PAPER

Uranyl nitrate as a recyclable homogeneous photocatalyst for selective cross-coupling of N-substituted amines and indoles†

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A homogeneous photocatalytic recyclable system for the selective radical–radical cross-coupling of N-substituted amines and indoles has been established. This system could conduct in water or acetonitrile, featuring the reuse of uranyl nitrate as the recyclable photocatalyst *via* a simple extraction. With this mild strategy in hand, good to excellent yields of cross-coupling products could be achieved even under the irradiation of sunlight, including 26 natural product derivatives and 16 natural product inspired re-engineered compounds. A radical–radical cross-coupling mechanism was newly proposed based on experimental evidence and reported literature. This strategy has been also applied to a gram scale synthesis to demonstrate its practical utility.

Introduction

In the past decades, great effort has been devoted to accessing sustainability in organic syntheses, such as by using metal-free strategies, green solvents, recyclable catalysts, photocatalysis, *etc* (Fig. 1A).[1] Among them, recycling and reusing the catalyst is a highly interesting alternative to achieve the goal of green synthesis. Generally, homogeneous catalysts have better activities, while they are rarely recycled because of the difficulty of separation from the solvent,[2] thereby resulting in the waste of catalysts and solvents in most homogeneous catalysis (Fig. 1B). To overcome these, several elegant strategies have been reported to achieve this goal, all these methods can be summed up in two main solutions, homogeneous catalysis and heterogeneous separation, and heterogenized (immobilized) homogeneous catalysts.[3] The most popular strategy is the water-based recycling catalysis system,[4] such as water-soluble catalysts in an aqueous/organic biphasic system,[5,6] even in switchable water.[7] However, application to diverse organic transformations are still underexplored.

Photoredox reactions in water have elicited increasing interest.[8–11] However, only a few examples regarding recycling

catalysts in water have been reported and mainly concentrated on micellar catalysis or heterogeneous catalysts in water.[12–15] Uranyl cations ($^{238}UO_2^{2+}$) were recently emerging as an ideal
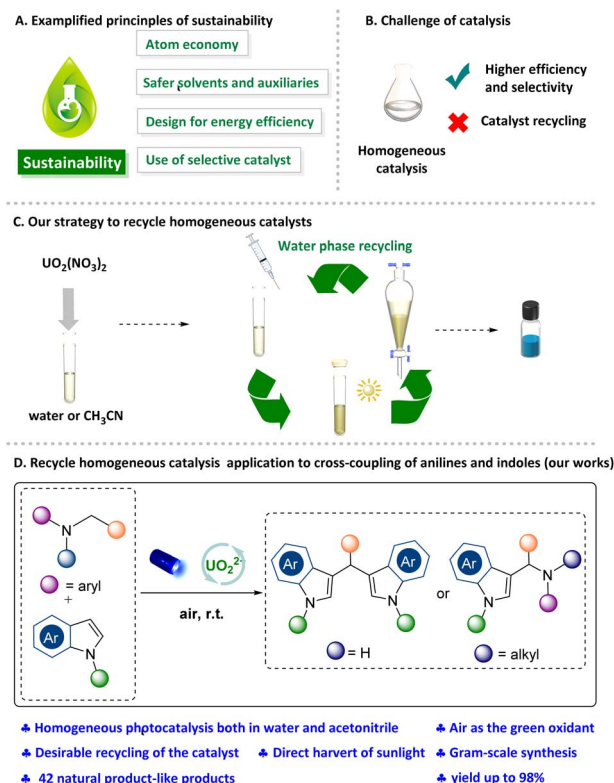

Fig. 1 Homogeneous photocatalyzed chemical transformation *via* a recyclable uranyl nitrate in water or CH_3CN.

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water-soluble photoredox catalysts.[16,17] It should be noted that uranyl cations have obvious solubility difference in solvents especially the excellent solubility in water and acetonitrile. However, it showed strongly limited solubility in many solvents such as dichloromethane and ethyl acetate. Although a few excellent organic transformations using uranyl cations were reported recently,[18–22] it is still untapped to recycle and reuse it in organic synthesis. Moreover, uranyl cations, activated by visible-light irradiation through ligand-to-metal charge transfer (LMCT), achieves the unique characteristic of excellent oxidizing ability ($E° = +2.36$ V $vs.$ SCE), were successfully used to selectively oxidation of sulfides,[18] the photocatalyzed hydrolysis of diaryl ethers,[19] activate the C–N bond of protogenetic anilines, tertiary anilines to form phenols via a single electron transfer (SET) process.[20]

