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Asymmetric addition of diethylzinc to *N*-(diphenylphosphinoyl) imines

Pedro Pinho and Pher G. Andersson*

Department of Organic Chemistry, Institute of Chemistry, Uppsala University, Box 531, S-751 21 Uppsala, Sweden

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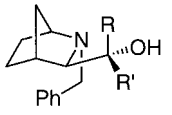
Abstract—The addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl) imines is a convenient method for the preparation of optically enriched amines. Herein we present our most recent results on this reaction, including solvent effects on the enantioselectivity and the extension of this method to a variety of *N*-(diphenylphosphinoyl) imines. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Since its introduction as a method to generate chiral secondary alcohols, the addition of organozinc reagents to prochiral aldehydes has seen a tremendous growth.[1] However, the corresponding addition to imines as a method for the preparation of chiral amines is not so well documented in the literature and only a limited number of publications have been devoted to the subject.[2] We have been, for some time, interested in the titled reaction[3a–c] and have recently reported on a very efficient chiral auxiliary (**1a**, Fig. 1) for this transformation.[3c]

The promising results obtained with the auxiliary **1a** for the addition of diethylzinc to *N*-(diphenylphosphinoyl)-benzalimine (**2a**, Fig. 2) encouraged us to further investigate the scope of the reaction. We now wish to present our most recent progress in the extension of this methodology as a tool to synthesize chiral building blocks from the easily prepared starting materials.[4] In a recent publication[3d] we described the preparation of chiral auxiliary **1b**, which proved to be even more efficient than its analogue **1a** in the addition of the alkylzinc reagent to imine **2a** (Fig. 2). Auxiliary **1b** was therefore prepared on a multigram scale



1a, R = R' = H
1b, R = Ph, R' = H

Figure 1. Chiral auxiliaries for the addition of diethylzinc to phosphinoyl imines.

for the evaluation of the addition reaction to phosphinoyl imines **2b–k** (Fig. 2).

2. Results and discussion

The addition of diethylzinc to phosphinoyl imine **2a** in the presence of one equivalent of the auxiliary **1b** in dry toluene afforded the addition product in >70% isolated yield and 97% optical purity over the (*S*)-isomer.[3d]

Due to the low number of publications dedicated to this transformation, solvent studies are rare and to our knowledge only one example can be found in the literature.[5] It was therefore considered appropriate to investigate the possible solvent effect on the reaction. Imine **2a** was chosen as the model substrate and the solvent influence on the stoichiometric addition reaction was studied. As observed from Table 1, solvents like THF, ether and dichloromethane proved to be unsuitable and no products were detected. Various aromatic solvents, however, proved to be adequate for the reaction, giving a range of yields and enantiomeric excesses of the product. At best, phosphinoyl amine **3a** was obtained with an optical purity of 98% when using chlorobenzene as solvent.

The addition of diethylzinc to phosphinoyl imines **2a–k** was thereafter performed in chlorobenzene and toluene. Although the reaction of diethylzinc with the ^{t}Bu substituted phosphinoyl imine (**2b**) did not lead to any addition product, all the aromatic substituted amines were obtained in good yields and selectivities. An exception being made for phosphinoyl imine **2f** which also failed to react. The results of the addition reactions to the different imines displayed in Fig. 2 are summarized in Table 2. At best, the addition product was obtained in 91% yield and 98% ee (entry 5, imine **2e**).

Keywords: asymmetric additions; diethylzinc; amino alcohols; chiral auxiliaries.

