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Phosphoric Acid-Catalyzed Asymmetric Synthesis of SPINOL Derivatives

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ABSTRACT: Axially chiral 1,1'-spirobiindane-7,7'-diol (SPINOL) is the most fundamental and important privileged structure to synthesize other chiral ligands containing a 1,1'-spirobiindane backbone. Driven by the development of enantioselective synthesis of axially chiral SPINOL derivatives, we have successfully developed the phosphoric acid-catalyzed asymmetric approach for the first time. This approach is a highly convergent and functional group tolerant to efficiently provide SPINOLs in good yield with excellent enantioselectivity, thus delivering a practical and straightforward access to this privileged structure. It should be emphasized that the catalyst loading could be decreased to only 0.1 mol% for the preparative scale synthesis. Furthermore, the 4,4'-dimethyl SPINOL-phosphoric acid was synthesized and applied to catalyze the model reaction for synthesis of enantioenriched SPINOL derivative.

INTRODUCTION

Axially chiral compounds are wide appearance in biologically active compounds, materials, organocatalysts and ligands. Accordingly, much attention has been paid to asymmetric construction of axially chiral compounds and great progress has been achieved in recent years. Among the well-known structures, axially chiral BINOL, BINAP and other biaryl derivatives have been extensively evaluated as versatile chiral ligands/catalysts. Owing to the importance of these structural motifs, the catalytic asymmetric construction of biaryl derivatives has been intensively investigated[1] and could be accessed by stereoselective oxidative/cross-coupling of two aryl counterparts,[2] asymmetric control of formation of an aromatic ring,[3] atroposelective functionalization of biaryl compounds,[4] and so on (Figure 1, left).[5]

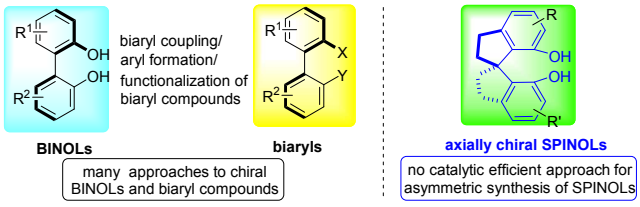


Figure 1. The existing approaches for catalytic asymmetric synthesis of axially chiral biaryls and SPINOLs.

In sharp contrast, the asymmetric synthesis of axially chiral 1,1'-spirobiindane-7,7'-diol (SPINOL) remains largely unexplored (Figure 1, right),[6] although it is the most fundamental and important privileged structure to synthesize other chiral ligands containing a 1,1'-spirobiindane backbone such as FuP, SDP, SpiroPAP, SPIDAM, SIPHOX, SpiroBOX, SCp, SITCP and CPA for asymmetric catalysis in recent years (Figure 2).[7] In this regard, there have only been a few synthetic attempts toward asymmetric synthesis of enantiopure SPINOL. Birman and co-workers firstly reported the successful outcome by using a classic resolution strategy.[6a] In 2002, Zhou and co-workers developed a more practical approach by employing cinchonidinium chloride as a resolution reagent.[6b] Quite recently, a promising method for kinetic resolution of SPINOL by *N*-heterocyclic carbene-catalyzed enantioselective acylation was reported by Zhao and co-workers,[6c] however, only one substrate was utilized with moderate result (less than 50% ee; selectivity factor, s = 3.4). The large scale production of optically pure SPINOL, however, still relies on conventional resolution, which requires the stoichiometric use of chiral reagents. Therefore, the development of a catalytic asymmetric synthetic approach to axially chiral SPINOL derivatives is very attractive and highly desirable.

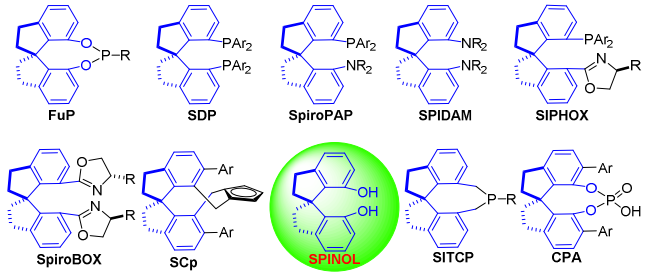


Figure 2. The useful ligands/organocatalysts with 1,1'-spirobiindane backbone derived from SPINOL.

