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Letter

1,10-Phenanthrolines derived from natural occurring ketones as ligands for asymmetric catalysis: enantioselective palladium catalyzed allylic substitution

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Abstract

A number of chiral C_1-symmetric 1,10-phenanthrolines derived from naturally occurring ketones were assessed in the enantioselective palladium catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethylmalonate. Enantioselectivity up to 96% was obtained with a new 1,10-phenanthroline derived from 5α-cholestan-4-one.

Keywords: Chiral 1,10-phenanthroline; Palladium complex; Allylic substitution; Enantioselectivity

1. Introduction

Chiral 1,10-phenanthrolines have recently found useful applications as ligands for palladium catalyzed allylic substitutions [1–3]. In particular, phenanthrolines **1** [1] and **2** [2] (Scheme 1) afforded 92% and 84% enantiomeric excesses in the enantioselective palladium catalysed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethylmalonate. Recently, in order to obtain an easy entry to this class of chiral ligands, we have applied the Friedländer methodology for the condensation of 8-aminoquinoline-7-carbaldehyde with naturally occurring aldehydes and ketones [4]. Moreover, by a modification of the Friedländer protocol, phenanthrolines derived from unreactive ketones such as camphor have been made available also [5].

With a number of easily available phenanthrolines in hand, continuing our interest in the synthesis and application in asymmetric catalysis of chiral pyridine derivatives [6,7], we were interested to investigate the potential utility of these compounds as chiral ligands for metal complexes in enantioselective catalysis.

In this paper, we report the application of a number of chiral C_1-symmetric phenanthrolines, specially those incorporated in a steroid backbone, in the enantioselective palladium catal-

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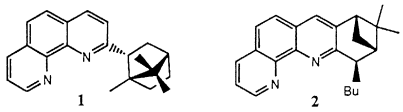


Scheme 1.

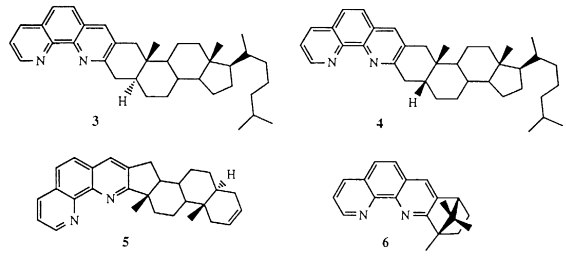
ysed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethylmalonate, which serves as a model substrate and reagent to compare the outcome of different ligands [8,9 (for more recent references on palladium-catalyzed allylic alkylation reactions, see Ref. [10]).

2. Results and discussion

Initially, the epimeric phenanthrolines **3** [4] and **4** [4] (Scheme 2) derived from α- and β-cholestan-3-one, respectively, were assessed in this process. The conditions of the catalytic alkylation entail the use of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as procatalyst and the generation of the nucleophile by the in situ treatment of dimethyl malonate with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate (KOAc) in a methylene chloride solution [11]. These phenanthrolines were able to provide effective palladium catalysts (Table 1). Total conversion of the starting material was achieved in less than 75 min to give high yields of dimethyl 1,3-diphenylprop-2-enylmalonate **12**. Surprisingly, both ligands gave **12** possessing the same sense of chirality and low enantiomeric excess, indicating that the different configuration at the C_5 carbon has a little effect on the stereoselectivity of the process. Then, since for an effective transfer of the chiral information from the catalyst to a product, it is necessary that there be a close interaction between the substrate and the ligand into the metal complex, we examined the phenathrolines **5** [4] and **6** [5] (Scheme 2) derived from 5α-androst-2-en-17-one and (+)-camphor, respectively. In the intermediate π-allyl palladium–phenanthroline complexes, the backbone of substituent on the heterocycle of these ligands is closer to the allylic termini and, therefore, it is expected to exert a larger influence on the stereoselectivity of the reaction. In fact, phenanthrolines **5** and **6** afforded a moderately high level of stereoselectivity (54% and 86%, respectively) with the former less effective, probably because of the presence on the stereocentre bonded to the heterocycle of not too much different methyl and methylene groups.

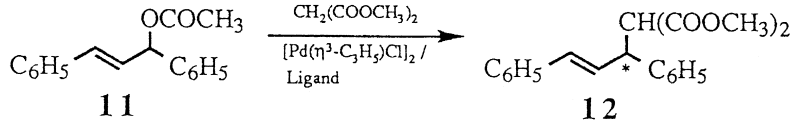
It has been reasoned out that one of the critical factors in controlling the selective addition of nucleophiles to π-allyl palladium intermediates is the nature of the ion pair of the attacking nucleophile [12,13]. Thus, according to several reports, the complexation of the cation with crown ether or employing tetraalkylammonium salts can have a dramatic effect on the enantioselectivity of the process. Very recently, Gilbertson and Chang [14] described a new method for the generation of malonate anion with a bulky counterions. This method, which proved to be superior to the BSA/KOAc procedure, involves the use as a base of BSA and of an appropriate tetraalkylammonium fluoride. In an effort to increase the enantioselectivity of the reaction, the ligand **3**, chosen to test this method, afforded an enantiomeric excess of 22% (Table 1, entry 3) which is twice as big as that obtained following the previous procedure (12%, entry 2). However, no change in the stereoselectivity was observed with ligand **6** (entry 7 versus 6).

Starting from these observations, we addressed our efforts to modify the structure of this kind of ligands in order to improve the



Scheme 2.

