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Novel Pd(PN,S)-complexes: Highly active catalysts designed for asymmetric allylic etherification

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ABSTRACT

Six novel thioether-aminophosphine type ligands with a general formula $(Ar^1)_2PN(R^1)CHR^2(CH_2)_nCH(R^3)SAr^2$ has been synthesized. The modular structure of the ligands and the new methodologies developed for their preparation enabled the systematic variation of their bridge length (n = 0 or 1), the substitution pattern of the backbone (R^2, R^3 = H or Me) as well as the P-, N- and S-substituents (Ar^1 = Ph or 3,5-$Me_2C_6H_3$, R^1 = Et or *i*Pr and Ar^2 = Ph, 4-MeC_6H_4, or 4-$MeOC_6H_4$, respectively). The ligands proved to be effective in Pd-catalyzed asymmetric allylic etherification reactions providing the products in high yields (up to 95%) and with good enantioselectivities (up to 86%) using unprecedentedly low (0.2 mol%) loadings of the chiral Pd-catalyst. Based on these findings, a new scalable protocol has been developed for the preparation of chiral allylic ethers. Furthermore, the Pd(II) coordination chemistry of the ligands was thoroughly investigated by 1D and 2D NMR methods as well as by X-ray crystallography with special attention to the conformation of the chelate ring and the stereoselectivity of the sulfur coordination. Based on these studies, the main factors determining activity and selectivity of the catalytic system have been identified.

Introduction

The palladium-catalyzed asymmetric allylic substitution represents one of the most versatile methodologies for the enantioselective construction of C-C and C-heteroatom bonds and thus for the efficient synthesis of biologically active chiral compounds.[1–5] These types of catalytic reactions typically operate under mild reaction conditions and coupling partners with a wide array of functional groups are well-tolerated. In the past several decades, the development of enantioselective C-C and C-N bond forming reactions using racemic allylic starting materials played a central role in this field of catalyst research. [6] More recently, however, the focus has been somewhat shifted towards the Pd-catalyzed enantioselective construction of C-O bond that facilitates the synthesis of chiral ethers and related derivatives. [7–9]

Despite extensive efforts, the direct utilization of alcohols as nucleophiles still represent a challenging direction of research. Amongst O-nucleophiles alcohols are usually considered as poor nucleophiles and when applied in an alkoxide form, elimination and deactivation of the metal catalyst may occur. [1] Their application, however, may open up new horizons towards the direct synthesis of optically active allylic ethers. [10] Indeed, in the last several years novel catalytic systems emerged that proved to be highly enantioselective (up to 99% *ee*) in asymmetric allylic etherification reactions utilizing alcohols as nucleophiles. [11–19] However, the practical use of these catalysts may be strongly limited by their low activity. A detailed survey of the literature clearly shows that generally 4-5 mol% (substrate/catalyst molar ratio (S/C) = 20-25) of the chiral catalyst is applied in the Pd-catalyzed allylic etherification using 1,3-diphenylallyl acetate as benchmark substrate. Furthermore, to the best of our knowledge there is no example for the application of the catalyst in less than 1 mol% (S/C = 100) concentration relative to the substrate in these types of catalytic transformations. [20] The high loading of the palladium catalyst required significantly increases the cost of each catalytic run due to the high world market price of this transition metal. Additionally, high metal loadings relative to the substrate increase the risk of poisoning subsequent reactions or contaminating the final product and also strongly hinder the scalability

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of the catalytic reaction. These facts clearly hamper the application of the present catalytic procedures for efficient palladium-mediated allylic etherification. As a result, there is a significant need to develop new synthetic protocols that employ low catalyst loadings, thus making Pd-catalyzed allylic etherification a cost-effective, safe and scalable synthetic methodology.

In the last several years, chiral phosphorus-thioether ligands became a privileged class of stereoselectors in transition metal catalysis. [21,22] The combination of a P,S heteroatom pair facilitates the stereoelectronic desymmetrization of the catalyst and the independent modification of the two functionalities enables subtle changes in the catalyst structure. Furthermore, by the proper choice of the ligand scaffold the donor sulfur-atom coordinates stereoselectively to the transition metal, thus promoting the successful stereochemical communication between the catalyst and the substrate. [23,24] In this context, thioether-aminophosphines and -phosphoramidites (PN,S ligands) offer themselves as promising candidates for stereoelectronic fine-tuning to improve catalyst activity and enantioselectivity. In these types of compounds, the nitrogen atom may strategically be functionalized by bulky substituents to further enhance steric control. Furthermore, the variation of the N-substituents can increase the modularity of the synthetic protocol and enables the electronic fine-tuning of the phosphorus donor. Indeed, Xiao and Chen et al. developed a library of highly modular thioether-phosphoramidites based on 1,2-diphenylethanediyl backbone (Fig. 1). [25] These ligands proved to be extremely efficient in Pd-catalyzed indole allylic alkylation as well as in the asymmetric construction of quaternary stereocenters using palladium-catalyzed decarboxylative [4+2] cycloaddition reactions. [26] In both types of catalytic processes very high yields (up to 99%) and *ees* (up to 98%) were achieved. Thioether-aminophosphines and -phosphoramidites were synthesized by Zeng and coworkers and were successfully used in Pd-catalyzed asymmetric allylic alkylation and in Cu-catalyzed conjugate additions. [27] Although with almost quantitative yields, only moderate *ees* could be obtained (up to 76% *ee* in the Cu-catalyzed process). Chan et al. developed a small library of ferrocene-based thioether-aminophosphine ligands (FerroNPS, Fig. 1). [28] These stereoselectors afforded high enantioselectivities (up to 96% *ee*) in the asymmetric allylic etherification of racemic 1,3-diphenyl-2-propenyl acetate with a wide array of alcohols.

Encouraged by these literature achievements we envisaged to synthesize a novel family of chiral thioether-aminophosphine ligands and to exploit their advantageous features provided by (i) their high modularity and convenient synthesis, (ii) the electronic differentiation induced by their different donoratoms as well as (iii) the stereolabile nature of the thioether function. Our additional aim was to systematically change the stereoelectronic features of the ligands in order to improve the activity and enantioselectvitiy of their Pd-complexes.

