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Selectivity and reactivity in asymmetric allylic alkylation*

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Abstract: 2-(1-Hydroxyalkyl)-6-oxazolyl-and 2-(1-alkoxyalkyl)-6-oxazolylpyridines serve as versatile ligands in the palladium-catalyzed allylic substitution of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate as nucleophile. The enantioselectivity of the reaction is dependent on the conformation of the ligands, as deduced by NMR, X-ray crystallography and DFT calculations of palladium(II) complexes of the ligands. The reactions are slow, requiring up to four days reaction time. However, with the use of microwave flash heating, reaction times are reduced to 2 min, with only minor loss in stereoselectivity.

INTRODUCTION

Asymmetric metal catalysis constitutes an important method for the preparation of enantiopure chiral compounds [1]. A complete understanding of the factors that govern the stereoselectivity in such processes is beyond the scope of today's knowledge, but among the factors which contribute to high stereoselectivity, the steric, electronic and kinetic properties of the reagents may be identified. Another factor which may play an important role is symmetry. In the design of new ligands, there is usually a need to consider all these factors. The palladium-catalyzed allylic substitution reaction has emerged as one of the most versatile asymmetric transformations for carbon-carbon as well as carbon-heteroatom bond formation [2]. A variety of chiral ligands have been designed for the process and high enantioselectivity has been achieved with a wide range of substrates [2].

(HYDROXYALKYL)- AND (ALKOXYALKYL)PYRIDINOOXAZOLINES

Chiral pyridinooxazolines have been employed in several types of asymmetric catalytic reactions; high enantioselectivity has been observed in rhodium-catalyzed hydrosilylations of ketones [3] and in condensations of allylic trichlorosilanes with aldehydes [4]. In the palladium-catalyzed allylic substitution of *rac*-1,3-diphenyl-2-propenyl acetate (CH_2Cl_2, r.t., BSA, KOAc) with **1** (R = H, Scheme 1) as ligand, moderate stereoselectivity (50% enantiomer excess; [5]) was observed. Substitution of the pyridine nucleus in the 6-position resulted in somewhat increased selectivity (**1**, R = Me: 74%; [6] **1** R = CH_2OH and R = CH_2OCH_3; 88 and 82% enantiomer excess, respectively, **2**: 73% enantiomer excess; [7]).

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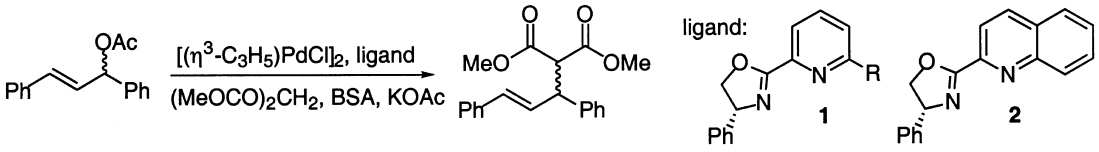


Scheme 1

Conformation of the ligands

2-(Hydroxymethyl)pyridine and 2-(methoxymethyl)pyridine adopt different conformations as free ligands. Hydrogen bonding stabilizes the *syn* planar conformation for the alcohol, whereas the alkylated ligand adopts an *anti* planar conformation due to electron-pair repulsion (A, Fig. 1) as well as to stereoelectronic stabilization originating from electron donation from the nitrogen lone pair into the anti-bonding carbon-oxygen σ-bond (B, Fig. 1); the barrier to rotation around the pyridine carbon-carbinol carbon bond amounts to 20–25 kJ/mol [8]. The stereoelectronic effect is manifested in a slightly elongated carbon–oxygen bond, as demonstrated by calculations of the variation in bond length upon rotation around the exocyclic carbon-carbon bond (Fig. 1 [9]).

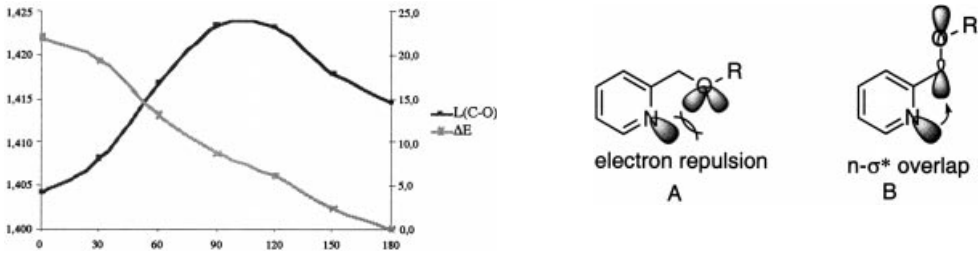


Fig. 1 C–O bond length and energy vs. the dihedral angle N-C-C-O in 2-(methoxymethyl)pyridine.

