Selective Transformation of Acyl Fluorides to Arylsilanes, Arylstannanes, 2-Substituted Propenes, and Esters

(フッ化アシルのアリールシラン、アリールスタンナン、2 位置換プロペンおよびエステルへの選択的な変換反応)

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Contents

Abstract

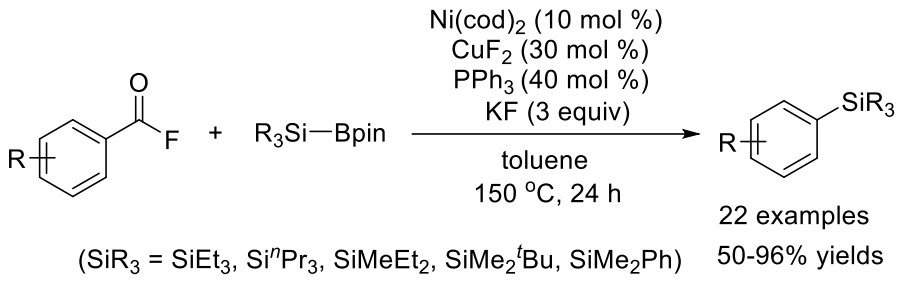
Recently, acyl fluorides as one of carboxylic acid derivatives have attracted much attention in organic synthesis, because they have many superiorities than other corresponding carboxylic derivatives, including easy availability, great stability, satisfying reactivity, versatile building blocks (aryl, acyl, and fluorine sources), controllable selectivity, and fluorination ability. However, transformations of acyl fluorides mainly focused on carbon-carbon bond formation to give various biaryl ketones and biaryls, other functionalizations of acyl fluorides into valuable adducts are still highly desired.

In this PhD Thesis, the Author focuses on functionalizations of acyl fluorides in carbonyl-retentive and decarbonylative manners. Initially, carbon-heteroatom bond-forming reactions of acyl fluorides were examined, as a result, a wide range of electronically and sterically (hetero)arylated silanes were obtained by nickel/copper-cocatalyzed decarbonylative silylation of acyl fluorides. Then, acyl fluorides serving as aryl sources were also discovered in ligand-free nickel-catalyzed decarbonylative stannylation of acyl fluorides. Subsequently, 2-substituted propenes were synthesized by methylenation of acyl halides with $AlMe_3$, assisted by a catalytic amount of 1,3-bis(diphenylphosphino)methane (DPPM). In addition, a diverse of acyl fluorides were designed to act as an acyl source to accept a methoxy group from tris(2,4,6-trimethoxyphenyl)phosphine (TMPP) via C(aryl)–OMe bond cleavage under transition-metal-free conditions. This PhD Thesis describes transformations of acyl fluorides in carbon-carbon and carbon-heteroatom bond formations, which also extended the utilization of carboxylic acids into other value-added compounds via acyl fluorides.

Chapter 2. Nickel/Copper-Cocatalyzed Decarbonylative Silylation of Acyl Fluorides

Since last year, decarbonylative transformations of acyl fluorides have attracted much attention due to their unique nature. However, main efforts focused on carbon-carbon bond formations in a decarbonylative manner, the carbon-heteroatom bond-forming reactions utilizing acyl fluorides are quite rare. Since organosilicon compounds are of a great importance in organic synthesis, drug discovery and materials science, various synthetic strategies have been established to construct a carbon-silicon bond. In this

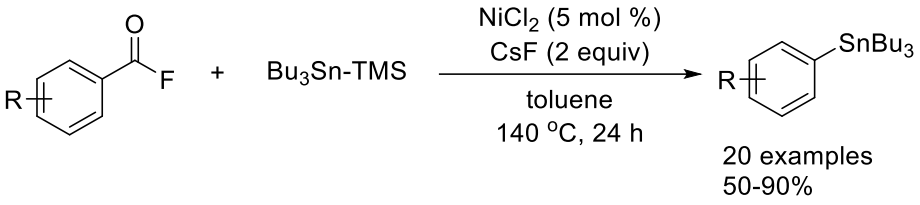
Chapter, the Author disclosed Ni/Cu-cocatalyzed decarbonylative silylation of acyl fluorides to afford various arylsilanes. The present transformation demonstrated high efficiency and good functional-group compatibility, which can provide a new access to arylsilanes starting from acyl fluorides via carbon-fluorine bond cleavage and carbon-silicon bond formation. Such transformation would not only extend the functionalization of acyl fluorides, but complement the synthetic route for arylsilanes.



Chapter 3. Nickel-Catalyzed Decarbonylative Stannylation of Acyl Fluorides under Ligand-Free Conditions

Arylstannanes as one of common organometallic reagents are extensively applied in Migita-Kosugi-Stille reaction, which has been utilized as a powerful method for C–C bond formation, especially, in natural product synthesis. Therefore, carbon-tin bond formation for the synthesis of an array of arylstannanes starting from acyl fluorides are highly desired.

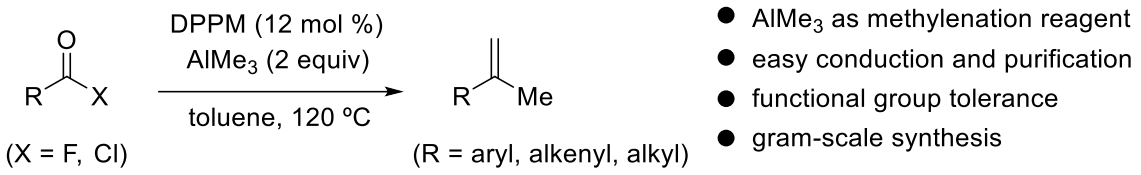
In Chapter 3, the Author discovered nickel-catalyzed decarbonylative stannylation of acyl fluorides under ligand-free conditions. A variety of aromatic acyl fluorides were capable of reacting with silylstannanes in the presence of cesium fluoride. One-pot decarbonylative stannylation/Migita-Kosugi-Stille reaction of benzoyl fluoride gave rise to the direct formation of the corresponding cross-coupled products, which further demonstrated the synthetic utility of the present method. This newly developed methodology with a good functional-group compatibility via C–F bond cleavage and C–Sn bond formation under the nickel catalysis opens a new area for the functionalization of acyl fluorides in terms of carbon-heteroatom bond formation.



Chapter 4. Bidentate Phosphine-Assisted Methylenation of Acyl Halides with $AlMe_3$

2-Substituted propenes as important building blocks are prevalent in natural and synthetic products, as well as catalytic asymmetric processes. Reported synthetic routes of 2-substituted propenes always start from ketones or aldehydes with various methylene transfer reagents, which generally require multi-step synthesis, harsh reaction condition as well as unsatisfactory yields of the target products. In addition, strong bases or acids are frequently used to activate intermediate alcohols to convert into methylenation products via basic elimination or acidic dehydration.

In this Chapter, the Author developed bidentate phosphine-assisted methylenation of trimethylaluminum with aryl, alkenyl, and alkyl-substituted acyl fluorides and acyl chlorides, affording an array of 2-substituted propene derivatives. The addition of a catalytic amount of DPPM increased an efficiency of the reactions. Trimethylaluminum as the methylenation reagent not only eliminates the pre-synthesis of the transfer reagent but provides an efficient method for the synthesis of a series of 2-substituted propenes.

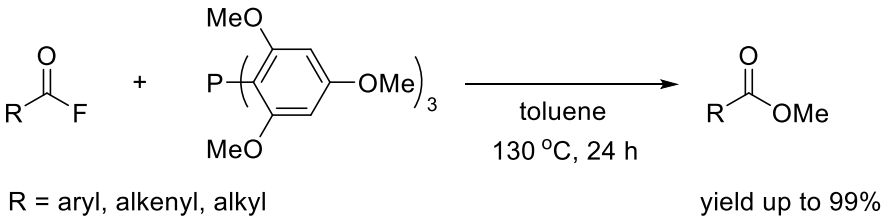


Chapter 5. Methoxylation of Acyl Fluorides by C–OMe Bond Cleavage in TMPP under Metal-Free Conditions

The C−O bond cleavage in ethers is one of the most fundamental transformations in organic synthesis, and ethers as one of the phenol derivatives are considered more economical and ecological alternative to aryl halides in transition metal-catalyzed cross-coupling reactions. Numerous studies on C(aryl)–O and O–Me bond cleavage

(demethylation) in aryl methyl ethers have been reported, where bond dissociation energies for C(aryl)–O and O–Me bonds are 100 kcal/mol and 65 kcal/mol, respectively. In these protocols, an eliminated methyl or methoxyl group is utilized as a leaving group. To the best of her knowledge, C(aryl)−OMe bond cleavage of phenol derivatives releasing alkoxy sources installed into the desired products has been unexplored.

In this Chapter, the Author described the transition-metal-free challenging C(aryl)–OMe bond cleavage in tris(2,4,6-trimethoxyphenyl)phosphine (TMPP), in which an OMe group was installed into acyl fluorides, affording a wide range of aryl, alkenyl and alkyl esters in high yields. Other OMe-substituted triarylphosphines afforded no trace of the target product under standard reaction conditions, which can be explained by unusual basicity and nucleophilicity of TMPP.



CHAPTER 1

General Introduction

1-1 Introduction

Fluoroorganic chemistry has become an important research field along with their application in materials, agrochemicals, fine chemicals as well as pharmaceuticals synthesis,[1] such as radiotracers labeled with ^{18}F nuclei,[2] high sensitivity of ^{19}F in nuclear magnetic resonance (NMR) experiments,[3] and ^{19}F magnetic resonance imaging (MRI).[4] Most importantly, more fluorinated drugs have been arise in best performing, top-selling drugs.[5] The introduction of a fluorine atom was benefited of the biologically relevant properties including metabolic stability, basicity, H-bond (HB) ability, lipophilicity, and bioavailability.[6]

Acyl fluorides as one of the carboxylic acid derivatives are composed of three components: aryl or alkyl skeleton, carbonyl group and a fluorine atom. The structure of acyl fluorides renders themselves as the unique and attractive electrophile in organic chemistry. Fluorine is the most electronegative element (χ = 4) in the periodic table,[7] which renders electron density substantially on fluorine, thus, the C–F bond is highly polarized. Moreover, fluorine has the smallest atomic radius among the Period 2 elements, its size (1.47 Å) is between hydrogen and oxygen.[8] The fluorine bounded to the carbon of an acyl moiety forms the strongest bond (C–F, 105.4 kcal mol^{-1}) in organic chemistry.[9] Compared with other carboxylic acid derivatives including amides, esters, aldehydes and other acyl halides, acyl fluorides have the highest wavenumber at 1867 cm^{-1}, which demonstrated that carbonyl C-O double bond of acyl fluorides are short and strong. In addition, the higher wavenumber declares that three lone pairs on fluorine are held tightly, they are reluctant to donate fluorine lone pair to carbonyl in acyl fluorides. Therefore, the stability and higher wavenumber of acyl fluorides is due to the electrostatic stability of the C–F bond, not resonance.

In terms of the electrophilicity or reactivity, acyl fluorides are comparable with activated esters but without steric concerns. Moreover, compared with highly active acyl chlorides, couplings with varying steric, electronic and functionalized partners, acyl fluorides provide less byproducts, and controllable selectivity.[10] Owing to their versatile building blocks, superior stability and distinct reactivity, various synthetic routes for acyl fluorides have been reported, which lay a solid foundation for the transformations of acyl fluorides to further

value-added adducts.

1-2 Synthesis of Acyl Fluorides

Efficiently synthetic routes of acyl fluorides are defined as utilization of cheap and stable fluorinating reagents, simple operation and easy-handle procedures, as well as wide functional-group compatibility. Up to date, four strategies have been developed for acyl fluorides synthesis, including 1) deoxyfluorination or halogen exchange of carboxylic acid derivatives by using different fluorinating reagents without the metal catalyst, 2) palladium-catalyzed fluorocarbonylation of aryl halides, 3) nucleophilic fluorination of acyl chlorides, and 4) acyl exchange reaction of carboxylic acid derivatives. These methods pose no problem for acyl fluoride synthesis and further transformations in various cross-coupling reactions.

1-2-1 Deoxyfluorination of Carboxylic Acid Derivatives

So far, many fluorinating reagents have been developed to synthesize acyl fluorides via deoxyfluorination of carboxylic acids or halogen exchange of acyl chlorides under the metal-free conditions. For the halogen exchange of acyl chlorides, the reported fluorinating sources include KF,[11] KHF_2,[12] HF,[13] SbF_3,[14] ZnF_2[15] and others.[16] In terms of deoxyfluorination of carboxylic acids, fluorinating reagents such as SF_4,[17] SeF_4,[18] cyanuric fluoride,[19] (diethylamino)sulfur trifluoride (DAST),[20] tetramethylfluoroformamidinium hexafluorophosphate,[21] benzyl fluoride[22] and so on[23] have been used in various acyl fluoride synthesis. Several selected examples on this topic are chosen to be introduced in this part.

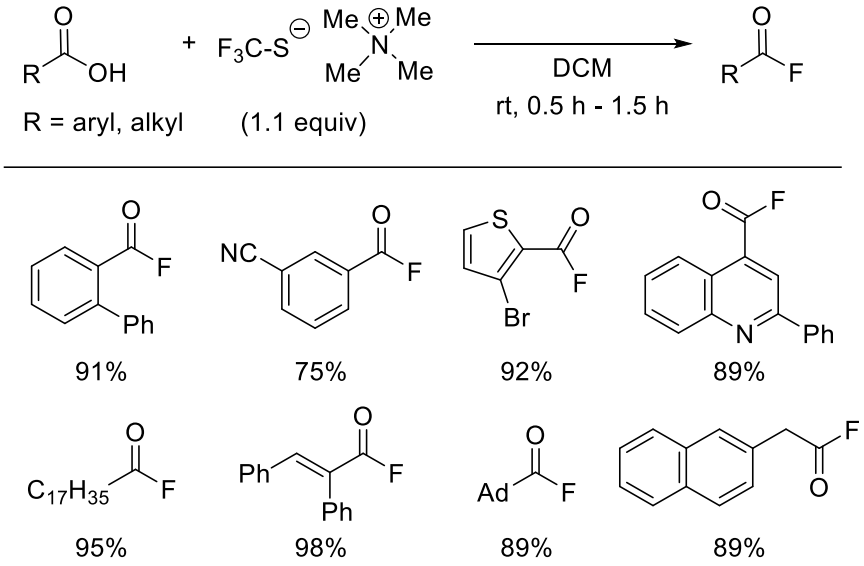
Pioneering works for the preparation of acyl fluorides from carboxylic acid derivatives such as carboxylic acids, carboxylic acid anhydrides, and acyl chlorides were contributed by Olah's group using HF or SeF_4/pyridine complex.[24]

More thermally stable and safer deoxofluorinating reagent Deoxo-Fluor ($(CH_3OCH_2CH_2)_2NSF_3$) than DAST ($(C_2H_5)_2NSF_3$) was designed and utilized in deoxyfluorination of carboxylic acids to form acyl fluorides in 1999.[25] The enhanced stability is rationalized by electron-rich alkoxy groups coordinated to the electron-deficient sulfur atom. Two substrates including benzoic acid and lauric acid were illustrated with Deoxo-Fluor reagent at 0 °C for 30 min to afford the corresponding acyl fluorides in 96%

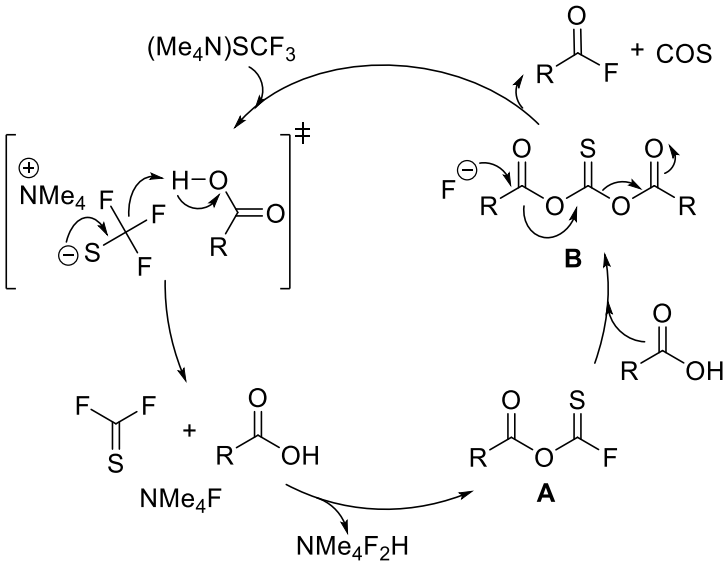
and 97% yields, respectively.

Bench-stable solid reagent $(Me_4N)SCF_3$ serving as the fluorine source was employed to selective deoxyfluorination of aromatic and aliphatic carboxylic acids at room temperature, in which additive and base-free conditions were enabled for high functional-group tolerance and easy purification of the target products (Scheme 1-1).[26] The salt $(Me_4N)HF_2$ forming as a byproduct could be easily removed by the addition of low polarity solvents, which highlighted the simplification and efficiency of this method.

Scheme 1-1. $(Me_4N)SCF_3$-Based Deoxyfluorination of Carboxylic Acids.



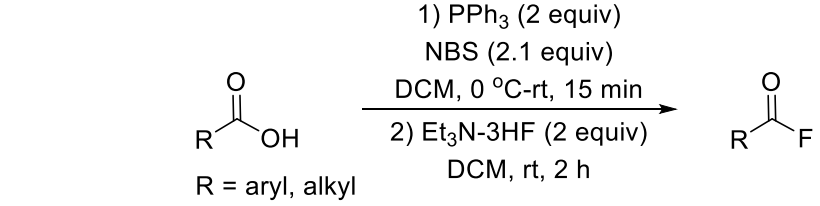
Scheme 1-2. Proposed Mechanism for $(Me_4N)SCF_3$-Based Deoxyfluorination of Carboxylic Acids.

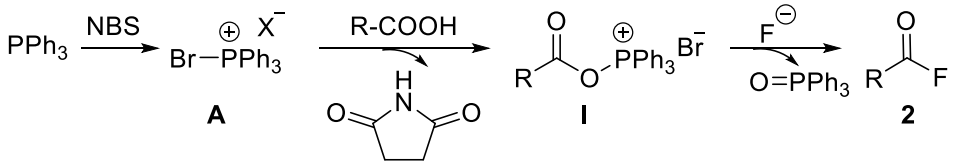


Combined with ReactIR and NMR spectroscopic analyses, proposed mechanism was shown in Scheme 1-2. $(Me_4N)SCF_3$ was activated by the carboxylic acid to form intermediate **A**, then reacted with a second molecule of carboxylic acid to produce intermediate **B**, which transformed to acyl fluorides and released the gaseous carbonyl sulfide (COS).

In 2019, a fast and simple method for deoxyfluorination of carboxylic acids is presented.[27] The protocol employed PPh_3, NBS, and Et_3N-3HF to afford acyl fluorides in excellent yields under mild conditions (Scheme 1-3). The protocol displays scalability, high functional-group tolerance, chemoselectivity, and easy purification of products. Deoxyfluorination of active pharmaceutical ingredients has also been established. A plausible mechanism was shown in Scheme 3. Bromophosphonium ion **A** was formed by oxidation of PPh_3 with NBS, then complex **A** reacted with carboxylic acids to afford acyloxyphosphonium intermediate **I**, which was identified by NMR spectroscopic methods. Acidic fluoride attacked at the C−acyl moiety of complex **I** to form acyl fluorides and triphenylphosphine oxide. Brønsted acidic conditions are essential for efficient C–F bond formation. When basic fluoride sources were employed, a fluoride ion was prone to attack at the phosphine center, which afforded Ph_3PF_2 as the major product along with minor acyl fluorides.

Scheme 1-3. HF-Mediated Deoxyfluorination of Carboxylic Acids.



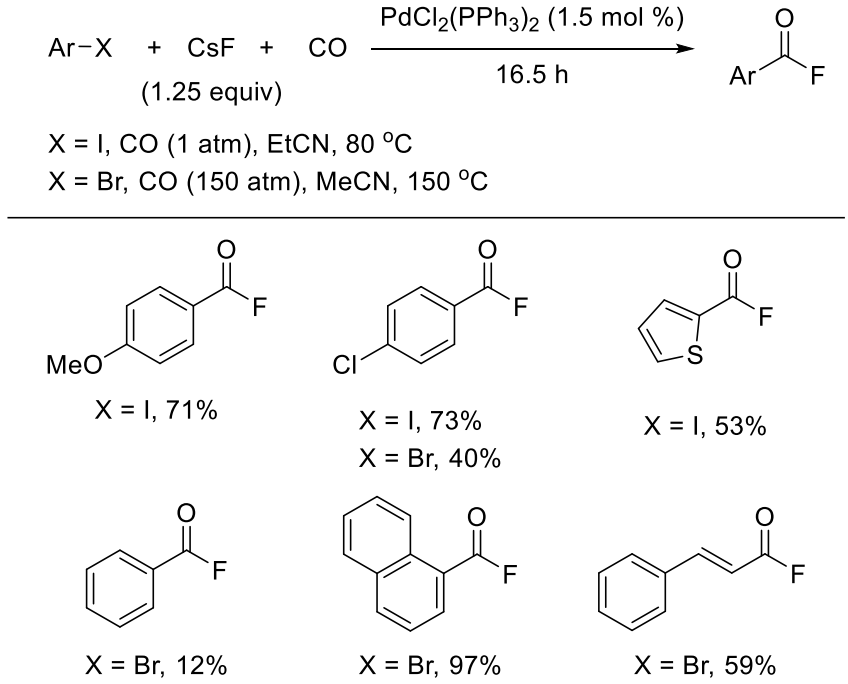


The deoxyfluorination of carboxylic acids is the most classical and reliable method to prepare acyl fluorides, which could extend to various acyl fluoride formations in a large scale synthesis, and the target acyl fluorides are stable enough to be isolated by column chromatography.

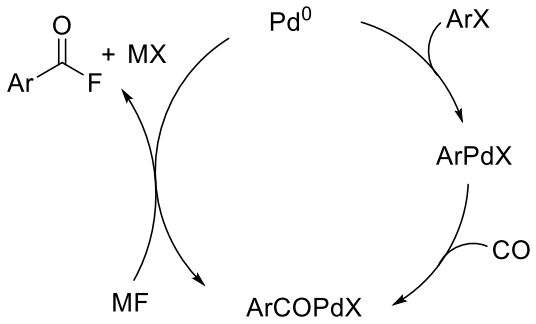
1-2-2 Palladium-Catalyzed Fluorocarbonylation of Aryl Halides

Another unique strategy to form acyl fluorides were designed via fluorocarbonylation of aryl halides. In 1987, Tanaka's group disclosed the carbonylation of aryl iodides or aryl/alkenyl bromides with cesium fluoride and a CO gas under the $PdCl_2(PPh_3)_2$ catalyst (Scheme 1-4).[28] Carbonylation of aryl iodides proceeded smoothly under an atmosphere of CO gas at 80 ℃ in EtCN. When aryl or alkenyl bromides as the substrates, higher CO pressure (150 atm) and temperature (150 ℃) were required.

Scheme 1-4. Pd-Catalyzed Carbonylative Fluoronation of Aryl Halides.



Scheme 1-5. Proposed Mechanism of Pd-Catalyzed Carbonylative Fluoronation.

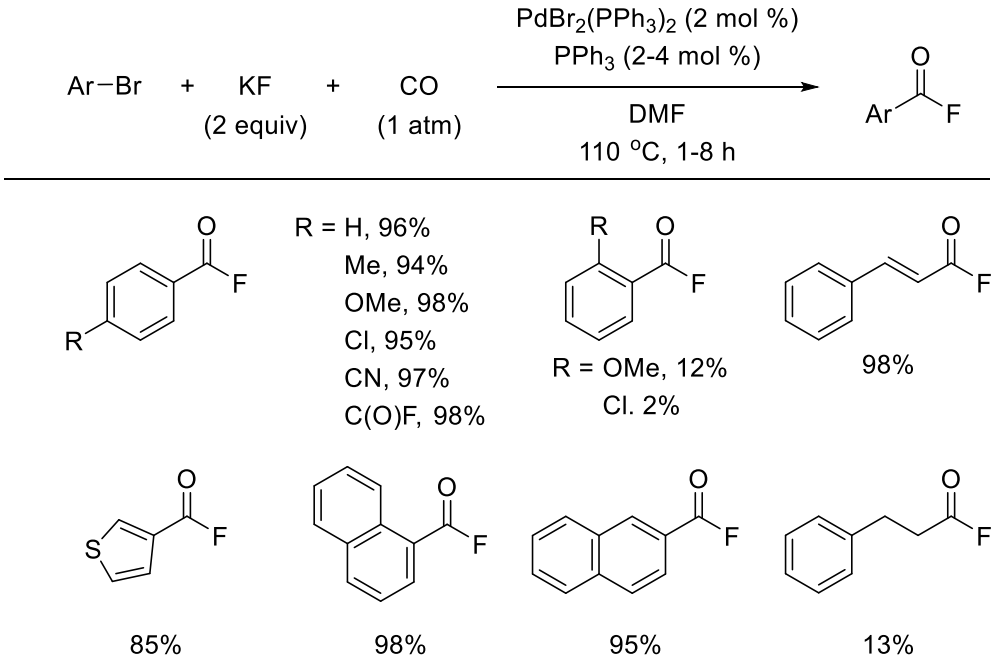


Classical mechanism was proposed as shown in Scheme 1-5. Oxidative addition of aryl

halides to the palladium(0) catalyst yielded arylpalladium(II) species, and subsequent CO insertion furnished acylpalladium intermediate, then finally nucleophilic attack of cesium fluoride to an acylpalladium complex gave the target acyl fluorides.

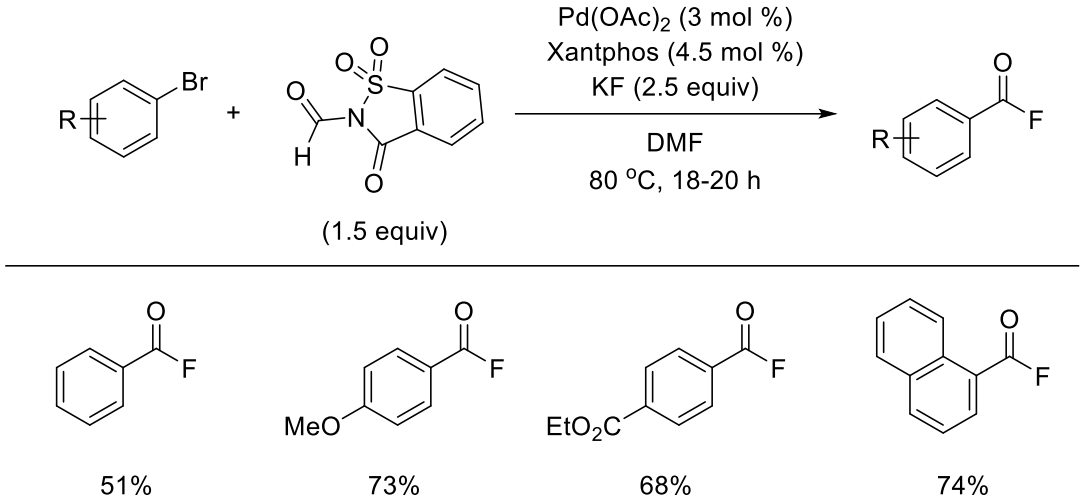
In 1992, an improved method by Okano's group was designed to complement the synthetic routes of acyl fluorides from readily available aryl bromides (Scheme 1-6).[29] This work was featured by carbonylation of aryl bromides under an atmosphere of CO gas at lower temperature. Although aryl bromides were well tolerated in the present transformation, the alkyl bromides except for benzylic bromides cannot be transformed to the corresponding acyl fluorides.

Scheme 1-6. Pd-Catalyzed Carbonylative Fluoronation of Aryl Bromides.



Due to the highly toxic nature and difficult handling of a CO gas, exploration of alternatives to a CO gas is highly desired. In 2013, Manabe employed *N*-formylsaccharin as a CO source in Pd-catalyzed carbonylation of aryl halides (Scheme 1-7).[30] Potassium fluoride played two roles in this reaction: one is acting as an activator to generate a CO gas from the crystalline *N*-formylsaccharin, the other is serving as a fluorine source in Pd-catalyzed fluorocarbonylation to synthesize acyl fluorides.

Scheme 1-7. Pd-Catalyzed Carbonylative Fluorination of Aryl Bromides without a CO Gas.



Palladium-catalyzed carbonylative fluorination of aryl halides also affords acyl fluorides. However, the utilization of noble palladium catalyst, toxic CO gas, as well as involvement of a large number reagents limited their application in the formation of acyl fluorides.

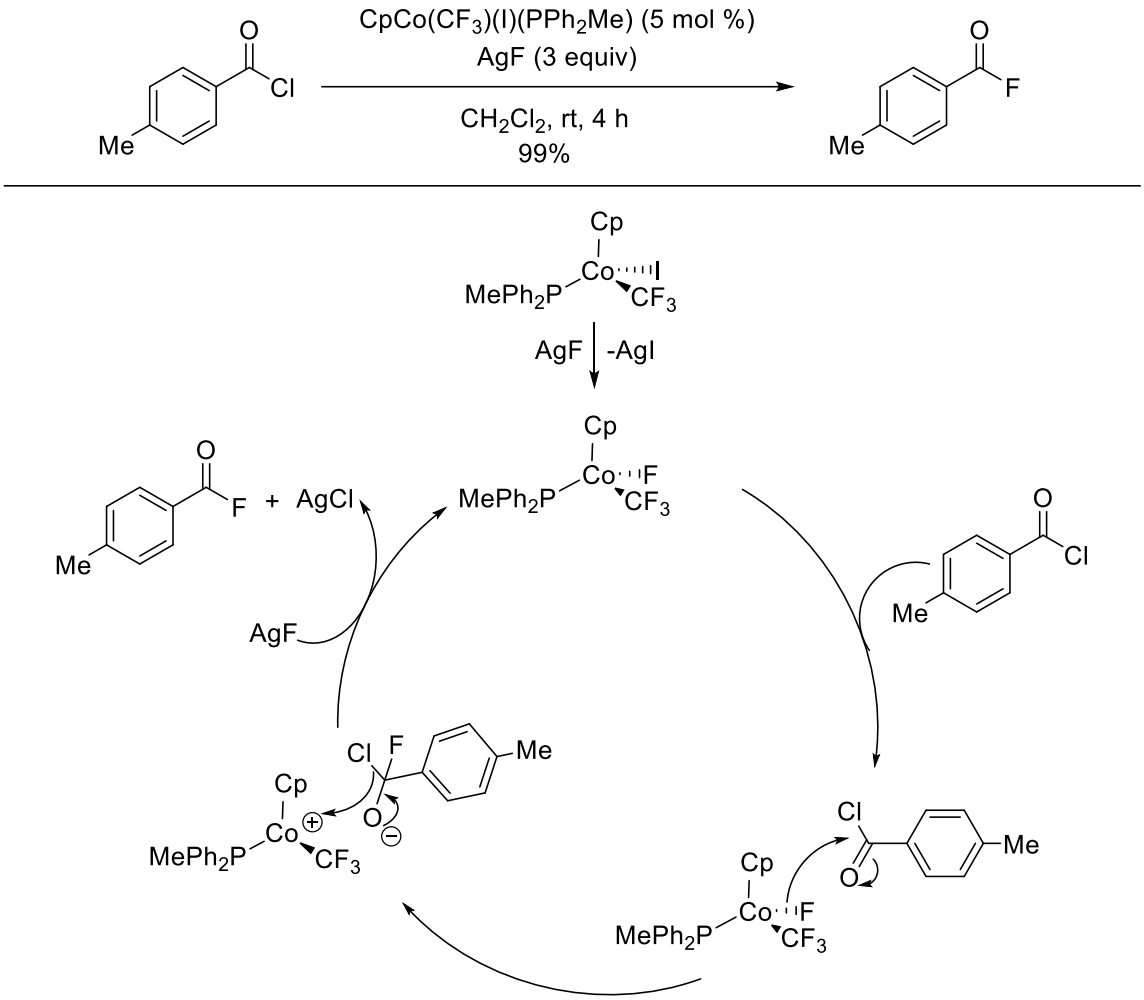
1-2-3 Nucleophilic Fluorination of Acyl Chlorides

Acyl fluorides could also be obtained from stoichiometric reactions of acyl chlorides with transition-metal complexes which are containing a naked fluorine atom via halogen exchange. First example was reported by Richmond and co-workers in 1994. A nucleophilic attack of benzoyl chloride and acetyl chloride to cobaltcenium fluoride $(Cp_2Co)F$ afforded benzoyl fluoride and acetyl fluoride quantitatively.[31] Apart from cobalt, late transition metal fluorides such as Bergman's $Cp^*Ir(Ph)(F)(PMe_3)$ [32] and Gray's fluoride complexes of bis(cyclometalated) Ir(III)[33] also participated in the stoichiometric acyl Cl/F replacement in high yields, due to the easily dissociation of a fluoride ion from the iridium center.

Fluorination of *p*-toluoyl chloride with AgF producing *p*-toluoyl fluoride in 99% yield was realized by adding a catalytic amount of $CpCo(CF_3)(I)(PPh_2Me)$ at room temperature. The author proposed mechanism as shown in Scheme 1-8.[34] Transmetalation between the iodocobalt complex and silver fluoride formed the fluorocobalt complex with an ionic Co−F bond, which reacted with an electrophilic carbon of acyl chloride to produce the corresponding acyl fluoride and chlorocobalt complex. Second transmetalation of AgF and the chlorocobalt complex regenerated the fluorocobalt complex to continue the catalytic

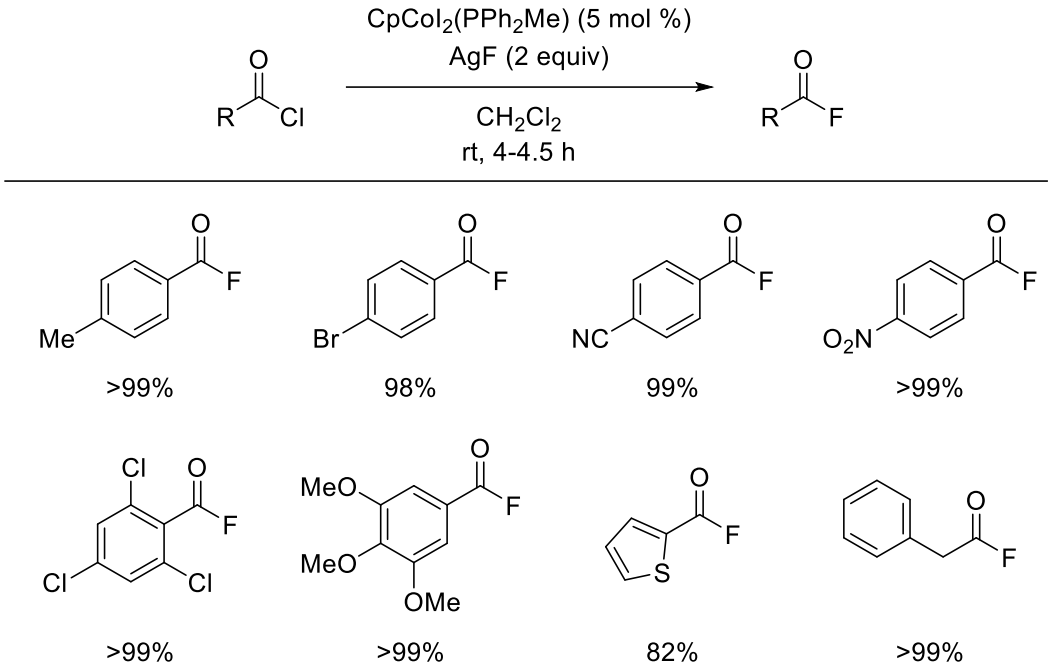
cycle.

Scheme 1-8. Proposed Mechanism for Co-Catalyzed Nucleophilic Fluorination of *p*-Toluoyl Chloride.



Two years later, similar cobalt complex $CpCoI_2(PPh_2Me)$ was reported in catalytic nucleophilic fluorination of acyl chlorides with AgF at room temperature for 4 to 4.5 h, in which a wide range of aromatic acyl fluorides regardless of electron-withdrawing and electron-donating functional groups, as well as 2-phenylacetyl chloride were all well tolerated with quantitative yields (Scheme 1-9).[35]

Scheme 1-9. Co-Catalyzed Nucleophilic Fluorination of Acyl Chlorides.



Although the synthesized cobalt and iridium complexes are readily promoted/catalyzed nucleophilic fluorination of acyl chlorides, the tedious pre-synthesis of these complexes and a stoichiometric addition of AgF render this method less used in acyl fluoride synthesis.

1-2-4 Acyl Transfer Reactions of Carboxylic Acid Derivatives

Yamaguchi's group also disclosed rhodium-catalyzed acyl transfer reaction between carboxylic acids derivatives and acyl fluorides[36]. Initial report pointed out that rhodium-catalyzed acyl exchange reactions of aryl esters, aryl thioesters or acylphosphine sulfide with acyl fluorides as fluoride precursors, produced acyl fluorides in equilibrium with the starting acyl fluorides. Using organic fluorides instead of acyl fluorides shifted the equilibrium with starting materials, including acyl transfer reactions of aryl esters with benzoylpentafluorobenzene and of aryl thioesters with hexafluorobenzene in the presence of $RhH(PPh_3)_4$ with different phosphine ligands.

1-3 Transformations of Acyl Fluorides

Acyl fluorides as one of carboxylic acid derivatives display many superiorities than other carboxylic acid derivatives, including ease availability, great stability, high reactivity and controllable selectivity. Therefore, the utilization of acyl fluorides as the acyl or aryl electrophiles are highly appealing and promising.[37]

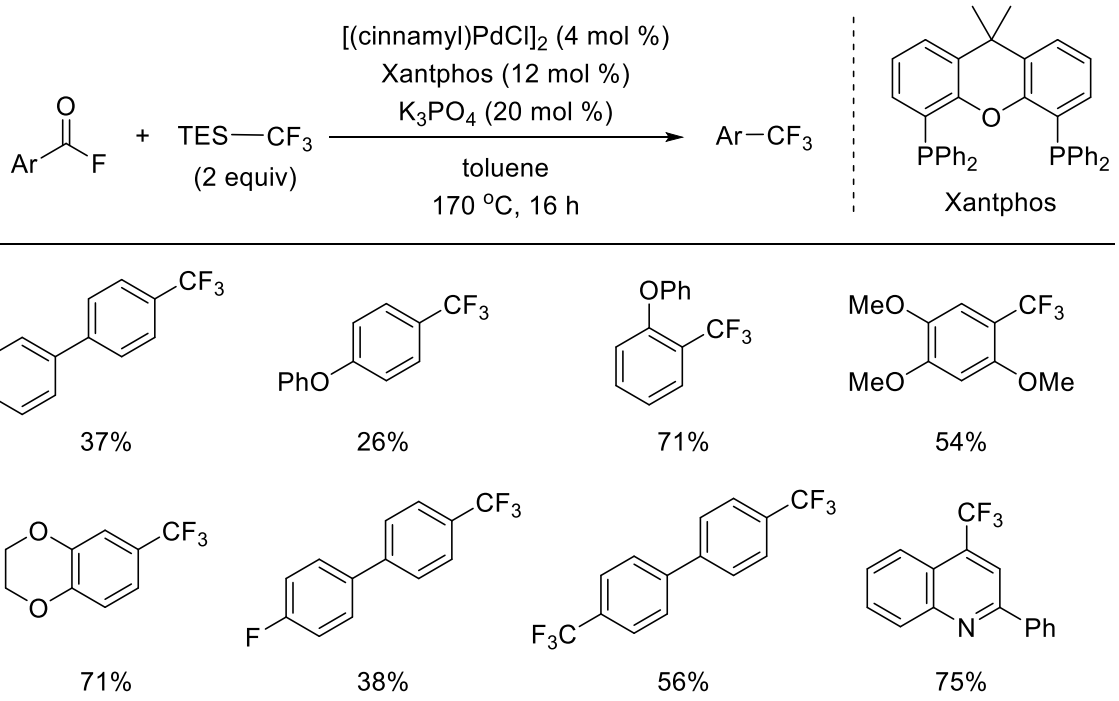
Recently, reactions of acyl fluorides serving as an arylation moiety via decarbonylative process for C−C bond formation have been extensively investigated, including trifluoromethylation,[38] reduction,[39] alkylation,[40] Suzuki-Miyaura type-arylation,[41] and direct C–H arylation.[42] Nishihara and coworkers have also reported the $Ni(cod)_2$/DPPE catalytic system for decarbonylative alkylation of acyl fluorides. The outcome suggested that utilization of acyl fluoride is the key to this transformation and other acyl halides cannot be participated.

Versatile building blocks of acyl fluorides rendered themselves applied in various transition-metal-catalyzed transformations, such as cross-couplings of Negishi,[43] Hiyama, [44] and Suzuki-Miyaura reactions[45] as the acyl fragment without a CO loss. Other reactions such as reductive coupling with vinyl triflates,[46] reduction,[39] C–H coupling with azoles,[47] and boroacylation of allenes[48] to give the corresponding ketones or aldehydes under carbonyl retentive manner also witnessed the role of acyl fluorides as the acylating sources.

1-3-1 Decarbonylative Transformations of Acyl Fluorides

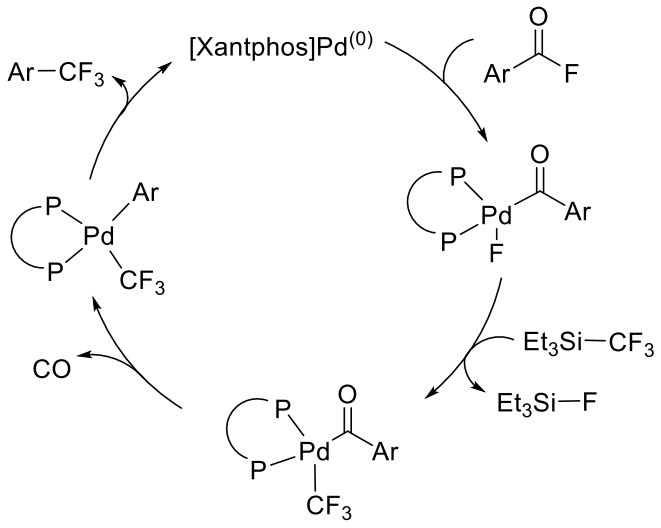
Since 2018, the decarbonylative transformations of acyl fluorides for carbon–carbon

Scheme 1-10. Pd-Catalyzed Decarbonylative Trifluoromethylation of Acyl Fluorides.



bond formation via transition-metal catalysis have attracted chemists' attention. Schoenebeck firstly reported decarbonylative trifluoromethylation of acid fluorides in the [(cinnamyl)PdCl]$_2$/xantphos catalytic system yielding trifluoromethylarenes (Scheme 1-10).[38] The challenges of this transformation are difficult reductive elimination of ArCF$_3$ from the corresponding palladium intermediate and ready transmetalation between the trifluoromethyl anions and weaker coordinating ligands. Unexpectedly, the utilization of acyl fluorides circumvents these challenges, realizing the first example of the use of a catalytic amount of xantphos in this transformation, and avoiding the addition of a stoichiometric amount of fluoride salts to activate trifluoromethylsilane.

Scheme 1-11. Proposed Mechanism for Pd-Catalyzed Decarbonylative Trifluoromethylation of Acyl Fluorides.

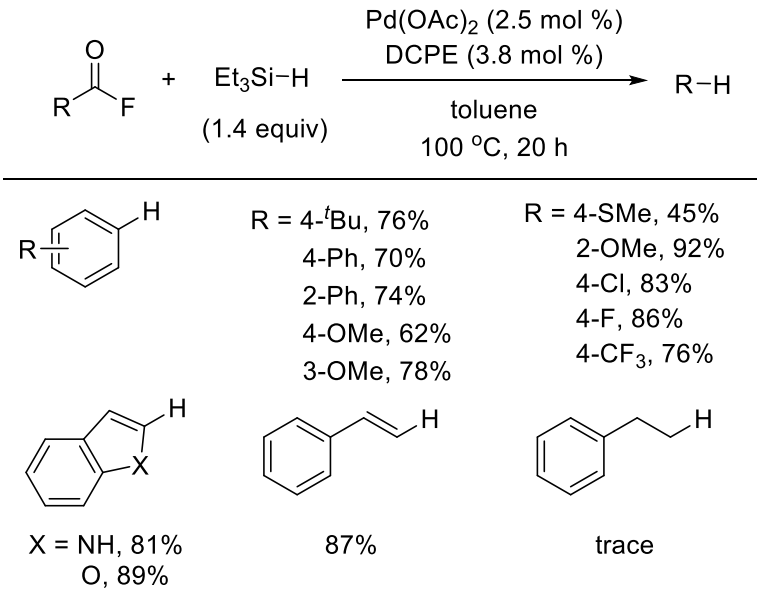


In this transformation, the author illustrated the favorable pathway based on the experimental results and computational data (Scheme 1-11). Initial step was oxidative addition of acyl fluorides to palladium(0) species to yield acylpalladium(II) species. Then, two possible pathways could be occurred: one is decarbonylation of acylpalladium species to furnish arylpalladium species with a CO loss, following transmetalation between the arylpalladium and Et$_3$Si–CF$_3$; the other is transmetalation of acylpalladium with Et$_3$Si–CF$_3$ prior to a decarbonylation step, followed by a CO gas extrusion affords arylpalladium species. Computational results demonstrated that a free energy barrier of decarbonylation of acylpalladium species is 27.3 kcal mol^{-1}. Whereas a lower activation free energy barrier of decarbonylation of already transmetalationed complex PhCO–Pd–CF$_3$ is 17.4 kcal mol^{-1},

which proved that decarbonylation of PhCO-Pd-CF_3 is more favorable than PhCO-Pd-F. Finally, reductive elimination gave the desire trifluoromethylarenes and regenerated the palladium catalyst. Therefore, the reaction sequence is oxidative addition, transmetalation, decarbonylation, and reductive elimination.

After that, palladium-catalyzed ligand-controlled decarbonylative reduction of acyl fluorides to arenes was developed by Sakai and Ogiwara (Scheme 1-12).[39] Various bidentate ligands were examined using 2-naphthoyl fluoride and triethylsilane as the model substrates under the $Pd(OAc)_2$ catalysis, and DCPE showed a superior result with the target product, naphthalene, in 82% yield (96:4 selectivity of naphthalene and 2-naphthyl aldehyde). The kinetic profiles suggested that the essential effect of Pd/P ratio for decarbonylative reduction was 1:2. An open coordination site at the palladium center was existed due to the 1:1 ratio of Pd/DCPE, which was favored for CO migration and insertion on palladium center.

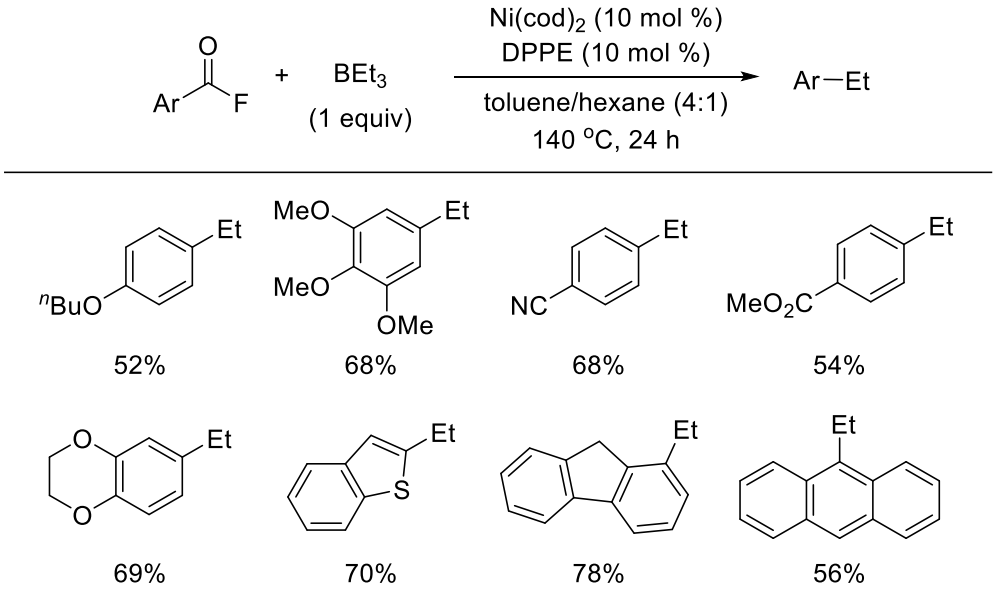
Scheme 1-12. Pd-Catalyzed Selectively Decarbonylative Reduction of Acyl Fluorides.



In 2018, Nishihara described the decarbonylative alkylation of acyl fluorides assisted by Lewis-acidic organoboranes under nickel catalysis (Scheme 1-13).[40] Triethylborane and trimethylboroxine as the alkyl sources were well tolerated in decarbonylative ethylation and methylation of acyl fluorides. Other alkylating reagents such as $SnMe_4$ and $SiMe_4$ to replace the alkylboranes were failed, which could be explained by the Lewis acidity of

organoboranes in acceleration of a transmetalation process. Notably, no alkylated products were observed when using other alternative carboxylic acid derivatives such as acyl chlorides, esters and thioesters, which further demonstrated the unique nature of acyl fluorides in this transformation.

Scheme 1-13. Ni-Catalyzed Decarbonylative Alkylation of Acyl Fluorides.

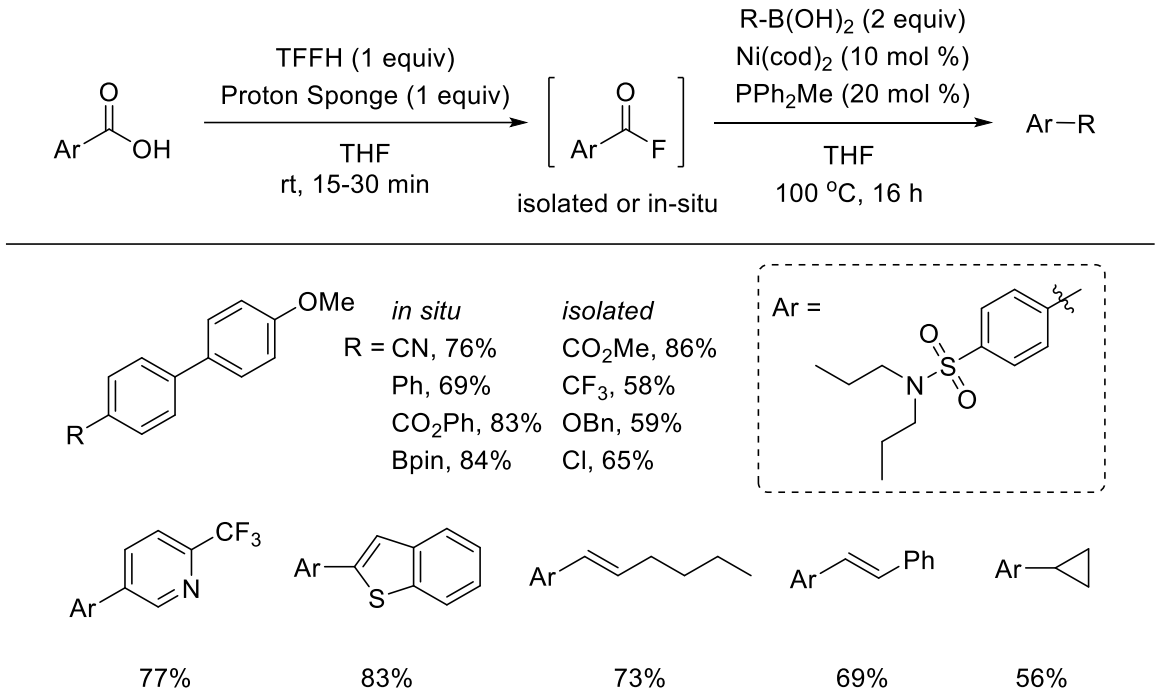


In 2018, Sanford's group reported $Ni(cod)_2/PPh_2Me$ catalytic system in decarbonylative Suzuki-Miyaura reaction of acyl fluorides without an exogenous base, which rendered a wide range of base-sensitive boronic acids and bioactive carboxylic acids were well compatible (Scheme 1-14).[41] In addition, isolated or in-situ formed acyl fluorides were prepared from the corresponding carboxylic acids under the optimized reaction conditions. This is the first example which demonstrates that fluorine from acyl fluorides could act as a mild base.

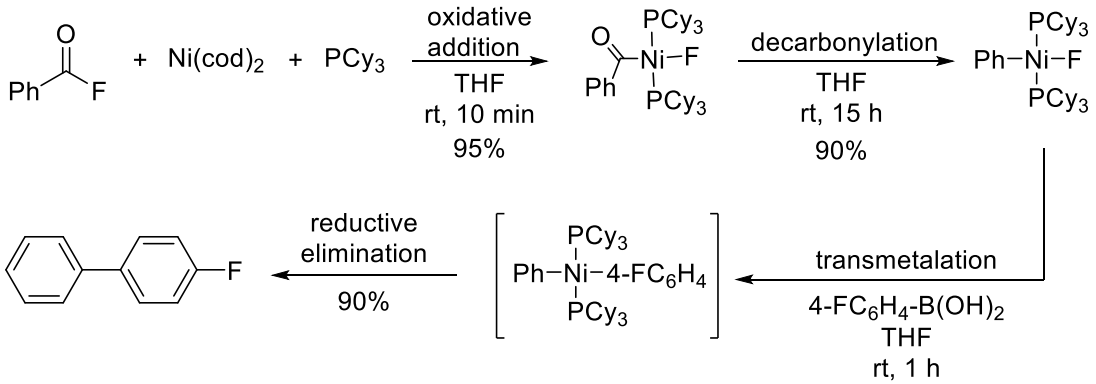
Extensive mechanistic experiments were performed to explain the possible pathway (Scheme 1-15). 1) Rapid oxidative addition of acyl fluorides to a Ni(0) catalyst to afford acylnickel fluoride species was observed at room temperature within 10 min using PCy_3 as the ligand. 2) Acylnickel fluoride species could undergo decarbonylation to yield 90% of arylnickel fluoride at room temperature after 15 h with the PCy_3 as the ligand. 3) Studies on acyl fluorides with a stoichiometric $Ni(cod)_2$ and phosphine ligands (PPh_2Me, PCy_3 and PEt_3) showed that the PPh_2Me proceeded much faster decarbonylation than PCy_3, and PEt_3

displaying very slow decarbonylation rate. 4) Comparison among the arylnickel fluoride, chloride, and bromide disclosed that only the former complex could participate in a transmetalation step with arylboronic acids. Subsequent reductive elimination afforded biaryls, which suggested that acyl fluorides as electrophiles could form the transmetalation active species.

Scheme 1-14. Base-Free Ni-Catalyzed Decarbonylative Suzuki-Miyaura Coupling of Acyl Fluorides.



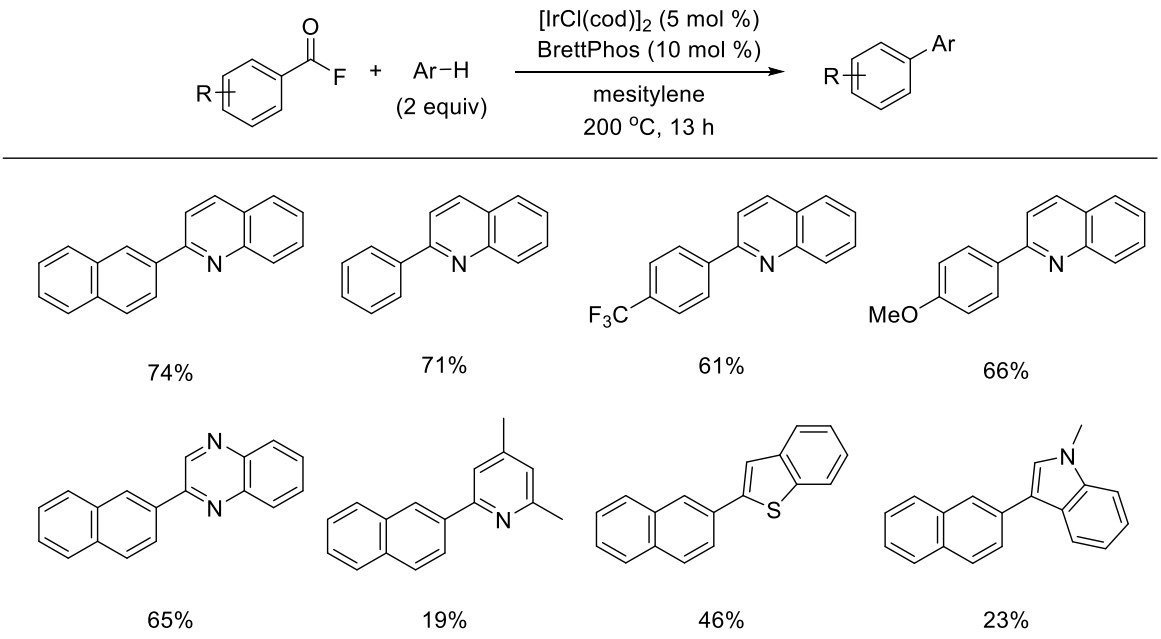
Scheme 1-15. Mechanistic Studies for Ni-Catalyzed Decarbonylative Suzuki-Miyaura Coupling of Acyl Fluorides.



Very recently, Tobius's group developed iridium/BrettPhos-catalyzed decarbonylative arylation of acyl fluorides with (hetero)arenes via C–H bond activation in mesitylene at 200 °C

for 13 h (Scheme 1-16).[42] A series of xylene, quinoline, and benzothiophene were well incorporated into acyl fluorides for biaryl synthesis in a decarbonylative manner. Besides benzoyl fluoride, other benzoic acid derivatives were evaluated, including benzoyl chloride, benzoate, benzoyl amide, benzoic acid, benzaldehyde, results showed only benzoyl fluoride could participate in this iridium-catalyzed arylation with (hetero)arenes, which indicated that fluorine played a key role in C–H activation. In this paper, the author assumed that the aryliridium species was formed from oxidative addition of acyl fluorides to iridium, followed by decarbonylation. For arenes, a fluorine atom of oxidative adduct abstracts a proton of arenes to yield a new aryliridium complex, followed by reductive elimination to give biaryls. In terms of heteroarenes, a nitrogen of quinoline coordinated to aryliridium species, then β-hydrogen elimination, followed by reductive elimination afforded heteroarenes.

Scheme 1-16. Ir-Catalyzed Decarbonylative Arylation of Acyl Fluorides via C–H Bond Activation.

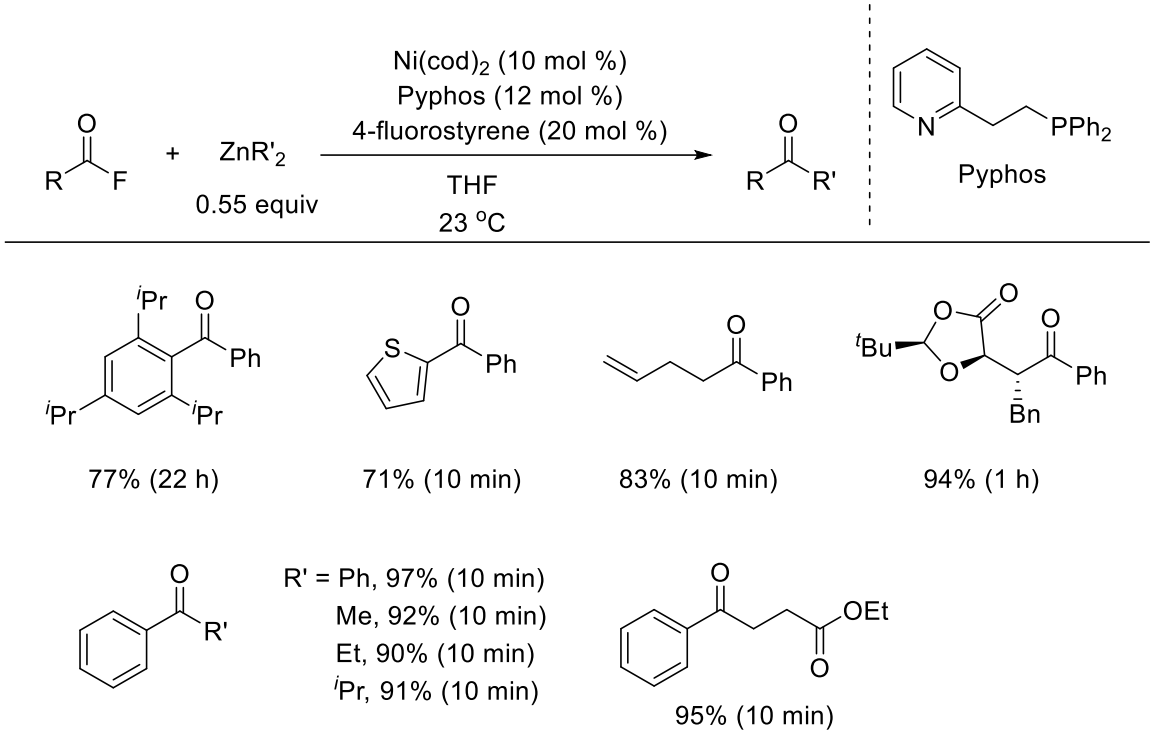


1-3-2 Carbonyl Retentive Transformations of Acyl Fluorides

Acyl fluorides acting as the acyl fragment without a CO loss in transition-metal-catalyzed cross-coupling reaction for the synthesis of biaryl ketones and aldehydes synthesis have been well documented. A pioneering work was disclosed by Rovis and Zhang in 2004.[43] They developed Ni/Pyphos-catalyzed Negishi reaction of acyl fluorides with organozinc

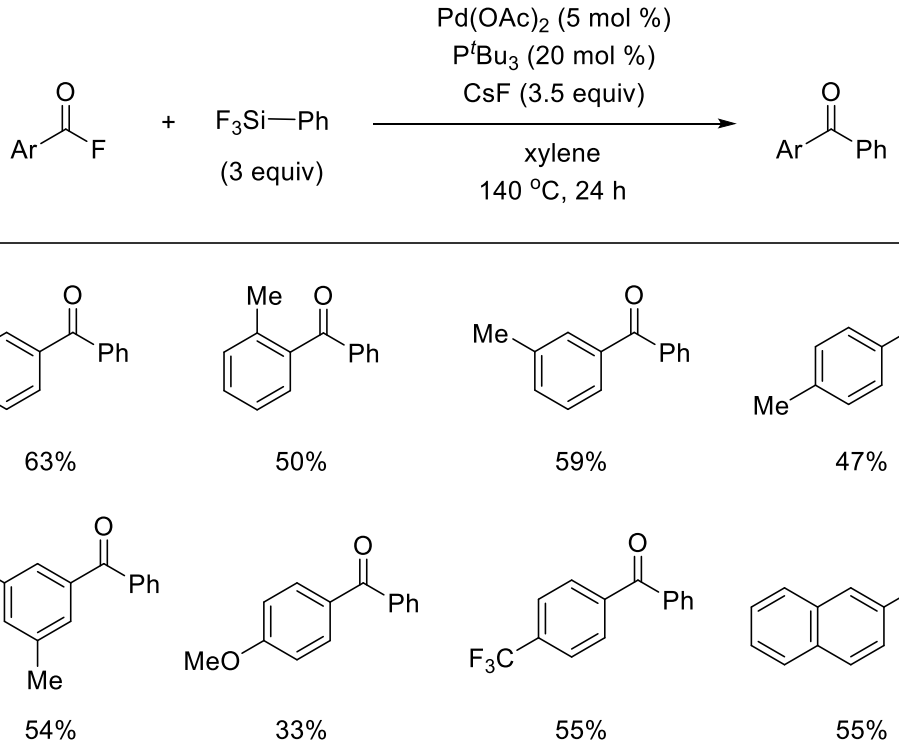
compounds in the presence of 20 mol % of 4-fluorostyrene at room temperature to afford a wide range of ketones. Notably, the reaction completed within 10 min in most cases. On the other hand, phenyl, methyl, ethyl, isopropyl, and alkyl ester-functionalized organozinc nucleophilies were also well tolerated in this reaction (Scheme 1-17).

Scheme 1-17. Ni-Catalyzed Negishi Coupling of Acyl Fluorides with Organozinc Reagents.

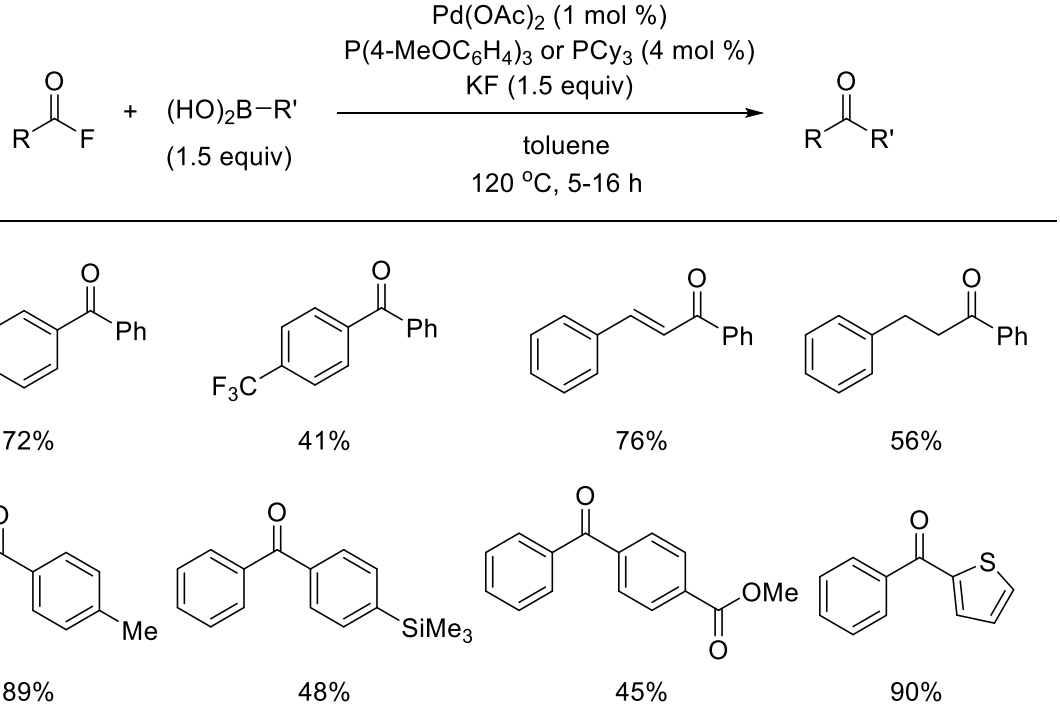


In 2016, Sakai and co-workers reported palladium-catalyzed acyl-aryl Hiyama coupling of acyl fluorides with aryltrifluorosilanes (Scheme 1-18).[44] A series of diaryl ketones were synthesized by using a $Pd(OAc)_2/P^tBu_3$ catalyst system in the presence of CsF at 140 °C for 24 h. The author believes that the proposed mechanism herein should be similar with the typical Hiyama cross-couplings. Initially, oxidative addition of acyl fluorides to palladium catalyst affords acyl palladium species. Subsequently, transmetalation between the acyl palladium species and pentacoordinated arylsilanes which was generated from arylsilanes and cesium fluoride, and the following reductive elimination of acyl(aryl)palladium complex results in the desired diaryl ketones, regenerating the palladium(0) catalyst.

Scheme 1-18. Pd-Catalyzed Hiyama Coupling of Acyl Fluorides with Arylsilanes.



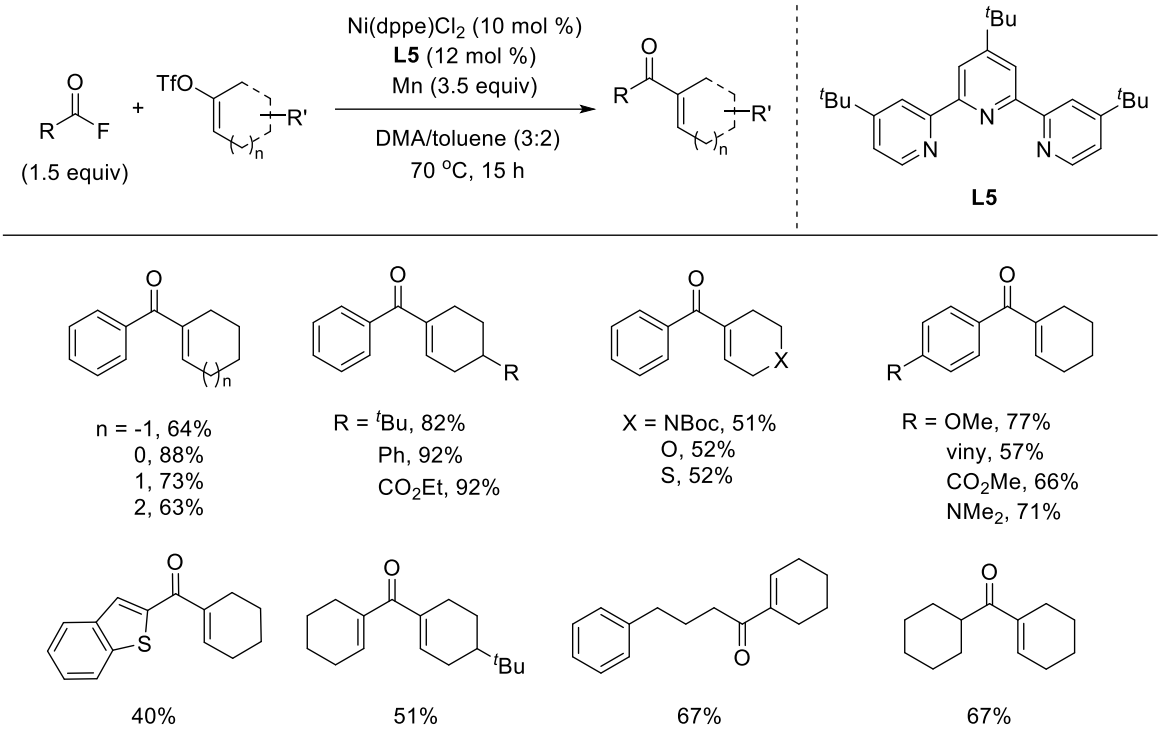
Scheme 1-19. Pd-Catalyzed Suzuki-Miyaura Coupling of Acyl Fluorides with Boronic Acids.



In 2017, Sakai and Ogiwara expanded the carbonyl retentive transformations of acyl fluorides into palladium-catalyzed Suzuki-Miyaura coupling with organoboron reagents

(Scheme 1-19).[45] Symmetrical and unsymmetrical ketones were obtained by the acyl coupling of acyl fluorides in the presence of $Pd(OAc)_2$ and $P(4\text{-}MeOC_6H_4)_3$ or PCy_3 under basic conditions in toluene at 120 °C for 20 h. Regardless of electronic effect, aryl, alkenyl, and alkyl acyl fluorides could be well incorporated to aryl/alkenylboronic acids.

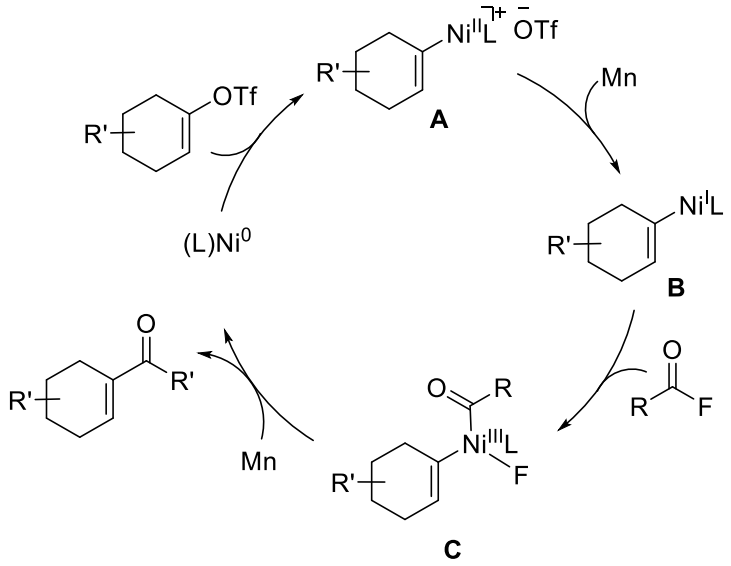
Scheme 1-20. Ni-Catalyzed Reductive Coupling of Acyl Fluorides with Vinyl Triflates.



Recently, first cross-electrophile reaction of acyl fluorides and reductive acylation of vinyl triflates was described by Shu's group.[46] Compared with conventional methods for ketone synthesis, this method is highlighted by the utilization of readily available, economic and stable electrophiles, acyl fluorides and vinyl triflates (Scheme 1-20), which avoided the involvement of acyl or vinyl metallic reagents. The utility of this protocol was demonstrated by the compatibility of aryl, vinyl, alkyl acyl fluorides with cyclic vinyl triflates, as well as late stage modification of complex molecules. The proposed mechanism assumed that vinyl triflates were favorable to oxidative addition to nickel(0) species to afford vinylnickel(II) intermediate **A**, which was reduced by Mn to yield vinylnickel(I) **B**. Then another oxidative addition of acyl fluorides to complex **B** furnished

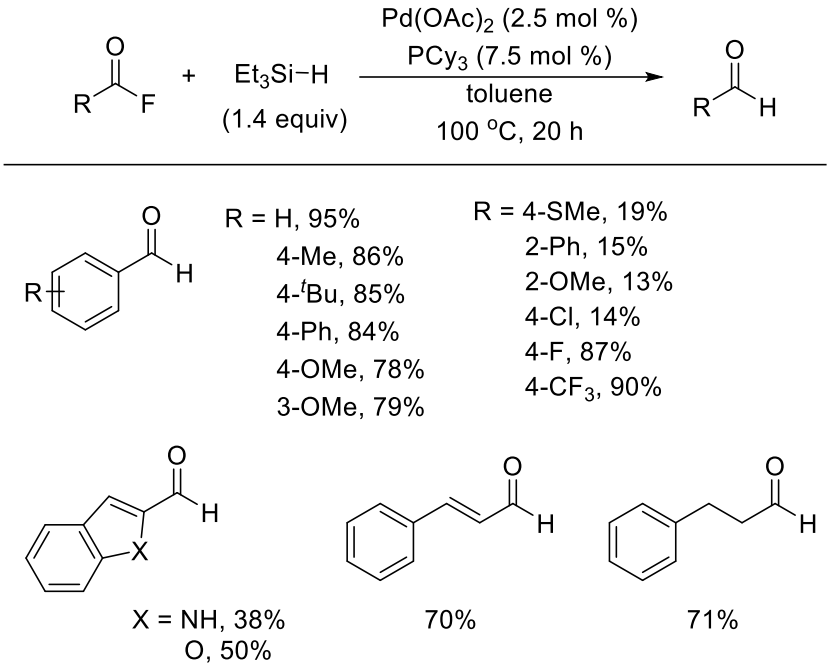
acylnickel(III) species **C**, and the following reductive elimination gave the desired enones, regenerating the Ni(0) catalyst in the presence of Mn (Scheme 1-21).

Scheme 1-21. Proposed Mechanism for Ni-Catalyzed Reductive Coupling of Acyl Fluorides with Vinyl Triflates.

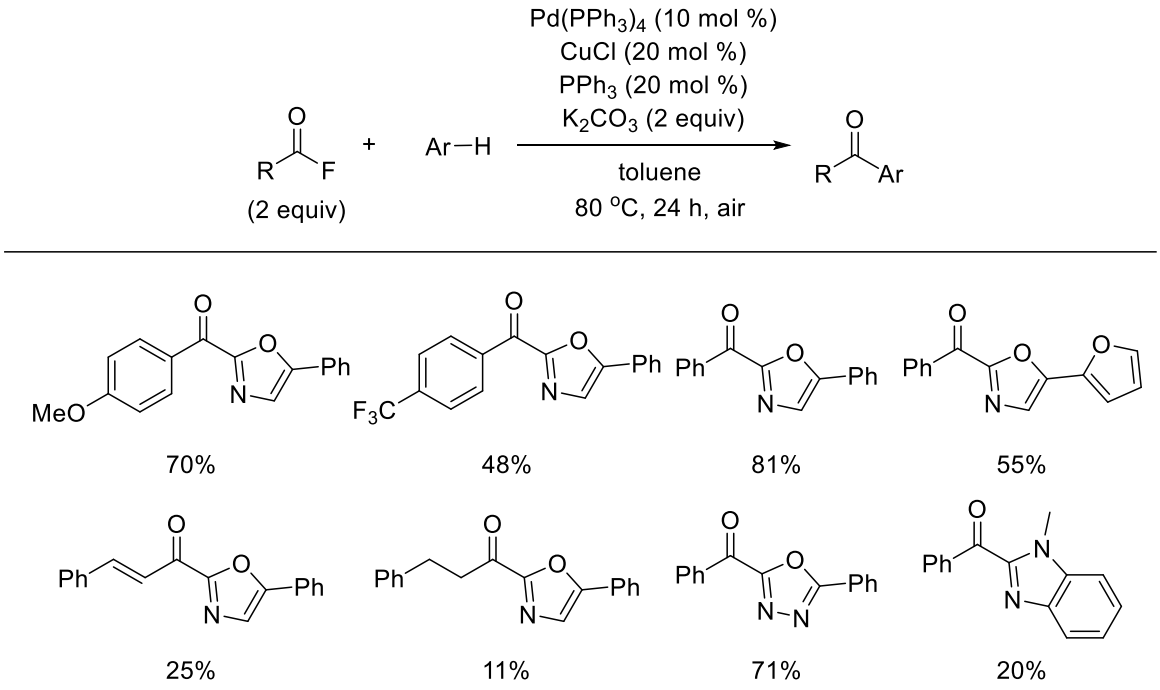


Selective reduction of acyl fluorides into aldehydes in a carbonyl retentive manner was controlled by the employed ligands (Scheme 1-22).[39] Screening of ligands in the reaction of 2-naphthoyl fluoride as the model substrate catalyzed by $Pd(OAc)_2$/P (Pd/P = 1:3) in the presence of 1.4 equiv of triethylsilane, non-decarbonylative progress was favored by using monodentate phosphine ligands such as electron-rich $P(4\text{-}MeOC_6H_4)_3$ giving the desired carbonyl retentive product, 2-naphthyl aldehyde, in 53% yield (with 85:15 selectivity of 2-naphthyl aldehyde and naphthalene). The best result was obtained by using PCy_3 as the ligand and no decarbonylative by-product naphthalene was observed. Alkyl, alkoxy, phenyl, fluorine, and trifluoromethyl groups at *para*-position were well tolerated under the optimized reaction conditions. However, benzoyl fluoride bearing methoxy and phenyl substituents at *ortho*-position gave the decreased yield and selectivity. The author believes that 1:3 ratio of palladium and phosphine was essential for the carbonyl retentive process due to the formation of coordinatively saturated acylpalladium complex bearing three monodentate phosphines.

Scheme 1-22. Pd-Catalyzed Selective Reduction of Acyl Fluorides.



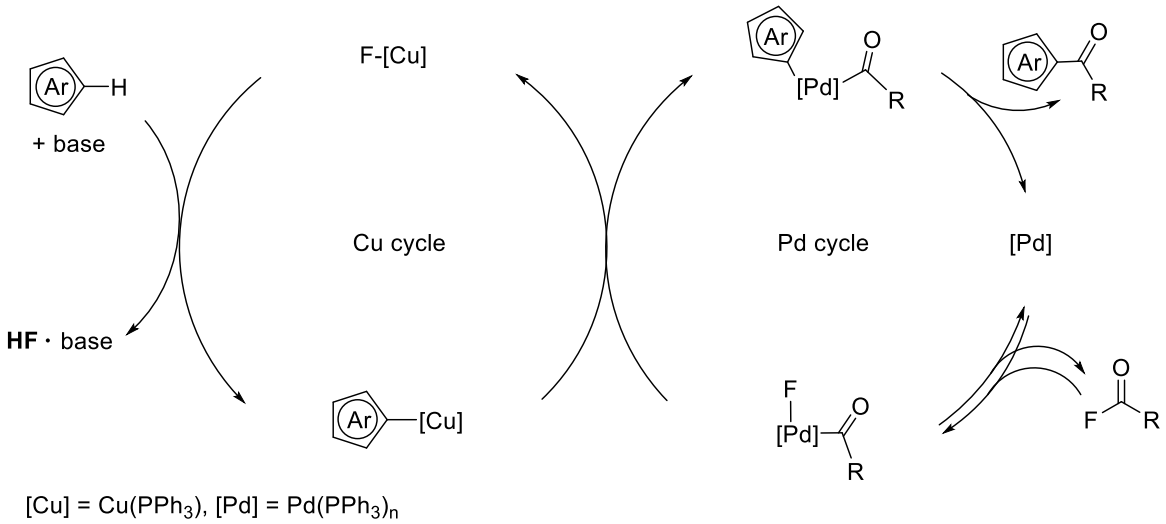
Scheme 1-23. Pd/Cu-Cocatalyzed C–H/C–F Coupling of Acyl Fluorides and Azoles.



Bimetallic palladium/copper catalytic system with triphenylphosphine-catalyzed acylation of azoles via C–H bond activation was developed in 2019 (Scheme 1-23).[47] The

combination of $Pd(PPh_3)_4$ with CuCl was essential to this reaction, as well as the presence of K_2CO_3. Notably, transformation could proceed smoothly at 80 ℃ under an atmosphere of air. Aroyl fluorides showed higher reactivity than vinyl and aliphatic acyl fluorides. In all substrates, small amounts of the decarbonylative coupling products were detected, especially by conducting the reaction in higher temperature like 140 ℃.

Scheme 1-24. Plausible Mechanism for Pd/Cu-Catalyzed C–H/C–F Coupling of Acyl Fluorides and Azoles.

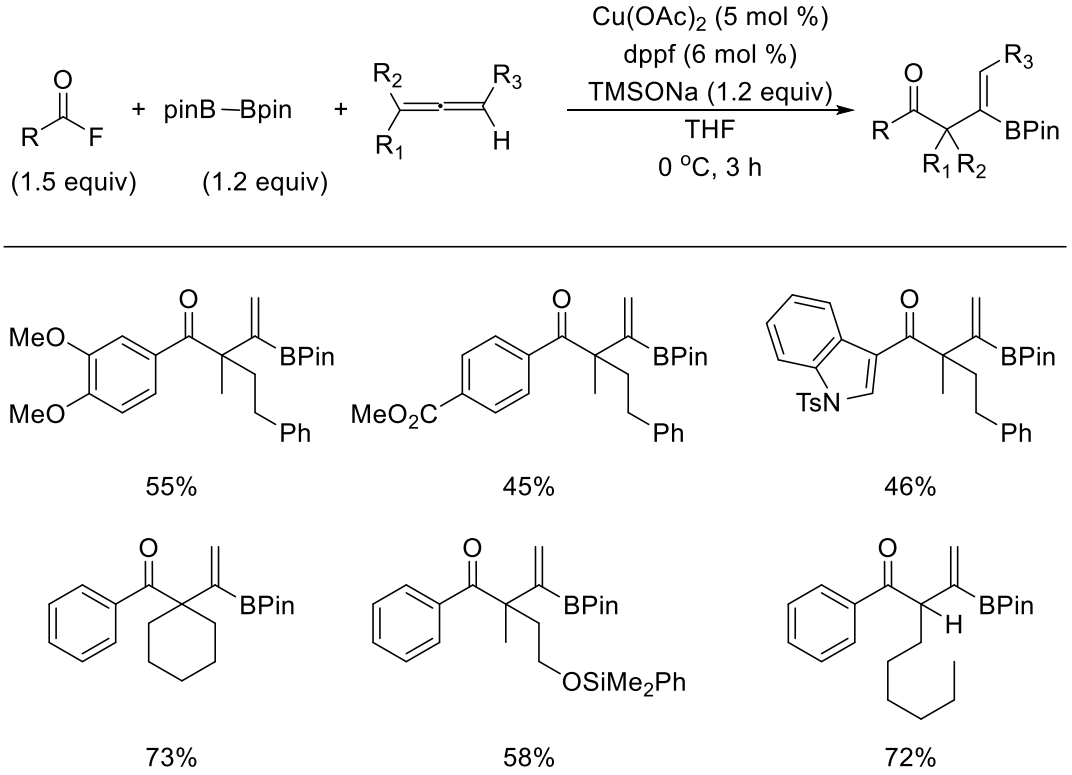


[Cu] = $Cu(PPh_3)$, [Pd] = $Pd(PPh_3)_n$

Plausible mechanism is illustrated in Scheme 1-24. In a palladium cycle, a reversible oxidative addition of acyl fluorides to palladium(0) species afforded acylpalladium(II) species. At the same time, $Cu(X)PPh_3$ activated aromatic C–H bond of azoles with the aid of the base to generate arylcopper species. Transmetalation of arylcopper species with acylpalladium complex furnished acyl(aryl)palladium(II) species, the following reductive elimination yielded ketones as the products.

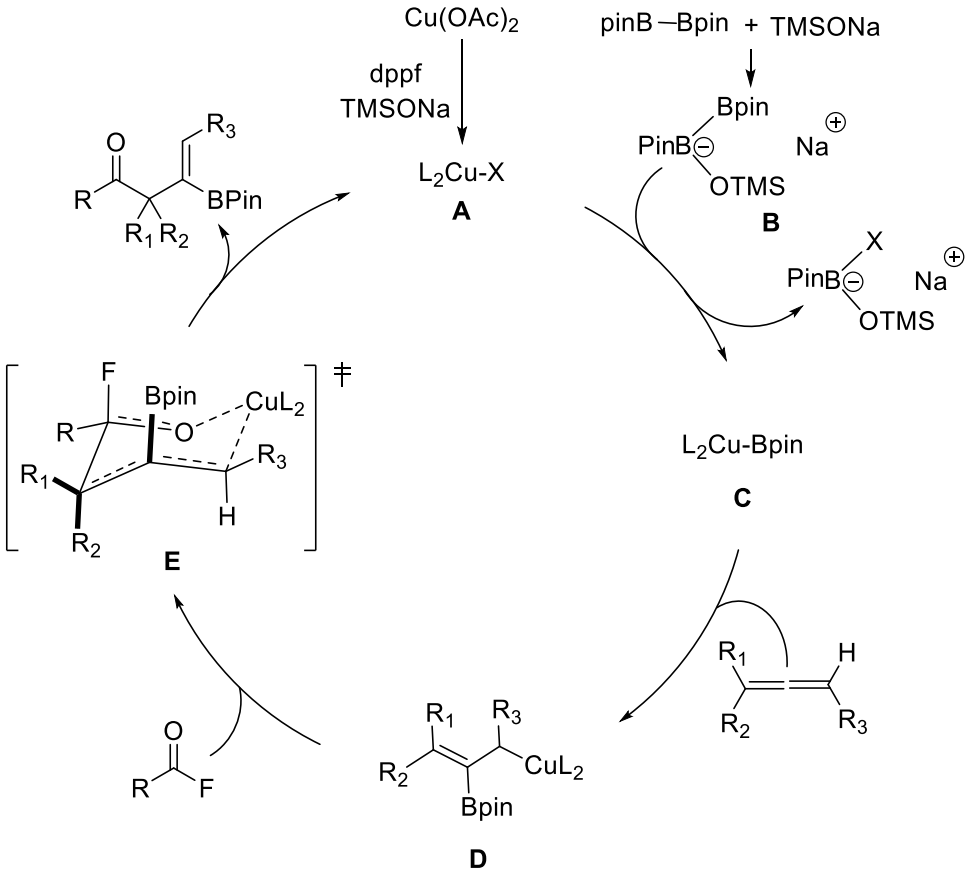
Copper-catalyzed three-component boroacylation reaction of acyl fluorides, allenes, and bis(pinacolato)diboron was reported in 2017 by Riant's group (Scheme 1-25).[48] In this transformation, acyl fluorides were proved to be an efficient acylating reagent than their corresponding carboxylic analogues such as acyl chlorides. This is the first example that copper was employed to functionalize acyl fluorides, resulting in a library of β-boryl β,γ-unsaturated ketones.

Scheme 1-25. Cu-Catalyzed Three-Component Boroacylation of Acyl Fluorides.



Based on the relative references and experimental results, the author proposed the mechanism as shown in Scheme 1-26. Initially, reduction of $Cu(OAc)_2$ by the DPPF ligand and potassium trimethylsilanolate (TMSONa) as a Lewis base generated Cu(I) species. Activation of diboron by TMSONa afforded complex **B**. Then Cu–B species **C** was produced through σ-bond metathesis between complexes **A** and **B**. Complex **C** regioselectively inserted into less-substituted C–C bond in allenes to yield the nucleophilic allylcopper species **D**, which reacted with electrophilic acyl fluorides via a six-membered **E** to form the target ketones and regenerated Cu(I) species.

Scheme 1-26. Proposed Catalytic Cycle for Cu-Catalyzed Boroacylation of Acyl Fluorides.


Cu(OAc)2
dppf
TMSONa
L2Cu-X
A
pinB–Bpin + TMSONa
Bpin
PinB
Na
OTMS
B
X
PinB
Na
OTMS
L2Cu-Bpin
C
R1
H
R2
R3
R1
R3
R2
CuL2
Bpin
D
O
R
F
F
Bpin
CuL2
R
O
R3
R1
H
R2
E
O
R
R3
BPin
R1 R2

1-4 Summary

A various synthetic routes and widespread transformations of acyl fluorides have been introduced in this Chapter, which makes a solid foundations for development of novel transformations of acyl fluorides. Encouraged by a unique nature of acyl fluorides in various carbonyl retentive and decarbonylative C−C bond-forming reactions, transformations of acyl fluorides in C−heteroatom bond-forming reactions and the synthesis other valuable compounds synthesis from acyl fluorides are worthy of exploration.

1-5 References

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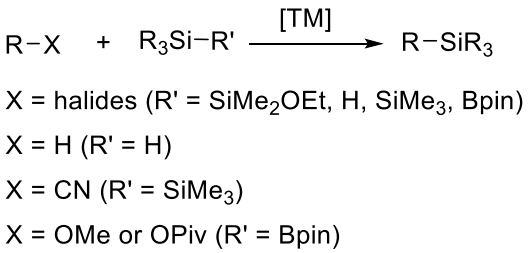
CHAPTER 2

Nickel/Copper-Cocatalyzed Decarbonylative Silylation of Acyl Fluorides

2-1 Introduction

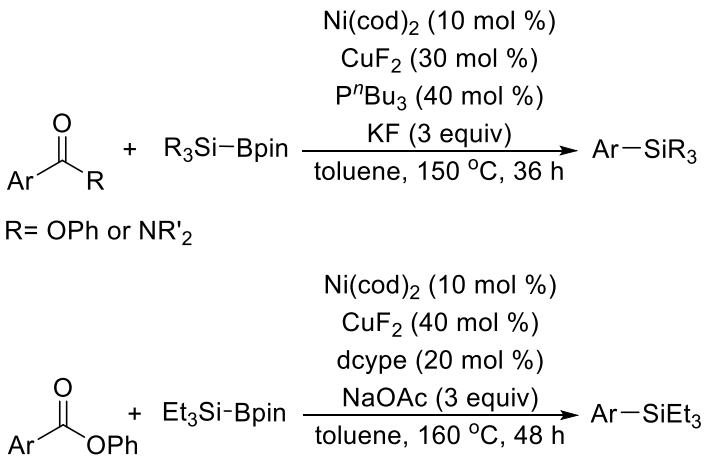
Since organosilicon compounds are of a great importance in organic synthesis,[1] drug discovery[2] and materials science,[3] various synthetic strategies have been established by constructing the carbon-silicon bond. Traditional synthetic methods of arylsilanes involve the reactions of Grignard or organolithium reagent with silyl electrophiles,[1a,4] in which ester and ketone functional groups cannot be incorporated. Alternatively, transition-metal-catalyzed silylation of aryl halides has been developed for the preparation of arylsilanes.[5] Although defluorosilylation of fluoroarenes via C−F bond activation has been reported recently, the synthesis of the starting materials requires multi-step reactions.[6] In addition, a direct C−H silylation of unreactive aromatic compounds with hydrosilanes were also investigated to obtain arylsilanes.[7] Furthermore, silylation of nitriles with disilanes via C−CN bond cleavage[8] and of pivalates or anisoles with silylboranes via C−O bond cleavage[9] provided a new access to arylsilanes (Scheme 2-1).

Scheme 2-1. Conventional Methods for Arylsilanes Synthesis.



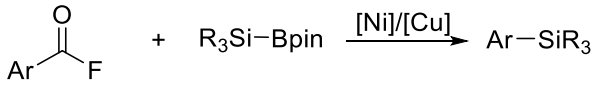
Utilizing decarboxylation/decarbonylation, transformations of carboxylic acid and their derivatives into valuable compounds under transition metal catalysis have drawn much attention owing to their natural abundance and easy availability.[10] Among them, early study found that palladium-catalyzed silylation of acyl chlorides bearing strong electron-withdrawing groups with hexamethyldisilanes gave a mixture of acylsilane and arylsilane, in which the selective decarbonylative silylation of acyl chlorides was observed with chlorinated disilanes.[11] Rueping[12] and Shi[13] independently succeeded in nickel/copper-cocatalyzed decarbonylative silylation of phenolic esters via C−O bond cleavage. Building up on the previous work, Reuping expanded the decarbonylation silylation strategy for arylamides via C−N bond cleavage (Scheme 2-2).[14]

Scheme 2-2. Decarbonylative Silylation of Phenolic Esters.



Due to the indispensable and versatile main group elements, namely, boron, silicon, and tin in cross-coupling chemistry,[15] carbon-heteroatom bond-forming reactions of acyl fluorides are highly desired. Encouraged by a unique nature of acyl fluorides in various decarbonylative C−C bond-forming reactions and our continuous interest of acyl halides in cross-coupling reactions,[16] we have developed nickel-catalyzed borylation[17] and stannylation[18] of acyl fluorides with diborons and silylstannanes, respectively, in a decarbonylation manner. In this Chapter, The Author reported a new approach to the synthesis of arylsilanes by nickel/copper-cocatalyzed decarbonylative silylation of acyl fluorides with silylboranes (Scheme 2-3).

Scheme 2-3. Ni/Cu-Catalyzed Decarbonylative Silylation of Acyl Fluorides.



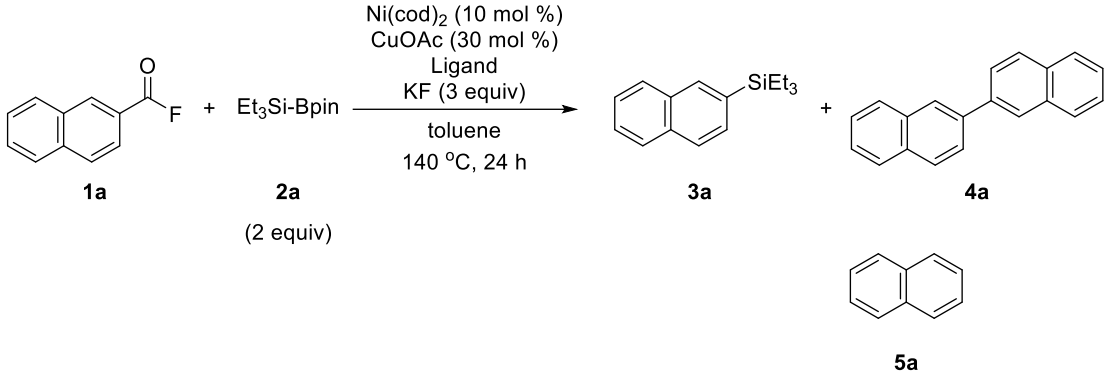
2-2 Results and Discussion

2-2-1 Decarbonylative Silylation of 2-Naphthoyl Fluoride with Et_3Si-Bpin

Initially, we chose Ni-catalyzed 2-naphthoyl fluoride (**1a**) and silylborane **2a** in the presence of KF as the model reaction, inexpensive and stable PPh_3 was preferred ligand due to its excellent performance in nickel-catalyzed decarbonylative borylation.[17] However, only 5 % silylated product **3a** was detected, along with the large amount of

silylborane unconsumed. At the same time, 22% of naphthalene derived from decarbonylative reduction and 58% of 2,2'-binaphthalene derived from decarbonylative homocoupling reaction were observed. This outcome revealed that nickel/PPh_3 catalytic system cannot efficiently activate **2a** to promote the transmetalation step with the oxidative addition adduct. Thus, CuOAc was added based on the reported profound effect of copper salts in activation of Si–B bond,[19] as expected, 85% of **3a** was obtained with 10% naphthalene byproduct (Table 2-1, entry 1). Notably, the introduction of copper salt inhibited the completing decarbonylative homocoupling reaction, as well as suppressed the decarbonylative reduction. However, the attempt to decrease the amount of PPh_3 was failed, the yield of desired product **3a** was decreased along with the decreasing loading of PPh_3 (entries 1-4). Therefore, the optimized ration of Ni/P is 1:4. Other monodentate phosphine ligands such as $P(OPh)_3$, P^nBu_3 and PCy_3 were also examined, moderate to poor activities were observed in this transformation (entries 5-7). Bidentate phosphine dcype which is proposed to facilitate reductive elimination step due to its *cis*-configuration, afforded decarbonylative silylation product **3a** in 50% of GC yield (entry 8). Even the P^nBu_3 and dcype showed excellent performances in $Ni(cod)_2/CuF_2$ catalytic system for decarbonylative silylation of phenolic esters, in our case, PPh_3 was well matched for the transformations of acyl fluorides.

Table 2-1. Optimization of Ligand in Ni/Cu Cocatalyzed Decarbonylative Silylation Reaction of **1a**.[a]



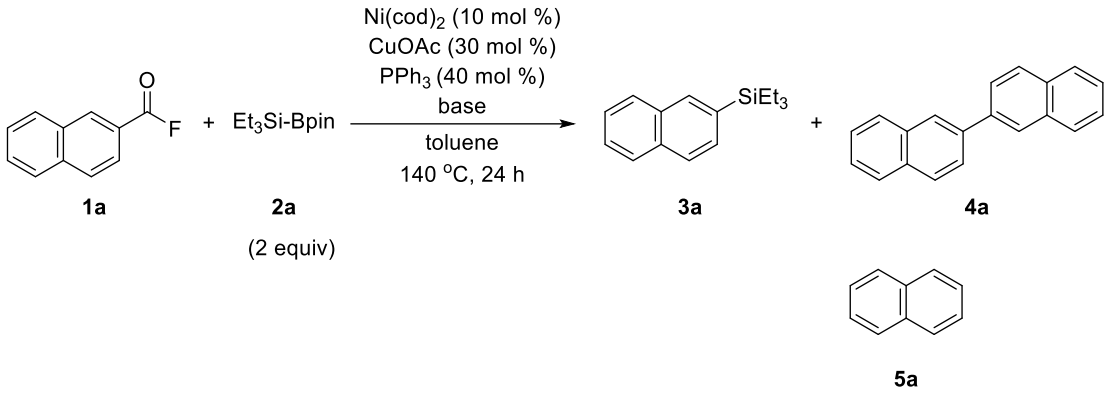
entry	ligand (mol %)	**1a** (%)[b]	**2a** (%)[b]	**3a** (%)[b]	**4a** (%)[b]	**5a** (%)[b]
1	PPh_3 (40)	0	63	85	0	10
2	PPh_3 (30)	0	0	53	0	11

3	PPh_3 (20)	0	41	49	6	15
4	PPh_3 (10)	12	68	48	6	10
5	$P(OPh)_3$ (40)	0	66	11	0	26
6	P^nBu_3 (40)	0	0	32	0	7
7	PCy_3 (40)	0	0	50	8	14
8	dcype (20)	0	0	50	0	16

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), CuOAc (0.06 mmol) and KF (0.6 mmol) in toluene (1.0 mL) at 140 ℃ for 24 h. [b]Determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard.

