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Visible-Light-Promoted Cascade Alkene Trifluoromethylation and Dearomatization of Indole Derivatives via Intermolecular Charge Transfer

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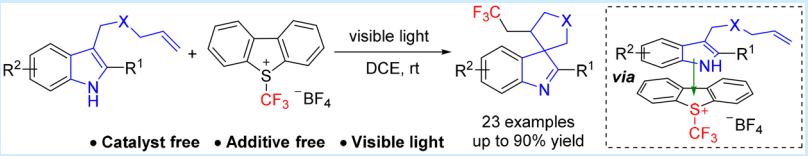
Supporting Information

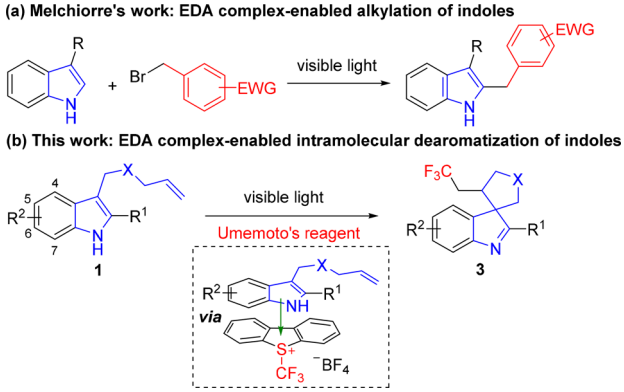


ABSTRACT: An intramolecular dearomatization of indole derivatives has been developed via an electron donor−acceptor complex formed between indole derivatives and Umemoto's reagent. Without the requirement of any catalyst and additive, diverse trifluoromethyl-substituted spiroindolenines bearing a quaternary stereogenic center were obtained in good yields (up to 90%) merely upon the illumination of two starting materials in 1,2-dichloroethane solution at room temperature. This work provides facile access to spiroindolenines bearing a trifluoromethyl group enabled by visible light.

Spiroindolenines, encountered as common substructures in alkaloid natural products, constitute an important class of biologically active molecules.[1] Meanwhile, they also occupy a prominent position in drug discovery research for new lead compounds.[2] Because of their high value in both synthetic and pharmaceutical chemistry, continuing efforts have been devoted to the development of their synthetic methods.[3] Among them, the dearomatization reaction of indole derivatives represents a straightforward and practical strategy to assemble such scaffolds.[4] For instance, alkylation reaction of indoles via intramolecular reactions including allylic substitution,[5] cross-coupling,[6] additions to alkynes,[7] and others[8] have been developed. Despite these great advances, the currently available approaches largely depend on the nucleophilic property of the indole moiety and the assistance of catalysts under thermal conditions. Developing new strategies beyond these thermal pathways in a catalyst-free fashion remains elusive but highly desirable.

Visible light, which is abundant and available in nature, has long been appreciated as a mild energy source to drive chemical transformations.[9] Of particular interest are the electron donor−acceptor (EDA, also called charge-transfer) complexes capable of absorbing visible light and promoting reactions involving open shell odd-electron species without any external photocatalyst.[10] However, due to the problems associated with unproductive, fast, and reversible electron transfer from the donor to the acceptor, the EDA complex-enabled synthetic chemistry is limited. In this regard, one recent elegant example from the Melchiorre group demonstrated that indoles are suitable electron donors combined with electron-deficient benzyl or phenacyl bromides as the acceptors, thus providing a novel strategy for the direct alkylation of indoles (a, Scheme 1).[11] Inspired by this pioneering work and as part of our continuing efforts toward dearomatization reactions, we began to explore the feasibility of indole derivatives as the electron donor in the intramolecular dearomatization reactions (b, Scheme 1). To achieve this, several challenges must be overcome: (a) possible competitive reactions including both intermolecular dearomatization and direct hydrofunctionalization of alkenes and (b) unfavorable energetic barrier and steric congestion caused during the

Scheme 1. EDA Complex Consisting of Indole As the Electron Donor



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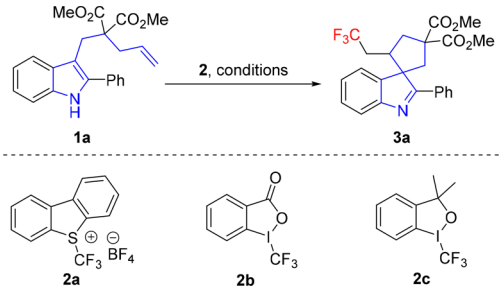
dearomatization process. Herein, we report the results from this work.

