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Direct Allylic C(sp³)–H and Vinylic C(sp²)–H Thiolation with Hydrogen Evolution by Quantum Dots and Visible Light

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Abstract: Direct allylic C-H thiolation is straightforward for allylic $C(sp^3)$ -S bond formation. However, strong interactions between thiol and transition metal catalysts lead to deactivation of the catalytic cycle or oxidation of sulfur atom under oxidative condition. Thus, direct allylic $C(sp^3)$ -H thiolation has proved difficult. Represented herein is an exceptional for direct, efficient, atom- and step-economic thiolation of allylic $C(sp^3)$ -H and thiol S-H under visible light irradiation. Radical trapping experiments and electron paramagnetic resonance (EPR) spectroscopy identified the allylic radical and thiyl radical generated on the surface of photocatalyst quantum dots (QDs). The C-S bond formation does not require external oxidants and radical initiators, and hydrogen (H_2) is produced as byproduct. When vinylic $C(sp^2)$ -H was used instead of allylic $C(sp^3)$ -H bond, the radical-radical cross-coupling of $C(sp^2)$ -H and S-H was achieved with liberation of H_2 . Such a unique transformation opens up a door toward direct C-H and S-H coupling for valuable organosulfur chemistry.

Wing to the importance of allylic sulfides in pharmaceuticals, agrochemicals and organic synthesis,^[1] the construction of allylic $C(sp^3)$ –S bond has received extensively attention and a great progress has been made by transition metal catalysis.^[2] For example, transition metal catalyzed allylic substitution reaction enables construction of allylic $C(sp^3)$ –S bond in organic synthesis.^[3] However, leaving group such as ester, carbonate and halide at the allylic position is always required, which put limits on the substrate scope and lead to tedious reaction steps for prefunctionalization and defunctionalization. Recent interest in allylic C–H bond activation has triggered the synthetic transformation for $C(sp^3)$ –X (X = C, O, N) bond formation.^[4] Common to these C–H bonds functionalization is the formation of high-active electrophiles,

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 π -allyl metal intermediates, with the assistance of transition metal catalyst. The π -allyl metal intermediates thus generated can be intercepted by carbon, oxygen and nitrogen nucleophiles leading to allylic C(sp³)–H alkylation, oxidation and amination^[5] (Scheme 1 A). Unfortunately, direct allylic C-(sp³)–H thiolation has not received the same level of success because sulfur nucleophiles can poison the catalyst system by precipitating the metals from the solution or tying up the metal complex in solution in an unreactive form.^[2a,6] Transition metal catalysed allylic C–H functionalization reactions involving radicals provide a powerful alternative,^[7] however, direct allylic C(sp³)–H thiolation with thiol via radical-radical cross-coupling pathway remains elusive.

(A) Direct allylic C(sp³)-H bond activation for C-X bond formation (*Previous work*)



(B) Direct allylic C(sp³)-H thiolation with hydrogen evolution (This work)



Scheme 1. Direct allylic C–H bond activation for C–S bond formation.

Herein, we report the first allylic $C(sp^3)$ -H thiolation via cross-coupling of allylic radical and thiyl radical, i.e., irradiation of a photocatalyst, quantum dots (QDs), by visible light results in direct allylic $C(sp^3)$ -H thiolation at extremely mild reaction condition (Scheme 1 B). The protocol presented here does not require pre-functionalization of both the coupling partners and any external oxidant or radical initiator, and produces hydrogen (H₂) as byproduct. Benefiting from the quantum confinement effects, rich surface-binding properties, broad and intense absorption spectra in the visible region,^[8] QDs offer new and versatile ways to serve as photocatalysts for chemical transformation.^[9] In this contribution, we found that QDs can activate allylic C–H bond^[10] to form allylic

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radical under visible light irradiation, and the hydrogen atom eliminated from the allylic C–H bond can be reduced for hydrogen evolution. Along with the previous works on the thiol activation to produce thiyl radicals on the surface of QDs,^[11] we envision that the allylic radical generated from allylic C–H bond might be captured by thiyl radical on the surface of QDs to achieve radical-radical cross-coupling for allylic C(sp³)–S bond formation. To our delight, this is indeed the case. Irradiation of the reaction mixture containing CdSe QDs, thiol and alkenes with blue LEDs ($\lambda = 450$ nm) resulted in the desired allylic C(sp³)–H thiolation product in excellent yield. Such a transformation facilitates the activation of allylic C(sp³)–H and thiol S–H bond without introducing extraneous functional groups and external oxidants or radical initiator.

