Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 929–936

TETRAHEDRON: *ASYMMETRY*

Diastereoselective cyclocarbonylation of isopulegol by palladium(II) complexes containing no chiral ligands

Géraldine Lenoble,[a] Ruth Naigre,[a] Thomas Chenal,[a,†] Martine Urrutigoïty,[a] Jean-Claude Daran [b] and Philippe Kalck [a,*]

[a] *Laboratoire de Catalyse, Chimie fine et Polymères, Ecole Nationale Supérieure de Chimie, 118 route de Narbonne, 31077 Toulouse Cedex, France*

[b] *Laboratoire de Chimie de Coordination, 205 route de Narbonne, 31052 Toulouse Cedex, France*

Received 19 January 1999; accepted 11 February 1999

Abstract

The cyclocarbonylation of isopulegol catalyzed by palladium(II) complexes containing no chiral ligands produces the two compounds (1*R*,5*R* or 5*S*,6*S*,9*R*)-5,9-dimethyl-2-oxabicyclo[4.4.0]decan-3-one with a diastereoisomeric excess up to 60%. X-Ray diffraction of the 5*S* stereoisomer, ^{1}H and ^{13}C NMR, and NOE measurements have allowed complete characterization of the two diastereoisomers. These results gave more details about the mechanism of cyclocarbonylation, and particularly the role of the OH group in the substrate.

1. Introduction

Asymmetric catalysis using transition metal complexes is a useful method in directly producing chiral compounds, provided efficient chiral ligands are introduced into the coordination sphere.[1] At the present time, hydrogenations and allylic isomerizations are the two best performing methods, and enantiomeric excesses higher than 99% have been obtained.[2,3] However, to date less interesting results have been obtained in hydroformylation,[4] although recently, 94–96% e.e.s have been reported.[5,6] For the asymmetric alkoxycarbonylation reactions of alkenes, the e.e. values remain in the 40–60% range.[7,8]

Stereodifferentiation due to the ligand itself is rather scarce in the literature. Indeed, palladium–copper systems catalyze the oxidative cyclocarbonylation of unsaturated chiral alcohols or diols: in the absence of chiral phosphorus ligands, it has been reported that an intramolecular transfer of the chirality to

* Corresponding author. Fax: +33-561-175-600; e-mail: pkalck@ensct.fr

† Present address: Laboratoire de Chimie Organique Appliquée, E.N.S.C. de Lille, BP 108, 59652 Villeneuve d'Ascq, France.

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00054-3

the substrate occurs which affords a 30% diastereoisomeric excess (d.e.) in the produced lactone.[9,10] Introduction of various additives in the reaction medium can increase the d.e. to 50%.[11,12]

It is worth mentioning that stereocontrol by the substrate has been largely investigated in association with chiral complexes to achieve a high diastereoselectivity through the so-called double asymmetric synthesis.[13–15]

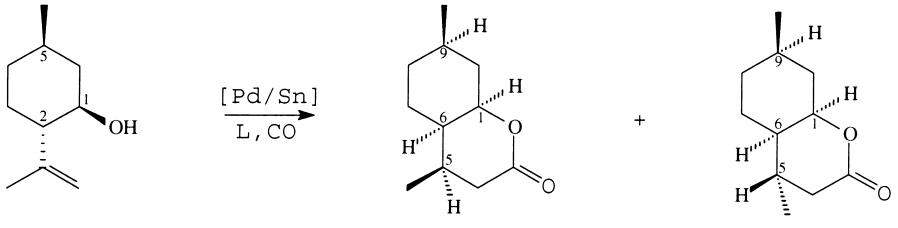
Previous studies[16,17] in our group have shown that (1*R*,2*S*,5*R*)-isopulegol can be readily carbonylated into the corresponding lactone with the $[PdCl_2(PPh_3)_2]/SnCl_2$ catalytic system. A study on the nature of the fate of the procatalyst led us to propose a palladium-hydride species in the catalytic cycle.

