

## Nucleophilic Displacements in Supercritical Carbon Dioxide Using Silica-Supported Phase-Transfer Agents

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### Introduction

Carbon dioxide in both its liquid and supercritical states is receiving more and more interest for organic reactions as an attractive environmentally friendly solvent.<sup>1</sup> Accordingly, several different reactions such as Diels–Alder cycloadditions,<sup>2</sup> reductions and couplings of organic halides,<sup>3</sup> cracking and rearrangements,<sup>4</sup> hydrogenations, hydroformylation, and oxidation processes,<sup>1,5</sup> and photochemical reactions<sup>6</sup> are claimed to proceed in supercritical CO<sub>2</sub> (scCO<sub>2</sub>).

However, the poor solubilizing power of the scCO<sub>2</sub> for many polar compounds may represent a severe limitation, especially for reactions involving ionic moieties.

In the case of catalytic processes carried out with neutral or ionic complexes of transition metals, elegant solutions have been achieved following three different approaches: (i) the incorporation of “CO<sub>2</sub>-philic” fragments (e.g., perfluorinated groups) into the catalysts, either as ligands of the metal or in the counteranions,<sup>5a,7–9</sup> (ii) the use of biphasic systems (scCO<sub>2</sub>-ethylene glycol, scCO<sub>2</sub>-water),<sup>10</sup> and (iii) the use of surfactant-stabilized water/CO<sub>2</sub> emulsions.<sup>11</sup>

When ionic or highly polar reagents are used, the introduction of polar cosolvents may overcome the solu-

bility problem. In fact, under solid–liquid phase-transfer catalysis conditions (SL-PTC), nucleophilic displacements have been reported in scCO<sub>2</sub>, providing that acetone is present as a cosolvent for the PT-catalyst.<sup>12</sup> Yet, reactions proceed at moderate rates (50 °C: after 48 h, 15–60% conversions). Similarly, the Glaser coupling of alkynes has been claimed in scCO<sub>2</sub> in the presence of MeOH as a “polar modifier” which enhances the solubility of the reactive salts (CuCl<sub>2</sub> and AcONa).<sup>13</sup>

As a phase-transfer solvent, scCO<sub>2</sub> has been described in the extraction/methylation of chlorinated benzoates (ArCO<sub>2</sub><sup>−</sup>: Ar = C<sub>6</sub>H<sub>3</sub>Cl<sub>2</sub> and C<sub>6</sub>H<sub>2</sub>Cl<sub>3</sub>) from aqueous solutions:<sup>14</sup> in this case, no cosolvents are required because of the high hydrophobic character of the nucleophiles.

Nucleophilic displacements have also been reported in water/scCO<sub>2</sub> microemulsions (w/c-me) prepared with fluorinated surfactants (perfluoropolyether ammonium carboxylates: PFPECO<sub>2</sub>NH<sub>4</sub>).<sup>15a,b</sup> More recently, electro-generated radicals and cations have been stabilized in the water core of similar w/c-me (PFPE-phosphate).<sup>16</sup>

In scCO<sub>2</sub>, efficient Diels–Alder reactions and enzymatic esterifications of polar substrates have been claimed with the use of amorphous silica gel,<sup>17,18</sup> whose promoting role, although not well understood, is explained through the adsorption of the reactants which come into closer contact to each other, on the silica surface.

A related, but conceptually different approach can be conceived with supported onium salts as reagents: as reported by us,<sup>19,20</sup> different anions (I<sup>−</sup>, Br<sup>−</sup>, SCN<sup>−</sup>) paired to bulky onium cations immobilized on alumina or silica gel, undergo fast nucleophilic substitutions in the presence of nonpolar media (*n*-heptane or toluene).

In this paper, we report for the first time that immobilized PT-agents provide also efficient anionic nucleophiles for reactions in scCO<sub>2</sub>.

### Results and Discussion

The S<sub>N</sub>2 displacement on *n*-octyl methanesulfonate (**1**) by bromide and iodide anions was chosen as a model reaction. All experiments were performed in scCO<sub>2</sub> as the solvent, at 50–70 °C and 130 bar (see Experimental Section). Silica-supported onium salts (**2a–e**) were used either as reagents or as catalysts (Scheme 1). The results are reported in Table 1.