Results and discussion

Synthesis of the new ligands

Recently, we have developed a class of simple alkane-diyl based thioether-amine type (S,N) chiral ligands with secondary amine functionality using ethyl (*S*)-lactate (**1**) [29] or the corresponding cyclic sulfates as starting materials (**2a-d**, Fig. 2). [30]

Ligands **1** and **2a-d** could be successfully applied in palladium-catalyzed asymmetric allylic alkylation reactions, but proved to be catalytically inactive in allylic etherification. A prosperous feature of this ligand class, however, is the possibility of a subsequent functionalization step due to the presence of the NH unit. Indeed, in a single step, the addition of 1.5 equiv. of chlorophosphine in the presence of Et_3N and DMAP (4-dimethylaminopyridine) results in the formation of the corresponding thioether-aminophosphine ligands in excellent yield (Fig. 3). Based on the methods leading to compounds **1** and **2a-e**, a highly modular synthetic procedure was developed for the synthesis of PN,S ligands that allows the easy modification of the S-, N- and P-substituents and the ligand backbone as well.

Palladium-catalyzed asymmetric allylic etherification

The novel ligands were tested in asymmetric allylic etherification reactions. In the first set of experiments, the allylic etherification of 1,3-diphenylallyl acetate as substrate with 4-methoxybenzyl alcohol was performed to screen ligands **L1** and **L2a-e** (Table 1). Based on the usual literature procedures, the catalytic reactions were carried out with the Pd-catalyst prepared *in situ* from $[Pd(\eta^3\text{-allyl})Cl]_2$ and the chiral ligand or with preformed $[Pd(\mathbf{L2})(\eta^3\text{-Ph}_2\text{-allyl})]BF_4$ complex in the case of **L2b** and **L2c** (entries 4 and 7, Table 1), at a substrate/Pd molar ratio of 20 (5 mol% catalyst relative to the substrate), at room temperature in toluene

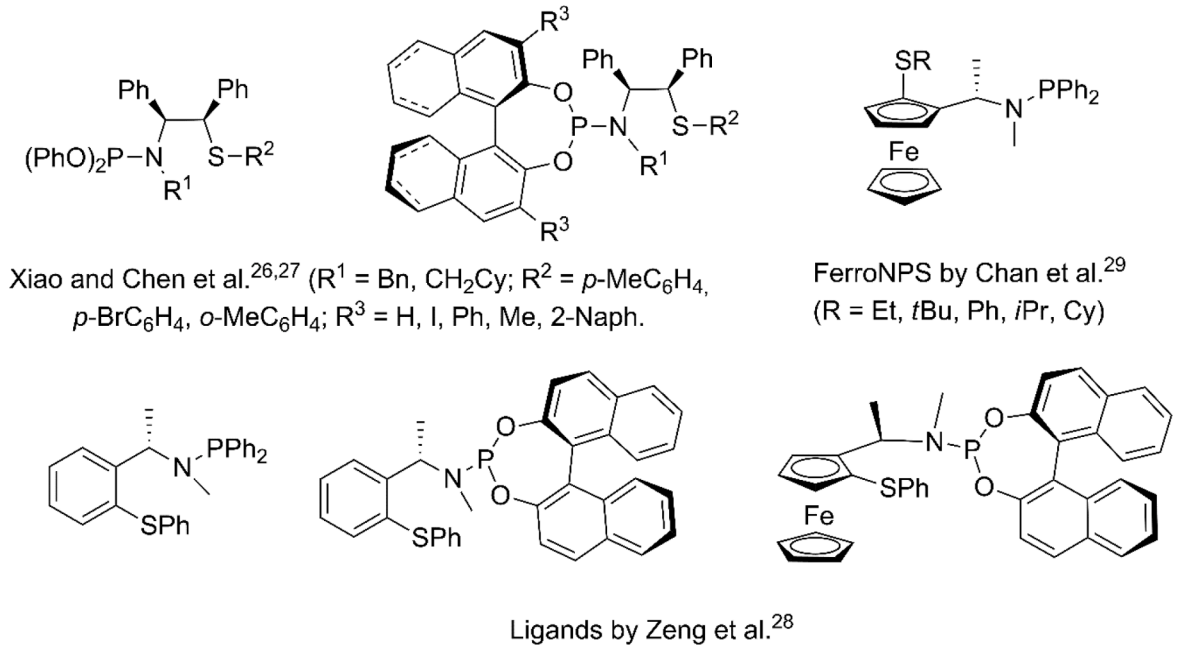


Fig. 1. Thioether-phosphoramidite and thioether-aminophosphine (PN,S) ligands used in asymmetric catalytic transformations.

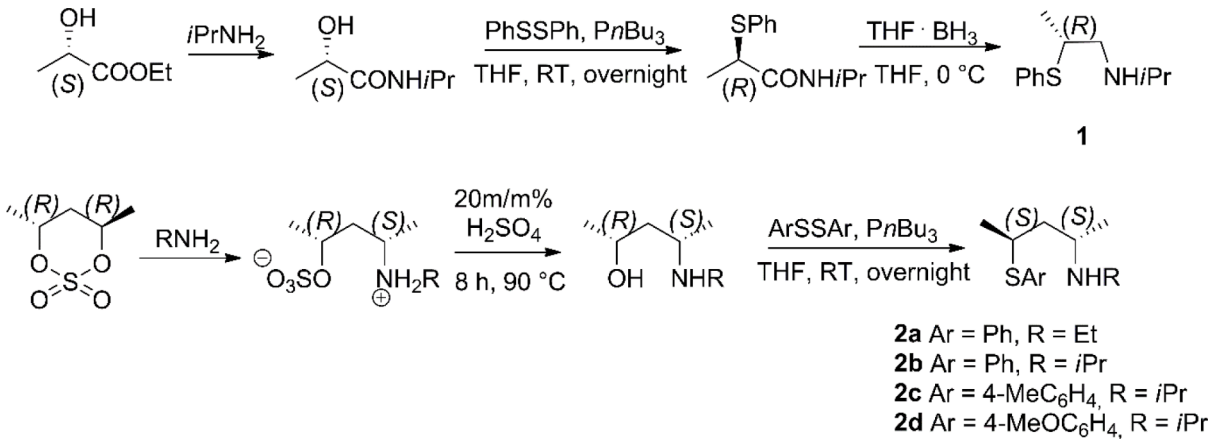


Fig. 2. Synthesis of alkanediyl based thioether-amines.

