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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

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, $-CH_3$, $-NO_2$, 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 O_2 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), $NaHCO_3$ (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 C_6F_5 substituents, did not provide the desired product. Installing a NO_2 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

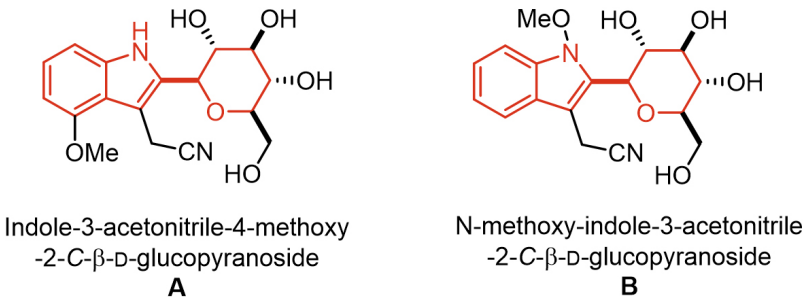
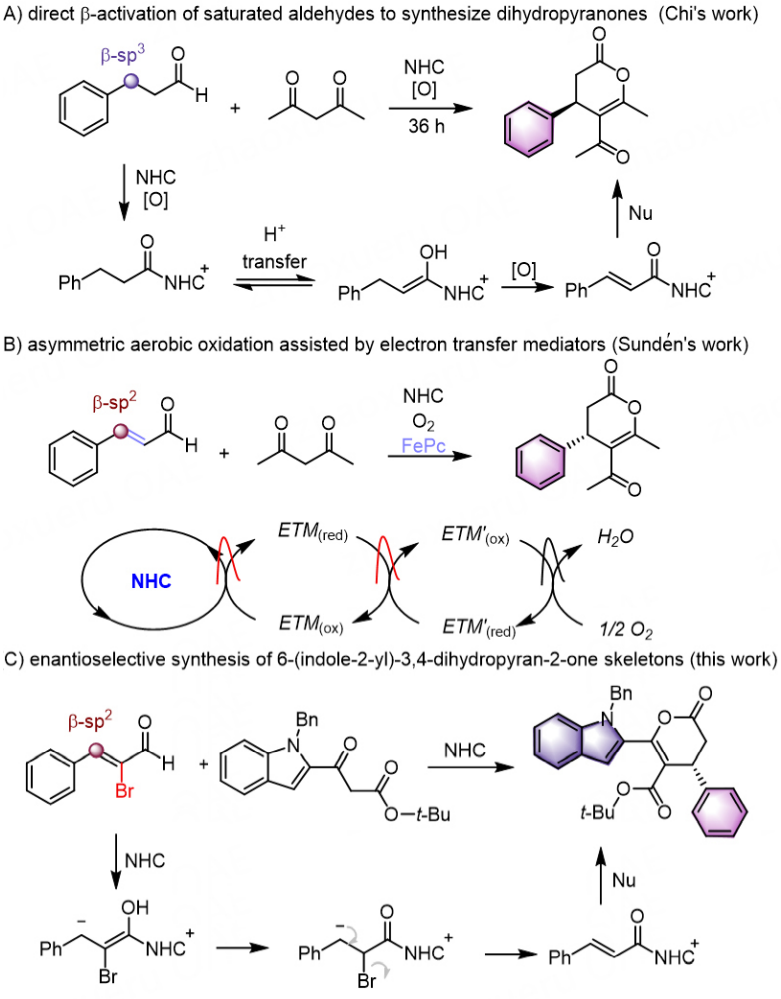
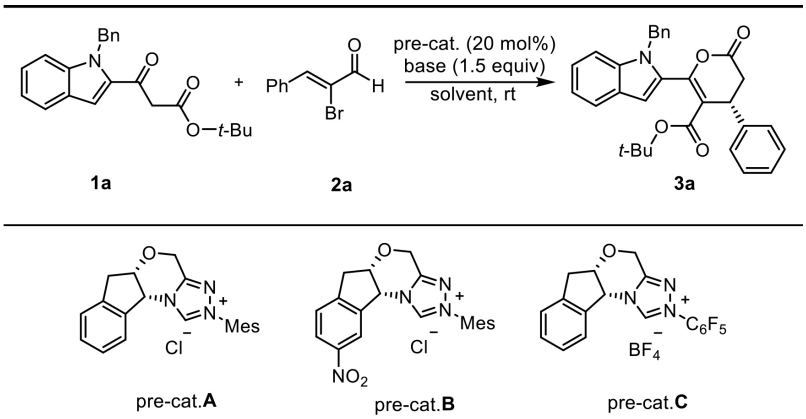


