Atroposelective synthesis of 2-arylindoles via chiral phosphoric acid-catalyzed direct amination of indoles

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Abstract

Indole-based atropisomers are a very important class of axially chiral compounds. However, the atroposelective synthesis of axially chiral 2-arylindole remains largely unexplored. In this study, we report the successful synthesis of atropisomeric 2-arylindoles using direct amination of indoles with p-quinonediimines in the presence of chiral phosphoric acid as a catalyst. Quinonediimine acts as an aminating reagent through formal polarity inversion of imine. The malonate group on the 2-aryl of 2-indoles was found to be essential for high enantioselectivity of the products. This could be due to the additional interaction between the ester group and the catalyst, as well as the intramolecular hydrogen bonding. Our findings provide a new strategy for the asymmetric construction of 2-arylindole atropisomers.

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Atroposelective synthesis of 2-arylindoles via chiral phosphoric acid-catalyzed direct amination of indoles

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Keywords

Chiral phosphoric acid | Quinonediimines | Direct amination |Axially chiral 2-Arylindole| Atroposelective synthesis

Comprehensive Summary

Indole-based atropisomers are a very important class of axially chiral compounds. However, the atroposelective synthesis of

Background and Originality Content

Indole-based atropisomers are a very important class of axially chiral compounds, many of them have become the core skeletons such as natural products, active drugs, and chiral catalysts or ligands (Scheme 1a),[1-6] and the development of catalytic asymmetric constructions within these frameworks has become an emerging research area.[7-20] In comparison to axially chiral biaryl compounds,[8] introducing a five-membered pyrrole component decreases the rotation barrier, thereby affecting the stability of the axial chirality configuration and making it difficult to control the enantioselectivity. [7,9] Therefore, the asymmetric synthesis of axially chiral indole-based frameworks presents certain challenges.[9]In this context, there have been some

synthetic attempts to achieve enantioselective synthesis of these axially chiral 2-arylindoles.[21-33] These attempts have primarily focused on the strategy of cyclization of arylethynylene (Scheme 1b). In 2019, the Yan group reported a strategy for constructing 2-arylindole atropoisomers through asymmetric cyclization of *o* -alkynylaniline by organocatalysis. [22] Li *et al.* [25] successfully synthesized axially chiral 2,3'-bisindole compounds via Rh(III) catalyzed C-H bond activation and nucleophilic cyclization in 2019. In 2020, the Zhu group developed an elegant method to construct axially chiral 2-arylindoles via asymmetric Cacchi reactions. [26] Although previous studies have achieved successful results, finding an efficient and selective method for generating axially chiral 2-arylindoles remains a continuing challenge. The development of new strategies will greatly expand the range of applications for these compounds and there is still significant demand in the field.

Recently, Zhong group utilized *p* -quinonediimines as electrophilic aminating reagents to achieve excellent results in the synthesis of N-sulfonyl-3-aminoindoles through organocatalytic atroposelective electrophilic amination of indoles.[34] Based on the aforementioned works, we envisaged that if 2-arylindoles could react with the electrophilic nitrogen center of *p* -quinonediimines to form direct amination products, the resulting bulky group would hinder the rotation of adjacent C2 axis and potentially stabilize the axial chirality of 2-arylindoles. It was evident that the steric hindrance provided by the aryl substituents of indoles could serve as another optimization parameter to prevent racemization of the product. Herein we report the successful synthesis of atropisomeric 2-arylindoles using *p* -quinonediimines as aminating reagents in the presence of chiral phosphoric acid as a catalyst (Scheme 1c).

Scheme 1 Research background of 2-arylindole atropoisomers

Results and Discussion

Before embarking on the atroposelective synthesis, we focused on discovering axially chiral 2-arylindoles with high configurational stability. Subsequently, we synthesized two compounds (**1** &**2**) and examined their potential to possess axial chirality through high-performance liquid chromatography (HPLC) analysis on a chiral stationary phase (Scheme 2a). The experimental results unequivocally showed that compound **1** was non-chiral, while compound **2** exhibited apparently axial chirality. Then, we carried out asymmetric synthesis of compound **2** in the presence of various chiral phosphoric acids (For details, see Table S1 in SI). The best result was obtained with 54% ee. Compound **2** exhibited low axial chirality stability during the subsequent racemization experiment, leading to rapid racemization at room temperature in*i* PrOH (ee drops gradually from 54% to 32% after 96 hours, Table S2 in SI for details). To increase the configurational stability, we introduce a malonate entity on the 2-aryl ring. Hopefully, this steric hindrance and intramolecular hydrogen bonding may increase the stability of product. Surprisingly, the compound **3** was proved to be configurationally stable and no racemization occurred at room temperature (rotation energy barrier to rotation of **3** was determined to be 121.55 KJ/mol, see Table S4 in SI).

