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Letter

Visible-Light-Induced Formation of Thiavinyl 1,3-Dipoles: A Metal-Free [3+2] Oxidative Cyclization with Alkynes as Easy Access to Thiophenes

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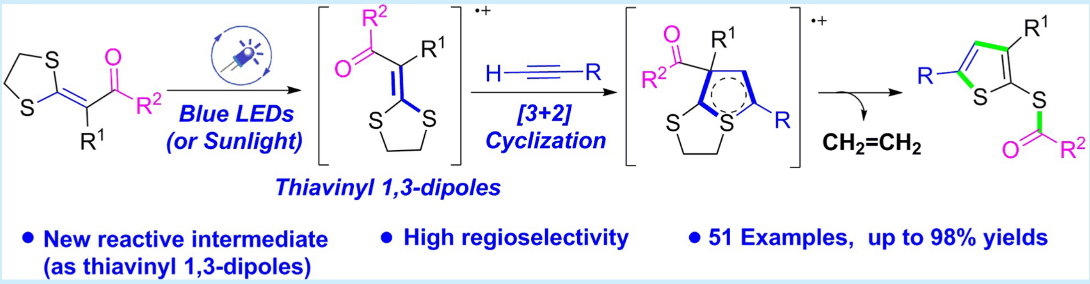

ABSTRACT: A visible-light-induced [3+2] oxidative cyclization of various alkynes with easily available ketene dithioacetals as the previously unknown thiavinyl 1,3-dipoles in the presence of an acridine photosensitizer is reported. A series of multisubstituted thiophenes were achieved regioselectively in ≤98% yields under very mild metal-free conditions without other additives. This reaction could tolerate a wide range of substrates and achieve good efficiency in large-scale syntheses. The reaction mechanism and their applications are described in detail to reveal the reactivity of the new 1,3-dipoles and the selectivity of the reactions.

Heterocyclizations are powerful tools for the synthesis of five-membered heterocycles[1−4] that are often found in natural products[5,6] and synthetic pharmaceuticals[7−9] and widely used in material science and organic synthesis.[10−17] Recent studies revealed that oxidative heterocyclizations[18−21] could evoke novel and useful catalytic transformations, which otherwise are difficult to achieve. For example, the cyclization of ketene dithioacetals,[22−26] a kind of electron-rich olefin, under electrochemical conditions afforded the cyclic amino acid derivatives (Scheme 1a, X = NH).[24] Similarly, (+)-nemorensic acid (Scheme 1a, X = O),[26] the necic acid portion of the macropyrrolizidine alkaloid nemorensine could also be achieved efficiently with the oxidative intramolecular cyclization mentioned above as the key step. In these heterocyclizations, the electron-rich ketene dithioacetal moieties of substrates were activated by losing an electron under electrolysis to generate the corresponding electrophilic radical cation, which further initiates the intramolecular cyclization. Clearly, these transformations efficiently avoid using additional oxidant or transition-metal catalysis, and more importantly, the polarity of the α-carbon atom on the ketene dithioacetal moiety can be reversed. However, considering the difficulty in restraining side reactions, and the limitation of substrates, more simple and efficient synthons and methods are strongly desired for the heterocyclization reactions.

In recent years, visible-light-promoted transformations proved to be efficient in organic synthesis[27−36] because they could provide clean and inexpensive energy sources and green catalytic environments.[37,38] With the aid of photosensitizers,[39−41] the substrates could be easily activated to active radical cations similar to the transformations under electrolysis mentioned above,[22−26] without additional oxidants. As part of our continuous efforts in the construction of carbo/heterocyclic compounds from easily available ketene dithioacetals,[42−46] we envisioned that visible-light-induced cyclizations of ketene dithioacetals with alkynes would lead to the novel [3+2] heterocyclization via the previously unknown thiavinyl 1,3-dipoles (Scheme 1b). To the best of our knowledge, there have been few studies on the photoredox reactions of ketene dithioacetals and the studies have been limited to the coupling reactions with aryldiazonium salts[47] or alkenes[48] or need an other photo-redox-active reactant.[49] There have been few reports about the visible-light-mediated synthesis of thiophenes,[13−17,50−54] with some syntheses of benzothiophenes from alkynes with o-methylthio-arene diazonium salts or 2-halothioanisoles.[55−57] We are glad to see that our proposed [3+2] oxidative cylization of ketene dithioacetals