In this paper, we report the investigation of various $PdCl_2L_2$ complexes in the cyclocarbonylation reaction, in which L_2 is (−)-DIOP or (+)-DIOP, bis(diphenylphosphino)ferrocene (dppf), bis(diphenylphosphino)butane (dppb), and 2 PPh_3. We show that the asymmetric induction on the C5 atom of the product is exclusively due to the presence of stereogenic carbon atoms in the substrate. One stereoisomer of the resulting lactone was isolated in a pure state and an X-ray crystal structure led to the assignment of the configuration of the C5 carbon atom and the ^1H and ^{13}C NMR spectra, were fully assigned using two-dimensional experiments. Also, the minor isomer has been completely assigned in NMR. Interestingly, a d.e. of 60% with dppb was obtained. The mechanism of this asymmetric cyclocarbonylation on the palladium center is discussed.

2. Results and discussion

2.1. Cyclocarbonylation reaction with $PdCl_2(PPh_3)_2/SnCl_2$

The carbonylation of isopulegol **1** (Scheme 1), was carried out at 65°C and 4 MPa for 16 h, with a catalytic system composed from $PdCl_2(PPh_3)_2$, an excess (greater than 2 equiv.) of PPh_3 and 2.5 equiv. of $SnCl_2 \cdot 2H_2O$. This selectively affords the corresponding lactone **2** with a 100% yield (Scheme 1). After evaporation of the toluene the crude product is purified on a silica column eluted with hexane/ethyl acetate to remove the catalytic components.



1 (1R,2S,5R)-isopulegol

2a(1R,5R,6S,9R) + **2b**(1R,5S,6S,9R) 5,9-dimethyl-2-oxabicyclo[4.4.0]decan-3-one

Scheme 1.

Evaporation of the eluent followed by a slow crystallization at −18°C gave white crystals suitable for an X-ray crystal structure analysis. As previously observed for this carbonylation reaction,[16,17] even in the presence of methanol the reaction leads exclusively to lactone **2**. NMR spectra show that two diastereoisomers are present in the reaction mixture in roughly a 62:38 ratio. The crystalline material belongs to the minor isomer **2b**.

2.2. X-Ray crystal structure of **2b**

The molecular structure of **2b**, shown on Fig. 1, reveals that the three preexisting stereogenic carbon atoms are maintained as C1(*R*), C6(*S*), and C9(*R*), and that the new C5 carbon atom has an *S* configuration. All the carbon–carbon, carbon–hydrogen and carbon–oxygen distances, and the chair conformations for the two rings, are as expected.

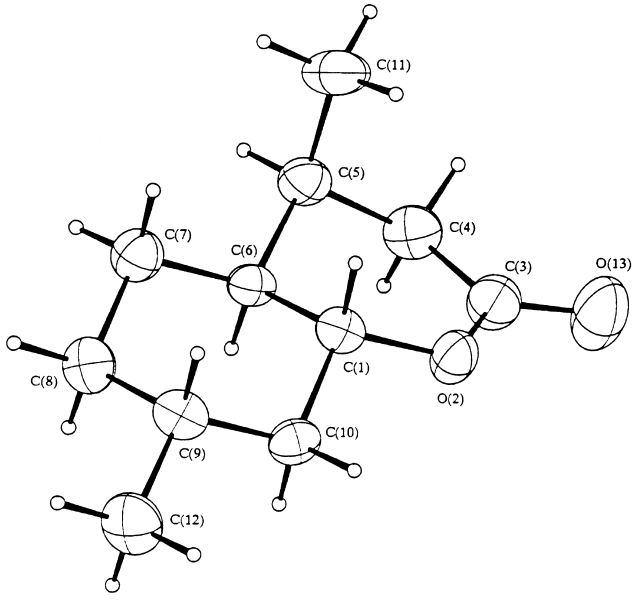


Figure 1. X-Ray structure of **2b**

2.3. NMR study of **2a** and **2b**

Crystalline material as analyzed by X-ray diffraction, was dissolved in $CDCl_3$ for a full ^1H and ^{13}C NMR investigation. The assignment of proton and carbon resonances (Tables 1 and 2) was helped by COSY (^1H,^1H), HMQC (^1H,^{13}C) ^1J and long-range experiments. More particularly, these analyses allowed us to clearly distinguish the two protons lying on the C4 carbon atom from the others CH_2 multiplets, and to assign H4*ax* from H4*eq* in the ABX system. The NOESY experiments (Fig. 2) show that H4*ax* is correlated to H6*ax* among others, and H4*eq* to the C11 methyl groups.