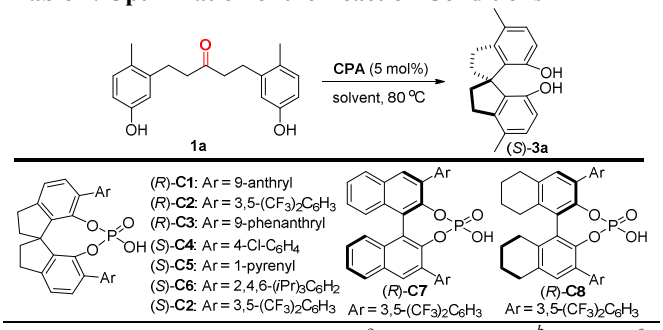
Since the pioneering reports of Akiyama and Terada, chiral phosphoric acids (CPAs) have demonstrated great potential to catalyze many reactions due to their capacity for synergistic dual acid and base activation.[8] More recently, List and co-workers have elegantly demonstrated the use of chiral confined phosphoric acid to synthesize an important spiroketal moiety by spiroketalizations.[9] Inspired by these successful examples and the previous efforts for synthesis of racemic SPINOL,[6a,10] we envisioned that phosphoric acid could acti-

vate the carbonyl and hydroxyl group in a cooperative manner via a bifunctional activation mode to give the final product SPINOLs with good stereocontrol. As part of our ongoing interest in asymmetric construction of axially chiral compounds[11] and phosphoric acid catalysis,[12] we describe herein the results of the investigation, leading to the first phosphoric acid-catalyzed enantioselective synthesis of axially chiral SPINOLs to provide a practical and straightforward synthetic route toward enantiopure SPINOL derivatives.

RESULTS AND DISCUSSION

To validate the feasibility of our proposed transformation, we initially investigated the reaction of 1,5-bis(5-hydroxy-2-methylphenyl)pentan-3-one **1a** in the presence of 9-anthryl-SPINOL-derived chiral phosphoric acid (*R*)-**C1**. Unfortunately, no reaction was observed at room temperature. To our delight, the reaction proceeded slowly to provide SPINOL derivative (*S*)-**3a** in 17% yield with 41% ee after stirring at 80 °C in a sealed vial for three days (Table 1, entry 1). This result encouraged us to further evaluate different chiral phosphoric acids for the transformation. As shown in Table 1, the electron properties and the steric bulk of substituents at the catalysts as well as the axially chiral backbone have very strong influences on the reactivity and enantioselectivity (Table 1, entries 2-8). Catalyst (*R*)-**C2** displayed the best result in terms of the chemical yield (60%) and stereocontrol (92% ee) (Table 1, entry 2). Upon optimizing the reaction conditions through variations of the solvent, temperature, catalyst loading, and concentration (Table 1, entries 9-13 and Table S1 in Supporting Information), we identified the following protocol as optimal: reaction of **1a** (0.1 mmol) in the presence of catalyst (*R*)-**C2** (10 mol%) in $CHCl_3$ (3 mL) at 120 °C for two days, the axially chiral (*S*)-**3a** was obtained in 98% isolated yield with 90% ee (Table 1, entry 13). The opposite enantiomer of (*R*)-**3a** could be obtained with similar result by using (*S*)-**C2** as chiral catalyst (Table 1, entry 14).

Table 1. Optimization of the Reaction Conditions[a]

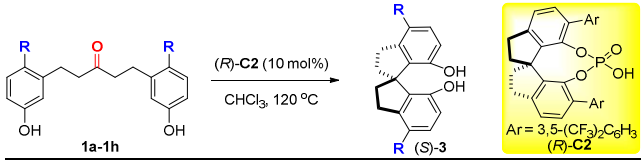


entry	CPA	solvent	T (°C)	yield (%)[b]	ee (%)[c]
1	(*R*)-**C1**	$CHCl_3$	80	17	41
2	(*R*)-**C2**	$CHCl_3$	80	60	92
3	(*R*)-**C3**	$CHCl_3$	80	23	40
4	(*S*)-**C4**	$CHCl_3$	80	40	-11
5	(*S*)-**C5**	$CHCl_3$	80	43	0
6	(*S*)-**C6**	$CHCl_3$	80	NR	-
7	(*R*)-**C7**	$CHCl_3$	80	trace	-36
8	(*R*)-**C8**	$CHCl_3$	80	48	-34
9	(*R*)-**C2**	DCE	80	54	83
10	(*R*)-**C2**	toluene	80	22	89
11[d]	(*R*)-**C2**	$CHCl_3$	60	13	94
12[d]	(*R*)-**C2**	$CHCl_3$	120	90	90
13[d,e]	(*R*)-**C2**	$CHCl_3$	120	98	90
14[d,e]	(*S*)-**C2**	$CHCl_3$	120	98	-90

