Monatsh Chem (2017) 148:2069–2077
DOI 10.1007/s00706-017-2029-2

ORIGINAL PAPER

Aminoalkyl-phosphine (P,N) ligands with pentane-2,4-diyl backbone in asymmetric allylic substitution reactions

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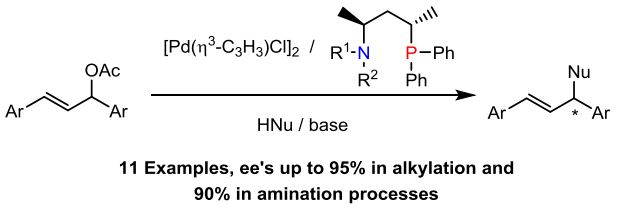
Received: 28 March 2017 / Accepted: 27 June 2017 / Published online: 20 October 2017

Abstract The asymmetric allylic substitution reaction of *rac*-1,3-diaryl-2-propenyl acetates with several C- and N-nucleophiles catalyzed by the palladium-complexes of eleven structurally analogous aminoalkyl-phosphines (P,N) with pentane-2,4-diyl backbone is reported. The role of the N-substituents and the influence of the ligand/palladium molar ratio on the activity and enantioselectivity of the catalytic system are studied. The solvent and the temperature dependence of the catalytic reaction were also assessed yielding enantioselectivities up to 95% in alkylation and 90% in amination processes under optimized reaction conditions.

Graphical abstract



Keywords Homogeneous catalysis · Alkylations · Chiral auxiliaries · Phosphorus compounds · Transition metals compounds

Introduction

Asymmetric allylic substitution provides an efficient route for the enantioselective formation of C,C- and C-heteroatom bonds [1–6]. From another point of view, the palladium-catalyzed asymmetric substitution of allylic substrates is a typical benchmark reaction for the comparison of new ligands. Consequently, there is a remarkable interest in this area, and a large number of new chiral ligands have been developed in the last few years [7–12]. Enantiomerically enriched alkylation and amination products are formed from racemic substrates by different reactivities of the two allyl termini in the intermediate π-allyl systems. Desymmetrization of the allyl system can be performed by electronic and steric effects induced by the ligand(s) bound to the metal center [13]. For C_2-symmetric systems, asymmetry arises only from steric interactions between the ligand and the substrate [14–17]. In the case of C_1-symmetric ligands non-steric factors may become dominant as, for example, in those containing two distinct donor groups that differ in their coordination to the metal center. Consequently, asymmetric induction may chiefly occur as a result of the different *trans* influences of the donor atoms [18–23]. In transition metal complexes modified by heterobidentate aminoalkyl-phosphine (P,N) ligands the difference in the *trans* influence between the P and N donor atoms distinguishes the two binding sites mainly, making the substituent *trans* to the phosphorus more labile. Besides the extensively applied libraries of chiral P,N ligands like phosphino-oxazolines (**a**) [24–26],

Electronic supplementary material The online version of this article (doi:10.1007/s00706-017-2029-2) contains supplementary material, which is available to authorized users.

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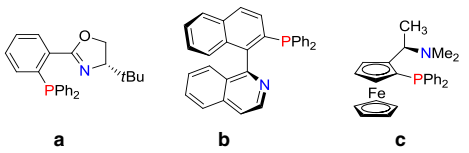


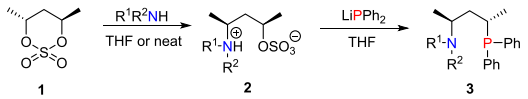
Fig. 1 Widely utilized P,N-type ligands for asymmetric catalytic synthesis

Quinap (**b**) and its congeners [27–29], or aminoalkyl-ferrocenes (**c**) [30, 31], alkane-diyl based aminoalkyl-phosphines emerged as a powerful class of P,N-type compounds with exceptional catalytic properties (Fig. 1) [32].

A systematic stereochemical fine-tuning of the coordinating subunits of this type of compounds can be implemented due to their structural modularity and to the versatility of the synthetic methodologies available for their preparation [33–35]. Additionally, aminoalkyl-phosphines with stereogenic nitrogen and chiral backbone may induce higher optical yields compared to achiral N-donors of similar ligand systems [36]. The coordination chemistry and catalytic properties of P,N ligands with stereogenic nitrogen, which are capable of forming five-membered chelates, have been previously investigated by several workgroups [37–47]. Six-membered chelate analogues of such systems having phosphinite [48] or aminophosphine [49, 50] functionalities are also known. However, in the case of six-membered aminoalkyl-phosphine chelate complexes containing stereogenic nitrogens there are still many important issues to be addressed concerning catalytic behaviour.