Though acyl fluorides could act as a mild base in some cases,[20] exogenous base is still required in the present silylation reaction (Table 2-2). Initially, different alkali metal halides including LiF, NaF, KF and CsF as the base were tested (entries 1-4). Among them, KF gave the superior results with **3a** in 85% yield, which demonstrated the suitable size of alkali metal cation is important in this transformation (entry 3). When employed 2 and 1 equiv KF in the certain reaction conditions, the yield of **3a** was decreased to 68% and 42%, respectively (entries 5-6). It may be due to the poor solubility for KF in toluene. The utilization of potassium acetate and potassium *tert*-butoxide instead of potassium fluoride were examined, and potassium acetate afforded the comparable result with potassium fluoride (entry 7), whereas no silylated product **3a** was detected when using potassium *tert*-butoxide as the base, because the byproduct *tert*-butyl 2-naphthoate was observed by the side reaction of 2-naphthoyl fluoride (**1a**) with *tert*-butoxide anion (entry 8).

Table 2-2. Optimization of Base.[a]



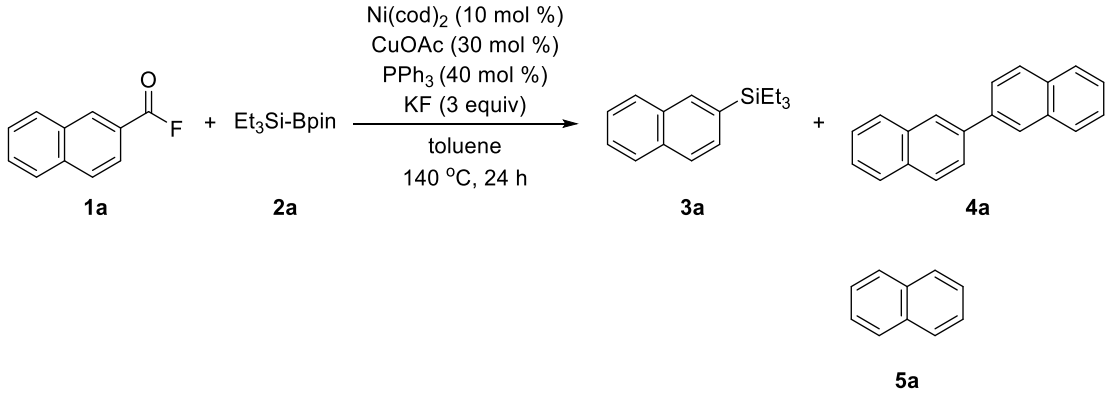
1a **2a** **3a** **4a** **5a**

entry	base (equiv)	**1a** (%)[b]	**2a** (%)[b]	**3a** (%)[b]	**4a** (%)[b]	**5a** (%)[b]
1	LiF (3)	0	14	45	0	0
2	NaF (3)	0	0	49	0	0
3	KF (3)	0	63	85	0	10
4	CsF (3)	0	0	18	0	8
5	KF (2)	0	27	68	6	13
6	KF (1)	0	0	42	16	16
7	KOAc (3)	0	0	71	6	5
8	KO^{t}Bu (3)	0	18	0	0	6

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), CuOAc (0.06 mmol) and PPh_3 (0.08 mmol) in toluene (1.0 mL) at 140 ℃ for 24 h. [b]Determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard.

From the result of Table 2-3, 63% silylborane **2a** was unconsumed in the reaction of **1a** with 2 equivalent of **2a** (entry 1). Therefore, the amount of silylborane **2a** was investigated, unfortunately, the yields of **3a** were dramatically reduced to 28% and 37% with the 1 and 1.5 equivalent of **2a** employed in this reaction, respectively (entries 2-3).

Table 2-3. Optimization the Amount of Silylborane **2a**.[a]

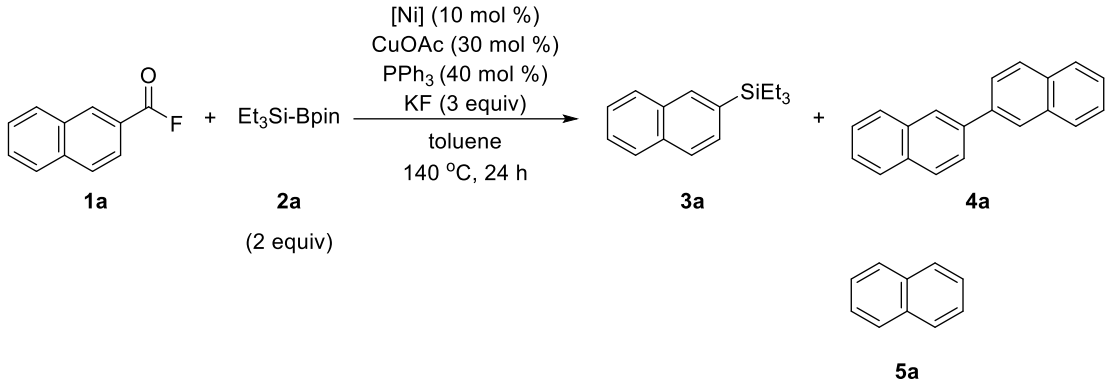


entry	**2a** (equiv)	**1a** (%)[b]	**2a** (%)[b]	**3a** (%)[b]	**4a** (%)[b]	**5a** (%)[b]
1	2	0	63	85	0	10
2	1	0	0	28	6	5
3	1.5	0	0	37	8	12

[a]Reaction conditions: **1a** (0.2 mmol), $Ni(cod)_2$ (0.02 mmol), CuOAc (0.06 mmol), PPh_3 (0.08 mmol) and KF (0. 6 mmol) in toluene (1.0 mL) at 140 ℃ for 24 h. [b]Determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard.

The moisture and oxygen-stable nickel sources were tried, such as nickel chloride and nickel acetate tetrahydrate, however, unsatisfactory results were obtained in terms of nickel (II) sources (Table 2-4).

Table 2-4. Optimization of Nickel Catalyst.[a]



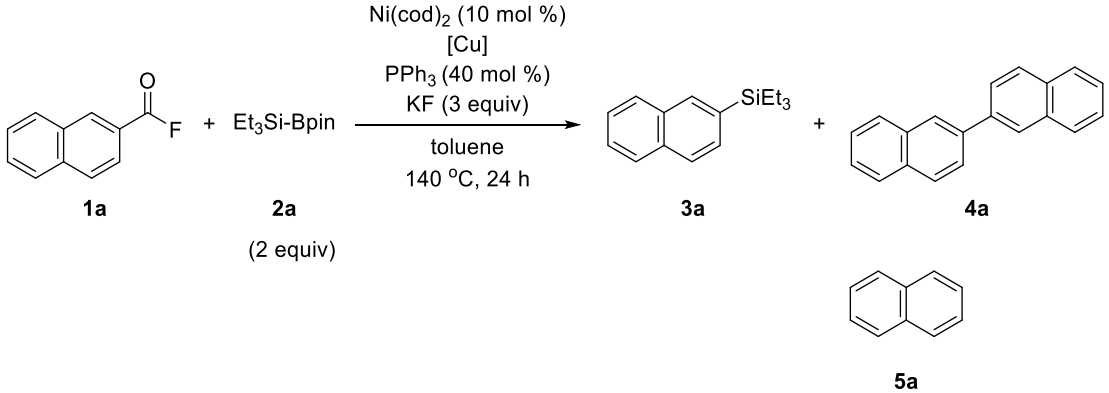
entry	[Ni]	**1a** (%)[b]	**2a** (%)[b]	**3a** (%)[b]	**4a** (%)[b]	**5a** (%)[b]
1	$Ni(cod)_2$	0	63	85	0	10

2	$NiCl_2$	0	0	21	0	15
3	$Ni(OAc)_2 \cdot 4H_2O$	0	0	0	0	8

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), CuOAc (0.06 mmol), PPh_3 (0.08 mmol) and KF (0.6 mmol) in toluene (1.0 mL) at 140 ℃ for 24 h. [b]Determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard.

Various cuprous and cupric salts were also examined (Table 2-5), among the four cupric salts (entries 1-4), 30 mol % of CuF_2 showed superior result with target product **3a** in 77% yield (entry 1). Notably, no desired product was detected using $CuCl_2$ as the cocatalyst (entry 2). Other cuprous salts such as CuI and CuOAc were examined, CuOAc showed comparable result with CuF_2 (entry 6). Attempt to employing silver acetate instead of copper salt was failed, the yield of **3a** was dramatically decreased to 13% (entry 7). Fluoride anion containing non-metal salts such as tetrabutylammonium difluorotriphenylsilicate (TBAT, entry 8) and tetra-*n*-butylammonium fluoride (TBAF, entry 9) gave poor conversions of this reaction. Elevating reaction temperature to 150 ℃ resulted in a slightly improvement to decarbonylative silylated product **3a** to 89% (entry 10).

Table 2-5. Optimization of Copper Salt.[a]



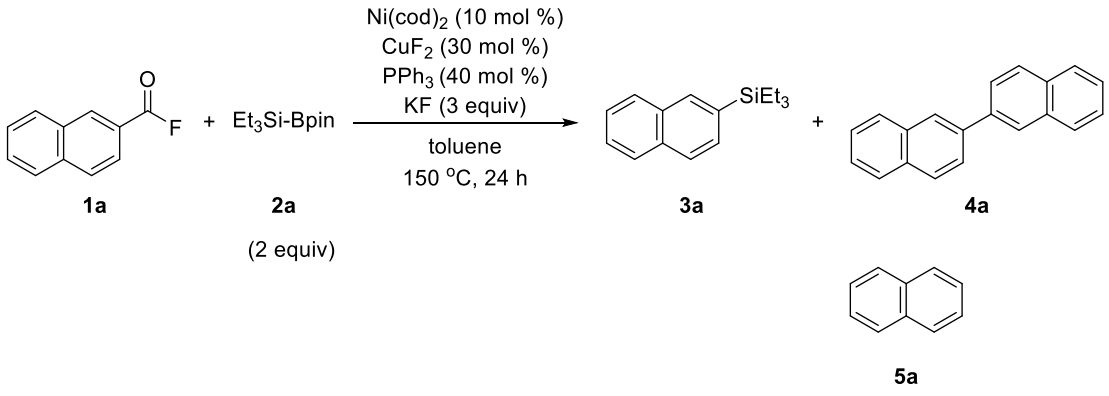
entry	[Cu] (mol %)	**1a** (%)[b]	**2a** (%)[b]	**3a** (%)[b]	**4a** (%)[b]	**5a** (%)[b]
1	CuF_2 (30)	0	60	77	0	6
2	$CuCl_2$ (30)	34	128	0	0	0
3	$Cu(OTf)_2$ (30)	0	0	3	0	0

4	$Cu(OAc)_2$ (30)	0	0	31	0	0
5	CuI (30)	60	148	15	0	0
6	CuOAc (30)	0	63	85	0	10
7	AgOAc (30)	0	38	13	10	3
8	TBAT (30)	0	131	31	0	19
9	TBAF (30)	43	132	9	0	0
10[c]	CuF_2 (30)	0	19	89	0	5

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), PPh_3 (0.08 mmol) and KF (0. 6 mmol) in toluene (1.0 mL) at 140 ℃ for 24 h. [b]Determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard. [c]150 ℃.

Control experiments in Table 2-6 confirmed the crucial factors of $Ni(cod)_2$, CuF_2 and PPh_3 to succeed this transformation, no or trace of **3a** was observed without one of them (entries 2-4). However, 46% conversion of **3a** was detected without KF (entry 5). In a sharp contrast, employing 2-naphthoyl chloride instead of **1a** under standard reaction conditions, **2a** was remained unreacted and no silylation product **3a** was formed (entry 6). This probably because the oxidative addition product Ar[Ni]Cl species cannot undergo ligand exchange with silylborane,[21] which further demonstrated the unique nature of acyl fluorides in the present reaction. It was noteworthy that no acylsilane was detected in all cases, which demonstrated that PPh_3 with weak electron-donating ability favors easily dissociation from nickel center, which is liable to facile CO migration and extrusion.

Table 2-6. Control Experiments.[a]



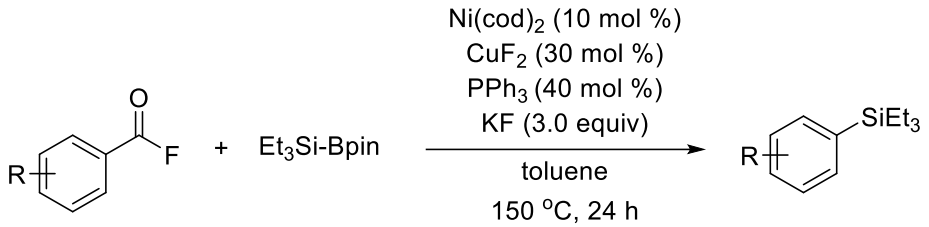
entry	deviation from standard conditions	**1a** (%)[b]	**2a** (%)[b]	**3a** (%)[b]	**4a** (%)[b]	**5a** (%)[b]
1	none	0	19	89 (85)	0	5
2	without $Ni(cod)_2$	0	3	0	0	0
3	without CuF_2	0	119	5	58	22
4	without PPh_3	0	31	<1	0	8
5	without KF	0	23	46	4	11
6	2-naphthoyl chloride instead of **1a**		186	0	0	5

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), CuF_2 (0.06 mmol), PPh_3 (0.08 mmol) and KF (0.6 mol) in toluene (1.0 mL) at 150 ℃ for 24 h. [b]Determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard. An isolated yield is given in parentheses.

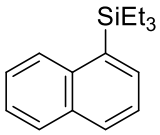
2-2-2 Nickel/Copper-Catalyzed Decarbonylative Silylation of Acyl Fluorides

With the optimized reaction conditions in hand, a wide range of acyl fluorides were investigated as shown in Table 2-7. The π-extended aromatic acyl fluorides could be accommodated, providing 1-naphthylsilane **3b** in 82% yield. The benzoyl fluoride substituted by a methyl group in the *para*-position was well tolerated in this reaction, affording the target product **3c** in 85% yield. A steric effect was illustrated by the phenyl-substituted substrates in the *ortho*-, *meta*-, and *para*-positions; *p*-phenylbenzoyl fluoride (**1d**) gained superiority than *m*-phenyl- (**1e**) and *o*-phenyl (**1f**) counterparts. Other electron-rich alkoxy groups such as *p*-methoxy (**3g**), 3,4,5-trimethoxy (**3h**) and *p*-butoxy (**3i**) were also well tolerated during the reaction, although the Ni-catalyzed silylation via C−O bond cleavage has been reported at lower temperature.[9] This protocol was also featured by acyl fluorides bearing functional groups at the *para*-position, including amine, fluoride, ketone, and methyl ester, resulting in the formation of the desired products **3j**-**3m** in 50-66% yields. In particular, phenolic ester skeleton (**3n**) was reported as a reactive electrophile under the nickel/copper cocatalysis in a decarbonylative silylation.[12,13] Therefore, our method could be a useful complement to other silylation processes that are inaccessible for compatibility of alkoxy and phenolic ester groups. Furthermore, the reaction could be extended to heteroatom-containing acyl fluorides, affording arylsilanes **3o** and **3p** in 71% and 65% yields, respectively.

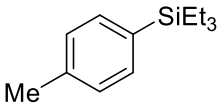
Table 2-7. Substrate Scope for Decarbonylative Silylation of Acyl Fluorides.[ab]



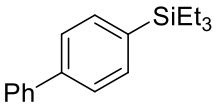
1 **2a** **3**



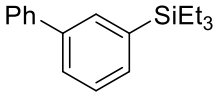
3b, 82%



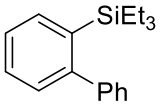
3c, 85%



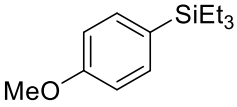
3d, 81%



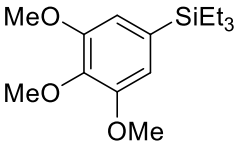
3e, 70%



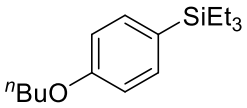
3f, 61%



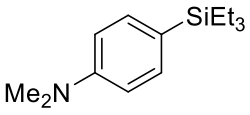
3g, 62%



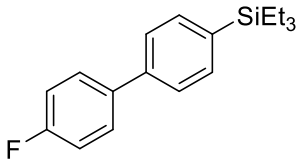
3h, 52%



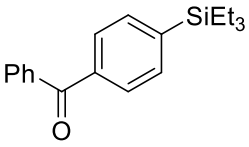
3i, 50%



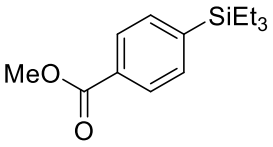
3j, 50%



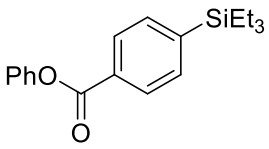
3k, 66%



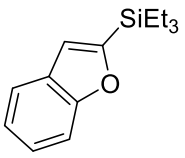
3l, 53%



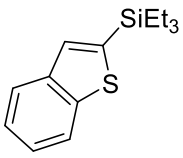
3m, 63%



3n, 60%



3o, 71%

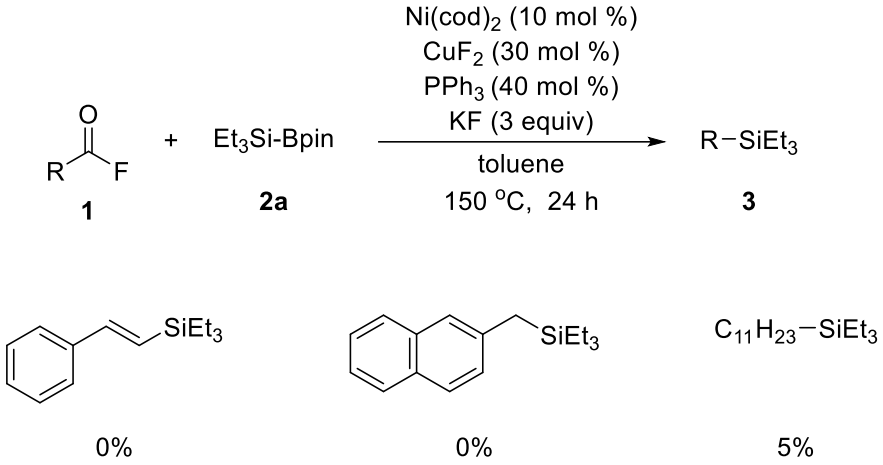


3p, 65%

[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), CuF_2 (0.06 mmol), PPh_3 (0.08 mmol), KF (0.6 mmol), toluene (1 mL), 150 °C, 24 h. [b]Isolated yields.

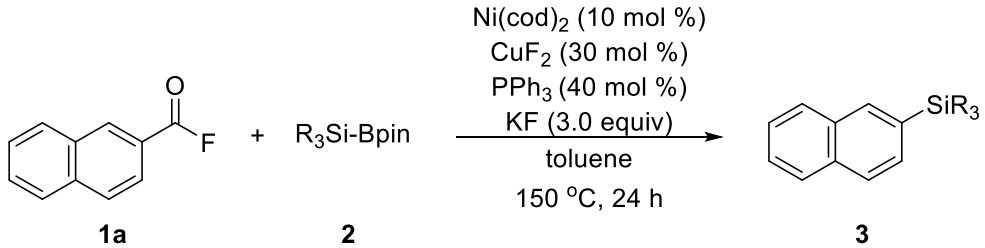
Unfortunately, other surrogate alkenyl and aliphatic acyl fluorides failed to participate this transformation. For example, only trace amount of decarbonylative silylation product was detected when employed dodecanoyl fluoride as the coupling partner (Scheme 2-4).

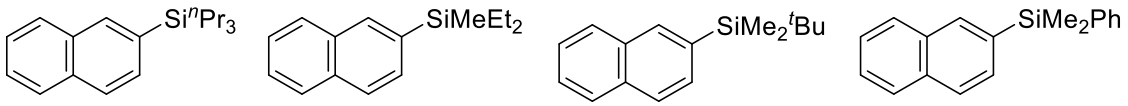
Scheme 2-4. Alkenyl and Aliphatic Precursors in Ni/Cu Cocatalyzed Decarbonylative Silylation.



Different silyl groups in organosilicon compounds can control the reactivity in Hiyama reaction to construct the new C−C bonds,[22] and in halogenation to provide new building blocks for further transformations.[6a,9b,23] Thus, electronic and steric effects of the silicon moiety on the present decarbonylative silylation were tested by using four types of silylboranes under the standard reaction conditions (Scheme 2-5). All of silylboranes are proved to be good coupling partners using 2-naphthoyl fluoride (**1a**), yielding the corresponding arylsilanes **3q**-**3t** in 63-96% yields. It is noteworthy that $^{n}Pr_3Si$-Bpin could be converted into the desired product **3q** in 64% with our method, whereas phenyl 2-naphthoate gave only 31% of **3q** with Rueping's protocol,[12] which further demonstrated the efficiency of our method.

Scheme 2-5. Evaluation of Different Silylboranes.[ab]





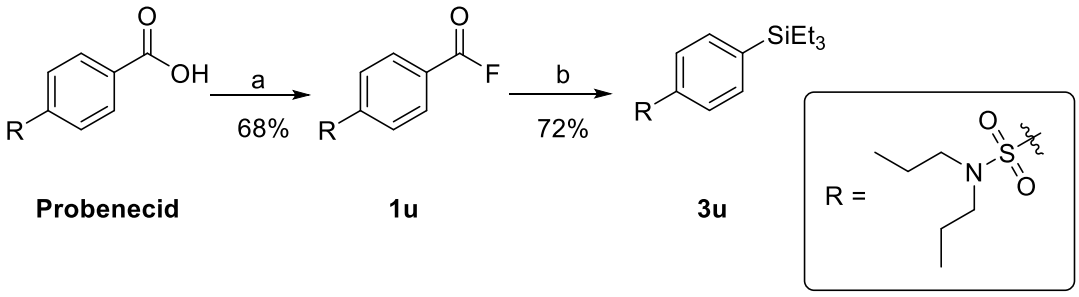
3q, 64% **3r**, 63% **3s**, 85% **3t**, 96%

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), CuF_2 (0.06 mmol), PPh_3 (0.08mmol), KF (0.6 mmol), toluene (1 mL), 150 ℃, 24 h. [b]Isolated yields.

Carboxylic acid-containing drug-probenecid, primarily used to treat gout and hyperuricemia[24] was also viable in nickel/copper-catalyzed decarbonylative silylation reaction. Deoxyfluorination of probenecid by conventional method,[25] followed decarbonylative silylation process furnished the target product **3u** in 72% yield (Scheme 2-6a), whereas the attempt of one-pot synthesis of **3u** without isolation of acyl fluoride (**1u**) provided an unsatisfactory result with the formation of **3u** in 28% yield. Besides, late-stage decarbonylative silylation of estrone derivative was conducted as shown in Scheme 2-6b, the etherification of estrone with methyl 4-(bromomethyl)benzoate (**4**), followed by hydrolysis afforded carboxylic acid **6**. Finally, compound **6** was subjected to the two-step deoxyfluorination/decarbonylative silylation to provide **3v** in 75% yield.

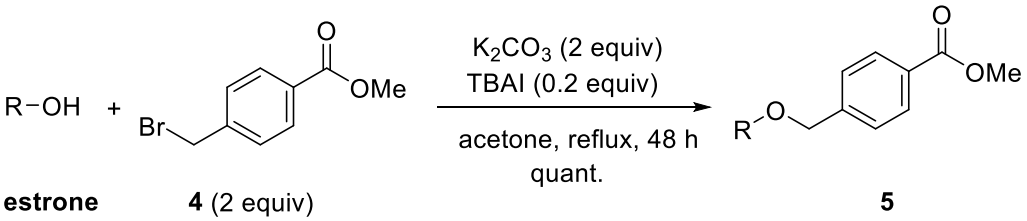
Scheme 2-6. Synthetic Applications.

(a) Two-step deoxyfluorination/decarbonylative silylation of probenecid

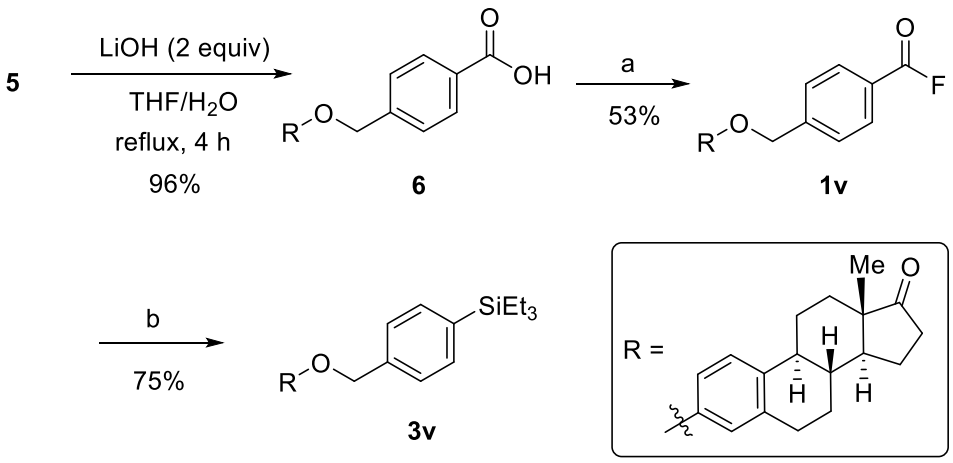


Probenecid **1u** **3u**

(b) Late-stage decarbonylative silylation of estrone derivative



estrone **4** (2 equiv) **5**

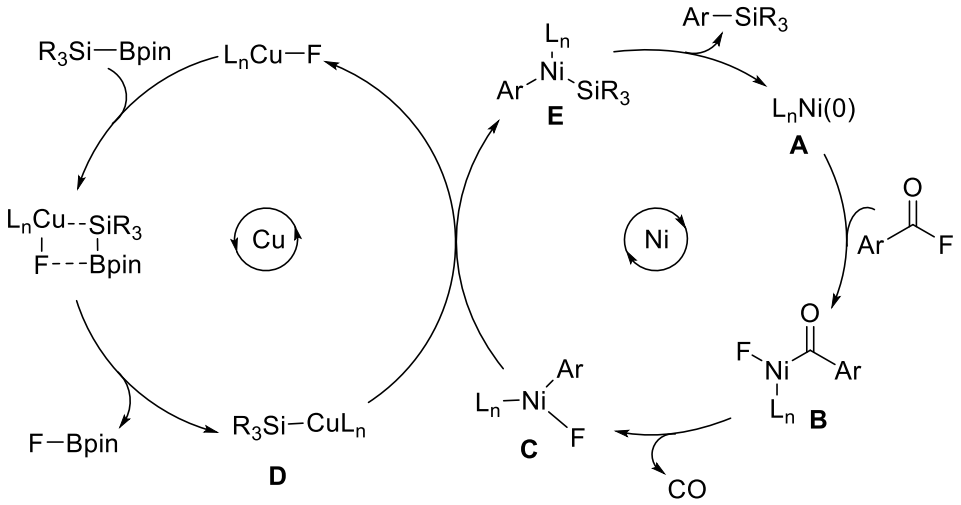


[a]Reaction conditions for deoxyfluorination of carboxylic acid: carboxylic acid (3 mmol), Deoxo-Fluor® reagent (3.3 mmol), CH_2Cl_2 (15 mL), 0 ℃, 30 min. [b]Reaction conditions for decarbonylative silylation: **1** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), CuF_2 (0.06 mmol), PPh_3 (0.08mmol), KF (0.6 mmol), toluene (1 mL), 150 ℃, 24 h.

2-2-3 Mechanistic Studies of Decarbonylative Silylation of Acyl Fluorides

Promoted by relative references and our previous work, a plausible mechanism was shown in Scheme 2-7. Oxidative addition of acyl fluorides to nickel(0) species **A** to yielded acyl nickel(II) species **B**. Subsequently, decarbonylation of complex **B** gave the aryl nickel species **C**.[17,20] In copper catalytic cycle, the favorable B–F over Si–F interaction and formation of active Cu–Si species were accounted for different electronegativity of B (2.051) and Si (1.916),[26] as well as bond dissociation energy (enthalpy) of diatomic B–F (732 kJ mol^{-1}) and Si–F (576.4 kJ mol^{-1}).[27] Therefore, fluorine anion activated silylborane by coordination to the boron atom to form silycopper species **D**,[19] which will facilitate the transfer of the silyl group to copper atom. Transmetalation between Ar[Ni]F species **C** and Cu-Si species **D** afforded intermediate **E**, followed reductive elimination of complex **E** yielding desired product arylsilane and regenerated nickel(0) species **A**.

Scheme 2-7. Proposed Mechanism.


R3Si—Bpin
LnCu—F
LnCu--SiR3
F---Bpin
Cu
F—Bpin
R3Si—CuLn
D
Ln
Ar
Ni
SiR3
E
Ar—SiR3
LnNi(0)
A
Ni
O
Ar
F
Ar
F
Ni
Ln
B
Ln—Ni
Ar
F
C
CO

2-3 Summary

The Author developed a bimetallic nickel/copper cocatalytic system for decarbonylative silylation reaction of acyl fluorides to a wide range of aryl and heteroaryl silanes, in which an inexpensive and stable PPh_3 showed high efficiency. The present transformation demonstrated high efficiency and good functional-group compatibility, which can provide a new access to arylsilanes starting from acyl fluorides via carbon-fluorine bond cleavage and carbon-silicon bond formation. Such transformation would not only extend the functionalization of acyl fluorides but complement the synthetic route for arylsilanes.

2-4 Experimental Section

2-4-1 General Instrumentation and Chemicals

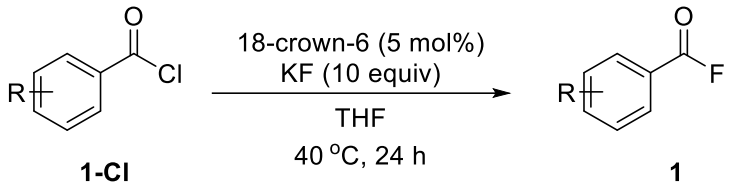
All the reactions were carried out under an Argon atmosphere using standard Schlenk techniques. Glassware was dried in an oven (150 °C) and heated under reduced pressure prior to use. Solvents were employed as eluents for all other routine operation, as well as dehydrated solvents were purchased from commercial suppliers and employed without any further purification. For thin layer chromatography (TLC) analyses throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. Silica gel column chromatography was carried out using silica gel 60 N (spherical, neutral, 40-100 μm) from Kanto Chemicals Co., Ltd. NMR spectra (^{1}H, ^{13}C{^{1}H} and ^{19}F{^{1}H}) were recorded on Varian INOVA-600 (600 MHz), Mercury-400 (400 MHz), or 300-NMR ASW (300 MHz) spectrometers. Chemical shifts (δ) are in parts per million related to $CDCl_3$ at 7.26 ppm for ^{1}H and at 77.16 ppm for ^{13}C{^{1}H}. The ^{19}F{^{1}H} NMR spectra were measured by using CCl_3F (δ = 0.00 ppm) as an external standard. The GC yields were determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard. GC analyses were performed on a Shimadzu GC-14A equipped with a flame ionization detector using Shimadzu Capillary Column (CBP1-M25-025) and Shimadzu C-R6A-Chromatopac integrator. Infrared spectra were recorded on a SHIMADZU IRP restige-21 spectrophotometer. HRMS analyses were obtained by using a double focusing magnetic sector mass spectrometer (JEOL JMS-700 MStation). Elemental analyses were carried out with a Perkin-Elmer 2400 CHN elemental analyzer at Okayama University.

Chemicals

Materials obtained from commercial suppliers were used without further purification. Bis(1,5-cyclooctadiene)nickel was purchased from Merck. Triphenylphosphine and potassium fluoride (purity > 95%) were obtained from Nacalai Tesque. *n*-Dodecane (purity > 99%) was purchased from Kanto Chemical Co. Acyl fluorides **1a**-**1v**[25,28] were synthesized from corresponding carboxylic acids or acyl chlorides, which was described in chapter 2. Silylboranes **2a**-**2e**[12,19g] were prepared according to the literatures and showed the identical spectra reported.

2-4-2 Experimental Procedures

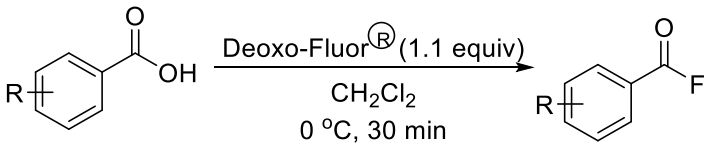
2-4-2-1 Representative Procedure for the Synthesis of Acyl Fluorides from Acyl Chlorides[28]



1-Cl **1**

To a 50 mL of Schlenk tube charged with a magnetic stirrer bar, were successively added acyl chloride **1-Cl** (4.0 mmol), 18-crown-6 (0.2 mmol, 5 mol %, 52.9 mg), KF (40 mmol, 10 equiv, 2.32 g) and THF (20 mL). After the reaction was stirred at 40 ºC for 24 h, the insoluble inorganic solid (KF or KCl) was filtered, and the volatiles were concentrated using a rotary evaporator. The crude product was purified by bulb-to-bulb distillation to afford the corresponding acyl fluorides **1**.

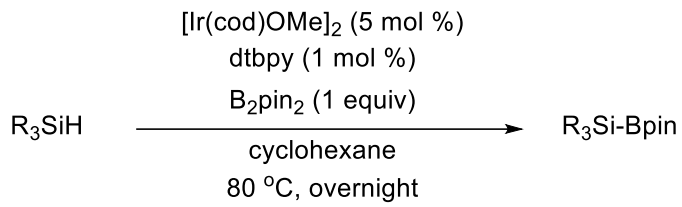
2-4-2-2 Representative Procedure for the Synthesis of Acyl Fluorides from Carboxylic Acids[25]



1-OH **1**

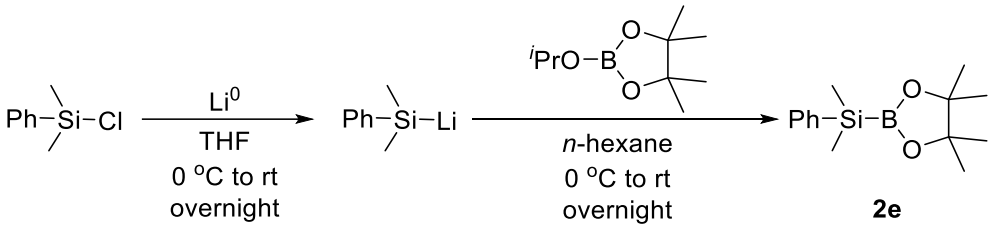
To a 20 mL of Schlenk tube charged with a magnetic stirrer bar, were successively added carboxylic acid **1-OH** (3.0 mmol) and CH_2Cl_2 (15 mL). After the mixture was stirred at 0 ºC, Deoxo-Fluor® reagent (3.3 mmol, 1.1 equiv, 608 μL) was slowly added to the reaction mixture. After the reaction mixture was stirred at 0 ºC for 30 min, the solution was slowly poured into saturated $NaHCO_3$, and after CO_2 evolution ceased it was extracted into CH_2Cl_2 (3 × 15 mL), and dried over $MgSO_4$. The crude product was purified by flash chromatography to afford the corresponding acyl fluorides **1**.

2-4-2-3 Representative Procedure for the Synthesis of Silylboranes from Silanes[12]



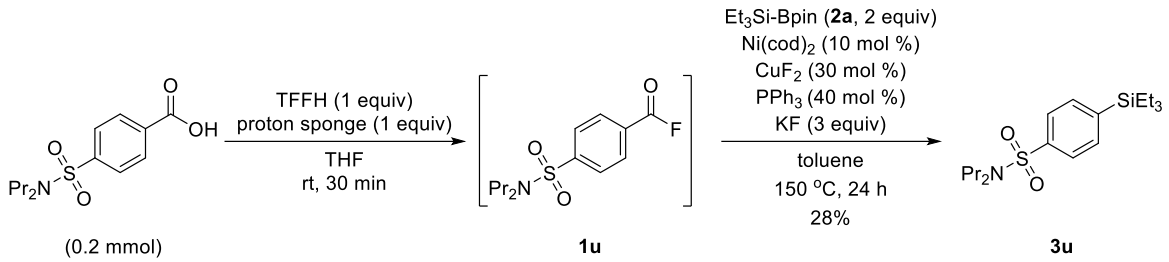
To a 20 mL of Schlenk tube charged with a magnetic stirrer bar, were successively added $[Ir(cod)OMe]_2$ (0.5 mol %, 13.2 mg), dtbpy (1 mol %, 10.8 mg) , B_2pin_2 (4.0 mmol, 1.02 g), cyclohexane (1.0 mL) and silane (4 equiv, 16.0 mmol). The resulting dark brown solution was heated at 80 ℃ overnight. After being cooled to room temperature, the crude reaction mixture was concentrated in vacuo, and the residue was purified by flash column chromatography to afford the corresponding silylboranes (**2a**-**2d**) in 30-60% yields.

2-4-2-4 Representative Procedure for the Synthesis of Silylborane (2e)[19g]



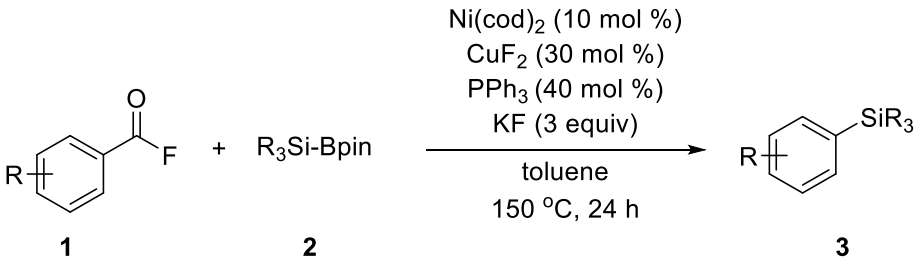
Metallic lithium (120 mmol, 826 mg) was added to THF (30 mL) under an argon flow. The flask was placed in an ice bath and dimethylphenylchlorosilane (30 mmol, 5 mL) was added dropwise. The red mixture was vigorously stirred overnight and added dropwise to a solution of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (60 mmol, 12.2 mL) in *n*-hexane (30 mL). The mixture was stirred overnight at room temperature, and the volatile materials were removed in *vacuo*. The residue was taken up in *n*-hexane (30 mL) and filtered through Celite under argon (Celite was dried in vacuo before use). The solvent was removed under reduced pressure and the product was purified by fractioned distillation (bp = 120 ℃ at 0.1 mbar).

2-4-2-5 One-Pot Reaction from Probenecid without Isolating the Corresponding Acyl Fluoride 1u



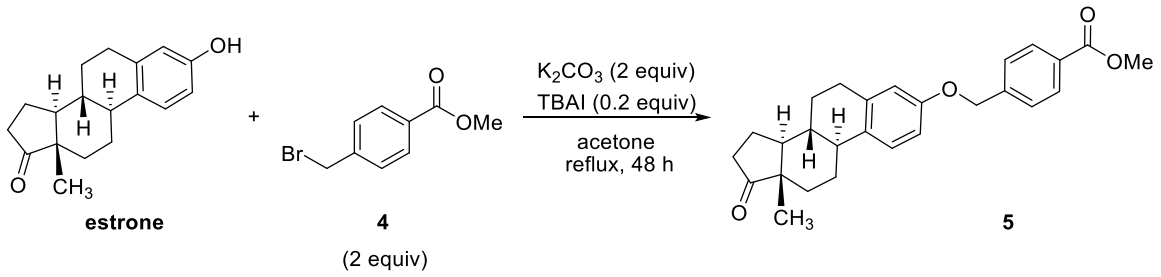
To a 20 mL of Schlenk tube charged with a magnetic stirrer bar, were successively added probenecid (0.2 mmol, 57.1 mg), TFFH (0.2 mmol, 1 equiv, 52.8 mg), proton sponge (0.2 mmol, 1 equiv, 42.9 mg) and THF (0.4 mL). After the reaction mixture was stirred at room temperature for 30 mins, a pre-mixed solution of $Ni(cod)_2$ (0.02 mmol, 10 mol %, 5.5 mg), PPh_3 (0.08 mmol, 40 mol %, 21.0 mg) in toluene (1 mL) was added. Then, KF (0.6 mmol, 3 equiv, 36.6 mg), Et_3Si-Bpin (**2a**) (0.4 mmol, 2 equiv, 96.9 mg) and CuF_2 (0.06 mmol, 30 mol %, 6.1 mg) were added. The mixture was heated at 150 ℃ with stirring for 24 h. After the reaction, *n*-dodecane was added as an internal standard and stirring the mixture vigorously. Take a portion of the mixture, diluted by Et_2O (2 mL), GC analysis was conducted using resulting organic phase.

2-4-2-6 Decarbonylative Silylation of Acyl Fluorides



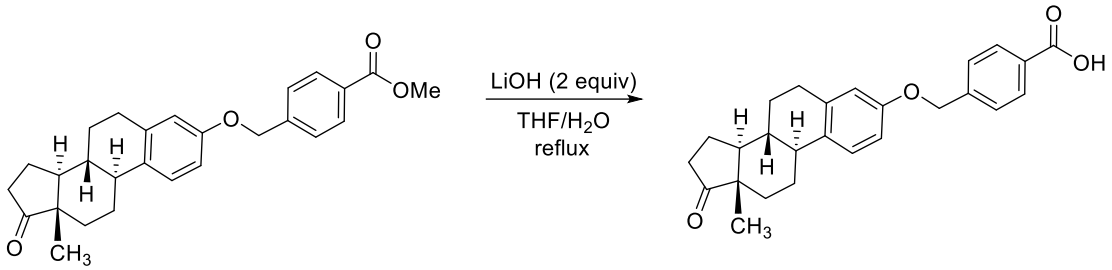
A 20 mL dried Schlenk tube containing a stirrer bar and KF (0.6 mmol, 3 equiv, 36.6 mg) was dried with a heat gun under reduced pressure and filled with argon after cooling to room temperature. To this vessel, were added $Ni(cod)_2$ (0.02 mmol, 10 mol %, 5.5 mg), PPh_3 (0.08 mmol, 40 mol %, 21.0 mg,), toluene (1 mL), acyl fluoride (**1**, 0.2 mmol), silylborane (**2**, 0.4 mmol, 2 equiv), and CuF_2 (0.06 mmol, 30 mol %, 6.1 mg). The mixture was heated at 150 ºC with stirring for 24 h. The solution was then cooled to room temperature, and the solvent was removed under vacuum. The decarbonylative silylation product **3** was purified by flash column chromatography on silica gel.

2-4-2-7 Synthesis of Methyl 4-((((8R,9S,13S,14S)-13-methyl-17-*oxo*-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-3-yl)oxy)methyl) benzoate (5)



Compound **5** was synthesized according to a modified procedure.[29] An oven-dried 50 mL of Schlenk tube containing a stirrer bar was charged with estrone (270 mg, 1 mmol), ester **4** (458.2 mg, 2 mmol, 2 equiv), K_2CO_3 (276.4 mg, 2 mmol, 2 equiv), TBAI (73.9 mg, 0.2 mmol, 0.2 equiv), and acetone (10 mL). After the reaction mixture was heated to reflux for 48 h, the solvent was removed under vacuum. The crude mixture was extracted with dichloromethane (10 mL × 3) and organic layers were combined, dried over Na_2SO_4, filtered. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane:EtOAc = 5:1) to afford **5** quantitatively (418 mg) as white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.91 (s, 3H), 1.39-1.65 (m, 6H), 1.93-1.97 (m, 1H), 1.98-2.08 (m, 2H), 2.14 (dt, J = 19.0, 8.8 Hz, 1H), 2.23-2.28 (m, 1H), 2.37-2.41 (m, 1H), 2.50 (dd, J = 19.0, 8.8 Hz, 1H), 2.88-2.91 (m, 2H), 3.92 (s, 3H), 5.10 (s, 2H), 6.72 (d, J = 2.6 Hz, 1H), 6.77 (dd, J = 8.6, 3.0 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 8.05 (dd, J = 7.2, 1.8 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 14.0, 21.7, 26.0, 26.6, 29.8, 31.7, 36.0, 38.4, 44.1, 48.1, 50.5, 52.3, 69.4, 112.4, 115.0, 126.5, 127.0, 129.6, 130.0, 132.7, 138.0, 142.6, 156.6, 167.0, 221.1. FT-IR (KBr): 2934, 2910, 2859, 2830, 1734, 1719, 1605, 1499, 1454, 1437, 1414, 1279, 1254, 1236, 1175, 1109, 1036 cm^{-1}. Anal. Calcd for $C_{27}H_{30}O_4$: C, 77.48; H, 7.23%. Found: C, 77.41; H, 7.25%. HRMS (FAB$^+$): Calcd for $C_{27}H_{30}O_4$: 418.2144. Found: 418.2150.

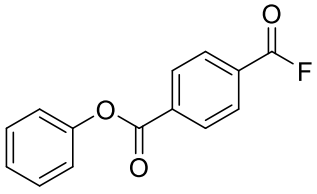
2-4-2-8 Synthesis of 4-((((8R,9S,13S,14S)-13-Methyl-17-oxo-7,8,9,11,12,13,14, 15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)oxy)methyl)benzoic acid (6)[30]



5 **6**

Compound **5** was subjected to hydrolysis according to the reported method.[31] A solution of ester **5** (418 g, 1 mmol) and lithium hydroxide monohydrate (84 mg, 2 mmol) in tetrahydrofuran (2 mL) and water (2 mL) was refluxed at 100 °C. After 4 h, the solvent was evaporated, and concentrated HCl was added to the residue. The precipitate was filtrated, washed with water, dried under vacuum to give a white solid (388.3 mg, 96%). ^{1}H NMR (600 MHz, $(CD_3)_2SO$): δ 0.81 (s, 3H), 1.30-1.39 (m, 3H), 1.44-1.57 (m, 3H), 1.72-1.77 (m, 1H), 1.89-1.96 (m, 2H), 2.05 (dt, J = 18.5, 8.5 Hz, 1H), 2.14-2.18 (m, 1H), 2.29-3.35 (m, 1H), 2.43 (dd, J = 18.5, 8.5 Hz, 1H), 2.79-2.82 (m, 2H), 3.36 (brs, 1H), 5.14 (s, 2H), 6.72 (d, J = 2.8 Hz, 1H), 6.76 (dd, J = 8.6, 2.8 Hz, 1H), 7.17 (d, J = 8.6 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.95 (d, J = 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $(CD_3)_2SO$): δ 13.6, 21.2, 25.5, 26.1, 29.2, 31.4, 35.4, 37.8, 43.5, 47.4, 49.6, 68.4, 112.3, 114.6, 126.4, 127.2, 129.5, 130.3, 132.2, 137.6, 142.4, 156.0, 167.2, 219.8. FT-IR (KBr): 2932, 2876, 1734, 1678, 1611, 1497, 1425, 1254, 1159, 1057, 1005, 860 cm^{-1}. Anal. Calcd for $C_{26}H_{28}O_4$: C, 77.20; H, 6.98%. Found: C, 77.03; H, 6.80%.

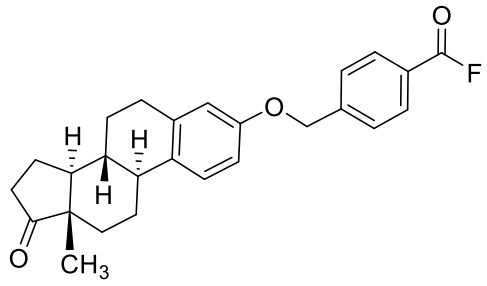
Phenyl 4-(fluorocarbonyl)benzoate (**1n**)



Purification: column chromatography (*n*-hexane/EtOAc = 10:1, R_f = 0.39). White solid. Isolated yield: 63% (461.6 mg). Melting point: 120-121 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22-7.24 (m, 2H), 7.28-7.33 (m, 1H), 7.43-7.47 (m, 2H), 8.19-8.22 (m, 2H), 8.27-8.36 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 121.6, 126.5, 129.3 (d, J = 61.9 Hz), 129.8, 130.8, 131.7 (d, J = 3.5 Hz), 135.7, 150.7,

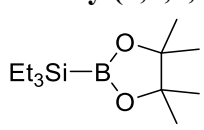
156.6 (d, J = 345.9 Hz), 163.9. $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ 20.3. FT-IR (neat, cm^{-1}): 689 (s), 718 (s), 1013 (s), 1082 (s), 1192 (s), 1225 (s), 1240 (s), 1267 (s), 1410 (s), 1491 (m), 1740 (s), 1817 (s). Anal. Calcd for $C_{14}H_9FO_3$: C, 68.57; H, 3.42%. Found: C, 68.85; H, 3.71%. HRMS (FAB^+): Calcd for $C_{14}H_9FO_3$: 244.0536. Found: 244.0532.

4-((((8*R*,9*S*,13*S*,14*S*)-13-Methyl-17-*oxo*-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-3-yl)oxy)methyl)benzoyl fluoride (1v)



Purification: column chromatography (*n*-hexane/EtOAc = 5:1, R_f = 0.40). White solid. Isolated yield: 53% (646.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (s, 3H), 1.39-1.49 (m, 2H), 1.53-1.68 (m, 6H), 1.94-2.19 (m, 4H), 2.22-2.28 (m, 1H), 2.37-2.42 (m, 1H), 2.47-2.54 (m, 1H), 2.88-2.92 (m, 2H), 5.14 (s, 2H), 6.72 (d, J = 2.8 Hz, 1H), 6.77 (dd, J = 8.6, 2.8 Hz, 1H), 7.22 (dd, J = 8.4, 3.2 Hz, 1H), 7.58-7.60 (m, 2H), 8.05 (d, J = 8.4 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 13.9, 21.7, 26.0, 26.6, 29.7, 31.7, 35.9, 38.4, 44.1, 48.1, 50.5, 69.0, 112.4, 115.0, 124.3 (J = 61.3 Hz), 126.6, 127.4, 131.8 (J = 3.8 Hz), 133.0, 138.1, 145.6, 156.35, 157.3 (J = 345.6 Hz), 220.9. $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ 18.3. FT-IR (KBr): 2924, 2857, 1780, 1734, 1612, 1495, 1456, 1375, 1256, 1240, 1159, 1061, 1032, 1001, 741 cm^{-1}. HRMS (FAB^+): Calcd for $C_{26}H_{27}FO_3$: 406.1944. Found: 406.1915.

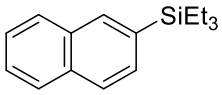
Triethyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)silane (2a)[12]



Purification: column chromatography (*n*-Hexane, R_f = 0.39). Colorless oil. Isolated yield: 60% (581.4 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.59 (q, J = 7.8 Hz, 6H),

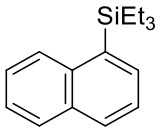
0.96 (t, J = 7.8 Hz, 9H), 1.22 (s, 12H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 3.1, 8.5, 25.2, 83.0. $^{11}B\{^{1}H\}$ NMR (192 MHz, $CDCl_3$) δ 35.1.

Triethyl(naphthalen-2-yl)silane (3a)[12]



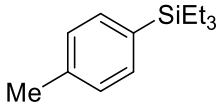
Purification: column chromatography (*n*-Hexane, R_f = 0.65). Colorless oil. Isolated yield: 85% (41.2 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89 (qd, J = 7.8, 1.2 Hz, 6H), 1.00-1.03 (m, 9H), 7.47-7.50 (sext, J = 3.0 Hz, 2H), 7.59 (dd, J = 8.4, 1.2 Hz, 1H), 7.82-7.86 (m, 3H), 8.00 (s, 1H).

Triethyl(naphthalen-1-yl)silane (3b)[12]



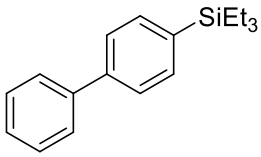
Purification: column chromatography (*n*-Hexane, R_f = 0.63). Colorless oil. Isolated yield: 82% (39.8 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.97-1.00 (m, 9H), 1.02-1.06 (m, 6H), 7.45-7.52 (m, 3H), 7.68 (dd, J = 7.2, 1.8 Hz, 1H), 7.86-7.88 (m, 2H), 8.10-8.12 (m, 1H).

Triethyl(p-tolyl)silane (3c)[12]



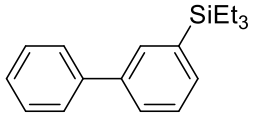
Purification: column chromatography (*n*-Hexane, R_f = 0.70). Colorless oil. Isolated yield: 85% (35.0 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.76-0.80 (m, 6H), 0.96 (t, J = 8.4 Hz, 9H), 2.35 (s, 3H), 7.18 (d, J = 7.2 Hz, 2H), 7.39 (d, J = 7.8 Hz, 2H).

[1,1'-Biphenyl]-4-yltriethylsilane (3d)[12]



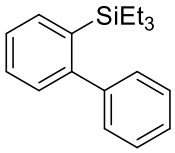
Purification: column chromatography (*n*-Hexane, R_f = 0.60). Colorless oil. Isolated yield: 81% (43.5 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.83-0.87 (m, 6H), 1.02 (t, *J* = 7.8 Hz, 9H), 7.35-7.37 (m, 1H), 7.44-7.47 (m, 2H), 7.58-7.64 (m, 6H).

[1,1'-Biphenyl]-3-yltriethylsilane (3e)[12]



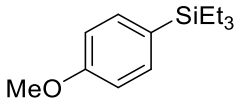
Purification: column chromatography (*n*-Hexane, R_f = 0.60). Colorless oil. Isolated yield: 70% (37.6 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.82-0.86 (m, 6H), 1.00 (t, *J* = 6.0 Hz, 9H), 7.36 (dt, *J* = 7.8, 7.2, 1.2 Hz, 1H), 7.42-7.49 (m, 4H), 7.57-7.61 (m, 3H), 7.70 (dt, *J* = 1.8, 0.6 Hz, 1H).

[1,1'-Biphenyl]-2-yltriethylsilane (3f)[12]



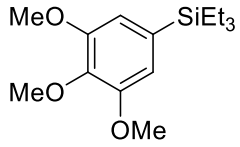
Purification: column chromatography (*n*-Hexane, R_f = 0.68). Colorless oil. Isolated yield: 61% (32.8 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.46 (q, *J* = 7.8 Hz, 6H), 0.81 (t, *J* = 7.8 Hz, 9H), 7.21-7.22 (m, 1H), 7.27-7.29 (m, 2H), 7.32-7.39 (m, 5H), 7.56-7.57 (m, 1H).

Triethyl(4-methoxyphenyl)silane (3g)[32]



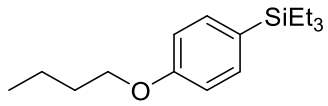
Purification: column chromatography (*n*-hexane/EtOAc = 50:1, R_f = 0.38). Colorless oil. Isolated yield: 62% (27.6 mg). ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 0.76 (qd, *J* = 7.8, 0.6 Hz, 6H), 0.95 (t, *J* = 7.8 Hz, 9H), 3.81 (s, 3H), 6.90-6.92 (m, 2H), 7.40-7.43 (m, 2H).

Triethyl(3,4,5-trimethoxyphenyl)silane (3h)



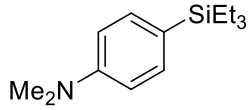
Purification: column chromatography (*n*-Hexane/EtOAc = 20:1, R_f = 0.53). Colorless oil. Isolated yield: 52% (29.4 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.76-0.80 (m, 6H), 0.98 (t, *J* = 7.8 Hz, 9H), 3.86 (s, 3H), 3.87 (s, 6H), 6.67 (s, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 3.6, 7.6, 56.3, 60.9, 110.9, 132.6, 139.0, 153.0. FT-IR (neat, cm^{-1}): 696 (s), 719 (s), 1003 (s), 1126 (s), 1306 (s), 1395 (s), 1464 (s), 1504 (s), 1570 (s), 2876 (s), 2911 (s), 2938 (s), 3019 (s). HRMS (FAB^+): Calcd for $C_{15}H_{26}O_3Si$: 282.1651. Found: 282.1679

(4-Butoxyphenyl)triethylsilane (3i)



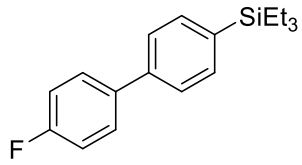
Purification: column chromatography (*n*-Hexane, R_f = 0.50). Colorless oil. Isolated yield: 50% (26.4 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.74-0.78 (m, 6H), 0.94-1.00 (m, 12H), 1.47-1.53 (m, 2H), 1.75-1.79 (m, 2H), 3.97 (t, *J* = 6.6 Hz, 2H), 6.89-6.91 (m, 2H), 7.39-7.41 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 3.7, 7.6, 14.0, 19.4, 31.5, 67.5, 114.1, 128.0, 135.7, 159.9. FT-IR (neat, cm^{-1}): 714 (s), 1007 (s), 1109 (s), 1182 (s), 1225 (s), 1244 (m), 1273 (s), 1503 (s), 1593 (s), 2873 (s), 2957 (s). HRMS (FAB^+): Calcd for $C_{16}H_{28}OSi$: 264.1909. Found: 264.1895.

N,N-Dimethyl-4-(triethylsilyl)aniline (3j)[12]



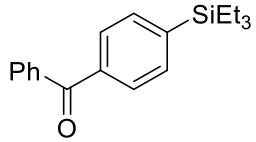
Purification: column chromatography (*n*-Hexane/EtOAc = 20:1, R_f = 0.63). Colorless oil. Isolated yield: 50% (23.5 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.74-0.78 (m, 6H), 0.97 (t, *J* = 8.4 Hz, 9H), 2.97 (s, 6H), 6.76 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H).

Triethyl(4'-fluoro-[1,1'-biphenyl]-4-yl)silane (3k)[12]



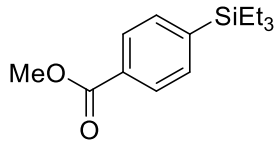
Purification: column chromatography (*n*-Hexane, R_f = 0.63). Colorless oil. Isolated yield: 66% (37.8 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.81-0.85 (m, 6H), 1.00 (t, *J* = 8.4 Hz, 9H), 7.12-7.15 (m, 2H), 7.53-7.58 (m, 6H). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -115.8.

Phenyl(4-(triethylsilyl)phenyl)methanone (3l)



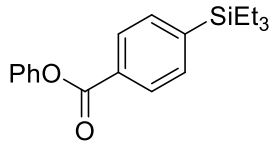
Purification: column chromatography (*n*-Hexane/EtOAc = 20:1, R_f = 0.67). Colorless oil. Isolated yield: 53% (31.4 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.82-0.86 (m, 6H), 0.97-1.00 (m, 9H), 7.47-7.50 (m, 2H), 7.58-7.62 (m, 3H), 7.75-7.77 (m, 2H), 7.81-7.83 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 3.4, 7.5, 128.4, 129.1, 130.2, 132.5, 134.2, 137.8, 143.7, 197.1. FT-IR (neat, cm^{-1}): 660 (s), 702 (s), 924 (s), 1283 (s), 1317 (s), 1655 (m), 2913 (s), 2957 (s), 3013 (s). HRMS (FAB$^+$): Calcd for $C_{19}H_{24}OSi$: 296.1596. Found: 296.1604.

Methyl 4-(triethylsilyl)benzoate (3m)[12]



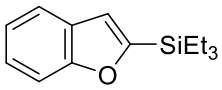
Purification: column chromatography (*n*-Hexane/EtOAc = 20:1, R_f = 0.70). Colorless oil. Isolated yield: 63% (31.6 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.79-0.83 (m, 6H), 0.96 (t, *J* = 7.2 Hz, 9H), 3.91 (s, 3H), 7.56-7.58 (m, 2H), 7.98-8.00 (m, 2H).

Phenyl 4-(triethylsilyl)benzoate (3n)[12]



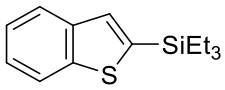
Purification: column chromatography (*n*-Hexane/EtOAc = 20:1, R_f = 0.70). Colorless oil. Isolated yield: 60% (37.5 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.83-0.87 (m, 6H), 0.97-1.00 (m, 9H), 7.21-7.23 (m, 2H), 7.27-7.29 (m, 1H), 7.42-7.45 (m, 2H), 7.64-7.66 (m, 2H), 8.16-8.18 (m, 2H).

Benzofuran-2-yltriethylsilane (3o)[12]



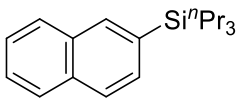
Purification: column chromatography (*n*-Hexane, R_f = 0.65). Colorless oil. Isolated yield: 71% (33.0 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.84-0.88 (m, 6H), 1.03 (t, *J* = 7.2 Hz, 9H), 6.99 (d, *J* = 0.6 Hz, 1H), 7.19-7.21 (m, 1H), 7.26-7.28 (m, 1H), 7.50-7.52 (m, 1H), 7.57-7.59 (m, 1H).

Benzo[b]thiophen-2-yltriethylsilane (3p)[12]



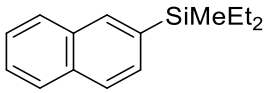
Purification: column chromatography (*n*-Hexane, R_f = 0.66). Colorless oil. Isolated yield: 65% (32.3 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.86-0.90 (m, 6H), 1.04 (t, *J* = 7.8 Hz, 9H), 7.30-7.36 (m, 2H), 7.47 (d, *J* = 0.6 Hz, 1H), 7.82-7.83 (dd, *J* = 6.6, 0.6 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H).

Naphthalen-2-yltripropylsilane (3q)[12]



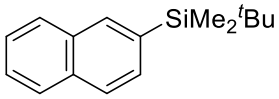
Purification: column chromatography (*n*-Hexane, R_f = 0.67). Colorless oil. Isolated yield: 64% (36.4 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89-0.92 (m, 6H), 1.01 (t, *J* = 7.2 Hz, 9H), 1.39-1.46 (m, 6H), 7.49-7.51 (m, 2H), 7.60 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.83-7.88 (m, 3H), 8.00 (s, 1H).

Diethyl(methyl)(naphthalen-2-yl)silane (3r)[12]



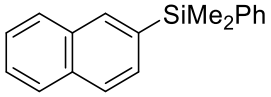
Purification: column chromatography (*n*-Hexane, R_f = 0.68). Colorless oil. Isolated yield: 63% (28.8 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.33 (s, 3H), 0.83-0.87 (m, 4H), 0.99 (t, *J* = 7.8 Hz, 6H), 7.47-7.50 (m, 2H), 7.59 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.83 (dd, *J* = 7.8, 4.2 Hz, 2H), 7.85 (dd, *J* = 6.0, 3.6 Hz, 1H), 8.00 (s, 1H).

Tert-butyldimethyl(naphthalen-2-yl)silane (3s)[12]



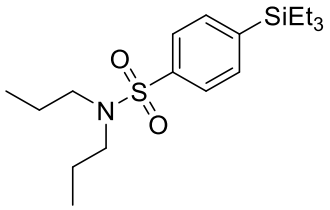
Purification: column chromatography (*n*-Hexane, R_f = 0.66). Colorless oil. Isolated yield: 85% (41.2 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.40 (s, 6H), 0.95 (s, 9H), 7.49-7.52 (m, 2H), 7.63 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.83-7.89 (m, 3H), 8.03 (s, 1H).

Dimethyl(naphthalen-2-yl)(phenyl)silane (3t)[12]



Purification: column chromatography (*n*-Hexane, R_f = 0.47). White solid. Isolated yield: 96% (50.4 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.68 (s, 6H), 7.38-7.42 (m, 3H), 7.50-7.54 (m, 2H), 7.60-7.64 (m, 3H), 7.85-7.87 (m, 3H), 8.08 (s, 1H).

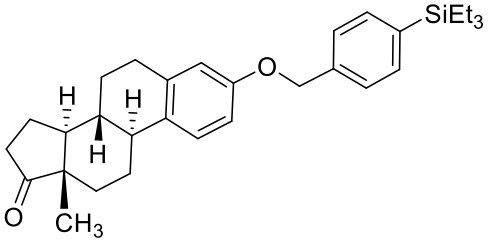
N,N-Dipropyl-4-(triethylsilyl)benzenesulfonamide (3u)



Purification: column chromatography (*n*-Hexane/EtOAc = 20:1, R_f = 0.60). Colorless oil. Isolated yield: 72% (51.9 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.79-0.83 (m, 6H), 0.86 (t, *J* = 7.8 Hz, 6H), 0.94-0.97 (m, 9H), 1.54-1.57 (m, 4H),

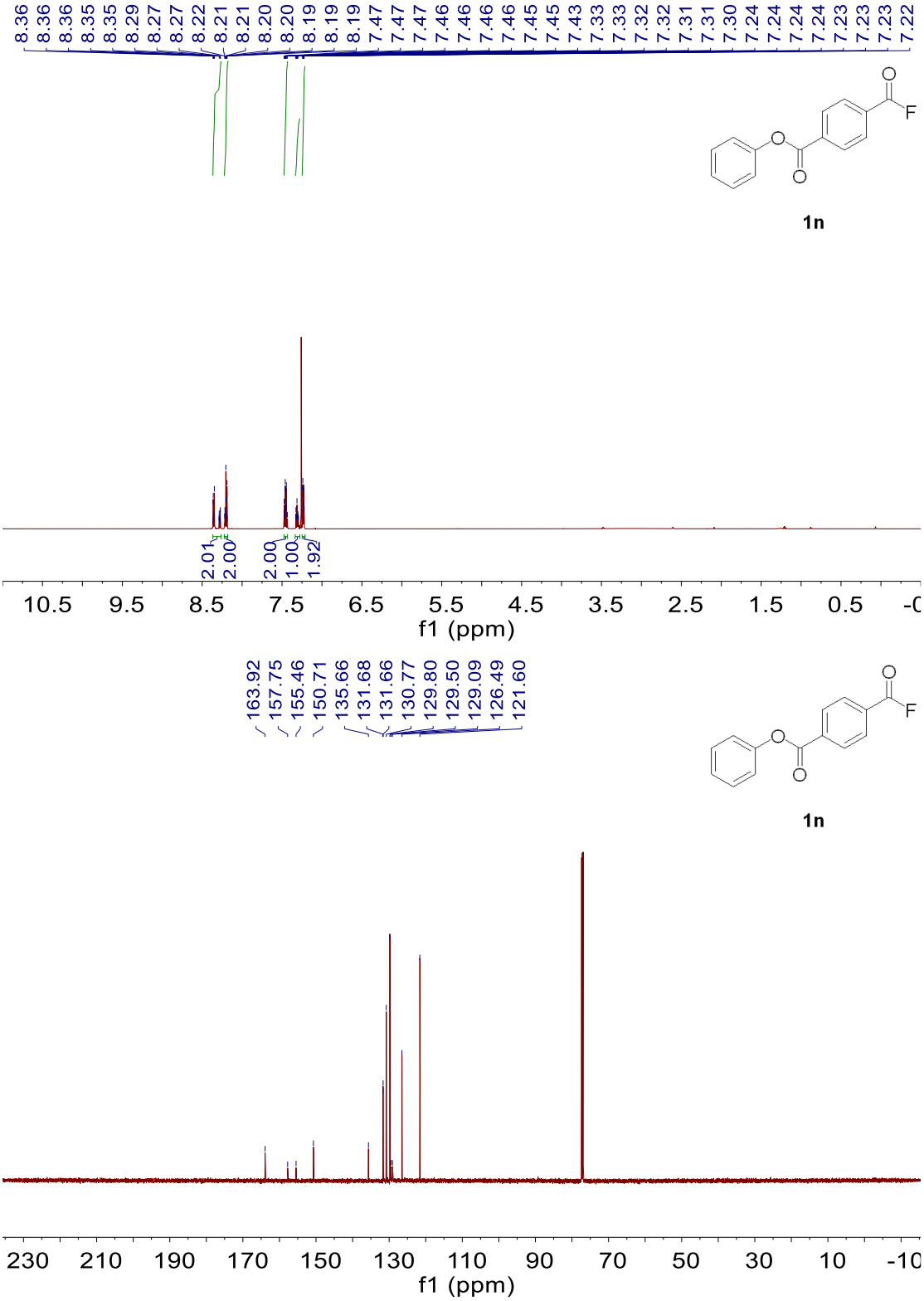
3.07-3.09 (m, 4H), 7.59-7.60 (m, 2H), 7.74-7.75 (m, 2H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 3.3, 7.4, 11.3, 22.3, 50.2, 126.0, 134.7, 140.3, 143.6. FT-IR (neat, cm^{-1}): 608 (s), 721 (s), 999 (s), 1109 (s), 1157 (s), 1225 (m), 1337 (s), 2876 (s), 2959 (s), 3028 (s). Anal. Calcd for $C_{18}H_{33}NO_2SSi$: C, 60.80; H, 9.35; N, 3.94%. Found: C, 60.89; H, 9.60; N, 3.76%.

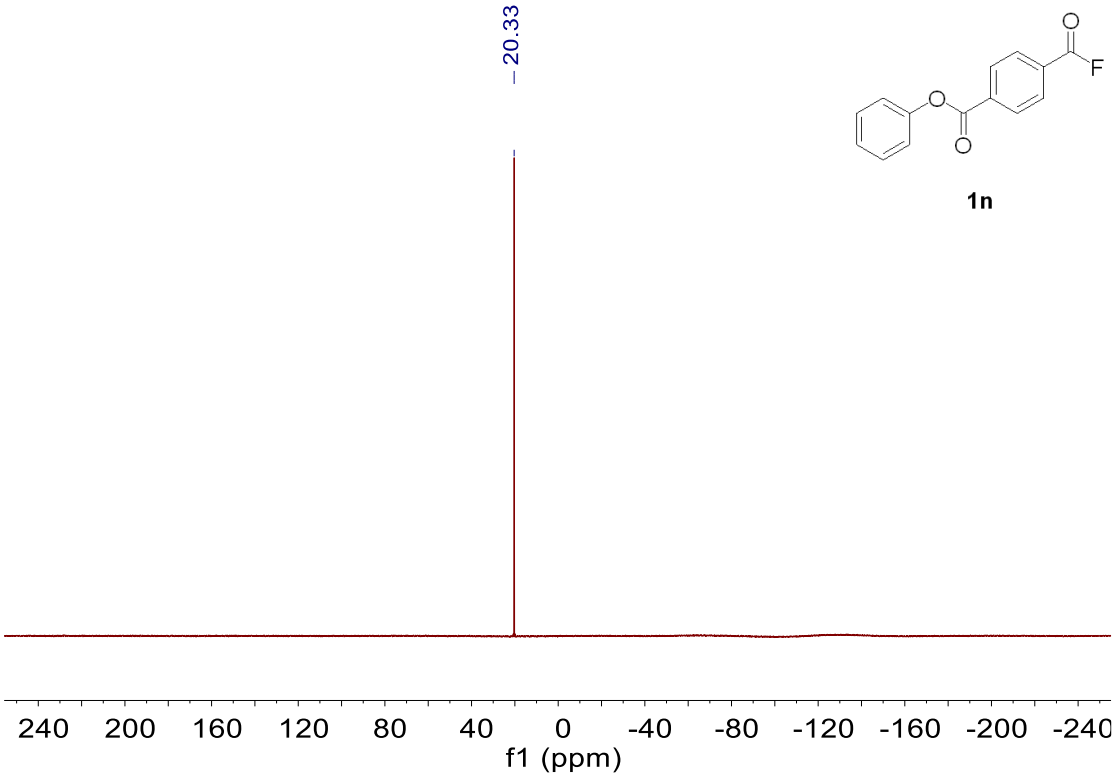
(8R,9S,13S,14S)-13-methyl-3-((4-(triethylsilyl)benzyl)oxy)-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (3v)



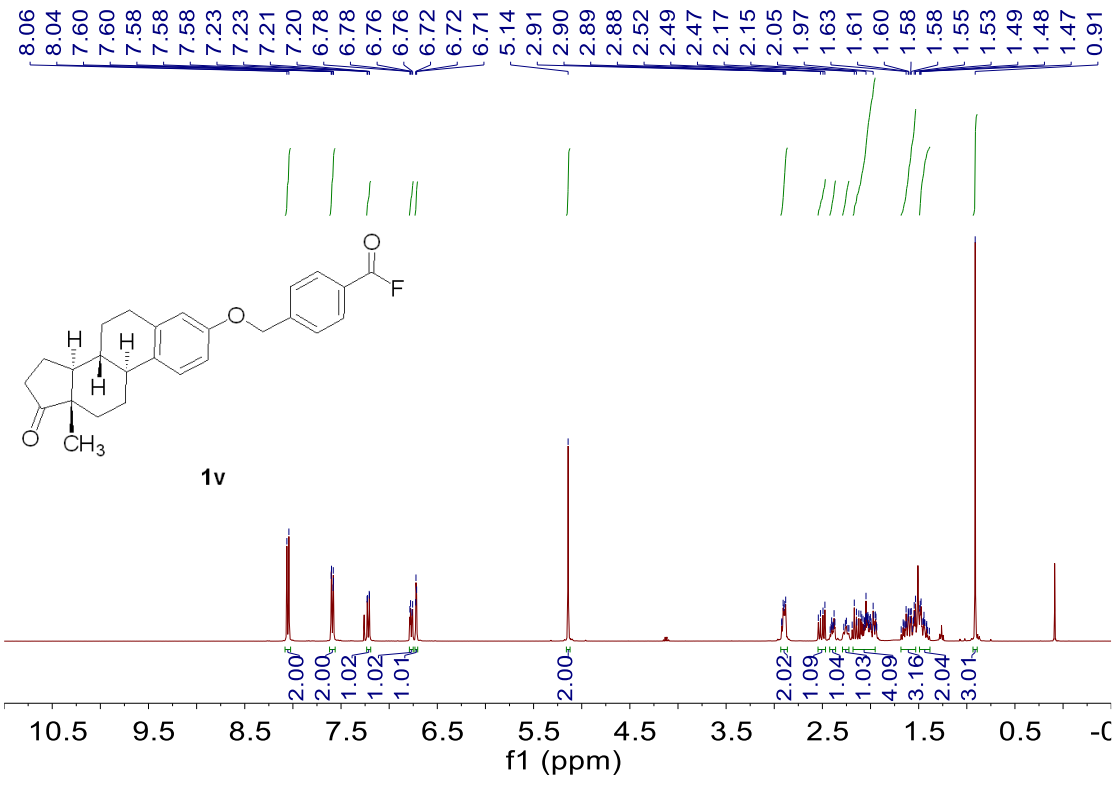
Purification: column chromatography (*n*-hexane/EtOAc = 10:1, R_f = 0.34). Colorless oil. Isolated yield: 75% (71.2 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.80 (qd, J = 7.8, 0.9 Hz, 6H), 0.92 (s, 3H), 0.97 (t, J = 8.4 Hz, 9H), 1.41-1.60 (m, 5H), 1.63-1.67 (m, 1H), 1.95-1.97 (m, 1H), 1.99-2.08 (m, 2H), 2.12-2.18 (m, 1H), 2.25-2.29 (m, 1H), 2.39-2.42 (m, 1H), 2.49-2.53 (m, 1H), 2.90-2.93 (m, 2H), 5.03 (s, 2H), 6.75 (d, J = 2.4 Hz, 1H), 6.81 (dd, J = 8.4, 3.0 Hz, 1H), 7.21 (dd, J = 8.4, 1.2 Hz, 1H), 7.42 (d, J = 7.8 Hz, 2H), 7.51 (d, J = 7.8 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 3.3, 7.4, 13.9, 21.6, 25.9, 26.6, 29.7, 31.6, 35.9, 38.4, 44.0, 48.0, 50.4, 70.0, 112.3, 114.8, 126.4, 126.8, 132.3, 134.5, 137.1, 137.6, 137.8, 156.9, 221.0. FT-IR (KBr): 3019, 2955, 2936, 2913, 2876, 2399, 2363, 2344, 1734, 1607, 1499, 1215, 1163, 1101, 1055, 1007, 930, 895, 770, 752, 669 cm^{-1}. HRMS (FAB^+): Calcd for $C_{31}H_{42}O_2Si$: 474.2954. Found: 474.2931.

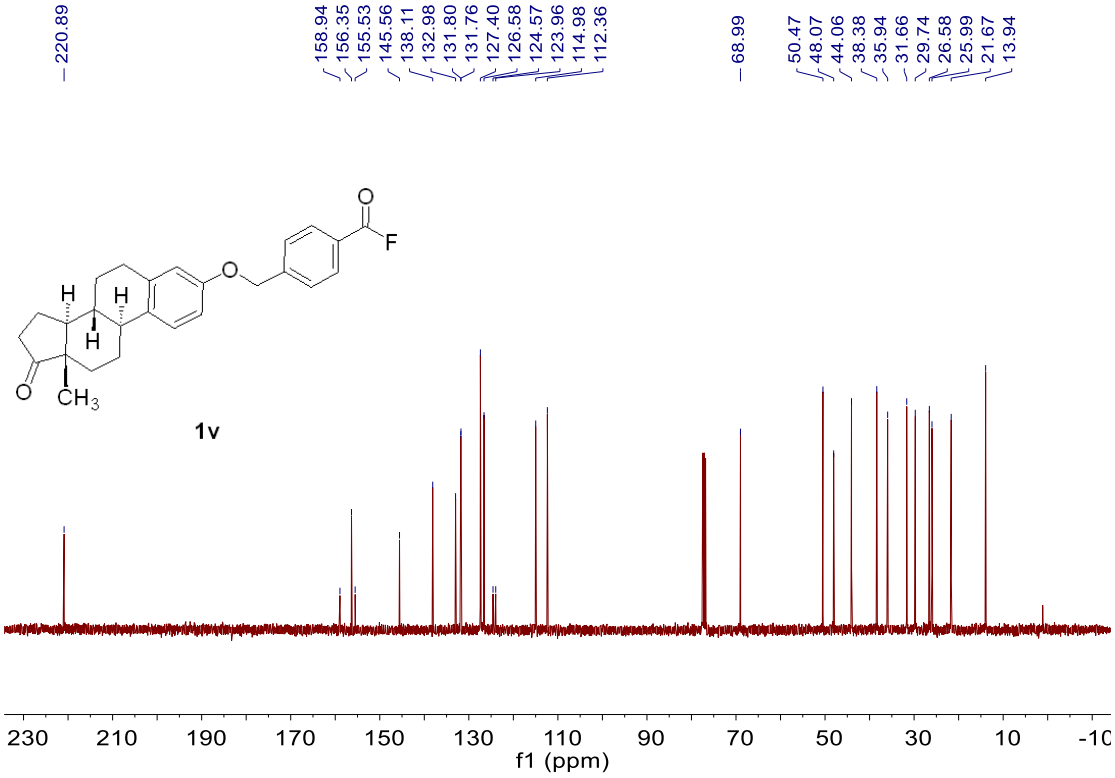
2-4-3 Copies of NMR Charts for Products

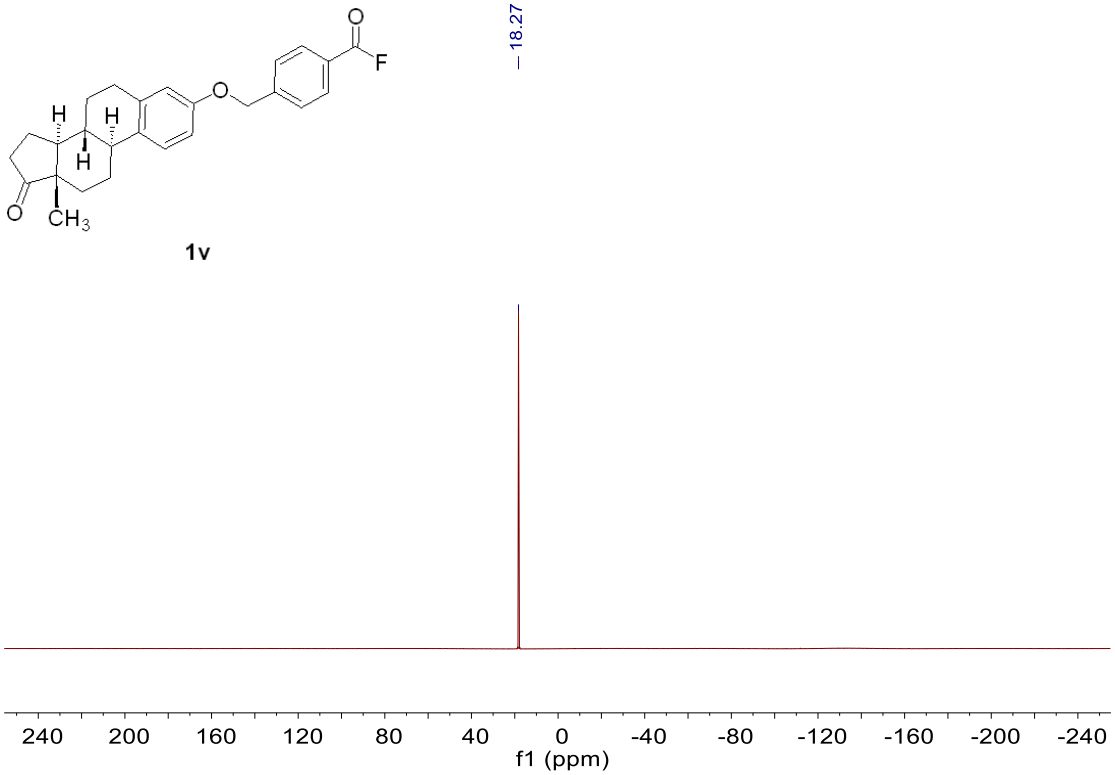




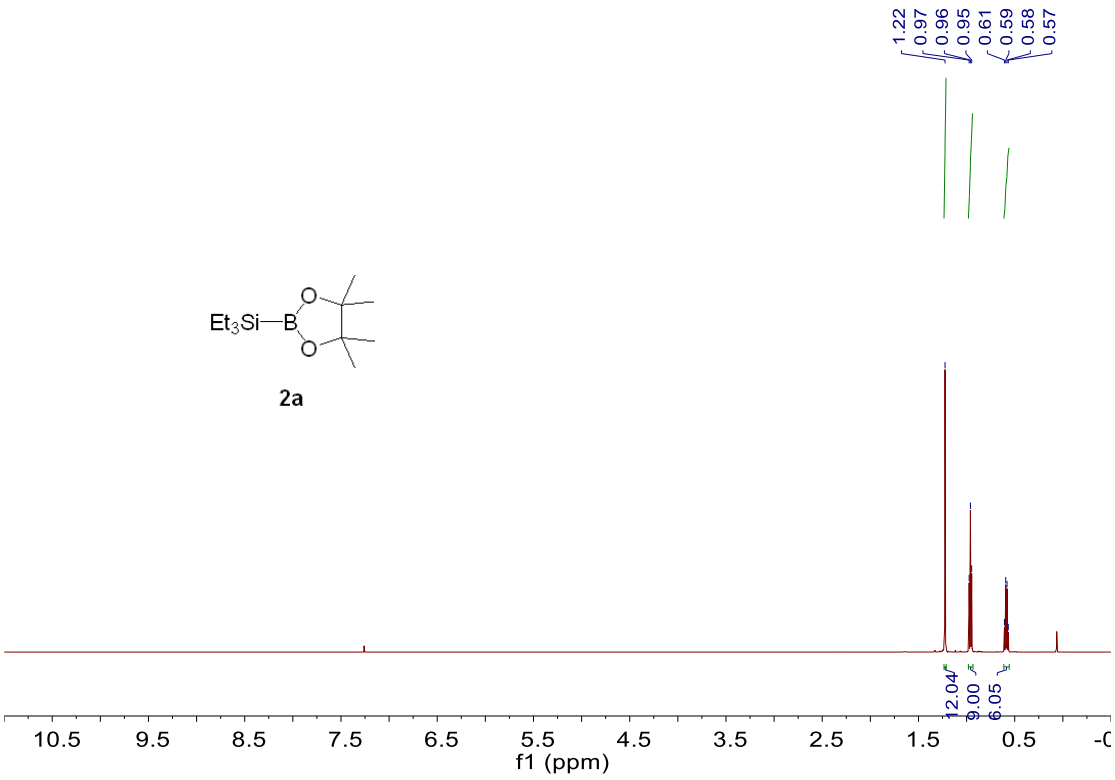
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz), and ^{19}F{^{1}H} NMR (376 MHz) spectra of **1n** ($CDCl_3$, rt).

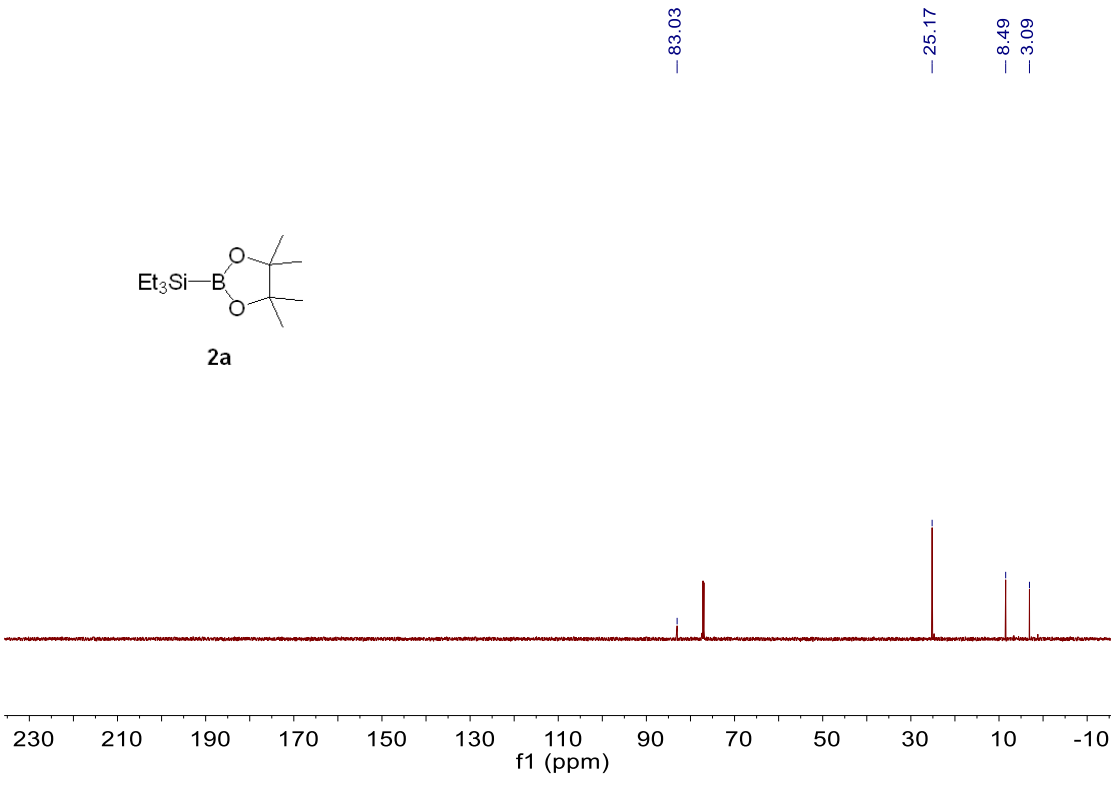


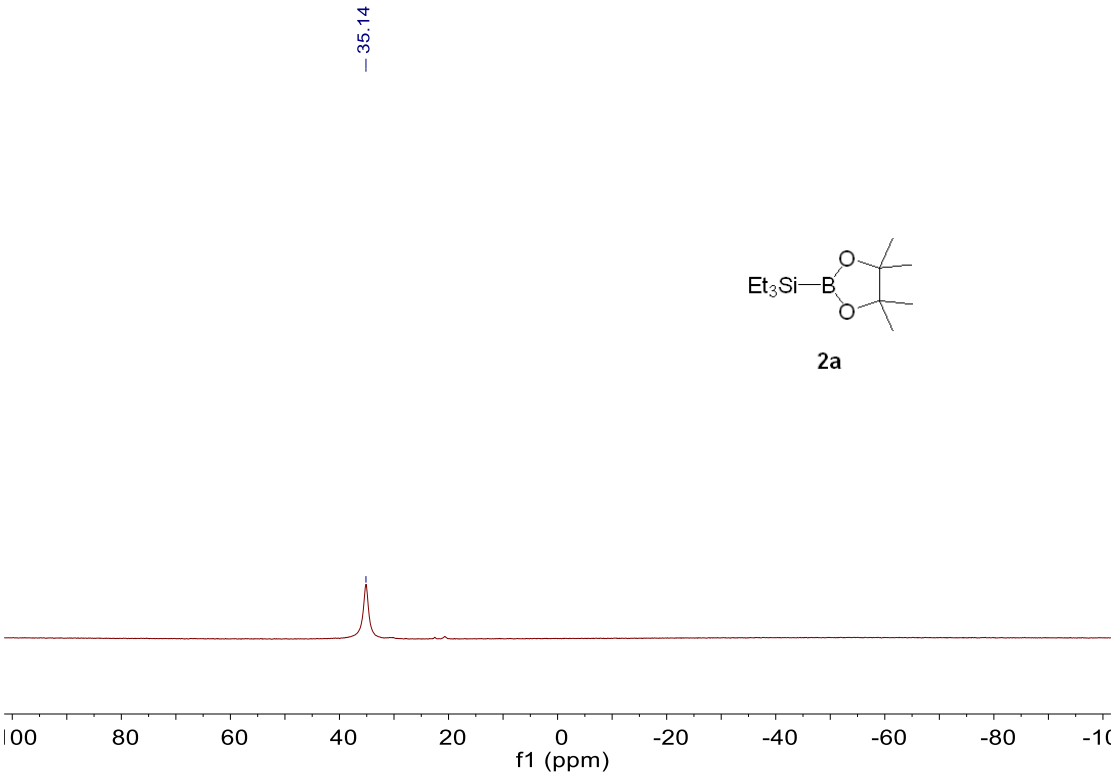




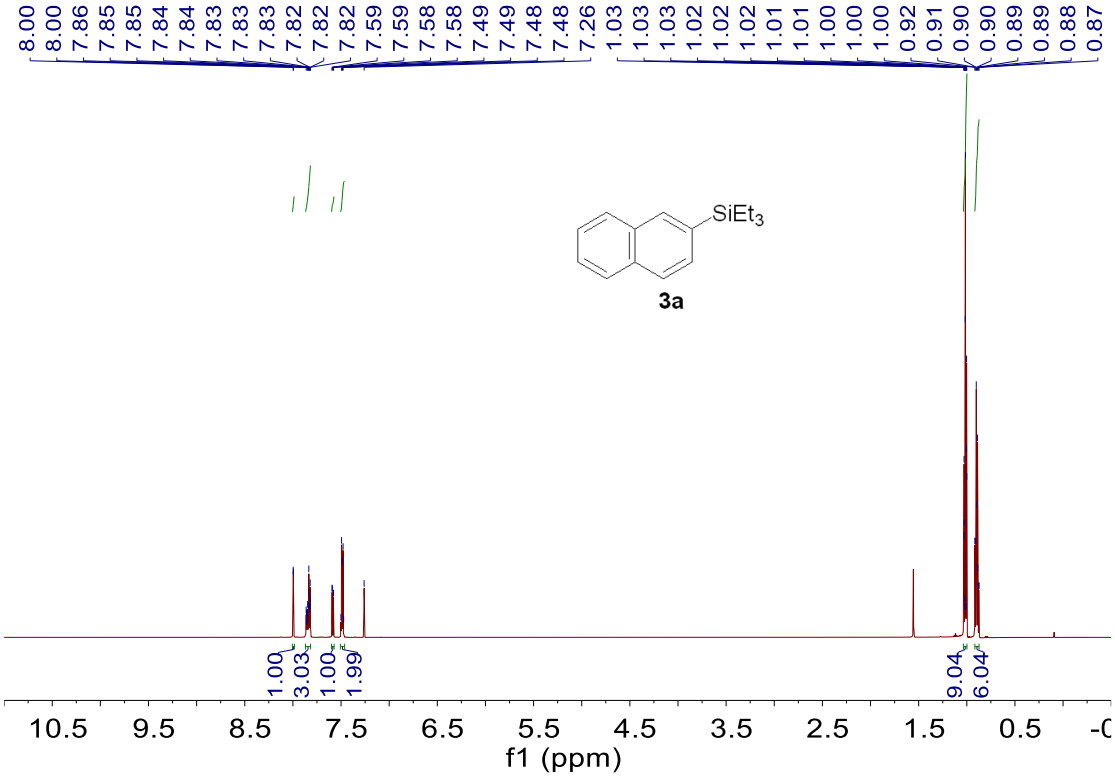
^{1}H NMR (400 MHz), ^{13}C{^{1}H} NMR (101 MHz), and ^{19}F{^{1}H} NMR (376 MHz) spectra of **1v** (rt., $CDCl_3$)


1.22
0.97
0.96
0.95
0.61
0.59
0.58
0.57
Et3Si—B
O
O
2a
12.04
9.00
6.05
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

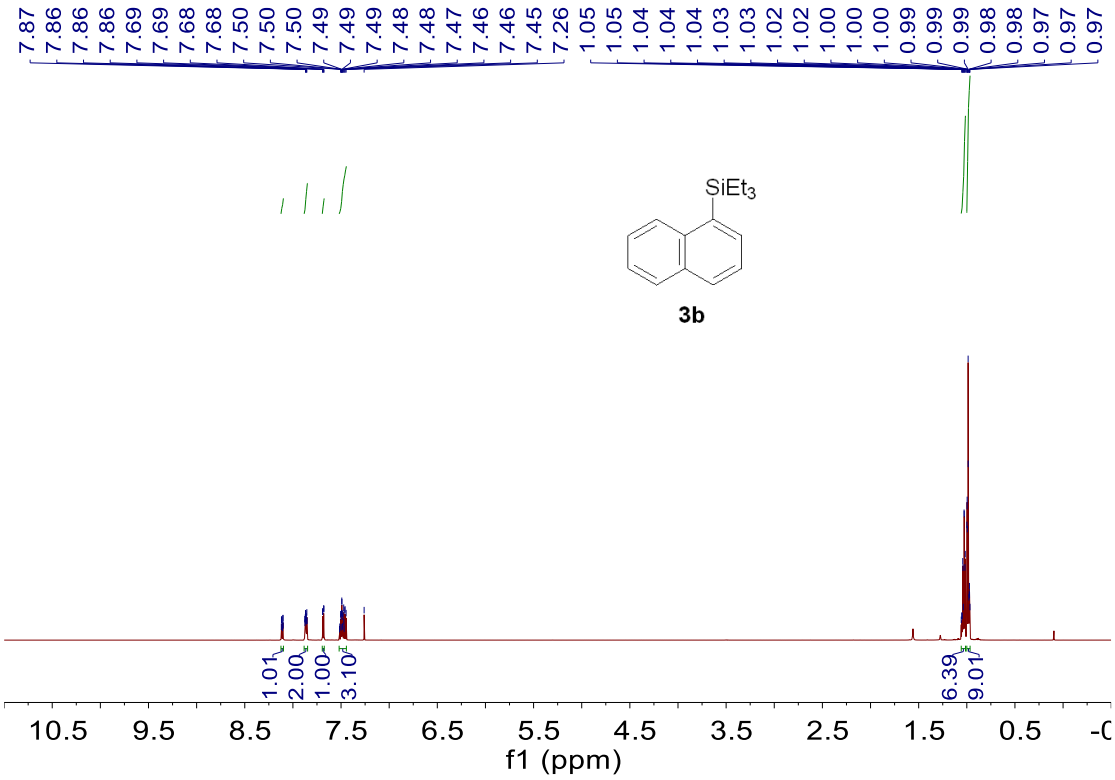

83.03
25.17
8.49
3.09
Et3Si—B
O
O
2a
230
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)



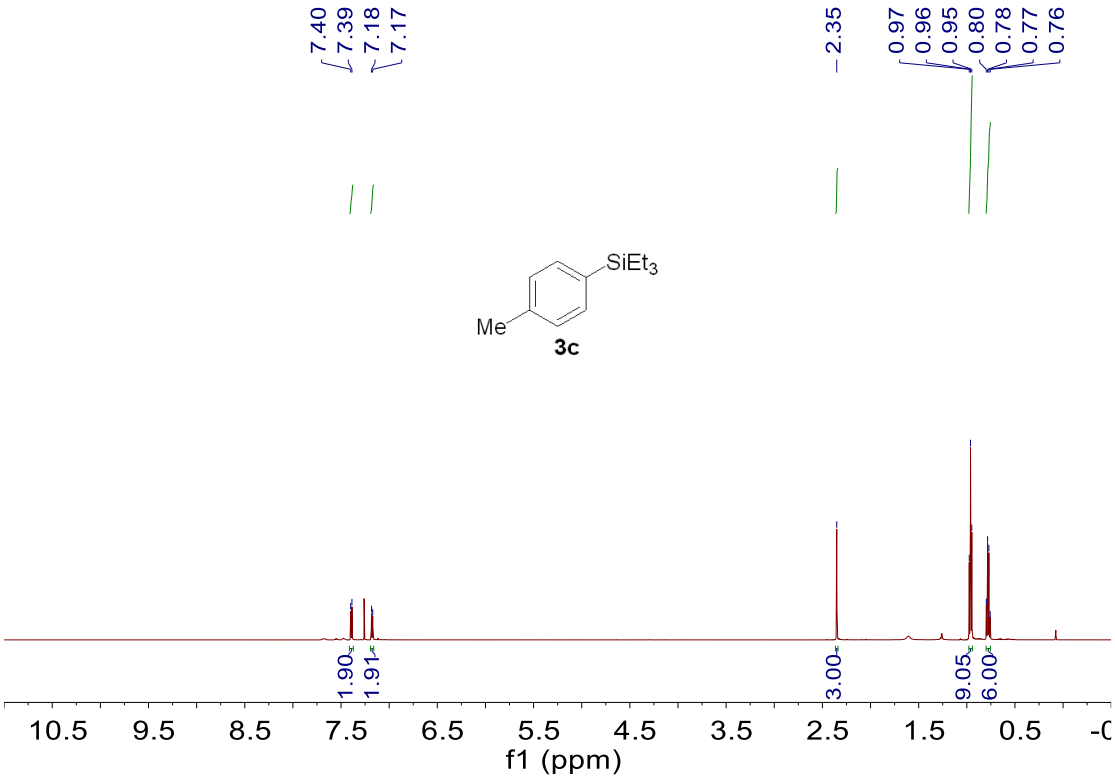
^{1}H NMR (600 MHz), ^{13}C{^{1}H} NMR (151 MHz), and ^{11}B{^{1}H} NMR (192 MHz) spectra of **2a** ($CDCl_3$, rt).



