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Mild and Expeditious Synthesis of Sulfenyl Enaminones of L-α-Amino Esters and Aryl/Alkyl Amines through NCS-Mediated Sulfenylation

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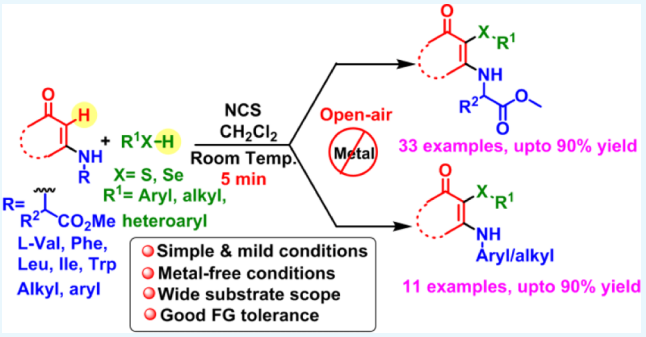
ABSTRACT: Sulfenylation or selenylation of enaminones of L-α-amino esters requires mild reaction conditions due to the presence of a racemization-prone chiral center and reactive side chains. An *N*-chlorosuccinimide (NCS)-mediated methodology has been developed for rapid sulfenylation of enaminones of L-α-amino esters and aryl/alkyl amines at room temperature in open air under metal-free conditions. Enaminones of L-α-amino esters bearing aliphatic, aromatic, and heterocyclic side chains react efficiently with diverse aryl/alkyl/heteroaryl thiols (R^1SH) in the presence of NCS to afford a library of biologically important sulfenyl enaminones in good-to-excellent yields (71−90%). Under similar reaction conditions, the enaminones also react with benzeneselenol to produce selenyl enaminones in good yield (73−83%). The NCS-mediated pathway generates sulfenyl chloride (R^1SCl) as an intermediate which leads to rapid sulfenylation of enaminones through cross-dehydrogenative coupling (CDC) under mild reaction conditions.



INTRODUCTION

Presently, C(sp^2)−H bond functionalization is considered as an essential transformation in organic synthesis,[1] and a wide range of reactions such as C−H alkylation,[2] alkenylation,[3] arylation,[4] and acylation[5] mostly based on transition-metal catalysis and oxidative coupling have been reported. Similarly, C−S, C−P, and C−N bond formation *via* transition-metal-catalyzed C−H functionalization has become popular in recent years.[6−8] On the other hand, nowadays, chemists are more concern about environmental pollution; therefore, metal-free C−H functionalization is also receiving considerable attention.[9] In this context, cross-dehydrogenative coupling (CDC) is considered as an effective strategy for construction of C−C and C-heteroatom bonds as it provides an atom economical and environmentally benign short synthetic pathway without any prerequisite functionalization of reactants.[10,11] Since aliphatic/heteroaromatic sulfides, diaryl sulfides, and their derivatives are widely present in biologically active compounds and natural products,[12] chemists are fascinated in developing efficient methods to create a C−S bond specially using a CDC strategy.

The sulfenyl enamines with a C−S bond show important biological and medicinal activities such as 5-fluoro-2′-deoxyuridine (FUDR) phosphorylase inhibitory,[13a] HIV-1 integrase inhibitory,[13b] and potential peptide-mimicking activities.[13c] Sulfenyl enamine 5-(phenylthio)acyclouridine (AC1NA056) is important for treatment of AIDS and cancer by improving oral uridine bioavailability with effective pharmacokinetic properties (Figure 1).[14] A cyclic thioenamine peptide acts as a potential β-turn mimic,[15] and NSC 128981 shows excellent growth inhibitory property against human carcinoma cells (Figure 1).[16] On the other hand, amino acids are important in the production of drug molecules[17] and peptide-based soft materials.[18] Amino acids are extensively used as β-lactam antibiotics,[19a] anticoagulants,[19b] reproductive medicines,[19c] and pesticides.[19d] Amino acid ester-based prodrugs are used to increase oral bioavailability and reduce toxicity of parent antiviral drugs (Figure 1).[20] *N*-functionalized amino acids are versatile building blocks in pharmaceutical industries and key starting materials for the development of peptide-based drug molecules.[21] Plakohypaphorine D, one of the indole alkaloids bearing *N*-functionalized L-tryptophan unit isolated from marine sponge, shows cytotoxic activity against leukemia and melanoma cells (Figure 1).[22] Moreover, organoselenium compounds also exhibit important biological and pharmacological activities such as anti-HIV, antiviral, anticancer, and antioxidant activities.[23] For example, (*E*)-2-

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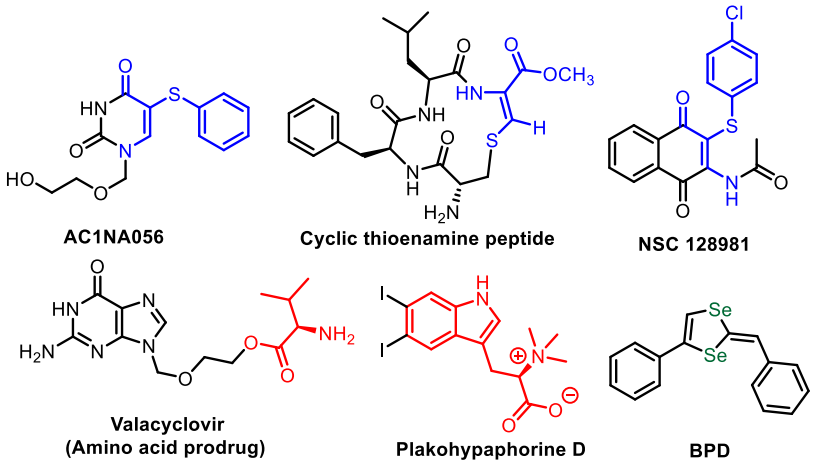
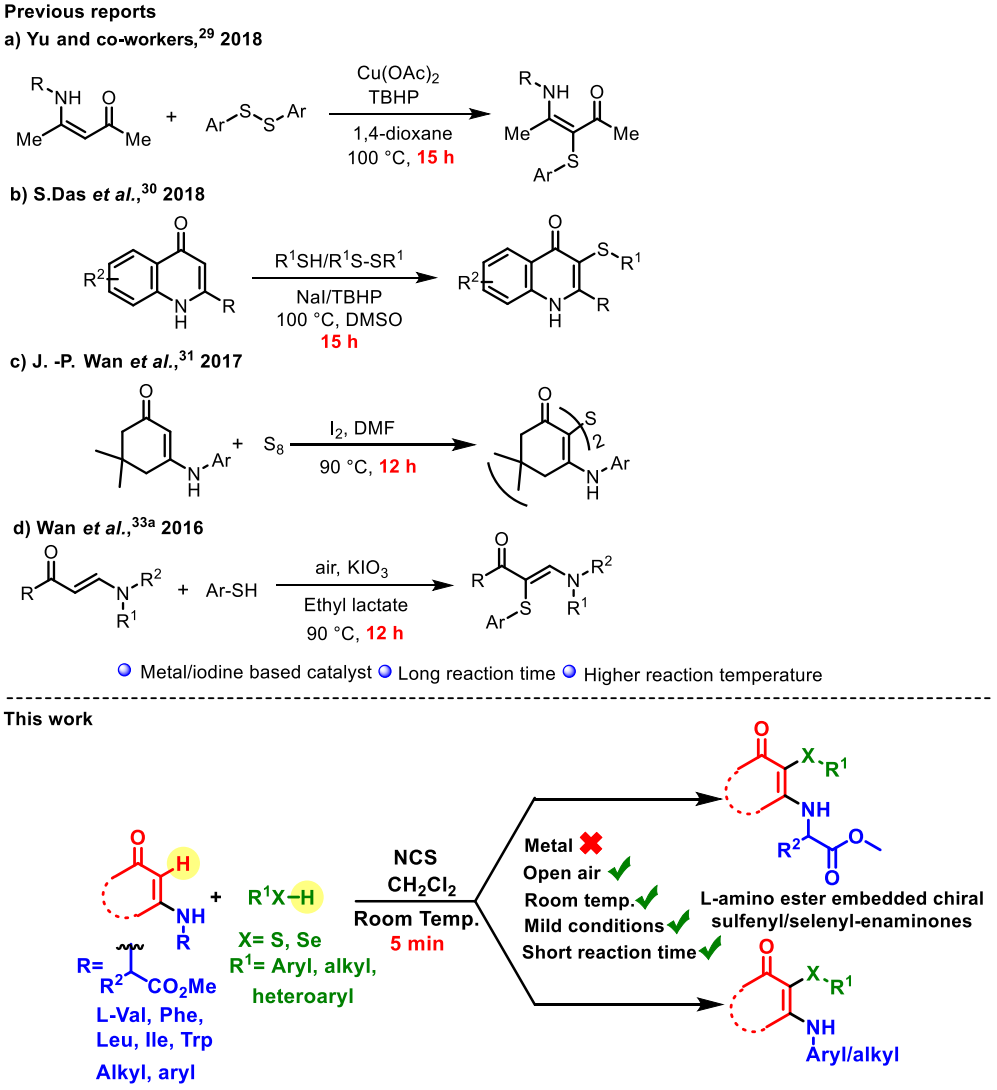


Figure 1. Some bioactive compounds bearing sulfenyl enamine, L-amino ester, *N*-alkyl-L-amino acid, and organoselenium moieties.

Scheme 1. Various Methodologies for Sulfenylation of Enaminones



benzylidene-4-phenyl-1,3-diselenole (BPD) acts as an antioxidant and a hepatoprotective agent against oxidative stress (Figure 1).[24] Because of all these important bioactivities, the synthesis of sulfenyl and selenyl enaminones of α-amino esters and aryl/alkyl amines is significant.

The creation of a C−S bond using transition-metal (Pd, Rh, Au, Cu, Ni, *etc.*) catalysts,[25] iodinating agents with oxidants,[26] photocatalysts,[27] and electrochemical oxidation[28] has drawn considerable attention in recent years. Sulfenylation of NH enaminones utilizing a variety of catalysts and reagents such as

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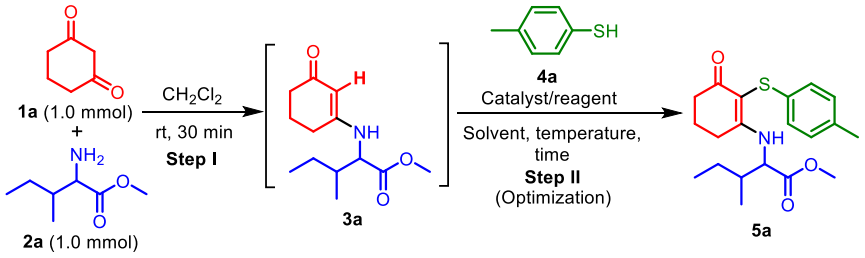
Table 1. Optimization of Reaction Conditions for Sulfenylation (Step II)[a]



entry	catalyst/reagent	oxidant (3.0 equiv)	amount of thiophenol **4a** (equiv)	solvent (2.0 mL)	temp (°C)	time	yield of **5a**[b] (%)
1			1.0	CH_2Cl_2	rt	24 h	
2	I_2 (10 mol %)	DMSO	1.0	CH_2Cl_2	rt	24 h	
3	I_2 (10 mol %)	DMSO	1.0	DCE	80	4 h	68
4	KIO_3 (10 mol %)	DMSO	1.0	DCE	80	6 h	24
5	NaI (3.0 equiv)	DMSO	1.0	DCE	80	6 h	trace
6	NCS (0.5 equiv)		1.0	CH_2Cl_2	rt	20 min	60
7	NCS (1.0 equiv)		1.0	CH_2Cl_2	rt	5 min	86
8	NCS (1.0 equiv)		1.2	CH_2Cl_2	rt	5 min	88
9	NCS (1.0 equiv)		**1.5**	**CH_2Cl_2**	**rt**	5 min	**90**
10	NCS (1.2 equiv)		1.5	CH_2Cl_2	rt	5 min	90
11	NCS (1.0 equiv)		1.5	CH_2Cl_2	rt	10 min	90
12	NCS (1.0 equiv)		1.5	CH_2Cl_2	rt	20 min	90
13	NBS (1.0 equiv)		1.5	CH_2Cl_2	rt	30 min	37
14	NIS (1.0 equiv)		1.5	CH_2Cl_2	rt	30 min	25
15[c]	NCS (1.0 equiv)		1.5	CH_2Cl_2	rt	5 min	87
16[d]	NCS (1.0 equiv)		1.5	CH_2Cl_2	rt	1 h	58
17	NCS (1.0 equiv)		1.5	CH_3CN	rt	30 min	72
18	NCS (1.0 equiv)		1.5	toluene	rt	30 min	78
19	NCS (1.0 equiv)		1.5	EtOH	rt	2 h	trace
20	NCS (1.0 equiv)		1.5	DMSO	rt	2 h	trace

[a]Reaction conditions: At first, a mixture of **1a** (1.0 mmol) and **2a** (1.0 mmol) was stirred in DCM (2.0 mL) at rt for 30 min (step I). Then, **4a**, catalyst/reagent, and oxidant were added to the same reaction mixture for further stirring at rt, step II (entries 1−2 and 6−16). In other cases (entries 3−5 and 17−20), the removal of solvent DCM was performed after step I followed by the addition of **4a**, catalyst/reagent, oxidant, and different solvents (2.0 mL) for further reaction (step II). [b]Isolated yield of product **5a**. [c]Reaction was carried out under a N_2 atmosphere (entry 15). [d]Reactants **1a**, **2a**, **4a**, and **NCS** were added at a time for reaction (entry 16).

