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NHC-catalyzed [12 + 2] reaction of polycyclic arylaldehydes for access to indole derivatives

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An *N*-heterocyclic carbene (NHC) catalyzed enantio- and diastereoselective [12 + 2] cycloaddition is disclosed to rapidly construct sophisticated molecules bearing tricyclic core and morpholine moiety. The success of our reaction relies on the NHC-catalyzed remote sp³ (C-H) bond activation of a 5*H*-benzo[*a*]pyrrolizine-3-carbaldehyde under oxidative conditions. Preliminary studies revealed that our products exhibit superior *in vitro* bioactivities against two plant pathogens to commercial Bismerthiazol (BT) and Thiodiazole Copper (TC).

Morpholine is a privileged structure in numerous commercial drugs and natural products due to its unique physicochemical, biological, and metabolic properties.[1] For example, pollenopyrroside A and pollenopyrroside B that contain pyrrole-fused morpholine moiety are natural products isolated from bee-collected rape pollen[2] or Chinese herbs (Figure 1a)[3]. Both of them have been used to treat central nervous system disorders, prostatitis, and diabetic nephropathy[4]. Tetracyclic butyrophenone that bears polycyclic core and morpholine moiety (Figure 1a) has proven orally bioavailable and highly efficacious as 5-HT_{2A} antagonists in rats[5]. Therefore, the development of synthetic methods to access morpholine derivatives containing complex polycyclic structures is of particular interest.

Due to the versatile activation model and excellent stereoselectivity, organocatalytic cycloadditions have become one of the most powerful and frequently used strategies to construct complex molecules, especially those bearing complex ring systems with medium and large multi-ring skeleton[6]. For example, in 2019, Jørgensen's group reported the chiral amine-catalyzed chem-, regio-, and stereoselective hetero-[6+4] / [6+2] cycloadditions to construct polycyclic pyrroles, imidazoles, and pyrazoles.[7] A variety of anti-bacterial N, O-acetals have also been facilely accessed through chiral *N*-heterocyclic carbene (NHC)-catalyzed enantioselective [10 + 2] cycloaddition reaction via the formation of an aza-fulvene-typed acyl azolium intermediate (Figure 1b).[8] Recently, Jørgensen and co-workers have achieved a chiral amine-catalyzed enantioselective [8 + 2] higher-order cycloaddition reaction to construct a chiral cycl[3.2.2]azine core that contained a fused aza-tricyclic ring structure (Figure 1b).[9]

Inspired by these seminal works and as part of our continuous interest in NHC-catalyzed remote activation to forge polycyclic molecules[10], we herein postulate a new method to construct morpholine-containing polycyclic molecules via an enantio- and diastereoselective [12 + 2] higher-order cycloaddition between 5*H*-benzo[*a*]pyrrolizine-3-carbaldehydes and 2π-electrophilic reagents (Figure 1c). In particular, an NHC-catalyzed remote C(sp³)-H bond activation of 5*H*-benzo[*a*]pyrrolizine-3-carbaldehydes was proposed to produce a 12π species that was trapped by an electron-deficient 2π components. A specific model reaction between 5*H*-benzo[*a*]pyrrolizine-3-carbaldehydes (**1a**) and *N*-benzyl-protected isatines (**2a**) was presented in Figure 1c. React the free carbene with aldehydes (**1a**) forms a Breslow intermediate followed by an oxidation reaction under the oxidative conditions to eventually generate an NHC-bound acyl azolium intermediate (**I**). Deprotonation of the intermediate **I** at C6 forms the carbon anion that is in equilibrium with a 12π species (**II**) via the tautomerization process. Subsequent addition of such a 12π species (**II**) to isatine based 2π electrophiles followed by regenerating the carbene eventually afford the target product **3**. A series of structurally complex molecules with tricyclic core and morpholine moiety were obtained in good yields with high optical purity from easily prepared starting materials via this NHC-catalyzed higher-order cycloaddition. Importantly, preliminary studies revealed that most of our products exhibited *in vitro* bioactivities against *Xanthomonas axonopodis* pv. *citri* (*Xac*) and

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Xanthomonas oryzae pv.*oryzae* (*Xoo*). Some of them even showed superior bioactivities to the commercial Bismerthiazol (BT) and Thiodiazole Copper (TC).

