Photoinduced dearomatization of (hetero)arenes catalyzed by polysulfide anions

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Abstract: The facile construction of C(sp³)-rich carbo- and heterocyclic compounds is a pivotal synthetic strategy to foster contemporary drug discovery programs. The downstream dearomatization of readily accessible two-dimensional (2D) planar arenes represents a direct pathway towards accessing three-dimensional (3D) aliphatic scaffolds. Here, we demonstrate that polysulfide anions are capable of catalyzing a dearomatization process of substituted naphthalenes, indoles, and other related heteroaromatic compounds in the presence of potassium formate and methanol under visible light irradiation. The developed protocol exhibits broad functional group tolerance, operational simplicity, scalability, and cost-effectiveness, representing a practical and sustainable alternative synthetic tool for the arene dearomatization.

Main text: The dearomatization of arenes, which converts readily available two-dimensional (2D) planar aromatic feedstocks into three-dimensional (3D) C(sp³)-rich ring derivatives,¹⁴ facilitates the expansion of the chemical spaces, especially in the context of medicinal chemistry programs within the pharmaceutical industry.⁵ The Birch reduction, which converts arenes into the corresponding 1,4-cyclohexadienes, is a well-established and widely recognized approach for achieving arene dearomatization (Figure 1a).⁶ The process typically necessitates the use of a super-stoichiometric quantity of pyrophoric lithium or sodium metal, in conjunction with liquid ammonia under cryogenic reaction conditions, to generate highly reducing solvated electrons. Despite recent developments in ammonia-free protocols⁷⁻⁹ and electrochemical variants,¹⁰ there remains a strong demand for the development of sustainable catalytic protocols that enable efficient Birch-type dearomatization of arenes under environmentally benign reaction conditions. Photoredox catalysis has emerged as an incredibly versatile tool for the generation of various radical and radical ion species through single-electron-transfer (SET). This process harnesses the high energy electronically excited states of visible-light absorbing redox catalysts, enabling novel reaction paradigms under milder reaction conditions, and making a significant contribution to the advancement of contemporary chemical synthesis.¹¹⁻¹⁴ In a recent notable study, Miyake employed a benzo[ghi]perylene imide as a precursor for the generation of photoexcited radical
anion species with highly reducing properties, employing the consecutive photoinduced electron-transfer (conPET) approach.\cite{15} This protocol successfully achieved photocatalytic conversions of non-activated benzene ($E_{\text{red}} = -3.4$ V vs SCE) and its alkyl-substituted derivatives into 1,4-cyclohexadienes at ambient temperature under visible light irradiation (Figure 1b).\cite{16} However, the highly reducing ability of this photocatalytic system simultaneously induced additional reductive processes on some susceptible functional groups present in the arene substrates, such as ketone deoxygenation and hydrodechlorination. On the other hand, König leveraged the dual roles of an iridium polypyridyl complex to execute a sequence of photoinduced triplet energy transfer and single-electron reduction in the presence of trialkylamines, which facilitated the dearomatization of sensitizable (herero)arenes (Figure 1c).\cite{17} Nonetheless, this system is limited to the reduction of only sensitizable (herero)arenes with triplet energy lower than that of the iridium photocatalyst ($E_T = 61.8$ kcal/mol). Similarly, Wang and Zheng utilized a boron carbonitride semiconductor (BCN), which served as a photoexcited sensitizer ($E_T = 51.0$ kcal/mol) and single-electron reductant for the Birch-type reduction of arenes in aqueous media.\cite{18} Interestingly, this system was also capable of dearomatizing arenes with a higher triplet energy such as naphthalene ($E_T = 60.6$ kcal/mol), benzene ($E_T = 84.3$ kcal/mol) and their derivatives\cite{19} as well as hydrodehalogenation of reductively inert alkyl chlorides, implying the presence of more strongly reducing species in the photocatalytic mechanism.

