A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202010598

Link to VoR: https://doi.org/10.1002/anie.202010598

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10.1002/anie.202010598

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Design and Atroposelective Construction of IAN analogues by Organocatalytic Asymmetric Heteroannulation of Alkynes

Lei Zhang,*[a],[b] Jiahua Shen,[a] San Wu,[b] Guofu Zhong,*[a] Yong-Bin Wang[b] and Bin Tan*[b]

Abstract: The organocatalytic atroposelective strategy for accessing enantioenriched axially chiral IAN analogues was developed for the first time. A class of novel atropisomeric C2-arylquinoline skeletons were synthesized with high enantiocontrol via chiral phosphoric-acid-catalyzed heteroannulation of *in-situ* generated vinylidene *ortho*-quinone methide (VQM) intermediates with *ortho*-aminophenones. The strategy tolerated a broad substrate scope, providing a facile organocatalytic approach to IAN analogues in good yields and excellent enantioselectivities under mild reaction conditions. Moreover, the synthetic utility of this methodology was illustrated through further transformations into IAN-type ligand and axially chiral thiourea.

The research on axially chiral biaryls have developed rapidly and gained considerable momentum in recent years because of their widespread appearance in natural products,[1] bioactive molecules,[2] and privileged chiral ligands and catalysts.[3] In sharp contrast, the asymmetric construction of axially chiral heterobiaryls was still underdeveloped,[4] even though it is scientifically important and of great significance in practical application.[5] For instance, the effective approaches to access axially chiral 2-arylpyridines (isoquinolines) are especially scanty, while they have emerged as essential backbone of numerous chiral catalysts and ligands in asymmetric catalysis (Figure 1).[6] This type of heteroaryl atropisomers ordinarily formed a chelate ring with metal atom through the coordination of nitrogen and other donor atoms, such as phosphorus, nitrogen, oxygen, and sulfur, providing the asymmetric induction in various metal-catalyzed enantioselective transformations (Figure 2a).[7] Conventionally, synthetic approaches for enantioenriched 2-arylpyridine/isoquinoline skeletons depend mainly on transition-metal mediated patterns, such as cross-coupling,[6i,r] (dynamic) kinetic resolution/transformation[6a,6g-h,6j-q,6s] and *de novo* construction of a (hetero)aromatic ring.[6c,6e-f] However, as the number of this type of axially chiral ligands and catalysts in asymmetric catalysis grows, a highly efficient organocatalytic approach to corresponding axially chiral heterobiaryl skeletons becomes an urgent need.

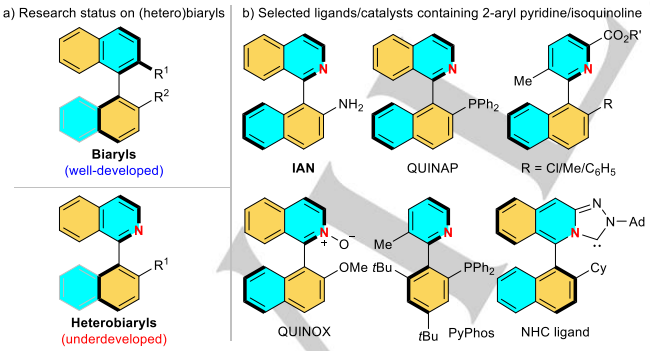

Figure 1. a) Current status of asymmetric synthesis of biaryl atropisomers; b) Selected ligands/catalysts with 2-arylpyridines/isoquinolines skeleton.

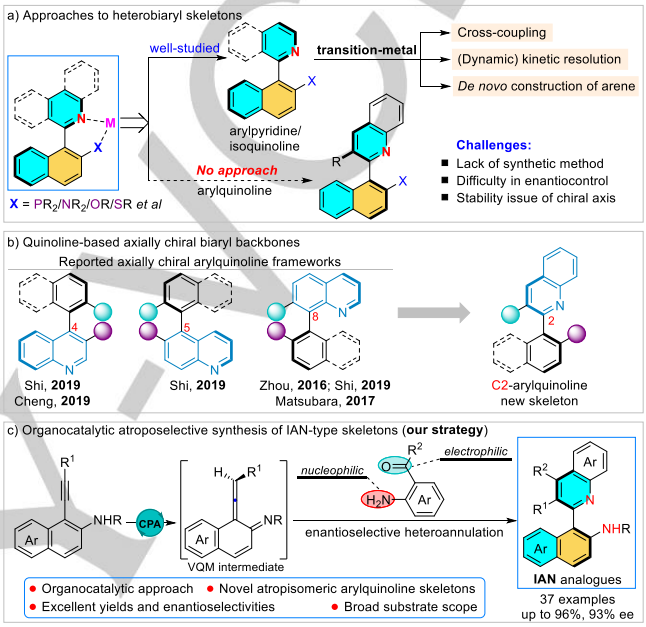

Figure 2. Previous work and our strategy.

