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Enantioselective synthesis of 6-(Indole-2-yl)-3,4-dihydropyran-2-one skeletons by *N*-Heterocyclic carbene-catalyzed asymmetric [3 + 3] cycloaddition of α -bromocinnamaldehyde

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Abstract

The enantioselective construction of chiral 6-(indole-2-yl)-3,4-dihydropyran-2-one skeleton was demonstrated by the formal [3 + 3] cycloaddition reaction of α -bromocinnamaldehyde with β -ketoester indole catalyzed by chiral *N*-heterocyclic carbene (NHC). The reaction proceeds smoothly via a vinyl acyl azolium intermediate (electron-poor enone) generated from NHC-aldehyde adducts, providing 6-(indole-2-yl)-3,4-dihydropyran-2-one derivatives in good yields with excellent enantioselectivities (up to 98% ee).

Keywords: Organocatalysis, enantioselective synthesis, *N*-heterocyclic carbene (NHC), acyl azolium intermediate, 6-(indole-2-yl)-3, 4-dihydropyran-2-one skeleton

INTRODUCTION

Indole skeletons are widely present in many important biomolecules and possess a heterocyclic structure with diverse properties. Their structural characteristics can offer unique features, such as modifying electron



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cloud density, adjusting steric hindrance, and realizing post-functionalization. In recent years, asymmetric catalytic reactions based on indole skeletons have emerged as a new research field^[1-9].

Indole-2-yl-pyrans are the basic structural framework for numerous biologically active natural products and drugs. Two novel alkaloids isolated from plant roots have an indole-C-glucoside core^[10]. Indole-C-glucopyranoside **A** showed cytotoxic activity against human myeloid leukemia HL60 cells ($IC_{50} = 1.3$ mM) and human hepatocellular carcinoma HepG2 cells. Isomer **B** showed cytotoxic activity against both HL60 cells and human myeloid leukemia Mata cells (IC_{50}) [Figure 1].

Given the importance of the indole skeleton, the selective functionalization of this skeleton catalyzed by *N*-heterocyclic carbene (NHC) has been gaining increasing interest in recent years. Armido Studer and other chemists reported intra- and intermolecular cycloaddition by NHC catalysis to construct spirocyclic indole skeletons by introducing formyl benzyl groups, -CHO, -OH, alkenyl groups, and other functional groups into the indole structure^[11-19]. Balanna *et al.* reported the NHC-catalyzed construction of the indole skeleton by introducing -CHO, -CH₃, -NO₂, and other groups into the indole structure^[20-23]. Liu *et al.* also reported the NHC-catalyzed construction of polycyclic substrates by designing the indole skeleton^[24-27]. Du *et al.* studied the construction of an axially chiral indole skeleton^[28]. In addition, Chi *et al.* and Gong *et al.* developed acyclic aldol reactions of the indole skeleton to form quaternary stereogenic centers by post-aldol stereochemistry control^[29,30].

Although the NHC-catalyzed synthesis of indole derivatives is widely studied, the application of NHC catalysis for the synthesis of indole-pyran skeletons has received limited attention. In 2013, Chi^[31] *et al.* developed the direct β -carbon functionalization of saturated aldehydes through oxidative NHC catalysis, leading to dihydropyranone with high enantioselectivity [Scheme 1A]. Subsequently, Sundén *et al.* used O₂ instead of high molecular weight stoichiometric oxidants and introduced a system of electron transfer mediators (ETMs) to realize β -carbon functionalization of unsaturated aldehydes [Scheme 1B]^[32]. Although preliminary achievements have been made in the construction of the dihydropyranone skeleton, the avoidance of any oxidants and additives remains a challenge. Our research group has reported the construction of spiroindole skeleton compounds catalyzed by NHC^[12]. Our continuous interest in NHC-catalyzed cycloaddition inspired us to construct chiral 6-(indole-2-yl)-3,4-dihydropyran-2-one derivatives by NHC-catalyzed [3 + 3] cycloaddition reactions between β -ketoester indole and α -bromocinnamaldehydes [Scheme 1C].

