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Thiourea catalyzed 1,6-conjugate addition of indoles to *para*-quinone methides

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ABSTRACT

An efficient thiourea catalyzed 1,6-conjugate addition of indoles to *para*-quinone methides (*p*-QMs) was developed. *p*-QMs was activated by a weak hydrogen-bond effect. The reaction is featured mild reaction conditions and wide substrate scope. A series of C-3 bisaryl methine substituted indoles are prepared in high yield.

Introduction

Indoles are ubiquitous structure motifs found in bioactive natural products and pharmaceuticals (Fig. 1) [1]. And nowadays there are a lot of convenient measures to prepare indole derivatives among which modification of an existed indole core is the most direct and rapid way to obtain new functionalized indole analogues [2]. The C3 position of indoles is innately electron-rich and favored to be modified by an electrophile. Many methods to modify indoles are based on this rule [3].

And recently *para*-quinone methides (*p*-QMs) with steric hindered substitutes located on the two *ortho* position of the ketone groups have attracted a lot of research interest and they are regarded as good 1,6-conjugate addition acceptors due to their unique electrophilic reactivity. A lot of carbon or heteroatom nucleophiles are tested on this 1,6-conjugate addition platform to prepare divergent diaryl methine substituted compounds and greatly improve the chemical space (Scheme 1) [4].

Due to our longstanding interest in total synthesis of indole alkaloids, our group also devoted to method developments for preparation of substituted indoles [5]. And we became interested in the combined chemical reactivity of electron-rich indoles and electron-poor *p*-QMs. Before we commenced our research, this chemistry has been initially explored by several groups (Scheme 2). Anand group developed a series of 1,6-additions to *p*-QMs using a Lewis acid/metal catalyst [6]. Then Anand's group reported an atom-economic preparation of unsymmetrical diarylindolylmethanes through palladium-catalyzed domino electrophilic cyclization/1,6-conjugate addition approach (Scheme 2, a) [7]. Yao and Lin reported a strong Lewis acid $BF_3{\cdot}Et_2O$ catalyzed 1,6-addition arylation of *p*-QMs to prepare unsymmetrical triarylmethane (Scheme 2, b) [8]. Among the explored substrates scope, only indole was tested to give the corresponding product. Recently Zhang, Mei and Shi's group reported an elegant chiral phosphoric acid (CPA)-catalyzed asymmetric conjugate addition of indoles to *p*-QMs and the corresponding C3-diaryl methine substituted indoles were obtained in modest to high yields and up to 96:4 *er* (Scheme 2, c) [9]. However, the reaction scope was limited to *ortho*-hydroxyphenyl substituted *p*-QMs. And a mechanism study indicated that *ortho*-hydroxyphenyl substituted *p*-QMs' transforming into *ortho*-quinone methides (*o*-QMs) was an essential step for the subsequent CPA catalyzed double activation of the generated *o*-QMs and indoles via two hydrogen bonds interfered effect. The failure of *ortho*-OMe phenyl and phenyl substituted *p*-QMs further valid the possible 1,4-conjugate reaction mechanism. And, Parthasarathy group reported the synthesis of diaryl indole via the addition reaction of indoles to *p*-QMs by heating (Scheme 2, d) [10]. More recently, Anand group has uncovered the application of the bis(amino)cyclopropenium ion in 1,6-conjugate addition reactions

