JOC The Journal of Organic Chemistry
Cite This: J. Org. Chem. 2019, 84, 2178−2190
Article
pubs.acs.org/joc

Copper-Catalyzed Radical C−C Bond Cleavage and [4+1] Annulation Cascade of Cycloketone Oxime Esters with Enaminothiones

Yuan He,[†,‡] Jiang Lou,[†,‡] Kaikai Wu,[†] Hongmei Wang,[*,§] and Zhengkun Yu[*,†,⊥]

[†]Chinese Academy of Sciences, Dalian Institute of Chemical Physics, 457 Zhongshan Road, Dalian 116023, People's Republic of China

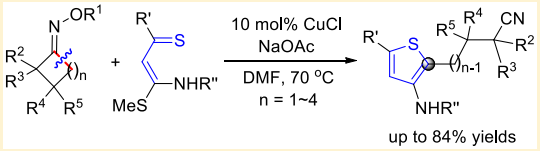
[‡]University of Chinese Academy of Sciences, Beijing 100049, People's Republic of China

[§]State Key Laboratory of NBC Protection for Civilian, Beijing 102205, People's Republic of China

[⊥]Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, State Key Laboratory of Organometallic Chemistry, 354 Fenglin Road, Shanghai 200032, People's Republic of China

Supporting Information

ABSTRACT: Carbon−carbon bond formation is among the most important reactions in organic synthesis. Reconstruction of a carbon−carbon bond through ring-opening C−C bond cleavage of a strained carbocycle usually occurs via a thermodynamically preferable pathway. However, carbon−carbon bond formation through thermodynamically less favorable C−C bond cleavage has seldom been documented. Herein, we disclose an unusual C−C bond cleavage of cycloketone oxime esters for [4+1] annulation. Under anaerobic copper(I) catalysis, cycloketone oxime esters underwent regioselective, thermodynamically less favorable radical C−C bond cleavage followed by annulation with enaminothiones; that is, α-thioxo ketene *N*,*S*-acetals efficiently affording 2-cyanoalkyl-aminothiophene derivatives. Cyclobutanone, -pentanone, -hexanone, and -heptanone oxime esters could act as the effective C1 building blocks in the annulation reaction. An iminyl radical mechanism is proposed for the rare C−C bond cleavage/[4+1] annulation cascade.



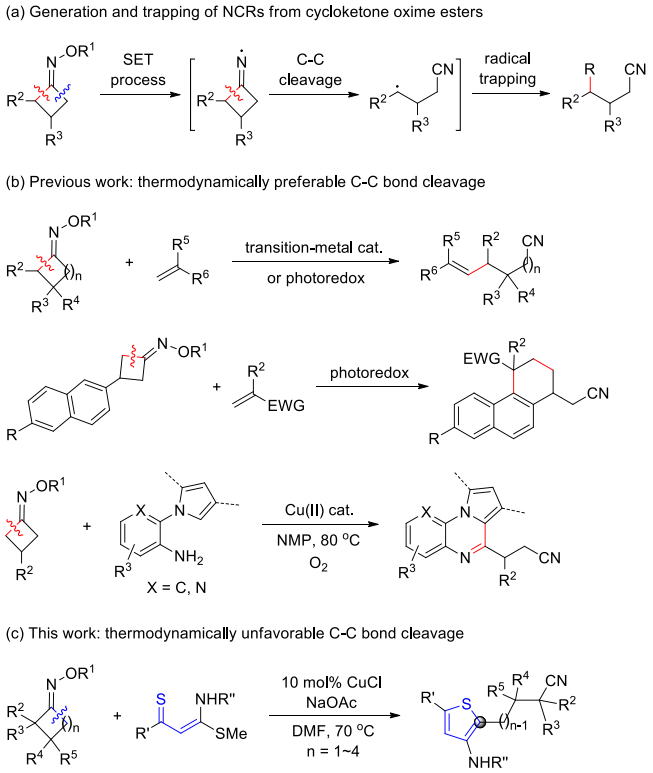
INTRODUCTION

Regioselective C−C bond cleavage has been a challenge in the construction of C−C and C-heteroatom bonds.[1] Continuous efforts have been devoted to ring-opening C−C bond cleavage of strained carbocycles.[2] In this regard, the ring-opening reactions of cycloketone oxime esters have recently been paid considerable attention because cyanoalkylation can be established via nitrogen-centered radicals (NCRs), that is, iminyl radicals,[3] by means of organotin hydride,[4] or under transition-metal catalysis,[5] photoinduction,[6] and microwave irradiation.[7] Oxime esters have been used as the diverse reagents for C−C and C-heteroatom bond formation as well as for *N*-heterocycle synthesis.[8] In the reaction of a cycloketone oxime ester, an iminyl radical is initially generated by a single-electron-transfer (SET) process to undergo regioselective C−C bond cleavage through β-elimination, producing the thermodynamically preferable alkyl radical, which is then trapped to form the corresponding cyanoalkylation product (Scheme 1a). Cycloketone oxime esters have been well investigated in the reactions with terminal alkenes or their surrogates, affording Heck-type cyanoalkylation products (Scheme 1b)[5a,e,f,h,6b,e] or cyanoalkylation-cyclization compounds.[5c,d,6a] A visible light-driven, copper-catalyzed three-component radical cross-coupling of cyclobutanone oxime esters, styrenes, and boronic acids;[9a] photoredox-catalyzed reactions of cycloketone oxime esters with styrenes in DMSO;[9b] and transition-metal-free C−C cleavage/borylation of cyclobutanone oxime esters, $B_2(OH)_4$, and pinacol[10] were achieved to give the corresponding cyanoalkylation/arylation, acylation, and cyanoalkylation/borylation products, respectively. The direct C−H cyanoalkylation of quinoxalin-2-(1*H*)-ones[5b] and heteroaromatic *N*-oxides[5e] was reported to yield the cyanoalkylation and cyanoalkyl-arylation products. The iminyl radicals generated in situ from cycloketone oxime esters could also be trapped by other reagents to produce the cyanoalkylation products with their alkyl-chains functionalized by acyloxy, aloxy, hydroxyl,[5g,6d] PhX (X = S, Se, and Te),[5i] fluoro,[6c] or TEMPO.[7] The radical C−C bond cleavage reaction of 2,4-unsubstituted cyclobutanone oxime esters has recently been employed to synthesize polycyclic *N*-heterocycles from the aerobic cyclization with 1-(2-aminophenyl)-pyrroles.[11] In all of these reactions, the regioselective ring-opening C−C bond cleavage occurred between the iminyl carbon and the vicinal sterically hindered carbon atoms in the cycloketone oxime esters (Scheme 1a,b). However, the ring-opening C−C bond cleavage between the iminyl carbon and the less sterically hindered carbon atoms is thermodynamically less favorable. To date, only two such examples have been documented in the intramolecular ring-opening reactions of strained cyclobutanone oxime esters, that is, the reaction of 2,2a,7,7a-tetrahydrocyclobuta[*a*]inden-1-one oxime ester with

Received: December 13, 2018
Published: January 11, 2019

DOI: 10.1021/acs.joc.8b03175
J. Org. Chem. 2019, 84, 2178−2190

Scheme 1. Cyanoalkylation by Means of Cycloketone Oxime Esters

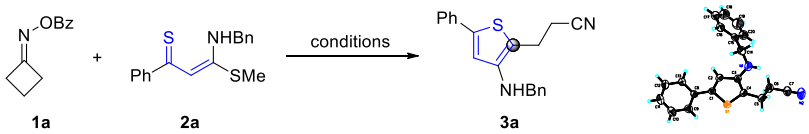


stoichiometric nBu$_3$SnH/AIBN leading to a thermodynamically less favorable nitrile (3%) as the byproduct,[12a] and palladium(0)-catalyzed ring-opening transformation of bicyclo[4.2.0]octan-7-one oxime ester under basic conditions to form 2-methylene-cyclohexane-carbonitrile via β-H elimination.[12b] Occurrence of such thermodynamically less favorable C−C bond cleavage in these 2-substituted cyclobutanone oxime esters is very dependent on the nature of the products or substituents on the cyclobutanone backbone.[12]

The thiophene ring ubiquitously exists in natural products, pharmaceuticals, and functional polymers,[13] and thiophene derivatives can function as versatile building blocks in organic synthesis and manufacturing of functional materials.[14] The cyanoalkyl moiety is also one of the important structural motifs, which are widely present in natural products and pharmaceutical drugs.[15] Synthesis of functionalized thiophenes are often achieved by modification of an existing thiophene ring or through ring-closure reactions.[16−18] In this area, considerable advance has been made in the establishment of amino-substituted thiophenes.[19,20] Base-promoted multiple-component Gewald reactions[21] and those of β-ketothioamides[22] have been employed for the synthesis of 2-aminothiophenes. 3-Aminothiophenes are also considered as the important small molecules for drug development,[23] but only a few methods have been reported for their synthesis.[24,25] Enaminothiones,[26] that is, α-thioxo ketene N,S-acetals, have been known to react with activated methylene compounds in the presence of stoichiometric Hg(OAc)$_2$[27] or with diazo compounds under Rh(II) catalysis,[28] affording 3-aminothiophenes.

Recently, we found that enaminothiones, which can be conveniently prepared from readily available α-oxo ketene N,S-acetals,[29] could be used for the construction of S-heterocycles by Cu(II) catalysis[26] or under transition-metal-free conditions[30] by using N-tosylhydrazones as the C1 building blocks. A copper-catalyzed three-component reaction of acyclic methyl aryl ketoxime acetate, aryl aldehyde, and elemental sulfur was used to furnish a fused thieno[3,2-d]thiazole core.[31] Intrigued by the regioselective reactivity of cycloketone oxime esters, we conceived that cycloketone oxime esters might be utilized as the C1 building blocks for the synthesis of aromatic S-heterocycles. Unexpectedly, our initial attempt revealed that

Table 1. Optimization of Reaction Conditions[a]

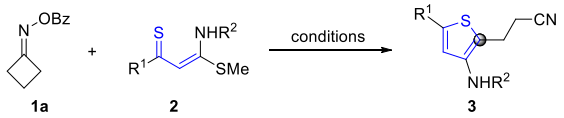


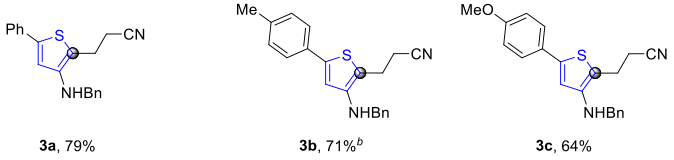
entry	catalyst	base	solvent	temp (°C)	yields[b] (%)
1	$CuCl_2$	Na_2CO_3	DMF	80	53
2	CuCl	Na_2CO_3	DMF	80	57
3	CuCl	K_2CO_3	DMF	80	46
4	CuCl	KOAc	DMF	80	65
5	CuCl	NaOAc	DMF	80	75
6	CuCl	CsOAc	DMF	80	59
7	CuCl	NaOAc	DMSO	80	63
8	CuCl	NaOAc	DMF	70	77 (79)[c]
9	CuCl	NaOAc	DMF	60	62
10[d]	CuCl	NaOAc	DMF	70	69
11[e]	CuCl	NaOAc	DMF	70	71
12[f]	CuCl	NaOAc	DMF	70	10
13		NaOAc	DMF	70	0
14	CuCl		DMF	70	trace

[a]Conditions: **1a** (0.30 mmol), **2a** (0.33 mmol), catalyst (0.03 mmol), base (0.30 mmol), solvent (2 mL), 0.1 MPa N_2, and 12 h. [b]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxylbenzene as the internal standard. [c]Isolated yield given in parentheses. [d]**1a** (0.33 mmol) and **2a** (0.30 mmol). [e]**2a** (0.30 mmol). [f]Under air atmosphere.

