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Atroposelective Synthesis of Axially Chiral 4-Aryl α-Carbolines via *N*-Heterocyclic Carbene Catalysis

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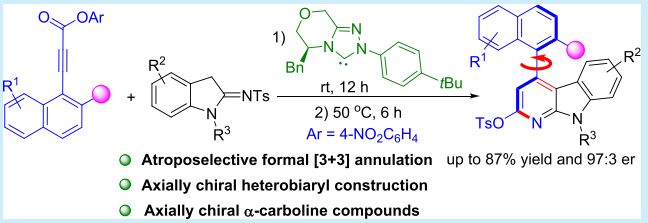
ABSTRACT: The first catalytic asymmetric construction of axially chiral 4-aryl α-carboline skeletons has been accomplished through an *N*-heterocyclic carbene (NHC)-catalyzed atroposelective formal [3 + 3] annulation of 4-nitrophenyl 3-arylpropiolates with 2-sulfonamidoindolines. The synthetic utility of the title compounds has been demonstrated by the diverse late-stage structural modifications. Density functional theory calculations were also conducted to illuminate the key factors for controlling the origin of the enantioselectivity. This strategy not only provides an efficient pathway to access axially chiral α-carboline atropisomers but also offers a novel catalytic enantioselective mode for the construction of axially chiral heterobiaryls by using NHC-bound alkynyl acylazoliums.



Axially chiral skeletons have been recognized as privileged structures because they not only are frequently found in numerous natural products and bioactive compounds[1] but also constitute the core structures of many chiral catalysts.[2] Therefore, the catalytic enantioselective synthesis of axially chiral molecules has attracted increasing interest among the scientific community.[3] Considerable efforts have been devoted to exploring efficient and enantioselective methods to access phenyl- and naphthyl-based biaryl atropisomers.[4] In contrast, the enantioselective construction of atropisomeric heterobiaryl skeletons is more challenging (Scheme 1a). In recent years, although significant progress has been made in the synthesis of a few atropisomeric heterobiaryls,[5] the development of more catalytic asymmetric approaches to access novel axially chiral heterobiaryls with structural diversity is still in high demand.

α-Carbolines (pyridoindoles) are privileged structural motifs embedded in a diverse array of natural alkaloids and bioactive compounds with wide-ranging pharmacological properties such as antitumor, anti-inflammatory, antibacterial, antimalarial, and central-nervous system-stimulating activities (Scheme 1b).[6] Compared with β-carbolines that have been intensively investigated, the synthetic approaches to α-carbolines are considerably less developed.[7] In particular, to the best of our knowledge, there is no example realizing the atroposelective synthesis of axially chiral α-carbolines to date. Therefore, the design and exploration of more general and efficient methods to synthesize functionalized α-carbolines, in particular, enantio-enriched axially chiral α-carbolines, are of great importance.

Over the past decade, *N*-heterocyclic carbene (NHC) catalysis has emerged as a powerful tool to realize numerous nontraditional chemical transformations.[8] The unique reactivity of NHCs has enabled the combination with different carbonyl compounds to access various centrally chiral molecules; however, the application of NHC catalysis in the synthesis of axially chiral molecules has been far less explored.[9] As a continuation of our research on the chemistry of NHC-bound alkynyl acylazolium,[10] we conceive that a new ring could be efficiently constructed through the [3 + *m*] annulation of a binucleophile with the β-activated alkynyl acylazolium, and the axially chirality could be concomitantly created between the newly formed ring and the 2,6-disubstituted aryl of the alkynyl acylazolium (Scheme 1c). To fulfill this target, a series of new 4-nitrophenyl 3-naphthylpropiolates **1** were well designed and synthesized as the alkynyl acylazolium precursors. After careful screening and selection of the substrates and reaction conditions, we demonstrate herein an atroposelective synthesis of novel 4-naphthyl α-carbolines **3** through an NHC-catalyzed formal [3 + 3] annulation of 4-nitrophenyl 3-naphthylpropiolates **1** with 2-sulfonamidoindolines **2** that serve as a type of suitable C−N 1,3-binucleophiles for the construction of the α-carboline skeleton. The unique structure of 3-(2-substituted naphth-1-yl)propiolates **2** was found to be one of the key factors for the success of this protocol.