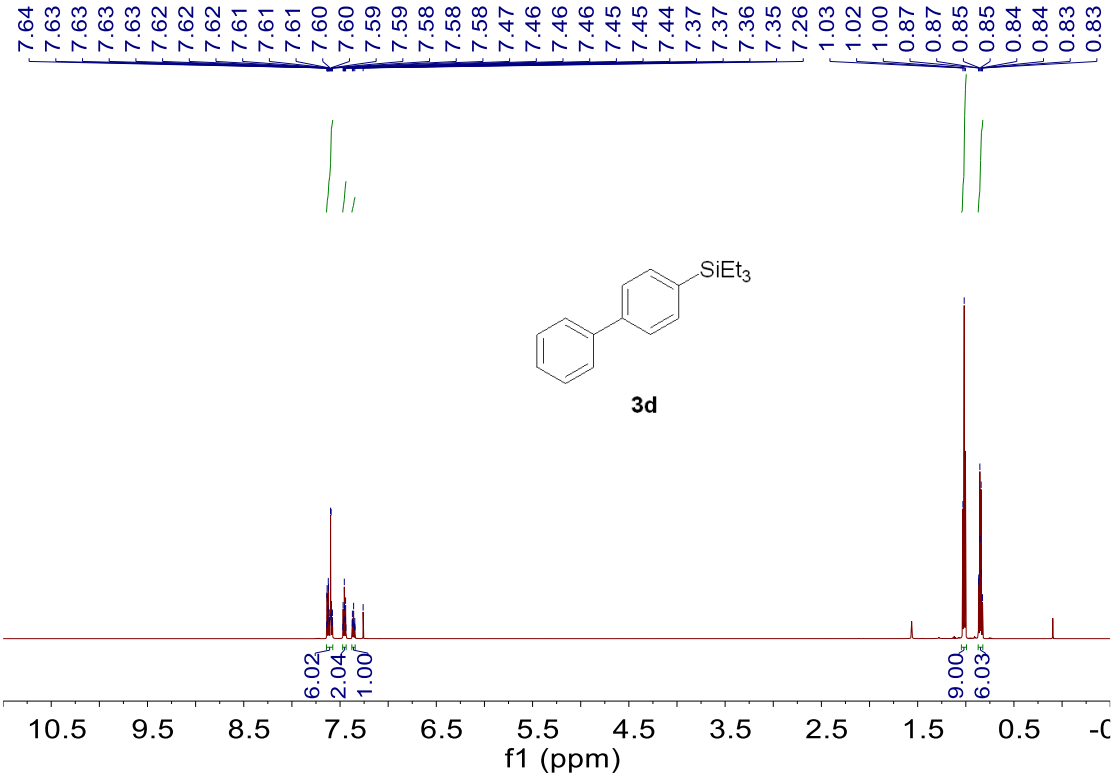
^{1}H NMR (600 MHz) spectrum of **3a** ($CDCl_3$, rt).



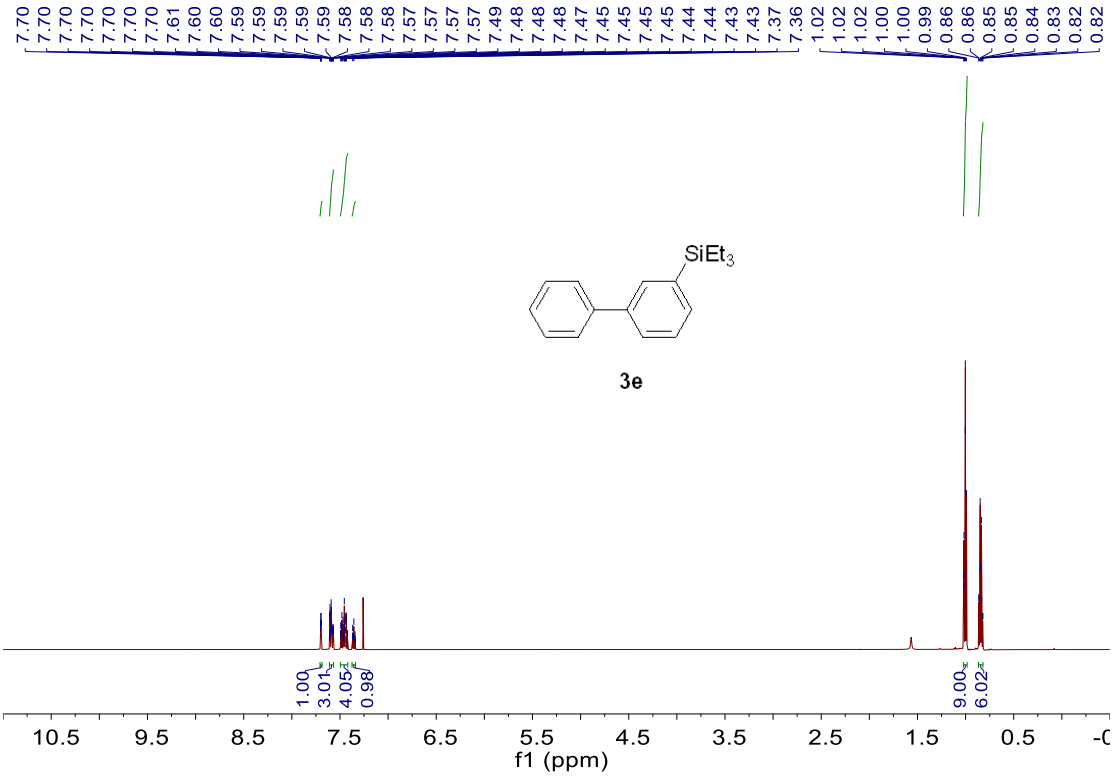
^{1}H NMR (600 MHz) spectrum of **3b** ($CDCl_3$, rt).



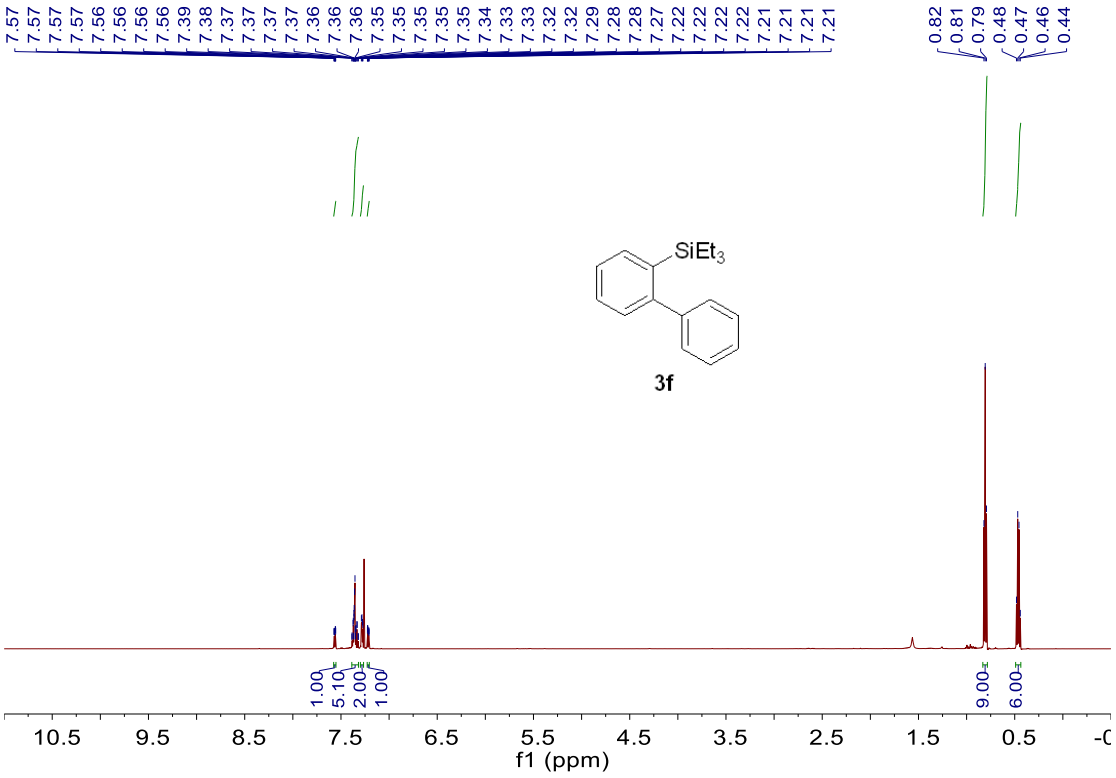
^{1}H NMR (600 MHz) spectrum of **3c** ($CDCl_3$, rt).



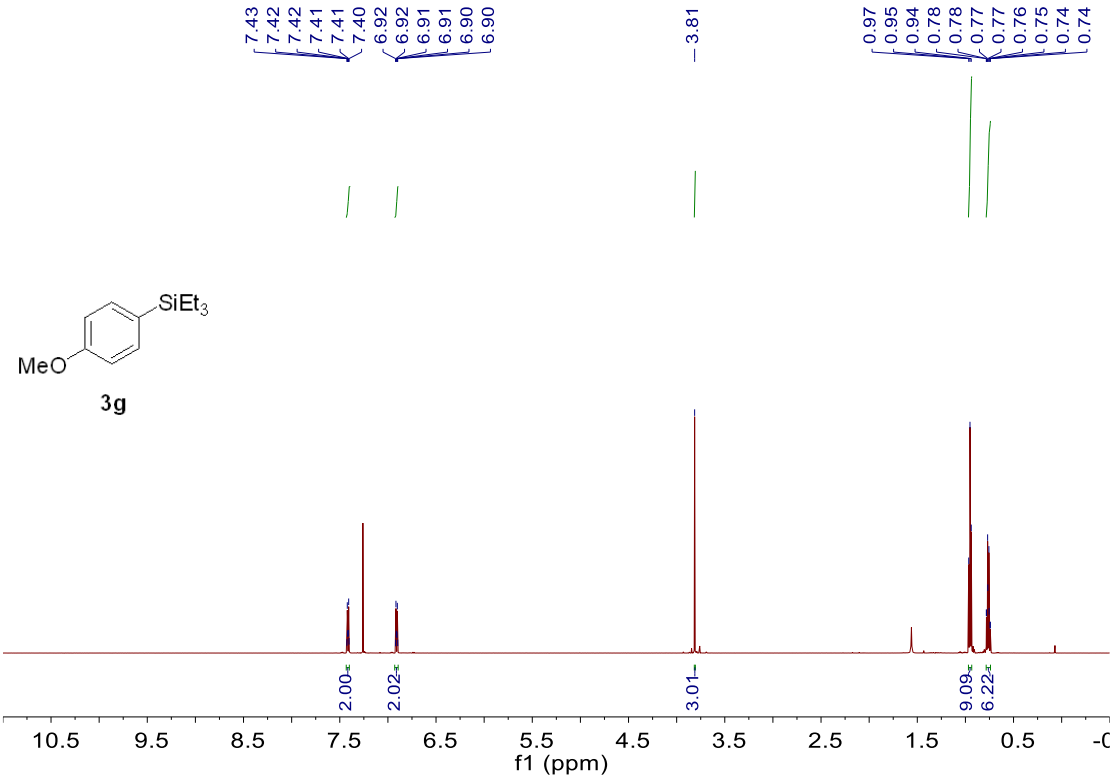
^{1}H NMR (600 MHz) spectrum of **3d** ($CDCl_3$, rt).



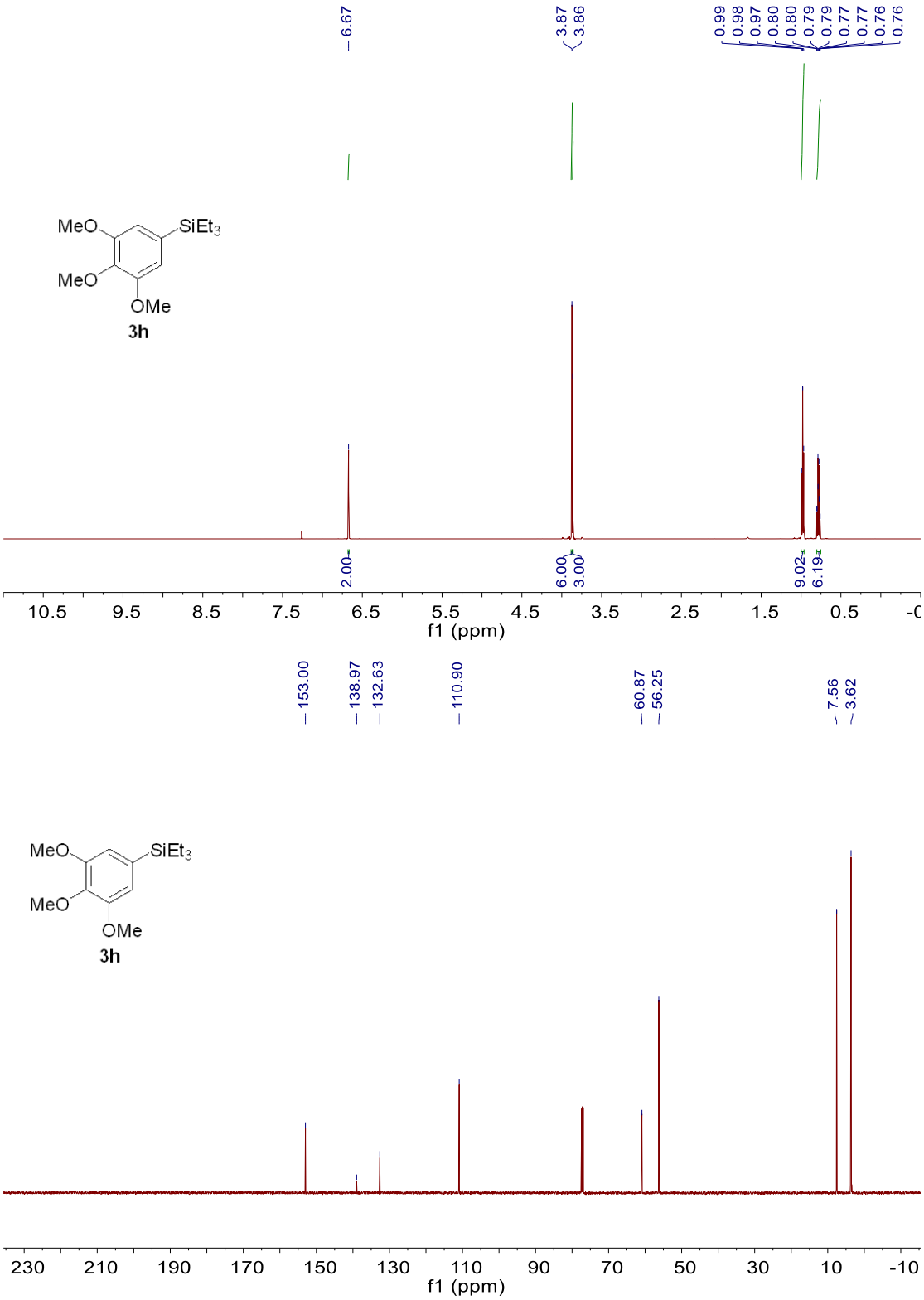
^{1}H NMR (600 MHz) spectrum of **3e** ($CDCl_3$, rt).



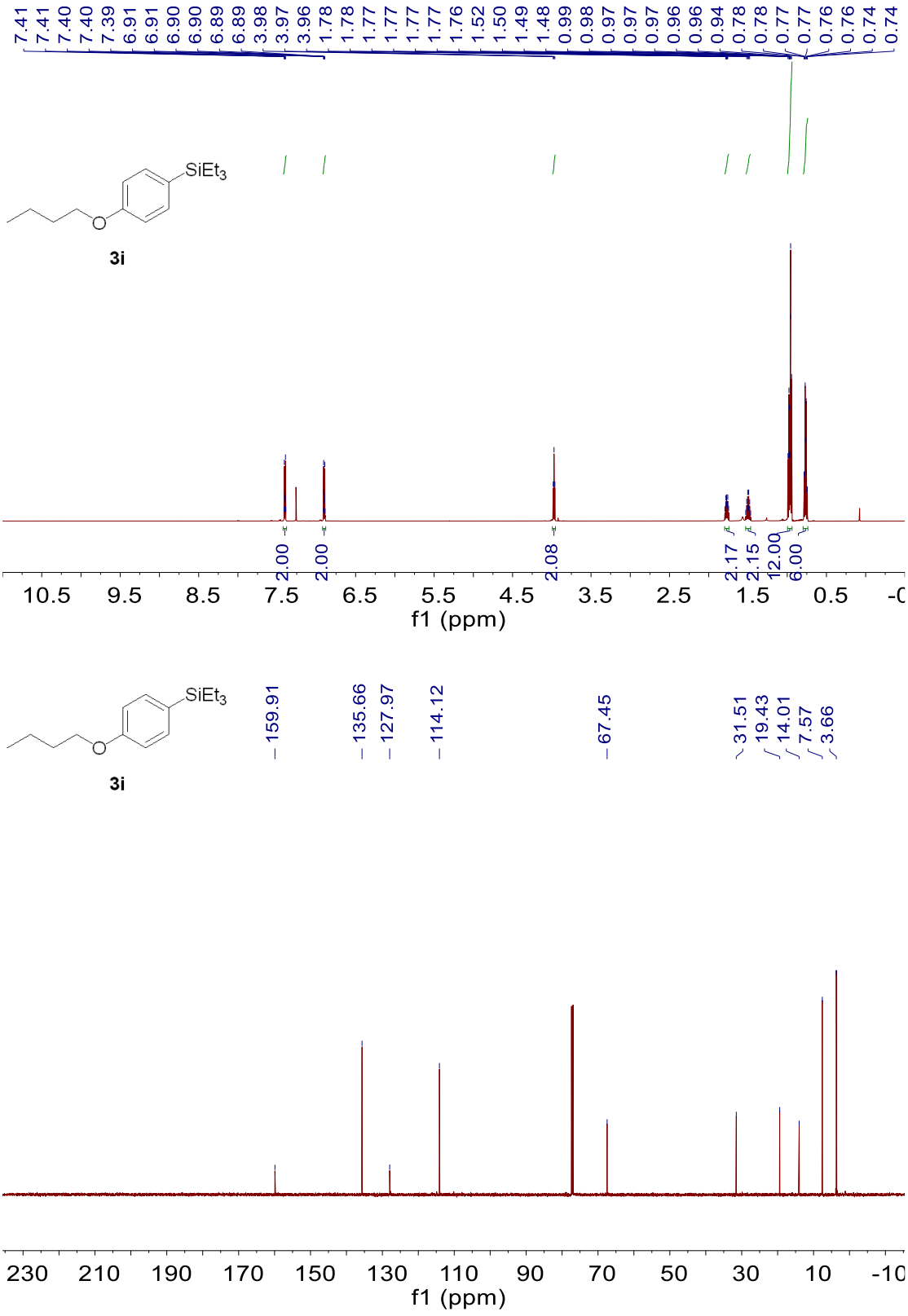
^{1}H NMR (600 MHz) spectrum of **3f** ($CDCl_3$, rt).



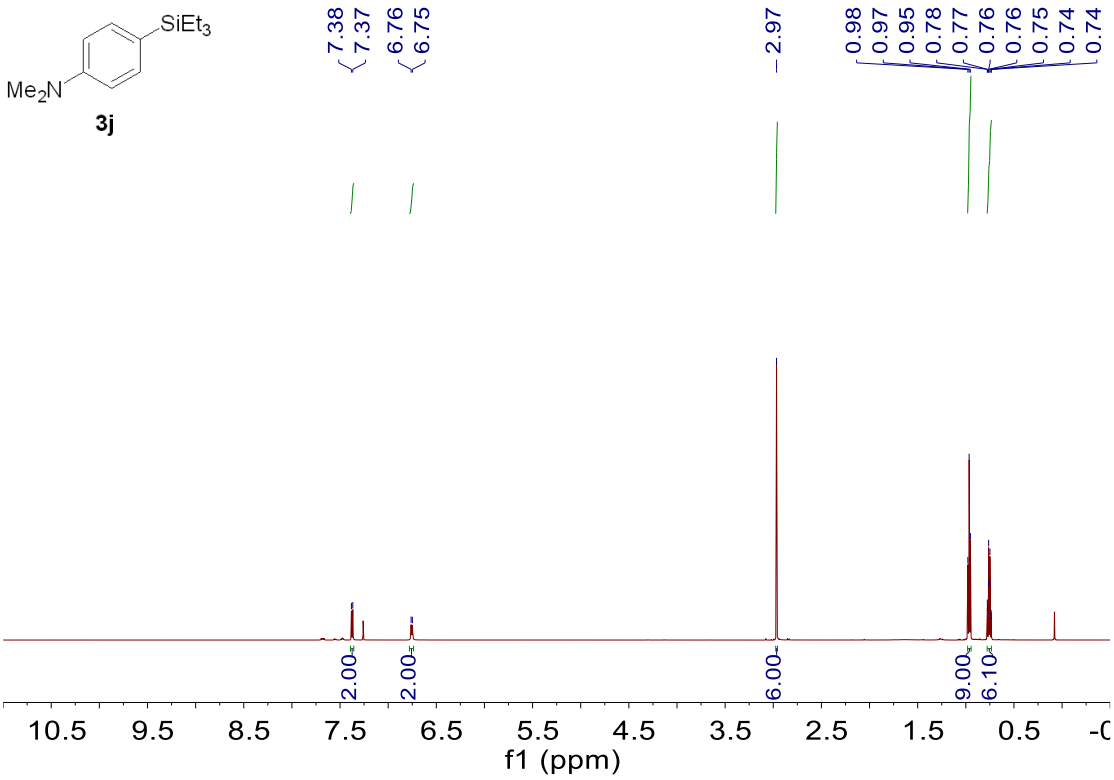
^{1}H NMR (600 MHz) spectrum of **3g** ($CDCl_3$, rt).



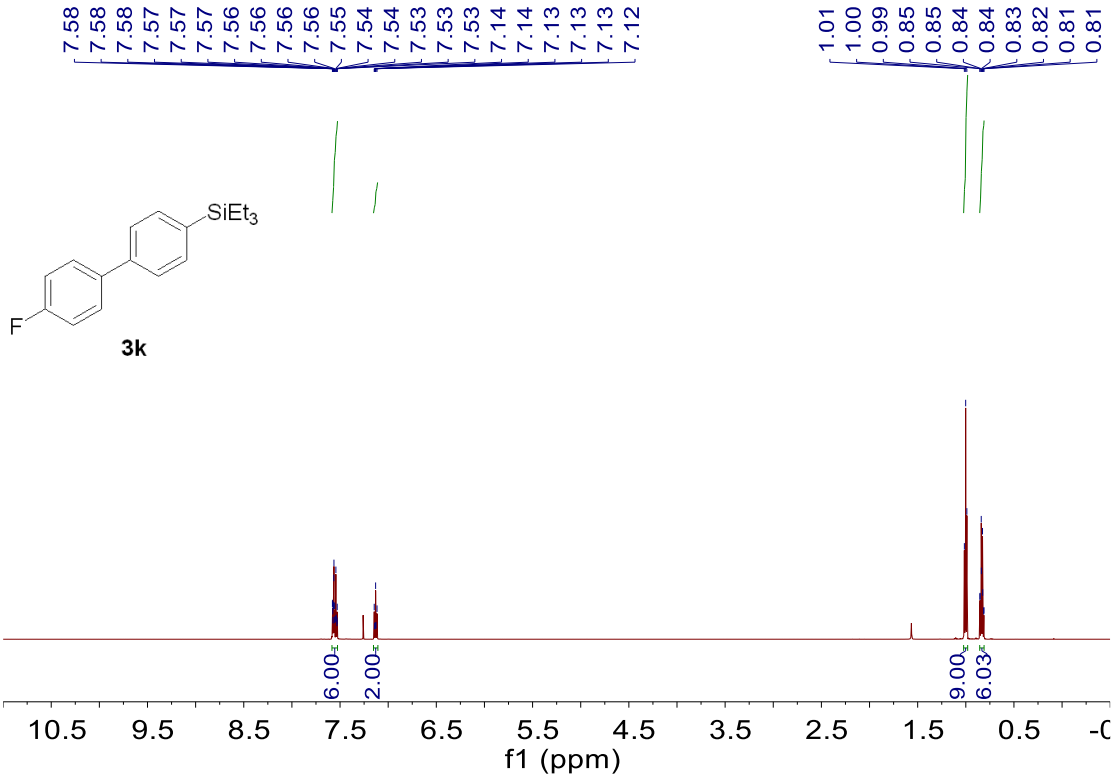
^{1}H NMR (600 MHz) and ^{13}C{^{1}H} NMR (151 MHz) spectra of **3h** ($CDCl_3$, rt).

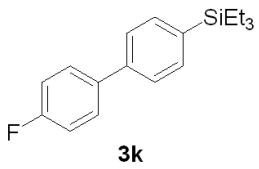


^{1}H NMR (600 MHz) and ^{13}C{^{1}H} NMR (151 MHz) spectra of **3i** ($CDCl_3$, rt).



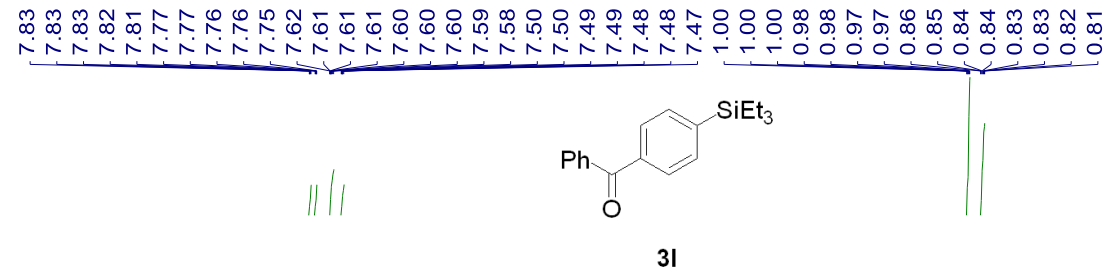
^{1}H NMR (600 MHz) spectrum of **3j** ($CDCl_3$, rt).



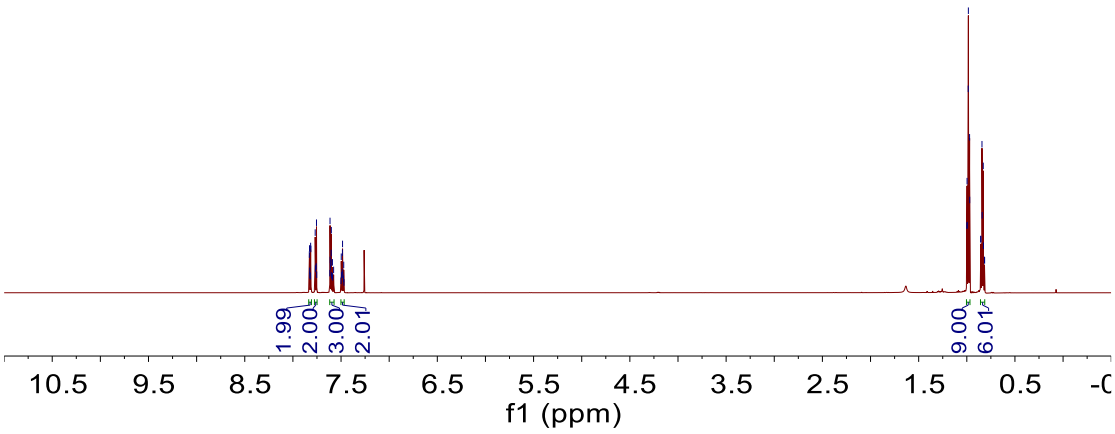


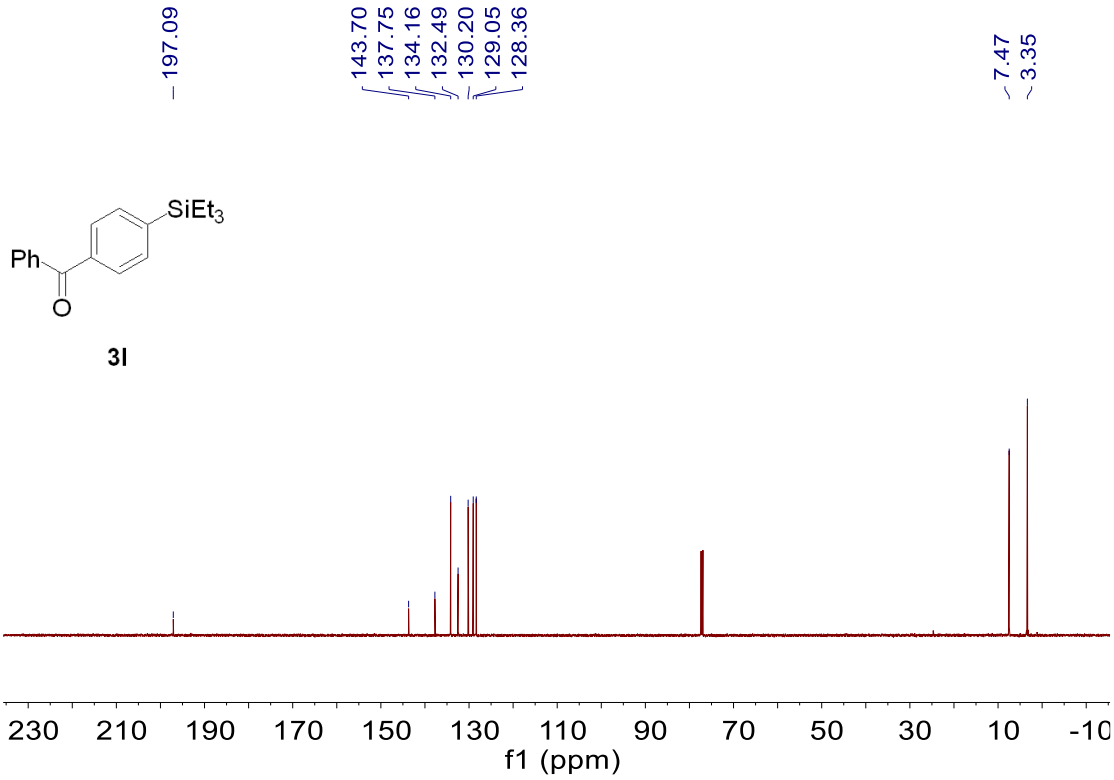
3k

^{1}H NMR (600 MHz) and ^{19}F{^{1}H} NMR (376 MHz) spectra of **3k** ($CDCl_3$, rt).

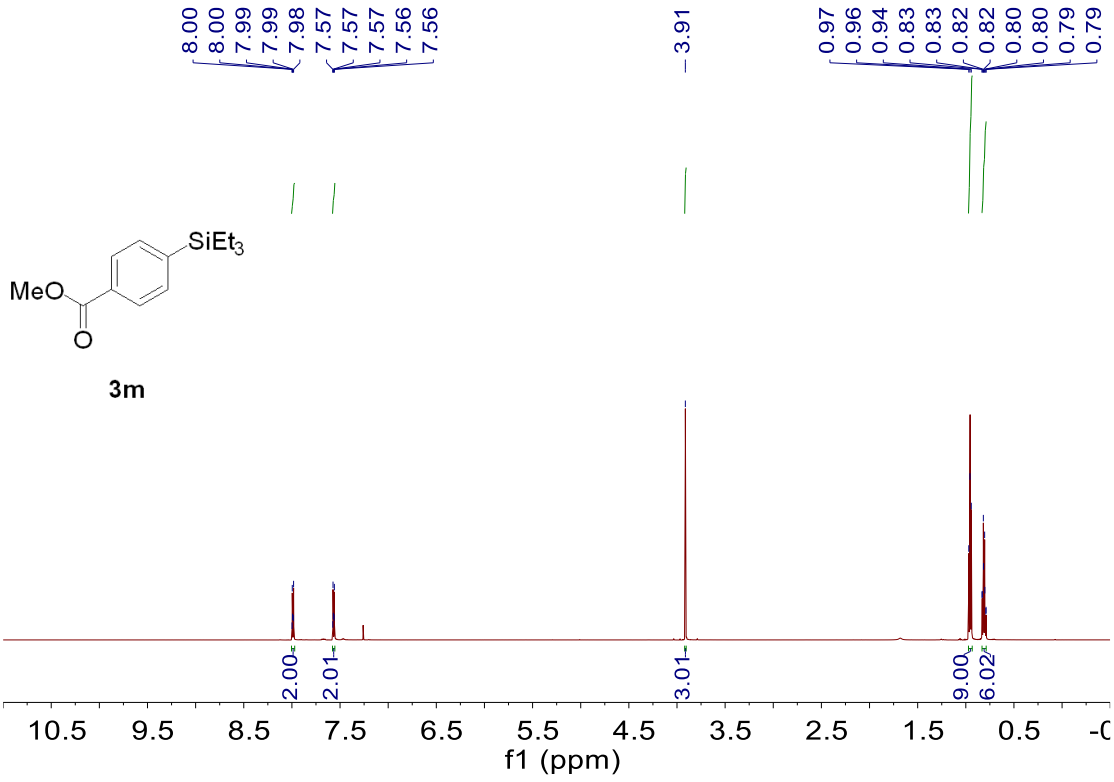


3l

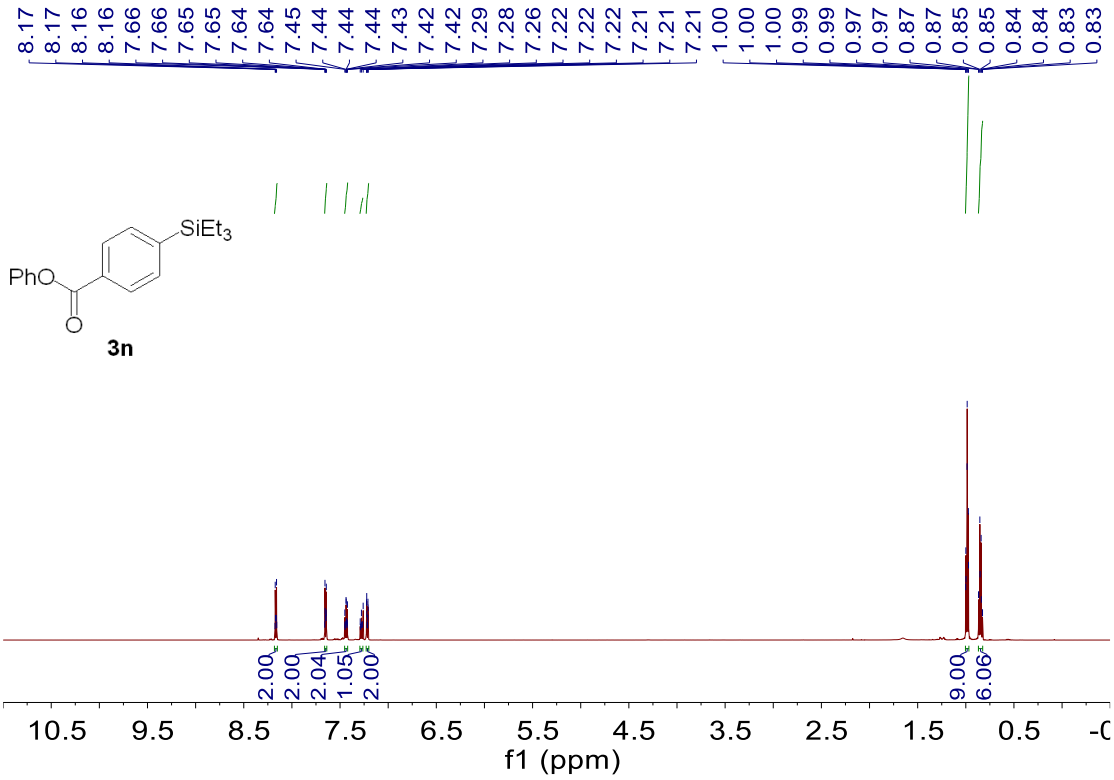




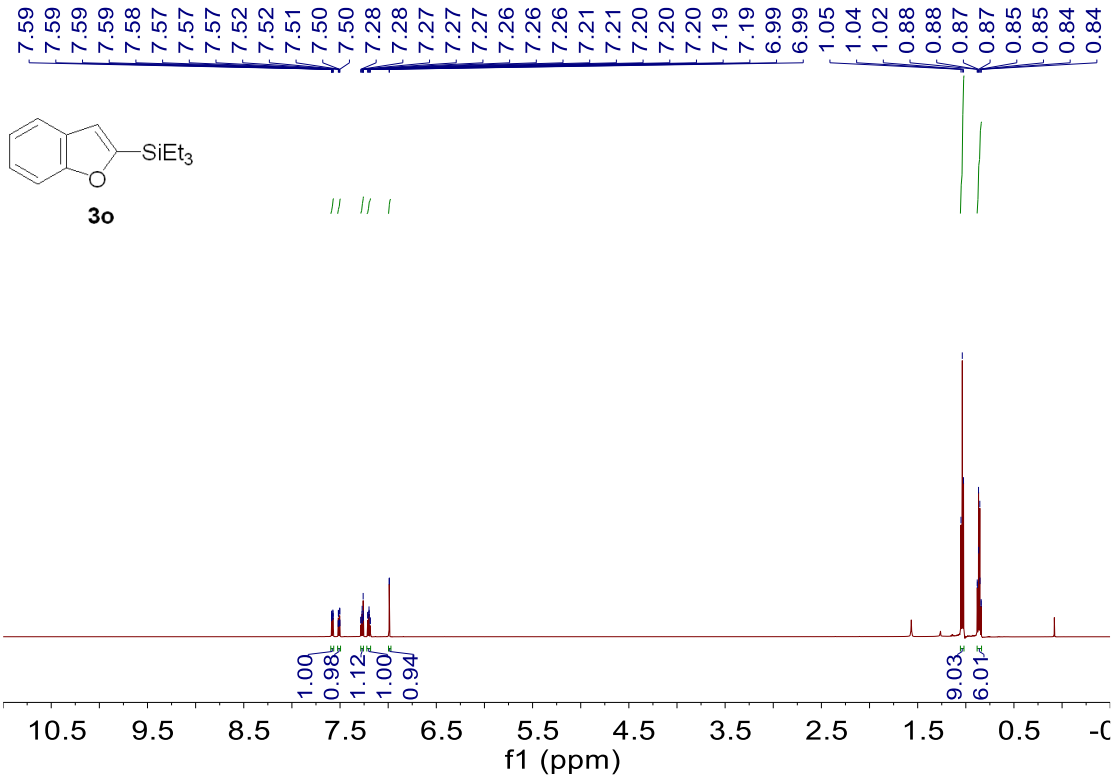
^{1}H NMR (600 MHz) and ^{13}C{^{1}H} NMR (151 MHz) spectra of **3l** ($CDCl_3$, rt).



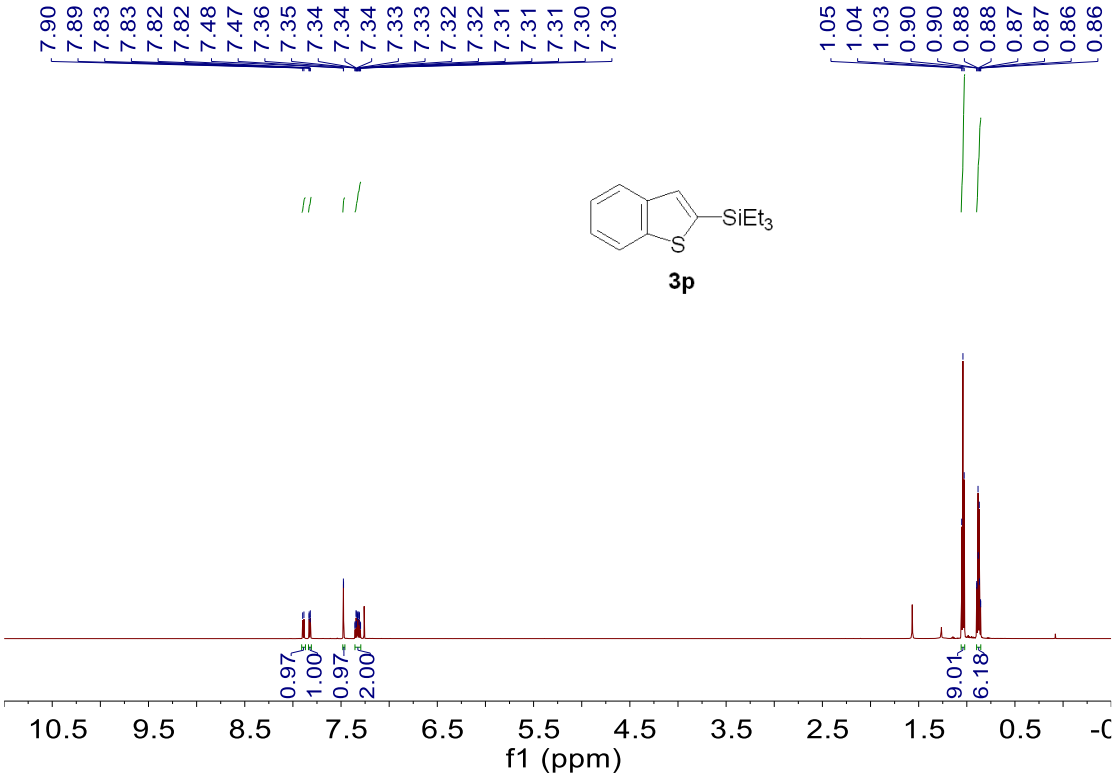
^{1}H NMR (600 MHz) spectrum of **3m** ($CDCl_3$, rt).



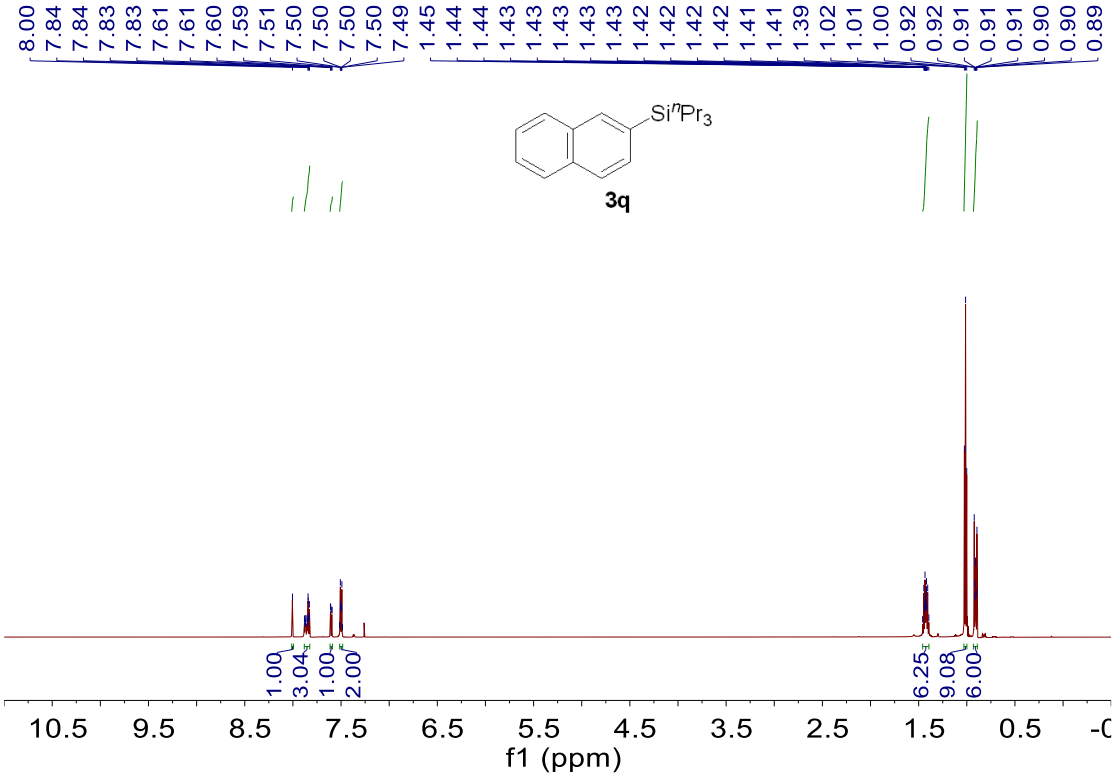
^{1}H NMR (600 MHz) spectrum of **3n** ($CDCl_3$, rt).



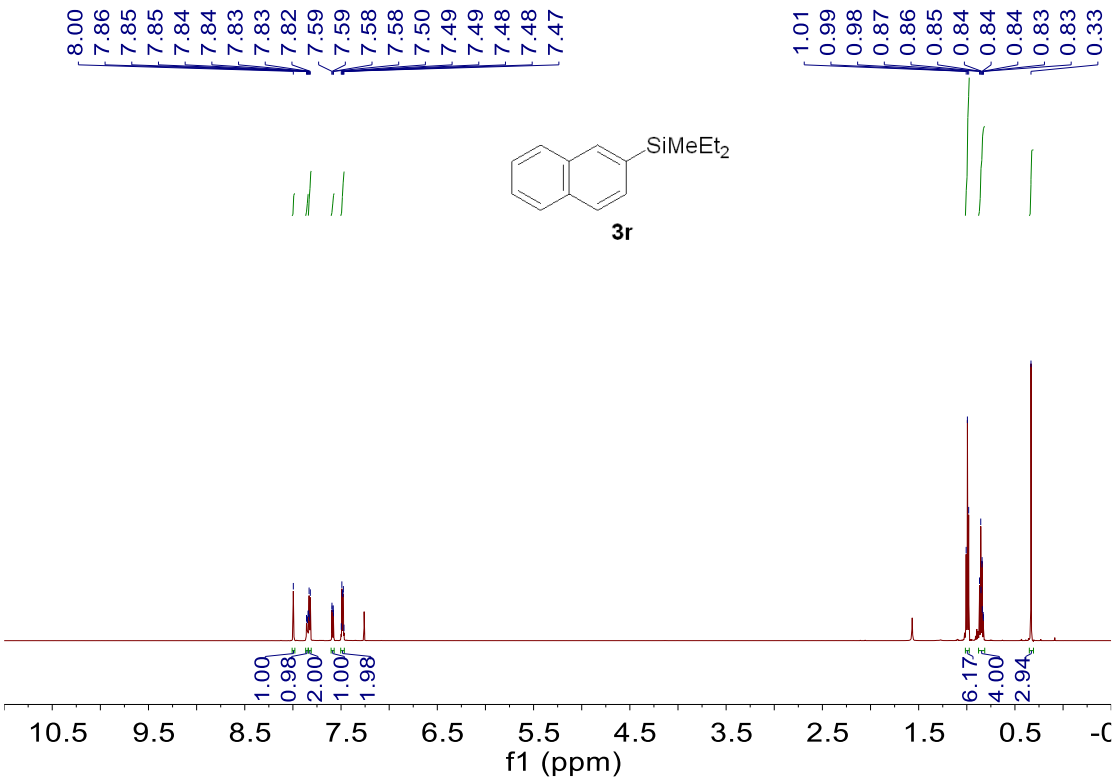
^{1}H NMR (600 MHz) spectrum of **3o** ($CDCl_3$, rt).



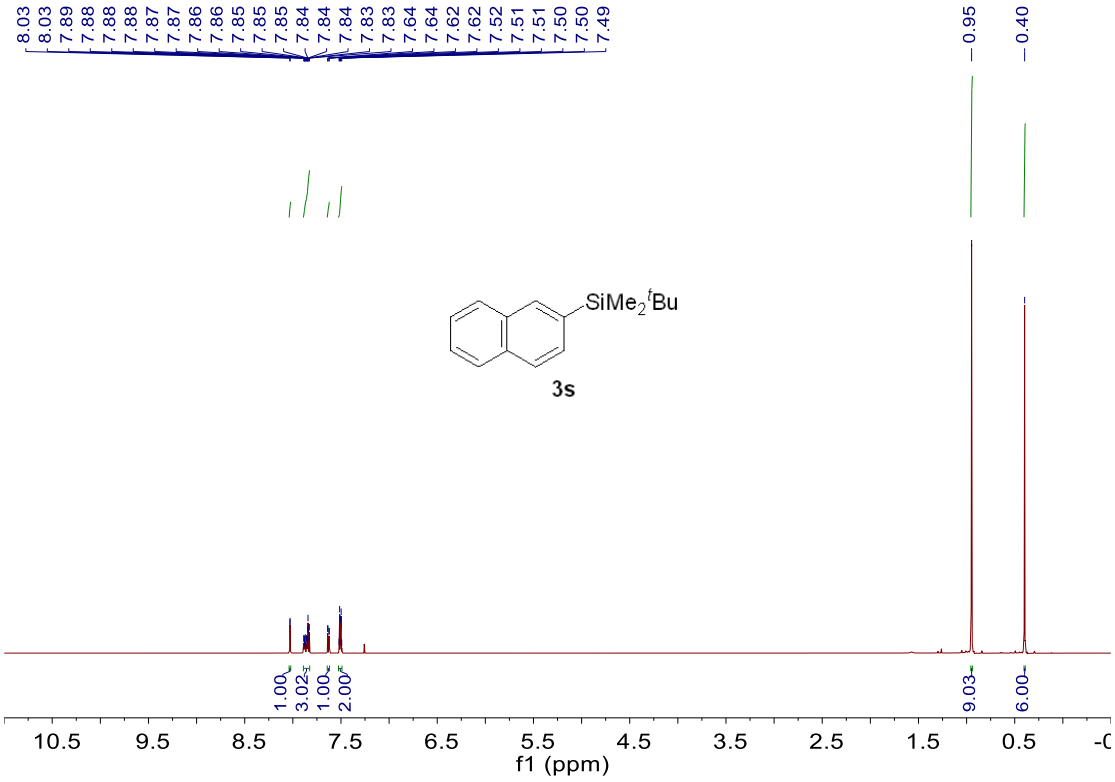
^{1}H NMR (600 MHz) spectrum of **3p** ($CDCl_3$, rt).



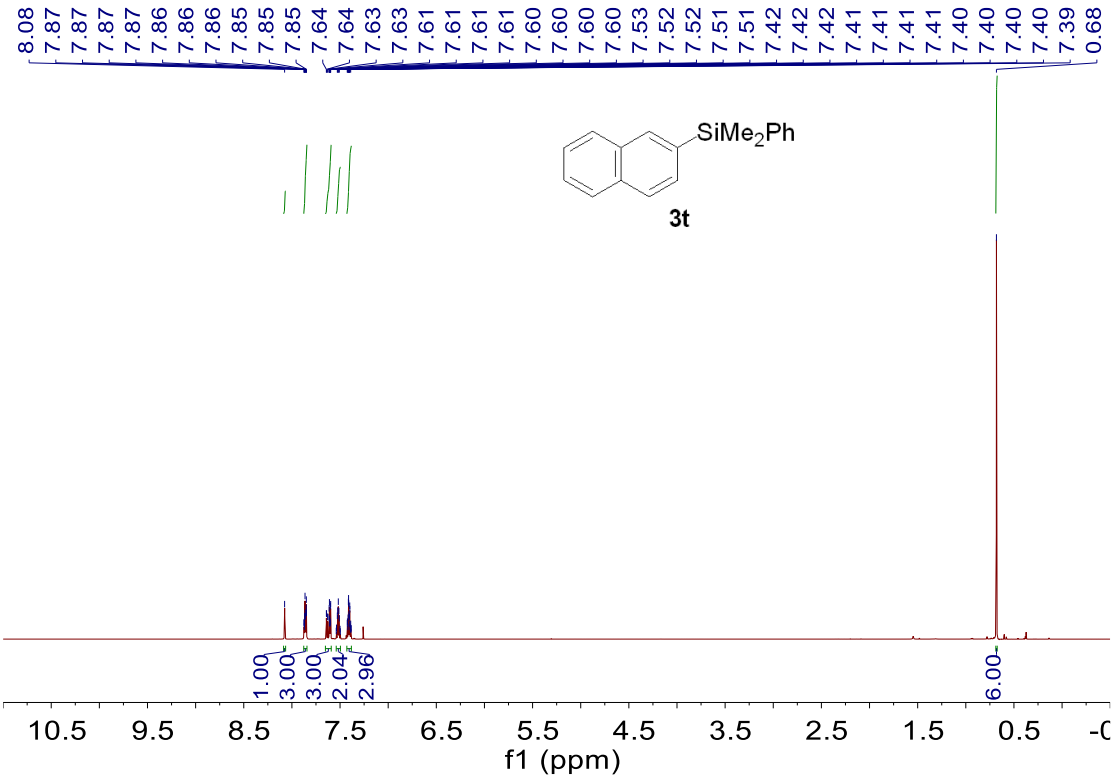
^{1}H NMR (600 MHz) spectrum of **3q** ($CDCl_3$, rt).



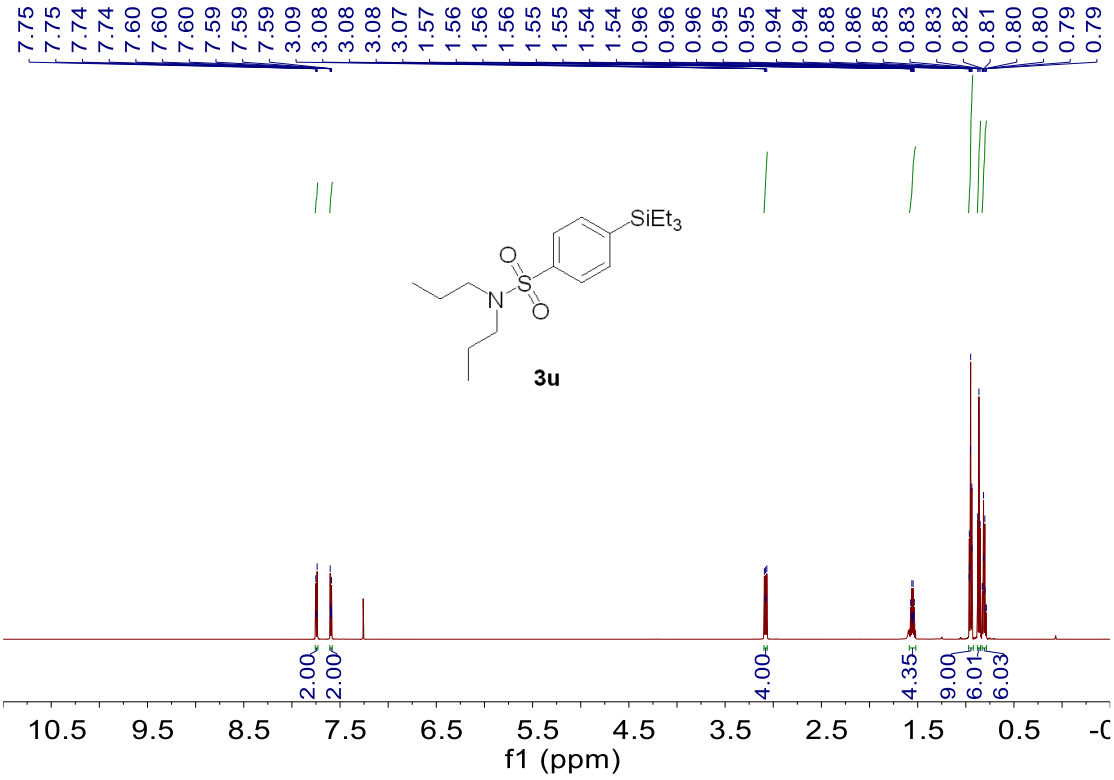
^{1}H NMR (600 MHz) spectrum of **3r** ($CDCl_3$, rt).

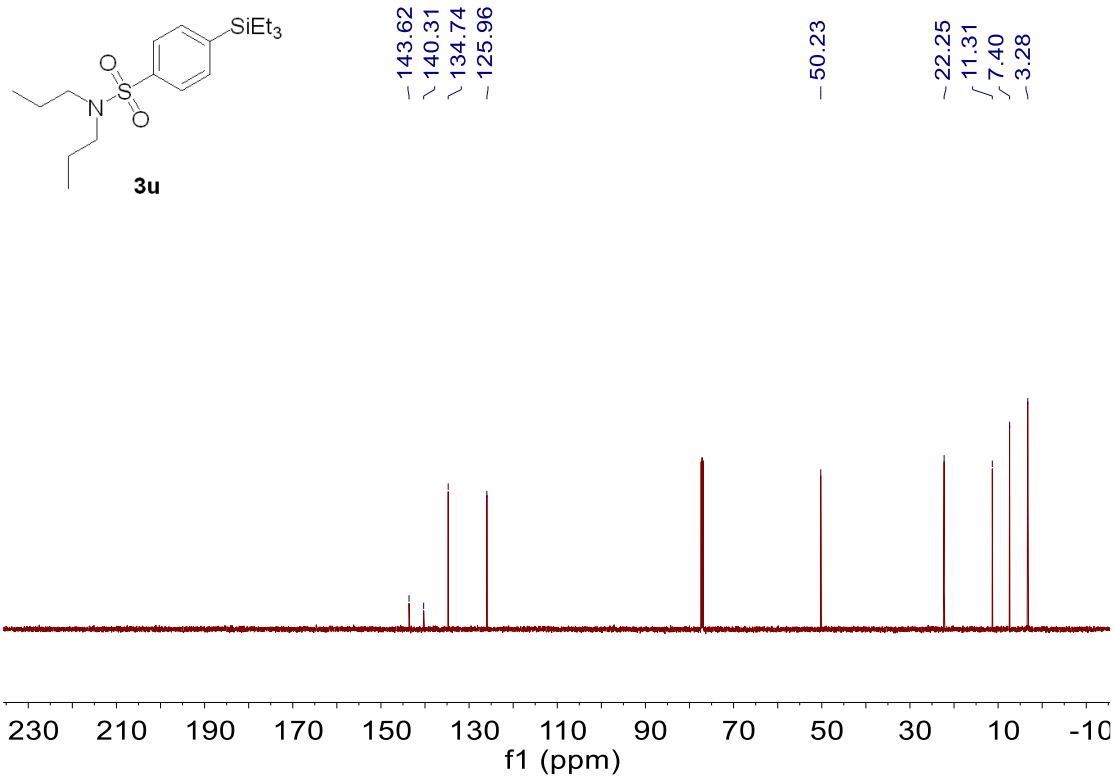


^{1}H NMR (600 MHz) spectrum of **3s** ($CDCl_3$, rt).

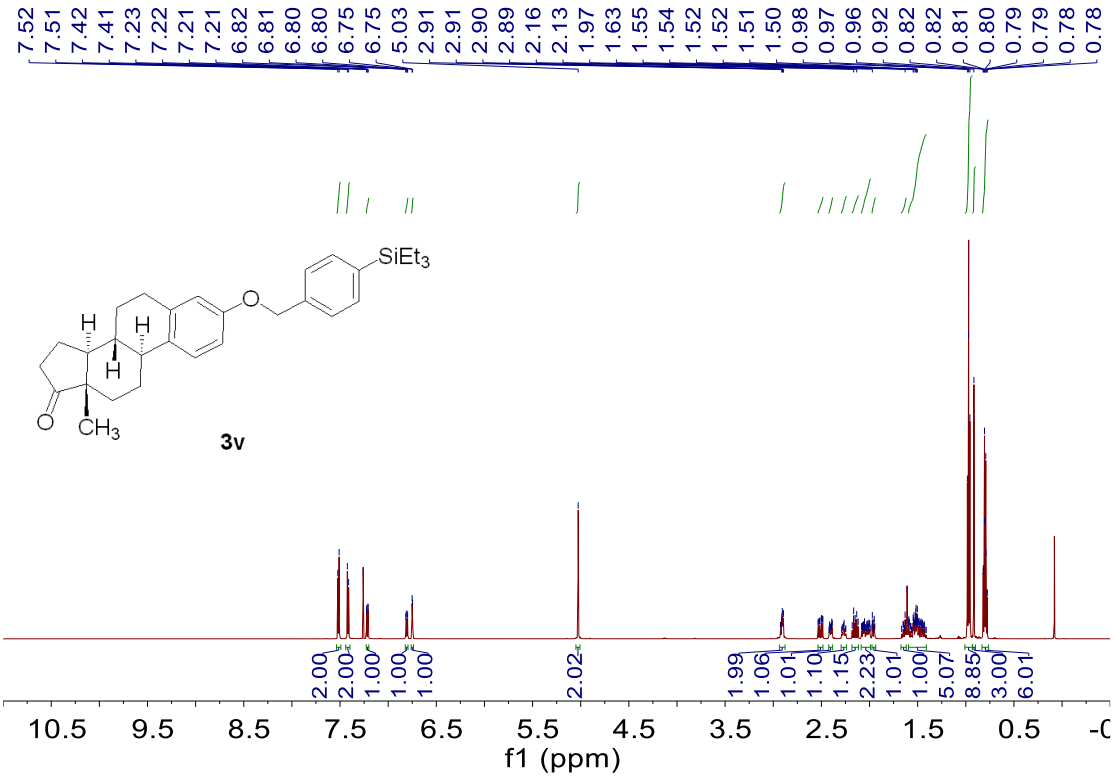


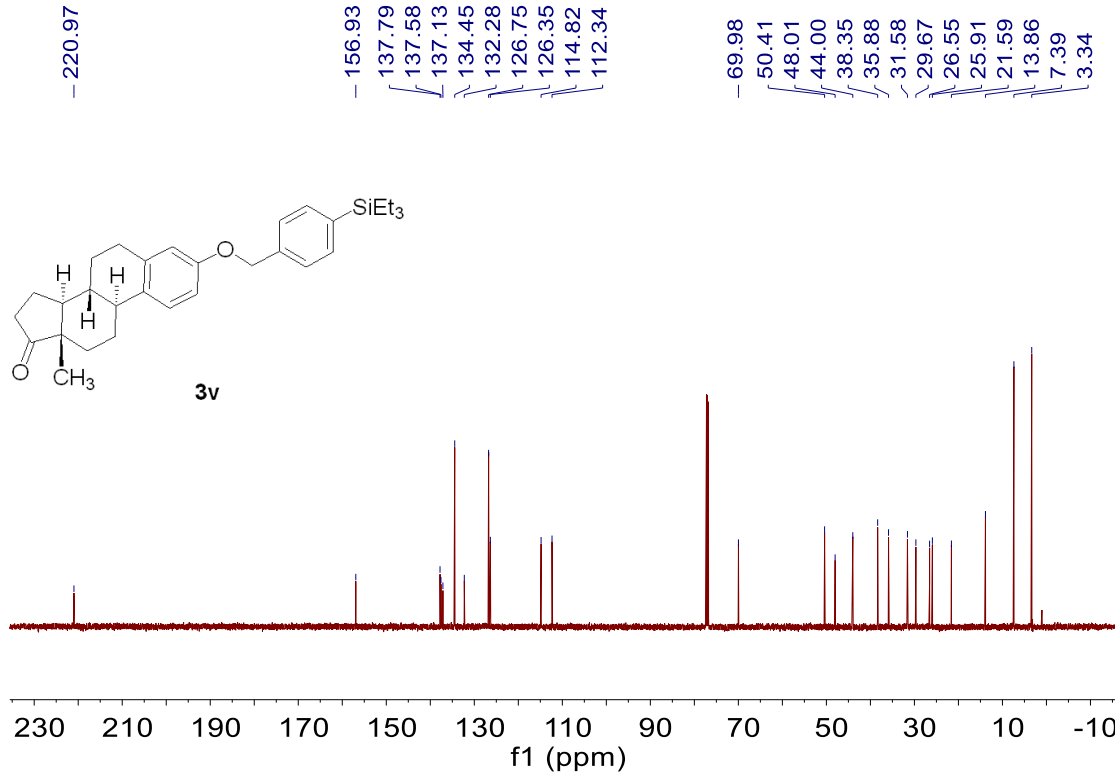
^{1}H NMR (600 MHz) spectrum of **3t** ($CDCl_3$, rt).



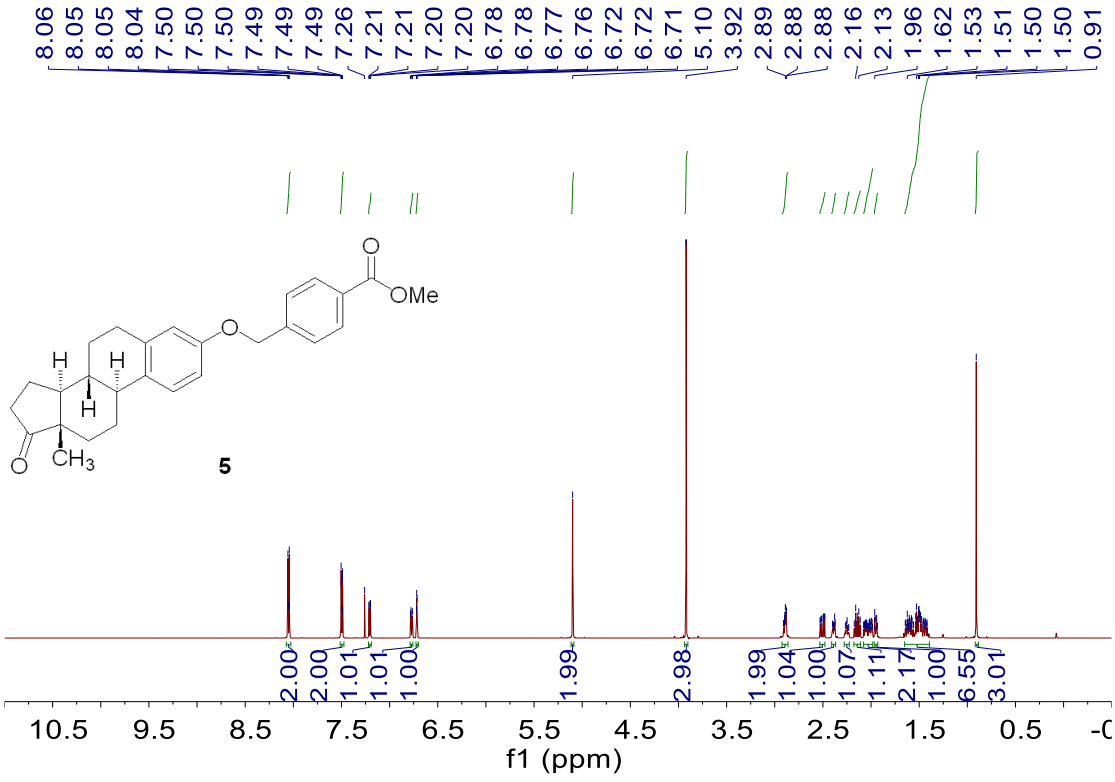


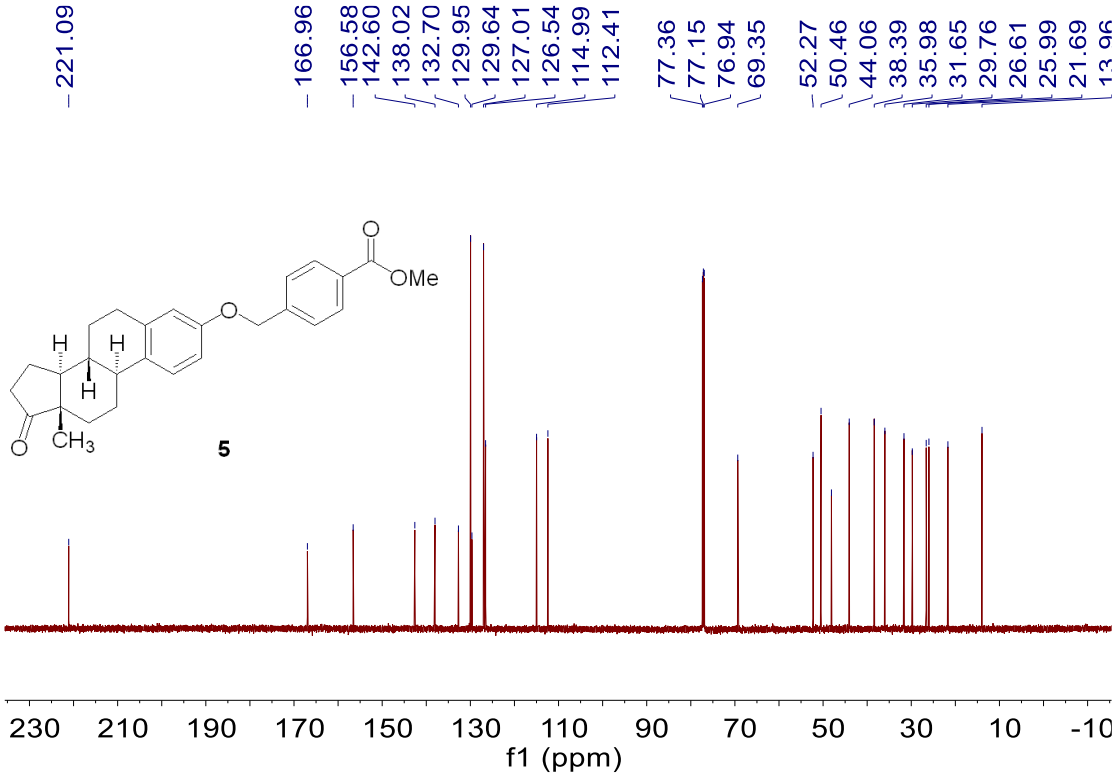
^{1}H NMR (600 MHz) and ^{13}C{^{1}H} NMR (151 MHz) spectra of **3u** ($CDCl_3$, rt).



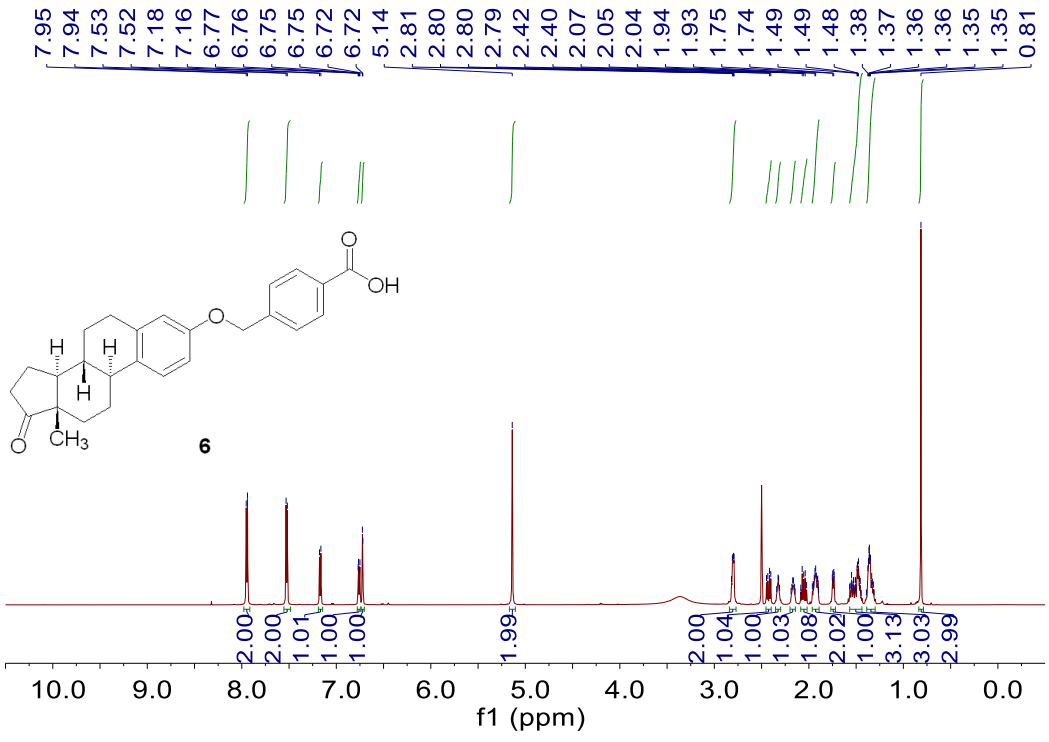


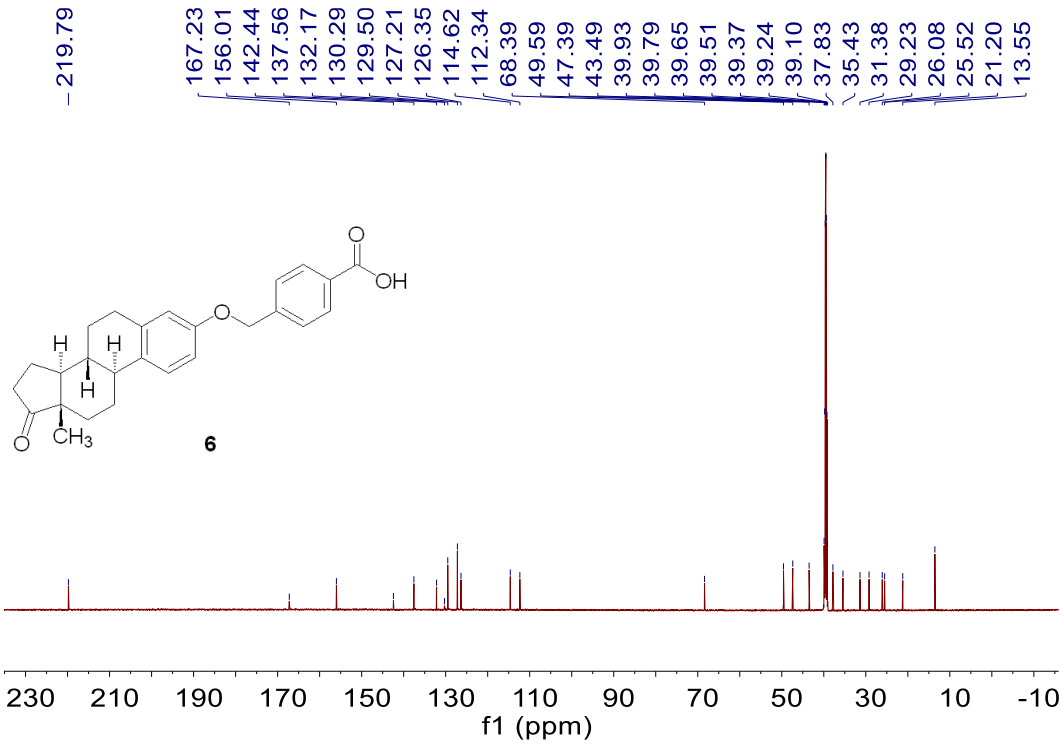
^{1}H NMR (600 MHz) and ^{13}C{^{1}H} NMR (151 MHz) spectra of **3v** ($CDCl_3$, rt).





^{1}H NMR (600 MHz) and ^{13}C NMR (151 MHz) spectra of **5** ($CDCl_3$, rt).





^{1}H NMR (600 MHz) and ^{13}C NMR (151 MHz) spectra of **6** ($(CD_3)_2SO$, rt).

2-5 References

1. (a) Hiyama, T. In Metal-Catalyzed Cross-Coupling Reactions; Diederich, F.; Stang, P. J.; Eds.; Wiley-VCH: Weinheim, **1998**; p 421. (b) For synthesis of arylsilane, see: The Chemistry of Organic Silicon Compounds; Patai, S.; Rappoport, Z.; Eds.; Wiley: New York, **2000**.
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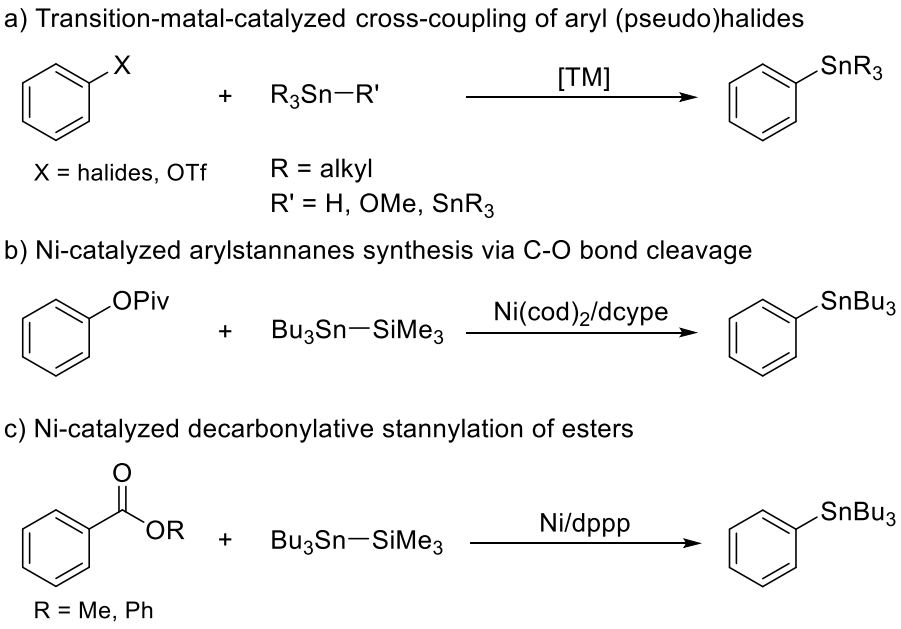
CHAPTER 3

Nickel-Catalyzed Decarbonylative Stannylation of Acyl Fluorides under Ligand-Free Conditions

3-1 Introduction

Arylstannanes as one of common organometallic reagents are extensively applied in Migita-Kosugi-Stille reaction,[1-3] which has been utilized as a powerful method for C–C bond formation, especially, in natural product synthesis.[4-6] Conventional synthetic methods of arylstannanes are the reactions of organometallic reagents such as arylzinc compounds with triorganotin halides.[7-9] Alternatively, catalytic cross-coupling reactions of aryl (pseudo)halides with tributyltin hydride,[10] tributylstannyl methoxide,[11] and hexaalkyldistannane[12,13] have been documented (Scheme 3-1a). Recent studies on arylstannanes synthesis utilizing air- and moisture-insensitive silylstannyl reagent, Bu_3Sn-$SiMe_3$, could prove that the C–O bond is also a powerful alternative to aryl halides (Scheme 3-1b).[14] In addition, Rueping and co-workers developed nickel-catalyzed stannylation of aromatic esters in a decarbonylative manner (Scheme 3-1c).[15]

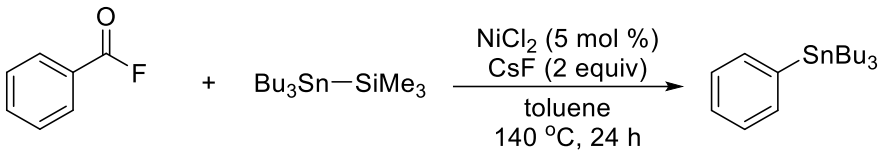
Scheme 3-1. Various Synthetic Routes for Arylstannanes.



Although these methods have made great contribution in the synthesis of arylstannanes, novel and practical methods to afford arylstannanes from more simple starting materials are still highly desirable. In this Chapter, the Author reported the first decarbonylative

stannylation of acyl fluorides with $Bu_3Sn–SiMe_3$ catalyzed by air-stable and inexpensive nickel(II) chloride under ligand and additive-free conditions (Scheme 3-2).

Scheme 3-2. Ni-Catalyzed Decarbonylative Stannylation of Acyl Fluorides.

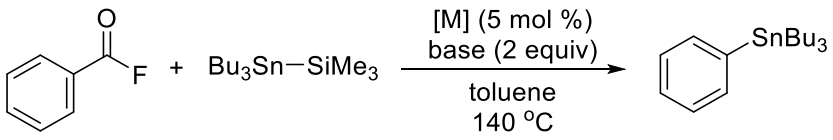


3-2 Results and Discussion

3-2-1 Decarbonylative Stannylation of Benzoyl Fluoride with $Bu_3Sn–SiMe_3$

We commenced our research by choosing benzoyl fluoride (**1a**) and 1.5 equiv of Bu_3Sn-$SiMe_3$ (**2**) as the model substrates, and the results are summarized in Table 3-1. Various transition metal sources were investigated to facilitate the decarbonylative stannylation reaction (entries 1-6). Among them, nickel(II) chloride displayed a superior result, affording the target product **3a** in 90% yield (entry 3). When cesium carbonate was employed in place of cesium fluoride, the yield of **3a** was dramatically dropped to 48% (entry 7) and no stannylation reaction occurred when potassium fluoride was used, along with silylstannane **2** recovered (entry 8). Additionally, amounts of **2** could be reduced to 1.2 equiv, which afforded 94% GC yield of **3a** (entries 3, 9, and 10). The yields of **3a** were slightly decreased as the reaction time was shortened (entries 9 *vs* 11-13). When benzoyl chloride was employed instead of **1a**, **3a** was obtained in 56% yield, suggesting the unique feature of the present reaction of acyl fluorides.

Table 3-1. Optimization the Reaction Condition.



1a **2** **3a**

entry	[M]	base	**2** (equiv)	time (h)	yield of **3a** (%)[a]
1	$FeCl_2$	CsF	1.5	24	29
2	$CoCl_2$	CsF	1.5	24	21

3	$NiCl_2$	CsF	1.5	24	90
4	$NiBr_2$	CsF	1.5	24	68
5	$Ni(cod)_2$	CsF	1.5	24	16
6	$PdCl_2$	CsF	1.5	24	4
7	$NiCl_2$	Cs_2CO_3	1.5	24	48
8	$NiCl_2$	KF	1.5	24	0
9	$NiCl_2$	CsF	1.2	24	94 (90)
10	$NiCl_2$	CsF	1.0	24	58
11	$NiCl_2$	CsF	1.2	18	91
12	$NiCl_2$	CsF	1.2	12	87
13	$NiCl_2$	CsF	1.2	6	76

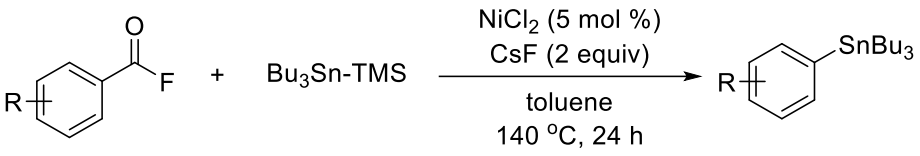
[a]Determined by GC analysis of the crude mixture using *n*-dodecane as an internal standard. An isolated yield is given in parentheses.

3-2-2 Nickel-Catalyzed Decarbonylative Stannylation of Acyl Fluoride

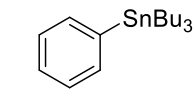
A generality of the decarbonylative stannylation was examined with the optimized reaction conditions as shown in Table 3-2. Acyl fluorides bearing electron-donating groups such as alkyl (**1b-1d**), phenyl (**1e-1g**), and alkoxy (**1h, 1i**) groups gave the corresponding products **3b-3i** in 56-85% yields regardless of the substitution positions. Other oxygen-containing functional groups such as benzyloxy (**1j**) and acetal (**1k**) were also well tolerated during the reaction. Acyl fluorides bearing electron-withdrawing groups such as trifluoromethyl (**1l**) and fluoro (**1m, 1n**) groups were also well compatible. In particular, an aryl chloride skeleton (**1o**) is known to a reactive electrophile in some nickel-catalyzed cross-coupling reactions.[11] Although 4-bromo- and 4-iodobenzoyl fluorides were employed as the substrates, no trace of the desired products was detected, presumably due to the bromo and iodo groups are highly reactive under the present reaction conditions. Acyl fluorides with fused aromatic systems (**1p-1r**) afforded arylstannanes in moderate to good yields. Heterocycles including benzothiophene and quinoline yielded **3s**

and **3t** in 62% and 84% yields, respectively. Unfortunately, however, the reactions employing surrogate aliphatic acyl fluorides gave no formation of the desired products.

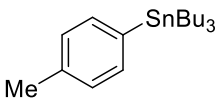
Table 3-2. Substrate Scope for Decarbonylative Stannylation of Acyl Fluorides.[a,b]



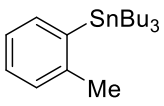
1 **2** **3**



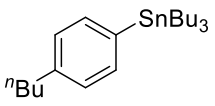
3a, 90%



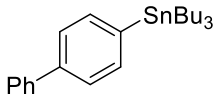
3b, 81%



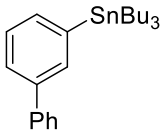
3c, 63%



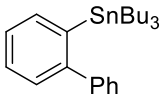
3d, 67%



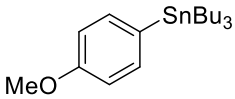
3e, 82%



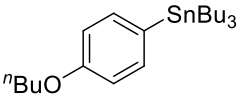
3f, 56%



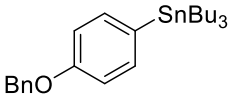
3g, 85%



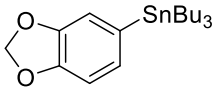
3h, 64%



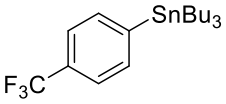
3i, 61%



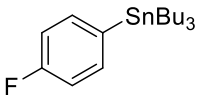
3j, 50%



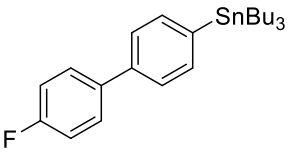
3k, 87%



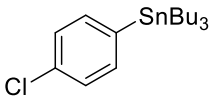
3l, 61%



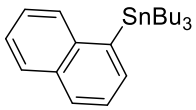
3m, 86%



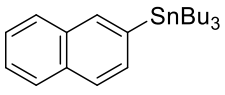
3n, 72%



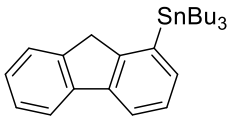
3o, 90%



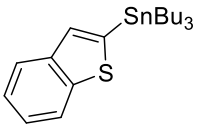
3p, 51%



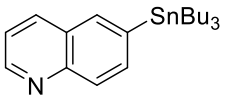
3q, 79%



3r, 82%



3s, 62%

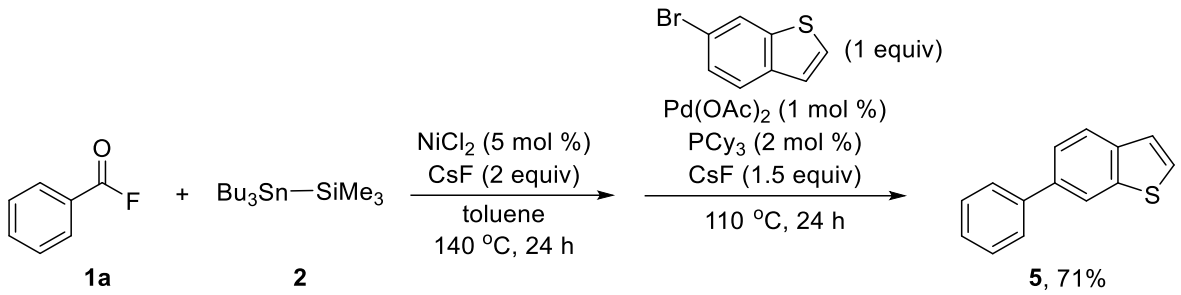


3t, 84%

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $NiCl_2$ (0.01 mmol), CsF (0.4 mmol), toluene (1 mL), 140 ℃, 24 h. [b]Isolated yields.

To demonstrate the synthetic utility of the present method, one-pot reaction of a successive decarbonylative stannylation/Migita-Kosugi-Stille reaction of **1a** was investigated (Scheme 3-3).[13] To our delight, with the aid of the additional palladium catalyst into the reaction mixture, 71% yield of compound **5** was obtained.

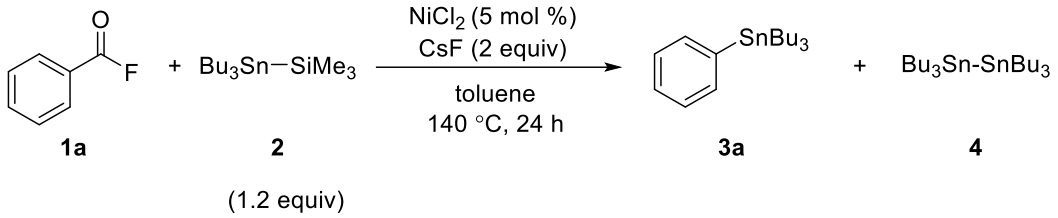
Scheme 3-3. One-Pot Reaction of Decarbonylative Stannylation/Migita-Kosugi-Stille Reaction of **1a**.



3-2-3 Mechanistic Studies of Decarbonylative Stannylation

To gain more detailed insights into the reaction mechanism, some control experiments were carried out (Table 3-3). Although arylstannane **3a** was obtained in 94% yield, along with the formation of hexabutylditin (**4;** 13%) under the optimized reaction conditions (entry 1), indicating that nickel(II) chloride was reduced to Ni(0) species. This hypothesis was further proved by the reaction of **1a** with **2** in the absence of cesium fluoride (entry 2). Without nickel(II) chloride, no target product **3a** was formed, and **4** was obtained quantitatively (entry 3). In some stannylation reactions, hexabutyldistannane (**4**) could also be used as a stannylating reagent.[12,13] Thus, the reaction of **1a** (0.2 mmol) with **4** (0.24 mmol) was evaluated under identical reaction conditions. However, neither the desired product **3a** nor a viable acyl stannane was delivered, along with decomposition of **1a** and the remained **4** unreacted, which suggests that the once formed **4** never be involved into the catalytic cycle because of its lower reactivity (entry 4).

Table 3-3. Control Experiments for Ni-Catalyzed Decarbonylative Stannylation.[a]

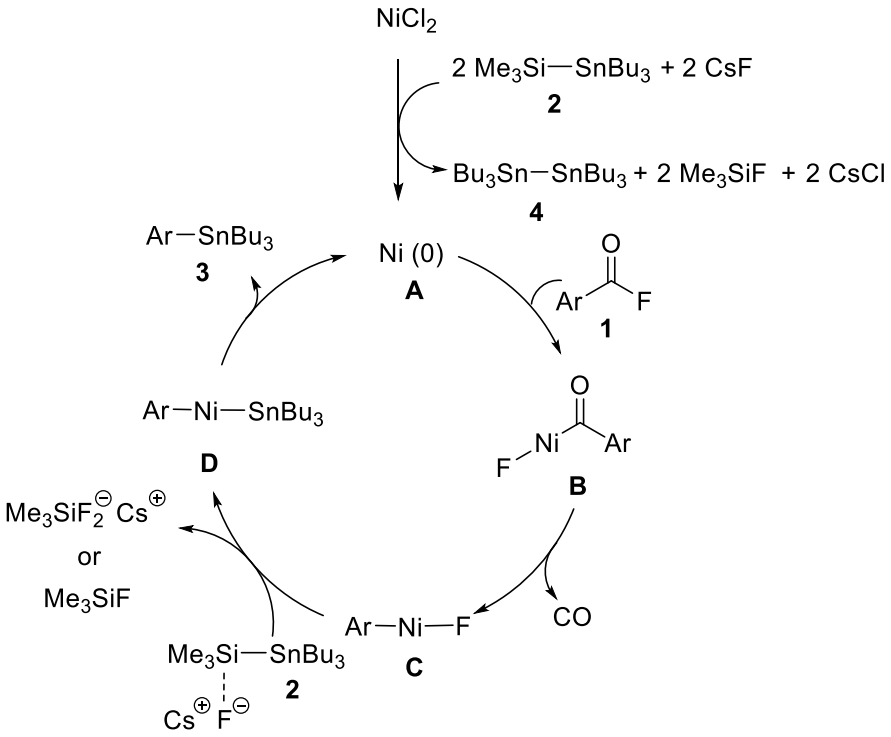


entry	deviation from standard conditions	GC yield (%)[b]		
		2	**3a**	**4**
1	none	0	94	13
2	without CsF	120	0	0
3	without $NiCl_2$	0	0	63
4	**4** instead of **2**	-	0	>99

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $NiCl_2$ (0.01 mmol), CsF (0.4 mmol), toluene (1 mL), 140 ℃, 24 h. [b]Determined by GC analysis of the crude mixture using *n*-dodecane as an internal standard.

Our proposed mechanism of the present decarbonylative stannylation is outlined in Scheme 3-4. Combining the related references[16,17] with our previous work,[18] it is assumed that oxidative addition of acyl fluorides **1** to Ni(0) species **A**, derived from reduction of Ni(II) chloride with **2**, yields acyl nickel (II) species **B**. Subsequently, decarbonylation of **B** delivers arylnickel(II) species **C**.[17,18] Transmetalation between the complex **C** and activated silylstannane **2** by cesium fluoride affords complex **D**.[14] Following reductive elimination gives the target product arylstannanes **3**, regenerating Ni(0) species **A**.

Scheme 3-4. Proposed Mechanism.


NiCl2
2 Me3Si—SnBu3 + 2 CsF
2
Bu3Sn—SnBu3 + 2 Me3SiF + 2 CsCl
4
Ar—SnBu3
3
Ni (0)
A
Ar
F
1
Ar—Ni—SnBu3
D
F
Ni
Ar
B
Me3SiF2 Cs
or
Me3SiF
Ar—Ni—F
C
CO
Me3Si—SnBu3
2
Cs F

3-3 Summary

The Author have developed an efficient and convenient method for inexpensive $NiCl_2$-catalyzed decarbonylative stannylation of a series of acyl fluorides, which is highlighted by the ligand and additive-free. A variety of aromatic acyl fluorides are capable of reacting with silylstannanes in the presence of cesium fluoride. One-pot decarbonylative stannylation/Migita-Kosugi-Stille reaction further demonstrated the synthetic applicability of our protocol because the isolation of toxic organotin compounds is not necessary. This newly developed methodology with a good functional-group compatibility via C–F bond cleavage and C–Sn bond formation under nickel catalysis opens a new area for the functionalization of acyl fluorides in terms of carbon-heteroatom bond formation.

3-4 Experimental Section

3-4-1 General Instrumentation and Chemicals

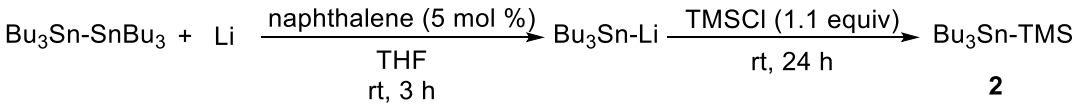
All the reactions were carried out under an argon atmosphere using standard Schlenk techniques. Glassware was dried in an oven (150 ℃) and heated under reduced pressure prior to use. Solvents were employed as eluents for all other routine operation, as well as dehydrated solvent were purchased from commercial suppliers and employed without any further purification. For thin layer chromatography (TLC) analyses throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. Silica gel column chromatography was carried out using silica gel 60 N (spherical, neutral, 40-100 μm) from Kanto Chemicals Co. Ltd. NMR spectra (^{1}H, ^{13}C{^{1}H} and ^{19}F{^{1}H}) were recorded on Varian INOVA-600 (600 MHz), Mercury-400 (400 MHz), or 300-NMR ASW (300 MHz) spectrometers. Chemical shifts (δ) are in parts per million relative to $CDCl_3$ at 7.26 ppm for ^{1}H and at 77.05 ppm for ^{13}C{^{1}H}. The ^{19}F{^{1}H} NMR spectra were measured by using CCl_3F (δ = 0.00 ppm) as an external standard. The NMR yields were determined using dibromomethane as an internal standard. The GC yields were determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard. GC analyses were performed on a Shimadzu GC-14A equipped with a flame ionization detector using Shimadzu Capillary Column (CBP1-M25-025) and Shimadzu C-R6A-Chromatopac integrator. Infrared spectra were recorded on a SHIMADZU IRPrestige-21 spectrophotometer. Elemental analyses were carried out with a Perkin-Elmer 2400 CHN elemental analyzer at Okayama University.

Chemicals

Materials obtained from commercial suppliers were used without further purification. Benzoyl fluoride **1a** (purity > 98%) and cesium fluoride were purchased from TCI. Nickel chloride was purchased from Wako. *n*-Dodecane (purity > 99%) was purchased from Kanto Chemical Co. Other acyl fluorides were synthesized from corresponding carboxylic acids or acyl chlorides, which was described in chapter 2.

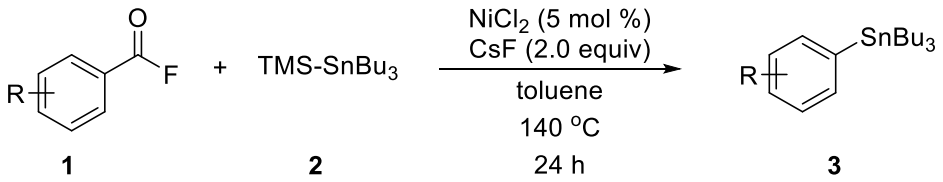
3-4-2 Experimental Procedures

3-4-2-1 Synthesis of Trimethyl(tributylstannyl)silane (2)[19]



To a solution of naphthalene (51.3 mg, 0.4 mmol) in THF (16 mL), was added lithium clippings (84 mg, 12 mmol) under an argon atmosphere. During the resulting mixture was stirred at room temperature for 1 h, the color turned to dark green. Then, hexabutylditin (2.02 mL, 4 mmol) was added dropwise and the mixture was stirred at room temperature for 3 h. The resulting solution (16 mL) was transferred via cannula to a Schlenk tube under Ar and then stored at room temperature. A THF solution prepared as described above was added via a cannula into the stirred solution of chlorotrimethylsilane (951 mg, 8.8 mmol) in THF at 0 ℃. The reaction was stirred at room temperature overnight followed by extraction with hexane. The organic phase was washed with brine and dried over Na_2SO_4. Removal of the solvent and purification by bulb-to-bulb distillation under reduced pressure provided $Bu_3Sn\text{-}SiMe_3$ as a colorless oil.

3-4-2-2 Representative Procedure for Ni-Catalyzed Decarbonylative Stannylation of Acyl Fluorides

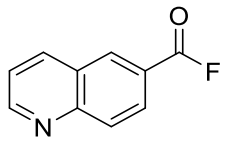


A 20 mL dried Schlenk tube containing a stirring bar and CsF (60.8 mg, 0.4 mmol, 2 equiv) was dried with a heat gun under reduced pressure and filled with Ar after cooling to room temperature. To this vessel, were added $NiCl_2$ (1.3 mg, 0.01 mmol, 5 mol %), toluene (1 mL), acyl fluorides (**1**) (0.2 mmol, 1 equiv) and trimethyl(tributylstannyl)silane (**2**) (87.2 mg, 0.24 mmol, 1.2 equiv). The mixture was heated at 140 ℃ with stirring for 24 h. The solution was then cooled to room temperature, and the solvent was removed under vacuum. The decarbonylative stannylation products **3** were purified by flash column chromatography on silica gel.

