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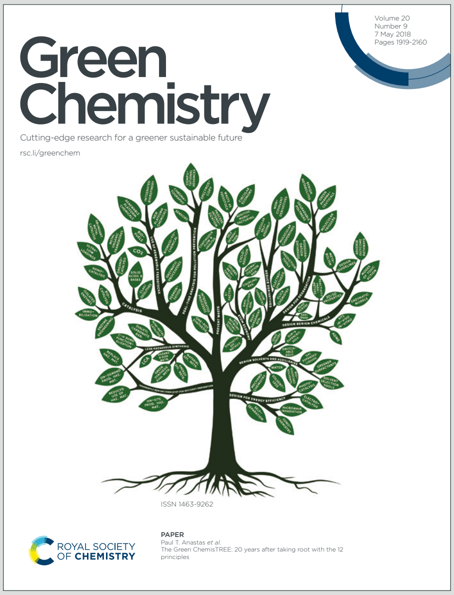

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Visible-Light-Induced Photocatalyst-Free C-3 Functionalization of Indoles with Diethyl Bromomalonate

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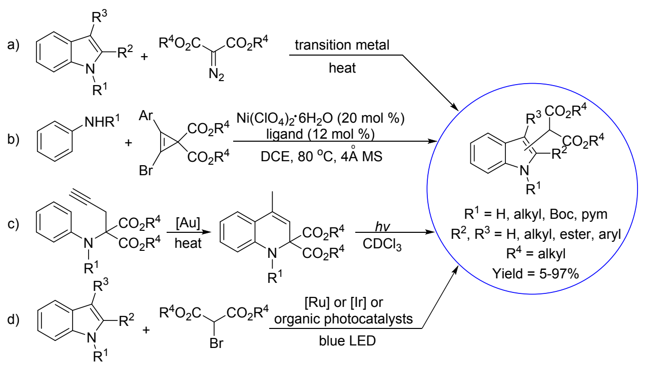
A visible-light induced green and efficient method is developed for the synthesis of α-indolyl diethyl malonates. The reaction proceeds without any photocatalysts or ligands in green solvent in short time. Moreover, the reaction mechanism has been clearly studied by control experiments, spectrophotometric studies and density functional theory (DFT) calculations. The results showed that the photocatalyst-free transformation may proceed *via* an XB-promoted radical process. The EDA complex formation of diethyl bromomalonate with base is the main reason for the reaction initiation.

Introduction

Indoles and their derivatives as one of important building blocks are widely present in natural products, medical preparations, bioactive molecules, optically active substances and useful intermediates for organic synthesis.[1] In particular, α-indolyl diethyl malonates not only possess the excellent properties of indoles, but also increase the possibility of modifying substituents due to the presence of the malonates.[2] The typical methods for the synthesis of these compounds are: 1) Ni-catalyzed [3+2] annulation of 2-bromocyclopenes with anilines; 2) transition-metal-catalyzed C2-alkylation of indoles with diazo compounds (Scheme 1, a and b).[3] In order to meet environmental protection requirements and improve the problem of heavy metal residues, the application of non-renewable energy and high-dose transition-metal catalysts still need to be solved.

