

Critical solvent effect on the chiral recognition of a catalytic species by a chiral substrate

Lisa Diab^{a,b}, Maryse Gouygou^{a,*}, Eric Manoury^{a,*},
Philippe Kalck^b, Martine Urrutigoity^{b,**}

^a *Laboratoire de Chimie de Coordination du CNRS, UPR 8241, 205 route de Narbonne, 31400 Toulouse Cedex 4, France*

^b *Laboratoire de Chimie de Coordination du CNRS, UPR 8241, Composante ENSIACET-INP, 118 route de Narbonne, 31077 Toulouse Cedex 4, France*

Received 27 July 2007; received in revised form 24 August 2007; accepted 24 August 2007

Available online 1 September 2007

Abstract

In the diastereoselective cyclocarbonylation of isopulegol and isolimonene catalysed by the non-chiral $[\text{PdCl}_2\text{L}_2]$ palladium complexes ($\text{L} = \text{PPh}_3$, $\text{L}_2 = \text{bis}(\text{diphenylphosphino})\text{-butane}$ or -ferrocene), the diastereoisomeric excess is enhanced by a factor of 1.5–2 when toluene is substituted by chloro-solvents. A less significant effect is noted when using more coordinating solvents such as acetonitrile and THF. In chloro-solvents reaction rates are faster than in toluene, isopropanol, acetonitrile or THF.

© 2007 Elsevier B.V. All rights reserved.

Keywords: Cyclocarbonylation; Monoterpenes; Palladium; Solvent effects; Diastereoselectivity

1. Introduction

Asymmetric catalysis provides a powerful tool to attain high enantioselectivities or diastereoselectivities when employing various functionalized prochiral substrates. Many examples of very efficient transition metal complexes have been reported, as well as numerous enantiomeric (or diastereoisomeric) excesses close to 100% [1]. These precatalyst complexes contain chiral ancillary ligands that govern the stereospecific approach of the substrate to the transition metal center. As for carbonylation reactions such as hydroformylation, alkoxy-carbonylation, alkene/CO co-polymerization, the results are somewhat less encouraging, and modest e.e. or d.e. values have been reported [2]. We were interested in the cyclocarbonylation reactions, especially those starting from terpenes, since cyclic compounds incorporating a carbonyl groups such as lactones, lactols, cycloalkanones, can be built in an elegant way [3]. As far as sustainable development is concerned, monoterpenes represent an abundant pool of natural substrates that contain most

of the time chiral carbon atoms in their backbone. Due to the presence of unsaturation(s) on it, direct functionalization often leads to tandem reactions by which new chiral centers are generated.

Moreover, we have recently observed the unusually strong influence given by the presence of stereogenic centers on the starting substrate. Indeed, the cyclocarbonylation of two representative substrates, isopulegol **1** and isolimonene **3**, affords the two lactone **2** and cyclopentanone **4** compounds, in which two diastereoisomers (**2a/2b** and **4a/4b** respectively) are formed with d.e. as high as 60% [4] (Scheme 1).

The goal of the present paper is to describe the role played by the solvent, which exerts a dramatic effect on both kinetics and diastereoselectivity. Whereas the addition of a slight excess of triphenylphosphine is needed when the $[\text{PdCl}_2\text{L}_2]$ catalyst precursor is used in toluene, using dichloromethane and 1,2-dichloroethane as solvents leads to higher reaction rates and better diastereoisomeric excesses (up to 87%) either in the presence or in the absence of added triphenylphosphine.

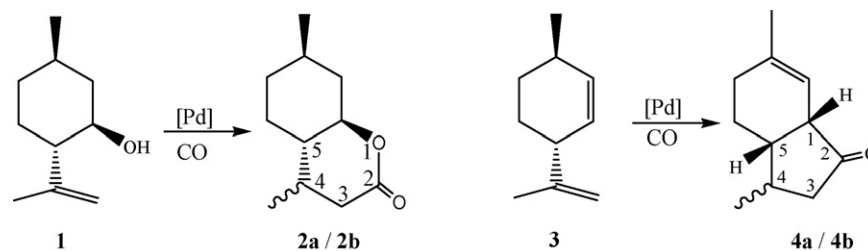
2. Results and discussion

Previous studies [4a] conducted by our group have shown that the cyclocarbonylation of isopulegol **1** catalysed by

* Corresponding authors. Tel.: +33 5 61 33 31 74; fax: +33 5 61 33 30 03.

