学位論文

Mechanistic Study on Palladium/Phosphine-Catalyzed Reactions of Acyl Fluorides, and Its Application to a Novel Fluorination Reaction

(フッ化アシルのパラジウム/ホスフィン触媒反応に関する反応機構解明と、新規フッ素化反応への応用)

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先端化学専攻　博士後期課程

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Preface

The studies presented in this thesis have been carried out under the direction of Professor Dr. Norio Sakai at the Department of Pure and Applied Chemistry, Faculty of Science and Technology, Tokyo University of Science (RIKADAI) during 2020-2023.

The objects of this thesis are a mechanistic study on palladium/phosphine-catalyzed reactions of acyl fluorides and its application to a novel fluorination reaction of acyl fluorides.

The author hopes that this basic work described in this thesis contributes to the further development of organometallic, organic fluorine, and organic synthetic chemistry.

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2023

Contents

Abbreviations

δ	Chemical shift
Ac	Acetyl; $COCH_3$
Ar	Aryl
Bu	Butyl; C_4H_9
cat.	Catalyst
cod	1,5-Cyclooctadiene
Cy	Cyclohexyl; C_6H_{11}
dba	Dibenzylideneacetone
DCYPBz	1,2-Bis(dicyclohexylphosphino)benzene
DMAP	4-(Dimethylamino)pyridine
DMF	*N*,*N*-Dimethylformamide
DPPBz	1,2-Bis(diphenylphosphino)benzene
DPPE	1,2-Bis(diphenylphosphino)ethane
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
DPPV	*Cis*-1,2-bis(diphenylphosphino)ethene
E	Electrophile
EI	Electron ionization
EWG	Electron-withdrawing group
equiv	Equivalents
Et	Ethyl; C_2H_5
et al.	et alii; and others
FAB	Fast atom bombardment
GC	Gas chromatography
HMDS	1,1,3,3-Hexamethyldisilazane
HRMS	High-resolution mass spectrometry

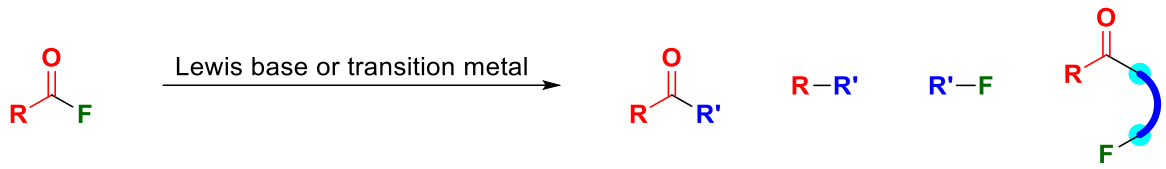
J	Coupling constant
LRMS	Low-resolution mass spectrometry
Me	Methyl; CH_3
mp	Melting point
MS	Mass spectrometry
NMP	*N*-Methylpyrrolidone
NMR	Nuclear magnetic resonance
Nu	Nucleophile
Ph	Phenyl; C_6H_5
R	Substituent
rt	Room temperature
t	Tertiary
T	Temperature
Tf	Triflyl; SO_2CF_3
THF	Tetrahydrofuran

Chapter 1.

General Introduction

1-1. Acyl fluorides as a divergent synthetic material

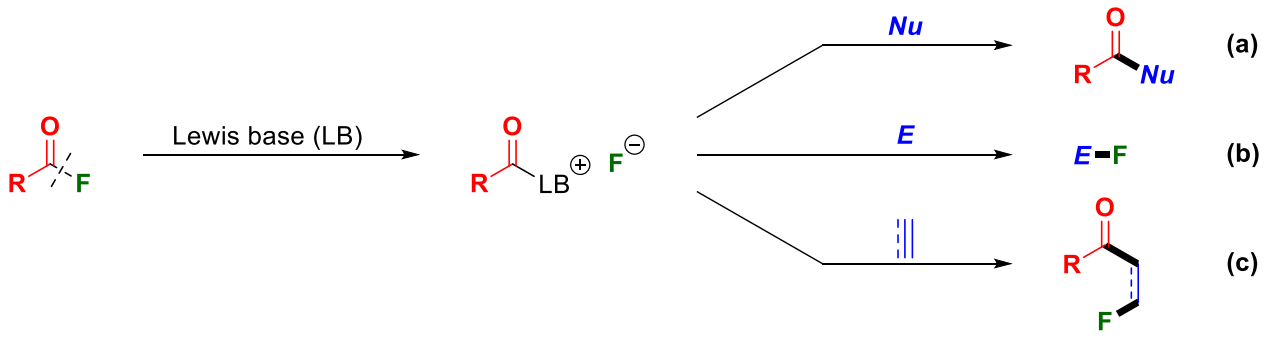
Acyl fluorides are carboxylic acid derivatives containing a fluorocarbonyl group. Because of the robust C–F bond, acyl fluorides display higher chemical stability than carboxylic acid derivatives, such as acyl chlorides and acid anhydrides.[1] On the other hand, they are more reactive than esters or amides. Such unique properties have enhanced the potential to utilize acyl fluorides as an easily-to-handled building block. For example, acyl fluorides have been traditionally used as a stable acylation reagent instead of acyl chlorides in peptide couplings, to derivatize amino acids into the corresponding amides without racemization.[2] In the last decades, further utilities of acyl fluorides have been actively explored in mainly catalyses, which revealed that acyl fluorides are a divergent synthon with the ability to provide an acyl, an aryl, and a fluorine source in the presence of a proper Lewis-base or transition-metal catalyst (Scheme 1-1).[3,4]



Scheme 1-1. Reactions of acyl fluorides in Lewis-base or transition-metal catalysis

1-1-1. Acyl fluorides in Lewis-base catalysis

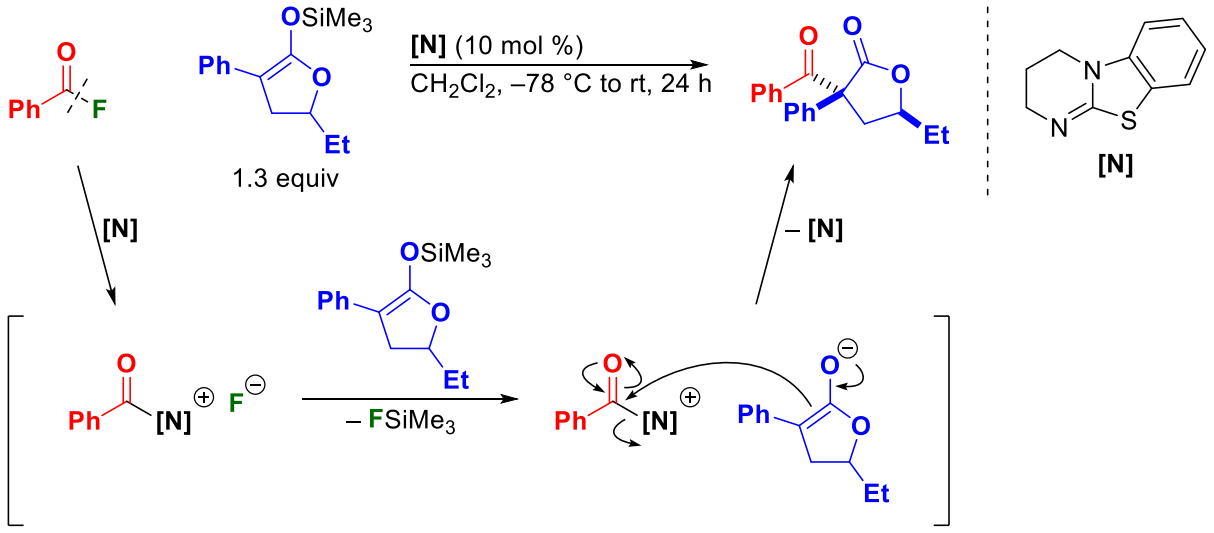
In Lewis-base-catalyzed reactions, acyl fluorides act as an acyl and a fluorine source. The reaction generally proceeds through a nucleophilic substitution to a carbonyl moiety of acyl fluorides by a Lewis base as an initiation step, generating an ion pair including a fluoride ion (Scheme 1-2). The ion pair reacts with nucleophiles, electrophiles, or unsaturated carbon–carbon bonds to be led to acylation (Scheme 1-2a), fluorination (Scheme 1-2b), or carbofluorination (Scheme 1-2c) respectively.



Scheme 1-2. Reactions of acyl fluorides in Lewis-base catalysis

1-1-1a. Acylation reaction

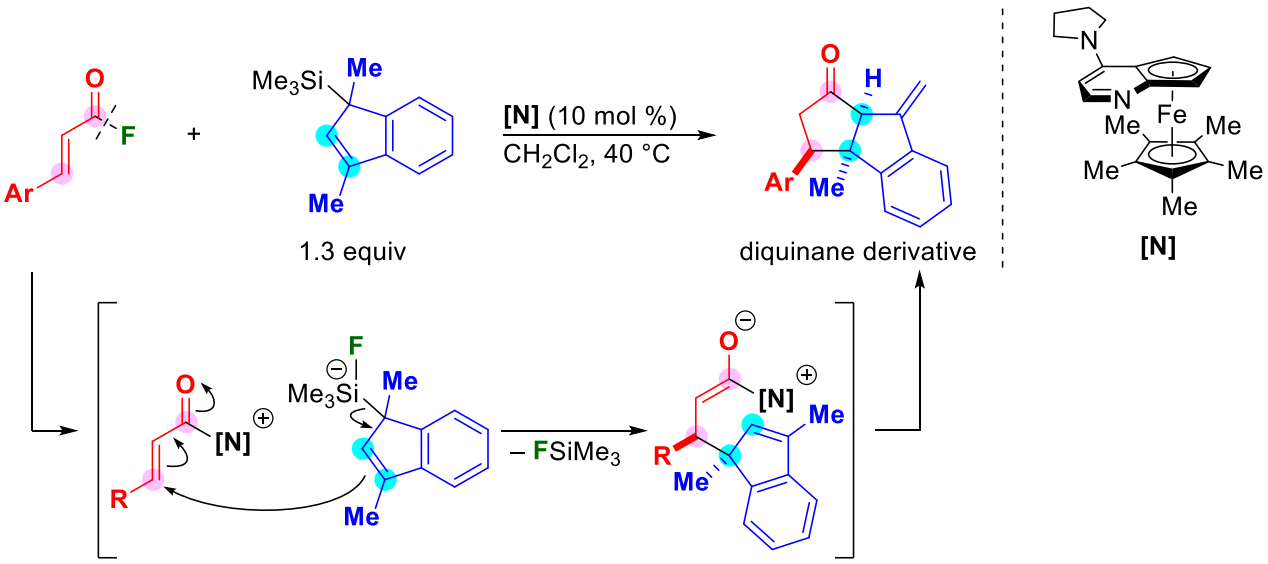
The acylation reaction as the most general reaction type provides a variety of carbonyl compounds such as ketones and esters (Scheme 1-2a).[5–11] For a simple acylation reaction, Smith *et al*. reported an isothiourea-catalyzed acylation of a ketene silyl acetal using benzoyl fluoride to give an *α*-keto-*γ*-lactone (Scheme 1-3).[5a] This reaction mechanism involves the formation of an acyl iminium fluoride from benzoyl fluoride and the isothiourea catalyst, and subsequent desilylation of the ketene silyl acetal by the fluoride ion generating a naked enolate with the release of $FSiMe_3$. Also, an enantioselective method using a thiourea derivative/pyridine catalyst was developed by Jacobsen *et al*. in the next year.[5b]



Scheme 1-3. Acylation of ketene silyl acetals by an isothiourea catalyst

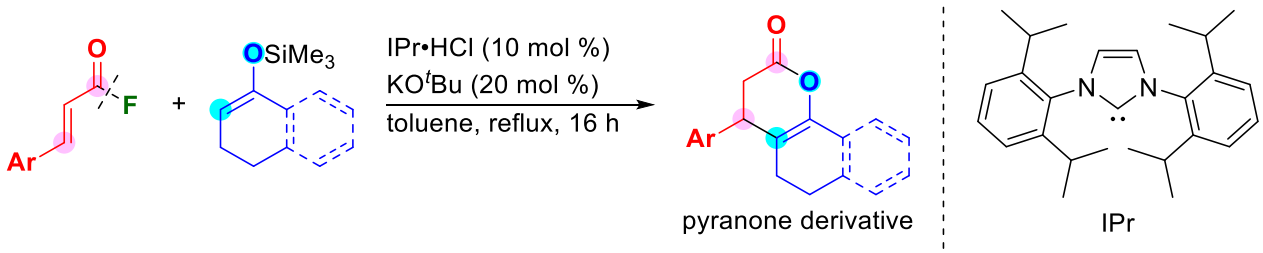
Among acylation reactions, annulation methods between *α*,*β*-unsaturated acyl fluorides and

silylated compounds utilizing the similar activation process with the dissociation of $FSiMe_3$ have been widely developed.[6–9] In 2006, Fu *et al*. initially reported a pyridine-derivative-catalyzed asymmetric [3 + 2] annulation (Scheme 1-4),[6] which is also a pioneering report of Lewis-base-catalyzed conversions of acyl fluorides. In this reaction, a combination of *α*,*β*-unsaturated acyl fluorides and silylated indenes efficiently provides diquinane derivatives that bear three contiguous stereocenters in the presence of a catalytic amount of a planar-chiral derivatives of DMAP **[N]**.



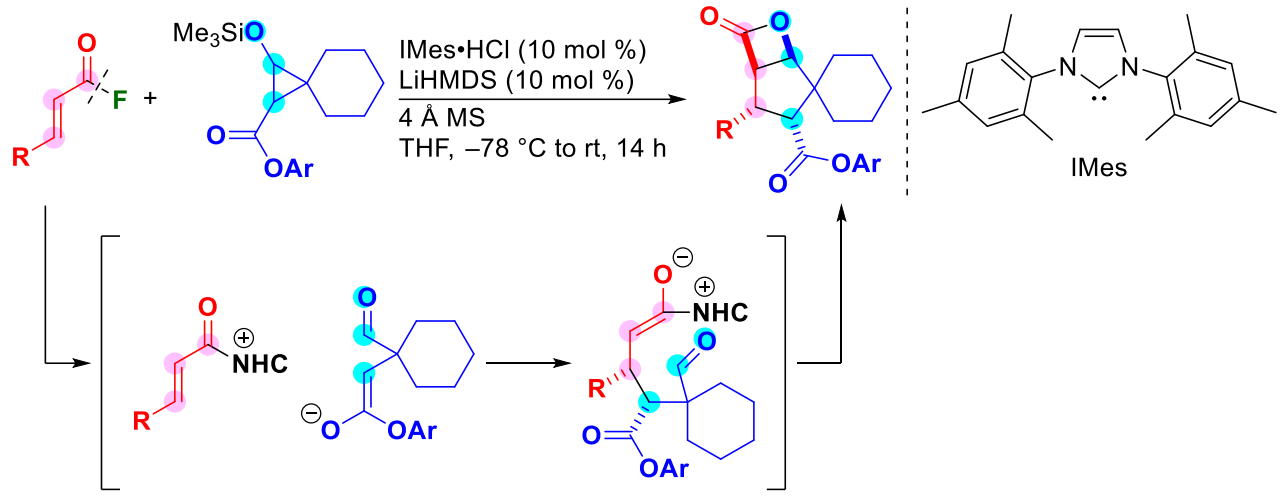
Scheme 1-4. Pioneering report of Lewis-base-catalyzed transformations of acyl fluorides

On the other hand, Lupton and co-workers have actively researched on cyclization reactions using silyl ethers to form lactone skeletons in the presence of an *N*-heterocyclic carbene (NHC) as a Lewis-base catalyst.[7–9] For example, a reaction system composed of *α*,*β*-unsaturated acyl fluorides and silyl enol ethers affords pyranone derivatives under 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) catalysis (Scheme 1-5).[7]



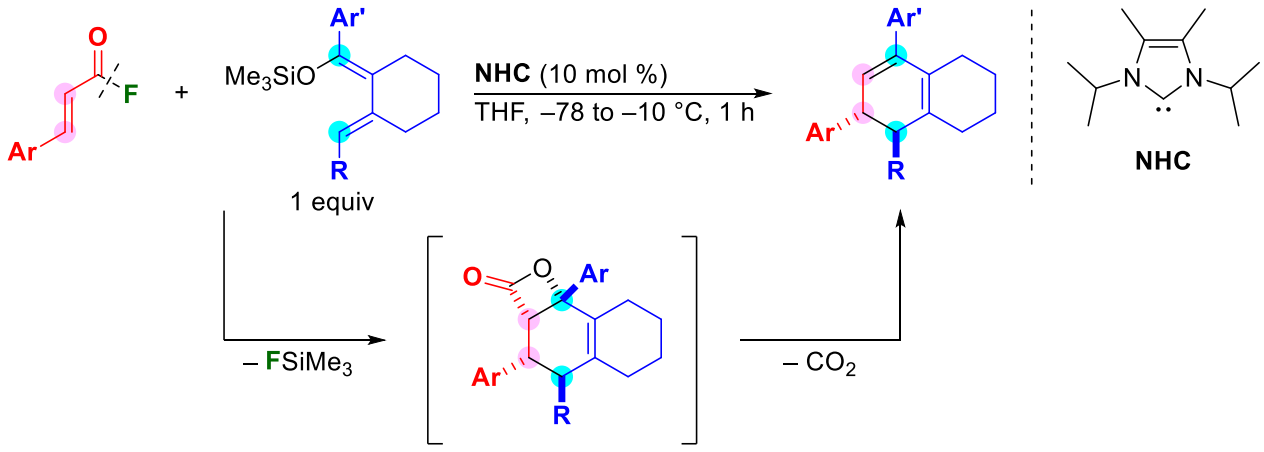
Scheme 1-5. NHC-catalyzed annulation of *α*,*β*-unsaturated acyl fluorides and enol silyl ethers

Additionally, they have developed various synthetic methods for the construction of *β*-lactone skeletons.[8] For example, was reported a [3 + 2] annulation reaction between *α*,*β*-unsaturated acyl fluorides and donor–acceptor cyclopropanes under NHC catalysis, to give *β*-lactone fused cyclopentanes (Scheme 1-6).[8a]



Scheme 1-6. NHC-catalyzed [3 + 2] annulation of *α*,*β*-unsaturated acyl fluorides and donor–acceptor cyclopropanes to form *β*-lactones

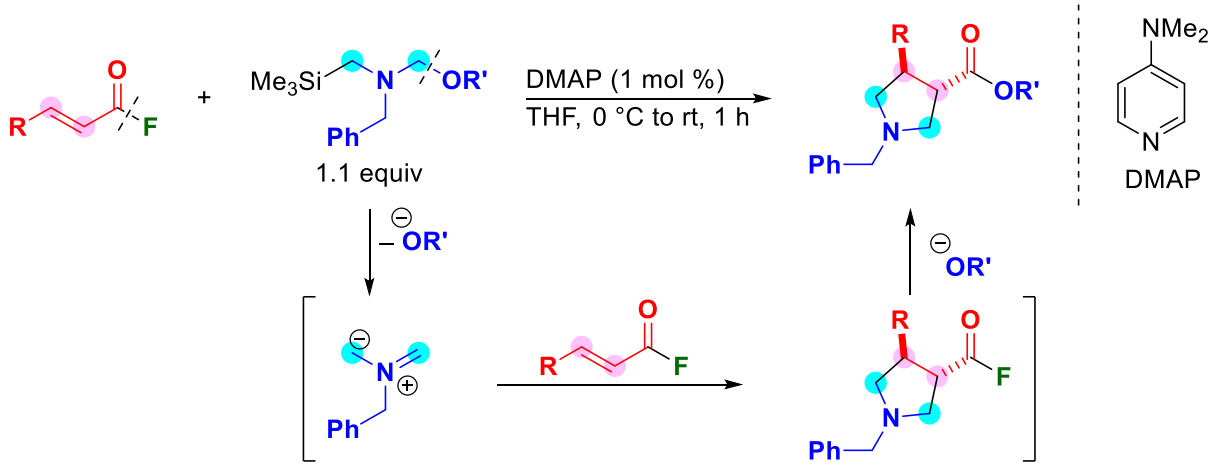
They have also established methods utilizing decarboxylation of *β*-lactones.[9] For instance, the formation of 1,3-cyclohexadiene derivatives by a [4 + 2] cycloaddition reaction of *α*,*β*-unsaturated acyl fluorides and silyl dienols through decarboxylation of *in-situ* generated *β*-lactones was found (Scheme 1-7).[9a]



Scheme 1-7. Decarboxylative [4 + 2] cycloaddition of *α*,*β*-unsaturated acyl fluorides and silyl

dienols to form 1,3-cyclohecxadienes

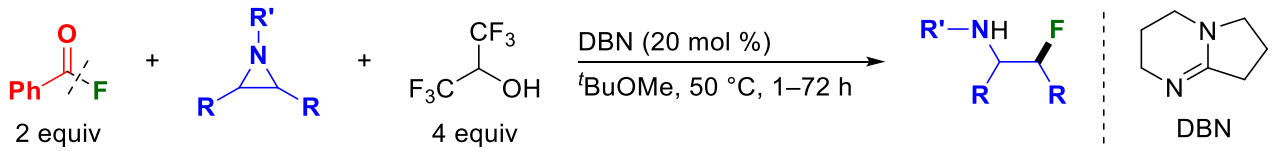
In 2012, Lupton *et al*. found a DMAP-catalyzed 1,3-dipolar cycloaddition reaction between *α,β*-unsaturated acyl fluorides and unstable azomethine ylides to provide various pyrrolidine derivatives (Scheme 1-8).[10] In this report, it was proposed that an *in-situ* generated azomethine ylide reacts with an acyl fluoride to form a cycloaddition intermediate, and the intermediate is then attacked by an alkoxylate to afford the final product.



Scheme 1-8. 1,3-Dipolar cycloaddition of azomethine ylides by DMAP catalysis

1-1-1b. Fluorination reaction

On the other hand, some fluorination reactions using acyl fluorides have been reported (Scheme 1-2b),[12,13] however, catalytic fluorination is very rare. For a representative example, Doyle *et al*. found a ring-opening fluorination reaction using an amine catalyst in 2012 (Scheme 1-9).[12a]



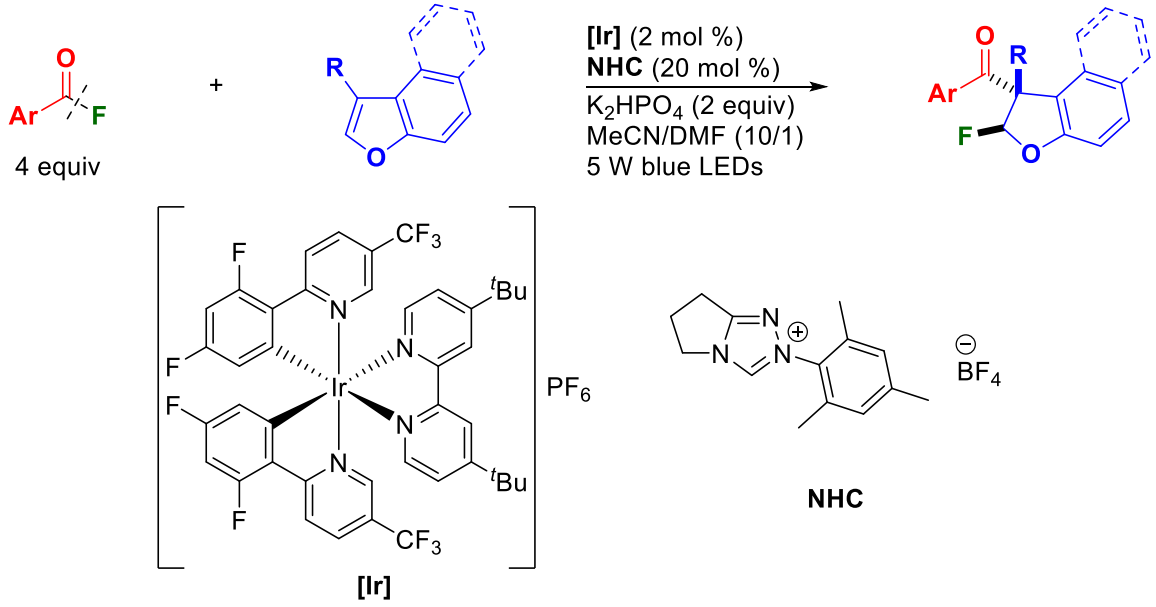
Scheme 1-9. Amine-catalyzed ring-opening fluorination of aziridines using benzoyl fluoride as a fluorination reagent

In this reaction, aziridine derivatives are regioselectively converted to *β*-fluoroamines in the

presence of 1,5-diaza[4.3.0]bicyclonon-5-ene (DBN) as a catalyst, benzoyl fluoride as a fluorinating reagent, and hexafluoroisopropanol. Although it is a Lewis-acid catalytic system, cobalt-catalyzed ring-opening fluorination reactions of epoxides and aziridines have been also developed by Doyle's group.[12b–12d]

1-1-1c. Carbofluorination reaction

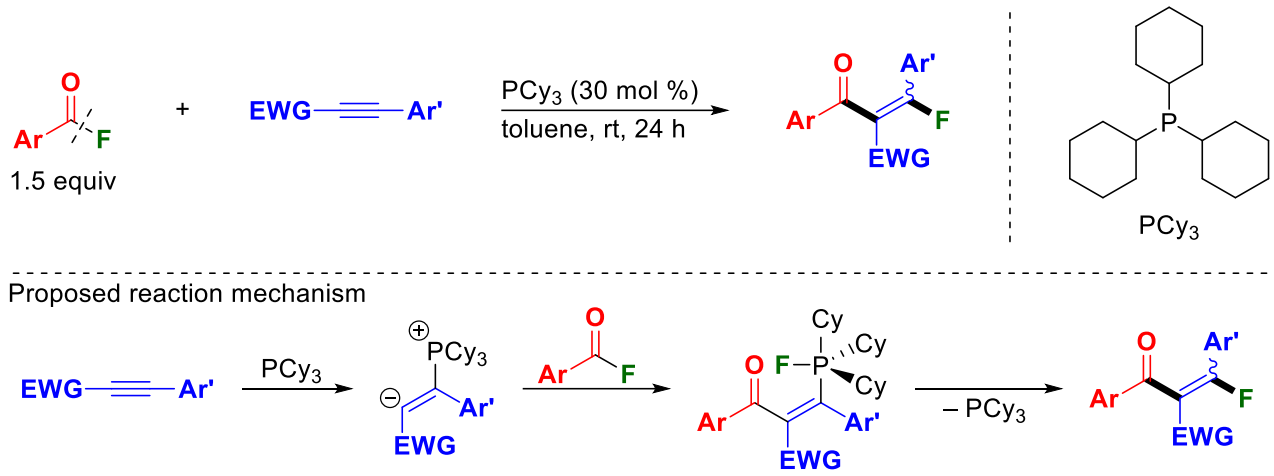
In recent years, carbofluorination reactions, that are an addition reaction of the acyl and the fluorine moiety of acyl fluorides to an unsaturated C–C bond, have been reported (Scheme 1-2c).[14] Because of both introductions of the acyl and the fluorine moiety, this type of reaction gives an atom-economical and straightforward manner. In 2022, aroylfluorination of benzofuran derivatives through reported by Studer *et al*. (Scheme 1-10),[14a] which proceeds under cooperative NHC and photoredox catalysis to furnish bifunctionalized dihydrobenzofurans.



Scheme 1-10. NHC/photoredox-catalyzed aroylfluorination of benzofurans

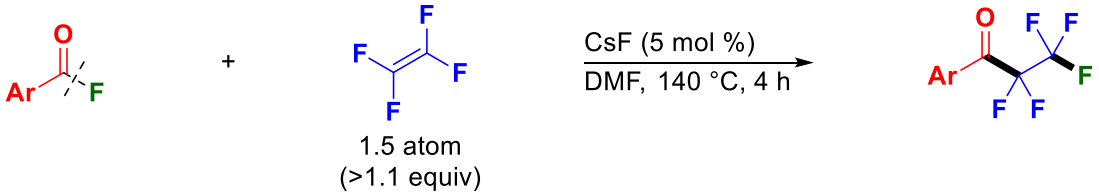
Although the nucleophilic substitution of a Lewis base into acyl fluorides is not involved, a phosphine-catalyzed acylfluorination reaction to electron-deficient alkynes has been also developed by Tobisu *et al*. in 2020, which is the first report of carbofluorination using acyl fluorides (Scheme 1-11).[14b] A reaction system composed of an aroyl fluoride, an electron-deficient alkyne,

and a catalytic amount of tricyclohexylphosphine (PCy_3) affords β-fluoro-α,β-unsaturated ketones. In this report, it is proposed that a nucleophilic addition of PCy_3 into an alkyne initially occurs to generate a carbanion species, and continuous nucleophilic acyl substitution and ligand coupling form the corresponding acylfluorinated product.



Scheme 1-11. Phosphine-catalyzed acylfluorination of electron-deficient alkynes

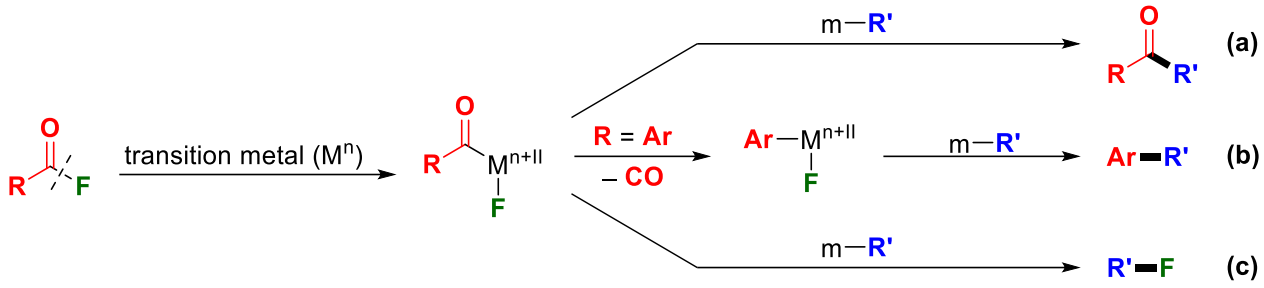
Also, CsF-catalyzed acylfluorination of tetrafluoroethylene to provide pentafluoroethyl ketones has been developed by Ogoshi *et al.* (Scheme 1-12).[14c]



Scheme 1-12. CsF-catalyzed acylfluorination of tetrafluoroethylene

1-1-2. Acyl fluorides in transition-metal catalysis

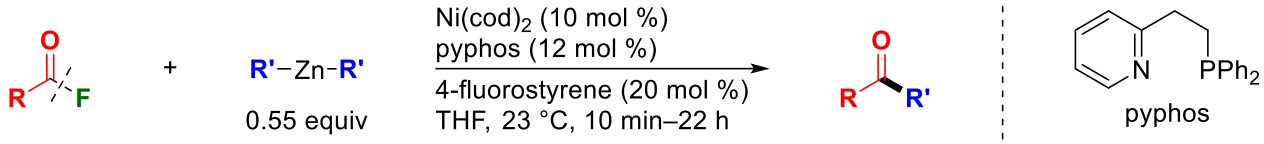
In transition-metal-catalyzed reactions, acyl fluorides behave as an acyl, an aryl, or a fluorine source. Such divergent reaction types have recently brought rapid enlargement of catalytic conversions of acyl fluorides. The difference of the reaction mode is originated from a reaction of an acyl metal fluoride species formed in an initial key step, that is oxidative addition of the acyl C–F bond to a low-valent transition metal (Scheme 1-13).



Scheme 1-13. Reactions of acyl fluorides in a transition-metal catalysis

1-1-2a. Acyl coupling

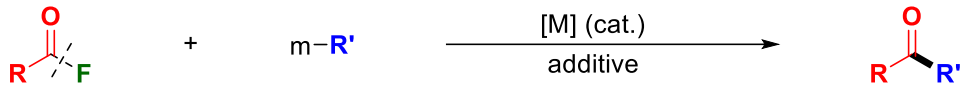
The acyl metal species reacts with organometal species to give the corresponding acylated products such as ketones (Scheme 1-13a).[15–18] For a pioneering example, in 2004, Rovis *et al.* reported the first acyl coupling using organozinc reagents under nickel catalysis and found that acyl fluorides could be applied to a transition-metal-catalyzed cross-coupling (Scheme 1-14).[15a] Several years after this report, various cross-coupling reactions have been vigorously developed.



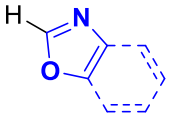
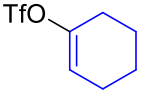
Scheme 1-14. Pioneering report of transition-metal-catalyzed transformations of acyl fluorides

Especially, acyl C–C bond formation reactions that furnish ketone derivatives have been well-researched (Table 1-1).[15b–15f] Our group has found this type of formations using various nucleophilic coupling partners, such as an organosilicon reagent,[15b] organoboron reagents,[15c] and heteroaromatic compounds,[15d] under a palladium/phosphine catalytic system. On the other hand, in 2019, Shu *et al.* developed a nickel-catalyzed reductive cross-coupling with vinyl triflates.[15f] This method provides a variety of enones from only carbon electrophiles.

