OL | Organic Letters

Letter

Cite This: Org. Lett. 2019, 21, 5026–5029

pubs.acs.org/OrgLett

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

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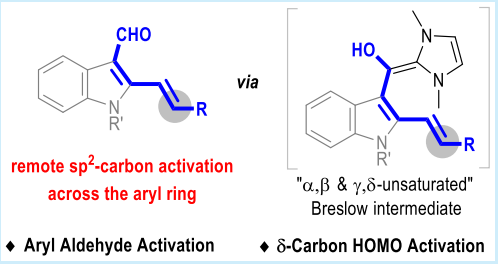
Supporting Information

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



Aromatic units are among the most common building blocks in natural and synthetic functional molecules. Developing asymmetric methods for efficient functionalization of the aromatic carbons or other atoms adjacent to the aromatic scaffolds is obviously important. Organic molecule catalysts have been shown to offer excellent controls on chemo- and stereoselectivities for many reactions.[1] However, employing organic catalysis for enantioselective transformation of aromatic compounds remains difficult.[2] Specifically, pushing the power of an N-heterocyclic carbene (abbreviated as NHC or carbene) catalyst across an all-carbon aromatic ring for the functionalization of the aromatic sp^2 carbons (Figure 1a, **A**) or benzylic sp^3 carbons (Figure 1a, **B**) is illusive. 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] The groups of Glorius and Rovis 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-sp^2 carbon (Figure 1a, **F**) via an extended Breslow intermediate (Figure 1a, **G**). Briefly, reaction of the NHC catalyst with 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-sp^2 carbon is then protonated to afford dienolate intermediate **II**, which subsequenlty reacts with imine substrate **2a** to generate intermediate **III** via an enantioselective formal [4+2] cycloaddition process. Elimination of the NHC catalyst finally gives chiral multicyclic 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 is found in pharmaceutically interesting bioactive molecules (Figure 1c).[6]

A Boc-protected indole aldehyde **1a** was chosen as a model substrate to react with cyclic sulfonic imine **2a** (Table 1). A multicyclic 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 and 2). Chiral amino-indanol-derived NHC catalyst **4b**, first introduced by Bode and co-workers,[7] gave desired product **3a** in a 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 product formation (e.g., entries 4 and 5). The solvents also had a clear influence on this catalytic transformation. The use of ethyl acetate as a solvent led to **3a** in a moderate yield with excellent enantioselectivity (entry 6). A few other solvents examined here gave only a trace amount of the desired product (e.g., entries 7 and 8). To our delight, the yield and er values of **3a** were further improved when a catalytic amount of Cs_2CO_3 was used as the base, **4b** as the

Received: May 7, 2019
Published: June 14, 2019

DOI: 10.1021/acs.orglett.9b01624
Org. Lett. 2019, 21, 5026–5029

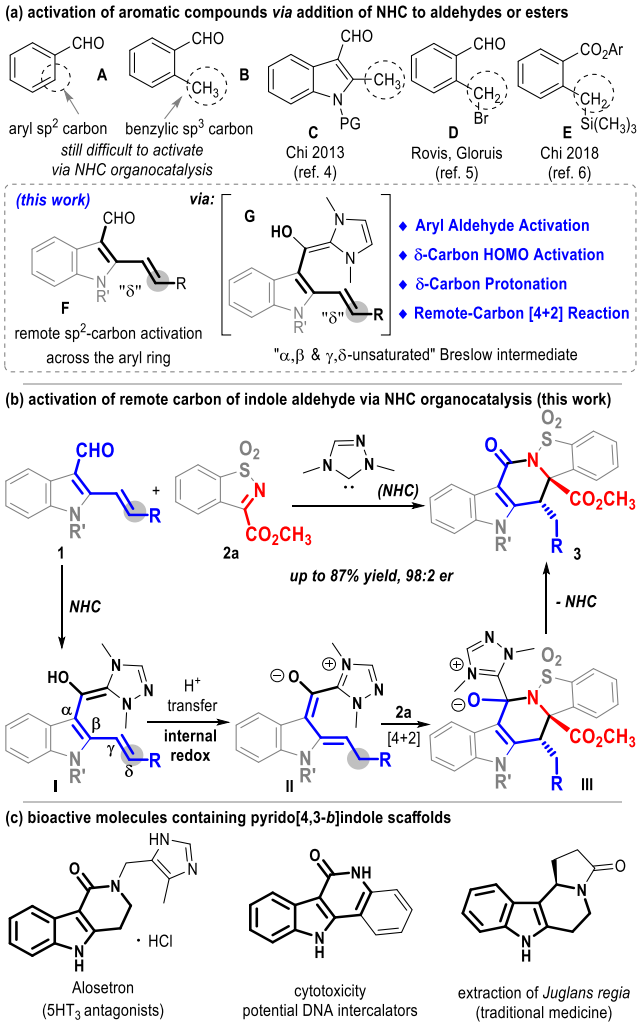
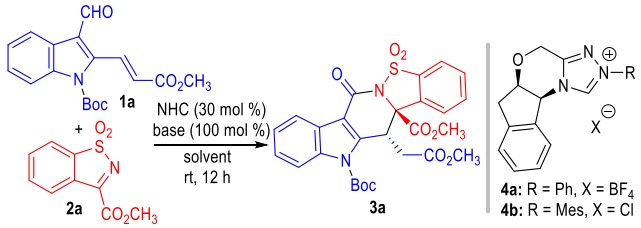


