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Highly Diastereoselective Oxa-[3+3] Cyclization with C, N-Cyclic Azomethine Imines via Copper-Catalyzed Aerobic Oxygenated C=C Bond of Indoles

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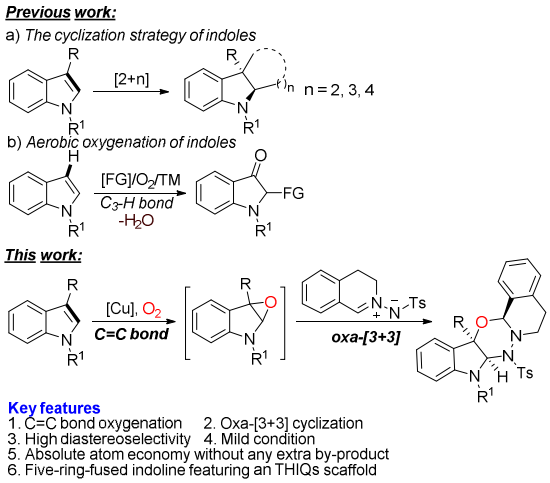
Herein, a copper-catalyzed highly diastereoselective aerobic oxygenated [3+3] cyclization of 3-substituted indoles with C,N-cyclic azomethine imines using oxygen as the sole oxidant under mild condition has been developed. This protocol provides a simple and convenient approach for constructing [2,3]-fused indoline *O*-heterocycles bearing the two pharmaceutically intriguing parts, tetrahydroisoquinoline and indoline. Good yield and excellent diastereoselectivity under mild reaction conditions were observed.

Indolines and tetrahydroisoquinolines (THIQs) have drawn much attention in industrial and academic research due to their privileged structural motifs in bioactive natural products and pharmaceuticals.[1-4] As a consequence, a considerable number of catalytic strategies dedicated to the preparation of either polycyclic indolines[5] or C1-functional tetrahydroisoquinolines have been reported.[6] Among them, the cyclization of indoles, including catalytic [2+2],[7] [2+3],[8] [2+4][9] cycloaddition and other annulation[10] reaction, provides an efficient method for constructing polycyclic structure of indoline derivatives (Scheme 1a).

The copper-catalyzed aerobic oxygenated strategy has emerged as an attractive and useful methodology for constructing C-C bond and C-heteroatom bond.[12] Recently, several copper-catalyzed aerobic oxygenation reactions on the cyclization of indoles have been developed via copper-catalyzed oxygenation of C3 C-H bond of indole by the groups of Li,[13] and Deng,[14] using TBHP and dioxygen as oxygen source, respectively (Scheme 1b). These reactions provide various polycyclic indolin-3-one derivatives with oxygen-atom incorporated. Although these elegant work for the construction of polycyclic indolines have been well-established, however, the [2,3]-fused indoline skeletons via copper-catalyzed aerobic oxygenation have not been discovered.



Scheme 1 Strategies for constructing indolines.

Herein, we report an aerobic oxygenation of indoles and oxa-[3+3] cyclization cascade with C,N-cyclic azomethine imines via oxygenation of the C=C bond of indole framework using copper catalysis under mild condition. The reaction provides a concise route to polycyclic [2,3]-fused indoline and C1-functional tetrahydroisoquinoline derivatives in a highly diastereoselective manner.

At the outset of our investigation, we began by carrying out this oxidation/1,3-dipolar cyclization cascade of idoles applying *N*-benzyl-3-methyl indole **1a** and C,N-cyclic azomethine imines **3a** as the model system in the presence of 10 mol% $Cu(CH_3CN)_4BF_4$ and dichloromethane at room temperature in air, after the complete consumption of **1a** in 24 h, the desired adduct **4a** was successfully isolated in 46% yield (Table 1, entry 1), meanwhile a byproduct **5** was isolated in only 3% yield. To our delight, the yield of adduct **4a** was improved to 70% yield when an oxygen balloon was employed (Table 1, entry 2). Subsequently, other transition metal catalysts were also evaluated with dioxygen as the oxidant, including $AgN(OTf)_2$, $AgSbF_6$, and $Pd(OAc)_2$, and $Pd(CH_3CN)_4(OTf)_2$ (Table 1, entries 3, 4; Table S1). However, they were found to be less efficient than copper salts. A survey of solvent effect using $Cu(CH_3CN)_4BF_4$ as the catalyst concluded that CH_2Cl_2 was the