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Scheme 1. Oxidative Cyclizations

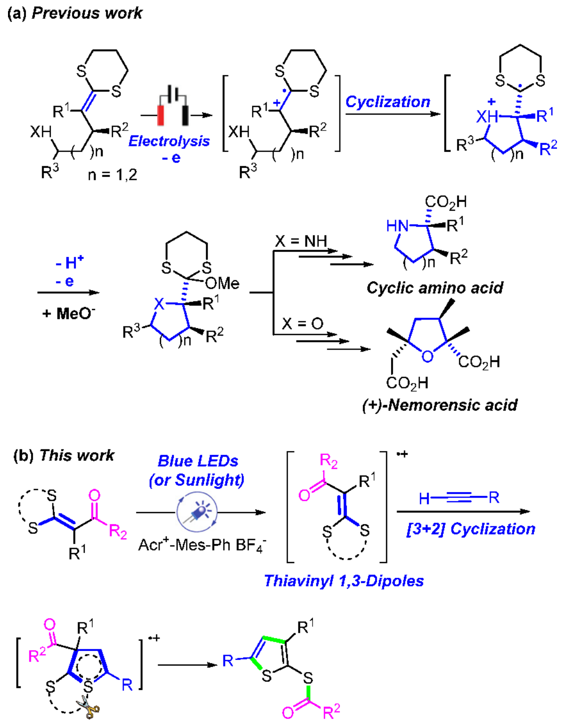
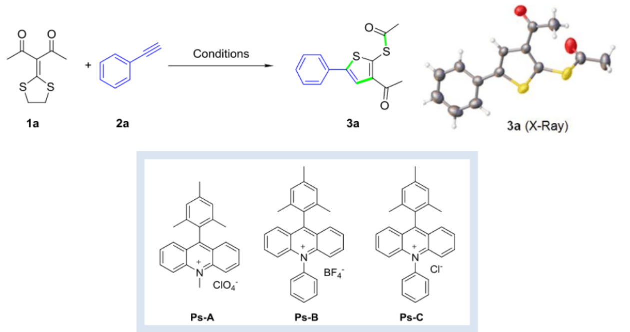


Table 1. Optimization of Reaction Conditions[a]



entry	1a:2a	catalyst (mol %)	solvent	*t* (h)	yield (%)[b]
1	1.3:1	Ps-A (3)	DCE	24	45
2	1.3:1	Ps-B (3)	DCE	24	58
3	1.3:1	Ps-C (3)	DCE	24	12
4	1.3:1	Ru(bpy)$_3$Cl$_2$ (3)	DCE	24	NR[c]
5	1.3:1	Ir(ppy)$_3$ (3)	DCE	24	NR[c]
6	1.3:1	Ps-B (5)	DCE	24	70
7	2:1	Ps-B (5)	DCE	24	84
8	2.5:1	Ps-B (5)	DCE	24	90
9	1:2	Ps-B (5)	DCE	24	64
10	2.5:1	Ps-B (5)	DCE	36	94
11	2.5:1	Ps-B (5)	CH$_3$CN	36	49
12	2.5:1	Ps-B (5)	THF	36	14
13	2.5:1	Ps-B (5)	EtOH	36	trace
14	2.5:1	–	DCE	36	trace
15[d]	2.5:1	Ps-B (5)	DCE	36	NR[c]
16[e]	2.5:1	Ps-B (5)	DCE	36	NO[f]

[a] Reaction conditions: **1a** or **2a** (0.3 mmol scale), solvent (2 mL). [b] Isolated yields. [c] No reaction was observed. [d] Without light. [e] TEMPO (1.0 equiv) was added. [f] No **3a** was observed.

and alkynes (Scheme 1b) could proceed smoothly under extremely simple and mild reaction conditions without using base, acid or oxidants.[58−60] Clearly, α-acyl ketene dithioacetals were activated by visible light to form a previously unknown thiavinyl 1,3-dipole intermediate that thus initiates this [3+2] cyclization.

