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The use of an ionic liquid in asymmetric catalytic allylic amination

Sergey E. Lyubimov,[a,*] Vadim A. Davankov[a] and Konstantin N. Gavrilov[b]

[a]*Institute of Organoelement Compounds, Russian Academy of Sciences, 28 Vavilov Street, 119991 Moscow, Russia*
[b]*Department of Chemistry, Ryazan State Pedagogic University, 46 Svoboda Street, Ryazan 390000, Russia*

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Abstract—Asymmetric amination of 1,3-diphenyl-2-propenyl acetate with di-*n*-propylamine catalysed by palladium/*P**-chiral diamidophosphites was carried out in [bdmim]BF_4^- ionic liquid, THF and CH_2Cl_2 with up to 90% ee. The catalyst can be reused three times without loss in enantioselectivity.

1. Introduction

Organic reactions catalysed by chiral transition metal complexes are the basis of modern asymmetric synthesis. This statement was substantiated by the fact that three leading researchers working in this field of chemistry were awarded the Nobel Prize in 2001. The key to obtaining high catalytic results is the targeted synthesis of optically active ligands. Of prime importance are phosphorus-containing compounds, including phosphite-type ligands. Chiral phosphites are stable towards oxidation, are readily obtainable, comparatively inexpensive and possess substantial π-acidity. Undoubted leaders among modern phosphite-type *P*-monodentate ligands are phosphite and phosphoramidite derivatives of BINOL. They have been used to achieve excellent results in enantioselective Rh-catalysed hydrogenations, Cu-catalysed additions of organozinc reagents, Ir-catalysed allylic substitutions and Pd-catalysed hydrosilylation-oxidations.[1] Nevertheless, in some catalytic processes, for example, in the Pd-catalysed diboration of allenes[2] and the Cu-catalysed conjugate addition of R_3Al to nitroalkenes[3] and cyclohexenones,[4] they demonstrated essentially lower asymmetric induction than TADDOL-, bis-phenol-based phosphites and phosphoramidites. Futhermore, the Pd-catalysed allylic substitution using BINOL-derived phosphites gave moderate or even low enantioselectivity.[5] Therefore, the development of novel *P*-monodentate chiral derivatives of phosphorus acids represents an important goal. Particularly promising are diamidophosphites with *P**-stereocentres, which provide excellent optical yields in the Pd-catalysed allylic substitution of 1,3-diphenyl-2-propenyl acetate.[5]

Along with the design of chiral ligands, another significant challenge in metal complex catalysis is recycling of the catalyst. The utilisation of ionic liquids (IL) as reaction media seems to be advantageous, since they combine the merits of homogeneous and heterogeneous catalysts. Despite the fact that the Pd-catalysed synthesis of *rac*-((*E*)-1,3-diphenylallyl)pyrrolidine from 1,3-diphenyl-2-propenyl acetate in an IL was reported as early as 1999,[6] no asymmetric allylic amination in an IL has been described until the present article. Also, in this letter we describe the first application of chiral phosphite ligands in catalytic reactions occurring in an IL.

The required palladium catalysts were prepared from *P**-chiral diamidophosphites **L1**–**L3**[5a] and BINOL-based phosphoramidite **L4**[7] (Scheme 1).

It should be noted that complex **1** represents a single stereoisomer, while **2** is a 74:26 mixture of (R_P)- and (S_P)-epimers,[5a] each of them in turn being a mixture of *exo* and *endo* isomers. Compounds **1**–**4** and **5**–**8**, as well as the complexes formed from $[Pd(allyl)Cl]_2$ and the corresponding ligands in situ, were tested in the asymmetric Pd-catalysed allylic amination using 1,3-diphenyl-2-propenyl acetate **9** as substrate (Scheme 2).

The catalytic results obtained in common organic solvents are summarised in Table 1.

Keywords: *P*-Monodentate phosphite ligands; Asymmetric Pd-catalysed amination; Ionic liquid.
* Corresponding author. Tel./fax: +7 095 135 6471; e-mail: lssp452@mail.ru

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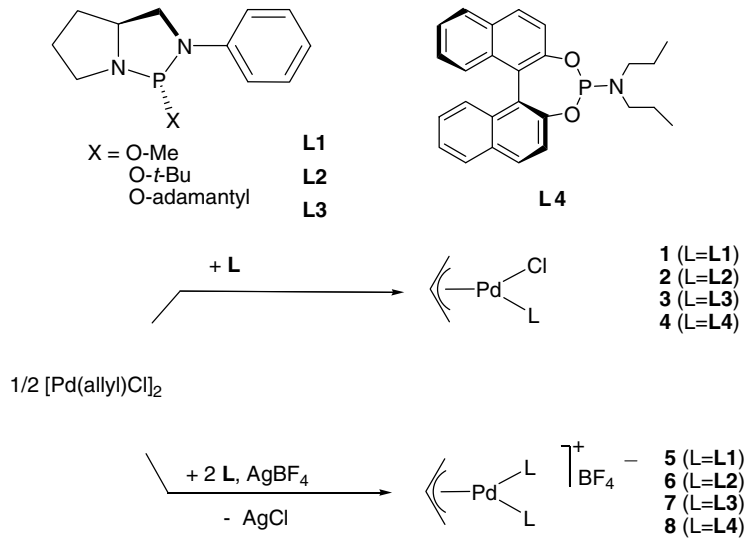
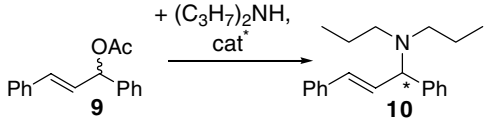


Scheme 1. Preparation of palladium catalysts.



