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Trisulfur-Radical-Anion-Triggered C(sp^2)−H Amination of Electron-Deficient Alkenes

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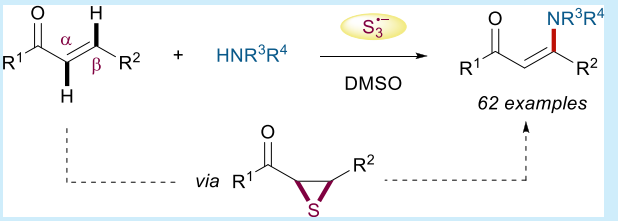
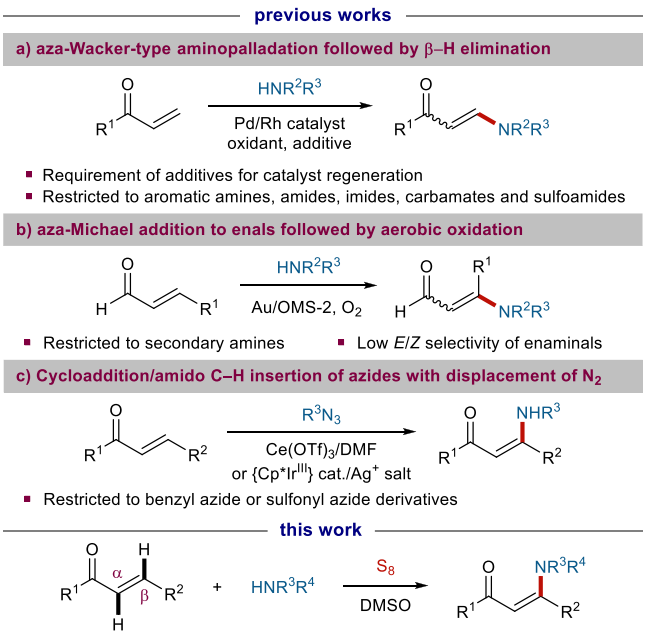
ABSTRACT: A trisulfur-radical-anion ($S_3^{\bullet-}$)-triggered C(sp^2)−H amination of α,β-unsaturated carbonyl derivatives with simple amines has been demonstrated. This protocol provides convenient access to a variety of synthetically valuable N-unprotected and secondary β-enaminones with absolute Z selectivity and tertiary β-enaminones with E selectivity. Mechanistic probe and electronic structure theory calculations suggest that $S_3^{\bullet-}$ initiates the nucleophilic attacks via a thiirane intermediate.



Enaminones are 1,3-difunctional frameworks ubiquitously found in the synthesis of N- and O-containing heterocycles, natural products, and pharmaceutical targets.[1] Owing to their structural features, β-enaminones are frequently used as expedient N,O-bidentate ligands in organoboron complexes and transition-metal catalysis.[2] In recent years, the β-enamine skeleton has been realized via the acid-catalyzed condensation of 1,3-diketones with amines,[3] aza-Michael addition of amines to ynones,[1d,4] aldol-type addition of carbonyl compounds to nitriles[5] or activated isocyanides,[6] and reductive ring opening of heterocycles.[7] More recently, several radical coupling strategies were developed through decarboxylation coupling of α-keto acids and α-imine radicals.[4a,8] However, the available methods are still arduous tasks due to the tedious multistep preparations, limited substrate scopes, and unavailability of starting materials or harsh reaction conditions. Additionally, practical and efficient syntheses of synthetically useful N-unprotected enaminones have scarcely been disclosed.

The intermolecular direct oxidative amination of alkenyl C(sp^2)−H bonds represents the most straightforward method for the synthesis of enamine derivatives (Scheme 1).[9] In this context, most attempts to couple the C(sp^2)−H bonds to N−H bonds were derived from the aza-Wacker process involving Pd or Rh catalysts.[10] These reactions, however, are limited by the preactivation of amino precursors for which only aromatic amines, amides, imides, carbamates, and sulfoamides were reactive substrates.[9c,10d] Furthermore, the presence of additives and oxidants is required to either prevent catalyst deactivation or regenerate the active Pd(II) species. Hence, the oxidative incorporation of highly nucleophilic amines remains less explored and hitherto challenging owing to the strong coordination of the aliphatic amines and precious-metal catalysts.[10f,g] Regarding the amido insertions for the construction of β-enamine functions, Xie et al. disclosed a $Ce(OTf)_3$-catalyzed 1,3-dipolar cycloaddition/N_2 extrusion

