

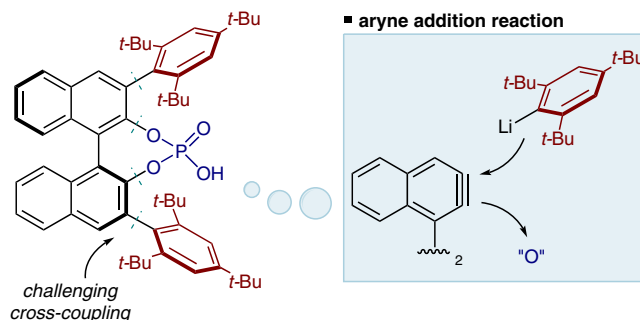
# An Approach to Highly Hindered BINOL Phosphates

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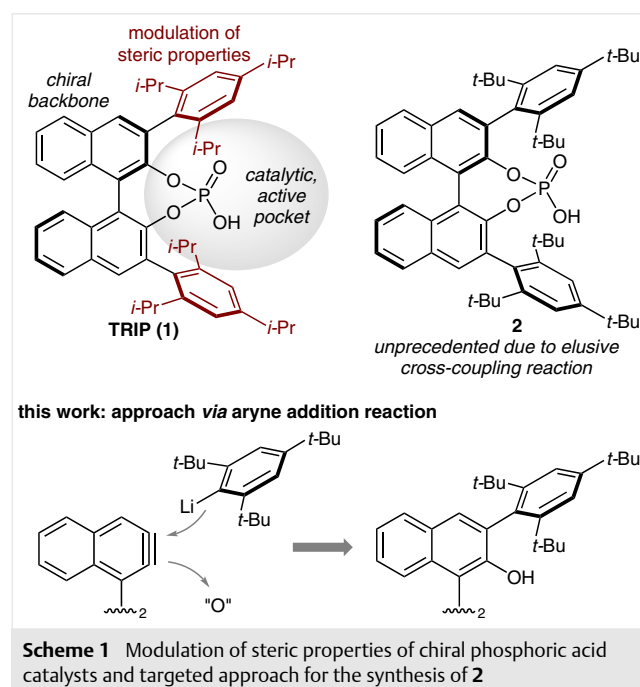
**Abstract** The synthesis of 3,3'-substituted BINOL-derived chiral phosphoric acid catalysts is still largely limited by the limitations of current cross-coupling methodologies. For this reason, despite the importance of sterically demanding catalysts in Brønsted acid catalysis, highly hindered congeners are still unprecedented. Exploiting the aryne addition reaction as key step, we report herein the development of a novel synthetic route to access this unexplored class of catalysts.

**Key words** phosphoric acids, confined catalysts, asymmetric organocatalysis, biaryl synthesis, aryne coupling reaction

Within the last ten years, chiral phosphoric acids have been recognized as privileged moieties in asymmetric Brønsted acid catalysis.<sup>1</sup> Introduced by Akiyama and Terada in 2004,<sup>2</sup> this research field has continuously grown, leading to the current stand out of phosphoric acids in modern organocatalysis.<sup>3</sup> One of the key aspects for their success relies on the facile structure modulation, which enables an optimization of the catalytic performance by allowing the fine tuning of electronic and steric properties. In particular, sterically demanding BINOL-derived phosphoric acids, such as TRIP,<sup>4</sup> are arguably among the most useful and successful catalysts. The acidic moiety of these compounds is placed in a significantly confined space, thus enabling an effective translation of the stereochemical information held in the chiral backbone to the catalytically active pocket (Scheme 1).<sup>5</sup> For this reason, efforts have been devoted towards the synthesis of even bulkier catalysts. Important advances were obtained by various modification of the *para* position of the aryl substituent of TRIP and, more recently, confined catalysts with a rigid polycyclic structure have been report-

ed.<sup>6,7</sup> In addition, a significantly narrower catalytic pocket could also be obtained in STRIP using substituted SPINOL as chiral backbone.<sup>8</sup>

Interestingly however, even more hindered phosphoric acid congeners with a quaternary carbon in the *ortho* position of the BINOL aryl substituent are entirely unknown.<sup>9</sup> Due to the limitations of biaryl synthesis via metal-catalyzed cross-coupling reaction, their preparation has been unsuccessful to date.<sup>10</sup> Nevertheless, given the remarkable activity and selectivity of TRIP, we wondered whether 3,3'-bis(2,4,6-tri-*tert*-butylphenyl)-BINOL-derived phosphoric acid **2** could further improve catalytic performances. How-