Table 1-1. Transition-metal-catalyzed acyl couplings to form C–C bond

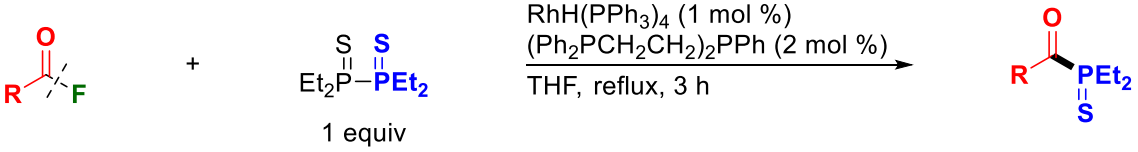


Variation of reagent combinations in C–C bond formations

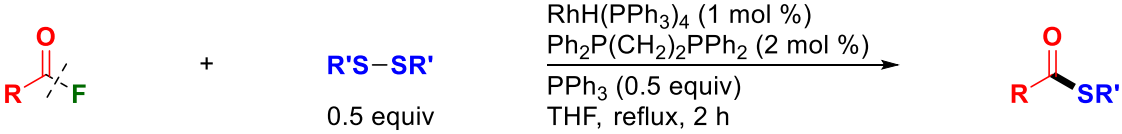
[M] (cat.):	Pd/P	Pd/P	Pd/Cu/P	Ni/N
m–R':	F_3Si—Ph	$(HO)_2B$–R'		
additive:	CsF	KF	K_2CO_3	Mn

On the other hand, acyl C–hetero atom bond formation reactions have been reported by Arisawa, Yamaguchi and co-workers (Scheme 1-15).[16]

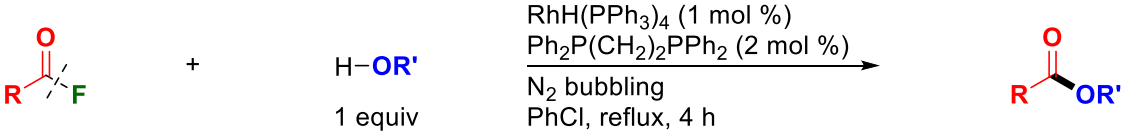
a) C–P



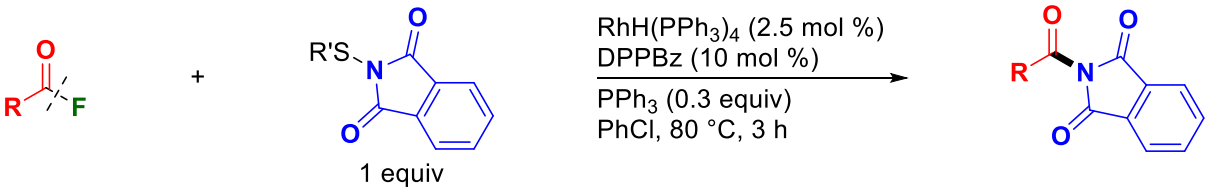
b) C–S



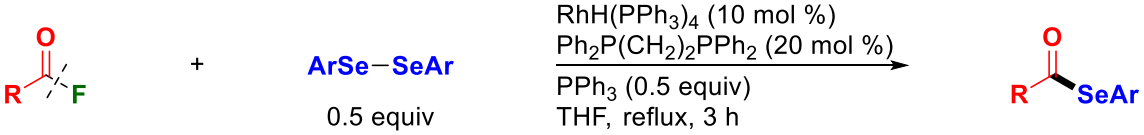
c) C–O



d) C–N



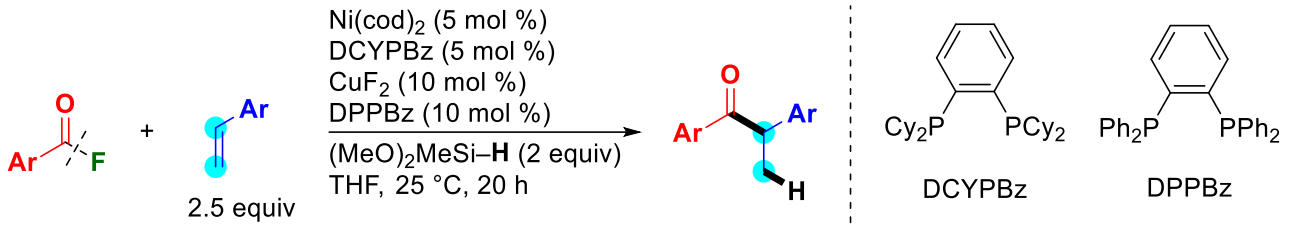
e) C–Se



Scheme 1-15. Rhodium-catalyzed acyl C–hetero atom bond formation reactions

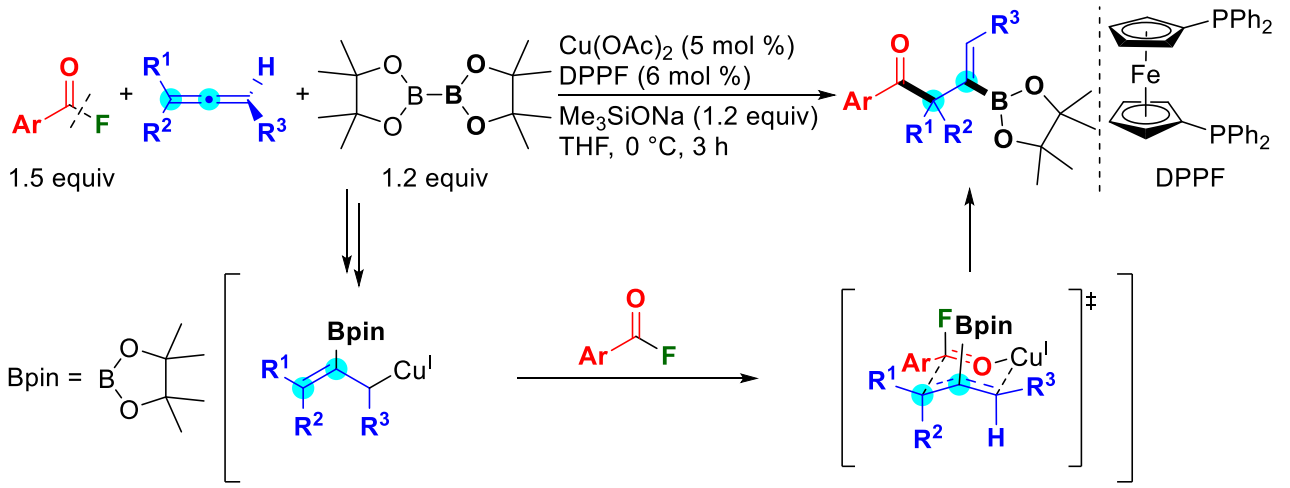
For example, a combination of acyl fluorides and a diphosphine sulfide gives acylphosphine sulfides through a C–F bond and a P–P bond cleavages by a rhodium catalyst (Scheme 1-15a).[16a] Besides, the formation of a C–S,[16b] a C–O,[16c] a C–N,[16d] or a C–Se bond[16e] using disulfides, alcohols, *N*-(organothio)phthalimides, or diselenides has been also found by them (Scheme 1-15b–e).

Also, for a three-component reaction, Sawamura *et. al.* reported a nickel-copper-catalyzed hydroacylation of vinyl arenes using a hydrosilane, forming branched ketones (Scheme 1-16).[17]



Scheme 1-16. Nickel-catalyzed hydroacylation of vinyl arenes

Although a reaction mechanism is different from the one as shown in Scheme 1-13a, a copper-catalyzed boroacylation of allenes are also known (Scheme 1-17).[18]

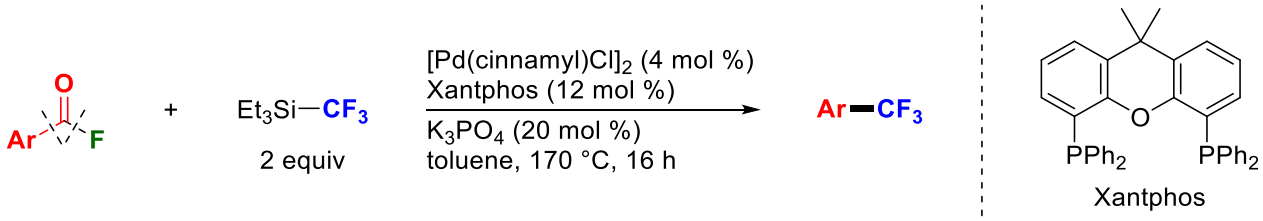


Scheme 1-17. Copper-catalyzed boroacylation of allenes

A reaction system including acyl fluorides, allenes, and a diborane affords *β*-boryl-*β*,*γ*-unsaturated ketones with the treatment of a copper/phosphine catalyst. In this reaction, mechanism involving a nucleophilic reaction of an allyl copper species with an acyl fluoride via a cyclic six-membered transient state was proposed.

1-1-2b. Decarbonylative coupling

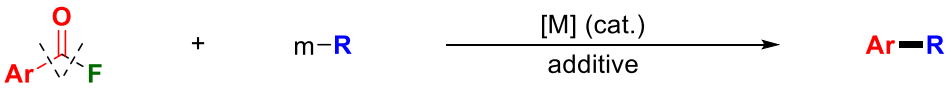
The acyl metal species can dissociate carbon monoxide from the metal center to form an aryl metal fluoride (Scheme 1-13b). This decarbonylation process provides various arylated products under palladium, nickel, or iridium catalysis.[19–21] In 2018, Schoenebeck *et al.* achieved the first decarbonylative coupling of acyl fluorides (Scheme 1-18).[19a] In this reaction, decarbonylation proceeds in the catalytic system that contains a catalytic amount of a palladium, a phosphine, and K_3PO_4 to selectively provide trifluoromethyl arenes from aroyl fluorides and a trifluoromethylsilane.



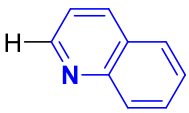
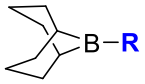
Scheme 1-18. Pioneering report of decarbonylative coupling reactions of acyl fluorides

Besides, decarbonylative C–C bond formation reactions with various combinations of a transition-metal catalyst and a coupling partner, such as organoboron reagents,[19b–19d] heteroaromatic compounds,[19e] alkynyl silanes,[19f] and a silyl cyanide,[19g] have been reported, and the variation was summarized in Table 1-2.

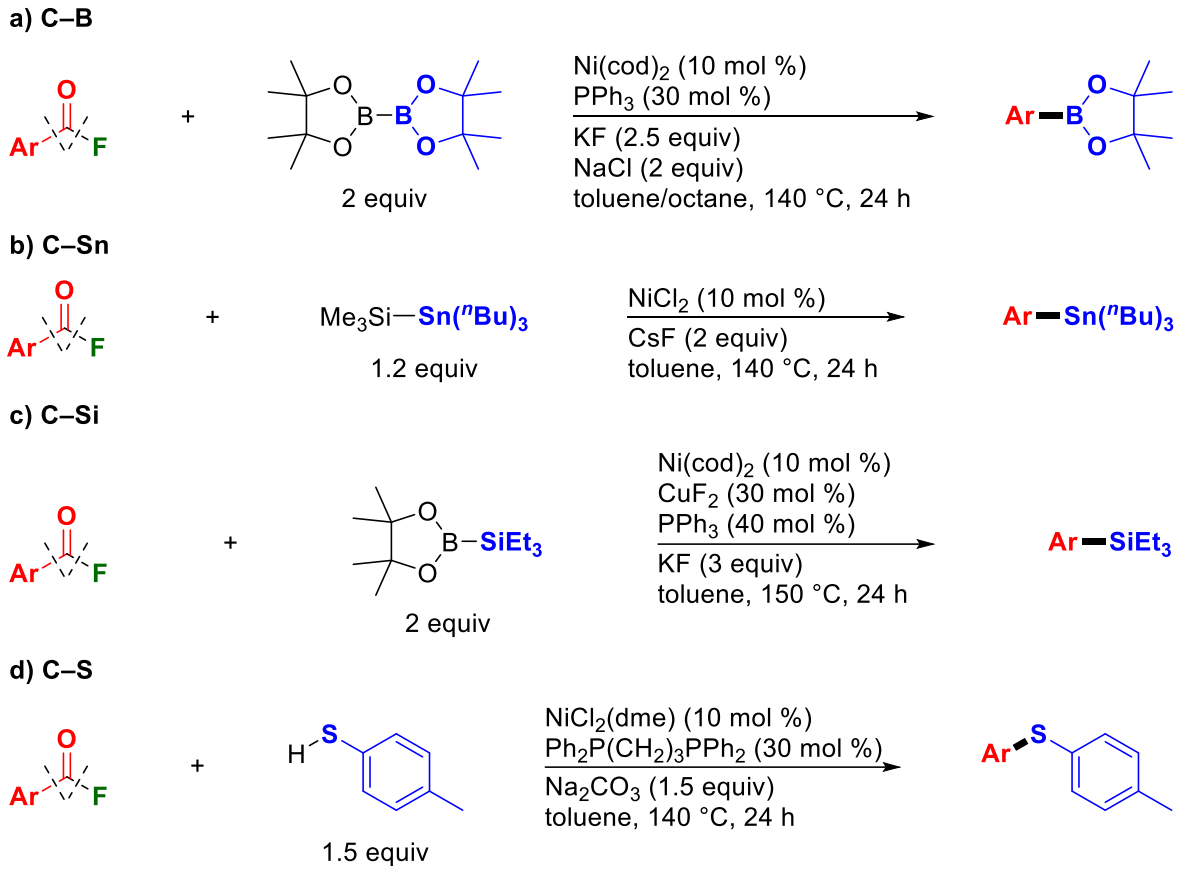
Table 1-2. Transition-metal-catalyzed decarbonylative couplings to form C–C bond



Variation of reagent combinations in C–C bond formations

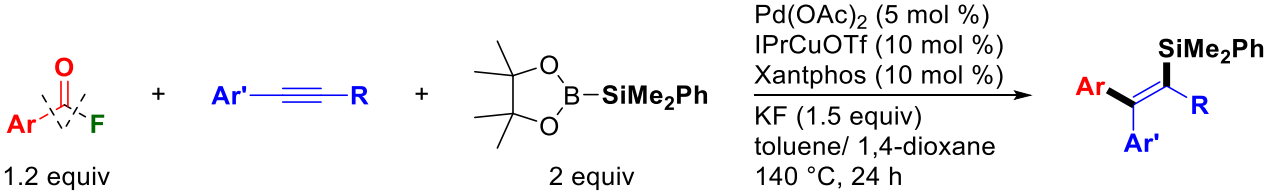
[M] (cat.):	Ni/P	Ir/P	Pd/Cu/P	Pd/P	Pd/P
m–R:	R'_2B–R		Me_3Si—≡—R'		Me_3Si—CN
additive:	—	—	—	KF	NaI

On the other hand, decarbonylative C–hetero atom bond formation reactions,[20] such as a C–B,[20a,20b] a C–Sn,[20c,20d] a C–Si,[20e] and a C–S bond formation,[20f] have been developed (Scheme 1-19). This type of strategy offers an aryl organometallic reagent used in cross-couplings for the formation a new aryl C–C bond.



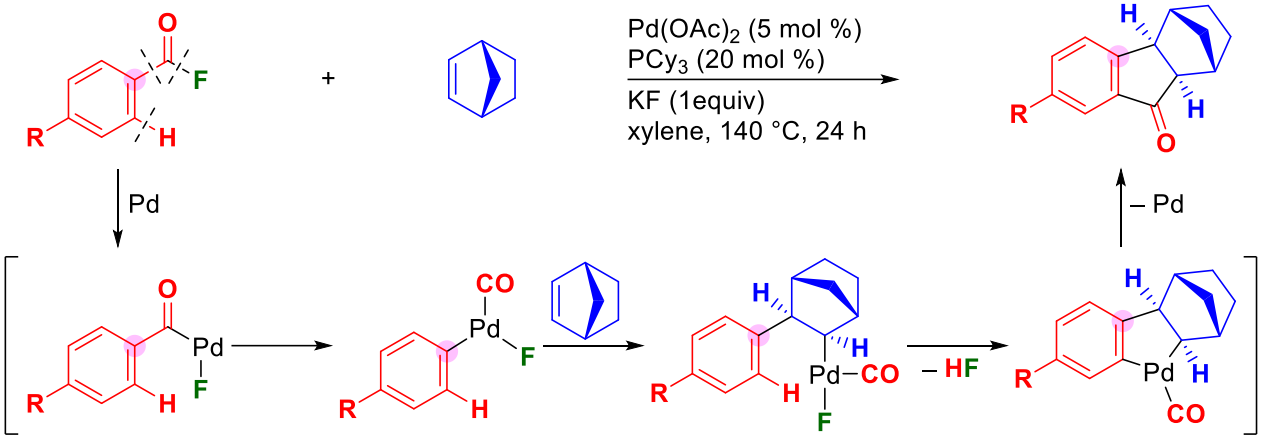
Scheme 1-19. Representative example of transition-metal-catalyzed decarbonylative C–hetero atom bond formation reactions

Furthermore, Nishihara *et al*. developed an arylsilylation reaction of internal alkynes as a three-component coupling reaction, which provides tetrasubstituted alkenylsilanes through a C–Si and a C–C bond formation by using a palladium/copper cocatalyst (Scheme 1-20).[21]



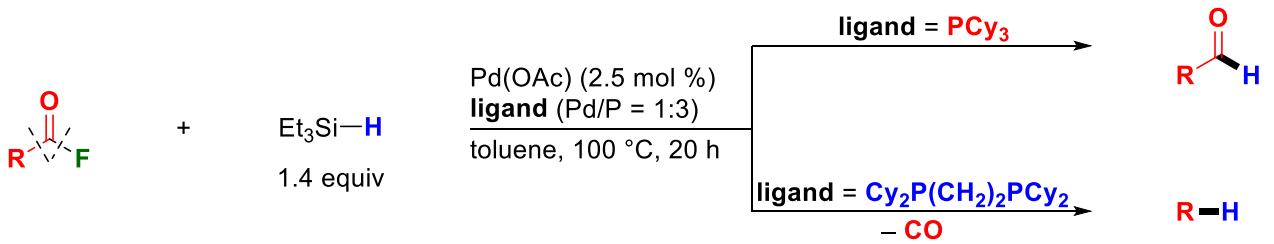
Scheme 1-20. Palladium/copper-cocatalyzed arylsilylation of internal alkynes

For another reaction type of decarbonylation, our group has developed a palladium-catalyzed annulation of aroyl fluorides with norbornene via decarbonylation and reinsertion of carbon monoxide (Scheme 1-21).[22] This method provides a variety of polycyclic ketones with a transfer of a carbonyl moiety of aroyl fluorides to the *ortho*-position. In this reaction, it was suggested that the generation of a metal-carbonyl species arising from the decarbonylation of the substrate is involved.



Scheme 1-21. Palladium-catalyzed annulation of acyl fluorides with norbornene via decarbonylation and insertion of carbon monoxide

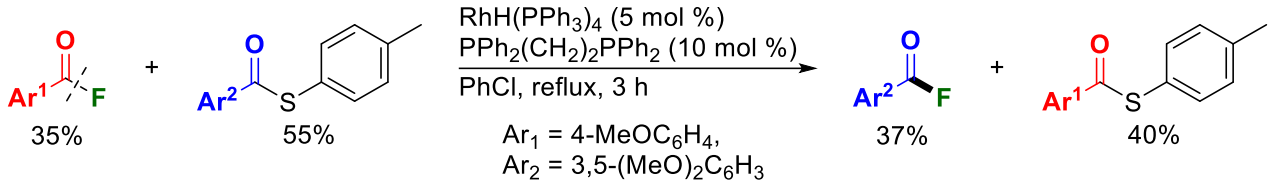
Additionally, our group has found a palladium-catalyzed C–H bond formation reaction using a hydrosilane. Control of decarbonylation of acyl fluoride was achieved by a change of only a phosphine ligand, and aldehydes or arenes were selectively synthesized (Scheme 1-22).[23] When PCy_3 was used as a monodentate phosphine ligand, aldehydes were obtained. In contrast, the use of $Cy_2P(CH_2)_2PCy_2$ as a bidentate phosphine ligand provides arenes via decarbonylation.



Scheme 1-22. Palladium-catalyzed reductive conversion of acyl fluorides with a hydrosilane via ligand-controlled decarbonylation

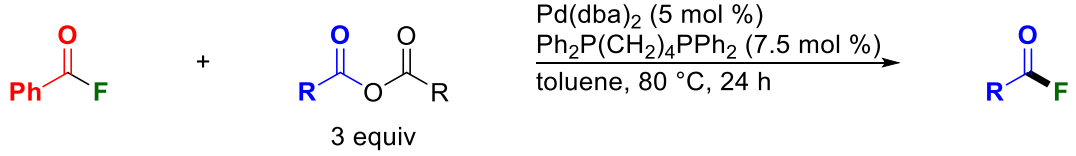
1-1-2c. Fluorination reaction

If the fluorine moiety of the metal fluoride species generated from acyl fluorides is introduced into a carbon framework, an organic fluorine compound is afforded (Scheme 1-13c). In 2011, Arisawa, Yamaguchi and co-workers initially reported a method to catalytically utilize acyl fluorides as a fluorine source, in which an acyl transfer reaction between an acyl fluoride and a thioester progress under a rhodium/phosphine catalytic system to afford another acyl fluoride in equilibrium (Scheme 1-23).[16b] Aside from this example, some cases using an ester,[16c] an acylphosphine sulfide,[16c] and an amide[16d] have been also demonstrated by them.



Scheme 1-23. Pioneering report of transition-metal-catalyzed fluorination using acyl fluorides

Our group has also developed a palladium/phosphine-catalyzed acyl-group exchange reaction (Scheme 1-24).[24] This method offers more complex and value-added acyl fluorides from acid anhydrides and the commercially available benzoyl fluoride.



Scheme 1-24. Palladium/phosphine-catalyzed acyl-group exchange reaction between acid anhydrides and benzoyl fluoride

However, the introduction of the fluorine moiety of the metal fluoride into organic molecules has been still a challenging issue,[25] and the fluoro group mainly acts as a leaving group at the present stage.

As mentioned above, the utility of acyl fluorides as a synthetic intermediate such as a carbon

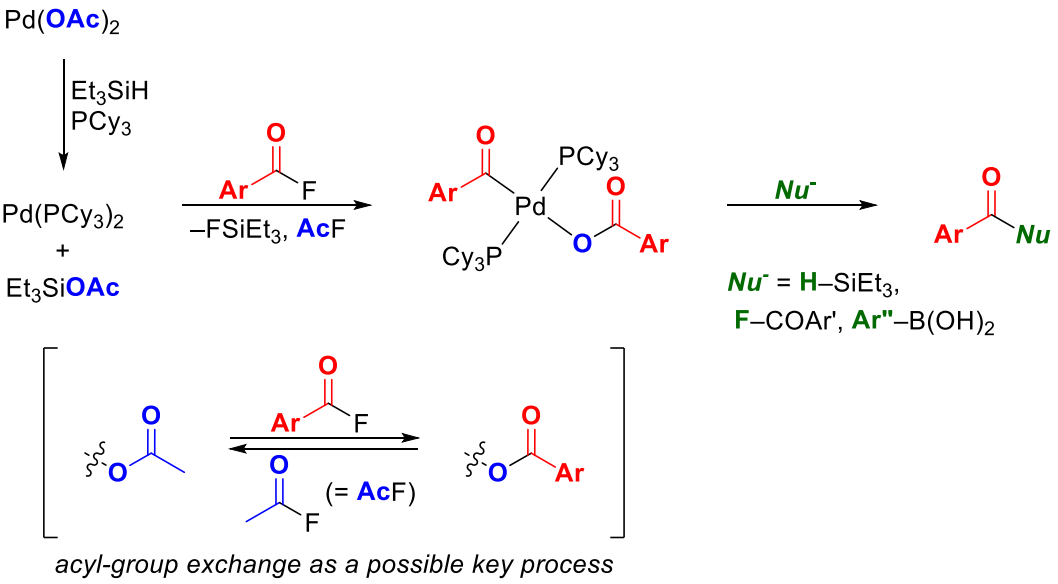
electrophile has been greatly extended in the last decade. However, further finding on a unique reaction of acyl fluorides is still an important issue. Especially, although a series of catalytic fluorination reactions has displayed the potential of utilization of acyl fluorides as an easily-to-handled, stable and facile available organic fluorination reagent, the reaction substrate that can be applied to the fluorination has been still limited whether the catalyst is a Lewis base or a transition metal.

In addition, regarding transition-metal-catalyzed conversions of acyl fluorides, experimental mechanistic insight has yet remained narrow and insufficient despite vigorous development. To also design novel catalytic transformation of acyl fluorides, it is significant to reveal an elementary process of the existing reactions.

1-2. This work

In this thesis, the author will describe a mechanistic study on palladium/phosphine-catalyzed conversions of acyl fluorides (Chapter 2) and its application to a fluorination reaction (Chapter 3).

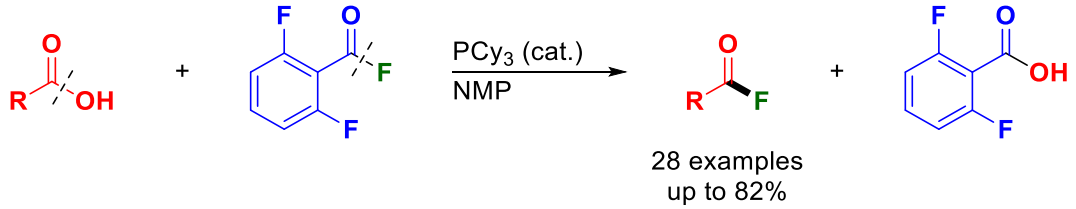
In Chapter 2, will be described the formation of benzoyl(benzoato)palladium complexes via a stoichiometric reaction between benzoyl fluorides, $Pd(OAc)_2$, a hydrosilane and a phosphine. NMR studies of the acyl palladium complex revealed the generation mechanism of the palladium complex involving an acyl-group exchange between acyl fluorides and an acetate group in the presence of a phosphine. And more, it was indicated that the complex is a reaction intermediate in a palladium-catalyzed reduction of acyl fluorides using a hydrosilane. Furthermore, the acyl(carboxylato)palladium complex provides some acylated products through a stoichiometric reaction with a coupling partner. This study is the first to experimentally investigate a reaction mechanism on a palladium-catalyzed reaction of acyl fluorides (Scheme 1-25).[26]



Scheme 1-25. Formation and reactivity of acyl(carboxylato)palladium complexes in stoichiometric reactions of acyl fluorides

In Chapter 3, will be described a phosphine-catalyzed acyl-group exchange reaction between carboxylic acids and an aroyl fluoride. Based on the phosphine-promoted acyl-group exchange

between acyl fluorides and carboxylate compounds found in Chapter 2, the author attempted its application to a catalytic fluorination of carboxylic acids to prepare acyl fluorides. Consequently, it was revealed that a combination of PCy_3 as a catalyst and 2,6-difluorobenzoyl fluoride is the best conditions for the acyl-group exchange. This method directly provided a wide variety of acyl fluorides from carboxylic acids in reasonable yields. This reaction is the first example of the synthesis of acyl fluorides from carboxylic acids utilizing an acyl fluoride as a fluorination reagent in the presence of only a phosphine catalyst (Scheme 1-26).[27]



Scheme 1-26. Phosphine-catalyzed acyl-group exchange reaction between carboxylic acids and an aroyl fluoride

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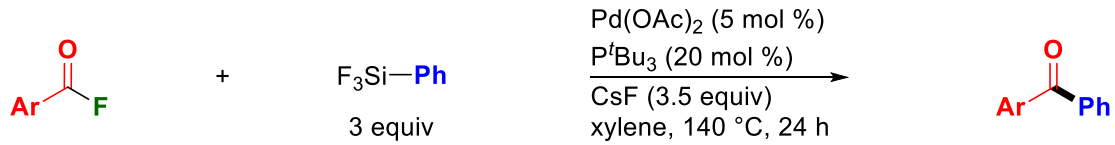
Chapter 2.

Mechanistic Study on Palladium/Phosphine-Catalyzed Reactions of Acyl Fluorides

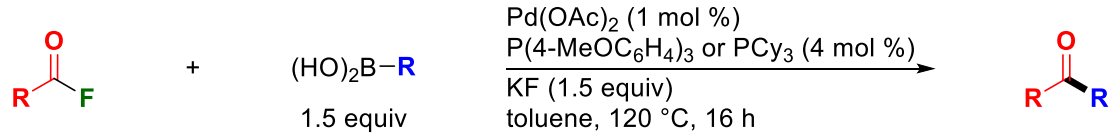
2-1. Introduction

Our group has reported several palladium/phosphine-catalyzed transformations of acyl fluorides via C(acyl)–F bond cleavage as a key step in several reactions (Scheme 2-1):[1]

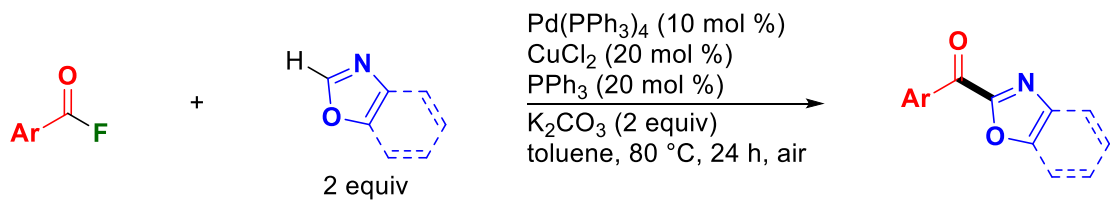
a) Organoslicon reagent



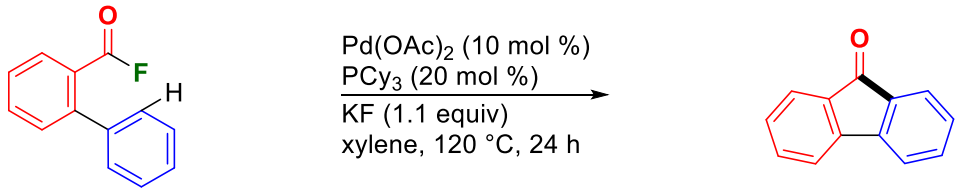
b) Organoboron reagent



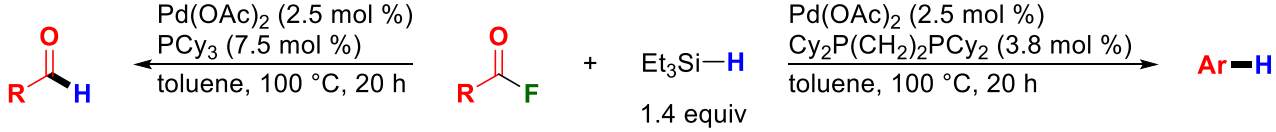
c) Hetroaromatic C–H bond



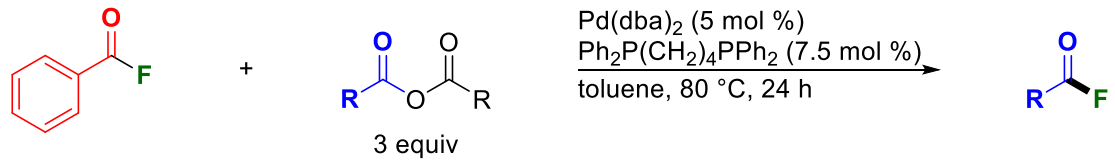
d) Intramolecular aromatic C–H bond



e) Hydrosilane

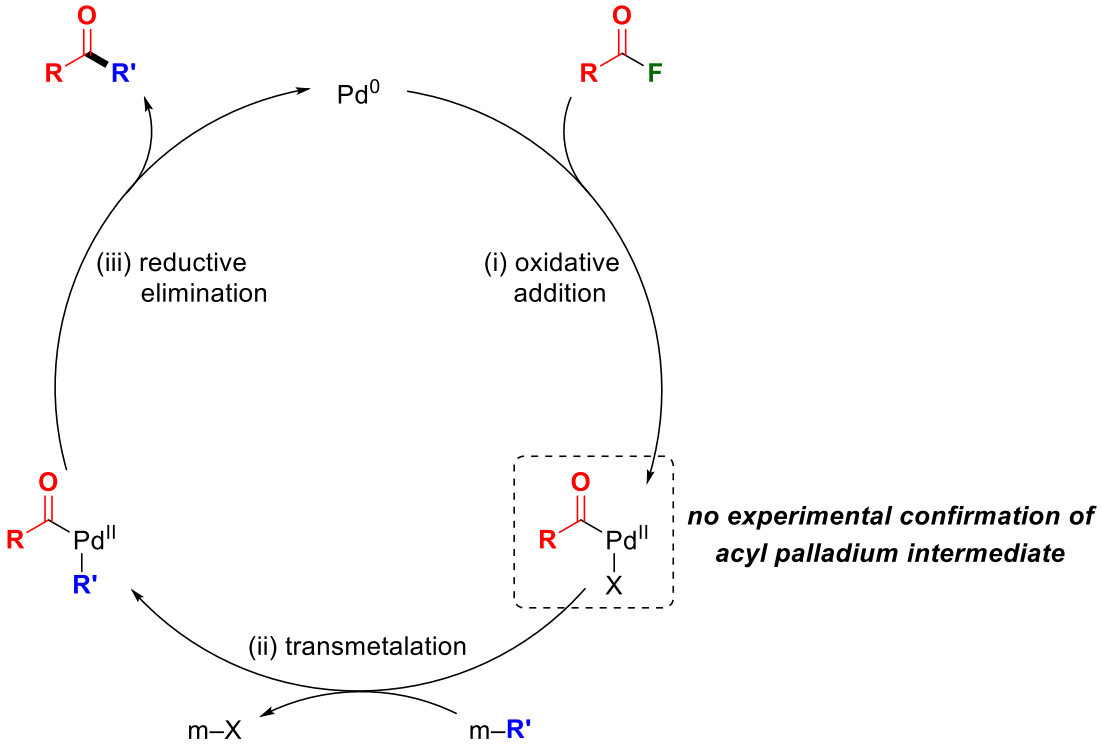


f) Acid anhydride



Scheme 2-1. Palladium-catalyzed coupling reactions of acyl fluorides (our previous works)

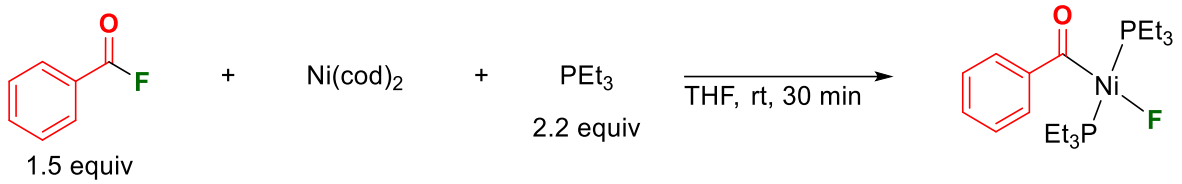
cross-coupling reactions with an organosilicon reagent (Scheme 2-1a),[1a] organoboron reagents (Scheme 2-1b),[1b] or aromatic C–H bonds (Scheme 2-1c and Scheme 2-1d)[1d,1g] (an acyl source); selective reduction with a hydrosilane (Scheme 2-1e) (an acyl and an aryl source);[1c] and, acyl-exchange reactions with acid anhydrides (Scheme 2-1f) (a fluorine and an acyl source).[1e] In these palladium-catalyzed reactions, acyl fluorides behave mainly as an acyl source with a reaction mechanism that is assumed to resemble the following known cross-coupling reactions using carboxylic acids (Scheme 2-2): (i) oxidative addition of acyl fluorides to Pd(0), which forms an acyl palladium intermediate; (ii) transmetalation between acyl palladium species and organometallic reagents; and, (iii) reductive elimination to form the desired acyl product and to regenerate the Pd(0).



