Asymmetric Synthesis of α-Aminophosphonate Esters by the Addition of Dialkyl Phosphites to *tert*-Butanesulfinyl Imines

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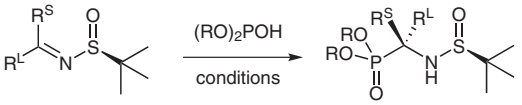
Abstract: The KHMDS-mediated addition of dialkyl phosphites to *N*-*tert*-butanesulfinyl aldimines and ketimines proceeds in uniformly high yields and diastereoselectivities and thereby enables the rapid and general asymmetric synthesis of α-aminophosphonate esters.

Key words: asymmetric synthesis, imines, amines, phosphorus, inhibitors

The serine protease GlpG is the archetypal member of the physiologically important rhomboid family of proteases that perform proteolysis within the hydrophobic environment of a membrane.[1] For the purpose of better understanding the molecular basis of substrate binding and proteolysis of the rhomboid membrane proteases, we have embarked on the synthesis of peptidyl phosphonate inhibitors for X-ray structural analysis of GlpG inhibitor complexes.[2] To prepare these peptidyl phosphonate inhibitors it is first necessary to synthesize the enantiomerically pure α-aminophosphonate ester precursors, for which several methods have been reported due to the importance of this mechanism-based protease inhibitor motif.[3]

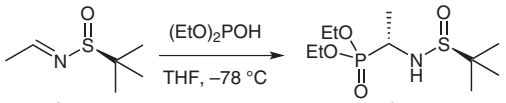
We elected to synthesize the α-aminophosphonate esters by the diastereoselective addition of dialkyl phosphites to *N*-*tert*-butanesulfinyl imines (Scheme 1).[4,5] However, repeated attempts to use the previously reported conditions of K_2CO_3 as base and CH_2Cl_2 as solvent for additions to *N*-*tert*-butanesulfinyl aldimines resulted in variable, but consistently poor reaction conversions,[6a] presumably due to the very poor solubility of K_2CO_3 in CH_2Cl_2. In contrast, multiple publications,[7] including the seminal work by Mikolajczyk[7a,e] and Davis,[7c,d] have reported that the addition of dialkyl phosphites to analogous *N*-toluenesulfinyl imines proceeds in high yields through the use of soluble amide bases in THF with the additions performed at low temperature to achieve high diastereoselectivity. Herein, we report our adaptation of these procedures for the asymmetric synthesis of *N*-*tert*-butanesulfinyl α-aminophosphonate esters by the addition of dialkyl phosphites to *N*-*tert*-butanesulfinyl imines using KHMDS as base in THF at –78 °C.

The addition of diethyl phosphite to sulfinyl imine **1a** was first explored at 0.1 M concentration using KHMDS in THF at –78 °C (Table 1, entry 1). The diethyl α-aminophosphonate **2a** was obtained in reasonable yield and with good diastereoselectivity.



Scheme 1 Asymmetric synthesis of *N*-*tert*-butanesulfinyl α-aminophosphonate esters

Table 1 Optimization of Reaction Conditions



1a **2a**

Entry	Base[a]	Concentration (M)	dr[b]	Yield (%)[c]
1	KHMDS	0.10	20:1	74
2	KHMDS	0.050	30:1	80
3	**KHMDS**	**0.025**	**49:1**	**95**
4	BuLi	0.025	6:1	19
5	LHMDS	0.025	9:1	62

[a] One equiv of base and 1.3 equiv of $(EtO)_2POH$ were used.
[b] Measured by ^{31}P NMR analysis of unpurified material.
[c] Based upon mass balance after purification by chromatography.

Moreover, the sense of induction was rigorously confirmed by cleavage of the sulfinyl group with HCl followed by comparison of the optical rotation of the resulting HCl salt of the α-aminophosphonate with the literature value.[8] Further optimization was then accomplished by varying the reaction concentration, with dilution of the reaction solution significantly improving both the yield and diastereoselectivity (entries 2 and 3). The more coordinating lithium counterion was next explored, but butyllithium (entry 4) or LHMDS (entry 5) as base resulted in lower yields and selectivities.