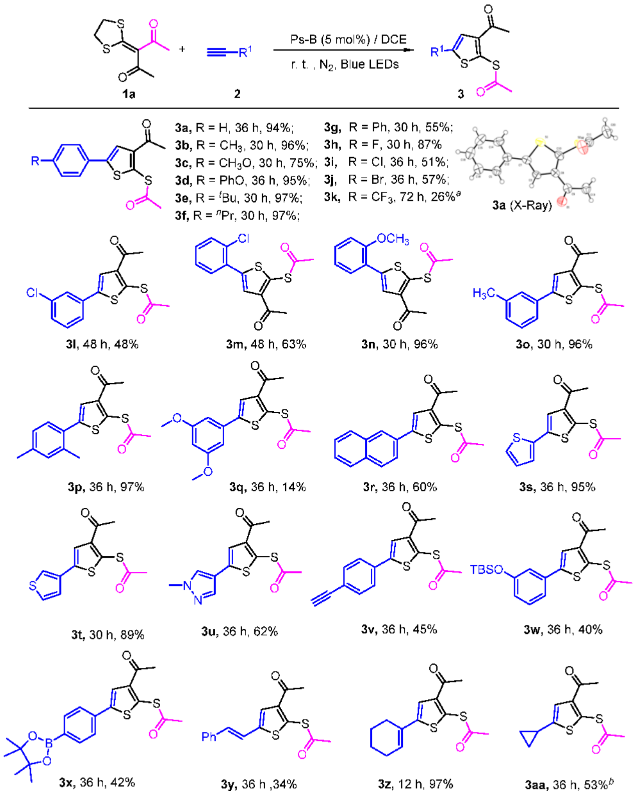
First, the catalytic construction of multisubstituted thiophenes was investigated by the reaction of α,α'-diacetyl ketene dithioacetal **1a** with phenylacetylene **2a** in the presence of an acridine photosensitizer without any other additives under blue light-emitting diode (LED) irradiation (Table 1). Multisubstituted thiophene **3a** (see the single-crystal analysis of **3a** in the Supporting Information) was obtained in 45% isolated yield in the presence of Acr$^+$-Mes ClO$_4^-$ (Ps-A, 3 mol %) in 1,2-dichloroethane (DCE) at room temperature (entry 1). The yield of **3a** was increased to 58% when Acr$^+$-Mes-Ph BF$_4^-$ (Ps-B, 3 mol %) was used as the photosensitizer (entry 2). An obvious decrease in the yield of **3a** was observed with Acr$^+$-Mes-Ph Cl$^-$ (Ps-C) as the photosensitizer (entry 3). No **3a** was observed when a photosensitizer like Ru(bpy)$_3$Cl$_2$ or Ir(ppy)$_3$ was applied (entry 4 or 5, respectively). **3a** was formed in a higher yield when the amount of Ps-B was increased to 5 mol % (entry 6 vs entry 2). Then, the **1a**/**2a** ratio was investigated with 5 mol % Ps-B in DCE (entries 7−9). With a 2.5/1 **1a**/**2a** ratio, **3a** was obtained in 90% yield (entry 8). We are glad to see that the yield of **3a** was increased to 94% when the reaction was performed for 36 h (entry 10). The effect of solvents was also examined, and DCE proved to be the optimal choice (entries 10−13). Furthermore, control experiments showed that nearly no the desired product was observed without the photosensitizer or in the dark (entries 14 and 15). When 1.0 equiv of TEMPO was added, product **3a** was not observed at all (entry 16).

With the optimal reaction conditions (Table 1, entry 10) in hand, the generality of this catalytic [3+2] oxidative cyclization was investigated. As shown in Scheme 2, the reactions of ketene dithioacetal **1a** with various alkynes **2** showed excellent tolerance to alkynes. The reactions of *para*-substituted arynes **2** bearing either electron-donating (**2b−g**) or electron-withdrawing substituents (**2h−j**) on the benzene ring afforded thiophenes **3b−j** in good to excellent yields. Moreover, 4-trifluoromethyl-substituted aryne **2k** could also give the desired **3k**. In addition, *ortho-*, *meta-*, or disubstituted arynes **2l−p** reacted smoothly to furnish thiophenes **3l−p**, respectively. The reaction of 3,5-dimethoxy-substituted aryne **2q** delivered the desired product **3q** in 14% yield. Furthermore, alkynes **2r−u** proved to be the suitable substrates for the [3+2] cyclization. All of these reactions showed high regioselectivity for the formation of multisubstituted thiophenes.

