

Application of molten salts in hydroalkoxycarbonylation of styrene

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Abstract

Hydroalkoxycarbonylation of styrene using palladium-based catalyst was studied in quaternary ammonium salts as reaction media. Under the reaction conditions applied, the catalyst-containing phase can be reused several times without a significant decrease in activity and selectivity as a function of the precursor and the halide counter ion used.

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1. Introduction

Due to its important industrial potential, transition-metal catalyzed carbonylation of olefins has been subject of interest in the last decades [1–3]. When used as substrate, styrene affords 2-arylpropionic esters, precursors of important anti-inflammatory agents [4]. In conventional organic solvents, the reaction can be carried out with very good chemo- and regioselectivities towards the target product, using palladium salts and a variety of mono- and bidentate phosphine ligands [5–7]. However, the problem of product isolation, catalyst recovery and losses by black palladium have been challenges for chemists. Ionic liquids – recognized as a novel class of environmental-friendly solvents – may constitute an alternative averting the imperfections of homogeneous catalysis. Nevertheless, they still have some deficiencies compared to the original reaction, mainly as regards catalyst activity and selectivity [8–10].

Although hydroformylation in ionic liquids was described as early as 1972 [11] and progressed intensively in the last decade [12–14] much less attention has been focused on palladium-catalyzed Reppe-type carbonylation. As only relevant example biphasic hydroesterification of styrene in 1-butyl-3-methylimidazolium/bmim/-salt and cyclohexane has been reported [15]. Despite of the remarkably high regioselectivities

(>99% iso product) obtained under mild conditions, formation of black palladium was observed.

In order to take advantage of the potential of green solvents we have focused mainly on the class of the quaternary ammonium salts as relatively cheap and easily manageable materials [16–18]. For our hydroalkoxycarbonylation experiments presented here we chose styrene as a substrate of potential pharmacological interest.

2. Experimental

2.1. Materials

Tetrabutylammonium bromide (Fluka, ≥98.0%, m.p. 101–103 °C) and chloride (Fluka, ≥97.0%, water content ≤1%), tetrabutylphosphonium bromide (Fluka, ≥98.0%), [bmim][BF₄] (Fluka, ≥97%, halogens ≤100 mg/kg), [bmim][PF₆] (Fluka, ≥96%), [bmim][Cl] (Fluka, ≥95%, m.p. ≈55 °C), [bmim][Br] (Fluka, ≥97%, m.p. ≈70 °C), styrene, PdCl₂, PdBr₂, triphenylphosphine (TPP), DIOP, tris(3-sulfophenyl)phosphine trisodium salt (TPPTS) and anhydrous CuCl₂ were commercially obtained from Sigma–Aldrich. Styrene was distilled prior to use, methanol was dried following the usual protocol and kept under argon, tetrabutylammonium bromide and chloride were crystallized from acetone/ether=2/1. Pd(PPh₃)₂Cl₂ was prepared according to published procedure [19].

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^{31}P NMR spectra were recorded in CDCl_3 or in molten salt phase (these latter were measured at 120°C) on a Varian Unity 300 (Palo Alto, CA) spectrometer at 121.4 MHz. GLC analyses were performed on a Hewlett-Packard 5917 gas chromatograph fitted with a 10 m HP-1 column. The ICP measurements were carried out on a Jobin Yvon instrument model Ultima (Horiba Group) with ultrasonic nebulizer. All manipulations related to synthesis steps were performed under argon using standard inert techniques.

