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Photoredox Catalysis Induced Bisindolylation of Ethers/Alcohols via Sequential C−H and C−O Bond Cleavage

Lu Ye,[†] Sai-Hu Cai,[†,‡] Ding-Xing Wang,[†] Yi-Qiu Wang,[†] Lin-Jie Lai,[†] Chao Feng,*,[†] and Teck-Peng Loh*,[‡,§]

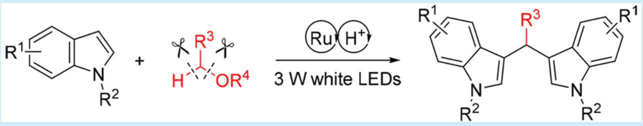
[†] Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Jiangsu National Synergetic Innovation Center for Advanced Materials, Nanjing Tech University, Nanjing 211816, P. R. China

[‡] Department of Chemistry, University of Science and Technology of China, Hefei 230026, P. R. China

[§] Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

Supporting Information

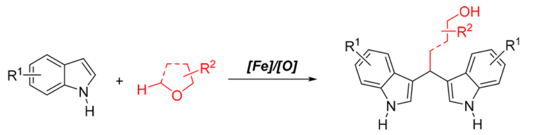
ABSTRACT: A visible-light-engaged 2-fold site-selective alkylation of indole derivatives with aliphatic ethers or alcohols has been accomplished for easy access to symmetric 3,3′-bisindolylmethane derivatives. The experimental data suggest a sequential photoredox catalysis induced radical addition and proton-mediated Friedel−Crafts alkylation mechanism.



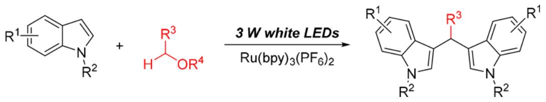
Bisindolylmethanes (BIMs) which consist of two indole motifs bridged by a single carbon at the 3 and 3′ positions are known as an important class of indole alkaloids[1] and frequently occur in marine[2] and terrestrial[3] natural sources. These BIM alkaloids possess diverse biological properties,[4] such as antifungal,[5] antimicrobial,[6] antiinflammatory,[7] antibacterial,[2b,8] antihyperlipidemic,[9] and anticancer[10] activity and also are found to serve as potential hypolipidemic and antiobesity agents.[11] Moreover, oxidized forms of BIMs have been utilized as dyes as well as colorimetric chemosensors.[12] Owing to their prevalence in natural resources and versatile biological activity, there has been significant interest in the synthesis of BIMs. Traditionally, Lewis acids or protic acids were used as catalysts to promote the electrophilic substitution reaction of indoles with various carbonyl compounds[13] or ethers (Scheme 1a).[14] In particular, a variety of organo,[15] transition-metal,[16] ionic liquid,[17] nanomaterial,[18] and solid acidic catalysts[19] have also been employed. Despite these achievements, the development of a more sustainable and mild protocol for the preparation of BIMs by circumventing the inherent drawbacks remains a compelling subject. Avoiding the necessity of high catalyst loading, expensive or highly toxic catalysts, harsh reaction conditions, and tedious workup procedures are desirable goals.

Scheme 1. One-Pot Synthesis of 3,3′-Bisindolylmethanes

(a) Iron-catalyzed bisindolylmethane synthesis (ref 14)



(b) Visible-light-induced bisindolylmethane synthesis (this work)



In recent years, photocatalysis chemistry has witnessed a significant renaissance, which could enable otherwise unattainable organic transformations to occur and allow very mild reaction conditions, thus attracting increasing attention from synthetic organic chemists.[20] In conjunction with our continuing efforts in the realm of visible-light photocatalysis,[21] we would report our recent work in visible-light-induced synthesis of symmetric 3,3′-bisindolylmethanes. The reaction proceeds through the successive alkylation of indole derivatives with ethers/alcohols mediated by an arenediazonium salt as a single-electron-transfer reagent (Scheme 1b).[22]

