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N-Heterocyclic Carbene-Catalyzed Regio- and Enantioselective C7-Alkylation of 4-Aminoindoles with α-Bromoenals

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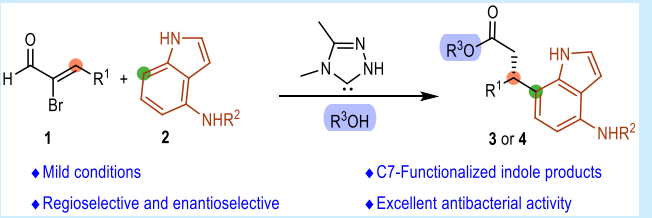
ABSTRACT: The first carbene-catalyzed regio- and enantioselective indole C7-alkylation reaction between 4-aminoindoles and α-bromoenals is disclosed. The corresponding indole products could be obtained in moderate to good yields with good to excellent enantioselectivities. The evaluation of antibacterial activity against *Psa* revealed that nine of the C7-functionalized indoles exhibited superior inhibitory activities compared to the positive controls TC and BT. Our approach provides an efficient strategy to introduce a chiral chain into the C7 position of indole compounds, with potential applications evaluated in pesticide development.



The indole core, as an electron-rich aromatic unit, widely exists in natural products, pharmaceuticals and agrochemicals with various biological activities.[1] In particular, C7-substituted indole derivatives have been proven to be of great significance in drug development (Figure 1). For example,

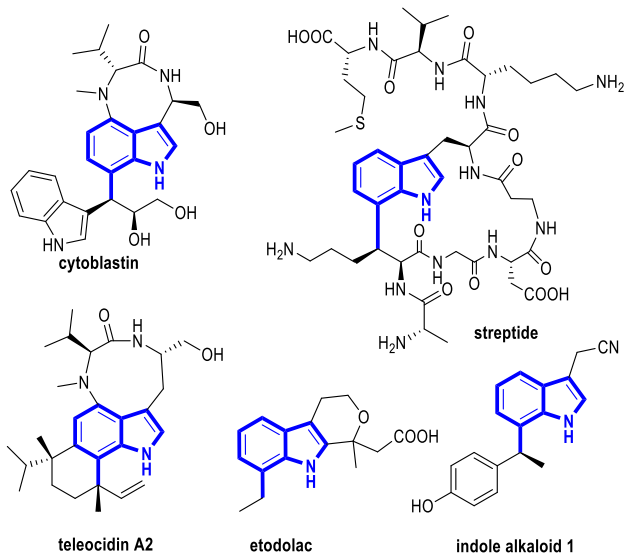


Figure 1. Bioactive C7-substituted indole derivatives.

cytoblastin isolated from the metabolites of bacterial *Streptoverticillium eurocidicum* possesses good immunomodulatory activity and low cytotoxicity and could effectively promote the proliferation of T cells.[2] Etodolac is used as an anti-inflammatory agent and selective COX-2 inhibitor proven to be effective in treating rheumatoid arthritis and osteoarthritis.[3] Indole alkaloid **1** exhibits strong antiviral activities against various influenza viruses.[4] Teleocidin A2 was discovered to exhibit efficacy against trypsin-induced PAR2-dependent intracellular Ca^{2+} mobilization and PAR2-activating peptide SLIGKV-NH_2 in tumors.[5] Streptide, a crucial macrocyclic peptide derivative, is initially isolated from *Streptococcus thermophilus*. It holds significance in the exploration of synthesizing ribosomal peptides and post-translationally modifying peptides.[6] Therefore, there has been considerable interest in developing efficient and enantioselective strategies for indole molecules with chiral side chains at the C7 position.

