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Trisulfur radical anion-triggered C(sp^2)–H amination of electron-deficient alkenes: rapid access to β-enamino ketones and highly functionalized thiazoles under transition metal-free conditions

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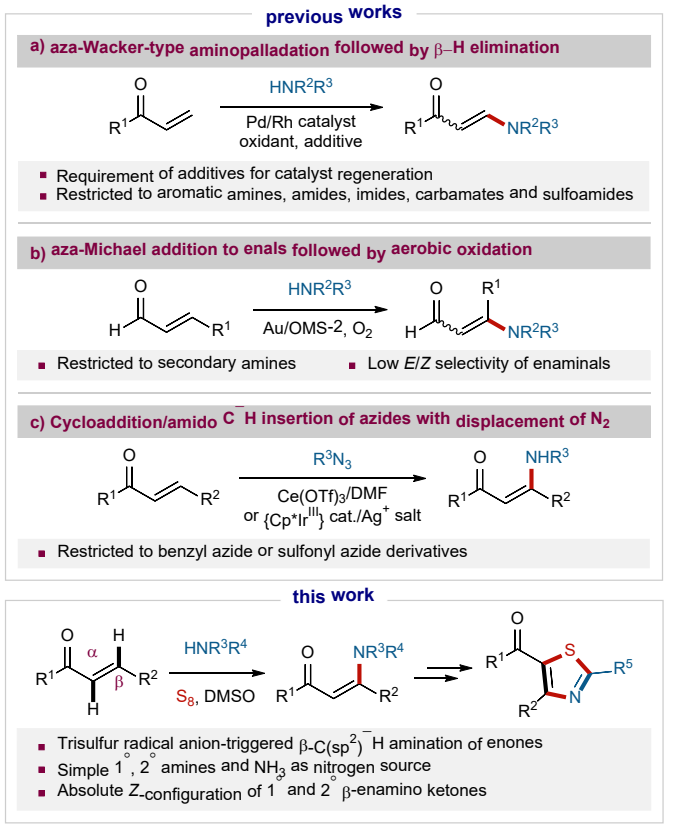
A novel trisulfur radical anion ($S_3^{\bullet-}$)-triggered C(sp^2)–H amination of α,β-unsaturated carbonyl derivatives with simple amines has been demonstrated. This protocol provides convenient access to a variety of synthetically valuable N-unprotected and secondary β-enaminones with absolute *Z*-selectivity, 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. Late-stage annulation of β-enaminone products generates three thiazoles substituted with different aryl-, aroyl- and styryl- functional groups.

Introduction

Enaminones are 1,3-difunctional frameworks ubiquitously found in the synthesis of N- and O-containing heterocycles, natural products, and pharmaceutical targets.[1-6] The β-enamino ketone fragments are also integral parts of various biologically active molecules.[7, 8] Owing to their structural features, β-enaminones are frequently used as expedient N,O-bidentate ligands in organoboron complexes and transition metal catalysis.[9-14] In particular, N-unprotected enaminones are versatile intermediates for the synthesis of chiral amines, β-amino acids, and their analogous diabetes treatment sitagliptin.[15-19] In recent years, the β-enamine skeleton has been realized *via* acid-catalysed condensation of 1,3-diketones with amines,[20, 21] aza-Michael addition of amines to ynones,[4, 22-24] aldol-type addition of carbonyl compounds to nitriles[25-27] or activated isocyanides,[28] and reductive ring-opening of heterocycles.[29, 30] More recently, several radical coupling strategies were developed through decarboxylation of α-keto acids and α-imine radicals, which are generated *in situ* from oxime esters and vinyl azides.[22, 31-35] However, available methods are still arduous tasks due to tedious multistep preparations, limited substrate scopes, and unavailability of starting materials and/or harsh reaction conditions. Although several protocols toward β-enaminones have been documented, practical and efficient syntheses of synthetically useful N-unsubstituted enaminones have scarcely been disclosed.

Intermolecular direct oxidative amination of alkenyl C(sp^2)–H bonds represents the most straightforward method for the



Scheme 1 Intermolecular alkenyl β-C(sp^2)–N bond formation reactions.