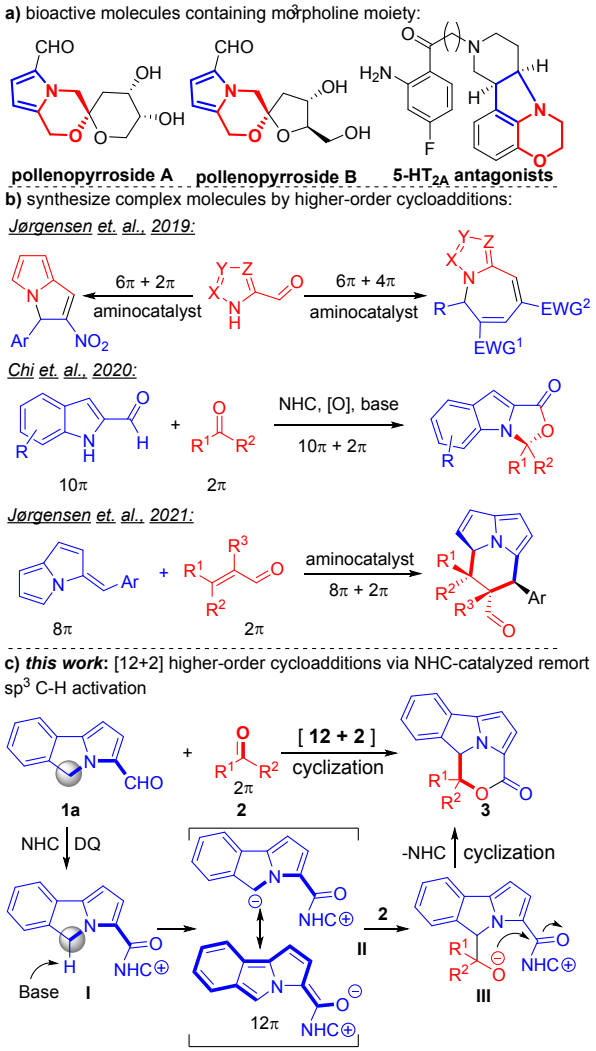
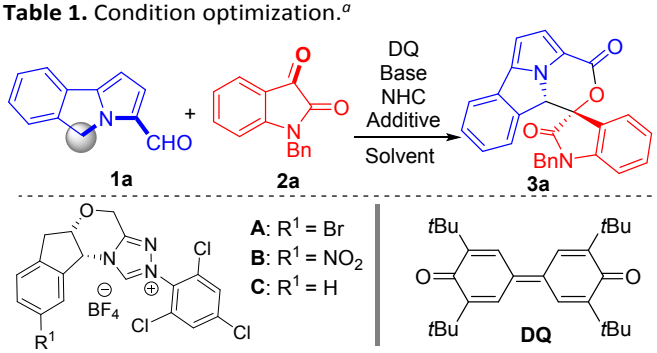


Figure 1. Morpholine moiety containing bioactive molecules and research background.

