Title	Studies on generation of organofluorine transition-metal complexes via C—F bond activation of perfluoroarenes or trifluoromethylketones and its application toward organic synthesis
Author(s)	土井, 良平
Citation	大阪大学, 2016, 博士論文
Version Type	VoR
URL	https://doi.org/10.18910/55933
rights	
Note	

Doctoral Dissertation

Studies on Generation of Organofluorine Transition-Metal Complexes via C−F Bond Activation of Perfluoroarenes or Trifluoromethylketones and its Application toward Organic Synthesis

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January 2016

Graduate School of Engineering

Osaka University

Contents

Preface and Acknowledgement

The study related to this doctoral dissertation has been conducted under the supervision of Professor Dr. Sensuke Ogoshi at the Department of Applied Chemistry, Faculty of Engineering, Osaka University, from April 2011 to March 2016. The thesis describes transition metal-catalyzed transformation of perfluoroarenes and trifluoromethylketones involving C−F bond cleavage as key steps.

I would like to express my deepest appreciation to Professor Dr. Sensuke Ogoshi for a number of suggestions, discussions, and encouragement. His advice both on research and on my career have been invaluable. I would like to express my gratitude to Professor Dr. Nobuaki Kambe and Professor Dr. Makoto Yasuda for their stimulating discussions. I would like to offer my special thanks to Professor Dr. Tetsuro Murahashi (Tokyo Institute of Technology), Associate Professor Dr. Masato Ohashi, Assistant Professor Dr. Yoichi Hoshimoto, Assistant Professor Dr. Tsubasa Hatanaka (Graduate School of Science, Osaka University), Project Assistant Professor Dr. Kotaro Kikushima, and Project Assistant Professor Dr. Kumar Ravindra for their continuous guidance, advice and assistance.

I would like to deeply acknowledge Professor Dr. Brian M. Stoltz (California Institute of Technology) for accepting me as a visiting student researcher and a number of great advices. I am also grateful for the Stoltz group members including my mentor Ms. Seo-Jung Han for their kind assistance and encouragement.

I would like to express my heartfelt appreciation to Mrs. Noriko Fujimoto for her total support with infinite tenderness.

It was really my pleasure to be a comrade of Mr. Ryohei Kamura, Mr. Yuki Tachibana and Mr. Hiromu Tokura during the master thesis study. I am deeply indebted to my senior alumni of Ogoshi group, Dr. Takashi Tamaki, Dr. Akira Nishimura, Mr. Tadashi Kambara, Mr. Tomoaki Taniguchi, Mr. Kentaro Usui, Dr. Hiroki Saijo, Ms. Haruka Suzuki, Mr. Ippei Takeda and Mr. Kohei Takase for their kind advices. I would like to express my thanks to the other colleagues in Ogoshi group, Mr. Kazuto Kinoshita, Mr. Hayato Hamada, Ms. Yukari Hayashi, Mr. Mitsutoshi Shibata, Mr. Atsushi Tanaka, Mr. Tomoya

Ohata, Mr. Seita Kimura, Mr. Hironobu Sakaguchi, Mr. Hayato Yabuki, Ms. Eri Tamai, Mr. Hiroaki Saito, Mr. Hiroshi Shirataki, Ms. Yukari Sasaoka, Mr. Takuya Kinoshita, Mr. Takuya Kawashima, Mr. Takuya Adachi, Mr. Yuta Ueda, Mr. Kyogo Maeda, Mr. Takahiro Asada, Mr. Akira Ohnishi, Mr. Ryohei Suzuki, Mr. Keita Ashida, Mr. Takaya Hinogami, Mr. Naoyoshi Ishida, and Mr. Yasuhiro Yamauchi, for their helpful assistance and dedication.

I would like to thank Dr. Nobuko Kanehisa for her helpful assistance for X-ray crystallographic analysis. I owe a very important debt to the committee of Instrumental Analysis Center, Graduate School of Engineering, Osaka University for the measurement of spectral and analytical data.

I would like to fully acknowledge scholarships from Hasegawa Shorai Foundation and Japan Student Service Organization, and Research Fellowship for Young Scientists from Japan Society for the Promotion of Science.

Finally, I would like to express my utmost gratitude to my parents, Mr. Ryosuke Doi and Mrs. Sayuri Doi as well as my brother Mr. Yusuke Doi for their affectionate support and warm encouragement.

Osaka, Japan
January 2016

Ryohei

Ryohei Doi

List of Abbreviations

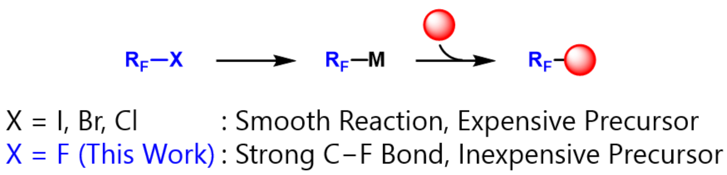
aq.	aqueous
Ar	aryl
br	broad
Bu	butyl
cat.	catalyst
CI	chemical ionization
cod	1,5-cyclooctadiene
Cy	cyclohexyl
°C	degrees Celsius
calcd	calculated
d	doublet
δ	chemical shift of NMR signal in ppm
dba	dibenzylideneacetone
EI	electron ionization
equiv	equivalent
Et	ethyl
GC	gas chromatography
h	hour(s)
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass specra
Hz	hertz
i	iso
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
J	coupling constant in NMR
L	ligand
M	Transition-metal
m	multiplet
Me	methyl
min	minute(s)
mL	milliliter
μL	microliter
MS	mass spectrometry
n	normal

NMR	nuclear magnetic resonance
o	ortho
ORTEP	Oak Ridge thermal ellipsoid plot
p	para
Ph	phenyl
Phen	1,10-phenanthroline
Pr	propyl
q	quartet
rt	room temperature
s	singlet
sec	secondary
t	triplet
t	tertiary
THF	tetrahydrofuran

Chapter 1

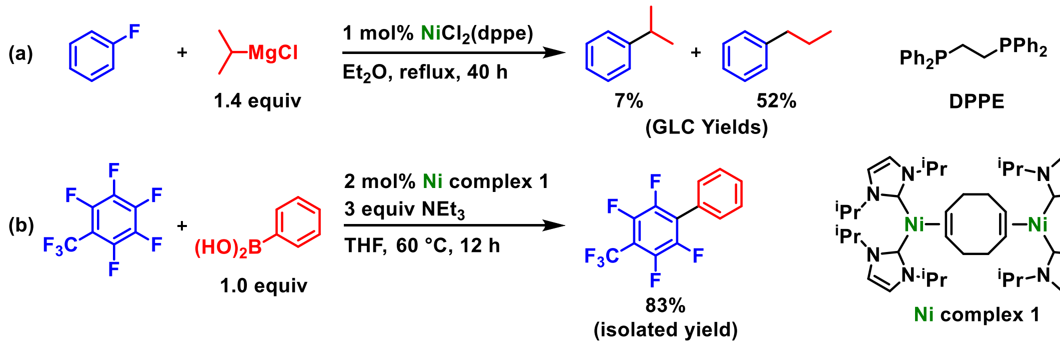
General Introduction

Transition-metal catalysts have been opened up novel pathways to synthesize a number of organic molecules by providing unique and efficient bond-forming methodologies.[1] Organic iodides, bromides, and chlorides have been frequently employed as a precursor for preparation or in situ generation of organotransition-metal complexes by facile and/or regioselective cleavage of carbon-halogen bond except for C−F bond which is one of the most stable bond that a carbon forms. Thus, numerous transition-metal catalyzed reactions have been reported to prepare desired organic compounds from organic halides via carbon-halogen bond cleavage. However, synthesis of organofluorine compounds via carbon-halogen bond cleavage by use of transition-metal catalysts requires the corresponding organofluorine building blocks containing other halogens, namely iodine, bromine, or chlorine which are not always readily available (Scheme 1.1).[2] Therefore, catalytic C−F bond cleavage enables us to access abundant poly- or perfluorinated building blocks to construct partially fluorinated compounds which are important synthetic targets as medicines, agrochemicals, and organic semiconductors.[3]



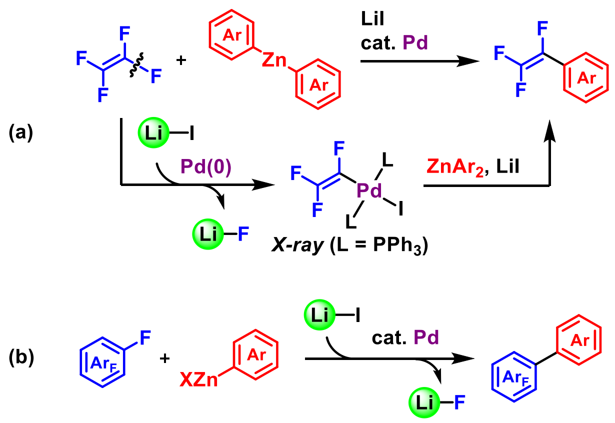
Scheme 1.1 Formation of organofluorine compounds via organotransition-metal complexes

Substitution of C−F bond into C−C bond catalyzed by transition-metal complexes was first reported by Kumada et al. in 1973 who disclosed Ni-catalyzed cross-coupling reaction of alkyl Grignard reagent with aryl fluoride to afford alkyl benzenes (Scheme 1.2a).[4] Since then, several nickel-catalyzed cross-coupling reactions have been developed. For instance, Radius et al. developed Ni(0)-NHC complex that is an efficient catalyst for Suzuki-Miyaura cross-coupling reaction of perfluoroarenes (Scheme 1.2b).[5]



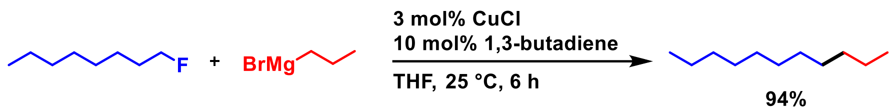
Scheme 1.2 Ni-catalyzed cross-coupling reaction of fluoroarenes with organometallic reagents

Contrary to the reactions using nickel catalyst, in 2011, our group has reported palladium-catalyzed coupling reaction of arylzinc reagent with tetrafluoroethylene which is a bulk organofluorine feedstock as a monomer of poly(tetrafluoroethylene) (Scheme 1.3a).[6] Addition of lithium iodide (LiI) drastically improved yields of the product, *α,β,β*-trifluorostyrene derivatives. The role of LiI is the promotion of C−F bond cleavage step. Indeed, stoichiometric reaction of palladium-tetrafluoroethylene complex with LiI afforded a novel trifluorovinylpalladium complex of which structure was determined by X-ray crystallography. This is a rare example of cross-coupling via C−F bond cleavage catalyzed by palladium.[7] Therefore, this methodology has been applied to cross-coupling reaction of perfluoroarenes (Scheme 1.3b). The details of the reactions and the dicussions are described in chapter 2.

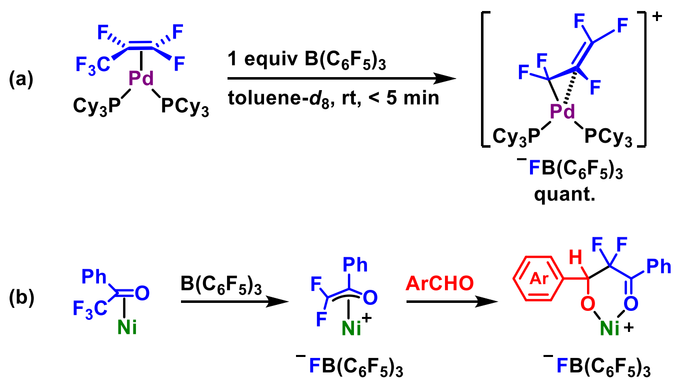


Scheme 1.3 Pd-catalyzed cross-coupling reaction of tetrafluoroethylene and perfluoroarenes with arylzinc reagents promoted by addition of LiI

Although transition metal-catalyzed or -mediated transformation via aromatic or vinylic C−F bond fission is well known, examples of aliphatic C−F bond cleavage by use of transition-metal complexes are quite rare. A pioneering work of cross-coupling reaction of alkyl fluoride with Grignard reagent has been developed by Kambe et al. in which combination of copper catalyst and 1,3-butadiene as an additive revealed to be efficient to afford cross-coupling product (Scheme 1.4).[8] However, only few examples that construct C−C bond via aliphatic C−F bond fission has been known yet.[9] Our group has found that stoichiometric aliphatic C−F bond activation of hexafluoropropene coordinated on Pd(0) was promoted by addition of tris(pentafluorophenyl)borane ($B(C_6F_5)_3$) (Scheme 1.5a).[10] In chapter 3, this strategy was expanded to the C−F bond activation of *α*,*α*,*α*-trifluoroacetophenone by using Ni(0)/$B(C_6F_5)_3$ system (Scheme 1.5b). Furthermore, the resulting novel nickel difluoro-enolate was fully characterized and its reactivity was investigated.

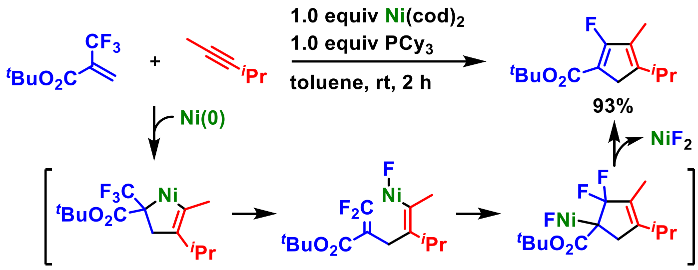


Scheme 1.4 Cu-catalyzed cross-coupling reaction of alkyl fluoride with Grignard reagents

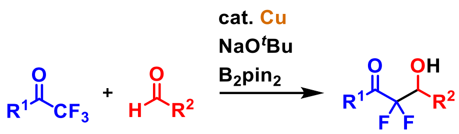


Scheme 1.5 Aliphatic C−F bond activation of hexafluoropropene on Pd(0) or trifluoroacetophenone on Ni(0) accelerated by addition of $B(C_6F_5)_3$

Another approach toward C−F bond cleavage is β-fluorine elimination. This process is known to proceed relatively under mild conditions.[11] For example, Ichikawa et al. developed Ni(0)-mediated cycloaddition of 2-trifluoromethyl-1-alkenes with alkynes through double C−F bond activation via β-fluorine elimination to afford monofluoro-cyclopentadiene (Scheme 1.6).[11j] However, transition-metal catalyzed C−C bond-forming reaction via β-fluorine elimination still remains elusive. In chapter 4, reaction of borylcopper complex with *α*,*α*,*α*-trifluoroacetophenone to generate copper difluoro-enolate *in situ* via 1,2-addition followed by β-fluorine elimination is described. In addition, copper-catalyzed formal Reformatsky reaction via C−F bond cleavage has been developed to give difluoro-compound from easily accessible trifluoromethylketone (Scheme 1.7).



Scheme 1.6 Ni-mediated cycloaddition of trifluoroalkene with alkyne along with a plausible reaction mechanism



Scheme 1.7 Cu-catalyzed formal Reformatsky reaction via C−F bond cleavage

Transformation of C−F bond is potentially an important technology to synthesize organofluorine compounds from inexpensive or abundant polyfluorinated precursors. On the other hand, C−F bond has been known as a very stable bond. Therefore, C−F bond activation still remains to be an academic challenge. In this thesis, reactions of abundant perfluoroarenes and trifluoromethylketones involving C−F bond cleavage by transition-metal complexes as key steps to give corresponding organofluorine compounds are described. These studies would contribute to development of synthetic chemistry of organofluorine compounds as well as organometallic chemistry by providing novel examples of stoichiometric C−F bond cleavage.

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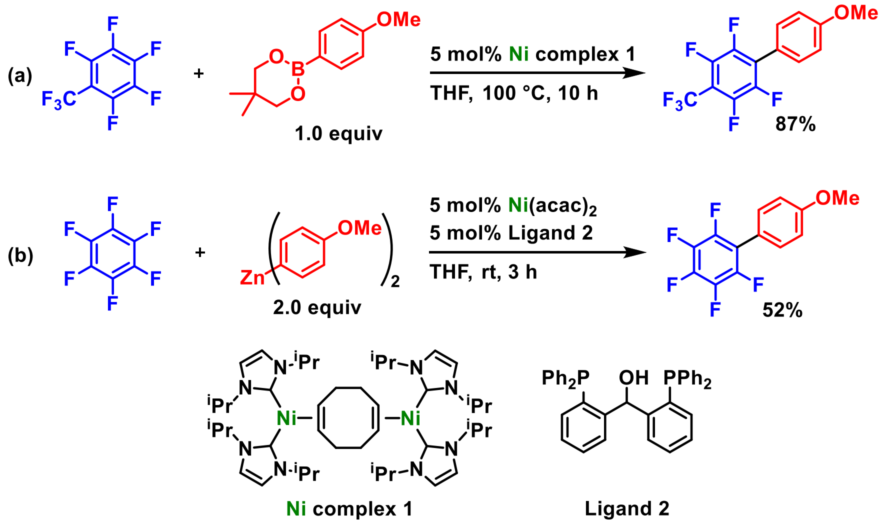
Chapter 2

Pd-Catalyzed Coupling Reaction of Perfluoroarenes with Arylzinc Reagents

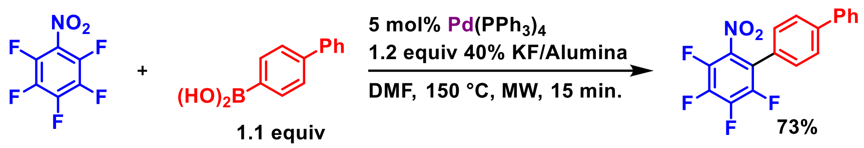
2.1 Introduction

Perfluoroarenes are unique functional groups featuring highly electron withdrawing nature, planar structure and high thermal stability derived from strong C−F bond. One of the most typical building blocks to install perfluoroarenes is a mixed halogen compound which is not readily available. Therefore, commercially available perfluoroarenes are fascinating alternative building blocks. Some cross-coupling reaction of perfluoroarenes with organometallic reagents to afford corresponding biaryls has been reported.[1-3] Our group demonstrated the reaction of perfluoroarenes with an aryl boronate catalyzed by Ni complex **1** developed by Radius et al. that proceeded even in the absence of additional base (Scheme 2.1a).[1m] Yoshikai and Nakamura et al. reported cross-coupling reactions of polyfluoroarenes with arylzinc reagents catalyzed by nickel ligated with alkoxydiphosphane **2** (Scheme 2.1b).[1l]



Scheme 2.1 Ni-catalyzed coupling reaction of perfluoroarenes with organometallic reagents

Contrary to these reports based on nickel catalyst, palladium-based catalyst system is quite rare.[2] Sandford et al. disclosed coupling reaction of perfluoronitrobenzene with aryl boronic acid in the presence of $Pd(PPh_3)_4$ under microwave irradiation (Scheme 2.2).[2d,e] However, the substrate scope is limited to the perfluoroarenes bearing nitro group as highly electron withdrawing group to activate C−F bond and as directing group for ortho selective activation.



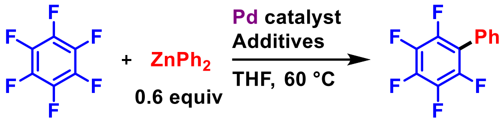
Scheme 2.2 Pd-catalyzed cross-coupling reaction of pentafluoronitrobenzene with aryl boronic acid

Herein, coupling reaction of perfluoroarenes with diarylzinc compounds catalyzed by Pd(0) in the presence of LiI is described. In addition, a possible reaction pathway based on mechanistic study using novel perfluoroaryl palladium complexes is discussed.

2.2 Result and Discussion

The reaction condition of coupling reaction of tetrafluoroethylene with arylzinc reagents were applied to the reaction of hexafluorobenzene (C_6F_6) with diphenylzinc ($ZnPh_2$) generated in situ by treatment of zinc chloride ($ZnCl_2$) with 2 equiv of phenylmagnesium bromide (PhMgBr).[4] In the presence of 5 mol% of tris(dibenzylideneacetone)palladium(0) ($Pd_2(dba)_3$), 20 mol% of triphenylphosphine (PPh_3) and 2.4 equiv of LiI, the reaction of C_6F_6 with $ZnPh_2$ gave trace amount of pentafluorophenyl benzene (**3a**) and C_6F_6 remained intact (Table 1, entry 1). The desired product **3a** was obtained in a 70% yield by using $Pd(PCy_3)_2$ (PCy_3 = tricyclohexylphosphine) as a catalyst precursor for the coupling reaction (entry 2). In the absence of a palladium catalyst, **3a** was not obtained at all (entry 3). An increase in the amount of LiI improved the yield of **3a** to 75%, while in the absence of LiI, the desired product **3a** was observed only 5% even after a prolonged reaction time (entry 4, 5). This result indicates that the addition of LiI is crucial for the occurrence of the coupling reaction. In the presence of PCy_3, palladium (II) acetate ($Pd(OAc)_2$) was also found to be an effective catalyst for the coupling reaction (entry 6). A mixture of 5 mol% of $Pd_2(dba)_3$ and 20 mol% of PCy_3 showed similar catalytic activity to give **3a** in 77% yield, whereas a greater palladium catalyst loading was required for smooth progress in the coupling reaction (entry 7). When either 1,2-bis(dicyclohexylphosphino)ethane (DCPE) or 1,4-bis(dicyclohexylphosphino)butane (DCPB) were employed, the coupling reaction retarded (entry 8, 9).

Table 2.1 Optimization of the reaction condition

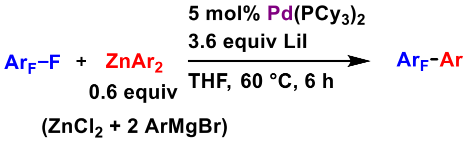


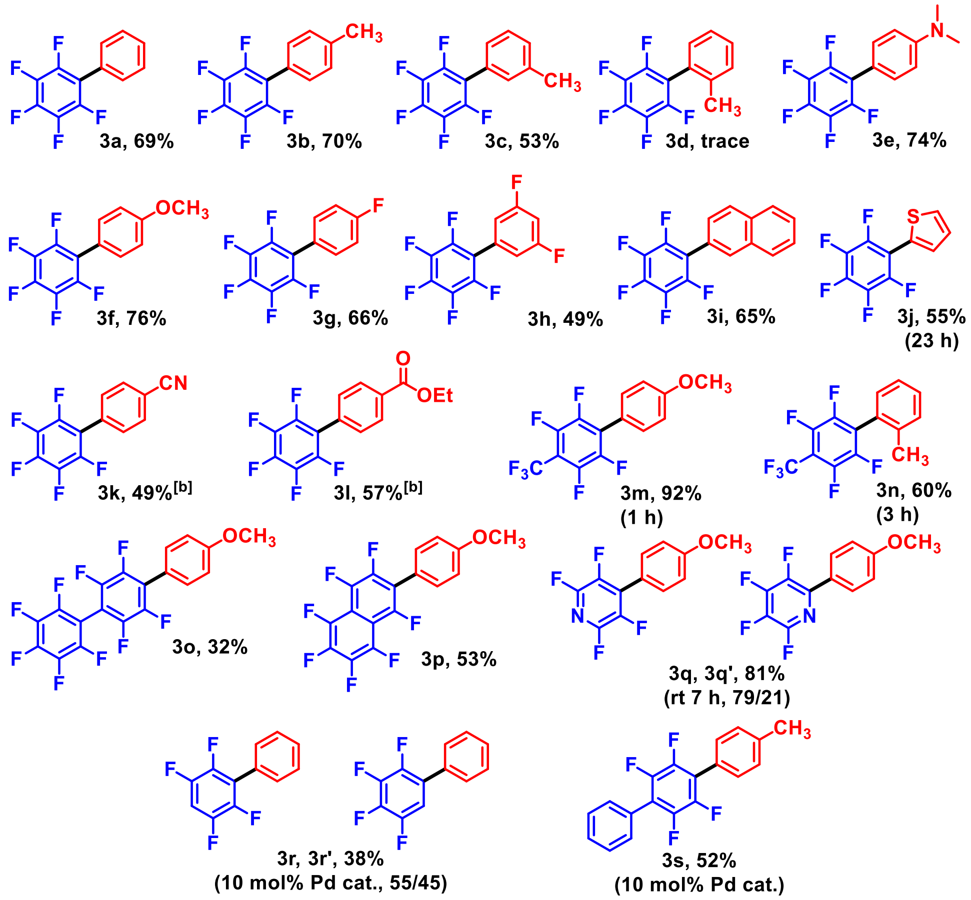
Entry	Catalyst (mol%)	Additive	Time (h)	Yield (%)[a]
1	$Pd_2(dba)_3$ (5) / PPh_3 (20)	LiI (2.4 equiv)	10	trace
2	$Pd(PCy_3)_2$ (5)	LiI (2.4 equiv)	4	70
3	none	LiI (2.4 equiv)	21	-
4	$Pd(PCy_3)_2$ (5)	LiI (3.6 equiv)	6	75
5	$Pd(PCy_3)_2$ (5)	none	10	5
6[b]	$Pd(OAc)_2$ (5) / PCy_3 (10)	LiI (2.4 equiv)	4	65
7	$Pd_2(dba)_3$ (5) / PCy_3 (20)	LiI (3.6 equiv)	4	77
8[b]	$Pd(OAc)_2$ (5) / DCPE (5)	LiI (2.4 equiv)	9	13
9[b]	$Pd(OAc)_2$ (5) / DCPB (5)	LiI (2.4 equiv)	15	trace

[a] GC yield estimated by use of tetradecane as an internal standard. [b] $ZnPh_2$ (0.7 equiv) was employed.

The substrate scope of the cross-coupling reaction of perfluoroarenes with arylzinc reagents in the presence of catalytic amount of $Pd(PCy_3)_2$ and LiI based on the result of optimization (Table 2.2). Both $(4\text{-}MeC_6H_5)_2Zn$ and $(3\text{-}MeC_6H_5)_2Zn$ reacted with C_6F_6 to give coupling products **3b** and **3c** in 70 and 53% yield, respectively. However, no coupling product was observed from the reaction of C_6F_6 with $(2\text{-}MeC_6H_5)_2Zn$. The arylzinc compounds bearing electron-donating groups such as $(4\text{-}Me_2NC_6H_4)_2Zn$ and $(4\text{-}MeOC_6H_4)_2Zn$ afforded the coupling compounds **3e** and **3f** in 74 and 76% yield, respectively. The reactions of aryl zinc reagents with electron-withdrawing groups, $(4\text{-}FC_6H_4)_2Zn$ and $(3,5\text{-}F_2C_6H_3)_2Zn$, also yielded the corresponding coupling products (**3g** and **3h**) in 66 and 49% yield, respectively. The reaction of C_6F_6 with $(2\text{-}C_{10}H_9)_2Zn$ under the same reaction conditions produced 2-pentafluorophenylnaphthalene (**3i**) in 65% yield after 8 h. When a thienyl group was introduced, the reaction gave 2-pentaphenylthiophene (**3j**) in 55% yield. Other functionalized aryl zinc species prepared according to Knochel's procedure, LiCl·(*p*-$EtCOOC_6H_4$)ZnI and LiCl·(p-NCC_6H_4)ZnI, were successfully applied to the coupling reaction with C_6F_6 to give **3k** and **3l**, respectively, in moderate isolated yields.[5]

Table 2.2 Pd-catalyzed coupling reaction of perfluoroarenes with arylzinc reagents in the presence of LiI[a]



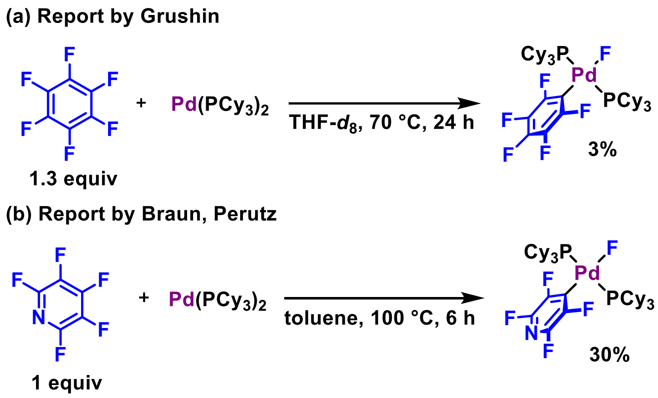


[a] Isolated yields. [b] Arylzinc reagent was prepared by reaction of corresponding aryl iodide with Zn (3 equiv) and LiCl (3 equiv) in THF.

Next, the reaction was applied to other perfluoroarenes. The coupling reaction of octafluorotoluene (C_7F_8) with $(4\text{-}MeOC_6H_4)_2Zn$, or $(2\text{-}MeC_6H_4)_2Zn$ occurred at the 4-position of C_7F_8 to give the corresponding products **3m** and **3n** in good-to-excellent yields. The reaction of C_7F_8 with $(4\text{-}MeOC_6H_4)_2Zn$ proceeded very smoothly, which allowed the confirmation of a background reaction. In the absence of $Pd(PCy_3)_2$, **3m** was obtained in 30% yield at 60 °C for 6 h, which indicates that the palladium-catalyzed coupling reaction proceeds much faster than the background reaction. Perfluorobiphenyl and Perfluoronaphthalene reacted with $(4\text{-}MeOC_6H_4)_2Zn$ to give corresponding products **3o** and **3p** in 32 and 53% yield, respectively. In contrast, the reaction of pentafluoropyridine

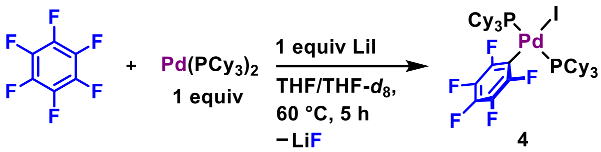
(C_5F_5N) with $ZnPh_2$ gave a mixture of tetrafluoro-4-phenylpyridine (**3q**) and tetrafluoro-2-phenylpyridine (**3q'**) in 65 and 17% yield, respectively. Pentafluorobenzene also participated in the coupling reaction with $ZnPh_2$, however, the reaction product was obtained as a mixture of two regioisomers, 2,3,5,6-tetrafluorobiphenyl (**3r**) and 2,3,4,5-tetrafluorobiphenyl (**3r'**), and the combined yield of the isomers was only 38 %. Pentafluorobiphenyl was also reactive to afford terphenyl **3s** in moderate yield with 10 mol% catalyst loading.

