Diastereofacial Selectivity in the Reaction of (*C*-1)-Metalated Alkyldiphenylphosphine Imides with Schiff Bases

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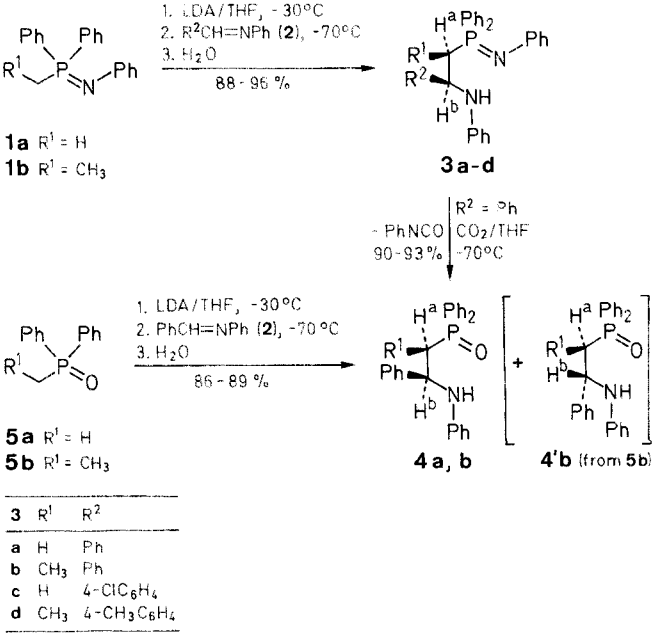
erythro-2-Anilinoalkyldiphenylphosphine phenylimides are obtained by reaction of (*C*-1)-metalated alkyldiphenylphosphine imides with aldimines in a diastereoselective fashion. Reaction of the products with carbon dioxide or with lithium aluminum hydride leads to 2-anilinoalkyldiphenylphosphine oxides or 2-anilinoalkyldiphenylphosphines, respectively.

Phosphine imide derivatives have attracted interest with regard to their widespread utility as key intermediates in the synthesis of natural products[1-3] and as ligands in transition-metal complexes.[4-6] Moreover, they have been found to possess interesting properties as organic semiconductors[7] and used as building blocks of backbone polymers.[8] In this context, we have reported the *C*-alkylation of alkyldiphenylphosphine imides with several electrophiles[9,10] and the application of the resultant functionalized alkyldiphenylphosphine imides to the preparation of new acyclic phosphine derivatives (e.g., phosphines,[11] phosphine oxides,[9,10] and phosphine sulfides[9]) and cyclic phosphorus compounds (λ^5-1,4-azaphosphorines,[12] 3-benzylidene- and 3-phenylimino-λ^5-3*H*-phospholes,[13] 2-oxo-1,2-dihydro-λ^5-1,3,4-diazaphosphorines,[11] and 4-oxo-1,4-dihydro-λ^5-1,2-benzazaphosphorines[14]).

We recently reported that the diastereoface selectivity of the additions of metalated alkyldiphenylphosphine imides[10] to aldehydes is higher than that of the corresponding phosphine oxides. In connection with our studies on alkyldiphenylphosphine imides, we now report the reaction of their lithiated derivatives with aldimines; the selectivity of the reaction of organometallic compounds with aldimines has hitherto hardly been explored.[15]

The reaction of alkyldiphenylphosphine phenylimides **1** with lithium diisopropylamide (LDA) in tetrahydrofuran followed by addition of *N*-phenylbenzaldimines **2** and aqueous work-up gave 2-anilinoalkyl(diphenyl)phosphine phenylimides **3** in high yields. In the case of aliphatic *N*-phenylaldimines, a complex product mixture was obtained, probably due to competitive metal–hydrogen exchange reactions between the metalated phosphine imide and the aldimine.

