

# Enantioselective Trapping of Phosphoramidate Ammonium Ylides with Imino Esters for Synthesis of 2, 3-Diaminosuccinic Acid Derivatives

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### General Remarks and Materials:

All reactions and manipulations were carried out under an argon atmosphere, in a flame-dried or oven-dried flask containing magnetic stir bar. All  $^1\text{H}$  NMR, and  $^{13}\text{C}$  NMR spectra were recorded using a Bruker 400 MHz or 500 MHz spectrometer in  $\text{CDCl}_3$ . Tetramethylsilane (TMS) served as an internal standard ( $\delta = 0$ ) for  $^1\text{H}$  NMR, and  $\text{CDCl}_3$  was used as internal standard ( $\delta = 77.0$ ) for  $^{13}\text{C}$  NMR. 85%  $\text{H}_3\text{PO}_4$  was used as external standard for  $^{31}\text{P}$  NMR. Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). HRMS (ESI) Mass spectra were recorded on IonSpec FT-ICR mass spectrometer. HPLC analysis was performed on Dalian Elite (UV230+ UV/Vis Detector and P230P High Pressure Pump). Chiralpak AD-H, IA was purchased from Daicel Chemical Industries, LTD. The racemic standards used in HPLC studies were prepared according to the general procedure by using racemic BINOL derived phosphoric acid catalysts. Dichloromethane (DCM), 1,2-dichloroethane (DCE) and toluene was distilled over calcium hydride. Glyoxylate derived imines were prepared from condensation of the corresponding aldehydes with amines according to the literature method.<sup>[1]</sup> Chiral phosphoric acids (PPAs) **5a-g** were prepared according to the literature procedure.<sup>[2]</sup>

### General Procedure for Optimization of Reaction Conditions (Table 1):

**Running the reaction at room temperature:** A mixture of  $\text{Rh}_2(\text{OAc})_4$  (0.004 mmol, 1.7mg), phosphoramidate **2** (0.26 mmol), imine **3a** (0.2 mmol), PPAs (as indicated in table 1), and 4Å MS (0.1 g) in 5.6 mL under an argon atmosphere was stirred under the indicated temperature in table 1. Diazo compound **1a** (0.26 mmol) in 2.8 mL toluene was then added over 1 h via a syringe pump at room temperature. After completion of the addition, the reaction mixture was filtrated and the filtrate evaporated *in vacuo* to give the crude product. And then the crude product was purified by flash chromatography on silica gel (EtOAc/light petroleum ether = 1:20 ~ 1:5) to give the pure product.

### General Procedure for the Enantioselective Three-Component Reactions (Table 2):

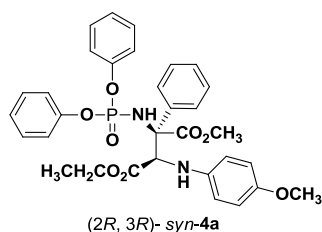
A mixture of  $\text{Rh}_2(\text{OAc})_4$  (0.004 mmol, 1.7mg), chiral phosphoric acid **5f** (2.5 mmol%), phosphoramidate **2** (0.26 mmol), imine **3** (0.2 mmol) and 4Å MS (0.1 g) in 5.6 mL of toluene under an argon atmosphere was stirred under rt. Diazo compound **1** (0.26 mmol) in 2.8 ml of toluene was then added over 1 h via a syringe pump. After completion of the addition, the reaction mixture was filtrated and evaporated *in vacuo* to give the crude product. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/light petroleum ether = 1:20 ~ 1:5) to give the pure product.

## References:

- [1] M. Mauksch; S. B. Tsogoeva; I. M. Martynova; S. Wei, *Angew. Chem.* 2007, **119**, 397; *Angew. Chem. Int. Ed.* 2007, **46**, 393.  
[2] (a) D. Uraguchi; M. Terada; *J. Am. Chem. Soc.* 2004, **126**, 5356. (b) T. Akiyama; H. Morita; J. Itoh; K. Fuchibe; *Org. Lett.* 2005, **7**, 2583. (c) R. I. Storer; D. E. Carrera; Y. Ni; D. W. C. MacMillan; *J. Am. Chem. Soc.* 2006, **128**, 84. (d) M. Yamanaka; J. Itoh; K. Fuchibe; T. Akiyama *J. Am. Chem. Soc.* 2007, **129**, 6756. (e) J. Jiang; J. Yu; X.-X. Sun; Q.-Q. Rao; L.-Z. Gong; *Angew. Chem. Int. Ed.* 2008, **47**, 2458.

## <sup>1</sup>H NMR, <sup>13</sup>C NMR data, <sup>31</sup>P NMR and HPLC data of compounds:

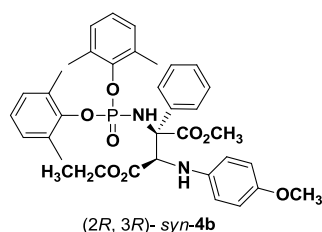
### (2*R*,3*R*)-4-ethyl 1-methyl 2-((diphenoxyphosphoryl)amino)-3-((4-methoxyphenyl)amino)-2-phenylsuccinate (4a).



(2*R*,3*R*)-*syn*-4a: 85% ee; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): 7.17-7.37 (m, 14H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 5.39 (d, *J* = 10.4 Hz, 1H), 5.18 (d, *J* = 8.4 Hz, 1H), 4.61 (d, *J* = 10.4 Hz, 1H), 3.98-4.02 (m, 1H), 3.86-3.86 (m, 4H), 3.74 (s, 3H), 1.02(t, *J* = 7.2 Hz,

3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 13.85, 53.71, 55.69, 61.39, 62.41, 67.31, 67.35, 114.77, 115.50, 120.27, 120.31, 120.40, 120.45, 124.83, 125.00, 127.64, 128.28, 128.53, 129.46, 129.60, 136.47, 139.87, 150.69 (d, *J*<sub>CP</sub> = 12.8 Hz), 150.79 (d, *J*<sub>CP</sub> = 11.3 Hz), 171.81; <sup>31</sup>P (162 MHz, CDCl<sub>3</sub>) δ -4.73; **HRMS** (ESI) Calcd. for C<sub>32</sub>H<sub>33</sub>N<sub>2</sub>NaO<sub>8</sub>P (M+Na)<sup>+</sup> 627.1867, Found: 627.1923; **HPLC** (Chiral AD-H, λ = 254 nm, hexane/2-propanol/MeOH = 80/10:5, Flow rate = 0.5 mL/min), t<sub>R</sub>(*syn*) = 16.52 min, 19.02 min.

### (2*R*,3*R*)-4-ethyl 1-methyl 2-((bis(2,6-dimethylphenoxy)phosphoryl)amino)-3-((4-methoxyphenyl)amino)-2-phenylsuccinate(4b)

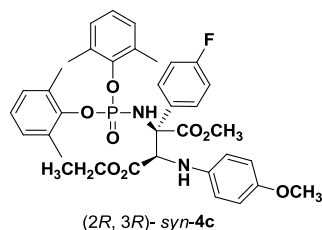


(2*R*, 3*R*)-*syn*-4b: 95% ee; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): 7.38-7.40 (m, 2H), 7.20-7.22(m, 3H), 6.89-6.97 (m, 6H), 6.68-6.76(m, 4H), 5.41 (d, *J* = 10.0 Hz, 1H), 5.25 (d, *J* = 6.4 Hz, 1H), 4.63(d, *J* = 10.4 Hz, 1H), 3.94-3.96(m, 1H), 3.71-3.74 (m, 7H), 2.22 (s, 6H), 2.15 (s, 6H), 0.93 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz,

CDCl<sub>3</sub>): δ 13.76, 17.23, 17.27, 53.54, 55.68, 61.26, 62.29, 67.27, 67.32, 114.75, 115.52, 124.77, 124.86, 127.50, 128.18, 128.30, 128.80, 128.99, 130.36, 130.39, 130.43, 136.83, 139.82, 148.24(d, *J*<sub>CP</sub> = 3.56 Hz), 148.33(d, *J*<sub>CP</sub> = 1.94 Hz), 152.89, 172.03; <sup>31</sup>P (162 MHz, CDCl<sub>3</sub>) δ -6.07; **HRMS**

(ESI) Calcd. for  $C_{36}H_{41}N_2NaO_8P$  ( $M+Na$ )<sup>+</sup> 683.2493, Found:683.2548; **HPLC** (Chiral AD-H,  $\lambda$  = 254 nm, hexane/2-propanol = 15/1, Flow rate = 1.0 mL/min),  $t_R(\text{syn})$  = 6.49 min, 8.05 min.

**(2R,3R)-4-ethyl 1-methyl 2-((bis(2,6-dimethylphenoxy)phosphoryl)amino)-2-(4-fluorophenyl)-3-((4-methoxyphenyl)amino)succinate(4c)**

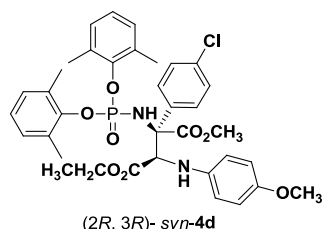


(2R, 3R)- *syn*-4c

(2R, 3R)-*syn*-4c: 91% ee; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): 7.32-7.35 (m, 2H), 6.96-6.98 (m, 3H), 6.82-6.90(m, 5H), 6.67-6.76 (m, 4H) , 5.39 (d,  $J$  = 10.8 Hz, 1H), 5.23 (d,  $J$  = 7.2 Hz, 2H), 4.54 (d,  $J$  = 10.0 Hz, 1H), 3.97-4.00 (m, 1H), 3.74-3.80(m, 7H), 2.25 (s, 6H), 2.15 (s, 6H), 1.57(s, 3H), 0.97 (t,  $J$  = 7.2 Hz, 3H ); <sup>13</sup>C

NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  13.79, 17.19, 17.28, 53.66, 55.67, 61.41, 62.35, 66.80, 66.84, 114.80, 115.03, 115.55, 124.85, 124.96, 128.86, 129.04, 129.53, 129.62, 130.30, 139.55, 148.08(d,  $J_{CP}$  =15.71 Hz), 148.29 (d,  $J_{CP}$  =14.90 Hz), 153.03, 171.84; <sup>31</sup>P (162 MHz, CDCl<sub>3</sub>)  $\delta$  -5.14; **HRMS** (ESI) Calcd. for  $C_{36}H_{40}FN_2NaO_8P$  ( $M+Na$ )<sup>+</sup> 701.2399, Found:701.2422; **HPLC** (Chiral AD-H,  $\lambda$  = 254 nm, hexane/2-propanol = 10/1, Flow rate = 1.0 mL/min),  $t_R(\text{syn})$  = 5.06 min, 6.17 min.

**(2R,3R)-4-ethyl 1-methyl 2-((bis(2,6-dimethylphenoxy)phosphoryl)amino)-2-(4-chlorophenyl)-3-((4-methoxyphenyl)amino)succinate(4d)**

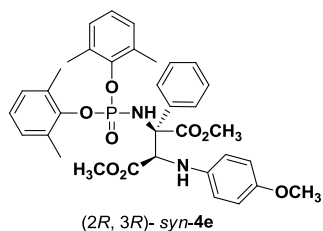


(2R, 3R)- *syn*-4d

(2R, 3R)-*syn*-4d: 90% ee; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): 7.27 (d,  $J$  = 9.2 Hz, 2H), 7.25 (d,  $J$  = 8.8 Hz, 2H), 6.90-7.00 (m, 6H) , 6.75 (d,  $J$  = 8.8 Hz, 2H), 6.68 (d,  $J$  = 8.8 Hz, 2H), 5.40 (d,  $J$  = 7.6 Hz, 1H), 5.22 (d,  $J$  = 7.6Hz, 1H), 4.52 (d,  $J$  =10.8 Hz, 1H), 3.98-4.00 (m, 1H), 3.74-3.79 (m, 7H), 2.26(s, 6H), 2.14 (s, 6H),

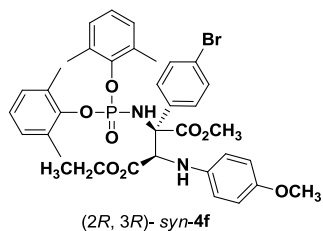
0.98 (t,  $J$  = 7.0 Hz, 3H ); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  13.80, 17.17, 17.29, 53.73, 55.68, 61.45, 62.15, 66.87, 66.92, 114.83, 115.54, 124.87, 124.99, 128.18, 128.90, 129.07, 130.28, 134.24, 135.40, 139.50, 148.25, 148.34, 153.05, 171.77; <sup>31</sup>P (162 MHz, CDCl<sub>3</sub>)  $\delta$  -6.12; **HRMS** (ESI) Calcd. for  $C_{36}H_{40}ClN_2NaO_8P$  ( $M+Na$ )<sup>+</sup> 717.2103, Found:717.2133; **HPLC** (Chiral IA,  $\lambda$  = 254 nm, hexane/2-propanol = 15/1, Flow rate = 1.0 mL/min),  $t_R(\text{syn})$  = 6.63 min, 7.37 min.

**(2R,3R)-dimethyl 2-((bis(2,6-dimethylphenoxy)phosphoryl)amino)-3-((4-methoxyphenyl)amino)-2-phenylsuccinate(4e)**



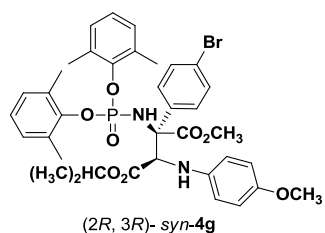
(2R, 3R)-*syn*-4e: 98% ee; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): 7.42-7.43(m, 2H), 7.25-7.28(m, 3H), 6.93-7.03(m, 6H), 6.79(d, *J* = 8.4 Hz, 2H), 6.72(d, *J* = 8.4 Hz, 2H), 5.54 (d, *J* = 10.4 Hz, 1H), 5.29 (d, *J* = 6.4 Hz, 1H), 4.68 (d, *J* = 10.8 Hz, 1H), 3.80(s, 3H), 3.77 (s, 3H), 3.39 (s, 3H) 2.27 (s, 6H), 2.18 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 17.23, 17.27, 52.05, 53.72, 55.67, 61.77, 67.38, 67.42, 114.86, 115.34, 124.79, 124.90, 127.52, 128.24, 128.34, 128.83, 129.09, 130.34, 130.37, 130.41, 136.84, 139.70, 148.22 (d, *J*<sub>CP</sub> = 8.10 Hz), 148.32 (d, *J*<sub>CP</sub> = 9.72 Hz), 152.90, 172.60; <sup>31</sup>P (162 MHz, CDCl<sub>3</sub>) δ -5.61; HRMS (ESI) Calcd. for C<sub>35</sub>H<sub>39</sub>N<sub>2</sub>NaO<sub>8</sub>P (M+Na)<sup>+</sup> 669.2336, Found:669.2354; HPLC (Chiral AD-H, λ = 254 nm, hexane/2-propanol = 30/1, Flow rate = 1.0 mL/min), t<sub>R</sub>(*syn*) = 14.56min, 18.96 min.

**(2R,3R)-4-ethyl 1-methyl 2-((bis(2,6-dimethylphenoxy)phosphoryl)amino)-2-(4-bromophenyl)-3-((4-methoxyphenyl)amino)succinate(4f)**



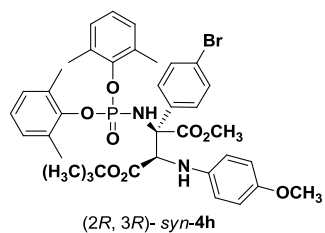
(2R, 3R)-*syn*-4f: 97% ee; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): 7.23-7.30 (m, 4H), 6.93-7.01(m, 4H), 6.78(d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 5.44 (d, *J* = 10.8 Hz, 1H), 5.24 (d, *J* = 7.2 Hz, 1H), 4.56 (d, *J* = 10.8 Hz, 1H), 3.99-4.07(m, 1H), 3.77-3.83 (m, 7H), 2.29 (s, 6H), 2.17 (s, 6H), 2.13 (s, 6H), 1.01 (t, *J* = 7.0 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 13.83, 17.19, 17.31, 53.76, 55.67, 61.46, 62.03, 66.92, 66.97, 114.84, 115.52, 122.58, 149.90, 124.99, 128.92, 129.06, 129.39, 130.28, 131.14, 135.95, 139.48, 147.97(d, *J*<sub>CP</sub> = 15.39 Hz), 148.30(d, *J*<sub>CP</sub> = 14.42 Hz), 153.06, 171.77; HRMS (ESI) Calcd. for C<sub>36</sub>H<sub>40</sub>BrN<sub>2</sub>NaO<sub>8</sub>P (M+Na)<sup>+</sup> 761.1598, Found:761.1587; <sup>31</sup>P (162 MHz, CDCl<sub>3</sub>) δ -6.12; HPLC (Chiral IA, λ = 254 nm, hexane/2-propanol = 10/1, Flow rate = 1.0 mL/min), t<sub>R</sub>(*syn*) = 5.55 min, 6.23 min.

**(2R,3R)-4-isopropyl 1-methyl 2-((bis(2,6-dimethylphenoxy)phosphoryl)amino)-2-(4-bromophenyl)-3-((4-methoxyphenyl)amino)succinate(4g)**



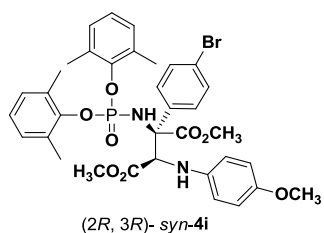
(2*R*, 3*R*)-*syn*-**4g**: 95% ee; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): 7.26-7.28 (m, 4H), 6.94-7.01 (m, 6H), 6.78(d, *J* = 8.4 Hz, 2H), 6.71(d, *J* = 8.4 Hz, 2H), 5.24-5.32 (m, 2H), 4.84 (m, 1H), 4.54 (d, *J* = 10.4 Hz, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 2.33 (s, 6H), 2.20 (s, 6H), 1.08 (d, *J* = 6.0 Hz, 3H), 1.00 (d, *J* = 6.0 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 17.23, 17.37, 21.40, 21.50, 53.51, 55.68, 62.90, 67.10, 67.14, 69.60, 114.75, 115.71, 122.50, 124.87, 125.00, 128.94, 129.04, 129.31, 130.26, 131.02, 136.03, 139.66, 147.94 (d, *J*<sub>CP</sub> = 15.23 Hz), 148.52 (d, *J*<sub>CP</sub> = 15.07 Hz), 153.09, 171.14; <sup>31</sup>P (162 MHz, CDCl<sub>3</sub>) δ -6.10; HRMS (ESI) Calcd. for C<sub>37</sub>H<sub>42</sub>BrN<sub>2</sub>NaO<sub>8</sub>P (M+Na)<sup>+</sup> 775.1754, Found: 775.1760; HPLC (Chiral IA, λ = 254 nm, hexane/2-propanol = 15/1, Flow rate = 1.0 mL/min), t<sub>R</sub>(*syn*) = 7.69 min, 9.74 min.

**(2*R*,3*R*)-4-tert-butyl 1-methyl 2-((bis(2,6-dimethylphenoxy)phosphoryl)amino)-2-(4-bromophenyl)-3-((4-methoxyphenyl)amino)succinate(4h)**



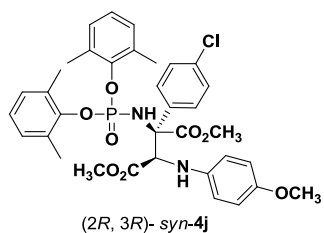
(2*R*, 3*R*)-*syn*-**4h**: 84% ee; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): 7.27-7.29 (m, 4H), 6.94-7.04 (m, 6H), 6.80 (d, *J* = 9.2 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 5.26 (d, *J* = 8.0 Hz, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 4.48 (d, *J* = 10.4 Hz, 1H), 3.78 (s, 3H), 3.65 (s, 3H), 2.37(s, 6H), 2.23(s, 6H), 1.30(s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 7.59, 16.17, 16.28, 16.44, 26.71, 28.68, 44.81, 52.31, 54.66, 81.81, 113.50, 113.70, 114.80, 121.36, 123.81, 123.93, 127.93, 128.02, 128.13, 128.40, 128.67, 129.20, 129.83, 129.89, 135.16, 138.84, 146.92 (d, *J*<sub>CP</sub> = 15.39 Hz), 147.69 (d, *J*<sub>CP</sub> = 15.55 Hz), 152.08, 169.68; <sup>31</sup>P (162 MHz, CDCl<sub>3</sub>) δ -6.12; HRMS (ESI) Calcd. for C<sub>38</sub>H<sub>45</sub>BrN<sub>2</sub>NaO<sub>8</sub>P (M+Na)<sup>+</sup> 767.2091, Found: 767.2083; HPLC (Chiral IA, λ = 254 nm, hexane/2-propanol = 15/1, Flow rate = 1.0 mL/min), t<sub>R</sub>(*syn*) = 7.11 min, 9.76 min.

**(2*R*,3*R*)-dimethyl 2-((bis(2,6-dimethylphenoxy)phosphoryl)amino)-2-(4-bromophenyl)-3-((4-methoxyphenyl)amino)succinate(4i)**



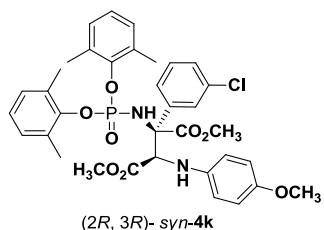
(2R, 3R)-syn-4i: 96% ee; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): 7.17-7.26 (m, 4H), 6.89-7.00 (m, 6H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 9.2 Hz, 2H), 5.49 (d, *J* = 10.8 Hz, 1H), 5.20 (d, *J* = 7.2 Hz, 1H), 4.54 (d, *J* = 10.8 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.39 (s, 3H), 2.26 (s, 6H), 2.13 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 17.18, 17.30, 52.22, 53.92, 55.69, 61.52, 67.05, 67.09, 114.94, 115.32, 122.62, 124.93, 125.02, 128.95, 129.14, 129.38, 130.26, 131.20, 139.39, 147.73(d, *J*<sub>CP</sub> = 15.55 Hz), 148.25 (d, *J*<sub>CP</sub> = 14.58 Hz), 153.06, 172.34; <sup>31</sup>P (162 MHz, CDCl<sub>3</sub>) δ -6.23; HRMS (ESI) Calcd. for C<sub>35</sub>H<sub>39</sub>BrN<sub>2</sub>O<sub>8</sub>P (M+H)<sup>+</sup> 725.1622, Found: 725.1615; HPLC (Chiral IA, λ = 254 nm, hexane/2-propanol = 30/1, Flow rate = 1.0 mL/min), t<sub>R</sub>(syn) = 11.24 min, 12.84 min.

**(2R,3R)-dimethyl 2-((bis(2,6-dimethylphenoxy)phosphoryl)amino)-2-(4-chlorophenyl)-3-((4-methoxyphenyl)amino)succinate(4j)**



(2R, 3R)-syn-4j: 96% ee; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): 7.25 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.90-6.98 (m, 6H), 6.76 (d, *J* = 9.2 Hz, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 5.54 (d, *J* = 10.8 Hz, 1H), 5.20 (d, *J* = 7.2 Hz, 1H), 4.53 (d, *J* = 10.8 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.40 (s, 3H), 2.26 (s, 6H), 2.13 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 17.16, 17.27, 52.19, 53.88, 55.66, 61.59, 66.96, 67.01, 114.91, 115.32, 124.89, 124.99, 128.24, 128.90, 129.05, 129.11, 130.25, 130.28, 134.26, 135.37, 139.38, 148.00(d, *J*<sub>CP</sub> = 15.55 Hz), 148.22 (d, *J*<sub>CP</sub> = 14.42 Hz), 153.03, 172.35; <sup>31</sup>P (162 MHz, CDCl<sub>3</sub>) δ -6.21; HRMS (ESI) Calcd. for C<sub>35</sub>H<sub>38</sub>ClN<sub>2</sub>O<sub>8</sub>P (M+Na)<sup>+</sup> 703.1947, Found: 703.1947; HPLC (Chiral IA, λ = 254 nm, hexane/2-propanol = 40/1, Flow rate = 1.0 mL/min), t<sub>R</sub>(syn) = 12.10 min, 15.12 min.

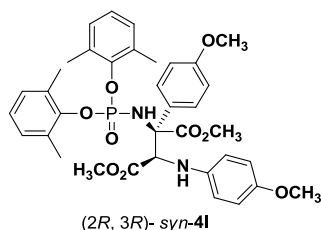
**(2R,3R)-dimethyl 2-((bis(2,6-dimethylphenoxy)phosphoryl)amino)-2-(3-chlorophenyl)-3-((4-methoxyphenyl)amino)succinate(4k)**



(2R, 3R)-syn-4k: 93% ee; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): 7.47(s, 1H), 7.17-7.37(m, 3H), 6.95-7.06(m, 6H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 5.52 (d, *J* = 10.8 Hz, 1H), 5.29 (d, *J* = 6.8 Hz, 1H), 4.55 (d, *J* = 10.8 Hz, 1H), 3.81 (s, 6H), 3.78 (s,

6H), 3.44 (s, 3H), 2.32 (s, 6H), 2.23(s, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  17.25, 17.29, 52.23, 53.84, 55.66, 62.16, 67.35, 67.39, 114.93, 115.67, 124.97, 125.03, 125.92, 127.95, 128.60, 128.91, 129.14, 129.36, 130.26, 130.29, 130.35, 134.12, 139.52, 148.13 (d,  $J_{\text{CP}}=15.71$  Hz), 148.29 (d,  $J_{\text{CP}}=14.90$  Hz), 153.23, 172.21;  $^{31}\text{P}$  (162 MHz,  $\text{CDCl}_3$ )  $\delta$  -5.93; **HRMS** (ESI) Calcd. for  $\text{C}_{35}\text{H}_{38}\text{ClN}_2\text{O}_8\text{P}$  ( $\text{M}+\text{Na}$ ) $^+$  703.1947, Found:703.1964; **HPLC** (Chiral AD-H,  $\lambda = 254$  nm, hexane/2-propanol = 30/1, Flow rate = 1.0 mL/min),  $t_{\text{R}}(\text{syn}) = 12.08$  min, 19.61 min.

