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Photoinduced EDA Complexes Enabled Radical Tandem Cyclization/Arylation of Unactivated Alkene with 2-Amino-1,4-naphthoquinones

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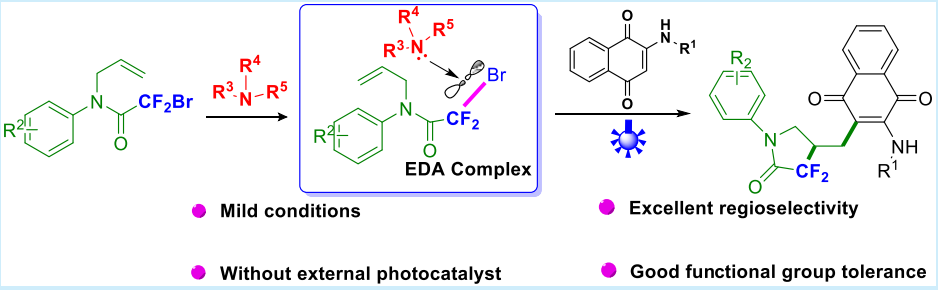

ABSTRACT: A visible-light-induced radical tandem cyclization/arylation between 2-amino-1, 4-naphthoquinone and *N*-allyl-2-bromo-2,2-difluoroacetamides has been developed without an external photocatalyst. The transformation could be carried out at room temperature and gave a variety of C-3-functionalized 2-amino-1,4-naphthoquinone derivatives in moderate to excellent yields. Moreover, mechanistic studies revealed that the reaction is driven by the formation of an electron donor−acceptor (EDA) complex.

Naphthoquinones, especially those containing an amino group at the two-position, are widely present among pharmacologically active compounds and synthetic molecules[1] (Figure 1) and have gained much attention owing to their

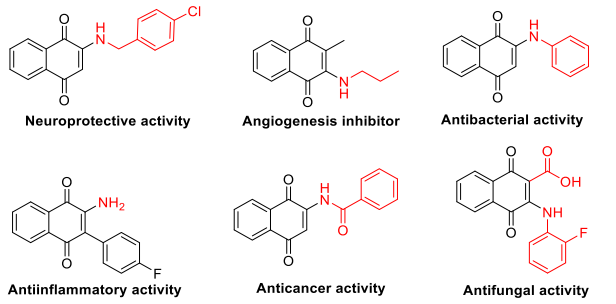

Figure 1. Examples of Bioactive Amino Naphthoquinone Derivatives

various biological activities such as antimalarial,[2] antiinflammatory,[3] anticancer,[4] antifungal,[5] and neuroprotective[6] properties. Therefore, the development of green and efficient methods to access such compounds is becoming one of the research interests in synthetic chemistry.[7] In the past few years, direct C−H functionalization at the C-3 position of 2-amino-1,4-naphthoquinones has served as an ideal and powerful method to afford the naphthoquinone derivatives. For example, in 2017, Yang and coworkers reported a novel method for the 3-trifluoromethylation of 2-amino-1,4-naphthoquinones by employing *tert*-butyl hydroperoxide (TBHP) as an oxidant and Zn $(SO_2CF_3)_2$ as a trifluoromethylation reagent[7a] (Scheme 1a). Zhang's group developed a copper-catalyzed three-component difunctionalization of aromatic alkenes to access 1,4-naphthoquinone derivatives, in which α-bromocarboxylates are used as radical precursors and 2-amino-1,4-naphthoquinones are used as radical trapping reagents[7b] (Scheme 1b). Subsequently, a silver-catalyzed three-component difunctionalization of alkenes was also reported by the same research group, providing an alternative method to access CF_3-functionalized alkyl-substituted quinone derivatives[7c] (Scheme 1c). Despite these achievements, developing novel and environmentally friendly methods for the construction of more complex 2-amino-1,4-naphthoquinone derivatives via direct C-3 functionalization is still in high demand.