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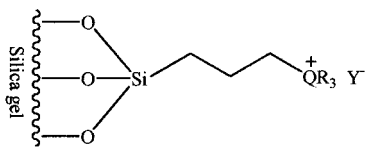
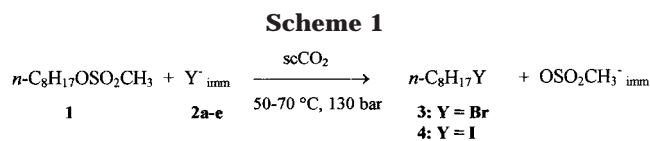
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Supported PT-agent	R, Q	Loading: mequiv Y/g
<b>2a</b>	Me, N	Br: 0.56
<b>2b</b>	<i>n</i> -Bu, N	Br: 0.19
<b>2c</b>	<i>n</i> -Bu, N	I: 0.30
<b>2d</b>	H, N	I: 0.58
<b>2e</b>	<i>n</i> -Bu, P	Br: 0.26

**(a) Bromide Displacements.** Entries 1–7 show a comparative investigation of the bromide displacements on **1** carried out with KBr, tetra-*n*-butylphosphonium bromide ( $\text{Bu}_4\text{P}^+\text{Br}^-$ ), and silicas **2a,b,e**. Potassium bromide is totally ineffective for the reaction. In the presence of catalytic amounts of  $\text{Bu}_4\text{P}^+\text{Br}^-$  (0.1 molar equiv with respect to **1**), when KBr is used as it is or in aqueous solution, only a 10% conversion is reached even for prolonged reaction times (entries 2a,b). This suggests that if solid–liquid (SL; entry 2a) or liquid–liquid (LL; entry 2b) phase-transfer catalysis (PTC) occurs, an impractically low reaction rate results. Under such conditions, the formation of octyl bromide (**3**) is due rather to the reaction of **1** with  $\text{Bu}_4\text{P}^+\text{Br}^-$  since the observed conversion (~10%) corresponds well to the quantity of the onium salt used. As proposed by Chandler et al.,<sup>12b</sup> because of the very low solubility of onium salts in  $\text{scCO}_2$ , the reaction may take place through the partition of **1** between the  $\text{CO}_2$  phase and the PT-agent itself.<sup>21</sup> In fact, reactions carried out using the onium salt as the reagent show, after 180 min, conversions of 39 and 95% in the presence of 1.1 and 2 molar equiv of  $\text{Bu}_4\text{P}^+\text{Br}^-$ , respectively (entries 3–4).

In contrast with the behavior of  $\text{Bu}_4\text{P}^+\text{Br}^-$ , bromide-exchanged silicas allow the bromide displacement on **1** to occur under LL-PTC conditions: in the presence of catalytic amounts of **2e** (0.1 and 0.05 molar equiv), conversions of 40 and 99% are achieved after 300 min, at 50 and 70 °C, respectively (entries 7a,b). *n*-Octyl bromide is isolated in 95% yield. The reaction takes place also with the use of silicas **2a,b,e** as reagents: conversions up to 80% can be reached with a reactivity comparable to or somewhat lower than that of the onium salt  $\text{Bu}_4\text{P}^+\text{Br}^-$  (entries 5, 6, and 7c).

**(b) Iodide Displacements.** Also iodide substitutions occurs with tetra-*n*-butylammonium iodide ( $\text{Bu}_4\text{N}^+\text{I}^-$ ) as a reagent (entries 8–9). However, the PT-promoted iodide displacement appears to be slower than the correspond-

ing bromide process (entries 3–4 and 8–9). As already reported for nucleophilic displacements in anhydrous apolar solvents,<sup>19</sup>  $\text{Br}^-$  is a better nucleophile than  $\text{I}^-$ , since  $\text{Br}^-$  is less polarizable in the absence of hydration.

Instead, iodide-immobilized silicas **2c–d** allow a significant enhancement of the reaction rate, yielding conversions that are more than three times higher than those achieved with  $\text{Bu}_4\text{N}^+\text{I}^-$  (entries 9–10 and 11–13). An even more striking result is manifest under LL-PTC conditions: while  $\text{Bu}_4\text{N}^+\text{I}^-$  is practically ineffective (entry 8), silica **2e** is a very active catalyst which allows a quantitative conversion after 3 h at 70 °C (entry 14; isolated yield 90%). It should be noted that on functionalized silica iodide substitutions occur more readily than bromide ones (entries 5–7 and 11–14). The same behavior was also observed for halide displacements on **1** carried out in apolar solvents.<sup>20</sup> Many factors may account for this situation: adsorption of the reagent, product, and nucleophile, as well as solvation-hydration of anions in the polar microenvironment provided by silicas, could come into play. Moreover, the fact that  $\text{CO}_2$  itself can adsorb on the silica surface<sup>22</sup> introduces a further alteration in the partitioning of species between solid and fluid phases.<sup>18</sup>

The chemical bonding of onium salts to the inorganic support is of fundamental importance for the reaction to proceed. In fact, when a mechanical mixture of  $\text{Bu}_4\text{N}^+\text{I}^-$  and silica gel is used, the iodide displacement is even slower than that performed with  $\text{Bu}_4\text{N}^+\text{I}^-$  alone (entries 8 and 13). This may be explicable through the following considerations: (i) immobilized onium salts distributed on the surface of the rigid solid support allow anionic nucleophiles to be highly available for the reaction; (ii) on the contrary, the nonlinked onium salt (entry 15) may adsorb on the non functionalized silica by forming agglomerated clusters into which nucleophiles are hidden; (iii) the presence of free acidic geminal silanol groups over the silica surface (entry 15)<sup>23</sup> could give an inhibition of the nucleophile activity.

