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Enantioselective synthesis of saddle-shaped eight-membered lactones with inherent chirality via organocatalytic high-order annulation

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Inherently chiral medium-ring derivatives have important applications in many research fields, such as materials science, molecular recognition, and asymmetric catalysis. However, the enantioselective assembly of these molecules, especially by organocatalytic strategies, remains a formidable challenge, and few methods are available. Here, we report the enantioselective NHC-catalyzed (NHC: N-heterocyclic carbenes) formal high-order (5 + 3) annulation of 1-(2-indolyl)naphthalen-2-ols with ynals. In the presence of an NHC pre-catalyst, base, Lewis acid and oxidant, this protocol enables the catalytic formation of C–C and C-O bonds, providing practical and facile access to an array of inherently chiral saddle-shaped eight-membered lactones featuring an oxocin-2-one scaffold with structural diversity in good efficiency and excellent enantiocontrol. Moreover, the scale-up preparation and representative late-stage transformations of the eight-membered lactones further demonstrate the application potential of this synthetic technology.

Chirality is a fundamental characteristic of nature and covers various basic macromolecules, such as proteins, sugars, amino acids, and enzymes. Moreover, chiral molecules have a wide presence in natural products, drugs, and organic materials. Generally, the vast majority of chiral molecules contain one or more chiral elements, namely, central chirality, axis chirality, or/and planar chirality (Fig. 1a)[1–8]. In addition to these substructures, which are responsible for generating chirality, the entire molecular architecture can also exhibit chirality, as exemplified by helicenes and helicene-like compounds, which are helically twisted structures (Fig. 1a)[9–14]. In contrast, other chiral molecules without the aforementioned chiral elements have been largely overlooked. In 1994, the Böhmer group reported that calix[4]arenes with nonsymmetric substituents have chirality because the skeleton is deprived of symmetry. Unlike conventional central, axial, planar, or helical chirality, this unique chirality is defined as the concept of "inherent chirality" to decipher the intrinsic nature of molecules with concave and rigid conformations (Fig. 1a)[15]. In addition to calix[4]arenes[16–18], inherent chirality has been discovered in some aromatic medium-sized rings with rigid nonplanar conformations[19–22]. For example, tetraphenylene derivatives, featuring an eight-membered polyarene composed of four alternating *ortho*-annulated benzenes, demonstrate a unique rigid saddle-shaped geometry and have inherent chirality with unsymmetrical substitution[23–27]. However, the application of asymmetric catalysis for the syntheses of these inherently chiral medium-sized cycles, especially those bearing a saddle-shaped eight-membered ring, is still in its infancy, and the corresponding literature documented thus far is quite limited. In 2009, Shibata and coworkers pioneered a Rh-catalyzed asymmetric cycloaddition of two triynes toward chiral eight-membered tetraphenylenes (Fig. 1b, left, 1st)[28]. In 2021, Luo, Zhu and coworkers reported elegant palladium-catalyzed double

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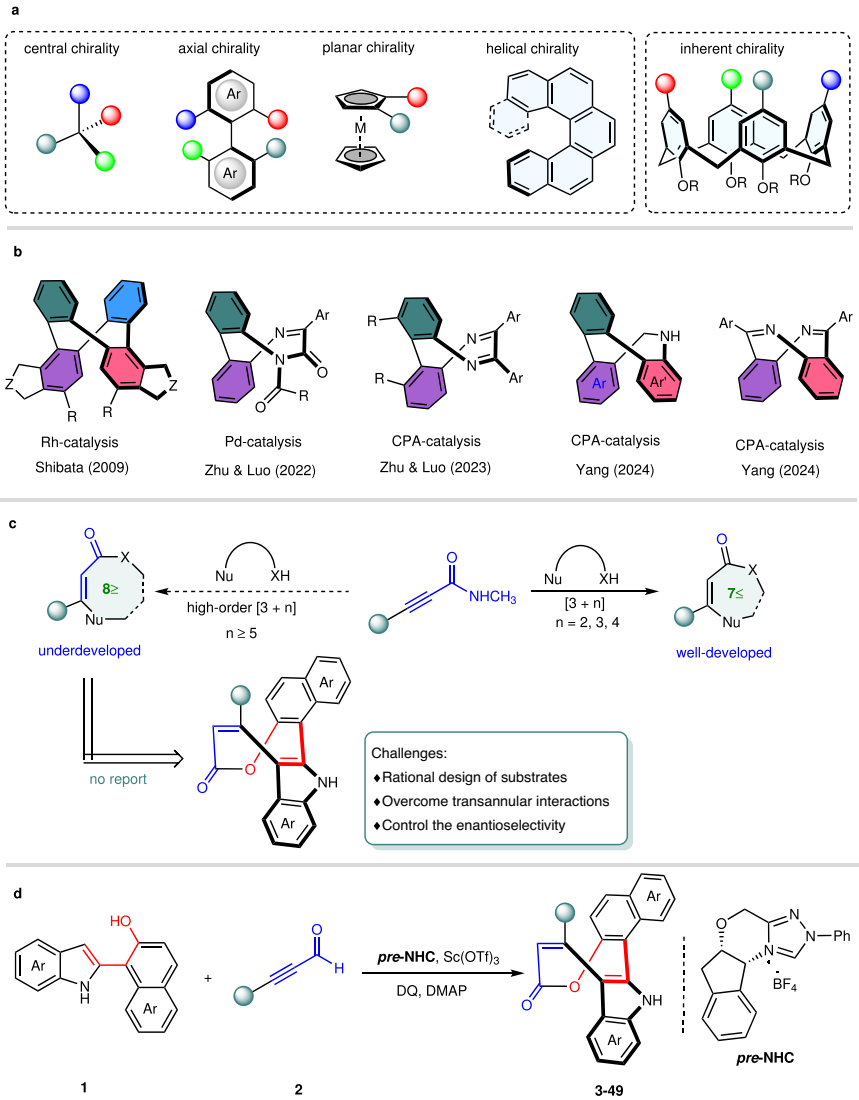

Fig. 1 | Background introduction and our strategy for synthesizing inherently chiral saddle-shaped eight-membered lactones. a Research status of the catalytic enantioselective synthesis of chemicals with different types of chirality. **b** (I) Strategies for the enantioselective synthesis of eight-membered rings. **c** Research advances in asymmetric transformations of alkynyl acyl azoliums. **d** Overview of this work.