\begin{itemize}
  \item **Figure 1.** Dearomatization of arenes. (a) Birch reduction. (b) Photocatalytic dearomatization via consecutive photoinduced single-electron-transfer. (c) Photocatalytic dearomatization via photoinduced triplet sensitization and single-electron-transfer.
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We have recently developed a potent photocatalytic system utilizing readily accessible and inexpensive polysulfide anions, which are commonly employed as charge transfer carriers in lithium-sulfur batteries.\textsuperscript{[20]} We observed that polysulfide dianions (S\textsubscript{2}n\textsuperscript{2–}), upon photoexcitation, exhibited remarkable capability for inducing SET reduction of aryl halides with reduction potentials (E\textsubscript{red}) as low as −2.5 V vs. SCE (Figure 2a). Consequently, this process leads to the formation of aryl radicals via mesolysis of the carbon-halogen bond in aryl halide anion radicals, enabling their participation in a variety of cross-coupling reactions under catalytic redox manifolds.\textsuperscript{[21,22]} Moreover, our findings have also highlighted the ability of polysulfide anions to facilitate successive SET and hydrogen-atom-transfer (HAT) processes, thus enabling α-C-H functionalization of α-secondary benzyamines with cyanoarenes or aryl ketones under visible light irradiation.\textsuperscript{[23]} These discoveries prompted us to explore the potential of photoexcited polysulfide anions as versatile and adaptable single-electron reductants for the dearomatization of diverse arenes. We hypothesized that by incorporating an appropriate proton donor and sacrificial reductant, a polar cross-over process involving sequential SET-reduction and protonation steps could be promoted, thereby facilitating the dearomatization process.

We embarked on our investigation using \textit{N,N}-dimethyl-1-naphtamide (I) (E\textsubscript{red} = −2.35 V vs. SCE) (Figure 2b). The reaction was performed using potassium polysulfide (K\textsubscript{2}S\textsubscript{x}, 10 mol%/S) and methanol (20 equiv) in DMSO, under irradiation with indigo light (427 nm, 40 W). Through screening of various sacrificial electron-donors, potassium formate (HCO\textsubscript{2}K, 5 equiv) was identified to enable an efficient photocatalytic dearomatization of 1, resulting in the formation of 1,4-dihydropathalene 2 in 74% yield, along with over-reduced tetrahydropathalene 3 in 7% yield. Additionally, the photoreduction of amide 1 in the presence of CD\textsubscript{3}OD provided deuterated dihydropathalene 2-d in 71% yield. We observed that the deuterium incorporation rate at the C(4) position exceeded 99%, whereas the rate at the C(1) position only reached 70%; this difference can be attributed to the resonance stabilization of the corresponding carbanion at the C(1) position with the amino carbonyl group.\textsuperscript{[24]} The method allowed for the construction of dihydropathalenes having pyrrolidine amide and secondary amide moieties (for 4 and 5). On the other hand, we observed that the photoreduction of methyl 1-naphtoate (6, E\textsubscript{red} = −1.89 vs. SCE) afforded tetrahydropathalene 8 in 90% yield as a sole product, presumably formed via the corresponding 1,4-dihydropathalene 7 (Figure 2c). We propose that these dearomatization processes of 1 and 6 were initiated with their SET reduction by photoexcited polysulfide anions [S\textsubscript{2}n\textsuperscript{2–}]* to form ketyl radical anions I, which then isomerized into dearomatized radical anions II (Figure 2d). The concomitantly formed polysulfide anion radical [S\textsubscript{n}•–] could undergo polarity-driven HAT\textsuperscript{[25-27]} with formate (bond dissociation energy = 86 kcal/mol)\textsuperscript{[28]} to regenerate polysulfide dianions upon subsequent deprotonation along with the formation of CO\textsubscript{2}•–. Further reduction of the resulting radical anions II either by the photoexcited polysulfide anions or by CO\textsubscript{2}•– (E\textsubscript{ox} = −2.2 V vs SCE)\textsuperscript{[29]} and subsequent protonation with MeOH, delivered 1,4-dihydropathalenes 2 and 7. We surmised that migration of the alkene moiety of ester 7 occurred rapidly to form conjugated alkene III, which could be smoothly reduced under the current reaction
conditions to form tetrahydronaphthalene 8. On the contrary, the alkene migration of amide 2 could be sluggish due to poor acidity of the $\alpha$-proton, thereby maintaining 2 as the major product.

