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1-Phosphanorbornadiene-imines and amines in enantioselective allylic *C*- and *N*-alkylation

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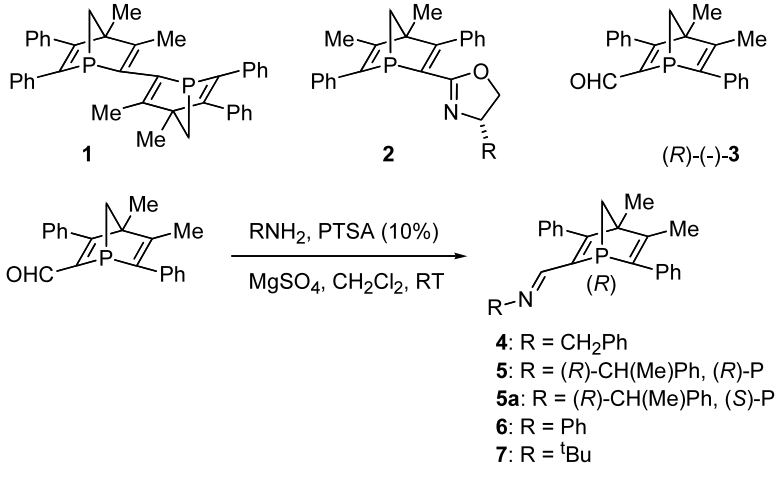
Abstract—The reaction of enantiopure 2-formyl-1-phosphanorbornadiene **3** with primary amines at room temperature in the presence of an acid catalyst gives the corresponding enantiopure imines **4-7** in quantitative yields. These imines are efficient ligands for the palladium-catalyzed enantioselective allylic *C*- and *N*- alkylations of dimethyl malonate and benzylamine by 1,3-diphenyl-prop-2-enyl acetate with ee's as high as 93 and 86–90%, respectively, and high reaction rates at room temperature (1 and 3 h, respectively, for quantitative conversions).

1. Introduction

Optically active phosphorus(III) centres have been used to some extent as ligands in transition metal-catalyzed enantioselective reactions.[1,2] Although high ee's and high efficiency have sometimes been achieved,[3–5] it must be recalled that a stereogenic phosphorus centre can racemise rather easily,[6] thus limiting the reliability of these ligands as inductors under industrial conditions. This instability of the chiral information is suppressed if phosphorus is located at the bridgehead of a bicyclic structure. This is the reason why the easily accessible 1-phosphanorbornadienes[7] are of special interest in asymmetric catalysis. Their effectiveness has been demonstrated in two cases, the 2,2′-dimeric structure BIPNOR **1**[8] and the 2-oxazolinyl derivatives **2**.[9] Nevertheless, the lengthy syntheses of these derivatives means high costs and thus, limited practical applicability. Recently, we have unveiled a very simple preparation of enantiopure 1-phosphanorbornadiene-2-carboxaldehydes **3**.[10] Herein we present a preliminary evaluation of their imine and amine derivatives in enantioselective catalysis.

2. Results and discussion

Our starting product has been the enantiopure aldehyde (*R*)-(−)-**3**. Since phosphine-imines have already found several uses in asymmetric catalysis,[11] we first decided to prepare a series of imine derivatives of **3** (Eq. (1)).



(1)

4: R = CH_2Ph
5: R = (*R*)-CH(Me)Ph, (*R*)-P
5a: R = (*R*)-CH(Me)Ph, (*S*)-P
6: R = Ph
7: R = ^tBu

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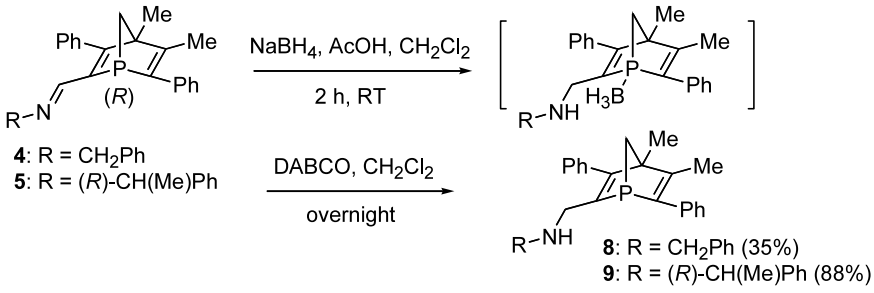


(2)

In all cases, the yield is almost quantitative. In addition to the imines derived from (*R*)-(−)-**3**, we have also prepared from (*S*)-(+)-**3**, the (*S*)-P, (*R*)-C diastereomer **5a** corresponding to **5**. These imines were subsequently reduced to the corresponding amines as shown (Eq. (2)).