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† Footnotes relating to the title and/or authors should appear here.
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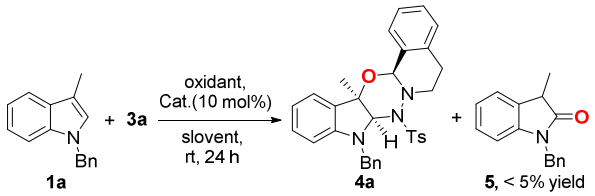
Table 1 Optimization of reaction conditions[a]

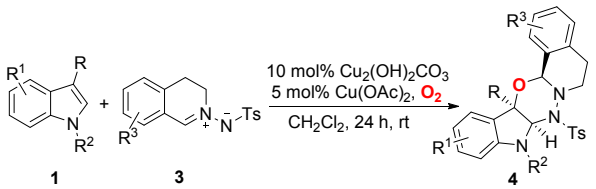


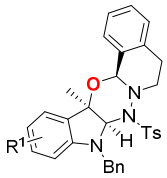
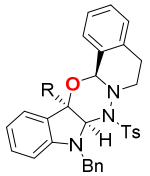
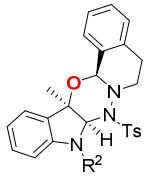
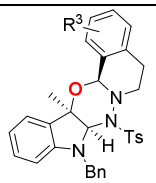
Entry	Oxidant	Cat.	Solvent	Yield (%)[b]
1	air	$Cu(CH_3CN)_4BF_4$	CH_2Cl_2	46
2	O_2	$Cu(CH_3CN)_4BF_4$	CH_2Cl_2	70
3	O_2	$AgSbF_6$	CH_2Cl_2	50
4	O_2	$Pd(OAc)_2$	CH_2Cl_2	63
5	O_2	$Cu(CH_3CN)_4BF_4$	$CHCl_3$	67
6	O_2	$Cu(CH_3CN)_4BF_4$	DCE	69
7	O_2	$Cu(CH_3CN)_4BF_4$	toluene	50
8	O_2	$Cu(CH_3CN)_4BF_4$	Et_2O	trace
9	O_2	$Cu(CH_3CN)_4BF_4$	THF	48
10	O_2	$Cu(CH_3CN)_4BF_4$	CH_3CN	45
11	O_2	$Cu(CH_3CN)_4PF_6$	CH_2Cl_2	73
12	O_2	CuI	CH_2Cl_2	69
13	O_2	$Cu(OAc)_2$	CH_2Cl_2	81
14[c]	O_2	$Cu_2(OH)_2CO_3$	CH_2Cl_2	79
15	O_2	$CuSO_4{\cdot}5H_2O$	CH_2Cl_2	77
16[d]	**O_2**	**$Cu_2(OH)_2CO_3$ + $Cu(OAc)_2$**	**CH_2Cl_2**	**88**
17[e]	O_2	$Cu_2(OH)_2CO_3$ + $Cu(OAc)_2$	CH_2Cl_2	84
18[f]	*m*-CPBA	$Cu_2(OH)_2CO_3$	CH_2Cl_2	46
19[g]	H_2O_2	$Cu_2(OH)_2CO_3$	CH_2Cl_2	N.D.
20[h]	*t*-BuOOH	$Cu_2(OH)_2CO_3$	CH_2Cl_2	N.D.
21[i]	O_2	----	CH_2Cl_2	56

