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Preliminary Communication

Asymmetric allylic alkylation with palladium coordinated to a new optically active pyrazolylmethane ligand *

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Abstract

The optically active pyrazole 4*R*-methyl-7*R*-isopropyl-4,5,6,7-tetrahydro-indazole, **3**, was prepared from (−)-menthone **1**, and used for the preparation of the ligands bis(4*R*-methyl-7*R*-isopropyl-4,5,6,7-tetrahydro-N^2-indazolyl)methane, **5**, bis(4*R*-methyl-7*R*-isopropyl-4,5,6,7-tetrahydro-N^1,N^2-indazolyl)methane, **6**, and bis(4*R*-methyl-7*R*-isopropyl-4,5,6,7-tetrahydro-N^1-indazolyl)methane, **7**. Their complexes $[Pd(\eta^3\text{-}C_3H_5)(LL)][PF_6]$ (LL = **5**, **6** and **7**); **9**, **10**, and **11**, respectively, were used as catalyst precursors for the reaction of *rac*-(*E*)-1,3-diphenyl-3-acetoxy-1-propene, **12**, with dimethylmalonate, **13**. When ligand **6** was used methyl 2-carbomethoxy-3,5-diphenyl-4-enoate, **15**, was obtained in 84% ee; it was shown that to achieve high ee value it is necessary to have 1 equivalent of chloride ion in the reaction mixture.

Pyrazole ligands have been used in organometallic chemistry since the seventies [1]. The earlier reports were centred mainly on the use of anionic polypyrazolate ligands, but during the last two years uncharged polypyrazolyl ligands have received increasing attention [2]. However, these investigations were mainly concerned with the coordination behaviour of the ligands and the structures of the complexes rather than their use in, for example, homogeneous catalysis. The latest development in this area is the synthesis of optically active pyrazoles and of their polypyrazolylborate or methane ligands [3]. Following the studies in our laboratory concerned with the cyclopropanation reaction of styrene using (+)- and (−)-bis(3-menthoxy-5-methyl-pyrazolyl)methane [4], we describe here the preparation of the optically active ligands **5–7** shown in Scheme 1 and their use in the palladium-catalysed enantioselective allylic alkylation.

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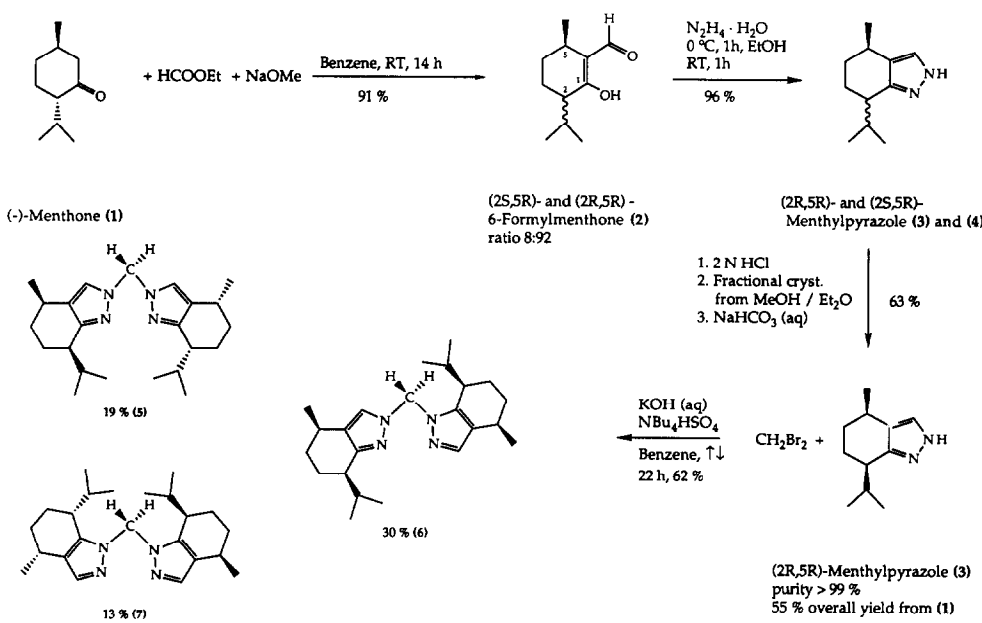
* Dedicated to Professor G.P. Chiusoli on the occasion of his 70th birthday and in recognition of his important contributions to organometallic chemistry and its application to organic synthesis.