** Corresponding author. Tel.: +33 5 62 88 56 98; fax: +33 5 62 88 56 00.

E-mail addresses: gouygou@lcc-toulouse.fr, manoury@lcc-toulouse.fr (M. Gouygou), Urrutigoity@ensiacet.fr (M. Urrutigoity).

Scheme 1. Cyclocarbonylation of isopulegol, **1**, and isolimonene, **2**, catalysed by $\{[\text{PdCl}_2(\text{PPh}_3)_2]/\text{SnCl}_2/\text{PPh}_3\}$ system.

various $[\text{PdCl}_2\text{L}_2]$ complexes ($\text{L}_2 = 2 \text{ PPh}_3$; bis(diphenylphosphino)butane, dppb; bis(diphenylphosphino)ferrocene, dppf; 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphosphino)butane DIOP) provides the corresponding lactone **2** in quantitative yield, with a diastereoselectivity ranging from 24 to 60%. These results were obtained when the reaction was performed at 80 °C under 40 bar of CO pressure using toluene as solvent and in the presence of 2 equiv. of triphenylphosphine and 2.5 equiv. of SnCl_2 (Table 1).

Under similar conditions (Table 2), isolimonene **3** can be cyclocarbonylated to the corresponding cyclopentanone **4a/4b** with a diastereoisomeric excess up to 69% [4b].

In this case, the palladium(II) catalytic system is less effective, giving lower conversion (71–95%) and lower chemoselectivity due to migration of the endocyclic double bond.

All of our experiments and the relevant results shown in Tables 1 and 2, (all the experiments have been reproduced in the present study), clearly show that non-chiral phosphine ancillary ligands assist the chiral recognition process. Indeed, whichever (+)-DIOP or (–)-DIOP ligand is used, the enantioselective excess at C_4 in lactone **2**, thus the *R/S* ratio, is exactly the same. Thus, these results clearly show that the stereo-induction

can be attributed to the chiral substrate itself [5]. Worthy of note is that such this stereodifferentiation can be also modulated by the nature of the ligand used (see Tables 1 and 2). From such results the question arises on the nature of the stereodetermining step. We can suppose that in the early stages of the catalytic process, for which the cycle shown in Scheme 2 has been proposed [6], two intermediates are formed according to the coordination mode of the isopropenyl moiety onto palladium in a pro-*R* or a pro-*S* mode. Such pentacoordinated intermediates would not possess the same energy so that one of them would react faster, providing the observed major diastereoisomer. Such pre-coordination of the substrate on the palladium center would be in competition with the coordination of the solvent and the relevant equilibrium would hence be affected by its nature.

In order to be able to improve the diastereoselectivity, we have studied the effect of the solvent. In the first set of experiments, the cyclocarbonylation of isopulegol was investigated for the $[\text{PdCl}_2(\text{PPh}_3)_2]/\text{SnCl}_2$ catalytic system in presence of an excess of triphenylphosphine. The reaction was carried out at 80 °C under CO pressure of 40 bar during 2 h in the presence of two supplementary equivalents of PPh_3 . The results are summarized in Table 3.