Scheme 1. Intermolecular Alkenyl β-C(sp^2)−N Bond Formation Reactions



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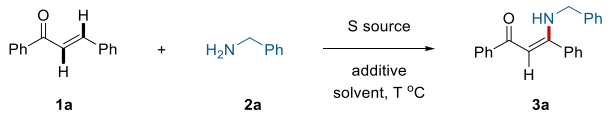
sequence of benzyl azides with chalcones.[11] In addition, Kim and coworkers reported an Ir(III)-catalyzed direct amidation of C(sp^2)−H bonds involving the carbonyl functionality as a weakly coordinating directing group.[12] The aryl C(sp^2)−N bond formation was found to be highly selective, such that olefinic amidation was exclusive for the aliphatic and terminal enone substrates. Therefore, the investigation of a novel system for the selective amination of the alkenyl C(sp^2)−H bonds, utilizing more versatile amine sources that are accessible and environmentally benign, is of prodigious synthetic value.[9a,c]

The S-centered, blue radical species $S_3^{\cdot-}$ has recently attracted significant interest in organic synthesis.[13] Despite remarkable advances in sulfur-mediated Willgerodt-type C−N bond formation,[14] direct incorporations of the trisulfur radical into alkenyl double bonds are rare.[15] Liu et al. developed a method using K_2S/DMF as a $S_3^{\cdot-}$ generator, which is trapped by the α,β-unsaturated *N*-sulfonylimines to produce isothiazoles.[15b] Other groups have employed the K_2S/DMSO system to assemble thiophenes, in which DMSO acts as an oxidant for the *in situ* formation of a conjugated system, which was further attacked by the reactive radical $S_3^{\cdot-}$.[15c,d] In the course of our development of efficient strategies for building C−heteroatom bonds, these results have inspired us to investigate the possibility of the incorporation of sulfur into enone systems.

We started this research by investigating the β-amination of (*E*)-1,3-diphenylprop-2-en-1-one **1a** with benzylamine **2a** and elemental sulfur in DMSO at 80 °C (Table 1). To our delight,

Table 1. Screening of Reaction Conditions[a]



1a 2a 3a

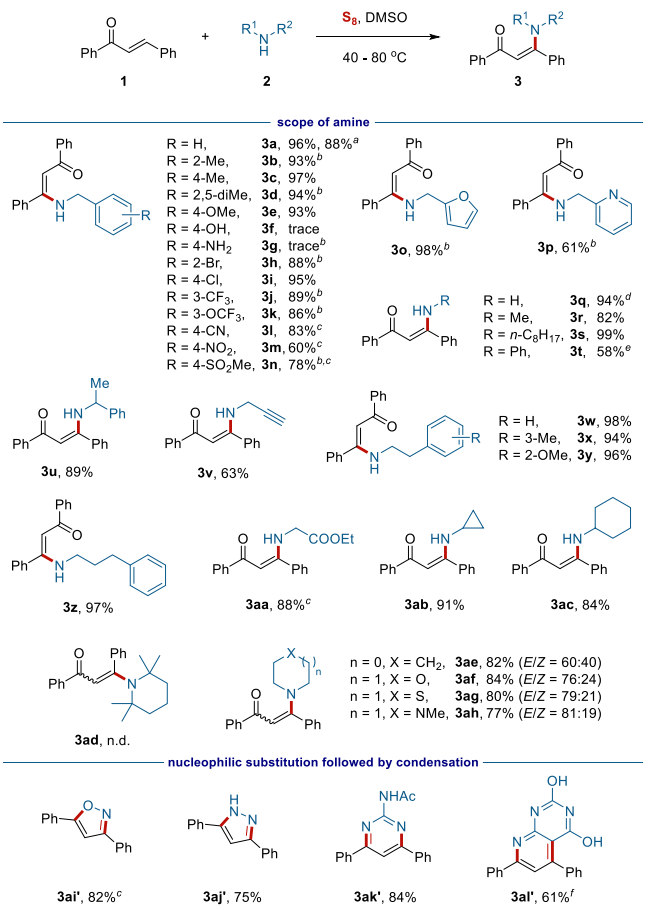
entry	S source (mmol)	solvent	temp (°C)	yield of **3a** (%)[b]
1	S_8 (1.0)	DMSO	rt	83
2	S_8 (1.0)	DMSO	40	97
3	S_8 (1.0)	DMSO	80	71
4		DMSO	40	n.d.
5	S_8 (0.6)	DMSO	40	98
6	S_8 (0.6)	neat	40	6
7	S_8 (0.6)	DMF	40	88
8	S_8 (0.6)	DMAc	40	93
9	S_8 (0.6)	CH_3CN	40	n.d.
10[c]	S_8 (0.6)	DMSO	40	98
11[c]	$Na_2S{\cdot}9H_2O$ (0.6)	DMSO	40	23
12[c]	K_2S (0.6)	DMSO	40	62

