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Steric versus electronic effects of the ligand in the enantioselective palladium-catalyzed allylic alkylation with chiral oxazolinylpyridines

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Abstract

Chiral oxazolinylpyridines bearing an oxazolinyl [bis(oxazolinyl)pyridines] or a cyano group in the 6-position of the pyridine ring were prepared and assessed in the enantioselective palladium-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate. The electronic and steric properties of substituents hardly affected either the catalytic activity or the enantioselectivity of the substitution reaction. Enantioselectivities up to 94% were obtained.

1. Introduction

Oxazolinylpyridine derivatives have been shown to induce high stereoselectivity in the enantioselective palladium-catalyzed allylic substitutions.[1] Thus, in the alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate, very high enantiomeric excesses have been obtained using oxazolinylpyridines with two stereocentres.[2] Recently, a number of chiral oxazolinylpyridines **1** with a single stereocentre having different substituents on the pyridine and oxazoline rings have been prepared and assessed in this process (Scheme 1: R,R′,R′′=alkyl, aryl; R′′′=electron-donating or withdrawing groups) and their effects on the catalytic activity and stereoselectivity (steric control and electronic control) have been disclosed.[3] Moreover, we have more recently attempted to obtain a ring-size control in this reaction, using the modified ligands **2** and **3**.[4]

Concerning the electronic control of the reaction, we synthesized, in order to differentiate the electronic effects from steric ones, oxazolinylpyridines in which the electronic differentiating substituents were in the 4-position of the pyridine ring. The results of this study showed that the catalytic activity was

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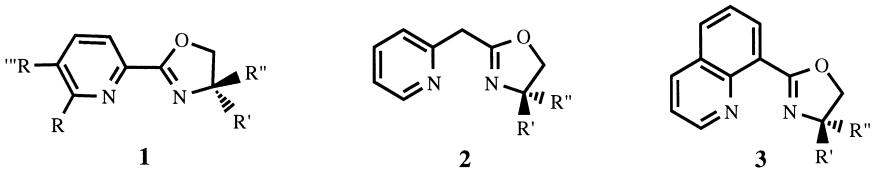


Scheme 1.

dramatically affected by the variation of the electronic property of the ligand but not the stereoselectivity, which depends mainly on steric effects.

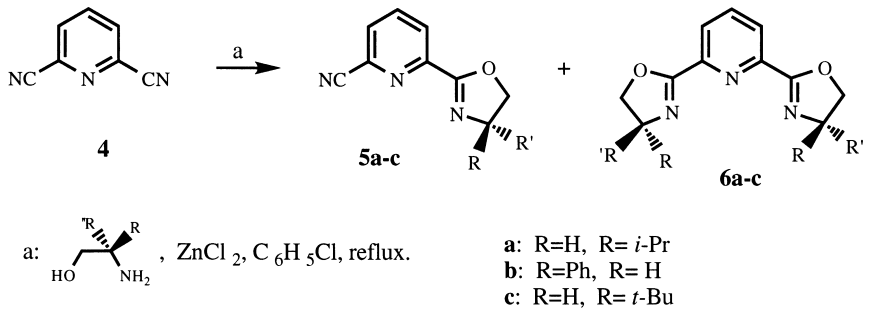
Pursuing our work in this field,[3,4] we have been evaluating the potential in this process of oxazolinylpyridines bearing an electronic differentiating substituent on the 6-position of the pyridine ring, taking into account that in this case both the electronic and steric properties of the substituent should be considered. The oxazolinyl and the cyano groups were selected for this purpose. In the former case we dealt with bis(oxazolinyl)pyridines, ligands extensively used for asymmetric reactions,[5] but whose use for enantioselective palladium-catalyzed allylic substitution has not been described.

We report here the synthesis of 2-cyano-6-(oxazolinyl)pyridines **5**, a new direct way to obtain bis(oxazolinyl)pyridines **6** and the results obtained with these ligands in the palladium-catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate.