Recently, visible light as one of clean energy source has been used for the production various organic compounds *via* the photocatalytic process.[4] In most cases, it is necessary to apply the photosensitizers to initiate the photoreactions because of the poor visible-light absorption of the reaction substrates.[5] With this concept, the photocatalytic approaches have been also used to achieve α-indolyl diethyl malonates (Scheme 1, c and d).[6] However, the difficulty in the purification of heavy metal residues still exists in these photocatalytic systems. Therefore, the development of the visible-light-induced photocatalyst-free approaches has been considered as one of the most effective ways.[7] Generally, the photocatalyst-free processes are realized by the following ways: 1) the modification of reaction substrates to increase their absorption in visible-light region;[8] 2) the photoexcitation of reaction intermediates;[9] 3) the addition of other radical initiators;[10] 4) the EDA (electron donor-acceptor) complexes construction between substrates, or between substrate and additive (such as base or oxidant).[11] In the type of EDA complexes, non-covalent interaction of terminal halogen atoms (R−X, formation σ-hole) with Lewis bases (LBs) plays an important role in non-covalent photocatalysis[12] due to higher directionality and larger polarizable interacting atoms of their halogen bonding (XB).[13] The formation of the halogen bonding complexes not only increases the visible-light absorption of the substrates, but also reduces the dissociation energy of C-X bond. It may be the main reason for the initiation of a single-electron-transfer (SET) transformation under mild reaction conditions.[14] Herein, a green and efficient XB-promoted photocatalyst-free method is developed to construct C-3 functionalization of indoles.



Scheme 1. Synthetic methods of α-indolyl diethyl malonates.

Results and discussion

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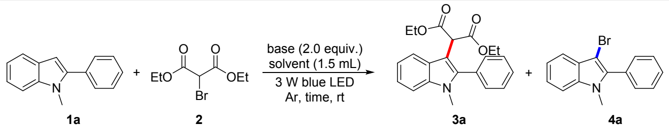
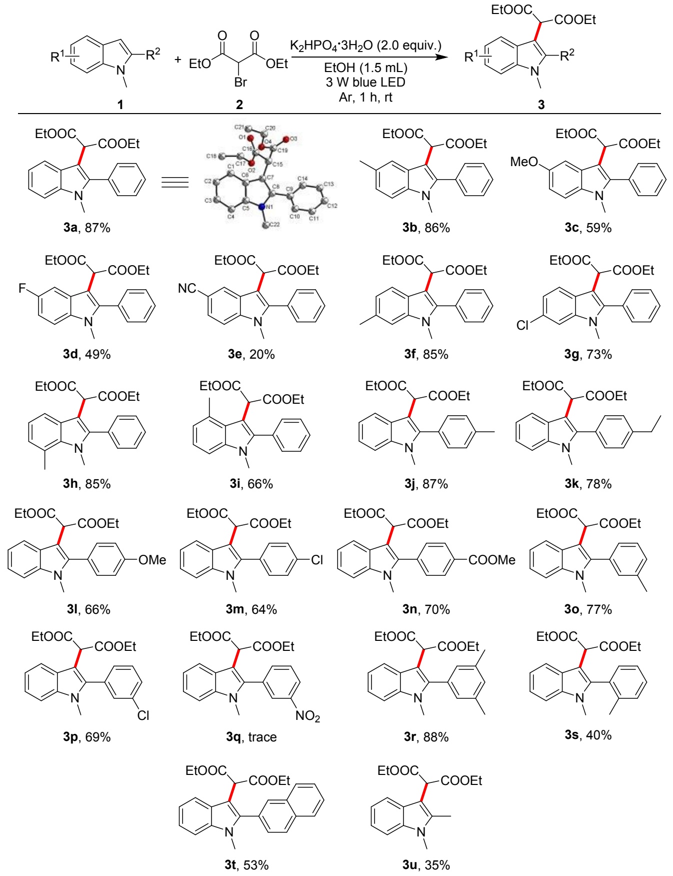
On the basis of our previous work,[15] the C-H activation of 1-methyl-2-phenylindole (**1a**) with diethyl bromomalonate (**2**) was chosen as the model reaction. In the presence of Ir(ppy)$_3$ or [Ir(ppy)$_2$(bpy)]PF$_6$ as a photocatalyst, 1-methyl-2-phenylindole (**1a**) was converted into diethyl 2-(1-methyl-2-phenyl-1*H*-indol-3-yl)malonate (**3a**) and 3-bromo-1-methyl-2-phenyl-1*H*-indole (**4a**) in 2 hours, using K$_2$HPO$_4$·3H$_2$O as base and DMF as solvent (Table 1, entries 1-2). Surprisingly, the model reaction could be carried out in the absence of any photocatalyst affording products **3a** in 81% and **4a** in 16% (entry 3). Other bases or solvents did not improve this transformation (entries 4-10). The compound **3a** could be selectively afforded when the transformation was carried out in EtOH (entries 10-11). A better result was achieved at shorter reaction time (entry 11). The transformation was not carried out without any base or in darkness (entries 12-13).

