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1-Dodecyloxy-4-perfluoroalkylbenzene as a Novel Efficient Additive in Aldol Reactions and Friedel–Crafts Alkylation in Supercritical Carbon Dioxide

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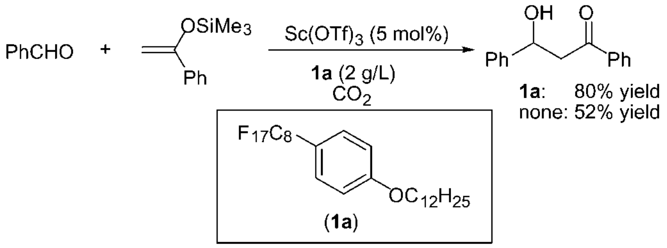
ABSTRACT



1-Dodecyloxy-4-perfluoroalkylbenzenes accelerated organic reactions such as aldol-type reactions and Friedel–Crafts alkylation in supercritical carbon dioxide. The perfluoroalkylbenzene worked as a surfactant in the system, and formation of emulsions during the reactions was observed.

Supercritical carbon dioxide ($scCO_2$)[1] is rapidly becoming attractive as a 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 or reactants are only sparingly soluble in $scCO_2$ and that they would not have sufficient reactivity and selectivity in many cases. Introduction of perfluorinated side chains in reactants and/or ligands or addition of liquid solvents was investigated to increase the solubility in $scCO_2$.[2] On the other hand, several reactions using water−CO_2 biphasic dispersions or surfactant-containing dispersion polymerization reactions have been studied.[3] Quite recently, we have developed Mannich and aldol reactions in a $scCO_2$/poly(ethylene glycol) derivatives (PEGs) system.[4] PEGs worked as surfactants in $scCO_2$, and reactants and catalysts were spread out in the reaction vessels to form emulsions. The reactions proceeded smoothly in this system to give improved product yields compared to those obtained under no additive conditions. In this paper, we report an alternative additive, 1-dodecyloxy-4-perfluoroalkylbenzene, which works as an efficient surfactant to accelerate several organic reactions in $scCO_2$.

Our finding that PEGs work as surfactants in $scCO_2$ was unexpected. We then started to design an alternative surfactant: a molecule that has a CO_2-philic unit and a lipophilic unit in the same molecule. We fixed a perfluoroalkyl chain

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[1] See, for example: (a) Noyori, R., Ed. Supercritical Fluids. *Chem. Rev.* **1999**, *99*, 353−634. (b) Symposium on supercritical fluids. *Ind. Eng. Chem. Res.* **2000**, *39*, 4441−4907.

[2] (a) Burk, M. J.; Feng, S.; Gross, M. F.; Tumas, W. *J. Am. Chem. Soc.* **1995**, *117*, 8277. (b) Kainz, S.; Koch, D.; Baumann, W.; Leitner, W. *Angew. Chem., Int. Ed. Eng.* **1997**, *36*, 1628. (c) Kainz, S.; Brinkmann, A.; Leitner, W.; Pfaltz, A. *J. Am. Chem. Soc.* **1999**, *121*, 6421. (d) Francio, G.; Leitner, W. *Chem. Commun.* **1999**, 1663. (e) Francio, G.; Wittmann, K.; Leitner, W. *J. Organomet. Chem.* **2001**, *621*, 130.