Initially, the reaction of *N,N*-dimethyl-1*H*-indole-1-carboxamide **1a** and tetrahydrofuran (THF) was examined (Table 1). We were pleased to find that the desired bis-indolylmethane **3aa** was obtained in 81% yield by using Ru(bpy)$_3$(PF$_6$)$_2$ as photocatalyst and DCE as solvent, while DCM and CH$_3$CN led to 72% and 69% isolated yield, respectively (Table 1, entries 1−3). No desired product was observed by conducting the reaction in DMF or under air (Table 1, entries 4 and 5). In addition, several photocatalysts were examined, which proved to be less effective for such a transformation (Table 1, entries 6−8). Control experiments showed that the visible-light-induced activation did not proceed, and the starting material was recovered completely without either light irradiation or the presence of photocatalyst (Table 1, entries 9 and 10). Moreover, arenediazonium salt was demonstrated to be a

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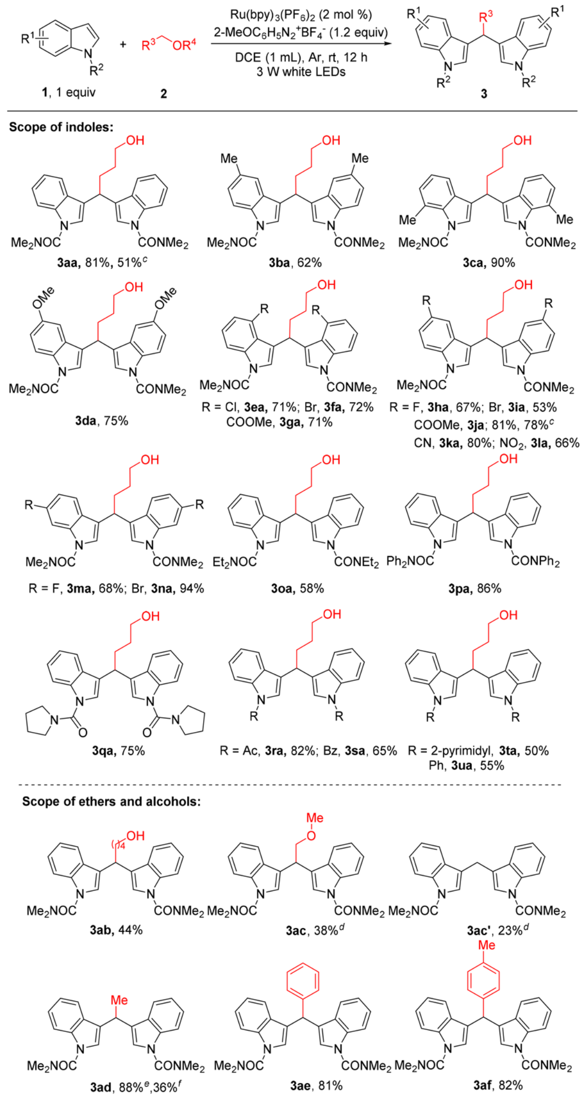
Table 1. Optimization of Reaction Conditions[a]

entry	photocatalyst	solvent	yield[b] (%)
1	**Ru(bpy)$_3$(PF$_6$)$_2$**	**DCE**	**81**
2	Ru(bpy)$_3$(PF$_6$)$_2$	DCM	72
3	Ru(bpy)$_3$(PF$_6$)$_2$	MeCN	69
4	Ru(bpy)$_3$(PF$_6$)$_2$	DMF	0
5[c]	Ru(bpy)$_3$(PF$_6$)$_2$	DCE	0
6	Ir(ppy)$_2$(dtbbpy)PF$_6$	DCE	75
7	[Ru(bpy)$_3$]Cl$_2$·H$_2$O	DCE	79
8	*fac*-Ir(ppy)$_3$	DCE	55
9[d]	Ru(bpy)$_3$(PF$_6$)$_2$	DCE	0
10		DCE	0
11[e]	Ru(bpy)$_3$(PF$_6$)$_2$	DCE	0