It was noticed that the reaction of 1,4-diethynylbenzene **2v** with **1a** afforded the corresponding thiophene **3v** in 45% yield with one alkynyl group remaining even when 10 equiv of **2v** was added. The borate moiety and silyl substitution on the benzene ring in **2w** and **2x** were tolerant to this reaction, giving more opportunities for further transformations. Reactions of enynes **2y** and **2z** and aliphilic alkyne **2aa** with **1a** could also give the desired thiophenes **3y**, **3z**, and **3aa**, respectively, showing the broad tolerance of this [3+2] heterocyclization to a wide variety of alkynes.

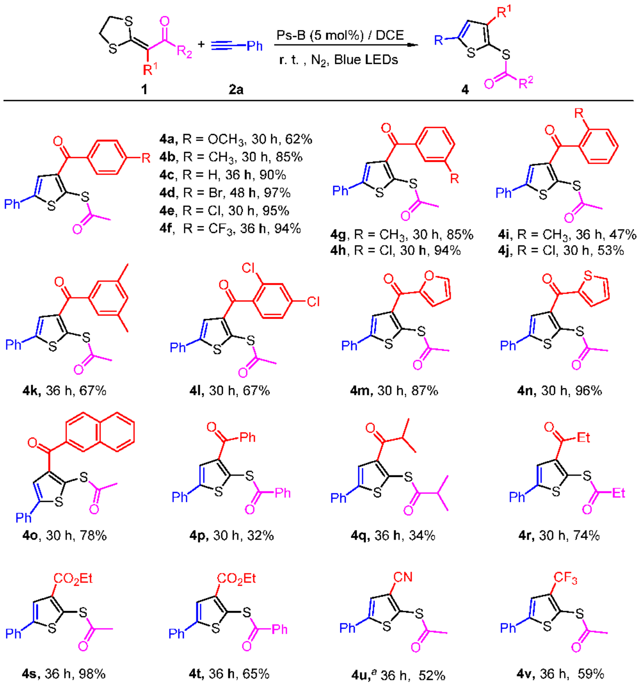
Next, the reactivity of selected ketene dithioacetals **1** as the thiavinyl 1,3-dipoles was investigated (Scheme 3). As a result, phenylacetylene **2a** could react with a wide variety of ketene dithioacetals **1** under the optimal reaction conditions. Multisubstituted thiophene **4c** could be obtained in 90%

Scheme 2. Synthesis of Multisubstituted Thiophenes from Ketene Dithioacetal 1a and Alkynes 2



[a]With 10 mol % Ps-B. [b]With 3 equiv of **2aa**.

Scheme 3. Synthesis of Multisubstituted Thiophenes from Ketene Dithioacetals 1 and Phenylacetylene 2a

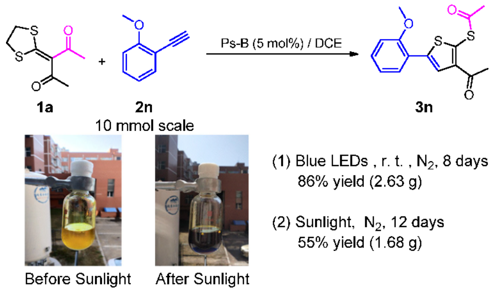


[a]With 10 equiv of ketene dithioacetal **1v**.

yield from the reaction of α-benzoyl-α'-acetyl ketene dithioacetal **1d** with **2a**. α-Aroyl-α'-acetyl ketene dithioacetals bearing *para*-, *meta*-, *ortho*-, and multisubstituted aroyls (**1b, 1c, 1e–m**) furnished thiophenes **4a, 4b, 4d–l**, respectively, in good to excellent yields. Reactions of **2a** with heteroaroyl- and 2-naphthoyl-substituted ketene dithioacetals (**1n–p**) proved to be efficient in affording the desired products **4m–o** in high yields. It was observed that various R^1 or R^2 groups on ketene dithioacetals were tolerant to this reaction, and multisubstituted thiophenes **4p–t** were produced smoothly from the reaction of α-symmetrically- or unsymmetrically substituted ketene dithioacetals **1** with **2a**. The structures of products **4b, 4c, 4e, 4m, 4s,** and **4t** were further confirmed by HMBC analysis (see the Supporting Information). It was deduced that the acetyl group is easier to transfer than the benzoyl group to the sulfur atom, and both of them are faster than the ester group. 3-Cyano-substituted thiophene **4u** (see the single-crystal analysis of **4u** in the Supporting Information) could also be obtained in 52% yield, although 10 equiv of **1v** was required. Fortunately, the trifluoromethyl group, which often shows special properties in organic reactions, could also be tolerant to this reaction, providing trifluoromethylated thiophene **4v** in 59% yield.

