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Addition of Carbene Catalyst to Indole Aryl Aldehyde Activates Remote δ -sp²-Carbon for Protonation and Formal [4 + 2] Reaction

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Supporting Information Placeholder

ABSTRACT: The addition of a carbene catalyst to an indole aryl aldehyde leads to the activation of a remote sp²-carbon that is five atoms away from the catalyst. The unsaturated Breslow intermediate formed between catalyst and substrate undergoes an internal redox reaction and remote carbon protonation to generate analogous azolium vinyl enolate intermediate. Subsequent [4+2] reaction with cyclic imine substrates eventually affords multi-cyclic pyridoindoles as nearly single diastereomers with excellent enantioselectivities.

Aromatic units are among the most common building blocks in natural and synthetic functional molecules. It is of obvious importance to develop asymmetric methods for efficient functionalization of the aromatic carbons or other atoms adjacent to the aromatic scaffolds. Organic molecule catalysts have been shown to offer excellent controls on chemo- and stereoselectivities for many reactions.¹ However, it remains difficult to employ organic catalysis for enantioselective transformation of aromatic compounds.² Specifically, it is illusive to push the power of N-heterocyclic carbene (abbreviated as NHC or carbene) catalyst across an all-carbon aromatic ring for the functionalization of the aromatic sp²-carbons (Figure 1a, A) or benzylic sp³-carbons (Figure 1a, B). In 2013, we found that by using indole aryl aldehyde as the substrate, addition of an NHC catalyst to the aldehyde could eventually lead to enantioselective functionalization of the indole benzylic carbon (Figure 1a, C).³ Glorius' and Rovis' groups have found that the introduction of an electronegative Br atom to an aryl aldehyde could lead to

NHC-mediated functionalization of its benzylic carbon (Figure 1a, D).⁴ Our lab recently found that the incorporation of a silicon atom to an aryl carboxylic ester (Figure 1a, E) could facilitate benzylic carbon functionalization via NHC organocatalysis.⁵

Here we disclose that the addition of an NHC catalyst to indole aryl aldehyde can lead to the functionalization of the remote δ -sp²-carbon (Figure 1a, F) via an extended Breslow intermediate (Figure 1a, G). Briefly, reaction of the NHC catalyst with the indole aldehyde substrate **1** forms an extended homoenolate intermediate **I** with two potentially nucleophilic carbons (Figure 1b, the β - and δ -carbons of intermediate **I**). The indole aldehyde δ -sp² carbon is then protonated to afford the dienolate intermediate **II**, which subsequently reacts with imine substrate **2a** to generate intermediate **III** via an enantioselective formal [4 + 2] cycloaddition process. Elimination of the NHC catalyst finally gives the chiral multi-cyclic pyrido[4,3-b]indole product **3** in good to excellent yields and er values. Interestingly, the

pyrido[4,3-*b*]indole structure formed in this transformation are found in pharmaceutically interesting bioactive molecules (Figure 1c).⁶

(a) activation of aromatic compounds via addition of NHC to aldehydes or esters

(b) activation of remote carbon of indole aldehyde via NHC organocatalysis (this work)

(c) bioactive molecules containing pyrido[4,3-*b*]indole scaffolds

Figure 1. Activation of the sp^2 - and Benzylic- sp^3 -Carbons of Aromatic Compounds and Bio-activities of Pyrido[4,3-*b*]indoles.

A Boc-protected indole aldehyde **1a** was chosen as a model substrate to react with cyclic sulfonic imine **2a** (Table 1). A multi-cyclic pyrido[4,3-*b*]indole product **3a** could be smoothly afforded under the catalysis of a variety of NHCs (e.g., Table 1, entries 1 to 2). The chiral amino-indanol-derived NHC catalyst **4b**, first introduced by Bode and co-workers,⁷ gave the desired product **3a** in promising isolated yield with excellent enantioselectivity (entry 2). The bases could significantly influence the reaction yields. The use of Cs_2CO_3 as the base could dramatically improve the product yield with little erosion of the er value (entry 3). Several organic bases tested here failed to facilitate the product formation (e.g., entries 4 to 5). The solvents also had clear influence on this catalytic transformation. The use of ethyl acetate as solvent led to **3a** with a moderate yield and excellent enantioselectivity (entry 6). A few other solvents examined here gave only trace amount of the desired product (e.g., entries 7 to 8). To our

delight, both the yield and er values of **3a** could be further improved when a catalytic amount of Cs_2CO_3 was used as the base, **4b** as the NHC pre-catalyst, and THF as the solvent (entry 9). Further decreasing the loading of the NHC catalyst **4b** would result in drop on the product yield (entry 10). Notably, all the products formed in this catalytic process were isolated as essentially single diastereomers.