* Corresponding author. E-mail: phera@kemi.uu.se

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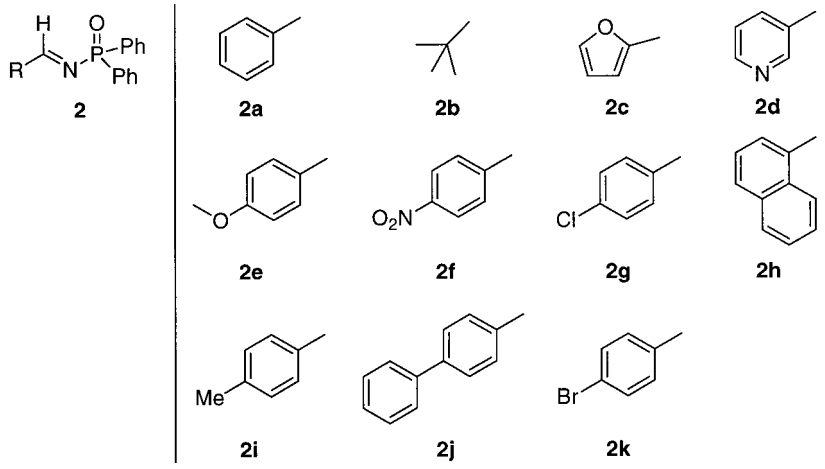


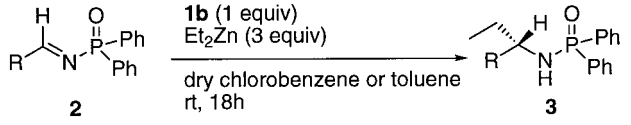
Figure 2. *N*-(diphenylphosphinoyl) imines.

Table 1. Results of the solvent study

Entry	Solvent	Yield (%)[a]	ee (%)[b]
1	Toluene	72	97
2	Dichloromethane	–	–
3	Diethylether	–	–
4	Tetrahydrofuran	–	–
5	Benzene	35	90
6	Ethylbenzene	38	90
7	Trifluorotoluene	52	95
8	Anisole	47	94
9	*p*-Methylanisole	43	92
10	**Chlorobenzene**	**75**	**98**
11	*o*-Dichlorobenzene	60	96
12	*m*-Dichlorobenzene	59	94
13	*o*-Chlorotoluene	57	90
14	*m*-Chlorotoluene	46	77
15	*p*-Chlorotoluene	69	95

[a] Refers to the isolated yield after flash chromatography.
[b] Determined by HPLC analysis on a chiral column (ChiralCel OD-H).

Table 2. Results of the addition reactions to imines **2**



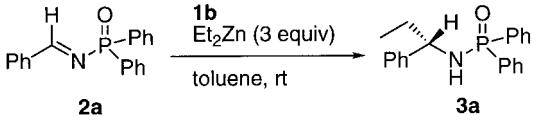
Entry	Imine	Yield (%)[a]	ee (%)[b]	
			Toluene	Chlorobenzene
1	**2a**	75	97	**98**
2	**2b**	–	–	–
3	**2c**	72	**91**	89
4	**2d**	70	77	**87**
5	**2e**	91	**98**	**98**
6	**2f**	–	–	–
7	**2g**	67	**95**	**95**
8	**2h**	65	**96**	92
9	**2i**	70	85	**97**
10	**2j**	70	90	**96**
11	**2k**	65	90	**94**

[a] Refers to the isolated yield after flash chromatography.
[b] Determined by HPLC analysis on a chiral column (ChiralCel OD-H or Chiralpak-AD) under the conditions described in Section 4.

Attention should be drawn to the products **3d** and **3i** which represent the reason for the change in the reaction solvent. The solvent effect was not very pronounced in the reaction of imine **2a**, but in the case of imines **2d** and **2i** the addition products were obtained with slightly higher enantiomeric excesses in chlorobenzene rather than toluene (entries 4 and 9, Table 2).