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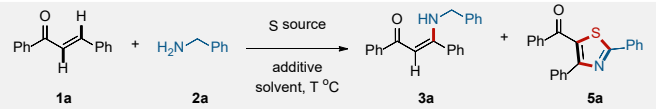
synthesis of enamine derivatives.[36-40] In this context, most attempts to couple the C(sp^2)–H bonds with N–H bonds were derived from the aza-Wacker process involving Pd or Rh catalysts.[41-50] A new C–N bond was forged through a classical aminopalladation pathway, followed by a β–hydride elimination to furnish the enamine moiety. These reactions, however, are limited by preactivation of amino precursors that only aromatic amines, amides, imides, carbamates, and sulfoamides were reactive substrates.[38, 44] 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 with and precious metal catalysts.[46, 47] In one representative example, Mizuno *et al.* employed a heterogeneous Au catalyst for the sequential conjugate addition and dehydrogenative oxidation of the secondary amines with α,β-unsaturated aldehydes.[51] Regarding the amido insertions for the construction of β-enamine functions, Xie *et al.* disclosed a Ce(OTf)$_3$-catalysed 1,3-dipolar cycloaddition/N_2 extrusion sequence of benzyl azides with chalcones.[52] In addition, Kim and co-workers reported an Ir(III)-catalysed direct amidation of C(sp^2)–H bonds, involving the carbonyl functionality as a weakly coordinating directing group.[53] 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, 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.[36, 38]

The *S*-centered, blue radical species $S_3^{\bullet -}$ has recently attracted significant interest in organic synthesis.[54-57] Although constructions of the C–S bonds *via* the interaction of $S_3^{\bullet -}$ with substituted acetylenes were well-demonstrated,[58-62] incorporations of this radical intermediate into alkenyl double bonds are rare.[63-66] Liu et al. developed a method using K_2S/DMF as a $S_3^{\bullet -}$ generator, which is trapped by the α,β-unsaturated *N*-sulfonylimines to produce isothiazoles in moderate yields.[64] Other groups have employed the K_2S/DMSO system for assembling of thiophenes, in which DMSO acts as both an oxidant and an electron-pair donor for the *in situ* formation of a conjugated system, which was further attacked by the active radical $S_3^{\bullet -}$.[65, 66] In the course of our development of efficient strategies for building C–heteroatom bonds, these results have inspired us to investigate the possibility on the incorporation of sulfur into enone systems. In this paper, we report the first C(sp^2)–H amination of α,β-unsaturated alkenes mediated by trisulfur radical anion. The reaction conditions may be altered to produce fully substituted thiazoles *via* multiple C–H bond cleavages and C–heteroatom bond formations.

Results and discussion

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, the

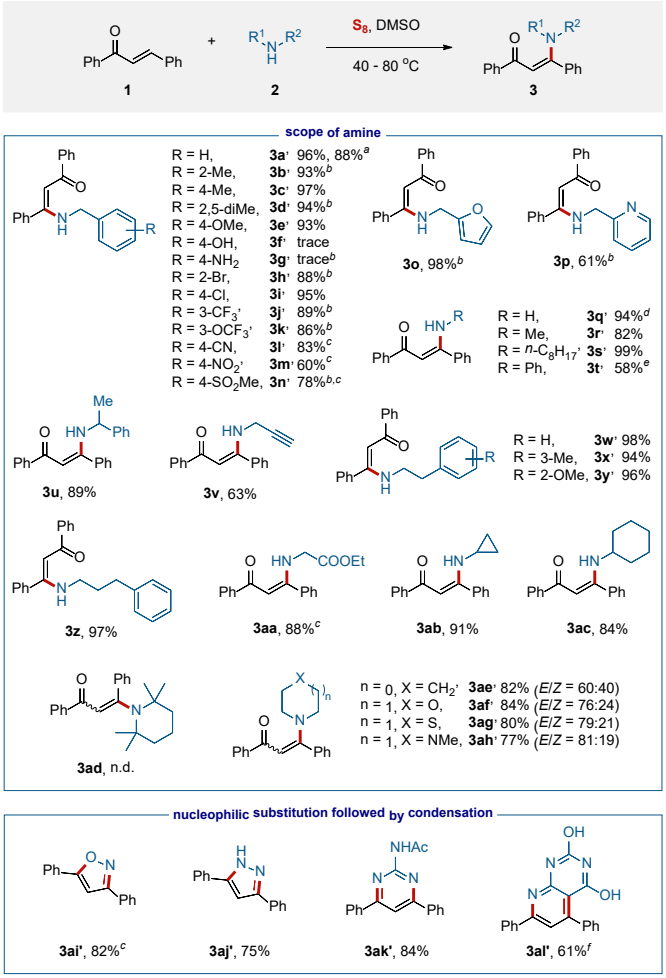
Table 1 Optimization studies of the regio- and chemoselective amination of enone **1a** with benzylamine **2a**[a]