Fascinated by the ability of the trifluoromethyl group in altering the intrinsic properties of organic compounds, our attempt was launched with the investigation of the reaction between indoles with Umemoto's reagent **2a**, with the goal of incorporating the CF_3 functionality into the spiroindolenines (Table 1).[12−14] However, the initial results were disappointing.

Table 1. Optimization of the Reaction Conditions[a]



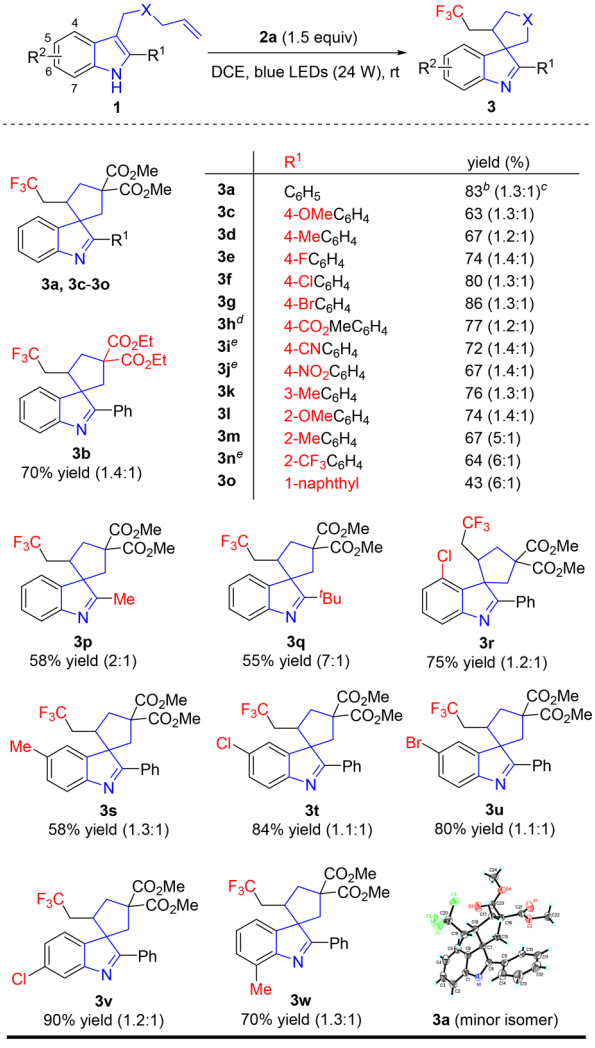
entry	2	solvent	base	time (h)	yield[b] (%)
1	**2a**	DMF		48	43
2	**2a**	CH_3CN		24	72
3	**2a**	MeOH		48	56
4	**2a**	$CHCl_3$		2	78
5	**2a**	DCM		2	80
6	**2a**	DCE		2	83
7	**2a**	1,4-dioxane		24	57
8	**2a**	Et_2O		24	nd
9	**2a**	toluene		24	nd
10	**2a**	DCE	K_2HPO_4	15	75
11	**2a**	DCE	K_2CO_3	15	77
12	**2a**	DCE	Cs_2CO_3	24	75
13	**2a**	DCE	^{t}BuOK	48	52[c]
14	**2a**	DCE	Et_3N	48	59[c]
15	**2b**	DCE		24	nd[c]
16	**2c**	DCE		24	54[c]
17[d]	**2a**	DCE		4	77
18[e]	**2a**	DCE		15	77
19[f]	**2a**	DCE		24	nd
20[g]	**2a**	DCE		24	nd

