New Aspects of Carbonylations Catalyzed by Transition-Metal Complexes

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Contents

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I. Introduction

Carbonylations of olefins, acetylenes, halides, alcohols, amines, nitro compounds, etc. promoted by transition-metal complexes are very important in both industrial and laboratory organic syntheses.[1] The mechanisms of those reactions have been studied extensively, especially for those associated with commercial processes such as hydroformylations of 1-alkenes.[1] Recently, the research on the utilization of carbon monoxide has substantially been promoted by the "C_1 chemistry" projects with regard to the establishment of chemical technology that enables production of gasoline, ethylene glycol, acetic acid, ethanol, methanol, etc. directly from carbon monoxide and hy-

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TABLE I. Hydroformylation of TFP[a]

cat.	TFP[b] cat.	press.,[c] atm (CO/H_2 = 1)	temp, °C	time, h	aldehydes[d] %	aldehydes[d] iso/n	alkane,[d] %
$Co_2(CO)_8$	50	130	100	20	95	7/93	0
$Co_2(CO)_8/PPh_3$	50	130	100	41	3	9/91	1
$PtCl_2(DIOP)/SnCl_2$	100	130	100	4	75	29/71	25
$Ru_3(CO)_{12}$	33	130	100	16	62	85/15	38
$Ru_3(CO)_{12}/PPh_3$	33	130	100	39	2k	92/8	1
$Rh_6(CO)_{16}$	1200	110	80	5	98	96/4	2
$Rh_6(CO)_{16}/PPh_3$	1200	110	80	22	93	97/3	7
$Rh_4(CO)_{12}$	1200	110	80	6	97	97/3	3
$Rh-C/P(OPh)_3$	1200	110	80	5	98	96/4	2
Rh-C	1200	110	80	5	96	96/4	4
$HRh(CO)(PPh_3)_3$	1200	110	80	5	95	95/5	5
$Rh-C/PPh_3$	1200	110	80	15	90	95/5	10
RhCl(dppb)	1200	110	80	22	42	97/3	<4
$RhCl(PPh_3)_3$	1200	110	80	22	30	96/4	<3
$RhCl(CO)(PPh_3)_2$	1200	110	80	22	23	95/5	<2
$RhCl_3 \cdot 3H_2O/PPh_3$	1200	110	80	22	17	96/4	<2

[a] All experiments were run with 130 mmol of TFP in 20 mL of toluene. [b] (mol of TFP)/(mol of metal). [c] Initial pressure at room temperature. [d] Determined by GLC.

drogen in the presence of appropriate catalysts. The use of carbon monoxide as a "one-carbon unit" has much potential in organic synthesis as well, and thus a variety of new carbonylations are currently being explored, which may eventually become commercial processes.

In our laboratory we have been interested in the development of (i) unique hydrocarbonylations of fluoro olefins, which will provide versatile intermediates for the synthesis of a variety of organofluorine compounds, and (ii) one-pot multistep processes exploiting the cobalt-catalyzed amidocarbonylation of aldehydes as a key unit reaction since this reaction can provide important fundamental biochemicals, i.e., *N*-acyl α-amino acids, from an aldehyde, amide, carbon monoxide, and hydrogen. We review here full accounts of our research on (i) the unique and remarkable effects of organofluorine substituents on the regioselectivity in the hydrocarbonylations of fluoro olefins and the application of the highly regioselective hydroformylation to the synthesis of fluoro amino acids, (ii) a novel ureidocarbonylation process that gives 5-(trifluoromethyl)dihydrouracils in one step, and (iii) the hydroformylation–amidocarbonylation of fluoro olefins catalyzed by Co–Rh mixed-metal systems.[2]

II. Hydrocarbonylations of Fluoro Olefins and Their Application to Fluoro Amino Acid Synthesis

A. Hydroformylation of Fluoro Olefins

Hydroformylation of alkenes is an important reaction for the practical synthesis of aldehydes, and detailed studies on the mechanism of the reaction as well as applications to organic syntheses have been extensively studied.[1] However, little had been known about the reactions of alkenes bearing perfluoroalkyl or perfluoroaryl substituents when we started research on this subject.[3] It has been shown that the introduction of a trifluoromethyl or a fluoro aromatic group into organic compounds often brings about unique chemical and biological properties.[4] Thus, the development of new synthetic methods that enable introduction of these fluoro groups effectively and selectively to the desired molecules from readily available materials is of significant synthetic importance. In this respect, commercially available fluoro olefins such as 3,3,3-trifluoropropene (TFP), vinyl fluoride (VF), and pentafluorostyrene (PFS) are important starting materials.

We have studied the hydroformylation of a variety of fluoro olefins as one of our approaches to the functionalizations of these building blocks by means of transition-metal catalysts and found unusually high regioselectivities and a remarkable dependency of the regioselectivities of the reaction on the catalyst metal species, which is unique in comparison with the hydroformylation of ordinary alkenes.[5,6] We review here a full account of our research on this subject, including a mechanism that can accommodate all the unique results obtained.

$$\underset{\mathbf{1}}{R_fCH{=}CH_2} + H_2 + CO \xrightarrow{\text{cat.}} \underset{\mathbf{2}\ (n)}{R_fCH_2CH_2CHO} + \underset{\mathbf{3}\ (iso)}{R_f(Me)CHCHO} \quad (1)$$

$$R_f = F,\ CF_3,\ C_2F_5,\ C_3F_7,\ C_8F_{17},\ C_6F_5$$

1. Remarkable Dependence of Regioselectivity on the Catalyst Metal Species

The hydroformylation of TFP was carried out with $Co_2(CO)_8$, $Ru_3(CO)_{12}$, $Rh_6(CO)_{16}$, and $PtCl_2(DIOP)/SnCl_2$, which are typical hydroformylation catalysts, at 100 °C and 100 atm (CO/H_2 = 1) for the Co, Pt, and Ru catalysts and at 80 °C and 110 atm (CO/H_2 = 1) for the Rh catalyst. Results are listed in Table I.

As Table I shows, the reaction of TFP catalyzed by $Co_2(CO)_8$ gives (trifluoromethyl)propanals (TFMPA) in 95% yield where a "normal" aldehyde $CF_3CH_2CH_2CHO$ (3-TFMPA) is formed with high regioselectivity (93%). In sharp contrast with $Co_2(CO)_8$, the rhodium carbonyl cluster $Rh_6(CO)_{16}$ exhibits extremely high catalytic activity and regioselectivity (96%) to give "iso" aldehyde, $CF_3(CH_3)CHCHO$ (2-TFMPA). The platinum catalyst, $PtCl_2(DIOP)/SnCl_2$, favors the formation of normal aldehyde (n/iso = 71/29), while $Ru_3(CO)_{12}$ gives iso aldehyde as the main product (n/iso = 15/85), and in both cases, a substantial amount of hydrogenated product, $CF_3CH_2CH_3$, is formed (25–38%). Addition of triphenylphosphine to the Co, Ru, and Rh catalysts considerably decreases the catalytic activities but somewhat increases the iso aldehyde selectivity. The

TABLE II. Hydroformylation of PFS[a]

cat.	PFS[b] cat.	press.,[c] atm (CO/H_2 = 1)	temp, °C	time, h	conv,[d] %	aldehydes[d] %	aldehydes[d] iso/n	alkane,[d] %
$Co_2(CO)_8$	21	80	90	12	67	54	21/79	9
	20	54[e]	120	16	81	59	10/90	22
$PtCl_2(DIOP)/SnCl_2$	100	80	90	4	100	76	49/51	20
$Ru_3(CO)_{12}$	33	80	90	17	49	22	74/26	25
$Rh_6(CO)_{16}$	5000	80	90	3	100	100	97/3	0
$Rh_4(CO)_{12}$	5000	82[e]	100	2	100	100	98/2	0
$HRh(CO)(PPh_3)_3$	5000	80	90	8	100	100	98/2	0
$RhCl(PPh_3)_3$	333	90	90	20	100	100	97/3	0

[a] Reactions were run with 30–100 mmol of PFS and 15–30 mL of benzene. [b] (mol of PFS)/(mol of metal). [c] Initial pressure at room temperature. [d] Determined by GLC. [e] Pressure at the given temperature.

result is in contrast to the cases of ordinary olefins, where the addition of triphenylphosphine increases normal aldehyde selectivity.[1]

Since $Rh_6(CO)_{16}$ gives excellent regioselectivity in the formation of 2-TFMPA, several other rhodium catalysts are employed to examine their catalytic activities as well as regioselectivities. Results are also listed in Table I. The results clearly indicate that the rhodium(I) complexes having chlorine as a ligand, such as $RhCl(PPh_3)_3$, are less active than $HRh(CO)(PPh_3)_3$, Rh–C, $Rh_4(CO)_{12}$, and $Rh_6(CO)_{16}$, but the regioselectivity is virtually the same in all cases examined.

Consequently, it is disclosed that the nature of the central metal of the catalyst plays a key role in determining the regioselectivity of the reaction. Moreover, it should be noted that the metal species dependency of the regioselectivity in the present reaction is remarkable compared with that reported for propene. The reported regioselectivities in the formation of butanal using cobalt, platinum, ruthenium, and rhodium catalysts are as follows:[1] $Co_2(CO)_8$[7] [150 atm; CO/H_2 = 1; 110 °C] 94%, iso/n = 20/80; $PtCl_2(PPh_3)_2/SnCl_2$[8] [89 atm; CO/H_2 = 1; 66 °C] 90%, iso/n = 13/87; $Ru_3(CO)_{12}$[7] [150 atm; CO/H_2 = 1; 110 °C] 40%, iso/n = 26/74; $Rh_6(CO)_{16}$[9] [120 atm; CO/H_2 = 1; 70 °C] 51%, iso/n = 49/51.

In a similar manner, the hydroformylation of PFS was carried out at 90 °C and 80 atm with the use of cobalt, platinum, ruthenium, and rhodium catalysts. The results are shown in Table II. Rhodium catalysts exhibit high catalytic activity to give iso aldehyde, $C_6F_5(CH_3)CHCHO$ (2-PFPPA), with excellent regioselectivity (97–98%) and quantitative yields, while $Co_2(CO)_8$ gives normal aldehyde (3-PFPPA) as the major product, with regioselectivity not as high as that observed in the reaction of TFP. The ruthenium catalyst, $Ru_3(CO)_{12}$, shows rather low catalytic activity, giving iso aldehyde as the major isomer, and a substantial amount of hydrogenated product, $C_6F_5CH_2CH_3$, is formed. The platinum catalyst, $PtCl_2(DIOP)/SnCl_2$, shows a high catalytic activity, but virtually no regioselectivity is observed and the hydrogenation of PFS takes place as a severe side reaction. On the whole, the metal species dependency of the regioselectivity is similar to that for TFP and it is also remarkable compared with that reported for styrene. The reported regioselectivities in the formation of phenylpropanal under typical conditions are as follows: $Co_2(CO)_8$[10] [80 atm; CO/H_2 = 1; 120 °C] 46%, iso/n = 59/41; $PtCl_2(DIOP)/SnCl_2$[11] [250 atm; CO/H_2 = 1; 100 °C] 60%, iso/n = 57/43; $Rh_2Cl_2(CO)_4$[11] [62 atm; CO/H_2 = 1; 130 °C] 93%, iso/n = 43/57; $Rh_2Cl_2(CO)_4/PPh_3$[12] [62 atm; CO/H_2 = 1; 130 °C] 98%, iso/n = 72/28.

TABLE III. Regioselectivities in the Hydroformylation of $R_fCH=CH_2$ Catalyzed by $Rh_4(CO)_{12}$[a]

$R_fCH=CH_2$	press.,[b] atm (CO/H_2 = 1)	temp, °C	time, h	aldehydes[c] iso:n
$FCH=CH_2$	110	80	6	100:0
$CF_3CH=CH_2$	110	80	6	96.6:3.4
$C_2F_5CH=CH_2$	110	80	6	83.1:16.9
	110	60	6	94.7:5.3
$C_3F_7CH=CH_2$	110	80	6	74.3:25.7
	110	60	6	91.0:9.0
$C_8F_{17}CH=CH_2$	110	80	6	72.8:27.2
	110	60	6	92.2:7.8

[a] Reactions were run with 0.065–0.40 mol % of $Rh_4(CO)_{12}$ in toluene. [b] Initial pressure at the given temperature. [c] Determined by GLC.

A kinetic study was performed for the $Rh_4(CO)_{12}$- and $Co_2(CO)_8$-catalyzed reactions of PFS. At 100 °C and 82 atm (CO/H_2 = 1) with 1.0×10^{-5} M catalyst concentration, the rhodium-catalyzed reaction is first order in PFS concentration, and the apparent rate constant for $Rh_4(CO)_{12}$ is calculated to be 6.2×10^{-4} s^{-1}; i.e., the turnover number is estimated to be 55 800 h^{-1} per rhodium metal. The cobalt-catalyzed reaction with 1.0×10^{-2} M catalyst concentration at 100 °C and 82 atm (CO/H_2 = 1) is also first order in PFS concentration, and the apparent rate constant is calculated to be 1.6×10^{-5} s^{-1}; i.e., the turnover number per cobalt metal is 2.88 h^{-1}. Thus, the rhodium catalyst is ca. 20 000 times more active than the cobalt catalyst per metal *provided that all metal species participate in the catalysis.*

Judging from the fact that the addition or the introduction of tertiary phosphines to the catalyst brings about only a slight change of regioselectivity, in sharp contrast with the hydroformylation of propene or styrene using the same catalysts, both TFP and PFS may well have a large binding constant with catalyst metal species, and thus they should act as important ligands that stabilize the catalysts during the reaction.

In order to examine the effects of perfluoroalkyl substituents longer than the trifluoromethyl group on the regioselectivity, the hydroformylation of other fluoro olefins of the type $R_fCH=CH_2$ was carried out, where R_f are C_2F_5 (PFB), C_3F_7 (HPFP), and C_8F_{17} (HPDFD). As Table III shows, the reactions give much lower regioselectivities than that for TFP under standard conditions, i.e., at 80 °C and 100 atm (CO/H_2 = 1): Higher selectivities (>90%) were achieved at 60 °C.

Next, the hydroformylation of allylpentafluorobenzene was carried out by using rhodium catalysts (eq 2). The reaction gives an iso/n ratio of 3/2 to 2/1, and

TABLE IV. Hydroformylation of (Pentafluoroallyl)benzene and Allylbenzene[a]

Ar	cat.	press.,[b] atm (CO/H_2 = 1)	temp, °C	time, h	conv, %	yield,[c] %	5:6:7:8
C_6F_5	$Co_2(CO)_8$	80	100	16	82	79	53:41:2:4
	$Rh_6(CO)_{16}$	80	95	13	100	100	41:59:0:0
	$HRh(CO)(PPh_3)_3$	80	95	3	100	94	39:61:0:0
Ph	$Co_2(CO)_8$	80	100	16	100	45	60:14:26:0
	$Rh_6(CO)_{16}$	80	95	3	100	76	47:52:1:0
	$HRh(CO)(PPh_3)_3$	80	95	3	100	78	50:48:2:0

[a] Reactions were run with 0.20–0.25 mol % (for rhodium) or 10 mol % (for cobalt) of catalyst in 1.0 mL of benzene. [b] Initial pressure at room temperature. [c] Determined by GLC.

the difference in the regioselectivity between allylpentafluorobenzene and allylbenzene is not as remarkable as that for PFS and styrene (Table IV).

$$ArCH_2CH{=}CH_2 \xrightarrow[\text{cat.}]{H_2,\ CO} \xrightarrow[\text{benzene}]{} \underset{5}{ArCH_2CH_2CH_2CHO} + \underset{6}{ArCH_2CH(CHO)CH_3} + \underset{7}{ArCH(CHO)CH_2CH_3} + \underset{8}{ArCH_2CH_2CH_3} \quad (2)$$

$$Ar = C_6F_5,\ C_6H_5$$

$$\text{cat.} = HRh(CO)(PPh_3)_3,\ Rh_6(CO)_{16},\ Co_2(CO)_8$$

The cobalt-catalyzed reactions of allylpentafluorobenzene and allylbenzene give rather complicated results because of the occurrence of severe isomerization, especially for allylbenzene, which leads to the formation of the other branched aldehyde (7) through the hydroformylation of (propen-1-yl)benzene generated in situ by the isomerization (Table IV). It should also be noted that only a negligible amount (1–2%) of isomerization was observed in the rhodium-catalyzed reactions of allylbenzene, and no isomerization was detected for allylpentafluorobenzene.