Most direct strategies to construct this structural motif involve transition-metal-catalyzed coupling reactions, with the corresponding C7-functionalized indoles obtained in an achiral form.[7] However, only a few examples have been achieved in the construction of chiral C7-functionalized indoles through asymmetric organocatalysis. A noteworthy exception arose from Zhao's group, wherein they achieved enantioselective and regioselective C7-alkylation of 4-aminoindoles under the catalysis of a chiral phosphoric acid in 2018 (Figure 2a).[8] Subsequently, some C7 Friedel−Crafts alkylation reactions of 4-aminoindoles were realized when the C7 position was activated to react with the C=C or C=X (X = O, NBoc) double bond through chiral phosphoric acid, as demonstrated by Zhao[9] and Antilla[10] (Figure 2a). *N*-Heterocyclic carbene (NHC) serves as an efficient organocatalyst, and various

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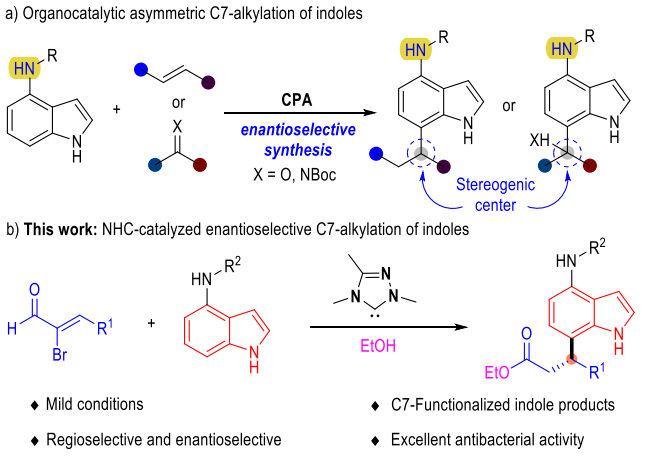


Figure 2. Organocatalytic enantioselective C7-alkylation of indole and our project design.

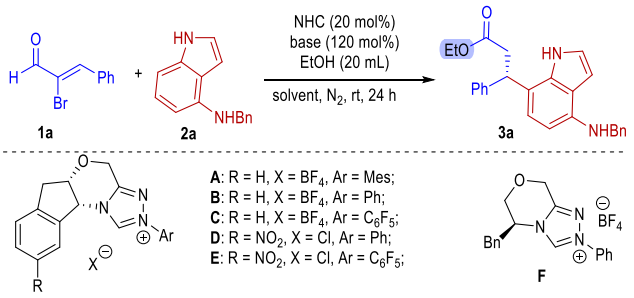
activation models and transformations focused on the C═C or C═X (X = O, NBoc) double bond have been achieved in past decades.[11] As far as our current knowledge extends, there is no documented instance of the enantioselective C7-alkylation of indoles through NHC catalysis.

Herein, we develop the first NHC-catalyzed regioselective and enantioselective alkylation reaction at the indole C7 position of 4-aminoindoles with α-bromoenals (Figure 2b). The corresponding C7-functionalized indole products were obtained in moderate to good yields and good to excellent enantioselectivities. Additionally, the chiral indole derivatives from our reaction show promising antibacterial activities against *Pseudomonas syringae* pv *actinidiae* (*Psa*) in an *in vitro* study, with inhibitory activity superior to the use of thiodiazole copper and bismerthiazol as positive controls.

We first investigated the optimal condition by selecting *N*-benzyl-1*H*-indol-4-amine **2a**[8−10] bearing a benzyl group as the model substrate to react with α-bromoenal **1a**.[12] Multifarious NHC precatalysts were screened under the condition where LiOAc served as the base in the solvent $CHCl_3$ (Table 1, entries 1−7). The aminoindanol-derived NHC catalysts **A**[13] and **B**,[14] featuring electron-rich groups *N*-Ph or *N*-Mes, were unable to promote this reaction. When NHC **C**[15] with a more electron deficient *N*-C_6F_5 group was used in this transformation, the C7-alkylated indole product **3a** was formed in good yield, albeit with a low er value (Table 1, entry 3). To our delight, installing the NO_2 moiety on the indane backbone of NHC **B** (to generate NHC **D**) proved to be efficient for this process, with the chiral product **3a** obtained in 35% yield with excellent enantioselectivity (Table 1, entry 4). Meanwhile, the examination of NHC **E**[16] and **F**[17] yielded unsatisfactory results, as indicated in entries 5 and 6, respectively.