DOI: 10.1021/acs.joc.8b03175
J. Org. Chem. 2019, 84, 2178−2190

Table 2. Scope of Enaminothiones (2)[a]

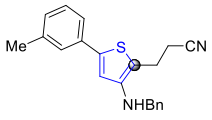




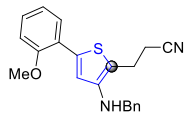
3a, 79%

3b, 71%[b]

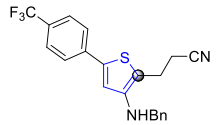
3c, 64%



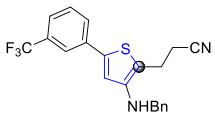
3d, 75%[b]



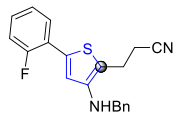
3e, 68%[b]



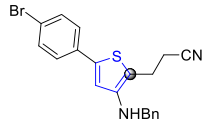
3f, 71%[b]



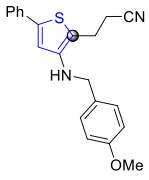
3g, 70%



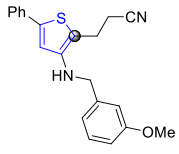
3h, 80%



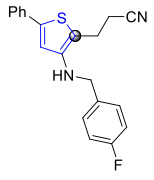
3i, 72%



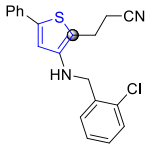
3j, 71%[b]



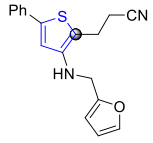
3k, 65%[b]



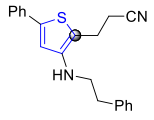
3l, 75%[b]



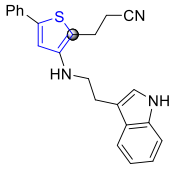
3m, 63%[b]



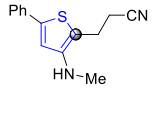
3n, 68%



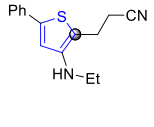
3o, 75%



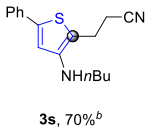
3p, 80%



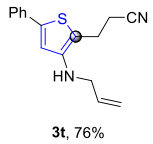
3q, 71%[b]



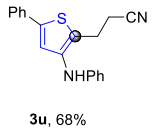
3r, 65%



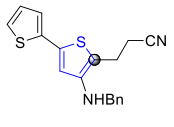
3s, 70%[b]



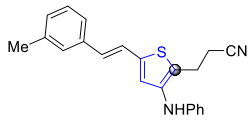
3t, 76%



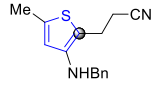
3u, 68%



3v, 75%



3w, 61%[b]



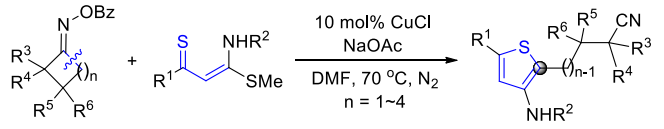
3x, 75%

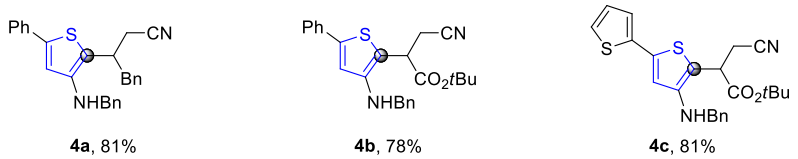
[a]Conditions: **1a** (0.30 mmol), **2** (0.33 mmol), CuCl (0.03 mmol), NaOAc (0.30 mmol), DMF (2 mL), 70 °C, 0.1 MPa N_2, and 12 h. [b]80 °C and 18 h.

2-substituted cyclobutanone oxime esters could undergo annulation with enaminothiones through thermodynamically less favorable radical ring-opening C−C bond cleavage, furnishing a thiophene ring (Scheme 1c). Herein, we disclose

DOI: 10.1021/acs.joc.8b03175
J. Org. Chem. 2019, 84, 2178−2190

Table 3. Scope of Cycloketone Oxime Esters (1)[a]





[a]Conditions: **1** (0.30 mmol), **2** (0.33 mmol), CuCl (0.03 mmol), NaOAc (0.30 mmol), DMF (2 mL), 70 °C, 0.1 MPa N_2, and 12 h. [b]80 °C and 18 h.

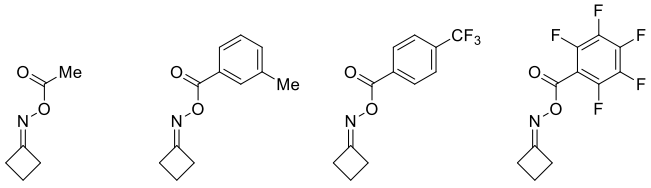
the unusual [4+1] annulation of cycloketone oxime esters with enaminothiones for the synthesis of 2-cyanoalkyl-3-amino-thiophene derivatives.

RESULTS AND DISCUSSION

Initially, the reaction of cyclobutanone oxime ester **1a** with enaminothione **2a** was conducted to screen the reaction conditions (Table 1). With 10 mol % $CuCl_2$ as the catalyst and Na_2CO_3 (1 equiv) as the base, the reaction underwent in DMF at 80 °C for 12 h to form the target 2-cyanoalkylthiophene product **3a** in 53% yield, while CuCl facilitated the reaction more efficiently (entries 1 and 2). Copper salts $CuBr_2$, $Cu(OAc)_2$, CuBr, CuI, and CuOAc were also screened as the catalysts to render the formation of **3a** in 43−51% yields, exhibiting a lower catalytic activity than CuCl. Among the screened bases Na_2CO_3, K_2CO_3, KOAc, NaOAC, and CsOAc, NaOAc was found to be the most effective promoter (entries 2−6). DMSO was a less effective solvent than DMF (entry 7). The best yield was obtained at 70 °C, resulting in **3a** in 79% isolated yield (entries 5, 8, and 9). Variation of the substrate

DOI: 10.1021/acs.joc.8b03175
J. Org. Chem. 2019, 84, 2178−2190

ratios by using an excess of **1a** or equimolar amount of **2a** did not improve the reaction efficiency (entries 10 and 11). An air atmosphere deteriorated the reaction, and the reaction could not occur without the catalyst or base promoter (entries 12−14). The analogs of **1a**, that is, cyclobutanone *O*-acetyl (**1A**), *O*-(3-methylbenzoyl) (**1B**), *O*-4-(trifluoromethyl)benzoyl (**1C**), and *O*-(perfluorobenzoyl) (**1D**) oxime esters, were also tested in the reaction with **2a**, producing **3a** in <1, 49, 61, and 27% yields, respectively, revealing that cyclobutanone oxime esters **1A**−**1D** could not be used as the effective C1 building blocks for the synthesis of **3a**. The molecular structure of compound **3a** was further confirmed by the X-ray single crystallographic determination (see the Supporting Information for details).



1A, <1% **1B**, 49% **1C**, 61% **1D**, 27%

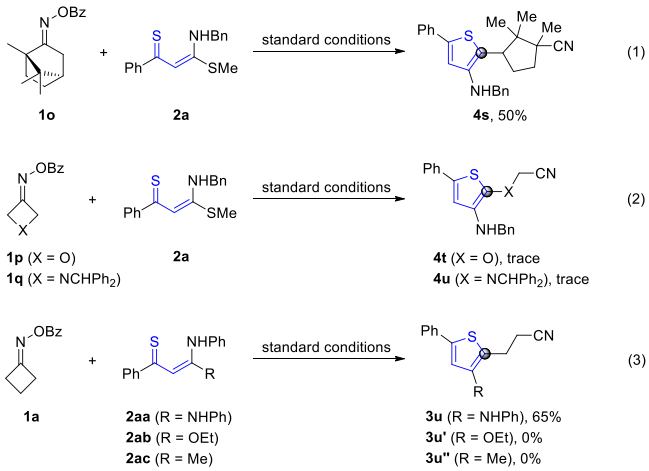
Under the optimal conditions, the scope of enaminothiones **2** was investigated by reacting with **1a** (Table 2). Electron-donating substituents, such as methyl and methoxy, on the aryl group of the thioaroyl moiety in **2** did not facilitate formation of the target products **3b**−**3e** (64−75%) in comparison to the formation of compound **3a** (79%). The substituent effects of the electron-withdrawing trifluoromethyl and fluoro groups varied to render the formation of **3f**−**3h** (70−80%). 4-Bromo-substituted enaminothione **2i** reacted with **1a** to give **3i** in 72% yield. Substituted benzylamino-based enaminothiones were also reacted to give the target products **3j**−**3m** in good yields (63−75%). 2-Furylmethylamino-derived enaminothiothione **2n** reacted with **1a** to afford **3n** in 68% yield. Other aliphatic non-benzylamine derived enaminothiones **2o**−**2t** efficiently reacted with **1a**, producing the target products **3o**−**3t** in 65−80% yields. However, cyclopropylamine-derived enaminothione failed to react with **1a** to give the corresponding product. Anilide-based enaminothione **2u** also reacted with **1a** to form product **3u** (68%). It is noteworthy, that 2-thienyl, styryl, and methyl-functionalized enaminothiones **2v**−**2x** exhibited a good reactivity to **1a**, and their reactions afforded **3v**−**3x** in 61−75% yields.

Next, the generality of cycloketone oxime esters **1** was examined as the C1 building blocks in the [4+1] annulation with enaminothiones **2** (Table 3). 3-Substituted cyclobutanone oxime esters **1b**−**1g** efficiently reacted with various enaminothiones to give the target 3-aminothiophene products **4a**−**4g** (70−81%). Functional groups, such as benzyl, CO_2tBu, 4-*t*Bu-phenyl, phenyl, methyl, and functionalized alkyl, could be tolerated as the 3-substituents on the cyclobutanone ring. It should be noted, that the 3,3-disubstituted 3-methyl-3-phenylcyclobutanone oxime ester (**1f**) did not exhibit an obvious steric effect on the generation of **4g** (76%). Unexpectedly, when 2-substituted cyclobutanone oxime esters were used as the C1 synthons, the C−C bond cleavage occurred between the iminyl carbon and the vicinal less sterically hindered 4-carbon atoms, affording **4h**−**4j** in 68−79% yields. Such transformations unambiguously proceeded through a thermodynamically less favorable ring-opening C−C bond cleavage pathway. However, the previously known C−C bond cleavage usually occurs between the iminyl carbon and the vicinal more sterically hindered 2-carbon atoms for 2-substituted cyclobutanone oxime esters and their analogs (Scheme 1a,b).[4−7,9,10] Unsubstituted cyclopentanone oxime ester **1j** also reacted well with **2a** to afford the ring-opening C−C cleavage/cyanoalkylation product **4k** (69%) by extending one carbon of the cyanoalkyl chain at the 2-position of the thiophene ring. 2,2-Dimethylcyclopentanone oxime ester **1k** reacted more efficiently with **2a** and its analogs than unsubstituted **1j** did, giving products **4l**−**4n** in 76−84% yields without exhibiting a negative steric impact on the reaction efficiency.

The six-membered cycloketone oxime esters, that is, 2-methyl and 2-phenylcyclohexanone oxime esters, showed a reactivity lower than those of the cyclobutanone and cyclopentanone oxime esters, leading to **4o**−**4q** in 51−61% yields.

This phenomenon is attributed to the lower ring tension of the six-membered carbocycle than those of the strained four- and five-membered carbocyclic rings. Interestingly, cycloheptanone oxime ester could also undergo the annulation reaction with **2a** through the ring-opening C−C bond cleavage, forming **4r** (45%) by elevating the reaction temperature and prolonging the reaction time.

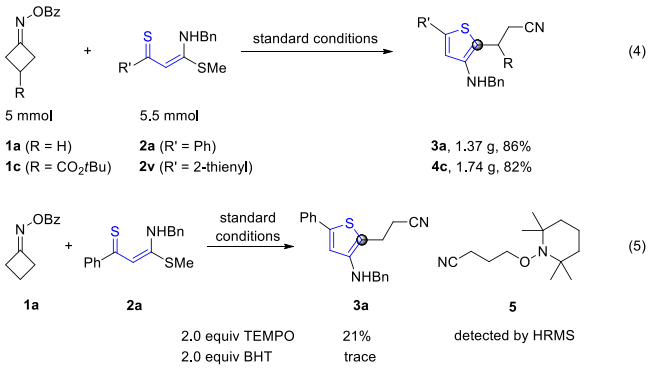
Bicyclic oxime ester **1o** derived from camphor reacted with enaminothione **2a** to yield the target product **4s** in 50% yield (eq 1). However, oxetan-3-one- and 1-Cbz-3-azetidinone-



derived oxime esters **1p** and **1q** hardly reacted with **2a** under the standard conditions (eq 2). α-Thioxo ketene *N*,*N*-acetal **2aa** reacted with **1a** to afford 3-arylaminothiophene **3u** (65%), whereas the corresponding ketene *N*,*O*-acetal (**2ab**) and enamine (**2ac**) exhibited no reactivity to **1a** (eq 3). These results have suggested that the alkylthio functionality in enaminothiones **2** plays a crucial role in executing the [4+1] annulation reaction.

To demonstrate the applicability of the present synthetic protocol, gram-scale preparation experiments were carried out by means of the reactions of **1a** with **2a**, and **1c** with **2v**, respectively (eq 4). Under the standard conditions, the target products **3a** and **4c** were obtained in 86 and 82% yields, respectively. It should be noted, that **3a** and **4c** were more efficiently obtained from the larger scale preparation, which has demonstrated the potential application of the synthetic protocol for the synthesis of 2-cyanoalkyl-3-aminothiophene derivatives.