isocyanide insertion for the synthesis of chiral saddle-shaped eight-membered dibenzo[e,g][1,4]diazocin-6(5H)-ones (Fig. 1b, left, 2nd)[29]. Later, the same group accomplished the highly enantioselective synthesis of eight-membered dibenzo[e,g][1,4]diazocines through chiral phosphoric acid (CPA)-catalyzed formal (4 + 4) annulation between [1,1′-biphenyl]−2,2′-diamines and benzyls (Fig. 1b, middle)[30]. In 2023, the Yang group described impressive CPA-catalyzed kinetic resolution and dynamic kinetic resolution approaches for the asymmetric synthesis of inherently chiral 9,10-dihydrotribenzoazocines[31] (Fig. 1b, right, 2nd). The same group subsequently achieved a CPA-catalyzed dimerization of 2-acylbenzoisocyanates toward inherently chiral saddle-shaped eight-membered [1,5]diazocines (Fig. 1b, right, 1st)[32]. Despite these limited advances, the development of innovative and general catalytic enantioselective strategies to access new families of chiral saddle-shaped eight-membered heterocycles is highly desirable but challenging, because of the unfavorable transannular interactions and entropic factors associated with constructing medium-sized rings.

N-heterocyclic carbene (NHC) catalysis represents an appealing protocol for the construction of central or/and atropisomeric chiral compounds[33–53], most of which involve the construction of axially chiral molecules through asymmetric (3 + 3) cycloaddition via the use of alkynyl acyl azolium as a C3 synthon[54–59]. To the best of our knowledge, no example of the enantioselective assembly of inherently chiral eight-membered lactones catalyzed by *N*-heterocyclic carbenes has been reported (Fig. 1c)[60,61], which might arise from the following three issues: (1) the lack of appropriate and available precursors; (2) overcoming unfavorable transannular interactions and entropic penalties associated with their medium-sized ring formation; and (3) efficient control of enantioselectivity. To continue our interest in building medium-sized rings[62–64] and achieve this goal, pro-axially chiral 1-(2-indolyl)naphthalen-2-ols **1** with 1,5-binucleophilic sites on biaryls were designed and synthesized (Fig. 1d). We speculated that the preformed 1-(2-indolyl)naphthalen-2-ols may react with chiral NHC-bounded alkynyl acyl azoliums as active intermediates generated from ynals[54], enabling catalytic formal (5 + 3) annulation to furnish saddle-shaped eight-membered lactones with inherent chirality (Fig. 1d)

In this work, we show efficient and practical access to highly enantioenriched saddle-shaped eight-membered lactones with inherent chirality starting from readily available 1-(2-indolyl)naphthalen-2-ols with 1,3-dielectrophilic α,β-alkynals through asymmetric oxidative NHC catalysis (Fig. 1d).

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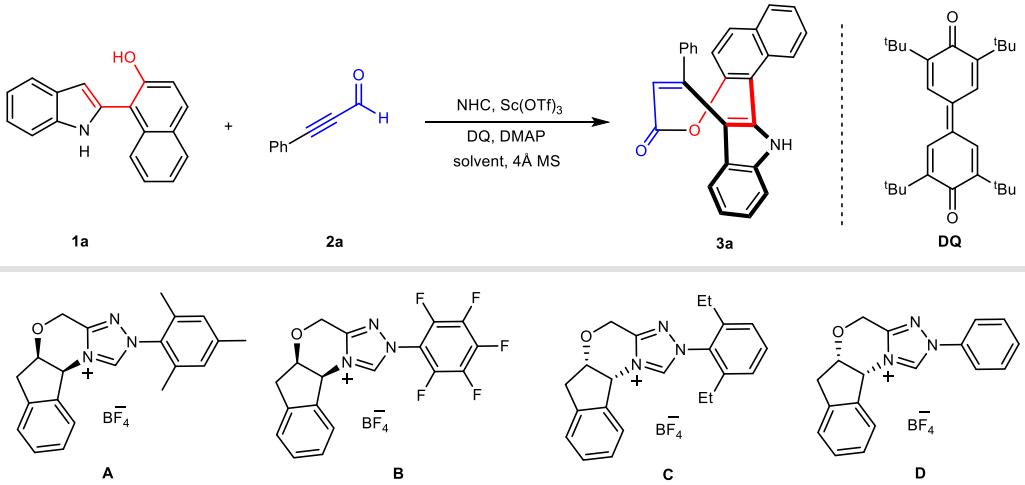
Table 1 | Optimization of reaction conditions.[a]



Entry	Cat. (mol%)	Base (equiv)	Solvent (mL)	Yield(%)[b]	ee(%)[c]
1	**A** (20)	DMAP (2.0)	THF (1.0)	10	−59
2	**B** (20)	DMAP (2.0)	THF (1.0)	12	−85
3	**C** (20)	DMAP (2.0)	THF (1.0)	25	87
4	**D** (20)	DMAP (2.0)	THF (1.0)	45	90
5	**D** (20)	Et_3N (2.0)	THF (1.0)	N.D.	-
6	**D** (20)	DABCO (2.0)	THF (1.0)	48	64
7	**D** (20)	K_2CO_3 (2.0)	THF (1.0)	34	79
8	**D** (20)	K_3PO_4 (2.0)	THF (1.0)	25	84
9	**D** (20)	DMAP (2.0)	toluene (1.0)	17	75
10	**D** (20)	DMAP (2.0)	CH_3CN (1.0)	35	70
11	**D** (20)	DMAP (2.0)	1,4-dioxane (1.0)	22	81
12	**D** (20)	DMAP (2.0)	DCE (1.0)	31	87
13[d]	**D** (20)	DMAP (2.0)	THF (1.0)	61	91
14[d]	**D** (20)	DMAP (2.0)	THF (0.5)	62	93
15[d]	**D** (15)	DMAP (2.0)	THF (0.5)	75	97
16[d]	**D** (15)	DMAP (1.0)	THF (0.5)	80	97
17[d,e]	**D** (15)	DMAP (1.0)	THF (0.5)	93	97

[a]Reaction conditions: **1a** (0.02 mmol), **2a** (0.06 mmol), DQ (2.0 equiv), NHC (20 mol%), base (x equiv), 4 Å MS (20 mg), $Sc(OTf)_3$ (20 mol%), solvent (x mL) at 20 °C for 3 days.
[b]Isolated yield of **3a**.
[c]The ee values were determined by HPLC.
[d]Use of DQ (3.0 equiv).
[e]Use of **2a** in 0.07 mmol.
THF tetrahydrofuran, *DCE* $ClCH_2CH_2Cl$, *N.D.* Not detected.