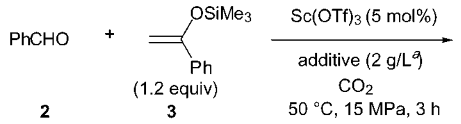
[3] (a) Canelas, D. A.; Betts, D. E.; DeSimone, J. M. *Macromolecules* **1996**, *29*, 2818. (b) Yong, Y.-M.; Hems, W. P.; van Nunen, J. L.; Holmes, M. A. B.; Steinke, J. H. G.; Taylor, P. L.; Segal, J. A.; Griffin, D. A. *Chem. Commun.* **1997**, 1811. (c) Jacobsen, G. B.; Lee, Jr., C. T.; Johnston, K. P. *J. Org. Chem.* **1999**, *64*, 1201. (d) Jacobsen, G. B.; Lee, Jr., C. T.; Johnston, K. P.; Tumas, W. *J. Am. Chem. Soc.* **1999**, *121*, 11902. (e) Bonilla, R. J.; James, B. R.; Jessop, P. G. *Chem. Commun.* **2000**, 941. (f) Giles, M. R.; Hay, J. N.; Howdle, S. M.; Winder, R. J. *Polymer* **2000**, *41*, 6715. (g) Wells, S. L.; Desimone, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 518. (h) Shim, J.-J.; Yates, M. Z.; Johnston, K. P. *Ind. Eng. Chem. Res.* **2001**, *40*, 536.

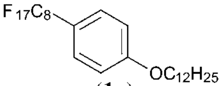
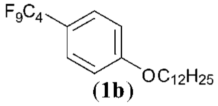
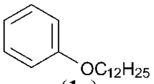
[4] Komoto, I.; Kobayashi, S. *Chem. Commun.* **2001**, 1842.

10.1021/ol0173127 CCC: $22.00

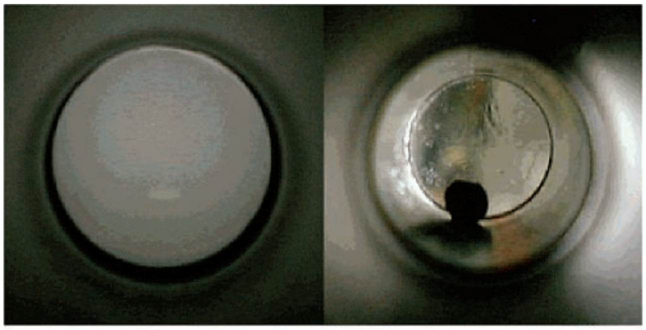
as a CO_2-philic domain, while an alkyl chain was thought to be suitable as a lipophlic domain. Based on this consideration, we synthesized 1-dodecyloxy-4-heptadecafluorooctylbenzene (**1a**), which was tested in the scandium triflate ($Sc(OTf)_3$)-catalyzed aldol reaction[5] of 1-trimethylsiloxy-1-phenylethene (**3**) with benzaldehyde in $scCO_2$. It was found that the reaction proceeded smoothly in the presence of a small amount of **1a** to afford the corresponding aldol adduct in 80% yield. It should be noted that the yield was better than that obtained using poly(ethylene glycol) dimethyl ether ($PEG(OMe)_2$) as an additive. In addition, lower yields were obtained when shorter perfluoroalkylbenzene **1b** and 1-dodecyloxybenzene (**1c**) were used (Table 1). We also observed an interesting tendency that the longer the perfluoroalkylsulfonyl chains of the scandium catalysts were, the lower the yields of the desired product in the presence of **1a** (Table 1, entries 6 and 7).[6] While the formation of emulsions was observed using **1a** (Figure 1a), substrates attached to the wall of the reaction vessel and did not spread out during the reaction without the additives (Figure 1b). These facts indicated that perfluoroalkylbenzenes acted as surfactants and that the catalysts and substrates would be packed into the emulsions.

Table 1. Effect of Additives and Catalysts



entry	catalyst	additive	yield (%)
1	$Sc(OTf)_3$	 (**1a**)	80
2	$Sc(OTf)_3$	 (**1b**)	61
3	$Sc(OTf)_3$	 (**1c**)	48
4	$Sc(OTf)_3$	$PEG(OMe)_2$[b]	72
5	$Sc(OTf)_3$	none	52
6	$Sc(OSO_2C_4F_9)_3$	**1a**	73
7	$Sc(OSO_2C_8F_{17})_3$	**1a**	51

[a] Additive (ca. 20 mg) was added in a 10 mL reaction vessel. [b] PEG (ca. 40 mg) was added in 10 mL reaction vessel.