DOI: 10.1021/acs.joc.8b03175
J. Org. Chem. 2019, 84, 2178−2190



Control experiments were conducted to probe into the reaction mechanism. The reaction of **1a** with **2a** was performed in the presence of two equivalents of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under the standard conditions, forming **3a** in 21% yield by ^{1}H NMR analysis of the reaction mixture, while 2,6-di-*tert*-butyl-4-methylphenyl (BHT) completely inhibited the reaction (eq 5). The adduct of the possible cyanoalkyl radical intermediate with TEMPO, that is, compound **5**, was detected in the reaction mixture by high-resolution mass spectrometry. These radical scavengers obviously inhibited the reaction, which implicates that the reaction may proceed through a radical pathway.[7]

A plausible mechanism is proposed in Scheme 2 by simplifying the core structure of the cycloketone oxime esters. The reaction is initiated by a single-electron-transfer (SET) process from cycloketone oxime ester **1** in the presence of a Cu(I) catalyst, generating cyclobutylidene iminyl radical **A** and a Cu(II) species. Iminyl radical **A** undergoes regioselective C−C bond cleavage via β-elimination to form the thermodynamically less favorable alkyl radical **B**,[12] which is then added to enaminothione **2** to result in radical **C**. A second SET process occurs to generate cation **D**/iminium **D′**, which undergo hydrogen abstraction by the carboxylate anion to furnish the five-membered *S*-heterocycle **E** with regeneration of the Cu(I) catalyst. Base-assisted aromatization through elimination of MeSH affords the target 2-cyanoalkyl-3-aminothiophene product **3** or **4**. Although generation of primary alkyl radical **B** is thermodynamically less favorable, production of the stable aromatic thiophene products of these types is kinetically preferred.

In conclusion, efficient copper(I)-catalyzed [4+1] annulation of enaminothiones (α-thioxo ketene *N*,*S*-acetals) with cycloketone oxime esters has been achieved to synthesize diverse 2-cyanoalkyl-3-aminothiophene derivatives. A rare thermodynamically less favorable C−C bond cleavage method has been developed for C−C bond construction with 2-substituted cycloketone oxime esters. Due to easy manipulations, readily available reactants, excellent regioselectivity, and mild reaction conditions, the present work offers a promising protocol to access a cyanoalkyl-thiophene motif.

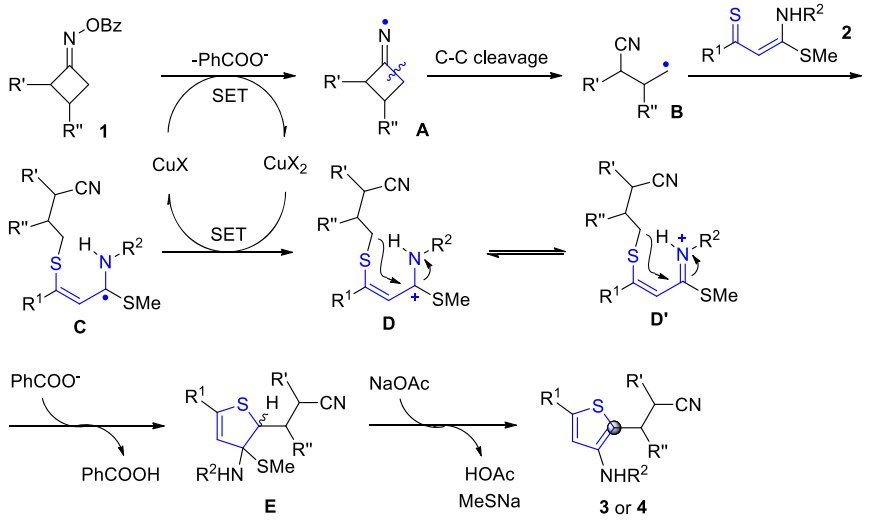
EXPERIMENTAL SECTION

General Considerations. The solvents were dried and distilled prior to use by the literature methods. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker DRX-400 spectrometer, and all chemical shift values refer to δ_{TMS} = 0.00 ppm or $CDCl_3$ (δ(^{1}H), 7.26 ppm, and δ(^{13}C), 77.16 ppm). The HRMS (ESI) analysis was obtained on a Waters GC-TOF CA156 mass spectrometer. X-ray crystallographic analysis was achieved by the Analysis Center, Dalian Institute of Chemical Physics, Chinese Academy of Sciences. All the chemical reagents were purchased from commercial sources and used as received unless otherwise indicated. The starting cycloketone oxime esters **1A**,[32a] **1C**,[6b] **1D**, **1a**, **1b**, **1e**−**1i**,[5h] **1j**, and **1n**;[32b] α-oxo ketene *N*,*S*-acetals;[32c,d] α-thioxo ketene *N*,*S*-acetals **2a**,[30] **2c**,[26] **2f**, **2h**−**2k**, **2m**, **2n**, **2p**, and **2q**;[30] **2r**;[26] **2t**−**2x**; and **2aa**−**2ac**[30] were prepared by the literature procedures, and their spectroscopic features are in good agreement with those reported in the literatures.

Preparation of Cycloketone Oxime Esters (1). Cycloketone oxime esters **1a** and **1g**−**1q** were prepared from the corresponding cycloketones by a two-step procedure. The cycloketones were commercially available or manufactured by the reduction of α,α-dichlorocyclobutanones synthesized from the corresponding alkenes by the reported procedure.[5h,6b]

Typical Procedure for the Preparation of ***1a*** *and* ***1g*****−****q****: Synthesis of Cyclobutanone Oxime Ester* ***1a****.* A mixture of cyclobutanone (350 mg, 5.0 mmol), hydroxylamine hydrochloride (695 mg, 10.0 mmol), and saturated aqueous sodium carbonate (10 mL) was stirred at 40 °C for 5 h. After being cooled to ambient temperature, the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and filtered, and all of the volatiles were evaporated under reduced pressure to give a crude oxime product which was directly used in the next step reaction without further purification.

Scheme 2. Proposed Reaction Mechanism



DOI: 10.1021/acs.joc.8b03175
J. Org. Chem. 2019, 84, 2178−2190

To a mixture of the crude cyclobutanone oxime, triethylamine (1.01 g, 10.0 mmol), and 10 mL dichloromethane was added benzoyl chloride (1.05 g, 7.5 mmol) at 0 °C. After, the reaction was continued at 0−25 °C for 6 h, and diethyl ether and water (20 mL each) were added. The organic layer was separated, washed with water (20 mL), dried over anhydrous $MgSO_4$, and filtered. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether (60−90 °C)/ethyl acetate = 30:1, v/v) to afford cyclobutanone oxime ester **1a** as a white solid (747 mg, 79%).

Cycloketone oxime esters **1b−1f** were prepared from the corresponding alkenes by a four-step procedure as follows.

*Typical Procedure for the Preparation of **1b−1f**: Synthesis of 3-Benzylcyclobutanone O-Benzoyl Oxime (**1b**).* Under an argon atmosphere, to a stirred mixture of allylbenzene (591 mg, 5.0 mmol) and zinc−copper couple (960 mg, 15.0 mmol) in anhydrous diethyl ether (10 mL) was added a solution of trichloroacetyl chloride (1.81 g, 10.0 mmol) and phosphorus oxychloride (843 mg, 5.5 mmol) in diethyl ether (10 mL) over 1 h. The suspension was stirred at reflux overnight. After being cooled to ambient temperature, the mixture was filtered through a short pad of Celite and rinsed with diethyl ether (20 mL). The combined filtrate was successively washed with water, saturated aqueous $NaHCO_3$, and brine (30 mL each); dried over anhydrous $MgSO_4$; and filtered, and all of the volatiles were removed under reduced pressure. The resultant crude product was directly used in the next step reaction without further purification.

A mixture of the crude 3-benzyl-2,2-dichlorocyclobutanone and zinc dust (1.30 g, 20.0 mmol) in acetic acid (10 mL) was stirred at ambient temperature for 2 h and then heated at 80 °C for 5 h. The resulting mixture was allowed to cool to ambient temperature, diluted with water (30 mL), and extracted with diethyl ether (3 × 20 mL). The combined organic phase was successively washed with saturated aqueous $NaHCO_3$ (3 × 30 mL), water (30 mL), and brine (30 mL); dried over anhydrous $MgSO_4$; and concentrated in vacuum to remove all the volatiles. The resultant residue was purified by flash silica gel column chromatography (eluent: petroleum ether (60−90 °C)/ethyl acetate, v/v = 20:1) to afford 3-benzylcyclobutanone.

To a stirred solution of 3-benzylcyclobutanone in 10 mL of pyridine was added hydroxylamine hydrochloride (695 mg, 10.0 mmol) at ambient temperature. After being stirred for 2 h, pyridine was removed under reduced pressure. The residue was diluted with water (20 mL) and extracted with EtOAc (20 mL). The aqueous phase was extracted with EtOAc (10 mL) and the combined organic extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and evaporated under reduced pressure to give the crude material, which was used in the next step reaction without further purification.

To a mixture of the resultant 3-benzylcyclobutanone oxime and triethylamine (1.01 g, 10.0 mmol) in 10 mL of dichloromethane was added benzoyl chloride (1.05 g, 7.5 mmol) at 0 °C. After being stirred at 0−25 °C for 6 h, water and diethyl ether (20 mL each) were added. The organic layer was separated and washed with water (20 mL), dried over anhydrous Na_2SO_4, and filtered, and all of the volatiles were evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether (60−90 °C)/ethyl acetate, v/v = 30:1) to afford 3-benzylcyclobutanone oxime ester **1b** as a white solid (768 mg, 55%).

*Cyclobutanone O-(3-Methylbenzoyl) Oxime (**1B**).* 720 mg, yield 71%, yellow solid. mp 294−295 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.33. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.81, 7.34 (m each, 2:2 H), 3.12 (t, J = 8.0 Hz, 4 H), 2.40 (s, 3 H), 2.11 (m, 2 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 169.1, 164.0, 138.1, 133.8, 129.9, 128.7, 128.2, 126.4, 31.7, 31.6, 21.0, 14.1. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{12}H_{14}NO_2$, 204.1025; found, 204.1024.

*tert-Butyl 3-((Benzoyloxy)imino)cyclobutanecarboxylate (**1c**).* 796 mg, yield 55%, yellow solid. mp 84−85 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.38. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.01, 7.58 (m each, 2:1 H), 7.46 (t, J = 7.7 Hz, 2 H), 3.35 (m, 4 H), 3.19 (m, 1 H), 1.49 (s, 9 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 172.5, 164.9, 163.9, 133.4, 129.7, 128.9, 128.6, 81.7, 35.8, 35.6, 32.1, 28.1. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{16}H_{20}NO_4$, 290.1392; found, 290.1391.

*3-(4-(tert-Butyl)phenyl)cyclobutanone O-Benzoyl Oxime (**1d**).* 820 mg, yield 51%, yellow solid. mp 130−131 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.45. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.98 (dd, J = 8.3 and 1.2 Hz, 2 H), 7.50, 7.31 (m each, 1:2 H), 7.39 (t, J = 7.9 Hz, 2 H), 7.15 (d, J = 8.2 Hz, 2 H), 3.56, 3.16 (m each, 3:2 H), 1.25 (s, 9 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 166.3, 164.0, 149.9, 140.0, 133.3, 129.6, 129.0, 128.5, 126.1, 125.6, 39.6, 39.5, 34.5, 32.1, 31.4. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{21}H_{24}NO_2$, 322.1807; found, 322.1807.

*(E)-2,2-Dimethylcyclopentanone O-benzoyl Oxime (**1k**).* 867 mg, yield 75%, yellow solid. mp 74−75 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.35. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.03, 7.57, 7.42 (m each, 2:1:2 H), 2.76 (t, J = 7.5 Hz, 2 H), 1.83, 1.70 (m each, 2:2 H), 1.30 (s, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 180.8, 164.0, 133.1, 129.6, 128.5, 43.4, 41.1, 29.0, 26.4, 20.7. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{14}H_{18}NO_2$, 232.1338; found, 232.1338.

*(E)-2-Methylcyclohexanone O-benzoyl Oxime (**1l**).* 821 mg, yield 71%, yellow solid. mp 69−70 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.60. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.95, 7.46, 7.35 (m each, 2:1:2 H), 2.79, 2.55, 2.31, 1.84, 1.67, 1.49 (m each, 1:1:1:1:2:3 H), 1.17 (d, J = 6.8 Hz, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 172.7, 164.4, 133.1, 129.7, 129.6, 128.6, 37.2, 35.0, 26.4, 25.8, 23.4, 17.2. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{14}H_{18}NO_2$, 232.1338; found, 232.1335.

*(E)-2-Phenylcyclohexanone O-benzoyl Oxime (**1m**).* 997 mg, yield 68%, yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.53. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.00, 7.50, 7.38, 7.29, 7.17 (m each, 2:1:2:4:1 H), 3.94 (t, J = 4.9 Hz, 1 H), 2.91, 2.44, 2.23, 1.99, 1.65 (m each, 1:1:1:1:4 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 171.5, 164.3, 139.1, 133.2, 129.7, 129.5, 128.7, 128.6, 127.8, 126.8, 45.5, 31.1, 26.5, 25.4, 22.2. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{19}H_{20}NO_2$, 294.1494; found, 294.1494.

*(1S,4R,E)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one O-benzoyl Oxime (**1o**).* 841 mg, yield 62%, yellow solid. mp 74−75 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.65. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.97, 7.47, 7.36 (m each, 2:1:2 H), 2.68, 1.89, 1.75, 1.52, 1.21 (m each, 1:1:2:1:1 H), 2.19 (d, J = 18.1 Hz, 1 H), 1.11, 0.88, 0.79 (s each, 3:3:3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 178.9, 164.1, 133.1, 129.6, 129.5, 128.5, 53.3, 48.8, 43.6, 35.0, 32.5, 27.2, 19.6, 18.5, 11.1. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{17}H_{22}NO_2$, 272.1651; found, 272.1651.

