International Journal of Research
Available at https://edupediapublications.org/journals
e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 05 Issue 01
January 2018

A study of Fluorine Chemistry at the Multidisciplinary

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ABSTRACT:

Over the last three decades, my engagement in "fluorine chemistry" has evolved substantially because of the multidisciplinary nature of the research programs. I began my research career as a synthetic chemist in organometallic chemistry and homogeneous catalysis directed toward organic synthesis. Then, I was brought into a very unique world of "fluorine chemistry" in the end of 1970s. The interface of fluorine chemistry and transition metal homogeneous catalysis first, which was followed by amino acids, peptides, and peptidomimetics for medicinal chemistry. Since then, the interfaces of fluorine chemistry and multidisciplinary fields of research involving medicinal chemistry, chemical biology, cancer biology, and molecular imaging. This perspective intends to cover my fruitful endeavor in the exploration of fluorine chemistry at the multidisciplinary interface of chemistry and biology in a chronological order to show the evolution of my research interest and strategy.

KEYWORDS: Fluorine, Chemistry, Multidisciplinary, nature, synthetic, homogeneous, medicinal, evolution.

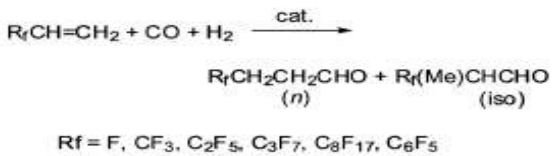
INTRODUCTION: The extraordinary potential of fluorine-containing biologically relevant molecules in peptide/protein chemistry, medicinal chemistry, chemical biology, pharmacology, drug discovery as well as diagnostic and therapeutic applications was recognized by researchers who are not in the traditional fluorine chemistry field, and thus a new wave of fluorine chemistry has been rapidly expanding its biomedical frontiers. In fact, the importance of fluorine in bioorganic and medicinal chemistry has been demonstrated by a large number of fluorinated compounds approved by the FDA for medical use. According to our survey in 2008, fluorine-containing drugs have received FDA approval for human diseases (of which, however, have been discontinued from the market), while 33 are currently in use for veterinary applications. These statistics make fluorine the "second-favorite heteroatom" after nitrogen in drug design. Small atomic radius, high electronegativity, nuclear spin of 1/ 2, and low polarizability of the C−F bond are among the special properties that render fluorine so attractive. These atomic properties translate

widely into equally appealing attributes of fluoroorganic compounds. Higher metabolic stability, often increased binding to target molecules, and increased lipophilicity and membrane permeability are some of the properties associated with the replacement of a C−H or C− O bond with a C−F bond in biologically active compounds. Because of the recognized value of fluorine, it is now a common practice in drug discovery to study fluoro-analogues of lead compounds under development. It should be noted that in 2006 the best and the second best selling drugs in the world were Lipitor (atorvastatin calcium) (by Pfizer/Astellas; $14.4 billion/year) and Advair (USA)/seretide(EU) (a mixture of fluticasone propionate and salmeterol) (by GlaxoSmithKline; $6.1 billion/year), which contain one and three fluorine atoms, respectively. These huge successes of fluorine-containing drugs keep stimulating research on fluorine in medicinal chemistry for drug discovery. As such, it is not an exaggeration to say that every new drug discovery and development today explores fluorine-containing drug candidates without exception.

