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Enantioselective Indole N-H Functionalization Enabled by Addition of Carbene Catalyst to Indole Aldehyde at Remote Site

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ABSTRACT: An enantioselective functionalization of the indole NH group is developed. The reaction stereo-selectivity is controlled by an N-heterocyclic carbene catalyst that adds to an aldehyde moiety at the C7-carbon of indole. The NH group participated in the carbene-catalyzed reaction is part of the heteroaromatic rings of the indole substrate. Our reactions afford multi-cyclic products bearing pyrroloquinazoline or oxazinoindole scaffolds widely presented in bioactive molecules. Our study shall encourage further exploration of carbene-catalyzed reactions of aromatic molecules and asymmetric transformation of heteroatoms in various functional molecules.

KEYWORDS: *N*-heterocyclic carbene, *N*-H functionalization, indoles, asymmetric catalysis, heterocyclic compounds

The selective functionalization of (hetero)aromatic molecules continues to be a research focus in synthetic chemistry. Most of the progress in this field comes from transition metal-catalyzed processes.^[1] It remains much less developed to use organic catalysts to activate and functionalize aromatic molecules. One important progress in this direction involves combined photoredox and organocatalysis for radical reactions, as pioneered by MacMillan,^[2a] Melchiorre^[2b] and Phipps.^[2c] Another type of elegant aromatic molecule functionalization reactions involve amino catalysis, as reported by Jørgensen,^[2d] Chen^[2e] and Xu.^[2f] *N*-heterocyclic carbene (NHC) organic catalysis has found impressive success for asymmetric reactions of aldehydes,^[3] esters,^[4] and related carbonyl compounds.^[5] We are interested in exploring NHCs for asymmetric transformation of aromatic molecules.^[6] Indeed, the benzylic carbons of indoles^[7] and benzenes^[8] could be activated and further converted enabled via addition of NHC catalysts to the adjacent aryl aldehyde moieties, as reported by Glorius,^[8a] Rovis,^[8b] and us.^[7,8c] We have also found that through addition of an NHC catalyst to an aldehyde at the ortho-carbon, the phenolic OH group could be functionalized enantioselectively.^[9] Recently, Scheidt and co-workers reported that carbene catalyst could enable an asymmetric decarboxylative annulations via *aza-o*-quinone methides (*aza-o*-QMs) intermediate (Figure 1a).^[10]

Here we disclose that the indole NH groups can undergo enantioselective addition to ketones under the influence of

Figure 1. Research background and related bioactive molecule scaffolds.

chiral NHC catalysts (Figure 1b). The enantioselectivity is controlled by the NHC catalyst that adds to a remote aryl aldehyde moiety on the C7-carbon of the indole. Key steps in this process include the formation of Breslow intermediate and acyl azolium ester intermediate^[4] (**I**) that upon proton transfer forms *aza-o*-QMs-containing intermediate **II**.^[11] Formal [4+2] reaction of **II** with a reactive ketone substrate forms the acetal product (**3a**) with 99% yield and 95:5 er. The products (e.g., **3a**) obtained from our method bear pyrroloquinazoline or oxazinoindole scaffolds that are widely presented in bioactive molecules (Figure 1c).^[12] Notably, the reactive nitrogen atom in our reaction is part of the aromatic ring of the substrate, which is different from previous studies involving oxygen^[9] or nitrogen^[10] atoms attached to benzenes as the reactive sites. It is also worth to note that asymmetric construction of aminal and *N,O*-acetal units as those in our product is of significant synthetic values.^[13] Our present study shall encourage further development of asymmetric heteroatom functionalization methods for heteroaromatic compounds.

Notably, asymmetric functionalization of indole involving NHC organocatalysis has attracted considerable attentions, with impressive studies reported by Enders,^[3h] Studer^[3i] and Biju.^[3j] In these previous studies,^[3h-j] the indole moiety behaves as a partner to react with another substrate that is activated by the NHC catalysts; the indole moiety itself is not activated by the catalyst. In our present study, activation of the indole substrate by the NHC catalyst is the critical step for the reaction to proceed.

