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# Carbene-catalyzed asymmetric Friedel–Crafts alkylation-annulation sequence and rapid synthesis of indole-fused polycyclic alkaloids

Muhammad Anwar<sup>1</sup>, Shuang Yang<sup>1,2</sup>, Weici Xu<sup>1</sup>, Jinggong Liu<sup>3</sup>, Saima Perveen<sup>1</sup>, Xiangwen Kong<sup>1</sup>, Syeda Tazeen Zehra<sup>1</sup> & Xinqiang Fang<sup>1,2</sup> 

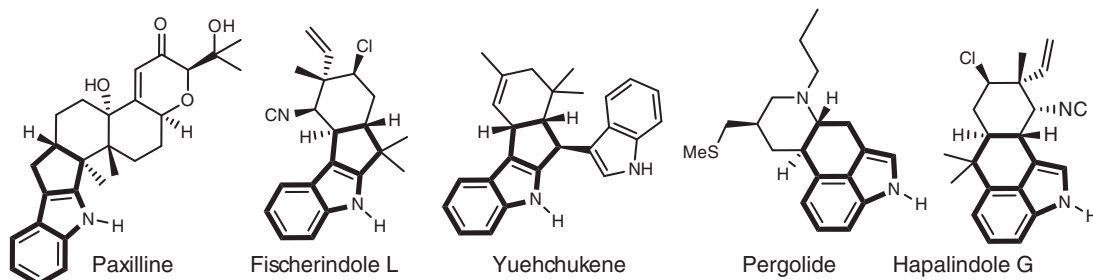
Organocatalyzed asymmetric Friedel–Craft reactions have enabled the rapid construction of chiral molecules with highly enantioselectivity enriching the toolbox of chemists for producing complex substances. Here, we report N-heterocyclic carbene-catalyzed asymmetric indole Friedel–Crafts alkylation-annulation with  $\alpha,\beta$ -unsaturated acyl azolium as the key intermediate, affording a large variety of indole-fused polycyclic alkaloids with excellent diastereo- and enantioselectivities. The reaction mechanism is also investigated, and the reaction products can be easily converted to highly functionalized indole frameworks with different core structures.

<sup>1</sup>State Key Laboratory of Structural Chemistry, and Key Laboratory of Coal to Ethylene Glycol and Its Related Technology, Fujian Institute of Research on the Structure of Matter, Center for Excellence in Molecular Synthesis, University of Chinese Academy of Sciences, 350100 Fuzhou, China. <sup>2</sup>Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, 200032 Shanghai, China. <sup>3</sup>Orthopedics Department, Guangdong Provincial Hospital of Traditional Chinese Medicine, 510120 Guangzhou, China. Correspondence and requests for materials should be addressed to X.F. (email: [xqfang@fjirsm.ac.cn](mailto:xqfang@fjirsm.ac.cn))

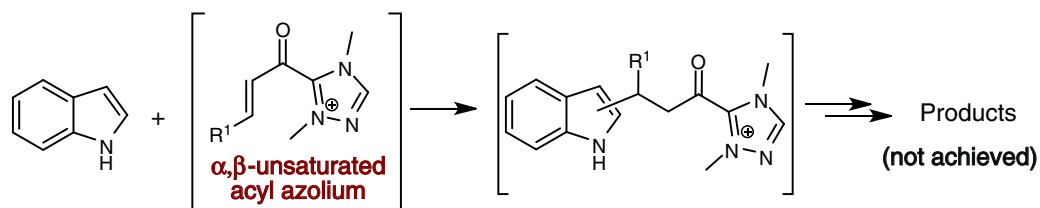
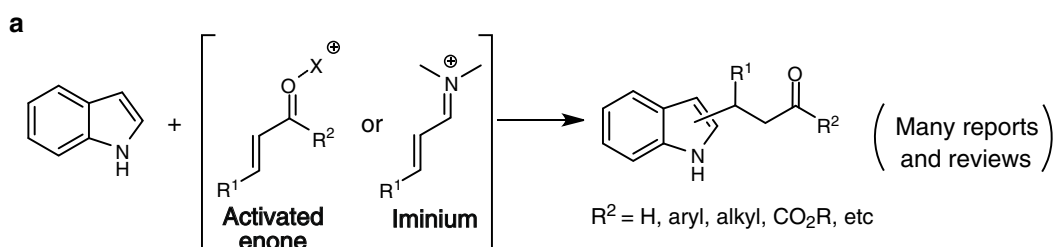
Indole-fused polycyclic scaffolds are ubiquitous in a large number of bioactive molecules and pharmaceuticals, such as paxilline (potassium channel blocker), fischerindole L (antifungal activity), yuehchukene (strong anti-implantation activity), pergolide (medicine in the treatment of Parkinson's disease), and hapalindole G (antimycotic activities) (Fig. 1)<sup>1–4</sup>. However, multiple steps have been used to make the key skeletons of these molecules, thus resulting in relatively low efficiency and atom

economy<sup>5–7</sup>. Therefore, developing a protocol that can rapidly construct these polycyclic indole units is still highly desirable.

