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PALLADIUM-CATALYZED DOUBLE CARBONYLATION OF ALKYL IODIDES BEARING PERFLUOROALKYL GROUP

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Abstract: *Double carbonylation of 1-perfluoroalkyl substituted 2-iodoalkanes are effectively catalyzed by palladium complexes in the presence of primary or secondary amines leading to the formation of the corresponding α-keto amides in good yields.*

Numerous efforts to introduce fluorine atoms into a variety of organic compounds have been made in search of biological active compounds. Fluorine-containing amino acids have been one of the promising candidates on this line.[1] Recently, much attention has been focused on double carbonylation of organic halides forming α-keto acid derivatives, which are useful synthons of α-amino acids. It is well known that dicobalt octacarbonyl is a good catalyst for the double carbonylation of benzylic halides[2] or α,ω-dihalides,[3] whereas palladium-phosphine complexes exhibit the catalytic activity for aryl or vinyl halides.[4] We examined the double carbonylation of 1-perfluoroalkyl substituted 2-iodoalkanes easily available by the addition of perfluoroalkyl iodides to olefins, and wish to report here the first example of palladium catalyzed double carbonylation of alkyl halides.

Initially, we examined the cobalt catalyzed conversion of 1-perfluoro-octyl-2-iodoethane (**1a**) into the corresponding α-keto acid using calcium hydroxide as base in t-BuOH under similar conditions to those reported.[2] No carbonylation took place under carbon monoxide pressure of less than 5 atm, and the starting iodide (**1a**) was recovered unchanged. When the reaction was carried out at 80 °C under 50 atm of CO in the presence of $Ca(OH)_2$, a mixture of the α-keto acid (**4a**) and the carboxylic acid (**5a**) was obtained (Eq. 1). In spite of our continuous efforts to optimize the reaction conditions, we could not achieve selective synthesis of the α-keto acid **4a**. As shown in Table 1, the highest yield of the doubly carbonylated product is only 29%.

Next we examined the palladium catalyzed carbonylation of **1**. Although no effective carbonylation of alkyl halides using palladium catalyst has been reported until now, we found that palladium-phosphine complexes are effective catalysts not only for mono but also for double carbonylation reaction of 1-perfluoroalkyl substituted 2-iodoalkanes (**1**) to afford the corresponding amides and α-keto amides. A general scheme of the present double carbonylation reaction is shown in Eq. 2.

$$C_8F_{17}CH_2CH_2I{+}CO + H_2O \xrightarrow[Ca(OH)_2,\ t\text{-}BuOH]{Co_2(CO)_8} C_8F_{17}CH_2CH_2C(=O)C(=O)OH + C_8F_{17}CH_2CH_2C(=O)OH \quad (1)$$

1a **4a** **5a**

Table 1. Cobalt-Catalyzed Double Carbonylation of **1a**[a)]

Run	H_2O(eq)	$Ca(OH)_2$(eq)	Temp.(°C)	Time(hr)	**4a**(%)[b)]	**5a**(%)[b)]
1	100	1.0	80	48	16	42
2	100	3.7	100	48	29	24
3	100	2.0	120	24	29	25
4	41	3.7	80	48	18	25
5	100	3.7	60	48	6	20

a) All reactions were run at 1.35 mmol scale of **1a** in t-BuOH (10 ml) in the presence of 10 mol% of $Co_2(CO)_8$ under 50 atm of CO pressure. b) Isolated yield. The products can be separated by silica gel column chromatography.

$$R_fCH_2CH(R^1)I + 2CO + HNR^2_2 \xrightarrow{\text{Pd cat.}} R_fCH_2CH(R^1)C(=O)C(=O)NR^2_2 + R_fCH_2CH(R^1)C(=O)NR^2_2 \quad (2)$$

