OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Organocatalytic Atroposelective Friedländer Quinoline Heteroannulation

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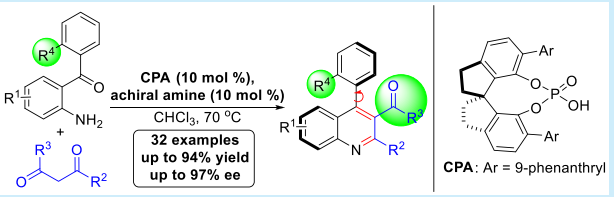
Supporting Information

ABSTRACT: An atroposelective Friedländer heteroannulation reaction of 2-aminoaryl ketones with α-methylene carbonyl derivatives has been developed for the first time with chiral phosphoric acid as an efficient organocatalyst. The desired enantioenriched axially chiral polysubstituted 4-arylquinoline architectures were prepared with good to high yields and enantioselectivities (up to 94% yield and up to 97% ee). Furthermore, the products can be readily derivatized to afford an array of new quinoline-containing heteroatropisomers, which hold great potential in asymmetric catalysis and drug discovery.



Quinolines and their derivatives have been tagged as "Privileged Scaffolds" owing to their widespread appearance in natural and synthetic products that exhibit remarkable pharmacological or physical properties (Figure 1).[1−3] While numerous synthetic methods have been developed toward their synthesis, the Friedländer heteroannulation reaction, discovered over 135 years ago, is still one of the most straightforward approaches to access polysubstituted quinolines.[4] This transformation is generally accomplished through a condensation/cyclodehydration sequence between 2-aminosubstituted aromatic carbonyl compounds and α-methylene carbonyl derivatives in the presence of acidic or basic catalysts.

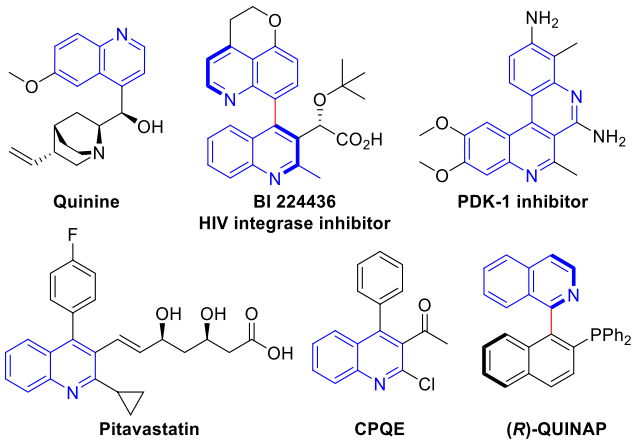


Figure 1. Selected privileged quinoline-containing natural product, bioactive molecules, and chiral ligand.

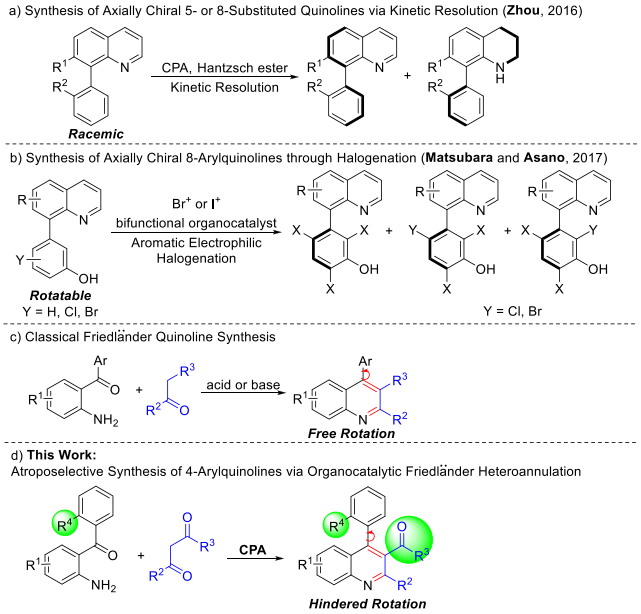
In recent decades, organocatalysis has emerged as an important tool in organic synthesis.[5] In this context, several organocatalytic Friedländer reactions for the preparation of quinolines with remote stereogenic centers have been disclosed.[6−8] On the other hand, axially chiral biaryl skeletons are frequently encountered in many natural products, bioactive compounds, and privileged chiral ligands and catalysts.[9] Besides, atropisomerism plays an important role in controlling the pharmacological properties of biological systems.[10] Accordingly, considerable efforts have been devoted to the search of efficient routes for the enantioselective construction of various atropisomeric aryl−aryl or aryl-heteroaryl structures.[11]

Despite such significant advances, the enantioselective synthesis of axially chiral quinoline-containing biaryl backbones, especially those by organocatalysis, remains rare. In 2016, the Zhou group realized an efficient kinetic resolution of axially chiral 5- or 8-substituted quinoline derivatives via chiral phosphoric acid (CPA) promoted asymmetric transfer hydrogenation (Scheme 1a).[12] Later, Matsubara, Asano and coworkers developed a bifunctional organocatalytic aromatic electrophilic halogenation reaction of prochiral 3-(quinolin-8-yl)phenols to access 8-arylquinoline atropisomers (Scheme 1b).[13] Surprisingly, the atroposelective formation of enantioenriched 4-arylquinoline derivatives in an organocatalytic and atom-efficient fashion from simple achiral substrates is almost unexplored to date.[14] Notably, 4-arylquinoline derivatives show a wide spectrum of bioactivities. For example, the HIV integrase inhibitor BI 224436 bearing a rotation inhibited axis is being investigated to target the LEDGF/p75 binding site[15] and has recently been the first noncatalytic site integrase inhibitor (NCINI) to advance into a phase Ia clinical trial.[16] The dibenzo[*c*,*f*][2,7]naphthyridine derivative represents a potent phosphoinositide-dependent kinase-1 (PDK-1) inhib-