Furthermore, the investigation on bases (Table 1, entries 7−10) indicated that using DMAP as a base resulted in excellent enantioselectivity for **3a** but with a significant decrease in product yield (Table 1, entry 7). Notably, the yield and enantioselectivity could be improved when $NaHCO_3$ was used as the base in this process (Table 1, entry 11). Then, various solvents were screened in the presence of NHC compound **D**. The unsatisfactory enantioselectivities and yields were obtained when $CHCl_3$ was switched to CH_2Cl_2, EtOAc, and THF (Table 1, entries 11−13, respectively). Finally, the yield of **3a** could be enhanced to 76%, with no significant impact on

Table 1. Optimization of Reaction Conditions[a]



entry	NHC	base	solvent	yield (%)[b]	er[c]
1	**A**	LiOAc	$CHCl_3$	<5	
2	**B**	LiOAc	$CHCl_3$	<5	
3	**C**	LiOAc	$CHCl_3$	60	56:44
4	**D**	LiOAc	$CHCl_3$	35	91:9
5	**E**	LiOAc	$CHCl_3$	45	76:24
6	**F**	LiOAc	$CHCl_3$	<5	
7	**D**	DMAP	$CHCl_3$	25	96:4
8	**D**	NEt_3/DBU/Li_2CO_3	$CHCl_3$	<5	
9	**D**	KOAc	$CHCl_3$	10	83:17
10	**D**	$NaHCO_3$	$CHCl_3$	45	95:5
11	**D**	$NaHCO_3$	DCE	45	83:17
12	**D**	$NaHCO_3$	EtOAc	25	97:3
13	**D**	$NaHCO_3$	THF	<5	
14[d]	**D**	$NaHCO_3$	$CHCl_3$	76	95:5

[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.10 mmol), base (0.12 mmol), and solvent (2.0 mL) under a N_2 atmosphere at rt for 24 h. [b]Isolated yield of **3a**. [c]The er values were determined via HPLC on chiral stationary phase. [d]**1a** (0.15 mmol), **2a** (0.10 mmol), **D** (0.02 mmol), $NaHCO_3$ (0.12 mmol), $CHCl_3$ (4.0 mL), and EtOH (0.30 mmol) under a N_2 atmosphere at 60 °C for 36 h.

optical purity, by using an excess amount of α-bromoenals **1a** in a diluted reaction system (Table 1, entry 14).

Having established optimized reaction conditions, we proceeded to examine the reaction scope using α-bromoenals **1** to react with *N*-benzyl-1*H*-indol-4-amine **2a**, as shown in Scheme 1. First, we examined the effect of α-bromoenals **1** with electron-withdrawing groups (F, Cl, Br, and CF_3) or an electron-donating group (OMe) on the benzene ring under the reaction conditions. These functional groups were well-tolerated, delivering the corresponding chiral C7-position indole derivatives in moderate to good yields with good enantioselectivities (**3b**−**3i**). To our delight, replacing the phenyl ring of **1a** with a 2-furyl group did not lead to any decrease in either the product yield or er value (**3j**). Additionally, this process could not be triggered when the phenyl ring of **1a** was switched to the alkyl moiety. The reason may be because the electrophilic ability of α-bromoenals **1** is weakened by the alkyl substituent.

