Homogeneous metal-based catalysis in supercritical carbon dioxide as reaction medium.

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ABSTRACT: Above 31.1 °C and 73.8 bar, carbon dioxide reaches the supercritical condition, being transformed into a fluid (*sc*CO_2) that has gained interest in the last decades as reaction medium for several transition metal-catalyzed organic transformations. The main feature of this fluid stands on its capability to dissolve large amounts of other gases such as hydrogen, carbon monoxide, ethylene or even methane and light alkanes. In this manner, very high concentrations of these reactants are available for catalysis. In this contribution a review of the main achievements of the use of transition metal complexes as catalysts in *sc*CO_2 is presented.

KEYWORDS (Word Style "BG_Keywords"). Supercritical carbon dioxide – homogenous catalysis – hydrogenation – hydroformylation – olefin metathesis – C-H activation – cycloaddition – oxidation – C-C bond formation

1. INTRODUCTION

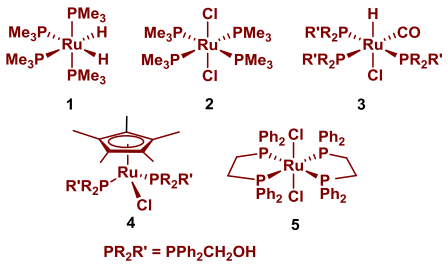
Supercritical carbon dioxide (*sc*CO_2) has been revealed in the last decades as an attractive solvent first for extraction/separation[1] processes and subsequently for synthetic purposes.[2] *sc*CO_2 displays a series of features such as a quite accessible critical point (31.1 ºC and 73.8 bar) in comparison with other substances (374.2 ºC and 220.5 bar for H_2O; 240.6 ºC and 79.9 bar for CH_3OH).[3] Tuning of the solvation properties by modifying temperature and pressure also constitutes an advantage when compared with traditional solvents.[4] No less important, although not significant on a global scale is its environmentally benign character and low cost. These and other properties have turned *sc*CO_2 into the solvent of choice for important industrial processes as caffeine extraction,[5] particle generation in pharmaceutical transformations[6] or polymer processing.[1]

The use of *sc*CO_2 to synthesize complex organic molecules emerged at the end of the 80's of the last century and currently constitutes an active research field.[7] Although the field of heterogeneous metal-based catalysts has been more extensively studied to date in this medium[8a,b] the homogeneous counterpart is gaining interest in the last decade. Actually, immobilized transition metal complexes have also been described as catalysts for some transformations in supercritical fluids.[8c] Soluble catalysts generally offer better possibilities to perform *in situ* mechanistic studies[8d] and, subsequently, to achieve catalyst improvements. Additionally, compared with heterogeneous catalysis, homogeneous transition-metal-based catalysts allows to use tailor-made catalysts on the basis of the plethora of ligands available and the development of new ligands to enhance at once selectivity and efficiency. The usual low solubility of catalysts in *sc*CO_2 constitutes a challenge that has required the smart design of ligands containing substituents to allow the necessary interaction between carbon dioxide molecules of the fluid and the catalyst with its consequent solubilization. The usual strategy consists of the introduction of CO_2-philic groups such as fluorinated functionalities, silanes, siloxanes or polyacetates, among others.[4a]

In this contribution the use of transition metal-based catalysts in *sc*CO_2 under homogeneous conditions is reviewed. The work has been organized by type of reaction including olefin hydrogenation, hydroformylation and hydrocarboxylation, olefin metathesis, alkane C-H functionalization by carbene insertion, carbon-carbon coupling processes, cycloaddition reactions and olefin and alcohol oxidations. Given the existence of a very recent compilation on polymerization reactions[1] in this medium, we have not included herein this transformation.

2. HYDROGENATION REACTIONS

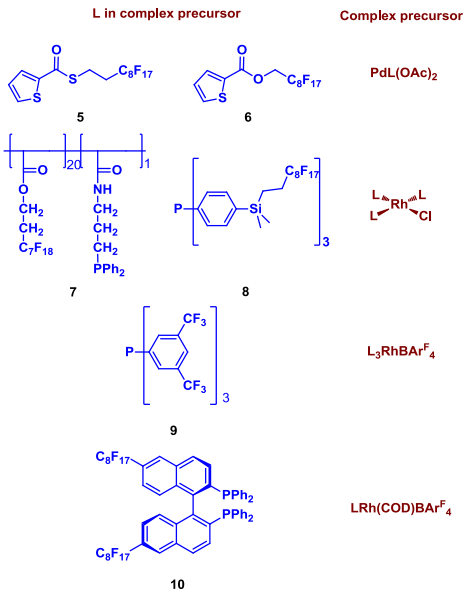
The first examples of hydrogenation reactions in *sc*CO_2 use carbon dioxide itself as the substrate with the aim of its reduction to methanol or formic acid, among others. These and other commodities are currently prepared[9] from carbon monoxide and therefore an alternate route based in carbon dioxide would be desirable from the point of view of safety. In this context, interesting advances in the field have arisen with the use of soluble metal catalysts. Nearly twenty years ago, Noyori and co-workers described the hydrogenation of carbon dioxide using a ruthenium catalyst bearing the quite simple trimethylphosphine ligand (catalysts **1** and **2**, Scheme 1).[10] The reactions were carried out in a mixture of hydrogen (85 bar) and CO_2, at a total pressure of 200-220 bar, at 50 ºC, thus ensuring supercritical conditions. Triethylamine was added as a base, a trace amount of water being also added as co-catalyst. A turnover number of 3700 with the noticeable turnover frequency of 1400 h^{-1} was achieved with catalyst **1**. The



Scheme 1. Ruthenium catalysts used in the hydrogenation of *sc*CO_2.

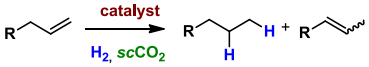
maximum turnover number of 7200 was reached with catalyst **2**.

This system was extended to the production of dimethylformamide or methylformate by adding dimethylamine or methanol to the reaction media.[11] In both cases the synthesis occurs in a two-step process. *sc*CO_2 is first reduced to formic acid in a fast reaction followed by thermal condensation with dimethylamine or methanol. The second step requires a higher temperature and thus these reactions were performed at 80-100 ^{o}C. The amount of alcohol added must be carefully measured in order to ensure a single phase reaction and good catalyst efficiency. Best results reported are collected in Table 1. Synthesis of formanilides from less basic amines such as anilines required the addition of one equivalent of DBU as a base.[12]



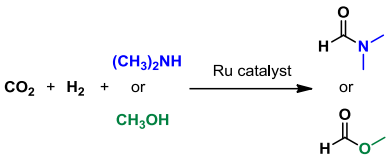
Scheme 2. Catalysts used in the hydrogenation of olefins in *sc*CO_2.

Table 2. Hydrogenation of 1-octene in *sc*CO_2.



Catalyst	TON	Octane selectivity (%)	Internal alkene selectivity (%)	Ref.
5	341	30	70	13a
6	52	62	38	13a
7	2800	64	36	13b,c

Table 1. Dimethylformamide and methylformate synthesis from *sc*CO_2.



Catalyst	Additive	TON	Ref.
2	CH_3OH	3500	11b
2	$(CH_3)_2NH$	420000	11c
3	$(CH_3)_2NH$	4800	11d
4	$(CH_3)_2NH$	3300	11d
5	$(CH_3)_2NH$	740000	11e

Only a scarce number of catalysts have been described for the hydrogenation of olefins in *sc*CO_2 when compared with the plethora of homogeneous catalysts known in conventional solvents. Scheme 2 shows several palladium- and rhodium-based catalysts that have been used in the hydrogenation of 1-octene.[13] It is worth mentioning that double bond isomerization appeared as a frequent side reaction in this transformation and thus mixtures of the reduced product and internal alkenes were obtained very often.

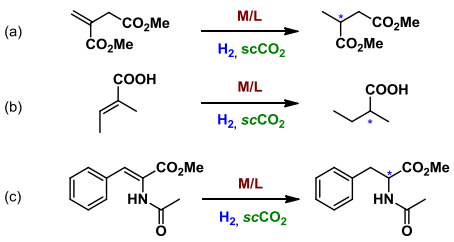
The catalytic activity of complexes bearing ligands **5-7** is shown in Table 2, and cannot be considered as competitors for those reported in conventional solvents. The low activity observed with tripodal ligands **5** and **6** was attributed to poisoning of palladium by carbon monoxide formed by the reaction of hydrogen with carbon dioxide.

Recycling of a soluble catalyst in *sc*CO_2 is not an easy task. Usually, depressurization of the reaction vessel leads to a mixture of the product and the catalyst. An approach to catalyst recycling in the homogeneous hydrogenation of olefins in *sc*CO_2 was based on the use of a membrane reactor.[14] The rhodium catalyzed hydrogenations using ligand **8**, a fluorinated analogue of Wilkinson's catalyst with a size of 2-4 nm, was used in the hydrogenation reaction of 1-butene. The vessel was equipped with a membrane with a pore size of 0.5-0.8 nm that allowed the flow of product molecules and retained the catalyst. Although catalyst activity (measured as TOF value) decreased to only 60 % of that observed for the same catalyst under batch conditions, high turnover numbers of 120000 could be achieved due to continuous use of the catalyst.

The selective hydrogenation of styrene to yield ethylbenzene has been studied using cationic complexes of Rh(I) with ligands **9** and **10**.[15] Complete selectivity to ethylbenzene was obtained in both cases, although bidentate ligand **10** provided better catalytic activity with a 96 % conversion after 3 hours using a 0.2 mol % of catalyst.