**(2R,3R)-dimethyl2-((bis(2,6-dimethylphenoxy)phosphoryl)amino)-2-(4-methoxyphenyl)-3-((4-methoxyphenyl)amino)succinate(4I)**

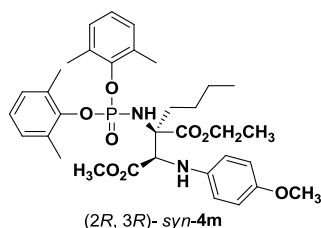


(2R, 3R)- syn-4I

(2R, 3R)-syn-4i: 94% ee;  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ): 7.27 (d,  $J = 8.8\text{Hz}$ , 2H), 6.88-6.97 (m, 6H), 6.66-6.75 (m, 6H), 5.48 (d,  $J = 10.4$  Hz, 1H), 5.21 (d,  $J = 6.4$  Hz, 1H), 4.62 (d,  $J = 10.4$  Hz, 1H), 3.77 (s, 3H), 3.71 (s, 6H), 3.36 (s, 3H), 2.23 (s, 6H), 2.15 (s, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  17.27, 17.30, 52.06, 53.72,

55.18, 55.67, 61.76, 66.99, 67.03, 113.55, 114.87, 115.27, 124.78, 124.90, 128.84, 128.88, 129.10, 130.33, 130.37, 130.42, 139.75, 148.23, 148.33(d,  $J_{\text{CP}}=3.24$  Hz), 152.86, 159.33, 172.66;  $^{31}\text{P}$  (162 MHz,  $\text{CDCl}_3$ )  $\delta$  -5.95; **HRMS** (ESI) Calcd. for  $\text{C}_{36}\text{H}_{42}\text{N}_2\text{O}_9\text{P}$  ( $\text{M}+\text{H}$ ) $^+$  677.2622, Found:677.2632; **HPLC** (Chiral IA,  $\lambda = 254$  nm, hexane/2-propanol = 20/1, Flow rate = 1.0 mL/min),  $t_{\text{R}}(\text{syn}) = 11.55$  min, 13.38 min.

**(2R,3R) -1-ethyl 4-methyl 2-((bis(2,6-dimethylphenoxy)phosphoryl)amino) -2-butyl-3-((4-methoxyphenyl)amino)succinate**



(2R, 3R)- syn-4m

(2R, 3R)-syn-4m: 79% ee;  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ): 6.97-7.04 (m, 9H), 6.62-6.77 (m, 6H), 4.84-4.89 (1.45, 2H), 4.65-4.72 (1.44, 2H), 4.35-4.40 (m, 4H), 3.87-3.92 (m, 2H), 3.75 (s, 6H), 2.48 (s, 6H), 2.42 (s, 3H), 2.32 (s, 3H), 2.27 (s, 7H), 1.38-1.42 (qt, H), 1.29 (s, 7H), 0.94-0.97 (t, 5H), 0.80-0.83 (t,

5H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.03, 14.12, 17.30, 17.60, 29.71, 36.48, 37.75, 55.71, 55.79, 61.10, 62.76, 62.82, 63.64, 65.11, 67.53, 67.59, 114.77, 115.64, 124.96, 125.03, 129.09, 130.3, 130.34, 130.57, 130.60, 142.08, 148.52, 152.26, 171.22, 171.54, 172.83, 173.01;  $^{31}\text{P}$  (162 MHz,

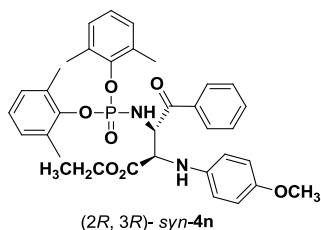


$\text{CDCl}_3$ )  $\delta$  -2.35; **HRMS** (ESI) Calcd. for  $\text{C}_{34}\text{H}_{45}\text{N}_2\text{NaO}_8\text{P}$  ( $\text{M}+\text{H}$ )<sup>+</sup> 663.2806, Found:663.2864;

**HPLC** (Chiral IA,  $\lambda$  = 254 nm, hexane/2-propanol = 50/1, Flow rate = 1.0 mL/min),  $t_{\text{R}}(\text{syn})$  = 8.03 min, 8.64 min.

### (2*R*,3*R*)-ethyl

### 3-((bis(2,6-dimethylphenoxy)phosphoryl)amino)-2-((4-methoxyphenyl)amino)-4-oxo-4-phenylbutanoate(4n)



(2*R*, 3*R*)-*syn*-4n: 85% ee; <sup>1</sup>H NMR (400MHz,  $\text{CDCl}_3$ ):

7.90-7.92 (d,  $J$  = 8Hz, 2H), 7.40-7.58 (m, 5H), 7.05-7.06 (d,  $J$  =

5.2Hz, 3H), 6.87 (s, 3H), 6.72-6.74 (t,  $J$  = 3Hz, 2H), 6.578-6.60

(t,  $J$  = 3Hz, 2H), 5.50-5.53 (t,  $J$  = 5.1Hz 1H), 4.67 (m, 1H),

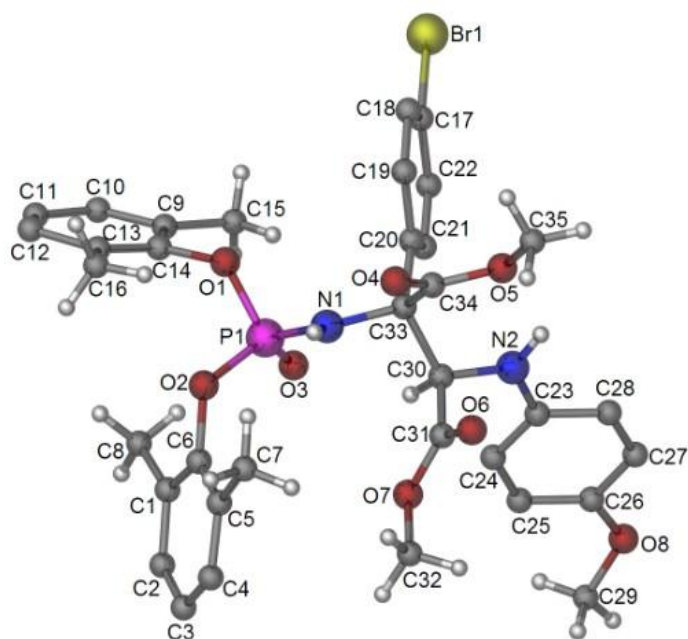
4.48-4.52 (t,  $J$  = 6.1Hz, 1H), 4.36-4.37 (d,  $J$  = 5.6Hz, 1H),

3.77-3.98 (m, 2H), 3.74 (s, 3H), 2.42 (s, 6H), 2.21 (s, 6H); <sup>31</sup>P (162 MHz,  $\text{CDCl}_3$ )  $\delta$  -0.94; **HRMS**

(ESI) Calcd. for  $\text{C}_{35}\text{H}_{39}\text{N}_2\text{O}_7\text{P}$  ( $\text{M}+\text{H}$ )<sup>+</sup> 631.2586, Found:631.2588; **HPLC** (Chiral IA,  $\lambda$  = 254 nm,

hexane/2-propanol = 6/1, Flow rate = 1.0 mL/min),  $t_{\text{R}}(\text{syn})$  = 12.30 min, 22.21 min.

### Single Crystal X-ray Structure Determinations of Compound *syn*-4i



Bond precision:

C-C = 0.0127 Å

Wavelength=0.71073

Cell: a=16.9476(6)

b=14.5627(5)

c=15.6857(5)

alpha=90

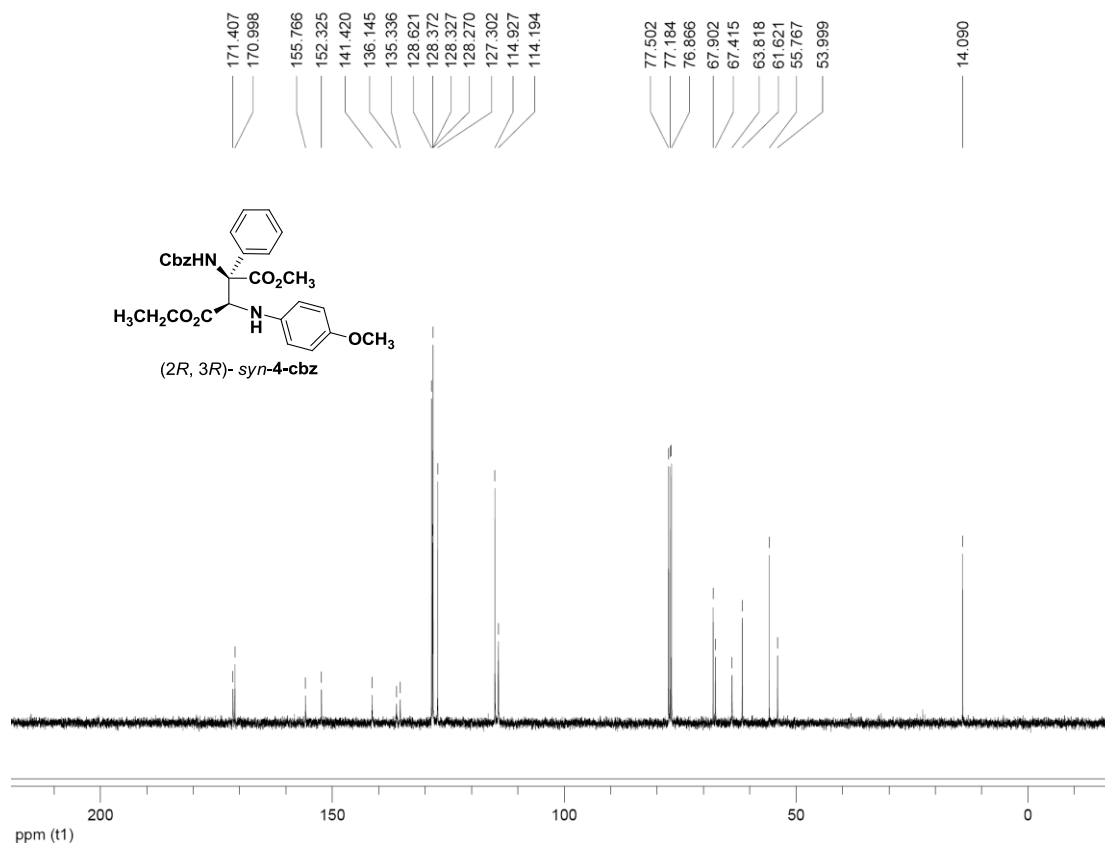
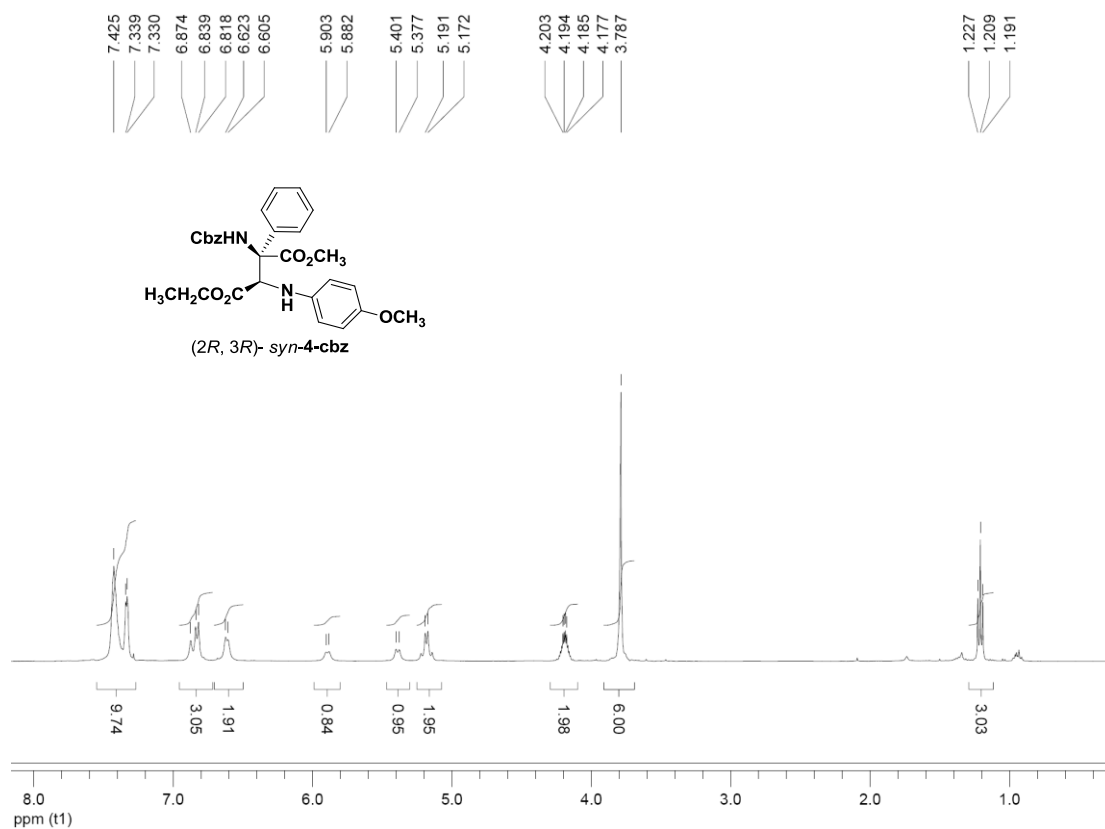
beta=116.620(1)

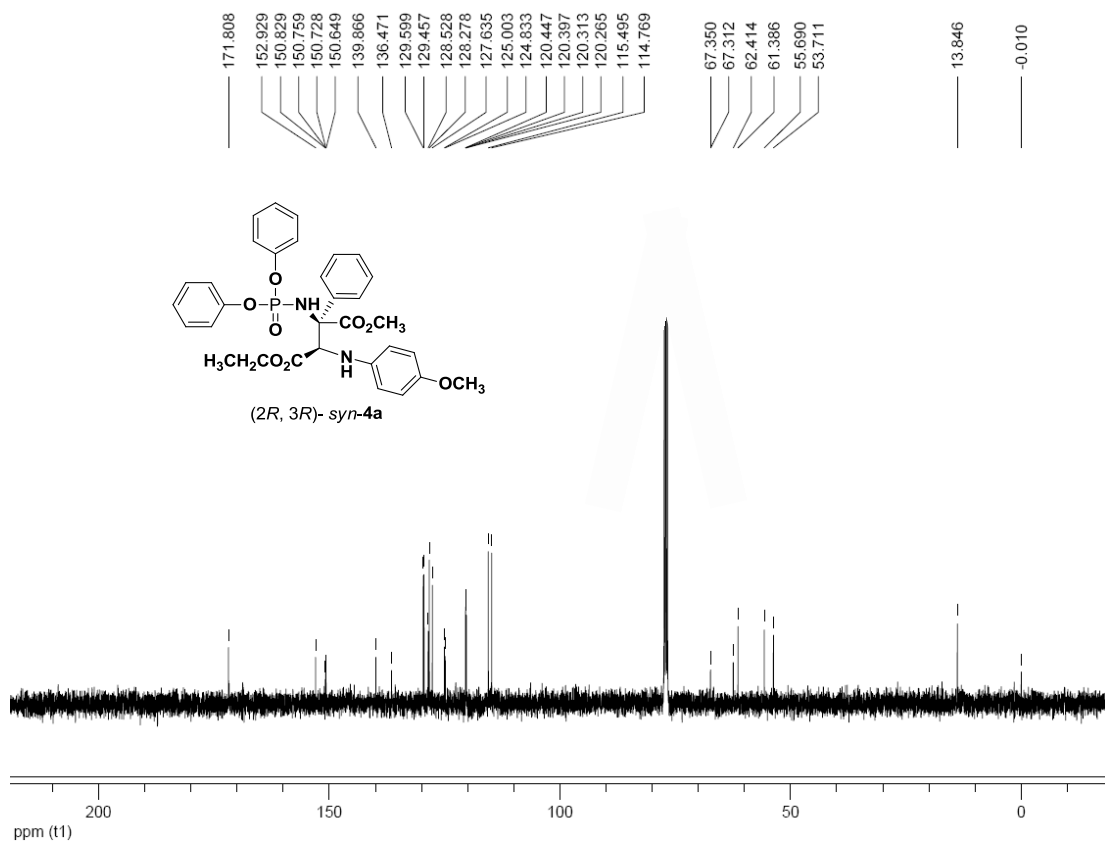
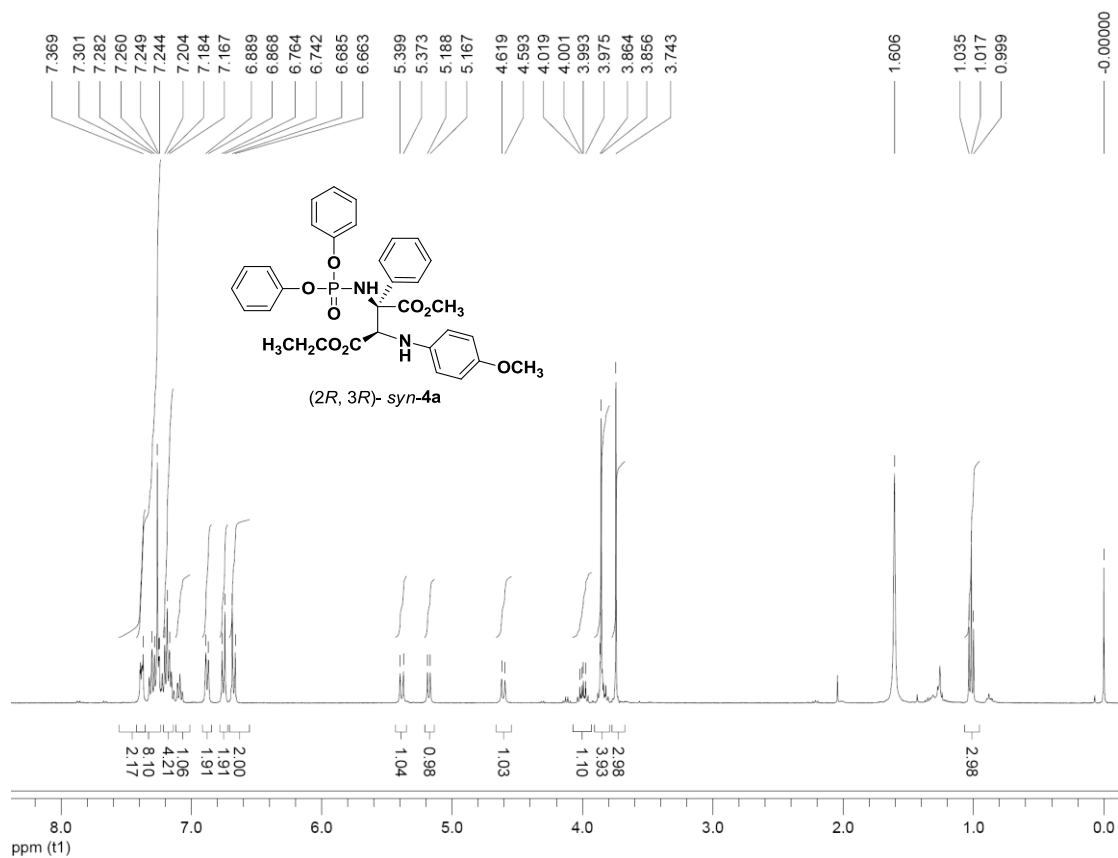
gamma=90

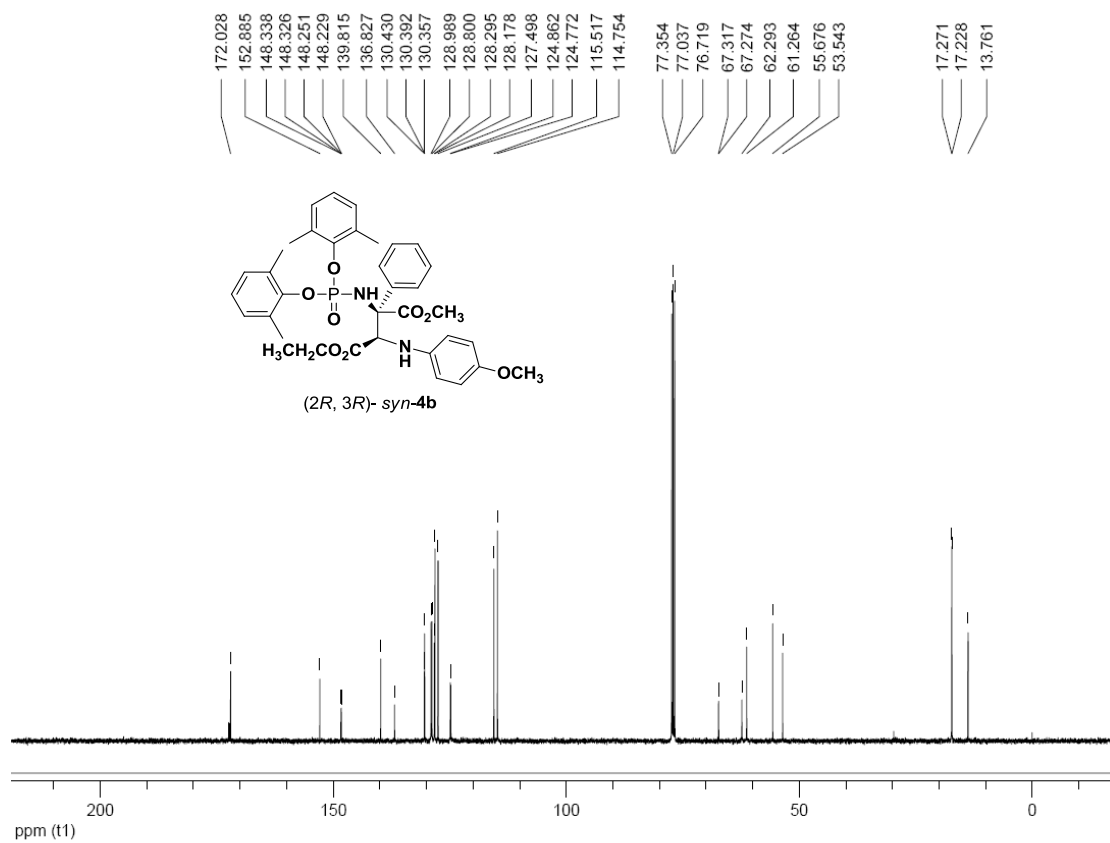
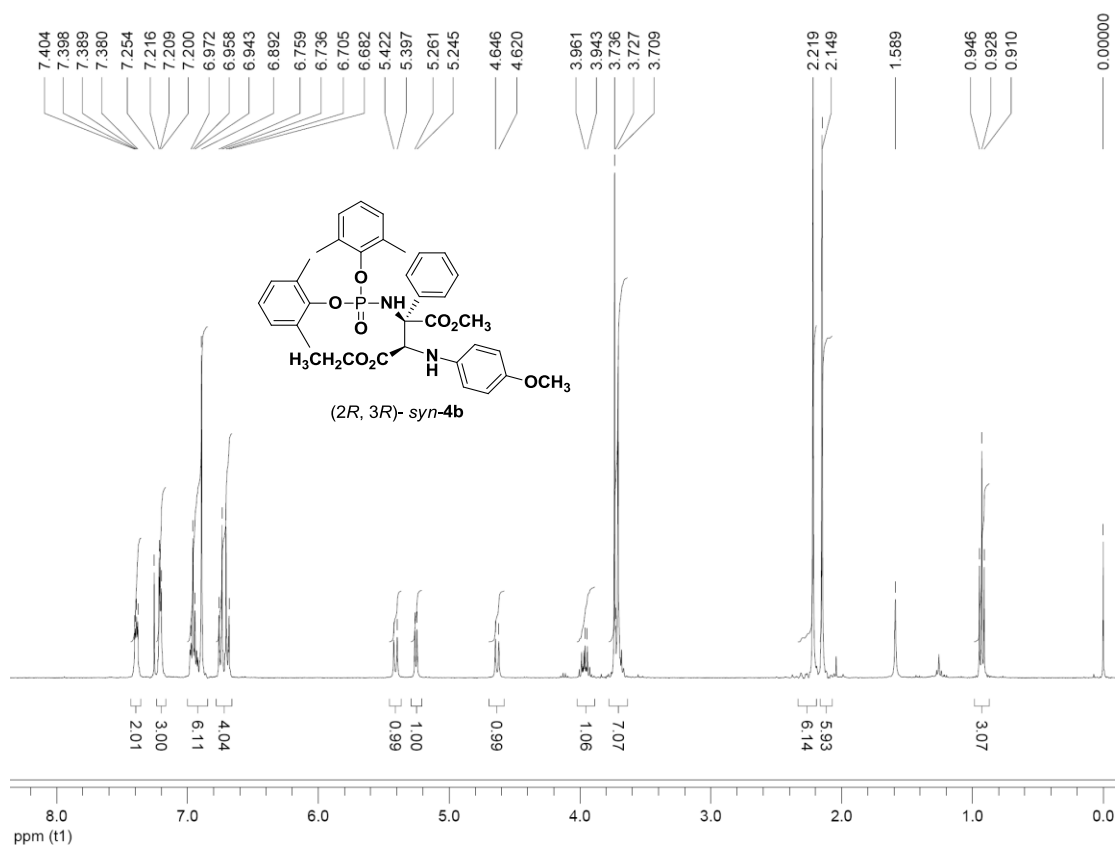
Temperature: 296 K