The initial reaction with $NaBH_4$ partly gives the P-BH_3 complexes of the amines. Monitoring the reaction mixture by ^{31}P NMR shows a broad resonance at ca. 35 ppm (versus ca. −15 ppm for the free amines) which demonstrates the preferential complexation of phosphorus rather than nitrogen.

Both the results of Pfaltz[12,13] with phosphinooxazolines and those of Gilbertson with **2**[9] suggested that the phosphanorbornadiene-imines **4**–**7** were ideally adapted to the enantioselective allylic alkylation reaction (Eq. (3)).

The optimisation of the reaction conditions was carried out with **5**. Quantitative conversion is observed in 1 h at RT in CH_2Cl_2. Other solvents (THF, DMF, toluene) give slower reactions and lower ee's. We have compared the efficiency of **4**-**9** using these optimised conditions (Table 1). Imines **4**–**7** are considerably more efficient than amines **8** and **9**, both in terms of reaction rates and enantioselectivities. It is interesting to note in that respect, that **5** induces the same enantioselectivity as **2** (R = ^{i}Pr or ^{t}Bu), while being much easier to synthesize.

We then turned our attention toward the related but less studied enantioselective allylic *N*-alkylation reaction (Eq. (4)).

The optimisation of the reaction conditions was carried out with **7** at RT in THF. The best Pd/L ratio was found to be 1/3. With a 1/1.5 ratio, the reaction becomes very slow (30% conversion in 20 h) and the enantioselectivity somewhat decreases (80% ee). The comparison between the various imine ligands is reported in Table 2. Both in terms of rates and enantioselectivities, our imine ligands compare favourably with the best ligands proposed in the literature.[14,15]

Table 1. Efficiency of ligands **4**–**9** in enantioselective allylic alkylation

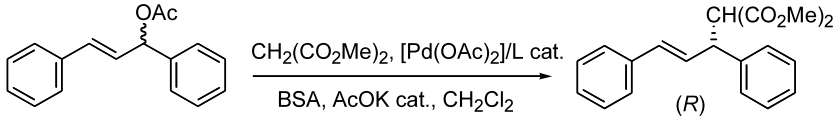
Entry	Ligand	Pd/L*	*t* (h)	Conversion[a]	Ee (%)[b]
1	**4**	3	1.5	100	87 (*R*)
2	**5**	3	1	100	93 (*R*)
3	**5a**	3	2	100	86 (*S*)
4	**6**	3	0.5	100	59 (*R*)
5	**7**	3	1	100	90 (*R*)
6	**8**	3	72	50	33 (*R*)
7	**9**	3	72	100	22 (*R*)

[a] Determined by ^1H NMR.
[b] Measured on a Chiralcel OD column:eluent hexane/^{i}PrOH:99/1 flow rate 0.8 mL/min.

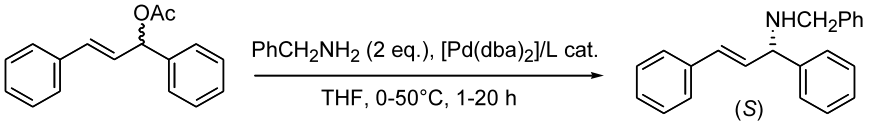
3. Experimental

3.1. General

All reactions were carried out under nitrogen by using standard techniques. Solvents were dried under nitrogen by standard procedures, distilled before use and stored under argon. The elemental analyses were performed by the Service de microanalyse du CNRS, Gif/Yvette, France. NMR spectra were recorded on a multinuclear Bruker AVANCE 300 MHz spectrometer operating at 300.13 for ^1H, 75.47 for ^{13}C and 121.50 MHz for ^{31}P. Chemical shifts are expressed in parts per million (ppm) downfield from internal tetramethylsilane (^1H and ^{13}C) and external 85% aqueous H_3PO_4(^{31}P).