Preparation of Enaminothiones (2). *Typical Procedure for the Preparation of **2**: Synthesis of (E)-3-(Benzylamino)-3-(methylthio)-1-phenylprop-2-ene-1-thione (**2a**).* A mixture of α-oxo ketene *N,S*-acetal, that is, (*E*)-3-(benzylamino)-3-(methylthio)-1-phenylprop-2-en-1-one (567 mg, 2.0 mmol), and Lawesson's reagent (404 mg, 2.0 mmol) in 5 mL toluene was stirred at 110 °C for 10 min. After being cooled to ambient temperature, the mixture was evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether (60−90 °C)/ethyl acetate, v/v = 50:1) to afford **2a** as a yellow solid (509 mg, 85%).

*(E)-3-(Benzylamino)-3-(methylthio)-1-(p-tolyl)prop-2-ene-1-thione (**2b**).* 552 mg, yield 88%, yellow solid. mp 85−86 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 6:1, v/v) = 0.45. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 14.86 (br, 1 H), 7.62 (d, J = 8.1 Hz, 2 H), 7.37 (m, 5 H), 7.15 (d, J = 8.1 Hz, 2 H), 6.56 (s, 1 H), 4.72 (d, J = 5.4 Hz, 2 H), 2.50 (s, 3 H), 2.36 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 198.2, 171.4, 146.5, 139.5, 135.6, 129.0, 128.8, 128.1, 127.8, 127.0, 106.8, 48.5, 21.3, 14.8. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{18}H_{20}NS_2$, 314.1037; found, 314.1038.

*(E)-3-(Benzylamino)-3-(methylthio)-1-(m-tolyl)prop-2-ene-1-thione (**2d**).* 533 mg, 85% yield, yellow solid. mp 87−88 °C

DOI: 10.1021/acs.joc.8b03175
J. Org. Chem. 2019, 84, 2178−2190

(recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 6:1, v/v) = 0.32. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 14.91 (br, 1 H), 7.58 (s, 1 H), 7.43 (m, 6 H), 7.27 (t, J = 6.7 Hz, 1 H), 7.21 (d, J = 7.5 Hz, 1 H), 6.59 (s, 1 H), 4.75 (s, 2 H), 2.52 (s, 3 H), 2.43 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 198.5, 171.5, 149.3, 137.7, 135.5, 129.9, 128.9, 127.9, 127.8, 123.8, 107.2, 48.4, 21.5, 14.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{18}H_{20}NS_2$, 314.1037; found, 314.1037.

*(E)-3-(Benzylamino)-1-(2-methoxyphenyl)-3-(methylthio)prop-2-ene-1-thione (**2e**).* 586 mg, yield 89%, yellow solid. mp 77−78 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 6:1, v/v) = 0.33. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 14.85 (br, 1 H), 7.57 (dd, J = 7.6 and 1.5 Hz, 1 H), 7.47 (d, J = 7.2 Hz, 2 H), 7.42 (t, J = 7.4 Hz, 2 H), 7.36 (t, J = 7.1 Hz, 1 H), 7.30 (m, 1 H), 7.02 (t, J = 7.5 Hz, 1 H), 6.95 (d, J = 8.3 Hz, 1 H), 6.58 (s, 1 H), 4.72 (s, 2 H), 3.85 (s, 3 H), 2.40 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 196.1, 171.0, 153.9, 139.4, 135.6, 130.2, 129.3, 129.0, 128.1, 127.9, 120.8, 111.6, 110.5, 56.0, 48.6, 14.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{18}H_{20}NOS_2$, 330.0986; found, 330.0986.

*(E)-3-(Benzylamino)-3-(methylthio)-1-(3-(trifluoromethyl)-phenyl)prop-2-ene-1-thione (**2g**).* 514 mg, yield 70%, yellow solid. mp 105−106 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 6:1, v/v) = 0.43. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 14.86 (br, 1 H), 7.95 (s, 1 H), 7.86 (d, J = 7.8 Hz, 1 H), 7.60 (d, J = 7.7 Hz, 1 H), 7.51−7.29 (m, 6 H), 6.55 (s, 1 H), 4.73 (d, J = 5.8 Hz, 2 H), 2.50 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 195.5, 172.2, 149.6, 135.2, 130.4 (J = 32.2 Hz), 130.1, 129.0, 128.6, 128.2, 127.7, 125.5 (q, J = 3.5 Hz), 123.7 (q, J = 3.9 Hz), 122.8 (q, J = 272.5 Hz), 107.4, 48.5, 14.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{18}H_{17}F_3NS_2$, 368.0755; found, 368.0757.

*(E)-3-((4-Fluorobenzyl)amino)-3-(methylthio)-1-phenylprop-2-ene-1-thione (**2l**).* 502 mg, yield 79%, yellow solid. mp 106−107 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 6:1, v/v) = 0.42. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 14.87 (br, 1 H), 7.70, 7.40, 7.08 (m each, 2:5:2 H), 6.57 (s, 1 H), 4.68 (d, J = 4.1 Hz, 2 H), 2.50 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 198.5, 171.5, 162.5 (d, J = 245.3 Hz), 149.1, 131.3 (d, J = 3.3 Hz), 129.6 (d, J = 8.2 Hz), 129.2, 128.1, 126.9, 115.9 (d, J = 21.7 Hz), 107.2, 47.7, 14.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{17}H_{17}FNS_2$, 318.0786; found, 318.0786.

*(E)-3-(Methylthio)-3-(phenethylamino)-1-phenylprop-2-ene-1-thione (**2o**).* 508 mg, yield 81%, yellow solid. mp 108−109 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 6:1, v/v) = 0.45. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 14.49 (br, 1 H), 7.61 (m, 2 H), 7.35−7.08 (m, 8 H), 6.44 (s, 1 H), 3.67 (m, 2 H), 3.01 (m, 2 H), 2.41 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 197.5, 171.4, 149.3, 137.8, 129.1, 129.0, 128.9, 128.1, 127.0, 127.0, 107.1, 46.5, 35.4, 14.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{18}H_{20}NS_2$, 314.1037; found, 314.1038.

*(E)-3-(Butylamino)-3-(methylthio)-1-phenylprop-2-ene-1-thione (**2s**).* 377 mg, yield 71%, yellow solid. mp 88−89 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 6:1, v/v) = 0.55. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 14.52 (br, 1 H), 7.79−7.62 (m, 2 H), 7.44−7.31 (m, 3 H), 6.54 (s, 1 H), 3.52 (m, 2 H), 2.52 (s, 3 H), 1.80 (m, 2 H), 1.56 (m, 2 H), 1.02 (t, J = 7.4 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 196.5, 171.4, 149.3, 129.0, 128.1, 126.9, 107.0, 44.6, 30.7, 20.3, 14.6, 13.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{14}H_{20}NS_2$, 266.1037; found, 266.1035.

*Typical Procedure for the Synthesis of Thiophenes **3** and **4**: Synthesis of 3-(3-(Benzylamino)-5-phenylthiophen-2-yl)-propanenitrile (**3a**).* Under a nitrogen atmosphere, a mixture of **1a** (57 mg, 0.3 mmol), **2a** (99 mg, 0.33 mmol), CuCl (3.0 mg, 0.03 mmol), and NaOAc (24 mg, 0.3 mmol) in 2 mL of DMF was stirred at 70 °C for 12 h. After being cooled to ambient temperature, the resultant mixture was purified by silica gel column chromatography (eluent: petroleum ether (60−90 °C)/ethyl acetate, v/v = 30:1) to afford **3a** as a yellow solid (75 mg, 79%).

*3-(3-(Benzylamino)-5-phenylthiophen-2-yl)propanenitrile (**3a**).* 76 mg, 79%; yellow solid. mp 104−105 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.38. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.55 (m, 2 H), 7.50−7.24 (m, 8 H), 6.99 (s, 1 H), 4.44 (s, 2 H) 3.54 (br, 1 H), 2.99 (t, J = 7.4 Hz, 2 H), 2.59 (t, J = 7.4 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 145.4, 140.8, 139.7, 134.3, 129.0, 128.8, 127.8, 127.6, 126.9, 125.4, 119.3, 115.6, 112.4, 51.5, 23.1, 18.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{20}H_{19}N_2S$, 319.1269; found, 319.1267.

*3-(3-(Benzylamino)-5-(p-tolyl)thiophen-2-yl)propanenitrile (**3b**).* 71 mg, 71%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.45. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.43−7.29 (m, 7 H), 7.15 (d, J = 7.9 Hz, 2 H), 6.91 (s, 1 H), 4.36 (s, 2 H), 2.97 (t, J = 7.4 Hz, 2 H), 2.57 (t, J = 7.4 Hz, 2 H), 2.35 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 145.4, 140.9, 139.7, 137.5, 131.6, 129.6, 128.8, 127.8, 127.5, 125.3, 119.3, 115.1, 111.9, 51.6, 23.1, 21.3, 18.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{21}H_{21}N_2S$, 333.1425; found, 333.1417.

*3-(3-(Benzylamino)-5-(4-methoxyphenyl)thiophen-2-yl)-propanenitrile (**3c**).* 67 mg, 64%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.31. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.32 (d, J = 8.9 Hz, 2 H), 7.25, 7.17 (m, 4:1 H), 6.76 (d, J = 8.9 Hz, 2 H), 6.72 (s, 1 H), 4.23 (s, 2 H), 3.69 (s, 3 H), 3.26 (br, 1 H), 2.81 (t, J = 7.4 Hz, 2 H), 2.41 (t, J = 7.4 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 159.2, 145.3, 140.6, 139.7, 128.7, 127.7, 127.4, 127.2, 126.6, 119.3, 114.6, 114.3, 111.2, 55.4, 51.4, 23.0, 18.6. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{21}H_{21}N_2OS$, 349.1375; found, 349.1357.

*3-(3-(Benzylamino)-5-(m-tolyl)thiophen-2-yl)propanenitrile (**3d**).* 75 mg, 75%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.25. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.28, 7.23, 7.14 (m each, 4:3:1 H), 6.98 (d, J = 7.6 Hz, 1 H), 6.85 (s, 1 H), 4.27 (s, 2 H), 2.85 (t, J = 7.4 Hz, 2 H), 2.46 (t, J = 7.4 Hz, 2 H), 2.28 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 145.4, 141.0, 139.7, 138.6, 134.2, 128.8, 128.4, 127.8, 127.6, 126.1, 122.6, 119.3, 115.5, 112.3, 51.6, 23.2, 21.5, 18.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{21}H_{21}N_2S$, 333.1425; found, 333.1425.

*3-(3-(Benzylamino)-5-(2-methoxyphenyl)thiophen-2-yl)-propanenitrile (**3e**).* 71 mg, 68%; yellow solid. mp 102−103 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.28. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.36−7.14 (m, 6 H), 6.99 (m, 2 H), 6.83 (s, 1 H), 6.79−6.65 (m, 1 H), 4.28 (s, 2 H), 3.75 (s, 3 H), 2.88 (t, J = 7.4 Hz, 2 H), 2.49 (t, J = 7.4 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 160.0, 145.4, 140.5, 139.6, 135.6, 129.9, 128.8, 127.7, 127.5, 119.3, 118.0, 115.8, 113.0, 112.5, 111.1, 55.4, 51.5, 23.1, 18.6. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{21}H_{21}N_2OS$, 349.1375; found, 349.1373.

*3-(3-(Benzylamino)-5-(4-(trifluoromethyl)phenyl)thiophen-2-yl)-propanenitrile (**3f**).* 82 mg, 71%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.33. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.49 (s, 4 H), 7.28 (m, 5 H), 6.91 (s, 1 H), 4.28 (s, 2 H), 2.89 (t, J = 7.3 Hz, 2 H), 2.50 (t, J = 7.3 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 145.8, 139.5, 138.9, 137.7, 129.2 (q, J = 32.6 Hz), 128.9, 127.7, 127.6, 125.9 (q, J = 3.8 Hz), 125.4, 124.2 (q, J = 270.2 Hz), 119.1, 116.6, 113.8, 51.4, 23.1, 18.6. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{21}H_{18}F_3N_2S$, 387.1143; found, 387.1142.

*3-(3-(Benzylamino)-5-(3-(trifluoromethyl)phenyl)thiophen-2-yl)-propanenitrile (**3g**).* 81 mg, 70%; yellow solid. mp 68−69 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.42. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.64 (s, 1 H), 7.56 (d, J = 7.6 Hz, 1 H, 7.40 (m, 2 H), 7.35−7.12 (m, 5 H), 6.91 (s, 1 H), 4.29 (s, 2 H), 2.90 (t, J = 7.3 Hz, 2 H), 2.50 (t, J = 7.3 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 145.8, 139.5, 139.0, 135.2, 131.4 (q, J = 32.5 Hz), 129.5, 128.9, 128.5 (q, J = 3.7 Hz), 127.8, 127.7, 124.0 (q, J = 270.6 Hz), 123.9 (q, J = 3.7 Hz), 122.0 (q, J = 3.7 Hz), 119.1, 116.5, 113.5, 51.6, 23.2, 18.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{21}H_{18}F_3N_2S$, 387.1143; found, 387.1144.

