Solid-Phase Organic Synthesis in the Presence of Compressed Carbon Dioxide**

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Solid-phase organic synthesis (SPOS) has been established as an important tool for preparative chemistry with a broad range of applications in modern organic synthesis.[1] In very few reaction steps, libraries of molecularly diverse compounds can be synthesized by taking advantage of the efficient removal of excess or unconsumed reagents by extraction and filtration as simple workup operations. However, solid-supported reactions are often characterized by slow reaction kinetics as a result of severe mass-transfer limitations. In particular, this effect is observed for reactions that occur under triphasic (g/l/s) conditions with gaseous reagents under elevated pressure (Figure 1 a). In most cases, standard methods for agitation under elevated pressure can not be applied owing to the mechanical instability of the solid supports and/or the typically small scales of parallel synthesis.[2]

Figure 1. Catalytic carbonylation of solid-supported substrates a) under conventional conditions, b) in an expanded liquid, and c) in scCO$_2$ (g = gas phase, l = liquid phase, s = solid phase).

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200801653.

Consequently, the use of SPOS has been limited for many synthetically useful catalytic processes that involve medium to high pressures of gaseous building blocks, such as hydrogenation or carbonylation reactions. To overcome this limitation, Marchetti and co-workers used a special reactor setup, whereby the solid support was incorporated in a stirrer device and thus agitated through the solution.[3] Breinbauer and co-workers addressed the problem at a molecular level by using soluble polymers as supports to remove one mass-transfer barrier.[4] The reaction products were separated after cleavage by dialysis over a period of 12–36 h.

We report herein an alternative approach, whereby the use of compressed carbon dioxide either as a supercritical fluid[5] or with expanded liquids (XPLs)[6] leads to an efficient enhancement in the mass-transfer properties in catalytic SPOS. The concept is readily applicable to small-scale and parallel synthesis, as demonstrated for two types of carbonylation reaction.

Under conventional SPOS conditions (Figure 1 a), mass transfer and the availability of the gaseous reagents are very low, whereas the catalyst concentration is high in the organic solvent. In contrast, supercritical conditions (Figure 1 c) result in a maximized gas availability and mass transfer, but at the same time in a decrease in catalyst concentration because of the larger volume of the supercritical phase. The situation in the expanded liquid (Figure 1 b) is intermediate, with significantly increased gas availability relative to the gas availability under conventional conditions and a higher catalyst concentration relative to supercritical conditions. The best operating conditions are difficult to predict and depend on the reaction system.

As a first benchmark reaction, the hydroformylation of polymer-supported 1-hexen-5-ol (**1**) was investigated. Trityl polystyrene resin was chosen as the support, as it enables the use of straightforward coupling and cleavage conditions.[1,2] [Rh(CO)$_2$(acac)] (**2**), which is known to exhibit high solubility and activity in hydroformylation reactions in conventional solvents and in scCO$_2$,[7] was used as an unmodified Rh catalyst for the carbonylation reaction. To prevent the formation of aldol condensation products under these conditions, the aldehyde **3** was reduced to the corresponding diol **4** with NaBH$_4$ prior to cleavage.[2a] The product **4** was cleaved from the resin with trifluoroacetic acid (TFA) in CH$_2$Cl$_2$. Representative results are summarized in Table 1.

First, the reaction was carried out using conventional conditions with toluene as the solvent under synthesis gas (40 bar) in a high-pressure view cell (10 mL stainless-steel reactor). No significant conversion occurred without agitation (Table 1, entry 1). The use of a magnetic stir bar was not possible, since grinding of the substrate beads resulted, as
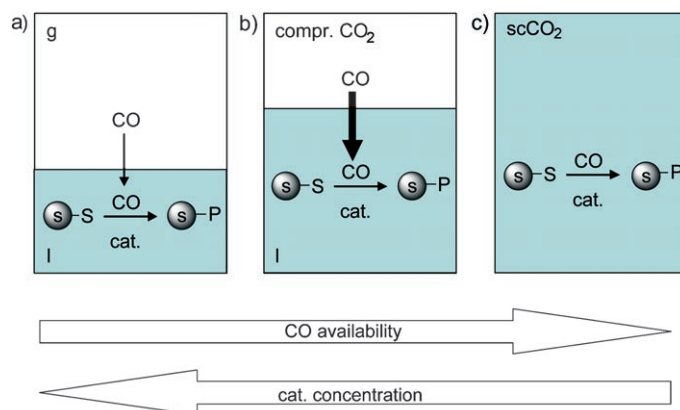
Table 1: Solid-supported hydroformylation in toluene and $scCO_2$.[a]