1 (R_f = perfluoroalkyl group) **2** **3**

Typical procedure is as follows. A mixture of $(Ph_3P)_2PdCl_2$ (24 mg, 0.03 mmol), $C_8F_{17}CH_2CH_2I$ (**1a**, 0.62 g, 1 mmol), and Et_2NH (0.52 ml, 5 mmol) in 1.5 ml of heptane in 50 ml of stainless steel autoclave was heated at 100 °C for 15 hr under carbon monoxide pressure (50 atm) with stirring. After evaporation of the solvent, the residue was submitted to a column chromatography on silica gel ($CHCl_3$) to give N,N-diethyl-4-perfluorooctyl-2-oxobutanamide (**2a**)[5)] in 56% yield (0.32 g) and N,N-diethyl-3-perfluorooctyl-propanamide (**3a**[6)]; 12%, 66 mg). Under the same reaction conditions as above, α-keto amides containing various kinds of perfluoroalkyl groups (**2**) were obtained in good yields in addition to amides (**3**). Representative results are summarized in Table 2. Aliphatic hydrocarbons are good solvents in the present reaction, and much less products were obtained in benzene or acetonitrile. Excess amounts (ca. 5 equiv. based on **1**) of diethylamine are suitable for the double carbonylation reaction. When two equivalents of diethylamine were used, singly carbonylated amide (**3a**) was formed as the main product in 50% yield as shown in Run 2. Primary amine such as tert-butylamine as well as secondary amines can be employed as reagents for the α-keto amides synthesis. In any case, no quaternary ammonium salt was formed at all under the present reaction conditions. On using cyclic amine such as piperidine (Run 8) or pyrrolidine, N-(3-fluoro-3-perfluoroalkyl-2-propenyl)-piperidine or

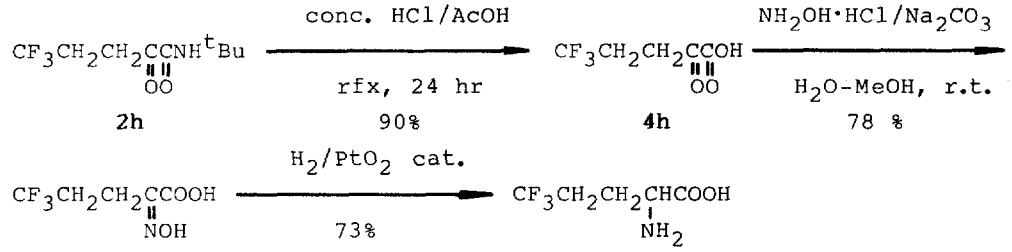
Table 2. Palladium-Catalyzed Double Carbonylation of **1**[a)]

Run	1	R_f	R^1	cat.[b)]	R^2_2NH(eq)	Products(Yield/%)	
1	**1a:**	$n\text{-}C_8F_{17}$	H	A	Et_2NH(5)	**2a:**56	**3a:**12
2		$n\text{-}C_8F_{17}$	H	A	Et_2NH(2)	38	50
3		$n\text{-}C_8F_{17}$	H	B	Et_2NH(5)	46	21
4		$n\text{-}C_8F_{17}$	H	C	Et_2NH(5)	24	5
5		$n\text{-}C_8F_{17}$	H	D	Et_2NH(5)	0	0
6		$n\text{-}C_8F_{17}$	H	E	Et_2NH(5)	3	4
7		$n\text{-}C_8F_{17}$	H	F	Et_2NH(5)	24	17
8		$n\text{-}C_8F_{17}$	H	G	Et_2NH(5)	0	13
9		$n\text{-}C_8F_{17}$	H	H	Et_2NH(5)	0	19
10[c)]		$n\text{-}C_8F_{17}$	H	A	piperidine(5)	**2b:**21	**3b:** -[d)]
11	**1b:**	$n\text{-}C_6F_{13}$	H	A	$t\text{-}BuNH_2$(5)	**2c:**36	**3c:** -[d)]
12	**1c:**	$n\text{-}C_4F_9$	H	A	$n\text{-}Pr_2NH$(5)	**2d:**56	**3d:**17
13	**1d:**	$i\text{-}C_3F_7$	H	A	Et_2NH(5)	**2e:**38	**3e:**22
14	**1e:**	C_2F_5	H	A	Et_2NH(5)	**2f:**36	**3f:** 1
15	**1f:**	CF_3	H	A	$n\text{-}Pr_2NH$(5)	**2g:**50	**3g:** 7
16		CF_3	H	A	$t\text{-}BuNH_2$(5)	**2h:**53	**3h:** -[d)]
17	**1g:**	CF_3	Me	A	Et_2NH(5)	**2i:**66	**3i:**14

a) All reactions were carried out in the presence of catalyst (3 mol%) in heptane solution at 100 °C under 50 atm of CO for 15 hr. b) A: $(Ph_3P)_2PdCl_2$, B: $(Cy_3P)_2PdCl_2$, C: $(Ph_2MeP)_2PdCl_2$, D: (dppe)$PdCl_2$, E: (dppp)$PdCl_2$, F: (dppb)$PdCl_2$, G: $Co_2(CO)_8$, H: $Rh_6(CO)_{16}$. c) N-(3-Fluoro-3-perfluoro-heptyl-2-propenyl)piperidine was obtained as a main product in 47% isolated yield. d) Not isolated.