Asymmetric indole functionalization has been a field of intense focus in the recent decade. Friedel–Crafts alkylation of indoles using enones/enals has been a powerful strategy to achieve the above purpose<sup>8–12</sup>. Carbonyl activation of enones by Lewis/Brønsted acids and activation of enals via iminiums are prevalent activation modes (Fig. 2a)<sup>8–12</sup>. However, exploiting new

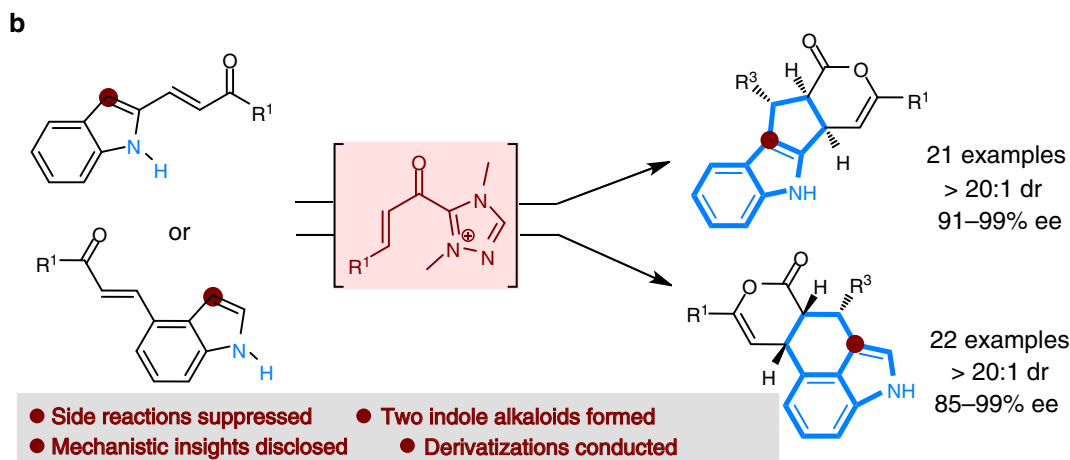


**Fig. 1** Selected indole-fused natural products and pharmaceuticals

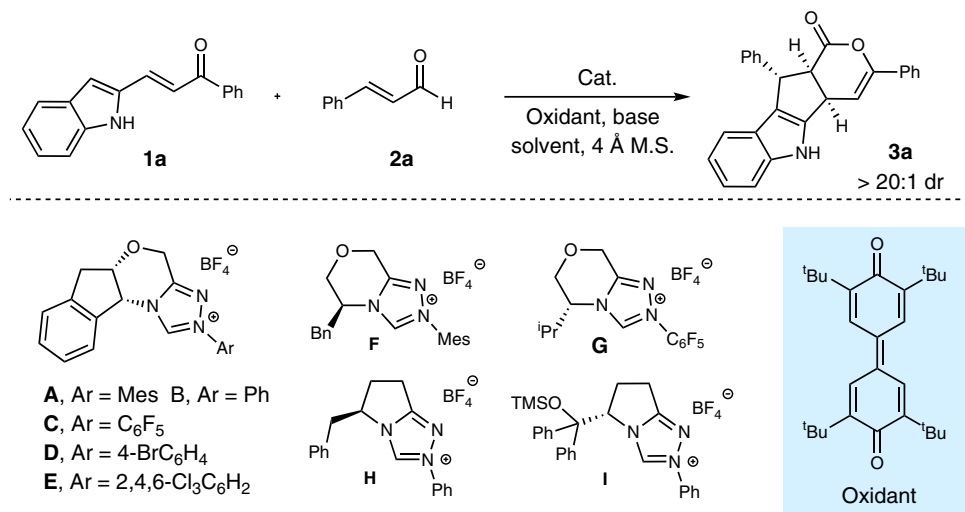


**Challenges of using  $\alpha,\beta$ -unsaturated acyl azolium:**

- Much lower electrophilicity ( $10^3$ – $10^6$  lower than iminiums)
- Aza-Michael addition      ● N-acylation      ● Catalyst recycling



**Fig. 2** Activation of enone/enals in indole Friedel–Crafts alkylation. **a** Activation modes of enones or enals in asymmetric indole Friedel–Crafts alkylation. **b** This work: NHC-catalyzed indole Friedel–Crafts alkylation and annulation