$Cu(OAc)_2$ as metal catalysts and NaI-TBHP/DMSO as iodine sources with oxidants has been reported (Scheme 1a,b).[29,30] Synthesis of sulfur-bridged NH enaminones has been achieved through I_2-mediated double C(sp^2)−H sulfenylation employing elemental sulfur (S_8) as a "S" source (Scheme 1c).[31] Sulfenylation and selenylation of tertiary enaminones have also been accomplished through palladium catalysis[32] and KIO_3 catalysis[33] (Scheme 1d). Although these methods are synthetically important, the requirement of transition-metal catalysts, long reaction time, and consumption of external thermal energy diminish their green credentials substantially. Moreover, for sulfenylation of enaminones of L-α-amino esters, drastic reaction conditions such as prolonged heating or heating in the presence of metal catalysts or oxidants should be avoided due to the presence of a racemization-prone chiral center and reactive side chains. Hence, the development of a metal-free room-temperature methodology for sulfenylation of enaminones/enamines becomes a chemist's objective.

N-chlorosuccinimide (NCS), known as less toxic, is a versatile reagent in organic synthesis with diverse applications such as chlorination, oxidation, halocyclizations, C−C bond formation, functional group transformations, and C−H functionalization and rearrangements.[34] In continuation of our effort in developing an efficient C−H sulfenylation method[35] and sustainable room-temperature reactions,[36] herein we report NCS-assisted metal-free sulfenylation and selenylation of enaminones of L-α-amino esters and aryl/alkyl amines at room temperature in open air (Scheme 1).

RESULTS AND DISCUSSION

The present synthesis was planned as a two-step one-pot process where initially L-α-amino esters were condensed with 1,3-diketones to generate enaminones (step I) and subsequently enaminones were reacted with thiols to form sulfenyl enaminones (step II). The optimization of reaction conditions was carried out employing 1,3-cyclohexanedione (**1a**), methyl L-isoleucinate (**2a**), and *p*-thiocresol (**4a**) as reactants for the synthesis of sulfenyl enaminone **5a** (Table 1). Initially, **1a** (1.0 mmol) was condensed with **2a** (1.0 mmol) in CH_2Cl_2 (DCM) to produce enaminone **3a** in quantitative yield upon 30 min of stirring at room temperature (step I). Then, 1.0 equiv of thiophenol **4a** was added to the reaction mixture and the resultant mixture was stirred further for 24 h at room temperature (step II). However, the reaction did not proceed at all to form the expected sulfenyl enaminone **5a** (Table 1, entry 1). Then, a catalytic amount of I_2 (10 mol %) with 3.0 equiv of DMSO as an oxidant was added to the reaction mixture which was stirred further for 24 h at room temperature. Again, the desired product **5a** was not formed even after prolonged stirring (Table 1, entry 2). At this point,

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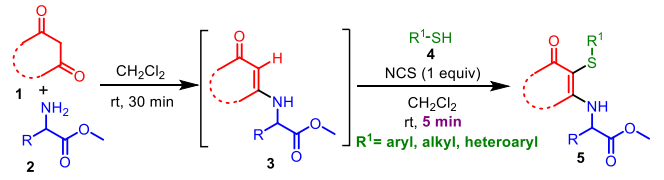
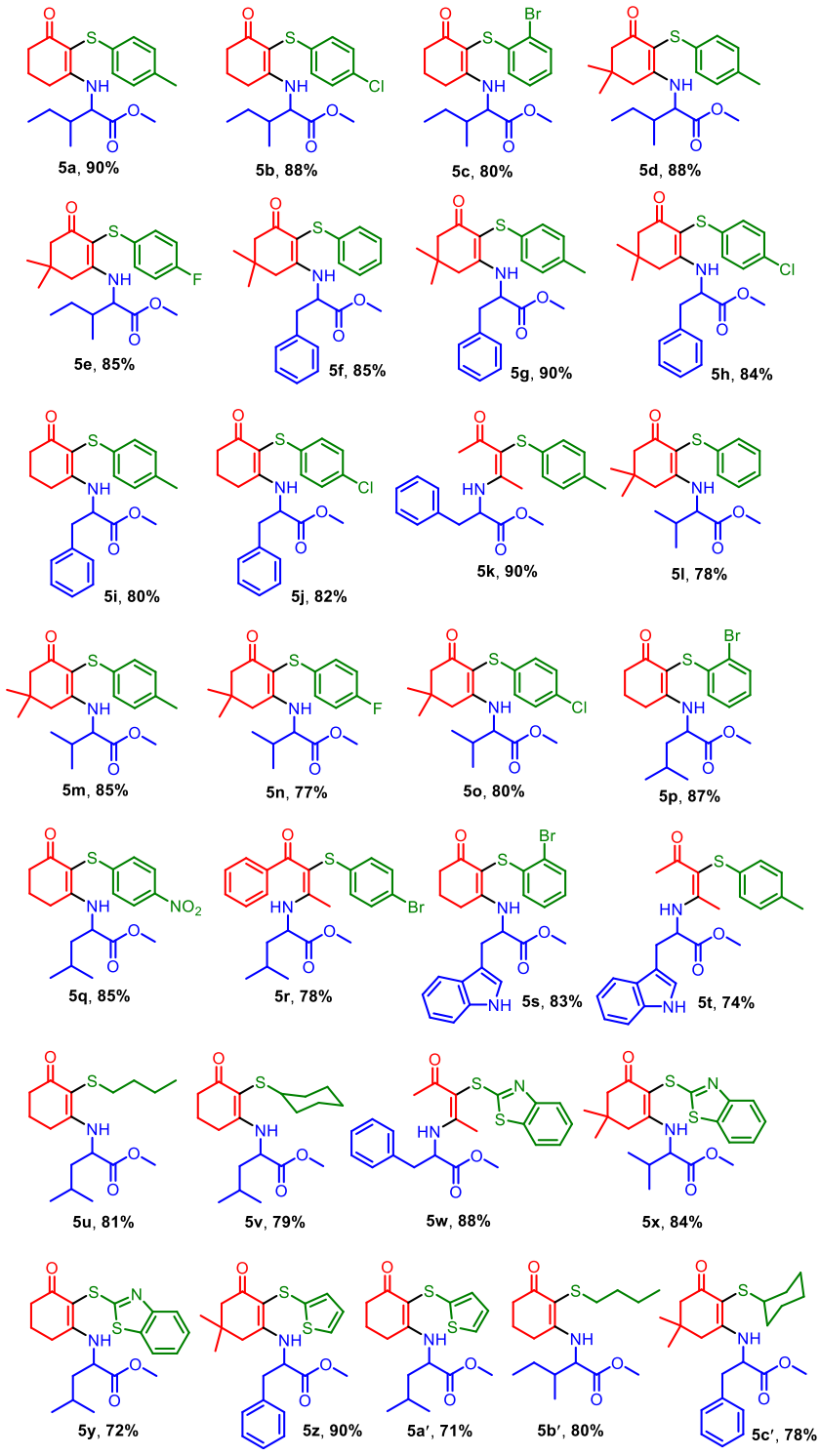
Table 2. Library Synthesis of α-Amino Ester-Embedded Sulfenyl Enaminones 5[a,b]





[a]Reaction conditions: initially, a mixture of **1** (1.0 mmol) and **2** (1.0 mmol) was stirred in DCM (2.0 mL) for 30 min at rt (step I). Then, thiol **4** (1.5 mmol) and NCS (1.0 mmol) were added to the same reaction mixture for further stirring at rt for 5 min in open air (step II). [b]Isolated yield of product **5**.

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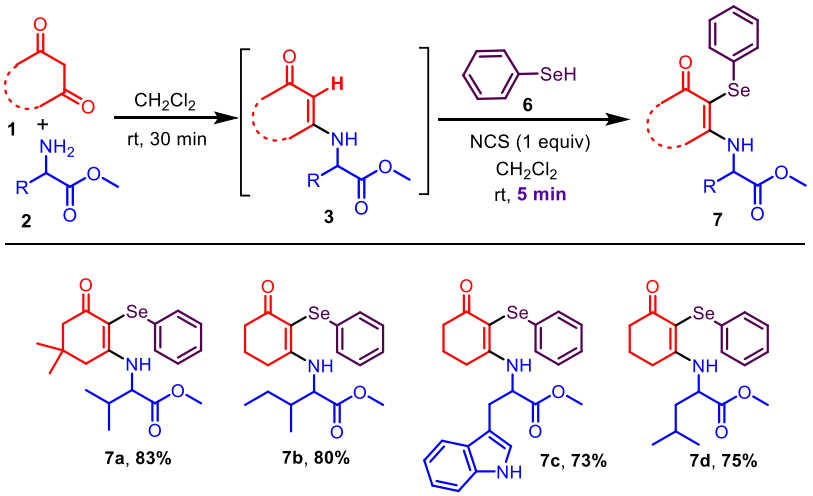
Table 3. Substrate Scope in Synthesis of α-Amino Ester-Embedded Selenyl Enaminones 7[a,b]



[a]Reaction conditions: initially, a mixture of **1** (1.0 mmol) and **2** (1.0 mmol) was stirred in DCM (2.0 mL) at rt for 30 min to produce **3**. Then, **6** (1.5 mmol) and NCS (1.0 mmol) were added to the same reaction mixture for further stirring at rt for 5 min in open air. [b]Isolated yield of product **7**.

we realized that probably some heating is necessary for successful sulfenylation of **3a**. Therefore, solvent DCM was removed under vacuum from the reaction mixture after initial condensation in step I and the intermediate **3a** was dissolved in higher boiling DCE (2 mL) for step II reaction. Then, **4a** (1.0 equiv) and I_2 (10 mol %) with 3.0 equiv of DMSO were added. Interestingly, after 4 h of stirring of the reaction mixture at 80 °C, the desired product **5a** was obtained in moderate yield, ∼68% (Table 1, entry 3). The other iodine sources such as KIO_3 and NaI in the presence of oxidant DMSO were less productive compared to the I_2/DMSO catalytic system (Table 1, entries 4 & 5).

