A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

GDCh

Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202008358

Link to VoR: https://doi.org/10.1002/anie.202008358

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Intermolecular Dearomatization of Naphthalene Derivatives via a Photoredox-Catalyzed 1,2-Hydroalkylation

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Dedicated to the 70th Anniversary of Shanghai Institute of Organic Chemistry

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Abstract: An intermolecular hydroalkylative dearomatization of naphthalenes with commercially available α-amino acids is achieved via visible-light photoredox catalysis. With an organic photocatalyst, a series of multi-substituted 1,2-dihydronaphthalenes are obtained in good to excellent yields. Intriguingly, by tuning the substituents at the C2 position of naphthalenes, formal dearomative [3 + 2] cycloadditions occur exclusively via a hydroalkylative dearomatization-cyclization sequence. This overall redox-neutral method features mild reaction conditions, good tolerance of functionalities, and operational simplicity. Diverse downstream elaborations of the products are demonstrated. Preliminary mechanistic studies suggest the involvement of a radical-radical coupling pathway.

As one of the most fundamental and abundant industrial feedstocks, aromatic compounds are widely used in almost all areas of molecular sciences. Among various applications, dearomatization reactions offer unique strategies to access highly functionalized three-dimensional molecules with added value.[1] Despite the significant progress that has been made, the known reports mainly involve the transformations of heterocycles, phenols, *etc*. Conversely, the more readily available non-activated arenes such as benzene, naphthalene, and their derivatives are less explored due to the challenge of overcoming dramatically improved resonance stabilization energy.[2] Of the limited options for dearomatization of arenes, conventional single-electron approaches such as Birch reduction,[3] radical dearomatization reactions[4-6] mediated by SmI_2/HMPA (hexamethylphosphoramide) [4] and Bu_3SnH/AIBN (azobisisobutyronitrile) [5] have long been recognized as reliable strategies. However, these reactions typically require harsh or dangerous reaction conditions and capitalize on stoichiometric methods. Moreover, viable partners to react with arenes are restricted with those derived from ketones or halide compounds. In this regard, to develop a mild and catalytic single-electron protocol for dearomatization of arenes, especially complementary to these established reaction types, is highly desirable.

Within the last decade, visible-light has been used as a green and sustainable energy to drive diverse chemical reactions.[7] Of particular note, the groups of Sheridan,[8a] Sarlah,[8b-e] Glorius,[8g] and Bach[8h] independently reported that dearomative cycloaddition of arenes with arenophiles or alkenes could be achieved by exploiting visible-light induced excited state reactivity.[8] As a distinct reactivity mode, visible-light photoredox catalysis has also provided a mild strategy for single-electron approaches. However, its applications in dearomatization of arenes are rather limited because of the significant perturbation of aromaticity. Until now, handful examples were disclosed by the groups of Wang and Samec,[9a] You and Cho,[9b] Jui,[9c] and Stephenson[9d]. Elegantly, with an intramolecular design, reactive radicals generated in different fashions [*via* single electron transfer (SET) oxidation, energy transfer, SET reduction, radical cascade, respectively] underwent cyclization to an aromatic nucleus, the dearomatized species were then quenched by oxidation or reduction/protonation, to deliver the corresponding dearomatized products.

Compared with intramolecular dearomatization reactions, intermolecular variants have the advantages of using readily available starting materials, but are confronted with added challenges associated with site-selective control coupled with unfavorable entropy reduction. To date, only König and coworkers reported a visible-light promoted Birch-type reduction of arenes via sensitized electron transfer, in which two hydrogen atoms were introduced in the final products enabled by the net reductive protocol (a, Scheme 1).[10,11] To further expand the reaction patterns, we have developed an intermolecular dearomatization of naphthalene derivatives via visible-light induced redox-neutral 1,2-hydroalkylation. By employing an organic photoredox catalyst, both hydrogen atom and external functionalities derived from N-aryl glycines are incorporated in dihydronaphthalenes with high yields. Interestingly, when tuning the groups at C2 position of naphthalenes, formal dearomative [3 + 2] cycloaddition products were generated exclusively via a hydroalkylative dearomatization-cyclization sequence (b, Scheme 1). Herein, we report our results from this study.