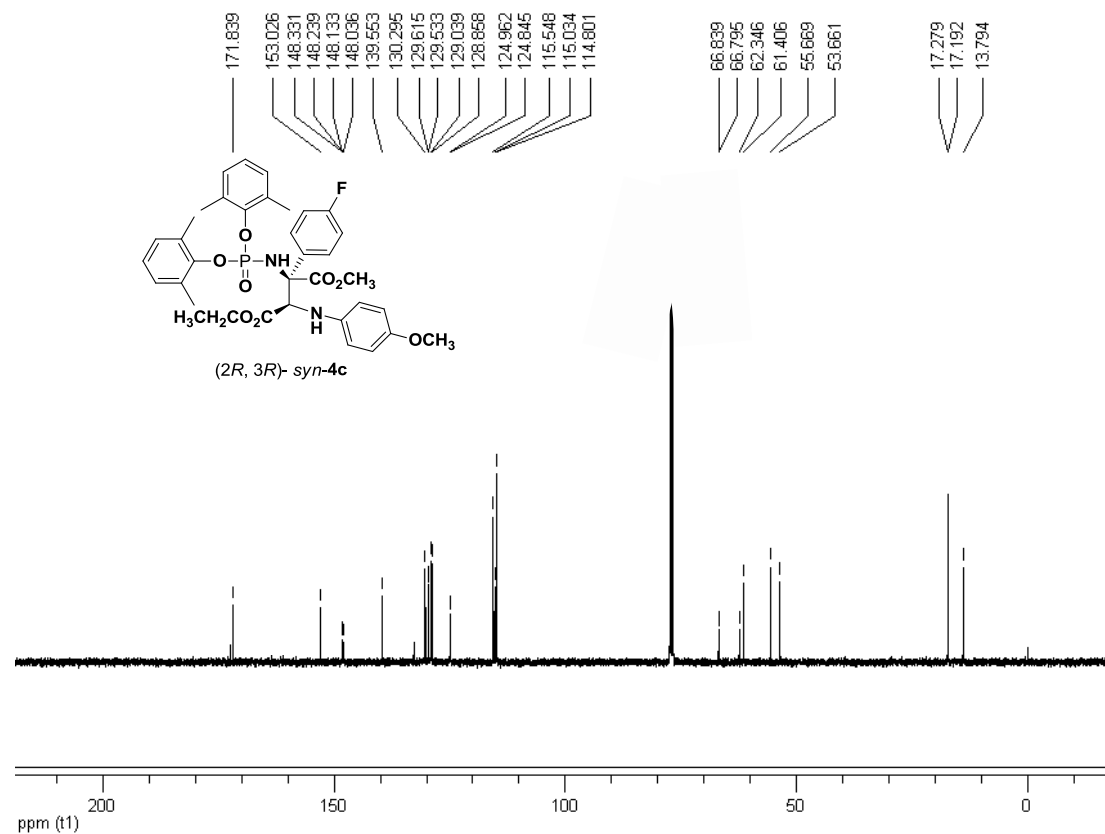
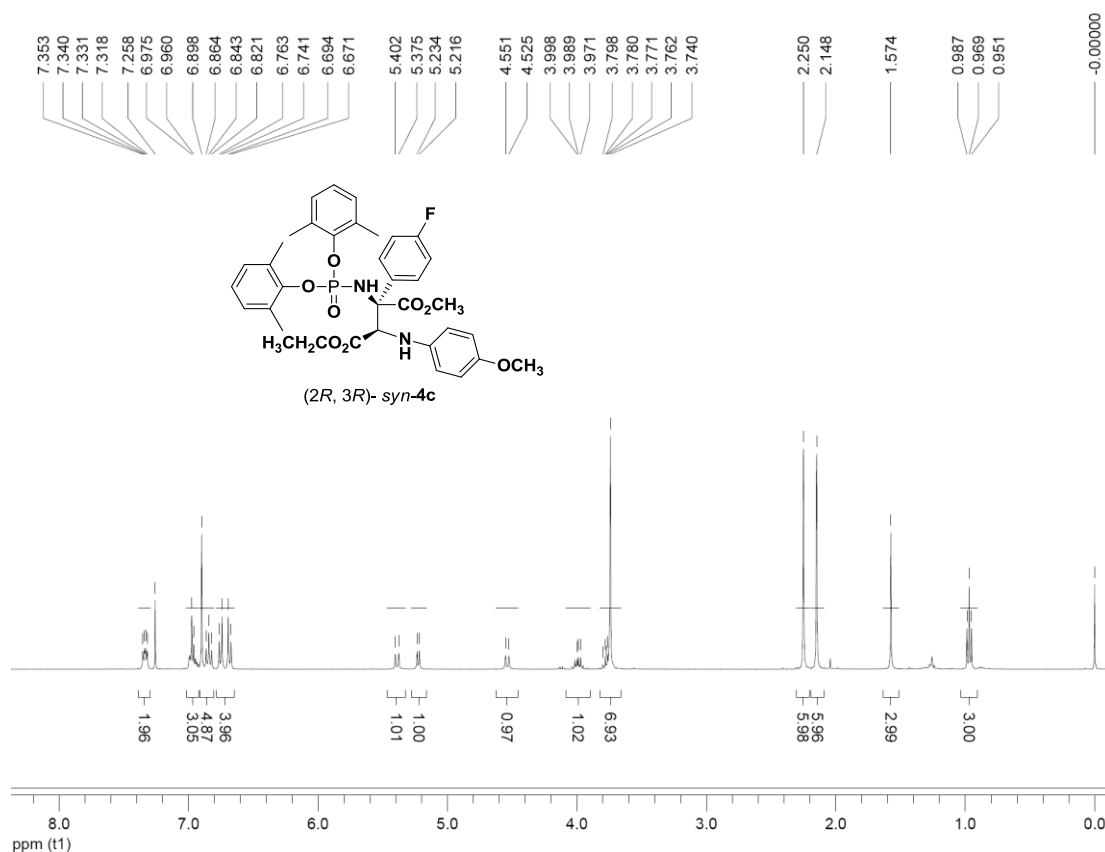
	Calculated	Reported
Volume	3460.9(2)	3460.9(2)
Space group	P 21/c	P2(1)/c
Hall group	-P 2ybc	?
Moiety formula	C35 H38 Br N2 O8 P	?
Sum formula	C35 H38 Br N2 O8 P	C35 H38 Br N2 O8 P
Mr	725.54	725.55
Dx,g cm-3	1.393	1.392
Z	4	4
Mu (mm-1)	1.287	1.287
F000	1504.0	1504.0
F000'	1503.92	
h,k,lmax	20,17,18	20,17,18
Nref	6100	6095
Tmin,Tmax	0.911,0.950	0.811,0.950
Tmin'	0.803	
Correction method= MULTI-SCAN		
Data completeness= 0.999		Theta(max)= 25.010
R(reflections)= 0.0752( 3424)		wR2(reflections)= 0.2318( 6095)
S = 1.040		Npar= 424

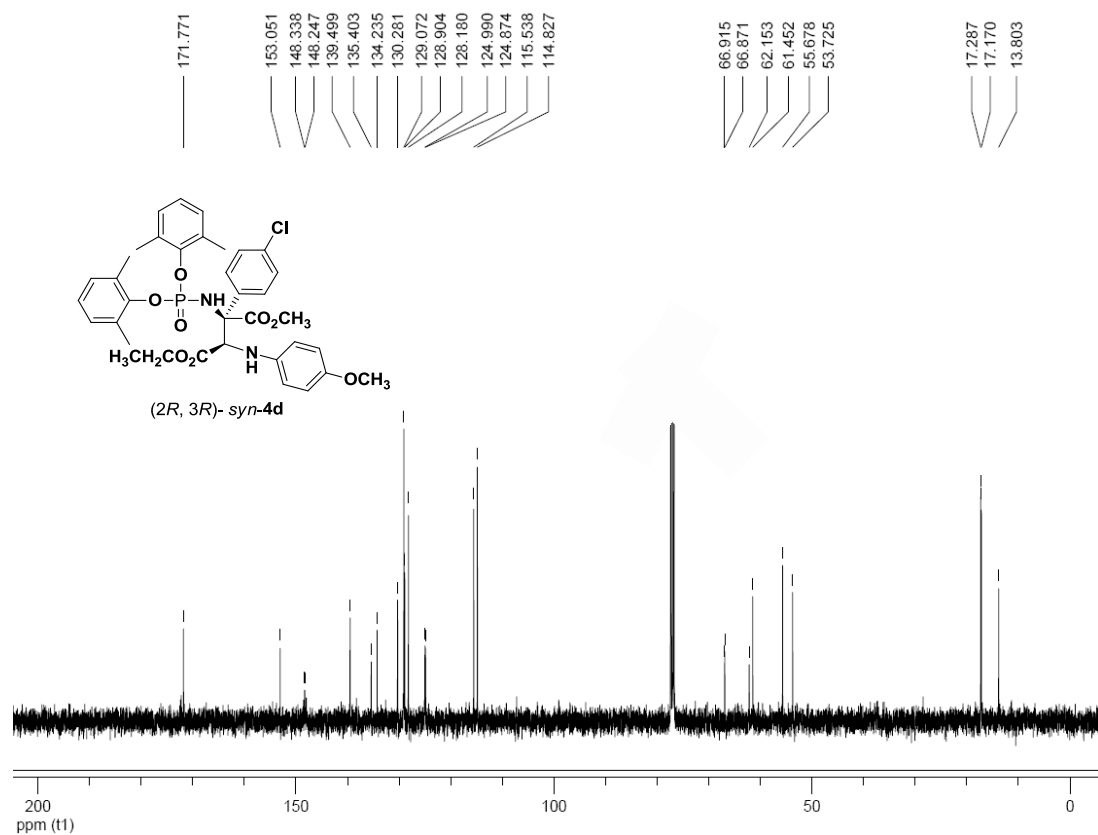
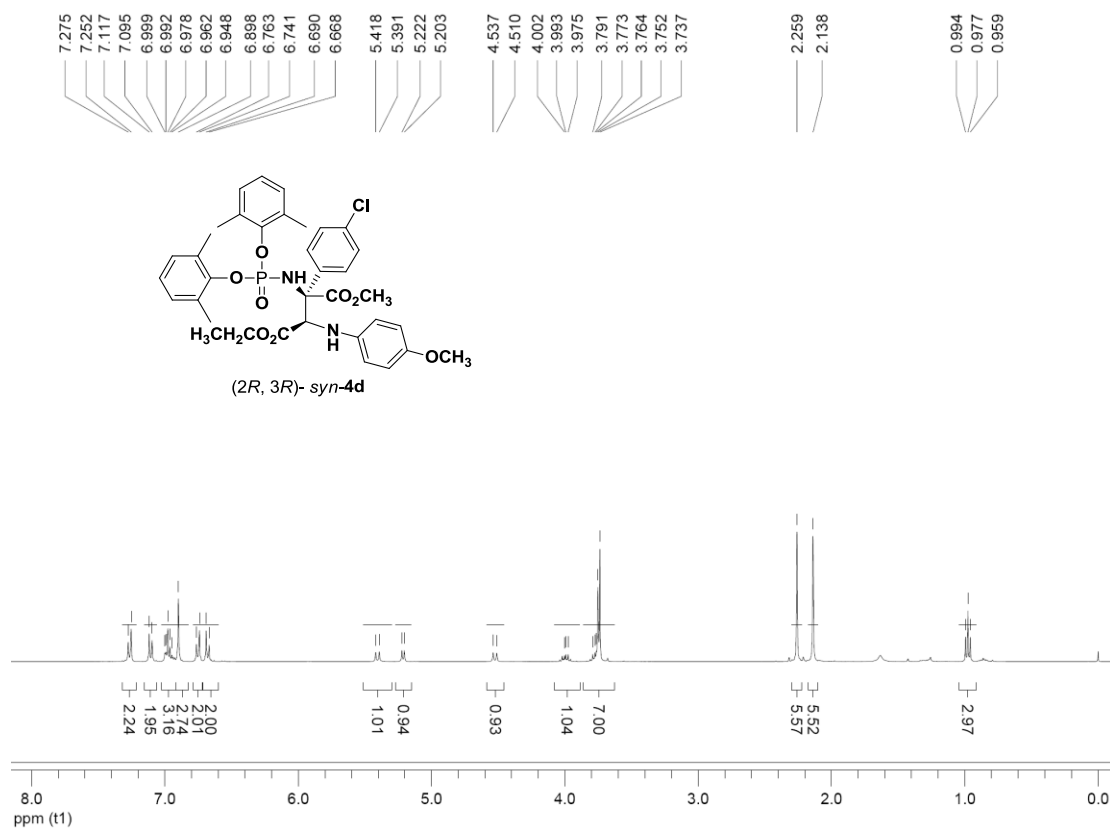
### $^1\text{H}$ NMR and $^{13}\text{C}$ NMR spectra for new compounds

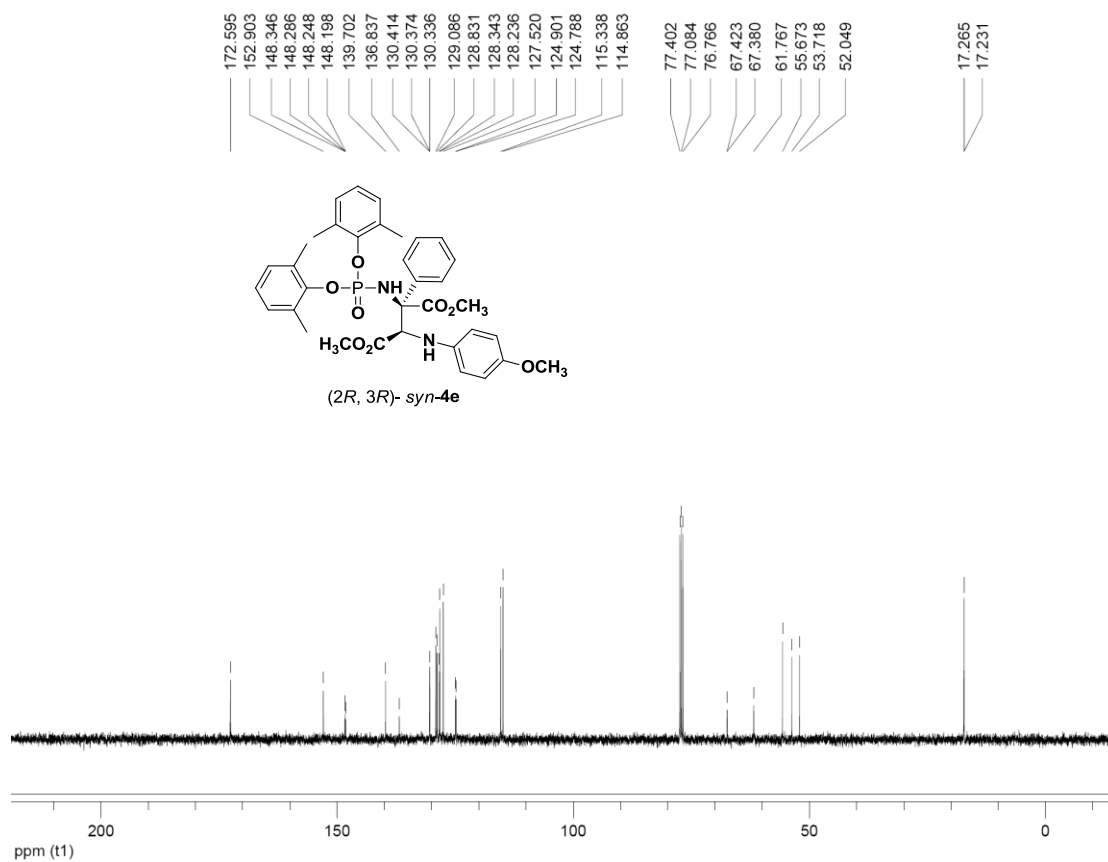
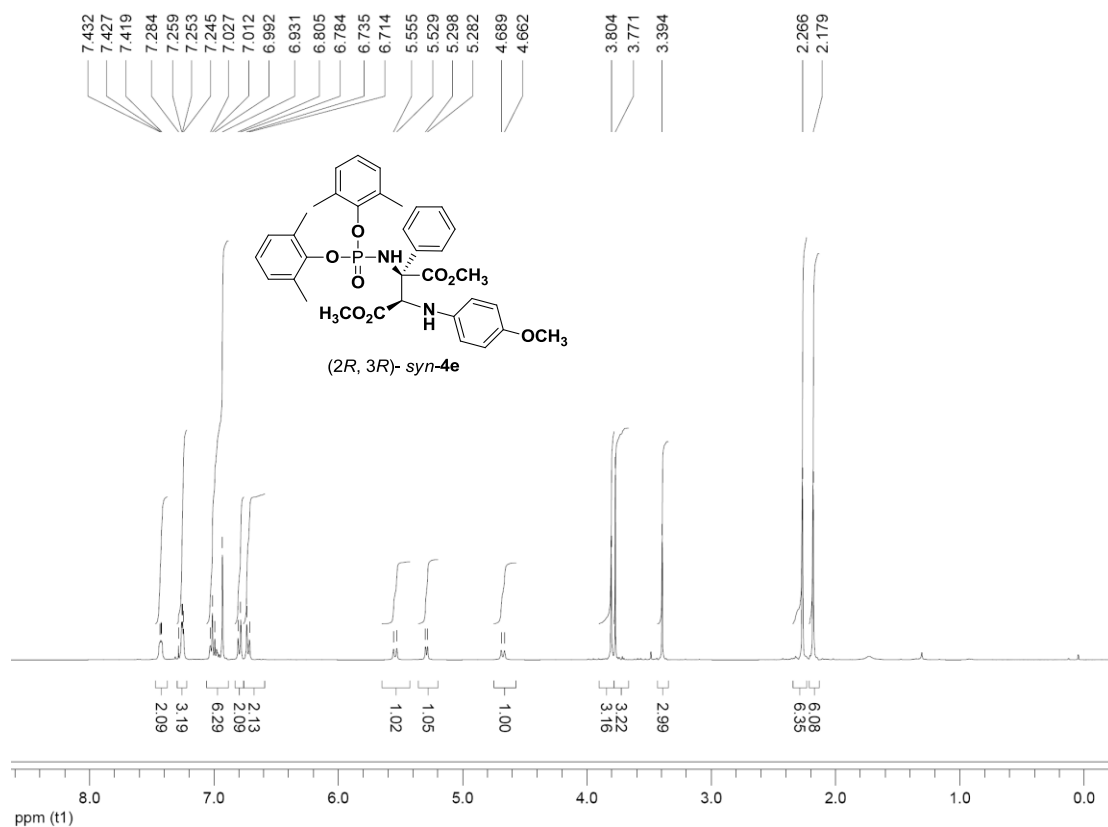




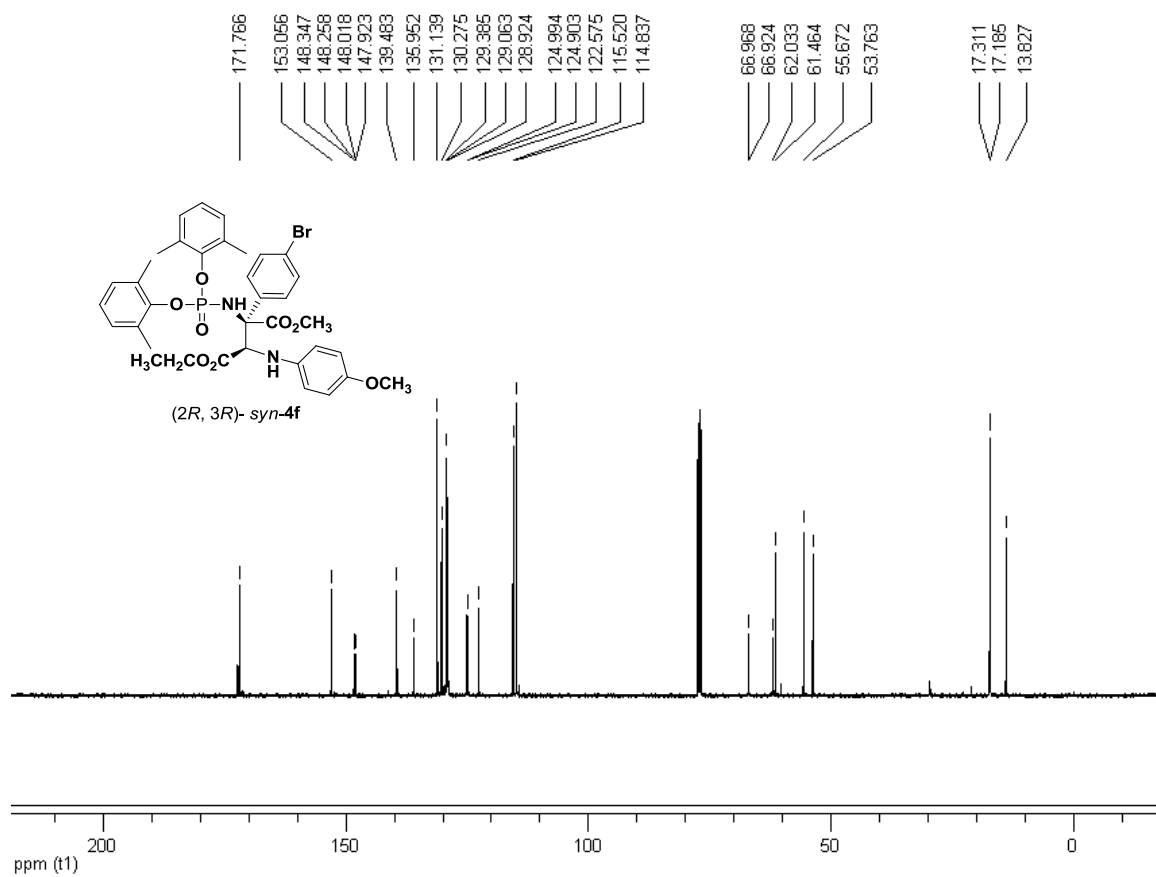
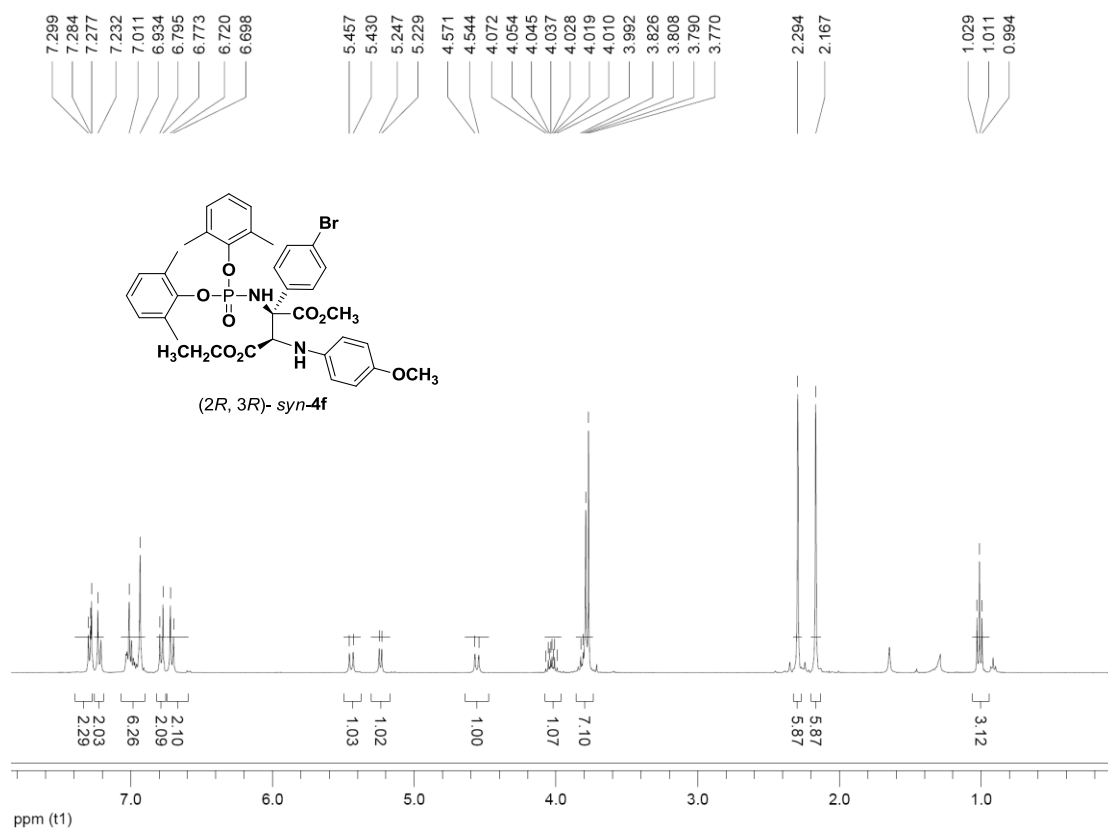


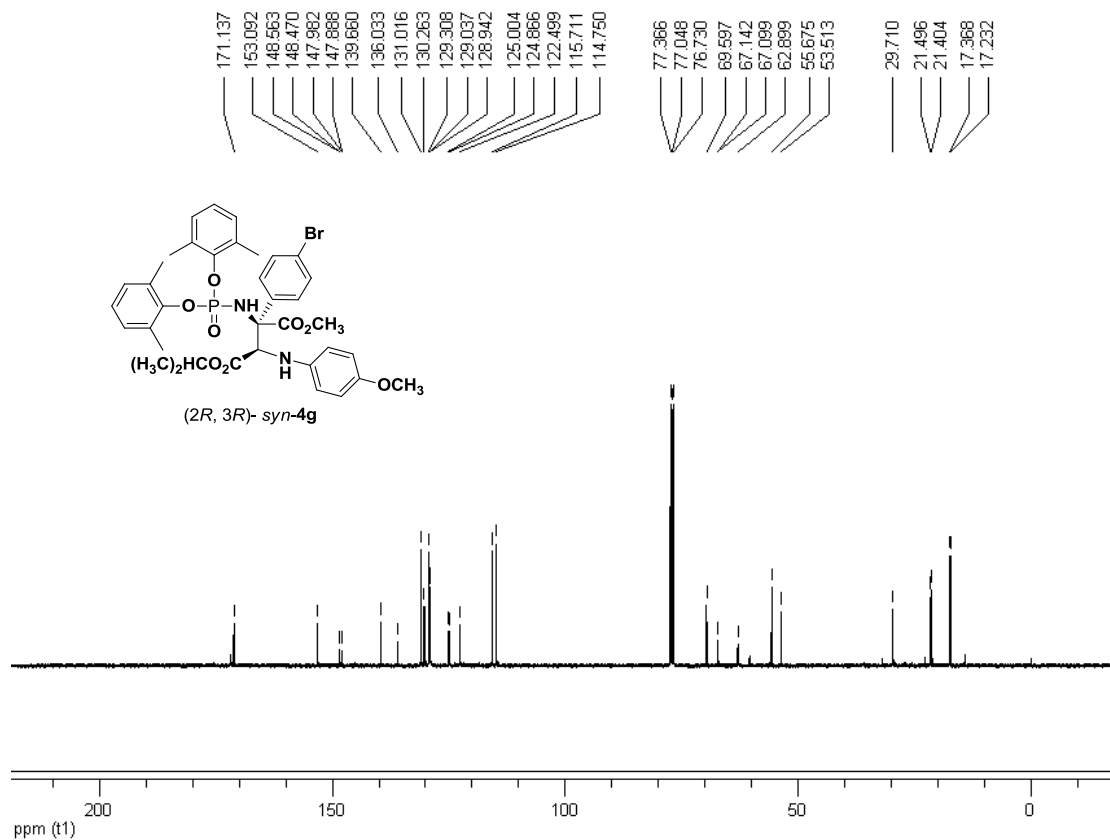
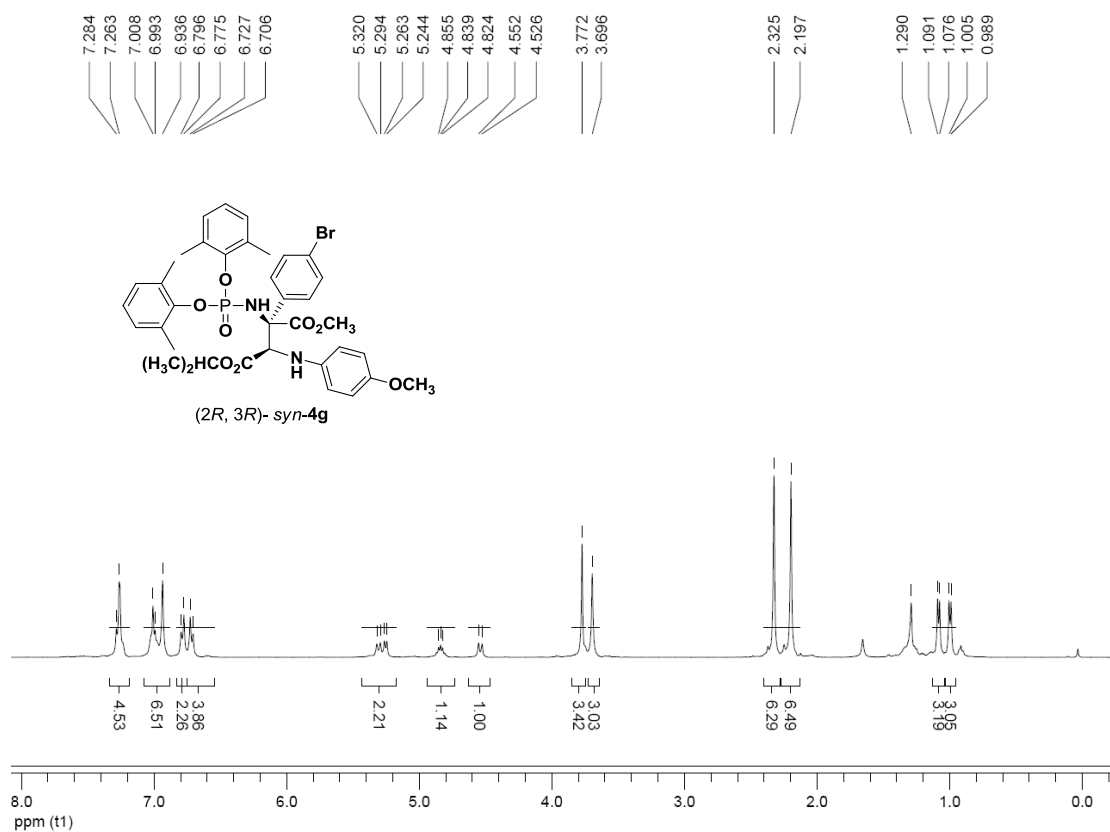