In toluene, the $[\text{PdCl}_2(\text{PPh}_3)_2]/\text{SnCl}_2/\text{PPh}_3$ system appears completely inactive after 2 h (run 1), and 16 h are necessary to exceed the induction period and to reach total conversion (run 3). When the experiment is carried out using 1,2-dichloroethane as

Table 1
Palladium-catalysed cyclocarbonylation of isopulegol in toluene (from Ref. [4a])

Complexes	Conversion (%)	Yield (%)	d.e. (%)
$[\text{PdCl}_2(\text{PPh}_3)_2]$	99	99	24
$[\text{PdCl}_2(\text{dppb})]$	83	82	60
$[\text{PdCl}_2(\text{dppf})]$	95	86	44
$[\text{PdCl}_2\{(-)\text{-diop}\}]$	97	96	62
$[\text{PdCl}_2\{(+)\text{-diop}\}]$	97	96	62

Conditions: substrate = 2.5 mmol; catalytic precursor = 5×10^{-2} mmol; $\text{SnCl}_2 \cdot 2\text{H}_2\text{O} = 2.5$ equiv.; excess of $\text{PPh}_3 = 2$ equiv.; CO pressure = 40 bar; $T = 80$ °C; $t = 16$ h.

Table 2
Palladium-catalysed cyclocarbonylation of isolimonene in toluene (from Ref. [4b])

Complexes	Conversion (%)	Yield (%)	d.e. (%)
$[\text{PdCl}_2(\text{PPh}_3)_2]$	95	86	12
$[\text{PdCl}_2(\text{dppb})]$	75	65	64
$[\text{PdCl}_2(\text{dppf})]$	71	68	69

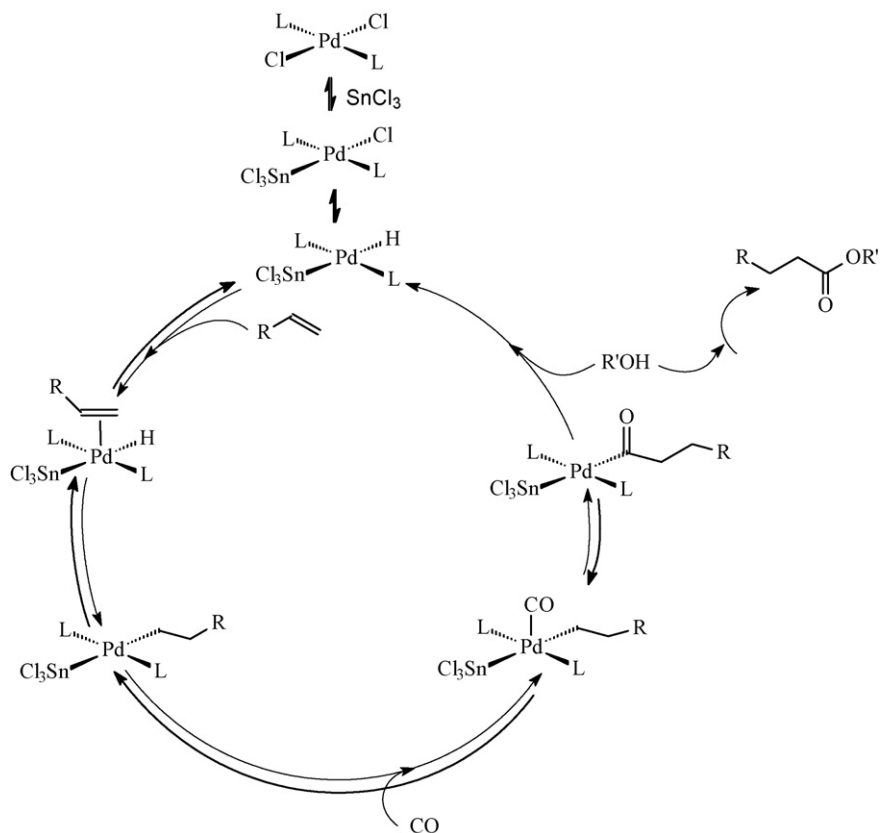
Conditions: substrate = 2.5 mmol; catalytic precursor = 5×10^{-2} mmol; $\text{SnCl}_2 \cdot 2\text{H}_2\text{O} = 2.5$ equiv.; excess of $\text{PPh}_3 = 2$ equiv.; CO pressure = 40 bar; $T = 80$ °C; $t = 16$ h.

