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Enantioselective palladium catalyzed allylic substitution with chiral pyridine ligands

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Abstract

Palladium complexes prepared in situ from $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and a number of chiral ligands with pyridine sp^2-nitrogen donators were assessed as chiral catalysts for the allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate. Enantioselectivity of up to 64% was obtained. © 1998 Elsevier Science B.V.

Keywords: Palladium; Allylic substitution; Catalysis; Enantioselectivity

1. Introduction

In the last few years, chiral derivatives with pyridine sp^2-nitrogen donators have attracted increasing interest because of their utility as chiral ligands in metal complexes for enantioselective catalysis [1–15]. Despite this, chiral pyridine derivatives has been scarcely used as ligands for enantioselective palladium-catalysed allylic substitutions [16,17].

Continuing our interest in the synthesis and application of chiral pyridine derivatives as ligands for metal complexes in enantioselective catalysis [18–22], we have evaluated the potential utility of these derivatives as ligands in the asymmetric palladium catalysed allylic substitutions [23–28].

In this paper we report the results of catalytic asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate by the complexes formed in situ from allylpalladium chloride dimer $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and ten different pyridine ligands.

These ligands were prepared according to reported procedures and their configurations are illustrated in Scheme 1. There are four 2,2′-bipyridines (**1**–**4**), two 2,2′:6,2″-terpyridines (**5**, **6**), two phenanthrolines (**7**, **8**) and two aminopyridines (**9**, **10**). Bipyridines, terpyridines and phenanthrolines present the 6,6-dimethylnorpynan-2-yl group as the common chiral substituent. Both monosubstituted and disubstituted C_2-symmetric derivatives have been tested.

Palladium catalysts where prepared in situ from allylpalladium chloride dimer $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and the ligands, using a molar ratio of palladium to ligand of 1 to 4. These catalysts

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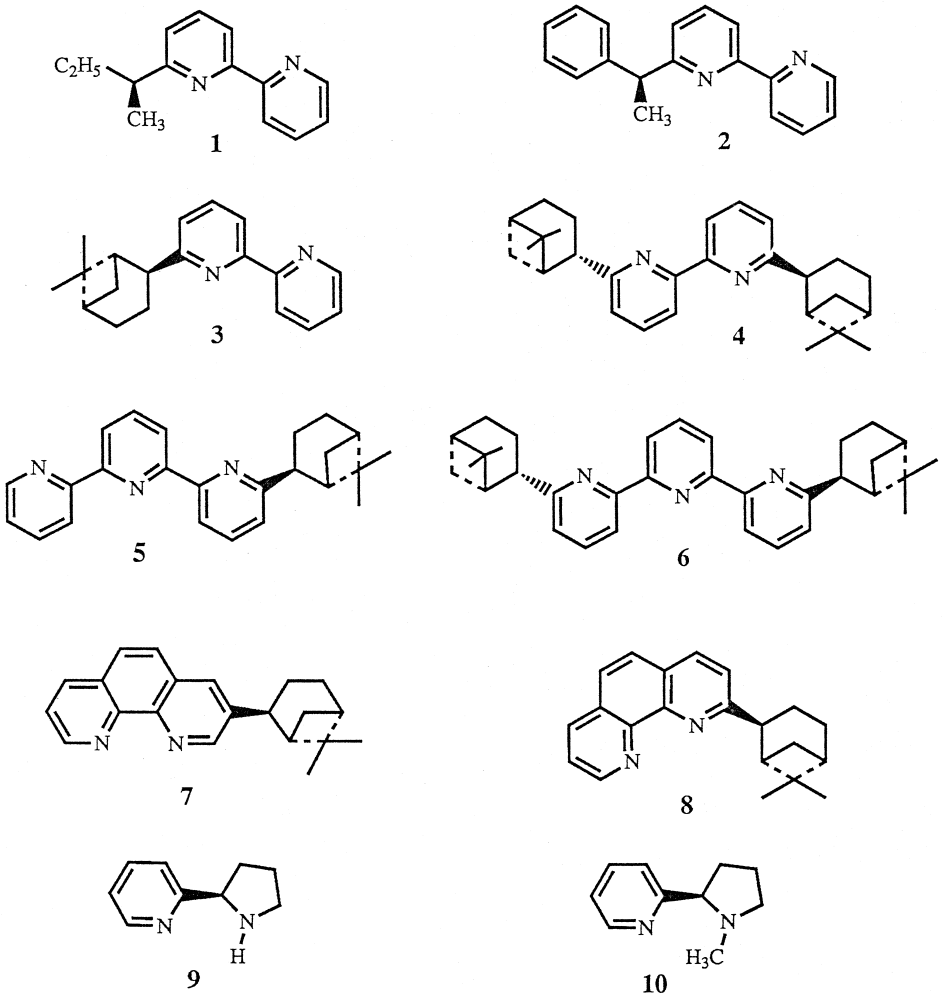


