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Enhanced product selectivity in the Mizoroki–Heck reaction using a supercritical carbon dioxide–liquid biphasic system

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Arylation of ethylene catalysed by Pd complexes bearing triphenyl phosphite ligands proceeds efficiently in a $scCO_2$–liquid biphasic system to give a mixture of arylated products; the selectivity of monoarylated products, styrene derivatives, can be improved by increasing the CO_2 pressure, where the monoarylated products are effectively extracted from the liquid reaction phase into the $scCO_2$ phase to prevent over-reactions to diarylated products.

There has been extensive interest in supercritical fluids (SCFs) as reaction media for molecular catalysis.[1] Their unique physical properties tuned by a small change in the pressure and temperature allows improved performance of molecular catalysts in terms of the reaction rates and selectivities.[2] Besides these benefits for catalysis, the use of SCFs can also offer great opportunities to solve the frequently encountered problem of efficient separation of the molecular catalysts by controlling the pressure of the media.[3] Recently, a biphasic reaction system consisting of a supercritical fluid phase and a solvent phase including H_2O was examined for the purpose of separating and recycling metal catalysts.[4] In the case where CO_2-insoluble substrates form the liquid phase under supercritical or subcritical CO_2 conditions, the high volatility of CO_2 allows it to help selectively remove the CO_2-soluble product from the reaction phase, resulting in a solvent-free reaction. However, the catalyst performance in such a multiphase system has not been systematically investigated except for a recent report on solvent-free synthesis under subcritical CO_2 conditions.[5,6] We now report Mizoroki–Heck arylation of ethylene in a CO_2–liquid biphasic system in which monoarylated products can be preferentially obtained in condensed CO_2 where the selectivity is controllable by a change in the pressure of CO_2.

The arylation of ethylene with aryl halides has been well investigated in liquid solvents.[7] In a single reaction phase, the initial products, styrene derivatives are subject to further reaction with aryl halides to afford stilbenes and 1,1-diphenylethylenes, resulting in a significant decrease in the selectivity for the monoarylation. If one of the desired products, styrene in this case, has high solubility in $scCO_2$ compared to that of the byproducts, the use of $scCO_2$ will enable the separation of the initial product from the liquid phase[8] to suppress the subsequent reactions of styrene (Fig. 1).

We first examined the phase behaviour of iodobenzene, ethylene, $N(C_2H_5)_3$ and styrene under subcritical and supercritical CO_2 conditions.† A visual inspection of these compounds in a window-equipped 50 mL reactor vessel confirmed that 1.0 mmol of styrene was completely dissolved in $scCO_2$ under 100 atm at 130 °C whereas some droplets of iodobenzene were observed under the same conditions. In the presence of subcritical CO_2 gas, these materials, except ethylene, precipitate to form the liquid phase where a neat reaction can be performed. Thus, the significant difference in the solubility of these compounds in $scCO_2$ should allow one to extract styrene preferentially from the liquid phase, leading to the efficient control of the styrene formation.[9]

The screening experiments with Pd catalyst bearing tertiary phosphine or phosphite ligands revealed that $PdCl_2\{P(OC_6H_5)_3\}_2$ (**1**) is the best choice of catalyst for the arylation because of its excellent activity[10] and suitable solubility (discussed later) under the reaction conditions at 130 °C and 100 atm.‡ Although complex **1** has been found to partially dissolve in $scCO_2$ under the same conditions,[11] it should stay in the liquid phase rather than the $scCO_2$ phase because of its higher solubility in the liquid substrates phase.

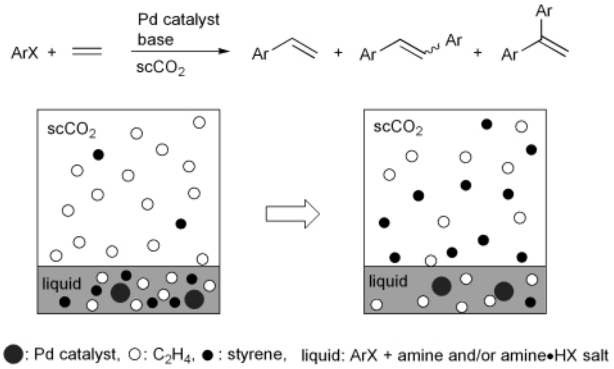

Fig. 1 Schematic illustration of phases during a $scCO_2$–liquid biphasic Mizoroki–Heck reaction. At the initial stage of the reaction, aryl halide, amine and some amine·HX salt are precipitated as a liquid containing the Pd catalyst. At the final stage of the reaction, an excess amount of amine and amine·HX salt form a liquid phase and monoarylated product is extracted into the $scCO_2$ phase. Ar = aryl group, X = I, Br in this case.

