N-Heterocyclic Carbene-Catalyzed Remote Enantioselective C-C Bond Formation via 1,6-Addition with Formyl Enynes

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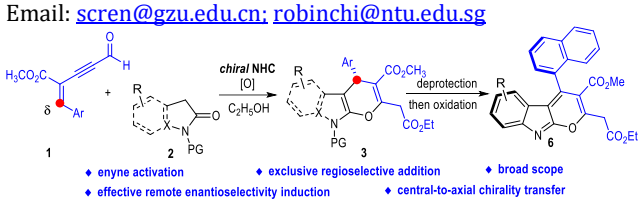


ABSTRACT: *N*-Heterocyclic carbenes (NHCs) have emerged as powerful organocatalysts in controlling the stereoselectivities of the reaction sites that are remote to the catalyst-binding position. Whereas the construction of stereogenic center at δ-position through NHC-catalysis remains an unmet goal. Herein, we report the NHC-catalyzed enantioselective 1,6-conjugated addition reaction of formyl enynes with nucleophilies through oxidative LUMO activation strategy. The reaction enables efficient chirality control at the δ-position of the formyl enyne substrates, providing access to high-value-added enantio-enriched pyrano[2,3-b]indole and pyrano[2,3-c]pyrazole derivatives. In addition, central-to-axial chirality transfer through the oxidation of our products was realized, enabling facile access to axially chiral pyrans.

KEYWORDS: *N*-heterocyclic carbene, organocatalysis, remote enantioselectivity induction, 1,6-conjugated addition, regio-selective

Controlling the stereoselectivities of the reaction sites that are remote to the catalyst-binding position represents one of the most challenging tasks in asymmetric synthesis.[1] Chiral N-heterocyclic carbenes (NHCs) have been extensively explored in the activation of various carbonyl compounds [2] to achieve effective chirality induction in the new bond formation process at a remote site to the chiral scaffold of the reaction catalyst (Figure 1a).[3,4] For instance, Ye and co-workers reported the pioneering work of utilizing chiral NHC to activate the remote γ-C(sp^3) of α,β-unsaturated acyl chloride and exert enantioselective control on the γ-position (Figure 1a, eq. 1).[3c] Chi and co-workers disclosed in 2012 the seminal report on the chirality control in the C-C bond formation at the remote enal γ-C(sp^3) via chiral NHC / Lewis acid co-catalyzed dienolate activation strategy (Figure 1a, eq. 1).[3d] Later, the same group reported the LUMO activation of the δ-C(sp^2) of a conjugated dienal substrate via formation of an NHC-bounded dienenyl acylazolium intermediate under oxidative conditions, with a diversity of multi-functional benzenes achieved in these transformations.[4b] In 2019, Zhu and co-workers successfully controlled the stereoselectivities in the dienal δ-C(sp^2) LUMO activation reactions and adopted this strategy in the atropoenantioselective synthesis of axially chiral biaryls (eq. 2).[4c] The stereoselectivity of the 1,6-conjugated addition reaction between dienenyl acylfluorides and silyl enol ethers can also be effectively induced by chiral NHCs to give a variety of structurally complex muliti-cyclic products in excellent optical purities, as recently disclosed by Lupton and co-workers (eq. 3).[4d] Chi and co-workers further extended the activation sites in the conjugated enone aryl aldehydes and successfully manage the enantioselectivity controls in the chiral C-S bond formation at the remote position via an NHC-catalyzed oxidative activation protocol.[5] Very recently, Ye and co-workers realized the chirality control in the C-C bond formation at the remote ε-C(sp^3) of 5-(chloromethyl)furfural via chiral NHC catalyzed remote Mannich-type reaction (eq.4).[6] Despite these advancements in NHC-catalyzed chirality control at remote sites, the construction of stereogenic center at δ-position through NHC-catalysis remains an unmet goal.

