Communication

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Atroposelective Synthesis of Axially Chiral Biaryldiols via Organocatalytic Arylation of 2-Naphthols

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Supporting Information Placeholder

ABSTRACT: The first phosphoric acid-catalyzed asymmetric direct arylative reactions of 2-naphthols with quinone derivatives have been developed, providing an efficient access to a class of axially chiral biaryldiols in good yields with excellent enantioselectivities under mild reaction conditions. This approach is highly convergent and functional group tolerant, providing the rapid construction of axially chiral compounds from simple, readily available starting materials. The excellent stereocontrol of the process stems from the efficient transfer of the stereochemical information of chiral phosphoric acid into the axis chirality of biaryldiol products. The preliminary results demonstrated that the resultant biaryldiols can act as an efficient chiral ligand in asymmetric transformations.

The axially chiral C_2-symmetric BINOL and their derivatives have been extensively evaluated as versatile chiral ligands/catalysts in asymmetric transformations.[1] In addition, their well-established conversions to the corresponding BINAP[2] and phosphoric acids[3] further expand their synthetic utility in various domains of asymmetric catalysis (Figure 1). As a result, the construction of these scaffolds has attracted considerable attention and the relatively practical methods have already been achieved.[1] Furthermore, recent studies have disclosed that the non-symmetric BINOL derivatives (biaryldiols) are also used as efficient chiral ligands or catalysts.[4] Noteworthy is that this motif is a prominent feature of many biological active natural products[5] like the famous Vancomycin, Knipholone and Gossypol (Figure 1). Compared with the successful application and synthesis of C_2-symmetric BINOLs, the application of these biaryldiols remains largely underexplored with respect to asymmetric synthesis and natural products synthesis, which is probably due to lack of reliable synthetic routes.[1a]

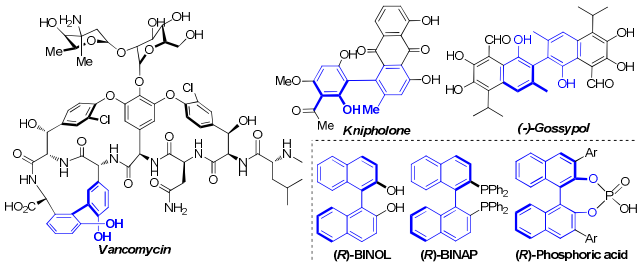
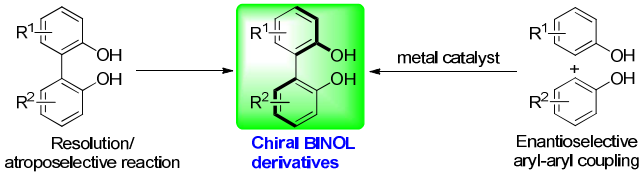


Figure 1. Selected natural products and ligands/catalysts involving axially chiral biaryldiols

In this context, there have only been a few synthetic attempts toward enantioselective synthesis of these axially chiral biaryldiols, which includes direct metal-catalyzed asymmetric oxidative cross-coupling reactions[6] and kinetic resolutions[7] (Scheme 1). Although the oxidative cross-coupling reactions represent a straightforward way to access non-symmetric biaryldiols from achiral precursors, the current catalytic systems can only produce desired products with certain specific substitution patterns in high enantioselectivity. Over the past several decades, the kinetic resolution of racemic starting materials has been one of the most powerful and reliable strategies for the synthesis of enantiopure compounds in both academia and industry. However, the catalytic kinetic resolution of these axially chiral biaryldiols has surprisingly underdeveloped[8] and accompanied with a limitation of no more than 50% yield. More recently, Akiyama achieved a significant breakthrough by using phosphoric acid to enable asymmetric atroposelective bromination, providing a more useful avenue to access these types of axially biaryldiol skeleton.[9] Despite these successful results, the development of efficient and highly enantioselective strategy for facile access to axially chiral biaryldiols would greatly expand the application scope and is still in great demand.

