

## A convenient synthetic approach to highly hindered 3,3'-bis(2,4,6-tri- tert-butylphenyl)-BINOL-derived phosphoric acids

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### SUPPORTING INFORMATION

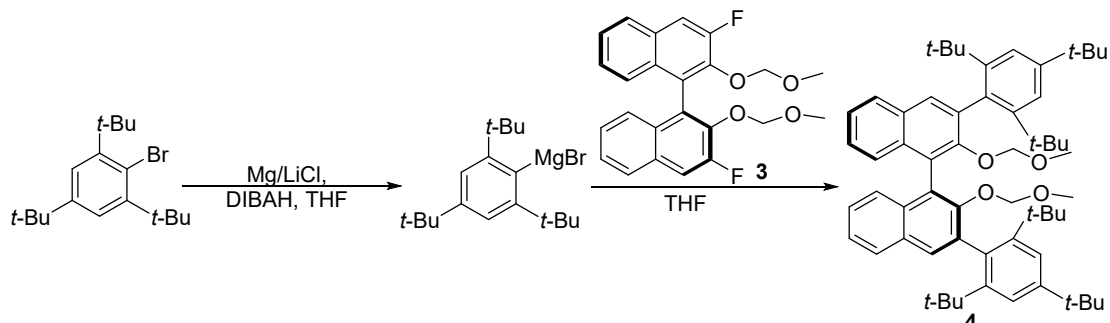
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## General information

All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring unless otherwise indicated. Reagents were purchased from Aldrich Chemical, Alfa Aesar, TCI, Adamas, Energy Chemical, or J&K at the highest commercial quality and used without further purification. Solvents were dried by passage through an activated alumina column under argon. Liquids and solutions were transferred via syringe. Reactions were monitored by UPLC/MS and thin layer chromatography (TLC) and visualization was accomplished with a 254 nm UV light and by staining with phosphomolybdic acid solution with heating. All Flash silica gel column chromatography was performed using Tsingdao Haiyang Chemicals silica gel (particle size 300-400 mesh).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on Varian Inova-400 spectrometers. Data for  $^1\text{H}$  NMR spectra are reported relative to  $\text{CDCl}_3$  (7.26 ppm),  $\text{CD}_2\text{Cl}_2$  (5.32 ppm) as an internal standard and are reported as follows: chemical shift ( $\delta$  ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, br = broad), coupling constant  $J$  (Hz), and integration. Data for  $^{13}\text{C}$  NMR spectra are reported relative to  $\text{CDCl}_3$  (77.00 ppm),  $\text{CD}_2\text{Cl}_2$  (53.84 ppm) as an internal standard and are reported in terms of chemical shift ( $\delta$  ppm). UPLC-MS analyses were performed on a Waters system (Column: BEH C18, 1.7  $\mu\text{m}$ , 2.1\*50 mm) with a Photodiode Array (PDA) detector and a Single Quadrupole (SQ) detector. High Resolution Mass spectra were obtained from on an Agilent 1290 LC-6540 QTOF Mass Spectrometer or an Agilent Technologies 7250 GCQTOF. HPLC analyses were carried out on Waters (Column Atlanits<sup>®</sup> HILIC Silica, 5  $\mu\text{m}$ , 4.6\*150 mm and 19\*150 mm) with 2998PDA and 3100MS detectors.