Single electron oxidation of amines provides an efficient way to access synthetically useful α-aminoalkyl radicals as reactive intermediates. The generated α-aminoalkyl radicals has been utilized in a variety of reaction systems to form several important bonds such as C–C, C–N, C–O, and C–P.[23,24] The presence of amines in numerous alkaloids, pharmaceuticals, and agrochemicals lends credence to the potential utility of this chemistry in construction of functional molecular libraries.[25] Inspired by these, we aim to develop an elegant and mild strategy enabling reuse the uranyl nitrate based on its specific solubleness and photochemical characteristics (Fig. 1C). Herein, two efficient radical cross-coupling reactions between anilines and indoles were developed using the uranyl nitrate as photocatalyst for multiple times with maintaining performance, which different from the previous works in term of mechanism (Fig. 1D).
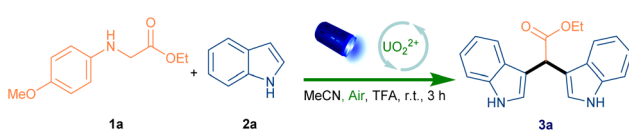
Our investigation into this new recyclable homogeneous photoredox catalysis began with SET oxidative cross-coupling of secondary anilines with indoles. We commenced our studies with secondary anilines N-aryl glycine ethyl ester (**1a**) and indole

(**2a**) as model substrates (Table 1). Uranyl cation was used as the photocatalyst under the irradiation of blue LEDs ($\lambda_{max} = 456$ nm), in which CH_3CN was added as the homogeneous phase. To our delight, we found that uranyl nitrate hexahydrate in CH_3CN under air atmosphere with TFA exhibited the best reactivity, and afforded desired product **3a** in 96% isolated yield (entry 1). Replacing the photocatalyst resulted in diminished efficiency (57% yield, entry 2). We also attended to changing the solvent into the water, however, only 20% desired product was detected (entry 3). Of note, the catalyst was recycled from water phase during the work-up, which exhibited comparable reactivity (entry 4). Moreover, the absence of the oxygen and the photocatalyst, visible light or acid, exhibited lower reactivity, respectively (entries 5–8). These control experiments indicated that photocatalyst, air, visible light and acid are essential for this reaction.

With the best-optimized conditions in hand, the scope was further explored to determine the generality (Scheme 1). Initially, we explored the scope of indoles in this tandem reaction. Various substrates bearing functional groups at the indoles motif (**1b–1k**) underwent smoothly and delivered expected disindoles products (**3b–3k**) in good to excellent yields. Specifically, electrically neutral or electron-rich indoles (**2b–2d**) performed well (**3b–3d**, 97–99% yields). It is worth noting that, halogen substituents on indoles, even a photosensitive iodine moiety (**3e–3h**, 74–95% yields) were well tolerated under the standard conditions. Notably the efficiency of the reaction was not impeded by strong electron-deficient substituents such as nitro (**3i**), cyano (**3j**) and ester (**3k**) (53–94% yields). Subsequently, the substrate scope of anilines for this photocatalytic coupling reaction was also evaluated. Firstly, a range of esters, including t-butyl ester, benzyl ester, icariidin ester, cholesteryl ester and 1,4-butyrolactone can be readily employed in this reaction to afford the products with good to excellent yield (**3l–3p**, 71–93% yields), and the structure of **3m** was further confirmed by a single crystal X-ray analysis. Perhaps most importantly, this transformation is not limited to glycine derivatives.[26] For example, N-benzyl or N-alkyl substituted anilines were found to be suitable substrates. The reaction of unsubstituted indole **2a** with N-benzyl-4-methoxyaniline (**1q**) selectively afforded 3,3'-(phenylmethylene)bis(1H-indole) (**3q**), which acts as an antibiotic natural product named turbomycin B in 54% isolated yield.[27] In addition, N-benzylic anilines bearing an electron-donating substituent such as methoxy and t-butyl groups or electron-deficient trifluoromethyl group could also be incorporated (**3r–3u** 41–66% yields). It is noteworthy that product **3r** is an orphan nuclear receptor inhibitor[28] and product **3t** acts as antitileukemic agent.[29] **3u** shows an inhibition of renal cell carcinoma.[30] Moreover, heteroaromatic N-benzylic anilines also reacted efficiently with **2a** to afford the arsindoline A (**3v**) and turbomycin A (**3w**) (74% and 65% yields respectively). Pleasingly, N-alkyl-anilines such as ethyl, n-butyl, 1-pentanol were also reactive and afforded vibrindole A (**3x**), ST-1385 (**3y**) and streptindole (**3z**) in 17%, 32% and 15% yields.

