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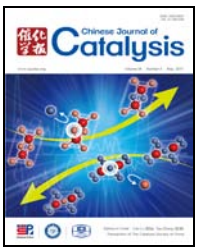

Article

Enantioselective synthesis of quaternary α-aminophosphonates by organocatalytic Friedel–Crafts reactions of indoles with cyclic α-ketiminophosphonates

Zhong Yan, Xiang Gao, Yong-Gui Zhou *

State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, Liaoning, China

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ABSTRACT

An efficient asymmetric Friedel–Crafts reaction has been developed for the synthesis of optically active quaternary α-aminophosphonates with up to 98% ee. The synthesis involves the reaction of cyclic α-ketiminophosphonates with indoles using an H8-BINOL-derived chiral phosphoric acid (CPA) catalyst that bears electron-withdrawing 3,5-ditrifluoromethylphenyl substituents on its 3- and 3′-positions. This Friedel–Crafts reaction of cyclic α-ketiminophosphonates was also successful with pyrrole.

1. Introduction

The construction of chiral tetrasubstituted carbon stereocenters remains a challenging and demanding topic in chemical synthesis [1–3]. Despite these challenges, the synthesis of optically active α-aminophosphonic acids and derivatives that bear quaternary α-stereogenic centers is of great interest owing to the inherent characteristics of these compounds, which can be used as building blocks for pharmaceutical targets, such as enzyme inhibitors [4] and antifungal [5], antibacterial [6] and antiviral agents [7]. Among the various synthetic routes to chiral α-aminophosphonic acids and their derivatives [8–14], catalytic asymmetric nucleophilic addition to α-ketiminophosphonates appears to be a particularly simple and reliable method. However, to date, application of this method has been limited to the asymmetric addition of only a small number of nucleophiles. In 2012, Palacios's group [15] reported the asymmetric cyanation of α-ketiminophosphonates catalyzed by cinchona alkaloids with up to 92% ee (Scheme 1, Eq 1). On the basis of enantioselective proline-catalyzed reactions between iminotrifluoroethylphosphonates and acetone, Onys'ko's group [16] developed an efficient synthetic route to chiral α-amino-γ-ketophosphonates with a free amine group (Scheme 1, Eq 2). Subsequently, Palacios's group [17] successfully documented the asymmetric synthesis of quaternary α-aminophosphonates through the enantioselective aza-Henry reaction of phosphorylated ketimines (Scheme 1, Eq 3). Recently, our group [18] reported an efficient and facile route to quaternary α-aminophosphonates by palladium-catalyzed enantioselective addition of arylboronic acids to cyclic α-ketiminophosphonates (Scheme 1, Eq 4). Despite these advances, the further development of efficient strategies for the synthesis of chiral tetrasubstituted carbon stereocenters is still required to satisfy the increasing demand for chiral quaternary α-aminophosphonic acids and their derivatives.

Over recent decades, the asymmetric Friedel–Crafts reaction

* Corresponding author. Tel: +86-411-84379220; E-mail: ygzhou@dicp.ac.cn
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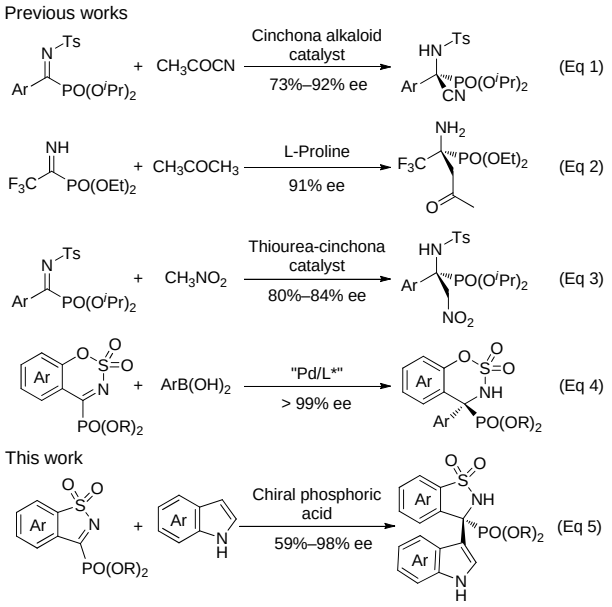


Scheme 1. Synthesis of chiral quaternary α-aminophosphonates by asymmetric nucleophilic addition to α-ketiminophosphonates.

has attracted much attention as a versatile C–C bond-forming process, and great progress has been reported in this field [19–21]. Notably, the asymmetric Friedel–Crafts reaction of indoles with imines provides easy access to optically active indolylalkylamine derivatives, which are found in various drugs and natural products with recognized pharmacological properties [22–42]. Considerable progress has been made in terms of promoting this transformation, for example, by employing chiral Lewis acids and organocatalysts. However, the literature contains only a few reports of the asymmetric addition of indoles to ketimine substrates. Using chiral phosphoric acids (CPA) as catalysts, Bolm's group [43] demonstrated that *N*-Boc-protected ethyl trifluoropyruvate imine could react with indoles to afford α-amino acids with excellent enantioselectivities. The syntheses of *N*-alkoxycarbonyl aryl α-imino esters and isatin-derived *N*-Boc ketimines were then reported by Hu's group [44] and Wang's group [45], respectively. In addition, the use of cyclic ketimines as electrophiles was described by the groups of Ma [46] and Rueping [47], and this reaction provided the corresponding cyclic indolyl α-tetrasubstituted amine derivatives with excellent enantioselectivities. Furthermore, using a $Cu(OTf)_2$-bisoxazoline complex as catalyst, Jia's group [48] successfully performed Friedel–Crafts alkylations of indoles and cyclic *N*-sulfonyl α-ketimino esters with high enantioselectivities. More recently, we developed a facile synthetic route to a series of cyclic α-ketiminophosphonates and subsequently achieved asymmetric hydrogenation [49] and addition of arylboronic acids to these molecules [18]. We envision that combining these cyclic ketimines and indoles in the presence of CPA will offer a new method for the synthesis of chiral quaternary α-aminophosphonates. Herein, we describe the CPA-catalyzed enantioselective Friedel–Crafts reaction of indoles with cyclic α-ketiminophosphonates with up to 98% enantioselectivity (Scheme 1, Eq 5).

2. Experimental

2.1. General methods

Commercially available reagents and solvents were used without further purification. ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and ^{31}P NMR spectra were recorded at room temperature in $CDCl_3$ on a 400 MHz instrument with tetramethylsilane (TMS) as the internal standard. Flash column chromatography was performed on silica gel (200–300 mesh). All reactions were monitored by thin-layer chromatographic analysis. Cyclic α-ketiminophosphonates **1** were synthesized according to the known literature procedure [49].

2.2. General procedure for the catalytic enantioselective Friedel–Crafts reaction

Cyclic α-ketiminophosphonates **1** (0.1 mmol) and CPA (*S*)-**4** (5 mol%) were placed in a Schlenk tube and mesitylene (2 mL) was added. The mixture was stirred at 30 °C for 10 min. Then, indoles **2** (0.3 mmol) were added. The resulting mixture was stirred at 30 °C until cyclic α-ketiminophosphonates **1** were completely consumed. The crude product was purified by flash chromatography on silica gel with a mixture of dichloromethane and methanol as the eluent to give chiral quaternary α-aminophosphonates **3**.