The reaction of iodobenzene with ethylene (10 atm) catalysed by the $P(OC_6H_5)_3$–Pd complex **1** (substrate/catalyst = 1000 : 1) at 130 °C in the presence of $N(C_2H_5)_3$ as a base proceeded rapidly to an almost quantitative conversion under solvent-free conditions (without CO_2). As listed in Table 1, styrene was obtained in 57% selectivity along with (*E*)-stilbene and 1,1-diphenylethylene in 31 and 11% yields, respectively. Notably, as illustrated in Fig. 2, the selectivity for the styrene formation was remarkably improved with an increase in the pressure of CO_2 above the critical pressure of 73 atm to attain over 80% at 100 atm and the same temperature. Further increase in the pressure above 100 atm resulted in the selectivity approaching 100% albeit with a significant drop in the yield. The decrease in the total efficiency at higher CO_2 pressures was

Table 1 Mizoroki–Heck reaction of iodobenzene with C_2H_4 in $scCO_2$[a]

Run	Medium	Conv. (%)	Styrene Yield (Sel.) (%)	1,1-Diphenylethylene : (*E*)-stilbene
1	—	95	54 (57)	2.8 : 1
2	CO_2, 25 (atm)	> 99	64 (65)	4 : 1
3	CO_2, 50	> 99	68 (69)	3.4 : 1
4	CO_2, 75	95	68 (71)	1.8 : 1
5	CO_2, 100	> 99	82 (83)	3.3 : 1
6	CO_2, 125	32	29 (92)	N.d.
7	CO_2, 150	19	18 (99)	N.d.

[a] Reaction was conducted at 130 °C for 18 h, in a 50 mL reaction vessel containing 10 μmol of Pd catalyst **1**, iodobenzene and triethylamine. Iodobenzene : **1** : $N(C_2H_5)_3$ = 1,000 : 1 : 1,400.

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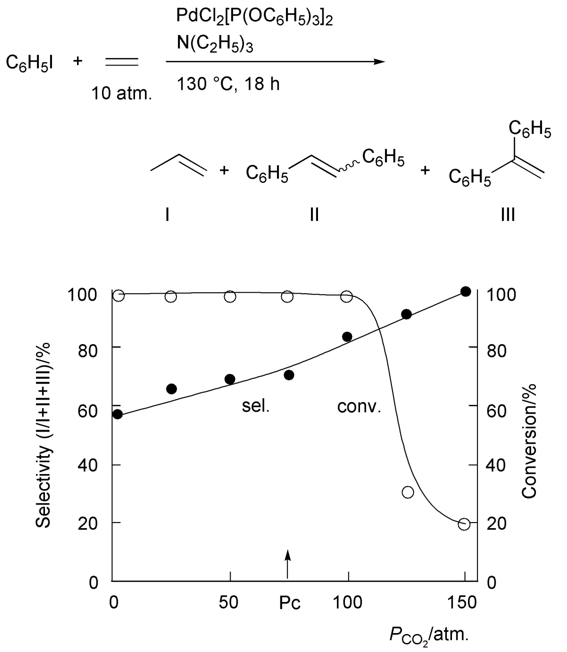
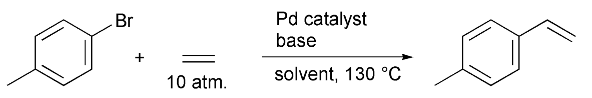


Fig. 2 Selectivity and conversion profile as a function of the CO_2 pressure for the reaction of iodobenzene **2a** and ethylene catalysed by Pd complex **1** in condensed CO_2. Condition: C_6H_5I : $N(C_2H_5)_3$: Pd catalyst = 1000 : 1400 : 1, C_2H_4 10 atm.

mainly due to the disappearance of the liquid phase since everything dissolved in the $scCO_2$, where the homogeneous reaction in $scCO_2$ possibly occurred. In fact, separate experiments showed that the arylation using CO_2-soluble trialkyl phosphite–Pd catalysts[12] in the homogeneous $scCO_2$ phase did not provide turnover numbers higher than those obtained in the liquid phase. These results, in addition to the phase behaviour discussed above, clearly indicate that below 100 atm of CO_2 pressure the reaction occurs rapidly mainly in the liquid phase to give the initial product styrene, which is effectively extracted in the $scCO_2$ phase because of its reasonably high vapor pressure (430 mmHg at 125 °C) and high solubility in $scCO_2$ under the reaction conditions. The use of supercritical or even subcritical gaseous CO_2 might help to separate the desired product from the liquid reaction phase into the $scCO_2$ or vapor phase to avoid further reactions which may produce undesired multiarylated products.