Quinolines are one of the prominent classes of heterocyclic systems and exist in many biologically active compounds.[8] Although many significant achievements have been achieved in developing efficient and practical approach for the construction of quinolines,[9] novel atropisomeric quinoline-containing ligands or catalysts have scarcely been explored, in sharp contrast to the isoquinoline analogues. A plausible explanation is that the current reports about quinoline-derived axially chiral frameworks mostly focused on aryl-C4-, C5- or C8-quinoline skeletons[6r],[10] and the dicisive nitrogen atom for coordination with metal center in such structures was always distant from the chiral axis, thus leading to the difficulty in stereoinduction (Figure 2b). To the best of our knowledge, there was no approach to access axially chiral C2-arylquinoline skeletons, in spite of their predictable catalytic and bioactive potentials. Consequently, we designed a new atropisomeric quinoline-containing skeleton like IAN, but how to assemble this structure in an atroposelective manner and control the stability of chiral axis remains a tough challenge.

Motivated by elegant studies from Yan group and our recent work involving the atroposelective vinylidene *ortho*-quinone methide (VQM) chemistry,[11] as well as our continuous interest in developing novel axially chiral scaffolds,[12] we envisaged that chiral phosphoric acid (CPA) catalyzed[13] enantioselective heteroannulation by trapping *in-situ* generated VQMs intermediates could afford the desired axially chiral C2-arylquinoline skeletons (Figure 2c). Nevertheless, the unprecedented organocatalytic atroposelective synthesis of IAN analogues is a particularly challenging attempt, and some

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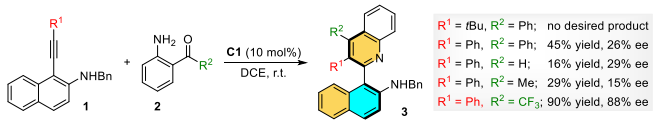
10.1002/anie.202010598

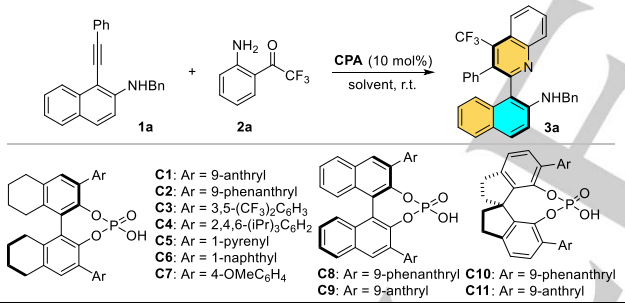
fundamental issues need to be solved. First, the selection of competent reactants should not only guarantee the final intramolecular cyclization, delivering the new quinoline ring, but also generate steric hindrance to ensure the configurational stability of products; second, the choice of a proper CPA which is capable of activating alkynes to afford VQMs intermediates and offering an effective interaction with reactants to control the atroposelectivity.

Scheme 1. Initial investigations.



To overcome the above-mentioned challenges, we initiated our studies by identifying suitable reactants. As is well known, *ortho*-carbonyl-substituted anilines have proven to be versatile reactants for diverse annulation reactions.[14] Then a preliminary study was conducted in the presence of **C1** to evaluate the effect of different types of reactants on the reactivity and stereoselectivity of the reaction (Scheme 1), and the results demonstrated that *ortho*-alkynyl-naphthylamines **1** bearing a bulky R^1 group were unfavorable for the formation of axially chiral IAN analogues (for details, see Supporting Information). Moreover, the R^2 group on the anilines derivatives has great influence on both the yields and enantioselectivities. The strategy can be carried out smoothly to give the expected axially chiral skeletons no matter the R^2 is phenyl, methyl or hydrogen atom. Despite making great efforts toward optimization of the reaction conditions, we have failed to obtain satisfactory yields and enantioselectivities. Fortunately, the dilemma has been solved significantly by introducing a CF_3-group into the aniline substrates (Scheme 1, $R^2 = CF_3$; 90% yield, 88% ee). Herein we report the first organocatalytic approach to access novel axially chiral C2-arylquinoline skeletons in high yields with excellent enantioselectivities, affording a practical metal-free avenue for the synthesis of enantioenriched IAN analogues.