[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.40 mmol), solvent (0.2 mL), under air, 12 h. n.d. = not detected. [b]Yields are GC yields using diphenyl ether as the internal standard. [c]DMSO (5.0 equiv) was used.

the enaminone product **3a** was obtained in 71% yield, as detected by GC-MS. Reaction conditions were then intensively screened to selectively maximize the yield of **3a**, with respect to the amount of sulfur, the additive, the solvent, and the temperature.[16] Absolute selectivity and a 97% yield of **3a** could be achieved by conducting the reaction at 40 °C, whereas a significant amount of annulation byproduct was observed at elevated temperatures.[17] Different amide-type solvents were also compatible, which delivered the enaminone products smoothly, and no traces of the coupling products were detected when the reaction was carried out in CH_3CN.[13d,18] Furthermore, the reaction was achievable by reducing the amount of DMSO to 5.0 equiv. An argon and carbon dioxide atmosphere could be used for air-sensitive substrates, although the enhancement was small in the case of **1a** and **2a**.[19] When other sulfur reagents such as $Na_2S{\cdot}9H_2O$ and K_2S were applied in the reaction, 23 and 62% yields of **3a** could be achieved, respectively.

Having these reaction conditions in hand, we then explored the reaction scope with respect to various primary and secondary amines, as depicted in Scheme 2. Benzylamines

Scheme 2. Substrate Scope for the Reaction of (*E*)-1,3-Diphenylprop-2-en-1-one with Various Amines[g]



[a]2 mmol scale. [b]Under a CO_2 atmosphere. [c]NaOAc (2.0 equiv) was added. [d]$(NH_4)_2CO_3$ (0.3 mmol), sulfur (0.6 mmol), DMSO (0.2 mL), under air, 60 °C, 12 h. [e]K_2CO_3 (0.2 mmol) was added. [f]80 °C, 12 h. [g]Reaction conditions: **1** (0.20 mmol), **2** (0.40 mmol), sulfur (0.60 mmol), DMSO (71 μL, 5.0 equiv), under air, 40 °C, 12 h.

bearing electron-donating groups were reactive toward the transformation, providing enaminones **3b−e** in excellent yields. Halo- and sulfonyl-substituted benzylamines were also compatible substrates and upon reactions with chalcone produced enaminones **3h−k** and **3n** in 78−95% isolated yields. Cyano and nitro functionalities remained intact during the course of the reactions. Unfortunately, reactions of **1a** with benzylamine containing free −OH and $-NH_2$ groups on the phenyl ring resulted in complex mixtures, presumably due to competitions between different nucleophilic sites. Additionally, heterocyclic benzylamines and other 1° aliphatic amines were well-tolerated, thereby generating the expected β-enaminones with high efficiency (61−97% isolated yields). Noticeably, the

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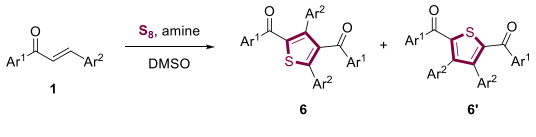
synthetically useful and transition-metal-sensitive propargylamine as well as glycine ester were also amenable to this amination process. The N-unprotected β-enaminone **3q** was successfully prepared from the treatment of chalcone **1a** at 60 °C with ammonia. In addition, the reaction conditions could be altered to achieve the full conversion of the aromatic amine **2t**, wherein the addition of K_2CO_3 (1.0 equiv) was found to be efficient. It is noteworthy that all secondary enaminones obtained were Z-selective. This was attributed to the strong intramolecular hydrogen bonding, as evident from the ^{1}H NMR spectroscopy. Secondary amines also exerted high reactivity, producing tertiary enaminones **3ae**–**ah** in satisfactory yields (77–84%).