## Synthetic procedures and spectral data.

### Synthesis of BINOL-derivative 4.



An oven-dried three-neck 250 mL round bottom flask, which was equipped with a magnetic stir bar and charged with magnesium shavings (432 mg, 18.0 mmol) and anhydrous LiCl (277 mg, 6.6 mmol), was fitted with a reflux condenser, glass stopper, and rubber septum. The flask was purged with argon and anhydrous THF (50 mL) and 2,4,6-tri-tert-butylbromobenzene (1.95g, 6.0 mmol) were added. Then DIBAL-H (1M in toluene, 60  $\mu$ L, 0.06 mmol) was added at room temperature via syringe and the mixture was heated to 50  $^{\circ}$ C for 1h. A separate oven-dried 250 mL round bottom flask, which was equipped with a magnetic stir bar and fitted with a septum, and (S)-3,3'-difluoro-2,2'- bis(methoxymethoxy)-1,1'-binaphthyl<sup>1</sup> (**3**, 410 mg, 1.0 mmol) was added, then the freshly prepared Grignard reagent was added via springe under argon. The resulting mixture was stirred at 50  $^{\circ}$ C for 4h, and then cooled down to room temperature and concentrated under reduced pressure, the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed with NH<sub>4</sub>Cl solution and brine. The organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was directly purified by flash chromatography on silica gel (PE/EA, 25:1) to afford the compound **4** (379.2 mg, 44%) as white solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.67-7.59 (m, 6H), 7.37 (m, 2H), 7.27 (m, 2H), 7.19 (m, 4H), 5.03 (d,  $J$  = 6.5 Hz, 2H), 4.89 (d,  $J$  = 6.5 Hz, 2H), 3.15 (s, 6H), 1.45 (s, 18H), 1.09 (s, 18H), 1.03 (s, 18H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  150.91, 148.70, 148.41, 148.38, 142.53, 134.50, 133.58, 133.23, 128.34, 126.05, 125.26, 123.42, 123.07, 123.03, 122.92, 121.32, 95.45, 55.75, 38.29, 38.19, 35.03, 33.53, 33.45, 31.56.

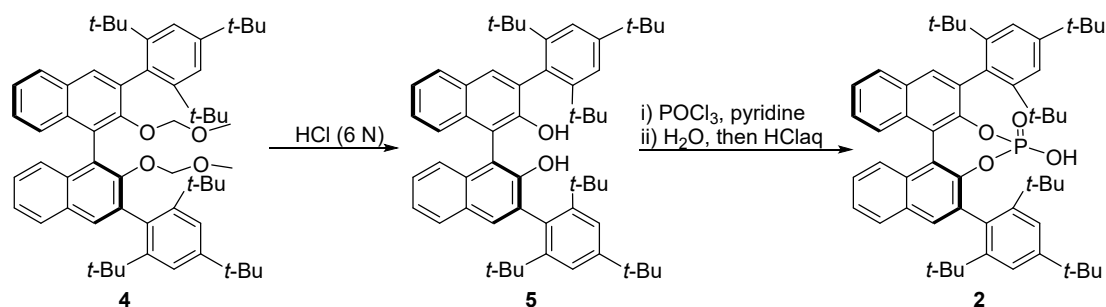
HRMS (m/z) calcd for C<sub>60</sub>H<sub>78</sub>O<sub>4</sub> [M+Na]<sup>+</sup>: 885.5798, found: 885.5797.

Followed the procedure above, *ent*-**4** was synthesized using (R)-3,3'-difluoro-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl and gave 362 mg product as white solid (42.0%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.64-7.62 (m, 6H), 7.37 (m, 2H), 7.27 (m, 2H), 7.18 (m, 2H), 5.02(d,  $J$  = 6.5 Hz, 2H), 4.88 (d,  $J$  = 6.5 Hz, 2H), 3.15 (s, 6H), 1.45 (s, 18H), 1.09 (s, 18H), 1.02 (s, 18H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  150.93, 148.73, 148.43, 148.40, 142.55, 134.52, 133.60, 133.25, 128.37, 126.07, 125.29, 123.44, 123.10, 123.06, 122.95, 121.34, 95.47, 55.78, 38.31, 38.21, 35.05, 33.55, 33.47, 31.58.

HRMS (m/z) calcd for C<sub>60</sub>H<sub>78</sub>O<sub>4</sub> [M+NH<sub>4</sub>]<sup>+</sup>: 880.6244, found: 880.6244.