[a]General conditions: **1a** (0.05 mmol), **2** (0.075 mmol), and base (0.075 mmol) in solvent (0.5 mL, 0.1 M) were stirred at room temperature under visible light. Unless otherwise noted, 24W blue LEDs were used as the light source. The product was observed in the form of two diastereoisomers, and the dr value was determined as 1.3:1 by ^{19}F NMR. [b]Isolated yield. [c]NMR yield determined by ^{19}F NMR with $PhCF_3$ as the internal standard. [d]Light source: 23W CFL. [e]DCE (0.25 mL, 0.2 M). [f]Open to air. [g]In dark. nd = not detected.

Different indoles including those bearing a nitrogen atom on the linkage or seven-membered carbon linked ones were not compatible. Gratifyingly, exposure of substrates **1a** and **2a** in DMF to blue LEDs provided the desired spiroindolenines in 43% yield after 2 days in the form of two diastereoisomers with a ratio of 1.3:1 (entry 1). Further experiments revealed the solvents had a profound effect on the reaction outcome and DCE gave the best yield with a much shorter reaction time (83% yield, entry 6). The reaction is quite robust and performs well in the presence of diverse bases including Et_3N, which might serve as a potential competitive electron donor (entries 10−14). Other trifluoromethylating reagents such as Togni's reagents **2b** and **2c** were also tested;[15] it was found that the reaction between **1a** and **2c** delivered the dearomative product in 54% NMR yield, while no reaction occurred between **1a** and **2b**. Varying the light source to 23W CFL or increasing the substrate concentration resulted in a slight drop in yield (entries 17 and 18). The reaction carried out in air merely led to a mixture without any observation of the desired product (entry 19). Finally, the control experiment verified that visible light is essential (entry 20).

With the optimized reaction conditions in hand, we next explored the substrate scope. As illustrated in Scheme 2,

Scheme 2. Substrate Scope[a]



	R^1	yield (%)
3a	C_6H_5	83[b] (1.3:1)[c]
3c	4-OMeC_6H_4	63 (1.3:1)
3d	4-MeC_6H_4	67 (1.2:1)
3e	4-FC_6H_4	74 (1.4:1)
3f	4-ClC_6H_4	80 (1.3:1)
3g	4-BrC_6H_4	86 (1.3:1)
3h[d]	4-CO_2MeC_6H_4	77 (1.2:1)
3i[e]	4-CNC_6H_4	72 (1.4:1)
3j[e]	4-$NO_2C_6H_4$	67 (1.4:1)
3k	3-MeC_6H_4	76 (1.3:1)
3l	2-OMeC_6H_4	74 (1.4:1)
3m	2-MeC_6H_4	67 (5:1)
3n[e]	2-$CF_3C_6H_4$	64 (6:1)
3o	1-naphthyl	43 (6:1)

[a]General conditions: **1** (0.20 mmol) and **2a** (0.30 mmol) in DCE (2.0 mL, 0.1 M) were stirred at room temperature under the irradiation of 24W blue LEDs. Unless otherwise noted, the reaction time was 2 h. [b]Isolated yield. [c]The product was observed in the form of two diastereoisomers, and the dr value was determined by ^{19}F NMR. [d]Reaction time: 8 h. [e]Reaction time: 12 h.

electron-donating or electron-withdrawing groups at various positions of the phenyl moiety (4-OMe, 4-Me, 4-F, 4-Cl, 4-Br, 4-CO_2Me, 4-CN, 4-NO_2, 3-Me, 2-OMe, 2-Me, 2-CF_3) or 1-naphthyl group at the C2 position of indole were well tolerated. The resultant dearomative products **3b−o** were obtained in 43−86% yields as diastereoisomeric mixtures (1.2:1 to 6:1). Typically, the substrates bearing strong

