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Controllable synthesis of pyrido[2,3-*b*]indol-4-ones or indolo[3,2-*b*]quinolines *via* formal intramolecular C(sp^2)–H functionalization†

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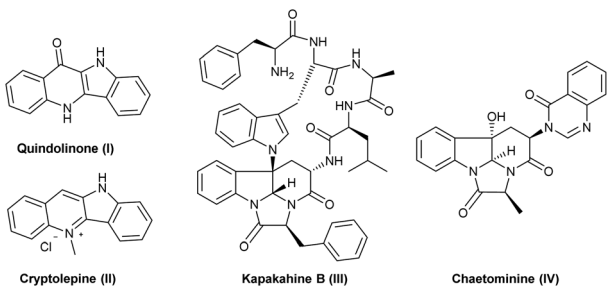
A novel Fe-catalyzed protocol for the controllable synthesis of pyrido[2,3-*b*]indol-4-ones or indolo[3,2-*b*]quinolines has been developed by using indole-2-carboxylic derivatives as starting materials. Indole-2-carboxenamines were transformed into pyrido[2,3-*b*]indol-4-ones through intramolecular N–H/C–H coupling, in which a carbonyl 1,2-migration was involved. Whereas, when indole-2-carboxarylamines were employed, indolo[3,2-*b*]quinolones were produced through direct N–H/C–H coupling. The desired products were obtained under mild reaction conditions in moderate to good yields with wide substrate scope. The natural product quindolinone was conveniently prepared by this reaction.

Introduction

Transition-metal catalyzed C–H bond functionalization has drawn great attention in synthetic organic chemistry due to its atom- and step-economic features. Indole structures have been widely used in selective C–H bond functionalization reactions because of their utility in the syntheses of bioactive compounds with an array of pharmaceutical properties.[1] On the other hand, the combination of two biologically active motifs into one molecule is highly appealing in drug discovery.[2] Indole-fused pyridones (including α-, β-, and γ-carbolinones) and indole-fused quinolinones are high-profile skeletons in a wide range of indole alkaloids with remarkable biological and pharmacological activities (Scheme 1).[3] Many elegant methodologies have been developed for the syntheses of β-carbolinones, such as intramolecular Heck reactions of 2- and 3-iodoindoles,[4] intramolecular C–H activation,[5] Au-catalyzed cycloismerization,[6] and cation-mediated [3 + 3] cyclization;[7] the synthesis approaches toward γ-carbolinones are also well established, including Pd-catalyzed intramolecular dehydrogenative annulation,[8] acid catalyzed intramolecular acylation of 2-substituted indole derivatives,[9] and amination of indole-3carboxylic acid.[10] However, compared with the intensively studied β- and γ-carbolinones, synthesis procedures for α-carbolinones are less exploited. Li *et al.* described the stereoselective synthesis of α-carbolinones through [4 + 2] annulations (Scheme 2a).[11] Ye and co-workers disclosed an efficient procedure to obtain α-carbolinones *via* N-heterocyclic carbene-catalyzed [3 + 3] annulation reactions (Scheme 2b).[12] Though these methods were effective, they focused on the synthesis of α-carbolinones of pyrido[2,3-*b*]indol-2-ones. Joule and co-workers[13] disclosed the base-promoted synthesis of indolo[3,2-*b*]quinolones using amide nitrogen as a nucleophile, in which the indole N should be protected with a phenylsulfonyl group (Scheme 2c). A transition-metal mediated or catalyzed synthesis procedure for isomeric pyrido[2,3-*b*]indol-4-one derivatives has never been reported, to the best of our knowledge. Thus, the development of straightforward and facile procedures for the synthesis of pyrido[2,3-*b*]indol-4-ones or indolo[3,2-*b*]quinolines from easily accessible starting materials is highly desirable.

Recently, we have developed an efficient procedure to γ-carbolinones *via* Pd-catalyzed dual C(sp^2)–H functionali-



Scheme 1 Some bioactive compounds with indole-fused heterocycles.