As is well known, nitrogen-containing heterocycles such as γ-lactam are key motifs in numerous bioactive molecules.[8] Meanwhile, because of the widespread application of difluoromethylene (CF_2)-containing molecules in pharmaceutical and agricultural chemicals,[9] the synthetic methods for the

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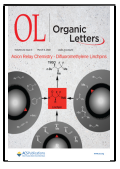

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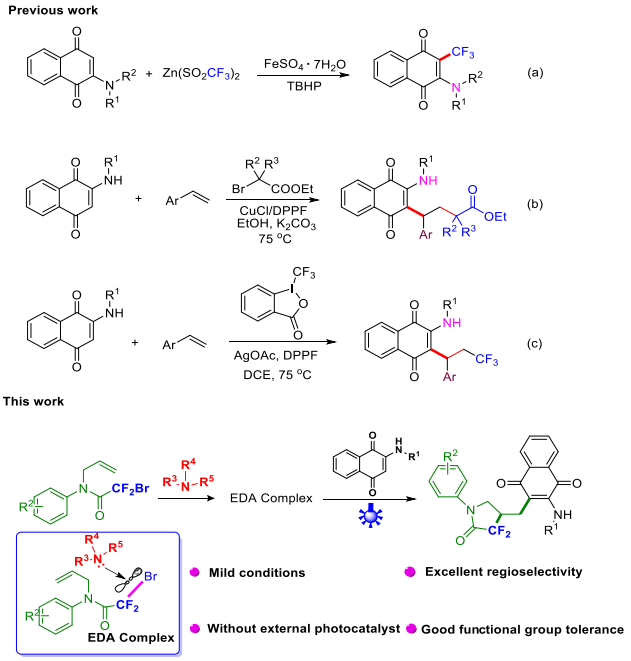
Scheme 1. C-3 Functionalization of 2-Amino-1,4-naphthoquinones

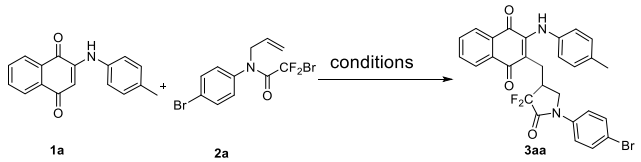


introduction of a CF_2 group into the γ-lactam have been extensively studied. In particular, the radical-mediated intermolecular 1,2-difunctionalization of alkenes and the intramolecular cyclization of *N*-allylhalodifluoroacetamide have become the most attractive approaches to α,α-difluoro-γ-lactams.[10] Considering the positive biological activities of 2-amino-1,4-naphthoquinones and α,α-difluoro-γ-lactams, we assume that combining the above two partners could lead to the discovery of a series of pharmacologically active compounds.

In the past decade, photoredox catalysis has become a hot area in organic chemistry due to its mild conditions, environmental friendliness, and low-energy irradiation.[11] However, traditionally, precious metal complexes or elaborate organic dyes are usually required in such approaches. Nowadays, with the growing demand for the discovery of greener synthetic methods, visible-light-induced organic transformations in the absence of photocatalysts have received great attention due to their excellent atomic economy and synthetic value, especially those photoinduced transformations mediated by the electron donor−acceptor (EDA) complex.[12] With our ongoing studies on photoinduced C−H functionalization,[13] herein, we developed an EDA-mediated, external catalyst-free, radical tandem cyclization/arylation of an unactivated alkene with 2-amino-1,4-naphthoquinones, providing a convenient and practical avenue to the naphthoquinone derivatives.

Initially, 2-(4-methylphenylamino)-1,4-naphthoquinone **1a** and *N*-allyl-2-bromo-*N*-(4-bromophenyl)-2,2-difluoroacetamide **2a** were chosen as the model substrates for the optimization of reaction conditions. In the process of the investigation of this model reaction, we observed a high-degree background reaction upon mixing two colorless reagents, **2a** and tetramethylethylenediamine (TMEDA), according to the color changes of the mixture, which implied that the EDA complex might be formed. To our delight, this transformation could be successfully initiated in the presence of TMEDA in MeCN with the irradiation of blue light-emitting diodes (LEDs) at room temperature, giving the desired product **3aa** in 28% yield without any external photocatalyst. Other electron donors including Et_3N, *N*,*N*-diisopropylethylamine (DIPEA), 4-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]-octane (DABCO), and *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (PMDETA) were then screened, and only PMDETA could give a better result (Table 1, entries 2−6).