(a) CO_2/**1a** (b) Without **1a**

Figure 1. Aldol reaction in a CO_2/**1a** system. In b, the black lump is a stirring bar.

Several examples of the $Sc(OTf)_3$-catalyzed aldol reaction of aldehydes with silicon enolates in the presence of **1a** in $scCO_2$ are shown in Table 2, entries 1−6. In all cases, the reactions proceeded smoothly to afford the aldol adducts in excellent yields. Aromatic as well as aliphatic and α,β-unsaturated aldehydes worked well. It is noted that the yields using **1a** are mostly better than those using $PEG(OMe)_2$ as an additive in $scCO_2$. Perfluorobenzene **1a** could be recovered quantitatively from the reaction mixture by simple extraction with a fluorous solvent (FC-72) (see below), and the Lewis acid catalyst ($Sc(OTf)_3$) was also recovered and reused without loss of activity. Furthermore, the $Yb(OTf)_3$-catalyzed Mannich-type reactions (imino aldol reactions) of imines with silicon enolates[7] also proceeded in the presence of a small amount of **1a** in $scCO_2$. The desired β-aminocarbonyl compounds were obtained in high yields in all cases under the conditions.

The present system was successively applied to other organic reactions. We also found that the CO_2/**1a** system was effective for Friedel−Crafts alkylation reaction of indoles.[8] Several examples are shown in Table 3, and in all cases, the alkylated indoles were obtained in high yields. We could confirm the formation of emulsions in the reaction of *N*-methylindole with MVK (Table 3, entry 3).

A typical experimental procedure is described for the reaction of aldehyde **2** with silicon enolate **5**: $Sc(OTf)_3$ (13 mg, 0.026 mmol), 1-dodecyloxy-4-heptadecafluorooctylbenzene **1a** (20 mg), and a small stirring bar were placed in a 10 mL stainless steel autoclave under argon atmosphere. Aldehyde **1** (54 mg, 0.51 mmol) and silicon enolate **5** (116 mg, 0.60 mmol) were mixed in a small ampule and put in the autoclave separately to prevent reaction 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

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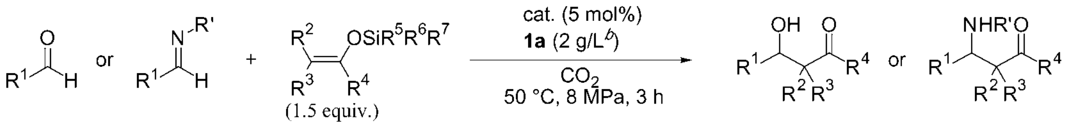
[5] Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Synlett* **1993**, 472.

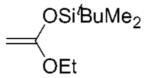
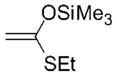
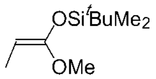
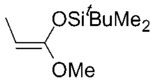
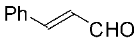
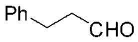
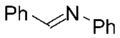
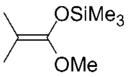
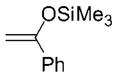
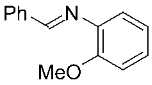
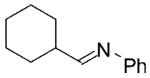
[6] We also confirmed that the longer perfluoroalkyl chains of the scandium catalysts were, the higher the yields of the desired products. Matsuo, J.; Tsuchiya, T.; Odashima, K.; Kobayashi, S. *Chem. Lett.* **2000**, 178.

[7] (a) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233. (b) Kobayashi, S.; Ishitani, H. *J. Chem. Soc., Chem. Commun.* **1995**, 1379.

[8] (a) Iqbal, Z.; Jacson, A. H.; Rao, K. R. N. *Tetrahedron Lett.* **1988**, *29*, 2577. (b) Dujardin, G.; Poirier, J.-M. *Bull. Soc. Chim. Fr.* **1994**, *131*, 900. (c) Harrington, P.; Kerr, M. A. *Synlett* **1996**, 1047. (d) Poupaert, J. H.; Bukuru, J.; Gozzo, A. *Monatsh. Chem.* **1999**, *130*, 929. (e) Manabe, K.; Aoyama, N. Kobayashi, S. *Adv. Synth. Catal.* **2001**, *343*, 174.

