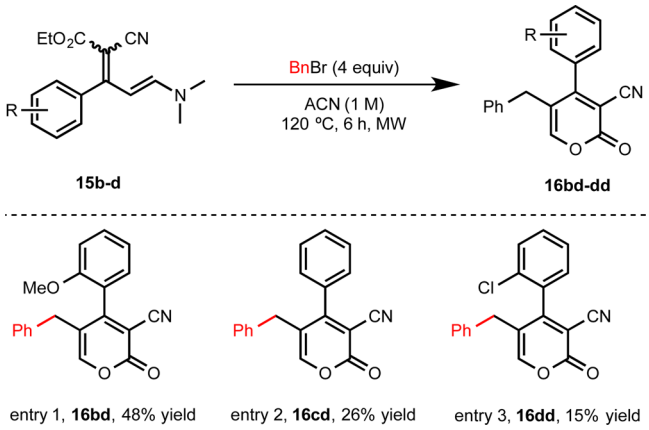
[a]Isolated yields. [b]Reaction concentration at 2.5 M.

byproduct formation was observed by ^{1}H NMR spectroscopy compared to the reaction shown in Scheme 8b. Interestingly, the product was not the expected pyridine. In contrast to the Pinner cyclization affording the 2-halonicotinoate,[2a] the cyclization of **15a** with allyl bromide gave exclusively 5-allyl-3-cyano-4-methyl-α-pyrone (**16aa**) due to the involvement of the ester in the cyclization. Despite less byproduct formation, the cyclization with allyl bromide to the corresponding α-pyrone (**16aa**) yield was low at 38% (Table 7, entry 1).[19] Baldwin et al. described the cyclization of **15a** under Pinner conditions and observed a fair yield (58%) of the desired 2-halonicotinoates from the ylidenecyanoacetate.[2a] The fair yield was originally assumed to be due the low yielding enamine formation with DMF-DMA. However, the results described here suggest that pyrone formation may have been a competing factor.

This unexpected result led us to investigate other organohalides (Table 7). The performance with propargyl bromide (entry 2) and cinnamyl bromide (entry 3) resulted in significantly slower reaction rates that contributed to lower yields of the desired product. Benzyl bromide was shown to produce **16ad** with the highest yield at 65% (entry 4) under much milder conditions (80 °C) than allyl bromide. Also, while methyl iodide was efficient in producing **16ae** at 50% yield (entry 5), ethyl iodide was much less reactive providing only a small amount of the desired product (entry 6). Further optimization of the reaction and purification conditions could result in significant yield improvements in the future for this novel approach to α-pyrones.

Other enamines derived from acetophenones were cyclized with benzyl bromide to determine how well the reaction tolerates varying electronics of the enamine backbone (Table 8). The reaction rates for all three substrates were much slower,

Table 8. Cyclization of Acetophenone-Derived Enamines (15b−d) to 16bd−dd with Benzyl Bromide[a]



[a]Isolated yields.

so an increase in temperature from 80 °C (Table 7, entry 4) to 120 °C was required. While the cyclization tolerated electron-rich substrates well (Table 8, entry 1), producing the highest yield at 48%, electron-poor substrates (entry 3) showed sluggish rates and poor yields. The effects in yield are likely due to the change in the nucleophilicity of the enamine.

The participation of benzyl bromide and methyl iodide in the cyclization to α-pyrones suggests that C-alkylation occurs which is opposite of what is proposed in Scheme 8a. Alkyl halides are known to undergo N-alkylation with aldehyde-derived enamines leading us to speculate both N- and C-alkylations were reversible at high temperatures.[20] We tested the validity of this hypothesis by performing the cyclization of **15a** with MeI-d_3 (Scheme 9a). The product ratio between labeled (**16ag**) and nonlabeled (**16ae**) 3-cyano-4,5-dimethyl-2-pyrone was 6:1 (Scheme 9a). The small percentage of nonlabeled α-pyrone present suggests N-alkylation is occurring and is reversible by a von Braun-like dealkylation leading to the scrambling of the methyl groups. Upon C-alkylation, the cyclization occurs followed by an irreversible nucleophilic dealkylation to drive the reaction forward. Dimethylamine then eliminates to afford the desired α-pyrone (Scheme 9b).

Reactivity toward Nucleophiles. The chemistry of these push−pull enamines toward nucleophiles has been explored, albeit rarely. Hiroshi and Ege[3a,2b] demonstrated that these types of enamines can react with a variety of amine-based nucleophiles such as ammonia,[3a,21a,11c,21b−d,3c] primary amines,[22,3g] hydrazine,[3e] diazonium salts,[23] and hydroxylamine.[24] The addition of carbon-based nucleophiles to these types of enamines has not been described in the literature prompting us to ascertain whether the chemoselectivity of the addition would be similar to that observed with the amine-based nucleophiles. We carried out a reactivity screen across a series of experiments using enaminomalononitrile **2a** and various organometallic nucleophiles. The reaction of this enamine with allylzinc bromide at room temperature for 16 h furnished the 2-allyl-substituted nicotinonitrile **17a** in 70% yield (Table 9, entry 1). The reaction between phenyl-substituted enaminomalononitrile and allylzinc bromide (entry 2) yielded the desired 1,3-substituted nicotinonitrile **17b** in 47% yield. The addition of allylzinc bromide to other enaminomalononitriles furnished the desired 2-allyl-substituted pyridine: a thiophene derivative (entry 3) is very well tolerated, however, the introduction of substitution at the β-position on the enamine led to decreased

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Scheme 9. (a) Deterium-Labeling Studies with MeI-d_3 and (b) Proposed Mechanism of α-Pyrone Formation

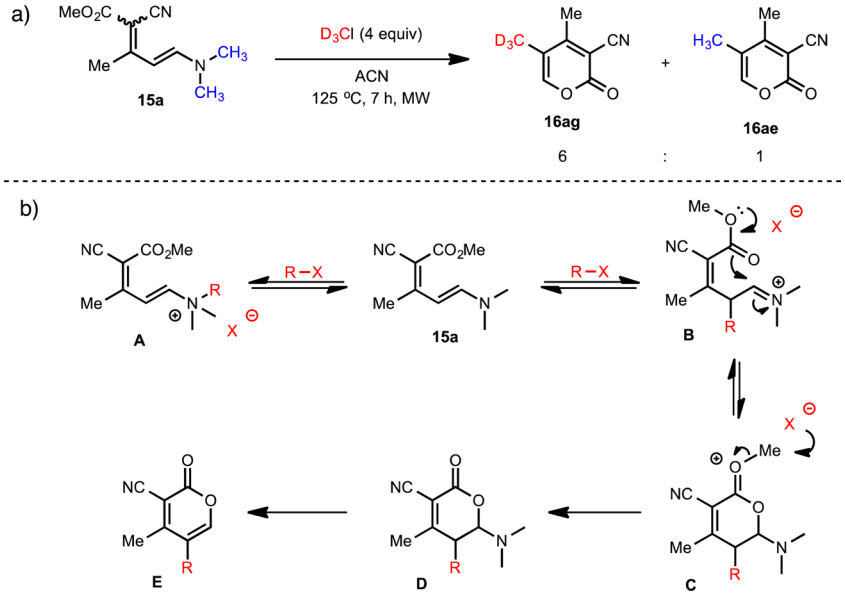
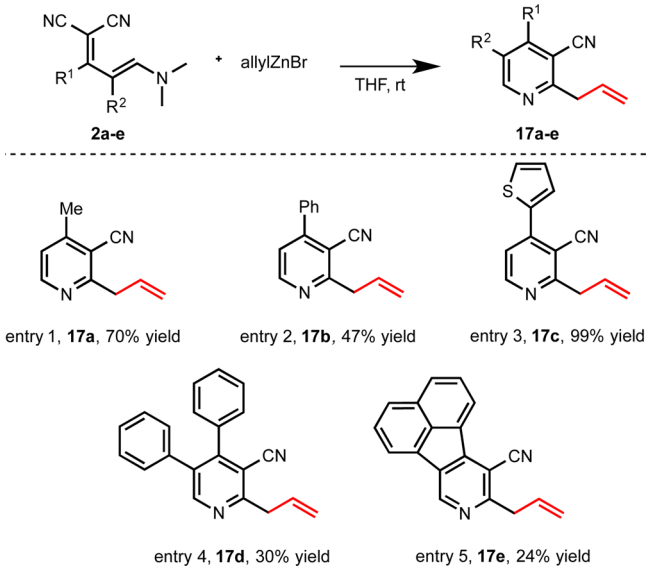


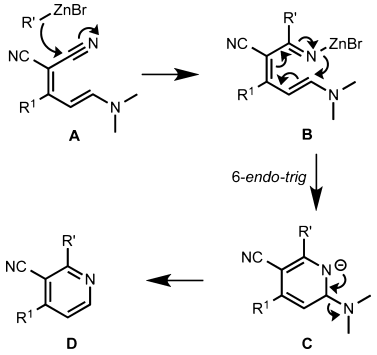
Table 9. Substrate Scope for Allylation of Enamines



yields for the formation of the diphenyl- (entry 4) and acenaphthenyl-derived (entry 5) nicotinonitriles **17d** and **17e**, respectively. Interestingly, the more reactive zinc species such as diethylzinc and benzyl zinc chloride did not participate in the reaction, conversely the Grignard reagents led to the formation of an intractable mixture of products. Other alkyl zinc reagents such as ethyl zinc iodide did not react, suggesting that the electronic properties of the nucleophile play a greater role than steric factors. We also suggest that aggregation and clustering effects may preclude certain organozinc halides from being viable nucleophiles toward enaminomalononitriles.[25]

On the basis of the above results and previous reports,[22b] a possible mechanism is proposed and shown in Scheme 10. First, the nucleophilic attack of the organozinc halide at the nitrile of **A** generates intermediate **B**. Subsequently, a Baldwin-favored 6-*endo-trig* cyclization furnishes cyclized intermediate **C**. The elimination of the dimethylamine then generates the desired nicotinonitrile **D**.