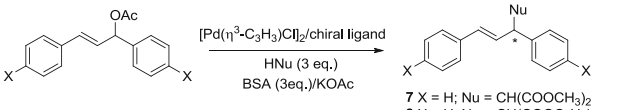
In previous studies we introduced a new methodology for the synthesis of modular P,N ligands **3a**–**3f** and **3i**–**3k** with pentane-2,4-diyl backbone associated with different nitrogen substituents (Scheme 1) [34, 35]. Recently, we have demonstrated, on a structural basis, the importance of the steric demand of N-substituent (**3a**, **3b**) in stereoselective coordination [51]. These two ligands were screened in asymmetric allylic substitution. It was found that beside the chiral backbone and the electronic differences in the donor atoms of the chelate, the stereoselective coordination of the nitrogen can also play an important role in efficient asymmetric catalysis. This allowed the establishment of a new stereocenter coordinated to the metal in one facile step. Based on these observations the careful stereoelectronic fine-tuning of the stereogenic nitrogen donor plays a crucial role in efficient catalyst design. Herein, we disclose a detailed account of the palladium-catalyzed asymmetric allylic substitution reaction of 1,3-diaryl-2-propenyl acetates with several C- and N-nucleophiles using a series of pentane-2,4-diyl based P,N ligands.

Scheme 1



3a R^1 = H, R^2 = Me; **3b** R^1 = H, R^2 = *i*Pr; **3c** R^1 = H, R^2 = *t*Bu; **3d** R^1 = H, R^2 = Cy; **3e** R^1 = H, R^2 = Bn; **3f** R^1 = H, R^2 = Ph; **3g** R^1 = H, R^2 = 2-Me-C_6H_4; **3h** R^1 = H, R^2 = 1-Ad; **3i** R^1, R^2 = -$(CH_2)_4$-; **3j** R^1, R^2 = -$(CH_2)_5$-; **3k** R^1, R^2 = -$(CH_2)_2O(CH_2)_2$-

Scheme 2



4 X = H, **5** X = OMe, **6** X = Br

7 X = H; Nu = $CH(COOCH_3)_2$
8 X = H; Nu = $CH(COOC_2H_5)_2$
9 X = H; Nu = $CH(COOCH_2Ph)_2$
10 X = OMe; Nu = $CH(COOCH_3)_2$
11 X = Br; Nu = $CH(COOCH_3)_2$

Results and discussion

The aminoalkyl-phosphines **3a**–**3k** were prepared in two simple steps according to Scheme 1. The family of ligands **3a**–**3f** and **3i**–**3k**, which were synthesized previously [34, 35], has been extended by the synthesis of two new compounds (**3g** and **3h**) with sterically unique 2-tolyl and 1-adamantyl N-groups. The low cost, ready availability, stereoelectronic properties, and relative ease of functionalisation of adamantane makes it an ideal candidate for incorporation into catalyst design [52]. The first step of the synthesis is the reaction of enantiomerically pure cyclic sulfate **1** and the corresponding primary amine mixed in THF leading to the corresponding aminoalkyl sulfates **2**. The addition of three equivalents of $LiPPh_2$ in THF provided the aminoalkyl-phosphines **3g** and **3h** in moderate yields, 56 and 51%, respectively. Both the ring-opening reaction of the cyclic sulfate with the amine and the second substitution reaction take place with complete inversion at the stereogenic centers.

First, the ligands were investigated in the palladium-catalyzed asymmetric allylic alkylation of the benchmark substrate 1,3-diphenyl-2-propenyl acetate with dimethyl malonate (Scheme 2, substrate **4** and HNu = $CH_2(COOCH_3)_2$). The substrate reacted with the nucleophile prepared in situ from dimethyl malonate (3 eq.) and *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 3 eq.) in the presence of 1 mol% catalyst and 5 mol% KOAc in CH_2Cl_2. The catalyst was synthesized in situ by the reaction of $[Pd(\eta^3\text{-}C_3H_3)Cl]_2$ and the chiral ligand in the same solvent.

