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Synthesis and Application of Chiral *P*,*N*-Ligands with *Pseudo-Meso* and *Pseudo-C*$_2$ Symmetry

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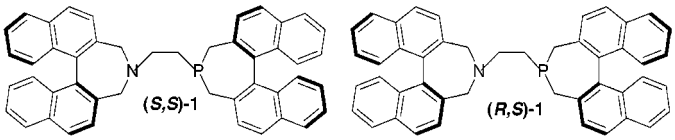
ABSTRACT



Two diastereoisomeric *P*,*N*-ligands, (*S*,*S*)-1 and (*R*,*S*)-1, were synthesized and assessed in palladium-catalyzed allylic alkylations. With *rac*-1,3-diphenylpropenyl acetate as substrate, ligand (*S*,*S*)-1, with "*pseudo*-C_2" symmetry, exhibited higher reactivity and higher enantioselectivity than the "*pseudo-meso*" ligand (*R*,*S*)-1, whereas reversal reactivity and selectivity were observed with *rac*-3-cyclohexenyl acetate.

Palladium-catalyzed asymmetric allylic alkylation is one of the most important C−C, C−O, C−N, and C−S bond forming reactions today. A large variety of chiral ligands have been designed and employed.[1] Factors such as the electronic and steric properties of the ligand as well as the size of the bite angle have proven to be crucial for selectivity.[2] In the choice of ligand structure, the benefits of C_2-symmetric ligands, originating mainly from the formation of one single π-allyl palladium complex and thus fewer reaction paths, have to be compared to those of asymmetric ligands, where electronic dissymmetry may lead to efficient enantiodiscrimination.

We have previously found dramatic differences in the selectivity as well as the reactivity of 2-(1-methoxyalkyl)-6-oxazolinylpyridines, such as **2a** and **2b** (Figure 1), containing sterically bulky groups either on different or on the same side of the coordination plane.[3] In the substitution of *rac*-1,3-diphenyl-2-propenyl acetate with malonate, the former resulted in high yields and >99% ee, whereas with the latter the ee achieved was merely 15%.[4]

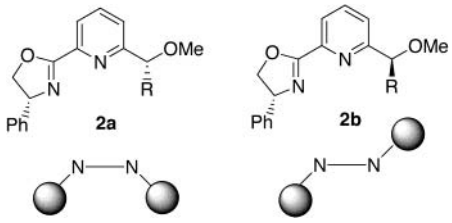


Figure 1.

As the difference in *trans* influence of the two nitrogen donor atoms is expected to be small in ligands such as **2a** and **2b**, the enantioselectivity is assumed to originate mainly from the different steric environments of the two allylic termini.

Recently, much attention has been devoted to *P*,*N*-ligands, and many of these have been successfully used in palladium-

(1) (a) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 2000; p 593. (b) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422.

(2) van Haaren, R. J.; Druijven, C. J. M.; van Strijdonck, G. P. F.; Oevering, H.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Chem*. Soc., *Dalton Trans.* **2000**, 1549−1554.

(3) Svensson, M.; Bremberg; U.; Hallman, K.; Csöregh, I.; Moberg, C. *Organometallics* **1999**, *18*, 4900−4907.

(4) (a) Nordström, K.; Macedo, E.; Moberg, C. *J. Org. Chem.* **1997**, *62*, 1604−1609. (b) Bremberg, U.; Rahm, F.; Moberg, C. *Tetrahedron: Asymmetry* **1998**, *9*, 3437−3443.

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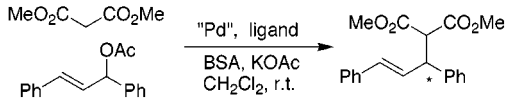
catalyzed allylic substitutions. The difference in *trans* influence between the two donor atoms is assumed to be the major enantiodifferentiating factor. Ligands containing two different coordinating atoms allow the design of "*pseudo*-C_2" and "*pseudo-meso*" ligands, provided they contain two stereocenters which may have different or the same absolute configuration.[5] Such ligands are of interest as they would allow efficient studies of steric as well as electronic factors.