The asymmetric hydrogenation of prochiral olefins probably provides the most practical route to optically pure organic compounds. The achievement of a good enantioselectivity in the hydrogenation reaction usually requires the presence in the olefin of a group capable of coordinating the metal center. This is the case of olefins with ester, ketone or amide moieties (Scheme 3). Scheme 4 shows ligands used in these reactions. Ligands **11**-**14** have been tested in the asymmetric hydrogenation of dimethyl itaconate, with the results shown in Scheme 3a, Table 3. Ligand **11** was used in the ruthenium-catalysed hydrogenation of dimethyl itaconate with good results.[16] High yields and enantioselectivities were obtained with catalyst loadings as low as 0.1 mol %. Despite the presence of fluorinated ponytails in the BINAP ligand, small amounts of methanol had to be added to ensure complete miscibility of the reaction mixture. Phosphite ligands **12**-**15** have also been used in the rhodium catalysed hydrogenation of dimethyl itaconate.[17] In the case of ligand **12**, the presence of the fluorinated chain in the ligand had a detrimental effect in reaction conversion as well as in enantioselectivity; the addition of one equivalent of $NaBAr^F_4$ (BAr_4^F = tetrakis(bis-3,5-trifluoromethyl-phenyl)-borate) barely improved the enantioselectivity of the reaction.[17a] Better results were obtained with the non-fluorinated phosphite ligands **13**-**15**.[17b-d] Generally, the catalysts were generated *in situ* from $[Rh(COD)_2]BF_4$ and two equivalents of the ligand. Only in the case of ligand **15** catalyst was presynthesized. It is worth mentioning that reaction rates were 7-10 times higher in scCO2 than in conventional solvents such as dichloromethane.

Ligand **16** was employed in the ruthenium-catalysed asymmetric hydrogenation of tiglic acid (Scheme 3b) with good results.[18] Enantioselectivities up to 89 % were obtained with a 99 % conversion with catalyst loadings as low as 0.7 mol %, although addition of a fluorinated alcohol as co-solvent was necessary. The use of a fluorinated derivative of BINAP ligand **17** did not report any improvement achieving only a 62 % *ee*.[19]



Scheme 3. Substrates commonly employed in the asymmetric hydrogenation of olefins in *sc*CO_2.

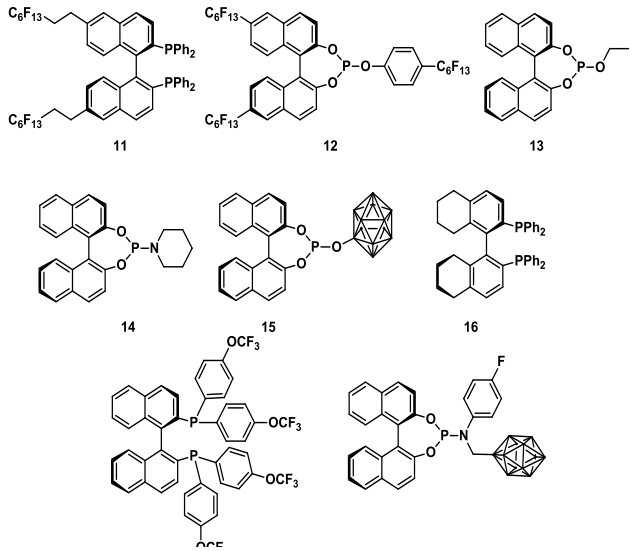
Table 3. Asymmetric hydrogenation of dimethyl itaconate in *sc*CO_2.

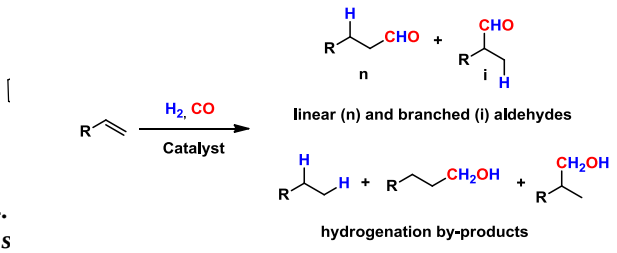
Ligand	Metal (mol %)	Conv. (%)	ee (%)	Ref.
11	[RuCl2(benzene)]2 (0.1 %)	92	93.6 (S)	15
12	[Rh(COD)2]BF4 (0.4 %) + NaBArF4	28	65 (S)	17a
13	[Rh(COD)2]BF4 (1 %)	100	90 (R)	17b
14	[Rh(COD)2]BF4 (1 %)	100	97.8 (R)	17c
15	[Rh(COD)2]BF4 (0.5 %)	100	93 (R)	17d

Asymmetric hydrogenation of α-enamides (Scheme 3c) has also been carried out with rhodium catalysts bearing ligands **18** and **19**. Although full conversions were achieved with ligand **18**, enantiomeric excess only reached a modest value of 52 %.[20] The enantioselectivity was improved up to reach 99.1% *ee* with Et-DuPHOS **19**, a result slightly better than those reported in conventional solvents.[21]

Ketones and imines can also be reduced to the corresponding alcohols and amines. In the first case (Scheme 5a), ligand **20** was tested in the ruthenium-catalyzed hydrogenation of ethyl acetylacetonate with moderated results.[22] Full conversions with enantiomeric excesses up to 74 % were observed with a catalyst loading of 0.2 mol %. However, trifluorotoluene had to be added as a co-solvent to increase the catalyst solubility despite the presence of fluorinated ponytails in this ligand. For imine reduction in *sc*CO_2 iridium was the metal of choice (Scheme 5b). A catalyst loading of 1 mol % of the complex formed *in situ* from two equivalents of ligand **14** and $[Ir(COD)_2]BAr^F_4$ afforded the amine with a conversion of 82 % and 90% *ee*.[23] Once again, the use of fluorinated ligands was detrimental probably due to electronic effects. A catalyst loading of only 0.09 % of pre-formed iridium complex (Scheme 5c) with a bidentate ligand bearing fluorinated chains afforded full conversion but a moderate 80 % *ee*.[24]

The reduction of levulinic acid to γ-valerolactone represents an important example as it is a key reaction in the transformation of biomass into fuel additives (Scheme 6, Top). The addition of CO_2 to the reaction mixture produces a single phase facilitating the reaction with gaseous hydrogen.[25]

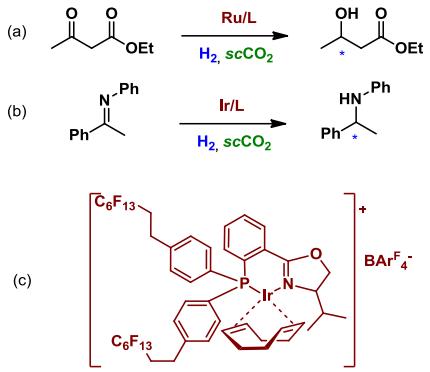




Scheme 4. olefins in *s*

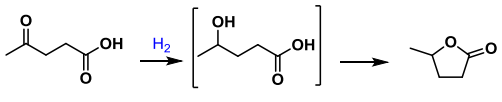
Scheme 7. The olefin hydroformylation reaction showing main and side products.

Chemoselectivity in hydrogenation reactions when several functional groups are present is often a challenge. One exam-

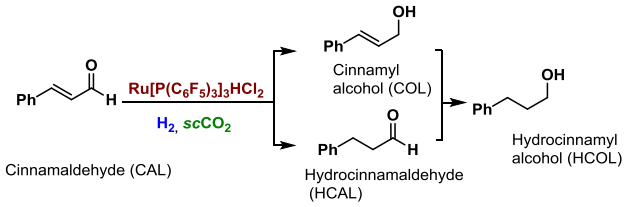


Scheme 5. Examples or reduction of ketones and imines in *sc*CO_2.

ple is the hydrogenation of the α,β–unsaturated cinnamaldehyde (Scheme 6, Bottom). The use of a ruthenium complex bearing tris(pentafluorophenyl)phosphine ligands in *sc*CO_2 allowed increasing the conversion with respect to conventional solvents.[26] The higher solubility of hydrogen in the supercriti-



Conditions	Conversion (%)	Selectivity (%)
$scCO_2$, 100 bar	98	97
neat	78	93



Conditions	Conversion (%)	Selectivity (%)		
		COL	HCAL	HCOL
$scCO_2$, 100 bar	26	31	48	21
Propanol	12	48	24	29
Benzene	4	15	42	43

Scheme 6. Top: Hydrogenation of levulinic acid. Botton: Hydrogenation of cinnamaldehyde.

cal media is probably responsible of this increment. However, chemoselectivity remained low, similar to that obtained in conventional nonpolar solvents.

3. HYDROFORMYLATION REACTIONS

Hydroformylation is an important industrial transformation to produce aldehydes from olefins and the so-called syngas, a mixture of carbon monoxide and molecular hydrogen. Aldehydes are employed in cosmetics, pharmaceutical and food industry and are also key intermediates in the production of alcohols, carboxylic acids, aldol products, diols, acetals, ethers, acrolein derivatives and esters.[27] In a typical hydroformylation reaction (Scheme 7), a terminal olefin is reacted with CO/H_2 in the presence of a transition metal catalyst to yield a mixture of linear and branched aldehydes besides other side products. Thus, the regioselection induced by the catalyst constitutes a parameter of industrial significance. The main drawback of the hydroformylation process is the low solubility of gases in the usual organic solvents used as reaction media which leads to low reaction rates. *sc*CO_2 is a good alternative solvent as it is complete miscible with H_2 and CO in almost any molar ratio thus allowing to use high gas concentrations during the catalytic reaction.