Results

Reaction optimization

To test our initial hypothesis, we began by studying the organocatalytic formal (5 + 3) annulation reaction of 1-(2-indolyl)naphthalen-2-ols with α,β-alkynals as test substrates to develop asymmetrical access to highly enantioenriched eight-membered lactones. Diverse NHC precatalysts, bases and solvents were evaluated at 20 °C, as depicted in Table 1. Initially, the reaction of 1-(2-indolyl)naphthalen-2-ol **1a** with **2a** was conducted under established conditions adapted from the previously reported enantioselective construction of the C-N axes of thiazine derivatives[57]. With NHC precursor **A** with an *N*-mesityl group and $Sc(OTf)_3$ as a Lewis acid catalyst, the reaction in THF in the presence of 3,3′,5,5′-tetra-tert-butyldiphenylquinone (DQ) as an oxidant and 4-dimethylaminopyridine (DMAP) as a base gave desired product **3a**, albeit with low yield (10%) and enantioselectivity (59% ee, entry 1). Preliminary results prompted us to further optimize the reaction conditions. Several other NHC precursors with an *N*-perfluorophenyl **B**, an *N*−2,6-diethylphenyl **C** or an *N*-phenyl **D** substituent were then examined (entries 2-4), demonstrating that all these catalysts displayed higher catalytic performances in terms of enantioselectivity than did **A**; moreover, to our delight, the latter precursor **D** proved to be the better choice for this asymmetric transformation, which furnished 45% yield and 90% ee (entry 4). The bases had important effects on the reaction efficiency and enantioselectivity (entries 5 − 8). The use of Et_3N completely suppressed the generation of **3a** (entry 5), whereas DABCO resulted in a slightly increased yield but a significant decrease in the ee value compared with that of DMAP (entry 6). Exchanging organic bases with inorganic bases, such as K_2CO_3 and K_3PO_4, did not improve either the chemical yield or the enantioselectivity (entries 7-8). The yields and ee values of product **3a** associated with the NHC precursor **D** and DMAP in several aprotic solvents were subsequently summarized as follows (entries 9 − 12): toluene (17%, 75% ee), CH_3CN (35%, 70% ee), 1,4-dioxane (22%, 81% ee), and DCE (31%, 87% ee). The above observations indicated that all these solvents were inferior to

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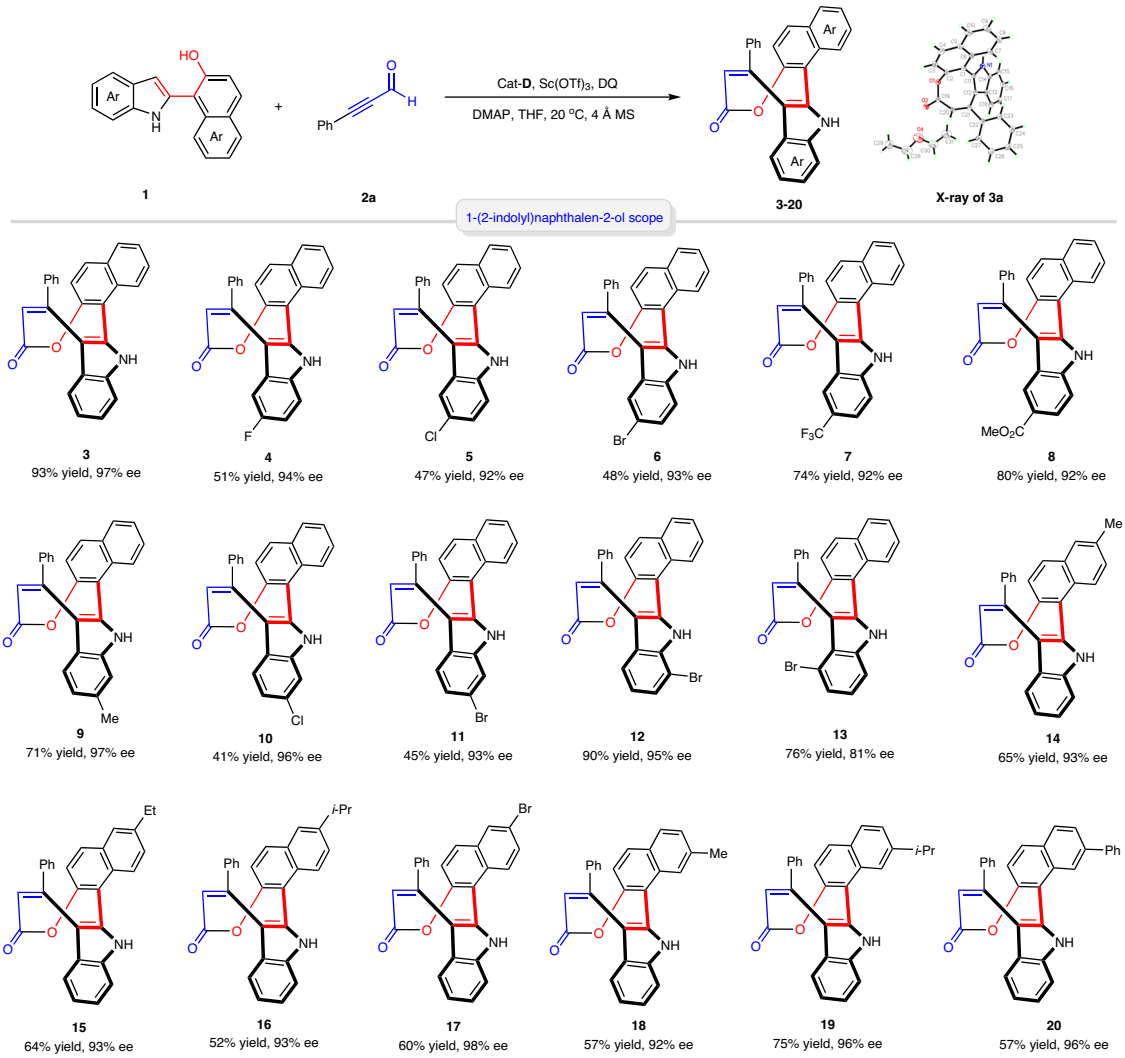

Fig. 2 | Scope of 1-(2-indolyl)naphthalen-2-ols. Reaction conditions: **1** (0.3 mmol), **2a** (1.05 mmol), NHC pre-catalyst **D** (15 mol%), $Sc(OTf)_3$ (20 mol%), DMAP (0.3 mmol), THF (7.5 mL), and 4 Å MS (300 mg) at 20 °C, for 3 days; the yield refers to the isolated yield based on **1**; ee values were determined by HPLC.