[a] Unless otherwise stated, all reactions were carried out with **1a** (0.1 mmol) and **CPA** (5 mol%) in 1 mL of solvent at 80 °C for three days under Ar. [b] Yield based on RPLC (for details, see supporting information). [c] Determined by chiral HPLC analysis. [d] Reaction was run in 3 mL of $CHCl_3$. [e] Reaction was run with 10 mol% of **CPA** for two days.

After an acceptable optimal reaction condition established, we turned our attention to the substrate scope. As shown in Table 2, the electronic properties of substituents on the aromatic rings have a significant effect on the reactivity of the transformation. Substrates bearing electron-donating groups (R = Me, *n*-Bu, Ph, 4-Me-Ph) at the aryl ring proceeded efficiently to afford the corresponding products (*S*)-**3a-3d** in 90-97% yield with 90-93% ee (Entries 1-4). To our disappointment, almost no desired SPINOL derivatives were detected when substrates bearing electron-withdrawing groups (R = F, Cl, Br, I) at the aryl ring were used under optimized reaction conditions. To our surprise, the expected products (*S*)-**3g** and (*S*)-**3h** were achieved with good enantioselectivity by increasing catalyst loading to 20 mol% and extending the reaction time to five days, albeit with very low yields (Table 2, entries 7 and 8), indicating that it is possible to expand the generality of the substrate scope by further investigation of the reaction parameters.

Table 2. The Substrate Scope with Respect to Ketones.[a]



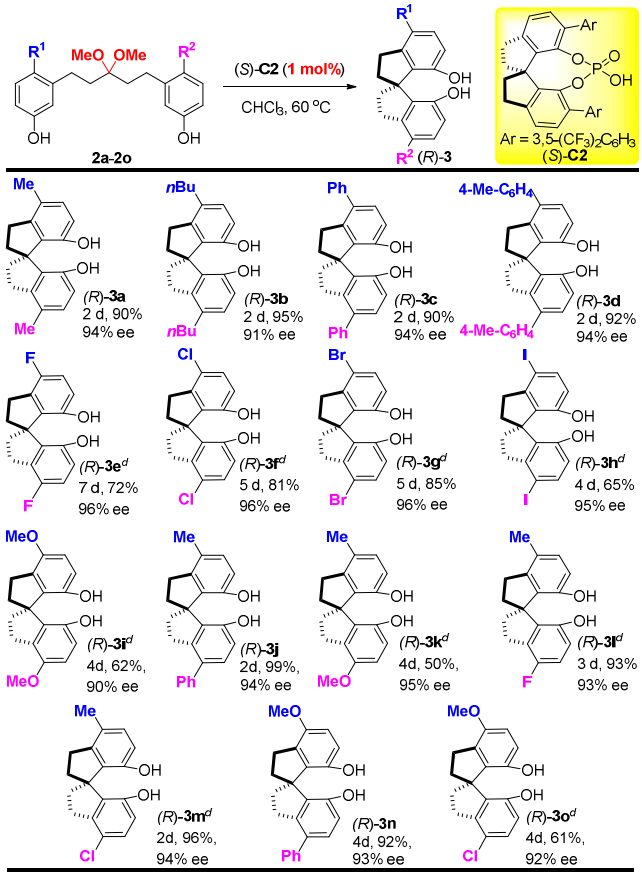
entry	substrate **1**	**3**	t (d)	yield (%)[b]	ee (%)[c]
1	**1a**, R = Me	(*S*)-**3a**	2	97	90
2	**1b**, R = *n*Bu	(*S*)-**3b**	2	95	91
3	**1c**, R = Ph	(*S*)-**3c**	2	90	92
4	**1d**, R = 4-Me-Ph	(*S*)-**3d**	2	92	93
5[d]	**1e**, R = F	(*S*)-**3e**	3	trace	-
6[d]	**1f**, R = Cl	(*S*)-**3f**	3	trace	-
7[d]	**1g**, R = Br	(*S*)-**3g**	5	19	93
8[d]	**1h**, R = I	(*S*)-**3h**	5	20	93