The hydroformylation of vinyl fluoride (VF) promoted by rhodium, ruthenium, and cobalt catalysts was also carried out (eq 3).

$$FCH{=}CH_2 + CO + H_2 \xrightarrow{\text{cat.}} \underset{\text{2-PFA}}{CH_3CHFCHO} \quad (3)$$

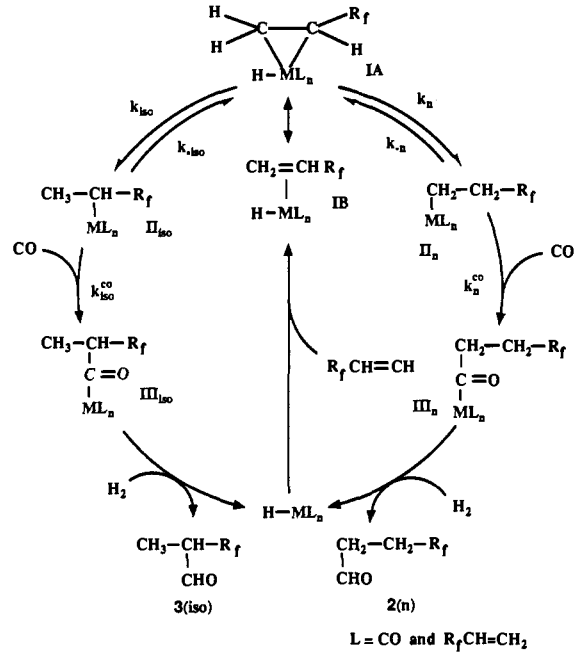
$$\text{cat.} = Rh_4(CO)_{12},\ HRh(CO)(PPh_3)_3,\ Ru_3(CO)_{12},\ Co_2(CO)_8$$

2. Mechanism of the Highly Regioselective Hydroformylation

The observed remarkable dependence of regioselectivity on the catalyst metal species may well be accommodated by considering the stability of isoalkylmetal species, the isomerization ability of isoalkylmetal species, and the relative rate of the migratory insertion of carbon monoxide into isoalkyl–metal and *n*-alkyl–metal bonds.

As Scheme I shows, when a substituent possessing a large "group electronegativity"[13] is introduced into an olefin, the metal–C^α bond of a π-olefin–metal complex (IA) should be stronger than the metal–C^β bond because of substantial stabilization of the formal negative charge developing on C^α. Therefore, the formation of isoalkylmetal species (II_{iso}) should be much more favorable than that of *n*-alkylmetal species (II_n) *regardless of the group VIII transition-metal species*. In fact, the results of the hydroformylations of vinyl fluoride (VF) provide

SCHEME I



strong supporting evidence for this: *regardless of the catalyst species employed*, the reaction of VF gives 2-fluoropropanal (2-FPA) exclusively (eq 3). Since the F substituent has a much stronger electronegativity than any perfluoroalkyl group, an (α-fluoroethyl)metal species (equivalent to the isoalkylmetal species in this discussion) should be much more favorable than the corresponding (β-fluoroethyl)metal species (equivalent to the *n*-alkylmetal species in this discussion).

The iso/n ratio of aldehydes should reflect the ratio of the intermediate iso- and *n*-acylmetal species (III_{iso} and III_n) (Scheme I) under sufficient pressure of hydrogen; i.e., under such conditions, the hydrogenolysis of the acylmetal species is not the rate-determining step. Thus it is deduced that in the rhodium-catalyzed reaction, the rate constants of carbon monoxide insertion, k_{iso}^{CO} and k_n^{CO}, are much larger than those of isomerization, k_{-i} and k_{-n}, viz., $k_{iso}^{CO} \gg k_{-i}$ and $k_n^{CO} \gg k_{-n}$, and thus the initially formed isoalkylrhodium species (II_{iso}, M = Rh) generates the isoacylrhodium species (III_{iso}, M = Rh) and gives the corresponding iso aldehyde with high regioselectivity. In sharp contrast with this, in the cobalt-catalyzed reaction, the following relations are deduced: $k_{-n} \gg k_n^{CO}$ and $k_{-i} \gg k_{iso}^{CO}$; $k_n^{CO} > k_{iso}^{CO}$ (the reason for this is that the carbon monoxide insertion to II_n (M = Co) is sterically less demanding than that to II_{iso} (M = Co)). Accordingly, the alkylmetal intermediates, II_{iso} and II_n (M = Co), should be in a preequilibrium, and then the reaction gives the corresponding normal aldehyde selectively: The substantial

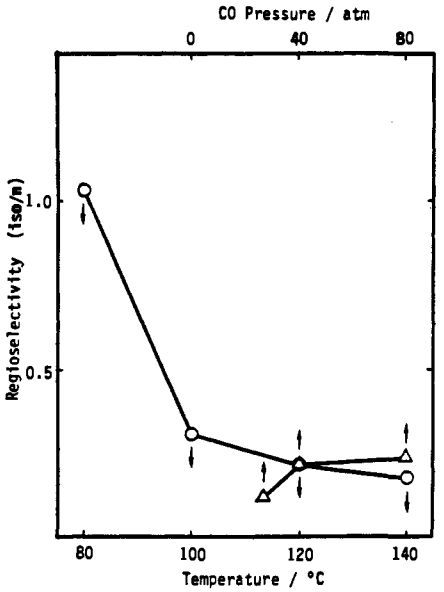


Figure 1. Effect of reaction temperature (O) and carbon monoxide pressure (△) on the regioselectivity of the hydroformylation of PFS catalyzed by $Co_2(CO)_8$.

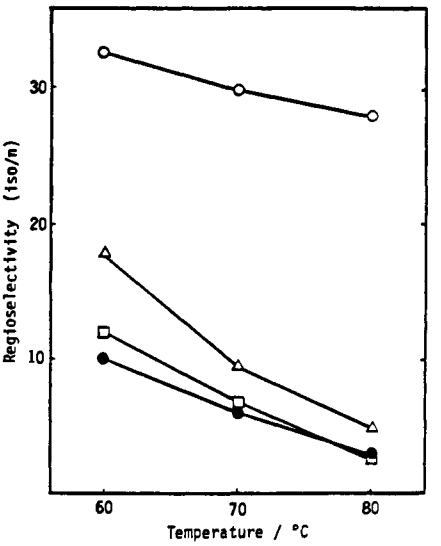


Figure 2. Effect of reaction temperature on the regioselectivity of the hydroformylation of TFP (O), PFB (△), HPFP (●), and HPDFD (□) catalyzed by $Rh_4(CO)_{12}$.

isomerization observed in the cobalt-catalyzed hydroformylation of allylbenzene strongly supports this proposed mechanism (vide supra).

The rhodium- and cobalt-catalyzed reactions are extremely selective cases, and the platinum- and ruthenium-catalyzed reactions are in between the two extreme cases.

Although the relation between rate constants of isomerization and those of carbon monoxide insertion for the rhodium- and cobalt-catalyzed reactions are deduced as described above based on the results obtained under standard conditions, it is very likely that the relations depend on reaction conditions such as temperature and pressure. For instance, *lower* temperatures and *higher* carbon monoxide pressures may change the relation of rate constants *in the cobalt case* to the following one: $k_{-i} \leq k_{iso}^{CO}$ and $k_{-n} \ll k_n^{CO}$. Since the formation of II_{iso} should be kinetically much more favorable than that of II_n (vide supra), i.e., $k_i > k_n$, the iso/n ratio of aldehydes should increase under those conditions. On the other hand, *in the rhodium case*, the relation of rate constants at *higher* temperatures and *lower* carbon monoxide pressures may become as follows: $k_{-i} \geq k_{iso}^{CO}$ and $k_{-n} \geq k_n^{CO}$. Then the iso/n ratio of aldehydes should decrease under those conditions.

In order to obtain supporting evidence for the proposed mechanism, we examined the effects of temperature and carbon monoxide pressure on the regioselectivity of the reactions catalyzed by $Co_2(CO)_8$ and $Rh_4(CO)_4$. The results for the cobalt-catalyzed reactions are shown in Figure 1. As Figure 1 shows, the expected effects of temperature and carbon monoxide pressure were indeed observed, viz., the iso aldehyde (2-PFPPA) becomes the major product at 80 °C. Thus it becomes evident that the isoalkylmetal species (II_{iso}, M = Co) is the favorable initial intermediate *even in the cobalt-catalyzed reaction at lower temperatures* as expected. A similar kinetically controlled formation of an isoalkylcobalt species was reported by Ungvary and Markó in the hydroformylation of styrene catalyzed by $HCo(CO)_4$.[14]

It should be noted that in the hydroformylations of ordinary 1-alkenes n/iso approaches 1 as the reaction temperature becomes higher, reflecting a decrease in selectivity. A remarkable dependence of regioselectivity on the reaction temperature similar to the PFS case was reported in the hydroformylations of methyl methacrylate with $Co_2(CO)_8$ by Falbe and Huppes[1b] and ethyl acrylate with $Rh_n(CO)_x$ by Takegami et al.[15] In those cases, an inversion of regioselectivity was observed by changing the reaction temperature; viz., the rhodium carbonyl behaved similarly to cobalt carbonyl. The $Co_2(CO)_8$-catalyzed reaction of ethyl acrylate was reported to give normal aldehyde in high selectivity and did not show such drastic change in regioselectivity as the rhodium-catalyzed reaction although the tendency was similar, i.e., the lower the temperature, the higher the iso aldehyde content. A similar dependence of regioselectivity on the reaction temperature was also reported by Botteghi et al.[16]

Clear effects of the reaction temperature on the regioselectivity were also observed in the $Rh_6(CO)_{16}$-catalyzed reaction of PFS: Results obtained with 80 atm of carbon monoxide and hydrogen ($CO/H_2 = 1$) are as follow: at 60 °C, iso/n = 199; at 70 °C, iso/n = 99; at 95 °C, iso/n = 49. Although the tendency is the same as to the cobalt case, it is apparent that there is a strong bias to the formation of iso aldehyde in the rhodium case.

The results with TFP, PFB, HPFP, and HPDFD as substrates and $Rh_4(CO)_{12}$ as catalyst are shown in Figures 2 and 3. Besides these kinetic aspects, we should take into account the fundamental difference between each isoalkylmetal intermediate. For example, why does rhodium prefer the isoalkylmetal intermediate much more than cobalt? Why is the k_i/k_{CO} ratio much larger for cobalt than for rhodium? In order to answer these questions, we should consider the size of the metal and the polarizability of the metal–carbon bond in each case. Since rhodium is substantially larger than cobalt, rhodium should be less sensitive to steric effects than cobalt and the rhodium–carbon bond should have more polarizability than the cobalt–carbon bond. Consequently, (i) the less sterically demanding *n*-alkylmetal

TABLE V. Hydroesterification of TFP[a]

entry	cat.	alcohol	solvent	yield, %	iso (10)/n (9)
1	$PdCl_2 + PPh_3$	EtOH	acetone	29	46/54
2	$PdCl_2 + 2PPh_3$	EtOH	acetone	62	49/51
3	$PdCl_2 + 4PPh_3$	EtOH	acetone	59	43/57
4	$PdCl_2 + 10PPh_3$	EtOH	acetone	23	31/69
5	$PdCl_2(PPh_3)_2$	EtOH	EtOH	74	49/51
6	$PdCl_2(PPh_3)_2$	EtOH	acetone	82	52/48
7	$PdCl_2(PPh_3)_2$	EtOH	THF	93	71/29
8	$PdCl_2(PPh_3)_2$	EtOH	toluene	96	77/23
9	$PdCl_2(PPh_3)_2$	EtOH	benzene	95	79/21
10	$PdCl_2(PPh_3)_2$	EtOH	acetonitrile	96	79/21
11	$PdCl_2(PPh_3)_2$	EtOH	triethylamine	0	
12	$PdCl_2(PPh_3)_2$	EtOH	NaOAc/EtOH[b]	0	
13	$PdCl_2(PPh_3)_2 + 5SnCl_2$	EtOH	benzene	6	
14	$PdCl_2$(dppb)[d]	EtOH	acetone[c]	12	<1/99
15	$PdCl_2$(dppb)[d]	EtOH	benzene[c]	13	1/99
16	$PdCl_2$(dppf)[e]	EtOH	acetone[c]	16	11/89
17	$PdCl_2$(dppf)[e]	EtOH	benzene[c]	50	23/77
18	$PdCl_2(PPh_3)_2$	MeOH	benzene	95	72/28
19	$PdCl_2(PPh_3)_2$	^{i}PrOH	benzene	93	79/21

[a] All reactions were run with 1.0 mol % of Pd catalyst at 100 °C and 110 atm of CO (initial pressure at 25 °C) for 40–70 h unless otherwise noted. Alcohol/solvent = 3/10 (v/v). [b] NaOAc (1.0 equiv of TFP) was added. [c] At 120 °C. [d] dppb = 1,4-bis(diphenylphosphino)butane. [e] dppf = 1,1′-bis(diphenylphosphino)ferrocene.

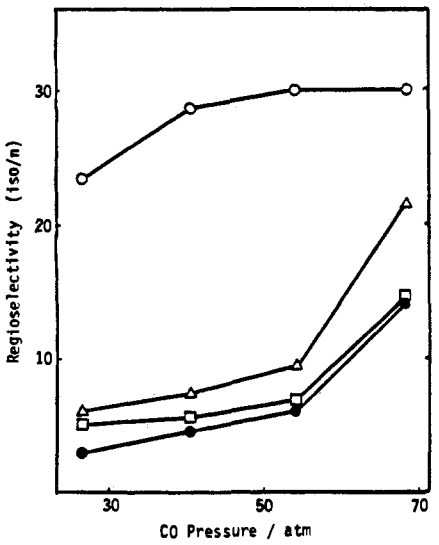


Figure 3. Effect of carbon monoxide pressure on the regioselectivity of the hydroformylation of TFP (○), PFB (△), HPFP (●), and HPDFD (□) catalyzed by $Rh_4(CO)_{12}$.

species is much more favorable for carbon monoxide insertion in the cobalt case than the rhodium case and thus cobalt has a much larger k_i/k_{CO} ratio than rhodium and (ii) the isoalkylrhodium species can obtain much larger stabilization than the isoalkylcobalt species because of the larger polarizability of the rhodium–carbon bond. According to this rationalization, the relative stability of II_{iso} can be estimated to increase in order $R_f(Me)CH-CoL_n < R_f(Me)CH-PtL_n < R_f(Me)CH-RuL_n < R_f(Me)CH-RhL_n$.