First hydroformylation reaction in *sc*CO_2 was carried out in high pressure NMR tubes by Rathke *et al*[28] in 1991 and involved the transformation of propylene into *n*- and *i*-butanal catalysed by $Co_2(CO)_8$. A complete study of the different reaction parameters performed later in stirred vessels,[29] demonstrated that albeit the catalyst is soluble in the supercritical media, CO_2 does not participate in the equilibrium exchange processes involving the cobalt carbonyl complex, H_2 and CO. In the presence of H_2, equilibration of $Co_2(CO)_8$ with $HCo(CO)_4$ was observed in *sc*CO_2 (eq 1). This hydride species interacts later with the olefin *en route* to the hydroformylation product. Comparable activation energy values for reactions in *sc*CO_2 or conventional organic solvents were found.

$$Co_2(CO)_8 + H_2 \rightleftharpoons 2\,HCo(CO)_4 \qquad (1)$$

Pressure and temperature affected this transformation in a different manner. At constant temperature, the observed rate increased linearly with the total pressure. On the other hand, maintaining constant the pressure, the reaction selectivity (*n*:*i*, linear to branched aldehydes ratio) can be affected by modifying the density of the reaction medium, the formation of the linear isomer being favoured at higher temperature.

These studies were conducted with relative high catalyst loading (2-12 %) and a large excess of syngas. Modified cobalt catalysts with fluorinated phosphines have been described (Figure 1) to increase the reaction efficiency.[30] Conversions up to 92 % were achieved in the hydroformylation of 1-octene with a catalyst loading of just 0.2 mol % and the stoichiometric amount of syngas. An excess of phosphine ligand allowed improving the selectivity towards the linear aldehyde up to 95.5 %. $Ru_3(CO)_{12}$, a polynuclear carbonyl cluster soluble in *sc*CO_2, has been used in the hydroformylation of ethylene.[31]

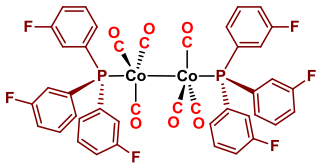
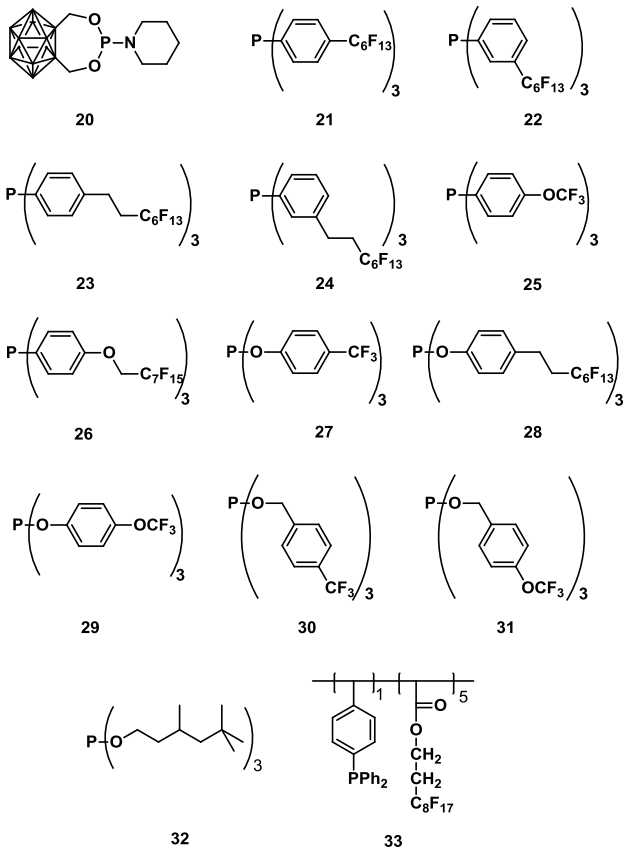


Figure 1. A Co-based catalyst for hydroformylation in $scCO_2$.

Without doubt, rhodium-based catalysts have proven being the best choice for this transformation. Some mechanistic studies have been carried out revealing the influence of pressure and ligand modification on catalyst activity and selectivity. The effect of temperature, olefin concentration and CO_2, CO and H_2 pressure in the hydroformylation of 1-octene have been monitored using isolated well-defined rhodium complexes containing phosphine ligands such as $HRh(CO)[P(p\text{-}CF_3C_6H_4)_3]_3$ and $HRh(CO)[P(3,5\text{-}(CF_3)_2C_6H_3)_3]_3$.[32] The reaction outcome was similar in $sc CO_2$ or conventional solvents. Dependence of activation energies on temperature and catalyst concentration was comparable in benzene, toluene and ethanol or $scCO_2$. As it happens in conventional solvents, high CO pressure has a detrimental effect in both regioselectivity and reaction rate due to the replacement of the phosphine ligands by CO. The main difference between conventional solvents and $scCO_2$ is the disappearance of the inhibitory effect of high olefin concentration in the latter. This effect was attributed to the difficulty of formation of dimeric rhodium species in the supercritical media. An intriguing result is the different reaction order of H_2 with both complexes, being 0.5 with $HRh(CO)[P(p\text{-}CF_3C_6H_4)_3]_3$ and 1 with $HRh(CO)[P(3,5\text{-}(CF_3)_2C_6H_3)_3]_3$. All previous studies in conventional solvents reported first-order rate in H_2 concentration what is commonly interpreted to mean that the oxidative addition of H_2 is the rate determining step. The authors ascribed this change to the different electronic character of the phosphine ligands used; decreasing basicity of the ligand should result in an increase of the catalytic activity. These results are endorsed by an additional study on the $HRh(CO)[P(3,5\text{-}(CF_3)_2C_6H_3)_3]_3$ catalyzed hydroformylation of ethylene in $scCO_2$ by *in situ* FTIR spectroscopy.[33]

In a typical hydroformylation experiment a rhodium catalyst precursor, the corresponding ligand and the alkene are charged into the reaction vessel before pressurization with syngas and CO_2. Catalyst loadings ranged within 0.025-0.5 mol %, with an excess of ligand being added (4-10 equiv with respect to rhodium). The CO/H_2 mixture is commonly introduced at 10-40 bar; temperatures in the 50-100 ^oC interval are employed. Selected results for the hydroformylation of 1-octene catalyzed by a series of rhodium-based systems with different phosphine and phosphite ligands, shown in Scheme 8, are summarized in Figure 2. Simple, phosphine-free rhodium complexes such as Rh(hfacac)COD[34] or $Rh(acac)(CO)_2$[34,35] catalyzed this olefin hydroformylation reaction. Complete conversions at 60-65 ^oC with good selectivity toward aldehydes were achieved but only at a moderate 1.5 linear:branched molar ratio. Use of triphenylphosphine as ligand became detrimental in catalyst activity due to poor solubility, albeit a certain increment in the linear aldehyde production was observed.[36] Several alkylphosphines and arylphosphines bearing bulky alkyl or carboxylate substituents have been also examined as ligands in this reaction. Triethylphosphine along with $Rh_2(OAc)_4$[37] enhanced the solubility of the catalyst and the *n*:*i* ratio improved up to 2.4, at the expense of a lower selectivity toward aldehyde-type products. Longer alkyl chains in the phosphine had a negative effect in solubility, catalytic activity and selectivity.[37]



Scheme 8. Ligands used in hydroformylation with rhodium-based catalyst precursors.

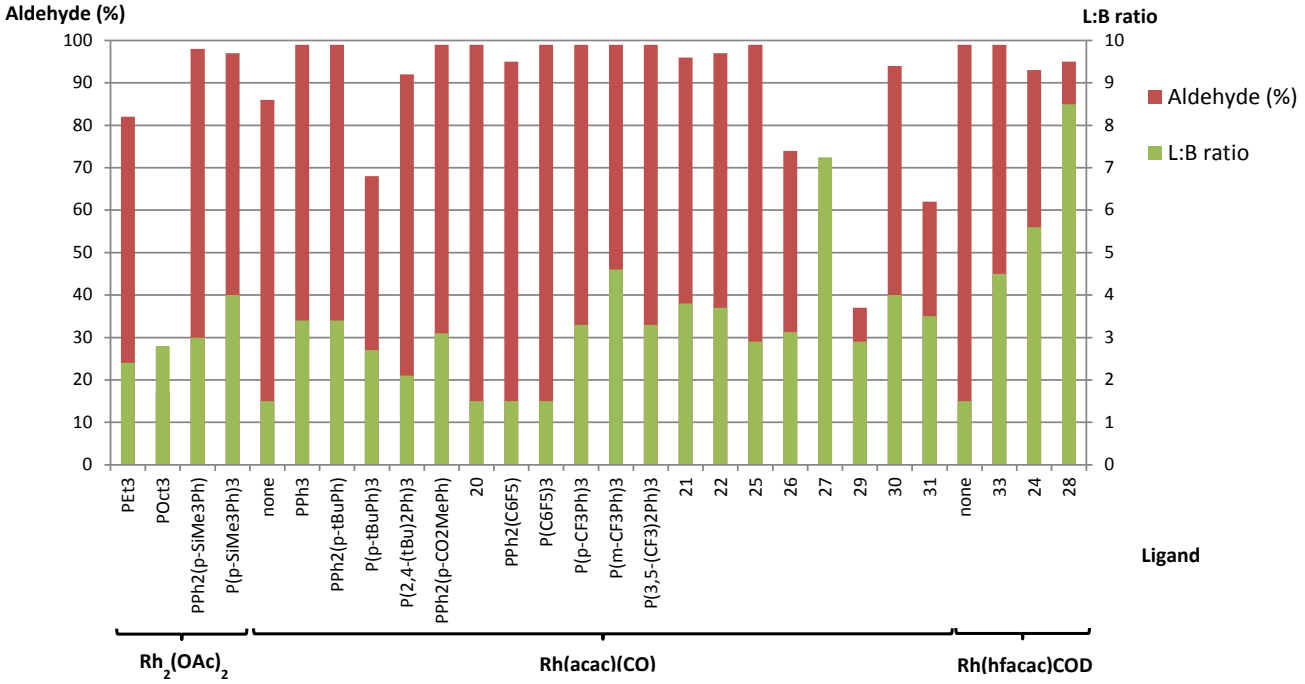


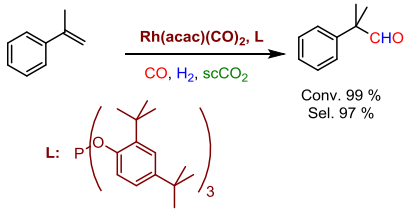
Figure 2. Catalytic hydroformylation of 1-octene in $scCO_2$ with several rhodium sources and the ligands shown in Scheme 8.