Scheme 1.

0022-328X/93/$6.00

TABLE 1. Spectroscopic and analytical data

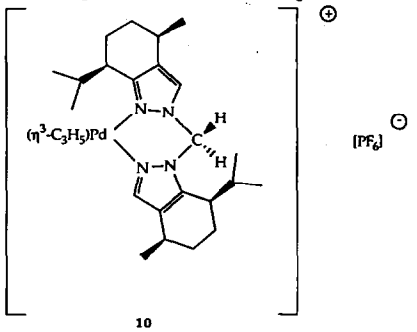
Compound	α_D^{20} (CH_2Cl_2)	M.p.	Elemental analysis (%)		^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm), coupling constants in Hz
			Found	Calcd.	
$C_{11}H_{18}N_2$ (3)	+27.93 ($c = 0.1$)	63	C, 73.93 H, 10.32 N, 75.17	C, 74.11 H, 10.18 N, 15.71	0.83 [d, 3H, CH_3(^{i}Pr), J(HH) 6.8], 1.02 [d, 3H, CH_3(^{i}Pr), J(HH) 6.8], 1.17 [d, 3H, CH_3(Me), J(HH) 6.9], 1.30–2.00 [m, 4H, 2×CH_2], 2.14 [m, 1H, CH(Me)$_2$], 2.62 [m, 1H, CHCH(Me)$_2$], 2.76 [m, 1H, CHMe], 7.34 [s, 1H, C=CH], 11.47 [br, 1H, NH]
$C_{23}H_{36}N_4$ (5)	+61.70 ($c = 0.1$)	72	C, 75.17 H, 9.85 N, 15.32	C, 74.45 H, 9.85 N, 15.20	0.82 [d, 6H, CH_3(^{i}Pr), J(HH) 6.8], 0.99 [d, 6H, CH_3(^{i}Pr), J(HH) 6.8], 1.10 [d, 6H, CH_3(Me), J(HH) 6.9], 1.20–1.85 [m, 8H, 4×CH_2], 2.16 [m, 2H, CH(Me)$_2$], 2.56 [m, 2H, CHCH(Me)$_2$], 2.71 [m, 2H, CHMe], 6.10 [s, 2H, CH_2 (methane)], 7.33 [s, 2H, CH=N]
$C_{23}H_{36}N_4$ (6)	+41.67 ($c = 0.1$)	108	C, 75.15 H, 9.88 N, 15.41	C, 74.45 H, 9.85 N, 15.20	0.83 [d, 3H, CH_3(^{i}Pr), J(HH) 6.8], 0.85 [d, 3H, CH_3(^{i}Pr), J(HH) 6.8], 0.97 [d, 3H, CH_3(^{i}Pr), J(HH) 6.8], 1.06 [d, 3H, CH_3(^{i}Pr), J(HH) 6.8], 1.08 [d, 3H, CH_3(Me), J(HH) 6.9], 1.18 [d, 3H, CH_3(Me), J(HH) 6.9], 1.25–2.00 [m, 8H, 4×CH_2], 2.16 [m, 2H, CH(Me)$_2$], 2.53 [m, 1H, CHCH(Me)$_2$], 2.93 [m, 1H, CHCH(Me)$_2$], 2.67 (m, 2H, CHMe], 6.11 [d, 1H, CH_2 (methane), J(HH) 14.1], 6.26 [d, 1H, CH_2 (methane), J(HH) 14.1], 7.19 [s, 1H, CH=N], 7.36 [s, 1H, CH=N]
$C_{23}H_{36}N_4$ (7)	+152.67 ($c = 0.1$)	118	C, 75.14 H, 9.89 N, 15.69	C, 74.45 H, 9.85 N, 15.20	0.88 [d, 6H, CH_3(^{i}Pr), J(HH) 6.8], 1.04 [d, 6H, CH_3(^{i}Pr), J(HH) 6.8], 1.16 [d, 6H, CH_3(Me), J(HH) 6.9], 1.20–2.00 [m, 8H, 4×CH_2], 2.13 [m, 2H, CH(Me)$_2$], 2.61 [m, 2H, CHMe], 2.77 [m, 2H, CHCH(Me)$_2$], 6.28 [s, 2H, CH_2 (methane)], 7.28 [s, 2H, CH=N]
