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Ag(I)-mediated *mono*-selective C(sp^2)–H chalcogenation of α-aminotropones and their peptides at room temperature

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This report describes an Ag(I)-mediated strategy for the *mono*-selective chalcogenation of α-aminotropones and their peptides with a range of disulfides and diselenides at ambient temperature. The method efficiently furnishes *mono*-chalcogenated aminotropone derivatives in moderate to good yields, while demonstrating compatibility with diverse substrates and functional groups, offering synthetic versatility in downstream applications.

Tropone and tropolone are constituents of various natural products, troponoids, possessing valuable bioactivities such as antimicrobial, antifungal, anti-protozoal, antibacterial, and anticancer.[1] Structurally, tropone has a non-benzenoid aromatic scaffold comprising six conjugated π-electrons in the seven-membered ring. Its distinctive electronic structure and inherent ring strain render it a valuable scaffold in meticulous synthesis design and a topic of particular interest in medicinal chemistry.[2,3] In particular, sulfur-containing tropone derivatives such as thiotropocin, tropodithietic acid (TDA), troposulfenin, and roseobacticides highlight their structural diversity (Fig. 1a).[4] An unusual aromaticity and strong biological relevance make these molecules attractive precursors for deliberate synthetic design and complicated architecture development. α-Aminotropone is a synthetic analogue of tropolone possessing unique structural and functional properties, including therapeutic value.[5] Notably, tropones and their analogues participate in diverse chemical reactions, including cycloaddition,[6] nucleophilic substitution,[7] α-alkylation,[8,9] metal-catalyzed transformations[10] *etc.* Despite the growing interest in tropolone chemistry, the majority of previous studies have primarily focused on cycloaddition reactions as a method for structural modification.[11] While these transformations have proven effective for generating complex frameworks from the core ring, they often lack precision in functionalizing specific positions on the ring. In contrast, site-selective C–H functionalization of the tropolone core remains significantly underexplored, specifically in the presence of a directing group.[3] The development of methodologies for precise and predictable C–H bond functionalization within this non-benzenoid aromatic framework would significantly broaden the synthetic utility of tropolones and enhance their application in medicinal chemistry. In the literature, Janik and co-workers have shown the Pd(0)-catalyzed synthesis of 5-aryl tropolone from 5-iodotropolone, which is derived from tropolone in multiple steps.[12] In 2022, our group reported a Pd(II)-catalyzed C7-olefination of α-aminotropones to synthesize various non-benzenoid cinnamate analogs.[13] Additionally, a series of alkylaminotroponyl sulfone (ATS) derivatives have been synthesized *via* a Cu(II)-mediated C(sp^2)–H functionalization of α-aminotropones with aryl sulfonyl hydrazides.[14] A couple of ATS derivatives exhibit promising anti-quorum-sensing (anti-QS) activity against pathogenic bacteria *Pseudomonas aeruginosa*. Recently, Bandini and

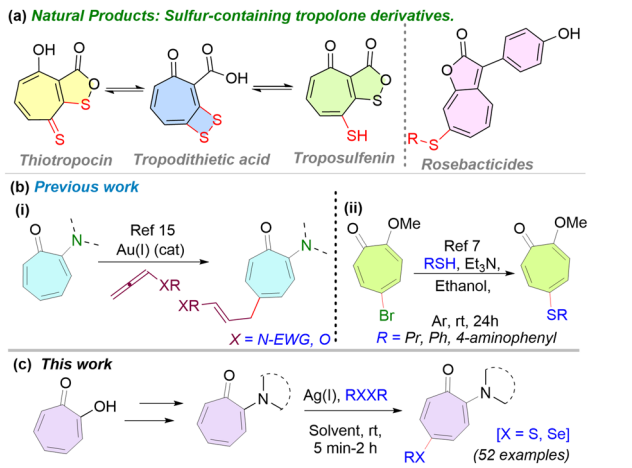

Fig. 1 (a) Troponyl natural products; (b) previous works-(i) Au(I)-catalyzed C–H alkylation; (ii) chalcogenation from bromotropolone; (c) this work-C5-chalcogenation of aminotropone derivatives.