We then selected **1a** as the model enal to investigate the effect of substituents on the benzyl moiety of *N*-benzyl-1*H*-indol-4-amine **2**, as shown in Scheme 2. It was found that electron-withdrawing substituents on the amine moiety of *N*-benzyl-1*H*-indol-4-amine **2** can slightly reduce the yield of the corresponding indole C7 functionalized products (**4a**−**4f**). The substituted benzyl group of **2** could be replaced with alky moieties, resulting in no erosion of the product yields or er values (**4g**−**4i**). Moreover, 4-diallylaminoindole **2k** could also be employed smoothly in this transformation to give **4j** in good yield and excellent enantioselectivity. It is noteworthy that the

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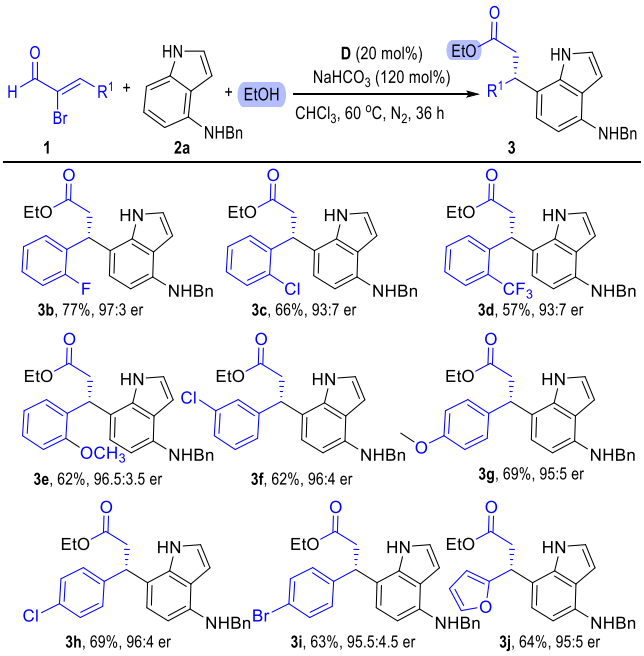
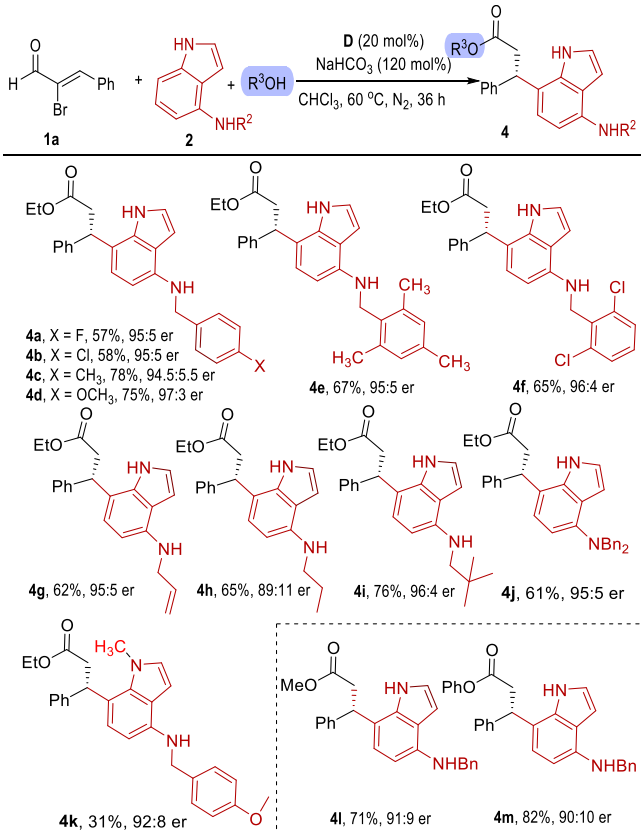
Scheme 1. Scope of α-Bromoenals 1[a]



[a]Yields represent isolated yields obtained after purification via column chromatography. Enantiomeric excess (er) values were determined through HPLC analysis employing a chiral stationary phase.

Scheme 2. Scope of 4-Aminoindoles 2 and Nucleophiles[a]



[a]Yields represent isolated yields obtained after purification via column chromatography. Enantiomeric excess (er) values were determined through HPLC analysis employing a chiral stationary phase.