To verify the practicality of this novel [3+2] oxidative cyclization, the scaled-up synthesis of **3n** was run (Scheme 4).

Scheme 4. Scaled-Up Synthesis of Polysubstituted Thiophenes 3n



(1) Blue LEDs , r. t. , N_2, 8 days
86% yield (2.63 g)

(2) Sunlight, N_2, 12 days
55% yield (1.68 g)

It was proved that 2.63 g of **3n** was obtained in 86% yield on a 10 mmol scale of **1a** with **2n**. Considering the efficiency of the solar synthesis, this catalytic transformation was also performed under natural sunlight irradiation. As a result, **3n** was also obtained in 55% yield after reaction for 12 days.

To shed light on the reaction mechanism, a series of control experiments were investigated (Figure 1; for details, see the Supporting Information). First, the reactions of **1a** and **2a** were investigated with the light off/on over a period of time under the optimal reaction conditions. The reaction proceeded well under visible light irradiation, but no further transformation was observed without light irradiation (Figure 1a), indicating the continuous irradiation of visible light is essential for this catalytic reaction.[61,62] Furthermore, the UV–vis absorption spectra (Figure 1b) confirmed that Acr^+-Mes-Ph BF_4^- (Ps-B) is the best photosensitizer as the sole catalyst tested in this [3+2] oxidative cyclization. The Stern–Volmer emission quenching studies (Figure 1c) determined that polarized ketene dithioacetals **1** more easily quench the excited photosensitizer than alkynes do.

Furthermore, the resulting gaseous phases of the reactions for **2a** with ketene dithioacetals **1x–z** bearing different 1,3-dithiolane moieties were analyzed by GC-MS. To our delight, propene, 2-butene, and styrene were clearly observed from the related GC-MS spectra (see the Supporting Information),

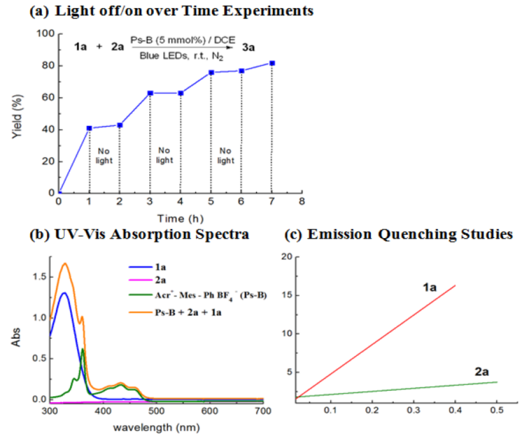
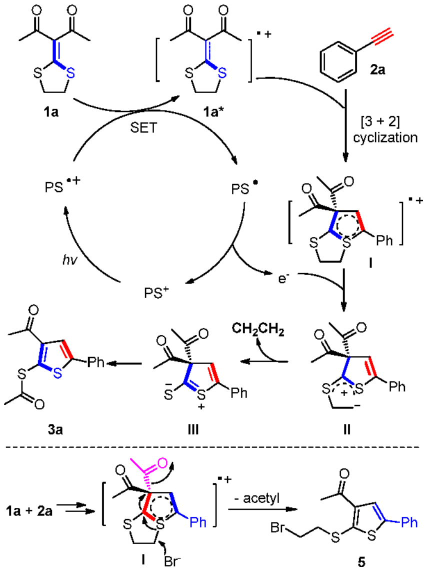


Figure 1. Mechanistic investigations. The yields in panel a were calculated from the ^1H NMR monitors with CH_2Br_2 as the internal standard.

elucidating the release of one molecule of alkene from C(sp^3)−S bond cleavage during the transformations, which may facilitate the final generation of the products.