Table 1. Optimization of reaction conditions[a,b]



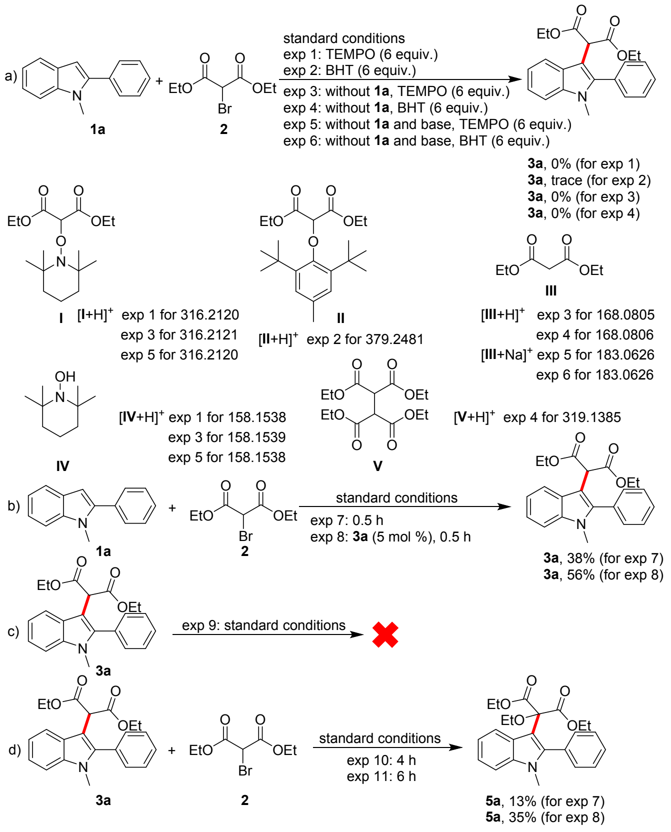
entry	base	conv. (%)	yield[b] (%)	
			3a	**4a**
1[c]	K$_2$HPO$_4$·3H$_2$O	89	79	10
2[d]	K$_2$HPO$_4$·3H$_2$O	92	77	15
3	K$_2$HPO$_4$·3H$_2$O	97	81	16
4	K$_3$PO$_4$·7H$_2$O		trace	
5	KH$_2$PO$_4$	90	67	23
6	CsOAc	54	24	30
7	Et$_3$N	59	36	23
8[e]	K$_2$HPO$_4$·3H$_2$O	48	13	35
9[f]	K$_2$HPO$_4$·3H$_2$O	88	76	12
10[g]	K$_2$HPO$_4$·3H$_2$O	81	75	6
11[g,h]	K$_2$HPO$_4$·3H$_2$O	90	87	3
12[g,h]	-		trace	
13[i]	K$_2$HPO$_4$·3H$_2$O		NR[j]	

[a]Reaction conditions: **1a** (0.2 mmol), **2** (3.0 equiv.), base (2.0 equiv.), DMF (1.5 mL), in a quartz tube under Ar at room temperature for 2 hours. [b]Isolated yield. [c]Ir(ppy)$_3$ (5 mol %). [d][Ir(ppy)$_2$(bpy)]PF$_6$ (5 mol %). [e]CH$_3$CN (1.5 mL) as solvent. [f]DMSO (1.5 mL) as solvent. [g]EtOH (1.5 mL) as solvent. [h]For 1 hour. [i]In darkness. [j]NR = No reaction.