In *P*,*N*-systems, chelates are usually formed, but monodentate coordination has occasionally been observed.[6] Recently, some *P*,*N*-ligands with *N*-aryl substituents have been shown to exhibit undesired coordination modes where the nitrogen atom, probably due to the presence of electron-withdrawing groups directly attached to nitrogen, does not take part in the coordination to palladium.[7]

In the present Letter, we describe the synthesis of *P*,*N*-ligands possessing "*pseudo*-C_2" and "*pseudo-meso*" symmetry and preliminary results from their use in palladium-catalyzed allylic alkylation reactions (Scheme 1).

Scheme 1



To optimize both steric and electronic properties, we decided to base this new class of ligands on a binaphthyl skeleton, more exactly on the 4,5-dihydro-3*H*-dinaphtho-[1,2-*c*:2′,1′-*e*]azepino and 4,5-dihydro-3*H*-dinaphtho[1,2-*c*:2′,1′-*e*]phosphepino series. We assumed that the coordination ability of the electron-rich nitrogen atom would be preserved in the catalytic reaction. The two ligands, (*S*,*S*)-**1** and (*R*,*S*)-**1**, thus carry the same binaphthyl groups, but they differ in their absolute configurations. In the latter ligand, the chirality originates solely from the different donor atoms.

For the preparation of the ligands, (*S*)-2,2′-di(bromomethyl)-1,1′-binaphthyl[8] **3** was reacted with (2-aminoethyl)-phosphonic acid diethyl ester in the presence of triethylamine in THF to give the amino-phosphonate **4** in 94% yield (Scheme 2). LAH reduction of **4** gave amino-phosphine **5**[9] (82%). To avoid an air-sensitive final product, we chose to protect the fairly air stable amino-phosphine **5** with borane. The protection of the phosphine also served to increase the acidity of the two hydrogen atoms on phosphorus. Addition of 2 equiv of BH_3·Me_2S complex in THF gave the *P*,*N*-bis protected borane **6** in quantitative yield. A total of 2 equiv was necessary to protect the phosphorus atom, as the first equivalent was trapped by the more electron-rich nitrogen atom. Reaction of phosphine−borane **6** with (*S*)- or (*R*)-**3** in THF in the presence of NaH gave "*pseudo*-C_2" and "*pseudo-meso*" ligand precursors (*S*,*S*)-**7** and (*R*,*S*)-**7** in 76 and 79% yields, respectively.[10] Selective *N*-deprotection with 1 equiv of DABCO[11] in CH_2Cl_2 resulted in the two ligands (*S*,*S*)-**1**−BH_3 and (*R*,*S*)-**1**−BH_3.

With the ligands in hand, we chose to first explore the reactivity and enantioselectivity in the palladium-catalyzed allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate as nucleophile in the presence of BSA and KOAc. We found that the catalyst could be generated in situ directly from the borane-protected ligand, using $Pd(OAc)_2$ as palladium source.

With (*S*,*S*)-**1** as ligand, total conversion was achieved after 6 h and an enantiomeric excess of 98% in favor of the (*S*)-enantiomer was observed. In contrast, when *pseudo-meso* ligand (*R*,*S*)-**1** was employed, 3 days of stirring were required to achieve a high yield of product, which, however, was obtained with low enantiomeric excess (37% of the (*R*)-enantiomer, Table 1).

Table 1

ligand	L:Pd	time (h)	yield (%)	ee (%)
(*S*,*S*)-**1**	1:1[a]	6	100	98 (*S*)
(*R*,*S*)-**1**	1:1[a]	72	95	37 (*R*)
(*S*,*S*)-**1**	2:1[b]	8	100	98 (*S*)
(*R*,*S*)-**1**	2:1[b]	8	100	59 (*S*)

[a] Palladium source: palladium acetate. [b] Palladium source: allylpalladium chloride dimer.

