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

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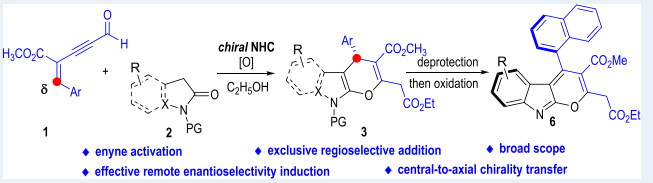
**ABSTRACT:** *N*-Heterocyclic carbenes (NHCs) have emerged as powerful organocatalysts in controlling the stereoselectivities of the reaction sites that are remote from the catalyst-binding position. Meanwhile, the construction of a stereogenic center at the $\delta$-position through NHC catalysis remains an unmet goal. Herein, we report the NHC-catalyzed enantioselective 1,6-conjugated addition reaction of formyl enynes with nucleophiles through an oxidative LUMO activation strategy. The reaction enables efficient chirality control at the $\delta$-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, regioselective*



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 $\gamma$-C($sp^3$) of $\alpha,\beta$-unsaturated acyl chloride and exert enantioselective control on the $\gamma$-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 $\gamma$-C($sp^3$) via a chiral NHC/Lewis acid cocatalyzed dienolate activation strategy (Figure 1a, eq 1).[3d] Later, the same group reported the LUMO activation of the $\delta$-C($sp^2$) of a conjugated dienal substrate via formation of an NHC-bounded dienenyl acylazolium intermediate under oxidative conditions, with a diversity of multifunctional benzenes achieved in these transformations.[4b] In 2019, Zhu and co-workers successfully controlled the stereoselectivities in the dienal $\delta$-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 multicyclic 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 managed 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 $\varepsilon$-C($sp^3$) of 5-(chloromethyl)furfural via a chiral NHC-catalyzed remote Mannich-type reaction (eq 4).[6] Despite these advancements in NHC-catalyzed chirality control at remote sites, the construction of the stereogenic center at the $\delta$-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 $\delta$-position of the carbonyl substrates (Figure 1b).[7]

Herein, we report the first NHC-catalyzed enantioselective 1,6-conjugated addition reaction of formyl enynes with nucleophiles through an oxidative LUMO activation strategy (Figure 2a). The aldehyde group of the formyl enyne substrate **1** can react with the chiral NHC catalyst under oxidative conditions to give the acylazolium intermediate **I**, with the

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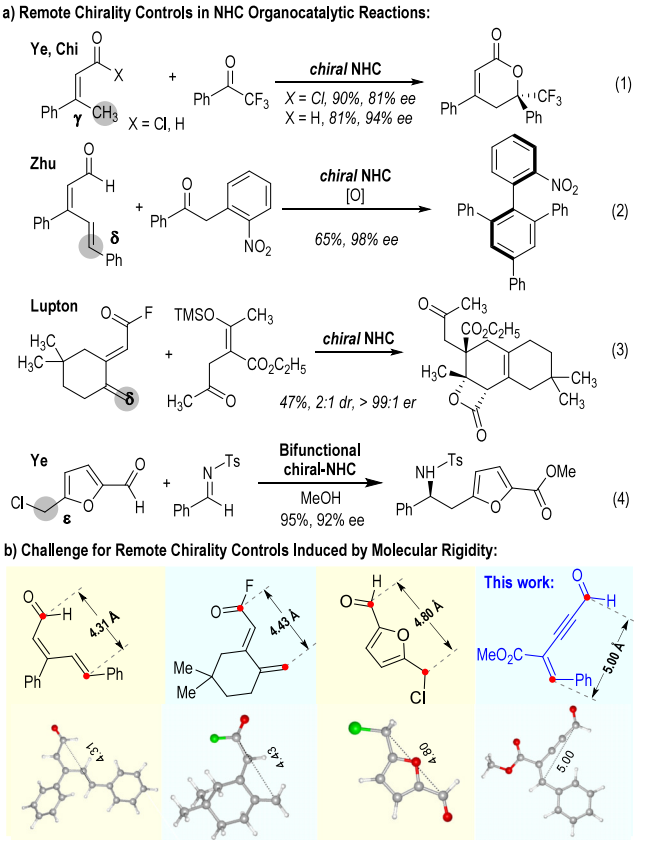


**Figure 1.** (a) (eqs 1−4) Remote chirality controls in NHC catalysis and (b) their challenges.

remote $\delta$-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 $\delta$-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. A 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 esterified 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 regioselective 1,6-addition reactions. The enantioselectivities in the C−C bond formation processes at the remote $\delta$-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]

## 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 catalysts in the presence of a stoichiometric amount of the DQ oxidant in THF (Table 1).