Scheme 2-2. A general mechanism for Pd-catalyzed reactions of acyl fluorides as the acyl source

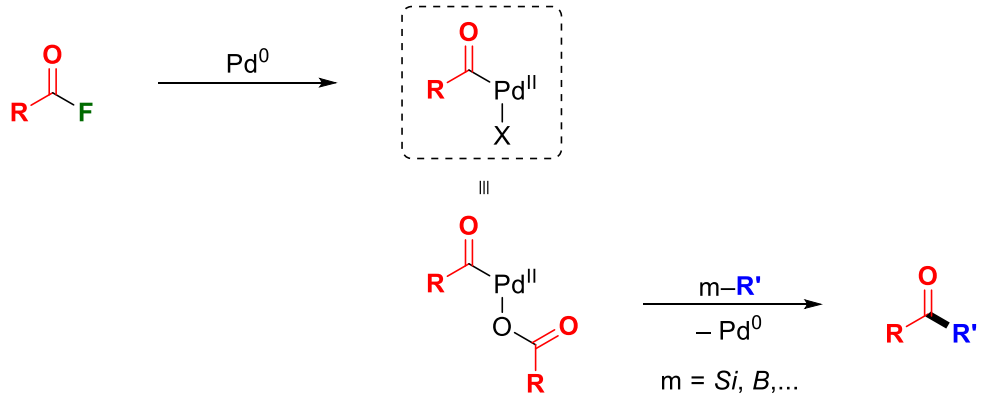
However, step (i), the formation of the acyl palladium intermediate from acyl fluorides and the Pd(0), has not been obvious though several mechanistic studies were performed including the DFT calculation for the ligand-selective C–H bond formation.[2] In the research, an acyl palladium fluoride, an oxidative-addition product of the acyl fluoride to the Pd(0), has been proposed as a key

intermediate. The actual reaction intermediate is uncertain, however, because no direct observation has been reported that the acyl fluoride and a low-valent palladium complex form an organopalladium complex (Scheme 2-2). Demonstration of a related organometallic intermediate in transition-metal-catalyzed transformations of acyl fluorides has been limited to nickel, in which an acyl nickel fluoride was isolated as a key intermediate via the oxidative addition of acyl fluorides to Ni(0) (Scheme 2-3).[3]



Scheme 2-3. Direct observation of oxidative addition of an acyl fluoride to a nickel (0)

Herein, the author found the reaction of acyl fluorides with a Pd(0) species to provide acyl(carboxylato)palladium complexes in the formation of an organopalladium complex (Scheme 2-4). The author also investigated the reactivity of the acyl palladium complexes with organometallic reagents such as hydrosilane and boronic acid. This study is the first to experimentally confirm a reaction intermediate for palladium-catalyzed transformations of acyl fluorides.



Scheme 2-4. Formation and reactivity of acyl(carboxylato)palladium complexes from Pd(0) and acyl fluorides (**this work**)

2-2. Results and Discussion

2-2-1. Observation of a reaction intermediate in the reduction of acyl fluorides

In our related previous research, a $Pd(OAc)_2$/phosphine catalytic system was often appropriate for the conversion of acyl fluorides.[1a–1c,1f,1g] Among them, the author selected the $Pd(OAc)_2/PCy_3$-catalyzed C–H bond formation reaction leading to aldehydes using a hydrosilane as a model reaction,[1c] because it proceeded using a combination of facile reactants under mild reaction conditions (Scheme 2-1e).

Initially, to observe the chemical behavior of each catalysis species in the palladium-catalyzed conversion of acyl fluorides, the time-course of the model reaction was monitored via ^{31}P NMR (Figure 2-1).

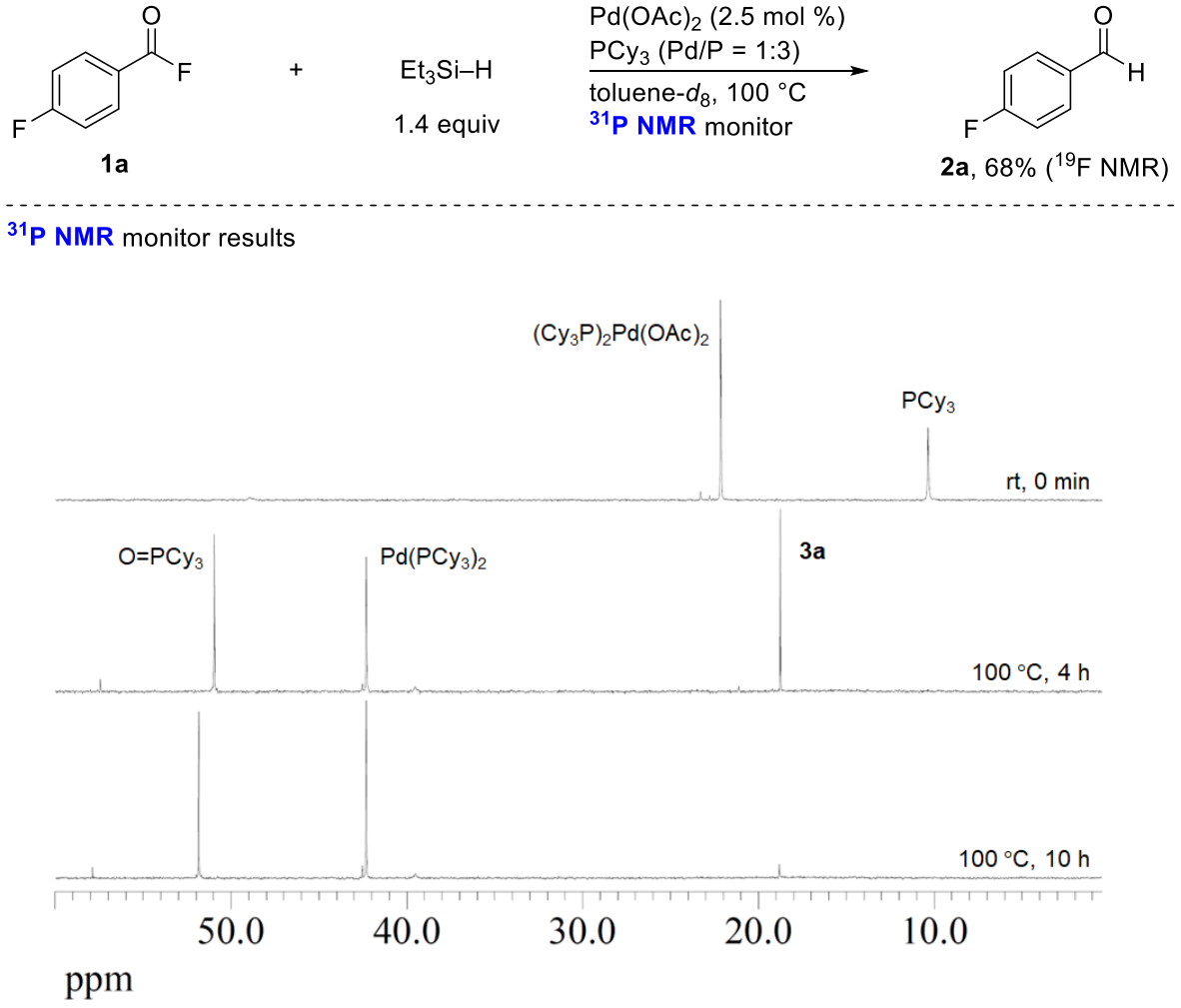


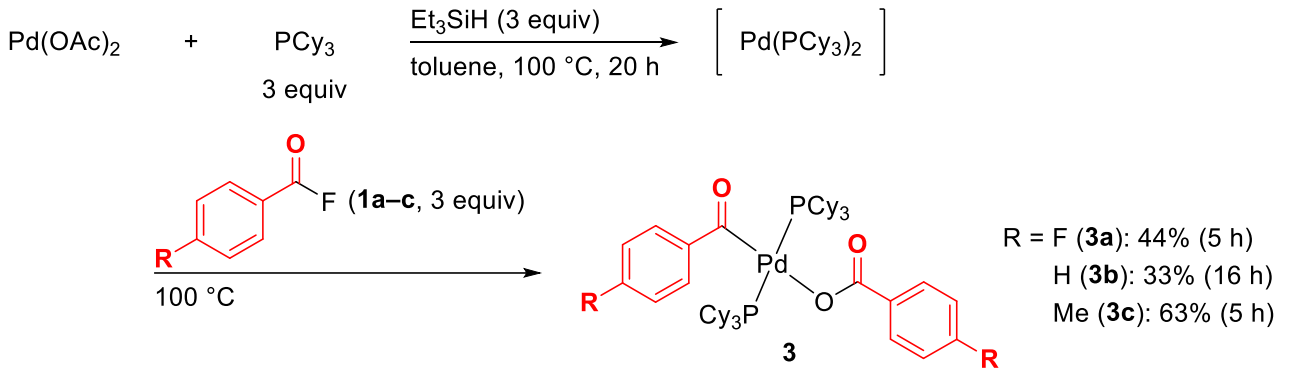
Figure 2-1. ^{31}P NMR time-course reaction monitoring of the $Pd(OAc)_2/PCy_3$-catalyzed reduction of an acyl fluoride.

For this reaction, 4-fluorobenzoyl fluoride (**1a**) and Et_3SiH were treated with a catalytic amount of $Pd(OAc)_2$ and PCy_3 in toluene-d_8, and the mixture was then heated at 100 °C. The signals of $(Cy_3P)_2Pd^{II}(OAc)_2$ (22.1 ppm)[4] and PCy_3 (10.4 ppm) were observed in the initial step. When the reaction mixture was then heated at 100 °C for 4 h, these signals disappeared and were replaced by two signals derived from $Pd^0(PCy_3)_2$ (42.3 ppm),[4b,5] and $O{=}PCy_3$ (50.0 ppm) and one new signal (18.9 ppm) from an unknown complex, which is referred to as **3a**. With further heating, the signal that corresponded to the unknown **3a** was completely consumed, and the signals of $Pd(PCy_3)_2$ and $O{=}PCy_3$ remained. Then, the corresponding aldehyde **2a** was produced in a 68% ^{19}F NMR yield. Consequently, it was presumed that complex **3a** must have been a catalytic intermediate of the model reaction.

To identify a structure of complex **3a**, isolation of complex **3a** was examined through a stepwise stoichiometric reaction (Scheme 2-5). To a solution of $Pd(OAc)_2$ and PCy_3 in toluene Et_3SiH was added, and the mixture was then treated at 100 °C for 20 h to generate $Pd(PCy_3)_2$, which is a zero-valent palladium species. Subsequently, 3 equiv of acyl fluoride **1a** was added, and the mixture was further heated at 100 °C for 5 h, isolating complex **3a** in a 44% yield. X-ray diffraction of a single crystal of **3a** unambiguously confirmed it to be a *trans*-bis(tricyclohexylphosphine)acyl(carboxylato)palladium complex (Figure 2-2).[6] The X-ray structure of **3a** revealed the following characteristics: (i) a square-planar geometry around the Pd atom; (ii) four coordination involving two molecules of PCy_3 and two anionic ligands, the 4-fluorobenzoyl group and the 4-fluorobenzoate group, at a *trans*-geometry; and, (iii) an η^1-type coordination of the 4-fluorobenzoate group to Pd. Also, ^1H, ^{13}C, ^{19}F and ^{31}P NMR spectroscopic data and the mass number were fully consistent with the structure obtained by X-ray crystallography. For instance, in the ^{19}F NMR spectrum, two singlets were observed at –112.0 and –107.5 ppm with an integral ratio of 1:1. Both signals were displayed in the C(aryl)–F region,[7] which exhibited the two different 4-fluorophenyl moieties. In the ^{31}P NMR spectrum, only one singlet arose at 18.9 ppm, indicating two equivalent PCy_3 ligands of **3a**.

Treating benzoyl fluoride (**1b**) in a similar manner for 16 h, provided benzoyl(benzoato)palladium

complex **3b** in a 33% isolated yield (Scheme 2-5). When 4-methylbenzoyl fluoride (**1c**) was employed for 5 h, the corresponding acyl(carboxylato)palladium complex **3c** successfully formed in a 63% yield.



Scheme 2-5. Synthesis of acyl(carboxylato)palladium complexes

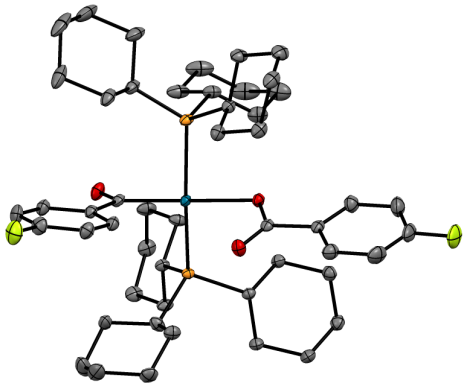


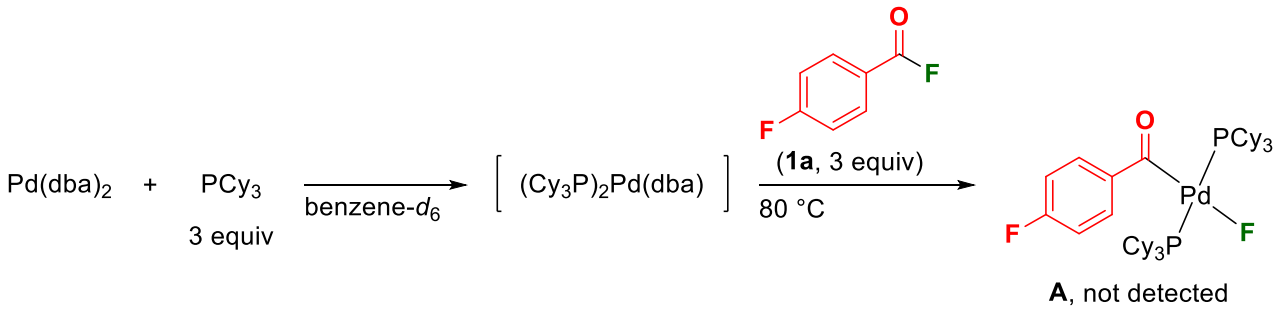
Figure 2-2. ORTEP drawing of complex **3a**.

2-2-2. Investigating the formation of acyl(carboxylato)palladium

As predicted based on the molecular structure of acyl(carboxylato)palladium complex **3** (Figure 2-2), two acyl moieties were induced from acyl fluoride **1**, but the origin of the O(carboxylate) atom bounded the Pd center remains elusive. Therefore, we next investigated the generation mechanism of acyl(carboxylato)palladium complex **3**.

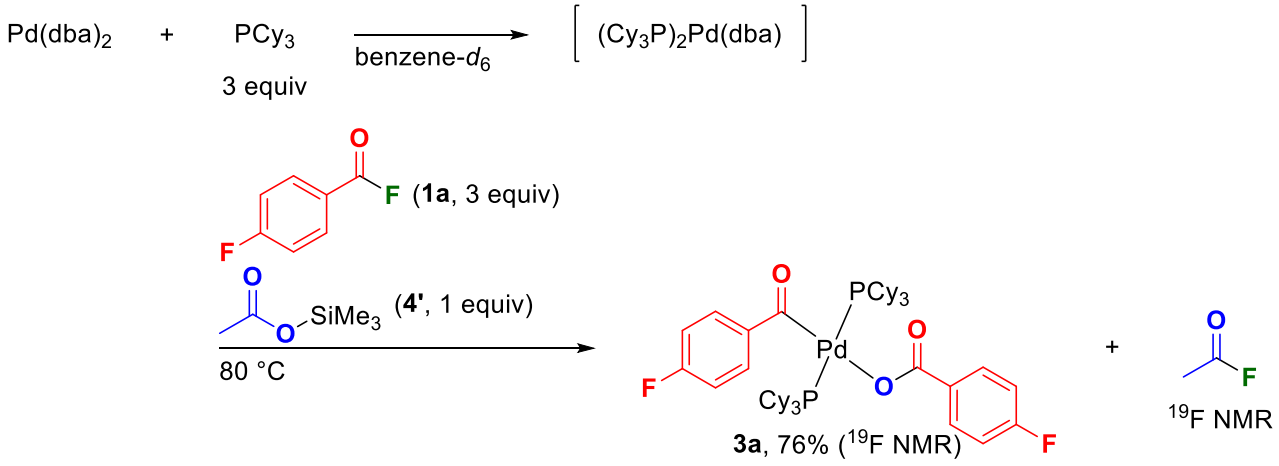
First, oxidative addition of acyl fluorides to a Pd(0) as an initial step was examined (Scheme 2-6). A zero-valent palladium, $Pd(dba)_2$, was treated with 3 equiv of PCy_3 in benzene-d_6 to in situ forms $(Cy_3P)_2Pd(dba)$, and 3 equiv of acyl fluoride **1a** was then added to the solution. But **1a** was not almost consumed and the corresponding acyl palladium fluoride **A**, an expected oxidative-addition

product, was not also detected. It is suggested that acyl fluorides cannot oxidatively add to a Pd(0) or formed acyl palladium fluoride **A** is not observed because of rapid reductive elimination to form acyl fluoride **1a** and the Pd(0)[8].



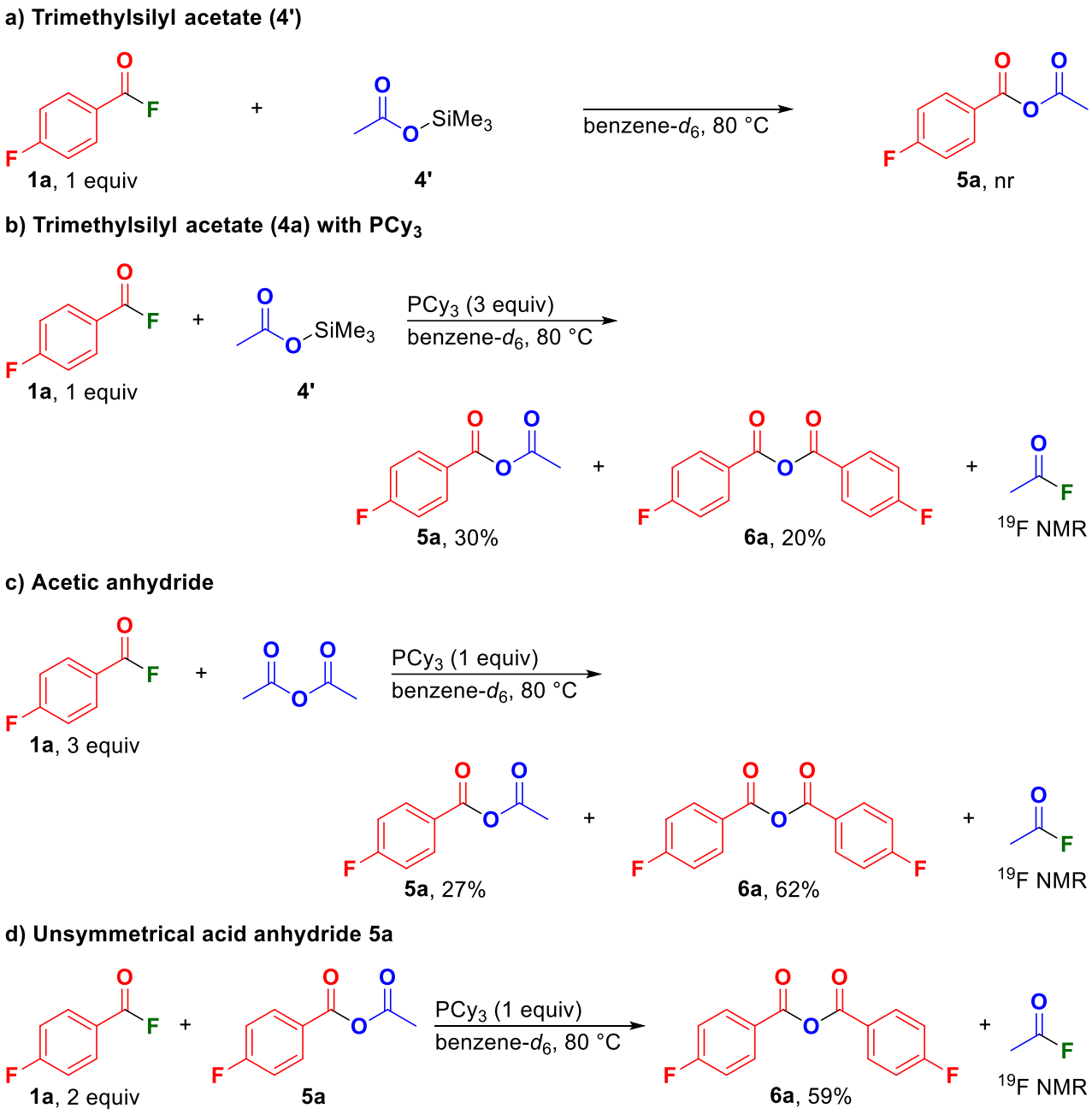
Scheme 2-6. Stoichiometric reaction of Pd(0) with acyl fluoride

Next, the origin of the O atom was investigated. The author expected that the O atom derives from a silyl ester **4** ($AcOSiEt_3$) which is generated through the reduction of $Pd(OAc)_2$ with PCy_3/Et_3SiH.[9,10] $Pd(dba)_2$ was treated with PCy_3 in benzene-d_6 generating $(Cy_3P)_2Pd(dba)$ before the addition of acyl fluoride **1a** and trimethylsilyl acetate (**4'**) with heating at 80 °C (Scheme 2-7). As a result, complex **3a** was obtained in a 76% yield with a release of acetyl fluoride (AcF)[11]. This process indirectly revealed that the source of the O atom is $Pd(OAc)_2$.



Scheme 2-7. Revealing the origin of O in acyl(carboxylato)palladium **3**

On the other hand, we assessed the reactivity of acyl fluorides towards silyl esters without palladium (Scheme 2-8).



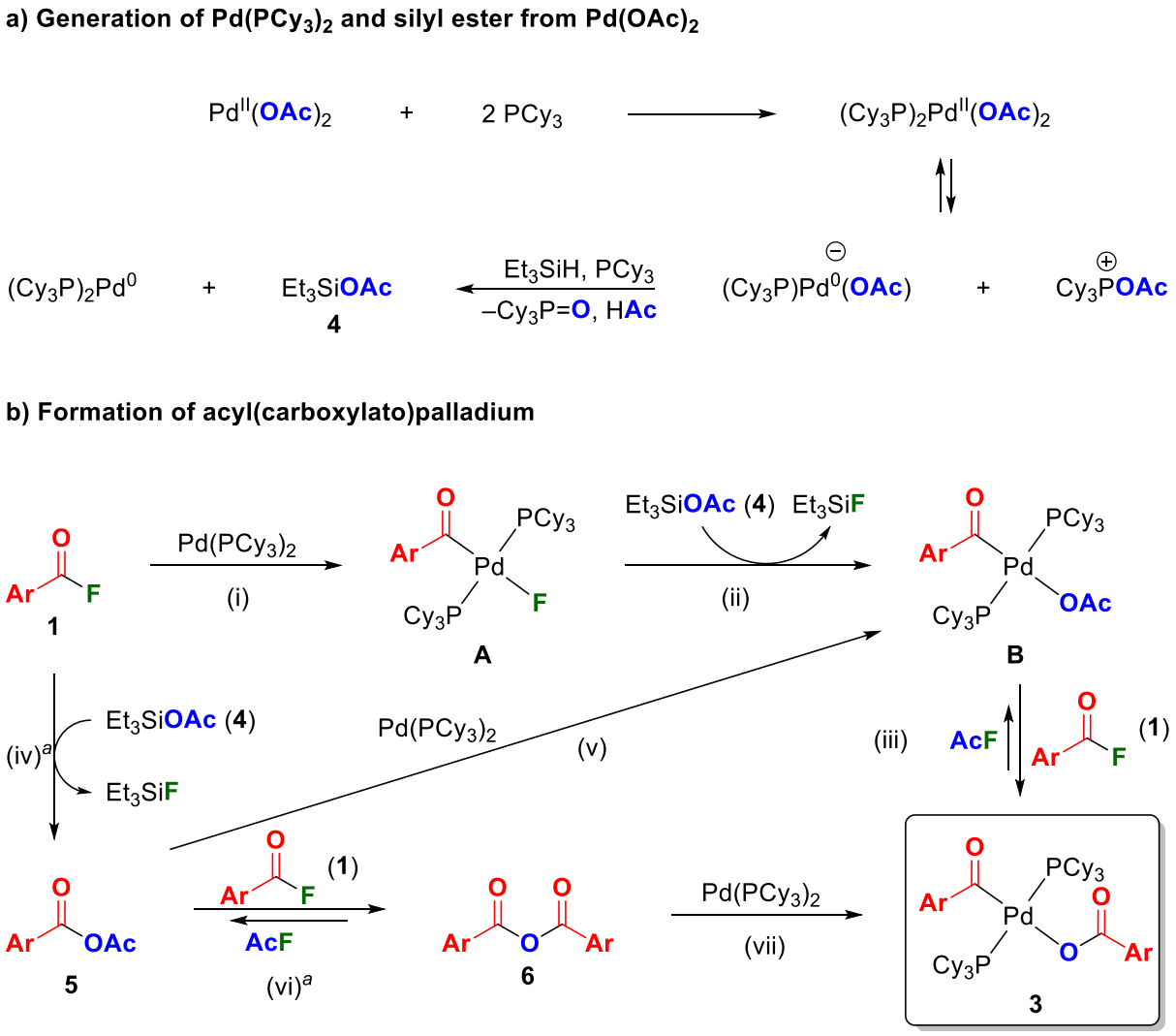
Scheme 2-8. Reactions of acyl fluoride without Pd species. Yields are determined by ^{19}F NMR

In the absence of palladium and phosphine, acyl fluoride **1a** was unreactive with silyl ester **4'** (Scheme 2-8a). In the presence of PCy_3, a reaction proceeded to give not only unsymmetrical acid anhydride **5a** but also symmetrical acid anhydride **6a** and acetyl fluoride (Scheme 2-8b). To confirm the reactivity of an acid anhydride with acyl fluoride, in the presence of PCy_3, a mixture of **1a** and acetic anhydride was heated (Scheme 2-8c). Consequently, **5a** and **6a** were afforded with the release of acetyl fluoride. Furthermore, treatment of prepared unsymmetrical anhydride **5a** with acyl

fluoride **1a** furnished the corresponding symmetrical anhydride **6a** and acetyl fluoride (Scheme 2-8d). These results showed an exchange of the acyl moieties between acyl fluoride and acid anhydride.

2-2-3. Proposed reaction mechanism in the generation of acyl(carboxylato)palladiums

On the basis of the results shown in Schemes 2-7 and 2-8, a generation mechanism of acyl(carboxylato)palladium complex **3** is proposed in Scheme 2-9.

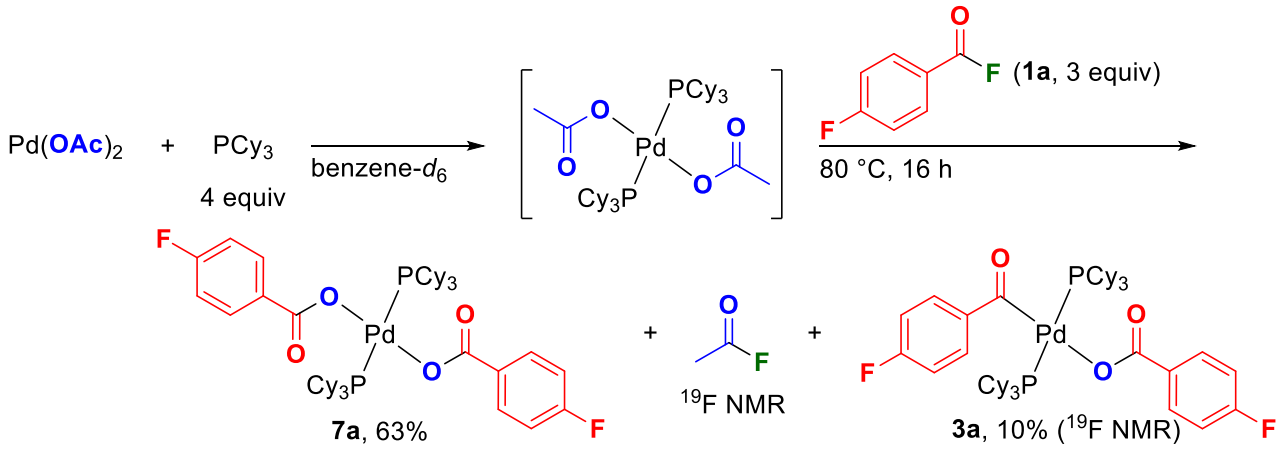


Scheme 2-9. Proposed generation mechanism for acy(carboxylato)palladium **3**

First, $Pd(OAc)_2$ and PCy_3 forms $(Cy_3P)_2Pd(OAc)_2$, and the palladium species is then treated with PCy_3 and Et_3SiH affording $Pd(PCy_3)_2$ with the liberation of acetaldehyde, $O{=}PCy_3$, and silyl ester

4 (Scheme 2-9a).[9] Next, acyl fluoride **1** oxidatively adds to $Pd(PCy_3)_2$ forming acyl palladium fluoride **A** (Scheme 2-9b, path i), and the subsequent transmetalation of **A** with silyl ester **4** affords acyl(acetato)palladium intermediate **B** (Scheme 2-9b, path ii). An acetyl moiety of **B** then replaces the acyl moiety of acyl fluoride **1**, giving the desired complex **3** with a release of acetyl fluoride (Scheme 2-9b, path iii). As another possibility for the generation of complex B, acyl fluoride **1** could react with silyl ester **4** forming unsymmetrical carboxylic anhydride **5** (Scheme 2-9b, path iv), and then the oxidative addition of **5** to $Pd(PCy_3)_2$ would provide complex **B** (Scheme 2-9b, path v). Although the acyl group exchange is reversible (Scheme 2-9b, path iii), acetyl fluoride is promptly released from the reaction system due to its volatility, which finally leads to the smooth formation of complex **3** as a single product. Alternatively, it is expected that formed acid anhydride **5** reacts with acyl fluoride **1** to form benzoic anhydride **6** (Scheme 2-9b, path vi), and then the oxidative addition of 6 to $Pd(PCy_3)_2$ would furnish complex **3** (Scheme 2-9b, path vii).

The mechanism for the acyl-exchange reaction between intermediate **B** and acyl fluoride **1** is uncertain (Scheme 2-9b, path iii), and, therefore, the author examined the reactivity of acyl fluoride against palladium acetate using $Pd(OAc)_2$ (Scheme 2-10).



Scheme 2-10. Reaction of palladium carboxylate with acyl fluoride

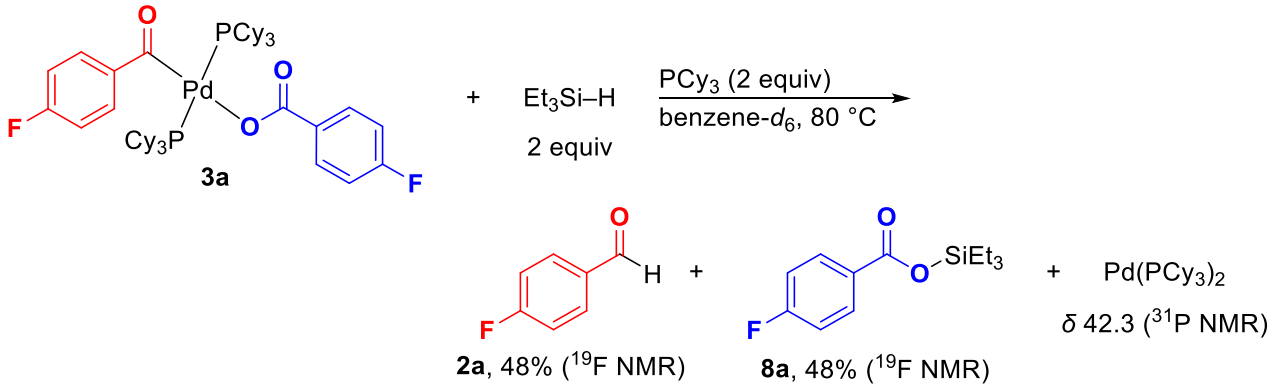
$Pd(OAc)_2$ was treated with 4 equiv of PCy_3 in benzene-d_6 to prepare $(Cy_3P)_2Pd(OAc)_2$, and acyl fluoride **1a** was then added to the solution. As a result, the acyl-exchange reaction proceeded to obtain palladium 4-fluorobenzoate **7a** in a good yield with the production of a small amount of

complex **3a**, in which acetyl fluoride was also observed in the ^{19}F NMR. Complex **7a** was characterized by ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectroscopy, and mass spectroscopy.

2-2-4. Reactivity of acyl(carboxylato)palladium in stoichiometric and catalytic reactions

The acyl(carboxylato)metal complex is well known as an oxidative-addition product of a carboxylic acid anhydride.[12] The complex demonstrated reductive elimination,[12a] its reactivity towards some reactants[12b–12d] including carboxylic acids, H_2, PhS–H, Me–I and a boronic acid, and decarbonylation[12e]. To display the effect of acyl(carboxylato)palladium complex **3** as a reaction intermediate, the author herein examined stoichiometric coupling reactions with various reagents used in our reported palladium-catalyzed reactions of acyl fluorides[1b,1c,1e] and a catalytic reaction, using complex **3a**.