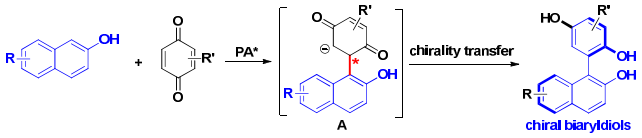
Scheme 1. The Existing Strategies for Atroposelective Synthesis of Axially Chiral Biaryldiols



Quinones have long served as useful synthetic precursors to construct densely functionalized aromatic rings.[10] Accordingly, their application in asymmetric organocatalysis has been on the increase as an expedient means to deliver a range of optically enriched compounds.[11] Motivated by these progresses and the recent development of synthesis of axial chiral compounds,[12] we envisioned that 2-naphthols could directly react with quinones to afford the chiral biarydiols, thus providing the possibility to develop a direct enantioselective arylation strategy to construct axially chiral non-symmetric biaryldiols. As shown in Scheme 2, we postulated that conjugated addition intermediates **A** could be generated from 2-naphthols and quinones, and subsequently aromatized with efficient central to axial chirality exchange[6e,12l,13] as a result of the restricted rotation to yield the final axial chiral compounds. In this scenario, several challenges had to be encountered:

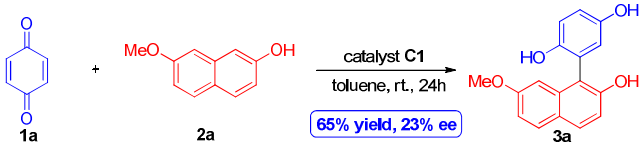
(1) the selection of reasonable catalyst to increase the reactivity, to efficiently control C/O chemoselectivity of the 2-naphthols; (2) the choice of chiral catalyst to efficiently induce stereocontrol in the conjugated addition step; (3) the use of mild reaction conditions to transfer the chirality and obviate the axial rotation. As part of our continued interest for asymmetric synthesis of axially chiral compounds[14] and phosphoric acid catalysis,[15] herein, we describe the novel chiral phosphoric acid-catalyzed highly enantioselective direct arylative reactions of 2-naphthols and quinone derivatives, providing a new synthetic route toward axially chiral biaryldiols bearing multiple substituent patterns; such structural motifs are important components of various biologically active natural products[5] and should have the potential application for asymmetric catalysis.[4]

Scheme 2. Our Strategy for Atroposelctive Synthesis of Axially Chiral Biaryldiols via Direct Arylation of 2-Naphthols



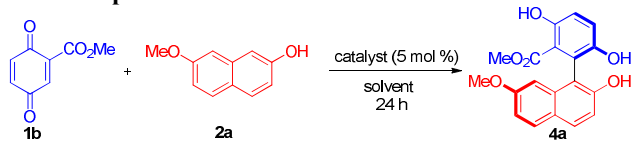
We initiated our studies by evaluating the reaction between quinone **1a** and 2-naphthol **2a** in toluene at room temperature in the presence of the typically used phosphoric acid catalyst (CPA) **C1** (Scheme 3). To our delight, the reaction proceeded smoothly and afforded the desired axially chiral biaryldiol **3a** in good yield, albeit with poor enantioselectivity (23% ee). However, after making great efforts on optimization of the reaction conditions, we could not improve the enantioselectivity by using the current model reaction.

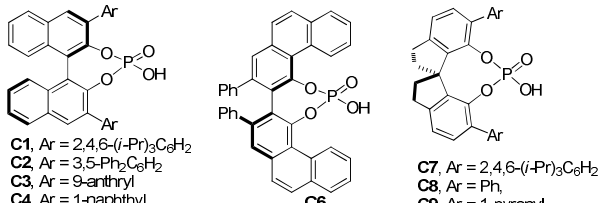
Scheme 3. Initial Results for Direct Synthesis of Biaryldiols