EXPERIMENTAL

To an oven-dried 10 mL vial, β -ketoester indole **1** (0.1 mmol, 1.0 equiv), β -bromo- α,β -unsaturated aldehyde **2** (0.1 mmol, 1.2 equiv), cat. **A** (7.4 mg, 0.02 mmol, 0.2 equiv), NaHCO₃ (12.6 mg, 0.15 mmol, 1.5 equiv) were added, followed by 1.5 mL of THF. The mixture was stirred overnight at room temperature. Once the reaction was completed (monitored by TLC), the desired product **3** was purified by silica gel column chromatography with EA/PE (1:10) as an eluent.

RESULTS AND DISCUSSION

In view of the fact that some enantioenriched indole and pyran derivatives are pharmaceutically attractive compounds, we chose β -ketoester indole **1a** and α -bromocinnamaldehyde **2a** as model reaction substrates to optimize the reaction conditions [Figure 2]. After evaluating triazolium pre-catalysts A-C, we found that pre-catalyst A gave the product **3a** in 67% yield and 45% *ee*, while pre-catalyst C, bearing C₆F₅ substituents, did not provide the desired product. Installing a NO₂ group to the indane moiety of pre-catalyst A (to get pre-catalyst B) led to a small improvement on the reaction yield but with a decrease in enantioselectivity

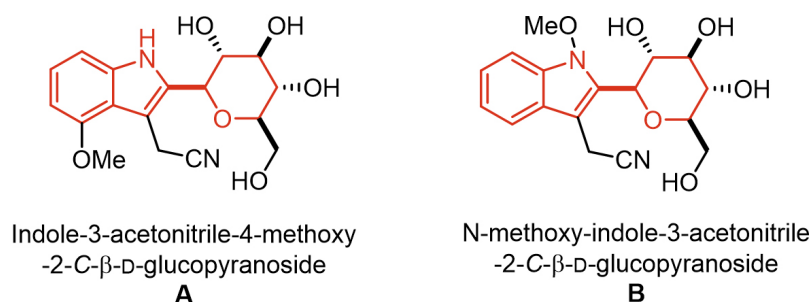
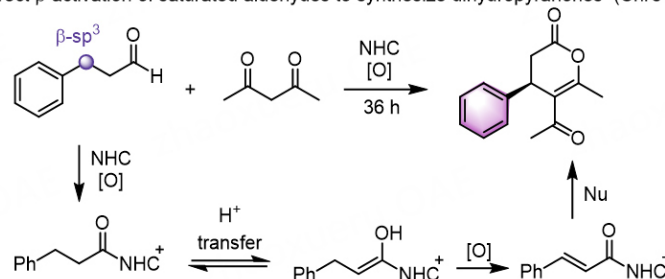
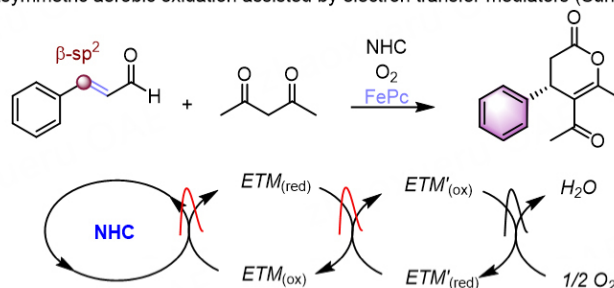


Figure 1. Representative natural products and bioactive compounds containing the indole-2-yl-pyrans skeleton.

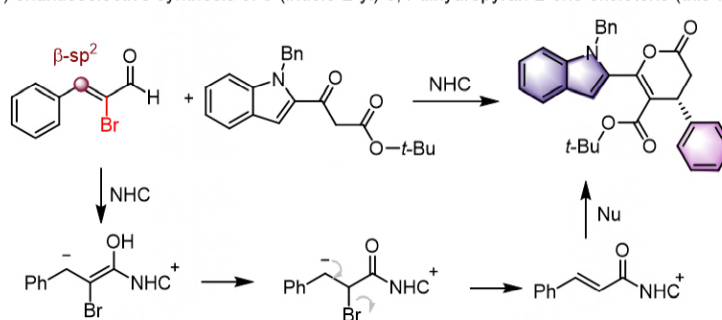
A) direct β -activation of saturated aldehydes to synthesize dihydropyranones (Chi's work)



B) asymmetric aerobic oxidation assisted by electron transfer mediators (Sundén's work)



C) enantioselective synthesis of 6-(indole-2-yl)-3,4-dihydropyran-2-one skeletons (this work)



Scheme 1. Profile of the construction of NHC-catalyzed construction of dihydropyranone.