10.1002/anie.202008358

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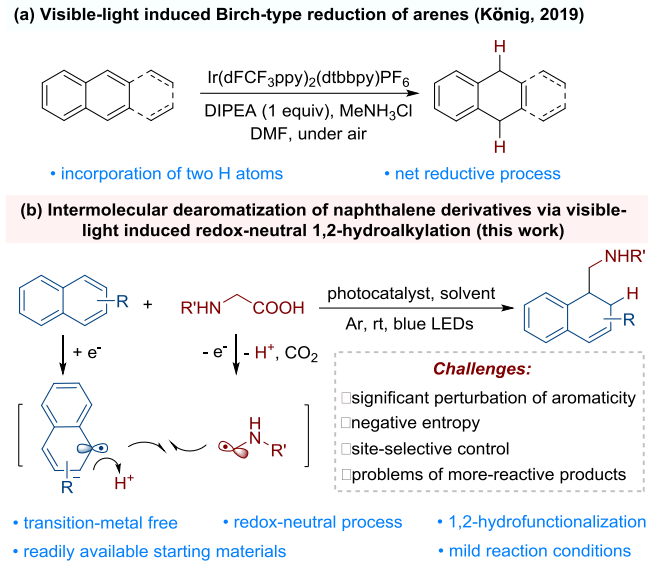
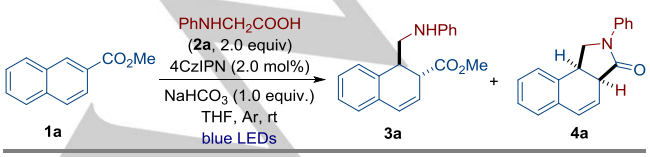
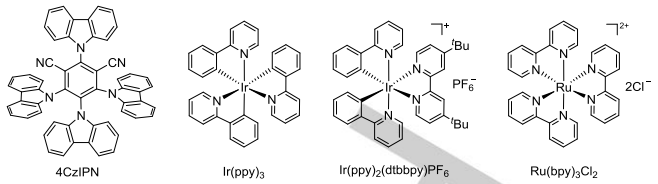


Scheme 1. Photoredox-Catalyzed Intermolecular Dearomatization of Arenes. DIPEA: diisopropylethylamine. DMF: N,N-dimethylformamide.

Due to their ready availability, α-amino acids are attractive starting materials for organic synthesis. In particular, they are frequently used as the precursors for valuable *a*-aminoalkyl radicals under visible-light photoredox catalysis, as illustrated by the groups of Das, Tan, MacMillan, Rueping, Jiang, and others.[12] Consequently, our attempt was launched with the model reaction of methyl 2-naphthoate (**1a**) and *N*-phenyl glycine (**2a**). Encouragingly, after a series of trials, we found that irradiation of a THF solution of **1a** and **2a** in the presence of 4CzIPN and $NaHCO_3$ with 24W blue LEDs gave the expected dearomative products **3a** and **4a** as a 2:1 mixture in 87% overall yield at room temperature (entry 1, Table 1).[13] While $Ir(ppy)_2(dtbbpy)PF_6$ and $Ru(bpy)_3Cl_2$ resulted in inferior results (60% and 30%, respectively), strongly reducing catalyst $Ir(ppy)_3$ failed to give any conversion (entries 2-4, Table 1). An evaluation of bases identified this reaction occurred with decreased efficiency in the presence of a mild inorganic base such as Na_2CO_3, K_2CO_3, or absence of a base. However, an organic base such as DBU inhibited this dearomative process (entries 5-8, Table 1). Moreover, solvents have a profound effect on the reaction outcome. Replacing THF with CH_3CN, DMF, CH_3OH, and CH_2Cl_2, which are commonly used in visible-light photoredox catalysis, merely resulted in poor yield or trace conversion (entries 9-12, Table 1). Finally, control experiments highlighted the importance of both 4CzIPN and visible light for promoting this hydroalkylative dearomatization reaction (entries 13-14, Table 1).

