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New 1,10-phenanthroline ligands for asymmetric catalysis: enantioselective palladium catalyzed allylic substitution

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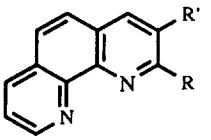
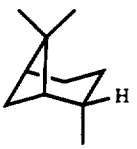
Abstract

A number of new chiral C_1-symmetric 1,10-phenathrolines have been prepared and assessed in the enantioselective palladium catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethylmalonate. Enantioselectivities up to 84% were obtained. © 1998 Elsevier Science Ltd. All rights reserved.

Recently, continuing our interest in the synthesis and application of chiral pyridine derivatives as ligands for metal complexes in enantioselective catalysis[1] we have evaluated the potential utility of a number of chiral ligands with sp^2-nitrogen donors as chiral controllers for enantioselective palladium catalyzed allylic substitutions.[2] This preliminary investigation indicated that in a series of alkyl C_1-symmetric phenanthroline–bipyridine–terpyridine, in which the same substituent was present on the heterocycle, the phenanthroline gave not only the more reactive catalytic species but also the higher enantioselection. Moreover, phenanthrolines gave catalysts whose reactivity and enantioselectivity was dependent on the distance of the chiral substituent from the heterocyclic nitrogen. Thus, between the 2- and 3-(2,2-dimethylnorpynan-2-yl)-1,10-phenanthroline (**1a** and **1b**, respectively) the best enantioselectivity (50% ee) was obtained with the ligand **1a**.



R: 2,2-dimethylnorpynan-2-yl=



1a: R= 2,2-dimethylnorpynan-2-yl, R'= H
1b: R= H, R'=2,2-dimethylnorpynan-2-yl

These promising results prompted us to prepare and assess in this catalytic process C_1-symmetric phenanthrolines in which the substituents on the stereocentre bound to the heterocyclic ring are arranged in a rigid backbone in such a way as to provide a more rigid array of the ligand around the metal

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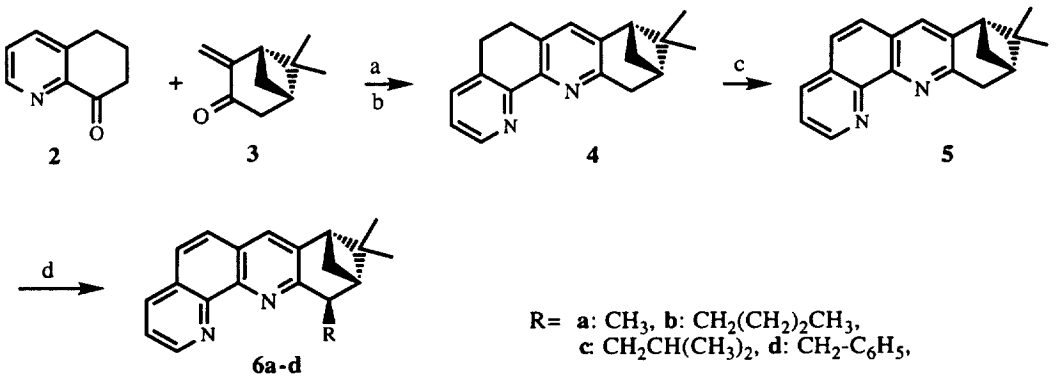
centre. In this communication we report the synthesis and application of a number of new chiral 1,10-phenanthrolines **5**,**6**[3] in the enantioselective palladium catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethylmalonate.

The dihydrophenathroline **4** was prepared by conjugate addition of the lithium enolate of tetrahydroquinolone **2** [generated by treatment with lithium diisopropylamine (LDA) at −78°C for 2 h] with (−)-pinocarvone **3**[4] (−78°C to room temperature) followed by azaanellation of the unisolated 1,5-dicarbonyl intermediate with the ammonium acetate/acetic acid system[5] (63% overall yield; Scheme 1). Then, the phenanthroline **5** was obtained by heating under reflux a decaline solution of **4** in the presence of 10% palladium on carbon (90% yield). Finally, the red solution of lithiated phenanthroline **5** (obtained by treatment with LDA at −40°C for 2 h) was quenched with the proper alkyl iodide to give ligands **6a–d** in 35–67% yield).[6] The use of alkyl iodide was necessary on account of the unexpectedly low reactivity of the lithium salt of **5**. Thus, the reaction with benzyl bromide, isopropyl iodide or acetone failed even if hexamethylphosphoric triamime (HMPA) or tetramethylethylenediamine were used as co-solvents.