Scheme 1.

(2.5 mol%) were treated according to the usual protocol with 1,3-diphenylprop-2-enyl acetate, three equivalent of the nucleophile, generated from dimethyl malonate with *N,O*-bis(trimethylsilyl)acetamide (BSA) and a small quantity of potassium acetate [29]. The reactions were carried out in methylene chloride at room temperature or at reflux temperature when the ligand provided an insufficiently reactive palladium catalyst.

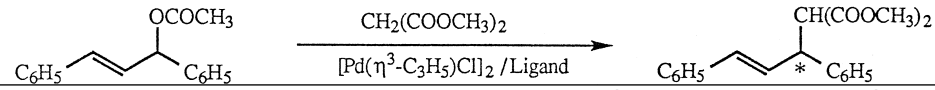
The following considerations can be made from the data reported in Table 1:

(1) 2,2′-Bipyridines are able to provide effective palladium catalysts but low enantiomeric excesses are achieved. The enantioselectivity increases as the substituent on the 6-position becomes larger (entry 1 versus 2, 3).

(2) The introduction of a second substituent in the 6′-position of the bipyridine **3** to give the related C_2-symmetric bipyridine **4** causes a drop both of the catalytic activity and of the enantioselectivity (entry 4 versus 5).

(3) The monosubstituted terpyridine **5** shows a comparable reactivity and enantioselectivity with respect to the related bipyridine (entry 7 versus 4), whereas the disubstituted C_2-symmetric terpyridine **6** is less reactive than the monosubstituted terpyridine **5** (entry 8 versus 7), but

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



Entry	Ligand	Temperature (°C)	Reaction time (h)	Conv.[b]	Yield[c]	% Ee[d]	Conf.[e]
1	**1**	r.t.	4	100	84	0	–
2	**2**	r.t.	5	100	82	2	R
3	**3**	r.t.	120	50	77	30	R
4	**3**	reflux	7	100	72	32	R
5	**4**	r.t.	120	11	n.d.	n.d.	n.d.
6	**4**	reflux	72	65	46	0	–
7	**5**	reflux	7	100	82	40	R
8	**6**	reflux	48	90	75	38	R
9	**7**	r.t.	1	100	84	14	S
10	**8**	r.t.	2	100	82	50	R
11	**9**	r.t.	24	100	72	64	R
12	**10**	r.t.	1	100	84	8	S

[a] Reaction of $[Pd(\eta^3\text{-}C_3H_5)C]_2$ (2.5 mol%) and the ligand (0.08 mmol) with 1,3-diphenyl-2-propenyl acetate (0.8 mmol), dimethyl malonate (2.4 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (2.4 mmol) and potassium acetate (3 mol%) in CH_2Cl_2 (4 ml) at room or refluxed temperature.
[b] Determined by ^{1}H-NMR of the crude reaction mixture.
[c] Isolated yields based on converted starting material.
[d] Determined by ^{1}H-NMR using $Eu(hfc)_3$ as chiral shift reagent.
[e] The assignment is based on the sign of the optical rotation [30].

more reactive than the C_2-symmetric bipyridine **4** (entry 8 versus 6). The stereochemical outcome is rather surprising on the base of a very recent study. Indeed, it has been demonstrated that in solution 2,2′:6′,2″-terpyridine allyl palladium(II) complexes are present in a dynamic equilibrium between η^1- and η^3-allyl isomeric forms. In the former case the terpyridine behaves as terdentate ligand whereas in the latter coordinates the palladium atom in a bidentate fashion [31]. If so, ligand **5** could form two η^3-allyl complexes according to whether the central pyridine coordinates the palladium together with the other substituted or unsubstituted pyridine, whereas with the C_2 symmetric ligand **6** can be formed only one palladium η^3-allyl complex. Both ligands **5** and **6** show the same enantioselective ability but they provides very different catalytic species.