DOI: 10.1021/acs.joc.8b03175
J. Org. Chem. 2019, 84, 2178−2190

*3-(3-(Benzylamino)-5-(2-fluorophenyl)thiophen-2-yl)-propanenitrile (**3h**).* 81 mg, 80%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.35. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.44 (m, 1 H), 7.35−7.15 (m, 5 H), 7.17−6.94 (m, 4 H), 4.27 (s, 2 H), 2.89 (t, J = 7.4 Hz, 2 H), 2.48 (t, J = 7.4 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 159.1 (d, J = 248.5 Hz), 145.2, 139.7, 133.7 (d, J = 31.8 Hz), 128.8, 128.6 (d, J = 8.4 Hz), 128.2 (d, J = 3.3 Hz), 127.8, 127.6, 124.5 (d, J = 3.4 Hz), 122.2 (d, J = 123.1 Hz), 119.2, 118.9 (d, J = 71.4 Hz), 116.5 (d, J = 222.7 Hz), 113.5 (d, J = 41.5 Hz), 51.6, 23.1, 18.6. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{20}H_{18}FN_2S$, 337.1175; found, 337.1173.

*3-(3-(Benzylamino)-5-(4-bromophenyl)thiophen-2-yl)-propanenitrile (**3i**).* 86 mg, 72%; yellow solid. mp 97−98 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.30. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.45 (d, J = 8.5 Hz, 2 H), 7.34 (m, 7 H), 6.92 (s, 1 H), 4.36 (s, 2 H), 3.38 (br, 1 H), 2.96 (t, J = 7.3 Hz, 2 H), 2.57 (t, J = 7.3 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 145.6, 141.3, 139.4, 132.0, 131.3, 128.8, 127.7, 127.6, 126.8, 121.3, 119.2, 115.8, 112.8, 51.4, 23.1, 18.6. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{20}H_{18}BrN_2S$, 397.0374; found, 397.0373.

*3-(3-((4-Methoxybenzyl)amino)-5-phenylthiophen-2-yl)-propanenitrile (**3j**).* 74 mg, 71%; yellow solid. mp 80−81 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.42. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.56, 7.33, 6.91 (m each, 2:5:2 H), 6.99 (s, 1 H), 4.32 (s, 2 H), 3.84 (s, 3 H), 2.97 (m, 3 H), 2.58 (t, J = 7.4 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 159.1, 145.5, 140.7, 134.3, 131.7, 129.0, 128.9, 127.5, 125.3, 119.3, 115.6, 114.2, 112.3, 55.4, 51.0, 23.1, 18.6. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{21}H_{21}N_2OS$, 349.1375; found, 349.1384.

*3-(3-((3-Methoxybenzyl)amino)-5-phenylthiophen-2-yl)-propanenitrile (**3k**).* 68 mg, 65%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.30. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.54, 7.34, 7.00, 6.86 (m each, 2:4:3:1 H), 4.37 (s, 2 H), 3.84 (s, 3 H), 3.53 (br, 1 H), 3.00 (t, J = 7.4 Hz, 2 H), 2.60 (t, J = 7.4 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 160.0, 145.4, 141.4, 140.7, 134.3, 129.8, 128.9, 127.5, 125.4, 119.9, 119.3, 115.5, 113.3, 112.9, 112.3, 55.3, 51.4, 23.1, 18.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{21}H_{21}N_2OS$, 349.1375; found, 349.1378.

*3-(3-((4-Fluorobenzyl)amino)-5-phenylthiophen-2-yl)-propanenitrile (**3l**).* 76 mg, 75%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.25. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.40, 7.24, 7.16, 6.95 (m each, 2:4:1:2: H), 6.81 (s, 1 H), 4.23 (s, 2 H), 3.06 (br, 1 H), 2.87 (t, J = 7.3 Hz, 2 H), 2.49 (t, J = 7.3 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 162.2 (d, J = 243.9 Hz,), 145.3, 140.8, 134.2, 135.4 (d, J = 31.4 Hz), 129.3 (d, J = 8.0 Hz), 128.9, 127.6, 125.4, 119.3, 115.7, 115.4 (d, J = 6.9 Hz), 112.6, 50.7, 23.1, 18.9. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{20}H_{18}FN_2S$, 337.1175; found, 337.1175.

*3-(3-((2-Chlorobenzyl)amino)-5-phenylthiophen-2-yl)-propanenitrile (**3m**).* 67 mg, 63%; yellow solid. mp 65−66 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.35. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.40, 7.30, 7.09 (m each, 2:2:3 H), 7.23 (t, J = 7.6 Hz, 2 H), 6.80 (s, 1 H), 4.34 (s, 2 H), 3.40 (br, 1 H), 2.86 (t, J = 7.4 Hz, 2 H), 2.45 (t, J = 7.4 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 144.9, 140.8, 137.0, 134.2, 133.4, 129.7, 129.6, 128.9, 128.8, 127.6, 127.2, 125.3, 119.2, 115.6, 113.1, 49.1, 23.1, 18.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{20}H_{18}ClN_2S$, 353.0879; found, 353.0879.

*3-(3-((Furan-2-ylmethyl)amino)-5-phenylthiophen-2-yl)-propanenitrile (**3n**).* 63 mg, 68%; yellow solid. mp 68−69 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.24. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.42 (d, J = 7.4 Hz, 2 H), 7.27 (m, 3 H), 7.16 (m, 1 H), 6.88 (s, 1 H), 6.23 (dd, J = 2.8, 2.0 Hz, 1 H), 6.13 (d, J = 3.1 Hz, 1H), 4.22 (s, 2 H), 3.37 (br, 1 H), 2.86 (t, J = 7.4 Hz, 2 H), 2.46 (t, J = 7.4 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 153.1, 144.7, 140.7, 134.3, 142.1, 128.9, 127.6, 125.4, 119.2, 115.9, 114.0, 110.5, 107.3, 44.5, 23.0, 18.6. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{18}H_{17}N_2OS$, 309.1062; found, 309.1059.

*3-(3-(Phenethylamino)-5-phenylthiophen-2-yl)propanenitrile (**3o**).* 75 mg, 75%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.40. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.44, 7.25, 7.14 (m each, 2:4:4 H), 6.85 (s, 1 H), 3.54 (br, 1 H), 3.35 (t, J = 6.9 Hz, 2 H), 2.80 (t, J = 6.9 Hz, 2 H), 2.73 (t, J = 7.4 Hz, 2 H), 2.38 (t, J = 7.4 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 145.1, 140.8, 139.2, 134.3, 128.9, 128.9, 128.8, 127.5, 126.6, 125.3, 119.1, 115.3, 112.0, 48.2, 36.2, 23.1, 18.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{21}H_{21}N_2S$, 333.1425; found, 333.1427.

*3-(3-((2-(1H-Indol-3-yl)ethyl)amino)-5-phenylthiophen-2-yl)-propanenitrile (**3p**).* 89 mg, 80%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.15. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.02 (br, 1 H), 7.53 (d, J = 8.0 Hz, 1 H), 7.42, 7.28, 7.17, 7.06 (m each, 2:3:2:1 H), 6.98 (d, J = 2.3 Hz, 1 H), 6.98 (s, 1 H), 3.44 (t, J = 6.5 Hz, 2 H), 3.01 (t, J = 6.4 Hz, 2 H), 2.67 (t, J = 7.4 Hz, 3 H), 2.30 (t, J = 7.4 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 145.5, 140.7, 136.6, 134.4, 128.9, 127.5, 127.5, 125.4, 122.5, 122.4, 119.7, 119.2, 118.8, 115.3, 113.2, 111.6, 111.5, 47.3, 25.7, 23.0, 18.2. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{23}H_{22}N_3S$, 372.1534; found, 372.1531.

*3-(3-(Methylamino)-5-phenylthiophen-2-yl)propanenitrile (**3q**).* 52 mg, 71%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.21.^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.45 (d, J = 7.3 Hz, 2 H), 7.26 (t, J = 7.7 Hz, 2 H), 7.16 (m, 1 H), 6.86 (s, 1 H), 3.20 (br, 1 H), 2.87 (t, J = 7.4 Hz, 2 H), 2.82 (s, 3 H), 2.52 (t, J = 7.4 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 146.9, 140.6, 134.4, 128.9, 127.5, 125.3, 119.3, 114.8, 111.1, 33.9, 23.1, 18.6. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{14}H_{15}N_2S$, 243.0956; found, 243.0957.

*3-(3-(Ethylamino)-5-phenylthiophen-2-yl)propanenitrile (**3r**).* 50 mg, 65%; yellow solid. mp 64−65 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.37. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.45, 7.26, 7.17 (m, 2:2:1 H), 6.85 (s, 1 H), 3.37 (br, 1 H), 3.12 (q, J = 7.1 Hz, 2 H), 2.89 (t, J = 7.4 Hz, 2 H), 2.53 (t, J = 7.4 Hz, 2 H), 1.16 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 145.7, 140.6, 134.4, 128.9, 127.5, 125.3, 119.3, 115.3, 111.6, 41.8, 23.1, 18.6, 15.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{15}H_{17}N_2S$, 257.1112; found, 257.1112.

*3-(3-(Butylamino)-5-phenylthiophen-2-yl)propanenitrile (**3s**).* 60 mg, 70%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.30. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.45, 7.14 (m each, 2:1 H), 7.26 (t, J = 7.4 Hz, 2 H), 6.85 (s, 1 H), 3.09 (t, J = 7.1 Hz, 2 H), 2.89 (t, J = 7.4 Hz, 2 H), 2.53 (t, J = 7.4 Hz, 2 H), 1.52, 1.35 (m each, 2:2 H), 0.88 (t, J = 7.3 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 145.6, 140.6, 134.3, 128.9, 127.5, 125.3, 119.3, 115.3, 111.9, 47.1, 32.5, 23.2, 20.3, 18.6, 14.0. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{17}H_{21}N_2S$, 285.1425; found, 285.1425.

*3-(5-Phenyl-3-(vinylamino)thiophen-2-yl)propanenitrile (**3t**).* 61 mg, 76%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.32. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.46 (m, 2 H), 7.27 (t, J = 7.6 Hz, 2 H), 7.19 (d, J = 7.0 Hz, 1 H), 6.85 (s, 1 H), 5.91 (m, 1 H), 5.22 (dd, J = 17.2 and 1.6 Hz, 1 H), 5.11 (dd, J = 10.3 and 1.4 Hz, 1 H), 3.74 (dt, J = 5.5 and 1.4 Hz, 2 H), 2.94 (m, 3 H), 2.56 (t, J = 7.4 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 145.3, 140.7, 134.4, 136.0, 129.0, 127.6, 125.4, 119.3, 116.6, 115.5, 112.2, 49.8, 23.2, 18.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{16}H_{17}N_2S$, 269.1112; found, 269.1110.

*3-(5-Phenyl-3-(phenylamino)thiophen-2-yl)propanenitrile (**3u**).* 62 mg, 68%; yellow solid. mp 89−90 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.45. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.57 (m, 2 H), 7.39 (t, J = 7.6 Hz, 2 H), 7.28 (m, 3 H), 7.20 (s, 1 H), 6.86 (t, J = 7.3 Hz, 1 H), 6.79 (d, J = 7.7 Hz, 2 H), 5.39 (s, 1 H), 3.13 (t, J = 7.2 Hz, 2 H), 2.68 (t, J = 7.2 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 146.1, 141.3, 138.5, 134.0, 129.6, 129.1, 128.7, 127.9, 125.5, 121.8, 119.5, 119.3, 114.7, 23.5, 19.3. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{19}H_{17}N_2S$, 305.1112; found, 305.1110.

DOI: 10.1021/acs.joc.8b03175
J. Org. Chem. 2019, 84, 2178−2190

*3-(4-(Benzylamino)-[2,2′-bithiophen]-5-yl)propanenitrile (**3v**).* 73 mg, 75%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.42. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.30 (m, 4 H), 7.23 (m, 1 H), 7.19 (s, 1 H), 7.10 (dd, J = 5.1 and 1.1 Hz, 1 H), 7.02 (dd, J = 3.6 and 1.1 Hz, 1 H), 6.91 (dd, J = 5.1 and 3.6 Hz, 1 H), 6.73 (br, 1 H), 4.26 (s, 2 H), 2.87 (t, J = 7.4 Hz, 2 H), 2.48 (t, J = 7.4 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 145.1, 139.6, 137.6, 134.1, 128.8, 127.9, 127.8, 127.6, 124.4, 123.4, 119.2, 116.2, 111.8, 51.5, 23.1, 18.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{18}H_{17}N_2S_2$, 325.0833; found, 325.0835.

*(E)-3-(5-(3-Methylstyryl)-3-(phenylamino)thiophen-2-yl)-propanenitrile (**3w**).* 63 mg, 61%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.35. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.22 (m, 5 H), 7.07 (m, 3 H), 6.90 (s, 1 H), 6.85 (d, J = 3.6 Hz, 1 H), 6.82 (d, J = 5.1 Hz, 1 H), 6.74 (m, 1 H), 6.72 (s, 1 H), 3.06 (t, J = 7.1 Hz, 2 H), 2.61 (t, J = 7.1 Hz, 2 H), 2.36 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 145.9, 139.8, 138.4, 138.1, 136.7, 129.5, 128.8, 128.7, 128.5, 127.7, 127.2, 124.3, 123.7, 121.3, 119.4, 119.2, 114.7, 23.6, 21.5, 19.1. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{22}H_{21}N_2S$, 345.1425; found, 345.1427.