Aromatic phosphines have also been tuned upon attachment of *tert*-butyl[35b,36b,e] or methoxycarbonyl[36a] groups at para position in the aromatic rings of triphenylphosphine. Substitution in only one of the three rings of the phosphine ligand led to good catalytic activity, with a *n*:*i* ratio of 3.4. However, subsequent substitution revealed negative for catalytic purposes. Such effect was not observed when the Me_3Si- group was attached. In this case the trisilylated phosphine provided high activity values with a selectivity *n*:*i* = 4.[36b] In contrast, the use of a phosphite ligand derived from carborane (ligand **20** in Scheme 8) did not significantly affect the results when compared with the unmodified rhodium precursor.[38]

In contrast, the use of fluorinated ligands was very effective. Actually, hydroformylation was more efficient with phosphines of low basicity in both $scCO_2$ and conventional organic solvents. Introduction of fluorinated moieties in the ligands not only increased the solubility of the catalyst but also decreased the electron density at the metal centre. Although substitution of $P(C_6F_5)_3$[35a,36c] for PPh_3 did not improve activity or selectivity of the catalyst, the incorporation of CF_3- substituents at the aryl rings was beneficial.[35a,36c-e] Best results were obtained with tris(*m*-trifluoromethylphenyl)phosphine as ligand leading under optimized reaction conditions to a linear:branched ratio of 4.6 (Figure 2). Long ponytails were also very effective to improve catalyst activity and selectivity.[34,35a,39] Better results were obtained when the fluorinated chains are attached to the *meta* position of the aryl ring through a non-fluorinated spacer, *i. e*. ligands **21** and **22** versus **23** and **24**. A maximum 5.6 *n*:*i* ratio was achieved with phosphine **25** whereas[35a] phosphite ligands (**27**-**31**) afforded the best results for this reaction.[34,39c,40] The linear:branched ratio was 8.5 with ligand **26** with a 99 % conversion and 95 % selectivity,[34] the amount of olefin isomerization being very low.

Aliphatic phosphite **32** was used as a modifier of $Rh(acac)(CO)_2$ in the hydroformylation of 1-octene. To increase catalyst solubility β-peracetylated cyclodextrine was added in a 6-fold excess with respect to catalyst precursor.[41] Although a positive effect on catalyst solubility was observed, the linear:branched ratio decreased from 4 to 1.3 when the oligosaccharide was present in the reaction media.

Hydorformylation of disubstituted alkenes has been developed using a bulky phophite ligand, tris(2,4-di-*tert*-butylphenyl)phosphite as a modifier of $Rh(acac)(CO)_2$. Hydroformylation takes place very selectively in the internal position of the alkene with very high conversion with just a 0.1 mol % of catalyst precursor (Scheme 9).[42]



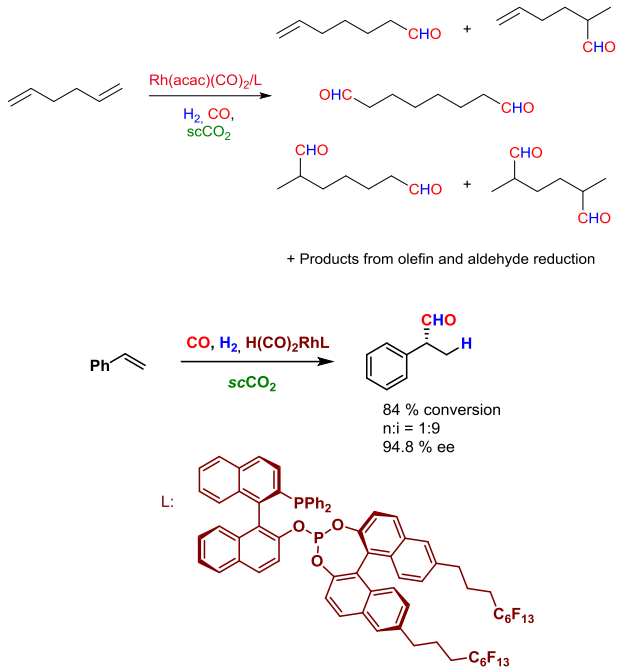
Scheme 9. Hydroformylation of disubstituted alkenes.

Ligands **21** and **33** have also been used in the hydroformylation reaction of acrylates,[43] a transformation of special interest as it yields synthetically valuable bifunctional compounds. Better catalytic activities were obtained when the reactions were performed in supercritical carbon dioxide instead of toluene.

Double hydroformylation of dienes has also been assayed. This reaction directly originates dialdehydes, a family of molecules relevant in the industrial preparation of cross-linked polymers. However, control of the selectivity is complicated in this case and mixtures of linear and branched dialdehydes

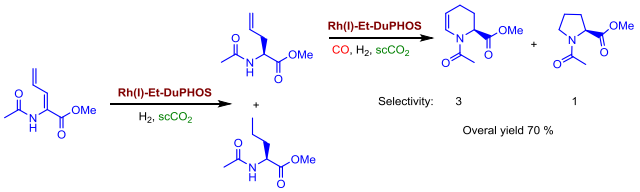
were obtained with a maximum selectivity of 60% for the linear isomers (Scheme 10, Top).[44]

Several approaches to the enantioselective hydroformylation of styrene in *sc*CO_2 have been reported.[45] In this case, the desired product is the branched aldehyde. The best result with a 94.8 % *ee* was obtained with a fluorinated derivative of BINAPHOS as the ligand (Scheme 10, Bottom). A racemic version has also been developed using a Wilkinson catalyst analogue bonded to a fluorinated polymer backbone which provides complete selectivity for the branched aldehyde.[46]



Scheme 10. Top: Double hydroformylation of dienes. Bottom: Enantioselective hydroformylation of styrene.

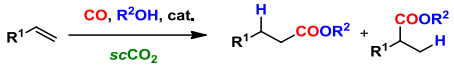
Cyclic α-amino acids have been prepared through a one-pot two-step enantioselective hydrogenation-hydroformylation reaction catalyzed by a Rh(I) complex bearing ligand Et-DuPHOS **19** (Scheme 11).[47] Initially, reactor vessel is charged with the prochiral dienamide and the catalyst and filled with hydrogen and *sc*CO_2. Careful control of H_2 and CO_2 pressure was necessary to avoid hydrogenation of the terminal double bond, a 88 % yield with 82 % selectivity for the desired enamide was obtained under optimized conditions. Reactor was then vented and pressurized again with a mixture of syngas and CO_2. Hydroformylation of the terminal alkene is followed by spontaneous condensation to yield the desired cyclic aminoacid. A secondary product is formed as a consequence of the hydroformylation in the internal position of alkene. Both



Scheme 11. Tandem hydrogenation-hydroformyl-ation-cyclization reaction.

products were obtained with enantiomeric excess of 98 %.

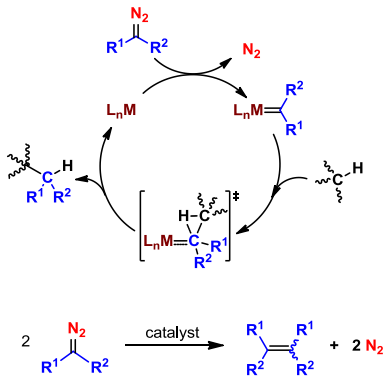
The hydroesterification of alkenes, a reaction closely related to the hydroformylation, has also been studied in supercritical carbon dioxide (Scheme 12). Only two examples of hydroesterification in *sc*CO_2 have been described. In the first the reaction with norbornene was catalyzed by a mixture of $PdCl_2$ and $CuCl_2$ that partially dissolved in *sc*CO_2 with the help of methanol, also present in the reaction media.[48] Carboxylation competed in this case with chlorination products. In the second report $PdCl_2(PhCN)_2$ was used as catalyst in the presence of tris(*p*-trifluoromethylphenyl)phosphine as ligand.[49] The linear ester was obtained with a selectivity of 86% but a low 25% conversion of alkene. Conversion was increased to 93 % with an aldehyde selectivity of 77 % by addition of small amounts of water and a fluorinated surfactant[50] to the reaction media.



Scheme 12. Hydroesterification reaction.

