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NHC-Catalyzed Chemo- and Enantioselective Reaction between Aldehydes and Enals for Access to Axially Chiral Arylaldehydes

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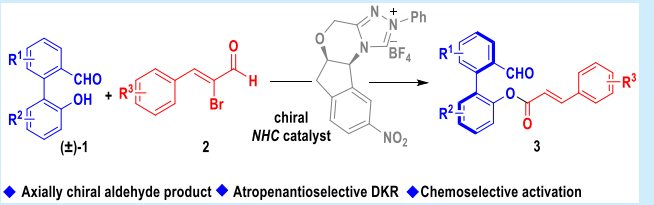
ABSTRACT: A chiral carbene-catalyzed chemo- and enantioselective reaction with racemic biaryl aldehydes and α-bromoenals is developed for access to axially chiral 2-arylbenzaldehydes through atroposelective dynamic kinetic resolution (DKR) processes. This atroposelective DKR strategy can tolerate a broad scope of substrates with diverse functionalities. The axially chiral 2-aryl benzaldehyde products generally afford moderate to good yields and enantioselectivities. The axially chiral molecules afforded from the current approach are variable through simple transformations to afford axially chiral functional molecules with excellent optical purities.



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Axial chirals are significant in naturally occurring molecules,[1] medicine,[2] and materials.[3] Axially chiral molecules have also been extensively explored as organic catalysts,[4] ligands,[5] and chiral auxiliaries[6] in organic synthesis (Figure 1a). The catalytic approaches for the synthesis of axially chiral molecules bearing diverse functionalities have been extensively developed in the past decade. For example, Tan and co-workers[7] have stimulated the application of chiral phosphoric acids (CPAs) as the reaction catalyst in the synthesis of various functional molecules possessing stereogenic axes. Maruoka and co-workers[8] have developed efficient methodologies in the construction of axially chiral molecules with asymmetric phase transfer catalysis (PTC). Yan and co-workers[9] have established a diversity of axially chiral functional structures with multifunctional chiral amines used as the reaction catalyst. Despite the significant achievements obtained in the construction of axially chiral molecules, investigations into facile strategies for the establishment of stereogenic axes in functional scaffolds are of great significance and interest.

N-Heterocyclic carbene (NHC) organocatalysis has been developed as one of the versatile approaches for asymmetric synthesis.[10] A great number of chiral structures possessing one or more stereogenic centers or axes have been facilely synthesized in optically active forms through NHC organocatalytic reactions.[11] Specifically, Zhao and co-workers[12] disclosed in 2014 a facile approach for the preparation of enantio-enriched BINOLs and NOBINs with NHC catalysts. They have also initialized the desymmetrization approaches for the establishment of axial chirals via NHC organocatalytic reactions. Wang and co-workers[13] reported the seminal denovo ring formation process to generate stereogenic axes in an atroposelective fashion. In contrast, the formation of axially chiral molecules via NHC-catalyzed dynamic kinetic resolution (DKR) processes has been relatively less explored (Figure 1b). Limited examples are from Wang's group and us. In 2021, Wang and co-workers[14] disclosed the DKR of the axially chiral 2-aryl benzaldehyde through an asymmetric esterification reaction under oxidative NHC organocatalytic conditions (Figure 1b, eq 1). We[15] have recently disclosed the atroposelective N−S bond cleavage reaction of sulfonyl imines bearing a stereogenic axis through an NHC-promoted DKR process (Figure 1b, eq 2). Both of the strategies developed by Wang and co-workers involved atroposelective transformations of the carbaldehyde group installed on the biaryl frameworks of the axially chiral substrates. Atroposelective transformation on reactive sites other than the carbaldehyde group has not been developed with the racemic 2-aryl benzaldehyde substrates for DKR reactions.