THF in terms of yield and ee value **3a**. An increase in the amount of DQ to 3.0 equivalents is beneficial for ensuring the yield of **3a** while maintaining enantioselectivity (entry 13). Furthermore, increasing the concentration of substrate slightly improved the enantioselectivity (entry 14). To our delight, the reaction was more efficient, delivering better yield (75%) and higher enantioselectivity (97% ee) while decreasing the catalyst loading to 15 mol% (entry 15). Furthermore, a decrease in the amount of DMAP slightly improved the yield (entry 16). Finally, slightly increasing the amount of substrate **2a** resulted in 93% yield without loss of enantioselectivity (entry 17).

Evaluation of the substrate scope

Using the optimized conditions, the generality of the NHC-catalyzed formal (5 + 3) annulation reaction with respect to an array of 1-(2-indolyl)naphthalen-2-ols with *α,β*-alkynals was examined (Fig. 2). To our delight, a number of 1-(2-indolyl)naphthalen-2-ols with different steric and electronic properties in both the indole and naphthalene rings were compatible, as shown in Fig. 2. For the indole ring, different substituents, such as fluoro (**1b**), chloro (**1c** and **1 h**), bromo (**1d, 1i** and **1j, 1k**), trifluoromethyl (**1e**), ester (**1 f**), and methyl (**1 g**), at the C4 to C7 positions were well tolerated in this reaction, furnishing the corresponding eight-membered lactones **4** – **13** in moderate to good yields (41%–90%) and excellent enantioselectivities (92%–97% ee). Of these groups, an obvious steric effect was observed because the C4 bromo analogue **1k**, which has strong steric hindrance, demonstrated significantly decreased enantioselectivity (**13**, 81% ee). Interestingly, even in a challenging case where the trifluoromethyl functional group was a strong electron-withdrawing group residing at the C5 position, this catalytic protocol was applicable, as product **7** was generated in 74% yield and 92% ee. For the naphthalene ring, either electronically rich (e.g., methyl, ethyl, isopropyl and phenyl) or deficient (e.g., bromo) substituents at different positions proceeded smoothly through organocatalytic formal (5 + 3) annulations with comparable efficiencies, accessing desired products **14** – **20** in 52-75% yields and 92-98% ee values.

The scope of the *α,β*-alkynals was proven to be quite broad (Fig. 3). Electronically rich and poor *α,β*-alkynals were compatible with the reaction conditions, and products **21** – **28**, which possessed *para*-, *meta*- and *ortho*-methyl, *para*-ethyl, *ortho*-fluoro, *para*-chloro, *meta*-bromo and *para*-nitro substituents, were all synthesized in acceptable yields and high enantioselectivities. Among them, incorporating *ortho*-methyl and *para*-nitro groups of the *α,β*-alkynals obviously decreased the enantioselectivity of the annulation reaction, and eight-membered lactone products **23** and **28** were formed with 80% and 84% ee, respectively. In addition to phenyl-substituted *α,β*-alkynal derivatives, heteroaryl *α,β*-alkynals such as 2-thienyl and 3-indolyl could also participate in this transformation, and compounds **29**-**45** were produced. Notably, a brief survey of the potential variations in the indole ring of

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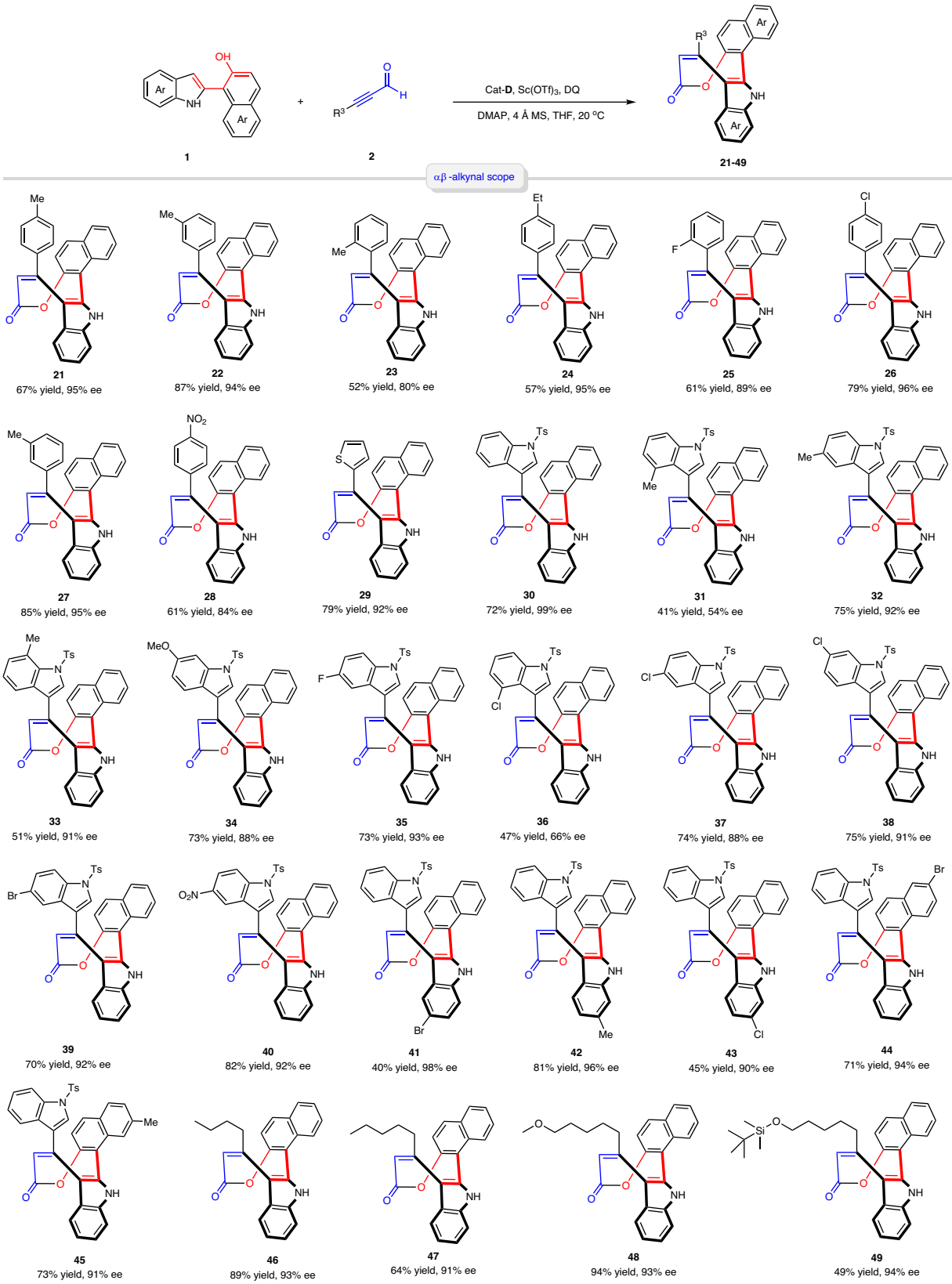

Fig. 3 | Scope of α,β-alkynals 2. Reaction conditions: **1** (0.3 mmol), **2** (1.05 mmol), NHC pre-catalyst **D** (15 mol%), $Sc(OTf)_3$ (20 mol%), DMAP (0.3 mmol), THF (7.5 mL), and 4 Å MS (300 mg) at 20 °C, for 3 days; the yield refers to the isolated yield based on **1**; ee values were determined by HPLC.