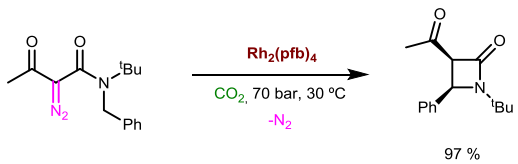
4. FUNCTIONALIZATION OF C-H BONDS THROUGH CARBENE INSERTION REACTIONS.

The use of diazocompounds as carbene precursors for the C-H bond functionalization of non-activated alkanes has become a useful tool for the transformation of these raw materials into value added products.[51] The reaction involves the transfer of a carbene moiety from the diazocompound to the alkane through the electrophilic attack of a metal carbene intermediate onto the C-H bond (Scheme 13). Complexes based on rhodium, gold, copper, silver and very recently zinc[51,52] have been described as catalysts for this transformation. Reactions are usually performed using the alkane both as substrate and as reaction media for two main reasons: 1) the use of a large excess of alkane diminishes the side dimerization reaction of the diazocompound that is also catalysed by the metal complex and 2) the presence of any other more reactive C-H bond must be avoided in order to ensure the functionalization of the low reactive C-H bonds of plain alkanes. This second reason is the major drawback that has limited the application of this reaction to gaseous alkanes until very recently.



Scheme 13. Catalytic cycle for alkane C-H functionalization by carbene insertion from diazo compound (top) and the coupling of two carbene groups (bottom).

In the event of facing



Scheme 15. Intramolecular C-H activation in compressed CO_2.

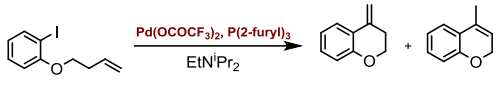
methane functionalization with this strategy, two issues must be solved. First, methane has the highest C-H bond dissociation energy of all the alkane series (105 Kcal mol^{-1} in front of 99 Kcal mol^{-1} corresponding to the primary C-H bond of *n*-hexane, for example),[53] and thus any other C-H bond in the reaction mixture would react in advance toward the electrophilic metallocarbene. The second problem stands on the nearly null polarity of methane, thus precluding its sole use under supercritical conditions since catalyst and diazocompound are insoluble. However, with *sc*CO_2 as the reaction medium, a catalytic system for the functionalization of the C-H bond of methane has been recently developed by Pérez, Asensio, Etienne and co-workers,[54] since methane is miscible with supercritical carbon dioxide in a wide extension. The catalyst is based on silver, and a highly fluorinated ligand, a perfluorotrisindazolylborate, became crucial for catalyst solubilisation (ligands **34**, Scheme 14). Introduction of the strong electron-withdrawing fluorine atoms in the ancillary ligand of the complex confers the metal carbene a strong electrophilic character at the same time that provides higher solubility in the supercritical media. The use of these catalysts allowed the functionalization of methane with ethyl diazoacetate in 29 % yield (diazo-based). The influence of the length of the fluorinated chains located in position 3 of the indazolyl rings has been also studied, with opposite effects: although complex solubility increased with the length of the chain, this was not traduced in higher transfer reaction efficiency but in the production of a major amount of dimerization products. This catalytic system was extended to the C2-C4 series of gaseous alkanes obtaining almost quantitative yields of insertion products.

The use of ligand **35** under the same conditions has allowed for the first time using copper as catalyst the functionalization of methane within this methodology.[55] An interesting effect of *sc*CO_2 was observed when this catalyst was used for the C-H activation of liquid alkanes (Scheme 14):[56] the selectivity varied when moving from neat alkanes to *sc*CO_2 as the reaction medium. This result has been attributed to the interaction of the molecules of CO_2 with the ancillary ligand thus withdrawing electron density from the complex and thus increasing the electrophilic nature of the carbene intermediate.

The high solubility of diazocompounds in compressed carbon dioxide has also been profited to develop an intramolecular C-H insertion catalysed by fluorinated complexes based on rhodium (II).[57] In the absence of any other C-H bond, the diazocompound is cyclized yielding β-lactams (Scheme 15).

5. CROSS COUPLING REACTIONS

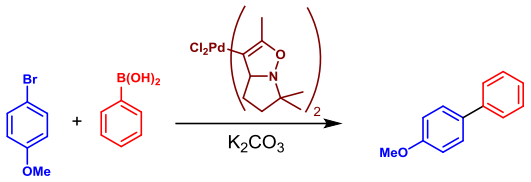
Palladium catalyzed cross-coupling reactions are among the most versatile carbon-carbon bond forming processes.[58] The first example of this transformation in *sc*CO_2 was described by Reiser and co-workers in 1996.[59] They studied the arylation of 2,3-dihydrofuran with iodobenzene catalysed by $Pd(OAc)_2/PPh_3$ (Scheme 16). Kinetic studies showed that although catalyst activity was only up to 3 times higher in *sc*CO_2, catalyst decomposition was very low resulting in a dramatic increase of the TON and TOF numbers. The prolonged lifetime of the catalyst has been explained in terms of its stabilization under high CO_2 pressure which reinforces the coordination of ligands.



Conditions	Conversion (%)	Selectivity (%)	
Neat	95	71	29
MeCN	95	24	76
Toluene	85	45	55
$scCO_2$	95	83	17

Scheme 17. Intramolecular Heck reaction in *sc*CO_2.

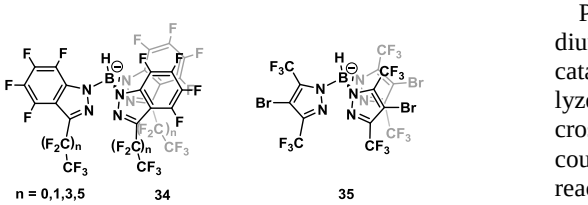
The effect of fluorination of phosphine ligands in cross-coupling reactions in *sc*CO_2 has also been investigated.[60] Fluorinated palladium catalysts were dissolved in *sc*CO_2 avoiding the addition of co-solvents but no improvement was found in terms of yields or catalyst lifetime, a feature that was ascribed to a detrimental electronic effect of the electron deficient phosphine ligands. This drawback has been challenged upon introduction of carbosilane dendrons or polydimethylsiloxane chains as solubilising agents (Figure 3).[61] Several ligands containing different number of trialkylsilyl groups or varying the siloxane chain were tested in the Heck reaction between iodobenzene and methyl acrylate and a direct relation was found between the silicon content and the solubility in *sc*CO_2 of the complexes. However, reaction efficiency of all ligands was very similar and lower in each case than that observed in reactions performed in conventional solvents such as toluene and DMF. Better results were obtained with simple tri-*tert*-butylphosphine.[62] The palladium catalyzed arylation of Merrifield resin was achieved in almost quantitative yield with this phosphine demonstrating the benefits of using low viscous *sc*CO_2 in heterogeneous reactions.

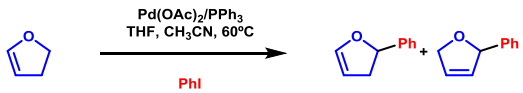


Conditions: catalyst loading 0.025 mol %	Yield (%)
MeOH, reflux	72
Toluene, reflux	67
THF, reflux	traces
$scCO_2$, 120 bar, 120 ºC	100

Scheme 18. Palladium catalyzed cross-coupling in *sc*CO_2.

The palladium source plays a crucial role in the reaction outcome.[63] The use of $Pd(OCOCF_3)_2$ and $Pd(hfacac)_2$ instead of the traditional $Pd(OAc)_2$ or $Pd_2(dba)_3$ allowed reducing catalyst loadings as well as the use of non-fluorinated phosphine ligands. Yields up to 96% were obtained in the Heck reaction between methyl acrylate and iodobenzene in *sc*CO_2





	cat. mol %	yield	TON	TOF	Selectivity	
1 atm	0.1	27 %	270	22	9	1
80 bar *sc*CO_2	0.001	100 %	> 100000	> 833	6	1

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Scheme 16. Heck coupling between 2,3-dihydrofurane and iodobenzene in scCO₂.

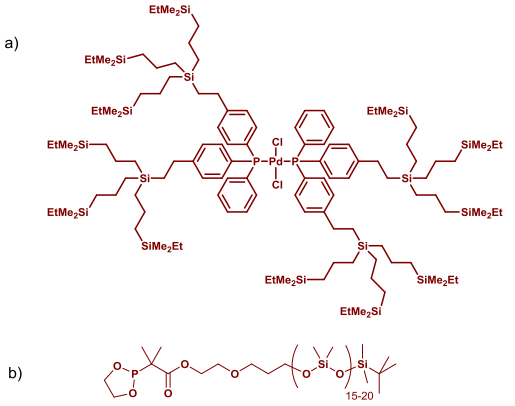


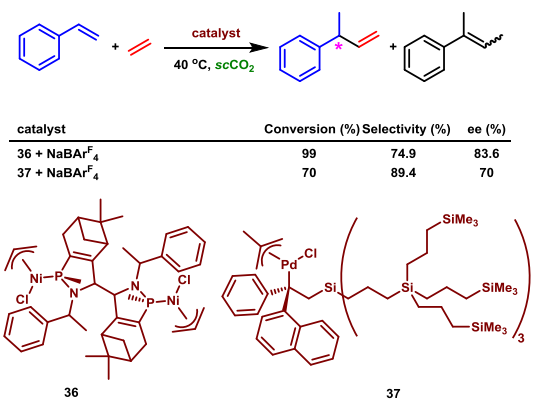
Figure 3. Example of palladium complex with a) carbosilane dendromer and b) polydimethylsiloxane used in the Heck coupling reaction in *sc*CO_2.

catalysed by $Pd(hfacac)_2$ in the presence of tris(2-furyl)phosphine. This phosphine has been used together with $Pd(OCOCF_3)_2$ in the intramolecular version of Heck reaction. In this case, the use of *sc*CO_2 reduced the undesired double bond isomerization common in conventional solvents (Scheme 17).[64]

Suzuki-Miyaura reactions have also been investigated in *sc*CO_2. In a similar way to Heck transfromations, the combination of an electron-rich phosphine and a fluorinated palladium source provides good catalytic activities.[65] A different approach implied the use of a oxadiazoline palladium(II) complex that provided an activity much higher in *sc*CO_2 than in conventional solvents achieving a TON of 4000 in the conversion of bromoarenes into biphenyls in 6 hours (Scheme 18).[66]

Enantioselective hydrovinylation of styrene is another example of improvement of catalyst efficiency when *sc*CO_2 is used as solvent. Two catalysts, one of them based on nickel and other being palladium carbosilane complex, have been described for this reaction (Scheme 19).[67,68] Conversion and selectivity were enhanced in both cases with respect to the corresponding values in reactions performed in dichloromethane. In addition, similar or slightly improved *ee* values were found in *sc*CO_2 but at much lower temperature.