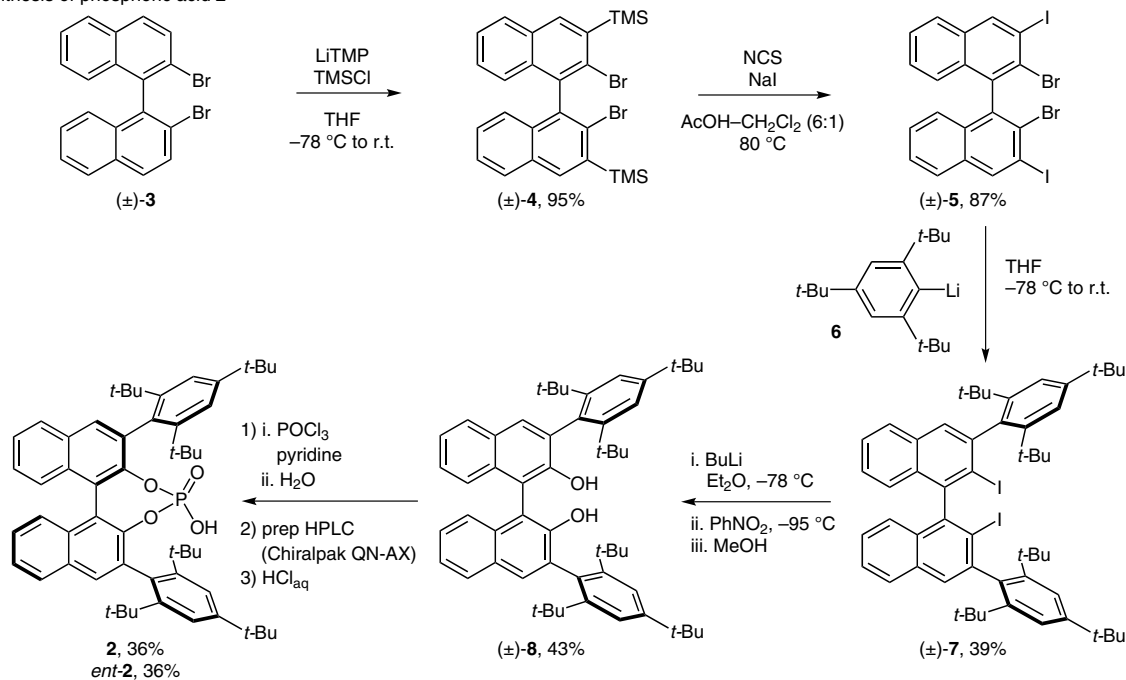
ever, not surprisingly, all our efforts to synthesize this compound using standard cross-coupling protocols failed.<sup>11</sup> Herein, we report the design and realization of a novel route towards this unexplored class of catalysts based on the aryne addition reaction (Scheme 1).

Arynes are characterized by a significantly low-lying LUMO, which make them susceptible to nucleophilic attack, and their extraordinary reactivity towards organolithium reagents was pioneered by Wittig in 1940.<sup>12,13</sup> Subsequent explorations have further improved this methodology,<sup>14</sup> which was recently utilized by the Buchwald group for the preparation of bulky phosphine ligands for metal catalysis.<sup>15</sup>

Following this idea, we began our exploration starting from commercially available 2,2'-dibromo binaphthol (**3**, Scheme 2, a). The investigations were performed using racemic material due to the envisioned low racemization bar-

rier of the postulated chiral aryne intermediate. Exploiting bromine as *ortho*-directing group, the initial silylation reaction was performed under cryogenic conditions to obtain compound **4** in excellent yield.<sup>16</sup> Subsequently, the conversion to the tetrahalogenated compound **5** was straightforwardly achieved using the convenient *ipso* desilylation–halogenation strategy disclosed by Wilbur et al.<sup>17</sup> We hypothesized that **5** could undergo an initial lithium–iodine exchange with 2,4,6-tri-*tert*-butyl lithiumbenzene **6**, followed by the generation of the desired aryne species via elimination of LiBr. In the presence of an excess of the organolithium reagent, such reactive intermediate would eventually be trapped leading to the desired hindered biaryl synthesis. Gratifyingly, using five equivalents of lithium arene **6**, our design was successful and compound **7** could be obtained in moderate yield, despite the poor solubility of **5** under the reaction conditions. Interestingly, the

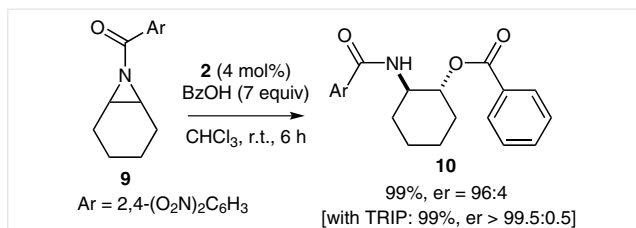
a) synthesis of phosphoric acid **2**



**Scheme 2** (a) Synthetic route to phosphate **2** using the aryne addition reaction as key step; (b) proposed mechanism for the biaryl coupling step.

