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Lewis acid catalysis in a supercritical carbon dioxide ($scCO_2$)-poly(ethylene glycol) derivatives (PEGs) system: remarkable effect of PEGS as additives on reactivity of $Ln(OTf)_3$-catalyzed Mannich and aldol reactions in $scCO_2$

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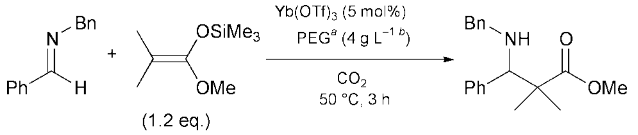
Use of poly(ethylene glycol) derivatives (PEGs) as additives in supercritical carbon dioxide ($scCO_2$) was found to be effective for Mannich and aldol reactions of silyl enolates with aldehydes and imines, and formation of emulsions was observed in these systems.

Supercritical fluids are becoming increasingly important solvent systems for organic chemistry and engineering.[1] In particular, supercritical carbon dioxide ($scCO_2$) is a widely used solvent due to its low cost, moderate critical conditions (T_c = 31 °C, P_c = 7.4 MPa), and environmentally benign nature. However, a problem is that catalysts and/or reactants have often only low solubility in $scCO_2$, and therefore, they would not have sufficient reactivity and/or selectivity. To increase the solubility of catalysts and reactants in $scCO_2$, a possible approach is to introduce perfluorinated side chains in the reactants or ligands, or in the anions in the case of cationic complexes.[2] Alternatively, emulsion systems such as water–CO_2, biphasic media with several kinds of surfactants or fluoropolymer or siloxane-containing polymer systems for polymerization reactions were investigated.[3]

On the other hand, we have recently developed several Lewis acid-catalyzed reactions in water.[4] Many organic materials are not soluble in water, and it was difficult to obtain sufficient reactivity and/or selectivity. To address this issue, we have developed surfactant molecules which create colloidal particles with organic molecules in water. It was demonstrated that substrates and catalysts were concentrated inside the particles, and that the desired reactions proceeded much faster in water than in organic solvents.

Bearing these results in mind, we investigated organic reactions in $scCO_2$ by using a specific molecule which worked as a 'surfactant' to form colloidal dispersions in $scCO_2$ and to accelerate the reactions.

Table 1 Mannich reaction in $scCO_2$



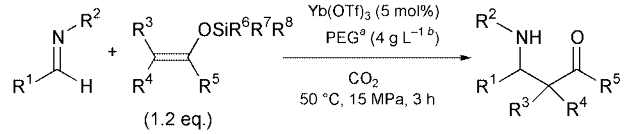
1 **2** **3**

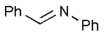
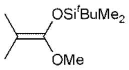
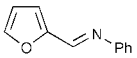
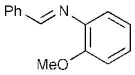
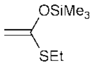
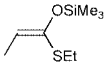
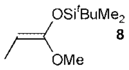
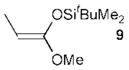
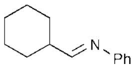
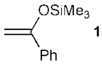
Entry	Pressure/MPa	M_w	Yield (%)
1	10	400	39
2	15	400	72 (10[c])
3	20	400	46
4	25	400	39
5	15	200	39
6	15	600	52
7	15	1000	20

[a] Poly(ethylene glycol) (average M_w was 400). [b] PEG (*ca.* 40 mg) was added in the 10 mL reaction vessel. [c] Without PEG.

First, we chose ytterbium-catalyzed Mannich reactions of silyl enolates with imines,[5] and tested several compounds as surfactants in $scCO_2$. Among those compounds, poly(ethylene glycol) (PEG) was found to be effective in the reaction of imine **1** with silyl enolate **2** (72% yield), while only 10% yield of the product **3** was obtained without PEG (Table 1, entry 2).†,‡ Addition of an organic solvent such as DCM or acetonitrile instead of PEG was not effective (36% or 35% yield, respectively). We also confirmed that the longer the perfluoroalkyl chains of the ytterbium catalysts were, the higher the yields of the desired products.[6] However, a reverse tendency was observed in the presence of PEG. $Yb(OTf)_3$ gave better yields than $Yb(OSO_2C_4F_9)_3$ or $Yb(OSO_2C_8F_{17})_3$ (64% or 40% respectively). It should be noted that emulsions were formed in Mannich reactions with PEG in $scCO_2$.§ On the other hand, substrates attached to the walls of the reaction vessel and did not disperse during the reaction without using PEG in $scCO_2$. These facts indicated that PEG would act as a surfactant-like molecule

Table 2 Mannich reaction in the CO_2–PEG system



Entry	Imine	Silyl enol ether	Yield (%)
1	 **4**	**2**	85
2	**4**		97
3		**2**	75
4	 **5**	 **6**	91
5	**5**	 **7** [d]	95[h]
6	**5**	 **8** [e]	68[i]
7	**5**	 **9** [f]	63[j]
8		**6**	89
9[c]	**4**	 **10** [g]	78[k]

[a] Poly(ethylene glycol) (average M_w was 400). [b] PEG (*ca.* 40 mg) was added in the 10 mL reaction vessel. [c] The reaction was carried out at 8 MPa. [d] *E*:*Z* = 3:97. [e] *E*:*Z* = 87:13. [f] *E*:*Z* = 7:93. [g] 1.5 eq. was used. [h] *Syn*:*anti* = 57:43. [i] *Syn*:*anti* = 38:62. [j] *Syn*:*anti* = 31:69. [k] The yield was determined by ^1H NMR analysis.

