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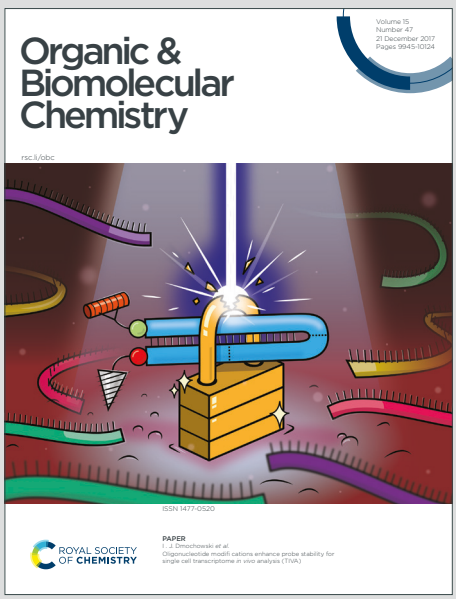

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COMMUNICATION

Visible-light-promoted radical cross-coupling of *para*-quinone methides with *N*-substituted anilines: An efficient approach to 2,2-diarylethylamines

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An efficient protocol to access 2,2-diarylethylamines *via* visible-light-promoted radical reactions of *para*-quinone methides (*p*-QMs) with *N*-alkyl anilines has been disclosed. The reactions featured metal-free, redox-neutral, mild reaction conditions, and wide functional groups compatibility.

Dopamine is a major neurotransmitter in the human brain. The dopamine deficiency is associated with several health conditions, including anxiety, depression and Parkinson's disease.[1] However, dopamine itself is too hydrophilic to cross the blood-brain barrier and thus cannot be used for the treatment of central nervous system diseases. Thus, the design and synthesis of dopamine analogues has received considerable attention among medicinal chemists. In particular, 2,2-diarylethylamine scaffold is a common structural motif in numerous dopamine receptor agonists. For example, **SKF-38393** and its derivatives, which are dopamine D1 receptor agonists could be used for the treatment of neurodegenerative disorders and cocaine addiction.[2] Diethanolamine (**MCN-4187**) has shown potential antidepressant activity (Fig. 1).[3] Consequently, many methods have been developed for the construction of the 2,2-diarylethylamine skeleton, such as ring-opening arylation of 2-arylaziridines (Scheme 1a),[4] hydrogenation of enamines (Scheme 1b),[5] aminoarylation of styrene (Scheme 1c),[6] and arylation of β-nitroalkenes followed by reduction (Scheme 1d).[7] Despite these significant advances, alternative and straightforward methods are still highly desirable.

In recent years, *para*-quinone methides (*p*-QMs) have emerged as versatile building blocks in organic synthesis. In particular, the 1,6-Michael addition of *p*-QMs with various nucleophiles has been extensively developed for the synthesis of diverse diarylmethane derivatives.[8-9] However, in sharp contrast, the radical-type addition or coupling reaction of *p*-QMs has less been explored,[10-11] albeit that diarylmethyl radicals could be generated from *p*-QMs was first demonstrated by Kurreck in 1985.[12] With the development of visible-light-promoted photoredox catalysis, a few photocatalytic radical transformations of *p*-QMs have recently been realized. The radical source is an important variable in these transformations. Up to now, various carbon radicals including tri-/difluoroalkyl,[11a-b] benzyl,[11c] cyanoalkyl[11d] and alkyl radicals[11e] have been used in these radical 1,6-addition reactions with *p*-QMs, which provide efficient approaches to construct diverse diaryl compounds.

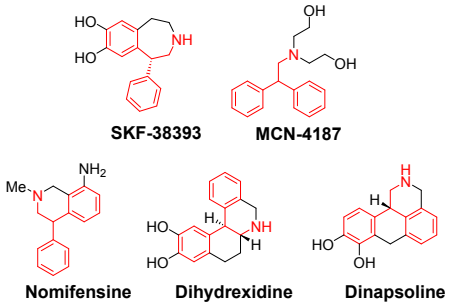

Fig. 1 Typical biologically active molecules with 2,2-diarylethylamine motif.