Figure 2. Dearomatization by polysulfide anions photocatalysis. All the reactions were performed on a 0.5 mmol scale using $K_2S$ (10 mol% / S), HCO$_2$K (5 equiv) and MeOH (20 equiv) in DMSO under irradiation with 427 nm light (Kessil lamp). The ambient temperature was monitored by the IR camera multiple times during the reaction, and the range was indicated. Isolated yields of the products were given. $^1$H NMR yields based on the internal standard were shown in parentheses. (a) Reactivity of polysulfide anions. (b) Dearomatization of 1-naphthamides. (c) Dearomatization of methyl 1-naphthoate (6). (d) Proposed mechanisms.
The formation of CO$_2^•–$ by HAT from formate could be confirmed by the reaction of $N,N$-dimethyl-2-naphtamide (9) ($E_{\text{red}} = −2.26$ V vs SCE) (Figure 3a). Under the current photocatalytic reaction conditions, the formation of tetrahydronaphthalene 10 and carboxylic acid 11 were formed in 39% and 41% yields, respectively. In this scenario, the initial hydrogenation of 9 could lead to the formation of dihydronaphthalenes 12 and/or 12’ possessing a conjugate alkene moiety. We reasoned that the subsequent single-electron reduction to 12 and/or 12’ by photoexcited polysulfide dianions enabled the hydrogenation of the conjugate alkenes in 12 and/or 12’ to form tetrahydronaphthalene 10. In addition, the competitive hydrocarboxylation$^{[30,31]}$ of the conjugate alkenes in 12 and/or 12’ by CO$_2^•–$ was also a viable alternative pathway, resulting in the formation of acid 11. To validate these reactivities, a series of control experiments were performed on several conjugated alkenes (Figure 3b). Despite its highly negative reduction potential ($E_{\text{red}} = −2.81$ V vs. SCE), dihydronaphthalene 13 could be hydrogenated and hydrocarboxylated to tetrahydronaphthalene 14 and carboxylic acid 15 in 35% and 21% yields, respectively. Similarly, when $\beta$-alkyl-$\alpha,\beta$-unsaturated amide 16 ($E_{\text{red}} = −2.51$ V vs. SCE) was employed, both hydrogenated and hydrocarboxylated products 17 and 18 were also obtained in 44% and 30% yields, respectively. These two experiments provided evidence that dihydronaphthalenes 12 and/or 12’ could be possible intermediates for the formation of 10 and 11. In contrast, the photoreduction of cinnamamide 19 only resulted in hydrogenation, likely due to its higher reduction potential ($E_{\text{red}} = −2.17$ V vs. SCE) and its steric hindrance obstructing the hydrocarboxylation pathway.
Figure 3. Dearomatization of 2-naphthamide 9 proves the formation of CO$_2$•–. All the reactions were performed on a 0.5 mmol scale using K$_2$S$_x$ (10 mol%/S), HCO$_2$K (5 equiv) and MeOH (20 equiv) in DMSO under irradiation with 427 nm or 390 nm light (Kessil lamp). The ambient temperature was monitored by the IR camera multiple times during the reaction, and the range was indicated. Isolated yields of the products were given. Carboxylic acids, if formed, were separated by acid-base extraction and their yields were measured by $^1$H NMR based on the internal standard (shown in parentheses). Further characterization was conducted by converting them into the corresponding methyl esters (see the Supporting Information). (a) Dearomatization of 2-naphthamide 9. (b) The reactions of conjugated alkenes.
We then evaluated the substituent effects for the photoinduced dearomatization of polyfunctionalized naphthalenes (Figure 4). Importantly, our studies revealed that the nature of substituents, their positions, and light intensity played a crucial role in dictating the resulting structures of the dearomatized products and their stereochemistry. Installation of a phenyl group at the C2 position of 1-naphthamide (for 21, Figure 4a) resulted in the formation of tetrahydronaphthalene 23 and carboxylic acid 24 in 59% and 20% yield, respectively. This dearomatative process was facilitated by the respective hydrogenation and hydrocarboxylation of the 1,4-dihydronaphthalene intermediate 22, which contains an arylalkene moiety. On the other hand, the photodearomatization of naphthalene 25, featuring a γ-lactone at the 1,2-juncture, proceeded in a diastereoselective manner to form 1,2-cis-tetrahydronaphthalene 28 in 68% yield, as well as carboxylic acid 29 in 6% yield (Figure 4b). Similar to the process observed with methyl 1-naphthoate (6) (Figure 1c), the reaction of 25 likely involved the initial formation of 1,4-dihydronaphthalene 26, followed by its isomerization to 3,4-dihydronaphthalene 27. Due to the presence of a conjugated alkene moiety, intermediate 27 could also be hydrogenated or hydrocarboxylated accordingly. Conversely, the reaction of naphthalenes 30 and 32, possessing a γ,γ-disubstituted-γ-lactone moiety, exclusively yielded the respective 1,2-cis-tetrahydronaphthalenes 31 and 33, without hydrocarboxylation. These outcomes were attributed to the sensitive nature of the hydrocarboxylation to steric effects (Figures 4c, d).