Scheme 10. Proposed Mechanism Cyclization with Organozinc Halides



In conclusion, we have extended the methodology to produce a class of push−pull enamines to better suit aldehyde-derived ylidenemalononitriles, include silyl group functionalities, and extend the sites for substitution by utilizing the *N*,*N*-dimethylacetamide acetal. Based on the existing mechanistic data, we propose that acetic anhydride provides acetate anions without introducing other base species that might catalyze the alkylidene dimerization. We have also demonstrated how cyanoacetate-derived enamine species can be used as an intermediate to α-pyrones, which differs from original pathways involving transition-metal catalysis or a series of condensation reactions. Lastly, we show the cyclization to nicotinonitriles can also be performed under basic conditions using certain organozinc compounds.

EXPERIMENTAL SECTION

General Information. Deuterated solvents were used as received, with the exception of deuterated chloroform which was stored over activated 4 Å molecular sieves. Alkyl halides were passed through basic alumina prior to use. Tetrahydrofuran, dichloromethane, acetonitrile, toluene, and benzene were obtained from a solvent system passing HPLC or reagent grade solvents through activated alumina or activated 5 Å molecular sieves. All other reagents were commercially available and used without further purification unless otherwise noted. All nonaqueous reactions were carried out in flame- or oven-dried

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(120 °C) glassware fitted with rubber septa under a positive pressure of argon with magnetic stirring, unless otherwise noted. Analytical thin layer chromatography (TLC) was performed using glass-backed silica gel $60F_{254}$ (250 μm thickness). Flash column chromatography was carried out using 60 Å Silica Gel (230−400 mesh). Microwave reactions were performed using a Biotage Initiator instrument. ^{1}H and ^{13}C were obtained on 400 or 600 MHz spectrometers. NMR chemical shifts are reported as δ values in ppm relative to TMS in $CDCl_3$ for all ^{1}H spectra and relative to $CDCl_3$ for all ^{13}C spectra. Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintuplet, sext = sextet, m = multiplet), coupling constants in Hertz (Hz), integration. The mass analyzer type TOF was used for HRMS measurements.

*Isopropylidenemalononitrile (**1a**).* Prepared according to the previously reported procedure.[1] ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.32 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 178.8, 111.8, 86.1, 24.5. Spectra were in accordance with those described in the literature.[1]

*(E)-2-(4-(Dimethylamino)but-3-en-2-ylidene)malononitrile (**2a**).* Prepared according to the previously reported procedure.[1] Yellow solid, mp 150−152 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, J = 12.7 Hz, 1H), 5.63 (d, J = 12.6 Hz, 1H), 3.23 (s, 3H), 2.99 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.3, 152.4, 116.9, 116.1, 97.2, 65.8, 45.9, 37.6, 17.3. Spectra were in accordance with those described in the literature.[1]

*Propylidenemalononitrile (**3a**).* Prepared according to the previously reported procedure.[6a] To a stirring solution of malononitrile (11.45 g, 173 mmol, 1 equiv) and propionaldehyde (12.5 mL, 173 mmol, 1 equiv) in $CHCl_3$ (100 mL) was added aluminum oxide (Brockmann I, activated basic) (24.6 g, 241 mmol, 1.4 equiv) slowly (reaction is very exothermic). After the addition of aluminum oxide was complete, the reaction stirred for 1 h at room temperature. The aluminum oxide was then filtered off by vacuum filtration using CH_2Cl_2 to rinse. The filtrate was concentrated *in vacuo* to yield a yellow oil. The oil was purified by short path distillation (70 °C, 1000 mTorr) to yield **3a** (12.65 g, 69% yield) as a clear, colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (t, J = 7.9 Hz, 1H), 2.62 (m, J = 7.6 Hz, 2H), 1.21 (t, J = 7.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 112.2, 110.5, 89.6, 26.4, 12.0. Spectra in accordance with those described in the literature.[6a]

*(E)-2-(3-(Dimethylamino)-2-methylallylidene)malononitrile (**4a**).* Prepared according to the previously reported procedure with some modifications.[6a] To a stirring solution of **3a** (1.06 g, 10 mmol, 1 equiv) and phthalic anhydride (1.48 g, 10 mmol, 1 equiv) in anhydrous CH_2Cl_2 (100 mL) was added DMF-DMA (2.7 mL, 20 mmol, 2 equiv). The reaction stirred for 20.5 h at room temperature. As the reaction proceeded, some product precipitated out. The reaction was concentrate *in vacuo*, and the resulting orange solid was recrystallized in CH_2Cl_2/hexanes to yield **4a** (0.99 g, 61%) as an orange solid, mp 185−190 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.86 (s, 1H), 6.75 (s, 1H), 3.23 (s, 6H), 2.25 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.9, 159.1, 119.0, 117.1, 106.7, 60.6, 44.2, 13.0; HRMS (ESI+) m/z: $[M + Na]^+$ calcd for $C_9H_{11}N_3Na$, 184.08507; found, 184.08647.

*2-Bromo-5-methylnicotinonitrile (**5a**).* To a stirring slurry of **4a** (0.806 g, 5 mmol, 1 equiv) in AcOH (3 mL) was added an HBr in AcOH (33 wt %) solution (5.5 mL, 31.4 mmol, 6.3 equiv). The reaction was stirred at 55 °C for 45 min. Once complete, the reaction was poured over a mixture of ice and Na_2CO_3 (20 g). Once the ice melted, the product was extracted using 3 × 50 mL CH_2Cl_2. The organic layers were combined, dried with $MgSO_4$, and then concentrated under vacuum to yield **5a** (0.85 g, 87%) as a tan solid, mp 110−113 °C; no additional purification was needed. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.40 (d, J = 1.7 Hz, 1H), 7.78 (d, J = 2.1 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.6, 142.7, 140.6, 133.1, 115.9, 113.7, 17.7. Spectra in accordance with those described in the literature.[6a]

*2-(1-(Trimethylsilyl)ethylidene)malononitrile (**7a**).* Prepared according to the previously reported procedure.[14] Acetyltrimethylsilane (2.00 g, 17.20 mmol), malononitrile (1.56 g, 23.57 mmol, 1.37 equiv), and ammonium acetate (358.0 mg, 4.644 mmol) were dissolved in acetic acid (0.83 mL, 13.76 mmol) and benzene (40 mL) in a 100 mL round-bottom flask attached to a Dean−Stark trap filled with benzene and 4 Å molecular sieves. The reaction mixture was stirred and heated to 95 °C for 36 h. The resulting orange solution was cooled and diluted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, water, brine, and dried over $MgSO_4$. The product was purified by column chromatography (ethyl acetate/hexanes) to give **7a** (2.712 g, 96% yield) as a pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.33 (s, 3H), 0.35 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 188.1, 113.4, 111.4, 94.6, 24.0, −2.1. Spectra in accordance with those described in the literature.[14]

*2-(3-Phenyl-1-(trimethylsilyl)propylidene)malononitrile (**7b**).* 3-phenyl-1-(trimethylsilyl)propan-1-one (590 mg, 2.84 mmol), malononitrile (260 mg, 3.90 mmol, 1.37 equiv), and ammonium acetate (60 mg, 0.770 mmol) were dissolved in acetic acid (0.14 mL, 2.280 mmol) and benzene (8 mL) in a 25 mL round-bottom flask attached to a Dean−Stark trap filled with benzene and 4 Å molecular sieves. The reaction mixture was stirred and heated to 95 °C for 36 h. The resulting orange solution was cooled and diluted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, water, brine, and dried over $MgSO_4$. The product was purified by column chromatography (ethyl acetate/hexanes) to give **7b** (354 mg, 49% yield) as a pale yellow solid, mp 58−61 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (t, J = 7.5 Hz, 2H), 7.26 (t, J = 7.5 Hz, 1H), 7.21−7.19 (m, 2H), 2.94−2.91 (m, 2H), 2.74−2.71 (m, 2H), 0.40 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.4, 140.7, 130.6, 130.2, 128.7, 114.9, 113.1, 97.4, 41.7, 36.8, 0.0. HRMS (ESI+) m/z: $[M + Na]^+$ calcd for $C_{15}H_{18}N_2SiNa$, 277.11369; found, 277.11368.

*2-(1-(Dimethyl(phenyl)silyl)hexylidene)malononitrile (**7c**).* 1-(dimethyl(phenyl)silyl)hexan-1-one (0.83 g, 3.54 mmol), malononitrile (0.32 g, 4.85 mmol, 1.37 equiv), and ammonium acetate (74 mg, 0.956 mmol, 0.27 equiv) were dissolved in acetic acid (0.16 mL, 2.83 mmol) and benzene (9 mL) in a 50 mL round-bottom flask attached to a Dean−Stark trap filled with benzene and 4 Å molecular sieves. The reaction mixture was stirred and heated to 95 °C for 36 h. The resulting orange solution was cooled and diluted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, water, brine, and dried over $MgSO_4$. The product was purified by column chromatography (ethyl acetate/hexanes) to give **7c** (524 mg, 52% yield) as a pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51−7.33 (m, 5H), 2.55 (t, J = 7.9 Hz, 2H), 1.31−1.28 (m, 2H), 1.21−1.18 (m, 4H), 0.82−0.81 (m, 3H), 0.66 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 190.5, 134.2, 133.2, 130.6, 128.4, 113.3, 111.6, 95.3, 38.2, 31.7, 28.5, 22.1, 13.8, −3.2; HRMS (ESI+) m/z: $[M + Na]^+$ calcd for $C_{17}H_{22}N_2SiNa$, 305.14499; found, 305.14486.