Received: May 16, 2019

DOI: 10.1021/acs.orglett.9b01731
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of Quinoline-Containing Heterobiaryl Atropisomers

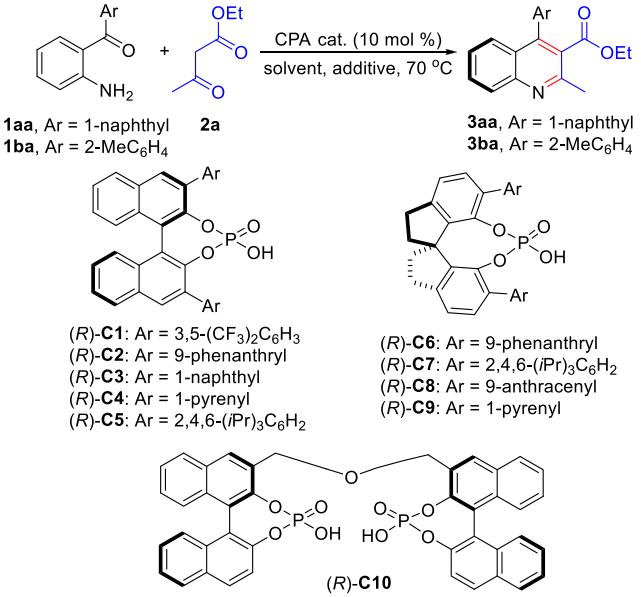


itor.[17] Pitavastatin is a well tolerated and effective alternative treatment for patients with hypercholesterolemia.[18] Even the structurally simple 4-phenyl chloroquinoline derivative **CPQE** was demonstrated to be a promising antioxidant and antidiabetic agent recently (Figure 1).[19] Therefore, the design and atroposelective construction of a new family of 4-arylquinolines is highly appealing, yet still challenging. We posited that catalytic asymmetric Friedländer heteroannulation reaction might allow a straightforward access to these valuable heterobiaryl atropisomers.

For a typical Friedländer heteroannulation, the 2,3-substituted 4-aryl quinolines produced from corresponding 2-aminoaryl ketones do not possess axial chirality because of the low rotational barrier between the two aromatic rings (Scheme 1c). We envisioned that if Ar was an aryl bearing *ortho*-substituents that could hinder the free rotation of the newly formed aryl-quinoline bond, the resulting 4-arylquinolines would be axially chiral. In order to reach this goal, the first task we encountered is selection of a suitable chiral catalyst prompt to efficiently promote the cascade process and induce axial enantiocontrol. Guided by our ongoing interest in Brønsted acid catalysis,[20] we designed a chiral phosphoric acid (CPA)[21] catalyzed asymmetric Friedländer heteroannulation reaction, which provided an efficient route for the synthesis of atropoisomeric 4-arylquinoline structures with good to high yields and enantioselectivities (Scheme 1d).

To validate our hypothesis, we first conducted the Friedländer heteroannulation reaction of (2-aminophenyl)-(naphthalen-1-yl)methanone **1aa** with ethyl acetoacetate **2a** in the presence of 10 mol % of BINOL-derived CPA (*R*)-**C1** in chloroform ($CHCl_3$) at 70 °C. After a 48 h reaction time, the desired axially chiral trisubstituted 4-aryquinoline **3aa** was obtained in 54% yield with 5% ee (Table 1, entry 1). To improve the results, a series of chiral phosphoric acids with different substituents and backbones were assessed (Table 1, entries 2−10). Among them, SPINOL-derived catalyst (*R*)-**C6** with a phenanthryl group was found to be the best in terms of enantioselectivity (79% yield, 72% ee, Table 1, entry 6).

Table 1. Reaction Condition Optimization[a]



entry	1	cat.	solvent	yield (%)[b]	ee (%)[c]
1	**1aa**	(*R*)-**C1**	$CHCl_3$	54	−5
2	**1aa**	(*R*)-**C2**	$CHCl_3$	50	−28
3	**1aa**	(*R*)-**C3**	$CHCl_3$	89	9
4	**1aa**	(*R*)-**C4**	$CHCl_3$	71	−17
5	**1aa**	(*R*)-**C5**	$CHCl_3$	70	−35
6	**1aa**	(*R*)-**C6**	**$CHCl_3$**	**79**	**72**
7	**1aa**	(*R*)-**C7**	$CHCl_3$	28	8
8	**1aa**	(*R*)-**C8**	$CHCl_3$	78	58
9	**1aa**	(*R*)-**C9**	$CHCl_3$	81	46
10	**1aa**	(*R*)-**C10**	$CHCl_3$	74	14
11	**1aa**	(*R*)-**C6**	THF	11	48
12	**1aa**	(*R*)-**C6**	EtOAc	70	44
13	**1aa**	(*R*)-**C6**	toluene	69	46
14	**1aa**	(*R*)-**C6**	DCE	66	68
15[d]	**1aa**	(*R*)-**C6**	$CHCl_3$	35	70
16[e]	**1aa**	(*R*)-**C6**	$CHCl_3$	94	69
17[f,g,h]	**1aa**	(*R*)-**C6**	**$CHCl_3$**	**92**	**74**
18[f,g]	**1ba**	(*R*)-**C6**	**$CHCl_3$**	**89**	**81**

