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Direct Tryptophols Synthesis from 2-Vinylanilines and Alkynes via C≡C Triple Bond Cleavage and Dioxygen Activation

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Supporting Information

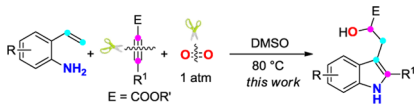
ABSTRACT: An unexpected metal-free C≡C triple bond cleavage, dioxygen activation, and reassembly into tryptophol derivatives has been developed. This chemistry provides a novel, simple, and efficient approach to highly valuable tryptophol derivatives from simple substrates under mild conditions. The mechanistic studies may promote the discovery of new methodologies through C−C bond cleavage and dioxygen activation.

With respect to simple and efficient methodologies, the synthesis of complex compounds by employing simple and readily available substrates as starting materials has always been desired.[1] A bond cleavage and reassembly strategy provides great opportunities to reach very incredible and more complex products. However, although the reactions through C−C bond cleavage have attracted considerable attention,[2] the transformations with unstrained C−C bond cleavage still remain a challenging issue.[3,4] Moreover, the cleavage and reassembly of the C≡C triple bond located in one product for the synthesis of more complex compounds is rarely achieved.[5,6]

Molecular oxygen is a green oxidant as well as an ideal oxygen source for the construction of oxygen-containing compounds because of its inexpensive, abundent, and environmentally benign character.[7] In the past decades, although many transition metals have been significantly applied in the oxygenation reactions with molecular oxygen,[8] only a few examples have been demonstrated on transition-metal-free dioxygen activation mediated by organic molecules.[9]

According to the atom economy concept, herein we report an unexpected metal-free C≡C triple bond cleavage, dioxygen activation, and reassembly into tryptophol derivatives (Scheme 1),

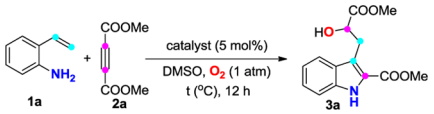
Scheme 1. Bond Cleavage for Tryptophols



which are common structural motifs in natural products and pharmaceutical drugs, as well as important intermediates and building blocks in organic synthesis.[10] The present novel tryptophol construction protocol has several significant advantages: (1) The incredible chemical bond cleavage of alkynes and molecular oxygen occurred and reassembled in one product molecule. To the best of our knowledge, this is the first direct synthesis of typtophol derivatives by an oxygenation strategy via O_2 activation as well as C−C bond cleavage from simple and readily available substrates; (2) this protocol is very simple under metal-free conditions, without the addition of any acid, base, or other additives, which avoids the strict transition-metal removal process from the products; (3) this chemistry provides a novel and simple strategy for the synthesis of complex and highly valuable tryptophol derivatives under very mild conditions; (4) a reasonable mechanism is proposed, which may promote the discovery of new methodologies for C−C bond cleavage and dioxygen activation.

When 2-vinylaniline **1a** and dimethyl acetylenedicarboxylate **2a** were initially investigated in our Pd-catalyzed dehydrogenative annulation for the corresponding indole synthesis,[11] to our delight, an unexpected tryptophol product **3a** was obtained in 58% yield in DMSO under a dioxygen atmosphere (Table 1, entry 1). In contrast, only a trace amount of **3a** was observed with a copper catalyst (entry 2). Further investigation (see Supporting Information (SI)) demonstrated that **3a** could be obtained without any metal catalyst in 60% yield (Table 1, entry 3). It seems that concentration of the reaction system plays an important role

Table 1. Optimization for the Tryptophols Synthesis[a]



entry	catalyst	t (°C)	yield of **3a**
1	$Pd(OAc)_2$	80	58%
2	$Cu(OAc)_2$	80	trace
3	–	80	60%
4	–	**80**	**89%**[b]
5	–	60	80%
6	–	120	16%
7	–	80	51%[c]
8	–	80	0%[d]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (0.01 mmol), DMSO (2 mL), stirred at 80 °C under O_2 for 12 h. Isolated yields. [b]DMSO (1.0 mL). [c]Under air. [d]Under Ar. DMSO = dimethyl sulfoxide.