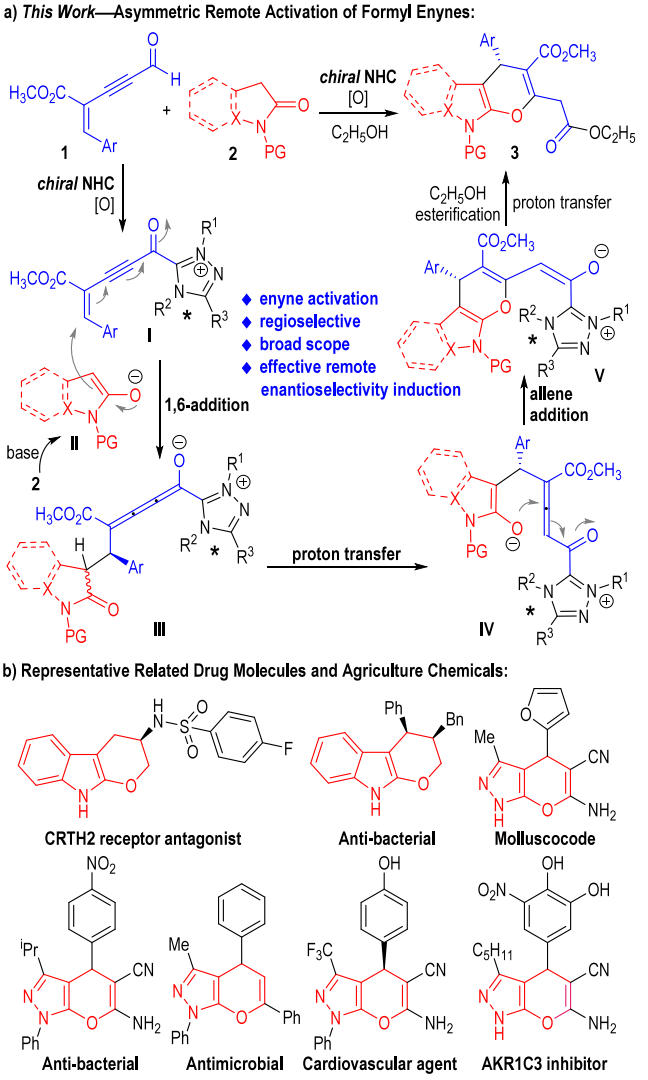


**Figure 2.** (a) Asymmetric remote activation of formyl enynes and (b) representative related biological molecules.

$K_2CO_3$ was used as the base to deprotonate the NHC precatalysts to initiate the reaction, and 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 tricyclic product **3a** afforded in good yields with promising enantioselectivities (Table 1, entries 1, 2, and 4). Meanwhile, 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 $K_2CO_3$ that 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**


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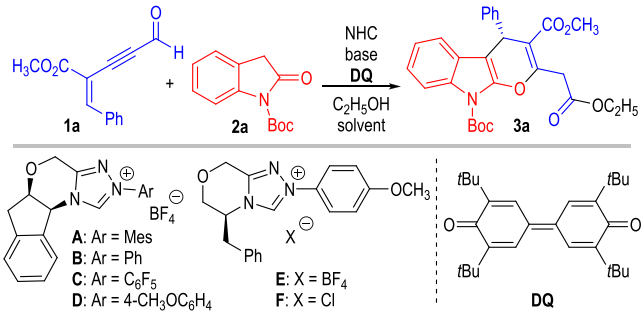
**Table 1. Condition Optimization**[a]