We start to search for suitable conditions for the proposed higher-order cycloaddition reactions using 5*H*-benzo[*a*]pyrrolizine-3-carbaldehydes (**1a**) and *N*-benzyl-protected isatin (**2a**) as the model substrates, and the results were summarized in Table 1. Initial studies (entries 1-3) revealed that in the presence of diisopropylethylamine (DIPEA) as a base, tetra-tert-butyldiphenylquinone (DQ) as the oxidant, and chloroform as the solvent, triazolium salts bearing *N*-C_6Cl_3 group could promote the reactions between **1a** and **2a** smoothly to afford **3a** in high yield (82%) with excellent diastereoselectivity (10:1 dr), although the enantioselectivity was not satisfactory (66:34 er). Further screening of the solvents showed that tetrahydrofuran (THF) gave **3a** with higher stereoselectivity, albeit with a lower yield (entry 5). We then explored the influence of the base on the enantioselectivity (entries 6-8). We were pleased to find that the target product **3a** was obtained in 16:1 dr and 85:15 er when (*t*-BuO)$_2$Mg was used as the base. Increasing the loading of the (*t*-BuO)$_2$Mg resulted in a slightly increased er value but a lower dr value (entry 10). Interestingly, the addition of triethylamine (TEA) or diisopropylethylamine (DIPEA) as an additive resulted in significant improvements both in the yields and dr values (entries 11 and 12). When the reaction was carried out at a lower temperature (-5 °C), the reaction gave a better result with **3a** isolated in 79% yield, > 20:1 dr, and 91:9 er (entry 13).

Table 1. Condition optimization.[a]