We have recently reported the photoredox-catalyzed decarboxylative radical 1,6-addition of arylacetic acids to *para*-quinone methides to access 1,1,2-triarylethanes.[11c] As part of our continuing interest for the synthesis of diaryl compounds, we envisioned that 2,2-diarylethylamines could be readily prepared by the photoredox-catalyzed radical 1,6-addition reaction of *p*-QMs with α-aminoalkyl radicals generated from *N*-alkyl anilines.[13] Herein, we report a visible-light-promoted radical reactions of *p*-QMs with *N*-alkyl anilines (Scheme 1e), providing a facile and efficient access to a wide range of 2,2-diarylethylamines.

Initially, we carried out the model reaction of *p*-QM (**1a**) (E_{red} = -0.20 V *vs.* SCE)[11a] with *N*,*N*-dimethylaniline (**2a**) in the presence of $[Ir\{dF(CF_3)_2ppy\}_2(bpy)]PF_6$ ($E_{ox}(Ir(IV/III^*)$ = -1.00 V *vs.* SCE)[14] and 1.2 equiv. of K_2HPO_4 in DMF (2 mL) under nitrogen atmosphere at 25

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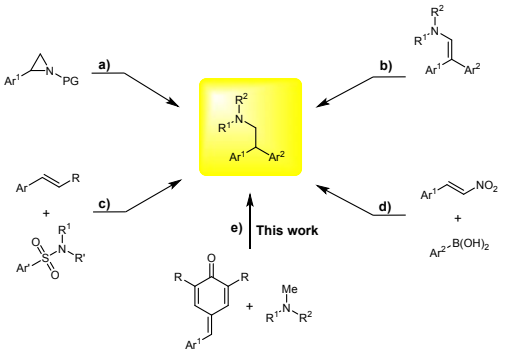
Electronic Supplementary Information (ESI) available: Synthetic details, additional spectroscopic data, and characterization of the new compounds.

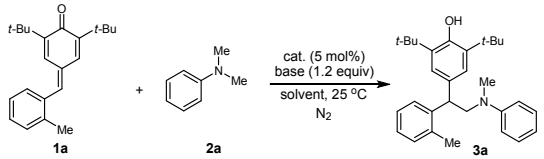
°C. As expected, the reaction did proceed under the irradiation of two 12

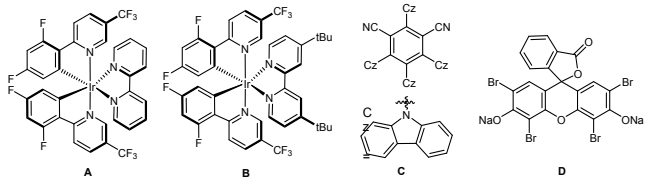


Scheme 1 Synthetic approaches of 2,2-diarylethylamines.

W green LED bulbs, providing the desired product **3a** in 45% yield (Table 1 entry 1). Inspired by this result, we then screened a series of photocatalysts with different redox potentials, including Ir-based photocatalysts (**A** and **B**), 4-CzIPN (**C**) and eosin Y (**D**), and found that 92% yield of **3a** was obtained when using Eosin Y (E_{ox}(EY $^{\bullet+}$/EY*) = -1.11 V *vs.* SCE)[15,16] (entry 4). Subsequently, different solvents were examined (entries 5-7), confirming that DMF was the optimal choice. Further investigation on the effect of bases was conducted, the yield was dramatically decreased to 53% in the absence of base (entry 8), which indicated that base played a considerable role in promoting the reaction. Among the bases screened,

Table 1 Optimization of the reaction conditions[a]