REVIEW OF LITERATURE: Although medicinal chemists have been introducing fluorine into bioactive molecules on the basis of experience and intuition, it is only recently that experimental and computational studies have been conducted to better understand how the introduction of fluorine into small drug molecules results in higher binding affinities and selectivity. An understanding of how the replacement of H with F affects the electronic nature and conformation of small molecules is crucial for predicting the interaction of fluoroorganic molecules with proteins and enzymes. In addition, 19F NMR has found numerous applications to molecular imaging and promoted the development of molecular probes for imaging. The sensitivity of 19F NMR spectroscopy, along with large 19F−1 H coupling constants and the virtual absence of 19F in living tissues, makes incorporation of fluorine into bioactive compounds a particularly powerful tool for the investigation of biological processes. Also, applications of 18F-PET (positron emission tomography), a powerful in vivo imaging technology in oncology, neurology, psychiatry, cardiology, and other medical specialties, have already become an essential part of medical care. In addition, 18F-PET has emerged as an important tool in drug development, especially for accurate measurements of pharmacokinetics and pharmacodynamics. There is a strong demand for developing new and efficient synthetic methods as well as expanding the availability of versatile fluorine-containing synthetic building blocks and intermediates to promote medicinal chemistry, chemical biology, and molecular imaging research. The limited availability of fluorochemicals for bioorganic and medicinal chemistry as well as pharmaceutical and agrochemical applications is mainly due to the exceptional properties and hazardous nature of fluorine and fluorochemical sources. Also, in many cases, synthetic methods developed for ordinary organic molecules do not work well for fluorochemicals because of their unique reactivity. Therefore, the new and efficient synthetic methods applicable to organ fluorine compounds, including 18F radiotracers, need to be continuously developed.

EXPLORATION OF ORGANOFLUORINE CHEMISTRY: In this paper, Clark demonstrated the capability of per fluorocarbons (PFCs) to deliver oxygen to a living mouse placed deep in a beaker filled with PFCs, which clearly implied the extraordinary nature of the world of "fluorine". Of course, fluoropolymers, especially "Teflons", fluorosilicones, coolants/refrigerants, extinguishers, aerosols, etc., were the representative fluorochemicals commonly used in daily life. As for pharmaceutical drugs, only 5-FU was widely recognized followed by 9α-fluorohydrocortisone at that time. We started our research program from the development of (i) unique hydrocarbonylations of fluoro-olefins that would provide versatile intermediates for the synthesis of a variety of organ fluorine compounds and (ii) one-pot multistep processes exploiting the cobalt-catalyzed amidocarbonylation of aldehydes as a key unit reaction since this reaction would furnish important fundamental biochemical, i.e., N-acyl α- amino acids, from an aldehyde, amide, carbon monoxide, and hydrogen. This research program proceeded smoothly, leading to successful findings of (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-(trifluoromethy1)dihydrouracils in one step, and (iii) the hydroformylation−amidocarbonylation of fluoroolefins catalyzed by Co−Rh mixed-metal systems.

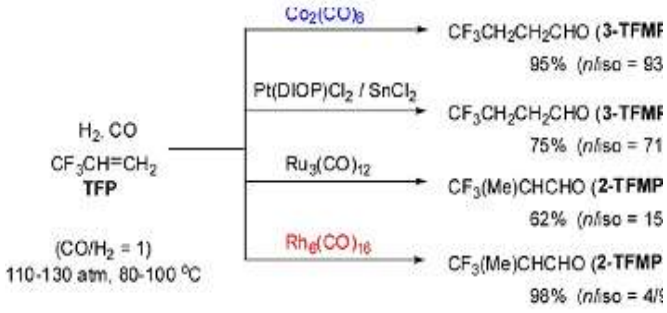
Hydroformylation of Fluoro-olefins: Hydroformylation of alkenes is important for the practical synthesis of aldehydes, and extensive studies were performed on the detailed mechanism of the reaction as well as applications to organic syntheses by the early 1980s. Little was known, however, about the reactions of alkenes bearing perfluoroalkyl or perfluoroaryl substituents when we started our investigation. It has been shown that the introduction of a trifluoromethyl or a fluoroaromatic group into organic compounds often brings about unique chemical and biological properties. Thus, the development of new synthetic methods that can introduce these fluoro groups efficiently and selectively to the desired molecules from readily available materials had an obvious significance. In this respect, commercially available fluoro-olefins such as trifluoropropene (TFP), vinyl fluoride (VF), and pentafluorostyrene (PFS) were recognized as very useful starting materials. Thus, we studied the hydroformylation of a variety of fluoro-olefins (eq 1) as one of our approaches to the functionalization of these building blocks by means of transition-metal catalysts.