### Synthesis of phosphoric acid 2.



HCl (6N in dioxane, 3.0 mL) was added to a solution of the compound **4** (260 mg, 0.3mmol) in dioxane (3.0 mL), the resulting solution was heated to 70 °C for 12 h. After cooling down to room temperature and quenched by addition of saturated sodium bicarbonate solution, the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> and organic phase washed with water and brine. The combined organics were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to yield the crude product **5** as a pink solid, which used next step without further purification.

To the suspension of the crude product **5** in anhydrous pyridine (3.0 mL) was added freshly distilled POCl<sub>3</sub> (84 μL, 3.8 mmol) in one portion, the resulting mixture was heated to 90 °C and stirred for 16h. After cooling down to room temperature, H<sub>2</sub>O (0.4 mL) was added and refluxed for 4h. Then mixture was cooled down to room temperature and diluted with 20 mL CH<sub>2</sub>Cl<sub>2</sub>, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×10 mL), combined organic layer was washed with 2N HCl, water, brine, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, then filtered and liberated of solvents under reduced pressure. The residue was purified by flash chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 100:1 to 20:1) to afford the compound **2** (196 mg, 78%) as white solid.

<sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 8.30 (s, 2H), 7.66 (d, *J* = 1.0 Hz, 2H), 7.60 (m, 4H), 7.37 (m, 4H), 7.28 (m, 4H), 1.41 (s, 18H), 1.01 (s, 18H), 0.91 (s, 18H). <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 149.65, 149.10, 148.57, 145.80, 145.71, 145.47, 135.90, 133.46, 131.78, 129.10, 127.16, 126.84, 125.47, 125.28, 123.64, 123.30, 120.98, 120.96, 38.48, 38.41, 35.32, 33.68, 33.54, 31.61.

HRMS (m/z) calcd for C<sub>56</sub>H<sub>69</sub>O<sub>4</sub>P [M+H]<sup>+</sup>: 837.5011, found: 837.5005

Followed the procedure above, *ent*-**2** was synthesized using *ent*-**4** and gave 190 mg product as white solid (76%).

<sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 7.66 (d, *J* = 0.9 Hz, 2H), 7.60 (m, 4H), 7.37 (m, 4H), 7.28 (m, 4H), 6.99 (s, 2H), 1.41 (s, 18H), 1.01 (s, 18H), 0.91 (s, 18H). <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 149.66, 149.12, 148.58, 145.80, 145.71, 145.48, 135.92, 135.90, 133.46, 131.78, 129.11, 127.17, 126.84, 125.47, 125.26, 123.64, 123.31, 120.98, 120.96, 38.48, 38.41, 35.33, 33.69, 33.54, 31.62.

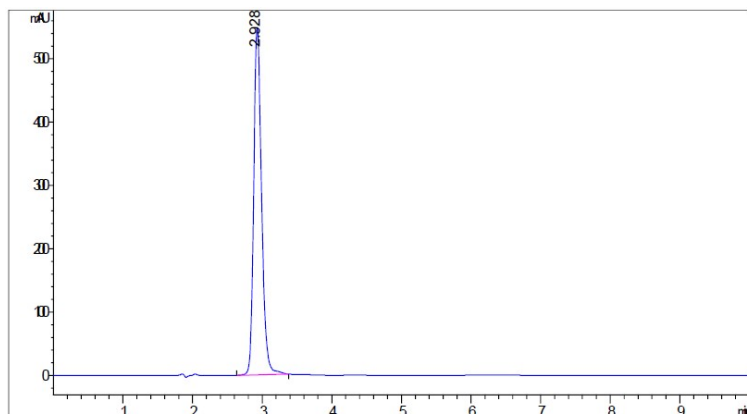
HRMS (m/z) calcd for C<sub>56</sub>H<sub>69</sub>O<sub>4</sub>P [M+H]<sup>+</sup>: 837.5011, found: 837.5008

## References

1. Y. Zhang, N. Li, B. Qu, S. Ma, H. Lee, N. C. Gonnella, J. Gao, W. Li, Z. Tan, J. T. Reeves, J. Wang, J. C. Lorenz, G. Li, D. C. Reeves, A. Premasiri, N. Grinberg, N. Haddad, B. Z. Lu, J. J. Song and C. H. Senanayake, *Org. Lett.*, 2013, **15**, 1710-1713.

