Direct regio- and diastereoselective diphosphonylation of cyclic enamines: One-pot synthesis of α,α’-bis(diphenylphosphoryl)- and α,α’-bis(diphenylphosphorothioyl)cycloalkanones

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1. Experimental procedures

General Considerations

Commercially available reagents and solvents were used without further purification. Acetonitrile was dried by distillation from sodium and stored over activated molecular sieves (4 Å°). When necessary the reactions were performed in oven-dried glassware under dry nitrogen. Melting points were determined in open glass capillaries and are uncorrected. All the compounds were characterized by IR, NMR and mass spectrometry. IR spectra were recorded on a Nicolet IR200 spectrometer. $^1$H, $^{31}$P, $^{13}$C and $^{13}$C APT NMR spectra were recorded on a 400 MHz-spectrometer. Chemical shifts ($\delta$) are reported in part per million (ppm) relative to the residual solvent peak. High-resolution-MS spectra were performed on a Thermo LTQ Orbitrap XL mass spectrometer. Single crystal X-ray diffraction analysis was done on a Rigaku Oxford Diffraction Supernova Dual Source (Cu at zero) diffractometer equipped with an Atlas CCD detector using $\omega$ scans and CuK$\alpha$ ($\lambda$ = 1.54184 Å) radiation. Column chromatography was performed on silica gel (70–230 mesh ASTM) using the reported eluent. Thin layer chromatography (TLC) was carried out on 5 x 20 cm plates with a layer thickness of 0.25 mm (Silica gel 60 F254). When necessary they were developed with KMnO$_4$ and SiO$_2$/I$_2$.

Synthesis of cyclic enamines 1

The starting cyclic enamines 1 were prepared according to the procedure reported by Stork [1] with slight modification:

A mixture of cyclic ketone (1 mol) and morpholine (1.7 mol) in dry toluene (30 mL) was heated at reflux, with Dean-Stark separation of water, for 4 h. The solvent was then removed under vacuum and the residue obtained was distilled under reduced pressure to give pure enamine 1 in more than 90% yield.

General procedure for the synthesis of $\alpha,\alpha'$-bis(diphenylphosphoryl)- and $\alpha,\alpha'$-bis(diphenylphosphorothioyl)cycloalkanones 2

To a well stirred solution of enamine 1 (1 mmol) and triethylamine (6.6 mmol) in dry acetonitrile (15 mL), maintained under an inert atmosphere (N$_2$) and cooled at 0 °C, P-chlorodiphenylphosphine (1 mmol) in dry acetonitrile (3 mL) was added dropwise within 15 min. The resulting solution was warmed up to room temperature and stirred for 1 h. The
reaction mixture was cooled again at 0 °C and the second portion of P-chlorodiphenylphosphine (5 mmol) in dry acetonitrile (15 mL) was added in the same manner as before. The mixture was allowed to warm up to room temperature and then refluxed for an extra 2 h. The reaction mixture was then cooled and treated with DMSO or sulfur as follows:

- Oxidation: DMSO (6 mmol) was added and the mixture was heated under reflux for 2 h. After cooling, 2N aqueous HCl solution (30 mL) was added dropwise at 0 °C and stirring was continued at room temperature for 12 h. The mixture was then extracted with CH₂Cl₂ (3 × 10 mL). The organic phase was dried over MgSO₄ and concentrated under vacuum. The residue obtained was chromatographed on a silica gel column using CH₂Cl₂ as eluent, or recrystallized from toluene (in the case of compounds 2a and 2c).

- Sulfurization: Ground sulfur (6 mmol) was added and the reaction mixture was stirred at room temperature until complete dissolution of the sulfur in 2 h. 2N aqueous HCl solution (30 mL) was then added dropwise at 0 °C and stirring was continued at room temperature for 12 h. The mixture was then extracted with CH₂Cl₂ (3 × 10 mL). The organic phase was dried over MgSO₄ and concentrated under vacuum. The residue obtained was chromatographed on a silica gel column using CH₂Cl₂ as eluent.

The compounds obtained were characterized by various spectroscopic tools including IR, NMR (¹H, ³¹P, ¹³C) spectroscopy, mass spectrometry and single crystal X-ray diffraction.

2. Spectral data of compounds 2a-g

trans-2,6-bis(diphenylphosphoryl)cyclohexanone (2a)

Yield (51 %); white solid; mp 249-250 °C; IR (neat): νP=O 1245 cm⁻¹; νC=O 1706 cm⁻¹.