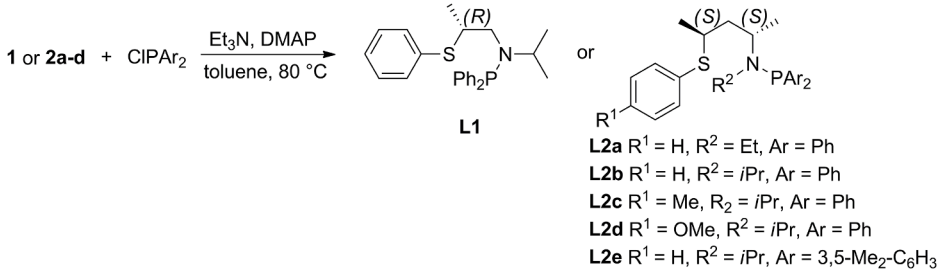


Fig. 3. Synthesis of thioether-aminophosphine L1 and L2a-e.

Table 1
Initial screening of the chiral ligands in asymmetric allylic etherification of 1,3-diphenylallyl acetate with 4-methoxybenzyl alcohol[a]

Entry	Ligand	Solvent	Yield (%)[b]	*Ee* (%)[c]
1	**L1**	toluene	97	40 (*R*)
2	**L2a** (R_1 = H, R_2 = Et, Ar = Ph)	toluene	96	60 (*S*)
3	**L2b** (R_1 = H, R_2 = *i*Pr, Ar = Ph)	toluene	96	80 (*S*)
4[d]	**L2b** (R_1 = H, R_2 = *i*Pr, Ar = Ph)	toluene	96	84 (*S*)
5	**L2b** (R_1 = H, R_2 = *i*Pr, Ar = Ph)	2-Me-THF	97	75 (*S*)
6	**L2c** (R_1 = Me, R_2 = *i*Pr, Ar = Ph)	toluene	95	86 (*S*)
7[d]	**L2c** (R_1 = Me, R_2 = *i*Pr, Ar = Ph)	toluene	96	86 (*S*)
8	**L2c** (R_1 = Me, R_2 = *i*Pr, Ar = Ph)	2-Me-THF	97	75 (*S*)
9	**L2c** (R_1 = Me, R_2 = *i*Pr, Ar = Ph)	MeCN	98	71 (*S*)
10	**L2c** (R_1 = Me, R_2 = *i*Pr, Ar = Ph)	MTBE	92	88 (*S*)
11	**L2d** (R_1 = OMe, R_2 = *i*Pr, Ar = Ph)	toluene	96	76 (*S*)
12	**L2e** (R_1 = H, R_2 = *i*Pr, Ar = 3,5-Me_2-C_6H_3)	toluene	96	83 (*S*)

[a]Reaction conditions: catalyst prepared *in situ* from 2.5 mol% of $[Pd(\eta^3\text{-allyl})Cl]_2$ and 5.25 mol% chiral ligand; substrate and alcohol: 0.25 mmol of 1,3-diphenylallyl acetate and 0.75 mmol of 4-methoxybenzyl alcohol; base: 0.75 mmol of Cs_2CO_3; solvent: 1.25 mL; temperature: RT; reaction time: 24 h.
[b]Yield of isolated product after column chromatography.
[c]Determined by HPLC on a chiral stationary phase.
[d]The reactions were carried out by using preformed [Pd(**L2b**)(η^3-Ph_2-allyl)]BF_4 (5 mol%) or of [Pd(**L2c**)(η^3-Ph_2-allyl)]BF_4 (5 mol%) complex instead of *in situ* formed catalysts.

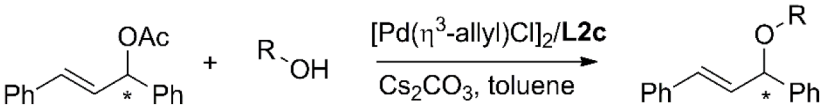
as solvent. Cesium-carbonate (Cs_2CO_3) was chosen as a base due to its mild basic nature, relatively high solubility in aprotic solvents and to the fact that Cs-salts are less prone to ion-pairing, thus providing higher reactivity and selectivity compared to other alkaline metal bases. [31–33]

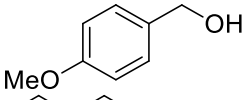
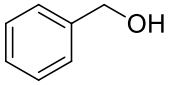
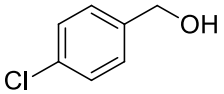
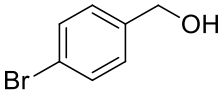
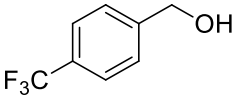
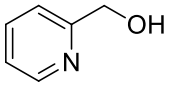
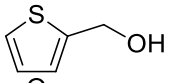
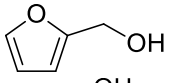
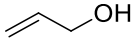
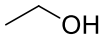
In each case, the reactions completed after 24 h as indicated by TLC and high isolated yields (up to 98%) and good enantioselectivities (up to 88%) could be obtained. Ligand **L1** possessing propane-1,2-diyl backbone and **L2a** having pentane-2,4-diyl bridge and N-ethyl substituent provided much lower *ee* (entries 1 and 2) compared to N-*i*Pr containing pentane-2,4-diyl based systems **L2b-e** (entries 3-12). These results emphasize the significant role of the backbone as well as the N-substituent in determining enantioselectivity. Interestingly, the S- and P-substituents seem to have a less significant effect on *ee*. Nevertheless, the best enantioselectivity in toluene (86%) could be obtained with ligand **L2c** containing S-tolyl and P-phenyl substituents (entries 6 and 7). It is noteworthy that the reaction proceeds smoothly without loss of enantioselectivity in alternative reaction media like 2-methyl tetrahydrofuran or methyl-*tert*-butyl ether (MTBE), although with some lower yield in the latter.

