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Notes

Supercritical Carbon Dioxide as a Reaction Medium for Silane-Mediated Free-Radical Carbonylation of Alkyl Halides

Yasuhisa Kishimoto and Takao Ikariya*

Graduate School of Science and Engineering,
Tokyo Institute of Technology and CREST, Japan Science
and Technology Corporation, 2-12-10 O-okayama,
Meguro-ku, Tokyo, 152-8552 Japan

tikariya@o.cc.titech.ac.jp

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Free-radical carbonylation has been extensively investigated as a promising tool for the introduction of a carbonyl group because of its potentially wide scope in organic synthetic chemistry.[1] Ryu and Sonoda reported a pioneering study of free-radical reductive carbonylation of organic halides with tri-*n*-butyltin hydride[2] or tris(trimethylsilyl)silane ($(TMS)_3SiH$)[3] in benzene, giving aldehydes or ketones in moderate to high yields. The outcome of this carbonylation is known to be dependent on the reactivity and stability of alkyl or acyl radical intermediates, which are expected to be strongly influenced by the solvent cage effect. Benzene is one of most useful nonpolar solvents for this radical reaction, but it is an environmentally hazardous compound. Ryu and Curran proposed organic/fluorous biphase systems as an alternative to benzene solvent for the free-radical carbonylation of alkyl halides, where a fluorous tin hydride reagent was used as a chain carrier.[4]

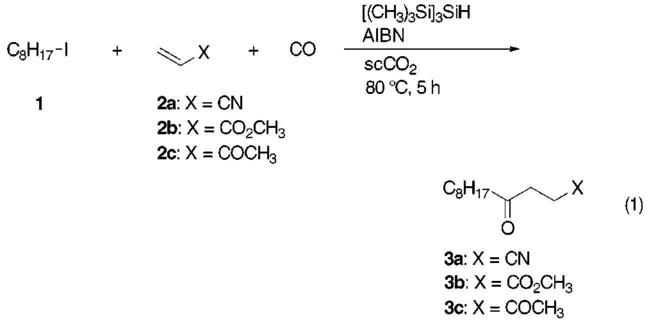
Supercritical carbon dioxide ($scCO_2$) is an emerging reaction medium for the free-radical reactions for a number of reasons, such as the pressure-tunable cage effect, the absence of radical chain transfer to the medium,[5] and unique properties such as high diffusivity and high miscibility of reactant gases.[6] These unique properties make it possible to attain high productivity in reactions with gaseous reactants and to avoid potential mass-transfer limitations.[7] In fact, DeSimone has reported that free-radical polymerization initiated by 2,2′-azobis(isobutyronitrile) (AIBN) in $scCO_2$ effectively proceeds with higher initiation efficiency than in benzene because of the weak cage effect in the supercritical medium.[8] We have recently demonstrated a discernible advantage of $scCO_2$ by performing the Ru(II)-catalyzed hydrogenation of CO_2[7] and the Pd(II)-catalyzed carbonylation of aryl iodides[9] in this medium. Thus, adopting $scCO_2$ as a reaction medium should allow for a highly efficient radical carbonylation. Herein, we report the first silane-mediated efficient free-radical carbonylation of organic halides to ketones in $scCO_2$.

Table 1. Tris(trimethylsilyl)silane-Mediated Free-Radical Coupling Reaction of 1-Iodooctane (1), Activated Olefin (2), and CO in $scCO_2$[a]

entry	olefin	AIBN equiv to **1**	P_{CO},[b] atm	P_{total}, atm	product yield, %[c]
1	**2a**	0.30	20	in benzene	**3a**, 60
2	**2a**	0.30	20	305	**3a**, 80
3	**2a**	0.30	20	230	**3a**, 66
4	**2a**	0.30	20	120	**3a**, 21
5	**2a**	0.30	2	300	**3a**, 40
6	**2a**	0.30	50	310	**3a**, 90
7	**2a**	0.075	20	295	**3a**, 66
8	**2b**	0.30	50	305	**3b**, 90[d]
9	**2c**	0.30	50	300	**3c**, 96[d]

[a] [**1**] = 1.3 mmol, [**2**] = 1.6 mmol, [$(TMS)_3SiH$] = 2.0 mmol, 80 °C, 5 h, in a 50 mL stainless steel autoclave. [b] Initial CO pressure at room temperature. [c] Isolated yield. [d] Determined by NMR analysis.