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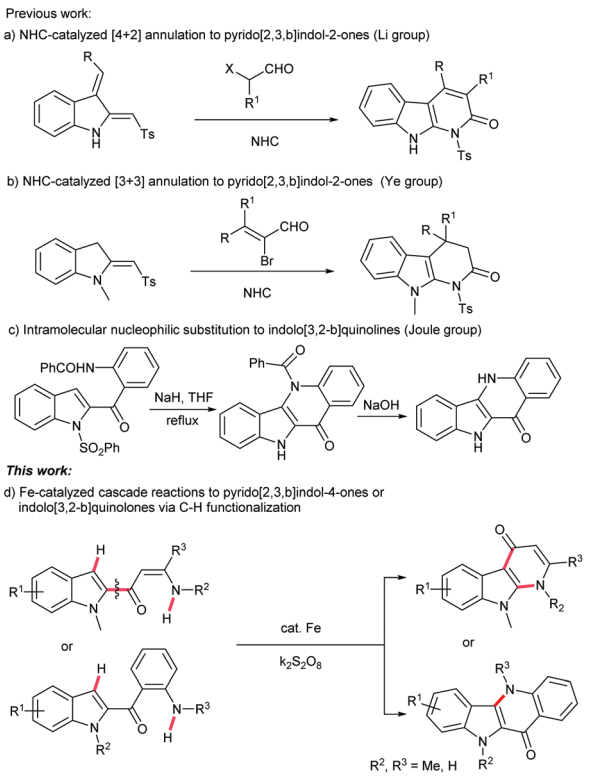


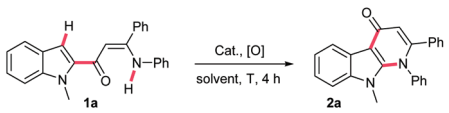
Scheme 2 Synthesis of indole-fused heterocycles.

zation of indole-2-carboxamides involving 1,2-acyl migration.[14] We have also reported novel methodologies for the synthesis heterocycles based on enaminone chemistry.[15] We envisioned that pyrido[2,3-*b*]indol-4-one derivatives might be generated *via* 1,2-acyl migration using 2-substituted indoles tethered to an enaminone moiety. Due to continuous interest in the C–H functionalization chemistry of substituted indole derivatives,[16] we herein report an efficient protocol for the selective synthesis of pyrido[2,3-*b*]indol-4-one through C3-H/N–H functionalization involving the 1,2-acyl migration from indole-2-enaminones. Furthermore, substrates of this methodology could be applied to indole-2-carboxarylamines, which afforded indolo[3,2-*b*]quinolones through the direct N–H/C–H coupling reaction (Scheme 2d). These compounds contain the same molecular skeleton as that of alkaloid quindolinone (Scheme 1, **I**), which could be converted into the cryptolepine alkaloid analogs showing antimalarial activities and strong antiplasmodial activities.[3i–k]

Results and discussion

We commenced feasibility studies with indole-2-carboxenamine **1a** as a model substrate (Table 1). It should be noted that when **1a** was subjected to our previous system[14a] $(Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (3.0 equiv.), and PivOH (6.0 equiv.) in DMF at 140 °C for 9 hours), no reaction occurred. We were encouraged to find that the desired pyrido[2,3,*b*]indol-4-one

Table 1 Optimization studies for the formation of **2a**[a]