After the oxidative deaminative dimerization of second anilines and indoles, we further examined the SET oxidation of tertiary anilines with indoles.[31–33] We initialed our studies with

Table 1 Optimization of SET oxidative cross-coupling of secondary anilines with indoles[a]

Entry	Conditions	Yield (%)
1	$UO_2(NO_3)_2 \cdot 6H_2O$	96
2	$UO_2(OAc)_2 \cdot 2H_2O$	57
3	H_2O instead of MeCN	20
4	Recycled catalyst[b]	91
5	Under Ar	22
6	Without $UO_2(NO_3)_2 \cdot 6H_2O$	0
7	Without light	26
8	Without TFA	18

[a] Reaction onditions: **1a** (1.0 equiv.), **2a** (2.1 equiv.), photocatalyst (4 mol%), TFA (2.0 equiv.), MeCN (0.05 M), room temperature, Blue LEDs(456 nm 40 W), 3 h. [b] Obtained by lyophilization of the water phase from extraction.
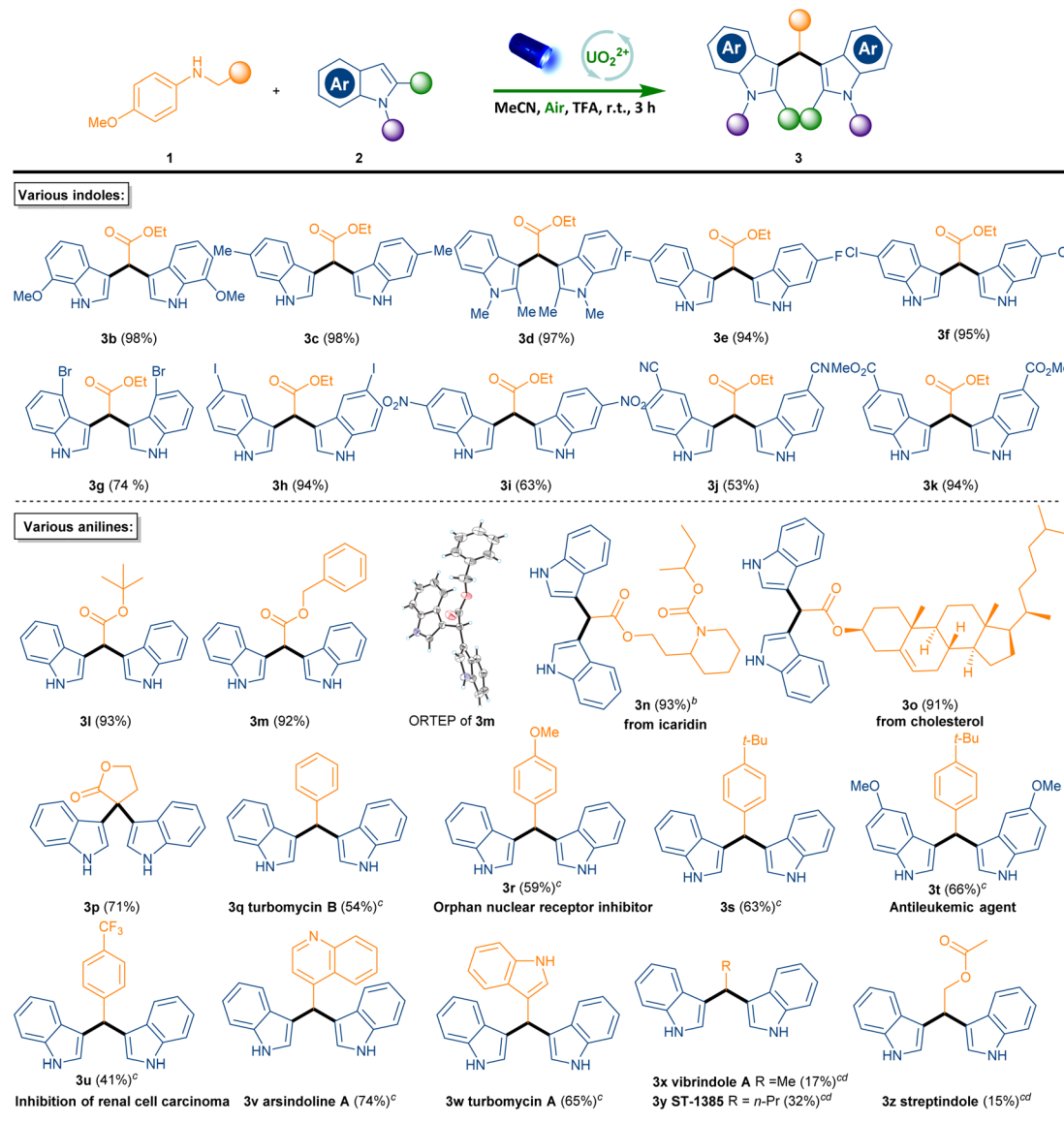
Scheme 1 Scope of indoles and anilines.[a] Reaction conditions: **1** (1.0 equiv.), **2** (2.1 equiv.), photocatalyst (4 mol%), TFA (2.0 equiv.), MeCN (0.05 M), room temperature, blue LEDs (456 nm, 40 W) for 3 h.[b] For 10 h.[c] For 16 h.[d] Photocatalyst (8 mol%).