*3-(3-(Benzylamino)-5-methylthiophen-2-yl)propanenitrile (**3x**).* 58 mg, 75%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.35. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.26, 7.20 (m each, 4:1 H), 6.32 (s, 1 H), 4.19 (s, 2 H), 3.02 (br, 1 H), 2.78 (t, J = 7.4 Hz, 2 H), 2.40 (t, J = 7.4 Hz, 2 H), 2.28 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 144.2, 139.9, 136.8, 128.7, 127.7, 127.4, 119.8, 119.4, 118.3, 51.5, 22.9, 18.8, 15.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{15}H_{17}N_2S$, 257.1112; found, 257.1112.

*3-(3-(Benzylamino)-5-phenylthiophen-2-yl)-4-phenylbutanenitrile (**4a**).* 99 mg, 81%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.42. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.48, 7.19, 7.03 (m each, 2:11:2 H), 6.77 (s, 1 H), 4.05 (dd, J = 39.7 and 13.8 Hz, 2 H), 3.31 (m, 1 H), 2.95 (m, 2 H), 2.49 (m, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 145.5, 140.6, 139.6, 138.4, 134.3, 129.2, 128.9, 128.7, 128.7, 127.7, 127.5, 127.4, 127.0, 125.3, 118.5, 117.7, 115.5, 51.4, 42.2, 37.1, 24.2. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{27}H_{25}N_2S$, 409.1738; found, 409.1739.

*tert-Butyl 2-(3-(Benzylamino)-5-phenylthiophen-2-yl)-3-cyanopropanoate (**4b**).* 98 mg, 78%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.45. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.41, 7.22 (m each, 2:8 H), 6.83 (s, 1 H), 4.30 (s, 2 H), 3.90 (dd, J = 8.7 and 6.9 Hz, 1 H), 2.82 (m, 2 H), 1.36 (s, 9 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 169.4, 146.5, 141.7, 139.6, 134.1, 128.9, 128.8, 127.8, 127.5, 127.4, 125.4, 117.8, 115.3, 108.4, 83.4, 50.7, 42.1, 27.9, 20.0. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{25}H_{27}N_2O_2S$, 419.1793; found, 419.1793.

*tert-Butyl 2-(4-(Benzylamino)-[2,2′-bithiophen]-5-yl)-3-cyanopropanoate (**4c**).* 103 mg, 81%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.45. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.27 (m, 5 H), 7.10 (dd, J = 5.1 and 1.1 Hz, 1 H), 7.01 (dd, J = 3.6 and 1.1 Hz, 1 H), 6.89 (dd, J = 5.1 and 3.6 Hz, 1 H), 6.83 (s, 1 H), 4.29 (s, 2 H), 3.88 (dd, J = 8.6 and 6.9 Hz, 1 H), 2.95 (dd, J = 16.7 and 6.9 Hz, 1 H), 2.68 (dd, J = 16.7 and 6.9 Hz, 1 H), 1.36 (s, 9 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 169.3, 146.2, 139.5, 137.2, 135.1, 128.8, 127.9, 127.5, 127.5, 124.6, 123.7, 117.7, 115.8, 107.7, 83.5, 50.8, 42.0, 28.0, 20.0. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{23}H_{25}N_2O_2S_2$, 425.1357; found, 425.1357.

*3-(3-(Benzylamino)-5-phenylthiophen-2-yl)-3-(4-(tert-butyl)-phenyl)propanenitrile (**4d**).* 99 mg, 73%; yellow solid. mp 94−95 °C (recrystallized from petroleum ether and ethyl acetate). R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.52. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.54, 7.18 (m each, 2:2 H), 7.43−7.25 (m, 10 H), 6.96 (s, 1 H), 4.45 (t, J = 7.5 Hz, 1 H), 4.38−4.17 (m, 2 H), 3.57 (br, 1 H), 3.06 (m, 2 H), 1.35 (s, 9 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 151.0, 144.9, 140.6, 139.6, 137.2, 134.3, 128.9, 128.7, 127.6, 127.4, 127.4, 127.2, 126.2, 125.4, 118.4, 116.5, 115.7, 51.0, 40.2, 34.7, 31.4, 25.0. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{30}H_{31}N_2S$, 451.2208; found, 451.2208.

*3-(4-(tert-Butyl)phenyl)-3-(3-((furan-2-ylmethyl)amino)-5-phenylthiophen-2-yl)propanenitrile (**4e**).* 100 mg, 76%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.61. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.56, 7.39, 7.29 (m each, 2:5:3 H), 7.00 (s, 1 H), 6.31 (dd, J = 3.1 and 1.9 Hz, 1 H), 6.22−5.90 (dd, J = 3.1 and 1.9 Hz, 1 H), 4.45 (t, J = 7.5 Hz, 1 H), 4.27 (s, 2 H), 3.05 (m, 2 H), 1.35 (s, 9 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 153.1, 150.9, 144.3, 142.0, 140.7, 137.1, 134.3, 128.9, 127.6, 127.1, 126.2, 125.4, 118.4, 118.3, 117.0, 116.0, 110.5, 44.3, 40.1, 34.6, 31.4, 25.0. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{28}H_{29}N_2OS$, 441.2001; found, 441.2000.

*Methyl 4-(3-(Benzylamino)-5-phenylthiophen-2-yl)-5-cyano-3,3-dimethyl-pentanoate (**4f**).* 91 mg, 70%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.32. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.55 (m, 2 H), 7.50−7.18 (m, 8 H), 6.95 (s, 1 H), 4.44 (s, 2 H), 3.77 (m, 1 H), 3.63 (s, 3 H), 2.82−2.25 (m, 4 H), 1.21 and 1.14 (s each, 3:3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 173.0, 147.9, 141.3, 140.1, 134.3, 128.8, 128.7, 127.5, 127.5, 127.2, 125.3, 119.2, 115.0, 113.2, 51.6, 51.1, 44.4, 42.0, 37.4, 25.5, 24.5, 21.3. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{26}H_{29}N_2O_2S$, 433.1950; found, 433.1950.

*3-(3-(Benzylamino)-5-phenylthiophen-2-yl)-3-phenylbutanenitrile (**4g**).* 93 mg, 76%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.42. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.45, 7.28, 7.14, 6.81 (m each, 2:8:4:2 H), 3.96 (s, 2 H), 3.11 (q, J = 16.2 Hz, 2 H), 2.83 (br, 1 H), 1.83 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 144.2, 144.0, 139.3, 139.1, 134.3, 129.3, 129.0, 128.6, 127.8, 127.5, 127.2, 127.2, 126.3, 125.3, 119.8, 117.8, 115.9, 50.5, 42.9, 29.6, 28.6. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{27}H_{25}N_2S$, 409.1738; found, 409.1738.

*3-(3-(Benzylamino)-5-phenylthiophen-2-yl)-2-methylpropanenitrile (**4h**).* 72 mg, 72%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.22. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.43, 7.28, 7.19 (m each, 2:7:1 H), 6.88 (s, 1 H), 4.30 (s, 2 H), 2.94, 2.76 (m each, 1:2 H), 1.30 (d, J = 6.7 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 146.0, 141.0, 139.7, 134.3, 128.9, 128.8, 127.7, 127.6, 127.5, 125.4, 122.9, 115.4, 111.1, 51.5, 31.2, 27.1, 17.6. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{21}H_{21}N_2S$, 333.1425; found, 333.1425.

*2-Benzyl-3-(3-(benzylamino)-5-phenylthiophen-2-yl)-propanenitrile (**4i**).* 97 mg, 79%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.42.^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.55 (m, 2 H), 7.40−7.26 (m, 13 H), 6.99 (s, 1 H), 4.37 (s, 2 H), 3.10−2.91 (m, 5 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 146.0, 140.9, 139.7, 136.7, 134.2, 129.1, 128.9, 128.8, 128.7, 127.7, 127.5, 127.4, 127.4, 125.3, 121.7, 115.4, 110.7, 51.3, 37.5, 35.0, 29.0. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{27}H_{25}N_2S$, 409.1738; found, 409.1732.

*2-((3-(Benzylamino)-5-phenylthiophen-2-yl)methyl)pent-4-enenitrile (**4j**).* 73 mg, 68%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.50. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.43, 7.28 (m, 2:8 H), 6.87 (s, 1 H), 5.76, 5.16 (m, 1:2 H), 4.29 (s, 2 H), 2.91 (m, 1:2:3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 146.1, 141.1, 139.7, 134.3, 132.9, 128.9, 128.8, 127.8, 127.6, 127.5, 125.4, 121.6, 119.6, 115.5, 111.0, 51.5, 35.4, 32.8, 28.9. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{23}H_{23}N_2S$, 359.1582; found, 359.1583.

*4-(3-(Benzylamino)-5-phenylthiophen-2-yl)butanenitrile (**4k**).* 69 mg, 69%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.18. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.43, 7.28 (m each, 2:8 H), 6.87 (s, 1 H), 4.28 (s, 2 H), 2.68, 2.30 (t, J = 7.1 Hz, 2:3 H), 1.87 (m, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 145.1, 140.0, 139.9, 134.5, 128.9, 128.8, 127.7, 127.5, 127.4, 125.3, 119.7, 115.6, 114.1, 51.6, 26.3, 25.1, 16.4. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{21}H_{21}N_2S$, 333.1425; found, 333.1424.

*4-(3-(Benzylamino)-5-phenylthiophen-2-yl)-2,2-dimethylbutanenitrile (**4l**).* 82 mg, 76%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.31. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.40 (m, 2 H), 7.32−7.06 (m, 8 H), 6.84 (s, 1 H), 4.27 (s, 2 H), 2.73−2.53 (m, 2 H), 1.79−1.58 (m, 2 H), 1.28 (m, 6 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 144.3, 140.0, 139.4, 134.6, 128.9, 128.7, 127.6, 127.4, 127.2, 125.2, 124.8, 115.6, 115.5, 51.6, 41.5, 32.4, 26.6, 22.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{23}H_{25}N_2S$, 361.1738; found, 361.1739.

DOI: 10.1021/acs.joc.8b03175
J. Org. Chem. 2019, 84, 2178−2190

*4-(3-(Benzylamino)-5-(2-fluorophenyl)thiophen-2-yl)-2,2-dimethylbutanenitrile (**4m**).* 95 mg, 84%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.35. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.42, 7.26, 7.19, 7.08, 7.00 (m, 1:4:1:1:3 H), 4.27 (s, 2 H), 3.15 (br, 1 H), 2.80−2.54 (m, 2 H), 1.79−1.57 (m, 2 H), 1.28 (s, 6 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 159.0 (d, J = 248.3 Hz), 144.1, 139.9, 132.4 (d, J = 3.3 Hz), 128.7, 128.2 (d, J = 8.3 Hz), 128.0 (d, J = 3.5 Hz), 127.7, 127.4, 124.7, 124.4 (d, J = 3.4 Hz), 122.4 (d, J = 12.4 Hz), 118.9 (d, J = 7.1 Hz), 116.6 (d, J = 4.3 Hz), 116.2, 51.6, 41.5, 32.5, 26.6, 22.6. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{23}H_{24}FN_2S$, 379.1644; found, 379.1645.

*2,2-Dimethyl-4-(5-phenyl-3-(phenylamino)thiophen-2-yl)-butanenitrile (**4n**).* 83 mg, 80%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.45. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.44, 7.26, 7.15, 6.70 (m each, 2:2:3:3 H), 7.09 (s, 1 H), 5.19 (br, 1 H), 2.81, 1.78, 1.25 (m each, 2:2:6 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 146.1, 139.8, 137.2, 134.3, 131.0, 129.4, 129.0, 127.6, 125.2, 124.8, 121.4, 119.2, 114.6, 41.9, 32.4, 26.6, 23.2. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{22}H_{23}N_2S$, 347.1582; found, 347.1582.

*5-(3-(Benzylamino)-5-phenylthiophen-2-yl)-2-methylpentanenitrile (**4o**).* 66 mg, 61%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.42. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.44, 7.21 (m each, 2:8 H), 6.87 (s, 1 H), 4.28 (s, 2 H), 2.54, 1.66, 1.23, 1.18 (m each, 3:4:3:1 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 144.4, 140.0, 139.4, 134.7, 128.9, 128.8, 127.8, 127.5, 127.2, 125.2, 123.0, 116.4, 115.5, 51.7, 33.4, 27.9, 26.0, 25.5, 18.1. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{23}H_{25}N_2S$, 361.1738; found, 361.1737.

*5-(3-(Benzylamino)-5-phenylthiophen-2-yl)-2-phenylpentanenitrile (**4p**).* 65 mg, 51%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.20. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.42, 7.23 (m each, 2:13 H), 6.86 (s, 1 H), 4.25 (s, 2 H), 2.55 (t, J = 7.2 Hz, 1 H), 3.71, 1.89, 1.72 (m, 2:2:2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 144.4, 139.9, 139.4, 135.8, 134.7, 129.2, 128.9, 128.8, 128.2, 127.8, 127.5, 127.4, 127.2, 125.2, 120.8, 116.2, 115.4, 51.7, 37.3, 35.1, 27.8, 25.8. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{28}H_{27}N_2S$, 423.1895; found, 423.1898.