Entry	Catalyst (mol %)	[O] (equiv.)	Solvent	*T* (°C)	Yield[b] (%)
1	$Fe(OTf)_3$ (10)	$(NH_4)_2S_2O_8$ (5)	DMSO	60	30
2	$Fe(OTf)_3$ (10)	TBHP	DMSO	60	Trace
3	$Fe(OTf)_3$ (10)	H_2O_2 (5)	DMSO	60	Trace
4	$Fe(OTf)_3$ (10)	DDQ (5)	DMSO	60	—
5	$Fe(OTf)_3$ (10)	Ag_2CO_3 (5)	DMSO	60	—
6	$Fe(OTf)_3$ (10)	$K_2S_2O_8$ (5)	DMSO	60	70
7	$Cu(OAc)_2$ (10)	$K_2S_2O_8$ (5)	DMSO	60	53
8	$Cu(OTf)_2$ (10)	$K_2S_2O_8$ (5)	DMSO	60	44
9	$Fe_2(SO_4)_3$ (10)	$K_2S_2O_8$ (5)	DMSO	60	56
10	$FeSO_4$ (10)	$K_2S_2O_8$ (5)	DMSO	60	47
11	$Sc(OTf)_3$ (10)	$K_2S_2O_8$ (5)	DMSO	60	59
12	AgOTf (10)	$K_2S_2O_8$ (5)	DMSO	60	41
13	$ZnCl_2$ (10)	$K_2S_2O_8$ (5)	DMSO	60	21
14	$Fe(OTf)_3$ (10)	$K_2S_2O_8$ (5)	DMF	60	34
15	$Fe(OTf)_3$ (10)	$K_2S_2O_8$ (5)	DMAc	60	Trace
16	$Fe(OTf)_3$ (10)	$K_2S_2O_8$ (5)	Toluene	60	—
17	$Fe(OTf)_3$ (10)	$K_2S_2O_8$ (5)	Dioxane	60	—
18	$Fe(OTf)_3$ (10)	$K_2S_2O_8$ (5)	DMSO	40	48[c]
19	$Fe(OTf)_3$ (10)	$K_2S_2O_8$ (5)	DMSO	80	57[d]
20	$Fe(OTf)_3$ (10)	$K_2S_2O_8$ (3)	DMSO	60	49
21	**$Fe(OTf)_3$ (10)**	**$K_2S_2O_8$ (4)**	**DMSO**	**60**	**74**
22	$Fe(OTf)_3$ (10)	$K_2S_2O_8$ (6)	DMSO	60	55
23	$Fe(OTf)_3$ (5)	$K_2S_2O_8$ (4)	DMSO	60	58
24	$Fe(OTf)_3$ (15)	$K_2S_2O_8$ (4)	DMSO	60	63
25	—	$K_2S_2O_8$ (4)	DMSO	60	47
26	$Fe(OTf)_3$ (10)	—	DMSO	60	—
27[e]	$Fe(OTf)_3$ (10)	$K_2S_2O_8$ (4)	DMSO	60	68

[a] Unless otherwise noted, all reactions were carried out under nitrogen on a 0.2 mmol scale in the solvent (2 mL) at 60 °C. [b] Isolated yields. [c] The reaction was carried out at 40 °C. [d] The reaction was carried out at 80 °C. [e] The reaction was carried out in air.