The scope and generality for the additions of dialkyl phosphites to *tert*-butanesulfinyl imines were next explored (Table 2). For each α-aminophosphonate addition product **2**, authentic diastereomer mixtures were prepared according to previously reported HCl-mediated sulfinyl group cleavage and subsequent base-mediated resulfinylation procedures for rigorous assignment of reaction diastereoselectivity.[9]

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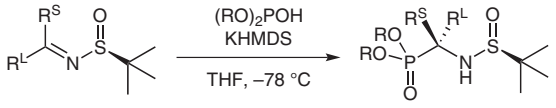
Table 2 Imine and Dialkylphosphite Substrate Scope[a]



Product	R^L	R^S	R	dr[b]	Yield (%)[c]
2b	Me	H	Me	49:1	95
2c	*i*-Pr	H	Me	24:1	91
2d	*i*-Bu	H	Me	49:1	95
2e	Bn	H	Me	20:1	92
2f	2-$MeOC_6H_4$	H	Me	49:1	96
2g	4-MeC_6H_4	H	Me	12:1	86
2h	*t*-Bu	Me	Me	99:1	94
2i	Me	H	Bn	99:1	90
2j	*i*-Pr	H	Bn	20:1	88
2k	Bn	H	Bn	30:1	96
2l	*t*-Bu	Me	Bn	99:1	91

[a] One equiv of base and 1.3 equiv of $(EtO)_2POH$ were used.
[b] Measured by ^{31}P NMR analysis of unpurified material.
[c] Based upon isolated yield of the major diastereomer after purification by chromatography.

Addition of dimethyl phosphite to *N*-sulfinyl aldimine **1a** provided α-aminophosphonate **2b** in the same yield and selectivity as observed for the addition of diethyl phosphite (see Table 1, entry 3). Moreover, dimethyl phosphite additions to branched alkyl imines were also effective, with α-branched product **2c** and β-branched products **2d** and **2e** each obtained in high yield and with high diastereoselectivity. Even additions to electron-rich aromatic aldimines proceeded in high yields (**2f** and **2g**). Notably, the *ortho*-substituted *N*-sulfinyl benzaldimine gave product **2f** with higher selectivity than that observed for the *para*-substituted *N*-sulfinyl benzaldimine derivative **2g**.

To evaluate the applicability of the method to sterically encumbered substrates, dimethyl phosphite addition to the ketimine derived from pinacolone was also explored. Product **2h** was obtained in very high yield and selectivity, and is consistent with the high selectivity previously reported for dialkyl phosphite additions to *N*-toluenesulfinyl ketimines.[7c]

Cleavage of both of the methyl groups from dimethyl α-aminophosphonates requires strongly acidic reaction conditions.[10] Therefore, the preparation of dibenzyl α-aminophosphonates was also investigated because the benzyl groups can be removed by hydrogenolysis under mild conditions.[11] The synthesis of dibenzyl α-aminophosphonates **2i** to **2l** proceeded in comparable yields and diastereoselectivities to that previously observed for the synthesis of the dimethyl α-aminophosphonates, thereby demonstrating that dibenzyl phosphite additions are equally effective to the more extensively studied dimethyl phosphite additions.

In summary, the addition of dialkyl phosphites to diverse *N*-*tert*-butanesulfinyl imines **1** with KHMDS as base in THF at –78 °C provides the desired α-aminophosphonate esters **2** in uniformly high yields and diastereoselectivities. This procedure should prove generally useful for the synthesis of α-aminophosphonates and related peptide derivatives. We are currently applying this procedure to the synthesis of mechanism-based peptidyl phosphonate inhibitors of the rhomboid membrane protease GlpG.

The *N*-*tert*-butanesulfinyl imines were all prepared according to previously reported conditions.[12] Commercial reagents were purchased from Sigma-Aldrich or Alfa Aesar and were used as received. All reactions were carried out under N_2 atmosphere, unless otherwise indicated. Reactions were monitored by TLC on EMD Silica Gel 60 F_{254} plates or using an Agilent 6120 Quadrupole LCMS. Visualization of the developed chromatogram was performed by fluorescence quenching or staining with $KMnO_4$ stain. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. ^1H, ^{19}F, ^{31}P, and ^{13}C NMR spectra were recorded on an Agilent Oxford AS400 NMR spectrometer. NMR spectra were internally referenced to residual protio solvent signals. Data for ^1H NMR spectra are reported as follows: chemical shift, multiplicity (standard abbreviations), coupling constant (Hz), and integration. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). High-resolution mass spectra were recorded on an Agilent 6550 iFunnel QTOF LCMS. IR spectra were collected on an Agilent Cary 630 FTIR Spectrometer using diamond ATR. Column chromatography was performed using Silicycle Silica-P Flash Silica Gel, using either glass columns or a Teledyne Isco Combi-Flash Rf. All salts were purchased from Aldrich and used without purification. Solvents were purchased from Brand-Nu Laboratories, Inc. and were used as received.