3-4-2-3 One-Pot Decarbonylative Stannylation/Migita-Kosugi-Stille Cross-Coupling Reaction of 1a

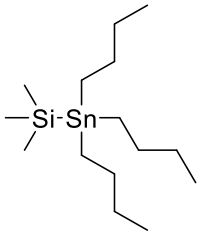
A 20 mL dried Schlenk tube containing a stirring bar and CsF (60.8 mg, 0.4 mmol, 2 equiv) was dried with a heat gun under reduced pressure and filled with Ar after cooling to room temperature. To this vessel, were added with $NiCl_2$ (1.3 mg, 0.01 mmol, 5 mol %), toluene (1 mL), benzoyl fluoride (**1a**) (24.8 mg, 0.2 mmol), and trimethyl(tributylstannyl)silane (**2**) (87.2 mg, 0.24 mmol, 1.2 equiv). The mixture was heated at 140 ºC with stirring for 24 h. The solution was then cooled to room temperature. 6-Bromobenzo[b]thiophene (42.6 mg, 0.2 mmol, 1 equiv), palladium acetate (0.4 mg, 0.002 mmol, 1 mol %), tricyclohexylphosphine (1.1 mg, 0.004 mmol, 2 mol %), and anhydrous cesium fluoride (45.6 mg, 0.3 mmol, 1.5 equiv) were added to the reaction mixture. The mixture was heated at 110 ℃ with stirring. After 24 h, the reaction mixture was cooled, the volatiles were evaporated under reduced pressure. The product was purified by flash chromatography on silica gel by elution with hexane, compound **5** was obtained in 71% yield (30 mg, 0.14 mmol) as white solid.[13]

Quinoline-6-carbonyl fluoride (**1t**)



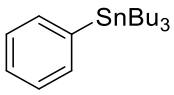
Yield: 55% (288.8 mg). White solid. Melting point: 104-105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 1H), 8.15-8.26 (m, 2H), 8.30 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.62 (d, *J* = 2.0 Hz, 1H), 9.08 (dd, *J* = 4.3, 1.9 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 122.5, 123.1, 127.4, 129.4 (d, *J* = 4.0 Hz), 130.8 (d, *J* = 1.4 Hz), 133.9 (d, *J* = 3.0 Hz), 137.6, 150.7, 153.8, 156.9 (d, *J* = 344.2 Hz). ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ 18.9. FT-IR (neat, cm^{-1}): 735 (s), 781 (s), 854 (s), 1011 (s), 1045 (s), 1171 (s), 1231 (s), 1622 (s), 1805 (s), 3051 (s). Anal. Calcd for $C_{14}H_9FO_3$: C, 68.57; H, 3.45%. Found: C, 68.50; H, 3.23%.

Trimethyl(tributylstannyl)silane (**2**)[19]



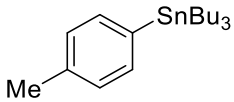
Yield: 92% (2.67 g). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.23 (s, $J_{H\text{-}Sn}$ = 26.4 Hz, 9H), 0.84-0.90 (m, 15H), 1.29 (sext, J = 7.3 Hz, 6H), 1.44-1.48 (m, 6H).

Tributyl(phenyl)stannane (3a)[15]



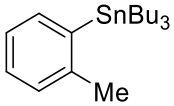
Yield: 90% (66.1 mg). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.91-0.95 (m, 9H), 1.03-1.16 (m, $J_{H\text{-}Sn}$ = 54.6 Hz, 6H), 1.33-1.41 (m, 6H), 1.53-1.63 (m, 6H), 7.32-7.36 (m, 3H), 7.46-7.54 (m, $J_{H\text{-}Sn}$ = 36.4 Hz, 2H).

Tributyl(p-tolyl)stannane (3b)[15]



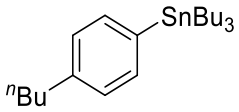
Yield: 81% (61.8 mg). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 9H), 1.00-1.10 (m, $J_{H\text{-}Sn}$ = 52.4 Hz, 6H), 1.31-1.38 (m, 6H), 1.48-1.59 (m, 6H), 2.35 (s, 3H), 7.17 (d, J = 7.2 Hz, 2H), 7.37 (d, J = 7.8 Hz, $J_{H\text{-}Sn}$ = 35.8 Hz, 2H).

Tributyl(o-tolyl)stannane (3c)[13]



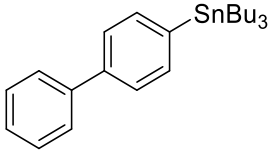
Yield: 63% (48.0 mg). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 9H), 1.01-1.14 (m, $J_{H\text{-}Sn}$ = 50.4 Hz, 6H), 1.34 (sext, J = 7.2 Hz, 6H), 1.47-1.58 (m, 6H), 2.40 (s, 3H), 7.12-7.17 (m, 1H), 7.17-7.25 (m, 2H), 7.40 (d, J = 6.8 Hz, $J_{H\text{-}Sn}$ = 42.8 Hz, 1H).

Tributyl(4-butylphenyl)stannane (3d)



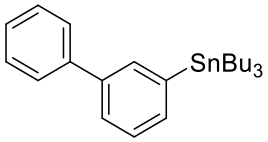
Yield: 67% (56.7 mg). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 7.6 Hz, 9H), 0.94 (t, J = 7.6 Hz, 3H), 0.99-1.12 (m, $J_{H\text{-}Sn}$ = 50.8 Hz, 6H), 1.29-1.40 (m, 8H), 1.50-1.64 (m, 8H), 2.60 (t, J = 7.8 Hz, 2H), 7.14-7.19 (m, 2H), 7.37 (d, J = 6.4 Hz, $J_{H\text{-}Sn}$ = 39.2 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 9.7 ($J_{C\text{-}Sn}$ = 338.7 Hz), 13.8, 14.1, 22.6, 27.6 ($J_{C\text{-}Sn}$ = 57.2 Hz), 29.3 ($J_{C\text{-}Sn}$ = 19.8 Hz), 33.8, 35.8, 128.3 ($J_{C\text{-}Sn}$ = 41.2 Hz), 136.5 ($J_{C\text{-}Sn}$ = 31.3 Hz), 138.3, 142.7. FT-IR (neat, cm^{-1}): 729 (m), 748 (m), 1070 (m), 1045 (m), 1377 (m), 1458 (m), 2855 (m), 2872 (m), 2928 (m), 2959 (m). Anal. Calcd for $C_{22}H_{40}Sn$: C, 62.43; H, 9.53%. Found: C, 62.30; H, 9.55%.

[1,1'-Biphenyl]-4-yltributylstannane (3e)[15]



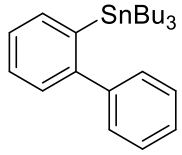
Yield: 82% (72.7 mg). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.93 (t, J = 7.5 Hz, 9H), 1.03-1.18 (m, $J_{H\text{-}Sn}$ = 43.2 Hz, 6H), 1.38 (sext, J = 7.5 Hz, 6H), 1.55-1.66 (m, 6H), 7.35-7.39 (m, 1H), 7.45-7.48 (m, 2H), 7.53-7.60 (m, 4H), 7.62-7.64 (m, 2H).

[1,1'-Biphenyl]-3-yltributylstannane (3f)[15]



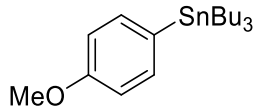
Yield: 56% (49.6 mg). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.91 (t, J = 7.5 Hz, 9H), 1.06-1.16 (m, $J_{H\text{-}Sn}$ = 50.8 Hz, 6H), 1.33-1.38 (m, 6H), 1.54-1.63 (m, 6H), 7.35-7.38 (m, 1H), 7.40-7.48 (m, 4H), 7.51-7.54 (m, 1H), 7.58-7.62 (m, 2H), 7.63-7.71 (d, J = 1.8 Hz, $J_{H\text{-}Sn}$ = 40.2 Hz, 1H).

[1,1'-Biphenyl]-2-yltributylstannane (3g)[15]



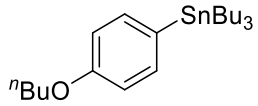
Yield: 85% (75.4 mg). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.69-0.77 (m, $J_{H\text{-}Sn}$ = 51.0 Hz, 6H), 0.84 (t, J = 7.3 Hz, 9H), 1.23 (sext, J = 7.8 Hz, 6H), 1.32-1.38 (m, 6H), 7.32-7.35 (m, 3H), 7.36-7.39 (m, 3H), 7.39-7.42 (m, 2H), 7.56 (d, J = 7.3 Hz, $J_{H\text{-}Sn}$ = 40.8 Hz, 1H).

Tributyl(4-methoxyphenyl)stannane (3h)[13]



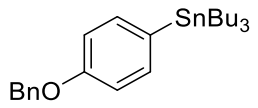
Yield: 64% (50.8 mg). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 7.2 Hz, 9H), 0.96-1.09 (m, $J_{H\text{-}Sn}$ = 51.2 Hz, 6H), 1.33 (sext, J = 7.6 Hz, 6H), 1.48-1.59 (m, 6H), 3.81 (s, 3H), 6.91 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, $J_{H\text{-}Sn}$ = 37.2 Hz, 2H).

(4-Butoxyphenyl)tributylstannane (3i)



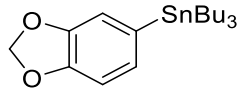
Yield: 61% (53.6 mg). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89 (t, J = 7.2 Hz, 9H), 0.98 (t, J = 7.2 Hz, 3H), 1.01-1.04 (m, $J_{H\text{-}Sn}$ = 51.6 Hz, 6H), 1.33 (sext, J = 7.8 Hz, 6H), 1.47-1.58 (m, 8H), 1.75-1.80 (m, 2H), 3.96 (t, J = 6.6 Hz, 2H), 6.90 (d, J = 8.5 Hz, $J_{H\text{-}Sn}$ = 61.8 Hz, 2H), 7.36 (d, J = 8.5 Hz, $J_{H\text{-}Sn}$ = 42.6 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 9.7 ($J_{C\text{-}Sn}$ = 333.0 Hz), 13.9, 14.0, 19.4, 27.6 ($J_{C\text{-}Sn}$ = 55.5 Hz), 29.2 ($J_{C\text{-}Sn}$ = 20.8 Hz), 31.5, 67.4, 114.6 ($J_{C\text{-}Sn}$ = 43.9 Hz), 131.8, 137.6 ($J_{C\text{-}Sn}$ = 34.7 Hz), 159.4. FT-IR (neat, cm^{-1}): 671 (m), 754 (m), 1072 (m), 1130 (m), 1207 (m), 1242 (m), 1273 (m), 1464 (m), 1495 (m), 1585 (m), 2855 (m), 2872 (m), 2928 (m), 2959 (m). Anal. Calcd for $C_{22}H_{40}OSn$: C, 60.15; H, 9.18%. Found: C, 60.09; H, 9.32%.

(4-(Benzyloxy)phenyl)tributylstannane (3j)[20]



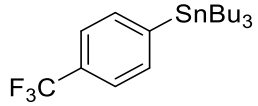
Yield: 50% (47.3 mg). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 9H), 0.98-1.10 (m, $J_{H\text{-}Sn}$ = 51.0 Hz, 6H), 1.34 (sext, J = 7.2 Hz, 6H), 1.52-1.57 (m, 6H), 5.07 (s, 2H), 7.00 (d, J = 8.5 Hz, 2H), 7.32-7.36 (m, 1H), 7.37-7.43 (m, 4H), 7.46 (d, J = 7.2 Hz, 2H).

Benzo[d][1,3]dioxol-5-yltributylstannane (3k)[11]



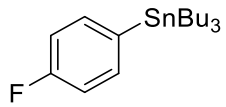
Yield: 87% (71.5 mg). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 9H), 0.99-1.08 (m, $J_{H\text{-}Sn}$ = 49.8 Hz, 6H), 1.33 (sext, J = 7.8 Hz, 6H), 1.50-1.58 (m, 6H), 5.92 (s, 2H), 6.86 (d, J = 7.4 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.94 (s, $J_{H\text{-}Sn}$ = 37.2 Hz, 1H).

Tributyl(4-(trifluoromethyl)phenyl)stannane (3l)[15]



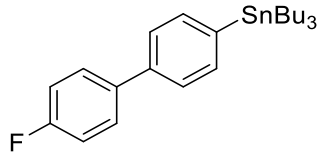
Yield: 61% (53.1 mg). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89 (m, J = 7.2 Hz, 9H), 1.04-1.15 (m, $J_{H\text{-}Sn}$ = 50.6 Hz, 6H), 1.33 (sext, J = 7.2 Hz, 6H), 1.50-1.57 (m, 6H), 7.55 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, $J_{H\text{-}Sn}$ = 34.8 Hz, 2H).

Tributyl(4-fluorophenyl)stannane (3m)[15]



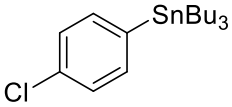
Yield: 86% (66.2 mg). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 9H), 0.98-1.12 (m, $J_{H\text{-}Sn}$ = 51.0 Hz, 6H), 1.33 (sext, J = 8.0 Hz, 6H), 1.47-1.60 (m, 6H), 7.00-7.08 (m, 2H), 7.35-7.48 (m, 2H).

Tributyl(4'-fluoro-[1,1'-biphenyl]-4-yl)stannane (3n)[15]



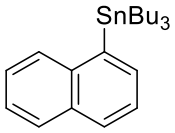
Yield: 72% (66.4 mg). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 9H), 1.05-1.15 (m, $J_{H\text{-}Sn}$ = 50.1 Hz, 6H), 1.36 (sext, J = 7.2 Hz, 6H), 1.54-1.62 (m, 6H), 7.13 (dd, J = 8.7 Hz, $J_{F\text{-}H}$ = 8.7 Hz, 2H), 7.51-7.53 (m, 2H), 7.54-7.57 (m, 4H).

Tributyl(4-chlorophenyl)stannane (3o)[19]



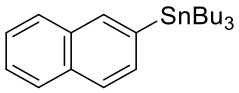
Yield: 90% (72.3 mg). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 9H), 1.00-1.10 (m, $J_{H\text{-}Sn}$ = 50.1 Hz, 6H), 1.32 (sext, J = 7.2 Hz, 6H), 1.47-1.56 (m, 6H), 7.28-7.33 (m, 2H), 7.34-7.42 (m, $J_{H\text{-}Sn}$ = 36.0 Hz, 2H).

Tributyl(naphthalen-1-yl)stannane (3p)[15]



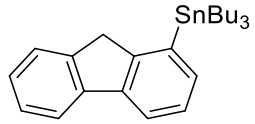
Yield: 51% (42.6 mg). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 9H), 1.19-1.22 (m, $J_{H\text{-}Sn}$ = 50.4 Hz, 6H), 1.35 (sext, J = 7.8 Hz, 6H), 1.54-1.60 (m, 6H), 7.42-7.51 (m, 3H), 7.63 (d, J = 6.6 Hz, $J_{H\text{-}Sn}$ = 46.2 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 7.2 Hz, 1H).

Tributyl(naphthalen-2-yl)stannane (3q)[15]



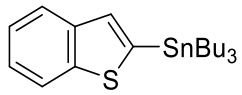
Yield: 79% (65.9 mg). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.92 (m, J = 7.2 Hz, 9H), 1.09-1.21 (m, $J_{H\text{-}Sn}$ = 50.1 Hz, 6H), 1.38 (sext, J = 7.2 Hz, 6H), 1.56-1.65 (m, 6H), 7.44-7.51 (m, 2H), 7.59 (d, J = 8.1 Hz, $J_{H\text{-}Sn}$ = 33.0 Hz, 1H), 7.79-7.87 (m, 3H), 7.96 (s, $J_{H\text{-}Sn}$ = 44.4 Hz, 1H).

Tributyl(9H-fluoren-1-yl)stannane (3r)



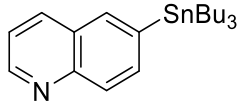
Yield: 82% (74.7mg). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 9H), 1.11-1.23 (m, $J_{H\text{-}Sn}$ = 51.0 Hz, 6H), 1.36 (sext, J = 7.2 Hz, 6H), 1.52-1.62 (m, 6H), 3.85 (s, 2H), 7.30-7.42 (m, 4H), 7.57 (d, J = 7.5 Hz, 1H), 7.76 (dd, J = 7.2, 1.2 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 9.8 ($J_{C\text{-}Sn}$ = 338.7 Hz), 13.8, 27.6 ($J_{C\text{-}Sn}$ = 60.1 Hz), 29.4 ($J_{C\text{-}Sn}$ = 19.6 Hz), 39.4, 119.9, 120.0, 125.0, 126.3, 126.6, 126.9, 135.0, 138.3, 140.3, 142.2, 143.0, 150.8. FT-IR (neat, cm^{-1}): 731 (m), 752 (m), 1207 (s), 1220 (m), 1225 (m), 1456 (m), 1464 (m), 1695 (m), 2855 (m), 2865 (m), 2926 (m), 2959 (m). Anal. Calcd for $C_{25}H_{36}Sn$: C, 65.95; H, 7.97%. Found: C, 66.06; H, 8.20%.

Benzo[b]thiophen-2-yltributylstannane (3s)[21]



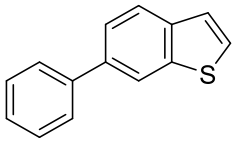
Yield: 62% (52.5 mg). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 9H), 1.12-1.20 (m, $J_{H\text{-}Sn}$ = 52.2 Hz, 6H), 1.36 (sext, J = 7.2 Hz, 6H), 1.56-1.64 (m, 6H), 7.27-7.29 (m, 1H), 7.32 (t, J = 6.6 Hz, 1H), 7.39 (s, $J_{H\text{-}Sn}$ = 24.0 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H).

6-(Tributylstannyl)quinoline (3t)[14]



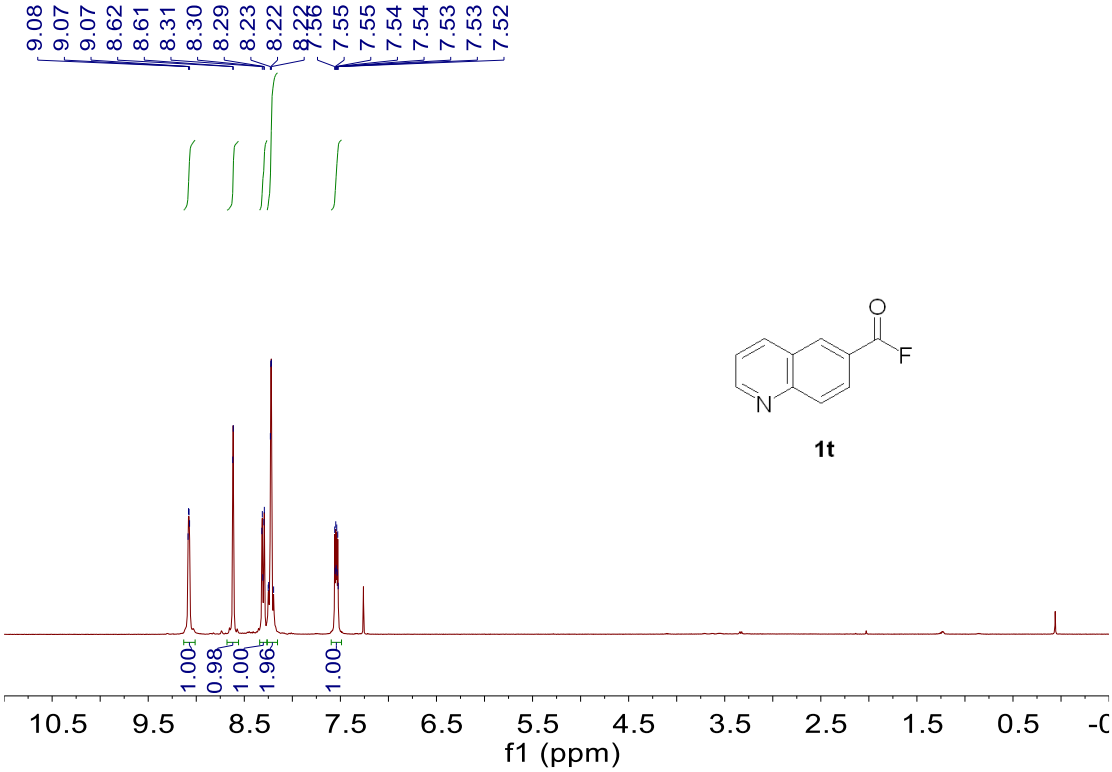
Yield: 84% (70.3 mg). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 9H), 1.08-1.20 (m, $J_{H\text{-}Sn}$ = 51.0 Hz, 6H), 1.36 (sext, J = 7.8 Hz, 6H), 1.53-1.64 (m, 6H), 7.39 (dd, J = 8.4, 4.2 Hz, 1H), 7.81 (d, J = 7.8 Hz, $J_{H\text{-}Sn}$ = 31.5 Hz, 1H), 7.91 (s, $J_{H\text{-}Sn}$ = 42.0 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 8.89 (dd, J = 8.4, 1.2 Hz, 1H).

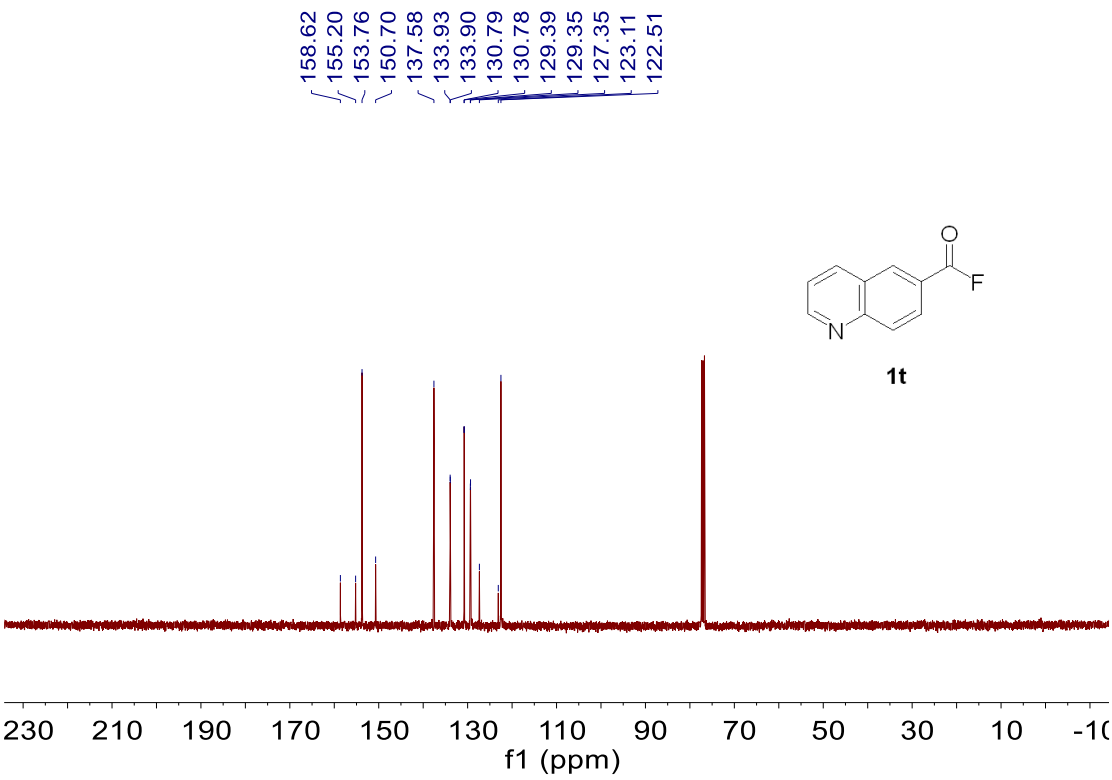
6-Phenylbenzo[b]thiophene (5)[22]

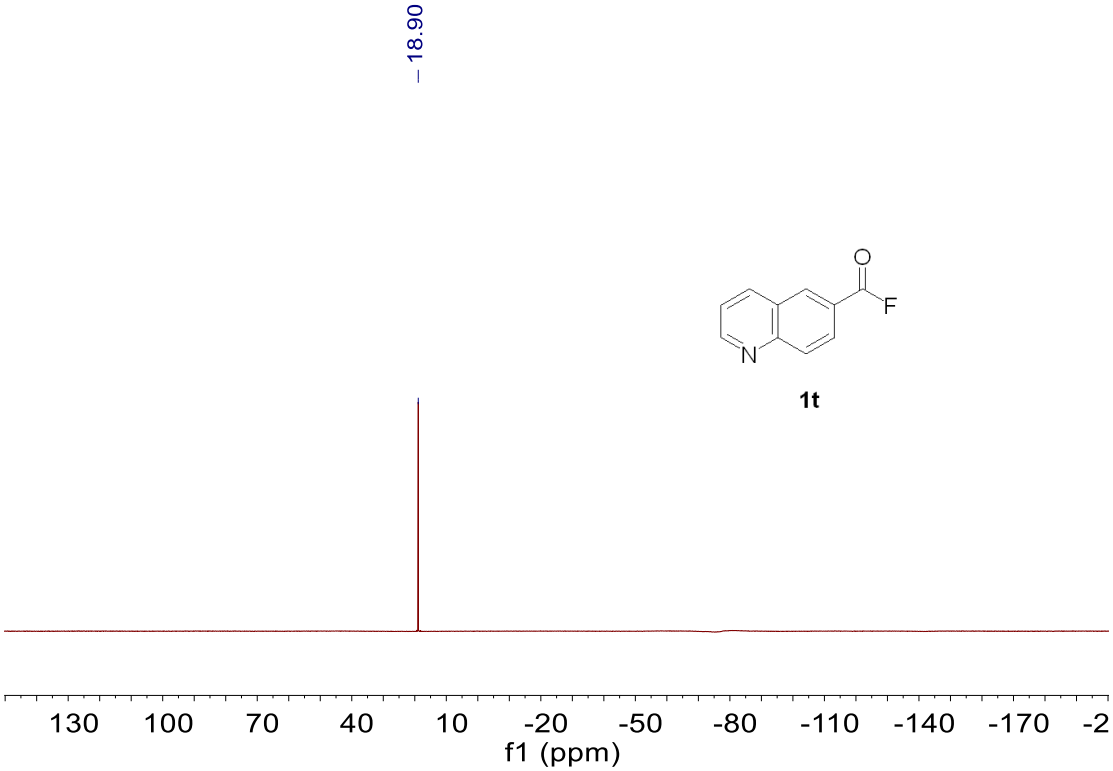


Yield: 71% (30.0 mg). White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.42 (m, 2H), 7.46-7.51 (m, 3H), 7.61 (dd, J = 8.4, 1.8 Hz, 1H), 7.66-7.9 (m, 2H), 7.95 (d, J = 8.4, 1H), 8.04 (d, J = 1.8 Hz, 1H).

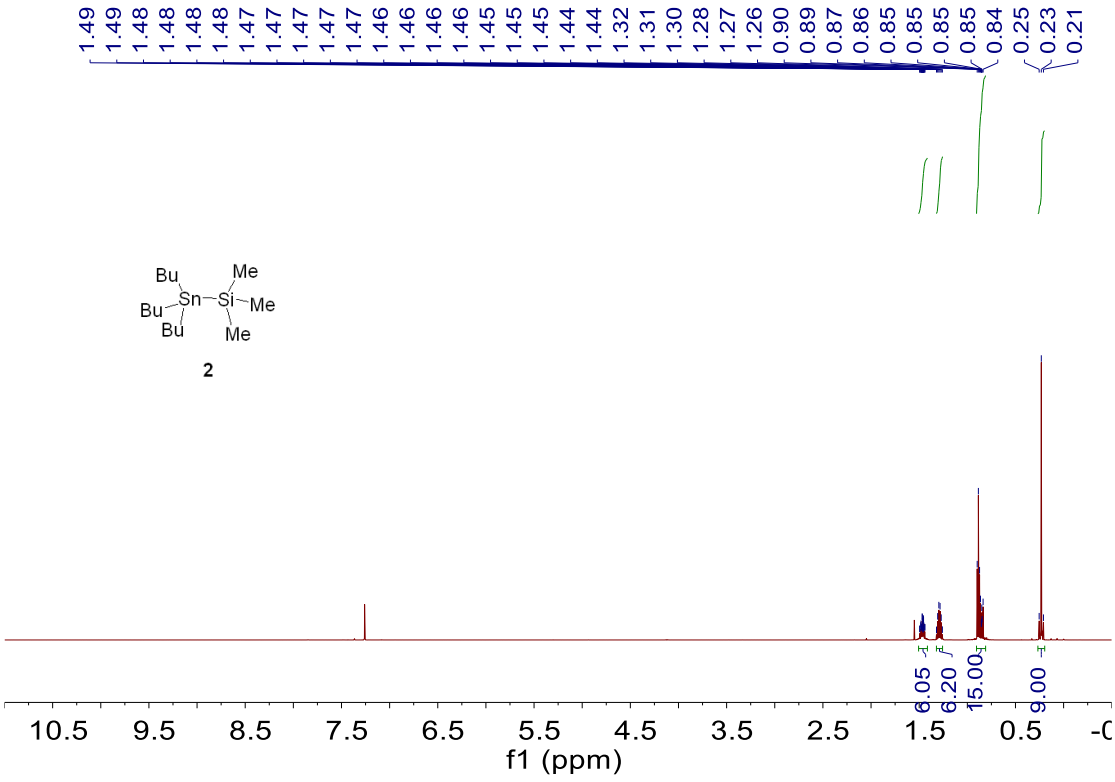
3-4-3 Copies of NMR Charts for Products



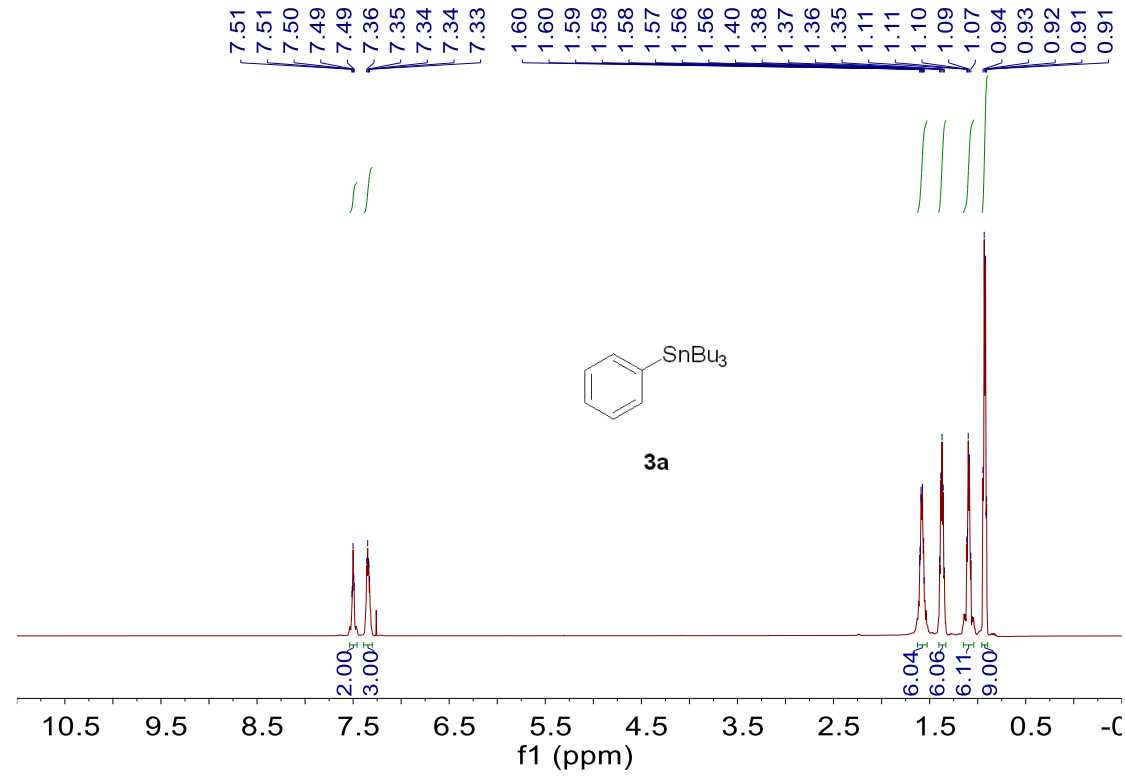




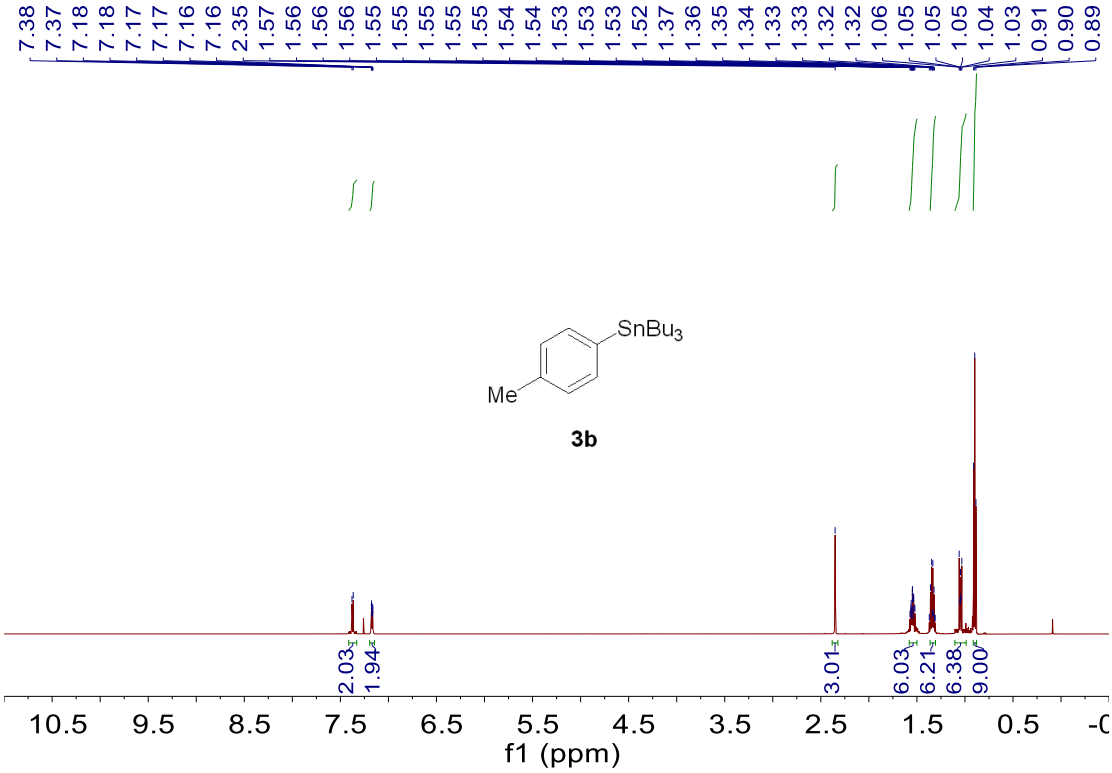
^{1}H NMR (400 MHz), ^{13}C{^{1}H} NMR (151 MHz) and ^{19}F{^{1}H} NMR (282 MHz) spectra of **1t** ($CDCl_3$, rt).



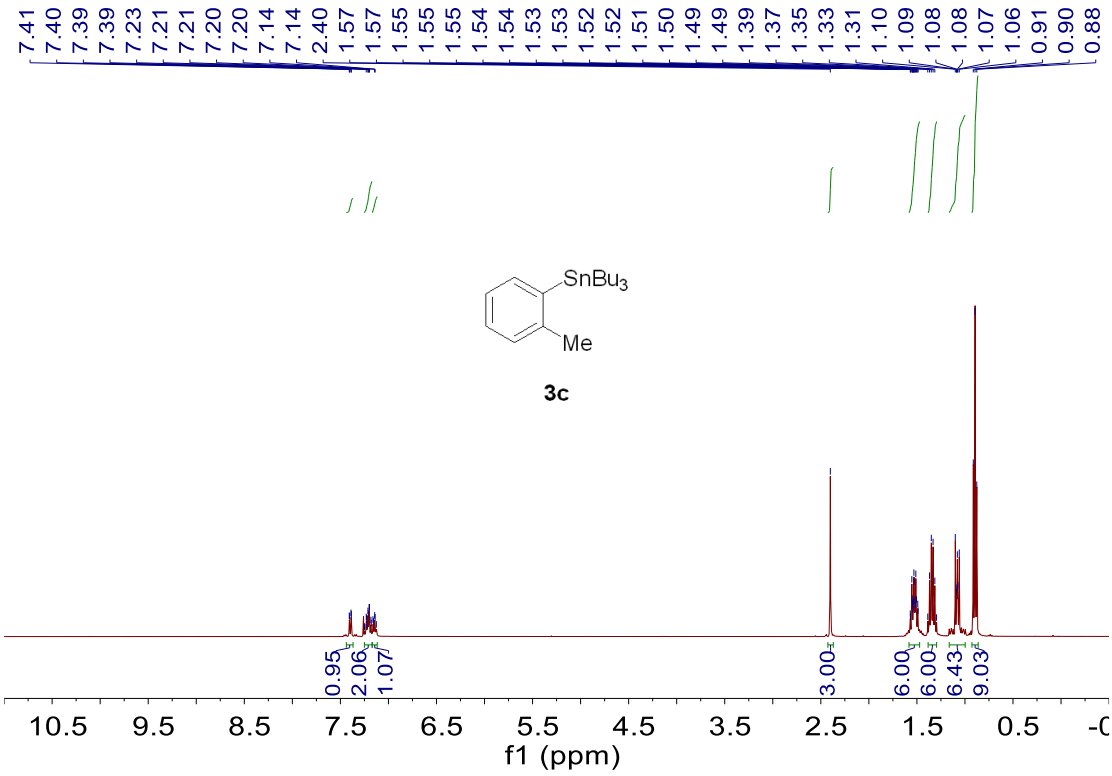
^{1}H NMR (600 MHz) spectrum of **2** ($CDCl_3$, rt).



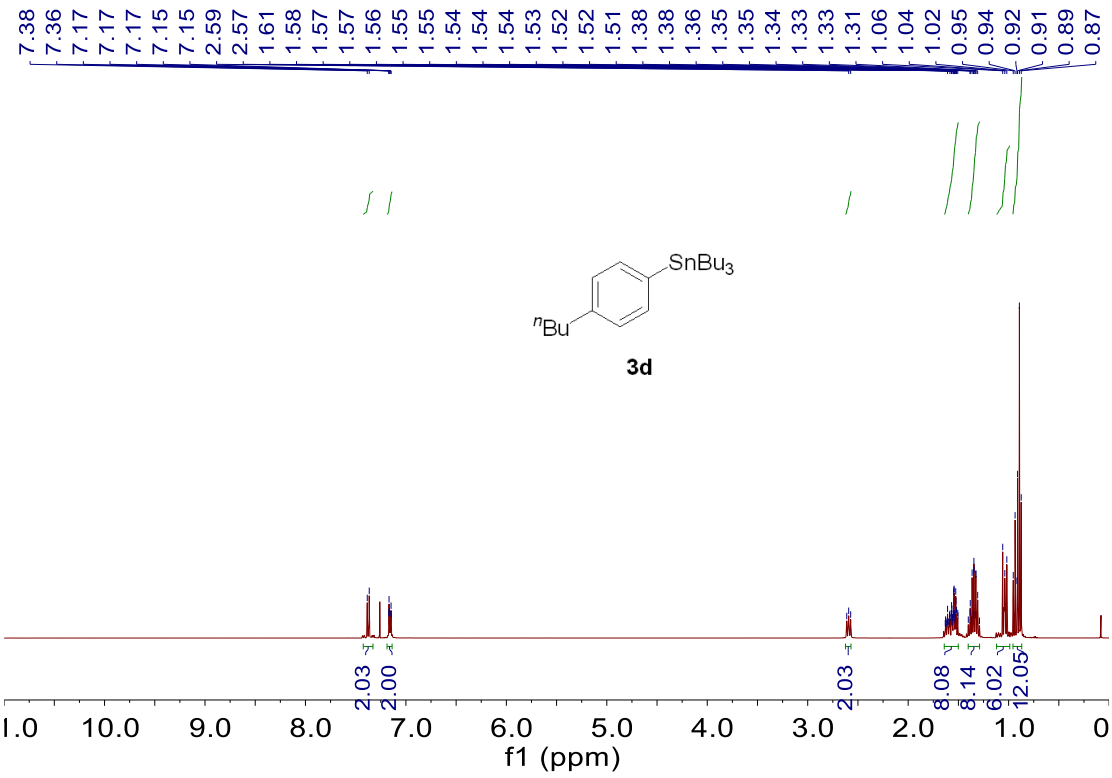
^{1}H NMR (600 MHz) spectrum of **3a** ($CDCl_3$, rt).

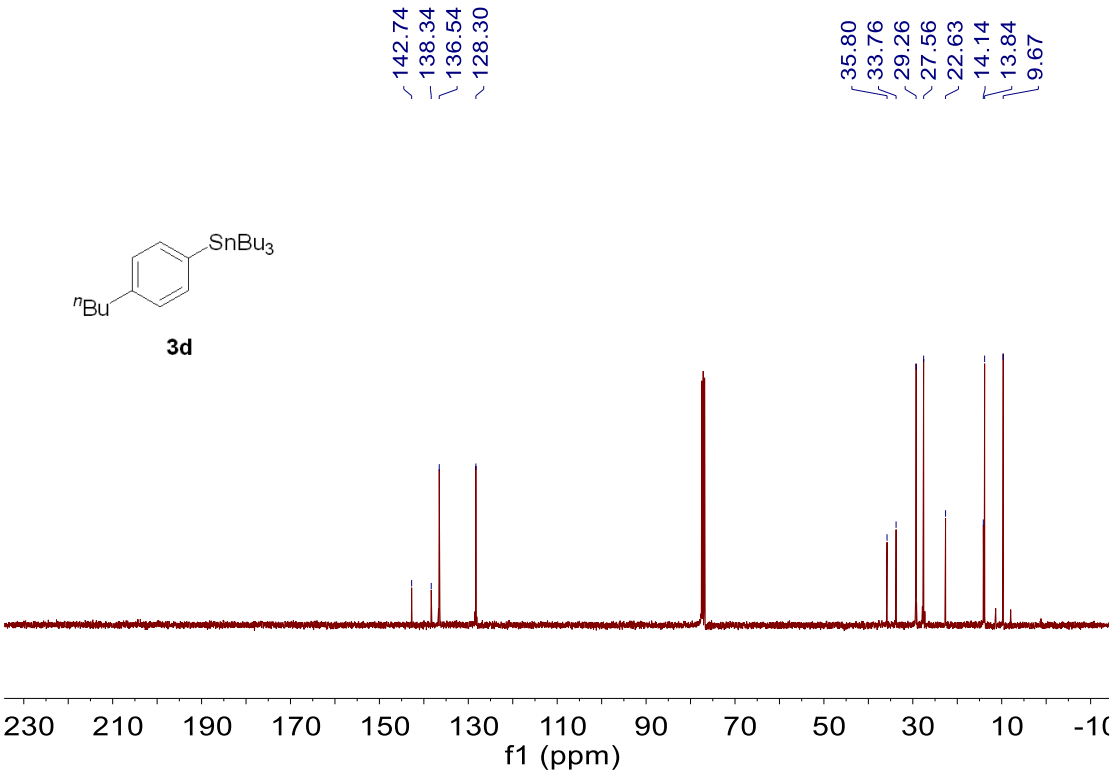


^{1}H NMR (600 MHz) spectrum of **3b** ($CDCl_3$, rt).

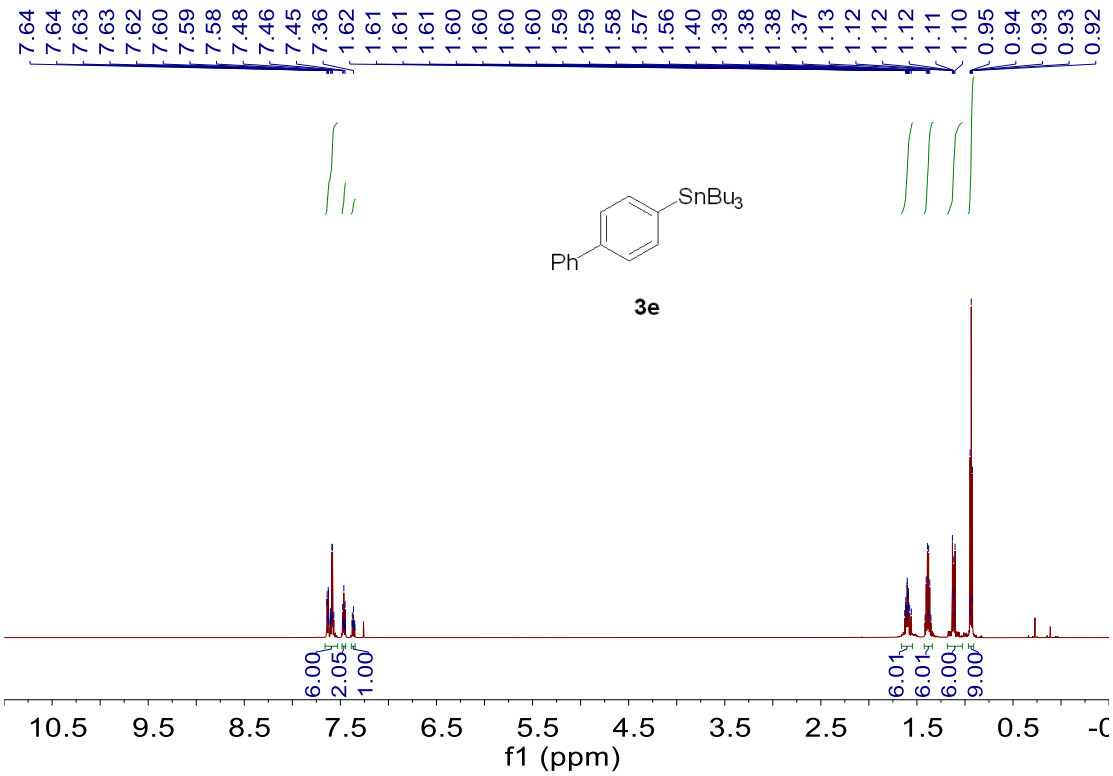


^{1}H NMR (400 MHz) spectrum of **3c** ($CDCl_3$, rt).

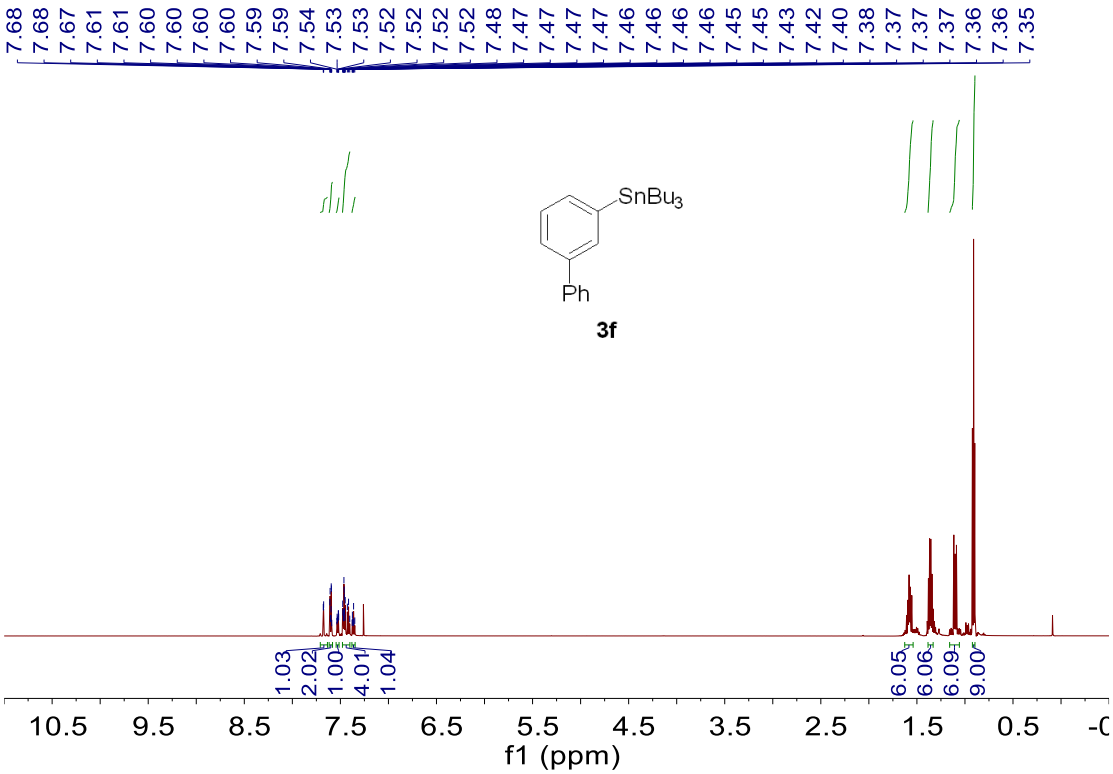




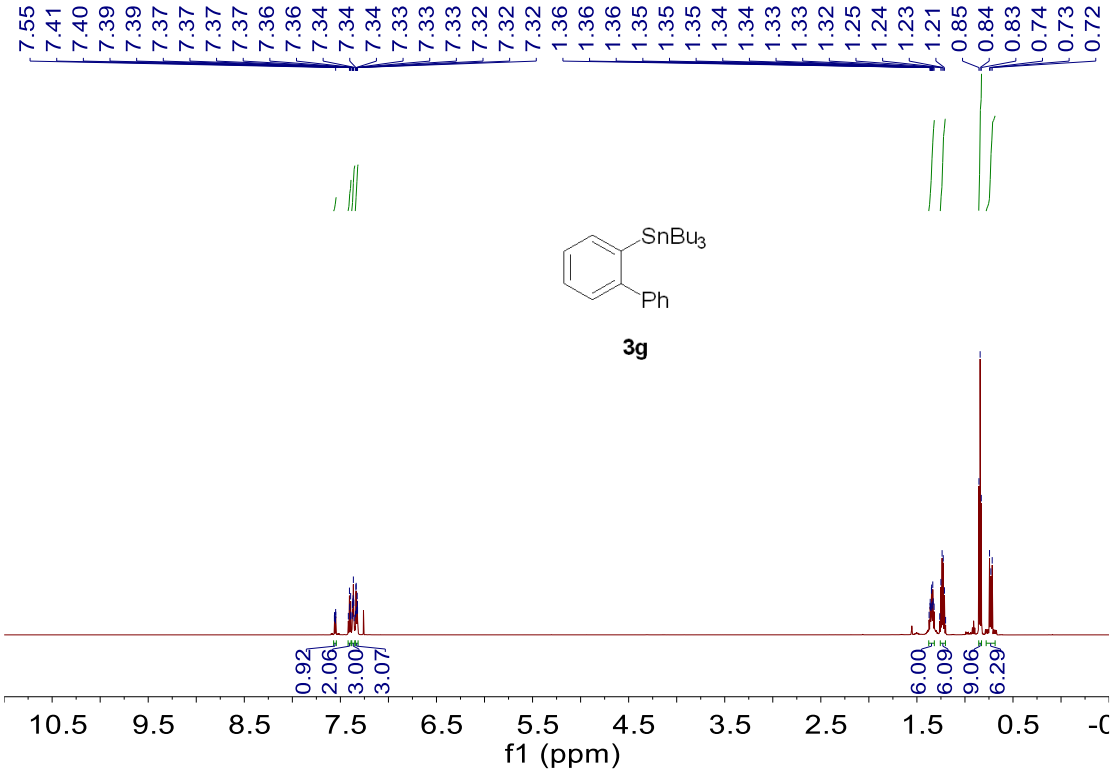
^{1}H NMR (400 MHz) and ^{13}C{^{1}H} NMR (101 MHz) spectra of **3d** ($CDCl_3$, rt).



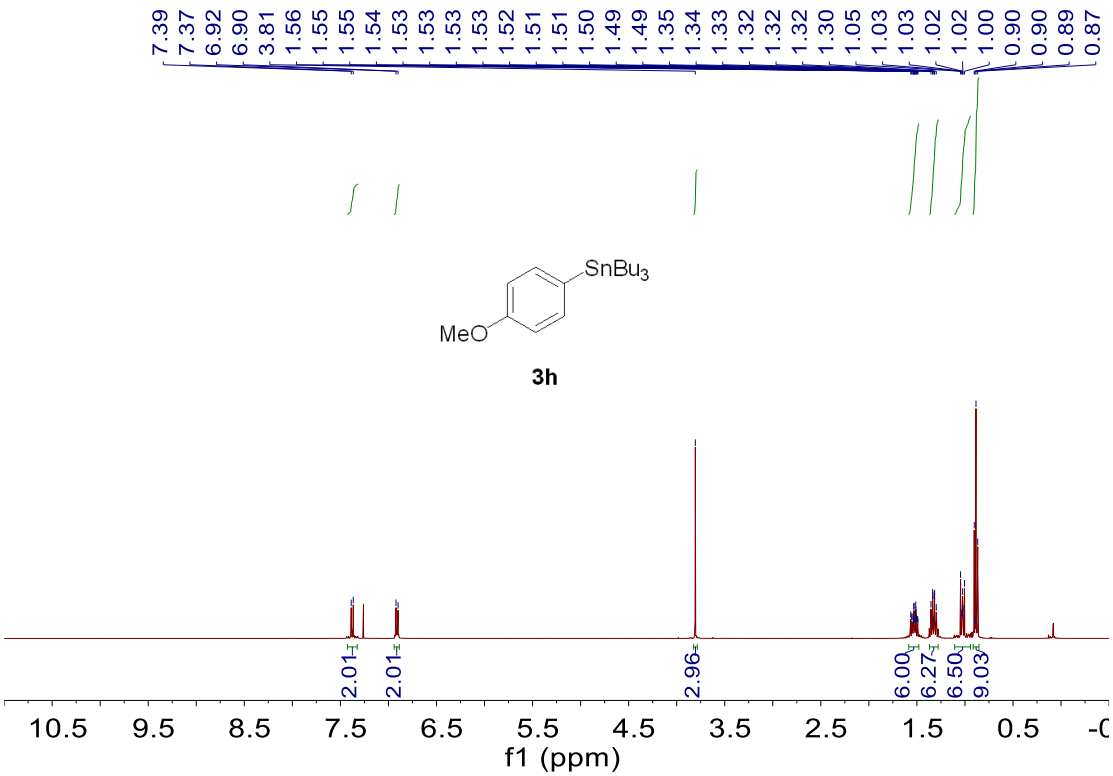
^{1}H NMR (600 MHz) spectrum of **3e** ($CDCl_3$, rt).



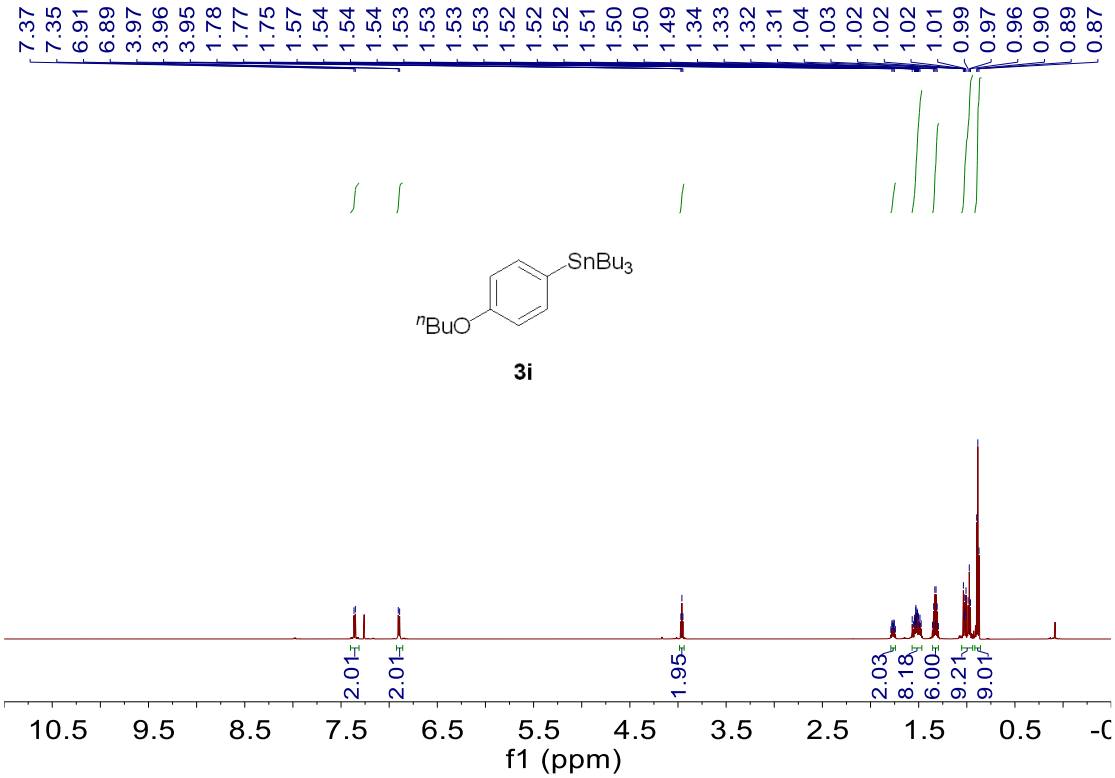
^{1}H NMR (600 MHz) spectrum of **3f** ($CDCl_3$, rt).

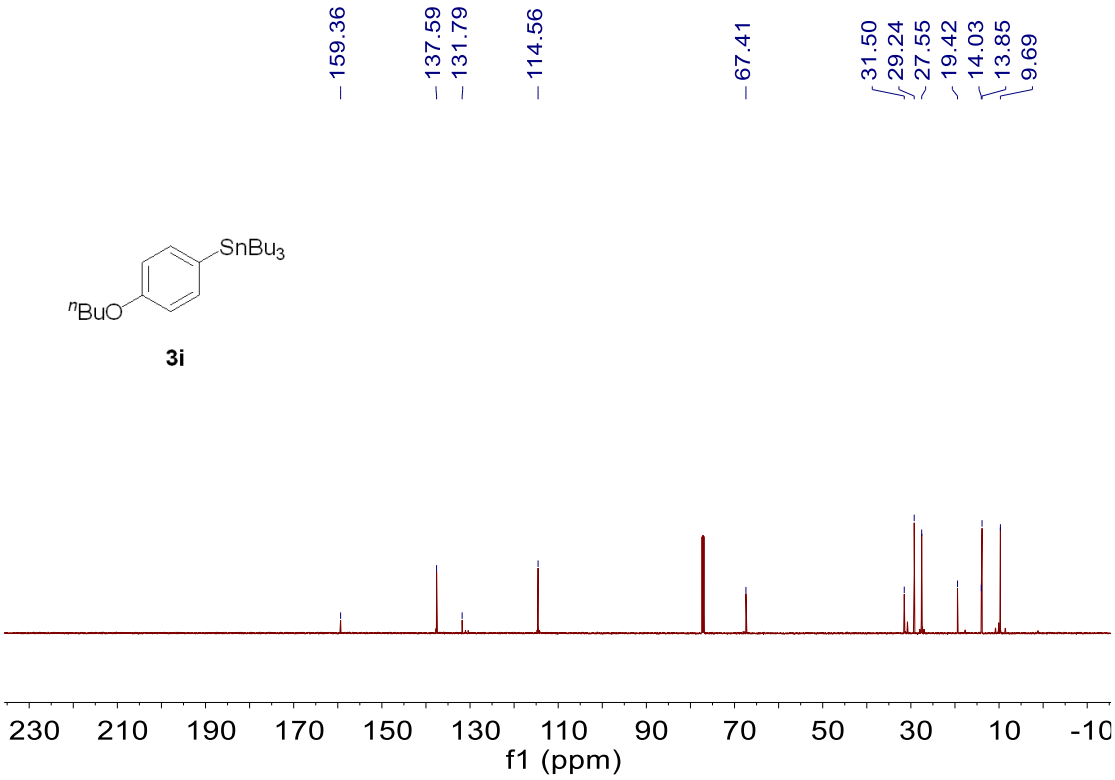


^{1}H NMR (600 MHz) spectrum of **3g** ($CDCl_3$, rt).

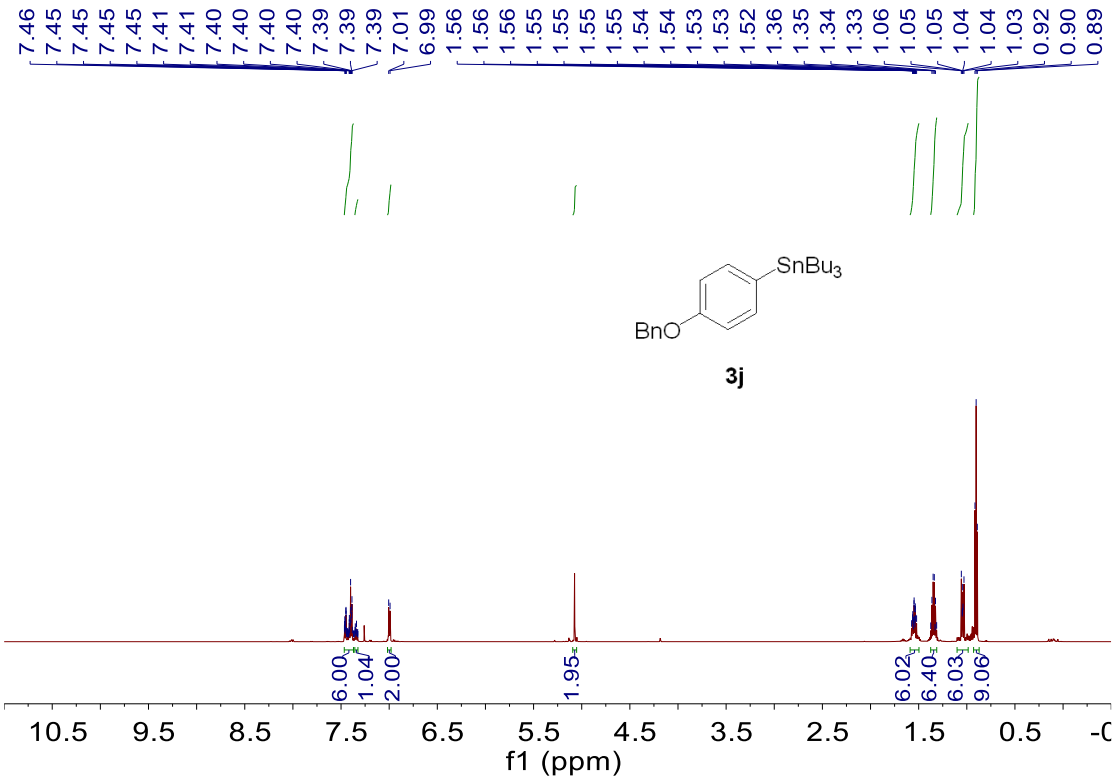


^{1}H NMR (400 MHz) spectrum of **3h** ($CDCl_3$, rt).

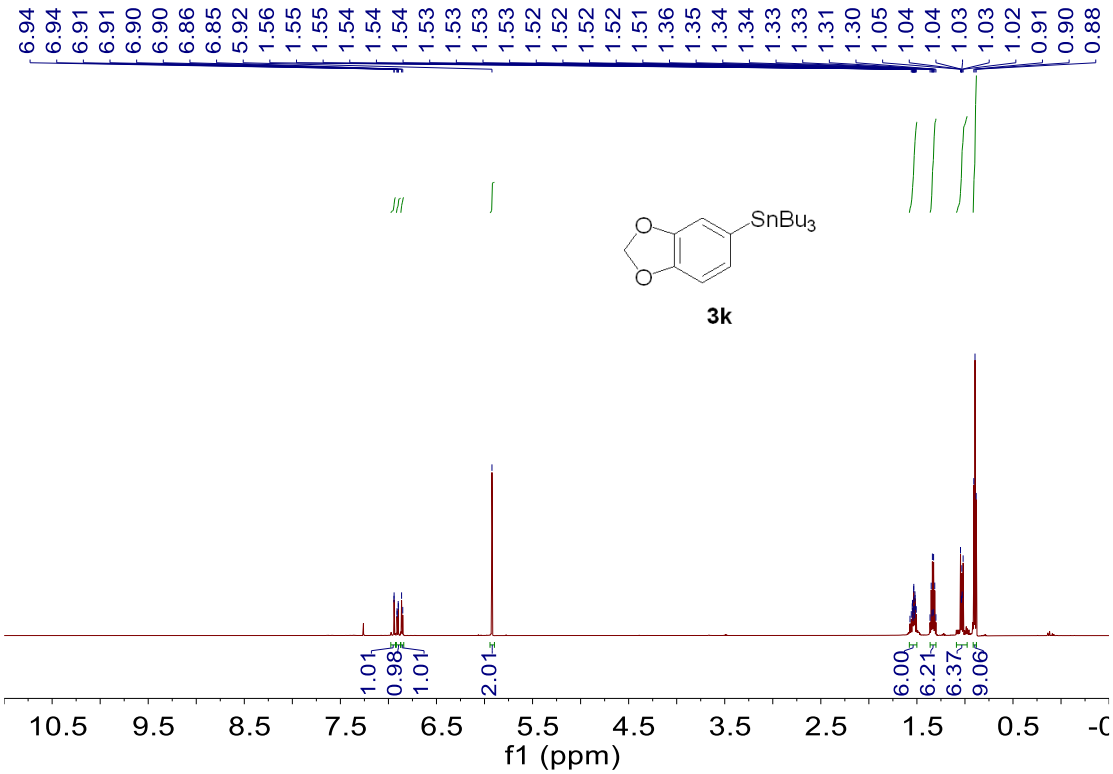




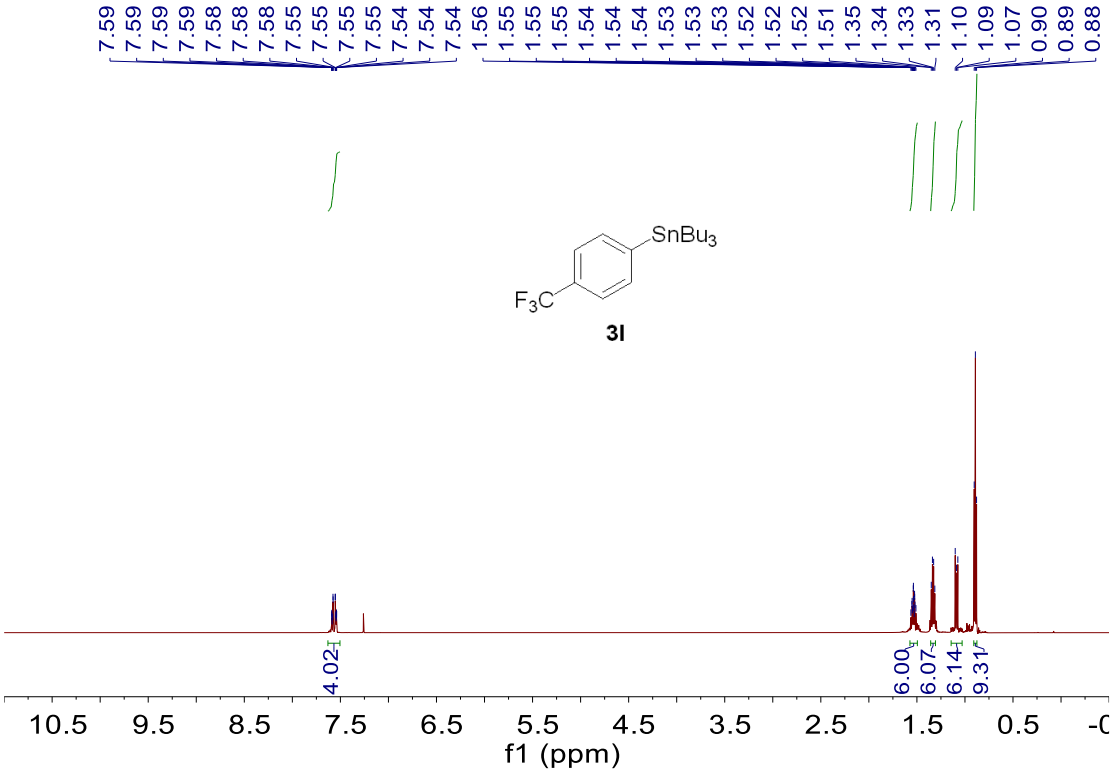
^{1}H NMR (600 MHz) and ^{13}C{^{1}H} NMR (151 MHz) spectra of **3i** ($CDCl_3$, rt).



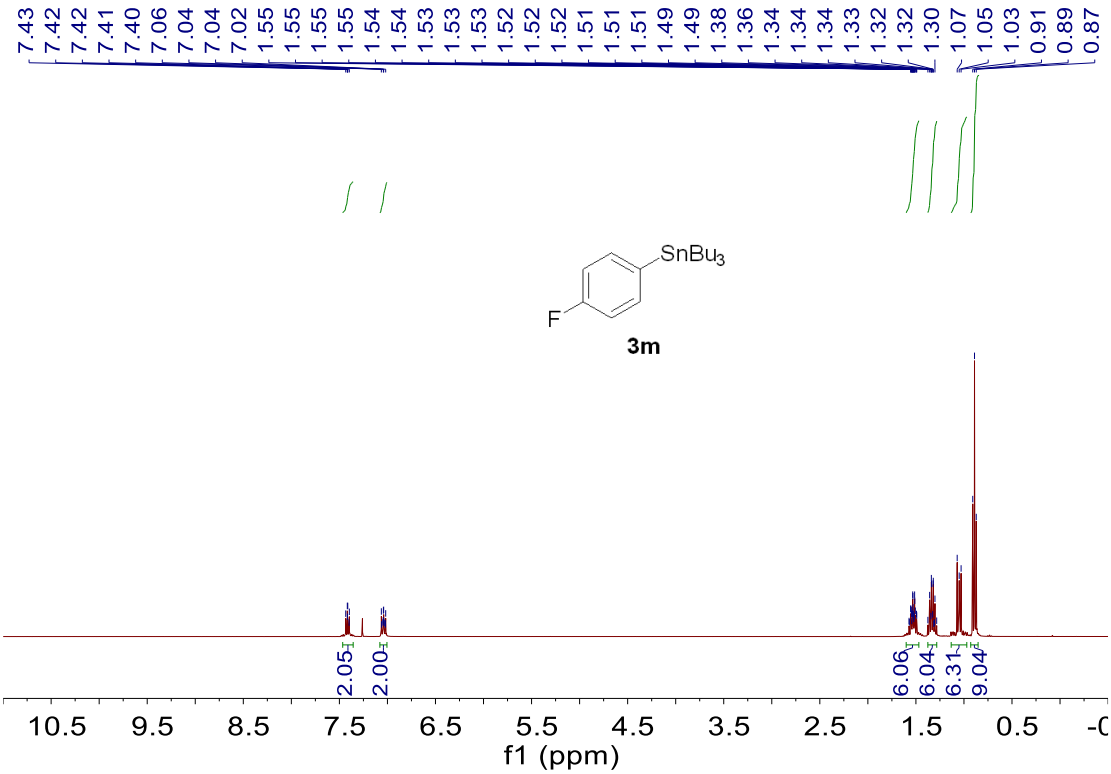
^{1}H NMR (600 MHz) spectrum of **3j** ($CDCl_3$, rt).



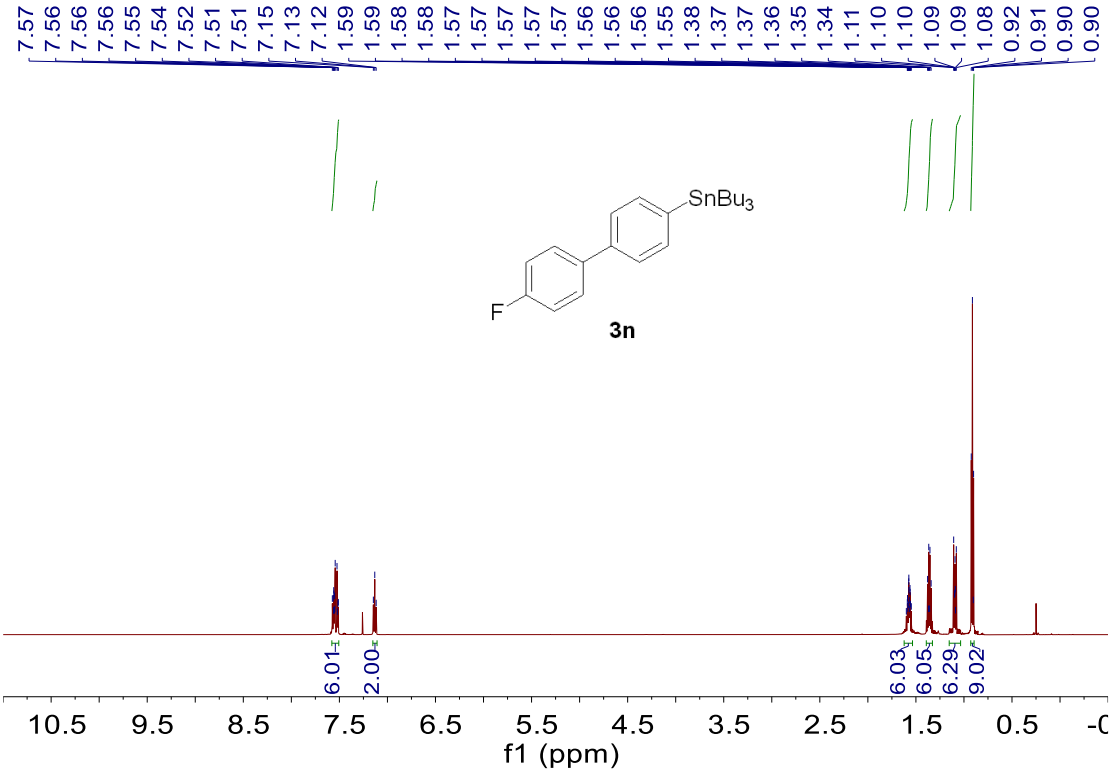
^{1}H NMR (600 MHz) spectrum of **3k** ($CDCl_3$, rt).



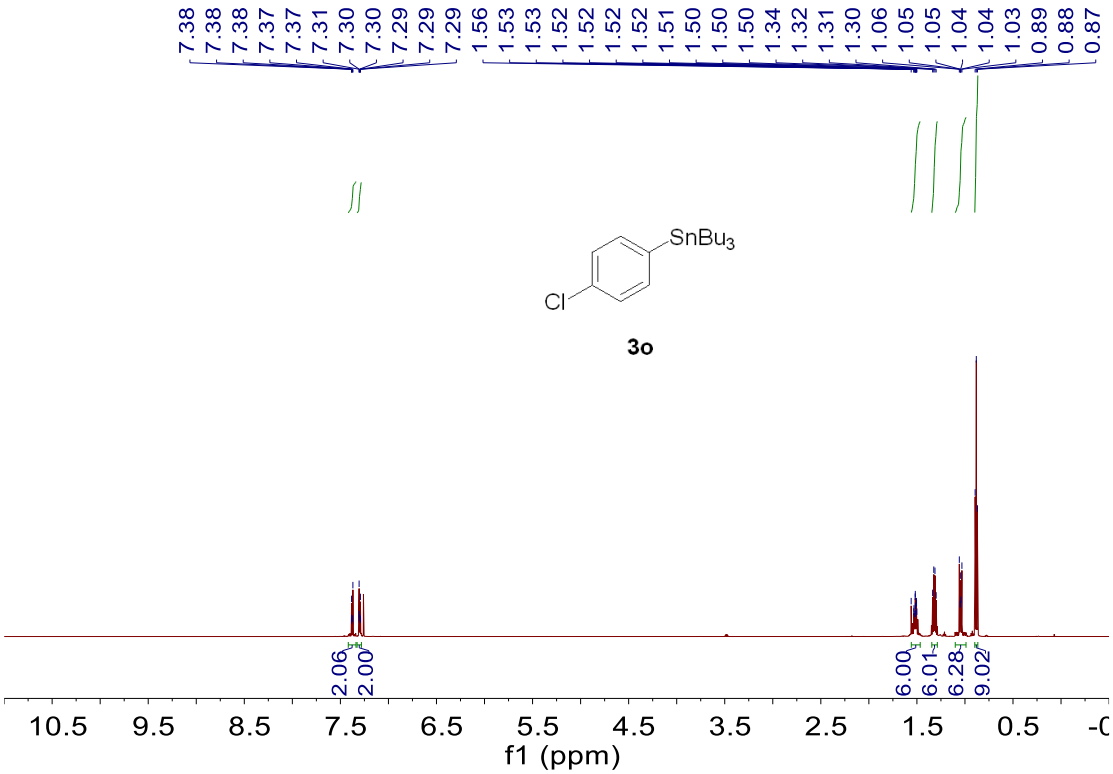
^{1}H NMR (600 MHz) spectrum of **3l** ($CDCl_3$, rt).



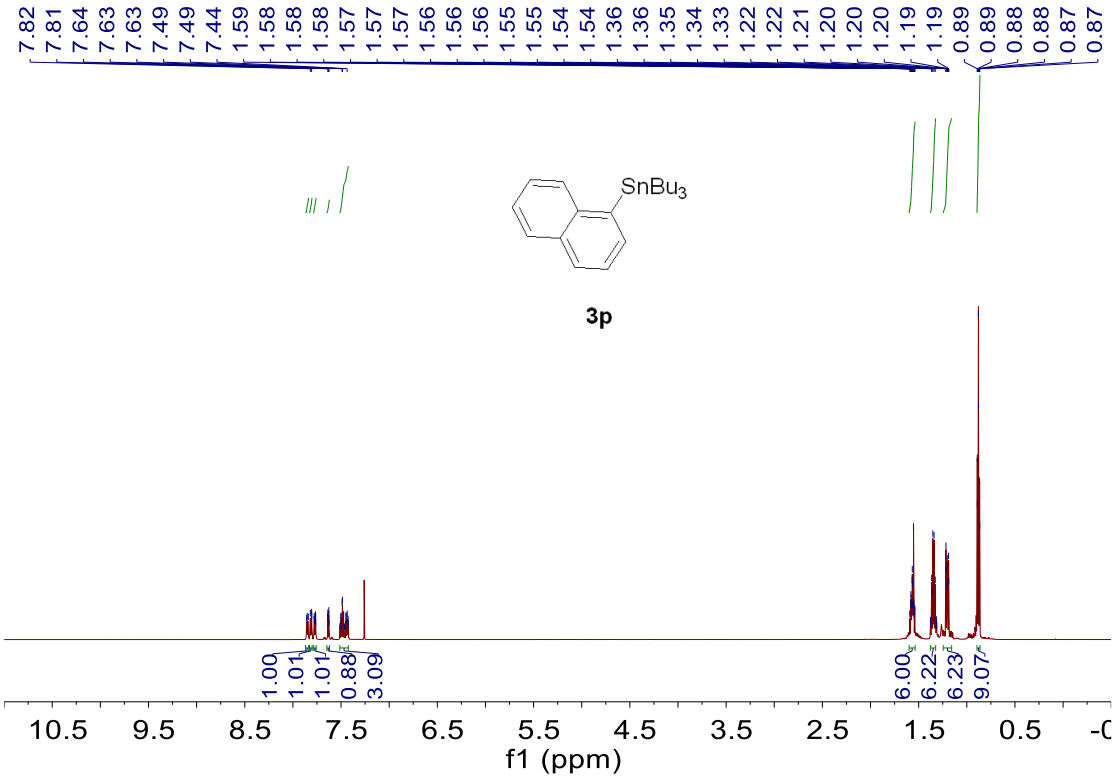
^{1}H NMR (400 MHz) spectrum of **3m** ($CDCl_3$, rt).



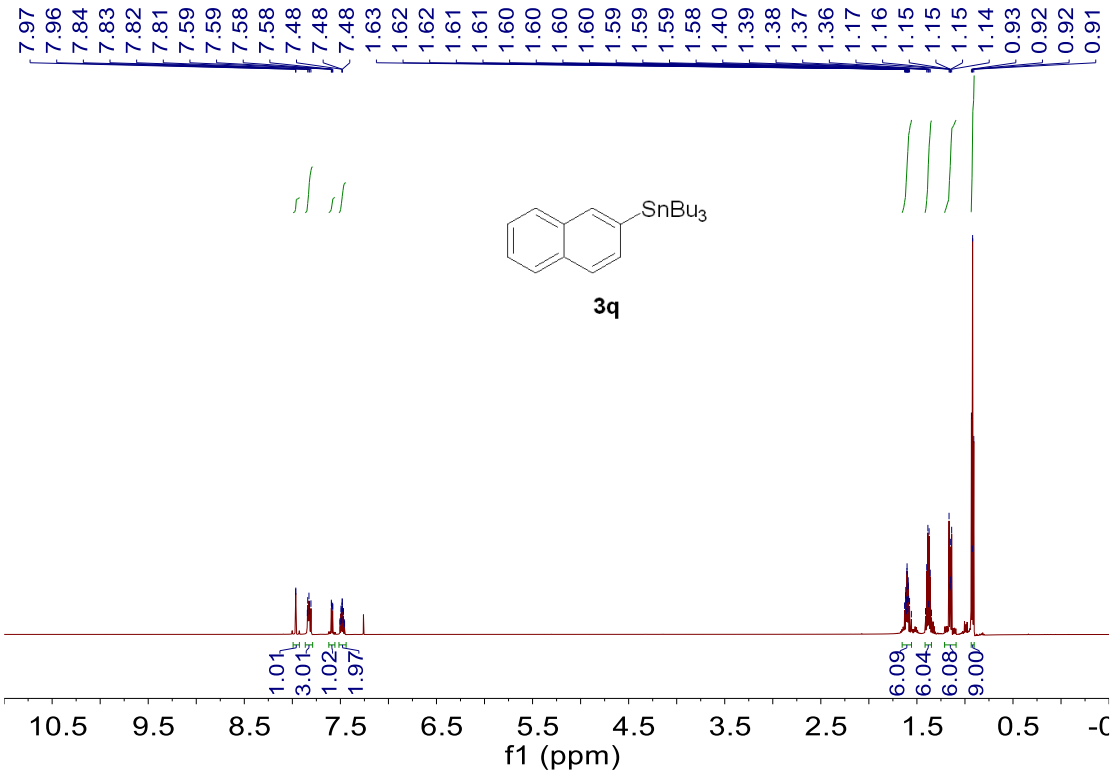
^{1}H NMR (600 MHz) spectrum of **3n** ($CDCl_3$, rt).



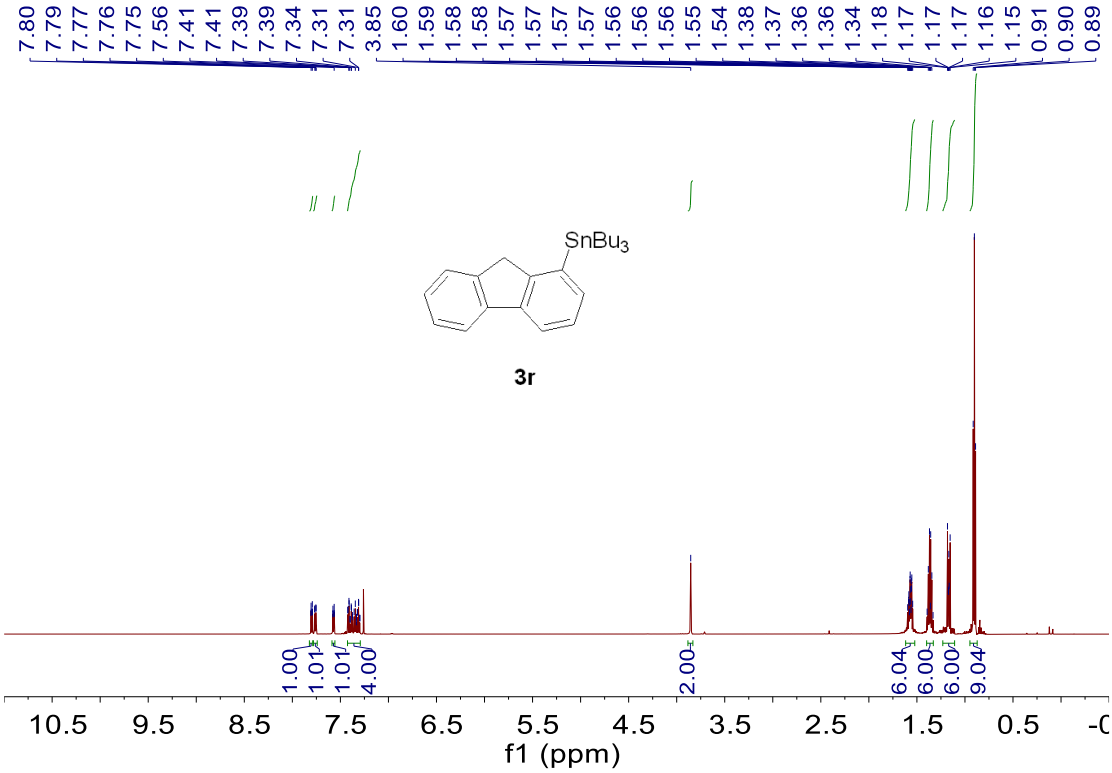
^{1}H NMR (600 MHz) spectrum of **3o** ($CDCl_3$, rt).

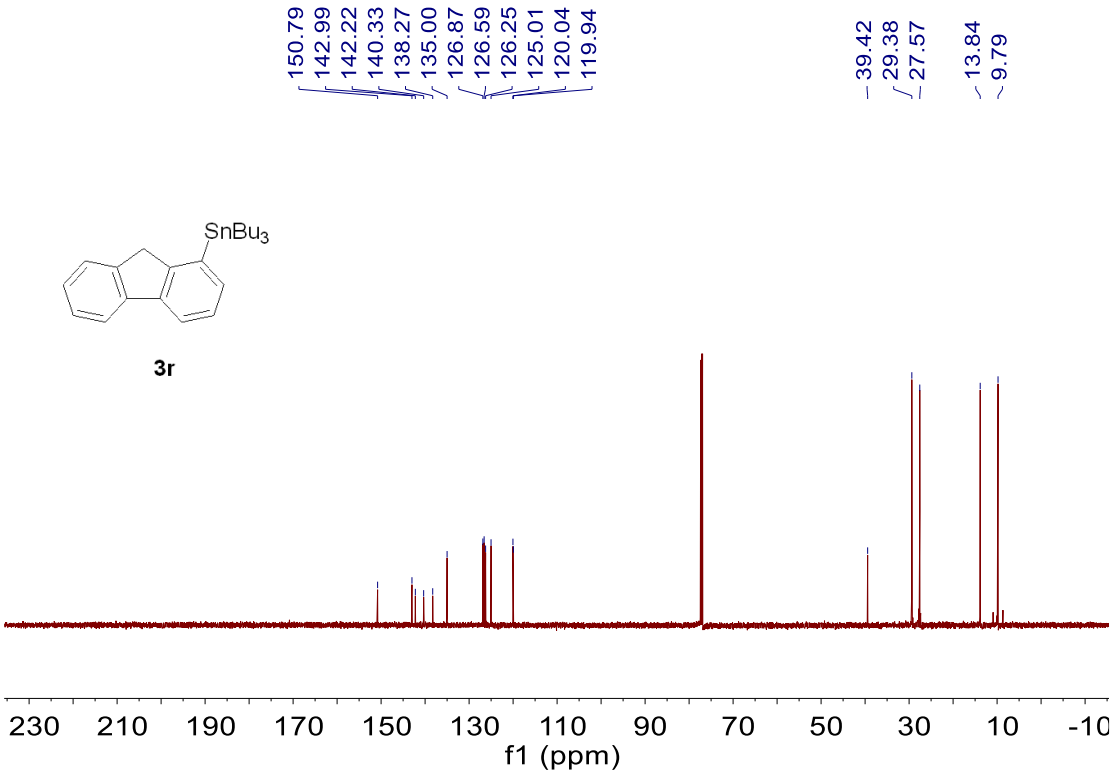


^{1}H NMR (600 MHz) spectrum of **3p** ($CDCl_3$, rt).

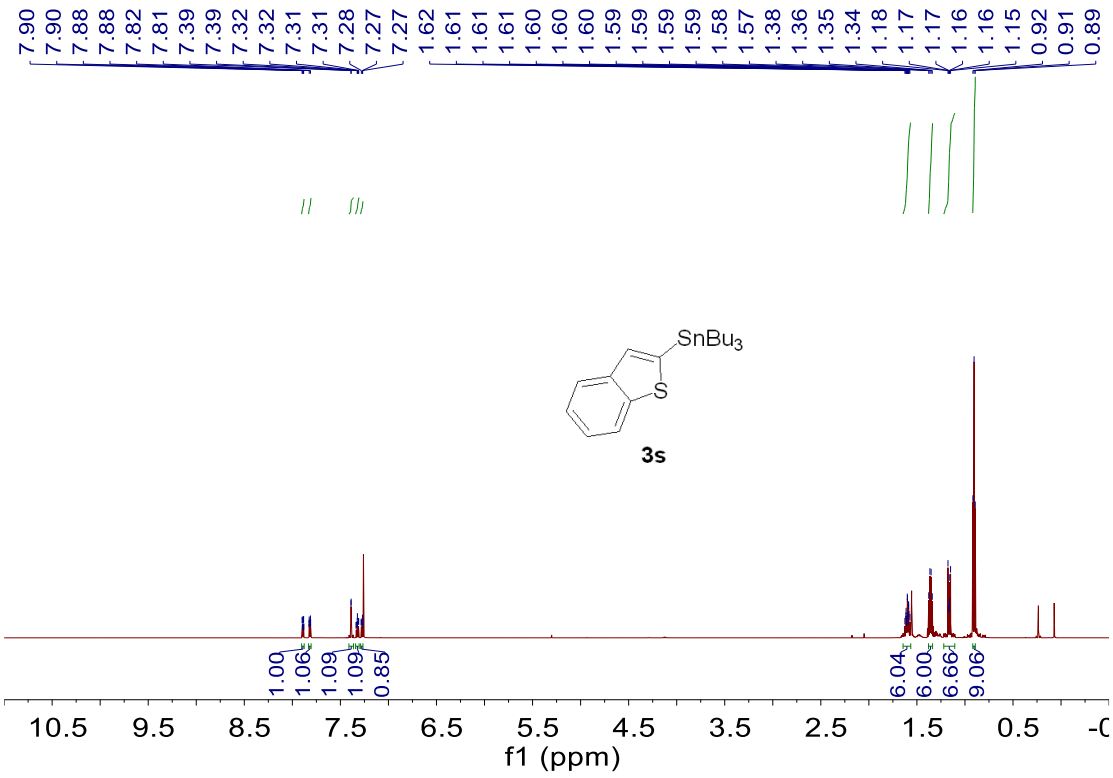


^{1}H NMR (600 MHz) spectrum of **3q** ($CDCl_3$, rt).

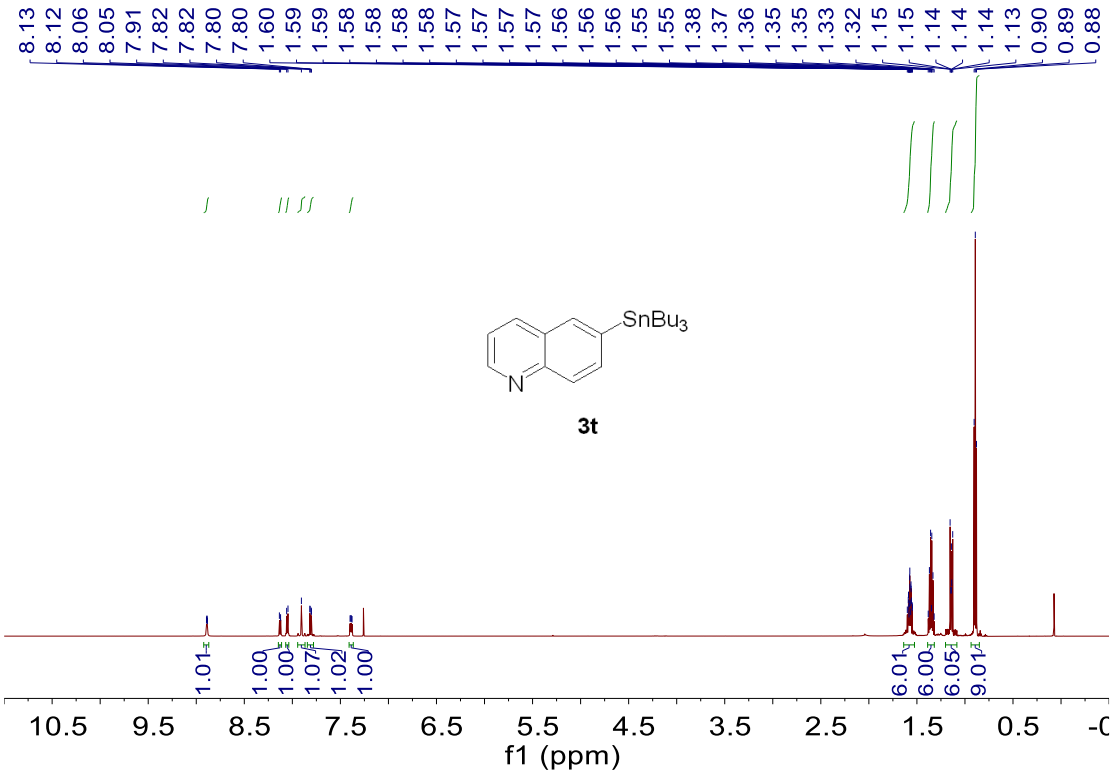




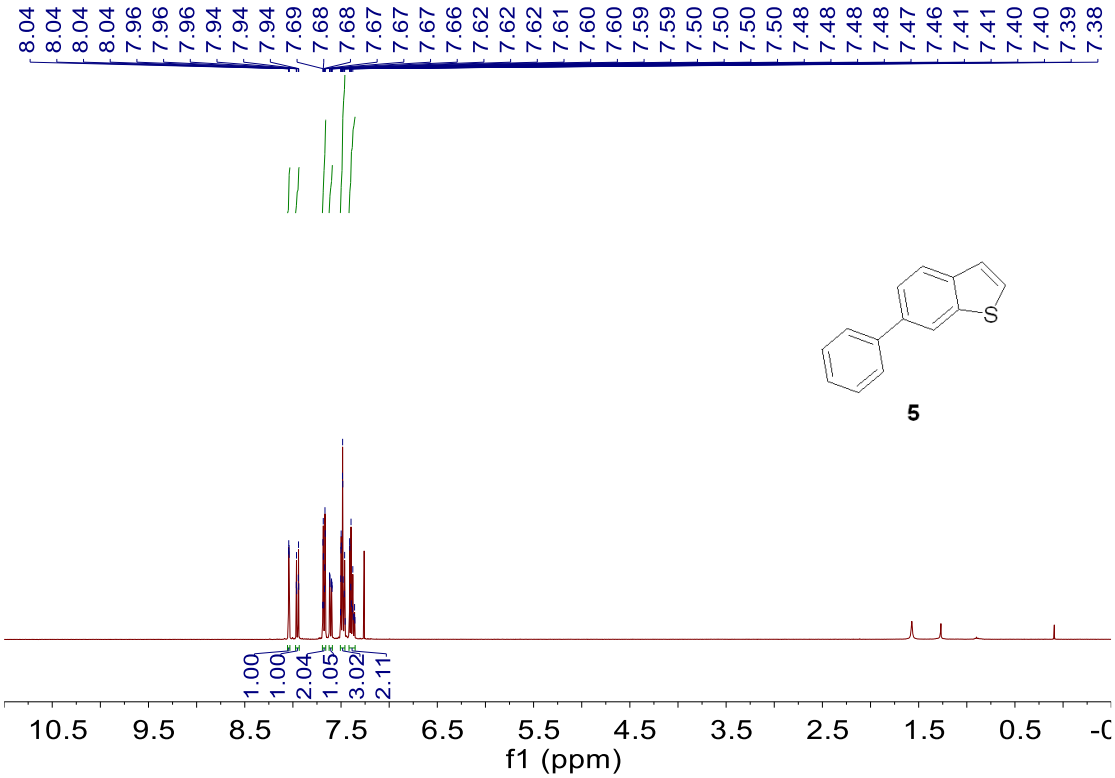
^{1}H NMR (600 MHz) and ^{13}C{^{1}H} NMR (151 MHz) spectra of **3r** ($CDCl_3$, rt).



^{1}H NMR (600 MHz) spectrum of **3s** ($CDCl_3$, rt).



^{1}H NMR (600 MHz) spectrum of **3t** ($CDCl_3$, rt).



^{1}H NMR (600 MHz) spectrum of **5** ($CDCl_3$, rt).

3-5 References

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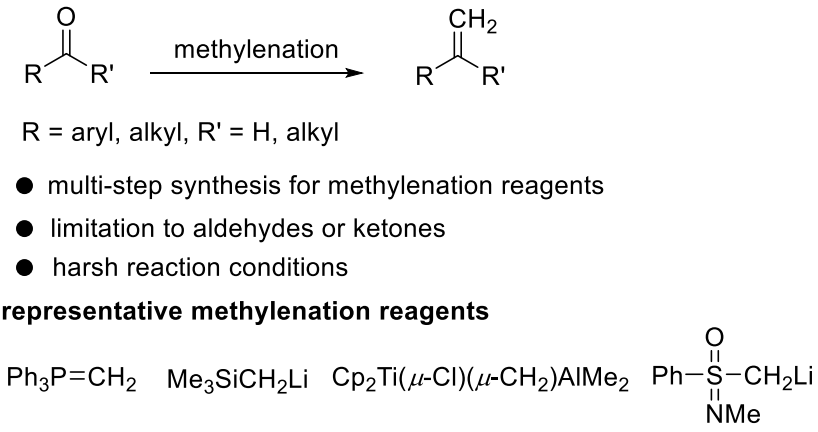
CHAPTER 4

Bidentate Phosphine-Assisted Methylenation of Acyl Halides with $AlMe_3$

4-1 Introduction

2-Substituted propenes including α-methylstyrenes are found to be prevalent in natural[1] and synthetic products,[2] as well as chiral building blocks in catalytic asymmetric processes.[3] Thus, direct and efficient synthesis of such products from the corresponding carbonyl compounds is an important class of organic transformations. Pioneering efforts on methylenation of aldehydes or ketones to the corresponding olefins have been well documented by Wittig,[4] Johnson,[5-7] Peterson,[8] Julia,[9-11] Tebbe,[12-14] and Takai.[15] In particular, an appropriate choice of reagents is a key issue to realize methylenation procedures (Scheme 4-1). Although phosphonium ylides are also well-known methylene transfer reagents, they suffered from tedious separation between triphenylphosphine oxide and the target products. In addition, the yields of target compounds were sometimes unsatisfactory due to the low reactivity of phosphonium ylides.[6,12,14] Other representative methylenation reagents such as sulfoximine,[5] silylcarbanion,[7] sulfone,[10] and titanium-aluminum complex[12] have been studied extensively. On the other hand, late-transition metal complexes such as Ni,[16] Cu,[17] Pd,[18] and Rh[19] have also been described to catalyze methylenation of aldehydes and ketones. However, acyl halides are still rare to be employed toward methylenation reactions, although they are cheap, stable, and wide abundant.[20-21]

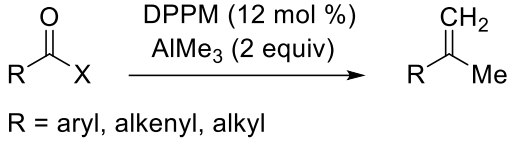
Scheme 4-1. Conventional Methods to Synthesize α-Methylstyrenes.



During our continuing studies on the transformation of acyl halides,[22] the Author discovered a simple and reliable method for the conversion of acyl halides (X = F and Cl)

to 2-substituted propenes, in which trimethylaluminum acts as the methylenation reagent (Scheme 4-2).

Scheme 4-2. Bidentate Phosphine-Assisted Methylenation of Acyl Halides with $AlMe_3$.