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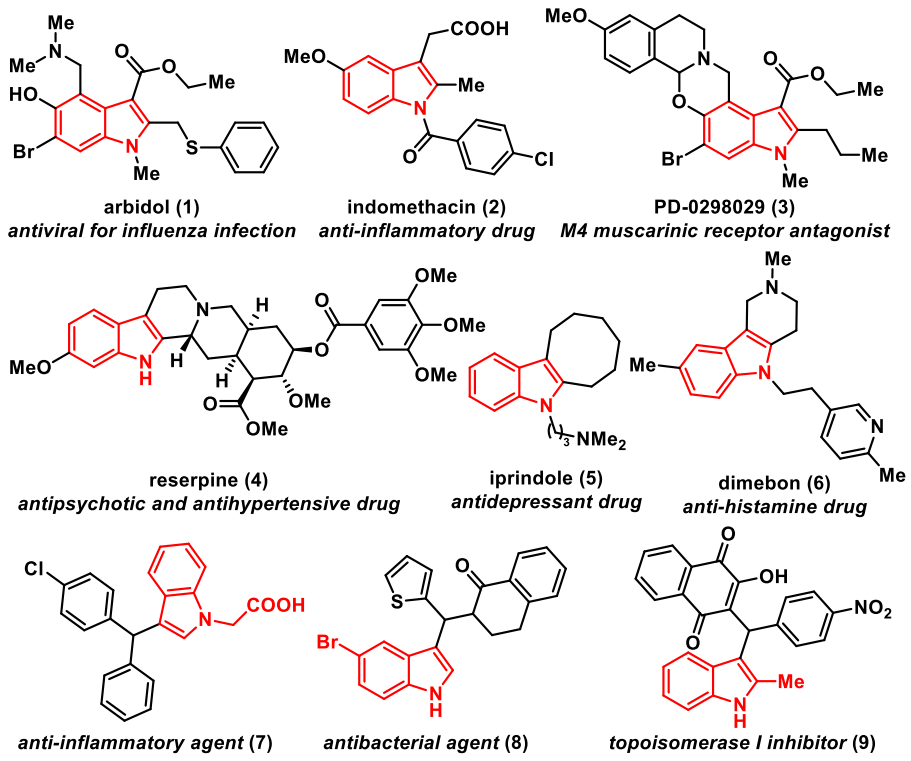
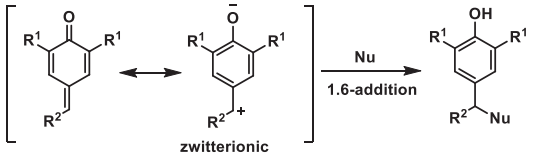


Fig. 1. Important indole compounds and bioactive indole compounds containing C-3 diaryl-methine substituent.



Scheme 1. *p*-QMs and their resonance structures.

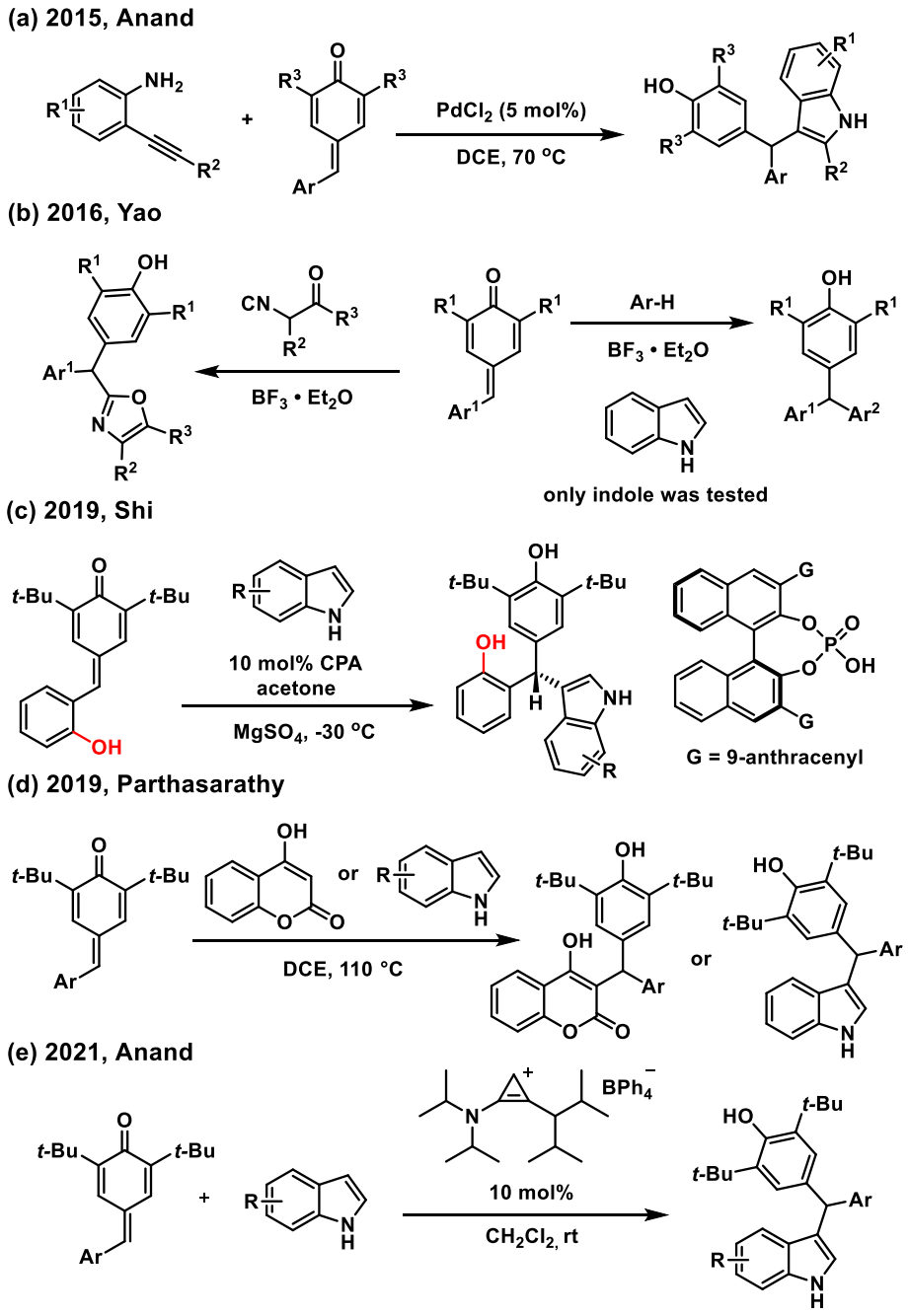
of *p*-QMs with various nucleophiles (Scheme 2, e) [11]. Although the above demonstrated works are elegant and effective to afford the substituted indoles in chiral or racemic form, they are limited in the specific substituted pattern in the substrates or harsh reaction condition. Herein we reported a thiourea catalyzed 1,6-conjugate addition of indoles to *p*-QMs in which *p*-QMs was activated by a weak hydrogen-bond effect. The mild reaction conditions tolerated a wide substrate scope and a series of C-3 bisaryl methine substituted indoles are prepared in high yields.

