Pergamon

Tetrahedron Letters 39 (1998) 5727–5730

TETRAHEDRON LETTERS

Chiral Phosphinooxazolines with a Bi- or Tricyclic Oxazoline Moiety - Applications in Pd-Catalyzed Allylic Alkylations

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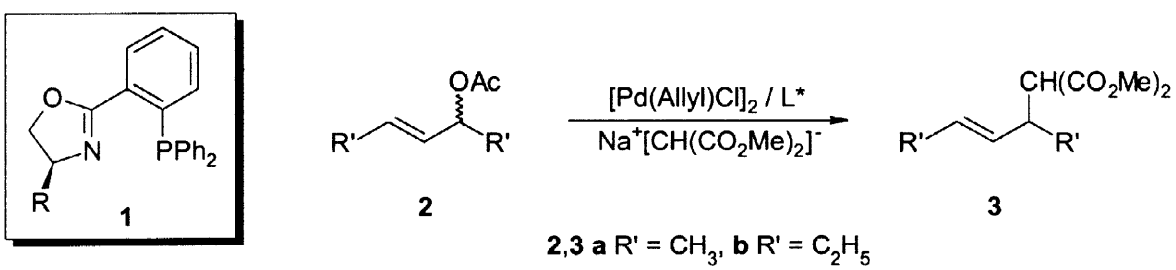
Received 14 May 1998; accepted 4 June 1998

Abstract: Phosphinooxazolines with a bi- or tricyclic oxazoline moiety are described. In Pd-catalyzed alkylations of 1,3-dimethylallyl acetate with sodium dimethyl malonate enantiomeric excess of up to 89.5 % was obtained. This is the best result so far achieved for this substrate with P,N-chelate ligands.

Pd-catalyzed allylic substitutions have been intensively studied over the last few years. As result, efficient chiral ligands are now available and considerable insight into the mechanisms of these reactions has been obtained.[1] The following types of chiral ligands are perhaps the most useful presently: phosphinooxazolines (PHOX) (Scheme 1),[2] modular C_2-diphosphines[3] and phosphinomyrtanic acids.[4] The two latter types are particularly useful for cyclic substrates.

Like numerous other P,N-chelate ligands, standard phosphinooxazolines (*i.e.* **1** with R = *i*Pr or *t*Bu) furnish excellent results with large acyclic substrates, in particular with derivatives of 1,3-diphenylallyl alcohol, but fail with cyclic substrates and give rise to low enantioselectivity with small acyclic substrates such as derivatives of 1,3-dimethylallyl alcohol. For this reason only a few of the many reports on allylic substitutions with P,N-ligands deal with the latter substrates.[2b,5] Recently, we were able to achieve high enantioselectivity for cyclic substrates with phosphinooxazolines that contain stereogenic phosphorus.[6] We here report new phosphinooxazolines which give excellent results in alkylations of small acyclic substrates.[7] The new ligands are of great interest for several other reactions as well.

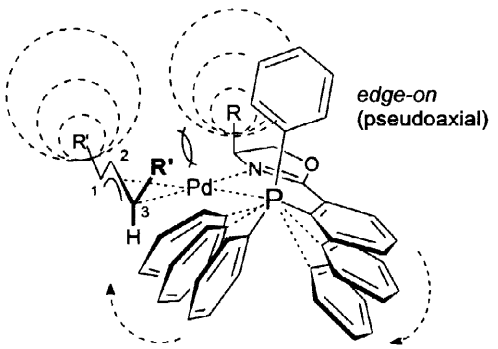


Scheme 1

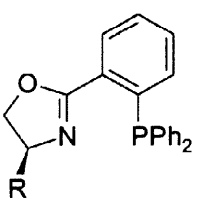
The new ligands were developed on the basis of the following observations concerning mechanistic aspects of allylic substitutions with (phosphinooxazoline)Pd complexes (cf. formula of *exo* complex below): (a) Differing σ-donor/π-acceptor capabilities of nitrogen and phosphorus give rise to selective attack of the nucleophile at the allylic carbon (C-1) in *trans* position relative to phosphorus (trans-effect). (b) In solution, (π-allyl)Pd complexes of PHOX ligands occur as mixtures of *exo* and *endo* isomers. Relative rates of reactions of *exo* and *endo* isomers with nucleophiles range from 9:1 to 1:1, respectively.[8] (c) As a rule, *exo* are more stable than *endo* isomers. Their relative stability is controlled by steric interactions between the pseudoequatorial phenyl group