N-phenyl-tetrahydroisoquinoline (**4a**) and 1,2-dimethyl-1*H*-indole (**2d**) as model substrates (Table 2). Under the same condition, the cross-coupling product **5a** was obtained in 96% yield within 6 h and the TFA was found to be useless (entry 1). The structure of **5a** was further confirmed by a single crystal X-ray analysis. To our delight, this transformation could be conducted in the water with same yield (entry 2). Therefore, the recycled water phase from extraction could be directly reused for the next reaction with same reactivity (entry 3). Later, the absence of oxygen and the photocatalyst exhibited lower reactivity, respectively (entries 4, 5). No formation of the product in the dark strongly proved the necessity of the light (entry 6). Furthermore, reducing the amount of **4a** or photocatalyst slightly decreased the yield (entries 7, 8). With the best-optimized conditions in hand, the scope was further explored to determine the generality (Scheme 2).

Firstly, various substrates bearing functional groups at the tetrahydroisoquinoline motif **4b–4d** underwent smoothly standard conditions and delivered expected cross-coupling products **5b–5d** in good to excellent yields. It was noteworthy that *N*-substituted 4,5,6,7-tetrahydrothieno [3,2-*c*] pyridine, a core structure of popular medicines such as (*S*)-clopidogrel[34] and prasugrel,[35] could afford the corresponding product in 76% yield (**5e**). Afterwards, a variety of *N*-aryl-tetrahydroisoquinolines containing diverse substituted aromatic rings was tolerated satisfactorily (**5f–5j**). Notably, the electronic properties of 4-substituted groups on the phenyl ring have an unobvious effect on the reaction performance. Interestingly, those products were highly potential intermediates for

Table 2 Optimization of the reaction conditions[a]

ORTEP of **5a**

Entry	Variations	Yield (%)
1	Acetonitrile as solvent, 6 h	95
2	—	96
3	Recycled water phase[b]	93
4	Under Ar	11
5	Without UO$_2$(NO$_3$)$_2$·6H$_2$O	23
6	Dark at 40 °C	0
7	**4a** (1.5 equiv.)	81
8	UO$_2$(NO$_3$)$_2$·6H$_2$O (4 mol%)	69

[a] Reaction conditions: **1a** (2.0 equiv.), **2a** (1.0 equiv.), UO$_2$(NO$_3$)$_2$·6H$_2$O (8 mol%) and H$_2$O (1.0 mL), blue LEDs (456 nm, 40 W), 18 h. [b] Water phase from extraction was directly used.

further functionalization. Meanwhile, various substituted indoles were examined under standard conditions. Among them, the indole and pyrrole without protection suppressed the reactivity greatly (**5k**, **5l**), probably due to the stability of indole radical.[36] However, indoles containing electron-donating groups proceeded efficiently (**5m–5o**). Indoles containing weak electron-withdrawing groups exhibited reactivity (**5p**). Moreover, stronger electron-withdrawing groups such as acyl group, nitro group at the 5 or 6 positions of indoles lead to no reaction at all (**5q–5s**).