*(E)-2-(3-(Dimethylamino)-1-(trimethylsilyl)allylidene)-malononitrile (**8a**).* Prepared according to the previously reported procedure.[6a] To a stirring solution of **7a** (500 mg, 3.04 mmol, 1 equiv) and acetic anhydride (58 μL, 0.609 mmol, 0.2 equiv) in toluene (8 mL) was added DMF-DMA (485 μL, 3.65 mmol, 1.2 equiv). The reaction stirred at overnight at room temperature. As the reaction proceeded, some product precipitated out. The reaction was concentrate *in vacuo*, and the product was purified by column chromatography (ethyl acetate/hexanes) to give **8a** (380 mg, 57% yield) as a yellow solid, mp 139−143 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, J = 12.7 Hz, 1H), 5.66 (d, J = 12.7 Hz, 1H), 3.19 (s, 3H), 2.98 (s, 3H), 0.42 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.2, 152.3, 117.6, 116.5, 101.5, 69.1, 45.2, 36.2, 0.0; HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{11}H_{18}N_3Si$, 220.12520; found, 220.12574.

*2-bromo-4-(trimethylsilyl)nicotinonitrile (**9a**).* Prepared according to the previously reported procedure with some modifications.[6a] To a stirred slurry of **8a** (80 mg, 0.365 mmol, 1.0 equiv) in toluene (1.0 mL) was added a 33 wt % solution of HBr in AcOH (370 μL, 2.298 mmol, 6.3 equiv) dropwise, and the reaction was allowed to stir at room temperature for 3 h. The reaction mixture was poured into a solution of sodium hydroxide (1 M) and extracted with ethyl acetate. The layers were separated, the aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (ethyl acetate/hexanes) to yield

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the **9a** (79 mg, 85%) as a white solid, mp 120−124 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (d, J = 4.7 Hz, 1H), 7.45 (d, J = 4.7 Hz, 1H), 0.47 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.3, 153.3, 147.4, 129.2, 120.2, 119.0, 0.00. Anal. calcd for $C_9H_{11}BrN_2Si$: C: 42.46; H: 4.34; Br: 31.31; N: 10.98; Si: 11.01. Found: C: 42.21; H: 4.28; Br: 31.05; N: 10.86.

*(E)-2-(4-(Dimethylamino)pent-3-en-2-ylidene)malononitrile (**10a**).* To a stirring solution of the alkylidene malononitrile **1a** (1.00 g, 9.42 mmol, 1.0 equiv) in toluene (19 mL) was added acetic anhydride (180 μL, 1.89 mmol, 0.2 equiv) followed by *N*,*N*-dimethylacetamide dimethylacetal (1.65 mL, 11.31 mmol, 1.2 equiv) dropwise. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure, and the crude material was purified by flash column chromatography on silica gel (ethyl acetate/hexanes as eluent) to yield the enamine **10a** (820 mg, 50%) as a greenish-yellow solid, mp 154−158 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.61 (s, 1H), 3.16 (s, 6H), 2.35 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.3, 161.8, 117.5, 117.1, 99.7, 41.5, 22.0, 19.1. HRMS (ESI+) m/z: $[M + Na]^+$ calcd for $C_{10}H_{13}N_3Na$, 198.10072; found, 198.10126.

*(E)-2-(5-(Dimethylamino)-2,2-dimethylhex-4-en-3-ylidene)-malononitrile (**10b**).* To a stirring solution of 2-(3,3-dimethylbutan-2-ylidene)malononitrile (505 mg, 3.41 mmol, 1.0 equiv) in toluene (13 mL) was added acetic anhydride (65 μL, 0.681 mmol, 0.2 equiv) followed by *N*,*N*-dimethylacetamide dimethylacetal (600 μL, 4.09 mmol, 1.2 equiv) dropwise. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure, and the crude material was purified by flash column chromatography on silica gel (ethyl acetate/hexanes as eluent) to yield the enamine **10b** (111 mg, 15%) as a yellow solid, mp 74−78 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.95 (s, 1H), 3.13 (s, 6H), 2.23 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 182.4, 163.6, 119.8, 118.3, 97.7, 63.8, 60.4, 41.2, 38.4, 29.4, 19.9. HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{13}H_{20}N_3$, 218.16572; found, 218.16588.

*(E)-2-(3-(Dimethylamino)-1-(trimethylsilyl)but-2-en-1-ylidene)-malononitrile (**10c**).* To a stirring solution of the alkylidene malononitrile **7a** (200 mg, 1.217 mmol, 1.0 equiv) in toluene (5 mL) was added acetic anhydride (23 μL, 0.243 mmol, 0.2 equiv) followed by *N*,*N*-dimethylacetamide dimethylacetal (195 mg, 1.461 mmol, 1.2 equiv) dropwise. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure, and the crude material was purified by flash column chromatography on silica gel (ethyl acetate/hexanes as eluent) to yield the enamine **10c** (219 mg, 77%) as a yellow solid, mp 109−112 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.06 (s, 1H), 3.13 (s, 6H), 2.18 (s, 1H), 0.32 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.4, 163.9, 120.0, 119.9, 104.3, 70.1, 42.6, 21.8, 0.0. HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{12}H_{20}N_3Si$, 234.14265; found, 234.14330.

*(E)-2-(3-(Dimethylamino)-1-phenylbut-2-en-1-ylidene)malono-nitrile (**10d**).* To a stirring solution of 2-(1-phenylethylidene)-malononitrile (960 mg, 5.70 mmol, 1.0 equiv) in toluene (11.4 mL) was added acetic anhydride (109 μL, 1.14 mmol, 0.2 equiv) followed by *N*,*N*-dimethylacetamide dimethylacetal (1.00 mL, 6.84 mmol, 1.2 equiv) dropwise. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure, and the crude material was purified by flash column chromatography on silica gel (ethyl acetate/hexanes as eluent) to yield the enamine **10d** (1.11 g, 82%) as a dark yellow solid, mp 171−174 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42−7.46 (m, 3H), 7.31−7.33 (m, 2H), 5.78 (s, 1H), 3.15 (s, 6H), 1.50 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ170.8, 163.6, 137.6, 130.3, 128.9, 128.7, 117.4, 117.3, 99.2, 64.8, 41.4, 18.9; HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{15}H_{16}N_3$, 238.13442; found, 238.13579.

*(E)-2-(3-(Dimethylamino)-1-(2-methoxyphenyl)but-2-en-1-ylidene)malononitrile (**10e**).* To a stirring solution of 2-(1-(2-methoxyphenyl)ethylidene)malononitrile (200 mg, 1.009 mmol, 1.0 equiv) in toluene (4 mL) was added acetic anhydride (19 μL, 0.202 mmol, 0.2 equiv) followed by *N*,*N*-dimethylacetamide dimethylacetal (161 mg, 1.211 mmol, 1.2 equiv) dropwise. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure, and the crude material was purified by flash column chromatography on silica gel (ethyl acetate/hexanes as eluent) to yield the enamine **10e** (229 mg, 85%) as a dark orange solid, mp 130−134 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (m, 1H), 7.04−6.97 (m, 3H), 5.89 (s, 1H), 3.86 (s, 3H), 3.14 (s, 6H), 1.55 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.7, 162.9, 156.0, 131.3, 129.5, 121, 2, 117.5, 117.2, 111.8, 99.0, 65.5, 55.9, 41.4, 17.3; HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{16}H_{18}N_3O$, 268.14499; found, 268.14579.

*(E)-2-(3-(Dimethylamino)-1-(thiophen-2-yl)but-2-en-1-ylidene)-malononitrile (**10f**).* To a stirring solution of 2-(1-(thiophen-2-yl)ethylidene)malononitrile (204 mg, 1.171 mmol, 1.0 equiv) in toluene (5 mL) was added acetic anhydride (22 μL, 0.234 mmol, 0.2 equiv) followed by *N*,*N*-dimethylacetamide dimethylacetal (206 μL, 1.405 mmol, 1.2 equiv) dropwise. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure, and the crude material was purified by flash column chromatography on silica gel (ethyl acetate/hexanes as eluent) to yield the enamine **10f** (242 mg, 85%) as a dark yellow solid, mp 146−148 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (m, 1H), 7.47 (m, 1H), 7.13 (m, 1H), 5.58 (s, 1H), 3.17 (s, 6H), 1.82 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.1, 161.3, 139. 2, 130.8, 130.7, 128.3, 117.8, 117.7, 99.4, 62.9, 41.4, 19.4. HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{13}H_{14}N_3S$, 244.09084; found, 244.09039.

*2-Bromo-4,6-dimethylnicotinonitrile (**11a**).* Prepared according to the previously reported procedure with some modifications.[6a] To a stirred slurry of the enamine **10a** (117 mg, 0.668 mmol, 1.0 equiv) in toluene (700 μL) was added a 33 wt % solution of HBr in AcOH (740 μL, 4.21 mmol, 6.3 equiv) dropwise, and the reaction was allowed to stir at room temperature for 3 h. The reaction mixture was poured into a solution of sodium hydroxide (1 M) and extracted with ethyl acetate. The layers were separated, the aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (ethyl acetate/hexanes) to yield pyridine **11a** (133 mg, 94%) as a white solid, mp 106−109 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.10 (s, 1H), 2.56 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.9, 154.1, 143.4, 123.5, 115.4, 111.7, 24.5, 20.7. HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_8H_8BrN_2$, 210.98709; found, 210.98707. Spectra in accordance with those described in the literature.[26]

*2-Bromo-4-(tert-butyl)-6-methylnicotinonitrile (**11b**).* Prepared according to the previously reported procedure with some modifications.[6a] To a stirred slurry of the enamine **10b** (66 mg, 0.304 mmol, 1.0 equiv) in toluene (700 μL) was added a 33 wt % solution of HBr in AcOH (740 μL, 4.21 mmol, 6.3 equiv) dropwise, and the reaction was allowed to stir at room temperature for 3 h. The reaction mixture was poured into a solution of sodium hydroxide (1 M) and extracted with ethyl acetate. The layers were separated, the aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (ethyl acetate/hexanes) to yield pyridine **11b** (133 mg, 94%) as a white solid, mp 137−140 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 (s, 1H), 2.60 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.0, 163.2, 146.5, 119.7, 117.5, 109.3, 36.2, 29.2, 24.9. HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{11}H_{14}BrN_2$, 253.03404; found, 253.03427.