The reductive carbonylation of 1-iodooctane (**1**) and acrylonitrile (**2a**) with CO_2-soluble $(TMS)_3SiH$ in $scCO_2$ (CO 20 atm, 305 atm total pressure) containing AIBN as a radical initiator (**1**/**2a**/$(TMS)_3SiH$/AIBN = 1:1.2:1.5:0.3) at 80 °C proceeded smoothly to give 1-cyano-3-undecanone (**3a**) in a good yield (80%) (eq 1).[10] Table 1 summarizes some representative results. The yield of **3a** was noticeably higher than that attained in benzene (entry 1 and 2). Organic halide **1** was completely consumed under these conditions. The reaction is known to proceed via formation of *n*-octyl radical followed by carbonylation of alkyl radical to acyl radical and its nucleophilic addition to acrylonitrile. Thus, the generated



(1)

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[10] Visual inspection revealed that the reaction systems containing 20 and 50 atm of CO were homogeneous above 200 and 220 atm of the total pressure, respectively.

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Table 2. Tris(trimethylsilyl)silane-Mediated Free-Radical Carbonylative Cyclization of 1-Iodo-4-hexene (4) in $scCO_2$[a]

entry	concn of **4** (M)	P_{CO}[b] (atm)	P_{total} (atm)	% yield[c] **5**	**6**	total	selectivity[c] **5**:**6**
1	0.025	50	in benzene	18	39	57	1:2.1
2	0.025	50	325	31	68	99	1:2.2
3	0.025	50	230	32	38	70	1:1.2
4	0.025	50	51	18	3	21	1:0.17
5	0.0083	2	315	14	38	52	1:3.2
6	0.0083	10	300	17	51	68	1:3.1
7	0.0083	50	295	16	40	56	1:2.5
8	0.0083	50	175	24	23	47	1:1.1

[a] [**4**] = 1.25 or 0.417 mmol, [**4**]/[$(TMS)_3SiH$]/[AIBN] = 1/1.4/0.12, 80 °C, 3 h, in a 50 mL stainless steel autoclave. [b] Initial CO pressure at room temperature. [c] Determined by ^1H NMR analysis.

β-keto radicals are quenched by the silane to give the ketone product.[2−4] The reduction product, *n*-octane, was obtained as a major byproduct, while nonyl aldehyde was not detected at all in the reacton mixture. Although a tri-*n*-butyltin hydride-assisted radical reaction of CO_2 was known to give tri-*n*-butyltin formate in $scCO_2$,[11] no evidence for the formation of either silyl formate, silyl ether, or alcohol via an undesirable hydrosilation of both CO_2 and the product ketone was observed in these experiments. At constant CO pressure of 20 atm, the yield of **3a** increased as the total pressure increased. The low yield at the total pressure of 120 atm (entry 4) was ascribed to the precipitation of liquid where the reduction of halide with the silane predominantly occurred. Because of the high solubility of CO in $scCO_2$, the carbonylation in $scCO_2$ (300 atm total pressure) efficiently occurred even at 2 atm of CO pressure (CO/halide = ca. 3:1), giving the product in a moderate yield, 40% (entry 5). An increase in the CO pressure to 50 atm at the same total pressure resulted in an improvement of the yield of **3a** (90%) (entry 6). Decreased AIBN concentration to 7.5 mol % showed no significant decrease in the yield of the product. The reaction of **1** and methyl acrylate (**2b**) or methyl vinyl ketone (**2c**) in the presence of 50 atm of CO in $scCO_2$ at 80 °C for 5 h smoothly proceeded in a similar way to afford methyl 4-oxododecanoate (**3b**) or 2,5-tridecanedione (**3c**) in 90 or 96% yield (by ^1H NMR), respectively.