Addition of Dialkyl Phosphites to *tert*-Butanesulfinyl Imines; General Procedure

To a flame-dried round-bottomed flask purged with N_2 and equipped with a magnetic stir bar was added THF (10 mL) and respective *tert*-butanesulfinyl imine (0.5 mmol). This solution was stirred and cooled to –78 °C in an acetone/dry ice bath. In another flame-dried round-bottomed flask equipped with a magnetic stir bar, was added the required phosphite (0.65 mmol, 1.3 equiv) and THF (10 mL). This solution was cooled to –78 °C, and then a solution of KHMDS (0.91M in THF, 550 μL, 0.5 mmol, 1.0 equiv) was added under N_2 pressure. The KHMDS-phosphite solution was then cannulated under N_2 pressure into the imine solution and the resulting reaction mixture was stirred for 20 min at –78 °C. The reaction was then quenched by the addition of sat. NH_4Cl (1 mL), and the reaction mixture was allowed to warm to r.t. The THF was removed under reduced pressure. Crude diastereomeric ratios were ascertained by ^{31}P NMR with comparison to authentic diastereomer mixture prepared according to previously reported desulfinylation/resulfinylation procedures.[9] The crude material was purified by silica gel chromatography to afford the desired *N*-sulfinyl α-aminophosphonate esters as single diastereomers.

Diethyl ((*R*)-1-{[(*S*)-*tert*-Butanesulfinyl]amino}ethyl)phosphonate (2a)

From (*S*,*E*)-*N*-ethylidene-2-methylpropane-2-sulfinamide (14 mg) and diethyl phosphite (15 μL). Crude dr was determined to be 49:1. The product was isolated as a colorless oil (27 mg, 95%) using a Teledyne Isco RediSep Rf 4 g column. Solvent gradient: 20% to 100% acetone in hexanes, 18 mL/min, for 25 min.

IR (ATR): 2961, 1452, 1232, 1028, 830 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.12–4.22 (m, 4 H), 3.64–3.73 (m, 2 H), 1.44 (dd, *J* = 20, 8 Hz, 3 H), 1.34 (t, *J* = 8 Hz, 6 H), 1.22 (s, 9 H).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 25.6.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_8H_{25}NO_4PS$: 286.3502; found: 286.3522.

Diethyl (*R*)-(1-Aminoethyl)phosphonate[8]
To a round-bottomed flask containing **2a** (54 mg) was added 4 M HCl in 1,4-dioxane (250 μL, 1 mmol, 5 equiv), and the reaction mixture was stirred at r.t. for 1 h. Volatiles were then removed under reduced pressure, affording the deprotected aminophosphonate quantitatively. Full characterization data are given in reference 8; $[\alpha]_D^{25}$ –5.3 (*c* 3.0, $CHCl_3$) {Lit.[8] $[\alpha]_D$ –5.4 (*c* 1.8, $CHCl_3$)}.

Dimethyl ((*R*)-1-{[(*S*)-*tert*-Butanesulfinyl]amino}ethyl)phosphonate (2b)
From (*S*,*E*)-*N*-ethylidene-2-methylpropane-2-sulfinamide (70 mg) and dimethyl phosphite (60 μL). Crude dr was determined to be 49:1. The product was isolated as a colorless oil (124 mg, 95%) using a Teledyne Isco RediSep Rf 40 g column. Solvent gradient: 20% to 100% acetone in hexanes, 40 mL/min, for 25 min; $[\alpha]_D^{20}$ +69.8 (*c* 1.6, $CHCl_3$).

IR (ATR): 2959, 1457, 1231, 1021, 826, 784 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.83 (d, *J* = 8 Hz, 3 H), 3.80 (d, *J* = 8 Hz, 3 H) 3.71 (m, 2 H), 1.44 (dd, *J* = 16, 8 Hz, 3 H), 1.22 (s, 9 H).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.1.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_8H_{21}NO_4PS$: 258.0929; found: 258.0974.

