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Applications of enantiopure 4,5-diphenyl substituted box and pybox ligands in asymmetric catalysis

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Abstract—Enantioselectivities of 95–98% have been obtained in the palladium-catalyzed alkylation of *rac*-3-acetoxy-1,3-diphenyl-1-propene with dimethyl malonate using 4,5-diphenyl substituted bis(oxazoline) as the chiral ligands, whatever the configuration at C-5. The copper-catalyzed allylic oxidation of various cycloalkenes gave the corresponding allylic esters with enantioselectivities up to 84% using the 4,5-diphenyl substituted bis(oxazoline). Lower enantioselectivities were obtained using the corresponding 4,5-diphenyl substituted pyridine-bis(oxazoline), the higher enantioselectivity being observed with the *cis*-stereoisomer.

1. Introduction

Asymmetric catalysis with chiral complexes has received considerable attention in recent years. Metal complexes of C_2-symmetric enantiopure ligands are among the most efficient chiral inducers used. In particular, bis(oxazoline) ligands (box) of general structure **A** with two oxazoline rings separated by a spacer (generally a single carbon atom) have found broad use in the asymmetric catalysis of a large variety of transformations during the past decade, such as cyclopropanations, ene-reactions, Diels–Alder and hetero-Diels–Alder reactions, allylic substitutions, aziridination reactions, and Mukayama aldol reactions.[1–5] The main reasons for the success of these ligands are their easy preparation and modification, their versatility, and the high enantioselectivities generally obtained. More recently, bis(oxazoline) ligands **B** with a pyridine ring as the spacer (pybox) have been synthesized; it was noted that these ligands generally acted as tridentate ligands.[6] Other chiral ligands with sp^2 nitrogens as the coordinating atoms such as 2,2′-bipyridines or 1,10-phenantrolines, have also been studied.[7,8]

So far, many variations have been made on the ligands **A** and **B**, including the modification of the R substituents on the bridging methylene unit of R^1, or the introduction of additional stereogenic centers on the oxazoline rings (R^2 or $R^3 \neq H$) (Fig. 1). In these studies it was noted that there was a reversal of facial selectivity in alkylation reactions by 4-alkyl- versus 4-aryl-substituted box ligands.[9–12] However if the influence of the substituent at the 4-position of chiral bis(oxazoline) or pyridine-bis(oxazoline) ligands on both the activity and the enantioselectivity of the reaction, has been studied in detail, there are few reports on the influence of a supplementary substituent at the stereogenic C-5 center. Recently, Pericàs et al.[13] prepared bis(oxazoline) ligands bearing Ar and OR groups of different steric and electronic nature at C-4 and C-5, respectively, and studied their behavior in palladium-catalyzed allylic substitution. 4-Ph-box and 4,5-di-Ph-box have also been used as ligands and their steric influences compared in Diels–Alder and hetero-Diels–Alder reactions,[14–21] in Michael additions,[22,23] and Mukayama–Michael and aldol reactions.[24,25] Conversely, there are only two

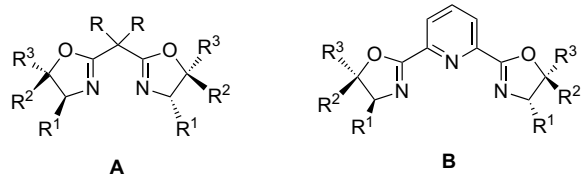

Figure 1.

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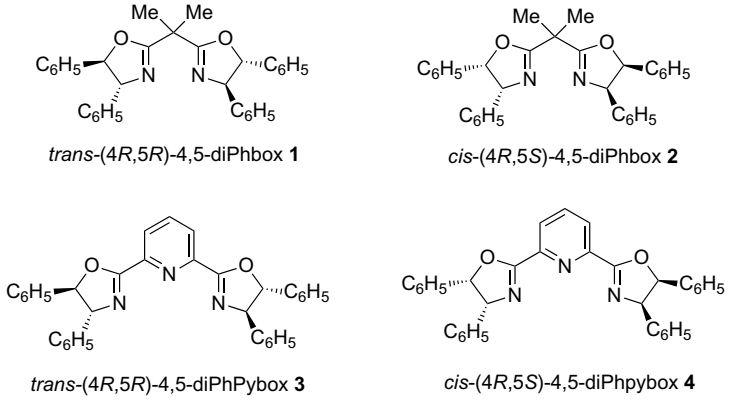


Figure 2.