To date, dienenyl and dienolate compounds have been extensively explored in NHC-catalyzed asymmetric reactions to form chiral C-C or C-X bonds.[3] Carbonyl compounds bearing enyne structures have not been studied

in the 1,6-conjugate addition reactions promoted by NHC organic catalysts. Noteworthily, the less flexibility of the alkyne moiety of the enyne structure will add difficulties to the chirality controls at the remote reactive δ-position of the carbonyl substrates (Figure 1b).[7]

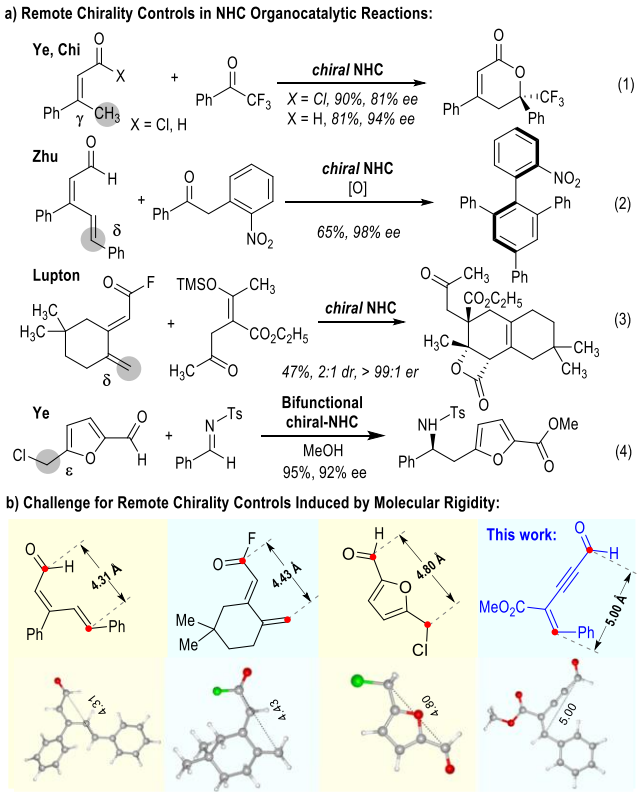


Figure 1. Remote chirality controls in NHC-catalysis and their challenges.

Herein, we report the first NHC-catalyzed enantioselective 1,6-conjugated addition reaction of formyl enynes with nucleophiles through oxidative LUMO activation strategy (Figure 2a). The aldehyde group of the formyl enyne substrate **1** can react with the chiral NHC catalyst under oxidative condition to give the acylazolium intermediate **I**, with the remote δ-C(sp^2) position to the binding catalyst well activated as an electrophile. The deprotonated oxindole or pyrazolone anion **II** (from **2**) can attack the δ-C(sp^2) of the acylazolium intermediate **I** through an asymmetric conjugated 1,6-addition process to give the azolium trienolate intermediate **III**, which can provide the allenyl acylazolium intermediate **IV** via a proton transfer process. Subsequent intramolecular nucleophilic O-addition reaction at the allene central C(sp) position of the intermediate **IV** leads to the formation of the 1,4-dihydropyran-derived azolium enolate intermediate **V**, which can be protonated and esterificated by the external ethanol and give the enantio-enriched 1,4-dihydropyrano[2,3-b]indole or 1,4-dihydropyrano[2,3-c]pyrazole **3** as the final product. It is worth noting that the conjugated formyl enynes are activated covalently by the chiral NHC organic catalyst for the first time and the activated enynyl acylazolium intermediate can react with a diversity of nucleophiles through exclusive regio-selective 1,6-addition reactions. The enantioselectivities in the C-C bond formation processes at the remote δ-C(sp^2) of the formyl enynes are effectively induced by the chiral scaffolds of the NHC organic catalysts. In addition, both the obtained pyrano[2,3-b]indole and pyrano[2,3-c]pyrazole scaffolds are privileged structures in medicines and agricultural chemicals (Figure 2b).[8]