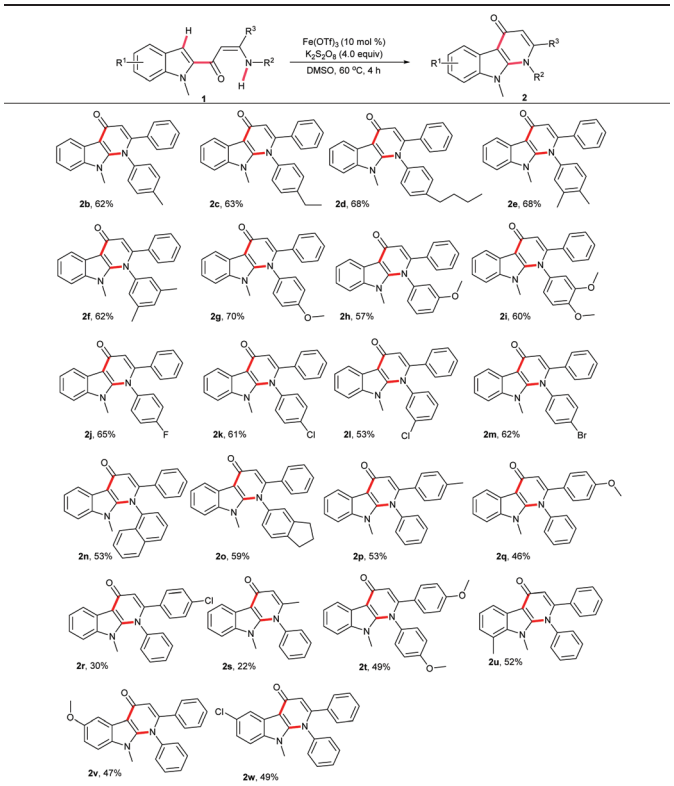
(**2a**) was formed in 30% yield in the presence of 10 mol% of $Fe(OTf)_3$ and 5.0 equiv. of $(NH_4)_2S_2O_8$ as an oxidant in DMSO (dimethyl sulfoxide) at 60 °C (entry 1). The structure of this product was further confirmed by X-ray crystal analysis (see the ESI†), and it meant that a rearrangement of the acyl group from C-2 to the C-3 position of the indole ring did occur as we expected. When the reaction was carried out using TBHP or H_2O_2 as the oxidant, only a trace amount of **2a** was detected (entries 2 and 3). DDQ or Ag_2CO_3 also gave no products (entries 4 and 5). Interestingly, $K_2S_2O_8$ resulted in a much higher yield of **2a** (entry 6). Other catalysts, such as $Cu(OAc)_2$, $Cu(OTf)_2$, $Fe_2(SO_4)_3$, $FeSO_4$, $Sc(OTf)_3$, AgOTf and $ZnCl_2$ afforded slightly lower yields (entries 7–13). Based on the optimal catalyst of $Fe(OTf)_3$, other solvents including DMF (*N*,*N*-dimethylformamide), DMAc (*N*,*N*-dimethylacetamide), toluene and dioxane were screened, and no better results were obtained (entries 14–17). Decreasing or increasing the reaction temperature in DMSO gave lower yields of the desired product, respectively (entries 18 and 19). 3.0 equiv. of $K_2S_2O_8$ rendered the corresponding **2a** in only 49% yield (entry 20). To our delight, the desired product **2a** was formed in 74% yield with 4.0 equiv. of $K_2S_2O_8$ (entry 21). Further increasing the amount

of $K_2S_2O_8$ to 6.0 equiv. provided 55% yield (entry 22). When Fe(OTf)$_3$ was reduced to 5 mol%, the corresponding **2a** was furnished in a lower yield of 58%. Whereas, increasing the catalyst loading to 15 mol% did not result in a better yield (entry 24 *vs.* entry 21). Surprisingly, **2a** could be obtained in the absence of Fe(OTf)$_3$, albeit in a low yield (entry 25). However, no reaction occurred without the addition of $K_2S_2O_8$ (entry 26). When the reaction was carried out in air, a lower yield of the desired product was observed (entry 27). Finally, the optimized reaction conditions were concluded to be 10 mol% Fe(OTf)$_3$ and 4.0 equiv. $K_2S_2O_8$ in DMSO at 60 °C under N_2 (entry 21).