$C_{26}H_{41}F_6N_4PPd$ (9)	+122.60 ($c = 1$)	140 (dec)	C, 47.09 H, 6.48 N, 8.51	C, 47.24 H, 6.25 N, 8.48	0.79 [d, 6H, CH_3(^{i}Pr), J(HH) 6.4], 1.01 [d, 6H, CH_3(^{i}Pr), J(HH) 6.4], 1.16 [d, 6H, CH_3(Me), J(HH) 6.4], 1.25–1.88 [m, 8H, 4×CH_2], 2.31 [m, 2H, CH(Me)$_2$], 2.51 [m, 2H, CHCH(Me)$_2$], 2.67 [m, 2H, CHMe], 3.14 [m, 2H, H^{anti} of allyl], 4.28 [m, 2H, H^{syn} of allyl], 5.73 [m, 1H, allyl], 6.28, 6.35 [d, 2H, CH_2 (methane)], 7.79 [s, 2H, CH=N]
$C_{26}H_{41}F_6N_4PPd$ (10) [a]	+62.50 ($c = 1$)	177 (dec)	C, 47.56 H, 6.20 N, 8.44	C, 47.24 H, 6.25 N, 8.48	0.67, 0.76, 0.65, 0.74 [d, 6H, CH_3(^{i}Pr), J(HH) 6.9], 1.00, 1.06, 1.02, 1.04 [d, 6H, CH_3(^{i}Pr), J(HH) 6.9], 1.17, 1.20, 1.16, 1.19 [d, 6H, CH_3)Me), J(HH) 6.7], 1.24–2.04 [m, 8H, 4×CH_2], 1.96, 2.32 [m, 2H, CH(Me)$_2$], 2.51, 2.97 [m, 2H, CHCH(Me)$_2$], 2.71 [m, 2H, CHMe], 3.10, 3.37, 3.23, 3.37 [d, 2H, H^{anti} of allyl, J(HH) 12.5], 4.27, 4.32, 4.41 [d, 2H, H^{syn} of allyl, J(HH) 7.1], 5.72 [m, 1H, allyl], 6.04, 6.44 [d, 2H, CH_2 (methane), J(HH) 15.1], 7.53, 7.69, 7.42, 7.73 [s, 2H, CH=N]
$C_{26}H_{41}F_6N_4PPd$ (11)	+46.20 ($c = 1$)	199 (dec)	C, 47.37 H, 6.30 N, 8.41	C, 47.24 H, 6.25 N, 8.48	0.83 [d, 6H, CH_3(^{i}Pr), J(HH) 6.8], 1.02 [d, 6H, CH_3(^{i}Pr), J(HH) 6.8], 1.22 [d, 6H, CH_3(Me), J(HH) 6.8], 1.33–2.07 [m, 8H+2H, 4×CH_2 and CH(Me)$_2$], 2.68 [m, 2H, CHMe], 2.83 [m, 2H, CHCH(Me)$_2$], 3.33 [dd, 2H, H^{anti} of allyl, J(HH) 3.0 and 12.4], 4.22 [dd, 2H, H^{syn} of allyl, J(HH) 3.0 and 6.6], 5.84 [tt, 1H, allyl, J(HH) 6.6 and 12.4], 6.09 [s broad, 2H, CH_2 (methane)], 7.52 [s, 2H, CH=N]

[a] Complex **10** shows in the ^{1}H NMR spectrum two sets of resonances due to two diastereomic forms (ratio 1:2).