B. Hydroesterification and Hydrocarboxylation of Fluoro Olefins

Hydrocarbonylations of olefins are known to serve as a convenient method for the synthesis of the corresponding esters or carboxylic acids.[1] In spite of extensive mechanistic studies as well as applications of the reactions to organic syntheses, little attention had been drawn to the reactions of fluoroolefins before we started the investigation on this subject. As described in section IIA, we found a remarkable effect of R_f substituents on the regioselectivity of transition-metal-catalyzed olefin hydroformylations. This finding compelled us to examine the hydroesterification and hydrocarboxylation of TFP and PFS.

1. Hydroesterification of Trifluoropropene and Pentafluorostyrene

First, the catalytic activities of typical transition-metal complexes such as $Co_2(CO)_8$, $Rh_6(CO)_{16}$, $H_2PtCl_6/SnCl_2$, and $PdCl_2(PPh_3)_2$ in the hydroesterification of TFP and PFS with methanol and carbon monoxide were screened at 100 °C and 110 atm, and it was found that only $PdCl_2(PPh_3)_2$ showed enough catalytic activity to promote the reaction under the given reaction conditions.[17] Thus, palladium complexes with phosphine ligands were chosen for the present study (eq 4).

$$\underset{\mathbf{1}}{R_fCH{=}CH_2} + CO + ROH \xrightarrow{[Pd]} \underset{\mathbf{9}\ (n)}{R_fCH_2CH_2COOR} + \underset{\mathbf{10}\ (iso)}{R_f(Me)CHCOOR} \quad (4)$$

$$R_f = CF_3,\ C_6F_5$$

Next, the effects of reaction variables on the conversion and regioselectivity of the reaction were studied. Table V summarizes the effects of the ratio of triphenylphosphine to palladium and the solvent effects on the reaction of TFP.[17]

As Table V shows, (i) a PPh_3/Pd ratio of 2 gives the best yield (entry 2), (ii) existence of triphenylphosphine is requisite,[18] but a large excess of it decreases the catalytic activity (entry 4), and (iii) the PPh_3/Pd ratio exerts substantial influence on the iso/n ratio. It is also shown that the regioselectivity depends on the nature of the solvent used, and a good iso/n ratio as well as a high yield is obtained when benzene, toluene, or acetonitrile is used as the solvent; e.g., $CF_3(CH_3)$-CHCOOEt is obtained in 96% yield with 79% regioselectivity (entry 10). In triethylamine or in the presence of sodium acetate, the reaction does not proceed at all. When a cis-chelating diphosphine such as 1,4-bis(di-

TABLE VI. Hydroesterification of PFS with Methanol[a]

entry	cat.	solvent	conditions: CO,[b] atm	conditions: temp, °C	conditions: time, h	conv, %	yield, %	iso (10)/n (9)
1	$PdCl_2(PPh_3)_2 + 5SnCl_2$	acetone	70	100	60	11	10	22/78
2	$PdCl_2(PPh_3)_2$	acetone	70	100	60	88	71	93/7
3	$PdCl_2(PPh_3)_2$	acetone	120	100	60	92	76	93/7
4	$PdCl_2(PPh_3)_2$	benzene	120	100	60	90	89	95/5
5	$PdCl_2(PPh_3)_2$	acetone	70	125	24	77	25	79/21
6	$PdCl_2(dppb)_2$[c]	acetone	100	125	24	53	5	
7	$PdCl_2(dppb)_2$[c]	acetone	120	100	60	9	0	

[a] All reactions were run with 1.0 mol % of Pd catalyst. Methanol/solvent = 1/4 (v/v). [b] Initial pressure at 25 °C. [c] dppb = 1,4-bis(diphenylphosphino)butane.

TABLE VII. Hydrocarboxylation of TFP[a]

entry	cat.	yield, %	iso (12)/n (11)
1	$PdCl_2(PPh_3)_2$	35	35/65
2	$PdCl_2(PPh_3)_2 + 5SnCl_2$	7	
3	$PdCl_2(dppb)$[b]	36	<1/99
4	$PdCl_2(dppb)$[b] + $5SnCl_2$	43	<1/99
5	$PdCl_2(dppb)$[b] + $10SnCl_2$	56	<1/99
6	$PdCl_2(dppf)$[c]	64	7/93
7	$PdCl_2(dppf)$[c] + $2SnCl_2$	79	3/97
8	$PdCl_2(dppf)$[c] + $5SnCl_2$	93	1/99
9	$PdCl_2(dppf)$[c] + $10SnCl_2$	92	6/94

[a] All reactions were run with 1.0 mol % of Pd catalyst in aqueous acetic acid ($AcOH/H_2O$ = 10/1 (viv)) at 125 °C and 110 atm of CO (initial pressure at 25 °C) for 70 h. [b] dppb = 1,4-bis(diphenylphosphino)butane. [c] dppf = 1,1′-bis(diphenylphosphino)ferrocene.

phenylphosphino)butane (dppb) or 1,1′-bis(diphenylphosphino)ferrocene (dppf) is employed as a ligand, which forms a cis chelate with palladium, the yield of the product is decreased, and the normal ester, $CF_3CH_2CH_2COOEt$, becomes predominant. The bulkiness of the alcohols does not have significant influence on the regioselectivity (entries 9, 18, and 19).

Table VI summarizes the results of the hydroesterification of PFS.[17] As Table VI shows, the type of phosphine ligands, the addition of $SnCl_2$, and the reaction temperature exert a marked influence on both the yield and regioselectivity of the reaction. Thus, the iso product, $C_6F_5(CH_3)CHCOOMe$, is obtained in 89% yield with 95% selectivity by using triphenylphosphine as the ligand (entry 4), whereas the yields of the products are very low (i) when cis-chelating ligands are employed (entries 6 and 7) and (ii) when $SnCl_2$ is added (entry 1) and the normal product, $C_6F_5CH_2CH_2COOMe$, is the predominant one. A decrease in both the yield and the iso/n ratio is observed on raising the reaction temperature to 125 °C (entry 5).

2. Hydrocarboxylation of Trifluoropropene and Pentafluorostyrene

The hydrocarboxylation of TFP and PFS (eq 5) is found to be effected also by phosphine–palladium complexes.[17]

$$\underset{\mathbf{1}}{R_fCH{=}CH_2} + CO + H_2O \xrightarrow[AcOH]{[Pd]} \underset{\mathbf{11}\ (n)}{R_fCH_2CH_2COOH} + \underset{\mathbf{12}\ (iso)}{R_f(Me)CHCOOH} \quad (5)$$

$$R_f = CF_3,\ C_6F_5$$

Typical results on the hydrocarboxylation of TFP are summarized in Table VII, and those of PFS are listed in Table VIII.[17]

As Table VII shows, the palladium complexes with cis-chelating diphosphines, e.g., dppb and dppf, give good results, and addition of $SnCl_2$ to these catalyst systems considerably promotes the reaction. These results are in sharp contrast with those obtained in the corresponding hydroesterification. With $PdCl_2(dppf)/SnCl_2$ as the catalyst, the normal product, $CF_3CH_2CH_2COOH$, is obtained in 93% yield with 99% regioselectivity (entry 8).

As Table VIII shows, the hydrocarboxylation of PFS proceeds much faster than that of TFP to give the normal acid 11 ($R_f = C_6F_5$) selectively. In this case, the palladium complexes bearing cis-chelating diphosphine realize much higher regioselectivity (up to 96%) than $PdCl_2(PPh_3)_2$ does. Addition of $SnCl_2$ does not increase the reaction rate in this case (entries 6 and 7).

3. Mechanisms of the Hydroesterification and Hydrocarboxylation

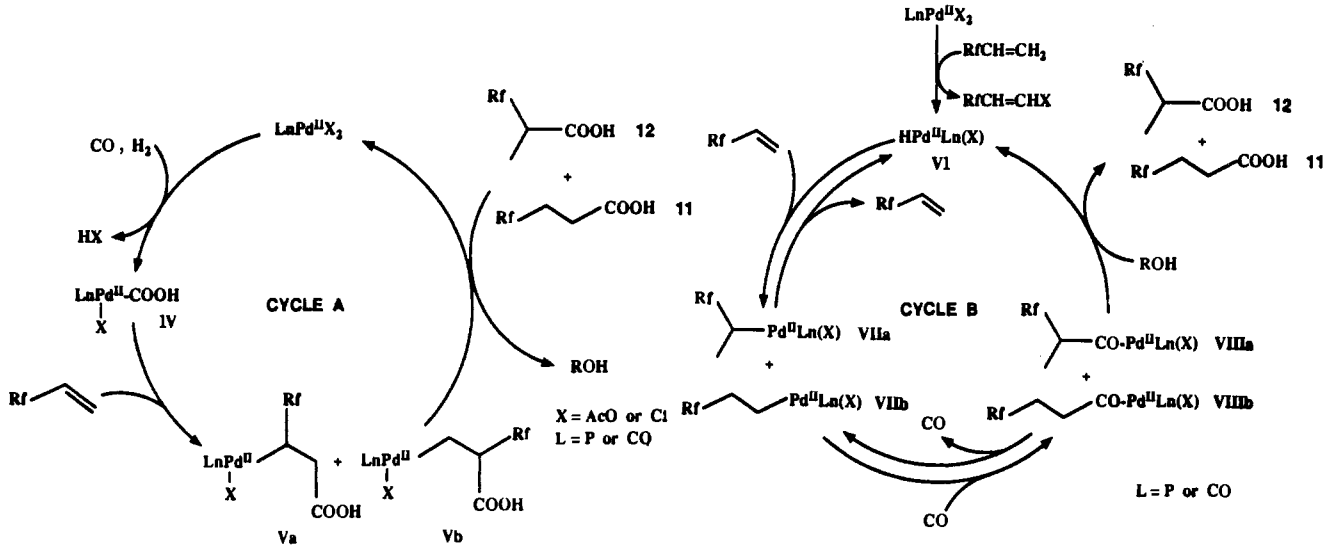
The mechanisms of hydroesterification and hydrocarboxylation catalyzed by transition-metal complexes have been extensively studied,[1] and two kinds of mechanisms have been proposed. One mechanism involves hydridometal and acylmetal intermediates followed by solvolysis (eq 6),[19a,b] and the other one involves (alkoxycarbonyl)- or (hydroxycarbonyl)metal and (2-

TABLE VIII. Hydrocarboxylation of PFS[a]

entry	cat.	conditions: CO,[b] atm	conditions: temp, °C	conditions: time, h	conv, %	yield, %	iso (12)/n (11)
1	$PdCl_2(PPh_3)_2$	100	125	24	100	90	27/73
2	$PdCl_2(dppb)$[c]	100	125	24	100	90	4/96
3	$PdCl_2(dppb)$[c]	100	100	48	100	90	<1/99
4	$PdCl_2(dppf)$[d]	100	125	24	100	89	1/99
5	$PdCl_2(dppf)$[d]	100	100	48	100	93	1/99
6	$PdCl_2(dppb)$[c] + $1/SnCl_2$	100	100	18	40	25	
7	$PdCl_2(dppf)$[c] + $1/SnCl_2$	100	100	18	32	29	

[a] All reactions were run with 1.0 mol % of Pd catalyst in aqueous acetic acid ($AcOH/H_2O$ = 40/3 (v/v)). [b] Initial pressure at 25 °C. [c] dppb = 1,4-bis(diphenylphosphino)butane. [d] dppf = 1,1′-bis(diphenylphosphino)ferrocene.

SCHEME II



(alkoxycarbonyl)alkyl)- or (2-(hydroxycarbonyl)alkyl)-metal intermediates followed by acid cleavage of the palladium–alkyl bond (eq 7).[19c]

$$\text{H-[M]} \underset{}{\overset{\text{RCH=CH}_2}{\rightleftharpoons}} \text{RCH}_2\text{CH}_2\text{-[M]} \overset{\text{CO}}{\rightleftharpoons} \text{RCH}_2\text{CH}_2\text{CO-[M]} \xrightarrow{\text{HOR}'} \text{RCH}_2\text{CH}_2\text{COOR}'' \quad (6)$$

$$\text{[M]-COOR}' \overset{\text{RCH=CH}_2}{\rightleftharpoons} \text{[M]-CHRCH}_2\text{COOR}' \xrightarrow{\text{H}^+} \text{RCH}_2\text{CH}_2\text{COOR}' \quad (7)$$

One of the characteristic features of the present reactions compared with the previously reported works is that the regioselectivity of the reaction dramatically changes when the hydrogen donor is changed from alcohol to water; e.g., when $PdCl_2(PPh_3)_2$ is used as a catalyst and PFS as the substrate, the iso/n ratio observed in the hydroesterification is 79/21 to 95/5 (entries 2–5 in Table VI) whereas that in the hydrocarboxylation is reversed to 27/73 (entry 1 in Table VIII). In addition to this, the catalytic activity of palladium complexes bearing cis-chelating ligands, e.g., $PdCl_2$(dppb), is by far lower than that of $PdCl_2(PPh_3)_2$ in the hydroesterification whereas the catalytic activities of those palladium complexes are comparable with each other in the hydrocarboxylation.

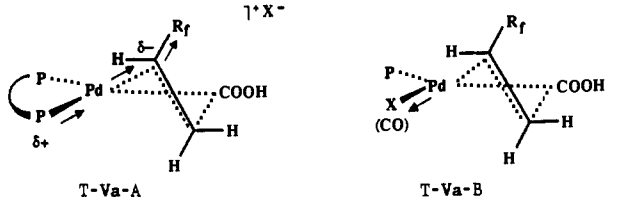
Possible mechanisms of the present hydroesterification and hydrocarboxylation, which can accommodate the characteristic features of the reactions mentioned above, are proposed in Scheme II.[17]

As for the possible mechanism of the hydrocarboxylation of TFP and PFS, the one involving (hydroxycarbonyl)palladium(II) species (IV) and (2-(hydroxycarbonyl)alkyl)palladium(II) intermediate (V) can well explain the observed regioselectivities (Scheme II, cycle A).

As discussed in section IIA2, an R_f substituent stabilizes a partial negative charge developing on the α-carbon of a palladium–alkyl bond through an inductive effect based on the large group electronegativity[13] of the R_f group. Accordingly, the (2-R_f-2-(hydroxycarbonyl)ethyl)palladium(II) intermediate (Va), in which R_f and palladium attach to the same carbon, should be much more favorable than Vb since the palladium–alkyl bond of Vb cannot earn any special stabilization. Thus, the hydrocarboxylation of TFP and PFS gives normal acids (6) selectively through Va followed by the protonative cleavage of the palladium–alkyl bond. It can be said that the insertion of $R_fCH{=}CH_2$ to IV is the regioselectivity-determining step.

For the difference between the regioselectivity achieved by the palladium catalysts with cis-chelating diphosphines and that by $PdCl_2(PPh_3)_2$, it is suggested that cis-chelating diphosphine behaves as a bidentate ligand throughout the catalytic cycle while two triphenylphosphines behave as trans ligands and probably liberate one triphenylphosphine to give a monophosphine complex.