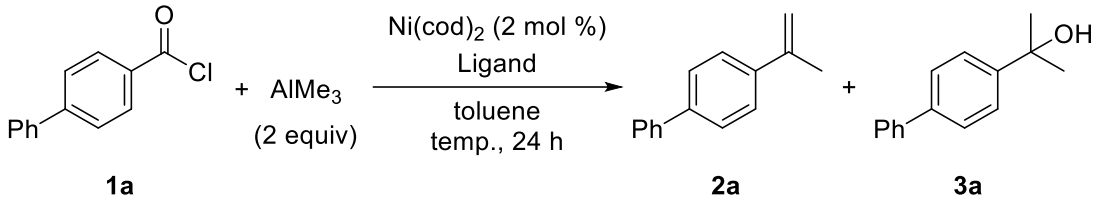


4-2 Results and Discussion

4-2-1 Methylenation of 4-Phenybenzoyl Chloride with $AlMe_3$

After a close look of literatures about the transformation of acyl chlorides to olefins[23] via ketones,[24] we found that one-step methylenation generating the corresponding alkenes from the corresponding carbonyl compounds is in high demand. With this consideration in mind, the author commenced the study by examining the reaction of acyl chloride **1a** and 2 equivalents of trimethylaluminum. Initially, the reaction was conducted in the presence of the Ni catalyst, various bidentate phosphine ligands were tested (Table 4-1, entries 1-4), such as DPPP, DPPB, Dcype, and DPPBz, among them, DPPP showed superior result with the selectively target product **2a** in 95% GC yield, and no alcohol byproduct **3a** was detected (entry 1). The amount of DPPP was then examined, when decreased the DPPP to 10 mol %, the desired product **2a** was slightly decreased to 92% (entry 5). However, when decreased the amount of DPPP to 2 mol %, the yield of **2a** was dramatically reduced to 45% (entry 6). From the screening of temperature, we found lower temperature was favored to the formation of byproduct **3a** (entries 7-9). Unexpectedly, control experiment in entry 10 demonstrated the DPPP could afford olefin **2a** in 83% yield, along with 18% byproduct alcohol **3a**, thus, the nickel catalyst is not necessary in this methylenation reaction. On the other hand, only 15% of **2a** was formed in the absence of DPPP, which further revealed that the addition of DPPP was crucial in the present transformation (entry 11). In order to suppress the side reaction to avoid the formation of alcohol, enlonged reaction time to 48 h, the conversion of olefin **2a** was obtained in 87% yield, along with 3% **3a** (entry 12).

Table 4-1. Optimization the Reaction Conditions in the Presence of Ni Catalyst.[a]



1a **2a** **3a**

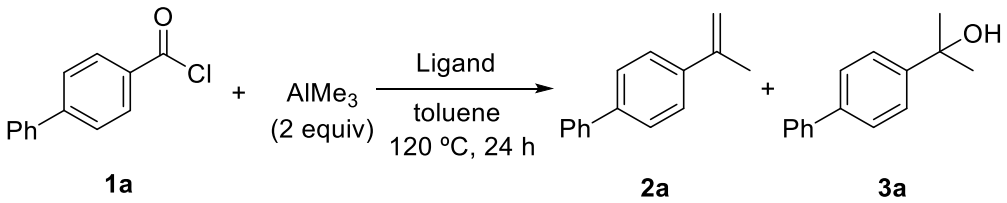
entry	ligand (mol %)	temp. (°C)	**2a** (%)[b]	**3a** (%)[b]
1	DPPP (12)	120	95	0
2	DPPB (12)	120	93	0
3	Dcype (12)	120	71	0
4	DPPBz (12)	120	71	0
5	DPPP (10)	120	92	0
6	DPPP (2)	120	45	0
7	DPPP (12)	110	86	14
8	DPPP (12)	60	37	55
9	DPPP (12)	rt	35	61
10[c]	DPPP (12)	120	83	18
11[c]	DPPP (0)	120	15	0
12[cd]	DPPP (12)	120	87	3

[a]Reaction conditions: **1a** (0.2 mmol), $AlMe_3$ (2 equiv), $Ni(cod)_2$ (0.004 mmol), toluene (0.5 mL), 24 h. [b]Determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard. [c]Without $Ni(cod)_2$. [d]48 h.

In order to realize the selectively methylenation of acyl chloride **1a** with $AlMe_3$ to 2-substituted propenes, screening several additives revealed the optimized condition, as shown in Table 4-2. Monodentate phosphine PPh_3 afforded 59% yield of **2a**, along with the alcohol **3a** in 7% yield (entry 1). Among bidentate phosphines investigated (entries 2-6), DPPM showed superior results; target product **2a** was selectively delivered in 90%

isolated yield (entry 2). While, nitrogen-containing bases such as triethylamine (entry 7) and tetramethylethylenediamine (TMEDA, entry 8) also resulted in the conversion of **2a** in 78% and 70% yields, respectively. In a sharp contrast, DPPM-free reaction conditions gave only 15% yield of **2a** (entry 11). The result shown in entry 12 suggested that 2 equivalents of $AlMe_3$ are essential for complete transformation into **3a**.

Table 4-2. Optimization for Methylenation of **1a** with $AlMe_3$.[a]



1a **2a** **3a**

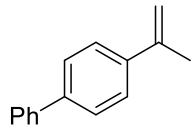
entry	additive	(mol %)	yield (%)[b]	
			2a	**3a**
1	PPh_3	24	59	7
2	**DPPM**	**12**	**93 (90)**	**0**
3	DPPE	12	54	8
4	DPPP	12	82	18
5	DPPB	12	3	3
6	Xantphos	12	57	10
7	Et_3N	24	78	22
8	TMEDA	12	70	3
9	DPPM	15	66	5
10	DPPM	2	60	0
11	DPPM	0	15	0
12[c]	DPPM	12	12	0

[a]Reactions were carried out with **1a** (0.2 mmol), $AlMe_3$ (2 equiv), toluene (0.5 mL) at 120 ℃ for 24 h. [b]GC yields. An isolated yield is given in parentheses. [c]$AlMe_3$ (1 equiv) was used.

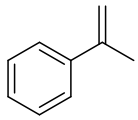
4-2-2 DPPM-Assisted Methylenation of Acyl Halides

With the optimized conditions in hand, a generality for methylenation of acyl chlorides **1** or fluorides **1'** with $AlMe_3$ was examined. The results are summarized in Table 4-3. Both benzoyl chloride (**1b**) and benzoyl fluoride (**1b'**) gave **2b** in 83% and 92% yields, respectively. Acyl halides bearing alkyl and phenyl groups in various positions afforded **2c-2f** in good to high yields. The substrates bearing oxygen functionalities reacted smoothly to afford the corresponding products **2g-2k** in 65-72% yields. Surprisingly, acyl chloride substituted by methoxycarbonyl group chemoselectively provided the target product **2l** in 76% yield. Functional compatibility of halogen-containing starting materials in this methylenation was further demonstrated. Due to the absence of any transition metals, it is noteworthy that bromide (**2o**) and iodide (**2p**) were well tolerated. Similarly, naphthoyl chlorides and fluorides readily yielded **2q** and **2r** in good yields. Sulfur-containing heterocycles posed no problem in this transformation to give **2s** and **2t**. Strikingly, this method employing alkenylated acyl chlorides could be applied for 1,3-dienes synthesis to afford **2u** and **2v**, which are versatile precursors for a variety of target molecules of industrial and biological significance. Additionally, the reactions of tertiary aliphatic acyl chloride **1w** could readily furnished **2w** in 75% yield. In some cases, an equimolar amount of $AlMe_3$ gave rise to the formation of **2** in comparable yields obtained with 2 equiv of $AlMe_3$ addition, indicating that $AlMe_3$ play a role of two methyl group-donating reagent. Unfortunately, acyl chlorides bearing strong electron-withdrawing functional groups such as nitro, cyano, and trifluoromethyl groups failed to participate this transformation.

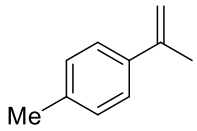
Table 4-3. Scope of Acyl Halides.[ab]



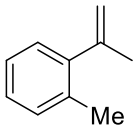
2a: 90% (from X = Cl)
92% (from X = F)



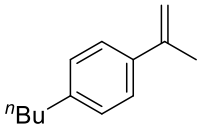
2b: 83% (from X = Cl)
92% (from X = F)



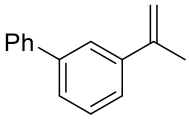
2c: 93% (from X = Cl)[c]



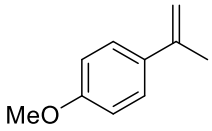
2d: 92% (from X = Cl)



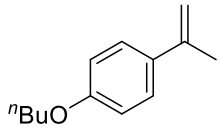
2e: 80% (from X = Cl)



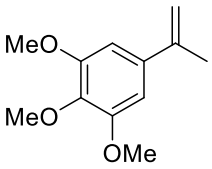
2f: 95% (from X = F)



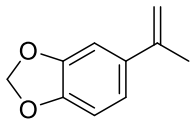
2g: 68% (from X = Cl)[c]
72% (from X = F)



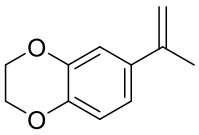
2h: 66% (from X = Cl)



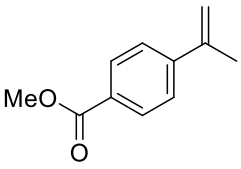
2i: 68% (from X = F)



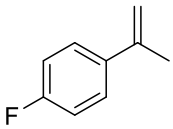
2j: 65% (from X = F)



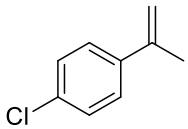
2k: 66%(from X = F)



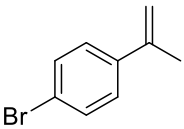
2l: 76% (from X = Cl)



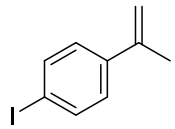
2m: 86% (from X = Cl)[c]



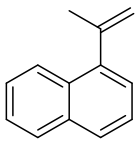
2n: 88% (from X = Cl)[c]



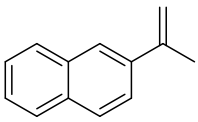
2o: 90% (from X = Cl)[c]



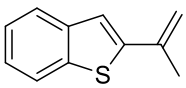
2p: 79% (from X = Cl)[c]



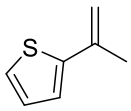
2q: 90% (from X = Cl)
94% (from X = F)



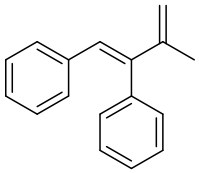
2r: 96% (from X = Cl)
95% (from X = F)



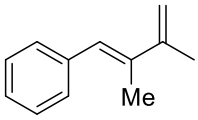
2s: 96% (from X = F)



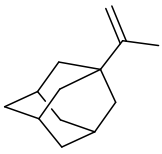
2t: 82%(from X = F)



2u: 76% (from X = Cl)



2v: 62% (from X = Cl)



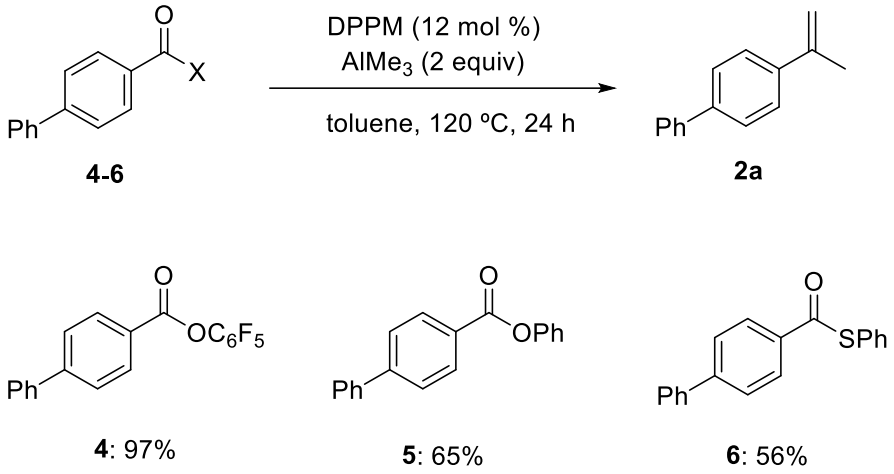
2w: 75% (from X = Cl)

[a]Reaction conditions: **1** (X = Cl) or **1'** (X = F) (0.2 mmol), $AlMe_3$ (2 equiv), DPPM (12 mol %), toluene (0.5 mL), 120 °C, 24 h. [b]Isolated yields. [c]1 mmol.

Next, a series of ester derivatives were also evaluated (Scheme 4-3). Perfluoro-phenolic ester **4** showed good reactivity with the aid of DPPM and afforded **2a**

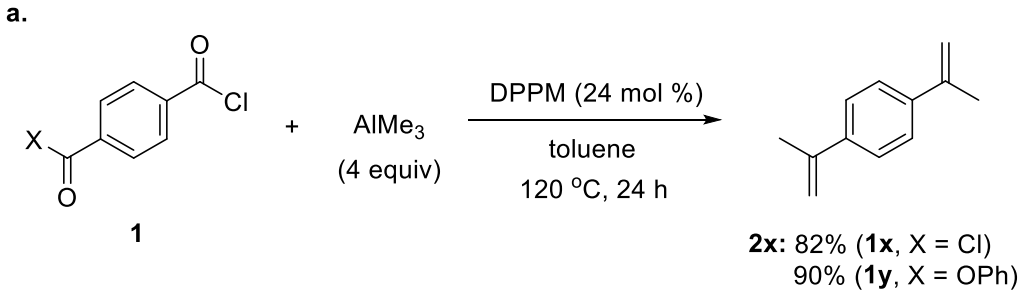
in 97% yield. In addition, the methylenation reactions of phenolic ester **5** and thioester **6** could also undergo to give **2a** in moderate yields, which is in a sharp contrast to the result for methyl ester (*vide supra*). Methylenation of challenging methyl benzoate and ethyl benzoate only afforded 15% and 5% yields of styrene, respectively.

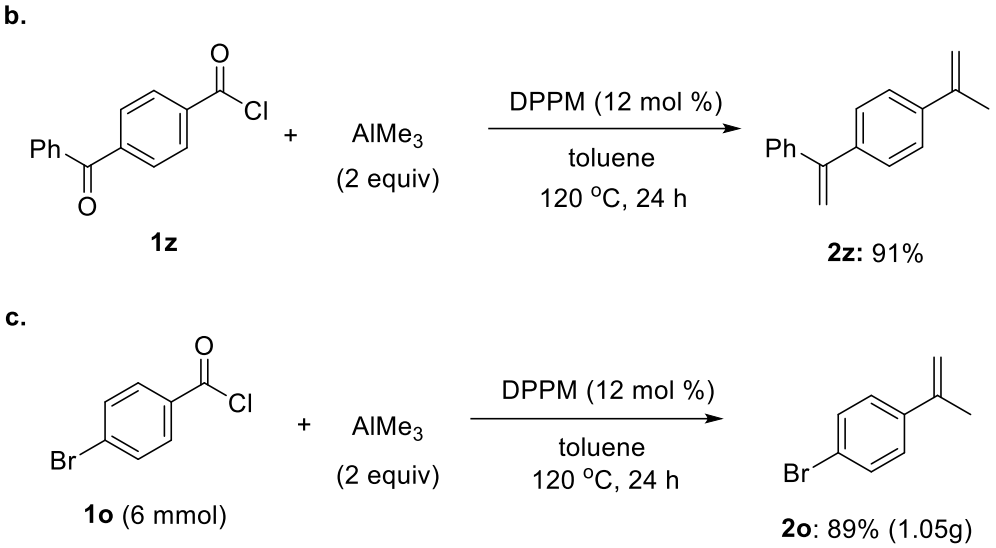
Scheme 4-3. Scope of Carboxylic Acid Derivatives.



Double methylenation with 4 equivalents of $AlMe_3$ was tested for the bifunctional acyl chloride **1x**. As a result, 1,4-diisopropenylbenzene (**2x**) was formed in 82% yield. In addition, with the use of phenolic ester **1y**, **2x** was delivered in 90% yield (Scheme 4-4a). As shown in Scheme 4-4b, acyl chloride **1z** with a keto group provided the unsymmetrical 1,4-methylenation product **2z** which has been frequently used in the polymerization.[25] Otherwise, **2z** is not readily synthesized by other synthetic methods. Large-scale synthesis of 4-bromo-2-propenylbenzene (**2o**) was successful without a loss in yield (89%, 1.05 g) (Scheme 4-4c).

Scheme 4-4. Synthetic Applications.

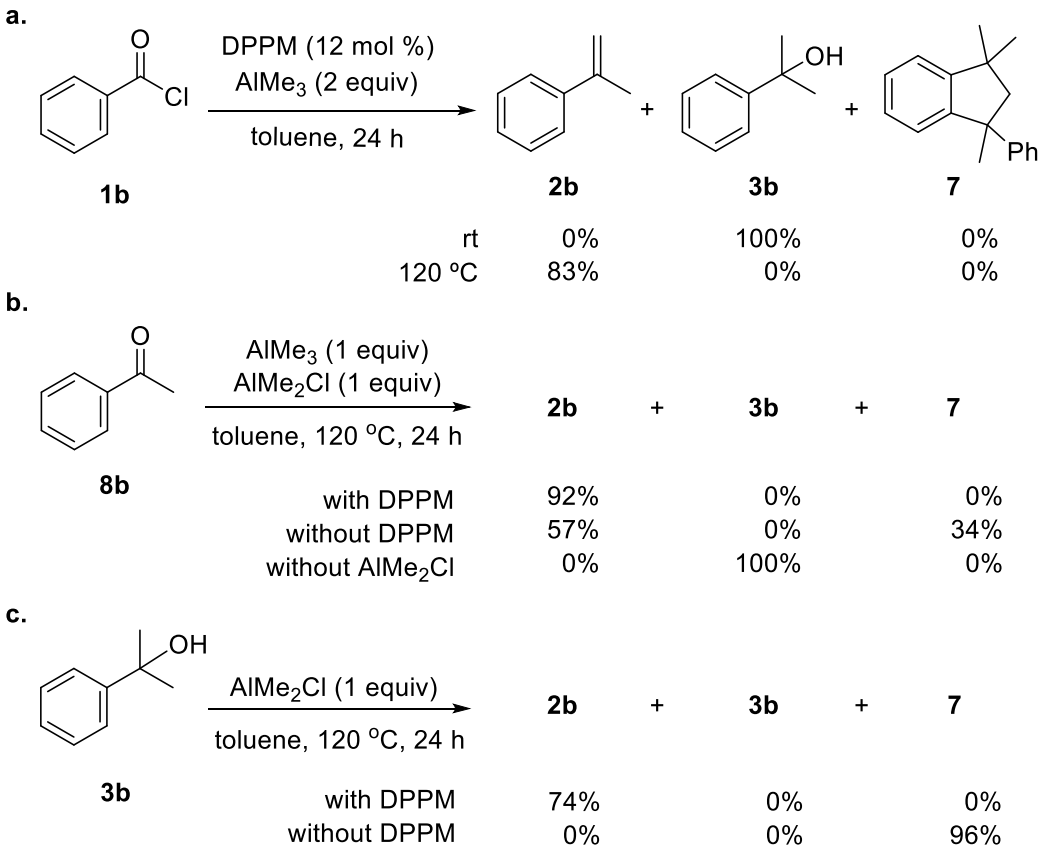




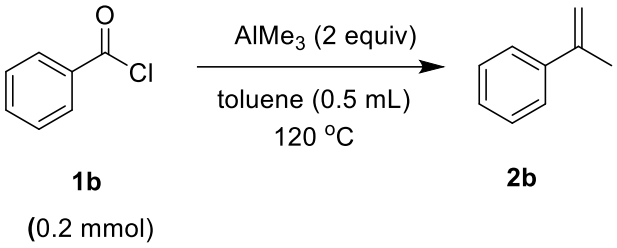
4-2-3 Mechanistic Studies of Methylenation of Benzoyl Halides

To shed light on the reaction mechanism, additional experiments were performed to prove the existence of intermediates and a role of DPPM. The reaction of **1b** with 2 equivalents of $AlMe_3$ was conducted (Scheme 4-5a). In the reaction at room temperature for 24 h, the starting material **1b** was completely consumed, along with the formation of alcohol **3b** quantitatively, but neither **2b**, nor 2,3-dihydro-1*H*-indene derivative **7**,[26] the dimerized product of **2b**, was observed. On the other hand, when the same reaction was carried out at 120 ℃, 83% yield of **2b** was obtained, which indicates that the high reaction temperature is important for transformation from **3b** into **2b**. The plausible intermediate acetophenone (**8b**) was subjected to the reaction with or without DPPM or $AlMe_2Cl$ (Scheme 4-5b). As a result, the reactions of **8b** with 1 equivalent of $AlMe_3$ in the presence of 12 mol % of DPPM afforded **2b** in 92% NMR yield, whereas the yield of **2b** was dropped to 57% without DPPM, along with 34% of **7**. Without $AlMe_2Cl$, only alcohol **3b** was obtained with or without DPPM. This result suggests that the in-situ formed $AlMe_2Cl$ plays an important role for transformation of **3b** to **2b**. Subsequently, the reactions of the intermediate alcohol **3b** with an equimolar amount of $AlMe_2Cl$ were elucidated (Scheme 4-5c). As expected, a single product **2b** was formed in 74% yield with the aid of 12 mol % of DPPM, whereas, without DPPM, byproduct **7** was obtained in 96% yield. Therefore, we concluded that the present methylenation is promoted by the in-situ formed $AlMe_2X$ (X = F or Cl).

Scheme 4-5. Mechanistic Studies.



The results mentioned above are also supported with the time course of the reaction of benzoyl fluorides (**1b'**) with 2 equivalents of $AlMe_3$ with or without DPPM. Initially, time course of the reaction of benzoyl chloride **1b** with $AlMe_3$ (2 equiv) in the presence of DPPM were performed in Figure 4-1. To a toluene (0.5 mL) solution of DPPM (9.2 mg, 0.024 mmol, 12 mol %), **1b** (28.1 mg, 0.2 mmol) in a 20-mL Schlenk tube, was added $AlMe_3$ (285 μL, 0.4 mmol, 2 equiv) under an argon atmosphere. Parallel experiments were stirred at 120 ℃ for 5 min, 30 min, 1 h, 1.5 h, 2 h, 3 h, 6 h, 12 h, and 24 h, respectively. The reaction mixtures were quenched with 1 M HCl solution, extracted with diethyl ether, and dried over $MgSO_4$, then the volatiles were removed by a rotary evaporator. These reactions were monitored by ^1H NMR spectroscopy at room temperature with CH_2Br_2 as the internal standard, and the results were shown in Figure 4-1 (black line). Similarly, time course of the reaction of benzoyl chloride **1b** with $AlMe_3$ (2 equiv) in the absence of DPPM were also performed, and the results were shown in Figure 4-1 (red line).



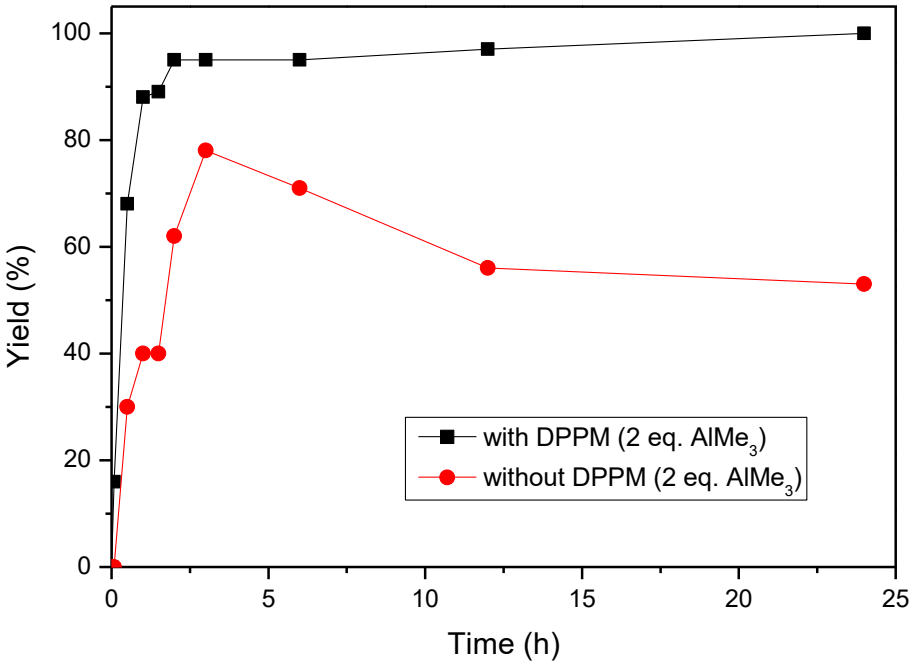
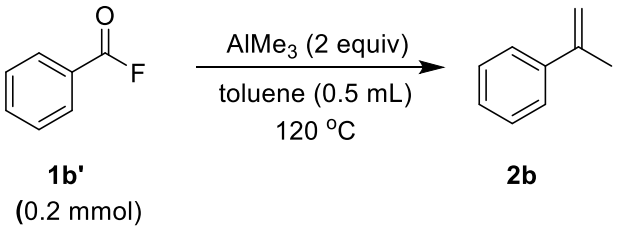


Figure 4-1. Time Course of the Reaction of Benzoyl Chloride (**1b**) with $AlMe_3$ (2 equiv) with or without DPPM.

Similarly, time course of the reaction of benzoyl fluoride **1b'** with $AlMe_3$ (2 equiv) in the presence of DPPM (black line) and in the absence of DPPM (red line) were performed and the results were shown in Figure 4-2.



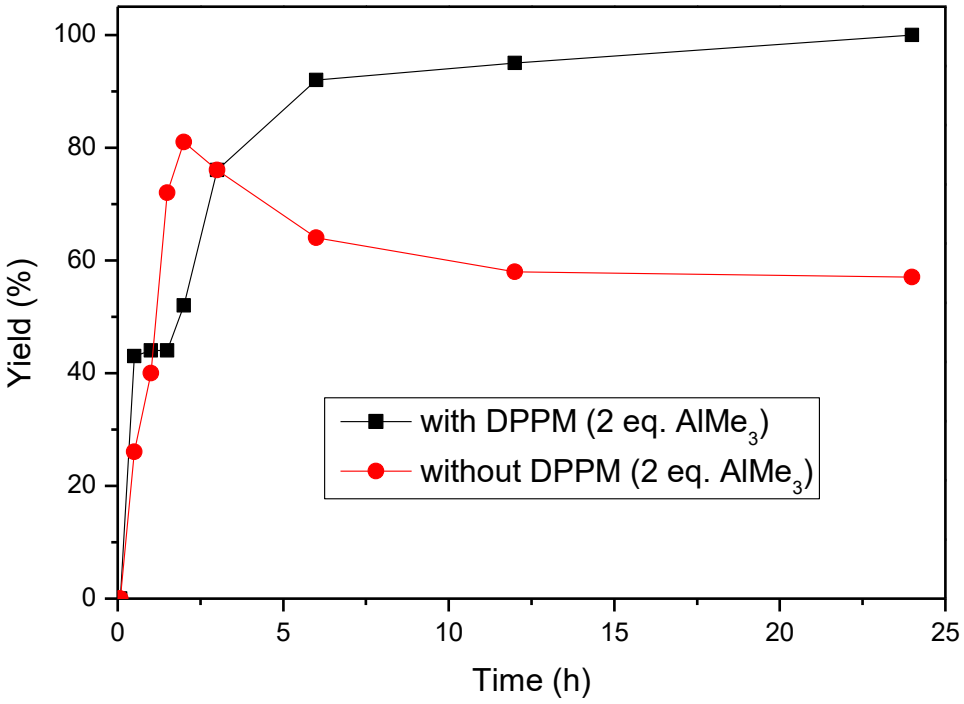
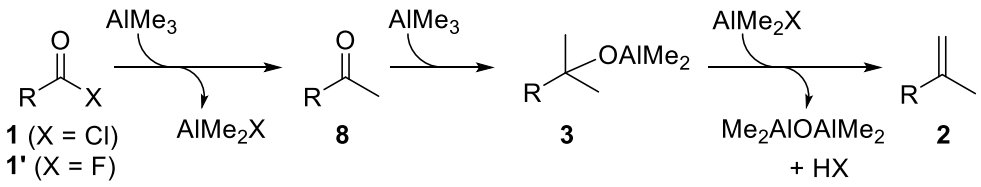


Figure 4-2. Time Course of the Reaction of Benzoyl Fluoride (**1b'**) with $AlMe_3$ (2 equiv) with or without DPPM.

With the results obtained shown in Scheme 4-5 and Figures 4-1 and 4-2 in hand, we proposed the reaction mechanism, as shown in Scheme 4-6. Acyl halides **1** or **1'** reacted with the first equivalent of $AlMe_3$ to afford ketone **8**, along with the formation of $AlMe_2X$. Successively, the formed ketone **8** reacted with the second equivalent of $AlMe_3$ to form intermediate **3**.[19a] Finally, in-situ resulting $AlMe_2X$[27] plays as Lewis acid to promote the elimination of $Me_2AlOAlMe_2$, giving rise to the products **2**. Although a role of DPPM has not been clarified, the bidentate nature of DPPM might support a nucleophilic attach of $AlMe_3$ to acyl halides and tune the acidity in the catalytic system, which retarded the Brønsted or Lewis acid-triggered dimerization of **2**.

Scheme 4-6. Reaction Mechanism.



4-3 Summary

The Author have developed a practicable, scalable, and one-step method to form 2-substituted propenes from various aryl, alkenyl, and alkyl acyl halides, as well as other esters. This bidentate phosphine-assisted methylenation of acyl fluorides and acyl chlorides features good functional tolerance of halogens and chemoselectivity for esters, which would be useful complement to other methylenation processes. The addition of a catalytic amount of DPPM increased an efficiency of the reactions. Trimethylaluminum as the methylenation reagent not only eliminates the pre-synthesis of methylene transfer reagent but provides an efficient method for the synthesis of a series of 2-substituted propenes.

4-4 Experimental Section

4-4-1 General Instrumentation and Chemicals

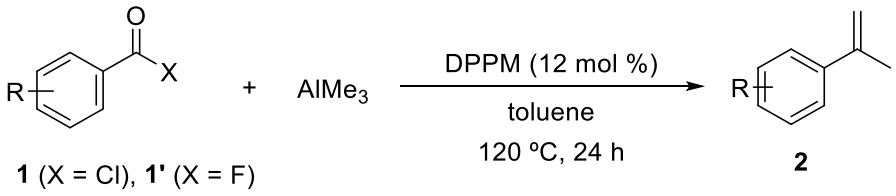
All the reactions were carried out under an Argon atmosphere using standard Schlenk techniques. Glassware was dried in an oven (150 ºC) and heated under reduced pressure prior to use. Solvents were employed as eluents for all other routine operation, as well as dehydrated solvent were purchased from commercial suppliers and employed without any further purification. For thin layer chromatography (TLC) analyses throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. Silica gel column chromatography was carried out using Silica gel 60 N (spherical, neutral, 40-100 μm) from Kanto Chemicals Co. Ltd. NMR spectra (^{1}H, and ^{19}F{^{1}H}) were recorded on Varian INOVA-600 (600 MHz) or Mercury-400 (400 MHz) spectrometers. Chemical shifts (δ) are in parts per million related to $CDCl_3$ at 7.26 ppm for ^{1}H. The GC yields were determined with *n*-dodecane as an internal standard. The NMR yields were determined by ^{1}H NMR spectra with dibromomethane as an internal standard.

Chemicals

Materials obtained from commercial suppliers were used without further purification. Trimethylaluminum (15% in hexane, ca. 1.4 mol/L), [1,1'-biphenyl]-4-carbonyl chloride (**1a**) and benzoyl fluoride (**1b'**) (purity > 98%) were purchased from Tokyo Chemical Industry Co., Ltd. Bis(1,5-cycloctadiene)nickel was purchased from Merck. *n*-Dodecane (purity > 99%) and dimethylaluminum chloride were purchased from Kanto Chemical Co., Ltd. Bis(diphenylphosphino)methane (DPPM) was purchased from Wako Pure Chemical Co., Ltd. Other acyl fluorides were synthesized from corresponding carboxylic acids or acyl chlorides, which was described in chapter 2.

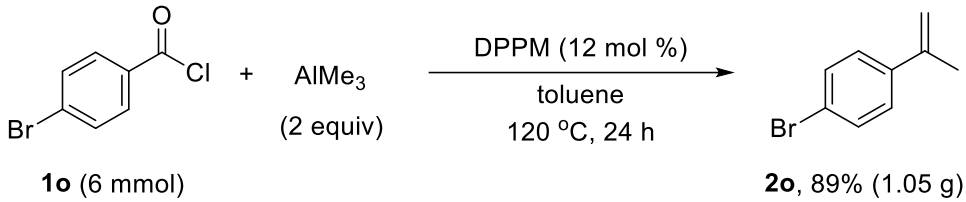
4-4-2 Experimental Procedures

4-4-2-1 Representative Procedure for Methylenation of Acyl Chlorides 1 or Acyl Fluorides 1'



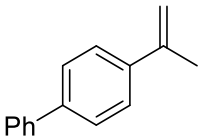
To a toluene (0.5 mL) solution of DPPM (9.2 mg, 0.024 mmol, 12 mol %,), acyl chlorides **1** or acyl fluorides **1'** (0.2 mmol) in a 20-mL Schlenk tube, was added $AlMe_3$ (285 μL, 0.4 mmol, 2 equiv) under an argon atmosphere. After being stirred at 120 ºC for 24 h, the reaction mixture was quenched with 1 M HCl solution, extracted with diethyl ether, and dried over $MgSO_4$. After the volatiles were removed under reduced pressure using a rotary evaporator, the crude product was purified by column chromatography on silica gel or bulb-to-bulb distillation to afford the desired products **2**.

4-4-2-2 Gram-Scale Synthesis



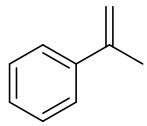
An oven-dried 50-mL Schlenk tube with a stirred bar was charged with 4-bromobenzoyl chloride (**1o**, 1.32 g, 6 mmol), trimethylaluminum (8.55 mL, 12 mmol, 2 equiv.), DPPM (276.8 mg, 0.72 mmol, 12 mol %), and toluene (5 mL) under an argon atmosphere. The reaction mixture was heated at 120 ºC with stirring. After 24 h, the reaction mixture was quenched with 1 M HCl solution, extracted with diethyl ether, and dried over $MgSO_4$. After the volatiles were removed by a rotary evaporator, the crude product was purified by column chromatography on silica gel to afford **2o** (1.05 g, 89%).

4-(Prop-1-en-2-yl)-1,1'-biphenyl (2a)[28]



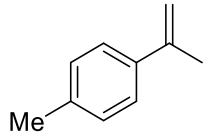
Purification: column chromatography (*n*-Hexane/Et_2O = 100:1, R_f = 0.73). White solid. Isolated yields were 90% (35.0 mg, from **1a**) and 92% (35.7 mg, from **1a'**). ^1H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 3H), 5.15 (m, 1H), 5.47 (s, 1H), 7.37 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.57-7.65 (m, 6H).

Prop-1-en-2-ylbenzene (2b)[29]



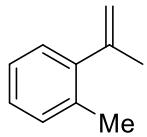
Purification: bulb-to-bulb distillation (50 ºC/20 mmHg). Colorless oil. Isolated yields were 83% (19.6 mg, from **1b**) and 92% (21.7 mg, from **1b'**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.19 (dd, J = 1.4, 0.8 Hz, 3H), 5.11-5.13 (m, 1H), 5.40-5.41 (m, 1H), 7.27-7.32 (m, 1H), 7.33-7.39 (m, 2H), 7.48-7.53 (m, 2H).

4-Methyl-2-(prop-1-en-2-yl)benzene (2c)[29]



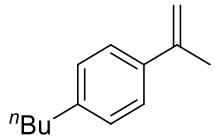
Purification: bulb-to-bulb distillation (60 ºC/20 mmHg). Colorless oil. Isolated yield was 93% (123.0 mg, from **1c**). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.14 (dd, J = 1.5, 0.8 Hz, 3H), 2.35 (s, 3H), 5.03-5.04 (m, 1H), 5.33-5.34 (m, 1H), 7.14 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H).

1-Methyl-2-(prop-1-en-2-yl)benzene (2d)[30]



Purification: bulb-to-bulb distillation (50 ºC/20 mmHg). Colorless oil. Isolated yields was 92% (24.3 mg, from **1d**). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.05 (dd, J = 1.5, 1.0 Hz, 3H), 2.33 (s, 3H), 4.85-4.86 (m, 1H), 5.20 (m, 1H), 7.11-7.20 (m, 4H).

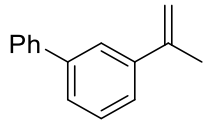
1-Butyl-4-(prop-1-en-2-yl)benzene (2e)[31]



Purification: column chromatography (*n*-Hexane, R_f = 0.56). Colorless oil. Isolated yield was 80% (27.9 mg, from **1e**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, J = 7.3 Hz, 3H), 1.38

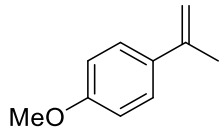
(sext, J = 8.0 Hz, 2H), 1.58-1.67 (m, 2H), 2.16 (dd, J = 1.5, 0.8 Hz, 3H), 2.62 (t, J = 8.0 Hz, 2H), 5.05-5.06 (m, 1H), 5.36-5.37 (m, 1H), 7.13-7.19 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H).

3-(Prop-1-en-2-yl)-1,1'-biphenyl (2f)[32]



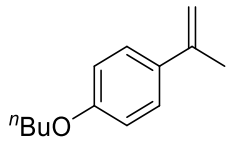
Purification: column chromatography (*n*-Hexane, R_f = 0.50). Colorless oil. Isolated yield was 95% (36.9 mg, from **1f'**). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.23 (s, 3H), 5.15-5.16 (m, 1H), 5.45 (s, 1H), 7.36-7.39 (m, 1H), 7.41-7.44 (m, 1H), 7.45-7.49 (m, 3H), 7.51-7.52 (m, 1H), 7.62-7.63 (m, 2H), 7.70 (t, J = 1.8 Hz, 1H).

1-Methoxy-4-(prop-1-en-2-yl)benzene (2g)[33]



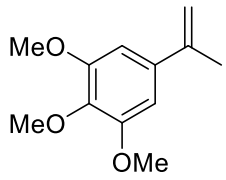
Purification: column chromatography (*n*-Hexane/Et_2O = 100:1, R_f = 0.47). Colorless oil. Isolated yields were 68% (100.8 mg, from **1g**) and 72% (21.3 mg, from **1g'**). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.16 (dd, J = 1.5, 0.8 Hz, 3H), 3.83 (s, 3H), 5.01-5.02 (m, 1H), 5.32 (dd, J = 1.5, 0.8 Hz, 1H), 6.89 (d, J = 8.9 Hz, 2H), 7.44 (d, J = 8.9 Hz, 2H).

1-Butoxy-4-(prop-1-en-2-yl)benzene (2h)[34]



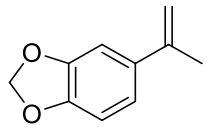
Purification: column chromatography (*n*-Hexane/Et_2O = 100:1, R_f = 0.63). Colorless oil. Isolated yield was 66% (22.8 mg, from **1h**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, J = 7.4 Hz, 3H), 1.51 (sext, J = 7.6 Hz, 2H), 1.75-1.82 (m, 2H), 2.14 (dd, J = 1.5, 0.8 Hz, 3H), 3.98 (t, J = 6.4 Hz, 2H), 4.99 (t, J = 1.5 Hz, 1H), 5.29 (dd, J = 1.5, 0.8 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H).

1,2,3-Trimethoxy-5-(prop-1-en-2-yl)benzene (2i)[35]



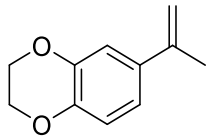
Purification: column chromatography (*n*-Hexane/Et_2O = 5:1, R_f = 0.56). Colorless oil. Isolated yield was 68% (28.3 mg, from **1i'**). ^1H NMR (400 MHz, $CDCl_3$): δ 2.14 (dd, *J* = 1.4, 0.7 Hz, 3H), 3.85 (s, 3H), 3.89 (s, 6H), 5.05-5.07 (m, 1H), 5.30 (dd, *J* = 1.4, 0.7 Hz, 1H), 6.68 (s, 2H).

5-(Prop-1-en-2-yl)benzo[d][1,3]dioxole (2j)[36]



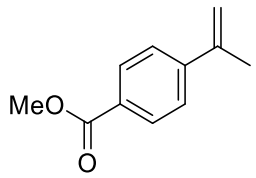
Purification: column chromatography (*n*-Hexane/Et_2O = 50:1, R_f = 0.75). Colorless oil. Isolated yield was 65% (21.1 mg, from **1j'**). ^1H NMR (600 MHz, $CDCl_3$): δ 2.11 (dd, *J* = 1.5, 0.8 Hz, 3H), 4.99-5.00 (m, 1H), 5.26 (dd, *J* = 1.5, 0.8 Hz, 1H), 5.95 (s, 2H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.94 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.99 (d, *J* = 1.8 Hz, 1H).

6-(Prop-1-en-2-yl)-2,3-dihydrobenzo[b][1,4]dioxine (2k)[37]



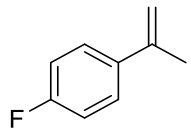
Purification: column chromatography (*n*-Hexane/Et_2O = 30:1, R_f = 0.56). Colorless oil. Isolated yield was 66% (23.3 mg, from **1k'**). ^1H NMR (400 MHz, $CDCl_3$): δ 2.10 (dd, *J* = 1.5, 0.8 Hz, 3H), 4.26 (s, 4H), 4.99-5.00 (m, 1H), 5.28 (dd, *J* = 1.6, 0.8 Hz, 1H), 6.80-6.84 (m, 1H), 6.97-7.00 (m, 1H), 7.00 (s, 1H).

Methyl 4-(prop-1-en-2-yl)benzoate (2l)[38]



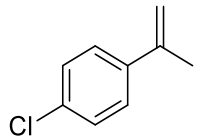
Purification: column chromatography (*n*-Hexane/Et_2O = 20:1, R_f = 0.52). White solid. Isolated yield was 76% (26.8 mg, from **1l**). ^1H NMR (600 MHz, $CDCl_3$): δ 2.17 (dd, J = 1.5, 0.8 Hz, 3H), 3.92 (s, 3H), 5.19-5.20 (m, 1H), 5.47 (m, 1H), 7.51-7.53 (m, 2H), 7.99-8.00 (m, 2H).

1-Fluoro-4-(prop-1-en-2-yl)benzene (2m)[39]



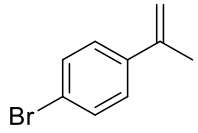
Purification: bulb-to-bulb distillation (55 ºC/20 mmHg). Colorless oil. Isolated yield was 86% (117.1 mg, from **1m**). ^1H NMR (600 MHz, $CDCl_3$): δ 2.14 (dd, J = 1.5, 0.8 Hz, 3H), 5.06 (t, J = 1.5 Hz, 1H), 5.30 (s, 1H), 6.99-7.03 (m, 2H), 7.41-7.44 (m, 2H); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -115.42 (tt, J = 10.4, 5.3 Hz).

1-Chloro-4-(prop-1-en-2-yl)benzene (2n)[33]



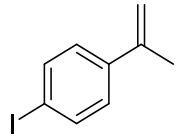
Purification: column chromatography (*n*-Hexane, R_f = 0.48). Colorless oil. Isolated yield was 88% (134.3 mg, from **1n**). ^1H NMR (400 MHz, $CDCl_3$): δ 2.15 (dd, J = 1.5, 0.8 Hz, 3H), 5.1-5.13 (m, 1H), 5.37-5.74 (m, 1H), 7.29-7.33 (m, 2H), 7.40-7.43 (m, 2H).

1-Bromo-4-(prop-1-en-2-yl)benzene (2o)[33]



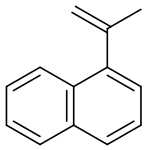
Purification: column chromatography (*n*-Hexane, R_f = 0.68). Colorless oil. Isolated yield was 90% (177.4 mg, from **1o**). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.14 (dd, J = 1.5, 0.8 Hz, 3H), 5.12 (m, 1H), 5.38 (m, 1H), 7.34 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 8.6 Hz, 2H).

1-Iodo-4-(prop-1-en-2-yl)benzene (2p)[32]



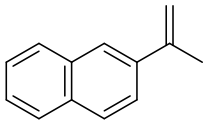
Purification: column chromatography (*n*-Hexane, R_f = 0.67). White solid. Isolated yield was 79% (192.8 mg, from **1p**). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.12 (m, 3H), 5.10 (m, 1H), 5.37 (m, 1H), 7.20 (d, J = 8.6 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H).

1-(Prop-1-en-2-yl)naphthalene (2q)[33]



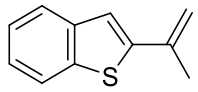
Purification: column chromatography (*n*-Hexane, R_f = 0.58). White solid. Isolated yields were 90% (30.3 mg, from **1q**) and 94% (31.6 mg, from **1q'**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (dd, J = 1.5, 0.9 Hz, 3H), 5.07-5.08 (m, 1H), 5.42-5.43 (m, 1H), 7.33 (dd, J = 7.2, 1.2 Hz, 1H), 7.43-7.51 (m, 3H), 7.77 (d, J = 8.4 Hz, 1H), 7.85-7.88 (m, 1H), 8.06-8.09 (m, 1H).

2-(Prop-1-en-2-yl)naphthalene (2r)[30]



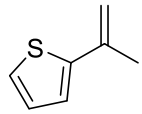
Purification: column chromatography (*n*-Hexane/Et_2O = 100:1, R_f = 0.73). White solid. Isolated yields were 96% (32.3 mg, from **1r**) and 95% (32.0 mg, from **1r'**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (dd, J = 1.5, 0.8 Hz, 3H), 5.20-5.22 (m, 1H), 5.55 (m, 1H), 7.44-7.50 (m, 2H), 7.69 (dd, J = 8.6, 1.9 Hz, 1H), 7.79-7.87 (m, 4H).

2-(Prop-1-en-2-yl)benzo[b]thiophene (2s)[40]



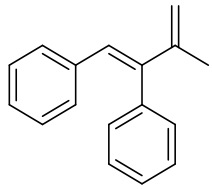
Purification: column chromatography (*n*-Hexane, R_f = 0.50). Colorless oil. Isolated yield was 96% (33.5 mg, from **1s'**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (dd, J = 1.5, 0.8 Hz, 3H), 5.12 (t, J = 1.3 Hz, 1H), 5.49 (m, 1H), 7.22 (s, 1H), 7.28-7.33 (m, 2H), 7.69-7.71 (m, 1H), 7.74-7.77 (m, 1H).

2-(Prop-1-en-2-yl)thiophene (2t)[41]



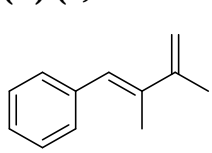
Purification: bulb-to-bulb distillation (60 ºC/20 mmHg). Colorless oil. Isolated yield was 82% (20.4 mg, from **1t'**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15 (dd, J = 1.5, 0.8 Hz, 3H), 4.95 (t, J = 1.4 Hz, 1H), 5.38 (s, 1H), 6.98 (dd, J = 5.1, 3.6 Hz, 1H), 7.03 (dd, J = 3.6, 1.2 Hz, 1H), 7.17 (dd, J = 5.1, 1.2 Hz, 1H).

(Z)-(3-Methylbuta-1,3-diene-1,2-diyl)dibenzene (2u)[42]



Purification: column chromatography (*n*-Hexane/Et_2O = 100:1, R_f = 0.70). Colorless oil. Isolated yield was 76% (33.5 mg, from **1u**). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.16 (d, J = 1.2 Hz, 3H), 4.72 (d, J = 1.7 Hz, 1H), 5.14 (s, 1H), 6.74 (s, 1H), 6.89 (dd, J = 10.8, 1.8 Hz, 2H), 7.08-7.11 (m, 3H), 7.18 (dd, J = 6.6, 1.2 Hz, 2H), 7.34-7.38 (m, 3H).

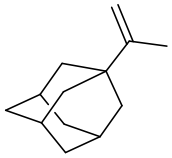
(E)-(2,3-Dimethylbuta-1,3-dien-1-yl)benzene (2v)[43]



Purification: column chromatography (*n*-Hexane, R_f = 0.59). Colorless oil. Isolated yield was 62% (19.6 mg, from **1v**). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.04 (d, J = 1.2 Hz, 3H),

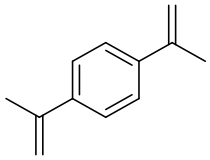
2.07 (d, J = 1.2 Hz, 3H), 5.09 (m, 1H), 5.21 (m, 1H), 6.68 (s, 1H), 7.24-7.25 (m, 1H), 7.28-7.30 (m, 2H), 7.34-7.37 (m, 2H).

(3r,5r,7r)-1-(Prop-1-en-2-yl)adamantine (2w)[44]



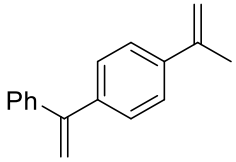
Purification: bulb-to-bulb distillation (90 ºC/5 mmHg). Colorless oil. Isolated yield was 75% (26.4 mg, from **1w**). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.64-1.67 (m, 9H), 1.70-1.73 (m, 6H), 1.99 (s, 3H), 4.67-4.69 (m, 2H).

1,4-Di(prop-1-en-2-yl)benzene (2x)[45]



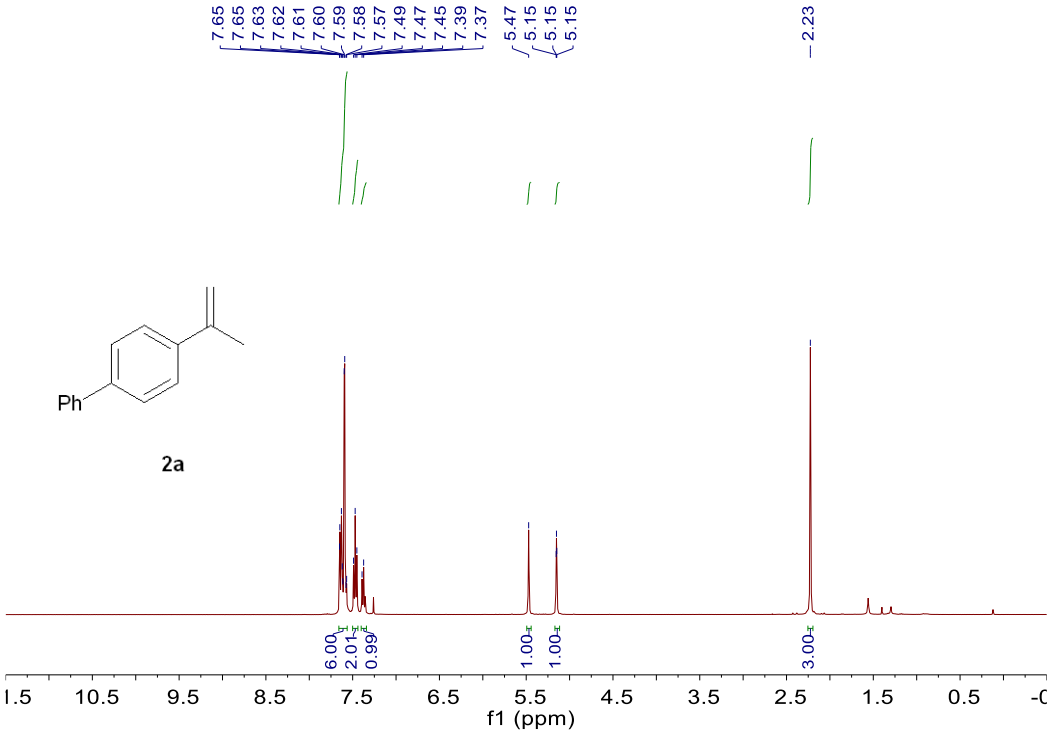
Purification: column chromatography (*n*-Hexane, R_f = 0.53). White solid. Isolated yields were 82% (26.0 mg, from **1x**) and 90% (28.5 mg, from **1y**). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.16 (dd, J = 1.5, 0.8 Hz, 6H), 5.08 (t, J = 1.5 Hz, 2H), 5.39 (s, 2H), 7.45 (s, 4H).

1-(1-Phenylvinyl)-4-(prop-1-en-2-yl)benzene (2z)[46]

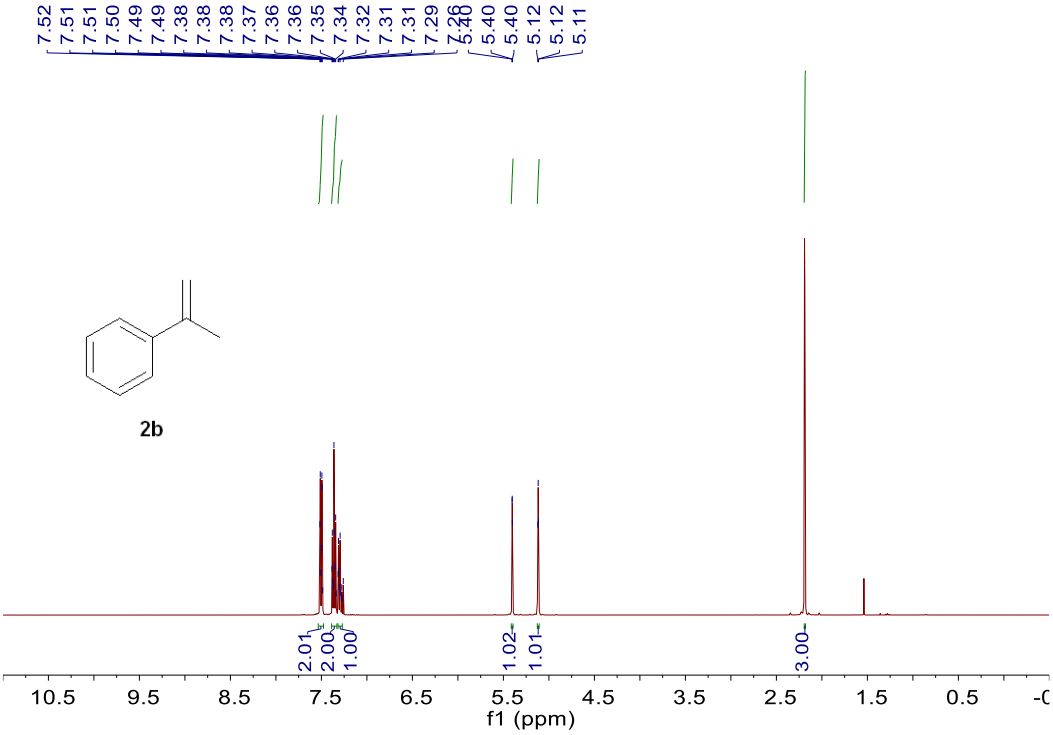


Purification: column chromatography (*n*-Hexane/Et_2O = 100:1, R_f = 0.77). White solid. Isolated yield was 91% (40.1 mg, from **1z**). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.20 (d, J = 1.4 Hz, 3H), 5.13 (t, J = 1.5 Hz, 1H), 5.45 (s, 1H), 5.48 (d, J = 1.2 Hz, 1H), 5.51 (d, J = 1.2 Hz, 1H), 7.34-7.39 (m, 7H), 7.47-7.48 (m, 2H).

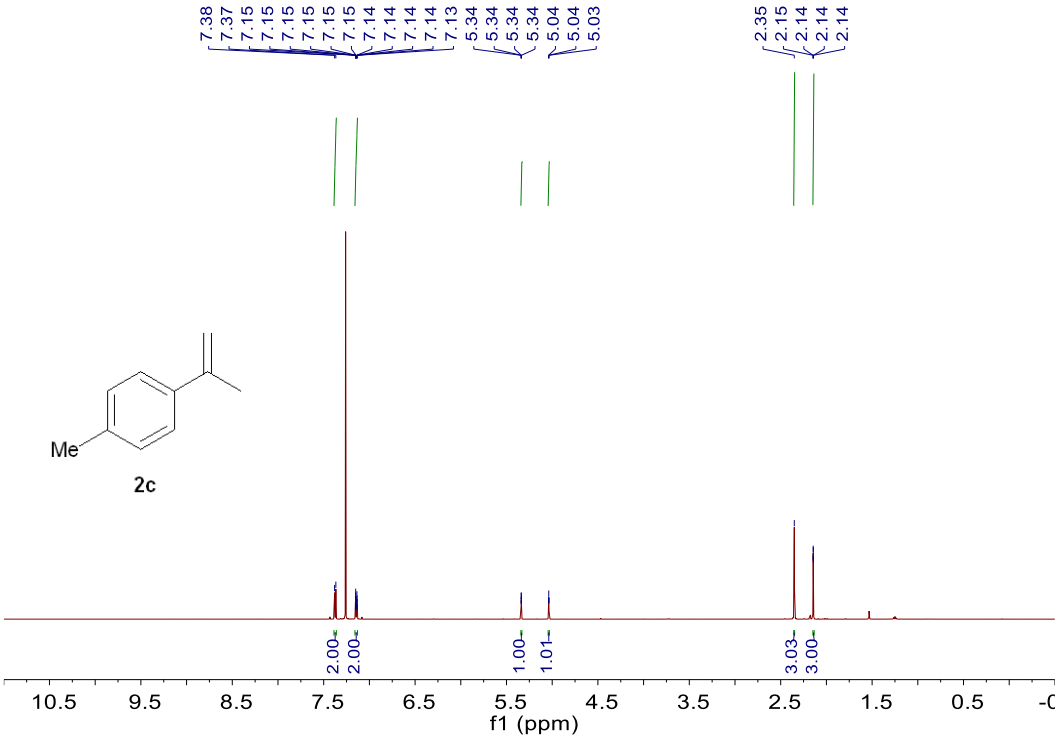
4-4-3 Copies of NMR Charts for Products



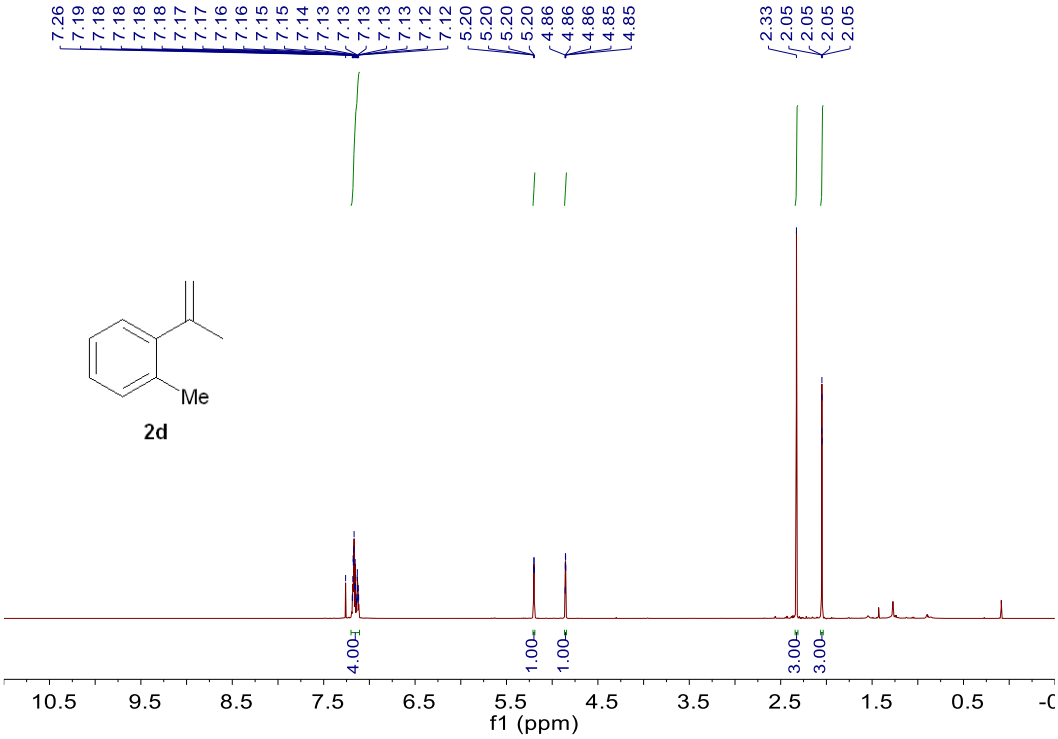
^{1}H NMR (400 MHz) spectrum of **2a** ($CDCl_3$, rt).



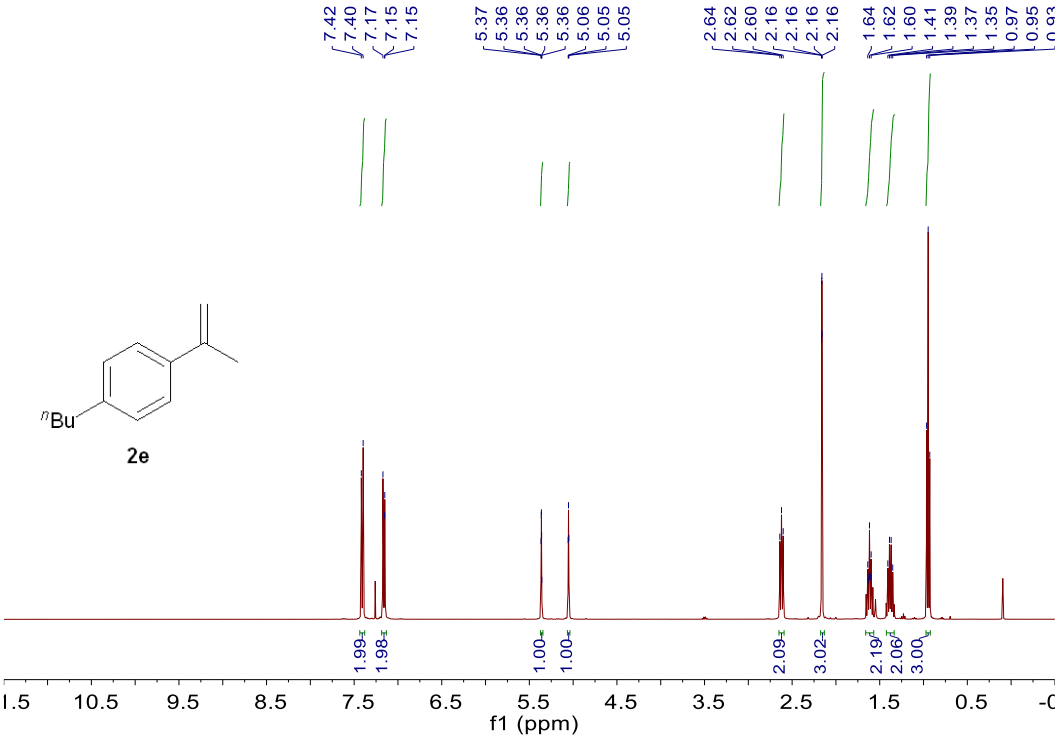
^{1}H NMR (400 MHz) spectrum of **2b** ($CDCl_3$, rt).



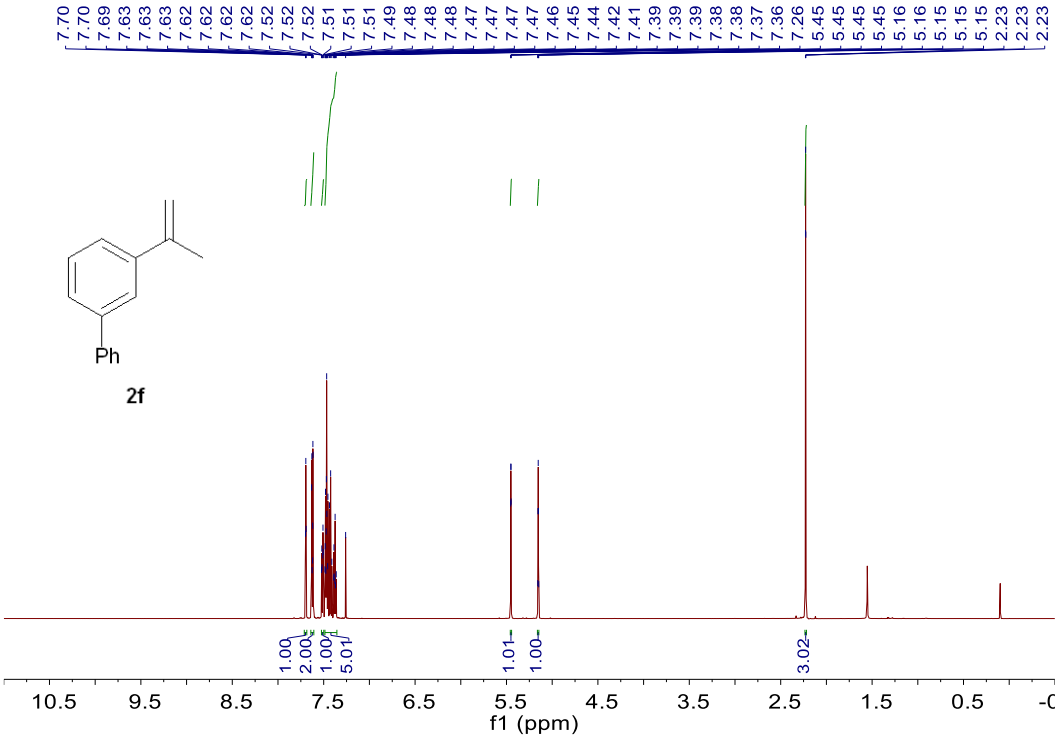
^{1}H NMR (600 MHz) spectrum of **2c** ($CDCl_3$, rt).



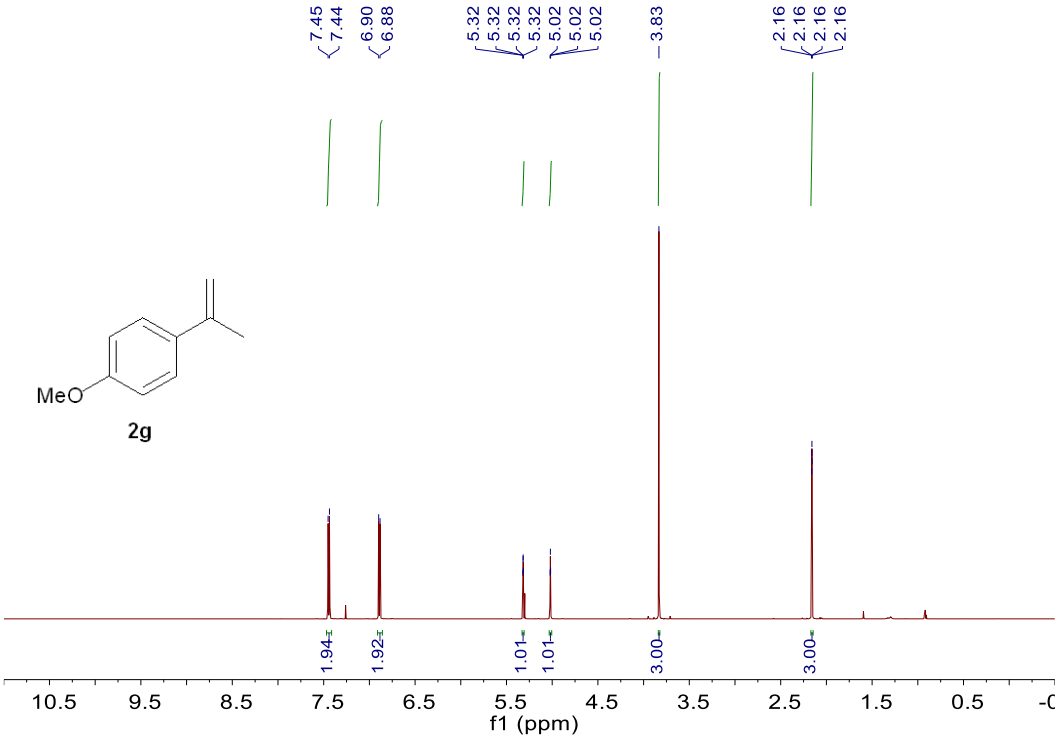
^{1}H NMR (600 MHz) spectrum of **2d** ($CDCl_3$, rt).



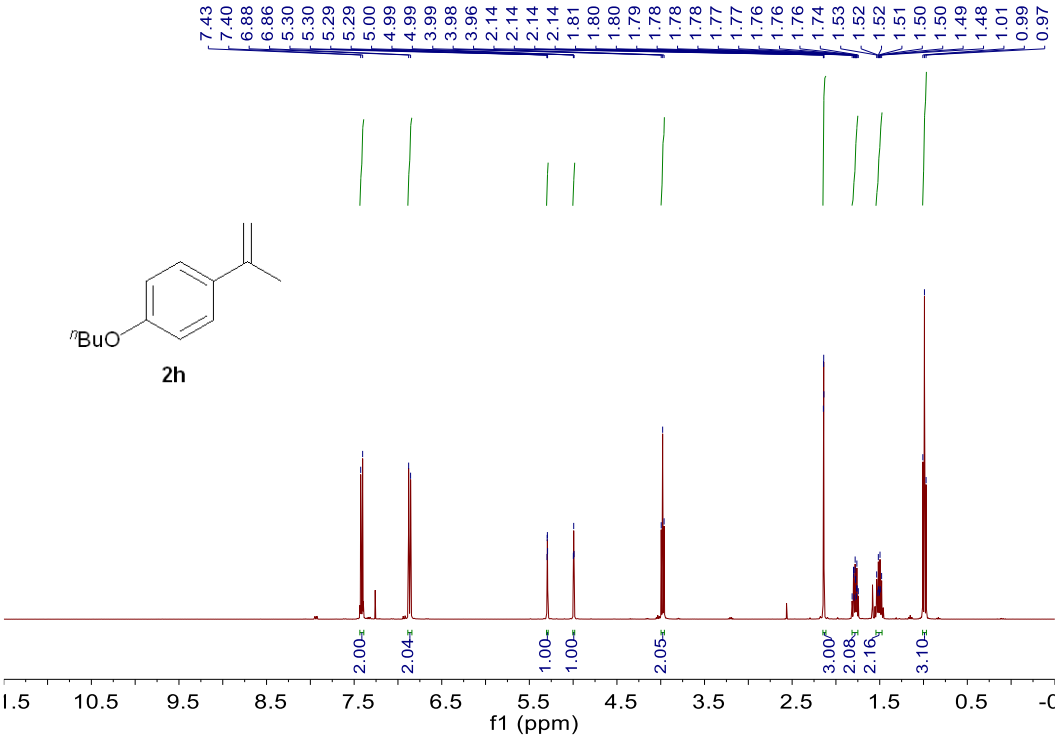
^{1}H NMR (400 MHz) spectrum of **2e** ($CDCl_3$, rt).



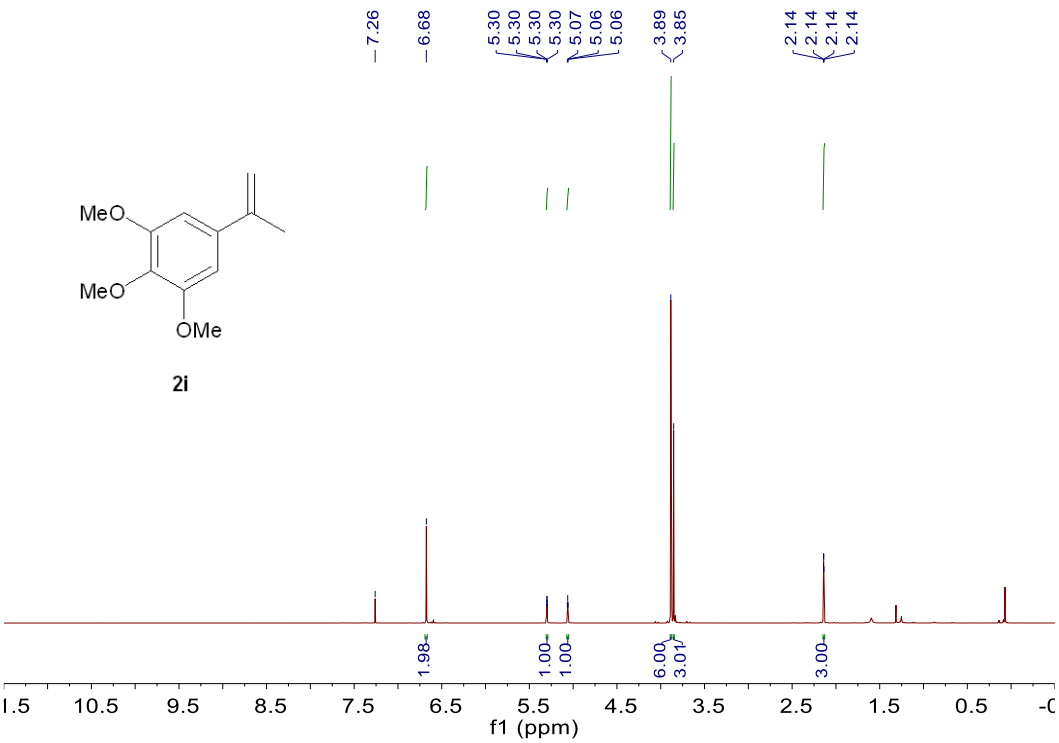
^{1}H NMR (600 MHz) spectrum of **2f** ($CDCl_3$, rt).



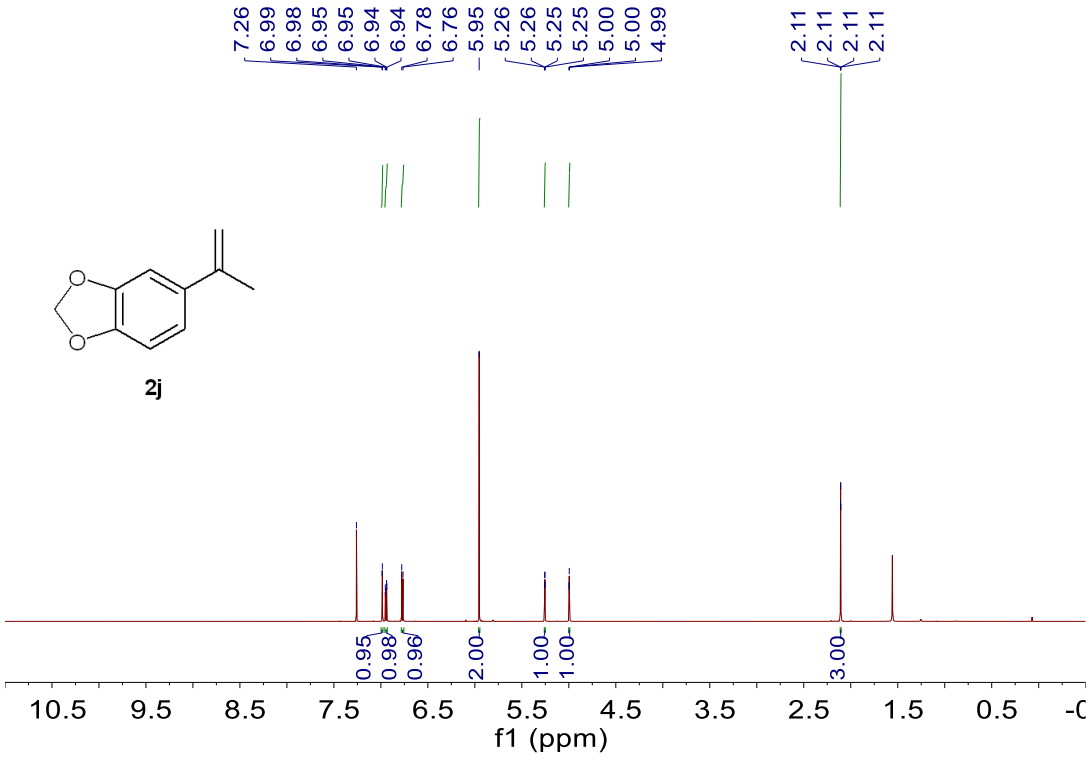
^{1}H NMR (600 MHz) spectrum of **2g** ($CDCl_3$, rt).



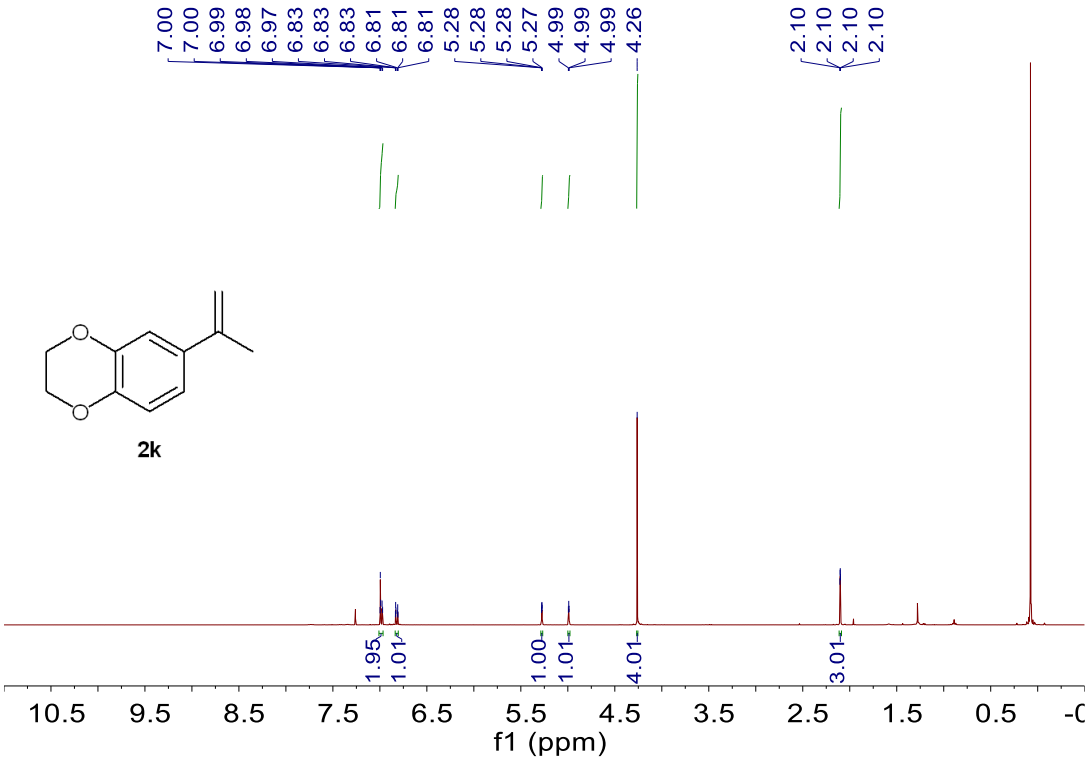
^{1}H NMR (400 MHz) spectrum of **2h** ($CDCl_3$, rt).



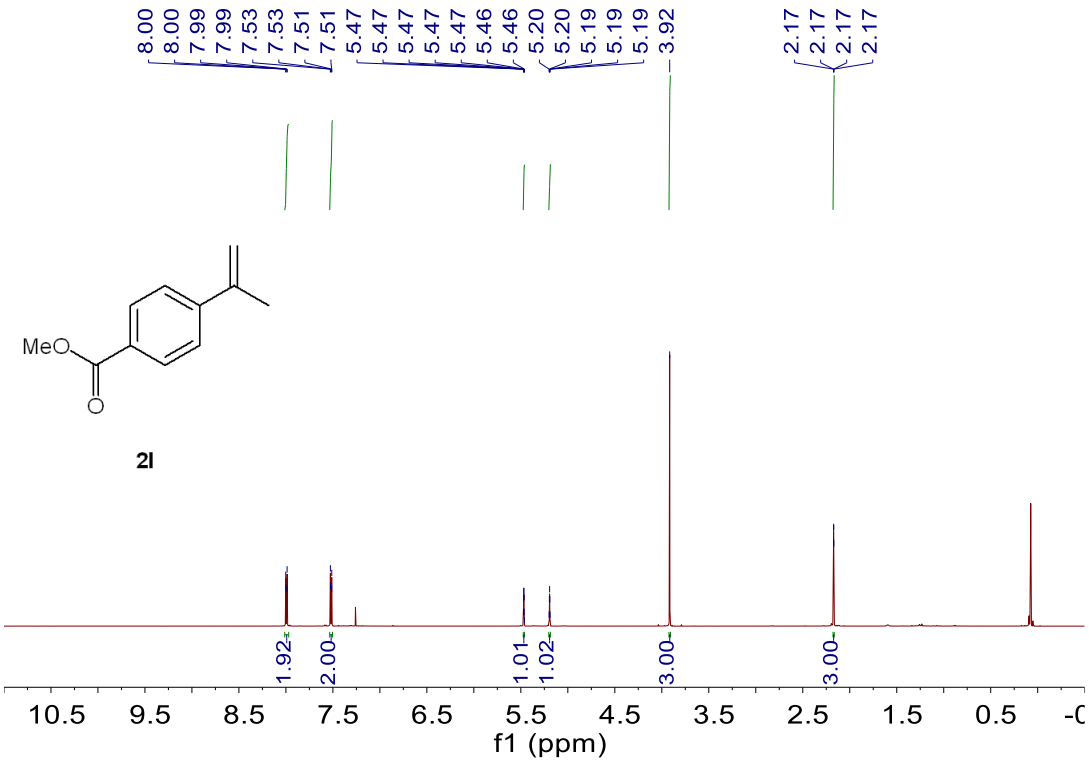
^{1}H NMR (400 MHz) spectrum of **2i** ($CDCl_3$, rt).



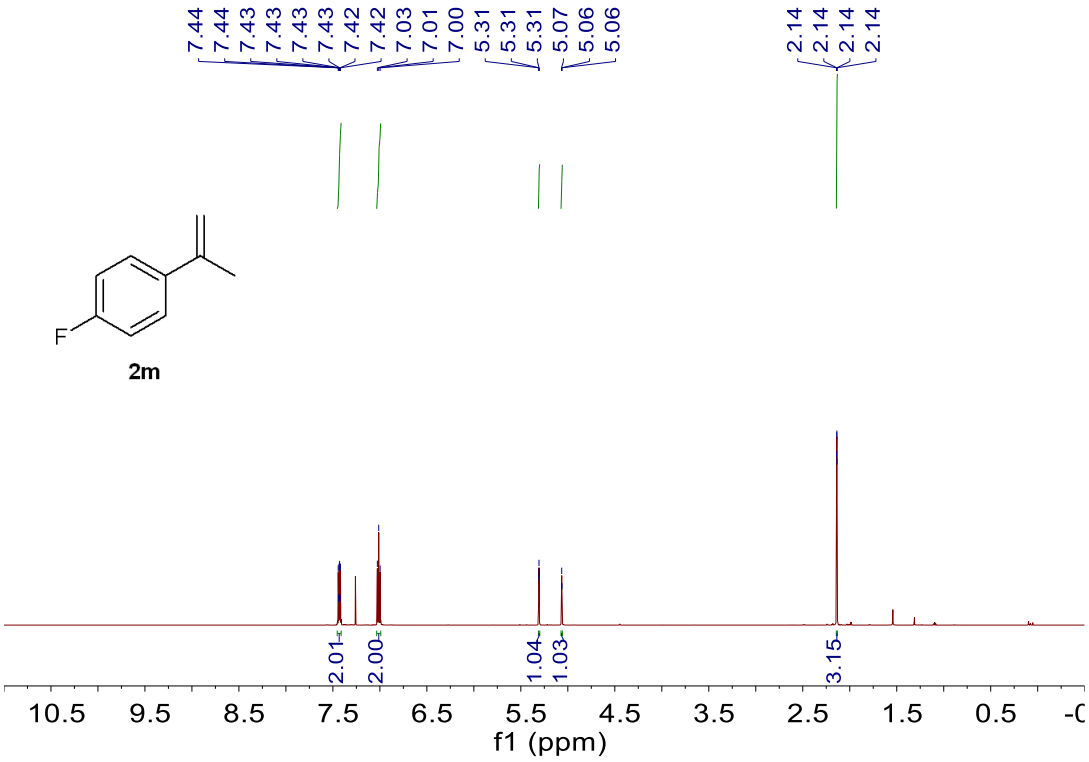
^{1}H NMR (600 MHz) spectrum of **2j** ($CDCl_3$, rt).



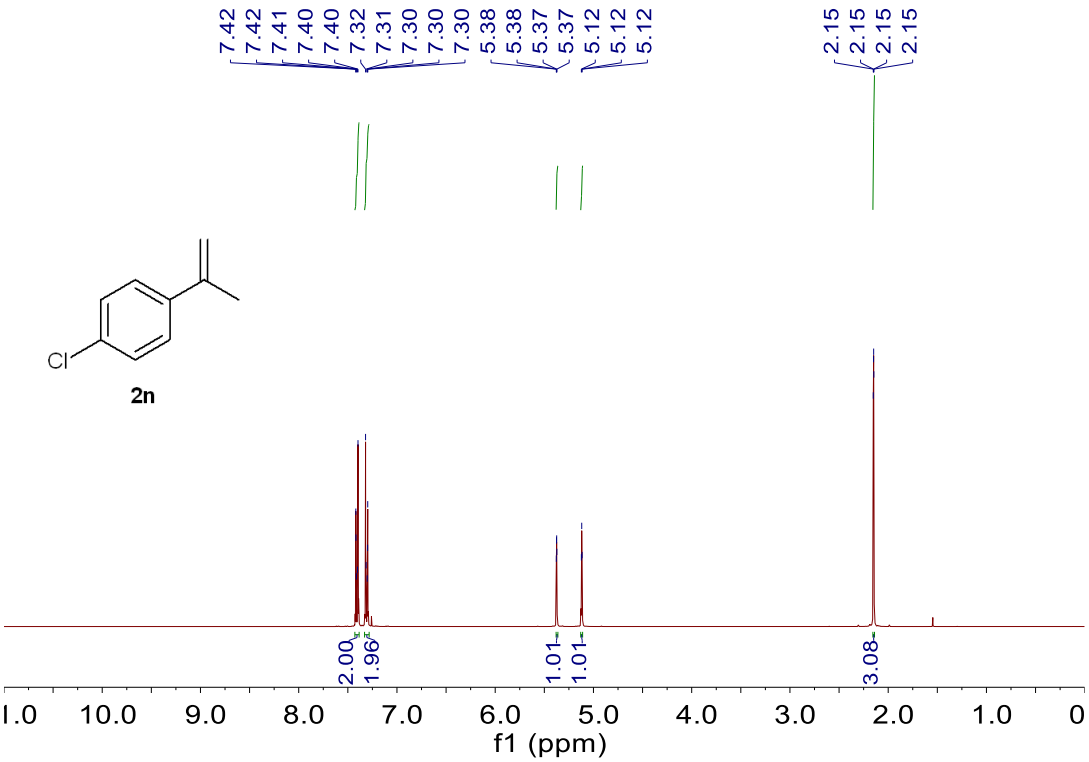
^{1}H NMR (400 MHz) spectrum of **2k** ($CDCl_3$, rt).



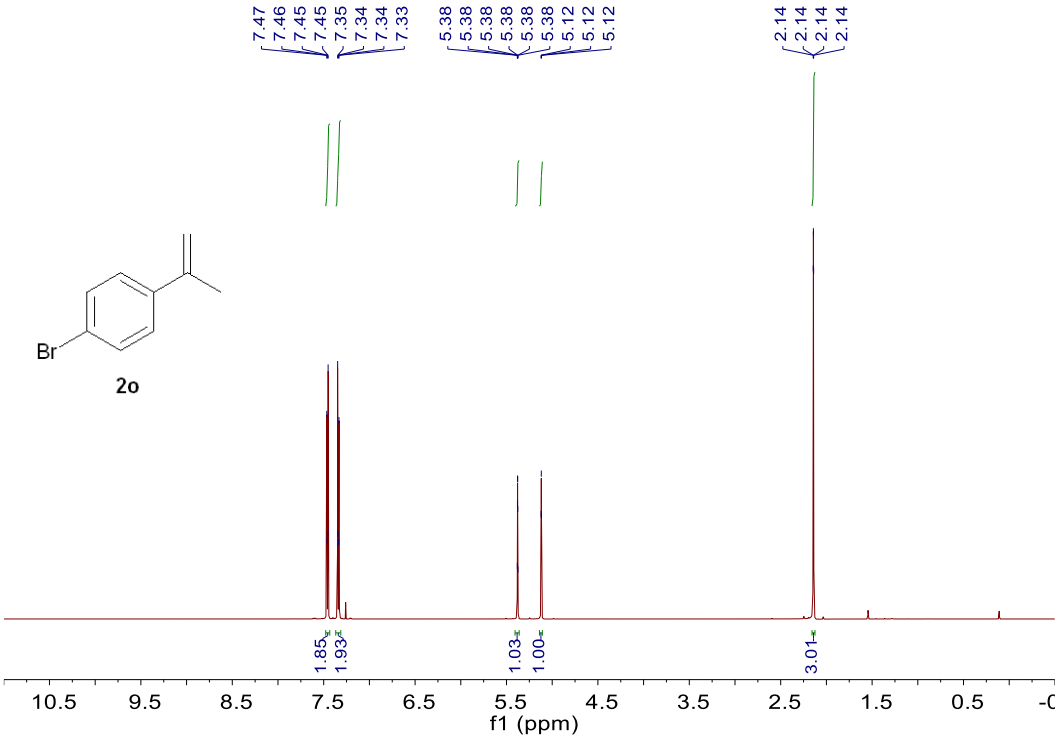
^{1}H NMR (600 MHz) spectrum of **2l** ($CDCl_3$, rt).



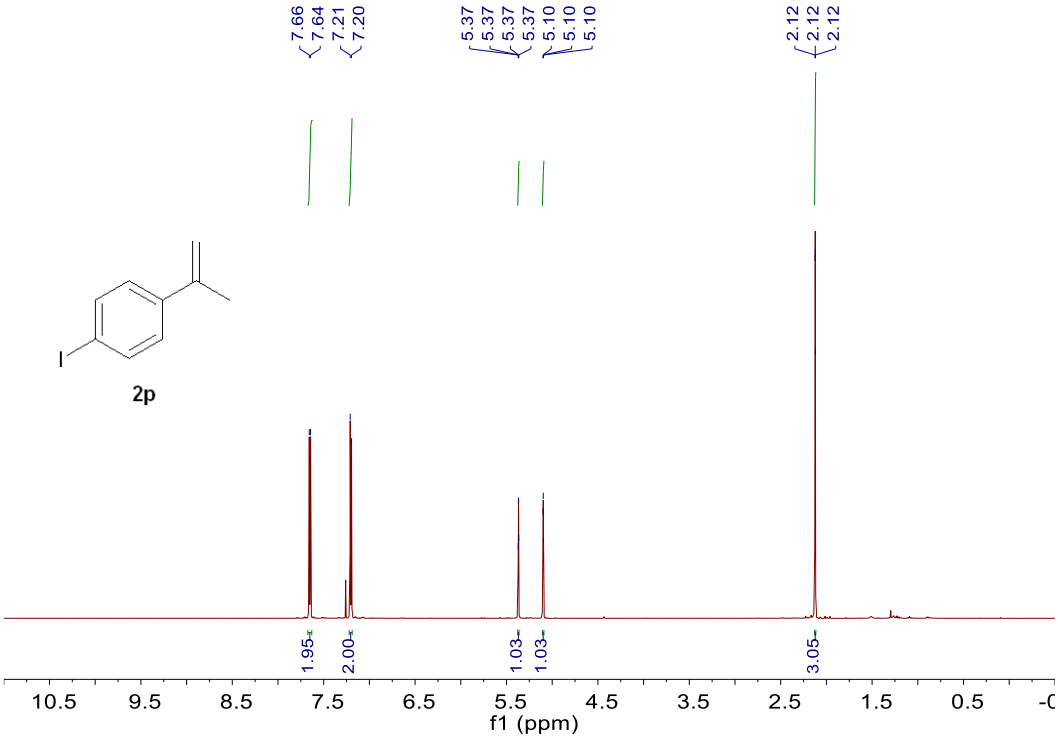
^{1}H NMR (600 MHz) spectrum of **2m** ($CDCl_3$, rt).



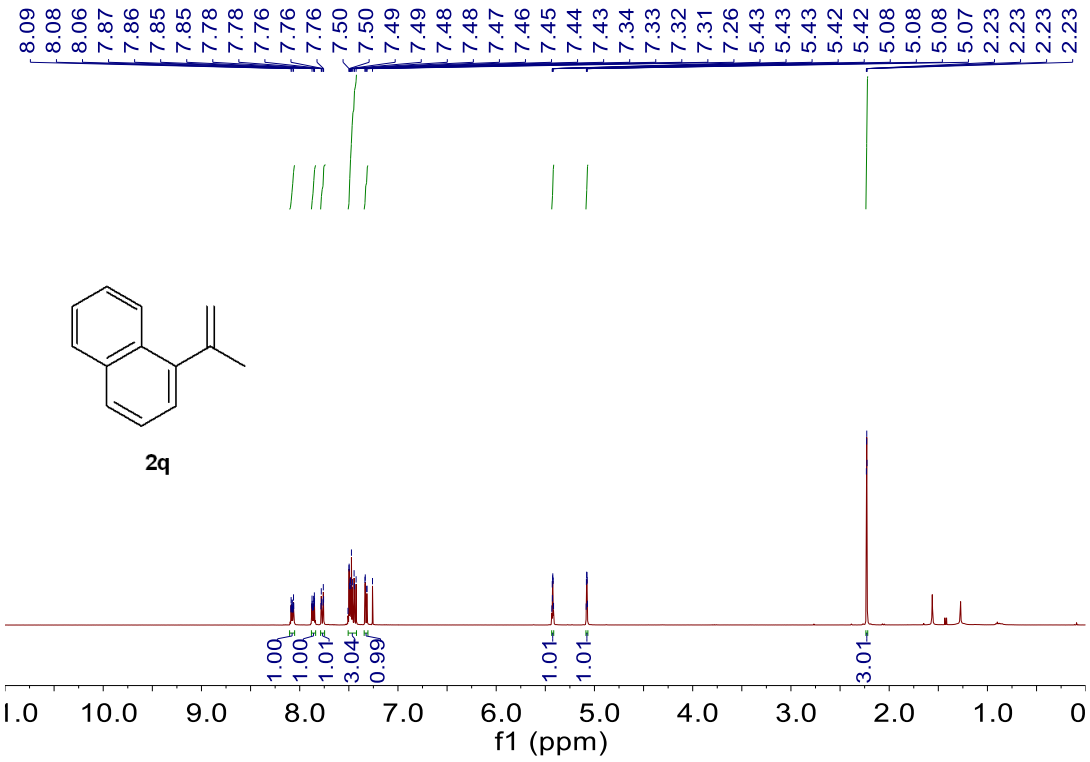
^{1}H NMR (400 MHz) spectrum of **2n** ($CDCl_3$, rt).



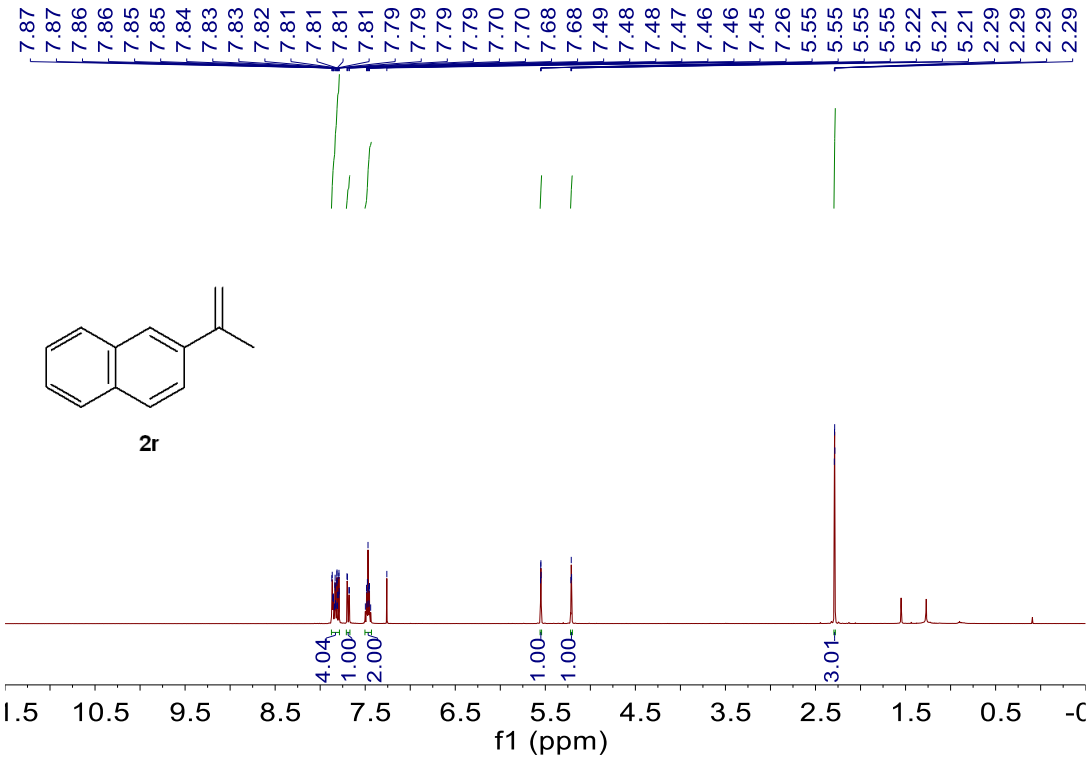
^{1}H NMR (600 MHz) spectrum of **2o** ($CDCl_3$, rt).



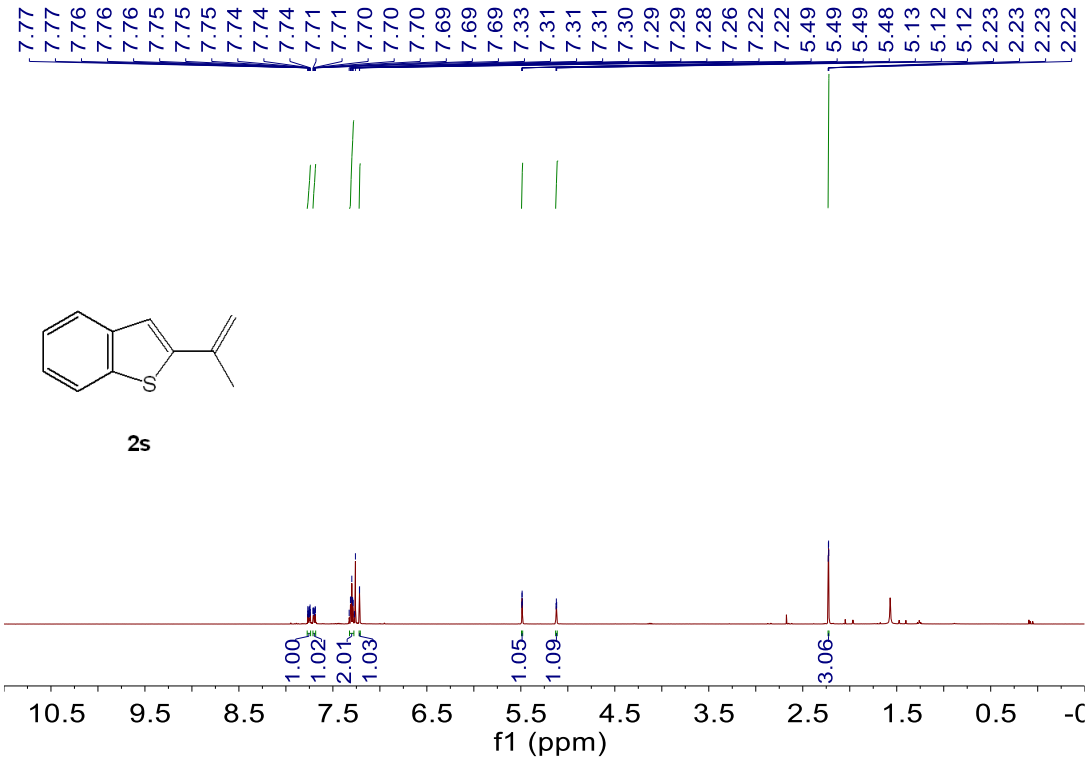
^{1}H NMR (600 MHz) spectrum of **2p** ($CDCl_3$, rt).