Another point of interest was the possibility to make the process catalytic. Unfortunately, a decrease in the amount of the auxiliary **1b**, rapidly decreased the optical purity of the product. This decrease was not dramatic when going from a full equivalent of **1b** (75% yield, 97% ee) to half the amount (68% yield, 92% ee), but when using only 25 mol% of the auxiliary the addition required a reaction time of two days to afford the product in 62% yield and 80% ee (Table 3). The addition of silylating agents has been previously reported to increase the catalytic activity of the amino alcohols allowing good results and shorter reaction times when using sub-stoichiometric amounts of the chiral auxiliary.[6] This was, however, not the case for our system. In the presence of TIPSCl a low enantiomeric excess of only 54% was obtained when using 25 mol% of **1b**, even if the reaction was completed in the usual 18 h. Finally, a full equivalent of methanol or triethylamine were added to the

Table 3. Influence of the amount of auxiliary and additives in the reaction outcome



Entry	Amount of **1b** (equiv.)	Additive	Yield (%)[a]	ee (%)[b]
1	1	–	75	97
2	0.5	–	68	92
3	0.25	–	62	80
4	0.25	TIPSCI	40	54
5	1	MeOH	50	90
6	1	Et_3N	50	93

[a] Refers to the isolated yield after flash chromatography.
[b] Determined by HPLC analysis on a chiral column (ChiralCel OD-H).

reaction mixture in order to eventually break the product-zinc-auxiliary chelate, but these additives proved to be ineffective. A drop in both the yield and enantioselectivity was observed even at stoichiometric levels of the auxiliary, 50% yield and 90% ee when methanol was used and 50% yield and 93% ee in the case of triethylamine.

3. Conclusions

The utility of the diethylzinc addition to phosphinoyl imines as a method for the preparation of optically active amines has been demonstrated. It has been shown that this methodology is extendable to substrates other than *N*-(diphenylphosphinoyl)benzalimine and that good enantioselectivities can be obtained using **1b** as a chiral auxiliary. Although the addition reaction is still performed using a full equivalent of the chiral auxiliary, it should be noted that approximately 90% of the auxiliary could be recovered during work-up and re-used without any loss of optical purity of the product.

4. Experimental

For general experimental information see Ref. 7. Flash chromatography was performed on silica gel (Matrex 60A, 37–70 μm). TLC's were performed on precoated plates, silica gel 60 F_{254}, purchased from Merck. HPLC analyses were carried out using a chiral column (ChiralCelOD-H or Chiralpak-AD), an UV detector and the appropriate mixture of ^{i}PrOH and hexane (see below).

Compounds **2a**,[4a–c,e] **2b**,[4g] **2c**,[4f] **2e**,[4d,e] **2f**,[4c,g] **2g**,[4c–e] **2h**,[4c–e] **2i**[4f,j] and **2k**[4b,c,g] were prepared following a literature procedure.[4e]

4.1. General procedure

4.1.1. *N*-(3-Pyridylmethylidene)-*P*,*P*-diphenylphosphinamide (2d). This compound was prepared following a literature procedure[4i] and was obtained in 65% yield as a white solid. Mp=129–130°C; IR (neat, cm^{-1}) 3435, 1620, 1199, 1125 and 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (7H, m), 7.94 (4H, m), 8.32 (1H, ddd, J=8.0, 6.0, 2.0 Hz), 8.78 (1H, dd, J=4.4, 2.0 Hz), 9.15 (1H, d, J=2.0 Hz) and 9.38 (1H, d, J_{H-P}=31.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.8, 128.5, 128.6, 131.5, 131.6, 132.0, 136.2, 151.9, 153.9 and 171.3 (d, J_{C-P}=7.6 Hz); MS (EI) *m/z* (rel. intensity) 306 (M^+, 100%), 201 (40), 182 (17) and 181 (52). HRMS: calcd for $C_{18}H_{15}N_2OP$ 306.0922, found 306.0923.