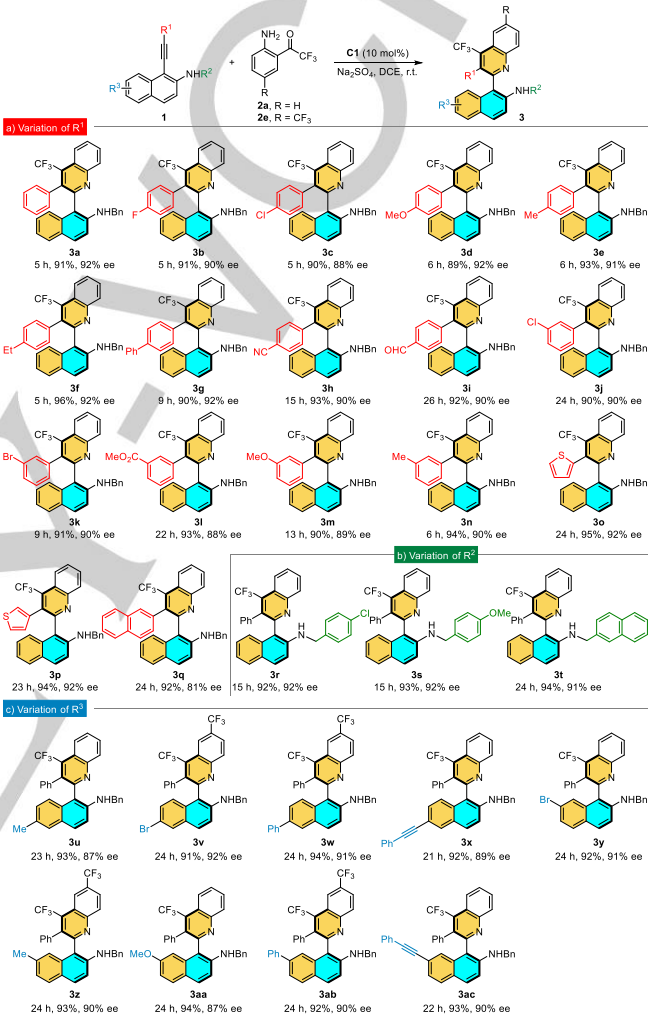
Table 1. Screening results of reaction conditions.[a]



entry	CPA	solvent	T (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**C1**	DCE	r.t.	3	90	88
2	**C2**	DCE	r.t.	6	85	83
3	**C3**	DCE	r.t.	3	83	18
4	**C4**	DCE	r.t.	48	82	14
5	**C5**	DCE	r.t.	48	80	52
6	**C6**	DCE	r.t.	4	77	70
7	**C7**	DCE	r.t.	24	86	36
8	**C8**	DCE	r.t.	17	87	48
9	**C9**	DCE	r.t.	4	84	53
10	**C10**	DCE	r.t.	24	77	3
11	**C11**	DCE	r.t.	24	74	45
12	**C1**	DCM	r.t.	5	82	82
13	**C1**	$CHCl_3$	r.t.	5	82	77
14	**C1**	toluene	r.t.	5	84	81
15	**C1**	THF	r.t.	24	86	59
16	**C1**	DCE	0	22	88	86
17[d]	**C1**	DCE	r.t.	5	91	90
18[d,e]	**C1**	DCE	r.t.	5	91	92

[a] Unless otherwise stated, all reactions were carried out with **1a** (0.12 mmol), *ortho*-trifluoroacetyl aniline **2a** (0.10 mmol), and **CPA** (10 mol%) in 3.0 mL of solvent. [b] Yields of isolated products. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Na_2SO_4 (33 mg) was added. [e] 5.4 mL of DCE.

Scheme 2. Substrate scope with respect to variation of 1-alkyne-2-naphthylamine.[a]



[a] Unless otherwise stated, all reactions were carried out with **1** (0.18 mmol), **2** (0.15 mmol), **C1** (10 mol%) and Na_2SO_4 (50 mg) in 8.0 mL of DCE. Isolated yields were provided. Ee values were determined by HPLC analysis using a chiral stationary phase.