(1)

Then, we found unusually high regioselectivities and a remarkable dependency of the regioselectivities of the reaction on the catalyst metal species, which was unique in

comparison with the hydroformylation of ordinary alkenes. The hydroformylation of TFP was carried out with $Co_2(CO)_8$, $Ru_3(CO)_{12}$, $Rh_6(CO)_{16}$, and PtCl, (DIOP)/SnC_{12}, 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 (Scheme 1). The reaction of TFP catalyzed by $Co_2(CO)_8$ gave (trifluoromethy)propanals (TFMPAs) in 95% yield, in which a "normal" (or linear) aldehyde, CF3CH2CH2CHO (3-TFMPA), was formed with high regioselectivity (93%). In sharp contrast with $Co_2(CO)_8$, Rhcarbonyl cluster $Rh_6(CO)_{16}$ exhibited extremely high catalytic activity and regioselectivity (96%) to give "iso" (or branched) aldehyde, CF3(CH3)CHCHO (2-TFMPA). The Pt catalyst, PtC_{l2} (DIOP)/SnC_{l2}, favored the formation of normal aldehyde (n/iso =71/29), while $Ru_3(CO)_{12}$ gave is aldehyde as the main product (n/iso =15/85). In both cases, a substantial amount of hydrogenated product, CF3CH2CH3, was formed (25−38%). Addition of PPh3 to the Co, Ru, and Rh catalysts considerably decreased the catalytic activities but somewhat increased the is aldehyde selectivity. The result made a sharp contrast to the cases of ordinary olefins, where the addition of PPh3 increased normal aldehyde se1ectivity.

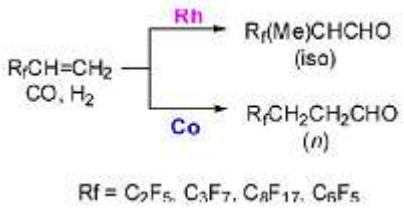


Scheme 1. Hydroformylation of TFP Catalyzed by Co, Pt, Ru, and Rh complexes

Since $Rh_6(CO)_{16}$ gave excellent regioselectivity for the formation of 2-TFMPA, several other Rh catalysts were employed and their catalytic activities as well as regioselectivity examined. The results clearly indicated that the Rh(I) complexes having chlorine as a ligand, such as RhC1(PPh3)3, were less active than $HRh(CO)(PPh_3)_3$, Rh−C, Rh4(CO)12, and $Rh_6(CO)_{16}$, but the regioselectivity was virtually the same in all cases examined. Consequently, it was concluded that the nature of the central metal of the catalyst played a key role in determining the regioselectivity of the reaction. It was noteworthy that the metal species dependency of the regioselectivity in the this reaction was remarkable compared to that reported for propene The reaction of PFS was carried out in a similar manner at 90 °C and 80 atm, using Co, Pt, Ru, and Rh catalysts. Rhodium catalysts exhibited high catalytic activity to give is aldehyde, C6F5(CH3)CHCHO (2-PFPPA), with excellent regioselectivity (97−98%) in quantitative yields, while $Co_2(CO)_8$ gave normal aldehyde (3-PFPPA) as the major product, with regioselectivity (79−90%) not as high as that observed in the reaction of TFP. The Ru catalyst, $Ru_3(CO)_{12}$, showed rather low catalytic activity (49% conversion), giving is aldehyde as the major isomer (22% yield, b/n = 74/26), accompanied by a substantial amount of hydrogenated product, $C_6F_5CH_2CH_3$ (25%). The Pt catalyst, PtC_{l2}(DIOP)/SnC_{l2}, showed a high catalytic activity (100% conversion in 4 h, 76% aldehyde yield), but virtually no regioselectivity was observed and the hydrogenation of PFS took place as a severe

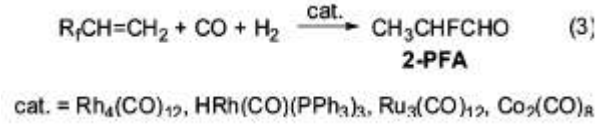
side reaction (20%). Thus, the dependency of regioselectivity on the metal species was similar to that for TFP, and the observed regioselectivity was also remarkably high compared with that reported for styrene.

In order to examine the effects of perfluoroalkyl substituents longer than the trifluoromethyl group on the regioselectivity, the reactions of other fluoro-olefins of the type Rf CH□CH2 catalyzed by $Rh_4(CO)_{12}$ were carried out, wherein Rf were C_2F_5 (PFB), C_3F_7 (HPFP), and C_8F_{17} (HPDFD) (eq 2). The reactions gave the corresponding branched aldehydes with lower regioselectivity (72−83%) than that for TFP under the standard conditions, i.e., at 80 °C and 100 atm (CO/H_2 = 1).