HPLC traces of single enantiomer **2** and *ent*-**2**: Chiralpak QN-AX, 0.46cm I.D. ×15cmL×5μm, eluent: Methanol/(0.1 M NH<sub>4</sub>OAc)<sub>aq</sub> = 90/10(v/v)

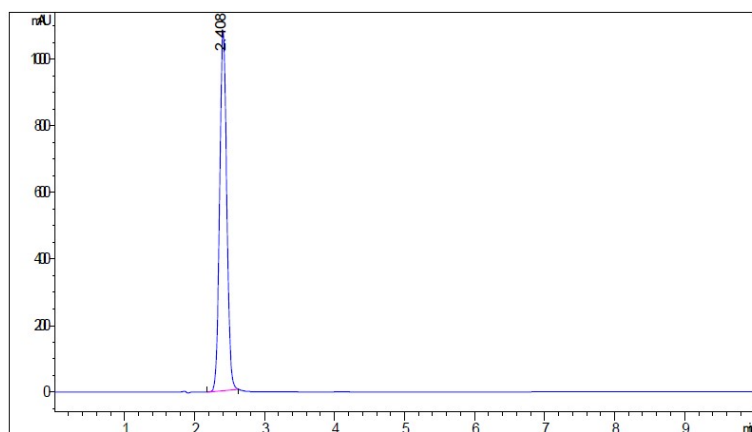
HPLC traces of **2**.



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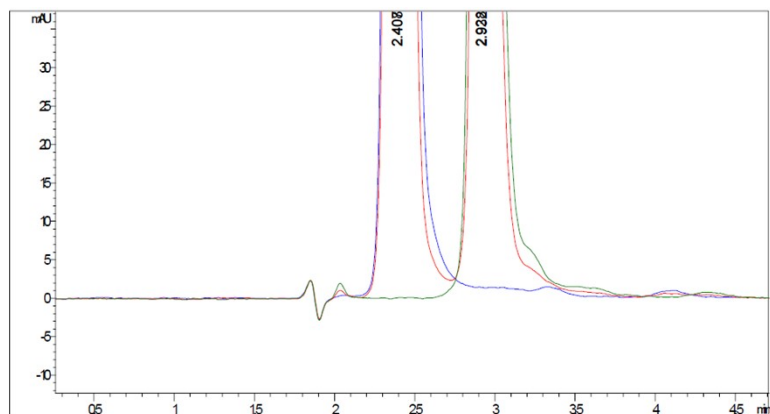
HPLC traces of *ent*-**2**