Our initial study chose 4-methoxybenzenthiol 1a and cyclohexene 2a as model substrates in the presence of CdSe QDs in CH₃CN at room temperature. Upon visible light irradiation of the reaction mixture ($\lambda = 450 \text{ nm}$) in argon atmosphere for 20 h, the desired allylic C(sp³)-H thiolation product **3a** and hydrogen (H_2) were obtained, respectively (Table 1, entry 1). Examination of a range of solvents including CH₃CN, acetone, DMF, DMSO, H₂O showed that CH₃CN was the best (entries 1-5). Increasing the amount of CdSe QDs from 8.0×10^{-5} M to 1.4×10^{-4} M improved the desired product 3a to 87% yield (entry 6). Even under aerobic condition, the photocatalytic allylic C(sp³)–H thiolation could proceed in 81% yield (entry 7). Both QDs and visible light were necessary for successful implementation of the reaction (entries 8 and 9). A higher yield (89%) could be achieved when thiol substrate 1a was reduced to 0.05 mmol (entry 10). Even though 50 equiv of alkene was used, the low yield of homocoupling product of 2a (1.4%) obtained in the crosscoupling of allylic C(sp³)-H thiolation indicated that the QDs reaction is in fact a surface reaction so that a large ratio of alkenes is to guarantee the interaction of QDs and substrates, and thereby realizing the allylic C(sp³)-H thiolation with higher efficiency. To summarize, the direct allylic $C(sp^3)$ -H

Table 1: Optimization of allylic C-H thiolation.

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Entry	Modification of reaction conditions ^[a]	Yield ^[b] [%]
1	None	75
2	Acetone instead of CH ₃ CN	74
3	DMF instead of CH ₃ CN	55
4	DMSO instead of CH₃CN	43
5	H ₂ O instead of CH ₃ CN	44
6	1.4×10 ⁻¹⁴ M CdSe QDs	87
7	In the air, 1.4×10^{-4} M CdSe QDs	81
8	Without CdSe QDs	n.d.
9	Without light	n.d.
10	1 a , 0.05 mmol	89
11	2.0 equiv TEMPO	n.d.

[a] Reaction condition: 0.1 mmol 1a, 5 mmol 2a, and CdSe QDs $(8.0 \times 10^{-5} \text{ M})$ which was dispersed by 4 mL CH₃CN were added into 10 mL reaction tube under room temperature. The solution was strictly deaerated and irradiated for 20 h by blue LEDs ($\lambda = 450 \text{ nm}$). [b] Yields detected by ¹H NMR using diphenylacetonitrile as an internal standard based on 1a. n.d. = no detected. H₂ was determined by GC-TCE.

thiolation with thiol proceeded under optimized condition, that is, irradiation of 4.0 mL degassed CH₃CN solution of 0.05 mmol 4-methoxybenzenthiol **1a**, 2.5 mmol cyclohexene **2a** and 8.0×10^{-5} M CdSe QDs by blue LED ($\lambda = 450$ nm).

Encouraged by the important result, we attempted to identify the reaction intermediates of the transformation. When a well-known radical scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), was added into the reaction system, the desired allylic $C(sp^3)$ -H thiolation was greatly suppressed, suggesting radicals involved in this transformation (entry 11). In order to further identify the radical intermediates formed in situ, we performed electron paramagnetic resonance (EPR) spectroscopy experiments. As shown in Scheme 2A, no spectral signal was detected when



Scheme 2. Mechanistic studies. A) Electron paramagnetic resonance spectroscopy experiments. (i), A solution containing CdSe QDs (dispersed by CH₃CN) and DMPO (0.2 M) was irradiated for 10 s with blue LEDs (λ =450 nm) under argon atmosphere. (ii), 4-methoxybenzenthiol **1a** was added into the solution containing CdSe QDs (dispersed by CH₃CN) and DMPO (0.2 M) under the irradiation of blue LEDs (λ =450 nm). (iii), Cyclohexene **2a** was added into the solution containing CdSe QDs (dispersed by CH₃CN) and DMPO (0.2 M) under the irradiation of blue LEDs (λ =450 nm). (iv), 1,1-diphenylethylene **4a** was added into the solution containing CdSe QDs (dispersed by CH₃CN) and DMPO (0.2 M) and DMPO (0.2 M) under the irradiation of blue LEDs (λ =450 nm). B) Control experiments.

a mixture of CdSe QDs and DMPO (5,5-dimethyl-1-pyrroline *N*-oxide) was irradiated with blue LEDs ($\lambda = 450$ nm) for 10 seconds under argon atmosphere (i). When 4-methoxybenzenthiol **1a** was presented into the mixture of CdSe QDs and DMPO, however, the thiyl radical signal was detected with coupling constants of $\alpha_N = 13.38$; $\alpha_H = 15.68^{[12]}$ (ii).