[a] Unless otherwise stated, all reactions were carried out with **1a-1h** (0.1 mmol) and (*R*)-**C2** (10 mol%) in 3 mL of $CHCl_3$ at 120 °C for two days under Ar. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] 20 mol% catalyst (*R*)-**C2** was used.

Considering the above-mentioned results, we thought that the improvement of the reactivity of ketones might be the key point to promote the outcome of this transformation. Thus, we turned our attention to investigating the reaction with a more reactive substrate (ketal **2a,** $R^1 = R^2$ = Me) (For details of optimization, see supporting information Table S2). Gratifyingly, the reaction proceeded very well by use of 1 mol% of catalyst

(*S*)-**C2** and the desired product (*R*)-**3a** was obtained in 90% yield with 94% ee in two days at 60 °C (Table 3, the first example). Remarkably, the scope of this catalytic system turned out to be very broad. Various ketals (**2a-2i**) with different substitution properties including electron-donating groups (R^1 = R^2 = Me, *n*-Bu, Ph, 4-Me-Ph, OMe) and electron-withdrawing groups (R^1 = R^2 = F, Cl, Br, I) at the aryl ring performed smoothly with high enantioselectivities and good to excellent chemical yields (90-96% ee, 62-95% yield). We have also investigated non-symmetrical substrates (**2j-2o**) and found them to be suitable substrates for delivering products **3j-3o** in good results. Thus, the current results demonstrated that this method is an efficient and straightforward process to access enantiomerically pure SPINOL derivatives.

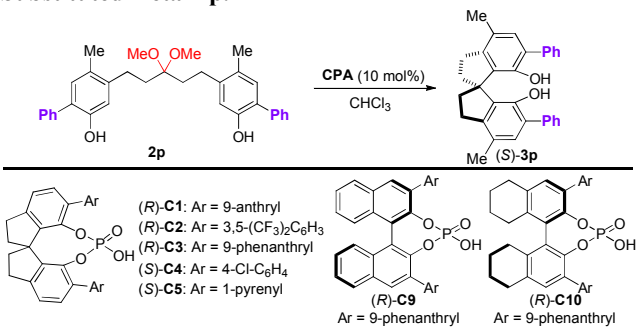
Table 3. The Substrate Scope with Respect to Ketals.[a,b,c]



[a] Unless otherwise stated, all reactions were carried out with **2a-2o** (0.1 mmol) and (*S*)-**C2** (1 mol%) in 3 mL of $CHCl_3$ at 60 °C under Ar. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] The reaction was run at 70 °C and 5 mol% (*S*)-**C2** was used.

Encouraged by these results, we therefore expanded the generality of the reaction with regard to the ketals bearing aromatic groups at the ortho position. When phenyl substituted ketal **2p** was investigated, the reaction proceeded very slowly under the optimized conditions and only trace amount of product could be formed after several days. To our delight, the expected SPINOL derivative (**3p**) was produced with 53% yield when the reaction was conducted at 100 °C, albeit with moderate enantioselectivity (45% ee). Encouraged by this result, we further screened the reaction condition by evaluating different chiral phosphoric acids for the transformation (Table 4, entries 1-7). The catalyst (*R*)-**C3** was proved to be optimal (Entry 3). The enantioselectivity could be improved to over 90% with good chemical yields after further modification of the reaction condition (Entries 8 and 9). Having identified the optimized conditions, we proceeded to investigate the substrates bearing other aromatic groups. Several substituted ketals (Ph, 4-Me-Ph, 3-F-Ph and 4-F-Ph) were successfully applied in the reaction (Table 5). The corresponding 6,6'-diaryl SPINOL derivatives **3p-3s** were isolated with moderate chemical yields (58-62%) and good enantioselectivities (83-95% ee).