Entry	S source (mmol)	Additive	Solvent	*T* (°C)	Yield of **3a** (%)	Yield of **5a** (%)
1	S_8 (1.0)	-	DMSO	rt	83	n.d.
2	S_8 (1.0)	-	DMSO	40	97	n.d.
3	S_8 (1.0)	-	DMSO	80	71	18
4	S_8 (1.0)	-	DMSO	140	n.d.	57
5	-	-	DMSO	40	n.d.	n.d.
6	S_8 (0.6)	-	DMSO	40	98	n.d.
7	S_8 (0.6)	-	neat	40	6	n.d.
8	S_8 (0.6)	-	DMF	40	88	n.d.
9	S_8 (0.6)	-	DMAc	40	93	n.d.
10	S_8 (0.6)	-	NMP	40	74	n.d.
11	S_8 (0.6)	-	CH_3CN	40	n.d.	n.d.
12	S_8 (0.6)	-	DMSO[c]	40	98 (99)[e,f]	n.d.
13	S_8 (0.6)	-	DMSO[d]	40	81	n.d.
14	Na_2S (0.6)	-	DMSO[c]	40	23	n.d.
15	K_2S (0.6)	-	DMSO[c]	40	62	n.d.
16[g]	S_8 (1.0)	-	DMSO[h]	140	n.d.	72
17[g]	S_8 (1.0)	I_2 (5 mol%)	DMSO[h]	140	n.d.	92
18[g]	S_8 (1.0)	KI (5 mol%)	DMSO[h]	140	n.d.	93
19[g]	S_8 (1.0)	KI (3 mol%)	DMSO[h]	140	n.d.	82

[a] Reaction conditions: **1a** (0.20 mmol, 1.0 equiv.), **2a** (0.40 mmol, 2.0 equiv.), solvent (0.2 mL), under air, 12 h; DMSO: dimethyl sulfoxide; DMF: *N*,*N*-dimethylformamide; DMAc: *N*,*N*-dimethylacetamide; NMP: *N*-methyl-2-pyrrolidone; n.d. = not detected. [b] Yields are GC yields using diphenyl ether as the internal standard. [c] DMSO (5.0 equiv.) was used. [d] DMSO (3.0 equiv.) was used. [e] Under argon atmosphere. [f] Under CO_2 atmosphere (amine substrate was transformed to carbamate salt prior to reaction). [g] **1a** (0.20 mmol, 1.0 equiv.), **2a** (0.40 mmol, 2.0 equiv.), DMSO (5.0 equiv.), under air, 12 h at 40 °C; then additive and DMSO were added and stirred for 3 h at 140 °C. [h] DMSO (2.0 mL) was used.

enaminone product **3a** was obtained in 71% as detected by GC-MS, along with a significant amount of the annulation product thiazole **5a**. Reaction conditions were then intensively screened to selectively maximize the yield of **3a** and **5a**, with respect to the amount of sulfur, additive, solvent, and temperature (see Supporting Information for full data). Temperature exhibited a considerable impact on the yield and selectivity of **3a**. While absolute selectivity and 97% yield of **3a** could be achieved by conducting the reaction at 40 °C, the annulation of **5a**, whose formation was envisaged to involve **3a** as an intermediate, was favoured at elevated temperatures. Different amide-type solvents were also compatible, which delivered the enaminone products smoothly with acceptable yields, and no traces of the coupling products were detected when the reaction was carried out in CH_3CN. It should be noted that electron-pair donating solvents were found efficient for the dissociation of cyclo-S_8.[57, 59] Furthermore, the reaction was achievable by reducing the amount of DMSO to 5.0 equiv. in combination with 3.0 equiv. of sulfur. Argon and carbon dioxide atmosphere could be used for