<Column Performance Report>

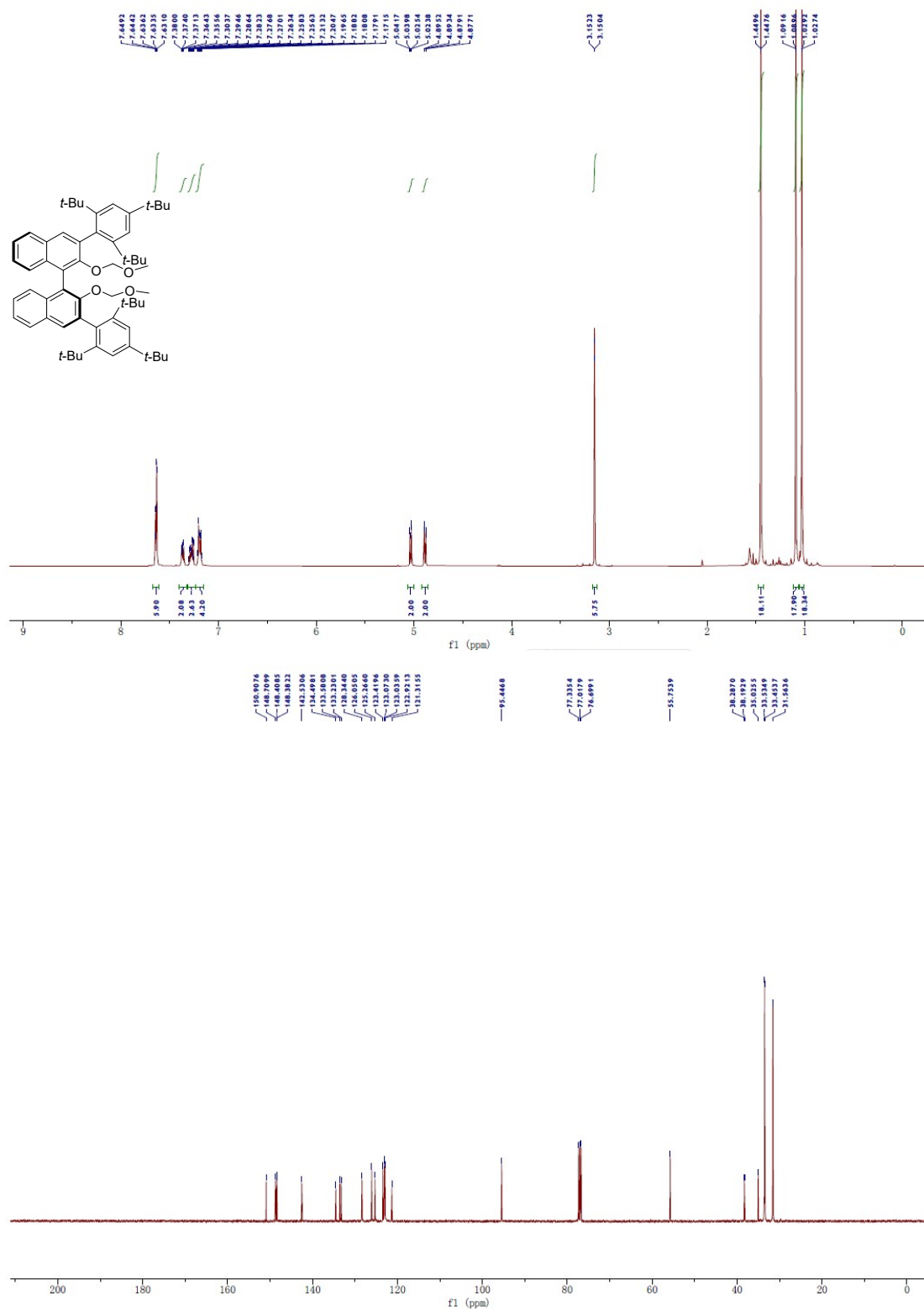
Peak No.	Time	Area	Area %	Plate number	Tailing	Resolution
1	2.408	7625.144	100.000	2696.418	1.054	

Overlay spectra of **2** and *ent*-**2**.