Since our objective was to develop a metal-free room-temperature method, next, we choose NCS as a promoter for sulfenylation. Therefore, 0.5 equiv of NCS and 1.0 equiv of thiophenol **4a** were added to the reaction mixture obtained from step I. Interestingly, we observed that the desired product **5a** was formed in 60% yield within 20 min of open air stirring of the reaction mixture at room temperature (Table 1, entry 6). To further improve the yield of **5a**, the amounts of NCS and **4a** were varied from 0.5 to 1.2 equiv and 1.0−1.5 equiv, respectively (Table 1, entries 6−10). It was observed that employment of 1.0 equiv of NCS and 1.5 equiv of **4a** produced **5a** in the highest yield (∼90%) within just 5 min of stirring (Table 1, entry 9). When the reaction time was increased from 5 to 10 and 20 min, the yield of **5a** was essentially the same (Table 1, entries 11 and 12). Next, we examined the performance of other *N*-halosuccinimides such as *N*-bromosuccinimide (NBS) and *N*-iodosuccinimide (NIS) in the sulfenylation process (step II). In both cases, the oxidized product of *p*-thiocresol (**4a**), that is, 1,2-di-*p*-tolyldisulfane (ArS-SAr), was formed as a major product instead of sulfenyl enaminone **5a** (Table 1, entries 13 and 14).[37] Additionally, when the reaction with NCS in DCM was carried out in the absence of air, that is, under a N_2 atmosphere, the product **5a** was formed in 87% yield (Table 1, entry 15), comparable to that of the open air reaction (Table 1, entry 9). The result indicates that there is no effect of aerial oxygen on the sulfenylation process. Furthermore, another reaction was carried out by adding reactants **1a**, **2a**, **4a**, and reagent NCS at a time in DCM. However, after 1 h of stirring of the mixture, the yield of product **5a** was found in a lower range (∼58%) possibly due to the formation of unwanted side products (Table 1, entry 16). To examine the effect of solvents on the NCS-mediated sulfenylation process (step II), different solvents such as CH_3CN, toluene, EtOH, and DMSO were employed after the removal of DCM. Although the reaction furnished **5a** in good yield in CH_3CN and toluene, 72−78% (Table 1, entries 17 and 18), unsatisfactory results were obtained in EtOH and DMSO (Table 1, entries 19 and 20). Therefore, finally, it was established that stirring of a mixture of **3a** (obtained from step I), **4a** (1.5 equiv), and NCS (1.0 equiv) in DCM at room temperature for 5 min produces sulfenyl enaminone **5a** in the maximum yield, ∼90% (Table 1, entry 9).

To explore the substrate scope and functional group tolerance, a variety of 1,3-dicarbonyls (**1**), methyl ester of L-α-amino acids (**2**), and aryl/alkyl/heteroaryl thiols (**4**) were reacted to produce different sulfenyl enaminones (**5**) under the optimized reaction conditions (Table 1, entry 9). It was evident from Table 2 that L-α-amino esters (**2**) bearing aliphatic, aromatic, and heterocyclic side chains underwent sulfenylation quite smoothly to produce a library of sulfenyl enaminones (**5**) in good-to-excellent yield (71−90%). Importantly, both cyclic and acyclic 1,3-dicarbonyls (**1**) such as 1,3-cyclohexanedione, dimedone, acetylacetone, and benzoylacetone participated well in the reaction (Table 2). Furthermore, different thiophenols (**4**) bearing electron-donating and -withdrawing groups were well-tolerated in the reactions to produce **5a−t**. Aliphatic thiols such as 1-butanethiol and cyclohexanethiol also participated significantly in the reaction to furnish sulfenylated products **5u**, **5v**, **5b′**, and **5c′** in very good yield, 78−81% (Table 2). The heterocyclic thiols such as 2-mercaptobenzothiazole and 2-thiophenethiol were found compatible with this reaction to produce the sulfenylated products **5w−z** and **5a′** in very good yield, 71−

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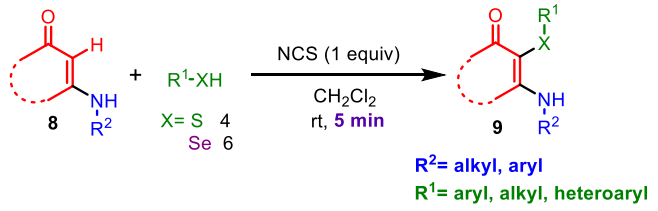
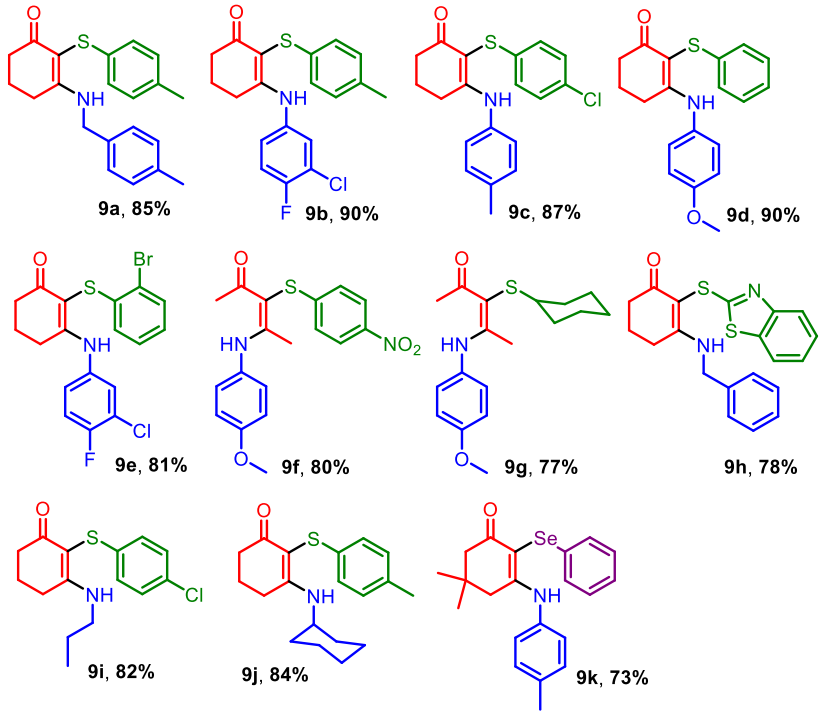
Table 4. Substrate Scope in Synthesis of β-Amino Sulfide/Selenide Derivatives 9[a,b]





[a]Reaction conditions: **8** (1.0 mmol) and NCS (1.0 mmol) were added to a solution of thiols **4** (1.5 mmol) or benzeneselenol **6** (1.5 mmol) in DCM and the mixture was stirred at rt for 5 min in open air. [b]Isolated yield of product **9**.

88% (Table 2). Benzeneselenol **6** also produced selenyl enaminones **7a−d** in very good yield (73−83%), under the same reaction conditions as that of sulfenylation (Table 3).

Furthermore, different aryl/alkyl/heteroaryl thiols (**4**) successfully reacted with enaminones of aryl and alkyl amines (**8**) to produce a series of β-amino sulfide derivatives **9a−j** in good-to-excellent yield, 77−90% (Table 4). When benzeneselenol **6** was employed, the corresponding selenyl enaminone **9k** was also formed in good yield, ~73% (Table 4). Therefore, successful synthesis of diverse sulfenyl and selenyl enaminones in good-to-excellent yield (71−90%) demonstrated a large substrate scope and high degree of functional group tolerance of this mild and eco-friendly synthesis (Tables 2−4). All the sulfenylated and selenylated products (**5**, **7**, and **9**) were characterized by ^{1}H and ^{13}C NMR and HRMS/elemental analyses. Furthermore, the X-ray crystal structure of sulfenyl enaminone **5w** corroborated the product formation and also established the preferred geometrical isomer of **5w** where the bulky heteroaryl sulfenyl and L-phenylalanyl groups are in *trans* disposition (Figure 2).

The industrial applicability of this sulfenylation approach was tested by gram-scale synthesis of sulfenyl enaminone **5a**. An one-pot sequential reactions of 1,3-cyclohexanedione **1a** (6.5 mmol), methyl L-isoleucinate **2a** (6.5 mmol) and *p*-thiocresol **4a** (9.75 mmol) in the presence of NCS (6.5 mmol)

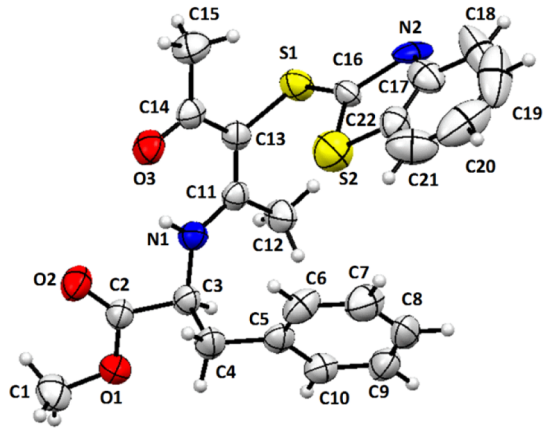


Figure 2. ORTEP diagram of compound **5w**; thermal ellipsoids are drawn at the 50% probability level (CCDC 2104278); crystal was grown in DMSO solvent.

under the optimized conditions afforded the desired sulfenylated product **5a** in very high yield, 86% (Scheme 2).

Some control experiments were carried out to decipher the mechanism of the sulfenylation reaction (Scheme 3). Initially, 1,3-cyclohexanedione (**1a**) and methyl L-isoleucinate (**2a**) were reacted at room temperature to afford a compound which

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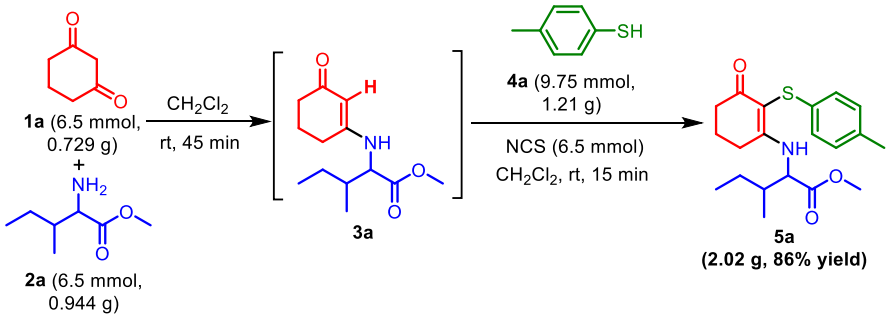
Scheme 2. Gram-Scale Synthesis



was isolated and characterized as enaminone **3a** by $^{1}H/^{13}C$ NMR and HRMS analysis (Scheme 3a). To gain more mechanistic insights, two reactions were performed sequentially. At first, **3a** was treated with NCS in DCM which afforded the chlorinated product methyl 2-((2-chloro-3-oxocyclohex-1-en-1-yl)amino)-3-methylpentanoate **3aa**. Then, **3aa** was exposed to *p*-thiocresol **4a** in DCM for sulfenylation at rt (Scheme 3b). Interestingly, the reaction did not proceed at all, which nullified the involvement of **3aa** as an intermediate in the sulfenylation reaction (Scheme 3b). Then, a reaction between enaminone **3a** and thiol **4a** was carried out in the presence of 0.5 equiv of radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) under the optimized conditions (Scheme 3c). After 10 min of stirring of the reaction mixture at rt, the sulfenylated product **5a** was formed in 76% yield which clearly suggested that the sulfenylation process does not follow a radical-mediated pathway. When dimeric 1,2-di-*p*-tolyldisulfane **4aa** was treated with enaminone **3a**, the desired product **5a** was not formed even after 2 h of stirring under the standard conditions (Scheme 3d). This result indicated that the disulfide **4aa** was not involved in this sulfenylation as an intermediate. To examine the role of visible light as a catalyst in sulfenylation, the reaction was carried out in a dark chamber. The formation of sulfenyl enaminone **5a** in high yield (~88%) nullified the role of visible light in the sulfenylation reaction (Scheme 3e). Next, 1.0 equiv of Et_3N was added as proton sponge to the reaction mixture during sulfenylation (Scheme 3f), and the formation of product **5a** in high yield (~87%) implied that the *in situ*-generated HCl neither inhibited nor catalyzed the sulfenylation process. Next, thiol **4a** was treated with NCS under standard conditions in the absence of enaminone **3a** (Scheme 3g). The formation of *p*-tolyl hypochlorothioite **4ab** (isolated and characterized by $^{1}H/^{13}C$ NMR) and succinimide (detected by LCMS, Supporting Information) clearly indicated the involvement of sulfenyl chloride (R^1SCl) as an intermediate in the sulfenylation reaction.

Based on the control experiments and the existing literature,[34c,37] a plausible mechanism of the sulfenylation reaction is depicted in Scheme 4. Initially, nucleophilic attack of the thiol (R^1SH) to the *N*-halosuccinimide produces sulfenyl halide R^1SX (**II**, X = Cl, Br, and I) and succinimide (**I**). Since NCS is a milder oxidizing agent than NBS and NIS, the generated sulfenyl chloride (R^1SCl) has a longer life period than sulfenyl bromide/iodide (R^1SBr/R^1SI).[37] The more reactive R^1SBr/R^1SI reacts rapidly with starting material thiols **4** (R^1SH) to furnish disulfide $R^1S\text{-}SR^1$ (**IV**) as a major product (Table 1, entries 13 and 14). The disulfide $R^1S\text{-}SR^1$ is significantly less reactive and requires drastic reaction conditions such as prolonged heating and external oxidants for sulfenylation of enaminones. On the other hand, the enaminone **3** undergoes nucleophilic displacement reaction smoothly with sulfenyl chloride (R^1SCl) at room temperature and produces the iminium ion intermediate **III**. Finally, dehydrochlorination of **III** affords the sulfenylated product **5**. The starting thiols **4** might be oxidized to disulfide $R^1S\text{-}SR^1$ when dimethyl sulfoxide (DMSO) was used as a solvent causing the formation of **5** in trace amounts (Table 1, entry 20).