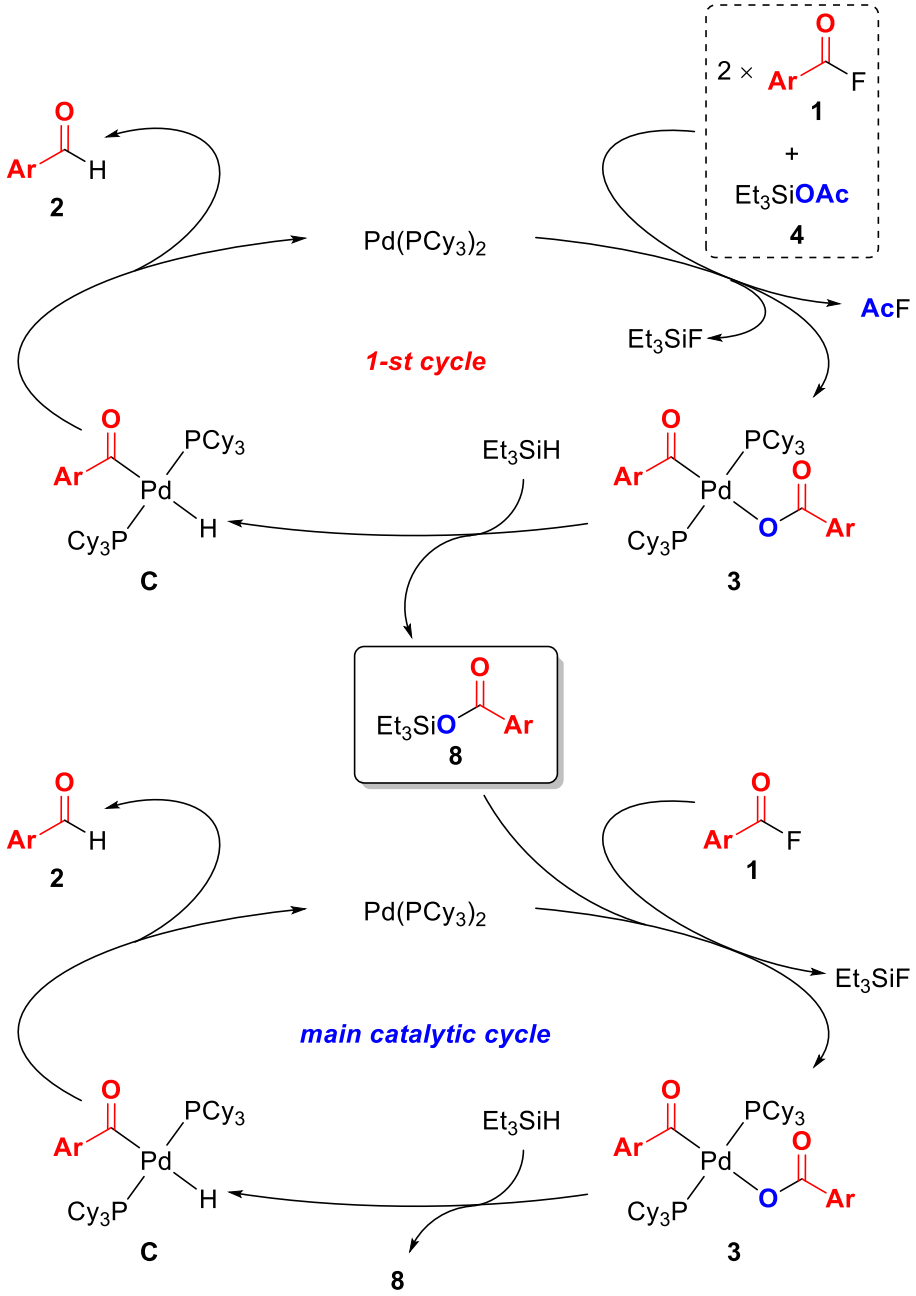
First, a stoichiometric reaction using a hydrosilane was carried out (Scheme 2-11). Complex **3a**, PCy_3 and Et_3SiH were mixed in benzene-d_6, and the resultant mixture was then heated at 80 °C. Consequently, the corresponding aldehyde **2a** and silyl benzoate **8a** were obtained in moderate ^{19}F NMR yields, and $Pd(PCy_3)_2$ was also observed in ^{31}P NMR. This result clearly showed that acyl(carboxylato)palladium **3** functioned as a key intermediate in the Pd-catalyzed formation of an aldehyde from acyl fluorides with hydrosilane.



Scheme 2-11. Stoichiometric reaction of an acyl(carboxylato)palladium complex with a hydrosilane

Based on these results, a reaction mechanism for the model reaction, the Pd-catalyzed reduction

of acyl fluorides leading to aldehydes, is assumed in Scheme 2-12.

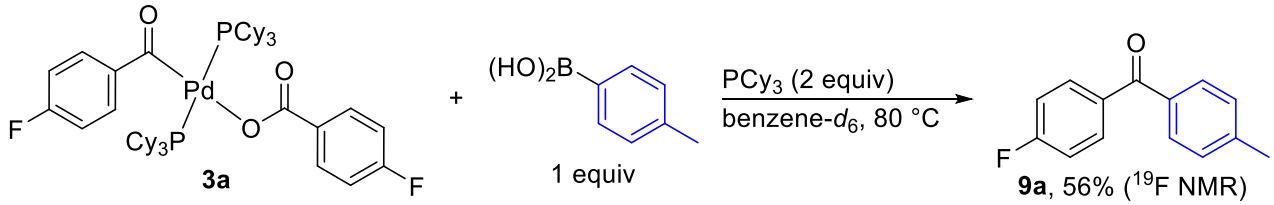


Scheme 2-12. Possible mechanism of the $Pd(OAc)_2/PCy_3$-catalyzed reduction of acyl fluorides with a hydrosilane

In the 1-st cycle, initially, in-situ generated $Pd(PCy_3)_2$ reacts with two equivalents of acyl fluoride **1** and silyl ester **4** to give acyl(carboxylato)palladium complex **3**, before complex **3** is converted to acyl palladium hydride **C** and silyl benzoate **8** by transmetalation with a hydrosilane. Reductive elimination of **C** then occurs to furnish the corresponding aldehyde **2**, and by regeneration of

$Pd(PCy_3)_2$, the first catalytic cycle is completed. From the second cycles onward (main catalytic cycle), the reaction of $Pd(PCy_3)_2$, acyl fluoride **1**, and silyl ester **8**, which was generated in the previous cycle, provides acyl(carboxylato)palladium complex **3**, and the subsequent reactions proceed to afford aldehyde **2** catalytically. Catalytic coupling reactions through an acyl(carboxylato)palladium intermediate have been reported by Yamamoto *et al.*,[12c,12d,13], deVries *et al.*,[14] Gooßen *et al.*,[15] and Szostak *et al.*,[16] in which acid anhydrides in situ generated from carboxylic acids and equimolar pivalic anhydride or carbonates has been used. Although this reduction of acyl fluorides also includes the formation of acid anhydride intermediate analogs from acyl fluorides, the intermediate is formed only with the catalytic amount, which is considered as one of its remarkable features.

And more, the author investigated the reactivity of acyl(carboxylato)palladium **3** towards other coupling partners such as a boronic acid and an acyl fluoride. Our group has developed catalytic coupling reactions of acyl fluorides with boronic acids[1b] or carboxylic acid anhydrides[1e]. When a coupling reaction with a boronic acid was tested (Scheme 2-13), the expected coupling reaction proceeded via a smooth transmetalation between complex **3a** and a boronic acid without additional reagents as a base, to give the corresponding ketone **9a** in a 56% yield.

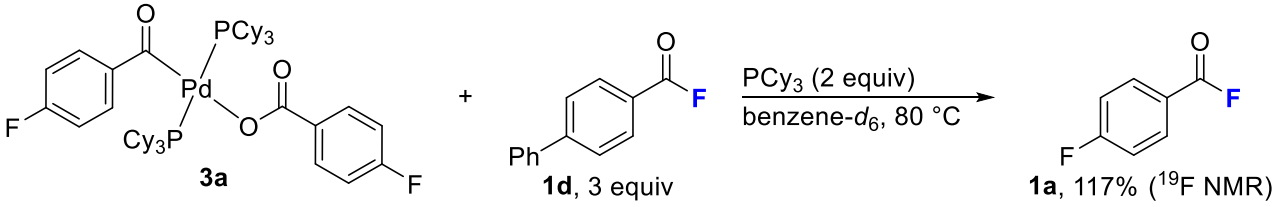


Scheme 2-13. Stoichiometric couplings of acyl(carboxylato)palladium complex **3** with boronic acid

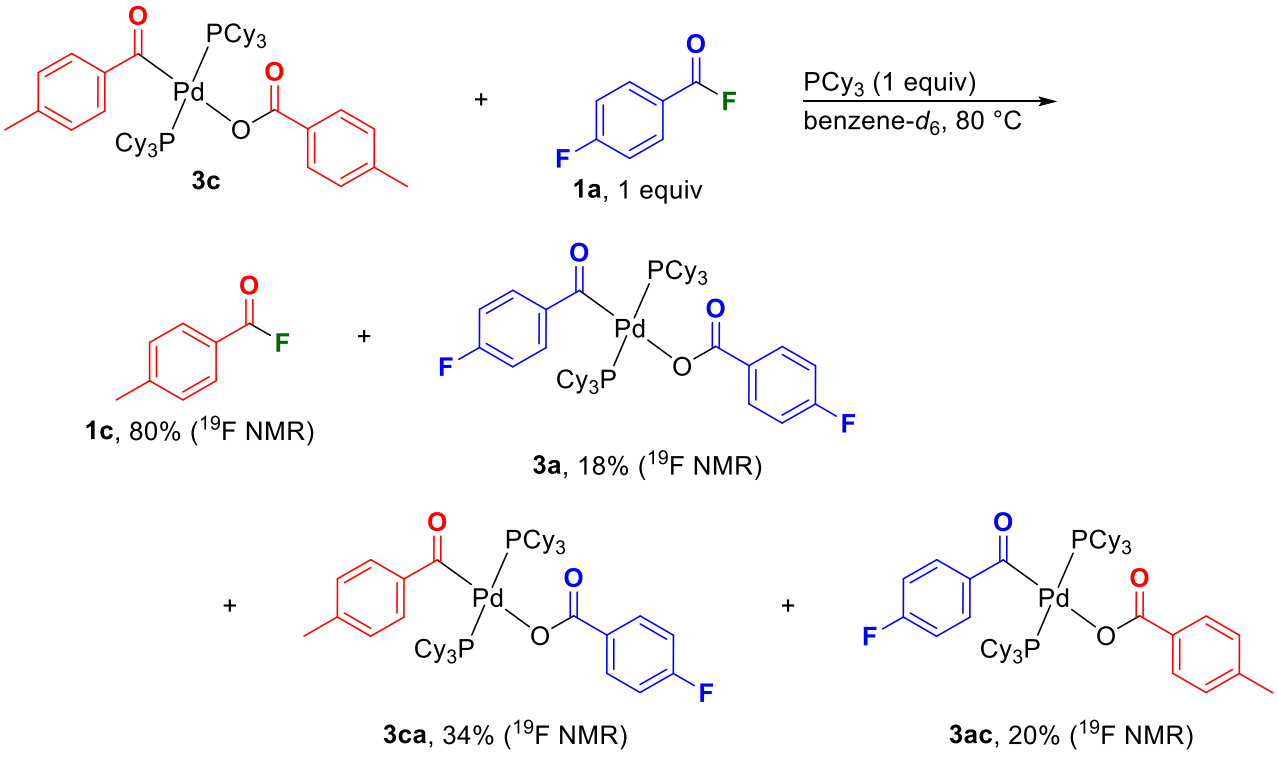
On the other hand, the reaction of **3a** with 4-phenylbenzoyl fluoride (**1d**) provided 4-fluorobenzoyl fluoride (**1a**) in a 117% yield (Scheme 2-14a), which suggested that both acyl parts of complex **3a** underwent an acyl-exchange reaction with acyl fluoride **1d**. Uncharacterized signals probably corresponded to acyl(carboxylato)palladium complexes were also observed besides to acyl fluoride product **1a** in the ^{19}F and ^{31}P NMR. To characterize those signals, 4-methylbenzoyl(4'-

methylbenzoato)palladium complex **3c** and 4-fluorobenzoyl fluoride (**1a**) were used as a substrate (Scheme 2-14b). When a mixture of **3c** and **1a** with PCy_3 in benzene-d_6 was heated at 80 °C, 4-methylbenzoyl fluoride (**1c**) generated in a high yield, in which 4-fluorobenzoyl(4'-fluorobenzoato)palladium complex **3a** and mixed acyl(carboxylato)palladium complexes, **3ca** and **3ac**, were also observed in 18%, 34%, and 20% ^{19}F NMR yields respectively. Complexes **3ca** and **3ac** were characterized by ^{1}H and ^{19}F NMR spectroscopy.

a) Reaction of acyl(carboxylato)palladium 3c with acyl fluoride 1a



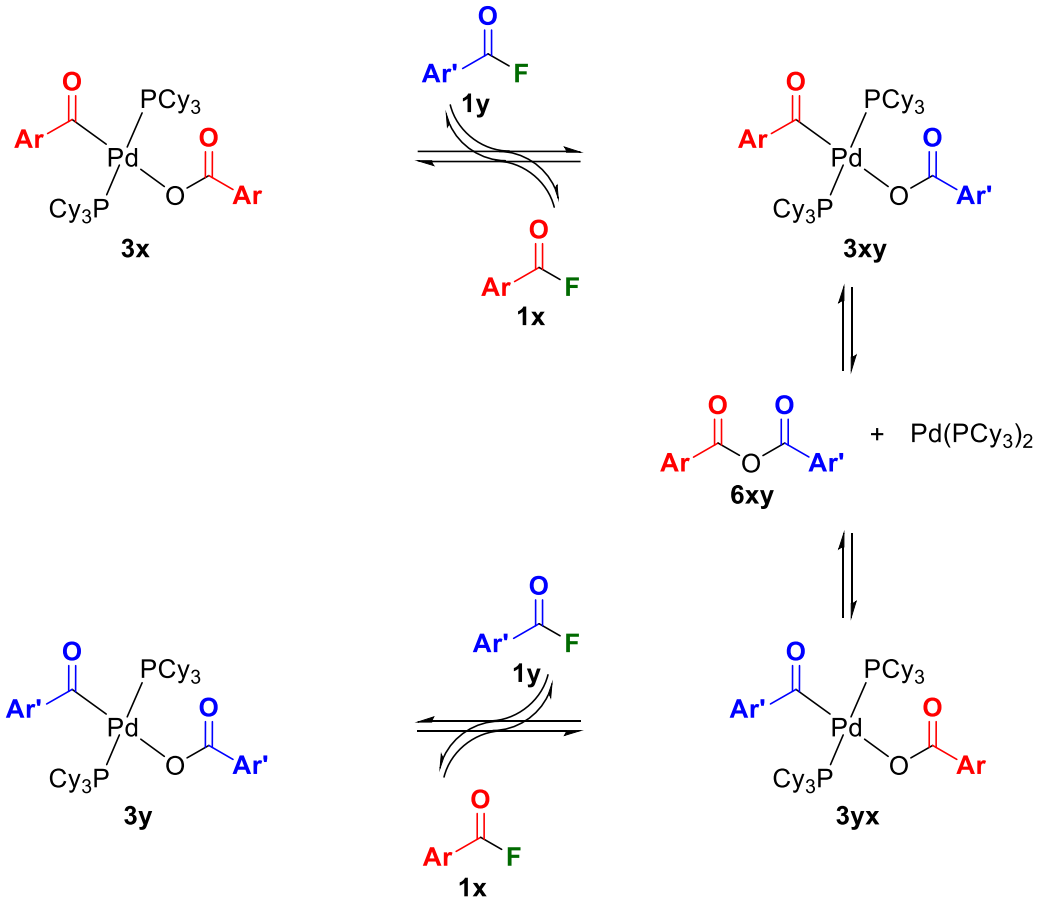
b) Reaction of acyl(carboxylato)palladium 3c with acyl fluoride 1a



Scheme 2-14. Stoichiometric couplings of acyl(carboxylato)palladium complex **3** with acyl fluorides

On the basis of this result, a mechanism of the acyl-exchange reaction is proposed in Scheme 2-

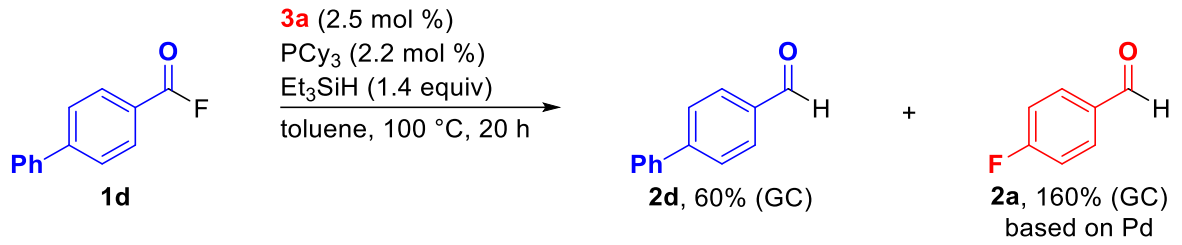
15. A combination of starting acyl(caboxylato)palladium **3x** and acyl fluoride **1y** provides reversibly acyl fluoride **1x** and acyl(carboxylato)palladiums **3xy**, **3yx** and **3y**, through the acyl exchange at carboxylate moieties and reductive elimination/oxidative addition between mixed anhydride **6xy** and $Pd(PCy_3)_2$. In the presence of excess starting acyl fluoride **1y**, it is expected that acyl fluoride **1x** derived from starting complex **3x** is obtained in more than equimolar amounts.



Scheme 2-15. Possible mechanism of acyl-group exchange reaction between acyl(carboxylato)palladiums and acyl fluorides

Finally, the author performed a reduction of acyl fluorides forming aldehydes using a catalytic amount of acyl(carboxylato)palladium **3** instead of $Pd(OAc)_2$ (Scheme 2-16). In the presence of 2.5 mol % of complex **3a** and PCy_3, a mixture of acyl fluoride **1d** and Et_3SiH in toluene was heated at 100 °C for 20 h. As a result, 60% of **1d** was effectively converted to aldehyde **2d**, and aldehyde **2a** was obtained in a 160% yield, which was calculated using an equivalent of palladium species **3a**. Production of aldehyde **2a** more than 100% yield proved that the acyl(carboxylato)palladium

complex exchanges both acyl groups with the acyl fluoride similar to Scheme 2-15.



Scheme 2-16. Catalytic reaction of an acyl(carboxylato)palladium complex with hydrosilane

2-3. Conclusions

In Chapter 2, the author found that the stoichiometric combination of $Pd(OAc)_2$, PCy_3, Et_3SiH and acyl fluorides forms the corresponding acyl(carboxylato)palladium complexes. The complex was isolated and was characterized via NMR spectroscopy and mass spectroscopy. The structure was unambiguously established via X-ray crystallography. Several mechanistic insights revealed that the *O* atom of the carboxylate moiety in the formed acyl(carboxylato)palladium complex is derived from $Pd(OAc)_2$. Also, the results showed that the acyl(carboxylato)palladium complex reacted with not only organometallic reagents, such as hydrosilanes and boronic acids, but also with acyl fluorides, which provided the coupling products. In addition, an acyl-group exchange reaction between palladium carboxylates and acyl fluorides could be significant information for the development of related catalytic reactions.

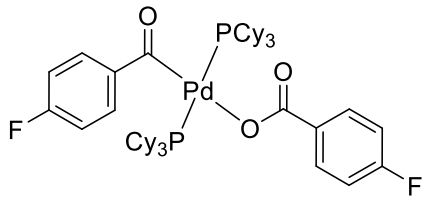
2-4. Experimental Section

General information

^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were recorded on a 500 MHz spectrometer. Chemical shifts in the ^{1}H and ^{13}C NMR spectra are reported in ppm relative to residual solvent peaks such as those of benzene (^{1}H, δ 7.15; ^{13}C, δ 128.0) or chloroform (^{1}H, δ 7.26; ^{13}C, δ 77.0). Chemical shifts in the ^{19}F NMR spectra are reported in ppm relative to the external reference, $CF_3C_6H_5$ (δ −62.6). Chemical shifts in the ^{31}P NMR spectra are reported in ppm relative to the external reference, H_3PO_4 (δ 0.00). GC analyses were performed using a DB-5 capillary column (30 m × 0.25 mm; film

thickness 0.25 μm). Benzene-d_6, toluene, and toluene-d_8 were distilled from Na/benzophenone ketyl prior to use. $Pd(OAc)_2$, $Pd(dba)_2$, PCy_3, benzoyl fluoride (**1b**), trimethylsilyl acetate (**4'**), acetic anhydride, and 4-methylphenylbronic acid were purchased from common commercial suppliers and used as received. Unless otherwise noted, all reactions were performed under an atmosphere of N_2.

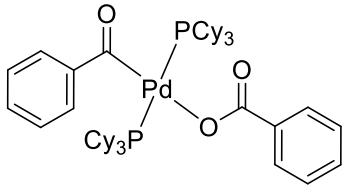
Synthesis of 3a



To a Schlenk tube in a glovebox, $Pd(OAc)_2$ (112 mg, 0.500 mmol), PCy_3 (423 mg, 1.51 mmol) and toluene (1 mL) were added. The tube was then sealed and removed from the glovebox, and the mixture was stirred until homogeneous. Et_3SiH (180 mg, 1.55 mmol) was then added to the stirred solution. The tube was placed in a preheated (100 °C) oil bath for 20 h, then removed from the oil bath and allowed to cool to room temperature. To the resulting reaction mixture, 4-fluorobenzoyl fluoride (**1a**; 201 mg, 1.41 mmol) was added. Then the tube was sealed and heated at 100 °C for 5 h. The solvent was removed under vacuum, and the resulting crude solid was dissolved in a minimal volume of toluene (1 mL) followed by the addition of hexane (10 mL). This solution was allowed to stand at 2 °C for 2 days. The supernatant was decanted, and the precipitates were dried *in vacuo* to afford a yellow green crystal complex (205 mg, 0.221 mmol, 44%); ^{1}H NMR (500 MHz, C_6D_6) δ 0.96–1.03 (m, 6 H), 1.11–1.28 (m, 12 H), 1.42 (q, J = 12.6 Hz, 6 H), 1.58 (d, J = 8.0 Hz, 12 H), 1.69–1.82 (m, 18 H), 2.03 (t, J = 12.6 Hz, 6 H), 2.31 (d, J = 12.0 Hz, 6 H), 6.66 (br, 1 H), 6.90 (t, J = 8.6 Hz, 2 H), 7.08 (br, 1 H), 7.67 (br, 1 H), 8.43 (dd, J = 6.3, 8.6 Hz, 2 H), 10.38 (br, 1 H); ^{13}C NMR (126 MHz, C_6D_6) δ 26.8, 28.1–28.2 (m, 2 C), 29.7, 30.1, 34.0 (t, J_{C-P} = 7.5 Hz), 114.6 (d, J_{C-F} = 20.9 Hz), 114.9, 115.7 (d, J_{C-F} = 23.8 Hz), 124.8 (d, J_{C-F} = 3.0 Hz), 132.2 (d, J_{C-F} = 8.5 Hz), 135.4, 140.6 (d, J_{C-F} = 7.5 Hz), 142.2 (td, J_{C-F} = 3.0 Hz, J_{C-P} = 11.9 Hz), 164.6 (d, J_{C-F} = 247.4 Hz), 165.6 (d, J_{C-F} = 253.3 Hz), 170.1, 226.0; ^{19}F NMR (471 MHz, C_6D_6) δ –111.98 (1 F), –107.45 (1 F); ^{31}P NMR (202 MHz, C_6D_6) δ 18.9; HRMS (FAB) calcd for [M – OCO(*p*-FC_6H_4)]$^+$

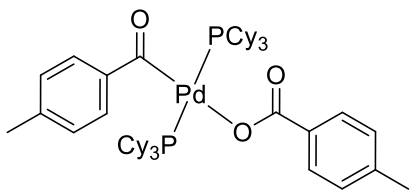
($C_{43}H_{70}FOP_2Pd$) *m*/*z* 789.3921, found 789.3912.

Synthesis of 3b



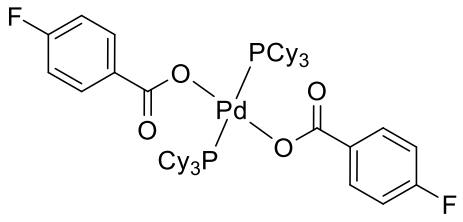
To a Schlenk tube in a glovebox, $Pd(OAc)_2$ (113 mg, 0.501 mmol), PCy_3 (424 mg, 1.51 mmol) and toluene (1 mL) were added. The tube was then sealed and removed from the glovebox, and the mixture was stirred until homogeneous. Et_3SiH (174 mg, 1.50 mmol) was then added to the stirred solution. The tube was placed in a preheated (100 °C) oil bath for 20 h, then removed from the oil bath and allowed to cool to room temperature. To the resulting reaction mixture, benzoyl fluoride (**1b**; 186 mg, 1.50 mmol) was added. Then the tube was sealed and heated at 100 °C for 16 h. The solvent was removed under vacuum, and the resulting crude solid was dissolved in a minimal volume of CH_2Cl_2 (1.5 mL) followed by the addition of Et_2O (10 mL). This solution was allowed to stand at 2 °C for 1 day. The supernatant was decanted, and the precipitates were dried in vacuo to afford a pale yellow solid complex (149 mg, 0.166 mmol, 33%); ^{1}H NMR (500 MHz, C_6D_6) δ 1.02–1.06 (m, 6 H), 1.13–1.26 (m, 12 H), 1.46 (q, J = 12.0 Hz, 6 H), 1.56–1.61 (m, 12 H), 1.71–1.90 (m, 18 H), 2.09 (t, J = 12.0 Hz, 6 H), 2.35 (d, J = 12.0 Hz, 6 H), 6.99 (br, 1 H), 7.17 (m, 1 H), 7.306–7.314 (m, 2 H), 7.60 (br, 1 H), 7.80 (br, 1 H), 8.596–8.608 (m, 2 H), 10.46 (br, 1 H); ^{13}C NMR (126 MHz, C_6D_6) δ 26.8, 28.1–28.2 (m, 2 C), 29.7, 30.1, 34.0 (t, J_{C-P} = 8.7 Hz), 122.5, 129.2, 130.0, 130.2, 131.9, 138.7, 139.2, 145.4 (t, J_{C-P} = 11.6 Hz), 171.3, 227.8; ^{31}P NMR (202 MHz , C_6D_6) δ 19.0; HRMS (FAB) calcd for $[M - OCOPh]^+$ ($C_{43}H_{71}OP_2Pd$) *m*/*z* 771.4031, found 771.4035.

Synthesis of 3c



To a Schlenk tube in a glovebox, $Pd(OAc)_2$ (67.1 mg, 0.299 mmol), PCy_3 (254 mg, 0.906 mmol) and toluene (0.6 mL) were added. The tube was then sealed and removed from the glovebox, and the mixture was stirred until homogeneous. Et_3SiH (101 mg, 0.869 mmol) was then added to the stirred solution. The tube was placed in a preheated (100 °C) oil bath for 20 h, then removed from the oil bath and allowed to cool to room temperature. To the resulting reaction mixture, 4-methylbenzoyl fluoride (**1c**; 123 mg, 0.893 mmol) was added. Then the tube was sealed and heated at 100 °C for 5 h. The solvent was removed under vacuum, and the resulting crude solid was dissolved in a minimal volume of CH_2Cl_2 (1 mL) followed by the addition of Et_2O (10 mL). This solution was allowed to stand at 2 °C for 1 day. The supernatant was decanted, and the precipitates were dried in vacuo to afford a yellow green solid complex (175 mg, 0.190 mmol, 63%); ^{1}H NMR (500 MHz, C_6D_6) δ 1.02–1.10 (m, 6 H), 1.15–1.29 (m, 12 H), 1.50 (q, J = 12.0 Hz, 6 H), 1.60 (t, J = 13.2 Hz, 12 H), 1.79–1.85 (m, 18 H), 2.02 (s, 3 H), 2.07 (s, 3 H), 2.12 (t, J = 12.0 Hz, 6 H), 2.38 (d, J = 12.0 Hz, 6 H), 6.86 (br, 1 H), 7.13 (d, J = 8.0 Hz, 2 H), 7.27 (br, 1 H), 7.76 (br, 1 H), 8.52 (d, J = 8.0 Hz, 2 H), 10.34 (br, 1 H); ^{13}C NMR (126 MHz, C_6D_6) δ 21.3, 21.4, 26.9, 28.2–28.3 (m, 2 C), 29.7, 30.2, 34.1 (t, $J_{C–P}$ = 7.5 Hz), 122.5, 128.6, 129.7, 130.3, 137.0, 138.6, 139.4, 142.0, 143.6 (t, $J_{C–P}$ = 11.9 Hz), 171.1, 227.6; ^{31}P NMR (202 MHz, C_6D_6) δ 18.9; HRMS (FAB) calcd for $[M – OCO(p\text{-}MeC_6H_4)]^+$ ($C_{44}H_{73}OP_2Pd$) m/z 785.4188, found 785.4181.

Synthesis of 7a

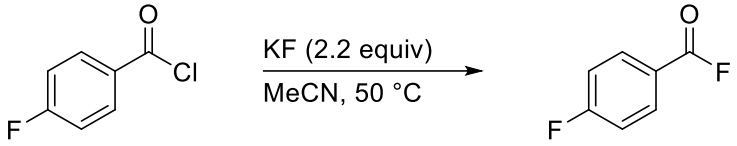


To a screw-capped NMR tube in a glovebox, $Pd(OAc)_2$ (13.4 mg, 0.0597 mmol), PCy_3 (66.5 mg, 0.0595 mmol) and benzene-d_6 (0.6 mL) were added. The tube was then sealed and removed from the glovebox, and the mixture was heated at 80 °C for 10 h. To the resulting reaction mixture, 4-fluorobenzoyl fluoride (**1a**; 27.6 mg, 0.194 mmol) was added. Then the tube was sealed and heated

at 80 °C for 16 h. This solution was allowed to stand at room temperature for 3 days. The supernatant was decanted, and the precipitates were dried *in vacuo* to afford a pale yellow solid complex (35.8 mg, 0.0379 mmol, 63%); ^{1}H NMR (500 MHz, C_6D_6) δ 1.00–1.07 (m, 12 H), 1.15–1.20 (m, 7 H), 1.54–1.56 (m, 7 H), 1.70–1.87 (m, 25 H), 1.96–1.98 (m, 6 H), 2.19–2.21 (m, 11 H), 6.85 (t, J = 8.6 Hz, 4 H), 8.27–8.30 (m, 4 H); ^{13}C NMR (126 MHz, C_6D_6) δ 26.8, 28.2 (t, J = 5.1 Hz), 30.0, 33.5 (t, J = 8.5 Hz), 114.8 (d, $J_{C–F}$ = 21.7 Hz), 132.3 (d, $J_{C–F}$ = 8.5 Hz), 132.6, 164.8 (d, $J_{C–F}$ = 249.9 Hz), 169.4; ^{19}F NMR (471 MHz, C_6D_6) δ –110.39; ^{31}P NMR (202 MHz, C_6D_6) δ 23.2; HRMS (FAB) calcd for $[M – OCO(p\text{-}FC_6H_4)]^+$ ($C_{43}H_{70}FO_2P_2Pd$) m/z 805.3886, found 805.3885.

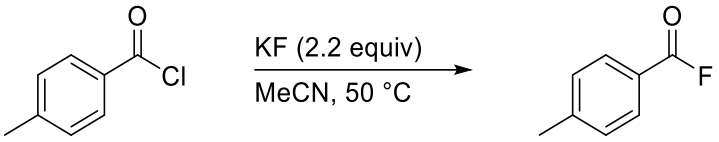
Preparation of acyl fluorides

4-Fluorobenzoyl fluoride (1a).[1c]



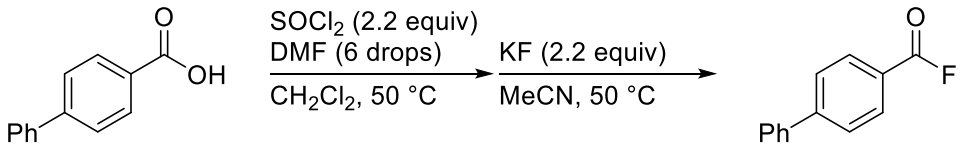
Based on a modified procedure found in the literature,[22] a two-necked flask equipped with a magnetic stir bar was charged with spray-dried KF (2.4 g, 42 mmol), and 4-fluorobenzoyl chloride (3.1 g, 19 mmol) in anhydrous MeCN (60 mL). The reaction mixture was stirred at 50 °C until conversion was completed (monitored by ^{1}H and ^{19}F NMR). The reaction suspension was allowed to settle, and the MeCN solution was decanted from the precipitate and then filtered. The precipitate was rinsed with MeCN, and the washes were filtered. The combined MeCN washes were concentrated *in vacuo*. For further purification, distillation under reduced pressure was performed, and 4-fluorobenzoyl fluoride was afforded as a colorless oil (1.5 g, 11 mmol, 56%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19–7.22 (m, 2 H), 8.07–8.09 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 116.5 (d, $J_{C–F}$ = 21.7 Hz), 121.2 (dd, $J_{C–F}$ = 3.6, 62.7 Hz), 134.2 (dd, $J_{C–F}$ = 3.6, 9.7 Hz), 156.4 (d, $J_{C–F}$ = 342.8 Hz), 167.1 (d, $J_{C–F}$ = 258.3 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ –100.48 (1 F), 18.08 (1 F); LRMS (EI) m/z (% relative intensity) 142 (M^+, 98), 123 (45), 114 (100), 95 (38), 94 (10), 75 (23), 74 (10), 63 (13), 57 (11), 50 (11).

4-Methylbenzoyl fluoride (1c).[1c]



Following the same manner as with the synthesis of **1a** using 4-methylbenzoyl chloride (1.8 g, 11 mmol), 4-methylbenzoyl fluoride was obtained as a colorless oil (1.1 g, 8.3 mmol, 72%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.46 (s, 3 H), 7.32 (d, J = 8.0 Hz, 2 H), 7.93 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.9, 122.1 (d, $J_{C–F}$ = 60.4 Hz), 129.8, 131.5 (d, $J_{C–F}$ = 3.6 Hz), 146.6, 157.5 (d, $J_{C–F}$ = 342.8 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 17.52; LRMS (EI) *m*/*z* (% relative intensity) 138 (M^+, 93), 119 (10), 110 (21), 109 (40), 91 (100), 65 (12), 63 (12).

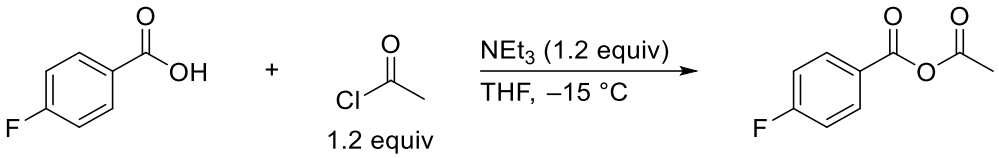
4-Phenylbenzoyl fluoride (1d).[1c]



Based on the modification of a procedure found in the literature,[17] a two-necked flask equipped with a magnetic stir bar was charged with 4-phenylbenzoic acid (3.9 g, 19 mmol) in anhydrous CH_2Cl_2 (60 mL), and then DMF (6 drops) and thionyl chloride (5.0 g, 42 mmol) were added to the solution. The reaction mixture was stirred at room temperature for 6 h. The resulting mixture was concentrated, and then KF (2.4 g, 42 mmol) and anhydrous MeCN (60 mL) were added. The mixture was stirred at 50 °C until complete conversion (monitored by ^{1}H and ^{19}F NMR). The reaction suspension was allowed to settle, and the MeCN solution was decanted from the precipitate and then filtered. The precipitate was rinsed with MeCN, and the washes were filtered. The combined MeCN washes were concentrated *in vacuo*. For further purification, silica gel column chromatography (hexane) and subsequent recrystallization (hexane) were performed, and 4-fluorobenzoyl fluoride was afforded as a colorless solid (2.0 g, 10 mmol, 52%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.46 (m, 1 H), 7.48–7.51 (m, 2 H), 7.63–7.65 (m, 2 H), 7.75 (d, J = 8.0 Hz, 2 H),

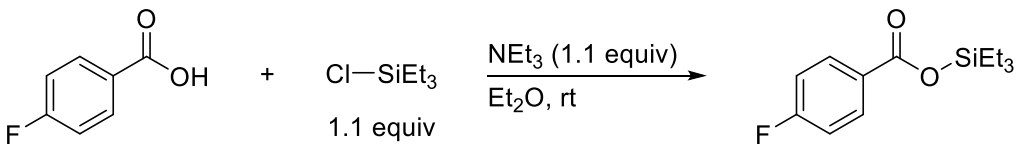
8.12 (d, J = 8.6 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 123.4 (d, $J_{C–F}$ = 61.6 Hz), 127.3, 127.6, 128.8, 129.1, 131.9 (d, $J_{C–F}$ = 4.8 Hz), 139.2, 148.1, 157.3 (d, $J_{C–F}$ = 342.8 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 18.24; LRMS (EI) m/z (% relative intensity) 201 (14), 200 (M^+, 100), 172 (43), 171 (16), 170 (10), 152 (22), 151 (10), 76 (15).