Scheme 2. Substrate scope. Reaction conditions: **1** (0.2 mmol), **2** (3.0 equiv.), K$_2$HPO$_4$·3H$_2$O (2.0 equiv.), EtOH (1.5 mL), in a quartz tube under Ar at room temperature for 1 hour, isolated yield.

As depicted in Scheme 2, various 2-substitutedindoles were accommodated to produce compounds **3**. Generally, the reactivity of 2-arylindoles with electron-donating groups at the C5, C6 and C7 positions were higher than that with electron-withdrawing groups (**3a**-**h**). The same electronic effect was observed for the 2-arylindoles bearing different substituents on the 2-aryl ring (**3j**-**r**). Although the methyl group at the C4 position might hinder the coupling reaction, the desired product **3i** was isolated in 66% yield. 1-Methyl-2-(*o*-tolyl)-1*H*-indole (**1s**) has a greater steric hindrance than 1,4-dimethyl-2-phenyl-1*H*-indole (**1i**), the corresponding compound **3s** was only obtained in a moderate yield. In addition, the optimized conditions were also suitable for *N*-methylindoles substituted with naphthalenyl (**3t**) or methyl (**3u**) group at C2 position.



Scheme 3. Control experiments.

To obtain a detailed mechanistic insight for this transformation, several control experiments were carried out under optimized reaction conditions (Scheme 3). The coupling reaction was completely quenched by excess amount of radical scavenger such as butylated hydroxytoluene (BHT) or 2,2,6,6-tetramethylpiperidine 1-oxide (TEMPO) (Scheme 3, a, exp 1-2), which indicated that the radical might be involved in this transformation. Meanwhile, five strong molecular ion peaks were obtained by ESI-MS and attributed to [**I**+H]$^+$ (exact mass: 316.2120), [**II**+H]$^+$ (exact mass: 379.2481), [**III**+H]$^+$ (exact mass: 168.0605), [**IV**+H]$^+$ (exact mass: 158.1538) and [**V**+H]$^+$ (exact mass: 319.1385) (see ESI Figure S1-15.). These results indicated that the C-Br bond cleavage of diethyl bromomalonate (**2**) might be *via* a homolytic process (Scheme 3, a, exp 3-6). It was found that product **3a** could serve as an additional photosensitizer in this coupling reaction (Scheme 3, b). The photodecomposition of product **3a** did not proceed directly without diethyl bromomalonate (**2**) (Scheme 3, c). However, the compound **3a** could be transformed into diethyl 2-ethoxy-2-(1-methyl-2-phenyl-1*H*-indol-3-yl)malonate (**5a**) in the presence of diethyl bromomalonate (**2**) (Scheme 3, d).

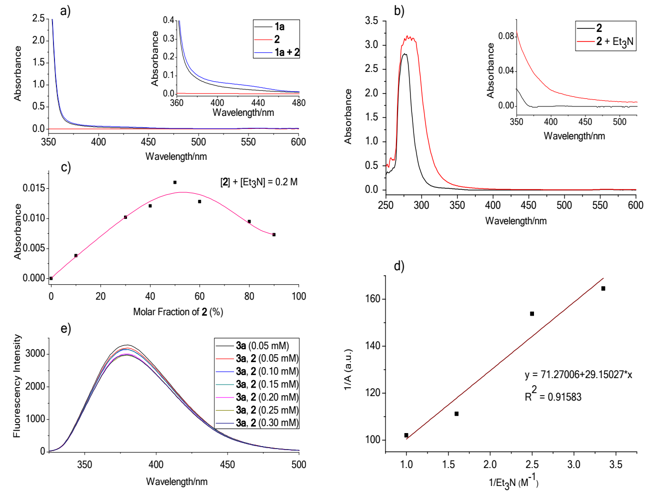


Figure 1. (a) The UV-Vis absorption spectra of **1a**, **2** and mixture of **1a** and **2** in DMF ([**1a**] = 0.13 M, [**2**] = 0.4 M); (b) The UV-Vis absorption spectra of **2** and mixture of **2** and triethylamine in DMF ([**2**] = 0.4 M, [Et_3N] = 0.27 M); (c) Job's plot of the EDA complexes for the ratio between **1a** and **2** with UV-Vis absorption spectra in DMF; (d) Benesi-Hildebrand plot for the interaction between **1a** and **2** in DMF ([**2**] = 0.05 M); (e) The luminescence quenching experiments of **3a** with **2** in EtOH.