2.2. Typical procedure

An amount of 4 g NBu_4Br or NBu_4Cl and 0.05 mmol PdCl_2 or PdBr_2 , respectively were weighed into a Schlenk tube under argon atmosphere. The mixture was stirred magnetically and heated in a 120°C oil bath until complete solvation of the precursor (deep red liquid). Then 0.1 mmol CuCl_2 and 0.2 mmol phosphine (or 0.1 mmol bis-phosphine) were added successively and the solution was stirred for 30 min. After cooling the resulted yellow pre-formed catalyst was used later as indicated. The pre-formed catalyst–salt mixture, 4 mmol styrene and 6 mmol alcohol were added into a 20 ml stainless steel autoclave which was then sealed and pressurized with 50 bar of CO and stirred magnetically at $108\text{--}110^\circ\text{C}$. When BMIM-type salts were used, all the components, including the catalyst precursor and the ionic liquid were added directly into the autoclave due to the low initial solubility of the palladium salts in the solvent. After 24 h the reaction vessel was cooled and $4 \times 5\text{ mL}$ portions of hexane were added for extraction of the products. The hexane fractions were combined, concentrated and analyzed by GC. The residual ammonium salt containing the catalyst precursor was recovered by decantation and reused in the following catalytic cycle. For BMIM-salts liquid–liquid extractions with hexane were applied. The palladium content of the products isolated was measured by ICP and it was found to be under the limit of quantification of the instrument in each case when NBu_4Br was used.

3. Results and discussion

Given the relatively high melting point of the ammonium salts used, hydroalkoxycarbonylation of styrene was carried out at 110°C starting with either $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ or an in situ system ($\text{PdCl}_2/\text{PPh}_3/\text{CuCl}_2$) [20] and pre-formed catalyst–salt mixtures as reaction media. Almost complete conversion and acceptable regioselectivity (Table 1) can be reached in both ammonium and phosphonium salts with the copper-containing system, while the other precursor leads to lower performances and palladium black formation. The optimal reaction conditions, i.e. CO pressure, Pd/Cu/P and substrate/alcohol ratios were determined previously. Practically no ether by-product formation could be noticed, as shown previously by Yun et al. [20]. Although not completely clarified, the role of copper in this system seems to be rather a re-oxidation of the palladium than formation of a bimetallic complex [6,21–23]. Our own ^{31}P NMR experiments did not support either the presence of copper in the coordination sphere of the palladium.

Substitution of PPh_3 to DIOP in the system above results in an undesired inversion of regioselectivity. Despite of a better solubility of TPPTS in the ionic liquids, a much lower conversion and regioselectivity was obtained. The reactions were carried out similarly in BMIM-type ionic liquids, the use of which resulted in all the cases in abundant palladium black precipitation and disappointingly low conversions, which can be accommodated in terms of the palladium-carbene formation observed by Herrmann et al. [24]. No improvement was achieved either when biphasic reactions were carried out. Due to its low solubility, the Pd/Cu system could not be employed successfully in these cases. It should be pointed out that carbonylation carried out in NBu_4Br demands a very precise control of both catalyst-containing salt pre-formation and reaction conditions. Every deviation from the standard protocol resulted in a sensible modification of conversion and regioselectivity, which was not characteristic for the BMIM-type media. When the bromide-salt was replaced by NBu_4Cl , this peculiarity of the reaction was not remarked any

Table 1
Hydroalkoxycarbonylation of styrene in ionic liquids using palladium-based catalysts

Nr. crt.	Catalyst precursor	Reaction medium	Conversion (%)	Regioselectivity ^a (%)
1 ^b	$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$	NBu_4Br	94.8	74
2 ^b	$\text{PdCl}_2/\text{CuCl}_2/\text{PPh}_3$	NBu_4Br	100	78
3 ^b	$\text{PdCl}_2/\text{CuCl}_2/\text{PPh}_3$	$\text{NBu}_4\text{Br}/\text{cyclohexane}$	98	78
4 ^b	$\text{PdCl}_2/\text{CuCl}_2/\text{DIOP}$	NBu_4Br	100	12
5 ^b	$\text{PdCl}_2/\text{CuCl}_2/\text{TPPTS}$	NBu_4Br	36	42
6 ^b	$\text{PdCl}_2/\text{CuCl}_2/\text{PPh}_3$	PBu_4Br	100	78
7 ^c	$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$	$[\text{bmim}][\text{BF}_4]$	48	92.3
8 ^c	$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$	$[\text{bmim}][\text{PF}_6]$	18	89
9 ^c	$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$	$[\text{bmim}][\text{BF}_4]/\text{cyclohexane}$	56	90.6
10 ^c	$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$	$[\text{bmim}][\text{PF}_6]/\text{cyclohexane}$	7	91
11 ^c	$\text{PdCl}_2/\text{CuCl}_2/\text{PPh}_3$	$[\text{bmim}][\text{BF}_4]$	30	93
12 ^c	$\text{PdCl}_2/\text{CuCl}_2/\text{PPh}_3$	$[\text{bmim}]\text{Cl}$	7	100
13 ^c	$\text{PdCl}_2/\text{CuCl}_2/\text{PPh}_3$	$[\text{bmim}]\text{Br}$	–	–