[a]Unless otherwise stated, all reactions were carried out with 2-aminoaryl ketones **1** (0.10 mmol), ethyl acetoacetate **2a** (0.30 mmol), catalyst CPA (10 mol %) and solvent (1.5 mL) in sealed tube at 70 °C for 48 h. [b]Isolated yield. [c]Determined by chiral stationary phase HPLC analysis. [d]The reaction was run at 50 °C for 5 d. [e]The reaction was run at 100 °C. [f]5 Å molecular sieves (150 mg) were added. [g]Glycine *tert*-butyl ester (10 mol %) was added. [h]The reaction was run for 24 h.

Subsequently, various solvents were examined (Table 1, entries 11−14). Better results were observed with halogenated solvents, and reactions in $CHCl_3$ gave slightly higher enantioselectivity.

We also studied the temperature profile of this reaction and found that the atroposelectivity was slightly diminished at both higher and lower temperatures (Table 1, entries 15−16; for details on the catalyst and temperature screening, see Supplementary Table S1). Further investigations on the additives revealed that the addition of 10 mol % of a primary amine, namely glycine *tert*-butyl ester, together with 5 Å molecular sieves led to an evident acceleration on the reaction rate without any negative effect on the enantioselectivity (92%

DOI: 10.1021/acs.orglett.9b01731
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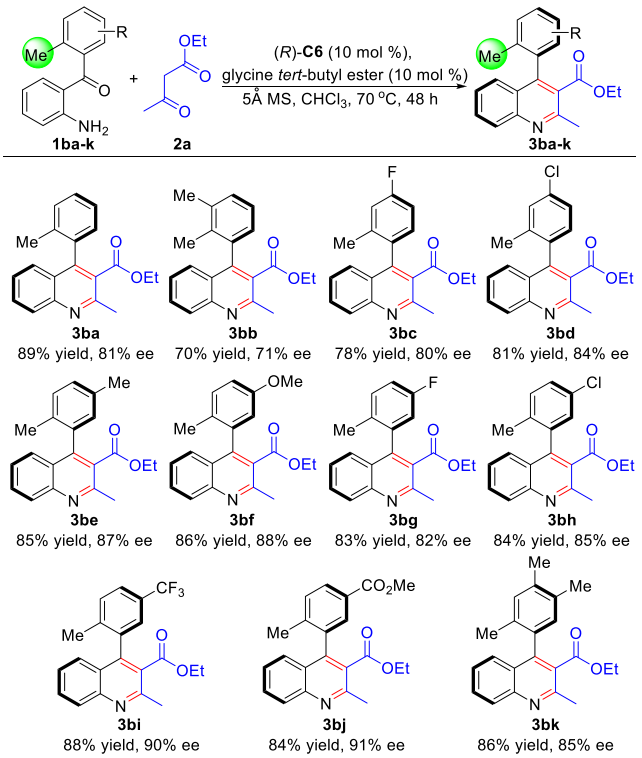
yield, 74% ee, Table 1, entry 17; for details on the additives screening, see Supplementary Table S2).

In view of the moderate result of the above model reaction of (2-aminophenyl)(naphthalen-1-yl)methanone **1aa** and the significant influence of the *ortho*-substituents of the 4-aryl group on the stereocontrol for the newly formed aryl-quinoline bond, we exchanged the Ar group of 2-aminoaryl ketone from 1-naphthyl (**1aa**) to 2-methylphenyl (**1ba**). Gratifyingly, the Friedländer heteroannulation of **1ba** with ethyl acetoacetate **2a** proceeded smoothly under the established optimal conditions and afforded the axially chiral 4-aryquinoline **3ba** in high yield (89%) with improved enantioselectivity (81% ee). Replacing the *o*-Me group with *i*Pr or CF_3 completely shut down the reaction, whereas the others (Ph, Cl, Br, and CO_2Et) led to poorer enantioselectivity, indicating that the functional group *ortho*- to the newly formed atropisomeric axis has a decisive effect on the reaction outcome.[22]

Continuing with the 4-(*o*-tolyl)quinoline scaffold, we sought out to explore a range of substitutions on the *o*-methyl phenyl ring (Scheme 2). In general, adding substitution with different