Based on these catalytic results we decided to expand the scope of the reaction with respect to the nucleophilic alcohols (Table 2). The catalytic tests were conducted under the same condition as in the first set of experiments. Again, high yields and good enantioselectivities could be obtained in the etherification process. As it was observed earlier, [28] benzylic alcohols with electron-donating substituents provided higher enantioselectivities and the *ee* slowly diminished as the substituent became more electron-deficient (entries 1-5, Table 2). Although with somewhat decreased activity and *ee*, the catalytic reaction took place with 2-pyridylmethanol (entry 6). In this case, however, the heteroatom may competitively coordinate to the metal center of the catalyst thus affecting both the activity and enantioselectivity. Interestingly, using 2-(hydroxymethyl)tiophene and 2-(hydroxymethyl)furane as nucleophiles high yields (97 and 98%, respectively) could be obtained (entries 7 and 8). Nevertheless, it was clearly proved that the Pd-catalyst modified by ligand **L2c** can effectively be used in the asymmetric allylic etherification with both aromatic and aliphatic alcohols to produce chiral allylic ethers in high yields and with good enantioselectivities (up to 88% *ee*).

In order to explore the potential of our catalytic system we

Table 2
Screening of nucleophilic reagents in the catalytic reaction[a]



Entry	Nucleophilic reagent (R-OH)	Yield (%)[b]	*Ee* (%)[c]
1		95	86
2		97	82
3		96	70
4		99	72
5		97	40
6		87	72
7		97	76
8		98	80
9		98	86
10		97	88
11	MeOH	97	81

[a]Reaction conditions: catalyst prepared *in situ* from 2.5 mol% of $[Pd(\eta^3\text{-allyl})Cl]_2$ and 5.25 mol% of **L2c**; substrate and alcohol: 0.25 mmol of 1,3-diphenylallyl acetate and 0.75 mmol of nucleophile; base: 0.75 mmol of Cs_2CO_3; solvent: 1.25 mL; temperature: RT; reaction time: 24 h.
[b]Yield of isolated product after column chromatography
[c]Determined by HPLC on a chiral stationary phase. The configuration of the prevailing enantiomer is (*S*).

investigated the effect of the substrate/catalyst (S/C) molar ratio on the yield and selectivity of the asymmetric allylic etherification of 1,3-diphenylallyl acetate with allyl alcohol using preformed [Pd(**L2c**)(η^3-Ph_2-allyl)]BF_4 as catalyst. Besides raising the S/C molar ratio by increasing the amount of the substrate, we decided to change the substrate/nucleophile/base ratio from 1/3/3 to 1/1.2/1.2 to enhance the effectiveness of the reaction and to reduce its environmental impact. Furthermore, the amount of toluene has not been proportionally increased relative to the substrate, in each case the reactions were performed in 2.5 mL of the solvent.

To our delight, the reactions proceeded smoothly even at a S/C ratio of 500 and unprecedentedly high yields could be obtained under these conditions (Table 3). Furthermore, the increase in the substrate/catalyst molar ratio does not affect the enantioselectivity, only a slight decrease in *ee* could be detected at a S/C ratio of 1000.

Encouraged by these promising results we extended this methodology to several other representative nucleophiles (Fig. 4). At S/C = 500 the reactions were performed under the same conditions as was described above. Although the catalytic reactions depend on the nucleophilic alcohol, it is indicated that high yields and good enantioselectivities can be obtained even by using only 0.2 mol% of the Pd-catalyst containing chiral thioether-aminophosphine **L2c**. Additionally, not only aromatic but aliphatic alcohols could be applied as nucleophiles. To the best of our knowledge this is the first report on the successful catalytic application of chiral Pd(II)-complexes in this benchmark allylic etherification reaction at catalyst loadings less than 1 mol%.

Coordination chemistry

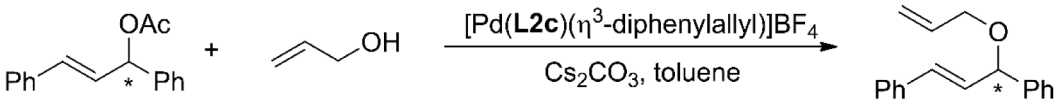
Synthesis of [Pd(PN,S)Cl_2] and [Pd(PN,S)(η^3-Ph_2-allyl)]BF_4 complexes

In order to evaluate the origin of the powerful catalytic properties of the novel bidentate thioether-aminophosphines, we decided to investigate their palladium coordination chemistry. Therefore, [Pd(PN,S)Cl_2] complexes of ligands **L1**, **L2a** and **L2b** and [Pd(PN,S)(η^3-Ph_2-allyl)]BF_4 type coordination compounds of **L2b** and **L2c** were synthesized. They can easily be prepared by using the suitably labile precursors [Pd(COD)Cl_2] or [Pd(COD)(η^3-Ph_2-allyl)]BF_4, respectively, by the addition of one molar equivalent of chiral ligand (Fig. 5). It is important to note that the two possible configurations of the coordinated sulfur donor and the different conformations associated with the C_1-symmetry seven-membered chelate ring as well as the isomerism of the diphenylallyl moiety in the [Pd(PN,S)(η^3-Ph_2-allyl)]BF_4 complexes enable the formation of stereoisomeric structures in the complexation reaction.

X-ray studies

X-ray structure analysis of single crystals grown by slow evaporation of the solvent from the solution of [Pd(**L2a**)Cl_2] and [Pd(**L2b**)Cl_2] in a

Table 3
The effect of substrate/catalyst molar ratio[a]



Entry	S/C molar ratio	Yield (%)[b]	*Ee* (%)[c]
1[d]	20	98	86
2[d]	100	98	86
3[d]	250	98	86
4	500	93	86
5	1000	64	83

[a]Reaction conditions: catalyst: 0.0025 mmol of preformed [Pd(η^3-PhCHCHCHPh)(**L2c**)]BF_4; substrate: diphenylallyl acetate; nucleophile: 1.2 equiv. allyl alcohol; base: 1.2 eqiv. of Cs_2CO_3; solvent: 2.5 mL of toluene; temperature: RT; reaction time: 24 h.
[b]Isolated yield.
[c]Determined by chiral HPLC. The configuration of the prevailing enantiomer is (*S*).
[d]Reaction time: 5 h.

