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Multiphase Systems for the Recycling of Alkoxycarbonylation Catalysts

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Abstract: This review evaluates the various multiphasic systems that have been developed for catalyst recycling in the context of alkoxycarbonylation of alkenes and alkynes. Immobilization of the catalyst on an insoluble support, such as silica, alumina, clay or a polymer, as well as immobilization in the inorganic phase of several liquid/liquid biphasic systems (aqueous/organic, ionic liquid/organic, fluorous/organic or supercritical CO_2/organic) has been described. In several cases detailed information on the efficiency of catalyst separation and recycling is available. Most of the work was focused on the alkoxycarbonylation reactions of alkenes, for which several efficient methods for catalyst recycling were demonstrated. The recycling of catalyst through specific precipitation from supercritical CO_2 or selective dissolution in a fluorous phase, has received only scant attention but offers many opportunities for further improvement.

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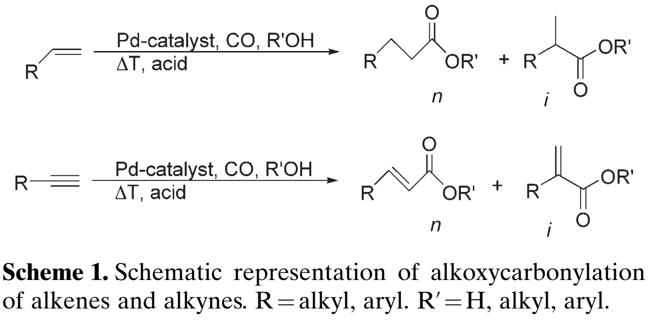
Keywords: alkenes; alkoxycarbonylation; alkynes; multiphase catalysis; recycling

1 Introduction

Nowadays, the alkoxycarbonylation[1] of alkenes and alkynes is a well-known process that is of interest to both academia and industry. In this reaction the unsaturated hydrocarbon is reacted with CO and an oxygen nucleophile (water or an alcohol) to produce the corresponding carboxylic acid derivatives (Scheme 1). The reaction is highly atom-efficient and as such fulfills the requirements of what is considered to be a sustainable chemical process. Complexes of several transition metals, in particular Ru, Pd, Pt or Co, catalyze alkoxycarbonylation reactions. Among these metal complexes, palladium/phosphine complexes are most frequently applied, because they afford high activity and selectivity under relatively mild conditions.[1]

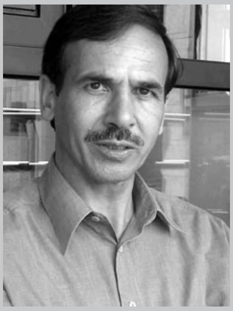
Alkoxycarbonylation of aryl-substituted alkenes and alkynes is especially relevant because the products formed are precursors to the important class of non-steroidal anti-inflammatory drugs (NSAIDs) such as Ibuprofen, Ketoprofen and Naproxen. For Naprox-



Scheme 1. Schematic representation of alkoxycarbonylation of alkenes and alkynes. R = alkyl, aryl. R' = H, alkyl, aryl.

Jeroen J. M. de Pater was born on March 12, 1977 in Gouda, The Netherlands. He received his "doctorandus" title (with distinction) in August 2000 from Utrecht University, after doing a major in the group for Organic Chemistry and Catalysis (with Prof. G. van Koten) on the preparation and application of perfluoroalkyl-functionalized *meta*-substituted triarylphosphine ligands. Subsequently, he did his PhD studies from September 2000 until November 2005 in the same group, in collaboration with the group for Molecular Inorganic Chemistry (with Prof. C. J. Elsevier), University of Amsterdam, on the subject of methoxycarbonylation reactions of alkenes and alkynes with fluorous palladium complexes. He obtained his PhD degree on November 7, 2005. From July until November 2005 he was employed as a post-doctoral researcher on a project for Ciba Specialties Inc. (Dr. A. Hafner, Dr. R. Pretôt). As of February 1, 2006, he accepted a position as research chemist at ARKEMA Vlissingen B.V.

Berth-Jan Deelman was born in 1966 in Groningen, The Netherlands. He obtained his PhD degree in 1994 from the University of Groningen where he had been working on reactivity studies of organometallic compounds of the lanthanides and yttrium (with Prof. J. H. Teuben). He then accepted a post-doctoral position at the University of Sussex, Brighton, UK (with Prof. M. F. Lappert) where he developed new non-cyclopentadienyl catalysts for olefin polymerization. Since 1996 he has been employed with ARKEMA Vlissingen B.V. where he currently holds the position of New Product Development Manager and he is head of the Process Development Group of Arkema Vlissingen. Since 1996 he has held a part-time lectureship position and, more recently, an associate professorship at Utrecht University. His research interests include the design of homogeneous catalysts for industrially relevant chemical processes, in particular for the production of organotins, combining rational design with high throughput screening methods in catalyst development, fluorous catalysts, fluorous biphasic catalyst recycling of homogenous catalysts and catalysis in unconventional reaction media.



Kees Elsevier was born in 1957 in Den Haag, The Netherlands. He obtained his masters and PhD in chemistry at Utrecht University (1984) with Dr. P. Vermeer and Professor H. J. T. Bos, on the topic of "transition-metal mediated synthesis of chiral allenes". Subsequently he moved to the University of Amsterdam, where he has developed his interests in organometallic chemistry and catalysis employing late transition-metal compounds. He became associate professor in 1991. He occupied the John van Geuns chair for developing transition-metal NMR spectroscopy from 1995 till 1999. Since 1999 he holds the chair of Molecular Inorganic Chemistry at the University of Amsterdam. He has been visiting professor twice at the Weizmann Institute of Science, Israel, and at the Universities of Strasbourg and Toulouse (France). He is co-author of about 180 scientific papers on various topics in organometallic chemistry, homogeneous catalysis, and (transition metal) NMR spectroscopy, including contributions to several books. He has lately focused on Pd-catalyzed hydrogenations, involving N-ligands and N-heterocyclic carbenes, as well as catalysis involving aggregates (micelles and vesicles) of metallo-amphiphiles. He has supervised 20 PhD graduates. Kees serves on the advisory board of several scientific journals and he is scientific director of the Holland Research School of Molecular Chemistry.