α,β-alkynals **2** was conducted. The effect of the electronic properties and positions of the substituents on the indole ring in this transformation was investigated. Various functional groups, such as methyl (C4, **2 l**; C5, **2 m**; C7, **2n**), methoxy (C6, **2o**), fluoro (C5, **2p**), chloro (C4, **2q**; C5, **2r**; C6, **2 s**), bromo (C5, **2t**), and nitro (C5, **2 u**) groups at different positions, were examined to demonstrate the compatibility of these asymmetrical annulations, and all of them were converted into the corresponding products **32-40**. These results indicated that the

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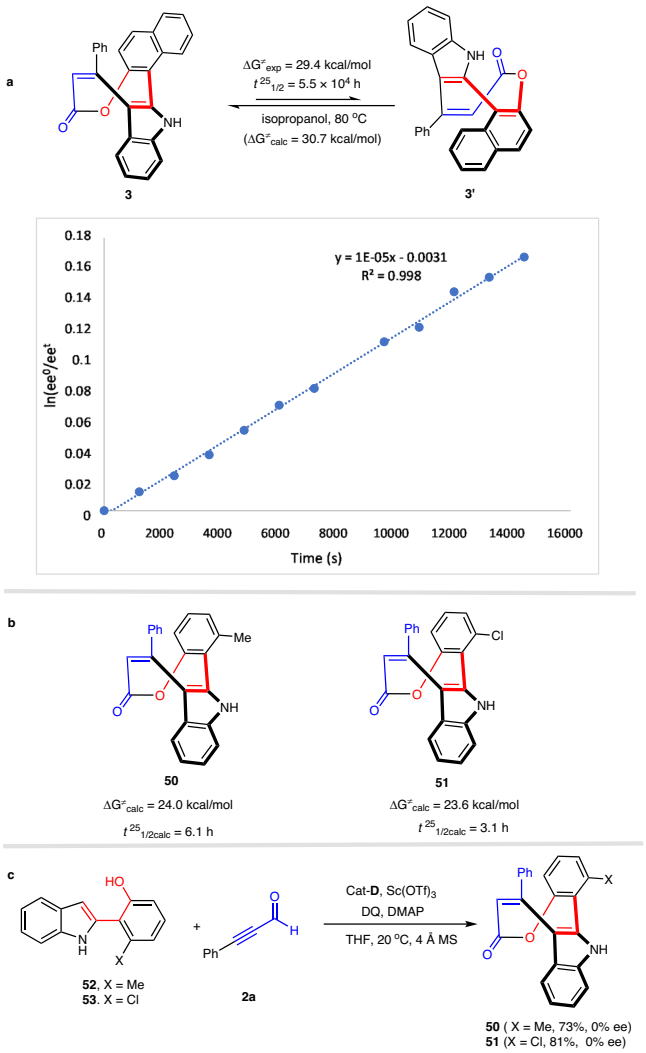

Fig. 4 | Study on product stability. a Experimental and DFT calculated determination of the enantiomerization barrier of **3**. **b** DFT calculations of the energy barriers of the enantiomerization of **50** and **51**. **c** Experimental validation.

position of the substituents on the indole ring has a profound impact on the enantioselectivity. Substrates bearing C4 substituents on the indole ring, probably due to steric hindrance, were reluctant to undergo this annulative process, as remarkable decreases in both chemical yields and enantioselectivities were observed (**31** and **36**). The variations in 1-(2-indolyl)naphthalen-2-ols were then investigated by combining 3-indole-substituted *α,β*-alkynal **2k**. Both electron-donating (methyl) and electron-withdrawing (chloro and bromo) groups in the indole or naphthalene ring were applicable, and compounds **41-45** were formed with ≥90% ee. Swapping the aryl moiety of *α,β*-alkynals with alkyl groups led to the formation of products **46-49** in moderate to excellent yields and high enantioselectivities. Several representative long-chain alkyl groups containing *n*-butyl, *n*-amyl, ether and TBS-protected alcohols all showed good reactivity profiles, producing corresponding products **46-49** with 91%–94% ee values.

Study of product stability and synthetic applications

To further investigate the conformational stability of eight-membered lactones, racemization experiments were performed (Fig. 4). Initially, the newly formed **3** was heated to 80 °C in isopropanol, and the ee decreased by 15.4% after 4 h. A racemization half-life of 5.5×10^4 h (at 25 °C) and a racemization barrier of 29.4 kcal/mol were calculated from these results, indicating the configurational stability of eight-membered lactones at relatively low temperatures. To verify the accuracy of the racemization barrier test, we further studied the racemization process of **3** by DFT calculations. As shown in Fig. 4 and Supplementary Fig. 20, the energy barrier of racemization is 30.7 kcal/mol, which supports the experimental results. Moreover, we changed the naphthalene ring to an *ortho*-substituted phenyl ring, such as *ortho*-methyl or *ortho*-chloro, and computationally investigated the possibility of synthesizing eight-membered lactones **50** and **51**. The computational results showed that the energy barriers to enantiomerization were 24.0 kcal/mol and 23.6 kcal/mol, respectively (see Supplementary Fig. 20), implying that the relatively lower calculated barrier to enantiomerization for these two compounds revealed their configurational lability and that the enantioselectivity was considered uncontrollable. To confirm this hypothesis, reactions of **52** and **53** were independently conducted under standard conditions, delivering products **50** and **51** in 73% and 81% yields, respectively, but without observation of enantioselectivity, which was in good agreement with the computational results.