We commenced our study by the reaction of ester **1a** with *N*-Me 2-sulfonamidoindoline **2a** using Cs_2CO_3 as the base in 1,2-dichloroethane (DCE) under the catalysis of NHC precursor **A** (Table 1, entry 1). Fortunately, a mixture of the

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Scheme 1. Catalytic Asymmetric Synthesis of Axially Chiral Biaryls and Our Work Design

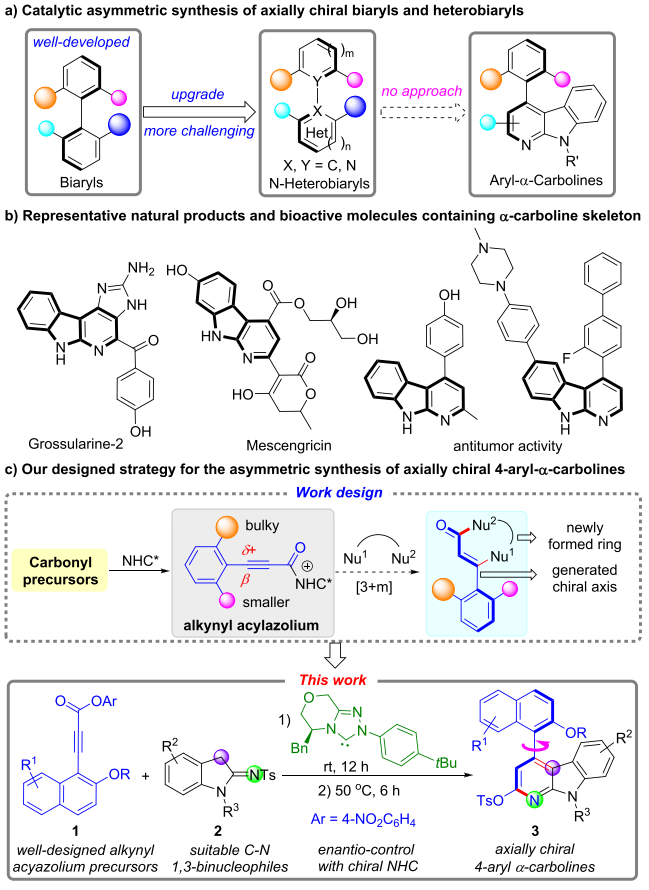
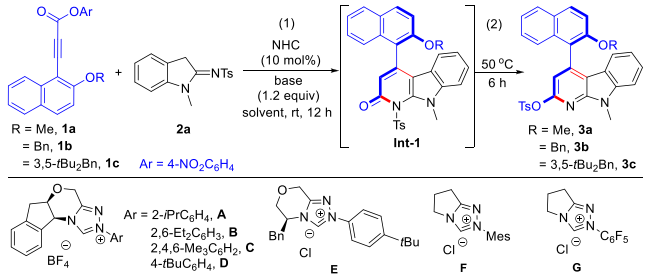


Table 1. Optimization of the Reaction Conditions[a]