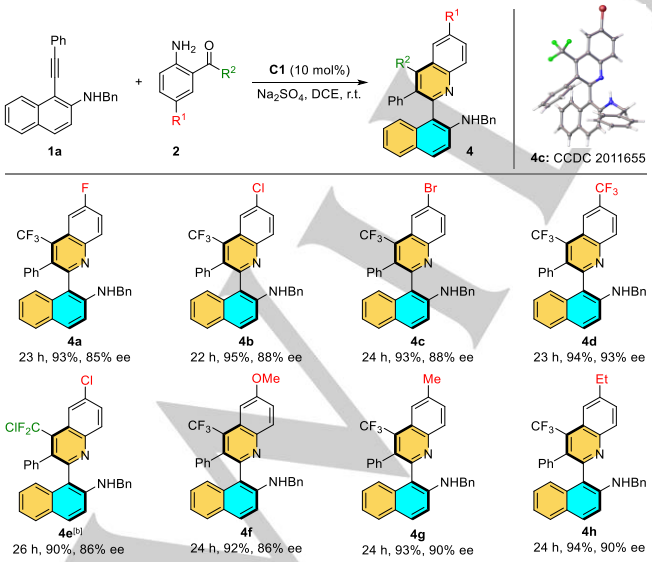
Based on our initial discovery, we utilized *N*-benzyl-1-(phenylethynyl)naphthalen-2-amine (**1a**) and *ortho*-trifluoroacetyl aniline (**2a**) as the model substrates to further optimize the reaction conditions in the presence of diversified CPA catalysts. Firstly, we set out to evaluate the electronic and steric effects of the substituents and axially chiral backbone on the CPA (Table 1, entries 1-11). **C1** with 9-anthryl at the 3,3'-position was found to be the best catalyst with respect to enantioselectivity for the model reaction (Table 1, entry 1). With the optimum catalyst identified, the influences of different solvents were then investigated (Table 1, entries 12-15). In addition, the enantioselectivity was also affected by the reaction temperature, different additives and concentration of reactants (Table 1, entries 16-18; for details, see Supporting Information). Based on

the above results, we identified the optimal conditions as follows: when **2a** was treated with 1.2 equivalent of **1a** in 1,2-dichloroethane at room temperature in the presence of 10 mol% of **C1**, the desired axially chiral arylquinoline **3a** was obtained in 91% isolated yield with 92% ee (Table 1, entry 18).

With the optimal reaction conditions in hand, we then explored the scope of substrates for this transformation. Firstly, the generality of 1-alkyne-2-naphthylamine derivatives **1** was evaluated. As summarized in Scheme 2, an array of 1-alkyne-2-naphthylamines bearing different R^1 were investigated. To our delight, the electronic and steric effects of the substituents at different positions of the aromatic rings has little impact on the reaction, affording the corresponding products in 89-96% yield with 88-92% ee (**3a**-**3n**). Moreover, no detrimental effects to the high catalytic efficiency and stereoselectivity of this process were detected with substrates bearing heteroaryl (**3o**-**3p**) or naphthyl (**3q**). Subsequently, the effect of the substituents on the R^2 was examined (**3r**-**3t**). Finally, 1-alkynyl-2-naphthylamine substrates with diverse R^3 substituents were also tested. The positions and the electronic properties of the substituents on the R^3 had a negligible impact on the chemical yields and enantioselectivities (**3u**-**3ac**). In addition, 1,6- and 1,7-bisalkynyl 2-naphthylamines (**3x** and **3ac**) proved to be efficiently transformed into the expected products, while the side products from the annulation of the 6- and 7-alkynyl groups were not detected.

To further expand the applicability of this transformation, various *ortho*-aminoacetophenone derivatives **2** were evaluated for this atroposelective annulation reaction. As shown in scheme 3, substrates **2b**-**2i** bearing either electron-rich or electron-deficient aromatic rings reacted smoothly with **1a** to afford the desired axially chiral products (**4a**-**4h**) in excellent chemical yields (90-95%) with high enantioselectivities (85-93% ee). It should be noted that the corresponding product **4e** was also obtained in 90% yield and 86% ee when replacing the CF_3 group

Scheme 3. Substrates scope in terms of variation of fluorinated *ortho*-aminophenones.[a]