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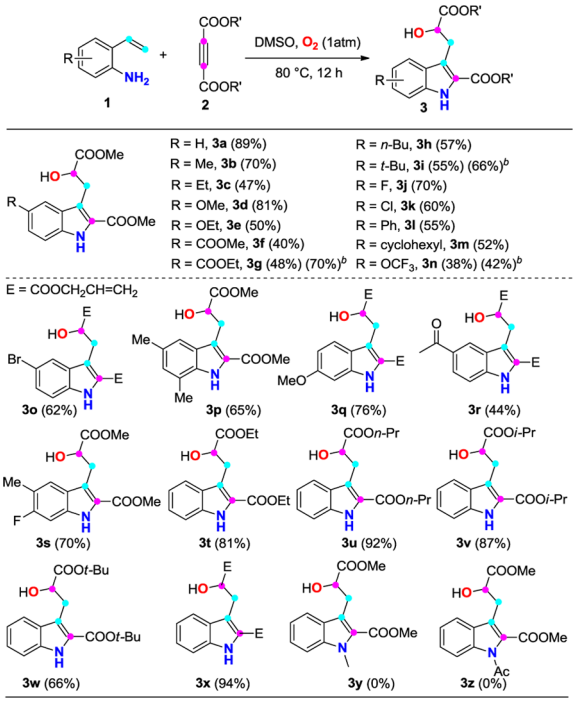
for high efficiency (cf. entries 3 and 4). Molecular oxygen is essential for this transformation. When the reaction was performed under air, the yield decreased signicantly (entry 7). No product was obtained uner an Ar atmosphere (entry 8). The reactions in other solvents such as THF, toluene, 1,4-dioxane, and DCE did not work (see SI).

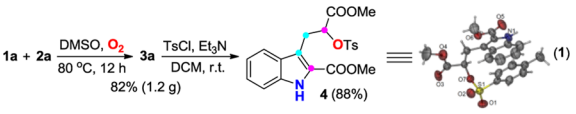
Various 2-vinylanilines containing different functional groups worked well leading to the desired tryptophols in moderate to good yields (Table 2). Notably, **1g**, which was prepared from

Table 2. Substrate Scope of this Transformation[a]



[a]Standard conditions: see entry 4, Table 1. Isolated yields. [b]At 120 °C for 24 h.

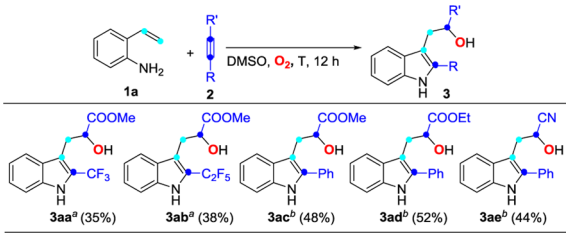
analgesic benzocaine, could smoothly generate **3g** in moderate yield. Unfortunately, the reactions of secondary amines and aliphatic homoallylamines stopped at the hydroamination step without the tryptophol products formation (**3y**; also see SI). The gram scale reaction afforded **3a** in 82% yield (eq 1). Moreover, the structure of **3a** was confirmed by the X-ray structure of its derivative **4** (eq 1).



For the scope of alkynes, to our delight, the fluoroalkyl alkynes worked well and regioselectively produced the corresponding tryptophol products **3aa** and **3ab** (Table 3). Furthermore, by using a simple tandem process, phenyl substituted alkynes could also be employed in this protocol (**3ac**–**3ae**). It is noteworthy that these reactions showed high regioselectivity with only one isomer detected.

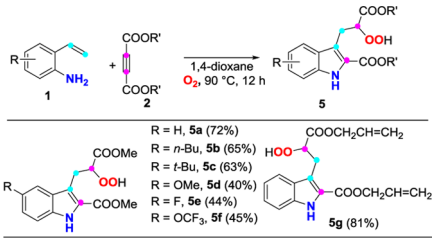
Interestingly, when the solvent was changed from DMSO to 1,4-dioxane, the corresponding peroxide tryptophol **5a** was obtained in 72% yield instead of **3a** (Table 4). Thus, the tryptophol products could be easily switched by the selection of solvent. A range of different substituents at the aromatic ring

Table 3. Substrate Scope of Alkynes[a]



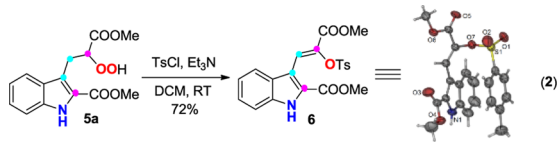
[a]Conditions see entry 6, Table 1. [b]Conditions: (1) **1a** (0.1 mmol), **2a** (0.09 mmol), $Cu(OTf)_2$ (10 mol %), 4 Å MS, THF (0.1 mL), stirred at 45 °C under Ar for 12 h; (2) DMSO (1 mL), stirred at 100 °C under O_2 for 12 h. Isolated yields.