[a]Unless otherwise noted, the reactions were carried out at room temperature under Ar atmosphere using **1a** (1 equiv, 0.1 mmol), THF (15 equiv, 1.5 mmol), Ru(bpy)$_3$(PF$_6$)$_2$ (2 mol %, 0.002 mmol), and 2-methoxybenzenediazonium tetrafluoroborate (1.2 equiv, 0.12 mmol) in solvent (1 mL) for 12 h. [b]Isolated yield. [c]Air conditions. [d]The reaction was run in the dark. [e]Without 2-methoxybenzenediazonium tetrafluoroborate.

Scheme 2. Reaction Scope[a,b]



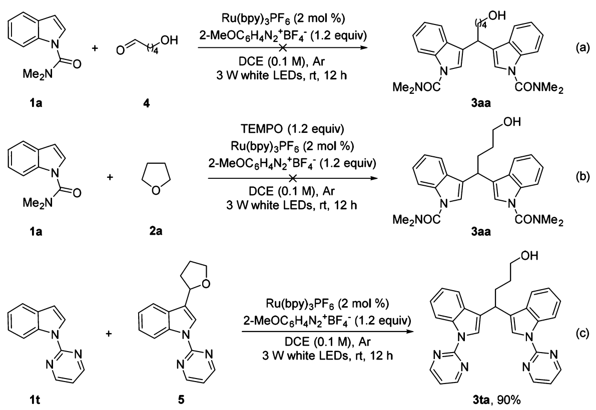
[a]Unless otherwise noted, the reactions were carried out at room temperature under Ar atmosphere using **1** (1 equiv, 0.1 mmol), THF (15 equiv, 1.5 mmol), Ru(bpy)$_3$(PF$_6$)$_2$ (2 mol %, 0.002 mmol), 2-methoxybenzenediazonium tetrafluoroborate (1.2 equiv, 0.12 mmol) in DCE (1 mL) for 12 h. [b]Isolated yield. [c]2.5 mmol scale. [d]Products obtained from dimethoxyethane. [e]Obtained from diethyl ether. [f]Obtained from ethanol.

necessary stoichiometric oxidant to furnish the desired product (Table 1, entry 11).

With the optimized conditions in hand, the substrate scopes with respect to indoles and ethers/alcohols were surveyed, and the results are shown in Scheme 2. It was found that diversely decorated *N*-protected indoles **1** were suitable substrates for this transformation, while *N*-H indoles afforded no products. Generally, both electron-donating and electron-withdrawing groups containing substrates worked well in this reaction. For example, substrates with methyl and methoxyl groups were all applicable and provided the desired products in moderate to excellent yields (62%−90%, **3aa**−**da**). *N*-Protected indoles bearing synthetically important substituents, such as CN, NO$_2$, and COOMe, were competent in this reaction, affording the corresponding products in moderate to excellent yields (53%−94%, **3ea**−**na**). It should be noted that halogen substituents remain intact after the reaction, which provides the opportunity for further derivatizations of the products. In addition, the substitution position was found to show little impact on the reaction efficiency. The influence of the *N*-protecting group of indoles to this reaction was also probed. For example, replacing the *N,N*-dimethylcarbamoyl group with *N,N*-diethylcarbamoyl, *N,N*-diphenylcarbamoyl, and pyrrolidine-1-carbonyl groups led to somewhat attenuated efficiency (**3oa**−**qa**). *N*-Acetyl and -benzoyl indoles worked smoothly in this transformation and furnished the desired products in good yields (**3ra**, **3sa**). Notably, the *N*-protecting group of indoles could also be changed to aryl groups, such as 2-pyrimidyl and phenyl, albeit with diminished reaction efficiency (**3ta**, **3ua**). When tetrahydropyran (THP) was employed instead of THF, the homologous product **3ab** was isolated in 44% yield. In addition, common acyclic ethers were also investigated in the reaction. Interestingly, dimethoxyethane gave two products, **3ac** and **3ac′**, through the cleavage of two kinds of C−O bonds. Diethyl ether afforded the desired product **3ad** in good yield. Furthermore, more challenging substrate alcohols were examined instead of ethers. To our delight, ethanol gave the product **3ad** successfully although in moderate yield. Then benzyl alcohol and 4-methyl benzyl alcohol were subjected to reaction and delivered the desired products in 81% and 82% yield (**3ae** and **3af**). The increased yields could probably be attributed to the activation of aryl group to benzylic C−H bond.