(*R*)-Diisopropyl (3-(1*H*-indol-3-yl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phosphonate (**3a**): 44 mg, 98% yield, 96% ee, $[\alpha]^{20}_D$ = +49.09 (*c* 0.66, THF), unknown compound, white solid, m.p. = 232–233 °C (decomp.), R_f = 0.30 (dichloromethane/methanol = 40/1). ^{1}H NMR (400 MHz, d6-DMSO): δ = 11.28 (s, 1H), 8.76 (s, 1H), 7.94 (d, *J* = 5.7 Hz, 1H), 7.77 (s, 1H), 7.74–7.61 (m, 2H), 7.51 (d, *J* = 5.5 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.03 (t, *J* = 7.3 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.77 (t, *J* = 7.3 Hz, 1H), 4.85–4.60 (m, 1H), 4.50–4.25 (m, 1H), 1.40–1.05 (m, 9H), 0.81 (d, *J* = 5.8 Hz, 3H); ^{13}C NMR (100 MHz, d6-DMSO): δ = 138.4 (d, J_{PC} = 4.5 Hz), 137.6, 136.8 (d, J_{PC} = 5.2 Hz), 134.0, 131.4, 127.8, 127.4 (d, J_{PC} = 2.6 Hz), 126.1 (d, J_{PC} = 11.5 Hz), 122.6, 122.0, 121.2, 120.1, 112.9, 111.6 (d, J_{PC} = 3.8 Hz), 73.6 (d, J_{PC} = 8.2 Hz), 73.4 (d, J_{PC} = 6.7 Hz), 64.7 (d, J_{PC} = 166.3 Hz), 25.3, 25.1 (d, J_{PC} = 2.7 Hz), 24.8 (d, J_{PC} = 5.4 Hz), 23.9 (d, J_{PC} = 5.5 Hz); ^{31}P NMR (162 MHz, d6-DMSO): δ = 16.4. HPLC: Chiralcel AD-H column, 230 nm, 30 °C, *n*-hexane/*i*-propanol = 70/30, flow 0.7 mL/min, retention time 14.9 min and 18.3 min (maj.). HRMS: Calculated for $C_{21}H_{26}N_2O_5PS$ $[M+H]^+$ 449.1295, found 449.1301.

(*R*)-Diisopropyl (3-(2-methyl-1*H*-indol-3-yl)-1,1-dioxido-2,3-dihydro-benzo[*d*]isothiazol-3-yl)phosphonate (**3b**): 42 mg, 91% yield, 59% ee, $[\alpha]^{20}_D$ = +18.29 (*c* 0.82, THF), unknown compound, yellow solid, m.p. = 200–201 °C (decomp.), R_f = 0.10 (dichloromethane/methanol = 40/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (s, 1H), 7.91–7.77 (m, 2H), 7.70–7.56 (m, 3H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 5.28 (d, *J* = 5.1 Hz, 1H), 4.86–4.74 (m, 1H), 4.49–4.35 (m, 1H), 2.19 (s, 3H), 1.29 (d, *J* = 6.2 Hz, 3H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.08 (d, *J* = 6.2 Hz, 3H), 0.79 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.0 (d, J_{PC} = 5.2 Hz), 135.7 (d, J_{PC} = 5.1 Hz), 135.2 (d, J_{PC} = 8.1 Hz), 134.9, 132.8 (d, J_{PC} = 2.1 Hz), 130.1 (d, J_{PC}

= 2.1 Hz), 128.1 (d, J_{PC} = 2.5 Hz), 127.1 (d, J_{PC} = 6.4 Hz), 121.7, 121.5, 121.0, 120.2, 110.4, 106.9 (d, J_{PC} = 3.2 Hz), 74.2 (d, J_{PC} = 8.1 Hz), 73.6 (d, J_{PC} = 7.7 Hz), 65.8 (d, J_{PC} = 165.9 Hz), 24.5 (d, J_{PC} = 2.7 Hz), 24.4 (d, J_{PC} = 3.3 Hz), 23.7 (d, J_{PC} = 5.7 Hz), 23.0 (d, J_{PC} = 5.9 Hz), 15.6; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 15.6. HPLC: Chiralcel AD-H column, 230 nm, 30 °C, *n*-hexane/*i*-propanol = 70/30, flow 0.7 mL/min, retention time 10.8 min (maj.) and 16.8 min. HRMS: Calculated for $C_{22}H_{28}N_2O_5PS$ $[M+H]^+$ 463.1451, found 463.1460.

(*R*)-Diisopropyl (3-(4-methyl-1*H*-indol-3-yl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phosphonate (**3c**): 42 mg, 91% yield, 87% ee, $[\alpha]^{20}_D$ = +9.64 (*c* 0.84, THF), unknown compound, yellow solid, m.p. = 193–194 °C (decomp.), R_f = 0.20 (dichloromethane/methanol = 80/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.60 (s, 1H), 8.12 (d, *J* = 2.7 Hz, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 7.1 Hz, 1H), 5.40 (d, *J* = 7.3 Hz, 1H), 4.98–4.85 (m, 1H), 4.40–4.28 (m, 1H), 1.72 (s, 3H), 1.35 (d, *J* = 6.1 Hz, 6H), 1.28 (d, *J* = 6.1 Hz, 3H), 0.74 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.4 (d, J_{PC} = 4.8 Hz), 137.7, 137.0 (d, J_{PC} = 4.9 Hz), 133.1 (d, J_{PC} = 2.9 Hz), 131.1, 130.2 (d, J_{PC} = 2.9 Hz), 129.7 (d, J_{PC} = 5.3 Hz), 127.3 (d, J_{PC} = 3.1 Hz), 124.2 (d, J_{PC} = 12.6 Hz), 123.3, 122.7, 122.0 (d, J_{PC} = 2.3 Hz), 109.7, 74.3 (d, J_{PC} = 1.7 Hz), 74.2 (d, J_{PC} = 3.0 Hz), 65.9 (d, J_{PC} = 159.1 Hz), 24.5 (d, J_{PC} = 2.8 Hz), 24.3 (d, J_{PC} = 4.2 Hz), 24.1 (d, J_{PC} = 4.4 Hz), 22.8 (d, J_{PC} = 5.9 Hz), 22.4; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 16.3. HPLC: Chiralcel AD-H column, 230 nm, 30 °C, *n*-hexane/*i*-propanol = 80/20, flow 0.7 mL/min, retention time 33.9 min and 37.1 min (maj.). HRMS Calculated for $C_{22}H_{28}N_2O_5PS$ $[M+H]^+$ 463.1451, found 463.1460.