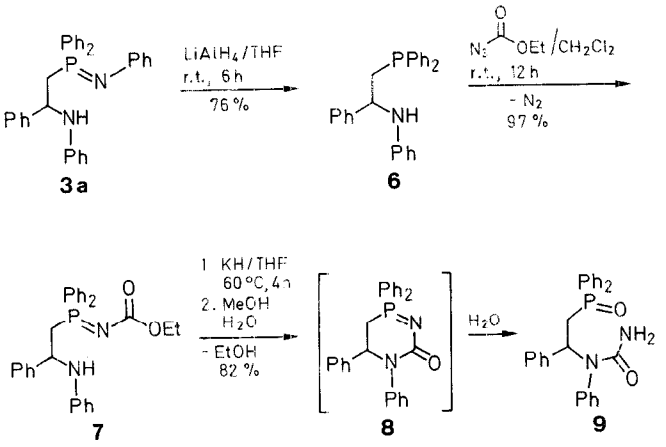
The spectral data of the crude product mixture, especially in the cases of **3b** and **3d**, allowed us to elucidate the stereoselectivity of the reaction and to assign the stereochemistry of compounds **3**. Thus, the IR spectra recorded at low concentrations (10^{-3} M) in tetrachloromethane show absorptions due to intramolecular hydrogen bonding of the amino group[16] at $\nu \approx 3240\ cm^{-1}$, while the ^{31}P-NMR spectra[17] of crude **3b** (δ = 13.9) show the diastereoisomer ratio (*erythro*/*threo*) to be higher than 98:2. The small vicinal H,H and H,P coupling constants ($^3J_{H^a,H^b}$ = 2.7 and $^3J_{P,H^b}$ = 7.3 Hz) observed in the ^{1}H-NMR spectrum of **3b** are in good agreement with the reported data given for the *erythro* isomer (*erythro*: $^3J_{H,H}$ = 2–4[18]; $^3J_{P,H}$ = 5–9[19,20]; *threo*: $^3J_{H,H}$ = 6–9[18]; $^3J_{P,H}$ = 15–20 Hz[19,20]). In addition, the values of the coupling constants of **3b** are very close to those observed for *erythro*-2-hydroxyalkylphosphine oxides[20,21] and imides[10] and support the stereochemical assignment. Aza-Wittig reactions of compounds **3** with carbon dioxide led to the corresponding *erythro*-2-anilinoalkylphosphine oxides **4** with loss of phenyl isocyanate.



3	R^1	R^2
a	H	Ph
b	CH_3	Ph
c	H	4-ClC_6H_4
d	CH_3	4-$CH_3C_6H_4$

Conversely, treatment of alkyldiphenylphosphine oxides **5a, b** with lithium diisopropylamide followed by the addition of aldimines afforded 2-anilino-2-phenylalkyl(diphenyl)phosphine oxides **4**, showing an *erythro*/*threo* ratio of (47:53) for **4b** as evidenced by ^{31}P-NMR spectrometry (δ = 37.4, 37.0). The stereochemical assignment was based on the chemical shifts and coupling constants observed in the ^{1}H-NMR spectra, and is in agreement with previously reported data.[10,18-21] Thus, signal of the H^b of the *erythro* isomer **4b** is found at δ = 4.27 and shows $^3J_{H^aH^b}$ = 2.8 and $^3J_{PH^b}$ = 6.9 Hz, while the signal of H^b of the *threo* isomer **4'b** is found downfield (δ = 4.52) with $^3J_{H^aH^b}$ = 6.3 and $^3J_{PH^b}$ = 18.2 Hz.

Functionalized alkyldiphenylphosphine imides are valuable intermediates in organic synthesis[11,22] and provide an access to functionalized phosphorus compounds which otherwise are not readily available. As in the case of simple phosphine imides,[11] 2-anilinoalkyl(diphenyl)phosphine imide **3a** may be reduced with lithium aluminum hydride to give 2-anilino-2-phenylethyl(diphenyl)alkylphosphine (**6**; δ_P = −22.7); the reaction of **6** with ethyl carbonoazidate in dichloromethane afforded the phosphine *N*-ethoxycarbonylimide **7** (δ_P = 21.7). The attempted cyclization of **7** with potassium hydride in tetrahydrofuran at 60 °C (6 h), followed by methanolysis and aqueous work-up, did not give the cyclic compound **8**, but the phosphine oxide **9**, probably via hydrolysis of intermediate **8**.



In summary, metalated alkyldiphenylphosphine imides show high diastereoselectivity in their reactions with *N*-phenyl aldimines, *erythro*-2-anilinoalkyldiphenylphosphine imides **3** being obtained. These products can be used as intermediates for the synthesis of the corresponding phosphine oxides **4** and for the preparation of the functionalized alkyldiphenylphosphine **6**. Hybrid ligands of this type are used to form complexes in organometal chemistry; they may undergo intramolecular chelate-assisted NH-oxidative addition.[23]