Figure 1. Activation of the sp^2 and benzylic sp^3 carbons of aromatic compounds and bioactivities of pyrido[4,3-*b*]indoles.

NHC precatalyst, and THF as the solvent (entry 9). Further decreasing the load of NHC catalyst **4b** would result in decrease in the product yield (entry 10). Notably, all of the products formed in this catalytic process were isolated as essentially single diastereomers.

With the optimized reaction condition in hand (as stated in Table 1, entry 9), we examined the substrate scope of this transformation (Scheme 1). Electron-donating groups were well tolerated at positions 5 and 6 of the indole aldehyde substrates, with the desired products produced in moderate to good isolated yields and excellent enantioselectivities (**3a**–**3f**). The er values of the products were decreased when substituents were installed at position 4 of the indole ring (**3g**). This decrease in the er value is probably due to the steric hindrance caused by substituents at position 4 (**3g**). Indole aldehydes bearing electron-withdrawing groups also worked well in this reaction, although the product yields slightly decreased (**3h**–**3k**). However, switching the ester groups on indole aldehyde **1** to other functional groups (e.g., CN, COPh, or Ph) resulted in no formation of the desired products. Similarly, both electron-donating (**3l**–**3p**) and electron-withdrawing (**3q**–**3s**) groups could be installed on the cyclic sulfonic imide substrates. Replacing the ester group on the imine molecules with a phenyl ring led to no product

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

[a]General 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 the chiral stationary phase. [d]Cs_2CO_3 (0.03 mmol) was used as the base. [e]**4b** (0.02 mmol) was used.

formation. Moreover, imine substrates derived from isatin or benzaldehyde were not effective for this [4+2] cycloaddition reaction. It is worth noting that all of our reaction products (**3a**–**3s**) were obtained as single diastereomers. Additionally, our catalytic reactions can be readily scaled without obvious erosion of either the reaction yield or the product optical purity (Scheme 2).

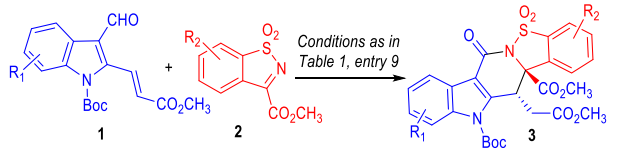
We have also carried out this internal redox [4+2] cycloaddition reaction with a deuterated starting material **1a′** (>99% D) to further understand the reaction mechanism (Scheme 3, eq 1). The δ carbon of substrate **1a′** was deuterated in 50% yield through this [4+2] reaction. A fully deuterated product (**3a′**) could be obtained from normal indole aldehyde **1a** by adding 10 equiv of D_2O to the reaction system (eq 2). This obseration (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, normal product **3a** did not go through proton exchange process with D_2O 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 that is present in the catalytic system may behave as a proton shuttle for this process.