Under the investigated conditions, in the presence of stoichiometric amounts of functionalized silica, the use of  $\text{scCO}_2$  as a solvent does not improve reaction rates with respect to conventional organic solvents: for instance, at 60 °C, iodide-exchanged silicas allow nucleophilic displacements on **1** to proceed quantitatively in 45–60 min, in anhydrous toluene<sup>20</sup> (compare to entry 12 of Table 1). However, it should be noted that the examined procedure has intrinsic benefits:  $\text{CO}_2$  has no environmental impact and, once the reaction is complete, it can be simply vented. Thus, products can be recovered by washing and filtering the functionalized silica which, eventually, can be regenerated through a simple protocol.<sup>20</sup>

## Conclusions

The combined utilization of  $\text{CO}_2$  and PT-catalysis is a field of research in its infancy. The present study demonstrates that in  $\text{scCO}_2$  a new procedure for the nucleophilic displacements on *n*-octylmethanesulfonate by halide anions ( $\text{I}^-$ ,  $\text{Br}^-$ ) can be carried out with the use of silica-supported PT-agents **2**. As reagents, compounds **2** can exhibit an activity even greater than that of

(21) Although we do not measure the solubility of  $\text{Bu}_4\text{P}^+\text{Br}^-$  in  $\text{scCO}_2$ , ref 12a reports a solubility of 0.21 mmol/l for tetra-*n*-heptylammonium bromide (THAB) in  $\text{CO}_2$ /5% acetone at 50 °C and 3000 psi.

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**Table 1.** Nucleophilic Displacements by Br<sup>-</sup> and I<sup>-</sup> on *n*-C<sub>8</sub>H<sub>17</sub>OSO<sub>2</sub>CH<sub>3</sub> in scCO<sub>2</sub> as the Solvent

entry	PT-agent	W <sup>a</sup> (molar ratio)	added salt <sup>b</sup> (molar ratio)	T (°C)	time (min)	product <sup>c</sup>	
						convn (%)	isolated yield (%)
1	none		KBr (2)	50	240	<b>3</b>	trace, < 1
2a	Bu <sub>4</sub> P <sup>+</sup> Br <sup>-</sup>	0.1	KBr (2)		360		12
2b	Bu <sub>4</sub> P <sup>+</sup> Br <sup>-</sup>		aq KBr (2) <sup>d</sup>		180		11
3	Bu <sub>4</sub> P <sup>+</sup> Br <sup>-</sup>	1.1			180		39
4	Bu <sub>4</sub> P <sup>+</sup> Br <sup>-</sup>	2			180		95
5	<b>2a</b>	1.1			180		31
6	<b>2b</b>	1.1			180		41
7a	<b>2e</b>	0.1	aq KBr (2.5) <sup>d</sup>	50	300		40
7b	<b>2e</b>	0.05	aq KBr (2.5) <sup>d</sup>	70			99
7c	<b>2e</b>	2		50			82
8	Bu <sub>4</sub> N <sup>+</sup> I <sup>-</sup>	0.1	aq KI (1.1) <sup>d</sup>		180	<b>4</b>	7
9	Bu <sub>4</sub> N <sup>+</sup> I <sup>-</sup>	1.1			180		19
10	Bu <sub>4</sub> N <sup>+</sup> I <sup>-</sup>	1.8			180		22
11	<b>2c</b>	1.1			180		60
12	<b>2c</b>	1.8			180		76
13	<b>2d</b>	1.1			180		60
14a	<b>2e</b>	0.05	aq KI (2.5) <sup>d</sup>	50	300		60
14b	<b>2e</b>		aq KI (2.5) <sup>d</sup>	70	180		100
15	Bu <sub>4</sub> N <sup>+</sup> I <sup>-</sup> / silica gel <sup>e</sup>	1.1			180		10