To shed light on the mechanism and uncover the unique photooxidation properties of excited uranyl cation, radical quenching experiments with 2,2,6,6-tetramethyl-1-piperinedinyloxy (TEMPO) as the radical quencher were carried out. Indeed, both reactions were suppressed and the TEMPO-trapped anilines and indole radical were detected by HRMS analysis, which indicated that the radical process was possible involved in our reaction (Scheme 3A and S2†). Furthermore, the uranyl cation was approved to serve as a photosensor via UV-vis absorption at 420 nm (Fig. 2A and C). Stern–Volmer analysis was further performed to uncover the species of active uranyl cation was quenched by **1a**, **2a**, **2d** and **4a** (Fig. 2B and D). Indole **2a** and **2d** have been widely shown to act as quenchers in visible-light mediated reactions, involved in the reaction in the form of allyl radicals.[36,37] Combining all of results, it was suggested that the reaction was initiated with excited uranyl cation. Most of reported literature[32] involved cross-coupling between the indoles and anilines gave a formal Mannich process, and in their system, the indole radical cannot form for the low excited state oxidation potential of photo-catalysts (E° = +1.16 V vs. SCE, for indole).[38] So alternative mechanistic pathways need to be considerd. To further confirm thepossible pathway, control experiments were carried out. The trimer of indole **2a**′, the dimer of tetrahydroisoquinoline (**4a**′)
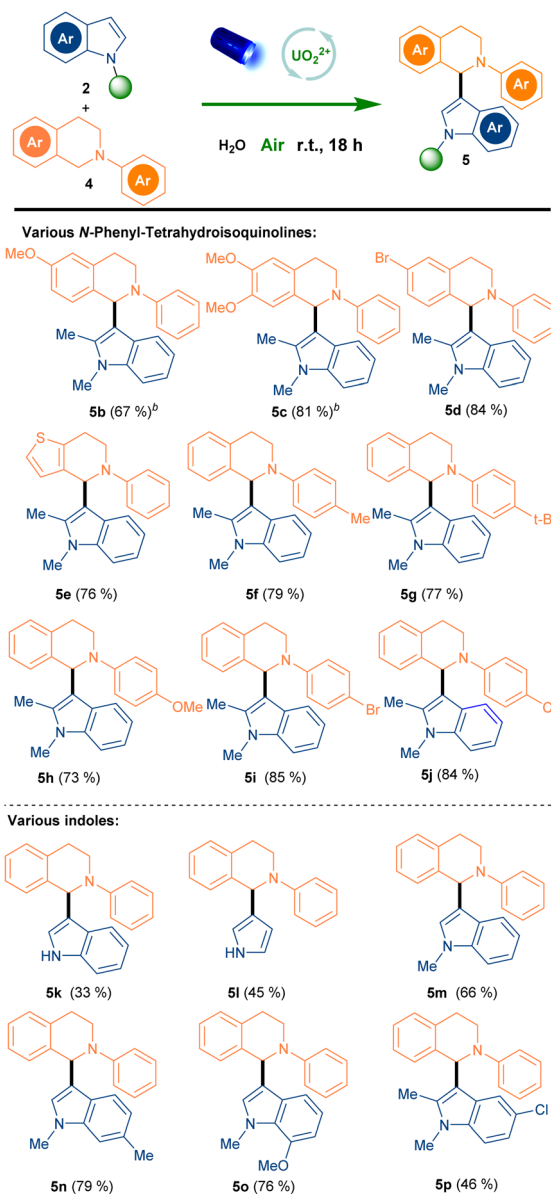
Scheme 2 Scope of tetrahydroisoquinolines and indoles.[a] Reaction conditions: **4** (2.0 equiv.), **2** (1.0 equiv.), photocatalyst (8 mol%), H$_2$O (1.0 mL), room temperature, blue LEDs (456 nm, 40 W) for 18 h.[b] **4** was added via a solution in MeCN (50 µL) (these tetrahydroisoquinolines need to be dispersed into water by MeCN).