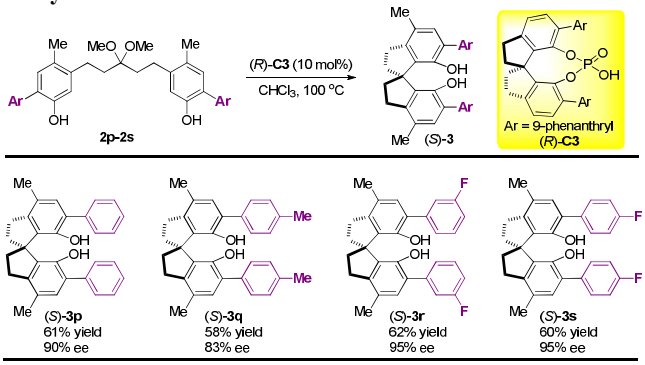
Table 4. Screening of the Reaction Conditions for Aryl Substituted Ketal 2p.[a]



entry	CPA	T (°C)	yield (%)[b]	ee (%)[c]
1	(*R*)-**C1**	100	55	80
2	(*R*)-**C2**	100	53	45
3	(*R*)-**C3**	100	60	88
4	(*S*)-**C4**	100	50	-67
5	(*S*)-**C5**	100	55	-84
6	(*R*)-**C9**	100	52	-72
7	(*R*)-**C10**	100	trace	-
8[d]	(*R*)-**C3**	100	61	90
9[e]	(*R*)-**C3**	100	60	91
10[d]	(*R*)-**C3**	120	61	88
11[d]	(*R*)-**C3**	80	20	92
12[d,f]	(*R*)-**C3**	100	13	90

[a] Unless otherwise stated, all reactions were carried out with **2p** (0.1 mmol) and **CPA** (10 mol%) in 3 mL of solvent at 100 °C for five days under Ar. [b] Isolated yield based on **2p**. [c] Determined by chiral HPLC analysis. [d] 5 mL of $CHCl_3$ was used. [e] 7 mL of $CHCl_3$ was used. [f] 1 mol% of (*R*)-**C3** was used.

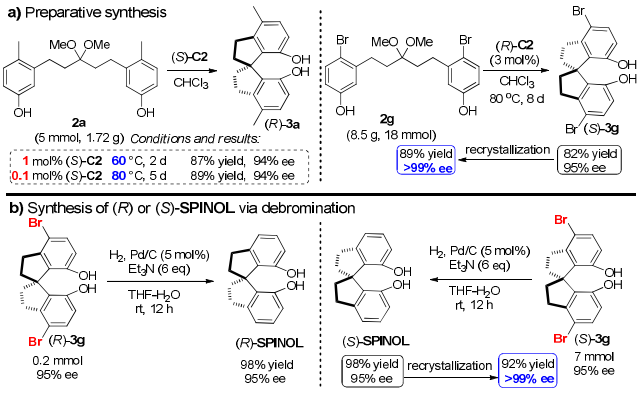
Table 5. The Substrate Scope in Terms of Synthesis of 6,6'-Diaryl-SPINOLs.[a]



[a] Unless otherwise stated, all reactions were carried out with **2p-2s** (0.1 mmol) and (*R*)-**C3** (10 mol%) in 5 mL of $CHCl_3$ at 100 °C for five days under Ar.

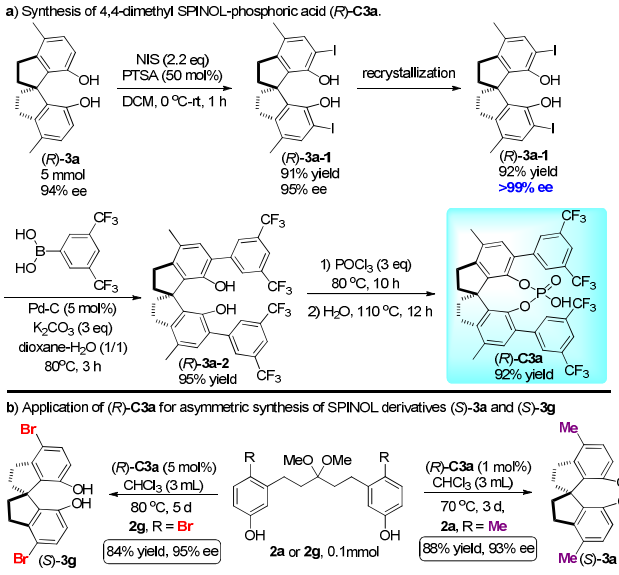
To further demonstrate the practicality of such process, we carried out a gram-scale synthesis of product (*R*)-**3a** and (*S*)-**3g** under the optimal reaction conditions. As displayed in Scheme 1a, there were almost no change in chemical yields and stereoselectivities. It is noteworthy that the catalyst loading can be decreased to 0.1 mol% for synthesis of (*R*)-**3a** without any influence on the outcome, albeit with a higher temperature and longer reaction time. It should be worth highlighting that the debromination of (*R*) or (*S*)-**3g** can be easily realized to synthesize the (*R*) or (*S*)-SPINOL in the presence of Pd/C catalyst without any effect on enantioselectivities (Scheme 1b).[6a] To our delight, the ee value could be improved to >99% after once recrystallization.