Gerard van Koten has been Professor of Organic Chemistry and Catalysis at the Debye Institute of the Utrecht University since 1986. In 2004 he became Distinguished Professor of the Utrecht University. In 2002 he was appointed by the Minister of Education, Culture and Science as chairman of the committee responsible for the renewal of the Chemistry Educational Programme at the Secondary School level in the Netherlands. From 2005 on he acts as Dean of the Utrecht Faculty of Science. He has been a member of COST Chemistry from 1995 on, served as Chairman of the TC Chemistry from 2000 to 2003 and is presently member of the Executive Board of the TC. His research interests comprise the study of fundamental processes in organometallic chemistry and the application of organometallic complexes as homogeneous catalysts. The preparation and use of the first examples of homogeneous metallodendrimer catalysts demonstrate his interest in supramolecular systems with (organometallic) catalytically active functionalities. He is author of more than 700 papers and 23 patents.

en a process which involves two palladium-catalyzed steps, starting from 2-bromo-6-methoxynaphthalene, has been patented. In the second step, a palladium-catalyzed carbonylation is used.[2] Since these products are used as drugs it is important that they are completely devoid of even traces of the used metal catalyst. In addition, interest into efficient catalyst recycling is stimulated by the fact that the metal catalyst is often expensive and has to be applied at relatively high catalyst loadings (0.1–5 mol%) to achieve high conversion of the substrate within reasonable reaction times. Therefore, separation and recycling of the catalyst from the reaction mixture are important issues that should be solved if alkoxycarbonylation is to be applied on a larger scale. Consequently, over the last decade a significant research effort has been devoted to finding adequate catalyst recycling methods.

In general, several methods exist for the recycling of a homogeneous catalyst. Firstly, immobilization of the homogenous catalyst on an insoluble support (e.g., silica, alumina) can be used.[3] In these cases the catalyst can be separated from the reaction mixture *via* a simple filtration.[4]

Secondly, attachment of the homogeneous catalyst is possible on macromolecular supports which are soluble in organic solvents and can be separated through nanofiltration.[4] Examples include attachment to dendrimers,[5] polymers[6] and rigid (fluoro)-organic backbones.[7]

Thirdly, the use of biphasic systems, such as aqueous biphasic systems[8] or fluorous biphasic systems, is chosen.[9] These systems consist of two phases, one composed of a common organic solvent and the second one of either water (aqueous biphasic) or a perfluoroalkane (fluorous biphasic). With these systems the homogeneous catalyst is functionalized with specific groups, which make the catalyst preferentially soluble in the second (aqueous or fluorous) phase. Catalyst recycling can be achieved *via* phase separation and re-use of the catalyst-containing phase. This category also includes the use of ionic liquids and supercritical CO_2, two recently used solvent systems that combine potential for catalyst recycling with being environmental friendly solvents.

To achieve effective recycling a number of conditions have to be met. The catalyst must be stable during both the reaction and the separation procedure. Ideally, catalyst leaching and, when using fluorous biphasic systems, leaching of fluorous solvent into the product solution must be prevented. In addition, the activity and selectivity of the catalyst should not be significantly affected when applying any of the above-mentioned immobilization approaches.

In this review we give an overview of recent advances made in the application of the different recycling techniques to the alkoxycarbonylation of alkenes and alkynes. Only palladium-based catalyst systems will be considered as essentially no work was done on catalyst recycling for other metals.

2 Alkoxycarbonylation and Recycling using Catalysts Immobilized on Insoluble Supports

The use of (in)organic materials, like silica, alumina and polymers, as supports for immobilizing homogeneous catalysts has been extensively studied after reports about the first successful applications appeared in the literature in the 1980s.[10] When inorganic supports are used the homogeneous catalyst is usually attached to this support material *via* so-called linkers. These linkers, besides acting as a means to attach the catalyst to the support, also have the advantage that the individual catalyst sites can be separated from each other, thus preventing possible intermolecular aggregation. Linkage of homogeneous catalysts to polymer supports is usually achieved by modifying the catalyst or one of its ligands with a polymerizable group, which can then be incorporated into the polymeric support material *via* simple polymerization techniques.

2.1 Immobilization on Silica and Montmorillonite

The first report on the use of an inorganic support in alkoxycarbonylation reactions appeared in 1991, when Crocker and Herold reported on the methoxycarbonylation of ethene by using Pd(II) complexes, such as $[Pd(PPh_3)_3(NCMe)]^{2+}$ and $[Pd(H_2O)_4]^{2+}$, that where intercalated in Montmorillonite-type clays by an ion exchange process.[11] Several different types of clay were used and it was observed that acidic clays had a promoting effect on the methoxycarbonylation reaction of ethene, reaching a maximum turnover rate of 115 mol product/(mol Pd·h). A couple of years later Alper et al. reported on the use of $[Pd(OAc)_2]$, immobilized on Montmorillonite clay.[12] This system displayed, with PPh_3 added as the phosphine ligand, a good activity and high selectivity towards formation of the *branched* ester under relatively mild conditions. They also investigated the influence of several reaction conditions (Pd/P ratio, effect of added acid) and tried different solvents to optimize the methoxycarbonylation reaction of styrene. Best results (activity and selectivity) were obtained with aromatic solvents such as benzene and toluene, giving high conversion and complete selectivity towards the *branched* product. Also other alkene substrates (with aliphatic as well as aromatic substituents) could be methoxycarbonylated efficiently. No example of catalyst recycling, however, was given in these two reports.