With the optimal conditions established, we explored the scope of this *N*-arylation reaction for the synthesis of pyrido[2,3-*b*]indol-4-ones using a series of indole-2-carboxenamines (Table 2). Firstly, we examined the electronic effects of various *N*-aryl substituents (R^2). The electron-donating aryl substituents (4-Me, 4-Et, 4-^{n}Bu, 3,4-diMe, 3,5-diMe, and 4-OMe) were efficiently converted to the desired products **2b–2f** in good yields. The –OMe group could even be conveniently incorporated at the 3- and/or 4-position of the aryl ring (**2g–2i**). The electron-withdrawing aryl groups (4-F or 4-Cl) smoothly resulted in the corresponding products in good yields (**2j**, **2k**). Other aryl substituents including the bulky 1-naphthyl and 5-dihydro-indenyl also afforded the desired **2n** and **2o** in 53% and 59% yields, respectively. When R^2 were alkyl groups, such as benzyl and *n*-butyl, no desired products could be obtained. Then, the effect of different groups (R^3) on the alkene moiety was investigated. It was found that the electron-donating aryl groups (4-Me, 4-OMe) worked well under the standard conditions, affording the desired products **2p** and **2q** in 53% and 46% yields, respectively. The electron-withdrawing aryl group 4-Cl gave a low yield of **2r**. For alkyl groups, a methyl substituted substrate resulted in only 22% of the carbolinone **2s**. Finally, we investigated the substituent (R^1) effect on the indole ring. Substrates with electron-rich (7-Me, 5-OMe) and electron-deficient (5-Cl) groups all gave the desired products **2u–2w** in moderate yields. However, no desired product could be detected when *N*-methyl was replaced with Ts, Boc or H. A gram-scale reaction for the synthesis of **2a** could be conducted as well, delivering the desired product in 58% yield (610 mg), which nicely demonstrated the practical utility of this methodology (see the ESI†).

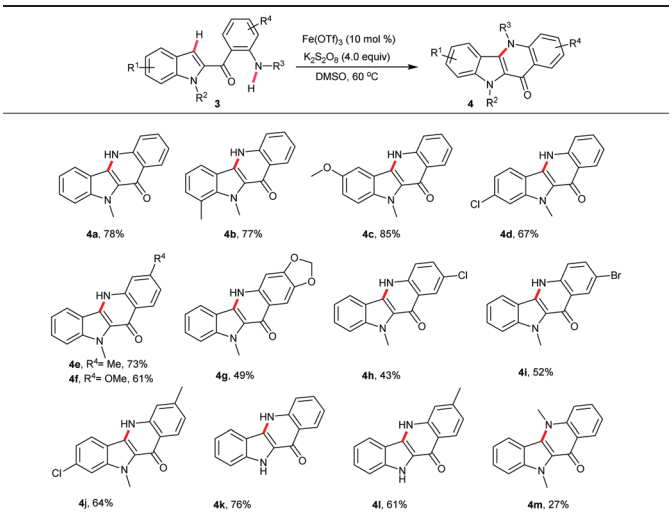
Next, we tried to further explore the substrate scope of this C–H/N–H coupling reaction. We reasoned that the replacement of the vinyl moiety in **1** with aryl groups might result in the formation of tetracyclic compounds, which contain a similar molecular skeleton to alkaloid quindolinone (Scheme 1, **I**). Then, substrate **3a** was prepared and subjected to the optimal reaction conditions. It is surprising that the corresponding product **4a** [17] has exactly the same molecular skeleton as that of alkaloid quindolinone (Scheme 1, **I**). This indicated that the direct C–H/N–H coupling occurred without acyl migration in this reaction. The substrate feasibility was also examined, and the results are shown in Table 3. R^1 substituents either with electron-donating (7-Me, 5-OMe) or electron-withdrawing (6-Cl) groups were suitable for the reaction, offering the corresponding indolo[3,2-*b*]quinolones in 67% to 85% yields (**4a–4d**) among which electron-rich aryl groups gave slightly higher yields (**4b**, 77% yield; **4c**, 85%) than those with electron-poor

Table 2 Scope of the indolyl enaminone **1**[a]



[a] Reaction conditions: **1** (0.3 mmol), Fe(OTf)$_3$ (10 mol%), $K_2S_2O_8$ (1.2 mmol) in DMSO (3 mL) at 60 °C under nitrogen unless otherwise noted. Isolated yields.