³¹P NMR (CD₃OD, 161.97 MHz) δ (ppm) = 33.3 (s, 2P). ¹H NMR (CD₃OD, 400.13 MHz): δ = 2.01-2.22 (m, 6H, 3 CH₂), 4.15-4.20 (m, 2H, 2 CH-P), 7.38-7.83 (m, 20H, Ar-H). ¹³C NMR (CD₃OD, 100.61 MHz): δ = 21.7 (t, CH₂, Jₐ=P = 6.0 Hz), 27.1 (s, 2 CH₂), 51.7 (d, 2 CH-P, J₀=P = 66.4 Hz), 201.7 (s, C=O), Ar-C: δ = 128.3, 128.4, 128.7, 128.8, 130.4, 129.9, 130.4, 130.5, 130.6, 130.9, 131.4, 131.8, 131.9, 132.2.
ESI-HRMS: calculated for C_{30}H_{28}O_{3}P_{2}: 499.15864 (M+H)^{+}; found: 499.15796.

**trans-2,6-bis(diphenylphosphoryl)-4-methylcyclohexanone (2b)**

Yield (60 %); white solid; mp 274-275 °C; IR (neat): ν_{P=O} 1211 cm^{-1}; ν_{C=O} 1706 cm^{-1}.

$^{31}$P NMR (CD_{3}OD, 161.97 MHz): $\delta$ (ppm) = 32.4 (s, 1P), 33.9 (s, 1P). $^1$H NMR (CD_{3}OD, 400.13 MHz): $\delta$ = 0.86 (d, 3H, $J = 8.0$ Hz, CH$_3$), 1.75-2.17 (m, 4H, 2 CH$_2$), 2.56-2.60 (m, 1H, CH-CH$_3$), 3.96-4.00 (m, 1H, CH-P), 7.31-7.91 (m, 20 H, Ar-H). $^{13}$C NMR (CD_{3}OD, 100.61 MHz): $\delta$ = 19.93 (s, CH$_3$), 28.28 (d, CH-CH$_3$, $^2J_{C-P}$ = 12.1 Hz), 33.83 (d, CH$_2$, $^2J_{C-P}$ = 2.0 Hz), 35.11 (d, CH$_2$, $^2J_{C-P}$ = 3.0 Hz), 50.90 (d, CH-P, $^1J_{C-P}$ = 74.5 Hz), 51.46 (dd, CH-P, $^1J_{C-P}$ = 57.3 Hz, $^3J_{C-P}$ = 3.0 Hz), 201.75 (t, C=O, $^2J_{C-P}$ = 3.0 Hz, chair conformation), 202.79 (s, C=O, boat conformation), Ar-C: $\delta$ = 128.1, 128.3, 128.4, 128.55, 128.59, 128.7, 128.9, 129.0, 129.2, 129.9, 130.2, 130.3, 130.35, 130.44, 130.6, 130.7, 130.8, 130.9, 131.45, 131.48, 131.6, 131.8, 131.92, 131.94, 132.20, 132.22, 132.44, 132.47.

ESI-HRMS: calculated for C$_{31}$H$_{30}$O$_{3}$P$_{2}$: 513.17429 (M+H)$^+$; found: 513.17318.

**trans-2,6-bis(diphenylphosphoryl)-4-ethylcyclohexanone (2c)**

Yield (65 %); white solid; mp 218-220 °C; IR (neat): ν_{P=O} 1207 cm^{-1}; ν_{C=O} 1707 cm^{-1}.