In 1997 Nozaki and co-workers reported on the activity and selectivity of Montmorillonite-diphenylphosphine-palladium(II) chloride complexes in the presence of chiral phosphines (Figure 1) for the asymmetric methoxycarbonylation of styrene.[13]

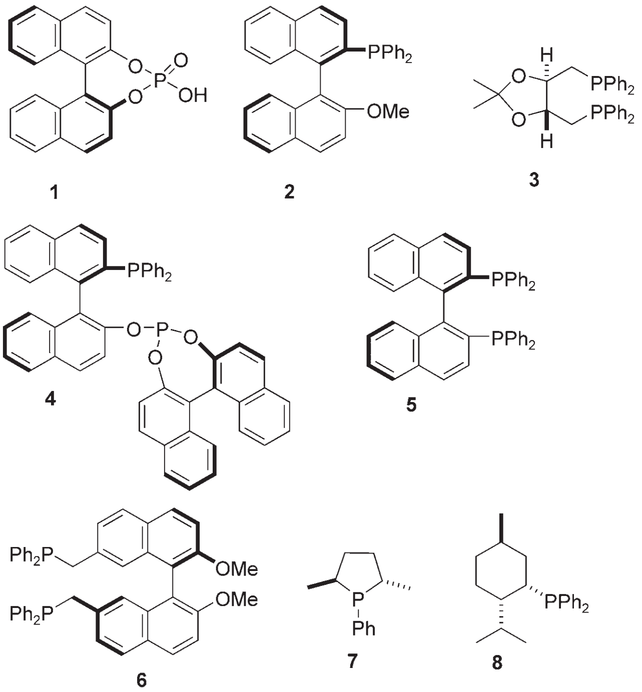


Figure 1. Chiral phosphines used by Nozaki et al. in combination with Montmorillonite.[13]

With some of the ligands good conversions [up to a turnover number (TON) of 500 mol substrate in 24 h] were observed, with excellent regioselectivity towards the *branched* product (more than 99%). However, the enantioselectivity was very low with only a few percent *ee* and a maximum of 12.0% with ligand **6**. Most interestingly, in all cases the non-immobilized homogeneous catalysts performed less well in terms of both activity and enantioselectivity. The catalytic system with the chiral ligand **8** was recycled, but each re-use led to a strong decrease in activity (TON of 385 in the first cycle and 165 in the second cycle).

Chaudhari et al. immobilized a pyridine-carboxylato-based palladium catalyst on both MCM-41 and MCM-48, which were modified with 3-aminopropyltrimethoxysilane to afford binding with the palladium complex (Figure 2).[14] These immobilized catalysts showed good activity [turnover frequency (TOF) up to 2600 h^{-1} with styrene as the substrate] and high selectivity (>99%) for the *branched* product when applied in the hydroxycarbonylation of styrene and 4-methylstyrene. Analysis of the still warm reaction mixture directly after filtration showed a very low degree (0.7 ppm) of palladium leaching. The immobilized catalysts were recycled three times without any apparent drop in activity or selectivity.

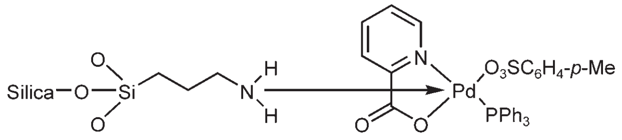
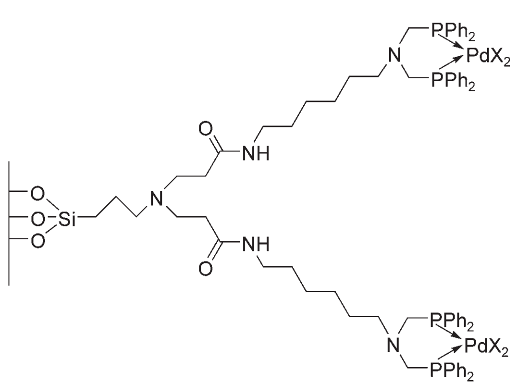


Figure 2. Immobilization of palladium catalysts on silica, as reported by Chaudhari et al.[14]

Zhang and Xia used a silica-supported chitosan-palladium complex in the alkoxycarbonylation of 6-methoxy-2-vinylnaphthalene.[15] They characterized the supported catalysts *via* TEM measurements, which showed an even dispersion of nanoparticles on the carrier surface. In catalysis, using dioxane as solvent, the use of several different alcohols did not affect the reaction rate, whereas selectivity towards the *branched* product was highest (95.3%) when methanol was present as alcohol. Addition of metal salts gave an improvement of the conversion. With 6-methoxy-2-vinylnaphthalene as a substrate, the catalyst was recycled three times; each cycle showed a decreased activity and selectivity, most likely due to the formation of inactive palladium clusters. Addition of *p*-benzoquinone prevented the formation of such clusters and restored the activity.

Reynhardt and Alper reported on the immobilization of palladium-complexes containing PAMAM dendrimers on silica and their use in the methoxycarbonylation of 1-decene in 2003.[16] Several palladium precursors as well as generations G(0) to G(4) PAMAM dendrimers were applied [see Figure 3 for a drawing of the G(1) palladium catalyst (**10**)]. Addition of free PPh$_3$ was needed in order to obtain a stable complex that could be recycled several times (up to five cycles), with the G(1) catalysts showing the best recycling (Table 1, entry 1). However, a significant loss of activity was observed after each recy-



X = Cl, OAc, (dba)$_{0.5}$, PPh$_3$ **10**

Figure 3. G(1) palladium catalysts immobilized on silica.[16]

Table 1. Recycling test[a] of G(1)–G(4) $Pd(PPh_3)_2$ catalysts in hexane/MeOH.[16]

Entry	Generation	Conversion [%] Run 1	Run 2	Run 3	Run 4	Run 5
1	1	87	73	61	55	44
2	2	87	78	55	36	
3[b]	1	>99	53	33		
4[b]	2	>99	83	57	35	
5[b]	3	>99	86	29		
6	3	83	84	36		
7	4	89	72	53	37	
8[b]	4	92	75	73	45	

[a] *Conditions:* 50 mg of catalyst (4.5 μmol of Pd), PPh_3 (25 equivs.), *p*-toluenesulfonic acid (35 equivs.), 1-decene (160 equivs.), hexane/MeOH (1:1 mixture, 5 mL), $P_{CO}=150$ psi, $T=115\,°C$, $t=22$ h.

[b] Hexane/MeOH (1:1 mixture, 5 mL), 1 drop of toluene.

cling step. Nevertheless, a wide variety of substrates could be efficiently methoxycarbonylated using these immobilized catalysts.