Due to the formation of the complex [R-Br···O(H)R] between diethyl bromomalonate (**2**) and ethanol,[16] the investigation of spectrum analysis was carried out in DMF to avoid the complex formation. Although the individual diethyl bromomalonate (**2**, 368 nm) does not absorb light in the visible region (400-700 nm), a weak absorption of reagent mixture (compounds **1a** with **2**) was detected in DMF (Fig. 1, a). To evaluate the function of base, we investigated the interaction of diethyl bromomalonate (**2**) with Et_3N instead of $K_2HPO_4{\cdot}3H_2O$ because of the poor solubility of inorganic salt in EtOH (see ESI Scheme S1.). Surprisingly, a more pronounced red shift was detected (Fig. 1, b), which could indicate EDA complex formation between compound **2** with base (Et_3N). According to the Gaussian calculation results, it is easy to form a σ-hole on the surface of the bromine atom of diethyl bromomalonate (**2**, Fig. 2),[12d, 17] which has the potential to interact with Lewis bases. Except that, the maximum absorption could reach the blue region of the visible range (~480 nm). Applying Job's method of continuous variations (see ESI Figure 22), a molar donor/acceptor ratio of 1:1 in solution for the EDA complex (Fig.1, c) was observed. Concomitantly, an association constant (K_{EDA}) of 2.4 ± 0.19 M^{-1} for the complex in DMF was determined by spectrophotometric analysis using the Benesi-Hildebrand method (see ESI Figure 23.). It might be a reason for the occurrence of photocatalytic transformation. Based on the results of the luminescence quenching experiments (Fig. 1, e), the energy transfer process might contribute to this transformation.

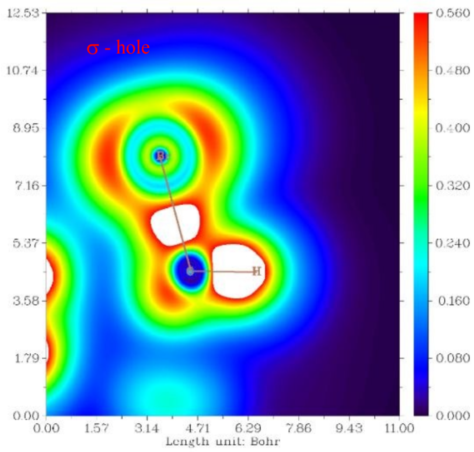


Figure 2. Color-filled map of valence electron density of diethyl bromomalonate (**2**).[18]

In order to better understand the detailed mechanism of this reaction, the free energy barriers in the rate determining addition step for C-C bond formation and the energy profiles of the reaction were also investigated using Et_3N and K_2HPO_4 as the bases, respectively (Fig. 3). Due to the high excitation energy, the compound **1a** could not be excited under the blue LED irradiation (E_{ex} = 3.0645 eV). On the other hand, the active diethyl malonate radical (**B**) was generated *via* two pathways under the blue LED irradiation (**λ** = 450 nm): 1) the homolysis of C-Br bond of diethyl bromomalonate **2** ($E_{C\text{-}Br}$ = 55.32 kcal/mol, Path **I**, see ESI); 2) the decomposition of complexes **A** (Path **II**, Figure 3). Although the reaction of both processes cannot be carried out spontaneously ($\Delta G > 0$), the decomposition of complexes **A** (path **II**) is more likely to occur than path **I**. The energy barriers of the nucleophilic attack by radical **B** on β-position of 1-methyl-2-phenylindole (**1a**) is not high (3.79 kcal/mol). Thus, the generated energy of blue LED is enough to promote the transformation. As described in the literatures, the intermediate **D** might be obtained *via* a SET process from the reaction of radical **C** with base[22]or substrate **2**[23]. According to the calculated results, we are more inclined to believe that the applied base is more suitable for the single electron transfer (SET) process. All the calculated results are consistent well with the experiments, indicating that our computations should be reasonable.