To shed light on the reaction mechanism, diverse controls reactions were performed. First, given aldehydes have been reported to react with aromatic compounds to yield diarylmethane derivatives through Friedel−Crafts reaction,[23] 5-hydroxypentaldehyde **4** which is able to be formed from the oxidation of THP[24] was examined in the reaction. As shown in Scheme 3a, the aldehyde **4** was found to be an unproductive reaction partner, which seems to rule out its participation in this transformation. Second, an experiment was carried out with

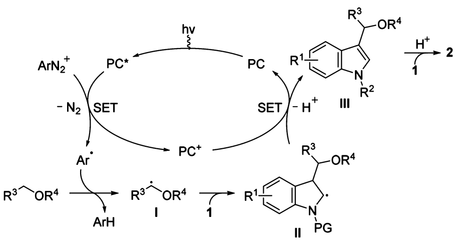
Scheme 3. Mechanistic Study



radical-trapping reagent to gain additional insight into the reaction mechanism. The reaction was inhibited in the presence of TEMPO, which reveals that a radical mechanism may operate in this reaction. Third, the monoindolylated THF **5** was prepared and subjected to the standard reaction conditions. In this reaction, the bisindolylated product **3ta** was obtained in 90% yield, which tentatively suggests the intermediacy of **5** in the present process (Scheme 3c). Finally, two types of kinetic isotope effect (KIE) experiments were carried out under the standard conditions, from which the KIE values were measured to be 3.3 and 1.7, respectively (see the Supporting Information for details). These results clearly demonstrate that C−H/D abstraction from the THF occurs during the rate-determining step of the reaction. The effect of photo irradiation on the reaction was further studied under "on/off" light conditions (see the Supporting Information for details). A dramatically decreased reaction rate was observed by turning off the light, which strongly suggests dependence of the present reaction on photoirradiation.

Based on our observations, we propose a plausible mechanism for bisindolylation process with ethers (Scheme 4). The activated photocatalyst PC* formed by irradiation donates an electron to the arenediazonium cation to yield an aryl radical by N_2 extrusion. Subsequently, the hydrogen atom abstraction from ether by the aryl radical furnishes the α-oxy-radical **I**.[25] Next, the addition of radical **I** to an indole derivative results in intermediate **II**, which gives the monoindolylated product **III** after transferring an electron to reduce the oxidized photocatalyst PC^+ and releasing a proton. The following Friedel−Crafts reaction of intermediate **III** with another indole substrate promoted by protons would lead to the desired bisindolylmethane skeleton. Also, when alcohols are employed a similar mechanism is still applicable.

Scheme 4. Mechanistic Proposal



In summary, a straightforward approach to a variety of elaborated 3,3′-bisindolylmethanes, based on a sequential alkylation strategy, is present. The reaction proceeds through photoinduced radical alkylation of indole followed by a Friedel−Crafts alkylation of the second indole substrate. The use of environmentally benign photoredox catalysis circumvents the employment of traditional strong oxidants or acids. Moreover, the mild conditions and the wide functional group tolerance of this method underline its potential for the synthesis of more complicated molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03073.

> Experimental procedures, characterization data, and NMR spectra of new and previously reported compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: iamcfeng@njtech.edu.cn.
*E-mail: teckpeng@ntu.edu.sg.

ORCID

Chao Feng: 0000-0003-4494-6845
Teck-Peng Loh: 0000-0002-2936-337X

Notes

The authors declare no competing financial interest.

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