2.2 Immobilization on Insoluble Polymeric Supports

The use of insoluble polymeric supports in the alkoxycarbonylation of alkenes was first reported by Crocker and Herold in 1991.[11] They tested several polymeric supports in the methoxycarbonylation of ethene, with Nafion-H giving the highest activity [turnover rate of 520 mol product/(mol Pd·h)]. In 1998 Liao et al. used a poly(*N*-vinyl-2-pyrrolidone) (PVP) polymer containing HCl which was impregnated with $[MCl_2]$ (N/M = 20/1, M = Ni, Pd) as the support material.[17] Addition of PPh_3 and a metal chloride salt was necessary to obtain a catalytically active system, with $NiCl_2$ giving the best results in terms of activity and selectivity (TON of 25 mol styrene per mol Pd, 99 % selectivity for the *branched* ester under optimized conditions). Colloidal palladium(0) particles are formed during the reactions with the palladium halide precursors, which are stabilized by the presence of the PVP polymer.

Tanaka et al. used several diphosphines (Figure 4), along with $[Pd(OAc)_2]$ or $[Pd_2(dba)_3]$ as the palladium source, in the methoxycarbonylation of styrene and vinyl acetate.[18] After tests with $MeSO_3H$ as acid to identify the best system, $[Pd(OAc)_2]$ with ligand **11**, several commercial polymeric sulfonic acids such as Amberlyst® -15 and Nafion® NR-50 were tested, all resulting in low activity (TON = 25). When a polymeric acid with low number of $-SO_3H$ functionality, such as PS-SO_3H-30 (SO_3H/Pd = 4.5), was used similar activity and selectivity were observed as with $MeSO_3H$. With PS-SO_3H-100 (SO_3H/Pd = 5.3) again low activity was observed. These results were explained by assuming that when the local acid concentration around palladium is high, two $-SO_3^-$ groups coordinate to palladium, this prevents formation of the Pd−H species (*vide infra*). By using a Wang-type resin modified with SO_3H groups, a TON of 500 and an 86 % selectivity for the *branched* ester were obtained. This modified resin could also be used for the methoxycarbonylation of vinyl acetate, giving good results in terms of conversion (TON of 350). In this reaction, the catalyst was recycled three times and showed no decrease in activity.

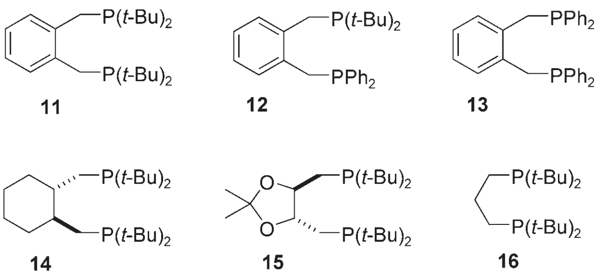


Figure 4. Diphosphines used by Tanaka et al. in combination with sulfonated polymers.[18]

Very recently a paper was published by Doherty et al., describing the first example of catalyst recycling in the alkoxycarbonylation reaction of alkynes.[19] They anchored the 2-(diphenylphosphine)pyridine ligand (2-pyPPh_2) onto several different insoluble polymeric supports (Figure 5). These supported ligands were tested in the methoxycarbonylation of phenylacetylene and propyne, using $[Pd(OAc)_2]$ as the palladium source and $MeSO_3H$ as the acid co-cat-

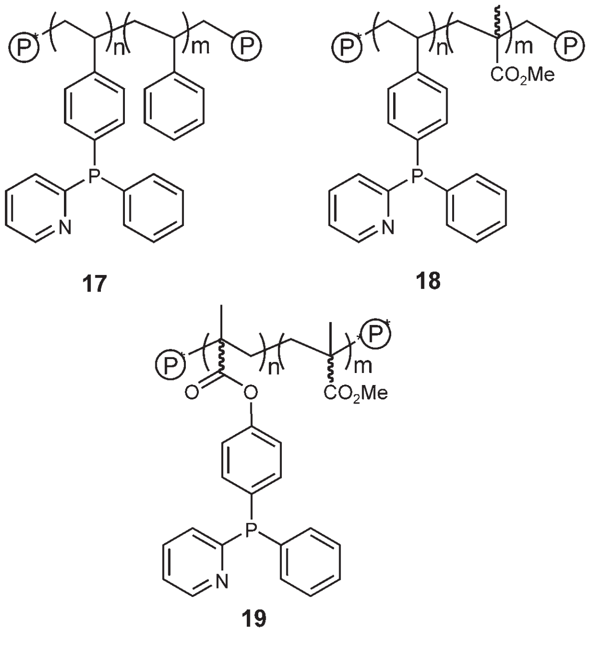


Figure 5. 2-(Diphenylphosphine)pyridine ligands anchored to several different insoluble polymeric supports.[19]

alyst. With phenylacetylene as substrate, ligands **17** and **19** gave the same activity and selectivity as their homogeneous counterpart 2-pyPPh$_2$, whereas the use of ligand **18** gave a somewhat lower activity. With propyne as the substrate only ligand **19** showed an activity comparable to that of the homogeneous counterpart. Although no recycling studies were performed, analysis of the reaction mixture after filtration showed that no palladium was collected, indicating that leaching was negligible.

3 Alkoxycarbonylation Reactions and Catalysts that can be Recycled using Biphasic Systems

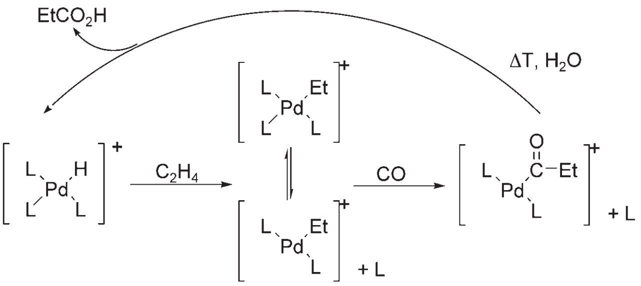
The use of biphasic systems in homogeneous catalysis, such as aqueous biphasic systems,[8] fluorous biphasic systems,[9] and ionic liquids,[20] has received considerably interest in the past two decades. Such systems provide the opportunity to recycle the catalyst through the relatively facile technique of liquid-liquid phase separation while maintaining the benefits of being able to use a homogeneous catalyst. Nowadays, the use of such biphasic systems has even been exploited commercially, for instance, in the Ruhrchemie/Rhône–Poulenc process for the aqueous biphasic hydroformylation of alkenes.[21] Recently, the use of biphasic solvent systems has also been investigated in the context of alkoxycarbonylation of alkenes and alkynes. Aqueous biphasic separation was the first technique to be used and most of the research has been focused on this approach. Nevertheless, also the use of ionic liquids and recently supercritical CO$_2$ has been investigated.