Preparation of acetic 4-fluorobenzoic anhydride (5a)



Based on a modified procedure found in the literature,[18] to a solution of 4-fluorobenzoic acid (1.41 g, 10.1 mmol) in anhydrous THF (10 mL), distilled NEt_3 (1.20 g, 11.9 mmol) in THF (20 mL) was added dropwise at –15 °C, and then acetyl chloride (0.93 g, 11.8 mmol) in THF (10 mL) was added at –15 °C. The reaction was monitored by GC. When the acid disappeared, the reaction was poured into ice-cold saturated $NaHCO_3$ aqueous solution. The organic layer was separated and was washed with brine, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum to give acetic 4-fluorobenzoic anhydride as an yellow oil (1.49 g, 8.19 mmol, 81%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 3 H), 7.08–7.13 (m, 2 H), 8.00–8.04 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.1, 115.9 (d, $J_{C–F}$ = 22.9 Hz), 124.7 (d, $J_{C–F}$ = 3.6 Hz), 133.0 (d, $J_{C–F}$ = 9.7 Hz), 161.0, 166.1, 166.4 (d, $J_{C–F}$ = 255.9 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ –102.57; LRMS (EI) m/z (% relative intensity) 182 (M^+, 4), 140 (19), 123 (100), 95 (28), 75 (13).

Preparation of triethylsilyl 4-fluorobenzoate (8a)



Based on a modified procedure found in the literature,[19] to a solution of 4-fluorobenzoic acid (1.38 g, 9.86 mmol) and triethylamine (1.12 g, 11.0 mmol) in Et_2O (20 mL), triethylsilyl chloride (1.59 g, 11.0 mmol) was slowly added at room temperature. Volatiles were removed under reduced pressure. Hexane (20 mL) was then added to the crude product and the filtration was performed to remove the white salt. The obtained crude oil was purified by distillation (125 °C, 0.2 kPa). Triethylsilyl 4-fluorobenzoate was obtained as a colorless oil (0.784 g, 3.08 mmol, 31%); ^{1}H NMR (500 MHz, C_6D_6) δ 0.82 (q, J = 8.0 Hz, 6 H), 0.99 (t, J = 8.0 Hz, 9 H), 6.64 (t, J = 8.6 Hz, 2 H), 7.99 (dd, J = 5.7 Hz, 8.6 Hz, 2 H); ^{13}C NMR (126 MHz, C_6D_6) δ 4.9, 6.7, 115.5 (d, J_{C-F} = 22.9 Hz), 132.9 (d, J_{C-F} = 9.7 Hz), 165.4, 166.0 (d, J_{C-F} = 252.3 Hz); ^{19}F NMR (471 MHz, C_6D_6) δ –106.06; HRMS (FAB) calcd for $[M]^+$ ($C_{13}H_{19}FO_2Si$) m/z 254.1138, found 254.1132.

X-ray crystallographic data of 3a

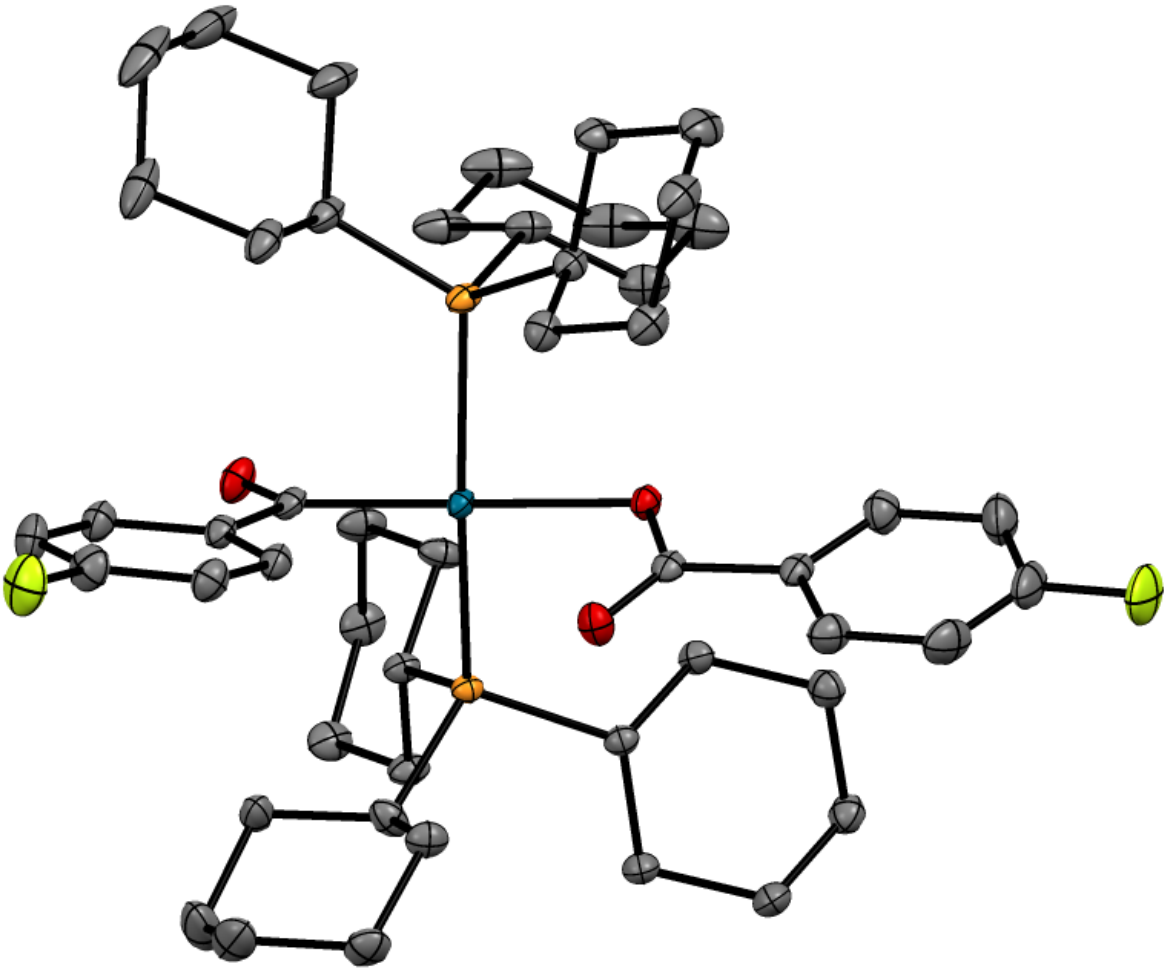


Figure 2-3. ORTEP drawing of **3a.**

Table 2-1. Crystal data and structure refinement for **3a**.

Empirical formula	$C_{53}H_{81}F_2O_3P_2Pd$	
Formula weight	972.51	
Temperature	100.01(10)	
Wavelength	1.54184 Å	
Crystal system	monoclinic	
Space group	*C*2/*c*	
Unit cell dimensions	a = 25.4755(3) Å	α = 90 °
	b = 17.2373(2) Å	β = 115.1530(10) °
	c = 25.5350(3) Å	γ = 90 °
V	10149.9(2) Å^3	
Z	8	
Density (calculated)	1.273 mg/mm^3	
Absorption coefficient	3.916 mm^{-1}	
F(000)	4136.0	
Crystal size	0.327 × 0.283 × 0.216 mm^3	
Theta range for data collection	6.402 to 154.204 °	
Index ranges	–32 <= h <= 30, –18 <= k <= 21, –31 <= l <= 31	
Reflections collected	31757	
Independent reflections	10354 [R(int) = 0.0304, R(sigma) = 0.0292]	
Data / restraints / parameters	10354 / 176 / 635	
Goodness-of-fit on F^2	1.032	
Final R indices [I > 2sigma(I)]	R_1 = 0.0273, wR_2 = 0.0681	
R indices (all data)	R_1 = 0.0286, wR_2 = 0.0690	
Largest diff. peak and hole	0.58 and –0.71 e. Å^{-3}	

Table 2-2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **3a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Pd(1)	6974(2)	5511(2)	5961(2)	12(4)
P(2)	7043(2)	5756(2)	6903(2)	12(8)
P(1)	6942(2)	4855(2)	5132(2)	15(8)
O(2)	7887(5)	5683(7)	6207(5)	15(2)
F(1)	4849(5)	7962(7)	4355(5)	35(3)
O(1)	5864(5)	4884(7)	5740(5)	21(3)
O(3)	7669(5)	6949(7)	6154(5)	21(2)
F(2)	10368(5)	7102(9)	6918(6)	47(4)
C(30)	8166(7)	5132(9)	7469(7)	17(3)
C(19)	6714(7)	4913(9)	7099(7)	15(3)
C(44)	8014(7)	6408(10)	6240(6)	15(3)
C(37)	6127(7)	5440(10)	5681(7)	16(3)
C(45)	8647(7)	6584(10)	6404(7)	16(3)
C(26)	7939(7)	6178(10)	8029(7)	18(3)
C(13)	7462(7)	5314(10)	4898(7)	16(3)
C(25)	7816(7)	5875(9)	7421(7)	14(3)
C(18)	7344(7)	6188(10)	4778(7)	19(3)
C(29)	8814(8)	5280(10)	7809(7)	20(3)
C(50)	9056(8)	5992(11)	6538(8)	24(4)
C(14)	7564(8)	4934(11)	4407(8)	22(4)
C(20)	6769(8)	4853(10)	7720(7)	18(3)
C(1)	7241(8)	3863(10)	5358(7)	20(3)
C(24)	6882(8)	4139(10)	6917(7)	19(3)
C(31)	6687(8)	6608(10)	7056(8)	19(3)

C(27)	8593(8)	6291(11)	8391(7)	22(4)
C(23)	6481(9)	3493(10)	6939(8)	22(4)
C(38)	5795(7)	6146(10)	5351(7)	16(3)
C(41)	5160(8)	7365(11)	4688(8)	25(4)
C(32)	6880(8)	7355(9)	6863(7)	19(3)
C(43)	5190(7)	6112(11)	5084(7)	20(3)
C(7)	6241(8)	4664(11)	4500(7)	22(4)
C(42)	4866(8)	6723(11)	4745(8)	25(4)
C(40)	5757(8)	7425(11)	4948(8)	21(3)
C(28)	8943(8)	5562(10)	8418(8)	21(3)
C(39)	6075(7)	6811(10)	5282(7)	18(3)
C(46)	8824(8)	7350(11)	6433(8)	24(4)
C(17)	7862(8)	6575(11)	4731(7)	21(3)
C(22)	6506(8)	3422(10)	7545(8)	23(4)
C(16)	7989(8)	6197(12)	4257(8)	26(4)
C(12)	6247(9)	4032(14)	4074(8)	32(5)
C(49)	9638(8)	6161(13)	6707(9)	31(4)
C(6)	7827(9)	3885(10)	5891(8)	25(4)
C(15)	8080(9)	5325(12)	4355(9)	27(4)
C(21)	6371(8)	4198(11)	7752(8)	23(4)
C(8)	5945(8)	5396(12)	4160(8)	25(4)
C(36)	6032(8)	6549(11)	6815(9)	21(4)
C(2)	6814(10)	3333(11)	5470(9)	28(4)
C(47)	9406(9)	7528(13)	6603(9)	32(4)
C(48)	9797(8)	6931(14)	6740(9)	31(4)
C(5)	8076(11)	3069(12)	6074(9)	34(5)
C(11)	5625(10)	3848(15)	3638(9)	41(6)

C(10)	5314(11)	4569(16)	3313(9)	46(7)
C(33)	6611(11)	8078(13)	6994(12)	24(5)
C(3)	7071(11)	2520(12)	5655(9)	36(5)
C(9)	5321(9)	5213(15)	3723(8)	36(5)
C(34)	5952(10)	8007(13)	6741(11)	32(6)
C(4)	7652(13)	2547(12)	6182(10)	41(6)
C(35)	5782(9)	7276(12)	6978(11)	37(5)
C(36A)	6301(6)	6646(9)	7349(7)	22(3)
C(34A)	6190(8)	8039(9)	7201(8)	31(3)
C(33A)	6422(9)	8003(10)	6750(9)	26(3)
C(52)	9874(16)	4205(2)	5478(15)	45(8)
C(53)	9752(12)	4880(19)	5066(12)	39(7)
C(51)	9362(2)	3953(3)	5590(2)	73(12)
C(54)	10080(20)	4010(20)	7617(17)	74(6)
C(57)	9363(17)	3440(30)	5911(17)	68(4)
C(56)	9559(17)	3870(20)	6390(16)	65(4)
C(55)	9640(20)	3720(30)	6993(18)	74(5)
C(58)	9448(18)	3590(30)	5418(18)	62(3)
C(59)	9687(18)	4440(20)	5485(19)	58(4)

Table 2-3. Bond lengths [Å] and angles [°] for **3a**.

Pd(1)–P(2)	2.3724(4)
Pd(1)–P(1)	2.3698(4)
Pd(1)–O(2)	2.1572(11)
Pd(1)–C(37)	1.9658(17)
P(2)–C(19)	1.8513(16)
P(2)–C(25)	1.8584(17)

P(2)–C(31)	1.8535(17)
P(1)–C(13)	1.8460(16)
P(1)–C(1)	1.8617(18)
P(1)–C(7)	1.8580(18)
O(2)–C(44)	1.285(2)
F(1)–C(41)	1.355(2)
O(1)–C(37)	1.215(2)
O(3)–C(44)	1.235(2)
F(2)–C(48)	1.359(2)
C(30)–C(25)	1.536(2)
C(30)–C(29)	1.524(2)
C(19)–C(20)	1.536(2)
C(19)–C(24)	1.535(2)
C(44)–C(45)	1.513(2)
C(37)–C(38)	1.518(2)
C(45)–C(50)	1.394(3)
C(45)–C(46)	1.388(3)
C(26)–C(25)	1.541(2)
C(26)–C(27)	1.535(2)
C(13)–C(18)	1.542(2)
C(13)–C(14)	1.532(2)
C(18)–C(17)	1.529(2)
C(29)–C(28)	1.526(2)
C(50)–C(49)	1.388(3)
C(14)–C(15)	1.535(2)
C(20)–C(21)	1.541(2)
C(1)–C(6)	1.535(3)

C(1)–C(2)	1.538(2)
C(24)–C(23)	1.528(2)
C(31)–C(32)	1.534(2)
C(31)–C(36)	1.516(2)
C(31)–C(36A)	1.468(12)
C(27)–C(28)	1.524(2)
C(23)–C(22)	1.525(2)
C(38)–C(43)	1.396(2)
C(38)–C(39)	1.401(2)
C(41)–C(42)	1.379(3)
C(41)–C(40)	1.383(3)
C(32)–C(33)	1.526(3)
C(32)–C(33A)	1.552(15)
C(43)–C(42)	1.391(3)
C(7)–C(12)	1.547(3)
C(7)–C(8)	1.536(3)
C(40)–C(39)	1.385(2)
C(46)–C(47)	1.390(3)
C(17)–C(16)	1.523(3)
C(22)–C(21)	1.531(3)
C(16)–C(15)	1.525(3)
C(12)–C(11)	1.533(3)
C(49)–C(48)	1.378(3)
C(6)–C(5)	1.533(3)
C(8)–C(9)	1.534(3)
C(36)–C(35)	1.541(3)
C(2)–C(3)	1.534(3)

C(47)–C(48)	1.371(3)
C(5)–C(4)	1.519(3)
C(11)–C(10)	1.518(4)
C(10)–C(9)	1.526(4)
C(33)–C(34)	1.526(3)
C(3)–C(4)	1.518(4)
C(34)–C(35)	1.538(3)
C(35)–C(36A)	1.661(14)
C(35)–C(34A)	1.622(15)
C(34A)–C(33A)	1.500(17)
C(52)–C(53)	1.510(5)
C(52)–C5(1)	1.513(6)
C(53)–C(53)[1]	1.496(6)
C(54)–C(55)	1.59(6)
C(57)–C(56)	1.33(6)
C(57)–C(58)	1.39(6)
C(56)–C(55)	1.49(5)
C(58)–C(59)	1.55(6)

P(1)–Pd(1)–P(2)	161.659(15)
O(2)–Pd(1)–P(2)	94.21(3)
O(2)–Pd(1)–P(1)	87.07(3)
C(37)–Pd(1)–P(2)	88.75(5)
C(37)–Pd(1)–P(1)	91.66(5)
C(37)–Pd(1)–O(2)	174.27(6)
C(19)–P(2)–Pd(1)	106.75(5)
C(19)–P(2)–C(25)	111.04(7)

C(19)–P(2)–C(31)	104.15(7)
C(25)–P(2)–Pd(1)	109.96(5)
C(31)–P(2)–Pd(1)	121.51(6)
C(31)–P(2)–C(25)	103.20(8)
C(13)–P(1)–Pd(1)	109.10(5)
C(13)–P(1)–C(1)	103.74(8)
C(13)–P(1)–C(7)	110.61(8)
C(1)–P(1)–Pd(1)	107.96(5)
C(7)–P(1)–Pd(1)	121.05(6)
C(7)–P(1)–C(1)	102.80(9)
C(44)–O(2)–Pd(1)	111.25(10)
C(29)–C(30)–C(25)	110.88(14)
C(20)–C(19)–P(2)	118.74(11)
C(24)–C(19)–P(2)	112.50(11)
C(24)–C(19)–C(20)	109.89(13)
O(2)–C(44)–C(45)	114.95(14)
O(3)–C(44)–O(2)	125.67(15)
O(3)–C(44)–C(45)	119.38(15)
O(1)–C(37)–Pd(1)	125.61(13)
O(1)–C(37)–C(38)	119.60(15)
C(38)–C(37)–Pd(1)	114.77(11)
C(50)–C(45)–C(44)	121.22(15)
C(46)–C(45)–C(44)	119.28(16)
C(46)–C(45)–C(50)	119.48(16)
C(27)–C(26)–C(25)	110.65(13)
C(18)–C(13)–P(1)	112.18(11)
C(14)–C(13)–P(1)	118.39(12)

C(14)–C(13)–C(18)	110.00(14)
C(30)–C(25)–P(2)	111.63(11)
C(30)–C(25)–C(26)	109.88(13)
C(26)–C(25)–P(2)	117.05(11)
C(17)–C(18)–C(13)	109.86(14)
C(30)–C(29)–C(28)	110.27(14)
C(49)–C(50)–C(45)	120.70(18)
C(13)–C(14)–C(15)	109.49(14)
C(19)–C(20)–C(21)	109.31(13)
C(6)–C(1)–P(1)	111.56(12)
C(6)–C(1)–C(2)	110.30(15)
C(2)–C(1)–P(1)	111.98(13)
C(23)–C(24)–C(19)	110.11(14)
C(32)–C(31)–P(2)	110.14(12)
C(36)–C(31)–P(2)	114.55(12)
C(36)–C(31)–C(32)	111.94(15)
C(36A)–C(31)–P(2)	129.6(6)
C(36A)–C(31)–C(32)	120.1(6)
C(28)–C(27)–C(26)	112.81(15)
C(22)–C(23)–C(24)	110.95(14)
C(43)–C(38)–C(37)	118.47(15)
C(43)–C(38)–C(39)	119.31(16)
C(39)–C(38)–C(37)	122.13(14)
F(1)–C(41)–C(42)	118.48(17)
F(1)–C(41)–C(40)	118.41(17)
C(42)–C(41)–C(40)	123.10(17)
C(31)–C(32)–C(33A)	110.2(8)

C(33)–C(32)–C(31)	112.32(15)
C(42)–C(43)–C(38)	120.80(16)
C(12)–C(7)–P(1)	116.32(14)
C(8)–C(7)–P(1)	113.88(13)
C(8)–C(7)–C(12)	109.30(16)
C(41)–C(42)–C(43)	117.94(17)
C(41)–C(40)–C(39)	118.36(16)
C(27)–C(28)–C(29)	110.34(14)
C(40)–C(39)–C(38)	120.48(16)
C(45)–C(46)–C(47)	120.38(19)
C(16)–C(17)–C(18)	110.99(14)
C(23)–C(22)–C(21)	111.18(14)
C(17)–C(16)–C(15)	111.18(15)
C(11)–C(12)–C(7)	109.88(18)
C(48)–C(49)–C(50)	117.9(2)
C(5)–C(6)–C(1)	111.56(16)
C(16)–C(15)–C(14)	111.75(16)
C(22)–C(21)–C(20)	111.93(14)
C(9)–C(8)–C(7)	110.35(17)
C(31)–C(36)–C(35)	110.31(16)
C(3)–C(2)–C(1)	110.93(18)
C(48)–C(47)–C(46)	118.48(19)
F(2)–C(48)–C(49)	118.3(2)
F(2)–C(48)–C(47)	118.7(2)
C(47)–C(48)–C(49)	123.00(18)
C(4)–C(5)–C(6)	111.31(19)
C(10)–C(11)–C(12)	111.48(19)

C(11)–C(10)–C(9)	111.56(18)
C(32)–C(33)–C(34)	110.96(18)
C(4)–C(3)–C(2)	111.90(17)
C(10)–C(9)–C(8)	110.7(2)
C(33)–C(34)–C(35)	110.02(18)
C(3)–C(4)–C(5)	110.96(17)
C(34)–C(35)–C(36)	110.02(18)
C(34A)–C(35)–C(36A)	95.4(9)
C(31)–C(36A)–C(35)	106.4(8)
C(33A)–C(34A)–C(35)	95.8(12)
C(34A)–C(33A)–C(32)	113.4(14)
C(53)–C(52)–C(51)	114.5(3)
C(53)[1]–C(53)–C(52)	115.3(3)
C(56)–C(57)–C(58)	126(4)
C(57)–C(56)–C(55)	134(4)
C(56)–C(55)–C(54)	135(4)
C(57)–C(58)–C(59)	107(4)

[1]2–X,1–Y,1–Z.

Table 2-4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for **3a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [$h^2a^{*2}U^{11}$ + ... + 2 hka*b*U^{12}].

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Pd(1)	11(6)	14(7)	10(6)	0(4)	4(5)	–3(4)
P(2)	14(18)	12(18)	11(17)	0(13)	6(15)	–1(14)
P(1)	17(19)	18(2)	11(17)	–2(14)	7(15)	–6(15)
O(2)	13(5)	18(6)	15(5)	–1(4)	6(4)	–3(4)
F(1)	27(6)	32(6)	37(6)	13(5)	3(5)	6(5)

O(1)	18(6)	24(6)	20(6)	3(5)	6(5)	–8(5)
O(3)	18(6)	20(6)	26(6)	3(5)	10(5)	1(5)
F(2)	19(6)	69(10)	53(8)	–16(7)	16(6)	–20(6)
C(30)	18(8)	15(8)	15(7)	0(6)	6(6)	1(6)
C(19)	18(7)	14(7)	13(7)	–1(6)	7(6)	–2(6)
C(44)	15(7)	19(8)	10(7)	0(6)	6(6)	–3(6)
C(37)	15(8)	20(8)	10(7)	–2(6)	4(6)	–5(6)
C(45)	16(8)	23(8)	12(7)	–2(6)	7(6)	–5(6)
C(26)	18(8)	21(8)	14(7)	–3(6)	6(6)	0(6)
C(13)	17(8)	19(8)	14(7)	0(6)	8(6)	–4(6)
C(25)	16(7)	13(7)	13(7)	0(6)	6(6)	–1(6)
C(18)	19(8)	21(8)	18(8)	3(6)	8(7)	–2(7)
C(29)	19(8)	20(8)	20(8)	1(6)	8(7)	3(7)
C(50)	19(8)	27(9)	26(9)	0(7)	11(7)	–3(7)
C(14)	27(9)	26(9)	21(8)	–5(7)	16(7)	–7(7)
C(20)	23(8)	20(8)	14(7)	–2(6)	10(7)	–5(7)
C(1)	31(9)	16(8)	19(8)	–3(6)	15(7)	–5(7)
C(24)	30(9)	14(8)	21(8)	–2(6)	17(7)	–3(7)
C(31)	21(8)	15(8)	26(9)	1(6)	15(7)	1(6)
C(27)	19(8)	26(9)	17(8)	–7(7)	5(7)	–2(7)
C(23)	33(10)	15(8)	23(8)	–3(6)	15(8)	–6(7)
C(38)	14(7)	21(8)	12(7)	–1(6)	5(6)	–3(6)
C(41)	23(9)	25(9)	21(8)	5(7)	5(7)	4(7)
C(32)	24(9)	14(8)	20(8)	0(6)	11(7)	–2(6)
C(43)	16(8)	25(9)	19(8)	0(7)	6(6)	–4(7)
C(7)	20(8)	33(9)	14(8)	–6(7)	8(7)	–11(7)
C(42)	14(8)	31(10)	25(9)	2(7)	3(7)	–1(7)

C(40)	20(8)	22(9)	21(8)	2(7)	7(7)	–4(7)
C(28)	17(8)	25(9)	17(8)	1(6)	5(7)	0(7)
C(39)	14(7)	23(9)	15(7)	0(6)	5(6)	–3(6)
C(46)	26(9)	24(9)	25(9)	–4(7)	14(8)	–7(7)
C(17)	23(9)	23(9)	18(8)	2(7)	9(7)	–7(7)
C(22)	28(9)	19(8)	24(9)	3(7)	14(8)	–6(7)
C(16)	26(9)	37(11)	18(8)	–1(7)	12(7)	–14(8)
C(12)	34(11)	44(12)	22(9)	–16(8)	15(8)	–19(9)
C(49)	17(9)	42(12)	34(10)	0(9)	10(8)	–1(8)
C(6)	35(10)	17(9)	24(9)	2(7)	14(8)	0(7)
C(15)	28(10)	36(10)	27(9)	–8(8)	20(8)	–9(8)
C(21)	28(9)	24(9)	21(8)	0(7)	15(7)	–7(7)
C(8)	20(9)	41(11)	14(8)	–1(7)	6(7)	–10(8)
C(36)	15(9)	19(10)	27(10)	–7(8)	7(8)	–2(7)
C(2)	45(12)	23(9)	27(9)	–8(7)	25(9)	–14(8)
C(47)	32(11)	33(11)	35(11)	–11(8)	18(9)	–18(9)
C(48)	17(9)	51(13)	28(10)	–10(9)	12(8)	–14(9)
C(5)	53(13)	23(10)	30(10)	6(8)	21(10)	8(9)
C(11)	42(13)	58(15)	24(10)	–20(10)	15(9)	–31(11)
C(10)	36(12)	82(19)	14(9)	–5(10)	5(9)	–34(12)
C(33)	29(12)	14(10)	27(12)	–4(9)	9(10)	–2(9)
C(3)	69(16)	19(9)	32(10)	–4(8)	34(11)	–12(10)
C(9)	21(9)	62(15)	18(9)	6(9)	1(8)	–16(10)
C(34)	28(12)	22(11)	38(13)	–6(9)	4(10)	9(9)
C(4)	80(18)	20(10)	32(11)	4(8)	32(12)	0(10)
C(35)	23(10)	29(11)	61(14)	–13(10)	19(10)	1(8)
C(36A)	27(6)	18(6)	28(6)	–7(5)	19(5)	–7(4)

C(34A)	33(6)	22(5)	40(6)	–1(5)	16(5)	4(4)
C(33A)	29(6)	15(5)	28(6)	–5(5)	7(5)	–3(4)
C(52)	42(18)	48(19)	39(15)	–4(14)	12(14)	–1(14)
C(53)	28(13)	55(18)	26(13)	–4(11)	3(10)	3(12)
C(51)	65(2)	86(3)	64(2)	16(2)	24(2)	–10(2)
C(54)	71(13)	92(13)	66(10)	3(11)	37(10)	–11(13)
C(57)	58(6)	84(7)	63(6)	5(6)	25(5)	–9(6)
C(56)	59(7)	82(7)	63(6)	6(6)	34(6)	–7(7)
C(55)	72(11)	91(11)	66(8)	4(9)	36(8)	–12(10)
C(58)	55(5)	72(6)	54(5)	0(5)	18(5)	–3(5)
C(59)	47(5)	67(5)	50(5)	1(5)	13(5)	–3(5)

Table 2-5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **3a**.

	x	*y*	*z*	*U*(eq)
H(30A)	8042	4724	7665	20
H(30B)	8089	4943	7076	20
H(19)	6288	4965	6852	18
H(26A)	7736	6678	7996	21
H(26B)	7788	5804	8226	21
H(13)	7845	5285	5244	19
H(25)	7979	6273	7246	17
H(18A)	6991	6263	4413	23
H(18B)	7276	6431	5096	23
H(29A)	8942	5676	7607	23
H(29B)	9031	4796	7832	23
H(50)	8935	5466	6514	28
H(14A)	7212	4987	4039	27

H(14B)	7644	4374	4488	27
H(20A)	6656	5351	7836	22
H(20B)	7176	4741	7990	22
H(1)	7309	3632	5032	24
H(24A)	6853	4183	6519	23
H(24B)	7289	4011	7179	23
H(31)	6835	6639	7486	23
H(31A)	6347	6557	6671	23
H(27A)	8730	6719	8222	26
H(27B)	8662	6443	8789	26
H(23A)	6078	3606	6659	27
H(23B)	6599	2995	6828	27
H(32A)	7308	7396	7062	23
H(32B)	6768	7329	6441	23
H(32C)	6930	7255	6505	23
H(32D)	7258	7526	7166	23
H(43)	4998	5666	5136	24
H(7)	5975	4464	4666	26
H(42)	4454	6699	4559	30
H(40)	5946	7877	4899	26
H(28A)	8843	5150	8630	25
H(28B)	9362	5677	8629	25
H(39)	6487	6841	5465	21
H(46)	8546	7756	6336	29
H(17A)	7779	7133	4643	26
H(17B)	8208	6531	5105	26
H(22A)	6897	3245	7817	27

H(22B)	6221	3028	7541	27
H(16A)	8341	6433	4253	31
H(16B)	7661	6293	3877	31
H(12A)	6475	4213	3866	39
H(12B)	6433	3555	4290	39
H(49)	9918	5760	6798	38
H(6A)	8104	4202	5804	30
H(6B)	7776	4135	6216	30
H(15A)	8436	5230	4712	33
H(15B)	8135	5091	4027	33
H(21A)	6421	4144	8156	27
H(21B)	59612	4339	7510	27
H(8A)	5940	5803	4431	30
H(8B)	6167	5596	3950	30
H(36A)	5925	6081	6973	25
H(36B)	5866	6498	6389	25
H(2A)	6723	3562	5776	34
H(2B)	6449	3293	5113	34
H(47)	9529	8052	6624	39
H(5A)	8167	2840	5766	41
H(5B)	8442	3103	6430	41
H(11A)	5634	3456	3358	49
H(11B)	5408	3624	3845	49
H(10A)	4908	4437	3054	55
H(10B)	5504	4757	3069	55
H(33A)	6717	8539	6828	29
H(33B)	6768	8150	7418	29

H(3A)	6797	2200	5745	43
H(3B)	7123	2270	5331	43
H(9A)	5092	5049	3937	43
H(9B)	5140	5686	3502	43
H(34A)	5791	7977	6314	38
H(34B)	5788	8472	6845	38
H(4A)	7814	2016	6274	49
H(4B)	7595	2744	6518	49
H(35A)	5354	7235	6815	45
H(35B)	5933	7313	7404	45
H(35C)	5629	7201	6555	45
H(35D)	5460	7275	7098	45
H(36C)	6517	6822	7753	27
H(36D)	6132	6129	7351	27
H(34C)	5965	8517	7173	37
H(34D)	6498	7978	7598	37
H(33C)	6598	8510	6736	31
H(33D)	6095	7915	6367	31
H(52A)	10197	4349	5852	54
H(52B)	10004	3758	5320	54
H(53A)	9420	4742	4698	47
H(53B)	9634	5331	5231	47
H(51A)	9028	3855	5220	109
H(51B)	9265	4364	5799	109
H(51C)	9461	3478	5822	109
H(54A)	9874	4311	7795	110
H(54B)	10379	4341	7579	110

H(54C)	10269	3563	7860	110
H(57A)	8938	3401	5779	82
H(57B)	9519	2910	6035	82
H(56A)	9312	4339	6274	78
H(56B)	9947	4040	6436	78
H(55A)	9666	3151	7027	89
H(55B)	9255	3854	6982	89
H(58A)	9078	3550	5068	74
H(58B)	9729	3223	5385	74
H(59A)	9754	4572	5146	86
H(59B)	9405	4796	5518	86
H(59C)	10053	4471	5834	86

References and Notes

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(5) $Pd(PCy_3)_2$ was characterized by the ^{31}P NMR spectra based on the follow literature. See: (a) Grushin, V. V.; Bensimon, C.; Alper, H. *Inorg. Chem.* **1994**, *33*, 4804–4806. (b) Mitchell, E. A.; Baird, M. C. *Organometallics* **2007**, *26*, 5230–5238. (c) Li, H.; Grasa, G. A.; Colacot, T. J. A *Org. Lett.* **2010**, *12*, 3332–3335.