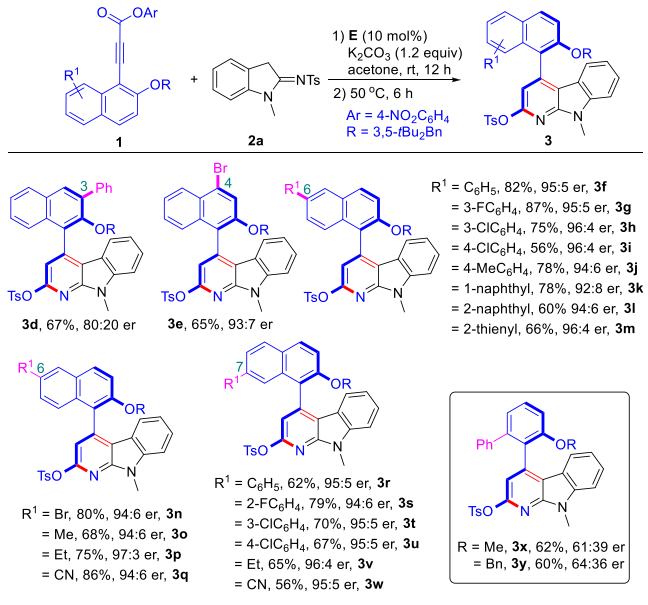
entry	NHC	base	solvent	3, yield (%)[b]	er[c]
1	**A**	Cs_2CO_3	DCE	**a**, 53	69:31
2	**B**	Cs_2CO_3	DCE	**a**, 47	74:26
3	**C**	Cs_2CO_3	DCE	**a**, 78	77:23
4	**D**	Cs_2CO_3	DCE	**a**, 25	79:21
5	**E**	Cs_2CO_3	DCE	**a**, 92	81:19
6	**E**	Cs_2CO_3	PhMe	**a**, 25	79:21
7	**E**	Cs_2CO_3	THF	**a**, 34	85:15
8	**E**	Cs_2CO_3	EtOAc	**a**, 60	79:21
9	**E**	Cs_2CO_3	acetone	**a**, 53	87:13
10	**E**	DBU	acetone	**a**, 42	87:13
11	**E**	DIPEA	acetone	**a**, 38	82:18
12	**E**	NaOAc	acetone	**a**, 47	84:16
13	**E**	K_2CO_3	acetone	**a**, 90	86:14
14	**E**	K_2CO_3	acetone	**b**, 82	92:8
15	***E***	***K_2CO_3***	***acetone***	***c*, 75**	95:5
16	**F**	K_2CO_3	acetone	**c**, 77	
17	**G**	K_2CO_3	acetone	**c**, 80	

[a](1) **1** (0.18 mmol), **2a** (0.12 mmol), base (0.144 mmol), NHC precursor (0.012 mmol), anhydrous solvent (4 mL), rt, 12 h; (2) 50 °C, N_2, 6 h. [b]Isolated yield of **3**. [c]er values were determined via high-performance liquid chromatography (HPLC) on a chiral stationary phase.

N-Ts product **Int-1** and *O*-Ts product **3a** was monitored by TLC (thin-layer chromatography) when the reaction was carried out at room temperature. To facilitate separation of the products, the reaction mixture was heated to 50 °C for another 6 h after completion of the reaction at room temperature to transform **Int-1** to product **3a** completely. Although product **3a** was isolated in moderate yield with a lower er value in the presence of catalyst **A** (entry 1), this result greatly encouraged us to realize our hypothesis by further screening a series of other chiral NHC precursors **B**–**E** (entries 2–5). As a result, the yield and er value of product **3a** could be enhanced to 92% and 81:19 er, respectively, in the presence of **E** (entry 5). Subsequent examination of the solvents and bases convinced us that K_2CO_3 and acetone were the optimal base and solvent, respectively (entry 13). Further investigation of the R group of substrates **1a**–**c** indicated that the volume of the R group had a great impact on the reaction yields and enantioselectivity (entries 13–15). In terms of product **3c** bearing a 3,5-tBu$_2$Bn group, the er value was enhanced to 95:5, although the yield was slightly decreased to 75% (entry 15). Therefore, the reaction conditions shown in entry 15 were established as the optimal ones for further scope exploration. Notably, the racemic product **3** could be obtained in the presence of the achiral NHC precursor **F** or **G** in good yield (entries 16 and 17).