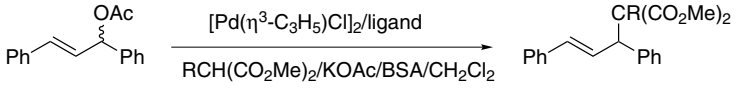
examples of the use of 4-Ph-Py-box together with 4,5-di-Ph-Py-box in Diels–[22] and Mukayama–Michael reaction.[24]

As part of a research project aimed at controlling the activity and enantioselectivity of catalytic reactions involving bis(oxazoline) ligands **1**–**4** by variation of the steric properties of the substituents, and in particular the substituent at the position 5, and with our previous results in the field of Diels–Alder reactions, we became interested in the use of such ligands both in allylic alkylations and oxidations. Herein we report the use of these ligands in these two fields (Fig. 2).

2. Results and discussion

We first examined chiral ligands **1** and **2** in the palladium-catalyzed allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate **5** with dimethyl malonate **6a** (Table 1). This reaction was carried in CH_2Cl_2 in the presence of a (π-allyl)-palladium-ligand complex generated in situ from 2 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 5 mol% of the appropriate chiral ligand. The nucleophile was generated from dimethyl malonate (3 equiv) in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (3 equiv) and 0.1 mol% of KOAc. When the reaction was performed at rt, the transformation was sluggish using *trans*-4,5-diPhbox **1** or *cis*-4,5-diPhbox **2** as the chiral ligand; ligand **1** gave the alkylated product **7a** with 30% chemical yield and 94% ee (Table 1, entry 1), while 40% chemical yield and 96% ee were obtained using ligand **2** (Table 1, entry 3), the same enantiomer being obtained using the two ligands. In order to obtain higher conversions, the reaction was performed at 35 °C. The alkylated product **7a** was obtained in 70% and 90% chemical yield using ligands **1** and **2**, respectively, with enantioselectivities of 97% and 98% (Table 1, entries 2 and 4). So not only the chemical yields were increased with increasing the reaction temperature, but the observed enantioselectivities were also a little higher. It is noteworthy that the bis(oxazoline) ligand bearing a unique phenyl substituent at C-4 gave an enantioselectivity up to 95% in the same alkylation reaction.[13] Hence it seems that there is a beneficial contribution on enantioselectivity, although low, of the phenyl substituent at C-5 for the two stereoisomers, the configuration of the newly created center being the same whatever the configuration at C-5 of the bis(oxazoline). This is in contrast with the results of Pericàs et al.[13] who find that the *trans*-bis(oxazoline) bearing a C_6H_5– and a

Table 1. Asymmetric allylic alkylation of *rac*-3-acetoxy-1,3-diphenyl-1-propene catalyzed by Pd/bis(oxazoline) catalyst[a]



(±)-**5** **7 a-b**

a: R = H; **b**: R = CH_3

Entry	Ligand	Nucleophile	*T* (°C)	Time (day)	Yield (%)[b]	Ee (%)[c] (config)[d]
1	**1**	$CH_2(CO_2Me)_2$	25	5	30	94 (*R*)
2	**1**	$CH_2(CO_2Me)_2$	35	5	70	97 (*R*)
3	**2**	$CH_2(CO_2Me)_2$	25	5	40	96 (*R*)
4	**2**	$CH_2(CO_2Me)_2$	35	3	90	98 (*R*)
5	**1**	$CH_3CH(CO_2Me)_2$	35	3	80	95 (*R*)
6	**2**	$CH_3CH(CO_2Me)_2$	35	3	65	95 (*R*)

[a] [Substrate]:[nucleophile]:[BSA]:[KOAc]:[Pd]:[ligand] = 25:75:75:2.5:1:2; THF.
[b] Isolated pure product.
[c] Determined by HPLC analysis (column Chiralpak AD 0.46 × 25 cm, eluent *i*-PrOH/*n*-hexane 4:6).
[d] Determined by comparison of the HPLC retention time with literature data.

$(C_6H_5)_2CHO$– substituents at C-4 and C-5, respectively, gave ees up to 96% in this reaction, when the *cis* analogue gave no reaction at all.

Under the above mentioned conditions, dimethyl methylmalonate **6b** afforded alkylated product **7b** in 80% chemical yield, and 95% ee (Table 1, entry 5), and 65% chemical yield and 95% ee (Table 1, entry 6), using bis(oxazoline) ligands **1** and **2**, respectively.

