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Palladium-catalyzed Heck coupling reactions using different fluorinated phosphine ligands in compressed carbon dioxide and conventional organic solvents

S. Fujita [a], K. Yuzawa [a], B.M. Bhanage [a,b], Y. Ikushima [b,c], M. Arai [a,b,*]

[a] *Division of Materials Science and Engineering, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan*
[b] *CREST, JST, Japan*
[c] *Supercritical Fluid Research Center, Institute of Advanced Industrial Science and Technology, Sendai 983-8551, Japan*

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Abstract

Palladium-catalyzed Heck reaction of iodobenzene and styrene was investigated in compressed CO_2 using different fluorinated phosphine compounds as ligands at a temperature of 70 °C. The reaction mixture is a single phase at 12 MPa but biphasic at 8 MPa, a little higher than the critical pressure of pure CO_2 under the reaction conditions used. Although the solubility of fluorinated ligands is very high in dense CO_2, they have marginal improvements in Heck conversion in this medium compared with a non-fluorinated ligand of triphenylphosphine. The activity of palladium complexes strongly depends on the kind of phosphine compound used, in the order of bis(pentafluorophenyl)phenylphosphine (III) $>$ triphenylphosphine (I), tris(pentafluorophenyl)phosphine (IV) $>$ diphenyl(pentafluorophenyl)phosphine (II), tris(*p*-fluorophenyl)phosphine (V) $>$ tris(*p*-trifluoromethyl phenyl)phosphine (VI), 1,2-bis[bis(pentafluorophenyl)phosphino]ethane (VII), for the homogeneous reaction at 12 MPa. This order of effectiveness of these ligands is different from those obtained in conventional organic solvents. Hexane, toluene, ethanol, and *N*-methylpyrrolidone (NMP) showed maximum conversions with the ligands VI, IV, V and VII, respectively. The conversion in CO_2 with the ligand III is comparable with those in polar solvents of ethanol and NMP, and larger than those in hexane and toluene in the presence of the best ligands. The dense CO_2 may affect the specific activity of palladium complex catalysts and/or the reactivity of reacting species. Small quantities of fluorinated products were observed to form at high pressure of CO_2 and this is direct evidence of P–C bond cleavage during Heck reaction in dense CO_2. The activity of palladium complexes with those ligands is higher in more polar solvent.

Keywords: Palladium; Fluorinated phosphines; Ligand effects; Supercritical carbon dioxide; Heck coupling

1. Introduction

Supercritical fluids have been attracting increasing attentions owing to their unique physical and chemical properties [1]. The use of supercritical fluids as reaction media could lead to solvent replacement, better chemistry, and new chemistry [1,2], and they will contribute environmentally benign methods for chemical synthesis and processing. Pressurized dense carbon dioxide allows various chemical substances to dissolve in it but it simply separates from them by depressurization. This enables the separation of carbon dioxide used as a solvent and/or a reactant from

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[*] Corresponding author. Present address: Division of Materials Science and Engineering, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan.
Fax: +81-11-706-6594.
E-mail address: marai@eng.hokudai.ac.jp (M. Arai).