3.1 Use of Aqueous Biphasic Systems in Alkoxycarbonylation Reactions of Alkenes

3.1.1 Palladium Complexes Based on Monodentate Phosphines

The first reports by Sheldon et al.,[22] Monflier et al.[23] and Xie et al.[24] on the use of aqueous biphasic systems for alkoxycarbonylation reactions of alkenes appeared almost simultaneously in 1997. All of these systems consisted of palladium TPPTS systems [TPPTS = P(C$_6$H$_4$-*m*-SO$_3$Na)$_3$]. Sheldon and co-workers, in their first reports, used [Pd(TPPTS)$_3$] (**20**) for the hydroxycarbonylation of propene, 4-isobutylstyrene and styrene.[22] With 4-isobutylstyrene only low turnover frequencies (TOFs) were obtained (maximum of 3 mol converted substrate per mol Pd per hour), which is probably due to the low solubility of the substrate in the aqueous phase (the substrate and formed product are in these cases in the organic phase). With styrene and, especially, propene high TOFs could be obtained (TOF$_{max}$ = 49 for styrene and 2507 for propene) under optimized conditions. Addition of acids of weakly coordinating anions (e.g., *para*-toluenesulfonic acid and triflic acid) provided active catalysts, whereas addition of acids of strongly coordinating anions, like HI, resulted in no reaction. A mechanism was proposed as well.

In later papers more detailed mechanistic and kinetic investigations were presented. ^{1}H and ^{31}P{^{1}H} NMR studies revealed that a palladium hydride intermediate is involved in the catalytic cycle.[25] Further consecutive reaction of this compound with ethene and CO, provided palladium-ethyl and palladium-acyl species (Scheme 2). The hydrolysis of the palladium-acyl bond was established as being the rate-determining step. Also it was found that the stability of the palladium system is significantly reduced in the absence of alkene.



Scheme 2. Mechanism for the stepwise hydroxycarbonylation of ethene, as proposed by Sheldon et al. L = TPPTS, the anion for the cationic palladium complexes is O$_2$CCF$_3$.[25]

In another study Sheldon et al. presented the results from the aqueous biphasic hydroxycarbonylation of several other alkenes.[26] High activities were observed when small alkenes such as propene were used, whereas for longer-chain alkenes activity dropped considerably, which was probably caused by the much lower solubility of the alkene in the aqueous phase. However, for some of the substrates (isobutene and cyclopentene) high selectivities towards one of the product isomers could be obtained.

Monflier et al., after having published their first paper on this topic in 1997, published a series of papers on the aqueous biphasic separation of alkoxycarbonylation catalysts.[23] By serving as a carrier for the olefin to dissolve in the aqueous phase, several derivatives of β-cyclodextrin were used successfully to overcome the problem of slow mass transfer that resulted when long-chain alkenes were used as substrate.[27] Per(2,6-di-*O*-methyl)-β-cyclodextrin provided the highest activity in the hydroxycarbonylation of 1-decene. The effects of several β-cyclodextrins on selectivity of the reaction as well as inhibition of the reaction by binding of the product to the β-cyclodextrin were investigated. The aqueous phase could be recycled four times resulting in only a slight loss of activity. However, the β-cyclodextrin was slowly esterified and hydrolyzed, leading to destruction of the β-cyclodextrin.

In a separate paper these authors also studied the hydroxycarbonylation of several substituted styrenes (see Figure 6) and vinylpyridines.[28] They observed that, a) conversion was higher when the substrate was more soluble in the aqueous phase, b) increase of the steric hindrance of the double bond led to lower initial activity (converted moles of olefin per mol of Pd per hour), low conversion (with **28** about 160 times lower initial activity compared to **24**) and a larger preference for the formation of the *linear* product and, c) the presence of electron-withdrawing groups lowered the activity of the catalyst. Furthermore, the presence of a pyridine group in the substrate led to both low activity and significant deposition of palladium metal. With styrene as the substrate, the system could be recycled five times without apparent loss of activity or selectivity.

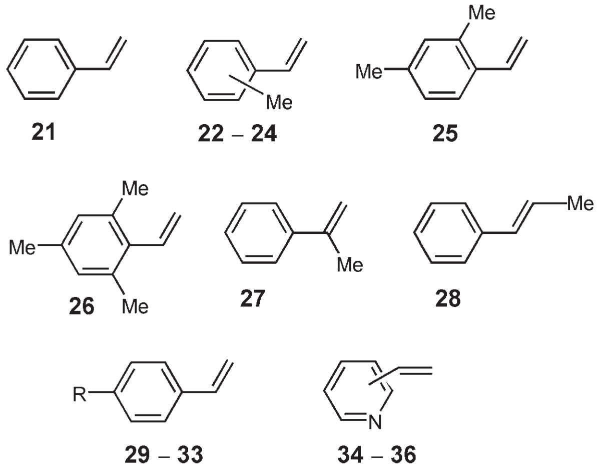


Figure 6. Substrates used by Monflier et al. **29**: R = Cl; **30**: R = Br; **31**: R = F; **32**: R = CF_3; **33**: R = C(O)Me.[28]

Also the effects of alkali metal salts and protective-colloid agents (polyvinyl alcohol) on the stability of a system consisting of [$PdCl_2$] and TPPTS were studied.[29] The presence of these additives increased the stability of the system by hampering formation of large clusters of palladium metal. They also synthesized and applied non-stabilized palladium colloids in the biphasic hydroxycarbonylation of propene. These palladium colloids had a much lower activity than the systems that have the alkali metal salts or the protective-colloid agent present.