^a Data based on GC: $[\text{iso}/(\text{iso} + \text{normal ester})] \times 100$.

^b Reaction conditions: see typical procedure.

^c Reaction conditions: 0.05 mmol Pd-salt, 2 ml $[\text{bmim}]$ -salt, 4 mmol styrene, 6 mmol MeOH and 2 ml cyclohexane (lines 9 and 10).

Table 2

Hydroalkoxycarbonylation of styrene in tetrabutylammonium salts containing chloride/bromide counterions

Nr. crt.	Catalyst precursor	Reaction medium	Conversion (%)	Regioselectivity (%)
1	PdCl ₂ /CuCl ₂ /PPh ₃	NBu ₄ Br	100	78
2 ^a	PdCl ₂ /CuCl ₂ /PPh ₃	NBu ₄ Cl	82	96
3	PdBr ₂ /CuCl ₂ /PPh ₃	NBu ₄ Cl	98	96
4	PdBr ₂ /CuCl ₂ /PPh ₃	NBu ₄ Br	34	68

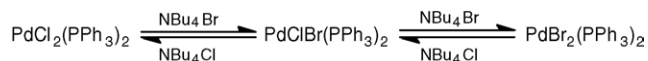
Reaction conditions: see typical procedure.

^a After 36 h reaction time.

more. On the basis of these observations we examined the effect of different anion combinations changing halides both in catalyst precursors and salts (Table 2). Although, the use of NBu₄Cl improves regioselectivity, it is deleterious from the point of view of conversion. The reaction slows further if bromides are used exclusively.

In order to gain an insight into the processes governing the pathways leading to the differences above, we carried out some ³¹P NMR experiments using the palladium and ammonium salts from above. The experiments were carried out in two different manners: both by investigating the effect of the ammonium salts successively added to a catalyst precursor solution and by examining the molten salts resulting from a reaction cycle.

As shown in Fig. 1a, on adding the first portion of NBu₄Br to the solution, two new signals appear at 23.2 and 22.1 ppm [this corresponding to Pd(PPh₃)₂Br₂] beside the signal given by the pure Pd(PPh₃)₂Cl₂ at 23.4 ppm. At the same time, the bright yellow solution turns to orange and some orange precipitate can be seen in the tube. The signal at 23.2 ppm can be assigned to the Pd(PPh₃)₂ClBr resulting in an equilibrium which is supposed to take place in the following way.



As more NBu₄Br is added, a shift of the equilibrium is observed towards the Pd(Br, Br) species developing by the intermediacy of Pd(Cl, Br). The same tendency is proved in the case of NBu₄I, while the NMR spectrum remains unchanged if NBu₄Cl is added.

The signals belonging to the species above are slightly shifted when they are examined in molten salt (Fig. 2). After two reaction cycles the same palladium complexes can be identified in the catalytically still active mixture when starting from Pd(Cl, Cl) and NBu₄Br (Fig. 2). As obvious from the spectra presented, the equilibrium, which is instantaneous in CHCl₃ (Fig. 1), is considerably slower in molten salt medium, completing only after many reaction cycles. The entire transformation of the chloride-containing Pd-species into Pd(Br, Br) takes place parallel with the observed lose in catalyst activity. This slow Cl–Br exchange in the coordination sphere of the palladium is supposed thus to be one of the reasons of the observed enhancement in catalyst activity compared to the PdBr₂/NBu₄Br and PdCl₂/NBu₄Cl systems which induce a much slower carbonylation reaction (see Table 2). The anion exchange, also taking place if the precursor

is Pd(Br, Br) dissolved in NBu₄Cl, seems to be relatively fast, ending by a predominance of Pd(Cl, Cl) species after a shorter period. The absence of the halide substitution is presumed to be related, again, to lower conversions already from the second cycle.