Table 3 Synthesis of indolo[3,2-*b*]quinolones[a]



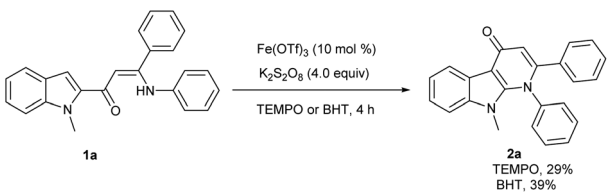
[a] Reaction conditions: **1** (0.2 mmol), Fe(OTf)$_3$ (10 mol%), $K_2S_2O_8$ (0.8 mmol) in DMSO (2 mL) at 60 °C under nitrogen unless otherwise noted. Isolated yields.

aryl groups (**4d**, 67% yield). For the R^4 substituents, good yields were obtained with either electron-rich or -poor aryl groups (**4e–4i**). It is noteworthy when R^2 is H, the reaction could also proceed smoothly, affording the desired products in high yields (**4k**, **4l**). The natural product quindolinone (**4k**)[18] was conveniently prepared in 76% yield in this reaction. Even when R^3 is a methyl group, the corresponding **4m** was obtained in 27% yield. However, no desired product could be detected when R^3 is a Ts group.

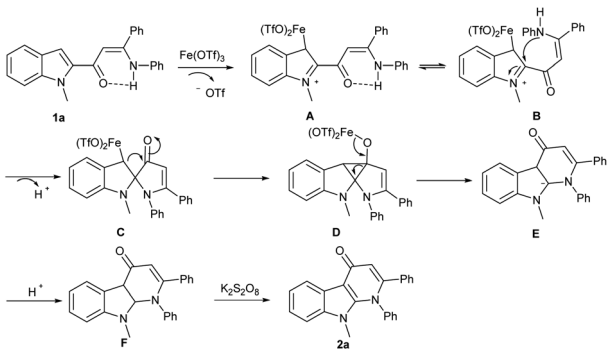
In order to gain further insight into the reaction mechanism, radical trapping experiments were employed using indole-2-carboxenamine **1a** as the substrate. The reaction was not inhibited by the addition of 2,2,6,6-tetramethylpiperidinoxy (TEMPO, 3.0 equiv.) or butylated hydroxytoluene (BHT, 2.0 equiv.), and **2a** was still obtained in moderate yields (Scheme 3).

The results suggested that a radical pathway might not be involved in this reaction.

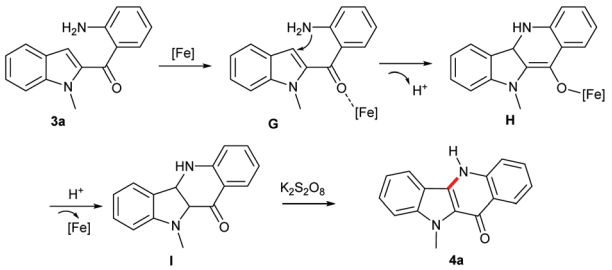
Based on the above observations and the reported literature,[14] a plausible reaction mechanism for the formation of **2a** is proposed (Scheme 4). Initially, substrate **1a** reacts with Fe $(OTf)_3$ to generate the iminium intermediate **A**, which may tautomerize to intermediate **B**. Then, a nucleophilic attack of the vinyl amine to the iminium moiety results in the spiro intermediate **C**, which is further converted to the intermediate **D** through nucleophilic addition. Subsequently, intermediate **D** undergoes 1,2-acyl migration to give intermediate **E**. Finally, the desired product **2a** is generated through protonation followed by oxidative aromatization.[19] A proposed reaction pathway to **4a** is shown in Scheme 6. It is interesting that intermediate **A** was formed from **1a** (Scheme 4), whereas, intermediate **G** was achieved through **3a** (Scheme 5) at the beginning of these reactions. We could see clearly from the ^{1}H NMR of **1a** that there is hydrogen bonding between the carbonyl oxygen and the hydrogen of amine (δ N–H 12.47 ppm), which prevents the coordination of carbonyl oxygen to the Fe catalyst, facilitating the formation of **A** from **1a**. On the other hand, there is no intramolecular hydrogen bonding between the carbonyl oxygen and the hydrogen of amine in **3a** (δ N–H 5.87 ppm). Thus, coordination of carbonyl oxygen to the Fe catalyst may occur to form intermediate **G**, which facilitates the next intramolecular Michael addition reaction (Scheme 5).