Chaudhari and co-workers used a new palladium complex, containing a pyridine carboxylate group and one TPPTS ligand (complex **37**, Figure 7), which has excellent water solubility.[30] This catalyst was applied in the biphasic hydroxycarbonylation of several vinylarenes in a toluene/water biphasic mixture at 115 °C. High activity (a maximum TOF of about 550 h^{-1} was reported) and high selectivity towards the *branched* product was obtained. Also with other substrates, e.g., 4-isobutyl styrene and 6-methoxy-2-vinylnaphthalene, high activities and selectivities were observed. The catalyst was recovered by phase separation and used again but gave a much lower activity in the second run. At lower reaction temperatures (85 °C), however, the catalyst could be recycled twice without loss of activity or selectivity. The use of LiCl as a promotor is necessary, since the alkene substrate has to be converted into an alkyl chloride intermediate, which acts as the active substrate. A possible explanation why this system is more active than previously reported aqueous biphasic systems is that the alkyl chloride has an improved solubility in water. Furthermore, miscibility of the two phases is enhanced by the presence of *para*-toluenesulfonic acid.

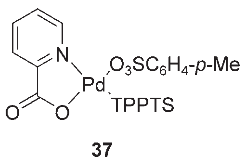


Figure 7. Water-soluble palladium complex from Chaudhari et al.[30]

3.1.2 Palladium Complexes Based on Bidentate Phosphines

There have been two reports on the use of aqueous biphasic systems for the recycling of palladium catalysts based on bidentate phosphines.[31,32] Van Leeuwen et al. reported on the use of a sulfonated diphosphine, 2,7-bis(SO_3Na)-Xantphos (**38**, Figure 8) to synthesize the corresponding neutral and dicationic palladium complexes (**39** and **40**), which were subsequently tested in the aqueous biphasic hydroxycarbonylation of ethene, styrene and propene.[31] The cationic complex, in the presence of *p*-toluenesulfonic acid (to avoid formation of palladium black), gave the highest activity with a reasonable selectivity (*n*/*i* = 65/35) towards the *linear* product in the biphasic carbonylation (olefin/water biphasic mixture) of both propene and styrene.

Claver, Sinou and co-workers used several sulfonated diphosphines, including several chiral ones

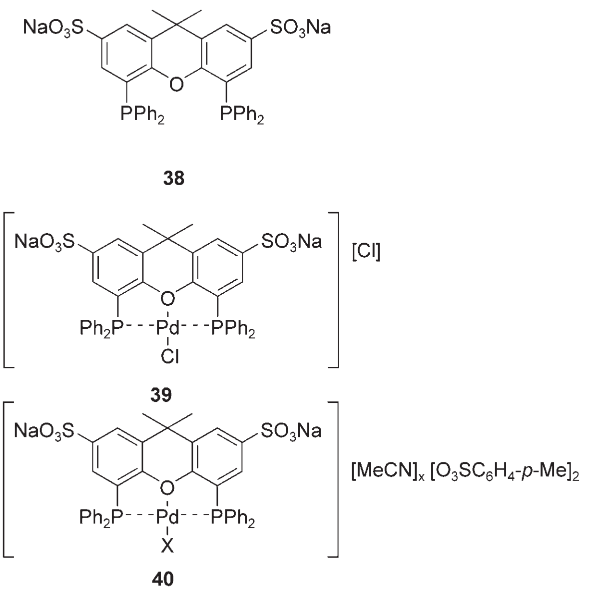


Figure 8. Structure of ligand **38** and derived palladium complexes **39** and **40**. X=MeCN or $O_3SC_6H_4$-*p*-Me.[31]

(Figure 9), in the aqueous biphasic hydroxycarbonylation of several styrene derivatives.[32] Using a biphasic reaction medium, comprising as the two phases water and the substrate, good activities with $[Pd(OAc)_2]$ as the palladium source (TONs of 63 in 16 h) and high selectivities for the *linear* acid (up to 81% with ligand **43**) were observed. Moderate enantioselectivities (maximum *ee* of 41% for the *S*-enantiomer) were observed. The acidity of the medium has no significant influence on the activity of the catalysts, but does have a marked influence on their stability. Recycling of the catalyst without loss of activity or selectivity was only possible in the case of acidic reaction media.

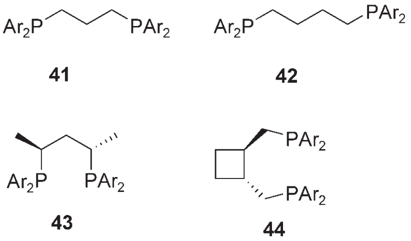


Figure 9. Diphosphines used by Claver, Masdeu et al. Ar=C_6H_4-*m*-SO_3.[32]

3.2 Use of Ionic Liquids in Alkoxycarbonylation Reactions of Alkenes

The first report on the use of ionic liquids in the alkoxycarbonylation of alkenes appeared in 1998, when Monteiro et al. used 1-*n*-butyl-3-methylimidazolium tetrafluoroborate salt as the ionic liquid and cyclohexane/isopropyl alcohol as the organic phase to perform the isopropoxycarbonylation of styrene derivatives.[33] Tests with $[PdCl_2(PhCN)_2]$ and several monodentate phosphines showed that the best regioselectivity towards the *branched* ester (for all substrates 99.5% or higher) was obtained with neomenthyldiphenylphosphine as the ligand, although for some substrates, e.g., α-methylstyrene, low conversions were observed. Recycling of the ionic liquid after full conversion and reuse in a second reaction led to complete inactivity in the second cycle, whereas recycling at low conversions led to *circa* 95% retention of palladium in the ionic liquid.