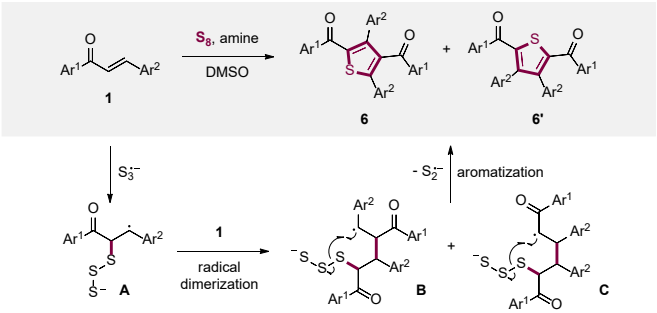
Scheme 2 Substrate scope for the reaction of (*E*)-1,3-diphenylprop-2-en-1-one with various amines. Reaction conditions: **1** (0.20 mmol, 1.0 equiv.), **2** (0.40 mmol, 2.0 equiv.), sulfur (0.60 mmol, 3.0 equiv.), DMSO (71 µL, 5.0 equiv.), under air, 12 h at 40 °C. [a] 2 mmol scale. [b] Under CO_2 atmosphere. [c] NaOAc (2.0 equiv.) was added. [d] $(NH_4)_2CO_3$ (0.3 mmol, 1.5 equiv.), sulfur (0.6 mmol, 3.0 equiv.), DMSO (0.2 mL), under air, 12 h at 60 °C. [e] K_2CO_3 (0.2 mmol, 1.0 equiv.) as additive. [f] Reaction carried out at 80 °C.

air-sensitive substrates, though the enhancement was small in the case of **1a** and **2a**. When other sulfur reagents such as $Na_2S.9H_2O$ and K_2S were applied in the reaction, 23% and 62% yields of **3a** could be achieved, respectively. Inspired by these results, we adjust reaction conditions to increase the yield and selectivity of **5a**. Gratifyingly, the yield of this annulation product could be significantly improved by performing the reaction in a one-pot two-step fashion. A series of additives were utilized, and the presence of KI (5 mol%) in the reaction mixture significantly accelerated the transformation, producing **5a** in 93% yield by further stirring the reaction mixture for 3 h at 140 °C.

Having these reaction conditions in hands, we then explored the reaction scope with respect to various primary and secondary amines as depicted in Scheme 2. Benzylamines bearing electron-donating groups were reactive toward the transformation, providing enaminones **3b**–**3e** in excellent yields. Halo- and sulfonyl-substituted benzylamines were also compatible substrates, upon reactions with chalcone produced enaminones **3h**–**3k** and **3n** in 78–95% isolated yields. Cyano and nitro functionalities remained intact during the course of reactions, giving the corresponding enaminones in acceptable yields. Unfortunately, reactions of **1a** with benzylamine containing free –OH and $-NH_2$ groups on the phenyl ring resulted in elusive complex mixtures, presumably due to nucleophilic competitions. Additionally, heterocyclic benzylamines and other 1° aliphatic amines were well-tolerated, thereby generating the expected β-enaminones in high efficiency (61–97% isolated yields). Noticeably, the 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 treatment of chalcone **1a** at 60 °C with ammonia, in the form of either saturated aqueous solution or carbonate salts. In addition, the reaction conditions could be altered to achieve full conversion of the aromatic and less nucleophilic 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 strong intramolecular hydrogen bonding as evident from the ^1H NMR spectroscopy. Secondary amines also exerted high reactivity, producing terminal enaminones **3ae**–**3ah** in high yields (77–84%) and good *E*/*Z* selectivity.

The sterically hindered 2,2,6,6-tetramethylpiperidine (TMP) did not favour the C(sp^2)–H amination pathway. Instead it induced 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 Table 2. The regioselectivity for the formation of tetrasubstituted thiophenes varied regarding the electronic nature of aryl substituents, apparently due to the stability of radical intermediates.[60] Indeed, reports on the formation of these thiophene derivatives are rare in the literature.[60, 67-69]