Table 3
Cyclocarbonylation of isopulegol catalysed by $\{[\text{PdCl}_2(\text{PPh}_3)_2]/\text{SnCl}_2/\text{PPh}_3\}$ system

Run	Solvent	Reaction time (h)	Conversion (%) ^a	d.e (%)
1	Toluene	2	0	–
2	Toluene	6	11	24
3	Toluene	16	100	24
4	1,2-Dichloroethane	0.33	72	60
5	1,2-Dichloroethane	1	100	61
6	Dichloromethane	2	93	70
7	Acetonitrile	2	61	36
8	Isopropanol	2	25	–8
9	Isopropanol	6	40	–8
10	Isopropanol	16	50	–8
11	THF	2	11	8

Conditions: substrate = 2.5 mmol; catalytic precursor = 5×10^{-2} mmol; $\text{SnCl}_2 \cdot 2\text{H}_2\text{O} = 2.5$ equiv.; excess of $\text{PPh}_3 = 2$ equiv.; CO pressure = 40 bar; $T = 80$ °C.

^a Yield (%).



Scheme 2. proposed catalytic cycle for the palladium(II)-catalysed cyclocarbonylation reaction.

solvent, the palladium(II) precursor is very active as complete conversion is attained within 1 h. In addition, the diastereoselectivity reaches 61% (run 5). Higher selectivities can even be reached using dichloromethane as solvent since run 6 shows a d.e. of 70% after 2 h. By contrast, in coordinating solvents such as acetonitrile, isopropanol or THF, the catalyst is less effective affording both lower conversions (11–61%) and lower diastereoselectivities (–8 to 36%) (runs 7–11). With isopropanol as solvent, the diastereoselectivity changes so dramatically that the other diastereoisomeric lactone **2b** becomes the major product of the reaction (runs 8–10).

Noteworthy, diastereoselectivities are constant during the whole course of the reaction either in toluene (runs 1–3), 1,2-dichloroethane (runs 4–5) and isopropanol (runs 8–10), showing that the same key catalytic species works till the end of the reaction.

These results show that the efficiency of the carbonylation process strongly depends on the nature of the solvent. The best catalyst performances in terms of both activity and diastereoselectivity are obtained when weakly coordinating solvents such as 1,2-dichloroethane or dichloromethane are used (runs 4–6).

In the light of these results, we revisited the cyclocarbonylation reaction of isopulegol in 1,2-dichloroethane using other $[\text{PdCl}_2\text{L}_2]$ palladium complexes (Table 4).

All of these palladium(II) catalytic systems are more active in 1,2-dichloroethane as complete conversions are obtained after 2 or 3 h. In addition better diastereoselectivities are observed.

With the $[\text{PdCl}_2(\text{dppb})]$ complex, the diastereoisomeric excess increases from 60 to 78% when toluene is replaced by 1,2-dichloroethane. A similar increase is observed with the $[\text{PdCl}_2(\text{dppf})]$ complex and the diastereoselectivity is enhanced from 32% in toluene to 66% in 1,2-dichloroethane.

We also studied the cyclocarbonylation reaction of isolimonene in 1,2-dichloroethane in the presence of the same $[\text{PdCl}_2\text{L}_2]$ precursors (Table 5).

When 1,2-dichloroethane is used, activities are only slightly increased, compared to the results in toluene, but chemoselectivities are significantly improved (see runs 15–17 and Table 2), and the cyclopentanones **4a/4b** are almost exclusively produced. The diastereoselectivities are not modified however, except for the case of $[\text{PdCl}_2(\text{PPh}_3)_2]$, for which d.e. increases from 12 (Table 2) to 40% (run 15).