When 1-iodo-4-hexene (**4**, 1.25 mmol, 0.025 M) was treated with $(TMS)_3SiH$ (1.4 equiv) in $scCO_2$ (CO 50 atm, total pressure 325 atm) at 80 °C, a mixture of 2-ethylcyclopentanone (**5**) and 2-methylcyclohexanone (**6**) was obtained in an excellent yield (99% based on the iodide) with a 1:2.2 molar ratio (entry 2 of Table 2). Homogeneity of the reaction mixture above the total pressure of ca. 220 atm (at 0.025 M of **4**) and above ca. 160 atm (at 0.0083 M of **4**) was visually confirmed. The yields of the ketone products in $scCO_2$ were higher than that attained in benzene at the same substrate concentration because of the high miscibility of CO (Table 2). Noticeably, the selectivity of the cyclization of the acyl radical generated from **4** and CO was found to be strongly dependent upon the viscosity of the reaction medium and the substrate concentration. Figure 1 shows the product ratio of **6**/**5** formed in the carbonylation in $scCO_2$ as a function of the viscosity of the reaction medium.[12,13] The product ratio monotonically increased regardless of the concentration of **4** by increasing the viscosities which are implicitly varied as a function of their densities related to total pressures of CO_2 and CO.[14] As shown in Table 2 and Figure 1, decreasing the total pressure from 325 to 230 atm (CO 50 atm, **4** 0.025 M) resulted in an increase in the five-membered cyclic ketone (**5**:**6** = 1:1.2) (entry 2 vs entry 3). Under 1 atm of CO_2, the five-membered ketone **5** was predominantly obtained in a low yield because the reaction occurred in the silane-rich liquid phase (entry 4).[15] At a lower substrate concentration, increasing the viscosity of the medium resulted in a remarkable increase in the formation of a six-membered cyclic ketone (**5**:**6** = 1:3.2) at 2 atm of CO and 315 atm of total pressure (**4** 0.0083 M) (Figure 1).

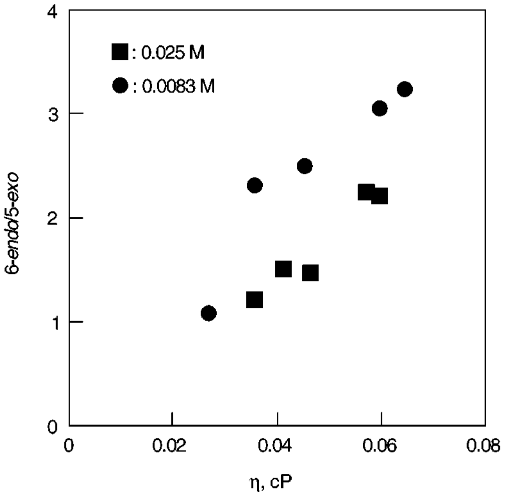

Figure 1. Dependence of 6-endo/5-exo-cyclized product ratio upon the viscosity of the medium. CO pressure = 2−50 atm, total pressure = 175−325 atm. Concentration of **4**: (■) 0.025 M, (●) 0.0083 M.

Many of the details of this cyclic carbonylation have been well investigated. As depicted in Scheme 1, the unsaturated acyl radical intermediate generated from the unsaturated alkyl radical and CO cyclizes to give the exocyclic and endocyclic β-keto radicals. The 5-*exo-trig* process is known to be kinetically more favored over the 6-*endo-trig* cyclization which gives the more stable six-membered radical.[16] Prior to reaction with a silane, the initially formed exocyclic radical slowly isomerizes to the ring-expanded isomer in a solvent cage. This rearrangement is known to proceed directly or via a cyclopropoxyl radical intermediate[16] and could be influenced by the solvent cage strength. The 5-*exo* to 6-*endo* selectivity

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[12] The viscosity of the reaction medium under each experimental condition was calculated from the density using Chung's method (see ref 13).

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[15] For the free-radical cyclization of 5-hexenoyl chloride in benzene, a similar trend has been observed: Brown, C. E.; Neville, A. G.; Rayner, D. M.; Ingold, K. U.; Lusztyk, J. *Aust. J. Chem.* **1995**, *48*, 363−379.

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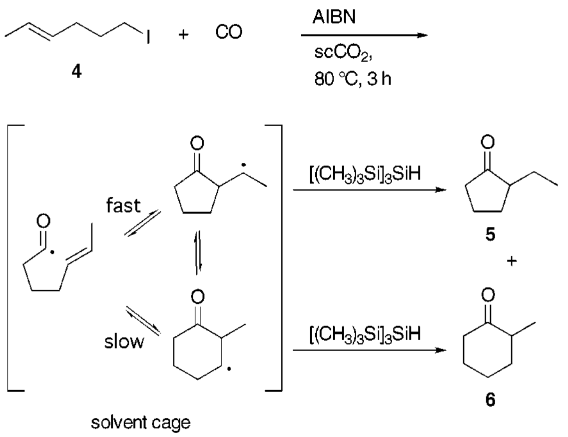
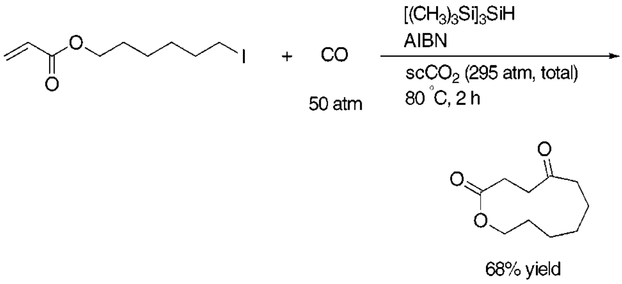
Scheme 1