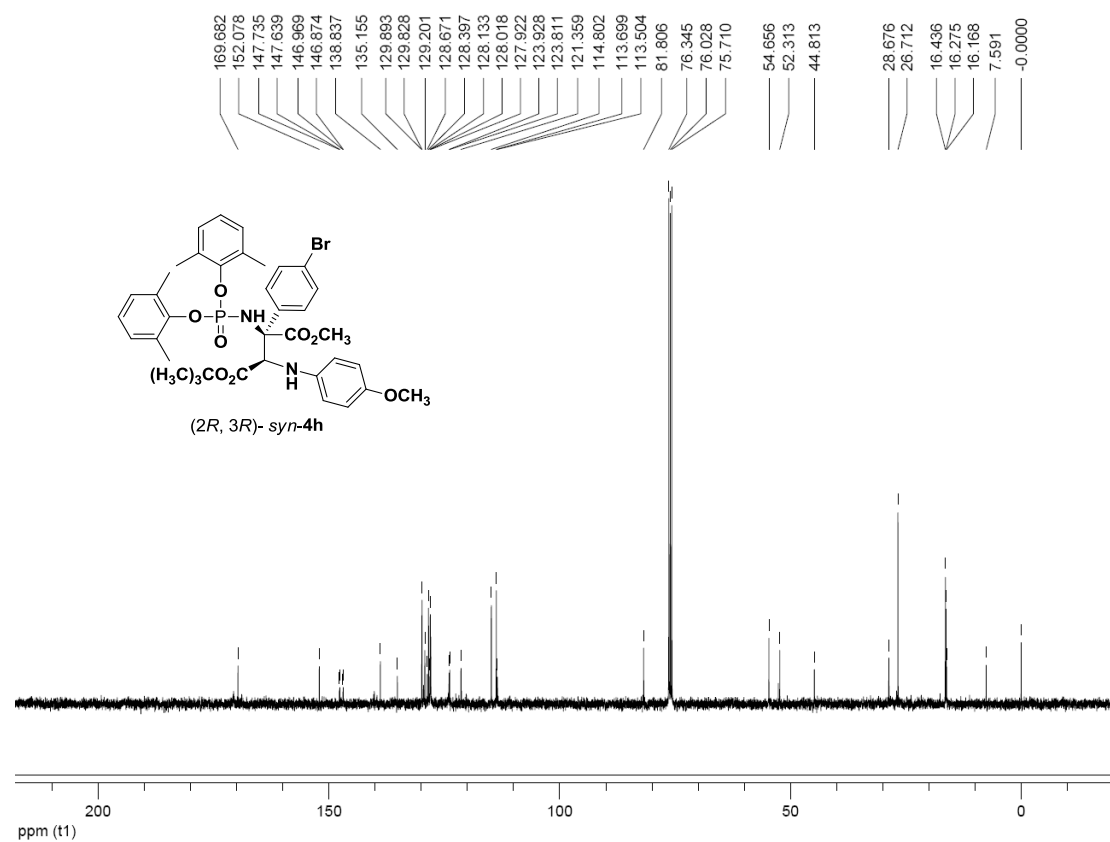
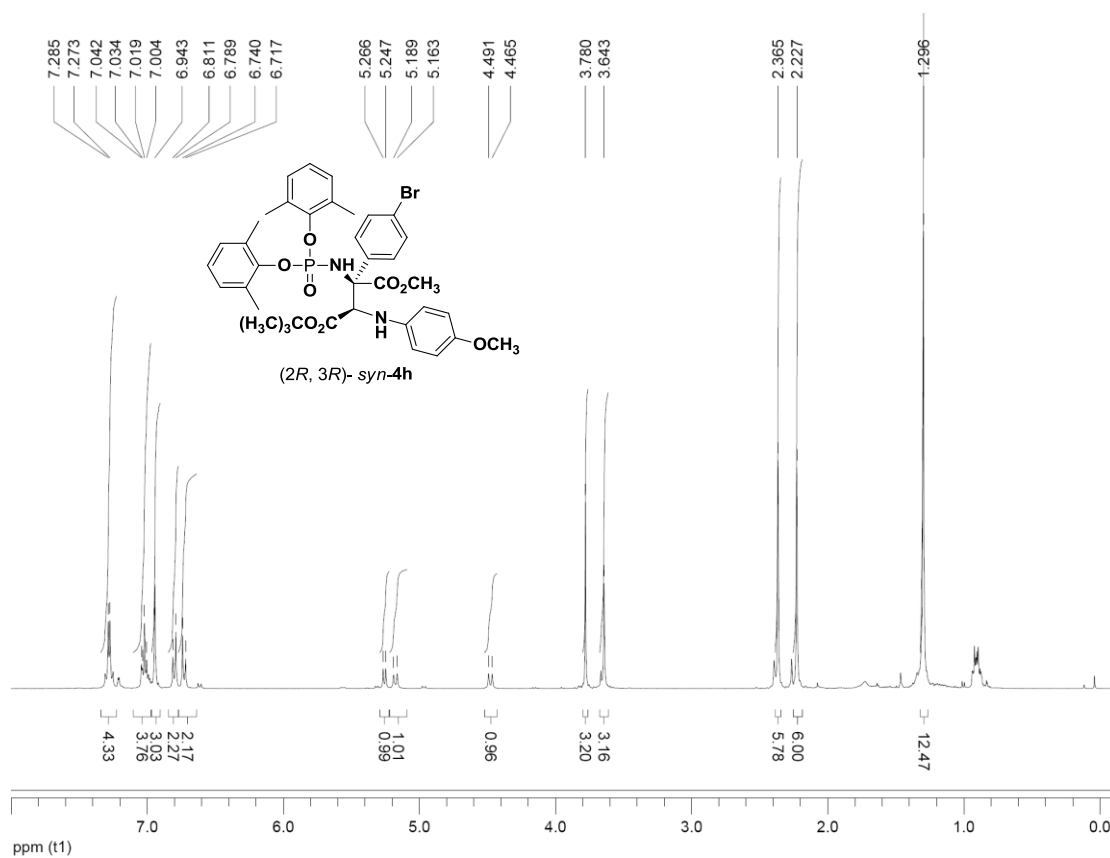


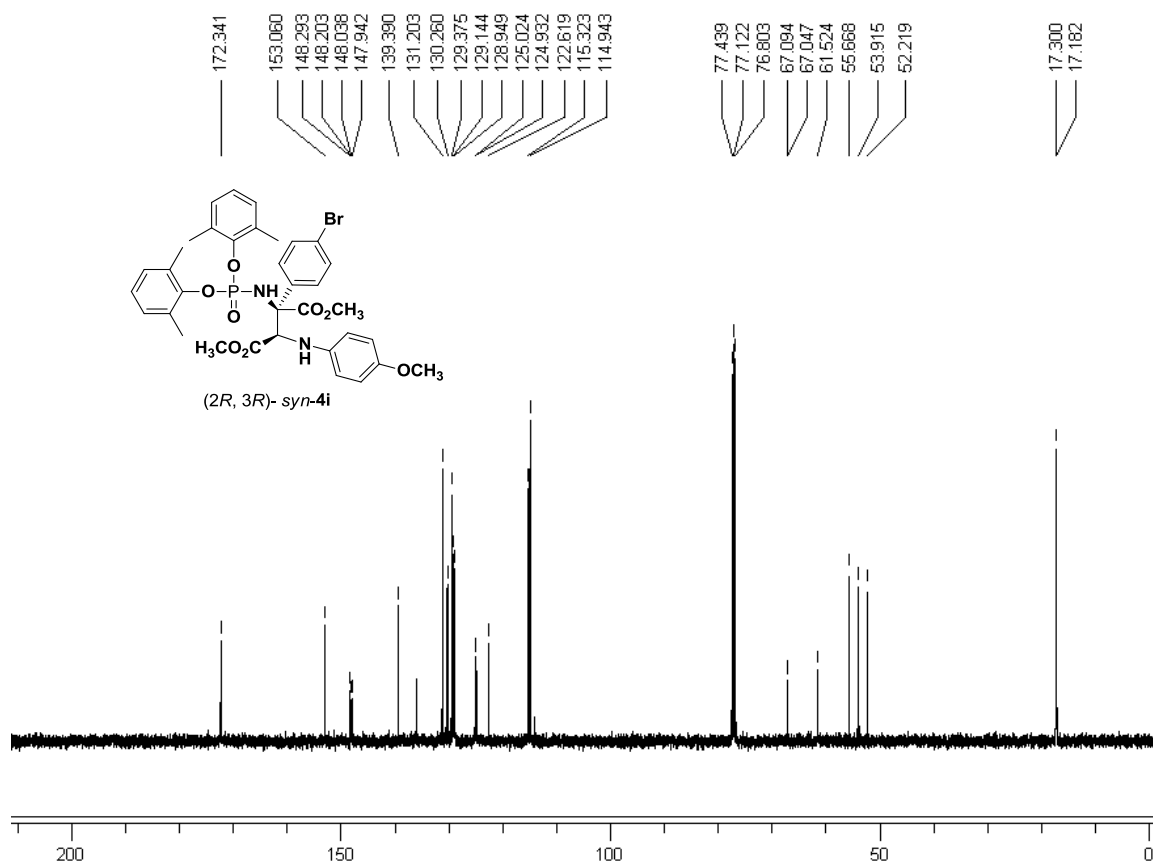
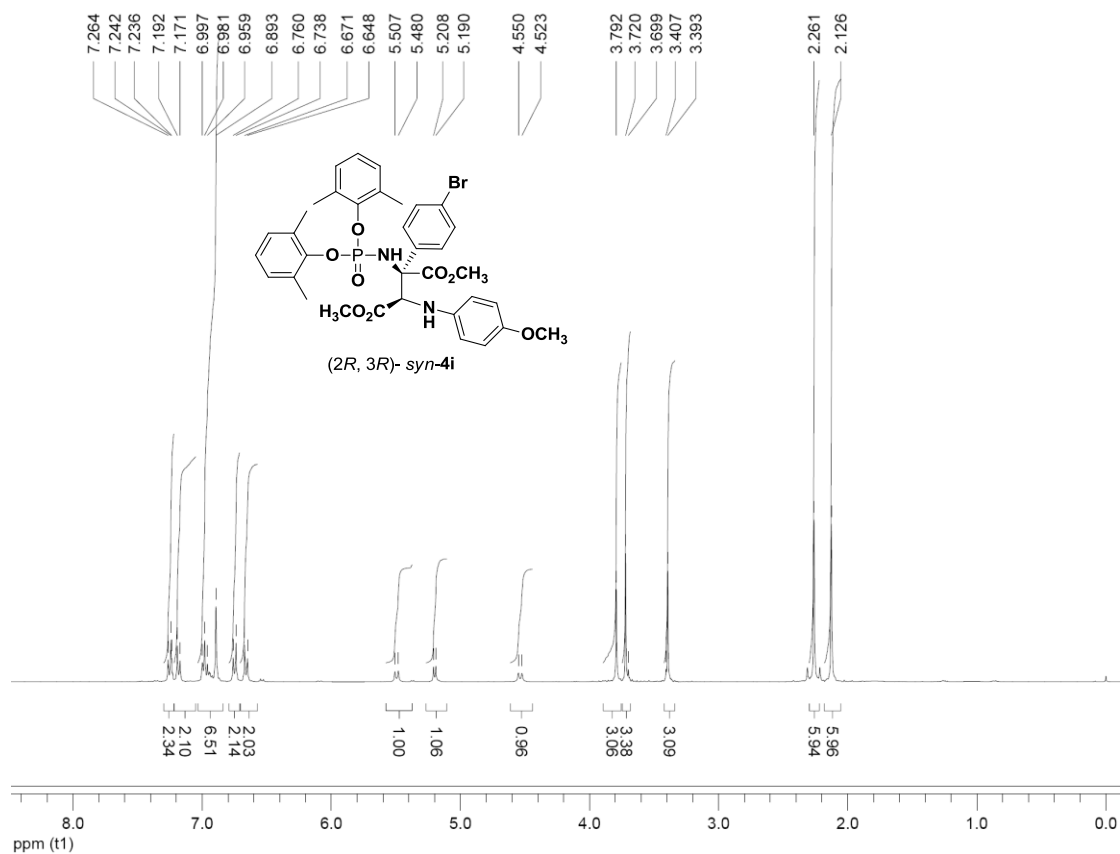


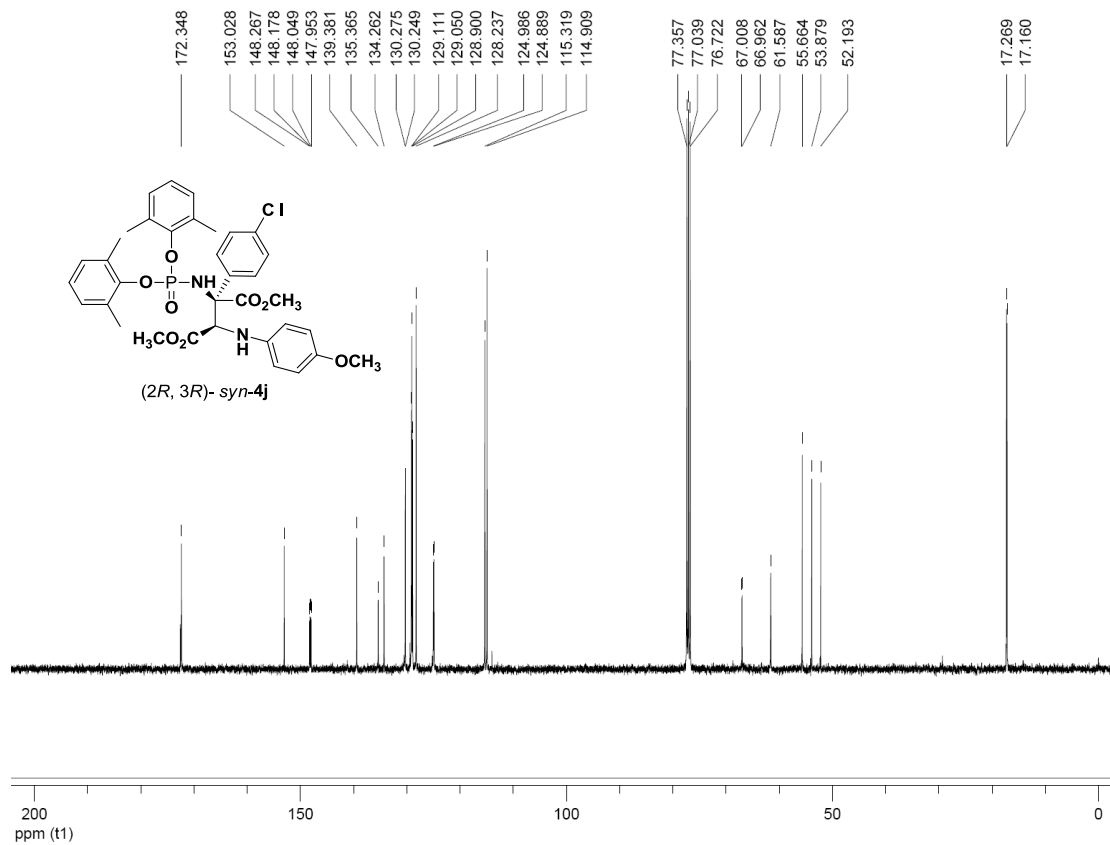
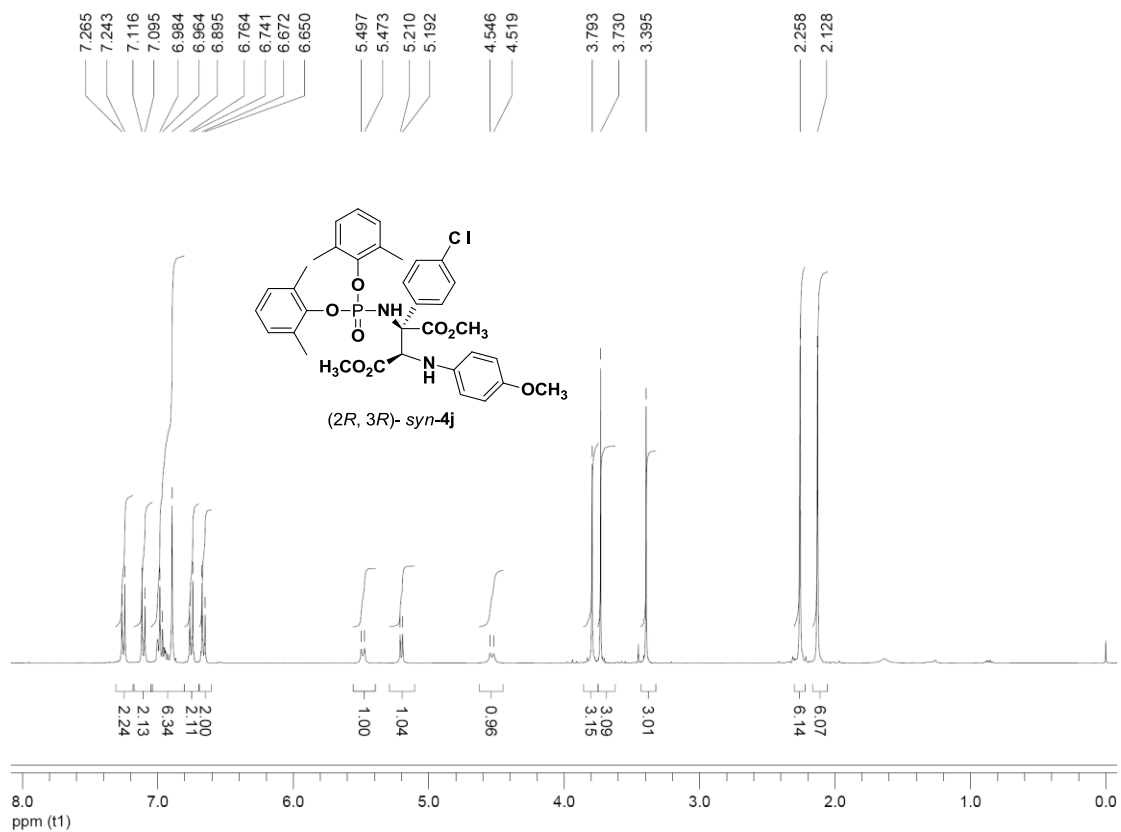


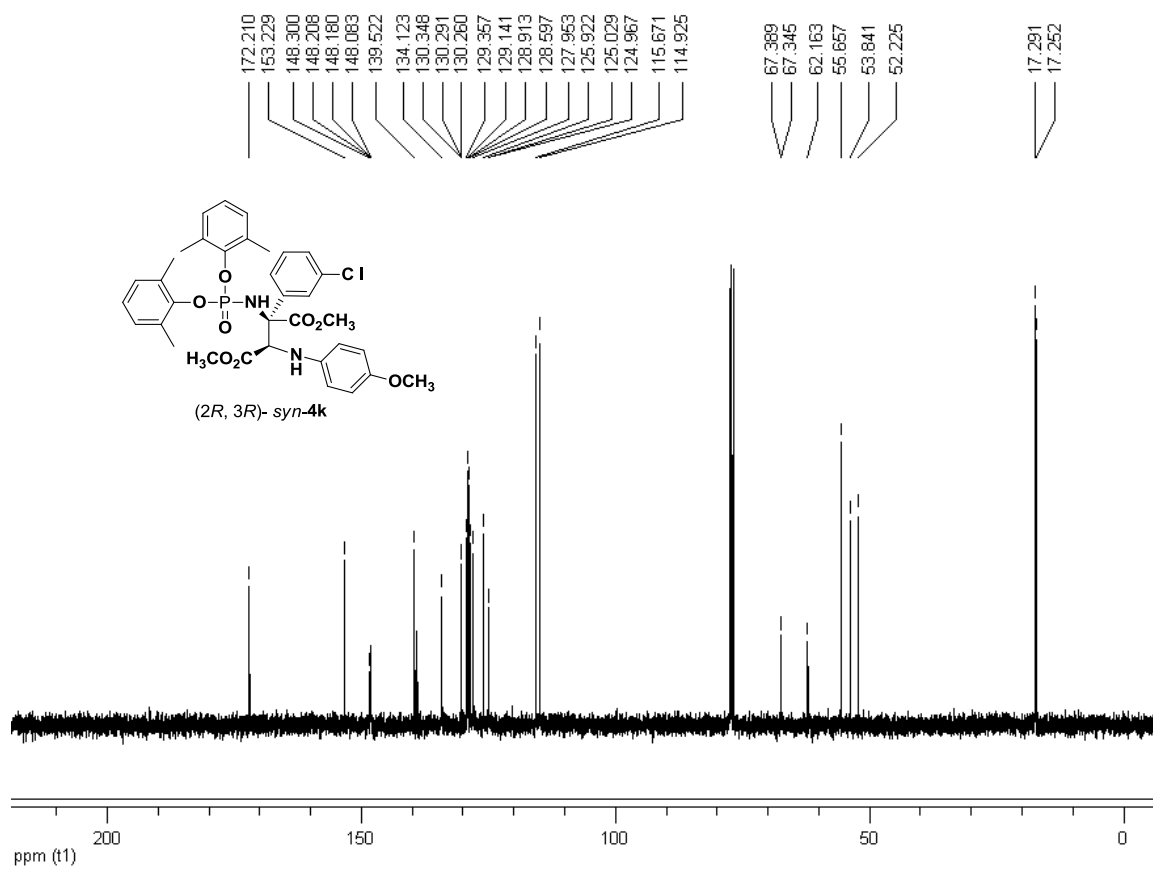
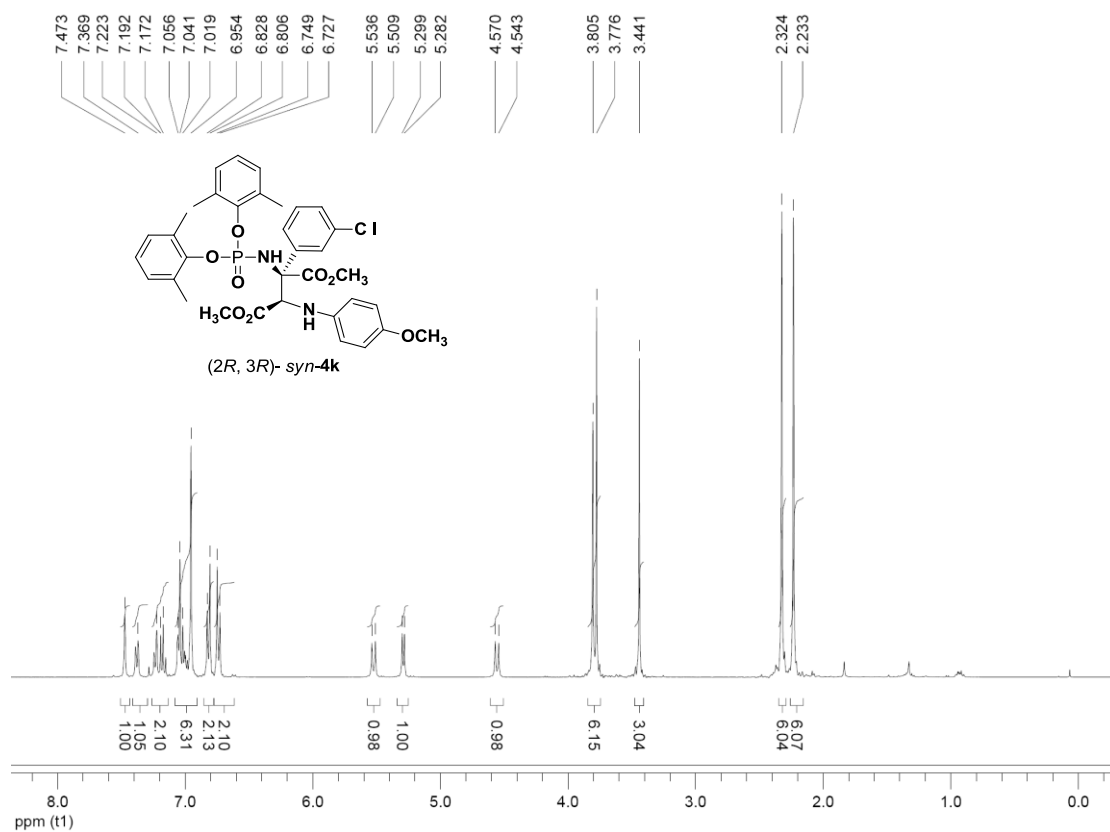