Table 1. Optimization of the Reaction Conditions[a]



entry	amines	solvent	yield (%)[b]
1	TMEDA	MeCN	28
2	Et_3N	MeCN	trace
3	DIPEA	MeCN	trace
4	DMAP	MeCN	NR
5	DABCO	MeCN	NR
6	PMDETA	MeCN	50
7	PMDETA	DMF	43
8	PMDETA	DCM	30
9	**PMDETA**	**DMSO**	**75**
10	PMDETA	DCE	15
11	PMDETA	EA	trace
12	PMDETA	dioxane	25
13	PMDETA	acetone	24
14[c]	PMDETA	DMSO	45
15[d]	PMDETA	DMSO	70
16[e]	PMDETA	DMSO	trace
17[f]	PMDETA	DMSO	48
18		DMSO	NR
19[g]	PMDETA	DMSO	NR
20[h]	PMDETA	DMSO	54

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), amine (0.4 mmol), solvent (2 mL), rt, under N_2, 3 W blue LEDs, 24−48 h. [b]Isolated yield. [c]PMDETA (0.2 mmol). [d]PMDETA (0.6 mmol). [e]Green LEDs. [f]White LEDs. [g]Without light. [h]Under air.

To further enhance the yield of **3aa**, several commonly used solvents such as dimethylformamide (DMF), dichloromethane (DCM), dimethyl sulfoxide (DMSO), diethylcarbamazine (DCE), ethyl acetate (EtOAc), dioxane, and acetone were also examined, and the experimental results indicated that DMSO displayed a higher efficiency compared with other solvents (Table 1, entries 7−13). Decreasing or increasing the amount of PMDETA did not lead to a significant improvement (Table 1, entries 14 and 15). Different light sources were then examined, and the results demonstrated that the blue light was still the best choice under the standard conditions compared with green or white lights (Table 1, entries 16 and 17). Finally, the control experiments indicated that the organoamine and irradiation were both essential for this reaction, and a decreased yield of **3aa** was obtained when this transform was carried out under air (Table 1, entries 18−20).

With the optimized conditions established, the substrate scope of 1,4-naphthoquinones incorporating amino groups at the two-position was originally evaluated (Scheme 2). The experimental results revealed that a variety of 2-amino-naphthoquinone derivatives were all suitable for this method,

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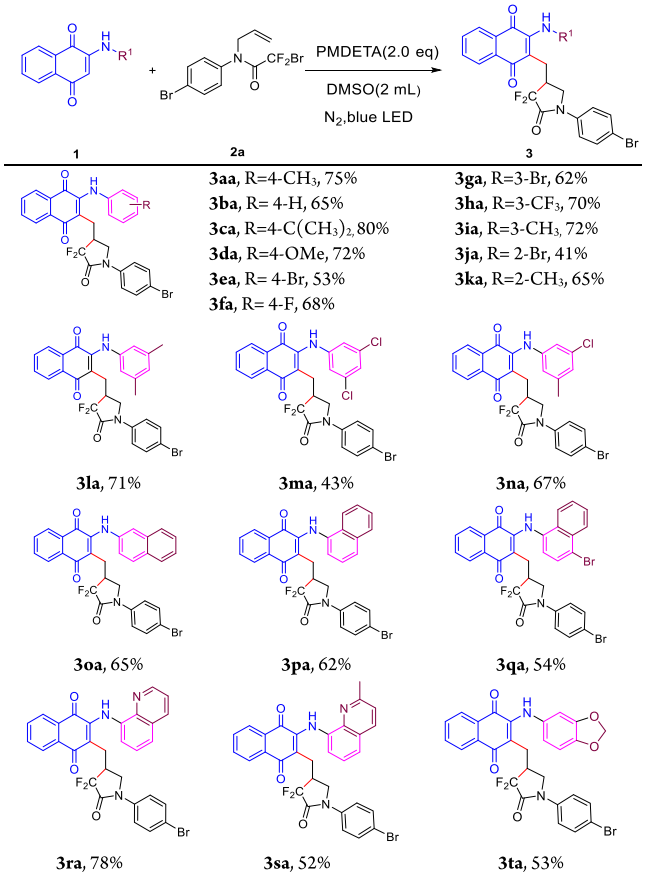
Scheme 2. Substrate Scope of 2-Aminonaphthoquinones Derivatives[a,b]