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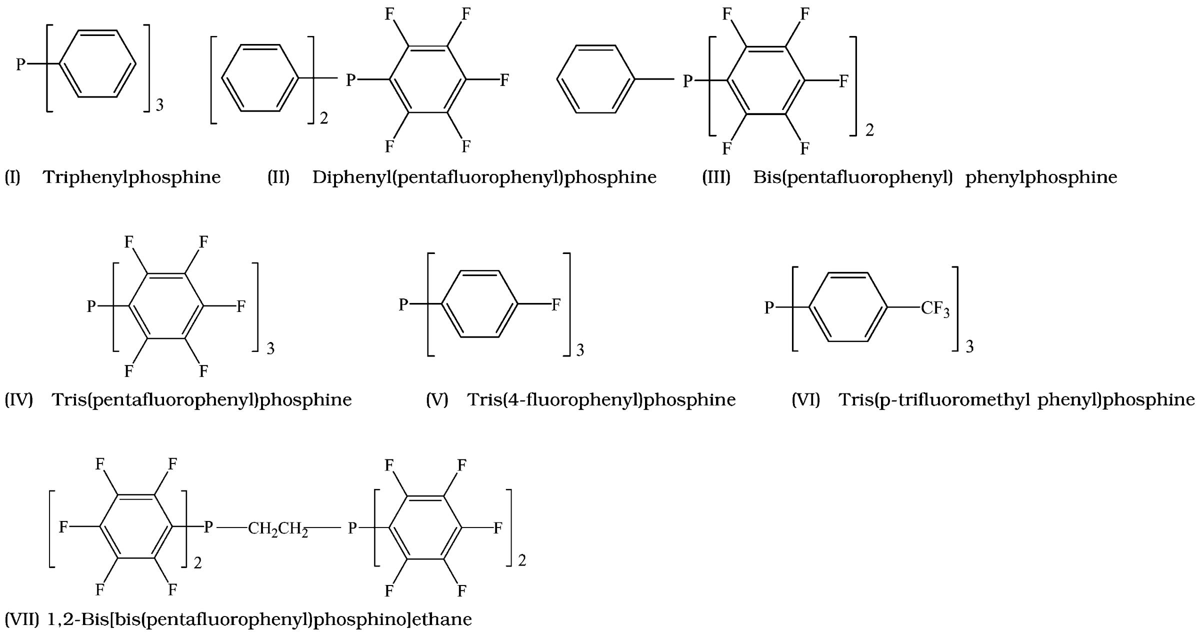
other reactants, products, and catalysts that are liquid or solid. These features of carbon dioxide are of both industrial significance and scientific interest.

Organometallic complexes are effective catalysts for various chemical transformations in conventional solvents [3]. Several research groups study those catalysts in dense carbon dioxide in an attempt to combine their high activities and its interesting properties. One can carry out homogeneous or heterogeneous catalytic reactions in dense carbon dioxide. For homogeneous reactions, organometallic complexes catalysts should be soluble to a certain extent in dense carbon dioxide. Often used metal complexes include phosphine compounds as ligands [3], which are less soluble in carbon dioxide. However, the fluorination of phosphine ligands leads to an increase in their solubility in carbon dioxide. Wagner et al. [4] reported, for example, that the solubility of triphenylphosphine in carbon dioxide is 5.16 mmol/l at 10.0 MPa and 310 K, whereas those of tris(*p*-fluorophenyl)phosphine and tris(pentafluorophenyl)phosphine are 60 mmol/l at 10.1 MPa and 310 K and 228 mmol/l at 9.5 MPa and 310 K, respectively. A few authors recently reported palladium-catalyzed Heck coupling reactions using fluorinated phosphine ligands. Morita et al. [5] showed the effective performance with tris[3,5-bis(trifluoromethyl)phenyl]phosphine ligand at an elevated pressure of 34 MPa and explained it by an increased solubility of the palladium complex. Carroll and Holmes [6] examined the solubility of palladium complexes using such fluorinated phosphine ligands as $(C_6F_{13}CH_2CH_2)_nPPh_{(3-n)}$ ($n = 1, 2$) and applied them to Heck and other carbon–carbon coupling reactions. Shezad et al. [7] reported the effectiveness of fluorinated palladium sources like $Pd(OCOCF_3)_2$ and $Pd(F_6\text{–}acac)_2$ for Heck coupling reactions. Kainz et al. [8] reported catalytic activity in dense carbon dioxide for rhodium catalysts containing perfluoroalkyl-substituted arylphosphines. Thus, homogeneous organometallic complexes are expected to achieve high catalytic performance in dense carbon dioxide as well as conventional solvents when using suitably selected ligands. For hydroformylation, several authors show the effectiveness of the combination of dense carbon dioxide and homogeneous metal complexes using modified phosphine ligands [9–12]. Very recently, Palo and Erkey [12] compared the activities of rhodium complexes with various fluorinated tertiary-phosphine compounds for hydroformylation of 1-octene.


(I) Triphenylphosphine
(II) Diphenyl(pentafluorophenyl)phosphine
(III) Bis(pentafluorophenyl) phenylphosphine
(IV) Tris(pentafluorophenyl)phosphine
(V) Tris(4-fluorophenyl)phosphine
(VI) Tris(p-trifluoromethyl phenyl)phosphine
(VII) 1,2-Bis[bis(pentafluorophenyl)phosphino]ethane

Scheme 1. Compounds used as ligands.