As confirmed by several catalytic experiments, the crystalline material corresponds exclusively to isomer **2b**. The other isomer **2a** is obtained as an oily mixture containing small amounts of **2b**, (generally 90:10). The NMR assignments (Tables 1 and 2) were determined in the same way as previously described, taking into account the signals due to **2b**. These are consistent with those of **2b**. Because of the inversion of the configuration on C5, the ABX system of CH_2 is still visible for the C4 atom, but now in the NOESY spectra H4*ax* is correlated to the methyl of C11.

2.4. Use of several diphosphine ligands on palladium

The introduction of the chiral ligand (−)-DIOP in the coordination sphere of palladium improved the diastereoisomeric excess since 81% of **2a** and 19% of **2b** were obtained, and thus a d.e. of 62% instead of 24% for PPh_3 was achieved (Table 3). However, starting from [$PdCl_2$(+)-DIOP] we obtained exactly the

Table 1
^{1}H NMR data (400 MHz, $CDCl_3$) of **2a** and **2b**

Proton	2a		2b	
	δ (ppm)	J (Hz)[a]	δ (ppm)	J (Hz)[a]
H1	3.75 (ddd)	4.2 / 10.5 / 10.5	4.13 (ddd)	4.3 / 11 /11
H4ax	2.55 (dd)	6.8 / 18	2.69 (dd)	6.6 / 17.6
H4eq	1.96 (dd)	9.4 / 17.8	2.41 (dd)	2.8 / 17.6
H5	1.45 (m)		2.07 (m)	
H6	0.8 (m)		1.60 (m)	
H7ax	1.10 (m)		1.27 (dddd)	3.5 / 12.9
H7eq	1.84 (m)		1.66 (m)	
H8ax	1.54 (m)		1.73 (m)	
H8eq	0.85 (m)		1.73 (m)	
H9	1.34 (m)		1.48 (m)	
H10ax	0.92 (m)		1.16 (ddd)	12 / 12 / 12
H10eq	1.86 (m)		2.13 (ddd)	1.6 / 12 / 12
CH_3 11	0.82 (d)	6.2	1.00 (d)	7.2
CH_3 12	0.77 (d)	6.5	0.97 (d)	6.6

[a]The numbers correspond to $J(^1H\text{-}^1H)$. d=doublet, dd=doublet of doublet, m=multiplet,ax=axial, eq=equatorial.

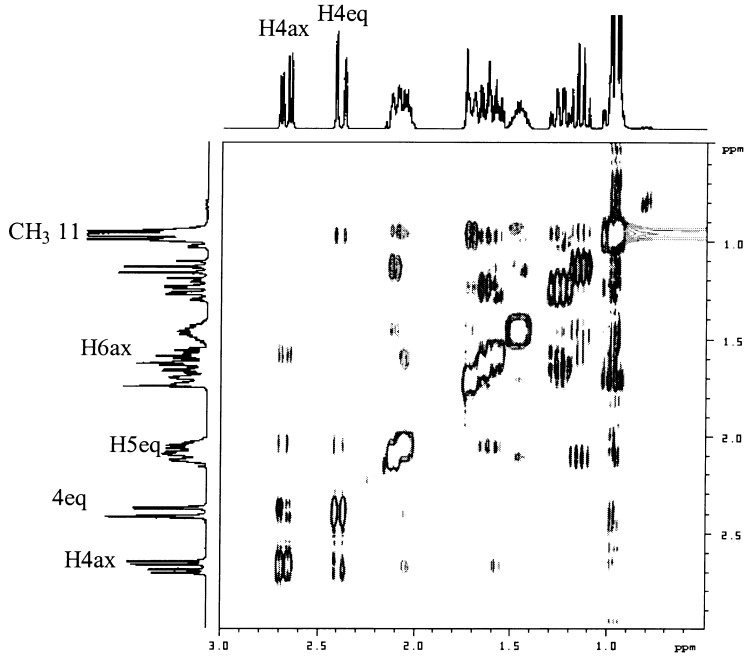
Table 2
^{13}C NMR parameters (δ, ppm) of **2a** and **2b**