To gain deeper insight into the reaction pathway, stoichiometric reactions of C_6F_6 with palladium(0) complexes were tested. In a previous report by Grushin et al., the reaction of C_6F_6 with $Pd(PCy_3)_2$ in THF at 70 °C for 24 h occurred very slowly to give a pentafluorophenylpalladium(II) fluoride, *trans*-$Pd(C_6F_5)F(PCy_3)_2$, in a 3% yield (Scheme 2.3a).[6] Braun and Perutz et al. also reported a reaction of $Pd(PCy_3)_2$ with highly reactive C_5F_5N to afford *trans*-$Pd(C_6F_4N)F(PCy_3)_2$ in 30% isolated yield (Scheme 2.3b).[7]



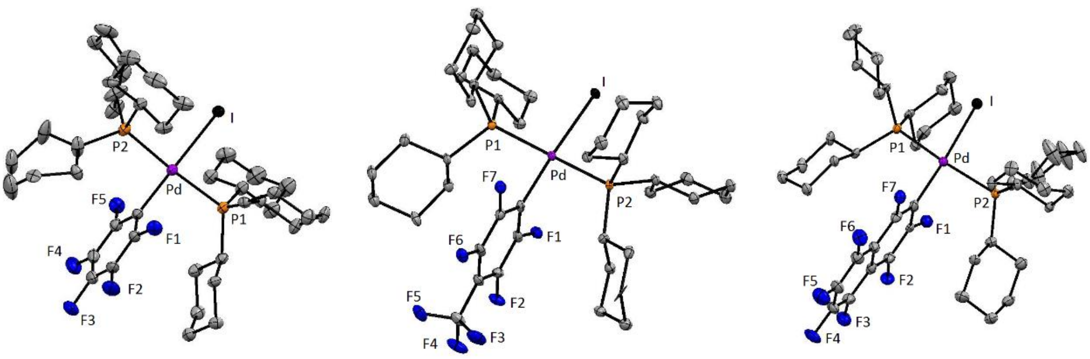
Scheme 2.3 C−F bond activation of perfluoroarenes with Pd(0)

On the other hand, in the presence of LiI the oxidative addition proceeded much faster to give a pentafluorophenylpalladium(II) iodide, *trans*-$Pd(C_6F_5)I(PCy_3)_2$ (**4**), which indicates that acceleration of the oxidative addition is an important role of LiI (Scheme 2.4). Addition of lithium bromide or chloride also promoted the reaction, although the yield decreased to 55% and 11% respectively. In contrast, even in the presence of LiI, the oxidative addition of C_6F_6 to $Pd(PPh_3)_4$ did not take place, which is consistent with the fact that PPh_3 is not a suitable auxiliary ligand for the catalytic reaction (Table 1, entry 1).



Scheme 2.4 C−F bond activation of C_6F_6

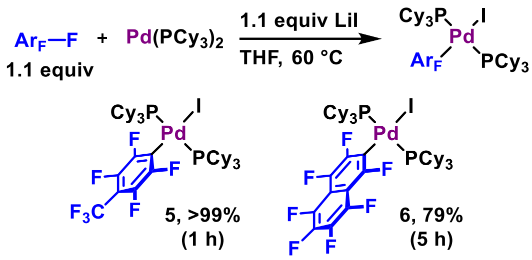
The ORTEP diagram of **4** unambiguously demonstrates that the palladium center in **4** adopts a square-planar coordination geometry and is coordinated by two PCy_3 ligands in a trans manner (Figure 2.1a). A similar coordination geometry was found in structurally well-defined Pd(II) complexes, such as *trans*-Pd(C_6F_5)Cl(PPh_3)$_2$ and *trans*-Pd(C_6F_5)I(PCy_2Fc)$_2$ (Fc= ferrocenyl).[8]



(a) Complex **4** (b) Complex **5** (c) Complex **6**

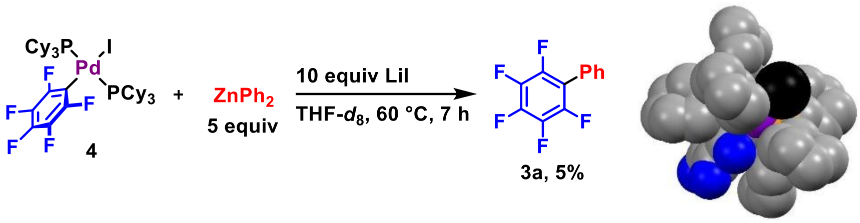
Figure 2.1 ORTEP representation of palladium complexes **4**, **5** and **6** with thermal ellipsoids at the 50% probability level. Hydrogen atoms were omitted for clarity. For **5**, one of the two independent molecules in a unit cell is depicted and solvated hexane was also omitted.

Similar oxidative-addition products, *trans*-Pd(4-$CF_3C_6F_4$)I(PCy_3)$_2$ (**5**) and *trans*-Pd(2-$C_{10}F_7$)I(PCy_3)$_2$ (**6**), can be isolated by treatment of either C_7F_8 or perfluoronaphthalene with Pd(PCy_3)$_2$ in the presence of LiI (Scheme 2.5). In the former reaction, the C−F bond at the 4-position of C_7F_8 was exclusively cleaved, whereas the C−F bond at the 2-position of perfluoronaphthalene was exclusively activated in the latter reaction. These regioselectivities of C−F bond fission were consistent with those observed in the corresponding catalytic process (Scheme 1). The ORTEP drawings of **5** and **6** are represented in Figure 2.1b and 2.1c, and definitely show that the palladium center in both **5** and **6** has the same coordination geometry as in **4**.



Scheme 2.5 Preparation of perfluoroarylpalladium complexes

To confirm whether or not **4** is an intermediate in the Pd-catalyzed cross-coupling reaction of C_6F_6 with diarylzinc compounds, a stoichiometric reaction of **4** with $ZnPh_2$ was examined. As a result, a yield of only 5% of **3a** was obtained from a stoichiometric reaction conducted at 60 °C for 7 h in the presence of an excess amount of LiI (Scheme 2.6), whereas **3a** was obtained in 69% yield under the catalytic reaction conditions mentioned above (60 °C, 6 h; Table 2.2). This result suggest that **4** is unlikely to be a reaction intermediate. The space filling model of the complex **4** based on the X-ray diffraction study implies the steric congestion around the palladium center caused by the two bulky PCy_3 ligands. Thus, it is assumed that oxidative addition of C_6F_6 to $Pd(PCy_3)_2$ in the presence of LiI might involve dissociation of a PCy_3 ligand to give a transient $Pd(C_6F_5)I(PCy_3)$ species (Figure 2.2). The resultant three-coordinate transient intermediate would undergo re-coordination of a PCy_3 ligand in the absence of $ZnPh_2$ to yield the thermodynamically favored, and unreactive, species **4**. On the other hand, in the presence of $ZnPh_2$, transmetalation between the transient iodopalladium(II) species and $ZnPh_2$ would occur smoothly to yield the coupling product **3a**. These assumptions are consistent with the results from kinetic studies performed by Hartwig and co-workers: the oxidative addition of chlorobenzene to $Pd(PCy_3)_2$, to give *trans*-$PdCl(PCy_3)_2(Ph)$ involved the dissociation of a PCy_3 ligand at the initial stage of the reaction.[9] Therefore, $Pd(C_6F_5)I(PCy_3)(py)]$ (**7**), in which pyridine acts as a labile ligand to generate a tentative threecoordinate $Pd(C_6F_5)I(PCy_3)$ species, was prepared as an alternative catalytic precursor.



Scheme 2.6 (Left) Reaction of complex **4** with $ZnPh_2$ in the presence of LiI.
(Right) Space filling model of the complex **4**.

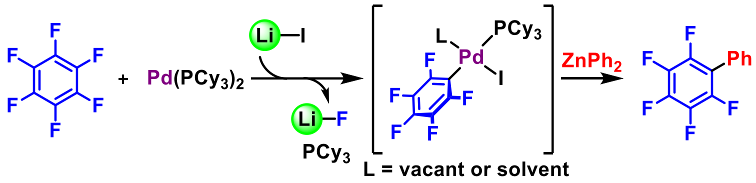


Figure 2.2 Working hypothesis on reaction mechanism

$Pd(C_6F_5)_2(py)_2$ (py = pyridine) was chosen as a starting material.[10] In accordance with the literature, treatment of $PdCl_2(py)_2$ with pentafluorophenyllithium (3 equiv), generated in situ by reaction of chloropentafluorobenzene with ^{n}BuLi at −78 °C, afforded $Pd(C_6F_5)_2(py)_2$ in 72% yield (Figure 2.3a).[11] X-ray diffraction study of $Pd(C_6F_5)_2(py)_2$ revealed that Pd(II) center had a square-planar geometry and was coordinated by two pentafluorophenyl group in the *cis* configuration, although a *trans* configuration was proposed in the original literature (Figure 2.3b). The transmetallation between $Pd(C_6F_5)_2(py)_2$ and $PdCl_2$ in acetone followed by treatment with pyridine gave $Pd(C_6F_5)Cl(py)_2$ (Figure 2.3c).[12]

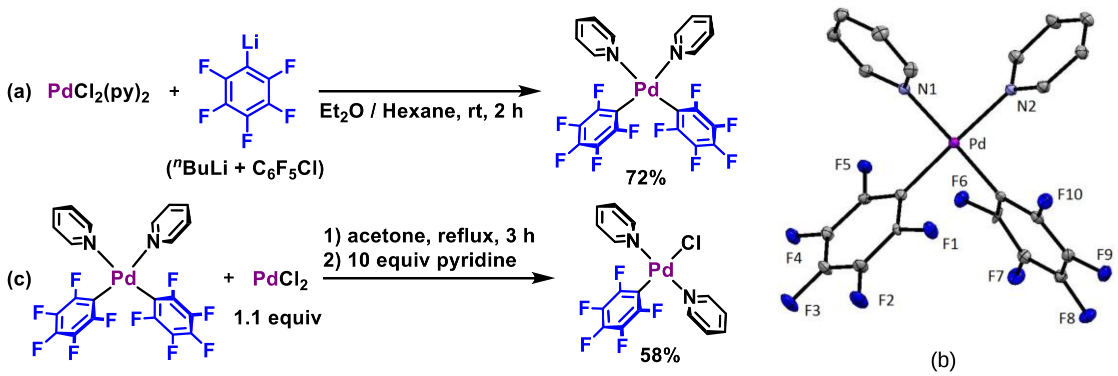
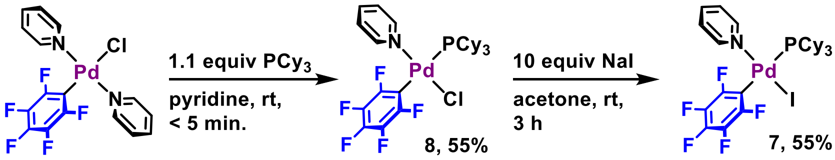
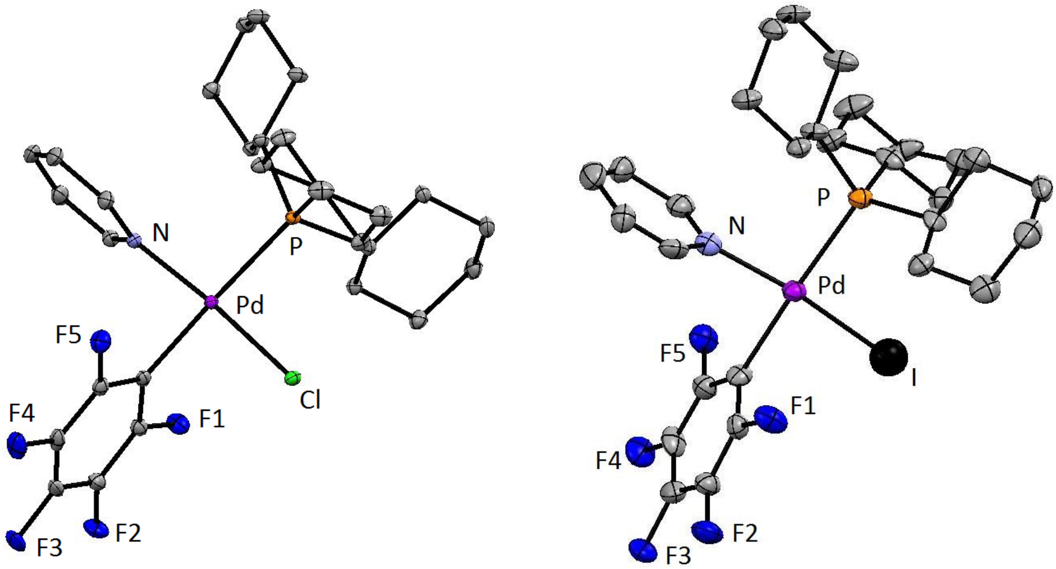


Figure 2.3 (a) Synthesis of $Pd(C_6F_5)_2(py)_2$. (b) ORTEP representation of $Pd(C_6F_5)_2(py)_2$ with thermal ellipsoids at the 50% probability level. Hydrogen atoms were omitted for clarity. (c) Preparation of $Pd(C_6F_5)Cl(py)_2$.

Treatment of $Pd(C_6F_5)Cl(py)_2$ with 1.1 equiv of PCy_3 in pyridine followed by addition of hexane caused white precipitation which was recrystallized from acetone to afford novel $Pd(C_6F_5)Cl(PCy_3)(py)$ (**8**) in a 55% yield as an acetone adduct (Scheme 2.7). Substitution of an iodide for the chloride in **8** was accomplished by reaction of **8** with excess sodium iodide to afford the desired Pd(II) iodide **7** in 55% yield. Pentafluorophenylpalladium halides **7** and **8** were characterized by NMR spectroscopy and combustion analysis as well as by X-ray diffraction analysis (Figure 2.4). The ^{1}H NMR spectra of these complexes clearly showed that both the pyridine and PCy_3 ligands were coordinated to the Pd(II) center in a ratio of 1 : 1. In addition, auxiliary ligands in **7** and **8** were situated in a mutual *cis* position with a square-planar geometry of Pd(II) as shown by X-ray diffraction study.



Scheme 2.7 Formation of complex **8** followed by treatment with NaI



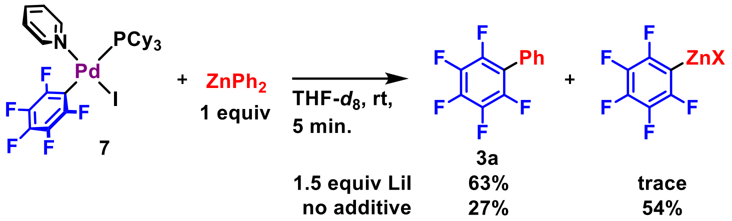
(a) Complex **8** (b) Complex **7**

Figure 2.4 ORTEP drawings of **8** and **7** with thermal ellipsoids at the 50% probability level. Hydrogen atoms and solvated molecules (acetone for **8** and THF for **9**) were removed for clarity.

The Pd−N bond lengths of 2.032(10) Å in **7** and 2.0407(13) Å in **8** were slightly shorter than those observed in $Pd(C_6F_5)_2(py)_2$ (2.093(2) and 2.105(3) Å), which reflects the difference in the trans influence between halides and a pentafluorophenyl ligand. On the other hand, the Pd−C_6F_5 bond lengths showed only slight differences (2.015(5) Å for **4**, 2.069(12) Å for **7**, 2.001(3) and 2.025(3) Å for $Pd(C_6F_5)_2(py)_2$, and 2.0519(16) Å for **8**). In addition, the bond lengths between the palladium and phosphorus atoms in **7** and **8** (2.359(3) and 2.3604(4) Å, respectively) were close in value to those observed in **4** (2.3691(16) and 2.3839(16) Å).

The reactivity of **7** toward $ZnPh_2$ in the presence or absence of LiI was evaluated (Scheme 2.8). In the presence of LiI (1.5 equiv), **8** reacted smoothly with $ZnPh_2$ in THF at room temperature to give the desired coupling product **3a** as the sole product in 63%

yield. On the other hand, in the absence of LiI, the reaction of **8** with $ZnPh_2$ under the same reaction conditions afforded a pentafluorophenylzinc species, C_6F_5ZnX (X=I or C_6F_5), as the major product (54%) and **3a** as the minor product (27 %). These observations suggest that a transient $Pd(C_6F_5)I(PCy_3)$ species, generated by dissociation of the labile pyridine ligand of **8**, could be crucial for the smooth occurrence of transmetalation between the palladium(II) species and $ZnPh_2$, and the existence of LiI is essential for selective transmetalation to generate **3a**.



Scheme 2.8 Reactivity of complex **7**

Based on these results, a plausible reaction mechanism was proposed in Figure 2.5. In the presence of LiI, oxidative addition of a C−F bond in C_6F_6 to Pd(0) would occur initiated by dissociation of a PCy_3 ligand to form a $Pd(C_6F_5)I(PCy_3)$ intermediate (**A**). Transmetalation between **A** and the arylzinc reagent in the presence of LiI would take place to give a bisarylpalladium(II) intermediate (**B**). The transmetalation step would progress in preference to the re-coordination of a PCy_3 ligand to give unreactive **4**. The role of LiI in this step might be rationalized by the formation of a reactive zincate, such as Li[ArZnXI] (X=Ar or I), which would enable the efficient formation of **B**.[4,13] Then, reductive elimination from **B**, followed by the re-coordination of a PCy_3 ligand would produce the coupling product **3**, along with regeneration of the Pd(0) species.

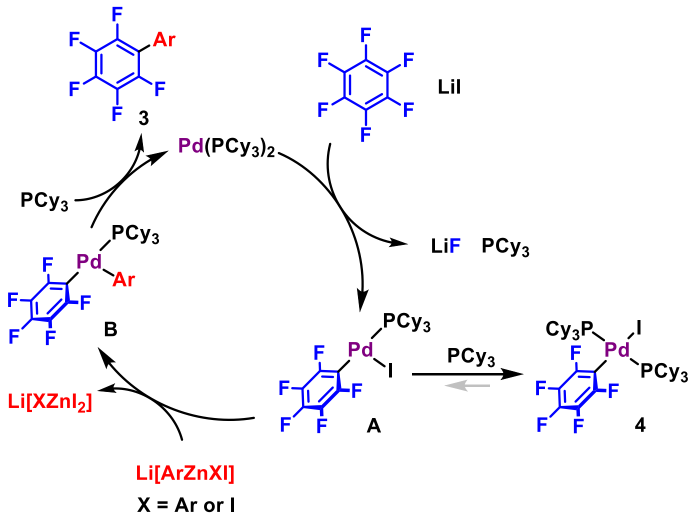


Figure 2.5 A plausible reaction mechanism

2.3 Conclusion

In chapter 2, Pd(0)/PCy_3-catalyzed cross-coupling reaction of perfluoroarenes with a variety of arylzinc reagents to afford the corresponding polyfluorobiaryls in good-to-excellent yields. Mechanistic investigation in which *trans*-$Pd(C_6F_5)I(PCy_3)_2$ and $Pd(C_6F_5)I(PCy_3)(py)$ were reacted with $ZnPh_2$ revealed both the catalytic reaction pathway and the role of LiI in the catalytic reaction. The key intermediate in this catalytic cycle is a transient, three-coordinated monophosphine palladium species $Pd(C_6F_5)I(PCy_3)$ which was generated by oxidative addition of C−F bond of C_6F_6 to $Pd(PCy_3)_2$ along with dissociation of a PCy_3 ligand. The role of LiI in this catalytic reaction was not only to accelerate the oxidative addition step, but also to activate a arylzinc reagent by formation of a zincate such as Li[ArZnXI] (X = Ar or I), which would enable an efficient transmetallation with the key intermediate.

2.4 Experimental Section

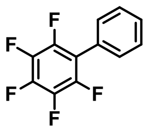
General statements for the experiments conducted in this thesis: All manipulations were conducted under a nitrogen atmosphere using standard Schlenk or dry box techniques. ^{1}H, ^{11}B, ^{19}F, ^{31}P, and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III 400 or on a Bruker Avance III 600. The chemical shifts in ^{1}H and ^{13}C NMR spectra were recorded relative to residual protonated solvent. The chemical shifts in the ^{31}P NMR spectra were recorded using 85% H_3PO_4 as an external standard. The chemical shifts in ^{19}F NMR spectra were referenced with respect to an external standard of $CFCl_3$. Recycling Preparative High Performance Liquid Chromatography (HPLC) was performed on Japan Analytical Industry LC9225NEXT equipped with JAIGEL-1H and JAIGEL-2H. Elemental analyses were performed at Instrumental Analysis Center, Faculty of Engineering, Osaka University. X-ray crystal data were collected by a Rigaku RAXIS-RAPID Imaging Plate diffractometer or Mercury 375R/M CCD (XtaL LAB mini) diffractometer.

Materials: The degassed and distilled solvents (toluene, hexane and pentane) used in this work were commercially available. THF, THF-d_8 and C_6D_6 were distilled from sodium benzophenone ketyl. All the Grignard reagents used in this work were purchased from Aldrich as THF solutions and their concentrations were determined by titration with absolute *m*-xylene solution of *sec*-BuOH in the presence of 1,10-phenanthroline as an indicator. *Trans*-bis(pyridine)dichloropalladium(II),[11] $Pd(PCy_3)_2$,[14] THF solution of LiCl•(*p*-cyanophenyl)zinc iodide,[5] and LiCl•(*p*-EtCOOPh)zinc iodide[5] were prepared by published procedures. $ZnCl_2$ (3N) was purchased from WAKO Pure Chemicals, and dried under vacuum with heating until melting. Other commercially available reagents were distilled and degassed prior to use.

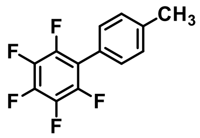
Experimental Details

General Procedure for Optimization of Catalytic Reaction: In a dry box, to a vial equipped with a stirring bar was placed $ZnCl_2$ (9.54 mg, 0.07 mmol), PhMgBr (1 M solution in THF, 140 μL, 0.14 mmol), LiI (32.1 mg, 0.24 mmol), and THF (160 μL). To the resulting mixture was added a THF solution of $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and PCy_3 (2.8 mg, 0.010 mmol), 1 (11.5 μL, 0.1 mmol), and tetradecane (26 μL, 0.1 mmol) as an internal standard. The vial was sealed, and heated with preheated sand bath with stirring. After the reaction, the solution was quenched with methanol and analyzed by GC. The yield was estimated by comparing peak areas of pentafluorobiphenyl with tetradecane with a sensitivity ratio determined by GC spectrum of isolated samples. The results are summarized in Table 2.1.

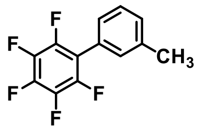
General Procedure for Pd-Catalyzed Coupling Reaction of Perfluoroarenes with Diarylzinc in the Presence of LiI: In a dry box, to a vial equipped with a stirring bar were added a THF solution of arylmagnesium halide (1.2 mmol) and $ZnCl_2$ (81.8 mg, 0.6 mmol). The mixture was diluted with THF to make the volume 5 mL and vigorously stirred until $ZnCl_2$ dissolve completely. To the solution were added $Pd(PCy_3)_2$ (33.3 mg, 0.05 mmol), LiI (321 mg, 2.4 mmol), and perfluroarenes (0.1 mmol). The reaction mixture was heated with stirring, and then quenched with 15 mL of 1M HCl aq. The water layer was separated and extracted with ether (5 mL × 4). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness. The resulting solid was purified by flash column chromatography to give pure product. The results are summarized in Table 2.2. Characterization of the products are described below.



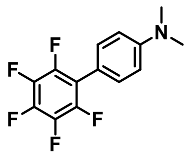
3a: By following the general procedure, a coupling reaction of phenylmagnesium bromide with C_6F_6 gave a white solid (168.5 mg, 69%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 7.39 – 7.44 (m, 2H), 7.46 – 7.52 (m, 3H). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −143.3 (dd, J = 7.8, 22.7 Hz, 2F), −155.7 (t, J = 20.6 Hz, 1F), −162.3 (dt, 7.8, 21.5 Hz, 2F). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 116.0 (dt, J = 4, 17 Hz), 126.5, 128.8, 129.4, 130.2, 138.0 (dm, J = 258 Hz), 142.0 (dm, J = 256 Hz), 144.3 (J = 249 Hz). HRMS: m/z calc. 244.0311 ($C_{12}H_5F_5$), found 244.0311. Spectral data of **3a** were identical to that of previously reported.[15]



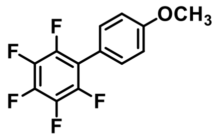
3b: By following the general procedure in 0.3 mmol scale, a coupling reaction of *4*-tolylmagnesium bromide with C_6F_6 gave a white solid purified by preparative thin layer chromatography (55 mg, 70%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 2.42 (s, 3H), 7.31 (s, 4H). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −143.4 (dd, 8.3 Hz, 21.23 Hz, 2F), −156.3 (t, 21.2 Hz, 1F), −162.6 (dt, 8.3 Hz, 21.2 Hz, 2F). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm,): 21.4, 116.1 (dt, 4 Hz, 17 Hz), 123.5, 129.6, 130.1, 138.0 (dm, 252 Hz), 139.6, 140.1 (dm, 254 Hz), 144.2 (dm, 246 Hz). HRMS: m/z calc. 258.0468 ($C_{13}H_7F_5$), found 258.0466. Spectral data of **3b** were identical to that of previously reported.[15]



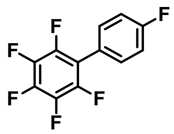
3c: By following the general procedure in 0.3 mmol scale, a coupling reaction of *3*-tolylmagnesium bromide with C_6F_6 gave white solid purified by preparative thin layer chromatography (41 mg, 53%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 2.42 (s, 3H), 7.20 - 7.22 (m, 2H), 7.27 (d, 7.4 Hz, 1H), 7.38 (t, 7.4 Hz, 1H). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −143.1 (dd, 8.2 Hz, 22.4 Hz, 2F), −155.9 (t, 22.4 Hz, 1F), −162.4 (dt, 8.23 Hz, 22.4 Hz). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 21.5, 116.2, 126.4, 127.3, 128.7, 130.2, 130.8, 137.9 (dm, 243 Hz), 138.6, 140.4 (dm, 255 Hz), 144.3 (dm, 251 Hz). HRMS: m/z calc. 258.0468 ($C_{13}H_7F_5$), found 258.0469. Spectral Data of **3c** were identical to that of previously reported.[15]



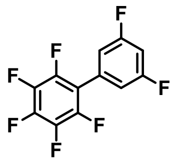
3e: By following the general procedure, a coupling reaction of *4-N,N*-dimethylaminophenylmagnesium bromide with C_6F_6 gave a white solid (211.2 mg, 74%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 3.02 (s, 6H), 6.79 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3, 2H). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −144.1 (dd, J = 7.7, 22.2 Hz, 2F), −158.1 (t, J = 22.2 Hz, 1F), −163.1 (dt, J = 7.7, 22.2 Hz, 2F). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 40.3, 112.0, 113.4, 116.4 (t, $J_{C\text{-}F}$ = 3, 16 Hz), 131.0, 137.5 (dm, $J_{C\text{-}F}$ = 249 Hz), 139.5 (dm, $J_{C\text{-}F}$ = 255 Hz), 144.3 (dm, $J_{C\text{-}F}$ = 245 Hz), 150.8. HRMS: m/z calc. 287.0733 ($C_{14}H_{10}F_5N$), found 287.0732. Spectral Data of **3d** were identical to that of previously reported.[16]



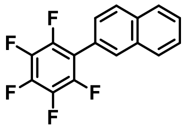
3f: By following general procedure, a coupling reaction of *4*-anisylmagnesium bromide with C_6F_6 gave a white solid (209.5 mg, 76%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 3.86 (s, 3H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −143.7 (dd, *J* = 8.2, 23.2 Hz, 2F), −156.6 (t, *J* = 21.2 Hz, 1F), −162.6 (dt, 7.7, 23.0 Hz, 2F). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 55.4, 114.3, 115.8 (m), 118.5, 131.5, 137.9 (dm, *J* = 251 Hz), 139.0 (dm, *J* = 253 Hz), 144.2 (dm, *J* = 246 Hz), 160.4. HRMS: m/z calc. 274.0417 ($C_{13}H_7F_5O$), found 274.0419. Spectral Data of **3f** were identical to that of previously reported.[15]



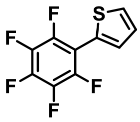
3g: By following the general procedure, a coupling reaction of *4*-fluorophenylmagnesium bromide with C_6F_6 gave a white solid (172.6 mg, 66%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 7.19 (m, 2H), 7.40 (m, 2H). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −111.3 (m, 1F), −143.4 (dd, *J* = 8.2, 22.7 Hz, 2F), −155.3 (t, *J* = 21.1 Hz, 1F), −162.1 (dt, *J* = 8.4, 21.8 Hz, 2F). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm, except for C_6F_5): 163.2 (d, J_{C-F} = 251 Hz), 132.1 (d, J_{C-F} = 8.8 Hz), 122.3, 116.0 (d, J_{C-F} = 22 Hz), 115.0 (d, J_{C-F} = 4 Hz). HRMS: m/z calc. 262.0217 ($C_{12}H_4F_6$), found 262.0223. Spectral Data of **3g** were identical to that of previously reported.[15]



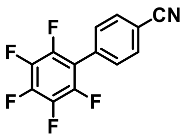
3h: By following the general procedure, a coupling reaction of *3,5*-difluorophenylmagnesium bromide with C_6F_6 gave a white solid (136.0 mg, 49%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 6.90-7.10 (m). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −161.34 (dt, 7.4 Hz, 21.6 Hz, 2F), −153.51 (t, 21.6 Hz, 1F), −142.66 (dd, 7.4 Hz, 21.6 Hz, 2F), −108.65 (t, 7.8 Hz, 2F). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 105.2 (t, 24 Hz), 113.5, 113.8, 129.2 (t, 10 Hz), 138.1 (dm, 253 Hz), 141.2 (dm, 255 Hz), 144.3 (dm, 253 Hz), 163.1 (dd, 250 Hz, 13 Hz). HRMS: m/z calc. 280.0123 ($C_{12}H_3F_7$), found 280.0125. Spectral Data of **3h** were identical to that of previously reported.[17]



3i: By following the general procedure, a coupling reaction of *2*-naphthylmagneisum bromide with C_6F_6 gave white solid (192.5 mg, 65%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 7.49 (dd, *J* = 1.5, 8.5 Hz, 1H), 7.56 (m, 2H), 7.88 – 7.97 (m, 4H). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −144.4 (dd, *J* = 8.1, 22.7 Hz, 2F), −156.8 (t, *J* = 22.7 Hz, 1F), −163.5 (dt, *J* = 8.1, 22.7 Hz, 2F). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 116.1 (dt, *J* = 4, 17 Hz), 123.9, 126.9, 127.2, 127.3, 127.9, 128.4, 128.5, 130.3, 133.2, 133.4, 138.1 (dm, *J* = 253 Hz), 140.6 (dm, *J* = 255 Hz), 144.5 (dm, *J* = 248 Hz). HRMS: m/z calc. 294.0468 ($C_{16}H_7F_5$), found 294.0465. Spectral Data of **3i** were identical to that of previously reported.[15]