The present work has been undertaken to study the effects of various fluorinated phosphine ligands (as shown in Scheme 1) in a test reaction of palladium-catalyzed Heck reaction of iodobenzene and styrene in dense carbon dioxide. We have measured the activities of various palladium complexes with the fluorinated phosphine ligands and compared these results with those in organic solvents of hexane, toluene, ethanol, and *N*-methylpyrrolidone (NMP). In addition, we have examined the phase behavior of those reaction mixtures by visual observation. The examination of phase behavior is important to see if the reaction is homogeneous or heterogeneous and then to consider if the activity in carbon dioxide is higher or lower than that in conventional solvents.

2. Experimental

2.1. Materials

Phosphine compounds used as ligands are shown in Scheme 1. All these compounds were used without further purification. Palladium acetate was used as Pd source, triethylamine as base, and iodobenzene and styrene as substrates. All these materials and conventional organic solvents were from Wako Pure Chemical Industries or Fluka Chemie AG. Carbon dioxide of 99.99% purity was used.

2.2. Experimental setup and procedures

The reaction experiments were carried out using a batch-type high-pressure reactor system as described previously [13,14], including a 50 ml stainless steel reactor vessel, a magnetic stirrer, a high-pressure liquid pump, and a back pressure regulator. The reaction mixture of organic substances was charged into the reactor vessel and it was immersed in a water bath maintained at a reaction temperature of 70 °C. Then liquid carbon dioxide was introduced up to near a reaction pressure. After the temperature of reaction mixture reached the desired temperature, small quantity of carbon dioxide was further introduced to attain the desired reaction pressure. After the reaction, the vessel was cooled with ice water to room temperature and it was depressurized to atmospheric pressure. The reaction mixture was removed with acetone and it was analyzed by gas chromatograph with a flame ionization detector or with a mass spectrometer. Typical reaction conditions are as follows: iodobenzene, styrene, triethylamine, 10 mmol; palladium acetate, 0.05 mmol; P(ligand)/Pd ratio, 2; time, 21 h.

The phase behavior of reaction mixtures was examined using a similar reactor of 10 ml attached with transparent windows, through which the mixture was seen by the naked eye and its change with pressure was recorded on video recorder using CCD camera. The temperature of the reactor was controlled using an electric heater enveloping it. Substrates (2 mmol), base (2 mmol) and ligand (0.02 mmol) were charged into the reactor. Liquid CO_2 was introduced to about 2 MPa and the reactor was heated. After the temperature went up to 70 °C, liquid CO_2 was further introduced at a rate of about 10 ml/min while stirring. The introduction of CO_2 was stopped at several different pressures and the mixture was maintained at each pressure for several minutes. The stirring was stopped and then the state of mixture was examined at several pressures. In addition, the concentration of chemical species in the gas phase was examined with infrared spectroscopy using a 1.5 ml reactor under similar conditions described above, using 0.4 mmol of substrates and triethylamine each and 0.004 mmol of ligands except for the ligand VII (0.002 mmol).

For conventional solvents of hexane, toluene, ethanol, and NMP, Heck reactions were conducted with a 100 ml autoclave under ambient atmosphere. A 50 ml of solvent was used for each run. Typical reaction conditions were the same as used for those in CO_2 except for reaction time, which was 4 h but a few runs were conducted for a longer time of 21 h.

3. Results and discussion

3.1. Heck reaction in CO_2

Fig. 1 shows the quantities of stilbene formed for Heck reactions using different phosphine ligands in CO_2 at pressures of 0.5, 8 and 12 MPa. The main product was stilbene with very minor by-products under the present conditions. The quantity of stilbene formed strongly depends on the kind of ligand used and CO_2 pressure applied. The highest activity was observed with the ligand VI at 8 MPa but the activity