isolation of the bis-iodinated product **7** suggests that the lithium–iodine exchange occurs more readily from aryllithium intermediate **III** rather than from **6**, thus effectively propagating a chain-type mechanism (Scheme 2, b).<sup>14a,18</sup> The following conversion into BINOL derivative **8** was found to be challenging, and several attempts to use organic peroxides as electrophilic source of oxygen were unsuccessful.<sup>19</sup> However, the desired compound could be obtained in satisfactory yield when using nitrobenzene, as reported by Power et al. for the synthesis of sterically hindered phenols.<sup>20</sup> At last, the phosphoric acid moiety was installed using conditions similar to those previously optimized for the synthesis of TRIP.<sup>4</sup> However, the formation of the phosphoryl chloride intermediate required longer reaction time (4 d), presumably due to steric reasons. Finally, a resolution of the racemic mixture via preparative HPLC on a chiral stationary phase delivered both enantiomers of the targeted phosphoric acid catalyst (**2** and *ent*-**2**).

Having obtained the first access to a long sought-after class of hindered phosphoric acid catalysts, we were eager to evaluate the catalytic activity of **2**. Therefore we investigated its performance in the asymmetric ring opening of aziridines with carboxylic acids (Scheme 3).<sup>21</sup> A good activity was observed, and aziridine **9** was converted into the desired protected amino alcohol **10** in near quantitative yield and excellent enantioselectivity (99% yield, *er* = 96:4). Even though in this specific case, TRIP outperforms the enantioselectivity of catalyst **2**, we are currently exploring this new catalyst in different reactions.



**Scheme 3** Preliminary exploration on the catalytic performance of catalyst **2**

In conclusion, we report the development of a novel synthetic approach to hindered BINOL-derived phosphoric acids.<sup>22</sup> Being based on the biaryl synthesis via aryne addition reaction, this procedure is complementary to the established routes and gives access to previously elusive catalysts. We believe that our strategy may find application for the preparation of several other bulky binaphthyl derivatives, and investigations towards this goal are in progress.

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## Supporting Information

Supporting information for this article is available online at <http://dx.doi.org/10.1055/s-0035-1560771>.

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(22) **Key Experimental Procedures**

**(±)-2,2'-Diiodo-3,3'-bis(2,4,6-tri-*tert*-butylphenyl)-1,1'-binaphthalene (7)**

A flame-dried, two-neck round-bottom flask was charged with a solution of 2,4,6-tri(*tert*-butyl)bromobenzene (2 g, 6.15 mmol, 5 equiv) in dry THF (10.5 mL) under an argon atmosphere. The solution was cooled down to  $-78^{\circ}\text{C}$  and BuLi (2.5 M in hexane, 2.45 mmol, 5.1 equiv) was added dropwise. The solution was then stirred at  $0^{\circ}\text{C}$  for 1 h. Next the reaction was cooled at  $-78^{\circ}\text{C}$ , and a solution of **5** in THF (814 mg, 1.23 mmol, 1 equiv) was added dropwise. The temperature was raised to r.t., and the reaction was vigorously stirred for 12 h.  $\text{CH}_2\text{Cl}_2$  was added, and the organic phase washed three times with  $\text{H}_2\text{O}$ . After anhydrication over  $\text{Na}_2\text{SO}_4$ , the solvent was evaporated in vacuo. Purification by column chromatography on silica gel (eluent: hexane- $\text{CH}_2\text{Cl}_2$ , 10:1) gave the desired compound in 39% yield.  $^1\text{H NMR}$  (500 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta = 7.99$  (s, 2 H), 7.83 (d, 2 H), 7.52–7.40 (m, 6 H), 7.18 (t, 2 H), 7.05 (d, 2 H), 1.29 (s, 18 H), 1.14 (s, 36 H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta = 149.5$ , 147.8,

147.5, 146.1, 145.8, 140.2, 132.6, 132.3, 131.8, 128.7, 127.2, 127.1, 127.0, 124.1, 123.9, 114.5, 38.9, 38.8, 35.2, 35.0, 34.1, 31.6. HRMS:  $m/z$  calcd for  $\text{C}_{56}\text{H}_{68}\text{I}_2$  [M]: 994.3410; found: 994.3405.

