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Synthesis and Evaluation of 5,5′-Bitetralone-Based Chiral Phosphoric Acids

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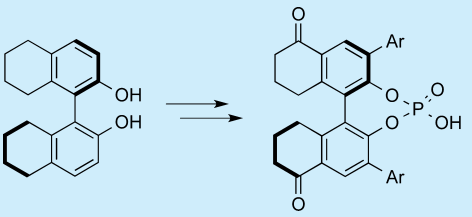
Supporting Information

ABSTRACT: A new type of phosphoric acid bearing a 5,5′-bitetralone scaffold was synthesized from BINOL and was shown to be a highly effective catalyst as illustrated in the asymmetric transfer hydrogenation of 2-phenylquinoline and the Friedel–Crafts reaction of 2,2,2-trifluoroacetophenone.



Chiral Brønsted acids have been shown to be highly effective catalysts for various organic transformations.[1] In particular, BINOL-based chiral phosphoric acids (**1** and **2**) (Figure 1) have attracted significant attention since Akiyama,

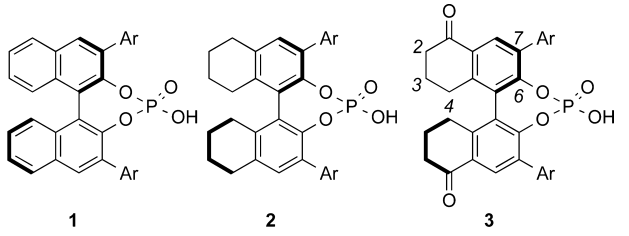
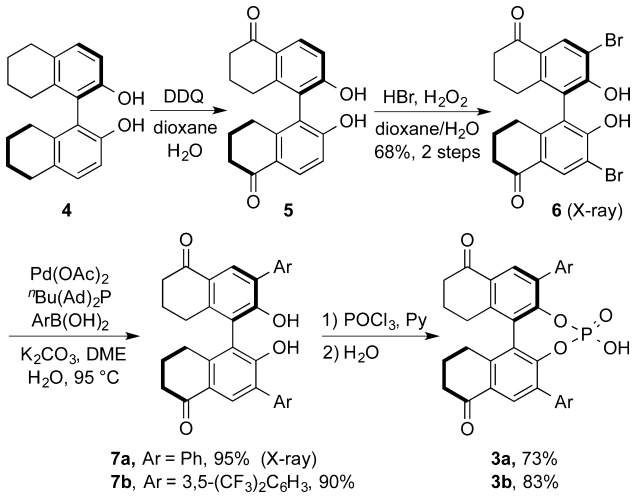


Figure 1. Chiral phosphoric acids.

Terada, and co-workers reported them a decade ago.[2,3] A variety of asymmetric processes can be catalyzed by these phosphoric acids.[4,5] In our previous studies on chiral acid-catalyzed asymmetric electrophilic addition reactions of olefins, promising results were also obtained with BINOL-based chiral phosphoric acids.[6] The catalyst acidity was found to be a crucial factor for the reaction outcome. It was envisioned that a catalyst with enhanced acidity while retaining the BINOL skeleton would benefit the reaction. Along this line, phosphoric acids bearing a 5,5′-bitetralone scaffold (**3**) were of interest since the introduction of the carbonyl group would enhance the acidity while the BINOL chiral framework would still be maintained. Herein, we report our preliminary studies on this subject.

Three phosphoric acids with commonly used aryl substituents were prepared. The synthesis of 5,5′-bitetralone-based chiral phosphoric acids **3a** and **3b** are outlined in Scheme 1. The oxidation of (*R*)-H_8-BINOL (**4**)[7] with DDQ in dioxane–H_2O at room temperature gave 5,5′-bitetralone-6,6′-diol (**5**),

Scheme 1. Synthesis of Phosphoric Acids 3a, 3b



which was subsequently brominated with HBr and H_2O_2[8] to afford compound **6** in 68% yield over two steps. The structure of **6** was confirmed by X-ray diffraction (see Supporting Information). The Ph and 3,5-$(CF_3)_2$-Ph groups were introduced via Suzuki coupling[9] of dibromide **6** with the corresponding arylboronic acids to give compounds **7a** and **7b** in 95% and 90% yield, respectively (Scheme 1). Phosphoric acids **3a** and **3b** were obtained in 73% and 83% yield, respectively, by treating **7a** and **7b** with $POCl_3$ in pyridine, followed by the one-pot hydrolysis.[10]