In addition, when the same anion is present both in the palladium precursor and the salt, the regioselectivity remains

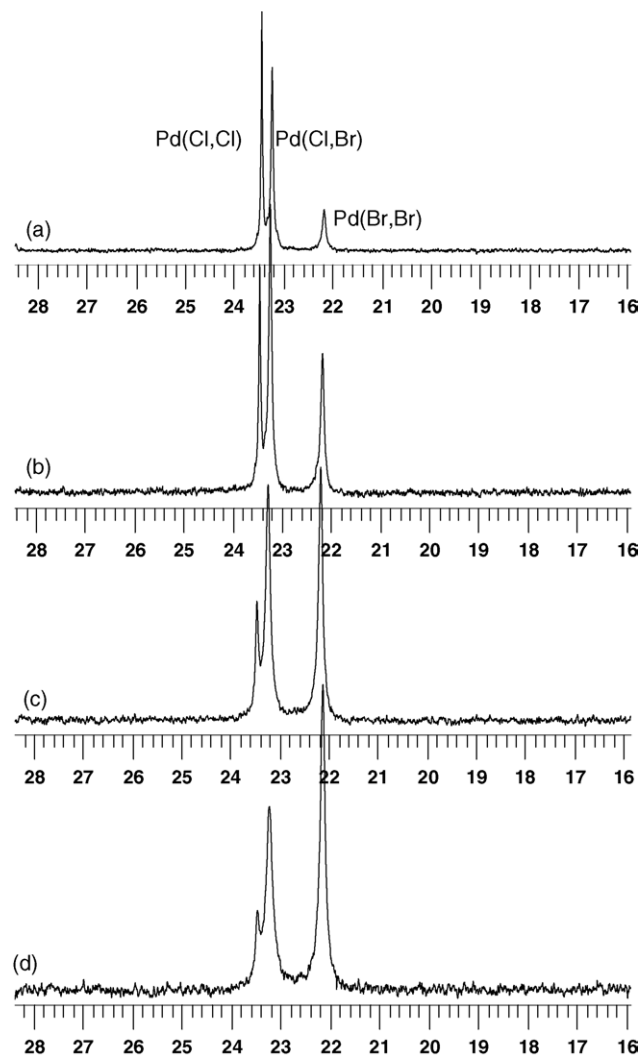


Fig. 1. ³¹P NMR spectra of the Pd(PPh₃)₂Cl₂ in CDCl₃: (a) 4.5 mg NBu₄Br added; (b) 11 mg NBu₄Br added; (c) 25 mg NBu₄Br added; (d) 46 mg NBu₄Br added to the solution.

