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Cleavage of C−C Bonds for the Synthesis of C2-Substituted Quinolines and Indoles by Catalyst-Controlled Tandem Annulation of 2-Vinylanilines and Alkynoates

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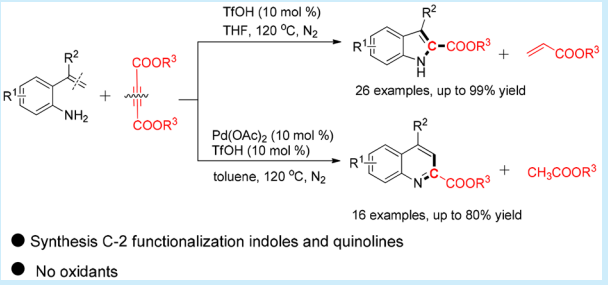
Supporting Information

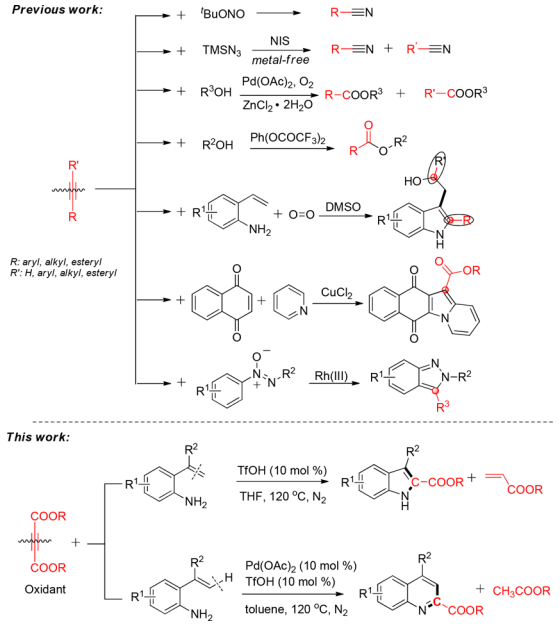
ABSTRACT: The strategy for the synthesis of C2-substituted indoles and quinolines from 2-vinylanilines and alkynoates through C−C bond cleavage is developed. With these general methods, 2-substituted indoles and quinolines can be accessed via tandem Michael addition and cyclization with no requirement of oxidant. This strategy not only provides a method for the synthesis C2-substituted indoles in good yields through the simultaneous cleavage of C═C and C≡C bonds under metal-free conditions but also provides a simple method for the generation of the C2-substituted quinolines in moderate yields via Pd-catalyzed C≡C bond cleavage.



Selective C−C bond cleavage is an invaluable and atom-economic tool for new heterocyclic compounds construction.[1] As compared to the highly developed C−C bond formations, the process of the selective cleavage of C−C bond remains a great challenge.[2] In the past decade, the direct cleavage of C═C and C≡C bonds have been significantly developed.[3] Alkynoates, as attractive substrates, have drawn much attention for their growing applications in the synthesis of *N*-heterocyclic compounds. To date, the C≡C bond cleavage of disubstituted acetylenes has been heavily studied.[4] The group of Jiang demonstrated a palladium-catalyzed cleavage reaction of C≡C triple bonds of alkynes to give carboxylic esters using molecular oxygen as the sole oxidant (Scheme 1).[5] Recently, the group of Jiao has developed an unexpected and efficient approach to synthesize highly valuable tryptophol derivatives through C≡C triple bond cleavage and dioxygen activation under metal-free conditions.[6] To our best knowledge, the formation of C2-substituted quinolines and indoles through the C−C bond cleavage of alkene and alkyne is very rare.

The substituted indole is a privileged heterocyclic scaffold prevalent in a wide range of interesting compounds, including natural products, medicinal agents, and agrochemicals.[7] Indole moieties have been disclosed to possess a diverse range of biological activities, such as anticancer, antiviral, and antibacterial.[8] The demand for efficient syntheses of indoles has burgeoned since the development of the classical Fischer indole synthesis.[9] Various methods have focused on the transition-metal-catalyzed cyclization to build new C−N/C−C bonds for rapid access to indole derivatives.[10] Although these significant developments have been achieved in the field of transition metal catalysis, the synthesis of C2 functional indoles remains a challenge due to the inherently poor nucleophilic reactivity of the C2 position.