4.1.2. *N*-Biphenylmethylidene-*P*,*P*-diphenylphosphinamide (2j). This compound was prepared following a literature procedure[4e] and was obtained in 55% yield as a pale yellow solid. Mp=121–122°C; IR (neat, cm^{-1}) 3234, 1602, 1185, 1125 and 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (9H, m), 7.63 (2H, app. d, J=7.2 Hz), 7.72 (2H, app. d, J=8.0 Hz), 7.93 (4H, m), 8.08 (2H, app. d, J=8.0 Hz) and 9.35 (1H, d, J_{H-P}=32.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.2, 127.6, 128.3, 128.4, 128.5, 129.0, 130.7, 131.5, 131.6, 131.8, 139.8, 146.4 and 173.2 (d, J_{C-P}=7.6 Hz); MS (EI) *m/z* (rel. intensity) 381 (M^+, 3%), 218 (12), 217 (31), 216 (100), 200 (20), 199 (57) and 152 (10). HRMS: calcd for $C_{25}H_{20}NOP$ 381.1282, found 381.1283.

4.2. General procedure for the addition reactions

A dry 25 mL round-bottom flask was loaded with a magnetic bar, chiral auxiliary **1b** (100 mg, 0.34 mmol) and *N*-(diphenylphosphinoyl) benzalimine **2a** (104 mg, 0.34 mmol). The reaction vessel was thereafter evacuated, placed under argon and dry chlorobenzene (3 mL) was added via syringe. After stirring for 10 min the solution was cooled to 0°C and diethylzinc (1.1 M in toluene or hexane, 0.95 mL, 1.04 mmol) was added dropwise. The ice-bath was removed and the reaction allowed to stir overnight at rt. The reaction mixture was then quenched by the addition of saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined extracts afforded a residue that was purified by flash chromatography on silica gel using a gradient of pentane/acetone.

Compounds **3a**,[3b,c,4h,6,8] **3c**,[4h] **3g**,[3b] **3h**[3b,c,4h,9] and **3i**[9] were obtained with the yields and enantioselectivities shown in Table 1. Racemic samples for HPLC comparison were prepared by addition of EtMgBr to imines **2** in THF/ether.

4.2.1. *N*-[1-(3-Pyridyl)propyl]-*P*,*P*-diphenylphosphinoylamide (3d). This compound was obtained as a low melting white solid in 70% yield and 87% ee; HPLC conditions: Chiralpak AD, 10% ^{i}PrOH in hexane, 1.0 mL/min, retention times 30.3 min (minor) and 47.6 min (major). R_f 0.10 (pentane/acetone: 1/1); $[\alpha]_D^{24}=-12.4$ (*c* 5.5, CH_2Cl_2); IR (neat, cm^{-1}) 3401, 1645, 1438, 1181 and 1124; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (3H, t, J=7.6 Hz), 1.89 (2H, ddq, J=13.0, 7.6, 5.6 Hz), 3.43 (1H, br s), 3.75 (1H, m), 7.51 (13H, m) and 8.41 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 32.1 (d, J_{C-P}=4.5 Hz), 54.8, 128.2, 128.3, 128.5, 131.6, 131.8, 131.9, 132.0, 134.2 and 135.6; MS (EI) *m/z* (rel. intensity) 337 (M^+, 8%), 308 (16), 307 (55), 231 (11), 219 (31), 216 (16), 201 (100), 183 (10), 173 (11), 169 (14), 168 (17) and 107 (10). HRMS calcd for $C_{20}H_{21}N_{20}P$ 336.1391, found 336.1392.