Table 4. Peroxide Tryptophol Synthesis[a]



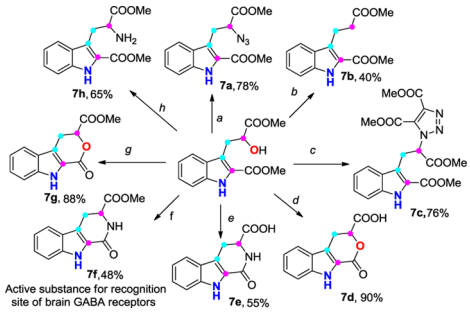
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), 1,4-dioxane (1 mL), stirred at 80 °C under O_2 for 12 h. Isolated yields.

were compatible to furnish highly functionalized peroxide tryptophol derivatives in moderate to good yields (**5b**–**f**). The structure of **5a** was confirmed by COSEY spectroscopy, and its derivative **6** generated from hydroperoxide[12] was further proved by X-ray analysis (eq 2).



The tryptophol products **3** could be further transferred to other important compounds (Scheme 2). For examples, the

Scheme 2. Further Transformations of Product 3a[a]



[a]Conditions: a–h, for details, please see SI.

nucleophilic substitution of **3a** with NaN_3 generated **7a** in 78% yield. The elimination reaction of **3a** provided **7b** in 40% yield, which could be used for further synthesis of biologically active molecules. Moreover, the Cu-catalyzed click reaction was employed to give triazole **7c** in 76% yield via intermediate **7a**. Due to the unique structure of **3a**, direct intramolecular

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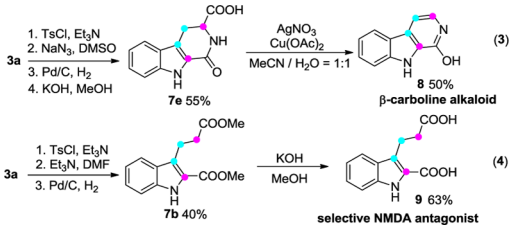
condensation was allowed to afford lactones **7d** in 90% yield. Lactam **7e** could be obtained in 55% yield under KOH/MeOH conditions, and further esterification of **7e** resulted in β-carboline skeleton **7f**, which has potential activity to bind brain GABA receptors.[13] Lactone **7g** could be highly efficiently prepared in 88% yield by direct intramolecular condensation of **3a**. In addition, as an important class of tryptophan derivatives, primary amine **7h** could be obtained via the reduction of **7a** in 65% yield. Thus, the presented methodology could be a complementary tool to access a useful library of tryptophols, lactones, lactams, and β-carboline alkaloids derivatives.

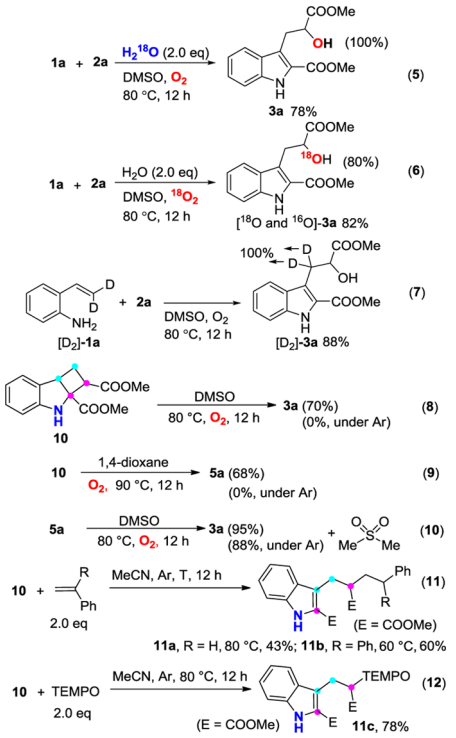
In addition, the present protocol also provides efficient synthetic routes to biologically active molecules synthesis. The direct silver- and copper-mediated oxidative decarboxylation of **7e** occurred to generate β-carboline alkaloids **8** in 50% yield (eq 3), which is separated from the stems of *picrasma quassioides*.[14] Moreover, the selective NMDA antagonist[15] **9** could be efficiently synthesized from **3a** via **7b** (eq 4).