Chiral ligands of the two types, with the same absolute configuration, thus have the substituents situated on different sides of the coordination plane (C and D, Fig. 2). In ligands carrying a further chiral center, such as (hydroxyalkyl)pyridinooxazolines (**3**) and (alkoxyalkyl)pyridinooxazolines (**4**), different topology for the two types of ligands is thus expected, *pseudo* C_2 (E) for (*R**,*R**)-**3** and *pseudo* meso (F) for (*R**,*R**)-**4**.

The conformation of the ligands in metal complexes is more difficult to predict, but some conclusions can be drawn from the results of the application of the ligands in asymmetric catalysis.

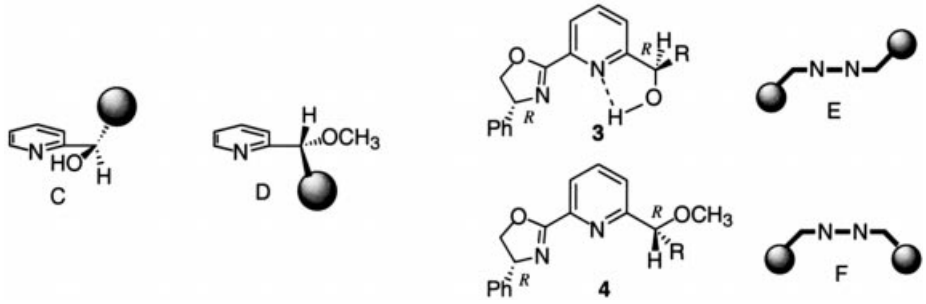


Fig. 2 Conformational preferences of the ligands.

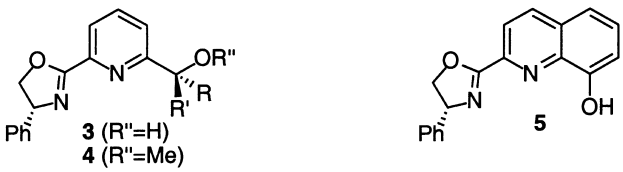
Chiral ligands in palladium-catalyzed alkylation

When ligands with the general structures **3** and **4** were subjected to the palladium-catalyzed allylation in Scheme 1, the enantioselectivity turned out to be highly dependent on the relative configuration at the two stereocenters in such a way that ligands with *R*,*R* configuration gave best results for alcohols **3**, whereas those with *R*,*S* configuration were more successful for ethers **4**. With sterically more bulky substituents at the benzylic carbon atom the effect was more pronounced (Table 1; Scheme 2). For example (*R*,*R*)-**3** (R = ^{t}Bu) afforded the product in 95% enantiomer excess and the diastereomer with (*R*,*S*) configuration in 90% enantiomer excess, whereas for (*R*,*R*)-**4** and (*R*,*S*)-**4** (R = ^{t}Bu) the selectivity was 15 and >99%, respectively [5]. With **5** as ligand, no product was obtained [7].

Table 1 Asymmetric alkylations according to Scheme 1 using ligands **3, 4** or **5**

Ligand	R	R′	% yield	% enantiomer excess	topology
3	H	H	93	88	
3	^{t}Bu	H	96	95	E
3	neom.	H	83	>99	E
3	H	^{t}Bu	96	90	F
3	H	neom.	*	39	F
4	H	H	99	82	
4	^{t}Bu	H	67	15	F
4	H	^{t}Bu	91	>99	F
5			–		

*not determined; neom. = neomenthyl.



Scheme 2

These results can be interpreted in terms of different conformations of the metal complexes of the two types of ligands, as those containing ligands with *pseudo* C_2 topology in the uncomplexed state always induced higher enantioselectivity than the diastereomers. Preliminary NOE studies indicated that different conformations were indeed adopted by metal complexes containing the two types of ligands [5].