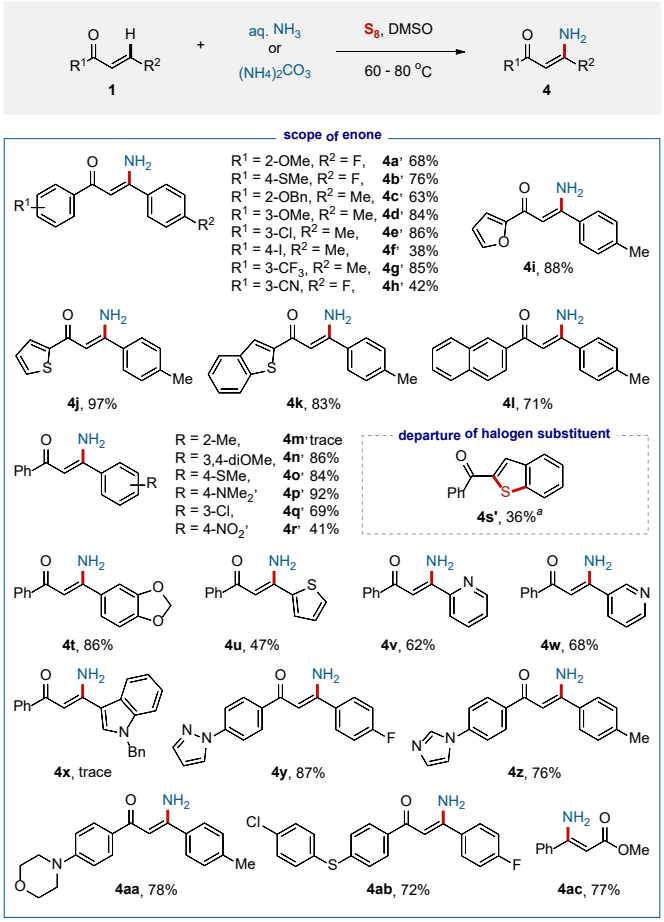
Table 2 Trisulfur radical anion-triggered thienannulation of enones



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

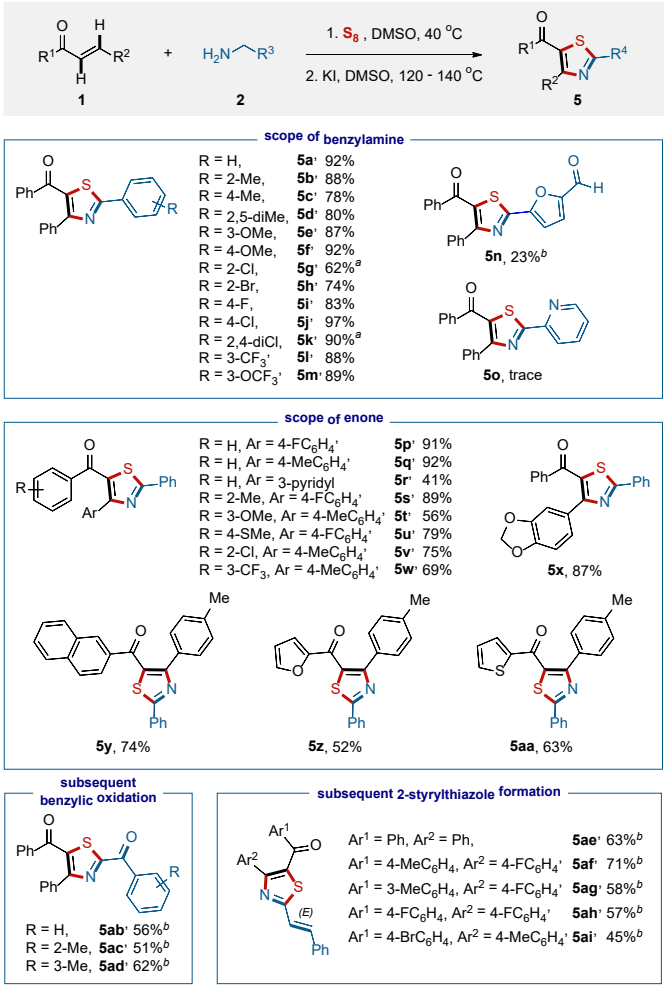
Ar^1	Ar^2	Product	Yield	Selectivity (6 : 6')
Ph	Ph	6a/6a'	94%	41 : 59
2-$OMeC_6H_4$	4-FC_6H_4	6b/6b'	89%	44 : 56
Ph		6c/6c'	98%	100 : 0

Reaction conditions: **1** (0.20 mmol, 1.0 equiv.), amine (0.40 mmol, 2.0 equiv.), sulfur (0.60 mmol, 3.0 equiv.), DMSO (0.2 mL), under air, 12 h at 40 °C. TMP = 2,2,6,6-tetramethylpiperidine; DABCO = 1,4-diazabicyclo[2.2.2]octane; DIPEA = *N*,*N*-diisopropylethylamine.