N1-methylated substrate **2l** can undergo the reaction with **2a** under standard conditions, yielding the desired indole C7 position-functionalized product **4k** with excellent enantioselectivity. In addition, methanol and phenol proved to be effective nucleophiles in lieu of ethanol, albeit with slightly reduced er values (**4l** and **4m**, respectively).

To further explore the synthetic potential of this reaction, the NHC-catalyzed asymmetric indole C7 alkylation reaction between **1a** and **2g** was successfully performed at gram scale, maintaining both the yield and optical purity with no erosion (Figure 3). Subsequently, the chiral product **4f** could be efficiently transformed into compound **5** through a hydrolysis reaction with lossless enantioselectivity and yield (Figure 3).[18]

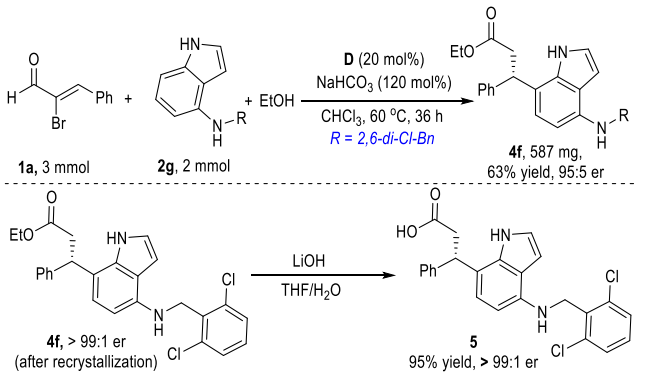


Figure 3. Gram-scale synthesis and synthetic transformations of **4f**.

Indole derivatives have been proven to exhibit various biological activities in numerous studies.[19] To delve deeper into the application of the C7-functionalized indole products, we evaluated their biological activity against *Psa*. *Psa* can infect *Actinidia* flowers, leading to browning and falling and ultimately causing the death of the whole plant. The optically enriched C7-functionalized indole products were tested *in vitro* for their antibacterial activity against *Psa* through turbidimetric tests at the concentrations of 100 and 50 μg/mL[20] (Table 2). Thiodiazole copper (TC) and bismerthiazol (BT), both commercial bactericides, were employed as positive controls. Nine of the indole products exhibited better inhibitory activities than TC and BT and have shown potential

Table 2. Preliminary Antibacterial Activities of the Target Compounds against *Psa*[a]

	inhibition rate (%)	
compounds	100 μg/mL	50 μg/mL
3b	58.35 ± 2.38	44.84 ± 2.13
3c	61.43 ± 1.97	49.65 ± 2.27
3d	57.58 ± 1.77	38.62 ± 1.57
3f	54.86 ± 2.75	38.48 ± 1.02
3h	57.88 ± 0.79	40.46 ± 1.28
3i	56.81 ± 2.53	39.12 ± 2.06
4a	59.12 ± 1.53	41.57 ± 1.68
4b	53.26 ± 1.67	39.75 ± 2.36
4f	60.45 ± 2.51	46.89 ± 1.72
TC[b]	50.53 ± 2.71	34.15 ± 2.38
BT[c]	46.45 ± 2.52	31.57 ± 2.15

[a]All data presented were averaged from three replicate experiments. [b]TC = thiodiazole copper. [c]BT = bismerthiazol.

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applications in the development of novel antibacterial lead compounds.

In conclusion, we developed the first NHC-catalyzed indole C7 position alkylation reaction of 4-aminoindoles with α-bromoenals, incorporating a chiral chain at the C7-position of indoles. The C7-alkylated indole products bearing diverse substituents and substitution patterns could be formed through our approach in generally moderate to good yields with good to excellent enantioselectivities. Notably, the target C7-functionalized indole products exhibit excellent antibacterial activity against *Psa*, demonstrating their potential applications for plant protection. Explorations of further applications of the chiral indoles obtained from our approach are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c04266.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 2290527 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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