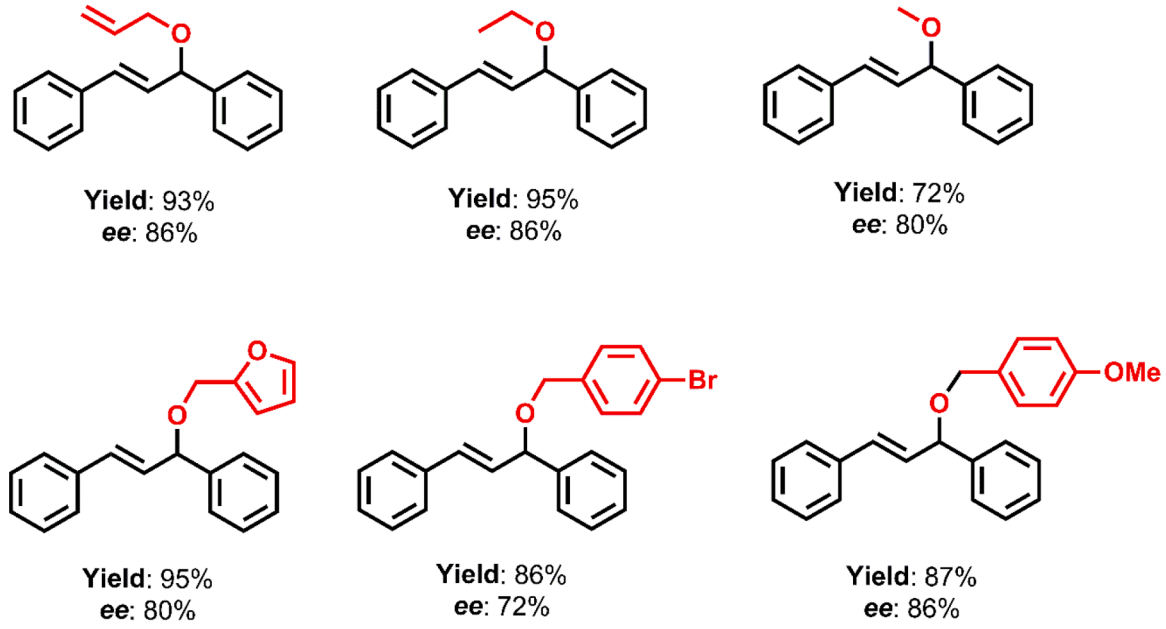


Fig. 4. Isolated yields and enantioselectivities of allylic ethers synthesized by asymmetric allylic etherification at a substrate/catalyst molar ratio of 500 (the additional reaction conditions are given in the footnote of Table 3).

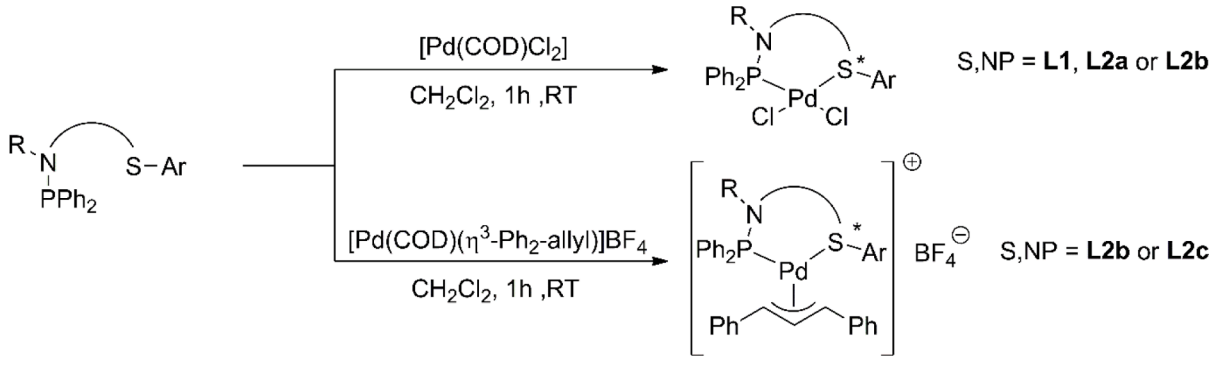


Fig. 5. Synthesis of Pd-complexes of the novel thioether-aminophosphines.

mixture of acetone and dichloromethane has been performed. In both cases, the coordination sphere of the seven-membered Pd-PN,S chelate has the usual slightly distorted square planar geometry (Fig. 6). The Pd-Cl length *trans* to P is somewhat longer than that *trans* to S indicating the larger *trans* influence of the phosphorus compared to the sulfur (Table 4).

In the distorted boat-like seven-membered chelate rings the coordinated sulfur donor has (*S*)-configuration with axially disposed Ph-substituent in both cases. The nitrogen atom has a trigonal planar geometry with bond angles of 119.9(7)°, 119.4(6)° and 118.5(6)° for [Pd(**L2a**)Cl_2] and 118.4(9)°, 118.9(10)° and 121.5(11)° for [Pd(**L2b**)Cl_2] around it. The N-atom is displaced by 0.132 and 0.101 Å from the PCC