**Fig. 3** Model system used for reaction optimization. Conditions used for optimization of the catalyst, base, solvent, and temperature can be found in Table 1

activation modes of enones/enals holds great importance to further promote the influence of this strategy. On the other side, N-heterocyclic carbene (NHC)-catalyzed reactions<sup>13–25</sup> mediated by  $\alpha,\beta$ -unsaturated acyl azoliums<sup>19,26–29</sup> have attracted increasing research interests owing to the great value in chiral cyclic molecule synthesis. Annulations of a series of carbon-based nucleophiles<sup>30–51</sup> with  $\alpha,\beta$ -unsaturated acyl azoliums have been reported by Studer, Lupton, Bode, Enders, Chi, Ye, You, Du, Hui, Biju, and other groups. Additionally, the use of heteroatoms (N or S) as nucleophiles to react with  $\alpha,\beta$ -unsaturated acyl azoliums has also been disclosed<sup>52–56</sup>. Despite these elegant reports, using  $\alpha,\beta$ -unsaturated acyl azolium as the basic enal activation mode to achieve indole Friedel–Crafts alkylation remains a significant challenge to date (Fig. 2a). The difficulties arise from: (1) according to Studer and Mayr’s study, such a reaction is unfavorable because the electrophilicity of  $\alpha,\beta$ -unsaturated acyl azoliums is  $10^3$ – $10^6$  lower than that of iminiums<sup>57</sup>; (2) the competitive aza-Michael addition<sup>52–54,56</sup> and N-acylation<sup>58</sup> reactions are easy to occur under basic conditions; (3) the difficulty in regenerating NHC catalyst. Recently, Studer et al. achieved the intramolecular dearomative indole acylation via NHC catalysis<sup>59</sup>.

Here we address these challenges by installing an enone unit into indoles to trigger the following annulation, which provides additional driving force for the Friedel–Crafts alkylation, and the protocol affords a series of indole-fused polycyclic alkaloids with excellent diastereo- and enantioselectivities (Fig. 2b).

## Results

**Optimization of the reaction conditions.** Readily available indole enone **1a** and enal **2a** were selected to test our hypothesis (Fig. 3). The reaction using catalyst **A**<sup>60–62</sup> with Cs<sub>2</sub>CO<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> led to the desired product **3a** with excellent 99% ee, but in only 15% yield, and **1a** was mostly recovered, indicating the low reactivity of  $\alpha,\beta$ -unsaturated acyl azolium towards **1a** (Table 1, entry 1). Then we tested catalysts<sup>60–62</sup> **B**, **C**, **D**, and **E**, but in all cases, trace amount of **3a** was formed (Table 1, entry 2). Catalyst **F** produced **3a** with slightly lower yield and ee (Table 1, entry 3), and catalysts **G**, **H**, and **I** retarded the reaction (Table 1, entry 4). To our delight, increasing the temperature to 40 °C enhanced the yield (Table 1, entry 5), but other bases, such as K<sub>2</sub>CO<sub>3</sub>, KOAc, KO<sup>t</sup>Bu, and DBU led to inferior results (Table 1, entries 6–9). CHCl<sub>3</sub> or DCE proved inefficient and THF and toluene impeded

**Table 1** Reaction condition optimization<sup>a</sup>

Entry	Cat.	Base	Solvent	Temp. (°C)	Yield ( <b>3a</b> , %) <sup>b</sup>	ee ( <b>3a</b> , %) <sup>c</sup>
1	<b>A</b>	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	rt	15	99
2	<b>B</b> , <b>C</b> , <b>D</b> , <b>E</b>	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	rt	Trace	–
3	<b>F</b>	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	rt	13	94
4	<b>G</b> , <b>H</b> , <b>I</b>	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	rt	Trace	–
5	<b>A</b>	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	40	41	94
6	<b>A</b>	K <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	40	23	96
7	<b>A</b>	KOAc	CH <sub>2</sub> Cl <sub>2</sub>	40	15	98
8	<b>A</b>	KO <sup>t</sup> Bu	CH <sub>2</sub> Cl <sub>2</sub>	40	21	56
9	<b>A</b>	DBU	CH <sub>2</sub> Cl <sub>2</sub>	40	Trace	–
10	<b>A</b>	Cs <sub>2</sub> CO <sub>3</sub>	CHCl <sub>3</sub>	40	16	99
11	<b>A</b>	Cs <sub>2</sub> CO <sub>3</sub>	DCE	40	18	97
12	<b>A</b>	Cs <sub>2</sub> CO <sub>3</sub>	THF	40	Trace	–
13	<b>A</b>	Cs <sub>2</sub> CO <sub>3</sub>	Toluene	40	Trace	–
14 <sup>d</sup>	<b>A</b>	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	50	61	99
15 <sup>e</sup>	<b>A</b>	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	50	76	99

<sup>a</sup>Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), NHC (0.04 mmol), oxidant (0.24 mmol), base (0.3 mmol), solvent (2 mL), 4 Å M.S. (200 mg), under argon atmosphere, rt