CONCLUSIONS

In summary, a two-step one-pot protocol has been developed for rapid synthesis of biologically important sulfenyl and selenyl enaminones of L-*α*-amino esters at room temperature through NCS-mediated sulfenylation and selenylation. The method is also suitable for sulfenylation and selenylation of enaminones of other aryl and alkyl amines. The employment of NCS is advantageous over NBS/NIS, as the *in situ*-generated sulfenyl chloride (R^1SCl) undergoes cross-dehydrogenative coupling with enaminones, whereas more reactive sulfenyl bromide/iodide (R^1SBr/R^1SI) produces oxidized product disulfides ($R^1S\text{-}SR^1$) as the major product. This NCS-mediated sulfenylation has several advantages such as mild and eco-friendly reaction conditions, operational simplicity, wider substrate scope, and avoidance of metal catalysts. The synthetic modification of natural amino acids is extremely important owing to their applications in proteomics, diagnosis, drug delivery, and so forth. In this context, the NCS-mediated mild and eco-friendly method may be useful for synthesis of sulfur- and selenium-containing bioactive *N*-functionalized L-*α*-amino acids/esters/peptides and related medicinally active molecules in the industry.

EXPERIMENTAL SECTION

General Remarks. All the chemicals and solvents were purchased from commercial suppliers and used without additional purification. Methyl L-amino esters **2** were synthesized from the corresponding L-amino acids according to the literature procedure.[38] Column chromatography was performed using silica gel (60−120 mesh, Merck). Melting points were determined in open capillary tubes. A Perkin-Elmer 782 spectrophotometer was used for recording IR spectra. ^{1}H (300/500 MHz) and ^{13}C NMR (75/126 MHz) spectra were recorded on Bruker instruments (300 MHz and DRX 500) in $CDCl_3$ and DMSO-d_6. The X-ray diffraction crystallography data were collected with MoK*α* radiation at 296 K using a Bruker APEX-II CCD System. HRMS spectra were obtained from Xevo G2-S QTof instrument. Elemental

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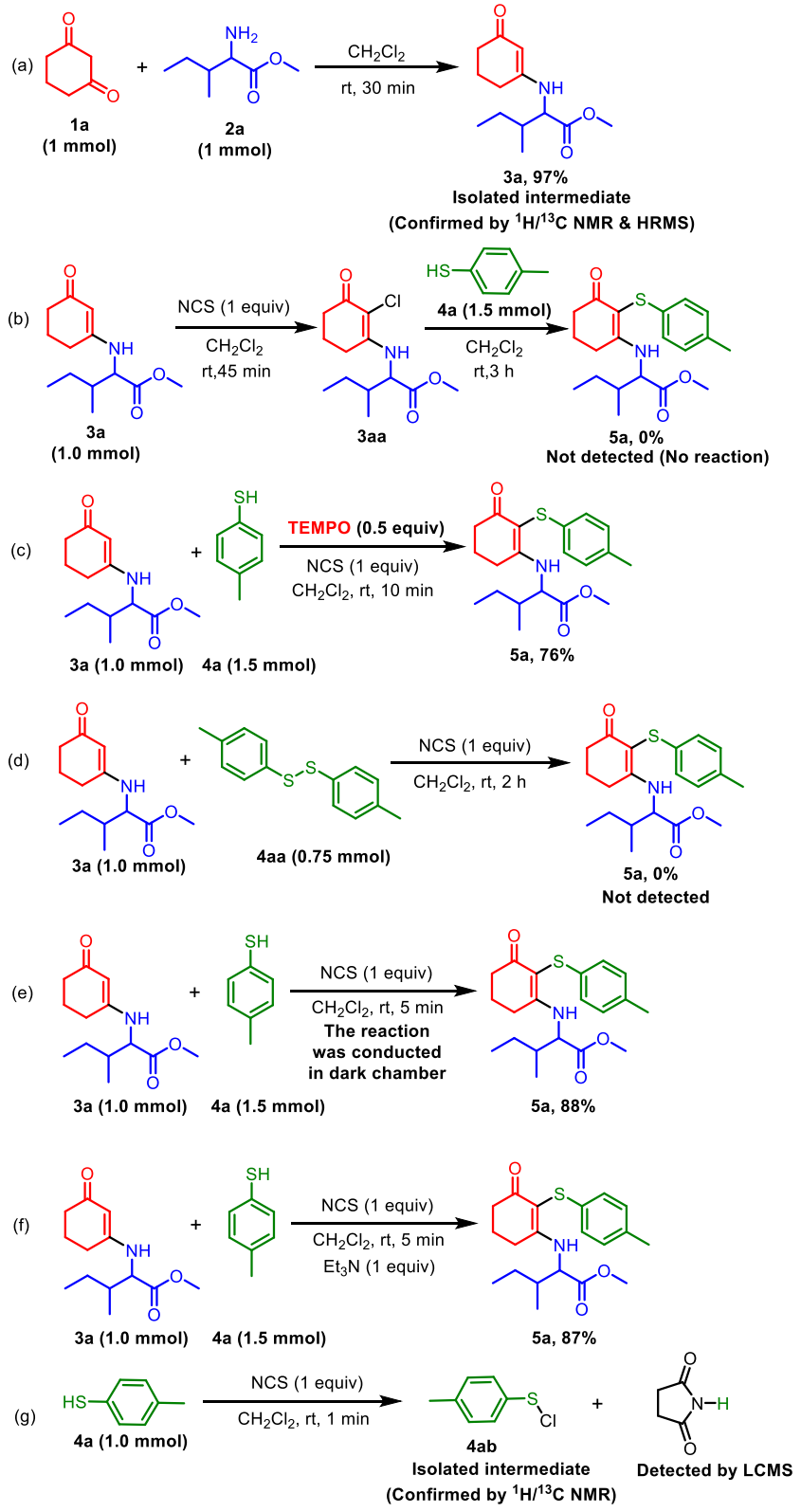
Scheme 3. Some Control Experiments



analyses (C, H, and N) were performed using a Perkin-Elmer 2400 elemental analyzer. LCMS was performed using a Shimadzu Prominence LC-20AD Binary pump, Shimadzu SIL-HTC autosampler, and applied biosystem API-2000 triple quadruple mass spectrometer equipped with an ESI source.

Experimental Procedure and Characterization Data of Isolated Intermediates. *Methyl-3-methyl-2-((3-oxocyclohex-1-en-1-yl)amino)pentanoate (**3a**).* A mixture of 1,3-cyclohexanedione, **1a** (1.0 mmol, 112 mg), and methyl L-isoleucinate, **2a** (1.0 mmol, 145 mg), in 2.0 mL of DCM was taken in a 50 mL round-bottom flask and the mixture was

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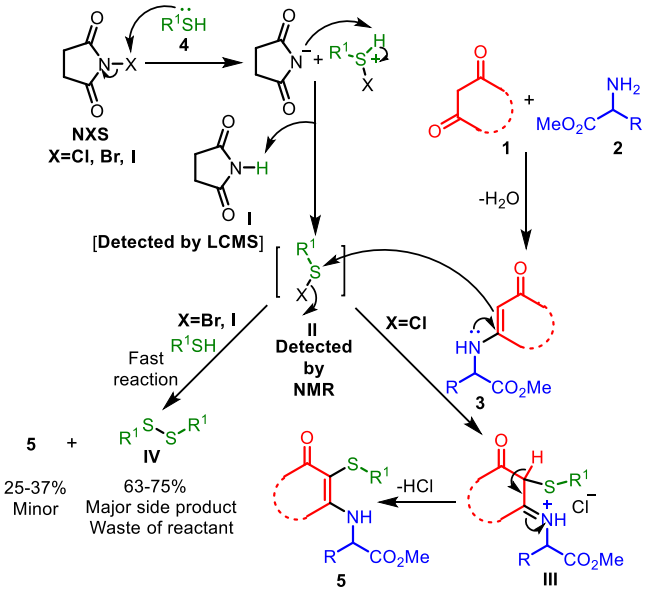
Scheme 4. Plausible Mechanism for Sulfenylation



stirred at rt (25−30 °C) for 30 min in open air. After completion of the reaction (observed by TLC monitoring), the reaction mixture was diluted with water and the organic layer was extracted with ethyl acetate (3 × 20 mL). The extracted organic part was dried over anhydrous sodium sulphate and concentrated *in vacuo*. The crude mass was purified by silica gel column chromatography using 40% ethyl acetate in hexane as an eluent to afford pure **3a**.

Yellow gum (232 mg, 97%); IR (Neat) $\bar{\nu}_{max}$: 3255, 2962, 1741, 1580, 1542 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 5.26−5.23 (m, 1H), 5.09 (s, 1H), 4.00−3.95 (m, 1H), 3.75 (s, 3H), 2.41−2.37 (m, 2H), 2.33−2.29 (m, 2H), 2.00−1.94 (m, 2H), 1.92−1.84 (m, 1H), 1.56−1.45 (m, 1H), 1.29−1.21 (m, 1H), 0.96−0.87 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 197.9, 172.00, 163.6, 97.6, 59.2, 52.3, 37.4, 36.2, 29.8, 25.8, 21.8, 15.0, 11.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{22}NO_3$, 240.1600; found, 240.1614.

*Methyl-2-((2-chloro-3-oxocyclohex-1-en-1-yl)amino)-3-methylpentanoate (**3aa**).* NCS (1.0 mmol, 133.5 mg) was added to a stirred solution of enaminone **3a** (1.0 mmol, 239 mg) in 2.0 mL of DCM taken in a 50 mL round-bottom flask. The resulting reaction mixture was stirred at rt (25−30 °C) for 45 min in open air. After completion of the reaction (checked by TLC monitoring), the reaction mixture was diluted with water and the organic layer was extracted with ethyl acetate (3 × 15 mL). The extracted organic part was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude mass was purified by silica gel column chromatography using 40% ethyl acetate in hexane as an eluent to afford pure **3aa**.

Yellow gum (232 mg, 85%); IR (Neat) $\bar{\nu}_{max}$: 3310, 2971, 1745, 1614, 1550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 5.91−5.88 (m, 1H), 4.03−3.98 (m, 1H), 3.72 (s, 3H), 2.48−2.39 (m, 4H), 1.99−1.91 (m, 2H), 1.89−1.79 (m, 1H), 1.54−1.40 (m, 1H), 1.26−1.13 (m, 1H), 0.92−0.87 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 187.9, 171.2, 158.3, 104.7, 60.1, 52.5, 38.9, 36.5, 26.3, 25.0, 20.6, 15.3, 11.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{21}ClNO_3$ 274.1211; found, 274.1212.

*1,2-Di-p-tolyldisulfane (**4aa**).*[39] The disulfide was produced as a major side product (**IV**, Scheme 4). Light yellow amorphous solid; mp 94−96 °C; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.59 (d, *J* = 7.8 Hz, 2H), 7.46 (d, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 7.5 Hz, 2H), 2.44 (s, 3H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 142.2, 140.9, 140.8, 135.4, 130.1, 129.7, 126.2, 124.3, 21.6, 21.4.

*p-Tolyl hypochlorothioite (**4ab**).*[40] NCS (1.0 mmol, 133.5 mg) was added to a stirred solution of *p*-thiocresol **4a** (1.0 mmol, 124 mg) in 2.0 mL of DCM taken in a 50 mL round-bottom flask. The resulting reaction mixture was stirred at rt (25−30 °C) for 1 min in open air. The reaction mixture became deep yellow-colored after the addition of NCS. After completion of the reaction (observed by TLC monitoring), the reaction mixture was diluted with water and the organic layer was extracted with ethyl acetate (2 × 15 mL). The extracted organic part was dried over anhydrous sodium sulphate and concentrated *in vacuo*. The crude mass was purified by silica gel column chromatography using 5% ethyl acetate in hexane as an eluent to afford pure **4ab**. Light yellow crystalline solid (135 mg, 85%); mp 44−46 °C; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.45 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 2.38 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 137.5, 133.9, 129.9, 128.6, 21.1.