Table 4
Palladium-catalysed cyclocarbonylation of isopulegol in 1,2-dichloroethane

Run	Reaction time (h)	Complexes	Conversion (%) ^a	d.e. (%)
12	2	$[\text{PdCl}_2(\text{PPh}_3)_2]$	99	60
13	3	$[\text{PdCl}_2(\text{dppb})]$	95	78
14	3	$[\text{PdCl}_2(\text{dppf})]$	99	66

Conditions: substrate = 2.5 mmol; catalytic precursor = 5×10^{-2} mmol; $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ = 2.5 equiv.; excess of PPh_3 = 2 equiv.; CO pressure = 40 bar; $T = 80^\circ\text{C}$.

^a Yield (%).

Table 5
Palladium-catalysed cyclocarbonylation of isolimonene in 1,2-dichloroethane

Run	Complexes	Conversion	Yield (%)	d.e. (%)
15	[PdCl ₂ (PPh ₃) ₂]	100	99	40
16	[PdCl ₂ (dppf)]	97	97	60
17	[PdCl ₂ (dppb)]	98	90	64

Conditions: substrate = 2.5 mmol; CO pressure = 40 bar; *T* = 80 °C; 2 equiv. PPh₃; SnCl₂·2H₂O = 2.5 equiv.; *t* = 16 h.

Table 6
Cyclocarbonylation of isopulegol catalysed by [PdCl₂L₂] without extra PPh₃

Run	Solvent	Complexes	Time (h)	Conversion (%) ^a	d.e. (%)
18	Toluene	[PdCl ₂ (PPh ₃) ₂]	16	11	20
19	Dichloromethane	[PdCl ₂ (PPh ₃) ₂]	2	97	70
20	1,2-Dichloroethane	[PdCl ₂ (PPh ₃) ₂]	2	100	70
21	1,2-Dichloroethane	[PdCl ₂ (dppb)]	3	52	85
22	1,2-Dichloroethane	[PdCl ₂ (dppb)]	6	64	87
23	Acetonitrile	[PdCl ₂ (PPh ₃) ₂]	3	33	39

Conditions: substrate = 2.5 mmol; catalytic precursor = 5×10^{-2} mmol; SnCl₂·2H₂O = 2.5 equiv.; CO pressure = 40 bar; *T* = 80 °C.

^a Yield (%).

In toluene, previous studies [4] revealed that the optimal phosphine/palladium ratio is equal to 4 for this cyclocarbonylation reaction. It is worth verifying if the addition of triphenylphosphine and its amount may be crucial when other solvents are employed. Therefore the cyclocarbonylation reaction of isopulegol was carried out in dichloromethane, 1,2-dichloroethane and acetonitrile with the aforementioned palladium complexes without added triphenylphosphine (see Table 6).

Both in toluene and acetonitrile, [PdCl₂(PPh₃)₂] is less active when PPh₃ is not added to the reaction mixture: compare runs 3 and 7 in Table 3 with 2 equiv. of PPh₃ added to runs 18 and 23; with no PPh₃; yet, diastereoselectivities are nearly the same in all the experiments. By contrast in 1,2-dichloroethane or dichloromethane (compare runs 5–6 to runs 19–20) the activity and diastereoselectivity are almost the same in the presence or in the absence of triphenylphosphine, except for 1,2-dichloroethane, in which the diastereoselectivity is slightly improved from 61 to 70% even with no PPh₃ added.

With [PdCl₂(dppb)] the comparison of run 13 to runs 21–22, shows a decrease in activity along with an increase in the diastereoisomeric excess (up to 87%).

3. Concluding remarks

Weakly coordinating solvents, such as 1,2-dichloroethane or dichloromethane, improve the diastereoselectivity induced by the substrate itself.

In view of the strong influence of the solvent on the catalytic performance of isopulegol and isolimonene cyclocarbonylation, we could envisage that one solvent molecule presents a specific interaction with one or several intermediate(s) in the catalytic cycle. In order to get a deeper insight into this peculiar effect, calculations and modelisation studies could be useful along with further experiments that are in progress.