Scheme 1. C≡C Bond Cleavage of Alkynoates



We initiated the investigation based on our experience in the construction of heterocyclic scaffolds,[11] examining the reaction of 2-(1-phenylvinyl)aniline **1a** with dimethyl but-2-ynedioate **2a**

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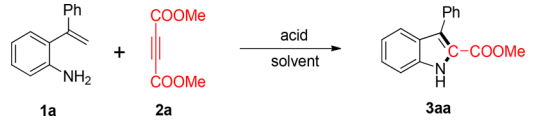
as the model reaction (Table 1). The use of AcOH as the catalyst in DMSO promoted the sequential cleavage and cyclization of **1a**

Table 1. Optimization of Reaction Conditions[a]



1a **2a** **3aa**

entry	acid	solvent	temp (°C)	yield (%)[b]
1	AcOH	DMSO	130	63
2	TfOH	DMF	120	61
3	**TfOH**	**THF**	**120**	**93**
4	TFA	THF	120	73
5	PivOH	THF	120	55
6	TfOH	MeCN	120	78
7	TfOH	toluene	120	70
8	–	THF	120	–
9	TfOH	THF	80	32
10	TfOH	THF	rt	–

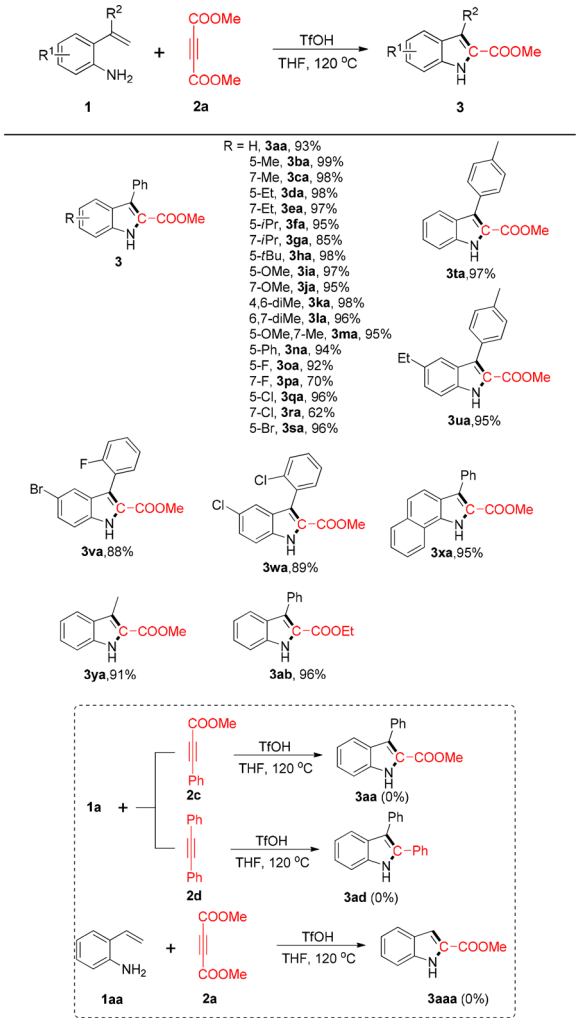
[a]All reactions were carried out in a nitrogen atmosphere using **1a** (0.30 mmol), **2a** (0.60 mmol), and acid (10 mol %) in 2 mL of solvent. [b]Isolated yield.

and **2a** to afford the C-2 functionalized indole **3aa** in 63% yield (Table 1, entry 1). Switching the solvent to THF significantly increased the yield of this process, and the yield of **3aa** was improved to 93%. Then the evaluation of various other acids, such as TfOH, TFA, PivOH, showed that TfOH was the best acid for this reaction (Table 1, entries 3–5). The temperature was also examined, and the yield was sharply decreased to 32% when the reaction temperature was reduced to 80 °C (Table 1, entry 9). Finally, the desired substituted indole cannot be detected in the absence of acid (Table 1, entry 10).

With suitable access to indole in hand, we proceeded to investigate the scope of the reaction using a variety of different 2-vinylaniline derivatives (Scheme 2). As shown in Scheme 2, the cleavage and cyclization proceeded efficiently with substrates bearing electron-deficient or electron-rich groups, providing the corresponding products in excellent yields. This access, which allowed substituting at random positions of the 2-vinylanines framework, illustrated the great generality and flexibility of this approach. The nature of the groups R^1 did not significantly affect the reaction. When R^1 was an electron-deficient group at the C7 position of the aryl ring, the yields of **3pa** and **3ra** were lowered to 70% and 62%, respectively. The substrate 2-(prop-1-en-2-yl)aniline **1t** can generate the desired product in satisfactory yield. The methodology also can be extended to diethyl but-2-ynedioate; the desired product **3ab** was afforded in 96% yield. The substrates, such as methyl 3-phenylpropiolate **2c** and 1,2-diphenylethyne **2d**, were also employed for this transformation, and no desired products were detected. Moreover, the substrate **1aa** also could not work under the optimized conditions.