Table 1. Optimization of the Reaction Conditions.[a]





Entry	Variations from the standard conditions	Yield (%) (**3a**:**4a**)[b]
1	none	90 (87)[c] (2:1)
2	$Ir(ppy)_3$ instead of 4CzIPN	0
3	$Ir(ppy)_2(dtbbpy)PF_6$ instead of 4CzIPN	60 (3.7:1)
4	$Ru(bpy)_3Cl_2$ instead of 4CzIPN	36 (2:1)
5	Na_2CO_3 instead of $NaHCO_3$	56 (3.5:1)
6	K_2CO_3 instead of $NaHCO_3$	41 (2.6:1)
7	DBU instead of $NaHCO_3$	<5
8	without $NaHCO_3$	56 (2.6:1)
9	CH_3CN instead of THF	50 (2.5:1)
10	DMF instead of THF	<5
11	CH_3OH instead of THF	<5
12	CH_2Cl_2 instead of THF	<5
13	w/o 4CzIPN	0
14	in dark	0

[a] Reaction conditions: unless otherwise noted, a solution of **1a** (0.2 mmol), **2a** (0.4 mmol), $NaHCO_3$ (0.2 mmol) and 4CzIPN (2 mol%) in THF (2.0 mL) was irradiated by 24W blue LEDs at room temperature under argon for 24 h. [b] The ratio of **3a**:**4a** was determined by ^1H NMR analysis of the crude reaction mixture. [c] Isolated yield is reported in the parenthesis. DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene. THF: tetrahydrofuran.

Having established the optimal reaction conditions, we next explored the generality of this protocol with respect to the naphthalene derivatives (Table 2). Incorporation of different esters instead of $-CO_2Me$ at C2 position of naphthalenes was well tolerated. As the ester group became bigger ($-CO_2Me$, $-CO_2Et$, $-CO_2{}^iPr$, $-CO_2{}^tBu$), a decreased yield (87 → 23%), albeit with slightly increased diastereoselectivity (2:1→4:1), was observed for the corresponding 1,2-hydroalkylative dearomatization products **3a**-**3d** and **4a** (entries 1-4). The amide analogue **1e** was also a viable substrate, furnishing **3e** and **4a** in 91% yield as a 1.1:1 mixture of diastereomers (entry 5). When additional aryl functionalities including $-C_6H_5$, $4\text{-}MeOC_6H_4$, $4\text{-}CF_3C_6H_4$, $4\text{-}TMSC_6H_4$ (TMS: trimethylsilyl), $2,4\text{-}F_2C_6H_3$ were introduced at the C3 position of methyl 2-naphthoate (**1f-1j**), the dearomatization reactions occurred in high yields (71-85%), and in most cases with significantly improved diastereoselectivities favoring the formation of products **3** with *trans*-selectivity (9:1-10:1) (entries 6-10). C3-OTf (Tf: triflate) substituted methyl 2-naphthoate (**1k**) provided dearomatization products in 65% yield with 5.9:1 diastereoselectivity (entry 11). Owing to the extremely mild conditions, diverse functionalities such as -OAc, -OTBS (TBS: tert-butyldimethylsilyl) and alkyne (**1l-1o**) were also found to be compatible with this protocol. Good yields were achieved for the corresponding hydroalkylative dearomatization products (55-78%, entries 12-15).

Table 2. Substrate Scope.[a]

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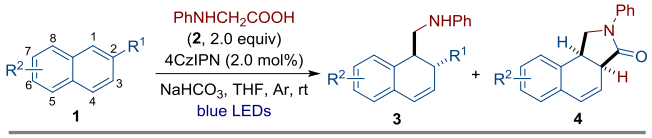
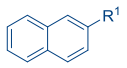
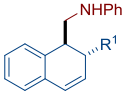
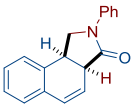
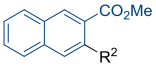
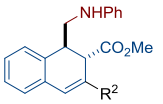
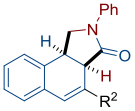
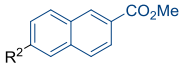
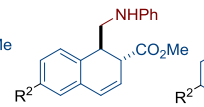
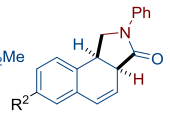
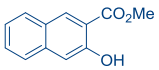
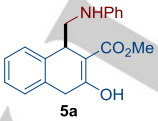
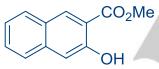
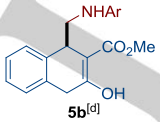
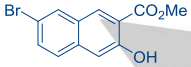
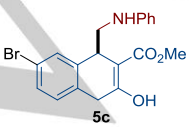
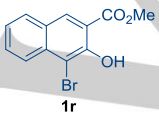
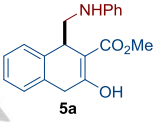