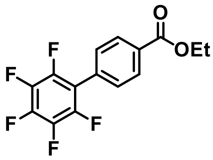


3j: Following the general procedure, a coupling reaction of *2*-thienylmagnesium bromide with C_6F_6 gave a white solid purified by preparative thin layer chromatography (138.4 mg, 55%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 7.19 (tm, 4.3 Hz, 1H), 7.52 (m, 1H), 7.55 (dd, 1.0 Hz, 5.2 Hz). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −140.0 (dd, 6.6 Hz, 21.3 Hz, 2F), −156.0 (t, 20.9 Hz, 1F), −162.2 (dt, 6.3 Hz, 21.4 Hz, 2F). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 111.1 (dt, 4 Hz, 15 Hz), 126.4, 127.4, 128.4 (t, 4 Hz), 130.2 (t, 5 Hz), 138.2 (dm, 253 Hz), 140.0 (dm, 257 Hz), 144.1 (dm, 246 Hz). HRMS: m/z calc. 249.9876 ($C_{10}H_3F_5S$), found 249.9880. Spectral Data of **3j** were identical to that of previously reported.[18]

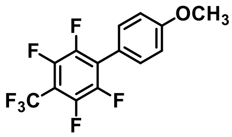


3k: To a reaction vessel equipped with a stirring bar was added LiCl•IZnC_6H_4CN (0.71 M THF solution, 1.7 mL, 1.2 mmol), LiI (481 mg, 3.6 mmol), and THF (3.3 mL). To the resulting solution was added $Pd(PCy_3)_2$ (33.3 mg, 0.05 mmol) and C_6F_6 (115 µL, 1.0 mmol). The reaction vessel was capped, and stirred at 60 ºC for 6 h. The reaction was quenched with 5 mL of sat. NH_4Cl aq. The water layer was separated and extracted with 5 mL of ether 3 times. The combined organic layer was filtered off, washed with 10 mL of brine, and dried over $MgSO_4$. The solution was concentrated in vacuo and purified by HPLC to give white crystalline powder (132.2 mg, 49%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 7.79 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 7.3 Hz, 2H). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −143.1 (m, 2F), −153.1 (m, 1F), −161.2 (m, 2F). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm):

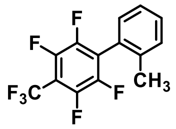
144.0 (dm, J = 255 Hz), 141.2 (dm, J = 251 Hz), 137.9 (dm, J = 255 Hz), 132.5, 131.1, 131.0, 118.1, 114.0 (m), 113.4. HRMS: m/z calc. 269.0264 ($C_{13}H_4F_5N$), found 269.0263. Spectral Data of **3k** were identical to that of previously reported.[18]



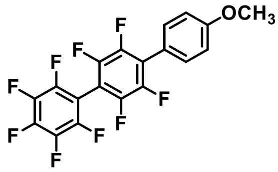
3l: To a reaction vessel equipped with a stirring bar was added LiCl•IZnC_6H_4COOEt (0.68 M THF solution, 1.8 mL, 1.2 mmol), LiI (481 mg, 3.6 mmol), and THF (3.2 mL). To the resulting solution was added Pd(PCy_3)$_2$ (33.3 mg, 0.05 mmol) and C_6F_6 (115 μL, 1.0 mmol). The reaction vessel was capped, and stirred at 60 °C for 6 h. The reaction was quenched with 5 mL of sat. NH_4Cl aq. The water layer was separated and extracted with 5 mL of ether 3 times. The combined organic layer was filtered off, washed with 10 mL of brine, and dried over $MgSO_4$. The solution was concentrated in vacuo and purified by flash column chromatography (eluent Hexane : EtOAc = 95 : 5) to give white crystalline powder (180.5 mg, 57%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 8.09 (m, 2H), 7.49 (m, 2H), 4.37 (m, 2H), 1.38 (m, 3H). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −142.9 (dd, 8.2 Hz, 23.1 Hz, 2F), −154.2 (t, 20.5 Hz, 1F), −161.6 (dt, 8.0 Hz, 22.6 Hz, 2F). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 166.0, 144.3 (dm, 247 Hz), 141.0 (dm, 253 Hz), 138.1 (dm, 239 Hz), 131.5, 130.9, 130.3, 130.0, 115.2 (m), 61.42, 14.44. HRMS: m/z calc. 316.0523 ($C_{15}H_9F_5O_2$), found 316.0523. Spectral Data of **3l** were identical to that of previously reported.[15]



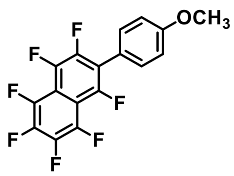
3m: By following the general procedure, a coupling reaction of 4-methoxyphenylmagnesium bromide and C_7F_8 gave a white solid (299.5 mg, 92%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 3.88 (s, 3H), 7.04 (dm, 8.9 Hz, 2H), 7.41 (dt, 8.9 Hz, 1.44 Hz, 2H). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −56.2 (t, 21.6 Hz, 3F), −141.2 (m, 2F), −142.1 (m, 2F). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 55.5, 107.8 (m), 114.4, 118.2, 123.0 (q, 274 Hz), 124.8 (t, 16 Hz), 131.6, 144.2 (dm, 247 Hz), 144.7 (dm, 260 Hz), 161.0. HRMS: m/z calc. 324.0385 ($C_{14}H_7F_7O$), found 324.0383. Spectral Data of **3m** were identical to that of previously reported.[1h]



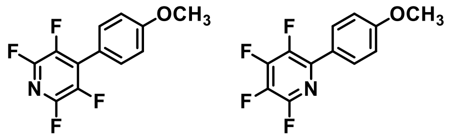
3n: By following the general procedure, a coupling reaction of 2-tolylmagnesium bromide and C_7F_8 gave a white solid (185.3 mg, 60%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 2.11 (s, 3H), 7.11 (d, 7.6 Hz, 2H), 7.20-7.34 (m, 3H). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −56.3 (t, 21.7 Hz, 3F), −138.7 (m, 2F), −140.8 (m, 2F). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 19.6, 108.9 (m), 120.9 (q, 274 Hz), 124.8, 125.6, 126.1, 130.0, 130.0, 130.7, 137.0, 144.1 (dm, 250 Hz). HRMS: m/z calc. 308.0436 ($C_{14}H_7F_7$), found 308.0431.



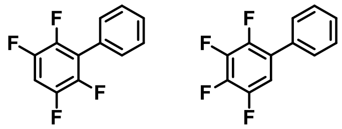
3o: By following the general procedure, a coupling reaction of *4*-methoxyphenylmagnesium bromide with $C_{12}F_{10}$ gave a white solid purified by HPLC (136.9 mg, 32%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 7.45 (d, 8.8 Hz, 2H), 7.03 (d, 8.8 Hz, 2H), 3.86 (s, 3H). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −137.4 (m, 2F), −139.1 (m, 2F), −143.1 (m, 2F), −150.6 (t, 21.0 Hz, 1F), −160.7 (m, 2F). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 160.7, 144.8 (dm, 252 Hz), 144.2 (dm, 248 Hz), 142.5 (dm, 258 Hz), 138.0 (dm, 253), 131.6 (t, 2 Hz), 122.9 (t, 16 Hz), 118.9, 114.3 (d, 6 Hz), 104.4 (t, 18 Hz), 102.7 (19 Hz), 55.6 (d, 39 Hz). HRMS: m/z calc. 422.0353 ($C_{19}H_7F_9O$), found 422.0350. Spectral Data of **3o** were identical to that of previously reported.[1h]



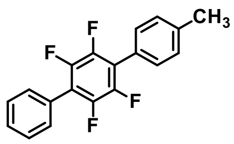
3p: By following the general procedure in 0.3 mmol scale, a coupling reaction of 4-methoxyphenylmagnesium bromide and $C_{10}F_8$ gave a white solid (57.5 mg, 56%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 3.88 (s, 3H), 7.06 (d, 9.3 Hz), 7.46 (d, 9.3 Hz). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −155.9 (m, 1F), −154.0 (t, 19.3 Hz, 1F), −149.0 (dtt, 57.8 Hz, 18.5 Hz, 3.7 Hz, 1F), −146.4 (dtd, 56.9 Hz, 17.7 Hz, 3.7 Hz, 1F), −144.0 (dt, 70.2 Hz, 16.7 Hz, 1F), −137.0 (m, 1F), −122.1 (ddd, 70.2 Hz, 19.2 Hz, 3.7 Hz, 1F). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 55.5, 108.2 (t, 16 Hz), 110.6 (m), 119.4 (t, 18 Hz), 144.3, 119.2 (m), 131.8 (t, 2 Hz), 137.5-150.5, 160.5. HRMS: m/z calc. 360.0385 ($C_{17}H_7F_7O$), found 360.0382.



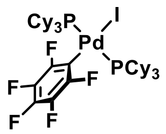
3q, 3q': By following the general procedure in 0.5 mmol, a coupling reaction of phenylmagnesium bromide with C_5F_5N gave a white solid (92.8 mg, 82%). <u>^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm)</u>: 7.92 (m), 7.57-7.46(m). <u>^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm)</u>: −82.6 (m, 1F), −90.6 (m, 2F), −138.4 (m, 1F), −145.1 (m), −158.6 (m). <u>HRMS</u>: m/z calc. 227.0358 ($C_{11}H_5F_4N$), found 227.0356, 227.0351.



3r, 3r': By following the general procedure in 0.5 mmol, a coupling reaction of phenylmagnesium bromide with pentafluorobenzene gave a white solid (42.5 mg, 38%). <u>^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm)</u>: 7.46 (m), 7.03 (m). <u>^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm)</u>: For 2,3,4,5-tetrafluorobiphenyl: −140.3 (m, 2F), −145.0 (m, 2F). For 2,3,5,6-tetrafluorobiphenyl: −140.7 (m, 1F), −144.9 (m, 1F), −156.3 (m ,1F), −158.2 (m, 1F). <u>HRMS</u>: m/z calc. 226.0406 ($C_{12}H_6F_4$), found 226.0398, 226.0405. Spectral Data of **3r** and **3r'** were identical to that of previously reported.[16]

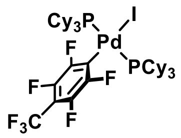


3s: Following the general procedure in 0.5 mmol, *4*-tolylmagnesium bromide and **3a** gave white solid purified by HPLC (82.0 mg, 52%). <u>^{1}H NMR (400.0 MHz, in $CDCl_3$, rt, δ/ppm)</u>: 7.52-7.28 (m, 9H), 1.54 (s, 3H). <u>^{19}F NMR (372 MHz, in $CDCl_3$, rt, δ/ppm)</u>: −144.6 (m). <u>HRMS</u>: m/z calc. 316.0875 (C19H12F4), found 316.0875.

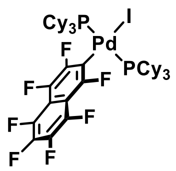


Isolation of **4**: In a dry box, to a reaction vial equipped with stirring bar were added $Pd(PCy_3)_2$ (202 mg, 0.3 mmol), LiI (41 mg, 0.3 mmol), C_6F_6 (34.5 μL, 0.3 mmol) and 5 mL portion of THF. The reaction mixture was stirred at 60 ºC for 5 h in a metal bath. Volatiles were removed *in vacuo*, and the resulting solid was extracted with Et_2O, filtered, and dried *in vacuo* yielding yellow solid of desired product (197 mg, 68%). Recrystallization from Et_2O at −35 ºC afforded good crystals, which was analyzed by X-ray diffraction. <u>^{1}H NMR (400 MHz, C_6D_6, rt)</u>: δ = 1.0–2.4 (m, 66 H; Cy group); <u>^{19}F</u>

NMR (376 MHz, C_6D_6, rt): δ = −111.2 (d, J = 27.4 Hz, 2 F), −164.7 (t, J = 20.1 Hz, 1 F), −166.0 (m, 2 F); ^{31}P NMR (162 MHz, C_6D_6, rt): δ = 29.3 (s); ^{13}C NMR (100 MHz, C_6D_6, rt): δ = 37.1 (t, J = 9.7 Hz), 30.8, 28.0 (t, J = 5.2 Hz), 26.7. The ^{13}C signals assignable to the C_6F_5 moiety could not be detected due to multiple ^{13}C-^{19}F couplings. Elemental Analysis: calcd (%) for $C_{42}H_{66}F_5IP_2Pd$: C, 52.48, H, 6.92; found: C, 52.45, H, 7.10. X-ray data: M = 961.19; colorless; monoclinic; $P2_1/c$ (no. 14); a = 16.474(11) Å, b = 16.227(10) Å, c = 17.847(12) Å, β = 116.358(6) º; V = 4275(5) Å^3; Z = 4; D_{calcd} = 1.493 g cm^{-3}; T = −120(0) ºC; R_1 (wR_2) = 0.0551 (0.1086).

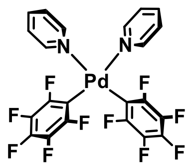


Complex **5**: In a dry box, to a vial equipped with a stirring bar were added $Pd(PCy_3)_2$ (334 mg, 0.5 mmol) and LiI (74 mg, 0.55 mmol) and the solid was dissolved in THF (8 mL). To the resulting solution was added C_7F_8 (77.5 μL, 0.55 mmol). The vial was sealed and the reaction mixture was heated at 60 ºC for 1 h with stirring. All volatiles were removed by evaporation and the resulting solid was extracted with hexane and filtered off. The hexane solution was dried out to yield **20** as yellow solid (515 mg, 102 % (Such an over 100% yield was due to the contamination by a small amount of hexane)). Purification was conducted by recrystallization from hot hexane to form yellow crystal. ^{1}H NMR (400 MHz, in C_6D_6, rt, δ/ppm): 1.04-2.39 (Cy Group). ^{19}F NMR (372 MHz, in C_6D_6, rt, δ/ppm): −58.7 (t, 21.0 Hz, 3F), −110.4 (m, 2F), −146.2 (m, 2F). ^{31}P NMR (162 MHz, in C_6D_6, rt, δ/ppm): 29.6 (s). ^{13}C NMR (100 MHz, in C_6D_6, rt, δ/ppm): 37.0 (t, 9.9 Hz), 30.6, 27.8 (t, 5.3 Hz), 26.5. The ^{13}C signals assignable to the p-CF_3-C_6F_4 moiety could not be detected due to multiple ^{13}C-^{19}F couplings. Elemental Analysis: calc. C, 51.07; H, 6.58, found: C, 51.29; H, 6.70.

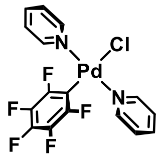


Complex **6**: In a dry box, to a vial equipped with a stirring bar were added $Pd(PCy_3)_2$ (334 mg, 0.5 mmol) and LiI (74 mg, 0.55 mmol) and the solid was dissolved in THF (8 mL). To the resulting solution was added $C_{10}F_8$ (150 mg, 0.55 mmol). The vial was capped and the reaction mixture was heated at 60 ºC for 5 h with stirring. All volatiles were removed by evaporation and the resulting solid was extracted with toluene and filtered off. The toluene solution was dried in vacuo and washed with small amount of hexane. The solid was dried out to yield **21** as yellow solid (414 mg, 79 %). Recrystallization from toluene/hexane gave yellow crystals. ^{1}H NMR (400 MHz, in C_6D_6, rt, δ/ppm): 0.99-2.40 (Cy Group). ^{19}F NMR (372 MHz, in C_6D_6, rt, δ/ppm): −90.3 (dd, 16.6 Hz, 66.7 Hz, 1F),

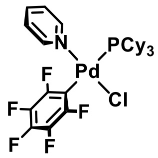
−104.57 (d, 27.9 Hz, 1F), −149.8 (dt, 66.3 Hz, 16.0 Hz, 1F), −150.8 (dt, 16.6 Hz, 55.1 Hz, 1F), −155.0 (m, 1F), −160.8 (t, 19.0 Hz, 1F), −161.0 (t, 18.1 Hz, 1F). ^{31}P NMR (162 MHz, in C_6D_6, rt, δ/ppm): 28.98 (s). ^{13}C NMR (100 MHz, in C_6D_6, rt, δ/ppm): 37.2 (t, 9.9 Hz), 30.8, 27.9 (t, 5.3 Hz), 26.7. The ^{13}C signals assignable to the *2*-$C_{10}F_7$ moiety could not be detected due to multiple ^{13}C-^{19}F couplings. Elemental Analysis: calc. C, 52.76; H, 6.35, found: C, 53.15; H, 6.81.



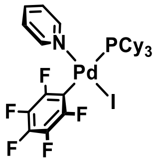
Preparation of $Pd(C_6F_5)_2(py)_2$:[10] To a two-necked round-bottomed flask equipped with a stirring bar were added absolute ether (20 mL, dried over benzophenon ketyl) and chloropentafluorobenzene (740 μL, 6.0 mmol). The solution was cooled to −78 ºC. To the solution was added Hexane solution of ^{n}BuLi (1.6 M, 3.8 mL, 6.0 mmol) dropwise with stirring (Caution! Pentafluorophenyllithium is very thermally unstable and in order to avoid explosion it must be prepared and reacted at low temperatures). The colorless solution was stirred for 30 min at this temperature. Then, to the solution was added $Pd(py)_2Cl_2$ (670 mg, 2.0 mmol). The resulting yellow suspension was stirred at this temperature for 1 h, and then warmed to room temperature and stirred for 2 h. The resulting white suspension was quenched with 5 mL of ether (containing a small amount of water) and evaporated to dryness. The residue was extracted with boiling acetone, and the acetone solution was filtered through a pad of celite and dried out. Recrystallization from hot acetone/ ethanol at −30 ºC overnight afforded 862 mg of white needle crystal (72%). ^{1}H NMR (400 MHz, $CDCl_3$, rt): δ = 8.74 (m, 4 H), 7.64 (tt, *J* = 7.8 Hz, 1.5 Hz, 2 H), 7.23 (m, 4 H); ^{19}F NMR (376 MHz, $CDCl_3$, rt): δ = −122.4 (m, 4 F), −160.4 (t, *J* = 19.5 Hz, 2 F), −162.5 (m, 4 F); ^{13}C NMR (100 MHz, $CDCl_3$, rt): δ = 153.4, 137.8, 125.4. The ^{13}C signals assignable to the C_6F_5 moiety could not be detected due to multiple ^{13}C-^{19}F couplings. Elemental Analysis: calcd (%) for $C_{22}H_{10}F_{10}N_2Pd$: C, 44.13, H, 1.68, N, 4.68; found C, 44.11, H, 1.89, N, 4.74. X-ray data: *M* = 598.72; yellow; monoclinic; $P2_1/c$ (# 14); a = 9.8891(10) Å, b = 16.9318(13) Å, c = 13.0111(12) Å, β = 109.524(3) º; V = 2053.3(3) Å^3; Z = 4; D_{calcd} = 1.937 g cm^{-3}; T = −150(0) ºC; R_1 (wR_2) = 0.0355 (0.0786).



Preparation of $Pd(C_6F_5)Cl(py)_2$:[12] To a round-bottomed flask equipped with a stirring bar were added $Pd(C_6F_5)_2(py)_2$ (599 mg, 1.0 mmol), $PdCl_2$ (195 mg, 1.1 mmol), and acetone (35 mL). The resulting reddish brown suspension was heated at reflux temperature for 3 h with vigorous stirring. After the reddish brown suspension of $PdCl_2$ disappeared, pyridine (1 mL) was added. After additional 30 min of reflux, volatiles were removed by evaporation. The resulting solid was extracted with Et_2O. The solution was evaporated to dryness and recrystallization from acetone afforded white needle crystal of $Pd(C_6F_5)Cl(py)_2$ (541 mg, 58%). ^{1}H NMR (400 MHz, C_6D_6, rt): δ = 8.60 (m, 4 H), 6.44 (tt, J = 7.8 Hz, 1.5 Hz, 2 H), 6.13 (m, 4 H); ^{19}F NMR (376 MHz, C_6D_6, rt): δ = −125.1 (m, 2 F), −162.0 (t, J = 20.2 Hz, 1 F), −164.9 (m, 2 F); ^{13}C NMR (100 MHz, C_6D_6, rt): δ = 153.4, 137.6, 124.7. The ^{13}C signals assignable to the C_6F_5 moiety could not be detected due to multiple ^{13}C-^{19}F couplings. Elemental Analysis: calcd (%) for $C_{16}H_{10}ClF_5N_2Pd$: C, 41.14, H, 2.16, N, 6.00; found C, 41.29, H, 2.38, N, 6.09. In the ^{1}H and ^{13}C NMR spectra, two pyridine rings were observed equivalently, indicating that two pyridine rings would occupy the trans positions of the square-planar Pd(II) geometry. The configuration of the product, however, was not mentioned in the original literature.[22]



Preparation of **8**: In a dry box, to a solution of $Pd(C_6F_5)Cl(py)_2$ (434 mg, 0.93 mmol) in 7 mL of pyridine was added PCy_3 (287 mg, 1.02 mmol). To the resulting yellow solution was added hexane to give yellowish white precipitate. The suspension was filtered off and washed with hexane to give yellowish white powder. This crude material was recrystallized from acetone by cooling to −35 ºC to yield yellow block crystal of 24·Acetone (320 mg, 52%). ^{1}H NMR (400 MHz, THF-d_8, rt): δ = 8.88 (m, 2 H), 7.85 (tt, J = 7.6 Hz, 1.5 Hz, 1 H), 7.45 (m, 2 H) , 2.1−1.0 (m, 33 H, Cy group); ^{19}F NMR (376 MHz, THF-d_8, rt): δ = −127.5 (m, 2 F), −169.3 (t, J = 19.6 Hz, 1 F), −170.5 (m, 2 F); ^{31}P NMR (162 MHz, THF-d_8, rt): δ = 17.7 (m); ^{13}C NMR (100 MHz, THF-d_8, rt): δ = 154.5, 139.2, 126.8, 33.6 (d, J_{C-P} = 17 Hz), 30.4, 28.3 (d, J_{C-P} = 11 Hz), 27.0. The ^{13}C signals assignable to the C_6F_5 moiety could not be detected due to multiple ^{13}C-^{19}F couplings. Elemental Analysis: calcd (%) for $C_{29}H_{38}ClF_5NPPd·(C_3H_6O)$: C, 52.90, H, 6.10, N, 1.93; found: C, 53.03, H, 6.29, N, 2.09. X-ray data: M = 726.50; colorless; monoclinic; $P2_1/c$ (n. 14); a = 9.8563(4) Å, b = 16.1075(7) Å, c = 20.7981(10) Å, β = 100.527(2) º; V = 3246.3(3) Å^3; Z = 4; D_{calcd} = 1.486 g cm^{-3}; T = −120(0) ºC; R_1 (wR_2) = 0.0241 (0.0281).



Preparation of **7**: In a dry box, to a solution of **8** (145 mg, 0.2 mmol) in 10 mL of acetone was added NaI (300 mg, 2.0 mmol). The resulting orange solution was stirred for 3 h. The solution turned to be orange suspension. Toluene (30 mL) was added, and resulting precipitates were removed by filtration. All volatiles were removed in vacuo, and the resulting solid was taken out of dry box. The solid was washed with ethanol until no yellow color was observed in washings, then washed with small amount of water and ethanol. The resulting solid was dissolved in acetone and dried in vacuo to give yellow powder (83 mg, 55%). The complex was recrystallized from THF/Hexane. ^{1}H NMR (400 MHz, Acetone-d_6, rt): δ = 8.86 (d, J = 5.2 Hz, 2 H), 7.98 (tt, J = 7.6 Hz, 1.5 Hz, 1 H), 7.62 (m, 2 H) , 2.1−1.0 (m, 33 H, Cy group); ^{19}F NMR (376 MHz, Acetone-d_6, rt): δ = −123.2 (m, 2 F), −167.3 (t, J = 18.6 Hz, 1 F), −168.7 (m, 2 F); ^{31}P NMR (162 MHz, Acetone-d_6, rt): δ = 21.0 (m); ^{13}C NMR (100 MHz, Acetone-d_6, rt): δ = 154.0, 140.0, 127.5, 35.1 (d, J_{C-P} = 18 Hz), 31.1, 28.5 (d, J_{C-P} = 10 Hz), 27.1. The ^{13}C signals assignable to the C_6F_5 moiety could not be detected due to multiple ^{13}C-^{19}F couplings. Elemental Analysis: calcd (%) for $C_{29}H_{38}F_5INPPd$: C, 45.84, H, 5.04, N, 1.84; found: C, 45.92, H, 5.65, N, 2.39. X-ray data: M = 831.98; colorless; monoclinic; $P2_1/n$ (no. 14); a = 9.9348(4) Å, b = 16.3295(7) Å, c = 21.2257(9) Å, β = 105.0560(10) °; V = 3325.2(2) Å^3; Z = 4; D_{calcd} = 1.646 g cm^{-3}; T = −150(0) °C; R_1 (wR_2) = 0.1348 (0.3479).

Reaction of **4** with $ZnPh_2$: In a dry box, the mixture of **4** (9.6 mg, 0.01 mmol), $ZnPh_2$ (11.0 mg, 0.05 mmol), and LiI (13.4 mg, 0.10 mmol) was dissolved in THF-d_8 (500 μL). To the reaction mixture was added $PhCF_3$ (10 μL) as an internal standard. The solution was transferred to a J-Young Tube, heated at 60 °C and analyzed by NMR spectroscopy.

Reaction of **7** with $ZnPh_2$: In a dry box, to a vial charged with **7** (7.6 mg, 0.01 mmol) was added THF-d_8 solution of $ZnPh_2$ (2.6 mg, 0.01 mmol), PCy_3 (2.80 mg, 0.01 mmol), and LiI (1.3 mg, 0.01 mmol). To the reaction mixture was added $PhCF_3$ (10 μL) as an internal standard. The solution was analyzed by ^{19}F NMR spectroscopy.

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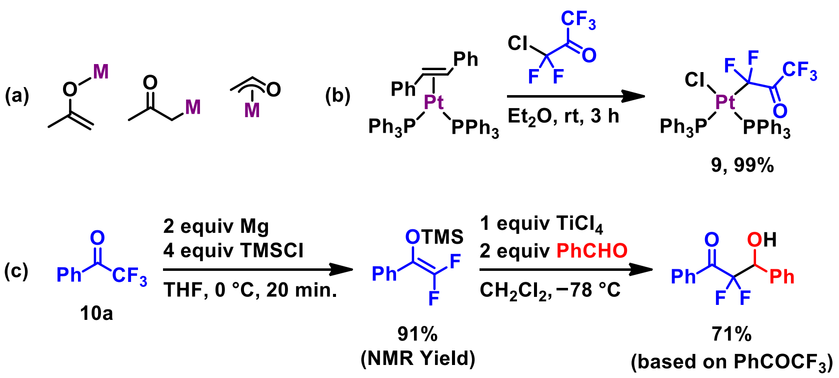
Chapter 3

Ni/B(C_6F_5)$_3$ Catalyst System for Highly Selective Crossed-Dimerization

3.1 Introduction

Transition metal-enolates continues to garner interest due to their important roles in various organic transformations.[1] Many transition metal-enolates have been prepared via the nucleophilic displacement of carbonyl compounds bearing a leaving group at the *α*-position, via the transmetallation of a transition-metal salt with the enolate of a main group element, and via the oxidative cyclization of *α*,*β*-unsaturated carbonyl compounds on Ni(0).[2-4] These reactions result in the formation of transition-metal enolates of which coordination modes are classified as *O*-bound or *C*-bound or η^3-oxallyl (Figure 3.1a). Despite numerous studies on their chemistry, only a few examples of transition-metal difluoro-enolates have been reported due to a lack of readily-accessible synthetic routes. To date, the oxidative addition of a C−Cl bond to Pt(0) is the only method that has been used to successfully obtain the fluorinated analogues of transition metal-enolates **9** of which reactivity remained elusive (Figure 3.1b).[5] Moreover, *α*-halogenated fluoroketones are neither easy to prepare nor commercially available. Therefore, trifluoromethylketones could be an ideal candidate for a precursor of transition-metal difluoro-enolates when using the well-established preparative procedure making use of inexpensive trifluoroacetic acid derivatives as starting materials.[6] Amii and Uneyama have reported a pioneering work that demonstrates an efficient synthetic method to synthesize silyl difluoro-enolates via the treatment of *α*,*α*,*α*-trifluoroacetophenone (**10a**) with magnesium metal and chlorotrimethylsilane via C−F bond activation (Figure 3.1c).[7]

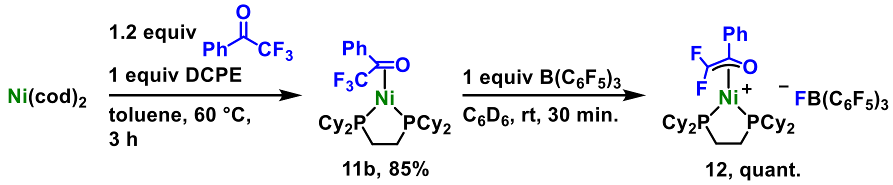


Scheme 3.1 (a) Coordination modes of transition-metal enolates. (b) Preparation of platinum difluoro-enolate **9** obtained via C−Cl bond cleavage. (c) Synthesis and reactivity of silyl difluoro-enolate from readily available trifluoroacetophenone.

There is no precedence for the synthesis of transition-metal difluoro-enolates from trifluoromethylketones. Herein, C−F bond activation of α,α,α-trifluoroacetophenone coordinated to Ni(0) promoted by the addition of $B(C_6F_5)_3$, which gives the first example of Ni(II) difluoro-enolate, is described. Furthermore, a unique catalytic activity of the nickel difluoro-enolate has been demonstrated for the crossed-dimerization of aldehydes with α-fluorinated ketones.

3.2 Result and Discussion

Our group reported the selective C−F bond activation of a CF_3 group of hexafluoropropylene on Pd(0) by the addition of $B(C_6F_5)_3$.[8] Thus, the C−F bond cleavage of trifluoroacetophenone **10a** was also expected by the combination of $B(C_6F_5)_3$ and low valent transition-metals. There are some reports dealing with η^2-ketone complexes of Ni(0), including the ones bearing **10a**.[9,10] For instance, Yamamoto *et al.* have described the synthesis of (η^2-$PhCOCF_3$)Ni(dppe)[10g] (**11a**, DPPE = 1,2-bis(diphenylphosphino)ethane). However, complex **11a** led to decomposition by treatment with $B(C_6F_5)_3$. Therefore, we decided to use a more electron-rich bidentate phosphine ligand DCPE that would make the nickel center more suitable for C−F bond activation by enhancing the electron density,[11] along with stabilization of the resultant Ni(II) complex. The reaction of $Ni(cod)_2$, DCPE and **10a** in toluene resulted in the formation of (η^2-$PhCOCF_3$)Ni(dcpe) (**11b**) in an 85% isolated yield. The ^{13}C NMR signal attributable to the carbonyl carbon in **11b** (73.8 ppm) was observed in the upfield region relative to that of **11a** (79.4 ppm).[10g] This upfield-shift would be invoked by the stronger electron-donating nature of the DCPE ligand that would enhance $d\rightarrow\pi^*$ back donation. Treatment of **11b** with $B(C_6F_5)_3$ in C_6D_6 afforded [($PhCOCF_2$)Ni(dcpe)][$FB(C_6F_5)_3$] (**12**) in a quantitative yield (Scheme 3.2). It is noteworthy that in the absence of $B(C_6F_5)_3$, complex **11b** was thermally stable and no decomposition was observed after heating the C_6D_6 solution of **3b** at 100 °C in a sealed NMR tube for a period of several days.