Figure 1. Representative natural products and bioactive compounds containing the indole-2-yl-pyrans skeleton.



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

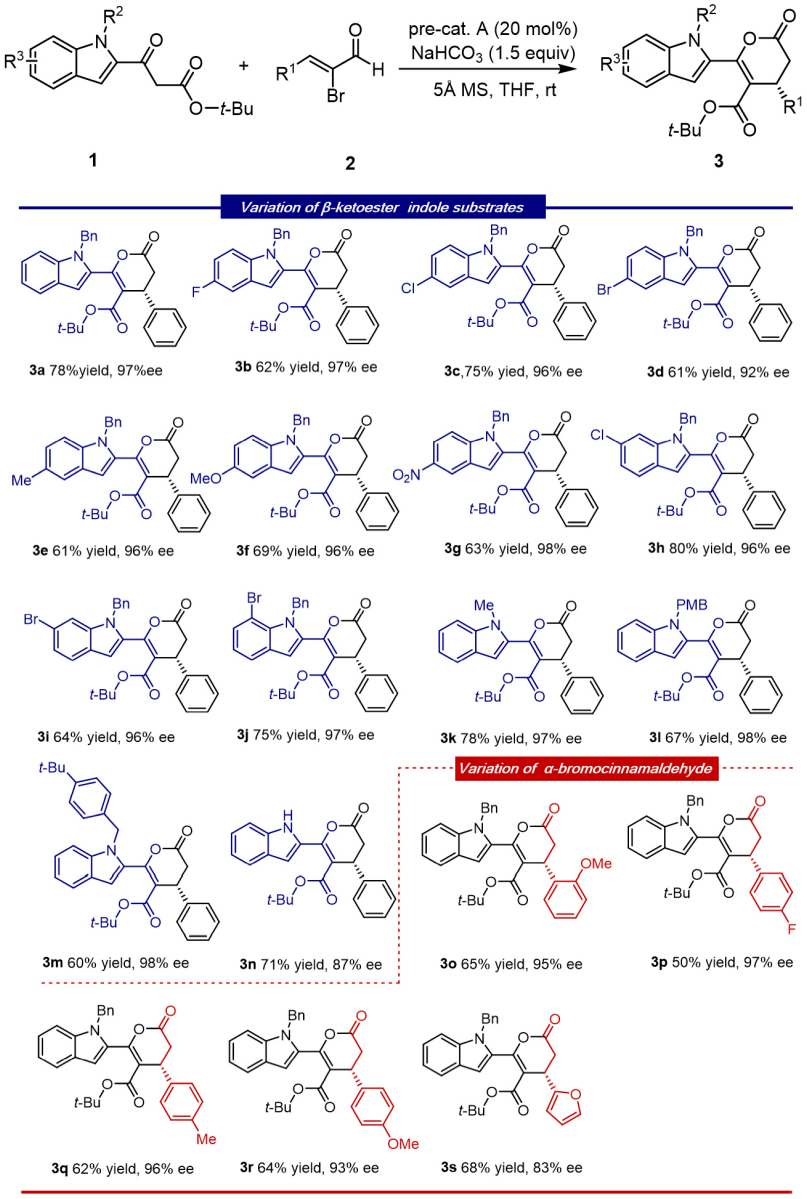


entry	solvent	pre-cat.	base	yield (%)[b]	*ee* (%)[c]
1	THF	A	TEA	67	45
2	THF	B	TEA	72	35
3	THF	C	TEA	trace	-
4	THF	A	NaOAc	85	87
5	THF	A	$NaHCO_3$	75	94
6	DCM	A	$NaHCO_3$	58	82
7	Toluene	A	$NaHCO_3$	52	77
8[d]	**THF**	**A**	**$NaHCO_3$**	**78**	**97**
9[e]	THF	A	$NaHCO_3$	68	97
10[f]	THF	A	$NaHCO_3$	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]. [a]Reaction conditions: pre-catalyst (20 mol%), base (1.5 equiv), **1a** (0.1 mmol), and **2a** (0.12 