Results and discussion

Initially, *p*-QM **1a** and indole **2a** were chose as model substrates to test the feasibility and screening the optimal reaction conditions of this 1,6-conjugate addition reaction which results are depicted in Table 1. MeCN soon proved to be a suitable solvent and the desired 1,6-conjugative addition product 3aa was obtained in 73% isolated yield (Table 1, entry **1**). No desired reaction occurred in more polar DMF or DMSO (Table 1, entries **2–3**). An alternative 1,6-conjugate reaction product **4a** was obtained in 42% yield when MeOH was used as solvent (Table 1, entry **4**). Ethyl acetate and toluene were both less effective than MeCN (Table 1, entries **5–6**). And finally CH_2Cl_2 and THF proved to be more suitable solvents than MeCN and in both cases the corresponding 1,6-adduct 3aa was obtained in 97% high yield (Table 1, entries **7–13**). Four common chiral H-bond donor catalysts (commercially available thioureas **C2, C3** and squaric acids **C4, C5**) were also tested in place of **C1** and they were all less effective and gave the desired 3aa in a lower yield and racemic form (Table 1). The less effectiveness in enantioselective induction might attribute to the poor basic character of tertiary amine group which couldn't form a tight interfered complex with indoles. And the optimal reaction conditions at this time turned out to be performing the reaction in CH_2Cl_2 or THF at ambient temperature using 10 mol% **C1** as catalyst.

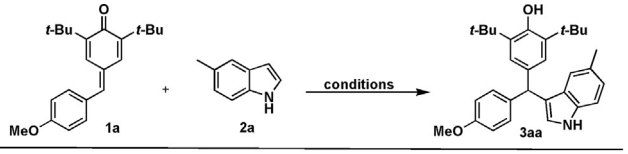
With the optimal reaction conditions in hand, the scope of *p*-QMs was firstly explored. As shown in Table 2, a variety of *p*-QMs bearing a single electron-donating or electron-withdrawing substituent at the aryl ring were readily converted to the corresponding 1,6-adducts in modest to high yields indicating that the electronic properties of *p*-QMs did not have a significant impact on the reaction outcome (Table 2, **3aa–3na**). *p*-QM 1e with 3,4-dimethoxyl phenyl substitute gave the corresponding 1,6-adduct 3ea in a little lower yield compared with its analogues with a single methoxyl substitutes 1a and 1f (Table 2, **3ea vs 3aa, 3fa**). And the *ortho*-OMe phenyl substituted *p*-QM 1f gave the corresponding 1,6-adduct 3fa in 91% yield which were slightly lower than 1a (with a *p*-OMe substitute) and 1 g (with a *m*-OMe substitute) revealed the 1,6-conjugate addition reaction was somewhat sensitive to the steric factors. And more importantly, heteroaryl substituted *p*-QMs were also compatible with the reaction conditions, leading to the corresponding indole derivatives 3oa-3ra in high yields which excellently demonstrate the mildness of the reaction conditions and wide potential applicability.