Table 1. Compounds **3**, **4**, **6**, **7**, **9** Prepared

Product	Yield[a] (%)	mp (°C)	Molecular Formula[b]	MS (70eV)[c] *m/z* (M^+)
3a	93	166–167	$C_{32}H_{29}N_2P$ (472.5)	472
3b	88	163–164	$C_{33}H_{31}N_2P$ (486.6)	486
3c	90	160–161	$C_{32}H_{28}ClN_2P$ (507.0)	508
3d	96	183–184	$C_{34}H_{33}N_2P$ (500.6)	500
4a	86 (90)[d]	205–206	$C_{26}H_{24}NOP$ (397.4)	397
4b	89[e] (94)[d]	226–227	$C_{27}H_{26}NOP$ (411.5)	411
6	76	127–128	$C_{26}H_{24}NP$ (381.4)	381
7	97	131–132	$C_{29}H_{29}N_2O_2P$ (468.5)	468
9	82	194–195	$C_{27}H_{25}N_2O_2P$ (440.5)	440

[a] Yield of isolated pure product.
[b] Satisfactory microanalyses: C ±0.30, H ±0.20, N ±0.25.
[c] Recorded on a Hewlett-Packard 5930A spectrometer.
[d] Yield from **3**.
[e] Isolated as an *erythro*/*threo* (47 : 53) mixture.

***erythro*-(2-Anilinoalkyl)diphenylphosphine *N*-Phenylimides 3; General Procedure:**

In a dried, argon-filled flask with addition funnel, a solution of the alkyldiphenylphosphine *N*-phenylimide **1** (5.0 mmol) in THF (40 mL) is added dropwise to a stirred solution of LDA (5.0 mmol) in THF (30 mL) at −30 °C. After 1 h, the mixture is cooled to −70 °C and then the *N*-phenylaldimine **2** (5.0 mmol) in THF (20 mL) is added dropwise. When the mixture has come to room temperature, it is poured into ice-water (100 mL) and the product extracted with CH_2Cl_2 (150 mL). The organic phase is dried (Na_2SO_4) and evaporated to afford the crude solid product **3** which is recrystallized from hexane/CH_2Cl_2 (5:1).

***erythro*-(2-Anilino-1-methyl-2-phenylethyl)diphenylphosphine Oxide (4b); Typical Procedure for the Conversion 3 → 4:**

Through a solution of phosphine imide **3b** (2.43 g, 5.0 mmol) in THF (50 mL) at −50 °C is bubbled excess CO_2. When the mixture has come to room temperature, the solvent is evaporated to afford a solid, which is washed with hot Et_2O (25 mL) and recrystallized from hexane/CH_2Cl_2 (5:1) to give pure **4b**; yield: 1.97 g (94%); mp 226–227 °C.

***erythro*-(2-Anilinoalkyl)diphenylphosphine Oxides 4; General Procedure for the Conversion 5 → 4:**

A solution of the alkyldiphenylphosphine oxide **5** (5.0 mmol) in THF (40 mL) is treated with LDA (5.0 mmol) in THF (30 mL) at −30 °C followed by the addition of the aldimine **2** (5.0 mmol) in THF (20 mL) at −70 °C as described for the preparation of **3**. Products **4** are purified by recrystallization from hexane/CH_2Cl_2 (5:1). In the case of **4b** (*erythro* isomer) part of the isolated product is the *threo* isomer **4'b**.

erythro/*threo*-(2-Anilino-1-methyl-2-phenylethyl)diphenylphosphine Oxide (**4b/4'b**); yield: 1.8 g (89%); mp 220–223 °C; *erythro*/*threo* ratio (**4b/4'b**): 47 : 53, according to ^{31}P-NMR analysis.

$C_{27}H_{26}NOP$	calc.	C 78.81	H 6.37	N 3.40
(411.5)	found	79.04	6.51	3.62

MS (70 eV): *m/z* = 411 (M^+, 5); 209 (100).