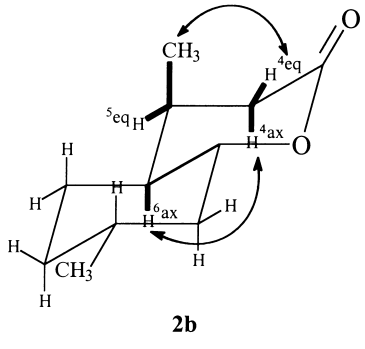
	2a	2b
C1	82.3	77.8
C3	171.3	171.2
C4	38.0	38.9
C5	31.7	28.8
C6	44.9	41.7
C7	27.7	27.2
C8	33.7	33.9
C9	30.9	30.8
C10	40.4	40.9
C11	19.0	14.7
C12	21.8	21.7

same major contribution of **2a** together with the same d.e. value. Thus, the chiral ligand appears to exert an influence on the formation of intermediate species in which the two phosphorus atoms are in mutual *cis* position; however, its chirality does not seem to play a role since the same **2a**:**2b** ratio is obtained.

To confirm this hypothesis a classic non-chiral diphosphine has been used. Whereas bis(diphenylphosphino)ethane and propane do not lead to any catalytic activity, presumably because the carbon chain between the two phosphorus atoms is too short, the use of dppb and dppf was successful. Indeed, $PdCl_2$(dppb), under the same conditions, shows the same performance as those of [$PdCl_2$DIOP]. $PdCl_2$(dppf) allows a good yield of lactone, but the diastereoisomeric excess is lower (Table 3).

Hence we come to the conclusion that the asymmetric induction is exerted by the substrate itself and that the phosphine ligands have essentially a steric effect during the cyclocarbonylation reaction.





2b

Figure 2. 2D NOESY spectrum (1 s mixing time), and scheme for the two correlations observed for H4

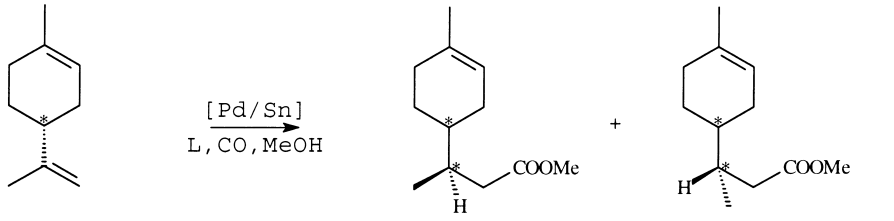
Table 3
Palladium-catalyzed carbonylation reactions

Catalytic precursor	Conversion (%)	Selectivity (%)	2a/2b	d.e. (%)
$[PdCl_2(PPh_3)_2]$[a]	100	100	62/38	24
$[PdCl_2$(–)-DIOP]	97	96	81/19	62
$[PdCl_2$(+)-DIOP]	97	96	81/19	62
$[PdCl_2$(dppb)]	83	99	80/20	60
$[PdCl_2$(dppf)]	95	90	72/28	44

Conditions : Catalytic precursor = 0.5 mmol, excess of diphosphine = 0.5 mmol, $SnCl_2$, $2H_2O$ = 1.25 mmol, isopulegol = 50 mmol, toluene = 25 mL, T = 97°C, CO pressure = 4 MPa, t = 22h.
[a] Excess of triphenylphosphine = 1 mmol , T = 65°C, t = 16h.

2.5. Approach of the reaction mechanism

It has been previously shown that the active species is a hydride intermediate $[Pd(H)(SnCl_3)L_2]$,[18] and that the substrate itself can be the hydrogen source.[16,18] We have observed that (+)-(*R*)-limonene gives, under the best conditions, a 5% d.e. using $[PdCl_2(-)\text{-DIOP}]$[19] (Scheme 2).