Initially, we intended to optimize the reaction conditions by studying the role of the temperature and solvent on the activity and selectivity of the catalytic process using ligand **3b**. According to the results achieved in different solvents and at different temperatures it is reasonable to assume that

Table 1 Optimization of reaction conditions: the effect of the solvent and temperature using ligand **3b**

Entry	Temp/°C	Solvent	Conversion[a]/%	*ee*[a]/%
1	−20	CH_2Cl_2	48	61
2	0	CH_2Cl_2	82	88
3	25	CH_2Cl_2	>99	92
4	40	CH_2Cl_2	>99	91
5[b,c]	25	CH_2Cl_2	>99	94
6[b]	25	THF	28	87
7[b]	25	Toluene	>99	92
8[b]	25	$CHCl_3$	>99	92

Reaction conditions: catalyst prepared in situ from 0.5 mol % of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and 1.5 mol % of ligand **3b**; substrate **4** 1.25 mmol; dimethyl malonate 3.75 mmol; solvent 10 cm^3; BSA 3.75 mmol; KOAc 7 mg; temperature RT; reaction time 1 h. Prevailing configuration of the product: (*R*)

[a] Conversion and enantiomeric excess were determined by chiral HPLC

[b] The L/Pd molar ratio was 1

[c] Ref. [51]

non-polar reaction media and ambient temperature have a positive effect on both the activity and the *ee* (Table 1).

After having promising results in hand for the model systems, we applied the optimised protocol for the alkylation reaction using our ligand library (**3a–3k**). The effect of the N-substituent was examined at 25 °C using CH_2Cl_2 as solvent and a metal-to-ligand molar ratio of 1 (Table 2). The enantioselectivity was strongly dependent on the nitrogen substituent. Ligands having alkyl or aralkyl substituted secondary amino functionality provided high activity and a trend in the variation of enantioselectivity can be observed. Increasing the steric demand of the N-substituent generally resulted in an increase in the product's optical purity (Table 2, entries 1–5 and 8), up to 94% *ee* with ligand **3b**. This might originate from the ligands capability for the stereoselective coordination [51]. Moreover, according to this trend the *ee* can roughly be considered as a function of branching at the first carbon center of the N-substituent [51].

Interestingly, palladium catalysts modified by ligands **3f** and **3g** with aryl substituents yielded only poor activities and selectivities (Table 2, entries 6 and 7). Ligands possessing endocyclic and non-stereogenic nitrogen atoms (**3i–3k**) afforded *ee*s up to 86% (Table 2, entries 9–11). However, a comparison of selectivities achieved with ligands **3b–3d**, **3h**, and **3i** (Table 2, entries 2–4, 8, and 9) emphasizes that high enantioselectivities can also be obtained by using ligands containing non-stereogenic nitrogen donor.

Ligand **3c** was also tested in the allylation of substrate **4** with dibenzyl and diethyl malonate and in the reaction of substrates **5** and **6** (Scheme 2) with dimethyl malonate (Table 2, entries 12–15). The results suggest that the *p*-substituents of the substrate and the structure of the malonate nucleophile have a minor effect on the enantioselectivity of the reaction.

Variation of the ligand/palladium molar ratio had a profound effect on the enantioselectivity. The relationship between L/Pd and *ee* was thoroughly screened by using ligands **3a–3c** having N-substituents of different steric properties. When the ligand-to-metal ratio was increased above 1, the enantioselectivity falls dramatically with ligand **3b** and especially with ligand **3c** (Fig. 2). In this latter case, the *ee* changes from 95 to 58% when varying the value of L/Pd from 0.25 to 2. The same trend was observed using ligand **3h**; the *ee* improved from 90 to 94% when the ligand-to-metal ratio was reduced from 1 to 0.5. In addition, we performed catalytic experiments at L/Pd molar ratio of 10 with ligands **3a–3c**, **3g**, and **3k** to shed light on the limits of selectivity change. In each case the reactions completed within 1 h yielding selectivities up to 36% (Table 2, entries 1–3, 7, and 11). The explanation for the pronounced effect can be the fact that at ligand-to-metal ratios less than or equal to 1:1 chelated allyl intermediates predominate. The attack of the nucleophile preferentially occurs *trans* to the phosphorus due to its better π-acceptor ability compared to that of N. At higher L/Pd ratios non-chelate species (e.g. bisphosphorous complexes) can form in appreciable amount that provide less enantiodiscrimination in contrast to the chelate complex [39, 53]. These species, however, might provide higher catalytic activities as in the case of ligands **3g** and **3k**, where increasing the L/Pd ratio from 1 to 10 results in completing the reaction in 1 h (Table 2, entries 7 and 11). Furthermore, the extent of change in the *ee* as a function of L/Pd ratio shows a high dependence on the nitrogen substituent. The higher sensitivity of the catalyst containing **3c** on the variation of L/Pd suggests that the chelate formed in

Table 2 Allylic alkylation reactions: screening of ligands, substrates and nucleophiles