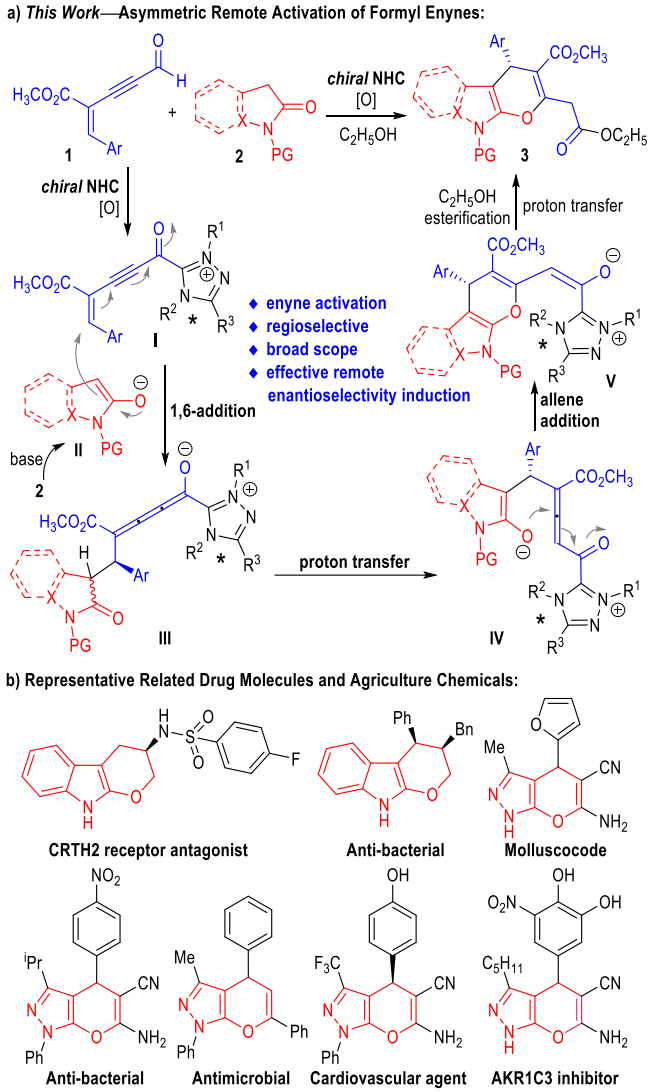


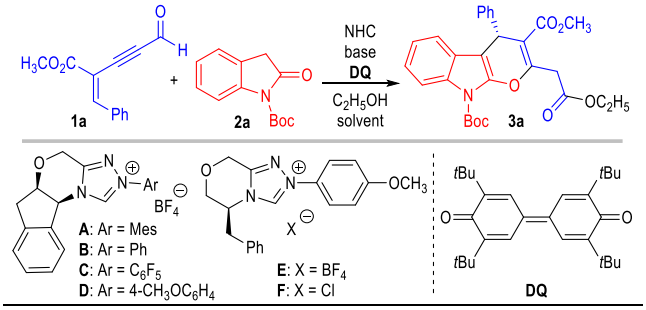
Figure 2. Asymmetric remote activation of formyl enynes and representative related biological molecules.

Results and Discussion

The conjugated 1,6-addition reaction between the formyl enyne **1a** and the oxindole **2a** was first evaluated using different chiral NHC organic catalyst in presence of a stoichiometric amount of the DQ oxidant in THF (Table 1). K_2CO_3 was used as the base to deprotonate the NHC pre-catalysts to initiate the reaction, and the ethanol was used to quench the reaction for liberation of the free NHC organic catalyst. The aminoindanol-derived NHC catalysts bearing electron-rich *N*-aryl substituents worked well for this asymmetric 1,6-addition reaction, with the desired tri-cycic product **3a** afforded in good yields with promising enantioselectivities (Table 1, entries 1, 2, 4). Whereas NHC

catalysts bearing electron-deficient *N*-aryl groups are not effective for this transformation (e.g., entry 3). Switching the NHC scaffold into the chiral morpholine resulted in dramatic improvements in the enantioselectivity with maintained yield (entry 5). Pleasingly, the yield and the er value of the product **3a** could be further increased when the triazolium chloride **F** was used instead of the tetrafluoroboronate salt **E** (entry 6).[9] Inorganic and organic bases other than K_2CO_3 we tested failed to increase the reaction outcomes (e.g., entries 7 to 10). Although a variety of organic solvents could be used as suitable media for this reaction (e.g., entries 11 to 14), the ether solvent of MTBE has provided the best enantioselectivity in the formation of the product **3a** with retention of the good reaction yield (entry 13). Finally, the er value of the product **3a** could be further increased to 96:4 when the reaction was carried out at a decreased 5 °C (entry 15).