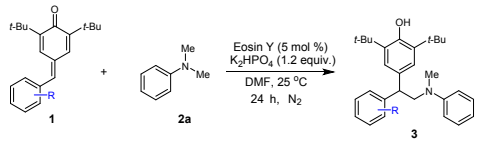


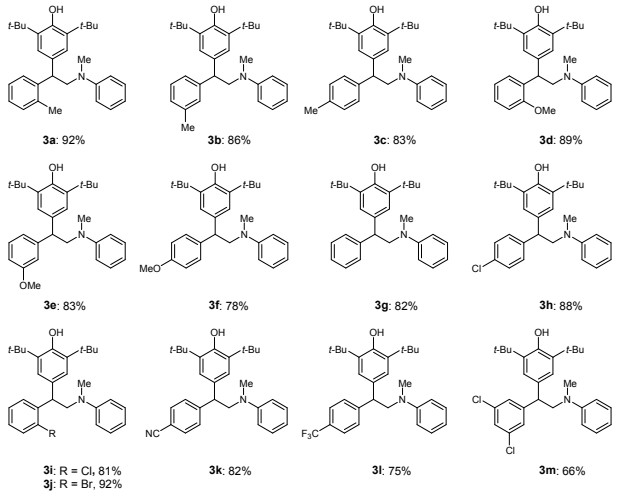
Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	**A**	K_2HPO_4	DMF	45
2	**B**	K_2HPO_4	DMF	50
3	**C**	K_2HPO_4	DMF	68
4	**D**	K_2HPO_4	DMF	92
5	**D**	K_2HPO_4	DMSO	52
6	**D**	K_2HPO_4	MeCN	30
7	**D**	K_2HPO_4	CH_2Cl_2	25
8	**D**	-	DMF	53
9	**D**	Na_2HPO_4	DMF	87
10	**D**	$NaHCO_3$	DMF	84
11	**D**	$K_3PO_4{\cdot}3H_2O$	DMF	24
12[c]	**D**	K_2HPO_4	DMF	-
13	-	K_2HPO_4	DMF	-
14[d]	**D**	K_2HPO_4	DMF	-

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), catalyst (0.005 mmol), base (1.2 equiv.), solvent (2 mL), under 12 W green LEDs for 24 h at 25 °C. [b] Isolated yield. [c] In dark. [d] Under air atmosphere.

K_2HPO_4 gave the highest yield (entry 4). Control experiments have shown that photocatalyst, nitrogen atmosphere and light irradiation are essential for the success of this transformation (entries 12-14).

Table 2 Scope of *para*-quinones[a,b]





[a] Reaction conditions: **1** (0.1 mmol), **2a** (0.12 mmol), Eosin Y (0.005 mmol), K_2HPO_4 (1.2 equiv.), DMF (2 mL), under 12 W green LEDs for 24 h at 25 °C. [b] Isolated yield.

With the optimal reaction conditions in hand (Table 1 entry 4), the substrate scope of *para*-quinones was further examined (Table 2). To our delight, a series of substituted *p*-QMs could smoothly react in this transformation, giving the corresponding products **3a**-**3m** in moderate to excellent yields (66-92%). It was found that the reaction could produce the desired products in high yields when the substituents on the phenyl ring were electron-donating groups such as methyl (**3a**-**3c**) and methoxyl (**3d**-**3f**). The yields could also be guaranteed when the substituents were electronically neutral (**3g**) or electron-withdrawing groups (**3h**-**3l**). The yield was slightly reduced for 3,5-dichloro-substituted substrate (**3m**, 66%). Moreover, the position of the substituents on the phenyl ring had little effect on the reaction outcome.

We next set out to explore the scope of the tertiary amines, and the results were summarized in Table 3. A series of *N*,*N*-dialkylanilines with electron-donating or -withdrawing substituents at the *para*-position of the benzene ring were reacted with *p*-QM **1a**, and the corresponding *β*,*β*-diarylethylamines **3n**-**3r** were generally afforded in moderate to good yields (42-79% yields). Furthermore, introduction of a

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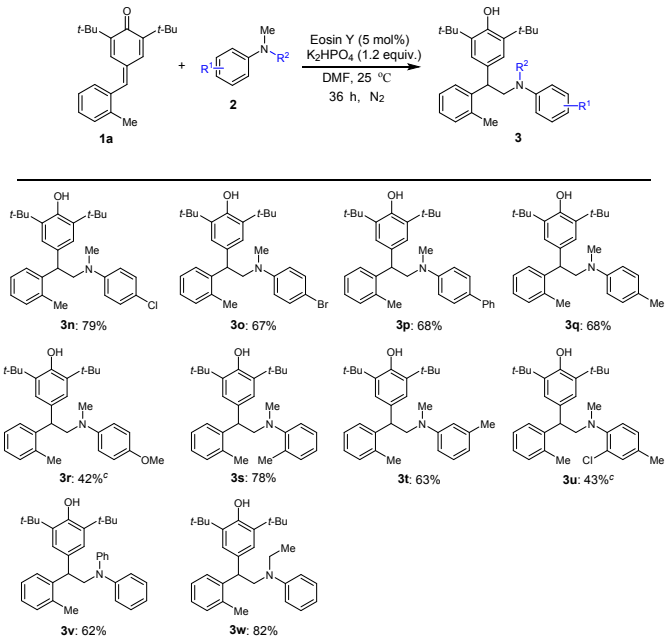
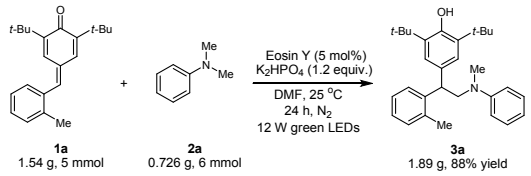
methyl group at the *ortho*- or *meta*-position did not significantly affect the yield of **3** (**3s**: 78% yield; **3t**: 63% yield). *N*,*N*-Dimethylanilines with bi-substituted *ortho*-chloro and *para*-methyl groups in the benzene ring was well tolerated and delivered the desired product **3u** in 43% yield after 48 hours. Moreover, *N*-methyldiphenylamine and *N*-ethyl-*N*-methyl aniline were also suitable substrates for this reaction, furnishing the desired products **3v** and **3w** in 62% and 82% yield, respectively.