(entry 2, 72% yield, 35% *ee*). Various inorganic bases could be used in this transformation (entries 4-5), and NaHCO_3 was found as the most efficient one that could give **3a** with good yield and excellent enantioselectivity (entry 5, 75% yield, 94% *ee*). Screening different reaction solvents did not show further improvements in either yields or enantioselectivities (entries 6-7). When 5 Å MS was used as the additive, the yield and the enantioselectivity increased slightly higher (entry 8, 78% yield, 97% *ee*). Further

1a + **2a** $\xrightarrow[\text{solvent, rt}]{\text{pre-cat. (20 mol\%), base (1.5 equiv)}}$ **3a**

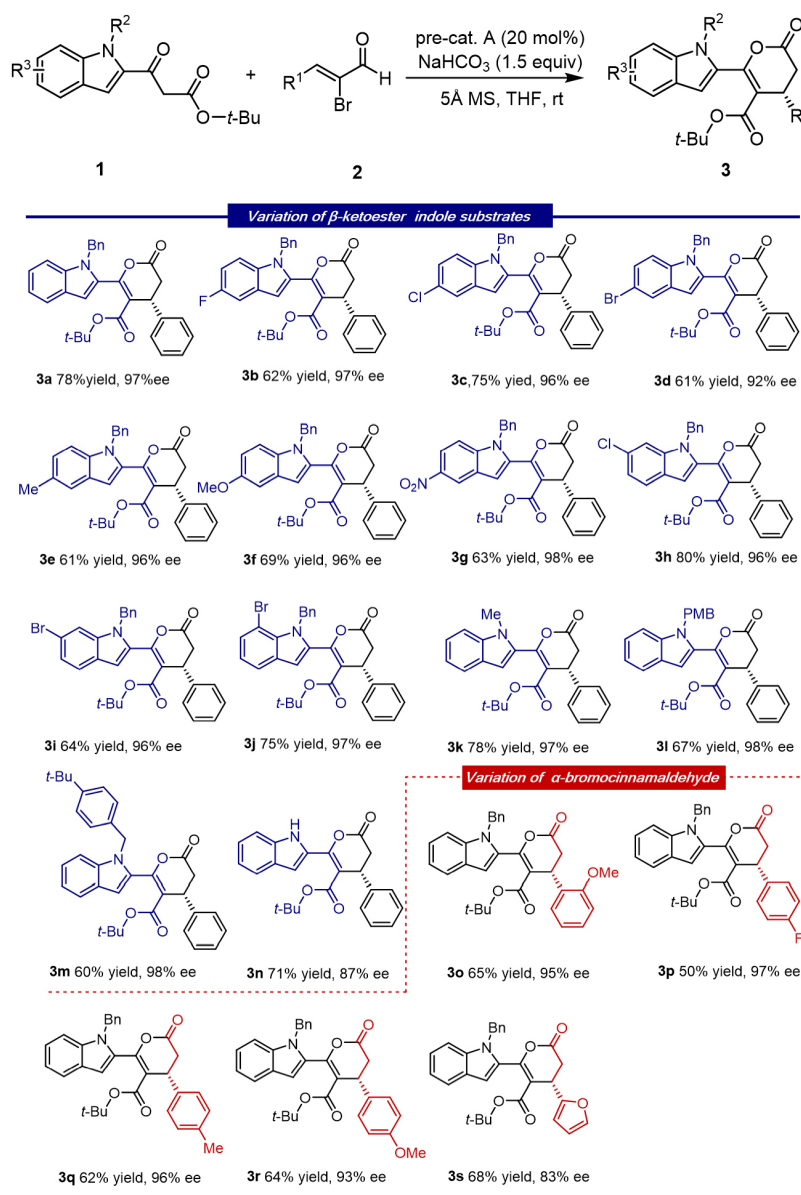
pre-cat. A **pre-cat. B** **pre-cat. C**

