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The Baylis–Hillman reaction in supercritical carbon dioxide: enhanced reaction rates, unprecedented ether formation, and a novel phase-dependent 3-component coupling

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The Baylis–Hillman reaction can be efficiently carried out in $scCO_2$ with enhanced reaction rates relative to comparable solution phase reactions; at low pressures, a novel dimerisation is observed which has led to the development of a novel one-pot three component coupling reaction to form highly functionalised ethers.

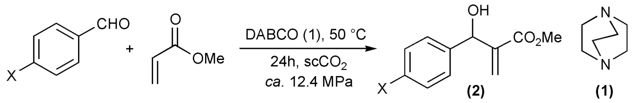
The Baylis–Hillman (B–H) reaction is a synthetically useful carbon–carbon bond-forming reaction between an aldehyde and an electrophilic alkene, usually in the presence of a tertiary amine.[1] One of its main attractions is the high degree of functionality present in the products and their resultant potential transformations. However the typical B–H reaction is notoriously slow in liquid solution unless particularly reactive substrates are chosen, and often fails to reach completion due to unfavourable equilibria.[2]

The reaction is usually catalysed by a tertiary amine, most commonly 1,4-diazabicyclo[2.2.2]octane (DABCO), but also 3-hydroxyquinuclidine (HQD)[3] and derivatives thereof,[4] diazabicyclo[5.4.0]undecene (DBU)[5] and phosphines.[6] The reaction can be accelerated by Lewis acids and/or various protic additives or solvents,[7] alongside physical methods such as microwave irradiation[8] and ultrasound.[9] Recent reports have also shown that the use of ionic liquids as solvents can be beneficial.[10] The B–H reaction is known to have a very high negative activation volume, and rates are known to be increased by high pressures (typically 5–15 kbar)[11] as can stereocontrol in appropriate cases.[12]

These factors, along with the high diffusion rates, possible clustering effects,[13] and consequent rate accelerations observed in supercritical fluids suggested to us that this reaction would be an ideal candidate for investigation in $scCO_2$, which is of increasing importance as an environmentally benign reaction medium.[14]

For our initial studies we chose to investigate DABCO (**1**) as catalyst, with methyl acrylate and a variety of aromatic aldehydes as substrates. The results of these studies are summarised in Table 1. To ensure consistency and have most potential for efficient reaction, we aimed for conditions where the initial reagents would form a homogeneous solution in $scCO_2$. Reactions on a 1 mmol scale in a 20 ml high pressure view cell (approx. 0.05 M aldehyde in $scCO_2$)[15] were homogeneous under all relevant conditions, at least during the initial stages of the reaction. If a higher reagent concentration was used (*e.g.* 3 mmol, 0.15 M aldehyde in $scCO_2$), a liquid layer was clearly visible at the bottom of the reactor, indicating lack of homogeneity, and allowing the possibility that a neat reaction may be occurring in the bottom of the reaction vessel under an atmosphere of CO_2.

Table 1 The Baylis–Hillman reaction in $scCO_2$



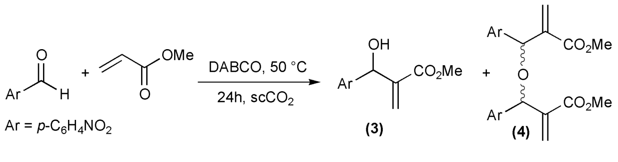
Entry[a]	X	Conversion (%)[b]
1	H	< 5
2	CF_3	17
3	CN	40 (35, 38[c])
4	NO_2	54 (48)
5[d]	NO_2	64 (62)
6	Pyridin-4-al	56 (48)

[a] Reaction performed in 20 ml view cell using aldehydes (1 mmol), methyl acrylate (2 mmol) and DABCO (1 mmol). [b] Isolated yields in parentheses. [c] Reaction performed at double concentration. [d] 4 eq. methyl acrylate.

In accord with observations from previous work, the reaction proceeded best with electrophilic aldehydes.[1,2] Yields could be further enhanced by working at higher concentrations (entry 3) whilst still retaining homogeneity, or using a larger excess of acrylate (entry 5). It is important to note that in comparable control experiments in conventional solvents, none of the substrates investigated gave significant conversions (< 5%) at similar concentrations (0.05 M) in either toluene or acetonitrile, thus demonstrating the unusual nature of the reaction medium and rate accelerations possible.

We have thus demonstrated that the B–H reaction can be efficiently carried out in $scCO_2$ with a range of electron-deficient aromatic aldehydes. However, in the course of this work, we noticed, on occasions, that small quantities of by-products were being formed. The outcomes of reactions performed in $scCO_2$ are known to vary with pressure, and in some cases, very substantial beneficial effects can be obtained by tuning the reaction medium to optimize a particular reaction pathway.[14,16,17] We thus decided to investigate the effect of pressure on an individual reaction in more detail, the results of which are shown in Fig. 1.