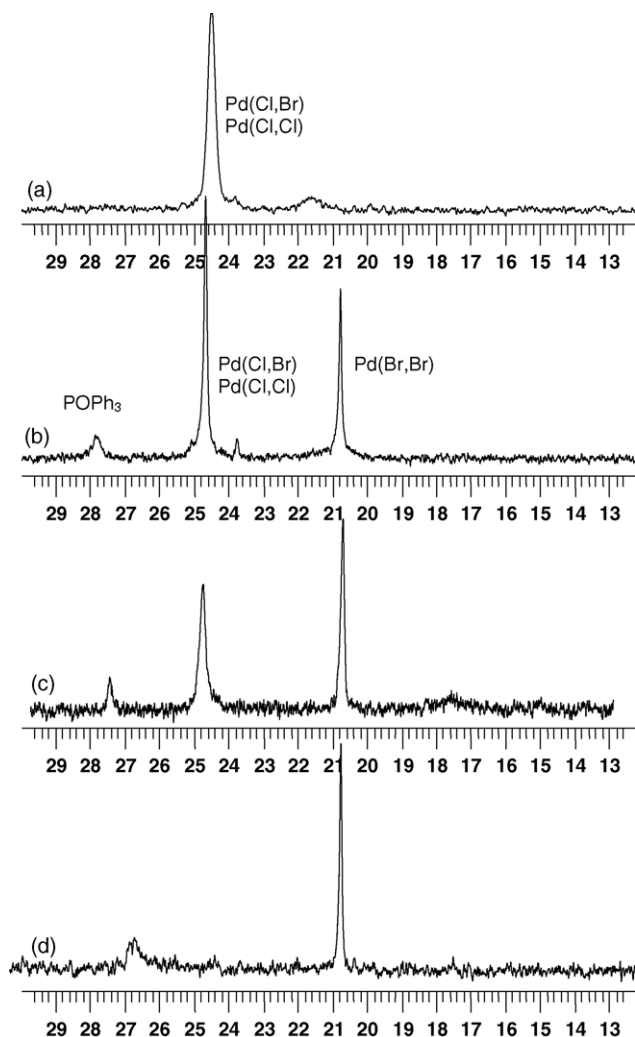


Fig. 2. ^{31}P NMR spectra of the reaction mixture: (a) before the reaction; (b) after one cycle; (c) after two cycles; (d) after the last cycle.

unchanged during recycling as also happens in the reaction carried out in $\text{PdBr}_2/\text{NBu}_4\text{Cl}$. On the other hand, by using $\text{PdCl}_2/\text{NBu}_4\text{Br}$ an enhanced reaction rate is combined with a decay of regioselectivity during the cycles. In our opinion, the spectroscopically proved slow $\text{Cl}-\text{Br}$ exchange amplifies the role of the $\text{Pd}(\text{Cl}, \text{Br})$ species which influences thus the performance of the reaction in a major way. The sufficiently long lifetime of this complex enables a higher conversion at the expense of regioselectivity. This phenomenon is believed to induce an unusual increase of the regioselectivity towards the branched ester [25] during more reaction cycles using DIOP as ligand (Fig. 3).

The recycling of the systems above was also tested (Fig. 3) and seems to depend as well on the halides present. The best performances were registered in our basic reaction, while the other systems were less efficient after the first cycle. The palladium leakage in the isolated products was also satisfactorily low after each reaction cycle and black palladium was not formed.

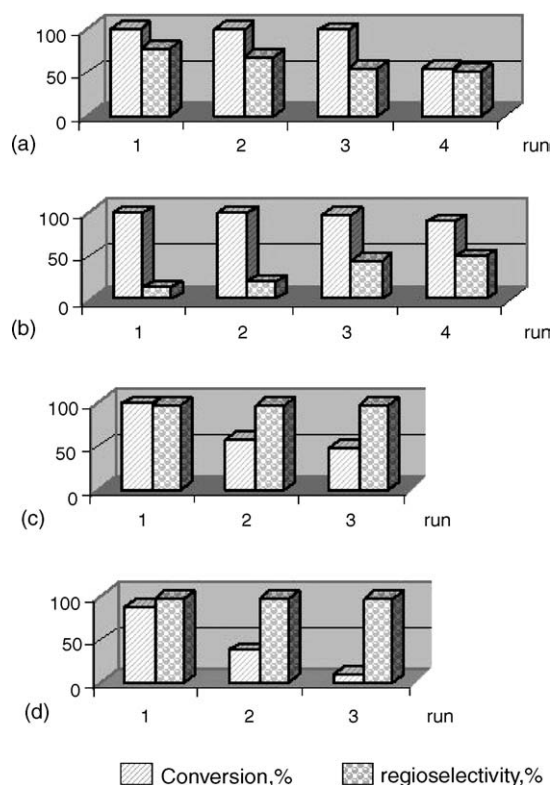


Fig. 3. Recycling of the catalyst-containing ionic liquids: (a) $\text{NBu}_4\text{Br}/\text{PdCl}_2/\text{CuCl}_2/\text{PPh}_3$ system; (b) $\text{NBu}_4\text{Br}/\text{PdCl}_2/\text{CuCl}_2/\text{DIOP}$ system; (c) $\text{NBu}_4\text{Cl}/\text{PdBr}_2/\text{CuCl}_2/\text{DIOP}$ system; (d) $\text{NBu}_4\text{Cl}/\text{PdCl}_2/\text{CuCl}_2/\text{PPh}_3$ system.