To gain some insight into the mechanism, some control experiments were investigated. When the reaction was carried out in the presence of 2.0 equiv of $H_2{}^{18}O$, no ^{18}O labeled product was detected (eq 5). In contrast, ^{18}O and ^{16}O products were detected in the ratio 4:1 when $^{18}O_2$ was filled in the reaction system (eq 6). These results demonstrate that the oxygen atom of hydroxyl in the product is mainly originated from molecular oxygen. The reaction of $[D_2]$-**1a** was tested under standard conditions, and $[D_2]$-**3a** was obtained in 82% yield (eq 7), which suggests that C≡C triple bond cleavage may be involved rather than C=C double bond cleavage of **1a**.

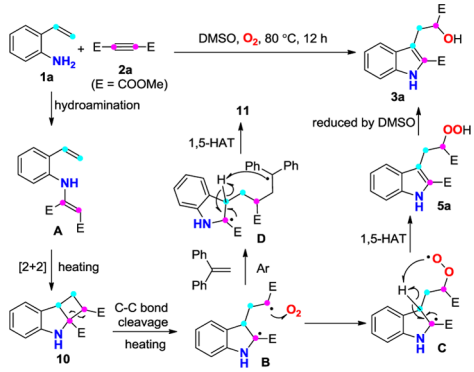
Since the different products were obtained in DMSO and 1,4-dioxane, we envisioned that products **3** and **5** were generated from the same intermediate. Then the possible intermediate **10** was synthesized in THF under Ar and further investigated in control experiments. Tryptophol product **3a** was obtained in 70% yield in the presence of O_2 (eq 8). Similarly, when 1,4-dioxane was employed as solvent, peroxide tryptophol **5a** was produced in 68% yield (eq 9). In contrast, both of these reactions did not work under Ar (eqs 8–9). These results demonstrate that **10** may be a possible intermediate for this novel transformation (for the detection of **10** under Ar, and in situ ^{1}H NMR experiment; see SI). In addition, **5a** could be highly efficiently converted into **3a** in either the presence or absence of O_2 in DMSO with the $CH_3SO_2CH_3$ as the byproduct detected by GC-MS (eq 10; also see SI), which indicates that DMSO can be a reductant to reduce the peroxide tryptophol **5a** to tryptophol **3a**.

To further understand the ring-opening mechanisms, styrenes and TEMPO, which were proven to be efficient radical traps, were allowed to react with **10** under Ar. The stryene-trapped products **11a–b** and TEMPO-trapped product **11c** were obtained in moderate yields (eqs 11–12), which demonstrate a radical pathway. Thus, homolytic cleavage of the C–C bond of intermediate **10** followed by the O_2-trapped process may be involved in this transformation.



On the basis of the above preliminary results, the proposed mechanism is illustrated in Scheme 3. Initially, enamine **A** is

Scheme 3. Proposed Mechanism



quickly formed by hydroamination of **2a** with **1a**.[16] Subsequently, intramolecular thermal [2 + 2] cyclization[17] occurs by heating to form the key intermediate **10**, which is highly reactive and easily undergoes C–C bond homolytic cleavage to generate radical intermediate **B**. And then the secondary carbon radical has priority over the tertiary carbon radical to be trapped by O_2 leading to peroxide radical intermediate **C**. A subsequent intramolecular 1,5-hydrogen atom transfer (1,5-HAT) process[18] enables the formation of peroxide tryptophol **5a**, which could be successfully obtained in 1,4-dioxane. Finally, the peroxide tryptophol **5a** is reduced by DMSO[19] to generate tryptophol procuct **3a**. In addition, the reactive intermediate **B** could be trapped by 1,1-diphenylethylene in the absence of O_2 to form intermediate **D**, which produces the product **11** through a similar 1,5-HAT process.

In summary, we have demonstrated a novel approach to tryptophol derivatives synthesis through a chemical bonds cleavage and reassembly strategy. This metal-free oxygenation chemistry is very easily operated using simple and readily available

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substrates under mild conditions, and provides an efficient protocol for complex and highly valuable tryptophol derivatives synthesis. The mechanism is reasonably proposed and may promote the discovery of new methodologies through C−C bond cleavage and dioxygen activation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08094.

Experimental procedures, analytical data for products, NMR spectra of products (PDF)
Crystallographic data (CIF, CIF)

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Notes

The authors declare no competing financial interest.

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