An Approach to Highly Hindered BINOL Phosphates

Mattia R. Monaco
Roberta Properzi
Benjamin List*

Max-Planck-Institut für Kohlenforschung,
Kaiser-Wilhelm-Platz 1, Mülheim an der Ruhr,
45470, Germany
list@kofo.mpg.de

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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.1 Introduced by Akiyama and Terada in 2004,2 this research field has continuously grown, leading to the current stand out of phosphoric acids in modern organocatalysis.3 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,4 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).5 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.6,7 In addition, a significantly narrower catalytic pocket could also be obtained in STRIP using substituted SPINOL as chiral backbone.8

Interestingly however, even more hindered phosphoric acid congeners with a quaternary carbon in the ortho position of the BINOL aryl substituent are entirely unknown.9 Due to the limitations of biaryl synthesis via metal-catalyzed cross-coupling reaction, their preparation has been unsuccessful to date.10 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-

Scheme 1 Modulation of steric properties of chiral phosphoric acid catalysts and targeted approach for the synthesis of 2
ever, not surprisingly, all our efforts to synthesize this com-
pound using standard cross-coupling protocols failed.11
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 1940.12,13 Subsequent
explorations have further improved this methodology,14
which was recently utilized by the Buchwald group for the
preparation of bulky phosphine ligands for metal cataly-
sis.15

Following this idea, we began our exploration starting
from commercially available 2-2′-dibromo binaphthol (3,
Scheme 2, a). The investigations were performed using ra-
cemic material due to the envisioned low racemization bar-
rier of the postulated chiral aryne intermediate. Exploiting
bromine as ortho-directing group, the initial silylation reac-
tion was performed under cryogenic conditions to obtain
compound 4 in excellent yield.16 Subsequently, the conver-
sion to the tetrahalogenated compound 5 was straightfor-
wardly achieved using the convenient ipso desilylation–ha-
genation strategy disclosed by Wilbur et al.17 We hypoth-
esized that 5 could undergo an initial lithium–iodine
exchange with 2,4,6-tri-tert-butyl lithiumbenzene 6, fol-
lowed by the generation of the desired aryne species via
elimination of LiBr. In the presence of an excess of the or-
ganolithium reagent, such reactive intermediate would
eventually be trapped leading to the desired hindered bi-
aryl synthesis. Gratifyingly, using five equivalents of lithi-
um arene 6, our design was successful and compound
7 could be obtained in moderate yield, despite the poor solu-
bility of 5 under the reaction conditions. Interestingly,

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).\textsuperscript{14a,18} 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.\textsuperscript{19} 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.\textsuperscript{20} At last, the phosphoric acid moiety was installed using conditions similar to those previously optimized for the synthesis of TRIP.\textsuperscript{4} 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).\textsuperscript{21} 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.

\begin{equation}
\text{Scheme 3 Preliminary exploration on the catalytic performance of catalyst 2}
\end{equation}

In conclusion, we report the development of a novel synthetica approach to hindered BINOL-derived phosphoric acids.\textsuperscript{22} 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.

\section*{Acknowledgment}

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\section*{Supporting Information}

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\section*{References and Notes}


(3) \textit{Asymmetric Organocatalysis}; List, B.; Maruoka, K., Eds.; Thieme: Stuttgart, 2012.


In a flame-dried, two-neck round-bottom flask, a 0.007 M solution of 2 in dry Et2O was added under an argon atmosphere. The stirred solution was cooled down to –78 °C, BuLi (2.5 M in hexanes, 4 equiv) was added dropwise, and the reaction was left at –78 °C for 1 h before being cooled down to –95 °C. Next a 2.8 M solution of nitrobenzene in Et2O 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. CH2Cl2 was added, and the organic phase was washed with H2O. After anhydridation over Na2SO4, the solvent was evaporated in vacuo. Purification by column chromatography on silica gel (eluent: mixtures hexane–CH2Cl2) gave the desired compound in 43% yield. 1H NMR (500 MHz, CD2Cl2): δ = 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). 13C NMR (125 MHz, CD2Cl2): δ = 152.8, 149.5, 149.5, 134.1, 133.4, 132.4, 130.4, 128.3, 127.8, 126.6, 124.7, 123.7, 123.3, 113.1, 38.1, 38.0, 35.1, 33.1, 33.0, 31.4. HRMS: m/z calc for C56H68I2 [M]: 994.3410; found: 994.3405.

(5)-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 Et2O was added under an argon atmosphere. The stirred solution was cooled down to –78 °C, BuLi (2.5 M in hexanes, 4 equiv) was added dropwise, and the reaction was left at –78 °C for 1 h before being cooled down to –95 °C. Next a 2.8 M solution of nitrobenzene in Et2O 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. CH2Cl2 was added, and the organic phase was washed with H2O. After anhydridation over Na2SO4, the solvent was evaporated in vacuo. Purification by column chromatography on silica gel (eluent: mixtures hexane–CH2Cl2) gave the desired compound in 43% yield. 1H NMR (500 MHz, CD2Cl2): δ = 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). 13C NMR (125 MHz, CD2Cl2): δ = 152.8, 149.5, 149.5, 134.1, 133.4, 132.4, 130.4, 128.3, 127.8, 126.6, 124.7, 123.7, 123.3, 113.1, 38.1, 38.0, 35.1, 33.1, 33.0, 31.4. HRMS: m/z calc for C56H70O2 [M + Na]: 797.5268; found: 797.5269.

3,3′-Bis(2,4,6-tri-tert-butylphenyl)-1,1′-binaphthyl-2,2′-diyl Hydrogenophosphate (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 °C, and 10 equiv of POCl3 were added. The reaction mixture was then heated up to 95 °C, and 10 additional equivalents of POCl3 were added after 24 h. After 4 d full consumption of starting material was observed (TLC eluent: hexane–CH2Cl2, 1:1). Then the reaction was cooled to 0 °C, and H2O (2.5 mL) were added dropwise (careful: exothermic reaction) before raising the temperature to 100 °C. After 4 h the reaction was cooled down to r.t., CH2Cl2 was added, and the organic phase was sequentially washed with a 3 M HCl (aq) solution, H2O, and brine. Then the organic phase was dried over anhydrous Na2SO4, and the solvent was evaporated in vacuo. Purification was accomplished by column chromatography (eluent: mixtures hexane–EtOAc). The isolated compound was subjected to preparative HPLC on chiral stationary phase [Chiralpak QN-AX, 5 μm, 150 x 29 mm; eluent: MeOH–NH4OAc (0.1 M,aq), 80:20] to achieve separation of the enantiomers. Both enantiomers were eventually dissolved in CH2Cl2 and subjected to an acidic wash with 6 M HCl (aq) solution [2: 36% yield; ent-2: 36% yield]. 1H NMR (500 MHz, CD2Cl2): δ = 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). 13C NMR (125 MHz, CD2Cl2) [overlapping signals]: δ = 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. 31P NMR (202 MHz, CD2Cl2): δ = -0.02 (s). HRMS: m/z calc for C56H56OP [M + H]: 835.4861; found: 835.4861.