observed in $scCO_2$ (Figure 1) can be interpreted in terms of the cage effect. At high viscosities, **6** was predominantly obtained because of the cage effect as observed in benzene. At low viscosities, the initially formed exocyclic radical predominantly reacts with the silane to give **5** because of a weak cage effect. A similar remarkable change in the selectivity with varying the pressure (or density) of the CO_2 medium has also been presented in the free-radical chlorination of alkanes,[17] and the photo-Fries rearrangement of naphthyl acetate.[18] The product ratio further increased at low substrate concentration (0.0083 M) probably because of the dilution effect as observed in solution.[16a,b]

The radical carbonylative ring-closing reaction of 6-iodohexyl acrylate (0.25 mmol) with 2 equiv of $(TMS)_3SiH$ in the presence of AIBN (0.2 equiv) in $scCO_2$ including CO (CO 50 atm, total pressure 295 atm) at 80 °C for 2 h afforded the eleven-membered macrolide in 68% isolated yield (eq 2). The yield of the macrolide is comparable to that achieved in benzene.[3b]



(2)

In conclusion, this free-radical carbonylation in $scCO_2$ is characterized by high efficiency and tunability of product distribution with pressure because of the characteristic properties of $scCO_2$ such as high miscibility of CO and controllable cage strength. Thus, $scCO_2$ can replace environmentally unacceptable benzene. This is the first example of free-radical carbonylation of organic halides in $scCO_2$.

Experimental Section

SAFETY WARNING: Operators of high-pressure equipment should take proper precautions to minimize the risk of personal injury.[7b]

Experimental Procedure for the Coupling Reaction of 1-Iodooctane (1), Olefin (2), and CO. A small vial containing AIBN (0.39 mmol) and a micromagnetic stirring bar were placed in a 50-mL stainless steel autoclave. After the autoclave was evacuated and then filled with argon, **1** (1.3 mmol), **2a** (1.6 mmol), and $(TMS)_3SiH$ (2.0 mmol) were charged into the autoclave (outside the vial) with a syringe. Then, CO was pressurized to 50 atm, and then CO_2 was added to the autoclave with an HPLC pump to attain the total pressure of approximately 220 atm. The temperature was raised to 80 °C and the pressure examined was achieved with the addition of more CO_2. After 5 h reaction, the vessel was cooled to approximately −78 °C, CO_2 and excess CO were vented, and the reactor was slowly warmed to room temperature. The remaining organic liquid was diluted with 20 mL of ether. 1,8-Diazabicyclo[5.4.0]-undecene (ca. 0.2 mL) was added to this solution to form a white precipitate, and a small portion of ether solution of I_2 was added until the color changed. The precipitate was filtered off through a plug of silica gel, and the precipitate was washed with ether (20 mL × 3). The combined ether solution was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The remained yellow oil was chromatographed on silica gel using hexane/ethyl acetate (from 100/0 to 95/5 v/v) as a mobile phase. A main fraction ($R_f = 0.34$, hexane/ethyl acetate 5/1 (v/v)) contained 229.1 mg of **3a** (90% yield).

1-Cyano-3-undecanone (3a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.75 (t, $COCH_2CH_2CN$, 2H), 2.53 (t, CH_2CN, 2H), 2.39 (t, $CH_2COCH_2CH_2CN$, 2H), 1.54 (br s, $CH_3(CH_2)_5CH_2CH_2CO$, 2H), 1.22 (br s, $CH_3(CH_2)_5CH_2CH_2CO$, 10H), 0.82 (t, CH_3, 3H); $^{13}C\{^1H\}$ NMR (75.45 MHz, $CDCl_3$) δ 206.4, 119.1, 42.4, 37.6, 31.7, 29.2, 29.1, 29.0, 23.6, 22.6, 14.0, 11.3; ESI HRMS calcd for $C_{12}H_{21}NOK$ (M + K) *m/z* 234.1260, found 234.1259.