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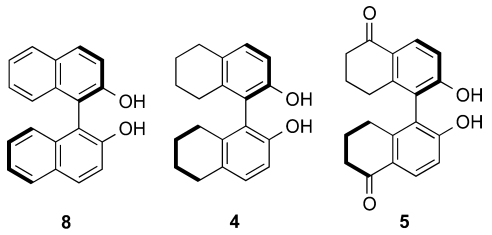
5,5′-Bitetralone-6,6′-diol (**5**), as a new chiral scaffold, could be potentially useful for other chiral ligands and catalysts. Its configurational stability under various conditions[11] was investigated along with BINOL (**8**) and H_8-BINOL (**4**). As shown in Table 1, compound **5** was configurationally stable up to 180 °C. The ee decreased to 92% at 200 °C for 24 h. No detectable racemization was observed when **5** was subjected to 6 N HCl in dioxane at 100 °C for 24 h or 10% NaOH in dioxane at 100 °C for 24 h. Comparable configurational stability was observed for H_8-BINOL (**4**). However, when **4** was subjected to the acidic and basic conditions, significant amounts of impurities were formed as judged by ^{1}H NMR and chiral HPLC analysis of the crude reaction mixture. BINOL (**8**) racemized readily at 150 °C and under the acidic conditions. The ee also dropped to 85% when **8** was treated with 10% NaOH at 100 °C for 24 h.[11]

Table 1. Studies on the Configurational Stability of Compounds 4, 5, and 8[a]



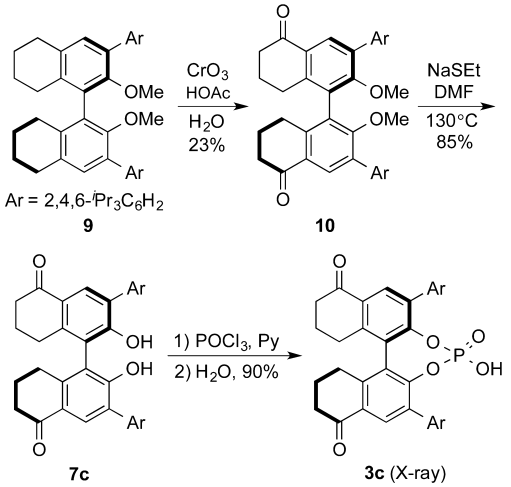
8 **4** **5**

entry	conditions	ee (%) (**8**)	ee (%) (**4**)	ee (%) (**5**)
1	starting material	>99	>99	>99
2	NMP, 150 °C, 24 h	42	>99	>99
3	NMP, 180 °C, 24 h	1	99	99
4	NMP, 200 °C, 24 h	0	96	92
5	6 N HCl, 100 °C, 24 h	9	>99	>99
6	10% NaOH, 100 °C, 24 h	85	>99	>99

[a]For more details, see Supporting Information.

The synthesis of 2,4,6-^{i}Pr$_3$Ph substituted phosphoric acid **3c** is described in Scheme 2. Diketone **10** was obtained in 23% yield from known methyl ether **9**[12] via oxidation with CrO_3 in HOAc–H_2O.[13] No desired product (**10**) was obtained when **9** was treated with DDQ. Compound **10** was demethylated with NaSEt in DMF at 130 °C to give compound **7c** in 85% yield.[14]

Scheme 2. Synthesis of Phosphoric Acid 3c



Treatment of **7c** with $POCl_3$ in pyridine and subsequent hydrolysis led to phosphoric acid **3c** in 90% yield.[10]

The X-ray structure of **3c** is shown in Figure 2. The torsion angle between the two phenyl planes of tetralone in **3c** is 62.00°, which is larger than that in BINOL-based **1c** (49.78°–51.29°)[10,15] and H_8-BINOL-based **2c** (57.70°) (Figure 3), indicating that phosphoric acid **3c** may have a larger chiral cavity, which could be beneficial for certain transformations.

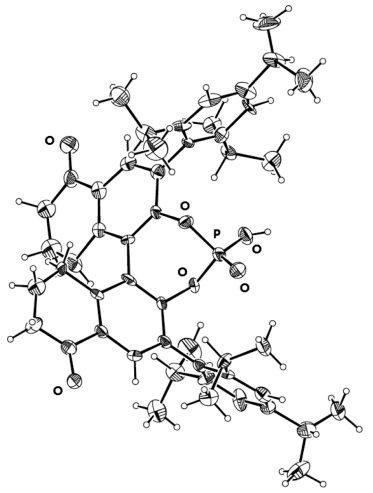


Figure 2. X-ray crystal structure of phosphoric acid **3c** (cocrystal CH_2Cl_2 was omitted for clarity).