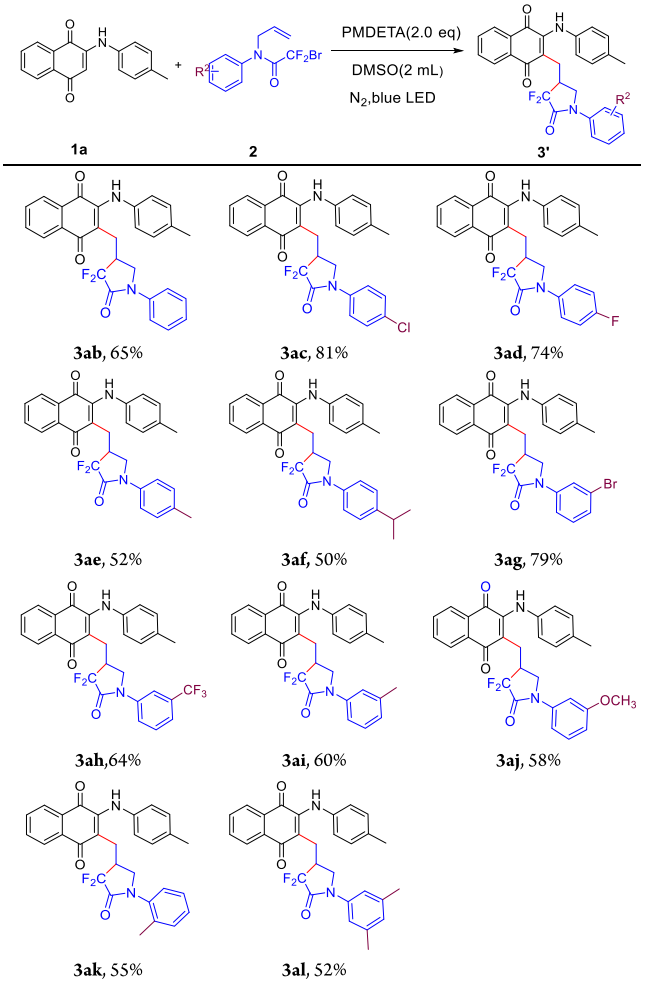


[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), amine (0.4 mmol), solvent (2 mL), rt, under N_2, 3 W blue LEDs, 24−48 h. [b]Isolated yield.