The observed stereochemistry in this palladium-catalyzed alkylation using 4,5-disubstituted box ligands is in agreement with the previous results using quite similar systems.[1,11,26,27] As previously postulated, the nucleophilic attack occurred on the longer, strained Pd–carbon bond of the *syn*/*syn* π-allyl ligand complex (Fig. 3). As can be seen, the substituents at C-5, and the configuration of this stereogenic center, are probably too far from the π-allyl ligand in order to have any important influence on the enantioselectivity of the process.

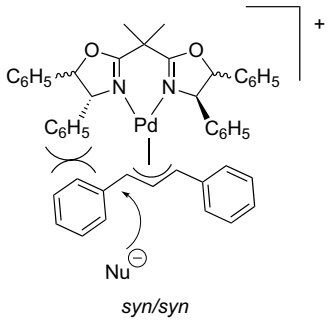


Figure 3.

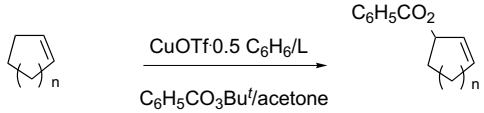
We also used 4,5-diPhpyboxes **3** and **4** as ligands in this alkylation reaction. However the conversion was low (less than 19%), whatever the conditions used.

We then turned our attention to the enantioselective copper-catalyzed allylic oxidation of cyclic olefins. The catalyst was prepared in situ from $CuOTf{\cdot}0.5C_6H_6$ and the appropriate ligand **1**–**4** in acetone, with the allylic oxidation of the alkene performed in the presence of *tert*-butyl perbenzoate for seven days. The results are summarized in Table 2.

It should be noted that all ligands **1**–**4** required several days to allow completion of this oxidation reaction as previously described for analogous box and pybox ligands, when the 2,2′-bipyridines and 1,10-phenantrolines gave the corresponding allylic esters within 30 min at room temperature.[7,8]

The oxidation of cyclopentene **8a** using 4,5-diPhbox ligands **1** and **2** showed good chemical yield and enantioselectivity; the corresponding allylic benzoate **9a** being obtained with ee up to 80% whatever the configuration at C-5 (Table 2, entries 1 and 2). This observed enantioselectivity is higher than those previously published (71%[28] and 69%[29] ee) using the monophenyl substituted

Table 2. Enantioselective copper-catalyzed allylic oxidation of cycloalkenes with bis(oxazolines)[a]



8 a-c **9** **a-c**

a: n = 1; **b**: n = 2; **c**: n = 3

Entry	Alkene	Ligand	Yield (%)[b]	Ee (%)[c] (*R*)[d]
1	*n* = 1	**1**	80	84
2	*n* = 1	**2**	70	80
3	*n* = 1	**3**	26	3
4	*n* = 1	**4**	37	15
5	*n* = 2	**1**	70	64
6	*n* = 2	**2**	78	61
7	*n* = 2	**3**	66	28
8	*n* = 2	**4**	60	36
9	*n* = 3	**1**	50	62
10	*n* = 3	**2**	50	80
11	*n* = 3	**3**	28	26
12	*n* = 3	**4**	42	48

[a] [Alkene]:[*tert*-butyl perbenzoate]:[$CuOTf{\cdot}0.5C_6H_6$]:[ligand] = 200:20:1:2.4; seven days.
[b] Isolated pure product.
[c] Determined by HPLC analysis (column Chiralpak AD 0.46 × 25 cm, eluent *i*-PrOH/*n*-hexane 1:150).
[d] Determined by comparison of the HPLC retention time with literature data.

4-Phbox under the same conditions. It seems that there is in this case a beneficial contribution on enantioselectivity of the phenyl substituent at C-5 for the two stereoisomers.

The use of cyclohexene **8b** as the olefin gave chemical yields in the same range, when the obtained enantioselectivities using **1** and **2** as the ligand were 64% and 61% ee, respectively (Table 2, entries 5 and 6). These results (conversion as well as enantioselectivity) are quite close to those observed using the monosubstituted 4-Phbox ligand (67%[28] and 59%[29] ee).

Moderate chemical yields (50%) were obtained in the oxidation of cycloheptene **8c**; however ees up to 80% were obtained using *cis*-4,5-diPhbox **2**, while ees of up to 62% were only obtained using *trans*-4,5-diPhbox **1**. It seems that in this case there is some influence of the stereogenic center at C-5 on the level of enantioselectivity.