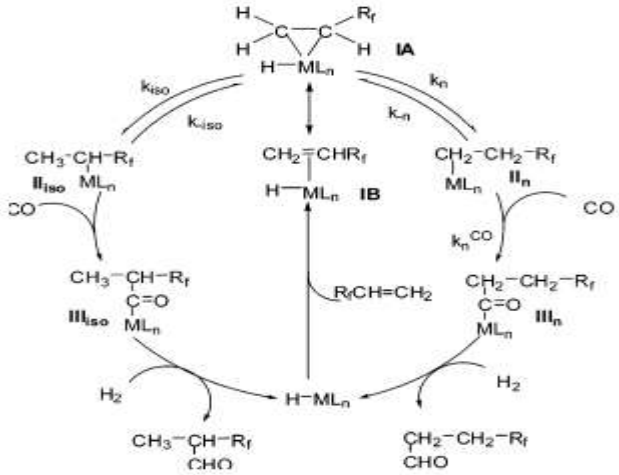
(2)

Nevertheless, higher selectivity (91−97%) was achieved when the reactions were carried out at 60 °C. The reaction of vinyl fluoride (VF) catalyzed by Rh, Ru, and Co complexes was also carried out (eq 3), which gave 3-fluoropropanal (2-FPA) exclusively regardless of the catalyst species used.



(3)

Mechanism of the Highly Regioselectivity Hydroformylation: The observed marked dependence of regioselectivity on the catalyst species was accommodated by taking into account the stability of isoalkyl−[M] species, the capability of isoalkyl− [M] species for isomerization, and the relative rate of the migratory insertion of CO into isoalkyl−[M] and n-alkyl−[M] bonds.29,30 As shown in Scheme 2, when a substituent bearing a strong "group electronegativity" is introduced into an olefin, the metal−Cα bond of a π-olefin−[M] complex (IA) should be stronger than the metal−Cβ bond because of substantial stabilization of the formal negative charge developing on Cα. Thus, the formation of isoalkyl−[M] species (IIiso) should be much more favorable than that of n-alkyl−[M] species (IIn) regardless of the group VIII transition-metal species.

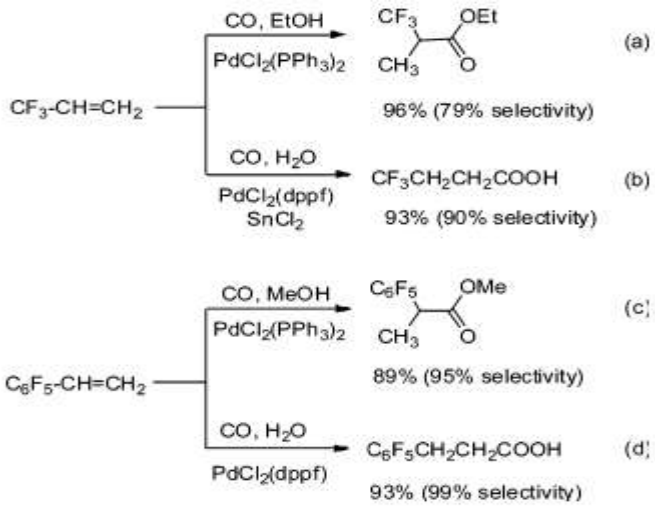


Scheme 2. Mechanism of Highly Regioselective Hydroformylation of Fluoro-olefins

The iso/n ratio of aldehydes should reflect the ratio of the intermediate iso- and n-acyl−[M] species (IIIiso and IIIn) (Scheme 2) under sufficient pressure of hydrogen. Thus, it is deduced that in the Rh-catalyzed reaction, kiso ≫ k-i and kn CO ≫ k-n, and thus the initially