With the optimized conditions in hand, we moved our attention to explore the reaction scope. Initially, 3-(naphthalen-1-yl)propiolates **1** bearing diverse substituents at different positions were used to examine the generality of this protocol (Scheme 2). Substrate **1d** bearing a phenyl group at the three-position of the naphthalene ring afforded the desired product **3d** in moderate yield with a decreased er value

Scheme 2. Substrate Scope with Respect to the 3-Arylpropiolates 1



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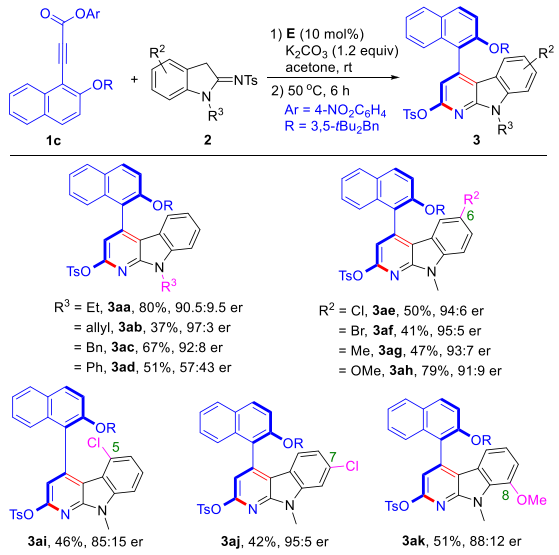
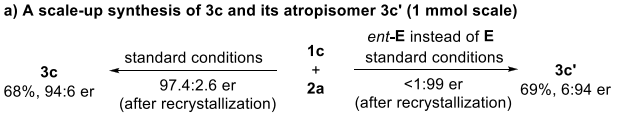
(80:20). When substrates bearing electron-withdrawing or electron-donating groups at the four-, six-, or seven-positions on the naphthalene rings were examined, moderate to high yields and high er values were regularly obtained (**3e**−**w**). Notably, this protocol could well accommodate a wide range of substituents on the naphthalene rings, including substituted phenyls, naphthyls, 2-thienyl, halogens, alkyls, and a cyano group. However, when a substituted phenyl ring replaced the naphthalene ring in propiolates, significantly decreased er values were observed (**3x** and **3y**). The absolute configuration structure of products **3** was determined by the X-ray crystallography of the atropisomer of **3s** (**3s′**) and was further established to be (R) by a comparison between the CD (circular dichroism) of **3c′** and its ECD (electrostatic circular dichroism).[11] In addition, the stability of product **3c** was investigated. (See the SI.) No racemization was observed after stirring **3c** at 150 °C for 24 h, indicating the high stability of this kind of axially chiral 4-aryl α-carboline.

Subsequently, the investigation of the scope of 2-sulfonamidoindolines **2** was conducted (Scheme 3). It was found that N-protecting groups of substrates **2** had great influence on the reaction yields and enantioselectivity. On one hand, the replacement of *N*-Me with *N*-Et or *N*-Bn led to slightly decreased er values (**3aa** and **3ac**), and the *N*-Ph substrate almost afforded the racemic product **3ad**. On the other hand, the *N*-allyl substrate resulted in a slightly increased er value but with a significantly decreased yield (**3ab**). Then, 2-sulfonamidoindolines **2** with different substituents on the benzene ring were tested. As a result, products **3ae**−**ah** and **3aj** with substituents at the six- or seven-positions were obtained in moderate yields with maintained enantioselectivities. However, five- or eight-substituted products (**3ai** and **3ak**) were obtained with decreased enantioselectivities.

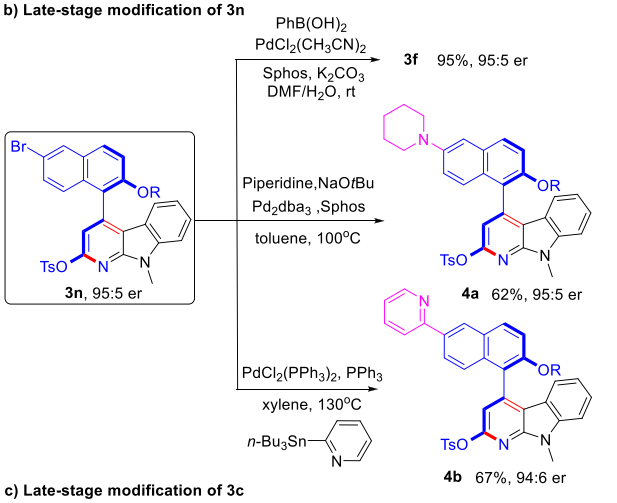
Scheme 3. Substrate Scope with Respect to the 2-Sulfonamidoindolines 2