Scheme 3.2 Formation of **11b** followed by treatment with $B(C_6F_5)_3$ to yield the nickel difluoro-enolate **12**.

Nickel complex **12** was fully characterized by NMR, combustion analysis and X-ray crystallography. The ^{19}F NMR spectrum of **12** exhibited a signal that was attributable to CF_2 at δ = −100 ppm (2F, dd, J_{PF} = 7, 18 Hz) as well as a set of resonances for the $[FB(C_6F_5)_3]$-counteranion.[12] The signal of CF_2 resembled to that of previously reported analogous platinum complex **9** (Scheme 3.1a).[5] Two sets of doublet of triplets with the same intensity were observed at δ = 80 (J_{PF} = 7 Hz, J_{PP} = 11 Hz) and 82 ppm (J_{PF} = 18 Hz, J_{PP} = 11 Hz) in the ^{31}P NMR spectrum. The existence of two ^{31}P resonances was probably due to a weak interaction between the carbonyl oxygen atom and the nickel center preventing a fluxional rotation around the Ni−C bond. Resonances derived from carbonyl and CF_2 moiety in ^{13}C NMR spectrum were not assigned. No signals were observed around 200 ppm probably due to a significant upfield shift of resonance of carbonyl carbon caused by the interaction of carbonyl group with nickel center. Signals derived from CF_2 were not observable because of weak intensity.

Fine crystals of **12** were obtained from the toluene/pentane layer at −35 °C. The ORTEP diagram of the cationic portion of **12** shows a difluoro-enolate complex of Ni(II) coordinated in an η^3-oxallyl fashion (Figure 3.1). The C−O bond distance of 1.313(3) Å was an intermediate between a typical C−O double bond (*ca.* 1.22 Å) and a single bond (*ca.* 1.44 Å). The bond length of the C1−C2 bond of 1.426(5) Å was within the range of standard C−C (*ca.* 1.54 Å) and C=C (*ca.* 1.34 Å) bond lengths. These bond distances were characteristic to those of η^3-oxallyl motif.

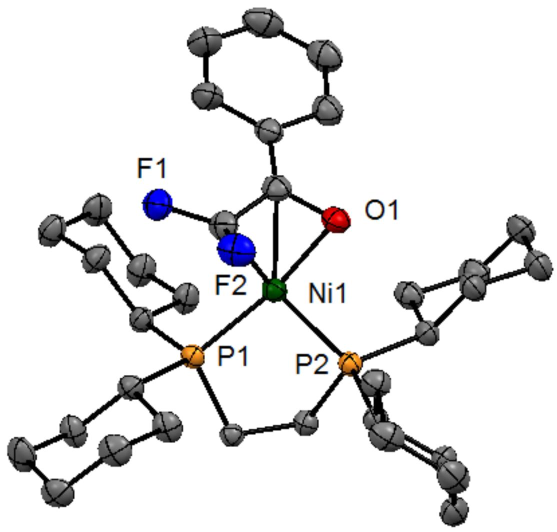
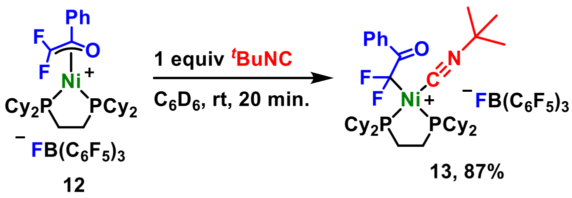


Figure 3.1 ORTEP diagram of cationic part of complex **12** with thermal ellipsoids at the 50% probability level. H atoms were omitted for clarity.

The reaction of **12** with ^{t}BuNC resulted in the coordination of isocyanide to the Ni(II) center to afford η^1-C-enolate **13** in an 87% yield (Scheme 3.3). ^{19}F NMR showed a signal of CF_2 at δ = −79 ppm (dd, J_{PF} = 22, 30 Hz). In the ^{31}P NMR spectrum, two signals were observed at δ = 79 (dt, J_{PP} = 29 Hz, J_{PF} = 22 Hz) and 78 ppm (dt, J_{PP} = 29 Hz, J_{PF} = 30 Hz). The ^{13}C NMR spectrum exhibited a resonance derived from carbonyl carbon at δ = 194.1 ppm as a triplet ($^2J_{CF}$ = 22.3 Hz). This characterization was unambiguously supported by X-ray analysis (Figure 3.2a).



Scheme 3.3 Treatment of ^{t}BuNC with **12**.

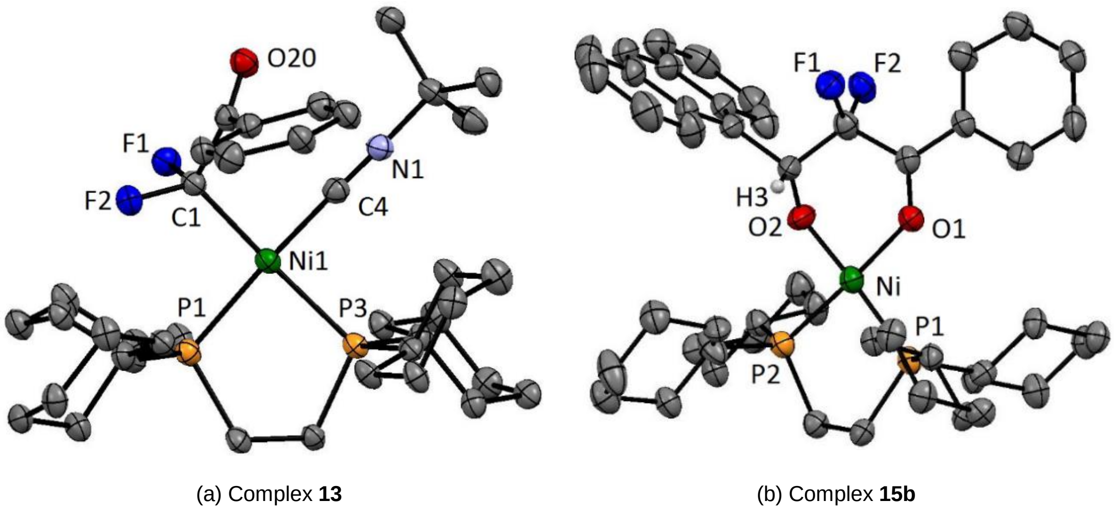
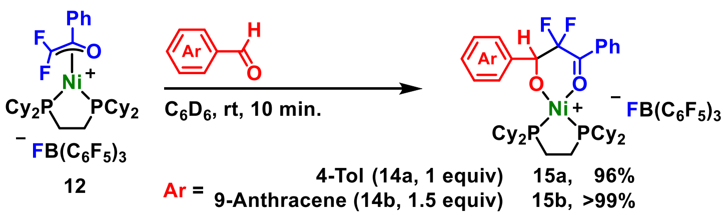


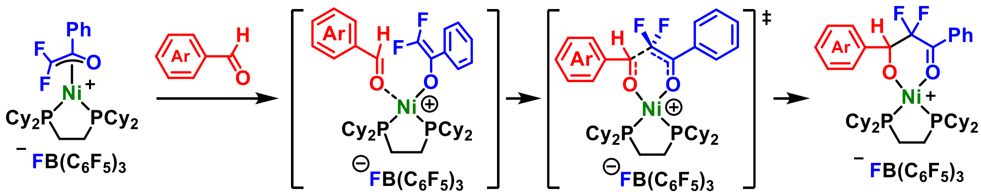
Figure 3.2 ORTEP diagram of cationic part of (a) complex **13** (b) complex **15b** with thermal ellipsoids at the 50% probability level. H atoms except for H3 of **15b** were omitted for clarity.

The solid-state structure of **13** showed the square planar geometry of the Ni(II) C-bound enolate. The C2−O bond distance of 1.219(10) Å and C1−C2 of 1.495(9) Å were typical values of a C−O double bond and a C−C single bond, respectively.



Scheme 3.4 Insertion of aldehyde **14a** and **14b** into Ni−C bond of **12**.

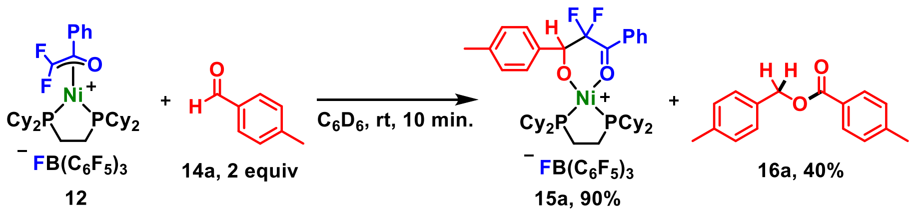
Transition-metal enolates are known as nucleophiles toward aldehydes. For instance, a C-bound nickel enolate reacted with an aldehyde to give aldol products according to a report of Bergman and Heathcock.[13] The complex **12** containing electron withdrawing fluorine atoms on an enolate moiety smoothly reacted with 1 equiv of *p*-tolualdehyde (**14a**) to allow the migratory insertion of the carbonyl group into the Ni−C bond in a quantitative yield (Scheme 3.4). This was in sharp contrast to the reactions of silyl difluoro-enolates with aldehydes that required the addition of Lewis acids and/or an excess amount of substrates and suffered from low yields.[14] This C−C bond formation might involve the Zimmerman-Traxler-type six membered transition-state initiated by coordination of an aldehyde giving an O-bound enolate intermediate **C** (Scheme 3.5). This is partly supported by the report of Cámpora et al. in which they concluded that only the O-bound enolate is sufficiently nucleophilic to afford the aldol product by a reaction with an aldehyde, based on observation of the difference of the reactivities between the O-bound Ni(II) enolate and its C-bound counterpart.[13c] The reaction, however, was too fast to observe any intermediates when the reaction of **12** with **14a** was monitored by means of NMR at –50 °C.



Scheme 3.5 A possible reaction pathway to give nickel alkoxide complex **15**.

The ^{19}F NMR spectrum of the resultant complex **15a** showed two signals that could be attributable to a diastereotopic CF_2 group at $\delta = -103$ (dd, J_{HF} = 9 Hz, J_{FF} = 270 Hz) and −118 ppm (dd, J_{HF} = 12 Hz, J_{FF} = 270 Hz). Small coupling of 9 and 12 Hz were attributable to the $^3J_{HF}$ coupling, and suggested a C−C bond formation between an enolate and an aldehyde. Furthermore, a signal derived from a formyl group to 4.9 ppm in ^{1}H NMR that was observed as a broad triplet with a coupling constant of *ca.* 10 Hz that resulted from the coupling of two fluorine atoms at 9 and 12 Hz. A large coupling constant of 270 Hz for $^2J_{FF}$ in the ^{19}F NMR is characteristic geminal coupling between two fluorine atoms bound to an sp^3-hybridized carbon. In the ^{31}P NMR spectrum, two signals derived from inequivalent phosphorus atoms were observed that indicated coordination of the carbonyl and newly formed carbinol oxygen atoms to the nickel center. The ^{13}C NMR spectrum of **7a** in CD_2Cl_2 gave signals attributable to CF_2 at 118.7 ppm as doublet of doublet bearing characteristic $^1J_{CF}$ coupling constants, 251 and 265 Hz, and α-carbons at 202.2 (t, $^2J_{CF}$ = 28.5 Hz, carbonyl group) and 73.5 ppm (t, $^2J_{CF}$ = 23.0 Hz, carbinol carbon). Although a single crystal of **7a** was not obtained, an analogous complex **7b**, generated by the reaction of **12** with 9-anthracenecarboxaldehyde (**14b**), was isolated and its single crystal was obtained. The molecular structure of **14b** was determined by X-ray crystallography to be consistent with that deduced by NMR spectroscopy (Figure 3.2b).

The reaction of **12** with 2 equiv of **14a** also resulted in the formation of **15a** and a homo-coupled ester **16a**, which was unexpectedly formed from the residual aldehyde (Scheme 3.6).

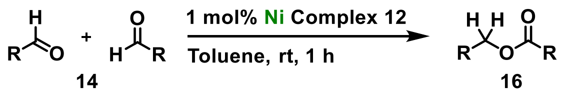


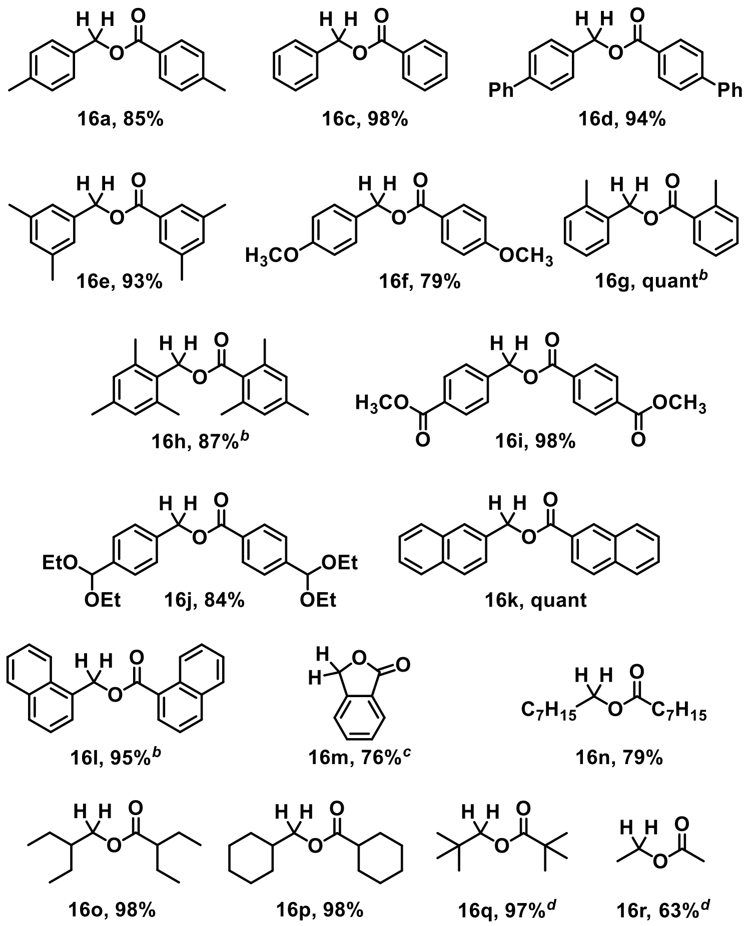
Scheme 3.6 Reaction of **12** with 2 equiv of **14a**

The dimerization of aldehydes to give an ester is known as the Tishchenko reaction, which is one of the most important methods of ester synthesis in an atom-economic and waste-free reaction manner.[15] The classical Tishchenko reactions catalyzed by aluminum alkoxides, however, suffer from narrow substrate scope. Thus, many catalyst systems have been developed to avoid side reactions such as the aldol reaction, the Cannizzaro reaction, the Meerwein-Pondorf-Verley reduction, and the Oppenauer oxidation. Encouraged by the results, the catalytic activity of **12** in a Tishchenko reaction was examined (Table 3.1).

In the presence of 1 mol% of **12**, the reactions of **14a**, benzaldehyde (**14c**), 4-biphenylcarboxyaldehyde (**14d**), 3,5-dimethylbenzaldehyde (**14e**), and 4-anisaldehyde (**14f**) yielded the corresponding esters **16a**,**c-f** in excellent isolated yields under room temperature for 1 h. Contrary to these results, 2-tolualdehyde (**14g**) did not react at ambient temperature. However, the reaction proceeded smoothly by heating at 60 °C for 1 h to give the corresponding ester **16g** in a quantitative yield. Even very bulky mesitaldehyde (**14h**) reacted under these conditions to give **16h** in an 87% yield. Aldehydes bearing either an ester **14i** or an acetal **14j** group were tolerated under these reaction conditions to afford **16i** and **16j** in 98 and 84% yields, respectively. The reaction of 2-naphthaldehyde (**14k**) gave the corresponding ester **16k** in a quantitative yield; however, the reaction of 1-naphthaldehyde (**14l**) required an elevated temperature to obtain **16l**. The intramolecular Tishchenko reaction of *o*-phthalaldehyde (**14m**) occurred to give phthalide **16m** in the presence of 2 mol% of **12**, and no oligomer was observed in the crude reaction mixture. Not only aromatic aldehydes, but also aliphatic aldehydes such as primary **14n**, secondary **14o** and **14p**, and tertiary alkylaldehyde **14q** were prone to esterification under the catalyst **12** to afford the corresponding esters **16n-q** in good to high yields. Furthermore, acetaldehyde (**14r**) was also transformed into ethyl acetate (**16r**) catalytically in moderate yield. Complex **12** proved to be an efficient catalyst for the Tishchenko reaction that is applicable toward both aromatic and aliphatic aldehydes.[16]

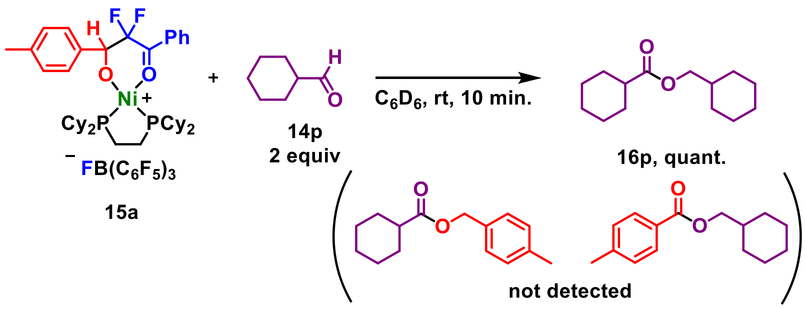
Table 3.1 Substrate scope of homo-esterification of aldehydes [a]





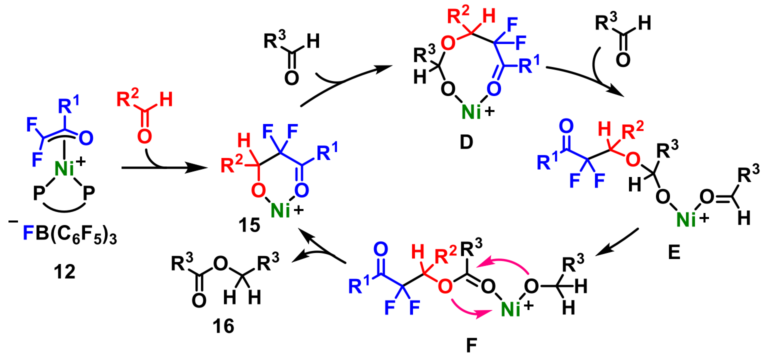
[a] Isolated Yields. [b] Reactions conducted at 60 °C. [c] 2 mol% catalyst loading. [d] NMR yield.

Although the reaction mechanism is ambiguous at this point, the nickel alkoxide complex **15** might be involved as an active catalyst. The reaction of **15a** with 2 equiv of aldehyde **14p** produced homo-esterification product **16p** quantitatively (Scheme 3.7). Note that ester products bearing a *p*-tolyl group derived from **15a** were not detected from the reaction mixture and complex **15a** was recovered. We also tested the reaction of **15a** with formyl proton deuterated **14k**-d_1, to afford the **16k**-d_2 and no significant scrambling was confirmed. This result exclude the possibility of nickel-hydride species as an active catalyst, although other metal hydrides often catalyze the Tishchenko reaction. To gain deeper insight into the mechanism, the reaction of **12** with 2 equiv of **14a** were monitored in toluene-d_8 by means of a variable temperature NMR from –50 to 25 °C. Formation of a nickel alkoxide complex **15a** was quite fast even at –50 °C and complete conversion of the starting complex **12** was confirmed by ^{19}F NMR. However, at this temperature, starting aldehyde **14a** was observed along with only trace amount of homo-Tishchenko product **16a**. Although the Tishchenko reaction mostly didn't proceed below –10 °C, the broadening of the signal derived from the formyl proton of **14a** was observed by raising the temperature.



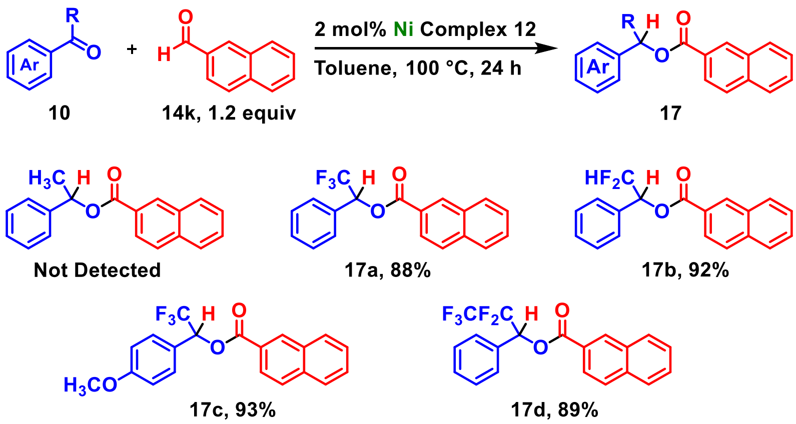
Scheme 3.7 Treatment of **15a** with 2 eq of **14p**.

A possible reaction mechanism is depicted in Scheme 3.8. Firstly, the reaction of **12** with an aldehyde generates the active catalyst **15**. Insertion of aldehyde into the Ni−O bond in **15** gives an intermediate **D**. The carbonyl group coordinated to the nickel center in an intermediate **D** is replaced by another aldehyde to generate an intermediate **E** which isomerize to **F** by β-hydrogen elimination-insertion sequence. Nucleophilic substitution of ester by alkoxide yields the homo-coupling product with regeneration of the active catalyst **15**.

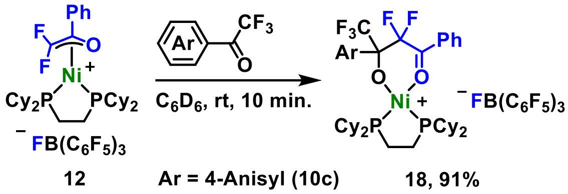


Scheme 3.8 A possible reaction pathway of the Tishchenko reaction.

Next, the crossed-dimerization of a ketone with an aldehyde were attempted (Scheme 3.9). In the presence of a catalytic amount of **12**, the reaction of acetophenone with aldehyde **14k** gave no coupling product and both starting materials were recovered. However, reaction of **10a** with **14k** gave the desired product **17a** in high yield. The crossed-dimerization of **10a** with aldehydes was reported by Connon's group utilizing thiophenoxide or selenoxide as catalysts.[17b,18] The reaction also proceeded with difluoroacetophenone (**10b**) to give the ester compound **17b** in a 92% yield. The reactions of 4'-methoxy-2,2,2-trifluoroacetophenone (**10c**) and 2,2,2,3,3-pentafluoropropiophenone (**10d**) were also successful. Note that no coupling product derived from nickel catalyst **12**, i.e. **17a**, was observed from these reaction mixtures by GCMS. The reaction of *α*-fluoroacetophenone resulted in recovery of starting material along with formation of some unidentified products that were not isolable.



Scheme 3.9 Crossed-dimerization of ketones with aldehyde **14k**



Scheme 3.10 Insertion of ketone **10c** into Ni−C bond of **12**.

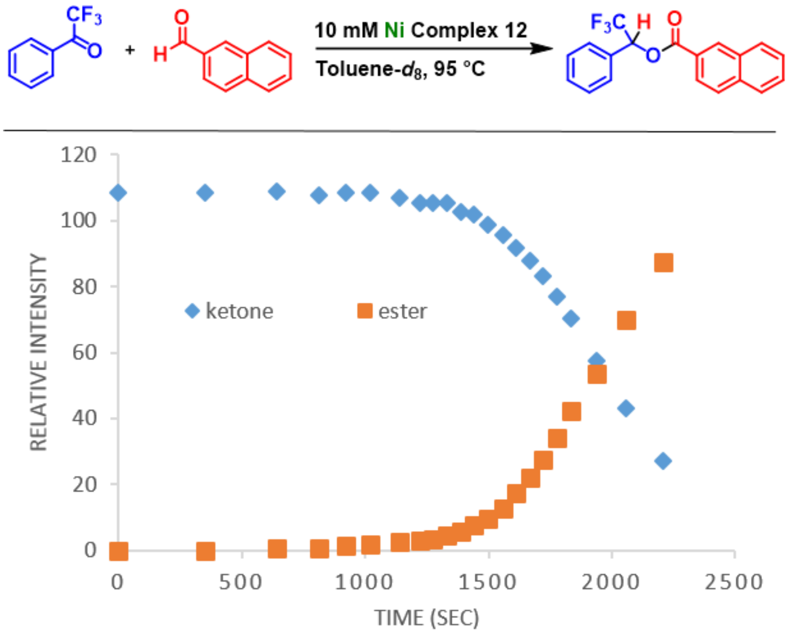
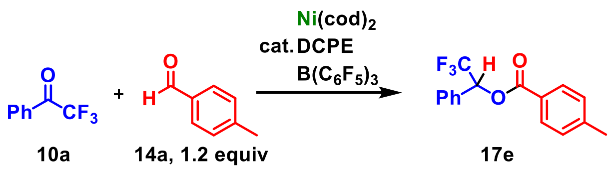


Figure 3.3 A reaction profile of ketone **10a** with aldehyde **14k** in the presence of a catalytic amount of nickel enolate **12**. The vertical axis shows intensities of ^{19}F resonance of ketone **10a** and ester **17a** relative to *α*,*α*,*α*-trifluorotoluene added as an internal standard, while the horizontal axis shows time in second.

In this crossed-dimerization reaction, a nickel alkoxide complex generated by insertion of a fluorinated ketone **10** to a nickel difluoro-enolate **12** would be involved as a resting state of the catalyst. The reaction of **10c** with **12** afforded a nickel alkoxide complex **18** that was characterized by NMR spectroscopy (Scheme 3.10). It is noteworthy that the complex **18** had no catalytic activity for Tishchenko reaction of aldehyde **14a** at room temperature, probably because the insertion of aldehyde to complex **18**, a possible initial step involved in the homo-Tishchenko reaction, might not occur. The difference of catalytic activities between alkoxide complexes **18** and **15a** might be rationalized by lower nucleophilicity of **18** bearing a highly electron withdrawing CF_3 group than that of complex **15a**. To gain further insight, the reaction of trifluoroacetophenone **10a** with aldehyde **14k** in the presence of catalytic amount of nickel enolate **12** was monitored by use of variable-temperature NMR at 95 °C (Figure 3.3). As a result, interestingly, an induction period that indicate formation of an active catalyst from nickel alkoxide species under the reaction condition was observed. Although the phenomenon is not fully understood at this point, the catalytic reaction might proceed in similar way of homo-esterification involving some active catalyst species.

These results indicated a possibility to develop a more practical catalyst system for the crossed-dimerization of a trifluoromethylketone with an aldehyde in which an active nickel catalyst was generated in situ from the reaction of Ni(0), trifluoromethylketone **10**, and $B(C_6F_5)_3$. In the presence of 10 mol% of $Ni(cod)_2$, DCPE, and $B(C_6F_5)_3$, the reaction of **10a** with **14a** in toluene at 100 °C resulted in the formation of the desired cross-coupled ester **17e** in an 88% yield (Table 3.2, run 1). The reaction did not work at all in the absence of $Ni(cod)_2$, DCPE, or $B(C_6F_5)_3$ (runs 2-4). Reactions with other ligands (DPPE, 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene (IPr), as well as 20 mol% of PCy_3) gave no desired product. The use of THF as a solvent allowed the reaction to proceed at lower temperature than that of the reaction conducted in toluene (runs 5, 6). The amount of catalyst loadings could be reduced to 2 mol%, and with this optimized reaction condition, the desired product was successfully isolated in an 88% yield (run 7).

Table 3.2 Optimization of the reaction condition of crossed-dimerization of a trifluoroacetophenone **10a** with an aldehyde



Entry	Catalyst Loadings	Conditions	Yield (%)[a,b]
1	10 mol%	Toluene, 100 °C, 4 h	88%
2	10 mol%[c]	Toluene, 100 °C, 4 h	ND
3	10 mol%[d]	Toluene, 100 °C, 4 h	ND
4	10 mol%[e]	Toluene, 100 °C, 4 h	ND
5	10 mol%	Toluene, 100 °C, 4 h	64%
6	10 mol%	THF, 60 °C, 4 h	87%
7	2 mol%	THF, 60 °C, 24 h	88%[f]

[a] Yields were determined by GC using tetradecane as an internal standard. [b] ND = not detected. [c] Without DCPE. [d] Without $B(C_6F_5)_3$. [e] Without $Ni(cod)_2$. [f] Isolated Yield.

With the optimized reaction conditions in hand, substrate scope was studied (Table 3.3). The reactions of **10a** with dimethylbenzaldehyde **14q** and **14e** gave corresponding cross-coupled esters **17f** and **17g** in 84 and 94% yields, respectively. A bulky aldehyde **14h** reacted to give ester **17h** in a high yield after an elongated reaction time. The reaction of **14d** was also successful, and the structure of the product **17i** was confirmed by X-ray crystallography (Figure 3.4). The ester and acetal groups on the aldehydes survived under these reaction conditions and gave the corresponding esters **17j** and **17k**. The reaction of *p*-formylbenzonitrile **14r** was unsuccessful under the optimized conditions listed above, and the starting materials were recovered. The reaction conducted in toluene at 100 °C, however, yielded the corresponding ester **17l** in a moderate yield. In the same manner, the reaction of **10a** with **14f** afforded a quantitative product **17m** in toluene at 100 °C. Naphthaldehydes **14k** and **14l** reacted with **10a** to give the corresponding esters **17e** and **17n** in THF at 60 °C for 24 h. Using an aldehyde bearing the phenanthrene structure **14s** required a much longer time to yield the ester product **17o**. The reaction of *p*-phthalaldehyde with 2 eq of **10a** resulted in the conversion of both aldehyde moieties to afford diester **17p** in a 40% yield. The reactions of **10a** with aliphatic aldehydes such as **14n** and **14m** were unsuccessful in delivering the required products **17q** and **17r**. The reaction of **10a** with **14q**, however, gave the corresponding ester **17s** in a 75% yield. Both trifluoroacetophenone bearing electron donating methoxy group **10c** and withdrawing CF_3 group **10e** reacted cleanly to give the desired product in high yields. The reaction of alkylketone **10f** with **14k** gave no coupling product. Difluorinated ketone **10b** reacted with **14k** to give the corresponding ester **17b** in a good yield. This result implies formation of an active nickel catalyst from *α,α*-difluorinated ketone. The reaction of **10d** conducted in THF resulted in a low conversion of starting materials. Therefore, the reaction in toluene at an elevated temperature (100 °C) was attempted to afford the desired ester **17d** in a 66% yield.