Scheme 2. Substrate Scope with Respect to (2-Aminophenyl)(*o*-tolyl)methanone 1b

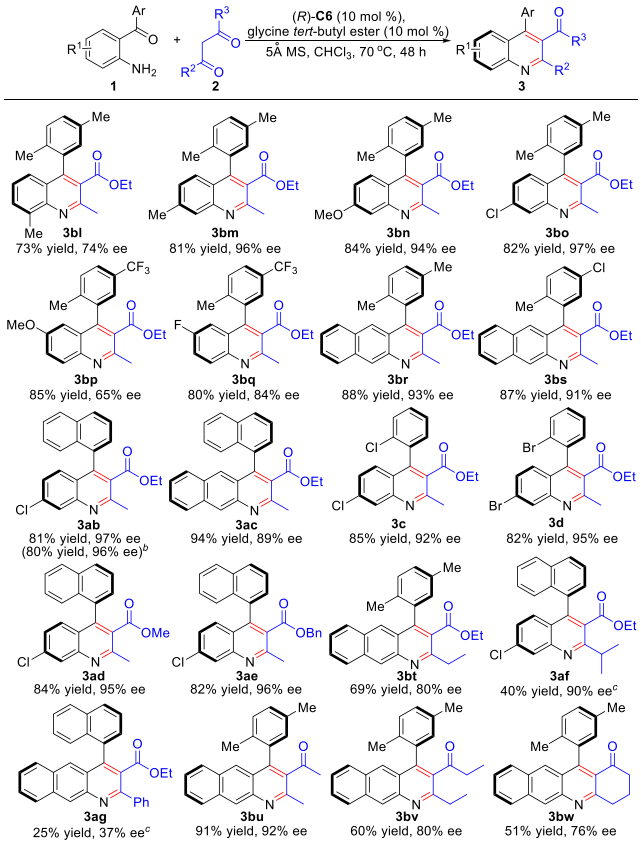


[a]All reactions were carried out with 2-aminoaryl ketones **1b** (0.10 mmol), ethyl acetoacetate **2a** (0.30 mmol), catalyst (*R*)-**C6** (10 mol %), glycine *tert*-butyl ester (10 mol %), and $CHCl_3$ (1.5 mL) in a sealed tube at 70 °C for 48 h. Yields refer to isolated pure compounds. The ee was determined by chiral stationary phase HPLC analysis.

electronic properties at the *ortho*-, *meta*-, and *para*- positions of the 2-methyl group had little effect on the reaction efficiency, giving **3ba**−**3bk** in good yields ranging from 70% to 89% and moderate to high ee values (71−91%). What is worthy of note is that incorporation of additional groups *para*- to the 2-methyl group resulted in an evident increase in the enantioselectivity (**3be**−**3bj**), and best results were obtained with a trifluoromethyl (**3bi**, 90% ee) or ester substituent (**3bj**, 91% ee).

Next, we evaluated the use of various aromatic amines (Scheme 3) and found that the atroposelectivity of this

Scheme 3. Substrate Scope with Respect to 2-Aminoaryl Ketones 1 and α-Methylene Carbonyl Derivatives 2



[a]Unless otherwise stated, all reactions were carried out with 2-aminoaryl ketones **1** (0.10 mmol), α-methylene carbonyl derivatives **2** (0.30 mmol), catalyst (*R*)-**C6** (10 mol %), glycine *tert*-butyl ester (10 mol %), and $CHCl_3$ (1.5 mL) in sealed tube at 70 °C for 48 h. Yields refer to isolated pure compounds. The ee was determined by chiral stationary phase HPLC analysis. [b]The reaction was performed at 1.0 mmol scale. [c]The reaction was run at 90 °C for 96 h.

catalytic asymmetric Friedländer reaction was very sensitive to substitutions on the phenyl ring of the newly formed quinoline. Compared with other positions (6- and 8-), higher enantioselectivities were obtained with 7-chloro (**3bo**, 97% ee) followed by 7-methyl (**3bm**, 96% ee) and 7-methoxy (**3bn**, 94% ee) substituted 4-arylquinolines. 2-Aminonaphthyl ketone was also a competent substrate, furnishing axially chiral benzo[*g*]quinoline derivatives with high optical purity (**3br**, 93% ee and **3bs**, 91% ee). At this stage, we deduced that installation of an appropriate substituent at the 7-position of the newly formed quinolines might be able to improve the enantioselectivity of other 4-arylquinolines. Pleasingly, adding a chloro-substituent to the initial model substrate **1aa** afforded significantly improved enantioselectivity (**3ab**, 97% ee vs **3aa**, 74% ee). A similar result was observed with 4-naphthylbenzo-[*g*]quinoline **3ac** (94%, 89% ee). Notably, these selectivities were conserved when different *o*-halogenated substrates were used, as exemplified by **3c** and **3d**, which contain a handle for the postfunctionalization. It bears mentioning that the

DOI: 10.1021/acs.orglett.9b01731
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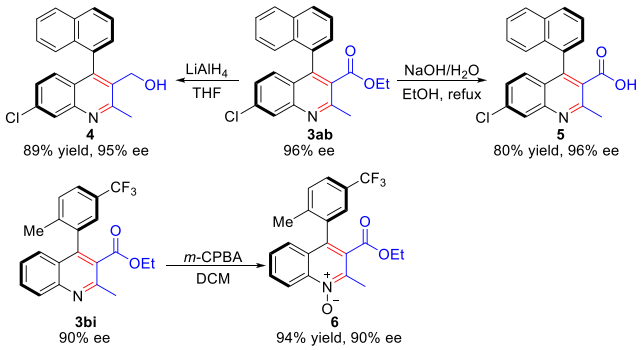
importance of the C7 position in 4-arylquinoline based drug candidates on the serum shifted potency has been established recently.[16]