*2-Bromo-6-methyl-4-(trimethylsilyl)nicotinonitrile (**11c**).* Prepared according to the previously reported procedure with some modifications.[6a] To a stirred slurry of the enamine **10c** (219 mg, 0.938 mmol, 1.0 equiv) in toluene (3.7 mL) was added a 33 wt % solution of HBr in AcOH (973 μL, 5.91 mmol, 6.3 equiv) dropwise, and the reaction was allowed to stir at room temperature for 3 h. The reaction mixture was poured into a solution of sodium hydroxide (1 M) and extracted with ethyl acetate. The layers were separated, the aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (ethyl acetate/hexanes) to yield pyridine

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11c (135 mg, 54%) as a white solid, mp 130−133 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (s, 1H), 2.60 (s, 3H), 0.45 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.1, 160.7, 146.6, 129.0, 119.4, 116.9, 26.4, 0.00. Anal. calcd for $C_{10}H_{13}BrN_2Si$: C: 44.61; H: 4.87; Br: 29.68; N: 10.41; Si: 10.43. Found: C: 44.49; H: 4.73; Br: 29.52; N: 10.34.

*2-Bromo-6-methyl-4-phenylnicotinonitrile (**11d**).* Prepared according to the previously reported procedure with some modifications.[6a] To a stirred slurry of the enamine **10d** (174 mg, 0.733 mmol, 1.0 equiv) in toluene (3.0 mL) was added a 33 wt % solution of HBr in AcOH (760 μL, 4.62 mmol, 6.3 equiv) dropwise, and the reaction was allowed to stir at room temperature for 3 h. The reaction mixture was poured into a solution of sodium hydroxide (1 M) and extracted with ethyl acetate. The layers were separated, the aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (ethyl acetate/hexanes) to yield pyridine **11d** (167 mg, 83%) as a white solid, mp 152−155 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45−7.48 (m, 1H), 7.21−7.23 (m, 1H), 7.03−7.08 (m, 2H), 3.86 (s, 3H), 2.64 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.1, 155.6, 144.8, 135.3, 130.5, 129.1, 128.4, 122.7, 116.1, 109.6, 24.7. HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{13}H_{10}BrN_2$, 273.00274; found, 273.00257.

*2-Bromo-4-(2-methoxyphenyl)-6-methylnicotinonitrile (**11e**).* Prepared according to the previously reported procedure with some modifications.[6a] To a stirred slurry of the enamine **10e** (222 mg, 0.830 mmol, 1.0 equiv) in toluene (3.3 mL) was added a 33 wt % solution of HBr in AcOH (861 μL, 5.23 mmol, 6.3 equiv) dropwise, and the reaction was allowed to stir at room temperature for 3 h. The reaction mixture was poured into a solution of sodium hydroxide (1 M) and extracted with ethyl acetate. The layers were separated, the aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (ethyl acetate/hexanes) to yield pyridine **11e** (212 mg, 83%) as a white solid, mp 138−140 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 (s, 1H), 2.60 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.8, 156.2, 153.6, 143.6, 131.8, 130.2, 124.5, 123.8, 121.0, 116.1, 111.7, 111.6, 55.5, 24.7. HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{14}H_{12}BrN_2O$, 303.01330; found, 303.01196.

*2-Bromo-6-methyl-4-(thiophen-2-yl)nicotinonitrile (**11f**).* Prepared according to the previously reported procedure with some modifications.[6a] To a stirred slurry of the enamine **10f** (127 mg, 0.522 mmol, 1.0 equiv) in toluene (3.7 mL) was added a 33 wt % solution of HBr in AcOH (580 μL, 3.29 mmol, 6.3 equiv) dropwise, and the reaction was allowed to stir at room temperature for 3 h. The reaction mixture was poured into a solution of sodium hydroxide (1 M) and extracted with ethyl acetate. The layers were separated, the aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (ethyl acetate/hexanes) to yield pyridine **11f** (134 mg, 92%) as a white solid, mp 105−108 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ7.92 (m, 1H), 7.58 (m, 1H), 7.35 (s, 1H), 7.21 (m, 1H), 2.63 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.1, 147.2, 145.6, 136.2, 130.2, 130.1, 129.0, 121.2, 116.7, 106.9, 24.7. Anal. calcd for $C_{11}H_7BrN_2S$: C: 47.33; H: 2.53; Br: 28.62; N: 10.04; S: 11.48. Found: C: 47.51; H: 2.47; Br: 28.68; N: 10.02; S: 11.46.

*(E)-2-(1-(Dimethylamino)-4,4-dimethylpent-1-en-3-ylidene)-malononitrile (**12**).* Prepared according to the general procedure with some modifications.[6a] A round-bottom flask containing 3,3-dimethylbutan-2-one (4.81 g, 48 mmol, 1 equiv), malononitrile (3.17 g, 48 mmol, 1 equiv), acetic acid (2.2 mL, 38 mmol, 0.8 equiv), ammonium acetate (0.74 g, 9.6 mmol, 0.2 equiv), and toluene (10 mL) was equipped with a Dean−Stark apparatus and heated to reflux. After refluxing for 6 h, the reaction was removed from heat and cooled to room temperature. The reaction was washed with saturated $NaHCO_3$ (2 × 50 mL) followed by water (50 mL). The organic layer was dried with $MgSO_4$ and then concentrated *in vacuo* to yield an orange oil. The oil was purified by column chromatography (silica gel, 1:9 EtOAc/hexanes, R_f = 0.27) and dried under high vacuum to yield 3,3-dimethylbutan-2-ylidenemalononitrile (3.25 g, 46%) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.33 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 189.4, 113.4, 113.0, 39.4, 28.8, 22.6. Prepared according to the general procedure with some modifications.[6a] To a stirring solution of 3,3-dimethylbutan-2-ylidenemalononitrile (0.74 g, 5 mmol, 1 equiv) and acetic anhydride (0.095 mL, 1 mmol, 0.2 equiv) in anhydrous toluene (5 mL) was added DMF-DMA (0.8 mL, 6 mmol, 1.2 equiv). The reaction stirred at room temperature for 22 h. Upon completion, solvent was removed under vacuum until crystals began to form, and the flask was set in the freezer. Once cool, the crystals were collected by vacuum filtration using cold toluene to rinse and dried under high vacuum to yield **12** (0.69 g, 68%) as a yellow solid, mp 118−123 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, J = 12.1 Hz, 1H), 4.94 (d, J = 12.1 Hz, 1H), 3.23 (bs, 3H), 2.99 (bs, 3H), 1.35 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.3, 153.8, 120.7, 118.5, 93.5, 60.4, 45.9 (br), 38.6, 37.4 (br), 29.6; HRMS (ESI+) m/z: $[M + Na]^+$ calcd for $C_{12}H_{17}N_3Na$, 226.13202; found, 226.13261.

*4-(tert-Butyl)-2-chloronicotinonitrile (**13b**).* Prepared according to the general procedure with some modifications.[6a] To a stirring solution of 3,3-dimethylbutan-2-ylidenemalononitrile (0.74 g, 5 mmol, 1 equiv) and acetic anhydride (0.095 mL, 1 mmol, 0.2 equiv) in anhydrous toluene (5 mL) was added DMF-DMA (0.8 mL, 6 mmol, 1.2 equiv). The reaction stirred at room temperature for 24 h, then the solvent was removed *in vacuo*. To the crude mixture was added acetyl chloride (2.2 mL, 31.4 mmol, 6.3 equiv). The mixture was cooled in an ice bath, and water (0.57 mL, 31.4 mmol, 6.3 equiv) was added dropwise. After the addition of water was complete, the reaction was heated to 55 °C and stirred for 45 min. Water (50 mL) was added dropwise while the reaction stirred vigorously to cause a solid to precipitate out. The solid was collected by vacuum filtration using water to rinse and dried under high vacuum over P_2O_5 to yield **13b** (0.70 g, 72%) as a tan solid, mp 95−98 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 (d, J = 5.4 Hz, 1H), 7.37 (d, J = 5.4 Hz, 1H), 1.54 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.7, 155.5, 152.2, 119.9, 115.9, 109.3, 36.5, 29.3; Anal. Calcd for $C_{10}H_{11}ClN_2$: C: 61.70; H: 5.70; N: 14.39. found: C: 61.91; H: 5.92; N: 14.28.

Deuterium Incorporation Experiment with DCl. To a 7 mL vial containing acetyl chloride (1.1 mL, 15.5 mmol, 6.3 equiv) at 0 °C was added D_2O (0.28 mL, 15.5 mmol, 6.3 equiv) dropwise. The solution was warmed up slowly to room temperature and transferred to a separate 7 mL vial containing **12** (0.5 g, 2.5 mmol, 1 equiv). The reaction was heated to 55 °C and stirred for 45 min. Water (5 mL) was added dropwise while the reaction stirred causing a solid to precipitate out. The solid was collected by vacuum filtration using water to rinse and dried under high vacuum over P_2O_5. The ratio of deuterated (**13a**) to nondeuterated product (**13b**) was determined by ^{1}H NMR. The reaction was performed in triplicate to obtain an average ratio of 8:1 of **13a** to **13b**. See ^{1}H NMR spectrum in Supporting Information.