<sup>b</sup>Isolated yields based on **1a**

<sup>c</sup>Determined via HPLC analysis on a chiral stationary phase

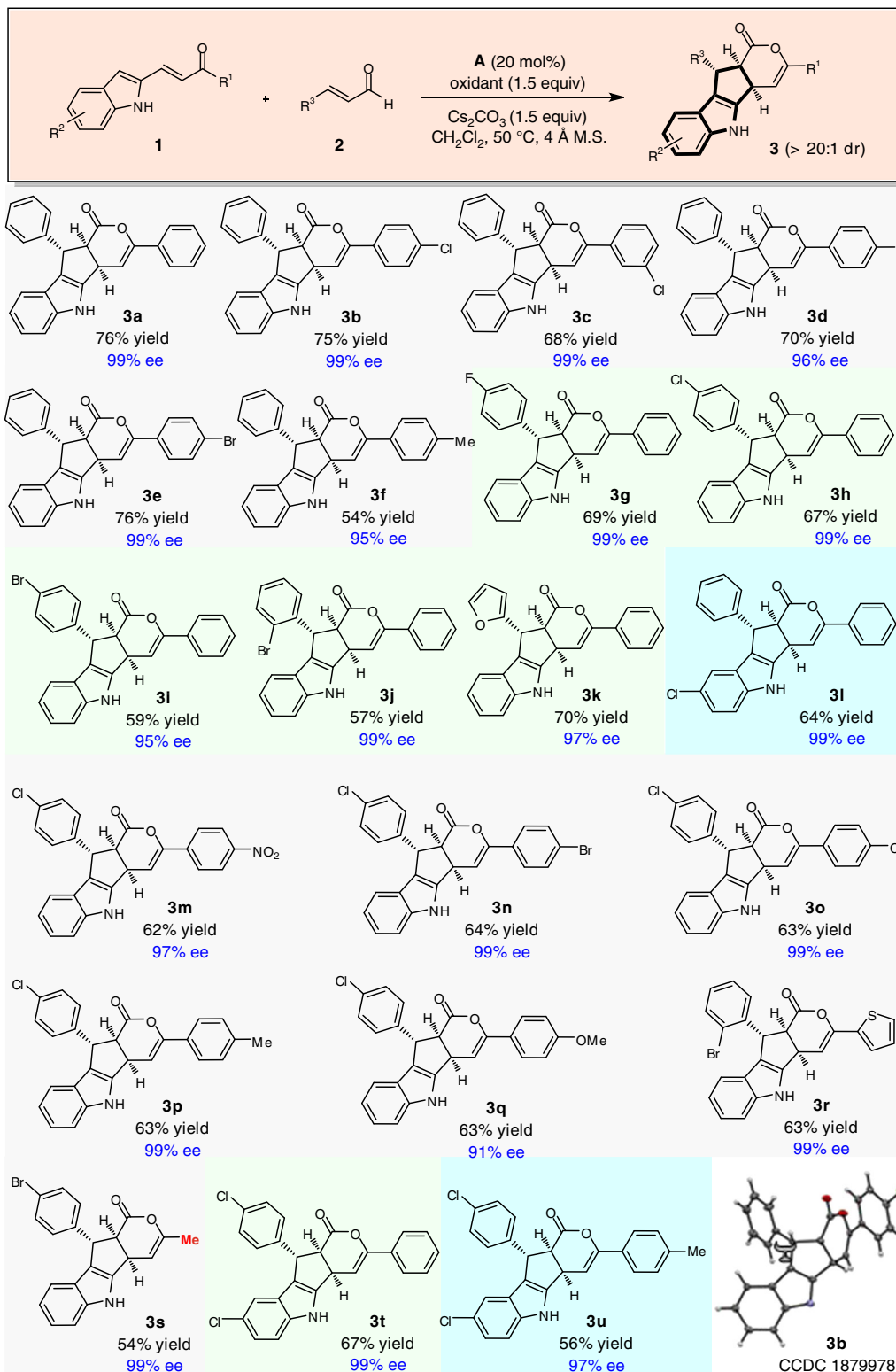
<sup>d</sup>Oxidant (0.3 mmol) and 4 Å M.S. (500 mg) were used

<sup>e</sup>Oxidant (0.3 mmol) and 4 Å M.S. (800 mg) were added

the reaction (Table 1, entries 10–13). Gratifyingly, using more oxidant and M.S. and higher temperature could further enhance the yield (Table 1, entry 14), and **3a** could be finally obtained in an acceptable 76% yield without affecting the enantioselectivity (Table 1, entry 15).