Methyl 4-oxododecanoate (3b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (s, CH_3O, 3H), 2.67 (t, $COCH_2CH_2COO$, 2H), 2.53 (t, $COCH_2CH_2COO$, 2H), 2.39 (t, $CH_2COCH_2CH_2COO$, 2H), 1.53 (m, $CH_3(CH_2)_5CH_2CH_2CO$, 2H), 1.22 (br s, $CH_3(CH_2)_5CH_2CH_2CO$, 10H), 0.82 (t, CH_3, 3H); $^{13}C\{^1H\}$ NMR (75.45 MHz, $CDCl_3$): δ 209.0, 173.2, 51.6, 42.7, 36.9, 31.7, 29.3, 29.1, 29.0, 27.6, 23.7, 22.5, 14.0. These spectroscopic data were consistent with those previously reported.[19]

2,5-Tridecanedione (3c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.64 (m, $COCH_2CH_2COCH_3$, 4H), 2.40 (t, $CH_2COCH_2CH_2COCH_3$, 2H), 2.15 (s, $COCH_3$, 3H), 1.53 (m, $CH_3(CH_2)_5CH_2CH_2CO$, 2H), 1.23 (br s, $CH_3(CH_2)_5CH_2CH_2CO$, 10H), 0.83 (t, CH_3, 3H); $^{13}C\{^1H\}$ NMR (75.45 MHz, $CDCl_3$) δ 209.6, 207.2, 42.8, 36.8, 36.0, 31.8, 29.9, 29.3, 29.2, 29.1, 23.8, 22.6, 14.0. The ^{1}H NMR data were consistent with those previously reported.[20]

Experimental Procedure for the Carbonylative Cyclization of 1-Iodo-4-hexene (4). A small vial containing AIBN (0.15 mmol) and a micromagnetic stirring bar were placed in a 50 mL stainless steel autoclave. After the autoclave was evacuated and then filled with argon, **4** (1.25 mmol) and $(TMS)_3SiH$ (1.75 mmol) were charged to the autoclave (outside the vial) with a syringe through an opening against a flow of argon. Then, CO was pressurized to 50 atm, and finally CO_2 was added to the autoclave with an HPLC pump to attain the total pressure of approximately 220 atm. The temperature was raised to 80 °C and the final desired pressure (325 atm) was achieved with the addition of more CO_2. After 5 h, the vessel was cooled to approximately −78 °C, CO_2 and excess CO were vented, and the reactor was slowly warmed to room temperature. ^{1}H NMR spectrum of the reaction mixture containing 0.5 mmol of benzene as an internal standard showed the yields of **5** and **6** to be 31% and 68%, respectively.

Carbonylative Cyclization of 6-Iodohexyl Acrylate. A small vial containing AIBN (0.05 mmol) and a micromagnetic stirring bar were placed in a 50 mL stainless steel autoclave. After the autoclave was evacuated and then filled with argon, 6-iodohexyl acrylate (0.25 mmol) and $(TMS)_3SiH$ (0.5 mmol) were charged to the autoclave (outside the vial) with a syringe through an opening against a flow of argon. Then, CO was pressurized to 50 atm, and finally CO_2 was added to the autoclave with an HPLC pump to attain the total pressure of approximately 220

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atm. The temperature was raised to 80 °C, and the final desired pressure (295 atm) was achieved with the addition of more CO_2. After 2 h, the vessel was cooled to approximately −78 °C, CO_2 and excess CO were vented, and the reactor was slowly warmed to room temperature. The residue was dissolved in 20 mL of acetonitrile and washed with pentane (3 × 15 mL). The acetonitrile layer was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel using hexane/ethyl acetate (from 100/0 to 95/5 v/v) as a mobile phase. A main fraction, eluted with hexane/ethyl acetate (95/5 v/v), contained 31.6 mg of the eleven-membered lactone (68% yield). Its ^1H NMR data were consistent with those previously reported.[3b]

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Supporting Information Available: Typical experimental procedures and ^1H and $^{13}C\{^1H\}$ NMR spectra of **3a**−**c**. This material is free of charge via the Internet at http://pubs.acs.org.

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