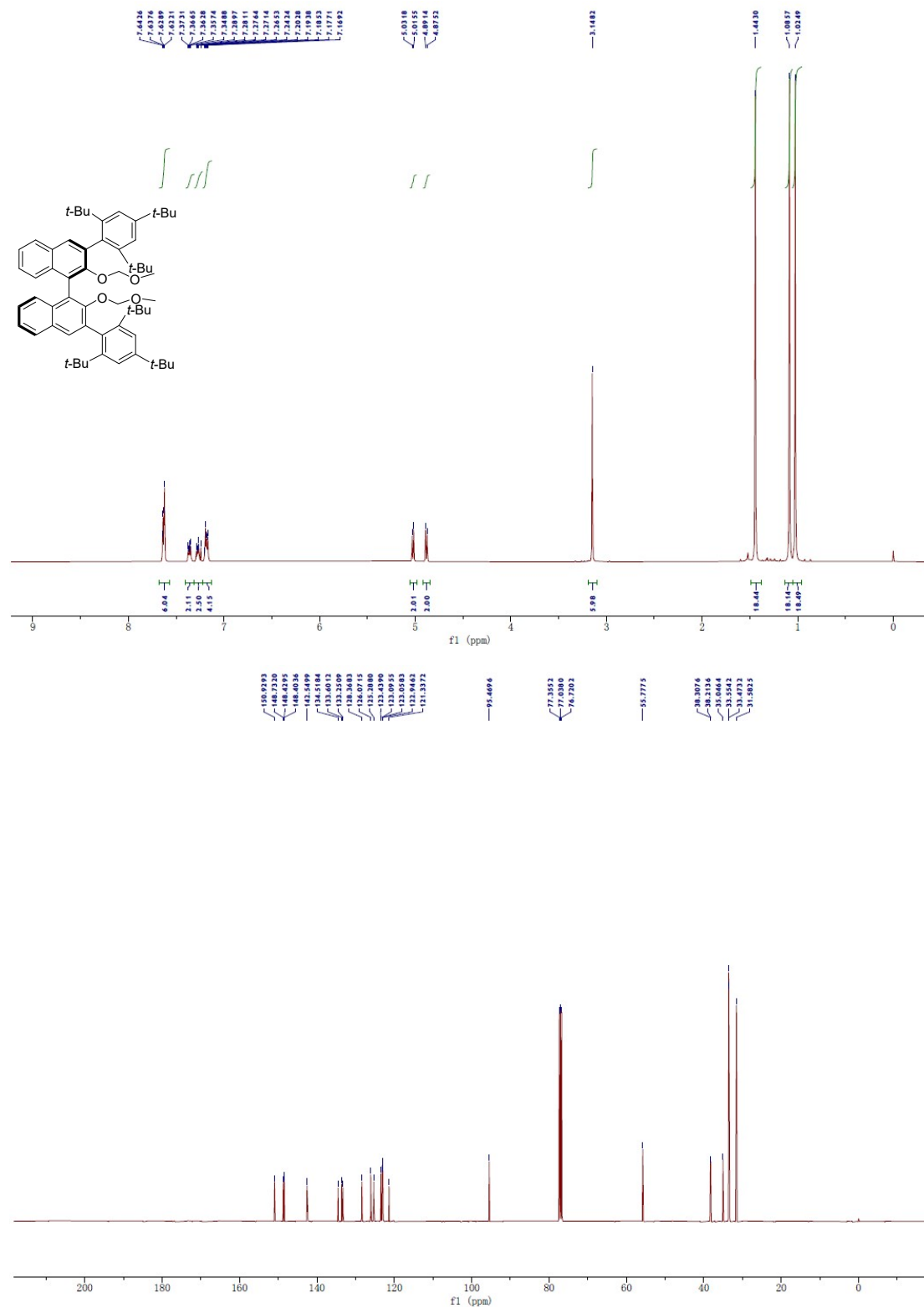


# Copies of NMR spectra

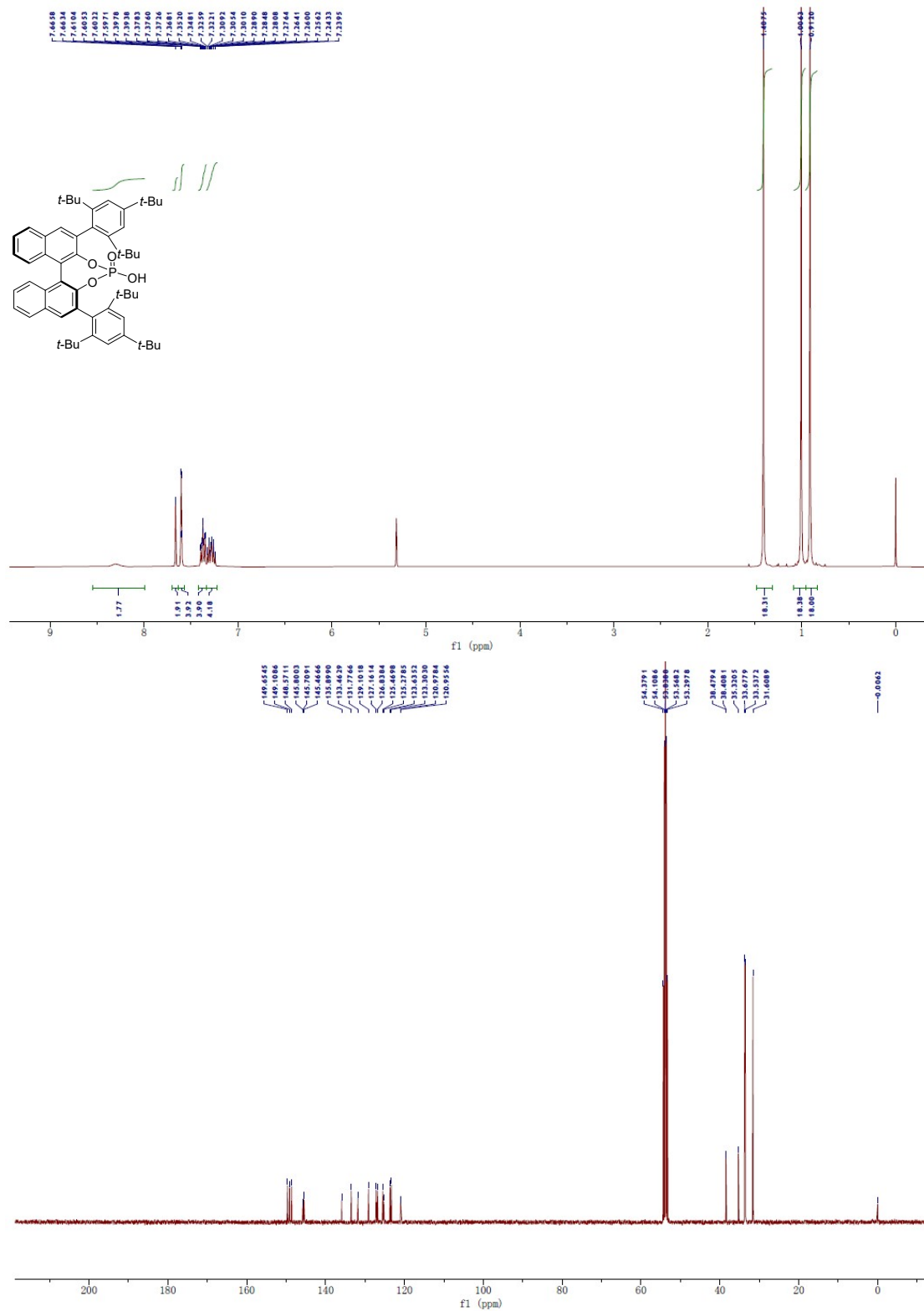
S-2,2'-bis(methoxymethoxy)-3,3'-bis(2,4,6-tri-tert-butylphenyl)-1,1'-binaphthalene **4**.



*R*-2,2'-bis(methoxymethoxy)-3,3'-bis(2,4,6-tri-*tert*-butylphenyl)-1,1'-binaphthalene *enti*-4.



S-3,3'-bis(2,4,6-tritertbutyl-phenyl)-BINOL-derived phosphoric acid **2**.





R-3,3'-bis(2,4,6-tritertbutyl-phenyl)-BINOL-derived phosphoric acid *enti*-2.