$^{31}$P NMR (CD_{3}OD, 161.97 MHz): $\delta$ (ppm) = 32.5 (s, 1P), 33.9 (s, 1P). $^1$H NMR (CD_{3}OD, 400.13 MHz): $\delta$ = 0.71 (t, 3H, $J = 8.0$ Hz, CH$_3$), 1.10-1.23 (m, 2H, CH$_2$-CH$_3$), 1.73-1.82 (m, 2H, CH$_2$), 2.07-2.15 (m, 2H, CH$_2$), 2.30-2.31 (m, 1H, CH-CH$_2$-CH$_3$), 3.97-4.01 (m, 1H, CH-P), 7.30-7.91 (m, 20 H, Ar-H). $^{13}$C NMR (CD_{3}OD, 100.61 MHz): $\delta$ = 10.3 (s, CH$_3$, chair conformation), 10.4 (s, CH$_3$, boat conformation), 27.8 (s, CH$_2$-CH$_3$, boat conformation), 28.1 (s, CH$_2$-CH$_3$, chair conformation), 31.8 (d, CH$_2$, $^2J_{C-P}$ = 2.0 Hz), 32.8 (d, CH$_2$, $^2J_{C-P}$ = 4.0 Hz), 34.7 (d, CH-CH$_2$-CH$_3$, $^2J_{C-P}$ = 11.1 Hz, chair conformation), 38.3 (t, CH-
CH$_2$-CH$_3$, $^3$J$_{C,P}$ = 11.1 Hz, boat conformation), 50.9 (d, CH-P, $^1$J$_{C,P}$ = 73.5 Hz), 51.4 (dd, CH-P, $^1$J$_{C,P}$ = 73.5 Hz, $^3$J$_{C,P}$ = 3.0 Hz), 202.0 (dd, C=O, $^2$J$_{C,P}$ = 5.0 Hz, $^3$J$_{C,P}$ = 3.0 Hz, chair conformation), 203.5 (t, C=O, $^2$J$_{C,P}$ = 5.0 Hz, boat conformation), Ar-C: δ = 128.05, 128.16, 128.23, 128.28, 128.32, 128.39, 128.41, 128.46, 128.51, 128.58, 128.60, 128.72, 128.77, 128.84, 128.97, 129.41, 129.67, 130.2, 130.4, 130.45, 130.5, 130.55, 130.59, 130.7, 130.8, 130.84, 130.9, 130.95, 131.0, 131.1, 131.25, 131.32, 131.4, 131.5, 131.52, 131.57, 131.61, 131.7, 131.8, 131.84, 131.94, 131.97, 132.2, 132.3, 132.48, 132.50, 132.61, 132.64, 133.0.

ESI-HRMS: calculated for C$_{32}$H$_{32}$O$_3$P$_2$: 527.18994 (M+H)$^+$; found: 527.19036.

**trans- and cis-2,5-bis(diphenylphosphoryl)cyclopentanone (2d)**

![2d](image)

Yield (58 %); white solid; mp 278-280 °C; IR (neat): ν$_{P=O}$ 1250 cm$^{-1}$; ν$_{C=O}$ 1732 cm$^{-1}$.

$^{31}$P NMR (CDCl$_3$, 161.97 MHz) δ (ppm) = 31.9 (s, 2P, 70 %, trans); 32.0 (s, 2P, 30 %, cis).

$^1$H NMR (CDCl$_3$, 400.13 MHz): δ = 2.32-2.46 (m, 4 H, 2 CH$_2$), 3.51-3.57 (m, 2 H, 2 CH-P), 7.26-7.77 (m, 20 H, Ar-H). $^{13}$C NMR (CDCl$_3$, 100.61 MHz): δ = 24.1 (d, 2 CH$_2$, $^2$J$_{C,P}$ = 2.0 Hz, cis), 24.2 (d, 2 CH$_2$, $^2$J$_{C,P}$ = 3.0 Hz, trans), 50.5 (d, 2 CH-P, $^1$J$_{C,P}$ = 64.4 Hz), 206.2 (t, C=O, $^2$J$_{C,P}$ = 5.0 Hz), Ar-C: δ = 128.4, 128.6, 128.7, 128.9, 130.7, 130.9, 131.0, 131.4, 131.5, 131.6, 131.7, 132.0, 132.6.

ESI-HRMS: calculated for C$_{29}$H$_{26}$O$_3$P$_2$: 485.14299 (M+H)$^+$; found: 485.14418.

**trans-2,6-bis(diphenylphosphorothioyl)cyclohexanone (2e)**

![2e](image)

Yield (53%); yellow solid; mp 252-254 °C; IR (neat): ν$_{P=S}$ 696 cm$^{-1}$; ν$_{C=O}$ 1733 cm$^{-1}$.

$^{31}$P NMR (CDCl$_3$, 161.97 MHz) δ (ppm) = 43.0 (s, 2P). $^1$H NMR (CD$_3$OD, 400.13 MHz): δ = 1.95-2.28 (m, 6 H, 3 CH$_2$), 4.15-4.20 (m, 2 H, 2 CH), 7.38-7.93 (m, 20 H, Ar-H). $^{13}$C NMR (CDCl$_3$, 100.61 MHz): δ = 21.3 (t, CH$_2$, $^3$J$_{C,P}$ = 8.0 Hz), 27.5 (s, 2 CH$_2$), 52.2 (d, 2 CH-P, $^1$J$_{C,P}$
= 50.3 Hz), 200.8 (t, C=O, $^2J_{C,P} = 4.0$ Hz), Ar-C: $\delta$ = 128.2, 128.3, 128.7, 128.8, 130.8, 130.9, 131.0, 131.26, 131.31, 131.4, 131.5, 131.6, 131.8.