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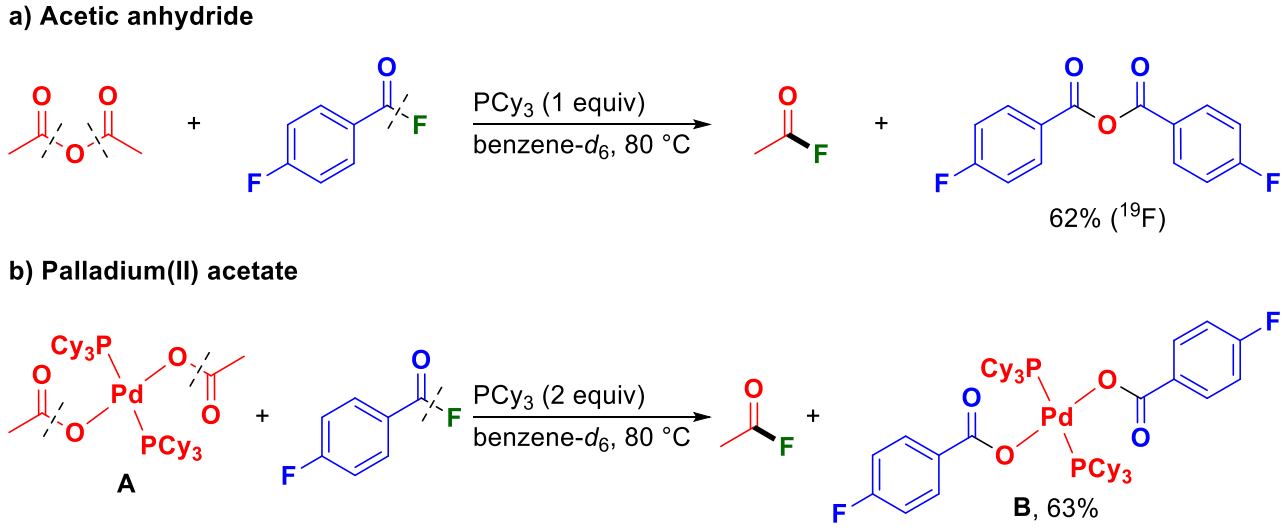
Chapter 3.

Phosphine-Catalyzed Acyl-Group Exchange Reaction between Carboxylic Acids and an Aroyl Fluoride

3-1. Introduction

3-1-1. Acyl-group exchange reaction for the synthesis of acyl fluorides

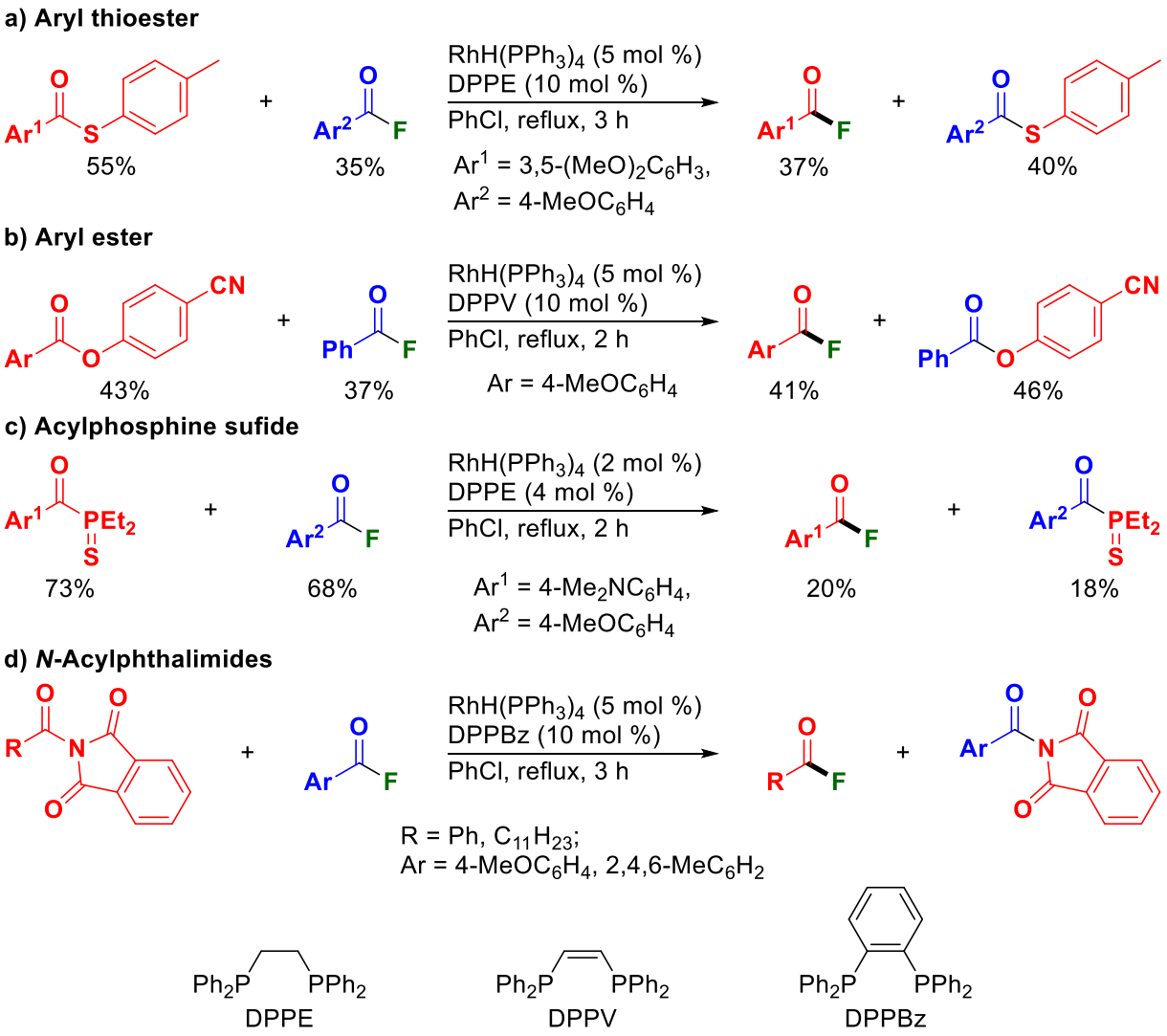
As shown in chapter 2, the author found that the acyl group-exchange reaction between acetic anhydride and acyl fluoride proceeded smoothly in the presence of only PCy_3 to form acetyl fluoride and the corresponding carboxylic anhydride (Scheme 3-1a). Similarly, the acyl-group exchange between palladium(II) acetate complex **A** and acyl fluoride proceeded to afford acetyl fluoride and palladium(II) benzoate complex **B** (Scheme 3-1b). These results imply that acyl fluorides potentially have fluorination ability to synthesize acyl fluorides from carboxylate compounds in the presence of only a phosphine. Thus, the author attempted to apply the phosphine-promoted acyl group-exchange to a fluorination reaction for the synthesis of acyl fluorides.



Scheme 3-1. Phosphine-promoted acyl-group exchange reactions between carboxylic acid derivatives and acyl fluorides.

Such synthetic methods of acyl fluorides by an acyl-group exchange between a carboxylic acid derivative and an acyl fluoride are known (Scheme 3-2).[1,2] Arisawa, Yamaguchi, and co-workers

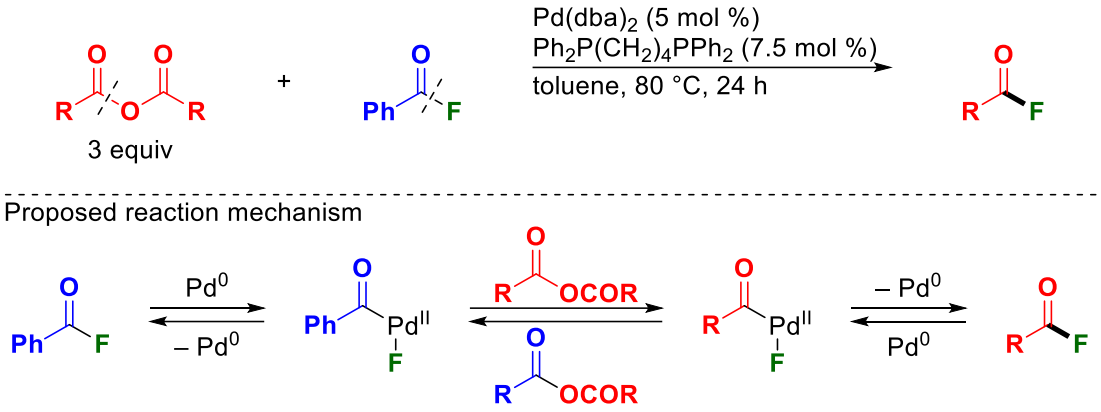
reported that acyl-group exchange between acyl fluorides and various carboxylic acid derivatives such as an aryl thioester, an aryl ester, an acylphosphine sulfide, and *N*-acylphthalimides occurred under a suitable rhodium/phosphine catalytic system.[1]



Scheme 3-2. Rhodium-catalyzed acyl-group exchange between carboxylic acid derivatives and acyl fluorides.

Our group separately developed a palladium/phosphine-catalyzed acyl-group exchange between benzoyl fluoride and acid anhydrides, for the synthesis of more complicated and value-added acyl fluorides (Scheme 3-3).[2] In this report, a reversible reaction pathway involving the acyl C–F bond cleavage/formation at the palladium center was proposed: (i) oxidative addition of the acyl C–F bond to form an acyl palladium fluoride, (ii) acyl exchange between the acyl palladium and an acid

anhydride, and (iii) reductive elimination to furnish the new C–F bond of the acyl fluoride. These acyl-exchange reactions have shown the great potential for the utility of acyl fluorides as fluorinating reagents in the synthesis of another acyl fluoride. On the other hand, besides the use of an activated carboxylic acid and a transition-metal catalyst, there is some room for improvement of the current methodologies by using a novel catalytic system.

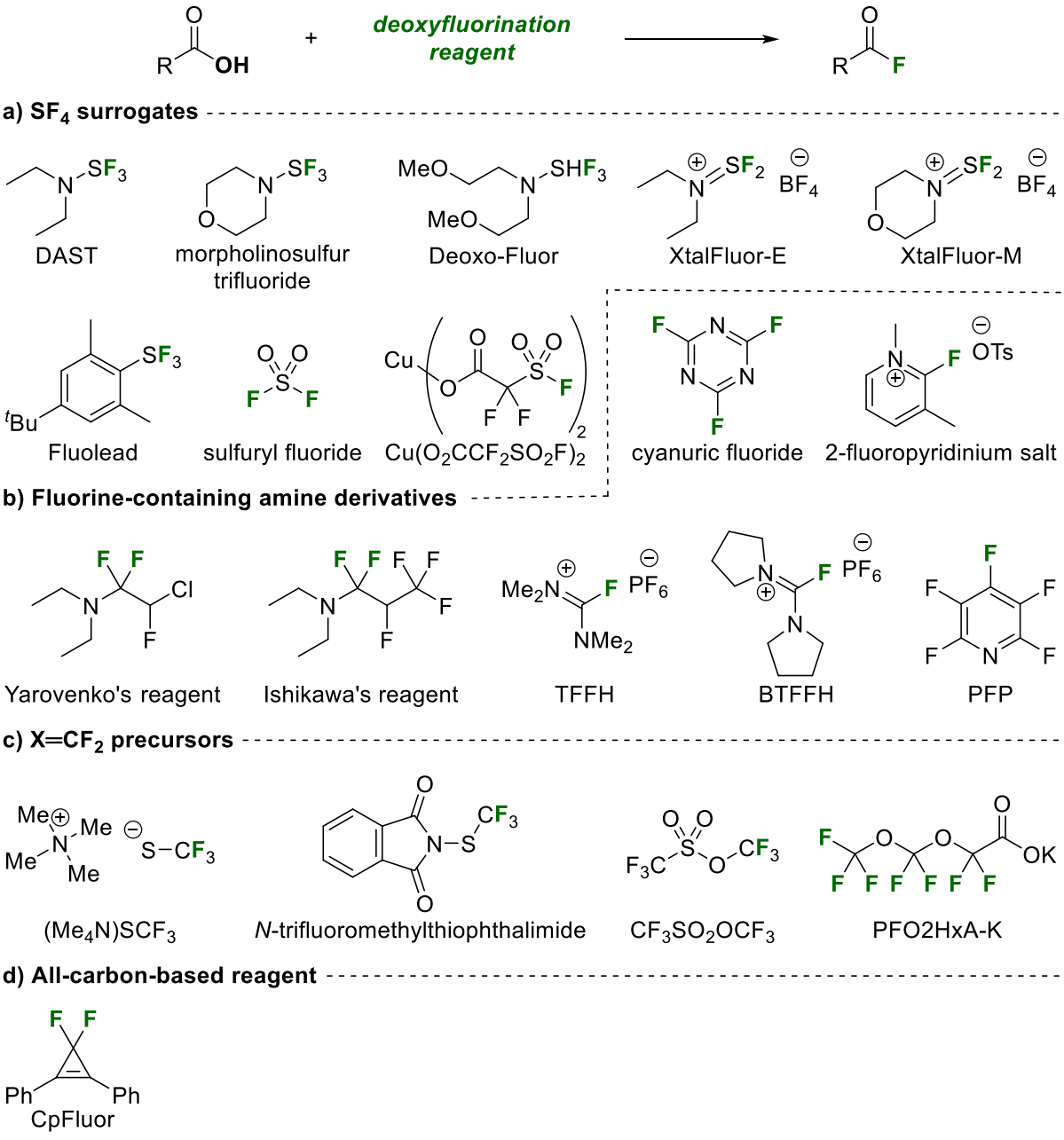


Scheme 3-3. Palladium-catalyzed acyl-group exchange between carboxylic acid anhydrides and benzoyl fluoride (our previous report).

3-1-2. Deoxyfluorination: Direct synthesis of acyl fluorides from carboxylic acids

Owing to the utility of acyl fluorides as a divergent synthetic material, a lot of synthetic methods have been developed.[3–5] Among them, deoxyfluorination of carboxylic acids has been extensively investigated because it offers direct access to acyl fluorides from ubiquitous carboxylic acids through a single-step process (Scheme 3-4).[6] To date, various deoxyfluorination reagents have been developed:[7–21] a) sulfur tetrafluoride (SF_4) surrogates[7–12] such as (diethylamino)sulfur trifluoride (DAST),[7] morpholinosulfur trifluoride,[7] bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor),[8] diethylaminodifluorosulfinium tetrafluoroborate (XtalFluor-E),[9] morpholinoaminodifluorosulfinium tetrafluoroborate (XtalFluor-M),[9] 4-*tert*-butyl-2,6-dimrthylphenylsulfur trifluoride (Fluolead),[10] sulfuryl fluoride,[11] and $Cu(O_2CCF_2SO_2F)_2$;[12] b) fluorine-containing amine derivatives[13–18] such as cyanuric fluoride,[13] a 2-fluoropyridinium salt,[14] (2-chrolo-1,1,2-trifluoroethyl)diethylamine (Yarovenko's reagent),[15a] (1,1,2,3,3,3-hexafluoropropyl)diethylamine (Ishikawa's reagent),[15b] tetramethylfluoroformamidinium

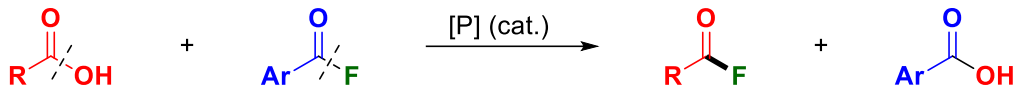
hexafluorophosphate (TFFH),[16] bis(tetramethylene)fluoroformamidinium hexafluorophosphate (BTFFH),[17] and pentafluoropyridine (PFP);[18] and, c) (thio)carbonyl difluoride (X=CF_2) precursors,[19,20] such as $(Me_4N)SCF_3$,[19a] *N*-trifluoromethylthiophthalimide,[19b] trifluoromethyl trifluoromethanesulfonate ($CF_3SO_2OCF_3$),[20a] a potasium salt of perfluoroalkyl ether carboxylic acid (PFO2HxA-K).[20b] In recent years, 3,3-difluoro-1,2-diphenylcyclopropene (CpFluor) has been disclosed as an alternative fluorinating reagent that has a C–F bond on a strained carbon framework that does not contain hetero atoms such as sulfur and/or nitrogen (Scheme 3-4d).[21]



Scheme 3-4. Representative deoxyfluorination reagents for the synthesis of acyl fluorides

However, the development of a new deoxyfluorination reagent for carboxylic acids is still demanded. Especially, a stable, easily-to-handled, and readily available deoxyfluorination reagent is highly desirable.[22]

With these backgrounds in mind, the author attempted to develop a metal-free phosphine-catalyzed acyl-group exchange reaction between carboxylic acids and acyl fluorides in Chapter 3 (Scheme 3-5). Herein, the author reports the detailed results.



Scheme 3-5. Phosphine-catalyzed acyl-group exchange reactions between carboxylic acids and acyl fluorides (**this work**).

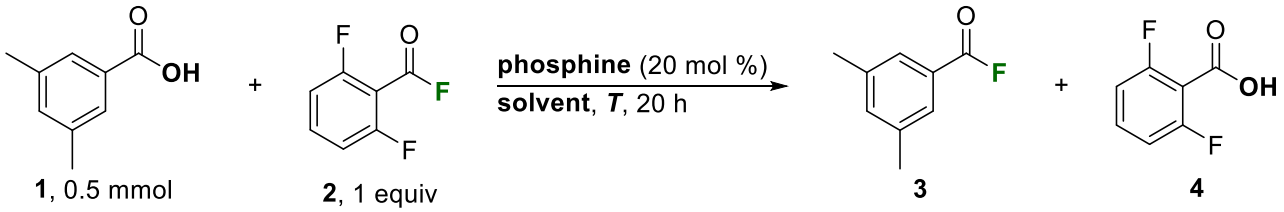
3-2. Results and Discussion

3-2-1. Optimization of the reaction conditions

As an initial attempt to catalytically exchange each acyl group between carboxylic acids and acyl fluorides, a toluene (0.5 mL) solution of equimolar 3,5-dimethylbenzoic acid (**1**) and 2,6-difluorobenzoyl fluoride (**2**) was treated with PCy_3 (20 mol %) at 80 °C for 20 h (Table 3-1, entry 1). **2** was intentionally utilized according to a working hypothesis whereby an electron-deficient acyl fluoride with a weak acyl C–F bond should effectively act as a better fluorinating agent. The expected 3,5-dimethylbenzoyl fluoride (**3**) was detected in 24% yield by gas chromatography (GC) along with 2,6-difluorobenzoic acid (**4**) in 51% yield. In this case, a mixture of acid anhydrides derived from **1** and/or **2** was also observed. When using 1,4-dioxane as an aprotic polar solvent, the selectivity of both products **3** and **4** was improved to yields of 47 and 51%, respectively (entry 2). Also, the use of DMF led to further improvement in the chemical yields (entry 3). Moreover, it was found that NMP was the optimal solvent for this deoxyfluorination, affording **3** in 68% yield (entry 4). Therefore, the author supposes that a high solubility of carboxylic acid **1** in these solvents increased the yield of **3**.[23] Next, the author examined the effect of a phosphine (entries 5–12). For example, among triarylphosphines, relatively electron-rich phosphines such as $P(4\text{-}MeOC_6H_4)_3$ and $P[2,4,6\text{-}(MeO)_3C_6H_2]_3$ gave **3** in good yields, but less electron-donating phosphines such as PPh_3 and $P(4\text{-}FC_6H_4)_3$ showed low yields (entries 5–8). In contrast, the use of $P(2\text{-}MeC_6H_4)_3$ with a bulky circumstance around the phosphorus atom center resulted in a rather low yield of **3** (entry 9). On the other hand, PCy_2Ph provided **3** in good yield, but $PCy_2(2\text{-}PhC_6H_4)$ was not suitable for this deoxyfluorination to afford **3** in only 8% yield (entries 10 and 11). Interestingly, acyl-group exchange slightly proceeded in the absence of a phosphine (entry 12). Thus, an electron-donating and not sterically demanding phosphine is required as a catalyst for the acyl-group-exchange reaction between an acyl fluoride and a carboxylic acid. The reaction temperature was then examined (entries 13 and 14). Surprisingly, the acyl-transfer reaction proceeded even at room temperature to afford **3** in moderate yield (entry 13). Although the reaction at 120 °C slightly decreased the yield of **3**, the desired acyl-group exchange reaction proceeded to some extent at high

temperature (entry 14). Therefore, it was shown that an acyl fluoride used in this work possessed high thermal stability. Also, the author examined the amount of PCy_3, and found that PCy_3 could be reduced to 10 mol % (entry 15). Finally, the use of 1.2 equiv of **2** resulted in the formation of **3** in satisfying yield (80% GC yield and 55% isolated yield) (entry 16).

Table 3-1. Optimization of the reaction conditions.

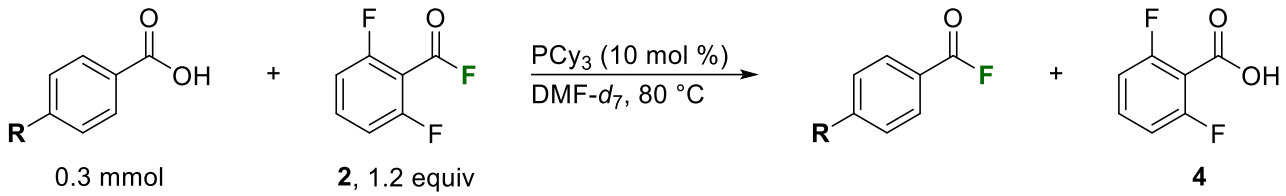


1, 0.5 mmol **2**, 1 equiv **3** **4**

entry	phosphine	solvent	*T* (°C)	GC yields (%)	
				3	**4**
1	PCy_3	toluene	80	24	51
2	PCy_3	1,4-dioxane	80	47	51
3	PCy_3	DMF	80	61	56
4	PCy_3	NMP	80	68	67
5	$P(4\text{-}FC_6H_4)_3$	NMP	80	10	15
6	PPh_3	NMP	80	16	16
7	$P(4\text{-}MeOC_6H_4)_3$	NMP	80	52	52
8	$P[2,4,6\text{-}(MeO)_3C_6H_2]_3$	NMP	80	69	50
9	$P(2\text{-}MeC_6H_4)_3$	NMP	80	3	4
10	PCy_2Ph	NMP	80	61	56
11	$PCy_2(2\text{-}PhC_6H_4)$	NMP	80	8	14
12	—	NMP	80	6	10
13	PCy_3	NMP	rt	45	38
14	PCy_3	NMP	120	49	54
15	PCy_3 (10 mol %)	NMP	80	64	66
16[a]	PCy_3 (10 mol %)	NMP	80	80 (55)[b]	63

[a] Acyl fluoride **2** (1.2 equiv) was used. [b] Isolated yield.

Also, to investigate substituent effects of benzoic acid derivatives to the reaction time and the yields, each reaction using three sorts of 4-substituted benzoic acids (CF_3, H, NMe_2) in the presence of acyl fluoride **2** (1.2 equiv) and PCy_3 (10 mol %) in DMF-d_7 at 80 °C was monitored by ^{19}F NMR spectroscopy, and the obtained concentration–time plots are displayed in Figure 3-1.



0.3 mmol **2**, 1.2 equiv **4**

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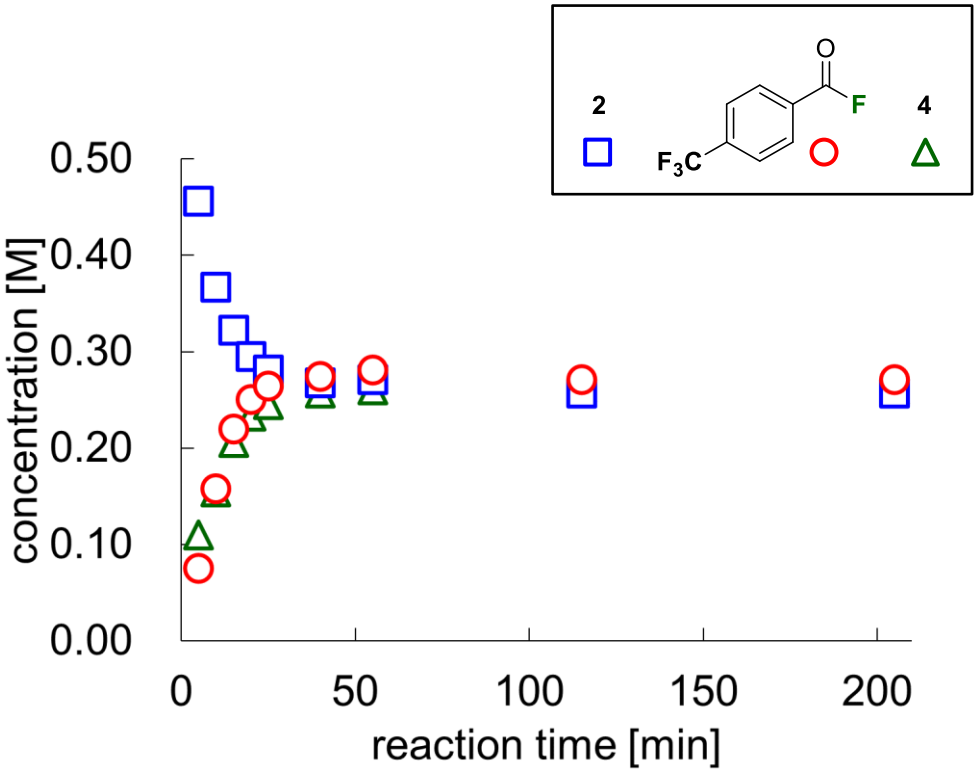
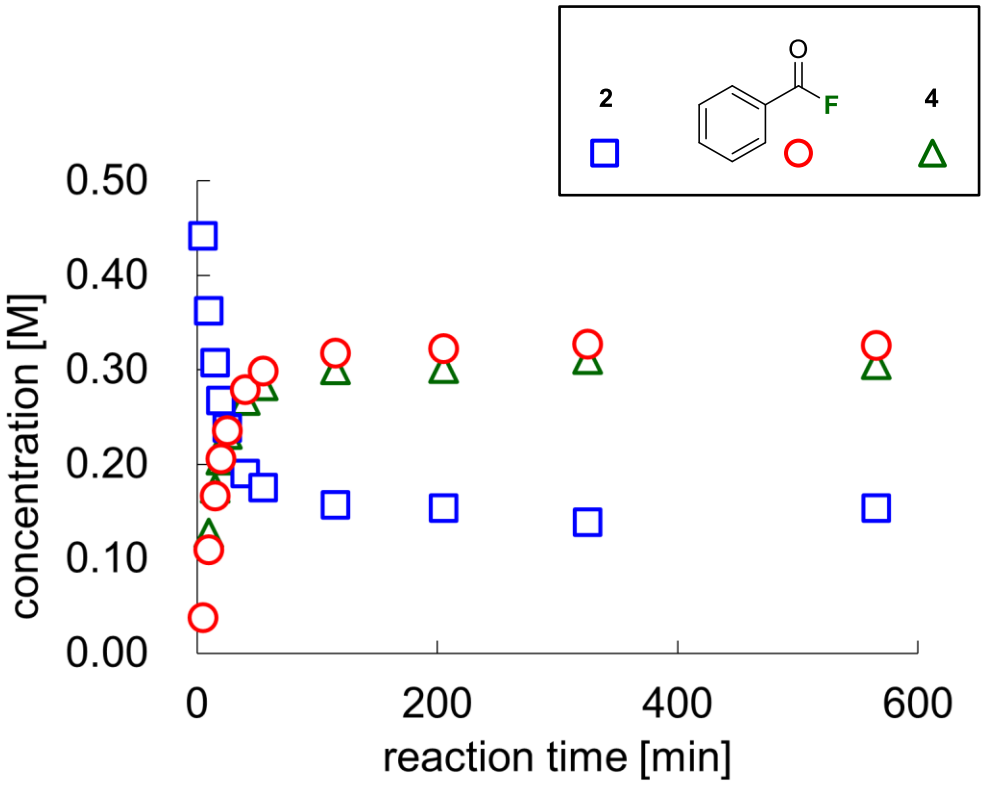
a) R = CF_3



b) R = H



c) R = NMe_2

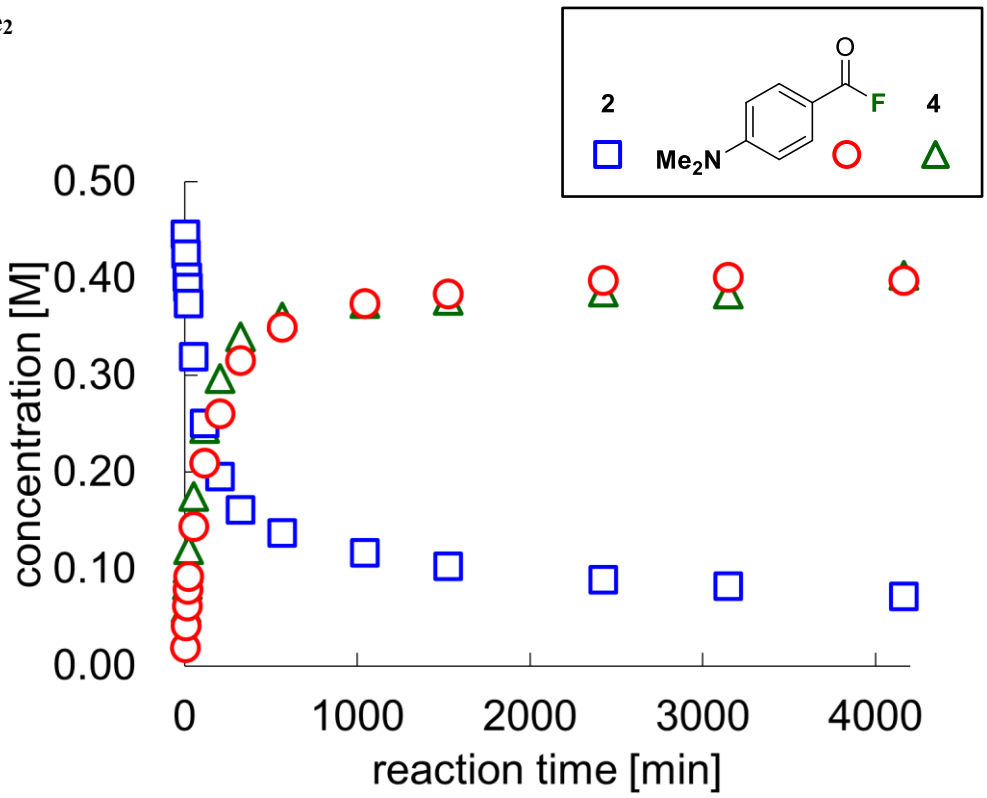


Figure 3-1. Concentration–time plots by a ^{19}F NMR monitor of the acyl-group exchange reaction using a 4-substituted benzoic acid; [**2**] (□, blue), [acyl fluoride product] (○, red), [**4**] (△, green).

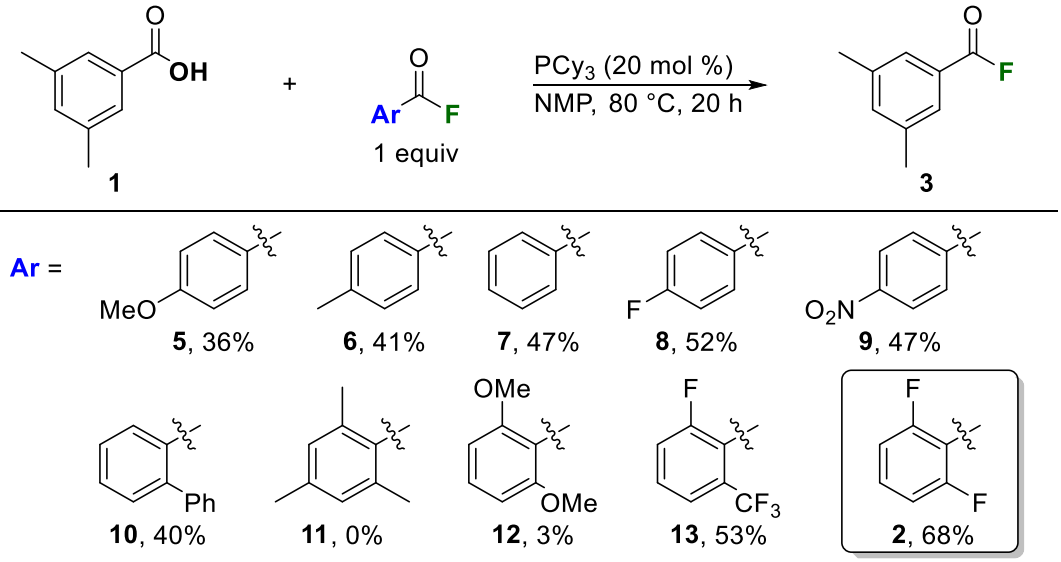
As shown in all plots, the reaction is considered to be in equilibrium between carboxylic acids and acyl fluorides. Also, the obtained plots revealed that the electron-donating group contributes the increase of the chemical yields of the products (NMe_2 > H > CF_3) although the longer reaction time is required. Based on these results, to correspond to any carboxylic acids, we set the optimal reaction time at 20 h.

3-2-2. Investigation of the fluorination ability of acyl fluorides

Then, the author investigated the fluorinating ability of aroyl fluorides with a variety of functional groups for acyl-group exchange under the reaction conditions of entry 4 in Table 3-1 (Table 3-2). When electron-donating aroyl fluorides such as 4-methoxybenzoyl fluoride (**5**) and 4-methylbenzoyl fluoride (**6**) were initially examined, the desired acyl fluoride **3** was formed in 36 and 41% yields. The use of either unsubstituted or electron-deficient benzoyl fluorides, such as

benzoyl fluoride (**7**;47%), 4-fluorobenzoyl fluoride (**8**; 52%), and 4-nitrobenzoyl fluoride (**9**; 47%), slightly improved the chemical yield of **3**. These results suggested that the electron density of the aroyl fluoride contributes to its fluorination ability. 2-Phenylbenzoyl fluoride **10** was also applicable although the yields of **3** were moderate. The author then examined 2,6-disubstituted benzoyl fluorides. When bulky and electron-rich substrates **11** or **12** were used, the desired acyl-exchange reaction was remarkably hindered. On the other hand, employment of electron-deficient 2-fluoro-6-(trifluoromethyl)benzoyl fluoride (**13**) furnished **3** in 53% yield. These results showed that various acyl fluorides except for bulky ones could be used as a fluorinating reagent in this acyl-group exchange reaction. Among them, it was revealed that 2,6-difluorobenzoyl fluoride (**2**) was the best reagent to afford the desired acyl fluoride **3** in 68% yield. In addition, the optimal acyl fluoride **2** can be easily prepared from a commercially available acyl chloride and fluoride salt and is an easily-to-handled solid reagent.

Table 3-2. Investigation of the fluorinating ability of acyl fluorides.



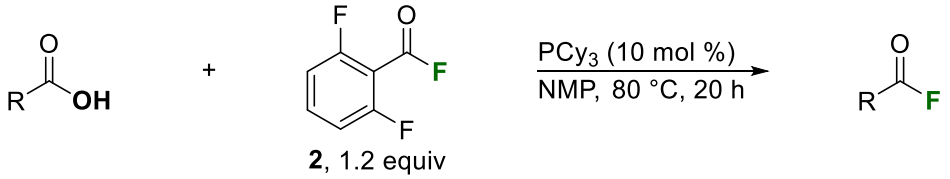
The yields of acyl fluoride **3** are shown as determined by GC analysis (internal standard: decane).