The sterically hindered 2,2,6,6-tetramethylpiperidine (TMP) did not favor the C(sp^2)–H amination pathway. Instead it induced the thienannulation of enone **1a** to produce an inseparable mixture of unsymmetrical (**6a**) and symmetrical (**6a′**) thiophenes, as confirmed by the NMR and HR-MS analyses. Accordingly, several enone substrates were examined in reactions with TMP, as summarized in Scheme 3.[20] Indeed, reports on the formation of these thiophene derivatives are rare in the literature.[21]

Scheme 3. Trisulfur-Radical-Anion-Triggered Thienannulation of Enones[a]



Amine	6a and 6a' (Ar^1 = Ar^2 = Ph)
$BnNH_2$	0%
aq. NH_3	trace
TMP	94%
DABCO	47%
DIPEA	23%
pyridine	trace

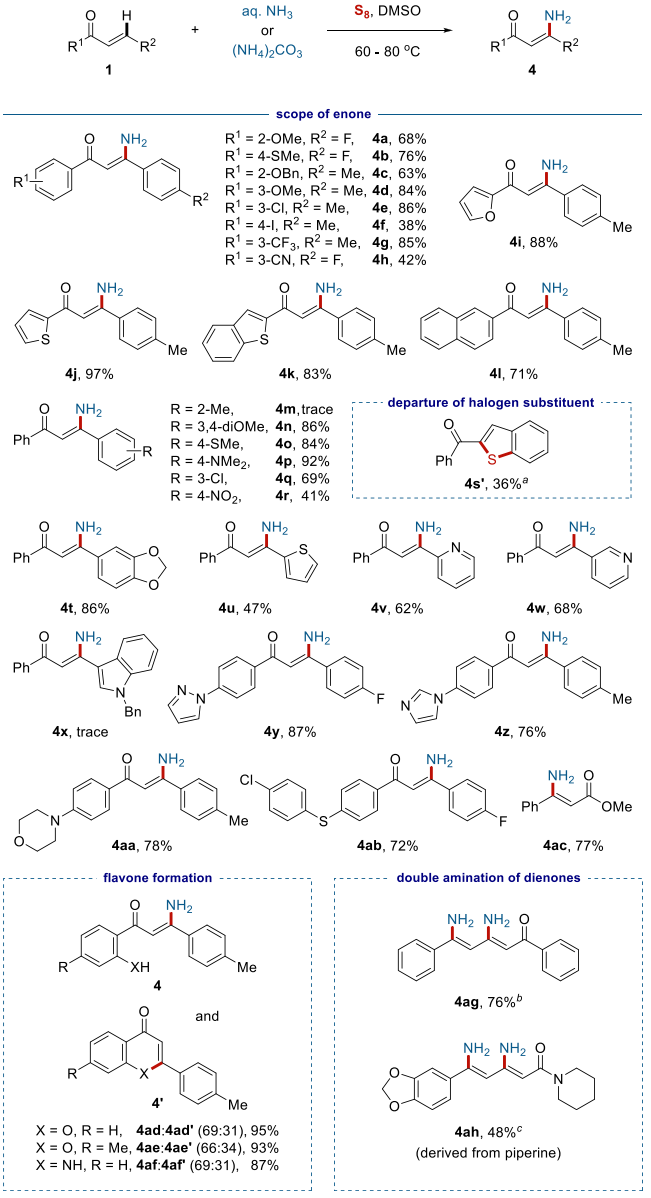
Ar^1	Ar^2	Product	Yield	Selectivity (6 : 6')
Ph	Ph	**6a/6a'**	94%	41 : 59
2-$OMeC_6H_4$	4-FC_6H_4	**6b/6b'**	89%	44 : 56
Ph		**6c/6c'**	98%	100 : 0

[a]Reaction conditions: **1** (0.20 mmol), amine (0.40 mmol), sulfur (0.60 mmol), DMSO (0.2 mL), under air, 12 h at 40 °C.