On the other hand, the addition of cyclohexene 2a into the solution of CdSe QDs and DMPO immediately led to new peaks, assigned to the typical spin adduct of allylic radicals with DMPO of $\alpha_N = 14.64$ and $\alpha_H = 19.93^{[13]}$ (iii). Compared to previous reported system,^[6b] where allylic C(sp³)-H bond was activated with the aid of disulfide as HAT reagent to form $C(sp^3)$ -S bond via ionic coupling process under air condition, our photochemical reaction realizes direct allylic C-H and S-H bonds activation to yield allylic radical and thiyl radical without external oxidants or radical initiators. More importantly, the allylic radical and thiyl radical thus generated can undergo radical-radical coupling on the surface of QDs for allylic (Csp³)–S bond construction. In contrast to a molecular photocatalyst that can only be coordinated by one substrate at a time, the QD photocatalyst can bind multiple substrates to simultaneously dictate C-H and S-H substrate activation for subsequent transformation.

To highlight the unique ability of QDs for photocatalytic allylic $C(sp^3)$ -H bond activation, we monitored the crosscoupling reaction of **1a** and **2a** shown in Figure S5. At the beginning of the reaction, a very small amounts of disulfides **1aa** were formed and then quickly consumed in 30 minutes. In the absence of the thiol coupling partner, homocoupling product **2aa** was formed (Scheme 2), indicating the activation of allylic $C(sp^3)$ -H bond by the QDs rather than by thiyl radical mediated HAT process. In addition, when disulfide **1aa** was used as substrate instead of thiol **1a**, the desired allylic sulfide **3a** was obtained smoothly in 74 % yield under standard condition.

With understanding the reaction mechanism, we investigated the generality of allylic $C(sp^3)$ -H thiolation. As shown in Scheme 3, a wide variety of thiophenols substrates reacted smoothly with cyclohexene to afford allylic $C(sp^3)$ -H thiolation products in good to excellent yields (3a-3v). Thiophenols bearing alkyl, alkoxy and methylthiol group could be transformed into the corresponding products in yields of 61-89% (3a-31). Ortho-substituted thiophenols did not lead to an obvious difference in reactivity as compared to unsubstituted variants (3a-3c). Halogenated thiophenols were compatible with the catalytic system, providing opportunities to further functionalize the formed allylic sulfide using the radical-radical cross-coupling chemistry (3m-3o). Notably, thiophenol containing free hydroxyl and amine group were well tolerated under our allylic $C(sp^3)$ -H thiolation condition, eliminating the need for protecting groups (3q-3v). Next, a variety of alkene 2, including cyclic, linear, and heterocyclic alkenes were examined. Unfunctionalized cyclic alkenes (five-, seven- and eight-membered rings) readily reacted with 4-methoxybenzenthiol to afford the allylic $C(sp^3)$ -H thiolation product in moderate yields (3w-3y), so did linear alkene (3z). Heterocyclic alkenes with allylic C(sp³)–H bond and α -oxy C(sp³)-H bond were suitable for selective allylic C-H thiolation at relatively weak C-H bond position (**3aa-3ab**).