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colleagues have reported an Au(I)-catalyzed direct C–H alkylation of α-substituted tropones at the C5 position using allenes as alkylating agents [Fig. 1b(i)].[15] Despite the well-established biological activity of sulfur-containing frameworks,[16] site-selective C–H chalcogenation of tropones remains largely unexplored. In 2014, Yamamoto and co-workers successfully synthesized a few sulfur-based tropones from 5-bromo-2-methoxytropone [Fig. 1b(ii)].[7] However, synthesizing the bromotropolone requires intricate reaction design and multiple steps. This underscores the need for a mild, efficient, and selective method for the C–H chalcogenation of tropolones. Previously, we have developed a site-selective chalcogenation strategy on tryptophan-containing peptides *via* an Ag(I)-mediated C(sp^2)–H functionalisation protocol.[17] Herein, we report the *mono*-selective C5-chalcogenation of α-aminotropones and their peptide derivatives at room temperature, employing various dichalcogenides through Ag(I)-mediated C(sp^2)–H functionalisation (Fig. 1c).

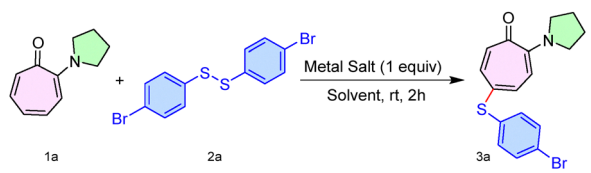
Initially, we synthesized various types of 2-aminotropone derivatives (**1**) from the commercially available *Tropolone* molecule by following the previous report.[13] One of the simple aminotropone derivatives (**1a**) was treated with diaryl disulfide (**2a**) in the presence of various Ag(I)-salts under different solvent conditions at room temperature. (Table S1, SI). Pleasingly, we optimized the reaction conditions for the substrate (**1a**) with the reagent (**2a**), using metal salt $AgCO_2CF_3$ (1.0 equiv.) in solvent toluene at room temperature, which produced the desired sulfenyl product **3a** in 76% yield (Table 1, entry 1). Increasing the amount of $AgCO_2CF_3$ (2 equiv.) failed to increase the yield. Also, decreasing the amount of $AgCO_2CF_3$ (0.5 equiv.) led to a drop in the product yield (entries 2 and 3). Furthermore, in the absence of $AgCO_2CF_3$, the formation of the product was not observed, while the use of AgOTf instead of $AgCO_2CF_3$ resulted in only a trace amount of the product while with AgOAc, reaction did not proceed (entries 4–6). Also, solvents like MeCN and xylene failed to increase the product yield (entries 7 and 8).

Having the optimal reaction conditions in hand, we next studied the substrate scope of the procedure using various disulfides (**2b–l**) with *N*,*N*-di-alkylaminotropone (**1a**) as a standard substrate (Scheme 1). To our delight, the simplest disulfide tested, namely diphenyl disulfide (**2b**), delivered the sulfenyl product (**3b**) in 73% yield. In contrast, aliphatic disulfides (**2j–k**) and cysteine-derived disulfides (**2l**) failed to provide a sulfenylated aminotropone under the optimized reaction conditions. Various aryl disulfides having electron-donating/withdrawing functionalities on the phenyl ring, such as 2-amino (**2c**), 2-chloro (**2d**), 3-chloro (**2e**), 3-fluoro (**2f**), 3-methoxy (**2g**), and 4-methyl (**2h**), produced the desired sulfenyl derivative **3c–h** in 76–72% yield. In addition, dinapthyl disulfide (**2i**) furnished **3i** in 75% yield. We also performed a gram-scale reaction of **1a** (5.71 mmol, 1.0 g) with **2a** (6.85 mmol, 2.58 g), furnishing the desired product **3a** (1.32 g) in 56% yield.