4. Experimental

4.1. General procedure

All reactions were carried out in dried solvents under N₂ atmosphere using standard Schlenk techniques. The catalyst precursor [PdCl₂L₂] (L = PPh₃, L₂ = dppb, dppf) was prepared according to a published procedure [7]. Compounds [PdCl₂], PPh₃, DIOP, dppb, dppf and SnCl₂·2H₂O were purchased from commercial sources and used without further purification. Carbon monoxide (CO, 99.99%) was supplied by Air Liquide. Carbonylation reactions were performed in a 250 ml inox (SOTELEM) autoclave magnetically stirred and electrically heated. The chemical, regioselectivity and diastereoisomeric excess of reactions were determined by gas-chromatographic (GC) analysis on a Perkin-Elmer instrument (split injector, Elite-5 30-m column (i.d. 0.25 mm, film thickness 0.25 μm), 1 bar H₂ as carrier gas, FID detector).

4.2. Typical procedure for cyclocarbonylation reactions

A mixture of [PdCl₂(PPh₃)₂] (35 mg, 0.05 mmol), or [PdCl₂(dppf)] (30.1 mg, 0.05 mmol) or [PdCl₂(dppb)] (33.7 mg, 0.05 mmol), SnCl₂·2H₂O (28 mg, 2.5 mmol) and PPh₃ (26 mg, 0.1 mmol) was introduced into a 250 ml autoclave under magnetic stirring. A solution of isopulegol or isolimonene (2.5 mmol) in the appropriate solvent (10 ml) was introduced into the evacuated autoclave by aspiration and then heated under CO pressure. At the end of the reaction, the autoclave was allowed to cool and then slowly depressurized. The crude mixture was removed from the autoclave and transferred to a Schlenk tube, and then treated with a few drops of CCl₄ to precipitate the palladium complex and the phosphine excess. The yellow to orange colored layer was separated by decantation, and concentrated by evaporation under reduced pressure. The

oily residue was purified by column chromatography on silicagel (petroleum ether/dichloromethane/ethyl acetate, 70:24:6 for cyclopentanone **4**, and hexane/ethylacetate, 96:4 for lactone **2**). The spectroscopic data for **2a** and **2b**, and **4a** and **4b** are consistent with those published in Ref. [4a,b], respectively.

Acknowledgments

The Ministère de l'Éducation Nationale, de la Recherche et de la Technologie is gratefully acknowledged for a research grant to LD. We thank the Institut National Polytechnique de Toulouse (ENSIACET) and the CNRS for financial support.

References

- [1] (a) I. Ojima, *Catalytic Asymmetric Synthesis*, 2nd ed., Wiley-VCH, New York, 2000;
- (b) E.N. Jacobsen, A. Pfaltz, H. Yamamoto, *Comprehensive Asymmetric Catalysis*, Springer-Verlag, Berlin, 1999;
- (c) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994.
- [2] M. Beller, *Catalytic Carbonylation Reactions Topics in Organometallic Chemistry*, 18, Springer-Verlag, Berlin, 2006.
- [3] (a) D.H. Nguyen, F. Hebrard, J. Duran, A. Polo, M. Urrutigoity, Ph. Kalck, *Appl. Organomet. Chem.* 19 (2005) 30;
- (b) S. Sirol, Ph. Kalck, *New J. Chem.* 21 (1997) 1129.
- [4] (a) G. Lenoble, R. Naigre, T. Chenal, M. Urrutigoity, J.C. Daran, Ph. Kalck, *Tetrahedron Asymmet.* 10 (1999) 929;
- (b) G. Lenoble, C. Lacaze-Dufaure, M. Urrutigoity, C. Mujoule, Ph. Kalck, *Eur. J. Inorg. Chem.* (2004) 791.
- [5] Ph. Kalck, M. Urrutigoity, *Coord. Chem. Rev.* 248 (2004) 2193.
- [6] H. Nguyen, G. Laurenzy, M. Urrutigoity, Ph. Kalck, *Eur. J. Inorg. Chem.* (2005) 4215.
- [7] D.R. Coulson, *Inorg. Synth.* 13 (1972) 121.