*Methyl (4E)-2-cyano-5-(dimethylamino)-3-methylpenta-2,4-dienoate (**15a**).* Prepared according to the general procedure with some modifications.[27] To a 20 mL microwave vial was added LiBr (2.61 g, 30 mmol, 3 equiv), acetone (15 mL, 204 mmol, 20.4 equiv), methyl cyanoacetate (0.9 mL, 10 mmol, 1 equiv), and powdered 5 Å molecular sieves (1.5 g) with a stir bar. The reaction was irradiated in the microwave at 120 °C for 4 h. The reaction was then filtered by vacuum filtration using DCM to rinse. The filtrate was concentrated *in vacuo* and then redissolved in water. The product was extracted from the mixture using DCM (3 × 20 mL). The organic layers were combined, dried with $MgSO_4$, and concentrated *in vacuo*. The resulting oil was purified by automated flash chromatography (silica gel, 1:9 EtOAc/hexanes, R_f = 0.32) to yield methyl 2-cyano-3-methylbut-2-enoate (0.58 g, 42%) as a clear, colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.78 (d, J = 4.1 Hz, 3H), 2.38 (d, J = 3.9 Hz, 3H), 2.28 (d, J = 3.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.2, 162.2, 162.2, 115.6, 104.5, 52.4, 27.3, 22.8. Spectra in accordance with those described in the literature.[28] To a stirring solution of methyl 2-cyano-

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3-methylbut-2-enoate (1.36 g, 9.7 mmol, 1 equiv) and acetic anhydride (0.18 mL, 1.9 mmol, 0.2 equiv) in anhydrous toluene (10 mL) was added DMF-DMA (1.6 mL, 11.7 mmol, 1.2 equiv). The reaction was heated to 45 °C and stirred for 16 h. The solvent was removed *in vacuo*, and the brown yellow solid was recrystallized in EtOAc/hexanes to yield **15a** (1.29 g, 68%, mixture of 2*E* and 2*Z* isomers) as a yellow solid, mp 86−88 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 and 7.34 (d, 1H), 7.10 and 5.73 (d, J = 13 Hz, 1H), 3.74 and 3.73 (s, 3H), 3.22 and 3.22 (s, 3H), 3.00 and 2.97 (s, 3H), 2.47 and 2.30 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.1, 165.9, 165.5, 165.4, 153.1, 152.3, 120.6, 119.7, 99.4, 98.5, 86.6, 85.6, 60.3, 55.7, 51.2, 45.5, 37.4, 18.9, 15.3, 14.1; HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{10}H_{15}N_2O_2$, 195.11335; found, 195.11450.

*5-Allyl-3-cyano-4-methyl-2-pyrone (**16aa**).* Allyl bromide (0.35 mL, 4 mmol, 4 equiv), **15a** (0.194 g, 1 mmol, 1 equiv), and anhydrous acetonitrile (1 mL) were placed in a 2 mL microwave vial equipped with a stir bar. The vial was irradiated for 6 h at 125 °C. Upon completion, the reaction was concentrated *in vacuo*, and the product was purified by automated flash chromatography (silica gel, 3:7 EtOAc/hexanes, R_f = 0.28) to yield **16aa** (67 mg, 38%) as a dark semisolid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (s, 1H), 5.85 (m, 1H), 5.24 (d, J = 10.2 Hz, 1H), 5.12 (d, J = 17.2 Hz, 1 H), 3.15 (d, J = 5.6 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.1, 158.0, 151.3, 133.2, 118.7, 118.2, 113.4, 101.8, 19.2; HRMS (ESI+) m/z: $[M + Na]^+$ calcd for $C_{10}H_9NO_2Na$, 198.05310; found, 198.05459.

*3-Cyano-4-methyl-5-propargyl-2-pyrone (**16ab**).* Propargyl bromide (80 wt % in toluene) (0.45 mL, 4 mmol, 4 equiv), **15a** (0.194 g, 1 mmol, 1 equiv), and anhydrous acetonitrile (0.4 mL) were placed in a 2 mL microwave vial equipped with a stir bar. The vial was irradiated for 7 h at 125 °C. Upon completion, the reaction was concentrated *in vacuo*, and the product was purified by automated flash chromatography (silica gel, 3:7 EtOAc/hexanes, R_f = 0.21) to yield **16ab** (25 mg, 15%) as a tan solid, mp 90−93 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (s, 1H), 3.30 (q, J = 1.3, 2H), 2.52 (s, 3H), 2.30 (t, J = 2.6, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.8, 157.7, 151.7, 115.5, 113.2, 102.0, 77.6, 73.4, 19.1, 18.1; HRMS (ESI+) m/z: $[M + Na]^+$ calcd for $C_{10}H_7NO_2Na$, 196.03745; found, 196.03873.

*5-Cinnamyl-3-cyano-4-methyl-2-pyrone (**16ac**).* Cinnamyl bromide (0.3 mL, 2 mmol, 4 equiv), **15a** (0.097 g, 0.5 mmol, 1 equiv), and anhydrous acetonitrile (0.5 mL) were placed in a 2 mL microwave vial equipped with a stir bar. The vial was irradiated for 6 h at 80 °C. Upon completion, the reaction was concentrated *in vacuo*, and the product was purified by automated flash chromatography (silica gel, 3:7 EtOAc/hexanes, R_f = 0.21) to yield **16ac** (32 mg, 25%) as an orange solid, mp 92−95 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.35−7.26 (m, 5H), 6.44 (d, J = 15.9 Hz, 1H), 6.16 (m, 1H), 3.29 (d, J = 6.3 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.9, 158.0, 151.4, 136.2, 133.8, 128.9, 128.2, 126.4, 124.3, 118.5, 113.4, 102.1, 30.9, 19.4; HRMS (ESI+) m/z: $[M + Na]^+$ calcd for $C_{16}H_{13}NO_2Na$, 274.08440; found, 274.08627.

*5-Benzyl-3-cyano-4-methyl-2-pyrone (**16ad**).* Benzyl bromide (0.24 mL, 2 mmol, 4 equiv), **15a** (0.097 g, 0.5 mmol, 1 equiv), and anhydrous acetonitrile (0.5 mL) were placed in a 2 mL microwave vial equipped with a stir bar. The vial was irradiated for 6 h at 80 °C. Upon completion, the reaction was concentrated *in vacuo*, and the product was purified by automated flash chromatography (silica gel, 3:7 EtOAc/hexanes, R_f = 0.21) to yield **16ad** (73 mg, 65%) as an orange-brown solid, mp 118−122 °C;. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (m, 3H), 7.28 (m, 1H), 7.15 (d, J = 7.4 Hz, 2H), 3.73 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.1, 158.0, 151.7, 136.2, 129.2, 128.4, 127.5, 119.2, 113.4, 102.1, 33.8, 19.6; HRMS (ESI+) m/z: $[M + Na]^+$ calcd for $C_{14}H_{11}NO_2Na$, 248.06875; found, 248.06904.

*3-Cyano-4,5-dimethyl-2-pyrone (**16ae**).* MeI (0.25 mL, 4 mmol, 4 equiv), **15a** (0.194 g, 1 mmol, 1 equiv), and anhydrous acetonitrile (0.4 mL) were placed in a 2 mL microwave vial equipped with a stir bar. The vial was irradiated for 7 h at 125 °C. Upon completion, the reaction was concentrated *in vacuo*, and the product was purified by automated flash chromatography (silica gel, 2:3 EtOAc/hexanes, R_f = 0.20) to yield **16ae** (76 mg, 51%) as a yellow solid, mp 65−67 °C;. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (s, 1H), 2.45 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.4, 158.3, 150.3, 116.2, 113.5, 101.4, 19.7, 13.3; HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_8H_8NO_2$, 150.05550; found, 150.05572.

*3-Cyano-5-ethyl-4-methyl-2-pyrone (**16af**).* Ethyl iodide (0.32 mL, 4 mmol, 4 equiv), **15a** (0.194 g, 1 mmol, 1 equiv), and anhydrous acetonitrile (0.4 mL) were placed in a 2 mL microwave vial equipped with a stir bar. The vial was irradiated for 7 h at 125 °C. Upon completion, the reaction was concentrated *in vacuo*, and the product was purified by automated flash chromatography (silica gel, 3:7 EtOAc/hexanes, R_f = 0.22) to yield **16af** (11 mg, 7%) as a tan solid. Product was not pure by NMR, so yield is assumed to be <5%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (s, 1H), 2.47 (s, 3H), 2.43 (m, 2H), 1.21 (t, J = 7.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.8, 158.2, 150.2, 121.5, 113.6, 101.9, 20.4, 19.0, 13.1; HRMS (ESI+) m/z: $[M + Na]^+$ calcd for $C_9H_9NO_2Na$, 186.05310; found, 186.05374.

Ethyl 2-Cyano-3-(2-methoxyphenyl)but-2-enoate. Prepared according to the general procedure with some modifications.[6a] A round-bottom flask containing 2′-methoxyacetophenone (6.6 mL, 48 mmol, 1 equiv), ethyl cyanoacetate (5.1 mL, 48 mmol, 1 equiv), acetic acid (3.0 mL, 53 mmol, 1.1 equiv), ammonium acetate (0.74 g, 9.6 mmol, 0.2 equiv), and toluene (30 mL) was equipped with a Dean−Stark apparatus and heated to reflux. After refluxing for 4 days, the reaction was removed from heat and cooled to room temperature. The reaction was washed with saturated $NaHCO_3$ (3 × 50 mL) followed by water (50 mL). The organic layer was dried with $MgSO_4$ and then concentrated *in vacuo* to yield a dark oil. The oil was purified by column chromatography (silica gel, 1:9 EtOAc/hexanes, R_f = 0.18) and dried under high vacuum to yield ethyl 2-cyano-3-(2-methoxyphenyl)but-2-enoate (6.71 g, 57%) as a yellow oil and a mixture of *E* and *Z* isomers. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36−6.90 (m, 4H), 4.33 and 4.08 (q, J = 7.1 Hz, 2H), 3.85 and 3.79 (s, 3H), 2.63 and 2.51 (s, 3H), 1.38 and 1.13 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.2, 168.1, 162.3, 161.3, 155.5, 154.9, 131.3, 130.5, 129.9, 128.4, 128.2, 127.1, 120.9, 120.6, 116.0, 115.8, 111.6, 111.0, 107.5, 106.9, 62.0, 61.7, 55.7, 55.6, 26.3, 23.2, 14.2, 13.9; HRMS (ESI+) m/z: $[M + Na]^+$ calcd for $C_{14}H_{15}NO_3Na$, 268.09496; found, 268.09435.