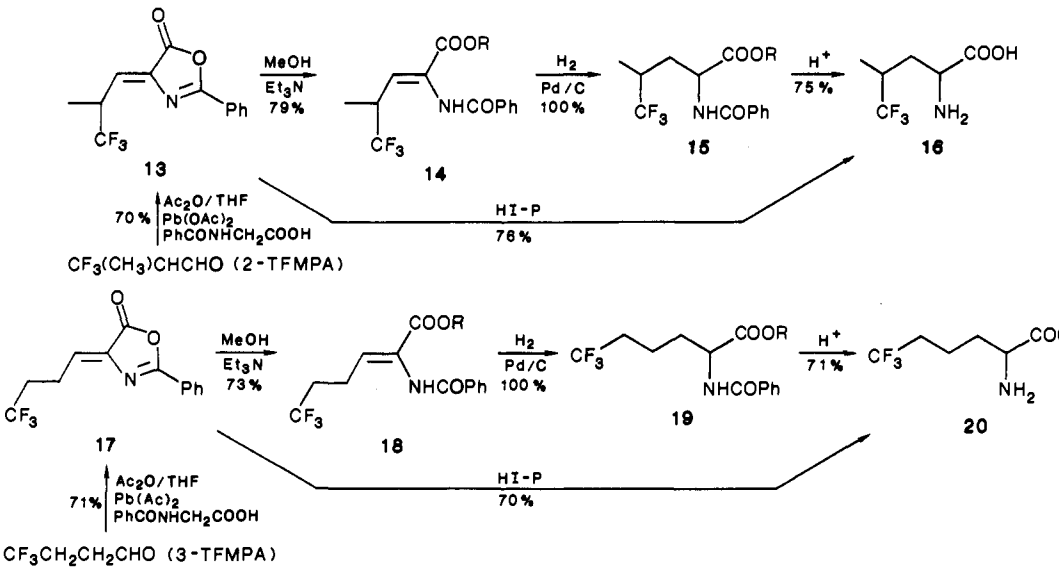
Because of the strong trans effect of the phosphine ligand, the transition state leading to Va (T-Va) would become much more favorable than that to Vb (T-Vb), especially in the case of the cis-chelating diphosphine complex since the electron-withdrawing R_f group is attached to the α-carbon of the palladium–alkyl complex in T-Va-A. On the other hand, the difference in



the preference between the two transition states, T-Va and T-Vb, would be much smaller for the triphenylphosphine complex since the trans effect of the phosphine ligand cannot necessarily be expected because of the ambiguity of the position of the phosphine ligand in the coordination sphere of T-Va-B. This would be the reason why excellent iso/n ratios are achieved by using cis-chelating diphosphines, dppb and dppf.

Similar regioselectivities were reported in the oxidative carbonylation[20] and dicarbonylation[21] of olefins bearing electron-withdrawing groups such as styrenes and α,β-unsaturated carbonyl compounds.

In the hydroesterification of TFP and PFS, the mechanism involving the (2-(alkoxycarbonyl)ethyl)-palladium(II) intermediate (V, in which COOH is replaced by COOR) could also be operative. However,



(8)

(9)

the protonative cleavage of this intermediate should be very slow because of the absence of acid as a solvent. Accordingly, the other mechanism involving hydridopalladium(II) (VI) and acylpalladium(II) (VIII) intermediates becomes predominant (Scheme II, cycle B). The regioselectivity of the reaction would be governed by the relative preference between the two alkylpalladium(II) intermediates VIIa and VIIb. Since an electron-withdrawing group on the α-carbon of a palladium–alkyl intermediate stabilizes the intermediate (vide infra), VIIa is more favorable than VIIb, and thus the iso ester **10** should be produced selectively. In fact, the results obtained for the reaction of PFS (Table VI) are well accommodated by taking into account the strong inductive and resonance stabilizing effects of the α-perfluorophenyl group in VIIa. The results obtained for the reaction of TFP (Table III) are rather complicated. The observed considerably large solvent effects on the regioselectivity may be due to the change in the preference of the two competitive catalytic cycles A and B. The acylpalladium(II) route (cycle B) is favorable in benzene, toluene, or THF while the two mechanisms may be almost equally operative in ethanol or acetone. The fact that trifluoromethyl is a much weaker stabilizer of negative charge than perfluorophenyl may be another reason why the highest iso/n ratio attained in TFP (79/21) is much lower than that realized in the case of PFS (95/5).

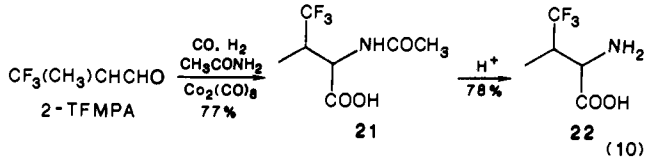
C. Use of Fluoro Aldehydes for the Synthesis of Fluoro Amino Acids

Recently, it has been shown that fluorinated analogues of naturally occurring biologically active compounds often exhibit unique physiological activities.[4] For example, fluorinated pyrimidines act as anticancer and antiviral agents, some fluoro aromatic compounds and CF_3 aromatic compounds are being used as nonsteroidal antiinflammatory drugs, as antifungal agents, as human antiparasitic agents, as central nervous system agents for psychopharmacology, as diuretics, and as antihypertensive agents, some fluoro amino acids act as "suicide substrate enzyme inactivators", showing strong antibacterial activities, and certain fluoro amino acids act as antihypertensive agents.[4d] Accordingly, we have applied the highly regioselective carbonylation processes mentioned above to the synthesis of fluorinated amino acids.

Trifluoroleucine (**16**) and trifluoronorleucine (**20**) are synthesized via azlactones starting from 2-TFMPA and 3-TFMPA, respectively (eq 8 and 9). For the preparation of the azlactones, a modified Erlenmeyer method[22] is employed; viz., the use of lead acetate, *N*-benzoylglycine, and acetic anhydride in tetrahydrofuran is crucial to obtain the azlactones in good yields. The azlactones are either converted to the corresponding dehydroamino acids, which are further hydrogenated and hydrolyzed to give the desired amino acids, or treated with hydriodic acid/red phosphorus to give directly the final amino acids.

Optically active (*S*)-*N*-benzoyltrifluoronorleucine methyl ester (**19**, 89% ee) is obtained quantitatively by the asymmetric hydrogenation of (*Z*)-*N*-benzoyldehydrotrifluoronorleucine methyl ester ((*Z*)-**18**) by using a chiral rhodium complex, [(diPAMP)Rh(NBD)]ClO_4 [diPAMP = (1*R*,2*R*)-1,2-ethanediylbis[(*o*-anisylphenyl)phosphine][23]; NBD = norbornadiene].

Trifluorovaline and trifluoronorvaline are synthesized via amidocarbonylation of 2-TFMPA and 3-TFMPA, respectively. The amidocarbonylation of TFMPA with acetamide catalyzed by cobalt carbonyl at 120 °C and 100 atm of carbon monoxide/hydrogen (1/1) gives *N*-acetyltrifluorovaline (**21**) or *N*-acetyltrifluoronorvaline (**23**) in good yield, which is further hydrolyzed to give the free amino acid (eq 10 and 11). For the



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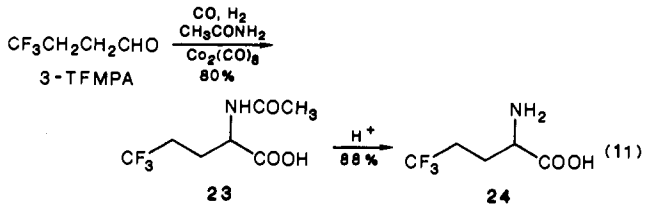
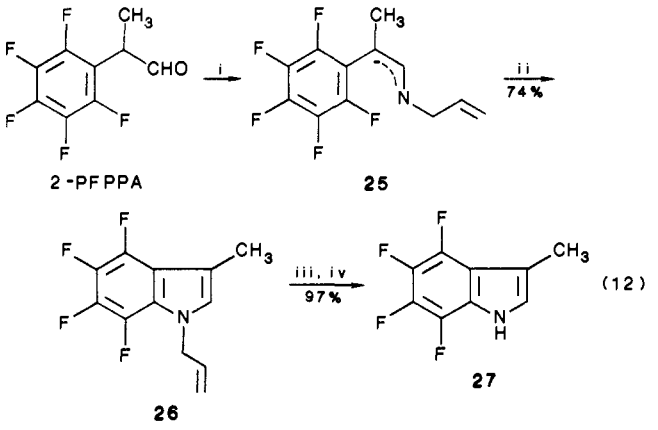


(11)

synthesis of these fluoro amino acids directly from TFP, see section IVC.

The indole skeleton is a very important ring system with regard to biologically active compounds such as tryptophan, tryptamine, indoleacetic acid, and alkaloids. Accordingly, tetrafluoro analogues of indoles were synthesized from 2-PFPPA.

The formation of a tetrafluoroindole ring is carried out by reacting 2-PFPPA with allylamine followed by cyclization by the action of lithium diisopropylamide (LDA), and the deprotection of the indole nitrogen gives 3-methyl-4,5,6,7-tetrafluoroindole (**27**) (72% from 2-PFPPA) (eq 12).[24]

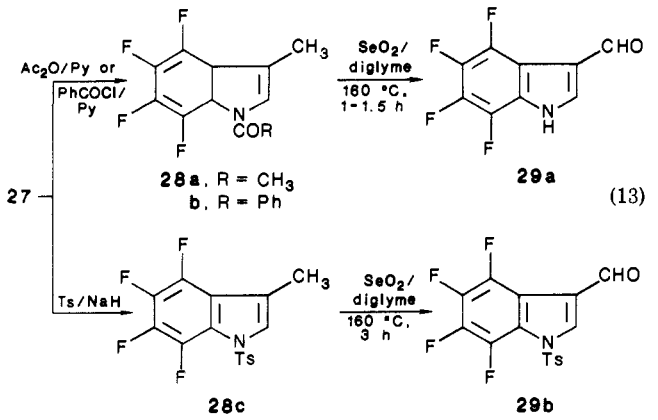


(12)

(i) $CH_2{=}CHCH_2NH_2$, $CHCl_3$, 0 °C to room temperature, 1 h; (ii) LDA, THF, −78 °C, 30 min and room temperature, 10 h; (iii) $RhCl_3{\cdot}3H_2O$ (1.0 mol %), EtOH, reflux, 14 h; (iv) conc. HCl aq, reflux, 20 min.

3-Formyl-4,5,6,7-tetrafluoroindoles (**29**) and 3-(acetoxymethyl)-4,5,6,7-tetrafluoroindoles (**30**) are the key intermediates for the synthesis of tetrafluoro analogues of tryptophan, tryptamine, and indoleacetic acid. The synthesis of **29** is realized through a unique selenium dioxide oxidation.

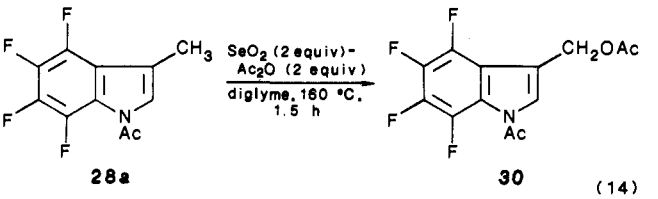
As the direct oxidation of **27** with selenium dioxide resulted in the decomposition of the indole skeleton, the 1-position of **27** was protected by the acetyl, benzoyl, or tosyl group (**28a–c**) and submitted to the selenium dioxide oxidation (eq 13). The oxidation of **28a** and



(13)

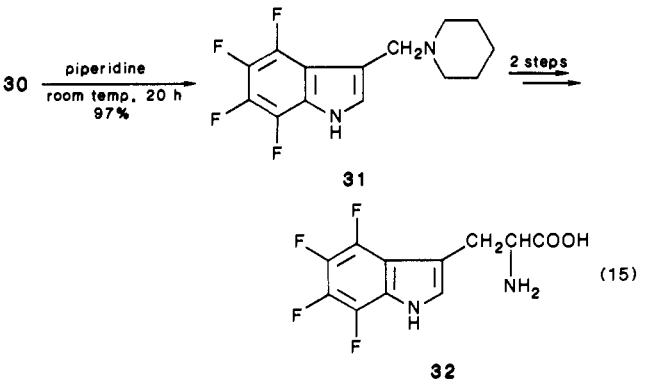
28b gives 3-formyl-4,5,6,7-tetrafluoroindole (**29b**) in 86% and 74% yields, respectively; the acetyl and benzoyl protecting groups are removed during the reaction. In contrast with this, the reaction of **28c** gives 1-tosyl-3-formyl-4,5,6,7-tetrafluoroindole (**29b**) in 81% yield; the 1-tosyl group is tolerant of the reaction.[24]

When the oxidation of **28a** was carried out in the presence of acetic anhydride, another unique reaction took place; viz., 1-acetyl-3-(acetoxymethyl)-4,5,6,7-tetrafluoroindole (**30a**) is obtained in 60% yield after purification. Similarly, the 1-benzoyl and 1-tosyl derivatives (**30b**, **32c**) are obtained in 40–60% yields (eq 14). In these reactions it turned out that a small amount of **29** was formed as a side product, which is separated by column chromatography on silica gel.[24]



(14)

The usefulness of **29** and **30** thus obtained has been demonstrated by the following examples: (i) the reaction of **30** with piperidine (large excess) at room temperature for 20 h gives 3-(piperidinomethyl)-4,5,6,7-tetrafluoroindole (**31**) in 97% yield, which is a known key intermediate[25] for the synthesis of 4,5,6,7-tetrafluorotryptophan (**32**) (eq 15), (ii) the reaction of N-



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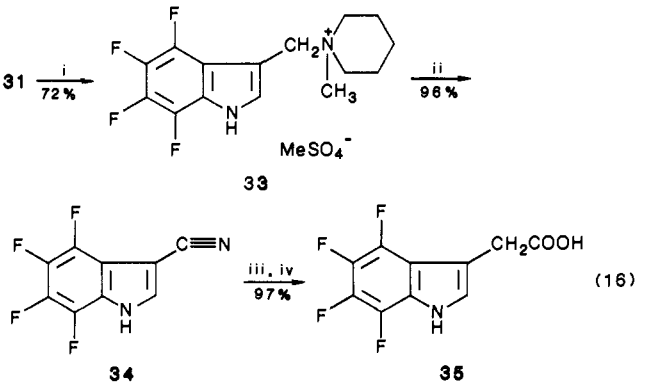
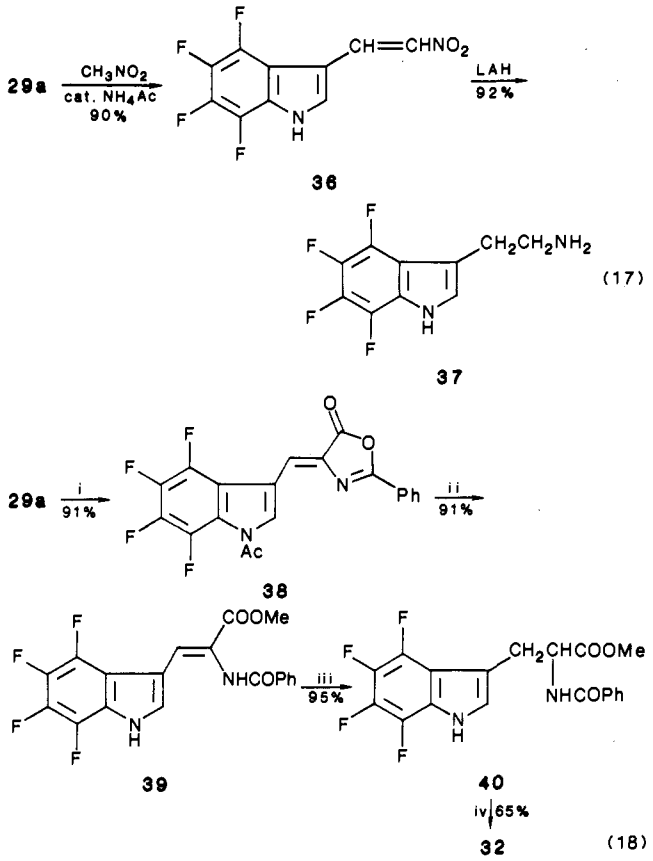


(16)

(i) Me_2SO_4/THF; (ii) KCN/DMF, H_2O; (iii) KOH (aq); (iv) H^+

methylated **31** (**33**) with potassium cyanide (4 equiv) in aqueous DMF under reflux for 2 h gives 3-(cyanomethyl)-4,5,6,7-tetrafluoroindole (**34**) in 96% yield, which is also known to be an excellent precursor[25a] of 4,5,6,7-tetrafluoroindoleacetic acid (**35**) (eq 16), (iii) 4,5,6,7-tetrafluorotryptamine (**37**) is obtained from **29a** through condensation with nitromethane followed by $LiAlH_4$ reduction in 83% overall yield (eq 17), and (iv) *N*-benzoyl-4,5,6,7-tetrafluorotryptophan (**32**) is obtained from **29a** through the Erlenmeyer azlactone method[26] in 51% overall yield (eq 18).