(*R*)-Diisopropyl (3-(5-methyl-1*H*-indol-3-yl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phosphonate (**3d**): 45 mg, 98% yield, 95% ee, $[\alpha]^{20}_D$ = +27.89 (*c* 0.90, THF), unknown compound, white solid, m.p. = 138–139 °C, R_f = 0.20 (dichloromethane/methanol = 80/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.85 (s, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.74 (s, 1H), 7.65–7.51 (m, 3H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.02 (s, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 5.33 (d, *J* = 4.8 Hz, 1H), 4.95–4.80 (m, 1H), 4.52–4.34 (m, 1H), 2.27 (s, 3H), 1.39–1.17 (m, 9H), 0.77 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8 (d, J_{PC} = 3.8 Hz), 135.5 (d, J_{PC} = 5.2 Hz), 135.0, 133.3 (d, J_{PC} = 2.3 Hz), 130.1 (d, J_{PC} = 2.5 Hz), 129.8, 127.3 (d, J_{PC} = 2.6 Hz), 126.1 (d, J_{PC} = 4.3 Hz), 125.0 (d, J_{PC} = 10.5 Hz), 124.4, 121.5 (d, J_{PC} = 1.7 Hz), 119.9, 111.4, 110.5, 74.0 (d, J_{PC} = 8.4 Hz), 73.7 (d, J_{PC} = 7.7 Hz), 64.8 (d, J_{PC} = 165.4 Hz), 24.5, 24.3 (d, J_{PC} = 3.7 Hz), 24.0 (d, J_{PC} = 5.1 Hz), 22.9 (d, J_{PC} = 5.9 Hz), 21.8; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 15.4 (d, *J* = 5.9 Hz). HPLC: Chiralcel AD-H column, 230 nm, 30 °C, *n*-hexane/*i*-propanol = 80/20, flow 0.7 mL/min, retention time 20.3 min (maj.) and 23.0 min. HRMS: Calculated for $C_{22}H_{28}N_2O_5PS$ $[M+H]^+$ 463.1451, found 463.1458.

(*R*)-Diisopropyl (3-(6-methyl-1*H*-indol-3-yl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phosphonate (**3e**): 43 mg, 93% yield, 94% ee, $[\alpha]^{20}_D$ = +32.44 (*c* 0.86, THF), unknown compound, white solid, m.p. = 240–241 °C (decomp.), R_f = 0.20 (dichloromethane/methanol = 80/1). ^{1}H NMR (400 MHz, $CDCl_3$); δ = 8.87 (s, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.75 (s, 1H), 7.65–7.48 (m, 3H), 7.12 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 5.37 (d, *J* = 3.5 Hz, 1H), 4.95–4.81 (m, 1H), 4.52–4.36 (m, 1H), 2.35 (s, 3H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.31–1.21 (m, 6H), 0.79 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8 (d, J_{PC} = 4.0 Hz), 137.2, 135.5 (d, J_{PC} = 5.0 Hz), 133.3 (d, J_{PC} = 2.5 Hz), 132.6, 130.2 (d, J_{PC} = 2.5 Hz), 127.2 (d, J_{PC} = 2.7 Hz), 125.6 (d, J_{PC} = 4.0 Hz), 122.6 (d, J_{PC} = 11.0 Hz), 122.3, 121.5 (d, J_{PC} = 1.9 Hz), 119.8, 111.7, 110.8 (d, J_{PC} = 3.6 Hz), 74.0 (d, J_{PC} = 8.3 Hz), 73.7 (d, J_{PC} = 7.7 Hz), 64.7 (d, J_{PC} = 166.0 Hz), 24.5 (d, J_{PC} = 2.7 Hz), 24.3 (d, J_{PC} = 3.6 Hz), 24.0 (d, J_{PC} = 5.2 Hz), 23.0 (d, J_{PC} = 5.8 Hz), 21.7; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 15.3 (d, *J* = 5.4 Hz). HPLC: Chiralcel AD-H column, 230 nm, 30 °C, *n*-hexane/*i*-propanol = 70/30, flow 0.7 mL/min, retention time 20.5 min (maj.) and 24.5 min. HRMS: Calculated for $C_{22}H_{28}N_2O_5PS$ $[M+H]^+$ 463.1451, found 463.1461.

(*R*)-Diisopropyl (3-(7-methyl-1*H*-indol-3-yl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phosphonate (**3f**): 44 mg, 96% yield, 95% ee, $[\alpha]^{20}_D$ = +60.11 (*c* 0.88, THF), unknown compound, white solid, m.p. = 213–214 °C, R_f = 0.20 (dichloromethane/methanol = 80/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.30 (s, 1H), 7.96 (d, *J* = 2.3 Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.56–7.46 (m, 2H), 6.99–6.91 (m, 2H), 6.89–6.81 (m, 1H), 5.31 (d, *J* = 5.3 Hz, 1H), 4.97–4.84 (m, 1H), 4.49–4.35 (m, 1H), 2.46 (s, 3H), 1.35 (d, *J* = 6.1 Hz, 3H), 1.32–1.25 (m, 6H), 0.79 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8 (d, J_{PC} = 3.8 Hz), 136.3, 135.6 (d, J_{PC} = 5.0 Hz), 133.3 (d, J_{PC} = 2.5 Hz), 130.2 (d, J_{PC} = 2.5 Hz), 127.2 (d, J_{PC} = 2.7 Hz), 126.2 (d, J_{PC} = 3.9 Hz), 124.3 (d, J_{PC} = 11.5 Hz), 123.3, 121.5 (d, J_{PC} = 2.0 Hz), 121.0, 120.8, 117.7, 111.2 (d, J_{PC} = 4.1 Hz), 74.1 (d, J_{PC} = 8.4 Hz), 73.8 (d, J_{PC} = 7.8 Hz), 64.8 (d, J_{PC} = 165.4 Hz), 24.5 (d, J_{PC} = 2.8 Hz), 24.3 (d, J_{PC} = 3.8 Hz), 24.1 (d, J_{PC} = 5.0 Hz), 22.9 (d, J_{PC} = 5.8 Hz), 16.7; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 15.2. HPLC: Chiralcel AD-H column, 230 nm, 30 °C, *n*-hexane/*i*-propanol = 70/30, flow 0.7 mL/min, retention time 18.5 min and 21.4 min (maj.). HRMS: Calculated for $C_{22}H_{28}N_2O_5PS$ $[M+H]^+$ 463.1451, found 463.1459.

(*R*)-Diisopropyl (3-(7-ethyl-1*H*-indol-3-yl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phosphonate (**3g**): 46 mg, 96% yield, 95% ee, $[\alpha]^{20}_D$ = +59.45 (*c* 0.92, THF), unknown compound, white solid, m.p. = 213–214 °C (decomp.), R_f = 0.20 (dichloromethane/methanol = 40/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.35 (s, 1H), 7.98 (s, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 7.66–7.42 (m, 3H), 7.05–6.83 (m, 3H), 5.26 (d, *J* = 4.6 Hz, 1H), 5.01–4.83 (m, 1H), 4.53–4.29 (m, 1H), 3.00–2.70 (m, 2H), 1.45–1.15 (m, 12H), 0.78 (d, *J* = 5.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8 (d, J_{PC} = 3.9 Hz), 135.6, 135.6 (d, J_{PC} = 5.3 Hz), 133.3 (d, J_{PC} = 2.2 Hz), 130.2 (d, J_{PC} = 2.5 Hz), 127.3 (d, J_{PC} = 2.6 Hz), 127.2, 126.1 (d, J_{PC} = 3.6 Hz), 124.5 (d, J_{PC} = 11.5 Hz), 121.5 (d, J_{PC} = 2.0 Hz), 121.3, 120.9, 117.7, 111.2 (d, J_{PC} = 4.2 Hz), 74.1 (d, J_{PC} = 8.4 Hz), 73.9 (d, J_{PC} = 7.6 Hz), 64.8 (d, J_{PC} = 165.4 Hz), 24.5 (d, J_{PC} = 2.6 Hz), 24.3 (d, J_{PC} = 3.8 Hz), 24.2 (d, J_{PC} = 5.0 Hz), 24.0, 22.9 (d, J_{PC} = 5.9 Hz), 14.0; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 15.2 (d, *J* = 5.8 Hz). HPLC: Chiralcel AD-H column, 230 nm, 30 °C, *n*-hexane/*i*-propanol = 70/30, flow 0.7 mL/min, retention time 16.1 min and 20.4 min (maj.). HRMS: Calculated for $C_{23}H_{30}N_2O_5PS$ $[M+H]^+$ 477.1608, found 477.1613.