mmol) in solvent (1.5 mL). [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]5Å molecular sieves (10 mg) were used as an additive at room temperature. [e]pre-catalyst (10 mol%). [f]The temperature was 0 °C. [g]The temperature was 35 °C. [h]THF = 3 mL. [i]THF = 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 ℃, 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 $NaHCO_3$, 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 (R^3) 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 NO_2. 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.

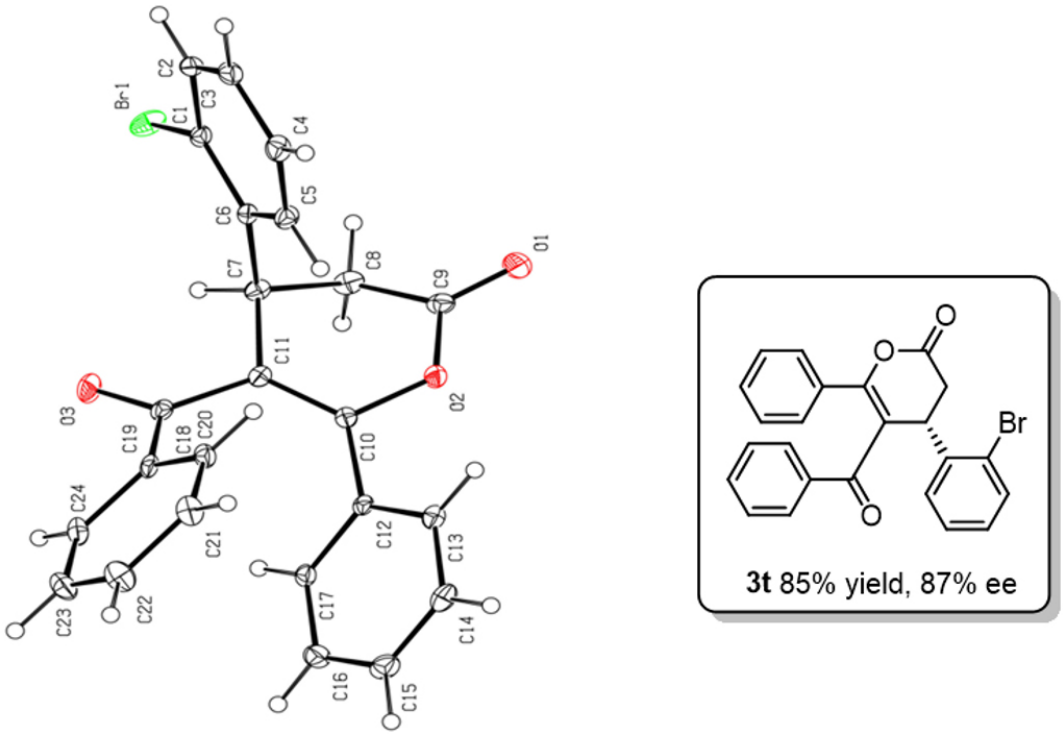


Figure 3. X-ray single crystal data for compound **3t**.