Entry	Ligand	Substrate	HNu	Conversion[a,b]/%	*ee*[a,b]/%
1[c]	R^1 = H, R^2 = Me (**3a**)	4	$CH_2(COOCH_3)_2$	>99 (>99)	24 (24)
2[c]	R^1 = H, R^2 = *i*Pr (**3b**)	4	$CH_2(COOCH_3)_2$	>99 (>99)	94 (36)
3	R^1 = H, R^2 = *t*Bu (**3c**)	4	$CH_2(COOCH_3)_2$	>99 (>99)	89 (28)
4	R^1 = H, R^2 = Cy (**3d**)	4	$CH_2(COOCH_3)_2$	>99	88
5	R^1 = H, R^2 = Bn (**3e**)	4	$CH_2(COOCH_3)_2$	>99	22
6	R^1 = H, R^2 = Ph (**3f**)	4	$CH_2(COOCH_3)_2$	30	13
7	R^1 = H, R^2 = 2-Me-C_6H_4 (**3g**)	4	$CH_2(COOCH_3)_2$	21 (>99)	8 (10)
8	R^1 = H, R^2 = 1-Ad (**3h**)	4	$CH_2(COOCH_3)_2$	>99	90
9	R^1, R^2 = –$(CH_2)_4$– (**3i**)	4	$CH_2(COOCH_3)_2$	>99	86
10	R^1, R^2 = –$(CH_2)_5$– (**3j**)	4	$CH_2(COOCH_3)_2$	23	76
11	R^1, R^2 = –$(CH_2)_2O(CH_2)_2$– (**3k**)	4	$CH_2(COOCH_3)_2$	31 (>99)	62 (18)
12	R^1 = H, R^2 = *t*Bu (**3c**)	4	$CH_2(COOCH_2CH_3)_2$	>99	88
13	R^1 = H, R^2 = *t*Bu (**3c**)	4	$CH_2(COOCH_2Ph)_2$	94	86
14	R^1 = H, R^2 = *t*Bu (**3c**)	5	$CH_2(COOCH_3)_2$	80	89
15	R^1 = H, R^2 = *t*Bu (**3c**)	6	$CH_2(COOCH_3)_2$	45	92

Reaction conditions: catalyst prepared in situ from 0.5 mol % of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and 1 mol % of chiral ligand; substrate 1.25 mmol; dimethyl malonate 3.75 mmol; solvent 10 cm^3 of CH_2Cl_2; BSA 3.75 mmol; KOAc 7 mg; temperature RT; reaction time 1 h. Prevailing configuration of the product: (*R*)

[a] Conversion and enantiomeric excess were determined by chiral HPLC

[b] Values in brackets were determined at an L/Pd molar ratio of 10

[c] Ref. [53]

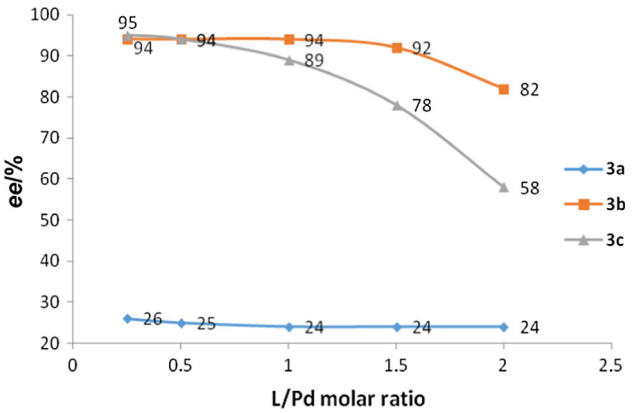
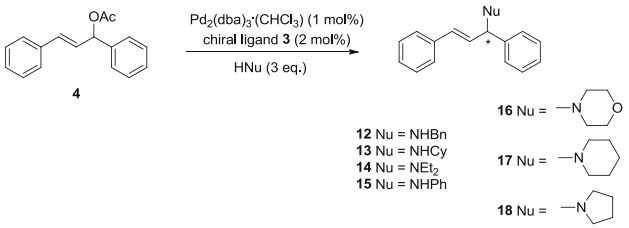


Fig. 2 The effect of ligand/palladium molar ratio (reaction conditions: catalyst prepared in situ from 0.5 mol% of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and calculated amount of chiral ligand according to the L/Pd ratio; substrate 1.25 mmol; dimethyl malonate 3.75 mmol; solvent 10 cm^3; BSA 3.75 mmol; KOAc 7 mg; temperature RT; reaction time 1 h. Prevailing configuration of the product: (*R*). In each case, the reaction proceeded with full conversion. Conversion and enantiomeric excess were determined by chiral HPLC)

this case is less stable. This can be interpreted by the stronger destabilizing effect of the sterically more demanding *t*Bu substituent compared to the *i*Pr group. According to this hypothesis, less strained chelates are less inclined to open that might result in the enhancement of enantioselectivity. These results reflect the importance of

Scheme 3

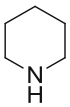
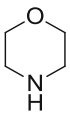
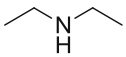
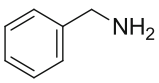
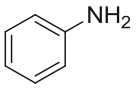
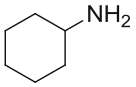


the molar ratio when hemilabile P,N-ligands are used for the modification of the catalyst.