(*R*)-Diisopropyl (3-(5-methoxy-1*H*-indol-3-yl)-1,1-dioxido-

2,3-dihydrobenzo[*d*]isothiazol-3-yl)phosphonate (**3h**): 47 mg, 98% yield, 94% ee, $[\alpha]^{20}_D$ = +34.25 (*c* 0.94, THF), unknown compound, white solid, m.p. = 232–233 °C (decomp.), R_f = 0.10 (dichloromethane/methanol = 80/1). ^{1}H NMR (400 MHz, d6-DMSO): δ = 11.08 (s, 1H), 8.73 (s, 1H), 7.98–7.88 (m, 1H), 7.73–7.62 (m, 3H), 7.54–7.43 (m, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 6.65 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.48 (d, *J* = 1.7 Hz, 1H), 4.78–4.64 (m, 1H), 4.41–4.25 (m, 1H), 3.46 (s, 3H), 1.25 (d, *J* = 6.1 Hz, 3H), 1.21–1.12 (m, 6H), 0.78 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, d6-DMSO): δ = 154.1, 138.4 (d, J_{PC} = 4.8 Hz), 136.9 (d, J_{PC} = 4.9 Hz), 134.0 (d, J_{PC} = 1.6 Hz), 132.6, 131.3 (d, J_{PC} = 2.0 Hz), 127.8 (d, J_{PC} = 2.4 Hz), 127.7 (d, J_{PC} = 3.5 Hz), 126.5 (d, J_{PC} = 11.4 Hz), 121.9, 113.4, 112.7, 111.3 (d, J_{FC} = 5.3 Hz), 103.2, 73.6 (d, J_{PC} = 8.0 Hz), 73.3 (d, J_{PC} = 7.5 Hz), 64.8 (d, J_{PC} = 165.8 Hz), 56.2, 25.3 (d, J_{PC} = 2.7 Hz), 25.1 (d, J_{PC} = 3.3 Hz), 24.8 (d, J_{PC} = 5.5 Hz), 23.9 (d, J_{PC} = 5.6 Hz); ^{31}P NMR (162 MHz, d6-DMSO): δ = 16.5. HPLC: Chiralcel OD-H column, 230 nm, 30 °C, *n*-hexane/*i*-propanol = 80/20, flow 0.7 mL/min, retention time 10.0 min and 12.5 min (maj.). HRMS: Calculated for $C_{22}H_{28}N_2O_6PS$ $[M+H]^+$ 479.1400, found 479.1408.

(*R*)-Diisopropyl (3-(5-fluoro-1*H*-indol-3-yl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phosphonate (**3i**): 44 mg, 94% yield, 93% ee, $[\alpha]^{20}_D$ = +25.79 (*c* 0.88, THF), unknown compound, white solid, m.p. = 233–234 °C (decomp.), R_f = 0.20 (dichloromethane/methanol = 80/1). ^{1}H NMR (400 MHz, d6-DMSO): δ = 11.36 (d, *J* = 2.0 Hz, 1H), 8.83 (s, 1H), 7.98–7.90 (m, 1H), 7.76 (d, *J* = 2.5 Hz, 1H), 7.73–7.65 (m, 2H), 7.57–7.50 (m, 1H), 7.37 (dd, *J* = 8.8, 4.8 Hz, 1H), 6.94–6.79 (m, 2H), 4.77–4.63 (m, 1H), 4.40–4.26 (m, 1H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.19 (d, *J* = 6.1 Hz, 3H), 1.13 (d, *J* = 6.2 Hz, 3H), 0.78 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, d6-DMSO): δ = 157.8 (d, J_{FC} = 231.1 Hz), 138.0 (d, J_{PC} = 4.7 Hz), 136.7 (d, J_{PC} = 5.0 Hz), 134.3, 134.1 (d, J_{PC} = 2.4 Hz), 131.5 (d, J_{PC} = 1.5 Hz), 129.1 (d, J_{PC} = 4.3 Hz), 127.7 (d, J_{PC} = 2.4 Hz), 126.2 (d, J_{PC} = 10.4 Hz), 122.1, 113.9 (d, J_{FC} = 10.2 Hz), 112.1, 110.9 (d, J_{FC} = 26.0 Hz), 106.2 (d, J_{FC} = 24.6 Hz), 73.7 (d, J_{PC} = 8.0 Hz), 73.5 (d, J_{PC} = 7.4 Hz), 64.5 (d, J_{PC} = 166.1 Hz), 25.3 (d, J_{PC} = 2.8 Hz), 25.1 (d, J_{PC} = 3.3 Hz), 24.7 (d, J_{PC} = 5.6 Hz), 23.9 (d, J_{PC} = 5.7 Hz); ^{19}F NMR (376 MHz, d6-DMSO): δ = −124.2; ^{31}P NMR (162 MHz, d6-DMSO): δ = 16.3 (t, *J* = 6.5 Hz). HPLC: Chiralcel AS-H column, 230 nm, 30 °C, *n*-hexane/*i*-propanol = 80/20, flow 0.7 mL/min, retention time 12.0 min (maj.) and 23.4 min. HRMS: Calculated for $C_{21}H_{25}FN_2O_5PS$ $[M+H]^+$ 467.1200, found 467.1205.

(*R*)-Diisopropyl (3-(6-fluoro-1*H*-indol-3-yl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phosphonate (**3j**): 40 mg, 85% yield, 95% ee, $[\alpha]^{20}_D$ = +43.65 (*c* 0.74, THF), unknown compound, white solid, m.p. = 233–234 °C (decomp.), R_f = 0.30 (dichloromethane/methanol = 40/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82 (s, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 1.8 Hz, 1H), 7.67–7.53 (m, 3H), 7.22 (dd, *J* = 8.9, 5.2 Hz, 1H), 7.00 (dd, *J* = 9.2, 2.0 Hz, 1H), 6.78–6.67 (m, 1H), 5.33 (d, *J* = 5.5 Hz, 1H), 4.92–4.79 (m, 1H), 4.50–4.34 (m, 1H), 1.34 (d, *J* = 6.2 Hz, 3H), 1.28 (d, *J* = 6.1 Hz, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 0.78 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2 (d, J_{FC} = 239.6 Hz), 137.5 (d, J_{PC} = 4.2 Hz), 136.8 (d, J_{FC} = 12.3 Hz), 135.4 (d, J_{PC} = 5.0 Hz), 133.4 (d, J_{PC} = 2.5 Hz), 130.4 (d, J_{PC} = 2.4 Hz), 127.1 (d, J_{PC} = 2.7 Hz), 126.3, 121.6 (d, J_{PC} = 1.8 Hz), 121.5 (d, J_{FC} = 9.9 Hz), 110.2, 109.5 (d, J_{FC} = 24.2 Hz), 97.9 (d, J_{FC} = 25.8 Hz), 74.1 (d, J_{PC} = 8.2 Hz), 73.9 (d, J_{PC} = 7.6 Hz), 64.4 (d, J_{PC} = 164.2 Hz), 24.5 (d, J_{PC} = 2.7 Hz), 24.3 (d, J_{PC} = 3.6 Hz), 24.0 (d, J_{PC} = 5.2 Hz), 23.0 (d, J_{PC} = 5.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −120.1; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 15.3. HPLC: Chiralcel AD-H column, 230 nm, 30 °C, *n*-hexane/*i*-propanol = 80/20, flow 0.7 mL/min, retention time 22.5 min (maj.) and 28.6 min. HRMS: Calculated for $C_{21}H_{25}FN_2O_5PS$ $[M+H]^+$ 467.1200, found 467.1207.