General Procedure for Synthesis of α-Amino Ester-Embedded Sulfenyl Enaminones (5). Initially, a mixture of 1,3-dicarbonyls **1** (1.0 mmol) and methyl L-amino esters **2** (1.0 mmol) in 2.0 mL of DCM was taken in a 50 mL round-bottom flask and the mixture was stirred at rt (25−30 °C) for 30 min in open air. Then, thiols **4** (1.5 mmol) and NCS (1.0 mmol, 133.5 mg) were added to the same reaction pot and the resulting mixture was stirred further for 5 min at rt. After completion of the reaction (observed by TLC monitoring), the reaction mixture was diluted with water and the organic layer was extracted with ethyl acetate (3 × 20 mL). The extracted organic part was dried over anhydrous sodium sulphate and concentrated *in vacuo*. The crude mass was purified by silica gel column chromatography using 10−50% ethyl acetate in hexane as an eluent to afford pure sulfenyl enaminones **5**.

Spectral Data. Characterization data of compounds **5a−z** and **5a′−c′**.

*Methyl-3-methyl-2-((3-oxo-2-(p-tolylthio)cyclohex-1-en-1-yl)amino)pentanoate (**5a**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 1/1). Yellow gum (325 mg, 90%); IR (neat) $\bar{\nu}_{max}$: 3311, 2960, 1740, 1635, 1555 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.02−6.96 (m, 3H), 6.93−6.90 (m, 2H), 3.99−3.94 (m, 1H), 3.62 (br s, 1H), 2.49−2.41 (m, 4H), 2.17 (s, 3H), 2.00−1.91 (m, 2H), 1.79−1.69 (m, 1H), 1.28−1.17 (m, 1H), 0.98−0.86 (m, 1H), 0.77−0.72 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.3, 170.7, 166.9, 134.8, 132.4, 129.2, 126.7, 100.5, 60.1, 52.1, 38.3, 36.6, 26.2, 24.4, 20.6, 20.5, 15.0, 11.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{28}NO_3S$ 362.1791; found, 362.1767.

*Methyl-2-((2-((4-chlorophenyl)thio)-3-oxocyclohex-1-en-1-yl)amino)-3-methylpentanoate (**5b**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 1/1). Yellow gum (336 mg, 88%); IR (neat) $\bar{\nu}_{max}$: 3314, 2954, 1745, 1644, 1557 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.12−7.07 (m, 2H), 7.05−7.00 (m, 2H), 6.95−6.92 (m, 1H), 4.01−3.96 (m, 1H), 3.64 (s, 3H), 2.51−2.44 (m, 4H), 2.03−1.95 (m, 2H), 1.81−1.73 (m, 1H),

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1.31−1.18 (m, 1H), 1.02−0.90 (m, 1H), 0.80−0.75 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.3, 170.8, 167.5, 134.9, 130.9, 128.7, 127.7, 99.8, 60.3, 52.4, 38.5, 36.8, 26.4, 24.7, 20.6, 15.2, 11.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{25}ClNO_3S$ 382.1244; found, 382.1215.

*Methyl-2-((2-((2-bromophenyl)thio)-3-oxocyclohex-1-en-1-yl)amino)-3-methylpentanoate (**5c**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 1/1). Yellow gum (341 mg, 80%); IR (neat) $\bar{\nu}_{max}$: 3350, 2935, 1741, 1642, 1552 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.39 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.08−7.02 (m, 1H), 6.90−6.78 (m, 3H), 3.96−3.91 (m, 1H), 3.61 (s, 3H), 2.55−2.47 (m, 4H), 2.06−1.97 (m, 2H), 1.83−1.74 (m, 1H), 1.31−1.17 (m, 1H), 1.03−0.88 (m, 1H), 0.78−0.71 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.5, 170.8, 167.8, 137.2, 132.6, 127.6, 126.4, 126.3, 121.9, 99.7, 60.7, 52.5, 38.4, 37.0, 26.6, 24.8, 20.8, 15.4, 11.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{25}BrNO_3S$, 426.0739; found, 426.0763.

*Methyl-2-((5,5-dimethyl-3-oxo-2-(p-tolylthio)cyclohex-1-en-1-yl)amino)-3-methylpentanoate (**5d**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Yellow liquid (342 mg, 88%); IR (neat) $\bar{\nu}_{max}$: 3325, 2972, 1740, 1650, 1555 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.04−6.98 (m, 3H), 6.93−6.90 (m, 2H), 4.02−3.95 (m, 1H), 3.61 (s, 3H), 2.31−2.28 (m, 4H), 2.16 (s, 3H), 1.80−1.70 (m, 1H), 1.28−1.16 (m, 1H), 1.03 (s, 3H), 1.01 (s, 3H), 0.93−0.87 (m, 1H), 0.79−0.69 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.1, 171.0, 165.7, 135.1, 132.9, 129.4, 127.3, 99.8, 60.3, 52.4, 50.3, 39.8, 38.5, 31.8, 28.5, 28.4, 24.6, 20.8, 15.2, 11.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{32}NO_3S$, 390.2104; found, 390.2108.

*Methyl-2-((2-((4-fluorophenyl)thio)-5,5-dimethyl-3-oxocyclohex-1-en-1-yl)amino)-3-methylpentanoate (**5e**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Yellow semisolid (334 mg, 85%); IR (neat) $\bar{\nu}_{max}$: 3322, 2970, 1738, 1654, 1545 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.13−7.06 (m, 2H), 7.00−6.97 (m, 1H), 6.84−6.76 (m, 2H), 4.01−3.96 (m, 1H), 3.61 (s, 3H), 2.35−2.23 (m, 4H), 1.81−1.71 (m, 1H), 1.31−1.20 (m, 1H), 1.01 (s, 3H), 0.99 (s, 3H), 0.95−0.84 (m, 1H), 0.78−0.72 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 191.9, 171.0, 165.8, 161.1 (d, $^1J_{C\text{-}F}$ = 242.2 Hz), 131.8 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 129.0 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 115.6 (d, $^2J_{C\text{-}F}$ = 21.75 Hz), 99.7, 60.3, 52.4, 50.4, 39.8, 38.5, 31.8, 29.5, 28.4, 24.7, 15.2, 11.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{29}FNO_3S$, 394.1853; found, 394.1847.

*Methyl-(5,5-dimethyl-3-oxo-2-(phenylthio)cyclohex-1-en-1-yl)phenylalaninate (**5f**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Yellow semisolid (348 mg, 85%); IR (neat) $\bar{\nu}_{max}$: 3318, 2950, 1745, 1635, 1557 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.22−7.17 (m, 5H), 7.14−7.09 (m, 4H), 6.94−6.92 (m, 2H), 4.41−4.37 (m, 1H), 3.71 (s, 3H), 3.13 (dd, J_1 = 13.5 Hz, J_2 = 4.5 Hz, 1H), 2.92−2.87 (m, 1H), 2.34−2.26 (m, 2H), 2.21−2.18 (m, 1H), 1.84−1.81 (m, 1H), 1.00 (s, 3H), 0.85 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ_C 192.2, 170.8, 165.7, 136.7, 135.0, 129.4, 128.9, 128.7, 127.5, 126.9, 125.4, 99.2, 57.3, 52.8, 50.3, 39.9, 39.8, 31.6, 28.7, 28.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{28}NO_3S$, 410.1791; found, 410.1776.

*Methyl-(5,5-dimethyl-3-oxo-2-(p-tolylthio)cyclohex-1-en-1-yl)phenylalaninate (**5g**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Yellowish white amorphous solid (381 mg, 90%); mp 86−88 °C; IR (KBr) $\bar{\nu}_{max}$: 3311, 2960, 1740, 1638, 1552 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.17−7.09 (m, 3H), 7.06−6.93 (m, 5H), 6.88−6.85 (m, 2H), 4.34−4.27 (m, 1H), 3.66 (s, 3H), 3.07 (dd, J_1 = 13.8 Hz, J_2 = 4.2 Hz, 1H), 2.85−2.78 (m, 1H), 2.26−2.14 (m, 5H), 2.12−2.07 (m, 1H), 1.73−1.67 (m, 1H), 0.91 (s, 3H), 0.75 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.0, 170.7, 165.2, 135.0, 134.9, 133.0, 129.3, 129.2, 128.6, 127.3, 127.2, 99.7, 57.0, 52.6, 50.1, 39.8, 39.5, 31.3, 28.4, 27.9, 20.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{30}NO_3S$, 424.1947; found, 424.1976.

*Methyl-(2-((4-chlorophenyl)thio)-5,5-dimethyl-3-oxocyclohex-1-en-1-yl)phenylalaninate (**5h**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Yellowish white amorphous solid (373 mg, 84%); mp 132−134 °C; IR (KBr) $\bar{\nu}_{max}$: 3360, 2975, 1740, 1650, 1530 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.17−7.06 (m, 5H), 6.98−6.94 (m, 3H), 6.90−6.87 (m, 2H), 4.37−4.30 (m, 1H), 3.67 (s, 3H), 3.09 (dd, J_1 = 13.8 Hz, J_2 = 4.2 Hz, 1H), 2.90−2.83 (m, 1H), 2.28−2.22 (m, 2H), 2.16−2.11 (m, 1H), 1.83−1.77 (m, 1H), 0.93 (s, 3H), 0.79 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.1, 170.8, 165.9, 135.4, 134.9, 131.1, 129.3, 128.9, 128.8, 128.2, 127.6, 98.9, 57.1, 52.9, 50.3, 39.9, 39.8, 31.6, 28.6, 28.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{27}ClNO_3S$, 444.1401; found, 444.1396.

*Methyl-(3-oxo-2-(p-tolylthio)cyclohex-1-en-1-yl)-phenylalaninate (**5i**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 1/1). Yellow gum (316 mg, 80%); IR (neat) $\bar{\nu}_{max}$: 3375, 2970, 1748, 1638, 1562 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.23−7.14 (m, 4H), 7.05−6.99 (m, 4H), 6.93−6.89 (m, 2H), 4.42−4.35 (m, 1H), 3.71 (s, 3H), 3.12 (dd, J_1 = 13.8 Hz, J_2 = 4.2 Hz, 1H), 2.91−2.84 (m, 1H), 2.41−2.36 (m, 2H), 2.26 (s, 3H), 2.02−2.01 (m, 1H), 1.96−1.79 (m, 2H), 1.75−1.66 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 193.0, 170.8, 167.6, 135.1, 135.0, 132.8, 129.5, 129.4, 128.8, 127.5, 127.1, 100.7, 57.3, 52.8, 40.0, 36.7, 26.3, 20.9, 20.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{26}NO_3S$, 396.1634; found, 396.1620.

*Methyl-(2-((4-chlorophenyl)thio)-3-oxocyclohex-1-en-1-yl)phenylalaninate (**5j**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 1/1). Yellow gum (340 mg, 82%); IR (neat) $\bar{\nu}_{max}$: 3326, 2981, 1745, 1634, 1551 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.22−7.10 (m, 5H), 7.03−6.97 (m, 3H), 6.93−6.89 (m, 2H), 4.43−4.35 (m, 1H), 3.70 (br s, 3H), 3.11 (dd, J_1 = 13.8 Hz, J_2 = 3.9 Hz, 1H), 2.94−2.86 (m, 1H), 2.39−2.28 (m, 3H), 2.06−1.96 (m, 1H), 1.89−1.83 (m, 1H), 1.78−1.69 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.5, 170.8, 167.9, 135.2, 134.8, 130.9, 129.2, 128.8, 128.7, 127.7, 127.5, 99.5, 57.1, 52.9, 39.7, 36.9, 26.4, 20.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{23}ClNO_3S$, 416.1088; found, 416.1063.

*Methyl-(E)-(4-oxo-3-(p-tolylthio)pent-2-en-2-yl)-phenylalaninate (**5k**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 9/1). White amorphous solid (345 mg, 90%); mp 100−102 °C; IR (KBr) $\bar{\nu}_{max}$: 3414, 2954, 1745, 1582 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 12.70 (br s, 1H), 7.28−7.15 (m, 5H), 6.97−6.95 (m, 2H), 6.78 (br s, 2H), 4.42−4.34 (m, 1H), 3.71 (s, 3H), 3.21 (dd, J_1 = 13.8 Hz, J_2 = 4.5 Hz, 1H), 3.01−2.93 (m,

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1H), 2.24 (s, 3H), 2.21 (s, 3H), 1.86 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 200.5, 170.9, 169.7, 136.6, 135.8, 134.1, 129.7, 129.4, 128.8, 127.4, 124.1, 95.0, 59.5, 52.8, 40.0, 29.1, 20.8, 17.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{26}NO_3S$, 384.1634; found, 384.1621.