After these preliminary investigations, we decided to study the influence of the ligand:palladium ratio on the outcome of the catalytic process. For this purpose, we needed to deprotect both nitrogen and phosphorus to obtain the free ligand. This was achieved by using the procedure previously described for **7**. After 8 h with 2 equiv of DABCO in toluene at room temperature, (*S*,*S*)-**1**−BH_3 and (*R*,*S*)-**1**−BH_3 were deprotected to give quantitatively free (*S*,*S*)-**1** and (*R*,*S*)-**1**, respectively. When 2 equiv (with respect to palladium) of the in situ deprotected ligands was used in the allylic alkylation of 1,3-diphenyl-2-propenyl acetate with allylpalladium chloride dimer as palladium source, the same level of enantioselectivity and total conversion were obtained as when (*S*,*S*)-**1** was used as ligand (Table 1). On the other hand, in the case of (*R*,*S*)-**1** total conversion was achieved within 8 h, and an enantiomeric excess of 59% with opposite stereoselection compared to that obtained using a ligand:palladium ratio of 1:1 was observed.

The two diastereoisomeric ligands thus differ considerably in their behavior. The results observed using (*S*,*S*)-**1** can be

(5) One example of a "*pseudo-meso*" ligand with the asymmetry in the ligand backbone has been reported: Trost, B. M.; *Acc. Chem. Res*. **1996**, *29*, 355−364.

(6) Amatore, C.; Fuxa, A.; Jutand, A. *Chem. Eur. J*. **2000**, *6*, 1474−1482.

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(8) Xiao, D.; Zhang, Z.; Zhang, X. *Org Lett*. **1999**, *1*, 1679−1681.

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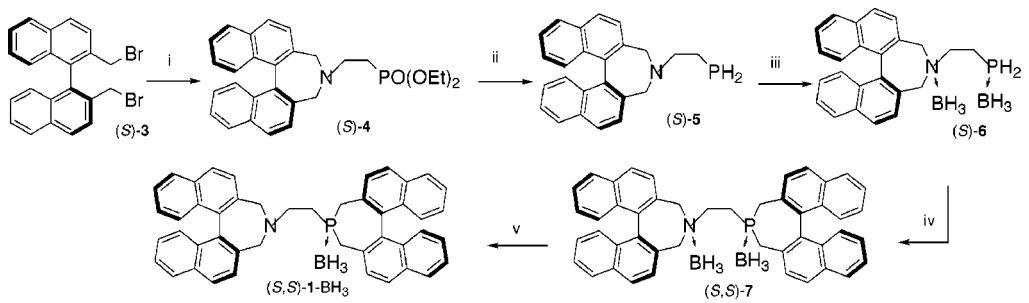
(10) Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc*. **1990**, *112*, 5244−5252.

(11) Brisset, H.; Gourdel, Y.; Pellon, P.; Le Corre, M. *Tetrahedron Lett*. **1993**, *34*, 4523−4526.

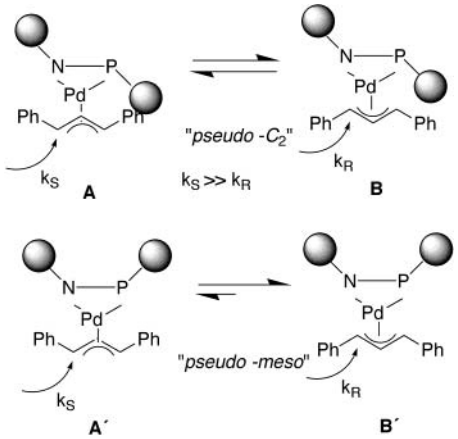
Scheme 2. Synthesis of the *Pseudo-*C_2 Ligand (*S*,*S*)-**1**



i) NH_2-CH_2-CH_2-$PO(OEt)_2$, NEt_3, THF, 94%; ii) $LiAlH_4$, THF, 91%; iii) BH_3.Me_2S, THF, 99%; iv) (*S*)-**3**, NaH, THF, 76%; v) DABCO, CH_2Cl_2, 96%.