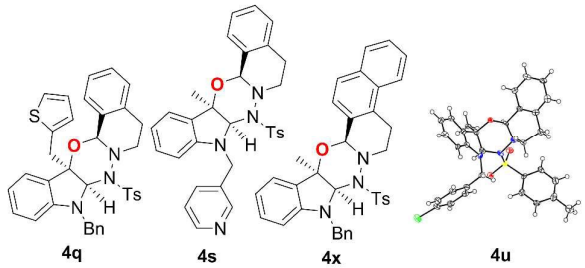
[a] Unless otherwise stated, reactions were conducted on a 0.2 mmol scale with **1a** (1.0 equiv), **3a** (1.5 equiv), and catalyst (0.1 equiv) in CH_2Cl_2 (1.0 mL) solvent at room temperature for 24 h. For all of cases, >99:1 dr values was detected. [b] Isolated yield. [c] **3a** (1.1 equiv) was used. [d] $Cu_2(OH)_2CO_3$ (10 mol%) + $Cu(OAc)_2$ (5 mol%) was used. [e] $Cu_2(OH)_2CO_3$ (5 mol%) + $Cu(OAc)_2$ (2.5 mol%) was used. [f] For 2 h. [g] H_2O_2 (30% in water) or [h] *t*-BuOOH (70% in water) was used. [i] For 36 h.

preferred medium for the reaction (Table 1, entries 5–10). We then employed a selection of copper salts as catalysts for the optimization of reaction conditions (Table 1, entries 11–17). It was shown a mixture of 5-mol% $Cu(OAc)_2$ and 10-mol% $Cu_2(OH)_2CO_3$ was able to increase the reaction yields to 88% (Table 1, entry 16). Furthermore, using basic $Cu_2(OH)_2CO_3$ as the catalyst seemed to be able to block the dimerization of 1,3-dipole substrate **3a**, which allowed for decreasing the utilization of **3a** from 1.5 equivalents to 1.1 equivalents. Lastly, a number of common oxidants were also used with $Cu_2(OH)_2CO_3$ as the catalyst. It was shown that the choice of oxidants is critical for this cascade process (Table 1, entries 18–20). Replacing dioxygen with *m*-CPBA resulted in a significant decrease of reaction yields (Table 1, entry 18). There was no product formed when H_2O_2 (30% in H_2O) or *t*-BuOOH (70% in H_2O) was applied to this reaction (Table 1, entries 19–20). In addition, without any catalyst, this reaction could also be carried out, but longer time and decrease in yield were shown (Table 1, entry21). The results indicated that copper-catalyst and increasing the amount of catalyst could accelerate this oxygenation reaction and improve isolated yield of **4a** (Table 1, entries 16–17, entry21).

Table 2 Scope of this aerobic oxidative cyclization[a]



Entry	Structure	Product(**4**)		Yield (%)[b]
1		R^1 = H	**4a**	88
2		R^1 = 5-Br	**4b**	70
3		R^1 = 5-F	**4c**	60
4		R^1 = 6-F	**4d**	66
5		R^1 = 6-Cl	**4e**	67
6		R^1 = 6-Me	**4f**	86
7		R^1 = 7-Me	**4g**	83
8		R^1 = 6-OMe	**4h**	64
9		R = Et	**4i**	83
10		R = Pr	**4j**	82
11		R = i-Pr	**4k**	81
12		R = n-hexane	**4l**	80
13		R = hexane	**4m**	70
14		R = -CH_2CN	**4n**	80
15		R = -$CH_2CH{=}CH_2$	**4o**	73
16		R = -Bn	**4p**	64
17		R	**4q**	42
18		R^2 = Me	**4r**	90
19		R^2	**4s**	45
20		R^2 = -Bn(2-CN)	**4t**	83
21		R^2 = -Bn(4-Cl)	**4u**	81
22		R^2 = H	**6**	14
23		R^3 = 4-Cl	**4v**	78
24		R^3 = 4-F	**4w**	73
25		R^3	**4x**	85
26		R^3 = 6-F	**4y**	66
27		R^3 = 4-Me	**4z**	86



[a] Unless otherwise stated, reactions were conducted on a 0.2 mmol scale with **1a** (1.0 equiv), **3a** (1.1 equiv), and catalyst (0.1 equiv) in CH_2Cl_2 (1.0 mL) solvent at room temperature for 24 h. For all of cases, >99:1 dr values was detected. [b] Isolated yield. Note: a relative configuration of product was exhibited.