Further efforts were focused toward testing the compatibility of various α-methylene carbonyl derivatives **2**. The transformation proceeded equally well with different alkyl acetoacetates (**3ad**, 95% ee and **3ae**, 96% ee). Variation of the R^2 group had a very strong influence on the reaction results. Ethyl propionylacetate smoothly underwent the reaction and provided product **3bt** in good yield and selectivity (80% ee). However, the reaction turned out to be very sluggish for sterically demanding β-keto esters. An elevated reaction temperature was required to achieve a better conversion. For example, the 2-isopropyl 4-arylquinoline **3af** was obtained in an acceptable yield with a high ee value of 90% after being heated at 90 °C for 4 days. However, utilizing ethyl benzoylacetate resulted in a dramatic drop in ee value to 37% (**3ag**). Besides, several 1,3-diones, including acetylacetone, heptane-3,5-dione, and cyclohexane-1,3-dione, were all tolerated in the catalytic process and afforded axially chiral quinolines **3bu**−**3bw** with good to high stereoselectivities (76−92% ee). The absolute configuration of **3ab** was assigned to be (*aS*) by single-crystal X-ray analysis,[23] and that of the remaining products were assigned by analogy. We also tested the configurational stability of the product by heating a solution of (*aS*)-**3ab** in toluene at 100 °C for 48 h. Chiral HPLC analysis showed that the ee was unaffected (see the Supporting Information for details).

Furthermore, the products can be readily derivatized to afford an array of new quinoline-containing heteroatropisomers (Scheme 4). The ester group in the chiral product **3ab** could

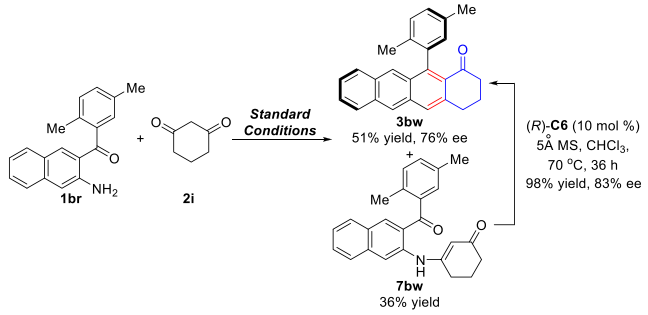
Scheme 4. Synthetic Applications



be readily reduced by $LiAlH_4$ at −20 °C or hydrolyzed with NaOH in refluxed ethanol to produce the corresponding axially chiral primary alcohol **4** and carboxylic acid **5** in high yields, respectively, without the loss of enantiopurity. Treatment of **3bi** with *m*-CPBA led to a quantitative formation of the quinoline *N*-oxide **6** with retained optical integrity.

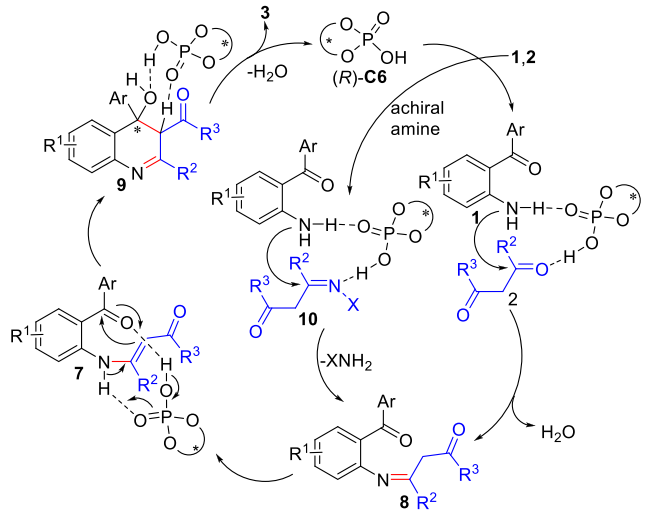
Two fundamentally different mechanisms exist for the classical Friedländer reaction. While most of the evidence favored the pathway involving the initial formation of the Schiff base intermediate,[24] a recent report has summarized that Friedländer reaction was initiated with an intermolecular aldol reaction under the typically used acidic or basic conditions.[25] Fortunately, an evident byproduct was observed in the reaction of utilizing 1,3-cyclohexanedione **2i** as a substrate, which was later demonstrated to be the enamine structure **7bw**.[26] When **7bw** was subjected to the standard protocol (without glycine *tert*-butyl ester additive), the axially chiral benzo[*g*]quinoline **3bw** could be isolated in quantitative yield with 83% ee after 36 h (Scheme 5).

Scheme 5. Isolation of Intermediate and Control Experiment



On the basis of the above experimental results, we propose the following catalytic process (Scheme 6). The first step is

Scheme 6. Proposed Catalytic Cycle



condensation of the primary amine group in 2-aminoaryl ketones **1** and **2** under promotion of CPA, leading to imine intermediates **8**, which then tautomerize to enamines **7**. Then, the intramolecular aldol reaction causes ring closure and gives compounds **9**, which finally lose water and furnish expected quinoline products **3**. It is obvious that CPA played an important role in the asymmetric induction by creating a suitable chiral environment in the cyclization step through cooperative hydrogen bonding interactions. The observation that adding a catalytic amount of achiral primary amine, such as glycine *tert*-butyl ester, could accelerate the reaction to a certain extent might be ascribed to the formation of imines **10**,[26] which was beneficial for the initial condensation to take place.

In summary, we have developed the first organocatalytic atroposelective Friedländer heteroannulation reaction to assemble stereochemically stable enantioenriched polysubstituted 4-arylquinolines in high yields with good to excellent enantioselectivities (up to 97% ee). The current study not only expands the existing state of the art of *N*-heteroatropisomers

DOI: 10.1021/acs.orglett.9b01731
Org. Lett. XXXX, XXX, XXX−XXX

construction but also provides a useful avenue to access axially chiral polysubstituted 4-arylquinoline scaffolds which might be of significance for future biological and medicinal studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01731.