The scope of the chalcogenation procedure was next extended for various *N*,*N*-dialkylaminotropones (**1b–f**) with disulfide **2a** (Scheme 2). Pleasingly, various *N*,*N*-dialkylaminotropones, such as piperidinyl tropone (**1b**), morpholinyl tropone (**1c**), *N*,*N*-dimethylaminotropone (**1d**), and *N*-ethyl-*N*-methylaminotropone (**1e**), were found to be effective in delivering the desired sulfenylated compounds (**3m–p**) in 67–78% yields. Subsequently, the troponyl amino acid derivative, proline-based aminotropone (**1f**), also produced the sulfenylated prolinyl tropone derivative (**3q**) in a better yield of 69% under the optimised reaction conditions, having the solvent system DCE/TFE (1 : 1, 2 mL) instead of toluene.

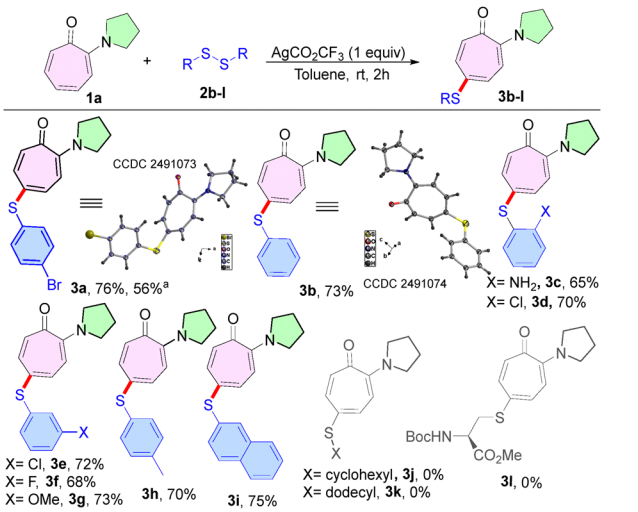
Encouraged by the aforementioned successful outcomes, we later tested the workability of various substituted diselenides with **1a** (Scheme 3). Interestingly, aryl diselenides bearing various functionalities on the aryl ring, like 2-methoxy (**2m**), 3-chloro (**2n**), 3-fluoro (**2o**), 3-trifluoromethyl (**2p**), 4-bromo (**2q**), 4-methoxy (**2r**), and 4-methyl (**2s**), afforded the selenylated products in good to moderate yields. Each one formed *mono*-substituted arylselenides (**3r–x**) as the major product with a good yield of 52–65%, while *di*-substituted products (**3r′–x′**) as

Table 1 Optimization of the reaction conditions[a]

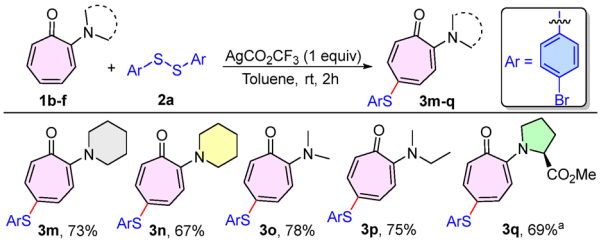


Entry	Deviation from standard conditions	Yield[b] (%)
1	None	76
2	2 equiv. $AgCO_2CF_3$	74
3	0.5 equiv. $AgCO_2CF_3$	59
4	Without $AgCO_2CF_3$	n.r.[c]
5	AgOTf instead of $AgCO_2CF_3$	Trace
6	AgOAc instead of $AgCO_2CF_3$	n.r.[c]
7	MeCN instead of toluene	41
8	Xylene instead of toluene	53