In the next set of experiments, we evaluated the efficiency of the catalytic system in asymmetric allylic amination reactions (Scheme 3). Using 1 mol% $Pd_2(dba)_3{\cdot}(CHCl_3)$ and 2 mol% of chiral ligand **3b** as catalyst, the reaction was performed in CH_2Cl_2 as solvent (Table 3). The catalytic process was particularly sensitive to the nature of the nucleophile. The use of heterocyclic amines as nucleophiles resulted in high activities and *ee*s up to 86% (Table 3, entries 3, 6 and 9).

One of the key principles of green chemistry is the elimination of solvents in chemical processes. When the amount of solvent was decreased the reaction proceeded significantly faster (entries 1–3, 4–6, and 7–9). Under

Table 3 Asymmetric allylic amination: scope of N-nucleophiles using ligand **3b**

Entry	HNu	Reaction time/h	Solvent	Conversion[a]/%	*ee*[a]/%
1[b]		0.5 min	Neat	>99	24
2		0.5	2 cm^3 CH_2Cl_2	>99	72
3		1	4 cm^3 CH_2Cl_2	>99	80
4[b]		0.5 min	Neat	>99	40
5		0.5	2 cm^3 CH_2Cl_2	>99	84
6		1	4 cm^3 CH_2Cl_2	>99	86
7[b]		0.5 min	Neat	>99	34
8		0.5	2 cm^3 CH_2Cl_2	>99	74
9		1	4 cm^3 CH_2Cl_2	>99	82
10		48	2 cm^3 CH_2Cl_2	53	74
11[c]		18	2 cm^3 CH_2Cl_2	>99	90
12		24	2 cm^3 CH_2Cl_2	>99	64
13[c]		24	2 cm^3 CH_2Cl_2	>99	78
14[c]		24	2 cm^3 CH_2Cl_2	>99	70
15[c]		24	2 cm^3 CH_2Cl_2	>99	61

Reaction conditions: catalyst prepared in situ from 1 mol% of $Pd_2(dba)_3.(CHCl_3)$ and 2 mol% of ligand **3b**; substrate 0.625 mmol; amine 1.88 mmol; solvent 2 cm^3 of CH_2Cl_2; temperature RT

[a] Conversion and enantiomeric excess were determined by chiral HPLC

[b] $[Pd(\eta^3\text{-}Ph_2\text{-}C_3H_3)(\mathbf{3b})]BF_4$ complex is used as catalyst and no solvent was applied

[c] 1.25 mmol Cs_2CO_3 was added as base

solvent-free conditions using preformed complex $[Pd(\eta^3\text{-}Ph_2\text{-}C_3H_3)(\mathbf{3b})]BF_4$ [51] as catalyst (entries 1, 4, and 7) moderate *ee*s (up to 40%) and complete conversions in 0.5 min was obtained resulting in a remarkably high turnover frequency of >12,000 1/h. The exact reason for such dramatic positive effect of the nucleophile concentration on catalytic activity remains unclear. However, this finding provides highly useful information for the development of catalytic systems.

Contrarily to the heterocyclic nucleophiles, reactions with non-cyclic amines took place with lower activity and selectivity (Table 3, entries 10 and 12). Recently, Bunt and

Table 4 Asymmetric allylic amination with different P,N-ligands

Entry	Ligand	Reaction time/h	Conversion[a]/%	*ee*[a]/%
1	R^1 = H, R^2 = Me (**3a**)	0.5	>99	20
2	R^1 = H, R^2 = *i*Pr (**3b**)	0.5	>99	84
3	R^1 = H, R^2 = *t*Bu (**3c**)	1	>99	54
4	R^1 = H, R^2 = Cy (**3d**)	1	97	88
5	R^1 = H, R^2 = 1-Ad (**3h**)	0.5	>99	62

Reaction conditions: catalyst prepared in situ from 1 mol% of $Pd_2(dba)_3.(CHCl_3)$ and 2 mol% of ligand **3b**; substrate 0.625 mmol; piperidine 1.88 mmol; solvent 2 cm^3 of CH_2Cl_2; temperature RT