## Scope of 1,2,3,4-tetrahydrocyclopenta[b]indole alkaloids.

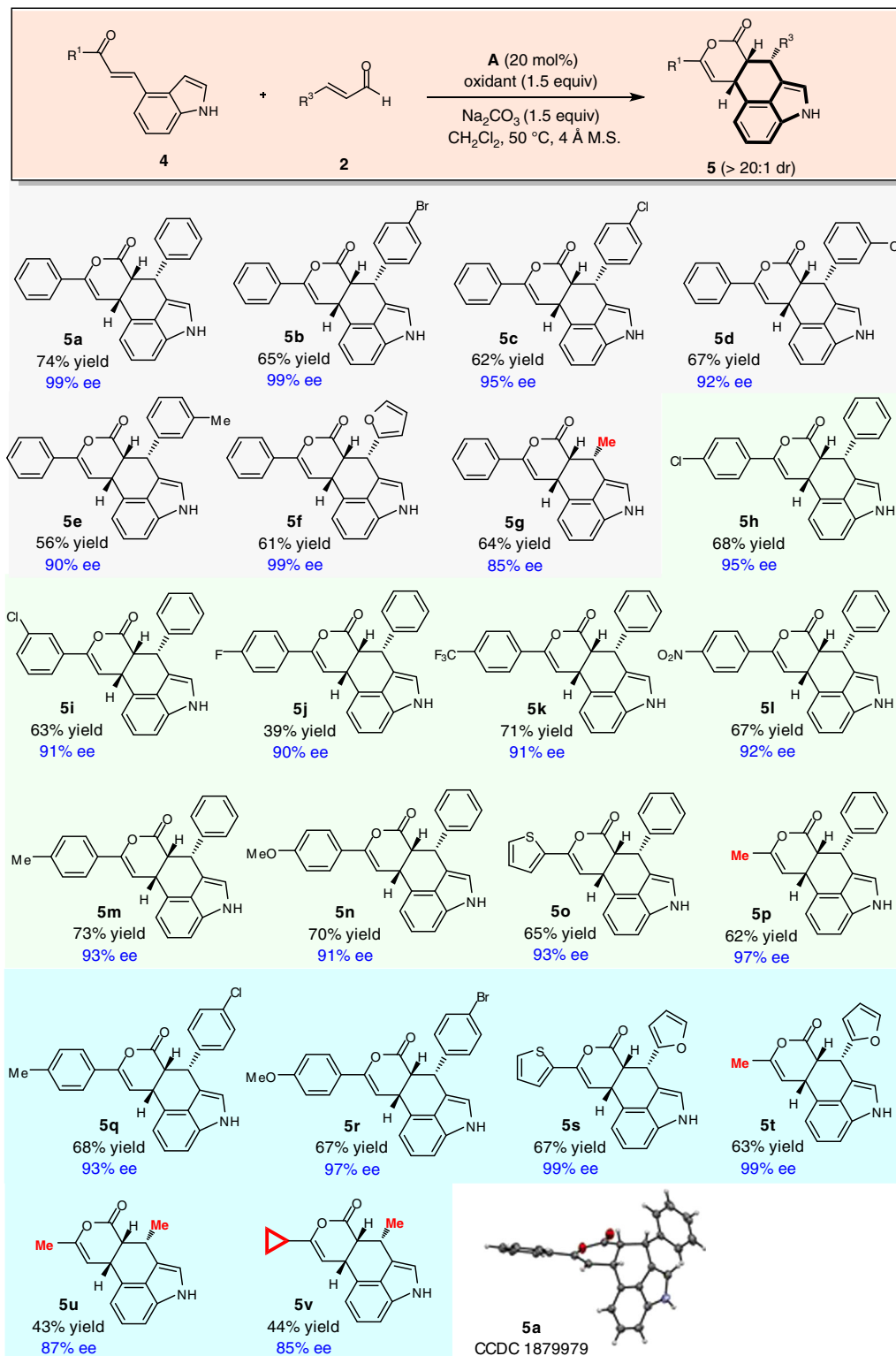
Having identified the optimal conditions, we then evaluated the generality and limitations of this protocol. We found that the reaction could tolerate the introduction of electron-withdrawing 4-Cl, 3-Cl, 4-F, 4-Br, and electron-donating 4-Me substituents into the phenyl rings of the enone units, delivering **3b–3f** with excellent 95–99% ee (Fig. 4, **3b–3f**). Then we tested aryl enals equipped with F, Cl, and Br groups at the phenyl rings, and they all worked well under the optimal conditions, releasing **3g–3j** with excellent 95–99% ee (Fig. 4, **3g–3j**). Furan-substituted enal



**Fig. 4** Scope of 1,2,3,4-tetrahydrocyclopenta[b]indole alkaloids. Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), **A** (0.04 mmol), oxidant (0.3 mmol),  $\text{Cs}_2\text{CO}_3$  (0.3 mmol),  $\text{CH}_2\text{Cl}_2$  (2 mL), 4 Å M.S. (800 mg), under argon atmosphere, 50 °C. All yields were isolated yields based on **1**. All ee values were determined via HPLC analysis on a chiral stationary phase

was surveyed and **3k** was formed smoothly in 70% yield with 97% ee (Fig. 4, **3k**). Enals with electron-rich aryl groups showed low conversion, but adding a Cl group into the indole ring had little influence on the outcome, affording **3l** with 99% ee (Fig. 4, **3l**). Moreover, varying simultaneously the substituent patterns