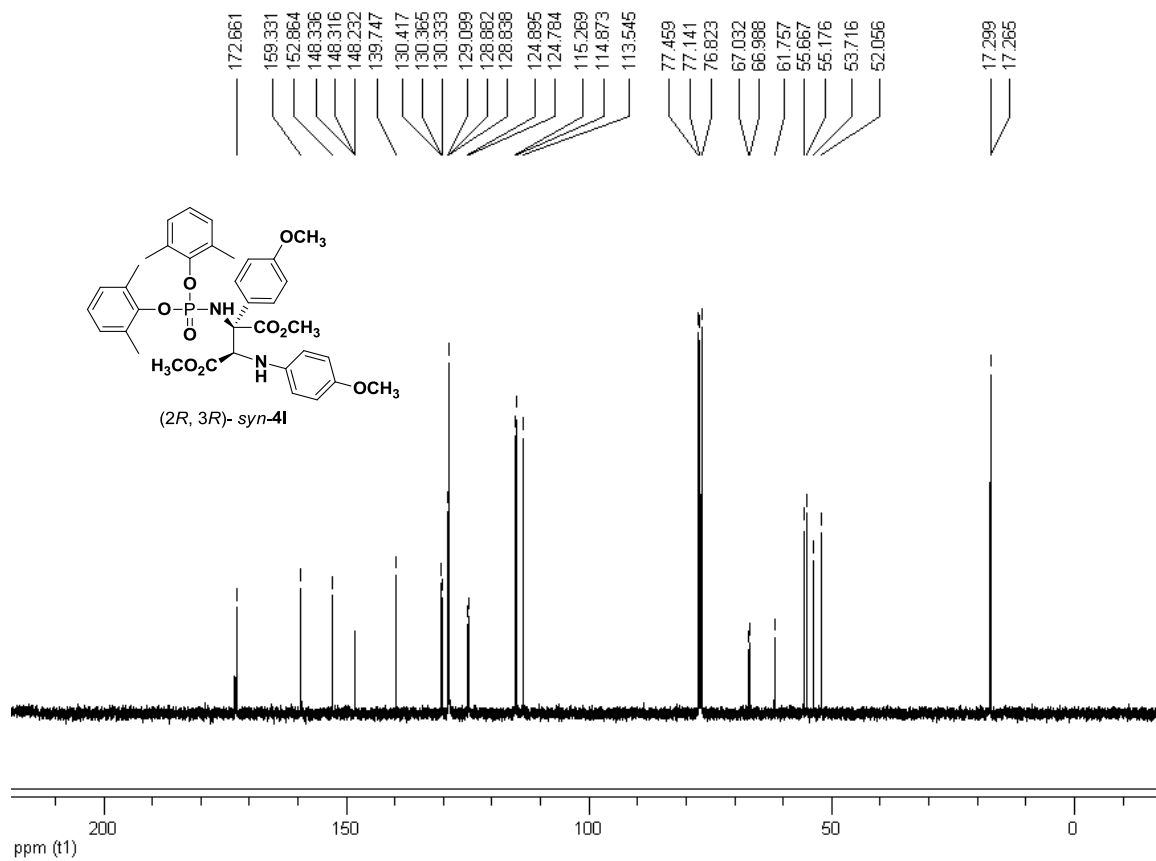
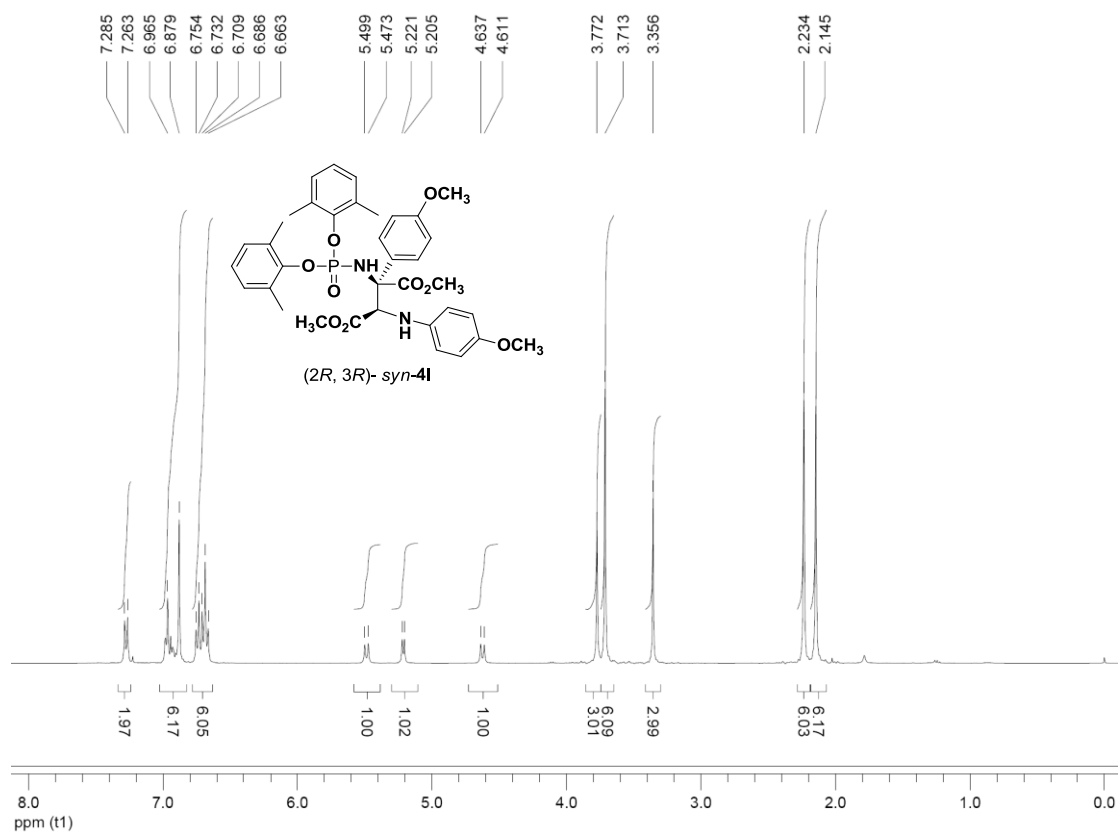


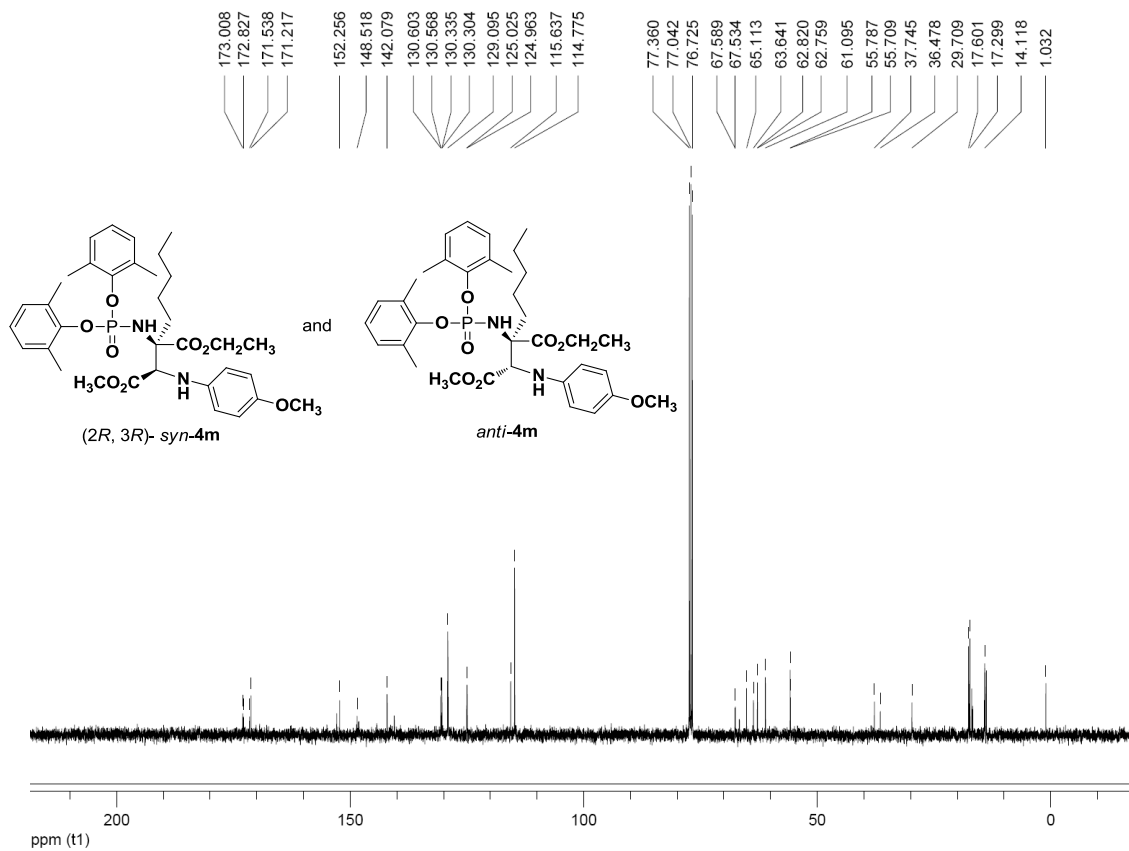
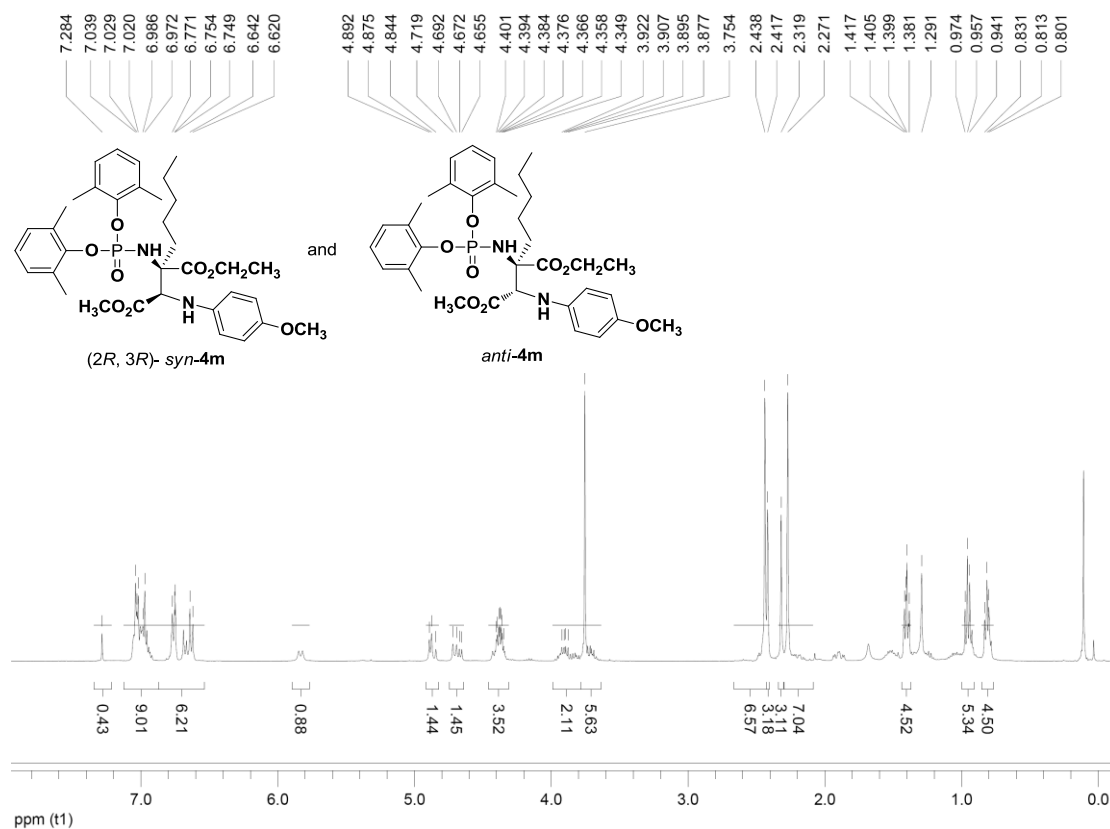






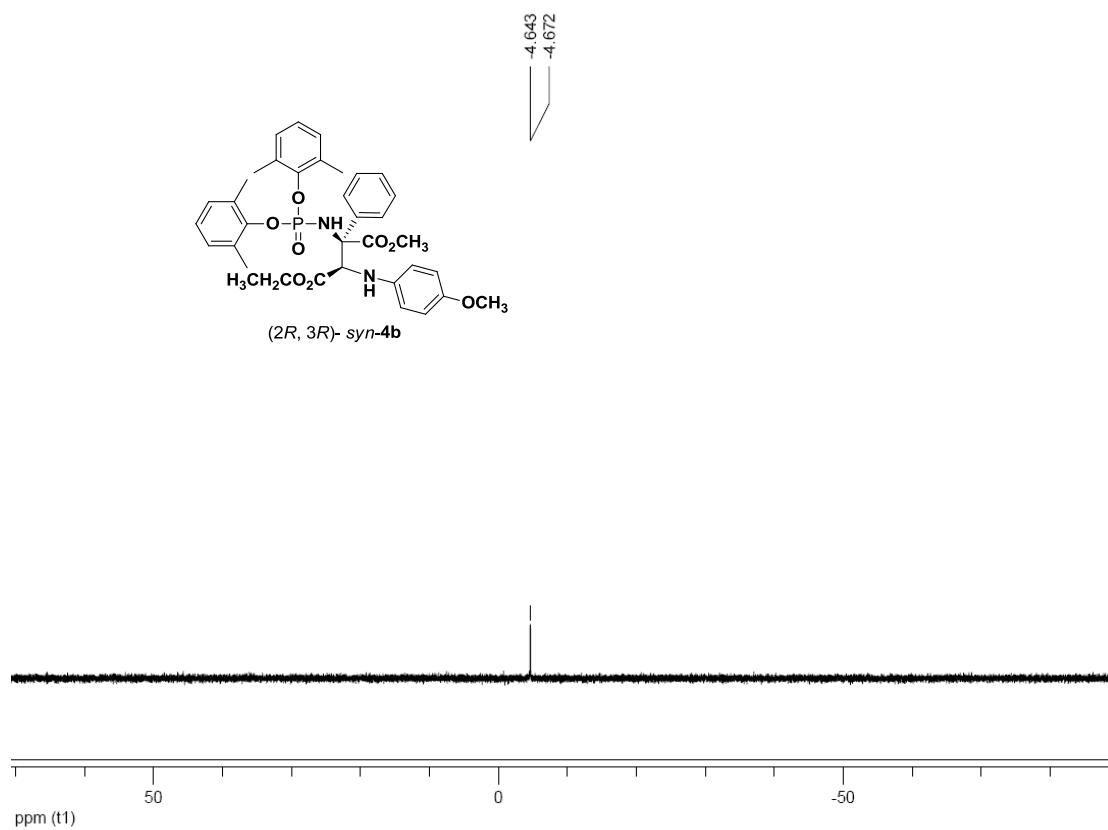
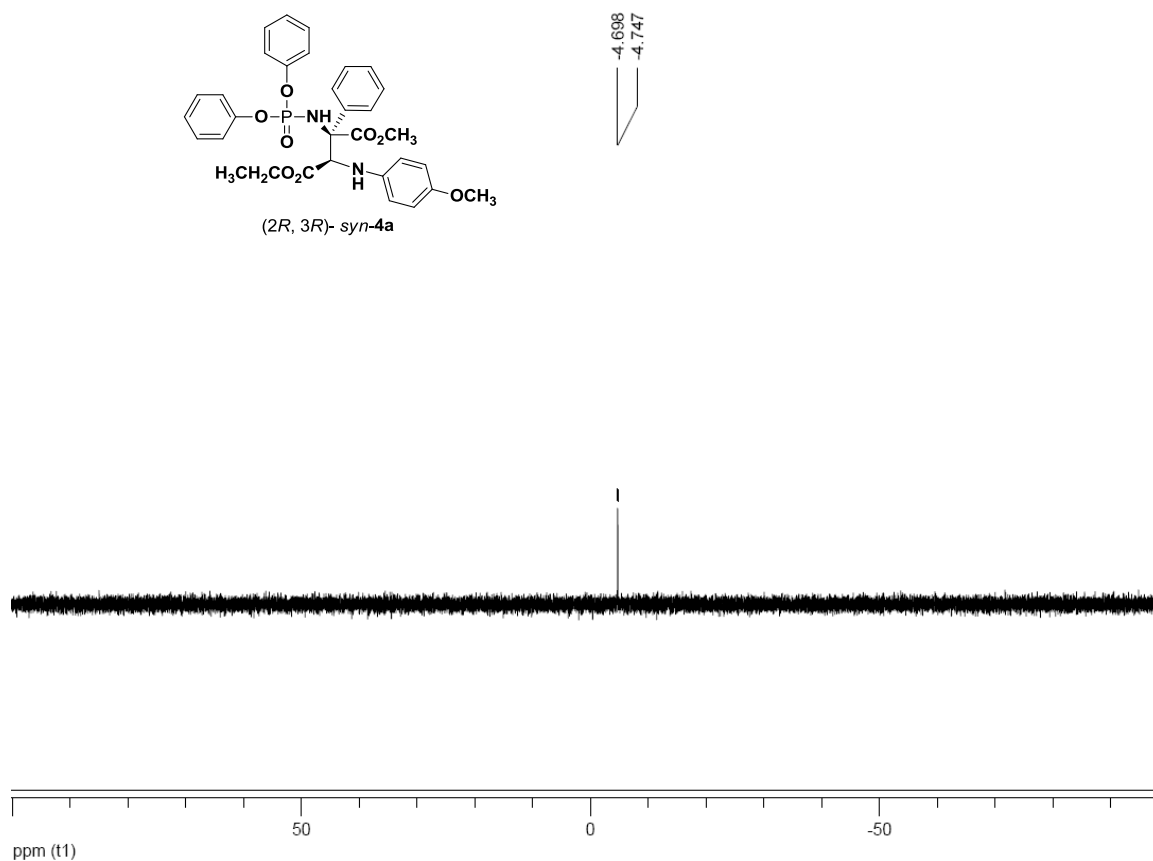


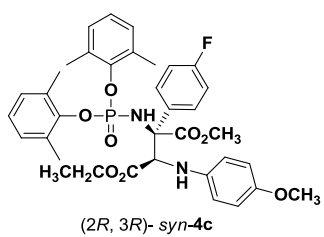




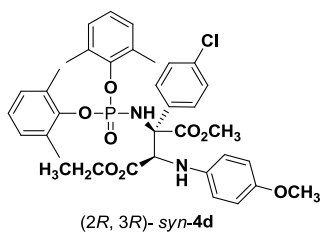
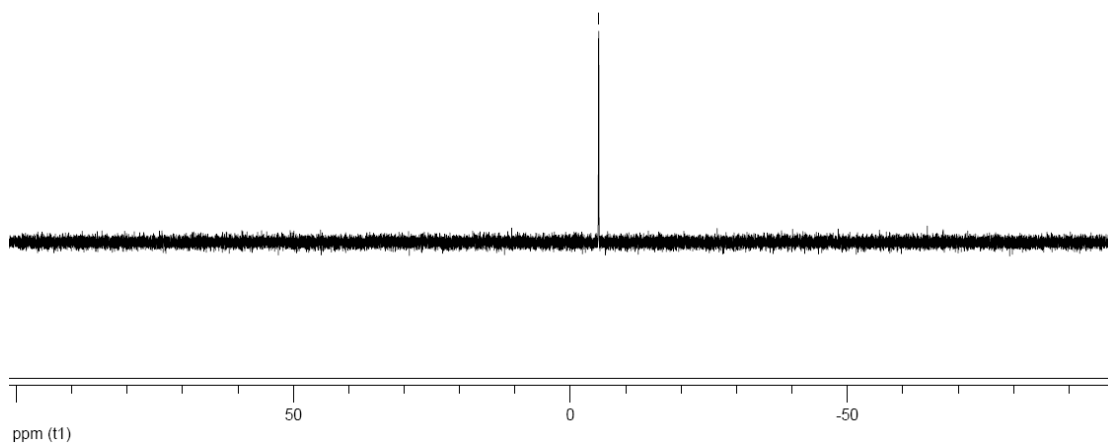


### Representative $^{31}\text{P}$ NMR spectra for new compounds

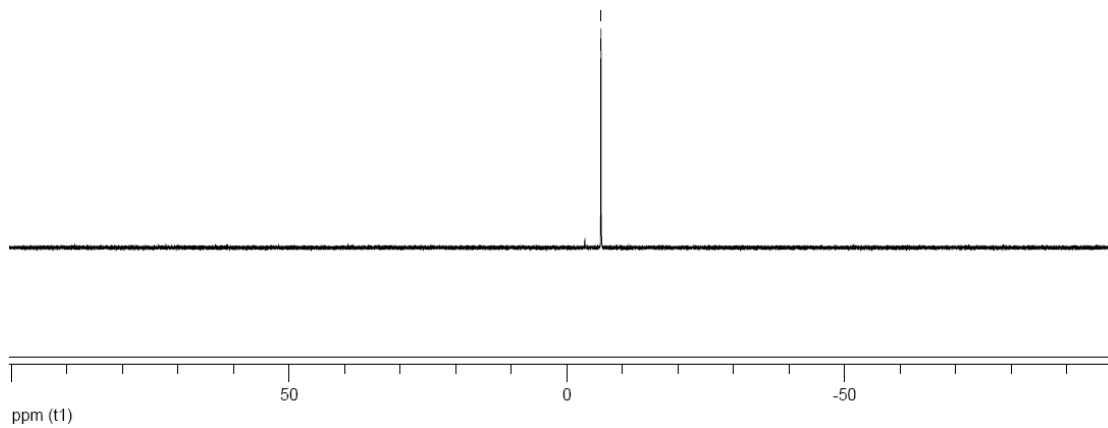


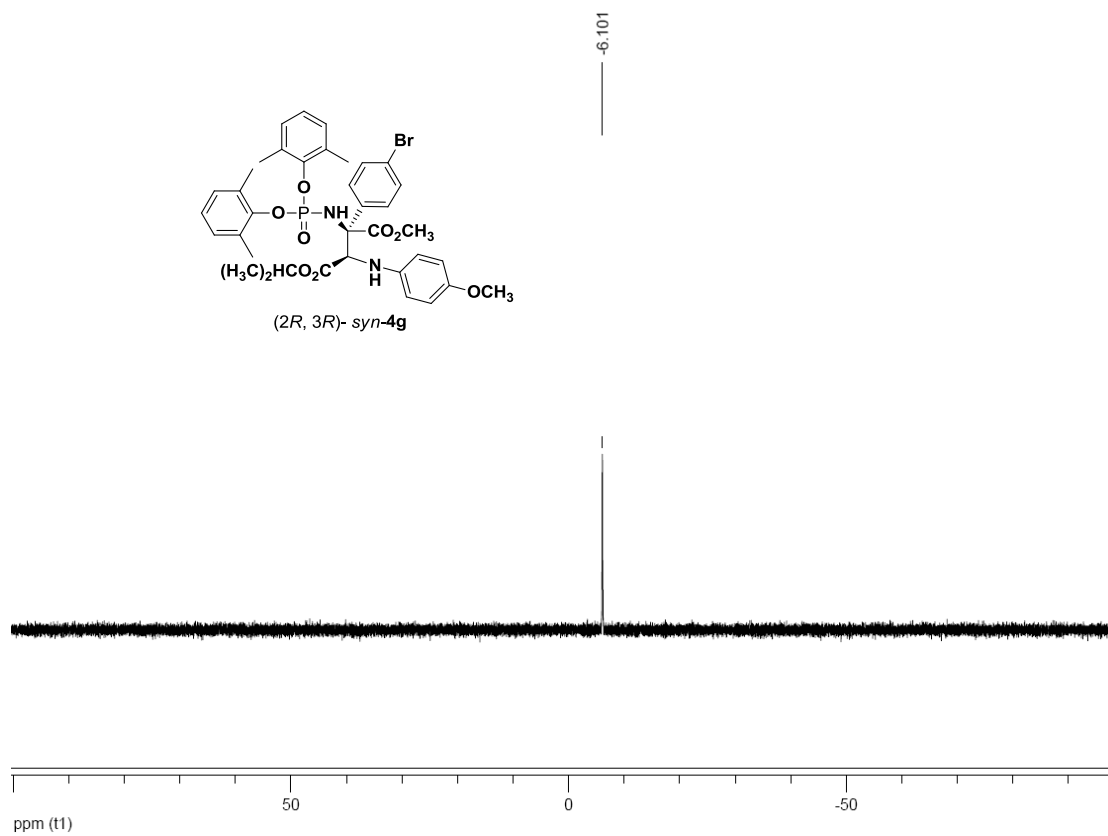
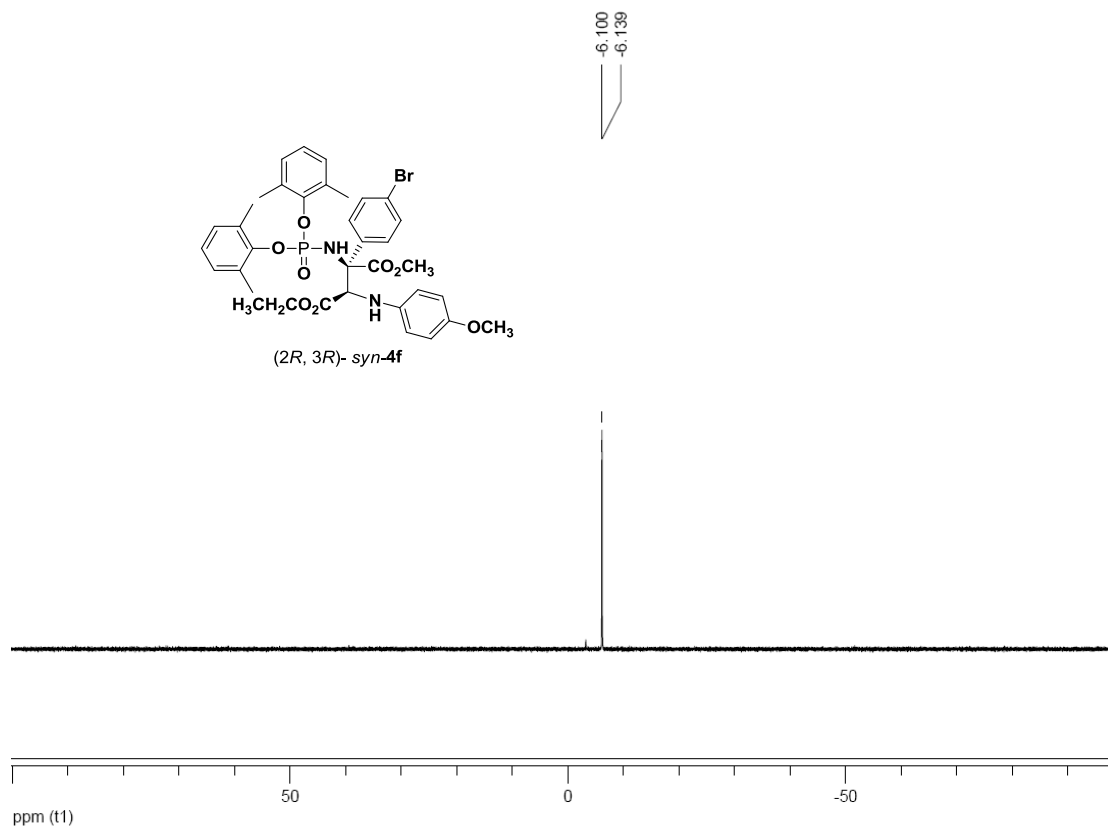