Table 2. Spectral Data of Compounds **3**, **4**, **6**, **7**, **9**

Compound	IR (KBr)[a] ν(cm^{-1})	^{1}H-NMR (80 MHz, $CDCl_3$/TMS)[b] δ, *J*(Hz)	^{13}C-NMR (20 MHz, $CDCl_3$/TMS)[b] δ, *J*(Hz)	^{31}P-NMR (30 MHz, $CDCl_3/H_3PO_{4ext}$)[b]
3a	3300 (NH); 1330 (P=N)	2.71 (m, 2H, CH_2); 4.28 (dt, 1H, $^3J_{H,H}$ = 9.8, $^3J_{P,H}$ = 2.8, CH); 5.08 (s, 1H, NH); 6.10–7.85 (m, 25 H_{arom})	37.0 (d, $^1J_{P,C}$ = 82.2, C-1); 55.2 (d, $^2J_{P,C}$ = 4.8, C-2); 113.8–150.6 (C_{arom})	+8.4
3b	3260 (NH); 1340 (P=N)	1.19 (dd, 3H, $^3J_{H,H}$ = 7.3, $^3J_{P,H}$ = 16, CH_3); 2.45 (dt, 1H, $^3J_{H,H}$ = $^3J_{P,H}$ = 7.3, $^3J_{H,H}$ = 2.7, CH); 4.37 (dd, 1H, $^3J_{H,H}$ = 2.7, $^3J_{P,H}$ = 7.3, CH); 5.08 (s, NH); 6.22–7.87 (m, 25 H_{arom})[c]	7.4 (CH_3); 39.6 (d, $^1J_{P,C}$ = 82.4, C-1); 58.3 (d, $^2J_{P,C}$ = 3.4, C-2); 114.1–150.8 (C_{arom})	+13.9
3c	3310 (NH); 1320 (P=N)	2.71 (m, 2H, CH_2); 4.27 (dt, 1H, $^3J_{H,H}$ = 9.5, $^3J_{P,H}$ = 2.9, CH); 6.14–7.83 (m, 20 H_{arom} + NH)	37.0 (d, $^1J_{P,C}$ = 82.2, C-1); 54.6 (d, $^2J_{P,C}$ = 4.8, C-2); 113.7–150.7 (C_{arom})	+8.2
3d	3320 (NH); 1330 (P=N)	1.2 (dd, 3H, $^3J_{PH}$ = 15.8, $^3J_{H,H}$ = 7.1, CH_3); 2.26 (s, 3H, *p*-CH_3); 2.52 (m, 1H, CH); 4.33 (dd, 1H, $^3J_{P,H}$ = 6.6, $^3J_{H,H}$ = 2.6, CH); 5.2 (s, 1H, NH); 6.16–7.9 (m, 24 H_{arom})	7.5 (CH_3); 20.9 (*p*-CH_3); 39.7 (d, $^1J_{P,C}$ = 83.5, C-1); 58.0 (d, $^2J_{P,C}$ = 3.2, C-2); 114.1–150.9 (C_{arom})	+13.8
4a	3300 (NH); 1180 (P=O)	2.61 (m, 2H, CH_2); 4.41 (m, 1H, CH); 5.47 (s, 1H, NH); 6.12–7.71 (m, 20 H_{arom})	38.2 (d, $^1J_{P,C}$ = 63.0, C-1); 54.4 (d, $^2J_{P,C}$ = 3.1, C-2); 112.8–146.1 (C_{arom})	+31.1
4b	3280 (NH); 1170 (P=O)	1.20 (dd, 3H, $^3J_{P,H}$ = 16.1, $^3J_{H,H}$ = 7.4, CH_3); 2.65 (dq, 1H, $^3J_{H,H}$ = 7.4, $^3J_{P,H}$ = 6.9, $^3J_{H,H}$ = 2.8, CH); 4.27 (dd, 1H, $^3J_{P,H}$ = 6.6, $^3J_{H,H}$ = 2.8, CH); 5.63 (s, 1H, NH); 6.3–7.8 (m, 20 H_{arom})[c]	6.7 (CH_3); 39.0 (d, $^1J_{P,C}$ = 67.1, C-1); 57.7 (d, $^2J_{P,C}$ = 1.7, C-2); 113.7–147.5 (C_{arom})	+37.4
6	3370 (NH)	2.47 (m, 2H, CH_2); 4.10 (m, 2H, CH + NH); 6.10–7.63 (m, 20 H_{arom})	38.8 (d, $^1J_{P,C}$ = 16.7, C-1); 55.9 (d, $^2J_{P,C}$ = 14.5, C-2); 113.3–146.7 (C_{arom})	−22.7
7	3310 (NH); 1320 (P=N)	1.26 (t, 3H, CH_3); 2.92 (m, 2H, CH_2); 4.12 (q, 2H, OCH_2); 4.40 (m, 1H, CH); 5.40 (m, 1H, NH); 6.42–7.81 (m, 20 H_{arom})	14.6 (CH_3); 35.6 (d, $^1J_{P,C}$ = 57.4, C-1); 53.4 (d, $^2J_{P,C}$ = 3.1, C-2); 61.4 (OCH_2); 113.3–146.5 (C_{arom}); 162.9 (CO)	+21.7
9	3320 (NH); 1190 (P=O)	2.71 (m, 2H, CH_2); 4.56 (m, 1H, CH); 5.6 (m, 2H, NH_2); 6.42–7.93 (m, 20 H_{arom})	38.6 (d, $^1J_{P,C}$ = 66.1, C-1); 54.5 (d, $^2J_{P,C}$ = 4.2, C-2); 113.8–147.3 (C_{arom} + CO)	+31.4