EI-HRMS: calculated for C$_{30}$H$_{28}$O$_1$P$_2$S$_2$: 530.1057 (M$^+$); found: 530.1066.

**trans-2,6-bis(diphenylphosphorothioyl)-4-methylcyclohexanone (2f)**

![Image of 2f](image)

Yield (61%); yellow solid; mp 272-273 °C; IR (neat): $\nu_{P=S}$ 701 cm$^{-1}$; $\nu_{C=O}$ 1706 cm$^{-1}$.

$^{31}$P NMR (CDCl$_3$, 161.97 MHz): $\delta$ (ppm) = 41.5 (s, 1P), 43.8 (s, 1P). $^1$H NMR (CDCl$_3$, 400.13 MHz): $\delta$ = 0.83 (d, 3H, $J = 8.0$ Hz, CH$_3$), 1.71-2.16 (m, 4H, 2 CH$_2$), 2.77-2.81 (m, 1H, CH-CH$_3$), 4.17-4.23 (m, 1H, CH-P), 5.03-5.10 (m, 1H, CH-P), 7.17-7.94 (m, 20 H, Ar-H). $^{13}$C NMR (CDCl$_3$, 100.61 MHz): $\delta$ = 21.3 (s, CH$_3$), 27.7 (dd, CH-CH$_3$, $^3J_{C,P} = 12.1$ Hz, 2.0 Hz), 34.4 (s, CH$_2$), 35.5 (s, CH$_2$), 51.7 (dd, CH-P, $^1J_{C,P} = 45.3$ Hz, $^3J_{C,P} = 3.0$ Hz), 51.8 (d, CH-P, $^1J_{C,P} = 55.3$ Hz), 200.9 (dd, C=O, $^2J_{C,P} = 5.0$ Hz, 3.0 Hz), Ar-C: $\delta$ = 128.1, 128.2, 128.3, 128.4, 128.6, 128.7, 128.8, 128.9, 130.2, 130.7, 130.95, 130.98, 131.1, 131.2, 131.3, 131.38, 131.44, 131.5, 131.6, 131.7, 131.80, 131.86, 131.9, 132.0, 132.2.

EI-HRMS: calculated for C$_{31}$H$_{30}$O$_1$P$_2$S$_2$: 544.1213 (M$^+$); found: 544.1220.

**trans- and cis-2,5-bis(diphenylphosphorothioyl)cyclopentanone (2g)**

![Image of 2g](image)

Yield (55 %); yellow solid; mp 232-233 °C; IR (neat): $\nu_{P=S}$ 698 cm$^{-1}$; $\nu_{C=O}$ 1709 cm$^{-1}$.

$^{31}$P NMR (CDCl$_3$, 161.97 MHz) $\delta$ (ppm) = 45.4 (s, 2P, 87%, trans), 45.6 (s, 2P, 13%, cis). $^1$H NMR (CDCl$_3$, 400.13 MHz): $\delta$ = 2.31-2.37 (m, 4 H, 2 CH$_2$), 3.89-3.96 (m, 2 H, 2 CH-P), 7.37-7.91 (m, 20 H, Ar-H). $^{13}$C NMR (CDCl$_3$, 100.61 MHz): $\delta$ = 24.2 (d, 2 CH$_2$, $^2J_{C,P} = 8.0$ Hz), 51.1 (d, 2 CH-P, $^1J_{C,P} = 51.3$ Hz), 205.0 (s, C=O), Ar-C: $\delta$ = 128.4, 128.6, 128.7, 128.8, 130.9, 131.0, 131.2, 131.3, 131.4, 131.5, 131.6, 131.7, 131.8, 131.9, 131.9, 132.0, 132.4.
EI-HRMS: calculated for C_{29}H_{26}O_1P_2S_2: 516.0900 (M^+); found: 516.0917.