Table 3 Scope of *N*,*N*-dialkylanilines[a,b]

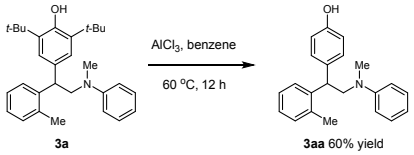


[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.12 mmol), Eosin Y (0.005 mmol), K_2HPO_4 (1.2 equiv.), DMF (2 mL), under 12 W green LEDs for 36 h at 25 °C. [b] Isolated yield. [c] 48 h.

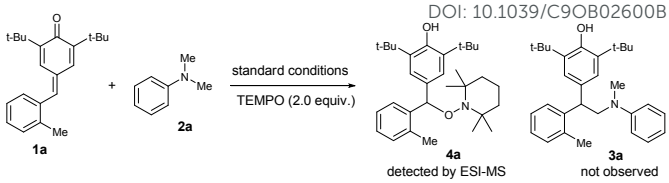
This photoredox process was amenable to gram-scale synthesis without significant yield loss (88% *vs.* 92%). Compound **3a** was synthesized on a 5 mmol scale without any specialized equipment using the same loading of photocatalyst (Scheme 2). Moreover, the bulky *tert*-butyl group could be successfully removed by $AlCl_3$ (60% yield, Scheme 3).[17]



Scheme 2 Gram-scale preparation of **3a**



Scheme 3 De-*tert*-butylation of 2,2-diarylethylamine **3a**



Scheme 4 Radical trapping experiment with TEMPO

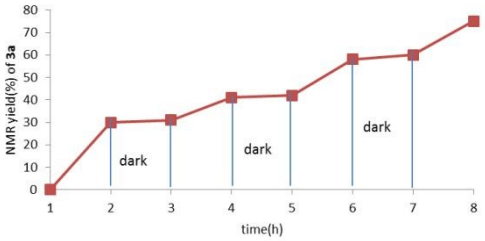


Fig. 2 Time profile for the reaction of **1a** with **2a**: light was switched off during the "dark" periods

In order to gain mechanistic insight into this reaction, several control experiments were performed. Radical trapping experiment was conducted with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) as radical scavenger under standard reaction conditions. TEMPO adduct can be detected by ESI-MS, while no product **3a** was observed (Scheme 4), which implied the involvement of a diarylmethyl radical. The Stern-Volmer studies of photocatalyst were also conducted and the details were shown in Supporting Information (Figs. S1-S4). This fluorescence quenching studies demonstrated that the excited photocatalyst Eosin Y* was quenched by *p*-QM **1a**. Moreover, in order to verify the effect of photo-irradiation, we investigated an on/off visible light irradiation experiment (Fig. 2). The graph showed that this reaction did not proceed during the "dark" period.

On the basis of our experimental results and literatures,[11a,13a] a plausible mechanistic pathway was illustrated in Fig. 3. The long-lived excited-stated EY* produced by light irradiation could engage in single electron transfer (SET) with *p*-QM **1a** followed by a protonation process to give radical intermediate **A** as well as the oxidized $EY^{\bullet+}$. $EY^{\bullet+}$ could convert the neutral amine **2a** into the radical cation *via* a single electron oxidation. Thereafter, because the C-H bonds adjacent to the nitrogen atom are greatly acidified (*pK*a *ca.* 8), it is easy to deprotonate and produce the *α*-aminoalkyl radical **B**.[18-19] Finally, the direct coupling of the radical intermediate **A** with *α*-aminoalkyl radical **B** gave the corresponding product **3a**.