(3)



(4)

Table 2. Efficiency of ligands **4**–**7** in enantioselective allylic N-alkylation

Entry[a]	Ligand	T (°C)	t (h)	Conversion[b]	Yield (%)[c]	Ee (%)[d]
1	**4**	50	5	100	87	79 (*S*)
2	**4**	20	2	100	91	83 (*S*)
3	**5**	50	5	79	64	72 (*S*)
4	**5**	20	3	100	89	86 (*S*)
5	**5**	0	24	100	100	89 (*S*)
6	**6**	50	1	100	88	67 (*S*)
7	**6**	20	2	100	85	73 (*S*)
8	**7**	50	2	100	88	78 (*S*)
9	**7**	20	3	100	90	86 (*S*)
10	**7**	0	20	100	94	90 (*S*)

[a] $[Pd(dba)_2]$ 2%, Pd/L = 1/3.
[b] Determined by TLC and NMR.
[c] Isolated yields.
[d] Measured on a Chiracel OD column, flow rate 1 mL/min, eluent:hexane/^{i}PrOH 200/1, t_R = 22.3 min, t_S = 24.3 min.

3.2. Synthesis of phosphanorbornadiene-imines 4–7

A mixture of aldehyde **3** (0.64 g, 2×10^{-3} mol), primary amine (1.2 equiv. for **4**, **5**, **5a**, **6**, and 5 equiv. for **7**), PTSA (0.1 equiv.) and $MgSO_4$ (0.1 g) in dry dichloromethane (14 mL) was stirred at room temperature for 3–12 h. Solid $NaHCO_3$ was then added, the reaction mixture was filtered and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude imines were obtained in quantitative yields. Compounds **4**, **6**, **7** were used as such, compound **5** was precipitated in pentane, compound **5a** was recrystallized from pure ethanol.

3.3. Characterization of imines 4–7

Compound **4**: yellow sticky solid, mp 60–70°C, $[\alpha]_D$ could not be measured. ^{31}P NMR (CH_2Cl_2) δ −22.3; ^{1}H NMR ($CDCl_3$) δ 8.06 (d, 1H, $^3J_{PH}$ = 8.3 Hz, CH = N), 7.36–7.11 (13H, Ph), 7.01 (d, 2H, $^3J_{HH}$ = 7.2 Hz, Ph), 4.80 (d, 1H, $^2J_{HH}$ = 13.8 Hz, CH_2N), 4.48 (d, 1H, $^2J_{HH}$ = 13.8 Hz, CH_2N), 2.10–2.01 (2H, P-CH_2), 2.04 (s, 3H, Me), 1.36 (s, 3H, Me), ^{13}C NMR ($CDCl_3$) δ 173.5 (s), 160.8 (d, $^2J_{PC}$ = 11.25 Hz, C=N), 157.0 (s), 152.4 (d, $^1J_{PC}$ = 24.75 Hz, C_α), 150.7 (d, $^1J_{PC}$ = 24.0 Hz, C_α), 140.3 (s), 139.3 (d, J_{PC} = 21.0 Hz, Ph or vinyl), 136.8 (s), 128.9–128.1 (Ph), 127.0 (s), 126.7 (s), 72.4 (d, $^2J_{PC}$ = 5.25 Hz, bridgehead C), 65.5 (s, CH_2N), 64.0 (s, bridge C), 20.6 (s, Me), 16.3 (s, Me).

Compound **5**: white solid, mp 67–68°C, $[\alpha]_D$ = −252 ($CHCl_3$, c = 1.0). ^{31}P NMR (CH_2Cl_2) δ −21.6, ^{1}H NMR ($CDCl_3$) δ 8.02 (d, 1H, $^3J_{PH}$ = 8.30 Hz, CH=N), 7.38–7.12 (13H, Ph), 7.01 (d, 2H, J_{HH} = 7.2 Hz, Ph), 4.27 (q, 1H, $^3J_{HH}$ = 6.56 Hz, CH-N), 2.05 (m, 2H, P-CH_2), 2.03 (s, 3H, Me), 1.55 (d, 3H, $^3J_{HH}$ = 6.56 Hz, *Me*CHN), 1.39 (s, 3H, Me), ^{13}C NMR ($CDCl_3$) δ 173.1 (s), 158.3 (d, $^2J_{PC}$ = 14.25 Hz, C = N), 156.5 (s), 152.9 (d, $^1J_{PC}$ = 24.0 Hz, C_α), 151.2 (d, $^1J_{PC}$ = 24.0 Hz, C_α), 146.5 (s), 139.6 (d, J_{PC} = 21.0 Hz, Ph or vinyl), 137.3 (s), 128.9–128.4 (Ph), 127.3 (s), 127.2 (s), 126.9 (s), 72.6 (d, $^2J_{PC}$ = 6.0 Hz, bridgehead C), 70.9 (s, CH-N), 63.9 (s, bridge C), 26.0 (s, *Me*CHN), 20.8 (s, Me), 16.5 (s, Me).