[a] Conversion and enantiomeric excess were determined by chiral HPLC

coworkers reported on the reversible nucleophilic addition in allylic amination reactions that might lower the enantioselectivity of the catalytic process [54]. However, the addition of a strong base (e.g. DBU or Cs_2CO_3) suppressed the proton driven reversibility and resulted in higher *ee*'s. Motivated by these findings, we decided to add Cs_2CO_3 to the catalytic reactions. This method clearly improved the performance of the catalytic system (entries 10–13), 90 and 78% *ee* could be obtained with diethylamine and benzylamine nucleophiles, respectively. For aniline and cyclohexylamine (entries 14 and 15) the reaction completed after 24 h with up to 70% *ee*. It is a noteworthy result since aromatic amines have not been used commonly in allylic amination, presumably because they are less nucleophilic than the more commonly used benzylamine or stabilized anionic nitrogen nucleophiles [55, 56]. However, recent studies proved the successful application of P,N ligands in the allylic aminations using aromatic amines [57]. The results achieved unambiguously prove that P,N-ligands with aliphatic backbone are capable of forming active and selective catalysts for allylic amination reactions.

Next, we studied the asymmetric allylic amination of 1,3-diphenyl-2-propenyl acetate with piperidine as nucleophile in the presence of palladium-catalysts modified by different P,N-compounds (Table 4). Ligands with bulky, tertiary N-groups (**3c** and **3h**, entries 3 and 5) gave only moderate selectivity compared to the catalysts having secondary nitrogen side chains (**3b** and **3d**, entries 2 and 4, Table 4). Similar to the effect of L/Pd ratio on the enantioselectivity, this phenomenon also emphasizes the significance of the substituent steric bulk in determining catalytic performance. However, it is important to note that the catalysts provided good enantioselectivities (up to 88%) and very high activities. Full conversions were achieved less than in 1 h under optimized conditions emphasizing the catalytic potential of P,N-type compounds with aliphatic backbone.

Conclusion

In summary, we have determined the beneficial features of pentane-2,4-diyl based aminoalkyl-phosphine (P,N) ligands in the palladium-catalyzed asymmetric allylic alkylation and amination of *rac*-1,3-diphenyl-2-propenyl acetate with several C- and N-nucleophiles giving high activities and enantioselectivities (up to 95% *ee* in alkylation and 90% *ee* in amination processes). The enantioselectivity of the asymmetric allylic alkylation with a series of analogous P,N ligands is strongly sensitive to the steric properties of the N-substituent. A general increase in enantioselectivity with the steric bulk of the substituents could be observed. The ligand-to-metal molar ratio has a profound effect on the enantioselectivity that was attributed to the possibility of the formation of less selective non-chelated species. It was observed that the catalyst with bulkier N-substituent (e.g. *t*Bu vs. *i*Pr) gives a more sensitive respond to the variation of L/Pd ratio. In amination reactions heterocyclic nucleophiles reacted smoothly with very high activities and good selectivities (up to 88%). Furthermore, under solvent-free conditions extremely high activities (TOF > 12,000/h) could be obtained with up to 40% enantioselectivity. The activity and selectivity of the reaction with non-heterocyclic amines could readily be enhanced by the addition of Cs_2CO_3, with diethylamine 90% *ee* was obtained. However, ligands with sterically more demanding N-sidechain provided lower selectivities. These results allowed us to conclude that chelates carrying sterically more demanding nitrogen substituents are more inclined to open. Consequently, the strategy, i.e. the variation of (1) the steric bulk of the substituent connected to the stereogenic nitrogen donor and of (2) the ligand-to-metal molar ratio in the Pd-complexes of pentane-2,4-diyl based ligands proved to be efficient means to enhance the catalyst activity/enantioselectivity.

Experimental

All manipulations were carried out under argon using Schlenk techniques. Solvents were purified, dried and deoxygenated by standard methods. Cyclic sulfate **1** was prepared according to the literature method [58]. All other starting materials were purchased from Sigma-Aldrich. $^{31}P\{^1H\}$, $^{13}C\{^1H\}$, and ^1H NMR spectra were recorded on a Bruker Avance 400 spectrometer (NMR Laboratory, University of Pannonia) operating at 161.98, 100.61, and 400.13 MHz, respectively. EI mass spectra were recorded on a Shimadzu GCMS QP2010 SE spectrometer.