Similarly, quinolines not only have been widely found in natural products with biological activities but also have also been broadly used in medical chemistry, drug synthesis, and functional compound materials as building blocks.[12] In the course of optimizing the experimental conditions, substituted quinoline was detected when the catalyst $Pd(OAc)_2$ was used. The product methyl 4-phenylquinoline-2-carboxylate **4aa** was isolated when compounds **1a** and **2a** were used as substrate (Scheme 3). Subsequently, we extensively screened acids, solvents, and other factors under argon. The results were summarized in Table S1

Scheme 2. Scope of 2-Vinylanilines and Alkynoates[a]



[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), and TfOH (10 mol %) in 2 mL of THF at 120 °C under N_2 for 8 h.

(Supporting Information). The highest yield of **4aa** was achieved when the reaction was operated with **1a** and **2a** (2 equiv), $Pd(OAc)_2$(10 mol %), and TfOH (10 mol %) in toluene at 120 °C under nitrogen (Table S1, entry 13).

The next step was to explore the generality of this approach to assemble a range of substituted quinolines under established optimal reaction conditions. As a result, the optimized conditions were consistent with various substituted 2-vinylanilines with Me, Et, *i*Pr, *t*Bu, Ph, F, and Br groups on the aryl ring and the desired quinolines were isolated in moderate yields. In general, the electron-withdrawing substituents R^1 at the aromatic ring (**4ka** and **4la**) led to a higher yield in this reaction than the electron-donating groups except *t*Bu. Moreover, these reaction conditions were also compatible with different substituents on aromatic rings, such as **1n** and **1o**, generating the desired products in 61% and 48% yields. Using 2-(prop-1-en-2-yl)aniline **1p** as substrate bearing a methyl group at the R^2 position afforded desired quinoline **4pa** in ideal yield.

The presumption of a radical mechanism guided the conceptual development of the indole formation reaction. To gain more insight into the reaction mechanism, some control experiments were conducted. Control experiments with added TEMPO gave the expected results. Only a trace amount of

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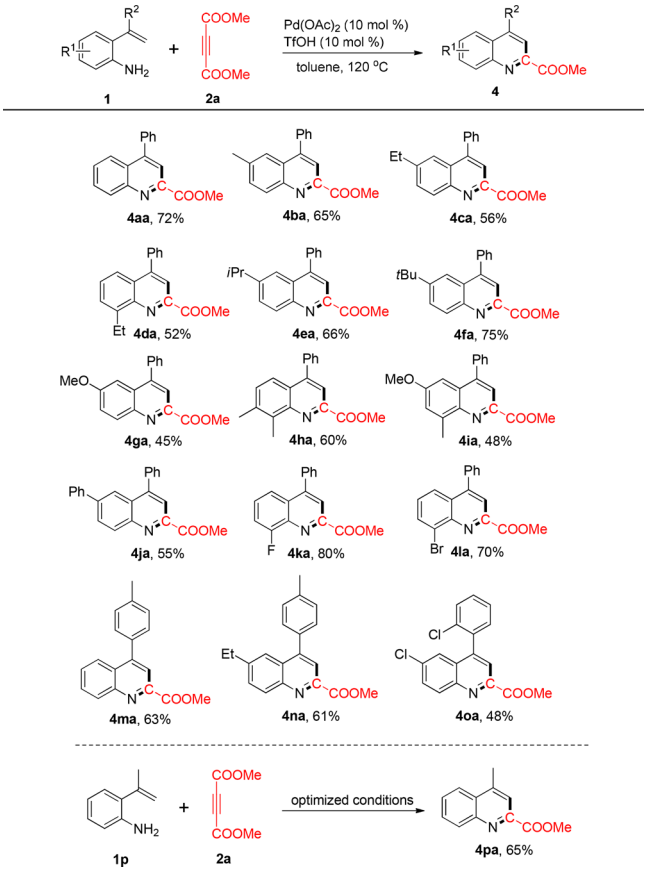
Scheme 3. Scope of Quinolines[a]