(+)-(R)-limonene

(3S, 1'R) methyl 3-[(4'-methyl)-cyclohex-3'-enyl)]butanoate

(3R, 1'R)

Scheme 2.

The main difference between the two substrates of interest here is the presence on isopulegol of an OH group which can interact with the palladium center during a crucial step. This step might be either after the hydride transfer or after the CO insertion, giving the complexes **3** and **4**, respectively, shown in Scheme 3. The coordination of carbon monoxide to complex **3** would require displacement of one of the phosphorus centers of the diphosphine ligand, and hence we consider that it is the stabilization of complex **4** which is the crucial difference between the catalytic cycles for isopulegol and limonene.

3a **4a**

Scheme 3. Only **3a** and **4a** have been represented

The last step, as is usually accepted, would be the cyclization giving lactone **2**, which restores the active palladium-hydride species.

3. Conclusion

This study on the cyclocarbonylation of isopulegol shows that the enantiodiscrimination may be attributed to the chiral substrate itself. Thus, non-chiral conventional ligands can be used as ancillary ligands on the active metal center. Further studies are in progress with similar observations on various other substrates and models of the two intermediates **3** and **4**, in order to obtain a deeper insight into the mechanism.

4. Experimental

4.1. General

GC Analyses were performed on a Carlo Erba MFC 500 apparatus equipped with a 50 m×0.32 mm capillary column and a flame ionization detector. Identification of the reaction products was checked by GC–MS on a Perkin–Elmer Q-MASS 910 mass spectrometer. The mixture of the two diastereoisomers were analyzed by NMR spectroscopy (Bruker AMX400 MHz), Infrared (Perkin–Elmer 1710 spectrophotometer) and elemental analysis.

$[PdCl_2(PPh_3)_2]$ was prepared according to the literature,[20] (yield 95%), $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ_p=23.47 ppm, IR ν=1481, 1436, 1099, 746, 693 cm^{-1}.

The palladium complexes $[PdCl_2(dppb)]$, $[PdCl_2(dppf)]$ and $[PdCl_2DIOP]$ were prepared using the same method: $[PdCl_2(PhCN)_2]$[21] (IR ν(C≡N)=2290–2225 cm^{-1}) and diphosphine were dissolved separately in 10 mL of hot acetone, then mixed and stirred for a few minutes. The solution was allowed to cool and crystallize. The product was filtered and dried: $[PdCl_2(dppb)]$ (yield 90%), $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ_p=63.75 ppm, IR ν=3054, 2925, 1484, 1435, 1101, 907, 745, 695 cm^{-1}; $[PdCl_2(dppf)]$ (yield 88%), $^{31}P\{^1H\}$NMR (CD_2Cl_2): δ_p=36.14 ppm; $[PdCl_2DIOP]$ (yield 85%), $^{31}P\{^1H\}$NMR (CD_2Cl_2): δ_p=16.47 ppm, IR ν=3053, 2932, 1482, 1436, 1101, 1238, 1056, 742, 698 cm^{-1}.

4.2. General method for cyclocarbonyation of (1R,2S,5R)-isopulegol

A mixture of 0.702 g (1 mmol) of dichlorobis(triphenylphosphine)palladium (II), 0.474 g (2.5 mmol) of hydrated tin(II) chloride and 0.524 g (2 mmol) of triphenylphosphine was introduced into a 250 mL stainless steel autoclave with mechanical stirring. A dinitrogen-saturated mixture of isopulegol (100 mmol) in 25 mL toluene was introduced into the evacuated autoclave by aspiration. It was heated to 65°C under 4 MPa of carbon monoxide at constant pressure. After 16 h, the autoclave was cooled and then slowly depressurized. The yellow-orange reaction mixture was analyzed by gas chromatography. After evaporation of the toluene, the oily residue was purified by column chromatography on silica gel (hexane:ethyl acetate, 96:4). The minor diastereoisomer crystallized on standing at −18°C, and was isolated by cold filtration.