Experimental procedures, NMR spectra, HPLC traces, X-ray and analytical data (PDF)

Accession Codes

CCDC 1906249 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.

■ ACKNOWLEDGMENTS

We are thankful for the financial support from the National Natural Science Foundation of China (Nos. 21602097 and 21601006).

■ REFERENCES

(1) (a) Morimoto, Y.; Matsuda, F.; Shirahama, H. Total synthesis of (±)-virantmycin and determination of its stereochemistry. *Synlett* **1991**, *1991*, 202−203. (b) Michael, J. P. Quinoline, quinazoline and acridone alkaloids. *Nat. Prod. Rep.* **1997**, *14*, 605−618. (c) Michael, J. P. Quinoline, quinazoline and acridone alkaloids. *Nat. Prod. Rep.* **2002**, *19*, 742−760.

(2) (a) Markees, D. G.; Dewey, V. C.; Kidder, G. W. Antiprotozoal 4-aryloxy-2-aminoquinolines and related compounds. *J. Med. Chem.* **1970**, *13*, 324−326. (b) Campbell, S. F.; Hardstone, J. D.; Palmer, M. J. 2,4-Diamino-6,7-dimethoxyquinoline Derivatives as α_1-Adrenoceptor Antagonists and Antihypertensive Agents. *J. Med. Chem.* **1988**, *31*, 1031−1035.

(3) (a) Zhang, X.; Shetty, A. S.; Jenekhe, S. A. Electroluminescence of multicomponent conjugated polymers. 1. Roles of polymer/polymer interface in emission enhancement and voltagetunable multicolor emission in semiconducting polymer/polymer heterojunctions. *Macromolecules* **2000**, *33*, 2069−2082. (b) Jenekhe, S. A.; Lu, L.; Alam, M. M. New conjugated polymers with donor-acceptor architectures: synthesis and photophysics of carbazole-quinoline and phenothiazine-quinoline copolymers and oligomers exhibiting large intramolecular charge transfer. *Macromolecules* **2001**, *34*, 7315−7324.

(4) (a) Cheng, C.-C.; Yan, S.-J. THE FRIEDLÄNDER SYNTHESIS OF QUINOLINES. *Org. React.* **1982**, *28*, 37−201. (b) Marco-Contelles, J.; Pérez-Mayoral, E.; Samadi, A.; Carreiras, M. C.; Soriano, E. Recent Advances in the Friedländer Reaction. *Chem. Rev.* **2009**, *109*, 2652−2671. (c) Fallah-Mehrjardi, M. Friedländer Synthesis of Poly-Substituted Quinolines: A Mini Review. *Mini-Rev. Org. Chem.* **2017**, *14*, 187−196.

(5) (a) *Comprehensive Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, Germany, 2013. (b) *Topics in Current Chemistry: Asymmetric Organocatalysis*; List, B., Ed.; Springer-Verlag: Berlin, Germany, 2009. (c) MacMillan, D. W. C. The Advent and Development of Organocatalysis. *Nature* **2008**, *455*, 304−308.

(6) Li, L.; Seidel, D. Catalytic Enantioselective Friedländer Condensations: Facile Access to Quinolines with Remote Stereogenic Centers. *Org. Lett.* **2010**, *12*, 5064−5067.

(7) Ren, L.; Lei, T.; Gong, L.-Z. Brønsted acid-catalyzed enantioselective Friedländer condensations: achiral amine promoter plays crucial role in the stereocontrol. *Chem. Commun.* **2011**, *47*, 11683−11685.

(8) Bañón-Caballero, A.; Guillena, G.; Nájera, C. Solvent-Free Enantioselective Friedländer Condensation with Wet 1,1'-Binaphthalene-2,2'-diamine-Derived Prolinamides as Organocatalysts. *J. Org. Chem.* **2013**, *78*, 5349−5356.

(9) For some reviews: (a) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193−3207. (b) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563−639. (c) *Privileged Chiral Ligands and Catalysts*; Zhou, Q.-L., Ed.; Wiley-VCH: Weinheim, Germany, 2011.

(10) For reviews: (a) Clayden, J.; Moran, W. J.; Edwards, P. J.; Laplante, S. R. The Challenge of Atropisomerism in Drug Discovery. *Angew. Chem., Int. Ed.* **2009**, *48*, 6398−6401. (b) Smyth, J. E.; Butler, N. M.; Keller, P. A. A twist of nature-the significance of atropisomers in biological systems. *Nat. Prod. Rep.* **2015**, *32*, 1562−1583. (c) Zask, A.; Murphy, J.; Ellestad, G. A. Biological Stereoselectivity of Atropisomeric Natural Products and Drugs. *Chirality* **2013**, *25*, 265−274.