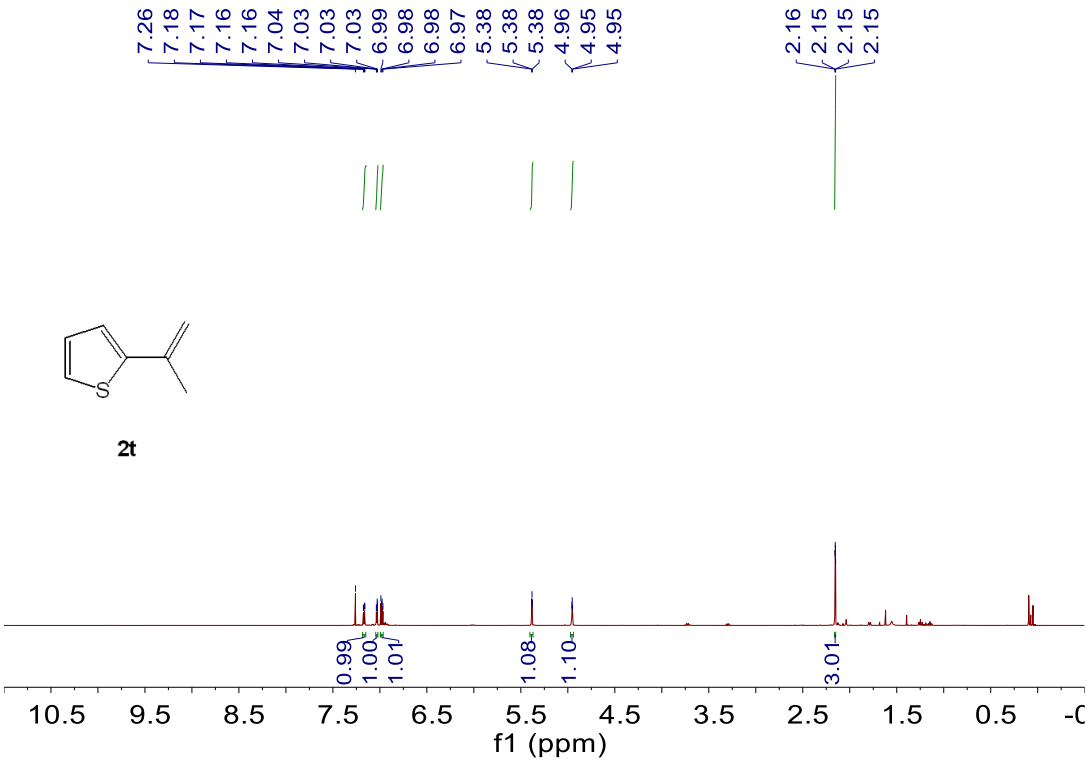
^{1}H NMR (400 MHz) spectrum of **2q** ($CDCl_3$, rt).



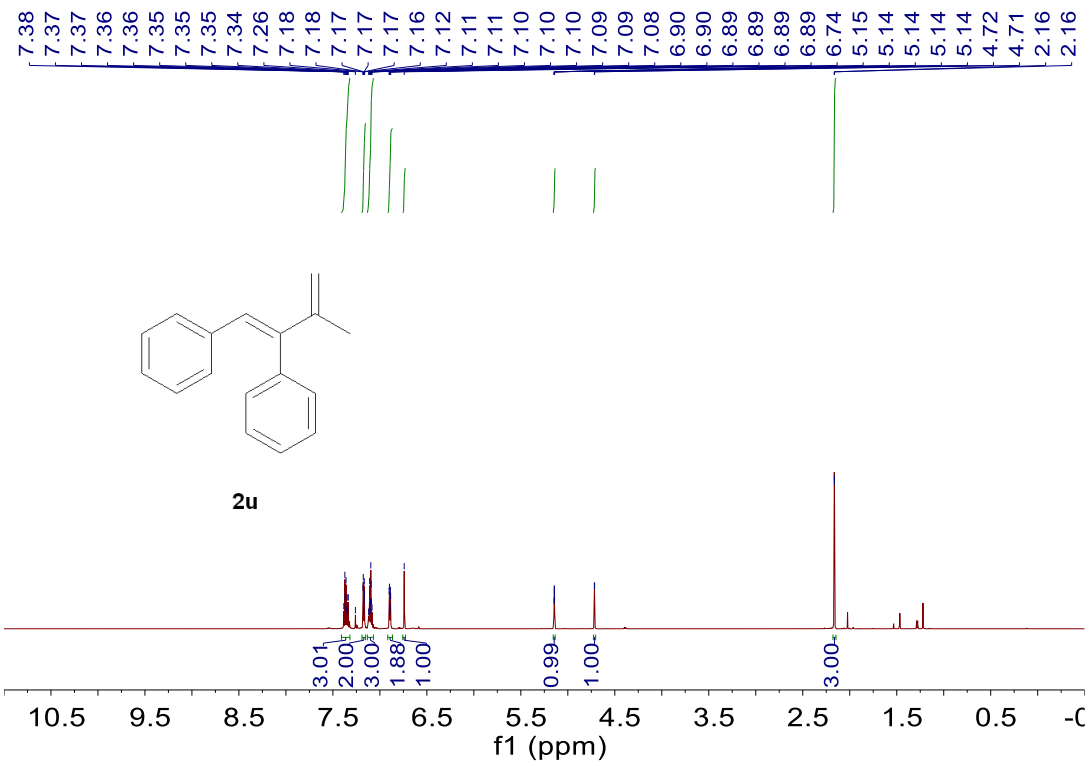
^{1}H NMR (400 MHz) spectrum of **2r** ($CDCl_3$, rt).



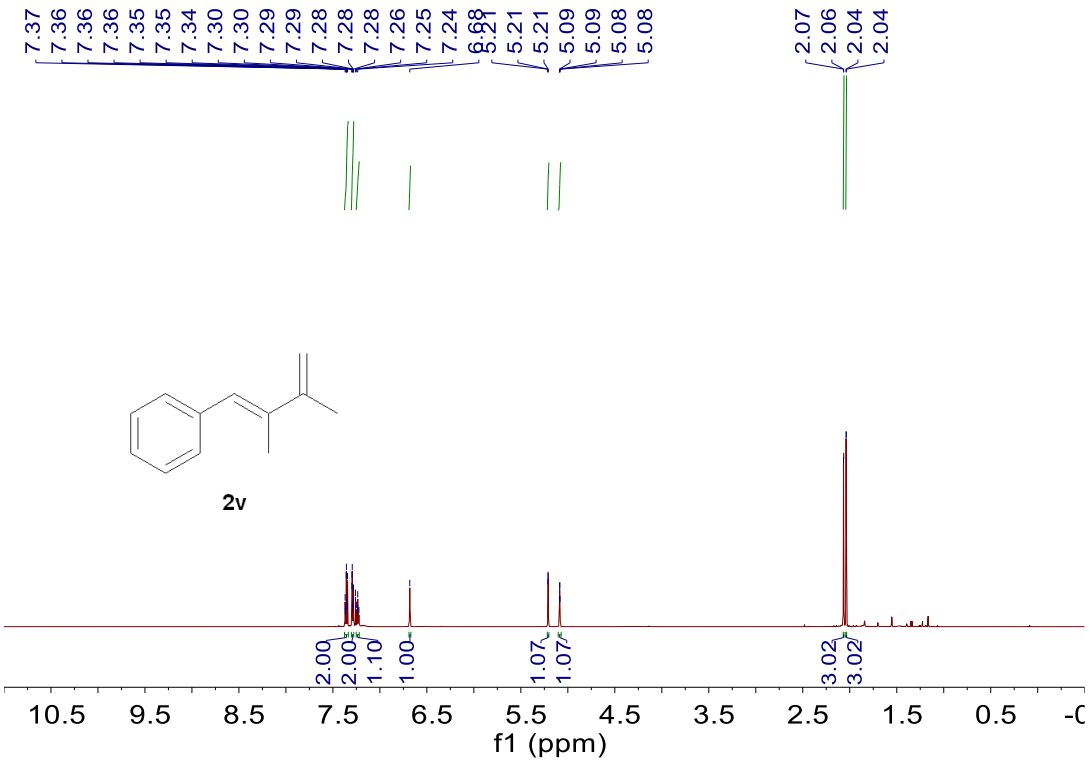
^{1}H NMR (400 MHz) spectrum of **2s** ($CDCl_3$, rt).



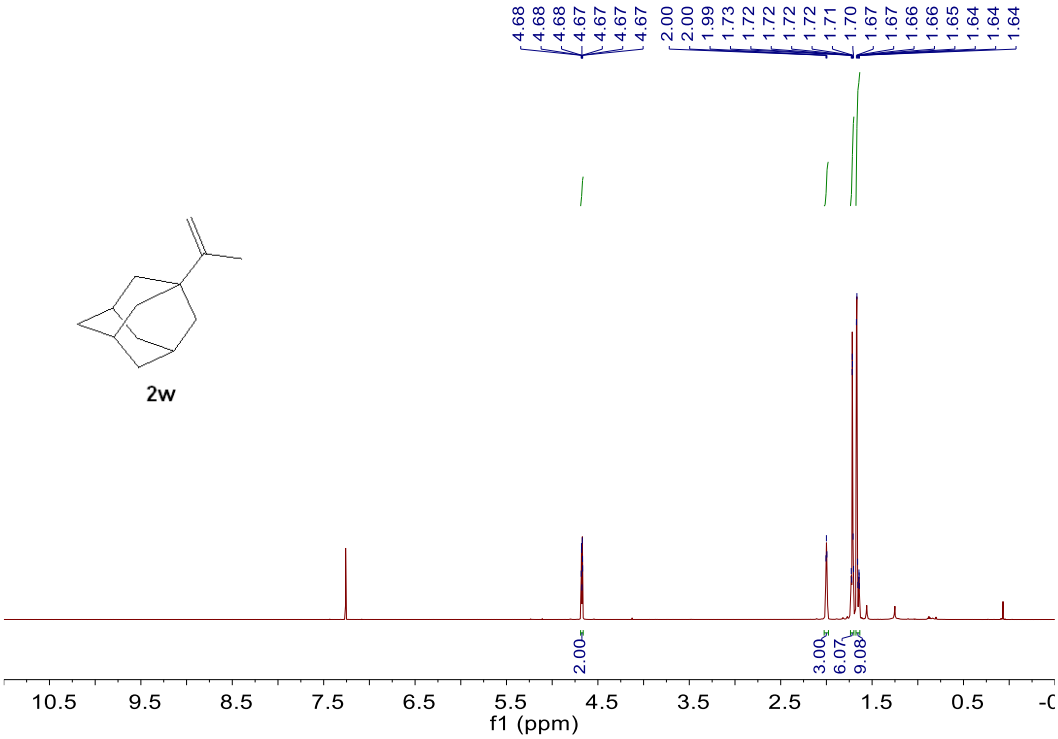
^{1}H NMR (400 MHz) spectrum of **2t** ($CDCl_3$, rt).



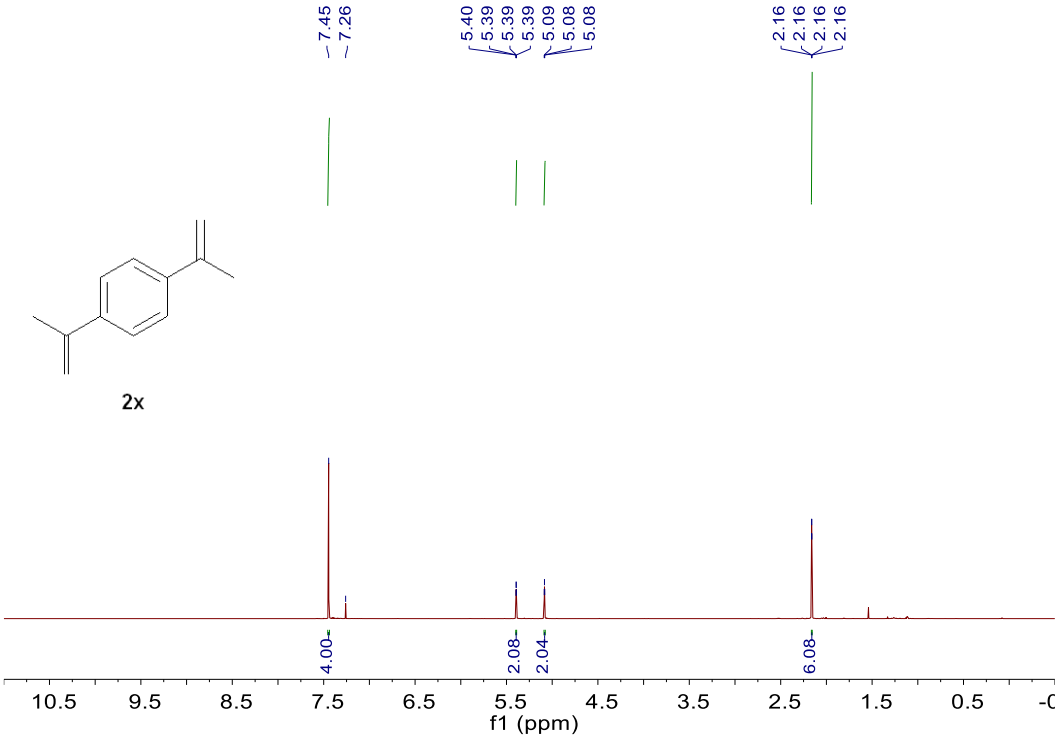
^{1}H NMR (600 MHz) spectrum of **2u** ($CDCl_3$, rt).



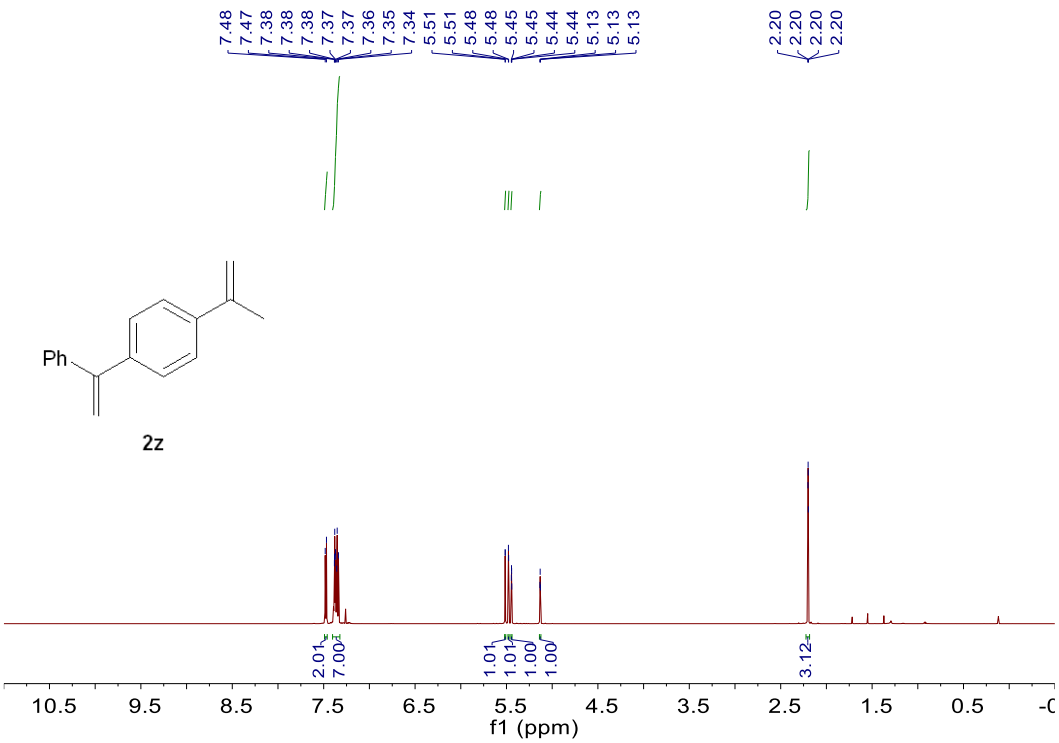
^{1}H NMR (600 MHz) spectrum of **2v** ($CDCl_3$, rt).



^{1}H NMR (600 MHz) spectrum of **2w** ($CDCl_3$, rt).



^{1}H NMR (600 MHz) spectrum of **2x** ($CDCl_3$, rt).



^{1}H NMR (600 MHz) spectrum of **2z** ($CDCl_3$, rt).

4-5 References

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CHAPTER 5

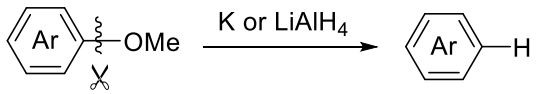
Methoxylation of Acyl Fluorides by C–OMe Bond Cleavage in TMPP under Metal-Free Conditions

5-1 Introduction

C-O bond cleavage in ether as a fundamental transformation in organic synthesis has been extensive studied.[1] Preparation and degradation of ethers have often been utilized as an efficient synthetic strategy of protection/deprotection of hydroxyl groups. With respect to unsymmetrical ethers consisting of a C(aryl)–O–Me scaffold, numerous studies on demethylation in aromatic methyl ethers have been explored, where bond dissociation energies for C(aryl)–O and O–Me bonds are 100 kcal/mol and 65 kcal/mol, respectively.[2] But, the eliminated methyl group have never been installed into the products. In terms of the usage of the methyl group in catalytic reactions, only two protocols have been realized to donate a methyl group to the target products. $RhH(CO)(PPh_3)_3$/dppe activated O–Me bond of aryl methyl ethers, in which thioesters acted as methyl group acceptors to give an array of esters.[3] In addition, $Rh_2(OAc)_4$-catalyzed methylation of aromatic carboxylic acids with bis/tris(*o*-alkoxyphenyl)phosphine via O–Me bonds cleavage to afford aryl esters.[4]

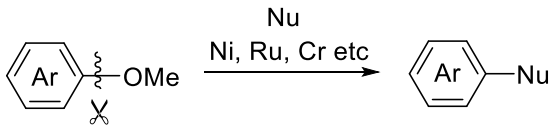
Although the cleavage patterns are affected by the reagents used, selective C(aryl)–OMe cleavage in anisole derivatives is relatively rare. Conventionally, reductive C(aryl)–OMe bond cleavage by potassium metal[5] and $LiAlH_4$/KO^{t}Bu[6] have been reported (Scheme 5-1).

Scheme 5-1. Reductive Cleavage of Anisole Derivatives.



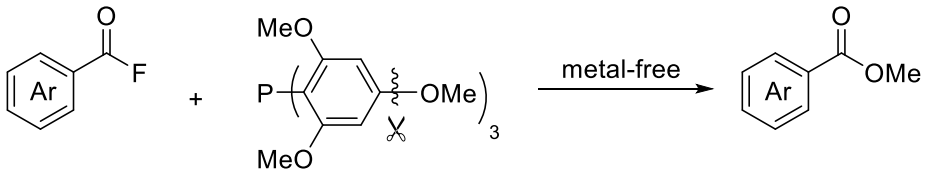
In the past decade, phenol derivatives have been utilized as cheap and sustained alternatives to conventional organic (pseudo)halides in transition-metal catalyzed cross-coupling reactions.[7] Extensive researches of phenol derivatives, especially simple and commercially available aryl methyl ethers as coupling partners are well documented (Scheme 5-2).[8-11] Very recently, KO^{t}Bu-promoted etherification of aryl methyl ethers via C(aryl)–OMe bond cleavage has also been disclosed.[12] In these reactions, however, an OMe group are utilized as leaving groups, and protocols where the eliminated OMe group is installed into the products are quite rare.

Scheme 5-2. Transition-Metal-Catalyzed Cross-Coupling Reactions via C–O Bond Cleavage.



Recently, utilization of acyl fluorides in transition-metal-catalyzed reactions has been extensively studied.[13] Transformations of acyl fluorides have well been documented by other research groups[14] and ourselves.[15] As a part of our continuing studies in transformations of acyl halides, we herein report an unprecedented methoxylation through C(aryl)–OMe bond cleavage of tris(2,4,6-trimethoxyphenyl)phosphine (TMPP, **2a**)[16] under transition-metal-free conditions, in which a diverse of acyl fluorides are subjected to methoxylation to give the corresponding aromatic esters in high yields (Scheme 5-3). In the previous studies, highly basic TMPP acts as an excellent ligand for stabilizing metal complexes by ligating with *ortho*-oxygen atoms,[17] and as a nucleophile for ring-opening of epoxides.[18] However, utilization of TMPP as a methoxylating agent via C(aryl)–OMe bond cleavage to offer a methoxy group to the products is of a great interest.

Scheme 5-3. Methoxylation of Acyl Fluorides with TMPP.

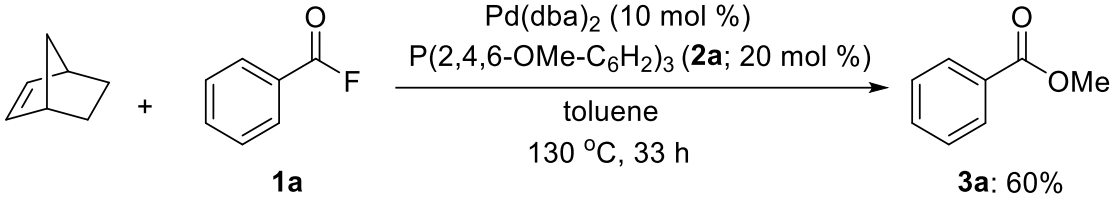


5-2 Results and Discussion

5-2-1 Optimization the Reaction Conditions of Methoxylation

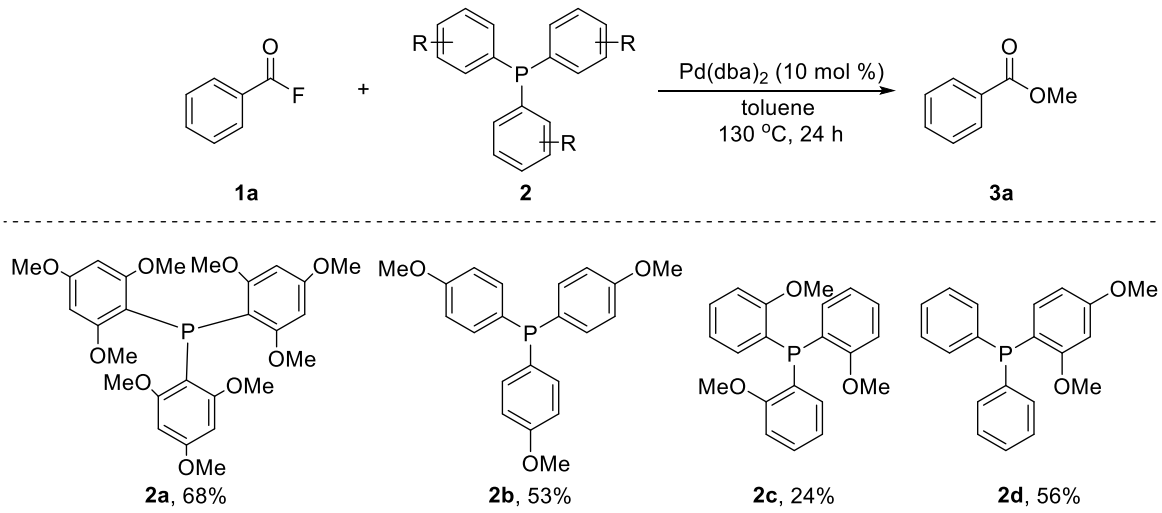
During the course of our studies on palladium-catalyzed addition reaction of benzoyl fluoride (**1a**) with 2-norbornene, we screened various phosphine ligands. To our surprise, when TMPP (**2a**) was employed as the ligand, the desired adduct was not detected, but the formation of methyl benzoate (**3a**) was observed in 60% NMR yield, based on the ligand added (Scheme 5-4).

Scheme 5-4. Attempt of Addition of norbornene.



Thus, we evaluated the performance of various OMe-substituted triarylphosphines **2** in palladium-catalyzed methoxylation of benzoyl fluoride (**1a**) in toluene at 130 ℃ for 24 h (Scheme 5-5). The steric alkyl bulky and highly basic tris(2,4,6-trimethoxyphenyl)phosphine (TMPP, **2a**) gave methyl benzoate (**3a**) in 68% yield. The *p*-OMe substituted triarylphosphine (**2b**) afforded **3a** with the yield of 53%, whereas, triarylphosphine bearing methoxy group at the *ortho* position **2c** furnished desired product **3a** in 24% yield. On the other hand, 56% target product was obtained when (2,4-dimethoxyphenyl)diphenylphosphine (**2d**) was employed in this transformation.

Scheme 5-5. Screening of Phosphines **2**.

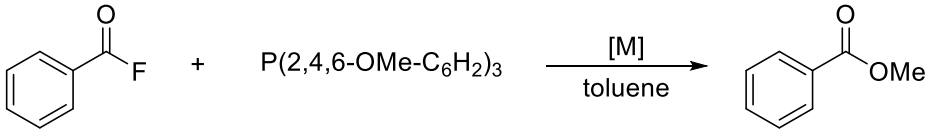


[a]Reaction conditions: **1a** (0.20 mmol), **2** (0.24 mmol), $Pd(dba)_2$ (10 mol %), toluene (0.5 mL), 130 ℃, 24 h. [b]NMR yield of **3a**.

Thus, we began our investigations by choosing benzoyl fluoride (**1a**) and TMPP (**2a**) as model substrates (Tables 5-1). Initially, the loading of the **2a** was examined in the presence of 10 mol % of $Pd(dba)_2$ at 130 ℃ for 24 h. As shown in entries 1-4, the

addition of 0.11 mmol of **2a** (F:OMe = 1:5) was found to be enough for this transformation, affording **3a** in 91% yield (entry 2). Other transition metal catalyst such as $Pd(OAc)_2$, $Ni(cod)_2$, $Ni(acac)_2$ were tested, and the results showed palladium catalyst was more efficient than nickel catalyst (entries 5-7). Even when the reaction was performed in air, target product was obtained without any loss (entry 8). Temperature seemed to be very important for this reaction, the reactions were conducted at 100 ℃ and 80 ℃ in air atmosphere, the yields of **3a** were reduced to 41% and 22%, respectively (entries 9-10). In contrast, the loading of the palladium catalyst had an ignorable effect on the conversion of **3a** as shown in entries 11-13, which suggested that the palladium catalyst does not require in this reaction. Based on this assumption, the reaction of **1a** with **2a** in the absence of the metal catalyst was tried under argon atmosphere. Expectedly, aryl $C(sp^2)$–OMe bond cleavage occurred without any transition metal catalyst, and 89% isolated yield of **3a** was obtained as shown in entry 15. Further screening the amount of **2a** and reaction temperature revealed that 0.11 mol of **2a** and high temperature (130 ℃) are key issues to succeed this reaction (entries 16-18). Similarly, a slight reduction of the yield of **3a** was observed when the reaction was conducted in air (entry 19). Interestingly, when viable surrogate of **1a**, benzoyl chloride was employed, **3a** was obtained only in 43% yield (entry 20). These results indicate that benzoyl fluoride (**1a**) showed specific reactivity for the reaction with TMPP.

Table 5-1. Screening the Reaction Conditions.[a]



1a 0.2 mmol **2a** **3a**

entry	**2a** (mmol)	[M]	[M] (mol%)	Temp. (ºC)	yield (%)[b]
1	0.24	$Pd(dba)_2$	10	130	68
2	0.11	$Pd(dba)_2$	10	130	91
3	0.07	$Pd(dba)_2$	10	130	80

4	0.06	$Pd(dba)_2$	10	130	63
5	0.11	$Pd(OAc)_2$	10	130	91
6	0.11	$Ni(cod)_2$	10	130	67
7	0.11	$Ni(acac)_2$	10	130	68
8[c]	0.11	$Pd(dba)_2$	10	130	91
9[c]	0.11	$Pd(dba)_2$	10	100	41
10[c]	0.11	$Pd(dba)_2$	10	80	22
11[c]	0.11	$Pd(dba)_2$	8	130	82
12[c]	0.11	$Pd(dba)_2$	5	130	79
13[c]	0.11	$Pd(dba)_2$	2.5	130	86
14[cd]	0.11	$Pd(dba)_2$	10	130	56
15	0.11	$Pd(dba)_2$	0	130	92 (89)
16	0.06	$Pd(dba)_2$	0	130	80
17	0.11	$Pd(dba)_2$	0	100	69
18	0.11	$Pd(dba)_2$	0	25	trace
19[c]	0.11	$Pd(dba)_2$	0	130	80
20	0.11	$Pd(dba)_2$	0	130	43 (43)

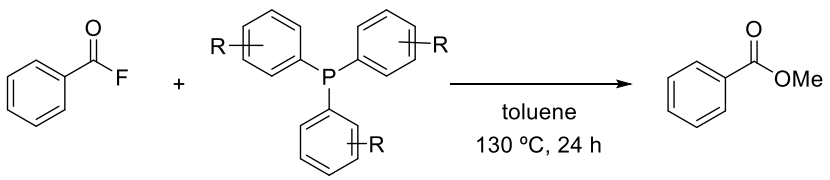
[a]Reaction conditions: **1a** (0.20 mmol), toluene (0.5 mL), 130 °C, 24 h. [b]NMR yields of **3a**. [c]In air. [d]1,4-dioxane instead of toluene. [e]Benzoyl chloride was employed instead of **1a**.

5-2-2 Methoxylation of Acyl Fluorides with TMPP under Metal-Free Conditions

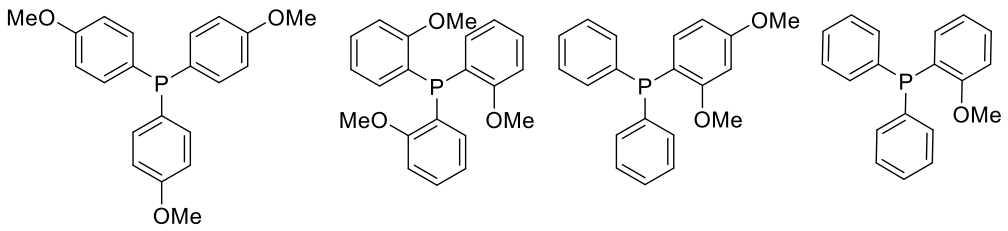
We next evaluated the reaction of benzoyl fluoride (**1a**) with various OMe-substituted triarylphosphines **2** in the absence of the metal catalyst (Scheme 5-6). Besides TMPP (**2a**), triarylphosphines **2b-2e** afford no trace of the target product **3a**. Combined with the

reported comparison among triarylphosphines, it can be explained by unusual basicity (pK_a = 11.02) and nucleophilicity of **2a**.[19] It is reported that 2,6-methoxy groups have a greater effect on the increase in basicity.

Scheme 5-6. Scope of Phosphines **2** in the Absence of the Metal Catalyst.[a,b]



1a **2** (R = H or OMe) **3a**



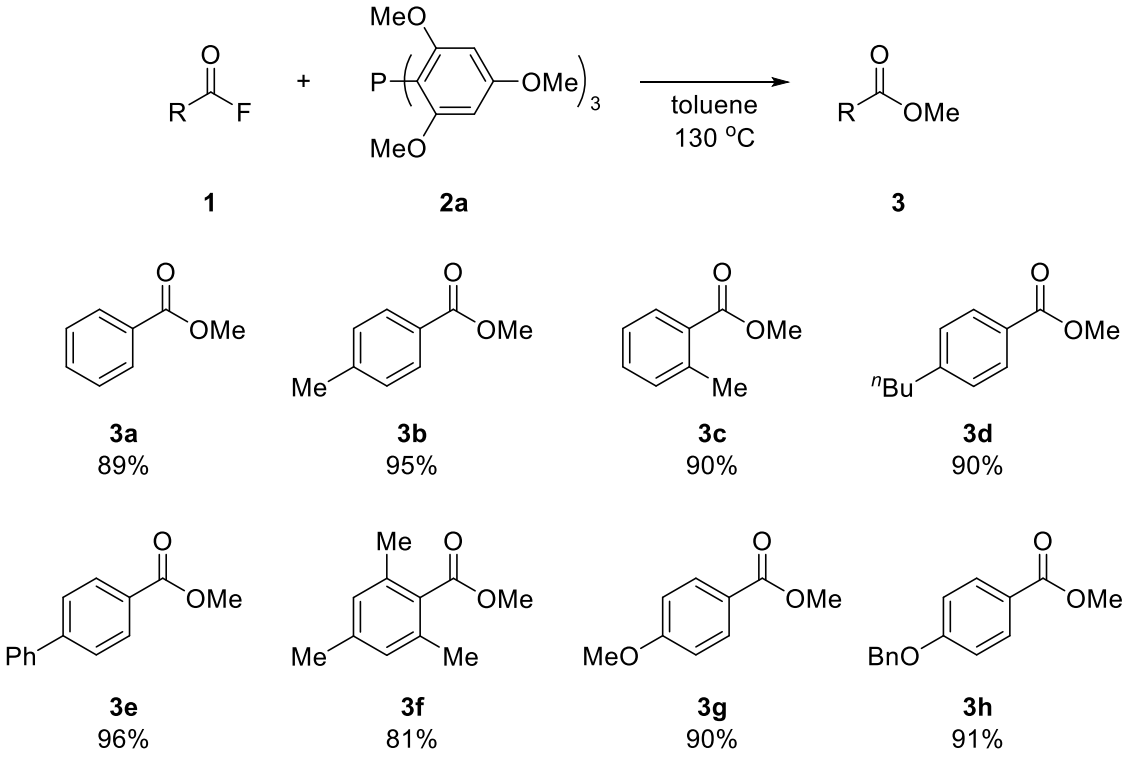
	2a	**2b**	**2c**	**2d**	**2e**
	89%	0%	0%	0%	0%
pK_a	11.02	4.75	4.47	n.r.	3.33

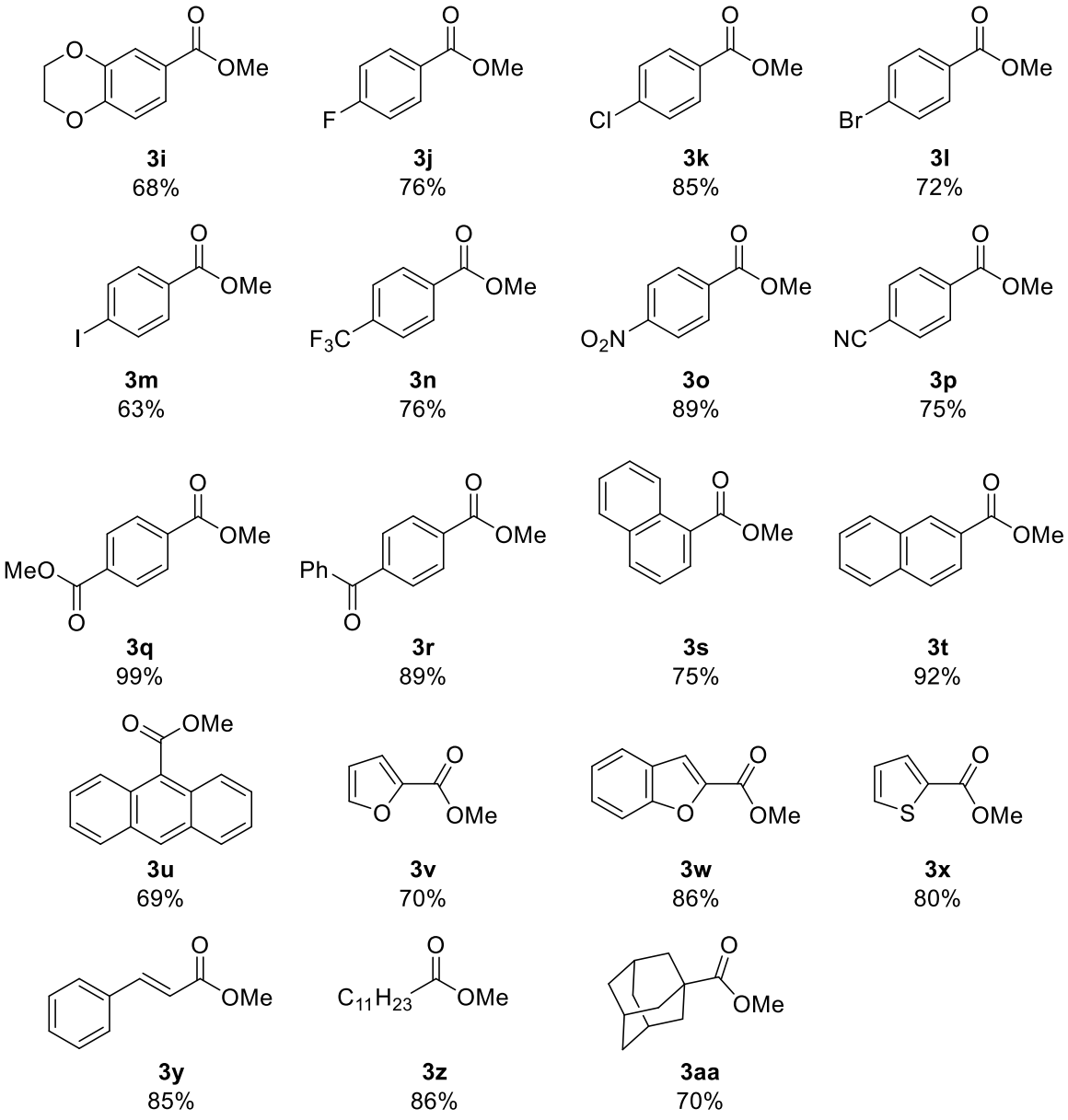
[a]Reaction conditions: **1a** (0.20 mmol), **2** [**2a** (0.11 mmol), **2b** (0.33 mmol), **2c** (0.33 mmol), **2d** (0.495 mmol), **2e** (0.99 mmol)], toluene (0.5 mL), 130 °C, 24 h. [b]Isolated yields.

With the optimized conditions in hand, we surveyed the scope of acyl fluorides **1**. As shown in Table 5-2, regardless of the electronic and steric nature of the substituents, methoxylation provided the desired products **3** in good to excellent yields. Benzoyl fluoride (**1a**) underwent the desired reaction to isolate methyl benzoate (**3a**) in 89% yield. Acyl fluorides bearing electron-rich methyl, *n*-butyl, phenyl in *para*- and *ortho*-positions proved to be very effective, affording **3b**-**3e** in 90-96% yields. Even the highly sterically congested acyl fluoride gave **3f** in 81% yield. Particularly, ethereal substrates bearing methoxy, benzyloxy, and ether groups can also be tolerated under the optimized reaction conditions, affording the target products **3g**-**3i** in 68-91% yields. Notably, acyl fluorides bearing halogen groups were also compatible to afford **3j**-**3m** in moderate to high yields. In particular, bromide and iodide are highly reactive for oxidative addition to transition

metals and the corresponding products **3l** and **3m** can be subjected to further transformations using cross-coupling techniques. The introduction of an electron-withdrawing group onto acyl fluorides led to a slight decrease in yield of the products **3n**-**3p**. Moreover, acyl fluorides-substituted by methoxycarbonyl and benzoyl groups were also good reaction partners to form the corresponding products **3q** and **3r** in 99% and 89% yields, respectively. The generality of the reaction was further extended by varying acyl fluorides with fused ring, affording **3s**-**3u** in 69-92% yields. Oxygen- and sulfur-containing heterocycles could be converted into the desired products **3v**-**3x** in 70-86% yields. Alkenoyl fluoride also gave **3y** in 85% yield. Additionally, the reactions of primary and tertiary aliphatic acyl fluorides **1z** and **1aa** could furnish **3z** and **3aa** in 86% and 70% yields, respectively.

Table 5-2. Scope of Acyl Fluorides **1**.[a,b]





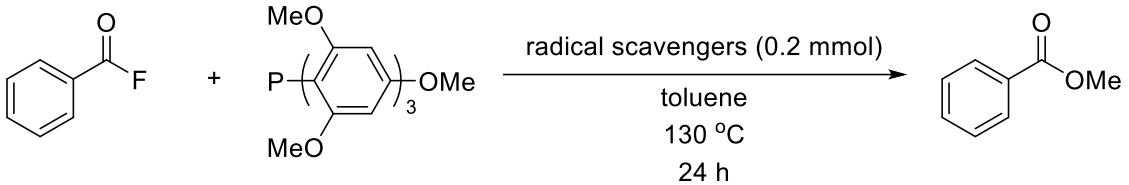
[a]Reaction conditions: **1** (0.20 mmol), **2a** (0.11 mmol), toluene (0.5 mL), 130 °C, 24 h. [b]Isolated yields.

5-2-3 Mechanistic Studies on Methoxylation of Benzoyl Fluoride with TMPP

Aryl C(sp^2)–OMe bond cleavage without transition-metal catalyst is challenging and has never been reported before, thus the reaction mechanism is attracting and worthy exploration. We initially checked the possibility of a radical pathway (Table 5-3), by addition of different radical scavengers including 2,2,6,6-tetramethyl-1-piperidinyloxy

(TEMPO), 2,6-bis(1,1-dimethylethyl)-4-methylphenol (BHT), and galvinoxyl. However, the yield of the desired product **3a** was decreased in some extent but never be inhibited, which could rule out the radical pathway of this reaction (entries 1-3). The possibility of light-induced methoxylation was also examined by performing the reaction of benzoyl fluoride (**1a**) and **2a** in dark under the standard reaction conditions, **3a** was obtained in 97% NMR yield, which further excluded the light induction (entry 4).

Table 5-3. Methoxylation of Benzoyl Fluoride in the Presence of Radical Scavenger.[a]



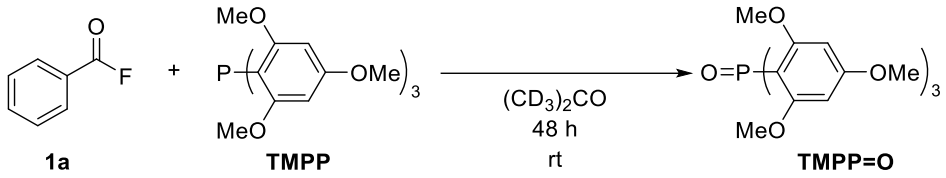
1a 0.2 mmol **2a** 0.11 mmol **3a**

entry	radical scavenger	yield (%)[b]
1	TEMPO	37
2	BHT	70
3	galvinoxyl	53
4[c]	-	97

[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.11 mmol), toluene (0.5 mL), 130 ℃, 24 h. [b]NMR yields. [c]In the dark.

Next interactions between benzoyl fluoride and TMPP were evaluated under different conditions. In atmospheric air, tris(2,4,6-trimethoxyphenyl)phosphine (TMPP, **2a**, 0.0275 mmol, 14.6 mg) and benzoyl fluoride (**1a**, 0.05 mmol, 6.2 mg) were placed in an NMR tube. $(CD_3)_2CO$ (0.5 mL) was then added at room temperature. After the resulting solution shaken well, the ^1H NMR analysis was performed as shown in Figure 5-1 (spectrum a), more than half of TMPP (dots) was transformed to tris(2,4,6-trimethoxyphenyl)phosphine oxide (TMPP=O, triangles) after 48 h. On the other hand, in air, only tris(2,4,6-trimethoxyphenyl)phosphine (TMPP, **2a**, 0.0275 mmol,

14.6 mg) was placed in an NMR tube in $(CD_3)_2CO$ (0.5 mL) at room temperature. After the resulting solution shaked well, the ^1H NMR analysis was performed as shown in Figure 5-1 (spectrum b), less than a half of TMPP (dots) was transformed to TMPP=O (triangles) after 48 h. From these two NMR charts, the addition of benzoyl fluoride promoted oxidation of TMPP to TMPP=O.



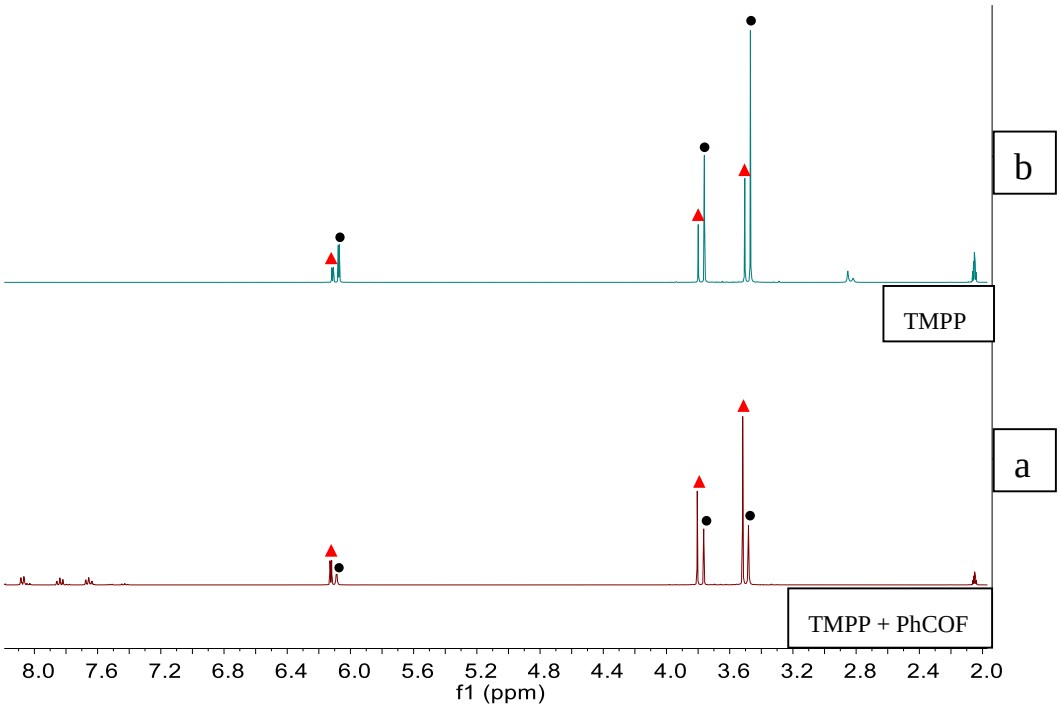


Figure 5-1. ^1H NMR spectra for oxidation of TMPP (**2a**) with or without benzoyl fluoride (**1a**).

Continuous monitoring the $(CD_3)_2CO$ solution of TMPP placed in an NMR tube in air was shown in Figures 5-2 and 5-3, the resonances of TMPP=O increased while the resonance of TMPP decreased gradually along with the time. After 20 days, TMPP=O was formed completely, and no TMPP was observed by the NMR analysis. This experiment provided the NMR data of TMPP=O, and helped us to identify all the phosphorus species under the standard reaction conditions.

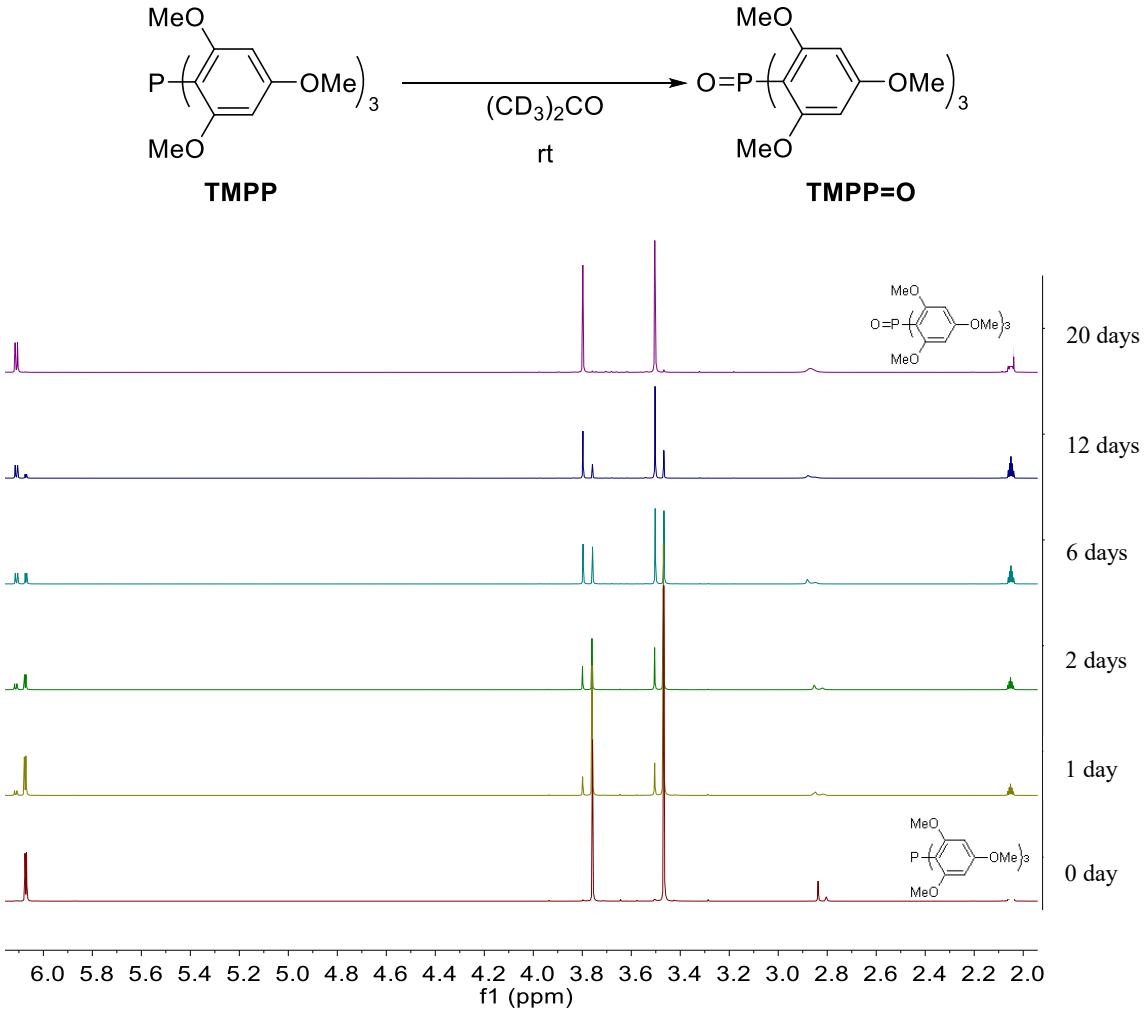
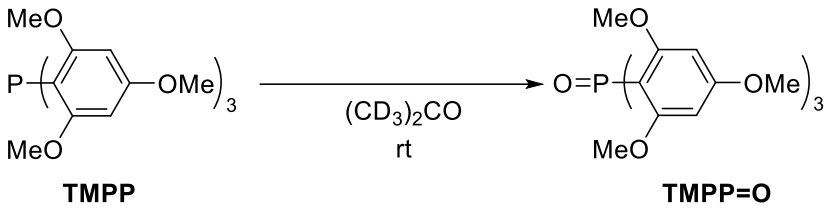


Figure 5-2. ^{1}H NMR spectra for oxidation of TMPP (**2a**) in $(CD_3)_2CO$ in air.



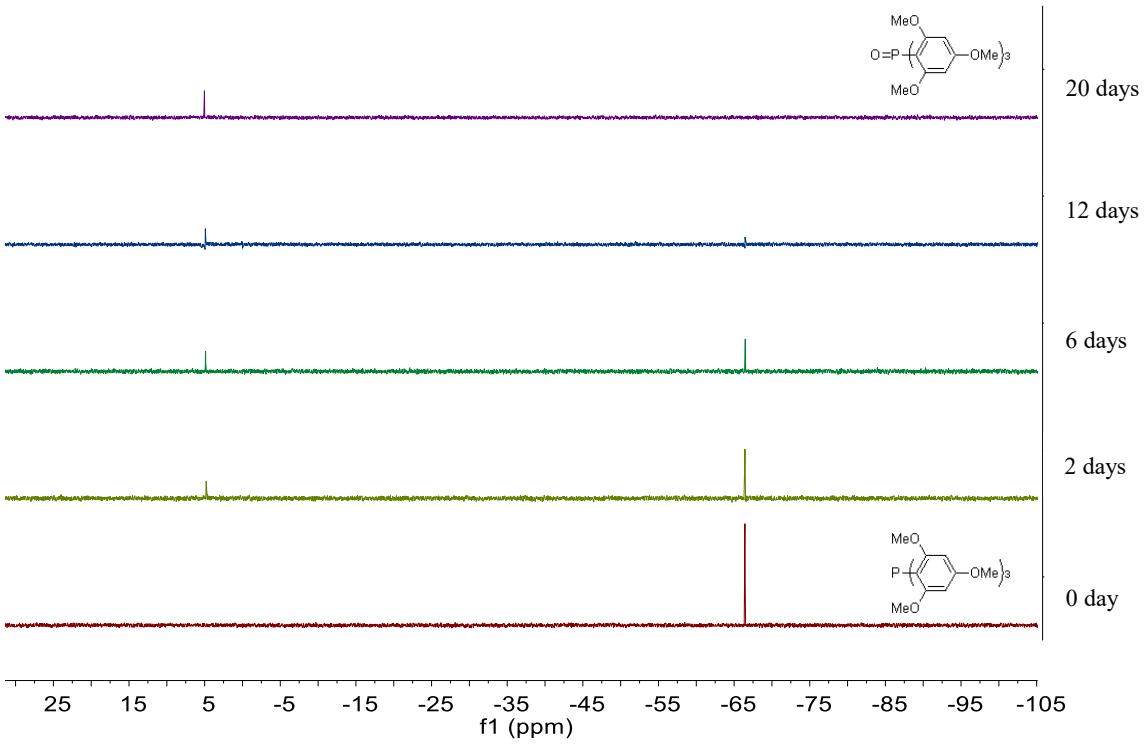
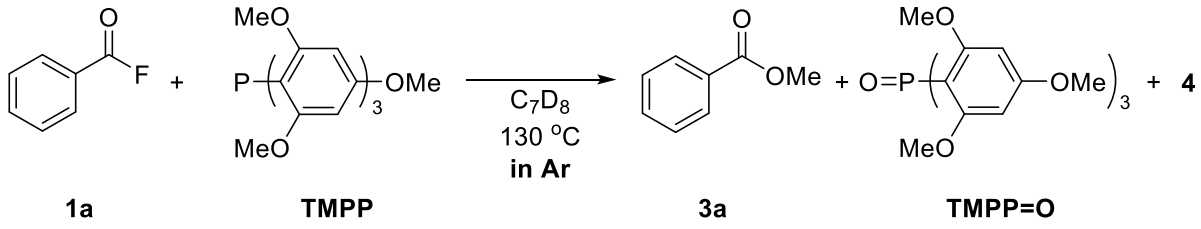


Figure 5-3. $^{31}P\{^{1}H\}$ NMR spectra for oxidation of TMPP (**2a**) in $(CD_3)_2CO$.

To shed light on the present methoxylation, the reaction of benzoyl fluoride (**1a**) with TMPP (**2a**) in C_7D_8 under an argon atmosphere was monitored by the ^{1}H NMR (Figure 5-4). When the reaction mixture was heated at 130 °C for 2 h, the new signals assignable to TMPP=O (triangles) and the product **3a** (squares) were observed. After 24 h, TMPP (**2a**) was completely consumed and white precipitates of **4** was formed in an NMR tube. The white precipitate was washed by $CHCl_3$, toluene and diethyl ether, and dried under vacuum. However, the isolation of complex **4** was failed.



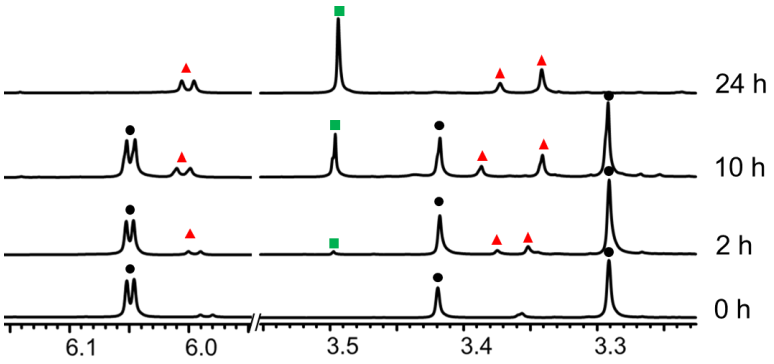
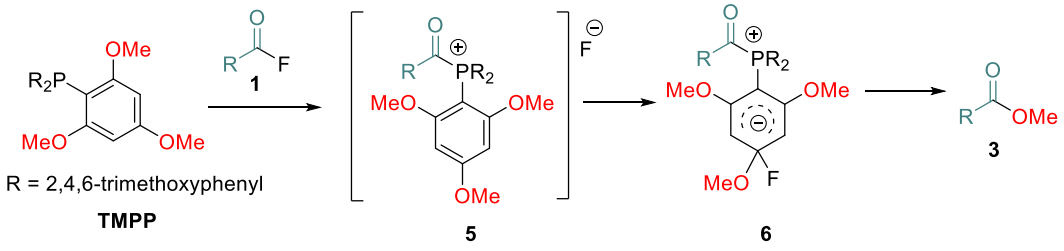


Figure 5-4. ^{1}H NMR spectra of a mixture of benzoyl fluoride (**1a**, 0.05 mmol) and TMPP (**2a**, 0.0275 mmol) in C_7D_8, showing TMPP (**2a**) (black dots), TMPP=O (triangles), and the product **3a** (squares).

A proposed catalytic cycle is outlined in Scheme 5-5. Benzoyl fluoride **1a** attacked TMPP to afford intermediate **5** species.[20] Then multiple methoxide groups and lone pair of phosphine rendered *para*-position methoxy group easily cleave to generate Meisenheimar complex **6** via aromatic nucleophilic substitution.[21] The desired products aromatic ester was furnished after work-up. Due to the formation of TMPP=O during the reaction process, the reaction using benzoyl fluoride with TMPP=O instead of TMPP was also tested, and no desired product was observed, which suggested that once formed TMPP=O can't participate in this reaction. The structure of **4** and detailed mechanism are still under investigation.

Scheme 5-5. Proposed Mechanism.



5-3 Summary

In conclusion, an unprecedented transformation of acyl fluorides with tris(2,4,6-trimethoxyphenyl)phosphine via C(aryl)–OMe bond cleavage has been realized. A wide range of substrates bearing electron-donating or -withdrawing substituents on the (hetero)aromatic rings, as well as alkenyl and alkyl acyl fluorides are well compatible. This transformation presents a new activation strategy for inert carbon-oxygen bonds. In addition, this reaction is featured by challenging aryl C(sp^2)–OMe bond cleavage under metal-free conditions, and a conventional leaving group (OMe) was successfully installed into desired products, utilizing TMPP as a methoxylating agent, esterification of acyl fluorides into a wide range of esters with a good substrate compatibility.

5-4 Experimental Section

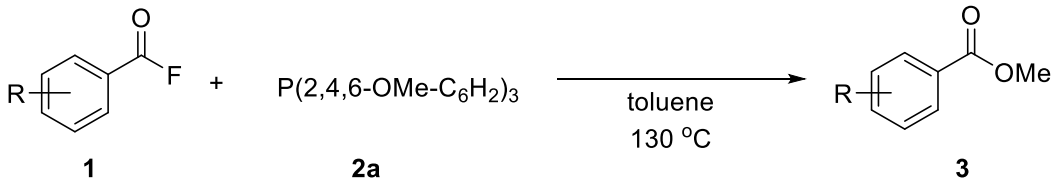
5-4-1 General Instrumentation and Chemicals

All the reactions were carried out under an argon atmosphere using standard Schlenk techniques. Glassware was dried in an oven (150 ℃) and heated under reduced pressure prior to use. Solvents were employed as eluents for all other routine operation, as well as dehydrated solvent were purchased from commercial suppliers and employed without any further purification. For thin layer chromatography (TLC) analyses throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. Silica gel column chromatography was carried out using Silica gel 60 N (spherical, neutral, 40-100 μm) from Kanto Chemicals Co. Ltd. NMR spectra (^{1}H, ^{13}C{^{1}H}, ^{31}P{^{1}H} and ^{19}F{^{1}H}) were recorded on Varian INOVA-600 (600 MHz), Mercury-400 (400 MHz), or 300-NMR ASW (300 MHz) spectrometers. Chemical shifts (δ) are in parts per million related to $CDCl_3$ at 7.26 ppm for ^{1}H and at 77.16 ppm for ^{13}C{^{1}H} NMR measurements. The GC yields were determined using *n*-dodecane as an internal standard. The NMR yields were determined by ^{1}H NMR spectra using dibromomethane as an internal standard.

Chemicals

Materials obtained from commercial suppliers were used without further purification. Benzoyl fluoride (**1a**) (purity > 98%) and dibromomethane (purity > 99%) were purchased from Tokyo Chemical Industry Co. Ltd. Bis(1,5-cycloctadiene)nickel and tris(2,4,6-trimethoxyphenyl)phosphine were purchased from Sigma-Aldrich Co. Ltd. Other acyl fluorides were synthesized from corresponding carboxylic acids or acyl chlorides, which was described in Chapter 2.

5-4-2 Experimental Procedures

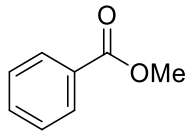


1 **2a** **3**

To a 20-mL Schlenk tube, were added acyl fluorides (**1**, 0.20 mmol), tris(2,4,6-trimethoxyphenyl)phosphine (**2a**, 61.5 mg, 0.11 mmol), and toluene (0.5 mL) at room temperature under an argon atmosphere. After being stirred at 130 ºC for 24 h, the

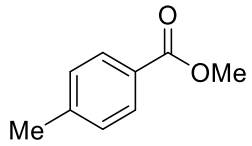
reaction mixture was quenched with 1 M HCl aq solution, extracted with diethyl ether, and dried over $MgSO_4$. After the volatiles were removed under vacuum, the crude product was purified by column chromatography on silica gel or bulb-to-bulb distillation to afford the products **3**.

Methyl benzoate (3a)[22]



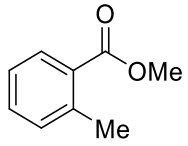
Purification: bulb-to-bulb distillation (60 ºC/5 mmHg). Colorless oil. Yield: 89% (24.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91 (s, 3H), 7.41-7.45 (m, 2H), 7.53-7.57 (m, 1H), 8.03-8.06 (m, 2H).

Methyl 4-methylbenzoate (3b)[22]



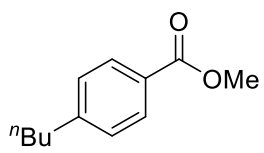
Purification: bulb-to-bulb distillation (80 ºC/5 mmHg). Colorless oil. Yield: 95% (28.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.90 (s, 3H), 7.24 (d, J = 8.0 Hz, 2H), 7.93 (d, J = 8.0 Hz, 2H).

Methyl 2-methylbenzoate (3c)[23]



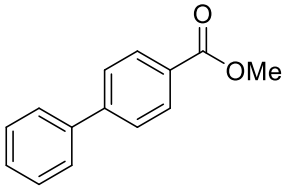
Purification: bulb-to-bulb distillation (85 ºC/5 mmHg). Colorless oil. Yield: 90% (27 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60 (s, 3H), 3.89 (s, 3H), 7.22-7.26 (m, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H).

Methyl 4-butylbenzoate (3d)[24]



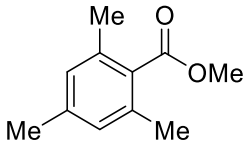
Purification: column chromatography (*n*-hexane/Et_2O = 20:1, R_f = 0.67). Colorless oil. Yield: 90% (34.6 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, J = 7.6 Hz, 3H), 1.35 (sext, J = 8.0 Hz, 2H), 1.57-1.65 (m, 2H), 2.66 (t, J = 7.6 Hz, 2H), 3.90 (s, 3H), 4.01 (s, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.94 (d, J = 8.0 Hz, 2H).

Methyl [1,1'-biphenyl]-4-carboxylate (3e)[25]



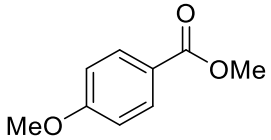
Purification: column chromatography (*n*-hexane/Et_2O = 10:1, R_f = 0.67). White solid. Yield: 96% (40.8 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 3.95 (s, 3H), 7.40 (t, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 8.11 (d, J = 8.0 Hz, 2H).

Methyl 2,4,6-trimethylbenzoate (3f)[26]



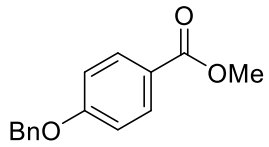
Purification: column chromatography (*n*-hexane/Et_2O = 20:1, R_f = 0.50). White solid. Yield: 81% (28.8 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 9H), 3.89 (s, 3H), 6.85 (s, 2H).

Methyl 4-methoxybenzoate (3g)[22]



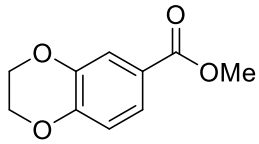
Purification: column chromatography (*n*-hexane/Et_2O = 10:1, R_f = 0.55). Colorless oil. Yield: 90% (29.9 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 3.88 (s, 3H), 6.91 (d, J = 8.0 Hz, 2H), 7.99 (d, J = 8.0 Hz, 2H).

Methyl 4-(benzyloxy)benzoate (3h)[27]



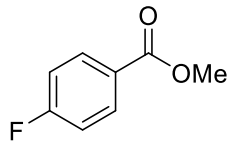
Purification: column chromatography (*n*-hexane/Et_2O = 10:1, R_f = 0.56). White solid. Yield: 91% (44.1 mg). ^1H NMR (600 MHz, $CDCl_3$) δ 3.89 (s, 3H), 5.11 (s, 2H), 7.00 (t, *J* = 6.0 Hz, 1H), 7.01 (t, *J* = 6.0 Hz, 1H), 7.34-7.37 (m, 1H), 7.39-7.45 (m, 2H), 8.01 (t, *J* = 6.0 Hz, 1H), 8.02 (t, *J* = 6.0 Hz, 1H).

Methyl 2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylate (3i)[28]



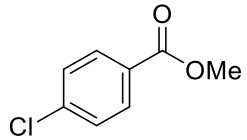
Purification: column chromatography (*n*-hexane/Et_2O = 50:1, R_f = 0.50). Colorless oil. Yield: 68% (26.4 mg). ^1H NMR (400 MHz, $CDCl_3$): *δ* 3.87 (s, 3H), 4.26-4.28 (m, 2H), 4.29-4.32 (m, 2H), 6.87-6.89 (m, 1H), 7.54-7.56 (m, 2H).

Methyl 4-fluorobenzoate (3j)[29]



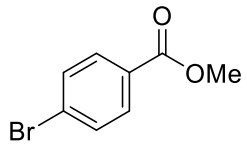
Purification: bulb-to-bulb distillation (60 ºC/20 mmHg). Colorless oil. Yield: 76% (23.4 mg). ^1H NMR (600 MHz, $CDCl_3$) δ 3.91 (s, 3H), 7.09-7.12 (m, 2H), 8.04-8.07 (m, 2H).

Methyl 4-chlorobenzoate (3k)[30]



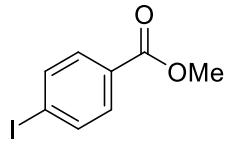
Purification: column chromatography (*n*-hexane/Et_2O = 20:1, R_f = 0.57). White solid. Yield: 85% (15.8 mg). ^1H NMR (400 MHz, $CDCl_3$): *δ* 3.92 (s, 3H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 2H).

Methyl 4-bromobenzoate (3l)[29]



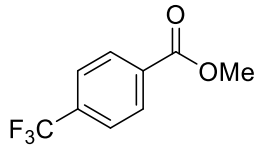
Purification: column chromatography (*n*-hexane/Et_2O = 20:1, R_f = 0.50). White solid. Yield: 72% (31.0 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.91 (s, 3H), 7.58 (d, *J* = 6.0 Hz, 2H), 7.90 (d, *J* = 6.0 Hz, 2H).

Methyl 4-iodobenzoate (3m)[29]



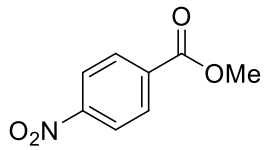
Purification: column chromatography (*n*-hexane/Et_2O = 20:1, R_f = 0.56). White solid. Yield: 63% (33.0 mg). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 3.91 (s, 3H), 7.75 (m, 2H), 7.80 (m, 2H).

Methyl 4-(trifluoromethyl)benzoate (3n)[22]



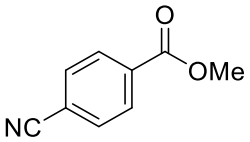
Purification: bulb-to-bulb distillation (65 ºC/5 mmHg). Colorless oil. Yield: 76% (31.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96 (s, 3H), 7.71 (d, *J* = 8.0 Hz, 2H), 8.15 (d, *J* = 8.0 Hz, 2H).

Methyl 4-nitrobenzoate (3o)[30]



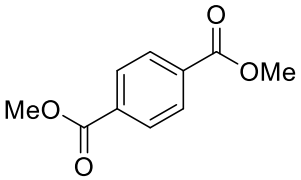
Purification: column chromatography (*n*-hexane/Et_2O = 10:1, R_f = 0.53). White solid. Yield: 89% (32.1 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.98 (s, 3H), 8.20-8.23 (m, 2H), 8.28-8.31 (m, 2H).

Methyl 4-cyanobenzoate (3p)[31]



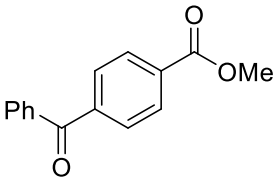
Purification: column chromatography (*n*-hexane/Et_2O = 10:1, R_f = 0.43). White solid. Yield: 75% (24.2 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 3.96 (s, 3H), 7.75 (d, J = 8.0 Hz, 2H), 8.14 (d, J = 8.0 Hz, 2H).

Dimethyl terephthalate (3q)[30]



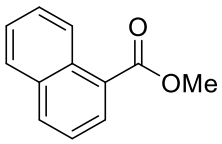
Purification: column chromatography (*n*-hexane/Et_2O = 10:1, R_f = 0.53). White solid. Yield: 99% (39.2 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 3.94 (s, 6H), 8.10 (s, 4H).

Methyl 4-benzoylbenzoate (3r)[32]



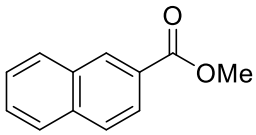
Purification: column chromatography (*n*-hexane/Et_2O = 10:1, R_f = 0.50). White solid. Yield: 89% (42.8 mg). ^1H NMR (600 MHz, $CDCl_3$) δ 3.96 (s, 3H), 7.47-7.51 (m, 2H), 7.58-7.64 (m, 1H), 7.75-7.86 (m, 4H), 8.12-8.17 (m, 2H).

Methyl 1-naphthoate (3s)[23]



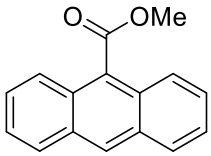
Purification: column chromatography (*n*-hexane/Et_2O = 20:1, R_f = 0.50). White solid. Yield: 75% (27.9 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 4.01 (s, 3H), 7.48-7.56 (m, 2H), 7.62 (dt, J = 8.0, 1.6 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 8.19 (dd, J = 8.0, 1.2 Hz, 1H), 8.91 (d, J = 8.0 Hz, 1H).

Methyl 2-naphthoate (3t)[33]



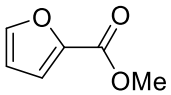
Purification: column chromatography (*n*-hexane/Et_2O = 10:1, R_f = 0.72). White solid. Yield: 92% (34.3 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 3.99 (s, 3H), 7.54-7.62 (m, 2H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.96 (d, *J* = 8.0 Hz, 1H), 8.07 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.62 (s, 1H).

Methyl anthracene-9-carboxylate (3u)[33]



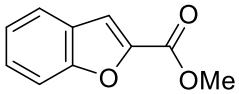
Purification: column chromatography (*n*-hexane/Et_2O = 10:1, R_f = 0.57). Yellow solid. Yield: 69% (32.6 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 4.19 (s, 3H), 7.48-7.57 (m, 4H), 8.02-8.05 (m, 4H), 8.54 (s, 1H).

Methyl furan-2-carboxylate (3v)[34]



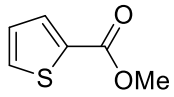
Purification: bulb-to-bulb distillation (70 ºC/20 mmHg). Colorless oil. Yield: 70% (17.7 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 6.47 (dd, *J* = 3.6, 1.6 Hz, 1H), 7.14 (dd, *J* = 3.6, 0.8 Hz, 1H), 7.54 (dd, *J* = 1.6, 0.8 Hz, 1H).

Methyl benzofuran-2-carboxylate (3w)[35]



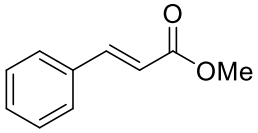
Purification: column chromatography (*n*-hexane/Et_2O = 10:1, R_f = 0.60). White solid. Yield: 86% (30.3 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 3.98 (s, 3H), 7.31 (td, *J* = 8.0, 0.8 Hz, 1H), 7.43-7.48 (m, 1H), 7.54 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.69 (dd, *J* = 8.0, 0.8 Hz, 1H).

Methyl thiophene-2-carboxylate (3x)[23]



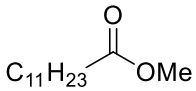
Purification: bulb-to-bulb distillation (65 ºC/5 mmHg). Colorless oil. Yield: 80% (22.7 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 3H), 7.10 (dd, J = 4.8, 3.6 Hz, 1H), 7.55 (dd, J = 4.8, 1.6 Hz, 1H), 7.80 (dd, J = 3.6, 1.6 Hz, 1H).

Methyl cinnamate (3y)[30]



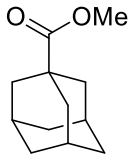
Purification: column chromatography (n-hexane/Et_2O = 10:1, R_f = 0.47). White solid. Yield: 85% (27.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H), 6.45 (d, J = 16.0 Hz, 1H), 7.38-7.40 (m, 3H), 7.52-7.54 (m, 2H), 7.70 (d, J = 16.0 Hz, 1H).

Methyl dodecanoate (3z)[36]



Purification: bulb-to-bulb distillation (100 ºC/5 mmHg). Colorless oil. Yield: 86% (36.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85-0.90 (m, 3H), 1.23-1.30 (m, 16H), 1.62 (td, J = 7.1, 3.0 Hz, 2H), 2.27-2.32 (m, 2H), 3.66 (s, 3H).

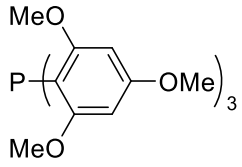
Methyl (3r,5r,7r)-adamantane-1-carboxylate (3aa)[37]



Purification: bulb-to-bulb distillation (100 ºC/5 mmHg). White solid. Yield: 70% (27.4 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.68-1.73 (m, 6H), 1.88-1.89 (m, 6H), 1.99-2.02 (m, 3H), 3.64 (s, 3H).

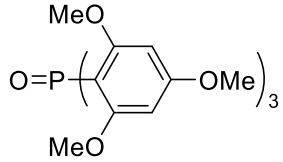
Relative Ether Phosphine Compounds' Data

Tris(2,4,6-trimethoxyphenyl)phosphine (TMPP)



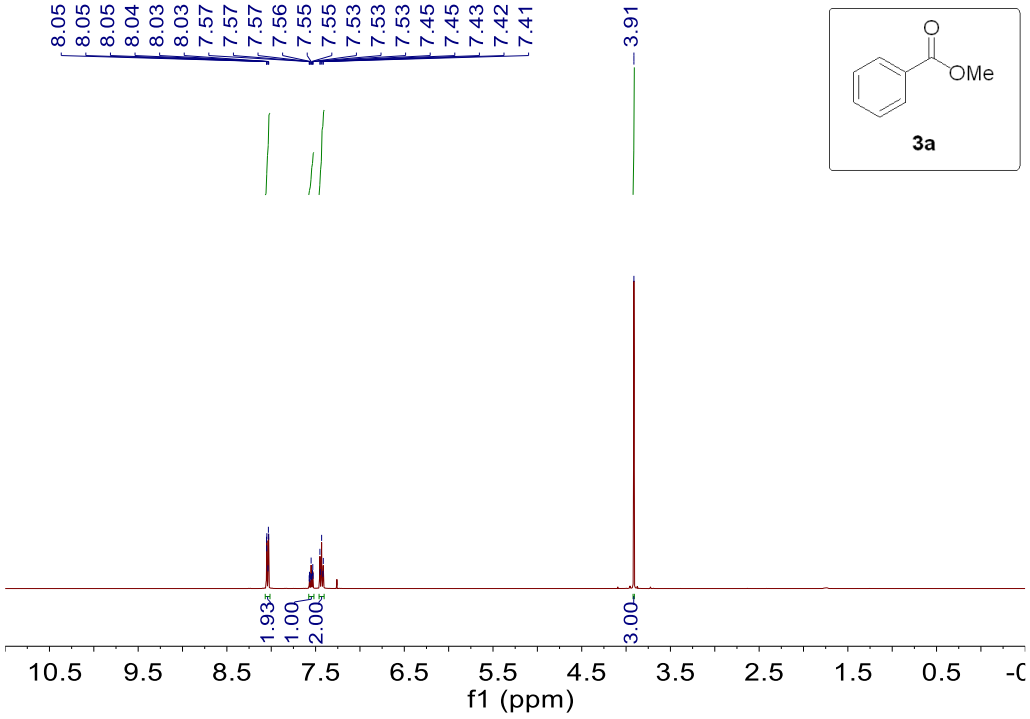
^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 3.47 (s, 18H), 3.76 (s, 9H), 6.07 (d, J = 2.4 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $(CD_3)_2CO$): δ 54.4, 55.1, 91.0, 160.8, 163.0, 163.1. ^{31}P{^{1}H} NMR (162 MHz, $(CD_3)_2CO$): δ -66.4. ^{1}H NMR (400 MHz, C_7D_8): δ 3.29 (s, 18H), 3.41 (s, 9H), 6.05 (d, $J_{P\text{-}H}$ = 2.0 Hz, 6H). ^{31}P{^{1}H} NMR (162 MHz, C_7D_8): δ -66.9.

Tris(2,4,6-trimethoxyphenyl)phosphine oxide (TMPP=O)

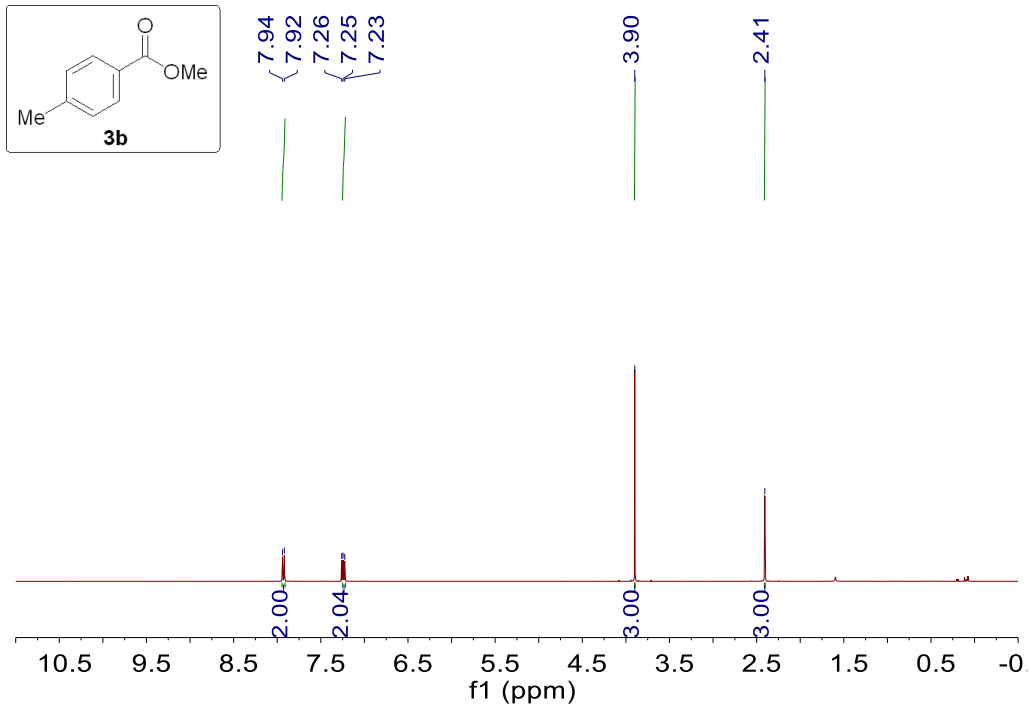


^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 3.50 (s, 18H), 3.80 (s, 9H), 6.11 (d, $J_{P\text{-}H}$ = 4.4 Hz, 6H). ^{31}P{^{1}H} NMR (162 MHz, $(CD_3)_2CO$): δ 5.0. ^{1}H NMR (400 MHz, C_7D_8): δ 3.35 (d, J = 1.6 Hz, 27H), 6.00 (d, $J_{P\text{-}H}$ = 4.0 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, C_7D_8): δ 54.6, 56.1, 92.2, 92.2, 137.5, 163.1, 164.2. ^{31}P{^{1}H} NMR (162 MHz, C_7D_8): δ 11.0.

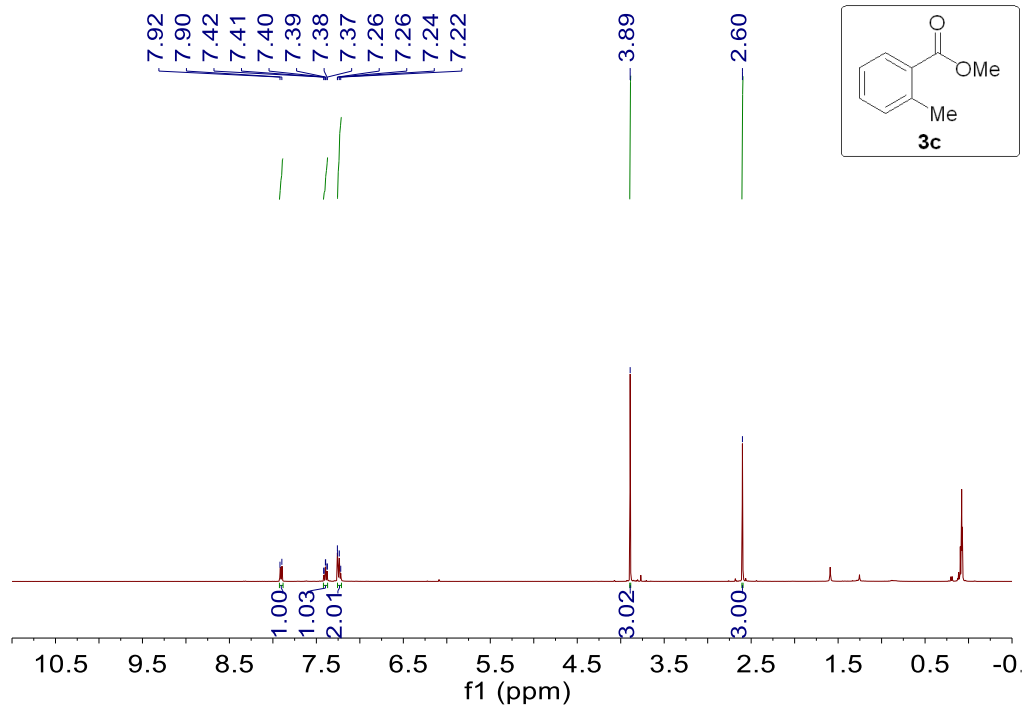
5-4-3 Copies of NMR Charts for Products



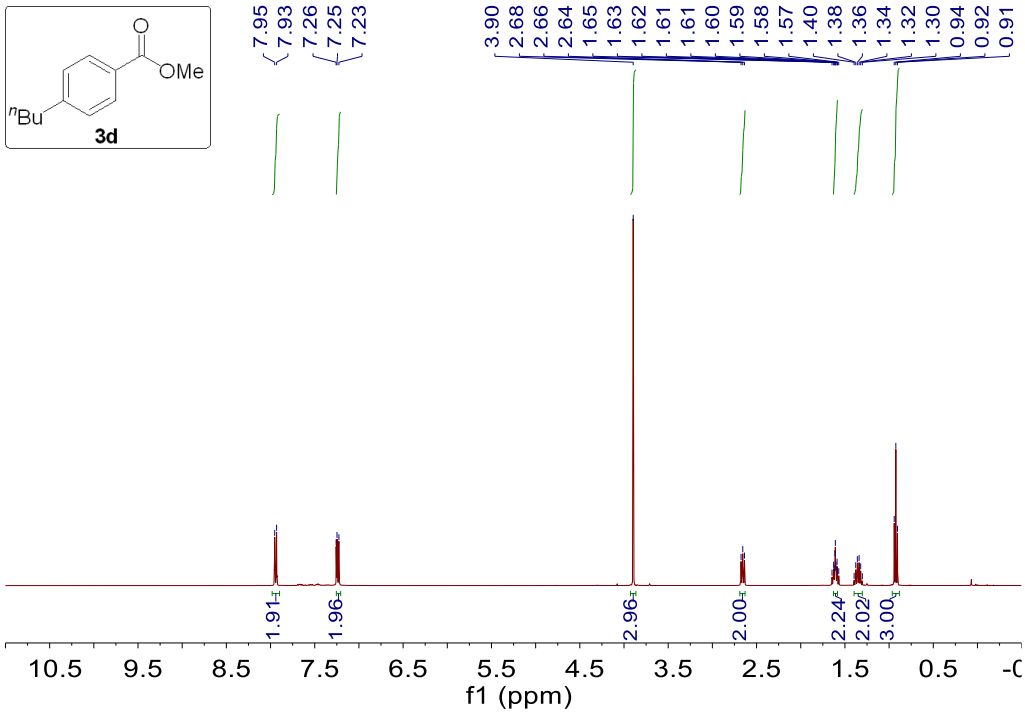
^{1}H NMR (400 MHz) spectrum of **3a** ($CDCl_3$, rt).



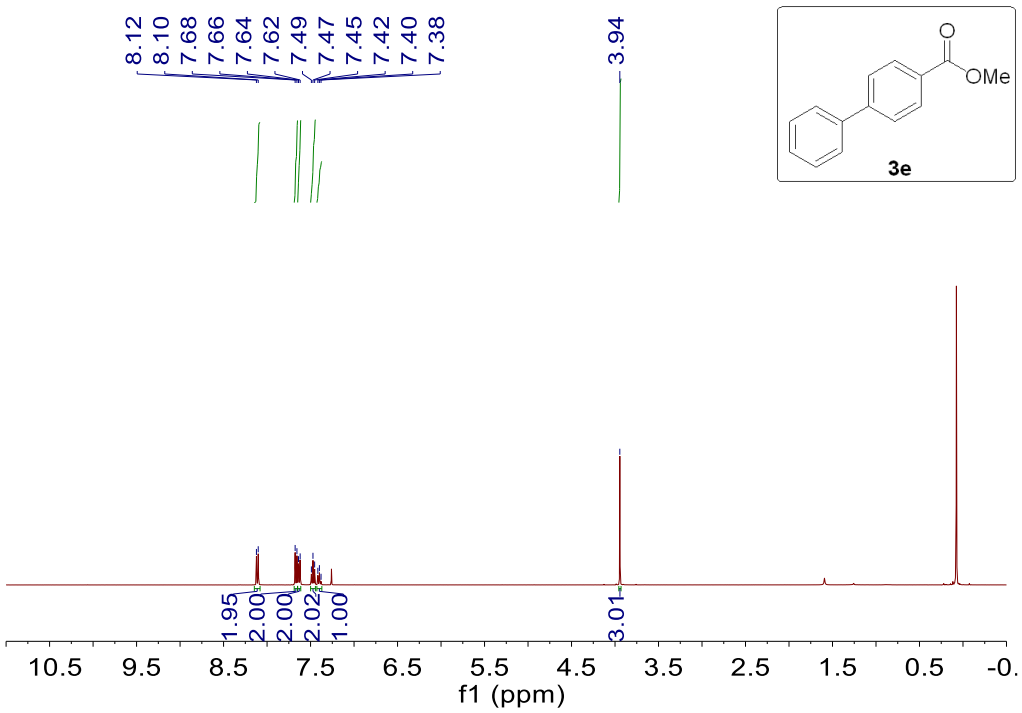
^{1}H NMR (400 MHz) spectrum of **3b** ($CDCl_3$, rt).



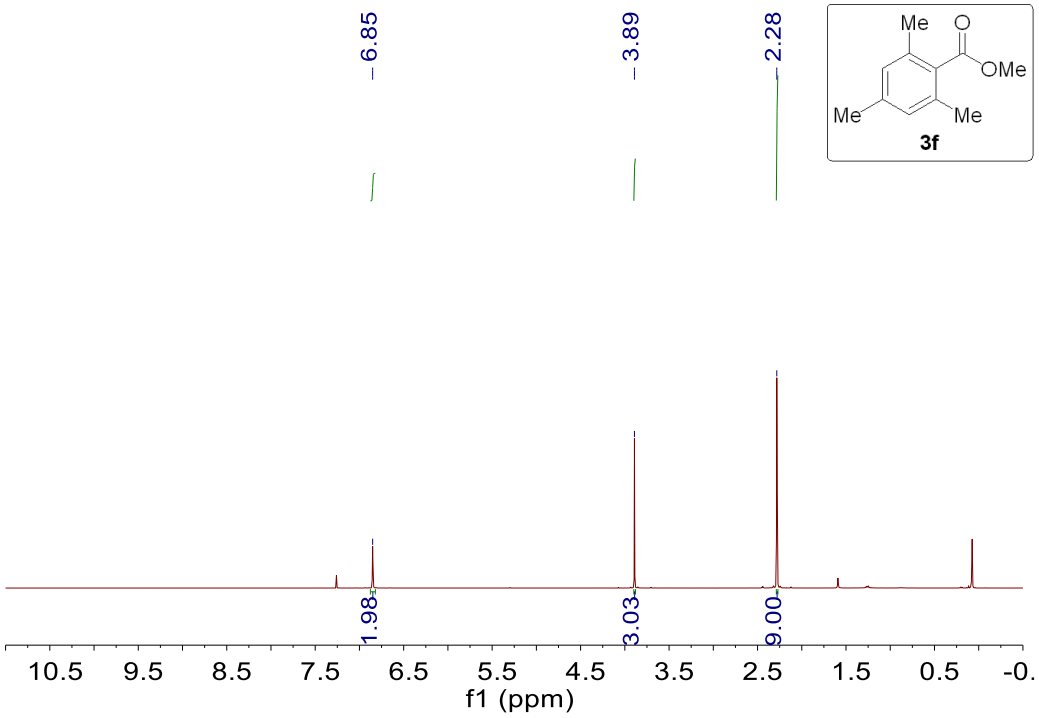
^{1}H NMR (400 MHz) spectrum of **3c** ($CDCl_3$, rt).



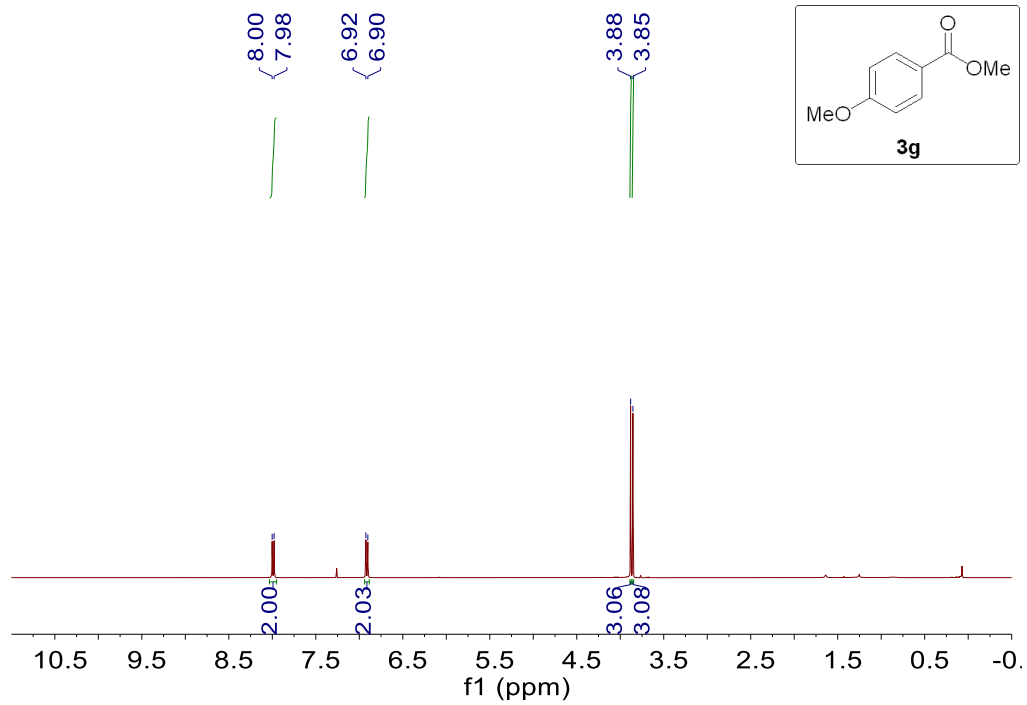
^{1}H NMR (400 MHz) spectrum of **3d** ($CDCl_3$, rt).



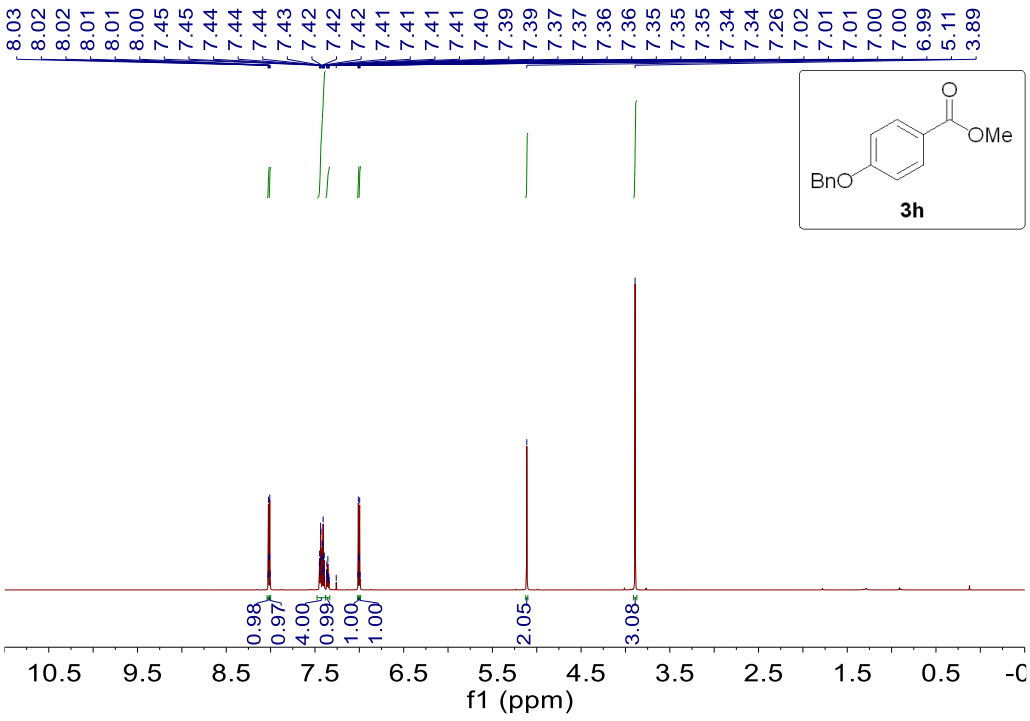
^{1}H NMR (400 MHz) spectrum of **3e** ($CDCl_3$, rt).



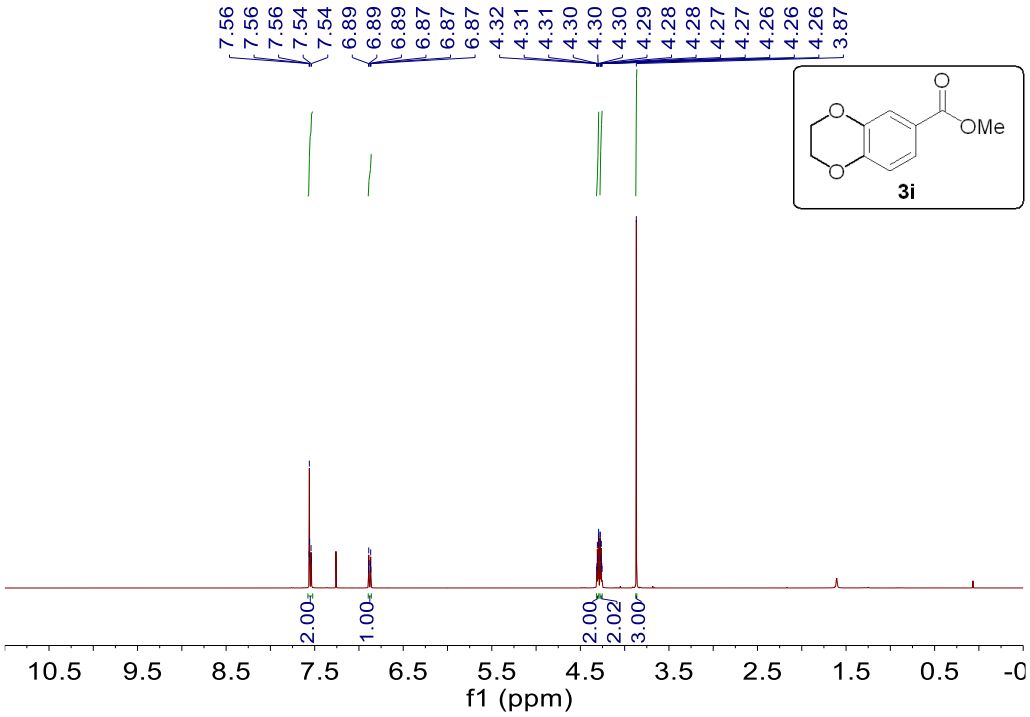
^{1}H NMR (400 MHz) spectrum of **3f** ($CDCl_3$, rt).