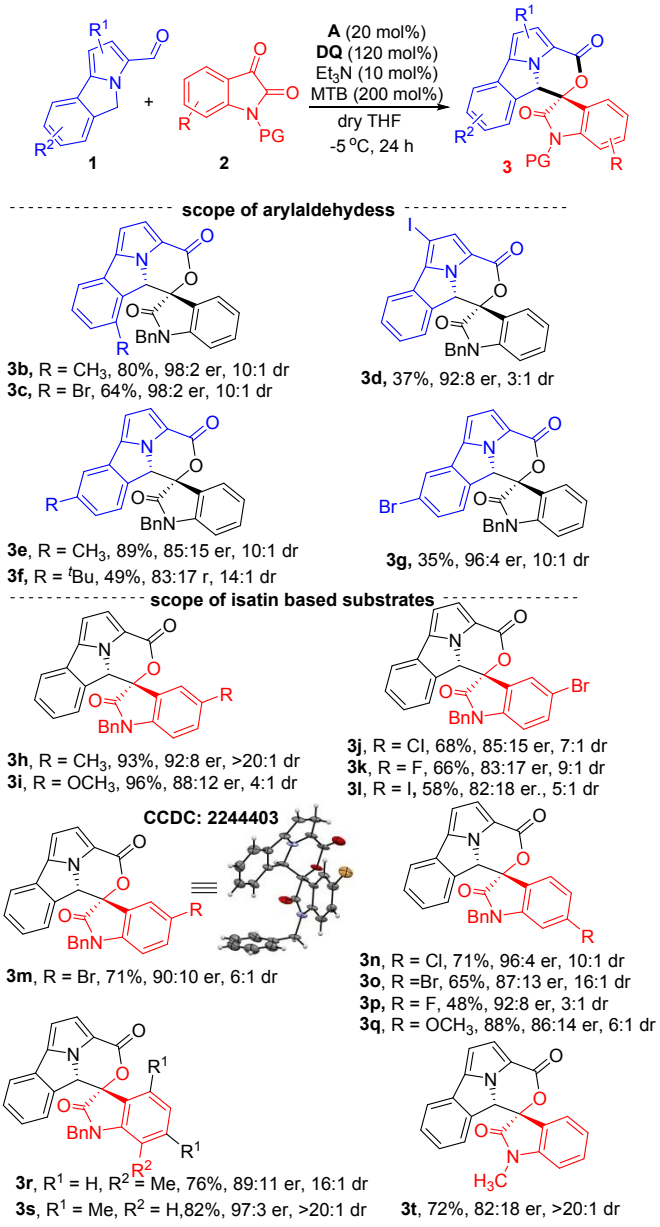


Ent.	NHC	Sol.	Base	Yield[b]%	e.r.[h](d.r.)[i]
1	**A**	$CHCl_3$	DIPEA	82	66:34 (10:1)
2	**B**	$CHCl_3$	DIPEA	86	65:35 (8:1)
3	**C**	$CHCl_3$	DIPEA	81	65:35 (8:1)
4	**A**	$PhCF_3$	DIPEA	56	66:34 (14:1)
5	**A**	THF	DIPEA	62	70:30 (>20:1)
6	**A**	THF	$NaHCO_3$	43	67:32 (13:1)
7	**A**	THF	DABCO	41	74:26 (2:1)
8	**A**	THF	MTB	56	85:15 (16:1)
9	**A**	THF[c]	MTB	55	86:14 (8:1)
10	**A**	THF[c]	MTB[d]	53	89:11 (6:1)
11[e]	**A**	THF[c]	MTB[d]	64	84:16 (15:1)
12[f]	**A**	THF[c]	MTB[d]	75	89:11 (>20:1)
13[f,g]	**A**	THF[c]	MTB[d]	79	91:9 (>20:1)

[a]General conditions: **1a** (0.12 mmol), **2a** (0.10 mmol), NHC (0.02 mmol), base (0.12 mmol), DQ (0.20 mmol) and additive (0.01 mmol) in solvent (1.0 mL) at 30 °C for 24 h. [b]Yields were determined by ^{1}H NMR. [c]THF (3 ml) was used. [d]MTB (0.20 mmol)was used, MTB = (*t*-BuO)$_2$Mg. [e]DIPEA (0.01 mmol) was used as an additive. [f]Et_3N (0.01 mmol) was used as an additive. [g]At -5 °C. [h]Enantiomeric ratio was determined by chiral HPLC analysis of the purified product. [i]The diastereomeric ratio was determined by ^{1}H NMR analysis.

With the optimized conditions in hand (Table 1, entry 13), we started to evaluate the generality of this NHC-catalyzed higher-order cycloaddition reaction. The scope of 5*H*-benzo[*a*]pyrrolizine-3-carbaldehyde was first investigated by using **2a** as a model reaction partner, and the results were summarized in Table 2. The steric effect of the substituent at the 6-position does not influence the reaction outcomes. For example, the substrate bearing a methyl at the 6-position was smoothly converted into the corresponding tricyclic products (**3b**) in an 80% yield and excellent stereoselectivities (10:1 dr, and 98:2 er). 6-Bromo substituted substrate proceeded successfully to produce **3c** in 64% yield with excellent

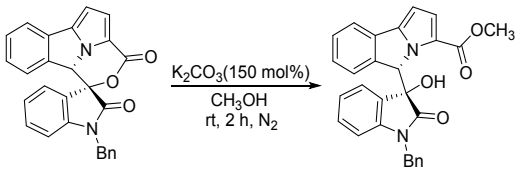
Table 2. Scope of 5*H*-benzo[*a*]pyrrolizine-3-carbaldehydes.[a]



[a]Reaction conditions: **1** (0.12 mmol), **2** (0.10 mmol), **A** (0.02 mmol), MTB (0.20 mmol), DQ (0.20 mmol) and Et_3N(0.02 mmol) in THF (3.0 mL) at -5 °C for 24 h.

stereoselectivity. Iodide is also well tolerated in our reaction and gave **3d** with good stereoselectivity, albeit with a lower yield. Such halide-containing products (**3b** and **3c**) provide opportunities for further functionalization. Substrates bearing substituents at 7-position were also explored and the corresponding targets (**3e**-**3g**) were given in moderate to good yields and good stereoselectivities. Simple *N*-substituted pyrrole-2-carboxaldehydes were not suitable substrates (see supplementary information for details).