Based on our initial investigations, we selected dimethyl 2-(3-bromo-2-(1H-indol-2-yl)phenyl)malonate **N-1c** and tosyl-substituted *p* -quinonesdiimine **E-1a** as model substrates to start systematic optimization studies. The reaction proceeded smoothly to give the axially chiral 2-arylindole **3**with 89% yield and 88% ee in the presence of chiral phosphoric acid (CPA) **C1** as catalyst. This preliminary result obviously demonstrated that the control of the axial chirality of 2-arylindole by using CPA-catalyzed direct amination of malonate substituted 2-arylindole is feasible. As shown in Scheme 2b, the electron properties and steric bulk of the substituents on the aromatic ring had a significant impact on the reactivity and enantioselectivity of the reaction. After screening of a range of CPAs, catalyst (*R*)-**C5** displayed the best results in terms of the enantioselectivity (95% ee). Thorough evaluation of other reaction parameters such as the solvent and catalyst loading (for details, see Table S3 in SI) culminated in the following optimal conditions: when**E-1a** (0.10 mmol) was treated with **N-1c** (0.15 mmol) in the presence of catalyst **C5** (10 mol%) in CH_2Cl_2 at 25 °C for 12 h, the axially chiral 2-arylindole **3** was obtained in 93% isolated yield with 95% ee (Scheme 2b).

Scheme 2 The exploration for atroposelective synthesis of the axially chiral 2-arylindoles

After the optimal reaction conditions established, we turn our attention to the substrate scope investigation.

Firstly, we have examined the substituted *p* -quinonesdiimines **E-1** and the results were depicted in Scheme 3a. The *p* -quinonediimines bearing a phenyl ring at the *para* -position (**4** -**7**) and a 2-naphthyl group (**8**) exhibited high reactivity and enantiocontrol in the reaction, resulting in the formation of products with excellent results. Additionally, the *p* -quinonediimines bearing an *ortho* -position substituent (Me) on the phenyl ring showed efficient transformation without compromising the yield (90%), albeit with slightly lower enantioselectivity (**9** , 82% ee).

To further explore the scope of this transformation, we then evaluated the use of various 2-arylindoles as nucleophiles (Scheme 3b). The replacement of Br with Cl in the reaction system did not significantly impact the reactivity and enantioselectivity, as expected. This suggests that Cl also effectively constrains the rotation of the chiral axis (**10**). However, when iodine atoms were used instead, the reaction was completely inhibited due to the large steric hindrance. The replacement of the halide group with a methyl group resulted in a considerable loss of enantiocontrol, with only 79% ee observed (**11**). However, when methoxy groups were introduced at C6 position of indole, there was an insignificant change in reaction outcome (**12**). The excellent enantiocontrol returned when substrate with a naphthyl was employed (**13** , 92% ee). The use of different malonate groups (Et and *i* Pr) proved to be amendable, resulting in corresponding products (**14** and **15**) with excellent results.

Scheme 3 Substrate generality for construction of axially chiral 2-arylindoles

Reaction conditions: In an oven dried Schlenk tube chiral phosphoric acid (*R*)-**C5** (10 mol%), **E-1** (0.10 mmol) and**N-1** (0.15 mmol) were dissolved in 4 mL of CH_2Cl_2. The mixture was stirred at 25°C until the reaction was completed.

To demonstrate the practicality of this transformation, a preparative-scale synthesis was conducted to efficiently produce 1.94 g of product **7** with 95% yield and 91% ee. As illustrated in Scheme 4a, there was only a minor variation in both chemical yield and stereoselectivity in the presence of 5 mol% of (*R*)-**C5** , suggesting that large-scale chemical production of axially chiral 2-arylindoles using this methodology may indeed be feasible. Furthermore, by treatment of **11** with $(Boc)_2O$, the protective product **16** could be easily obtained with 96% ee after recrystallization. The absolute configuration of **16** was determined to be *S* by X-ray crystallographic analysis and stereochemistry of other products was assigned by analogy (Scheme 4b).

Scheme 4 Large-scale synthesis and transformation

The compound **17** with stable configuration was synthesized with fairly poor enantioselectivity when the malonate entity was replaced by isopropyl under the optimal conditions. This result could be attributed to the loss of the ester-CPA catalyst interaction and the intermolecular hydrogen bonding within the indole substrate. Based on the experimental results and the reported literatures,[34] a possible reaction mechanism was illustrated. As shown in Scheme 5b, initially, imine **E** is activated by chiral phosphoric acid to generate intermediate **A** . The driving force of aromaticity caused **A** to undergo isomerization and transform into intermediate **B** . Subsequently, 2-arylindole**N** attacked the latter to produce the final product with an axially chiral 2-arylindole moiety. The bifunctional CPA catalyst was responsible for simultaneously activating both 2-arylindole and intermediate **B** through multiple hydrogen bonding interactions.

Scheme 5 Control experiment and reaction mechanism

Conclusions

In summary, we have synthesized a series of axially chiral 2-arylindoles through the direct amination of 2-arylindoles with*p* -quinonediimines as aminating reagents. The reaction was carried out with excellent yields and high enantioselectivities under the catalysis of chiral phosphoric acid. It is worth noting that this method exhibits synthetic practicality, as the products could be obtained through gram-scale reactions with nearly identical yields and enantioselectivities. This method is an effective supplement to the existing strategies for the enantioselective synthesis of 2-arylindole atropisomers. The application of 2-arylindole atropisomers in asymmetric synthesis is currently being explored in our group.

Experimental

In an oven dried Schlenk tube chiral phosphoric acid (*R*)-**C5** (10 mol%), **E-1** (0.10 mmol) and**N-1** (0.15 mmol) were dissolved in 4 mL CH_2Cl_2. The mixture was stirred at 25°C until the reaction was completed (about 12 h). Solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc = 30/1) to give the pure product.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2023xxxxx.

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Left to Right: Wen Bao, Ye-Hui Chen, Yu-Wei Liu, Shao-Hua Xiang, and Bin Tan

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