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



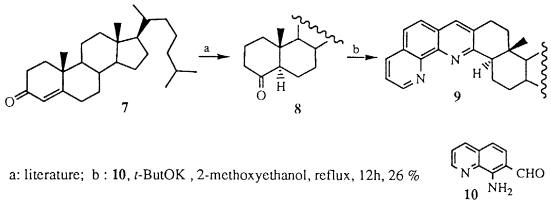
Ligand	Method[a]	React. time, min	% Yield[b]	% Ee[c]	Conf.[d]
1	A	50	93	12	S
1	B	30	90	22	S
2	A	75	88	4	S
3	A	95	90	54	S
4	A	180	89	86	S
4	B	120	93	85	S
7	A	75	88	94	R
7	B	60	92	96	R

[a] *Method 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 **11** (0.8 mmol), $CH_2(COOMe)_2$ (2.4 mmol), N,O-bis(trimethylsilyl)acetamide (BSA) (2.4 mmol) and KOAc (3.5% mol) in CH_2Cl_2 (2 ml) at room temperature. *Method B:* Reaction of the ligand (0.08 mmol, 10 mol%) and $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ (8 mg, 2.5 mol%) in CH_2Cl_2 (1 ml) for 30 min. followed by a solution of **11** (0.8 mmol) in CH_2Cl_2 (0.5 ml). Then, a solution of dimethyl malonate (2.4 mmol), BSA (2.4 mmol) and tetrabutylammomium fluoride trihydrate (2.4 mmol) in CH_2Cl_2 (3.5 ml) was added over 1 h. [b] Isolated yields. [c] Determined by ^{1}H-NMR using $Eu(hfc)_3$as chiral shift reagent. [d] The assignment is based on the sign of the optical rotation [17].

stereoselectivity of the process. To this end we decided to synthesize the 5α-cholestan[4,3-*b*]-1,10-phenanthroline (**9**) (Scheme 3), which was obtained by heating under reflux a 2-methoxyethanol solution of 5α-cholestan-4-one (**8**) and 8-aminoquinoline-7-carbaldehyde (**10**) in the presence of potassium *t*-butoxide. The ketone **8** was in turn prepared through a four-step reaction sequence starting from 4-cholesten-3-one (**7**) [15].

As expected, the phenanthroline **9** gave a much higher enantioselectivity (94%) than the related phenanthrolines **3** and **4**. Moreover, the enantiomeric excess increased to 96% using tetrabutylammonium fluoride, generating, in the model reaction studied, the highest reported induction for phenanthroline based ligands.

We are currently investigating further applications of these ligands to asymmetric synthesis.



Scheme 3.

3. Experimental section

3.1. 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. 5α-Cholesta[2,3-*b*]1,10-phenanthroline (**3**) [4], 5β-cholesta[2,3-*b*]-1,10-phenanthroline (**4**) [4],

5α-androstadieno[17,16-b]-1,10-phenanthroline (**5**) [4], 1,7,7-trimethyl[2.2.1]bicyclo heptano-[2,3-*b*]-1,10-phenanthroline (**6**) [5], 5α-cholestan-4-one (**8**) [15] and 8-aminoquinoline-7-carbaldehyde (**10**) [16] were prepared following literature procedures.

3.2. 5α-cholestan[4,3-b]-1,10-phenanthroline (9)

A mixture of 8-aminoquinoline-7-carbaldehyde (0.67 g, 3.88 mmol), 5α-cholestan-4-one (1.5 g, 3.88 mmol) and potassium *t*-butoxide (0.87 g, 7.76 mmol) in 2-methoxyethanol (30 ml) was heated under reflux overnight. The solvent was evaporated and the residue was taken up in water and extracted with ethyl ether. The organic phase was dried over anhydrous Na_2SO_4 and the solvent evaporated. The residue was purified by chromatography on neutral alumina eluting with CH_2Cl_2 to give pure **9**: 0.52 g (26% yield); mp 202-4°C; $[\alpha]^{20}{}_D$ −3.7 (c 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 9.17 (d, 1 H, $J = 3.3$ Hz); 8.21 (d, 1 H, $J = 7.8$ Hz); 7.88 (s, 1 H); 7.69 (m, 2 H); 7.56 (dd, 1 H, $J = 7.8$, 4.2 Hz); 3.27 (d, 1 H, $J = 9.9$ Hz); 3.09 (m, 2 H); 2.75 (d, 1 H, $J = 9.0$ Hz); 2.20–1.40 (m, 25 H); 0.93 (d, 3 H, $J = 6.3$ Hz); 0.87 (dd, 6 H, $J = 6.6$, 0.9 Hz); 0.83 (s, 3 H); 0.72 (s, 3 H). Anal. Calcd. for $C_{37}H_{50}N_2$: C, 84.99; H, 9.65; N, 5.36. Found: C, 84.77; H, 9.55; N, 5.55.

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

Method A: A solution of ligand (0.08 mmol, 10 mol%) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (8 mg, 2.5 mol%) in dry CH_2Cl_2 (2 ml) was stirred at room temperature for 30 min. This solution was treated successively with a solution of rac-(*E*)-1,3-diphenyl-2-propenyl acetate (**11**) (0.8 mmol) in CH_2Cl_2 (1 ml), dimethyl malonate (2.4 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (2.4 mmol) and anhydrous potassium acetate (3.5 mol%). The reaction mixture was stirred for the appropriate time 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. *Method B:* A solution of ligand (0.08 mmol, 10 mol%) and $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ (8 mg, 2.5 mol%) in dry CH_2Cl_2 (1 ml) was stirred at room temperature for 30 min and then a solution of **11** (0.8 mmol) in CH_2Cl_2 (0.5 ml). After 5 min, a solution of dimethyl malonate (2.4 mmol), BSA (2.4 mmol) and tetrabutylammonium fluoride trihydrate (2.4 mmol) in CH_2Cl_2 (3.5 ml) was added over 1 h and stirring continued at r.t. for the appropriate time. The reaction was treated as reported above.

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