-pyrrolidine was obtained as the main product in addition to α-keto amide. In sharp contrast to the double carbonylation of aryl halides,[4)] $(Ph_2MeP)_2PdCl_2$ and (dppp)$PdCl_2$ catalysts were less effective for the present reaction. Among the Pd(II)-phosphine complexes examined as a catalyst, we found that $(Ph_3P)_2PdCl_2$ and $(Cy_3P)_2PdCl_2$, which have relatively bulky phosphine ligands, show potent activities for the double carbonylation reaction (Table 2, Run 1, 3-7). Cobalt and rhodium carbonyl complexes gave only amide **3a** in poor yields. Judging from the analogy between the present reaction and the double carbonylation of aryl halides, the mechanism of the double carbonylation of 1-perfluoroalkyl substituted 2-iodoalkanes may be similar to that proposed by Ozawa *et al.*[4)]

Perfluoroalkyl group containing α-keto amides obtained here can be easily converted into the corresponding α-amino acids. Typical example is outlined in Eq. 3. α-Keto acid **4h** prepared by hydrolysis of **2h** under acidic conditions (conc. HCl/AcOH)[7)] was treated with $NH_2OH{\cdot}HCl$ in the presence of Na_2CO_3 in an aqueous methanol solution to form oxime **6**,[8)] successive hydrogenation by PtO_2 catalyst[9)] afforded trifluoronorvaline (**7**) in good yield.



$CF_3CH_2CH_2CCNH^tBu$ (O, O) (**2h**) → $CF_3CH_2CH_2CCOH$ (O, O) (**4h**) → $CF_3CH_2CH_2CCOH$ (NOH) (**6**) → $CF_3CH_2CH_2CHCOOH$ (NH_2) (**7** (trifluoronorvaline)) (3)

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5) **2a:** mp 52.5-53 °C; IR (KBr) ν(C=O) 1726 and 1640 cm^{-1}; ^{1}H-NMR ($CDCl_3$, TMS) δ 1.20 (3H, t, J = 7.2Hz), 1.22 (3H, t, J = 7.1Hz), 2.50 (2H, tt, J = 18.9 and 7.4Hz), 3.15 (2H, t, J = 7.4Hz), 3.31 (2H, q, J = 7.1Hz), 3.44 (2H, q, J = 7.2Hz); ^{13}C-NMR ($CDCl_3$, TMS, except for R_f group) δ 12.62 (s), 14.55 (s), 24.71 (t, J = 22.3Hz), 31.12 (t), 40.07 (s), 42.34 (s), 165.42 (s), 197.44 (s); ^{19}F-NMR ($CDCl_3$, $CFCl_3$) δ -81.5 (3F, t, J = 10Hz), -114.6 (2F, m), -122.2 (6F, m), -123.1 (2F, m), -123.8 (2F, m), -126.6 (2F, m); Anal. Calcd for $C_{16}H_{14}F_{17}NO_2$ C:33.41, H:2.45, N:2.43; Found C:33.32, H:2.47, N:2.43.

6) **3a:** IR (KBr) ν(C=O) 1640 cm^{-1}; ^{1}H-NMR ($CDCl_3$, TMS) δ 1.13 (3H, t, J = 7.2Hz), 1.21 (3H, t, J = 7.1Hz), 2.45-2.65 (4H, m), 3.33 (2H, q, J = 7.2Hz), 3.40 (2H, q, J = 7.1Hz); ^{13}C-NMR ($CDCl_3$, TMS, except for R_f group) δ 13.05 (s), 14.22 (s), 24.12 (s), 27.02 (t), 40.62 (s), 42.00 (s), 168.93 (s); ^{19}F-NMR ($CDCl_3$, $CFCl_3$) δ -81.5 (3F, t, J = 10Hz), -114.8 (2F, m), -122.1 (6F, m), -123.1 (2F, m), -124.0 (2F, m), -126.5 (2F, m).

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