*Methyl-(5,5-dimethyl-3-oxo-2-(phenylthio)cyclohex-1-en-1-yl)valinate (**5l**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Yellow gum (282 mg, 78%); IR (neat) $\bar{\nu}_{max}$: 3373, 2965, 1741, 1632, 1546 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.15−7.13 (m, 4H), 7.05−6.96 (m, 2H), 3.97−3.92 (m, 1H), 3.65 (s, 3H), 2.40−2.34 (m, 4H), 2.13−2.04 (m, 1H), 1.09 (s, 3H), 1.07 (s, 3H), 0.82−0.75 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 191.9, 170.8, 165.6, 136.3, 128.6, 126.6, 125.2, 99.1, 61.1, 52.3, 50.3, 39.8, 31.8, 31.7, 28.5, 28.3, 18.6, 17.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{28}NO_3S$, 362.1791; found, 362.1767.

*Methyl-(5,5-dimethyl-3-oxo-2-(p-tolylthio)cyclohex-1-en-1-yl)valinate (**5m**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Yellow gum (320 mg, 85%); IR (neat) $\bar{\nu}_{max}$: 3328, 2974, 1740, 1640, 1555 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.03−6.99 (m, 3H), 6.92−6.89 (m, 2H), 3.99−3.93 (m, 1H), 3.60 (s, 3H), 2.37−2.24 (m, 4H), 2.15 (s, 3H), 2.09−1.98 (m, 1H), 1.02 (s, 3H), 1.00 (s, 3H), 0.78−0.72 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.1, 171.0, 165.9, 135.1, 132.9, 129.4, 127.2, 99.7, 61.0, 52.4, 50.3, 39.8, 31.8, 31.7, 28.5, 28.3, 20.8, 18.6, 17.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{30}NO_3S$, 376.1947; found, 376.1934.

*Methyl-(2-((4-fluorophenyl)thio)-5,5-dimethyl-3-oxocyclohex-1-en-1-yl)valinate (**5n**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Light yellow gum (292 mg, 77%); IR (neat) $\bar{\nu}_{max}$: 3335, 2982, 1745, 1635, 1564 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.17−7.10 (m, 2H), 7.04−6.99 (m, 1H), 6.88−6.80 (m, 2H), 3.99−3.93 (m, 1H), 3.64 (br s, 3H), 2.38−2.25 (m, 4H), 2.13−2.04 (m, 1H), 1.06−1.02 (m, 6H), 0.83−0.76 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 191.9, 171.0, 165.9, 161.2 (d, $^1J_{C\text{-}F}$ = 243.0 Hz), 131.7 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 129.0 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 115.7 (d, $^2J_{C\text{-}F}$ = 21.7 Hz), 99.8, 61.1, 52.5, 50.4, 39.9, 31.9, 31.8, 28.6, 28.4, 18.7, 17.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{27}FNO_3S$, 380.1696; found, 380.1682.

*Methyl-(2-((4-chlorophenyl)thio)-5,5-dimethyl-3-oxocyclohex-1-en-1-yl)valinate (**5o**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Yellow semisolid (316 mg, 80%); IR (neat) $\bar{\nu}_{max}$: 3325, 2980, 1740, 1641, 1548 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.12−7.03 (m, 4H), 6.95−6.92 (m, 1H), 3.97−3.92 (m, 1H), 3.65 (br s, 3H), 2.34−2.31 (m, 4H), 2.12−2.04 (m, 1H), 1.06−1.03 (m, 6H), 0.83−0.76 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 191.9, 171.0, 166.1, 135.3, 131.1, 128.8, 128.1, 98.9, 61.1, 52.5, 50.4, 39.9, 31.9, 31.8, 28.6, 28.4, 18.8, 17.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{27}ClNO_3S$, 396.1401; found, 396.1387.

*Methyl-(2-((2-bromophenyl)thio)-3-oxocyclohex-1-en-1-yl)leucinate (**5p**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 1/1). Yellow gum (370 mg, 87%); IR (neat) $\bar{\nu}_{max}$: 3364, 2984, 1747, 1652, 1542 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.40 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.10−7.05 (m, 1H), 6.92−6.86 (m, 1H), 6.83−6.80 (m, 1H), 6.67−6.64 (m, 1H), 4.16−4.08 (m, 1H), 3.63 (s, 3H), 2.55−2.47 (m, 4H), 2.07−1.98 (m, 2H), 1.67−1.49 (m, 2H), 1.40−1.29 (m, 1H), 0.80−0.75 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.4, 171.8, 168.1, 137.2, 132.6, 127.6, 126.4, 126.3, 121.7, 99.4, 54.6, 52.7, 41.6, 37.0, 26.6, 24.6, 22.6, 21.6, 20.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{25}BrNO_3S$, 426.0739; found, 426.0753.

*Methyl-(2-((4-nitrophenyl)thio)-3-oxocyclohex-1-en-1-yl)-leucinate (**5q**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 1/1). Yellow semisolid (332 mg, 85%); IR (neat) $\bar{\nu}_{max}$: 3330, 2961, 1745, 1628, 1563 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.98 (d, J = 9.0 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 6.60−6.57 (m, 1H), 4.19−4.11 (m, 1H), 3.66 (s, 3H), 2.58−2.48 (m, 4H), 2.09−2.01 (m, 2H), 1.69−1.60 (m, 1H), 1.57−1.51 (m, 1H), 1.48−1.40 (m, 1H), 0.82−0.79 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 191.9, 171.7, 168.5, 146.5, 145.1, 125.4, 123.8, 97.5, 54.4, 52.7, 41.6, 36.8, 26.6, 24.6, 22.5, 21.7, 20.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{25}N_2O_5S$, 393.1485; found, 393.1472.

*Methyl-(E)-(3-((4-bromophenyl)thio)-4-oxo-4-phenylbut-2-en-2-yl)leucinate (**5r**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 9/1). Brown semisolid (371 mg, 78%); IR (neat) $\bar{\nu}_{max}$: 3434, 2954, 1745, 1571 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 13.03−13.00 (m, 1H), 7.39−7.24 (m, 7H), 6.96−6.91 (m, 2H), 4.41−4.34 (m, 1H), 3.82 (s, 3H), 2.29 (s, 3H), 1.91−1.88 (m, 2H), 1.31−1.25 (m, 1H), 1.05−0.99 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 197.5, 171.7, 142.3, 140.5, 131.8, 129.1, 128.2, 127.3, 126.6, 125.8, 117.8, 93.7, 56.3, 52.8, 41.6, 24.9, 22.7, 21.8, 17.6; Anal. Calcd for $C_{23}H_{26}BrNO_3S$: C, 57.98; H, 5.50; N, 2.94. Found: C, 57.87; H, 5.63; N, 2.86.

*Methyl-(2-((2-bromophenyl)thio)-3-oxocyclohex-1-en-1-yl)tryptophanate (**5s**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 1/1). Yellow amorphous solid (414 mg, 83%); mp 128−130 °C; IR (KBr) $\bar{\nu}_{max}$: 3390, 2954, 1745, 1628, 1542 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 9.00−8.96 (m, 1H), 7.58−7.50 (m, 2H), 7.40−7.37 (m, 1H), 7.31−7.28 (m, 1H), 7.20−7.15 (m, 1H), 7.10−7.05 (m, 1H), 7.02−6.96 (m, 1H), 6.50 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H), 5.09 (br s, 1H), 5.05−5.03 (m, 1H), 4.43−4.37 (m, 1H), 3.71 (s, 3H), 3.52−3.45 (m, 1H), 3.37−3.30 (m, 1H), 2.29−2.22 (m, 2H), 2.16−2.03 (m, 2H), 1.93−1.83 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 197.8, 171.6, 163.1, 138.3, 137.4, 132.9, 128.2, 127.8, 126.8, 124.1, 122.0, 120.3, 119.8, 119.0, 117.9, 111.6, 100.0, 97.9, 55.2, 52.8, 36.3, 29.6, 26.7, 21.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{24}BrN_2O_3S$, 499.0692; found, 499.0679.

*Methyl-(E)-(4-oxo-3-(p-tolylthio)pent-2-en-2-yl)-tryptophanate (**5t**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 9/1). Brown gum (312 mg, 74%); IR (neat) $\bar{\nu}_{max}$: 3417, 2952, 2923, 1745, 1579 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 12.68−12.65 (m, 1H), 8.31 (br s, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 7.14−7.02 (m, 3H), 6.95−6.93 (m, 2H), 6.79−6.75 (m, 2H), 4.53−4.46 (m, 1H), 3.65 (s, 3H), 3.40−3.34 (m, 1H), 3.26−3.18 (m, 1H), 2.23 (s, 3H), 2.20 (s, 3H), 1.90 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 200.5, 171.4, 169.9, 136.6, 136.2, 134.1, 129.7, 126.9, 124.1, 124.0, 122.2, 119.7, 118.2, 111.5, 109.3, 94.9, 58.3, 52.8, 29.5, 29.1, 20.8, 17.3; Anal. Calcd for $C_{24}H_{26}N_2O_3S$: C, 68.22; H, 6.20; N, 6.63. Found: C, 68.10; H, 6.33; N, 6.49.

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*Methyl-(2-(butylthio)-3-oxocyclohex-1-en-1-yl)leucinate (**5u**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Yellow gum (265 mg, 81%); IR (neat) $\bar{\nu}_{max}$: 3330, 1738, 1642, 1550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 6.97−6.94 (m, 1H), 4.19−4.12 (m, 1H), 3.73 (s, 3H), 2.55−2.50 (m, 2H), 2.46−2.31 (m, 4H), 1.98−1.89 (m, 2H), 1.75−1.62 (m, 3H), 1.50−1.29 (m, 4H), 0.99−0.91 (m, 6H), 0.86−0.82 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.6, 172.4, 166.8, 102.1, 54.4, 52.6, 42.1, 36.9, 33.6, 31.8, 26.2, 24.7, 22.7, 22.0, 21.9, 20.8, 13.7; Anal. Calcd for $C_{17}H_{29}NO_3S$: C, 62.35; H, 8.93; N, 4.28. Found: C, 62.26; H, 9.05; N, 4.19.

*Methyl-(2-(cyclohexylthio)-3-oxocyclohex-1-en-1-yl)-leucinate (**5v**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Yellow liquid (280 mg, 79%); IR (neat) $\bar{\nu}_{max}$: 3345, 1747, 1638, 1538 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.00−6.97 (m, 1H), 4.17−4.10 (m, 1H), 3.71 (s, 3H), 2.88−2.79 (m, 1H), 2.45−2.36 (m, 4H), 1.99−1.86 (m, 2H), 1.83−1.82 (m, 2H), 1.73−1.60 (m, 5H), 1.53−1.49 (m, 1H), 1.28−1.14 (m, 5H), 0.94−0.89 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.8, 172.3, 167.2, 101.1, 54.4, 52.5, 45.4, 42.1, 36.9, 33.3, 26.2, 26.1, 25.8, 24.7, 22.6, 21.9, 20.8; Anal. Calcd for $C_{19}H_{31}NO_3S$: C, 64.55; H, 8.84; N, 3.96. Found: C, 64.43; H, 8.97; N, 3.88.

*Methyl-(E)-(3-(benzo[d]thiazol-2-ylthio)-4-oxopent-2-en-2-yl)phenylalaninate (**5w**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 9/1). White amorphous solid (375 mg, 88%); mp 126−128 °C; IR (KBr) $\bar{\nu}_{max}$: 3385, 2924, 1745, 1628, 1556 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 13.01−12.92 (m, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.75−7.69 (m, 1H), 7.43−7.23 (m, 7H), 4.58−4.48 (m, 1H), 3.81 (br s, 3H), 3.38−3.29 (m, 1H), 3.14−3.06 (m, 1H), 2.41 (br s, 3H), 2.06 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 199.5, 170.4, 170.1, 155.4, 135.7, 135.2, 129.5, 129.3, 128.9, 127.3, 126.1, 123.8, 121.5, 120.8, 95.4, 59.6, 52.9, 39.8, 29.0, 17.1; Anal. Calcd for $C_{22}H_{22}N_2O_3S_2$: C, 61.95; H, 5.20; N, 6.57. Found: C, 61.87; H, 5.31; N, 6.46.