Scheme 1. Preparative Synthesis and Debromination.



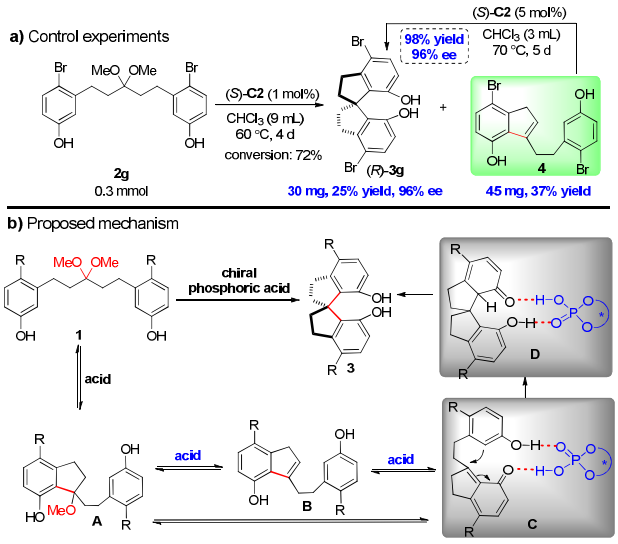
After the practical approach to synthesize the SPINOL derivatives established, we are interested in exploring the application of 4,4'-disubstituted SPINOLs in asymmetric catalysis. Inspired by the pioneering works of Zhou[13a] and Wan[13b] that 4,4'-disubstituted SPINOLs and their derived compounds could be utilized as efficient chiral ligands for addition reaction and hydrogenation, we envisioned that 4,4'-disubstituted SPINOL-derived phosphoric acids might be acted as organocatalysts to catalyze the model reaction. According to Wang's elegant synthetic procedure for synthesis of SPINOL-phosphoric acid,[7h] we have synthesized the 4,4'-dimethyl SPINOL-phosphoric acid (*R*)-**C3a** by using modified reaction procedures (Scheme 2a, for synthetic details, see Supplementary information). To really investigate the potential application of the resultant new chiral phosphoric acid in the field of asymmetric catalysis, we chose the synthesis of (*S*)-**3a** and (*S*)-**3g** from ketal **2a** and **2g** respectively as model reactions. Gratifyingly, the reactions proceeded smoothly and the corresponding products were obtained in good results (Scheme 2b), demonstrating that the newly developed phosphoric acid has the potential application in asymmetric synthesis. Further work encompassing the application of other 4,4'-disubstituted SPINOL-derived phosphoric acids for enantioselective reactions is currently in progress in our laboratory.

Scheme 2. Synthesis and Application of 4,4'-Dimethyl SPINOL-Phosphoric Acid (*R*)-C3a.



To gain further insight into the reaction mechanism, we conducted control experiments to rationalize the current reaction process and its stereochemistry. Fortunately, when ketal **2g** was tested under the similar reaction conditions by using 1 mol% of catalyst (*S*)-**C2** for just four days, the key intermediate **4** was formed in 37% yield and accompanied with formation of the desired product in 25% yield with 96% ee (Scheme 3a). Furthermore, treating the intermediate **4** with 5 mol% of (*S*)-**C2** at 70 °C for five days, the final product (*R*)-**3g** was formed in almost quantitative yield with the same enantioselectivity (Scheme 3a). On the basis of the above observations and previous reports,[14a,b] the reaction may initially form an intermediate **B** *in situ* generated from **A** and further go through an active *o*-QM intermediate[14] **C** to deliver the SPINOL derivative. The excellent stereocontrol was attributed to the simultaneous interaction between the bifunctional phosphoric acid and intermediate **C** via hydrogen bonding (Scheme 3b). At the present stage, the ion pair interactions[10,15] between the substrate and the catalyst cannot be ruled out from the reaction process with respect to the excellent enantioselection observed in the reaction. Therefore, further investigations are necessary to unambiguously elucidate the mechanism.