Ethyl 2-Cyano-3-phenylbut-2-enoate. Prepared according to the general procedure with some modifications.[6a] A round-bottom flask containing acetophenone (5.6 mL, 48 mmol, 1 equiv), ethyl cyanoacetate (5.1 mL, 48 mmol, 1 equiv), acetic acid (3.0 mL, 53 mmol, 1.1 equiv), ammonium acetate (0.74 g, 9.6 mmol, 0.2 equiv), and toluene (30 mL) was equipped with a Dean−Stark apparatus and heated to reflux. After refluxing for 4 days, the reaction was removed from heat and cooled to room temperature. The reaction was washed with saturated $NaHCO_3$ (3 × 50 mL) followed by water (50 mL). The organic layer was dried with $MgSO_4$ and then concentrated *in vacuo* to yield a dark oil. The oil was purified by column chromatography (silica gel, 1:9 EtOAc/hexanes, R_f = 0.26) and dried under high vacuum to yield ethyl 2-cyano-3-phenylbut-2-enoate (1.52 g, 15%) as a yellow oil and a mixture of *E* and *Z* isomers. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47−7.16 (m, 5H), 4.34 and 4.09 (q, J = 7.1 Hz, 2H), 2.70 and 2.55 (s, 3H), 1.38 and 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.5, 169.8, 162.5, 161.5, 140.4, 139.1, 130.5, 129.6, 128.8, 128.4, 127.2, 126.3, 116.3, 115.7, 106.3, 105.3, 62.2, 62.0, 27.0, 23.4, 14.2, 13.8; Anal. calcd for $C_{13}H_{13}NO_2$: C: 72.54; H: 6.09; N: 6.51. Found: C: 72.68; H: 6.10; N: 6.45.

Ethyl 2-Cyano-3-(2-chlorophenyl)but-2-enoate. Prepared according to the general procedure with some modifications.[6a] A round-bottom flask containing 2′-chloroacetophenone (6.2 mL, 48 mmol, 1 equiv), ethyl cyanoacetate (5.1 mL, 48 mmol, 1 equiv), acetic acid (3.0 mL, 53 mmol, 1.1 equiv), ammonium acetate (0.74 g, 9.6 mmol, 0.2 equiv), and toluene (30 mL) was equipped with a Dean−Stark apparatus and heated to reflux. After refluxing for 4 days, the reaction was removed from heat and cooled to room temperature. The reaction was washed with saturated $NaHCO_3$ (3 × 50 mL) followed by water (50 mL). The organic layer was dried with $MgSO_4$ and then concentrated *in vacuo* to yield a dark oil. The oil was purified by column chromatography (silica gel, 1:19 EtOAc/hexanes, R_f = 0.20) and dried under high vacuum to yield ethyl ethyl 2-cyano-3-(2-

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chlorophenyl)but-2-enoate (3.93 g, 33%) as a yellow oil and a mixture of *E* and *Z* isomers. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47−7.03 (m, 4H), 4.35 and 4.09 (q, J = 7 Hz, 2H), 2.65 and 2.52 (s, 3H), 1.38 and 1.12 (t, J = 7 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.0, 168.0, 161.6, 160.4, 139.6, 138.3, 130.7, 130.4, 130.3, 129.9, 129.8, 129.6, 127.4, 126.9, 126.7, 115.0, 114.9, 108.6, 108.3; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.51−7.31 (m, 4H), 4.31 and 3.99 (q, J = 7 Hz, 2H), 2.60 and 2.49 (s, 3H), 1.30 and 0.97 (t, J = 7 Hz, 3H). Spectra in accordance with those described in the literature.[29]

*Ethyl (4E)-2-Cyano-5-(dimethylamino)-3-(2-methoxyphenyl)-penta-2,4-dienoate (**15b**).* Prepared according to the general procedure with some modifications.[6a] To a stirring solution of ethyl 2-cyano-3-(2-methoxyphenyl)but-2-enoate (6.71 g, 27.4 mmol, 1 equiv) and acetic anhydride (0.5 mL, 5.5 mmol, 0.2 equiv) in anhydrous toluene (27 mL) was added DMF-DMA (4.4 mL, 32.8 mmol, 1.2 equiv). After stirring at room temperature for 24 h, the solvent was removed *in vacuo*. The resulting light brown solid was recrystallized in DCM/heptane to produce **15b** as a mixture of 2*E* and 2*Z* isomers (3.7 g, 45%) as yellow crystals, mp 118−120 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 and 7.05−6.90 (m, 4H), 7.24 and 6.50 (d, J = 12.7 and 12.4 Hz, 1H), 6.57 and 5.92 (d, J = 12.7 and 12.4 Hz, 1H), 4.24 and 3.98 (m and q, J = 7.0 Hz, 2H), 3.83 and 3.75 (s, 3H), 2.99−2.95 (s, 6H), 1.32 and 1.09 (t, J = 7.1 and 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.4, 165.9, 165.5, 163.7, 156.2, 156.1, 156.0, 154.7, 130.2, 129.9, 129.4, 128.9, 126.7, 125.8, 120.4, 120.1, 119.9, 119.5, 111.6, 110.8, 99.7, 99.2, 87.1, 86.3, 59.9, 59.7, 55.9, 55.7, 45.4, 37.5, 37.4, 14.4, 14.1; HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{17}H_{21}N_2O_3$, 301.15522; found, 301.15441.

*Ethyl (4E)-2-Cyano-5-(dimethylamino)-3-phenylpenta-2,4-dienoate (**15c**).* Prepared according to the general procedure with some modifications.[6a] To a stirring solution of ethyl 2-cyano-3-phenylbut-2-enoate (1.52 g, 7.1 mmol, 1 equiv) and acetic anhydride (0.13 mL, 1.4 mmol, 0.2 equiv) in anhydrous toluene (7 mL) was added DMF-DMA (1.1 mL, 8.5 mmol, 1.2 equiv). After stirring at room temperature for 24 h, the solvent was removed *in vacuo*. The resulting light brown solid was recrystallized in DCM/heptane to produce **15c** (1.27 g, 67%) as yellow crystals, mp 133−138 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36−7.02 (m, 5H), 7.15 and 6.38 (d, J = 12.7 and 12.4, 1H), 6.48 and 5.84 (d, J = 12.7 and 12.4, 1H), 4.19 and 3.90 (q, J = 7.1 Hz, 2H), 2.93−2.87 (s, 6H), 1.27 and 1.02 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.1, 169.1, 165.3, 163.7, 156.8, 155.8, 137.7, 136.8, 128.6, 128.5, 128.0, 127.8, 127.7, 127.5, 119.9, 119.3, 100.2, 99.5, 85.0, 59.8, 59.6, 45.4, 37.3, 37.2, 14.3, 13.9; HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{16}H_{19}N_2O_2$, 271.14465; found, 271.14456.

*Ethyl (4E)-2-Cyano-5-(dimethylamino)-3-(2-chlorophenyl)penta-2,4-dienoate (**15d**).* Prepared according to the general procedure with some modifications.[6a] To a stirring solution of ethyl 2-cyano-3-(2-chlorophenyl)but-2-enoate (3.93 g, 15.7 mmol, 1 equiv) and acetic anhydride (0.3 mL, 3.2 mmol, 0.2 equiv) in anhydrous toluene (16 mL) was added DMF-DMA (2.5 mL, 18.9 mmol, 1.2 equiv). After stirring at room temperature for 24 h, the solvent was removed *in vacuo*. The resulting light brown solid was recrystallized in DCM/toluene to produce **15d** (3.01 g, 63%) as yellow/green crystals, mp 179−183 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47−7.04 (m, 4H), 7.21 and 6.35 (d, J = 13 Hz, 1H), 6.42 and 5.91 (d, J = 13 Hz, 1H), 4.26 and 4.01 (m and q, J = 7.1 Hz, 2H), 3.02−2.98 (s, 6H), 1.34 and 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.9, 165.4, 165.4, 163.6, 155.9, 154.7, 136.8, 136.1, 132.3, 132.1, 130.3, 130.1, 130.0, 129.3, 127.0, 126.4, 119.3, 119.1, 99.3, 98.9, 87.6, 86.7, 60.4, 60.2, 45.8, 37.7, 37.6, 14.5, 14.2; HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{16}H_{18}ClN_2O_2$, 305.10568; found, 305.10747.

*5-Benzyl-3-cyano-4-(2-methoxyphenyl)-2-pyrone (**16bd**).* Benzyl bromide (0.24 mL, 2 mmol, 4 equiv), **15b** (0.15 g, 0.5 mmol, 1 equiv), and anhydrous acetonitrile (0.5 mL) were placed in a 2 mL microwave vial equipped with a stir bar. The vial was irradiated for 6 h at 120 °C. Upon completion, the reaction was concentrated *in vacuo*, and the product was purified by automated flash chromatography (silica gel, 3:7 EtOAc/hexanes, R_f = 0.29) to yield **16bd** (75 mg, 48%) as a yellow semisolid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (m, 1H), 7.38 (s, 1H), 7.16 (m, 3H), 6.99 (t, J = 7.4 Hz, 1H), 6.94 (m, 2H), 6.79 (m, 2H), 3.71 (s, 3H), 3.44 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.4, 158.4, 155.3, 151.8, 136.8, 132.2, 128.7, 128.6, 128.5, 126.9, 122.0, 121.1, 120.6, 113.4, 111.4, 103.3, 55.6, 34.0; HRMS (ESI+) m/z: $[M + Na]^+$ calcd for $C_{20}H_{15}NO_3Na$, 340.09496; found, 340.09571.