*Methyl-(2-(benzo[d]thiazol-2-ylthio)-5,5-dimethyl-3-oxocyclohex-1-en-1-yl)valinate (**5x**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Yellow semisolid (350 mg, 84%); IR (neat) $\bar{\nu}_{max}$: 3344, 2973, 1745, 1644, 1547 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.82 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.67 (dd, J_1 = 8.1 Hz, J_2 = 1.5 Hz, 1H), 7.39−7.34 (m, 1H), 7.28−7.21 (m, 1H), 7.05−6.99 (m, 1H), 4.06−4.01 (m, 1H), 3.64 (s, 3H), 2.46−2.45 (m, 4H), 2.20−2.09 (m, 1H), 1.20 (s, 3H), 1.17 (s, 3H), 0.96−0.85 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 191.1, 170.6, 169.8, 167.3, 154.3, 135.4, 125.9, 124.1, 121.6, 120.8, 97.7, 61.6, 52.6, 50.4, 40.3, 32.0, 31.9, 28.8, 28.5, 18.8, 17.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{27}N_2O_3S_2$, 419.1464; found, 419.1473.

*Methyl-(2-(benzo[d]thiazol-2-ylthio)-3-oxocyclohex-1-en-1-yl)leucinate (**5y**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 1/1). Yellow gum (290 mg, 72%); IR (neat) $\bar{\nu}_{max}$: 3322, 2985, 1736, 1631, 1542 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.86 (d, J = 8.1 Hz, 1H), 7.70−7.67 (m, 1H), 7.42−7.37 (m, 1H), 7.29−7.24 (m, 1H), 6.81−6.78 (m, 1H), 4.26−4.19 (m, 1H), 3.68 (s, 3H), 2.67−2.59 (m, 4H), 2.19−2.10 (m, 2H), 1.74−1.61 (m, 2H), 1.54−1.42 (m, 1H), 0.86−0.82 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 191.4, 171.5, 170.2, 168.7, 154.2, 135.3, 126.0, 124.1, 121.6, 120.7, 99.3, 54.8, 52.8, 41.6, 36.9, 26.9, 24.6, 22.5, 21.5, 20.5; HRMS (ESI-TOF) m/z: $[M\text{-}CH_3 + H]^+$ calcd for $C_{19}H_{23}N_2O_3S_2$, 391.1151; found, 391.1145.

*Methyl-(5,5-dimethyl-3-oxo-2-(thiophen-2-ylthio)-cyclohex-1-en-1-yl)phenylalaninate (**5z**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Light yellow gum (374 mg, 90%); IR (neat) $\bar{\nu}_{max}$: 3324, 2981, 1745, 1638, 1549 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.24−7.16 (m, 3H), 7.14−7.07 (m, 2H), 7.05−6.92 (m, 3H), 6.82−6.79 (m, 1H), 4.37−4.30 (m, 1H), 3.73 and 3.71 (2 s, 3H, rotamers), 3.16−3.09 (m, 1H), 3.00−2.88 (m, 1H), 2.21−2.11 (m, 2H), 2.07−2.01 (m, 1H), 1.70−1.62 (m, 1H), 0.91 and 0.85 (2 s, 3H, rotamers), 0.78 and 0.71 (2 s, 3H, rotamers); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 191.7, 170.9, 164.6, 155.9, 135.9, 135.1, 130.3, 129.5, 129.0, 127.71 and 127.60 (rotamers), 127.0, 102.6, 57.34 and 57.04 (rotamers), 52.9, 50.2, 40.36 and 40.24 (rotamers), 39.73 and 39.64 (rotamers), 31.92 and 31.56 (rotamers), 28.51 and 28.37 (rotamers), 28.12 and 28.02 (rotamers); Anal. Calcd for $C_{22}H_{25}NO_3S_2$: C, 63.59; H, 6.06; N, 3.37. Found: C, 63.47; H, 6.14; N, 3.29.

*Methyl-(3-oxo-2-(thiophen-2-ylthio)cyclohex-1-en-1-yl)-leucinate (**5a′**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 1/1). Brownish yellow semisolid (250 mg, 71%); IR (neat) $\bar{\nu}_{max}$: 3373, 2946, 1748, 1663, 1529 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.14−7.12 (m, 1H), 7.09−7.07 (m, 1H), 6.97−6.94 (m, 1H), 6.85−6.82 (m, 1H), 4.22−4.14 (m, 1H), 3.75 and 3.73 (2 s, 3H, rotamers), 2.51−2.40 (m, 4H), 2.01−1.90 (m, 2H), 1.78−1.65 (m, 2H), 1.62−1.53 (m, 1H), 0.95−0.84 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.1, 178.1, 172.0, 166.5, 135.7, 130.3, 127.09 and 126.90 (rotamers), 103.7, 54.52 and 54.35 (rotamers), 52.7, 42.1, 36.74 and 36.51 (rotamers), 29.6, 24.69 and 24.59 (rotamers), 22.7, 21.9, 20.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{24}NO_3S_2$, 354.1198; found, 354.1168.

*Methyl-2-((2-(butylthio)-3-oxocyclohex-1-en-1-yl)amino)-3-methylpentanoate (**5b′**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Light yellow gum (262 mg, 80%); IR (neat) $\bar{\nu}_{max}$: 3332, 1737, 1642, 1552 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.23−7.20 (m, 1H), 4.08−4.03 (m, 1H), 3.78 (s, 3H), 2.77 (s, 2H), 2.61−2.56 (m, 2H), 2.47−2.43 (m, 3H), 2.02−1.93 (m, 3H), 1.53−1.29 (m, 5H), 1.00−0.95 (m, 6H), 0.91−0.86 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.7, 171.4, 166.9, 102.2, 60.5, 52.4, 38.7, 36.9, 33.7, 32.0, 29.6, 25.1, 22.1, 20.9, 15.6, 13.7, 11.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{30}NO_3S$, 328.1947; found, 328.1925.

*Methyl-(2-(cyclohexylthio)-5,5-dimethyl-3-oxocyclohex-1-en-1-yl)phenylalaninate (**5c′**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/1). Yellow gum (324 mg, 78%); IR (neat) $\bar{\nu}_{max}$: 3326, 1745, 1634, 1551 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.37−7.29 (m, 3H), 7.22−7.18 (m, 3H), 4.46−4.39 (m, 1H), 3.79 (s, 3H), 3.24 (dd, J_1 = 13.8 Hz, J_2 = 4.8 Hz, 1H), 3.11−3.04 (m, 1H), 2.83−2.78 (m, 1H), 2.25−2.10 (m, 4H), 1.83−1.80 (m, 2H), 1.69−1.67 (m, 2H), 1.57 (br s, 1H), 1.25−1.13 (m, 5H), 0.99 (s, 3H), 0.88 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.5, 171.4, 165.3, 135.3, 129.4, 128.9, 127.6, 100.2, 57.1, 52.7, 50.4, 47.4, 45.5, 39.7, 33.4, 31.6, 28.6, 28.2, 26.0, 25.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{34}NO_3S$, 416.2260; found, 416.2271.

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General Procedure for Synthesis of α-Amino Ester-Embedded Selenyl Enaminones (7). At first, a mixture of 1,3-dicarbonyls **1** (1.0 mmol) and methyl L-amino esters **2** (1.0 mmol) in 2.0 mL of DCM was taken in a 50 mL round-bottom flask and the mixture was stirred at rt (25−30 °C) for 30 min in open air. Next, benzeneselenol **6** (1.5 mmol, 235 mg) and NCS (1.0 mmol, 133.5 mg) were added to the same reaction pot and the resulting mixture was further stirred for 5 min at rt. After completion of the reaction (observed by TLC monitoring), the reaction mixture was diluted with water and the organic layer was extracted with ethyl acetate (3 × 20 mL). The extracted organic part was dried over anhydrous sodium sulphate and concentrated *in vacuo*. The crude mass was purified by silica gel column chromatography using 40−50% ethyl acetate in hexane as an eluent to afford pure selenyl enaminones **7**.

Spectral Data. Characterization data of compounds **7a**−**d**.

*Methyl-(5,5-dimethyl-3-oxo-2-(phenylselanyl)cyclohex-1-en-1-yl)valinate (**7a**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Light yellow gum (338 mg, 83%); IR (neat) $\overline{\nu}_{max}$: 3299, 2960, 1741, 1632, 1557 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.35−7.31 (m, 2H), 7.19−7.09 (m, 3H), 6.98−6.95 (m, 1H), 4.00−3.94 (m, 1H), 3.69 (s, 3H), 2.43 (br s, 2H), 2.37−2.36 (m, 2H), 2.16−2.05 (m, 1H), 1.12 (s, 3H), 1.10 (s, 3H), 0.86−0.80 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 191.9, 171.2, 165.0, 131.6, 129.8, 128.9, 126.1, 100.1, 61.5, 52.4, 50.4, 40.1, 32.1, 31.9, 28.6, 28.4, 18.8, 17.5; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{28}NO_3Se$, 410.1235; found, 410.1244.

*Methyl-3-methyl-2-((3-oxo-2-(phenylselanyl)cyclohex-1-en-1-yl)amino)pentanoate (**7b**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Brown gum (315 mg, 80%); IR (neat) $\overline{\nu}_{max}$: 3320, 2982, 1739, 1643, 1567 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.25−7.21 (m, 2H), 7.12−7.02 (m, 3H), 6.91−6.88 (m, 1H), 3.99−3.92 (m, 1H), 3.62 (s, 3H), 2.50−2.43 (m, 4H), 1.99−1.95 (m, 2H), 1.78−1.69 (m, 1H), 1.22−1.16 (m, 1H), 0.92−0.86 (m, 1H), 0.77−0.70 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.4, 171.1, 166.6, 131.3, 129.5, 129.0, 126.1, 101.1, 60.7, 52.4, 38.6, 36.6, 26.5, 24.7, 21.1, 15.3, 11.4; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{26}NO_3Se$, 396.1079; found, 396.1068.

*Methyl-(3-oxo-2-(phenylselanyl)cyclohex-1-en-1-yl)-tryptophanate (**7c**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 1/1). Light yellow amorphous solid (340 mg, 73%); mp 80−82 °C; IR (KBr) $\overline{\nu}_{max}$: 3316, 2974, 1745, 1622, 1563 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ_H 11.65−11.63 (m, 1H), 7.60−7.45 (m, 1H), 7.35−7.32 (m, 1H), 7.24−7.19 (m, 3H), 7.17−7.11 (m, 4H), 7.09−6.97 (m, 2H), 4.68−4.52 (m, 1H), 3.68 and 3.61 (2 s, 3H, rotamers), 2.43−2.32 (m, 1H), 2.24−2.06 (m, 3H), 1.73−1.64 (m, 1H), 1.63−1.48 (m, 1H), 1.40−1.24 (m, 1H), 0.96−0.82 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ_C 190.7, 171.7, 168.3, 138.2, 132.5, 130.0, 129.8, 129.6, 129.3, 129.1, 127.2, 120.8, 119.7, 116.9, 116.2, 98.9, 56.4, 53.0, 37.1, 32.8, 29.7, 20.9; Anal. Calcd for $C_{24}H_{24}N_2O_3Se$: C, 61.67; H, 5.18; N, 5.99. Found: C, 61.58; H, 5.29; N, 5.88.

*Methyl-(3-oxo-2-(phenylselanyl)cyclohex-1-en-1-yl)-leucinate (**7d**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 1/1). Light yellow gum (295 mg, 75%); IR (neat) $\overline{\nu}_{max}$: 3290, 2968, 1744, 1647, 1560 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.29−7.25 (m, 2H), 7.18−7.08 (m, 3H), 6.74−6.71 (m, 1H), 4.18−4.10 (m, 1H), 3.68 (s, 3H), 2.56−2.51 (m, 4H), 2.08−1.99 (m, 2H), 1.67−1.48 (m, 2H), 1.43−1.30 (m, 1H), 0.83−0.78 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.4, 172.1, 166.7, 131.4, 129.3, 129.0, 126.0, 101.0, 54.6, 52.7, 41.8, 36.8, 26.5, 24.4, 22.7, 21.7, 21.0; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{26}NO_3Se$, 396.1079; found, 396.1063.

General Procedure for Synthesis of Enaminones of Aryl and Alkyl Amines (8).[41] In a 50 mL round-bottom flask, aryl/alkyl amines (2.0 mmol) were mixed with 1,3-diketone compounds (2.0 mmol) in 10 mL of benzene. The resulting reaction mixture was refluxed using Dean−Stark trap for 1.5 h. After completion of the reaction (checked by TLC monitoring), benzene was removed from the reaction mixture under reduced pressure. The crude mass containing enaminones **8** was washed with hexane (3 × 15 mL) and used for sulfenylation/selenylation reaction without further purification.