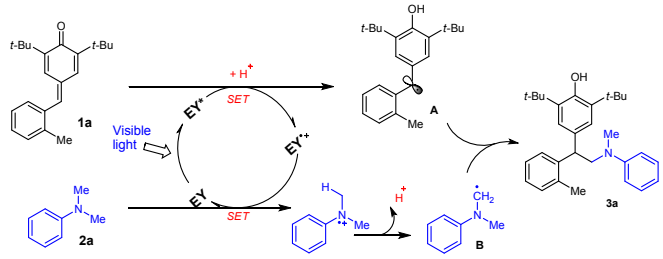


Fig. 3 Proposed mechanism

In summary, we have developed a novel photocatalytic radical cross-coupling reaction of *para*-quinone methides with *N*-alkyl anilines. A variety of 2,2-diarylethylamine derivatives with pharmaceutical potential were obtained in high efficiency (23 examples, up to 92% yield). Metal-free, redox-neutral, high atom economy, and mild conditions make this synthetic method a worthy one.

Experimental Section

General information

All the commercial reagents were used as such without further purification. All solvents were used as commercial anhydrous grade without further purification. The flash column chromatography was carried out over silica gel (230-400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 MHz spectrometer or Bruker Avance-500 MHz spectrometer. Chemical shifts in ^{1}H NMR spectra were reported in parts per million (ppm, δ) downfield from the internal standard Me_4Si (TMS, δ = 0 ppm). Chemical shifts in ^{13}C NMR spectra were reported relative to the central line of the chloroform signal (δ = 77.0 ppm). Peaks were labelled as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). High resolution mass spectra were obtained with a Shimadzu LCMS-IT-TOF mass spectrometer. Chemical yields refer to pure isolated substances.

Procedure for the synthesis of *p*-QMs 1[9]

All reactants **1** are known compounds. In a dry 100 mL round-bottom flask, a solution of phenols (25.0 mmol) and the corresponding aldehydes (25.0 mmol) in toluene (100 mL) was heated to reflux. Piperidine (50.0 mmol, 4.95 mL) was dropwise added within 1 h. The reaction mixture was continued to reflux for 12-18 h. After cooling just below the boiling point of the reaction mixture, acetic anhydride (50.0 mmol, 2.55 g) was added and the stirring was continued for 15 min. Then the reaction mixture was cooled to room temperature, poured into water and extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4 and solvents were removed under reduced pressure. The crude products were purified by flash column chromatography and further recrystallized from *n*-hexane, affording the desired *p*-QMs **1a**-**1m**.

Procedure for the synthesis of tertiary amines 2[20]

All reactants **2** are known compounds. Amine (1.0 g) and aldehyde (8.0 equiv.) was stirred in methanol (15 mL) to which pre-prepared methanol (5 mL) solution of sodium cyanoborohydride (1.0 equiv.) and zinc chloride (0.5 equiv.) was added at room temperature. The resulted reaction mixture was stirred overnight at room temperature and basified with 0.1 N NaOH (20 mL). Methanol was evaporated and aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate. Further, the organic layer was evaporated to dryness and subjected for silica gel column chromatography using ethyl acetate/hexane as eluent. Yield of *tert*-amines **2** were approx. 80-90%.

Procedure for the synthesis of compound 3

To a solution of **1a** (30.8 mg, 0.1 mmol) and **2a** (14.5 mg, 0.12 mmol) in DMF (2 mL), K_2HPO_4 (20.9 mg, 0.12 mmol) and Eosin Y (3.4 mg, 0.005 mmol) were added. The reaction mixture was degassed by bubbling nitrogen stream for 15 min and then stirred and irradiated with two 12 W Green LED bulbs with a fan placed nearby for cooling. After 24 hours, the mixture was extracted with ethyl acetate, and the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to afford the title compound **3a**.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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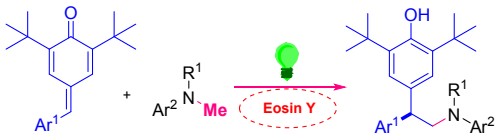

- ***metal-free***
- ***mild reaction conditions***
- ***redox-neutral***
- ***23 examples, up to 92% yield***
- ***gram-scale preparation***

A series of 2,2-diarylethylamines were accessed via visible-light-promoted radical cross-coupling of *p*-QMs with *N*-alkyl anilines