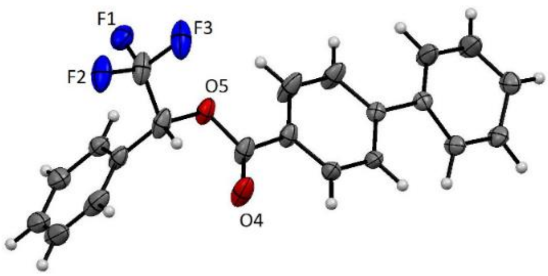
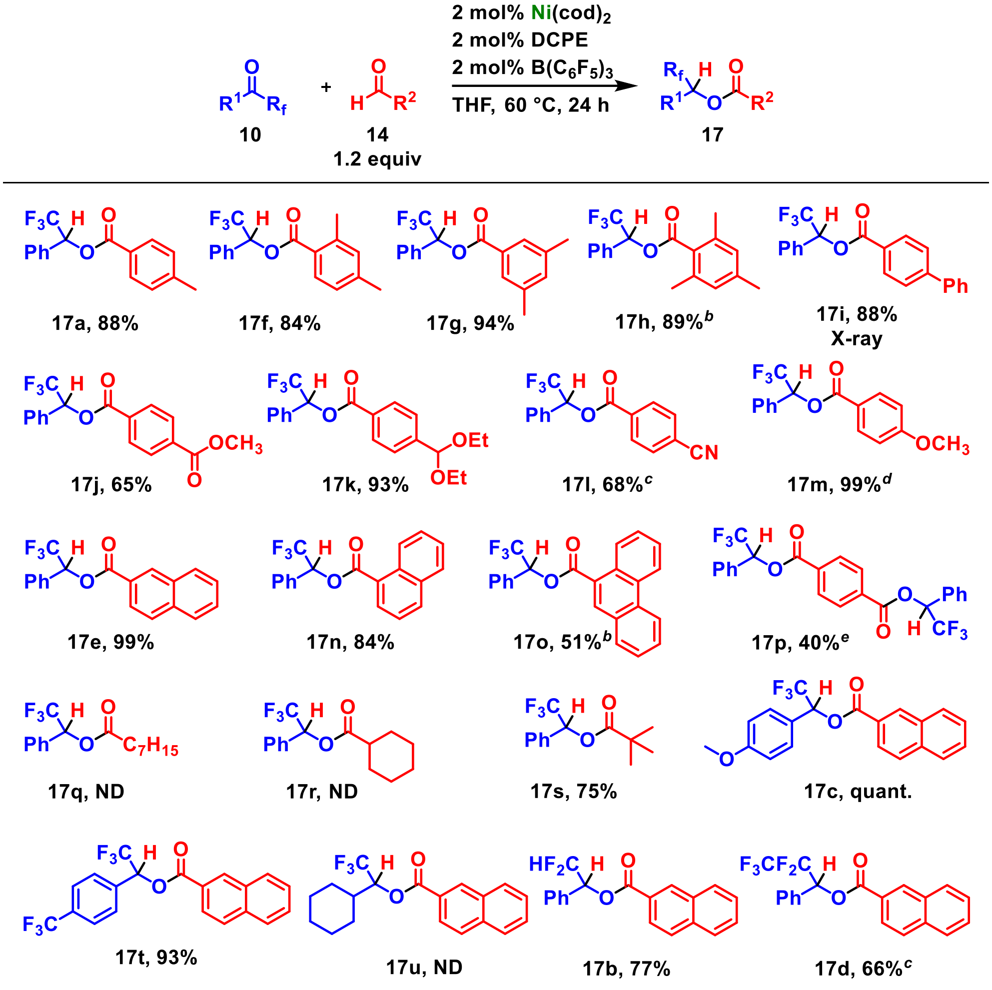


Figure 3.4 Molecular structure of **17i**.

Table 3.3 Substrate scope of crossed-dimerization of trifluoroacetophenone **10** with aldehydes **14** by using *in situ* generated catalyst. [a]



[a] Isolated Yields. ND = not detected. [b] 50 h. [c] Reactions conducted at 100 °C in toluene. [d] Reactions conducted at 100 °C in toluene for 48 h. [e] 4 mol% catalyst loading.

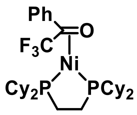
3.3 Conclusion

In chapter 3, a fluorinated analogue of nickel enolate **12** was synthesized via the C−F bond activation of trifluoroacetophenone, which was drastically accelerated by the addition of $B(C_6F_5)_3$. The combination of Ni(0) with an highly electron-donating DCPE ligand might be the key to successful activation of the C−F bond. The reaction of **12** with ^{t}BuNC resulted in coordination to give nickel *C*-bound enolate **13**. The complex **12** was reactive to aldehydes and the resultant complexes **15** were fully characterized. Furthermore, complex **12** had unique catalytic activities toward either the dimerization of aldehydes or the crossed-dimerization of trifluoroacetophenone with aldehydes. The established method was further improved in a practical sense by the in situ generation of a nickel difluoro-enolate catalyst. Thus, efficient $Ni(cod)_2$/DCPE/$B(C_6F_5)_3$ catalyst system for the highly selective crossed-dimerization of trifluoroacetophenones with aldehydes were developed.

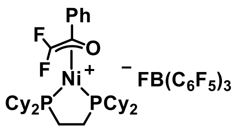
3.4 Experimental Section

Materials: Toluene, THF, THF-d_8 and C_6D_6 were distilled from sodium benzophenone ketyl. CD_2Cl_2 was dried over CaH_2 and purified by bulb to bulb distillation. Difluoroacetophenone[19], fluoroacetophenone[20], 4-trifluoromethyl trifluoroacetophenone[21], cyclohexyl trifluoromethyl ketone[21] and 2,2,2,3,3-pentafluoropropiophenone[22] were prepared by following the previously reported procedures. Other commercially available reagents were distilled and degassed prior to use.

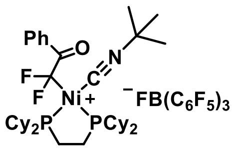
Experimental Details



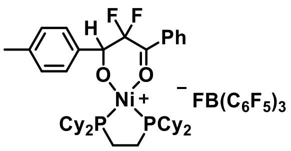
Preparation of **11b**: To the Schlenk flask containing Ni(cod)$_2$ (275 mg, 1.0 mmol) and stirring bar was added solution of DCPE (422.6 mg, 1.0 mmol) dissolved in toluene (10 mL), followed by addition of α,α,α-trifluoroacetophenone (163 μL, 1.2 mmol) to give a brown solution. The flask was sealed, and the reaction mixture was stirred at 60 ºC for 3 h. The color of the solution turned orange. The solution was cooled to −35 ºC to cause yellow precipitate, which was collected by filtration, washed with pentane, and extracted with THF. The extract was evaporated to dryness to give a yellow solid of title compound (557.1 mg, 85%). <u>^{1}H NMR (400 MHz, in C_6D_6, rt, δ/ppm)</u>: 0.74-2.10 (m, 51H), 7.07 (t, 7.2 Hz, 1H), 7.22 (t, 7.6 Hz, 2H), 8.09 (d, 7.8 Hz, 2H). <u>^{13}C NMR (151 MHz, in C_6D_6, rt, δ/ppm)</u>: 144.5, 127.8, 127.0 (q, $^1J_{CF}$ = 279 Hz), 124.4, 124.2, 73.8 (dq, J = 29.2, 32.7 Hz), 34.4 (m), 33.7 (dd, J = 16.3, 36.1 Hz), 29.6-25.5 (m), 22.2 (dd, J = 17.7, 25.3 Hz), 19.3 (dd, J = 11.4, 22.8 Hz). <u>^{19}F NMR (376 MHz, in C_6D_6, rt, δ/ppm)</u>: −64.9 (d, 12.8 Hz). <u>^{31}P NMR (162 MHz, in C_6D_6, rt, δ/ppm)</u>: 64.6 (d, 49.4 Hz, 1P), 65.9 (dq, 49.4 Hz, 13.0 Hz, 1P). <u>^{13}C NMR (151 MHz, in CD_2Cl_2, rt, δ/ppm)</u>: 144.5, 127.8, 126.9 (q, J = 279.2 Hz), 124.4, 124.1, 73.8 (dq, J = 3.5 Hz, 29.2 Hz), 34.4 (dd, J = 2.6 Hz, 21.3 Hz), 34.2 (dd, J = 3.1 Hz, 22.3 Hz), 33.8, 33.7, 33.6, 33.5, 29.7-29.4 (m), 29.1, 29.0 (m), 28.4, 28.3, 27.6-26.6 (m), 26.3, 26.2, 25.5, 22.2 (dd, J = 17.7 Hz, 25.3 Hz), 19.3 (dd, J = 11.4 Hz, 22.8 Hz). <u>Elemental Analysis</u>: calc. C, 62.31; H, 8.15; F, 8.70; Ni, 8.96; O, 2.44; P, 9.45, found C, 62.07; H, 8.36.



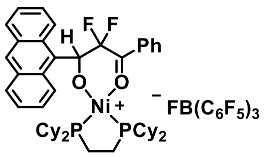
Preparation of **12**: To a vial equipped with a stirring bar was placed (η^2-PhCOCF$_3$)Ni(dcpe) (**11b**) (197 mg, 0.30 mmol) and B(C_6F_5)$_3$ (168 mg, 0.33 mmol). To the solid was added 8 mL of toluene and the mixture was vigorously stirred for 10 min to give a red solution. The reaction mixture was poured into stirring cold pentane (100 mL, −35 ºC) to cause yellow precipitate. Solvent was removed by decantation and the resulting solid was washed with pentane three times. The residue was dried *in vacuo* to give yellow powder of the title compound (309.2 mg, 88%). Recrystallization from toluene/pentane at −35 ºC afforded yellow crystals suitable for X-ray crystallography. ^{1}H NMR (400 MHz, in C_6D_6, rt, δ/ppm): 7.70 (d, 7.6 Hz, 2H), 7.08 (t, 7.6 Hz, 1H), 6.98 (t, 7.6 Hz, 1H), 2.1-0.8 (m, 48H). ^{13}C NMR (151 MHz, in C_6D_6, rt, δ/ppm): 148.6 (dm, $^{1}J_{CF}$ = 242 Hz), 139.1 (dm, $^{1}J_{CF}$ = 245 Hz), 137.1 (dm, $^{1}J_{CF}$ = 260 Hz), 134.5, 129.7 (d, J = 4.6 Hz), 127.9, 124.6 (br), 34.8 (d, J_{CP} = 26.2 Hz), 34.2 (d, J_{CP} = 21.5 Hz), 28.9-28.3 (m), 26.3-26.1 (m), 25.4, 25.3, 23.4 (dd, J = 10.9, 31.1 Hz), 18.5 (dd, J = 5.1, 29.3 Hz). ^{19}F NMR (376 MHz, in C_6D_6, rt, δ/ppm): −100.2 (dd, 7.3 Hz, 17.8 Hz, 2F), −137.4 (m, 6F), −164.4 (t, 20.4 Hz, 3F), −169.0 (m, 6F), −190.8 (s, 1F). ^{31}P NMR (162 MHz, in $CDCl_3$, rt, δ/ppm): 83.2 (m, 1P), 80.0 (m, 1P). Elemental Analysis: calc. C, 53.50; H, 4.58; B, 0.93; F, 29.29; Ni, 5.03; O, 1.37; P, 5.31, found C, 53.21; H, 4.64. X-ray data: *M* = 1167.42, yellow, triclinic, P-1 (#2), a = 11.6106(7) Å, b = 14.4297(8) Å, c = 15.6884(8) Å, α = 86.394(2) º, β = 88.475(3) º, γ = 72.090(2) º, V = 2496.0(2) Å^3, Z = 2, D_{calc} = 1.553 g/cm^3, T = −150 ºC, $R_1(wR_2)$ = 0.0468 (0.1160).



Preparation of **13**: To a suspension of [($PhCOCF_2$)Ni(dcpe)][$FB(C_6F_5)_3$] (**12**) (58.5 mg, 0.05 mmol) in 1.5 mL of $PhCF_3$ in a round-bottomed flask was added ^{t}BuNC (5.5 µL, 0.05 mmol) to give yellow solution. The reaction mixture was concentrated *in vacuo* and 2 mL of pentane was added to cause a yellow viscous precipitate. Solvent was removed by decantation and the residue was washed with 2 mL of pentane four times to yield yellow powder (49 mg, 78%). Crystals suitable for X-ray analysis were grown in CH_2Cl_2/pentane mixture. ^{1}H NMR (400 MHz, in CD_2Cl_2, rt, δ/ppm): 8.00 (d, J = 7.6 Hz, 2H), 7.55 (m, 1H), 7.43 (m, 2H), 2.2-1.2 (m, dcpe and ^{t}Bu group). ^{13}C NMR (151 MHz, in CD_2Cl_2, rt, δ/ppm): 194.1 (t, $^{2}J_{CF}$ = 22.3 Hz), 147.9 (dm, $^{1}J_{CF}$ = 238 Hz), 138.6 (dm, $^{1}J_{CF}$ = 245 Hz), 136.6 (dm, $^{1}J_{CF}$ = 247 Hz), 133.8, 133.7, 129.7, 128.7, 123.7 (br), 60.0 (CN*C*(CH_3)$_3$), 36.7 (d, J_{CP} = 22.2 Hz, P*C*H), 35.2 (d, J_{CP} = 21.4 Hz, P*C*H), 30.6, 29.9, 29.2 (CNC(*C*H_3)$_3$), 28.99, 28.96, 28.92, 28.90, 27.27, 27.18, 27.00, 26.91, 26.90, 26.84, 26.66, 26.59, 25.71, 25.49, 21.2 (dd, J_{CP} = 15.0, 29.0 Hz), 20.2 (dd, J_{CP} = 9.5, 25.7 Hz). The signals may comprise four singlets and six doublets due to methylene groups of DEPE deduced by comparison of the spectra with DEPT135. However, it was impossible to attribute each signals fully and correctly. Resonances derived from carbons bound to nickel were not detected probably due to low intensity of these signals as well as complicated coupling pattern with fluorine and phosphorus atoms. ^{19}F-^{13}C HSQC spectrum indicated existence of a signal of CF_2 at around 138 ppm in ^{13}C NMR spectrum, however it was overlapped with signals derived from $FB(C_6F_5)_3$. ^{19}F NMR (376 MHz, in CD_2Cl_2, rt, δ/ppm): −80.9 (dd, J = 24.0, 29.3 Hz, 2F), −138.6 (m, 6F), −165.8 (m, 3F), −170.1 (m, 6F), −193.9 (br, 1F). ^{31}P NMR (162 MHz, in CD_2Cl_2, rt, δ/ppm): 79.1 (dt, J = 28.6, 22.0 Hz), 77.7 (dt, J = 29.6, 29.9 Hz). Elemental Analysis: calc. C, 54.75; H, 5.00; B, 0.86; F, 27.35; N, 1.12; Ni, 4.69; O, 1.28; P, 4.95, found C, 54.82; H, 5.00; N, 1.25. X-ray data: M = 1250.55, yellow, triclinic, P-1 (#2), a = 12.0326(9) Å, b = 13.883(2) Å, c = 17.516(2) Å, α = 84.588(3) °, β = 79.578(3) °, γ = 73.801(3) °, V = 2760.4(4) Å^3, Z = 2, D_{calc} = 1.504 g/cm^3, T = −150 ºC, $R_1(wR_2)$ = 0.0794 (0.2755).

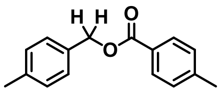


Preparation of **15a**: To a solution of $[(PhCOCF_2)Ni(dcpe)][FB(C_6F_5)_3]$ (**12**) prepared in situ from $(PhCOCF_3)Ni(dcpe)$ (**11b**) (163 mg, 0.25 mmol) with $B(C_6F_5)_3$ (128 mg, 0.25 mmol) in 4 mL of toluene was added 4-tolualdehyde (30 μL, 0.25 mmol) and the reaction mixture was stirred for 15 min. to give red solution. All volatiles were evaporated in vacuo and the residue was thoroughly washed with hexane followed by dry out in vacuo to yield red powder of title compound (218 mg, 68%). ^1H NMR (400 MHz, in C_6D_6, rt, δ/ppm): 7.46 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 6.84 (m, 3H), 6.70 (m, 2H), 4.92 (t, J_{HF} = 10.4 Hz, 1H), 1.9-0.86 (m). ^{13}C NMR (151 MHz, in CD_2Cl_2, rt, δ/ppm): 202.2 (t, $^2J_{CF}$ = 28.5 Hz), 147.9 (dm, $^1J_{CF}$ = 238 Hz), 138.7 (dm, $^1J_{CF}$ = 242 Hz), 138.4, 138.0, 136.6 (dm, $^1J_{CF}$ = 257 Hz), 135.0 (d, J = 4.2 Hz), 131.4, 131.3, 129.4, 128.7, 127.3, 123.9 (br), 118.7 (dd, $^1J_{CF}$ = 251, 265 Hz), 73.5 (t, $^2J_{CF}$ = 23.0 Hz), 35.5 (d, J_{CP} = 25.5 Hz), 34.2-34.0 (m), 29.8, 29.7, 29.2, 29.0, 28.8, 28.7, 28.4, 28.1, 27.2-26.5 (m), 25.7, 21.0 (dd, J_{CF} = 10.5, 30.9 Hz), 20.7, 20.0 (dd, J_{CP} = 6.5, 32.8 Hz). ^{19}F NMR (376 MHz, in C_6D_6, rt, δ/ppm): −102.6 (dd, J_{HF} = 9.4 Hz, J_{FF} = 269.6 Hz, 1F), −108.7 (dd, J_{HF} = 12.0 Hz, J_{FF} = 269.6 Hz, 1F), −137.5 (m, 6F), −164.6 (m, 3F), −169.1 (m, 6F), −190.9 (br, 1F). ^{31}P NMR (162 MHz, in C_6D_6, rt, δ/ppm): 88.2 (d, J_{PP} = 59.8 Hz, 1P), 77.6 (d, J_{PP} = 59.8 Hz, 1P). Elemental Analysis: calc. for $C_{60}H_{61}BF_{18}NiO_2P_2$, C, 55.97; H, 4.78; B, 0.84; F, 26.56; Ni, 4.56; O, 2.49; P, 4.81, found C, 55.70; H, 4.74.

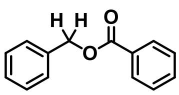


Preparation of **15b**: To a vial equipped with a stirring bar was placed complex **12** (116.7 mg, 0.10 mmol) and 9-anthracenecarboxaldehyde (22.7 mg, 0.11 mmol). Addition of 2.5 mL of toluene to the mixture with vigorous stirring gave deep red solution. After 30 min, yellow precipitate occurred which was collected by filtration after cooling the mixture to −35 °C, washed with Et_2O, and dried in vacuo (92.5 mg, 67%). The compound was recrystallized from CH_2Cl_2/pentane to afford red platelet crystals suitable for X-ray crystallography. ^{1}H NMR (400 MHz, in CD_2Cl_2, rt, δ/ppm): 0.24-2.51 (m, 48H), 6.63 (d, J_{HF} = 32.0 Hz, 1H), 7.30-7.54 (m, 6H), 7.78-8.16 (m, 6H), 8.43 (s, 1H), 9.13 (m, 1H). ^{13}C NMR (151 MHz, in CD_2Cl_2, rt, δ/ppm): 201.4 (t, $^2J_{CF}$ = 33.6 Hz), 147.9 (dm, $^1J_{CF}$ = 238 Hz), 138.8, 138.7 (dm, $^1J_{CF}$ = 242 Hz), 136.6 (dm, $^1J_{CF}$ = 257 Hz), 132.3, 132.2, 131.0, 130.7, 130.6, 129.8, 129.6, 129.4, 129.3, 128.9, 128.9, 128.4, 128.0, 126.6, 124.9, 124.5, 125.4, 123.9 (br), 122.8, 116.1 (dd, $^1J_{CF}$ = 258.2, 267.4 Hz), 69.8 (t, $^2J_{CF}$ = 23.3 Hz), 35.9 (d, J_{CP} = 26.4 Hz), 34.3 (d, J_{CP} = 21.3 Hz), 33.8 (t, J = 22.2 Hz), 30.3, 29.9, 29.2, 28.9, 28.8, 27.7, 27.1-25.0 (m), 21.1 (m), 19.7 (m). ^{19}F NMR (376 MHz, in CD_2Cl_2, rt, δ/ppm): −194.2 (br, 1F), −170.1 (m, 6F), −165.8 (m, 3F), −138.7 (m, 6F), −110.5 (ddd, J_{HF} = 5.2 Hz, 31.6 Hz, J_{FF} = 316.6 Hz, 1F), −100.0 (d, J_{FF} = 316.6 Hz, 1F). ^{31}P NMR (162 MHz, in CD_2Cl_2, rt, δ/ppm): 75.9 (d, J_{PP} = 55.7 Hz, 1P), 86.0 (d, J_{PP} = 55.7 Hz, 1P). Elemental Analysis: calc. for $C_{67}H_{63}BF_{18}NiO_2P_2$; C, 58.58; H, 4.62; B, 0.79; F, 24.89; Ni, 4.27; O, 2.33; P, 4.51, found C, 58.34; H, 4.52.

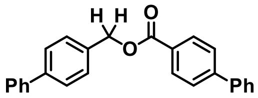
General Procedure for Homo-Esterification of Aldehydes: In a glove box, to a reaction vessel equipped with a stirring bar was placed [(η^3-$PhCOCF_2$)Ni(dcpe)][$FB(C_6F_5)_3$] (11.7 mg, 0.01 mmol). The solid was dissolved in 0.5 mL of toluene. To the solution was added an aldehyde (1.0 mmol). The reaction mixture was stirred at ambient temperature for 1 h. The results are summarized in Table 3.1 and identification of the products are as follows.



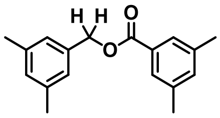
16a[23]: The product was obtained by following the general procedure and purified by kugelrohr distillation to give colorless liquid (101.6 mg, 85%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 2.36 (s, 3H), 2.40 (s, 3H), 5.31 (s, 2H), 7.19 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.95 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 21.3, 21.8, 66.6, 127.6, 128.4, 129.1, 129.3, 129.8, 133.3, 138.1, 143.7, 166.6.



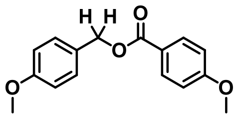
16c[24]: The product was obtained by following the general procedure and purified by kugelrohr distillation to give colorless liquid (104.3 mg, 98%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 5.39 (s, 2H), 7.35-7.50 (m, 7H), 7.59 (m, 1H), 8.10-8.12 (m, 2H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 66.7, 128.2, 128.3, 128.4, 128.7, 129.8, 130.2, 133.1, 136.1, 166.5.



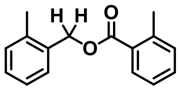
16d[25]: The product was obtained by following the general procedure and purified by short silica column (eluent; Hexane : EtOAc = 80 : 20) to give white solid (171.7 mg, 94%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 5.35 (s, 2H), 7.28-7.60 (m, 16H), 8.10 (m, 2H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 66.6, 127.1, 127.2, 127.3, 127.4, 127.5, 128.3, 128.8, 128.9, 129.0, 130.4, 135.2, 140.0, 140.8, 141.3, 145.9, 166.4.



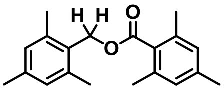
16e[26]: The product was obtained by following the general procedure and purified by kugelrohr distillation to give colorless liquid (124.6 mg, 93%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 2.34 (s, 6H), 2.36 (s, 6H), 5.28 (s, 2H), 6.98 (s, 1H), 7.06 (s, 2H), 7.19 (s, 1H), 7.70 (s, 2H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 21.2, 21.3, 66.7, 126.2, 127.5, 129.9, 130.1, 134.7, 136.0, 138.0, 138.2, 166.9.



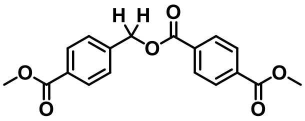
16f[26]: The product was obtained by following the general procedure and purified by silica gel column chromatography (eluent; Hexane : EtOAc = 90 : 10) to give colorless oil. ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 3.80 (s, 3H), 3.84 (s, 3H), 5.27 (s, 2H), 6.90 (m, 4H), 7.38 (m, 2H), 8.01 (m, 2H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 55.3, 55.4, 66.3, 113.6, 113.9, 122.7, 128.5, 130.0, 131.7, 159.6, 163.4, 166.3.



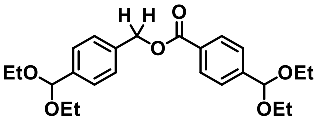
16g[23]: The product was obtained by following the general procedure (reaction was conducted at 60 ºC) and purified by kugelrohr distillation to give colorless liquid (120.2 mg, 100%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 2.49 (s, 3H), 2.68 (s, 3H), 5.42 (s, 2H), 7.26-7.50 (m, 7H), 8.00 (d, J = 6.8 Hz). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 19.1, 21.9, 65.0, 125.8, 126.1, 128.6, 129.3, 129.5, 130.4, 130.7, 131.8, 132.1, 134.1, 137.0, 140.5, 167.4.



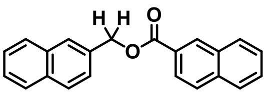
16h[16a]: The product was obtained by following the general procedure (reaction was conducted at 60 ºC) and purified by kugelrohr distillation to give colorless liquid (128.5 mg, 87%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 2.14-2.32 (m, 18H), 5.29 (s, 2H), 6.73 (m, 4H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 19.6, 19.7, 21.0, 21.1, 61.4, 128.3, 128.8, 129.1, 131.2, 134.9, 138.2, 138.5, 139.1, 170.5.



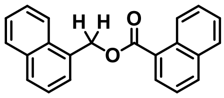
16i[23]: The product was obtained by following the general procedure and purified by passing through a short silica column (eluent; hexane : EtOAc = 80 : 20) to give white solid (161.4 mg, 98%) ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 3.93 (s, 3H), 3.95 (s, 3H), 5.43 (s, 2H), 7.51 (m, 2H), 8.07 (m, 2H), 8.12 (m, 4H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 52.2, 52.5, 66.4, 127.8, 129.6, 129.7, 130.0, 130.2, 133.6, 134.2, 140.7, 165.5, 166.2, 166.7.



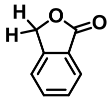
16j: The product was obtained by following the general procedure and purified by silica gel column chromatography (eluent; hexane : EtOAc = 90 : 10) to give colorless oil (174.5 mg, 84%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 1.21 (t, J = 7.0 Hz, 6H), 1.22 (t, J = 7.1 Hz, 6H), 3.56 (m, 8H), 5.34 (s, 2H), 5.49 (s, 1H), 5.52 (s, 1H), 7.41-7.54 (m, 6H), 8.04 (m, 2H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 15.1, 15.2, 61.1, 66.4, 100.8, 101.3, 126.8, 127.0, 128.0, 129.7, 130.0, 136.1, 139.2, 144.2, 166.2. HRMS (FAB+): m/z calc. 416.2199 (C24H32O6), found 439.2100 (C24H32O6Na1).



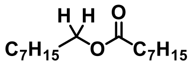
16k[26]: The product was obtained by following the general procedure and the crude mixture was purified by short silica column with toluene as eluent to afford title compound as white solid in quantitative yield (156.5 mg, 100%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 5.62 (s, 2H), 7.52-7.64 (m, 5H), 7.89-77.98 (m, 7H), 7.15 (d, J = 8.6 Hz, 1H), 8.70 (s, 1H) ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 67.1, 125.4, 126.1, 126.3, 126.4, 126.7, 127.4, 127.5, 127.8, 128.1, 128.2, 128.3, 128.6, 129.5, 131.3, 132.6, 133.2, 133.3, 133.6, 135.7, 166.7.



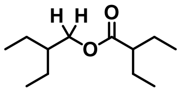
16l[28]: The product was obtained by following the general procedure (reaction was conducted at 60 ºC) and purified by column chromatography (eluent; Hexane : EtOAc = 90 : 10) to give colorless oil (148.7 mg, 95%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 5.81 (s, 2H), 7.07-8.10 (m, 13H), 8.9 (d, J = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 65.2, 123.7, 124.5, 125.3, 125.4, 128.9, 126.0, 126.3, 126.7, 126.9, 127.7, 127.9, 128.3, 128.6, 128.8, 129.1, 129.4, 130.6, 131.5, 131.6, 131.8, 133.6, 133.8, 167.4.



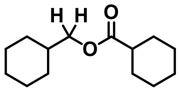
16m[29]: The product was obtained by following the general procedure (2 mol% of nickel catalyst was used) and purified by kugelrohr distillation to give white solid (51.0 mg, 76%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 5.35 (s, 2H), 7.55 (m, 2H), 7.71 (dt, J = 1 Hz, 7.5 Hz, 1H), 7.92 (d, 7.6 Hz, 1H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 69.7, 122.2, 125.7, 129.1, 134.1, 146.6, 171.1.



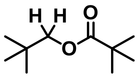
16n[30]: The product was obtained by following the general procedure and purified by kugelrohr distillation to give colorless liquid (92.6 mg, 81%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 0.91 (m, 6H), 1.32, (m, 14H), 1.64 (m, 4H), 2.32 (t, J = 7.6 Hz, 2H), 4.09 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 14.02, 14.06, 22.50, 22.59, 25.00, 25.90, 28.67, 28.84, 28.93, 31.48, 31.74, 34.43, 64.40, 174.02.



16o[17b]: The product was obtained by following the general procedure and purified by kugelrohr distillation to give colorless liquid (98.1 mg, 98%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 0.92 (dt, J = 2.5 Hz, 7.4 Hz, 12H), 1.40 (dt, J = 14.8 Hz, 7.5 Hz, 4H), 1.49-1.77 (m, 5H), 2.24 (m, 1H), 4.03 (d, J = 5.7 Hz, 2H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 11.0, 11.8, 23.4, 25.1, 40.3, 49.2, 66.0, 176.5.