formed isoalkyl−[Rh] species (IIiso, M = Rh) generates the isoacyl-[Rh] species (IIIiso, M = Rh) and gives the isoaldehyde with high regioselectivity. In sharp contrast, the rate constants in the Co-catalyzed reaction are k-n ≫ kn CO and k-i ≫ kisoCO; kn CO > kisoCO. This is because the CO insertion to IIn (M = Co) is sterically less demanding than that to IIiso (M = Co). Accordingly, the alkyl−[M] intermediates, IIiso and IIn (M = Co), should be in a pre-equilibrium, and then the reaction gives the normal aldehyde selectively. The Rh- and Co-catalyzed reactions are extremely selective cases, and the Ptand Ru-catalyzed reactions are in between the two extreme cases. In addition to these kinetic aspects, we should take into account the fundamental difference between each isoalkyl−[M] intermediate, i.e., the size of the metal and the polarizability of the metal−carbon bond. Thus, the relative stability of IIiso can be estimated to increase in the order Rf(Me)CH-CoLn < Rf(Me)CH-PtLn < Rf(Me)CHRuLn < Rf(Me)CH-RhLn. 30 It is worth noting that these mechanistic details were revealed because of the use of fluoro-olefins as unique substrates for the hydroformylation reaction. In this case, organometallic chemistry and catalysis research greatly benefited from fluorine compounds. In turn, fluorine chemistry also benefited from the discovery of highly regioselective hydroformylation processes, which provided versatile fluorinecontaining aldehydes. In fact, immediately after the discovery of highly regioselective hydroformylation of TFP by Rh-catalyzed process, I envisioned that we should be able to produce a series of "CF3-chemicals" from TFMAs.

Hydroesterification and Hydrocarboxylation of Fluoro-olefins: Hydrocarbonylations of olefins serves as a convenient method for the synthesis of the corresponding esters or carboxylic acids.22,36 Despite extensive mechanistic studies as well as applications of the reactions to organic syntheses, little attention had been paid to the reactions of fluoro-olefins before we started the investigation on this subject. The screening of typical transition-metal complexes in the hydrocarbonylations of TFP and PFS revealed that only Pd complexes with phosphine ligands showed sufficient catalytic activity to promote the reaction under the given reaction conditions.37 As Scheme 3 shows, the Pd-complex-catalyzed hydroesterification of TFP and PFS gave branched esters, Rf (Me)CHCOOR, in good to excellent regioselectivity, while the corresponding hydrocarboxylation afforded linear acids, Rf CH2CH2COOH, in excellent yield and regioselectivity. Plausible mechanisms were proposed to accommodate the observed marked difference in regioselectivity for these two reactions.



Scheme 3. Pd-Catalyzed Hydroesterification and Hydrocarboxylation of TFP and PFS

CONCLUSION: This Perspective has covered the evolution of my research endeavor on fluorine chemistry not as a specialist in this field, but as an explorer of its interfaces with multidisciplinary fields in chemistry. Laboratory started exploring the interface of fluorine chemistry and transition-metal catalysis, especially hydrocarbonylations and amidocarbonylation, which opened highly efficient synthetic routes to a variety of organofluorine compounds. Among them, CF3-containing enantiopure amino acids were successfully applied to the enzyme inhibitor design, leading to the discovery of highly potent ACE inhibitor and enkephalin analogues. This line of research brought us into the field of medicinal chemistry. Also, trifluoromethacrylic acid was the key compound for the synthesis of trifluorothymine and this process was incorporated into the commercial process for the production of antiviral drug, trifluridine. We also introduced fluorine chemistry to the "β-lactam synthon method" and demonstrated the versatile and robust utility of fluorine-containing N-acyl-β-lactams as key intermediates to a library of fluorine-containing α-hydroxyl-β- amino acids and their peptides. Through expansion of this chemistry, we synthesized novel fluorine-containing taxoids and used them as excellent probes for the identification of bioactive conformations of paclitaxel and taxoids by means of 19F NMR in solution and solid phase. We also designed and developed a series of fluorine-containing taxoids, which are highly potent in vitro and in vivo, especially against multidrug resistant tumors through strategic incorporation of fluorine for potency and metabolic stability. Thus, laboratory has been exploring the interfaces of fluorine chemistry and multidisciplinary field of research involving medicinal chemistry, chemical biology, cancer biology, and molecular imaging. When we explore new areas of research, naturally we enjoy and struggle with many "first" findings, successes, and problems.

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