(2S,4S)-4-(Diphenylphosphino)-N-(2-methylphenyl)-2-pentanamine (**3g**, $C_{24}H_{28}NP$)

At first (2*S*,4*R*)-2-(2-methylphenyl)amino-4-sulfatopentane was synthesized that was used without further purification in the next step. *o*-Toluidine (2.46 g, 23.02 mmol) was added to a solution of 3 g **1** (18.06 mmol) in 6 cm^3 THF and the mixture was stirred for 48 h at room temperature. After that 60 cm^3 ether was added to the mixture. The suspension formed was stirred for 30 min and then filtered. The solid was washed two times with ether, and dried by azeotropic distillation with toluene. The residual solvent was evaporated by vacuum to give (2*S*,4*R*)-2-(2-methylphenyl)amino-4-sulfatopentane as a white powder. Yield: 4.3 g, 87%; m.p.: 220 °C, $[\alpha]_D^{22} = +24°$ ($c = 1.105$, DMSO); ^1H NMR (400 MHz, DMSO-d_6): $\delta = 8.70$ (s, 2H, NH_2^+), 7.59–7.38 (m, 4H, aromatic), 4.27 (m, 1H, NCH), 2.98 (m, 1H, PCH), 1.85 (m, 1H, CH_2, diast.), 1.63 (m, 1H, CH_2, diast.), 1.51 (d, 3H, CH_3), 1.18 (d, ^3J(H,H) = 5.7 Hz, 3H, CH_3, overlapped), 1.17 (d, ^3J(H,H) = 6.1 Hz, 3H, CH_3, overlapped) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): $\delta = 133.92$ (broad s, 1C), 132.87 (s, 1C), 131.77 (broad s, 1C), 128.82 (broad s, 1C), 127.65 (s, 1C), 124.25 (broad s, 1C), 70.48 (s), 55.14 (s), 41.06 (s), 22.50 (s), 17.52 (s), 17.01 (s) ppm.

$LiPPh_2$·1,4-dioxane adduct (26.4 g, 94.2 mmol) was dissolved in 80 cm^3 THF under argon and the red solution was cooled to −10 °C. **2g** (4.3 g, 15.7 mmol) was added dropwise to this solution in small portions. The reaction mixture was stirred at room temperature for 24 h. The color of the reaction mixture remained red. After evaporation of the solvent, 80 cm^3 deoxygenated water and 60 cm^3 ether were added to the residue and the mixture was stirred until the two phases became clear solutions. The pH of the mixture was then adjusted to 1 with 10% deoxygenated aqueous HCl solution. The two phases were then separated and the aqueous phase was washed three times with 30 cm^3 portions of ether. The pH was then adjusted to about 9–10 with dropwise addition of a solution of Na_2CO_3. The product was then extracted four times with 30 cm^3 portions of ether. After drying with $MgSO_4$ the solvent was evaporated to give **3g** as a transparent oil. The crude product was then chromatographed on silica using *n*-hexane/EtOAc 15/1 as eluent to yield the product as a white powder. Yield: 3.2 g, 56%; m.p.: 87 °C; $[\alpha]_D^{22} = -54°$ ($c = 0.985$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.57$–6.57 (m, 14H, aromatic), 3.68 (m, 1H, NCH), 2.53 (m, 1H, PCH), 2.11 (s, 3H, CH_3), 1.74 (m, 1H, CH_2, diast.), 1.53 (m, 1H, CH_2, diast.), 1.21 (d, ^3J(H,H) = 6.2 Hz, 3H, CH_3), 1.16 (dd, ^3J(P,H) = 14.8 Hz, ^3J(H,H) = 6.9 Hz, 3H, CH_3) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 145.71$ (broad s, 1C), 137.66 (d, J(P,C) = 14.0 Hz, 1C), 137.57 (d, J(P,C) = 15.0 Hz, 1C), 134.43 (d, J(P,C) = 19.5 Hz, 2C), 134.20 (d, J(P,C) = 19.1 Hz, 2C), 130.94 (s, 1C), 129.49 (s, 1C), 129.44 (s, 1C), 129.08 (d, J(P,C) = 6.9 Hz, 2C), 128.98 (d, J(P,C) = 7.2 Hz, 2C), 127.74 (s, 1C), 122.42 (broad s, 1C), 117.14 (broad s, 1C), 110.83 (broad s, 1C), 47.18 (broad s, 1C), 41.65 (d, J(P,C) = 17.3 Hz, 1C), 28.12 (d, J(P,C) = 10.3 Hz, 1C), 21.11 (broad s, 1C), 18.31 (s, 1C), 17.21 (d, J(P,C) = 15.4 Hz) ppm; $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): $\delta = 0.47$ (s) ppm; EI-MS: $m/z = 361$ (M^+, calculated 361.2).