| 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 |

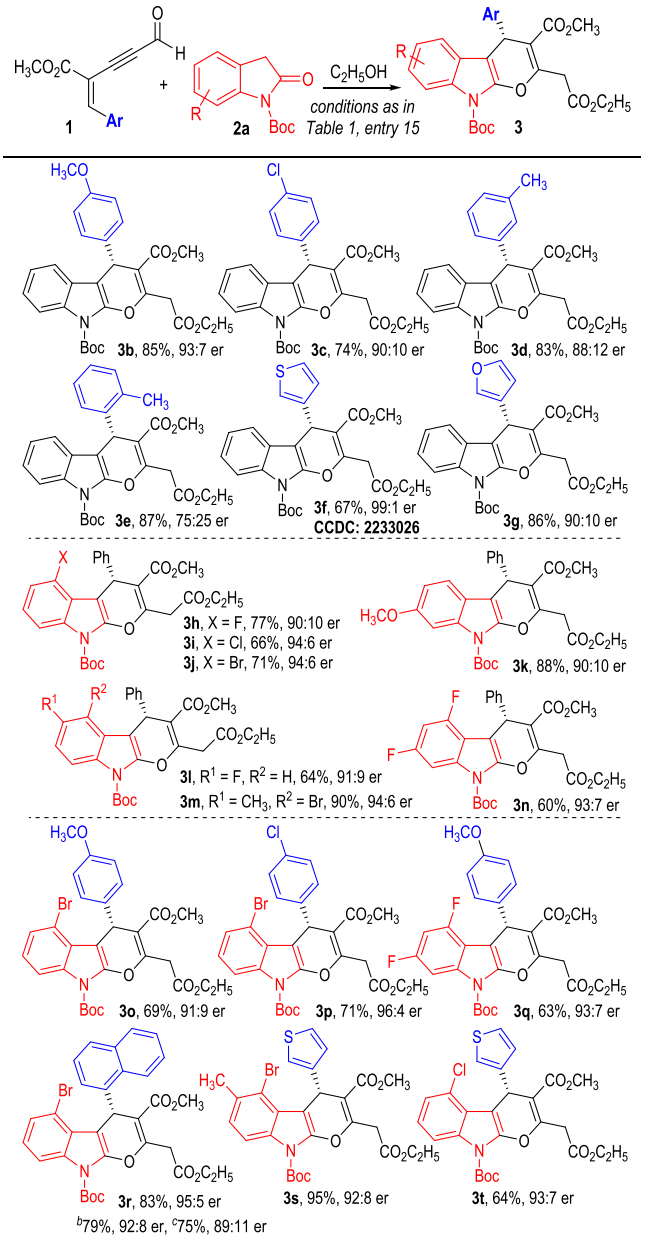
[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.10 mmol), NHC (0.02 mmol), DQ (0.15 mmol), base (0.05 mmol), EtOH (100 uL), and solvent (3.0 mL) at room temperature for 12 h. [b]Isolated yield of **3a**. [c]The er values were determined via HPLC on a chiral stationary phase. [d]The reaction was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

could be further increased to 96:4 when the reaction was carried out at a decreased temperature of 5 °C (entry 15).

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 with good er values (**3b** and **3c**). Installing substituents on the meta- or ortho-positions of the phenyl ring of **1a** resulted in serious erosion of 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 rings such as the 3-thiofuryl and the 3-furyl groups, with the corresponding fused tricyclic products given in good yields with 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 at 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 enantio-enriched tricyclic products in

**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 a 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.

moderate to excellent yields (**3k** to **3n**). To our delight, we can also obtain a series of optically enriched multifunctionalized pyrano[2,3-*b*]indole products from both the enyne and oxindole substrates bearing various substitution patterns. For example, enynes **1** bearing para-substituents on the phenyl rings can react with 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 multifunctionalized oxindoles can also react with the enynes bearing a 1-naphthyl or 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