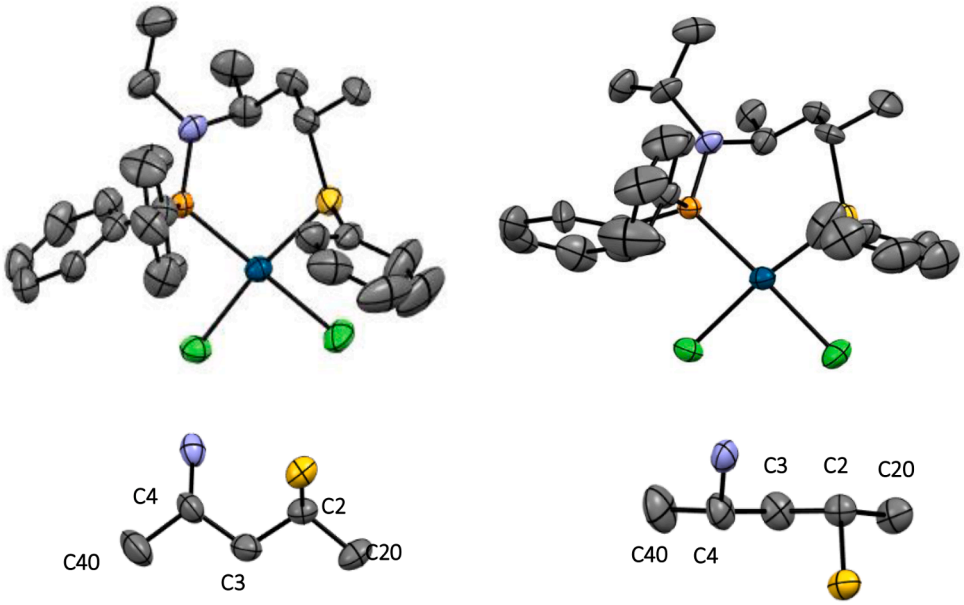


Fig. 6. X-ray structures of [Pd(L2a)Cl_2] and [Pd(L2b)Cl_2] (top) and the pentane-2,4-diyl moiety of the chelate in [Pd(L2a)Cl_2] from different perspectives (bottom) (ORTEP views at 50% probability level, hydrogen atoms are omitted for clarity).

Table 4
Selected bond lengths (Å), bond angles (°) and torsion angles (°) of complexes [Pd(L2a)Cl_2] and [Pd(L2b)Cl_2][a].

	[Pd(**L2a**)Cl_2]	[Pd(**L2b**)Cl_2]
Bond lengths (Å)		
Pd-S	2.305(2)	2.315(3)
Pd-P	2.263(2)	2.258(4)
P-N	1.673(7)	1.665(11)
Pd-Cl (*trans* to S)	2.301(2)	2.301(4)
Pd-Cl (*trans* to P)	2.360(2)	2.360(4)
Bond angles (°)		
P-Pd-S	97.59(7)	99.24(12)
Cl-Pd-Cl	90.73(8)	90.17(15)
P-N-C4	119.4(6)	118.4(9)
P-N-C(alkyl)	118.5(6)	118.9(10)
C4-N-C(alkyl)	119.9(7)	121.5(11)
Torsion angles (°)		
C20-C2-C3-C4	175.7(7)°	175.9(13)
C40-C4-C3-C2	177.5(8)°,	178.1(12)

[a]Complexes were crystallized via slow evaporation of the solvent from their solution in acetone/dichloromethane mixture.

plane and the P-N bond length is 1.673(7) and 1.665(11) Å, for the complexes [Pd(**L2a**)Cl_2] and [Pd(**L2b**)Cl_2], respectively. These are clear indications that the P-N bond has a considerable double bond character. [34] It is particularly interesting that the torsion angles C20-C2-C3-C4 and C40-C4-C3-C2 in the pentane-2,4-diyl moiety are very close to 180° (Fig. 6, Table 4). In other words, the pentane-2,4-diyl framework adopts a nearly planar zig-zag conformation so that both methyl groups are directed equatorially in the chelate. It is important to note that the same arrangement of the backbone has been observed for uncoordinated pentane-2,4-diyl based phosphine-phosphoramidite ligands. [35]

NMR analysis

[Pd(PN,S)Cl_2] type complexes of ligands **L1, L2a** and **L2b** have been characterized by ^{1}H, ^{13}C{^{1}H}, ^{31}P{^{1}H}, ^{1}H-^{1}H NOESY, ^{1}H-^{1}H COSY and HSQC NMR techniques using CD_2Cl_2 as solvent in order to have a deeper insight into their solution phase behavior. The ligands coordinated in a bidentate fashion in each case as was shown by the significant coordination shift of the corresponding signals relative to the free ligand in the ^{1}H, ^{13}C{^{1}H} and ^{31}P{^{1}H} NMR spectra of the complexes. At room temperature only one set of signals could be observed for each complex in the 1D spectra. Upon cooling the samples to 193 K, however, the signals of complexes [Pd(**L1**)Cl_2] and [Pd(**L2a**)Cl_2] split, indicating the presence of two equilibrating isomers in a ratio of ~9:1 in both cases. These isomers may differ in their chelate conformation, in the configuration of the sulfur donor or both. In contrast to compound [Pd(**L2a**)Cl_2] with N-ethyl substituent and pentane-2,4-diyl backbone, complex [Pd(**L2b**)Cl_2] having N-isopropyl group exists in solution as a single diastereomer. The detailed NMR analysis of [Pd(**L2b**)Cl_2] and the major isomer of [Pd(**L2a**)Cl_2] proves that they have the same chelate conformation and sulfur atom configuration as observed in their solid state X-ray structures. It was unambiguously proved by the characteristic coupling pattern of the (*S,S*)-pentane-2,4-diyl framework, where the same coupling constants could be observed for both methylene protons H^b and H^c (Fig. 7). The couplings of H^b with the adjacent CH's, H^a and H^d are significantly different (~2 and ~14 Hz, respectively) that strongly suggests their *syn*- and *anti*-positions relative to H^b, respectively. As the same argument is valid for H^c, the planar arrangement of the pentane-2,4-diyl moiety can nicely be deduced from the solution phase ^{1}H NMR data. Additionally, the indicative NOESY crosspeaks between the corresponding ^{1}H signals provide further support for this backbone conformation (Fig. 7) and for the axial arrangement of the S-Ph substituent. These observations together with our earlier findings [35] underline the significance of the pentane-2,4-diyl backbone in the stabilization of ring conformation and provide unambiguous evidence for its enhanced conformational rigidity. Obviously, the increased double bond character of the P-N bond and its sterically crowded environment may also largely contribute to the remarkable conformational rigidity of the seven-membered chelate in [Pd(**L2a**)Cl_2] and [Pd(**L2b**)Cl_2]. Although the exact stereochemical characterization of the equilibrating [Pd(**L1**)Cl_2] isomers and the minor isomer of [Pd(**L2a**)Cl_2] could not be carried out, their solution phase dynamics proves that both the chelate ring size and the N-alkyl substituent has a substantial role in determining the stereoselectivity of the coordination, a major factor affecting enantioselectivity in catalysis. In this context, it is important to recall that the *ee* values achieved by using ligands **L1** (40% *ee*) and **L2a** (60% *ee*) are considerably lower than those obtained by the application of pentane-2,4-diyl based ligands having N-*i*Pr substituents (*ee*s up to 86%) under identical conditions (Table 1).