Table 2. Aldol and Mannich Reactions in a CO_2/1a System



entry	cat.	electrophile	silyl enol ether	yield (%)[a]
1	$Sc(OTf)_3$	PhCHO **2**	 **6**	90 (90)
2	$Sc(OTf)_3$	**2**	 **7**[c]	87 (84)
3	$Sc(OTf)_3$	**2**	 **8**[d]	97[f] (82[g])
4	$Sc(OTf)_3$	**2**	 [e]	98[h] (91[i])
5	$Sc(OTf)_3$		**6**	99 (89)
6	$Sc(OTf)_3$		**6**	92 (78)
7	$Yb(OTf)_3$	 **4**	 [c]	97 (85[j, k])
8	$Yb(OTf)_3$	**4**	 **3**	61 (78)
9	$Yb(OTf)_3$	 **5**	**6**	73 (63[j])
10	$Yb(OTf)_3$	**5**	**8**[d]	82[l] (63[j, m])
11	$Yb(OTf)_3$		**7**	90 (89[j])

[a] Parentheses are the product yields in the case using PEGs. [b] Additive (ca. 20 mg) was added in a 10 mL reaction vessel. [c] 1.2 equiv was used. [d] *E*/*Z* = 87/13. [e] *E*/*Z* = 93/7. [f] Syn/anti = 40/60. [g] Syn/anti = 33/67. [h] Syn/anti = 50/50. [i] Syn/anti = 31/69. [j] PEG (ca. 40 mg) was added in a 10 mL reaction vessel. [k] Reaction was carried out at 15 Mpa. [l] Syn/anti = 40/60. [m] Syn/anti = 31/69.

was cooled with ice and then the pressure was released. After hydrolytic workup with water and dichloromethane, the organic layer was dried with anhydrous Na_2SO_4. The aqueous layer was concentrated in vacuo to give a crystalline residue, which was dried under reduced pressure at 200 °C for 4 h to afford 13 mg (quantitative recovery) of $Sc(OTf)_3$ as colorless crystals. The organic layer was concentrated, and the residue was treated with an aqueous HCl/THF solution (10 mL, 1 N aqueous HCl/THF = 1:9) at 0 °C for 1 h. After addition of water, the mixture was extracted with dichloromethane and the organic layer was dried with anhydrous Na_2SO_4. After filtration and concentration, dichloromethane (5 mL) was added to the residue and extracted with perfluorohexanes (FC-72, 15 mL) several times. The fluorous layer was concentrated to give **1a** (20 mg, quantitative recovery). The dichloromethane layer was concentrated, and the residue was subjected to preparative TLC (hexane/ethyl acetate) to give the aldol adduct as a pale yellow oil (92 mg, 80% yield).

1-Dodecyloxy-4-heptadecafluorooctylbenzene **1a** was synthesized as follows: 4-iodophenol (1.00 g, 4.6 mmol), 1-bromododecane (2.28 g, 9.2 mmol), DMF (5 mL), and K_2CO_3 (1.28 g, 9.2 mmol) were mixed and stirred at 150 °C for 2 h. After aqueous workup with aqaqueous HCl and dichloromethane (to adjust under pH 7), the organic layer was washed with water and then dried with anhydrous Na_2SO_4. After removal of the solvents, the residue was purified by column chromatography (silica gel) to give 4-dodecyloxy iodobenzene (1.72 g, 97% yield) as a white solid. 4-Dodecyloxyiodobenzene (0.15 mg, 0.40 mmol), 1-iodoheptadecafluorooctane (4.37 g, 8.0 mmol), activated copper (0.51 g, 8.0 mmol), and pyridine (4 mL) were mixed in a glass autoclave, and the mixture was stirred at 150 °C for 48 h.[9] A small amount of aqueous 1 N HCl was added after cooling to room temperature, and the mixture was treated with Celite filtration eluted by ethyl ether. After being washed with aqueous 1 N HCl (five times) and water (five times), the mixture was dried with anhydrous Na_2SO_4 and