entry	substrates (1)	products		yield (3:4)
	 1a-1e	 3a-3e	 4a	
1	**1a**, R^1 = CO_2Me	**3a**	**4a**	87% (2:1)
2	**1b**, R^1 = CO_2Et	**3b**	**4a**	78% (2:1)
3	**1c**, R^1 = $CO_2{}^iPr$	**3c**	**4a**	61% (4:1)
4	**1d**, R^1 = $CO_2{}^tBu$	**3d**	**4a**	23%[b](4:1)
5	**1e**, R^1 = 	**3e**	**4a**	91%[b] (1.1:1)
	 1f-1k	 3f-3k	 4f-4k	
6	**1f**, R^2 = C_6H_5	**3f**	**4f**	79%[c] (9.6:1)
7	**1g**, R^2 = 4-$MeOC_6H_4$	**3g**	**4g**	85%[c] (10:1)
8	**1h**, R^2 = 4-$CF_3OC_6H_4$	**3h**	**4h**	79%[c] (9:1)
9	**1i**, R^2 = 4-$TMSC_6H_4$	**3i**	**4i**	71%[c] (10:1)
10	**1j**, R^2 = 2,4-$F_2C_6H_3$	**3j**	**4j**	85%[c] (1.8:1)
11	**1k**, R^2 = OTf	**3k**	**4k**	65%[b] (5.9:1)
	 1l-1o	 3l-3o	 4l-4o	
12	**1l**, R^2 = OTf	**3l**	**4l**	68%[c] (1.4:1)
13	**1m**, R^2 = OAc	**3m**	**4m**	65%[b] (1.7:1)
14	**1n**, R^2 = OTBS	**3n**	**4n**	55%[c] (2.1:1)
15	**1o**, R^2 =	**3o**	**4o**	78%[c] (1.7:1)

entry	substrates (1)	products (5)	yield (5)
16	 1p	 5a	99%
17	 1p	 5b[d] (Ar = 4-ClC_6H_4)	99%
18	 1q	 5c	92%
19	 1r	 5a	63%

[a] Reaction conditions: as entry 1, Table 1. The ratio of **3**:**4** was determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Additional **2a** (0.4 mmol) were added after 12 h. [c] Additional **2a** (0.4 mmol), $NaHCO_3$ (0.2 mmol) and 4CzIPN (2 mol%) were added after 12 h. [d] **2b** (Ar = 4-ClC_6H_4) was used.

Strikingly, the reactions between free C3-OH substituted methyl 2-naphthoates (**1p**-**1q**) and N-aryl glycines (**2a**-**2b**) provided exclusive 1,4-hydrofunctionalization products with uniformly excellent yields (92-99%, **5a**-**5c**, entries 16-18). However, when C4-Br substituted substrate **1r** was tested under standard conditions, debromination rather than protonation took place to deliver the same product as that obtained from the reaction of **1p** with **2a** (entry 19 *vs* entry 16).