To improve reaction results, we modified the design of the quinone substrate to provide its potential interaction for hydrogen bonding formation with catalysts. Specifically, we installed an ester group into quinone skeleton to facilitate access of the catalyst to the ketone-ester moiety[16] for multiple hydrogen-bonding, thus enabling the simultaneous activation of a nucleophile and an electrophile in a suitable spatial configuration. The quinone derivative **1b** was tested for this reaction, using CPA **C1** as a catalyst, the enantioselectivity was improved up to 57% ee (Table 1, entry 1). Encouraged by this promising result, a detailed optimization study was first done with different CPAs (**C1-C9**). Several BINOL, SPINOL, and VAPOL-derived catalysts were investigated, which displayed remarkable effects on the outcome of the reaction (Table 1, entries 1-9). The results clearly demonstrated that CPA with a very bulky substituted group in the 3,3'-position gave rise to good enantiocontrol. It should be noted that almost no ee of product **4a** was obtained with VAPOL-derived phosphoric acid **C6** as the catalyst, which is most likely due to the less steric hindrance with the starting material. Of the solvents tested for the reaction catalyzed by **C1** (Table 1, entries 10-13), dichloromethane (DCM) proved optimal with respect to the enantioselectivity (Table 1, entry 10). Attempts to optimize the reaction by conducting it in different temperature succeeded to provide the desired improvement in enantioselectivity and found the best results can be obtained with up to 90% yield in 93% ee at the temperature of -78 °C (Table 1, entry 16). The lower catalyst loading has a negative effect on the results while the higher loading does not improve the chemical yield and stereoselectivity (Table 1, entries 17, 18). The reaction concentration has a fairly influence on the chemical yield and enantioselectivity. When more or less concentrated solution was employed, the chemical yield and ee of the product decreased (Table 1, entry 19, 20).

Table 1. Optimization of the Reaction Conditions[a]





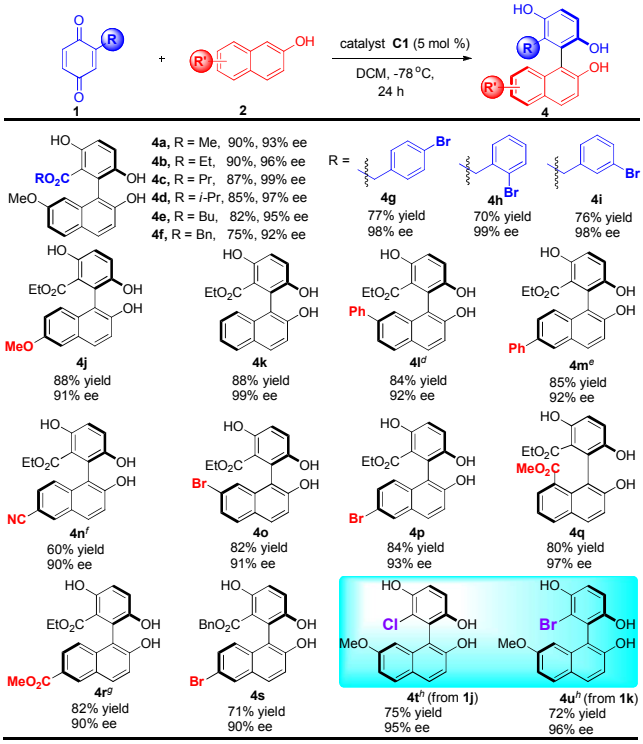
entry	catalyst	solvent	T (°C)	yield (%)[b]	ee (%)[c]
1	**C1**	toluene	25	90	57
2	**C2**	toluene	25	85	3
3	**C3**	toluene	25	87	6
4	**C4**	toluene	25	85	3
5	**C5**	toluene	25	83	10
6	**C6**	toluene	25	83	0
7	**C7**	toluene	25	88	-41
8	**C8**	toluene	25	81	-4
9	**C9**	toluene	25	87	-7
10	**C1**	DCM	25	92	72
11	**C1**	DCE	25	90	65
12	**C1**	$CHCl_3$	25	89	70
13	**C1**	EtOAc	25	84	57
14	**C1**	DCM	0	92	80
15	**C1**	DCM	-40	92	85
16	**C1**	DCM	-78	90	93
17[d]	**C1**	DCM	-78	88	85
18[e]	**C1**	DCM	-78	90	93
19[f]	**C1**	DCM	-78	85	88
20[g]	**C1**	DCM	-78	89	93

[a] The reaction was carried out with 2-methoxycarbonyl-1,4-benzoquinone **1b** (0.10 mmol), 7-methoxyl-2-naphthol **2a** (0.12 mmol) and catalyst (5 mol %) in 2 mL of solvent for 24 h under Ar. [b] Isolated yield based on **1b**. [c] ee values were determined by HPLC analysis using a chiral stationary phase. . [d] 2.5 mol % of **C1** was employed. [e] 10 mol % of **C1** was employed. [f] 1 mL of DCM was employed. [g] 3 mL of DCM was employed for 48 h.