2. Results and discussion

2.1. Synthesis of ligands

2-Cyano-6-(oxazolinyl)pyridines **5** were prepared by heating under reflux a chlorobenzene solution of 2,6-dicyanopyridine **4** with the appropriate aminoalcohol in the presence of a catalytic amount of zinc chloride.[6] To obtain the preferential formation of mono-oxazolines **5**, a 1:1 molar ratio of **4** and the appropriate aminoalcohol was used (Scheme 2). Notwithstanding this, ligands **5** were obtained in low yield (26–44% yield) because of the formation of a relevant amount of the compounds of bis-anellation **6** (20–30% yield). Instead, the formation of the bis(oxazolinyl)pyridines **6** was exclusive if a 1:3 molar ratio between **4** and the aminoalcohol was used. The bis(oxazolinyl)pyridine **6a** was obtained in 60% yield when **4** was allowed to react with (*S*)-(+)-2-amino-3-methyl-1-butanol. Therefore, this method opens a direct access to this very important class of ligands which up to now have been obtained through long reaction sequences.[7] Moreover, it is important to note that this route appears particularly attractive because **4** is easily accessible from a variety of pyridine derivatives.[8]



Scheme 2.

2.2. Palladium-catalyzed allylic alkylation

Allylic substitutions were carried out employing Trost's procedure, which demands the use of $[Pd(\eta^3\text{–}C_3H_5)Cl]_2$ as the procatalyst and a mixture of dimethyl malonate, *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate in methylene chloride at room or reflux temperature.[9]

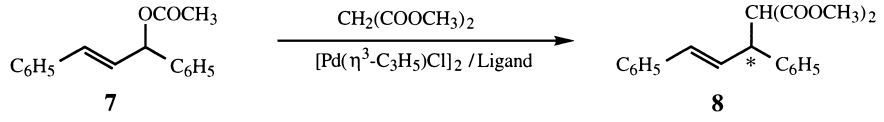
The results obtained in a set of experiments with the new ligands are summarized in Table 1, in which the results previously obtained with the related ligands **1a**–**c** bearing the methyl instead of the cyano group (Scheme 1: **1a**: R=Me, R′′=*i*-Pr, R′=R′′′=H_2; **1b**: R=Me, R′′′=Ph, R′=R′′=H; **1c**: R=Me, R′′=*t*-Bu, R′=R′′′=H) are reported too. According to Table 1 the following considerations can be made:

(i) The bis(oxazolinyl)pyridine **6a**, which was selected to determine the reactivity of this class of ligands, provided a very ineffective palladium catalyst. Thus, no reaction was obtained after 7 days at room temperature (entry 8) whereas 80% of the starting material was converted after 2 days (entry 9) at reflux. This catalytic outcome could be rationalized considering that this ligand behaves as the analogue 2,2′:6′,2′′-terpyridine which forms allyl palladium(II) complexes that in solution are present in a dynamic equilibrium between η^1- and η^3-allyl isomeric forms.[10] In the former case the terpyridine behaves as a terdentate ligand, whereas in the latter it coordinates the palladium atom in a bidentate fashion. Likewise, ligand **6a** could form η^1- and η^3-allyl palladium complexes of which the former, catalytically unreactive, is prevailing at room temperature, whereas the latter, catalytically reactive, is slowly formed at higher temperatures. In this case, ligand **6a** forms, on account of its C_2-symmetry, only one palladium η^3-allyl complex where the central pyridine coordinates the palladium with either of the oxazoline nitrogens. The low enantioselectivity (26%) obtained in this process indicates that the steric and electronic effects of the substitution are detrimental to the stereoselectivity of the reaction. On this basis the use of this kind of ligand was abandoned.

(ii) A dramatic effect on the catalytic activity is observed by the presence in the pyridine ring of a cyano group. This electron-withdrawing substituent decreases the reaction rate with respect to the related 6-methyl substituted oxazolinylpyridines **1a**–**c** (entries 2, 5 and 7 versus 1, 4 and 6). The results obtained can be tentatively explained considering the catalytic cycle of the reaction which begins by the oxidative addition of the allylic substrate to the palladium(0) catalyst. The rate of this step is dependent on the nature of the ligand and, in general, decreases with reducing basicity (ability to donate electrons to the metal) of the ligand, which decreases the electronic density on the palladium and so its nucleophilic ability. These considerations are consistent with the observation that the cyano group drastically decreases the reaction rate. However, the rate of the oxidative addition step can be decreased not only by reducing the electronic density on the palladium but also by improving the steric requirement of the ligand, as we observed previously when the steric demands of both the substituent on the oxazoline and the pyridine rings were increased.[3a] Though both these factors should be considered we prefer the former explanation because the steric demands of the cyano and the methyl groups are not so different to justify a dramatic change in the reactivity.