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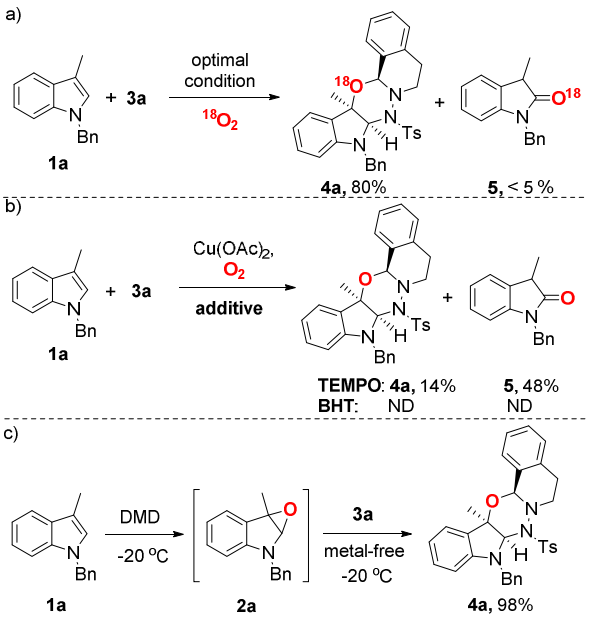
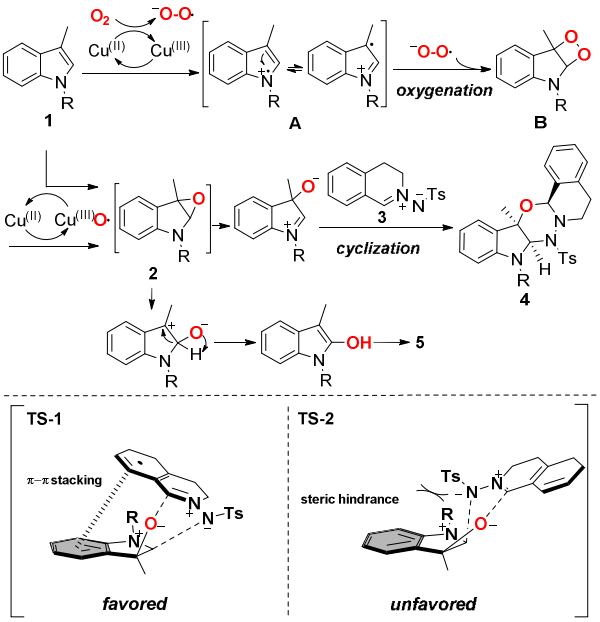
With the established optimal reaction conditions in hand, the substrate scope of the oxidation/cyclization cascade reaction was investigated by using various indole substrates **1** and C,N-cyclic azomethine imine **3** (Table 2). Both electron donating and electron-withdrawing substituents in the C5-, C6-, and C7-position of 1 were all compatible with the standard reaction conditions (**4b**–**4h**) in yields ranging from 60% to 83%. Besides, azomethine imine with methyl group substituent on aryl ring exhibited relatively higher reactivity than that of with halogen substituents. It appeared that the electronic effect of the C3-position of **1** had significant influence on the reaction process. Substrates with electron-neutral substituents or weak electron-withdrawing substituents at the C3-position gave 42% to 83% yields (**4i**–**4q**). In addition, the *N*-substituent of indoles seemed to be crucial for reaction yields and product stability, substrates with an electron-neutral group at *N*-position of **1** (**4r**–**4u**) gave 45% to 90% yields. Otherwise, only 14% yield of **6** and *N*1-substitued product in moderate yield have been obtained when hydrogen atom at *N*-position of **1** (see the Supporting Information); however, there was no desired product formed when R group of **1** was changed to acyl or ester group. We inferred that electrophilic effect of protecting groups block the electron transfer from lone pair. Lastly, various structurally diverse C,N-cyclic azomethine imines **3** were synthesized to further explore the generality of this reaction. The substitution impact on aryl groups of appeared to be limited (**4v**–**4z**) with 66%–86% yields. It is worth noting that azomethine imine **3x** with condensed-ring system also could be tolerated, and converted into the desired product **4x** with a satisfactory yield. However, the reaction didn't work when p-methylbenzene sulfonyl was replaced with benzoyl or with other 1,3-dipolrs such as nitrone, azomethine ylides etc.. This is due to strong electrical absorption of Ts group was more favourable to forming active 1,3-dipoles, and C,N-cyclic azomethine imines played roles in this oxygenation/cyclization. The relative configurations of the adduct products were unambiguously determined by X-ray crystallography (**4u** and **4y**; see the Supporting Information). For all cases, the values of diastereoselectivities were above 99:1.