rationalized by assuming a different reactivity of the two possible π-allylpalladium complexes A and B (Scheme 3),

Scheme 3



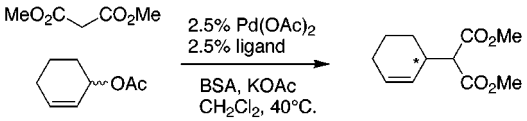
with attack of the nucleophile preferentially taking place *trans to* phosphorus in A.[12] This seems reasonable, as rotation of the allyl fragment to form an olefin−Pd complex would be unfavorable due to steric repulsion in B, which is thus expected to be considerably less reactive than A.[13] The fact that the same results were obtained when a 2:1 ligand:metal ratio was used suggests that a 1:1 complex is the catalytically active species.

From the *pseudo-meso* ligand, also two complexes, A′ and B′, are expected. The two complexes are assumed to differ considerably in energy, with A′ suffering from severe steric congestion. Nucleophilic attack *trans* to phosphorus in the major complex results in the observed product. This process is, however, unfavorable, as rotation of the allyl fragment to form an olefin complex is sterically difficult. This explains the low reactivity of the catalytic system containing (*R*,*S*)-**1**. The different results obtained with an excess of ligand indicate that the stoichiometry of the catalyst varies with the amount of ligand added. A 2:1 complex, in which only the phosphorus atom takes part in coordination to palladium, has C_2 symmetry and is expected to yield the (*S*) enantiomer as the major product, in accordance with what was observed.

The study of this new class of ligands was extended to a sterically less demanding substrate. Thus (*S*,*S*)-**1**−BH_3 and (*R*,*S*)-**1**−BH_3 were tested in the palladium-mediated substitution of *rac*-3-cyclohexenyl acetate, employing a ligand:metal ratio of 1:1. In this case, we needed to run the reactions at 40 °C to obtain satisfactory conversion to product, as only traces were detected at room temperature.

As expected,[13] with both ligands products with (*R*) absolut configuration were obtained, although with low enantioselectivity. Interestingly, with the cyclic substrate, the *pseudo-meso* ligand (*R*,*S*)-**1** resulted in somewhat higher enantioselectivity (26%) than the diastereoisomer *(S,S)*-**1** (12%, Table 2). The former ligand also exhibited higher reactivity (70% conversion after 24 h compared to 40% for (*S*,*S*)-**1**). These results show that in the case of the cyclic substrate the behavior, in terms of reactivity and enantioselectivity, of these ligands is opposite from what was observed with the more activated open substrate.

Table 2



ligand	Pd/L	time (h)	convn (%)	ee (%)
(*S*,*S*)-**1**	1/1	24	40	12 (*R*)
(*R*,*S*)-**1**	1/1	24	70	26 (*R*)

In conclusion, we have synthesized two new chiral *P*,*N*-ligands with *pseudo-meso* and *pseudo-*C_2 topology. In a preliminary study, we have demonstrated their different behavior in palladium-catalyzed allylic alkylations with different type of substrates. These results confirm

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(13) Saitoh, A.; Achiwa, K.; Tanaka, K.; Morimoto, T. *J. Org. Chem*. **2000**, *65*, 4227−4240

that symmetry has an important influence on the course of the reaction in terms of kinetics and enantioselectivity.

Acknowledgment. We gratefully thank Mr. Hervé Cousin for determination of enantiomeric excesses on the cyclic substrates and Dr. Krister Zetterberg for valuable discussion. This work was supported financially by the Göran Gustafsson Foundation for Research in Sciences and Medicine and by the Swedish Natural Science Research Council.

Supporting Information Available: Spectroscopic data as well as experimental procedures for the synthesis of (*S*,*S*)-**1**−BH_3 and (*R*,*S*)-**1**−BH_3 and general procedures for the catalytic reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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