Enantioselective allylic alkylation is a convenient route to chiral products with high complexity. Some advances have been done in the development of this transformation in *sc*CO_2. The use of a chiral diamidophosphite ligand containing a carborane moiety in the palladium catalysed alkylation of allylic acetates led to moderate conversions but good enantioselectivities (Scheme 20).[69] Better results were obtained with a bidentate diamidophosphite ligand.[70] The monodentate diamidophosphite ligand was successfully applied to the allylic amination of unsymmetrically substituted allyl acetates.[71] In this case, the products derived from direct substitution of malonate for acetate was obtained with regioselectivities up to 99 % and complete conversions. The S_N2' reaction, a common side product in this kind of transformation, is in this case very disfavoured.

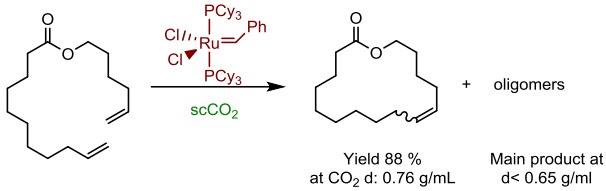


Scheme 19. Enantioselective hydrovinylation of styrene in *sc*CO_2.

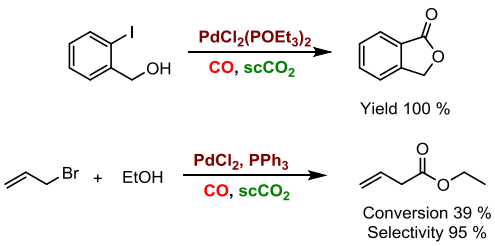
In situ formation of carbamic ammonium salts by reaction of the amines with the solvent is a major drawback in palladium catalyzed aminations of arylhalides in *sc*CO_2 ~~presents the~~. This problem has been overcome by using trimethylsilylamines as surrogates.[72] This procedure could only be applied to aromatic amines and moderated yields were obtained. More nucleophilic aliphatic silylamines showed unreactive due to the formation of silylcarbamates under the reaction conditions.

Carbonylation of aryliodides has been developed in *sc*CO_2 in both inter- and intramolecular versions (Scheme 21).[73] Low conversions in the intermolecular version can be ascribed to low catalyst solubility. Nevertheless, use of $scCO_2$ in this transformation has the beneficial effect of olefin isomerization inhibition, a common side reaction.

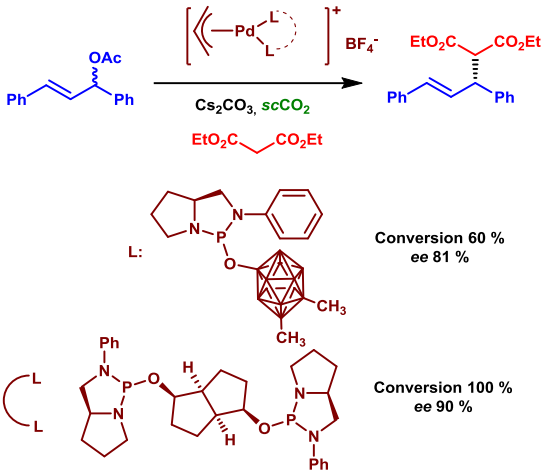
Coupling of terminal alkynes is an important reaction as it yields 1,3-diynes, valuable products due to their physical and electronical properties and as precursors in the synthesis of natural products. Homocoupling of terminal alkynes was first attempted using stoichiometric copper(II) chloride.[74] A catalytic method was later developed using 5 mol % of copper(I) chloride, oxygen and DBU as a base. In order to obtain good yields large excess of base had to be added (250-fold with respect to the alkyne).[75] Good results have been obtained in the copper(I) chloride catalyzed unsymmetrical coupling between bromoalkynols and terminal alkynes with sodium acetate as a base.[76] Small amounts of methanol were added to the reaction mixture in order to increase catalyst solibility.



Scheme 22. RCM in *sc*CO_2.



Scheme 21. Carbonylation reactions in $scCO_2$.



Scheme 20. Enantioselective allylic alkylation.

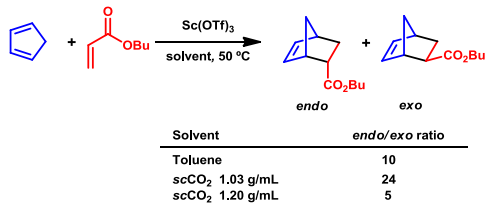
6. OLEFIN METATHESIS

Grubbs catalyst has good activity in *sc*CO_2 in the ring closing metathesis of olefins.[77] Reaction selectivity is strongly dependent on reaction media. Reactions performed in supercritical carbon dioxide with densities below 0.65 g/mL^{-1} gave oligomers as the main products while the desired macrocycles were obtained in good yield under higher density–conditions (Scheme 22).

The authors emphasized the beneficial effect of *sc*CO_2 as reaction media in the ring closing methathesis of dienes bearing free amine substituents, which usually present low reactivity due to catalyst deactivation. However, under the reaction conditions carbamic acids are formed playing the CO_2 two roles: solvent and temporary protecting group.

7. CYCLOADDITION REACTIONS

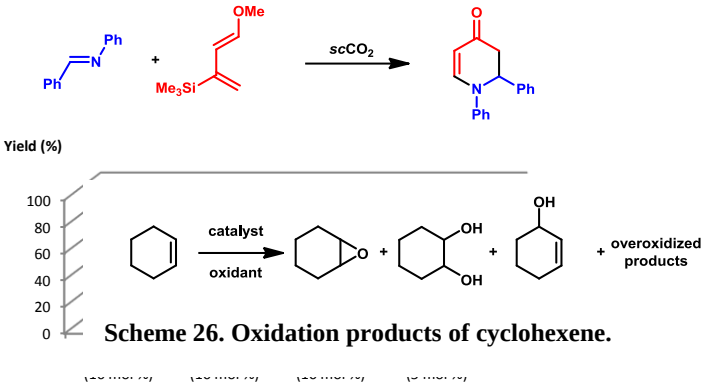
Diels-Alder cycloadditions are among the first reactions performed in scCO2.[78] These pioneer works studied the solvating power of *sc*CO_2 through its effect on the rate and selectivity of well-known Diels-Alder reactions. It was shown that reaction time, regio- and diastereoselectivity were influenced by pressure and temperature changes. The use of Lewis acid catalysts in cycloaddition reactions performed in *sc*CO_2 allowed obtaining better diasteroselectivity through pressure and temperature modifications. Rayner and coworkers found that the diastereoselectivity of the reaction between cyclopentadiene and *n*-butylacrylate in the presence of scandium triflate was strongly affected by *sc*CO*2* density (Scheme 23).[79] Cycloaddition efficiency was improved by increasing catalyst solubility. As an example, in the *aza*-Diels-Alder reaction between benzyliden(phenyl)imine and Danishefsky's diene, the use of metal salts derived from long chain perfluorinated sulfonic acids led to better catalyst solubility and higher reaction yields (Scheme 24).[80] This catalytic system has also been successfully applied to Mannich [78b] and Friedel-Craft acylation reactions.[81]



Solvent	*endo/exo* ratio
Toluene	10
scCO_2 1.03 g/mL	24
scCO_2 1.20 g/mL	5

Scheme 23. Sc(OTf)$_3$-catalysed Diels-Alder reaction.

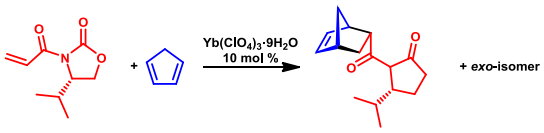
Some approaches have been explored toward the development of an enantioselective version of the Diels-Alder cycloaddition in *sc*CO_2. Thus, the diastereoselectivity of the reaction between Evans's chiral dienophile and cyclopentadiene in the presence of a Lewis acid catalyst was clearly improved in this medium (Scheme 25).[82] The influence of the unique solvation characteristics of *sc*CO_2 in this reaction is outstanding; the induction of good enantio- or diastereoselectivity in common solvents usually requires low temperatures while reactions in *sc*CO_2 take place at least at 40 °C to ensure supercritical conditions. By contrast, use of chiral ligands in the presence of $(CF_3SO_3)_3Sc$ has had little success, with no effect of the supercritical medium in the reaction outcome.[83]



Scheme 26. Oxidation products of cyclohexene.