Next, we wondered if the tricyclic lactam-fused 1,2-dihydronaphthalene products **4** could be formed exclusively via a hydroalkylative dearomatization-cyclization sequence. Gratifyingly, by changing the substituents at the C2 position of naphthalenes to *N*-acylpyrazole or pentafluorophenyl ester, the expected transformations proceeded smoothly to afford the formal dearomative [3 + 2] cycloaddition products **4** with excellent diastereoselectivity (Scheme 2). It was believed the incorporation of good leaving groups (A and B) in the substrates **1** made the cyclization process more feasible, which might act as a driving force for the cascade. Remarkably, this method has a good tolerance of diverse functional groups. Naphthalenes **1** bearing halogen, cyclopropane, alkyne, amide, methoxy, acetate, triflate, silylether, and even free hydroxyl groups at different positions all provided the desired tricyclic products **4** in good to excellent yields with exclusive selectivity (64-98%, **4s**-**4y**). The easily convertible functionalities such as halogen, triflate, and alkyne offer handles for further derivatization. Lastly, comparable results were achieved with N-*p*-chlorophenyl glycine (**1b**) as the hydrofunctionalization reagent (77-95%, **4z**-**4ab**).

To demonstrate the potential utilities of this method, synthetic transformations of the products obtained herein were investigated (Scheme 3). Initially, the reaction of **1a'** with **2a** was performed on a 5 mmol scale, furnishing **4a** in 85% yield (1.12 g), which showed comparable efficiency with that of 0.2 mmol scale reaction (eq 1). Exposure of **4a** to Pd/C catalyzed hydrogenation delivered tetrahydronaphthalene **6** in 98% yield (eq 2). Instead, the lactam moiety was selectively reduced in the presence of 9-BBN, generating the tricyclic functionalized scaffold incorporating a pyrrolidine ring (**7**) in 82% yield (eq 3). Aziridination of the C=C bond of **4a** proceeded smoothly to give multi-substituted tetrahydronaphthalene compound **8** possessing lactam and aziridine rings simultaneously, with a single *all-cis*-fused configuration (57% yield, >20:1 dr). Similarly, epoxidation of **4a** was successfully executed, leading to the epoxide-fused analog **9** in 91% yield with exclusive selectivity, whose structure and relative configuration were verified by the X-ray crystallographic analysis (eq 5).