Conformation of the ligands in metal complexes

Further studies of some metal complexes gave a closer insight into the conformational preferences of the two types of ligands when bound to metal ions. Of particular interest were studies of complexes containing alcohol ligands of type **3**. A NOE study of a complex prepared from **3** (R = R′ = H) and $PdCl_2$ showed no correlation between the hydroxy proton and the proton in 3-position of the pyridine ring, indicating that the conformation is not anti [10]. X-ray crystallography showed two conformations to be

present in the solid state. In addition to that observed in solution, one having the hydroxy group essentially in an *anti*- planar conformation was observed. DFT calculations (B3LYP, using ligand with achiral, unsubstituted oxazoline ring) confirmed the existence of two conformational minima, that of lowest energy with the hydroxy proton taking part in hydrogen bonding to the chloride ion, and with a N-C-C-O dihedral angle of 73° (A, Fig. 3). About 9.2 kJ/mol above this minimum, another conformational minimum with a dihedral angle of 178° was found (B, Fig. 3). The transition state for rotation was found at 18.4 kJ/mol, with a dihedral angle of 149° (C, Fig. 3).

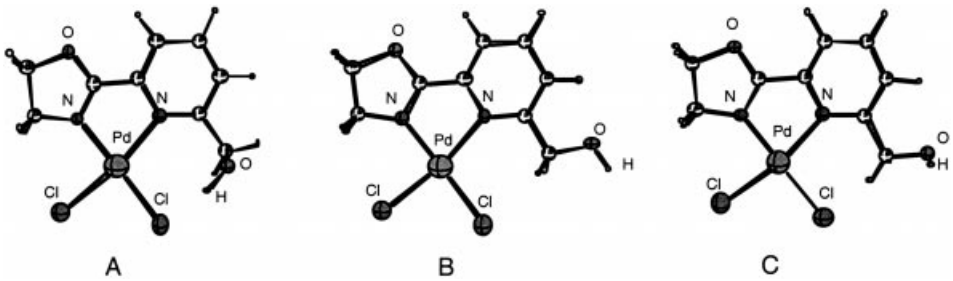


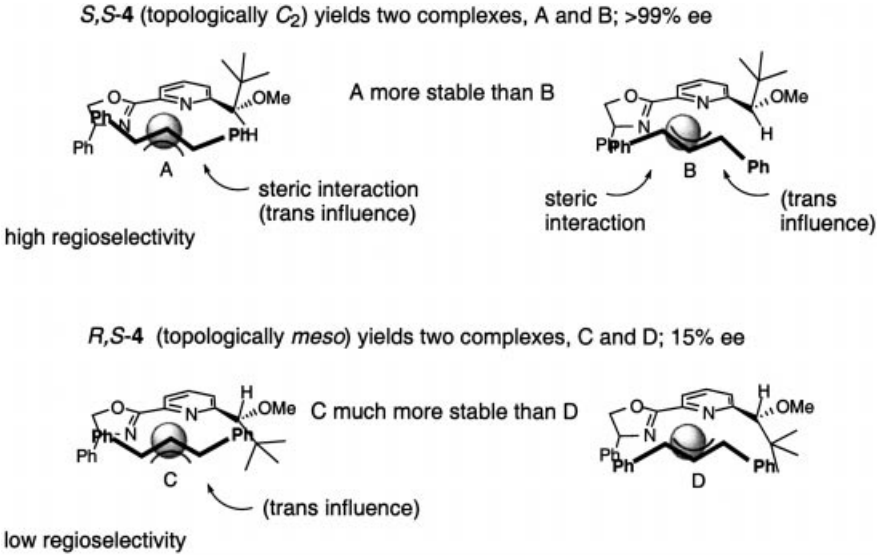
Fig. 3 Conformational minima (A and B) and TS (C) according to DFT computations.

In the calculations on complexes where the chloride ions were exchanged for an allyl or a 1,3-diphenylallyl group, conformational minima at 71° and 179°, and at 85° and 178°, respectively, were found [10]. In each case the latter was the most stable one (by 11.7 and 7.1 kJ/mol, respectively), but the relative energy of the two conformations is expected to be different in the complexes with chiral ligand **3**. Calculations on the $PdCl_2$ complex of the corresponding methyl ether yielded a single conformational minimum close to 180°. Results from NOESY studies of the Pd(II) allyl complex of **3** ($R = R' = H$) and of the Pd(II) chloride complex of **4** ($R = R' = H$) were in agreement with the calculated structures. From the experimental and theoretical studies it was thus concluded that Pd(II) complexes of ligands **3** exhibit two conformational minima, but those of **4** only one.