Scheme 3. Control Experiments and Proposed Mechanism.



CONCLUSION

We have successfully developed the asymmetric synthesis of SPINOL derivatives by means of chiral phosphoric acid for the first time. With this methodology, a wide range of axially chiral SPINOLs were synthesized in good results with high level of enantioselectivity, delivering a practical and straightforward approach to this fundamental and important privileged structure. Notably, the preparative scale synthesis can be conducted very well with only 0.1 mol% of catalyst loading. Furthermore, the 4,4'-dimethyl SPINOL-phosphoric acid was synthesized and applied to catalyze the model reaction for synthesis of enantioenriched SPINOL derivative, indicating that the newly developed phosphoric acid has the potential application in asymmetric synthesis. Application of this strategy to other substrate classes and mechanistic studies for better understanding the asymmetric induction in this transformation are ongoing in our laboratory.

METHODS

General procedure for the asymmetric synthesis of the SPINOL Derivatives (*R*)-3a-3o from ketal substrates. Under argon atmosphere, **2** (0.1 mmol), (*S*)-**C2** (1 mol% or 5 mol%) and 3 mL of anhydrous $CHCl_3$ were added to a 10 mL oven-dried ***pressure Schlenk tube (purchased from Beijing Synthware Glass)*** with a magnetic stirring bar. Then the sealed reaction proceeded at 60℃ or 70℃ (the temperature of oil bath) until the substrate was consumed completely. After evaporation of the solvent, the residue was purified by flash chromatography eluted with PE/EA (8/1-4/1) to afford the product (*R*)-**3**.

General procedure for the asymmetric synthesis of the 6,6'-diaryl-SPINOL Derivatives (*S*)-3p-3s. Under argon atmosphere, **2** (0.1 mmol), (*R*)-**C3** (10 mol%) and 5 mL of anhydrous $CHCl_3$ were added to a 10 mL oven-dried ***pressure Schlenk tube (purchased from Beijing Synthware Glass)*** with a magnetic stirring bar. Then the sealed reaction proceeded at 100℃(the temperature of oil bath) for five days. After evaporation of the solvent, the residue was purified by flash chromatography eluted with PE/EA (50/1-20/1) to afford the corresponding product (*S*)-**3**.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization of all new compounds, Table S1, Table S2. 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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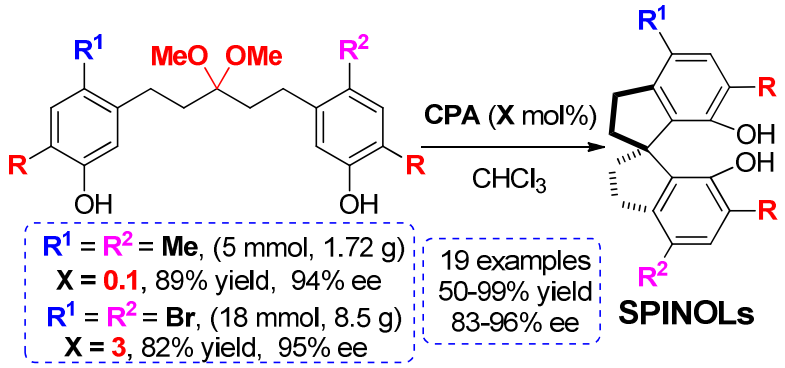
R1
MeO OMe
R2
R
R
OH
OH
CPA (X mol%)
CHCl3
R1 = R2 = Me, (5 mmol, 1.72 g)
X = 0.1, 89% yield, 94% ee
R1 = R2 = Br, (18 mmol, 8.5 g)
X = 3, 82% yield, 95% ee
19 examples
50-99% yield
83-96% ee
SPINOLs