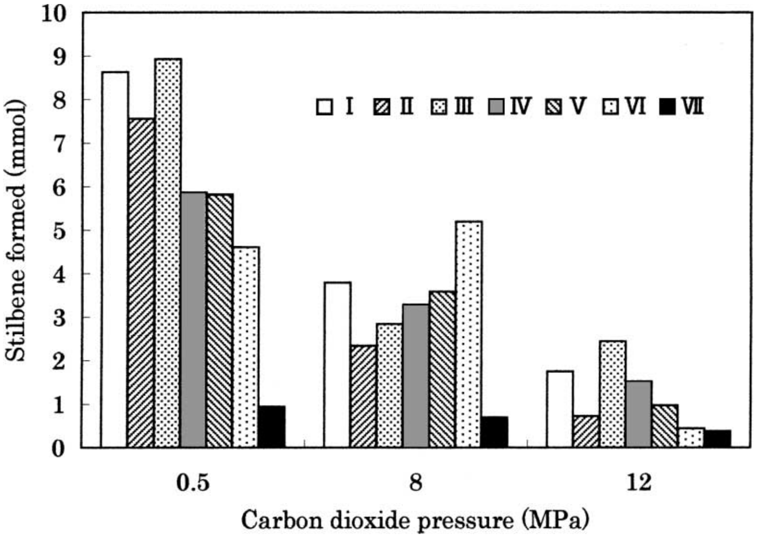


Fig. 1. Influence of ligands of I–VII on palladium-catalyzed Heck reactions in a medium of carbon dioxide at 0.5, 8 and 12 MPa. Reaction conditions: substrates, base, 10 mmol; Pd(OAc)2, 0.05 mmol; P(ligand)/Pd = 2; reaction volume, 50 ml; temperature, 70 °C; time, 21 h.

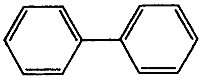
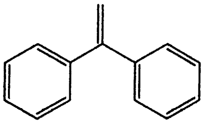
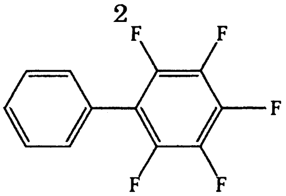
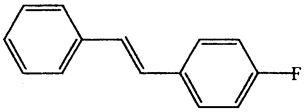
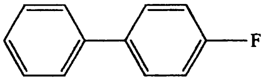
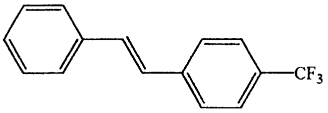
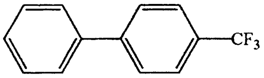
with this ligand considerably decreased to the lowest level at 12 MPa. The activity with the ligand III did not change so much with pressure and it was the highest at 12 MPa. Some fluorinated compounds were less effective ligands compared with non-fluorinated ligand I, triphenylphosphine, by contraries. The compound VII was much less effective irrespective of CO_2 pressure. At 0.5 MPa, the reacting species were not soluble in gaseous CO_2, and so the reaction occurred in the liquid phase (solvent-less). The reacting species are concentrated in this case and this is a reason for the higher conversions obtained compared with the reactions at higher CO_2 pressures. The order of effectiveness of ligands is very similar between this solvent-less reaction and the reaction at 12 MPa, in which the reaction mixture is a single phase as described below.

Table 1 lists by-products formed during reactions at high CO_2 pressures, which were very minor but detected by GC–MS. The formation of those by-products indicates that phosphine compounds were involved as one of reactants and that P–C bonds of the ligands should have been cleaved. It was previously reported the cleavage of P–C bond occurred in Heck reactions catalyzed by Pd complexes with phosphine compounds in an organic solvent at temperatures above 120 °C [15]. We did not detect such by-products as shown in Table 1 in the conventional solvents at a lower temperature of 70 °C. The same reaction temperature was used for the runs with CO_2 and so highly compressed CO_2 atmosphere may cause the P–C cleavage.

3.2. Heck reaction in conventional solvents

The effectiveness of the fluorinated phoshine ligands in conventional organic solvents is shown in Fig. 2. In the case of hexane, the quantity of stilbene formed did not change so much with the phosphine ligand used. When compared with the result for triphenylphosphine, the fluorinated ligands III and IV were more effective for toluene, II, III, V, and VI for ethanol, and IV, V, and VII for NMP. The compound V was commonly effective for the two polar solvents of ethanol and NMP. The phosphine ligands are useful for ethanol to enhance the activity of Pd but not for NMP, which functions by itself as an effective ligand and gives the highest rate of reaction in the absence of ligands [16,17]. In the case of ethanol, small black particles were observed to form for all the ligands examined and so the precipitation of the metal occurred during the reaction. The activity of palladium complexes with those fluorinated phoshines is higher in more polar solvent, similar to the case of triphenylphosphine.