The stoichiometric and catalytic versions of this reaction have been extensively studied during the past 20 years [5]. Although until recently the complexes employed for this purpose contained exclusively phosphine ligands [6], there have now been two reports of the very successful use of optically active nitrogen ligands [7].

The ligands were synthesized from optically pure (2*R*, 5*R*)-menthylpyrazole **3**, as shown in Scheme 1 [8]. Their analytical and spectroscopic data are listed in Table 1.

The complexes $[Pd(\eta^3\text{-}C_3H_5)(LL)][PF_6]$ (LL = **5**, **6** and **7**); **9**, **10**, and **11**, respectively [9*], were prepared by treating $[Pd_2(\mu\text{-}Cl)_2(\eta^3\text{-}C_3H_5)_2]$ (**8**) with the ligands in the presence of $Ag[PF_6]$.



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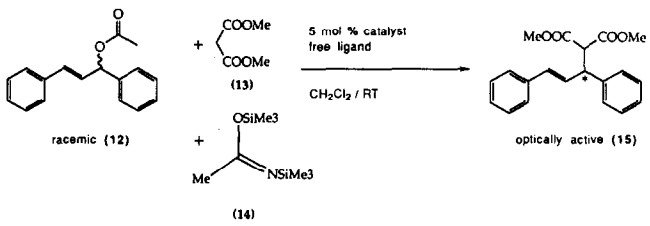
The allylic alkylation test reaction investigated is shown below, and the results of the corresponding experiments (see Scheme 2) are summarized in Table 2 [10*].

As can be seen from the table (entries 1–3), the catalyst containing ligand **6** gives ee values that are significantly higher than those observed for the complexes containing the two other ligands. It should be noted that ligand **6** is asymmetric, whereas compounds **5** and **7** are C_2-symmetric. C_2-symmetry has been accepted as an important feature of ligands used in asymmetric homogeneous catalysis; in particular for systems involving square-planar coordination geometry at the metal centre [12]. Indeed, many of the successful ligands used in asymmetric allylic alkylation were designed by following this approach. It is, therefore, surprising that the asymmetric ligand **6** clearly gives the best stereoselectivities. The structural isomerism of this ligand system allows the creation of different asymmetric environments at the metal centre, by keeping the same absolute configurations at the ligand stereogenic centres. To our knowledge this is the first report concerning the influence on stereoselectivity in a homogeneous catalytic reaction using different structural combinations of the same chirotopic ligand building blocks. The observed enantioselectivities when ligands **5**, **6** and **7** were used possibly reflect the "degree of chirality" [13] of the corresponding palladium-complexes, and indicate that C_2-symmetry is not relevant in this system.



Scheme 2.

* Reference number with asterisk indicates a note in the list of references.

TABLE 2. Reaction parameters and yields of the enantioselective allylic alkylation [a] of *rac*-(*E*)-1,3-diphenyl-3-acetoxy-1-propene with dimethylmalonate

Entry	cat [b]	Ligand	mol % [c]	Hal. [d]	mol %	Time h	Conv. % [f]	Yield % [g]	% ee
1	**9**	**5**	10	–	–	166	100	75	33 (*S*)
2	**10**	**6**	10	–	–	121	100	90	66 (*S*)
3	**11**	**7**	10	–	–	103	100	85	11 (*R*)
4	**10**	**6**	10	Cl	5	65	100	85	83 (*S*)
5	**10**	**6**	10	Cl	10	168	83	54	65 (*S*)
6	**10**	**6**	10	Br	5	38	100	88	67 (*S*)
7	**10**	**6**	10	Br	10	72	100	87	66 (*S*)
8	**10**	**6**	10	J	5	268	29	4	51 (*S*)
9	**10**	**6**	10	J	10	268	10	3	25 (*S*)
10	**8**	**5**	15	–	– e	282	34	23	39 (*S*)
11	**8**	**6**	15	–	– e	104	100	70	84 (*S*)
12	**8**	**7**	15	–	– e	15	100	75	38 (*R*)
13	**8**	**6**	15	Cl	5	168	51	37	65 (*S*)