Table 1. Condition Optimization.[a]

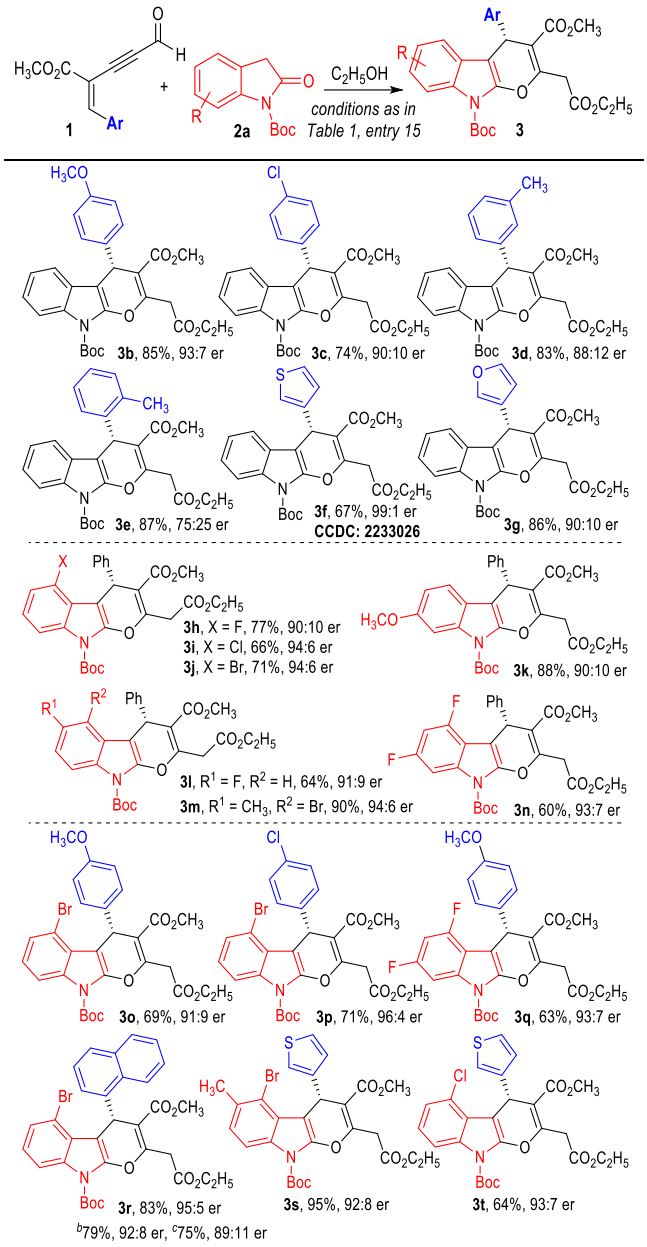


Entry	NHC	Base	Solvent	Yield [%][b]	Er[c]
1	**A**	K_2CO_3	THF	84	60:40
2	**B**	K_2CO_3	THF	76	64:36
3	**C**	K_2CO_3	THF	0	--
4	**D**	K_2CO_3	THF	78	65:35
5	**E**	K_2CO_3	THF	83	79:21
6	**F**	K_2CO_3	THF	87	84:16
7	**F**	Cs_2CO_3	THF	74	82:18
8	**F**	K_3PO_4	THF	79	82:18
9	**F**	TEA	THF	64	76:24
10	**F**	DBU	THF	35	65:35
11	**F**	K_2CO_3	CH_2Cl_2	87	79:21
12	**F**	K_2CO_3	toluene	92	79:21
13	**F**	K_2CO_3	MTBE	86	86:14
14	**F**	K_2CO_3	dioxane	93	81:19
15[d]	**F**	K_2CO_3	MTBE	78	96:4