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

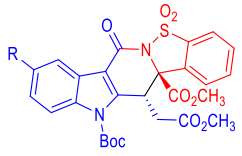
The absolute configurations of chiral pyrido[4,3-*b*]indole products **3** were estimated according to the X-ray analysis on the single crystals of **3a** (Figure 2a). A rationale for the reaction stereoselectivity is illustrated in Figure 2b.[8] The re face of the γ carbon of dienolate intermediate **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 the steric effect. The [4+2] reaction between the most favorable faces of substrates

DOI: 10.1021/acs.orglett.9b01624
Org. Lett. 2019, 21, 5026–5029

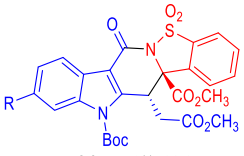
Scheme 1. Scope of Reactions[a]



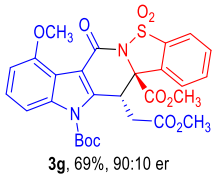
scope of indole aldehyde:



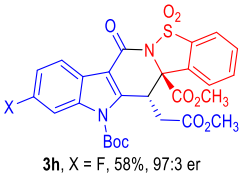
3a, R = H, 82%, 97:3 er
3b, R = OCH_3, 87%, 97:3 er
3c, R = CH_3, 60%, 98:2 er



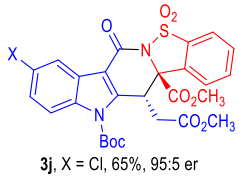
3d, R = OCH_3, 79%, 98:2 er
3e, R = CH_3, 43%, 98:2 er
3f, R = $C(CH_3)_3$, 71%, 97:3 er



3g, 69%, 90:10 er

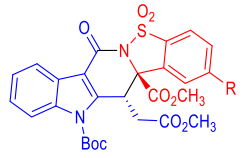


3h, X = F, 58%, 97:3 er
3i, X = Cl, 66%, 96:4 er

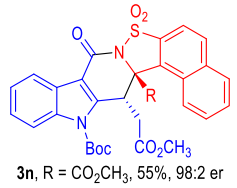


3j, X = Cl, 65%, 95:5 er
3k, X = Br, 64%, 94:6 er

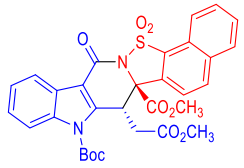
scope of sulfonic imide:



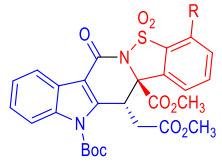
3l, R = OCH_3, 71%, 98:2 er
3m, R = CH_3, 68%, 98:2 er



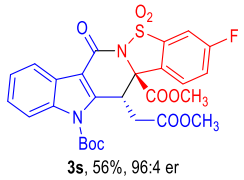
3n, R = CO_2CH_3, 55%, 98:2 er



3o, 65%, 95:5 er

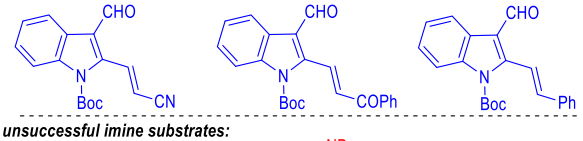


3p, R = OCF_3, 38%, 96:4 er
3q, R = CF_3, 64%, 97:3 er
3r, R = Cl, 62%, 97:3 er

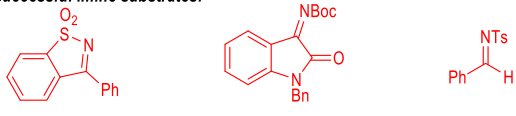


3s, 56%, 96:4 er

unsuccessful indole substrates:

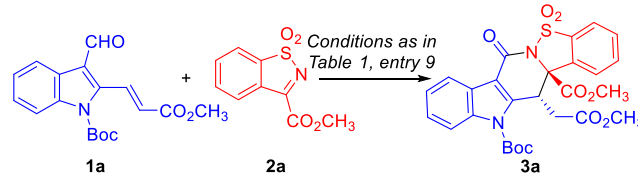


unsuccessful imine substrates:

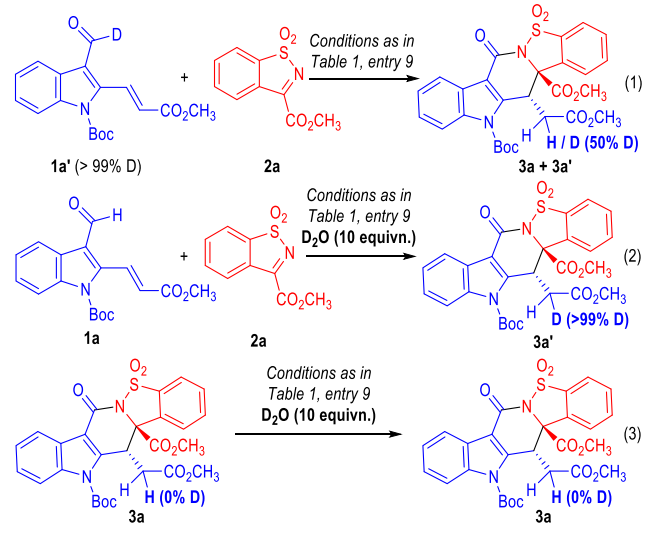


[a]Reaction conditions as stated in entry 9 of Table 1. Yields are isolated yields after purification by column chromatography. The er values were determined via HPLC on a chiral stationary phase.

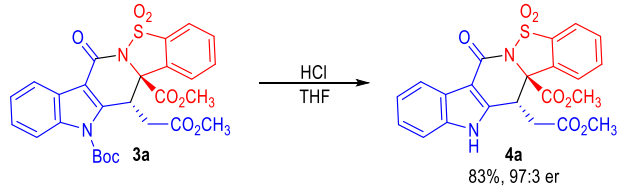
Scheme 2. Gram Scale Synthesis of 3a



Scheme 3. Isotope Labeling Experiment



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



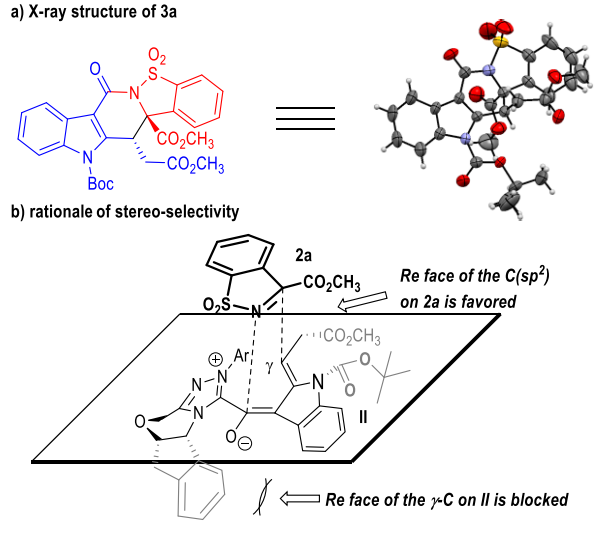


Figure 2. X-ray analysis of **3a** and rationale for stereoselectivity.

2a and intermediate **II** led to product **3a** in an enantio- and diastereoselective manner.

In summary, we have developed an organic catalytic method for remote carbon functionalizatoin 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 an azolium vinyl enolate intermediate. Subsequent formal cycloaddition with cyclic imines affords multicyclic pyrido[4,3-*b*]indoles as single diastereomers with

DOI: 10.1021/acs.orglett.9b01624
Org. Lett. 2019, 21, 5026−5029

excellent enantioselectivities. Further investigations into remote carbon activation of aryl aldehydes for broader reactions and investigations of the bioactivities of heterocyclic compounds are in progress in our laborotories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01624.

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

Accession Codes

CCDC 1817493 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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Author Contributions

‖P.Z., S.W., and C.M. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge financial support from the National Natural Science Foundation of China (21772029, 21472028, and 21807019), the Natural Science Foundation of Guizhou University (GZU[2017]35), the Opening Foundation of the Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University (2018GDGP0101), and Guizhou University, the Guizhou Province First-Class Disciplines Project (YiLiu Xueke Jianshe Xiangmu) [GNYL(2017)008], Guizhou University of Traditional Chinese Medicine, the Singapore National Research Foundation (NRF-NRFI2016-06), the Ministry of Education of Singapore (MOE2013-T2-2-003, MOE2016-T2-1-032, and RG108/16), an A*STAR Individual Research Grant (A1783c0008), a Nanyang Research Award Grant, and Nanyang Technological University.

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