Key results of condition optimization using indole-7-carbaldehyde **1a** and trifluoroacetophenone **2a** as model substrates are summarized in Table 1. The aminoindanol-derived triazolium pre-catalyst (**A**) with an *N*-mesityl substituent,^[14] an excellent catalyst in a large set of reactions, was ineffective here (entry 1). Replacing the *N*-mesityl unit with an *N*-(2,6-diethylphenyl) group (pre-catalyst **B**)^[15] gave similar results (entry 2). We then found that when the electron-deficient trichlorophenyl was used as the *N*-substituent of the pre-catalyst (**C**),^[16] the reaction could proceed to form **3a** with an encouraging 90:10 er, albeit in a low yield (8%) (entry 3). The product yield was dramatically improved when NHC pre-catalyst

Table 1: Optimization of the Reaction Conditions^a

<p>A: Ar = Mes B: Ar = 2,6-Et₂C₆H₃ C: Ar = 2,4,6-Cl₃C₆H₂ D: Ar = C₆F₅ E: Ar = C₆F₅, R = NO₂ F: Ar = C₆F₅</p> <p>DQ (oxidant)</p>						
entry	NHC	base	solvent	t (h)	yield (%) ^b	<i>e.r.</i> ^c
1	A	Cs ₂ CO ₃	CH ₂ Cl ₂	24	trace	-

2	B	Cs ₂ CO ₃	CH ₂ Cl ₂	24	trace	-
3	C	Cs ₂ CO ₃	CH ₂ Cl ₂	24	8	90:10
4	D	Cs ₂ CO ₃	CH ₂ Cl ₂	3	90	95.5:4.5
5	E	Cs ₂ CO ₃	CH ₂ Cl ₂	3	74	3.5:96.5
6	F	Cs ₂ CO ₃	CH ₂ Cl ₂	3	70	91:9
7	D	K ₂ CO ₃	CH ₂ Cl ₂	12	24	95.5:4.5
8	D	DBU	CH ₂ Cl ₂	12	51	95:5
9	D	DIEA	CH ₂ Cl ₂	3	99	95.5:4.5
10	D	DIEA	THF	3	56	95.5:4.5
11	D	DIEA	toluene	3	57	92:8

^a Reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), base (1.0 equiv), NHC (20 mol%), and DQ (1.2 equiv) in solvent (1.0 mL) at rt; ^b Isolated yield; ^c Enantiomeric ratio of **3a** was determined via HPLC on a chiral stationary phase.

D with an *N*-pentafluorophenyl group was used as the reaction catalyst.^[17] The product was obtained in 90% yield and 95.5:4.5 er, with Cs₂CO₃ as the base, CH₂Cl₂ as the solvent and DQ as the oxidant (entry 4).^[18] Installing a NO₂ group on the indane moiety of catalyst **D** (to get catalyst **E**) led to a small improvement on the product er value but with drop on the reaction yield (entry 5). Phenylalanine-derived catalyst **F**^[19] was also efficient for this transformation, with the product **3a** afforded in 70% yield and 91:9 er (entry 6). Various organic and inorganic bases could be used in this transformation (entries 7-9), and DIEA was found as the most efficient one that could give **3a** in quantitative yield without erosion of the er value (entry 9). Screening of different reaction solvents did not show further improvements in either the product yields or enantioselectivities (entries 10-11).

Having established the optimal reaction conditions, we set out to explore the generality of this protocol. First, the scope of electron-deficient ketone substrates was examined (Table 2). Aromatic trifluoromethyl ketones with halogen atoms (**3b-d**), electron-donating (**3e** and **3f**) and electron-withdrawing (**3g**) groups on the *para*-position of the phenyl rings were well tolerated, with all of the target products obtained in excellent yields and er values. Substitutions on the *meta*-position of the phenyl rings resulted in slight drops on the enantioselectivities (**3h** and **3i**). The benzene ring of the trifluoromethyl ketone **2a** could be switched into fused aromatic groups such as 2-naphthalene group and 3-indolene group, with corresponding products afforded in excellent yields and enantioselectivities (**3j** and **3k**). To our great delight, aliphatic trifluoromethyl ketones 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 (**3l** and **3m**). Furthermore, difluoromethyl ketone and α -ketoester were also found as suitable reactants in this catalytic transformation, and both of the target products could be obtained in good yields with excellent er values (**3n** and **3o**).

Table 2: Scope of acyclic ketones^a

^a Reaction conditions: **1a** (0.15 mmol), **2** (0.1 mmol), DIEA (1.0 equiv), NHC **D** (20 mol%), and DQ (1.2 equiv) in CH₂Cl₂ (1.0 mL) at rt.