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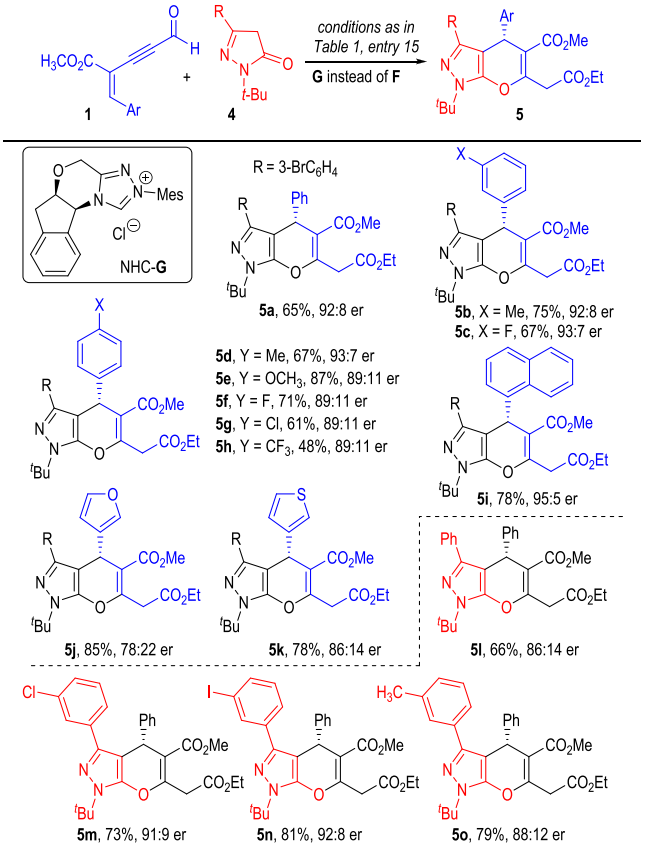
potential utility of our method, with the target **3r** obtained in slightly dropped yields and enantioselectivity.

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

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

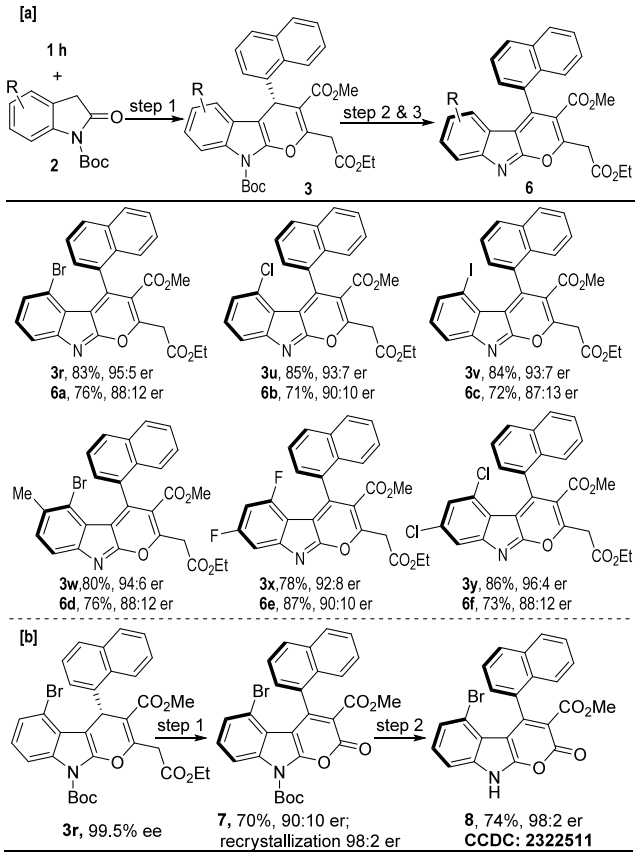



[a]Reaction conditions as stated in Table 1, entry 15, NHC-**G** instead of NHC-**F**. Yields are isolated yields after purification by column chromatography. er values were determined via HPLC on a chiral stationary phase.

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 an increased reaction yield and enantioselectivity (**5i**) obtained. Switching the phenyl ring to heterocyclic arenes such as furan (**5j**) and thiofuryl (**5k**) resulted in serious erosion of 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, the nonsubstituted phenyl ring (**5l**) and the methyl-substituted phenyl ring (**5o**) led to drops in enantioselectivities.

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, indole-fused 1,4-dihydropyran

**Scheme 3. 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.

**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 the Supporting Information for details).[14] Interestingly, the central-to-axial transfer process of compound **3r** can also occur upon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treatment of **3r** with DDQ directly at room temperature. An axially chiral 2*H*-pyran-2-one derivative **7** was generated, albeit with a slight loss of the ee value. Treatment of 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** (Supporting Information, Tables S3 and S6).

## CONCLUSIONS

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 highly regioselective 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

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c04733.

Experimental procedures and spectral data for all new compounds; experimental details, materials and methods, characterization data, NMR spectra for all compounds, chromatograms for chiral separations, information on X-ray diffraction experiments, X-ray crystallographic data for **3f**, X-ray crystallographic data for *racemic*-**7**, and X-ray crystallographic data for **8** (PDF)

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### Notes

The authors declare no competing financial interest.

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