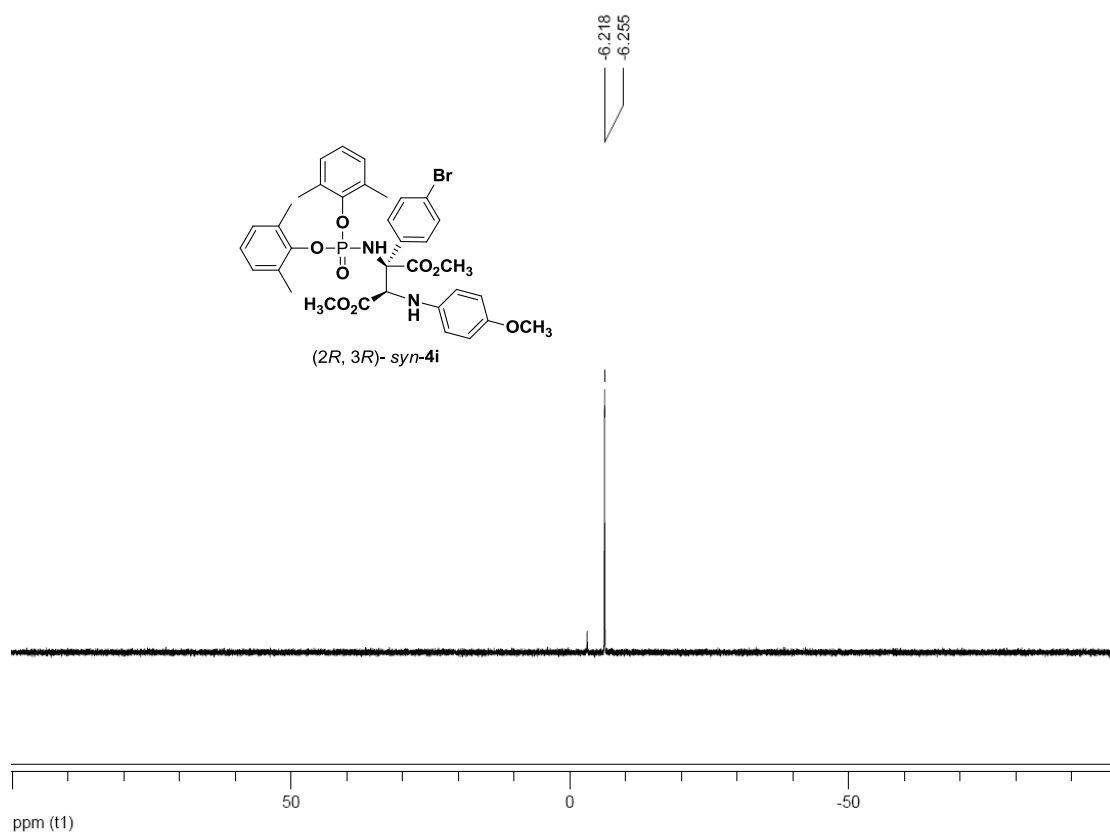
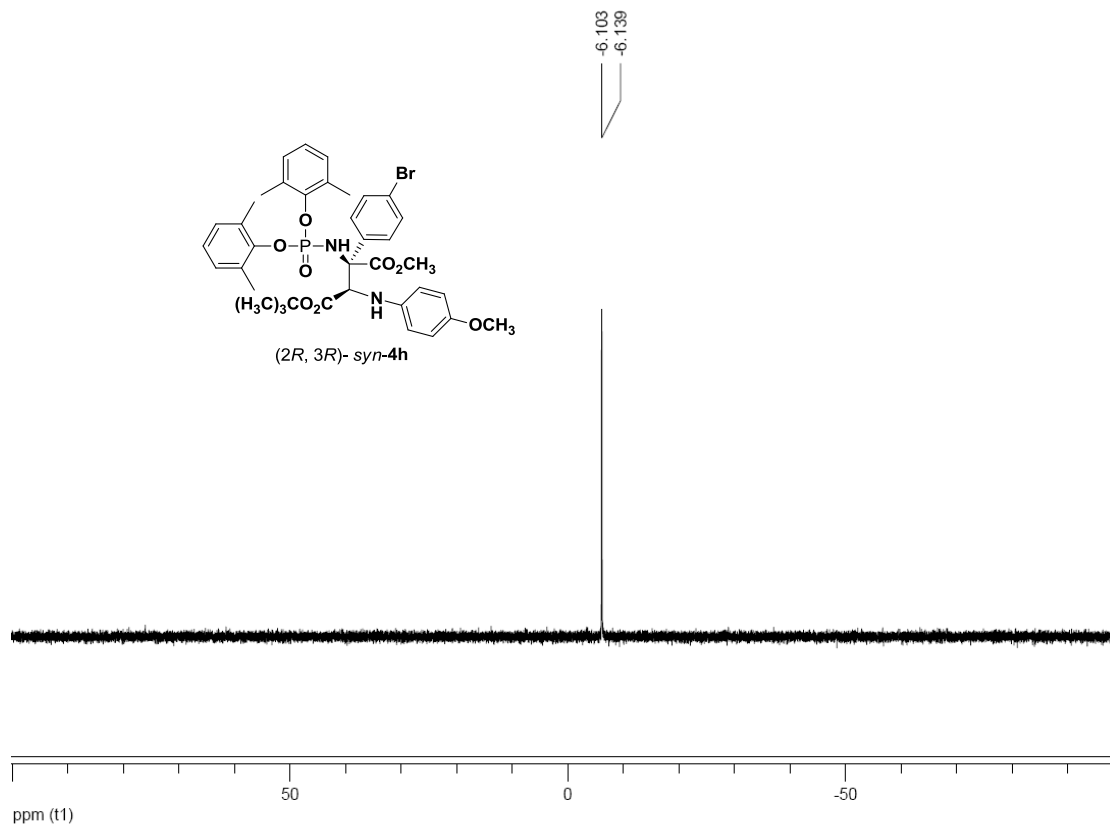
-5.118  
-5.153

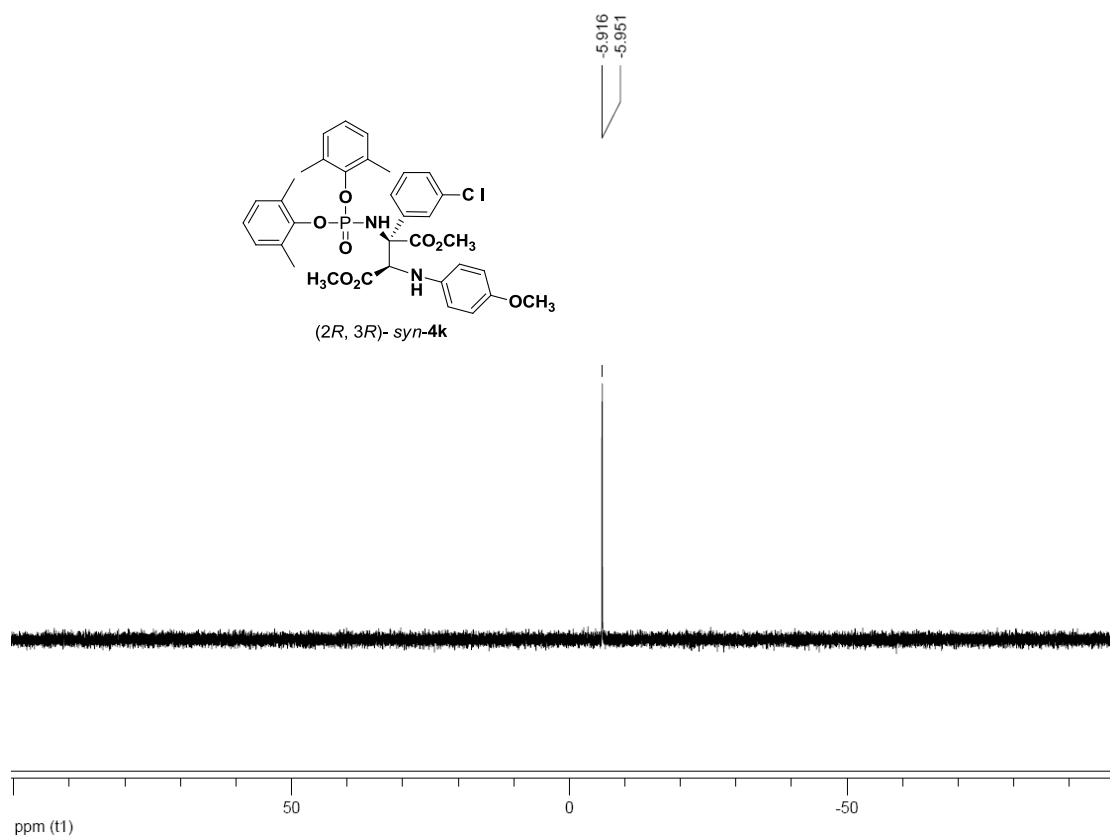
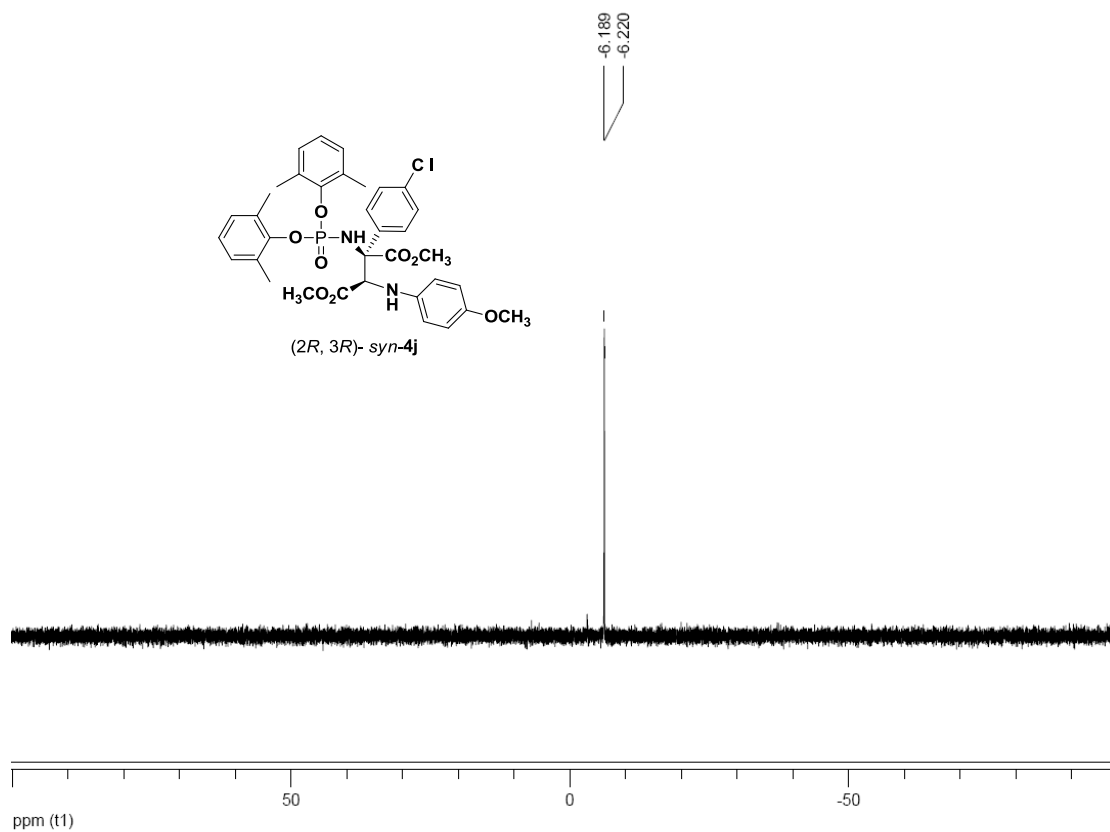


-6.100  
-6.139



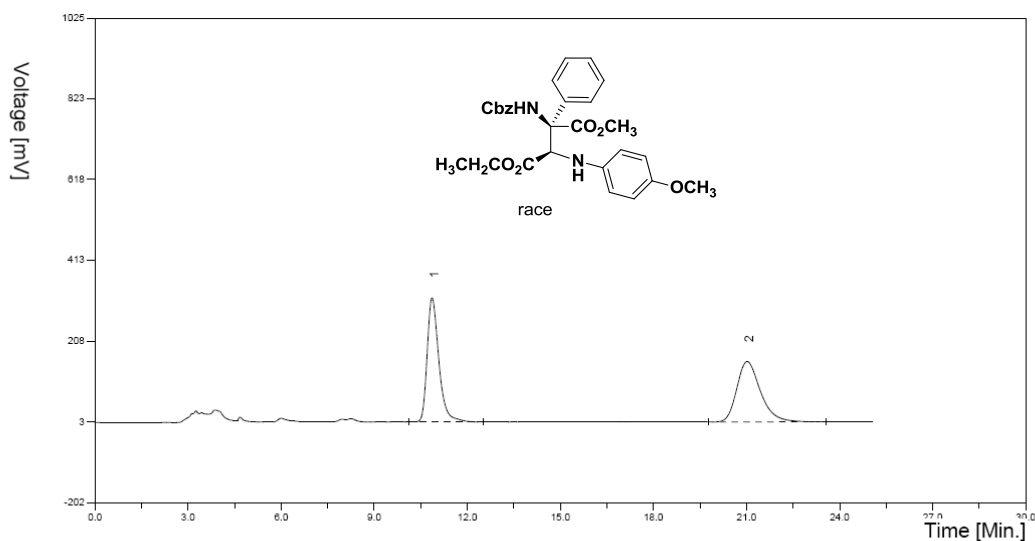






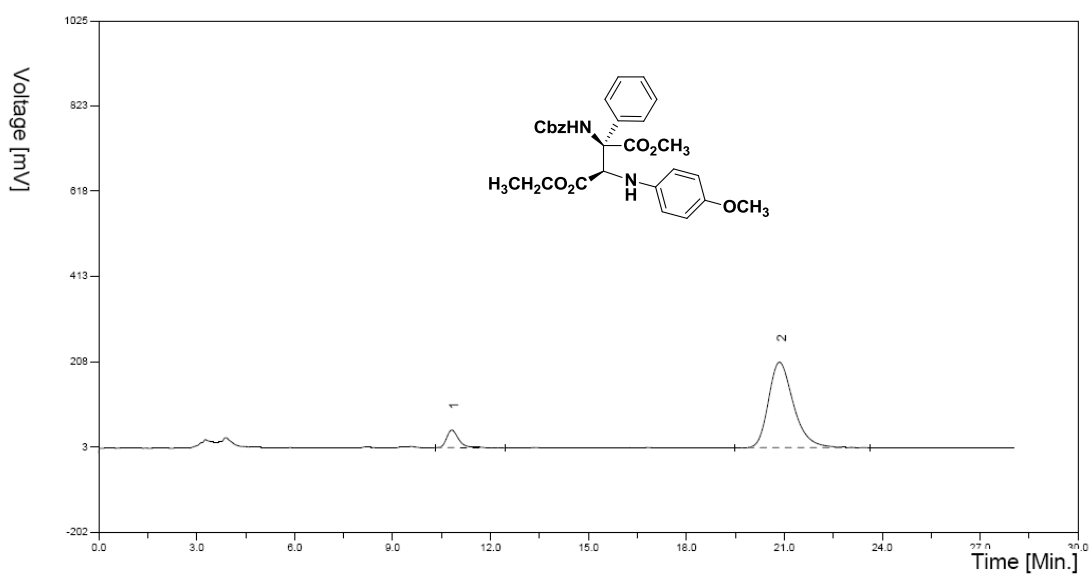
### HPLC spectra of compounds

Chiralpak Column: AD-H  
 M.P: *n*-Hex/*i*-PrOH=70:30  
 UV: 254nm  
 1.0 ml/min  
 Injection Volume: 20µl



组分表

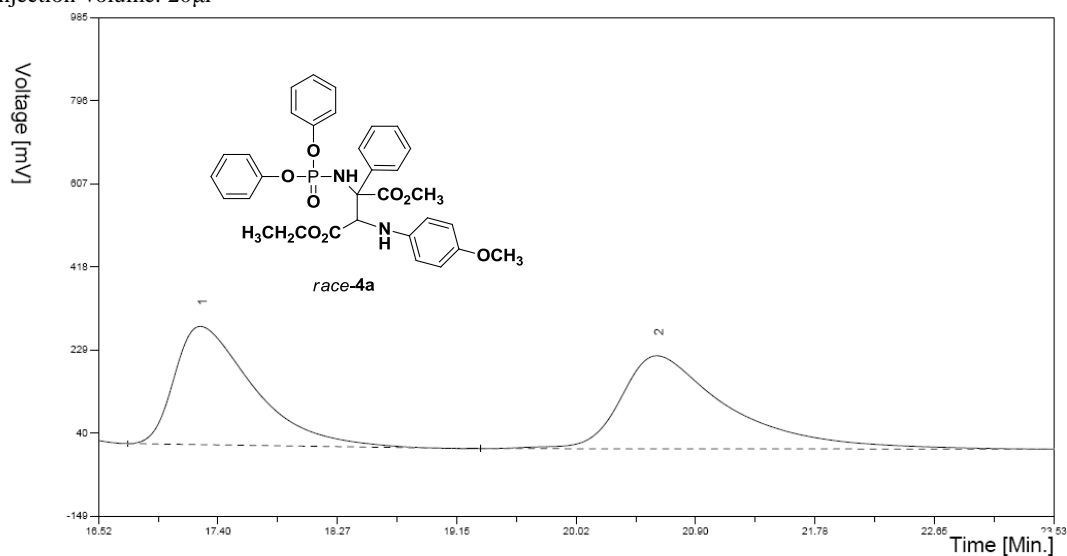
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1	Unknown	10.86	314.63	8256.14	50.4579
2	Unknown	21.02	153.22	8106.29	49.5421
合计			467.85	16362.43	100



组分表

#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	10.81	42.45	1106.67	9.1951
2	Unknown	20.85	205.30	10928.68	90.8049
合计			247.75	12035.34	100

Chiralpak Column: AD-H  
 M.P: *n*-Hex/*i*-PrOH/MeOH=80:10:5  
 UV: 254nm  
 0.5 ml/min  
 Injection Volume: 20µl

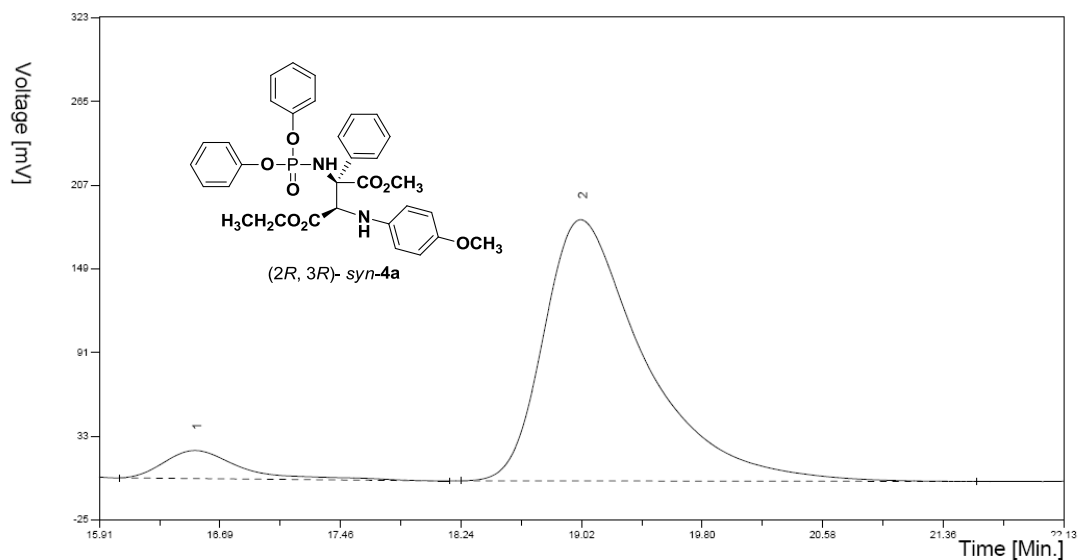


组分表

#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	17.27	267.63	10254.97	48.7958
2	Unknown	20.62	206.74	10761.12	51.2042

合计

474.37 21016.09 100



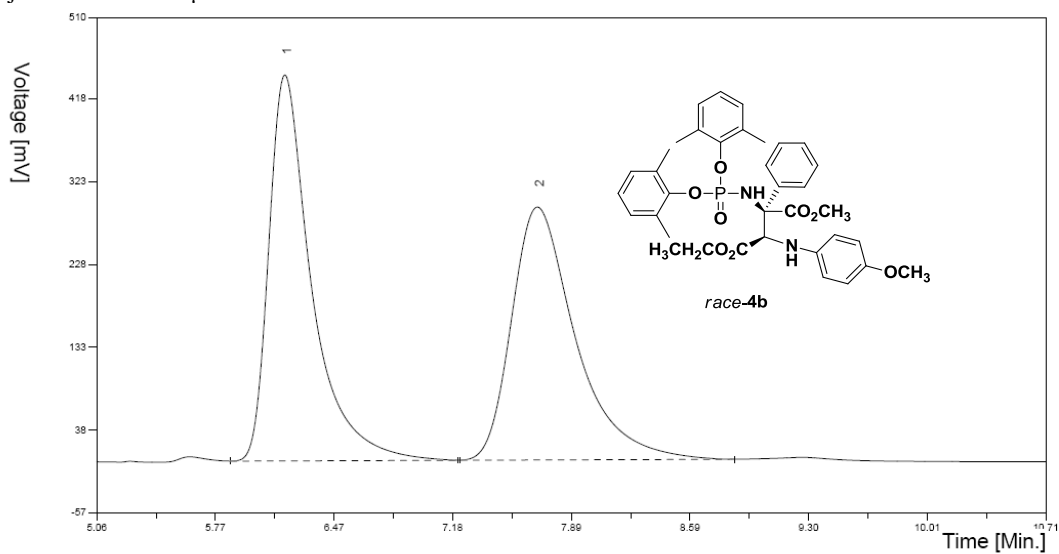
组分表

#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	16.52	19.41	667.92	7.5343
2	Unknown	19.02	180.99	8197.15	92.4657

合计

200.40 8865.08 100

Chiralpak Column: AD-H  
 M.P: *n*-Hex/*i*-PrOH=15:1  
 UV: 254nm  
 1.0 ml/min  
 Injection Volume: 20µl

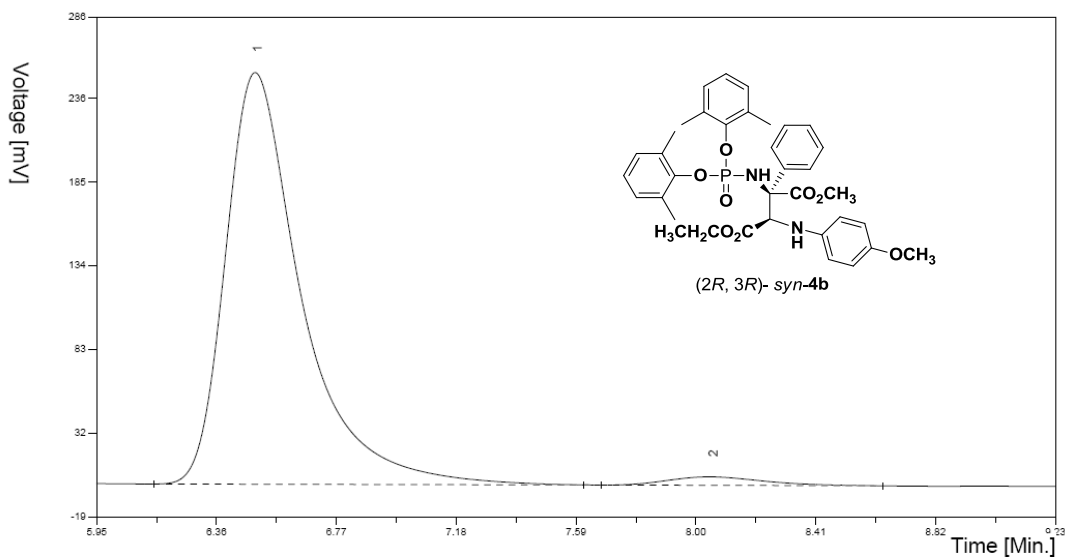


组分表

#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	6.18	442.47	7824.72	50.5479
2	Unknown	7.69	290.01	7855.08	49.4521