Herein, we show an NHC-catalyzed DKR reaction for access to enantio-enriched 2-aryl benzaldehydes through the asymmetric acylation reaction of the phenol fragment existing in the racemic 2-aryl benzaldehyde substrate (Figure 1c). The 2-bromo cinnamaldehyde **1a** was preferably attacked by the chiral NHC molecule to the 2-aryl benzaldehyde **2a**. The afforded chiral α,β-unsaturated acylazolium **I**[11f] could enantioselectivity react with the (*S*)-enantiomer of the racemic 2-aryl benzaldehyde substrate **2a** through an asymmetric acylation process to give the intermediate **II**. Meanwhile, the remaining (*R*)-**2a** could be racemized through an intramolecular semiacetal formation step. Elimination of the chiral

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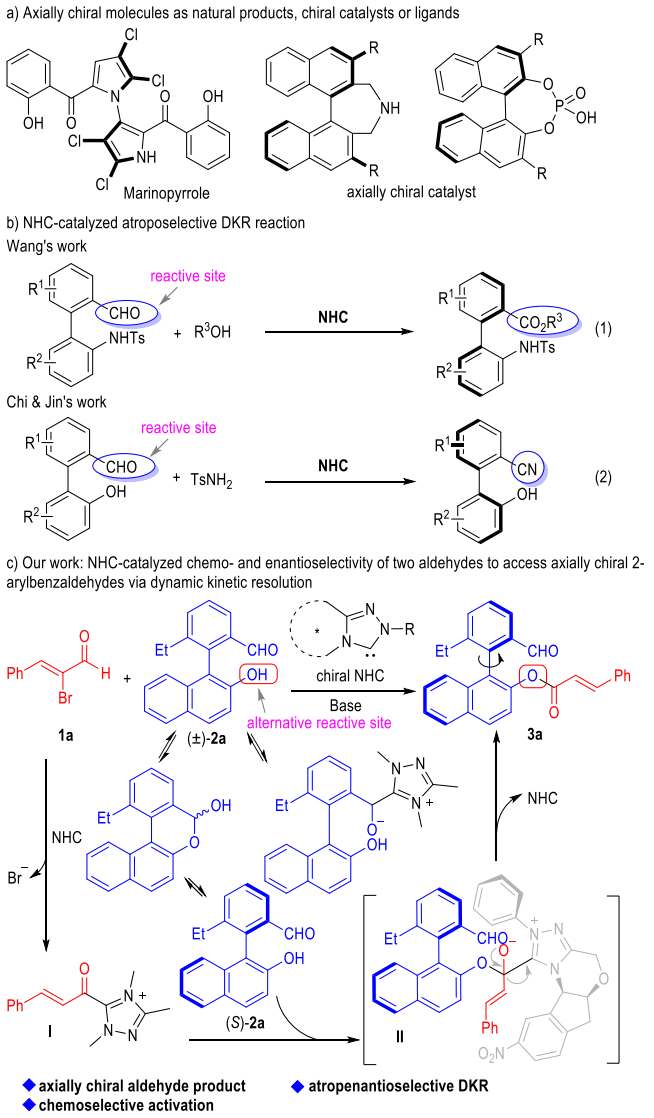


Figure 1. Enantioselective access to axially chiral molecules via NHC organocatalysis and our project design.

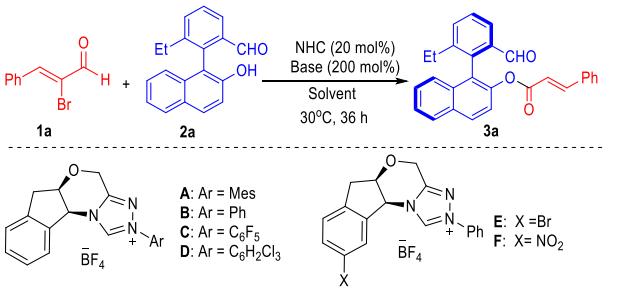
NHC catalyst from the stereospecific intermediate **II** gives the optically pure axially chiral 2-aryl benzaldehyde product **3a** in good yield.

Different NHC organocatalysts were first examined for the reaction of the α-bromoenal **1a** and the 2-aryl benzaldehyde **2a** with Cs_2CO_3 in THF at 30 °C for 36 h (Table 1, entries 1 to 6). The NHC precatalyst **A**[16] bearing an *N*-mesityl group provided the axially chiral arylaldehyde product **3a** in a poor yield and optical purity (entry 1). In contrast, the NHC catalysts **B**, **C**, and **D** could provide the product **3a** in good yields (entries 2 to 4).[17] Introducing substituents onto the indanol scaffold of the chiral NHC catalyst resulted in a slight increase in the product er values. The reaction solvent proved to be important to the reaction enantioselectivities (entries 7 to 9). The product er values could be improved if the basic additive was changed into organic bases with weak bases (entries 10 to 12). Finally, the target **3a** was afforded in 82% yield and 92:8 er under the catalysis of the NHC **F**[18] in the presence of $NH(C_2H_5)_2$ in mesitylene.