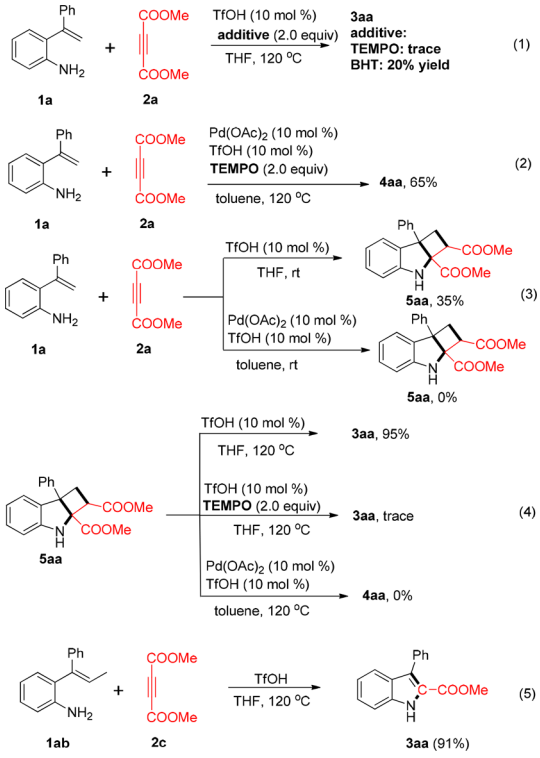


[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (10 mol %), and TfOH (10 mol %) in 2 mL of toluene at 120 °C under N_2.

desired product **3aa** was detected when TEMPO was employed under the standard conditions to synthesize the indoles. When BHT was added, the desired product **3aa** was generated in 20% yield (Scheme 4). Therefore, these results suggested that this reaction proceeded via a free radical process. The result of entry 2 in Scheme 4 suggested that the transformation to form the quinoline was not a radical pathway under the standard conditions because no suppression occurred with the addition of TEMPO. It is worth noting that the compound **5aa** was isolated in 35% yield when the reaction was conducted under room temperature with TfOH (10 mol %) in THF, while the **5aa** was not detected with the standard conditions of generating quinoline at room temperature. In a follow-up study, the compound **5aa** was also employed as substrate for this reaction, giving the desired indole **3aa** in 95% yield and **4aa** in 0% yield.

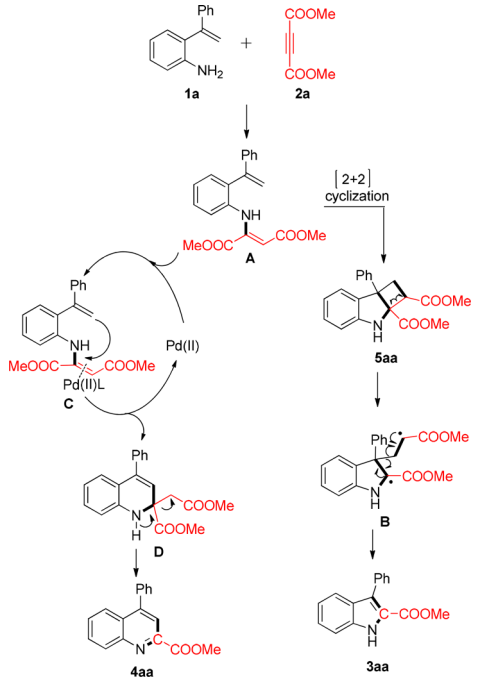
Obviously, a dramatic decrease in the yield (trace) of the reaction to form indole with **5aa** was observed in the presence of TEMPO as a potent radical inhibitor. Given these data, a proposed mechanism for the formation of indoles proceeding through the Michael addition and cyclization of 2-vinylanilines and alkynoates could be envisioned, and an important intermediate **5aa** was indeed synthesized under the optimized reaction conditions. In order to certify the C═C cleavage of the substrate **1a** for the synthesis of indole, the compound **1ab** was employed for this reaction under optimized conditions. According to our expectation, the desired indole **3aa** was isolated in 91% yield.

Scheme 4. Control Experiments



On the basis of the results described above, the proposed mechanism is illustrated in Scheme 5. The proposed mechanism for the synthesis of the indole is described as follows: generally, enamine **A** is quickly formed by Michael addition of **1** and **2**.[13] Later, intramolecular thermal [2 + 2] cyclization[14] occurs to form the key intermediate **5aa**, which is highly reactive and easily undergoes C−C bond homolytic cleavage to generate biradical intermediate **B**.[6] Then the desired indole **3aa** is afforded through

Scheme 5. Proposed Mechanism



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cleavage of C−C bonds. The proposed mechanism for the synthesis of the quinolines is also shown as follows: the enamine **A** is coordinated with Pd catalysis to generate the intermediate **C**. Then, the intermediate **D** is formed through the intramolecular nucleophilic addition. Finally, the quinoline is produced through cleavage of the C≡C bond.

In summary, we have demonstrated a novel and convenient method to synthesize the C2-substituted indoles and quinoline from 2-vinylanilines and alkynoates through cleavage of C−C bonds. Furthermore, this protocol shows good functional group compatibility and various substituted 2-vinylanilines proceed smoothly with alkynoates, generating the desired products in moderate to good yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00260.

Experimental methods and ^{1}H and ^{13}C NMR spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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