and 2-indole-substituted 3-oxindole (**2d**′) were obtained under standard reaction conditions (CH$_3$CN or water as solvent, respectively) in the absence of a coupling partner, respectively.[32a,37c–e,39] (Scheme 3B–D) The mixture of **4ab** and **4ab**′ could be isolated under O$_2$ atmosphere,[32a,39] even in the presence of a solvent amount of nucleophile (acetone), and formal Mannich product was not detected.[32f,40] (Scheme 3E). Although cross coupling reaction involved indole radical is rarely reported,[26a,41] In our uranyl nitrate system, the radical–radical coupling process was preferred. Moreover, the Manich type reaction between unactivated indoles and imines need very harsh condition.[37c,42] On the basis of the above results and
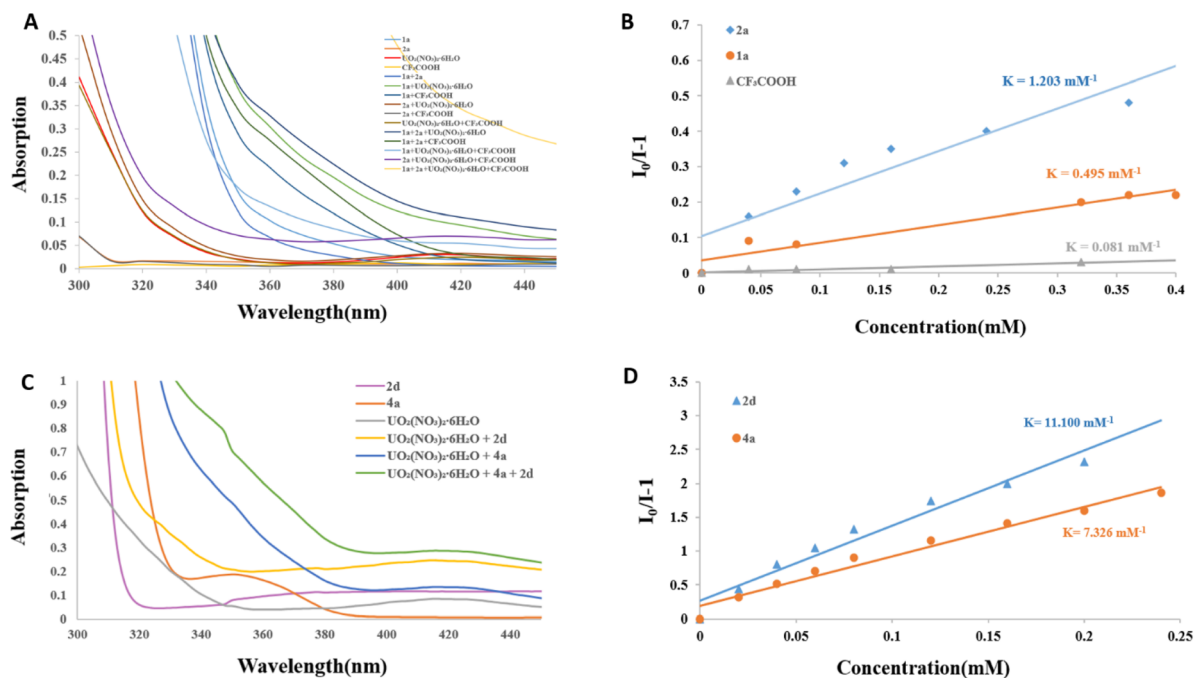
Fig. 2 UV-vis experiments and Stern–Volmer plot of fluorescence quenching experiment.