When using box ligands **1** and **2** associated with copper, the highest enantioselectivities were obtained in the oxidation of cyclopentene and cyclohexene, in agreement with the published results concerning this class of ligands.[24,25,30,31]

When 4,5-diPhpyboxes **3** or **4** were used as the ligand, low to moderate conversions were observed: 26% and 37% for cyclopentene **8a**, 66% and 60% for cyclohexene **8b**, and 28% and 42% for cycloheptene **8c**, using **3** and **4**, respectively. The obtained enantioselectivities (3% and 15% ee, 28% and 36% ee, 26% and 48% ee, in the

presence of **3** and **4**, respectively) are generally lower than those published in the literature using 4-*i*-Prpybox as the chiral ligand.[32,33] However we noticed that the *trans*-4,5-diPhpybox ligand **3** gave lower enantioselectivities than the *cis* isomer. In this case, the stereogenic center at C-5 plays an important role on the enantioselectivity of the allylic oxidation. Although the obtained enantioselectivities are low, we observed the following sequence of enantioselectivity cyclopentene < cyclohexene < cycloheptene, which is in agreement with the other copper–pybox complexes.[6,32,33]

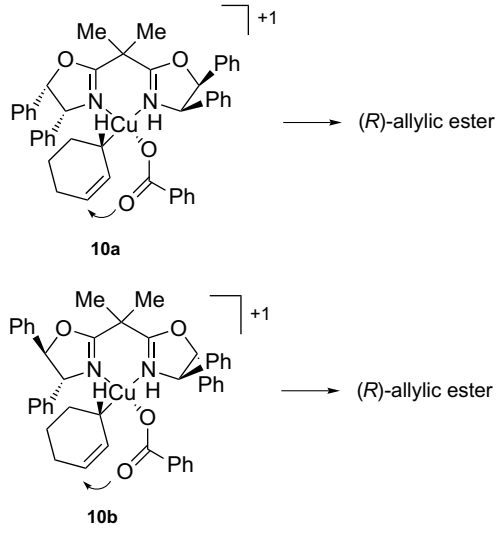


Figure 4.

These results could be rationalized according to Figures 4 and 5. In the case of the 4,5-diphenylbis(oxazoline) ligands **1** and **2**, we can propose the intermediates **10a** and **10b** (Fig. 4), where the benzoate and the cyclohexenyl ligands are in the less hindered quadrant of the copper complex. These intermediates have been put forward by Zavitsas and co-workers,[34,35] and more recently by Andrus and Zhou.[36] The rearrangement of these intermediates gave the (*R*)-enantiomer, whatever the chirality at C-5.

For *cis*-4,5-diphenylpybox **4**, we proposed transition state model **11** (Fig. 5), postulated by Singh and coworkers.[33] The preferred transition state is that where the benzoate ligand is on the upper less hindered quadrant, and the transfer of the benzoate ligand to the cyclohexyl ligand affords the (*R*)-allylic benzoate. For *trans*-4,5-diphenylpybox **3**, the two transition states **12** and **13** are possible (Fig. 5); however, as postulated by Singh, transition state **12**, could be a little more stabilized by some attractive interaction between the two phenyl rings of the benzoate moiety and at C-5. So in this case, the (*R*)-enantiomer would also be formed, although with lower enantioselectivity.

3. Conclusion

4,5-Diphenyl substituted bis(oxazolines) ligands gave enantioselectivities in the range 95–98% ee in the palladium-catalyzed alkylation of *rac*-3-acetoxy-1,3-diphenyl-1-propene with dimethyl malonate derivatives; there