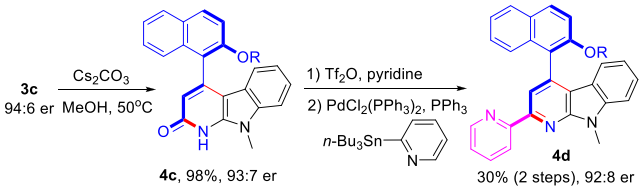
Scheme 4a) A scale-up synthesis of 3c and its atropisomer 3c' (1 mmol scale)



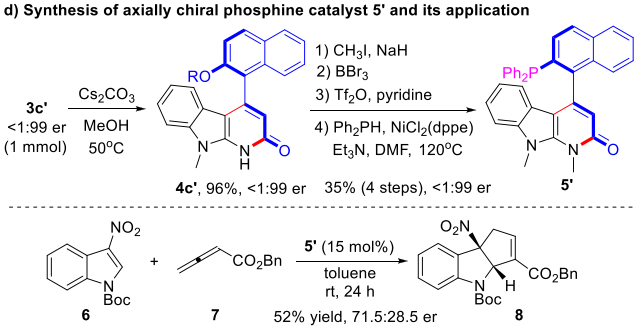
Scheme 4b) Late-stage modification of 3n



Scheme 4c) Late-stage modification of 3c



Scheme 4d) Synthesis of axially chiral phosphine catalyst 5' and its application



To further explore the synthetic utility of this methodology, a scale-up synthesis of **3c** and its atropisomer **3c′** on a 1 mmol scale was then carried out (Scheme 4a). Product **3c** was obtained in an almost maintained yield with almost maintained enantioselectivity under standard conditions. The reaction of **1c** with **2a** in the presence of the NHC precursor *ent*-**E** could also give **3c′** in a similar yield with similar enantioselectivity. It is noteworthy that the er values of the filtrates of **3c** and **3c′** could be enhanced to 97.4:2.6 and <1:99, respectively after one recrystallization.

The late-stage modification of the products was then conducted to demonstrate the utility of the developed protocol. Three classical coupling reactions of **3n** with $PhB(OH)_2$, piperidine, and 2-(tributylstannyl)pyridine afforded the corresponding products **3f**, **4a**, and **4b**, respectively, in moderate yields with maintained er values (Scheme 4b). Removal of the tosyl group of **3c** afforded product **4c** in an excellent yield with maintained enantioselectivity. **4c** was subsequently transformed to an *O*-triflate-protected intermediate that could couple with the two-position substituted pyridine reagent to get the 2-(pyridin-2-yl) α-carboline **4d** with almost maintained enantioselectivity (Scheme 4c). Moreover, the axially chiral 4-naphthyl-α-carboline **3c′** obtained after recrystallization with a higher optical purity was used for the synthesis of the axially chiral phosphine **5′**, and the enantioselectivity was retained even after five steps (Scheme 4d). A preliminary application of phosphine **5′** as an

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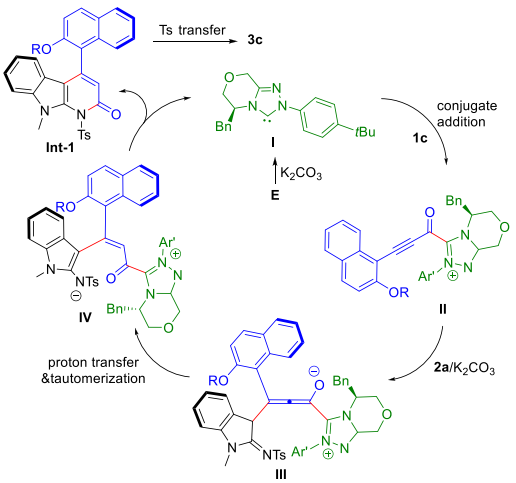
organocatalyst in the dearomatization of 3-nitroindole **6** with allenoate **7** indicated that **5′** could promote the reaction, although the enantioselectivity of product **8** still needed to be improved. Thus the synthesized axially chiral 4-naphthyl-α-carbolines should have potential in the exploration of a new class of chiral organocatalysts or ligands through further structural modification.