As it is known that 4,5,6,7-tetrafluorotryptophan (**32**) exhibits strong activities in the inhibition of both tryptophanyl hydroxamate and aminoacyl t-RNA formation,[27] tetrafluoro analogues of tryptamine, indoleacetic acid, and other indole derivatives are expected



(17)

(18)

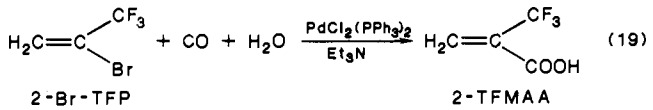
(i) $PhCONHCH_2COOH$, $AcONa/Ac_2O$, THF, reflux 12 h; (ii) MeOH, cat. Et_3N, reflux 1 h; (iii) $H_2/Pd-C$/MeOH, 50 °C, 17 h; (iv) concentrated HCl(aq), reflux 10 h.

to have unique physiological activities.

III. Carbonylations of (Trifluoromethyl)vinyl Bromide

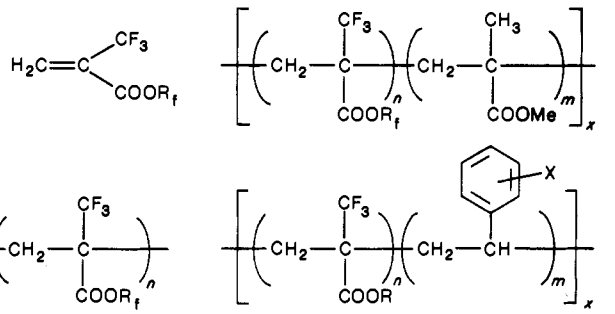
A. Carboxylation and Amidation of 2-Bromotrifluoropropene

The bromination of TFP promoted by photoirradiation followed by dehydrobromination on potassium hydroxide gives 2-bromo-3,3,3-trifluoropropene (2-Br-TFP) in high yield.[28] The carboxylation of 2-Br-TFP, i.e., a Heck type reaction,[29] catalyzed by a palladium catalyst, e.g., $PdCl_2(PPh_3)_2$ or $PdCl_2$(dppf), in the presence of triethylamine in DMF or THF gives 2-(trifluoromethyl)acrylic acid (2-TFMAA) in 65–78% yield (eq 19).[30]



(19)

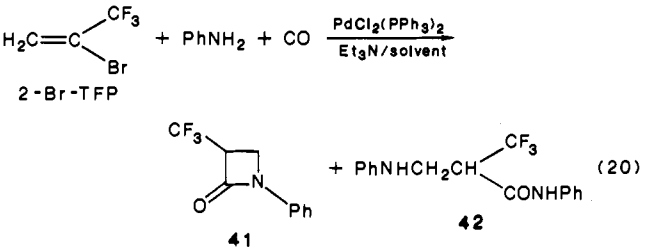
From 2-TFMAA a variety of trifluoromethacrylates, $CH_2{=}C(CF_3)COOR$, can readily be prepared, which are interesting monomers for fluorine-containing polymethacrylates. Copolymerizations with, e.g., methyl methacrylate (MMA) and styrenes are also possible. In fact, the homo- and copolymerizations of methyl trifluoromethacrylate (MTFMA) were reported[31] with regard to the development of new radiation-sensitive polymers for resists in microelectronic fabrication processes; MTFMA was prepared from trifluoroacetone. Copolymers of TFMA esters with styrene and substituted styrenes were also reported.[32] We synthesized a variety of new trifluoromethacrylates bearing polyfluoroalkyl ester moieties, which are currently being evaluated as monomers for potential photoresists and as a component of optical fibers.



R_f = CH_2CF_3, $CH_2CH(CH_3)CF_3$, $(CH_2)_3CF_3$, $CH_2CH_2(C_6F_5)$, $CH(CF_3)_2$

The amidation of 2-Br-TFP with carbon monoxide (50 atm) and diethylamine catalyzed by $PdCl_2(PPh_3)_2$ in the presence of triethylamine (11 mmol) in THF at 100 °C for 7 h gives the expected *N,N*-diethyl-2-(trifluoromethyl)acryloylamide, $CH_2{=}C(CF_3)CONEt_2$, in 50% isolated yield. The formation of a trace amount of a Michael adduct, $Et_2NCH_2CH(CF_3)CONEt_2$, is detected.

However, when aniline is used as an amine for the amidation under similar conditions (80 °C, 40 atm of CO, 15 h), the reaction gives a β-lactam, 1-phenyl-3-(trifluoromethyl)azetidin-2-one (**24**) (26%), and a Michael adduct, 3-(phenylamino)-2-(trifluoromethyl)-propionanilide (**25**) (13%) (eq 20). No trace of 2-(trifluoromethyl)acryloylanilide is detected.



(20)

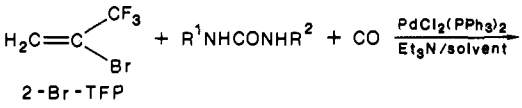
The formation of the β-lactam can be rationalized by considering either an amidation followed by cyclization through an intramolecular Michael addition or a Michael addition of aniline followed by an intramolecular amidation. Since it is reasonable to assume that the formation of a strained four-membered ring is not a low-energy process, the relatively low yield for the β-lactam formation can be ascribed to this unfavorable cyclization. These considerations led us to the development of a novel "ureidocarbonylation" process.

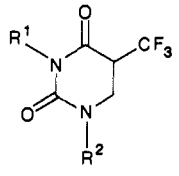
B. "Ureidocarbonylation" of 2-Bromotrifluoropropene Catalyzed by a Palladium–Phosphine Complex

It has been shown that the palladium complex catalyzed amidation of vinyl halides is a convenient method for the synthesis of α,β-unsaturated amides.[29] Mori et al. applied this method to the synthesis of a 3-methylidene β-lactam, which is a key intermediate of nocardicine, through an intramolecular amidation.[33]

As described above, the combination of 2-Br-TFP, aniline, and carbon monoxide in the presence of a palladium catalyst and triethylamine gives 3-trifluoro-

methyl β-lactam, 41. Now, what will happen when a combination of 2-Br-TFP, a urea, carbon monoxide, and triethylamine is subjected to the catalysis of a palladium–phosphine complex? If both nitrogen termini of a urea have sufficient nucleophilicity, the reaction may give the dihydrouracil skeleton in one step. Actually, the reaction proceeded as predicted, and this novel carbonylation process was named "ureidocarbonylation". A general scheme of the ureidocarbonylation is shown in eq 21.[34]





(21)

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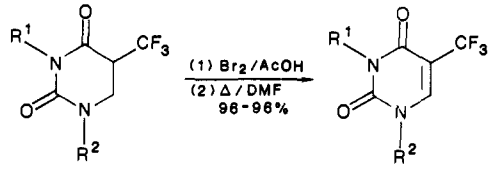
Typically, the ureidocarbonylation is run by heating a mixture of 2-Br-TFP, a urea, $PdCl_2(PPh_3)_2$, and triethylamine in DMF or THF in a stainless steel autoclave with stirring at 100 °C. The reaction with 1,3-dimethylurea gives 1,3-dimethyl-5-(trifluoromethyl)-5,6-dihydrouracil (**43a**) in 70% isolated yield. In a similar manner, the reaction with methylurea gives a mixture of 3-methyl-5-(trifluoromethyl)dihydrouracil (**43b**) and 1-methyl-5-(trifluoromethyl)dihydrouracil (**43c**), which are readily separated by column chromatography on silica gel to afford **43b** and **43c** in 51% and 9% yields, respectively. When unsubstituted urea is employed, the yield of 5-(trifluoromethyl)dihydrouracil (**43d**) is lower than those of the substituted ones, although the reaction conditions are not optimized. It is found that 2,3-dibromo-1,1,1-trifluoropropane can be used instead of 2-Br-TFP.

5-(Trifluoromethyl)-5,6-dihydrouracils (**43**) thus obtained are readily converted to the corresponding 5-(trifluoromethyl)uracils (**44a–d**) by treating with bromine[35] in nearly quantitative yields (eq 22).

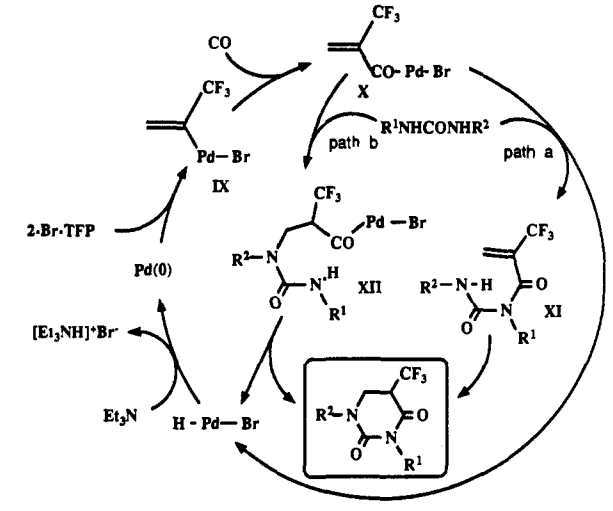


(22)

43 44

The present reaction may involve a (2-(trifluoromethyl)propenoyl)palladium(II) intermediate (X, Scheme III), which further reacts with a urea either in the manner of the amidation of the intermediate X to form (2-(trifluoromethyl)propenoyl)urea (XI) followed by an intramolecular Michael addition to give **43** (path a) or through a Michael type addition of a urea to the intermediate X, first to form the intermediate XII followed by an intramolecular amidation to give **43** (path b). As a trace of neither (2-(trifluoromethyl)-propenoyl)urea (XI) nor (3-ureido-2-(trifluoromethyl)-propanoyl)urea is detected in the reaction mixture in every case examined, it is strongly suggested that the cyclization step is very fast. As we have found that the Michael type addition of ureas to 2-(trifluoromethyl)-

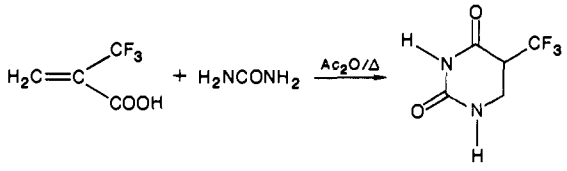
SCHEME III



acrylic acid (2-TFMAA) proceeds smoothly (vide infra), path b may be the operating process.

As 5-(trifluoromethyl)uracil derivatives such as 5-(trifluoromethyl)uridine have been found to have antitumor and antiviral activities[36] and the effective routes to these compounds are still to be explored in spite of extensive synthetic studies, our novel ureidocarbonylation of 2-Br-TFP may serve as an efficient new synthetic route to the analogues of these compounds. In fact, the new 5-(trifluoromethyl)dihydrouracils, **43a–c**, exhibit substantial antitumor activity toward the tumor cells of ascitic mastocarcinoma MM2 of inbred mice.[30]

Another simple method for the synthesis of **43** consists of heating a mixture of 2-TFMAA and a urea in the presence of acetic anhydride at 80–100 °C, which affords **43** directly in good yield. 5-(Trifluoromethyl)-5,6-dihydrouracil (**43d**) was obtained in 67% yield by using this method (eq 23).[30]



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IV. Hydroformylation–Amidocarbonylation of Fluoro Olefins: Highly Regioselective Synthesis of Fluoro Amino Acids

As an approach to the design of multifunctional multicatalyst systems that can promote multistep synthesis in one pot, the efficiency of homogeneous heterobimetallic catalyst systems for amino acid synthesis was examined, which can sequentially promote catalytic processes, including amidocarbonylation as the key unit reaction. The cobalt-catalyzed amidocarbonylation of aldehydes was discovered in 1971 by Wakamatsu et al.,[37] developed by Ajinomoto's research group, and later reinvestigated in more detail by Pino et al.[38] Further applications of this reaction, e.g., to the synthesis of heterocyclic compounds are being developed by Izawa et al.[39]

We have demonstrated successful examples of isomerization–amidocarbonylation and hydroformylation–

amidocarbonylation. The isomerization–amidocarbonylation gives *N*-acyl α-amino acids directly either from allylic alcohols[40,41] or from oxiranes,[41] and the hydroformylation–amidocarbonylation provides fluorinated *N*-acyl α-amino acids directly from fluoro olefins. Since the isomerization–amidocarbonylation has already been fully reviewed[2] and new data have become available for the hydroformylation–amidocarbonylation, we focus on the recent advance in the hydroformylation–amidocarbonylation of fluoro olefins.

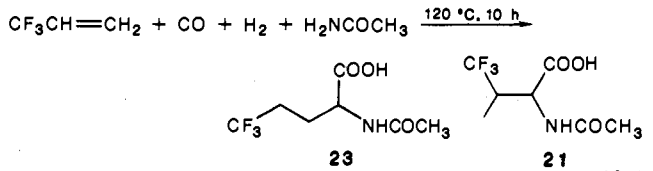
As amidocarbonylation requires both H_2 and CO, and since the reaction conditions are almost the same as those of hydroformylation except for the coexistence of an amide, it is logically possible to combine the two reactions. In fact, the possible synthesis of *N*-acyl α-amino acids through hydroformylation–amidocarbonylation of olefins was suggested by Wakamatsu in his review in 1974.[42] However, it was only recently that the proposed process was actually examined by Stern et al. and appeared as a patent.[43] The process is claimed to be useful for the production of C_9–C_{31} straight-chain (n) *N*-acyl α-amino acids althrough the process gives a mixture of straight-chain (n) and branched (iso) isomers.

If excellent regioselectivities are realized in the hydroformylation of olefins, *N*-acyl α-amino acids can be synthesized with high regioselectivity. As described in section IIA, such high regioselectivities (>93%) are achieved in the hydroformylation of fluoro olefins such as TFP and PFS.[5,6] Accordingly, these reactions are applied to the hydroformylation–amidocarbonylation process. As there is an increasing interest in the incorporation of fluoro amino acids into physiologically active peptides, an efficient synthesis of fluoro amino acids has an important significance in medicinal chemistry and pharmacology (see also IC).