a: LDA, THF, -78 °C, 2h; then **3** from -78 °C to slowly r.t.; b: AcOH, $AcONH_4$, THF, reflux, 2h; c: 10% Pd/C, decaline, reflux, 3h; d: LDA, THF, -40 °C, 2h; then CH_3I or $CH_3(CH_2)_2CH_2I$ or $(CH_3)_2CHCH_2I$ or $C_6H_5CH_2I$

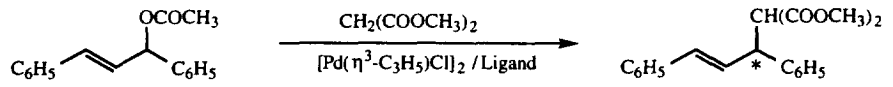
Scheme 1.

To test the ability of new ligands to provide asymmetric induction in the palladium catalyzed allylic substitutions we examined the alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate which serves as a model substrate to compare the outcome of different ligands.[7] Allylic substitutions were carried out at room temperature employing $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as a procatalyst in a methylene chloride solution of dimethyl malonate, *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate.[8] The results of the catalytic reaction are reported in Table 1.

1,10-Phenanthrolines **5–6** were able to provide effective palladium catalysts. Total conversion of the starting material was achieved with these ligands in less than 45 min to give high yields of dimethyl 1,3-diphenylprop-2-enylmalonate **8**. The introduction of alkyl groups at the 11-position of phenanthroline **5** was crucial for the stereoselectivity of the process. Thus, phenanthroline **5** gave a much lower enantiomeric excess than the 11-substituted phenanthroline **6**. The best stereoselectivity (84% ee) was obtained with the *n*-butyl substituted ligand **6b**, whereas a drop of enantioselectivity was observed with a branched substituent (entry 3 versus 4 and 5).

In all cases, the absolute configuration of the substitution product **8** was controlled by the absolute configuration at the stereogenic centre at the 11-position of the heterocyclic ring, resulting in the preferred formation of (*R*)-**8**. Moreover, since the 11-unsubstituted phenanthroline **5** gave the same sense of

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



7 8

Entry	Ligand	Temperature	React. time, min[b]	Yield[c]	% Ee[d]	Conf.[e]
1	**5**	r.t.	30	93	4	R
2	**6a**	r.t.	35	95	78	R
3	**6b**	r.t.	25	93	84	R
4	**6c**	r.t.	45	91	70	R
5	**6d**	r.t.	25	88	34	R

[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 temperature. [b]Determined by TLC analysis (SiO_2; light petroleum:ether:3/1; R_f **7** = 0.42; R_f **8** = 0.30. [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.

enantioselection than the 11-substituted one, it is reasonable to assume that in phenanthroline **6** the stereocentre at the 11-position and those at the 8,10-positions are not in a mismatching relation.

Finally, since the enantiomeric excess of ligands **5** and **6** is 91%, a higher asymmetric induction can be foreseen, excluding asymmetric amplification processes, if the same ligands could be used in enantiomerically pure form. Thus, for the enantiomerically pure ligand **6b** an enantiomeric excess of 92% should be expected.

In conclusion, in this paper we have reported the first synthesis of phenanthroline ligands[9] in which the substituent on the stereocentre bonded to the heterocyclic ring is arranged in a rigid backbone, and good preliminary results have been obtained with these ligands in enantioselective allylation reactions.[10]