entry	solvent	pre-cat.	base	yield (%) ^b	ee (%) ^c
1	THF	A	TEA	67	45
2	THF	B	TEA	72	35
3	THF	C	TEA	trace	-
4	THF	A	NaOAc	85	87
5	THF	A	NaHCO ₃	75	94
6	DCM	A	NaHCO ₃	58	82
7	Toluene	A	NaHCO ₃	52	77
8^d	THF	A	NaHCO₃	78	97
9 ^e	THF	A	NaHCO ₃	68	97
10 ^f	THF	A	NaHCO ₃	8	92
11 ^g	THF	A	NaHCO ₃	67	93
12 ^h	THF	A	NaHCO ₃	33	93
13 ⁱ	THF	A	NaHCO ₃	42	92

Figure 2. Optimization of the reaction conditions^a. ^aReaction conditions: pre-catalyst (20 mol%), base (1.5 equiv), **1a** (0.1 mmol), and **2a** (0.12 mmol) in solvent (1.5 mL). ^bIsolated yield. ^cDetermined by chiral HPLC analysis. ^d5Å molecular sieves (10 mg) were used as an additive at room temperature. ^epre-catalyst (10 mol%). ^fThe temperature was 0 °C. ^gThe temperature was 35 °C. ^hTHF = 3 mL. ⁱTHF = 1 mL. Mes = 2,4,6-trimethylphenyl.

optimization studies revealed that high enantioselectivity with low reaction yield (entry 9, 68% yield, 97% *ee*) was delivered when the reaction was performed with 10 mol% pre-catalyst A. Then, the reaction temperature was investigated. When the reaction proceeded at 0 °C, the yield was dramatically decreased to 8%, and the enantioselectivity was slightly decreased to 92% [Figure 2] (entry 10). Higher reaction temperature did not result in better yield or enantioselectivity [Figure 2] (entry 11). While the changing of reactant concentration led to lower yields (entries 12–13). The best reaction condition was established with a 20 mol% pre-catalyst, 1.5 equiv NaHCO₃, and 1.0:1.2 reactant ratio at room temperature.

After establishing the optimized reaction conditions, the scope of the reaction was examined. First, we studied variations of the β-ketoester indoles [Scheme 2]. Substrates with electron-releasing and electron-withdrawing groups on the benzene ring of the indole group of 1,3-dicarbonyl compound (R³) underwent a cycloaddition reaction, affording the compounds in moderate to good yields (61%–80% yield) and excellent enantioselectivities (**3a–3j**, 92%–98% *ee*). It is worth mentioning that the enantioselectivity of the reaction can reach 98% when the C5 position of the indol-phenyls is NO₂. Subsequently, we investigated different N-protecting groups on the indole skeleton, such as Me, PMB, or tert-butyl benzyl. To our great delight, β-



Scheme 2. Substrates scope. Reaction conditions: pre-cat. **A** (20 mol%), NaHCO_3 (1.5 equiv), **1** (0.1 mmol), and **2** (0.12 mmol) in THF (1.5 mL).

ketoester indoles with different N-protecting groups also worked well in this process under the current reaction condition, and the desired products were generated in good to excellent yields and optical purities (**3k-3m**, 97%-98% ee). However, the N-electron withdrawing protecting group (such as Boc) showed lower reaction activity and enantioselectivities. Furthermore, the enantioselectivity of the reaction has a slight decrease without an N-protecting group (**3n**, 87% ee). This may be due to the steric resistance effect of the N-protecting group. Encouraged by these results, the generality of α -bromocinnamaldehyde **2** was further investigated with β -ketoester indole **1a** [Scheme 2]. Substituents with different electronic properties at the orthoposition (**3o**, 65% yield, 95% ee) and the paraposition (**3p-3r**, 93-97% ee) of the phenyl group were well tolerated. Para-F on the phenyl ring led to some decrease in reaction yield (**3p**, 50% yield). Replacement of the phenyl substituent with 2-furanyl had little effect on the reaction outcomes (**3s**, 68% yield, 83% ee). In addition, trace desired products were obtained by employing alkyl-substituted aliphatic aldehydes.