A. Hydroformylation–Amidocarbonylation of Trifluoropropene

The hydroformylation–amidocarbonylation of TFP was studied in the first place since the reaction should give normal or iso *N*-acetyl α-amino acid, *N*-acetyltrifluoronorvaline (**23**) or *N*-acetyltrifluorovaline (**21**), directly from TFP is the extremely regioselective hydroformylation was successfully combined with amidocarbonylation.

As eq 24 shows, $Co_2(CO)_8$-catalyzed reaction (initial pressure at 25 °C: CO, 80 atm; H_2, 50 atm) at 120 °C for 10 h gives *N*-acetyltrifluoronorvaline (**23**) with 96%

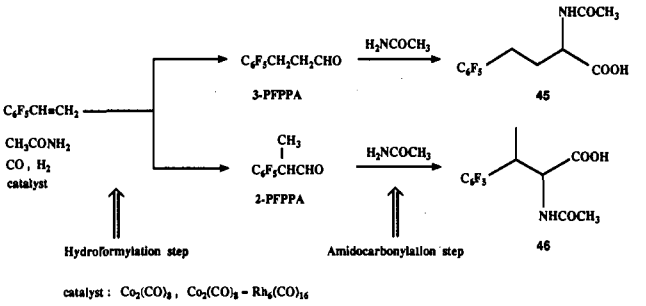


(24)

catalyst	yield, %		
$Co_2(CO)_8$	83	96	4
$Co_2(CO)_8$–$Rh_6(CO)_{16}$	87	6	94

selectivity while the reaction catalyzed by the $Rh_6(CO)_{16}$–$Co_2(CO)_8$ binary system ($Co_2(CO)_8/Rh_6(CO)_{16}$ = 50) under the same conditions gives *N*-acetyltrifluorovaline (**21**) with 94% selectivity.[41] The latter result clearly indicates that the rhodium-catalyzed hydroformylation takes place exclusively in the first step

SCHEME IV



to give 2-TFMPA highly selectively, which is effectively incorporated into the subsequent cobalt-catalyzed amidocarbonylation.

B. Hydroformylation–Amidocarbonylation of Pentafluorostyrene

In contrast to the results obtained for the reactions of TFP, the attempted highly regioselective hydroformylation–amidocarbonylation of PFS catalyzed by the Co–Rh binary system as well as $Co_2(CO)_8$ under similar conditions to those for TFP gave unexpected results. The detailed study of the reaction revealed interesting mechanistic aspects of Co–Rh mixed-metal catalyst systems, including a novel $CoRh(CO)_7$-catalyzed process.[44]

The hydroformylation–amidocarbonylation of PFS catalyzed by $Co_2(CO)_8$ was carried out at 120 °C and 130 atm of CO and H_2 (CO/H_2 = 1.6) with acetamide (2.0 equiv) in dioxane to give *N*-acetyl-4-(pentafluorophenyl)homoalanine (**45**, Scheme IV) with 90–92% regioselectivity (ca. 30% yield). This selectivity is much higher than that (79%) of the simple hydroformylation in benzene. The reaction catalyzed by a Co–Rh binary system [$Co_2(CO)_8/Rh_6(CO)_{16}$ = 50; CO, 80 atm; H_2, 50 atm; 120 °C; acetamide, 2.0 equiv; dioxane] gives *N*-acetyl-3-(pentafluorophenyl)homoalanine (**46**) with only ca. 80% regioselectivity (70% yield), which is much lower than the excellent regioselectivity (98%) of the simple hydroformylation in benzene.[5,6]

To interpret the results obtained, the following three possibilities were initially considered. (a) The regioselectivity of the cobalt-catalyzed hydroformylation of PFS is affected by acetamide and/or dioxane to give the normal aldehyde (3-PFPPA) in much higher selectivity (90–92%) since an amide could conceivably coordinate to the cobalt carbonyl to modify its regioselectivity; a similar solvent effect of dioxane is conceivable as well. (b) There is a kinetic selection of the normal aldehyde (3-PFPPA) in preference to the iso aldehyde (2-PFPPA) in the amidocarbonylation step; viz., a considerable amount of 2-PFPPA should remain unreacted. (c) In the Co–Rh binary system the rhodium catalyst is somewhat deactivated by forming less active or inactive Rh–Co mixed cluster(s) or the cobalt catalyst acquires special activation for the hydroformylation so that the Co–Rh binary system gives a much lower iso/n ratio than the single rhodium catalyst since there should be a 10^3–10^4 difference between the activity of rhodium catalysts and $Co_2(CO)_8$ for the hydroformylation as long as the two catalysts work independently.[1] A series of experiments were carried out to clarify these anomalies.[44]

1. Hydroformylation of Pentafluorostyrene in the Presence of Acetamide

It was found that (a) the cobalt-catalyzed hydroformylation of PFS was substantially slower than the amidocarbonylation of the aldehydes since no trace of 2-PFPPA or 3-PFPPA was detected in the GLC analysis of the reaction mixture even at low conversion and (b) dioxane did not have any favorable solvent effects on the increase of normal selectivity (n-selectivity) for the hydroformylation of PFS. Thus, it became evident that the hydroformylation was the regioselectivity-determining step and the presence of acetamide to $Co_2(CO)_8$ substantially increased the n-selectivity, possibly by forming an active species like $HCo(CO)_n(CH_3CONH_2)_m$. In fact, Izawa et al. also independently found that the addition of acetamide to $Co_2(CO)_8$ changed the regioselectivity in the hydroformylation of isobutene. (Note: Izawa et al. found that the hydroformylation of isobutene catalyzed by $Co_2(CO)_8$ in the *absence* of acetamide followed by amidocarbonylation with acetamide gave 60% of *N*-acetylleucine and 1.6% of *N*-acetyl-*tert*-butylglycine whereas the hydroformylation–amidocarbonylation of isobutene, which included hydroformylation in the *presence* of acetamide, gave 17% of *N*-acetylleucine and 22% of *N*-acetyl-*tert*-butylglycine.[48]) However, the addition of acetamide seemed to enhance the hydrogenation and polymerization of PFS. Remarkable effects of other amides added to the reaction system on the regioselectivity of the reaction also were observed.[44] It was found that the n-selectivity of PFPPA could be increased by elevating temperature and lowering the CO pressure and vice versa, and a considerably large amount of hydrogenation product, $C_6F_5C_2H_5$, was formed (25–50%) at higher temperatures.

In the $Rh_6(CO)_{16}$-catalyzed hydroformylation of PFS, it was found that (a) neither acetamide nor dioxane had any appreciable effect on the regioselectivity, (b) the iso/n ratio was clearly dependent on the reaction temperature (the lower the temperature, the higher is the selectivity (e.g., iso/n = 98/2 at 95 °C; iso/n = 99.5/0.5 at 60 °C)), and (c) the formation of the hydrogenation product was negligible and thus the aldehyde selectivity is extremely high.[44]

2. Kinetic Selection of Iso and Normal Aldehydes in Amidocarbonylation

A competitive reaction of iso aldehyde (2-PFPPA) and normal aldehyde (3-PFPPA) with acetamide was carried out in the presence of $Co_2(CO)_8$ (0.1 equiv) in dioxane at 125 °C. It is found that 3-PFPPA reacts 2.5 times faster than 2-PFPPA. Accordingly, it turns out that there is, actually, a kinetic selection of the aldehydes. However, this kinetic selection does not affect the iso/n ratio of amino acids, **45** and **46**, in the $Co_2(CO)_8$-catalyzed reaction since the hydroformylation step is considerably slower than the amidocarbonylation step as mentioned above. In the Co–Rh mixed-metal system, this kinetic selection could somewhat affect the iso/n ratio at low conversion since $CoRh(CO)_7$-catalyzed or $Rh_4(CO)_{12}$-catalyzed hydroformylation is much faster than the $Co_2(CO)_8$-catalyzed amidocarbonylation. However, the kinetic selection should not affect the final iso/n ratio since the 2-PFPPA should be consumed eventually. Actually, no aldehydes were detected after the reaction unless the reaction was quenched at an early stage. Consequently, the possibility of the kinetic selection being responsible for the observed anomalies is ruled out.[47]

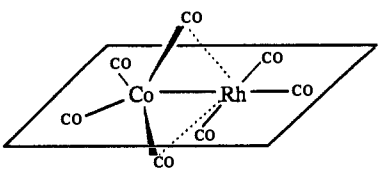
3. Dependence of Regioselectivity on the Co/Rh Ratio

The hydroformylation of PFS in dioxane catalyzed by the Co–Rh mixed-metal system was closely examined with various Co/Rh ratios. The reactions were run with the Co/Rh atomic ratio of 1–100 with the use of $Co_2(CO)_8$ and $Rh_4(CO)_{12}$ or $Rh_6(CO)_{16}$. The Co–Rh mixed clusters, $Co_2Rh_2(CO)_{12}$ and $Co_3Rh(CO)_{12}$, were also used.

The regioselectivities were examined by carrying out the reactions at 95 °C and 82 atm (CO/H_2 = 1) with $Co_2(CO)_8/Rh_6(CO)_{16}$ ratios of 10, 50, and 200, respectively. If the cobalt and rhodium catalysts worked independently, the ratio of normal aldehyde formation should increase at higher Co/Rh ratios and eventually the normal aldehyde should become a major product. However, contrary to this assumption, an interesting leveling phenomenon of regioselectivity was observed; viz., the iso/n ratio decreases from 94/6 at Co_2/Rh_6 = 10 to 88/12 at Co_2/Rh_6 = 50, but the ratio does not continue to significantly decrease with a further increase of Co/Rh ratio; iso/n was 87/13 even at a Co_2/Rh_6 ratio of 200! Under the same reaction conditions, the reaction catalyzed by $Co_3Rh(CO)_{12}$ (Co/Rh = 3) gives an iso/n ratio of 96/4 and the reaction catalyzed by $Co_2Rh_2(CO)_{12}$ (Co/Rh = 1) gives a 98/2 ratio.

This leveling phenomenon of the regioselectivity is best interpreted by taking into account the formation of and the catalysis by a Co/Rh mixed-metal complex. Thus, $Rh_6(CO)_{16}$ and $Co_2(CO)_8$ form a mixed-metal complex that competes with the rhodium catalyst(s) in the system up to a point where practically almost all the rhodium catalyst(s) is converted to the Co–Rh mixed-metal complex in the presence of a large excess of $Co_2(CO)_8$. The Co–Rh complex then becomes the most efficient catalyst species and governs the reaction and the regioselectivity.

When we almost reached the conclusion that "some Co–Rh mixed-metal complex" was the active catalyst species in the hydroformylation of PFS, Horváth, Bor, and Pino[46,47] reported the synthesis, equilibrium study, isolation, characterization, and some reactions of an interesting coordinatively unsaturated Co–Rh mixed-metal complex, $CoRh(CO)_7$, previously postulated as an active catalyst species in the hydroformylation of diketene.[47] It is reported[46,47] that the Co–Rh mixed-metal



The proposed structure of $CoRh(CO)_7$ by Horváth et al.

systems, e.g., $Co_2(CO)_8$–$Rh_4(CO)_{12}$, $Co_2(CO)_8$–$Rh_6(CO)_{16}$, $Co_3Rh(CO)_{12}$, and $Co_2Rh_2(CO)_{12}$, generate an equilibrium mixture under CO pressure in which $CoRh(CO)_7$, $Co_2(CO)_8$, and $Rh_4(CO)_{12}$ are the three major components in hexane (eq 25) and $CoRh(CO)_7$ is an unusually stable complex. This is in sharp contrast to other known mixed clusters such as $HCoRu_3(CO)_{13}$ and

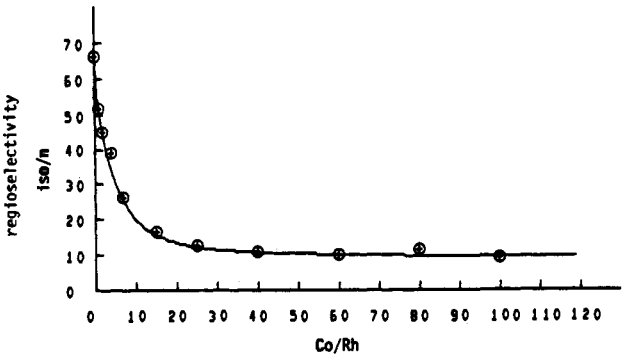


Figure 4. Dependence of regioselectivity on the Co/Rh ratio for the reactions in dioxane at 80 °C and 82 atm ($CO/H_2 = 1$). The concentration of $Rh_4(CO)_{12}$ is kept at 1.0×10^{-3} M and the amount of $Co_2(CO)_8$ is changed. The Co/Rh ratio indicated is based on the metals; i.e., a Co/Rh ratio of 100 is equal to a $Co_2(CO)_8/Rh_4(CO)_{12}$ ratio of 200.

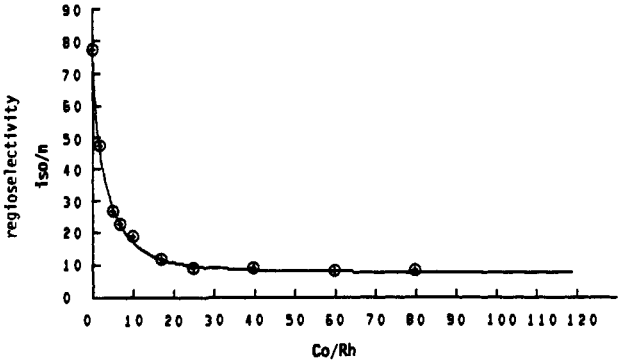


Figure 5. Dependence of regioselectivity on the Co/Rh ratio for the reactions in hexane at 80 °C and 82 atm ($CO/H_2 = 1$). For other conditions, see the caption for Figure 4.

$H_2FeRu_3(CO)_{13}$, which decompose easily to the corresponding homonuclear species under 1 atm of CO at 25–70 °C.[48]

$$Rh_4(CO)_{12} + 2Co_2(CO)_8 \overset{K_1}{\rightleftharpoons} 4CoRh(CO)_7 \quad (25)$$

These reports led us to the close reexamination of the dependence of the regioselectivity on the Co/Rh ratio in order to obtain unambiguous evidence for the catalysis of "some Co–Rh mixed-metal complex", i.e., $CoRh(CO)_7$ catalysis, using $Co_2(CO)_8$ and $Rh_4(CO)_{12}$ as catalyst precursors. The equilibrium constant, K_1, for eq 25 was estimated to be 3.5×10^{-3} M at 84 °C in hexane.[47]

All reactions are run by mixing $Co_2(CO)_8$, $Rh_4(CO)_{12}$, and PFS in dioxane or hexane, in advance, at 80 °C and 41 atm of CO for 12 h and then starting the reaction by introducing H_2 (41 atm) so that the Co–Rh mixed-metal system reaches equilibrium before the hydroformylation begins. In the controlled experiments, the iso/n ratios for the $Rh_4(CO)_{12}$-catalyzed reaction are 66 in dioxane and 76 in hexane; those for the $Co_2(CO)_8$-catalyzed reaction are 0.67 in dioxane and 0.47 in hexane at 80 °C and 82 atm ($CO/H_2 = 1$). Under the given conditions the cobalt-catalyzed reaction is very slow so that the formation of aldehydes is only 4.1% yield after 16 h in dioxane (4.0×10^{-2} M of $Co_2(CO)_8$) and 6.0% after 6 h in hexane (0.10 M of $Co_2(CO)_8$) at 1.0 M concentration of PFS. The results are shown in Figures 4 and 5.