Table 1
By-products formed during palladium-catalyzed Heck reactions in dense carbon dioxide using different ligands

Ligand	By-products
I	 1  2
II–IV, VII	1 2 
V	1 2  
VI	1 2  

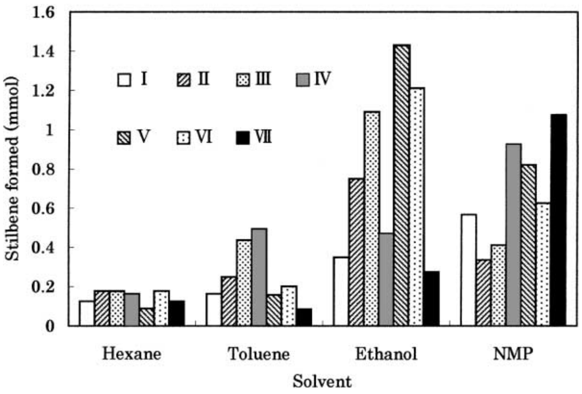


Fig. 2. Influence of ligands of I–VII on palladium-catalyzed Heck reactions in conventional organic solvents. Reaction conditions: substrates, base, 10 mmol; Pd(OAc)$_2$, 0.05 mmol; P(ligand)/Pd = 2; solvent, 50 ml; temperature, 70 °C; time, 4 h.

3.3. Phase behavior of reaction mixture with CO$_2$

The state of reaction mixture was examined by the naked eye through a transparent window using substrates, base, CO$_2$ and ligand at 70 °C. The catalyst, Pd(OAc)$_2$, was not used because the examination was often disturbed by solid materials like stilbene formed, which deposited on the window, when the catalyst existed. Fig. 3 shows pictures of two selected reaction mixtures with the ligands I and III at CO$_2$ pressures of 0.5, 8.0 and 12.0 MPa. For the reaction mixtures with the other ligands, very similar changes with pressure were also observed. At 0.5 MPa, there are two phases, CO$_2$ gas and a liquid phase, in which all the reacting species are soluble. When CO$_2$ pressure is as low as ambient pressure, the solubility of substrates, catalyst, and base in it is negligible and so the reaction should proceed in the liquid phase (solvent-less reaction). At a higher pressure of 8 MPa slightly higher than the critical pressure of CO$_2$, two phases are still present. In this case, however, the reacting species should be distributed to these two phases and the Heck reaction should occur in the CO$_2$ and liquid phases. The quantity of the ligands used was lower than their solubility in pure CO$_2$ at 8 MPa [4] but they should exist in the CO$_2$ and liquid phases under the reaction conditions used. As the pressure is raised to 12 MPa or above, the mixture changes into a single phase; namely, the reaction takes place in this homogeneous phase at the