We subsequently focused on investigating the substituent effect on 2-naphthoates. The photoreduction of 2-naphthoate 34, bearing an aryl group at the C3 position, afforded 2,3-cis-tetrahydronaphthalene 35 as a major diastereomer (Figure 4e). Interestingly, installing an o-tolyl group at the C3 position (for 36, Figure 4f) induced selective semi-hydrogenation to form 1,2-dihydronaphthalene 37 while maintaining the conjugate alkene intact, possibly due to the non-planar arrangement of the tolyl group. We found that the photodearomatization of naphthalene 38, featuring a γ-lactone at the 2,3-juncture, could be controlled by the light intensity (Figure 4g). Specifically, irradiation with a 40W lamp gave 1,4-dihydronaphthalene 39 as the major product in 65% yield, whereas irradiation with two 40W lamps yielded 2,3-cis-tetrahydronaphthalene 40 in 66% yield along with acid 41 in 26% yield via hydrocarboxylation of 39. On the contrary, the reduction of naphthalene 42 fused with a γ-spirocyclic-γ-lactone afforded only 1,4-dihydronaphthalene 43, even under irradiation with two 40W lamps (Figure 4h). The method proved to be useful for the facile construction of the basic framework of aryltetralin lignan lactones. For phenyl naphthalene lactone 44 was converted selectively into 1,4-dihydronaphthalene 45 under photoirradiation with a 40W lamp for 6 h, whereas longer irradiation with two 40W lamps for 18 h resulted in overreduction to form tetrahydronaphthalene 46 without undergoing hydrocarboxylation (Figure 4i). These results suggested that the transformation from 45 to 46 might proceed via the intermediate 3,4-dihydronaphthalene 47, which possesses a highly conjugated alkene similar to cinnamate 19 (Figure 3b). Furthermore, polyoxygenated aryl naphthalene lactone 48, known as deoxyhydropodophyllotoxin, could also be slowly hydrogenated to the corresponding 1,4-dihydronaphthalene 49, which is a key intermediate for the total synthesis of podophyllotoxin reported by Meyers (Figure 4j).
Figure 4. Substrate scope on the dearomatization of naphthalenes. All the reactions were performed on a 0.5 mmol scale using K$_2$S$_x$ (10 mol%/S), HCO$_2$K (5 equiv) and MeOH (20 equiv) in DMSO under irradiation with 427 nm or 390 nm light (Kessil lamp). The ambient temperature was monitored by the IR camera multiple times during the reaction, and the range was indicated. Isolated yields of the products were given. Carboxylic acids, if formed, were separated by acid-base extraction and their yields were measured by $^1$H NMR based on the internal standard (shown in parentheses). Further characterization was conducted by converting them into the corresponding methyl esters.
Further investigations revealed that the photodearomatization of methyl 3-methoxy-2-naphthoate (50), a push-pull naphthalene, resulted in selective semi-1,2-reduction to provide 1,2-dihydronaphthalene 51 bearing an enol ether moiety (Figure 5a). The reaction proceeded more efficiently by irradiation with two 40W lamps, and when conducted in the presence of CD$_3$OD, deuterated 1,2-dihydronaphthalene 51-d was obtained with deuterium incorporation rate at the C(1), C(2) and C(4) at >99%, 80%, and 8%, respectively. The reaction could be performed on a 10 mmol scale of 50 without a detrimental impact on the yield of 51, despite the longer reaction time required. Subsequent studies on substituent compatibility of push-pull naphthalenes (Figure 5b) revealed that installation of allyl and phenyl groups at the C4 position did not diminish the process efficiency, providing the corresponding 1,2-dihydronaphthalenes 52 and 53 in excellent yields. In turn, the installation of a phenyl group at the C1 position enabled diastereoselective 1,2-reduction to form 1,2-trans-dihydronaphthalene 54. Switching the position of the methoxy group to the C4 position also resulted in