A remarkable advantage of this biphasic system can be demonstrated by the reaction of *p*-bromotoluene substrate/catalyst = 100) and ethylene (10 atm) catalysed by complex **1** in the presence of (DBU) and 1-ethylpiperidine (Table 2). A mixture of these bases serves as an efficient promoter for the less reactive bromoarenes possibly because of their strong basicity. Although the reaction of the bromoarene proceeded much more slowly than that of iodoarene, it reacted with ethylene under neat conditions without CO_2 to give products in moderate selectivity as shown in Table 2 (Run 1). Using CH_3CN as a liquid solvent, the reaction proceeded to 74% conversion after 96 h to give the monoarylated product in 82% selectivity (Runs 2 and 3). In contrast to these liquid phase reactions, the outcome of the reaction in the $scCO_2$–liquid biphasic system was significantly improved, the styrene selectivity increasing from 68 to 88% at near complete conversion after 18 h (Run 4).[13]

Table 2 Pd-catalysed reaction of *p*-bromotoluene and ethylene in $scCO_2$ and other media[a]



Run	Medium	Time/h	Conversion (%)	Selectivity (%)
1		18	100	68
2	CH_3CN, 10 mL	18	14	100
3	CH_3CN, 10 mL	96	74	82
4	CO_2, 100 atm	18	97	88

[a] Reaction was conducted at 130 °C for 18 h, in a 50 mL reaction vessel containing 100 μmol of Pd catalyst **1**. Base = DBU + 1-ethylpiperidine, *p*-bromotoluene:**1**:DBU:1-ethylpiperidine = 100:1:140:150.

In conclusion, the arylation of ethylene catalysed by Pd complex with phosphite ligands selectively afforded monoarylated products in the $scCO_2$–liquid biphasic system. A combination of the rapid reaction in the liquid phase and the extraction of the product with $scCO_2$ provided a significant improvement in the product selectivity.

Notes and references

† Safety warning: Operators of high-pressure equipment should take proper precautions to minimize the risk of personal injury.

‡ Standard procedure for the arylation: The reactor was charged with argon gas and was placed in the oven at 130 °C before introduction of reagents. A mixture of the substrate (1.0 mmol), base (1.4 mmol) and DMF (0.01 mL) solution of Pd catalyst (0.01 mmol) was added into the reactor with a syringe through an opening against the flow of CO_2. Subsequently, C_2H_4 (10 atm) was introduced, and then CO_2 (0–150 atm) was added with an HPLC pump. After stirring for 18 h, the reactor was cooled in a bath of methanol with dry ice. The mixture of C_2H_4 and CO_2 was vented, and the reactor was slowly warmed to rt. The yields of products were determined by GC analyses.

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10 Some examples of the catalytic activity of $PdCl_2L_2$ complexes under the same conditions (conversion after 18 h), L = CH_3CN 13%, $P(OC_2H_5)_3$ 44%, $P(n\text{-}C_4H_9)_3$ 52%, $P(OC_6H_5)_3$ 94%, T. Ikariya, to be published.

11 Some examples of the solubility of $PdCl_2L_2$ complexes (mol L^{-1} at 200 atm and 80 °C): L = $P(n\text{-}C_4H_9)_3$ 5.6×10^{-3}; $P(OC_2H_5)_3$ 8.8×10^{-4}; CH_3CN 2.5×10^{-5}; $P(OC_6H_5)_3$ 7.5×10^{-5}. T. Ikariya, to be published.

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13 The homogeneous Mizoroki–Heck reaction of aryl iodides and activated olefins such as methyl acrylate in $scCO_2$ has been studied by several groups. However, there are no examples of simple bromoarene as the substrate; (*a*) M. A. Carroll and A. B. Holmes, *Chem. Commun.*, 1998, 1395; (*b*) D. K. Morita, D. R. Pesiri, S. A. David, W. H. Glaze and W. Tumas, *Chem. Commun.*, 1998, 1397; (*c*) N. Shezad, R. S. Oakes, A. A. Clifford and C. M. Rayner, *Tetrahedron Lett.*, 1999, **40**, 2221.