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.10 mmol), NHC (0.02 mmol), DQ (0.15 mmol), base (0.05 mmol), EtOH (100 uL), solvent (3.0 mL) at room temperature for 12 h. [b] Isolated yield of **3a**. [c] The er values were determined *via* HPLC on chiral stationary phase. [d] The reaction was stirred at 5 °C for 12 h and $NaBF_4$ (0.02 mmol) used.

Having identified an optimal reaction condition for the NHC-organocatalytic asymmetric 1,6-addition reaction, we then examined the substrate scope using both the formyl enyne **1** and the oxindole **2** bearing various substituents (**Scheme 1**). The phenyl group on the enyne substrate **1a** can tolerate both electron-donating and electron-withdrawing groups on the *para*-position, with the target pyrano[2,3-b]indole products afforded in good yields and er values (**3b** and **3c**). Installing substituents on the meta- or ortho-positions of the phenyl ring of **1a** resulted in serious erosions on the product optical purities, although the yields were not affected (**3d** and **3e**). The phenyl rings of the enyne substrate **1** could be switched into heteroaryl

Scheme 1. Scope of Enynes 1 and Oxindoles 2[a]



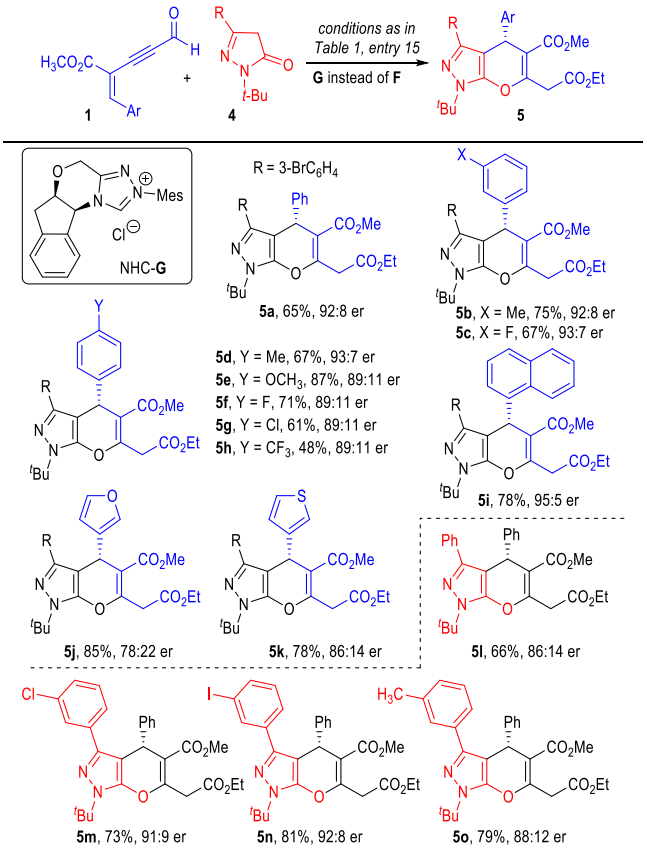
[a] Reaction conditions as stated in Table 1, entry 15. Yields are isolated yields after purification by column chromatography. Er values were determined *via* HPLC on chiral stationary phase. [b] The

reaction was carried out in a 1.0 mmol scale. [c] The reaction was carried out in a 4.0 mmol (1.06 g) scale.

rings such as the 3-thiofuryl and the 3-furyl groups, with the corresponding fused tricyclic products given in good yields and good to excellent optical purities (**3f** and **3g**). The absolute configuration of **3f** was determined by X-ray diffraction analysis of its single crystals, and those of other similar products were assigned by analogy.