Scheme 24. *Aza*-Diels-Alder reactions with Danishefsky's diene.

Cyclotrimerization of alkynes is a versatile procedure to obtain polysubstituted benzenes. Two catalysts have been employed in this reaction in *sc*CO_2. Low 22 % yield was obtained in the photochemically activated cyclotrimerization of phenylacetylene catalyzed by $CpCo(CO)_2$.[84] Yield increased to 70 % when the same catalyst was activated thermally at 150 °C. High yields and good regioselectivities were obtained when



Conditions	Yield (%)	*endo/exo*	*de* (%, *endo*)
CH_2Cl_2, 0°C, 2h	90	75/25	61
scCO_2, 40°C, 100 bar, 0.5h	49	83/17	77

Scheme 25. Reaction between Evans's diene and cyclopentadiene.

$PdCl_2$ was used as catalyst in the cyclotrimerization of internal alkynes.[85] However, two equivalents of $CuCl_2$ had to be added as co-catalyst and small amounts of methanol were necessary to increase catalyst solubility.

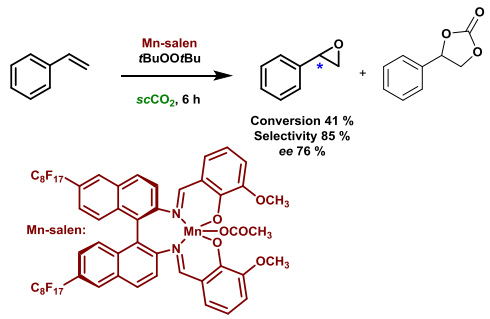
8. OXIDATION REACTIONS

Catalytic oxidation of alkenes is an important synthetic transformation to obtain epoxides, diols, allylic alcohols, ketones and other products with industrial relevance (Scheme

26). First attempts to develop this reaction in *sc*CO_2 were based on $Mo(CO)_6$ as the catalyst precursor and *tert*-butylhydroperoxide as the oxidant.[86] Complete conversion of cyclohexene was attained with only one equivalent of 70 % aqueous tBuOOH. *anti*-1,2-Cyclohexanediol was obtained by *in situ* hydrolysis of the intermediate oxirane formed. Reactions performed with an anhydrous solution of alkylhydroperoxide in decane yielded exclusively cyclohexene oxide but three equiv. of oxidant had to be added to achieve quantitative yields. An attempt to develop a catalyst to use air as oxidant in this reaction involved the use of highly fluorinated iron-porphyrin complexes.[87] The reaction in *sc*CO_2 was cleaner due to the absence of the frequent solvent-derived oxidation products found in conventional solvents, but the epoxide was obtained only with a modest 23% selectivity due to the preferential allylic oxidation under these conditions.

A vanadium(IV)-salen complex bearing bulky *tert*-butyl substituents was used in the diastereoselective epoxidation of allylic alcohols with *t*BuOOH.[88] A moderate 70 % *de* was obtained although with good selectivities, ring opening and isomerization reactions were always under 10 %.

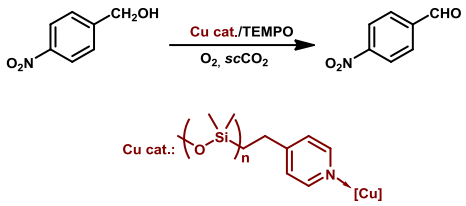
The enantioselective epoxidation of styrene in *sc*CO_2 has been developed using a manganese-salen complex bearing a fluorinated binaphtyl moiety (Scheme 27).[89] The epoxide was obtained with a selectivity up to 85 % and 76% *ee* avoiding the cleavage oxidation products typical in aromatic alkene oxidations. Prolonged reaction times caused the formation of only cyclic carbonates by reaction with *sc*CO_2.



Scheme 27. Enantioselective epoxidation catalyzed by a Mn-salen complex.

Wacker oxidation of terminal alkenes to methylketones has been developed in *sc*CO_2 using the catalytic system formed by $PdCl_2$ and $CuCl_2$ (Scheme 28).[90] Although moderate conversions were obtained, even in presence of small amounts of methanol as cosolvent, the methyl ketone was obtained with a remarkable selectivity higher than that observed in conventional solvents as alcohols or HMPA. This result is another proof of the capability of *sc*CO_2 to diminish double bond isomerization. When acrylates are used as starting material, important synthetic intermediates 3,3-dialkoxypropanoates are directly obtained,.[91]

The solubility of polydimethylsiloxanes has been taken as an advantage for the development of homogeneous metal catalysts. A polydimethylsiloxane functionalized at the chain-end with pyridine has been used as ligand in the copper-based aerobic oxidation of alcohols to aldehydes (Scheme 29).[92] Complete oxidation to the corresponding aldehyde from the electron deficient *p*-nitrobenzyl alcohol was achieved in only 4 hours using a 3.5 mol % of copper catalyst loading and TEMPO in only 7 % as co-catalyst. However, the authors reported similar efficiencies for insoluble catalysts in scCO2 such as $[Cu(OAc)_2(H_2O)]_2$ or $[Cu(OAc)_2(py)]_2$ indicating that catalyst solubility is not an important factor in these reactions. The CuCl catalyzed aerobic oxidation of cyclohexanol to cyclohexanone has also been developed in the presence of 1,10-phenantroline.[93] Athough conversion remained around 30 % the selectivity for the desired product increased from 70 to 90 % in *sc*CO_2 instead of conventional solvents as toluene or fluorobenzene.



Scheme 28. Wacker oxidations in *sc*CO_2.

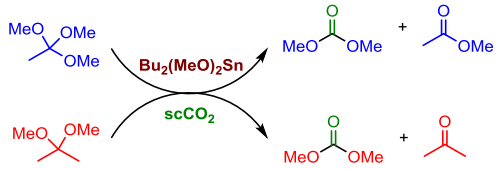
Scheme 29. Copper catalyzed aerobic oxidation of alcohols.

A Fe(III)-tetraphenylporphirine complex has been succesfully used in the direct oxidation of cyclohexane to cyclohexanol in *sc*CO_2. Conversions of 15 % were obtained with selectivities up to 99 %.[94]

9. MISCELLANEA

CO_2 is a perfect C1 building block as is abundant, cheap and safe. Methods for the synthesis of carbonates, carbamates and ureas have been developed using *sc*CO_2 as starting material avoiding the use of toxic phosgene.

Synthesis of dimethylcarbonate from methanol and CO_2 catalyzed by dialkyldialkoxystannanes presents as major drawback catalyst deactivation due to reaction with water formed as concomitant product. This inconvenient has been overcome using trimethylorthoformate or the dimethylacetal of acetone as methanol source.[95] Although high conversions have been achieved with 1.7 mol % of dibutyldimethoxystanne and dimethylacetal of acetone, this procedure has the inconvenient of the formation of stoichiometric amounts of acetone, difficult to separate from the desired dimethylcarbonate (Scheme 30). A first attempt to synthesize dimethylcarbonate directly from methanol and CO_2 used a special vessel were the reaction mixture was circulated through a second reactor bearing molecular sieves 3A at room temperature. Long recirculation periods of 72 hours were necessary in order to obtain conversions of 50 %.[96]

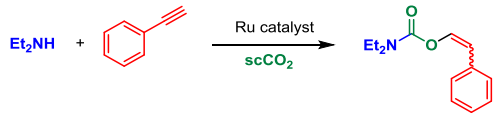


Scheme 30. Synthesis of dimethylcarbonate from trimethylortoformate or 2,2-dimethoxypropane.

scCO_2 has also been reacted with epoxides to yield cyclic carbonates.[97] Although good conversion of 2-methyloxirane can be obtained with 1 mol % of lithium bromide, better catalytic activities were obtained when an aluminium salen complex was used.

Spontaneous reaction between amines and CO_2 to yield carbamic acid has been profited for the synthesis of vinylcarbamates in *sc*CO_2.[98] Although formation of carbamic acids from amines and *sc*CO_2 is readily accomplished, reverse decarboxylation takes places easily during depressurization. To effectively fix CO_2 is necessary to trap these intermediates. An effective procedure is the reaction with terminal alkynes to yield vinylcarbamates. Results are summarized in table 4. In all cases reaction efficiency was higher in *sc*CO_2 than in conventional solvents as toluene or acetonitrile.

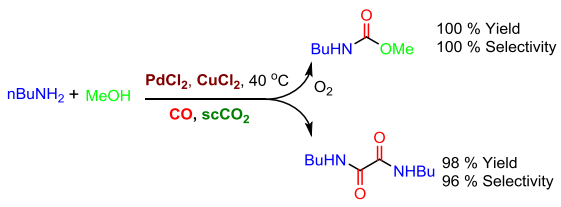
Table 4. Synthesis of vinyl carbamates in *sc*CO_2.



Catalyst	Yield (%)	Z:E ratio	TOF	Ref.
$RuCl_2(C_5H_5N)_4$	35	3.8-8.3:1	43	98a
$RuCl_2(\eta_6\text{-}C_6H_6)(PMe_3)$	80	3.8-8.3:1	148	98a
trans-$RuCl_2(POEt_3)_4$	86	85:1	3	98b

The synthesis of symmetric and non-symmetric ureas from secondary amines and carbon dioxide proceeds smoothly without the need of metal catalysts. [99] However, this procedure cannot be applied to primary amines. Synthesis of symmetric ureas from monosubstituted amines and CO_2 has been performed catalyzed by ruthenium.[12] Moderated yields were obtained with catalyst **2** without the need of any additive, but long reaction times were needed.