*5-Benzyl-3-cyano-4-phenyl-2-pyrone (**16cd**).* Benzyl bromide (0.24 mL, 2 mmol, 4 equiv), **15c** (0.135 g, 0.5 mmol, 1 equiv), and anhydrous acetonitrile (0.5 mL) were placed in a 2 mL microwave vial equipped with a stir bar. The vial was irradiated for 6 h at 120 °C. Upon completion, the reaction was concentrated *in vacuo*, and the product was purified by automated flash chromatography (silica gel, 3:7 EtOAc/hexanes, R_f = 0.31) to yield **16cd** (37 mg, 26%) as an orange semisolid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (m, 1H), 7.43 (m, 3H), 7.18 (m, 3H), 7.14 (d, J = 7.2 Hz, 2H), 6.80 (m, 2H), 3.52 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.0, 158.1, 152.6, 136.6, 132.9, 130.6, 129.1, 128.8, 128.6, 127.1, 119.5, 113.3, 102.3, 34.0; HRMS (ESI+) m/z: $[M + Na]^+$ calcd for $C_{19}H_{13}NO_2Na$, 310.08440; found, 310.08491.

*5-Benzyl-3-cyano-4-(2-chlorophenyl)-2-pyrone (**16dd**).* Benzyl bromide (0.24 mL, 2 mmol, 4 equiv), **15d** (0.152 g, 0.5 mmol, 1 equiv), and anhydrous acetonitrile (0.5 mL) were placed in a 2 mL microwave vial equipped with a stir bar. The vial was irradiated for 6 h at 120 °C. Upon completion, the reaction was concentrated *in vacuo*, and the product was purified by automated flash chromatography (silica gel, 3:7 EtOAc/hexanes, R_f = 0.33) to yield **16dd** (76 mg, 15%) as a yellow semisolid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 (d, J = 8.0 Hz, 1H), 7.43 (m, 2H), 7.28 (t, J = 8.0 Hz, 2H), 7.19 (m, 2H), 6.93 (m, 1H), 6.80 (m, 2H), 3.45 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.7, 157.8, 152.6, 136.2, 132.1, 131.8, 131.2, 130.3, 128.9, 128.8, 128.7, 127.6, 127.3, 119.9, 112.6, 103.5, 34.1; HRMS (ESI+) m/z: $[M + Na]^+$ calcd for $C_{19}H_{12}ClNO_2Na$, 344.04543; found, 344.04535.

Deuterium Incorporation Experiment with MeI-d_3. MeI-d_3 (0.12 mL, 2 mmol, 4 equiv), **15a** (0.0.97 g, 0.5 mmol, 1 equiv), and acetonitrile (0.5 mL) were placed in a 2 mL microwave vial equipped with a stir bar. The vial was irradiated for 7 h at 125 °C. Upon completion, the reaction was concentrated *in vacuo*, and the product was purified by automated flash chromatography (silica gel, 2:3 EtOAc/hexanes, R_f = 0.20). The resulting yellow solid was observed by ^{1}H NMR to determine the ratio between deuterated (**16ag**) and nondeuterated (**16ae**) product. See Supporting Information for ^{1}H NMR spectrum.

*Typical Procedure for the Preparation of Polysubstituted Nicotinonitriles **17a−e**.* Allylzinc bromide was prepared under an argon atmosphere by using a modified version of Knochel's procedure.[30] In a flame-dried round-bottom flask fitted with a magnetic stir bar and a dropping funnel was placed zinc powder (0.78g, 12 mmol, 1.2 equiv), and the flask was flushed with argon. The zinc was heated under vacuum at 70 °C for 1 h and then flushed again with argon. A solution of dibromoethane (0.1 mL, 1.2 mmol, 0.1 equiv) in THF (2 mL) was added at 70 °C, and the reaction mixture was allowed to stir for 10 min and then cooled to room temperature. A solution of chlorotrimethylsilane (0.1 mL, 0.8 mmol, 0.1 equiv) in THF (1 mL) was added. The reaction mixture was allowed to stir for 15 min after which a solution of allyl bromide (0.87 mL, 10 mmol, 1 equiv) in THF (5 mL) was added dropwise over 25 min. The reaction mixture was stirred for 30 min and used immediately.

*2-Allyl-4-methylnicotinonitrile (**17a**).* To a solution of the enamine **2a** (100 mg, 0.620 mmol, 1.0 equiv) in THF (3 mL) was added a freshly prepared and titrated 1.25 M solution of allylzincate (1.5 mL, 1.861 mmol, 3.0 equiv) in THF dropwise. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched with a saturated solution of ammonium chloride and diluted with ethyl acetate. The layers were separated, the aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (ethyl acetate in hexanes as eluent) to yield pyridine **17a** (69 mg, 70%) as a semisolid; IR (neat) ν = 2229, 1731, 1531, 1416, 1183, 1100, 913, 731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J = 5.1 Hz, 1H), 7.14 (d, J = 5.1 Hz, 1H), 6.02−6.07 (m, 1H), 5.18−5.25 (m, 2H), 3.81

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(d, J = 6.7 Hz, 2H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 151.8, 151.6, 133.5, 122.5, 117.9, 115.7, 109.9, 41.6, 20.5; HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{10}H_{11}N_2$, 159.09222; found, 159.09237.

*2-Allyl-4-phenylnicotinonitrile (**17b**).* To a solution of 2-(3-(dimethylamino)-1-phenylallylidene)malononitrile (92 mg, 0.412 mmol, 1.0 equiv) in THF (2 mL) was added a freshly prepared and titrated 1.25 M solution of allylzincate (1.0 mL, 1.236 mmol, 3.0 equiv) in THF dropwise. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched with a saturated solution of ammonium chloride and diluted with ethyl acetate. The layers were separated, the aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (ethyl acetate in hexanes as eluent) to yield pyridine **17b** (43 mg, 47%) as a white solid; mp 50−52 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (d, J = 5.2 Hz, 1H), 7.50−7.59 (m, 5H), 7.31 (d, J = 5.2 Hz, 1H), 6.08−6.16 (m, 1H), 5.22−5.30 (m, 2H), 3.91 (d, J = 6.8 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.1, 153.7, 151.9, 136.0, 133.5, 130.0, 129.0, 128.5, 121.7, 118.1, 116.4, 107.7, 41.8; HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{15}H_{13}N_2$, 221.10763; found, 221.10787.

*2-Allyl-4-(thiophen-2-yl)nicotinonitrile (**17c**).* To a solution of (*E*)-2-(3-(dimethylamino)-1-(thiophen-2-yl)allylidene)malononitrile (103 mg, 0.449 mmol, 1.0 equiv) in THF (3 mL) was added a freshly prepared and titrated 1.25 M solution of allylzincate (1.1 mL, 1.348 mmol, 3.0 equiv) in THF dropwise. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched with a saturated solution of ammonium chloride and diluted with ethyl acetate. The layers were separated, the aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (ethyl acetate in hexanes as eluent) to yield pyridine **17c** (102 mg, 99%) as a white solid; mp 61−63 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (d, J = 5.3 Hz, 1H), 7.90−7.91 (m, 1H), 7.56−7.57 (m, 1H), 7.40 (d, J = 5.3 Hz, 1H), 7.21−7.23 (m, 1H), 6.07−6.13 (m, 1H), 5.22−5.30 (m, 2H), 3.89 (d, J = 6.7 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.7, 152.0, 145.2, 137.3, 133.4, 129.6, 129.5, 128.8, 120.4, 118.1, 116.9, 105.2, 41.8; HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{13}H_{11}N_2S$, 227.06429; found, 227.06374.

*2-Allyl-4,5-diphenylnicotinonitrile (**17d**).* To a solution of 2-(3-(dimethylamino)-1,2-diphenylallylidene)malononitrile (93 mg, 0.310 mmol, 1.0 equiv) in THF (2 mL) was added a freshly prepared and titrated 1.25 M solution of allylzincate (0.75 mL, 0.929 mmol, 3.0 equiv) in THF dropwise. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched with a saturated solution of ammonium chloride and diluted with ethyl acetate. The layers were separated, the aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (ethyl acetate in hexanes as eluent) to yield pyridine **17d** (28 mg, 30%) as a white solid; mp 104−106 °C;^{1}H NMR (600 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.31−7.36 (m, 3H), 7.22−7.27 (m, 3H), 7.16−7.18 (m, 2H), 7.03−7.05 (m, 2H), 6.13−6.18 (m, 1H), 5.24−5.35 (m, 2H), 3.94 (d, J = 6.7 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.5, 152.9, 152.0, 135.8, 135.0, 134.6, 133.5, 129.6, 129.5, 129.1, 128.5, 128.4, 127.9, 118.2, 116.2, 109.5, 41.6; HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{21}H_{17}N_2$, 297.13878; found, 297.13917.

*9-Allylacenaphtho[1,2-c]pyridine-10-carbonitrile (**17e**).* To a solution of 2-(2-((dimethylamino)methylene)acenaphthylen-1(2*H*)-ylidene)malononitrile (97 mg, 0.358 mmol, 1.0 equiv) in THF (1.5 mL) was added a freshly prepared and titrated 1.25 M solution of allylzincate (0.87 mL, 1.08 mmol, 3.0 equiv) in THF dropwise. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched with a saturated solution of ammonium chloride and diluted with ethyl acetate. The layers were separated, the aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (ethyl acetate in hexanes as eluent) to yield pyridine **17e** (23 mg, 24%) as a white solid; mp 130−131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.64 (d, J = 7.1 Hz, 1H), 8.02−8.14 (m, 2H), 8.01 (d, J = 8.0 Hz, 1H), 7.82 (t, J = 7.2 Hz, 1H), 7.76 (d, J = 7.2 Hz, 1H), 6.14−6.19 (m, 1H), 5.24−5.33 (m, 2H), 3.97 (d, J = 6.7 Hz, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 148.5, 144.5, 133.9, 132.4, 132.4, 132.2, 132.0, 131.9, 130.9, 130.0, 128.6, 128.5, 128.3, 125.6, 122.2, 117.9, 116.2, 101.9, 41.4; HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{19}H_{13}N_2$, 269.10787; found, 269.10889.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01169.

^{1}H NMR spectra of deuterium incorporation experiments and ^{1}H and ^{13}C NMR spectra of products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*Email: mcquade@chem.fsu.edu.