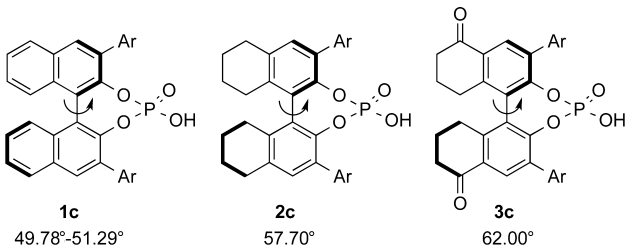


Figure 3. Torsion angles of phosphoric acids **1c**, **2c**, and **3c** (Ar = 2,4,6-^{i}Pr$_3$C$_6$H$_2$).

The catalytic properties of phosphoric acid **3c** was evaluated with previously reported asymmetric transfer hydrogenation of 2-phenylquinoline (**11**) with the Hantzsch dihydropyridines (**12**) (Scheme 3).[5g,15a,16,17] The reaction was carried out in benzene at room temperature with 0.2 mol % phosphoric acids **1c**, **2c**, and **3c**. Catalyst **3c** was found to be slightly more active than **1c** and **2c** while the same high enantioselectivity was achieved. A similar behavior was observed for catalyst **3c** in the asymmetric Friedel–Crafts reaction[18,19] of 2,2,2-trifluoroacetophenone (**15**) with indole (**14**) (Scheme 4). These results indicated that the introduction of the carbonyl group enhanced the activity of the phosphoric acid but did not deteriorate the enantioselectivity, as initially hoped. The potential of the newly synthesized phosphoric acids in asymmetric catalysis awaits further exploration.

In summary, we have developed a new type of phosphoric acid bearing a 5,5′-bitetralone scaffold from BINOL. As illustrated in asymmetric transfer hydrogenation of 2-phenylquinoline and the Friedel–Crafts reaction of 2,2,2-trifluoroacetophenone, the newly synthesized phosphoric acid catalyst displayed the same enantioselectivity as the corresponding

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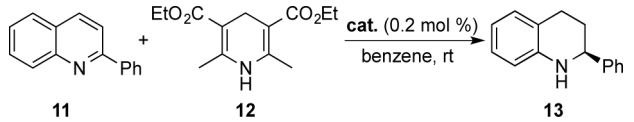
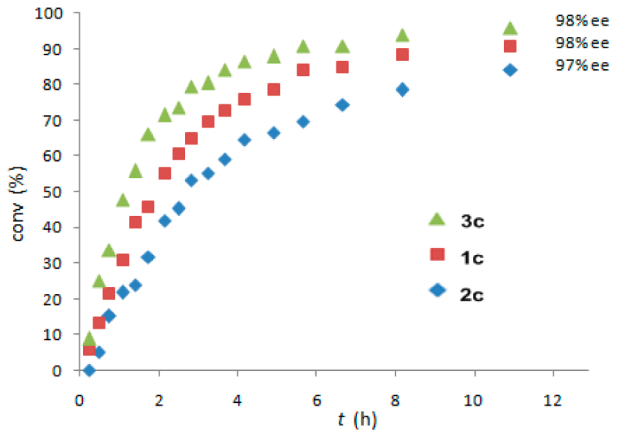
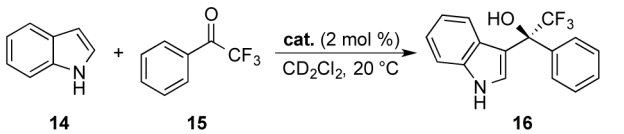
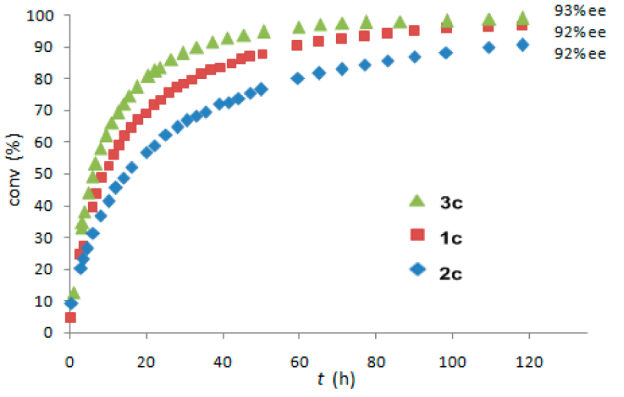
Scheme 3. Asymmetric Transfer Hydrogenation of 2-Phenylquinoline 11





Scheme 4. Asymmetric Friedel–Crafts Reaction of 2,2,2-Trifluoroacetophenone 15





BINOL and H_8-BINOL-based phosphoric acids, but with enhanced catalytic activity. The larger torsion angle and stronger acidity associated with 5,5′-bitetralone-based phosphoric acid could provide additional opportunities for asymmetric transformations. Furthermore, the 5,5′-bitetralone scaffold provides a novel chiral framework for the development of new chiral ligands and catalysts. All these studies are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02400.

Experimental procedures, characterization data, X-ray structures, HPLC data for the determination of enantiomeric excess, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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