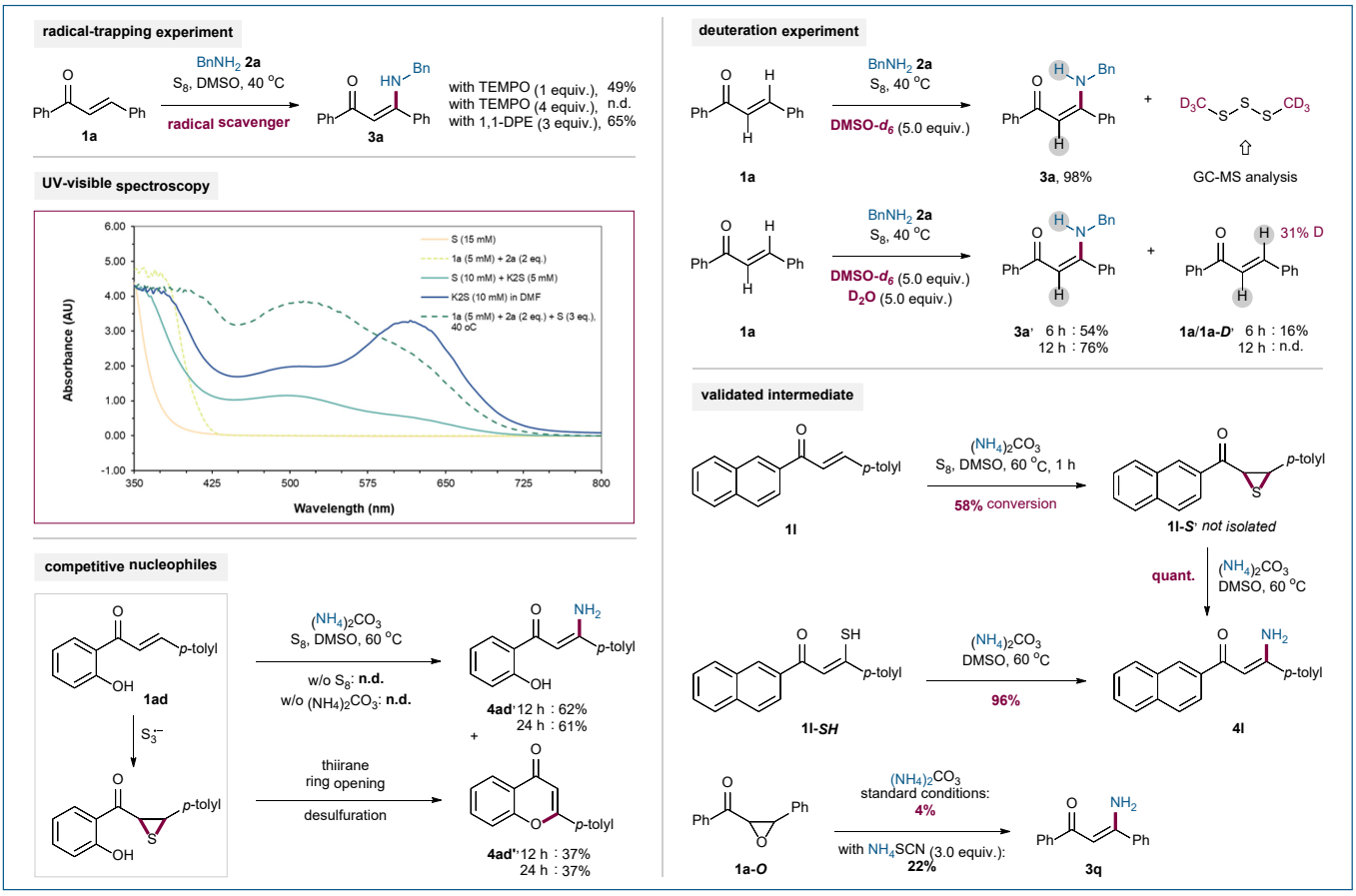
Scheme 3 Substrate scope for the reaction of enones with ammonia. Reaction conditions: **1** (0.20 mmol, 1.0 equiv.), $(NH_4)_2CO_3$ (0.30 mmol, 1.5 equiv.), sulfur (0.60 mmol, 3.0 equiv.), DMSO (0.2 mL), under air, 12 h at 60 °C. [a] 2-chlorochalcone was used as substrate. [b] 6 h at 60 °C. [c] 12 h at 80 °C.