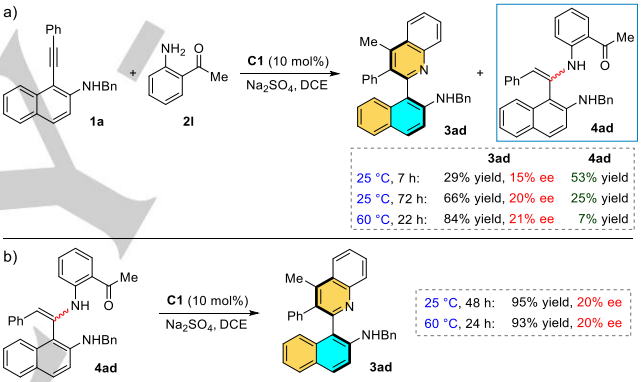


[a] Unless otherwise stated, all reactions were carried out with **1a** (0.144 mmol), fluorinated *ortho*-aminophenones **2** (0.12 mmol), **C1** (10 mol%) and Na_2SO_4 (40 mg) in 10.0 mL of solvent. Isolated yields were provided. Ee values were determined by HPLC analysis using a chiral stationary phase. [b] The corresponding product **4i** was obtained in 91% yield with 61% ee when CF_2Cl group was replaced with C_2F_5.

with CF_2Cl. The absolute configuration of **4c** (CCDC 2011655) has been determined by X-ray crystallographic analysis (see Supplementary Figure) and those of other products were assigned by analogy.

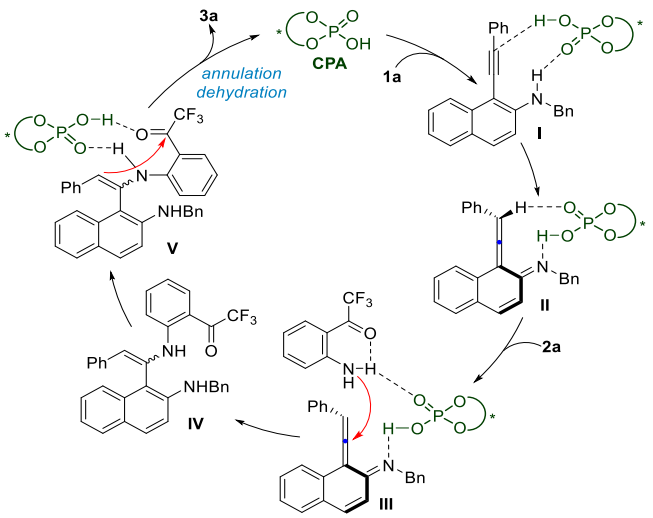
To gain further insight into the reaction mechanism, we performed control experiments to isolate the key intermediate of the process. After a lot of explorations, fortunately, when **1a** and 2-acetylaniline (**2l**) were tested under the optimal conditions, the key intermediate **4ad** was obtained in 53% yield and accompanied with formation of the final product **3ad** in 29% yield with 15% ee. Prolonging the reaction time or increasing the reaction temperature, the final axially chiral arylquinoline **3ad** was obtained as the principal product with approximately 20% ee (Scheme 4a). In addition, by treating the intermediate **4ad** with 10 mol% of **C1** at room temperature or 60 °C, the desired product **3ad** could be formed smoothly in excellent yields with the same enantioselectivities (Scheme 4b). Worthy of note is that the intermediate **4ad** was demonstrated to be the enamine structure by the analysis of NMR and mass spectrometry (for details, see Supporting Inforamtion).

Scheme 4. Control experiments and isolation of intermediate.



Based on the results of control experiments and literature precedent,[11g],[15] a possible reaction pathway of this asymmetric heteroannulation reaction has been proposed in Scheme 5. The dual hydrogen-bonding between *ortho*-alkynyl-naphthylamine **1a** and CPA was the pivotal interaction to form the complex **I**. The π−π interaction according to a recent report efficiently assists the formation of this intermediate.[16] Next, the activated alkyne