Shaughnessy and co-workers used several ionic liquids (Figure 10), with $[PdCl_2(PPh_3)_2]$ as the catalyst precursor, to perform the methoxycarbonylation reaction of styrene and several other alkenes.[34]

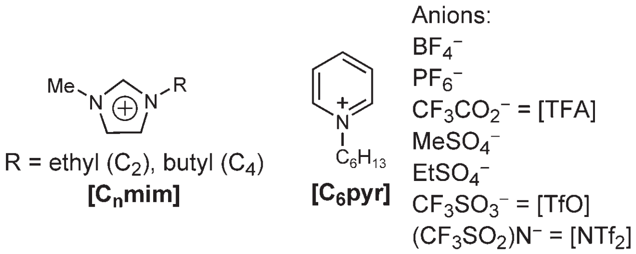


Figure 10. Ionic liquids used by Shaughnessy.[34]

The reaction was first optimized, using $[C_4mim][NTf_2]$ as the ionic liquid and styrene as the substrate, to determine the best conditions (like CO pressure, ionic liquid:MeOH ratio, temperature). Then, all ionic liquids were tested under these optimized conditions (Table 2), showing that the anion used has only a small effect on activity and linear-to-branched ratio, with the exception of the $[PF_6]^-$ and $[TFA]^-$ anions. Best results were obtained with $[C_2mim][EtSO_4]$. Addition of chloride led to a strong decrease in catalyst activity. Several other substrates could also be used, giving good conversions, except for 4-*tert*-butylstyrene.

Recycling studies, performed at 70°C with $[C_4mim][NTf_2]$ as the ionic liquid showed that after 5 runs the activity went from 85 to 60% conversion, while the linear-to-branched ratio increased from 4.3 to 9.8 from the first to the sixth run. The authors explained the observed results by stating that the use of ionic liquids causes a larger preference for the cationic catalytic cycle, which leads to the formation of the *linear* product.

Rangits and Kollár used $[PdCl_2(PPh_3)_2]$ as a catalyst in the alkoxycarbonylation of styrene in $[BMIM][BF_4]$ and $[BMIM][PF_6]$ ionic liquids.[35] Several different al-

Table 2. Use of different liquids[a] in methoxycarbonylation of styrene.[34]

Ionic Liquid	Yield [%][b]	*l*:*b* ratio
$[C_6pyr][NTf_2]$	51	5.0
$[C_6pyr][MeSO_3]$	48	4.5
$[C_2mim][EtSO_3]$	70	6.8
$[C_4mim][PF_6]$	13	5.4
$[C_4mim][TfO]$	50	5.5
$[C_4mim][BF_4]$	51	5.7
$[C_4mim][MeSO_3]$	50	5.6
$[C_4mim][TFA]$	0	–
$[C_4mim][NTf_2]$	60	5.0
$[C_4mim][NTf_2]$[c]	22	5.2

[a] Ionic liquid (4 mL), methanol (4 mL), 90 °C, 200 psi CO, styrene (0.50 mL), $[PdCl_2(PPh_3)_2]$ (1.2 mol %), PPh_3 (2.3 mol %), $t=3$ h.

[b] Yields were determined by GC analysis.

[c] Addition of 0.5 weight % $[C_4mim][Cl]$ relative to $[C_4mim][NTf_2]$.

cohols were used as well as addition of several different bidentate phosphines. In the absence of bidentate phosphines, high conversions and moderate to high selectivities towards the *branched* product (up to 100 % when benzyl alcohol was used) could be achieved. Addition of bidentate phosphines, however, led to both a lower activity as well as a lower preference for the *branched* ester. Furthermore, higher selectivities towards the *branched* product were usually observed when $[BMIM][BF_4]$ was used as the ionic liquid. Recycling of the catalyst, with $[BMIM][PF_6]$ as the ionic liquid, showed that in the first three cycles a decrease in activity of about 5–10 % per cycle was observed and an even higher loss in activity when further cycles were performed. In both ionic liquids, especially $[BMIM][PF_6]$, dimerization/oligomerization of styrene was enhanced, probably due to the formation of acids (HF) by reaction of the anion with H_2O.

3.3 Use of Supercritical CO_2 in Alkoxycarbonylation Reactions

Jiang and co-workers were the first to report on this topic when they published their work on the use of $[PdCl_2]$ in the presence of $[CuCl_2]$ and amine bases for the methoxycarbonylation of norbornene in supercritical CO_2 ($scCO_2$).[36] They observed that, when using different bases and copper salts, the ratio of the products obtained (see Figure 11) varied substantially. The highest selectivity towards the diester product **45** was observed with Et_3N was used as a base, yielding a selectivity of 96 %. Also raising the temperature had a great effect on selectivity, for instance at 85 °C product **47** became the major product formed. Also dicyclopentadiene could be methoxycarbonylated in $scCO_2$ under the same conditions.

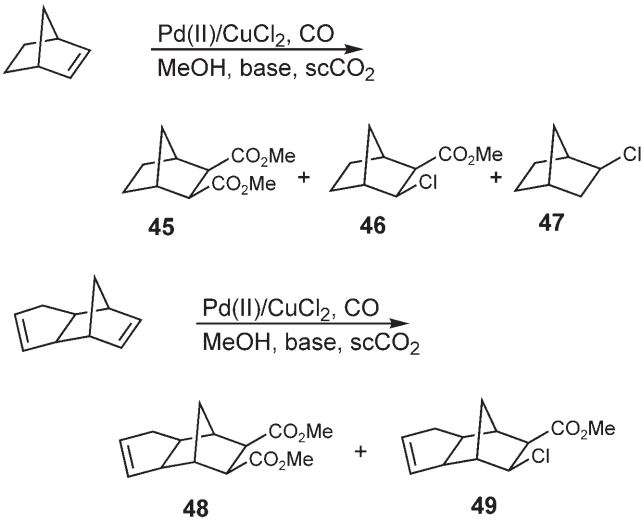


Figure 11. Substrates and products formed in the methoxycarbonylation of alkenes in $scCO_2$, reported by Jiang et al.[36]

Jiang et al. also published several papers on the methoxycarbonylation of acetylenes in $scCO_2$.[37] In one of these papers they used phenylacetylene as the substrate, with $[PdCl_2]$ as the catalyst and $[CuCl_2]$ as additive, and observed that the dicarbonylated product was formed (Figure 12, top) as well as some homocoupling product.[37a] Variation of the amount of MeOH added had a significant influence on both the conversion and the selectivity towards the desired diester product, with an optimum at 1–2 mL of MeOH (4–8 % of the total volume) added (100 % conversion,