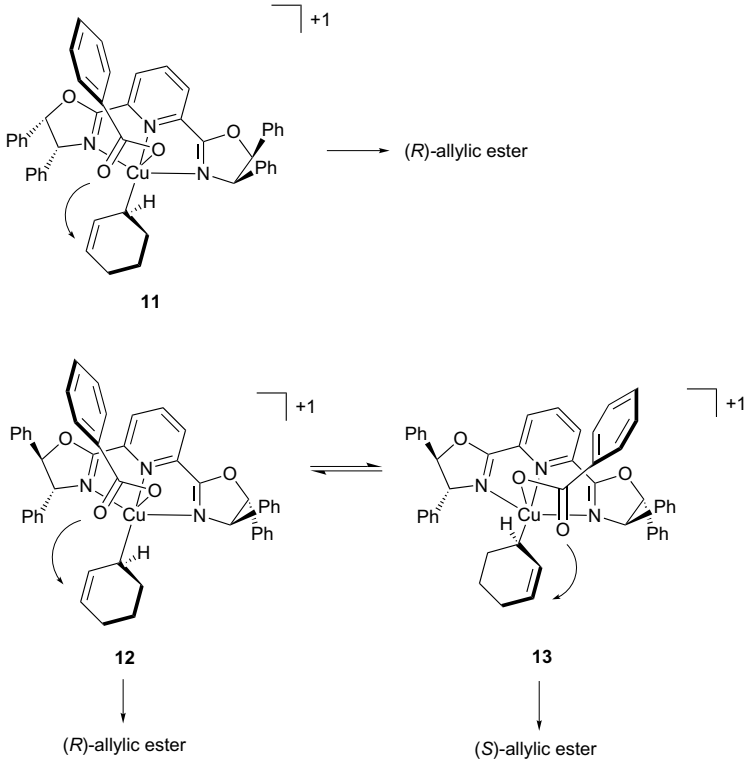


Figure 5.

is no influence of the stereogenic center at C-5 on the enantioselectivity of the reaction.

The same ligands gave enantioselectivities up to 84% in the copper-catalyzed allylic oxidation of various cycloalkenes, with again practically no influence of the stereogenic center at C-5 on the selectivity. The corresponding 4,5-diphenyl substituted pyridine-bis(oxazolines) gave lower ees in this reaction, the higher enantioselectivity being observed with the *cis*-stereoisomer. The configuration of the newly created center can be rationalized using the appropriate transition states.

4. Experimental

4.1. General

Solvents were purified by standard methods and dried if necessary. All commercially available reagents were used as received. Ligands **1**,[37] **2**,[37] **3**,[24] and **4**[38] have already been prepared. Reactions involving organometallic catalysis were carried out in a Schlenk tube under an inert atmosphere. All reactions were monitored by TLC (TLC plates G_{F254} Merck); detection was effected by UV absorbance. Column chromatography was performed on silica gel 60 (230–240 mesh, Merck). NMR spectra were recorded with a Bruker AMX 300 spectrometer. Enantiomeric excesses were determined by HPLC with a Chiralpak AD column (25 cm × 4.6 cm) using different ratios of hexane/*i*-propanol as the eluent.

4.2. Procedure for the catalytic allylic alkylation

Ligand (50 μmol, 5 mol%) and $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (7.3 mg, 20 μmol, 2%) were dissolved in CH_2Cl_2 (8 mL) under nitrogen in a Schlenk tube. The reaction mixture was stirred for 1 h, and *rac*-1,3-(*E*)-diphenyl-2-propenyl acetate **5** (252 mg, 1 mmol) in CH_2Cl_2 (3 mL) then transferred into another reaction vessel containing *N*,*O*-bis(trimethylsilyl)acetamide (610 mg, 3 mmol), KOAc (9.8 mg, 0.1 mmol, 10 mol%), and the nucleophile (3 mmol) in CH_2Cl_2 (6 mL). The reaction mixture was stirred at the desired temperature for the appropriate time. Diethyl ether (20 mL) was added, and the solution washed with a saturated aqueous solution of NH_4Cl (2 × 10 mL). The solvent was evaporated, and the residue purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate 5:1) to afford alkylated product **6**. The enantioselectivity was determined by HPLC with a Chiralpak AD (25 cm × 0.46 cm) and eluting with hexane/*i*-PrOH (8:2).

4.3. Procedure for the catalytic allylic oxidation

To a stirred solution of $CuOTF{\cdot}0.5C_6H_6$ (12.6 mg, 50 μmol, 2.5 mol%) in anhydrous acetone (4 mL) was added the bis(oxazoline) (120 μmol, 6 mol%). After stirring for 1 h at rt, the alkene (10 mmol, 10 equiv) in acetone (2 mL) was added to this solution, followed by the dropwise addition of *tert*-butyl perbenzoate (182 mg, 1 mmol, 1 equiv). The resulting solution was then stirred at rt for seven days. The solvent was then removed under reduced pressure, and the residue purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 10:1) to give the corresponding allylic benzoate. The ee was determined by HPLC using a Chiralpak AD (25 cm × 0.46 cm) and eluting with hexane/*i*-PrOH (150:1).

Acknowledgements

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