合计

732.48 15479.80 100



组分表

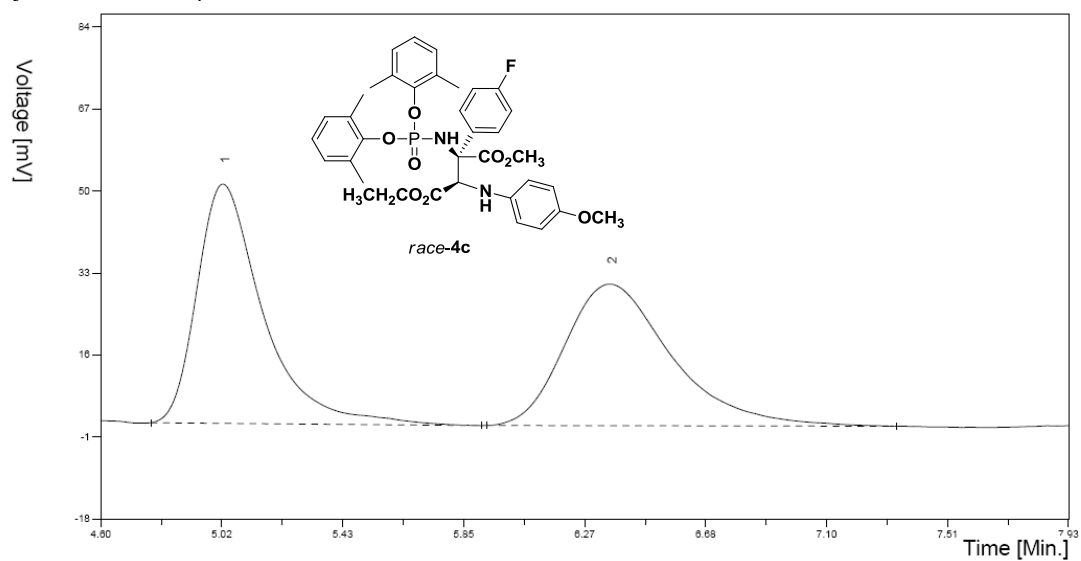
#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	6.49	250.62	4525.93	97.5203
2	Unknown	8.05	5.16	115.09	2.4797

合计

255.77 4641.01 100



Chiralpak Column: AD-H  
 M.P: *n*-Hex/*i*-PrOH=10:1  
 UV: 254nm  
 1.0 ml/min  
 Injection Volume: 20µl

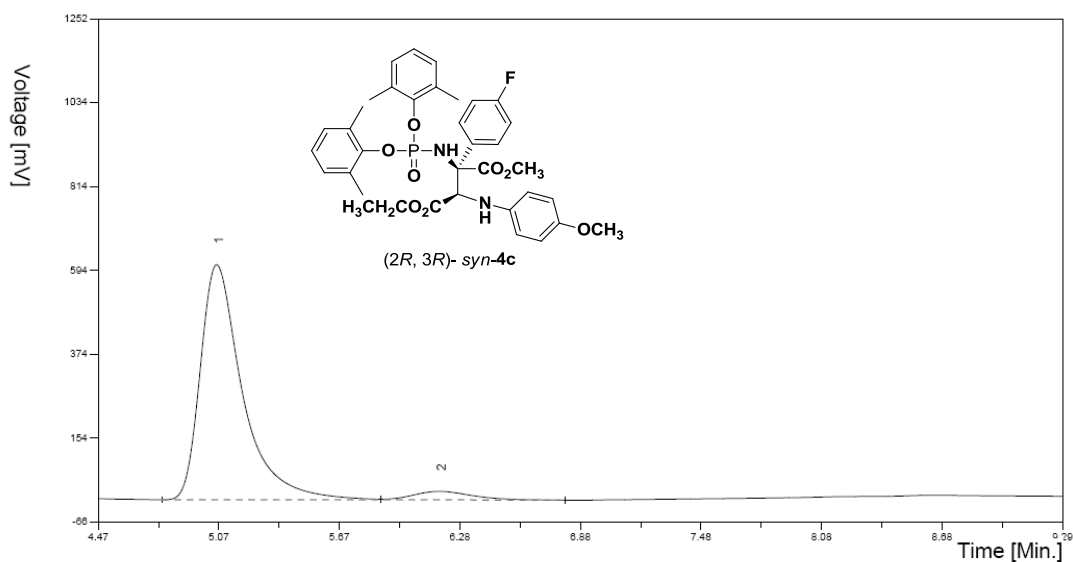


组分表

#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	5.02	49.57	783.30	51.1789
2	Unknown	6.35	29.34	747.21	48.8211

合计

78.92 1530.51 100



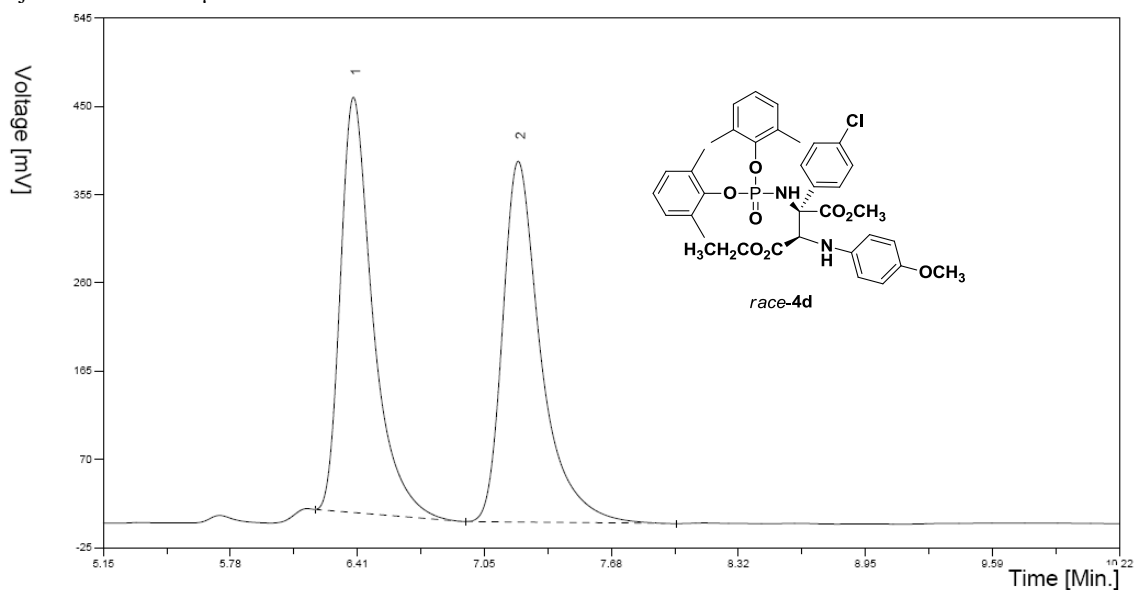
组分表

#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	5.06	616.28	9017.85	95.2450
2	Unknown	6.17	22.40	450.21	4.7550

合计

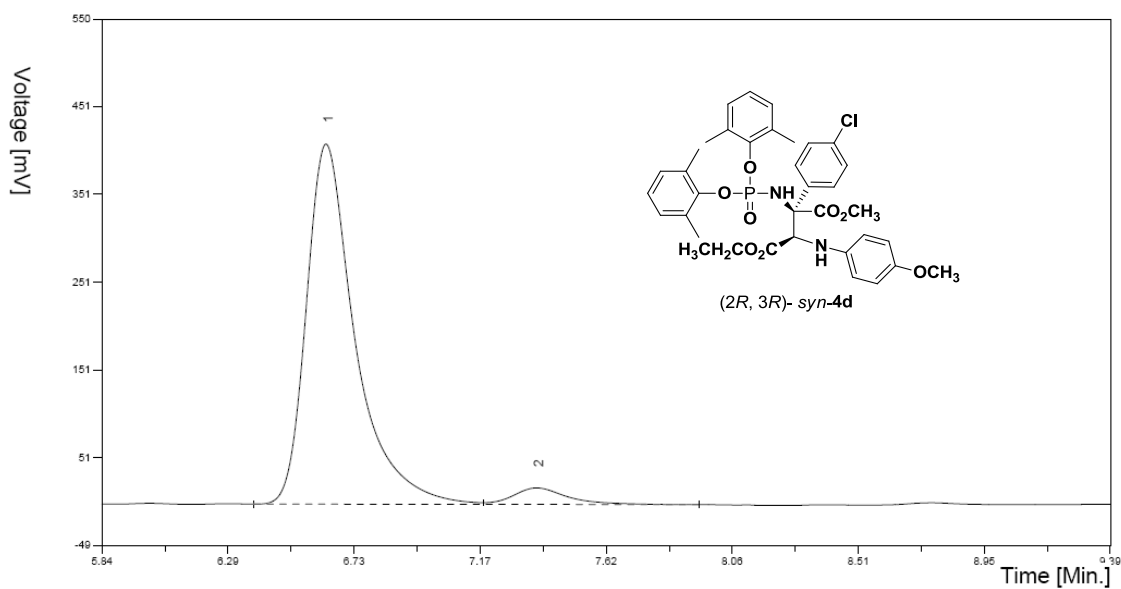
638.68 9468.06 100

Chiralpak Column: IA  
 M.P: *n*-Hex/*i*-PrOH=15:1  
 UV: 254nm  
 1.0 ml/min  
 Injection Volume: 20µl



组分表

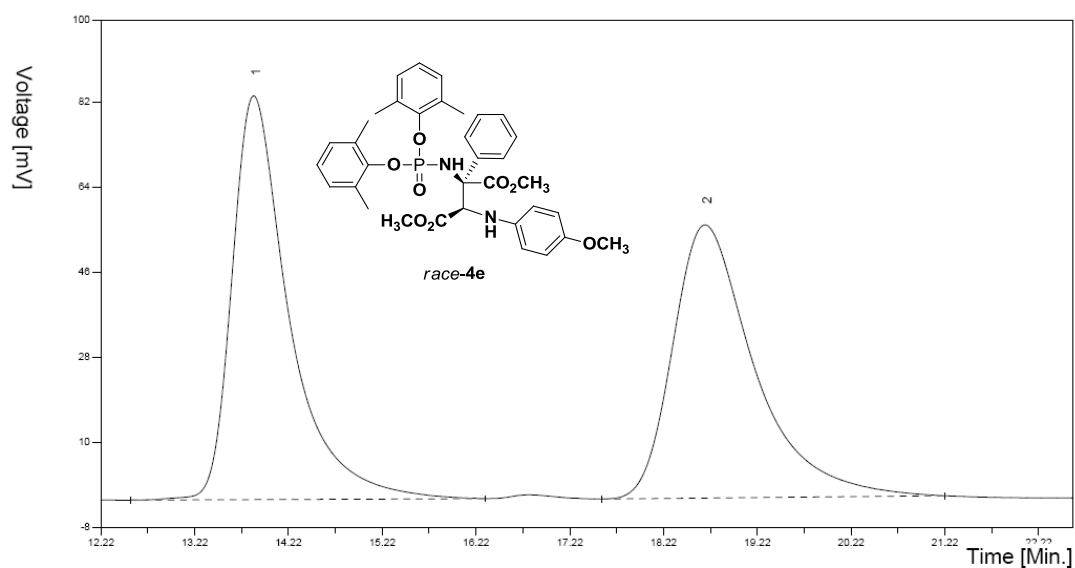
#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	6.39	444.88	4876.44	49.7090
2	Unknown	7.22	383.00	4933.54	50.2910
合计			827.88	9809.99	100



组分表

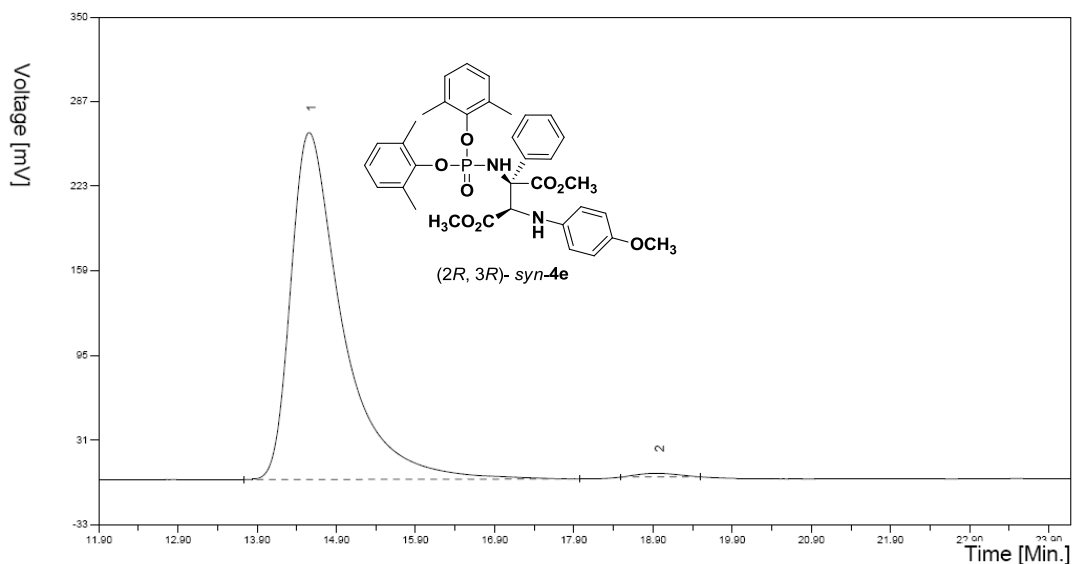
#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	6.63	410.13	4882.33	95.1096
2	Unknown	7.37	18.77	251.04	4.8904
合计			428.90	5133.37	100

Chiralpak Column: AD-H  
 M.P: *n*-Hex/*i*-PrOH=30:1  
 UV: 254nm  
 1.0 ml/min  
 Injection Volume: 20µl



组分表

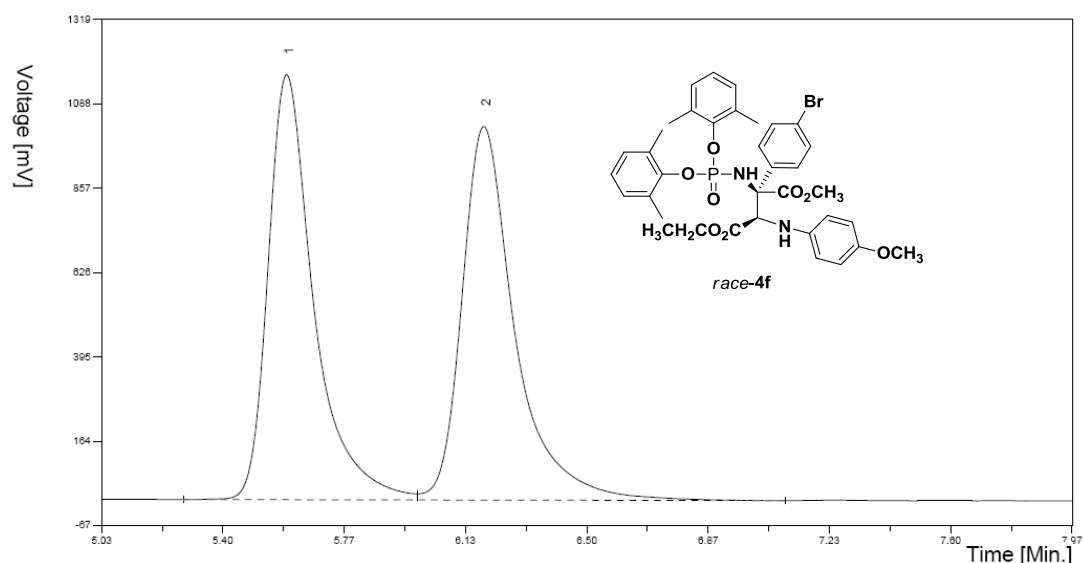
#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	13.85	85.35	3614.40	50.8745
2	Unknown	18.66	57.75	3490.14	49.1255
合计			143.10	7104.54	100



组分表

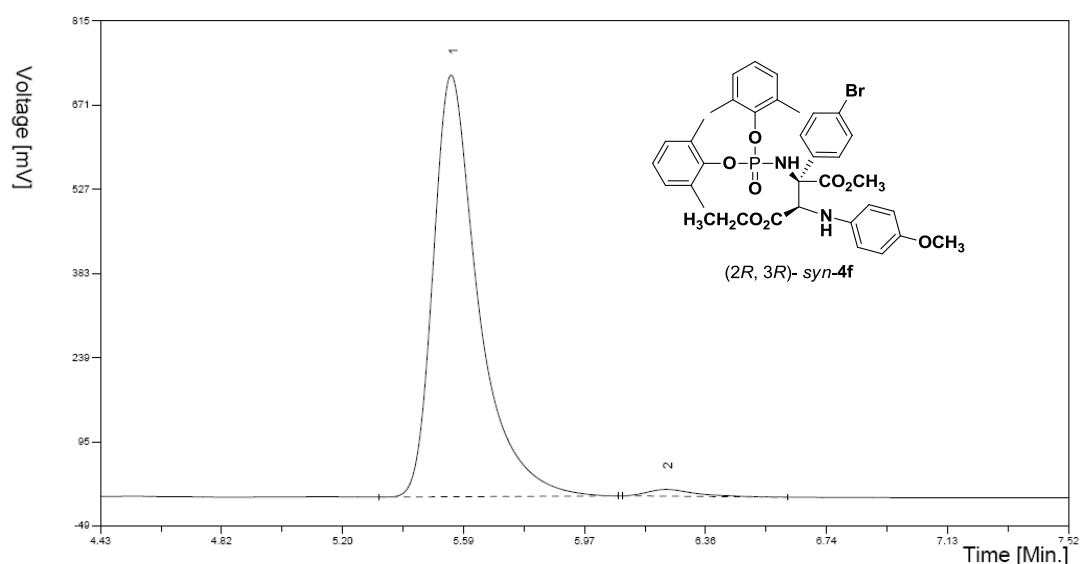
#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	14.56	262.03	11885.62	99.1931
2	Unknown	18.96	2.71	96.68	0.8069
合计			264.74	11982.31	100

Chiralpak Column: IA  
 M.P: *n*-Hex/*i*-PrOH=10:1  
 UV: 254nm  
 1.0 ml/min  
 Injection Volume: 20µl



组分表

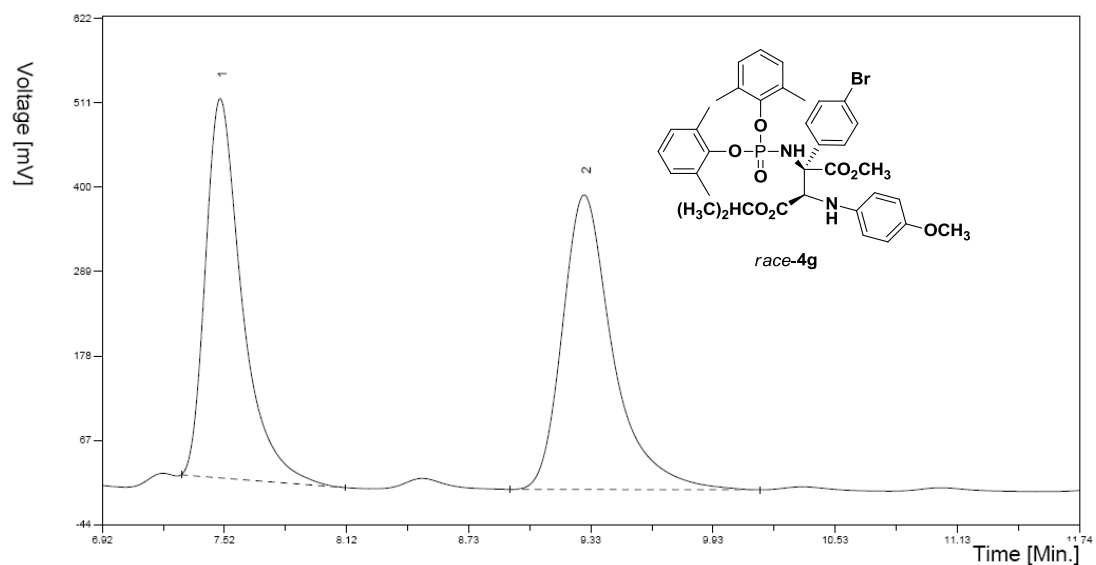
#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	5.59	1163.88	11190.90	49.5337
2	Unknown	6.19	1023.00	11401.58	50.4663
合计			2186.88	22592.47	100



组分表

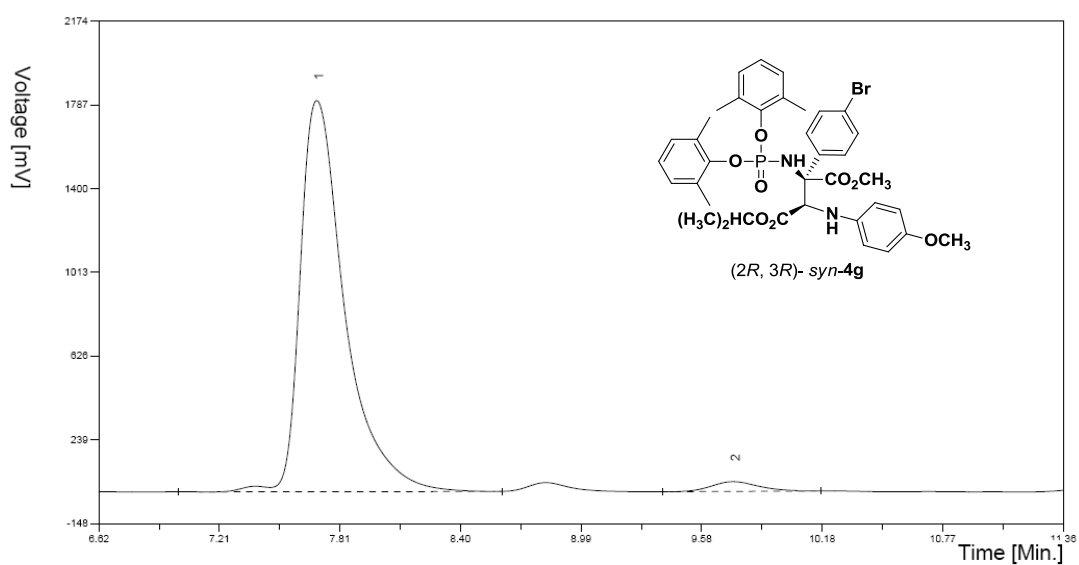
#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	5.55	721.13	7199.58	98.3333
2	Unknown	6.23	11.40	122.03	1.6667
合计			732.53	7321.61	100

Chiralpak Column:IA  
 M.P: *n*-Hex/*i*-PrOH=15:1  
 UV: 254nm  
 1.0 ml/min  
 Injection Volume: 20µl



组分表

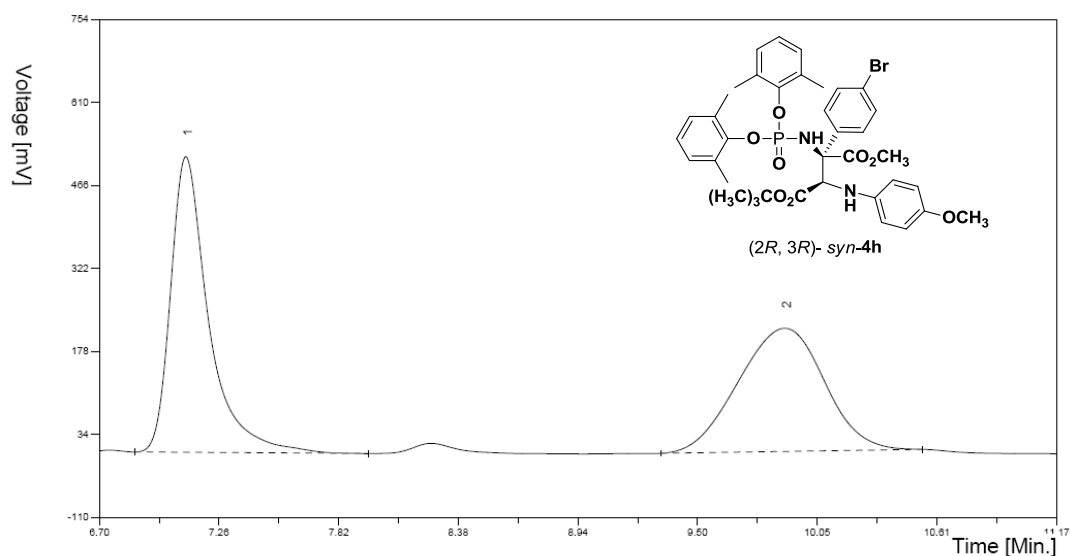
#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	7.50	498.73	6240.39	48.1782
2	Unknown	9.30	387.49	6712.34	51.8218
合计			886.22	12952.73	100



组分表

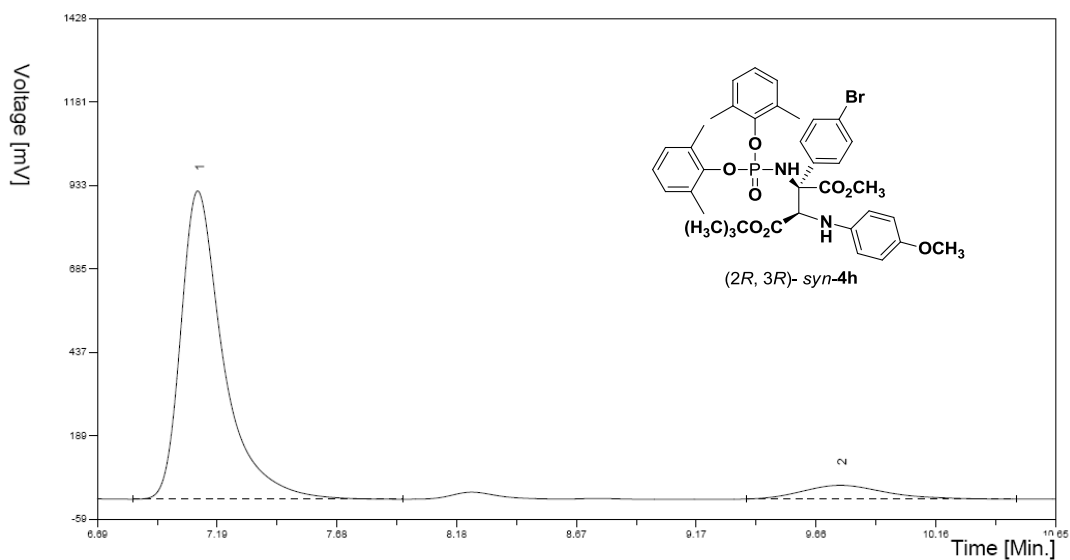
#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	7.69	1806.29	27457.25	97.4150
2	Unknown	9.74	45.18	728.60	2.5850
合计			1851.47	28185.85	100

Chiralpak Column:IA  
 M.P: *n*-Hex/*i*-PrOH=15:1  
 UV: 254nm  
 1.0 ml/min  
 Injection Volume: 20µl