0040-4039/98/$19.00
PII: S0040-4039(98)01173-3

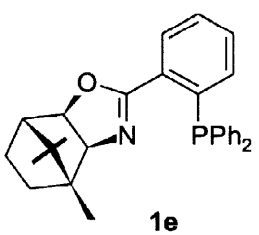
at phosphorus and the substituent at C-3 (R') of the π-allyl system. (d) Enantioselectivity of the substitution reaction increases with increasing steric bulk of substituent R of the oxazoline moiety and R' of the substrate. The reason is not interaction between R and R', but rather repulsion between R or R' and the palladium ion which leads to bending of the ligand plane (N-C-C-C-P) relative to the coordination plane (P, N, C-1, C-3). Increase of bending causes the pseudoequatorial phenyl ring at P to be pushed further towards the π-allyl system; this leads to an increase in the crucial interaction between the P-phenyl group and the substituent R' at C-3 thus destabilizing the *endo* π-allyl complex.



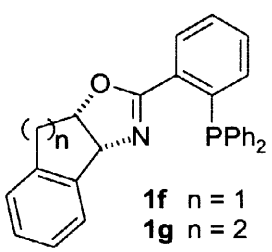
These observations suggested that better suited ligands might be obtained by using larger substituents at the oxazoline moiety. This was achieved by simply increasing the size of substituents R in the series **1a-d**;[10] ligand **1d** derived from penicillamine is particularly interesting because of the possibility for further variation in the substituent at sulfur. A more successful concept involved incorporation of the substituent R into a ring in order to provide a conformational situation with maximal steric interaction between R and the palladium ion (ligands **1e-g**).[9]



ent-**1a** R = Ph
1b R = *i*Pr
1c R = *t*Bu
ent-**1d** R = CMe_2SiBu

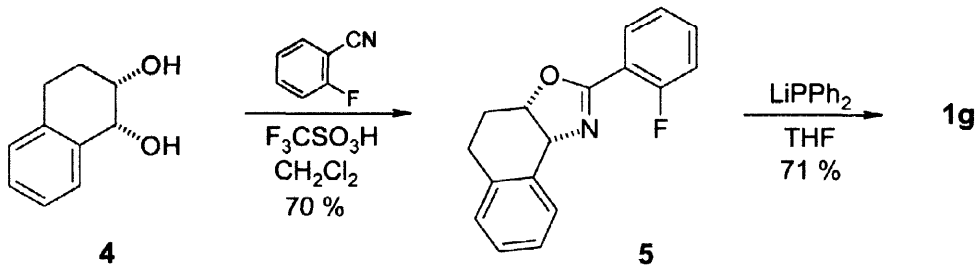


1e



1f n = 1
1g n = 2

Preparation of the phosphinooxazolines **1a-1d** is well documented.[10] Ligands **1e** and **1f** were obtained in 56 % (corr. 84 %) and 67 % yield by reaction of 2-diphenylphosphinobenzonitrile[11] with (2*S*,3*R*)-3-hydroxy-bornylamine[12] and (1*R*,2*S*)-1-amino-2-indanol,[13] respectively. The oxazoline **1g** was prepared in 50 % yield from (1*R*,2*S*)-1,2,3,4-tetrahydro-1,2-naphthalindiol (**4**)[14] by applying a method developed at Merck Research Laboratories involving a Ritter-type cyclization with 2-fluorobenzonitrile;[15] the ligand is then obtained by subsequent nucleophilic substitution of fluoride with lithium diphenylphosphide (Scheme 2). Careful analysis of the crude product indicated that both regio- and stereoselectivity of the reaction are very high. The Ritter-type reaction of the diol **4** with 2-diphenylphosphinobenzonitrile, to give **1g** directly, could not be accomplished.



Scheme 2

Results obtained in Pd-catalyzed allylic alkylations (cf. Scheme 1) under control of the new ligands are summarized in Table 1. The following conclusions are apparent: (i) As anticipated, enantioselectivity increases in the series of ligands **1b-1d** containing substituents of increasing steric bulk. (ii) Incorporation of the phenyl group into a ring leads to enhanced selectivity, as demonstrated by comparison of the results obtained with *ent*-**1a** and with **1f** and **1g**. (iii) Of particular importance is the observation that the fastest reaction is induced by phosphinooxazoline **1g**; this indicates that the intermediary (π-allyl)palladium complexes are highly strained.[16] (iv) That excellent yields can be obtained with **1f** and **1g** after a reaction time of up to 48 h (entries 9 and 11) indicates excellent stability of the intermediary (phosphinooxazoline)Pd^0 complexes.