STERIC AND ELECTRONIC EFFECTS—SYMMETRY

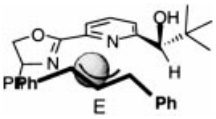
The enantioselectivity in the alkylation of *meso* substrates is determined by the regiochemistry of the nucleophilic attack at the intermediate π-allylpalladium complex, an event that occurs outside the coordination sphere of the metal ion, distal from the chiral ligand. Several investigations point to an early transition state for the reaction, and the transition state is therefore expected to resemble the intermediate π-allylpalladium complex [11]. With C_1-symmetric ligands, at least two π-allylpalladium complexes are formed. The barrier to interconversion of the complexes is small, leading to Curtin–Hammet conditions, but it has been observed that the major complex leads to the major product [11a]. The allylic terminus most prone to be attacked by the nucleophile is that having the longest bond to palladium, as explained by relief of bond strain upon nucleophilic attack as well as by increased cationic character at that site [12].

With C_2-symmetric ligands the asymmetry in the π-allyl palladium complex originates solely in the different steric environments at the two allylic termini, whereas with C_1-symmetric ligands donor atoms with different *trans* influence may be employed, leading to electronic desymmetrization as well. With ligands **3** and **4**, the enantioselectivity of those isomers having *pseudo* C_2 symmetry originates mainly in different steric environments at the allylic termini, as the difference in *trans* influence between the pyridine and the oxazoline moieties is expected to be small [13]. Two isomeric complexes are formed (Scheme 3), attack on each leading preferentially to the same enantiomer. For the *pseudo* meso ligands, the energy difference between the two complexes is expected to be larger. The *trans* influence is assumed to be the major enantiodifferentiating factor. With a small difference in *trans* influence, low enantioselectivity is expected.



Scheme 3

For the alcohol ligands **3**, the conformational analysis was less straightforward, since the relative contribution of the different conformations in the stereocontrolling step was unknown. A DFT calculation on the olefin complex obtained after nucleophilic attack gave some insight into the conformational preferences of the ligand during reaction. In the olefin complex, the hydroxy group was found to be closer to the metal than in the high energy conformation of the π-allyl complexes (having N-C-C-O dihedral angles of about 71–85°). Therefore, in the stereocontrolling step (*R,R*)-**3** was assumed to adopt a pseudo C_2-symmetric conformation, with the hydroxy group occupying the space above the coordination plane (E, Scheme 4 [10]).



Scheme 4

MICROWAVE FLASH HEATING

Chiral nitrogen-containing ligands often exhibit high enantioselectivity in asymmetric metal-catalyzed processes. The ligands are often stable and they are commonly easier to prepare than their phosphorus analogs. However, a serious drawback with nitrogen-containing ligands, particularly sterically demanding *N*,*N*-ligands, is their low reactivity compared to *N*,*P*- or *P*,*P*-ligands. An increase in reaction temperature, resulting in enhanced reactivity and thus shorter reaction times, is commonly accompanied by loss in selectivity.

Microwave heating has the ability to greatly accelerate chemical reactions by superheating, especially if closed microwave-transparent reaction vessels are used [14]. With the introduction of single mode cavities, reproducible results could be obtained, the method thereby becoming more attractive [15]. Recently microwave flash heating was successfully employed for several metal-catalyzed processes by some of us [16]. Selective Heck, Stille and Suzuki coupling reactions were thus accomplished in high yields in 1.5–12 min. The dramatic reduction in reaction times experienced with the palladium-catalyzed coupling reactions using microwave flash heating encouraged us to explore whether the comparatively slow asymmetric palladium-catalyzed allylic alkylations might be sped up with this technology. Reactions using ligand **2** in acetonitrile, usually requiring 3 days for complete reaction, gave indeed close to

quantitative yields within down to 2 min, with only minor loss in stereoselectivity (Table 2; [17]). Reaction times were significantly reduced by thermal heating as well (Table 2). However, a more pronounced decrease in both yield and selectivity was observed in the thermally heated reactions compared to those heated by microwave radiation.