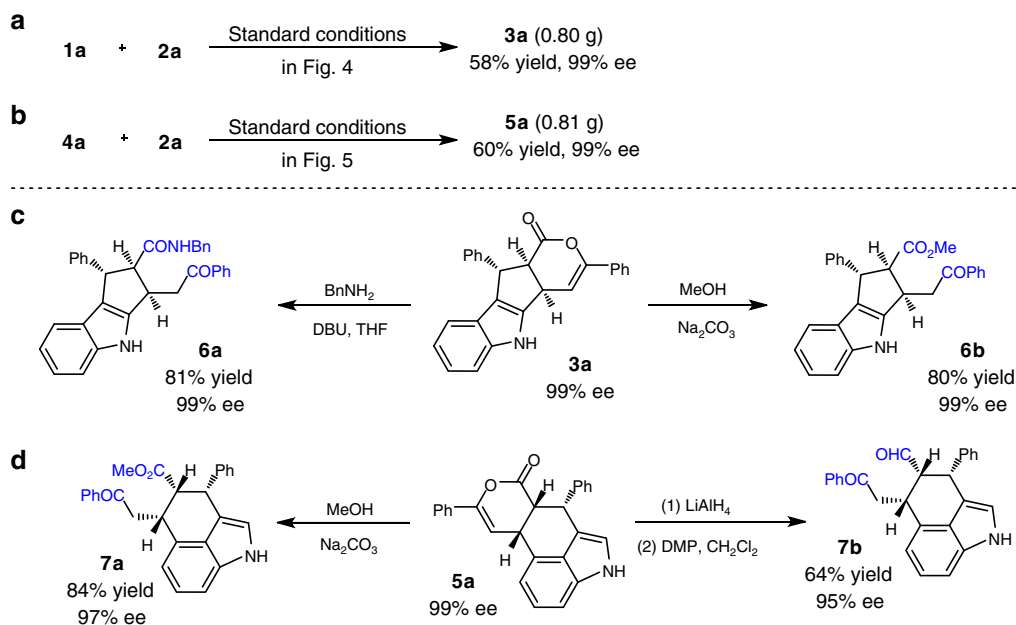
of both enones and enals proved possible, delivering **3m–3r** with 91–99% ee (Fig. 4, **3m–3r**). Furthermore, methyl enone also worked well, forming **3s** with 99% ee (Fig. 4, **3s**). Additionally, enone with a Cl atom at the indole moiety could also cyclize with 4-Cl- $\text{C}_6\text{H}_4$ -substituted enal, affording **3t** in 67% yield with



**Fig. 5** Scope of 1,3,4,5-tetrahydrobenzo[cd]indole alkaloids. Reaction conditions: **4** (0.2 mmol), **2** (0.3 mmol), **A** (0.04 mmol), oxidant (0.3 mmol),  $\text{Na}_2\text{CO}_3$  (0.3 mmol),  $\text{CH}_2\text{Cl}_2$  (2 mL), 4 Å M.S. (800 mg), under argon atmosphere, 50 °C. All yields were isolated yields based on **4**. All ee values were determined via HPLC analysis on a chiral stationary phase

99% ee (Fig. 4, **3t**). Finally, when three substituted groups were introduced into the phenyl ring of enal, indole, and ketone unit, respectively, product **3u** was also liberated with excellent 97% ee (Fig. 4, **3u**). In all cases, the products were obtained as single-diastereoisomers, and the absolute configuration of **3b** was determined by the single crystal X-ray structure analysis (Fig. 4).

**Scope of 1,3,4,5-tetrahydrobenzo[cd]indole alkaloids.** Next we investigated the possibility of making 1,3,4,5-tetrahydrobenzo[cd]indoles, which are also key units in many bioactive molecules. Indole enone **4a** could react with **2a** smoothly under slightly modified conditions, releasing **5a** in 74% yield with excellent 99% ee (Fig. 5, **5a**;  $\text{Cs}_2\text{CO}_3$  led to 55% yield). Then we surveyed a series



**Fig. 6** Scale-up synthesis and product derivatizations. **a** Scale-up synthesis of **3a**. **b** Scale-up synthesis of **5a**. **c** Product derivatizations of **3a**. **d** Product derivatizations of **5a**

of enals bearing substituents with different electronic properties, and in all cases, the corresponding products were formed with excellent ee (Fig. 5, **5b–5e**). Furan-substituted enal also worked well, affording **5f** in 99% ee (Fig. 5, **5f**). Aliphatic methyl enal proved amenable and **5g** was formed with 85% ee in 64% yield (Fig. 5, **5g**). Moreover, the reaction tolerated a variety of enones with both electron-poor and electron-rich aryl substituents, allowing access to **5h–5n** with 90–95% ee (Fig. 5, **5h–5n**). The reactions using thiophene or methyl-substituted enones proved successful, delivering **5o** and **5p** with excellent 93% and 97% ee, respectively (Fig. 5, **5o** and **5p**). Finally, we investigated the simultaneous variations of both enal and enone substituents, and different combination modes, such as aryl/aryl, aryl/alkyl, and alkyl/alkyl were all tolerated, and good to excellent ee values of the products were observed (Fig. 5, **5q–5v**). The absolute configuration of **5a** was determined by the single crystal X-ray structure analysis (Fig. 5)<sup>17</sup>.

**Scale-up synthesis and product derivatizations.** Scale-up synthesis of **3a** and **5a** proved possible, with no erosion of the ee detected (Fig. 6a, b). Furthermore, various simple reactions can be used to afford amide **6a**, ester **6b/7a**, and aldehyde **7b** (Fig. 6c, d). The newly formed functional groups in these compounds can be readily used for further transformations.