We then examined the scope of isatin-based substrates (**2**) using **1a** as the model aldehyde (Table 2). Various substituents on the benzene ring of isatin were proven to be tolerated under our reaction conditions, giving the desired target molecules in good to high yields with good to excellent stereoselectivities. In particular, substrates containing electron-donating groups such as methyl and methoxyl at 5-position proceeded well to produce **3h** and **3i** in 93% and 96% yield respectively with good enantioselectivities. Electron-withdrawing groups such as chlorine, bromine, fluorine, and iodine atoms at the same position were also well tolerated and gave the corresponding products in good yields and slightly lower stereoselectivities. The absolute configuration of **3m** was confirmed by X-ray analysis as shown in Table 2. Isatins bearing chlorine and bromine atom at the 6-position were competent reactants, affording the corresponding products (**3n** and **3o**) in 71% and 65% isolated yield respectively with good to excellent stereoselectivities. Although the 6-fluoro substituted isatin only gave **3p** in 48% yield and 3:1 dr under the standard conditions, the enantioselectivity of the major diastereoisomer was good. The disubstituted reactant 4,6-dimethyl isatin was also explored to deliver **3s** in excellent yield and stereoselectivity. The *N*-protecting group could be switched into methyl group to give **3t** in 72% yield (>20:1 dr, and 82:18 er).



Scheme 1. Synthetic transformation.

To test the potential utility of our reactions, the reaction was conducted in 1 mmol scale. As a result, the desired **3a** was isolated in a slightly improved yield (86%) without any loss of the enantio- and diastereoselectivity (91:9 er, >20:1 dr). Further transformation of our product was also explored. For example, the tricyclic core in **3a** could be easily opened to afford **4** in an 88% isolated yield with high optical purity in the presence of potassium carbonate in methanol (Scheme 1).

Table 3. Anti-bacterial activities of our products (**3**).

compounds	Inhibition rate[a] (%) of 100 μg/mL	
	Xac	Xoo
3c	75.26±1.84	79.05±1.54
3d	77.84±5.25	78.65±12.69
3f	77.49±2 22	76.67±5.85
3i	70.53±3.54	80.05±2. 91
3l	78. 95±1.11	77.84±5.55
3m	56.14±2.46	82.25±1.89
3o	56.37±5.4	79.14±1.91
3s	72.11±7.42	67.57±5.03
BT[b]	45.73±4.92	53.69±2.8
TC[c]	54.33±3.29	59.73±1.9

[a]All data were average data of three replicates. [b]BT = Bismerthiazol [c]TC = Thiodiazole Copper.

Our products are characterized by the combination of tricyclic core, morpholine moiety, and spiral oxindole structure, which are all widely existing in bioactive molecules.[11] Upon our continuous interest in searching for unique scaffolds bearing

antiviral and antibacterial activities in agricultural applications,[12] the *in vitro* bioactivities against *Xanthomonas axonopodis* pv. *citri* (*Xac*) and *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) of our products were evaluated by the turbidimeter test. To our delight, most of the tested compounds exhibited promising antibacterial activities (for more details, see SI). Moreover, some of them showed superior bioactivities (Table 3) to the commercial Bismerthiazol (BT) and Thiodiazole Copper (TC).[13]

Conclusions

In summary, we have developed the enantio- and diastereoselective [12 + 2] higher-order cycloadditions between 5*H*-benzo[*a*]pyrrolizine-3-carbaldehydes and isatine-based electrophiles via NHC-catalyzed remote C(sp^3)-H activation process. Our reactions are characterized by rapidly constructing sophisticated tricyclic core bearing morpholine moiety under mild conditions from readily available starting materials. The bioactivities of the enantioenriched products against two plant pathogens (*Xac* and *Xoo*) were investigated. Some of our products exhibit superior bioactivities to the commercial Bismerthiazol (BT) and Thiodiazole Copper, which provides opportunities to develop new pesticides.

Author contributions

J.H. conducted most of the experiments. J.Z. contributed to designs and some experiments. S.-C. R. and Y.R. C. conceptualized and directed the project and drafted the manuscript with assistance from all co-authors. C. M. and Y. L. contributed to part of the experiments and/or discussions.

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