Entry	1 [mg]	2 [mg]	Substrate/Rh	Toluene [mL]	$p(CO/H_2)$ [bar]	CO_2 [g]	p_{tot} [bar][b]	Agitation	Yield of 4 [%]	4a/4b
1	250	10	10:1.5	5	40	–	45	no	<1	–
2	250	10	10:1.5	5	40	–	45	yes	>98	1.2:1
3	250	9	10:1.4	–	30	8.0	200	no	10	–
4	1000	10	10:0.4	1[c]	40	8.5	250	no	>98	1.2:1

[a] Reaction conditions: $V_{reactor} = 10$ mL, $T = 60\,°C$, $t = 24$ h. acac = acetylacetonate. [b] Total pressure at the reaction temperature. [c] A single phase was observed (by visual inspection).

reported previously.[2] The use of a modified shaker to shake the entire reactor setup resulted in quantitative conversion after the standard reaction time of 24 h, a result that shows the importance of mass transfer for the system (Table 1, entry 2).

Initial experiments with the non-agitated reactor and supercritical CO_2 ($scCO_2$) as the only solvent were disappointing, despite the fact that a homogeneous phase containing the dissolved catalyst was observed as expected (Table 1, entry 3). It is most likely that the poor swelling properties of the resin in $scCO_2$[8] hinder the accessibility of the substrate under these conditions. Indeed, the addition of small amounts of organic cosolvents, such as 1-hexene, CH_2Cl_2, or toluene, resulted in excellent performance of the system and led to quantitative conversion without the need for mechanical agitation (Table 1, entry 4). No liquid phase was observed by visual inspection, and the supercritical phase showed the typical coloration of the rhodium catalyst.

To demonstrate the applicability of the method to parallel synthesis, we carried out the hydroformylation of the supported allylic alcohol **5**, 1-hexen-5-ol (**1**), and 1-decen-9-ol (**6**). The solid-supported substrates were introduced into the reactor by using a simple glass liner with three compartments (Figure 2). Following the reaction under the standard reaction conditions, the three materials were subjected separately to cleavage and workup (Scheme 1). Quantitative yields and typical *n/iso* ratios were observed in all cases, without any indication of cross-contamination between the materials in the reactor.

The ready access to solid-supported hydroformylation products makes more-complex diversification processes possible, as demonstrated for the Hantzsch synthesis of pyridines

Figure 2. Experimental setup to show the simple compartmentalization for parallel hydroformylation reactions in $scCO_2$.
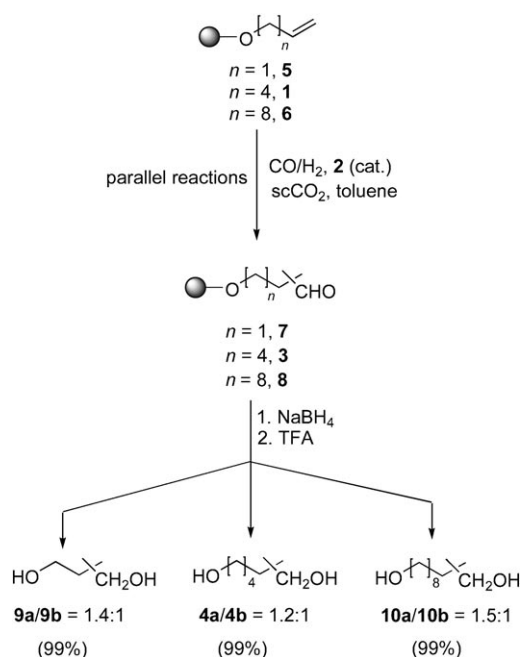
Scheme 1. Parallel SPOS: Hydroformylation in $scCO_2$. Reaction conditions: $V_{reactor} = 10$ mL, $p(CO/H_2) = 40$ bar, $T = 60\,°C$, $t = 24$ h, total pressure (p_{tot}) = 230 bar.

from an allylic alcohol starting material. After the hydroformylation of **5** in $scCO_2$ under the previously described conditions, the solid-supported aldehydes **7a,b** were subjected directly and without further purification to multicomponent coupling with methyl acetoacetate (**11**) and methyl 3-aminocrotonate (**12**). Aromatization with ceric ammonium nitrate and subsequent cleavage of the anchoring group with TFA gave the two isomeric pyridines **14a,b** in 99% yield and a 1.4:1 ratio (Scheme 2). The ratio of **14a** to **14b** corresponds well with the *n/iso* ratio of the products **7a,b** of the hydroformylation step. The branched product **13b** underwent cyclization under the workup conditions.