Next, we turned our attention to investigate the scope of indole-7-carbaldehydes **1** with trifluoroacetophenone **2a** as the

Table 3: Scope of indole-7-carbaldehydes^a

^a Reaction conditions: **1** (0.15 mmol), **2a** (0.1 mmol), DIEA (1.0 equiv), NHC **D** (20 mol%), and DQ (1.2 equiv) in CH₂Cl₂ (1.0 mL) at rt.

model substrate. The results are summarized in Table 3. Installing a methyl group at the indole 3-position (**3p**) or chloro-

atom at 4-position (**3q**), the products were obtained in excellent yields with good enantioselectivities. Substitutions on the indole 5- and 6-positions could give the desired products in excellent yields and optical purities, regardless of the electronic properties (**3r** to **3w**).

To further demonstrate the generality and utility of our synthetic protocol, we next explored the reaction using isatin derivatives as the substrates to construct spiro-cyclic compounds **5** (Table 4). It has been well documented that many indole- and isatin-containing molecules exhibited interesting and important bioactivities, such as antitumor, anti-HIV and antimicrobial activities.^[20] After identification of the optimal reaction conditions (see SI), we found that NHC precatalyst **E** could give the product **5a** in excellent yield and enantioselectivity. A wide range of isatin substrates were then smoothly converted into the spiro-cyclic compounds **5** in good yields with excellent enantioselectivities (**5a-i**). In addition, indole-7-carbaldehydes bearing various substituents were employed in this process, which provided the products in good to excellent yields with excellent er values (**5j-p**).

Table 4: Asymmetric N-H functionalization of indole-7-carbaldehydes with isatins^a

^a Reaction conditions: **1** (0.15 mmol), **4** (0.1 mmol), DIEA (1.0 equiv), NHC **E** (20 mol%), and DQ (1.2 equiv) in CH₂Cl₂ (1.0 mL) at rt.

Imine substrates were also tested for this catalytic transformation. After screening of different imine electrophiles (see SI), the electron deficient imine **6** could react smoothly with indole-7-carbaldehyde **1a** and give product **7** in 95% yield and 83:17 er. The er value of the afforded product could be improved to 97:3 after a simple recrystallization from ethyl acetate (Scheme 1a). To evaluate the practicality of our method, a

scale-up reaction was carried out. By treating of **1i** (3.0 mmol, 0.3 M) and **2a** (2.0 mmol, 0.2 M) using 5 mol% NHC precatalyst **D**, product **3w** (0.66 g) was obtained with 94% yield and 96.5:3.5 er value that are comparable to the small-scale reaction (96% yield, 96.5:3.5 er) (Scheme 1b).

Scheme 1. (a) Asymmetric N-H functionalization of indole-7-carbaldehyde **1a with imine **6** and (b) Scale-up synthesis with a lower catalyst loading.**

The plausible [4 + 2] annulation pathway is shown in Figure 2. The addition of NHC to aldehyde **1a** forms Breslow intermediate, which undergoes oxidation reaction to generate acylazolium ester intermediate **I**. After deprotonation of intermediate **I**, the analogous *aza-o*-QMs intermediate (**II**) is formed. Finally, a formal [4 + 2] annulation reaction between intermediate **II** and trifluoroacetophone **2a** provides the desired product **3a** and regenerates the NHC catalyst. We calculated Mulliken atomic charges for intermediate **II** and found that the O and N atoms have partial negative charges of -0.481 and -0.631, respectively. These fractional charges indicate that **II** cannot be described as either of the two extreme resonance structures depicted in Figure 2. The real state of analogous *aza-o*-QMs intermediate should lie somewhere in between.

Figure 2. Proposed catalytic cycle for formal [4 + 2] cycloaddition.

In summary, we have realized the first enantioselective functionalization of indole N-H group through NHC catalysis. The addition of the NHC catalyst to the aldehyde moiety at a remote site of indole (indole-7-carbaldehydes) initiates the reaction and controls the stereo-selectivity. Our study demonstrates that the nitrogen atom in heteroaromatic molecules can undergo asymmetric formal cycloaddition reactions with the catalysis of NHCs. The multi-cyclic *N,O*-acetal and aminor products could be obtained in up to quantitative yields with excellent er values. Further development of asymmetric heteroatom functionalization and their synthetic applications are in progress in our laboratories.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, analytical and spectroscopic data for new compounds, and copies of NMR and HPLC spectra (PDF)

Crystallographic data for **3k** (CIF)

Crystallographic data for **5a** (CIF)

Crystallographic data for **7** (CIF)

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Notes

The authors declare no competing financial interests.

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