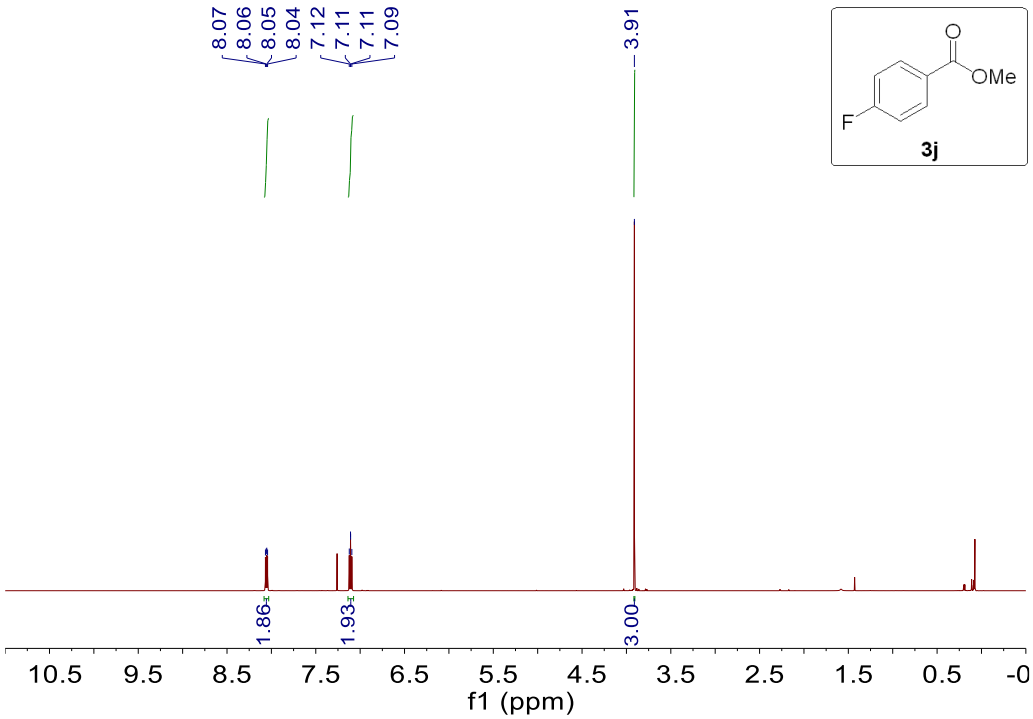
^{1}H NMR (400 MHz) spectrum of **3g** ($CDCl_3$, rt).



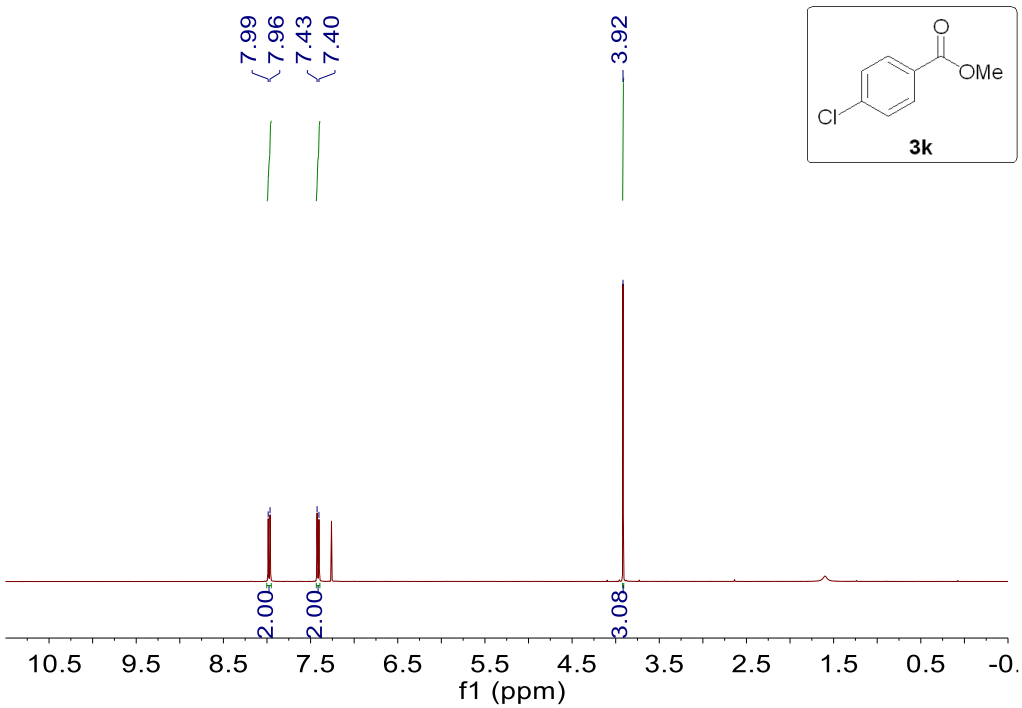
^{1}H NMR (600 MHz) spectrum of **3h** ($CDCl_3$, rt).



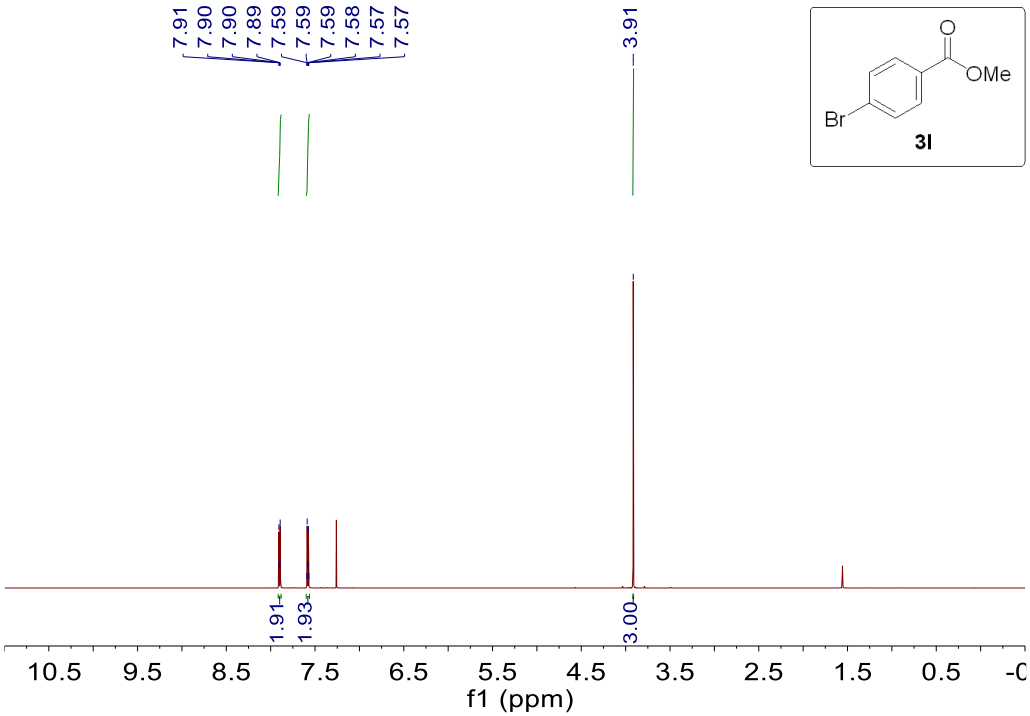
^{1}H NMR (400 MHz) spectrum of **3i** ($CDCl_3$, rt).



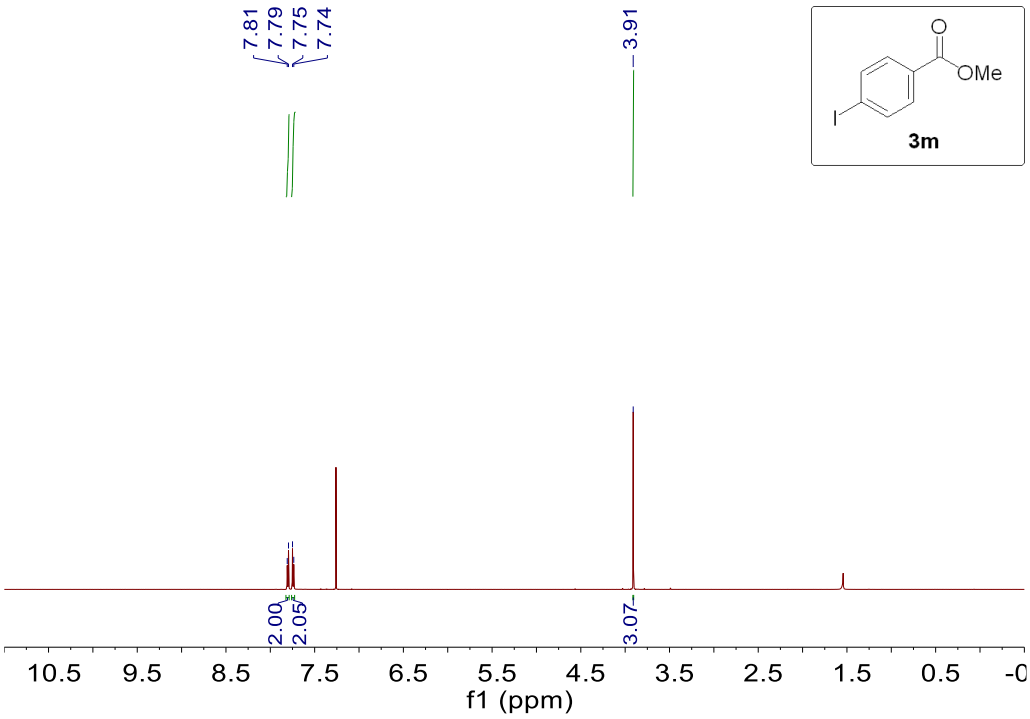
^{1}H NMR (600 MHz) spectrum of **3j** ($CDCl_3$, rt).



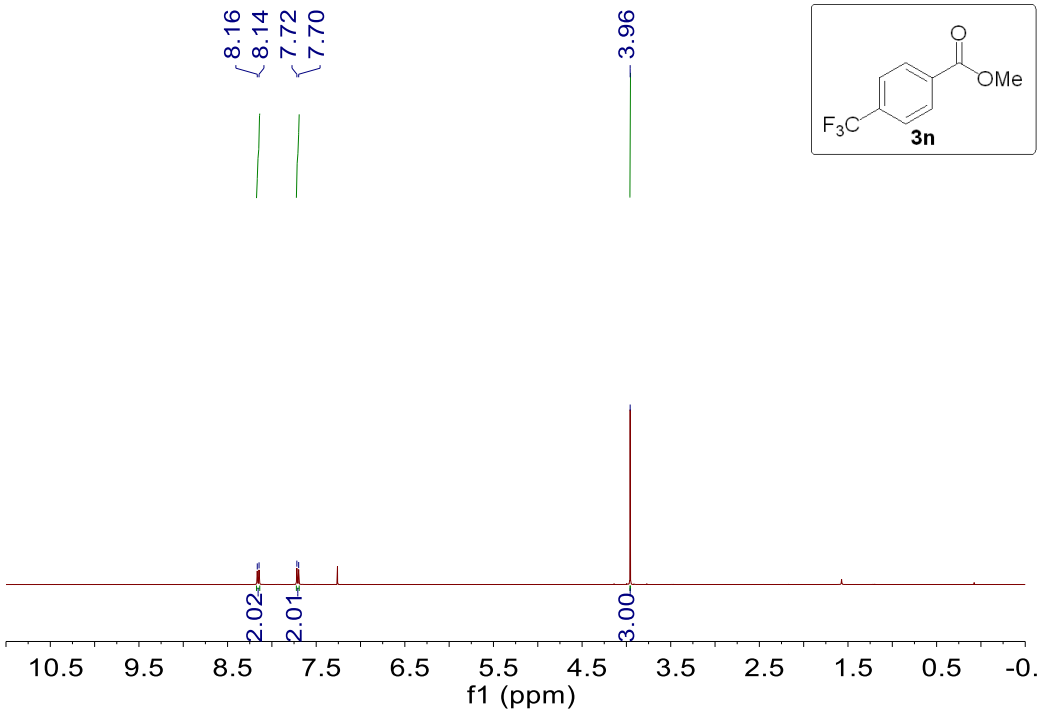
^{1}H NMR (400 MHz) spectrum of **3k** ($CDCl_3$, rt).



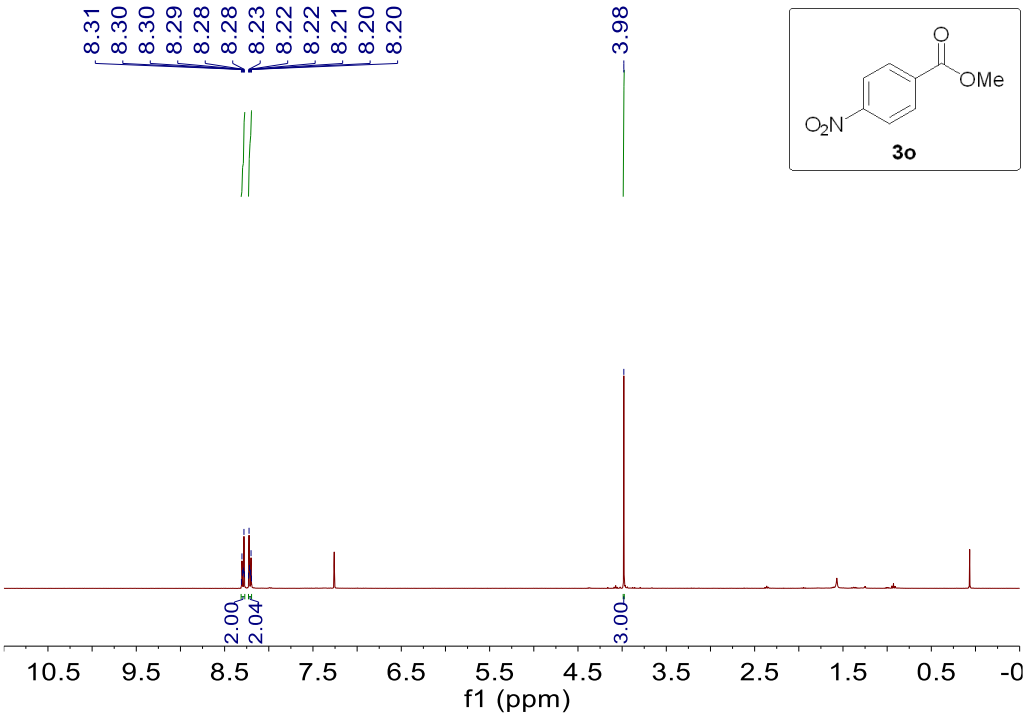
^{1}H NMR (600 MHz) spectrum of **3l** ($CDCl_3$, rt).



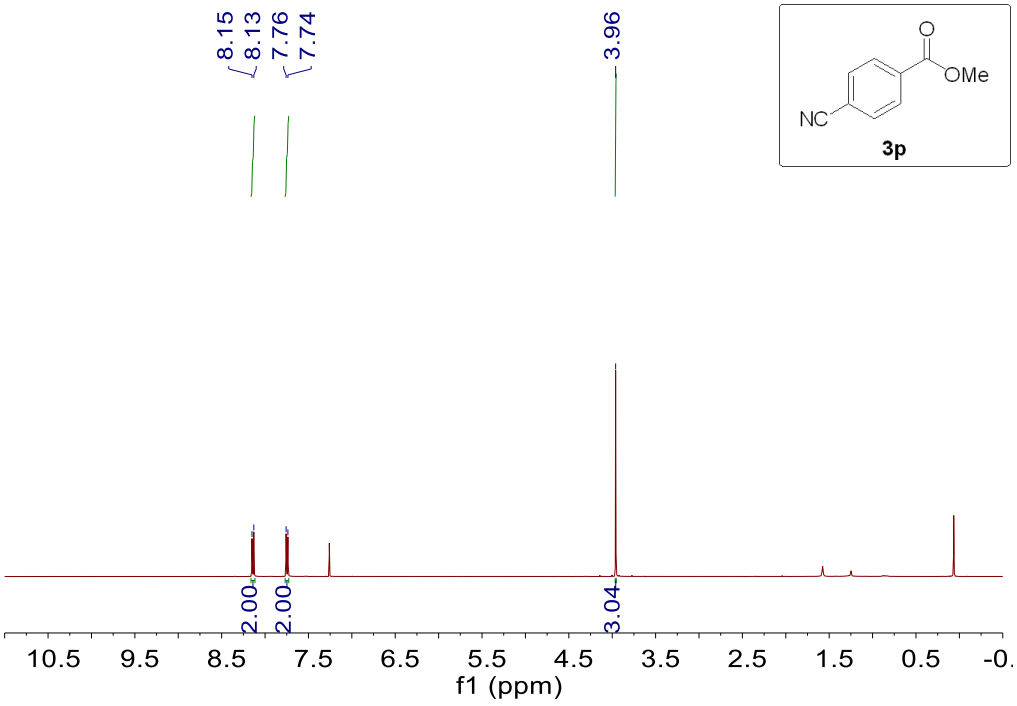
^{1}H NMR (600 MHz) spectrum of **3m** ($CDCl_3$, rt).



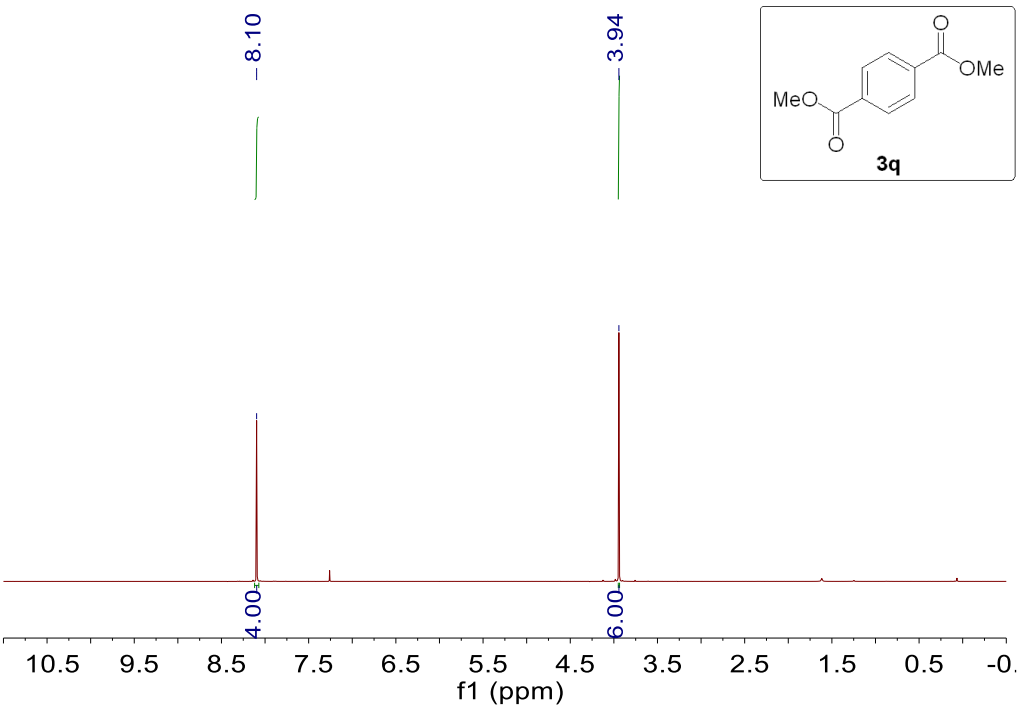
^{1}H NMR (400 MHz) spectrum of **3n** ($CDCl_3$, rt).



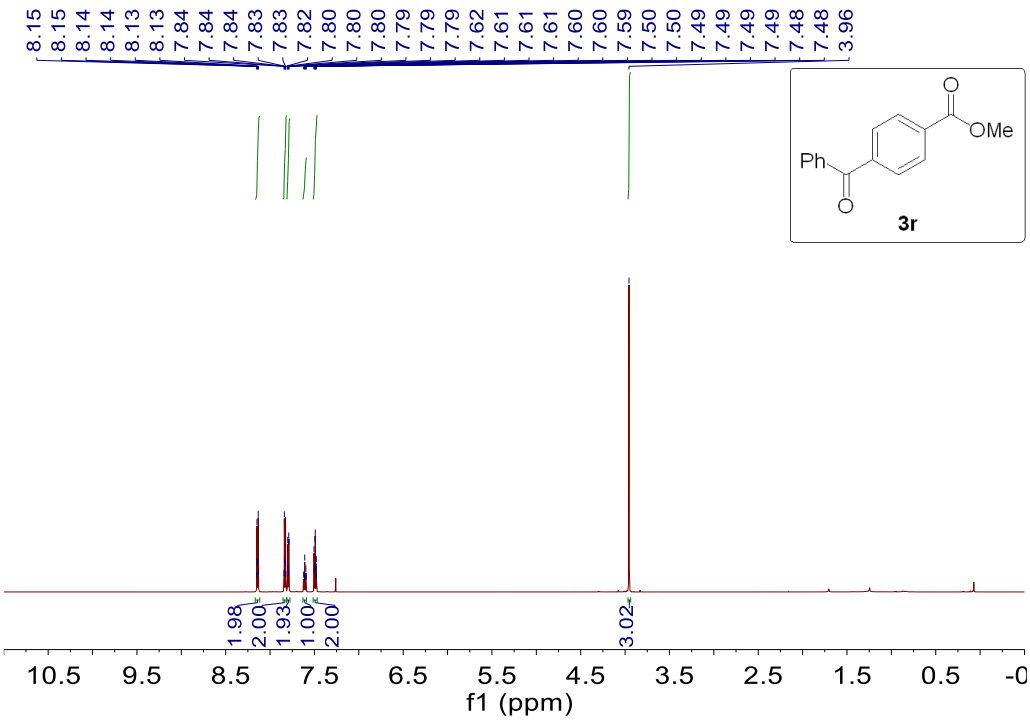
^{1}H NMR (400 MHz) spectrum of **3o** ($CDCl_3$, rt).



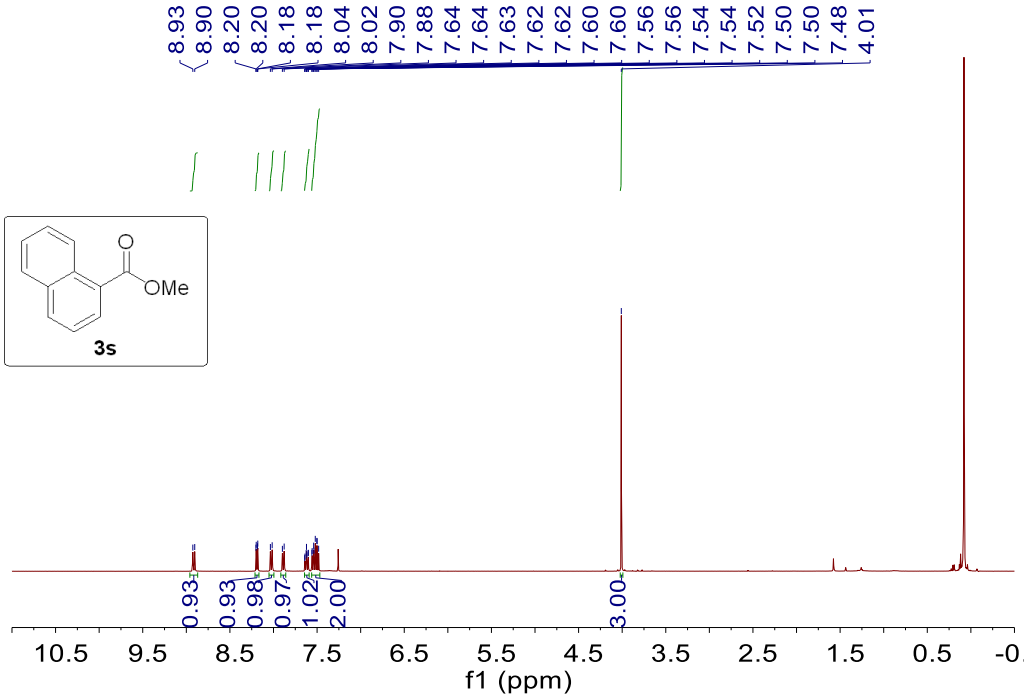
^{1}H NMR (400 MHz) spectrum of **3p** ($CDCl_3$, rt).



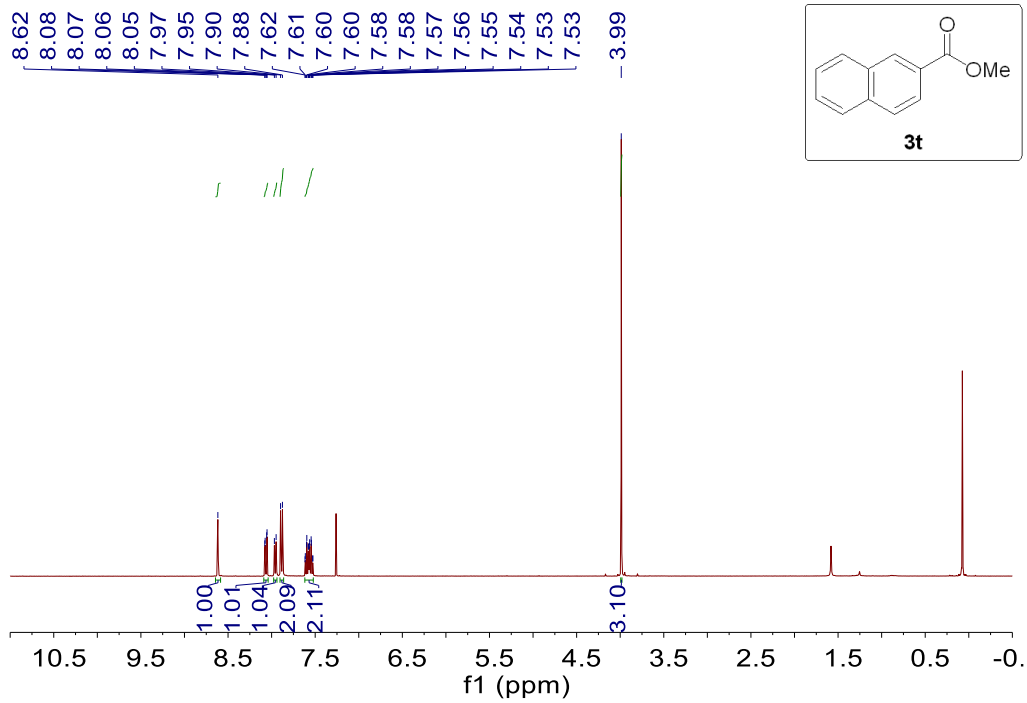
^{1}H NMR (400 MHz) spectrum of **3q** ($CDCl_3$, rt).



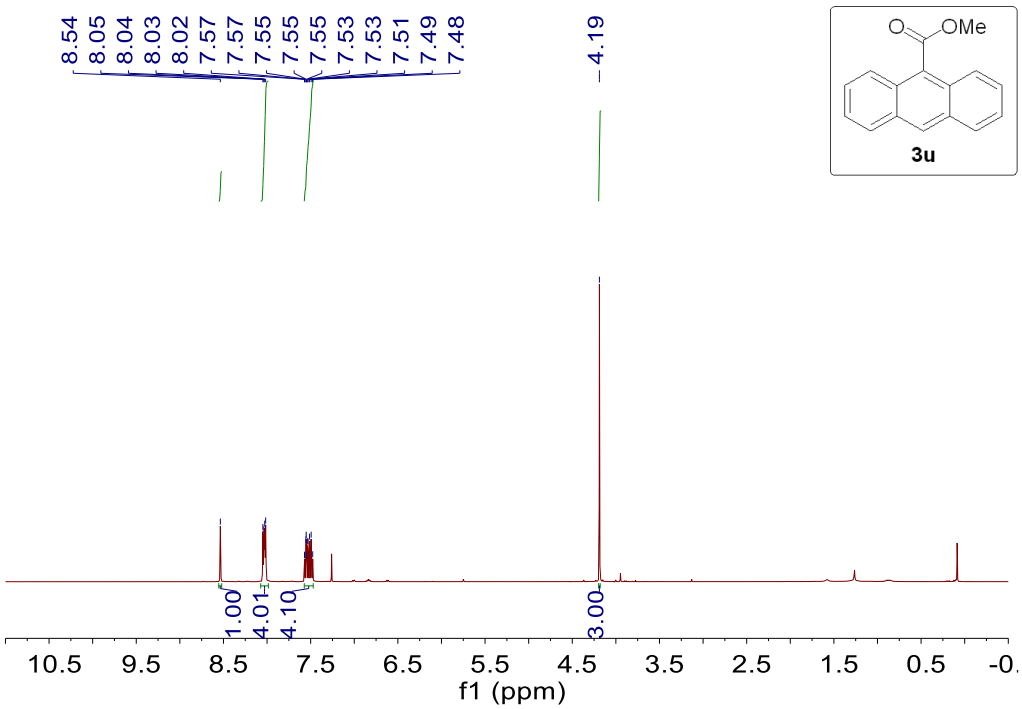
^{1}H NMR (600 MHz) spectrum of **3r** ($CDCl_3$, rt).



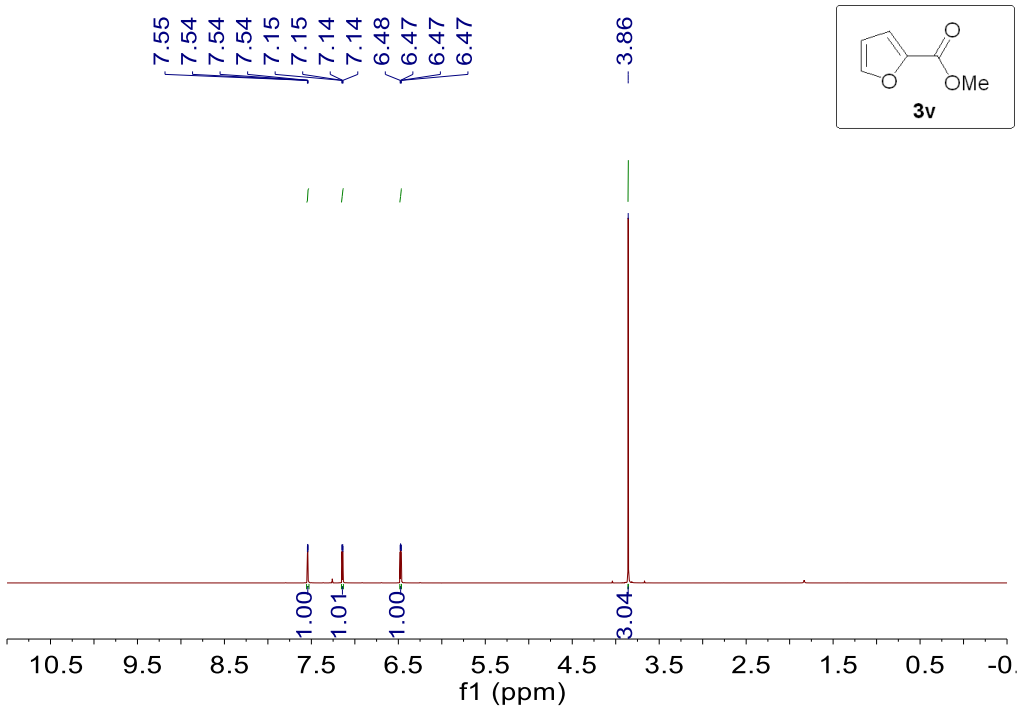
^{1}H NMR (400 MHz) spectrum of **3s** ($CDCl_3$, rt).



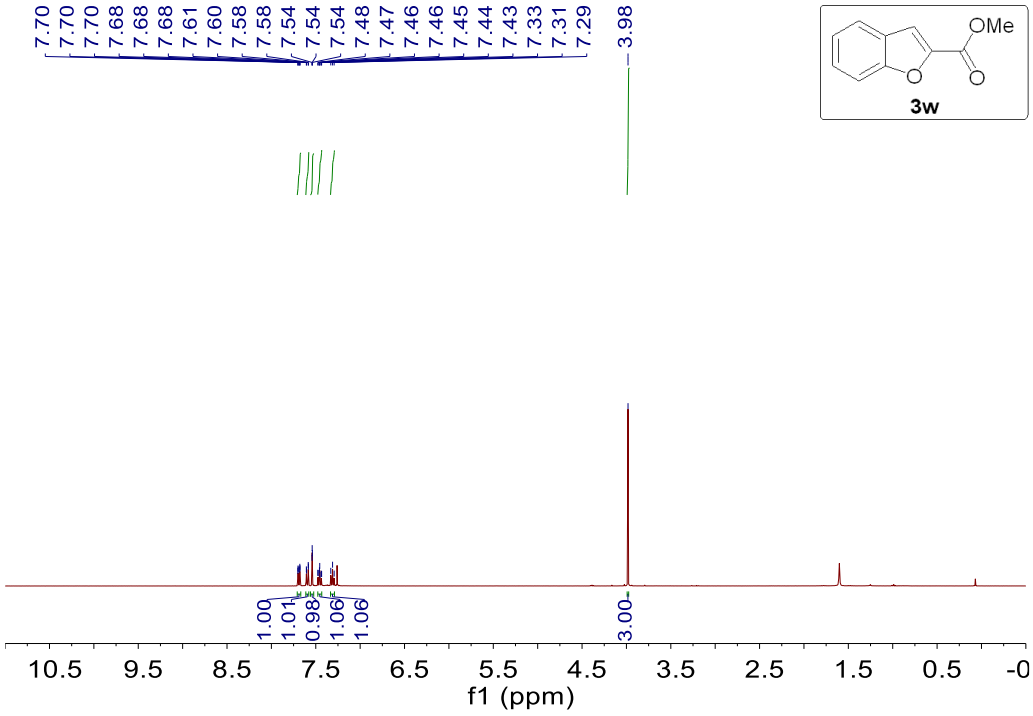
^{1}H NMR (400 MHz) spectrum of **3t** ($CDCl_3$, rt).



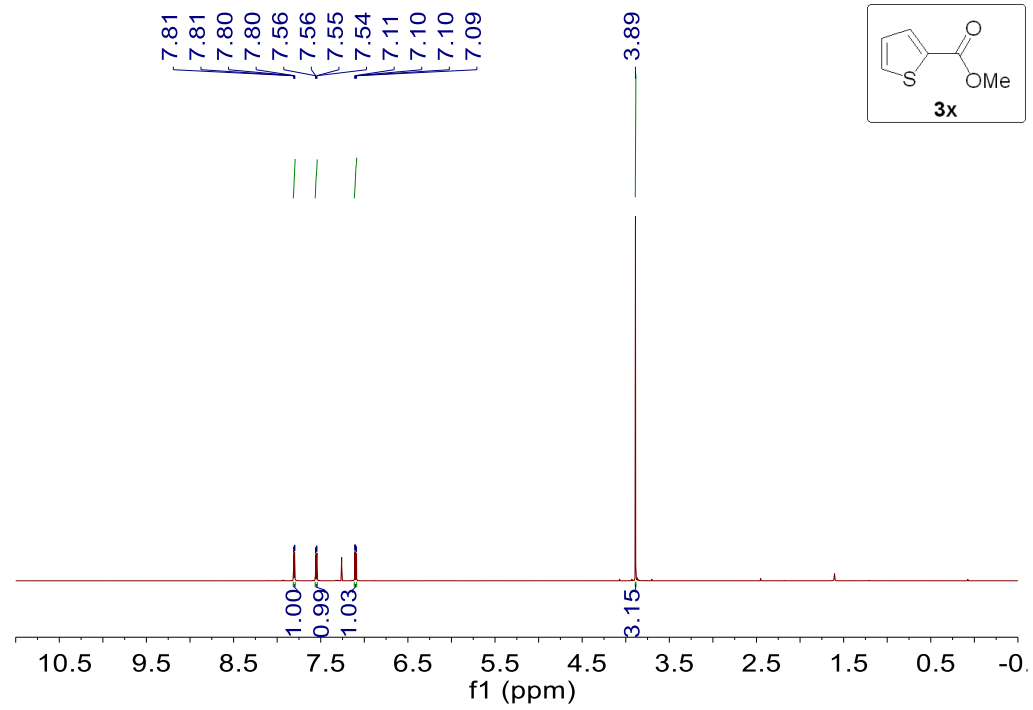
^{1}H NMR (400 MHz) spectrum of **3u** ($CDCl_3$, rt).



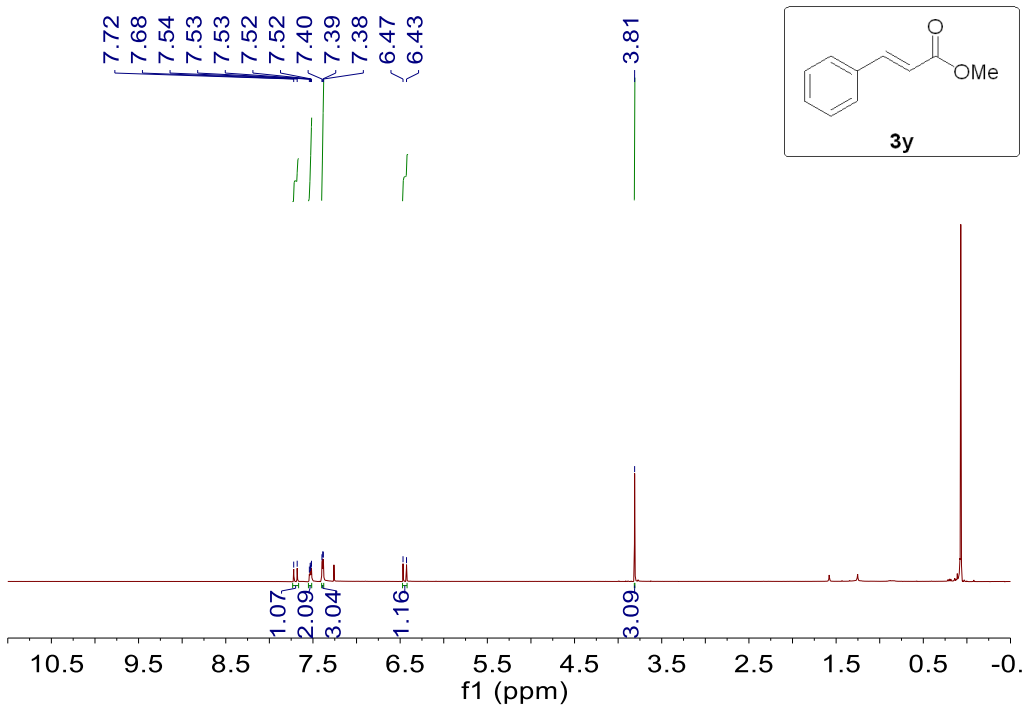
^{1}H NMR (400 MHz) spectrum of **3v** ($CDCl_3$, rt).



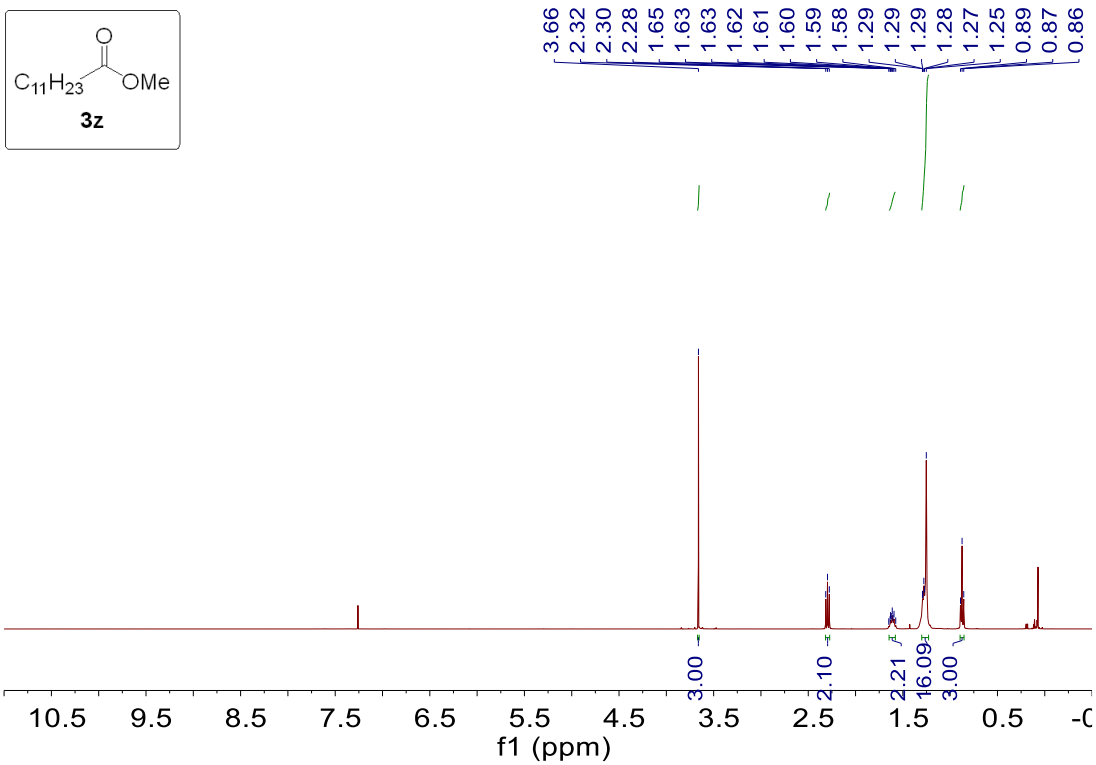
^{1}H NMR (400 MHz) spectrum of **3w** ($CDCl_3$, rt).



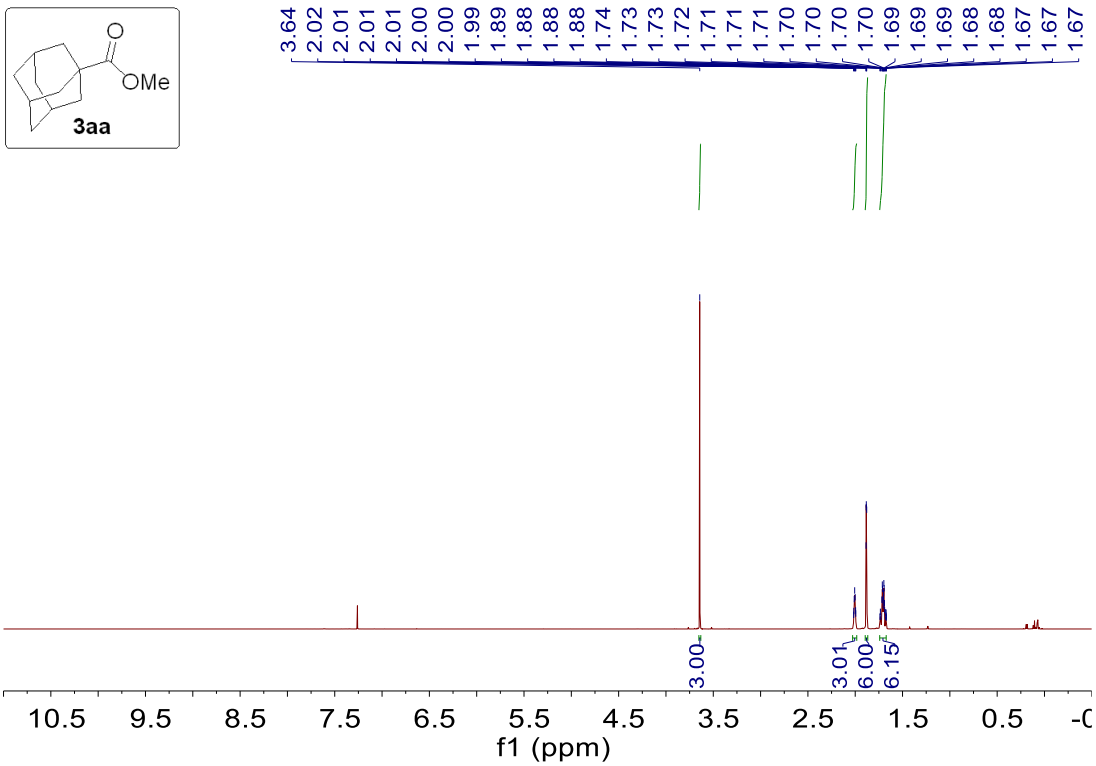
^{1}H NMR (400 MHz) spectrum of **3x** ($CDCl_3$, rt).



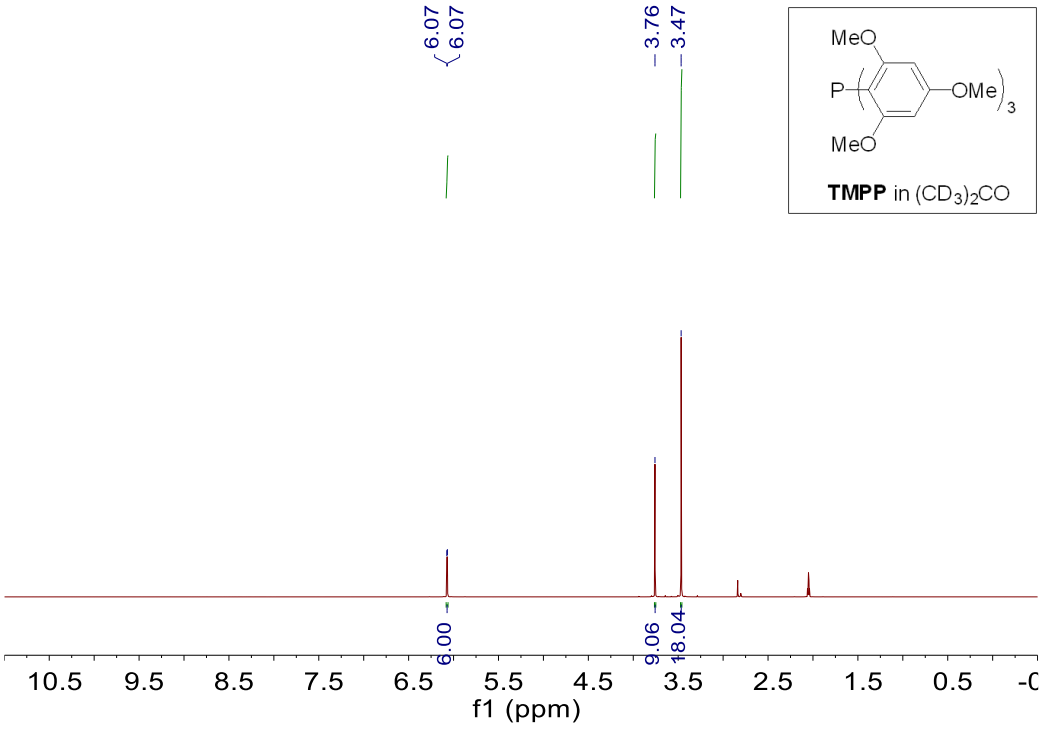
^{1}H NMR (400 MHz) spectrum of **3y** ($CDCl_3$, rt).

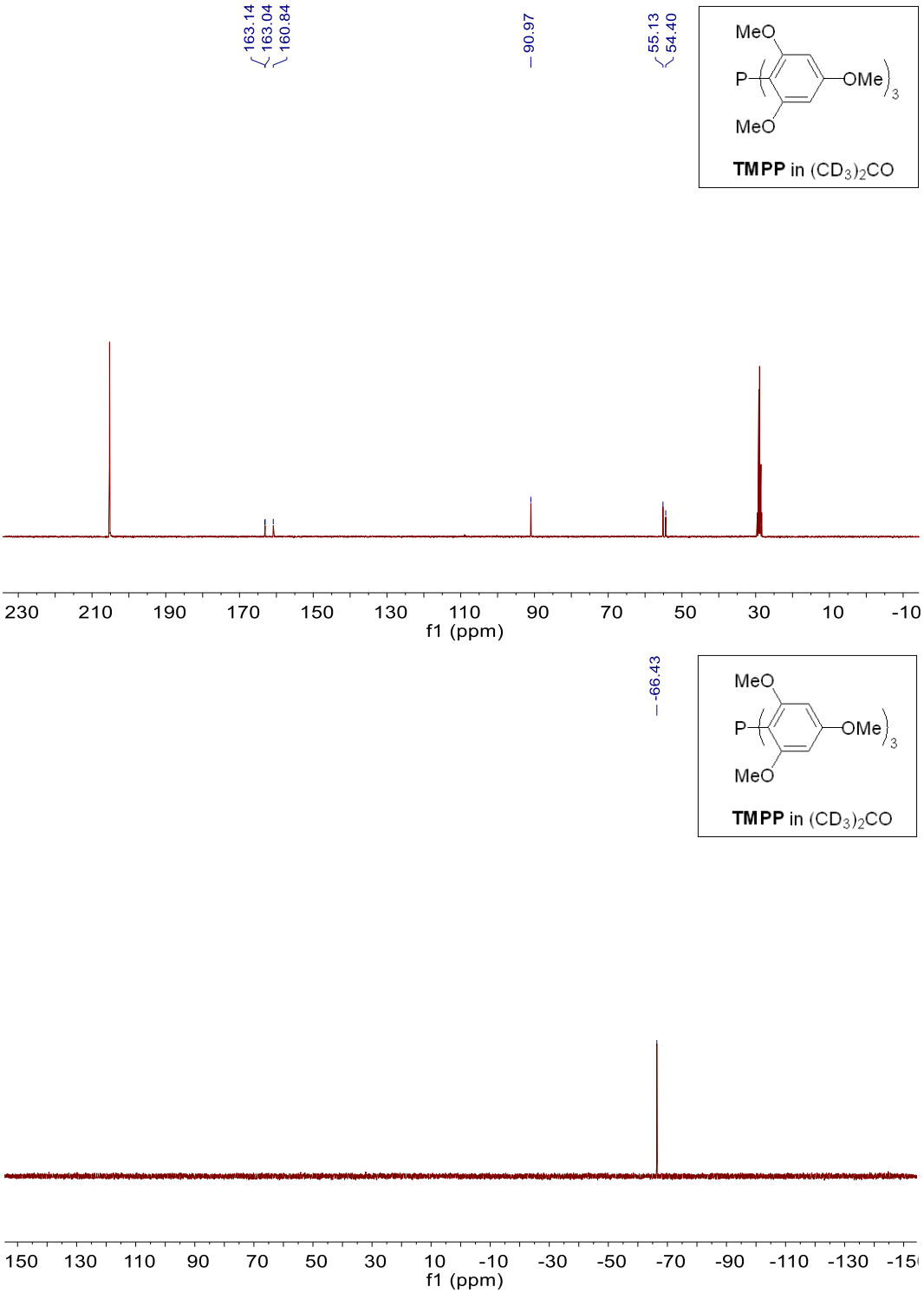


^{1}H NMR (400 MHz) spectrum of **3z** ($CDCl_3$, rt).

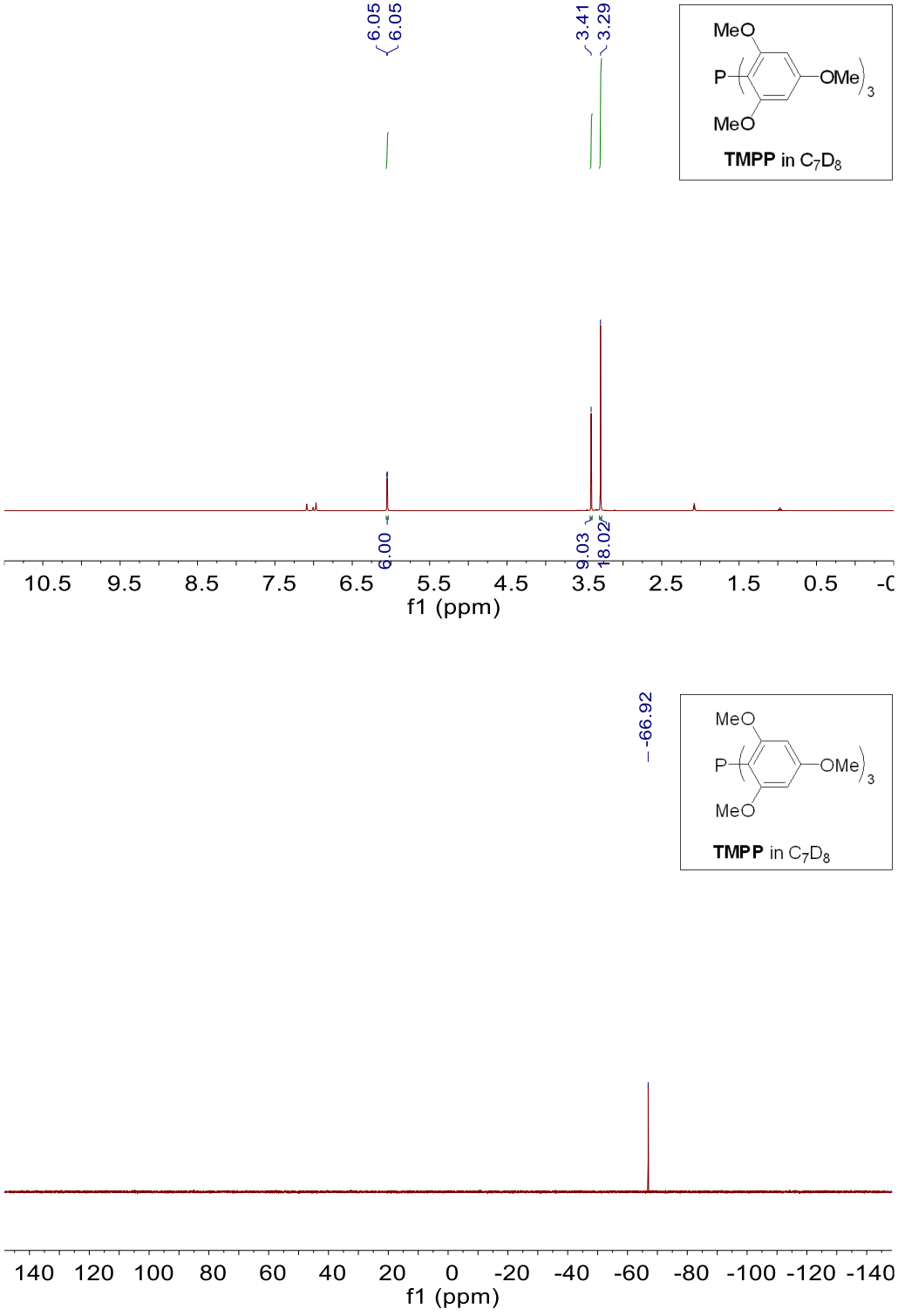


^{1}H NMR (600 MHz) spectrum of **3aa** ($CDCl_3$, rt).

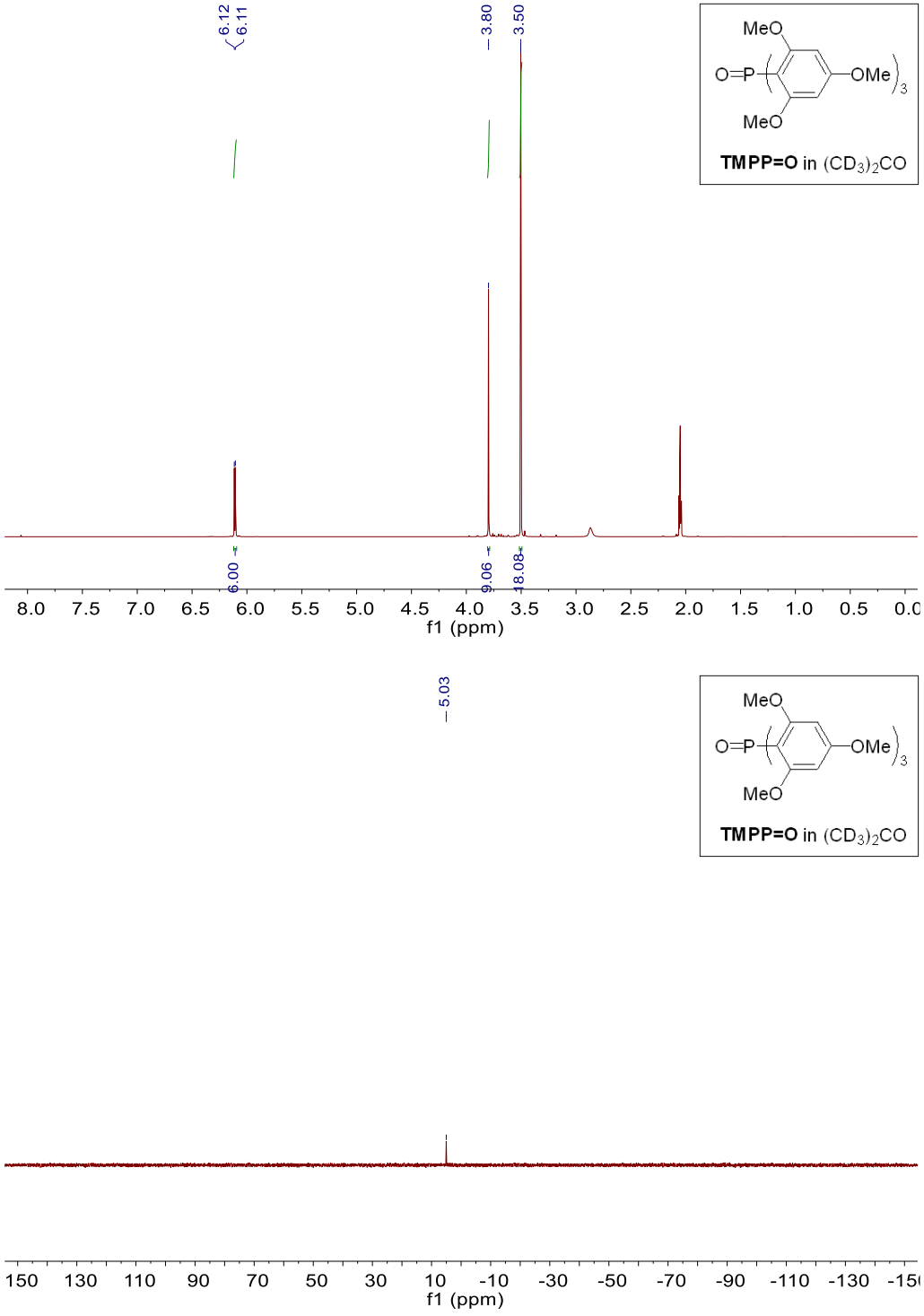




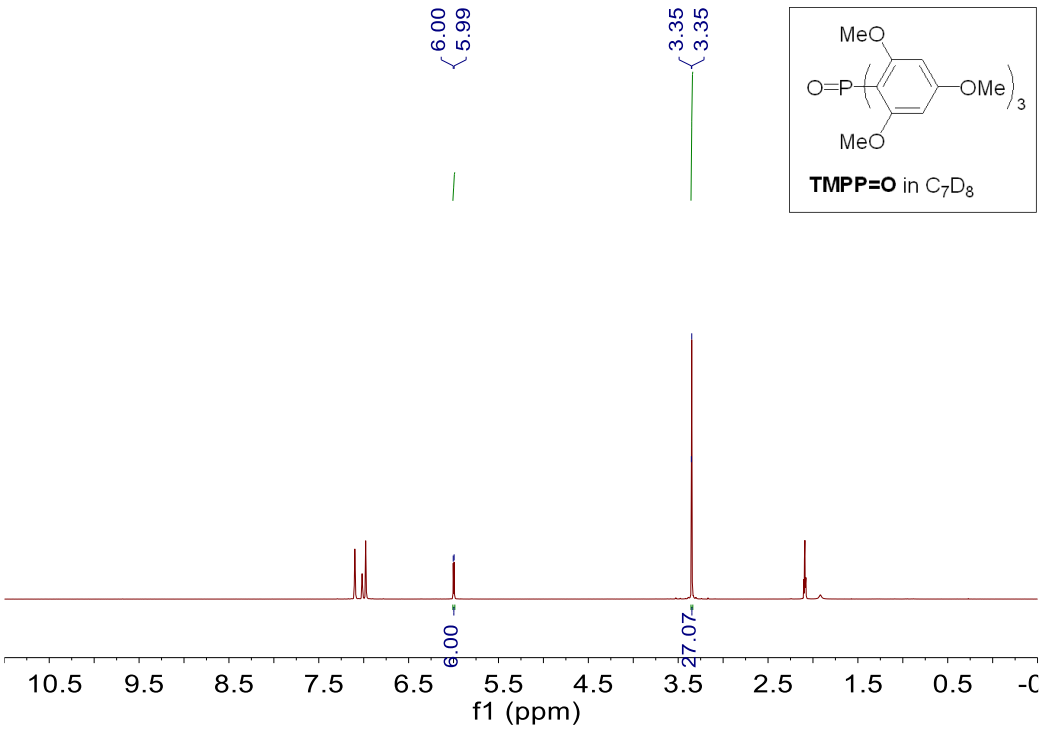
^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz) and ^{31}P NMR (162 MHz) spectra of **TMPP** ($(CD_3)_2CO$, rt).

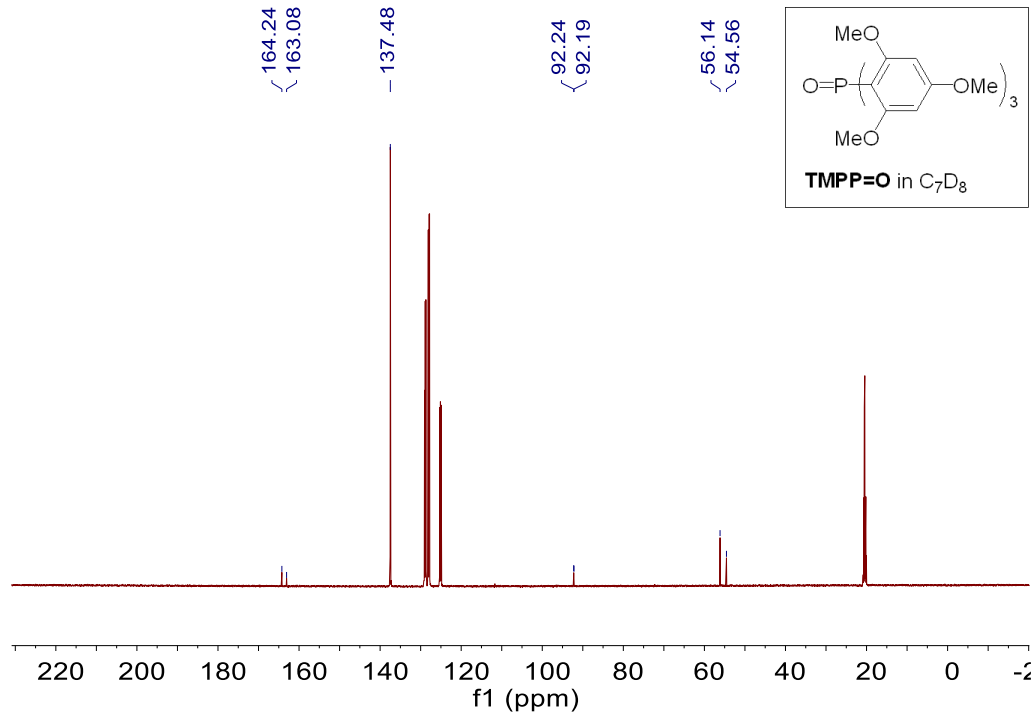


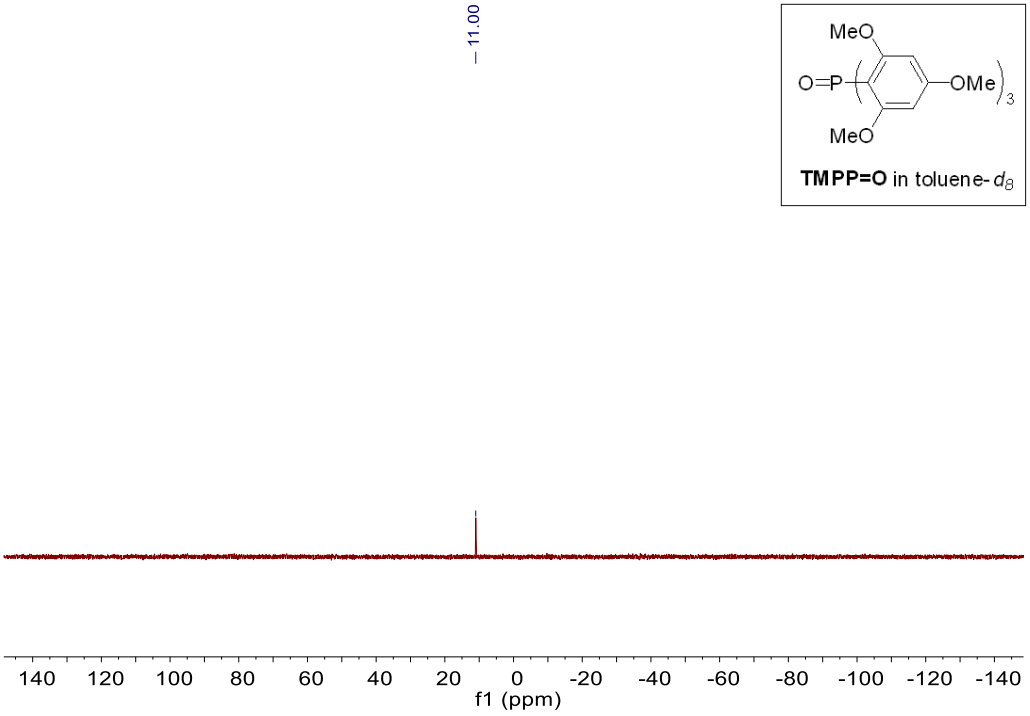
^{1}H NMR (400 MHz) and ^{31}P NMR (162 MHz) spectra of **TMPP** (C_7D_8, rt).



^{1}H NMR (400 MHz) and ^{31}P NMR (162 MHz) spectra of **TMPP=O** ($(CD_3)_2CO$, rt).


6.00
5.99
3.35
3.35
MeO
O=P
OMe
3
MeO
TMPP=O in C7D8
6.00
27.07
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)


164.24
163.08
137.48
92.24
92.19
56.14
54.56
MeO
O=P
OMe
3
MeO
TMPP=O in C7D8
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)



^{1}H NMR (400 MHz), ^{13}C NMR (151 MHz), and ^{31}P NMR (162 MHz) spectra of **TMPP=O** (C_7D_8, rt).

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Conclusion

In this PhD Thesis, the Author focuses on the functionalizations of acyl fluorides serving as acyl and aryl sources to construct carbon-carbon and carbon-heteroatom bonds. Nickel/copper-cocatalyzed decarbonylative silylation of acyl fluorides with an inexpensive and stable mono-phosphine PPh_3 was disclosed, affording a wide range of electronically and sterically (hetero)arylated silanes. Subsequently, we discovered a practical method to synthesize various arylstannanes via ligand-free nickel-catalyzed decarbonylative stannylation of acyl fluorides. In addition, a direct and efficient method for the conversion of acyl halides to 2-substituted propenes has been developed, in which $AlMe_3$ acts as a methylenating reagent with the aid of a catalytic amount of 1,3-bis(diphenylphosphino)methane (DPPM) to adjust an acidity of the catalytic reaction system to retard dimerization of the products. Then, an unprecedented process for C(aryl)–OMe bond cleavage of tris(2,4,6-trimethoxyphenyl)phosphine (TMPP) under transition-metal-free conditions, in which a diverse of acyl fluorides were subjected to esterification to give the corresponding aromatic esters in high yields. This PhD thesis expands the chemistry of acyl fluorides as carboxylic acid derivatives in terms of carbon-carbon and carbon-heteroatom bond formations and develops efficient methods to synthesize useful compounds in organic synthesis including arylsilanes, arylstannanes, 2-substituted propenes, as well as aromatic esters.

Chapter 2. Nickel/Copper-Cocatalyzed Decarbonylative Silylation of Acyl Fluorides

In this Chapter, the Author discloses the nickel/copper-catalyzed decarbonylative silylation of acyl fluorides with an inexpensive and stable mono-phosphine PPh_3. The experimental results revealed that the presence of the nickel catalyst, the copper salt, PPh_3, and acyl fluorides are all key components to this transformation. Notably, no decarbonylative silylation products and an unreacted silylborane were observed by employing acyl chlorides instead of acyl fluorides, which further demonstrated the unique advantages of acyl fluorides as the substrates. A wide range of electronically and sterically (hetero)arylated acyl fluorides were well tolerated in the present reaction, including alkoxyl, halogen, amine, and ester-containing functional groups, which are subjected to be silylated under transition-metal catalytic system. On the other hand, the utility of this method was further proved by good performance of different silylboranes as

coupling partners. Moreover, carboxylic acid-containing drug-probenecid and bioactive estrone derivatives are also viable in two-step deoxyfluorination and decarbonylative silylation reactions. Such transformation not only extended the functionalization of acyl fluorides in carbon-heteroatom bond formation, but a useful complement to other silylation processes.

Chapter 3. Nickel-Catalyzed Decarbonylative Stannylation of Acyl Fluorides under Ligand-Free Conditions

In Chapter 3, the Author discovered a practical method to synthesize various arylstannanes via ligand-free nickel-catalyzed decarbonylative stannylation of acyl fluorides. The experimental results revealed that the presence of cesium fluoride is vital to activate trimethyl(tributylstannyl)silane to facilitate a transmetalation step. A wide range of electronically and sterically (hetero)arylated acyl fluorides were well tolerated in the present reaction, especially for halogens and oxygen-containing functional groups. A sequential decarbonylative stannylation/Migita-Kosugi-Stille reaction in one-pot further demonstrated the utility of this method. This newly developed methodology showed good functional-group compatibility via C–F bond cleavage and C–Sn bond formation, which also extended the functionalization of acyl fluorides in carbon-heteroatom bond formation.

Chapter 4. Bidentate Phosphine-Assisted Methylenation of Acyl Halides with $AlMe_3$

In this Chapter, the Author developed 1,3-bis(diphenylphosphaneyl)methane (DPPM) assisted methylenation of acyl halides and $AlMe_3$ to 2-substituted propenes. A wide range of electronically and sterically aryl, alkenyl, and aliphatic acyl chlorides and fluorides are well tolerated, especially for halogens, methyl ester, and ether-containing functional groups. Other carbonyl compounds such as phenolic ester and thioester also undergo smoothly methylenation. Furthermore, double methylenation of two carbonyl-containing compounds and gram-scale synthesis provided satisfactory results, which can offer a direct route to divinylated molecules not readily available by other synthetic methods. Mechanistic studies demonstrated that the methylenation process of acyl halides was promoted by the in-situ formed Lewis acid $AlMe_2X$ (X = F, Cl), a

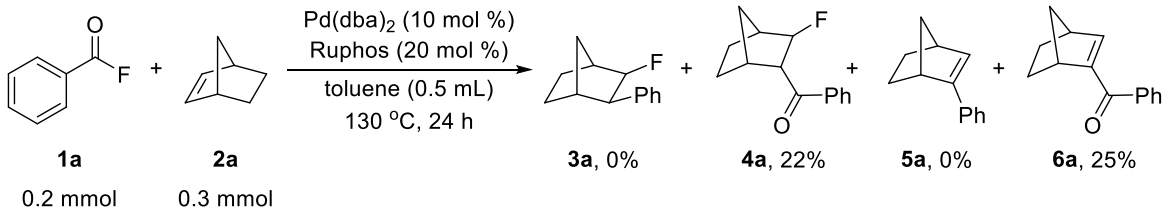
catalytic amount of DPPM could retard the dimerization of the products to the formation of 2,3-dihydro-1*H*-indene derivative.

Chapter 5. Methoxylation of Acyl Fluorides by C–OMe Bond Cleavage in TMPP under Metal-Free Conditions

In this Chapter, the Author described methoxylation of acyl fluorides with tris(2,4,6-trimethoxyphenyl)phosphine (TMPP) to afford a wide range of esters in high yields. Notably, an inert C(aryl)–OMe bond was cleaved under transition-metal-free conditions. This transformation is featured by a challenging aryl C(sp^2)–OMe bond cleavage under metal-free conditions, installation of conventional leaving group (OMe) into the desired products, utilization of TMPP as a methoxylating agent.

Future Perspective

This Thesis describes the studies of carbonyl retentive and decarbonylative transformations of acyl fluorides. Although the role of acyl fluorides as aryl and acyl sources has been disclosed, the addition of acyl fluorides as fluorine and aryl or acyl sources to unsaturated compounds such as alkynes or alkenes has not been investigated. Such transformations are atom-economical and highly appealing. The Author attempted the addition of acyl fluorides to norbornene via the palladium/Ruphos catalytic system in toluene at 130 ℃ for 24 h. Unfortunately, no decarbonylative product **3a** was formed, and carbonyl retentive product **4a** and byproduct **6a** were observed in 22% and 25% yields, respectively. In the future, the design of new and suitable ligand is a crucial key to succeed this transformation.



1a 0.2 mmol + **2a** 0.3 mmol → **3a**, 0% + **4a**, 22% + **5a**, 0% + **6a**, 25%

List of Publications

Publications Related to the Ph.D Thesis

Chapter 2

1) Nickel/Copper-Cocatalyzed Decarbonylative Silylation of Acyl Fluorides
Xiu Wang, Zhenhua Wang, Yasushi Nishihara
Chem. Commun. **2019***, 55,* 10507-10510.

Chapter 3

2) Nickel-Catalyzed Decarbonylative Stannylation of Acyl Fluorides under Ligand-Free Conditions
Xiu Wang, Zhenhua Wang, Li Liu, Yuya Asanuma, Yasushi Nishihara
Molecules **2019**, *24*, 1671.

Chapter 4

3) Synthesis of 2-Substituted Propenes by Bidentate Phosphine Assisted Methylenation of Acyl Fluorides and Acyl Chlorides with $AlMe_3$
Xiu Wang, Zhenhua Wang, Yuya Asanuma, Yasushi Nishihara
Org. Lett. **2019**, *21*, 3640-3643.

Chapter 5

4) Methoxylation of Acyl Fluorides by C–OMe Bond Cleavage in Tris(2,4,6-trimethoxyphenyl)-phosphine under Metal-Free Conditions
Xiu Wang, Zhenhua Wang, Yasushi Nishihara
manuscript preparation

Other Publications

5) Nickel-catalysed decarbonylative borylation of aroyl fluorides
Zhenhua Wang, Xiu Wang, Yasushi Nishihara
Chem. Commun. **2018**, *54*, 13969-13972.

6) PPh_3-Assisted Esterification of Acyl Fluorides with Ethers via C(sp^3)–O Bond Cleavage Accelerated by TBAT
Zhenhua Wang, Xiu Wang, Yasushi Nishihara
Catalysts **2019**, *9*, 574.

7) Nickel-Catalyzed Decarbonylative Cyanation of Acyl Chlorides
Zhenhua Wang, Xiu Wang, Yasuyuki Ura, Yasushi Nishihara
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Nickel/copper-cocatalyzed decarbonylative silylation of acyl fluorides†

Xiu Wang,[a] Zhenhua Wang[a] and Yasushi Nishihara *[b]

Ni/Cu-cocatalyzed decarbonylative silylation of acyl fluorides with silylboranes has been developed to afford various arylsilanes with high efficiency and good functional-group compatibility *via* carbon–fluorine bond cleavage and carbon–silicon bond formation. Such transformation can not only extend the functionalization type of acyl fluorides but complement the synthetic route for arylsilanes.

Since organosilicon compounds are of great importance in organic synthesis,[1] drug discovery[2] and materials science,[3] various synthetic strategies have been established by constructing the C–Si bond. Traditional synthetic methods of arylsilanes involve the reactions of Grignard or organolithium reagents with silyl electrophiles,[1a,4] in which ester and ketone functional groups cannot be incorporated. Alternatively, transition-metal-catalyzed silylation of aryl halides has been developed for the preparation of arylsilanes.[5] Although defluorosilylation of fluoroarenes *via* C–F bond activation has been reported recently, the synthesis of the starting materials requires multi-step reactions.[6]

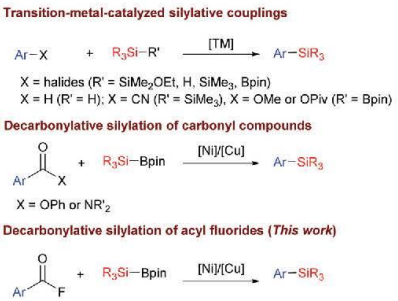
In addition, a direct C–H silylation of unreactive aromatic compounds with hydrosilanes was also investigated to obtain arylsilanes.[7] Furthermore, silylation of nitriles with disilanes *via* C–CN bond cleavage[8] and of pivalates or anisoles with silylboranes *via* C–O bond cleavage[9] provided a new access to arylsilanes (Scheme 1a).

Utilizing decarboxylation/decarbonylation, transformations of carboxylic acid and their derivatives into valuable compounds under transition metal catalysis have drawn much attention owing to their natural abundance and easy availability.[10] Among them, an early study found that palladium-catalyzed silylation of acyl chlorides bearing strong electron-withdrawing groups with hexamethyldisilanes gave a mixture of acylsilane and arylsilane, in which the selective decarbonylative silylation of acyl chlorides was observed with chlorinated disilanes.[11]

Rueping[12] and Shi[13] independently succeeded in nickel/copper-cocatalyzed decarbonylative silylation of phenolic esters *via* C–O bond cleavage. Building upon the previous work, Reuping expanded the decarbonylation silylation strategy for arylamides *via* C–N bond cleavage (Scheme 1b).[14] However, phenolic esters and arylamides are generally prepared from the corresponding carboxylic acids *via* acyl chlorides in two steps, and a large amount of waste derived from phenols and amines is generated after the reaction.[12,14]

On the other hand, acyl fluorides display much superiority over the corresponding carboxylic derivatives, showing great stability and high reactivity.[15] Moreover, acyl fluorides acting as the acyl fragment without a CO loss in transition-metal-catalyzed transformations have been witnessed in cross-couplings of Negishi,[16] Hiyama,[17] Suzuki–Miyaura,[18] and other reactions such as reductive coupling with vinyl triflates,[19] reduction,[20] boroacylation of allenes,[21] and C–H coupling with azoles[22] to give the corresponding ketones or aldehydes.

Recently, reactions of acyl fluorides serving as an arylation moiety *via* a decarbonylative process for C–C bond formation have



Scheme 1 Synthetic routes for arylsilanes.

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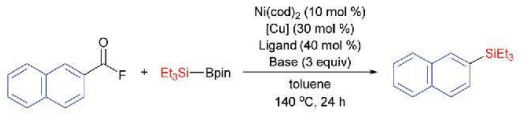
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data and copies of ^{1}H, $^{13}C\{^{1}H\}$ and $^{19}F\{^{1}H\}$ NMR spectra. See DOI: 10.1039/c9cc05325e

been extensively investigated, including trifluoromethylation,[23] reduction,[20b] Suzuki–Miyaura type-arylation,[24] and direct C–H arylation.[25] We have also reported the $Ni(cod)_2$/DPPE catalytic system for decarbonylative alkylation of acyl fluorides.[26] The outcome suggested that utilization of acyl fluoride is the key to this transformation and other acyl halides cannot be participated.

Due to the indispensable and versatile main group elements, namely, boron, silicon, and tin in cross-coupling chemistry,[27] carbon–heteroatom bond-forming reactions of acyl fluorides are highly desired. Encouraged by the unique nature of acyl fluorides in various decarbonylative C–C bond-forming reactions and our continuous interest in acyl halides in cross-coupling reactions,[26,28] we have developed nickel-catalyzed borylation[29] and stannylation[30] of acyl fluorides with diborons and silylstannanes, respectively, in a decarbonylation manner. Herein, we report our new approach to the synthesis of arylsilanes by nickel/copper-cocatalyzed decarbonylative silylation of acyl fluorides with silylboranes (Scheme 1c).

Initially, we chose the reaction of 2-naphthoyl fluoride (**1a**) with silylborane **2a** under basic conditions as the model reaction. An inexpensive PPh_3 ligand was preferable due to its excellent performance in nickel-catalyzed decarbonylative borylation.[29] However, only 5% of silylated product **3a** was detected, along with a large amount of unconsumed **2a** (Table 1, entry 1), where 22% of naphthalene from decarbonylative reduction and 58% of 2,2′-binaphthalene derived from decarbonylative homocoupling were observed. This outcome revealed that the nickel/PPh_3 catalytic system cannot efficiently activate **2a** to promote transmetalation of the oxidative adduct. Thus, CuOAc was added because of the reported profound effect of copper salts in activation of the Si–B bond.[31] As expected, 85% of **3a** was obtained, along with 10% of naphthalene as a by-product (entry 2). Notably, cooperation of the copper salt suppressed the competitive decarbonylative homocoupling and reduction.

Table 1 Optimization of the reaction conditions[a]



1a 2a 3a

Entry	[Cu]	Ligand	Base	3a[b] (%)
1	—	PPh_3	KF	5
2	CuOAc	PPh_3	KF	85
3	CuOAc	PCy_3	KF	50
4	CuOAc	P^nBu_3	KF	32
5	CuOAc	$P(OPh)_3$	KF	11
6	CuOAc	PPh_3	CsF	18
7	CuOAc	PPh_3	NaF	49
8	CuOAc	PPh_3	LiF	45
9	CuOAc	PPh_3	KOAc	71
10	$Cu(OAc)_2$	PPh_3	KF	31
11	$CuCl_2$	PPh_3	KF	0
12	CuF_2	PPh_3	KF	77
13[c]	CuF_2	PPh_3	KF	89 (85)
14[d]	CuF_2	PPh_3	KF	0
15	CuF_2	—	KF	<1
16	CuF_2	PPh_3	—	46
17[e]	CuF_2	PPh_3	KF	0

[a] **1a** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol) in toluene (1.0 mL) at 140 °C for 24 h. [b] Determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard. The isolated yield is given in parentheses. [c] 150 °C. [d] Without $Ni(cod)_2$. [e] 2-Naphthoyl chloride instead of **1a**.

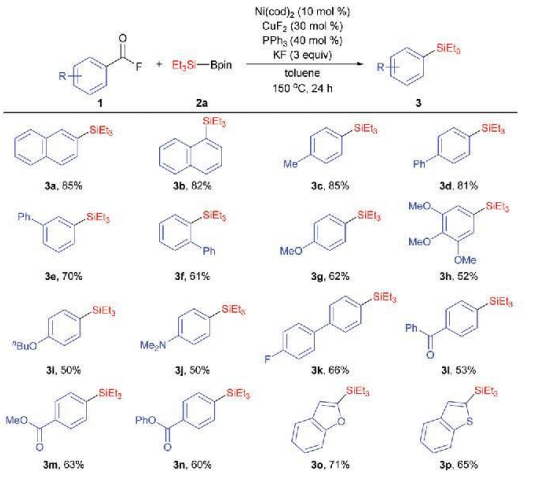
Other monodentate phosphine ligands such as PCy_3, P^nBu_3, and $P(OPh)_3$ showed moderate to poor activities in this transformation (entries 3–5). Although acyl fluorides could act as a mild base in some cases,[24] an exogenous base is still required in the present silylation reaction. Among the bases used, KF gave the best result (entry 2 and entries 6–9). Various cuprous and cupric salts were also examined (entries 10–13 and Table S5, ESI†), and CuF_2 showed a superior result with the target product **3a** in 89% yield (entry 13). Screening of the reaction temperatures demonstrated that a higher reaction temperature greatly increased the conversion of **1a** to the decarbonylative silylation product **3a**, suppressing the formation of the homocoupled product (Table S6, ESI†). Control experiments shown in entries 14 and 15 confirmed the crucial factors of $Ni(cod)_2$ and PPh_3 to succeed in this transformation; no or a trace of **3a** was observed. In the absence of KF, only 46% formation of **3a** was detected (entry 16). In sharp contrast, upon employing 2-naphthoyl chloride instead of **1a** under the optimized reaction conditions, **2a** remained unreacted and no silylation product **3a** was formed (entry 17). We reasoned that the oxidative adduct $NiAr(Cl)(PPh_3)_2$ cannot undergo ligand exchange with silylboranes.[24] This different reactivity demonstrated the unique nature of acyl fluorides in the present silylation. It is noteworthy that no acylsilane in a retentive fashion was detected in all cases, suggesting that PPh_3 with a weak coordinating ability favors easy dissociation from a nickel center, which is favorable for facile CO migration and extrusion.

With the optimized reaction conditions in hand, a wide range of acyl fluorides were investigated as shown in Table 2. The π-extended aromatic acyl fluorides could be accommodated, affording naphthylsilanes **3a** and **3b** in 85% and 82% yields, respectively. The benzoyl fluoride with a methyl group substituted at the *para*-position was well tolerated in this reaction, affording the target product **3c** in 85% yield.

A steric effect was illustrated by the phenyl-substituted substrates at the *ortho*-, *meta*-, and *para*-positions; *p*-phenylbenzoyl fluoride (**1d**) led to a higher yield than its *m*-phenyl- (**1e**) and *o*-phenyl (**1f**) counterparts. Other electron-rich alkoxy groups such as *p*-methoxy (**3g**), 3,4,5-trimethoxy (**3h**) and *p*-butoxy (**3i**) were also well tolerated during the reaction, although the Ni-catalyzed silylation *via* C–O bond cleavage has been reported at a lower temperature.[9]

This protocol tolerated acyl fluorides bearing functional groups at the *para*-position, including amine, fluoride, ketone, and methyl ester, resulting in the formation of the desired products **3j**–**3m** in 50–66% yields. In particular, the phenolic ester skeleton (**3n**) was reported as a reactive electrophile under the nickel/copper co-catalysis in a decarbonylative silylation.[12,13] Therefore, our method could be a useful complement to other

Table 2 Decarbonylative silylation of acyl fluorides[a,b]

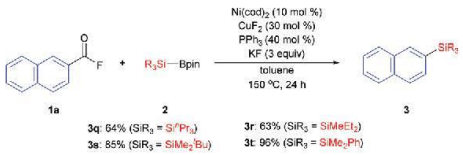


[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), CuF_2 (0.06 mmol), PPh_3 (0.08 mmol), KF (0.6 mmol), toluene (1 mL), 150 °C, 24 h. [b] Isolated yields.

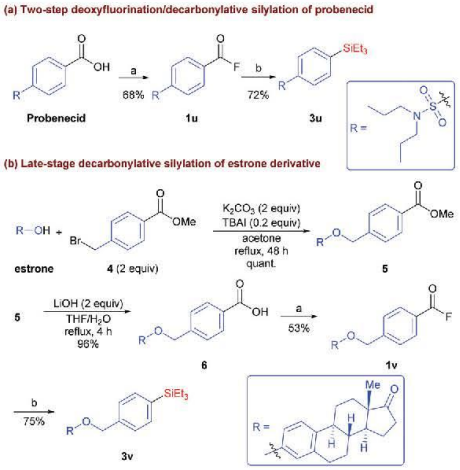
silylation processes that are inaccessible for compatibility of alkoxy and phenolic ester groups.

Furthermore, the reaction could be extended to heteroatom-containing acyl fluorides, affording arylsilanes **3o** and **3p** in 71% and 65% yields, respectively. Unfortunately, other surrogate alkenyl and aliphatic acyl fluorides failed to participate in this transformation. For example, only a trace amount of the decarbonylative silylation product was detected when dodecanoyl fluoride was employed as the coupling partner (Scheme S1, ESI†).

Different silyl groups in organosilicon compounds can control the reactivity in the Hiyama reaction to construct new C–C bonds,[32] and in halogenation to provide new building blocks for further transformations.[6a,9b,33] Thus, electronic and steric effects of the silicon moiety on the present decarbonylative silylation were tested by using four types of silylboranes under the standard reaction conditions (Scheme 2). All of the silylboranes are proved to be good coupling partners using 2-naphthoyl fluoride (**1a**), yielding the corresponding arylsilanes **3q**–**3t** in 63–96% yields. It is noteworthy that $^{n}Pr_3Si$–Bpin could be converted into the desired product **3q** in 64% yield with our method, whereas phenyl 2-naphthoate gave only 31% of **3q** with Rueping's protocol,[12] which further demonstrated the efficiency of our method.



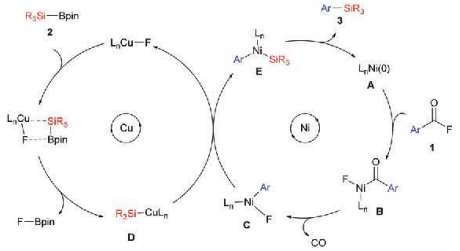
Scheme 2 Evaluation of different silylboranes.



Scheme 3 Synthetic applications. [a] Reaction conditions for deoxyfluorination of carboxylic acid: carboxylic acid (3 mmol), Deoxo-Fluor® reagent (3.3 mmol), CH_2Cl_2 (15 mL), 0 °C, 30 min. [b] Reaction conditions for decarbonylative silylation: **1** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), CuF_2 (0.06 mmol), PPh_3 (0.08 mmol), KF (0.6 mmol), toluene (1 mL), 150 °C, 24 h.

Carboxylic acid-containing drug probenecid, primarily used to treat gout and hyperuricemia,[34] was also viable in the nickel/copper-catalyzed decarbonylative silylation reaction. Deoxyfluorination of probenecid by a conventional method,[35] followed by the decarbonylative silylation process furnished the target product **3u** in 72% yield (Scheme 3a), whereas the attempt of one-pot synthesis of **3u** without isolation of acyl fluoride (**1u**) provided an unsatisfactory result with the formation of **3u** in 28% yield (Scheme S2, ESI†). Besides, the late-stage decarbonylative silylation of an estrone derivative was conducted as shown in Scheme 3b, the etherification of estrone with methyl 4-(bromomethyl)benzoate (**4**), followed by hydrolysis affording carboxylic acid **6**. Finally, compound **6** was subjected to the two-step deoxyfluorination/decarbonylative silylation to provide **3v** in 75% yield.

Considering the related references and our previous work, a plausible mechanism is shown in Scheme 4. Oxidative addition of acyl fluorides **1** to the nickel(0) catalyst **A** yields acylnickel(II)



Scheme 4 Proposed mechanism.

complex **B**. Subsequently, decarbonylation of complex **B** gave the arylnickel species **C**.[24,29]

In the copper catalytic cycle, the formation of the active Cu–Si species from silylboranes **2** can be explained by the more Lewis acidic boron as well as the bond dissociation energy of diatomic B–F (732 kJ mol $^{-1}$) and Si–F (576 kJ mol $^{-1}$).[36] Therefore, a fluoride ion activates silylborane by construction of the stronger B–F bond to generate silylcopper species **D**.[31] Transmetalation between aryl(fluoro)nickel(II) complex **C** and silylcopper species **D** afforded complex **E**, and the subsequent reductive elimination of **E** yields the desired arylsilanes **3**, regenerating nickel(0) species **A**.

In summary, we have developed a nickel/copper co-catalyst system for the decarbonylative silylation reaction of acyl fluorides to synthesize a wide range of aryl and heteroarylsilanes, in which an inexpensive and stable PPh_3 ligand is indispensable. This study can expand the chemistry of acyl fluorides in terms of carbon–heteroatom bond formations, as well as a useful complement to other silylation processes.

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Conflicts of interest

There are no conflicts to declare.

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Nickel-Catalyzed Decarbonylative Stannylation of Acyl Fluorides under Ligand-Free Conditions

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Abstract: Nickel-catalyzed decarbonylative stannylation of acyl fluorides under ligand-free conditions was disclosed. A variety of aromatic acyl fluorides are capable of reacting with silylstannanes in the presence of cesium fluoride. A one-pot decarbonylative stannylation/Migita-Kosugi-Stille reaction of benzoyl fluoride, giving rise to the direct formation of the corresponding cross-coupled products, further demonstrated the synthetic utility of the present method. This newly developed methodology with a good functional-group compatibility via C–F bond cleavage and C–Sn bond formation under nickel catalysis opens a new area for the functionalization of acyl fluorides in terms of carbon-heteroatom bond formation.

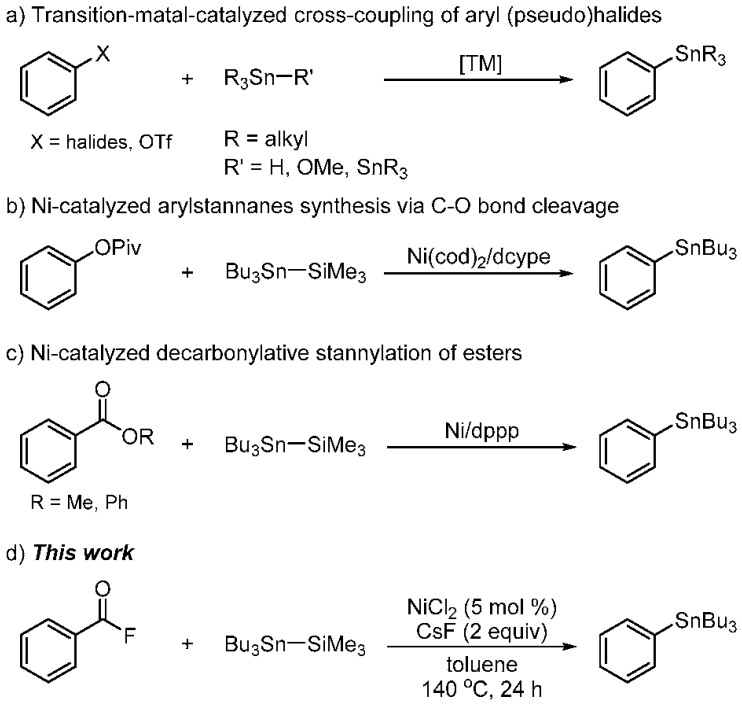
Keywords: nickel; acyl fluorides; stannylation; decarbonylation; carbon-tin bond formation

1. Introduction

Acyl fluorides as one of carboxylic acid derivatives have attracted much attention in organic synthesis, due to their great stability, easy availability, and unique intrinsic nature [1–3]. Conventionally, transition metal-catalyzed transformations of acyl fluorides with organometallic reagents (Zn, Si, and B) have focused on the synthesis of biaryl ketones in a carbonyl-group retentive manner [4–6]. In a sharp contrast, recently, decarbonylative transformations of carboxylic acid derivatives [7,8], especially acyl fluorides have been studied intensively [9]. Sakai and Ogiwara have disclosed that the auxiliary ligand of the palladium catalyst can control the reaction type of reduction of acyl fluorides [10]. However, transition-metal catalyzed decarbonylative transformations of acyl fluorides are mainly C–C bond formation, such as palladium-catalyzed trifluoromethylation [11], nickel-catalyzed Suzuki-Miyaura reaction [12], iridium-catalyzed arylation via C–H bond activation [13], and our recent work on nickel-catalyzed ethylation with BEt_3 [14] and DPPM-assisted methylenation with $AlMe_3$ [15]. Therefore, the development of carbon-heteroatom bond-forming reactions of acyl fluorides are of great importance. Very recently, we successfully demonstrated the first nickel-catalyzed decarbonylative borylation of acyl fluorides with diboron, forming the C–B bond [16], and the related decarbonylative borylation catalyzed by palladium have been reported [17,18].

Arylstannanes as one of common organometallic reagents are extensively applied in Migita-Kosugi-Stille reaction [19–21], which has been utilized as a powerful method for C–C bond formation, especially, in natural product synthesis [22–24]. Conventional synthetic methods of arylstannanes are the reactions of organometallic reagents such as arylzinc compounds with triorganotin halides [25–27]. Alternatively, catalytic cross-coupling reactions of aryl (pseudo)halides with tributyltin hydride [28], tributylstannyl methoxide [29], and hexaalkyldistannane [30,31] have been documented (Scheme 1a).

Recent studies on arylstannanes synthesis utilizing air- and moisture-insensitive silylstannyl reagent, Bu_3Sn-$SiMe_3$, could prove that the C–O bond is also a powerful alternative to aryl halides (Scheme 1b) [32]. In addition, Rueping and co-workers developed nickel-catalyzed stannylation of aromatic esters in a decarbonylative manner (Scheme 1c) [33]. Although these methods have made a great contribution to the synthesis of arylstannanes, novel and practical methods to afford arylstannanes from more simple starting materials remain highly desirable. Herein, we report the first decarbonylative stannylation of acyl fluorides with Bu_3Sn-$SiMe_3$ catalyzed by air-stable and inexpensive nickel(II) chloride under ligand and additive-free conditions (Scheme 1d).

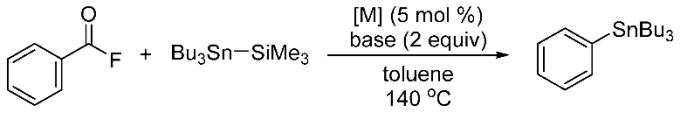


Scheme 1. Various synthetic routes for arylstannanes.

2. Results and Discussion

We commenced our research by choosing benzoyl fluoride (**1a**) and 1.5 equiv of Bu_3Sn-$SiMe_3$ (**2**) as the model substrates, and the results are summarized in Table 1. Various transition metal sources were investigated to facilitate the decarbonylative stannylation reaction (entries 1–6). Among them, nickel(II) chloride displayed a superior result, affording the target product **3a** in 90% yield (entry 3). When cesium carbonate was employed in place of cesium fluoride, the yield of **3a** was dramatically dropped to 48% (entry 7) and no stannylation reaction occurred when potassium fluoride was used, along with silylstannane **2** recovered (entry 8). Additionally, amounts of **2** could be reduced to 1.2 equiv, which afforded 94% GC yield of **3a** (entries 3, 9, and 10). The yields of **3a** were slightly decreased as the reaction time was shortened (entries 9 vs. 11–13). When benzoyl chloride was employed instead of **1a**, **3a** was obtained in 56% yield, suggesting the unique feature of the present reaction of acyl fluorides.

Table 1. Optimization of the reaction conditions.



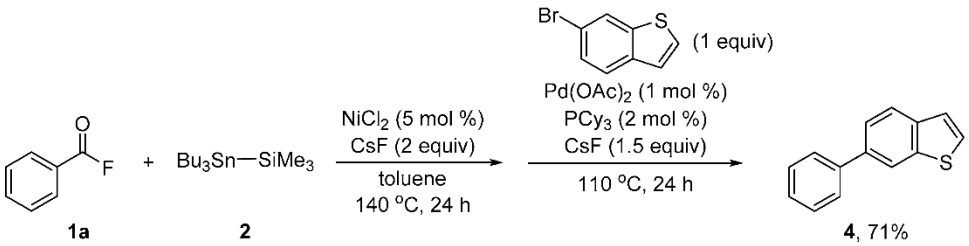
1a **2** **3a**

Entry	[M]	Base	2 (equiv)	Time (h)	Yield of 3a (%) [1]
1	$FeCl_2$	CsF	1.5	24	29
2	$CoCl_2$	CsF	1.5	24	21
3	$NiCl_2$	CsF	1.5	24	90
4	$NiBr_2$	CsF	1.5	24	68
5	$Ni(cod)_2$	CsF	1.5	24	16
6	$PdCl_2$	CsF	1.5	24	4
7	$NiCl_2$	Cs_2CO_3	1.5	24	48
8	$NiCl_2$	KF	1.5	24	0
9	$NiCl_2$	CsF	1.2	24	94 (90)
10	$NiCl_2$	CsF	1.0	24	58
11	$NiCl_2$	CsF	1.2	18	91
12	$NiCl_2$	CsF	1.2	12	87
13	$NiCl_2$	CsF	1.2	6	76

[1] Determined by GC analysis of the crude mixture using *n*-dodecane as an internal standard. An isolated yield is given in parentheses.