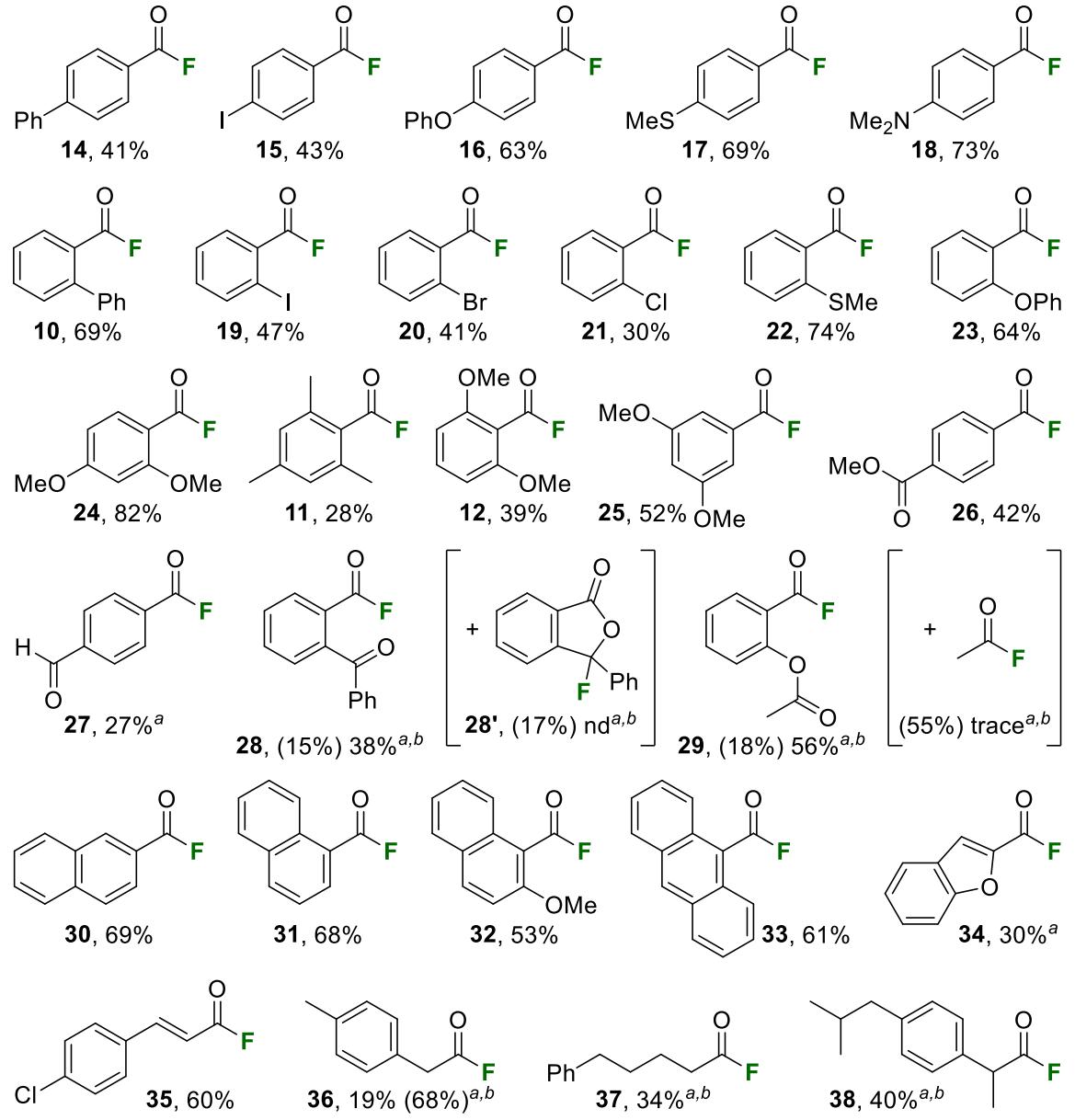
3-2-3. Substrate scope

Then, the author examined the substrate scope of carboxylic acids under optimal conditions (Table

3-1, entry 16), and the results are summarized in Table 3-3. First, 4-substituted benzoic acids were assessed. The use of a benzoic acid bearing a phenyl or an iodo group afforded the corresponding acyl fluoride **14** or **15** in 41 and 43% yields, respectively. In contrast, benzoic acids containing an electron-donating group, such as a phenoxy, a methylthio, or a dimethylamino group, showed a high reactivity, and gave **16**–**18** in good yields. Next, 2-substituted benzoic acids were examined. The reaction with 2-phenylbenzoic acid proceeded, leading to 2-phenylbenzoyl fluoride **10**. Less reactivity was gained by using 2-halogen-substituted benzoic acids, and the corresponding acyl fluorides **19**–**21** were obtained in 30–40% yields. The use of 2-methylthio- and 2-phenoxybenzoic acid furnished the desired acyl fluorides **22** and **23** in good yields. Moreover, the reaction with 2,4-dimethoxybenzoic acid successfully proceeded to afford acyl fluoride **24** in 82% yield. Therefore, the reactivity of 2-substituted benzoic acids is significantly affected by the electronic effect of a functional group rather than by the steric effect. However, when 2,6-disubstituted benzoic acids were used, the yields of acyl fluorides **11** and **12** were decreased to low yields, probably due to the fact that their steric hindrances rather than the electronic effect strongly influenced the reactivity. The employment of 3,5-dimethoxybenzoic acids gave the corresponding product **25** in moderate yield. Benzoic acids containing another carbonyl group were also examined. The author found that 4-methoxycarbonyl- and 4-formyl groups tolerated the catalytic conditions to afford the desired acyl fluorides **26** and **27**. However, the use of 2-benzoyl- and 2-acetoxybenzoic acid under the standard conditions produced the corresponding acyl fluorides **28** and **29** in low yields. During deoxyfluorination with 2-benzoylbenzoic acid, ^{19}F NMR measurement revealed an initial formation of the desired acyl fluoride **28**, which then was followed by an intramolecular cyclization[24] of **28** to give an undesirable γ-fluoro-γ-butyrolactone **28'**. In the case with 2-acetoxybenzoic acid, ^{19}F NMR measurement of the crude material revealed the formation of acetyl fluoride[4k] as a byproduct, clearly indicating the substitution of a fluoride ion on the acetoxy moiety. Interestingly, reaction conditions at room temperature suppressed these undesired side reactions and improved the yields of **28** and **29**. Furthermore, various naphthoyl fluorides **30**–**32** could be prepared in good yields from carboxylic acids. Anthracene-ring-substituted acyl fluoride **33** could also be synthesized.

Table 3-3. Substrate scope.





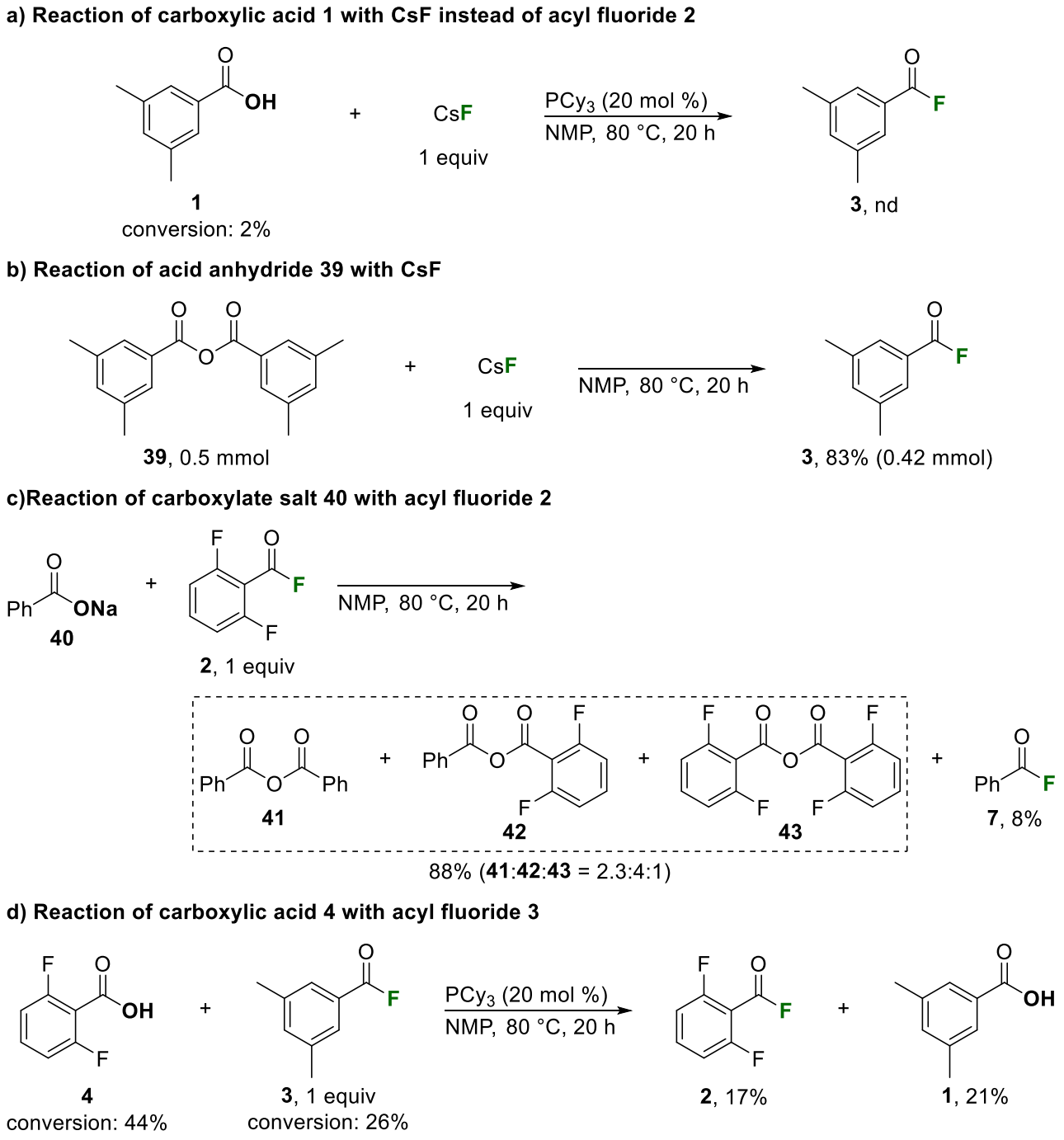
Isolated yields are shown. ^{19}F NMR yields are shown in parentheses (internal standard: PhF).
[a] Acyl fluoride **2** (2 mmol) was used. [b] Reaction was carried out at room temperature.

Heteroaromatic acyl fluoride **34** was also obtained by the reaction with corresponding carboxylic acid. Furthermore, the use of a cinnamic acid provided cinnamoyl fluoride **35** in 60% yield. Finally, this catalytic deoxyfluorination could also be applied to aliphatic carboxylic acids. 4-

Methylphenylacetyl fluoride **36** was yielded from the corresponding carboxylic acid, however, the chemical yield was low owing to the difficulty of isolation derived from the instability and the high volatility. 5-Phenylpentanoic acid furnished straight-chain aliphatic acyl fluoride **37**. To prove the further utility of this method, ibuprofen, an active pharmaceutical ingredient, was examined, in which the desired acyl fluoride **38** was obtained in moderate yield.

3-2-4. Mechanistic insights

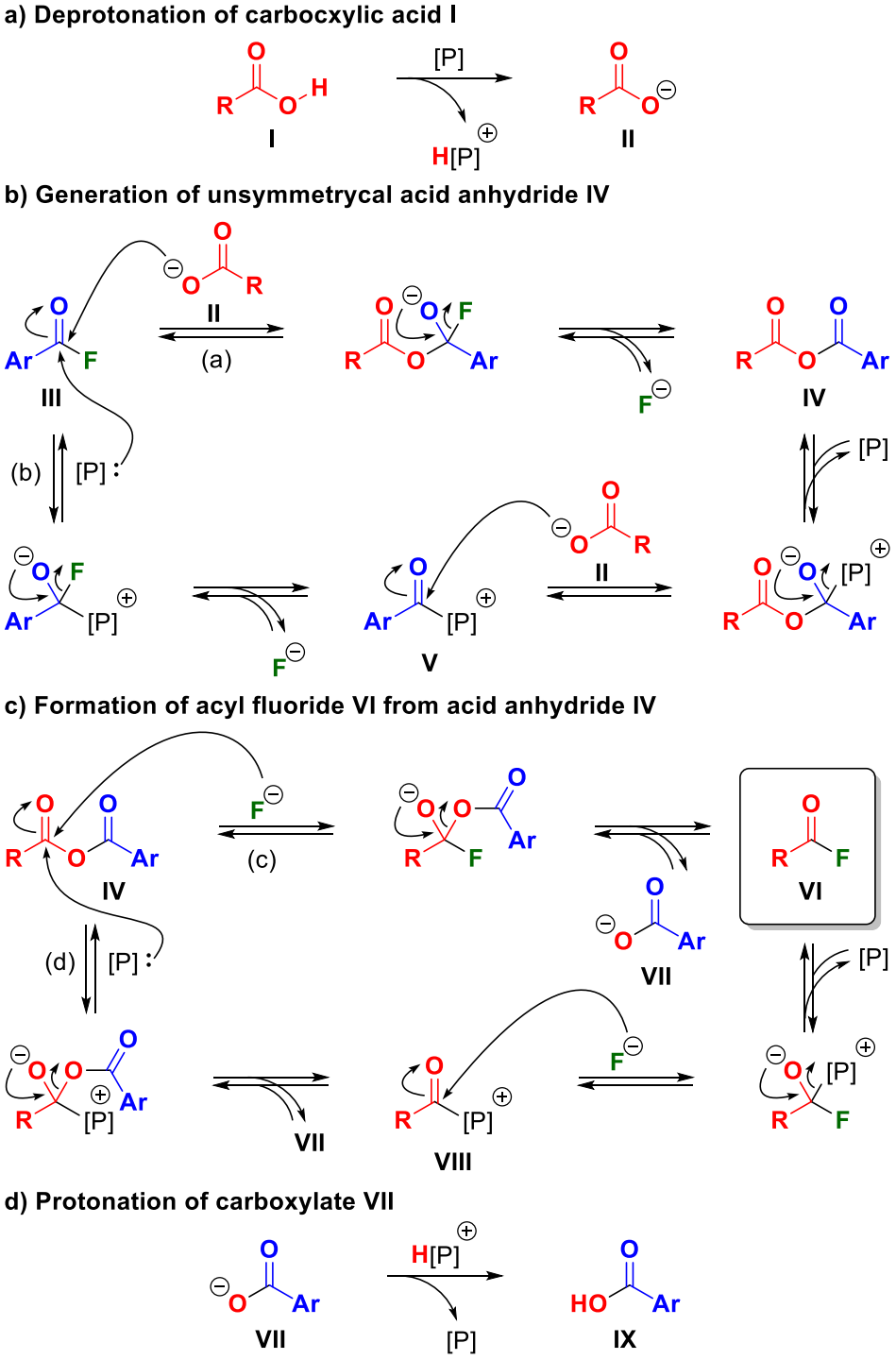
To reveal the reaction mechanism for the phosphine-catalyzed acyl-group exchange between carboxylic acids and an aroyl fluoride, several control experiments were carried out (Scheme 3-6). When CsF was used instead of acyl fluoride **2**, the desired product **3** could not be obtained (Scheme 3-6a). That result supported that in the catalytic system, direct substitution of the OH group by a fluoride ion is unlikely and a carboxylic acid anhydride intermediate should involve. As expected, the reaction of acid anhydride **39** with CsF effectively afforded acyl fluoride **3** (Scheme 3-6b). As mentioned later, one of the roles of PCy_3 should be a base, that produces a carboxylate anion from a carboxylic acid. Thus, when a control experiment using sodium benzoate (**40**) and acyl fluoride **2** was performed in the absence of PCy_3, three acid anhydrides **41**–**43** and benzoyl fluoride (**7**) were detected (Scheme 3-6c).[25] Then, to check the backward reaction of the acyl-group exchange reaction, 2,6-difluorobenzoic acid (**4**) and 3,5-dimethylbenzoyl fluoride (**3**) were treated with a catalytic amount of PCy_3 in NMP at 80 °C for 20 h (Scheme 3-6d). Consequently, the corresponding products **2** and **1** were formed in about 20% yields, while 60–70% of starting materials remained. This result clearly indicated that the catalytic reaction is equilibrium, which moderately favors the formation of **3** and **4**.[26]



Scheme 3-6. Control experiments.

On the basis of the results shown in Scheme 6 and Figure 3-1, a reaction mechanism of the phosphine-catalyzed acyl-group exchange between carboxylic acids and an aroyl fluoride is proposed in Scheme 3-7. First, carboxylic acid **I** is deprotonated by PCy_3 to generate carboxylate ion **II** (Scheme 3-7a).[27] Carboxylate **II** nucleophilically attacks a carbonyl carbon of acyl fluoride **III** to furnish unsymmetrical carboxylic acid anhydride **IV** with the release of a fluoride ion

(Scheme 3-7b, path a). As another path for the generation of acid anhydride **IV**, acyl fluoride **III** reacts with PCy_3 to provide acyl phosphonium salt **V**[28] and subsequent nucleophilic substitution between **V** and **II** proceeds leading to acid anhydride **IV** (Scheme 3-7b, path b). Acid anhydride **IV** is then attacked by the fluoride ion, producing the desired acyl fluoride **VI** and carboxylate **VII** (Scheme 3-7c, path c).

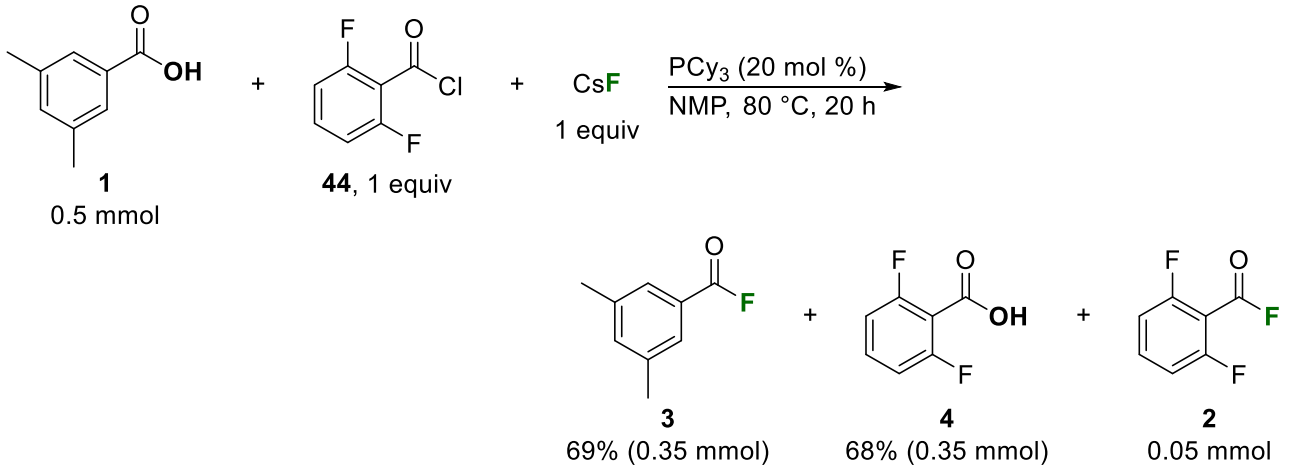


Scheme 3-7. Proposed reaction mechanism. [P] = PCy_3, Ar = 2,6-$F_2C_6H_3$.

In this fluorination process, there is also the possibility that a reaction of acid anhydride **IV** with PCy_3 forms acyl phosphonium salt **VIII** and nucleophilic attack by the fluoride ion then occurs to afford acyl fluoride **VI** (Scheme 3-7c, path d). Released carboxylate **VII** is finally protonated by the phosphonium salt ($H[P]^+$) to form the corresponding carboxylic acid **IX** with the regeneration of a phosphine catalyst (Scheme 3-7d).[29,30]

3-2-5. Application of the phosphine-catalyzed acyl-group exchange reaction

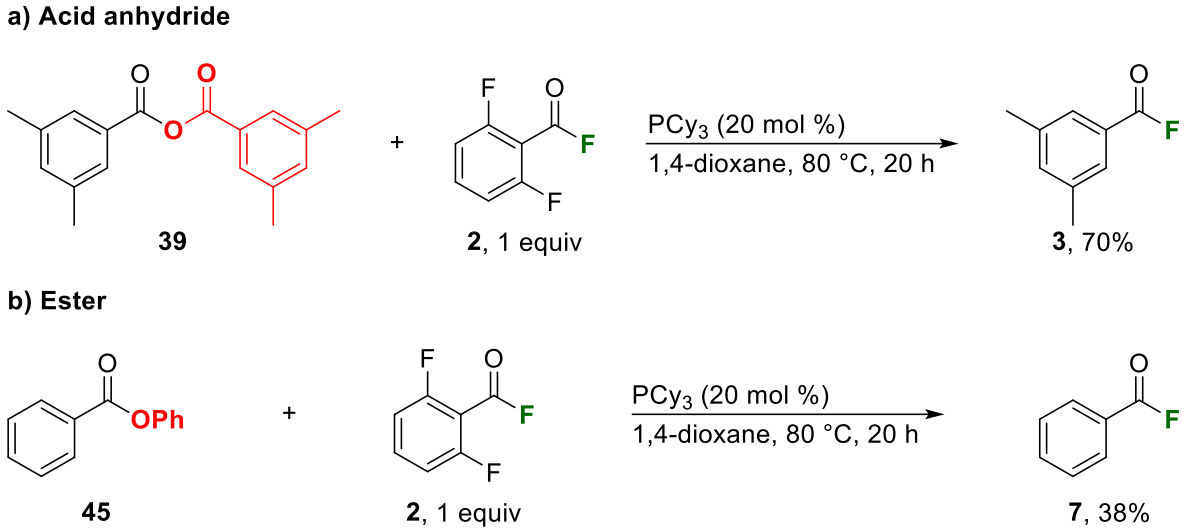
Finally, applications of this reaction were examined. As described above, acyl fluoride **2**, a fluorination reagent, is easy to prepare from the corresponding acyl chloride and a fluoride salt as commercially available reagents. To simplify a series of synthetic methods, the author thus examined a one-pot synthesis of the desired acyl fluoride via the in-situ generation of acyl fluoride **2** and the subsequent acyl-group exchange with a carboxylic acid (Scheme 3-8). When carboxylic acid **1** was treated with 1 equiv of acyl chloride **44** and CsF in the presence of a catalytic amount of PCy_3 in NMP at 80 °C for 20 h, the desired acyl fluoride **3** was obtained in good yield. Also, an equivalent amount of carboxylic acid **4** and a small amount (10%) of acyl fluoride **2** remained in the reaction pot.



Scheme 3-8. One-pot synthesis of acyl fluoride using acyl chloride and CsF

Moreover, the fluorination of carboxylic acid derivatives besides a carboxylic acid was investigated using this catalytic system (Scheme 3-9). When acid anhydride **39** and ester **45** were

used, the desired acyl fluorides **3** and **7** were obtained in 70 and 38% yields, respectively.



Scheme 3-9. Expansion to other carboxylic acid derivatives.

3-3. Conclusions

In Chapter 3, the author developed a novel method for the synthesis of acyl fluorides. This method involves a phosphine-catalyzed acyl-group exchange between carboxylic acids and 2,6-difluorobenzoyl fluoride. This study is the first to demonstrate that acyl fluorides have the ability to function as a deoxyfluorination reagent by using a phosphine catalyst. Also, the acyl fluoride reagent is a solid reagent that is easily prepared, purified, handled, and stored for long-term use. Additionally, the synthetic cost and effort are lower than that of commercially available conventional deoxyfluorination reagents. Moreover, this study revealed that a series of acyl-group exchanges involving carboxylic acid derivatives could proceed in the presence of only a phosphine catalyst under metal-free conditions.

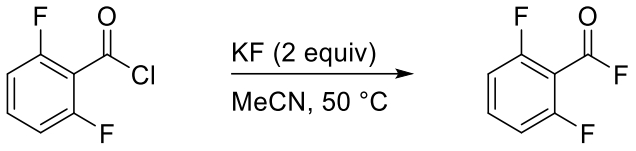
3-4. Experimental Section

General information

^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were recorded on a 500 MHz spectrometer. Chemical shifts in the ^{1}H and ^{13}C NMR spectra are reported in ppm relative to residual solvent peaks such as that of chloroform (^{1}H, δ 7.26; ^{13}C, δ 77.0). Chemical shifts in the ^{19}F NMR spectra are reported in ppm

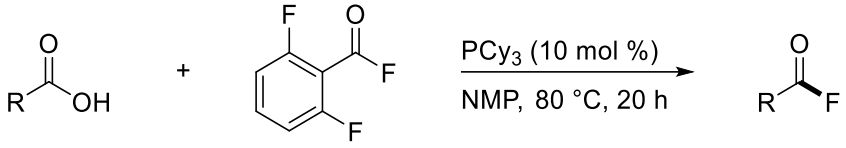
relative to the external reference, $CF_3C_6H_5$ (δ −62.6). GC analyses were performed using a DB-5 capillary column (30 m × 0.25 mm; film thickness 0.25 μm). NMP was distilled from CaH_2 prior to use. Carboxylic acids, PCy_3, sodium benzoate **40**, acyl chloride **44**, ester **45**, and CsF were purchased from common commercial suppliers and used as received. Acyl fluorides **2**, **5**–**9**, and **13** were prepared via a modified method found in the literature,[4g] and 3,5-dimethylbenzoic anhydride (**39**) was synthesized from 3,5-dimethylbenzoic acid (**1**) using thionyl chloride, pyridine and DMF in DCM. Unless otherwise noted, all reactions were performed under an atmosphere of N_2.

Preparation of 2,6-difluorobenzoyl fluoride (2) as a fluorinating reagent[4n]



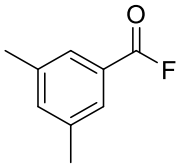
Based on a modified procedure found in the literature,[4g] a two-necked flask equipped with a magnetic stir bar was charged with spray-dried KF (11.6 g, 200 mmol), and 2,6-fluorobenzoyl chloride (**44**; 17.5 g, 98.9 mmol) in anhydrous MeCN (300 mL). The reaction mixture was stirred at 50 °C until conversion was completed (monitored by ^{1}H and ^{19}F NMR). The reaction suspension was allowed to settle, and the MeCN solution was decanted from the precipitate and then filtered. The precipitate was rinsed with MeCN, and the washes were filtered. The combined MeCN washes were concentrated in vacuo. For further purification, distillation under reduced pressure was performed and the resultant colorless oil was then solidified. 2,6-Difluorobenzoyl fluoride (**2**) was afforded as a colorless solid (11.4 g, 71.1 mmol, 72%): mp 33.8–34.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (t, J = 8.6 Hz, 2 H), 7.65 (tt, J = 5.7 Hz, 8.6 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 104.7 (dt, $J_{C–F}$ = 14.5, 62.8 Hz), 112.8 (dd, $J_{C–F}$ = 2.4, 21.7 Hz), 136.6 (t, $J_{C–F}$ = 10.9 Hz), 150.7 (d, $J_{C–F}$ = 345.3 Hz), 162.4 (dd, $J_{C–F}$ = 3.6, 246.4 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ –105.09 (d, J = 29.3 Hz, 2 F), 47.57 (t, J = 29.3 Hz, 1 F); LRMS (EI) m/z (% relative intensity) 160 (M^+, 100), 141 (78), 132 (84), 113 (39), 81 (13), 63 (36).

General procedure for the synthesis of acyl fluorides from carboxylic acids



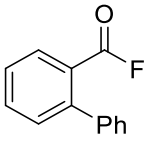
A carboxylic acid (1 mmol) and 2,6-difluorobenzoyl fluoride (**2**; 192 mg, 1.20 mmol) were placed in a screw-capped vial with a stir bar. Then, in a N_2-filled glovebox, PCy_3 (28.0 mg, 0.100 mmol) and NMP (1 mL) were added. The vial was then sealed and removed from the glovebox, before the mixture was stirred at 80 °C for 20 h. Thereafter, the mixture was analyzed by ^{19}F NMR spectroscopy using fluorobenzene (δ −112.98) as an internal standard. The crude reaction mixture was purified via column chromatography on silica gel to afford the corresponding acyl fluoride.

3,5-Dimethylbenzoyl fluoride (3)[31]



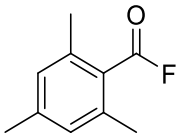
Following the general procedure using 3,5-dimethylbenzoic acid (149 mg, 0.993 mmol), column chromatography (hexane) afforded 3,5-dimethylbenzoyl fluoride (**3**) as a colorless oil (83.1 mg, 0.546 mmol, 55%): ^1H NMR (500 MHz, $CDCl_3$) δ 2.38 (s, 6 H), 7.32 (s, 1 H), 7.65 (s, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.0, 124.7 (d, $J_{C–F}$ = 59.2 Hz), 129.0 (d, $J_{C–F}$ = 3.6 Hz), 137.0, 138.8, 157.7 (d, $J_{C–F}$ = 344.1 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 18.43; LRMS (EI) *m*/*z* (% relative intensity) 152 (M^+, 92), 151 (10), 137 (42), 132 (10), 109 (29), 105 (100), 104 (12), 103 (13), 77 (20), 51 (11).

2-Phenylbenzoyl fluoride (10)[19a]



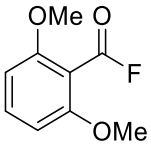
Following the general procedure using 2-phenylbenzoic acid (198 mg, 1.00 mmol), column chromatography (hexane) afforded 2-phenylbenzoyl fluoride (**10**) as a colorless oil (138 mg, 0.689 mmol, 69%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.40 (m, 2 H), 7.45–7.55 (m, 5 H), 7.71 (td, J = 1.2 Hz, 8.0 Hz, 1 H), 8.09 (dd, J = 1.2 Hz, 8.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 124.0 (d, $J_{C–F}$ = 56.7 Hz), 127.5, 127.8, 128.2, 128.3, 131.6 (d, $J_{C–F}$ = 2.4 Hz), 132.0 (d, $J_{C–F}$ = 2.4 Hz), 133.8, 140.0, 145.3, 157.4 (d, $J_{C–F}$ = 347.7 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 35.26; LRMS (EI) *m*/*z* (% relative intensity) 201 (14), 200 (M^+, 100), 199 (64), 181 (15), 180 (14), 172 (10), 171 (19), 170 (19), 152 (28), 151 (16), 104 (15), 85 (14), 76 (22).

2,4,6-Trimethylbenzoyl fluoride (11)[32]



Following the general procedure using 2,4,6-trimethylbenzoic acid (165 mg, 1.00 mmol), column chromatography (hexane) afforded 2,4,6-trimethylbenzoyl fluoride (**11**) as a colorless solid (45.9 mg, 0.276 mmol, 28%): mp 33.6–33.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.32 (s, 3 H), 2.45 (d, J = 3.4 Hz, 6 H), 6.94 (s, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.2 (d, $J_{C–F}$ = 3.6 Hz), 21.3, 123.4 (d, $J_{C–F}$ = 53.1 Hz), 129.6, 139.5, 142.7, 158.5 (d, $J_{C–F}$ = 352.5 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 52.59; LRMS (EI) *m*/*z* (% relative intensity) 167 (11), 166 (M^+, 100), 151 (34), 147 (14), 146 (83), 138 (12), 123 (37), 119 (58), 118 (38), 117 (35), 115 (20), 103 (19), 91 (21), 77 (18), 51 (12).

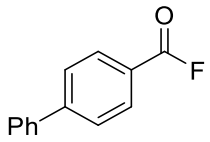
2,6-Dimethoxybenzoyl fluoride (12)[33]



Following the general procedure using 2,6-dimethoxybenzoic acid (182 mg, 1.00 mmol), column chromatography (hexane to hexane/EtOAc 97/3, v/v) afforded 2,6-dimethoxybenzoyl fluoride (**12**)

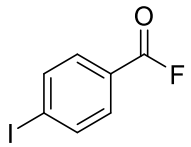
as a colorless solid (71.7 mg, 0.389 mmol, 39%): mp 64.3–65.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86 (s, 6 H), 6.58 (d, J = 8.6 Hz, 2 H), 7.40 (t, J = 8.6 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 56.1, 103.9, 106.7 (d, $J_{C–F}$ = 57.9 Hz), 133.8, 155.4 (d, $J_{C–F}$ = 350.1 Hz), 159.1; ^{19}F NMR (471 MHz, $CDCl_3$) δ 53.75; LRMS (EI) *m*/*z* (% relative intensity) 185 (11), 184 (M^+, 100), 15 **Scheme 2-1.** Formation of acyl metal species via oxidative addition of carboxylic acid derivatives 3 (24), 136 (10), 135 (38), 125 (10), 123 (11), 121 (18), 118 (17), 113 (17), 110 (11), 107 (42), 105 (14), 79 (14), 77 (13), 70 (10), 63 (10).

4-Phenylbenzoyl fluoride (14)[34]



Following the general procedure using 4-phenylbenzoic acid (198 mg, 0.999 mmol), column chromatography (hexane) afforded 4-phenylbenzoyl fluoride (**14**) as a colorless solid (81.9 mg, 0.409 mmol, 41%): mp 93.4–94.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.52 (m, 3 H), 7.64–7.65 (m, 2 H), 7.75 (d, J = 8.0 Hz, 2 H), 8.12 (d, J = 8.6 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 123.4 (d, $J_{C–F}$ = 61.6 Hz), 127.3, 127.6, 128.8, 129.1, 131.9 (d, $J_{C–F}$ = 4.8 Hz), 139.2, 148.1, 157.3 (d, $J_{C–F}$ = 342.8 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 18.27; LRMS (EI) *m*/*z* (% relative intensity) 201 (15), 200 (M^+, 100), 172 (42), 171 (15), 170 (10), 152 (22), 151 (10), 76 (14).

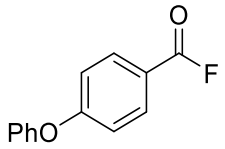
4-Iodobenzoyl fluoride (15)[4m]



Following the general procedure using 4-iodobenzoic acid (198 mg, 0.999 mmol), column chromatography (hexane) afforded 4-iodobenzoyl fluoride (**15**) as a colorless solid (109 mg, 0.434 mmol, 43%): mp 120.6–121.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 8.6 Hz, 2 H), 7.91

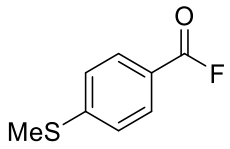
(dd, J = 1.1 Hz, 8.0 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 104.0, 124.3 (d, $J_{C–F}$ = 62.8 Hz), 132.4 (d, $J_{C–F}$ = 3.6 Hz), 138.5, 157.0 (d, $J_{C–F}$ = 344.1 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 18.39; LRMS (EI) *m*/*z* (% relative intensity) 250 (M^+, 100), 222 (14), 123 (25), 95 (51), 76 (10), 75 (33), 74 (13), 50 (16).