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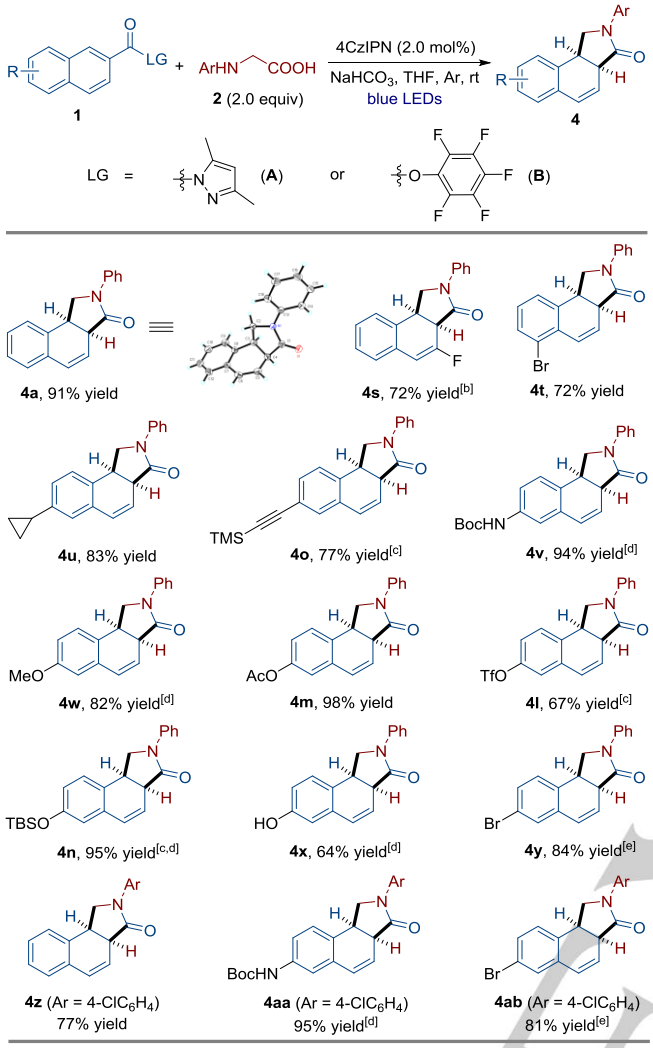
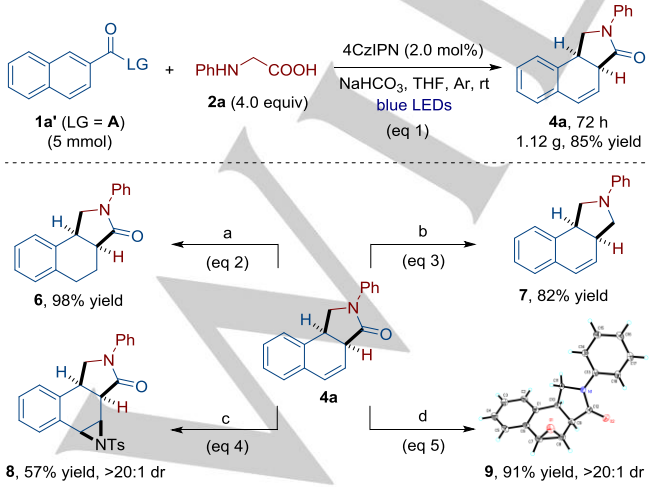
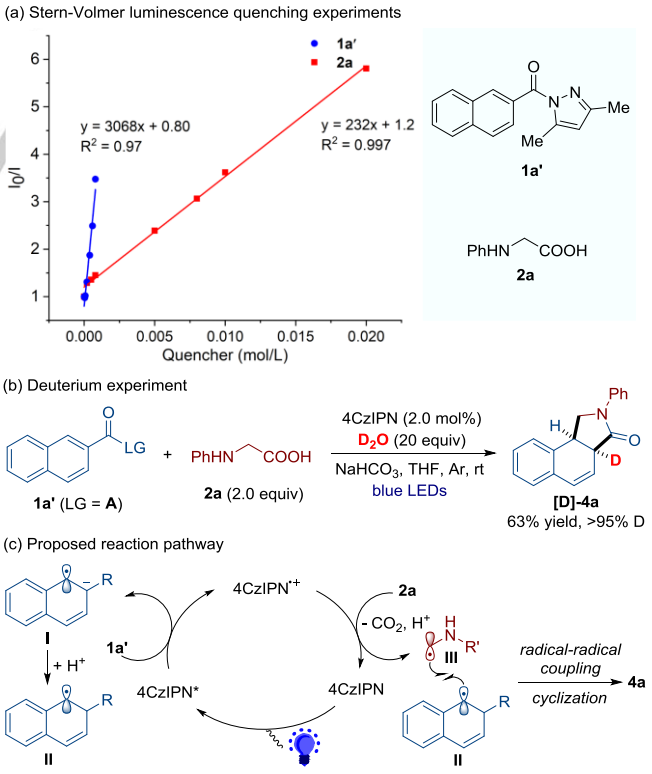


Scheme 2. Scope of Lactam-Fused 1,2-Dihydronaphthalenes.[a] [a] Reaction conditions: as entry 1, Table 1. Unless otherwise noted, **1** (LG = **A**) was used. [b] The reaction was conducted at 60 °C and additional **2a** (0.4 mmol), $NaHCO_3$ (0.2 mmol), 4CzIPN (2 mol%) were added after 24 h. [c] **1** (LG = **B**) was used. [d] Additional **2** (0.4 mmol), $NaHCO_3$ (0.2 mmol) and 4CzIPN (2 mol%) were added after 12 h. [e] **2** (0.3 mmol) was used.



Scheme 3. Gram-Scale Reaction and Synthetic Transformations. Reaction conditions: (a) Pd/C (10%), H_2, MeOH, rt, 24 h. (b) 9-BBN (4.0 equiv), THF, Ar, 65 °C, 3 h. (c) TsNClNa (1.5 equiv), $PhNMe_3Br_3$ (0.3 equiv), Ar, rt, CH_3CN, 24 h. (d) CH_3O_3Re (1.5 mol%), pyrazole (12 mol%), H_2O_2, MnO_2 (8 mol%), DCM, 0 °C-rt, 24 h. 9-BBN: 9-borabicyclo[3.3.1]nonane