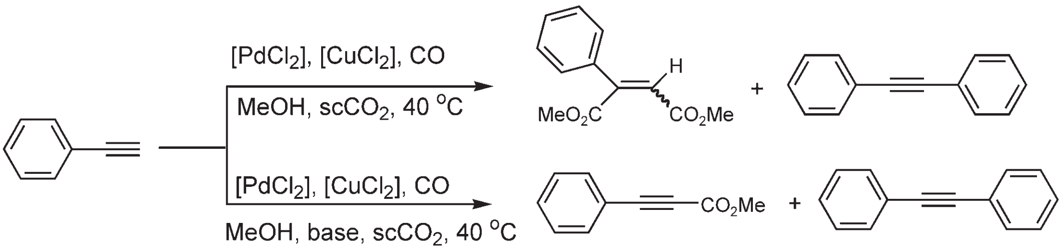
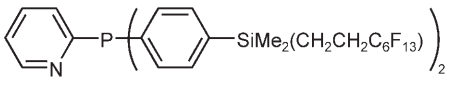


Figure 12. Dimethoxycarbonylation of phenylacetylene (top) and methoxycarbonylation of phenylacetylene (bottom), in $scCO_2$, reported by Jiang et al.[37]

75–72% selectivity towards the diester). Also the CO_2 pressure had a large influence on the activity of the system; optimum activity was achieved at a CO_2 pressure of 140 bar. Besides phenylacetylene, several other terminal alkynes could also be dicarbonylated in good yields.

The same authors also reported on the methoxycarbonylation of several terminal alkynes in $scCO_2$ (Figure 12, bottom).[37b] Using $[PdCl_2]$ and $[CuCl_2]$ as additive they first sought the optimal conditions, using phenylacetylene as the model substrate. The highest selectivity towards the desired mono-ester product (63%, with a conversion of 100%) was achieved using NaOAc as the base and a CO_2 partial pressure of 75 bar (CO partial pressure was 60 bar). Besides MeOH, also isopropyl alcohol and *n*-butanol were used as alcohols, giving the mono-esters along with large amounts of homo-coupling product. With 1-heptyne as the alkyne similar results were obtained.

Deelman, Elsevier and Van Koten et al. recently reported on the methoxycarbonylation of phenylacetylene[38] by 1*H*,1*H*,2*H*,2*H*-perfluoroalkylsilyl-substituted 2-[bis(4-aryl)phosphino]pyridine ligands (Figure 13) with $[Pd(OAc)_2]$. Besides catalytic reactions in MeOH and $MeOH/CF_3C_6H_5$ also reactions were performed in $scCO_2$ with both ligand **50** and the non-functionalized ligand 2-[diphenylphosphino]pyridine. A turnover number (TON) of 2000 mol substrate per mol [Pd] (50 min reaction time) with a high selectivity (>99% *versus* 97–98% in MeOH) towards the *branched* ester was observed when ligand **50** was used, whereas with the parent 2-[diphenylphosphino]-pyridine ligand under the same conditions only a TON of 120 was achieved. This work represents the first case of the use of a fluorous alkoxycarbonylation catalyst.



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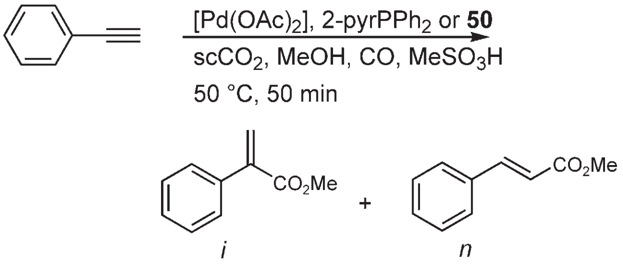

Figure 13. Functionalized 2-[bis(4-aryl)phosphino]pyridine ligands used by Deelman, Elsevier, van Koten et al.[38]

So far no studies that address the recycling of alkoxycarbonylation catalysts from supercritical CO_2 solutions have been reported. However, this may well become feasible in the near future by, e.g., nanofiltration[7e,39] or selective precipitation of the catalyst by variation of the pressure.[40]

4 Conclusions

Over the last decade, several techniques for the recycling of catalysts have been demonstrated in the context of alkoxycarbonylation reactions. Most of the attention was given to alkenes although alkynes can undergo alkoxycarbonylation as well. Initial studies focused on the use of aqueous biphasic systems and of insoluble (in)organic supports, giving rise in some cases to catalytic systems that combine high activity and selectivity with good recyclability. More recently, ionic liquid systems have been successfully applied for catalyst recovery. In some cases the selectivity of the catalysis was affected and more of the *linear* product was formed. It appears that the ionic liquid favors an ionic mechanism over the neutral mechanism. Whatever the recycling method, it is clear that the limited stability of the Pd(II) systems is often responsible for the loss of activity upon repeated recycling of the catalyst system.

The use of phase-vanishing approaches such supercritical CO_2 (pressure-dependent solubility of catalyst) and fluorous biphasic solvent systems (temperature-dependent miscibility of the two phases) offers the advantage of overcoming the mass transport limitation encountered in other multiphasic approaches, especially for higher molecular weight alkenes. So far these new techniques have received only limited attention but this is no doubt the result of the fact that this field is relatively young. First results obtained in supercritical CO_2 indicate that alkoxycarbonylation in this medium is feasible and that selectivities can be comparable or even higher than in conventional solvent systems. No examples of catalyst recycling using the fluorous biphasic approach have been demonstrated yet. However, lightly fluorous catalysts have been successfully applied in biphasic solvent mixtures.[41] Hence more examples of catalyst recycling based on these new techniques can be expected in the near future.

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[1] Besides the term alkoxycarbonylation also hydroesterification and hydroalkoxycarbonylation are used in literature to describe this reaction. Furthermore, one can find terms describing specific types of reactions, such as hydroxycarbonylation (formation of carboxylic esters),

methoxycarbonylation (formation of methyl esters) etc. We will use alkoxycarbonylation as a standard term and in the text specify which reaction is meant. For a recent review on alkoxycarbonylation reactions of alkenes and alkynes, see: G. Kiss, *Chem. Rev.* **2001**, *101*, 3435–3456.

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