(2S,4S)-4-(Diphenylphosphino)-N-(1-adamantyl)-2-pentanamine (**3h**, $C_{27}H_{36}NP$)

At first (2*S*,4*R*)-2-(1-adamantyl)amino-4-sulfatopentane was synthesized that was used without further purification in the next step. 1-Adamantylamine (3.5 g, 23.02 mmol) was added to a solution of 3 g **1** (18.06 mmol) in 6 cm^3 THF and the mixture was stirred for 24 h at room temperature. After that 20 cm^3 ether was added to the mixture. The suspension formed was stirred for 30 min and then filtered. The solid was washed two times with ether, dried by azeotropic distillation with toluene. The residual solvent was evaporated by vacuum to give (2*S*,4*R*)-2-(1-adamantyl)amino-4-sulfatopentane as a white powder. Yield: 3.2 g, 56%; m.p.: 230–234 °C; $[\alpha]_D^{22} = +4°$ ($c = 1.00$, DMSO); ^1H NMR (400 MHz, DMSO-d_6): $\delta = 6.46$ (broad s, 2H, NH_2^+), 4.22 (m, 1H, NCH), 3.55 (m, 1H, PCH), 2.08 (m, 3H, adamantyl CH), 1.84–1.56 (broad m, 12H, CH_2), 1.22 (d, ^3J(H,H) = 6.4 Hz, 3H, CH_3), 1.19 (d, ^3J(H,H) = 6.2 Hz, 3H, CH_3) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): $\delta = 70.76$ (s, 1C), 56.99 (s, 1C), 45.64 (s, 1C), 44.65 (s, 1C), 39.82 (s, 3C) 35.91 (s, 3C), 29.20 (s, 3C), 22.41 (s, 1C), 21.25 (s, 1C) ppm.

$LiPPh_2$·1,4-dioxane adduct (6 g, 21.4 mmol) was dissolved in 30 cm^3 THF under argon and the red solution was cooled to −10 °C. **2 h** (2.3 g, 7.1 mmol) was added dropwise to the red solution in small portions. The reaction mixture was stirred at room temperature for 24 h. The color of the reaction mixture remained red. After evaporation of the solvent, 80 cm^3 deoxygenated water and 60 cm^3 ether were added to

the residue and the mixture was stirred until the two phases became clear solutions. The pH of the mixture was then adjusted to 1 with 10% deoxygenated aqueous HCl solution. The two phases were then separated and the aqueous phase was washed three times with 30 cm^3 portions of ether. The pH was then adjusted to about 9–10 with dropwise addition of a solution of Na_2CO_3. The product was then extracted four times with 30 cm^3 portions of ether. After drying with $MgSO_4$ the solvent was evaporated to give **3h** as a transparent oil. The crude product was then chromatographed on silica using $CHCl_3$/MeOH 6/1 as eluent to yield the product as a white powder. Yield: 1.5 g, 51%; m.p.: 72–74 °C; $[\alpha]_D^{22} = -104°$ ($c = 1.265$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.51$–7.27 (m, 10H, aromatic), 3.06 (m, 1H, NCH), 2.37 (m, 1H, PCH), 2.01 (m, 3H, adamantyl CH), 1.59 (m, 12H, adamantyl CH_2), 1.39 (m, 2H, CH_2), 1.05 (dd, ^3J(P,H) = 14.8 Hz, ^3J(H,H) = 6.8 Hz, 3H, CH_3), 1.03 (d, ^3J(H,H) = 6.8 Hz, 3H, CH_3) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 137.25$ (d, J(P,C) = 15.0 Hz, 1C), 137.15 (d, J(P,C) = 13.9 Hz, 1C), 133.94 (d, J(P,C) = 19.1 Hz, 2C), 133.75 (d, J(P,C) = 18.5 Hz, 2C), 128.83 (s, 1C), 128.77 (s, 1C), 128.46 (d, J(P,C) = 6.9 Hz, 2C), 128.37 (d, J(P,C) = 7.1 Hz, 2C), 51.93 (broad s, 1C), 43.62 (m, 3C), 43.21 (broad s, 1C), 36.76 (s, 3C), 29.74 (s, 3C), 27.80 (d, J(P,C) = 9.9 Hz, 1C), 23.44 (s, 1C), 16.39 (d, J(P,C) = 15.1 Hz) ppm; EI-MS: $m/z = 405$ (M^+, calculated 405.3).

Acknowledgements We thank Mr. Béla Édes for skilful assistance in analytical measurements and synthetic experiments and Dr. Imre Tóth for his useful comments on the manuscript. The research was supported by the 'National Excellence Program' in the framework of the Project TÁMOP-4.2.4.A/2-11/1-2012-0001 and by the National Research, Development and Innovation Office—NKFIH, K 115539.

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