A scale-up experiment using **1a** (1.0 mmol) with **2a** under standard conditions afforded **3** in a reduced yield (73%) without an obvious decrease in enantioselectivity (97% ee, Fig. 5a). The potential synthetic utility of the current developed protocol for accessing other chiral molecules was further highlighted by late-stage transformations. *N*-acetylation of **3** was carried out in the presence of DMAP and Et_3N to produce *N*-acetyl product **54** with a remarkable 98% ee by using Ac_2O as an acetylation reagent (Fig. 5b)[65]. Similarly, the use of Bc_2O led to the formation of *N*-Boc product **55** without a loss of enantioselectivity[66]. Next, ring opening of the oxocin-2-one framework occurred readily in the presence of different esterification reagents, affording axially chiral biaryls **56** and **57** without loss of enantioselectivity. Owing to the presence of two chiral axes in these two compounds, we performed DFT studies to calculate the rotational barriers of these chiral axes and determine whether they are biaxial chiral compounds. DFT calculations for compounds **56** demonstrate that the rotation barriers of C(indole)-C(Np) and C(indole)-C(alkene) axes are 37.7 and 21.4 kcal/mol, respectively, indicating that compound **56** has only one rotationally hindered chiral axis. A similar phenomenon was observed for compounds **57** and **59**, in which the high rotation barriers of C(indole)-C(Np) axis were calculated (**57**, 52.3 kcal/mol; **59**, 41.5 kcal/mol) and associated with the low rotation barriers of C(indole)-C(alkene) axis (**57**, 21.2 kcal/mol; **59**, 21.9 kcal/mol). The presence of lithium ethoxide in Et_2O resulted in axially chiral biaryls **56**, whereas compound **57** was afforded by using methanol as the esterification reagent and Et_3N as the base (Fig. 5b). In addition, treatment of **3** with methyl iodide gave *N*-methyl product **58** with significantly decreased enantioselectivity (82% ee). The reason may be that the free N-H bond of product **3** loses a proton in the presence of K_2CO_3, decreasing the steric hindrance and causing racemization. After simple recrystallization, the ee of *N*-methyl product **58** improved to 99%, and this was followed by ring-opening with methanol and Et_3N to access axially chiral biaryls **59** in 95% yield and 99% ee. Interestingly, de-esterification of **59** proceeded smoothly in the presence of diisopropylethylamine (DIPEA), triflic anhydride (Tf_2O) and triflic acid (TfOH), affording terminal olefin **60** in 57% yield and 99% ee. The reaction of **3** with chlorodiphenylphosphine furnished monophosphine product **61** in 89% yield and 95% ee[67]. The synthesized monophosphine product **61** was subsequently used as a chiral ligand for the asymmetric Pd-catalyzed allylic substitution of dimethyl malonate and the Tsuji-Trost reaction, and the desired product **62** was obtained in 85% yield but with very poor enantioselectivity (Fig. 5c)[67].

Possible reaction pathways

To gain mechanistic insights into this process, several control experiments were conducted. **1a** reacted with **2a** under standard conditions without $Sc(OTf)_3$, and product **3** was afforded in both decreased yield and enantioselectivity (81%, 80% ee), showing that $Sc(OTf)_3$ had a

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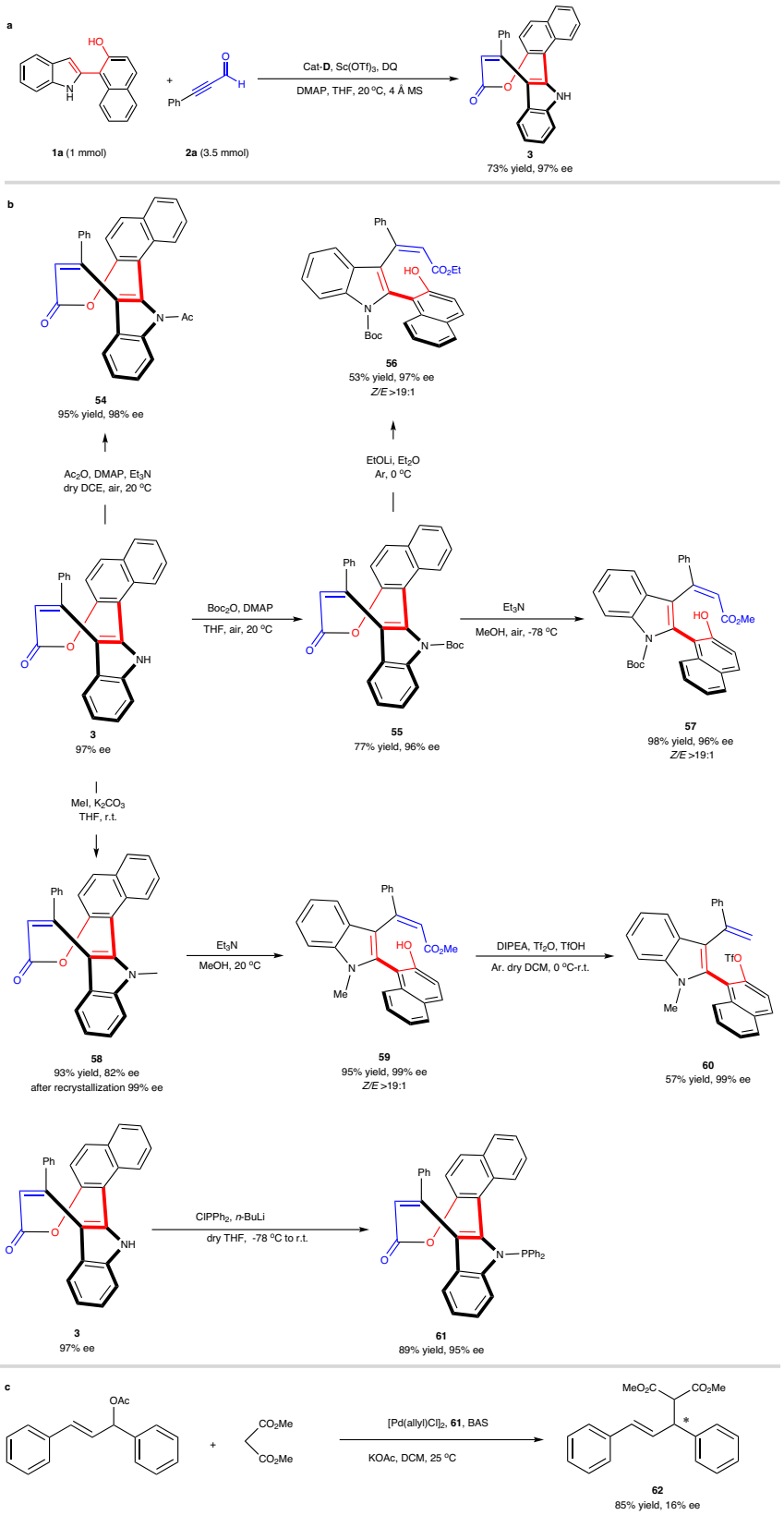