Then the scope of indoles were accessed which results were summarized in Table 3. Indoles **2a-2g** with an electron-donating methyl group located at the N1, C2, C4, C5, C6 or C7 positions (Table 3, **3aa–3ag**) and **2h** with stronger donating methoxyl group at the C4 (Table 3, **3ah**) all proceeded well under the optimal conditions affording the corresponding 1,6-adducts in high yields. Indole **2i** with an electron-withdrawing methoxyl carbonyl substitute at the C4 position didn't react at all which indicated that the



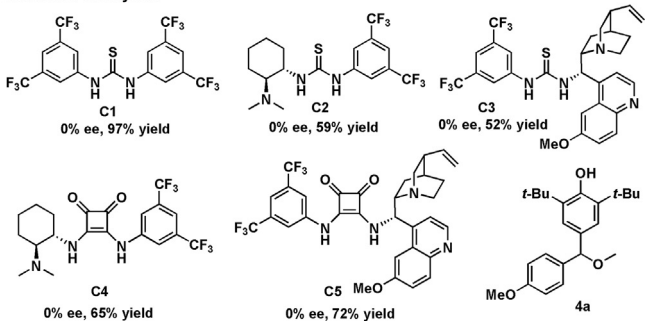
Scheme 2. Previous works.

Table 1
Optimization of reaction conditions.



Entry[a]	Catalyst	Solvent	Yield(%) [b]
1	C1	MeCN	73
2	C1	DMF	N.R.
3	C1	DMSO	N.R.
4	C1	MeOH	42(4a)
5	C1	EA	62
6	C1	Toluene	54
7	C1	1,4-dioxane	78
8	C1	THF	97
9	C1	DCE	83
10	C1	$CHCl_3$	65
11	C1	CCl_4	76
12	C1	DCM	97
13	C1	DCM	75

screened catalysts:



[a]Standard conditions: **1a** (0.5 mmol, 1.0 equiv.), **2a** (0.75 mmol, 1.5 equiv.) and catalyst (10 mol%) were add into the solvents (1.5 mL), the mixture was stirred at room temperature for 20–60 h. [b] Isolated Yields.

Table 2
The scope of *p*-QMs.