Then the scope of the α-bromoenal substrates **1** was examined (Scheme 1). Electron-donating and electron-withdrawing groups were well tolerated on the phenyl 4-position in **1a**, with the axially chiral aryl aldehyde products afforded in good yields and enantioselectivities (Scheme 1, **3b** to **3e**). Introducing substituents onto the 2- or 3-positions of the enal phenyl rings resulted in loss in the product enantioselectivities, although the yields were not affected (for details, see Supporting Information, Table S2). Switching the phenyl substituent in **1a** into a furyl group or a naphthyl group occurs without obvious erosion on the reaction er values (**3f**, **3g**). The linear α-bromoenals also worked well in this DKR process and gave the desired products in moderate to good yields and optical purities (**3h** to **3l**).

The NHC-catalyzed DKR reaction also showed good tolerance to substituents on both aromatic rings of substrate **2** (Scheme 2). For example, the 3-ethyl group on the ring **A** of the benzaldehyde substrate could be changed into a 3-methyl group without erosion of either the product yield or enantioselectivity (e.g., **3m**, **3q**, **3r**, and **3s**). The ring **A** in **2a** could also be changed into a naphthyl ring to give the target product **3n** with retention of a good product yield and optical purity. The ring **B** could tolerate substituents on the 6- or 7-position, and the desired products were given in good yields and optical purities (**3o** and **3p**). Switching the naphthyl ring B into a 6-methylphenyl group resulted in an obvious increase in the reaction yield with little impact on the enantioselectivity (**3q** and **3r**). Switching the 6-methyl group of phenyl ring B into a 6-methoxyl group afforded the axially chiral biphenyl products **3s** and **3t** in good yields and enantioselectivities. The enantioselectivity of the DKR process was obviously decreased

Table 1. Condition Optimization[a]



Entry	NHC	Solvent	Base	Yield (%[b])	er[c]
1	**A**	THF	Cs_2CO_3	15	55:45
2	**B**	THF	Cs_2CO_3	80	62:38
3	**C**	THF	Cs_2CO_3	78	56:44
4	**D**	THF	Cs_2CO_3	85	51:49
5	**E**	THF	Cs_2CO_3	82	65:35
6	**F**	THF	Cs_2CO_3	80	67:33
7	**F**	DCM	Cs_2CO_3	80	64:36
8	**F**	Toluene	Cs_2CO_3	80	68:32
9	**F**	Mesitylene	Cs_2CO_3	82	70:30
10	**F**	Mesitylene	DBU	60	75:25
11	**F**	Mesitylene	Et_3N	52	86:14
12[d]	**F**	Mesitylene	$NH(Et)_2$	70	92:8
13	**F**	Mesitylene	$NH(Et)_2$	82	92:8

[a]General conditions: **1a** (0.20 mmol), **2a** (0.10 mmol), NHC-**F** (0.02 mmol), base (0.20 mmol), and solvent (2.0 mL) at 30 °C for 36 h. [b]Yields of isolated products after column chromatography. [c]The er values of **3a** were determined by HPLC using a chiral stationary phase. [d]**1a** (0.20 mmol), **2a** (0.10 mmol), NHC-**F** (0.02 mmol), base (0.20 mmol), and solvent (2.0 mL) at 0 °C for 72 h.