Author Contributions

†These authors contributed equally.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Bryson, T. A.; Wisowaty, J. C.; Dunlap, R. B.; Fisher, R. R.; Ellis, P. D. *J. Org. Chem.* **1974**, *39*, 3436. (b) Bryson, T. A.; Donelson, D. M.; Dunlap, R. B.; Fisher, R. R.; Ellis, P. D. *J. Org. Chem.* **1976**, *41*, 2066.

(2) (a) Baldwin, J. J.; Raab, A. W.; Ponticello, G. S. *J. Org. Chem.* **1978**, *43*, 2529. (b) Ege, G.; Frey, H. O.; Schuck, E. *Synthesis* **1979**, *1979*, 376.

(3) (a) Kurihara, H.; Mishima, H. *J. Heterocycl. Chem.* **1977**, *14*, 1077. (b) Prager, R. H.; Tsopelas, C.; Heisler, T. *Aust. J. Chem.* **1991**, *44*, 277. (c) Church, R.; Trust, R.; Albright, J. D.; Powell, D. *J. Org. Chem.* **1995**, *60*, 3750. (d) Schönfeld, F.; Troschütz, R. *Heterocycles* **2001**, *55*, 1679. (e) Sayed, S. M.; Khalil, M. A.; Ahmed, M. A.; Raslan, M. A. *Synth. Commun.* **2002**, *32*, 481. (f) Skofic, P.; Dambrot, C.; Kozelj, M.; Golobic, A.; Barrio, J. R.; Petric, A. *Acta Chim. Slov.* **2005**, *52*, 391. (g) Longstreet, A. R.; Jo, M.; Chandler, R. R.; Hanson, K.; Zhan, N.; Hrudka, J. J.; Mattoussi, H.; Shatruk, M.; McQuade, D. T. *J. Am. Chem. Soc.* **2014**, *136*, 15493. (h) Petersen, I. N.; Kristensen, J. L. *Synthesis* **2014**, *46*, 1469.

(4) Prager, R. H.; Tsopelas, C. *Heterocycles* **1989**, *29*, 847.

(5) Petersen, I. N.; Crestey, F.; Kristensen, J. L. *Chem. Commun.* **2012**, *48*, 9092.

(6) (a) Longstreet, A. R.; Campbell, B. S.; Gupton, B. F.; McQuade, D. T. *Org. Lett.* **2013**, *15*, 5298. (b) Longstreet, A. R.; Opalka, S. M.; Campbell, B. S.; Gupton, B. F.; McQuade, D. T. *Beilstein J. Org. Chem.* **2013**, *9*, 2570.

DOI: 10.1021/acs.joc.5b01169
J. Org. Chem. 2015, 80, 8583−8596

(7) (a) Cope, A. C.; Hoyle, K. E. *J. Am. Chem. Soc.* **1941**, *63*, 733. (b) Williams, J. K. *J. Org. Chem.* **1963**, *28*, 1054. (c) Weir, M. R. S.; Hyne, J. B. *Can. J. Chem.* **1964**, *42*, 1440.
(8) Vorbrüggen, H. *Synlett* **2008**, *2008*, 1603.
(9) (a) von Schenering, H. G.; Schmidt, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 356. (b) Bredereck, H.; Simchen, G.; Rebsdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieshaber, P. *Chem. Ber.* **1968**, *101*, 41. (c) Csihony, S.; Beaudette, T. T.; Sentman, A. C.; Nyce, G. W.; Waymouth, R. M.; Hedrick, J. L. *Adv. Synth. Catal.* **2004**, *346*, 1081.
(10) (a) Wasserman, H. H.; Ives, J. L. *J. Org. Chem.* **1978**, *43*, 3238. (b) Wawer, I.; Osek, J. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1669.
(11) (a) Granik, V. G.; Grizik, S. I.; Soloveva, N. P.; Anisimova, O. S.; Sheinker, Y. N. *Zh. Org. Khim.* **1984**, *20*, 673. (b) Mittelbach, M.; Kastner, G.; Junek, H. *Arch. Pharm.* **1985**, *318*, 481. (c) Mittelbach, M. *Monatsh. Chem.* **1987**, *118*, 617.
(12) (a) Yano, S.; Ohno, T.; Ogawa, K. *Heterocycles* **1993**, *36*, 145. (b) Hao, L.-h.; Zhou, J.; Sun, Y.-l.; Wang, Y.-q.; Zeng, Z.-j. *J. Shenyang Pharm. Univ.* **2005**, *6*, 005. (c) Stocks, M. J.; Barber, S.; Ford, R.; Leroux, F.; St-Gallay, S.; Teague, S.; Xue, Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3459. (d) Ferlin, M. G.; Di Marco, V. B.; Dean, A. *Tetrahedron* **2006**, *62*, 6222. (e) Sasikumar, T. K.; Qiang, L.; Burnett, D. A.; Greenlee, W. J.; Li, C.; Heimark, L.; Pramanik, B.; Grilli, M.; Bertorelli, R.; Lozza, G.; Reggiani, A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3199. (f) Bogdanowicz, A.; Foks, H.; Gobis, K.; Kędzia, A.; Kwapisz, E.; Olczak, A.; Główka, M. L. *J. Heterocycl. Chem.* **2013**, *50*, 544. (g) Zhang, Z.; Liu, C.; Li, X.; Song, T.; Wu, Z.; Liang, X.; Zhao, Y.; Shen, X.; Chen, H. *Eur. J. Med. Chem.* **2013**, *60*, 410.
(13) Zheng, G. Z.; Bhatia, P.; Daanen, J.; Kolasa, T.; Patel, M.; Latshaw, S.; El Kouhen, O. F.; Chang, R.; Uchic, M. E.; Miller, L.; Nakane, M.; Lehto, S. G.; Honore, M. P.; Moreland, R. B.; Brioni, J. D.; Stewart, A. O. *J. Med. Chem.* **2005**, *48*, 7374.
(14) Leung, C. Y.; Langille, A. M.; Mancuso, J.; Tsantrizos, Y. S. *Bioorg. Med. Chem.* **2013**, *21*, 2229.
(15) (a) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553. (b) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem.* **2001**, *66*, 7527. (c) Rooke, D. A.; Ferreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 11926.
(16) (a) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527. (b) Clark, C. T.; Milgram, B. C.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 3977.
(17) (a) Yershov, L. V.; Granik, V. G. *Khim. Geterotsikl. Soedin.* **1985**, 646. (b) Shin, M. S.; Lee, S. J.; Chin, S. M.; Lee, S. H.; Pore, D. M.; Park, Y.; Lee, S. G.; Hwang, K. J. *Bull. Korean Chem. Soc.* **2011**, *32*, 3152.
(18) Brannock, K.; Burpitt, R. *J. Org. Chem.* **1961**, *26*, 3576.
(19) The product would degrade slowly at room temperature. Higher yields were also obtained when the product was isolated quickly upon reaction completion.
(20) (a) Hodgson, D. M.; Bray, C. D.; Kindon, N. D. *J. Am. Chem. Soc.* **2004**, *126*, 6870. (b) Hodgson, D. M.; Kaka, N. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 9958.
(21) (a) Degraw, J. I.; Tagawa, H.; Christie, P. H.; Lawson, J. A.; Brown, E. G.; Kisliuk, R. L.; Gaumont, Y. *J. Heterocycl. Chem.* **1986**, *23*, 1. (b) Su, T. L.; Watanabe, K. A. *J. Org. Chem.* **1989**, *54*, 220. (c) DeGraw, J. I.; Christie, P. H.; Kisliuk, R. L.; Gaumont, Y.; Sirotnak, F. M. *J. Med. Chem.* **1990**, *33*, 673. (d) Hagen, V.; Jänsch, H. J. *J. Prakt. Chem.* **1990**, *332*, 748.
(22) (a) Lacroix, A.; Fleury, J.-P. *Tetrahedron Lett.* **1978**, *19*, 3469. (b) Villemin, D.; Belhadj, Z.; Cheikh, N.; Choukchou-Braham, N.; Bar, N.; Lohier, J.-F. *Tetrahedron Lett.* **2013**, *54*, 1664.
(23) Al-Omran, F.; Khalik, M. M. A.; Abou-Elkhair, A.; Elnagdi, M. H. *Synthesis* **1997**, *1997*, 91.
(24) Degraw, J. I.; Tagawa, H. *J. Heterocycl. Chem.* **1982**, *19*, 1461.
(25) (a) Koszinowski, K.; Bohrer, P. *Organometallics* **2009**, *28*, 100. (b) Fleckenstein, J. E.; Koszinowski, K. *Organometallics* **2011**, *30*, 5018.
(26) Kumar, S.; Johansson, H.; Kanda, T.; Engman, L.; Muller, T.; Bergenudd, H.; Jonsson, M.; Pedulli, G. F.; Amorati, R.; Valgimigli, L. *J. Org. Chem.* **2010**, *75*, 716.
(27) Zhu, J.-L.; Huang, P.-W.; You, R.-Y.; Lee, F.-Y.; Tsao, S.-W.; Chen, I. C. *Synthesis* **2011**, *2011*, 715.
(28) Valla, A.; Andriamialisoa, Z.; Valla, B.; Labia, R.; Le Guillou, R.; Dufossé, L.; Cartier, D. *Eur. J. Org. Chem.* **2007**, *2007*, 711.
(29) Jimonet, P.; Ribeill, Y.; Bohme, G. A.; Boireau, A.; Chevé, M.; Damour, D.; Doble, A.; Genevois-Borella, A.; Herman, F.; Imperato, A.; Le Guern, S.; Manfré, F.; Pratt, J.; Randle, J. C. R.; Stutzmann, J.-M.; Mignani, S. *J. Med. Chem.* **2000**, *43*, 2371.
(30) (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390. (b) Zhang, Y.; Jia, X.; Wang, J.-X. *Eur. J. Org. Chem.* **2009**, *2009*, 2983.

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