In spite of elegant protocol for allylic C(sp³)-H activation by HAT with the generated thiyl radical,^[7c] our approach is the direct cross-coupling of allylic C(sp³)-H and S-H bond with hydrogen evolution. Strikingly, a facile thiyl radical addition to olefins^[14] is negligible. To examine the possibility for such an addition process, we introduced vinylic $C(sp^2)$ -H to replace allylic $C(sp^3)$ -H for the thiolation. To our surprise, when vinylic $C(sp^2)$ -H was added into the mixture of CdSe QDs and DMPO, a typical set of vinyl radical signals was observed with coupling constants of $\alpha_N = 14.64$; $\alpha_H = 19.42^{[13]}$ (Scheme 2, iv). On the basis of the result, we explored vinylic C(sp²)-H thiolation by irradiation of the reaction mixture containing CdSe QDs, 4-methoxythiophenol 1a and 1,1diphenylethylene 4a. The cross-coupling product 5, a significant scaffold found in natural products and pharmaceutical molecules,^[15] was exclusively obtained (Scheme 2B). Different from vinyl sulfides, which are typically prepared via the addition reaction of thiols to alkynes and cross-coupling reactions of vinyl halides with thiols,^[2a,16] the protocol presented constructs vinylic C(sp²)-S bond via direct radical-radical cross-coupling of C-H and S-H (see details for reaction optimization in Supporting Information). As shown in Scheme 3, a wide range of thiol and vinylic $C(sp^2)$ -H participated in the reaction, providing vinyl sulfides with high efficiency. Thiophenol substrates bearing alkoxy, methylthio, alkyl, aryl and F group furnished the desired vinylic $C(sp^2)$ -H thiolation products in yields ranging from 61–89% (5a–5l). Heterocyclic thiols, prevalent in natural products and pharmaceuticals, were also effective (5m). When thiolactic acid was employed as a coupling partner, the corresponding product with decarboxylation was obtained in 90% yield (5n). Also, alkyl thiols 8-mercaptomaleone was successfully coupled to vinylic C(sp²)-H bonds to afford the vinyl sulfides in moderate yields (50). On the other hand, the scope of 1,1diarylethylene substrates 4 for the vinyl $C(sp^2)$ -H thiolation protocol was examined. A range of 1,1-diarylethylene derivatives bearing OMe, Me, 'Bu, F, Cl, and NMe₂ groups produced the desired thiolation products in moderate to good yields (5p-5u). Although styrene failed to yield the cross-coupling product (see details in Supporting Information), unsymmetrical substituted 1,1-diarylethylene substrates enable to couple with 4-methoxythiophenol to afford the corresponding product in excellent yields (5v-5x).

To evaluate the scalability of this C–S bonds forming protocol, we used 4-methoxythiophenol **1a** and 1,1-diarylethylene **4u** to perform a large-scale reaction, and obtained 0.74 g (91 % yield) of the cross-coupling product **5u** under the standard conditions. Under sunlight irradiation, the direct allylic C(sp³)–H thiolation and vinylic C(sp²)–H thiolation could also be achieved in 77 % and 95 % yields, respectively (**3a** and **5u**), demonstrating the practical potential for construction of C–S bonds using solar energy.

In summary, a general, efficient and selective allylic $C(sp^3)$ -H or vinylic $C(sp^2)$ -H thiolation with thiol via radicalradical cross-coupling has been established for the first time. Mechanistic studies revealed the allylic radical (or vinylic radical) and thiyl radical generated on the surface of QDs



Communications





Scheme 3. Substrate scope. [a] Standard conditions: 0.05 mmol of thiophenol 1 (1.0 equiv), 2.5 mmol of alkenes 2 (50.0 equiv), CdSe QDs (8.0×10^{-5} M), in 4 mL of CH₃CN under Ar, irradiation with blue LEDs ($\lambda = 450$ nm) for 20 h at room temperature; Isolated yield; H₂ was determined by GC-TCE. [b] Sun light instead of blue LEDs ($\lambda = 450$ nm), see details in Supporting information. [c] Reaction conditions: 0.1 mmol of thiophenol 1 (1.0 equiv), 0.3 mmol of alkene 4 (3.0 equiv), DMAP (1.0 equiv), CdSe QDs (1.2×10^{-4} M) in 4 mL of CH₃CN under Ar, irradiation with blue LEDs ($\lambda = 450$ nm) for 12 h at room temperature; Isolated yield; H₂ was determined by GC-TCE. [d] Reaction was performed on a large scale, see details in Supporting Information [e] Ratio of isomers was determined by ¹H NMR analysis.

upon irradiation by visible light, which enable direct radicalradical cross-coupling for allylic $C(sp^3)$ -H or vinylic $C(sp^2)$ -H thiolation at extremely mild condition. The atom- and stepeconomic protocol bypasses external oxidants or radical initiators and pre-functionalization of both the coupling partners, employs readily available chemical feedstocks and compatible with a variety of functional groups, and produces hydrogen (H₂) as the byproduct. All of the features highlight the photocatalysis with QDs and visible light promising in both academic and industrial settings.

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Conflict of interest

The authors declare no conflict of interest.

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