(11) (a) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. Atroposelective Synthesis of Axially Chiral Biaryl Compounds. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384−5427. (b) Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivaguru, J. Nonbiaryl and Heterobiaryl Atropisomers: Molecular Templates with Promise for Atroposelective Chemical Transformations. *Chem. Rev.* **2015**, *115*, 11239−11300. (c) Wallace, T. W. Biaryl synthesis with control of axial chirality. *Org. Biomol. Chem.* **2006**, *4*, 3197−3210. (d) Zhang, D.; Wang, Q. Palladium catalyzed asymmetric Suzuki-Miyaura coupling reactions to axially chiral biaryl compounds: Chiral ligands and recent advances. *Coord. Chem. Rev.* **2015**, *286*, 1−16. (e) Wencel-Delord, J.; Panossian, A.; Leroux, F. R.; Colobert, F. Recent advances and new concepts for the synthesis of axially stereoenriched biaryls. *Chem. Soc. Rev.* **2015**, *44*, 3418−3430. (f) Baudoin, O. The Asymmetric Suzuki Coupling Route to Axially Chiral Biaryls. *Eur. J. Org. Chem.* **2005**, *2005*, 4223−4229. (g) Li, Y.-M.; Kwong, F.-Y.; Yu, W.-Y.; Chan, A. S. C. Recent advances in developing new axially chiral phosphine ligands for asymmetric catalysis. *Coord. Chem. Rev.* **2007**, *251*, 2119−2144. (h) Renzi, P. Organocatalytic synthesis of axially chiral atropisomers. *Org. Biomol. Chem.* **2017**, *15*, 4506−4516. (i) Loxq, P.; Manoury, E.; Poli, R.; Deydier, E.; Labande, A. Synthesis of axially chiral biaryl compounds by asymmetric catalytic reactions with transition metals. *Coord. Chem. Rev.* **2016**, *308*, 131−190. (j) Zilate, B.; Castrogiovanni, A.; Sparr, C. Catalyst-Controlled Stereoselective Synthesis of Atropisomers. *ACS Catal.* **2018**, *8*, 2981−2988. (k) Wang, Y.-B.; Tan, B. Construction of Axially Chiral Compounds via Asymmetric Organocatalysis. *Acc. Chem. Res.* **2018**, *51*, 534−547. (l) Bonne, D.; Rodriguez, J. A Bird's Eye View of Atropisomers Featuring a Five-Membered Ring. *Eur. J. Org. Chem.* **2018**, *2018*, 2417−2431.

(12) Wang, J.; Chen, M.-W.; Ji, Y.; Hu, S.-B.; Zhou, Y.-G. Kinetic Resolution of Axially Chiral 5- or 8-Substituted Quinolines via Asymmetric Transfer Hydrogenation. *J. Am. Chem. Soc.* **2016**, *138*, 10413−10416.

(13) Miyaji, R.; Asano, K.; Matsubara, S. Induction of Axial Chirality in 8-Arylquinolines through Halogenation Reactions Using Bifunctional Organocatalysts. *Chem. - Eur. J.* **2017**, *23*, 9996−10000.

(14) For some representative work on the construction of axial chirality involving organocatalytic annulation, see: (a) Link, A.; Sparr, C. Organocatalytic Atroposelective Aldol Condensation: Synthesis of

DOI: 10.1021/acs.orglett.9b01731
Org. Lett. XXXX, XXX, XXX−XXX

Axially Chiral Biaryls by Arene Formation. *Angew. Chem., Int. Ed.* **2014**, *53*, 5458−5461. (b) Fäseke, V. C.; Sparr, C. Stereoselective Arene-Forming Aldol Condensation: Synthesis of Axially Chiral Aromatic Amides. *Angew. Chem., Int. Ed.* **2016**, *55*, 7261−7264. (c) Zhang, L.; Zhang, J.; Ma, J.; Cheng, D.-J.; Tan, B. Highly Atroposelective Synthesis of Arylpyrroles by Catalytic Asymmetric Paal-Knorr Reaction. *J. Am. Chem. Soc.* **2017**, *139*, 1714−1717. (d) Wang, Y.-B.; Zheng, S.-C.; Hu, Y.-M.; Tan, B. Brønsted acid-catalysed enantioselective construction of axially chiral arylquinazolinones. *Nat. Commun.* **2017**, *8*, 15489. (e) Zhao, C.; Guo, D.; Munkerup, K.; Huang, K.-W.; Li, F.; Wang, J. Enantioselective [3 + 3] atroposelective annulation catalyzed by *N*-heterocyclic carbenes. *Nat. Commun.* **2018**, *9*, 611. (f) Liu, Y.; Wu, X.; Li, S.; Xue, L.; Shan, C.; Zhao, Z.; Yan, H. Organocatalytic Atroposelective Intramolecular [4 + 2] Cycloaddition: Synthesis of Axially Chiral Heterobiaryls. *Angew. Chem., Int. Ed.* **2018**, *57*, 6491−6495.

(15) Christ, F.; Voet, A.; Marchand, A.; Nicolet, S.; Desimmie, B. A.; Marchand, D.; Bardiot, D.; Van der Veken, N. J.; Van Remoortel, B.; Strelkov, S. V.; De Maeyer, M.; Chaltin, P.; Debyser, Z. Rational design of small-molecule inhibitors of the LEDGF/p75-integrase interaction and HIV replication. *Nat. Chem. Biol.* **2010**, *6*, 442−448.