and the corresponding products **3aa**−**3ta** were obtained in 41−80% yields. First, the 2-aminonaphthoquinones without a substituent on the benzene ring could give the desired product **3ba** in 65% yield. Substituents with different electronic effects on this reaction were then investigated. The experimental results indicated that the 1,4-naphthoquinone derivatives containing electron-donating groups (4-methyl **1a**, isopropyl **1c**, methoxy **1d**) showed good reactivity for this transformation, providing the desired products in moderate to good yields. The substrates bearing those electron-withdrawing groups (4-bromo **1e**, 4-fluoro **1f**) showed a slightly lower reactivity, giving the products **3ea** and **3fa** in 53 and 68% yields. In addition, the effect of the position of substituents on the phenyl was then studied. Three-substituted derivatives exhibited good tolerance for this reaction, providing the products **3ga**−**3ia** in 62−72% yields. However, two-substituted compounds, such as **1j** or **1k**, afforded the corresponding products in lower yields compared with the three- or four-substituted compounds, which was attributed to steric effects. Substrates with a multisubstituted phenylamino were also suitable for the reaction, and the corresponding products **3la**, **3ma**, and **3na** were obtained in yields of 71, 43, and 67%, respectively. Moreover, this transformation also showed good tolerance when the aniline group was replaced by other aromatic amine, affording the products **3oa**−**3ta** in satisfying yields (52−78%). For example, compounds **1o**−**1q** bearing a naphthalene group could undergo this tandem reaction smoothly, giving the corresponding products (**3oa**−**3qa**) in moderate yields. We also found that a substrate with an R^1 group as a quinoline moiety also could work satisfactorily, furnishing products **3ra** and **3sa** in 78 and 52% yields, respectively. Finally, the 3,4-methylenedioxyphenyl-containing derivative **2t** was tested for this reaction, and the desired products **3ta** was obtained in 53% yield.

After examining the substrate scope of 2-amino-1,4-naphthoquinone, we next turned our attention to explore the scope of *N*-allyl-2-bromo-2,2-difluoroacetamides with different substituents on the benzene ring (Scheme 3). When acetamide

Scheme 3. Scope of *N*-Allyl-2-bromo-2,2-difluoroacetamines[a,b]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), amine (0.4 mmol), solvent (2 mL), rt, under N_2, 3 W blue LEDs, 24−48 h. [b]Isolated yield.

2b without a substituent on the benzene ring was used as the substrate under identical conditions, the target product **3ab** was obtained in 65% yield. Bromodifluoroacetamide bearing either electron-withdrawing groups (4-chloro **2c**, 4-fluoro **2d**) or electron-donating groups (4-methyl **2e**, 4-isopropyl **2f**) furnished the corresponding products in moderate to good yields (50−81%). In addition, meta-substituted compounds such as **3ag** (−Br), **3ah** (−CF_3), **3ai** (−CH_3), and **3aj** (−OCH_3) also performed well for this reaction, giving the

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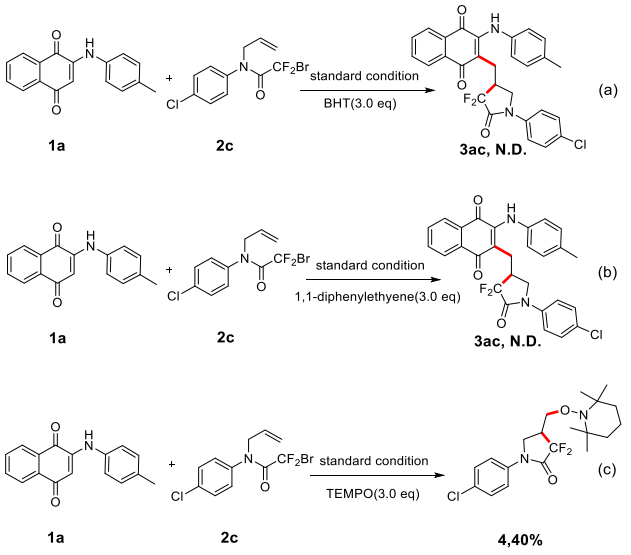
desired products **3ag**−**3aj** in 79, 64, 60, and 58% yields, respectively. Additionally, the ortho-substituted compound **2k** underwent this tandem process well and afforded the desired product **3ak** in 55% yield. Finally, the disubstituted bromodifluoroacetamide **2l** containing methyl groups in the three- and five-positions was also a suitable substrate for this reaction and gave the corresponding product **3al** in 52% yield.