selective 1,2-trans-reduction to afford 55. Notably, the method was capable of constructing tetrasubstituted 1,2-trans-dihydronaphthalenes having phenyl, thienyl, ethyl and cyclopropyl moieties at the C(1) position (for 56-59). The present protocol was found applicable to the semi-hydrogenation of 2-methoxy-3-phenylnaphthalene (60), despite slower reaction rate, providing dihydronaphthalene 61, which was isolated as ketone 62 upon hydrolysis of the enol ether moiety of 61 (Figure 5c). In addition, the reaction of 3-pyrrolidinyl-1-naphthoate 63 under the current reaction conditions provided 1,2-dihydronaphthalene 64 with an enamine moiety, which was detected by the $^1$H NMR analysis but isolated as hydrolyzed ketone 65 after silica gel chromatography (Figure 5d). Treatment of enamine 64 with sodium cyanoborohydride (NaBH$_3$CN) in the presence of acetic acid (AcOH) allowed for the retention of the pyrrolidinyl moiety in tetrahydronaphthalene 66. On the other hand, the reduction 67 bearing a phenylamine moiety at the C3 position resulted in semi-1,4-reduction to form enaminoester 70, likely via alkene migration from the initially formed 1,2-dihydronaphthalene 68 through imine intermediate 69 (Figure 5e).
Figure 5. Dearomatization of push-pull naphthalenes. All the reactions were performed on a 0.5 mmol scale, unless otherwise noted, using K$_2$S$_x$ (10-20 mol%/S), HCO$_2$K (5 equiv) and MeOH (20 equiv) in DMSO under irradiation with 427 nm light (Kessil lamp). The ambient temperature was monitored by the IR camera multiple times during the reaction, and the range was indicated. Isolated yields of the products were given. (a) Dearomatization of naphthalene 50. (b) Substrate scope. (c) Dearomatization of 2-methoxy-3-phenylnaphthalene 60. (d) Dearomatization of 3-pyrrolidinyl-1-naphthoate 59. (e) Dearomatization of 3-(phenylamino)-2-naphthoate 67.
Finally, we investigated the application of this dearomative reaction protocol for heteroaromatic compounds.[36] The reaction of N-methyl indole-2-carboxylate 71 proceeded slowly to afford N-methyl indoline-2-carboxylate 72 in 63% yield, after irradiation with 427 nm light of higher intensity (two 40W lamps) for 48 h (Figure 6a). Replacement of a methyl group to a t-butoxycarbonyl group (Boc) at the indole nitrogen (for 73) accelerated the dearomatization, providing the corresponding indoline 74 in 86% yield within 6 h. Notably, the reduction potential of N-Boc indole 73 ($E_{\text{red}} = -2.11$ V vs SCE) was only slightly more positive than that of N-methyl indole 71 ($E_{\text{red}} = -2.27$ V vs SCE). We surmised that this drastic difference in the reaction rate could be attributed to the potential occurrence of the unproductive back-electron-transfer (BET) from the putative radical intermediate 75; this undesirable BET process was effectively mitigated by the N-Boc moiety. We then explored the scope and limitation of this protocol for the other heteroaromatic compounds (Figure 6b). The method was amenable to constructing indoline-2-carboxamide 76. The dearomatization of 3-phenyl indole-2-carboxylate proceeded smoothly to form the corresponding 2,3-trans-indoline 77 in a diastereoselective manner. Moreover, N-Boc indole-4-carboxylate was converted into the corresponding indoline 78 in 69% yield, along with 22% yield of indoline-2-carboxylic acid 79 via hydrocarboxylation with concomitantly generated CO$_2^–$.[37,38] Benzofuran-2-carboxylate was also efficiently dearomatized to form dihydrobenzofuran 80 in 96% yield. In contrast, the dearomatization of benzothiophene-2-carboxylate into dihydrobenzothiophene 81 was accompanied by the formation of thiophenol 82 in 13% yield, as a result of the subsequent C-S bond mesolysis of 81. This reductive ring-opening could be suppressed by using carboxamide instead of ester, thereby providing 83 as a sole product.