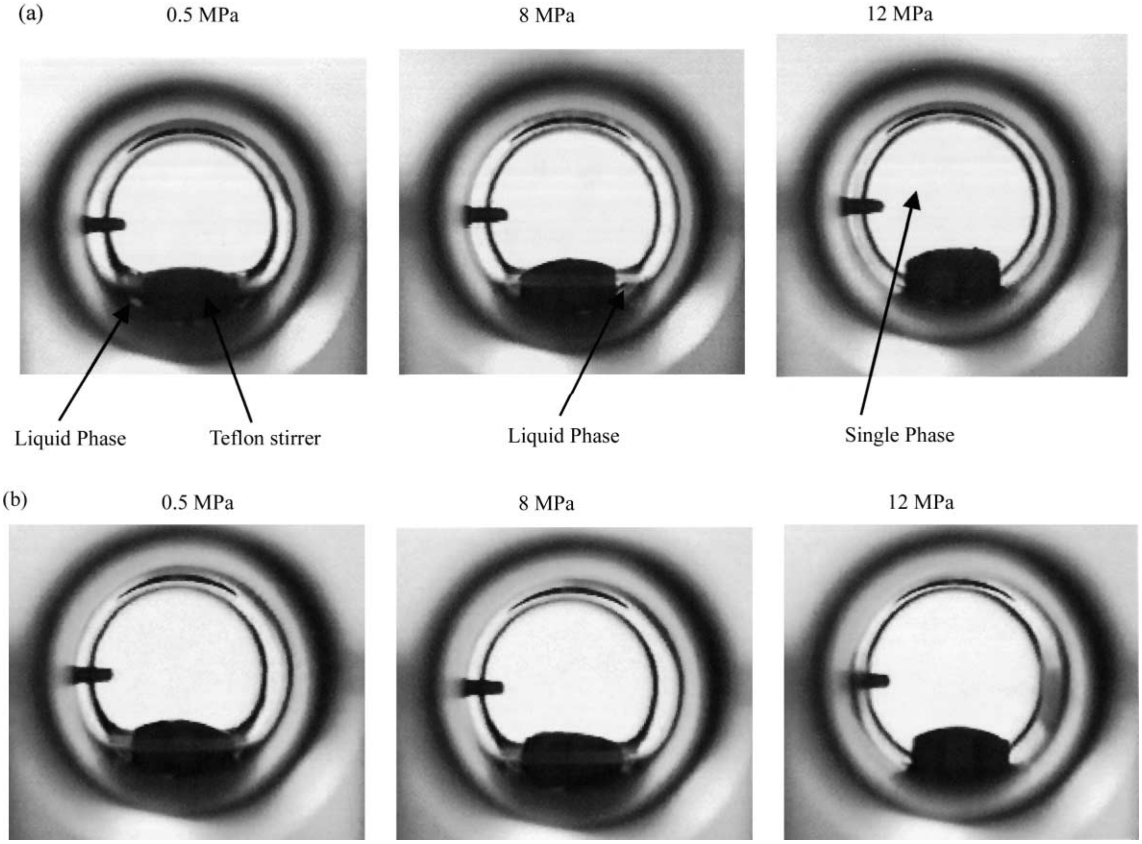


Fig. 3. Visual observations of reaction mixtures with (a) ligand I and (b) ligand III in CO_2 at 70 °C and at 0.5, 8, and 12 MPa. Conditions: reactor volume, 10 ml; temperature, 70 °C; substrates, base, 2 mmol; ligand, 0.02 mmol.

elevated pressures. The same changes with increasing pressure were also observed for all the ligands examined. Thus one can assume that the reaction mixture is in a single phase at a high CO_2 pressure of 12 MPa or above.

In addition, the relative concentrations of substrates, base, and ligands in the CO_2 gas phase were examined with IR measurements under similar conditions described above. Table 2 shows the ratio of the absorption intensity with respect to the intensity at 12 or 16 MPa, at which the reaction mixture is proved to be homogeneous from visual observations. All those chemical species are present in the CO_2 gas phase at 8 MPa while the ligands cannot be detected at 0.5 MPa, at which some quantities of the substrates and base are soluble in the gas phase since they can partly evaporate at 70 °C.

3.4. Comparison of activities

For comparison of the activities of Pd complexes using different fluorinated phosphine compounds in CO_2, we should use the results at a high CO_2 pressure of 12 MPa, at which the reaction mixture is in a single phase. Fig. 1 indicates that the activity of Pd complex is in the order of III $>$ I, IV $>$ II, V $>$ VI, VII. The maximum and minimum turnover numbers (TONs) are 48 and 6, respectively, for III and VI. The TON would be enhanced since reaction conditions have not yet been optimized. An asymmetrically fluorinated phosphine compound III is effective, whereas the other compounds are similarly or less effective compared with triphenylphosphine. Although the fluorination increases the solubility of phosphine compounds in dense CO_2, it has positive

Table 2
Relative quantities of chemical species in the gas phase at different CO_2 pressures at 70 °C estimated from IR measurements

Substance	Wavenumber[a] (cm^{-1})	Relative quantity			
		0.5 MPa	8 MPa	12 MPa	16 MPa
Styrene	1633	0.02	0.20	1	
Iodobenzene	1576	0.02	0.16	1	
Triethylamine	1211	0.15	0.50	1	
Ligand I	1025	0.00	0.05	1	
	3064	0.00	0.01	1	
Ligand II	981	0.00	0.02	1	
	3066	0.00	0.05	1	
Ligand III	981	0.00	0.18	1	
	3069	0.00	0.18	1	
Ligand IV	985	0.00	0.15	1	
	1640	0.00	0.16	1	
Ligand V	1015	0.00	0.08	1	
	1590	0.00	0.05	1	
Ligand VI	1017	0.00	0.23	1	
	1324	0.00	0.26	1	
Ligand VII	981	0.00	0.00	0.05	1
	1518	0.00	0.02	0.09	1

[a] From K. Nakanishi and P. Solomon, Infrared Absorption Spectroscopy, Emerson-Adams Press, 1998.