Dimethyl ((*R*)-1-{[(*S*)-*tert*-Butanesulfinyl]amino}-2-methylpropyl)phosphonate (2c)[6a]
From (*S*,*E*)-2-methyl-*N*-(2-methylpropylidene)propane-2-sulfinamide (88 mg) and dimethyl phosphite (60 μL). Crude dr was determined to be 24:1. The product was isolated as an amorphous solid (129 mg, 91%) using a Teledyne Isco RediSep Rf 40 g column. Solvent gradient: 20% to 100% acetone in hexanes, 40 mL/min, for 25 min.

IR (ATR): 2958, 1466, 1234, 1024, 827, 786 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.83 (d, *J* = 12 Hz, 3 H), 3.77 (d, *J* = 12 Hz, 3 H) 3.70 (dd, *J* = 12 Hz, 8 Hz, 1 H), 3.44 (ddd, *J* = 20, 12, 4 Hz, 1 H), 2.17–2.24 (m, 1 H), 1.25 (s, 9 H), 0.99 (dd, *J* = 8, 4 Hz, 3 H), 0.97 (d, *J* = 8 Hz, 3 H).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.44.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{25}NO_4PS$: 286.1242; found: 286.1225.

Dimethyl ((*R*)-1-{[(*S*)-*tert*-Butanesulfinyl]amino}-3-methylbutyl)phosphonate (2d)
From (*S*,*E*)-2-methyl-*N*-(3-methylbutylidene)propane-2-sulfinamide (100 mg) and dimethyl phosphite (60 μL). Crude dr was determined to be 49:1. The product was isolated as an amorphous solid (142 mg, 95%) using a Teledyne Isco RediSep Rf 40 g column. Solvent gradient: 20% to 100% acetone in hexanes, 40 mL/min, for 25 min; $[\alpha]_D^{20}$ +66.5 (*c* 1.8, $CHCl_3$).

IR (ATR): 2954, 2869, 1469, 1258, 1231, 1023, 829, 807 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.85 (d, *J* = 8 Hz, 3 H), 3.79 (d, *J* = 8 Hz, 3 H), 3.53–3.65 (m, 2 H), 1.77–1.83 (m, 1 H), 1.66 (m, 1 H), 1.56 (m, 1 H), 1.23 (s, 9 H), 0.94 (d, *J* = 8 Hz, 3 H), 0.89 (d, *J* = 8 Hz, 3 H).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.5.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{27}NO_4PS$: 300.1400; found: 300.1381.

Dimethyl ((*R*)-1-{[(*S*)-*tert*-Butanesulfinyl]amino}-2-phenylethyl)phosphonate (2e)
From (*S*,*E*)-2-methyl-*N*-(2-phenylethylidene)propane-2-sulfinamide (110 mg) and dimethyl phosphite (60 μL). Crude dr was determined to be 20:1. The product was isolated as a white solid (153 mg, 92%) using a Teledyne Isco RediSep Rf 40 g column. Solvent gradient: 20% to 100% acetone in hexanes, 40 mL/min, for 25 min; mp 52–55 °C; $[\alpha]_D^{20}$ +58.8 (*c* 1.7, $CHCl_3$).

IR (ATR): 3181, 2949, 2846, 1456, 1363, 1247, 1233, 1072, 1033 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.30 (m, 2 H), 7.19–7.22 (m, 3 H), 3.83 (d, *J* = 12 Hz, 3 H), 3.79 (d, *J* = 12 Hz, 3 H), 3.60 (t, *J* = 8 Hz, 1 H), 3.24 (ddd, *J* = 16, 8, 6 Hz, 1 H), 2.83–2.92 (m, 1 H), 0.95 (s, 9 H).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.35.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{25}NOPS$: 334.1241; found: 334.1236.