**Mechanistic studies.** A series of experiments were conducted to gain more mechanistic insights (Fig. 7). The reaction using N-methyl indole enone **1a'** or **4a'** failed to deliver any products (Fig. 7a), indicating the vital role of indole N–H in the reaction. However, both  $\text{Cs}_2\text{CO}_3$  and  $\text{Na}_2\text{CO}_3$  cannot deprotonate indole N–H, showing that the nitrogen anion is not involved in the reaction (Fig. 7b). With catalytic amount of base or even without base, the reaction can still occur, albeit in lower yields (Fig. 7c). Using anion substrate **4aa** we got N-acylation product **8a** in 51% yield, and no annulation product was detected (Fig. 7d), which further excluded the existence of nitrogen anion in the catalytic cycle. Then, N-deuterium **4ab** and 3-deuterium **4ac** were used, but the reaction only led to **5a**, indicating that proton transfer from indole to enal-derived intermediates may not occur

(Fig. 7e). Furthermore, the reaction using deuterium enal **2a-d<sub>1</sub>** resulted in no erosion of D atom in the product, but the reaction was obviously sluggish, and N-acylation product was also formed (Fig. 7f). However, using **2a-d<sub>3</sub>** we observed apparent D/H exchange during the reaction and only 63% deuterium was kept at the  $\alpha$ -position of the ester moiety, indicating the probable equilibrium between azolium enolate and acyl azolium intermediates. Using **4m** as the reference, we could estimate the KIE of the reaction to be 2.0, indicating that indole 3-position addition/C–H bond cleavage (from **I** to **II**) is possibly involved in the rate-determining step (RDS) (Fig. 7g).

A plausible mechanism was proposed in Fig. 7h. The reaction of enal and NHC under oxidative conditions affords unsaturated acyl azolium **I**. The Friedel–Crafts reaction of indole enone and **I** results in enolate **II** (see the Supplementary Material for more details of this step); **II** can be protonated to produce **III**, and the process is reversible. Then the Michael addition happens to form a new enolate **IV**, and after lactonization, product **3a** is produced, together with the regeneration of free carbene. Similar process happens when enone **4a** is used, producing **5a** as the final product.