Fig. 5 | Scale-up reaction and synthetic transformations. a Scale-up experiment. **b** Chemical transformations of compound **3**. **c** Application of compound **61**. The yields are the isolated yields after purification by column chromatography. The ee values were determined by HPLC. The *Z*/*E* ratios were determined by ^{1}H MNR.

positive effect on the efficiency of this transformation in terms of yield and ee (Fig. 6a). This interesting observation enabled us to further understand this process. From these results, we reasoned that Sc^{3+} may act as a linker to fix alkynyl acyl azolium **I** and naphthalen-2-olate **III**, which enables the intermolecular nucleophilic addition pathway in the absence of scandium to occur in an intramolecular pattern and thereby facilitates the Michael addition of indole to alkynyl acyl azolium (Fig. 7), thus leading to improvements in both the yield and the

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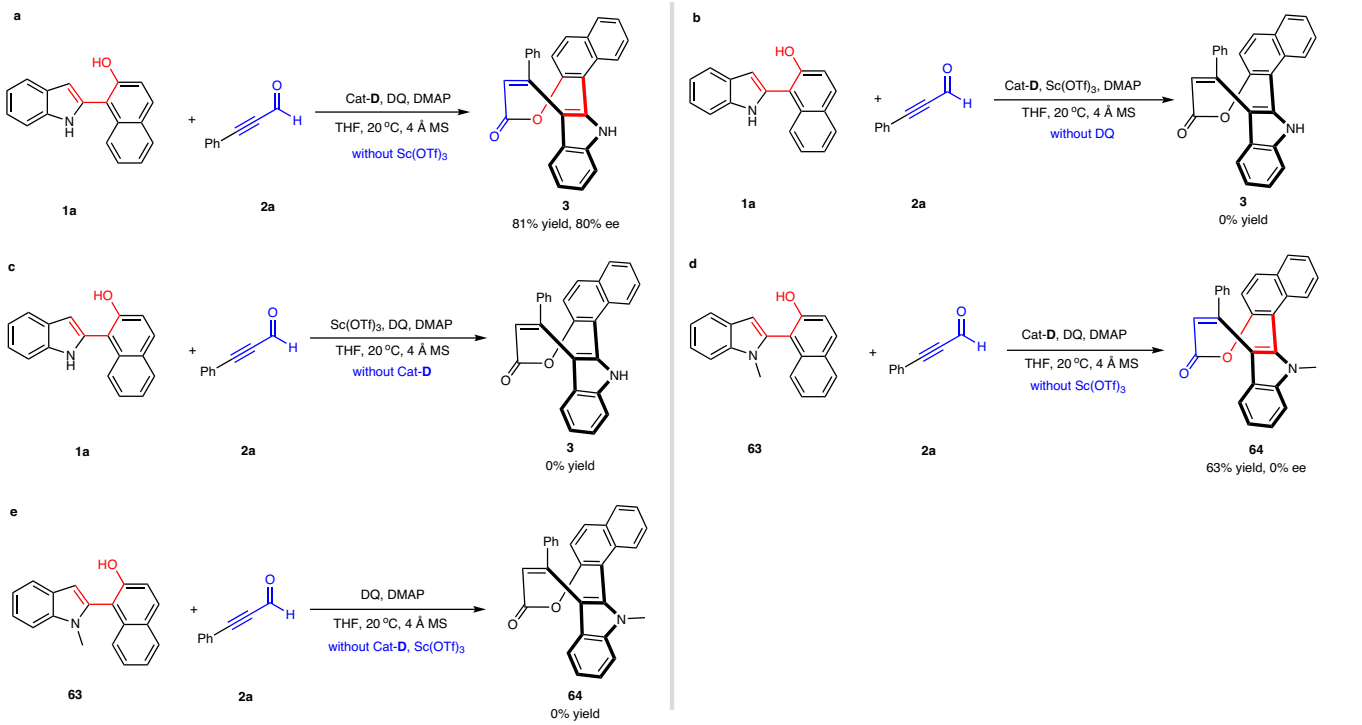

Fig. 6 | Investigation of the mechanism. a Control reaction of **1a** with **2a** without $Sc(OTf)_3$. **b** Control reaction of **1a** with **2a** without DQ. **c** Control reaction of **1a** with **2a** without Cat-**D**. **d** Control reaction of **63** with **2a** without Cat-**D** and $Sc(OTf)_3$. **e** Control reaction of **63** with **2a** without $Sc(OTf)_3$.