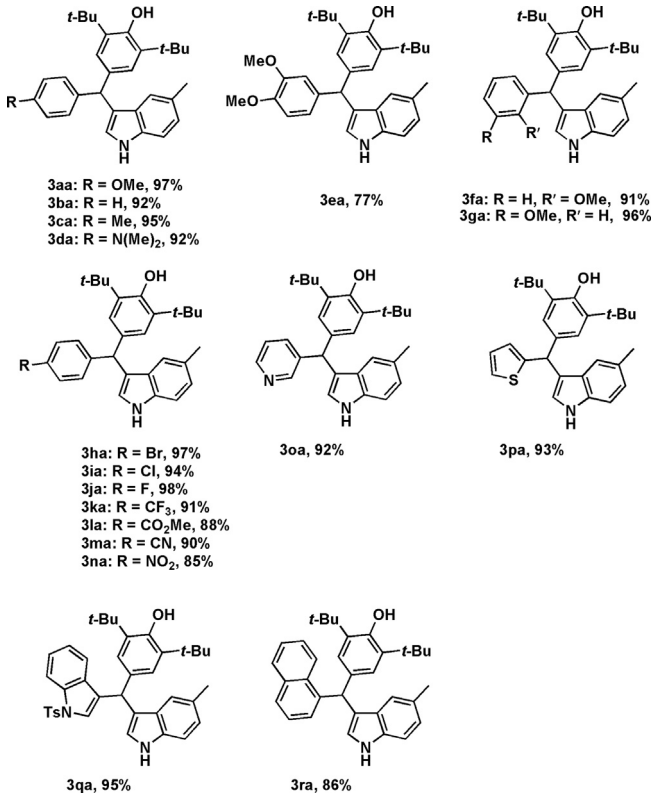
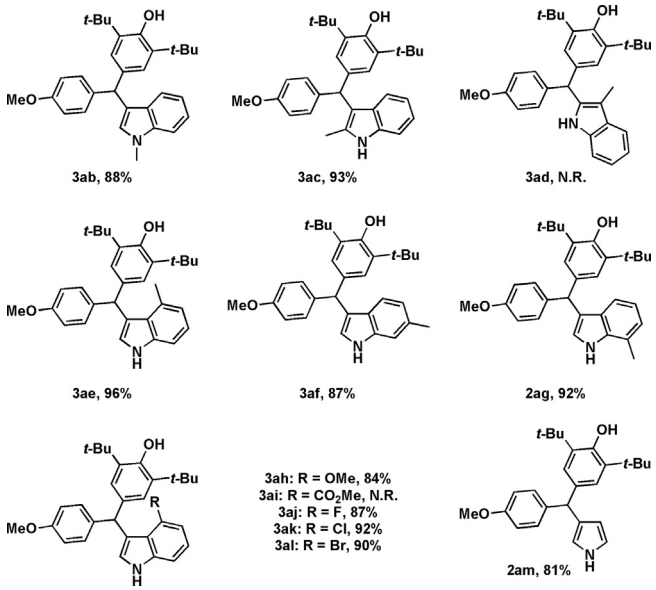


Table 3
The scope of indoles.

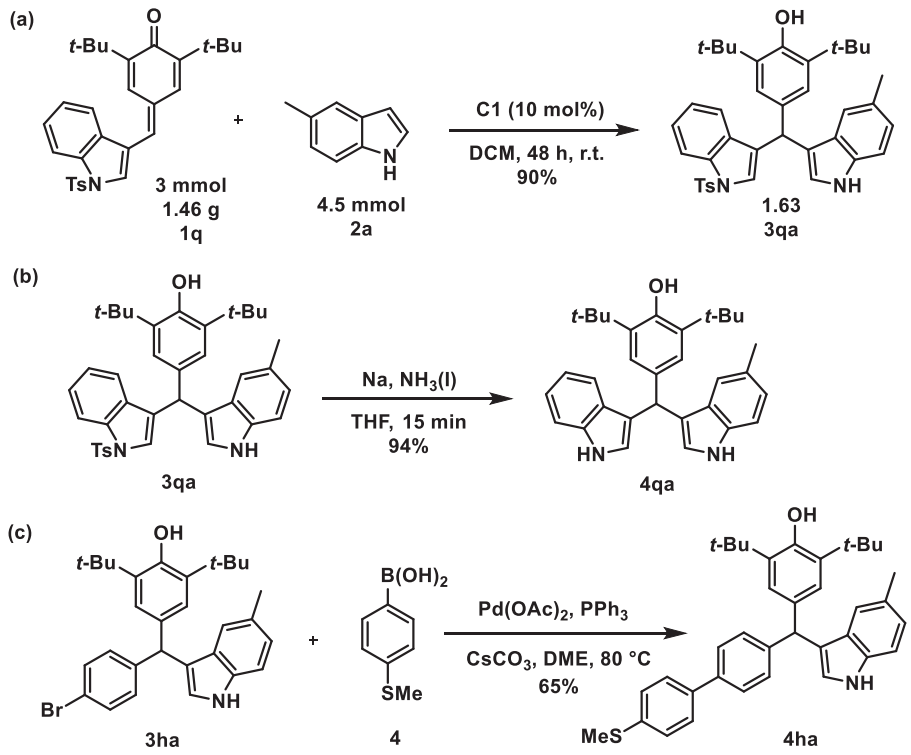


electron effect of the indoles' substitutes had a significant effect on this reaction (Table 3, **3ai**). To our delight, indoles with F, Cl or Br substitutes at the C4 succeeded in the 1,6-addition reaction and the corresponding adducts could be obtained in 87–92% yield (Table 3, **3aj–3al**). Several other nucleophiles, such as 7-azaindole, benzimidazole, pyrrole, imidazole, 2-phenyl indole and carbazole were also tried under the standard reaction conditions. They all failed to give the desired adducts except for pyrrole which proceeded smoothly at the C-3 position to afford the corresponding 1,6- conjugate adduct **2am** in 81% yield.