Procedures for the synthesis of carbamates and ureas from monosubstituted amines have been developed through palladium catalyzed oxidative carbonylation (Scheme 31).[100] The synthesis of carbamates from primary amines, methanol and



Conditions	Yield (%)	TON
neat	36	18000
$scCO_2$, 170 bar	96	43500

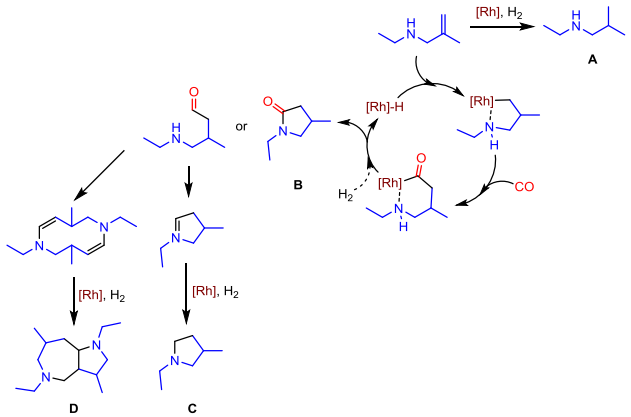
Scheme 31. Synthesis of Top: carbamates and oxalyldiamines and Bottom: aromatic ureas.

CO_2 is catalyzed by $PdCl_2$ in the presence of $CuCl_2$. If oxygen is not present in the reaction mixture, selectivity changes sharply and oxalyldiamines are obtained as major products (Scheme 31, Top) In the case of the synthesis of ureas, the use of *sc*CO_2 as solvent dramatically increased the catalyst efficiency (Scheme 31, Bottom). Under the reaction conditions two phases are formed, one of them rich in amine where the catalyst is dissolved and a supercritical phase completely miscible with carbon monoxide. The interaction of the amine-containing phase with carbon dioxide has two positives effects on the reaction efficiency. First, the expansion of the liquid phase strongly increases the solubility of carbon monoxide in this phase. Additionally, amines react with carbon dioxide to form carbamates which are more active substrates than amines itself in the oxidative carbonylation, especially in the case of aromatic amines.

CO2 has been used as temporary protecting group by formation of carbamic acids in the rhodium catalyzed hydroaminomethylation in supercritical carbon dioxide (Scheme 32). [101] In conventional solvents **B** is the main product obtained by rapid nucleophilic attack of the nitrogen atom to the carbonyl group in the rhodium acyl intermediate. By contrast, i~~I~~nteraction of the amine with CO_2 reduces the intramolecular cyclization reaction rate thus allowing the hydrogenolysis of the acyl rhodium species to take place. The resulting ~~A~~aminoaldehyde suffers condensation followed by hydrogenation to yield desired product **C**. A new product **D** was isolated under supercritical conditions coming from the condensation of two molecules of aminoladehyde followed by intramolecular Mannich cyclization and hydrogenation. Careful control of reaction conditions allowed to reach a 77 % conversion and a selectivity of 76 % in the desired pyrrolidine.

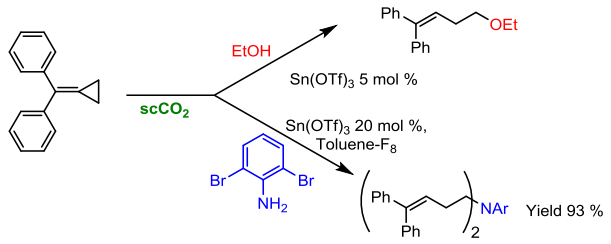
Cyclopentenones can be readily synthesized by Pauson-Khand carbonylative cyclization of enynes. The intra- and intermolecular versions of this $Co_2(CO)_8$ catalyzed transformation has been studied in *sc*CO_2. [102] Although good yields have been achieved with catalyst loadings of 2-5 mol %, a long reaction time of 2-3 days was necessary.

Intermediate carbocations formed in Lewis acid catalyzed ring-opening of methylenecyclopropanes are trapped by a nucleophile, generally an amine or alcohol. This type of transformation has been assayed in *sc*CO_2 in the presence of small amounts of perfluorotoluene as co-solvent using $Sn(OTf)_3$ as the catalyst (Scheme 33).[103] The reaction of primary aromatic amines required the use of high catalyst loadings and dialkyla-



Scheme 32. Rhodium catalyzed hydroaminomethylation

tion of the amine occurred preferably. Better yields were obtained with lower catalyst loading in absence of co-solvent when an alcohol was used as nucleophile. This difference in

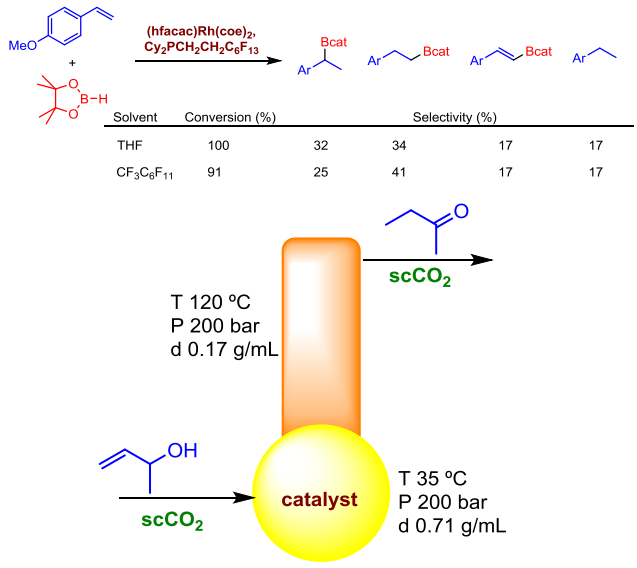


Scheme 33. Lewis acid catalyzed methylenecyclopropane ring-opening.

reactivity is most sure due to the carbamate formation in the case of the amines that reduces its reactivity.

Complete selectivity for the Markovnikov addition product was obtained in the hydroboration of vinyl arenes catalyzed by Rh(I) in *sc*CO_2.[104] This transformation is greatly solvent dependent and the selectivity for the desired product increased from 25-30 % in conventional solvents as THF or perfluoromethylcyclohexane to 100 % in *sc*CO_2 (Scheme 34).

Possibility of selective product separation by pressure or temperature tuning is often appealed as a benefit of the use of *sc*CO_2 as reaction medium. A special reactor design has allowed performing a homogeneous metal-catalyzed reaction in *sc*CO_2 under continuous flow conditions.[105] The apparatus is formed by a vessel were the reaction takes place connected to a vertical heat exchanger at a higher temperature (Scheme 35). A solution of the starting allylic alcohol in *sc*CO_2 is feed in o the reaction zone. In this part, isomerization to the corresponding ketone catalyzed by $Rh(COD)_2BAr^F_4$ in the presence of ligand **24** takes place. When this supercritical solution enters the upper part of the reactor, isobaric increase of temperature induces a density reduction and only more volatile ketone is soluble under this conditions. Catalyst and starting alcohol



Scheme 35. Special reaction vessel for continuous flow homogeneous catalysis.

condense and return to the reaction zone.

9. CONCLUSIONS

We have aimed to provide to the reader the state of the art of the use of $scCO_2$ as the solvent for soluble, transition-metal catalyzed reactions. A frequently asked question refers to whether the design of catalysts for such medium and the development of the experimental setup is worth or not in terms of the catalytic outcome. Several issues should be taken into consideration. The use of $scCO_2$ instead of organic solvents is an advantage not only from the perspective of green chemistry (always assuming that CO_2 can be recycled after use) but also regarding separation, usually achieved through controlled depressurization. However, such advantages would imply no improvement unless the reaction outcome is noticeably better. In this sense, the main advances of this strategy have been observed with transformations involving gases as reactants. The *sc*CO_2 fluid can dissolve a large amount of gaseous reactants when compared with the solubility of these reagents in common solvents, and this factor is crucial toward reaction kinetics. On those basis, from a productive point of view, reaching high conversion rates would make the design of more elaborated, in many cases fluorine-containing, ligands worth of development. The capability of dissolving large amount of gases and the lack of C-H bonds are unique in this solvent. These properties have made possible, yet from a purely academic interest, the functionalization of methane and other inert gaseous alkanes.

In most of the results presented in this contribution we have found that a certain improvement in the reaction outcome has been developed when carried out in *sc*CO_2 compared with those observed in conventional solvents. However, this methodology is yet far from being highly developed probably due to the need of using special ligands containing certain substituents to favor the catalyst solubilization and of specific high pressure hardware. We hope that given the advances in the area, in the next years the development of more effective catalytic systems for new or already described transformations will take place.

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Funding Sources

Support for this work was provided by the MINECO (CTQ2014-52769-C03-1-R and CTQ2014-52769-C03-2-R), and the Junta de Andalucía (P10-FQM-06292).

ACKNOWLEDGMENT

Support for this work was provided by the MINECO (CTQ2014-52769-CO3-1-R and CTQ2014-52769-CO3-2-R), and the Junta de Andalucía (P10-FQM-06292).A. O. thanks MINECO for Juan de la Cierva fellowship (JCI-2011-09184).

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SYNOPSIS TOC

The use of supercritical carbon dioxide ($scCO_2$) as reaction medium as an alternative for conventional organic solvents frequently induces a beneficial effect (activity, reaction rate, TON/TOF values) in transition metal catalyzed reactions. The main advances in the area are described in this Review Article

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