(iii) In contrast, the enantioselectivity of the substitution reaction appears to be favourably affected by the presence of the cyano group. Thus, an improved stereoselectivity has always been obtained with ligands **5a**–**c** with respect to the related **1a**–**c**. The best enantioselectivity (94% ee) has been obtained with the ligand **5c** bearing the *tert*-butyl group on the oxazoline moiety. The stereochemical result can be tentatively explained by considering the related π-allyl palladium complexes. The accepted mechanism for palladium-catalyzed allylic substitutions, which proceed through a *meso* η^3-allyl intermediate, foresees that the nucleophile attacks the allylic termini of two alternative

Table 1
Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate[a]

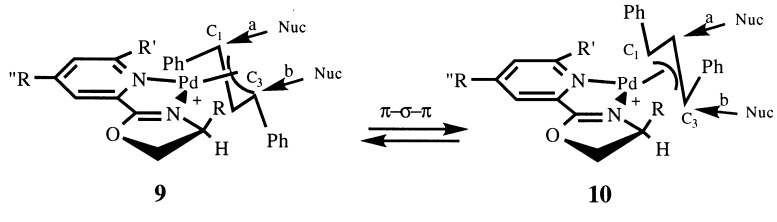


7 8

Entry	Ligand	Temperature (°C)	React. time (h)	Conv.[b]	Yield[c]	% Ee[d]	Conf.[e]
1	**1a**	r.t.	1	100	93	70	S[f]
2	**5a**	r.t.	96	100	84	80	S
3	**5a**	reflux	7	100	73	66	S
4	**1b**	r.t.	4.5	100	81	74	R[f]
5	**5b**	r.t.	48	100	78	88	R
6	**1c**	r.t.	2.3	100	92	91	S[f]
7	**5c**	r.t.	168	74	77	94	S
8	**6a**	r.t.	168	0	--	--	--
9	**6a**	reflux	48	80	45	26	S

[a]Reaction of the ligand (10 mol %) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %) with 1,3-diphenylprop-2-enyl acetate (0.4 mmol), $CH_2(COOMe)_2$ (1.2 mmol), N,O-bis(trimethylsilyl)acetamide (BSA) (1.2 mmol) and KOAc (3.5 % mol) in CH_2Cl_2 (2 ml) at room or reflux temperature. [b]Determined by ^{1}H-NMR of the crude reaction mixture. [c]Isolated yields. [d]Determined by ^{1}H-NMR using Eu(hfc)$_3$ as chiral shift reagent. [e]The assignement is based on the sign of the optical rotation: Leutenegger, U.; Umbricht, G.; Fahrni, C.; Matt, P.V.; Pfaltz, A. *Tetrahedron*, **1992**, *48*, 2143. [f]Data taken from ref.3a

diastereomeric π-allyl palladium complexes which interconvert through a π–σ–π mechanism and which are present at the equilibrium in a different ratio (for instance **9** and **10** for ligands with (*S*) configuration: Scheme 3). Because both ligands **1a–c** and **5a–c** give the substitution product **8** with the same prevailing configuration, it is reasonable to assume that the reactive transition states are always the same.



9 **10**

Scheme 3.

Since it has usually been observed that the prevailing reaction product comes from a nucleophilic attack on one terminus of the allylic unit of the most abundant complex[11] (in this case the allylic terminus *trans* to the oxazoline nitrogen in the more stable diastereomer **9**), the ability of the ligand to stabilize one of the two diasteromeric complexes is a crucial point in determining the stereochemical outcome. Thus, the better stereochemical results obtained with ligands **5a–c** with respect to ligands **1a–c** seem to indicate that the cyano group is able to better stabilize the reactive diasteromeric complex.

3. Conclusions

In this paper the catalytic activity in the palladium-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate using chiral oxazolinylpyridines bearing, on the 6-position of the pyridine ring, a substituent which has both electronic and steric properties, is reported. The results obtained show that bis(oxazolinyl)pyridines are unable to give a catalytic active palladium catalyst. In contrast, an improved stereoselectivity is obtained by the cyano group, whose favourable steric demand overcomes its electron withdrawing property which reduces the catalytic activity. An interesting and direct way to obtain bis(oxazolinyl)pyridines, a very important class of ligands, is also reported.