reported literature,[26a,41] we proposed a plausible radical–radical coupling mechanism as shown in Scheme 4. Firstly, the excited $*UO_2^{2+}$ ion is generated upon the irradiation of blue light. In this process, excited $*UO_2^{2+}$ promotes the SET oxidation of indole **2a** and 2°, 3° anilines (**1a** and **4a**) to generate corresponding radical cations. Meanwhile, UO_2^+ intermediate
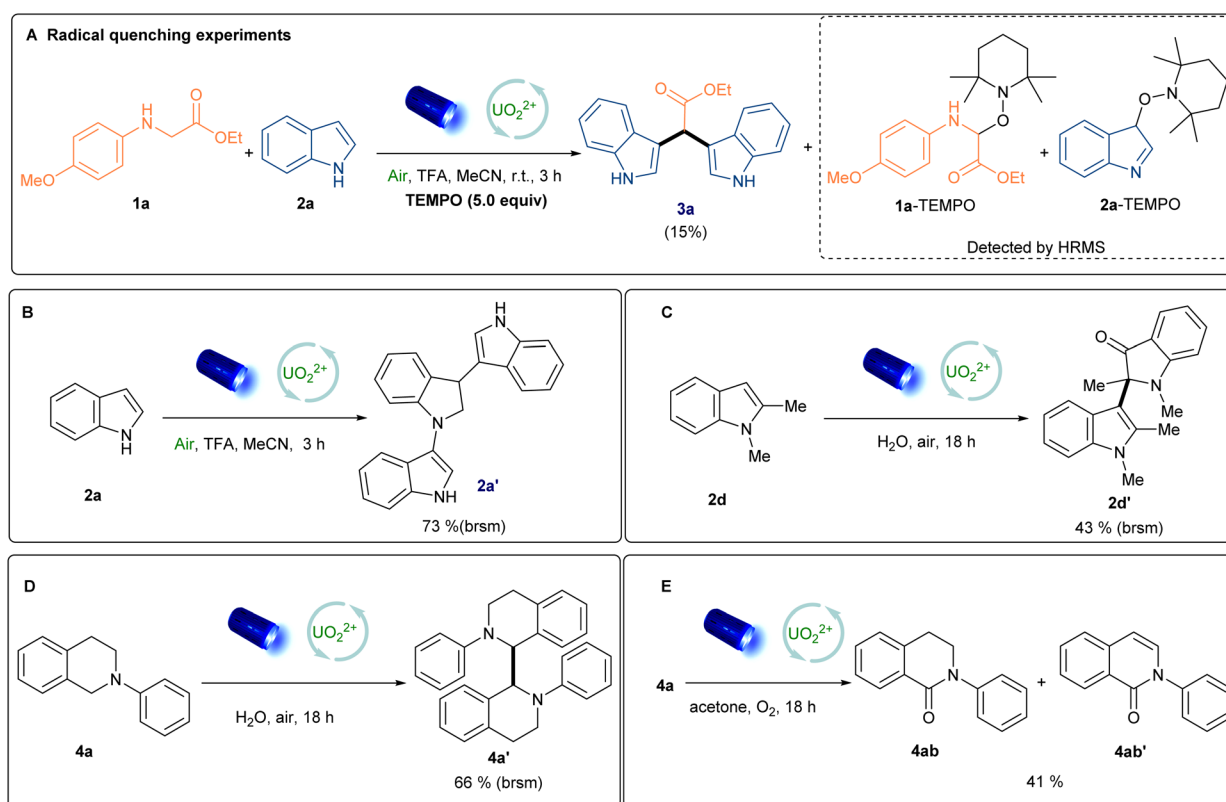
**Scheme 3** Radical quenching experiments and control experiments.
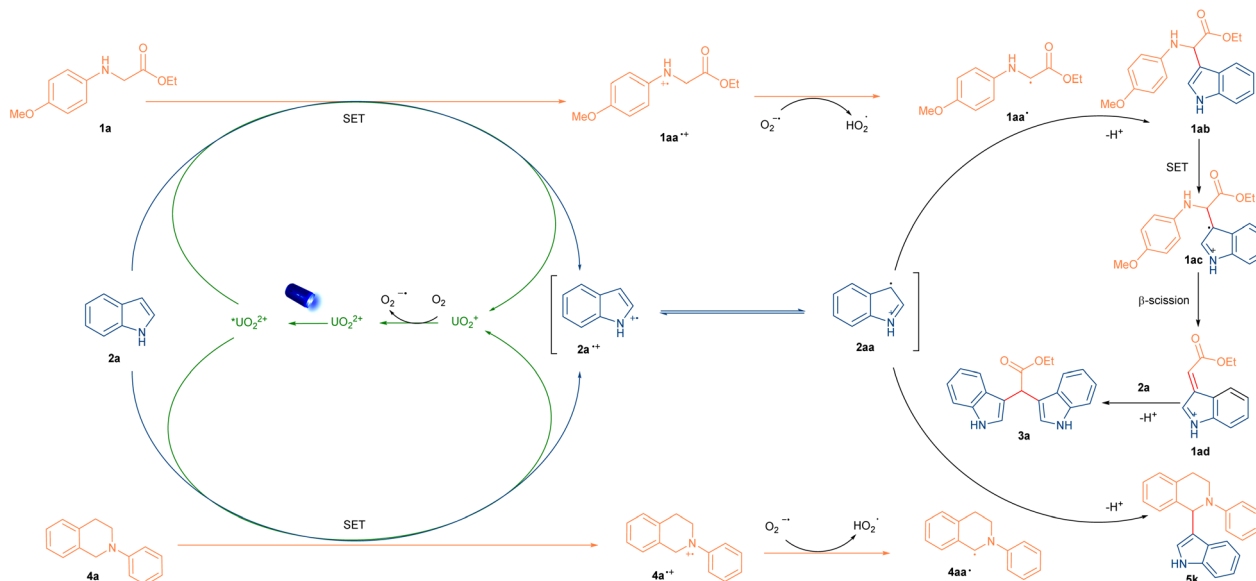
Scheme 4 Proposed mechanism of cross coupling reactions of *N*-substituted amines and indoles.

