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Suppression of double bond isomerisation in intramolecular Heck reactions using supercritical carbon dioxide

Najam Shezad, Anthony A. Clifford and Christopher M. Rayner*

School of Chemistry, University of Leeds, Leeds LS2 9JT, UK

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Abstract—The modified reagent system [Pd($OCOCF_3$)$_2$/P(2-furyl)$_3$/EtN^{i}Pr$_2$] gives enhanced conversions compared with standard conditions [Pd(OAc)$_2$/PPh$_3$/NEt$_3$] for intramolecular Heck cyclisations, and when used in scCO$_2$ results in the suppression of double bond isomerisation to minimal levels, which is otherwise a serious competing side reaction in conventional solvents.

The use of supercritical carbon dioxide (scCO$_2$) as an environmentally friendly non-toxic alternative to common organic solvents is an area of significant current interest.[1] Alongside the environmental aspects, scCO$_2$ also has additional benefits as a reaction medium, such as its ready availability, ease of removal and disposal and/or recycling. Other advantages which are particularly relevant for carrying out reactions in scCO$_2$ are: fine control of solvent properties by changes in temperature and pressure; the ability to homogenise reaction substrates, electrically neutral metal complexes and gases like oxygen and hydrogen; enhanced diffusion rates; and potential for product processing.

More recently it has become apparent that there are more significant benefits to carrying out reactions in scCO$_2$. In our own laboratories we have recently reported that dramatic enhancements of stereoselectivity are possible compared to those obtained in conventional solvents in two totally unrelated classes of reactions, simply by switching to scCO$_2$ and optimising the pressure and hence density of the reaction medium.[2,3]

We have also recently reported methods to carry out Heck, Suzuki and Stille reactions in scCO$_2$ using commercially available palladium sources [Pd($OCOCF_3$)$_2$ and Pd(F$_6$-acac)$_2$] with a range of commercially available phosphine ligands (e.g. P(2-furyl)$_3$ (TFP), P(*o*-tolyl)$_3$), including those that are often considered to be poor ligands for coupling reactions under conventional conditions such as PCy$_3$ and PBu$_3$.[4] The reactions proceed at moderate temperature (80°C) with 2% catalyst loading, and are usually complete within 15–24 h, which are the mildest reaction conditions so far reported for such reactions in scCO$_2$. Previous procedures relied on the use of perfluorinated phosphine ligands in conjunction with Pd($OCOCH_3$)$_2$ or Pd$_2$(dba)$_3$,[5] or a heterogeneous Pd/C catalyst.[6] Whilst these various methods are of interest, it is likely that scCO$_2$ would only be chosen as a reaction medium if it offered specific advantages over conventional solvents. No studies so far have demonstrated that this is the case.

Our methodology, utilising simple, readily available reagents, provides an excellent opportunity for studying a range of Pd-mediated processes on a variety of interesting substrates to try to identify areas where scCO$_2$ may offer advantages. Intramolecular Heck reactions are of fundamental importance for the construction of complex carbocyclic and heterocyclic molecules.[7] However, it is known that in many cases, further reaction of the initial products, in particular, isomerisation of double bonds to form thermodynamically more favoured alkenes, is a serious problem. Separation of such isomers can be difficult, particularly on a large scale. Methods have been developed to overcome such unwanted side reactions that involve the use of additives in the Heck reaction, either expensive silver salts,[8] or toxic thallium salts,[9] which have obvious cost and environmental disadvantages, particularly on a large scale. We now wish to report that carrying out such reactions in scCO$_2$ or in the absence of solvent, also significantly reduces double bond isomerisation.

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* Corresponding author. E-mail: c.m.rayner@chem.leeds.ac.uk

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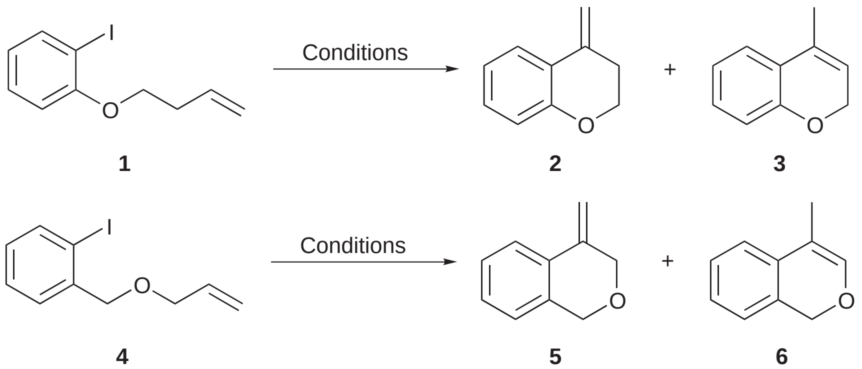

Scheme 1.

We chose to study the intramolecular Heck cyclisation of two related substrates **1** and **4** (Scheme 1).[10] Reactions were carried out in conventional solvents (toluene, MeCN), in $scCO_2$ at a variety of pressures, and in the absence of solvent for comparison. The results are summarised in Table 1.

Reactions in conventional solvents using $Pd(OAc)_2$/PPh_3/NEt_3 with the aryl butenyl ether **1** (entries 1 and 2) gave moderate conversions, with the major product being the isomerised trisubstituted alkene **3**, rather than the initially formed exocyclic alkene **2**. Note that isomerisation is occurring at less than complete conversion indicating that the relative rate of isomerisation is comparable to that for the cyclisation, and hence is a serious competing process. Using our modified reagent system, $Pd(OCOCF_3)_2$/$P(2\text{-furyl})_3$/EtN^iPr_2 in conventional solvents (entries 3 and 4), higher conversions were observed, but the isomerised product **3** was still the major product.