After the optimal reaction conditions being established, we set out to explore the substrate scope with respect to various quinones and 2-naphthols as reactants (Table 2). As regarding to the quinone derivatives, the phosphoric acid-catalyzed direct arylation reaction proceeded smoothly with a variety of quinone esters to afford the desired products under mild reaction condition. All of the investigated reactions were complete within 24 hours and gave products (**4a-4i**) in good yields (70-90%) and with excellent enantioselectivities (92-99% ee). For the use of 2-naphthols, the position and the electronic properties of the substituents on the aro-

matic ring appeared to have a very limited effect on stereoselectivity. Regardless of the type of substituents on the aromatic rings, bearing electron-withdrawing (Table 2, products **4n-4s**), electron-donating (Table 2, product **4j**), or neutral (**4k-4m**) groups at the different positions, the reactions of these 2-naphthols gave the axially chiral biaryldiols with very high stereoselectivities and good reactivity. It is noteworthy that the use of a steric hindrance 8-substituted naphthanol, also afforded the desired product **4q** in excellent stereocontrol (97% ee) under the standard reaction conditions, demonstrating that the substrate scope could not be only limited to less bulky 2-naphthols. It should be noted that changing the ester group to the more useful halogen group, such as Cl or Br at the quinone moiety, has almost no influence on the reaction efficiency and stereoselectivity with excellent results (**4t**, **4u**), which is very important for chiral ligands or catalysts design because halides are very reactive for further modifications in many transition metal-catalyzed reactions.[17]

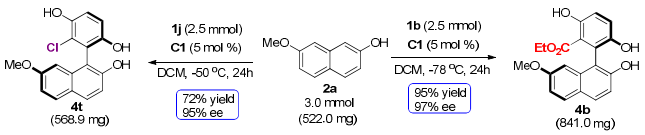
Table 2. Substrates Scope of the Direct Arylation Reaction[a,b,c]



[a] The reaction was carried out with quinone esters **1** (0.10 mmol), 2-naphthol **2** (0.12 mmol) and catalyst **C1** (5 mol %) in 2 mL of DCM at -78°C for 24 h under Ar. [b] Isolated yields based on quinone esters. [c] ee values were determined by HPLC analysis using a chiral stationary phase. [d] Reaction at -20 °C for 72 h. [e] Reaction at -78 °C for 48 h. [f] Reaction at -25 °C with 10 mol % of **C1** for 60 h. [g] Reaction at -10 °C with 10 mol% of **C1** for 48 h. [h] Reaction at -40 °C for 24 h.

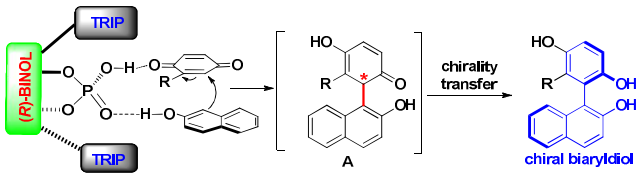
To demonstrate the utility of the direct arylative reaction, preparative scale synthesis of product **4b** and **4t** was carried out. As displayed in Scheme 4, there was almost no change in reactivity and stereoselectivity, suggesting that this method should have the potential for large-scale chemical production.

Scheme 4. Preparative Synthesis of 4b and 4t.