reacted with O_2 to produce the superoxide radical anion ($O_2^{\cdot-}$) and further regenerate UO_2^{2+}. The α-aminoalkyl radicals **1aa**$^{\cdot}$ and **4aa**$^{\cdot}$ were subsequently formed after the deprotonation from HOO$^{\cdot}$ radical. Rradical **4aa**$^{\cdot}$ could further coupled with intermediate **2aa** to generate desirable product **5a**. For reaction with **2o** anilines, **1aa**$^{\cdot}$ will further react with **2aa** to form the intermediate the **1ab**, which undergoes an SET oxidative and β-scission to generate the **1ad**. Then it will be trapped by the purposely added nucleophile indole **2a** to afford desired product **3a** after deprotonation. However, alternative mechanistic pathways should not be fully excluded.

After the understanding of the reaction mechanism, the recyclability of UO_2^{2+} in the system was further investigated and a convenient recycle process was showcased. The simple work-
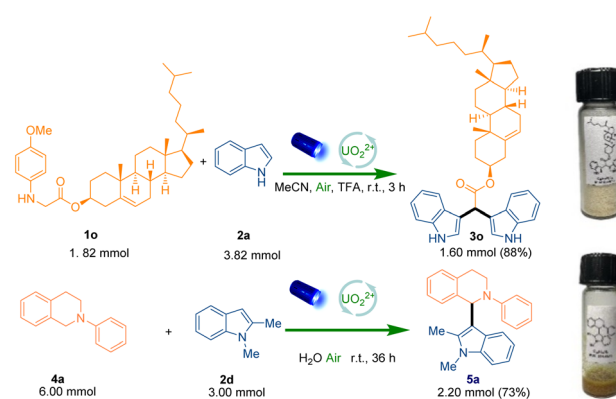
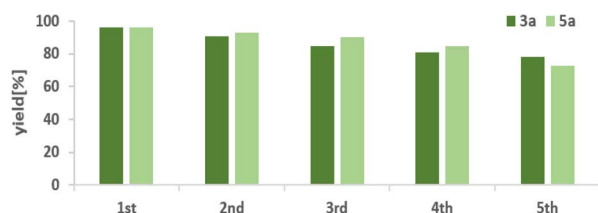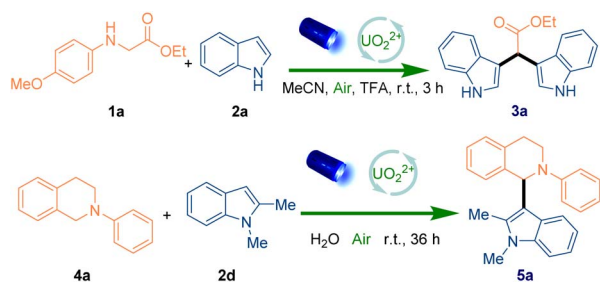**Scheme 5** Gram-scale synthesis **3o** and **5a**.

up (extraction with water and dichloromethane three times) was carried out to remove the organic reagents after the completion of reaction, and then the water phase containing the water-soluble photocatalyst could be reused for the next reaction cycle. Delightedly, five recycling cycles were performed which showed the stable performance of recycled homogeneous photocatalytic system (Fig. 3). To further exploit other characteristics of sustainability, the reactions were also conducted in excellent yield *via* harvesting the sunlight (95% and 94% yield respectively) (Scheme S6 and S7†). Finally, gram-scale (3.0 mmol) reactions (Scheme 5) were carried out, which afforded the target product in 88% and 73% yield respectively.

Conclusions

In summary, we have developed a highly mild and environmentally benign strategy for the construction of two types of natural product-like libraries by the selective cross-coupling of anilines and indoles. The homogeneous catalysis system is

Fig. 3 Recyclability of UO_2^{2+} in the reactions for the generation of **3a** and **5a**.

keeping comparable performance after 5 recycling cycles *via* using water (acetonitrile)-soluble depleted uranium as the recycled photocatalyst. Although cross coupling reaction involved indole radical is rarely reported, in our uranyl nitrate system, the radical–radical coupling process was preferred based on experimental evidences and reported literature. Moreover, the reaction *via* harvesting the sunlight and gram-scale reaction strongly proved the practicability of this system. We believe this method enables the development of uranium enrichment catalysis and represents a lower-cost, milder organic transformation process.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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