Substituents are also well tolerated on each position of the nucleophilic oxindole substrate **2**. For instance, oxindoles bearing various halogen atoms on the 4-position generally gave the target products in moderate to good yields with good optical purities (**3h** to **3j**). Introducing functional groups on the 5- and 6-positions on the indole rings also led to the formation of the

Scheme 2. Scpoe of Enynes 1 and Pyrazolone 4[a]

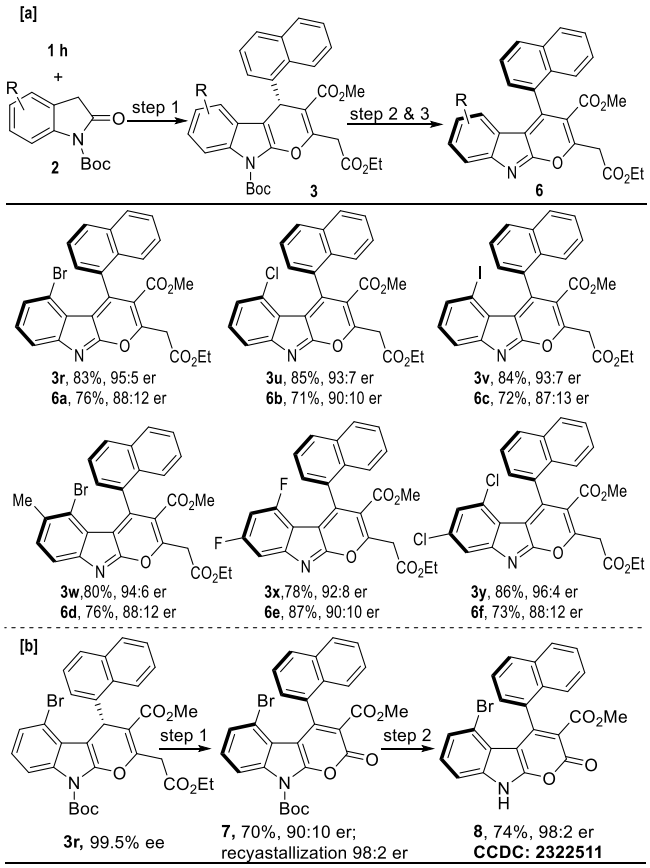


[a] Reaction conditions as stated in Table 1, entry 15, NHC-**G** instead of NHC-**F**. Yields are isolated yields after purification by column chromatography. Er values were determined *via* HPLC on chiral stationary phase.

enantio-enriched tricyclic products in moderate to excellent yields (**3k** to **3n**). To our delight, we can also obtain a series of optically enriched multi-functionalized pyrano[2,3-b]indole products from both the enyne and oxindole substrates bearing various substitution patterns. For example, the enynes **1** bearing *para*-substituents on the phenyl rings can react with the halogenated oxindole substrate **2** to give the chiral pyrano[2,3-b]indole products in moderate yields with good to excellent optical purities (**3o** to **3q**). The multi-functionalized oxindoles can also react with the enynes bearing a 1-naphthyl or a 2-thiofuryl group and lead to the formation of the corresponding pyrano[2,3-b]indole products in good to excellent yields and enantioselectivities (**3r** to **3t**). In addition, a large-scale reaction was conducted to test the potential utility of our method, with the target **3r** obtained in slightly dropped yields and enantioselectivity.