The promising catalytic features of the novel pentane-2,4-diyl based ligands with N-*i*Pr substituent prompted us to investigate their coordination properties using the ionic complex [Pd(**L2b**)(η^3-Ph_2-allyl)]BF_4.

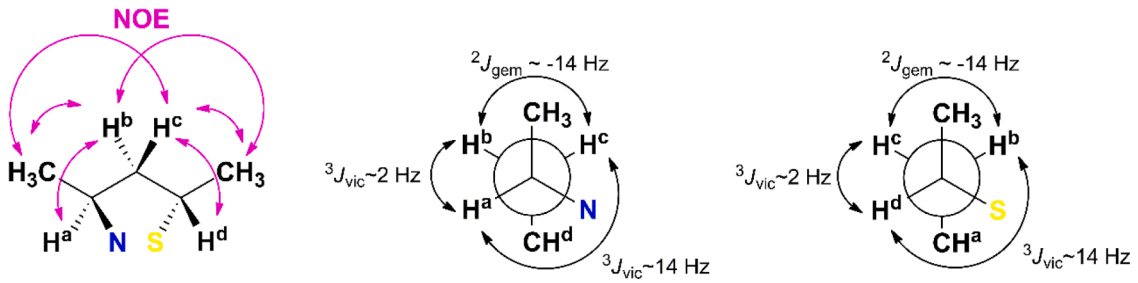


Fig. 7. NOE interactions and the characteristic coupling pattern of the (S,S)-pentane-2,4-diyl skeleton stabilized in planar zig-zag conformation in the major isomer of [Pd(L2b)Cl_2].

The ^{1}H and ^{31}P NMR spectra of [Pd(**L2b**)(η^3-Ph_2-allyl)]BF_4 revealed the presence of two isomers in 8.6:1.4 molar ratio at room temperature in CD_2Cl_2. These isomers can be assigned as the *exo*- and *endo*-complexes (Fig. 8), respectively, based on their characteristic coupling patterns and the ^{1}H and ^{13}C chemical shifts of the corresponding allylic NMR signals. [36] The preference of the *exo*-isomer over the *endo* can mainly be attributed to the more pronounced repulsion between the face positioned equatorial P–Ph group and the allylic Ph substituent in the latter (Fig. 8). [36] The structural analysis of the diphenylallyl-complex by ^{1}H and ^{1}H-^{1}H NOESY techniques evidenced that the chelate ring adopts the same conformation both in the *exo*- and *endo*-isomers as in [Pd(**L2b**)Cl_2]. This can for instance be deduced from the very similar coupling patterns and chemical shifts of the diastereotopic CH_2 protons in the backbone. To our great surprise, however, upon cooling the solution to 193 K the ^{31}P signal of the *exo*-isomer splits, indicating a fast equilibrium between two isomers that are present in a molar ratio of 1.6:7. This process can be attributed to the inversion of the coordinated sulfur atom as the typical coupling patterns and chemical shifts of the backbone hydrogens and the allylic protons are very similar in the two species thus excluding the possibility of changes in the ring conformation or in the allylic moiety. Consequently, the NMR data suggest that the *exo*-form of [Pd(**L2b**)(η^3-Ph_2-allyl)]$^+$ dominates in the solution phase that exhibits fluxional behavior due to its stereolabile sulfur atom. It is, however, interesting to note that the above dynamic behavior of chiral ligand **L2b** cannot be observed in [Pd(**L2b**)Cl_2]. It demonstrates the fact that the co-ligand of the complex (i.e. Cl vs. diphenylallyl) has a remarkable effect on the stereoselectivity of sulfur coordination and on its dynamics as well. Additionally, the observed configurational lability in the *exo*-isomer point out that the sulfur has a sterically less hindered environment and that the substrate-complex is prone to structural changes despite its rigid chelate ring. Furthermore, the stereolability of the catalyst may strongly contribute to the acceleration of certain transitions in the catalytic cycle through the adaptation of the ligand's structure thus increasing the rate of the overall process [37,38].

In order to strengthen this concept, we have synthesized phosphine-aminophosphine ligand **L3**, analogously to compounds **L2a-e**, using the corresponding aminophosphine (**3**) [36] as starting material (Fig. 9). **L3** can be considered as a structural analogue of **L2b** as they differ only in one of their coordinating functionalities: **L3** contains a sterically more demanding PPh_2 function instead of the SPh moiety.

In contrast to their structural similarities, however, **L3** exhibits quite different coordination behavior in its Pd-diphenylallyl complex compared to **L2b**. In the ^{31}P NMR spectrum of [Pd(**L3**)(η^3-Ph_2-allyl)]BF_4 two pairs of doublets appear indicating the presence of two diastereomers in a molar ratio of 10:2, that are identified as the corresponding *exo* and *endo* isomers, respectively. The chelate ring in both the *exo*- and *endo*-isomers of [Pd(**L3**)(η^3-Ph_2-allyl)]BF_4 adopts the same conformation as was found in [Pd(**L2b**)(η^3-Ph_2-allyl)]BF_4. Consequently, both donor phosphorus atoms must have an axially and an equatorially disposed Ph group, as depicted in Fig. 8. Unlike in the solution of [Pd(**L2b**)(η^3-Ph_2-allyl)]BF_4, however, no dynamic behavior could be observed: upon cooling the sample to 193 K the spectrum still exhibited the same signal sets. This also confirms the fact that the solution phase dynamics of complex [Pd(**L2b**)(η^3-Ph_2-allyl)]BF_4 can be attributed to the sulfur inversion. The catalytic features of the two diphenylallyl-complexes, [Pd(**L2b**)(η^3-Ph_2-allyl)]BF_4 and [Pd(**L3**)(η^3-Ph_2-allyl)]BF_4 are also remarkably different. First, in the allylic etherification using allyl alcohol as nucleophile the thioether-containing