Based on the above results, a possible radical mechanism is proposed (Scheme 4). The photodecomposition of compound

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2 (Path **I**) or complexes **A** (Path **II**) forms radical **B**. Subsequently, the β-dicarbonyl radical **B** attacks on C-3 position of 2-substitutedindoles **1** to generate the intermediate **C**. The cation **D** is afforded *via* the SET process. In the presence of base, the elimination of C3 proton of **D** results in the formation of product **3**.

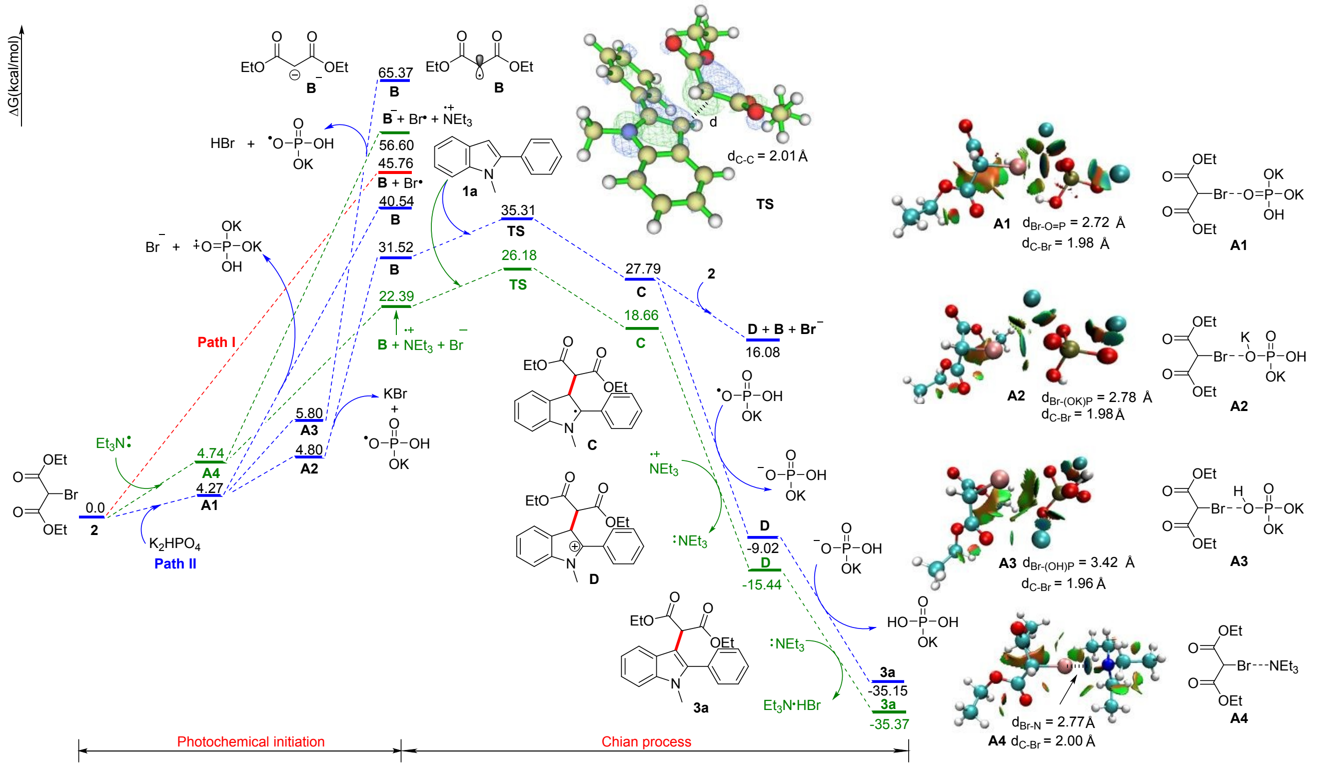
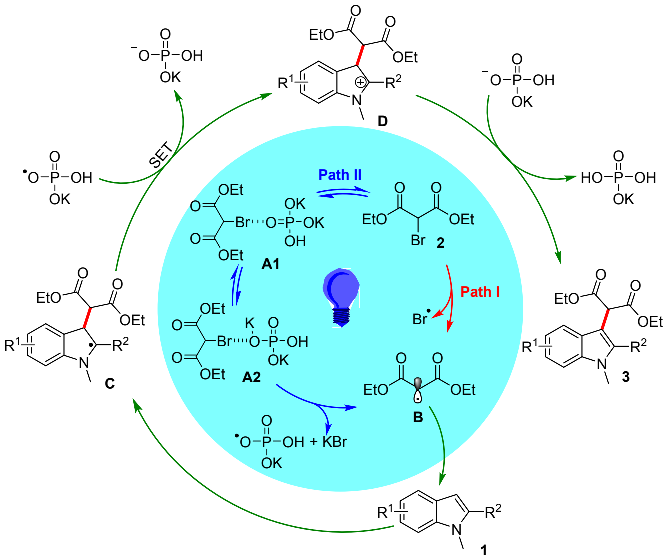