The cobalt-catalyzed Pauson–Khand reaction (PKR) was investigated as a second benchmark reaction. This [2+2+1] cycloaddition of alkynes with alkenes and carbon monoxide is a versatile synthetic approach to cyclopentenones with various substitution patterns.[9] The use of $scCO_2$ as the solvent for the PKR under homogeneous conditions with
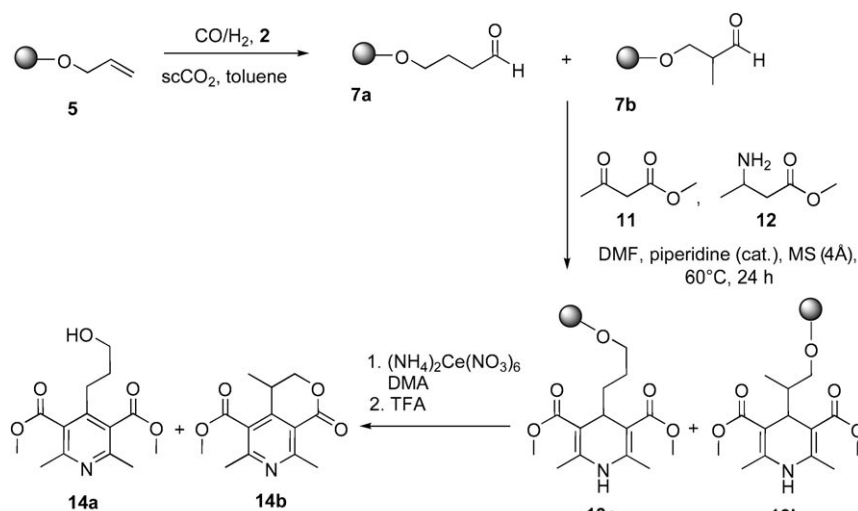
Scheme 2. Solid-phase catalytic hydroformylation in scCO$_2$ and Hantzsch synthesis. DMA = dimethylacetamide, DMF = *N*,*N*-dimethylformamide, MS = molecular sieves.

[Co$_2$(CO)$_8$] (**15**) as the catalyst was described by Jeong and Hwang.[10]

PKRs with solid-supported substrates under conventional conditions have been reported, but reactions were found to be sluggish, and stoichiometric amounts of the catalyst were required.[11] We first studied the PKR of solid-supported 1-pentyn-5-ol (**16**) using THF with a catalytic amount of catalyst **15** (0.1 equiv) and norbornene (**17a**; 10 equiv) under CO (20 bar) at 120°C (Scheme 3). After 17 h, cleavage by TFA in CH$_2$Cl$_2$ gave the polycyclic product **18a** in 80% yield, even without agitation during the reaction.
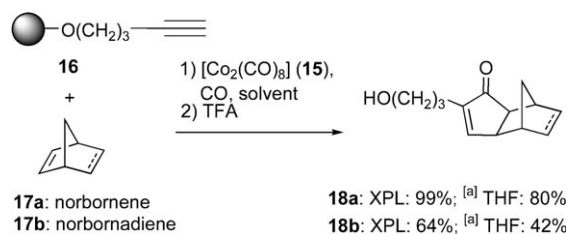
Scheme 3. Pauson–Khand reaction on a solid support. Reaction conditions: **15** (0.1 equiv), **17a/b** (10 equiv), p(CO) = 20 bar, T = 120°C. [a] p_{tot} = 120 bar.

The application of compressed carbon dioxide led to a significant increase in yield to quantitative formation of **18a** (Scheme 3). A similar increase in yield was observed when norbornadiene (**17b**) was used as the substrate. The highest yields were observed under the conditions of an expanded liquid (XPL) rather than under homogeneous supercritical conditions (Figure 3). This behavior can be rationalized by considering the effects illustrated in Figure 1. Initially, the application of compressed CO$_2$ enhances the mass-transfer properties and leads to an increase in reaction rate in the XPL. This positive effect is offset, however, by the sharp decrease in the concentration of both the catalyst and the

soluble substrate upon passing into the supercritical phase, which occupies the entire reactor volume.