Compound **5a**: white yellow pasty solid, $[\alpha]_D$ = +119 (CH_2Cl_2, c = 1.0). ^{31}P NMR (CH_2Cl_2) δ −22.0, ^{1}H NMR ($CDCl_3$) δ 8.31 (d, 1H, $^3J_{PH}$ = 8.40 Hz, CH = N), 7.44–7.00 (15H, Ph), 4.31 (q, 1H, $^3J_{HH}$ = 6.56 Hz, CH-N), 2.08 (s, 3H, Me), 2.00 (m, 2H, P-CH_2), 1.45 (d, 3H, $^3J_{HH}$ = 6.56 Hz, *Me*CHN), 1.38 (s, 3H, Me), ^{13}C NMR ($CDCl_3$) δ 172.9 (s), 158.0 (d, $^2J_{PC}$ = 15.75 Hz, C=N), 157.4 (s), 153.0 (d, $^1J_{PC}$ = 24.0 Hz, C_α), 151.2 (d, $^1J_{PC}$ = 24.0 Hz, C_α), 146.4 (s), 139.8 (d, J_{PC} = 21.0 Hz, Ph or vinyl), 137.3 (s), 129.0–128.4 (Ph), 127.3 (s), 127.2 (s), 126.9 (s), 72.6 (d, $^2J_{PC}$ = 6.0 Hz, bridgehead C), 70.3 (s, CH-N), 64.3 (s, bridge C), 25.8 (s, *Me*CHN), 20.8 (s, Me), 16.6 (s, Me).

Compound **6**: yellow solid, mp 166°C, $[\alpha]_D$ = −158 (acetone, c = 1.0). ^{31}P NMR (CH_2Cl_2) δ −23.2, ^{1}H NMR ($CDCl_3$) δ 8.14 (d, 1H, $^3J_{PH}$ = 8.40 Hz, CH = N), 7.41–7.04 (15H, Ph), 2.14 (m, 2H, P-CH_2), 2.10 (s, 3H, Me), 1.42 (s, 3H, Me), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.8 (s), 159.3 (d, $^2J_{PC}$ = 15.5 Hz, C=N), 157.4 (s), 153.4 (s), 153.1 (d, $^1J_{PC}$ = 25.5 Hz, C_α), 150.9 (d, $^1J_{PC}$ = 24.0 Hz, C_α), 139.5 (d, J_{PC} = 21.0 Hz, Ph or vinyl), 137.0 (s), 130–128.5 (Ph), 127.1 (s), 126.1 (s), 121.5 (s), 72.9 (d, J_{PC} = 6.0 Hz, bridgehead C), 64.7 (s, bridge C), 20.9 (s, Me), 16.6 (s, Me).

Compound **7**: white solid, mp 124°C, $[\alpha]_D$ = −158 ($CHCl_3$, c = 0.9). ^{31}P NMR (CH_2Cl_2) δ −22.5, ^{1}H NMR ($CDCl_3$) δ 7.86 (d, 1H, $^3J_{PH}$ = 8.0 Hz, CH=N), 7.32–7.10 (8H, Ph), 6.95 (d, 2H, J_{HH} = 7.5 Hz, Ph), 1.99 (s, 3H, Me), 1.95 (m, 2H, P-CH_2), 1.32 (s, 3H, Me), 1.08 (s, 9H, ^{t}Bu), ^{13}C NMR ($CDCl_3$) δ 171.6 (s), 157.5 (s), 154.0 (d, $^2J_{PC}$ = 15.0 Hz, C=N), 153.6 (d, $^1J_{PC}$ = 23.25 Hz, C_α), 151.2 (d, $^1J_{PC}$ = 24.0 Hz, C_α), 139.8 (d, J_{PC} = 21.0 Hz, Ph or vinyl), 137.5 (s), 128.8 (d, J_{PC} = 8.25 Hz, Ph), 128.8 (s), 128.7 (s), 128.3 (s), 126.8 (s), 72.5 (d, J_{PC} = 6.0 Hz, bridgehead C), 63.9 (s, bridge C), 58.1 (s, Me_3C-N), 30.4 (s, Me_3C-N), 20.9 (s, Me), 16.5 (s, Me).