*5-(3-(Phenethylamino)-5-phenylthiophen-2-yl)-2-phenylpentanenitrile (**4q**).* 72 mg, 55%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.28. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.45, 7.27, 7.15 (m each, 2:8:5 H), 6.87 (s, 1 H), 3.69, 3.35, 2.80, 2.41, 1.70 (m each, 1:2:2:2:5 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 144.1, 139.4, 139.3, 135.7, 134.7, 129.2, 128.9, 128.9, 128.7, 128.2, 127.3, 127.2, 126.6, 125.2, 120.8, 116.1, 115.3, 48.4, 37.2, 36.3, 35.0, 27.7, 25.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{29}H_{29}N_2S$, 437.2051; found, 437.2051.

*6-(3-(Benzylamino)-5-phenylthiophen-2-yl)hexanenitrile (**4r**).* 49 mg, 45%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.12. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.42, 7.25, 7.13 (m each, 2:7:1 H), 6.87 (s, 1 H), 4.26 (s, 2 H), 3.73 (br, 1 H), 2.50 (t, J = 7.4 Hz, 2 H), 2.22, 1.56, 1.42 (m each, 2:4:2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 144.1, 140.0, 139.1, 134.7, 128.9, 128.7, 127.8, 127.4, 127.1, 125.2, 119.8, 117.4, 115.5, 51.8, 29.8, 28.3, 26.3, 25.3, 17.2. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{23}H_{25}N_2S$, 361.1738; found, 361.1739.

*3-(3-(Benzylamino)-5-phenylthiophen-2-yl)-1,2,2-trimethylcyclopentanecarbonitrile (**4s**).* 60 mg, 50%; yellow liquid. R_f (petroleum ether/ethyl acetate = 4:1, v/v) = 0.65. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.31, 7.18 (m each, 9:1 H), 6.04 (s, 1 H), 4.78 (br, 1 H), 4.36 (s, 2 H), 2.86, 1.90, 1.19 (m each, 1:2:5 H), 0.86, 0.54 (s each, 3:3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 170.0, 157.7, 143.9, 139.6, 139.4, 128.7, 128.6, 128.6, 128.4, 127.9, 127.8, 127.3, 100.2, 56.4, 54.2, 49.7, 47.6, 32.2, 26.7, 20.2, 19.5, 10.7. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{26}H_{29}N_2S$, 401.2051; found, 401.2051.

*Typical Procedure for the Gram-Scale Synthesis: Synthesis of 3-(3-(Benzylamino)-5-phenylthiophen-2-yl)propanenitrile (**3a**).* Under a nitrogen atmosphere, a mixture of **1a** (0.95 g, 5.0 mmol), **2a** (1.65 g, 5.5 mmol), CuCl (50 mg, 0.5 mmol), and NaOAc (680 mg, 5.0 mmol) in 20 mL of DMF was stirred at 70 °C for 12 h. After being cooled to ambient temperature, the resultant mixture was purified by silica gel column chromatography (eluent: petroleum ether (60−90 °C)/ethyl acetate, v/v = 30:1) to afford **3a** as a yellow solid (1.37 g, 86%).

TEMPO or BHT-Trapping Radical Experiments. Under a nitrogen atmosphere, a mixture of cyclobutanone oxime ester **1a** (57 mg, 0.3 mmoL), enaminothione **2a** (99 mg, 0.33 mmol), CuCl (3 mg, 0.03 mmol), NaOAc (24 mg, 0.3 mmol), and TEMPO or BHT (0.6 mmol) in DMF (2 mL) was stirred at 70 °C for 12 h. The reaction mixture was analyzed by proton NMR and HRMS (ESI) analyses. HRMS (ESI-TOF) (m/z): [M + H]$^+$ calcd for $C_{13}H_{25}N_2O$, 225.1961; found, 225.1957.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b03175.

X-ray crystallographic data for compound **3a** (CIF)

Experimental procedures for the starting materials **1** and **2**, NMR spectra of the substrates and products, and X-ray crystallographic analysis for compound **3a** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: wanghongmei@dicp.ac.cn.

*E-mail: zkyu@dicp.ac.cn.

ORCID

Yuan He: 0000-0001-6600-8433

Jiang Lou: 0000-0002-5653-1359

Kaikai Wu: 0000-0003-1950-5343

Hongmei Wang: 0000-0003-1057-334X

Zhengkun Yu: 0000-0002-9908-0017

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (21871253 and 21472185) and the National Basic Research Program of China (2015CB856600) for support of our research.

■ REFERENCES

(1) (a) Jun, C. H. Transition Metal-Catalyzed Carbon−Carbon Bond Activation. *Chem. Soc. Rev.* **2004**, *33*, 610−618. (b) Chen, F.; Wang, T.; Jiao, N. Recent Advances in Transition-Metal-Catalyzed Functionalization of Unstrained Carbon−Carbon Bonds. *Chem. Rev.* **2014**, *114*, 8613−8661. (c) Marek, I.; Masarwa, A.; Delaye, P. O.; Leibeling, M. Selective Carbon−Carbon Bond Cleavage for the Stereoselective Synthesis of Acyclic Systems. *Angew. Chem., Int. Ed.* **2015**, *54*, 414−429.

(2) Fumagalli, G.; Stanton, S.; Bower, J. F. Recent Methodologies that Exploit C−C Single-Bond Cleavage of Strained Ring Systems by Transition Metal Complexes. *Chem. Rev.* **2017**, *117*, 9404−9432.

(3) (a) Zard, S. Z. Iminyl Radicals: A Fresh Look at a Forgotten Species (and Some of its Relatives). *Synlett* **1996**, *1996*, 1148−1154. (b) Zard, S. Z. Recent Progress in the Generation and Use of Nitrogen-Centred Radicals. *Chem. Soc. Rev.* **2008**, *37*, 1603−1618.

(4) (a) Boivin, J.; Fouquet, E.; Zard, S. Z. Ring Opening Induced by Iminyl Radicals Derived from Cyclobutanones: New Aspects of Tin Hydride Cleavage of S-Phenyl Sulfenylimines. *J. Am. Chem. Soc.* **1991**, *113*, 1055−1057. (b) Boivin, J.; Fouquet, E.; Zard, S. Z. A New and Synthetically Useful Source of Iminyl Radicals. *Tetrahedron Lett.* **1991**, *32*, 4299−4302. (c) Boivin, J.; Schiano, A.-M.; Zard, S. Z. A Novel and Practical Access to 13-Epi-17-ketosteroids. *Tetrahedron Lett.* **1992**, *33*, 7849−7852. (d) Boivin, J.; Fouquet, E.; Zard, S. Z.

DOI: 10.1021/acs.joc.8b03175
J. Org. Chem. 2019, 84, 2178−2190

Iminyl Radicals: Part II. Ring Opening of Cyclobutyl- and Cyclopentyliminyl Radicals. *Tetrahedron* **1994**, *50*, 1757−1768.
(5) (a) Zhao, J.-F.; Duan, X.-H.; Gu, Y.-R.; Gao, P.; Guo, L.-N. Iron-Catalyzed Decarboxylative Olefination of Cycloketone Oxime Esters with α,β-Unsaturated Carboxylic Acids *via* C−C Bond Cleavage. *Org. Lett.* **2018**, *20*, 4614−4617. (b) Yang, L.; Gao, P.; Duan, X.-H.; Gu, Y.-R.; Guo, L.-N. Direct C−H Cyanoalkylation of Quinoxalin-2(1H)-ones *via* Radical C−C Bond Cleavage. *Org. Lett.* **2018**, *20*, 1034−1037. (c) Zhang, J.-Y.; Duan, X.-H.; Yang, J.-C.; Guo, L.-N. Redox-Neutral Cyanoalkylation/Cyclization of Olefinic 1,3-Dicarbonyls with Cycloketone Oxime Esters: Access to Cyanoalkylated Dihydrofurans. *J. Org. Chem.* **2018**, *83*, 4239−4249. (d) Wu, J.; Zhang, J.-Y.; Gao, P.; Xu, S.-L.; Guo, L.-N. Copper-Catalyzed Redox-Neutral Cyanoalkylarylation of Activated Alkenes with Cyclobutanone Oxime Esters. *J. Org. Chem.* **2018**, *83*, 1046−1055. (e) Gu, Y.-R.; Duan, X.-H.; Yang, L.; Guo, L.-N. Direct C−H Cyanoalkylation of Heteroaromatic *N*-Oxides and Quinones *via* C−C Bond Cleavage of Cyclobutanone Oximes. *Org. Lett.* **2017**, *19*, 5908−5911. (f) Zhao, J.-F.; Gao, P.; Duan, X.-H.; Guo, L.-N. Iron-Catalyzed Ring-Opening/Allylation of Cyclobutanone Oxime Esters with Allylic Sulfones. *Adv. Synth. Catal.* **2018**, *360*, 1775−1779. (g) Ai, W. Y.; Liu, Y. Q.; Wang, Q.; Lu, Z. L.; Liu, Q. Cu-Catalyzed Redox-Neutral Ring Cleavage of Cycloketone *O*-Acyl Oximes: Chemodivergent Access to Distal Oxygenated Nitriles. *Org. Lett.* **2018**, *20*, 409−412. (h) Zhao, B. L.; Shi, Z. Z. Copper-Catalyzed Intermolecular Heck-Like Coupling of Cyclobutanone Oximes Initiated by Selective C−C Bond Cleavage. *Angew. Chem., Int. Ed.* **2017**, *56*, 12727−12731. (i) Nishimura, T.; Yoshinaka, T.; Nishiguchi, Y.; Maeda, Y.; Uemura, S. Iridium-Catalyzed Ring Cleavage Reaction of Cyclobutanone *O*-Benzoyloximes Providing Nitriles. *Org. Lett.* **2005**, *7*, 2425−2427.
(6) (a) Wang, P.-Z.; Yu, X.-Y.; Li, C.-Y.; He, B.-Q.; Chen, J.-R.; Xiao, W.-J. A Photocatalytic Iminyl Radical-Mediated C−C Bond Cleavage/Addition/Cyclization Cascade for the Synthesis of 1,2,3,4-Tetrahydrophenanthrenes. *Chem. Commun.* **2018**, *54*, 9925−9928. (b) Yu, X.-Y.; Chen, J.-R.; Wang, P.-Z.; Yang, M.-N.; Liang, D.; Xiao, W.-J. A Visible-Light-Driven Iminyl Radical-Mediated C−C Single Bond Cleavage/Radical Addition Cascade of Oxime Esters. *Angew. Chem., Int. Ed.* **2018**, *57*, 738−743. (c) Dauncey, E. M.; Morcillo, S. P.; Douglas, J. J.; Sheikh, N. S.; Leonori, D. Photoinduced Remote Functionalisations by Iminyl Radical Promoted C−C and C−H Bond Cleavage Cascades. *Angew. Chem., Int. Ed.* **2018**, *57*, 744−748. (d) Li, L. Y.; Chen, H. G.; Mei, M. J.; Zhou, L. Visible-Light Promoted γ-Cyanoalkyl Radical Generation: Three-Component Cyanopropylation /Etherification of Unactivated Alkenes. *Chem. Commun.* **2017**, *53*, 11544−11547. (e) Shen, X.; Zhao, J.-J.; Yu, S. Y. Photoredox-Catalyzed Intermolecular Remote C−H and C−C Vinylation *via* Iminyl Radicals. *Org. Lett.* **2018**, *20*, 5523−5527.
(7) Jackman, M. M.; Im, S.; Bohman, S. R.; Lo, C. C. L.; Garrity, A. L.; Castle, S. L. Synthesis of Functionalized Nitriles by Microwave-Promoted Fragmentations of Cyclic Iminyl Radicals. *Chem. - Eur. J.* **2018**, *24*, 594−598.
(8) (a) Vulovic, B.; Watson, D. A. Heck-Like Reactions Involving Heteroatomic Electrophiles. *Eur. J. Org. Chem.* **2017**, *2017*, 4996−5009. (b) Tang, X. D.; Wu, W. Q.; Zeng, W.; Jiang, H. F. Copper-Catalyzed Oxidative Carbon−Carbon and/or Carbon−Heteroatom Bond Formation with O_2 or Internal Oxidants. *Acc. Chem. Res.* **2018**, *51*, 1092−1105.
(9) (a) Yu, X.-Y.; Zhao, Q.-Q.; Chen, J.; Chen, J.-R.; Xiao, W.-J. Copper-Catalyzed Radical Cross-Coupling of Redox-Active Oxime Esters, Styrenes, and Boronic Acids. *Angew. Chem., Int. Ed.* **2018**, *57*, 15505−15509. (b) He, B.-Q.; Yu, X.-Y.; Wang, P.-Z.; Chen, J.-R.; Xiao, W.-J. A Photoredox Catalyzed Iminyl Radical-Triggered C−C Bond Cleavage/Addition/Kornblum Oxidation Cascade of Oxime Esters and Styrenes: Synthesis of Ketonitriles. *Chem. Commun.* **2018**, *54*, 12262−12265.
(10) Zhang, J.-J.; Duan, X.-H.; Wu, Y.; Yang, J.-C.; Guo, L.-N. Transition-Metal Free C−C Bond Cleavage/Borylation of Cycloketone Oxime Esters. *Chem. Sci.* **2019**, *10*, 161−166.
(11) An, Z. Y.; Jiang, Y.; Guan, X.; Yan, R. L. Copper-Catalyzed Tandem Aerobic Oxidative Cyclization for the Synthesis of 4-Cyanoalkylpyrrolo[1,2-a]- quinoxalines from 1-(2-Aminophenyl) pyrroles and Cyclobutanone Oxime Esters. *Chem. Commun.* **2018**, *54*, 10738−10741.
(12) (a) Boivin, J.; Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Schiano, A.-M.; Zard, S. Z. Iminyl, Amidyl, and Carbamyl Radicals from *O*-Benzoyl Oximes and *O*-Benzoyl Hydroxamic Acid Derivatives. *Tetrahedron* **1995**, *51*, 6517−6528. (b) Nishimura, T.; Nishiguchi, Y.; Maeda, Y.; Uemura, S. Palladium-Catalyzed Transformation of Cyclobutanone *O*-Benzoyloximes to Nitriles *via* C−C Bond Cleavage. *J. Org. Chem.* **2004**, *69*, 5342−5347. (c) Kurouchi, H.; Singleton, D. A. Labelling and Determination of the Energy in Reactive Intermediates in Solution Enabled by Energy-dependent Reaction Selectivity. *Nat. Chem.* **2018**, *10*, 237−241.
(13) (a) Feldman, A. W.; Romesberg, F. E. Expansion of the Genetic Alphabet: A Chemist's Approach to Synthetic Biology. *Acc. Chem. Res.* **2018**, *51*, 394−403. (b) Wang, C. L.; Dong, H. L.; Hu, W. P.; Liu, Y.; Zhu, D. B. Semiconducting π-Conjugated Systems in Field-Effect Transistors: A Material Odyssey of Organic Electronics. *Chem. Rev.* **2012**, *112*, 2208−2267. (c) Takimiya, K.; Osaka, I.; Mori, T.; Nakano, M. Organic Semiconductors Based on [1]Benzothieno[3,2-*b*][1]benzothiophene Substructure. *Acc. Chem. Res.* **2014**, *47*, 1493−1502. (d) Lepri, S.; Nannetti, G.; Muratore, G.; Cruciani, G.; Ruzziconi, R.; Mercorelli, B.; Palu, G.; Loregian, A.; Goracci, L. Optimization of Small-Molecule Inhibitors of Influenza Virus Polymerase: From Thiophene-3-carboxamide to Polyamido Scaffolds. *J. Med. Chem.* **2014**, *57*, 4337−4350.
(14) (a) Meng, L. K.; Fujikawa, T.; Kuwayama, M.; Segawa, Y.; Itami, K. Thiophene-Fused π-Systems from Diarylacetylenes and Elemental Sulfur. *J. Am. Chem. Soc.* **2016**, *138*, 10351−10355. (b) Zhang, C.; Zhu, X. Thieno[3,4-b]thiophene-Based Novel Small-Molecule Optoelectronic Materials. *Acc. Chem. Res.* **2017**, *50*, 1342−1350.
(15) (a) Fleming, F. F. Nitrile-Containing Natural Products. *Nat. Prod. Rep.* **1999**, *16*, 597−606. (b) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. Nitrile-Containing Pharmaceuticals: Efficacious Roles of the Nitrile Pharmacophore. *J. Med. Chem.* **2010**, *53*, 7902−7917.
(16) Beletskaya, I. P.; Ananikov, V. P. Transition-Metal-Catalyzed C−S, C−Se, and C−Te Bond Formation via Cross-Coupling and Atom-Economic Addition Reactions. *Chem. Rev.* **2011**, *111*, 1596−1636.
(17) (a) Hassanpour, A.; De Carufel, C. A.; Bourgault, S.; Forgione, P. Synthesis of 2,5-Diaryl-Substituted Thiophenes as Helical Mimetics: Towards the Modulation of Islet Amyloid Polypeptide (IAPP) Amyloid Fibril Formation and Cytotoxicity. *Chem. - Eur. J.* **2014**, *20*, 2522−2528. (b) Song, C. L.; Yi, H.; Dou, B.; Li, Y. Y.; Singh, A. K.; Lei, A. W. Visible-Light-Mediated C2-Amination of Thiophenes by Using DDQ as an Organophotocatalyst. *Chem. Commun.* **2017**, *53*, 3689−3692.
(18) Han, T.; Wang, Y.; Li, H.-L.; Luo, X.-Y.; Deng, W.-P. Synthesis of Polysubstituted 3-Aminothiophenes from Thioamides and Allenes *via* Tandem Thio-Michael Addition/Oxidative Annulation and 1,2-Sulfur Migration. *J. Org. Chem.* **2018**, *83*, 1538−1542.
(19) (a) Mancuso, R.; Gabriele, B. Recent Advances in the Synthesis of Thiophene Derivatives by Cyclization of Functionalized Alkynes. *Molecules* **2014**, *19*, 15687−15719. (b) Wu, B.; Yoshikai, N. Versatile Synthesis of Benzothiophenes and Benzoselenophenes by Rapid Assembly of Arylzinc Reagents, Alkynes, and Elemental Chalcogens. *Angew. Chem., Int. Ed.* **2013**, *52*, 10496−10499.
(20) Seed, A. Synthesis of Self-Organizing Mesogenic Materials Containing a Sulfur-Based Five-Membered Heterocyclic Core. *Chem. Soc. Rev.* **2007**, *36*, 2046−2069.
(21) (a) Huang, Y. J.; Dömling, A. The Gewald Multicomponent Reaction. *Mol. Diversity* **2011**, *15*, 3−33. (b) Thomas, J.; Jana, S.; Sonawane, M.; Fiey, B.; Balzarini, J.; Liekens, S.; Dehaen, W. A New Four-Component Reaction Involving the Michael Addition and the