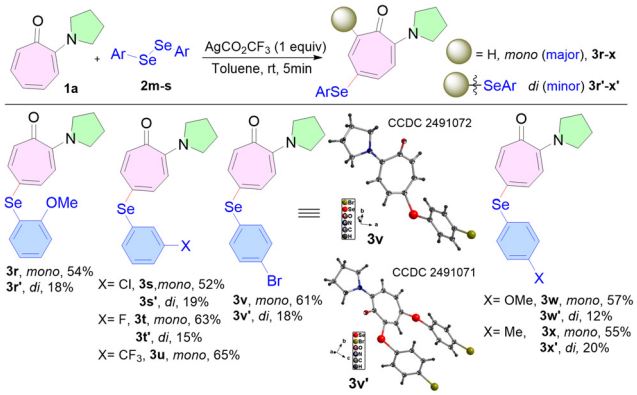
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), $AgCO_2CF_3$ (1 equiv.) in toluene (2 mL) at rt for 2 h under air. [b] Isolated yield. [c] n.r. = no reaction.



Scheme 1 Variation of the disulfide partners. [a] Gram scale yield.



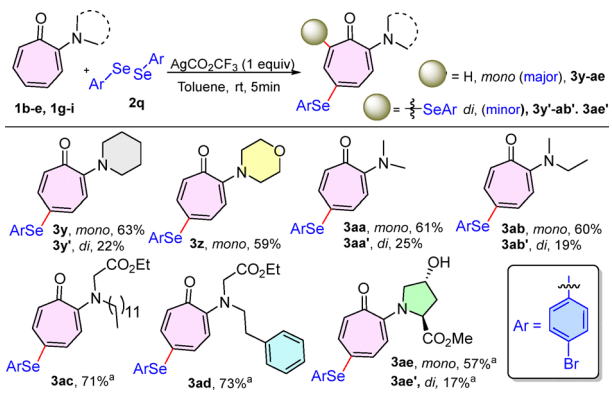
Scheme 2 Scope of aminotropone for sulfenylation. [a] Reaction conditions: DCE/TFE (1 : 1).



Scheme 3 Variation of diselenides.

minor ones with a yield of 12–20% under the optimized reaction conditions within 5 min. These results reveal a greater reactivity of diselenides towards *N*,*N*-dialkylaminotropone as compared to disulfides.

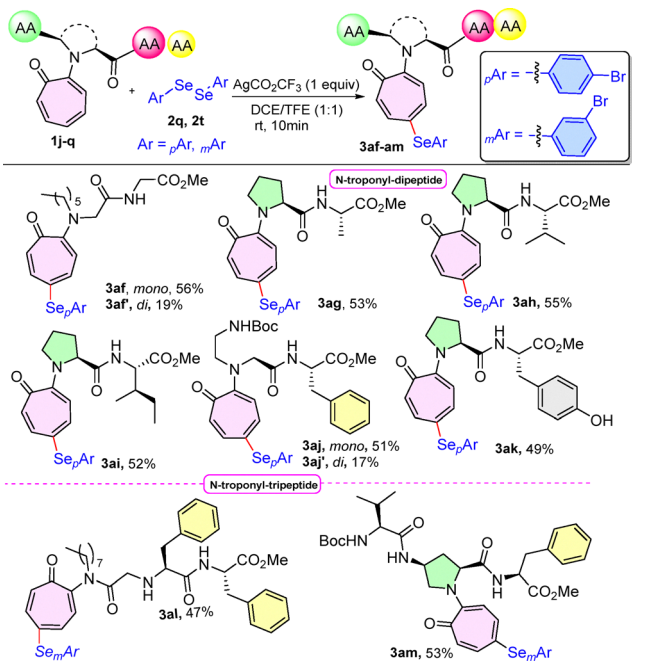
Next, the scope of the methodology was investigated for a series of *N*,*N*-di-alkylaminotropone (**1b–e**) with diselenide (**2q**) (Scheme 4). Several *N*,*N*-di-alkylaminotropones, such as piperidinyl tropone (**1b**), morpholinyl tropone (**1c**), *N*,*N*-dimethylaminotropone (**1d**), and *N*-ethyl-*N*-methylaminotropone (**1e**) produced the selenylated compounds (**3**) under the optimized reaction conditions within 5 min. In all the above cases, we observed the formation of *mono*-substituted **3y-ab** as a major product with