[a] At room temperature. [b] Catalyst precursor, 5 mol% of Pd. [c] Added ligand. [d] Additional halogen: NEt_4Cl, NEt_4Br and NBu_4J, freshly dried at 100°C *in vacuo*. [e] The reaction mixture already contains 5 mol % chloride as the catalyst precursor **8** was used. [f] Measured by GC analysis. [g] Isolated yield after column chromatography.

It was further found that the enantioselectivity is significantly improved if the reaction is carried out in the presence of halide (see entries 4–9), especially chloride. It is important to note that best results are obtainable by using Pd: Cl ratios of 1 : 1; higher proportions of halide have a deleterious effect on both activity and stereoselectivity. The source of Cl^- is irrelevant in respect to its effect on selectivity (*cf.* entries 4 and 11). This observation indicates that complex **10** and one equivalent of NEt_4Cl, as well as precursor **8** and ligand **6**, form *in situ* the same catalytically active species. The effect of bromide on the enantioselection is negligible, although the reaction rate is raised. Finally, the more nucleophilic iodide was found to be a poison for the catalyst. The exact nature of this halide effect is still obscure. Studies directed toward the elucidation of these observations, as well as further modifications of the ligand system, are currently being carried out.

Acknowledgments

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9 Typical procedure for the preparation of complex **9**: ligand **5** (400 mg, 1.085 mmol) was added to a solution of $[Pd_2(\mu\text{-}Cl)_2(\eta^3\text{-}C_3H_5)_2]$ (**8**) (180 mg, 0.492 mmol) in CH_2Cl_2 (4 ml, freshly distilled from CaH_2). A solution of $Ag[PF_6]$ (249 mg, 0.987 mmol) in MeOH (1 ml, freshly distilled from $Mg(OMe)_2$) was added and the mixture was stirred in the dark for 1 h. The AgCl precipitate was filtered off on a Celite plug. The filtrate was evaporated under reduced pressure, the residue was dried *in vacuo* and washed twice with Et_2O (2 ml), affording a white powder: 624 mg of **9** (96%). Recrystallisation from CH_2Cl_2/Et_2O at $-20°C$ afforded colourless crystals. Complexes **10** and **11** were similarly prepared. The complexes were characterised by NMR spectroscopy and elemental analysis (see Table 1).

10 Typical procedure for the catalytic allylic alkylation reaction. The catalyst precursor **8** (20.0 mg, 0.030 mmol) and ligand **6** (22.3 mg, 0.060 mmol) were dissolved in CH_2Cl_2 (3 ml, freshly distilled from CaH_2). *rac*-(*E*)-1,3-Diphenyl-3-acetoxy-1-propene, **12**, (153 mg, 0.600 mmol), dimethylmalonate (**13**) (139 μl, 1.200 mmol), *N,O*-bis(trimethylsilyl)acetamide (**14**) (295 μl, 1.200 mmol) and anhydrous potassium acetate (3 mg, 0.030 mmol) were added successively. The mixture was then degassed by three freeze-thaw cycles. After approximately one hour of stirring at room temperature it turned pale yellow and murky. The reaction was monitored by TLC analysis. The appearance of a black precipitate indicated completion of the reaction. Filtration through Celite and evaporation of the filtrate gave a yellow oil, which was chromatographed (silica gel, hexane/EtOAc 5:1 v/v) to afford methyl 2-carbomethoxy-3,5-diphenyl-4-enoate, **15**, as a colourless oil (175 mg, 90%). The enantiomeric excess was determined by ^1H NMR spectroscopy using 0.5 equivalent of the shift reagent $Eu(hfc)_3$ in $CDCl_3$, which caused a splitting of the CO_2CH_3-singlet at lower field [11].

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