Figure 4 (solvent, dioxane) shows a clear leveling phenomenon that is essentially the same as that observed for $Co_2(CO)_8$–$Rh_6(CO)_{16}$. The iso/n ratio sharply decreases from 66 (Rh 100%) to 16 (Co/Rh = 15), the decrease slows down at higher Co/Rh ratios and becomes nearly constant, 10, at Co/Rh = 40, and the ratio is 9.5 at Co/Rh = 100. At this stage was made a working hypothesis that the catalyst species giving an iso/n ratio of 10 would be $CoRh(CO)_7$.

In hexane, as Figure 5 shows, the same type of clear leveling phenomenon of regioselectivity is observed as well. In this case, the regioselectivity at the leveled region is 7.5, which $CoRh(CO)_7$ is assumed to give. Thus, it is apparent that there is a solvent effect on the regioselectivity. As mentioned above, the E.T.H. group obtained all the data for the equilibrium between $Co_2(CO)_8$, $Rh_4(CO)_{12}$, and $CoRh(CO)_7$ in hexane based on the high-pressure IR studies, and these three species were found to be the only predominant species in hexane under carbon monoxide pressure.[46,47] Therefore it is possible to consider that these three species are either the active catalytic species or the direct precursors of the active catalytic species in hexane.

Although it seems reasonable to assume that the three major species existing in the Co–Rh mixed-metal system in dioxane under carbon monoxide pressure are the same as those in hexane, there might be some solvent effects that would change the major species. Therefore, a high-pressure IR study of the $Co_2(CO)_8$–$Rh_4(CO)_{12}$ system in dioxane was carried out in order to directly observe active catalytic species in the actual reaction system.

4. High-Pressure IR Study of the Co–Rh Mixed-Metal System under the Reaction Conditions

As Figure 6 shows, the IR spectrum of the reaction mixture of $Co_2(CO)_8$ and $Rh_4(CO)_{12}$ (1:1 metal ratio) in dioxane at 80 °C and 41 atm of carbon monoxide displays the clear formation of $CoRh(CO)_7$ together with $Co_2(CO)_8$ and $Rh_6(CO)_{16}$ (system 1) (Figure 6a; bold line). The bands at 1850 cm^{-1} (B) and 1808 cm^{-1} (D) are assigned to $Co_2(CO)_8$ and $Rh_6(CO)_{16}$, respectively. The band at 1940 cm^{-1} (A) is attributed to $CoRh(CO)_7$ as evidently shown in the IR spectrum of $CoRh(CO)_7$ obtained quantitatively from the reaction of $Co_2Rh_2(CO)_{12}$ with carbon monoxide at 25 °C and 41 atm (Figure 6a; dotted line). The IR spectrum of $CoRh(CO)_7$ measured previously in hexane[46] is virtually superimposable on that in dioxane, which indicates no change in the structure of this Co–Rh mixed complex in those two solvents. It should be noted that $Rh_4(CO)_{12}$ disappeared completely when it was dissolved in dioxane at 80 °C and 41 atm of carbon monoxide for 20 h although $Rh_4(CO)_{12}$ is stable in dioxane at 25 °C and 41 atm of carbon monoxide. The result clearly indicates a substantial solvent effect on the structure of the major species of rhodium carbonyls as we suspected before the high-pressure IR study. Under the same conditions, $Co_2Rh_2(CO)_{12}$ shows exactly the same spectrum as system 1. When hydrogen (41 atm) was introduced to system 1, the spectrum of the reaction mixture displayed a new intense absorption of $HCo(CO)_4$ in place of the substantially diminished $Co_2(CO)_8$, $CoRh(CO)_7$, and $Rh_6(CO)_{16}$ (system 2) (Figure 6b). The band at 2114 cm^{-1} is assigned to $HCo(CO)_4$.

Next a high-pressure IR study of the Co–Rh mixed-metal systems was carried out with a Co/Rh metal ratio

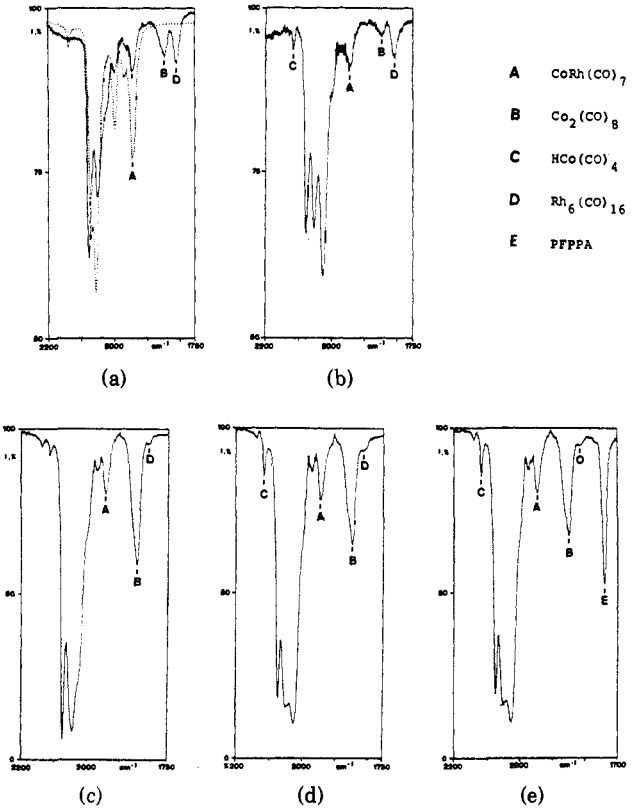


Figure 6. High-pressure IR spectra of the Co–Rh mixed-metal systems in dioxane. (a) Spectrum for the mixture of $Co_2(CO)_8$ and $Rh_4(CO)_{12}$ (2:1 molar ratio; 1:1 metal ratio) at 80 °C and 41 atm of CO (bold line) (system 1), and the reference spectrum of $CoRh(CO)_7$ generated from $Co_2Rh_2(CO)_{12}$ at 25 °C and 41 atm of CO (dotted line). (b) Spectrum of the mixture of $Co_2(CO)_8$ and $Rh_4(CO)_{12}$ (1:1 metal ratio) at 80 °C and 82 atm (CO/H_2 = 1), i.e., system 1 plus hydrogen (system 2). (c) Spectrum of the mixture of $Co_2(CO)_8$ and $Rh_4(CO)_{12}$ (80:1 molar ratio; 40:1 metal ratio) at 80 °C and 41 atm of CO (system 3). (d) Spectrum of the mixture of $Co_2(CO)_8$ and $Rh_4(CO)_{12}$ (40:1 metal ratio) at 80 °C and 82 atm (CO/H_2 = 1), i.e., system 3 plus hydrogen (system 4). (e) Spectrum of the mixture of $Co_2(CO)_8$ and $Rh_4(CO)_{12}$ (40:1 metal ratio) at 80 °C and 82 atm (CO/H_2 = 1) 1 h after the addition of PFS to system 4 (system 5).

of 40 under the same conditions as described above (system 3). At this Co/Rh ratio, $CoRh(CO)_7$ should become the predominant catalyst species based on the results depicted in Figure 4. Indeed, as shown in Figure 6c, $Rh_6(CO)_{16}$ diminishes to a trace amount and $CoRh(CO)_7$ and $Co_2(CO)_8$ become the two major components in this system. The addition of hydrogen (41 atm) to system 3 brings about the formation of $HCo(CO)_4$ without affecting the $CoRh(CO)_7$ concentration (Figure 6d) (system 4). Finally, PFS was added to system 4, and the IR spectrum of this real reaction system was measured 1 h after the addition of PFS. As Figure 6e shows, an intense aldehyde peak (E) appears together with those of $CoRh(CO)_7$, $HCo(CO)_4$, and $Co_2(CO)_8$ and a peak due to a trace amount of $Rh_6(CO)_{16}$. The ratio and the appearance of the metal carbonyl peaks did not change during the reaction.

Consequently, the IR study provides strongly supporting evidence for the $CoRh(CO)_7$ catalysis that is hypothesized.

5. Evaluation of Relative Activities of Catalytic Species

(a) Reactions in Hexane. On the basis of the equilibrium constant K_1 (3.5×10^{-3} M at 84 °C) reported for eq 25,[47] the relative concentrations of $CoRh(CO)_7$, $Co_2(CO)_{12}$, and $Rh_4(CO)_{12}$ at a given Co/Rh ratio can be calculated by eq 26, where a is the concentration of $CoRh(CO)_7$, b is the initial concentration of $Co_2(CO)_8$, and c is the initial concentration of $Rh_4(CO)_{12}$.

$$K_1 = \frac{[CoRh(CO)_7]^4}{[Rh_4(CO)_{12}][Co_2(CO)_8)]^2} = \frac{a^4}{(c - a/4)(b - a/2)^2} = 0.0035 \quad (26)$$

The relative catalytic activity of $Rh_4(CO)_{12}$ vs $CoRh(CO)_7$ as well as $Co_2(CO)_8$ can be estimated based on the calculated relative concentrations of these three species and the observed iso/n ratios of PFPPA. (Note: As for the kinetics of cobalt- and rhodium-catalyzed hydroformylation of olefins, it has been shown that the following equation is basic:

$$\frac{d(\text{aldehyde})}{dt} = k[\text{olefin}]^x[\text{cat.}]^y\frac{P_{H_2}}{P_{CO}} \quad (27)$$

where $x = y = 1$ for cobalt catalysts; when rhodium catalysts are used, x and y vary depending on the reaction conditions.[49] Under the reaction conditions used in our experiments, Heil and Markó reported that the rate is first order in concentration of olefin and of $Rh_4(CO)_{12}$.[49b] Accordingly, we assumed the first-order relation of the reaction rate with the catalyst concentration for $CoRh(CO)_7$ in the calculations.

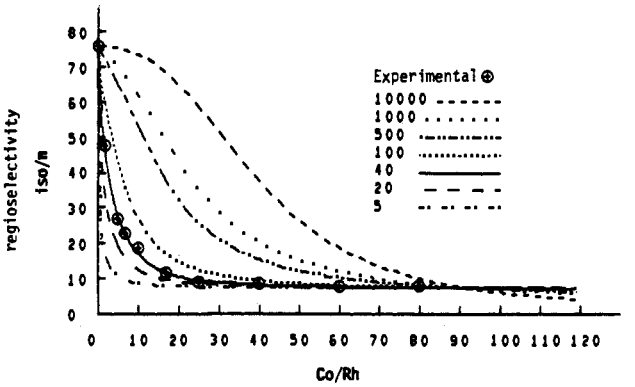


Figure 7. Calculated dependence of regioselectivity on the Co/Rh ratio for the reactions in hexane with several hypothetical relative catalytic activity ratios for $Rh_4(CO)_{12}$ versus $CoRh(CO)_7$. The regioselectivity of each catalyst used for the calculation is 76 for $Rh_4(CO)_{12}$, 7.5 for $CoRh(CO)_7$, and 0.47 for $Co_2(CO)_8$. The y value in eq 3 set for this display is 8400.

The results of the calculations and the computer plotting for the iso/n ratio vs Co/Rh ratios with several given relative catalytic activities are shown in Figure 7. The calculations were performed based on the following assumptions and treatments. (i) The rate constants, k_1, k_2, and k_3, are defined for the unit reactions that give iso aldehyde (2-PFPPA) catalyzed by $Rh_4(CO)_{12}$, $CoRh(CO)_7$, and $Co_2(CO)_8$, respectively. Similarly, $k_{1'}$, $k_{2'}$, and $k_{3'}$ are defined as the rate constants for the unit reactions giving normal aldehyde (3-PFPPA) catalyzed by $Rh_4(CO)_{12}$, $CoRh(CO)_7$, and $Co_2(CO)_8$, respectively. (ii) The observed iso/n ratios should be described by using the relative concentrations

of the three catalyst species as follows based on the observed iso/n ratios ($=k_{iso}/k_n$) for each catalyst species, i.e., 76 for $Rh_4(CO)_{12}$ ($k_1/k_{1'}$), 7.5 for $CoRh(CO)_7$ ($k_2/k_{2'}$), and 0.47 for $Co_2(CO)_8$ ($k_3/k_{3'}$), and also based on the assumption that the rate of the reaction is first order in concentration of the catalyst in each case for the three catalysts (eq 28).

$$\text{iso/n} = 76(c - a/4)/Z + 7.5(a/x)/Z + 0.47\{(b - a/2)/y\}/Z \quad (28)$$

$$Z = (c - a/4) + (a/x) + (b - a/2)/y$$

$$x = k_{2'}/k_{1'}; \qquad y = k_{3'}/k_{1'}$$

(iii) The relative catalytic activities are defined as $(k_1 + k_{1'})/(k_2 + k_{2'})$ for $Rh_4(CO)_{12}/CoRh(CO)_7$ and $(k_1 + k_{1'})/(k_3 + k_{3'})$ for $Rh_4(CO)_{12}/Co_2(CO)_8$. Since the observed iso/n ratios are 76 for $Rh_4(CO)_{12}$, 7.5 for $CoRh(CO)_7$, and 0.47 for $Co_2(CO)_8$, we can derive the following equations: $k_1 = 76k_{1'}$; $k_2 = 7.5k_{2'}$; $k_3 = 0.47k_{3'}$. Thus, the relative catalytic activities can be described as follows: $(77/8.5)k_{1'}/k_{2'}$ ($=9.06x$) for $Rh_4(CO)_{12}/CoRh(CO)_7$; $(77/1.47)k_{2'}/k_{3'}$ ($=52.4y$) for $Rh_4(CO)_{12}/Co_2(CO)_8$.

As Figure 7 shows, the relative catalytic activity of 40 for $Rh_4(CO)_{12}/CoRh(CO)_7$, i.e., 10 per rhodium metal, almost perfectly fits the experimental results. The relative catalytic activity for $Rh_4(CO)_{12}/Co_2(CO)_8$ is calculated to be ca. 440 000, i.e., ca. 220 000 per metal, which indicates that $Co_2(CO)_8$ is nearly inactive under the given reaction conditions. This may well be partly ascribed to a low conversion of $Co_2(CO)_8$ to $HCo(CO)_4$, which is the real active catalyst species, under these conditions besides the inherent activity difference between the rhodium catalyst and the cobalt catalyst (vide infra).

(b) Reactions in Dioxane. Since the high-pressure IR study revealed that the rhodium species existing in the catalytic reaction system in dioxane was $Rh_6(CO)_{16}$ instead of $Rh_4(CO)_{12}$, eq 29 should be modified and an equilibrium constant for the modified equation should be determined. Nevertheless, we may be able to assume that (i) the concentration of $Rh_6(CO)_{16}$ can be represented by $Rh_4(CO)_{12}$, i.e., $[Rh_6(CO)_{16}] = {}^2/_3[Rh_4(CO)_{12}]$, since it has been shown[46] that $Rh_6(CO)_{16}$ should be converted to $Rh_4(CO)_{12}$ to react with $Co_2(CO)_8$ forming $CoRh(CO)_7$ and (ii) the K_1 value in dioxane is not very different from that in hexane.