4. Experimental

4.1. General methods

Boiling points are uncorrected. Melting points were determined on a Buchi 510 capillary apparatus and are uncorrected. The ^{1}H NMR (300 MHz) spectra were obtained with a Varian VXR-300 spectrometer. Optical rotations were measured with a Perkin–Elmer 241 polarimeter in a 1 dm tube. Elemental analyses were performed on a Perkin–Elmer 240 B analyser. (*R*)-(−)-2-Amino-2-phenylethanol, (*S*)-(+)-2-amino-3,3-dimethyl-1-butanol and (*S*)-(+)-2-amino-3-methyl-1-butanol were commercial products (Aldrich A.G.). 2,6-Dicyanopyridine **4** was prepared following the literature procedure.[8]

4.2. General procedure for the preparation of oxazolinylmethylpyridines *5*

In a 25 ml two-necked flask, zinc chloride (14 mg, 0.10 mmol) was melted under high vacuum and cooled under argon. After cooling to room temperature, anhydrous chlorobenzene (10 ml) was added followed by the 2,6-dicyanopyridine **4** (2 mmol) and the aminoalcohol (2.0 mmol). The resulting mixture was heated under reflux for 24 h and then the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 ml) and the resulting solution was washed with water (3×4 ml). The aqueous solution was extracted with CH_2Cl_2 (10 ml), the combined organic phases were dried over anhydrous Na_2SO_4 and the solvent evaporated. The residue was purified by chromatography on a silica gel column.

4.3. (S)-2-Cyano-6-[4,5-dihydro-4-(1-methylethyl)oxazol-2-yl]pyridine *5a*

Chromatographic eluent: benzene:acetone=8:2; 0.135 g (31%); mp 154°C; $[\alpha]_D^{25}$ −58.7 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.31 (d, 1H, *J*=7.8 Hz), 7.95 (t, 1H, *J*=7.8 Hz), 7.80 (d, 1H, *J*=7.8 Hz), 4.56 (t, 1H, *J*=9.0 Hz), 4.30–4.12 (m, 2H), 1.97–1.86 (m, 1H), 1.06 (d, 3H, *J*=6.6), 0.96 (d, 3H, *J*=6.6 Hz). Anal. calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.86; H, 6.19; N, 19.32.

4.4. (R)-2-Cyano-6-(4,5-dihydro-4-phenyloxazol-2-yl)pyridine *5b*

Chromatographic eluent: petroleum ether:ethyl acetate=1:2; 0.502 g (26%); mp 121–122°C; $[\alpha]_D^{25}$ +123.5 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.39 (dd, 1H, *J*=7.8, *J*=1.0 Hz), 7.98 (t, 1H, *J*=7.8 Hz), 7.84 (dd, 1H, *J*=7.8, 1.0 Hz), 7.40–7.29 (m, 5H), 5.48 (dd, 1H, *J*=10.3, 8.6 Hz), 4.94 (dd, 1H, *J*=10.3, *J*=9.0

Hz), 4.44 (t, 1H, *J*=8.6 Hz). Anal. calcd for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45; N, 16.86. Found: C, 72.18; H, 4.55; N, 16.77.

*4.5. (S)-2-Cyano-6-[4,5-dihydro-4-(1,1-dimethylethyl)oxazol-2-yl]pyridine **5c***

Chromatographic eluent: benzene:acetone=8:2; 0.202 g (44%); mp 154–156°C; $[\alpha]_D^{25}$ −86.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.35 (dd, 1H, *J*=7.8, 0.9 Hz), 7.95 (t, 1H, *J*=7.8 Hz), 7.81 (dd, 1H, *J*=7.8, 0.9 Hz), 4.50 (dd, 1H, *J*=10.5, 8.7 Hz), 4.36 (t, 1H, *J*=8.7 Hz), 4.15 (dd, 1H, *J*=10.5, 8.7 Hz), 0.98 (s, 9H). Anal. calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.15; H, 6.71; N, 18.35.