(*R*)-Diisopropyl (3-(5-chloro-1*H*-indol-3-yl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phosphonate (**3k**): 47 mg, 98% yield, 95% ee, $[\alpha]^{20}_D$ = −5.11 (*c* 0.94, THF), unknown compound, yellow solid, m.p. = 225–226 °C (decomp.), R_f = 0.20 (dichloromethane/methanol = 80/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.09 (s, 1H), 7.89 (d, *J* = 7.4 Hz, 1H), 7.71–7.51 (m, 4H), 7.30 (s, 1H), 7.17 (d, *J* = 8.7 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 1H), 5.56 (d, *J* = 5.4 Hz, 1H), 4.90–4.75 (m, 1H), 4.49–4.32 (m, 1H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.27 (d, *J* = 6.1 Hz, 3H), 1.19 (d, *J* = 6.1 Hz, 3H), 0.75 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.2 (d, J_{PC} = 4.3 Hz), 135.5 (d, J_{PC} = 5.2 Hz), 135.1, 133.4 (d, J_{PC} = 2.3 Hz), 130.4 (d, J_{PC} = 2.2 Hz), 127.1 (d, J_{PC} = 4.9 Hz), 127.1 (d, J_{PC} = 2.9 Hz), 126.2, 125.9 (d, J_{PC} = 9.1 Hz), 123.1, 121.8 (d, J_{PC} = 1.5 Hz), 120.1, 112.7, 111.1 (d, J_{PC} = 3.5 Hz), 74.2 (d, J_{PC} = 8.2 Hz), 74.0 (d, J_{PC} = 7.7 Hz), 64.2 (d, J_{PC} = 165.2 Hz), 24.5 (d, J_{PC} = 2.7 Hz), 24.3 (d, J_{PC} = 3.6 Hz), 23.9 (d, J_{PC} = 5.3 Hz), 23.0 (d, J_{PC} = 5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 15.3 (d, *J* = 5.9 Hz). HPLC: Chiralcel AD-H column, 230 nm, 30 °C, *n*-hexane/*i*-propanol = 80/20, flow 0.7 mL/min, retention time 21.3 min and 22.9 min (maj.). HRMS: Calculated for $C_{21}H_{25}ClN_2O_5PS$ $[M+H]^+$ 483.0905, found 483.0910.

(*R*)-Diisopropyl (3-(5-bromo-1*H*-indol-3-yl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phosphonate (**3l**): 52 mg, 98% yield, 96% ee, $[\alpha]^{20}_D$ = −15.48 (*c* 1.04, THF), unknown compound, yellow solid, m.p. = 231–232 °C (decomp.), R_f = 0.20 (dichloromethane/methanol = 80/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.23 (s, 1H), 7.89 (d, *J* = 7.4 Hz, 1H), 7.70–7.55 (m, 3H), 7.50 (s, 1H), 7.45 (s, 1H), 7.17–7.05 (m, 2H), 5.71 (d, *J* = 5.2 Hz, 1H), 4.89–4.74 (m, 1H), 4.47–4.33 (m, 1H), 1.32 (d, *J* = 6.1 Hz, 3H), 1.26 (d, *J* = 6.1 Hz, 3H), 1.18 (d, *J* = 6.2 Hz, 3H), 0.74 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.2 (d, J_{PC} = 4.3 Hz), 135.5 (d, J_{PC} = 5.3 Hz), 135.4, 133.3 (d, J_{PC} = 2.2 Hz), 130.4 (d, J_{PC} = 2.1 Hz), 127.1 (d, J_{PC} = 2.6 Hz), 127.0 (d, J_{PC} = 4.8 Hz), 126.5 (d, J_{PC} = 8.9 Hz), 125.6, 123.2, 121.7 (d, J_{PC} = 1.6 Hz), 113.7, 113.2, 110.9, 74.3 (d, J_{PC} = 8.3 Hz), 74.0 (d, J_{PC} = 7.8 Hz), 64.2 (d, J_{PC} = 165.7 Hz), 24.5 (d, J_{PC} = 2.7 Hz), 24.3 (d, J_{PC} = 3.6 Hz), 23.9 (d, J_{PC} = 5.3 Hz), 23.0 (d, J_{PC} = 5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 15.3 (d, *J* = 5.8 Hz). HPLC: Chiralcel AD-H column, 230 nm, 30 °C, *n*-hexane/*i*-propanol = 80/20, flow 0.7 mL/min, retention time 21.9 min and 27.1 min (maj.). HRMS: Calculated for $C_{21}H_{25}BrN_2O_5PS$ $[M+H]^+$ 527.0400, found 527.0409.

(*R*)-Diisopropyl (3-(5-cyano-1*H*-indol-3-yl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phosphonate (3m): 44 mg, 94% yield, 91% ee, $[\alpha]^{20}_D$ = −29.32 (*c* 0.74, THF), unknown compound, white solid, m.p. = 215–216 °C (decomp.), R_f = 0.10 (dichloromethane/methanol = 40/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.64 (s, 1H), 7.90 (d, *J* = 7.0 Hz, 1H), 7.77–7.51 (m, 5H), 7.24–7.12 (m, 2H), 6.05 (d, *J* = 3.3 Hz, 1H), 4.88–4.70 (m,

1H), 4.54–4.34 (m, 1H), 1.31 (d, *J* = 6.1 Hz, 3H), 1.26 (d, *J* = 6.1 Hz, 3H), 1.15 (d, *J* = 6.1 Hz, 3H), 0.79 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 136.9 (d, J_{PC} = 5.2 Hz), 135.4 (d, J_{PC} = 5.2 Hz), 133.5 (d, J_{PC} = 1.6 Hz), 130.7, 128.1 (d, J_{PC} = 4.9 Hz), 126.9 (d, J_{PC} = 2.4 Hz), 126.4, 125.3, 124.6 (d, J_{PC} = 8.7 Hz), 121.9, 120.6, 112.8, 112.3, 103.4, 74.5 (d, J_{PC} = 8.0 Hz), 74.2 (d, J_{PC} = 7.7 Hz), 63.8 (d, J_{PC} = 165.5 Hz), 24.4 (d, J_{PC} = 2.7 Hz), 24.3 (d, J_{PC} = 3.4 Hz), 23.8 (d, J_{PC} = 5.5 Hz), 23.1 (d, J_{PC} = 5.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 15.2 (d, *J* = 5.7 Hz). HPLC: Chiralcel AS-H column, 230 nm, 30 °C, *n*-hexane/*i*-propanol = 70/30, flow 0.7 mL/min, retention time 9.2 min (maj.) and 13.9 min. HRMS: Calculated for $C_{22}H_{25}N_3O_5PS$ $[M+H]^+$ 474.1247, found 474.1255.