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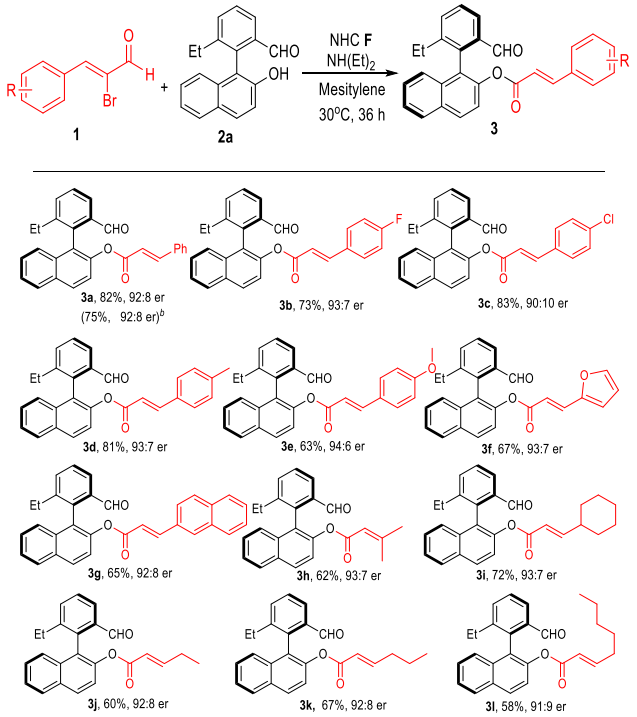
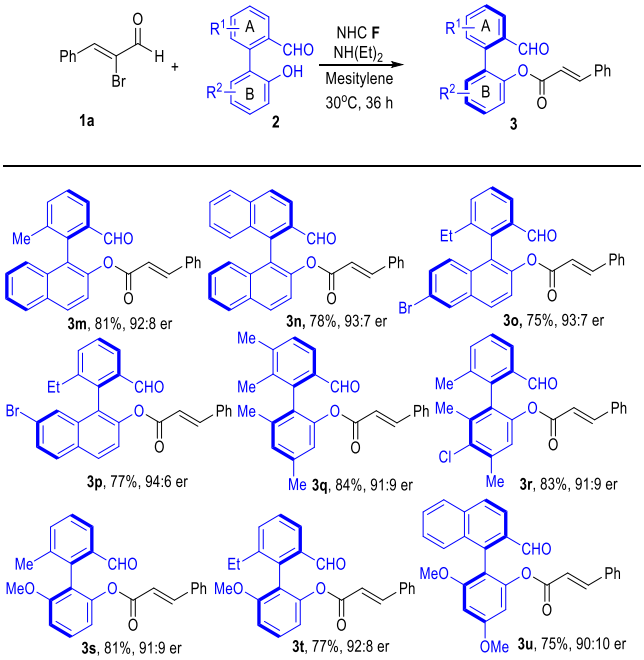
Scheme 1. Substrate Scope of α-Bromoenal 1[a]



[a]Reaction conditions: **1** (0.20 mmol), **1a** (0.10 mmol), **F** (0.02 mmol), $NH(Et)_2$ (0.20 mmol), mesitylene (2.0 mL), 30 °C, 36 h. Yields were isolated yields. er values were determined via HPLC using a chiral stationary phase. [b]The reaction was carried out at the 1 g scale. Reaction conditions: **1** (7.24 mmol), **2a** (3.62 mmol), **F** (0.36 mmol), $NH(Et)_2$ (7.24 mmol), mesitylene (72.0 mL), 30 °C, 36 h.

Scheme 2. Substrate Scope of 2-Arylbenzaldehyde 2[a]



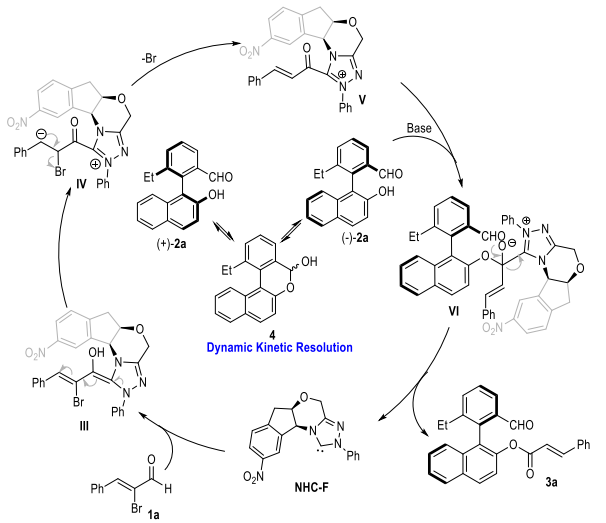
[a]Reaction conditions: **1a** (0.20 mmol), **2** (0.10 mmol), **F** (0.02 mmol), $NH(Et)_2$ (0.20 mmol), mesitylene (2.0 mL), 30 °C, 36 h. Yields were isolated yields. er values were determined via HPLC using a chiral stationary phase.

when using substrate **2** bearing a naphthyl ring A and a 6-methoxylphenyl ring B (**3u**).