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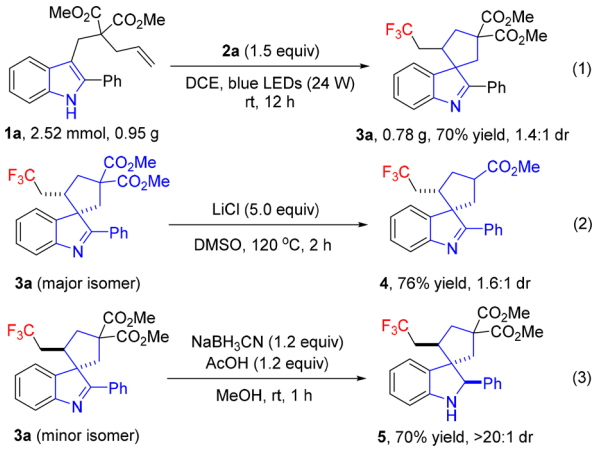
electron-withdrawing groups such as $-CO_2Me$, $-CN$, $-NO_2$, and $-CF_3$ required a prolonged reaction time. It is worth noting that the diastereoselectivity is highly dependent on specific structure. For example, the incorporation of a substituent at the *ortho*-position of the phenyl moiety could dramatically increase the diastereoselectivity of the products. Furthermore, the reactions between indoles bearing an aliphatic group such as Me- or ^{t}Bu- at the C2 position and Umemoto's reagent **2a** proceeded smoothly, delivering the corresponding spiroindolenines **3p** and **3q** in 58% and 55% yields with 2:1 and 7:1 dr, respectively. Meanwhile, indoles bearing 4-Cl, 5-Me, 5-Cl, 5-Br, 6-Cl, 7-Me were all compatible with this protocol, in all cases, leading to their corresponding products in good to excellent yields (58−90%, 1.1:1−1.3:1 dr, **3r**−**w**). The structure of the minor isomer in **3a** has been confirmed by X-ray diffraction analysis.[16]

To our great delight, the reaction of **1a** in a 2.52 mmol scale with **2a** also proceeded smoothly, delivering product **3a** in 70% yield within 12 h, which highlights the robustness and practicality of this method (eq 1, Scheme 3). Furthermore,

Scheme 3. Gram-Scale Reaction and Transformations of Product 3a



several transformations based on spiroindolenine **3a** were carried out. Upon the treatment with LiCl, selective removal of one of the methyl ester groups in **3a** occurred at 120 °C to give compound **4** in 76% yield with 1.6:1 dr (eq 2, Scheme 3). Interestingly, the spirocycle **5** bearing three contiguous stereogenic centers could be obtained in 70% yield as a single diastereoisomer through the reduction of the imine moiety of **3a** in the presence of $NaBH_3CN$ and AcOH (eq 3, Scheme 3).

To gain insight into the reaction process, a series of mechanistic experiments were performed. First, UV/vis absorption spectrometry showed a bathochromic shift by mixing the DCE solution of indole **1a** with Umemoto's reagent **2a**, which was consistent with the sharp color change visually (a, Figure 1). Then, a 1:1 ratio between **1a** and **2a** in the EDA complex was established based on the Job's plot with UV/vis absorption experiments, in which maximal absorption appeared at 50% molar fraction of indole **1a** (b, Figure 1).[17] Meanwhile, the association constant K_{EDA} was calculated to be 4.5 M^{-1} in DCE via the nonlinear curve-fitting methodology (c, Figure 1).[18] All of these above results support the formation of a donor−acceptor complex between **1a** and **2a**. Next, the reaction was monitored by electron paramagnetic resonance (EPR) spectroscopy. Upon the addition of free radical spin-