To further study the reaction mechanism, a series of control experiments were conducted, as shown in Scheme 4. When the

Scheme 4. Radical Inhibitor Experiment



reaction was performed in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 1,1-diphenylethylene, the transformation was found to be completely inhibited, and no product was detected (Scheme 4a,b). These results suggested that the reaction might proceed via a radical mechanism. To confirm the formation of a difluoroacetamide radical, another radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was then applied to the same reaction system. As expected, the target product **3ac** was not detected, whereas the radical-captured product **4** was isolated in a yield of 40%. To explore whether this photochemical reaction was mediated by the EDA complex of the *N*-allyl-2-bromo-2,2-difluoroacetamines and PMDETA, the UV−visible (UV−vis) analysis of the different reaction components was carried out. After mixing the *N*-allyl-2-bromo-2,2-difluoro-acetamines and PMDETA, the optical absorption spectrum obviously shifted to the visible region (Figure 2). Finally, the results of the light on−off experiment demonstrated that visible light is a necessary component of the reaction (Figure 3).

According to the above experiments and literature reports, a possible mechanism for this visible-light-mediated cyclization/arylation between 2-amino-1,4-naphthoquinone and *N*-allyl-2-bromo-2,2-difluoroacetamides is proposed (Scheme 5). This reaction was initiated by the formation of an EDA complex between the organoamine and *N*-allyl-2-bromo-2,2-difluoro-acetamines. Irradiation of the EDA complex with visible light triggers a single-electron transfer (SET) process to form amino radical cation **A**, accompanied by the generation of difluoroalkyl radical (**B**) after releasing a bromide anion from the *N*-allyl-2-bromo-2,2-difluoroacetamide radical anion. The acquired radical **B** then immediately underwent an intra-

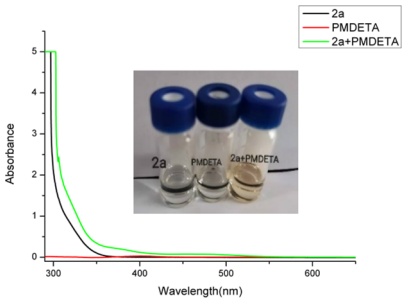


Figure 2. UV−vis absorption spectra. Insert: Photos of 2, PMDETA, and 2 + PMDETA in DMSO (0.02 M).

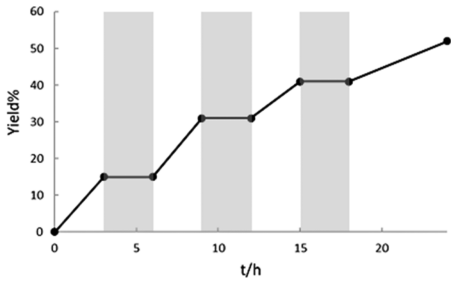
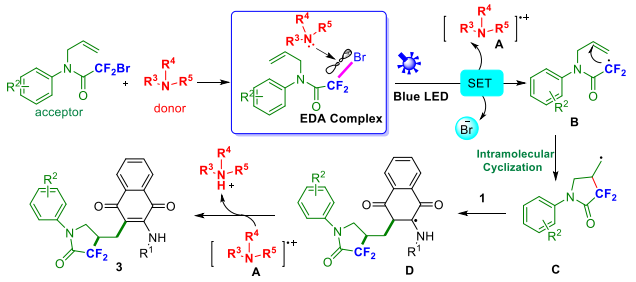


Figure 3. Light on−off experiment.

Scheme 5. Proposed Mechanism



molecular cyclization process to form the cyclic radical intermediate **C**, which was subsequently trapped by the 2-amino-1,4-naphthoquinone to form another radical **D**. The target product **3** could be obtained via a hydrogen atom abstract process from radical **D** to amino radical cation **A**.

In conclusion, we have developed an EDA-complex-mediated radical tandem cyclization/arylation of unactivated alkenes with 2-amino-1,4-naphthoquinone analogues by the irradiation of blue LEDs. The mechanistic studies have demonstrated that *N*-allylbromodifluoroacetamide was capable of generating an EDA complex with organoamine, which was the key step for triggering this transformation. Furthermore, this protocol features external photocatalyst-free, mild conditions, good functional group tolerance, and excellent regioselectivity, providing a novel environmentally friendly method to naphthoquinone derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00268.

Experimental details and spectroscopic data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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