On switching to $scCO_2$, complete conversions were observed at moderate pressures (entries 5–7), with the initial exocyclic alkene **2** predominating, and essentially the reverse of the isomer ratio observed at complete conversion in MeCN.[†] This clearly demonstrates that the double bond migration has, to a large extent, been suppressed by using $scCO_2$ as the reaction medium. At higher pressures, the rate of reaction falls off rapidly, with a slight increase in the degree of isomerisation (entry 8). Interestingly, if the reaction is carried out in the absence of solvent (entry 9), good conversions are obtained, and reduced levels of isomerisation are observed compared to conventional conditions, although not as good as those observed in $scCO_2$. Although neat conditions would appear attractive, there are considerable problems due to exotherms, reaction selectivity, and efficient mixing, which make them impracticable, particularly on a large scale. We thus believe that $scCO_2$ really offers the best opportunity to exploit this effect.

Similar results were noted with the alternative substrate **4**. In conventional solvents, the isomerised product is predominant (entries 10 and 11), whereas in $scCO_2$, little isomerisation is observed (entries 12 and 13). Again, the rate of reaction decreases significantly at higher pressures as before (entries 14 and 15), but note that in this case, the degree of isomerisation actually decreases. For the neat reaction, isomerisation is reduced to levels similar to those obtained in $scCO_2$, but at a lower conversion.

These results clearly show that levels of double bond isomerisation are significantly reduced in $scCO_2$ and neat conditions, compared to those observed in conventional solvents. The similarity of results in $scCO_2$ and neat initially caused concern; the possibility of the reactions apparently occurring in $scCO_2$ actually being neat but under an atmosphere of CO_2 needed to be addressed. Fortunately, the base and substrates are all miscible with the $scCO_2$ with no sign of a neat liquid phase when viewed in reaction vessels fitted with sapphire windows under typical reaction conditions.[6,11] Whilst many of the catalyst systems we have devised have high solubility in $scCO_2$,[4,11] the $Pd(OCOCF_3)_2$/$P(2\text{-furyl})_3$ system is somewhat borderline, with small traces of solid being visible. An active heterogeneous Pd-catalyst cannot thus be discounted,[6] but in any case, would be very different to a neat reaction. Some precipitation is also observed as the reaction proceeds, which is believed to be $EtN^iPr_2{\cdot}HI$ and metallic palladium typical of that observed during Heck reactions.[5,7]

The precise reason for the reduced levels of double bond isomerisation in $scCO_2$ and under neat conditions is not yet known, although $scCO_2$ is a relatively non-polar solvent, which would appear to favour the non-isomerised product (cf. entries 1 and 2; 3 and 4; 10 and 11).[8,9] Other possible explanations currently under consideration are based on enhanced rates of decomposition of the palladium hydride species which are usually responsible for isomerisation. This could be due to the enhanced diffusion rates usually observed in supercritical fluids[1] or reversible insertion of CO_2 into the Pd-H bond.[12] The higher concentration of base under neat conditions may also be expected to increase the rate of decomposition of I-Pd-H species again reducing isomerisation. An alternative explanation involving clustering effects[13] is also possible, where the high local concentrations of reagents in clusters mimic neat reac-

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[†] Apparatus used is as previously described.[2] As with all reactions under high pressure, appropriate safety precautions must be taken.

Table 1. Variation of double bond isomerisation for intramolecular Heck reactions

Entry	Substrate	Solvent	Pressure	Conversion	% Exocyclic	% Endocyclic
1	**1**	Toluene[a]	–	25	50	50
2	**1**	MeCN[a]	–	67	33	67
3	**1**	Toluene	–	85	45	55
4	**1**	MeCN	–	>95	24	76
5	**1**	$scCO_2$	1290	>95	83	17
6	**1**	$scCO_2$	1430	>95	78	22
7	**1**	$scCO_2$	1785	90	76	24
8	**1**	$scCO_2$	2100	36	64	36
9	**1**	Neat	–	>95	71	29
10	**4**	Toluene	–	90	46	54
11	**4**	MeCN	–	>95	20	80
12	**4**	$scCO_2$	1215	>95	85	15
13	**4**	$scCO_2$	1898	>95	88	12
14	**4**	$scCO_2$	2700	28	93	7
15	**4**	$scCO_2$	3554	19	91	9
16	**4**	Neat	–	69	92	8

Conditions: $Pd(OCOCF_3)_2$ (5 mol%), P(2-furyl)$_3$ (10 mol%), $EtN^{i}Pr_2$ (1.5 equiv.), $scCO_2$ or solvent, 5 h, 80°C. Isolated yields of product mixtures are typically 70–80% at complete conversion.

[a] $Pd(OAc)_2$, (5 mol%), PPh_3 (10 mol%), NEt_3 (1.5 equiv.) used.

tion conditions. However, clustering is usually most important around the critical point of CO_2, which is someway off typical reaction conditions.

In summary, we have shown that the extent of double bond migration following an intramolecular Heck reaction is significantly reduced when the reaction is carried out in $scCO_2$ or neat, whereas in conventional solvents, it is the major pathway. We are currently working to determine the origin of this effect. We believe this work provides a further example of how using $scCO_2$ as a reaction medium provides additional advantages for synthetic organic chemistry over conventional solvents in addition to environmental factors. Such advantages are of crucial importance if this technology is to be adopted by industry.

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