(16) Fader, L. D.; Malenfant, E.; Parisien, M.; Carson, R.; Bilodeau, F.; Landry, S.; Pesant, M.; Brochu, C.; Morin, S.; Chabot, C.; Halmos, T.; Bousquet, Y.; Bailey, M. D.; Kawai, S. H.; Coulombe, R.; LaPlante, S.; Jakalian, A.; Bhardwaj, P. K.; Wernic, D.; Schroeder, P.; Paul Edwards, M. P.; Garneau, M.; Duan, J.; Cordingley, M.; Bethell, R.; Mason, S. W.; Bös, M.; Bonneau, P.; Poupart, M.-A.; Faucher, A.-M.; Simoneau, B.; Fenwick, C.; Yoakim, C.; Tsantrizos, Y. Discovery of BI 224436, a Noncatalytic Site Integrase Inhibitor (NCINI) of HIV-1. *ACS Med. Chem. Lett.* **2014**, *5*, 422−427.

(17) Gopalsamy, A.; Shi, M.; Boschelli, D. H.; Williamson, R.; Olland, A.; Hu, Y.; Krishnamurthy, G.; Han, X.; Arndt, K.; Guo, B. Discovery of Dibenzo[*c*,*f*][2,7]naphthyridines as Potent and Selective 3-Phosphoinositide-Dependent Kinase-1 Inhibitors. *J. Med. Chem.* **2007**, *50*, 5547−5549.

(18) Saito, Y. Pitavastatin: An overview. *Atheroscler. Suppl.* **2011**, *12*, 271−276.

(19) Murugavel, S.; Jacob Prasanna Stephen, C. S.; Subashini, R.; AnanthaKrishnan, D. Synthesis, structural elucidation, antioxidant, CT-DNA binding and molecular docking studies of novel chloroquinoline derivatives: Promising antioxidant and anti-diabetic agents. *J. Photochem. Photobiol., B* **2017**, *173*, 216−230.

(20) (a) Cheng, D.-J.; Wu, H.-B.; Tian, S.-K. Catalytic Asymmetric Pictet-Spengler-Type Reaction for the Synthesis of Optically Active Indolo[3,4-*cd*][1]benzazepines. *Org. Lett.* **2011**, *13*, 5636−5639. (b) Cheng, D.-J.; Tian, Y.; Tian, S.-K. Catalytic Asymmetric Synthesis of Dihydroquinazolinones from Imines and 2-Aminobenzamides. *Adv. Synth. Catal.* **2012**, *354*, 995−999. (c) Cheng, D.-J.; Yan, L.; Tian, S.-K.; Wu, M.-Y.; Wang, L.-X.; Fan, Z.-L.; Zheng, S.-C.; Liu, X.-Y.; Tan, B. Highly Enantioselective Kinetic Resolution of Axially Chiral BINAM Derivatives Catalyzed by a Brønsted Acid. *Angew. Chem., Int. Ed.* **2014**, *53*, 3684−3687. (d) Shao, Y.-D.; Cheng, D.-J. Catalytic Asymmetric 1,2-Difunctionalization of Indolenines with α-(Benzothiazol-2-ylsulfonyl) Carbonyl Compounds. *Adv. Synth. Catal.* **2017**, *359*, 2549−2556.

(21) For some reviews: (a) Akiyama, T. Stronger Brønsted Acids. *Chem. Rev.* **2007**, *107*, 5744−5758. (b) Terada, M. Binaphthol-derived phosphoric acid as a versatile catalyst for enantioselective carbon−carbon bond forming reactions. *Chem. Commun.* **2008**, *35*, 4097−4112. (c) Terada, M. Chiral Phosphoric Acids as Versatile Catalysts for Enantioselective Transformations. *Synthesis* **2010**, *2010*, 1929−1982. (d) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. Chiral BINOL-derived phosphoric acids: privileged Brønsted acid organocatalysts for C−C bond formation reactions. *Org. Biomol. Chem.* **2010**, *8*, 5262−5276. (e) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2014**, *114*, 9047−9153. (f) Held, F. E.; Grau, D.; Tsogoeva, S. B. Enantioselective Cycloaddition Reactions Catalyzed by BINOL-Derived Phosphoric Acids and *N*-Triflyl Phosphoramides: Recent Advances. *Molecules* **2015**, *20*, 16103−16126.

(22) Besides, different alkyl acetoacetates were tested and best results were obtained with the ethyl group (for details, see Supplementary Table S3).

(23) See the Supporting Information for details.

(24) (a) Schofield, K.; Theobald, R. S. Reactions of methazonic acid. Part I. The preparation of 3-nitrolepidines and 3-nitro-4-arylquinolines. *J. Chem. Soc.* **1950**, 395−402. (b) Fehnel, E. A.; Deyrup, J. A.; Davidson, M. B. Quinoline Analogs of Podophyllotoxin. II. Friedländer Reactions with Tetronic Acid: A General Method for the Preparation of 2-Hydroxymethyl-3-quinolinecarboxylic Acid Lactones[1]. *J. Org. Chem.* **1958**, *23*, 1996−2001. (c) Tamura, Y.; Tsugoshi, T.; Mohri, S.-i.; Kita, Y. Michael addition to 1,3-bis(alkoxycarbonyl)allenes: synthesis of heterocyclic compounds having glutaconate structure in the molecules. *J. Org. Chem.* **1985**, *50*, 1542−1544.

(25) Muchowski, J. M.; Maddox, M. L. Concerning the mechanism of the Friedländer quinoline synthesis. *Can. J. Chem.* **2004**, *82*, 461−478.

(26) Additionally, ESI-mass spectroscopic analysis of the reaction mixture also allowed us to identify tentatively similar key acyclic intermediate. For details on the mechanistic studies, please see the Supporting Information.

DOI: 10.1021/acs.orglett.9b01731
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