On the basis of this working hypothesis, the relative ratio of $[CoRh(CO)_7]$, $[Rh_6(CO)_{16}]$, and $[Co_2(CO)_8]$ at the given Co/Rh ratio can be calculated, and the relative catalyst activities for these three species can be estimated in a manner similar to the hexane case described above. The calculations were performed by using a modified eq 26 in which only the numbers were changed based on the iso/n ratio of 66 for the rhodium-catalyzed reaction ($k_1/k_{1'}$) and 10 for the $CoRh(CO)_7$-catalyzed reaction ($k_2/k_{2'}$), and 0.67 for the cobalt-catalyzed reaction ($k_3/k_{3'}$) at 80 °C and 80 atm ($CO/H_2 = 1$). The results of the calculations and the computer plotting for the iso/n ratio vs Co/Rh ratio with several given relative catalytic activities are shown in Figure 8. As Figure 8 shows, the relative catalytic activity of 54 for $Rh_6(CO)_{16}/CoRh(CO)_7$ shows a very good agreement with the experimental resutls; i.e., the relative activity per rhodium metal is 9. The relative

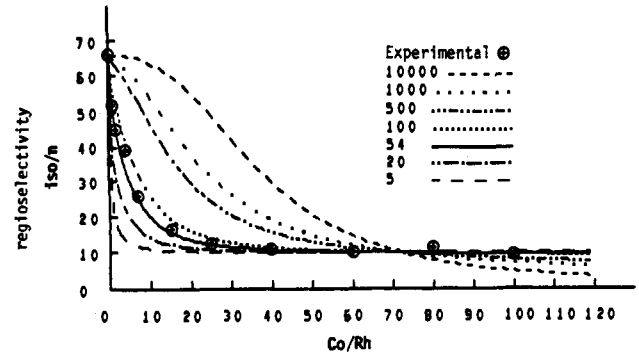


Figure 8. Calculated dependence of regioselectivity on the Co/Rh ratio for the reactions in dioxane with several hypothetical relative catalytic activity ratios for $Rh_6(CO)_{16}$ versus $CoRh(CO)_7$. The regioselectivity of each catalyst used for the calculation is 66 for $Rh_6(CO)_{16}$, 10 for $CoRh(CO)_7$, and 0.67 for $Co_2(CO)_8$. The y value in eq 3 for this display is 6600.

catalytic activity for $Rh_6(CO)_{16}/Co_2(CO)_8$ is calculated to be ca. 400 000, i.e., 133 000 per metal. Thus, the results of the calculations are very similar to those of the hexane case.

6. Kinetic Study of Rh, Co–Rh, and Co Catalyst Systems

Kinetic studies of $CoRh(CO)_7$, rhodium carbonyl, and cobalt carbonyl catalyst systems were performed in order to obtain independent supporting evidence for the relative catalytic activities estimated based on the analysis of the regioselectivity of the reactions.

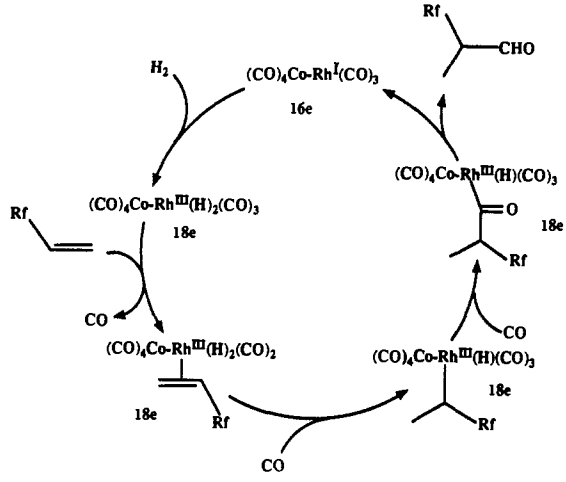
(a) Reactions in Hexane. The rhodium-catalyzed reaction was carried out with PFS (5.0×10^{-2} M) and $Rh_4(CO)_{12}$ (5.0×10^{-5} M) in hexane at 80 °C and 82 atm ($CO/H_2 = 1$). The reaction is first order in PFS concentration, and the rate constant for $Rh_4(CO)_{12}$ is calculated to be 6.1×10^{-4} s^{-1}; i.e., the turnover number is estimated to be 10 980 h^{-1} per rhodium.

The cobalt-catalyzed reaction was carried out at 80 °C and 82 atm ($CO/H_2 = 1$) with PFS (1.0 M) and $Co_2(CO)_8$ (5.0×10^{-2} M) in hexane. The formation of aldehydes after 6 h was 6.0%. The calculated rate constant is 2.8×10^{-6} s^{-1}; i.e., the turnover number is estimated to be 5.0×10^{-2} h^{-1} per cobalt. Thus, the relative catalytic activity of $Rh_4(CO)_{12}$ vs $Co_2(CO)_8$ is calculated to be 439 000. The value estimated based on the regioselectivity analysis is 440 000 (vide supra).

As $CoRh(CO)_7$ should become a predominant catalyst species at a Co/Rh ratio of 40 (see Figure 7), the reaction was carried out with PFS (0.25 M), $Rh_4(CO)_{12}$ (1.0×10^{-3} M) and $Co_2(CO)_8$ (8.0×10^{-2}) in hexane at 80 °C and 82 atm ($CO/H_2 = 1$). The reaction is first order in PFS concentration like the cases of the rhodium carbonyl and cobalt carbonyl, and *the regioselectivity does not change throughout the reaction.* The calculated rate constant is 6.8×10^{-4} s^{-1}; i.e., the estimated turnover number per $CoRh(CO)_7$ is 612 h^{-1}. Accordingly, the relative activity ratio of $Rh_4(CO)_{12}$ to $CoRh(CO)_7$ *per rhodium* is 17.9. The estimated value based on the regioselectivity analysis is 10 (vide supra).

(b) Reactions in Dioxane. The rhodium-catalyzed reaction was carried out under the same conditions as those employed for the reaction in hexane except for the solvent. The reaction is clearly first order in PFS concentration and the rate constant for $Rh_4(CO)_{12}$ is calculated to be 1.9×10^{-4} s^{-1}; i.e., the turnover number

SCHEME V



is estimated to be 3420 h^{-1} per rhodium.

The cobalt-catalyzed reaction was performed in two ways. First, the reaction was carried out at 80 °C and 82 atm (CO/H_2 = 1) with PFS (1.0 M) and $Co_2(CO)_8$ (5.0×10^{-2} M) in dioxane. The conversion after 6 h was only 4.1% and the calculated rate constant is ca. 7.1×10^{-7} s^{-1}; i.e., the turnover number is estimated to be 2.6×10^{-2} h^{-1} per cobalt. Thus, the relative catalytic activity of $Rh_6(CO)_{16}$ vs $Co_2(CO)_8$ is calculated to be 398000. The estimated value based on the regioselectivity analysis is 400000 (vide supra). Second, the reactions were carried out at 100 °C and at 120 °C under 82 atm of carbon monoxide and hydrogen (CO/H_2 = 1) with PFS (0.20 M) and $Co_2(CO)_8$ (6.0×10^{-3} M) in dioxane. The reaction is first order in PFS concentration, and the estimated turnover numbers at 100 and 120 °C are 2.3 and 9.2 h^{-1} per cobalt, respectively. The activation energy estimated based on the Arrhenius plot is 81.5 kJ mol^{-1} and the frequency factor is calculated to be 3.5×10^8 mol^{-1} L s^{-1}. These results suggest that only a part of $Co_2(CO)_8$ is converted to $HCo(CO)_4$, the active catalyst species, at 80 °C and thus, the *apparent* rate constant and turnover number at 80 °C is much smaller than the value expected from the given concentration of $Co_2(CO)_8$. This observation corresponds well to the high-pressure IR study mentioned above (see Figure 6c).

The reaction with the Co/Rh ratio of 40 was carried out in dioxane under the same conditions as those employed for the reaction in hexane. The reaction is first order in PFS concentration and the regioselectivity does not change throughout the reaction, the same as for the reaction in hexane. The calculated rate constant is 1.0×10^{-3} s^{-1}; i.e., the estimated turnover number per $CoRh(CO)_7$ is 900 h^{-1}. Accordingly, the relative activity ratio of $Rh_4(CO)_{12}$ (or $Rh_6(CO)_{16}$) to $CoRh(CO)_7$ *per rhodium* is 3.8. The estimated value based on the regioselectivity analysis is 9 (vide supra).

7. Possible Catalytic Cycle of $CoRh(CO)_7$

Although further detailed studies are necessary to understand the mechanism of $CoRh(CO)_7$ catalysis, our current working hypothesis is that *the active site of $CoRh(CO)_7$ is the rhodium moiety* since the rhodium moiety is coordinatively unsaturated and the cobalt moiety acts as a ligand for the rhodium moiety, which is responsible for the distinct regioselectivity of this mixed-metal complex in comparison with simple rhodium and cobalt complexes. A proposed catalytic cycle is shown in Scheme V. In fact, Horváth[50] and Roberts et al.[51] isolated phosphine complexes of the type $(CO)_4CoRh(CO)_{3-n}(PR_3)_n$ (n = 1, 2), which implies the feasibility of the rhodium moiety for ligand substitution and thus the rhodium moiety as the reaction site in catalysis. (Note: It has also been shown that $Co_2Rh_2(CO)_{12}$ reacts with various nucleophiles such as tetrahydrofuran, acetonitrile, and triethylphosphine to give the corresponding $(CO)_4CoRh(CO)_2Nu$.[50])

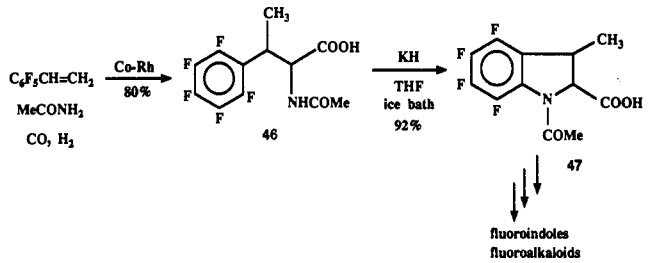
8. New Scale for the Analysis of the Catalysis of Mixed-Metal Systems

In order to investigate the catalysis of complicated mixed-metal systems like this, an introduction of a new scale besides the conventional kinetic measurements is necessary and powerful. We have demonstrated here a relevant example by introducing "regioselectivity" as an excellent scale together with the equilibrium of components and the spectroscopic identification of catalytic species or their direct precursors in the actual reaction system: $CoRh(CO)_7$, $Rh_4(CO)_{12}$ (or $Rh_6(CO)_{16}$), and $Co_2(CO)_8$ have substantially different regioselectivities with respect to each other in the hydroformylation of PFS so that we can successfully analyze a rather complicated reaction. The estimated relative catalytic activity of $CoRh(CO)_7$ vs $Rh_4(CO)_{12}$ and $Rh_6(CO)_{16}$ based on the regioselectivity analysis showed a good agreement with that estimated by kinetic measurements in hexane as well as in dioxane in spite of several assumptions. Consequently, this study has provided a rare successful example of the elucidation of mixed-metal catalysis, in which actual active catalyst species and their direct precursors are detected spectroscopically and the observation corresponds almost perfectly to the mechanism proposed based on the regioselectivity analysis. (Note: At this point, one may be curious about the reason why excellent regioselectivities were achieved in the hydroformylation–amidocarbonylation of TFP using $Rh_6(CO)_{16}$–$Co_2(CO)_8$ in which $CoRh(CO)_7$ should be generated as well. On the basis of our preliminary study on the hydroformylation of TFP catalyzed by Co–Rh mixed-metal systems using $Rh_4(CO)_{12}$–$Co_2(CO)_{12}$ in a similar manner to the PFS case, it is strongly suggested that the high iso/n ratio (94/6) obtained in the hydroformylation–amidocarbonylation of TFP using $Rh_6(CO)_{16}$ (0.1 mol %)–$Co_2(CO)_8$ (5 mol %) (vide supra)[41] is ascribed to the very fast hydroformylation of TFP by rhodium species before the Co–Rh mixed-metal system reached an equilibrium.)

9. Highly Regioselective Synthesis of Fluoro Amino Acids

From the synthetic viewpoint, a highly regioselective production of the fluoro amino acids, **45** and **46**, is the ultimate goal. As for the synthesis of **46**, it can be said that the process is practical. For example, the $Co_3Rh(CO)_{12}$ catalyst (1.0 mol %) gives **46** in 74% yield with 92% regioselectivity at 110 °C and 1200 psi (82.8 bar) (CO/H_2 = 3/1) and the $Co_2(CO)_8$ (5.0 mol %)–$Rh_4(CO)_{12}$ (0.05 mol %) catalyst system gives **46** in 80% yield with 98.2% regioselectivity at 60 °C for 6 h and then 125 °C for 5 h under 75 atm of CO and 48 atm of H_2. With regard to the synthesis of **45**, however, the

SCHEME VI



single $Co_2(CO)_8$-catalyzed process is not very efficient yet; although the regioselectivity of the reaction is high, 90–94%, the chemical yield is low, 30–35%, mainly due to the hydrogenation of PFS (30–55%). Accordingly, we should search for another mixed-metal system that suppresses the hydrogenation without affecting high straight-chain selectivity of cobalt carbonyl to overcome this problem.

N-Acetyl-3-pentafluorophenylhomoalanine (**46**) thus obtained can serve as a good precursor for fluoroindoles. Base-promoted cyclization of **46** gives *N*-acetyl-2-(hydroxycarbonyl)-3-methyl-2,3-dihydro-4,5,6,7-tetrafluoroindole (**47**) in 92% yield, which can be transformed to a variety of fluoroindoles and fluoro alkaloids (Scheme VI).

V. Conclusion

It is demonstrated that carbonylations promoted by homogeneous transition-metal catalysts, including mixed-metal catalysts, have excellent applicability to the functionalization of olefins, vinylic halides, allylic alcohols, oxiranes, and aldehydes.

Highly regioselective hydrocarbonylations of fluoro olefins has opened a new research area in the interface of organofluorine chemistry and homogeneous catalysis. From a synthetic viewpoint, the hydroformylation products, 3-R_f-propanal and 2-R_f-propanal (R_f = F, perfluoroalkyl, and perfluorophenyl), are versatile building blocks for the synthesis of a variety of fluorine-containing compounds. For instance, 2- and 3-TFMPA and 2- and 3-PFPPA have been successfully converted to the corresponding biologically active fluoro amino acids and related compounds such as trifluorovaline, trifluoronorvaline, trifluoroleucine, trifluoronorleucine, tetrafluorotryptophan, tetrafluoroindoleacetic acid, tetrafluorotryptamine, and tetrafluoroindoles. 2-FPA is an excellent precursor of monofluorinated compounds such as 3-fluorohomoalanine, which is known to be a strong enzyme inhibitor of cystathionases.[52]

The successful application of homogeneous binary catalyst systems to the hydroformylation–amidocarbonylation processes, which give fluorinated *N*-acyl α-amino acids directly from fluoro olefins, provides us with strong encouragement for the further development of multicatalyst systems for multistep reactions in one pot.

The finding of novel $CoRh(CO)_7$-catalyzed hydroformylation is noteworthy. It should also be mentioned that we have found a way to use any of the active catalyst species selectively among catalytic species in an equilibrium mixture like the one shown in eq 25 by choosing appropriate conditions such as metal–metal ratio, pressure, and temperature. This approach has opened a new aspect of homogeneous catalysis, which, in principle, is applicable to a variety of multistep catalytic processes.

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VI. References and Notes

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