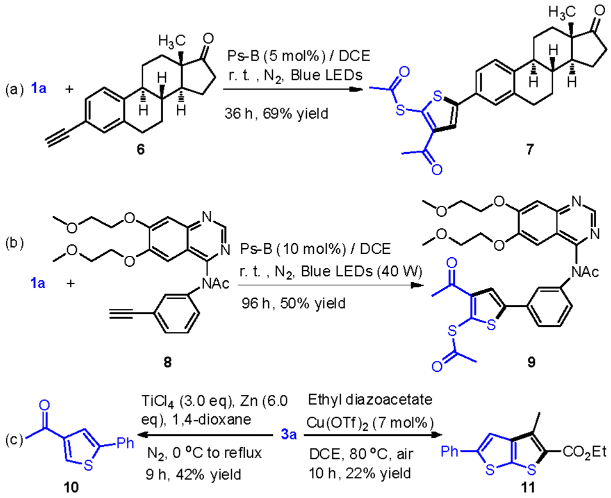
On the basis of the experimental results, mechanistic studies mentioned above (Schemes 2−4, Figure 1, and Table 1), and related reports,[63,64] a plausible catalytic mechanism for this visible-light-induced synthesis of multisubstituted thiophenes **3** and **4** is proposed with the formation of **3a** as an example (Scheme 5). The photosensitizer is excited at first under blue LED (or sunlight) irradiation. Then, single-electron transfer (SET) from ketene dithioacetal **1a** to the excited state of the photosensitizer leads to the formation of radical cation intermediate **1a*** acting as the electrophilic thiavinyl 1,3-dipole equivalent, which undergoes [3+2] cyclization with alkynes **2a** to afford cyclic intermediate **I** in a regioselective manner. The subsequent SET process between **I** and the photosensitizer facilitates the cleavage of the C(sp^3)−S bond to form intermediate **II**, which releases a relatively stable small molecule (ethylene) to form intermediate **III**. Finally, **III** undergoes a sequential intramolecular nucleophilic acyl transfer driven by aromatization to afford **3a**. To further elucidate the proposed mechanism, the catching experiment for intermediate **I** was performed by the addition of $CuBr_2$ (1.0 equiv) under otherwise standard reaction conditions (Table 1, entry 10). 2-Bromoethylthio-substituted thiophene **5** was obtained in 47% yield, providing strong support for the proposed catalytic [3+2] cyclization with ketene dithioacetals **1** as the previously unknown thiavinyl 1,3-dipoles (Scheme 5).

Scheme 5. Proposed Reaction Mechanism



Then, the practicality of this catalytic synthesis of multisubstituted thiophenes was further elucidated by the reaction of **1a** with alkyne-containing natural products. The reaction of estrone **6**[65,66] with **1a** gave thiophene **7** in 69% yield with the estrone moiety intact (Scheme 6a). The reaction of N-protected erlotinib **8**[67] with **1a** could also proceed smoothly using 10 mol % Ps-B under 40 W blue LED irradiation (Scheme 6b). Furthermore, the transformations of the multisubstituted thiophenes were tested. In the presence of $TiCl_4$ and Zn, the reduction of thiophene **3a** gave 2,4-disubstituted thiophenes **10**, instead of the expected McMurry cyclization product.[68−70] In addition, thieno[2,3-*b*]thiophene **11** was achieved when **3a** was treated with ethyl diazoacetate in the presence of $Cu(OTf)_2$ (Scheme 6c).[14]

Scheme 6. Applications for the Facile Synthesis of Thiophenes



In conclusion, a visible-light-induced catalytic [3+2] oxidative cyclization of alkynes with ketene dithioacetals under very mild metal-free conditions without using a base or an oxidant was developed. We found that the easily available ketene dithioacetals can be activated to form a thiavinyl 1,3-dipole equivalent. The previously unknown thiavinyl 1,3-dipole-triggered highly regioselective [3+2] cyclization provides a new access to multisubstituted thiophenes in ≤98% yields. The reaction shows a wide tolerance to both ketene dithioacetals and alkynes, including natural products. The catalytic reaction mechanism is described in detail to reveal the reactivity of the new 1,3-dipoles and the selectivity of the reactions. Further investigation of the thiavinyl 1,3-dipole is in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00915.

General procedures, detailed mechanistic studies, compound characterization, and NMR spectra (PDF)

Accession Codes

CCDC 2054299–2054300 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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