Table 1. Optimization of Reaction Conditions.^a

entry	NHC	base	solvent	yield (%) ^b	er ^c
1	4a	K_2CO_3	THF	30	80:20
2	4b	K_2CO_3	THF	35	96:4
3	4b	Cs_2CO_3	THF	80	93:7
4	4b	DBU	THF	<5	-
5	4b	Et_3N	THF	<5	-
6	4b	Cs_2CO_3	EtOAc	40	96:4
7	4b	Cs_2CO_3	Toluene	<5	-
8	4b	Cs_2CO_3	CH_2Cl_2	<5	-
9 ^d	4b	Cs_2CO_3	THF	82	97:3
10 ^{d,e}	4b	Cs_2CO_3	THF	40	97:3

^aGeneral conditions (unless otherwise specified): **1a** (0.1 mmol), **2a** (0.09 mmol), NHC (0.03 mmol), base (0.1 mmol), solvent (2.0 mL), RT, 12 h. ^b Isolated yield of **3a**. ^c The er values were determined via HPLC on chiral stationary phase. ^d Cs_2CO_3 (0.03 mmol) was used as the base. ^e **4b** (0.02 mmol) was used.

With the optimized reaction condition at hand (as stated in Table 1, entry 9), we then examined the substrate scope of this transformation (Scheme 1). Electron-donating groups were well tolerated on the 5- and 6-positions of the indole aldehyde substrates, with the desired products afforded in moderate to good isolated yields and excellent enantioselectivities (**3a** to **3f**). The er values of the products were decreased when substituents were installed on the 4-position of the indole ring (**3g**). This decrease in er value is probably due to the steric hindrance caused by the 4-substituents (**3g**). Indole aldehydes bearing electron-withdrawing groups also worked well in this reaction, although the product yields slightly decreased (**3h** to **3k**). However, switching the ester groups on the indole aldehyde **1** into other functional groups (e.g., CN, C(=O)Ph, Ph) resulted in no formation of the desired products. Similarly, both electron-donating (**3l** to **3p**) and electron-withdrawing groups (**3q** to **3s**) could be installed on the cyclic sulfonic imine substrates. Replacing the ester group on the imine molecules with a phenyl ring led to no product formation. Moreover, imine substrates derived from isatin or benzaldehyde were not effective for this [4 + 2] cycloaddition reaction. It's worth to note that all our reaction products (**3a-s**) are obtained as single diastereomers. Additionally, our catalytic reactions are readily scalable without obvious erosions of either the reaction yield or the product optical purity (Scheme 2).

Scheme 1. Scope of Reactions ^a

scope of indole aldehyde:

scope of sulfonic imide:

unsuccessful indole substrates:

unsuccessful imine substrates:

^aReaction conditions as stated in Table 1, entry 9. Yields are isolated yields after purification by column chromatography. Er values were determined via HPLC on chiral stationary phase.

Scheme 2. Gram Scale Synthesis of **3a**.

We have also carried out this internal redox [4 + 2] cycloaddition reaction with a deuterated starting material **1a'** (> 99% D) to further understand the reaction mechanism (Scheme 3, eq. 1). The δ -carbon of the substrate **1a'** was deuterated in 50% yield through this [4 + 2] reaction. A fully deuterated product (**3a'**) could be obtained from the normal indole aldehyde **1a** by adding 10 equivn. of D₂O into the reaction system (eq. 2). This observation (partial deuteration) indicates that the internal redox transformation likely went through a deprotonation / protonation process (from intermediate **I** to **II**; as shown in Figure 1b). As a technical note, the normal product **3a** did not go through proton exchanging process with D₂O under the identical catalytic condition (eq. 3). This indicates that the proton shift from intermediate **I** to **II** goes through an intermolecular proton transfer process and the moisture existed in the catalytic system may behave as a proton shuttle for this process.

Scheme 3. Isotope Labelling Experiment

The Boc protecting group of the chiral product **3a** could be easily removed under acidic condition to give the free indole derivative **4a** in good yield with retention of the optical purity (Scheme 4).

Scheme 4. Removal of Boc Protection Group of **3a**

The absolute configurations of the chiral pyrido[4,3-b]indole products **3** were estimated according to the X-ray analysis on the single crystals of **3a** (Figure 2a). A rational for the reaction stereoselectivity is illustrated in Figure 2b.⁸ The Re face of the γ -carbon of the dienolate intermediate **II** is blocked by the chiral motif of the NHC catalyst, and the Re face of the sp^2 -carbon on substrate **2a** is favored due to steric effect. The [4 + 2] reaction between the most favorable faces of substrates **2a** and intermediate **II** led to product **3a** in an enantio- and diastereoselective manner.

a) X-ray structure of **3a**

Figure 2. X-ray Analysis of **3a and Rational of Stereo-Selectivity.**

In summary, we have developed an organic catalytic method for remote carbon functionalization of indole aryl aldehydes. The analogous δ - sp^2 -carbon of the indol aryl aldehyde is protonated via a carbene catalyst-enabled internal redox process to generate azolium vinyl enolate intermediate. Subsequent formal cycloaddition reaction with cyclic imines affords multi-cyclic pyrido[4,3-b]indoles as single diastereomers with excellent enantioselectivities. Further investigations into remote-carbon activation of aryl aldehydes for broader reactions, and investigations of heterocyclic compounds for bioactivities are in progress in our laboratories.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interests.

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