Dimethyl ((*R*)-{[(*S*)-*tert*-Butanesulfinyl]amino}(2-methoxyphenyl)methyl)phosphonate (2f)
From (*S*,*E*)-2-methyl-*N*-(4-methoxybenzylidene)propane-2-sulfinamide (120 mg) and dimethyl phosphite (60 μL). Crude dr was determined to be 49:1. The product was isolated as a white solid (167 mg, 96%) using a Teledyne Isco RediSep Rf 40 g column. Solvent gradient: 20% to 100% acetone in hexanes, 40 mL/min, for 25 min; mp 57–60 °C; $[\alpha]_D^{20}$ +109.8 (*c* 0.8, $CHCl_3$).

IR (ATR): 3168, 2953, 1493, 1462, 1235, 1062, 1022, 760 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.45 (dt, *J* = 6, 2 Hz, 1 H), 7.26–7.30 (m, 1 H), 6.97 (t, *J* = 6 Hz, 1 H), 6.89 (d, *J* = 8 Hz, 1 H), 5.38 (dd, *J* = 16, 4 Hz, 1 H), 4.19 (dd, *J* = 6, 2 Hz, 1 H), 3.86 (s, 3 H), 3.81 (d, *J* = 8 Hz, 3 H), 3.52 (d, *J* = 8 Hz, 3 H), 1.19 (s, 9 H).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 24.4.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{25}O_5PS$: 350.1191; found: 350.1190.

Dimethyl ((*R*)-{[(*S*)-*tert*-Butanesulfinyl]amino}(*p*-tolyl)methyl)phosphonate (2g)[6a]
From (*S*,*E*)-2-methyl-*N*-(4-methylbenzylidene)propane-2-sulfinamide (110 mg) and dimethyl phosphite (60 μL). Crude dr was determined to be 12:1. The product was isolated as a white solid (143 mg, 86%) using a Teledyne Isco RediSep Rf 40 g column. Solvent gradient: 20% to 100% acetone in hexanes, 40 mL/min, for 25 min; mp 28–30 °C; $[\alpha]_D^{20}$ +112.1 (*c* 1.2, $CHCl_3$).

IR (ATR): 3220, 2957, 1579, 1457, 1362, 1021 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (dd, *J* = 8, 2 Hz, 2 H), 7.19 (d, *J* = 8 Hz, 2 H), 5.01 (d, *J* = 8 Hz, 1 H), 3.72 (d, *J* = 12 Hz, 3 H), 3.67 (d, *J* = 12 Hz, 3 H), 2.35 (d, *J* = 2 Hz, 3 H), 1.23 (s, 9 H).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 23.58.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{24}NO_4PS$ + Na: 356.1061; found: 356.1044.

Dimethyl ((*R*)-2-{[(*S*)-*tert*-Butanesulfinyl]amino}-3,3-dimethylbutan-2-yl)phosphonate (2h)[6a]
From (*S*,*E*)-*N*-(3,3-dimethylbutan-2-ylidene)-2-methylpropane-2-sulfinamide (100 mg) and dimethyl phosphite (60 μL). Crude dr was determined to be 99:1. The product was isolated as an amorphous solid (147 mg, 94%) using a Teledyne Isco RediSep Rf 40 g column. Solvent gradient: 20% to 100% acetone in hexanes, 40 mL/min, for 25 min; $[\alpha]_D^{20}$ +38.9 (*c* 0.9, $CHCl_3$).

IR (ATR): 2954, 1472, 1379, 1242, 1073, 1018, 827, 801 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.89 (d, *J* = 8 Hz, 1 H), 3.83 (d, *J* = 8 Hz, 3 H), 3.77 (d, *J* = 8 Hz, 3 H), 1.54 (d, *J* = 16 Hz, 3 H), 1.22 (s, 9 H), 1.05 (s, 9 H).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 29.71.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{29}NOPS$: 314.1555; found: 314.1547.

Dibenzyl ((*R*)-1-{[(*S*)-*tert*-Butanesulfinyl]amino}ethyl)phosphonate (2i)

From (*S*,*E*)-*N*-ethylidene-2-methylpropane-2-sulfinamide (70 mg) and dibenzyl phosphite (140 μL). Crude dr was determined to be 99:1. The product was isolated as a colorless oil (184 mg, 90%) using a Teledyne Isco RediSep Rf 40 g column. Solvent gradient: 20% to 100% EtOAc in hexanes, 40 mL/min, for 25 min; $[\alpha]_D^{20}$ +35.8 (*c* 1.1, $CHCl_3$).