or negative effects on the catalytic activity of Pd complexes with them depending on the location and extent of fluorination. Palo and Erkey [12] studied rhodium-catalyzed hydroformylation in dense CO_2 using fluorinated tertiary-phosphine ligands. The activity of rhodium complexes was found to be in the series $[2,5\text{-}(CF_3)_2C_6H_3]_3P > [4\text{-}CF_3C_6H_4]_3P$, $[3\text{-}CF_3C_6H_4]_3P > [4\text{-}CF_3OC_6H_4]_3P > [4\text{-}F(CF_2)_4(CH_2)_3C_6H_4]_3P$, increasing with decreasing basicity of the phosphine compound. The very weakly basic ligand IV (see Scheme 1) was not able to complex with rhodium ($Rh(CO)_2(acac)$). It is difficult to simply relate our results with the basicity of the phosphine ligands. The order of activity at 8 MPa is different from that at 12 MPa as discussed above. At this pressure, a little higher than the critical pressure of pure CO_2, the reaction mixture is not a single phase and the reaction is likely to take place in the CO_2-rich phase and in the liquid solution. The overall rate of reaction depends on the distribution of the reacting chemical species between those two phases and the specific activity of Pd complexes in each phase.

For toluene, a similar trend can be seen from Fig. 2, the activity being III, IV > II > I, V, VI > VII. This order is also similar to that observed for a more polar solvent of NMP except for VII, which is very effective. Table 3 shows results on homogeneous reactions in different solvents using the best ligands. A longer reaction time of 21 h was used for all the runs. The rate of Heck reaction decreases after the middle stage of reaction [16] and so the longer time increases the production of stilbene but not so much for the conventional solvents (for which the data obtained with reaction time of 4 h are given in Fig. 2). Table 3 indicates that the quantity of stilbene formed in CO_2 at 12 MPa is comparable with those in polar organic solvents of ethanol and NMP. When the ligand III is selected, CO_2 is the best solvent. As shown in Table 3, the concentrations (mole fractions) of the reacting species in 12 MPa CO_2 are comparable with those in conventional solvents. The concentrations were estimated using the data of Moriyoshi et al. [18]. The TON values are, however, different and so the dense CO_2 is likely to affect the specific activity of a molecular Pd complex catalyst and/or the reactivity of reacting species. Although the concentrations are known, it is difficult to estimate the rate of Heck reaction owing to the complexity of the rate expression for homogeneous Heck

Table 3
Results on homogeneous Heck reactions in carbon dioxide and conventional organic solvents with the best ligands

Solvent	Ligand	Mole fraction		Stilbene formed (mmol)	TON[a]
		Catalyst ($\times 10^4$)	Substrate ($\times 10^2$)		
CO_2, 0.5 MPa[b]	III	16.6	33.2	8.93	178.6
CO_2, 12 MPa	III	1.18	2.35	2.44	48.8
Hexane	VI	1.20	2.40	0.307	6.1
Toluene	IV	1.00	2.00	0.584	11.7
Ethanol	V	0.564	1.13	1.53	30.6
NMP	VII	0.912	1.82	2.84	56.8

[a] Moles of stilbene formed divided by moles of Pd used.

[b] Solvent-less reaction, reaction volume, 3.66 ml. Reaction conditions: temperature, 70 °C; time, 21 h; substrates, base, 10 mmol; $Pd(OAc)_2$, 0.05 mmol; P(of ligand)/Pd = 2; organic solvent, 50 ml; reactor volume (for 12 MPa CO_2), 50 ml.

reaction [19]. It is useful to further examine the details of the phase behavior and the chemical state of the complexes in dense CO_2 with the help of high-pressure spectroscopy techniques [1,20]. The study in line with this direction is in progress in our laboratory.

4. Conclusion

The present results demonstrate that differences in the extent and location of fluorination of phosphine compounds have a significant effect on the activity of Pd-based Heck coupling catalysts in dense CO_2 as well as conventional organic solvents. The reaction mixture in dense CO_2 is homogeneous at 12 MPa but it consists of two phases at 8 MPa. The TONs obtained in 12 MPa CO_2 are comparable with those obtained in such an organic solvent as NMP, which is one of the effective conventional solvents. The specific activity of Pd-phosphine complexes may be modified with changing reaction medium from organic solvent to compressed CO_2.

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