The points indicated by squares in Fig. 1 indicate the percentage of the Baylis–Hillman product (**3**) in the crude reaction mixture. At high pressures, the conversion is small, and similar to the yield obtained in toluene solution at comparable



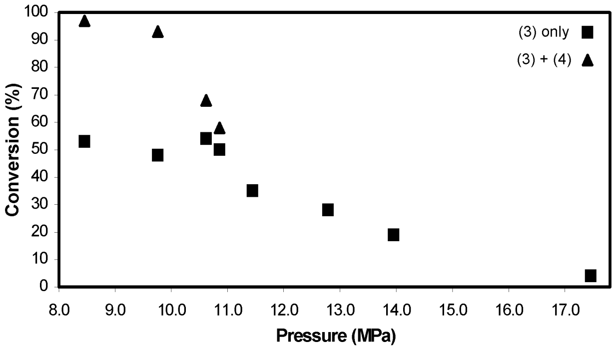


Fig. 1 Effect of pressure of $scCO_2$ on the product distribution between the Baylis–Hillman product (**3**) and dimer (**4**).

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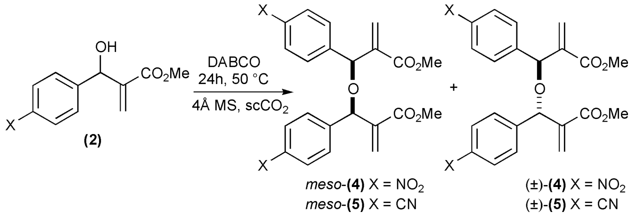
concentrations. As the pressure is reduced, the yield increases to a maximum of around 50%, clearly demonstrating that this effect is very different to the high-pressure accelerations previously reported.[11,12] An explanation similar to that used by Leitner *et al.*, based on ideas of concentration, can be used to explain our observations, with a high CO_2 density mimicking more dilute solutions with consequent rate retardation.[18] However, other effects may also be operating, and this is currently under investigation.[19]

The additional products present in the reaction mixtures were identified as dimers of the original Baylis–Hillman adducts, with both possible stereoisomers, the *meso* and C_2-symmetrical, being formed (Table 2).[20] The points indicated by triangles in Fig. 1 show the total conversion of the aldehyde to the Baylis–Hillman product (**3**) and its dimer (**4**). Note that the extent of dimerisation increases as the pressure decreases, with almost all the starting aldehyde reacting at the lowest pressures investigated (*cf.* Table 1).

Table 2 Formation of dimeric ethers from Baylis–Hillman products



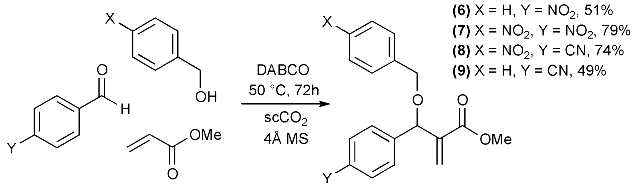
Entry[a]	X	Pressure/MPa	Ratio (*meso* : ±)[c]	Yield (%)
1	NO_2	13.7	58:42	82
2	CN	13.6	69:31	78
3	NO_2[b]	8.93	58:42	52
4	CN[b]	9.27	63:37	45

[a] Combined isolated yield of both diastereoisomers. [b] Reaction carried out over 72 h directly from aldehydes without isolation of initial B–H product. [c] Assigned using chiral lanthanide shift reagents.[20]

To the best of our knowledge, such a dimerisation is totally unprecedented in B–H chemistry. The yields for such a reaction could be optimized by isolating the initial B–H product, and resubjecting it to the standard reaction conditions at higher pressure (13.7 MPa, 2000 psi), in the presence of molecular sieves to remove the water by-product formed. Using this procedure, good yields of dimer can be obtained (Table 2, entries 1 and 2). Lower, but still acceptable yields, can be obtained directly from the original B–H precursors at lower pressures (entries 3 and 4).

A closer analysis of the phase behaviour of the reaction in Fig. 1 suggests the origin of the ether formation. In general, at pressures around 11.0 MPa and below, as the reaction proceeds, the initial B–H product begins to separate as an oil at the bottom of the reactor. This is also the pressure below which significant dimerisation is observed. This suggests that the dimerisation reaction is occurring in the liquid layer at the bottom of the reactor, which may also help to explain why it has not been observed in previous studies of the B–H reaction. It is in effect, a solventless reaction occurring under an atmosphere of $scCO_2$.[21]

A potentially more useful variant of this reaction would be if a different alcohol could be used in the etherification step for form an unsymmetrical ether. This would represent a novel one-pot 3-component coupling protocol by tandem B–H reaction and subsequent etherification. Our preliminary studies indicate that this process is indeed feasible (Scheme 1).



Scheme 1 One-pot three-component coupling by Baylis–Hillman reaction and *in situ* etherification.

Interestingly, the reaction works well from the initial B–H precursors, and is particularly efficient with *p*-nitrobenzylalcohol, which we believe is due to its relative insolubility in $scCO_2$ compared to benzyl alcohol, which is consistent with the neat reaction explanation. Preliminary investigations suggest that both DABCO and high pressure CO_2 are required for efficient etherification, however further studies to confirm the mechanism, and to expand the scope of the reaction are currently under way.

In summary, the Baylis–Hillman reaction can be efficiently carried out in $scCO_2$. Enhanced reaction rates are observed relative to comparable solution phase reactions. At low pressures, an unprecedented dimerisation is observed which has led to the development of a novel one-pot three component coupling reaction to form highly functionalised ethers derived from B–H products. The results described here provide another important example of how the unique properties of $scCO_2$ can lead to the development of unprecedented reactions of importance to the synthetic chemistry community.

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