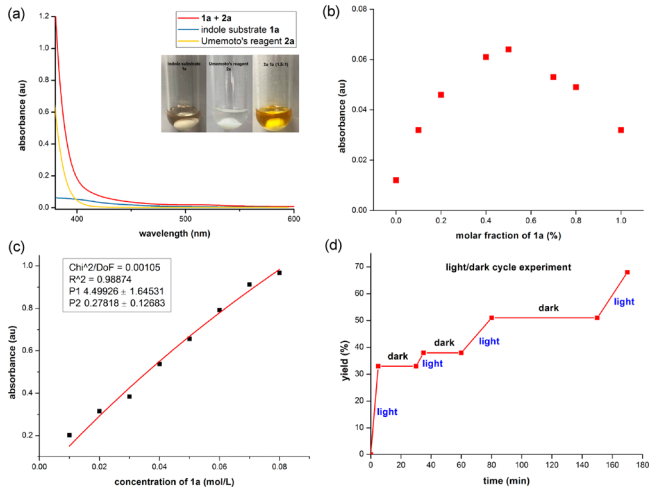
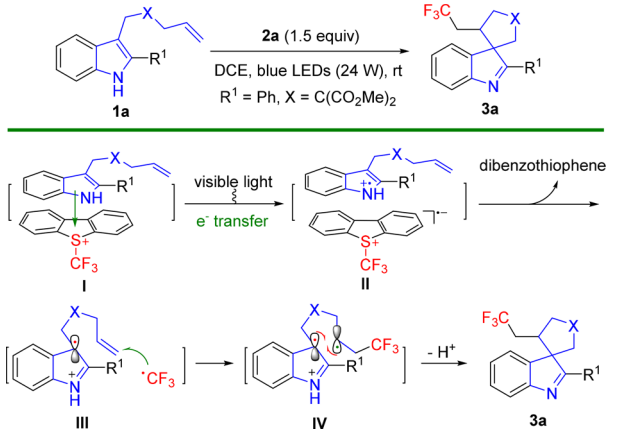


Figure 1. (a) Optical absorption spectra of the reaction components. (b) Job's plot between **1a** and **2a** (measured wavelength: 425 nm). (c) Determination of the association constant (K_{EDA}): nonlinear curve-fitting methodology (measured wavelength: 425 nm). (d) Light/dark cycle experiments for the model reaction.

trapping agent 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO), the spectrum recorded was identified as EPR signals of adduct CF_3-DMPO.[16] In addition, the light-dark interval experiment verified that constant illumination of light is an essential element for product formation (d, Figure 1).

On the basis of all these experimental results, a plausible mechanism was proposed. As exemplified by the reaction between **1a** and **2a**, the combination of two starting materials delivers the transient complex **I**, which upon visible-light irradiation undergoes single-electron transfer from donor to acceptor (**II**). The CF_3 radical generated through S-CF_3 bond cleavage then proceeds via an addition to terminal alkene (**III**) to afford the intermediate **IV**. Ultimately, the radical−radical recombination occurs to provide the desired product **3a** after deprotonation (Scheme 4). Herein, the substituents intro-

Scheme 4. Proposed Mechanism



duced at the C-2 position might render the radicals coupling process in a diastereoselective manner due to the effect of geometrical preferences. Notably, the radical chain mechanism might also be operative in this case.[19]

In summary, we here introduced a novel method for the intramolecular dearomatization reaction of indoles enabled by visible-light promoted intermolecular charge transfer. Upon

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mixing two starting materials in DCE solution, the cascade sequence involving trifluoromethylation of alkenes coupled with indole dearomatization is achieved merely by illumination of visible light. This method features extremely mild and simple reaction conditions—no heating and is free of catalyst and additives—allowing access to a wide range of spiroindolenines bearing trifluoromethyl (CF_3) group in good yields. The amenable capability to scale-up and flexible manipulation of the resultant products further demonstrate its synthetic utility. In addition, mechanistic studies suggest an unprecedented EDA complex formed between the indole substrate and Umemoto's reagent. To the best of our knowledge, this work constitutes a previously elusive reaction type in EDA complex-enabled chemical transformations. Further exploration of visible-light promoted dearomatization reactions are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01899.

Experimental procedures and analysis data for all new compounds (PDF)

Accession Codes

CCDC 1844566 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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