4.2.1. (1R,5S,6S,9R)-5,9-[Dimethyl-2-oxabicyclo[4.4.0]decan-3-one]

Mass spectrum: m/z=183 (MH^+, 12%), 138 (M^+-CO_2, 6%), 122 ($M^+-CH_2C(OH)_2$, 31%), 96 (138–CH_2CHCH_3, 100%), 81 (96–CH_3, 85%). IR ν(C=O)=1731 cm^{-1}. Elemental anal. calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95; O, 17.56. Found: C, 71.78; H, 9.94; O, 18.26.

4.2.2. (1R,5R,6S,9R)-5,9-[Dimethyl-2-oxabicyclo[4.4.0]decan-3-one]

Mass spectrum: m/z=183 (MH^+, 18%), 138 (M^+-CO_2, 7%), 122 ($M^+-CH_2C(OH)_2$, 30%), 96 (138–CH_2CHCH_3, 41%), 95 (96–H, 100%), 81 (96–CH_3, 62%).

Acknowledgements

The authors are grateful to Engelhard-Comptoir Lyon-Alemand-Louyot for generous loan of palladium salt. We also thank F. Lacassin for NMR analyses, and N. Wheatley for helpful discussions.

References

1. (a) Chaloner, P. A. *Handbook of Coordination Catalysis in Organic Chemistry*; Butterworth: London, 1986; (b) Ojima, I. In *Catalytic Asymmetric Synthesis*; Department of Chemistry, State University of New York at Stony Brook. VCH Publishers: New York, 1993.
2. (a) Noyori, R. *Chem. Soc. Rev*. **1989**, *18*, 187; (b) Noyori, R. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B.; Herrmann, W. A., Eds. VCH Publishers: New York, 1996; p. 552.
3. Sheldon, R. *Chemistry and Industry* **1990**, 212.
4. Botteghi, C.; Paganelli, S.; Schionato, A.; Marchetti, M. *Chirality* **1991**, *3*, 355.
5. Horiuchi, T.; Ohta, T.; Shirakawa, E.; Nozaki, K.; Takaya H. *J. Org. Chem*. **1997**, *62*, 4285.
6. Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H. *J. Am. Chem. Soc.* **1997**, *119*, 4413.
7. Consiglio, G.; Pino, P. *Chimia* **1976**, *30*, 193.
8. Consiglio, G.; Kollár, L.; Kölliker, R. *J. Organomet. Chem*. **1990**, *396*, 375.
9. Alper, H.; Leonard, D. *J. Chem. Soc., Chem. Commun*. **1985**, 511.
10. Toda, S.; Miyamoto, M.; Kinoshita, H.; Inomata, K. *Bull. Chem. Soc. Jpn*. **1991**, *64*, 3600.
11. Tamaru, Y.; Kobayashi, T.; Kawamura, S.-I.; Ochiai, H.; Hojo, M.; Yoshida, Z. I. *Tetrahedron Lett*. **1985**, *26*, 3207.
12. Tamaru, Y.; Hojo, M.; Yoshida, Z. I. *Tetrahedron Lett*. **1987**, *28*, 325.
13. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl*. **1985**, *24*, 1.
14. Horeau, A.; Kagan, H. B.; Vigneron, J. P. *Bull. Soc. Chim. Fr*. **1968**, 3795.
15. Brown, J. M. *Chem. Soc. Rev*. **1993**, 25.
16. Naigre, R.; Chenal, T.; Ciprès, I.; Kalck, Ph.; Daran, J.-C.; Vaissermann, J. *J. Organomet. Chem*. **1994**, *480*, 91.
17. Chenal, T.; Ciprès, I.; Jenck, J.; Kalck, Ph.; Pérès, Y. *J. Mol. Catal*. **1993**, *78*, 351.
18. Knifton, J. F. *J. Org. Chem*. **1976**, *41*, 2885.
19. Naigre, R. PhD Thesis, Institut National Polytechnique de Toulouse (France) 1994.
20. Coulson, D. R.; Satek, L. C.; Orim, S. O. *Inorg. Synth*. **1972**, *13*, 121.
21. Jenkins, J. M.; Verkade, J. C. *Inorg. Synth*. **1968**, *11*, 108.