Scheme 2. Palladium catalysed allylic amination.

Table 1. Enantioselective allylic amination of **9** in organic solvents

Entry	Catalyst	Solvent	Conv. [%][a]	ee [%][b]
1	**1**	THF	99	37 (+)
2	**1**	CH_2Cl_2	100	50 (+)
3	[Pd(allyl)Cl]$_2$/4**L1**	THF	100	13 (+)
4	[Pd(allyl)Cl]$_2$/4**L1**	CH_2Cl_2	100	19 (+)
5	**5**	THF	100	1 (+)
6	**5**	CH_2Cl_2	100	2 (+)
7	**2**	THF	99	65 (+)
8	**2**	CH_2Cl_2	100	71 (+)
9	[Pd(allyl)Cl]$_2$/4**L2**	THF	100	**90** (+)
10	[Pd(allyl)Cl]$_2$/4**L2**	CH_2Cl_2	100	78 (+)
11	**6**	THF	100	29 (+)
12	**6**	CH_2Cl_2	100	11 (+)
13	**3**	THF	98	81 (+)
14	**3**	CH_2Cl_2	100	75 (+)
15	[Pd(allyl)Cl]$_2$/4**L3**	THF	99	77 (+)
16	[Pd(allyl)Cl]$_2$/4**L3**	CH_2Cl_2	100	74 (+)
17	**7**	THF	97	74 (+)
18	**7**	CH_2Cl_2	99	25 (+)
19	**4**	THF	30	51 (−)
20	**4**	CH_2Cl_2	87	60 (−)
21	**8**	THF	48	56 (−)
22	**8**	CH_2Cl_2	38	54 (−)

The sign of specific rotation of the product **10** is given in parentheses.
[a] Determined by HPLC (Daicel Chiralcel OD-H).
[b] Determined by HPLC (Daicel Chiralcel OD-H, C_6H_{14}/*i*-PrOH/Et_2NH = 1000/1/1, 0.4 ml/min, 254 nm).

The highest asymmetric induction among diamidophosphites **L1**–**L3** (90% ee) involved ligand **L2**, when its cationic complex $[Pd(allyl)(\mathbf{L2})_2]^+Cl^-$ was used in situ (Table 1, entry 9). Interestingly, the iso-structural complex **6** showed low stereoselectivity (Table 1, entries 11 and 12), probably due to the dramatic influence of the counter-ion. Ligand **L3** provided similar enantioselectivity (up to 81% ee, Table 1, entry 13), but in this case the most efficient was neutral catalyst **3**. For ligand **L1**, the neutral complex also worked better than the cationic compounds, however, this least bulky diamidophosphite afforded only moderate enantioselectivity (up to 50% ee, Table 1, entry 2). In comparison to *P**-chiral diamidophosphites **L2** and **L3**, BINOL-based phosphoramidite **L4** was found to be poorly stereoselective providing not more than 60% ee (Table 1, entries 19–22).

In general, the 90% enantioselectivity achieved in this reaction sufficiently exceeds the best previously reported result (74% ee) obtained with planar-chiral cyclopentadienylruthenium complexes.[8]

Cationic complexes **5**–**8** were also tested as catalysts for allylic amination in an IL medium (1-butyl-2,3-dimethylimidazolium tetrafluoroborate). As in common organic solvents, complex **5** afforded almost racemic **10** (Table 2, entry 1). In contrast, complex **6** provided good enantioselectivity (up to 77% ee), which remained unchanged

Table 2. Catalytic results obtained in ionic liquid medium

Entry	Catalyst	Cycle	Conv. [%][a]	ee [%][b]
1	**5**	1	100	3 (+)
2	**6**	1	100	77 (+)
3	**6**	2	71	75 (+)
4	**6**	3	45	76 (+)
5	**7**	1	100	**84** (+)
6	**7**	2	10	68 (+)
7	**8**	1	97	50 (−)
8	**8**	2	40	51 (−)
9	**8**	3	10	51 (−)

The sign of specific rotation of the product **10** is given in parentheses.
[a] Determined by HPLC (Daicel Chiralcel OD-H).
[b] Determined by HPLC (Daicel Chiralcel OD-H, C_6H_{14}/*i*-PrOH/Et_2NH = 1000/1/1, 0.4 ml/min, 254 nm).

during three consecutive catalytic cycles (compare Table 1, entries 11 and 12 and Table 2, entries 2–4), though a gradual decrease of conversion was observed, probably due to partial leaching of the catalyst. The highest enantioselectivity in the IL medium was achieved with complex **7**. In the first catalytic cycle, 84% ee and quantitative conversion were obtained, however, a second cycle suffered from a considerable drop in both activity and selectivity of the recovered catalyst (Table 2, entries 5 and 6). BINOL-based phosphoramidite **L4**, complex **8**, showed almost the same moderate asymmetric induction in the IL as in THF or CH_2Cl_2 (Table 1, entries 21 and 22 and Table 2, entries 7–9).