(*R*)-Diisopropyl (3-(1*H*-indol-3-yl)-5-methyl-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phosphonate (**3n**): 40 mg, 87% yield, 96% ee, $[\alpha]^{20}_D$ = +36.75 (*c* 0.74, THF), unknown compound, white solid, m.p. = 235–236 °C (decomp.), R_f = 0.30 (dichloromethane/methanol = 40/1). ^{1}H NMR (400 MHz, d6-DMSO): δ = 11.22 (s, 1H), 8.62 (s, 1H), 7.86–7.70 (m, 2H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.25 (s, 1H), 7.06–6.90 (m, 2H), 6.75 (t, *J* = 7.6 Hz, 1H), 4.78–4.62 (m, 1H), 4.43–4.27 (m, 1H), 2.32 (s, 3H), 1.26 (d, *J* = 6.1 Hz, 3H), 1.19 (d, *J* = 6.1 Hz, 3H), 1.15 (d, *J* = 6.2 Hz, 3H), 0.83 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, d6-DMSO): δ = 144.1 (d, J_{PC} = 2.4 Hz), 138.8 (d, J_{PC} = 4.3 Hz), 137.6, 134.4 (d, J_{PC} = 5.0 Hz), 132.2 (d, J_{PC} = 2.4 Hz), 127.6 (d, J_{PC} = 2.6 Hz), 127.4 (d, J_{PC} = 3.4 Hz), 126.1 (d, J_{PC} = 11.8 Hz), 122.6, 121.8 (d, J_{PC} = 1.7 Hz), 121.2, 120.1, 112.9, 111.7 (d, J_{PC} = 5.0 Hz), 73.6 (d, J_{PC} = 8.1 Hz), 73.3 (d, J_{PC} = 7.4 Hz), 64.6 (d, J_{PC} = 165.2 Hz), 25.3 (d, J_{PC} = 2.9 Hz), 25.2 (d, J_{PC} = 3.2 Hz), 24.8 (d, J_{PC} = 5.5 Hz), 24.0 (d, J_{PC} = 5.4 Hz), 22.5; ^{31}P NMR (162 MHz, d6-DMSO): δ = 16.5. HPLC: Chiralcel AD-H column, 230 nm, 30 °C, *n*-hexane/*i*-propanol = 70/30, flow 0.7 mL/min, retention time 13.7 min and 17.2 min (maj.). HRMS Calculated for $C_{22}H_{28}N_2O_5PS$ $[M+H]^+$ 463.1451, found 463.1456.

(*R*)-Diisopropyl (5-methyl-3-(5-methyl-1*H*-indol-3-yl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-3-yl)-phosphonate (**3o**): 42 mg, 88% yield, 94% ee, $[\alpha]^{20}_D$ = +11.87 (*c* 0.80, THF), unknown compound, white solid, m.p. = 235–236 °C (decomp.), R_f = 0.20 (dichloromethane/methanol = 40/1). ^{1}H NMR (400 MHz, d6-DMSO): δ = 11.08 (s, 1H), 8.58 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 2.2 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.27 (s, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 6.91 (s, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 4.77–4.63 (m, 1H), 4.39–4.26 (m, 1H), 2.33 (s, 3H), 2.15 (s, 3H), 1.26 (d, *J* = 6.1 Hz, 3H), 1.18 (d, *J* = 6.1 Hz, 3H), 1.15 (d, *J* = 6.2 Hz, 3H), 0.80 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, d6-DMSO): δ = 144.0 (d, J_{PC} = 2.4 Hz), 138.8 (d, J_{PC} = 4.5 Hz), 135.9, 134.4 (d, J_{PC} = 5.0 Hz), 132.1 (d, J_{PC} = 2.2 Hz), 128.3, 127.7 (d, J_{PC} = 2.3 Hz), 127.2 (d, J_{PC} = 3.8 Hz), 126.4 (d, J_{PC} = 11.1 Hz), 124.1, 121.8, 121.2, 112.5, 111.2 (d, J_{PC} = 4.8 Hz), 73.6 (d, J_{PC} = 8.0 Hz), 73.3 (d, J_{PC} = 7.6 Hz), 64.7 (d, J_{PC} = 165.6 Hz), 25.3 (d, J_{PC} = 2.8 Hz), 25.2 (d, J_{PC} = 3.3 Hz), 24.8 (d, J_{PC} = 5.5 Hz), 23.9 (d, J_{PC} = 5.5 Hz), 22.7, 22.5; ^{31}P NMR (162 MHz, d6-DMSO): δ = 16.6. HPLC: Chiralcel AS-H column, 230 nm, 30 °C, *n*-hexane/*i*-propanol = 80/20, flow 0.7 mL/min, retention time 8.9 min (maj.) and 12.9 min. HRMS: Calculated for $C_{23}H_{30}N_2O_5PS$ $[M+H]^+$ 477.1608, found 477.1613.

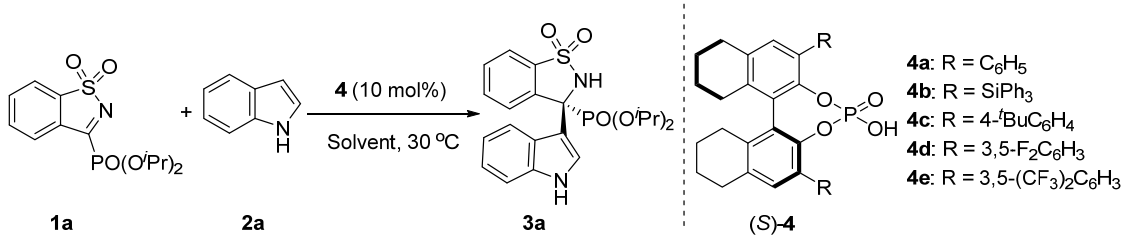
(*R*)-Diethyl (3-(1*H*-indol-3-yl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phosphonate (**3p**): 36 mg, 86% yield, 98% ee, $[\alpha]^{20}_D$ = +55.00 (*c* 0.72, THF), unknown compound, white solid, m.p. = 251–252 °C, R_f = 0.20 (dichloromethane/methanol = 40/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.78 (s, 1H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.87 (s, 1H), 7.63 (t, *J* = 7.0 Hz, 1H), 7.59–7.49 (m, 2H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 5.50 (s, 1H), 4.42–4.22 (m, 2H), 4.04–3.88 (m, 1H), 3.87–3.67 (m, 1H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.12 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.6 (d, J_{PC} = 3.9 Hz), 136.7, 135.5 (d, J_{PC} = 4.7 Hz), 133.4 (d, J_{PC} = 2.4 Hz), 130.4 (d, J_{PC} = 2.5 Hz), 127.4 (d, J_{PC} = 2.7 Hz), 126.4 (d, J_{PC} = 3.9 Hz), 124.6 (d, J_{PC} = 11.7 Hz), 122.9, 121.5 (d, J_{PC} = 2.1 Hz), 120.7, 119.9, 111.8, 110.7 (d, J_{PC} = 4.3 Hz), 65.6 (d, J_{PC} = 7.6 Hz), 64.5 (d, J_{PC} = 165.8 Hz), 64.2 (d, J_{PC} = 7.5 Hz), 16.7 (d, J_{PC} = 5.3 Hz), 16.3 (d, J_{PC} = 5.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 17.2. HPLC: Chiralcel AS-H column, 230 nm, 30 °C, *n*-hexane/*i*-propanol = 80/20, flow 0.7 mL/min, retention time 23.3 min (maj.) and 30.9 min. HRMS: Calculated for $C_{19}H_{22}N_2O_5PS$ $[M+H]^+$ 421.0982, found 421.0987.