**(±)-3,3'-Bis(2,4,6-tri-*tert*-butylphenyl)-[1,1'-binaphthalene]-2,2'-diol (8)**

In a flame-dried, two-neck round-bottom flask, a 0.007 M solution of **7** in dry  $\text{Et}_2\text{O}$  was added under an argon atmosphere. The stirred solution was cooled down to  $-78^{\circ}\text{C}$ , BuLi (2.5 M in hexanes, 4 equiv) was added dropwise, and the reaction was left at  $-78^{\circ}\text{C}$  for 1 h before being cooled down to  $-95^{\circ}\text{C}$ . Next a 2.8 M solution of nitrobenzene in  $\text{Et}_2\text{O}$  was added dropwise. After 30 min MeOH was added (1:1 with the reaction solvent), and the temperature was raised to r.t. and stirred for 2 additional hours.  $\text{CH}_2\text{Cl}_2$  was added, and the organic phase was washed with  $\text{H}_2\text{O}$ . After anhydrication over  $\text{Na}_2\text{SO}_4$ , the solvent was evaporated in vacuo. Purification by column chromatography on silica gel (eluent: mixtures hexane- $\text{CH}_2\text{Cl}_2$ ) gave the desired compound in 43% yield.  $^1\text{H NMR}$  (500 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta = 7.82$ –7.75 (m, 4 H), 7.58–7.48 (m, 4 H), 7.29 (t, 2 H), 7.20 (t, 2 H), 7.10 (d, 2 H), 4.89 (s, 2 H), 1.29 (s, 18 H), 1.14 (s, 18 H), 1.05 (s, 18 H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta = 152.8$ , 149.5, 149.5, 134.1, 133.5, 132.4, 130.4, 128.3, 127.8, 126.6, 124.7, 123.7, 123.3, 123.3, 113.1, 38.1, 38.0, 35.1, 33.1, 33.0, 31.4. HRMS:  $m/z$  calcd for  $\text{C}_{56}\text{H}_{70}\text{O}_2$  [M + Na]: 797.5268; found: 797.5269.

**3,3'-Bis(2,4,6-tri-*tert*-butylphenyl)-1,1'-binaphthyl-2,2'-diyl Hydrogenphosphate (2)**

In a flame-dried, two-neck round-bottom flask, equipped with a reflux condenser, a 0.025 M solution of **8** in dry pyridine was added under Ar atmosphere. Then the stirred solution was cooled down to  $0^{\circ}\text{C}$ , and 10 equiv of  $\text{POCl}_3$  were added. The reaction mixture was then heated up to  $95^{\circ}\text{C}$ , and 10 additional equivalents of  $\text{POCl}_3$  were added after 24 h. After 4 d full consumption of starting material was observed (TLC eluent: hexane- $\text{CH}_2\text{Cl}_2$ , 1:1). Then the reaction was cooled to  $0^{\circ}\text{C}$ , and  $\text{H}_2\text{O}$  (2.5 mL) were added dropwise [careful: exothermic reaction] before raising the temperature to  $100^{\circ}\text{C}$ . After 4 h the reaction was cooled down to r.t.,  $\text{CH}_2\text{Cl}_2$  was added, and the organic phase was sequentially washed with a 3 M HCl (aq) solution,  $\text{H}_2\text{O}$ , and brine. Then the organic phase was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and the solvent was evaporated in vacuo. Purification was accomplished by column chromatography (eluent: mixtures hexane- $\text{EtOAc}$ ). The isolated compound was subjected to preparative HPLC on chiral stationary phase [Chiralpak QN-AX, 5  $\mu\text{m}$ ,  $150 \times 29$  mm; eluent: MeOH- $\text{NH}_4\text{OAc}$  (0.1 M, aq), 80:20] to achieve separation of the enantiomers. Both enantiomers were eventually dissolved in  $\text{CH}_2\text{Cl}_2$  and subjected to an acidic wash with 6 M HCl (aq) solution (**2**: 36% yield; *ent*-**2**: 36% yield).  $^1\text{H NMR}$  (500 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta = 7.83$  (s, 2 H), 7.74 (d,  $J = 8.2$  Hz, 2 H), 7.40–7.33 (m, 6 H), 7.09 (t,  $J = 8.2$  Hz, 2 H), 6.87 (d,  $J = 8.2$  Hz, 2 H), 6.32 (br s, 1 H), 1.21 (s, 18 H), 0.97 (s, 18 H), 0.88 (s, 18 H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CD}_2\text{Cl}_2$ ) [overlapping signals]:  $\delta = 149.3$ , 149.0, 148.7, 148.5, 148.4, 135.7, 135.7, 135.3, 133.2, 130.4, 130.3, 128.4, 127.6, 126.4, 125.9, 124.3, 123.5, 121.5, 38.9, 38.5, 35.1, 34.3, 33.6, 31.6.  $^{31}\text{P NMR}$  (202 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta = -0.02$  (s). HRMS:  $m/z$  calcd for  $\text{C}_{56}\text{H}_{69}\text{O}_4\text{P}$  [M - H]: 835.4861; found: 835.4861.