IR (ATR): 3449, 2955, 1455, 1228, 989, 733, 695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.37 (m, 10 H), 4.95–5.14 (m, 4 H), 3.69–3.73 (m, 2 H), 1.42 (dd, *J* = 20, 8 Hz, 3 H), 1.17 (s, 9 H).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 26.60.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{29}NO_4PS$: 410.1555; found: 410.1553.

Dibenzyl ((*R*)-1-{[(*S*)-*tert*-Butanesulfinyl]amino}-2-methylpropyl)phosphonate (2j)

From (*S*,*E*)-2-methyl-*N*-(2-methylpropylidene)propane-2-sulfinamide (88 mg) and dibenzyl phosphite (140 μL). Crude dr was determined to be 20:1. The product was isolated as a colorless oil (192 mg, 88%) using a Teledyne Isco RediSep Rf 40 g column. Solvent gradient: 20% to 100% EtOAc in hexanes, 40 mL/min, for 25 min; $[\alpha]_D^{20}$ +30.4 (*c* 0.4, $CHCl_3$).

IR (ATR): 2961, 1456, 1232, 1010, 990, 727, 695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.40 (m, 10 H), 5.13–5.15 (m, 2 H), 4.97 (dd, *J* = 12, 8 Hz, 1 H), 4.85 (dd, *J* = 12, 8 Hz, 1 H), 3.90 (dd, *J* = 10, 8 Hz, 1 H), 3.48 (ddd, *J* = 16, 8, 2 Hz, 1 H), 2.22 (m, 1 H), 1.26 (s, 9 H), 0.97 (d, *J* = 4 Hz, 3 H), 0.96 (dd, *J* = 8, 2 Hz, 3 H).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 26.00.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{33}NO_4PS$: 438.1868; found: 438.1835.

Dibenzyl ((*R*)-1-{[(*S*)-*tert*-Butanesulfinyl]amino}-2-phenylethyl)phosphonate (2k)

From (*S*,*E*)-2-methyl-*N*-(2-phenylethylidene)propane-2-sulfinamide (110 mg) and dibenzyl phosphite (140 μL). Crude dr was determined to be 30:1. The product was isolated as a light yellow oil (232 mg, 96%) using a Teledyne Isco RediSep Rf 40 g column. Solvent gradient: 20% to 100% acetone in hexanes, 40 mL/min, for 25 min; $[\alpha]_D^{20}$ +38.6 (*c* 0.7, $CHCl_3$).

IR (ATR): 3175, 2920, 1455, 1239, 988, 736, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13–7.37 (m, 15 H), 5.13–5.10 (m, 2 H), 4.92 (ddd, *J* = 36, 12, 8 Hz, 2 H), 3.79–3.88 (m, 1 H), 3.65 (t, *J* = 8 Hz, 1 H), 3.21 (ddd, *J* = 12, 8, 4 Hz, 1 H), 2.82–2.91 (m, 1 H), 0.95 (s, 9 H).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 25.62.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{33}NOPS$: 486.1868; found: 486.1843.

Dibenzyl ((*R*)-2-{[(*S*)-*tert*-Butanesulfinyl]amino}-3,3-dimethylbutan-2-yl)phosphonate (2l)[6a]

From (*S*,*E*)-*N*-(3,3-dimethylbutan-2-ylidene)-2-methylpropane-2-sulfinamide (100 mg) and dibenzyl phosphite (140 μL). Crude dr was determined to be 99:1. The product was isolated as a light yellow oil (205 mg, 91%) using a Teledyne Isco RediSep Rf 40 g column. Solvent gradient: 20% to 100% EtOAc in hexanes, 40 mL/min, for 25 min.

IR (ATR): 2957, 1455, 1379, 1240, 1213, 1072, 986, 732, 695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.42 (m, 10 H), 5.09–5.20 (m, 2 H), 4.90 (dd, *J* = 12, 8 Hz, 1 H), 4.77 (dd, *J* = 12, 8 Hz, 1 H), 4.12 (d, *J* = 8 Hz, 1 H), 1.61 (d, *J* = 16 Hz, 3 H), 1.26 (s, 9 H), 1.08 (s, 9 H).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.35.

HRMS: *m*/*z* [M + Na]$^+$calcd for $C_{24}H_{36}NOPS$ + Na: 488.2000; found: 488.1999.

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Supporting Information

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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