Scheme 2 The control experiments of oxygenation



Scheme 3 A proposed reaction mechanism and transition states.

For studying the mechanism of this oxidative transformation, a series of control experiments have been conducted. The isotope labelling experiment with $^{18}O_2$ revealed that oxygen would be involved in the indole oxygenation (Scheme 2a). Compound **5** as the by-product in model reaction was found to be dominating when 2, 2, 6, 6-Tetramethyl-1-oxylpiperid-ine (TEMPO) was used, and the steric hindrance of methyl group at 3-position of indole could give the best explain for this result. Introducing the radical scavenger-butylated hydroxytoluene (BHT), the transformation was prevented completely (Scheme 2b). These observations support a probably radical mechanism. To further understand the mechanism of this aerobic oxygenated cyclization, we also performed this reaction process with dimethyldioxirane (DMD), which could oxidize indole into oxireno[2,3-b]indole.[15] The results showed that **1a** can be transformed to intermediate **2a** by DMD as the oxidant under -20 °C, moreover, the intermediate **2a** can interact with **3a**, giving the desired adduct **4a** in high yield without any metal catalysis in total 2 h (Scheme 2c), and the similar results have been found with *m*-CPBA as the oxidant. These results indicated that this transformation maybe progress via intermediate **2** under copper-based catalytic system.

On the basis of above results from the mechanistic studies, a plausible mechanism of this aerobic oxygenation/cyclization have been proposed (Scheme 3). Originally, copper (II) is oxidized by molecular oxygen to afford a higher valence copper (III) with the generation of the oxygen radical anion. Subsequently, an electron of nitrogen on indole ring of **1** is

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trapped by trivalent copper to get the nitrogen kation radical intermediate **A**, and trivalent copper return back to cupric. Intermediate **A** is easily attracted by oxygen radical anion leading to indoline peroxide intermediate **B**[16] which the molecular mass can be detected by LC-MS during reaction. Under the assist of cupric reduction, **B** transfered to intermediate **2** and the cupric turn to cupper (III)-oxygen radical, which products intermediate **2** and cupric again by reacting with substrate **1**.[17] In addition, the C-O bond at 2-position of intermediate **2** is much easier disrupted than 3-position by the effect of electron-donation of lone-pairs of nitrogen atom and the nucleophilic attack of substrate **3** result in preferring to dipolar form. Finally, a subsequent oxa-[3+3] cyclization between dipolar intermediate **2** and **3** enables the formation of adduct **4** in a high diastereoselectivity due to π-π stacking and steric hindrance effect between -Ts group and *N*-protected group R (Scheme 3), this point was further supported by the control experiment without any catalyst. Otherwise, the intermediate **2** was processed through 1,3-proton transformation and tautomerism of enol form to offer byproduct **5**.

In conclusion, we have reported a novel copper-catalyzed aerobic oxidative 1,3-dipolar cyclization for efficiently introducing indole- and THIQ-based substructures into complex molecules. This protocol represents an elegant example of aerobic oxygenation and 1,3-dipolar cyclization of indoles in good yields and excellent diastereoselectivities under mild reaction conditions. A diverse range of complex alkaloid-type pentacycles for diversity-oriented synthesis and drug discovery could be constructed in one single step.

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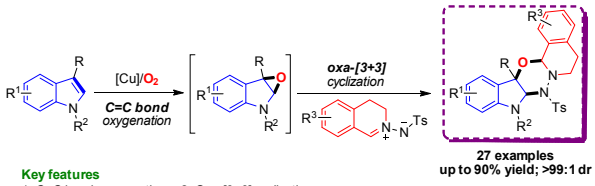

Key features

1. C=C bond oxygenation 2. Oxa-[3+3] cyclization
3. High diastereoselectivity 4. Mild condition
5. Absolute atom economy without any by-product
6. Five-ring-[2,3]-fused indoline featuring an THIQs scaffold