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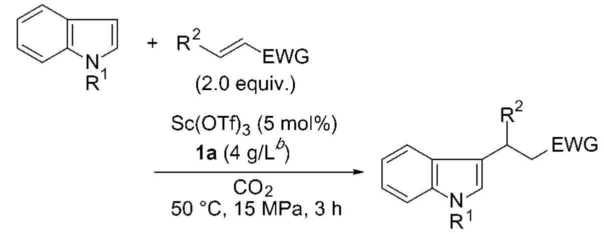
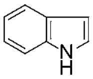
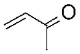
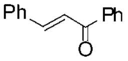
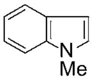
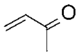
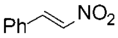
(9) (a) McLoughlin, V. C. R.; Thrower, J. *Tetrahedron* **1969**, *25*, 5921. (b) Kobayashi, Y.; Kumadaki, I.; Sato, S.; Hara, N.; Chikami, E. *Chem. Pharm. Bull.* **1970**, *18*, 2334. (c) Wiedenfeld, D.; Niyogi, S.; Charkrabarti, D. *J. Fluorine Chem.* **2000**, *104*, 303.

Table 3. Friedel−Crafts Alkylation of Indol Derivatives in a CO_2/1a System



entry	indoles	alkylating reagent	yield (%)[a]
1	 **9**		69 (58)
2	**9**		92 (74)
3			77 (59)
4	**9**		84 (71)

[a] Parentheses are the product yields without the additive. [b] **1a** (ca. 20 mg) was added in a 10 mL reaction vessel.

then concentrated. The residue was subjected to column chromatography (silica gel) to give **1a** (85 mg, 32% yield) as a white solid.[10] 4-Dodecyloxyiodobenzene (55%) was recovered.

In summary, we have found that fundamental carbon−carbon bond-forming reactions such as aldol-type reactions and Friedel−Crafts alkylation proceed smoothly in the presence of a small amount of perfluoroalkylbenzene **1a** in $scCO_2$. In $scCO_2$, **1a** works as a surfactant to form emulsions. In most cases, perfluoroalkylbenzene **1a** is more effective than PEGs, which also work as surfactants as we have previously found. Further investigations to apply this new system to other synthetic reactions are now in progress.

Acknowledgment. This work was partially supported by CREST, Japan Science and Technology Corporation (JST), and a Grant-in-Aid for Scientific Research from the Japan Society of the Promotion of Science.

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[10] Experimental data: mp 54−55 °C; ^{1}H NMR (CDCl$_3$) δ 0.88 (t, J = 6.9 Hz, 3 H), 1.24−1.50 (m, 18 H), 1.80 (dq, J = 6.9, 6.9 Hz, 2 H), 3.99 (t, J = 6.5 Hz, 2 H), 6.96 (d, J = 8.8 Hz, 2 H), 7.48 (d, J = 8.8 Hz, 2 H); ^{13}C NMR (CDCl$_3$) δ 14.1, 22.7, 26.0, 29.1, 29.4, 29.59, 29.63, 29.68, 29.71, 32.0, 68.3, 105−119 (m), 114.5, 120.6 (t, J = 24.8 Hz), 128.4 (t, J = 6.2 Hz), 162.0; ^{19}F NMR (CDCl$_3$) δ −126.4 (bs, 2 F), −123.0 (bs, 2 F), −122.2 (bs, 6 F), −121.6 (bs, 2 F), −110.0 (t, J = 14.6 Hz, 2 F), −81.1 (t, J = 10.0 Hz, 3 F); IR (cm^{-1}) (KBr) 2921, 2853, 1615, 1518, 1475, 1370, 1257, 1211, 1144, 1112, 1090, 1051, 1017, 952, 845, 661, 559; MS (m/z) 680 (M^+). Anal. Calcd for $C_{26}H_{29}F_{17}O$: C, 45.89; H, 4.30. Found: C, 46.04; H, 4.60.