Interestingly, the reaction of chalcone **1a** with hydroxylamine produced 3,5-diphenylisoxazole **3ai′** in 82% yield. The formation of **3ai′** certainly proceeded via a β-amination followed by a 5-exo-trig cyclization. We note that isoxazole **3ai′** was usually prepared by the oxidation of the corresponding isoxazoline or by transamination with a preformed enaminone.[8a,22] Likewise, pyrazole **3aj′** was successfully formed upon reaction with hydrazine hydrate. Nevertheless, pyrimidine **3ak′** or fused quinoline **3al′** was generated in good yield from 1-acetylguanidine and 6-aminouracil under slightly modified conditions.

Considering the importance of β-functionalized N-unsubstituted enaminones, the reactions of ammonia with enones were next investigated (Scheme 4). After extensive screening, we found that the use of sulfur (3.0 equiv) in DMSO and $(NH_4)_2CO_3$ (1.5 equiv) was effective for the direct aminative C(sp^2)–H functionalization. A variety of enones bearing electron-donating, electron-withdrawing, and heteroaryl substituents delivered products (**4a**–**ab**) in reasonable yields (38–97%). The reaction of (*E*)-2-methylchalcone resulted in a complex mixture, whereas 2-benzoylbenzothiophene **4s′** was unexpectedly derived from (*E*)-2-chlorochalcone.[23] A cinnamate ester was also reactive, whereas attempts to functionalize

Scheme 4. Substrate Scope for the Reaction of Enones with Ammonia[d]



[a]2-Chlorochalcone was used as the substrate. [b]60 °C, 6 h. [c]80 °C, 12 h. [d]Reaction conditions: **1** (0.20 mmol), $(NH_4)_2CO_3$ (0.30 mmol), sulfur (0.60 mmol), DMSO (0.2 mL), under air, 12 h at 60 °C.

other olefins such as β-nitrostyrenes or styryl sulfones were unsuccessful (results not shown). Specifically, substituted 2-hydroxystyryl and 2-aminostyryl ketones could also be smoothly transformed into the corresponding β-enaminones (**4ad′**–**af′**) and flavones (**4ad′**–**af′**) in an approximately 2:1 ratio. This amination cascade was also amenable to longer conjugated systems. By moderately increasing the reaction temperature, the alkaloid piperine and cinnamylideneacetophenone were efficiently converted to the targeted N,N′-unprotected diamines **4ag** and **4ah**.

To better understand the reaction pathways, a series of experiments were conducted to probe the elementary steps of the amination process (Scheme 5). First, the presence of a radical scavenger significantly influenced the transformation. As a further support, a characteristic absorption peak of $S_3^{\bullet-}$ at

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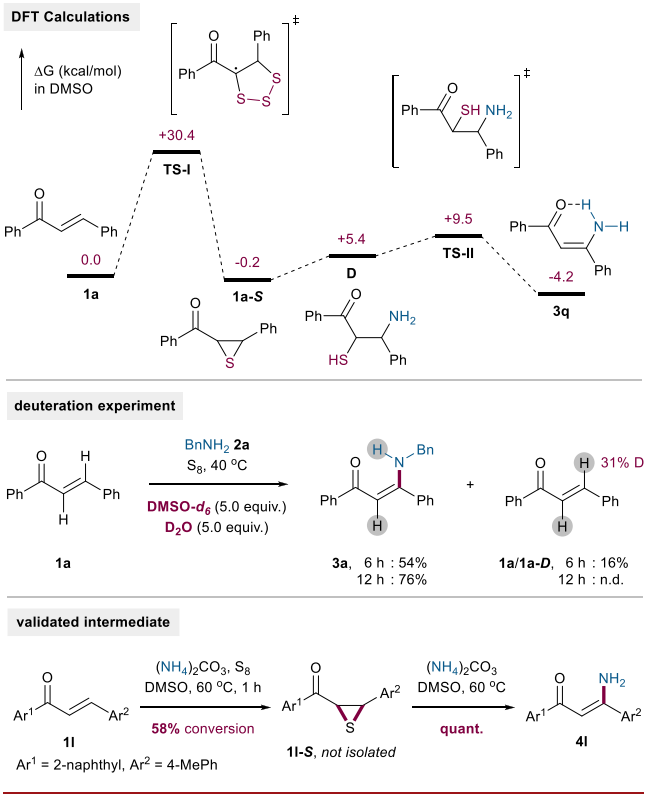
Scheme 5. Mechanistic Studies