Preliminary mechanistic studies were then conducted to probe the reaction pathway. Based on the Stern-Volmer luminescence quenching studies of each component, it was found that both **1a'** and **2a** quenched the photocatalyst 4CzIPN*, respectively (a, Scheme 4). In addition, the base did not have a great impact on quenching efficiency. However, the oxidative quenching of 4CzIPN* by naphthalene derivative **1a'** proceeded at significant higher rate than its reductive quenching by **2a**, which suggested the former was likely the initiation point of the photoredox catalytic cycle. When D_2O (20 equiv) was added to the reaction mixture, exclusive deuterium incorporation at the C2-position of the dearomative product was observed (b, Scheme 4). Along with the occurrence of debromination for the reaction of **1r** with **2a** (entry 19, Table 2), these experiments largely indicated the generation of radical anion intermediates. Accordingly, on the basis of the experimental observations, the catalytic cycle was proposed as follows: naphthalene **1a'** oxidatively quenches the photoexcited species 4CzIPN* to deliver $4CzIPN^{\bullet+}$ and the naphthalene radical anion **I**. Protonation at the C2-position of **I** gives radical **II**. In the meantime, single-electron oxidation of **2a** by $4CzIPN^{\bullet+}$ completes the photocatalytic cycle and upon the release of CO_2, affords α-amino radical **III**. Finally, the recombination of radical **II** and α-amino radical **III** forges the C−C bond, which is followed by a spontaneous cyclization, to provide the final product **4a** (c, Scheme 4). At this stage, an alternative pathway involving radical addition could not be fully excluded (See the SI for details).



Scheme 4. Mechanistic Studies.

In conclusion, we have developed the first catalytic intermolecular hydroalkylative dearomatization of naphthalene derivatives with commercially available α-amino acids via visible-light photoredox catalysis. By employing an organic photocatalyst and simple starting materials, the intermolecular process occurs with high site-selectivity, furnishing substituted 1,2-dihydronaphthalenes in good to excellent yields. Interestingly, with the adjustment of the substituents at the C2 position of naphthalenes, formal dearomative [3 + 2] cycloadditions are achieved via a hydroalkylative dearomatization-cyclization sequence. An array of lactam-fused 1,2-dihydronaphthalenes are obtained in high yields with exclusive diastereoselectivity. Different from previously described strategies, this method is entirely redox-neutral and requires no need for stoichiometric external oxidants or reductants. The extremely mild conditions render this method compatible with diverse functionalities and amenable to scale-up with a simple operation. In addition, diversification of dihydronaphthalene products is demonstrated, further showcasing the potential synthetic utility. Preliminary mechanistic studies suggest a radical-radical coupling pathway is operative. We anticipate this method would provide a new platform for single-electron dearomatization reactions.

Acknowledgements

We thank MOST (2016YFA0202900), the NSFC (21821002 and 21801248), the Chinese Academy of Sciences (QYZDY-SSW-SLH012), the Youth Innovation Promotion Association (2019255) of CAS and Shanghai Sailing Program (18YF1428900) for generous financial support. We also thank Prof. Wei-Shi Li for assistance with the luminescence quenching experiments. Dr. Yuan-Zheng Cheng thanks AstraZeneca and Pharmaron for a postdoctoral fellowship.

Keywords: dearomatization • naphthalene • photocatalysis • radical • redox-neutral

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[14] CCDC 1986696 and 1986697 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

10.1002/anie.202008358

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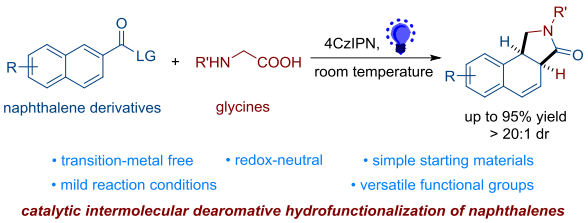

The development of dearomative functionalization strategies for arenes is intrinsically challenging and remains a largely unsolved synthetic problem due to the particularly high resonance energy. In this manuscript, we have developed the first catalytic intermolecular hydroalkylative dearomatization of naphthalene derivatives with commercially available α-amino acids via a photoredox-neutral process.