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2. Chelucci, G.; Caria, V.; Saba, A. *J. Mol. Catal. A*, **1998**, *130*, 51.
3. The name tentatively attributed to **5** is 8,10-methano-9,9-dimethyl-8,9,10,11-tetrahydrobenzo[*b*] [1,10]phenanthroline.
4. (−)-Pinocarvone was prepared from (1*R*)-(+)-α-pinene (91% ee by GLC, Aldrich): Mihelich, E. D.; Eickhoff, D. J. *J. Org. Chem.*, **1983**, *48*, 4135.
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6. All compounds showed satisfactory spectroscopic and analytical data. Compound **5** was isolated in 90% yield: mp 229–230°C; $[\alpha]_D^{25}$ +102.6 (*c* 1.4, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 9.22 (dd, 1H, J=4.2, 1.5), 8.25 (dd, 1H, J=8.1, 1.8), 7.74 (s, 3H), 7.60 (dd, 1H, J=8.1, 4.5), 3.61 (d, 2H, J=3.9), 3.06 (t, 1H, J=5.7), 2.84 (m, 1H), 2.52 (m, 1H), 1.51 (s, 3H), 1.42 (d, 1H, J=9.6), 0.74 (s, 3H). Compound **6a** was isolated in 67% yield after flash chromatography (petroleum ether/ethyl acetate): mp 77–78°C; $[\alpha]_D^{25}$ +2.3 (*c* 0.7 $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 9.19 (dd, 1H, J=4.2, 1.5), 8.20 (dd,

1H, J=8.1, 1.8), 7.71 (s, 2H), 7.68 (s, 1H), 7.56 (dd, 1H, J=8.1, 4.2), 3.66 (m, 1H), 3.02 (t, 1H, J=5.4), 2.68 (m, 1H), 2.27 (m, 1H), 1.64 (d, 3H, J=6.9), 1.48 (s, 3H), 1.45 (d, 1H, J=10.2), 0.68 (s, 3H). Compound **6b**: was isolated in 43% yield after chromatographic purification on Al_2O_3 (petroleum ether:ethyl acetate=1:1): mp 65–66°C; $[\alpha]_D^{25}$ −33.9 (*c* 1.3, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 9.18 (dd, 1H, J=4.2, 1.5), 8.17 (dd, 1H, J=8.1, 1.8), 7.67 (s, 2H), 7.65 (s, 1H), 7.53 (dd, 1H, J=8.1, 4.5), 3.60 (m, 1H), 2.99 (t, 1H, J=5.7), 2.19 (m, 1H), 2.52–2.40 (m, 2H), 1.80 (m, 1H), 1.66 (m, 1H), 1.48 (s, 3H), 1.44 (d, 1H, J=9.6), 1.09 (d, 3H, J=6.6), 1.00 (d, 3H, J=6.6), 0.65 (s, 3H). Compound **6c**: was isolated in 35% yield after chromatographic purification on Al_2O_3 (petroleum ether:ethyl acetate=1:1): mp 72–73°C; $[\alpha]_D^{25}$ −49.1 (*c* 0.9 $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 9.19 (dd, 1H, J=4.2, 1.5), 8.20 (dd, 1H, J=8.1, 1.8), 7.71 (s, 2H), 7.68 (s, 1H), 7.56 (dd, 1H, J=8.1, 4.2), 3.66 (m, 1H), 3.02 (t, 1H, J=5.4), 2.62 (m, 1H), 2.27 (m, 1H), 1.64 (d, 3H, J=6.9), 1.48 (s, 3H), 1.45 (d, 1H, J=10.2), 0.68 (s, 3H). Compound **6d**: was isolated in 55% yield after chromatographic purification on Al_2O_3 (petroleum ether:ethyl acetate=1:1): mp 70–71°C; $[\alpha]_D^{25}$ +56.1 (*c* 1.1 $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 9.20 (dd, 1H, J=4.5, 1.8), 8.18 (dd, 1H, J=8.1, 1.8), 7.70 (s, 1H), 7.69 (s, 2H), 7.54 (dd, 1H, J=8.1, 4.2), 7.40–7.18 (m, 5H), 4.22 (dd, 1H, J=13.5, 4.23), 3.86 (m, 1H), 3.00 (t, 1H, J=5.7), 2.83 (dd, 1H, J=13.5, 11.7), 2.60 (m, 1H), 2.14 (m, 1H), 1.54 (d, 1H, J=9.9), 1.36 (s, 3H), 0.64 (s, 3H).

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