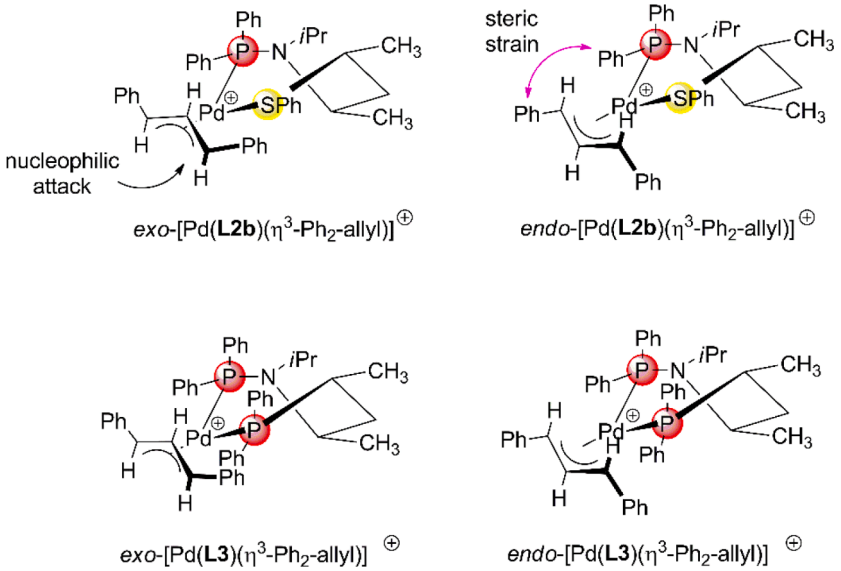


Fig. 8. The *exo* (major)- and *endo* (minor)- isomers of cations [Pd(**L2b**)(η^3-Ph_2-allyl)]$^+$ (top) and [Pd(**L3**)(η^3-Ph_2-allyl)]$^+$ (bottom).

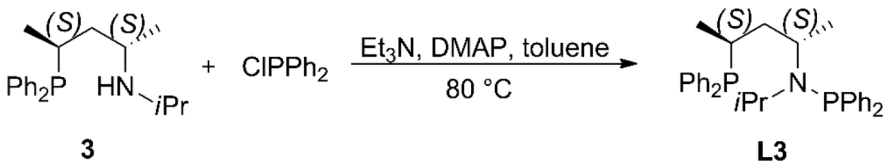


Fig. 9. Synthesis of chiral phosphine-aminophosphine ligand L3.

catalyst provided the product with 93% yield after 24 h at a substrate/catalyst molar ratio of 500. In contrast, the catalytic system containing **L3** as chiral selector resulted only 30% isolated yield under the same conditions. In other words, the stereochemically rather labile catalyst with a sterically less hindered sulfur environment outperformed the sterically more congested and rigid system in terms of activity. Additionally, the enantioselectivity achieved by the latter (20% *ee*) is considerably lower than that provided by **L2b** (84% *ee*). The higher enantioselectivity achieved by using the thioether containing catalyst can mainly be attributed to the remarkably different electronic nature of its donoratoms. Assuming that the *exo*-isomer is more reactive than the *endo*, and that the nucleophilic attack on the diphenylallyl-moiety takes place at the allyl carbon *trans* to the phosphorus and opposite to the Pd (Fig. 8), [16,39] allylic ethers with (*S*) configuration will be produced. Indeed, the prevailing configuration of the optically active allylic products is (*S*) when using **L2b-e** as chiral ligands.

Obviously, the stereochemical lability of the Pd(PN,S) complexes may also be responsible for the imperfect enantioselectivity observed in the catalytic reactions. [23] It is, however, reasonable to assume that it is the balanced flexibility of these Pd(PN,S) catalysts, i.e. the expressed rigidity of the chelate together with the rather non-rigid nature of the chiral pocket, that enables the catalytic system to provide very high activities and relatively high enantioselectivities at the same time.

Conclusions

In summary, six novel, optically active alkane-diyl based thioether-aminophosphines **L1** and **L2a-e** with modular structure have been synthesized in a simple step starting from the corresponding thioether-amines. Based on the new ligand family, a cost-effective, safe and scalable synthetic protocol has been developed for the Pd-catalyzed asymmetric allylic etherification using catalyst loadings as low as 0.2 mol%. In addition, the substrate/base/nucleophile ratio was significantly improved to 1/1.2/1.2 from the ratio of 1/3/3 used generally in literature procedures, while the amount of the solvent could be kept at a minimum. The optically active allylic ethers could be isolated in high yields (up to 95%) with good enantioselectivities (up to 86% *ee*). Furthermore, combined spectroscopic and X-ray studies, and comparative experiments were performed in order to shed light on the success of this small ligand family in asymmetric allylic etherification reactions. The (i) stereoelectronic heterogeneity of the donor atoms, (ii) the sterically less hindered environment around the thioether moiety and (iii) the carefully balanced stereochemical lability of the catalyst have been identified as the major factors exerting a profound effect on the activity and the enantioselectivity. We strongly believe that our findings will promote the use of chiral PN,S type ligands in asymmetric allylic etherification reactions as an efficient tool for the synthesis of optically active chiral building blocks even on an industrial scale.

CRediT authorship contribution statement

Máté M. Major: Methodology, Investigation. **Mária Guóth:** Investigation. **Szabolcs Balogh:** Investigation, Validation. **József Simon:** Investigation, Validation. **Attila C. Bényei:** Investigation, Validation, Conceptualization. **József Bakos:** Writing – review & editing, Supervision, Conceptualization. **Gergely Farkas:** Writing – original draft, Supervision, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.mcat.2021.111763.

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