Interestingly, the reaction of chalcone **1a** with hydroxylamine produced 3,5-diphenylisoxazole **3ai'** in 82% yield, while the expected enaminone coupling product was detected in only trace quantity. The formation of **3ai'** certainly proceeded *via* a chemoselective β-amination followed by a *5-exo-trig* cyclization. Noted that isoxazole **3ai'** was usually prepared by oxidation of the corresponding isoxazoline or by transamination with a preformed enaminone.[31, 70, 71] Likewise, pyrazole **3aj'** was successfully formed upon reaction with hydrazine hydrate. Nevertheless, pyrimidine **3ak'** or fused quinoline **3al'** was generated in good yields from a coupling partner containing a geminal nucleophile under slightly modified conditions.



Scheme 4 Substrate scope for the reaction of enones with ammonia. Reaction conditions: **1** (0.20 mmol, 1.0 equiv.), **2** (0.40 mmol, 2.0 equiv.), sulfur (1.0 mmol, 5.0 equiv.) DMSO (71 µL, 5.0 equiv.), 12 h at 40 °C; then KI (5 mol%) and DMSO (2.0 mL) were added and stirred for 3 h at 140 °C. [a] NaOAc (2.0 equiv.) was added. [b] 8 h at 120 °C.

Considering the importance of β-functionalized N-unsubstituted enaminones, the reactions of ammonia with enones were next investigated (Scheme 3). 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 with R^1 bearing electron-donating, electron-withdrawing and heteroaryl substituents delivered products (**4a–4l** and **4y–4ab**) in reasonable yields (38–97%). The electronic properties and steric effects of substituents on R^2 group exhibited noticeable impacts on the product formation, where electron-rich enaminones were synthesized in high yields (**4n–4p** and **4t**). The reaction of (*E*)-2-methylchalcone resulted in a sluggish mixture, while 2-benzoylbenzo[*b*]thiophene **4s'** was unexpectedly derived from (*E*)-2-chlorochalcone, possibly through an initial C(sp^2)–H sulfuration followed by a S_NAr mechanism. Note that the benzothiophene **4s'** was not formed using a similar DIPEA and sulfur-mediated strategy.[72] A cinnamate ester was also reactive, and the resulting β-enamine **4ac** was obtained in 77% yield. Unfortunately, attempts to functionalize other olefins such as β-nitrostyrenes or styryl sulfones were unsuccessful (results



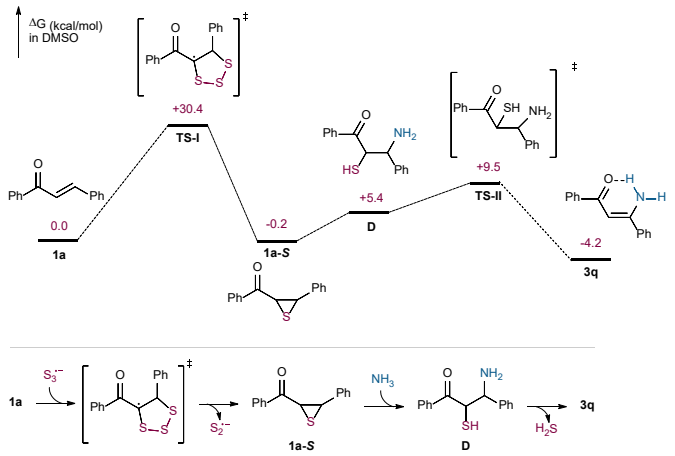
Scheme 5 Mechanistic probes. TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy; 1,1-DPE = 1,1-diphenylethylene.

not shown). Specifically, substituted 2-hydroxystyryl ketones could also be smoothly transformed into the corresponding β-enaminones (**4ad** and **4ae**) and flavones (**4ad'** and **4ae'**) in approximately 2:1 ratio. A control reaction indicated that the resulting enaminone was unlikely an intermediate for the formation of flavone annulation product (Scheme 5). 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**.

Upon successful β-aminations of enones, we employed this methodology in the consecutive assembly of poly-substituted thiazoles.[73] As shown in Scheme 4, the reaction of benzylamines and enones exhibited broad tolerance of functionalities with yields of thiazoles ranging from 41 to 97% (**5a**–**5m** and **5p**–**5aa**). Notably, furfural-derived thiazole **5n** was isolated as the main product in case of furfurylamine, albeit in low yield. Similar successive formylations were not observed for products **5z** and **5aa**, probably due to the deactivating effect from the attached carbonyl groups.[74-76] Complementary to the above results, sequential KI/S_8/DMSO-mediated oxidations were observed for amines bearing multiple activated methylene groups. In this account, phenethylamines were accommodated to generate twofold aroyl-decorated thiazoles **5ab**–**5ad** with generally moderate yields.[20, 77] Thereafter, the structurally significant 2-styrylthiazoles **5ae**–**5ai** were also furnished from 3-phenyl-1-propylamine with compatibility of various enones.[65, 78] These observations demonstrated the utility and versatility of the present KI/S_8/DMSO system for generating molecular complexity in a controllable manner.