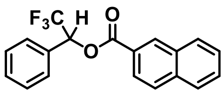


16p[26]: The product was obtained by following the general procedure and purified by kugelrohr distillation to give colorless liquid (109.4 mg, 98%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 0.97 (m, 2H), 1.13-1.36 (m, 6H), 1.46 (m, 2H), 1.59-1.80 (m, 9H), 1.92 (m, 2H), 2.30 (tt, *J* = 3.6 Hz, 11.3 Hz, 1H), 3.88 (d, *J* = 6.5 Hz, 2H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 25.5, 25.7, 25.8, 26.4, 29.1, 29.7, 37.2, 43.3, 69.3, 176.2.

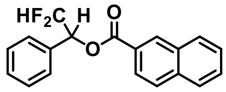


16q[26]: The product was obtained by following the general procedure (CH_2Cl_2 was used as solvent instead of toluene) and purified by distillation to give colorless liquid (19.3 mg, 22%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 0.88 (s, 9H), 1.15 (s, 9H), 3.68, (s, 2H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 26.5, 27.3, 31.5, 39.0, 73.6, 178.6. The low isolated yield was due to relatively high volatility of the product. The reaction also proceed in C_6D_6, and after the reaction, bis(trimethylsilyl)benzene (12.92 mg, 0.0582 mmol) was added as an internal standard, and the NMR yield was estimated to be 97% by comparison of peak areas.

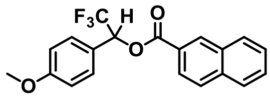
Crossed-Dimerization Catalyzed by Ni Complex **12**: To a vial equipped with a stirring bar was placed **12** (11.7 mg, 0.01 mmol). The solid was dissolved in 0.5 mL of toluene and to the solution was added 0.5 mmol of ketone followed by addition of 2-naphthaldehyde (93.7 mg, 0.6 mmol). The reaction mixture was stirred for 24 h at 100 °C. The product was obtained by kugelrohr distillation. The results are summarized in Scheme 3.9 and the characterization of the products are as follows.



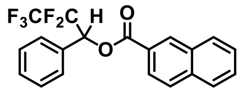
17a[28]: The product was obtained by following the general procedure to afford a white solid (144.8 mg, 88%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 6.44 (q, *J* = 6.8 Hz, 1H), 7.44 (m, 3H), 7.61 (m, 4H), 7.92 (t, *J* = 8.6 Hz, 2H), 8.01 (d, *J* = 8.1 Hz, 1H), 8.12 (dd, *J* = 1.7 Hz, 8.6 Hz, 1H), 8.71 (d, *J* = 0.8 Hz, 1H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 72.7 (q, *J* = 32.9 Hz), 123.5 (q, *J* = 279 Hz), 124.9, 126.0, 127.1, 128.0, 128.2, 128.6, 128.9, 128.9, 129.6, 130.1, 131.5, 132.0, 132.5, 136.0, 164.7. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −75.7 (d, *J* = 6.8 Hz). HRMS: m/z calc. 330.0868 (C19H13F3O2), found 330.0870.



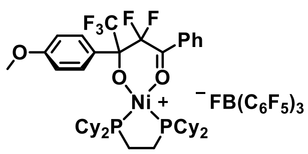
17b: The product was obtained by following the general procedure to afford colorless liquid (144.2 mg, 92%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 8.71 (s, 1H), 8.12 (m, 1H), 8.00 (m, 1H), 7.90 (m, 2H), 7.68-7.53 (m, 4H), 7.47-7.37 (m, 3H), 6.25 (dt, J_{HH} = 3.6, J_{HF} = 11.4 Hz, 1H), 6.13 (dt, J_{HH} = 3.6 Hz, J_{HF} = 55.1 Hz, 1H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 165.1, 135.9, 132.8 (m), 132.47, 131.7, 129.5, 129.4, 128.8, 128.7, 128.4, 127.8, 126.9, 126.4, 125.2, 114.0 (t, J_{CF} = 244.0 Hz), 74.1 (t, J_{CF} = 25.5 Hz). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −126.3 (m, 1F), −127.8 (m, 1F). HRMS: m/z calc. 312.0962 (C19H14F2O2), found 312.0959.



17c: The product was obtained by following the general procedure and further purified by HPLC to give colorless liquid (167.7 mg, 93%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 8.60 (s, 1H), 8.02-7.79 (m, 4H), 7.54-7.44 (m, 4H), 6.86 (m, 2H), 6.30 (q, J_{HF} = 6.8 Hz), 3.86 (s, 3H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 164.6, 160.8, 135.9, 132.4, 131.9, 129.6, 129.5, 128.8, 128.5, 127.9, 126.9, 126.0, 125.2, 123.5 (q, J_{CF} = 278.7 Hz), 123.4, 114.2, 72.3 (q, J_{CF} = 124.8 Hz), 55.3. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −75.8 (d, J_{HF} = 6.8 Hz). HRMS: m/z calc. 360.0973 (C20H15F3O3), found 360.0971.



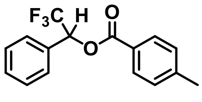
17d: The product was obtained by following the general procedure to afford colorless liquid (168.6 mg, 89%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 8.69 (s, 1H), 8.10 (m, 1H), 8.00 (m, 1H), 7.91 (m, 2H), 7.60 (m 4H), 7.44 (m, 3H), 6.54 (dd, J = 7.0 Hz, 17.5 Hz, 1H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm, except for CF_2CF_3): 164.3, 136.0, 132.9, 132.5, 131.9, 130.9, 130.1, 129.6, 128.9, 128.7, 128.6, 128.4, 127.9, 127.0, 125.8, 125.1, 71.6 (dd, J = 22.0 Hz, 30.5 Hz). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −81.6 (s, 3F), −119.8 (dd, J = 7.0 Hz, 278.2 Hz, 1F), −126.1 (dd, J = 17.5 Hz, 278.2 Hz, 1F). HRMS: m/z calc. 380.0836 (C20H13F5O2), found 380.0835.



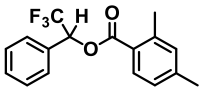
Preparation of **18**: To a round bottomed flask was placed nickel complex **12** (58.4 mg, 0.05 mmol) and toluene (1.5 mL) was added. To the resulting suspension was added *p*-anisyltrifluoromethylketone (8.5 μL, 0.05 mmol) to give a red solution. All volatiles were evaporated in vacuo, and resulting reddish oil was washed successively with pentane and dried out to yield orange powder of title compound (64.6 mg, 94%). ^{1}H NMR (400 MHz, in C_6D_6, rt, δ/ppm): 0.85-2.17 (m, 48H), 3.06 (s, 3H), 6.58 (d, J = 8.8 Hz, 2H), 6.68 (t, J = 7.6 Hz, 2H), 6.86 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 7.6 Hz, 2H), 7.77 (d, J = 8.2 Hz, 2H). ^{13}C NMR (151 MHz, in C_6D_6, rt, δ/ppm): 201.5 (dd, J_{CF} = 24.2, 26.7 Hz), 160.8, 148.6 (d, J_{CF} = 234.1 Hz), 139.1 (d, J_{CF} = 246.5 Hz), 137.2 (d, J_{CF} = 246.1 Hz), 131.2, 130.5, 130.4, 129.2, 128.9, 125.8, 118.9 (dd, J_{CF} = 262.6, 227.1 Hz), 113.6, 54.3, 35.8 (d, J_{CP} = 22.6 Hz), 34.1 (m), 29.4-25.4 (m), 20.8 (dd, J_{CP} = 23.3, 31.5 Hz), 20.3 (dd, J_{CP} = 6.4, 33.5 Hz). The sample for ^{13}C NMR was contaminated with small amount of toluene. Signals attributable to CF_3 and its α-carbon were not be attributable. ^{19}F NMR (376 MHz, in C_6D_6, rt, δ/ppm): −190.8 (br, 1F), −169.1 (m, 6F), −164.4 (t, J = 20.4 Hz, 3F), −137.6 (m, 6F), −121.1 (br, 1F), −108.7 (d, J_{FF} = 256.1 Hz, 1F), −75.7 (t, J = 10.1 Hz, 3F). ^{31}P NMR (162 MHz, in C_6D_6, rt, δ/ppm): 80.9 (d, J_{PP} = 61.9 Hz, 1P), 88.6 (d, J_{PP} = 61.9 Hz, 1P). Elemental Analysis: calc. for C61H60BF21NiO3P2; C, 53.42; H, 4.41; B, 0.79; F, 29.09; Ni, 4.28; O, 3.50; P, 4.52, found C, 53.36; H, 4.14.

Optimization of the Reaction Condition for Crossed-Dimerization: To a vial equipped with a stirring bar was placed Ni(cod)$_2$ (2.75 mg, 0.01 mmol), DCPE (4.22 mg, 0.01 mmol), and $B(C_6F_5)_3$ (5.12 mg, 0.01 mmol). To the solid was added Toluene (500 μL), 2,2,2-trifluoroacetophenone (13.6 μL, 0.1 mmol), and *p*-tolualdehyde (14.2 μL, 0.12 mmol). The mixture was stirred for 4 h at 100 ºC. The reaction mixture was diluted with Et_2O and analyzed by gas chromatography using tetradecane as an internal standard. The results are summarized in Table 3.2.

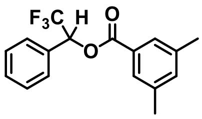
General Procedure for Crossed-Dimerization of ketone with aldehyde: In a dry box, to a vial equipped with a stirring bar was placed Ni(cod)$_2$ (5.50 mg, 0.02 mmol), 1,2-bis(dicyclohexylphosphino)ethane (8.44 mg, 0.02 mmol) and tris(pentafluorophenyl)borane (10.24 mg, 0.02 mmol). The solids were dissolved in 1 mL of THF. To the solution were added ketone (1.0 mmol) followed by aldehyde (1.2 mmol). The reaction mixture was stirred at 60 ºC for 24 h. The results are summarized in Table 3.3 and the characterization of the products are described below.



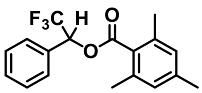
17a[28]: The product was obtained by following the general procedure and purified by column chromatography (eluent; Hexane : EtOAc = 90 : 10) followed by kugelrohr distillation to give colorless liquid (260.3 mg, 88%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 2.43 (s, 3H), 6.36 (q, J = 6.9 Hz, 1H), 7.28 (m, 2H), 7.41 (m, 3H), 7.55 (m, 2H), 8.02 (m, 2H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 21.8, 72.4 (q, J = 33 Hz), 123.5 (q, J = 280 Hz), 126.1, 128.1, 128.8, 129.5, 130.0, 130.2, 131.6, 144.9, 164.5. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −75.8 (d, J = 6.9 Hz). HRMS: m/z calc. 294.0868 (C16H13F3O2), found 294.0869.



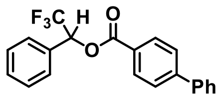
17f: The product was obtained by following the general procedure and purified by kugelrohr distillation to give colorless liquid (259.3 mg, 84%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 2.38 (s, 3H), 2.59 (s, 3H), 6.34 (q, J = 7.0 Hz), 7.09-7.12 (m, 2H), 7.42 (m, 3H), 7.54 (m, 2H), 8.00 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 21.5, 22.0, 72.1 (q, J = 32.8 Hz), 123.5 (q, J = 279 Hz), 124.9, 126.8, 128.2, 128.8, 129.9, 131.4, 131.6, 132.8, 141.4, 143.8, 164.9. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −75.7 (d, J = 6.9 Hz). HRMS: m/z calc. 308.1024 (C17H15F3O2), found 308.1025.



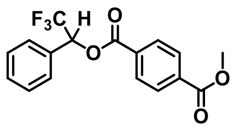
17g: The product was obtained by following the general procedure and purified by kugelrohr distillation to give colorless liquid (289.2 mg, 94%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 2.39 (s, 6H), 6.36 (q, J = 6.9 Hz, 1H), 7.25 (s, 1H), 7.43 (m, 3H), 7.56 (m, 2H), 7.74 (s, 2H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 21.4, 72.4 (q, J = 32.9 Hz), 123.6 (q, J = 279 Hz), 127.7, 127.9, 127.2, 128.7, 128.9, 130.0, 131.6, 135.7, 138.6, 164.9. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −75.7 (d, J = 6.9 Hz). HRMS: m/z calc. 308.1024 (C17H15F3O2), found 308.1023.



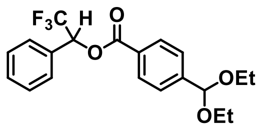
17h: The product was obtained by following the general procedure and purified by kugelrohr distillation to give colorless liquid (287.2 mg, 89%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 2.23 (s, 6H), 2.30 (s, 3H), 6.40 (q, J = 7.0 Hz, 1H), 6.88 (s, 2H), 7.43 (m, 3H), 7.53 (m, 2H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 19.7, 21.1, 72.2 (q, J = 33.0 Hz), 120.5 (q, J = 279 Hz), 128.3, 128.5, 128.7, 129.0, 129.9, 131.1, 135.6, 140.1, 167.8. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −75.3 (d, 6.8 Hz). HRMS: m/z calc. 322.1181 (C18H17F3O2), found 322.1183.



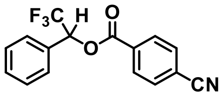
17i: The product was obtained by following the general procedure and purified by column chromatography (eluent; Hexane : EtOAc = 90 : 10) followed by kugelrohr distillation to give white solid (313.6 mg, 88%). The compound was recrystallized from toluene. ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 6.38 (q, J = 6.8 Hz, 1H), 7.38-7.43 (m. 4H), 7.47 (m, 2H), 7.56 (m, 2H), 7.61 (m, 2H), 7.69 (m, 2H), 8.18 (m, 2H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 72.5 (q, J = 33.0 Hz), 123.4 (q, J = 279 Hz), 127.3, 127.3, 128.0, 128.4, 128.8, 129.0, 130.0, 130.6, 131.4, 139.8, 146.7, 164.3. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −75.7 (d, J = 6.8 Hz). HRMS: m/z calc. 356.1024 (C21H15F3O2), found 356.1021. X-ray data: M = 356.34, colorless, monoclinic, $P2_1/c$ (#14), a = 20.0039(7) Å, b = 5.7737(2) Å, c = 15.3278(7) Å, β = 106.523(2) º, V = 1697.2(2) Å^3, Z = 4, D_{calc} = 1.394 g/cm^3, T = −150 ºC, $R_1(wR_2)$ = 0.0604 (0.1755).



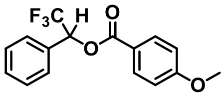
17j: The product was obtained by following the general procedure and purified by preparative thin layer chromatography followed by kugelrohr distillation to give colorless oil (218.7 mg, 65%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 3.96 (s, 3H), 6.37 (q, J = 6.8 Hz, 1H), 7.42 (m, 3H), 7.56 (m, 2H), 8.16 (m, 4H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 52.6, 72.8 (q, J = 33.0 Hz), 123.2 (q, J = 279 Hz), 128.0, 128.9, 129.8, 130.3, 130.1, 131.0, 132.4, 134.8, 163.7, 166.1. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −75.7 (d, J = 6.8 Hz). HRMS: m/z calc. 338.0766 (C17H13F3O4), found 338.0768.



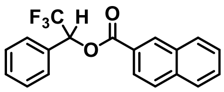
17k: The product was obtained by following the general procedure and purified by kugelrohr distillation to give colorless liquid (353.9 mg, 93%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 1.24 (t, J = 7.0 Hz, 6H), 3.58 (m, 4H), 5.55 (s, 1H), 6.35 (q, J = 6.8 Hz, 1H), 7.42 (m, 3H), 7.53 (m, 2H), 7.60 (m, 2H), 8.12 (m, 2H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 15.2, 61.2, 72.5 (q, J = 33.0 Hz), 123.3 (q, J = 279 Hz), 127.0, 128.0, 128.6, 128.8, 129.9, 130.0, 131.3, 145.1, 164.2. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −75.8 (d, J = 6.8 Hz). HRMS (CI+): m/z calc. 383.1470 (C20H22F3O4), found 383.1471.



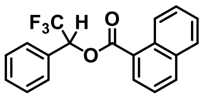
17l[28]: The product was obtained by following the general procedure (reaction conducted in toluene at 100 °C) and purified by kugelrohr distillation to give colorless viscous oil (207.6 mg, 68%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 6.36 (q, *J* = 6.8 Hz, 1H), 7.42-7.48 (m, 3H), 7.55 (m, 2H), 7.80 (m, 2H), 8.22 (m, 2H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 73.2 (q, *J* = 33.4 Hz), 117.4, 117.7, 123.1 (q, *J* = 279 Hz), 128.0, 128.9, 130.3, 130.5, 130.7, 132.5, 162.9. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −75.7 (d, *J* = 6.8 Hz). HRMS: m/z calc. 305.0664 (C16H10F3NO2), found 305.0665.



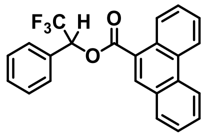
17m: The product was obtained by following the general procedure (reaction conducted in toluene at 100 °C) and purified by kugelrohr distillation to give pale green oil (307.8 mg, 99%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 3.88 (s, 3H), 6.35 (q, *J* = 6.9 Hz, 1H), 6.96 (m, 2H), 7.42 (m, 3H), 7.54 (m, 2H), 8.08 (m, 2H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 55.5, 72.2 (q, *J* = 32.8 Hz), 113.9, 121.0, 123.4 (q, *J* = 279 Hz), 127.6, 128.0, 128.7, 129.9, 131.6, 132.2, 164.0, 164.1. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −75.8 (d, *J* = 6.8 Hz). HRMS: m/z calc. 310.0817 (C16H13F3O3), found 310.0815.



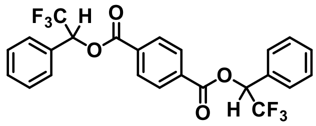
17e: The product was obtained by following the general procedure and purified by kugelrohr distillation to give white solid (328.6 mg, 99%).



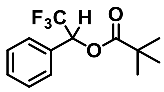
17n: The product was obtained by following the general procedure and purified by kugelrohr distillation to give colorless oil (276.5 mg, 84%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 6.51 (q, *J* = 6.9 Hz, 1H), 7.45 (m, 3H), 7.53-7.67 (m, 5H), 7.91 (d, *J* = 7.7 Hz, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 8.40 (dd, *J* = 1.2 Hz, 7.3 Hz, 1H), 8.92 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 164.9, 134.5, 133.9, 131.6, 131.5, 131.1, 130.0, 128.8, 128.7, 128.3, 128.2, 126.5, 125.6, 125.2, 124.5, 123.6 (q, *J* = 279.0 Hz), 72.5 (q, *J* = 32.9 Hz). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −75.5 (d, *J* = 6.8 Hz). HRMS: m/z calc. 330.0868 (C19H13F3O2), found 330.0869.



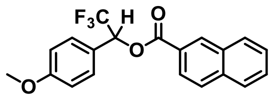
17o: The reaction was conducted by following the general procedure. The reaction mixture was passed through a short silica column (eluent; Hexane : EtOAc = 90 : 10), and purified by HPLC followed by kugelrohr distillation to give white solid (194.2 mg, 51%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 6.52 (q, J = 6.9 Hz, 1H), 7.46 (m, 3H), 7.61-7.74 (m, 5H), 7.80 (m, 1H), 8.05 (m, 1H), 8.73 (m, 2H), 8.89 (m, 1H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 72.6 (q, J = 33.0 Hz), 122.7, 122.9, 123.5 (q, J = 279 Hz), 124.4, 126.4, 127.2, 127.2, 127.7, 128.2, 128.9, 129.6, 129.8, 130.0, 130.4, 130.7, 131.4, 132.6, 133.6, 165.0. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −75.5 (d, J = 7.0 Hz). HRMS: m/z calc. 380.1024 (C23H15F3O2), found 380.1026.



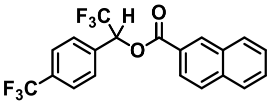
17p: The reaction was conducted in the presence of excess amount of trifluoroacetophenone (1.2 mmol) and 4 mol% of catalyst system and crude material was purified by column chromatography followed by HPLC to give colorless oil (97 mg, 40%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 6.29 (q, J_{HF} = 6.8 Hz), 7.34 (m, 6H), 7.47 (m, 4H), 8.14 (s, 4H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 73.0 (q, J_{CF} = 33.3 Hz), 123.2 (q, J_{CF} = 278.9 Hz), 128.0, 128.9, 130.1, 130.2, 131.0, 133.3, 163.4. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −75.8 (d, J_{HF} = 6.5 Hz). HRMS: m/z calc. 482.0953 (C24H16F6O4), found 482.0956.



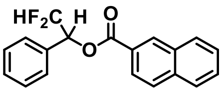
17s: The product was obtained by following the general procedure and purified by kugelrohr distillation to give colorless liquid (194.4 mg, 75%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 1.32 (s, 9H), 6.17 (q, J_{HF} = 6.9 Hz, 1H), 7.45-7.50 (m, 5H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 26.9, 38.9, 71.7 (q, J_{CF} = 32.8 Hz), 123.3 (q, J_{CF} = 278.8 Hz), 127.5, 128.7, 129.8, 131.5, 176.1. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −76.2 (d, J_{HF} = 6.8 Hz). HRMS: m/z calc. 260.1024 (C13H15F3O2), found 260.1026.



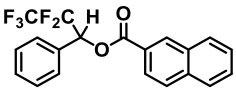
17c: The product was obtained by following the general procedure and purified by kugelrohr distillation to give colorless oil (359.5 mg, 100%).



17t: The product was obtained by following the general procedure and purified by kugelrohr distillation to afford white solid (369.4 mg, 93%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 8.70 (s, 1H), 8.11 (m, 1H), 8.00 (m, 1H), 7.92 (m, 2H), 7.72 (m, 4H), 7.61 (m, 2H), 6.47 (q, J = 6.7 Hz, 1H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 164.4, 136.1, 135.3, 132.4, 132.3, 132.0, 129.6, 129.0, 128.7, 128.5, 127.9, 127.1, 125.8 (q, J = 3.7 Hz), 125.5, 125.1, 123.7 (q, J = 270.2 Hz), 123.1 (q, J = 279.1 Hz), 72.1 (q, J = 33.4 Hz). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): −62.9 (s, 3F), −75.5 (d, J = 6.7 Hz, 3F). HRMS: m/z calc. 398.0741 (C20H12F6O2), found 398.0740.



17b: The product was obtained by following the general procedure and purified by kugelrohr distillation to afford colorless liquid (240.3 mg, 77%).



17d: The product was obtained by following the general procedure with 0.5 mmol of 1,1,1,2,2-pentafluoropropiophenone in toluene at 100 °C and purified by kugelrohr distillation to afford colorless liquid (124.8 mg, 66%).

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Chapter 4

Cu-Catalyzed Formal Reformatsky Reaction via C−F Bond Cleavage

4.1 Introduction

The Reformatsky reaction is an efficient C−C bond-forming reaction where an enolate is generated from an α-halocarbonyl compound by use of a reductant such as Zn(0) or Sm(II).[1] Since the first report by Sergey Reformatsky in 1887, a plethora of improved methods has been developed and widely applied in organic synthesis.[2] One of the most important applications of the Reformatsky reaction is the synthesis of difluoromethylene compounds that are important intermediates or products in medicinal chemistry as a bioisostere for an oxygen atom.[3,4] However, a classic Reformatsky reaction via a zinc difluoro-enolate requires the use of relatively expensive α-bromo-α,α-difluorocarbonyl compounds as starting materials (Figure 1, path a). Other synthetic methods to obtain difluoromethylene compounds require the utilization of hazardous and expensive fluorination reagents.[5] Amii and Uneyama have developed a method to generate silyl difluoro-enolate by the reaction of magnesium, trimethylsilyl chloride and α,α,α-trifluoroacetophenones (Figure 1, path c).[6,7] However, the protocol requires multi-step reactions to afford a difluoromethylene compound, and the addition of a Lewis acid is indispensable for the C−C bond-forming step due to low reactivity of the silyl enolates.[8] Herein, Cu-catalyzed formal Reformatsky reaction via a C−F bond cleavage is discussed that enables the direct conversion of α,α,α-trifluoromethylketones into difluoromethylene compounds by using a copper catalyst and less-toxic diboron as a reductant (Figure 1, path b). A possible reaction mechanism concerning the reactivity and equilibrium of difluoro-enolate is also discussed based on the mechanistic studies.

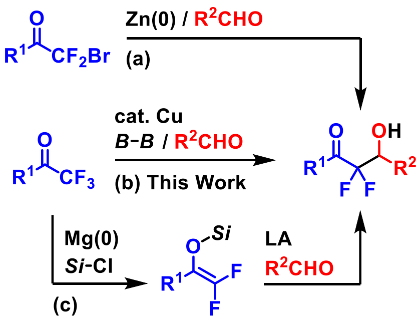


Figure 4.1 (a) Reformatsky reaction of α-bromo-α,α-difluorocarbonyl compounds. (b) This work: copper-catalyzed formal Reformatsky reaction via C−F bond cleavage. (c) Generation of silyl difluoro-enolate followed by Mukaiyama-aldol reaction (LA = Lewis Acid).

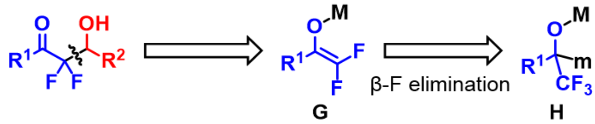
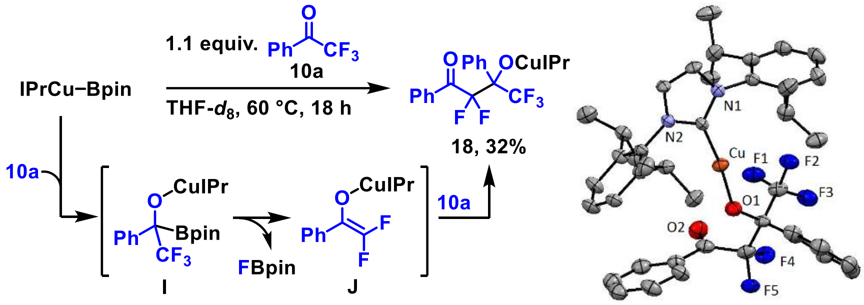


Figure 4.2 Retrosynthetic Analysis of the difluoro-enolate **G**

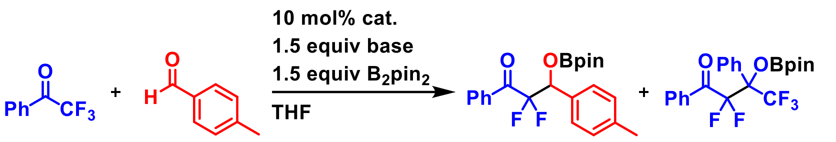


Scheme 4.1 Reaction of (IPr)CuBpin with **10a** via formation of copper difluoro-enolate **J** and the molecular structure of **18** with 50% thermal ellipsoids. Hydrogen atoms were removed for clarity.

4.2 Result and Discussion

As an efficient method for cleaving a C−F bond, β-fluorine elimination is known to proceed under relatively mild reaction conditions.[9] With this strategy in mind, the retrosynthetic analysis suggested α-metallated alkoxide **H** as a synthon of a difluoro-enolate **G** (Figure 4.2). Sadighi et al. reported that the 1,2-addition of (IPr)CuBpin (pin = 2,3-dimethyl-2,3-butanediolate) to an aldehyde generates an α-borylated copper alkoxide in situ.[10,11] Inspired by this reaction, the reaction of (IPr)CuBpin with trifluoromethylketone **10a** was conducted to observe the copper alkoxide **18** in a 32% yield (Scheme 4.1). The molecular structure of **18** was confirmed by X-ray crystallography. This result suggests the formation of the copper difluoro-enolate **J** via the intermediate **I**. Motivated by this outcome, copper-catalyzed formal Reformatsky reaction via C−F bond cleavage has been developed. The reaction of trifluoromethylketone **10a** with aldehyde **14a** in the presence of a catalytic amount of CuCl, IPr and NaO^{t}Bu and 1.5 equiv. of bis(pinacolato)diboron (B_2pin_2) that afforded a trace amount of borate ester of cross-adduct **19** along with a 4% yield of that of homo-adduct **20** (Table 4.1, entry 1).[12] The yield of **19** was improved to 32 and 56%, respectively by increasing the amount of NaO^{t}Bu to 0.6 and 1.5 equiv. Several auxiliary ligands were screened. Various phosphine ligands were tested, however the yields were compatible to that obtained in the absence of a ligand (entry 4-9). Contrary to these results, nitrogen based ligands such as 1,10-phenanthroline (Phen), 2,2'-bipyridine and 4,7-diphenyl-1,10-phenanthroline (bathophenanthroline, BPhen) delivered the desired product **19** in 81-82% yields (entry 10-12). The choice of an inorganic base was also crucial; a reaction using LiO^{t}Bu resulted in 62% yield and KO^{t}Bu gave only trace amount of the product **19** (entry 10, 13-14). The reaction even proceeded at 30 °C, and no reaction occurred in the absence of copper catalyst (entry 15-16).