3. NMR and mass Spectra of compounds 2a-g

trans-2,6-bis(diphenylphosphoryl)cyclohexanone (2a)
N2 bis(diphenyloxyphosphoryl)cyclohexa-1-one P

N2 bis(diphenyloxyphosphoryl)cyclohexa-1-one APT
trans-2,6-bis(diphenylphosphoryl)-4-m ethylcyclohexanone (2b)
trans-2,6-bis(diphenylphosphoryl)-4-ethylcyclohexanone (2c)
trans and cis-2,5-bis(diphenylphosphoryl)cyclopentanone (2d)
trans-2,6-bis(diphenylphosphorothioyl)cyclohexanone (2e)
trans-2,6-bis(diphenylphosphorothioyl)-4-methylcyclohexanone (2f)

![Chemical Structure](image)
trans and cis-2,5-bis(diphenylphosphorothioyl)cyclopentanone (2g)
4. Single crystal X-ray diffraction analysis

For the structures of compounds 2a, 2b and 2g, X-ray intensity data were collected at 100 K, on a Rigaku Oxford Diffraction Supernova Dual Source (Cu at zero) diffractometer equipped with an Atlas CCD detector using ω scans and CuKα (λ = 1.54184 Å) radiation. The images were interpreted and integrated with the program CrysAlisPro (Rigaku Oxford Diffraction) [2]. Using Olex2 [3], the structure was solved by direct methods using the ShelXS [4] structure solution program and refined by full-matrix least-squares on F² using the ShelXL [5] program package. Non-hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode and isotropic temperature factors fixed at 1.2 times U(eq) of the parent atoms (1.5 times for methyl groups).

Crystal data for compound 2a. C₃₀H₂₈O₃P₂, M = 498.46, triclinic, space group P-1 (No. 2), a = 8.8812(2) Å, b = 11.4466(3) Å, c = 13.2360(3) Å, α = 95.8308(19), β = 108.188(2), γ = 92.146(2), V = 1268.32(5) Å³, Z = 2, T = 100 K, ρcalc = 1.305 g cm⁻³, μ(Cu-Kα) = 1.796 mm⁻¹, F(000) = 524, 48860 reflections measured, 5168 unique (Rint = 0.0876) which were used in all
calculations. The final $R_1$ was 0.0516 ($I > 2\sigma(I)$) and $wR_2$ was 0.1410 (all data). (Figure 1).

**Crystal data for compound 2b.** C$_{31}$H$_{30}$O$_3$P$_2$, $M = 512.49$, triclinic, space group $P-1$ (No. 2), $a = 8.9003(3)$ Å, $b = 11.8231(5)$ Å, $c = 13.6022(4)$ Å, $\alpha = 108.476(3)$, $\beta = 107.746(3)$, $\gamma = 90.192(3)$, $V = 1285.04(9)$ Å$^3$, $Z = 2$, $T = 100$ K, $\rho_{\text{calc}} = 1.324$ g cm$^{-3}$, $\mu(\text{Cu-K}\alpha) = 1.786$ mm$^{-1}$, $F(000) = 540$, 24036 reflections measured, 5221 unique ($R_{\text{int}} = 0.0499$) which were used in all calculations. The final $R_1$ was 0.0519 ($I > 2\sigma(I)$) and $wR_2$ was 0.1461 (all data). The 4-methylcyclohexan-1-one ring is mainly observed in the chair conformation. However, a very slight disorder was observed for this ring, adopting a boat conformation. The disorder was properly refined in two PARTS with final occupancy factors of 0.94 and 0.06, for the chair and boat conformations, respectively (Figure 2).

**Crystal data for compound 2g.** C$_{29}$H$_{26}$OP$_2$S$_2$, $M = 516.56$, orthorhombic, space group $Fdd2$ (No. 43), $a = 27.7465(7)$ Å, $b = 19.1707(7)$ Å, $c = 9.4982(3)$ Å, $V = 5052.3(3)$ Å$^3$, $Z = 8$, $T = 100$ K, $\rho_{\text{calc}} = 1.358$ g cm$^{-3}$, $\mu(\text{Cu-K}\alpha) = 3.266$ mm$^{-1}$, $F(000) = 2160$, 9674 reflections measured, 2499 unique ($R_{\text{int}} = 0.0541$) which were used in all calculations. The final $R_1$ was 0.0561 ($I > 2\sigma(I)$) and $wR_2$ was 0.1562 (all data). The asymmetric unit consists of only half a trans-2,5-bis(diphenylphosphorothioyl)cyclopentanone molecule, i.e. the total molecule is generated through a two-fold crystallographic axis (Figure 3).

CCDC 1527521-1527523 contain the supplementary crystallographic data for this paper and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

Figure 1. Asymmetric unit of the crystal structure of 2a, showing thermal displacement ellipsoids at the 50% probability level.
Figure 2. Asymmetric unit of the crystal structure of 2b, showing thermal displacement ellipsoids at the 50% probability level. The slight disorder of the 4-methylcyclohexan-1-one ring (occupancy factor of 0.06) is shown in yellow.
Figure 3. Asymmetric unit of the crystal structure of 2g, showing thermal displacement ellipsoids at the 50% probability level.