Scheme 4 Scope of aminotropones for selenylation. [a] Reaction conditions: DCE/TFE (1 : 1).

yields of 59–63%, while the *di*-substituted product (**3y′-ab′**) as a minor one with yields of 12–25%. Also, *N*-troponyl alkylglycinate esters (**1g–h**) provided **3ac–ad** with 71–73% yields under the optimised reaction conditions having solvent system DCE/TFE (1 : 1, 2 mL) instead of toluene. Furthermore, proline-based aminotropone *N*-troponyl-4′-OH-proline ester **1i** furnished the major *mono*-substituted selenylated derivative **3ae** in a good yield of 57% and minor *di*-substituted product **3ae′** with 17% yield.

With these exciting results, late-stage selenylation of structurally more complex aminotropone derivatives such as *N*-troponyl dipeptides (**1j–1o**) was treated with diselenides (**2q**) under the optimised reaction conditions in solvent system DCE/TFE (1 : 1, 2 mL) for 10 min (Scheme 5). Various troponyl-containing dipeptides such as *N*-troponyl-hexyl-Gly-OMe (**1j**), *N*-troponyl- Pro-Ala-OMe (**1k**), *N*-troponyl-Pro-Val-OMe (**1l**), *N*-troponyl-Pro-Ile-OMe (**1m**), BocNH-troponyl-ethyl-Gly-Phe-OMe (**1n**), and *N*-troponyl-Pro-Tyr-OMe (**1o**) were compatible to provide the respective selenylated products (**3af–3ak**) in good yields of 49–56%. In the case of **1j** and **1n**, minor *di*-substituted products **3af′** and **3aj′** were obtained in 19% and 17% yields, respectively. Notably, troponyl peptides (**3aj–3ak**) produced the aryl selenylation only at the C5 position of the troponyl-ring, though two phenyl/phenol rings were present. Pleasingly, we also noticed that the selenylation of troponyl-containing tripeptide, *N*-troponyl-octyl-Phe-Phe-OMe (**1p**) at the C5-position of the troponyl ring afforded the target peptides **3al** in a good yield of 47% using diselenide (**2t**), even in the presence of two phenyl rings of phenylalanine. These results strongly support that site-selective aryl selenylation occurs only at the C5-position of the tropone ring. Furthermore, we also tried the reaction conditions with tripeptides having aminotropones in the middle,



Scheme 5 Scope of *N*-troponyl peptide partners.

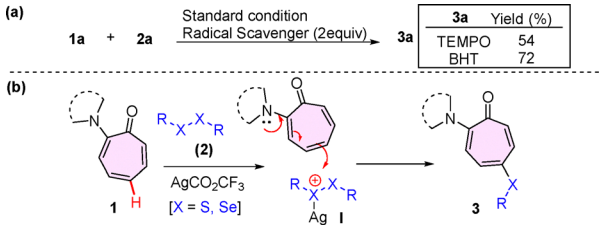


Fig. 2 (a) Radical scavenger experiments. (b) Plausible reaction mechanism.

Boc-Val-*N*-troponyl-Pro-Phe-OMe (**1q**) with diselenide (**2t**), which provided the desired product **3am** in a good yield of 53%.