In conclusion, we have developed a photocatalytic protocol for the dearomatization of substituted naphthalenes, indoles, and related heteroaromatic compounds via a radical-polar crossover mechanism induced by single-electron-transfer from photoexcited polysulfide anions. Fine-tuning of arene substrates, light intensity and wavelength enables the controlled synthesis of various aliphatic cyclic structures. The versatility and efficacy of this photocatalytic methodology highlight its potential as a promising strategy for a wide range of synthetic applications. Further investigations are warranted to fully explore the synthetic utility of this protocol.
Figure 6. Dearomatization of heteroaromatic compounds. All the reactions were performed on a 0.5 mmol scale using K₂Sₓ (10 mol%/S), HCO₂K (5 equiv) and MeOH (20 equiv) in DMSO under irradiation with 427 nm light (Kessil lamp). The ambient temperature was monitored by the IR camera multiple times during the reaction, and the range was indicated. Isolated yields of the products were given. (a) Dearomatization of indoles 71 and 73. (b) Substrate scope. Carboxylic acid 79 was separated by acid-base extraction and its yield was measured by ¹H NMR based on the internal standard. Further characterization was conducted by converting it into the corresponding methyl ester. Thiophenol 82 was obtained as an inseparable mixture with 81 and its yield was measured by ¹H NMR based on the internal standard. They were separated by flash column chromatography after converting 82 into the corresponding acetate.

References


**Acknowledgments**

Financial support was provided by Nanyang Technological University (NTU Singapore) and the Singapore National Research Foundation (NRF-CRP27-2021-0001). We thank Saif A. Khan (National University of Singapore), Jie Wu (National University of Singapore), Edwin K. L. Yeow (NTU Singapore), Joel M. Hawkins (Pfizer), François Lévesque (Merck), Lee Edwards (GSK), Jean-Philippe Krieger (Syngenta) and Farhan Bou Hamdan (Syngenta) for helpful discussion.

**Author contributions**


**Competing interests**

The authors declare no competing interest.

**Additional information**

All data are available in the supplementary information.

**TOC graphics**