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 the reaction was completely suppressed by the addition of 4.0 equiv. of TEMPO. As a further support, a characteristic absorption peak at 550–700 nm was detected in the UV-visible spectrum of the reaction mixture, which was identical to the absorption peak of $S_3^{\bullet -}$ recorded from the DMF solution of K_2S. These observations suggest that a radical pathway is likely involved in the reaction, which may be ascribed to the formation of $S_3^{\bullet -}$.[55, 63, 79]

As our next series of inquiries, we interrogated the reaction of enone **1a** with benzylamine **2a** in deuterated solvents. The standard reaction occurred in DMSO-d_6 gave mostly no deuterated products. Upon adding D_2O to the identical reaction system, the formation of β-deuterated chalcone **1a** was observed by the ^{1}H NMR spectrum, 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.[80] In another control experiment, the



Scheme 6 Computational study of the reaction mechanism.

thiirane **1l-*S*** was observed using GC-MS by quenching the reaction of naphthyl chalcone **1l** after 1 hour, whereas the enthiol isomer **1l-*SH*** was obtained from flash chromatography of the reaction mass on silica gel.[81] Both the thiirane and the thiolation intermediate gave almost full conversion to the enaminone product **4l** upon further treatment with $(NH_4)_2CO_3$. Additionally, the independently synthesized oxirane **1a-*O*** was found unreactive under standard conditions, whilst the replacement of the amine source with NH_4SCN provided the expected enaminone **3q** in modest yield. These results support that a mechanism involving a thiirane intermediate was operative.

To further explore reaction mechanisms for the overall amination process, density functional theory (DFT) calculations were carried out to obtain structures and energies of important intermediates relevant to this work. The calculations were performed using the quantum chemistry program packages Q-Chem 5.2 and Gaussian 16.[82, 83] The reaction intermediates considered here include both local minima and saddle points (e.g., transition states.) Geometry optimizations in the gas phase were carried out at the M06-2X/6-31+G* level of theory, employing the M06-2X functional[84] and the 6-31+G* basis set. After the stationary points were found, standard normal mode analysis and frequency calculations were carried out on these structures using the same level of theory and basis set. This provides free energy corrections in the gas phase. Solvation free energies were obtained using the polarizable continuum model (PCM) with dimethyl sulfoxide (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 the model compounds. In addition, second order Møller-Plesset (MP2) perturbation theory[85] 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 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), [86, 87] are discussed. Based on 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 free energy difference −4.2 kcal/mol. The reaction mechanism is illustrated in Scheme 6 and can be summarized as follows. Initially, a trisulfur radical anion ($S_3^{\bullet -}$), which is generated from the base-induced dissociation of elemental sulfur,[57, 58, 60, 63] rapidly attacks the α- or β-position of the α,β-unsaturated carbonyl **1a** and forms a cyclic transition state **TS-I** where the two end sulfur atoms of the trisulfur anion are linked to the α- or β-carbons of **1a**, respectively. Calculation results support the α-regioselectivity of the $S_3^{\bullet -}$ radical addition step, as much lower activation energy is required in comparison to the β-addition.[80] The initial α-sulfuration is also suggested by the mode of formation for thiophene derivatives (Table 2) and benzothiophene **4s'**. 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 to 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**. Control experiments showed that this sulfur extrusion sequence occurred spontaneously by treatment of the thiirane intermediate with $(NH_4)_2CO_3$. Elemental sulfur or polysulfide anions could be regenerated by oxidative nature of DMSO.[65, 66] While 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.

Conclusions

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 nucleophilic ring-opening reaction of a thiirane intermediate. This protocol provides a simple access to β-enaminones under mild, oxidant- and metal-free conditions. The late-stage variations of enaminone products were successfully controlled to afford an array of trisubstituted thiazoles. This study was complementary to the progress in C–H bond functionalization for the generation of molecular diversity and complexity from simple precursors.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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