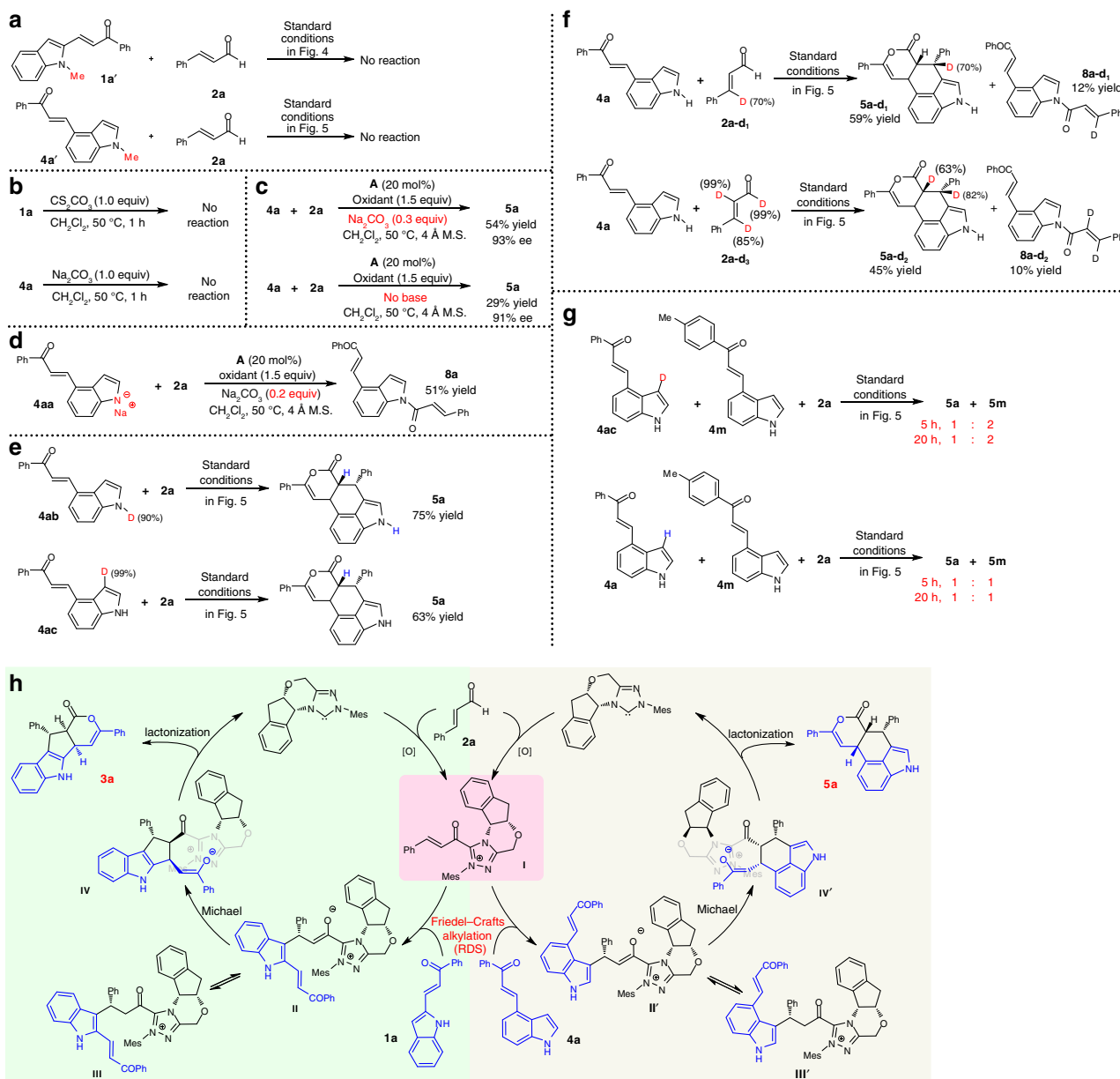
## Discussion

In summary, we have disclosed the NHC-catalyzed asymmetric indole Friedel–Crafts alkylation-annulation using  $\alpha,\beta$ -unsaturated acyl azoliums for the first time, and the protocol afforded a large variety of indole-fused polycyclic alkaloids with excellent diastereo- and enantioselectivities. The competitive side reactions were suppressed, and mechanistic studies revealed that indole 3-position C–H bond cleavage is involved in the rate-determining step, and rapid equilibrium between azolium enolate and acyl azolium exists. This work further expands the application of NHC catalysis, and is also a valuable addition to the field of indole Friedel–Crafts alkylation. Further studies on NHC-catalyzed annulation reactions are ongoing in our group.

## Methods

**General procedure for the annulation reaction of **1** and **2**.** Substrate **1a** (247.10 mg 1.00 mmol), oxidant (612.45 mg, 1.50 mmol), 4 Å M.S. (2.00 g),  $\text{Cs}_2\text{CO}_3$  (488.69 mg, 1.50 mmol) and catalyst (83.84 mg, 0.20 mmol) were added to  $\text{CH}_2\text{Cl}_2$





**Fig. 7** Mechanistic studies and proposed mechanism. **a** Reactions using N-methyl-substituted indole enones. **b** Reactions in the absence of catalyst. **c** Reactions of **4a** with **2a** with catalytic amount of base or without base. **d** Reaction of indole anion. **e** Reactions of deuterium-indole substrates. **f** Reactions of **4a** with deuterium-enals. **g** Evaluation of the KIE of the reaction. **h** Proposed mechanism

(5 mL) at room temperature under argon atmosphere. After 15 min, **2a** (198.09 mg, 1.50 mmol) was added into the reaction system. The reaction was stirred at 50 °C for 20 h. After that the residue was filtered on celite, the solvent was removed under reduced pressure and the residue was purified by flash chromatography with petroleum ether/ethyl acetate (v:v = 10:1) as eluent to afford the product **3a** (271.5 mg, 72% yield).

**General procedure for the annulation reaction of 4 and 2.** Substrate **4a** (247.10 mg, 1.00 mmol), oxidant (612.45 mg, 1.50 mmol), 4 Å M.S. (3.00 g), Na<sub>2</sub>CO<sub>3</sub> (159.00 mg, 1.50 mmol) and catalyst (83.84 mg, 0.20 mmol) were added to CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at room temperature under argon atmosphere. After 15 min, **2a** (198.08 mg, 1.50 mmol) was added into the reaction system. The reaction was stirred at 50 °C for 20 h. After that the residue was filtered on celite, the solvent was removed under reduced pressure and the residue was purified by flash chromatography with petroleum ether/ethyl acetate (v:v = 10:1) as eluent to afford the product **5a** (279.0 mg, 74% yield).

**Typical procedure for the preparation of substrates.** See Supplementary methods for more details.

**Procedure for the product derivatizations.** See Supplementary methods for more details.

**Deuterium experiments.** See Supplementary Figs. 1–6.

**Proposed indole Friedel-Crafts alkylation mechanism.** See Supplementary Fig. 7.

**<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of substrates and products.** See Supplementary Figs. 8–79.

**HPLC spectra of products.** See Supplementary Figs. 80–126.

**Crystallography.** The CIF files for compounds **3b** and **5a** are available in Supplementary Data 1 and 2. Crystal data and structure refinement are shown in Supplementary Tables 1 and 2.

## Data availability

Data for the crystal structures reported in this paper have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under the deposition numbers CCDC 1879978 (**3b**) and CCDC 1879979 (**5a**). Copies of these data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif). All other data supporting the findings of this study, including compound characterization, are available within the paper and its Supplementary Information files, or from the corresponding authors on request.

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## Author contributions

X.F. designed the project. M.A. conducted most of the experiments. S.P., X.K. and S.T.Z. conducted part of the experiments. X.F. wrote the manuscript. M.A. and S.Y. prepared the Supplementary Material. J.L. tested the single crystal structures. W.X. and S.Y. contributed to discussions.

## Additional information

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