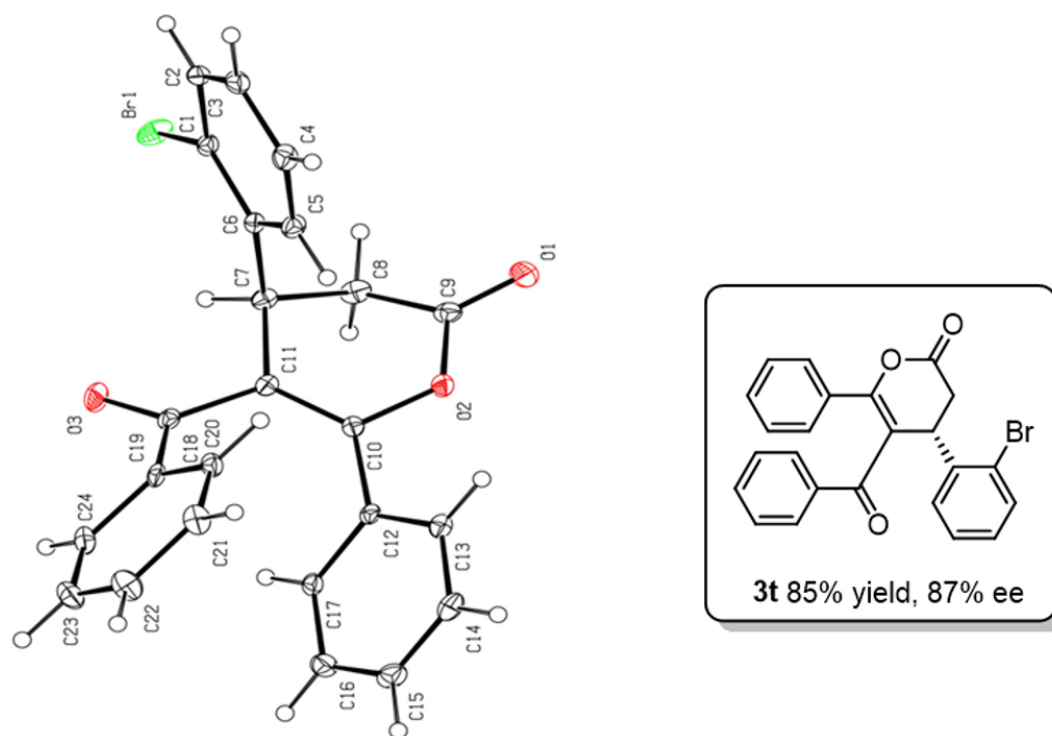


Figure 3. X-ray single crystal data for compound **3t**.

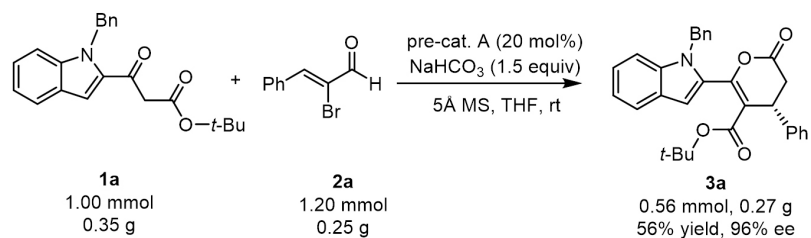
To demonstrate the practical nature of the present catalytic asymmetric strategy, a gram-scale preparation of compound **3a** was performed [Scheme 3]. Under the standard reaction conditions, amplifying the model reaction to 1.00 mmol straightforwardly gave optically pure 6-(indole-2-yl)-3,4-dihydropyran-2-one **3a** without the loss of enantioselectivity in modest yield (56% yield and 96% *ee*).

The absolute configuration of the cycloadduct **3t** was determined by X-ray crystallographic analysis as an (*S*)-configuration [Figure 3]. The absolute configuration of all other products was assigned accordingly (CCDC 2243010, please see the SI for details).