Table 1. Pd-Catalyzed Allylic Alkylations of 1,3-Dimethyl- and 1,3-Diethylallyl Acetate with Sodium Dimethyl Malonate (cf. Scheme 1)[a]

Entry	Ligand	Substrate R'	Temp. [°C]	Reaction time [h]	Yield[b] [%]	ee [%][c] (Config.)
1	*ent*-**1a**	CH_3	rt	0.5	93	56 (*R*)
2	**1b**	CH_3	rt	1	99	57 (*S*)
3	**1c**	CH_3	rt	0.3	93	68 (*S*)[d]
4	**1c**	C_2H_5	rt	4	88	77 (S)[e]
5	*ent*-**1d**	CH_3	rt	2	92	75 (*R*)[e]
6	*ent*-**1d**	C_2H_5	rt	4	90	85 (*R*)[e]
7	**1e**	CH_3	rt	0.5	95	58 (*S*)
8	**1f**	CH_3	rt	1	95	76 (*R*)
9	**1f**	CH_3	-20	48	96	82 (*R*)
10	**1g**	CH_3	rt	0.1	95	70 (*R*)
11	**1g**	CH_3	-20	24	97	85 (*R*)
12	**1g**	CH_3	-40	48	21	89.5 (*R*)

(a) Reaction conditions: 1.0 mmol of substrate, 1.5 mmol of nucleophile, 1.0 mol-% of $[Pd(C_3H_5)Cl]_2$, Pd:L = 1:1.1, 4 ml of THF; (b) Isolated, purified product; (c) GLC: He, 25 m permethyl-β-cyclodextrin, WCOT fused silica, Cp-cyclodextrin-B-236-M-19 (Chrompack), **3a**: temp. 85 °C: (-)-(*S*)-**3a**: t_R = 29.0 min, (+)(*R*)-**3a**: t_R = 29.7 min; **3b**: temp. 90 °C, (-)-(*S*)-**3b**: t_R = 52.8 min, (+)(*R*)-**3b**: t_R = 53.6 min. (d) In previous work (ref. 2b) ee of 71 % was obtained for the same reaction. (e) These data are taken from ref. 17.

In conclusion, palladium catalyzed allylic alkylations of 1,3-dimethylallyl acetate with the new, sterically demanding phosphinooxazoline ligands yield products with up to 89.5 %ee. The new ligand **1g** is accessible in two steps from the commercially available diol **4**; other, even more bulky ligands were obtained via the same route.[18] The new phosphinooxazolines may well be useful for transition metal catalyzed reactions other than allylic substitutions.

Acknowledgements. This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (SFB 247). We thank Dr. M. Kiefer,[17] BASF AG, Luwigshafen, Prof. Y. Langlois, Paris, and Dr. D. G. Morris, Glasgow, for unpublished procedures and Tobias Illg for skillful technical assistance.

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12. The preparation of the requisite *exo,exo*-2-amino-3-bornanol from (1*R*)-2,3-bornandione is problematic, cf. D. G. Morris, K. S. Ryder, *Synthesis* **1997**, 620-621. We have further simplified the preparation of this compound by directly reducing the oxime of *exo*-3-hydroxy-2-bornanone with $NaBH_4/NiCl_2$ (88 % yield, diastereoselectivity >95:5) according to a general method of J. Ipaktschi (*Chem. Ber.* **1984**, *117*, 856-858); *exo*-3-hydroxy-2-bornanone was prepared from (1*R*)-2,3-bornandione by reduction with L-Selectride according to an unpublished procedure kindly communicated by Prof. Y. Langlois, Paris.
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16. This statement may appear paradoxical. However, one must bear in mind that the first step in the catalytic cycle, oxidative addition, is fast compared to the second step, nucleophilic substitution. As a consequence, steric strain gives rise to increase of the energy content of the π-allyl complex and, therefore, reduction of the activation energy because interactions between the allylic moiety and the ligand are lower in the transition state than in the ground state.
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