Figure 3. Density functional theory calculations. Computed Gibbs free energy profile for the C-H functionalization of **1a** with **2**, and spin density of transition states **TS1**. Energies are given in kcal/mol. Calculated by Gaussian 16 program using B3LYP-D3BJ/6-311+G(d,p)/EtOH (PCM).[19] NonCovalent Interaction (NCI) analysis was carried out using Multiwfn Version 3.7(dev)[17a, 20] and VMD version 1.9.3 programs.[21]



Scheme 4. The proposed mechanism.

Conclusions

In summary, we have developed a green and mild XB-promoted radical reaction of 2-substitutedindoles with diethyl bromomalonate under blue LED irradiation without any photocatalysts or ligands. The reaction mechanism is systematically verified by experimental and calculational methods. The results of our investigation indicated that the photocatalyst-free transformation might proceed *via* a radical process. The complex formation of diethyl bromomalonate with base is the main reason for the reaction initiation. The reaction mechanism was more deeply analysed and discussed by theoretical method using the Gaussian calculation. The advantages of this method meet the requirements of sustainable and green synthetic chemistry, and it provides a straight forward way to create valuable α-indolyl diethyl malonates.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

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Visible-Light-Induced Photocatalyst-Free C-3 Functionalization of Indoles with Diethyl Bromomalonate

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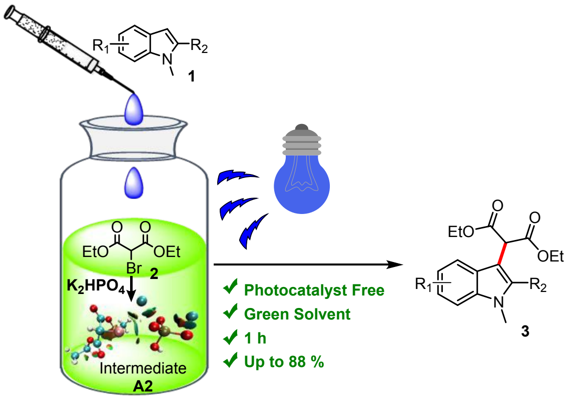

A visible-light-induced and XB-promoted green approach to construct α-indolyl diethyl malonates was developed.