The simple glass liner used for parallel hydroformylation reactions can not be used for parallel PKRs, as the presence of a liquid phase is necessary for optimum performance. However, commercially available micro-x-kans[12] proved efficient for the compartmentalization of the substrate beads under XPL conditions. As a proof of principle, parallel PKRs were carried out with solid-supported **16** and 10-undecyn-1-ol (**19**). The corresponding cyclopentenones **18a** and **20** were obtained in 67% yield (Scheme 4).

In summary, we have shown that compressed carbon dioxide can be used to overcome the mass-transfer limitation in solid-phase organic synthesis
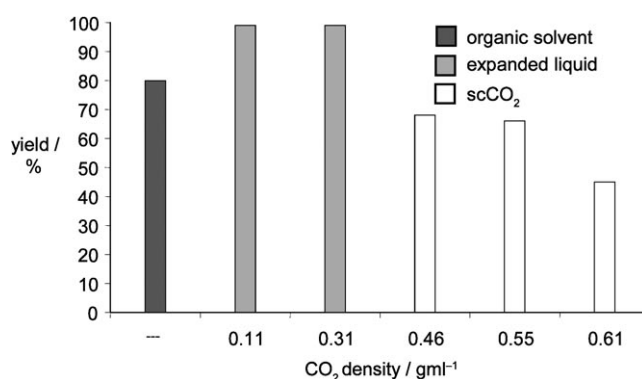

Figure 3. PKRs on a solid support. Reaction conditions: **15** (0.1 equiv), **17a** (10 equiv), p(CO) = 20 bar, T = 120°C, t = 17 h.

with pressurized gaseous reagents. Depending on the relative importance of mass-transfer resistance and catalyst/substrate concentration, the optimum conditions may be found in the homogeneous supercritical state (Figure 1 c, hydroformylation) or under conditions of expanded liquids (Figure 1 b, Pauson–Khand reaction). The reactions can be carried out in
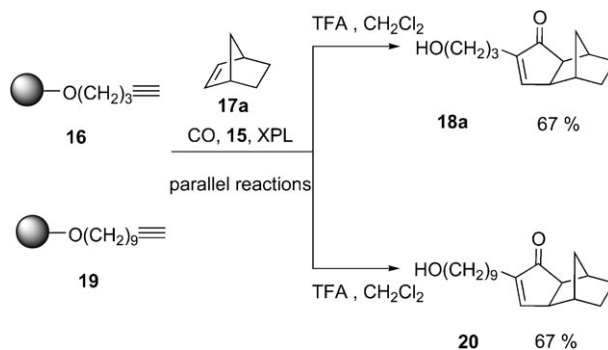
Scheme 4. Parallel PKRs of the solid-supported alkynols **16** and **19** with **17a** under XPL conditions.

standard high-pressure vessels, which are also required for these reactions with pressurized gaseous reagents under conventional conditions. As the use of compressed CO_2 removes the need for mechanical agitation, simple and commercially available receptacles can be utilized for the compartmentalization of substrate-loaded beads. As a result, parallelization is straightforward. Thus, the use of compressed CO_2 should lead to a significant expansion in the range of catalytic reactions that can be applied to generate molecular diversity through SPOS methodologies.

Experimental Section

Safety warning: Experiments with compressed gases must be carried out only with appropriate equipment and under rigorous safety precautions.

Parallel hydroformylation in scCO$_2$: Catalyst **2** (10 mg, 0.03 mmol) and toluene (1 mL) were placed in a high-pressure view cell ($V = 10$ mL, see Figure 2) under an inert atmosphere. The solid-supported olefins **1**, **5**, and **6** (250 mg each, 1 mmol g^{-1} loading) were placed inside the cell in a glass liner with three compartments. The cell was pressurized with synthesis gas (40 bar) and CO_2 (8.0 g) and heated to 60 °C for 24 h ($p_{tot} = 230$ bar). Reduction and cleavage were carried out as described in the Supporting Information.[2]

Parallel Pauson–Khand reactions in an XPL: A high-pressure view cell was loaded with **17 a** (230 mg, 2.49 mmol), **15** (9.0 mg, 0.02 mmol), and THF (4 mL) under inert conditions. Two micro-x-kans, one filled with **16** and the other with **19** (42 mg each, loading: 0.7 mmol g^{-1}), were placed in the reactor. The reactor was pressurized with CO (17 bar) and CO_2 (2.4 g), and the mixture was heated at 120 °C for 72 h. Workup and cleavage were carried out as described in the Supporting Information.

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