3.4. Synthesis of phosphanorbornadiene-amines 8, 9

To a solution of phosphanorbornadiene-imine **4** or **5** (2×10^{-3} mol) in dichloromethane (20 mL) was added solid $NaBH_4$ (0.15 g) in one portion. Then acetic acid (1 mL) was added and the mixture stirred at room temperature for 2 h. After hydrolysis with 3N HCl, neutralization with 20% KOH, three extractions of the aqueous phase with CH_2Cl_2, the organic phase was dried over $MgSO_4$. The organic residue in CH_2Cl_2 (20 mL) was treated with DABCO (0.27 g, 2.4×10^{-3} mol) for 12 h at rt. After evaporation, the organic residue was purified by chromatography on silica gel with CH_2Cl_2/AcOEt 95/5. Amines **8** and **9** were obtained in 35 and 88% yields, respectively.

3.5. Characterization of amines 8, 9

Compound **8**: colorless oil, $[\alpha]_D=-135$ (CH_2Cl_2, $c=0.9$). ^{31}P NMR (CH_2Cl_2) δ −16.7, ^1H NMR ($CDCl_3$) δ 7.43–6.94 (15H, Ph), 3.45 (m, 4H, CH_2-N), 2.11 (s, 3H, Me), 2.04 (d, 2H, $^2J_{PH}=9.66$ Hz, P-CH_2), 1.51 (s broad, 1H, NH), 1.33 (s, 3H, Me), ^{13}C NMR ($CDCl_3$) δ 163.5 (s), 157.8 (s), 153.5 (d, $^1J_{PC}=25.5$ Hz, C_α), 149.6 (d, $^1J_{PC}=22.5$ Hz, C_α), 141.0 (s), 139.9 (d, $^2J_{PC}=20.25$ Hz, Ph or vinyl), 138.3 (s), 128.9–128.7 (Ph), 128.5 (s), 127.6 (s), 127.3 (s), 126.8 (s), 71.7 (d, $^2J_{PC}=5.25$ Hz, bridgehead C), 66.7 (s, bridge C), 53.6 (s, Ph*C*H_2N), 49.1 (d, $^2J_{PC}=19.5$ Hz, CH_2N), 21.4 (s, Me), 16.4 (s, Me).

Compound **9**: colorless oil, $[\alpha]_D=-125$ (CH_2Cl_2, $c=1.1$). ^{31}P NMR (CH_2Cl_2) δ −16.7, ^1H NMR ($CDCl_3$) δ 7.37–7.10 (13H, Ph), 6.86 (m, 2H, Ph), 3.67 (q, 1H, $^3J_{HH}=6.55$ Hz, CH–N), 3.35 (dd, $^2J_{HH}=13.6$ Hz, $^3J_{PH}=7.8$ Hz, CH_2N), 3.24 (dd, $^2J_{HH}=13.6$ Hz, $^3J_{PH}=10.1$ Hz, CH_2N), 2.05 (s, 3H, Me), 2.04 (d, 2H, $^2J_{PH}=9.40$ Hz, CH_2P), 1.31 (s, 3H, Me), 1.19 (d, 3H, $^3J_{HH}=6.55$ Hz, *Me*CHN), ^{13}C NMR ($CDCl_3$) δ 163.0 (s), 158.0 (s), 153.6 (d, $^1J_{PC}=26.25$ Hz, C_α), 149.7 (d, $^1J_{PC}=22.50$ Hz, C_α), 146.3 (s), 139.9 (d, $J_{PC}=22.50$ Hz, Ph or vinyl), 138.2 (s), 128.9–128.4 (Ph), 127.5 (s), 127.2 (s), 126.8 (s), 71.7 (d, $^2J_{PC}=5.25$ Hz, bridgehead C), 66.7 (s, CH_2P), 57.8 (s, CH-N), 47.5 (d,$^2J_{PC}=20.25$ Hz, CH_2-N), 24.7 (s, *Me*CHN), 21.3 (s, Me), 16.4 (s, Me).

Acknowledgements

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