General Procedure for Synthesis of β-Amino Sulfide/Selenide Derivatives (9). Enaminones **8** (1.0 mmol) and NCS (1.0 mmol, 133.5 mg) were added to a stirred solution of thiols **4** (1.5 mmol) or benzeneselenol **6** (1.5 mmol, 235 mg) in 2.0 mL of DCM taken in a 50 mL round-bottom flask. The resulting mixture was stirred for 5 min at rt in open air. After completion of the reaction (observed by TLC monitoring), the reaction mixture was diluted with water and the organic layer was extracted with ethyl acetate (3 × 20 mL). The extracted organic part was dried over anhydrous sodium sulphate and concentrated *in vacuo*. The crude mass was purified by silica gel column chromatography using 10−50% ethyl acetate in hexane as an eluent to afford pure sulfide/selenide derivatives **9**.

Spectral Data. Characterization data of compounds **9a**−**k**.

*3-((4-Methylbenzyl)amino)-2-(p-tolylthio)cyclohex-2-en-1-one (**9a**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 1/1). White amorphous solid (286 mg, 85%); mp 132−134 °C; IR (KBr) $\overline{\nu}_{max}$: 3433, 2928, 1630, 1558 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.14−7.01 (m, 7H), 6.98−6.96 (m, 2H), 4.45 (br s, 1H), 4.43 (br s, 1H), 2.64−2.60 (m, 2H), 2.57−2.53 (m, 2H), 2.35 (s, 3H), 2.30 (s, 3H), 2.08−2.00 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.4, 168.6, 137.6, 135.0, 133.9, 132.9, 129.7, 129.6, 126.6, 126.5, 99.4, 47.0, 37.0, 26.5, 21.1, 20.9, 20.8; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{24}NOS$ 338.1579; found, 338.1585.

*3-((3-Chloro-4-fluorophenyl)amino)-2-(p-tolylthio)-cyclohex-2-en-1-one (**9b**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). White amorphous solid (325 mg, 90%); mp 144−146 °C; IR (KBr) $\overline{\nu}_{max}$: 3420, 2945, 1637, 1547 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.25 (br s, 1H), 7.19−7.15 (m, 2H), 7.13−7.12 (m, 1H), 7.10−7.05 (m, 3H), 7.00−6.95 (m, 1H), 2.63−2.59 (m, 4H), 2.30 (s, 3H), 2.08−2.03 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.4, 166.5, 156.7 (d, $^1J_{C-F}$ = 249.0 Hz), 135.4, 134.1, 132.2, 129.8, 128.2, 126.6, 125.8 (d, $^3J_{C-F}$ = 6.75 Hz), 121.8 (d, $^2J_{C-F}$ = 18.75 Hz), 117.2 (d, $^2J_{C-F}$ = 21.75 Hz), 102.2, 37.3, 27.8, 21.3, 20.9; Anal. Calcd for $C_{19}H_{17}ClFNOS$: C, 63.07; H, 4.74; N, 3.87. Found: C, 63.01; H, 4.83; N, 3.76.

*2-((4-Chlorophenyl)thio)-3-(p-tolylamino)cyclohex-2-en-1-one (**9c**).* The product was purified by column chromatog-

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raphy on silica gel (eluted with hexane/EtOAc, 3/2). White amorphous solid (300 mg, 87%); mp 176−178 °C; IR (KBr) $\overline{\nu}_{max}$: 3410, 2952, 1638, 1562 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.26 (br s, 1H), 7.25−7.18 (m, 4H), 7.15−7.11 (m, 2H), 6.98−6.96 (m, 1H), 2.66−2.59 (m, 4H), 2.37 (s, 3H), 2.07−2.01 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.8, 168.0, 137.2, 135.0, 134.5, 131.0, 130.1, 129.0, 127.3, 125.8, 99.5, 37.4, 27.9, 26.9, 21.3; Anal. Calcd for $C_{19}H_{18}ClNOS$: C, 66.37; H, 5.28; N, 4.07. Found: C, 66.28; H, 5.36; N, 3.98.

*3-((4-Methoxyphenyl)amino)-2-(phenylthio)cyclohex-2-en-1-one (**9d**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Light gray amorphous solid (292 mg, 90%); mp 126−128 °C; IR (KBr) $\overline{\nu}_{max}$: 3431, 2919, 1635, 1560 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.21 (br s, 1H), 7.28−7.15 (m, 4H), 7.13−7.07 (m, 1H), 7.01−6.97 (m, 2H), 3.81 (s, 3H), 2.62−2.56 (m, 4H), 2.06−1.98 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.9, 168.2, 158.6, 136.3, 130.0, 128.9, 127.6, 125.9, 125.2, 114.6, 99.4, 55.5, 37.4, 27.8, 21.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{20}NO_2S$, 326.1215; found, 326.1232.

*2-((2-Bromophenyl)thio)-3-((3-chloro-4-fluorophenyl)-amino)cyclohex-2-en-1-one (**9e**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Light gray amorphous solid (345 mg, 81%); mp 152−154 °C; IR (KBr) $\overline{\nu}_{max}$: 3445, 2940, 1640, 1537 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.14 (br s, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.12−7.02 (m, 3H), 6.95−6.81 (m, 3H), 2.56−2.49 (m, 4H), 2.02−1.94 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.8, 167.6, 156.8 (d, $^1J_{C\text{-}F}$ = 244.5 Hz), 136.8, 133.9, 132.9, 128.4, 127.9, 126.5, 126.2, 126.1 (d, $^3J_{C\text{-}F}$ = 2.25 Hz), 121.8, 121.6 (d, $^3J_{C\text{-}F}$ = 5.25 Hz), 117.2 (d, $^2J_{C\text{-}F}$ = 22.5 Hz), 100.3, 37.4, 28.0, 21.3; Anal. Calcd for $C_{18}H_{14}BrClFNOS$: C, 50.66; H, 3.31; N, 3.28. Found: C, 50.57; H, 3.43; N, 3.20.

*(E)-4-((4-Methoxyphenyl)amino)-3-((4-nitrophenyl)thio)-pent-3-en-2-one (**9f**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 9/1). Yellow amorphous solid (286 mg, 80%); mp 120−122 °C; IR (KBr) $\overline{\nu}_{max}$: 3450, 2954, 1582 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 13.89 (s, 1H), 8.14 (d, J = 9.0 Hz, 2H), 7.29−7.26 (m, 2H), 7.09 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 3.84 (s, 3H), 2.35 (s, 3H), 2.18 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 199.7, 169.8, 158.6, 150.6, 145.0, 130.7, 127.0, 124.3, 123.9, 114.5, 93.1, 55.5, 28.7, 18.6; Anal. Calcd for $C_{18}H_{18}N_2O_4S$: C, 60.32; H, 5.06; N, 7.82. Found: C, 60.38; H, 5.14; N, 7.71.

*(E)-3-(Cyclohexylthio)-4-((4-methoxyphenyl)amino)pent-3-en-2-one (**9g**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 9/1). Brown semisolid (246 mg, 77%); IR (neat) $\overline{\nu}_{max}$: 3443, 2950, 1577 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 13.74 (s, 1H), 7.07−7.02 (m, 2H), 6.92−6.88 (m, 2H), 3.83 (s, 3H), 2.53 (s, 3H), 2.32 (s, 3H), 1.97−1.94 (m, 2H), 1.79 (br s, 2H), 1.65 (br s, 1H), 1.35−1.23 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 200.6, 168.5, 158.1, 131.7, 127.0, 114.3, 98.1, 55.5, 48.9, 33.1, 29.3, 26.3, 25.9, 19.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{26}NO_2S$, 320.1685; found, 320.1662.

*2-(Benzo[d]thiazol-2-ylthio)-3-(benzylamino)cyclohex-2-en-1-one (**9h**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). White amorphous solid (285 mg, 78%); mp 140−142 °C; IR (KBr) $\overline{\nu}_{max}$: 3433, 2924, 1628, 1555 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.85 (d, J = 8.1 Hz, 1H), 7.72−7.69 (m, 1H), 7.44−7.38 (m, 1H), 7.32−7.27 (m, 4H), 7.23−7.14 (m, 3H), 4.56−4.54 (m, 2H), 2.72−2.68 (m, 2H), 2.63−2.58 (m, 2H), 2.12−2.08 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 191.4, 170.0, 154.1, 136.4, 135.3, 129.1, 128.1, 126.6, 126.1, 126.1, 124.2, 121.6, 120.8, 98.1, 47.4, 36.9, 26.9, 20.5; Anal. Calcd for $C_{20}H_{18}N_2OS_2$: C, 65.54; H, 4.95; N, 7.64. Found: C, 65.47; H, 5.03; N, 7.53.

*2-((4-Chlorophenyl)thio)-3-(propylamino)cyclohex-2-en-1-one (**9i**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Light yellow gum (242 mg, 82%); IR (KBr) $\overline{\nu}_{max}$: 3438, 2923, 1630, 1555 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.11−7.07 (m, 2H), 6.99−6.94 (m, 2H), 6.71−6.67 (m, 1H), 3.20−3.14 (m, 2H), 2.62−2.58 (m, 2H), 2.50−2.45 (m, 2H), 2.04−1.98 (m, 2H), 1.55−1.43 (m, 2H), 0.83−0.78 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.6, 169.4, 135.4, 130.6, 128.8, 127.1, 97.0, 45.2, 36.8, 26.4, 23.2, 20.7, 11.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{19}ClNOS$, 296.0877; found, 296.0860.

*3-(Cyclohexylamino)-2-(p-tolylthio)cyclohex-2-en-1-one (**9j**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 1/1). Yellow gum (265 mg, 84%); IR (KBr) $\overline{\nu}_{max}$: 3435, 2930, 1628, 1572 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 6.88−6.81 (m, 4H), 6.61−6.58 (m, 1H), 3.32−3.22 (m, 1H), 2.53−2.49 (m, 2H), 2.37−2.33 (m, 2H), 2.08 (s, 3H), 1.90−1.84 (m, 2H), 1.66−1.59 (m, 2H), 1.52−1.36 (m, 3H), 1.18−0.94 (m, 5H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.5, 167.9, 134.6, 132.9, 129.4, 126.2, 97.8, 51.8, 36.8, 33.5, 29.5, 26.3, 24.9, 24.1, 20.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{26}NOS$, 316.1736; found, 316.1716.

*5,5-Dimethyl-2-(phenylselanyl)-3-(p-tolylamino)cyclohex-2-en-1-one (**9k**).* The product was purified by column chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Yellow gum (280 mg, 73%); IR (KBr) $\overline{\nu}_{max}$: 3450, 2942, 1635, 1550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.22 (br s, 1H), 7.38−7.35 (m, 2H), 7.24−7.17 (m, 5H), 6.93−6.91 (m, 2H), 2.48−2.46 (m, 4H), 2.37 (s, 3H), 1.08 (br s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C 192.4, 165.1, 136.9, 134.9, 131.6, 130.0, 129.4, 129.1, 126.1, 125.9, 99.9, 50.8, 41.1, 40.8, 32.4, 28.3, 21.0; Anal. Calcd for $C_{21}H_{23}NOSe$: C, 65.62; H, 6.03; N, 3.64. Found: C, 65.55; H, 6.12; N, 3.57.

Single-Crystal X-ray Structure Analysis of 5w (CCDC 2104278). $C_{22}H_{22}N_2O_3S_2$, M = 426.54, monoclinic, a = 10.618(2) Å, b = 8.0686(16) Å, c = 12.470(3) Å, α = 90.00°, β = 101.467(3)°, γ = 90.00°, V = 1047.0(4) $Å^3$, T = 296(2) K, space group P 21, Z = 2, μ(MoKα) = 0.280 mm^{-1}, 22071 reflections measured, 4876 independent reflections (R_{int} = 0.0454). The final R_1 values were 0.0818 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.2307 ($I > 2\sigma(I)$). The final R_1 values were 0.1003 (all data). The final $wR(F^2)$ values were 0.2603 (all data). The goodness of fit on F^2 was 1.071.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c05058.

Copies of ^1H and ^{13}C NMR spectra of all compounds and LCMS spectra of intermediates (PDF)

X-ray crystal structure of **5w** (CIF)

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Notes

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