In summary, we have shown that P^*-chiral diamidophosphites yield the highest enantioselectivity reported so far in the Pd-catalysed allylic amination of 1,3-diphenyl-2-propenyl acetate with dipropylamine. The reaction proceeds smoothly in common organic solvents and also in an IL. In the latter case, it was possible to recycle successfully the chiral catalyst residing in the IL several times with removal of the reaction product via extraction. Of note is the successful utilisation of an IL as a solvent for the asymmetric catalytic allylic amination, as well as the first combination of an IL with metal complexes of chiral phosphite-type ligands.

2. General procedure for the preparation of Pd-complexes 1, 2 and 4

A solution of the relevant ligand (0.4 mmol) in $CHCl_3$ (15 ml) was added dropwise over 40 min to a vigorously stirred solution of $[Pd(allyl)Cl]_2$ (0.073 g, 0.2 mmol) in $CHCl_3$ (15 ml). The mixture was stirred for an additional 1 h after which the solvent was evaporated under reduced pressure (40 Torr). The residue was washed with ether (2×10 ml) and dried in vacuum (1 Torr, 1 h). Yields: 84% (**1**), 81% (**2**) and 87% (**4**).

Characterisation data for **1**: ^{31}P {H} NMR, 162.0 MHz ($CDCl_3$): $\delta = 123.8$ ppm. IR (Nujol): ν (Pd–Cl) = 268 cm^{-1}. ESI-MS (CH_3CN): m/z (%): 424 (100) $[M-Cl+CH_3CN]^+$, 383 (23) $[M-Cl]^+$. $C_{15}H_{22}ClN_2OPPd$: calcd C 42.98, H 5.29, N 6.68%; found C 43.21, H 5.40, N 6.42%.

For **2**: ^{31}P {H} NMR, 162.0 MHz ($CDCl_3$): $\delta = 111.7$ (39%), 111.4 (35%) and 98.4 (16%), 98.2 (10%) ppm. IR (Nujol): ν (Pd–Cl) = 271 cm^{-1}. ESI-MS (CH_3CN): m/z (%): 466 (100) $[M-Cl+CH_3CN]^+$, 410 (41) $[M-Cl-CH_3]^+$. $C_{18}H_{28}ClN_2OPPd$: calcd C 46.87, H 6.12, N 6.07%; found C 47.02, H 6.06, N 6.18%.

For **4**: ^{31}P {H} NMR, 162.0 MHz ($CDCl_3$): $\delta =$ 148.3 ppm. IR (Nujol): ν (Pd–Cl) = 294 cm^{-1}. ESI-MS (acetone): m/z (%): 598 (100) $[M]^+$, 555 (12) $[M-C_3H_7]^+$. $C_{29}H_{31}ClNO_2PPd$: calcd C 58.21, H 5.22, P 5.18%; found C 58.05, H 5.35, P 4.97%.

3. Pd-catalysed allylic amination of 1,3-diphenyl-2-propenyl acetate with dipropylamine

Method A: A solution of $[Pd(allyl)Cl]_2$ (0.0037 g, 0.01 mmol) and appropriate ligand (0.04 mmol) in 5 ml of the appropriate solvent was stirred for 40 min [alternatively, the pre-synthesised complex **1**–**8** (0.02 mmol) was dissolved in the appropriate solvent (5 ml)]. 1,3-Diphenyl-2-propenyl acetate (0.1 ml, 0.5 mmol) was added and the solution stirred for 15 min, then freshly distilled di-*n*-propylamine (0.2 ml, 1.5 mmol) was added and the reaction mixture stirred for a further 48 h. The resulting solution was filtered through Celite. The solvent was removed under vacuum (40 Torr), and the residue dried under vacuum (10 Torr, 12 h) to give (*E*)-1,3-diphenyl-*N*,*N*-di-*n*-propylprop-2-en-1-amine (**10**) as a colourless crystalline solid. All spectroscopic data for compound **10** were in good agreement with the published data.[8]

Method B: Complex **5**–**8** (0.02 mmol) was dissolved in $[bdmim]BF_4$ (1 ml). 1,3-Diphenyl-2-propenyl acetate (0.1 ml, 0.5 mmol) was added and the solution stirred for 15 min, then freshly distilled di-*n*-propylamine (0.2 ml, 1.5 mmol) was added and the reaction mixture stirred for a further 48 h. The mixture was extracted with Et_2O (7×4 ml) and the combined extracts filtered through a short column of silica gel. The solvent was removed under vacuum (40 Torr), and the residue dried in vacuo (10 Torr, 12 h) to afford (*E*)-1,3-diphenyl-*N*,*N*-di-*n*-propylprop-2-en-1-amine (**10**) as a colourless crystalline solid.

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