*4.6. 2,6-Bis[(4S)-(+)-isopropyl-2-oxazolin-2-yl]pyridine **6a***

The procedure used for the synthesis of **5** was followed. In this case a 1:3 ratio of 2,6-dicyanopyridine (**4**) (2.0 mmol) and of (*S*)-(+)-2-amino-3-methyl-1-butanol (6.0 mmol) was used. After usual work-up the residue was purified by flash chromatography (ethyl acetate) to give **6a** (0.36 g, 60% yield) whose spectroscopic data were consistent with an authentic sample (Aldrich A.G.).

4.7. Allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate: general procedure

A solution of ligand (0.04 mmol, 10 mol%) and $[\{Pd(\eta^3\text{–}C_3H_5)Cl\}_2]$ (4 mg, 2.5 mol%) in dry CH_2Cl_2 (2 ml) was stirred at room temperature for 15 min. This solution was treated successively with a solution of *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate (0.4 mmol) in CH_2Cl_2 (1 ml), dimethyl malonate (1.2 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (1.2 mmol) and anhydrous potassium acetate (3.5 mol%). The reaction mixture was stirred for the appropriate time (see Table 1) until conversion was complete as shown by TLC analysis (light petroleum:ether=3:1). The reaction mixture was diluted with ether (25 ml), washed with ice-cold saturated aqueous ammonium chloride. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (light petroleum:ether=3:1) to afford dimethyl 1,3-diphenylprop-2-enyl malonate. The enantiomeric excess was determined from the ^{1}H NMR spectrum in the presence of enantiomerically pure shift reagent Eu(hfc)$_3$; splitting of the signals for one of the two methoxy groups was observed.

Acknowledgements

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References

1. For reviews, see: Trost, M. B.; Van Vranken, D. L. *Chem. Rev*. **1996**, *96*, 395. Hayashi, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993. Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089. For more recent references on palladium-catalyzed allylic alkylation reactions, see: Koning, B.; Meetsma, A.; Kellogg, R. M. *J. Org. Chem*. **1998**, *63*, 1604.
2. Chelucci, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2667. Nordström, K.; Macedo, E.; Moberg, C. *J. Org. Chem*. **1997**, *62*, 1604.
3. (a) Chelucci, G.; Medici, S.; Saba, A. *Tetrahedron: Asymmetry* **1999**, *10*, 543. (b) Chelucci, G.; Deriu, S.; Saba, A.; Valenti, R. *Tetrahedron: Asymmetry* **1999**, *10*, 1457. (c) Brenberg, U.; Rahn, F.; Moberg, C. *Tetrahedron: Asymmetry* **1998**, *9*, 3437.

4. Chelucci, G.; Gladiali, S.; Saba, A. *Tetrahedron: Asymmetry* **1999**, *10*, 1393.
5. Nishiyama, H.; Soeda, N.; Naito, T.; Motoyama, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 2865, and references cited therein.
6. Bolm, C.; Veickhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber*. **1991**, *124*, 1173.
7. Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500.
8. The dinitrile **4** is easily accessible from a variety of pyridine derivatives: (a) from 2,6-dibromopyridine by cyanation with CuCN (44%) [Pearse, G. A.; Wisowaty, J. *J. Heterocyclic Chem*. **1973**, *10*, 647]; (b) from the *N*-oxide of 2-pyridinecarbonitrile by cyanation with KCN (84%) [Tani, H. *Chem. Pharm. Bull*. **1959**, *7*, 930]; (c) from 2,6-pyridinedicarboxamide by dehydration (52%) [Bancks, R.; Brookes, R. *Chem. Ind. (London)* **1974**, *15*, 617]; (d) from 2,6-dimethylpyridine by oxidative ammonolysis (75%) [Glubokovskikh, L. K.; Kan, I. I.; Suvorov, B. V.; Berstenev, S. V. *Izv. Akad. Nauk. Kaz. SSR, Ser. Khim*. **1985**, *3*, 90; C.A. **1986**, *104*, 88395g].
9. Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.
10. Ramdeehul, S.; Barloy, L.; Osborn., J. A.; De Cian, A.; Fischer, J. *Organometallics* **1986**, *15*, 5442.
11. Blöchl, P. E.; Togni, A. *Organometallics* **1996**, *15*, 4125.