To understand the reaction mechanism, we conducted radical trapping experiments in the presence of radical scavengers, TEMPO and BHT [Fig. (2a)]. The reaction of aminotropone (**1a**) with disulfide (**2a**) under the optimized conditions in the presence of TEMPO and BHT delivered the respective C5-sulfenylated peptide (**3a)** in a good yield of 54% and 72%. Hence, these results exclude the involvement of a single-electron-transfer (SET) process in the mono-selective chalcogenation of the troponyl ring. Previously, we have reported the chalcogenation of tryptophan at the C2-position through electrophilic substitution reactions at the positively charged S/Se centre of the disulfides/diselenides-Ag(I) complex.[17] Also, the role of the Ag(I) ion is purely activating the electrophile, not to coordinate with the amine group of the aminotropones. The amine groups of aminotropones are tertiary and bulky in nature, which may not be feasible for coordination with Ag(I). In the literature, similar observations are noticed with Au(I) catalyzed alkylation at the C-5 position of the tropone ring in aminotropone derivatives.[15] Herein, we propose a plausible mechanism. Initially, dichalcogenides (**2**) give an active electrophilic cationic intermediate (**I**) with Ag(I) salt ($AgCO_2CF_3$). Next, nucleophile aminotropones (**1**) participate in the electrophilic substitution reaction at the C5 position of tropone with electrophilic, positively charged S/Se intermediate (**I**), which facilitates the formation of the target chalcogenated aminotropone product (**3**) along with organosulfide byproduct formation [Fig. 2(b)].

To demonstrate the practical utility of the protocol, various post-synthetic transformations were conducted through reported procedures, such as oxidation of aryl sulfide[18] with oxone, borylation of aryl bromide,[19] and olefination of the tropone ring.[13] For example, the oxidation of **3a** with oxone afforded the desired sulfone **4** in excellent yield (Scheme 6a). Also, borylation of a bromo-substituted thiolated compound **3a** using bis(pinacolato)diboron and a Pd catalyst was investigated to obtain the corresponding borylated derivative **5** in 53% yield (Scheme 6b). Moreover, Pd catalyzed C(sp^2)–H olefination at the C7-position of the aminotropone derivative in the presence of ethyl acrylate starting from **3a** was effectively accomplished to give the expected product **6** without affecting the sulfenyl moiety (Scheme 6c). Finally, the removal of the amino group of the sulfenyl aminotropone **3a** product was successfully achieved by hydrolysis under alkaline conditions[15] in 86% yield (Scheme 6d). The chalcogenated troponyl compounds (**4–6**) could serve as a synthon for a variety of further modifications (Scheme 6).

In conclusion, we have established an efficient synthetic protocol for site-selective silver-mediated chalcogenation of α-aminotropones with dichalcogenides (disulfides/diselenides) at ambient temperature. The method features broad substrate applicability and tolerance to diverse functionalities, and enables valuable post-synthetic transformations, thereby offering a practical route for the synthesis of chalcogenated aminotropones.

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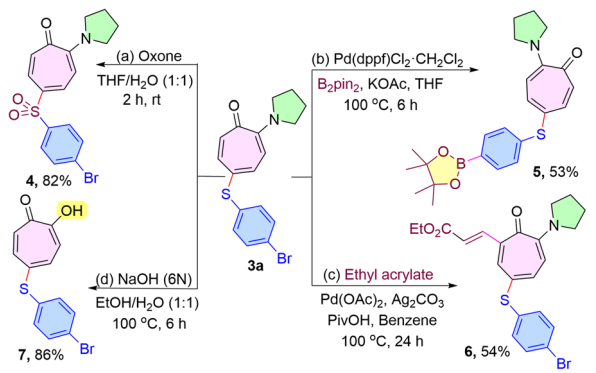
Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: general experimental procedures, NMR data/spectra (^{1}H, ^{13}C, ^{11}B, ^{19}F) and HRMS of newly synthesized substrates (**1e**, **1i**, **1k–m**, **1o**, **1q**) and products (**3a-am**, **4**, **5**, **6**, **7**) and crystal data (**3a**, **3b**, **3v**, and **3v′**). See DOI: https://doi.org/10.1039/d5cc05556c.

CCDC 2491071–2491074 contain the supplementary crystallographic data for this paper.[20a–d]



Scheme 6 Post synthetic utilities.

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