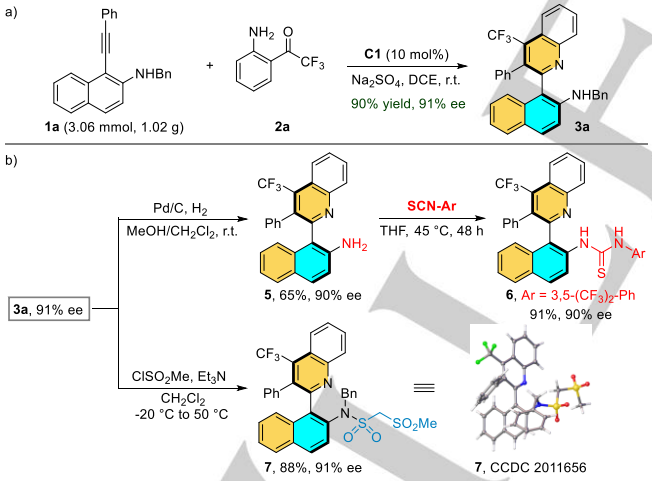
Scheme 5. Proposed reaction mechanism.



undergoes a concerted 1,5-H transfer to form the key VQM intermediate **II**. Association with *ortho*-trifluoroacetyl aniline **2a** results in a stabilized complex **III**, which features an additional hydrogen-bonding between the substrates and CPA. Subsequently, the attack of *ortho*-trifluoroacetyl aniline **2a** to the VQM intermediate results in the formation of the enamine intermediate **IV**. The intramolecular aldol reaction, followed by dehydration affords the desired axially chiral product **3a**. Obviously, CPA plays an important role in the asymmetric induction by creating an appropriate chiral environment in the final cyclization process.

To demonstrate the practicality of this method, a preparative scale synthesis of product **3a** was carried out under the optimal reaction conditions and there was almost no deterioration in chemical yield (90%) and enantioselectivity (91% ee), thus indicating that large-scale chemical production of enantioenriched IAN analogues could be achieved (Scheme 6). Subsequently, a variety of synthetic transformations were then performed based on the generated products **3a**. Axially chiral IAN analogue **5**, bearing a free amine group on the naphthalene ring, was obtained without loss of stereochemical integrity through the debenzylation of **3a**. Furthermore, treatment of **5** with bis(trifluoromethyl)phenyl isothiocyanate led to an atropisomeric thiourea **6** with complete retention of enantiopurity, which could potentially serve as an efficient organocatalyst in asymmetric transformations. Apart from that, upon treatment of **3a** with methanesulfonyl chloride in dichloromethane from -20 °C to 50 °C for 10 hours, the corresponding atropisomeric sulfonamide **7** was obtained in 88% yield without any erosion of the enantioselectivity.

Scheme 6. Gram-scale synthesis and synthetic transformations.



In summary, we have developed the first organocatalytic enantioselective construction of axially chiral IAN analogues through the asymmetric heteroannulation of alkynes with *ortho*-aminophenones via an active VQM intermediate. This transformation accommodated broad substrate scope with excellent yields and enantioselectivities (up to 96% yield, 93% *ee*) in the presence of CPA. Moreover, the reaction could be scaled up without any loss of yield and enantioselectivity. On the whole, the strategy not only offered a new type of axially chiral C2-arylquinoline skeletons, but also provided an efficient metal-free approach to the atroposelective synthesis of IAN-type *N*,*N*-ligands. The synthetic utility of this methodology was illustrated through further transformations into atropisomeric thiourea and sulfonamide. Further applications of the axially chiral C2-arylquinoline skeletons in asymmetric catalysis are currently underway in our laboratory.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (NSFC) (No. 21373073, 21672048, 21825105) and Hangzhou Normal University for financial support. G.Z. acknowledges a Qianjiang Scholar award from Zhejiang Province, China.

Conflict of interest

The authors declare no conflict of interest.

Keywords: chiral phosphoric acid • atroposelective • arylquinolines • heteroannulation • axial chirality

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[17] CCDC 2011655 (**4c**) and 2011656 (**7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

10.1002/anie.202010598

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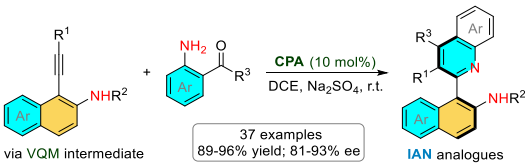
The first organocatalytic strategy for accessing enantioenriched axially chiral IAN analogues has been developed. A class of novel atropisomeric C2-arylquinoline skeletons were synthesized with high enantiocontrol via chiral phosphoric-acid-catalyzed heteroannulation of alkynes. The synthetic utility of this methodology was illustrated through further transformations into IAN-type ligand and axially chiral thiourea.



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