It is noteworthy that the atroposelective DKR process, catalyzed by NHC, can still achieve a high separation yield and enantioselectivity for the production of axial chiral 2-arylbenzaldehyde product **3a**, even when the catalyst amount is reduced by half (1.1 g, 75%, 92:8 er, Scheme 1, see Supporting Information for details).

The chiral catalyst **F** could attack the α-bromoenal **1a** and give the Breslow intermediate **III**, which then affords the α,β-unsaturated acylazolium intermediate **V** through debromination (Scheme 3). Then, in the presence of external bases, (*S*)-

Scheme 3. Postulated Reaction Mechanism



2a could react with intermediate **VI** to afford the axially chiral 2-aryl benzaldehyde **3a** via O-acylation, with liberation of the recyclable NHC catalyst. Noteworthily, the less reactive (*R*)-**2a** could be racemized into its (*S*)-enantiomer through an intramolecular semiacetal formation process, so that the enantio-enriched (*S*)-**3a** was obtained in a good isolated yield.

The product **3a** was amenable in various transformations (Figure 2). For instance, the aldehyde group of **3a** can react with 1,3-propanediol and 1,3-ethanedithiol under acidic conditions to give the acetal product **5** and thioacetal product **6** in moderate yield and enantioselectivity, respectively. The secondary alcohol product **7**, as a single diastereomer, could be given in 75% yield and excellent enantioselectivity via a nucleophilic addition reaction between **3a** and a Grignard reagent. Similarly, the axially chiral biaryl benzaldoxime **8** could be easily obtained from the reaction with hydroxylamine in moderate yield and with moderate er value. The aldehyde group of **3a** can also be transformed to the double bond to afford the axially chiral biaryl alkene compound **9** through reported procedures. Reduction of **3a** in THF/CH_3OH with $NaBH_4$ afforded the product **10** in 85% yield with retention of the product er value.

In summary, we have developed an NHC-catalyzed chemo- and enantioselective strategy for quick access to axially chiral aryl aldehyde molecules. The reactions between racemic 2-aryl benzaldehydes and α-bromoenals can give the enantio-enriched axially chiral aryl aldehydes in good isolated yields through DKR processes. A broad scope of substrates bearing various substituents and substitution patterns are well tolerated

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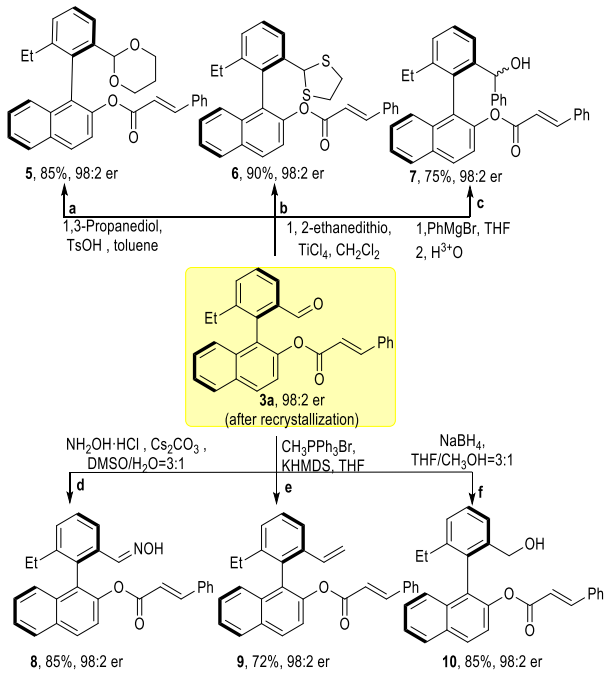

Figure 2. Synthetic transformation of axially chiral biaryl aldehyde product **3a**.

in this transformation. Most of the axially chiral aryl aldehydes were afforded in moderate to good yields and enantioselectivities under mild conditions. The axially chiral 2-aryl benzaldehyde products obtained from our method can be easily converted to various functional molecules. In-depth explorations of the efficient construction of the axially chiral biaryl structures are in progress in our laboratories.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c04189.

Experimental procedures and spectral data, for all new compounds, and X-ray crystallography of compound **3e** (PDF)

Accession Codes

CCDC 2252780 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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Notes

The authors declare no competing financial interest.

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