<sup>a</sup> All reactions were carried out at 130 bar. W: molar ratio between the nucleophile (Br<sup>-</sup> or I<sup>-</sup>) and the substrate. <sup>b</sup> Molar ratio between the added salt (KBr or KI) and the substrate. <sup>c</sup> Products were identified by GC/MS and by comparison to authentic samples. <sup>d</sup> Aqueous solutions (0.5 mL) of KBr and KI were used. <sup>e</sup> A mechanical mixture of Bu<sub>4</sub>N<sup>+</sup>I<sup>-</sup> (1.1 molar equiv with respect to **1**) and silica gel was used for the reaction: 0.13 equiv of I<sup>-</sup>/g of silica.

conventional onium salts. However, the major advantage is evident under LL-PTC conditions: in the presence of immiscible scCO<sub>2</sub>/aqueous phases, both Bu<sub>4</sub>P<sup>+</sup>Br<sup>-</sup> and Bu<sub>4</sub>N<sup>+</sup>I<sup>-</sup> are inactive, while catalytic amounts of silicas **2** afford products (*n*-octyl halides) in quantitative yields. Inorganic matrixes (i.e., silica gel) are particularly suitable supports because they have rigid structures that do not swell; swelling may occur with organic polymeric resins.<sup>24</sup> Finally, as far as the anion nucleophilicity is concerned, the behavior of functionalized silicas in scCO<sub>2</sub> seems to parallel a trend already reported for nonpolar solvents:<sup>20</sup> iodide displacements appear faster than bromide ones, while the opposite is true in the case of onium salts.

### Experimental Section

**SAFETY WARNING:** Operators of high-pressure equipments should take proper precautions to minimize the risks of personal injury.<sup>25</sup>

Silica-supported PT-agents **2a–e** were synthesized and analyzed as previously described:<sup>26</sup> the loading of the onium salts was 0.56, 0.19, 0.30, 0.58, and 0.26 mequiv per gram of silica, for **2a–e**, respectively. *n*-Octyl methanesulfonate (**1**) was also prepared according to established procedures.<sup>27</sup> Before each reaction, compounds **2a–e** were dehydrated by heating them under vacuum at 60 °C, overnight. All reactions were performed using a 25 mL stainless steel (hastelloy) cell equipped with sapphire windows which allowed the visual observation of the mixture.

**Nucleophilic Displacements with Silicas 2a–e and Onium Salts as Reagents.** In a typical experiment, the reactor

was charged with the substrate (**1**, in the range of 30–100 mg) and the silica-supported reagent **2** (no more than 1 g in order to ensure the reaction mixture to be stirred) or the onium salt (Bu<sub>4</sub>P<sup>+</sup>Br<sup>-</sup> or Bu<sub>4</sub>N<sup>+</sup>I<sup>-</sup>), according to the amounts reported in Table 1. The autoclave was then pressurized with CO<sub>2</sub> (SFC/SFE grade) at approximately 60 bar by using an automatic syringe pump (ISCO model 260 D), and it was electrically heated at the desired temperature (50 °C), while the reaction mixture was magnetically stirred. The final pressure of 130 bar was reached by slowly adding the remaining CO<sub>2</sub> to the reactor. Under these conditions, previous tests assured that compound **1** was completely soluble in scCO<sub>2</sub>.<sup>28</sup> The reaction was allowed to proceed for the reported time (see Table 1); then, after cooling, CO<sub>2</sub> was slowly vented by bubbling it into acetone (5 mL). The content of the cell was washed with additional acetone (5 mL), and the combined acetone solutions were analyzed by GC/MS (HP 5890, series II, fitted with a 30 m HP5MS column).

**Nucleophilic Displacements with Silica 2e and Onium Salts as Catalysts. LL-PTC Conditions.** According to the above-described procedure, a mixture of **1** (200 mg, 0.96 mmol), the onium salt (Bu<sub>4</sub>P<sup>+</sup>Br<sup>-</sup> or Bu<sub>4</sub>N<sup>+</sup>I<sup>-</sup>) or silica **2e** (0.05–0.1 molar equiv of I<sup>-</sup> or Br<sup>-</sup> with respect to **1**), and an aqueous solution of KX (0.5 mL; 2.1–4.8 M; X = Br<sup>-</sup>, I<sup>-</sup>) was made to react. In the case of silica **2e**, the acetone solutions recovered at the end of the reactions of entries 7b and 14b in Table 1 were dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. After rotary evaporation, *n*-octyl bromide and *n*-octyl iodide were isolated in 95 and 90% yields, respectively (>95% pure by GC).

**SL-PTC Conditions.** The same procedure was applied with Bu<sub>4</sub>P<sup>+</sup>Br<sup>-</sup> in the presence of solid KBr (entry 2a of Table 1).

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(28) In a 25 mL reactor, a complete miscibility was warranted up to 500 mg of **1**.