DOI: 10.1021/acs.joc.8b03175
J. Org. Chem. 2019, 84, 2178−2190

Gewald Reaction, Leading to Diverse Biologically Active 2-Aminothiophenes. *Org. Biomol. Chem.* **2017**, *15*, 3892−3900.
(22) (a) Guo, W.-S.; Wen, L.-R.; Li, M. *β*-Ketothioamides: Efficient Reagents in the Synthesis of Heterocycles. *Org. Biomol. Chem.* **2015**, *13*, 1942−1953. (b) Luo, X.-Y.; Ge, L.-S.; An, X.-L.; Jin, J.-H.; Wang, Y.; Sun, P.-P.; Deng, W.-P. Regioselective Metal-Free One-Pot Synthesis of Functionalized 2-Aminothiophene Derivatives. *J. Org. Chem.* **2015**, *80*, 4611−4617. (c) Wen, L.-R.; He, T.; Lan, M.-C.; Li, M. Three-Component Cascade Annulation of *β*-Ketothioamides Promoted by CF_3CH_2OH: A Regioselective Synthesis of Tetrasubstituted Thiophenes. *J. Org. Chem.* **2013**, *78*, 10617−10628.
(23) Huang, J. J.; Wu, X. W.; Jia, J. M.; Guo, X. K.; Xue, X.; Jiang, Z. Y.; Zhang, S. L.; Zhang, X. J.; Sun, H. P.; You, Q. D. Novel IKK*β* Inhibitors Discovery Based on the Co-crystal Structure by Using Binding-Conformation-Based and Ligand-Based Method. *Eur. J. Med. Chem.* **2013**, *63*, 269−278.
(24) Ogawa, K.; Radke, K. R.; Rothstein, S. D.; Rasmussen, S. C. Synthesis of Secondary and Tertiary Aminothiophenes via Palladium-Catalyzed Amination. *J. Org. Chem.* **2001**, *66*, 9067−9070.
(25) (a) Chen, B. H.; Ni, H. C.; Guo, X.; Zhang, G. L.; Yu, Y. P. Facile Preparation of 3,5-Disubstituted-4-Aminothiophene-2-Carbaldehyde from A Novel Unexpected Domino Reaction of Vinyl Azides and 1,4-Dithiane-2,5-diol. *RSC Adv.* **2014**, *4*, 44462−44465. (b) Chavan, S. M.; Toche, R. B.; Patil, V. M.; Aware, P. B.; Patil, P. S. Reactions of Ketene Dithioacetal for A New Versatile Synthesis of 4,5-Substituted 3-Aminothiophene-2-Carboxylate Derivatives. *J. Sulfur Chem.* **2016**, *37*, 426−437.
(26) Huang, F.; Liu, Z. Q.; Wang, Q. N.; Lou, J.; Yu, Z. K. Copper-Catalyzed Formal Carbene Migratory Insertion into Internal Olefinic C = C Bonds with *N*-Tosylhydrazones to Access Iminofuran and *2*(3H)-Furanone Derivatives. *Org. Lett.* **2017**, *19*, 3660−3663.
(27) (a) Lee, J. S.; Lee, D. J.; Kim, B. S.; Kim, K. Reactions of Thiobenzoylketene *S,N*-Acetals with Silyl Enol Ethers of Cyclic Ketones in the Presence of Desilylating Reagents: Formation and Desulfurization of Thienolactams. *J. Chem. Soc., Perkin Trans.* **2001**, *1*, 2774−2780. (b) Kim, B. S.; Kim, K. A Facile and Convenient Synthesis of 3-Alkylamino-5-Arylthiophenes with A Variety of Substituents at C-2 and Studies of Reaction Mechanisms. *J. Org. Chem.* **2000**, *65*, 3690−3699. (c) Kim, B. S.; Choi, K. S.; Kim, K. Reactions of Thioaroylketene *S,N*-Acetals with 1,3-Dicarbonyl Compounds in the Presence of Mercury(II) Acetate: A General Route to 2-Acyl- and 2-Aroyl-3-(Alkylamino)-5-Arylthiophenes and 2-(Ethoxycarbonyl)-3- (Methylamino)-5-Arylthiophenes. *J. Org. Chem.* **1998**, *63*, 6086−6087. (d) Kim, K.; Kim, B. S.; Choi, K. S. Thioaroylketene *S,N*-Acetals: Versatile Intermediates for the Synthesis of 3-Alkylamino-5-Arylthiophenes with a Variety of Functional Group at C-2. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, *153*, 393−394.
(28) Song, H. M.; Kim, K. Rhodium(II)-Mediated Reactions of Thiobenzoylketene *S,N*-Acetals with *α*-Diazo Carbonyl Compounds: Synthesis of 2-Substituted 3-Alkylamino-5-Phenylthiophenes. *J. Chem. Soc., Perkin Trans.* **2002**, *1*, 2414−2417.
(29) Zhang, L.; Dong, J. H.; Xu, X. X.; Liu, Q. Chemistry of Ketene *N,S*-Acetals: An Overview. *Chem. Rev.* **2016**, *116*, 287−322.
(30) Liu, Z. Q.; Wu, P.; He, Y.; Yang, T.; Yu, Z. K. [4 + 1] Cycloaddition of Enaminothiones and Aldehyde *N*-Tosylhydrazones toward 3-Aminothiophenes. *Adv. Synth. Catal.* **2018**, *360*, 4381−4392.
(31) Huang, H. W.; Xu, Z. H.; Ji, X. C.; Li, B.; Deng, G.−J. Thiophene-Fused Heteroaromatic Systems Enabled by Internal Oxidant-Induced Cascade Bis-Heteroannulation. *Org. Lett.* **2018**, *20*, 4917−4920.
(32) (a) Yang, H.-B.; Pathipati, S. R.; Selander, N. Nickel-Catalyzed 1,2-Aminoarylation of Oxime Ester-Tethered Alkenes with Boronic Acids. *ACS Catal.* **2017**, *7*, 8441−8445. (b) Sato, S.; Takeda, N.; Ueda, M.; Miyata, O. Sequential [3,3]-Sigmatropic Rearrangement/Nucleophilic Arylation of *N*-(Benzoyloxy)enamides towards the Preparation of Cyclic *β*-Aryl-*β*-amino Alcohols. *Synthesis* **2016**, *48*, 882−892. (c) Huang, F.; Wu, P.; Wang, L. D.; Chen, J. P.; Sun, C. L.; Yu, Z. K. Copper-Mediated Intramolecular Oxidative C−H/C−H Cross-Coupling of *α*-Oxo Ketene *N,S*-Acetals for Indole Synthesis. *J. Org. Chem.* **2014**, *79*, 10553−10560. (d) Huang, F.; Wu, P.; Wang, L. D.; Chen, J. P.; Sun, C. L.; Yu, Z. K. Copper-Mediated Intramolecular Oxidative C−H/N−H Cross-Coupling of *α*-Alkenoyl Ketene *N,S*-Acetals to Synthesize Pyrrolone Derivatives. *Chem. Commun.* **2014**, *50*, 12479−12481.

DOI: 10.1021/acs.joc.8b03175
J. Org. Chem. 2019, 84, 2178−2190