(*R*)-Diisopropyl (1,1-dioxido-3-(1*H*-pyrrol-3-yl)-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phosphonate (**6**): 39 mg, 98% yield, 84% ee, $[\alpha]^{20}_D$ = −26.28 (*c* 0.78, THF), unknown compound, white solid, m.p. = 181–182 °C, R_f = 0.20 (dichloromethane/methanol = 40/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.74 (s, 1H), 7.84 (dd, *J* = 15.4, 7.6 Hz, 2H), 7.74–7.53 (m, 2H), 6.78 (s, 1H), 6.47 (s, 1H), 6.12 (d, *J* = 12.2 Hz, 2H), 4.88–4.67 (m, 1H), 4.63–4.43 (m, 1H), 1.39–1.21 (m, 6H), 1.10 (d, *J* = 6.0 Hz, 3H), 0.97 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.9 (d, J_{PC} = 5.4 Hz), 134.9 (d, J_{PC} = 5.1 Hz), 133.2 (d, J_{PC} = 2.1 Hz), 130.3 (d, J_{PC} = 2.0 Hz), 126.6, 126.5, 121.7 (d, J_{PC} = 1.1 Hz), 119.9, 109.0 (d, J_{PC} = 1.6 Hz), 108.9 (d, J_{PC} = 4.6 Hz), 75.2 (d, J_{PC} = 7.8 Hz), 74.3 (d, J_{PC} = 7.7 Hz), 63.2 (d, J_{PC} = 167.2 Hz), 24.5 (d, J_{PC} = 2.5 Hz), 24.4 (d, J_{PC} = 2.9 Hz), 23.5 (d, J_{PC} = 6.2 Hz), 23.3 (d, J_{PC} = 5.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 14.8. HPLC: Chiralcel AS-H column, 230 nm, 30 °C, *n*-hexane/*i*-propanol = 70/30, flow 0.7 mL/min, retention time 9.3 min (maj.) and 17.8 min. HRMS: Calculated for $C_{17}H_{24}N_2O_5PS$ $[M+H]^+$ 399.1138, found 399.1141.

3. Results and discussion

Initially, diisopropyl (1,1-dioxidobenzo[*d*]isothiazol-3-yl)phosphonate **1a** was chosen as the model substrate. We tested the Friedel–Crafts reaction of indole **2a** with **1a** in the presence of 10 mol% of H8-BINOL-derived CPA (*S*)-**4a** as an organocatalyst in dichloromethane at room temperature. Desired product **3a** was achieved in 76% yield, but with only 22% ee (Table 1, entry 1). A survey of organic solvents indicated that mesitylene was optimal in terms of enantioselectivity and yield (Table 1, entries 1–4). Next, to enhance the enantioselectivity of the reaction, CPA with various substituents at the 3 and 3′-positions of the H8-BINOL scaffold were evaluated, and electron-withdrawing 3,5-ditrifluoromethylphenyl-substituted catalyst (*S*)-**4e** was found to give the highest yield and enantioselectivity (98% yield, 96% ee, Table 1, entries 4–8). When we lowered the reaction temperature to 0 °C, both the activity and enantioselectivity slightly decreased (Table 1, entry 9). Addi-

Table 1
Evaluation of the reaction parameters [a].



1a 2a 3a (*S*)-**4**

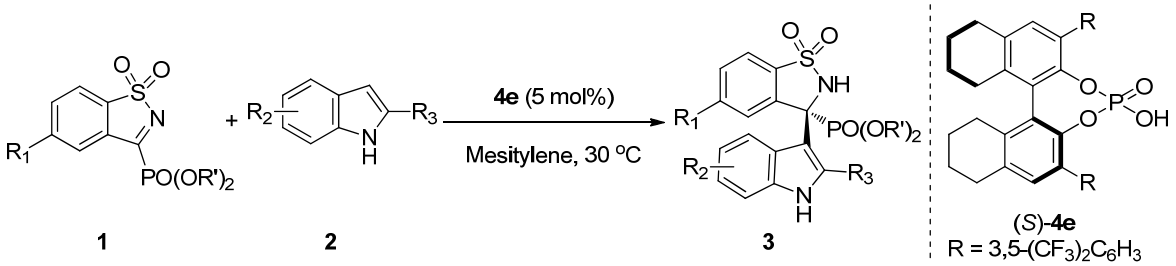
Entry	CPA	Solvent	*t*/h	Yield [b] (%)	ee [c] (%)
1	**4a**	CH_2Cl_2	24	76	22
2	**4a**	Et_2O	24	73	13
3	**4a**	Toluene	24	91	41
4	**4a**	Mesitylene	24	96	61
5	**4b**	Mesitylene	4	91	55
6	**4c**	Mesitylene	10	89	57
7	**4d**	Mesitylene	8	93	80
8	**4e**	Mesitylene	2	98	96
9 [d]	**4e**	Mesitylene	3	96	93
10 [e]	**4e**	Mesitylene	4	98	96

[a] Reaction conditions: **1** (0.1 mmol), **2** (0.3 mmol), (*S*)-**4** (10 mol%), purified solvent (2.0 mL), 30 °C.
[b] Isolated yield. [c] Determined by HPLC. [d] Reaction temperature = 0 °C. [e] Catalyst loading = 5 mol%.

tionally, the catalyst loading could be reduced to 5 mol% with retention of the enantioselectivity and slight lowering of activity (Table 1, entry 10). The optimal reaction conditions were thus established: 5 mol% CPA (*S*)-**4e** as the catalyst, mesitylene as the solvent and a reaction temperature of 30 °C.

With the optimal conditions in hand, we investigated the substrate scope for the reaction, and the results (Table 2) show that the Friedel–Crafts reaction is suitable for a wide array of indoles. The steric effect of the substituents is particularly clear; when a methyl group was introduced at the 2-position of

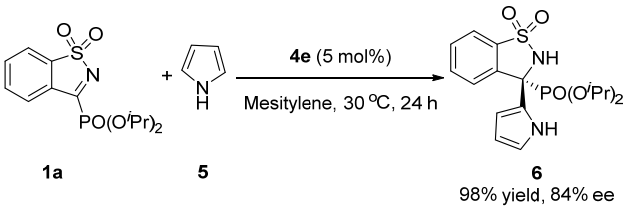
Table 2
Scope of the catalytic enantioselective Friedel–Crafts reaction [a].



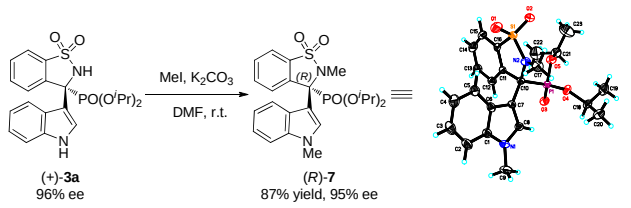
1 2 3

Entry	R′	R_1	R_2	R_3	Yield [b] (%)	ee [c] (%)
1	^{i}Pr	H	H	H	98 (**3a**)	96 (*R*)
2	^{i}Pr	H	H	Me	91 (**3b**)	59 (+)
3	^{i}Pr	H	4-Me	H	91 (**3c**)	87 (+)
4	^{i}Pr	H	5-Me	H	98 (**3d**)	95 (+)
5	^{i}Pr	H	6-Me	H	93 (**3e**)	94 (+)
6	^{i}Pr	H	7-Me	H	96 (**3f**)	95 (+)
7	^{i}Pr	H	7-Et	H	96 (**3g**)	95 (+)
8	^{i}Pr	H	5-MeO	H	98 (**3h**)	93 (+)
9	^{i}Pr	H	5-F	H	94 (**3i**)	94 (+)
10	^{i}Pr	H	6-F	H	85 (**3j**)	95 (+)
11	^{i}Pr	H	5-Cl	H	98 (**3k**)	95 (–)
12	^{i}Pr	H	5-Br	H	98 (**3l**)	96 (–)
13	^{i}Pr	H	5-CN	H	94 (**3m**)	91 (–)
14	^{i}Pr	Me	H	H	87 (**3n**)	96 (+)
15	^{i}Pr	Me	5-Me	H	88 (**3o**)	94 (+)
16	Et	H	H	H	86 (**3p**)	98 (+)

[a] Reaction conditions: **1** (0.1 mmol), **2** (0.3 mmol), (*S*)-**4e** (5 mol%), mesitylene (2.0 mL), 30 °C, 12 h.
[b] Isolated yield. [c] Determined by HPLC.