4-Phenoxybenzoyl fluoride (16)[33]



Following the general procedure using 4-phenoxybenzoic acid (213 mg, 0.994 mmol), column chromatography (hexane) afforded 4-phenoxybenzoyl fluoride (**16**) as a colorless oil (136 mg, 0.631 mmol, 63%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (d, J = 8.6 Hz, 2 H), 7.09 (d, J = 7.5 Hz, 2 H), 7.24 (t, J = 7.5 Hz, 1 H), 7.42 (t, J = 7.5 Hz, 2 H), 7.98 (d, J = 8.6 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 117.3, 118.4 (d, $J_{C–F}$ = 61.6 Hz), 120.6, 125.2, 130.2 (d, $J_{C–F}$ = 1.2 Hz), 133.8 (d, $J_{C–F}$ = 3.6 Hz), 154.6, 157.0 (d, $J_{C–F}$ = 340.4 Hz), 164.0 (d, $J_{C–F}$ = 1.2 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 16.90; LRMS (EI) *m*/*z* (% relative intensity) 217 (15), 216 (M^+, 100), 188 (14), 169 (11), 168 (11), 141 (16), 77 (48), 51 (22).

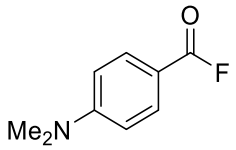
4-(Methylthio)benzoyl fluoride (17)[35]



Following the general procedure using 4-(methylthio)benzoic acid (169 mg, 1.00 mmol), column chromatography (hexane) afforded 4-(methylthio)benzoyl fluoride (**17**) as a colorless solid (117 mg, 0.687 mmol, 69%): mp 49.5–50.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.53 (s, 3 H), 7.29 (dd, J = 1.2 Hz, 8.6 Hz, 2 H), 7.91 (d, J = 8.6 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.5, 120.4 (d, $J_{C–F}$ = 61.6 Hz), 125.0, 131.5 (d, $J_{C–F}$ = 3.6 Hz), 149.3, 157.3 (d, $J_{C–F}$ = 341.6 Hz); ^{19}F NMR (471

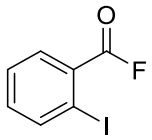
MHz, $CDCl_3$) δ 16.71; LRMS (EI) *m*/*z* (% relative intensity) 171 (10), 170 (M^+, 100), 142 (24), 127 (24), 109 (13), 83 (14).

4-(Dimethylamino)benzoyl fluoride (18)[32]



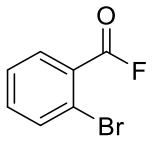
Following the general procedure using 4-(dimethylamino)benzoic acid (165.2 mg, 1.00 mmol), column chromatography (hexane to hexane/EtOAc 97/3, v/v) afforded 4-(dimethylamino)benzoyl fluoride (**18**) as a colorless solid (123 mg, 0.733 mmol, 73%): mp 126.0–126.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.08 (s, 6 H), 6.64–6.66 (m, 2 H), 7.84–7.86 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 39.9, 110.1 (d, $J_{C–F}$ = 61.6 Hz), 110.9, 133.4, 154.5, 158.2 (d, $J_{C–F}$ = 334.4 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 12.41; LRMS (EI) *m*/*z* (% relative intensity) 167 (M^+, 75), 166 (100), 150 (10), 118 (16).

2-Iodobenzoyl fluoride (19)[36]



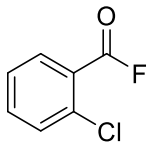
Following the general procedure using 2-iodobenzoic acid (247 mg, 0.997 mmol), column chromatography (hexane) afforded 2-iodobenzoyl fluoride (**19**) as a colorless solid (116 mg, 0.464 mmol, 47%): mp 42.1–43.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, J = 8.0 Hz, 1 H), 7.51 (t, J = 8.0 Hz, 1 H), 8.02 (d, J = 8.0 Hz, 1 H), 8.13 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 97.1 (d, $J_{C–F}$ = 6.0 Hz), 128.3 (d, $J_{C–F}$ = 61.6 Hz), 128.4, 133.4 (d, $J_{C–F}$ = 2.4 Hz), 135.1, 142.6 (d, $J_{C–F}$ = 3.6 Hz), 156.4 (d, $J_{C–F}$ = 345.3 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 28.78; LRMS (EI) *m*/*z* (% relative intensity) 250 (M^+, 100), 222 (14), 104 (13), 95 (41), 76 (15), 75 (31), 74 (10), 50 (15).

2-Bromobenzoyl fluoride (20)[22d]



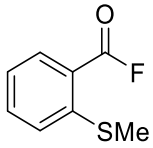
Following the general procedure using 2-bromobenzoic acid (201 mg, 1.00 mmol), column chromatography (hexane) afforded 2-bromobenzoyl fluoride (**20**) as a colorless solid (82.8 mg, 0.408 mmol, 41%): mp 30.5–30.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.51 (m, 2 H), 7.77–7.79 (m, 1 H), 8.02 (dd, J = 2.3 Hz, 7.5 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 124.8 (d, $J_{C–F}$ = 4.8 Hz), 125.4 (d, $J_{C–F}$ = 61.6 Hz), 127.6, 133.7, 135.3, 135.5 (d, $J_{C–F}$ = 3.6 Hz), 154.8 (d, $J_{C–F}$ = 345.3 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 31.61; LRMS (EI) *m*/*z* (% relative intensity) 204 (99), 203 (11), 202 (M^+, 100), 185 (24), 183 (24), 176 (45), 174 (46), 157 (17), 155 (16), 195 (79), 94 (11), 76 (19), 75 (69), 74 (27), 69 (10), 50 (34), 23 (15).

2-Chlorobenzoyl fluoride (21)[4m]



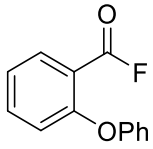
Following the general procedure using 2-chlorobenzoic acid (157 mg, 1.00 mmol), column chromatography (hexane) afforded 2-chlorobenzoyl fluoride (**21**) as a colorless solid (48.1 mg, 0.303 mmol, 30%): mp 28.5–29.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.43 (m, 1 H), 7.55–7.61 (m, 2 H), 8.02 (dd, J = 1.7 Hz, 8.02 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 123.6 (d, $J_{C–F}$ = 61.6 Hz), 127.1, 132.0 (d, $J_{C–F}$ = 3.6 Hz), 133.6 (d, $J_{C–F}$ = 2.4 Hz), 135.4, 136.8 (d, $J_{C–F}$ = 4.8 Hz), 154.4 (d, $J_{C–F}$ = 345.3 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 32.33; LRMS (EI) *m*/*z* (% relative intensity) 160 (32), 158 (M^+, 100), 139 (29), 132 (29), 130 (93), 123 (20), 111 (27), 95 (43), 75 (41), 74 (18), 50 (18).

2-(Methylthio)benzoyl fluoride (22)



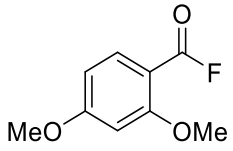
Following the general procedure using 2-(methylthio)benzoic acid (168 mg, 0.997 mmol), column chromatography (hexane) afforded 2-(methylthio)benzoyl fluoride (**22**) as a colorless solid (125 mg, 0.737 mmol, 74%): mp 49.4–50.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.50 (s, 3 H), 7.22 (t, J = 8.0 Hz, 1 H), 7.32 (d, J = 8.0 Hz, 1 H), 7.58–7.62 (m, 1 H), 8.01 (dd, J = 1.7 Hz, 8.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.1, 120.5 (d, $J_{C–F}$ = 59.2 Hz), 123.6, 124.4 (d, $J_{C–F}$ = 2.4 Hz), 133.2, 134.8, 147.2 (d, $J_{C–F}$ = 7.2 Hz), 155.7 (d, $J_{C–F}$ = 342.8 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 24.44; HRMS (FAB) calcd for $[M]^+$ (C_8H_7FOS) m/z 170.0202, found 170.0202.

2-Phenoxybenzoyl fluoride (23)[37]



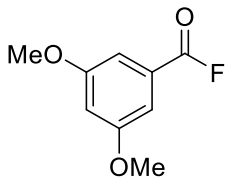
Following the general procedure using 2-phenoxybenzoic acid (214 mg, 0.998 mmol), column chromatography (hexane) afforded 2-phenylbenzoyl fluoride (**23**) as a colorless oil (138 mg, 0.640 mmol, 64%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (d, J = 8.0 Hz, 1 H), 7.05–7.07 (m, 2 H), 7.18–7.21 (m, 2 H), 7.34–7.41 (m, 2 H), 7.55–7.59 (m, 1 H), 8.01 (dd, J = 1.7 Hz, 8.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 115.7 (d, $J_{C–F}$ = 59.2 Hz), 119.0 (d, $J_{C–F}$ = 2.4 Hz), 119.5, 122.9, 124.4, 130.0, 133.5 (d, $J_{C–F}$ = 2.4 Hz), 136.3, 154.8 (d, $J_{C–F}$ = 344.0 Hz), 155.7, 159.3 (d, $J_{C–F}$ = 2.4 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 32.30; LRMS (EI) m/z (% relative intensity) 216 (M^+, 44), 120 (100), 92 (28), 77 (19), 51 (16).

2,4-Dimethoxybenzoyl fluoride (24)



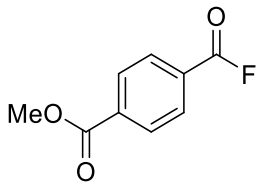
Following the general procedure using 2,4-dimethoxybenzoic acid (183 mg, 1.00 mmol), column chromatography (hexane to hexane/EtOAc 97/3, v/v) afforded 2,4-dimethoxybenzoyl fluoride (**24**) as a colorless solid (151 mg, 0.819 mmol, 82%): mp 57.0–58.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (s, 3 H), 3.91 (s, 3 H), 6.48–6.49 (m, 1 H), 6.53 (dd, J = 2.3 Hz, 8.6 Hz, 1 H), 7.87 (d, J = 8.6 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.7, 56.0, 98.7 (d, $J_{C–F}$ = 3.6 Hz), 105.4, 105.6 (d, $J_{C–F}$ = 59.2 Hz), 135.8 (d, $J_{C–F}$ = 2.4 Hz), 154.7 (d, $J_{C–F}$ = 338.0 Hz), 163.7 (d, $J_{C–F}$ = 4.8 Hz), 166.6; ^{19}F NMR (471 MHz, $CDCl_3$) δ 28.09; HRMS (FAB) calcd for $[M]^+$ ($C_9H_9FO_3$) m/z 184.0536, found 184.0535.

3,5-Dimethoxybenzoyl fluoride (25)[32]



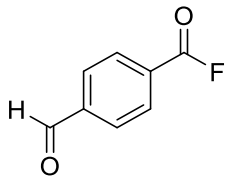
Following the general procedure using 3,5-dimethoxybenzoic acid (181 mg, 0.994 mmol), column chromatography (hexane to hexane/EtOAc 99/1, v/v) afforded 3,5-dimethoxybenzoyl fluoride (**25**) as a colorless solid (95.2 mg, 0.517 mmol, 52%): mp 51.0–52.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (s, 6 H), 6.75 (t, J = 2.3 Hz, 1 H), 7.15 (d, J = 2.3 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.6, 108.7, 108.8 (d, $J_{C–F}$ = 3.6 Hz), 126.5 (d, $J_{C–F}$ = 61.6 Hz), 157.2 (d, $J_{C–F}$ = 345.3 Hz), 161.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ 18.80; LRMS (EI) m/z (% relative intensity) 184 (M^+, 100), 155 (10), 154 (19), 135 (17), 113 (19), 96 (14), 63 (10).

4-(Methoxycarbonyl)benzoyl fluoride (26)[38]



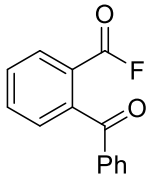
Following the general procedure using 4-(methoxycarbonyl)benzoic acid (181 mg, 1.00 mmol), column chromatography (hexane to hexane/EtOAc 9/1, v/v) afforded 4-(methoxycarbonyl)benzoyl fluoride (**26**) as a colorless solid (77.6 mg, 0.426 mmol, 42%): mp 65.7–66.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.96 (s, 3 H), 8.10 (d, J = 8.6 Hz, 2 H), 8.17 (d, J = 8.6 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 52.7, 128.5 (d, $J_{C–F}$ = 61.6 Hz), 130.0, 131.3 (d, $J_{C–F}$ = 2.4 Hz), 136.0, 156.5 (d, $J_{C–F}$ = 345.3 Hz), 165.6; ^{19}F NMR (471 MHz, $CDCl_3$) δ 20.14; LRMS (EI) *m*/*z* (% relative intensity) 182 (M^+, 23), 151 (100), 123 (29), 95 (28), 75 (18).

4-Formylbenzoyl fluoride (27)[5e]



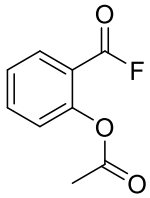
4-Formylbenzoic acid (150 mg, 1.00 mmol) and 2,6-difluorobenzoyl fluoride (**2**; 320 mg, 2.00 mmol) were placed in a screw-capped vial with a stir bar. Then, in a N_2-filled glovebox, PCy_3 (28.2 mg, 0.101 mmol) and NMP (1 mL) were added. The vial was then sealed and removed from the glovebox, before the mixture was stirred at 80 °C for 20 h. Column chromatography on silica gel (hexane) afforded 4-formylbenzoyl fluoride (**27**) as a colorless solid (41.3 mg, 0.271 mmol, 27%): mp 90.2–92.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 8.0 Hz, 2 H), 8.22 (d, J = 8.0 Hz, 2 H), 10.15 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 129.7 (d, $J_{C–F}$ = 61.6 Hz), 129.8, 132.0 (d, $J_{C–F}$ = 3.6 Hz), 140.6, 156.3 (d, $J_{C–F}$ = 346.5 Hz), 191.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ 20.67; LRMS (EI) *m*/*z* (% relative intensity) 152 (M+, 76), 151 (100), 123 (40), 96 (11), 95 (40), 75 (23), 50 (11).

2-Benzoylbenzoyl fluoride (28)



2-Benzoylbenzoic acid (226 mg, 0.998 mmol) and 2,6-difluorobenzoyl fluoride (**2**; 320 mg, 2.00 mmol) were placed in a screw-capped vial with a stir bar. Then, in a N_2-filled glovebox, PCy_3 (28.0 mg, 0.100 mmol) and NMP (1 mL) were added. The vial was then sealed and removed from the glovebox, before the mixture was stirred at room temperature for 20 h. Column chromatography on silica gel (hexane to hexane/EtOAc 9/1, v/v) afforded 2-benzoylbenzoyl fluoride (**28**) as a colorless solid (85.5 mg, 0.375 mmol, 38%): mp 36.8 °C (decomp.); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.49 (m, 3 H), 7.58–7.61 (m, 1 H), 7.66 (t, J = 8.0 Hz, 1 H), 7.76–7.80 (m, 3 H), 8.09 (dd, J = 1.2 Hz, 8.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 123.4 (d, $J_{C–F}$ = 61.6 Hz), 128.3, 128.6, 129.6, 130.0, 131.9, 133.7, 134.6, 136.1, 143.6 (d, $J_{C–F}$ = 4.8 Hz), 156.0 (d, $J_{C–F}$ = 346.5 Hz), 195.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ 27.34; HRMS (FAB) calcd for $[M + H]^+$ ($C_{14}H_{10}FO_2$) m/z 229.0665, found 229.0667.

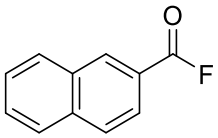
2-Acetoxybenzoyl fluoride (29)[39]



2-Acetoxybenzoic acid (180 mg, 0.999 mmol) and 2,6-difluorobenzoyl fluoride (**2**; 320 mg, 2.00 mmol) were placed in a screw-capped vial with a stir bar. Then, in a N_2-filled glovebox, PCy_3 (28.0 mg, 0.100 mmol) and NMP (1 mL) were added. The vial was then sealed and removed from the glovebox, before the mixture was stirred at room temperature for 20 h. Column chromatography on silica gel (hexane to hexane/EtOAc 99/1, v/v) afforded 2-acetoxybenzoyl fluoride (**29**) as a colorless solid (102 mg, 0.608 mmol, 61%): mp 39.9–41.7 °C (decomp.); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3 H), 7.20–7.21 (m, 1 H), 7.38–7.41 (m, 1 H), 7.72 (td, J = 1.7 Hz, 8.0 Hz, 1 H),

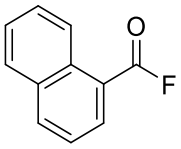
8.03 (dd, J = 1.7 Hz, 8.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.8, 118.1 (d, $J_{C–F}$ = 60.4 Hz), 124.4 (d, $J_{C–F}$ = 3.6 Hz), 126.5, 133.0, 136.5, 152.4 (d, $J_{C–F}$ = 4.8 Hz), 154.0 (d, $J_{C–F}$ = 346.5 Hz), 169.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ 28.56; LRMS (EI) m/z (% relative intensity) 182 (M^+, 4), 140 (64), 121 (10), 120 (100), 92 (40), 64 (10), 63 (13).

2-Naphthoyl fluoride (30)[40]



Following the general procedure using 2-naphthoic acid (172 mg, 1.00 mmol), column chromatography (hexane) afforded 2-naphthoyl fluoride (**30**) as a colorless solid (121 mg, 0.696 mmol, 69%): mp 51.6–52.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.63 (m, 1 H), 7.67–7.70 (m, 1 H), 7.91–8.01 (m, 4 H), 8.63 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 121.9 (d, $J_{C–F}$ = 60.4 Hz), 125.6 (d, $J_{C–F}$ = 3.6 Hz), 127.3, 127.9, 129.0, 129.6, 129.7, 132.2, 134.0 (d, $J_{C–F}$ = 2.4 Hz), 136.4, 157.6 (d, $J_{C–F}$ = 344.6 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 18.18; LRMS (EI) m/z (% relative intensity) 175 (12), 174 (M^+, 100), 146 (72), 127 (21), 126 (23), 125 (10), 73 (14), 63 (11).

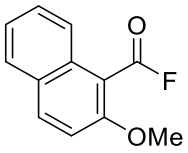
1-Naphthoyl fluoride (31)[3c]



Following the general procedure using 1-naphthoic acid (172 mg, 0.998 mmol), column chromatography (hexane) afforded 1-naphthoyl fluoride (**31**) as a colorless solid (118 mg, 0.675 mmol, 68%): mp 63.0–63.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (t, J = 8.0 Hz, 1 H), 7.61 (t, J = 8.0 Hz, 1 H), 7.72 (t, J = 8.0 Hz, 1 H), 7.94 (d, J = 8.0 Hz, 1 H), 8.17 (d, J = 8.0 Hz, 1 H), 8.35 (d, J = 8.0 Hz, 1 H), 9.02 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 120.3 (d, $J_{C–F}$ = 55.5 Hz), 124.4, 125.1, 126.9, 128.9, 129.2, 132.0 (d, $J_{C–F}$ = 7.2 Hz), 133.6, 133.8 (d, $J_{C–F}$ = 3.6 Hz),

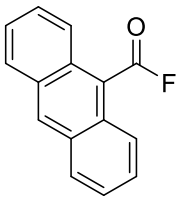
136.6, 156.4 (d, $J_{C–F}$ = 345.3 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 30.02; LRMS (EI) *m*/*z* (% relative intensity) 175 (12), 174 (M^+, 100), 147 (11), 146 (97), 145 (15), 127 (21), 126 (31), 125 (13), 75 (10), 73 (16), 63 (13).

2-Methoxy-1-naphthoyl fluoride (32)[33]



Following the general procedure using 2-methoxy-1-naphthoic acid (203 mg, 1.00 mmol), column chromatography (hexane to hexane/EtOAc 97/3, v/v) afforded 2-methoxy-1-naphthoyl fluoride (**32**) as a white solid (109 mg, 0.533 mmol, 53%): mp 77.4–78.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.03 (s, 3 H), 7.30 (d, *J* = 9.2 Hz, 1 H), 7.41–7.44 (m, 1 H), 7.59 (ddd, *J* = 1.7 Hz, 6.9 Hz, 8.6 Hz, 1 H), 7.81 (d, *J* = 8.6 Hz, 1 H), 8.01 (d, *J* = 9.2 Hz, 1 H), 8.12 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 56.7, 109.8 (d, $J_{C–F}$ = 55.5 Hz), 112.6, 123.6, 124.6, 128.3, 128.5, 128.9, 131.6, 135.2, 157.1 (d, $J_{C–F}$ = 351.3 Hz), 158.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ 53.72; LRMS (EI) *m*/*z* (% relative intensity) 205 (13), 204 (M^+, 100), 176 (14), 173 (18), 161 (15), 155 (16), 133 (81), 127 (10).

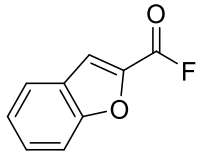
Anthracene-9-carbonyl fluoride (33)[41]



Following the general procedure using 9-anthracenecarboxylic acid (221 mg, 0.996 mmol), column chromatography (hexane) afforded 9-anthracenecarbonyl fluoride (**33**) as a yellow solid (136 mg, 0.608 mmol, 61%): mp 107.2–108.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.54 (m, 2 H), 7.62–7.65 (m, 2 H), 8.02 (d, *J* = 9.2 Hz, 2 H), 8.30 (dd, *J* = 2.3 Hz, 9.2 Hz, 2 H), 8.61 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 119.9 (d, $J_{C–F}$ = 55.5 Hz), 124.6 (d, $J_{C–F}$ = 2.4 Hz), 125.8, 128.5, 128.9, 130.1,

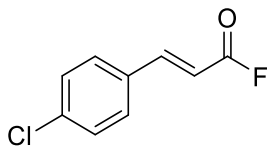
130.7, 133.1, 158.4 (d, $J_{C–F}$ = 353.7 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.76; LRMS (EI) *m*/*z* (% relative intensity) 225 (16), 224 (M^+, 100), 197 (14), 196 (95), 194 (12), 176 (17), 175 (11), 98 (31), 97 (11), 88 (17), 85 (17).

Benzofuran-2-carbonyl fluoride (34)[38]



Benzofuran-2-carboxylic acid (162 mg, 1.00 mmol) and 2,6-difluorobenzoyl fluoride (**2**; 321 mg, 2.01 mmol) were placed in a screw-capped vial with a stir bar. Then, in a N_2-filled glovebox, PCy_3 (28.2 mg, 0.101 mmol) and NMP (1 mL) were added. The vial was then sealed and removed from the glovebox, before the mixture was stirred at 80 °C for 20 h. Column chromatography on silica gel (hexane) afforded benzofuran-2-carbonyl fluoride (**34**) as a colorless solid (49.5 mg, 0.302 mmol, 30%): mp 91.9–92.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.40 (m, 1 H), 7.54–7.63 (m, 2 H), 7.75–7.77 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 112.6, 119.3, 123.5, 124.6, 126.2, 129.5,139.8 (d, $J_{C–F}$ = 89.3 Hz), 149.4 (d, $J_{C–F}$ = 329.6 Hz), 156.9; ^{19}F NMR (471 MHz, $CDCl_3$) δ 17.49; LRMS (EI) *m*/*z* (% relative intensity) 164 (M^+, 100), 136 (48), 108 (74), 107 (32), 89 (12), 63 (20), 62 (11).

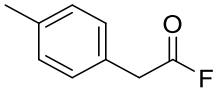
***trans*-4-Chlorocinnamoyl fluoride (35)**[22c]



Following the general procedure using *trans*-4-chlorocinnamic acid (182 mg, 0.999 mmol), column chromatography (hexane) afforded trans-4-chlorocinnamoyl fluoride (**35**) as a colorless solid (110 mg, 0.598 mmol, 60%): mp 84.6–85.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.34 (dd, J = 6.8 Hz, 16.0 Hz, 1 H), 7.41 (dt, J = 2.3 Hz, 8.6 Hz, 2 H), 7.15 (dt, J = 2.3 Hz, 8.6 Hz, 2 H) 7.78 (d, J = 16.0 Hz,

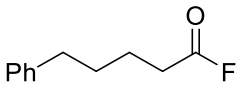
1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 112.6 (d, $J_{C–F}$ = 67.6 Hz), 129.5, 129.8, 131.5, 137.9, 149.8 (d, $J_{C–F}$ = 6.0 Hz), 156.8 (d, $J_{C–F}$ = 338.0 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 26.06; LRMS (EI) *m*/*z* (% relative intensity) 186 (33), 185 (17), 184 (M^+, 100), 183 (19), 158 (22), 156 (71), 149 (72), 137 (10), 136 (23), 121 (40), 120 (14), 102 (19), 101 (57), 75 (33), 74 (20), 60 (11), 51 (20), 50 (16).

4-Methylphenylacetyl fluoride (36)



4-Methylphenylacetic acid (151 mg, 1.01 mmol) and 2,6-difluorobenzoyl fluoride (**2**; 319 mg, 1.99 mmol) were placed in a screw-capped vial with a stir bar. Then, in a N_2-filled glovebox, PCy_3 (27.5 mg, 0.100 mmol) and NMP (1 mL) were added. The vial was then sealed and removed from the glovebox, before the mixture was stirred for 20 h at room temperature. Column chromatography on silica gel (hexane) afforded 4-methylphenylacetyl fluoride (**36**) as a colorless oil (29.8 mg, 0.196 mmol, 19%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 3.78 (d, J = 2.3 Hz, 2 H), 7.18 (s, 4 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.1, 38.6 (d, $J_{C–F}$ = 54.3 Hz), 127.7 (d, $J_{C–F}$ = 2.4 Hz), 129.1, 129.6, 137.8, 161.6 (d, $J_{C–F}$ = 362.2 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 44.64; HRMS (FAB) calcd for $[M]^+$ (C_9H_9FO) *m*/*z* 152.0637, found 152.0637.

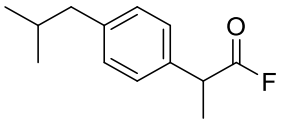
5-Phenylpentanoyl fluoride (37)[9c]



5-Phenylpentanoic acid (180 mg, 1.01 mmol) and 2,6-difluorobenzoyl fluoride (**2**; 323 mg, 2.00 mmol) were placed in a screw-capped vial with a stir bar. Then, in a N_2-filled glovebox, PCy_3 (28.0 mg, 0.100 mmol) and NMP (1 mL) were added. The vial was then sealed and removed from the glovebox, before the mixture was stirred for 20 h at room temperature. Column chromatography on silica gel (hexane) afforded 5-phenylpentanoyl fluoride (**37**) as a colorless oil (61.4 mg, 0.341 mmol,

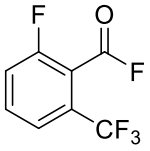
34%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.71–1.74 (m, 4 H), 2.51–2.54 (m, 2 H), 2.65–2.67 (m, 2 H), 7.18–7.22 (m, 3 H), 7.28–7.31 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.5, 30.3, 32.0 (d, $J_{C–F}$ = 50.7 Hz), 35.3, 126.0, 128.3, 128.4, 141.5, 163.4 (d, $J_{C–F}$ = 361.0 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 45.66; LRMS (EI) *m*/*z* (% relative intensity) 180 (M^+, 17), 104 (12), 92 (15), 91 (100), 65 (10).

2-(4-Isobutylphenyl)propanoyl fluoride (38)[22c]



2-(4-Isobutylphenyl)propanoic acid (205 mg, 1.00 mmol) and 2,6-difluorobenzoyl fluoride (**2**; 320 mg, 2.00 mmol) were placed in a screw-capped vial with a stir bar. Then, in a N_2-filled glovebox, PCy_3 (28.1 mg, 0.100 mmol) and NMP (1 mL) were added. The vial was then sealed and removed from the glovebox, before the mixture was stirred for 20 h at room temperature. Column chromatography on silica gel (hexane) afforded 2-(4-isobutylphenyl)propanoyl fluoride (**38**) as a colorless oil (83.1 mg, 0.399 mmol, 40%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, J = 6.9 Hz, 6 H), 1.58 (d, J = 6.9 Hz, 3 H), 1.86 (sep, J = 6.9 Hz, 1 H), 2.47 (d, J = 6.9 Hz, 2 H), 3.82–3.87 (m, 1 H), 7.15 (d, J = 8.0 Hz, 2 H), 7.20 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.0, 22.3, 30.1, 43.9 (d, $J_{C–F}$ = 49.5 Hz), 45.0, 127.2, 129.7, 134.5, 141.6, 164.4 (d, $J_{C–F}$ = 367.0 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.38; LRMS (EI) *m*/*z* (% relative intensity) 208 (M^+, 39), 166 (40), 165 (71), 119 (42), 118 (23), 117 (24), 115 (12), 109 (100), 91 (38).

6. Spectral data of 2-fluoro-6-(trifluoromethyl)benzoyl fluoride (13)



A colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (t, J = 8.6 Hz, 1 H), 7.62 (d, J = 8.0 Hz, 1 H), 7.73 (td, J = 5.2, 8.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 114.9 (ddd, $J_{C–F}$ = 2.4, 18.1, 66.4 Hz), 120.4 (d, $J_{C–F}$ = 21.7 Hz), 122.1 (dq, $J_{C–F}$ = 3.6, 274.0 Hz), 122.6 (quin, $J_{C–F}$ = 4.5 Hz), 130.5

(dq, J_{C-F} = 1.2, 33.8 Hz), 134.3 (d, J_{C-F} = 8.5 Hz), 152.5 (d, J_{C-F} = 352.5 Hz), 160.3 (d, J_{C-F} = 257.1 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ –108.97 (s, 1 F), –59.98 (s, 3 F), 55.59 (s, 1 F); LRMS (EI) *m*/*z* (% relative intensity) 210 (M^+, 100), 191 (64), 182 (74), 181 (11), 163 (72), 143 (13), 141 (15), 132, (40), 113 (23), 75 (13), 69 (13), 63 (19); HRMS (FAB) calcd for $[M + H]^+$ ($C_8H_4F_5O$) *m*/*z* 211.0182, found 211.0182.

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(26) The author computationally assessed free energies of the products (acyl fluoride **3** and carboxylic acid **4**) and the starting materials (carboxylic acid **1** and acyl fluoride **2**). Consequently, the relative free energy of the products (ΔG) was to be –0.7 kcal mol^{-1}, indicating that the products were slightly more thermodynamically stable than the starting materials. The result strongly supports the experimental result of Scheme 3-6d. The free energies were given by density functional theory (DFT) calculations with B3LYP/6-31G(d) level of theory which were carried out using Gaussian09 software package.

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(29) To monitor this catalytic reaction with ^{19}F NMR, a mixture of 3,5-dimethylbenzoic acid (**1**; 0.3 mmol), 2,6-difluorobenzoyl fluoride (**2**; 0.3 mmol), PCy_3 (0.03 mmol) and DMF-d_7 (0.6 mL) was heated at 80 °C. Full production of 3,5-dimethylbenzoyl fluoride (**3**) and 2,6-difluorobenzoic acid (**4**) was completed within 3 h. On the other hand, regarding the monitor by ^{31}P NMR, no remarkable change for time-course of the phosphine was observed.

(30) In this acyl-group exchange reaction of 3,5-dimethylbenzoic acid (**1**; 0.5 mmol) with 2,6-difluorobenzoyl fluoride (**2**; 0.5 mmol) in NMP (0.5 mL), a good base and a good nucleophilic catalyst, 4-(dimethylamino)pyridine (DMAP) or 1,4-diazabicyclo[2.2.2]octane (DABCO) (0.1 mmol), was used instead of PCy_3 to afford 3,5-dimethylbenzoyl fluoride (**3**) in 71% or 54% GC

yields respectively. This result suggested that a phosphine catalyst also bears a role as a base and a nucleophile.

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Chapter 4.

Conclusions

The author examined mechanistic study on the palladium/phosphine-catalyzed transformation of acyl fluorides and its application to the fluorination reaction.

In Chapter 2, the formation of acyl(carboxylato)palladium complexes from a combination of $Pd(OAc)_2$, PCy_3, Et_3SiH, and bimolecular of acyl fluorides was found. The NMR stoichiometric mechanistic study on its formation revealed that the "OAc" of $Pd(OAc)_2$ acts as the O source of the acyl(carboxylato)palladium complex and a phosphine-promoted acyl-group exchange process of acyl fluorides with carboxylate compounds is involved. Also, the acy(carboxylato)palladium complex reacted with some coupling partners, such as a hydrosilane or a boronic acid, to give the corresponding carbonyl compounds, which proved that the acy(carboxylato)palladium species is one of the reaction intermediates in $Pd(OAc)_2/PCy_3$-catalyzed transformations of acyl fluorides. This study is the first to experimentally investigate a reaction mechanism on a palladium-catalyzed reaction of acyl fluorides.

In Chapter 3, the phosphine-catalyzed direct synthesis of acyl fluorides from carboxylic acids was developed. On the basis of the phosphine-promoted acyl-group exchange of acyl fluoride that was found in Chapter 2, the author revealed that an acyl-group exchange between carboxylic acids and 2,6-difluorobenzoyl fluoride efficiently proceeds in the presence of a catalytic amount of tricyclohexylphosphine (PCy_3) only. The present method provided various acyl fluorides, such as an aromatic, a heteroaromatic, a vinylic, and an aliphatic one. This finding is the first example of utilization of acyl fluorides as a fluorination reagent of carboxylic acids.

These transformations are unique to acyl fluorides, and the author, therefore, believes that these findings would be a significant knowledge for organometallic, organic fluorine, and organic synthetic chemistry.

List of Publication

Publications related to this thesis

Chapter 2

1. Formation, Characterization and Reactivity of Acyl Palladium Complexes in $Pd(OAc)_2/PCy_3$-Catalyzed Transformation of Acyl Fluorides

   Hiroyuki Hattori, Yohei Ogiwara, Norio Sakai

   Organometallics, Vol. 41, Issue 12, pp. 1509–1518 (2022)

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Chapter 3

2. Phosphine-Catalyzed Acyl-Group Exchange Reaction between Carboxylic Acids and an Aroyl Fluoride

   Hiroyuki Hattori, Kento Ishida, Yohei Ogiwara, Norio Sakai

   European Journal of Organic Chemistry, Vol. 2022, Issue 46, p. e202201118 (2022)

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Other publication

1. Palladium-Catalyzed Reductive Conversion of Acyl Fluorides via Ligand-Controlled Decarbonylation

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   Organic Letters, Vol. 20, Issue 14, pp. 4204–4208 (2018)

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