A plausible mechanism for the synthesis of product **3c** in the presence of the NHC precursor **E** is depicted in Scheme 5. The

Scheme 5. Proposed Reaction Mechanism



catalytic cycle starts with the addition of chiral NHC **I** to ester **1c** to give the key alkynyl acylazolium intermediate **II**. The subsequent conjugate addition of substrate **2a** to **II** under basic condition generates the allenolate intermediate **III**, which undergoes sequential proton transfer and tautomerization to form intermediate **IV**. The intramolecular nucleophilic attack of the nitrogen anion on the acylazolium of **IV** gives rise to the annulation intermediate **Int-1** with the loss of NHC **I** in the next catalytic cycle. Then, tosyl transfer from nitrogen to oxygen results in the formation of the more stable aromatized product **3c**.

To explore the origin of the stereoselectivity in this reaction, density functional theory (DFT) calculations were performed at the M06-2X/6-31G(d, p)//$SMD_{acetone}$ level in Gaussian 09. As shown in Figure 1, two different reaction modes would lead to the corresponding diastereoisomer transition states for the formation of the allenolate intermediates, that is, **TS1R** and **TS1S**. The energy barrier of **TS1R** is 1.8 kcal/mol lower than that of **TS1S**, so the pathway corresponding to the R isomer should be dominant. The calculated result is consistent with

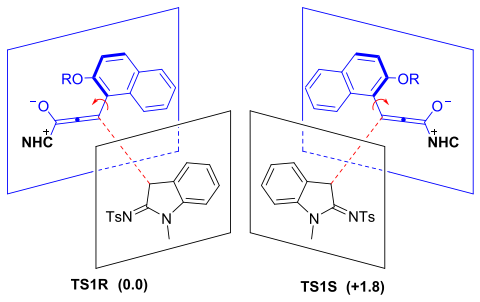


Figure 1. 2-D structures and relative free energies (kcal/mol) of **TS1R** and **TS1S**.

the experimental observation. Further analysis of the transition states **TS1R** and **TS1S** using noncovalent interation (NCI) and atoms in molecules (AIM) methods indicated that the strength of the noncovalent interactions (that is, LP$\cdots\pi$ and the C−H···N hydrogen bond) is stronger in **TS1R** than in **TS1S**, which should be responsible for the energetic favorability of the R-configurational isomer pathway. (See Figure S2.)

In summary, we have documented an NHC-catalyzed atroposelective formal [3 + 3] annulation of 4-nitrophenyl 3-arylpropiolates **1** with 2-sulfonamidoindolines **2**, which features the efficient construction of the α-carboline skeleton with the concomitant creation of the axial chirality to afford a new class of 4-aryl α-carboline atropisomers **3** with high enantioselectivity. The synthetic utility of this protocol was also demonstrated by the versatile late-stage modification of the products. Moreover, DFT calculations were conducted to illuminate that the LP$\cdots\pi$ and C−H···N hydrogen-bond interactions should be the key factors for controlling the origin of the enantioselectivity. We believe that this method not only provides a solution to the challenges in the asymmetric synthesis of axially chiral aryl-α-carbolines but also paves the way for the further investigation and application of alkynyl acylazoliums in the construction of other axially chiral molecules with structural diversity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01221.

All experimental procedures, characterization, X-ray crystallographic data, CD, ECD, nuclear magnetic resonance (NMR), and HPLC spectra, and DFT calculations (PDF)

Accession Codes

CCDC 2059256 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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(11) For detailed experiments and discussion of the determination of the absolute configuration, please see the SI (Figures S1 and S2).

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