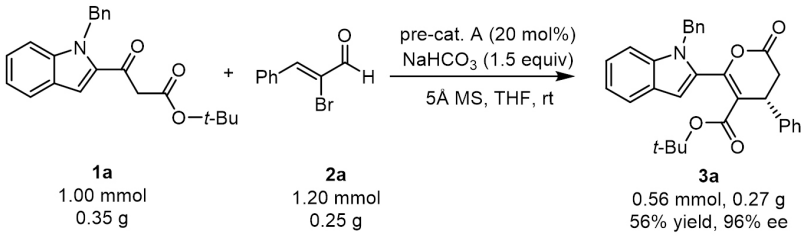
To demonstrate the practical nature of the present catalytic asymmetric strategy, a gram-scale preparation of compound **3a** was performed [Scheme 3]. Under the standard reaction conditions, amplifying the model reaction to 1.00 mmol straightforwardly gave optically pure 6-(indole-2-yl)-3,4-dihydropyran-2-one **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).

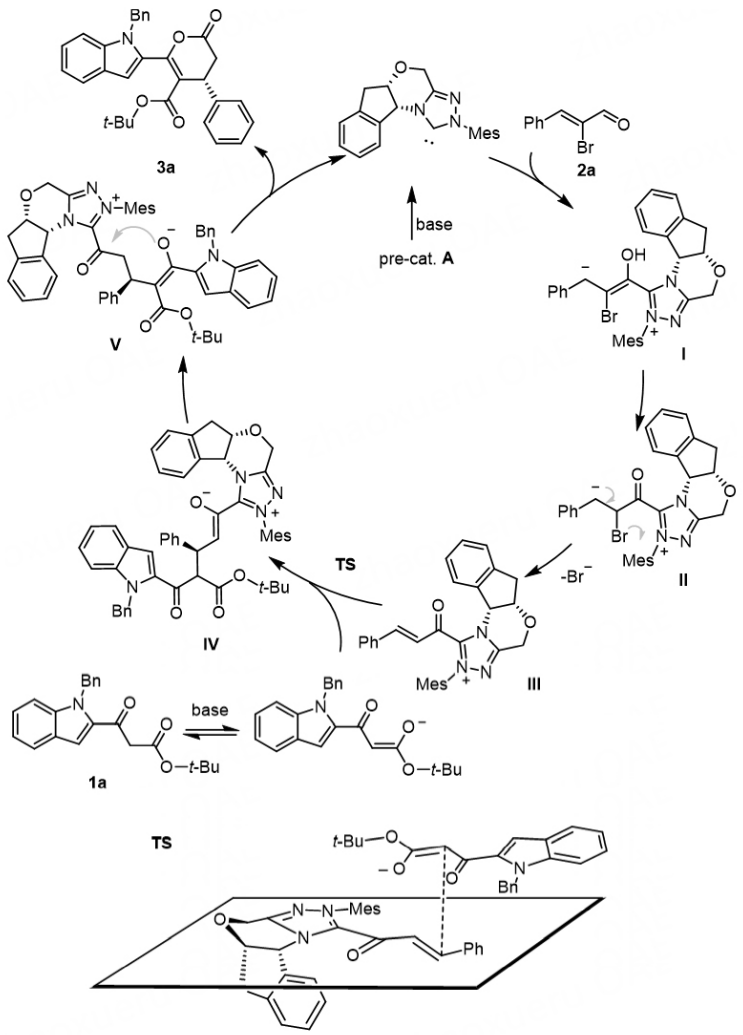
The plausible catalytic cyclic for this [3 + 3] cycloaddition pathway is shown in Scheme 4. The cycloaddition reaction begins with the addition of NHC to α-bromocinnamaldehyde **2a**, forming a Breslow intermediate, which undergoes tautomerization and debromination to generate form α, β-unsaturated acylazolium **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
Not applicable.

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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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