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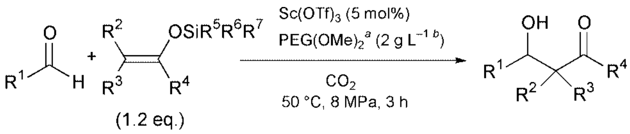
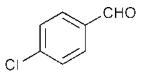
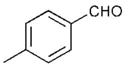
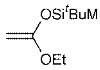
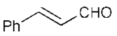
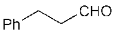
Table 3 Aldol reaction in CO_2–PEG(OMe)$_2$ system



Entry	Aldehyde	Silyl enol ether	Yield (%)
1[c,d,e]	PhCHO **11**	**10**	38
2[c,e]	**11**	**10**	72 (52[j])
3		**10**	93
4		**10**	89
5	**11**	 **12** [f]	90
6		**12**[f]	89
7		**12**[f]	78
8	**11**	**8**[f,g]	82[k]
9	**11**	**9**[f,h]	91[l]
10	**11**	**6**	84
11	**11**	**7**[i]	91[m]

[a] Poly(ethylene glycol) dimethyl ether (average M_w was 500). [b] PEG(OMe)$_2$ (*ca*. 20 mg) was added in the 10 mL reaction vessel. [c] The reaction was carried out at 15 MPa. [d] Poly(ethylene glycol) (average M_w was 400) was added. [e] Additive (4 g L^{-1}). [f] 1.5 eq. was used. [g] $E:Z = 87:13$. [h] $E:Z = 7:93$. [i] $E:Z = 3:97$. [j] Without PEG(OMe)$_2$. [k] *Syn*:*anti* = 33:67. [l] *Syn*:*anti* = 31:69. [m] *Syn*:*anti* = 26:74.

in $scCO_2$ and that the catalyst and substrates would be packed into the emulsions. The effects of pressure and average molecular weight (M_w) of PEGs on yields were examined, and the results are summarized in Table 1. The highest yield of the adduct was obtained at 15 MPa using PEG of M_w = 400. Several examples of Mannich reactions in the CO_2–PEG system are shown in Table 2. In most cases, the reaction proceeded smoothly at 50 °C/15 MPa for 3 h to afford the corresponding β-amino carbonyl derivatives in high yields. It is noteworthy that various substrates including imines derived from aromatic and heterocyclic as well as aliphatic aldehydes and silyl enolates derived from esters, thioesters, and a ketone are applicable in this system.

We also found that the CO_2–PEG system was effective for scandium-catalyzed aldol reactions of silyl enolates with aldehydes.[7] In this reaction, poly(ethylene glycol) dimethyl ether (PEG(OMe)$_2$, average M_w = 500) was more efficient than PEG (Table 3, entries 1 and 2). We examined several examples of the aldol reactions in the CO_2–PEG(OMe)$_2$ system. Not only benzaldehyde, but also substituted aromatic, aliphatic, and α,β-unsaturated aldehydes were applicable to this medium. In addition, various silyl enolates derived from a ketone, esters, and thioesters also worked well to afford the corresponding aldol adducts in high yields. We also observed that the CO_2–PEG(OMe)$_2$ medium formed emulsions in these aldol reactions.

A typical experimental procedure is described for the reaction of imine **1** with silyl enolate **2**: Yb(OTf)$_3$ (16 mg, 0.026 mmol) and a small stirring bar were placed in a 10 mL stainless steel autoclave under argon atmosphere. Imine **1** (103 mg, 0.53 mmol), silyl enolate **2** (113 mg, 0.65 mmol) and poly(ethylene glycol) (44 mg, average M_w = 400) were mixed in a small ampoule and put in the autoclave separately to prevent reactions under neat conditions before the autoclave was filled with CO_2. CO_2 was cooled at −10 °C and charged with a HPLC pump. During the introduction of CO_2, the autoclave was heated and then pressure and temperature were adjusted to 15 MPa, and 50 °C. The mixture was stirred for 3 h, and the reactor was cooled with ice and then the pressure was released. After hydrolytic work-up with aqueous $NaHCO_3$ and ethyl ether, the organic layer was dried with anhydrous Na_2SO_4. After being concentrated, the residue was subjected to preparative TLC to give **3** as a pale yellow oil (113 mg, 72% yield).

In summary, we have found that use of PEGs as additives was effective for Mannich and aldol reactions in $scCO_2$. PEGs would work as surfactants in the reaction media, and formation of emulsions was observed in these cases. The PEGs media are, as far as we know, the first example to accelerate reactions by forming emulsions in a single $scCO_2$ phase. Further investigations on the mechanism of these reactions as well as on applications to other synthetic reactions in $scCO_2$ are now in progress.

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Notes and references

† An example using PEG as a phase-transfer catalyst between a $scCO_2$ phase and a solid KCl salt phase in the cyanation reaction of benzyl chloride was reported.[8]

‡ Poly(butylene oxide)-*block*-poly(ethylene oxide) was used as a surfactant in a water–CO_2 system.[3c]

§ Emulsions formed during 8 MPa to 15 MPa at 50 °C.

1 See for example: *Supercritical Fluids*, in *Chem. Rev*., ed. R. Noyori, 1999, **99**, 353–634; *Symposium on Supercritical Fluids* in *Ind. Eng. Chem. Res*., 2000, **39**, 4441–4907.

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