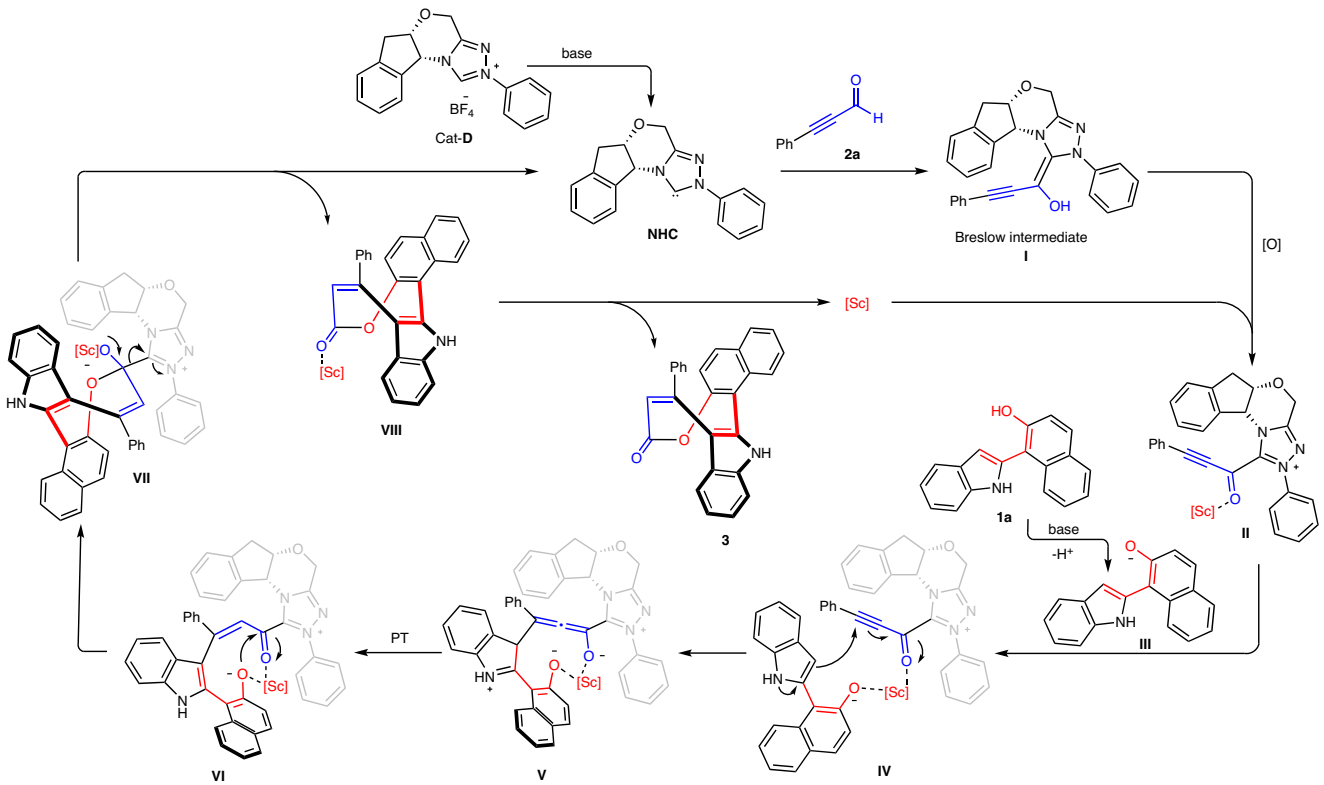

Fig. 7 | Proposed reaction pathway.

enantioselectivity. Without DQ or the NHC catalyst, the reaction did not proceed, and the starting materials were recovered (Fig. 6b and c), suggesting that alkynyl acyl azolium may be a key intermediate and that the NHC catalyst is crucial for this transformation. To confirm the role of the free N-H bond in substrate **1,** *N*-methyl-protected 1-(2-indolyl)naphthalen-2-ol **63** was reacted with **2a** in the absence of $Sc(OTf)_3$ under standard conditions, furnishing corresponding product **64** in 63% yield but without observation of the ee (Fig. 6d). The

above reaction did not work without an NHC catalyst (Fig. 6e). These results implied that the substituent at the *N*-atom of 1-(2-indolyl) naphthalen-2-ol severely affects the enantioselective control of this transformation.

Based on the above experimental results and previous reports[54–59], a proposed mechanism is depicted in Fig. 7. With 1-(2-indolyl)naphthalen-2-ol **1a** and 3-phenylpropiolaldehyde **2a** as representative examples, this process might initially involve in-situ-generation of a free NHC catalyst from precatalyst **D** under basic conditions, and the subsequent addition of the NHC catalyst to **2a** gives Breslow intermediate **I**. Then, intermediate **I** is oxidized by DQ, followed by coordination of $Sc(OTf)_3$ to yield the alkynyl acyl azolium-[Sc]-complex **II**. Intermediate **II** captures naphthalen-2-olate **III**, derived from **1a** under basic conditions, by coordination, affording [Sc]-complex **IV**. Michael addition of indole to alkynyl acyl azolium yields allenolate intermediate **V**, which undergoes proton transfer (PT) and subsequent lactonization to afford product **3** and simultaneously regenerates the NHC catalyst and [Sc]-complex for the next catalytic cycles.

Discussion

In summary, we developed an oxidative NHC catalytic formal (5 + 3) annulation strategy starting from 1-(2-indolyl)naphthalen-2-ol and *α,β*-alkynals with the aid of $Sc(OTf)_3$, and used this process to produce a wide range of challenging inherently chiral saddle-shaped eight-membered lactones with structural diversity in moderate to good yields and high enantioselectivities. The stabilities of the inherently chiral eight-membered lactones were evaluated *via* both experimental and computational methods, which demonstrated that these molecules are quite stable at relatively low temperatures. Both the indole and oxocin-2-one scaffolds in our eight-membered rings are commonly used structural motifs in bioactive and other functional molecules and can be easily derivatized into a series of functionally diverse chiral molecules, in which preliminary deconstructive esterification of the oxocin-2-one ring to axially chiral biaryls was showcased. We believe that our developed methodology will inspire more investigations on inherently chiral medium-ring skeletons, especially those bearing eight-membered rings. Further studies on the enantioselective synthesis of inherently chiral medium-ring-embedded molecules, especially those with potential applications in pharmaceutical and medical chemistry, are currently underway in our laboratories.

Methods

General procedure for the NHC-catalyzed domino reaction of 1-(2-indolyl)naphthalen-2-ols and *α,β*-alkynals. Chiral NHC pre-catalyst **D** (0.045 mmol, 15 mol%, 17 mg), DMAP (0.3 mmol, 1.0 equiv, 37 mg), $Sc(OTf)_3$ (0.06 mmol, 20 mol%, 30 mg), 4 Å molecular sieves (300 mg), DQ (0.9 mmol, 3.0 equiv, 368 mg) and substituted 1-(2-indolyl)naphthalen-2-ols **1** (0.3 mmol) was added to a 20 mL vial equipped with a magnetic stir bar. After that, THF (7.5 mL) and *α,β*-alkynals **2** (1.05 mmol, 3.5 equiv) were added, and the reaction mixture was allowed to stir for 3 days at 20 °C. After consumption of 1-(2-indolyl) naphthalen-2-ols **1**(monitored by TLC), the reaction mixture was directly subjected to column chromatography on silica gel (eluent, petroleum ether/ethyl acetate = 20:1 V/V) to afford desired products **3-49**.

Data availability

The data generated in this study are provided in the Supplementary Information file. For the experimental procedures, data of NMR and HRMS analysis and computational details, see Supplementary Methods and Figures in Supplementary Information file. The authors declare that all these data supporting the findings of this study are available within the article and Supplementary Information files and are also available from the corresponding author upon request. The X-ray crystallographic coordinates for structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number CCDC 2330705 (**3**) and 2330706 (**60**). The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. Source data are provided with this paper.

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Author contributions

S.Q.S. and C.C.C. contributed equally to this work. S.Q.S. and C.C.C. conducted and analyzed the experimental studies. L.L.X. and J.P.Z. checked the experimental data. J.W. conducted the DFT computational study. B.J., W.J.H. and J.W. discussed the reaction mechanism. All the authors wrote the manuscript. B.J. and W.J.H. conceived and supervised the project.

Competing interests

The authors declare no competing interests.

Additional information

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