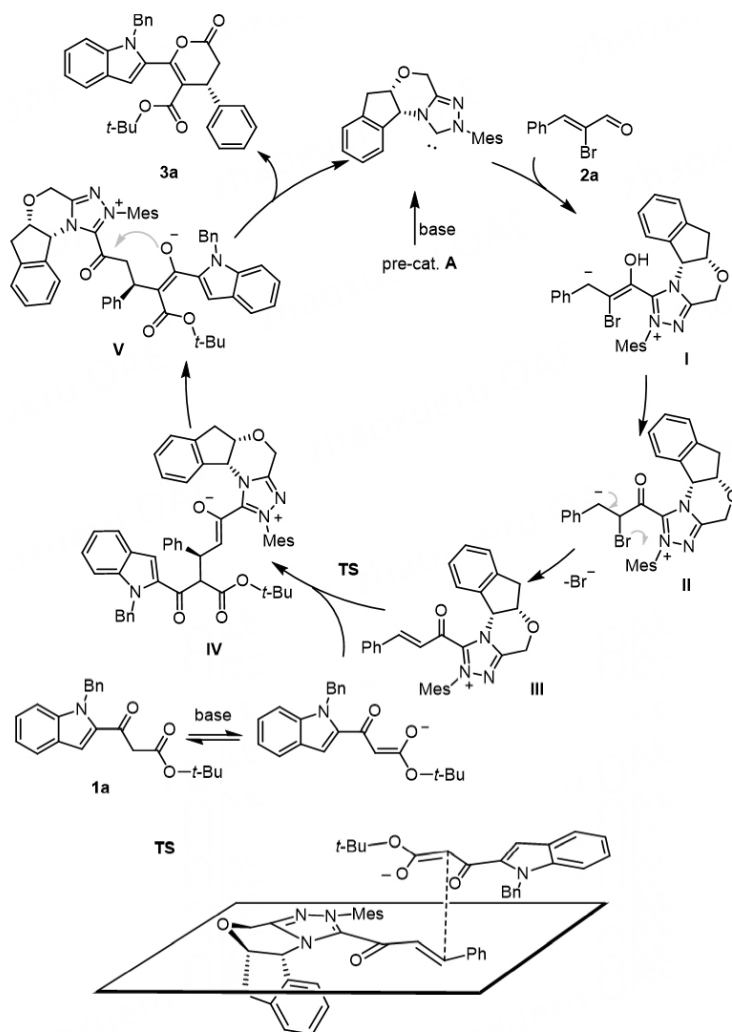
The plausible catalytic cyclic for this [3 + 3] cycloaddition pathway is shown in Scheme 4. The cycloaddition reaction begins with the addition of NHC to α -bromocinnamaldehyde **2a**, forming a Breslow intermediate, which undergoes tautomerization and debromination to generate form α , β -unsaturated acylazolium **III**. The Michael addition of enolate generated by β -ketoester indole **1a** to intermediate **III** led to intermediate **IV**. Intermediate **IV** undergoes tautomerization and intramolecular esterification to give the desired product **3a** and regenerate the NHC catalyst.

CONCLUSIONS

In conclusion, we have developed a mild NHC-catalyzed efficient [3 + 3] cycloaddition reaction between α -bromocinnamaldehyde and β -ketoester indole, avoiding the use of high molecular weight stoichiometric oxidants. This reaction resulted in the highly enantioselective construction of 6-(indole-2-yl)-3,4-dihydropyran-2-one skeleton in good yields and exhibiting excellent enantioselectivities.



Scheme 3. A gram scale reaction.



Scheme 4. Proposed catalytic pathway and transition state.

DECLARATIONS

Authors' contributions

Designing the experiments, writing the manuscript, and being responsible for the whole work: Yang L
 Performing the experiments: He G

Manuscript writing and picture drawing, [Supplementary Materials](#): Chen X

Synthesizing the substrates and data review: Xia S

Co-directing this project: Zhong G

Directing this project and revising the manuscript: Yang L

Availability of data and materials

The data supporting this article have been included as part of the Supplementary Materials.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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