550−700 nm was detected in the UV−visible spectrum of the reaction mixture.[24] These observations suggest that a radical pathway is likely involved, which may be ascribed to the formation of $S_3^{\bullet-}$.[13b,25] Upon adding D_2O to the identical reaction system, the formation of β-deuterated chalcone **1a** was observed by GC-MS and ^1H NMR analyses, possibly via a consecutive H-abstraction/elimination process. From these, we hypothesize that the amination reaction is triggered by a radical sulfuration of enone at the α-position.[26] In another control experiment, the thiirane **1l-*S*** was observed using GC-MS by quenching the reaction of naphthyl chalcone **1l** after 1 h, which gave almost full conversion to the enaminone product **4l** upon further treatment with $(NH_4)_2CO_3$.[27] These results support the notion that a mechanism involving a thiirane intermediate is operative.

To further explore the reaction mechanisms for the overall amination process, density functional theory (DFT) calculations were performed using the quantum chemistry program packages Q-Chem 5.2 and Gaussian 16.[28] The reaction intermediates considered here include both local minima and saddle points. Geometry optimizations in the gas phase were carried out at the M06-2X/6-31+G* level of theory, employing the M06-2X functional[29] and the 6-31+G* basis set. Solvation free energies were obtained using the polarizable continuum model (PCM) with DMSO as the solvent. Geometry optimizations were also performed within the PCM framework, which yielded very similar structures to those obtained in the gas phase for all of the model compounds. In addition, second-order Møller−Plesset (MP2) perturbation theory[30] was used to recalculate the single-point electronic energies for the M06-2X/6-31+G* optimized structures using a larger basis set 6-311++G**. The final free-energy values for all of the model compounds thus use electronic energies obtained at the MP2/6-311++G**//M06-2X/6-31+G* level of theory and gas-phase and solvation free-energy corrections at the M06-2X/6-31+G* level of theory. In the Supporting Information, results from another two DFT functionals, B3LYP and B3LYP with Grimme's empirical dispersion correction (B3LYP-GD3),[31] are discussed. On the basis of the calibration calculations at the MP2/6-311++G** level of theory, we conclude that the M06-2X functional is more accurate than the other two functionals for the compounds considered in this work.

The overall reaction from **1a** to **3q** is exothermic with a free-energy difference of −4.2 kcal/mol. The reaction mechanism is illustrated in Scheme 5 and can be summarized as follows. Initially, a trisulfur radical anion, which is generated from the base-induced dissociation of elemental sulfur, rapidly attacks the α- or β-position of the α,β-unsaturated carbonyl **1a** and forms a cyclic transition state **TS-I**. The reaction then proceeds downhill, dissociating to $S_2^{\bullet-}$ and a thiirane intermediate **1a-*S***. The thiirane ring undergoes nucleophilic attack by NH_3 to form an adduct **D**, which rearranges to form the second transition state **TS-II** and finally dissociates to the product **3q**. Calculations also suggest a possible attack of NH_3 on the α-carbon of **1a-*S***, which forms a different isomeric adduct **D′** (see the Supporting Information for details) with a slightly higher energy. Nevertheless, both **D** and **D′** go through the transition state **TS-II** to reach the final product **3q**. Elemental sulfur or polysulfide anions could be regenerated by the oxidative nature of DMSO.[15c,d] Whereas the elimination of H_2S from **TS-II** leads to the final product **3q**, removing NH_3 from **TS-II** goes back to **1a-*S***, as confirmed by the calculation.

In summary, we have developed a trisulfur radical-enabled C(sp^2)−H amination of enones with simple amines via a radical sulfuration and sulfur extrusion cascade. Detailed control experiments and DFT calculations probe the installation of amine functionalities through the nucleophilic ring-opening reaction of a thiirane intermediate. This protocol provides simple access to β-enaminones under mild, oxidant- and metal-free conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03846.

Experimental procedures, mechanistic study, computational calculation details, characterization data, and ^1H NMR and ^{13}C NMR spectra for all new products (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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