[a] Recorded on a Perkin-Elmer 298 IR spectrophotometer.
[b] Recorded on a Varian FT-80A spectrometer.
[c] Recorded on a Bruker 300AC spectrometer.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.20 (dd, 3H, $^3J_{P,H}$ = 16.0, $^3J_{H,H}$ = 7.4 Hz, CH_3); 2.65 (dq, 1H, $^3J_{H,H}$ = 7.4, $^3J_{P,H}$ = 6.9, $^3J_{H,H}$ = 2.8 Hz, CH); 4.27 (dd, 1H, $^3J_{P,H}$ = 6.9, $^3J_{H,H}$ = 2.8 Hz, CH); 5.63 (s, 1H, NH); 6.3–7.8 (m, 20 H_{arom}) [for the *erythro* isomer **4b**].

δ = 1.13 (dd, 3H, $^3J_{P,H}$ = 15.5, $^3J_{H,H}$ = 7.4 Hz, CH_3); 2.93 (m, 1H, $^3J_{H,H}$ = 7.4, $^3J_{P,H}$ = 7.0, $^3J_{H,H}$ = 6.3 Hz, CH); 4.52 (dd, 1H, $J_{P,H}$ = 18.2, $^3J_{H,H}$ = 6.3 Hz, CH); 6.21–7.8 (m, 20 H_{arom} + NH) [for the *threo*-isomer **4'b**].

^{31}P-NMR ($CDCl_3$/85% H_3PO_{4ext}): δ = 37.4 (*erythro*); 37.0 (*threo*).

(2-Anilino-2-phenylethyl)diphenylphosphine (6):
In a dried, argon-filled round-bottomed flask fitted with stirrer and addition funnel, a solution of phosphine imide **3a** (4.72 g, 10.0 mmol) in THF (50 mL) is added dropwise to a stirred suspension of $LiAlH_4$ (0.38 g, 10.0 mmol) in THF (40 mL), and stirring is continued at room temperature for 6 h. The mixture is then quenched with MeOH (20 mL) and ice-water (80 mL), and CH_2Cl_2 (300 mL) is added. The organic phase is separated, washed with H_2O (50 mL), and dried (Na_2SO_4). The solvent is evaporated and the crude solid product **6** is recrystallized from hexane/CH_2Cl_2 (8:1); yield: 2.9 g (76%); mp 127–128°C.

(2-Anilino-2-phenylethyl)diphenylphosphine *N*-Ethoxycarbonylimide (7):
Phosphine **6** (1.9 g, 5.0 mmol) is dissolved in CH_2Cl_2 (25 mL) and a solution of ethyl carbonoazidate (0.63 g, 5.5 mmol) in CH_2Cl_2 (20 mL) is added dropwise over 30 min, with stirring at room temperature. After 12 h, the solvent is evaporated and the residual oil is taken up in Et_2O (20 mL). This solution is agitated until a crystalline solid forms. The solid product **7** is isolated by suction; yield: 2.27 g (97%); mp 131–132°C (hexane/CH_2Cl_2, 6:1).

***N*-(2-Diphenylphosphinoyl-1-phenylethyl)-*N*-phenylurea (9):**
In a dried, argon-filled round-bottomed flask with stirrer and addition funnel, a solution of phosphine imide **7** (2.1 g, 4.5 mmol) in THF (20 mL) is added dropwise to a stirred suspension of KH (0.2 g, 5.0 mmol) in THF (30 mL). The mixture is stirred at 60°C for 4 h, then quenched with MeOH (10 mL) and H_2O (10 mL), and extracted with CH_2Cl_2 (80 mL). The organic phase is separated and dried (Na_2SO_4), the solvent is evaporated, and the residual oil is taken up in Et_2O (10 mL). This solution is agitated until a crystalline yellow solid forms. The solid product **9** is isolated by suction and recrystallized from hexane/CH_2Cl_2 (4:1); yield: 1.8 g (82%); mp 194–195°C.

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