4.2.2. *N*-[1-(4-Methoxyphenyl)propyl]-*P*,*P*-diphenylphosphinoylamide (3e). This compound was obtained as a white solid in 91% yield and 98% ee; HPLC conditions: ChiralCel OD-H, 5% ^{i}PrOH in hexane, 0.5 mL/min, retention times 36.3 min (minor) and 40.5 min (major). R_f 0.20 (pentane/acetone: 2/1), mp=112–113°C; $[\alpha]_D^{24}=-29.3$ (*c* 2.97, CH_2Cl_2); IR (neat, cm^{-1}) 3208, 1612, 1513 and 1180; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (3H, t, J=7.6 Hz), 1.90 (2H, ddq, J=13.0, 7.6, 5.6 Hz), 3.16 (1H, m), 3.79 (3H, s), 4.05 (1H, m), 6.81 (2H, m), 7.07 (2H, m), 7.41 (6H, m) and 7.81 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6, 32.5 (d, J_{C-P}=3.8 Hz), 55.2, 56.6, 113.8, 127.6, 128.29, 128.33, 128.5, 131.75, 131.84 and 132.5; MS (EI) *m/z* (rel. intensity) 365 (M^+, 5%), 337 (21), 336 (96), 219 (14), 201 (61), 165 (13) and 164 (100). Anal. Calcd for $C_{22}H_{24}NO_2P$: C, 72.31; H, 6.62; N, 3.83. Found: C, 72.11; H, 6.62; N, 3.86.

4.2.3. *N*-(1-Biphenylpropyl)-*P*,*P*-diphenylphosphinoylamide (3j). This compound was obtained as a white solid in 70% yield and 97% ee; HPLC conditions: Chiralpak AD,

10% ^{i}PrOH in hexane, 1.0 mL/min, retention times 33.0 min (major) and 37.1 min (minor). R_f 0.27 (pentane/acetone: 2/1), mp=150–151°C; $[\alpha]_D^{24}=-76.1$ (*c* 4.61, CH_2Cl_2); IR (neat, cm^{-1}) 3181, 1438 and 1187; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (3H, t, *J*=7.6 Hz), 1.95 (2H, ddq, *J*=13.0, 7.6, 5.6 Hz), 3.27 (1H, m), 4.15 (1H, m), 7.41 (15H, m) and 7.83 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6, 32.4 (d, J_{C-P}=3.8 Hz), 56.8, 127.0, 127.1, 127.2, 128.2, 128.3, 128.4, 128.5, 128.7, 131.8, 131.9, 132.5 and 132.6; MS (EI) *m*/*z* (rel. intensity) 412 (M^+, 4%), 383 (15), 382 (60), 219 (23), 211 (21), 210 (100), 202 (12) and 201 (68). Anal. Calcd for $C_{27}H_{26}NOP$: C, 78.81; H, 6.37; N, 3.40. Found: C, 78.63; H, 6.50; N, 3.47.

4.1.6. *N*-[1-(4-Bromophenyl)propyl]-*P*,*P*-diphenylphosphinoylamide (3k). This compound was obtained as a white solid in 65% yield and 94% ee; HPLC conditions: ChiralCel OD-H, 5% ^{i}PrOH in hexane, 0.5 mL/min, retention times 27.8 min (minor) and 32.7 min (major). R_f 0.21 (pentane/acetone: 2/1), mp=131–132°C; $[\alpha]_D^{24}=-45.8$ (*c* 4.03, CH_2Cl_2); IR (neat, cm^{-1}) 3153, 1438 and 1186; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (3H, t, *J*=7.6 Hz), 1.85 (2H, ddq, *J*=13.0, 7.6, 5.6 Hz), 3.24 (1H, m), 4.06 (1H, m), 7.02 (2H, app. d, *J*=8.4 Hz), 7.39 (8H, m) and 7.79 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 32.3 (d, J_{C-P}=3.8 Hz), 56.5, 128.2, 128.3, 128.4, 131.5, 131.7, 131.8, 132.4 and 132.5; MS (EI) *m*/*z* (rel. intensity) 416 and 414 (M^+, 2%), 386 (13), 385 (60), 384 (14), 323 (60), 219 (51), 214 (23), 212 (23), 202 (14), 201 (100). Anal. Calcd for $C_{21}H_{21}BrNOP$: C, 60.88; H, 5.11; N, 3.38. Found: C, 61.02; H, 5.18; N, 3.47.

Acknowledgements

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