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

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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 α,β-unsaturated acyl azolium as the key intermediate, affording a large variety of indole-fused polycyclic alkaloids with excellent diastereomeric 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.
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)1–4. However, multiple steps have been used to make the key skeletons of these molecules, thus resulting in relatively low efficiency and atom economy5–7. 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 purpose8–12. Carbonyl activation of enones by Lewis/Brønsted acids and activation of enals via iminiums are prevalent activation modes (Fig. 2a)8–12. However, exploiting new
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\(^{13–25}\) mediated by \(\alpha,\beta\)-unsaturated acyl azoliums\(^{19,26–29}\) have attracted increasing research interests owing to the great value in chiral cyclic molecule synthesis. Annulations of a series of carbon-based nucleophiles\(^{30–51}\) with \(\alpha,\beta\)-unsaturated acyl azoliums have been reported by Studer, Lupton, Bode, Enders, Chi, Ye, You, Du, Hui, 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\(^{52–56}\). Despite these elegant reports, using \(\alpha,\beta\)-unsaturated acyl azolium as the basic 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 of the electrophilicity of \(\alpha,\beta\)-unsaturated acyl azoliums is \(10^4–10^6\) lower than that of iminiums\(^{57}\); (2) the competitive aza-Michael addition\(^{52–54,56}\) and N-acylation\(^{58}\) reactions are easy to occur under basic conditions; (3) the difficulty in regenerating NHC catalysis. Recently, Studer et al. achieved the intramolecular deamortative indole acylation via NHC catalysis\(^{59}\).

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\(^{60–62}\) with Cs\(_2\)CO\(_3\) in CH\(_2\)Cl\(_2\) 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 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 2), 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\(_2\)CO\(_3\), KOAc, KO\(_2\)Bu, and DBU led to inferior results (Table 1, entries 6–9). CH\(_2\)Cl\(_2\) or DCE proved inefficient and THF and toluene impeded 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

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**Table 1 Reaction condition optimization**

| Entry | Cat. | Base    | Solvent | Temp. (°C) | Yield (3a, %) b | ee (3a, %) c |
|-------|------|---------|---------|------------|----------------|--------------|
| 1     | A    | Cs\(_2\)CO\(_3\) | CH\(_2\)Cl\(_2\) | rt | 15 | 99 |
| 2     | B, C | Cs\(_2\)CO\(_3\) | CH\(_2\)Cl\(_2\) | rt | Trace | - |
| 3     | F    | Cs\(_2\)CO\(_3\) | CH\(_2\)Cl\(_2\) | rt | 13 | 94 |
| 4     | G, H | Cs\(_2\)CO\(_3\) | CH\(_2\)Cl\(_2\) | rt | Trace | - |
| 5     | A    | Cs\(_2\)CO\(_3\) | CH\(_2\)Cl\(_2\) | 40 | 41 | 94 |
| 6     | A    | K\(_2\)CO\(_3\) | CH\(_2\)Cl\(_2\) | 40 | 23 | 96 |
| 7     | A    | KOAc | CH\(_2\)Cl\(_2\) | 40 | 15 | 98 |
| 8     | A    | KO\(_2\)Bu | CH\(_2\)Cl\(_2\) | 40 | 21 | 56 |
| 9     | A    | DBU | CH\(_2\)Cl\(_2\) | 40 | Trace | - |
| 10    | A    | Cs\(_2\)CO\(_3\) | CH\(_3\)Cl | 40 | 16 | 99 |
| 11    | A    | Cs\(_2\)CO\(_3\) | DCE  | 40 | 18 | 97 |
| 12    | A    | Cs\(_2\)CO\(_3\) | THF  | 40 | Trace | - |
| 13    | A    | Cs\(_2\)CO\(_3\) | Toluene | 40 | Trace | - |
| 14    | A    | Cs\(_2\)CO\(_3\) | CH\(_2\)Cl\(_2\) | 50 | 61 | 99 |
| 15    | A    | Cs\(_2\)CO\(_3\) | CH\(_2\)Cl\(_2\) | 50 | 76 | 99 |

aReaction conditions: 1a (0.3 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
bIsolated yields based on 1a
cDetermined via HPLC analysis on a chiral stationary phase
\(\text{Oxidant (0.3 mmol) and 4 Å M.S. (500 mg) were used}
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**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.
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-C₆H₄-substituted enal, affording 3t in 67% yield with

**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), Cs₂CO₃ (0.3 mmol), CH₂Cl₂ (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.
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; Cs₂CO₃ led to 55% yield). Then we surveyed a series

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**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), Na₂CO₃ (0.3 mmol), CH₂Cl₂ (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.
However, both Cs2CO3 and Na2CO3 cannot deprotonate indole (Fig. 7a), indicating the vital role of indole N in derivatizations of from indole to enal-derived intermediates may not occur.

The reaction using N-d. The newly formed functional groups in these compounds can yield, and no annulation product was detected (Fig.7d), which further excluded the existence of nitrogen anion in the catalytic process.

In summary, we have disclosed the NHC-catalyzed asymmetric indole Friedel–Crafts alkylation-annulation using a,β-unsaturated acyl azolium for the first time, and the protocol afforded a large variety of indole-fused polycyclic alkaloids with excellent dia-stereo- 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 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.

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), Cs2CO3 (488.69 mg, 1.50 mmol) and catalyst (83.84 mg, 0.20 mmol) were added to CH2Cl2
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

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.

1H NMR and 13C 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.
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.

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