Table 4.1. Optimization of the Reaction Conditions

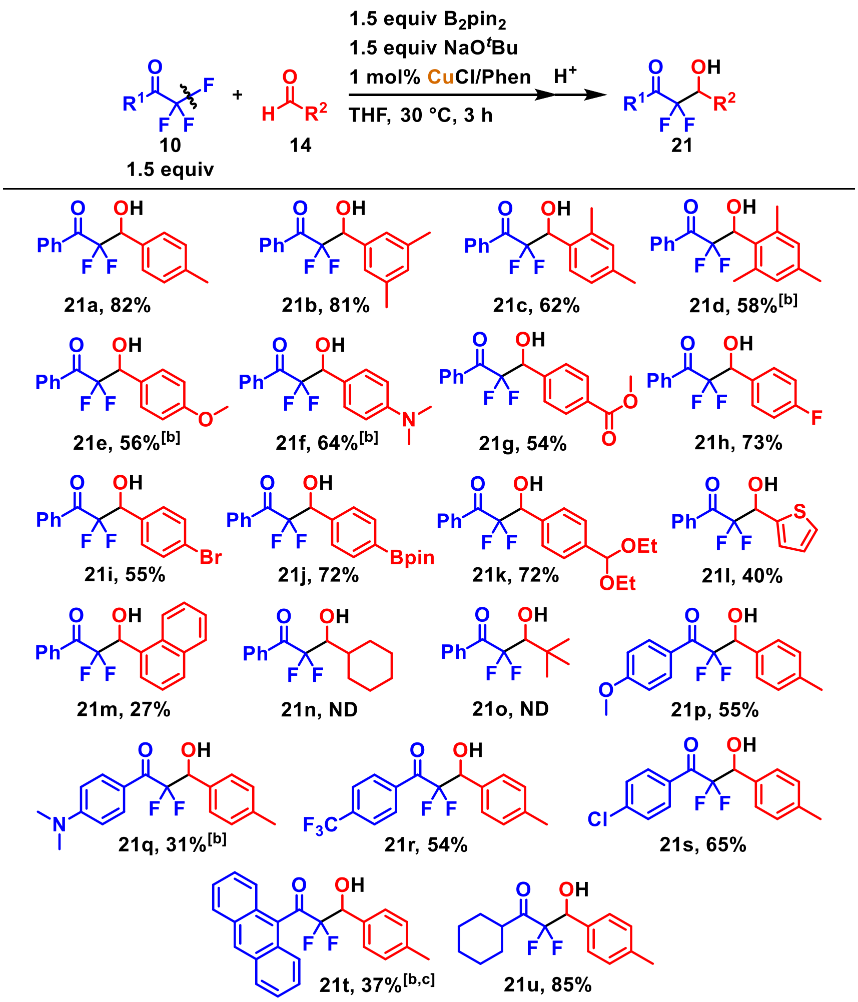


Run	Ligand	Base	Yield[a]	
			19	20
1	IPr	NaO^{t}Bu (0.1 eq)	trace	4
2	IPr	NaO^{t}Bu (0.6 eq)	32	ND
3	IPr	NaO^{t}Bu	56	ND
4	PPh_3[b]	NaO^{t}Bu	56	ND
5	DCPE	NaO^{t}Bu	49	3
6	DPPE	NaO^{t}Bu	62	3
7	*rac*-BINAP	NaO^{t}Bu	61	ND
8	Xantphos	NaO^{t}Bu	53	1
9	-	NaO^{t}Bu	63	ND
10	Phen	NaO^{t}Bu	82	4
11	Bpy	NaO^{t}Bu	81	ND
12	BPhen	NaO^{t}Bu	82	trace
13	Phen	LiO^{t}Bu	62	ND
14	Phen	KO^{t}Bu	trace	ND
15[c]	Phen	NaO^{t}Bu	83	5
16[c,d]	Phen	NaO^{t}Bu	ND	ND

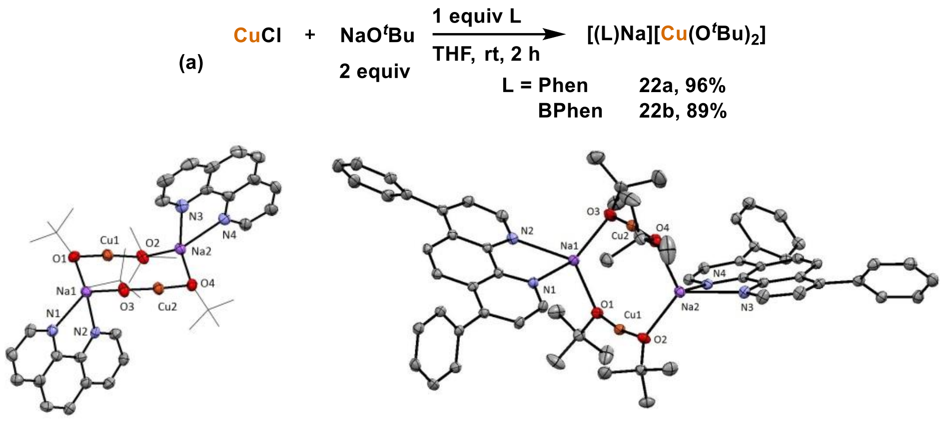
[a] Yields based on aldehyde were estimated by comparison of peak areas in ^{19}F NMR with $PhCF_3$ added as an internal standard. ND = not detected. [b] Reaction conducted with a 20 mol% ligand loading. [c] Reaction conducted at 30 °C. [d] CuCl was not added.

The catalyst loadings could be reduced to 1 mol%, and with these reaction conditions the corresponding alcohol product **21a** was isolated in an 82% yield after aqueous work up (Table 4.2). With this opimized condition in hand, the substrate scope of this reaction was investigated. The reaction was affected by the steric hinderance of benzaldehydes (**21b**, **21c**, **21d**). The reactions of benzaldehydes bearing an electron-donating methoxy (**14f**) and an *N*,*N*-dimethylamino group (**14l**) gave the corresponding products **21e** and **21f** in 56 and 64% yields, respectively. Functional groups such as ester (**21g**), fluorine and bromine attached to the aromatic ring (**21h**, **21i**), Bpin (**21j**) and acetal (**21k**) survived under the reaction conditions. 2-Thiophenecarboxaldehyde and 1-naphthaldehyde also gave the desired products **21l** and **21m**, respectively. Contrary to aromatic aldehydes, aliphatic aldehydes such as **21n** and **21o** could not be applied to these reaction conditions. The scope of trifluoromethyl ketone was also examined. The reactions of trifluoroacetophenones bearing an electron-donating methoxy, *N*,*N*-dimethylamino group and an electron-withdrawing CF_3 group afforded the desired products **21p**, **21q** and **21r** in moderate yields. The reaction of **14m** bearing chlorine at the 4-position of the benzene ring afforded the product **21s**, and the C−Cl bond was not reduced under the same reaction conditions. Bulky ketone **10g** afforded the corresponding product **21t** in a 37% yield even at 60 °C. Cyclohexyl trifluoromethyl ketone reacted with **14a** to yield coupling product **21u** in an 85% yield. Although NMR analysis of crude samples indicated full conversions of aldehydes, the formation of some unidentified by-products was observed, which might decrease the yields. Ethyl trifluoroacetate could not be applied under the reaction conditions.

Table 4.2 Substrate Scope[a]



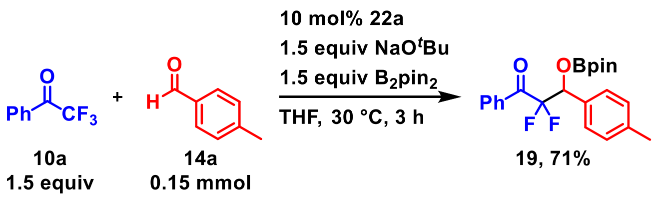
[a] Isolated yields of purified products. ND = not detected. [b] Reaction was conducted at 60 °C. [c] Reaction time was 24 h.



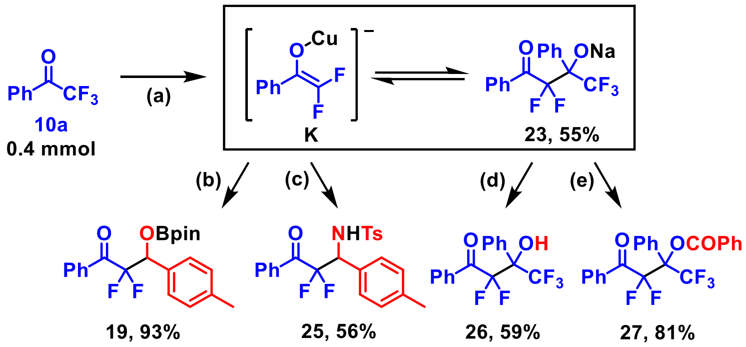
(b) Complex **22a** (c) Complex **22b**

Figure 4.3 (a) Formation of complexes **22** by reaction of CuCl, NaO^{t}Bu and ligand. (b) Crystal structure of complex **22a** with 50% thermal ellipsoids. Proton atoms and unidentified solvated molecule (probably toluene) were omitted for clarity. The ^{t}Bu groups were described as wires for clarity. (c) The crystal structure of complex **22b** depicted with 50% thermal ellipsoids. Hydrogen atoms were omitted for clarity.

To gain deeper insights into the reaction mechanism, a mixture of CuCl and Phen was treated with excess NaO^{t}Bu in THF-d_8. NMR analysis of the reaction mixture indicated the formation of a complex bearing two ^{t}BuO groups relative to Phen. In fact, [(L)Na][Cu(O^{t}Bu)$_2$] (**22**, where L = Phen or BPhen) was successfully isolated by the reaction of CuCl, ligand and 2 equiv. of NaO^{t}Bu (Figure 4.3a).[13] The crystal structures of complexes **22** were determined by X-ray crystallography (Figure 4.3b,c). The complexes formed dimers via coordination of ^{t}BuO groups to sodium atoms. The copper atoms adopted a two-coordinate linear structure while the conformation of the sodium atoms could be described as a distorted tetrahedral coordinated by Phen or BPhen and two ^{t}BuO groups. It is noteworthy that complex **22a** acts as a catalyst for the formal Reformatsky reaction via C−F bond cleavage (Scheme 4.2).

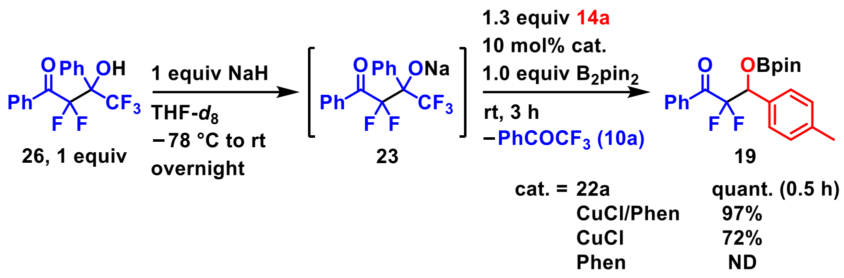


Scheme 4.2 Reaction of **10a** with **14a** catalyzed by **22a**



Scheme 4.3 Generation, reactivity and equilibrium of **23**. Conditions: (a) 5 mol% CuCl/Phen, 1 equiv. B_2pin_2, 1 equiv. NaO^{t}Bu, THF-d_8, rt, 30 min. (b) 0.27 mmol aldehyde **14a**, rt, 12 h. Yield is based on **14a**. (c) 0.2 mmol imine **24**, rt 5 h, then NaOHaq. Isolated yield is described. (d) Excess ^{i}PrOH, rt, 5 min. Yield is based on **10a**. (e) 0.2 mmol benzoyl chloride, rt, 9 h. Yield is based on benzoyl chloride.

In the catalytic reaction, the addition of a difluoro-enolate to either trifluoromethylketone **10** or aldehyde **14** could occur. The reaction in the absence of an aldehyde was monitored by NMR to observe formation of the sodium alkoxide of homo-adduct **23** in a 55% NMR yield along with some unidentified products (Scheme 4.3a). It merits note that homo-adduct borate ester **20** was not detected even though ^{11}B NMR analysis revealed the existence of an enough amount of residual B_2pin_2. These observations indicate the sluggish transmetallation of **23** with B_2pin_2 under the catalytic reaction conditions. The addition of aldehyde **14a** resulted in the formation of cross-adduct **19** in a high yield even at room temperature (Scheme 4.3b). An analogous reaction with *N*-(4-methylbenzylidene)-4-methylbenzenesulfonamide (**24**) afforded the corresponding product **25** (Scheme 4.3c). On the other hand, protonolysis of the reaction mixture did not afford $PhCOCF_2H$, but did afford the alcohol **26** (Scheme 4.3d). The alkoxide **23** was also trapped by the addition of benzoyl chloride to deliver ester **27** (Scheme 4.3e). These observations indicate that in the presence of anionic copper species like **22a**, **23** is in equilibrium with an anionic copper difluoro-enolate **K** that produces cross-adduct **19** via a reaction with aldehyde **14a**. In fact, in the presence of a catalytic amount of anionic copper complex **22a** and a stoichiometric amount of B_2pin_2, the reaction of aldehyde **14a** with homo-adduct **23** that was generated by treatment of corresponding alcohol **26** with NaH yielded cross-adduct **19** quantitatively (Scheme 4.4). In this case, the formation of trifluoromethylketone **10a** was confirmed by means of ^{19}F NMR analysis. The reaction also proceeded in the presence of 10 mol% of CuCl/Phen or CuCl, whereas the product was not obtained at all in the absence of CuCl.



Scheme 4.4 Copper-catalyzed reaction of alkoxide **23** with aldehyde **14a** in the presence of B_2pin_2

A plausible reaction mechanism is depicted in Figure 4.4. First, the reaction of CuCl, Phen and NaO^{t}Bu gives the cuprate **22a**. Reaction of **22a** with B_2pin_2 affords an anionic borylcopper species **L** which reacts with **10** to give intermediate **M**. β-Fluorine elimination of an intermediate **M** affords copper difluoro-enolate **N**. In this step, NaO^{t}Bu would act as a promoter of β-fluorine elimination since the β-fluorine elimination of a fluoroalkyl copper complex is promoted by the addition of sodium salt.[6l] The reaction of the enolate **N** with aldehyde **14** gives alkoxide **O** that reacts with B_2pin_2 to generate thermodynamically favored borate ester of cross-adduct **P** along with regeneration of borylcopper catalyst.[12] The enolate **N** also can react with trifluoromethylketone **10** to form an alkoxide **Q** which is in equilibrium between **R** and **22a** in the presence of NaO^{t}Bu. The selective formation of cross-adduct **P** could be rationalized by the equilibrium and the difference of basicity between copper alkoxide intermediates **O** and **Q**. The alkoxide **O** is sufficiently basic to give a thermodynamically stable borate ester of cross-adduct **P**, while the reaction of the alkoxide **Q** with B_2pin_2 is much slower probably due to electron withdrawing nature of five fluorine atoms attached to the β-carbons.

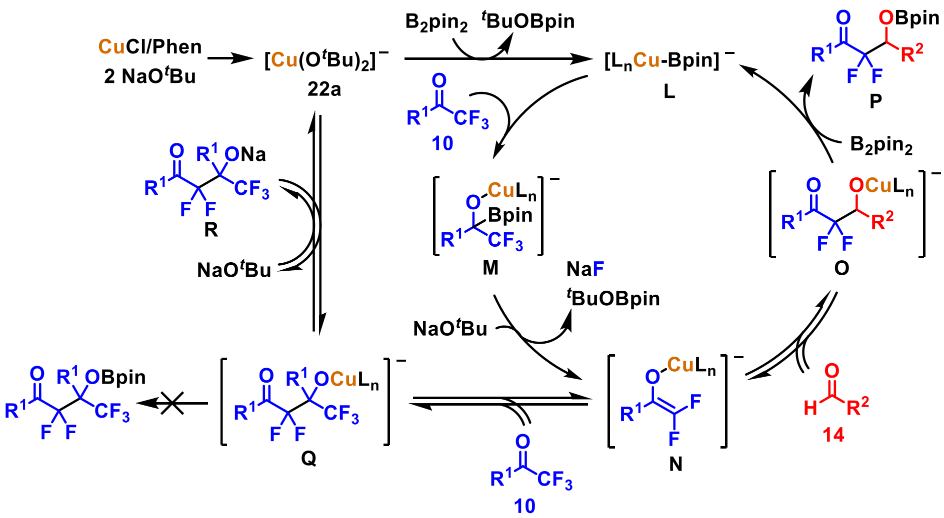


Figure 4.4 A plausible reaction mechanism

4.3 Conclusion

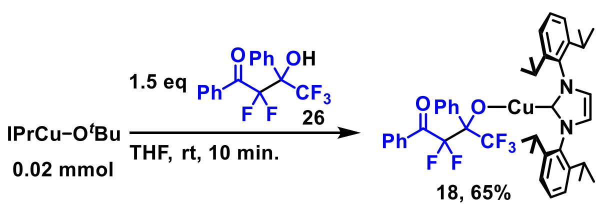
In chapter 4, the copper-catalyzed formal Reformatsky reaction of trifluoromethylketone with aldehyde via C−F bond cleavage using B_2pin_2 as a reductant in the presence of NaO^{t}Bu. This novel methodology is a potential alternative to the known procedures for synthesis of difluoro-compounds by circumventing the use of expensive mixed-halogen compounds and lengthy procedures, although further exploration on improvement of yields, scopes, and extension to an asymmetric version is desired. The catalytic reaction was highly selective to give the cross-adducts, although the copper difluoro-enolate generated in situ reacts with either trifluoromethylketone to give the homo-adducts or aldehyde to give the cross-adducts. The high selectivity was rationalized by mechanistic investigation that revealed the existence of an equilibrium between alkoxides of homo-adducts and those of cross-adducts of which much more facile transformation occurs to give thermodynamically stable borate esters than those of homo-adducts.

4.4 Experimental Detail

Materials: The degassed and distilled solvents (hexane, pentane) used in this work were commercially available. THF and THF-d_8 were distilled from sodium benzophenone ketyl. C_6D_6 was degassed and stored over activated molecular sieves (3A) in a glove box. IPrCuBpin[14] and IPrCuO^{t}Bu[14] were obtained by the literature procedures. CuCl (purity: ≥99.995%) was purchased from Sigma-Aldrich and stored in a glove box without further purification. B_2pin_2 was obtained from Matrix Scientific and recrystallized from dry pentane or hexane in a glove box. Other commercially available reagents were distilled and degassed prior to use.

Experimental Details

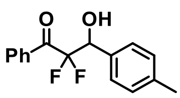
Reaction of (IPr)CuBpin with **10a**: To a solution of IPrCuBpin (17.4 mg, 0.03 mmol) in THF-d_8 (500 μL) was added **10a** (4.5 μL, 0.033 mmol) and $PhCF_3$ (5 μL as an internal standard). The resulting solution was transferred into a J. Young tube and analyzed by NMR. It is noteworthy that a signal derived from FBpin was observed at –150.3 ppm.[16]



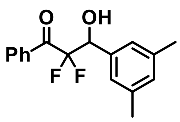
Preparation and Characterization of **18**: A screw-capped test tube equipped with a stirring bar was placed IPrCuO^{t}Bu (31.4 mg, 0.06 mmol) and alcohol **26** (29.7 mg, 0.09 mmol). The mixture was dissolved in 1.5 mL of THF and stirred for 10 min at ambient temperature. Then, the solution was concentrated in vacuo. The resulting oily material was treated with pentane to give white precipitate that was washed with pentane three times and dried in vacuo (30.3 mg, 65%). Fine crystals were obtained by diffusion of pentane into the THF solution of the complex. ^{1}H NMR (400 MHz, in THF-d_8, rt, δ/ppm): 7.92 (d, J = 7.6 Hz, 2H), 7.50-7.28 (m, 11H), 7.15 (m, 2H), 7.07 (m, 1H), 6.97 (m, 2H), 2.53 (m, 4H), 1.18-1.06 (m, 24H). ^{19}F NMR (376 MHz, in THF-d_8, rt, δ/ppm): –79.2 (dd, J = 6.5, 13.0 Hz, 3F), 107.3 (dd, J = 6.1, 244.0 Hz, 1F), –113.0 (dq, J = 243.7, 12.9 Hz, 1F). ^{13}C NMR (151 MHz, in THF-d_8, rt, δ/ppm): 191.4 (t, J = 29.0 Hz), 181.6, 146.5, 145.4, 140.4, 136.3, 135.9, 132.5, 131.9, 130.9, 128.5, 127.9, 127.8, 127.4, 126.6 (q, J = 291.4 Hz), 124.8, 124.7, 124.5, 118.9 (dd, J = 268.5, 271.0 Hz), 82.7 (m), 29.52, 29.51, 24.7, 24.6, 24.1, 24.0. Elemental Analysis: calc. C, 66.10; H, 5.93; Cu, 8.13; F, 12.16; N, 3.59; O, 4.10, found C, 66.09; H, 5.97; N, 3.61. X-ray data: M = 781.39, colorless, block, monoclinic, P2$_1$/c (#14), a = 12.2792(3) Å, b = 15.7535(4) Å, c = 20.5477(4) Å, β = 98.126(2)°, V = 3934.9(2) Å^3, Z = 4, D$_{calc}$ = 1.319 g/cm^3, T = −150 ºC, R_1(wR_2) = 0.0941 (0.3135).

Optimization of the reaction conditions: A screw-capped test tube equipped with a stirrer bar was charged with CuCl (1.5 mg, 0.015 mmol), ligand (0.015 mmol), and NaO^{t}Bu (0.1 eq: 1.4 mg, 0.6 eq: 8.7 mg, 1.5 eq 21.6 mg) and B$_2$pin$_2$ (57.1 mg, 0.225 mmol). The solids were suspended in 300 μL of THF and then **1a** (30 μL, 0.225 mmol), **2b** (18 μL, 0.15 mmol) and PhCF$_3$ (5 μL, an internal standard) was added. The tube was capped and heated at 60 °C for 3 h. The reaction mixture was diluted with 500 μL of C$_6$D$_6$ in a dry box, transferred into a NMR tube which was capped, sealed and analyzed by ^{19}F NMR. The results are summarized in Table 4.1.

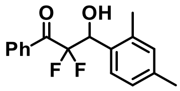
General procedure for substrate scope: A screw-capped test tube equipped with a stirrer bar was charged with CuCl (1.0 mg, 0.01 mmol), Phen (1.8 mg, 0.01 mmol), NaO^{t}Bu (144.2 mg, 1.5 mmol) and B$_2$pin$_2$ (381.3 mg, 1.5 mmol). The solids were suspended in 2 mL of THF and then trifluoromethylketone (1.5 mmol) and aldehyde (1.0 mmol) were added. The tube was capped and heated at 30 °C with stirring for 3 h. Aqueous work-up and purification delivers desired alcohol. The results are summarized in Table 4.2 and the characterization of the products are mentioned below.



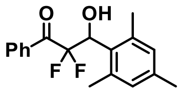
21a[17]: A screw-capped test tube equipped with a stirrer bar was charged with CuCl (1.0 mg, 0.01 mmol), Phen (1.8 mg, 0.01 mmol), NaO^{t}Bu (144.2 mg, 1.5 mmol) and B$_2$pin$_2$ (381.3 mg, 1.5 mmol). The solids were suspended in 2 mL of THF and then **10a** (261 mg, 1.5 mmol), **14a** (120 mg, 1.0 mmol) and PhCF$_3$ (30 μL, an internal standard) were added. The tube was capped and heated at 30 °C with stirring for 3 h. A portion of the reaction mixture was diluted with 500 μL of C_6D_6 in a dry box, transferred into a NMR tube which was capped, sealed and analyzed by ^{19}F NMR. The yield was estimated to be 88% by comparison of the peak area of the internal standard with that of the product. The NMR sample was combined with the reaction mixture and then, the whole mixture was quenched with 0.5 mL of ^{i}PrOH. The solution was evaporated to dryness, and then the resulting brown oil was extracted with hexane. The extract was filtered off, concentrated *in vacuo* and purified by column chromatography (hexane : EtOAc = 96 : 4) to afford colorless oil (227.0 mg, 82%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 8.06 (d, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.38 (d, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.34 (dd, *J* = 5.6 Hz, 18.6 Hz, 1H), 3.06 (br, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 191.0 (dd, *J* = 28.3 Hz, 31.3 Hz), 138.9, 134.5, 132.6, 131.8, 130.3 (t, *J* = 3.2 Hz), 129.1, 128.7, 128.0, 115.8 (dd, *J* = 254.9 Hz, 262.9 Hz), 73.3 (dd, *J* = 23.0 Hz, 28.4 Hz), 21.3. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): –104.9 (dd, J_{HF} = 5.6 Hz, J_{FF} = 289.7 Hz, 1F), −116.4 (dd, J_{HF} = 18.6 Hz, J_{FF} = 289.7 Hz, 1F). HRMS: m/z calc. 276.0962 (C16H14F2O2), found 276.0964.



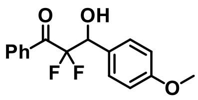
21b: A screw-capped test tube equipped with a stirrer bar was charged with CuCl (1.0 mg, 0.01 mmol), Phen (1.8 mg, 0.01 mmol), NaO^{t}Bu (144.2 mg, 1.5 mmol) and B_2pin_2 (381.3 mg, 1.5 mmol). The solids were suspended in 2 mL of THF and then **10a** (261 mg, 1.5 mmol), **14b** (134 mg, 1.0 mmol) were added. The tube was capped and heated at 30 °C with stirring for 3 h. The reaction mixture was quenched with ^{i}PrOH (1 mL). The solution was evaporated to dryness, and then the resulting brown oil was extracted with hexane. The extract was filtered off, concentrated *in vacuo*. Crude material was purified by column chromatography (Hexane : EtOAc = 96 : 4) followed by HPLC to afford the alcohol **21b** (234.7 mg, 81%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 8.04 (d, *J* = 7.5 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 6.90 (m, 2H), 5.30 (dd, *J* = 2.8, 18.3 Hz, 1H), 3.80 (s, 3H), 3.15 (br, 1H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 191.0 (dd, *J* = 28.8 Hz, 31.7 Hz), 137.9, 134.6, 134.5, 132.6, 130.8, 130.3 (dd, *J* = 3.2 Hz), 128.7, 125.9, 115.9 (dd, *J* = 254.8 Hz, 262.9 Hz), 73.4 (dd, *J* = 23.1 Hz, 28.6 Hz), 21.3. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): –104.6 (dd, *J* = 5.3 Hz, 288.7 Hz, 1F), −116.6 (dd, *J* = 19.0 Hz, 288.8 Hz, 1F). HRMS (EI+): m/z calc. 290.1118 (C17H16F2O2), found 290.1118.



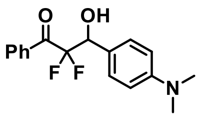
21c: By following the general procedure, the reaction of **10a** with **14d** resulted in formation of desired alcohol **21c** (90.4 mg, 62%) after column chromatography (Hexane : EtOAc = 96 : 4) followed by HPLC. <u>^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm)</u>: 8.07 (d, *J* = 7.7 Hz, 2H), 7.64-7.46 (m, 4H), 7.08 (d, *J* = 7.8 Hz, 1H), 7.02 (s, 1H), 5.64 (d, *J* = 20.1 Hz, 1H), 2.91 (m, 1H), 2.35 (s, 3H), 2.32 (s, 3H). <u>^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm)</u>: 191.1 (dd, *J* = 29.0, 31.9 Hz),138.6, 136.6, 134.5, 132.5, 131.2, 130.4, 130.3 (t, *J* = 3.0 Hz), 128.6, 128.0, 126.9, 116.5 (dd, *J* = 253.7, 263.5 Hz), 69.0 (dd, *J* = 22.5, 30.0 Hz), 21.1, 19.5 (d, *J* = 2.7 Hz). <u>^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm)</u>: –104.2 (d, *J* = 291.7 Hz, 1F), –117.0 (dd, *J* = 20.0, 291.7, 1F). <u>HRMS (EI+)</u>: m/z calc. 290.1118 (C17H16F2O2), found 290.1123.



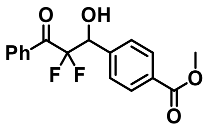
21d[18]: The reaction of **10a** with **14e** conducted at 60 °C resulted in formation of desired alcohol **21d** (88.9 mg, 58%) after column chromatography (Hexane : EtOAc = 96 : 4) followed HPLC. <u>^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm)</u>: 8.01 (d, *J* = 7.6 Hz, 2H), 7.54 (m, 1H), 7.40 (m, 2H), 6.80 (s, 2H), 5.82 (ddd, *J* = 3.1, 3.8, 26.3 Hz, 1H), 2.80 (d, *J* = 4.8 Hz, 1H), 2.39 (br, 6H), 2.19 (s, 3H). <u>^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm)</u>: 191.7 (dd, *J* = 28.5, 32.9 Hz), 138.2, 134.6, 132.6, 130.3 (dd, *J* = 2.5, 3.8 Hz), 128.7, 127.7, 117.7 (dd, *J* = 251.6, 266.7 Hz), 70.6 (dd, *J* = 22.9, 30.7 Hz), 21.3, 20.9. <u>^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm)</u>: –102.0 (dd, *J* =1.8, 279.9 Hz, 1F), −114.7 (dd, *J* = 26.1, 291.2 Hz, 1F). <u>HRMS (EI+)</u>: m/z calc. 304.1275 (C18H18F2O2), found 304.1276.



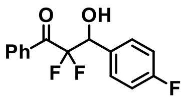
21e: The reaction of **10a** with **14f** was conducted at 60 °C and quenched by 5% NaOHaq. After stirring the mixture for several minutes, the organic layer was separated. The water layer was washed with ether three times, and the combined organic layer was dried over $MgSO_4$. The alcohol **14f** (82.4 mg, 56%) was obtained after column chromatography (Hexane : EtOAc = 96 : 4) followed by HPLC. <u>^{1}H NMR (600 MHz, in $CDCl_3$, rt, δ/ppm)</u>: 8.05 (d, *J* = 8.2 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.47 (t, 8.0 Hz, 2H), 6.90 (m, 2H), 5.28 (dt, *J* = 19.0 Hz, 5.1 Hz, 1H), 3.80 (s, 3H), 3.15 (d, 4.7 Hz, 1H). <u>^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm)</u>: 191.0 (dd, *J* = 28.8 Hz, 30.6 Hz), 160.1, 134.5, 132.5, 130.3 (dd, *J* = 3.1 Hz), 129.3, 128.6, 126.8, 115.9 (dd, *J* = 254.5 Hz, 262.3 Hz), 113.7, 73.0 (dd, *J* = 22.8 Hz, 28.2 Hz), 55.4. <u>^{19}F NMR (565 MHz, in $CDCl_3$, rt, δ/ppm)</u>: –105.0 (dd, *J* = 5.6 Hz, 288.4 Hz, 1F), −116.2 (dd, *J* = 18.4 Hz, 288.4 Hz, 1F). <u>HRMS(EI+)</u>: m/z calc. 292.0911 (C16H14F2O3), found 292.0913.



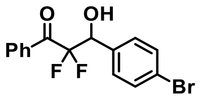
21f[18]: The reaction of **10a** with **14g** was conducted at 60 °C and quenched by 5% NaOHaq. After aqueous work up, the alcohol **21f** (97.5 mg, 64%) was obtained after HPLC. ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 8.05 (d, *J* = 7.4 Hz, 2H), 7.61 (m, 1H), 7.46 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.9 Hz, 2H), 5.25 (d, *J* = 18.0 Hz, 1H), 2.96 (s, 6H), 2.81 (s, 1H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 191.3 (dd, *J* = 28.7, 31.1 Hz), 151.1, 134.4, 132.8, 130.2 (t, *J* = 2.9 Hz), 129.0, 128.6, 122.1, 116.2 (dd, *J* = 253.9, 262.5 Hz), 112.1, 73.4 (dd, *J* = 22.9, 28.6 Hz), 40.4. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): –105.4 (dd, *J* = 5.3, 285.3 Hz, 1F), –116.4 (dd, *J* = 18.2, 2851, 1F). HRMS (EI+): m/z calc. 305.1227 (C17H17F2NO2), found 305.1234.