Pyrazolones were also suitable nucleophiles for this NHC-catalyzed enantioselective [3+3] annulation reaction. The NHC catalyst **G** [10] was adopted as the reaction catalyst for the reactions between the enynes **1** and the dihydropyrazolones **4** under otherwise identical conditions as stated in Entry 15, Table 1. The target pyrano[2,3-c]pyrazole products **5** were generally afforded in moderate to good yields and enantioselectivities (Scheme 2). Specifically, various functional groups such as halogens, methyl, methoxy, and trifluoromethyl at the *meta*- or *para*-position of the phenyl ring on the formyl enynes were well tolerated to give the corresponding products in good yields and enantioselectivities, regardless of their electronic properties (**5b**-**5h**). The phenyl ring of the formyl enyne **1** can be switched into 1-naphthyl with increased reaction yield and enantioselectivity (**5i**) obtained. Switching the phenyl ring to heterocyclic arenes such as furan (**5j**) and thiofuryl (**5k**) resulted in serious erosions on the enantioselectivities, albeit with retention or improvement of the reaction yields. This phenomenon may be ascribed to the decreased steric hindrance of the five-membered heteroarenes compared to the phenyl rings. Finally, the scope of pyrazolones was explored by using formyl enyne **1a** as a model substrate. Introducing electron-withdrawing groups such as chlorine (**5m**) and iodine (**5n**) atoms at the *meta*-position of the phenyl ring on the pyrazolones benefits the reaction yield and enantioselectivity. In contrast, non-substituted phenyl ring (**5l**) and methyl-substituted phenyl ring (**5o**) led to drops in enantioselectivities.

Scheme 3. The Transformations of Products 3



[a] Step 1: standard conditions listed in Table 1, entry 15; Step 2: HCO_2H, DMF, 120 °C; Step 3: DDQ, EtOAc, r.t. [b] Step 1: DDQ, DCM, r.t.,12 h; Step 2: TFA/DCM (v/v = 1:3), r.t., 12 h.

Atropisomeric compounds have attracted substantial attention recently due to their wide applications in natural product chemistry, catalyst or ligand design, and drug discovery.[11] Central-to-axial chirality transfer represents an efficient strategy for the construction of axially chiral compounds.[12] We were very interested in the construction of axially chiral molecules based on our currently developed enantioselective [3+3] annulation reaction via an additional central-to-axial transfer process. As shown in **Scheme 3**, the indole-fused 1,4-dihydropyran **3r** was subjected to a sequence of deprotection and oxidation processes. To our delight, deprotected **3r** reacted with DDQ smoothly to afford the desired axially chiral 4-(1-naphthyl) substituted pyrano[2,3-b]indole skeleton **6a** in 76% yield, albeit with slightly decreased optical purity.[13] The generality of this central-to-axial chirality transfer was then investigated by using different oxindoles. In general, this three-step protocol proceeded smoothly to afford the target axially chiral compounds **6b** to **6f** in moderate to good yields and optical purities. It is worth noting that the obtained pyrano[2,3-b]indole skeleton is one of the key structures in natural products and drug molecules (see **Figure S1** in supplementary information for details).[14] Interestingly, the central-to-axial transfer process of compound **3r** can also occur upon treatment of **3r** with DDQ directly under room temperature. An axially chiral 2*H*-pyran-2-one derivative **7** was generated, albeit with a slight loss of the ee value. Treatment compound **7** with trifluoroacetic acid led to the deprotection of the indole nitrogen to form **8**, whose structure and absolute configuration were further confirmed via X-ray diffraction analysis of the corresponding single crystal. The absolute configuration of compounds (**6**) was assigned by structural analogy with compound **8** (Supportting Information, **Table S3**, **Table S6**).

Conclusion

In summary, we have disclosed the first NHC-catalyzed 1,6-addition reaction of formyl enynes. The reaction can tolerate diverse substitution patterns, with the target pyrano[2,3-b]indole and pyrano[2,3-c]pyrazole products generally afforded in good to excellent yields and optical purities. The reactions took place in a high regio-selective fashion, with the enantioselectivity in the C-C bond formation at the remote C(sp^2) of the enyne structure well controlled by the NHC organic catalyst. In addition, the 1,4-dihydropyrano[2,3-b]indoles were successfully converted to axially chiral pyran derivatives via a central-to-axial chirality transfer process. Further investigations into the biological activity test of our products are in progress in our laboratory.

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.

Experimental details, materials and methods, characterization data, NMR spectra for all compounds, chromatograms for chiral separations, and information on X-ray diffraction experiments (PDF)

X-ray crystallographic data for **3f** (cif)

X-ray crystallographic data for *Racemic*-**7** (cif)

X-ray crystallographic data for **8** (cif)

AUTHOR INFORMATION

Notes

The authors declare no competing financial interests.

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