组分表

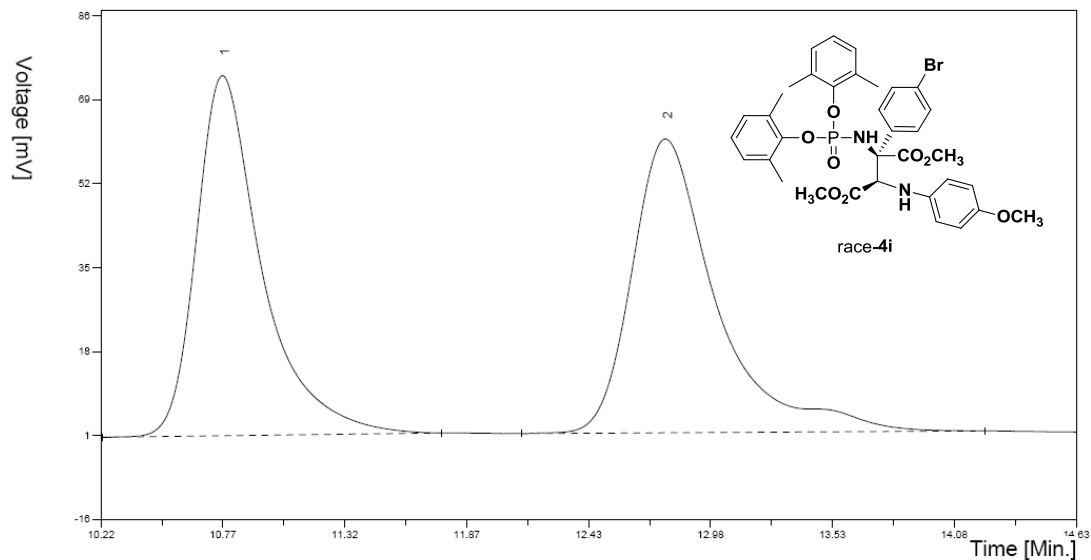
#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	7.11	512.70	6317.23	51.4247
2	Unknown	9.90	213.56	5967.21	48.5753
合计			726.27	12284.43	100



组分表

#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	7.11	915.37	11144.16	92.1224
2	Unknown	9.76	40.39	952.96	7.8776
合计			955.77	12097.12	100

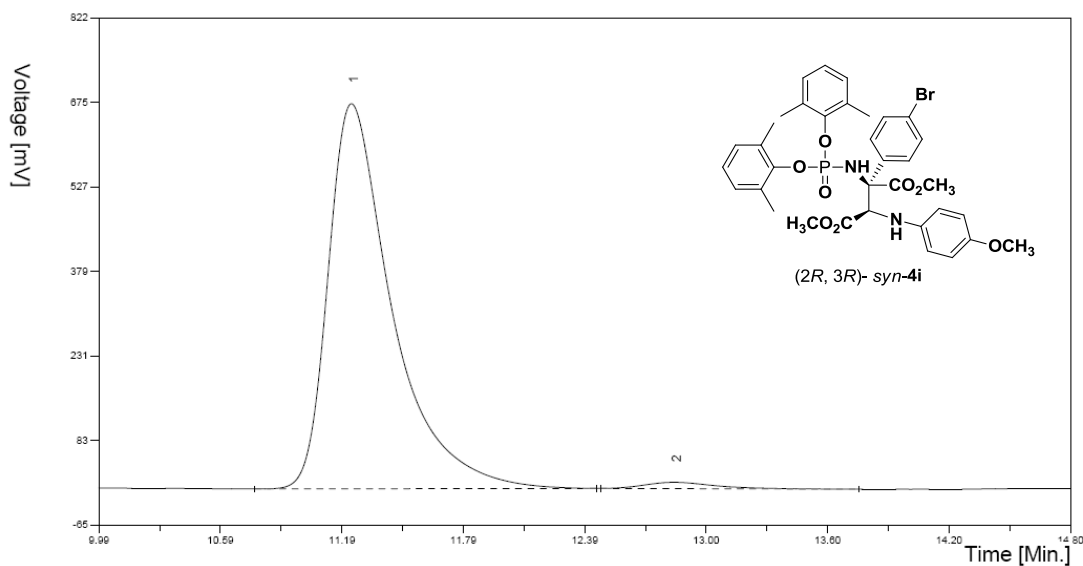
Chiralpak Column:IA  
 M.P: *n*-Hex/*i*-PrOH=30:1  
 UV: 254nm  
 1.0 ml/min  
 Injection Volume: 20µl



组分表

#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	10.77	72.89	1498.89	48.6340
2	Unknown	12.77	59.48	1583.09	51.3660

合计 132.37 3081.98 100

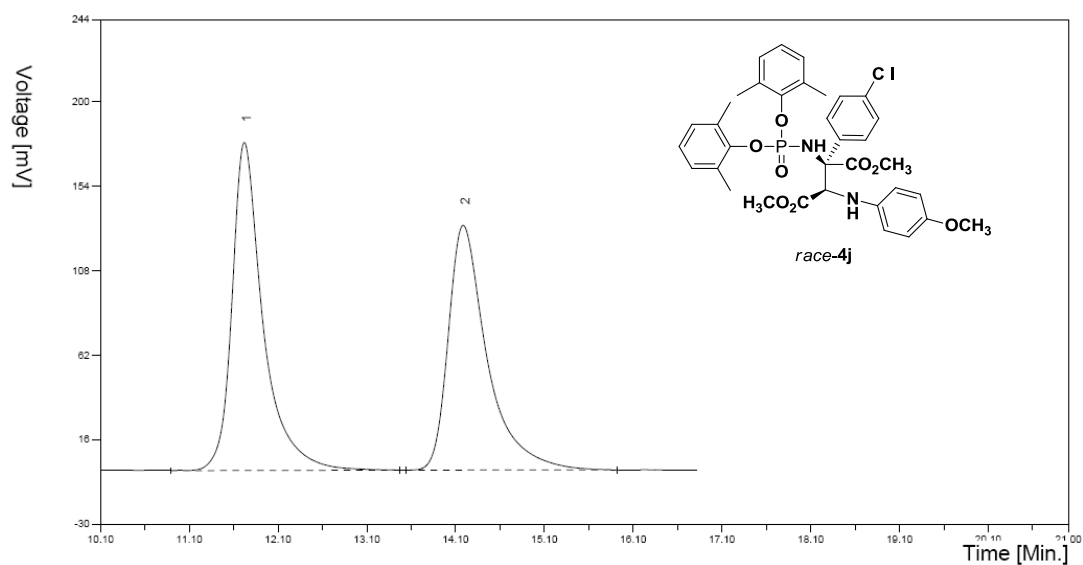


组分表

#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	11.19	673.78	14801.49	98.2217
2	Unknown	12.84	11.05	267.98	1.7783

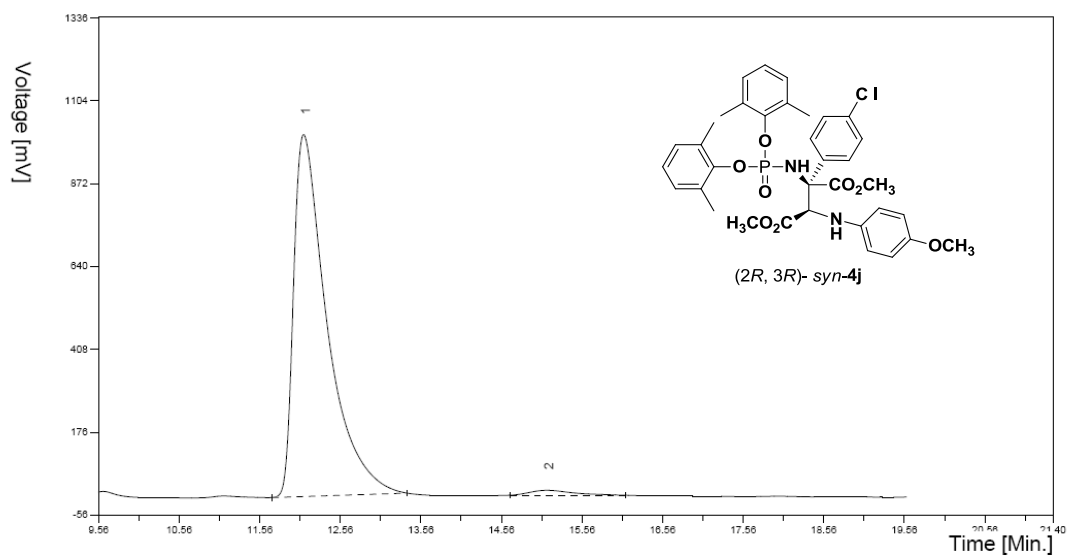
合计 684.83 15069.47 100

Chiralpak Column:IA  
 M.P: *n*-Hex/*i*-PrOH=40:1  
 UV: 254nm  
 1.0 ml/min  
 Injection Volume: 20µl



组分表

#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	11.72	178.52	4352.56	51.8177
2	Unknown	14.18	133.19	4047.19	48.1823
合计			311.71	8399.75	100

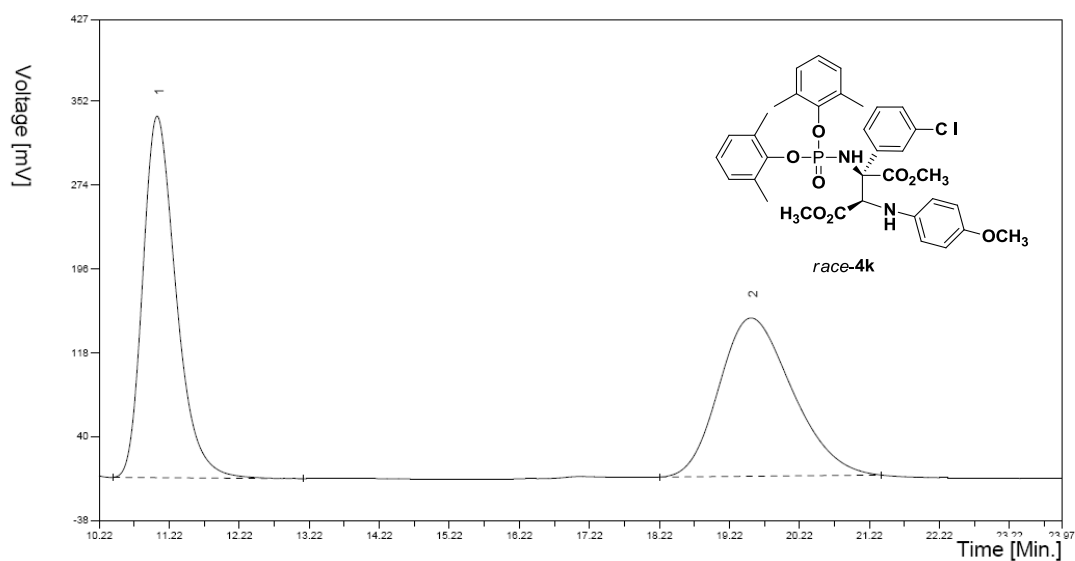


组分表

#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	12.10	1013.36	29198.24	98.2392
2	Unknown	15.12	13.78	523.35	1.7608
合计			1027.14	29721.59	100

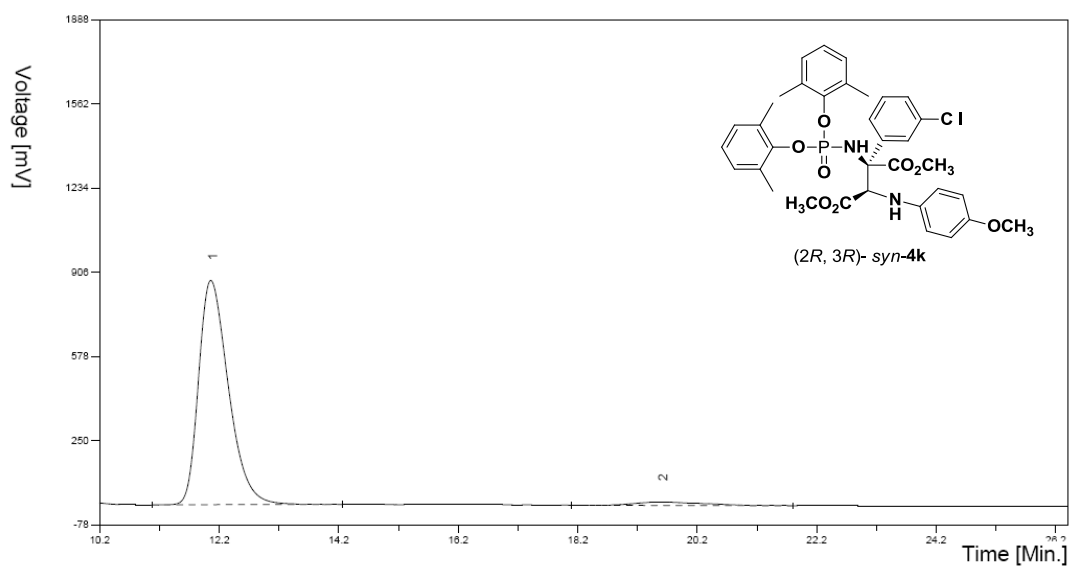


Chiralpak Column:AD-H  
 M.P: *n*-Hex/*i*-PrOH=30:1  
 UV: 254nm  
 1.0 ml/min  
 Injection Volume: 20µl



组分表

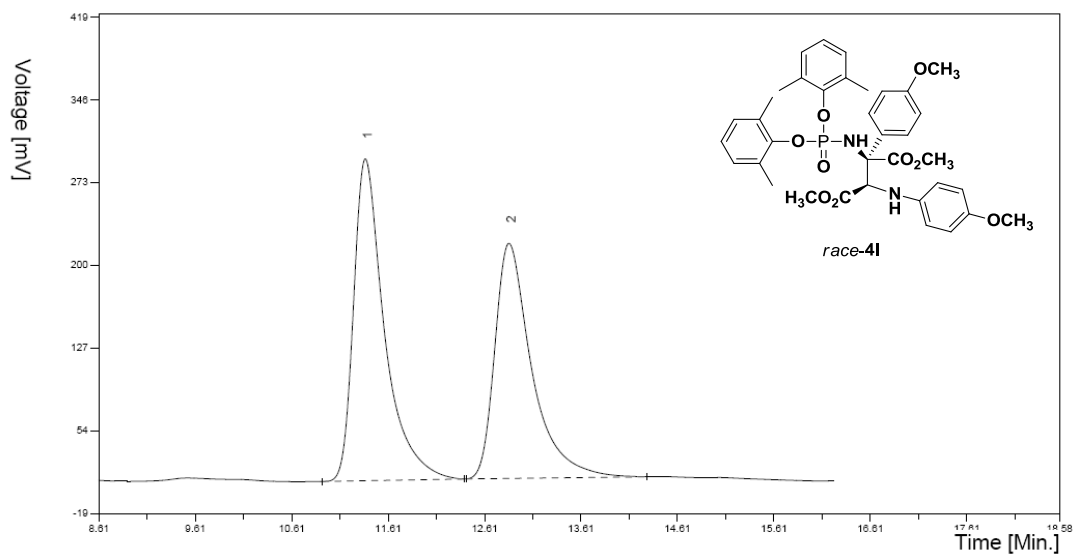
#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	11.05	335.92	11092.90	50.9303
2	Unknown	19.53	147.09	10687.64	49.0697
合计			483.01	21780.54	100



组分表

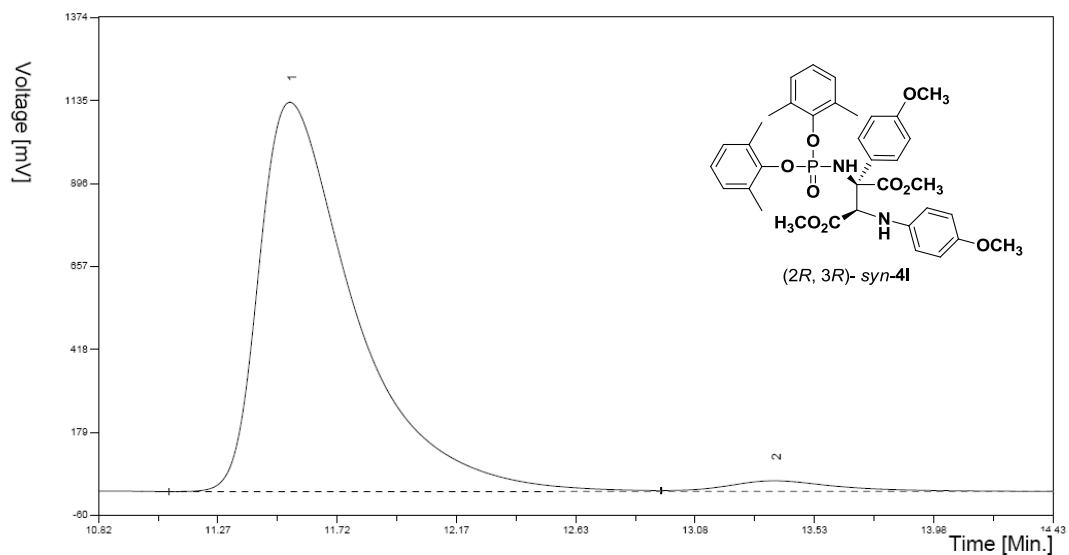
#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	12.08	873.03	30319.90	96.6175
2	Unknown	19.61	13.39	1061.47	3.3825
合计			886.43	31381.37	100

Chiralpak Column: IA  
 M.P: *n*-Hex/*i*-PrOH=20:1  
 UV: 254nm  
 1.0 ml/min  
 Injection Volume: 20µl



组分表

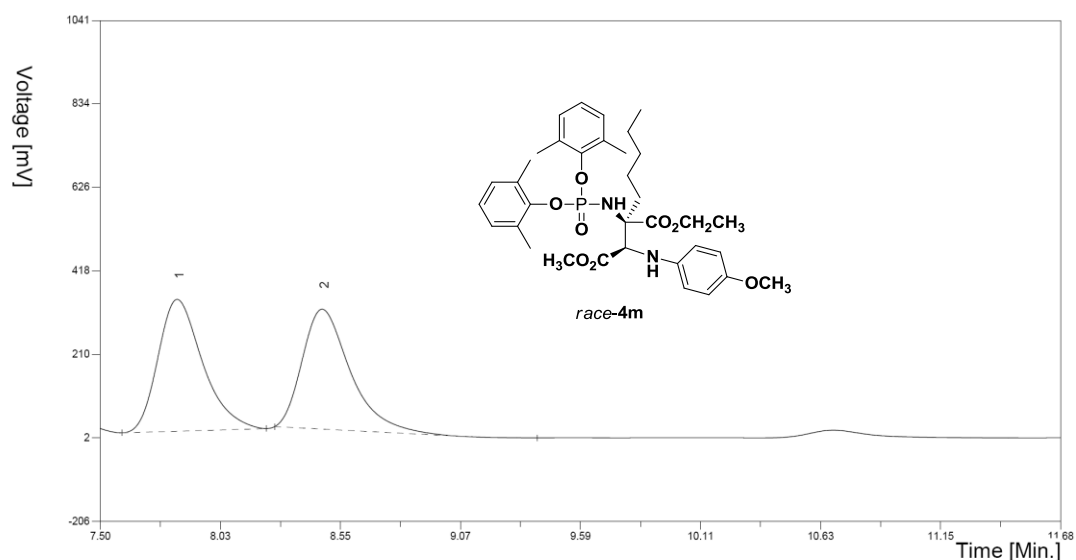
#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	11.38	283.83	6293.74	53.3346
2	Unknown	12.87	207.31	5506.74	46.6654
合计			491.14	11800.49	100



组分表

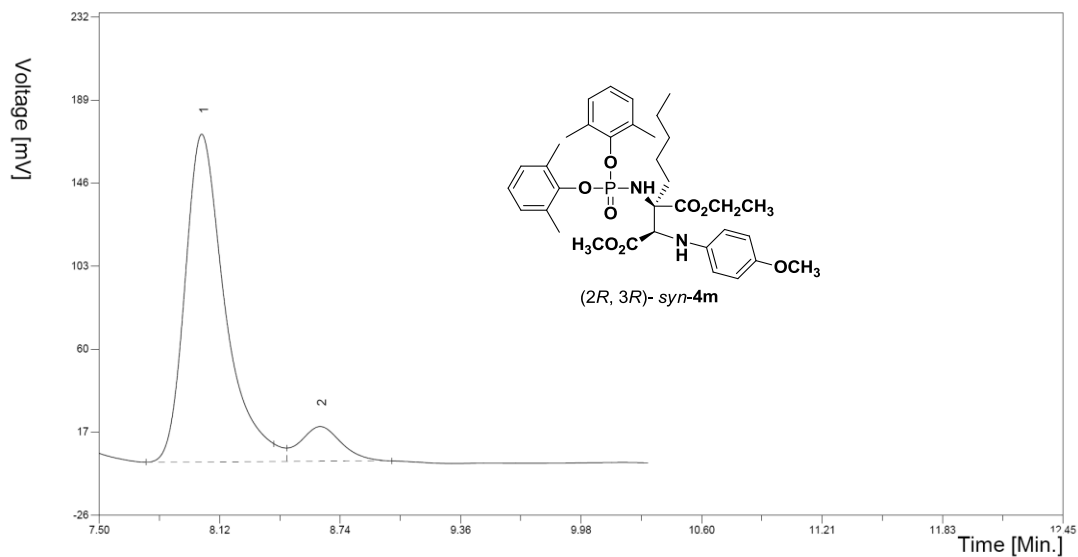
#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	11.55	1121.45	28281.51	96.9596
2	Unknown	13.38	30.55	886.83	3.0404
合计			1152.00	29168.34	100

Chiralpak Column:IA  
 M.P: *n*-Hex/*i*-PrOH=50:1  
 UV: 254nm  
 1.0 ml/min  
 Injection Volume: 20µl



组分表

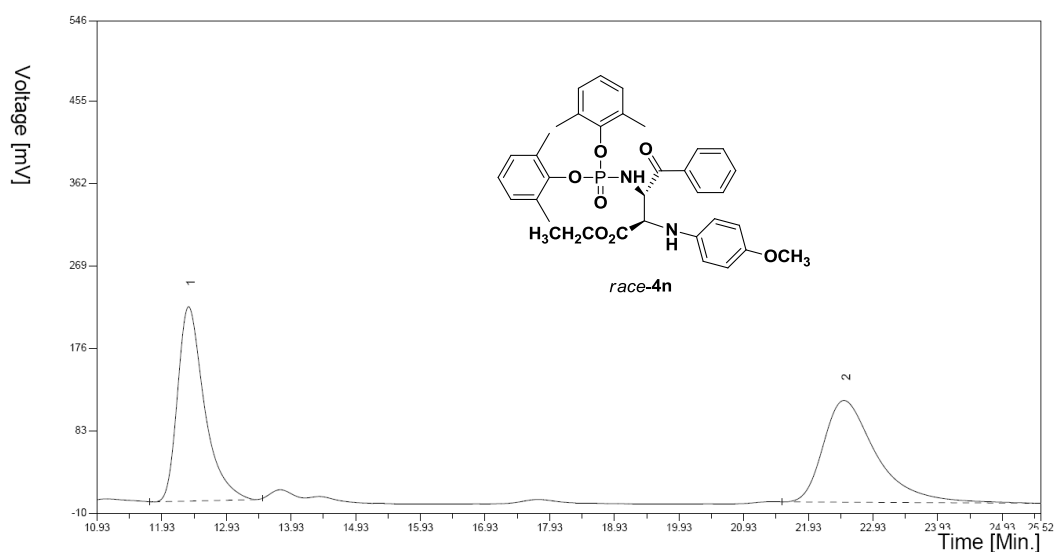
#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	7.84	327.86	4412.10	51.3673
2	Unknown	8.47	297.24	4177.22	48.6327
合计			625.10	8589.32	100



组分表

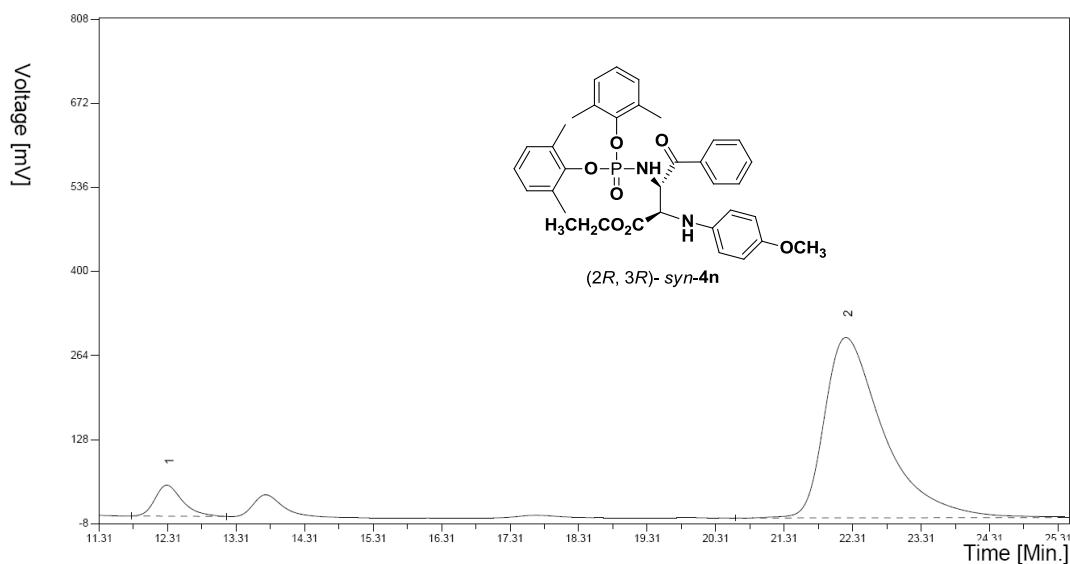
#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	8.03	169.68	2421.84	89.1115
2	Unknown	8.64	17.99	295.92	10.8885
合计			187.67	2717.76	100

Chiralpak Column:IA  
 M.P: *n*-Hex/*i*-PrOH=6:1  
 UV: 254nm  
 1.0 ml/min  
 Injection Volume: 20µl



组分表

#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	12.35	218.66	6250.77	48.9002
2	Unknown	22.48	114.73	6531.94	51.0998
合计			333.40	12782.70	100



组分表

#	组分名	保留时间(min)	峰高(mv)	峰面积(mv.sec)	面积百分比(%)
1	Unknown	12.30	50.06	1394.68	7.3507
2	Unknown	22.21	291.66	17578.78	92.6493
合计			341.73	18973.46	100