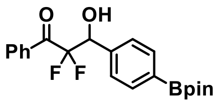
21g[18]: The reaction of **10a** with **14h** was quenched by 5% NaOHaq. After aqueous work up, the alcohol **21g** (86.4 mg, 54%) was obtained after column chromatography (Hexane : EtOAc = 95 : 5). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 8.03 (m, 4H), 7.65-7.45 (m, 5H), 5.43 (d, *J* = 17.8 Hz, 1H), 3.90 (s, 3H), 3.35 (s, 1H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 190.6 (dd, *J* = 29.0, 30.8 Hz), 166.8, 139.7, 134.8, 132.2, 130.6, 130.3 (t, *J* = 3.0 Hz), 129.5, 128.8, 128.2, 115.5 (dd, *J* = 255.7, 263.1 Hz), 72.8 (dd, *J* = 25.2, 30.7 Hz), 52.3, 52.2. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): –104.0 (dd, *J* = 3.6, 295.3 Hz, 1F), –116.5 (dd, *J* = 19.0, 295.3, 1F). HRMS (CI+): m/z calc. 321.0938 (C17H14F2O4+H), found 321.0936.



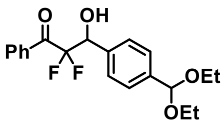
21h[17]: The reaction of **10a** with **14i** was quenched by 5% NaOHaq. After aqueous work up, the alcohol **21h** (102.0 mg, 73%) was obtained after column chromatography (Hexane : EtOAc = 96 : 4) followed by HPLC. ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 8.04 (d, *J* = 8.0 Hz, 2H), 7.63 (m, 1H), 7.47 (m, 4H), 7.07 (m, 2H), 5.36 (dt, *J* = 18.8, 4.5 Hz, 1H), 3.15 (d, *J* = 4.3 Hz, 1H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 190.9 (dd, *J* = 29.0, 31.0 Hz), 163.1 (d, *J* = 246.0 Hz), 134.8, 132.3 (m), 130.5, 130.3 (t, *J* = 3.2 Hz), 130.0 (d, *J* = 8.4 Hz), 128.7, 115.5 (dd, *J* = 256.2, 263.3 Hz), 115.3 (d, *J* = 21.6 Hz), 72.6 (dd, *J* = 23.0, 28.6 Hz). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): –104.6 (dd, *J* = 5.0, 294.4 Hz, 1F), –112.8 (m, 1F), –116.8 (dd, *J* = 18.7, 294.6, 1F). HRMS (CI+): m/z calc. 281.0789 (C15H11F3O2+H), found 281.0790.



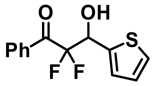
21i[17]: By following the general procedure, the reaction of **10a** with **14j** afforded the desired alcohol **21i** (94.4 mg, 55%) after HPLC. ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 8.05 (d, *J* = 7.4 Hz, 2H), 7.66-7.35 (m, 7H), 5.34 (d, *J* = 18.8 Hz, 1H), 3.23 (d, *J* = 4.1 Hz, 1H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 190.7 (dd, *J* = 29.3, 31.4 Hz), 134.9, 133.7, 132.2, 131.5, 130.3 (t, *J* = 3.1 Hz), 129.9, 128.8, 123.2, 115.4 (dd, *J* = 255.4, 263.9 Hz), 72.6 (dd, *J* = 23.0, 28.5 Hz). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): –104.2 (dd, *J* = 295.4, 3.2 Hz, 1F), –116.7 (dd, *J* = 18.8, 295.4, 1F). HRMS (CI+): m/z calc. 340.9989 (C15H11BrF2O2+H), found 340.9996.



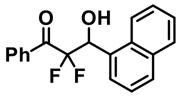
21j: The reaction of **10a** with **14k** was quenched by 5% NaOHaq. After standard aqueous workup, purification of crude product by column chromatography (Hexane : EtOAc = 95 : 5) afforded the desired product **21j** as a white solid (93.8 mg, 72%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 8.05 (d, *J* = 7.7 Hz, 1H), 7.81 (d, *J* = 7.52 Hz, 1H), 7.62 (m, 1H), 7.47 (m, 4H), 5.36 (d, *J* = 18.8 Hz, 1H), 3.29 (d, *J* = 3.2 Hz, 1H), 1.33 (s, 12 H). ^{11}B NMR (128 MHz, in $CDCl_3$, rt, δ/ppm): 30.2 (br). ^{13}C NMR (151 MHz, in $CDCl_3$, rt, δ/ppm): 190.9 (dd, *J* = 28.9, 31.3 Hz), 137.8, 134.7, 134.5, 132.5, 130.3, 130.2, 128.7, 127.4, 115.8 (dd, *J* = 256.7, 264.9 Hz), 84.0, 73.3 (dd, *J* = 23.1, 28.6 Hz), 24.8. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): –104.4 (dd, *J* = 4.4, 290.0 Hz, 1F), –116.5 (dd, *J* = 18.8, 290.1, 1F). HRMS (FAB+): m/z calc. 389.1736 (C21H23BF2O4+H), found 389.1742.



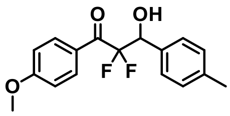
21k: By following the general procedure, the reaction of **10a** with **14l** afforded the desired product **21k** (130.3 mg, 72%) after HPLC. ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 8.02 (d, *J* = 7.7 Hz, 2H), 7.59 (m, 1H), 7.45 (m, 6H), 5.47 (s, 1H), 5.32 (d, *J* = 14.0 Hz, 1H), 3.51 (m, 4H), 1.20 (t, *J* = 7.0 Hz). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 191.1 (dd, *J* = 28.6, 31.3 Hz), 139.7, 135.1, 134.5, 132.6, 130.2 (m), 128.6, 128.0, 126.6, 116.0 (dd, *J* = 256.6, 264.4 Hz), 101.2, 73.0 (dd, *J* = 23.1, 28.6 Hz), 61.12, 61.11, 15.1. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): –104.9 (dd, *J* = 5.3, 286.5 Hz, 1F), –116.3 (dd, *J* = 18.5, 286.5, 1F). HRMS (FAB+): m/z calc. 387.1384 (C20H22F2O4+Na), found 387.1388.



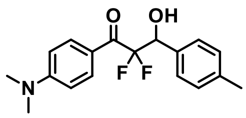
21l[19]: By following the general procedure, the reaction of **10a** with **14m** afforded the desired product **21l** (53.1 mg, 40%) after purification by column chromatography (Hexane : EtOAc = 95 : 5). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm):8.07 (d, *J* = 7.7 Hz, 2H), 7.63 (m, 1H), 7.47 (m, 2H), 7.36 (d, *J* = 4.9 Hz, 1H), 7.17 (m, 1H), 7.02 (m, 1H), 5.63 (dt, *J* = 5.1, 17.0 Hz, 1H), 3.25 (d, *J* = 5.0 Hz). ^{13}C NMR (151 MHz, in $CDCl_3$, rt, δ/ppm): 190.5 (dd, *J* = 29.1, 31.2 Hz), 137.2, 134.7, 132.3, 130.2 (t, *J* = 2.8 Hz), 128.7, 127.5, 126.81, 126.80, 115.1 (dd, *J* = 257.9. 264.9 Hz), 70.2 (dd, *J* = 24.3, 29.1 Hz). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): –104.0 (dd, *J* = 5.5, 291.3 Hz, 1F), –115.6 (dd, *J* = 17.1, 291.3, 1F). HRMS (EI+): m/z calc. 268.0370 (C13H10F2O2S), found 268.0372.



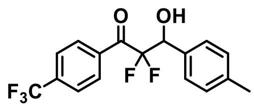
21m: By following the general procedure, the reaction of **10a** with **14n** afforded the desired product **21m** (42.1 mg, 27%) after purification by HPLC. ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 8.05 (m, 3H), 7.87 (m, 3H), 7.63-7.43 (m, 6H), 6.29 (dm, *J* = 19.7 Hz, 1H), 3.23 (m, 1H). ^{13}C NMR (151 MHz, in $CDCl_3$, rt, δ/ppm): 191.2 (dd, *J* = 29.0, 31.8 Hz), 134.7, 133.7, 132.5, 131.7, 131.0, 130.4 (t, *J* = 3.3 Hz), 129.8, 128.9, 128.8, 126.8, 126.6, 125.8, 125.3, 123.5, 116.5 (dd, *J* = 256.7, 266.0 Hz), 69.1 (dd, *J* = 23.1, 29.6 Hz). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): –102.6 (d, *J* = 292.3 Hz, 1F), –116.6 (dd, *J* = 19.7, 292.3, 1F). HRMS (EI+): m/z calc. 312.0962 (C19H14F2O2), found 312.0968.



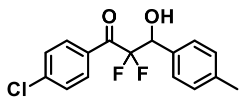
21p[17]: The reaction time of 2’,2’,2’-trifluoro-4-methoxyacetophenone with **14a** was elongated to 5 h. The reaction was quenched by 5% NaOHaq. After standard aqueous workup, purification of crude product by HPLC afforded the desired product **21p** as a white solid (84.1 mg, 55%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 8.06 (d, *J* = 8.7 Hz, 2H), 7.38 (d, *J* = 7.7 Hz, 2H), 7.19 (d, *J* = 7.7 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 5.31 (dt, *J* = 19.0, 4.5 Hz, 1H), 3.87 (s, 3H), 3.20 (d, *J* = 4.5 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 189.2 (dd, *J* = 28.9, 30.6 Hz), 164.8, 138.8, 132.9 (t, *J* = 3.4 Hz), 131.9, 129.0, 128.1, 125.2, 115.9 (dd, *J* = 254.8, 262.9 Hz), 114.0, 73.2 (dd, *J* = 23.1, 28.5 Hz), 55.6, 21.2. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): –103.9 (dd, *J* = 4.6, 291.6 Hz, 1F), –115.9 (dd, *J* = 19.0, 291.6, 1F). HRMS (EI+): m/z calc. 306.1068 (C17H16F2O3), found 306.1071.



21q: The reaction of 2',2',2'-trifluoro-4-(*N*,*N*-dimethylamino)acetophenone with **14a** was conducted at 60 °C. The reaction was quenched by 5% NaOHaq. After standard aqueous workup, purification of crude product by HPLC afforded the desired product **21q** as a yellow oil (50.0 mg, 31%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 7.90 (m, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.09 (d, *J* = 7.9 Hz, 2H), 6.51 (m, 2H), 5.21 (dt, *J* = 19.7, 4.3 Hz, 1H), 3.41 (d, *J* = 4.2 Hz, 1H), 2.98 (s, 6H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 188.1 (t, *J* = 29.6 Hz), 154.4, 138.6, 133.0 (t, *J* = 2.9 Hz), 132.2, 128.9, 128.2, 119.7 (t, *J* = 2.8 Hz), 116.0 (dd, *J* = 255.7, 263.8 Hz), 110.8, 73.5 (t, *J* = 23.6 Hz), 40.0 (d, *J* = 1.6 Hz), 21.3 (d, *J* = 3.1 Hz). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): –102.8 (dd, *J* = 4.4, 293.5 Hz, 1F), –115.5 (dd, *J* = 19.7, 293.5 Hz, 1F). HRMS (EI+): m/z calc. 319.1384 (C18H19F2NO2), found 319.1389.

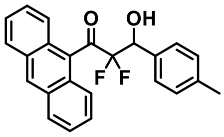


21r: The reaction of 2',2',2'-trifluoro-4-trifluoromethylacetophenone with **14a** was conducted at 60 °C and quenched by 5% NaOHaq. After standard aqueous workup, purification of crude product by HPLC afforded the desired product **21r** as a white solid (93.0 mg, 54%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 8.12 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 5.32 (dt, *J* = 18.2, 4.8 Hz, 1H), 2.92 (d, *J* = 4.5 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 190.5 (dd, *J* = 28.7, 32.5 Hz), 139.3, 135.5, 135.3 (m), 131.5, 130.5 (t, *J* = 3.0 Hz), 129.2, 127.9, 125.6 (q, *J* = 3.6 Hz), 123.4 (q, *J* = 271.3 Hz), 115.9 (dd, *J* = 254.2, 262.3 Hz), 114.0, 73.2 (dd, *J* = 23.2, 28.8 Hz), 21.2. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): –63.4 (s, 3F), –105.4 (dd, *J* = 5.6, 286.0 Hz, 1F), –116.8 (dd, *J* = 18.3, 286.2, 1F). HRMS (EI+): m/z calc. 344.0836 (C17H13F5O2), found 344.0831.

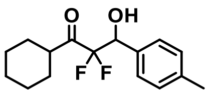


21s: The reaction of 4-chloro-2',2',2'-trifluoroacetophenone with **14a** was quenched by 5% NaOHaq. After standard aqueous workup, purification of crude product by HPLC afforded the desired product **21s** as a white solid (101.6 mg, 65%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 7.98 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 5.30 (dt, *J* = 4.9, 18.4 Hz, 1H), 3.00 (d, *J* = 4.5 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 190.0 (dd,

J = 29.0, 31.7 Hz), 141.4, 139.2, 131.8 (t, J = 3.1 Hz), 131.0 (m), 129.2, 129.1, 128.1, 115.9 (dd, J = 254.3, 262.2 Hz), 73.3 (dd, J = 23.2, 28.4 Hz), 21.3. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): –104.9 (dd, J = 5.7, 288.3 Hz, 1F), –116.4 (dd, J = 18.4, 288.3, 1F). HRMS (EI+): m/z calc. 306.1068 (C17H16F2O3), found 306.1071.



21t: The reaction of **10g** with **14a** was conducted at 60 °C for 24 h. Then, the reaction was quenched by 5% NaOHaq. After standard aqueous workup, purification of crude product by HPLC afforded the desired product **21t** as a yellow solid (43.8 mg, 23%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 8.55 (s, 1H), 8.01 (d, J = 8.2 Hz, 2H), 7.81 (br, 2H), 7.48-4.40 (m, 6H), 7.19 (d, J = 7.5 Hz, 2H), 5.62 (dt, J = 18.4, 4.9 Hz, 1H), 2.80 (d, J = 4.6 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 201.4 (dd, J = 28.9, 35.9 Hz), 139.3, 132.1, 130.8, 130.3, 129.9, 129.3, 129.0, 128.7, 128.2, 127.0, 125.6, 124.9, 114.9 (dd, J = 254.2, 263.2 Hz), 73.2 (dd, J = 22.7, 29.7 Hz), 21.3. ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): –106.1 (dd, J = 3.5, 278.9 Hz, 1F), –120.9 (dd, J = 18.4, 278.9 Hz, 1F). HRMS (EI+): m/z calc. 376.1275 (C24H18F2O2), found 376.1273.



21u: The reaction of Cyclohexyl trifluoromethyl ketone with **14a** was quenched by 5% NaOHaq. After standard aqueous workup, purification of crude product by HPLC afforded the desired product **3ob** as a white solid (120.1 mg, 85%). ^{1}H NMR (600 MHz, in $CDCl_3$, rt, δ/ppm): 7.30 (dd, J = 8.0 Hz, 2H), 7.19 (dd, J = 8.0 Hz, 2H), 5.11 (ddd, J = 4.9, 7.6, 16.8 Hz, 1H), 2.80 (d, J = 4.9 Hz, 1H), 2.76 (m, 1H), 2.36 (s, 3H), 1.84-1.66 (m, 6H), 1.36-1.27 (m, 2H), 1.24-1.15 (m, 2H). ^{13}C NMR (151 MHz, in $CDCl_3$, rt, δ/ppm): 205.6 (dd, J = 26.5, 30.2 Hz), 138.9, 131.9, 129.1, 127.7, 115.1 (dd, J = 256.7, 263.4 Hz), 72.9 (dd, J = 24.1, 28.5 Hz), 45.8, 27.9, 27.7, 25.6, 25.4, 25.3, 21.2. ^{19}F NMR (564 MHz, in $CDCl_3$, rt, δ/ppm): –112.2 (dd, J = 7.0, 271.0 Hz, 1F), –122.7 (dd, J = 16.8, 271.0 Hz, 1F). HRMS (EI+): m/z calc. 282.1431 (C16H20F2O2), found 282.1428.

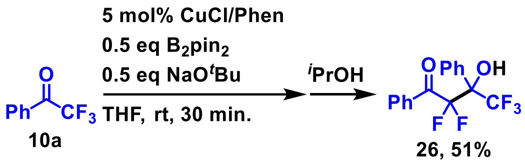
Preparation of [(Phen)Na][Cu(O^{t}Bu)$_2$] (**22a**): To a round-bottomed flask equipped with a stirring bar was placed 1,10-phenanthroline (0.54 g, 3.0 mmol), CuCl (0.30 g, 3.0 mmol) and NaO^{t}Bu (0.58 g, 6.0 mmol). To the mixture was added 30 mL of THF and the reaction mixture was stirred for 2 h. The resulting yellow suspension was passed through a pad of Celite and concentrated *in vacuo* to yield off-white powder of **22a** (1.19 g, 96%). Recrystallization from toluene/pentane afforded pale-yellow needle crystals. ^{1}H NMR (600 MHz, in THF-d_8, rt, δ/ppm): 9.38 (s, 2H), 8.35 (d, J = 7.6 Hz, 2H), 7.85

(s, 2H), 7.67 (d, J = 5.2 Hz), 1.15 (s, 18H). ^{13}C NMR (151 MHz, in THF-d_8, rt, δ/ppm): 151.6, 146.8, 137.1, 129.7, 127.4, 124.0, 68.8, 36.9. Elemental analysis gave no satisfactory result probably due to extremely high sensitivity of the complex to the air. Single crystals of complex **22a** was obtained by recrystallization from toluene/pentane in a glove box, but the crystals gradually got darken even when the crystals were suspended in a degassed Paratone. Although the X-ray data was sufficiently refined, R values were larger than those of complex **22b**. X-ray data: M = 1744.03, yellow, tetragonal, $P4_12_12$ (#92), a = 17.6815(4) Å, c = 28.8227(6) Å, V = 9011.0(3) Å^3, Z = 4, D_{calc} = 1.285 g/cm^3, T = −150 ºC, $R_1(wR_2)$ = 0.0910 (0.2656).

Preparation of [(BPhen)Na][Cu(O^{t}Bu)$_2$] (**22b**): Complex **22b** was prepared by an analogous method of **5a**. The reaction of BPhen (332 mg, 1.0 mmol), CuCl (99.0 mg, 1.0 mmol) and NaO^{t}Bu (192 mg, 2.0 mmol) afforded purple powder of the title compound (501.5 mg, 89%). ^{1}H NMR (400 MHz, in THF-d_8, rt, δ/ppm): 9.47 (s, 2H), 7.86 (s, 2H), 7.64 (s, 2H), 7.5 (m, 10 H), 1.22 (s, 18H). ^{13}C NMR (100 MHz, in THF-d_8, rt, δ/ppm): 151.2, 149.5, 147.4, 138.8, 130.5, 129.4, 129.3, 127.1, 124.7, 124.4, 68.8, 36.9. Elemental Analysis: C, 68.01; H, 6.06; Cu, 11.24; N, 4.96; Na, 4.07; O, 5.66, found C, 68.23; H, 6.11; N, 5.17. X-ray data: M = 1130.34, blue, monoclinic, $P2_1/c$ (#14), a = 12.6477(4) Å, b = 19.3207(5) Å c = 24.0282(7) Å, β = 90.474(2)°, V = 5871.4(3) Å^3, Z = 4, D_{calc} = 1.279 g/cm^3, T = −150 ºC, $R_1(wR_2)$ = 0.0516 (0.1609).

Reaction of **10a** with **14a** catalyzed by **22a**: A screw-capped test tube equipped with a stirrer bar was charged with complex **5a** (6.2 mg, 0.015 mmol), NaO^{t}Bu (22.0 mg, 0.225 mmol) and B_2pin_2 (57.1 mg, 0.225 mmol). The solids were suspended in 300 μL of THF and then **1a** (30 μL, 0.225 mmol), **2b** (18 μL, 0.15 mmol) and $PhCF_3$ (5 μL, an internal standard) was added. The tube was capped and heated at 30 °C for 3 h. The reaction mixture was diluted with 500 μL of C_6D_6 in a dry box, transferred into a NMR tube which was capped, sealed and analyzed by ^{19}F NMR. The desired product **19** was estimated to be formed in 71%.

Generation, reactivity and equilibrium of **23**: (a, d) A screw-capped test tube equipped with a stirring bar was placed CuCl (2.0 mg, 0.02 mmol), 1,10-phenanthroline (3.6 mg, 0.02 mmol), B_2pin_2 (101.5 mg, 0.4 mmol) and NaO^{t}Bu (38.4 mg, 0.4 mmol). The solids were suspended in 0.5 mL of THF/THF-d_8 (1:4) and stirred well. To the resulting suspension was added **10a** (70 mg, 0.4 mmol) and $PhCF_3$ (10 μL as an internal standard). The brown viscous mixture was stirred for 30 min. to give a dark brown solution that was transferred into a J. Young tube and analyzed by NMR. Then, to the tube was added 0.1 mL of ^{i}PrOH and well shaken before additional NMR analysis.



Isolation and characterization of **26**[20]: To a vial equipped with a stirring bar was placed CuCl (1.0 mg, 0.01 mmol), Phen (1.8 mg, 0.01 mmol), B_2pin_2 (253.9 mg, 1.0 mmol) and NaO^{t}Bu (96.1 mg, 1.0 mmol). The solids were suspended in 1.5 mL of THF and then, **1a** (272 μL, 2 mmol) was added. The reaction mixture was stirred at 30 °C for 3 h and then, quenched by addition of ^{i}PrOH (1 mL). The resulting brown solution was concentrated. Hexane was added to the brown oil and filtered off to give colorless crude material that was purified by flash column chromatography (hexane : EtOAc = 96 : 4) to afford colorless liquid (167.2 mg, 51%). The product was solidified on standing or scratching by use of a spatula. ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 7.91 (d, J = 7.6 Hz, 2H), 7.72 (m, 2H), 7.63 (m, 1H), 7.46-7.39 (m, 5H), 4.84 (s, 1H). ^{19}F NMR (376 MHz, in $CDCl_3$, rt, δ/ppm): –73.2 (m, 3F), –105.3 (dq, 294.9, 9.1 Hz, 1F), –106.0 (dq, J = 294.9 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, in $CDCl_3$, rt, δ/ppm): 190.8 (d, J = 30.7 Hz), 135.0, 132.3, 131.5, 130.2 (t, J = 3.6 Hz), 129.8, 128.7, 128.5, 127.0. Signals derived from CF$_3$, COH, CF$_2$ were not able to be assigned due to low intensities. HRMS (EI+): m/z calc. 330.0679 (C16H11F5O2), found 330.0676.

(b) A screw-capped test tube equipped with a stirring bar was placed CuCl (2.0 mg, 0.02 mmol), 1,10-phenanthroline (3.6 mg, 0.02 mmol), B_2pin_2 (101.5 mg, 0.4 mmol) and NaO^{t}Bu (38.4 mg, 0.4 mmol). The solids were suspended in 0.5 mL of THF-d_8 and stirred well. To the resulting suspension was added **10a** (70 mg, 0.4 mmol) and $PhCF_3$ (10 μL as an internal standard). The brown viscous mixture was stirred for 30 min. to give a dark brown solution that was transferred into a J. Young tube and analyzed by NMR. Then, to the solution was added **14a** (31.8 μL, 0.27 mmol).

(c) A screw-capped test tube equipped with a stirring bar was placed CuCl (2.0 mg, 0.02 mmol), 1,10-phenanthroline (3.6 mg, 0.02 mmol), B_2pin_2 (101.5 mg, 0.4 mmol) and NaO^{t}Bu (38.4 mg, 0.4 mmol). The solids were suspended in 0.5 mL of THF-d_8 and stirred well. To the resulting suspension was added **10a** (70 mg, 0.4 mmol) and $PhCF_3$ (10 μL as an internal standard). The brown viscous mixture was stirred for 30 min. to give a dark brown solution. To the solution was added imine **24** (54.6 mg, 0.2 mmol) and then, the solution was transferred into a J. Young tube. After 5 h, white precipitation was observed. The reaction mixture was treated with NaOHaq. Water layer was separated and extracted with ether three times. Then, the combined organic layer was dried over $MgSO_4$ and then purified by HPLC to afford white solid of compound **25**[7h] (48.3 mg, 56%). ^{1}H NMR (400 MHz, in $CDCl_3$, rt, δ/ppm): 7.86 (d, J = 7.5 Hz, 2H), 7.61-7.52 (m, 3H), 7.41 (t, J = 7.7 Hz, 2H), 7.06 (m, 4H), 6.98 (m, 2H), 5.73 (d, J = 9.7 Hz), 5.17 (m , 1H), 2.32 (s, 3H), 2.26 (s, 3H). ^{19}F NMR (376 MHz, in

CDCl$_3$, rt, δ/ppm): –104.7 (dd, *J* = 279.2, 12.2 Hz, 1F), –105.9 (dd, *J* = 279.1, 13.1 Hz, 1F). ^{13}C NMR (151 MHz, in CDCl$_3$, rt, δ/ppm): 188.9 (dd, *J* = 28.9 Hz), 143.5, 138.8, 137.4, 132.3, 130.0 (t, *J* = 3.0 Hz), 129.7, 129.4, 129.3, 128.8, 128.5, 127.2, 116.3 (t, *J* = 261.6 Hz), 59.9 (t, *J* = 24.8 Hz), 21.6, 21.2. HRMS (CI+): m/z calc. 430.1288 (C23H21F2NO3S+H), found 430.1285.

(e) A screw-capped test tube equipped with a stirring bar was placed CuCl (2.0 mg, 0.02 mmol), 1,10-phenanthroline (3.6 mg, 0.02 mmol), B_2pin_2 (101.5 mg, 0.4 mmol) and NaO^{t}Bu (38.4 mg, 0.4 mmol). The solids were suspended in 0.5 mL of THF-d_8 and stirred well. To the resulting suspension was added **10a** (70 mg, 0.4 mmol) and $PhCF_3$ (10 µL as an internal standard). The brown viscous mixture was stirred for 30 min. to give a dark brown solution that was transferred into a J. Young tube and analyzed by NMR. Then, benzoyl chloride (23 µL, 0.2 mmol) was added. After 9 h, the mixture was concentrated in vacuo and then extracted with hexane. The extract was filtered off and then purified by preparative thin layer chromatography followed by HPLC to afford white solid of **27** (50.1 mg, 58%). ^{1}H NMR (600 MHz, in CDCl$_3$, rt, δ/ppm): 7.91 (d, *J* = 7.3 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.43-7.33 (m, 9H). ^{19}F NMR (565 MHz, in CDCl$_3$, rt, δ/ppm): –63.3 (t, *J* = 12.7 Hz, 3F), –103.5 (dq, *J* = 268.0, 11.2 Hz, 1F), –107.2 (dq, *J* = 268.0, 14.9 Hz, 1F). ^{13}C NMR (151 MHz, in CDCl$_3$, rt, δ/ppm): 186.8 (t, *J* = 27.7 Hz), 162.5, 134.3, 134.1, 133.9, 130.4, 130.2 (t, *J* = 4.3 Hz), 129.9, 128.8, 128.7, 128.3, 128.2, 128.0, 127.4, 122.8 (q, *J* = 291.1 Hz), 115.2 (dd, *J* = 267.7, 273.2 Hz), 85.6 (m). HRMS (EI+): m/z calc. 434.0941 (C23H15F5O3), found 434.0932.

Copper-catalyzed reaction of alkoxide **23** with aldehyde **14a**: To a vial equipped with a stirring bar was placed NaH (4.8 mg, 0.2 mmol). The vial was cooled to −78 °C. To the solid was added THF-d_8 solution of alcohol **4a** (66 mg, 0.2 mmol, 0.4 M) that was cooled to −78 °C in advance. The reaction mixture was stirred for 1 h at the temperature, and then gradually warmed to room temperature overnight. Then, the resulting solution was added into a test tube containing CuCl (2.0 mg, 0.02 mmol), Phen (3.6 mg, 0.02 mmol), B_2pin_2 (50.8 mg, 0.2 mmol) and $PhCF_3$ (5 µL as an internal standard). The reaction mixture turned brown that was transferred to a J. Young tube and analyzed by NMR. Other related experiments were conducted analogously.

4.5 References and Notes

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Concluding Remarks

In this thesis, transformation reactions of abundant perfluoroarenes and trifluoromethylketones were developed by use of palladium, nickel, and copper catalysts involving cleavage of C−F bond as key steps. Related fluorine containing organotransition-metal complexes were synthesized along with full characterization and evaluation of their reactivity.

In chapter 2, Pd-catalyzed coupling reaction of perfluoroarenes with arylzinc reagents promoted by addition of LiI was described. One of the roles of LiI in this catalytic reaction was to promote the oxidative addition of C−F bond of perfluoroarenes to palladium, and the other was to enhance reactivity of arylzinc reagent by forming ate complex to facilitate transmetallation step. A transient three coordinate palladium complex was proposed as a key intermediate that was supported by comparison of the reactivity of bisphosphine and monophosphine palladium complexes.

In chapter 3, a well-defined nickel difluoro-enolate complex was synthesized via C−F bond activation of trifluoromethyl group of trifluoroacetophenone coordinated to Ni(0) accelerated by addition of $B(C_6F_5)_3$. The nickel difluoro-enolate showed unique catalytic activity toward dimerization of aldehydes as well as highly selective crossed-dimerization of trifluoroacetophenones with aldehydes to afford a variety of esters.

In chapter 4, Cu-catalyzed formal Reformatsky reaction via C−F bond cleavage of trifluoromethylketones with aldehydes was developed. The key process of the reaction is the formation of a copper difluoro-enolate via 1,2-addition of a borylcopper intermediate to trifluoromethylketones followed by β-fluorine elimination. The catalytic reaction was highly selective to give the cross-adducts and showed wide functional group compatibility. Mechanistic studies including the isolation and characterization of a possible anionic copper alkoxide intermediate suggested existence of unique equilibrium of copper difluoro-enolate species that is a key phenomenon to observe high selectivity of the catalytic reaction to afford cross-adduct.

The studies in this thesis will provide a new strategy toward synthesis of organofluorine compounds from relatively inexpensive and abundant starting materials. Mechanistic investigation conducted in this study would be a unique approach toward understanding reaction mechanism involving fluorinated or even non-fluorinated organotransition-metal catalyst.

List of Publications

1. "Copper-Catalyzed Reaction of Trifluoromethylketones with Aldehydes via Copper Difluoro-Enolate"
R. Doi, M. Ohashi, S. Ogoshi *Angew. Chem. Int. Ed.* **2016**, *55*, 341-344.

2. "Synthesis, Characterization and Unique Catalytic Activity of a Fluorinated Nickel Enolate"
R. Doi, K. Kikushima, M. Ohashi, S. Ogoshi *J. Am. Chem. Soc.* **2015**, *137*, 3276-3282.

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Supplementary Publications

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