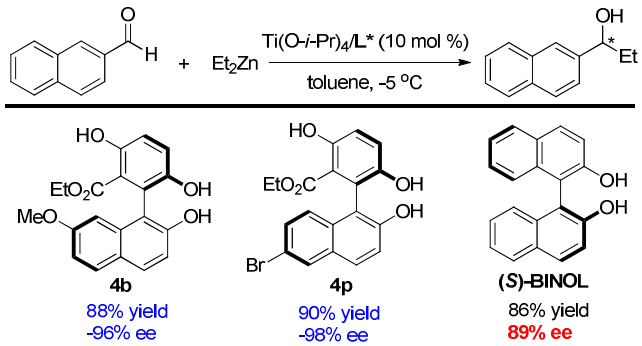
Based on the experimental results, a possible reaction process is illustrated in Scheme 5. The chiral phosphoric acid **C1** performed as a bifunctional organocatalyst to simultaneously activate 2-naphthols and quinone derivatives by multiple hydrogen-bonding activation and promote the first step of enantioselective conjugated addition to form the intermediate **A**. The following step is just to transfer its central chirality information into its axial chirality and affords the final chiral biaryldiol.[6e,12l,13] The ester moiety or halogen in the 2-position of the quinone might play a very important role to control the stereoinduction via additional interactions. In addition, these groups could help to increase the stablity of the obtained products. However, the exact role of these moieties remains unclear and deserves further investigations. In order to confirm the absolute configuration (AC) of compounds **4**, the ECD spectra were calculated by the TD-DFT method, which has been proven to be useful in predicting ECD spectra and assigning the AC of organic molecules. The *R* configuration could be reliably assigned to compound **4b** (For details, see Supporting Information Figure S1).

Scheme 5. Proposed Reaction Process



An indication for the configurational stability of the product was obtained by heating a solution of **4b** in DCE at 80 °C for 24 hours. HPLC analysis showed an unaffected enantiomeric exess. Therefore, the obtained axially chiral compounds may have potential applications as asymmetric organocatalysts/ligands. To further investigate the utility of the obtained chiral biaryldiols, the efficiency of (*R*)-**4** as ligands for enantioselective addition of diethylzinc to aldehydes was verified, which is one of the most reliable methods to prepare chiral *sec*-alcohols and also a standard reaction to test the reactivity and enantioselectivity of newly designed chiral ligands.[18] As shown in the Table 3, the mixture prepared by allowing a toluene solution of **4b** or **4p** and titanium tetraisopropoxide to stand at -5 °C gave excellent chemical yields and enantiomeric excesses (96% or 99% ee). It should be noted that the enantioselectivity for this model reaction was just 89% ee with (*S*)-BINOL as chiral ligand under the same reaction conditions, further demonstrating the useful utility of the obtained non-symmetrical biaryldiols.

Table 3. Preliminary Application in Addition of Diethylzinc to Aldehyde[a,b,c]



[a] Reaction conditions, see supporting information. [b] Isolated yields. [c] ee values were determined by HPLC analysis using a chiral stationary phase.

In summary, we have successfully developed the first phosphoric acid-catalyzed asymmetric direct arylative reactions of 2-naphthols with quinone derivatives, giving an efficient access to a class of axially chiral biaryldiols in good yields with excellent enantioselectivities under mild reaction conditions. This new approach is highly convergent and functional group tolerant, which allows for the rapid construction of axially chiral compounds from simple, readily available starting materials. The excellent stereocontrol of the process stems from the efficient transfer of the stereochemical information of chiral phosphoric acid into the axis chirality of biaryldiol products. The application of this strategy to other substrate classes and mechanistic investigations addressing the intricacies of the chirality transfer are currently underway in our laboratory and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization of all new compounds, Figure S1. This information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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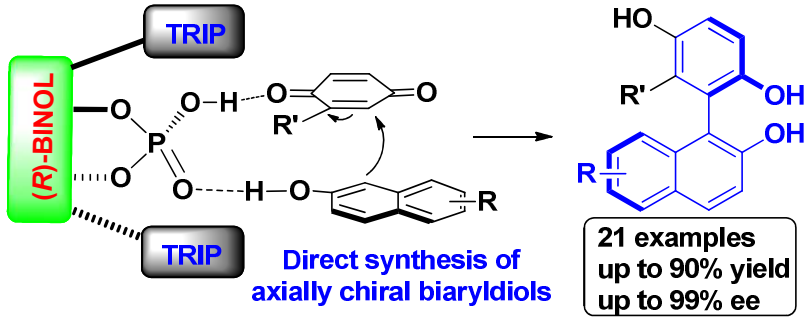
TRIP
(R)-BINOL
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Direct synthesis of
axially chiral biaryldiols
HO
R'
OH
OH
R
21 examples
up to 90% yield
up to 99% ee