(4) Phenanthrolines give very active catalysts whose reactivity and enantioselectivity depend on the distance of the chiral substituent from the heterocycle nitrogen (entry 9 versus 10). In the phenanthroline–bipyridine–terpyridine series in which the same substituent is present on the heterocycle, the phenanthroline **8** gives not only the more reactive catalytic species but also the more enantioselection (entry 10 versus 4 and 7).

(5) The aminopyridines **9**–**10** which differ only in the methyl substitution at the pyrrolidine nitrogen are effective ligands with the secondary amine **9** which affords a better enantioselection but with a slower reaction rate. Moreover, these ligands gave opposite configuration of dimethyl 1,3-diphenylprop-2-enylmalonate, indicating that the steric course of the reaction depends on both the stereogenic centres: that on carbon and that on the pyrrolidine nitrogen atom (which is formed after coordination to palladium).

In conclusion, this preliminary investigation indicates that chiral bipyridines and phenanthrolines are active ligands for palladium catalysed asymmetric allylic alkylation, whereas terpyridines do not appear to be useful ligands for this catalytic process. Moreover, the use of C_2-symmetric ligands is detrimental for both catalytic activity and enantioselectivity. Finally,

the potential utility of aminopyridines has been confirmed [32] [1]. Further studies aim at the synthesis and application of new chiral bipyridines and phenanthrolines for palladium catalysed asymmetric allylic alkylation are under way in our laboratory.

2. Experimental

2.1. Materials

Dimethyl malonate, *N*,*O*-bis(trimethylsilyl)acetamide and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ were purchased from Aldrich. *Rac*-(E)-1,3-diphenyl-2-propenyl acetate [33] and the pyridine ligands **1**–**10** were prepared according to reported procedures: (*S*)-6-(2-methylpropyl)-2-(2-pyridinyl)pyridine **1** [34], (*S*)-6-(2-phenylethyl)-2-(2-pyridinyl)pyridine **2** [35], 6-[6,6-dimethylnorpynan-2-yl]-2,2′-bipyridine **3** [35,36], 6,6′-bis-[6,6-dimethylnorpynan-2-yl]-2,2′-bipyridine **4** [36], 6-[6,6-dimethylnorpynan-2-yl]-2,2′:6′,2″-terpyridine **5** [37], 6,6′-bis-[6,6-dimethylnorpynan-2-yl]-2,2′:6,2″-terpyridine **6** [37], 3-[6,6-dimethylnorpynan-2-yl]-5,6-dihydro-1,10-phenanthroline **7** [38], 2-[6,6-dimethylnorpynan-2-yl]-5,6-dihydro-1,10-phenanthroline **8** [39], 2-[1-methyl-2-pyrrolidinyl]pyridine **9** [40] and 2-(2-pyrrolidinyl)pyridine **10** [39].

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

A solution of the ligand (0.08 mmol, 10 mol%) and $[Pd(\eta^3\text{-}C_3H_5)C]_2$ (8 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 (0.202 g, 0.8 mmol) in CH_2Cl_2 (2 ml), dimethyl malonate (0.316 g, 2.4 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (0.488 g, 2.4 mmol) and anhydrous potassium acetate (2.4 mg, 3 mol %). The reaction mixture was stirred at room or reflux temperature 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-enylmalonate. 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.

[1] Recently, we have reported that diastereomeric pure 8-amino substituted (5*S*,7*S*)-2-phenyl-5,6,7,8-tetrahydro-6,6-dimethylmethanoquinolines are active ligands in enantioselective palladium catalysed allylic substitutions, enantioselectivities up to 68% were obtained.

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