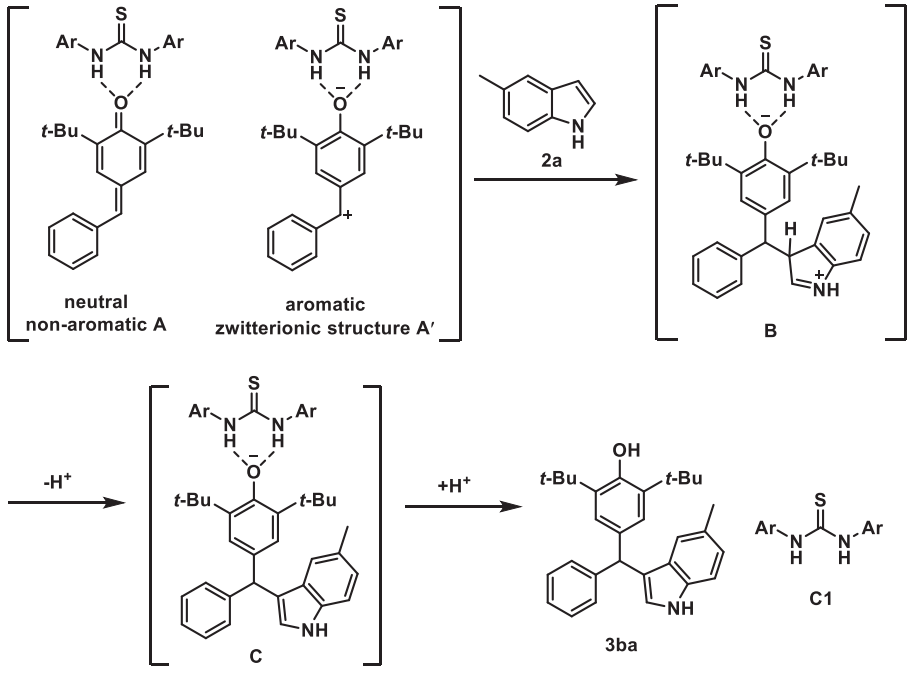
To demonstrate the practical value of this reaction, scale-up experiments and derivative transformations were subsequently carried out. As shown in Scheme 3, the gram-scale conjugate addition reaction of **1q** and **2a** underwent smoothly in the presence of 10 mol% **C1** affording the desired 1,6-adduct **3qa** in 90% high yield (Scheme 3, **a**). A sequential removal of Ts protecting group of **3qa** gave **4qa** in 94% isolated yield (Scheme 3, **b**). And a Suzuki coupling reaction between **3ha** and 4-methylthio-phenylboronic acid **5** generated more complex indole derivative **4ha** in a modest yield (Scheme 3, **c**).

On the basis of experimental results and relevant literature reports [4e,12], a possible reaction mechanism was proposed which was depicted in Scheme 4. Initially, thiourea catalyst **C1** and *p*-QM **1b** form a complex via the weak H-bond effect. The complex undergoes resonance between neutral non-aromatic structure **A** and zwitterionic structure **A′** which display remarkable chemical reactivity as a reactive acceptor for 1,6-addition reactions. Then indole **2a** attacks the C6 of the reactive complex affording **B** which was deprotonated to give the more stable **C**. Finally protonation of **C** affords the product **3ba** and releases the thiourea catalyst **C1**.

In summary, an efficient preparation of 3-diaryl methine substituted indoles via a thiourea catalyzed 1,6-conjugate addition of indoles to *p*-QMs was developed. *p*-QMs are activated by a weak and mild hydrogen-bond effect. The reaction features with wide substrates scope and mild reaction conditions. Further scale up experiments and derivative transformations of the obtained 3-diaryl methine substituted indoles increase the practical value of the developed method.



Scheme 3. Scale-up preparation and derivative transformation of the obtained products.



Scheme 4. Possible mechanism.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153315.

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