Table 2 Asymmetric alkylations according to Scheme 1 using ligand **2** at room temperature, with thermal heating and with microwave flash heating

Conditions	Temp (°C)/ power (W)	Time (min)	% enantiomer yield	excess
	Room temp	4300	99	77
Thermal heating	100 °C	19	97	62
Thermal heating	140 °C	6.3	93	60
Thermal heating	180 °C	4.5	93	56
Microwave flash heating	35 W	15	99	65
Microwave flash heating	70 W	7.5	99	64
Microwave flash heating	120 W	3.5	99	63
Microwave flash heating	250 W	3.0	99	65
Microwave flash heating	500 W	2.0	99	65

CONCLUSIONS

The consideration of various factors such as the steric, electronic and kinetic properties and the symmetry of the reagents in metal-catalyzed reactions is essential in rational ligand design. Experimental and theoretical investigations of catalytically active metal complexes were used to get an insight into the enantiocontrolling events in palladium-catalyzed reactions using chiral pyridinooxazolines as ligands. Another factor which may be important to consider in ligand design is the reactivity of the metal complexes used in the catalytic reactions. The low reactivity exhibited by the ligands under study was overcome by employing microwave flash heating.

REFERENCES

1 R. Noyori. *Asymmetric Catalysis in Organic Synthesis.* Wiley, New York (1994); J. Seyden-Penne. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis.* Wiley, New York (1995).

2 B. M. Trost, D. L. Van Vranken. *Chem. Rev.* **96**, 395 (1996).

3 H. Brunner, U. Obermann, U. *Chem. Ber.* **122**, 499 (1989); H. Brunner, P. Brandl. *Tetrahedron: Asymmetry* **2**, 919 (1991); H. Brunner, R. Störiko, B. Nuber. *Tetrahedron: Asymmetry* **9**, 407 (1998).

4 R. M. Angell, A. G. M. Barrett, D. C. Braddock, S. Swallow, B. D. Vickery. *Chem. Commun.* 919 (1997).

5 K. Nordström, E. Macedo, C. Moberg. *J. Org. Chem.* **62**, 1604 (1997).

6 G. Chelucci, S. Medici, A. Saba. *Tetrahedron: Asymmetry* **8**, 3183 (1997).

7 U. Bremberg, F. Rahm, C. Moberg. *Tetrahedron: Asymmetry* **9**, 3437 (1998).

8 P.-O. Norrby, K. Wärnmark, B. Åkermark, C. Moberg, P.-O. Norrby, C. Moberg. *J. Comput. Chem.* **16**, 620 (1995); C. Moberg, H. Adolfsson, K. Wärnmark, P.-O. Norrby, K.-M. Marstokk, H. Møllendal. *Chem. Eur. J.* **2**, 136 (1996).

9 P.-O. Norrby, C. Moberg. Unpublished results: Fully relaxed scan of 2-(methoxymethyl) pyridine at the B3LYP/6-31+G* level. This bond is even longer in a conformation with the carbon-oxygen bond essentially perpendicular to the plane of the aromatic ring due to π-σ^* overlap.

10 M. Svensson, U. Bremberg, K. Hallman, I. Csöregh, C. Moberg. *Organometallics* **18**, 4900 (1999).

11 (a) P. B. Mackenzie, J. Whelan, B. Bosnich. *J. Am. Chem. Soc.* **107**, 2046 (1985). (b) D. Müller, G. Umbricht, B. Weber, A. Pfaltz. *Helv. Chim. Acta* **74**, 232 (1991).

12 J. D. Oslob, B. Åkermark, P. Helquist, P.-O. Norrby. *Organometallics* **16**, 3015 (1997).

13 DFT calculations on a Pd(II) allyl complex of 2-oxazolylpyridine revealed only a minor difference in Pd–C bond lengths, that *trans* to the oxazoline being about 2% shorter than that trans to pyridine: M. Svensson, C. Moberg, U. Bremberg. Unpublished results.

14 C. Gabriel, S. Gabriel, E. H. Grant, B. S. J. Halstead, D. M. P. Mingos. *Chem. Soc. Rev.* **27**, 213 (1998).

15 S. Stone-Elander, N. Elander. *Appl. Radiat. Isot.* **44**, 889 (1993); F. Langa, P. de la Cruz, A. de la Hoz, A. Díaz-Ortiz, E. Díez-Barra. *Contemp. Org. Synth.* **373** (1997).

16 M. Larhed, G. Lindeberg, A. Hallberg. *Tetrahedron Lett.* **37**, 8219 (1996); M. Larhed, A. Hallberg. *J. Org. Chem.* **61**, 9582 (1996).

17 U. Bremberg, M. Larhed, C. Moberg, A. Hallberg. *J. Org. Chem.* **64**, 1082 (1999).