4. Conclusions

Hydroalkoxycarbonylation of styrene in ionic liquids was investigated using palladium catalysts. The reaction was performed with good conversion, chemo- and regioselectivity in molten ammonium and phosphonium salts. The reaction media could be used during some more cycles without significant palladium contamination of the product. An anion exchange between the starting palladium precursor and the ammonium salt is supposed to influence the outcome of carbonylation leading to an improved reaction rate and a lower regioselectivity in the case of a $\text{PdCl}_2/\text{PPh}_3/\text{CuCl}_2-\text{NBu}_4\text{Br}$ system. The chloride–bromide exchange in the coordination sphere of the palladium was followed and proved by ^{31}P NMR spectroscopy.

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References

- [1] M. Beller, C. Bolm, *Transition Metals for Organic Synthesis*, vols. 1–2, Wiley-VCH, New York, 1998.
- [2] G. Kiss, *Chem. Rev.* 101 (2001) 3435.
- [3] *Applied Catalysis with Organometallic Compounds*, Second and Completely Revised and Enlarged Edition, 2002.
- [4] J. Tsuji, *Palladium reagents and catalysts*, Wiley (1995).

- [5] S. Oi, M. Nomura, T. Aiko, Y. Inoue, *J. Mol. Catal. A: Chem.* 115 (1997) 289.
- [6] H. Zhou, J. Hou, J. Cheng, S. Lu, H. Fu, H. Wang, *J. Organomet. Chem.* 543 (1997) 227.
- [7] C. Benedek, G. Szalontai, Á. Gömöry, S. Törös, B. Heil, *J. Organomet. Chem.* 579 (1999) 147.
- [8] H. Zhao, S.V. Malhotra, *Aldrichim. Acta* 35 (2002) 75.
- [9] D.E. Kaufmann, N. Nouroozian, H. Henze, *Synth. Lett.* (1996) 1091.
- [10] T. Welton, *Coord. Chem. Rev.* 248 (2004) 2459.
- [11] G.W. Parshall, *J. Am. Chem. Soc.* 94 (1972) 8716.
- [12] C.M. Gordon, *Appl. Catal. A: Gen.* 222 (2001) 101.
- [13] P. Wasserscheid, T. Welton, *Ionic Liquids in Synthesis*, Wiley-VCH, Weinheim, 2003.
- [14] P. Wasserscheid, W. Keim, *Angew. Chem. Int. Ed.* 39 (2000) 3772.
- [15] D. Zim, R.F. de Souza, J. Dupont, A.L. Monteiro, *Tetrahedron Lett.* 39 (1998) 7071.
- [16] J.F. Knifton, *J. Mol. Catal.* 43 (1987) 65.
- [17] N. Karodia, S. Guise, C. Newlands, J.A. Anderson, *Chem. Commun.* (1998) 2341.
- [18] K. Selvakumar, A. Zapf, M. Beller, *Org. Lett.* 4 (2002) 3031.
- [19] H. Itatani, J.C. Bailar, *J. Am. Oil Chem. Soc.* 44 (1967) 147.
- [20] H.S. Yun, K.H. Lee, J.S. Lee, *J. Mol. Catal. A: Chem.* 95 (1995) 11.
- [21] H. Alper, J.B. Woel, B. Despeyroux, D.J.H. Smith, *J. Chem. Soc. Chem. Commun.* (1983) 1270.
- [22] H. Alper, F.W. Hartstock, B. Despeyroux, *J. Chem. Soc. Chem. Commun.* (1984) 905.
- [23] H. Alper, D. Leonard, *J. Chem. Soc. Chem. Commun.* (1985) 511.
- [24] W.A. Herrmann, K. Öfele, D.V. Preysing, S.K. Schneider, *J. Organomet. Chem.* 687 (2003) 229.
- [25] G. Consiglio, M. Marchetti, *Chimia* 30 (1976) 26.