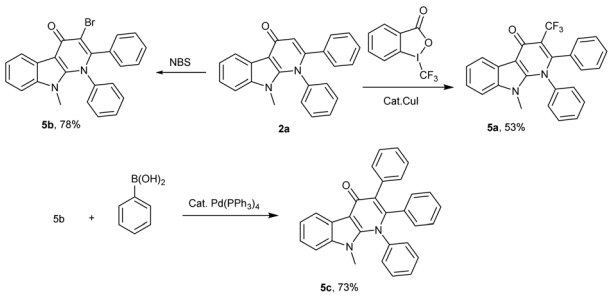
Scheme 3 Control experiment.



Scheme 4 Proposed reaction mechanism for **2a**.



Scheme 5 Possible reaction pathway to **4a**.



Scheme 6 Further modification of pyrido[2,3,*b*]indol-4-one.

To demonstrate the versatility of this C–H/N–H coupling reaction, transformations of the thus formed pyrido[2,3,*b*]indol-4-ones were performed. As shown in Scheme 6, **2a** could be easily converted to the corresponding 3-trifluoromethyl derivative **5a** in 53% yield. It also reacted readily with NBS to give 3-bromo derivative **5b** in 78% yield. X-ray crystal analysis confirms the structure of **5b** (see the ESI†). Moreover, **5b** underwent Suzuki coupling smoothly to give the phenylated product **5c**.

Conclusions

In summary, we have developed an atom-economical Fe-catalyzed protocol for the controllable synthesis of pyrido[2,3-*b*]indol-4-ones or indolo[3,2-*b*]quinolines through C–H/N–H coupling reactions. The intramolecular hydrogen bonding between the carbonyl oxygen and the hydrogen of amine in the starting materials may account for the selectivity of the outcomes.

Experimental

General procedure for the synthesis of 9-methyl-1,2-diphenyl-1,9-dihydro-4*H*-pyrido[2,3-*b*]indol-4-one

A typical procedure for the synthesis of **2a** is as follows: indolyl enaminone **1a** (0.2 mmol, 70.5 mg), $Fe(OTf)_3$ (0.02 mmol, 10.1 mg), $K_2S_2O_8$ (0.8 mmol, 216.3 mg) and DMSO (2.0 mL) were placed in an Schlenk tube under N_2. Then the reaction mixture was allowed to react at 60 °C for 4 h. After the reaction was completed as monitored by thin-layer chromatography, the reaction mixture was then quenched with water, and the water layers were extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by chromatography on silica gel (dichloromethane/ethyl acetate = 1 : 1) afforded the desired compound **2a**.

General procedure for the synthesis of 10-methyl-5,10-dihydro-11*H*-indolo[3,2-*b*]quinolin-11-one

A typical procedure for the synthesis of **4a** is as follows: the substrate **3a** (0.2 mmol, 50.1 mg), $Fe(OTf)_3$ (0.02 mmol, 10.1 mg), $K_2S_2O_8$ (0.8 mmol, 216.3 mg) and DMSO (2.0 mL) were placed in a Schlenk tube under N_2. Then the reaction mixture was allowed to react at 60 °C for 2 h. After the reaction was completed as monitored by thin-layer chromatography, the reaction mixture was then quenched with water, and the water layers were extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by chromatography on silica gel (petroleum ether/ethyl acetate = 4 : 1) afforded the desired compound **4a**.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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