Scheme 2. Asymmetric Friedel–Crafts reaction of pyrrole with cyclic α-ketiminophosphonates.



Scheme 3. Assignment of the absolute configuration of (+)-**3a** by X-ray diffraction analysis.

the indole, only a moderate enantioselectivity of 59% ee was obtained (Table 2, entry 2). In contrast, using 4-methyl indole as the nucleophile gave the product in 91% yield and 87% ee (Table 2, entry 3). Excellent enantioselectivities and yields were obtained for indoles with both electron-donating and electron-withdrawing substituents on their 5, 6, or 7-positions (Table 2, entries 4–13). Further research was conducted with other cyclic α-ketiminophosphonates; when a methyl group was introduced onto the phenyl ring of substrate **1** or the isopropyl group was replaced with an ethyl group, the desired products were obtained in uniformly high enantioselectivities but slightly reduced yields compared with those of the unsubstituted substrate. Notably, no reactivity was observed for the analogous six-membered cyclic and simple acyclic α-ketiminophosphonates under the optimal conditions described above, which may be a consequence of their lower reactivity compared with that of the five-membered cyclic substrates.

Pyrrole was also tested as a nucleophile in the catalytic enantioselective Friedel–Crafts reaction. In the presence of 5 mol% of CPA (*S*)-**4e**, the reaction of pyrrole with **1a** proceeded smoothly to afford product **6** in 98% yield and 84% ee (Scheme 2). However, no reactivity was observed for 2-naphthanol, *N*,*N*-dimethylaniline or furan.

Owing to its poor solubility, compound (+)-**3a** was transformed into methylated product **7**, which could be easily recrystallized from chloroform and petroleum ether. On the basis of single crystal X-ray diffraction analysis, the absolute configuration of product (+)-**7** was determined to be *R* (Scheme 3). The absolute configuration of (+)-**3a** was thus unambiguously determined to be *R*.

4. Conclusions

In summary, we have developed an efficient enantioselective Friedel–Crafts reaction of indoles and cyclic α-ketiminophosphonates that is catalyzed by an (*S*)-H8-BINOL-derived chiral phosphoric acid bearing electron-withdrawing 3,5-ditrifluoromethylphenyl substituents at the 3- and 3′-positions. This method provides facile access to optically active quaternary α-aminophosphonates in high yields and enantioselectivities. In addition, good enantioselectivity was achieved with pyrrole in the same reaction. The further application of this enantioselective protocol to other reactions is ongoing in our laboratory.

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Graphical Abstract

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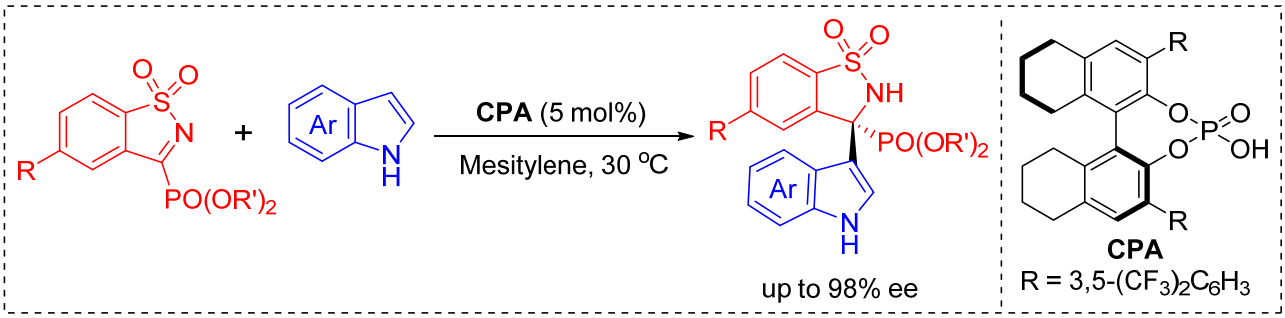
Enantioselective synthesis of quaternary α-aminophosphonates by organocatalytic Friedel–Crafts reactions of indoles with cyclic α-ketiminophosphonates

Zhong Yan, Xiang Gao, Yong-Gui Zhou *
Dalian Institute of Chemical Physics, Chinese Academy of Sciences



An efficient enantioselective Friedel–Crafts reaction of indoles and cyclic α-ketiminophosphonates was developed using a chiral phosphoric acid (CPA) catalyst. This reaction provides facile access to optically active quaternary α-aminophosphonates in high yields and up to 98% enantioselectivity.

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有机催化吲哚与环状酮亚胺膦酸酯的傅-克反应合成含手性季碳胺基膦酸衍生物

严 忠, 高 翔, 周永贵*
中国科学院大连化学物理研究所催化基础国家重点实验室, 辽宁大连116023

摘要: 在有机合成中, 季碳中心的构建始终是一项充满挑战的课题. 含手性季碳中心的胺基膦酸化合物以其多样的生物活性, 如酶抑制剂、抗真菌剂、抗菌剂和抗病毒剂等, 受到了科研工作者的广泛关注. 目前已有许多合成策略报道, 其中亲核试剂与α-酮亚胺膦酸酯的不对称加成策略为含手性季碳中心胺基膦酸衍生物的合成提供了一条简洁有效的路径, 但是却鲜有报道, 已有的报道也仅局限于乙酰氰、丙酮、硝基甲烷和芳基硼酸作亲核试剂. 为满足多样的手性胺基膦酸衍生物的合成需求, 新的合成策略和亲核源仍有待进一步发展. 值得一提的是, 不对称傅-克反应是一种非常有效的构建碳-碳键的合成方法, 并已有广泛报道. 基于吲哚与亚胺底物的傅-克反应经验, 我们研究组发展了一种有机催化吲哚与环状酮亚胺膦酸酯傅-克反应合成含手性季碳胺基膦酸衍生物的方法, 使用的有机催化剂是手性磷酸. 通过对溶剂、催化剂和温度的筛选发现, 使用在3,3′-位引入吸电子的3,5-二三氟甲基苯基取代的H8-BINOL衍生的手性磷酸作催化剂, 反应温度为30 °C, 溶剂

为均三甲苯时, 最高能以98%对映选择性得到含手性季碳胺基膦酸酯化合物. 该反应操作简单, 条件温和, 不仅适用于吲哚衍生物, 对吡咯也能取得较好结果. 总之, 该方法提供了一条简洁有效的合成手性胺基膦酸衍生物的途径.

关键词: 傅-克反应; 季碳胺基膦酸酯; 吲哚; 手性磷酸

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*通讯联系人. 电话: (0411)84379220; 电子信箱: ygzhou@dicp.ac.cn

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