A generality of the decarbonylative stannylation was examined with the optimized reaction conditions (Table 2). Acyl fluorides bearing electron-donating groups such as alkyl (**1b**–**1d**), phenyl (**1e**–**1g**), and alkoxy (**1h, 1i**) groups gave the corresponding products **3b**–**3i** in 56%–85% yields regardless of the substitution positions. Other oxygen-containing functional groups such as benzyloxy (**1j**) and acetal (**1k**) were also well tolerated during the reaction. Acyl fluorides bearing electron-withdrawing groups such as trifluoromethyl (**1l**) and fluoro (**1m, 1n**) groups were also well compatible. In particular, an aryl chloride skeleton (**1o**) is known to a reactive electrophile in some nickel-catalyzed cross-coupling reactions [29]. Although 4-bromo- and 4-iodobenzoyl fluorides were employed as the substrates, no trace of the desired products was detected, presumably due to the bromo and iodo groups are highly reactive under the present reaction conditions. Acyl fluorides with fused aromatic systems (**1p**–**1r**) afforded arylstannanes in moderate to good yields. Heterocycles including benzothiophene and quinoline yielded **3s** and **3t** in 62% and 84% yields, respectively. Unfortunately, however, the reactions employing surrogate aliphatic acyl fluorides gave no formation of the desired products.

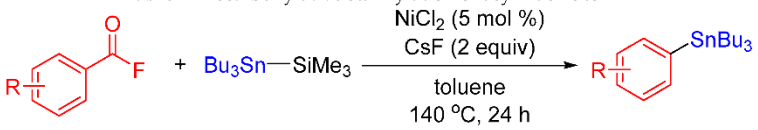
To demonstrate the synthetic utility of the present method, one-pot reaction of a successive decarbonylative stannylation/Migita-Kosugi-Stille reaction of **1a** was investigated (Scheme 2) [31]. To our delight, with the aid of the additional palladium catalyst into the reaction mixture, 71% yield of compound **4** was obtained.

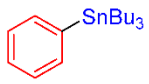
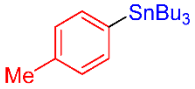
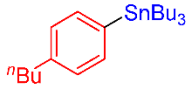
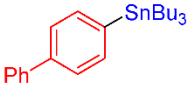
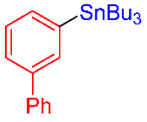
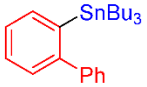
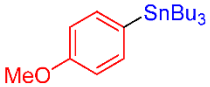
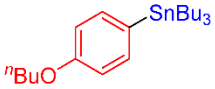
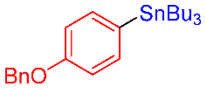
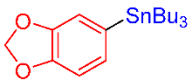
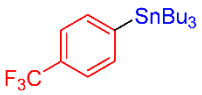
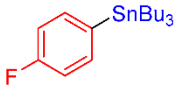
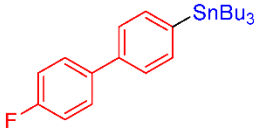
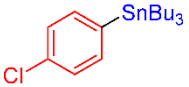
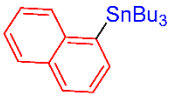
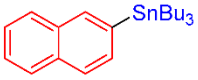
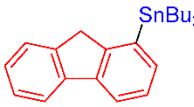
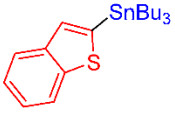
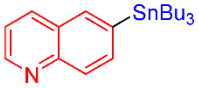


1a **2** **4**, 71%

Scheme 2. One-pot reaction of decarbonylative stannylation/Migita-Kosugi-Stille reaction of **1a**.

Table 2. Decarbonylative stannylation of acyl fluorides [a,b].

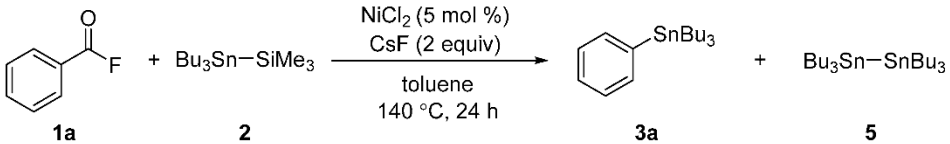


1	2		3
 **3a**, 90%	 **3b**, 81%	 **3c**, 63%	 **3d**, 67%
 **3e**, 82%	 **3f**, 56%	 **3g**, 85%	 **3h**, 64%
 **3i**, 61%	 **3j**, 50%	 **3k**, 87%	 **3l**, 61%
 **3m**, 86%	 **3n**, 72%	 **3o**, 90%	 **3p**, 51%
 **3q**, 79%	 **3r**, 82%	 **3s**, 62%	 **3t**, 84%

[a] *Reaction conditions*: **1** (0.2 mmol), **2** (0.24 mmol), $NiCl_2$ (0.01 mmol), CsF (0.4 mmol), toluene (1 mL), 140 °C, 24 h.
[b] Isolated yields.

To gain more detailed insights into the reaction mechanism, some control experiments were carried out (Table 3). Although arylstannane **3a** was obtained in 94% yield, along with the formation of hexabutylditin (**5**; 13%) under the optimized reaction conditions (entry 1), indicating that nickel(II) chloride was reduced to Ni(0) species. This hypothesis was further proved by the reaction of **1a** with **2** in the absence of cesium fluoride (entry 2). Without nickel(II) chloride, no target product **3a** was formed, and **5** was obtained quantitatively (entry 3). In some stannylation reactions, hexabutyldistannane (**5**) could also be used as a stannylating reagent [30,31]. Thus, the reaction of **1a** (0.2 mmol) with **5** (0.24 mmol) was evaluated under identical reaction conditions. However, neither the desired product **3a** nor a viable acyl stannane was delivered, along with decomposition of **1a** and the remained **5** unreacted, which suggests that the once formed **5** never be involved into the catalytic cycle because of its lower reactivity (entry 4).

Table 3. Control experiments for Ni-catalyzed decarbonylative stannylation.



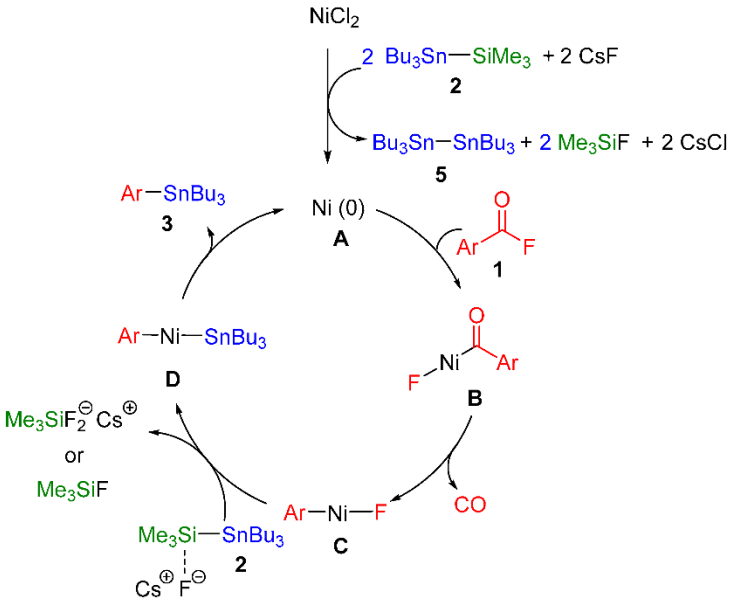
1a **2** **3a** **5**

0.2 mmol 1.2 equiv

Entry	Deviation from Standard Conditions	GC Yield (%) [1]		
		2	3a	5
1	none	0	94	13
2	without CsF	120	0	0
3	without $NiCl_2$	0	0	63
4 [2]	**5** instead of **2**	-	0	>99

[1] Determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard. [2] 4 (0.24 mmol) was added.

Our proposed mechanism of the present decarbonylative stannylation is outlined in Scheme 3. Combining the related references [12,34] with our previous work [16], it is assumed that oxidative addition of acyl fluorides **1** to Ni(0) species **A**, derived from reduction of Ni(II) chloride with **2**, yields acyl nickel(II) species **B**. Subsequently, decarbonylation of **B** delivers arylnickel(II) species **C** [12,16]. Transmetalation between the complex **C** and activated silylstannane **2** by cesium fluoride affords complex **D** [32]. Following reductive elimination gives the target product arylstannanes **3**, regenerating Ni(0) species **A**.



Scheme 3. Proposed mechanism.

3. Experimental Sections

3.1. General

Unless otherwise noted, all the reactions were carried out under an argon atmosphere using standard Schlenk techniques. Glassware was dried in an oven (150 °C) and heated under reduced pressure prior to use. Solvents were employed as eluents for all other routine operation, as well as dehydrated solvent were purchased from commercial suppliers and employed without any further purification. For thin layer chromatography (TLC) analyses throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. Silica gel column chromatography was carried out using silica gel 60 N (spherical, neutral, 40–100 μm) from Kanto Chemicals Co., Inc. (Tokyo, Japan). NMR spectra (^{1}H, ^{13}C{^{1}H} and ^{19}F{^{1}H}) were recorded on Varian INOVA-600 (600 MHz), Mercury-400 (400 MHz), or 300-NMR ASW (300 MHz) spectrometers (Agilent Technologies International Japan, Ltd., Tokyo, Japan). Chemical shifts (δ) are in parts per million relative to $CDCl_3$ at 7.26 ppm for ^{1}H and at 77.16 ppm for ^{13}C{^{1}H}. The ^{19}F{^{1}H} NMR spectra were measured by using CCl_3F (δ= 0.00 ppm) as an external standard. The NMR yields were determined using dibromomethane as an internal standard. The GC yields were determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard. GC analyses were performed on a Shimadzu GC-14A equipped with a flame ionization detector using Shimadzu Capillary Column (CBP1-M25-025) and Shimadzu C-R6A-Chromatopac integrator (Kyoto, Japan). Infrared spectra were recorded on a SHIMADZU IRPrestige-21 spectrophotometer. Elemental analyses were carried out with a Perkin-Elmer 2400 CHN elemental analyzer (Perkin-Elmer, Waltham, MA, USA) at Okayama University. ^{1}H NMR, ^{13}C{^{1}H} NMR, ^{19}F{^{1}H} NMR spectra of the compounds **1t**, **2**, **3a**–**t** and **4** can be found at the Supplementary Materials.

3.2. Experimental Method

3.2.1. Representative Procedure for the Synthesis of Acyl Fluorides from Acyl Chlorides

To a 50 mL of Schlenk tube charged with a magnetic stir bar, were successively added acyl chloride (4.0 mmol), 18-crown-6 (52.9 mg, 0.2 mmol, 5 mol %), KF (2.32 g, 40 mmol, 10 equiv), and THF (20 mL). After the reaction was stirred at 40 °C for 24 h, insoluble inorganic solid (KF or KCl) was filtered, and the volatiles were concentrated using a rotary evaporator. The crude product was purified by bulb-to-bulb distillation to afford the corresponding acyl fluorides **1** [35].

3.2.2. Representative Procedure for the Synthesis of Acyl Fluorides from Carboxylic Acids

To a 20 mL of Schlenk tube charged with a magnetic stir bar, were successively added carboxylic acid (3.0 mmol) and CH_2Cl_2 (15 mL). After the mixture was stirred at 0 °C for 30 min, Deoxo-Fluor® reagent (608 μL, 3.3 mmol, 1.1 equiv) was slowly added to the reaction mixture. After the reaction mixture was stirred at 0 °C for 30 min, the solution was slowly poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 (3 × 15 mL), and dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel to afford the corresponding acyl fluorides **1** [36].

3.2.3. Synthesis of Trimethyl(tributylstannyl)silane (**2**)

To a solution of naphthalene (51.3 mg, 0.4 mmol) in THF (16 mL), was added lithium clippings (84 mg, 12 mmol) under an argon atmosphere. During the resulting mixture was stirred at room temperature for 1 h, the color turned to dark green. Then, hexabutylditin (2.02 mL, 4 mmol) was added dropwise and the mixture was stirred at room temperature for 3 h. The resulting solution (16 mL) was transferred via cannula to a Schlenk tube under Ar and then stored at room temperature. A THF solution prepared as described above was added via a cannula into the stirred solution of chlorotrimethylsilane (951 mg, 8.8 mmol) in THF at 0 °C. The reaction was stirred at room temperature overnight followed by extraction with hexane. The organic phase was washed with brine and dried

over Na_2SO_4. Removal of the solvent and purification by bulb-to-bulb distillation under reduced pressure provided Bu_3Sn-$SiMe_3$ as a colorless oil [37].

3.2.4. Representative Procedure for Ni-catalyzed Decarbonylative Stannylation of Acyl Fluorides

A 20 mL dried Schlenk tube containing a stirring bar and CsF (60.8 mg, 0.4 mmol, 2 equiv) was dried with a heat gun under reduced pressure and filled with Ar after cooling to room temperature. To this vessel, were added $NiCl_2$ (1.3 mg, 0.01 mmol, 5 mol %), toluene (1 mL), acyl fluorides (**1**) (0.2 mmol, 1 equiv) and trimethyl(tributylstannyl)silane (**2**) (87.2 mg, 0.24 mmol, 1.2 equiv). The mixture was heated at 140 °C with stirring for 24 h. The solution was then cooled to room temperature, and the solvent was removed under vacuum. The decarbonylative stannylation products **3** were purified by flash column chromatography on silica gel.

3.2.5. One-Pot Decarbonylative Stannylation/Migita-Kosugi-Stille Cross-Coupling Reaction of **1a**

A 20 mL dried Schlenk tube containing a stirring bar and CsF (60.8 mg, 0.4 mmol, 2 equiv) was dried with a heat gun under reduced pressure and filled with Ar after cooling to room temperature. To this vessel, were added with $NiCl_2$ (1.3 mg, 0.01 mmol, 5 mol %), toluene (1 mL), benzoyl fluoride (**1a**) (24.8 mg, 0.2 mmol), and trimethyl(tributylstannyl)silane (**2**) (87.2 mg, 0.24 mmol, 1.2 equiv). The mixture was heated at 140 °C with stirring for 24 h. The solution was then cooled to room temperature. 6-Bromobenzo[*b*]thiophene (42.6 mg, 0.2 mmol, 1 equiv), palladium acetate (0.4 mg, 0.002 mmol, 1 mol %), tricyclohexylphosphine (1.1 mg, 0.004 mmol, 2 mol %), and anhydrous cesium fluoride (45.6 mg, 0.3 mmol, 1.5 equiv) were added to the reaction mixture. The mixture was heated at 110 °C with stirring. After 24 h, the reaction mixture was cooled, the volatiles were evaporated under reduced pressure. The product was purified by flash chromatography on silica gel by elution with hexane, compound **4** was obtained in 71% yield (30 mg, 0.14 mmol) as white solid [31].

3.3. Characterization Data of Starting Materials and Products

Quinoline-6-carbonyl fluoride (**1t**). Yield: 55% (288.8 mg); white solid; melting point: 104–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.56 (m, 1H), 8.20–8.25 (m, 2H), 8.30 (dd, J = 8.4, 1.9 Hz, 1H), 8.62 (d, J = 1.9 Hz, 1H), 9.08 (dd, J = 4.3, 1.9 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 122.5, 123.1, 127.4, 129.4 (d, $J_{C\text{-}F}$ = 4.0 Hz), 130.8 (d, $J_{C\text{-}F}$ = 1.4 Hz), 133.9 (d, $J_{C\text{-}F}$ = 3.0 Hz), 137.6, 150.7, 153.8, 156.9 (d, $J_{C\text{-}F}$ = 344.2 Hz); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ 18.9; FT-IR (neat, cm^{-1}): 735 (s), 781 (s), 854 (s), 1011 (s), 1045 (s), 1171 (s), 1231 (s), 1622 (s), 1805 (s); Anal. Calcd for $C_{14}H_9FO_3$: C, 68.57; H, 3.45; N, 8.00%. Found: C, 68.50; H, 3.23; N, 7.95%.

Trimethyl(tributylstannyl)silane (**2**) [37]. Yield: 92% (2.67 g); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.23 (s, $J_{H\text{-}Sn}$ = 26.4 Hz, 9H), 0.84–0.90 (m, 15H), 1.29 (sext, J = 7.3 Hz, 6H), 1.44–1.48 (m, 6H).

Tributyl(phenyl)stannane (**3a**) [33]. Yield: 90% (66.1 mg); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.91–0.95 (m, 9H), 1.03–1.16 (m, $J_{H\text{-}Sn}$ = 54.6 Hz, 6H), 1.33–1.41 (m, 6H), 1.53–1.63 (m, 6H), 7.32–7.36 (m, 3H), 7.46–7.54 (m, $J_{H\text{-}Sn}$ = 36.4 Hz, 2H).

Tributyl(p-tolyl)stannane (**3b**) [33]. Yield: 81% (61.8 mg); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 9H), 1.00–1.10 (m, $J_{H\text{-}Sn}$ = 52.4 Hz, 6H), 1.31–1.38 (m, 6H), 1.48–1.59 (m, 6H), 2.35 (s, 3H), 7.17 (d, J = 7.2 Hz, 2H), 7.37 (d, J = 7.8 Hz, $J_{H\text{-}Sn}$ = 35.8 Hz, 2H).

Tributyl(o-tolyl)stannane (**3c**) [31]. Yield: 63% (48.0 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 9H), 1.01–1.14 (m, $J_{H\text{-}Sn}$ = 50.4 Hz, 6H), 1.34 (sext, J = 7.2 Hz, 6H), 1.47–1.58 (m, 6H), 2.40 (s, 3H), 7.12–7.17 (m, 1H), 7.17–7.25 (m, 2H), 7.40 (d, J = 6.8 Hz, $J_{H\text{-}Sn}$ = 42.8 Hz, 1H).

Tributyl(4-butylphenyl)stannane (**3d**). Yield: 67% (56.7 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 7.6 Hz, 9H), 0.94 (t, J = 7.6 Hz, 3H), 0.99–1.12 (m, $J_{H\text{-}Sn}$ = 50.8 Hz, 6H), 1.29–1.40 (m, 8H), 1.50–1.64 (m, 8H), 2.60 (t, J = 7.8 Hz, 2H), 7.14–7.19 (m, 2H), 7.37 (d, J = 6.4 Hz, $J_{H\text{-}Sn}$ = 39.2 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 9.7 ($J_{C\text{-}Sn}$ = 338.7 Hz), 13.8, 14.1, 22.6, 27.6 ($J_{C\text{-}Sn}$ = 57.2 Hz), 29.3

($J_{C\text{-}Sn}$ = 19.8 Hz), 33.8, 35.8, 128.3 ($J_{C\text{-}Sn}$ = 41.2 Hz), 136.5 ($J_{C\text{-}Sn}$ = 31.3 Hz), 138.3, 142.7; FT-IR (neat, cm^{-1}): 729 (m), 748 (m), 1070 (m), 1045 (m), 1377 (m), 1458 (m), 2855 (m), 2872 (m), 2928 (m), 2959 (m); Anal. Calcd for $C_{22}H_{40}Sn$: C, 62.43; H, 9.53%. Found: C, 62.30; H, 9.55%.

[1,1′-Biphenyl]-4-yltributylstannane (**3e**) [33]. Yield: 82% (72.7 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.93 (t, J = 7.5 Hz, 9H), 1.03–1.18 (m, $J_{H\text{-}Sn}$ = 43.2 Hz, 6H), 1.38 (sext, J = 7.5 Hz, 6H), 1.55–1.66 (m, 6H), 7.35–7.39 (m, 1H), 7.45–7.48 (m, 2H), 7.53–7.60 (m, 4H), 7.62–7.64 (m, 2H).

[1,1′-Biphenyl]-3-yltributylstannane (**3f**) [33]. Yield: 56% (49.6 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.91 (t, J = 7.5 Hz, 9H), 1.06–1.16 (m, $J_{H\text{-}Sn}$ = 50.8 Hz, 6H), 1.33–1.38 (m, 6H), 1.54–1.63 (m, 6H), 7.35–7.38 (m, 1H), 7.40–7.48 (m, 4H), 7.51–7.54 (m, 1H), 7.58–7.62 (m, 2H), 7.63–7.71 (d, J = 1.8 Hz, $J_{H\text{-}Sn}$ = 40.2 Hz, 1H).

[1,1′-Biphenyl]-2-yltributylstannane (**3g**) [33]. Yield: 85% (75.4 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.69–0.77 (m, $J_{H\text{-}Sn}$ = 51.0 Hz, 6H), 0.84 (t, J = 7.3 Hz, 9H), 1.23 (sext, J = 7.8 Hz, 6H), 1.32–1.38 (m, 6H), 7.32–7.35 (m, 3H), 7.36–7.39 (m, 3H), 7.39–7.42 (m, 2H), 7.56 (d, J = 7.3 Hz, $J_{H\text{-}Sn}$ = 40.8 Hz, 1H).

Tributyl(4-methoxyphenyl)stannane (**3h**) [31]. Yield: 64% (50.8 mg); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 7.2 Hz, 9H), 0.96–1.09 (m, $J_{H\text{-}Sn}$ = 51.2 Hz, 6H), 1.33 (sext, J = 7.6 Hz, 6H), 1.48–1.59 (m, 6H), 3.81 (s, 3H), 6.91 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, $J_{H\text{-}Sn}$ = 37.2 Hz, 2H).

(4-Butoxyphenyl)tributylstannane (**3i**). Yield: 61% (53.6 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.89 (t, J = 7.2 Hz, 9H), 0.98 (t, J = 7.2 Hz, 3H), 1.01–1.04 (m, $J_{H\text{-}Sn}$ = 51.6 Hz, 6H), 1.33 (sext, J = 7.8 Hz, 6H), 1.47–1.58 (m, 8H), 1.75–1.80 (m, 2H), 3.96 (t, J = 6.6 Hz, 2H), 6.90 (d, J = 8.5 Hz, $J_{H\text{-}Sn}$ = 61.8 Hz, 2H), 7.36 (d, J = 8.5 Hz, $J_{H\text{-}Sn}$ = 42.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 9.7 ($J_{C\text{-}Sn}$ = 333.0 Hz), 13.9, 14.0, 19.4, 27.6 ($J_{C\text{-}Sn}$ = 55.5 Hz), 29.2 ($J_{C\text{-}Sn}$ = 20.8 Hz), 31.5, 67.4, 114.6 ($J_{C\text{-}Sn}$ = 43.9 Hz), 131.8, 137.6 ($J_{C\text{-}Sn}$ = 34.7 Hz), 159.4; FT-IR (neat, cm^{-1}): 671 (m), 754 (m), 1072 (m), 1130 (m), 1207 (m), 1242 (m), 1273 (m), 1464 (m), 1495 (m), 1585 (m), 2855 (m), 2872 (m), 2928 (m), 2959 (m); Anal. Calcd for $C_{22}H_{40}OSn$: C, 60.15; H, 9.18%. Found: C, 60.09; H, 9.32%.

(4-(Benzyloxy)phenyl)tributylstannane (**3j**) [38]. Yield: 50% (47.3 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 9H), 0.98–1.10 (m, $J_{H\text{-}Sn}$ = 51.0 Hz, 6H), 1.34 (sext, J = 7.2 Hz, 6H), 1.52–1.57 (m, 6H), 5.07 (s, 2H), 7.00 (d, J = 8.5 Hz, 2H), 7.32–7.36 (m, 1H), 7.37–7.43 (m, 4H), 7.46 (d, J = 7.2 Hz, 2H).

Benzo[d][1,3]dioxol-5-yltributylstannane (**3k**) [29]. Yield: 87% (71.5 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 9H), 0.99–1.08 (m, $J_{H\text{-}Sn}$ = 49.8 Hz, 6H), 1.33 (sext, J = 7.8 Hz, 6H), 1.50–1.58 (m, 6H), 5.92 (s, 2H), 6.86 (d, J = 7.4 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.94 (s, $J_{H\text{-}Sn}$ = 37.2 Hz, 1H).

Tributyl(4-(trifluoromethyl)phenyl)stannane (**3l**) [33]. Yield: 61% (53.1 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.89 (m, J = 7.2 Hz, 9H), 1.04–1.15 (m, $J_{H\text{-}Sn}$ = 50.6 Hz, 6H), 1.33 (sext, J = 7.2 Hz, 6H), 1.50–1.57 (m, 6H), 7.55 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, $J_{H\text{-}Sn}$ = 34.8 Hz, 2H).

Tributyl(4-fluorophenyl)stannane (**3m**) [33]. Yield: 86% (66.2 mg); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 9H), 0.98–1.12 (m, $J_{H\text{-}Sn}$ = 51.0 Hz, 6H), 1.33 (sext, J = 8.0 Hz, 6H), 1.47–1.60 (m, 6H), 7.00–7.08 (m, 2H), 7.35–7.48 (m, 2H).

Tributyl(4′-fluoro-[1,1′-biphenyl]-4-yl)stannane (**3n**) [33]. Yield: 72% (66.4 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 9H), 1.05–1.15 (m, $J_{H\text{-}Sn}$ = 50.1 Hz, 6H), 1.36 (sext, J = 7.2 Hz, 6H), 1.54–1.62 (m, 6H), 7.13 (dd, J = 8.7 Hz, $J_{F\text{-}H}$ = 8.7 Hz, 2H), 7.51–7.53 (m, 2H), 7.54–7.57 (m, 4H).

Tributyl(4-chlorophenyl)stannane (**3o**) [37]. Yield: 90% (72.3 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 9H), 1.00–1.10 (m, $J_{H\text{-}Sn}$ = 50.1 Hz, 6H), 1.32 (sext, J = 7.2 Hz, 6H), 1.47–1.56 (m, 6H), 7.28–7.33 (m, 2H), 7.34–7.42 (m, $J_{H\text{-}Sn}$ = 36.0 Hz, 2H).

Tributyl(naphthalen-1-yl)stannane (**3p**) [33]. Yield: 51% (42.6 mg); colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 9H), 1.19–1.22 (m, $J_{H\text{-}Sn}$ = 50.4 Hz, 6H), 1.35 (sext, J = 7.8 Hz, 6H), 1.54–1.60

(m, 6H), 7.42–7.51 (m, 3H), 7.63 (d, J = 6.6 Hz, $J_{H\text{-}Sn}$ = 46.2 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 7.2 Hz, 1H).

Tributyl(naphthalen-2-yl)stannane (**3q**) [33]. Yield: 79% (65.9 mg); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.92 (m, J = 7.2 Hz, 9H), 1.09–1.21 (m, $J_{H\text{-}Sn}$ = 50.1 Hz, 6H), 1.38 (sext, J = 7.2 Hz, 6H), 1.56–1.65 (m, 6H), 7.44–7.51 (m, 2H), 7.59 (d, J = 8.1 Hz, $J_{H\text{-}Sn}$ = 33.0 Hz, 1H), 7.79–7.87 (m, 3H), 7.96 (s, $J_{H\text{-}Sn}$ = 44.4 Hz, 1H).

Tributyl(9H-fluoren-1-yl)stannane (**3r**). Yield: 82% (74.7 mg); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 9H), 1.11–1.23 (m, $J_{H\text{-}Sn}$ = 51.0 Hz, 6H), 1.36 (sext, J = 7.2 Hz, 6H), 1.52–1.62 (m, 6H), 3.85 (s, 2H), 7.30–7.42 (m, 4H), 7.57 (d, J = 7.5 Hz, 1H), 7.76 (dd, J = 7.2, 1.2 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 9.8 ($J_{C\text{-}Sn}$ = 338.7 Hz), 13.8, 27.6 ($J_{C\text{-}Sn}$ = 60.1 Hz), 29.4 ($J_{C\text{-}Sn}$ = 19.6 Hz), 39.4, 119.9, 120.0, 125.0, 126.3, 126.6, 126.9, 135.0, 138.3, 140.3, 142.2, 143.0, 150.8; FT-IR (neat, cm^{-1}): 731 (m), 752 (m), 1207 (s), 1220 (m), 1225 (m), 1456 (m), 1464 (m), 1695 (m), 2855 (m), 2865 (m), 2926 (m), 2959 (m); Anal. Calcd for $C_{25}H_{36}Sn$: C, 65.95; H, 7.97%. Found: C, 66.06; H, 8.20%.

Benzo[b]thiophen-2-yltributylstannane (**3s**) [39]. Yield: 62% (52.5 mg); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 9H), 1.12–1.20 (m, $J_{H\text{-}Sn}$ = 52.2 Hz, 6H), 1.36 (sext, J = 7.2 Hz, 6H), 1.56–1.64 (m, 6H), 7.27–7.29 (m, 1H), 7.32 (t, J = 6.6 Hz, 1H), 7.39 (s, $J_{H\text{-}Sn}$ = 24.0 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H).

6-(Tributylstannyl)quinoline (**3t**) [32]. Yield: 84% (70.3 mg); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 9H), 1.08–1.20 (m, $J_{H\text{-}Sn}$ = 51.0 Hz, 6H), 1.36 (sext, J = 7.8 Hz, 6H), 1.53–1.64 (m, 6H), 7.39 (dd, J = 8.4, 4.2 Hz, 1H), 7.81 (d, J = 7.8 Hz, $J_{H\text{-}Sn}$ = 31.5 Hz, 1H), 7.91 (s, $J_{H\text{-}Sn}$ = 42.0 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 8.89 (dd, J = 8.4, 1.2 Hz, 1H).

6-Phenylbenzo[b]thiophene (**4**) [40]. Yield: 71% (30.0 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.42 (m, 2H), 7.46–7.51 (m, 3H), 7.61 (dd, J = 8.4, 1.8 Hz, 1H), 7.66–7.90 (m, 2H), 7.95 (d, J = 8.4, 1H), 8.04 (d, J = 1.8 Hz, 1H).

4. Summary

In summary, we have developed an efficient and convenient method for the inexpensive $NiCl_2$-catalyzed decarbonylative stannylation of a series of acyl fluorides, which is notable for being both ligand and additive-free. A one-pot decarbonylative stannylation/Migita-Kosugi-Stille reaction further demonstrated the synthetic applicability of our protocol because the isolation of toxic organotin compounds is not necessary. This study can expand the chemistry of acyl fluorides in terms of carbon-heteroatom bond formations.

Supplementary Materials: The following are available online. ^{1}H NMR, ^{13}C{^{1}H} NMR, ^{19}F{^{1}H} NMR spectra of representative starting materials and final products.

Author Contributions: X.W. developed above reactions and wrote the manuscript; X.W., Z.W. and L.L. prepared starting materials and expanded the substrates scope; Y.A. conducted the additional experiments required by reviewers; Y.N. supervised the project and revised the manuscript.

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Sample Availability: Samples of the compounds **3a**–**3t** are available from the authors.

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Synthesis of 2-Substituted Propenes by Bidentate Phosphine-Assisted Methylenation of Acyl Fluorides and Acyl Chlorides with $AlMe_3$

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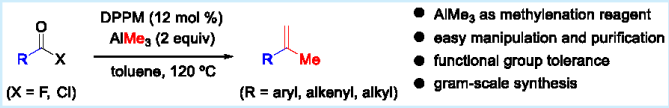
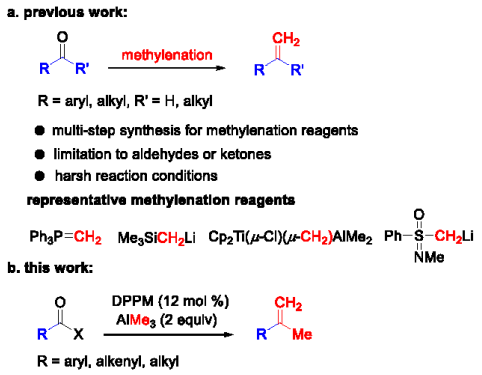
Supporting Information



ABSTRACT: Bidentate phosphine-assisted methylenation of acyl fluorides and acyl chlorides with substituted with aryl, alkenyl, and alkyl groups trimethylaluminum afforded an array of 2-substituted propene derivatives. The addition of a catalytic amount of DPPM increased an efficiency of the reactions. Trimethylaluminum as the methylenation reagent not only eliminates the presynthesis of methylene transfer reagent, but provides an efficient method for the synthesis of a series of 2-substituted propenes.

2-Substituted propenes including α-methylstyrenes are found to be prevalent in natural[1] and synthetic products,[2] as well as chiral building blocks in catalytic asymmetric processes.[3] Thus, direct and efficient synthesis of such products from the corresponding carbonyl compounds is an important class of organic transformations. Pioneering efforts on methylenation of aldehydes or ketones to the corresponding olefins have been well-documented by Wittig,[4] Johnson,[5−7] Peterson,[8] Julia,[9−11] Tebbe,[12−14] and Takai.[15] In particular, an appropriate choice of reagents is a key issue to realize methylenation procedures (Scheme 1a). Although phosphonium ylides are also well-known methylene transfer reagents, they suffered from tedious separation between triphenylphosphine oxide and the target products. In addition, the yields of target compounds were sometimes unsatisfactory, because of the low reactivity of phosphonium ylides.[6,12,14] Other representative methylenation reagents such as sulfoximine,[5] silylcarbanion,[7] sulfone,[10] and titanium−aluminum complex[12] have been studied extensively. On the other hand, late-transition-metal complexes such as Ni,[16] Cu,[17] Pd,[18] and Rh[19] have also been described to catalyze methylenation of aldehydes and ketones. However, acyl halides are still rare to be employed toward methylenation reactions, although they are inexpensive, stable, and widely abundant.[20,21] During our continuing studies on the transformation of acyl halides,[22] we discovered a simple and reliable method for the conversion of acyl halides (X = F and Cl) to 2-substituted propenes, in which trimethylaluminum acts as the methylenation reagent (Scheme 1b).

Scheme 1. Methylenation of Carbonyl Compounds



After a close look at the literature about the transformation of acyl chlorides to olefins[23] via ketones,[24] we found that one-step methylenation generating the corresponding alkenes from the corresponding carbonyl compounds is in high demand. With this consideration in mind, we commenced the study by examining the reaction of acyl chloride **1a** and 2 equiv of trimethylaluminum. Initially, the reaction was conducted in the presence of the Ni catalyst, but after extensive optimization of reaction conditions, we finally found that the nickel catalyst is not necessary (see Tables S1−S4 in the Supporting Information). Screening several additives revealed the optimized condition, as shown in Table 1. Monodentate phosphine PPh_3 afforded 59% yield of **2a**, along with the alcohol **3a** in 7% yield (Table 1, entry 1). Among bidentate

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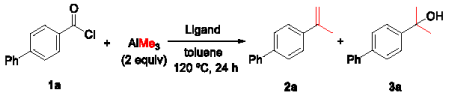
Table 1. Optimization for Methylenation of 4-Phenybenzoyl Chloride (1a) with $AlMe_3$[a]



1a 2a 3a

entry	additive	amount (mol %)	Yield[b] (%) 2a	3a
1	PPh_3	24	59	7
2	DPPM	12	93 (90)	0
3	DPPE	12	54	8
4	DPPP	12	82	18
5	DPPB	12	3	3
6	Xantphos	12	57	10
7	Et_3N	24	78	22
8	TMEDA	12	70	3
9	DPPM	2	60	0
10	DPPM	0	15	0
11[c]	DPPM	12	12	0

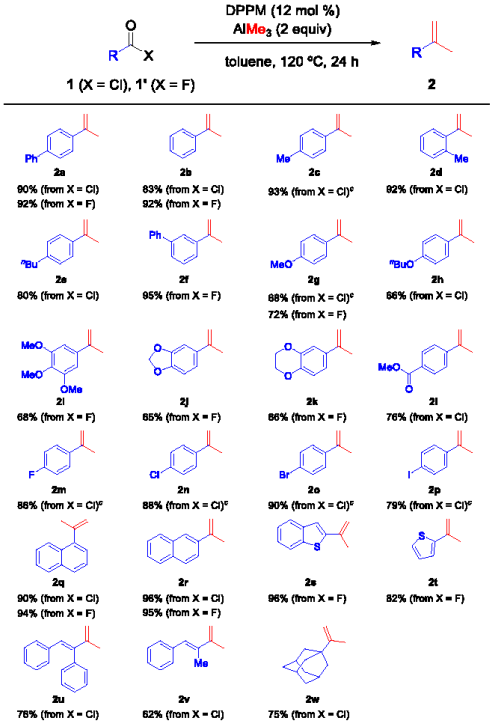
[a]Reactions were performed with **1a** (0.2 mmol), $AlMe_3$ (2 equiv), toluene (0.5 mL) at 120 °C for 24 h. [b]GC yields. An isolated yield is given in parentheses. [c]$AlMe_3$ (1 equiv) was used.

phosphines investigated (entries 2−6), DPPM showed superior results; target product **2a** was selectively delivered in 90% isolated yield (Table 1, entry 2). Meanwhile, nitrogen-containing bases such as triethylamine (Table 1, entry 7) and tetramethylethylenediamine (TMEDA; see Table 1, entry 8) also resulted in the conversion of **2a** in 78% and 70% yields, respectively. In a sharp contrast, DPPM-free reaction conditions gave only 15% yield of **2a** (Table 1, entry 10). The result shown in entry 11 suggested that 2 equiv of $AlMe_3$ are essential for complete transformation into **2a**.

With the optimized conditions of entry 2 (in Table 1) in hand, a generality for methylenation of acyl chlorides **1** or fluorides **1′** with $AlMe_3$ was examined. The results are summarized in Scheme 2. Both benzoyl chloride (**1b**) and benzoyl fluoride (**1b′**) gave **2b** in 83% and 92% yields, respectively. Acyl halides bearing alkyl and phenyl groups in various positions afforded **2c**−**2f** in good to high yields. The substrates bearing oxygen functionalities reacted smoothly to afford the corresponding products **2g**−**2k** in 65%−72% yields. Surprisingly, acyl chloride substituted by methoxycarbonyl group chemoselectively provided the target product **2l** in 76% yield. Functional compatibility of halogen-containing starting materials in this methylenation was further demonstrated. Because of the absence of any transition metals, it is noteworthy that bromide (**2o**) and iodide (**2p**) were well-tolerated. Similarly, naphthoyl chlorides and fluorides readily yielded **2q** and **2r** in good yields. Sulfur-containing heterocycles posed no problem in this transformation to give **2s** and **2t**. Strikingly, this method employing alkenylated acyl chlorides could be applied for 1,3-dienes synthesis to afford **2u** and **2v**. In addition, the reactions of tertiary aliphatic acyl chloride **1w** could readily furnished **2w** in 75% yield. In some cases, an equimolar amount of $AlMe_3$ gave rise to the formation of **2** in comparable yields obtained with 2 equiv of $AlMe_3$ addition, indicating that $AlMe_3$ play a role in two methyl-group-donating reagents.

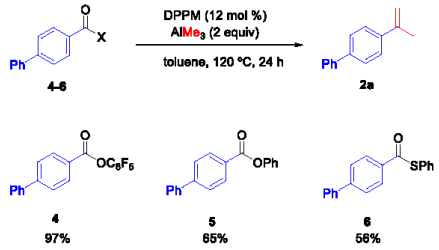
Next, a series of ester derivatives was also evaluated (Scheme 3). Perfluoro-phenolic ester **4** showed good reactivity with the aid of DPPM and afforded **2a** in 97% yield. In addition, the

Scheme 2. Scope of Acyl Halides[a,b]



[a]Reaction conditions: **1** (X = Cl) or **1′** (X = F) (0.2 mmol), $AlMe_3$ (2 equiv), DPPM (12 mol %), toluene (0.5 mL), 120 °C, 24 h. [b]Isolated yields. [c]One mmol.

Scheme 3. Scope of Carboxylic Acid Derivatives



methylenation reactions of phenolic ester **5** and thioester **6** could also undergo to give **2a** in moderate yields, which is in sharp contrast to the result for methyl ester (vide supra).

Double methylenation with 4 equiv of $AlMe_3$ was tested for the bifunctional acyl chloride **1x**. As a result, 1,4-diisopropenylbenzene (**2x**) was formed in 82% yield. In addition, with the use of phenolic ester **1y**, **2x** was delivered in 90% yield (Scheme 4a). As shown in Scheme 4b, acyl chloride **1z** with a keto group provided the unsymmetrical 1,4-methylenation product **2z**, which has been frequently used in the polymerization.[25] Otherwise, **2z** is not readily synthesized by other synthetic methods. Large-scale synthesis of 4-bromo-

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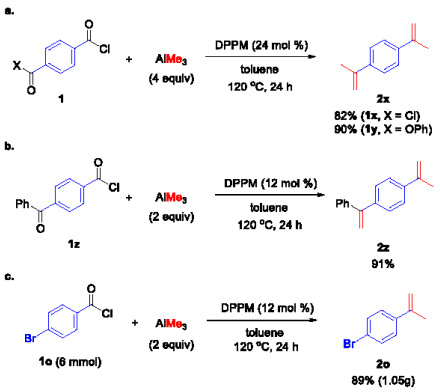
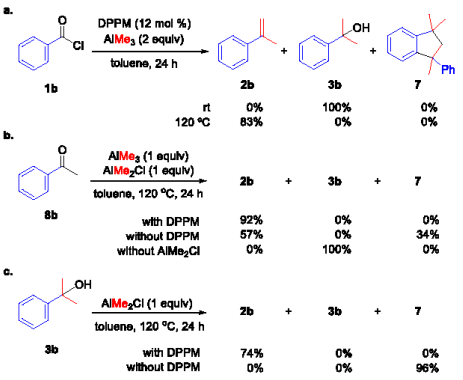
Scheme 4. Application



2-propenylbenzene (**2o**) was successful without a loss in yield (89%, 1.05 g) (Scheme 4c).

To shed light on the reaction mechanism, additional experiments were performed to prove the existence of intermediates and a role of DPPM. The reaction of **1b** with 2 equiv of $AlMe_3$ was conducted (Scheme 5a). In the reaction

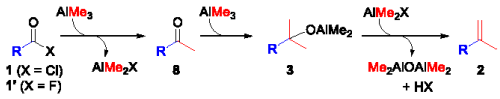
Scheme 5. Mechanistic Studies



at room temperature for 24 h, the starting material **1b** was completely consumed, along with the formation of alcohol **3b** quantitatively, but neither **2b**, nor 2,3-dihydro-1*H*-indene derivative **7**,[26] the dimerized product of **2b**, was observed. On the other hand, when the same reaction was performed at 120 °C, 83% yield of **2b** was obtained, which indicates that the high reaction temperature is important for transformation from **3b** to **2b**. The plausible intermediate acetophenone (**8b**) was subjected to the reaction with or without DPPM or $AlMe_2Cl$ (Scheme 5b). As a result, the reactions of **8b** with 1 equiv of $AlMe_3$ in the presence of 12 mol % DPPM afforded **2b** in 92% NMR yield, whereas the yield of **2b** decreased to 57% without DPPM, along with 34% of **7**. Without $AlMe_2Cl$, only alcohol **3b** was obtained with or without DPPM. This result suggests that the in-situ-formed $AlMe_2Cl$ plays an important role for transformation of **3b** to **2b**. Subsequently, the reactions of the intermediate alcohol **3b** with an equimolar amount of $AlMe_2Cl$ were elucidated (Scheme 5c). As expected, a single product **2b** was formed in 74% yield with the aid of 12 mol % of DPPM, whereas, without DPPM, byproduct **7** was obtained in 96% yield. These results are also supported with the time course of the reactions of benzoyl chloride (**1b**) or benzoyl fluoride (**1b′**) with 2 equiv of $AlMe_3$ with or without DPPM (see Figures S1 and S2 in the Supporting Information). Therefore, we concluded that the present methylenation is promoted by the in-situ-formed $AlMe_2X$ (X = F or Cl).

With the results obtained shown in Scheme 5 in hand, we propose the reaction mechanism, as shown in Scheme 6. Acyl

Scheme 6. Reaction Mechanism



halides **1** or **1′** react with the first equivalent of $AlMe_3$ to afford ketone **8**, along with the formation of $AlMe_2X$. Successively, the formed ketone **8** reacts with the second equivalent of $AlMe_3$ to form intermediate **3**.[24c] Finally, the $AlMe_2X$[27] formed in situ acts as a Lewis acid to promote the elimination of $Me_2AlOAlMe_2$, giving rise to the products **2**. Although a role of DPPM has not been clarified, the bidentate nature of DPPM might support a nucleophilic attach of $AlMe_3$ to acyl halides and tune the acidity in the catalytic system, which retards the Brønsted or Lewis acid-triggered dimerization of **2**.

In summary, we have developed a practicable, scalable, and one-step method to form 2-substituted propenes from various aryl, alkenyl, and alkyl acyl halides, as well as other esters. This protocol features good functional tolerance of halogens and chemoselectivity for esters, which would be a useful complement to other methylenation processes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01059.

More-detailed results of methylenation and ^{1}H NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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Nickel-catalysed decarbonylative borylation of aroyl fluorides†

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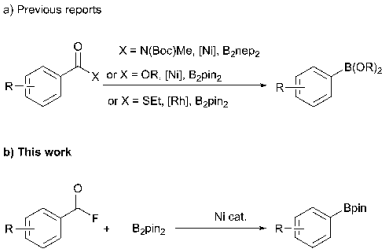
The first $Ni(cod)_2/PPh_3$ catalyst system has been established for decarbonylative borylation of aroyl fluorides with bis(pinacolato)-diboron. A wide range of functional groups in the substrates were well tolerated. The ease of access of the starting aroyl fluorides indicates that these results might become an alternative to the existing decarbonylation events.

Arylboronic acids and arylboronates are versatile synthetic reagents in synthetic organic chemistry.[1] These compounds are conventionally synthesized by organolithium or magnesium compounds, which are not compatible with functional groups.[2] The further development of transition-metal-catalysed borylation reactions has allowed the synthesis of arylboronates from numerous aryl iodides, bromides, chlorides, or triflates.[3] In recent years, much effort has been devoted to the synthesis of arylboronates *via* C–X (X = H,[4] halogen,[5] SR,[6] OR,[7] CN,[8] or NR_2[9]) bond activation.

Taking into account the growing concerns on the environmental and sustainable events of our society, carboxylic acid as an aromatic feedstock alternative is in high demand. In particular, facile diversification of carboxylic acids into organoboron compounds shows high value.[10] As such, several attempts have succeeded in the transformation of carboxylic acid derivatives such as amides,[11,12] esters,[13–15] thioesters,[16,17] and chloride[18] into the corresponding arylboronates in a decarbonylative manner (Scheme 1a). Very recently, the decarboxylative borylation of aliphatic and aromatic *N*-hydroxyphthalimide esters, derived from the corresponding carboxylic acids, were also disclosed.[19]

On the other hand, aroyl fluorides easily prepared from the corresponding carboxylic acids,[20] arguably one of the simplest and most atom-economical derivatives in the aroyl acid series, have received considerably less attention, presumably due to their low reactivity. In some cases, however, aroyl fluorides were found to be a cross-coupling partner with organozinc,[21] -silicon,[22] and -boron[23] nucleophiles to generate various ketones without decarbonylation. Recently, Ogiwara and Sakai reported palladium-catalysed reduction of sp^2 and sp^3 acid fluorides in a retentive or decarbonylative manner.[24] This report suggested that the retentive or decarbonylative pathway could be controlled by the ligands employed. Encouraged by the decarbonylative C–C bond formation, namely, trifluoromethylation of acid fluorides under a $[(cinnamyl)PdCl]_2$/xantphos catalytic system,[25] we also disclosed decarbonylative alkylation of aroyl fluorides catalysed by $Ni(cod)_2$/DPPE.[26] To the best of our knowledge, however, the decarbonylative borylation of acid fluorides has been virtually unexplored.[27] Herein we report our results on the utilization of aroyl fluorides as the electrophilic component in a nickel-catalysed decarbonylative borylation reaction (Scheme 1b).



Scheme 1 Decarbonylative borylation of carboxylic acid derivatives.

Our initial studies involved the evaluation of various ligands and bases in the borylation reaction of benzoyl fluoride (**1a**) with bis(pinacolato)diboron (**2a**, (B_2pin_2) catalysed by $Ni(cod)_2$ (Tables S1–S4, ESI†)). To our delight, 33% of desired product **3a** was obtained when a stable and inexpensive ligand PPh_3 was employed. Extensive screening of the reaction conditions (see the ESI†) revealed that a mixture of 10 mol% of $Ni(cod)_2$, 30 mol% of PPh_3, 2.5 equiv. of KF, and 2.0 equiv. of NaCl as the additive

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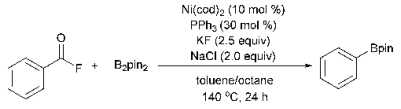
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data and copies of ^1H, $^{13}C\{^1H\}$ and $^{19}F\{^1H\}$ NMR spectra. See DOI: 10.1039/c8cc08504h

at 140 °C for 24 h in a mixed solvent system, toluene and octane (v/v = 2/1), provided the best result, affording **3a** in 83% yield (Table 1, entry 1). Other air-stable Ni(II) salts other than $Ni(cod)_2$ resulted in a lower yield of **3a** (entries 2 and 3). Palladium catalysts such as $Pd(OAc)_2$ and $Pd(dba)_2$ were inefficient (entries 4 and 5). Although $[Rh(OH)(cod)]_2$ was reported to be efficient in decarbonylative borylation of aromatic thioesters,[16] it showed moderate reactivity (entry 6). Replacement of PPh_3 with other monodentate phosphine ligands under identical reaction conditions decreased the yield (entries 7–9). Interestingly, the yield of **3a** was increased in the order of CsF < NaF < KF (Table S4, ESI†), suggesting that a countercation is important to some extent.[28] A similar tendency was observed in the additives; NaCl and KCl afforded good yields, while LiCl, CsCl and TBAC (tetrabutylammonium chloride) gave poor results (entries 10–13). This revealed that suitable countercations may play a vital role in this transformation. These results are associated with recent publications that demonstrate the important role of countercations in C–O bond activation in reactions of aryl ethers.[29] When no NaCl was added, the yield was slightly decreased to 67% (entry 14). No desired product was detected in the absence of $Ni(cod)_2$ or PPh_3 in the decarbonylative borylation process (entries 15 and 16). The KF additive was found to be essential to proceed the reaction (entry 17), suggesting that an external activator of B_2pin_2 is required. When we applied certain conditions to the analogous benzoyl chloride at 140 °C (entry 18) and even at room temperature, 50 °C, or 80 °C, no decarbonylative borylation product was detected. It is indicated that a fluoride moiety plays a crucial role and conversion of benzoyl fluoride *in situ* into benzoyl chloride in the presence of NaCl can be ruled out during this transformation.

With the optimized conditions in hand, the generality of the reaction was subsequently investigated (Table 2). A wide range of electronically and sterically diverse aroyl fluorides with bis(pinacolato)diboron (**2a**) were smoothly converted into the corresponding arylboronates. Aroyl fluorides bearing electron-donating alkyl and alkoxy groups in the *para*-position afforded arylboronates **3b**–**3f** in 50–82% yields. High chemoselectivity of this decarbonylative borylation was demonstrated by the synthesis of **3i** bearing the ester functionality unreacted. This result suggests that this methodology is complementary to the decarbonylative borylation of aromatic esters.[13–15] Moreover, the introduction of electron-withdrawing groups onto benzoyl fluoride led to a slight decrease in the yields of products **3k** and **3l**. Reaction of benzoyl fluoride with *ortho*-substituents under the identical reaction conditions proceeds smoothly to yield **3n**–**3p**. Naphthyl (**3q** and **3r**), anthracenyl (**3s**), and biphenyl (**3g**, **3m**, and **3t**)-containing arylboronates were successfully obtained in good to high yields. On the other hand, although the decarbonylative borylation using vinyl and benzyl precursors have been elucidated, no traces of the desired products **3** were detected.

To evaluate the utility of this decarbonylative borylation reaction, reactions of a series of diborons have been carried out (Table 3). Using bis(hexylene glycolato)diboron (**2b**) and bis(neopentyl glycolato)diboron (**2c**, B_2nep_2) instead of **2a** with benzoyl fluoride (**1a**) gave the corresponding arylboronates **4b** and **4c** in 54% and 55% yields, respectively. The reaction of

Table 1 Optimization of the reaction conditions[a]

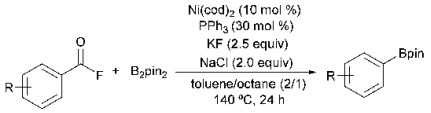


1a 2a 3a

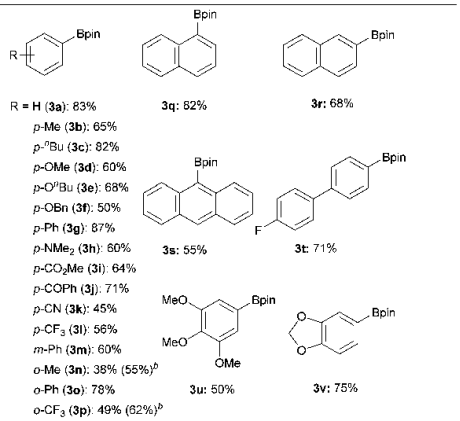
Entry	Deviation from standard conditions	Yield[b] (%)
1	None	85 (83)[c]
2	$NiCl_2$ instead of $Ni(cod)_2$	52
3	$Ni(OAc)_2{\cdot}4H_2O$ instead of $Ni(cod)_2$	4
4	$Pd(OAc)_2$ instead of $Ni(cod)_2$	16
5	$Pd(dba)_2$ instead of $Ni(cod)_2$	23
6	$[Rh(OH)(cod)]_2$ instead of $Ni(cod)_2$	50
7	PCy_3 instead of PPh_3	16
8	$P(OPh)_3$ instead of PPh_3	46
9	P^nBu_3 instead of PPh_3	71
10	LiCl instead of NaCl	5
11	KCl instead of NaCl	79
12	CsCl instead of NaCl	23
13	TBAC instead of NaCl	25
14	Without NaCl	67
15	Without $Ni(cod)_2$	0
16	Without PPh_3	0
17	Without KF	<1
18	Benzoyl chloride instead of **1a**	0

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), PPh_3 (0.06 mmol), KF (0.5 mmol), NaCl (0.4 mmol), toluene (0.66 mL), octane (0.33 mL), 140 °C, 24 h. [b] Determined by GC analysis. [c] An isolated yield is shown in parentheses.

Table 2 Decarbonylative borylation of aroyl fluorides[a,b]

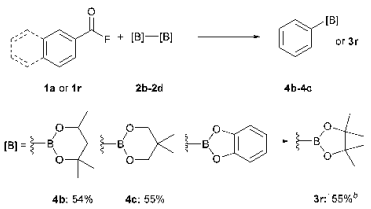


1a-1v 2a 3a-3v



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (0.02 mmol), PPh_3 (0.06 mmol), KF (0.5 mmol), NaCl (0.4 mmol), toluene (0.66 mL), octane (0.33 mL), 140 °C, 24 h. [b] $Ni(cod)_2$ (0.06 mmol), PPh_3 (0.18 mmol).

Table 3 Elucidation of other diborons[a,b]

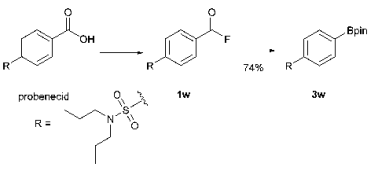


[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), Ni(cod)$_2$ (0.02 mmol), PPh_3 (0.06 mmol), KF (0.5 mmol), NaCl (0.4 mmol), toluene (0.66 mL), octane (0.33 mL), 140 °C, 24 h. [b] **1r** (0.2 mmol), **2d** (0.4 mmol), then pinacol (4 equiv.) and NEt_3 (0.5 mL) at room temperature for 1 h.

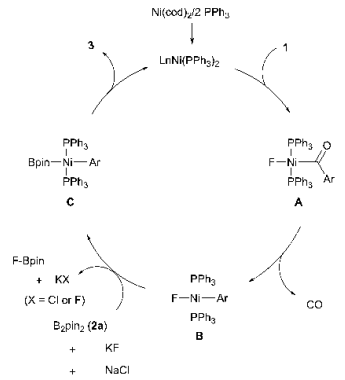
2-naphthoyl fluoride (**1r**) with bis(catecholato)diboron (**2d**, B_2cat_2), followed by the replacement with pinacol also yielded **3r** in 55% yield.

This nickel-catalysed decarbonylative borylation was also viable with complex molecular precursors bearing functional groups. For example, a carboxylic acid-containing drug, probenecid,[30] primarily used to treat gout and hyperuricemia, could be subjected to the two-step fluorination/decarbonylative borylation sequences. After fluorination of probenecid by conventional methods,[20c] aroyl fluoride **1w** was smoothly converted into the target arylboronate **3w** in 74% yield (Scheme 2),whereas the attempt to elucidate the one-pot synthesis of arylboronates without isolation of aroyl fluorides was found to be unsuccessful. To our delight, this decarbonylative borylation is applicable to a large-scale synthesis. The 10-mmol scale experiment provided 1.19 g of **3a** in 58% yield.

The proposed mechanism of decarbonylative borylation of aroyl fluorides is shown in Scheme 3. Initially, oxidative addition of aroyl fluorides to Ni(0) generates the acyl-nickel(II) intermediate **A**.[31–33] Although our attempt to isolate **A** was unsuccessful, we found some clues for arylnickel species **B**. The reaction of Ni(cod)$_2$/2 PPh_3 with benzoyl fluoride in C_6D_6 at rt provided a characteristic broad singlet at −409.9 ppm in the $^{19}F\{^1H\}$ NMR spectrum and a doublet at 15.1 ppm with a J_{P-F} of 44 Hz in the $^{31}P\{^1H\}$ NMR spectrum even after 1 h. Considering the results obtained by Sanford,[33] the formed oxidative adduct Ni(COPh)F(PCy_3)$_2$ caused decarbonylation to form Ni(Ph)F(PCy_3)$_2$ at room temperature within 10 min, in our case, the *in situ* generated Ni(COPh)F(PPh_3)$_2$ must be more unstable due to the weak coordination ability of PPh_3 than PCy_3. We thus concluded that



Scheme 2 Two-step borylation of probenecid.[a] [a]Reaction conditions: **1w** (0.2 mmol), **2a** (0.4 mmol), Ni(cod)$_2$ (0.02 mmol), PPh_3 (0.06 mmol), KF (0.5 mmol), NaCl (0.4 mmol), toluene (0.66 mL), octane (0.33 mL), 140 °C, 24 h.



Scheme 3 Proposed mechanism.

the subsequent extrusion of carbon monoxide forming **B** could take place prior to transmetalation. Transmetalation between complex **B** and B_2pin_2 assisted by external KF (and NaCl) affords borylnickel(II) intermediate **C**. Finally, reductive elimination delivers the targeted arylboronates **3**, regenerating the Ni(0) species to complete a catalytic cycle.

In summary, we have developed the first decarbonylative borylation of aroyl fluorides with the assistance of an abundant and inexpensive metal Ni/PPh_3 catalytic system with B_2pin_2 as a coupling nucleophile, which is capable of producing various aromatic boronates. Importantly, this method realized that carboxylic acids can be converted into a wide array of arylboronates *via* aroyl fluorides. Currently, we are investigating the theoretical calculations to determine the reaction mechanism including a decarbonylation step, and other transition-metal-catalysed transformations of aroyl fluorides.

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Conflicts of interest

There are no conflicts to declare.

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PPh_3-Assisted Esterification of Acyl Fluorides with Ethers via C(sp^3)–O Bond Cleavage Accelerated by TBAT

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Abstract: We describe the (triphenylphosphine (PPh_3)-assisted methoxylation of acyl fluorides with cyclopentyl methyl ether (CPME) accelerated by tetrabutylammonium difluorotriphenysilicate (TBAT) via regiospecific C–OMe bond cleavage. Easily available CPME is utilized not only as the solvent, but a methoxylating agent in this transformation. The present method is featured by C–O and C–F bond cleavage under metal-free conditions, good functional-group tolerance, and wide substrate scope. Mechanistic studies revealed that the radical process was not involved.

Keywords: Acyl fluorides; cyclopentyl methyl ether (CPME); tetrabutylammonium difluorotriphenysilicate (TBAT); carbon-oxygen bond cleavage; esterification

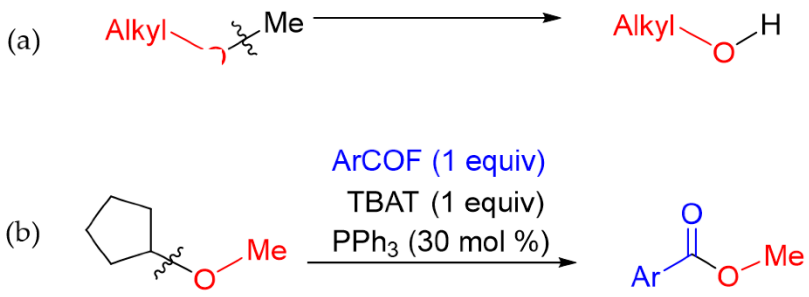
1. Introduction

The C–O bond cleavage in ethers is one of the most fundamental transformations in organic synthesis and has been widely applied in the manufacturing of fine chemicals as well as the synthesis of polyfunctional molecules [1–5]. Particularly, the preparation and degradation of ethers have often been considered important synthetic strategies for the protection/deprotection of hydroxyl groups. Although numerous studies on demethylation in aromatic methyl ethers have been reported [6–10], demethylation of viable aliphatic surrogates has been relatively less explored. Typically, various reagents have been utilized to convert aliphatic methyl ethers into the corresponding alcohols via demethylation (Scheme 1a), employing $BF_3{\cdot}Et_2O$/$(CH_3CO)_2O$ [11], BCl_3 [12], BBr_3 [13], $BF_3{\cdot}Et_2O$/EtSH [14], Me_3SiI [15], hydrobromic acid/phase-transfer-catalysts [16], BBr_3/NaI/15-crown-5 [17], $(CH_3)_2BBr$ [18], $AlCl_3$/NaI/CH_3CN [19], or BI_3/*N*,*N*-diethylaniline [20].

On the other hand, since 2005, cyclopentyl methyl ether (CPME) [21,22] has become the common solvent in organic reactions [23–25]. Compared with other conventional ethereal solvents such as diethyl ether (Et_2O), tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), 1,4-dioxane, methyl *tert*-butyl ether (MTBE), and 2-MeTHF, CPME displays many advantages, such as low cost, high-boiling point (106 °C), low polarity, lower miscibility with water (1.1 g/100 g), low tendency to form peroxides, narrow explosion range, and stability under strong acidic and basic conditions. With these characteristics of CPME in mind, the utility of CPME as a potential reactant in various organic transformations are attractive. However, to the best of our knowledge, the selective C–O bond cleavage in CPME [26] and the utilization of released methoxy group as a methoxylating agent [27] has been unexplored.

Numerous examples for utilization of acyl fluorides in synthetic organic chemistry have been reported [28], while recently, unique reactivity of acyl fluorides has been extensively disclosed due to their strong electrophilicity and high stability [29,30]. Transformations of acyl fluorides into other

valuable molecules have been well demonstrated by others [31–36] and our group [37–40]. As a part of our ongoing interest in the functionalization of acyl halides, we herein report the nucleophilic methoxylation of acyl fluorides with CPME assisted by PPh_3 via both C–OMe and C–F bonds cleavage under metal-free conditions (Scheme 1b).

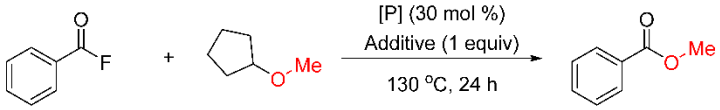


Scheme 1. C–O cleavage in alkyl methyl ethers. (**a**) Conventional demethylation of aliphatic methyl ethers (deprotection), (**b**) This work.

2. Results and Discussion

When we conducted the reaction of benzoyl fluoride (**1a**) with CPME (**2a**), giving rise to methyl benzoate (**3a**) in the presence of a catalytic amount of PPh_3, various additives were screened. As shown in Table, tetrabutylammonium difluorotriphenylsilicate (TBAT) [41] as the additive sufficiently increased the yield of **3a** in 74% yield (Table 1, entry 1). PPh_3 showed superior result than other monodentate phosphine ligands (entries 2–5). Compared to TBAT, several tetrabutylammonium halides such as tetrabutylammonium fluoride, -chloride, -bromide, and -iodide were tested, but they were found to be inferior (entries 6–9). Markedly, tetrabutylammonium trifluoromethanesulfonate (NBu_4OTf) did not work at all (entry 10). With regard to other fluoride sources, poor results were obtained when potassium fluoride (KF) or cesium fluoride (CsF) was employed (entries 11–12). Interestingly, in the presence of 18-crown-6, KF gave 34% of **3a** (entry 13), which might prove the importance of a naked fluoride ion. Notably, no trace of **3a** was detected with fluorotriphenysilane (entry 14) or without TBAT (entry 15), indicating that TBAT uniquely accelerated this methoxylation event (Table S1). Careful control experiments resulted in an unexpected accelerating effect on methoxylation with 30 mol % of PPh_3 (entry 1 *vs* entry 16), suggesting that an addition of PPh_3 can enhance the electrophilicity of acyl fluorides, to some extents (Table S2) [42]. It is noteworthy that the identical reaction with benzoyl chloride afforded the lower yield of **3a** (entry 17), suggesting a unique feature of acyl fluoride in this transformation.

Table 1. Optimization of the reaction conditions.



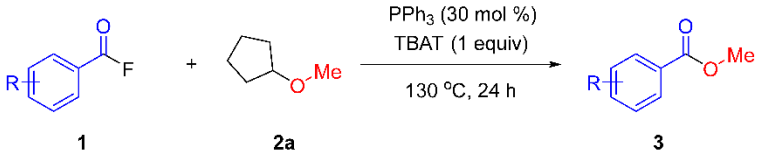
1a **2a** **3a**

Entry	[P]	Additive	Yield of 3a (%) [1]
1	PPh_3	TBAT	74 (74)
2	$P(OPh)_3$	TBAT	40

3	PCy_3	TBAT	50
4	P^tBu_3	TBAT	45
5	$P(4\text{-}F\text{-}C_6H_4)_3$	TBAT	55
6	PPh_3	NBu_4F	46
7	PPh_3	NBu_4Cl	30
8	PPh_3	NBu_4Br	14
9	PPh_3	NBu_4I	25
10	PPh_3	NBu_4OTf	0
11	PPh_3	KF	12
12	PPh_3	CsF	14
13	PPh_3	18-crown-6/KF	34
14	PPh_3	Ph_3SiF	0
15	PPh_3	-	0
16	-	TBAT	53
17[2]	PPh_3	TBAT	50

[1] Determined by gas chromatography (GC) analysis of the crude mixture using *n*-dodecane as an internal standard. An isolated yield is given in parentheses. [2] Benzoyl chloride was employed instead of **1a**.

With the optimized reaction conditions in hand, we investigated the scope and limitation of the methoxylation of an array of acyl fluorides **1** with CPME. As shown in Figure 1, this protocol displayed remarkable tolerance towards the substitution pattern and a steric effect. Both electron-donating and sterically encumbering substituents in any positions of the aryl ring gave good results. Another interesting feature of this reaction is that alkyl aryl ethers such as **3c** and **3d** were inert under the conditions. Acyl fluorides bearing electron-donating groups provided the corresponding products **3e–3g** in 64–90% isolated yields. When acyl fluorides with electron-withdrawing groups were employed, except for 4-nitrobenzoyl fluoride (**1i**), the desired products **3h**, **3j**, and **3k** were obtained in good yields. Particularly, an ester group can also be tolerated, affording the target product **3l** in 75% yield, which is noteworthy because the esters are known to be incompatible with Me_3SiI [15]. Either more sterically hindered (**3n**) or more electron-rich (**3o**) products were successfully formed in this transformation. Polyaromatic products including naphthalenes (**3p**–**3q**) and anthracene (**3r**) motifs also exhibited moderate to good levels of reactivity. Moreover, oxygen- (**3s** and **3t**), sulfur-containing heterocycles (**3u**) did not interfere toward the ester formation. To our delight, the primary and tertiary alkylated acyl fluorides also could accommodate under optimal conditions, afforded corresponding ester **3v** and **3w** in moderate yields.



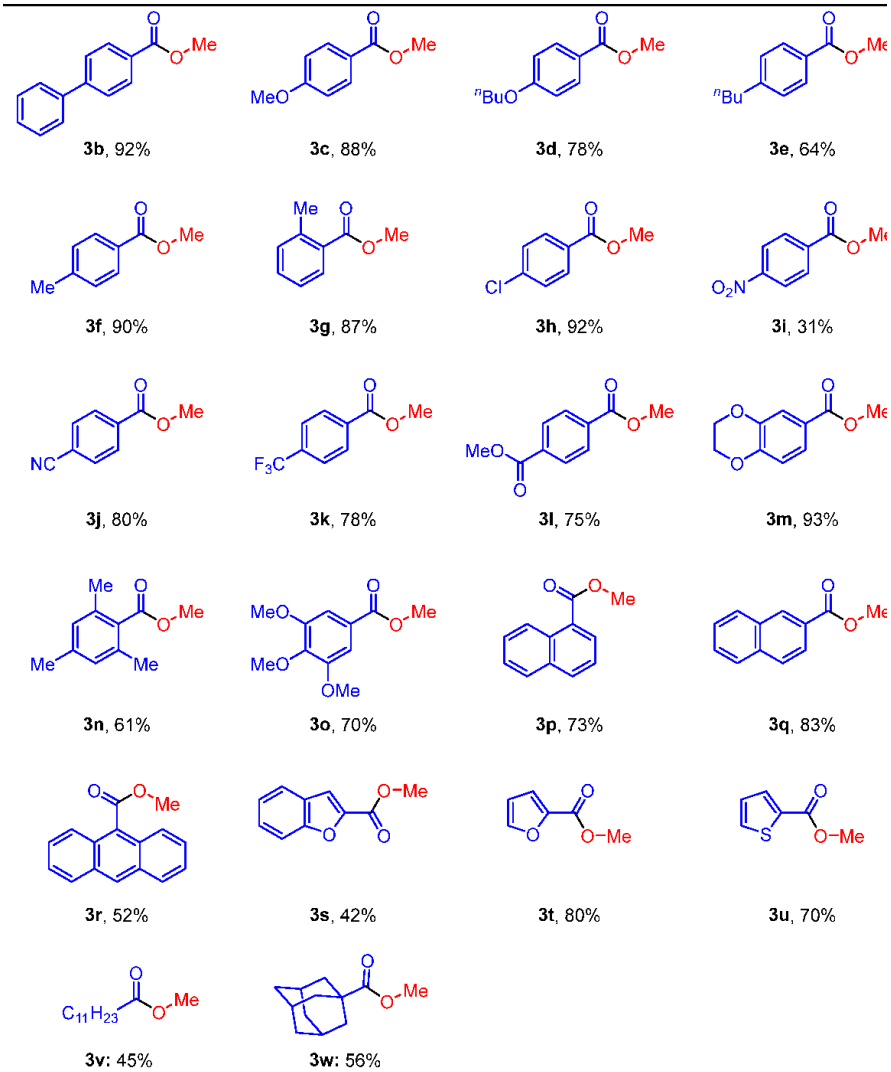
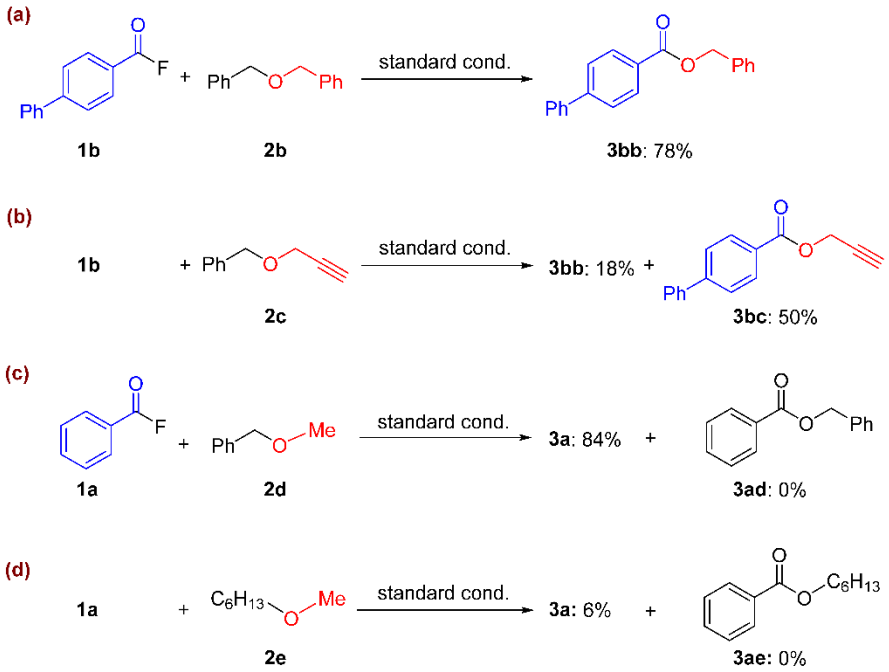


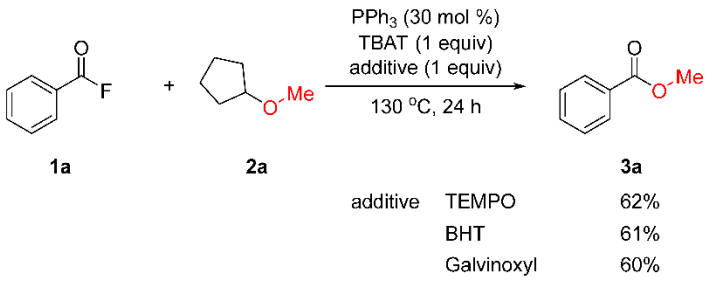
Figure 1. Methoxylation of acyl fluorides **1** with CPME (**2a**) [a,b]. [a] Reaction conditions: acyl fluorides **1** (0.2 mmol), **2a** (2 mL), PPh_3 (0.06 mmol), TBAT (0.2 mmol), 130 °C, 24 h. [b] Isolated yields.

Given a regiospecific cleavage of C–O bond in CPME, we reasoned that other ethers could also be applied in alkoxylation of acyl fluorides (Scheme 2). Dibenzyl ether (**2b**) was also a good substrate, resulting in the formation of **3bb** in 78% yield (Scheme 2a). When benzyl propargyl ether (**2c**) was employed, a propargyl group was installed preferentially into the product to afford **3bc** in 50% yield, along with 18% of **3bb** (Scheme 2b). Subsequently, unsymmetrical benzyl methyl ether (**2d**) smoothly gave **3a** in 84% yield with a high regiospecificity (Scheme 2c). In a sharp contrast, *n*-hexyl methyl ether failed to undergo the reaction, leading to only 6% of **3a** and no competitive product **3ae** was detected (Scheme 2d). Although the cleavage patterns highly depend on the reagents added [1–5], the regiospecific C–O bond cleavage in this transformation can be explained by the stability of the resulting carbocations.



Scheme 2. (**a**) Alkoxylation of **1b** with dibenzyl ether (**2b**). (**b**) Alkoxylation of acyl fluorides **1b** with benzyl propargyl ether (**2c**). (**c**) Alkoxylation of acyl fluorides **1a** with benzyl methyl ether (**2d**). (d) Alkoxylation of acyl fluorides **1a** with hexyl methyl ether (**2e**).

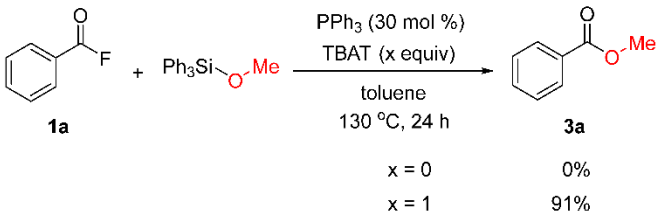
To clarify the reaction mechanism, we performed the methoxylation in the presence of radical scavengers (Scheme 3). Consequently, in the presence of equimolar amount of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), 2,6-di-tert-butyl-4-methylphenol (BHT), or 9,10-dihydroanthracene (DHA), the reaction proceeded with comparable efficiency to that without a radical scavenger, ruling out a radical pathway of this transformation.



Scheme 3. Methoxylation of **1a** with **2a** in the presence of radical scavengers.

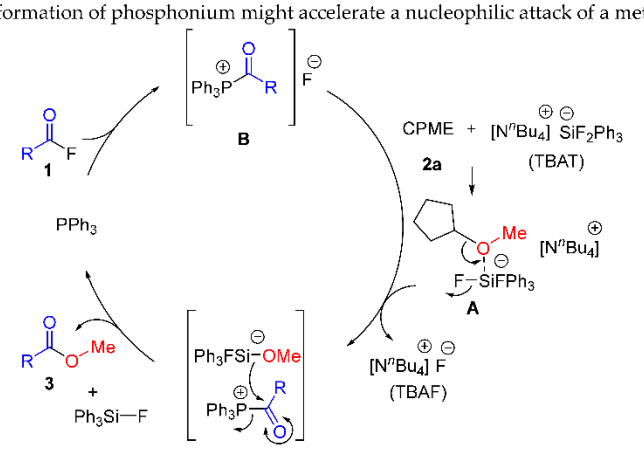
Next, we hypothesized that this PPh_3-assisted transformation might proceed via methoxytriphenylsilane (Ph_3SiOMe) as the intermediate [43]. When we carried out the reaction using Ph_3SiOMe instead of CPME under the optimized conditions (Scheme 4), no desired product **3a** was formed in the absence of TBAT, along with the recovered **1a** (91%) and Ph_3SiOMe (95%). In a sharp contrast, the reaction of **1a** with Ph_3SiOMe in the presence of TBAT, 91% of **3a** was obtained. These results indicate that the reaction of TBAT with CPME generates many nucleophilic pentacoordinate

silicates [44]. Hypervalent silicates are the key organosilicon species to promote the nucleophilic substitution step, which is normally reluctant with less nucleophilic tetracoordinate organosilicon compounds [45].



Scheme 4. Methoxylation of **1a** with Ph_3SiOMe.

A plausible reaction mechanism is outlined in Scheme 5. Initially, CPME (**2a**) interacts with TBAT to form a hypervalent silicate **A**, which is supposed to cleave C–OMe bond, affording silicate [$Ph_3FSiOMe$] . Meanwhile, acyl fluorides **1** react with PPh_3 to generate phosphonium **B** which can be more electrophilic to participate in methoxylation by nucleophilic attack of a methoxide ion to a carbonyl group, giving the desired product **3** and Ph_3SiF which was confirmed by $^{19}F\{^1H\}$ nuclear magnetic resonance (NMR) spectrum. Although a role of a catalytic amount of PPh_3 has not been clarified, the formation of phosphonium might accelerate a nucleophilic attack of a methoxide to **1**.



Scheme 5. Proposed mechanism.

3. Experimental Sections

3.1. General

Unless otherwise noted, all the reactions were carried out under an argon atmosphere using standard Schlenk techniques. Glassware was dried in an oven (150 °C) and heated under reduced pressure prior to use. Solvents were employed as eluents for all other routine operation, as well as dehydrated solvent were purchased from commercial suppliers and employed without any further purification. For thin layer chromatography (TLC) analyses throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. Silica gel column chromatography was carried out using Silica gel 60 N (spherical, neutral, 40-100 µm) from Kanto Chemicals Co., Inc. (Tokyo, Japan) NMR spectra (^1H and $^{19}F\{^1H\}$) were recorded on Varian INOVA-600 (600 MHz) or Mercury-400 (400 MHz) spectrometers (Agilent Technologies International Japan, Ltd., Tokyo, Japan). Chemical shifts (δ) are in parts per million relative to $CDCl_3$ at 7.26 ppm for ^1H. The $^{19}F\{^1H\}$ NMR spectra were

measured by using CCl_3F (= 0.00 ppm) as an external standard. The NMR yields were determined using dibromomethane as an internal standard. The GC yields were determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard.

3.2. Experimental Method

3.2.1. Representative Procedure for the Synthesis of Acyl Fluorides from Acyl Chlorides

To a 50 mL of Schlenk tube charged with a magnetic stir bar, were successively added acyl chlorides (4 mmol), 18-crown-6 (52.9 mg, 0.2 mmol, 5 mol %), KF (2.32 g, 40 mmol, 10 equivalents), and THF (20 mL). After the reaction mixture was stirred at 40 °C for 24 h, insoluble inorganic solid (KF or KCl) was filtered, and the volatiles were removed using a rotary evaporator. The crude product was purified by bulb-to-bulb distillation to afford the corresponding acyl fluorides **1** [46].

3.2.2. Representative Procedure for the Synthesis of Acyl Fluorides from Carboxylic Acids

To a 20 mL of Schlenk tube charged with a magnetic stir bar, were successively added carboxylic acids (3.0 mmol) and CH_2Cl_2 (15 mL). After the mixture was stirred at 0 °C for 30 min, Deoxo-Fluor® reagent (608 µL, 1.1 equivalents, 3.3 mmol) was slowly added to the reaction mixture. After the reaction mixture was stirred at 0 °C for 30 min, the solution was slowly poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 (3 × 15 mL), and dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel to afford the corresponding acyl fluorides **1** [47].

3.2.3. Synthesis of Methoxytriphenylsilane

To methanol (2 mL), were added chlorotriphenylsilane (1.179 g, 4 mmol) and triethylamine (607.1 mg, 6 mmol, 1.5 equiv). The reaction mixture was stirred under argon for 72 h until full conversion. Next, the reaction mixture was evaporated to dryness, dissolved in diethyl ether (100 mL), and washed with H_2O (1 × 5 mL, 2 × 2.5 mL). Organic phase was dried over sodium sulfate and evaporated. The crude product was purified by flash chromatography (*n*-hexane: EtOAc = 40:1) to afford methoxytriphenylsilane in 95% yield [48].

3.2.4. General Methods for the Synthesis of Benzyl Ethers **2b**–**2d**

To a solution of the corresponding alcohol (20 mmol) in DMF (20 mL), was added sodium hydride (1.2 g, 30 mmol, 60% in paraffin oil, 1.5 equivalents) at 0 °C under argon. After the reaction mixture was stirred for 30 min, benzyl bromide (2.95 mL, 30 mmol, 1.5 equivalents) was added to the reaction mixture at 0 °C and the solution was stirred at room temperature for 5 h. Then the reaction mixture was quenched with H_2O (10 mL) and extracted with Et_2O (20 mL × 2). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by silica-gel column chromatography (*n*-hexane: EtOAc = 40:1) to give the corresponding benzyl ether derivatives **2b**–**2d** [49].

3.2.5. Representative Procedure for Methoxylation of Acyl Fluorides **1** with CPME (2a)

To a 20 mL Schlenk tube containing PPh_3 (15.7 mg, 0.06 mmol, 30 mol %,) and TBAT (108 mg, 0.2 mmol, 1 equivalents), were added [1,1'-biphenyl]-4-carbonyl fluoride (**1b**) (40.0 mg, 0.2 mmol,) and CPME (2.0 mL). Subsequently, the resulting mixture was heated at 130 °C. After 24 h, cyclopentyl methyl ether (**2a**) was removed by a rotary evaporator (for the high-boiling-point ethers were removed by bulb-to-bulb distillation), and the residue was purified by column chromatography (*n*-hexane: EtOAc = 20:1) to afford methyl [1,1'-biphenyl]-4-carboxylate (**3b**) (39 mg, 0.184 mmol) in 92% yield. Spectroscopic data for methyl esters matched with those previously reported in the literature, and ^1H and $^{19}F\{^1H\}$ NMR spectra of representative starting materials and the prepared products are shown in Supplementary Materials.

3.3. Characterization Data of Starting Materials and Products

Methoxytriphenylsilane [48]. Yield: 95% (1.1 g); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H), 7.37–7.47 (m, 9H), 7.60–7.67 (m, 6H).

((Prop-2-yn-1-yloxy)methyl)benzene (**2c**) [49]. Yield: 80% (2.34 g); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.47 (s, 1H), 4.18 (d, *J* = 2.4 Hz, 2H), 4.62 (s, 2H), 7.29–7.33 (m, 1H), 7.34–7.39 (m, 4H).

Methyl benzoate (**3a**) [50]. Yield: 74% (20.2 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.42-7.47 (m, 2H), 7.53–7.58 (m, 1H), 8.02-8.07 (m, 2H).

Methyl [1,1'-biphenyl]-4-carboxylate (**3b**) [51]. Yield: 92% (39.1 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.61–7.68 (m, 4H), 8.11 (d, *J* = 8.2 Hz, 2H).

Methyl 4-methoxybenzoate (**3c**) [50]. Yield: 88% (29.2 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 3.88 (s, 3H), 6.91 (d, *J* = 8.9 Hz, 2H), 7.99 (d, *J* = 9.0 Hz, 2H).

Methyl 4-butoxybenzoate (**3d**) [52]. Yield: 78% (32.5 mg); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.4 Hz, 3H), 1.46–1.53 (m, 2H), 1.78 (ddt, *J* = 9.1, 7.7, 6.5 Hz, 2H), 3.88 (s, 3H), 4.01 (s, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 7.92–8.03 (m, 2H).

Methyl 4-butylbenzoate (**3e**) [53]. Yield: 64% (24.6 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.31–1.40 (m, 2H), 1.55–1.67 (m, 2H), 2.63-2.68 (m, 2H), 3.90 (s, 3H), 7.24 (dt, *J* = 8.6, 0.6 Hz, 2H), 7.90–7.98 (m, 2H).

Methyl 4-methylbenzoate (**3f**) [50]. Yield: 90% (27.0 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.90 (s, 3H), 7.24 (dt, *J* = 8.0, 0.6 Hz, 2H), 7.89–7.97 (m, 2H).

Methyl 2-methylbenzoate (**3g**) [54]. Yield: 87% (26.2 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (s, 3H), 3.89 (s, 3H), 7.22–7.26 (m, 2H), 7.39 (td, *J* = 7.5, 1.3 Hz, 1H), 7.91 (dd, *J* = 8.2, 1.2 Hz, 1H).

Methyl 4-chlorobenzoate (**3h**) [50]. Yield: 92% (31.4 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.95–8.00 (m, 2H).

Methyl 4-nitrobenzoate (**3i**) [55]. Yield: 31% (11.3 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 8.19–8.23 (m, 2H), 8.26–8.31 (m, 2H).

Methyl 4-cyanobenzoate (**3j**) [56]. Yield: 80% (25.8 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 7.71–7.77 (m, 2H), 8.10–8.17 (m, 2H).

Methyl 4-(trifluoromethyl)benzoate (**3k**) [50]. Yield: 78% (32.0 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 7.69–7.73 (m, 2H), 8.11–8.18 (m, 2H).

Dimethyl terephthalate (**3l**) [55]. Yield: 75% (29.0 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 6H), 8.10 (s, 4H).

Methyl 2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylate (**3m**) [57]. Yield: 93% (36.1 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 4.25–4.28 (m, 2H), 4.29–4.32 (m, 2H), 6.86–6.90 (m, 1H), 7.52–7.58 (m, 2H).

Methyl 2,4,6-trimethylbenzoate (**3n**) [58]. Yield: 61% (21.8 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 9H), 3.89 (s, 3H), 6.85 (s, 2H).

Methyl 3,4,5-trimethoxybenzoate (**3o**) [59]. Yield: 70% (31.7 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (d, *J* = 1.0 Hz, 12H), 7.29 (s, 2H).

Methyl 1-naphthoate (**3p**) [54]. Yield: 73% (27.2 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 3H), 7.48–7.56 (m, 2H), 7.62 (ddd, *J* = 8.6, 6.8, 1.5 Hz, 1H), 7.89 (ddd, *J* = 8.2, 1.4, 0.7 Hz, 1H), 8.02 (ddd, *J* = 8.3, 1.4, 0.7 Hz, 1H), 8.19 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.89–8.95 (m, 1H).

Methyl 2-naphthoate (**3q**) [60]. Yield: 83% (31.0 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (s, 3H), 7.57 (dddd, *J* = 19.6, 8.1, 6.9, 1.4 Hz, 2H), 7.88 (dt, *J* = 8.0, 1.2 Hz, 2H), 7.95 (ddt, *J* = 8.0, 1.4, 0.7 Hz, 1H), 8.07 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.62 (dd, *J* = 1.6, 0.8 Hz, 1H).

Methyl anthracene-9-carboxylate (**3r**) [54]. Yield: 52% (24.6 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (s, 3H), 7.47-7.57 (m, 4H), 8.03 (dd, *J* = 8.4, 4.1 Hz, 4H), 8.54 (s, 1H).

Methyl benzofuran-2-carboxylate (**3s**) [61]. Yield: 42% (14.8 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.31 (ddd, *J* = 7.9, 7.2, 0.8 Hz, 1H), 7.46 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.54 (t, *J* = 0.7 Hz, 1H), 7.59 (dq, *J* = 8.3, 0.8 Hz, 1H), 7.69 (ddd, *J* = 7.9, 1.4, 0.7 Hz, 1H).

Methyl furan-2-carboxylate (**3t**) [62]. Yield: 80% (20.2 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.47 (dd, *J* = 3.5, 1.8 Hz, 1H), 7.14 (dd, *J* = 3.5, 0.9 Hz, 1H), 7.54 (dd, *J* = 1.7, 0.9 Hz, 1H).

Methyl thiophene-2-carboxylate (**3u**) [54]. Yield: 70% (20 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 7.55 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.80 (dd, *J* = 3.7, 1.3 Hz, 1H).

Methyl dodecanoate (**3v**) [63]. Yield: 45% (19.4 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85–0.90 (m, 3H), 1.23–1.30 (m, 16H), 1.62 (td, *J* = 7.1, 3.0 Hz, 2H), 2.27-2.32 (m, 2H), 3.66 (s, 3H).

Methyl (3r,5r,7r)-adamantane-1-carboxylate (**3w**) [64]. Yield: 56% (21.8 mg); white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.68–1.73 (m, 6H), 1.88–1.89 (m, 6H), 1.99–2.02 (m, 3H), 3.64 (s, 3H).

Benzyl [1,1'-biphenyl]-4-carboxylate (**3bb**) [65]. Yield: 78% (45.1 mg); white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.40 (s, 2H), 7.33–7.43 (m, 4H), 7.45–7.49 (m, 4H), 7.61-7.64 (m, 2H), 7.65–7.68 (m, 2H), 8.13–8.17 (m, 2H).

Prop-2-yn-1-yl [1,1'-biphenyl]-4-carboxylate (**3bc**) [66]. Yield: 50% (23.6 mg); white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.54 (t, *J* = 2.4 Hz, 1H), 4.96 (d, *J* = 2.5 Hz, 2H), 7.39-7.43 (m, 1H), 7.45–7.50 (m, 2H), 7.61–7.64 (m, 2H), 7.66–7.70 (m, 2H), 8.12-8.18 (m, 2H).

4. Summary

In summary, we report the PPh_3-assisted methoxylation via the regiospecific cleavage of the inert C–OMe bond in CPME. This protocol demonstrated the utility of CPME as a methoxylating reagent, good functional group tolerance, and metal-free conditions. Furthermore, the regiospecific cleavage of aliphatic ethers, even in the presence of aromatic ethers, is quite difficult to achieve by conventional reagents. We believe that our study constitutes an important contribution towards a more practical use of readily available aliphatic ethers as coupling partners. Further explorations of related transformations via C–O scission are currently underway in our laboratory.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1. Details of screening the amounts of TBAT and PPh3 (Table S1), the effect of PPh_3 (Table S2), and ^{1}H and ^{19}F{^{1}H} NMR spectra of representative starting materials and final products.

Author Contributions: Z.W. developed above reactions and wrote the manuscript; Z.W. and X.W. prepared starting materials and expanded the substrates scope; Y.N. supervised the project and revised the manuscript.

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Nickel-Catalyzed Decarbonylative Cyanation of Acyl Chlorides

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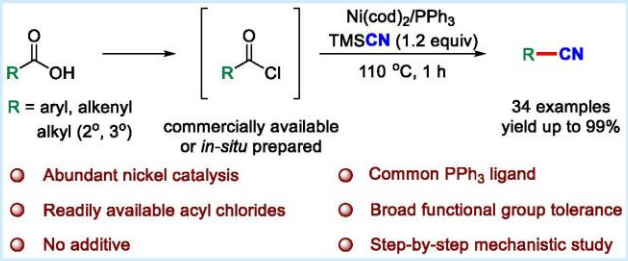
Supporting Information

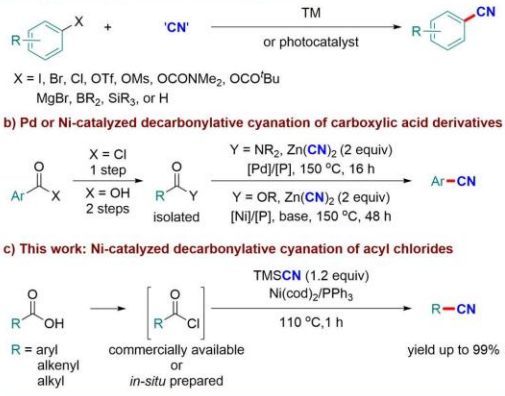


ABSTRACT: Ni-catalyzed decarbonylative cyanation of acyl chlorides with trimethylsilyl cyanide has been achieved. This transformation is applicable to the synthesis of an array of nitrile compounds bearing a wide range of functional groups under neutral conditions. The step-by-step experimental studies revealed that the reaction sequences of the present catalytic reaction are oxidative addition, transmetalation, decarbonylation, and reductive elimination.

Nitriles are prevalent in natural products, pharmaceuticals, agrochemicals, dyes, and herbicides[1] as well as important intermediates.[2] In particular, arylnitriles can be obtained via the classical methods of Sandmeyer[3] and Rosenmund−von Braun[4] reactions by the treatment of diazonium salts or aryl halides with CuCN, and various synthetic routes to arylnitriles have been further developed.[5−7] Alternatively, transition-metal (TM)-catalyzed nucleophilic cyanation of "preactivated" aryl halides[8] and phenol derivatives[9] and electrophilic cyanation of organometallic reagents[10] with various CN sources have well been developed (Scheme 1a). Higher atom-economy cyanation of arene C−H bonds by TM-catalyzed,[11] TM-mediated,[12] or photoinduced[13] reactions with the aid of suitable directing groups or electron-rich (hetero)arenes has been achieved.

On the contrary, carboxylic acids are potential candidates as electrophiles because they are naturally abundant and readily available.[14] However, the direct transformation of carboxylic acids and their derivatives to nitriles has various drawbacks, for example, the requirement of additional preparatory steps, the use of excess reagents, harsh conditions, and the narrow range substrates.[15] Recently, two pioneering studies on decarbonylative cyanation have been disclosed (Scheme 1b). Szostak demonstrated the Pd-catalyzed decarbonylative cyanation of amides with $Zn(CN)_2$, affording a wide range of arylnitriles.[16] Subsequently, Rueping developed the Ni-catalyzed cyanation of phenolic esters or amides with $Zn(CN)_2$ in which 2 equiv of base were required to reach higher yields.[17] However, all of the starting materials, amides, and esters in the above-mentioned

Scheme 1. Synthetic Routes for Nitriles



reactions need to be presynthesized from the corresponding acyl chlorides. Therefore, a direct and mild protocol of decarbonylative cyanation of acyl chlorides to nitriles is of great interest because acyl chlorides are commercially available

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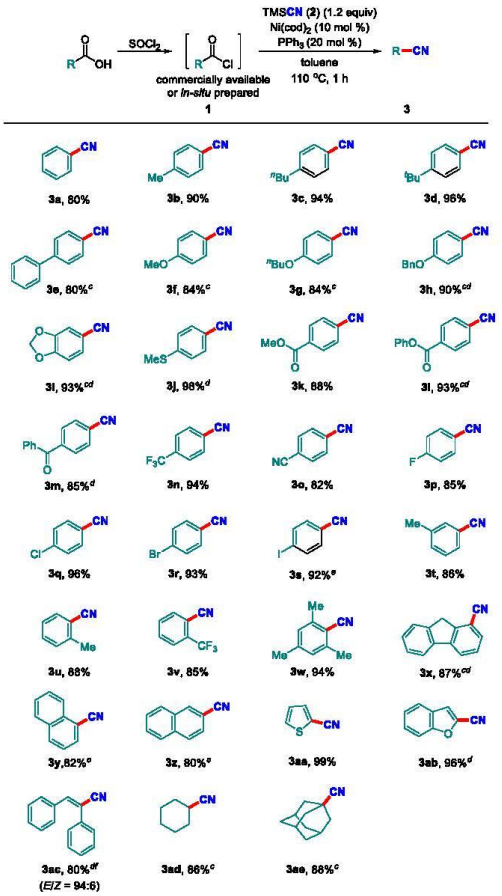
or could be easily prepared from the abundant carboxylic acids.[18] Although catalytic decarbonylative-type reactions of acyl chlorides could accommodate transformations for C−X bond construction,[19] including arylation,[20] chlorination,[21] silylation,[22] Mizoroki−Heck reaction,[23] and difluoromethylation,[24] to the best of our knowledge, decarbonylative cyanation of acyl chlorides has been virtually unexplored. In our continuing interests in the nickel-catalyzed decarbonylative transformation of acyl halides,[25] we herein report the establishment of an efficient and practical synthetic method of nitriles from carboxylic acids via acyl chlorides (Scheme 1c).

We commenced the model reaction of benzoyl chloride (**1a**) with trimethylsilyl cyanide (TMSCN, **2**) as the substrates. After the extensive optimization of reaction parameters (Tables S1−S10), an inexpensive catalytic system of $Ni(cod)_2$ and PPh_3 effectively facilitated the decarbonylative cyanation of **1a** to afford benzonitrile (**3a**) in 80% yield (Table S10, entry 1). Notably, the exogenous base was not necessary, and this transformation could afford satisfying yields of the corresponding nitriles at 110 °C within 1 h. The previously reported palladium- or nickel-catalyzed decarbonylative cyanation of carboxylic acid derivatives required an extended reaction time (16−48 h) and high temperature (150 °C).[16,17] Although triphenylphosphite gave benzonitrile (**3a**) in 72% yield (Table S10, entry 2), monodentate phosphine ligands such as PEt_3, $PnBu_3$, or PCy_3 were found to be inferior (Table S10, entries 3−5). These ligand effects indicate that less electron-donating phosphine ligands are highly suitable for the present reaction regardless of the cone angles. $Zn(CN)_2$ that has been successfully used in the Ni- or Pd-catalyzed decarbonylative cyanation reaction[16,17] gave no products. Because no formation of benzoyl cyanide was detected, the highly selective formation of **3a** rather than benzoyl cyanide might be a consequence of the unfavorable reductive elimination between the benzoyl group and the cyano group, both of which are electron-poor ligands. Decarbonylation triggers reductive elimination between an electron-rich aryl ligand and an electron-deficient cyano ligand by a favorable electronic synergy.

The optimized reaction conditions were applied for various acyl chlorides, and the results are summarized in Scheme 2. It is noteworthy that the acyl chlorides used were not only commercially available but in situ prepared from corresponding carboxylic acids for the one-pot protocol (denoted as footnote *d*), which demonstrates a practicability of the present transformation. Initially, a qualitative assessment of the electronic trend of the decarbonylative cyanation reaction was examined. Electron-donating alkyl groups installed in the *para* position of acyl chloride could give the corresponding nitriles **3b−d** in 90−96% yield. When the substrates bearing ether **3f−h** and acetal **3i** groups were employed, the higher temperature was required to gain satisfying results. Methylthio (**3j**), methoxycarbonyl (**3k**), phenoxycarbonyl (**3l**), and benzoyl (**3m**) groups were well tolerated to give the desired products in good to excellent yield. On the contrary, a series of electron-deficient *para*-substituted acyl chlorides having trifluoromethyl, cyano, and halogens smoothly furnished **3n−s** in 82−96% yield. Although bromide and iodide are known to be reactive for oxidative addition to nickel catalysts, they were compatible during the reactions. Sterically hindered *ortho* substituents were also productive for the formation of arylnitriles **3u** and **3v**, regardless of the electronic nature of the substituents. Even more sterically hindered 2,4,6-trimethylbenzoyl chloride (**1w**) was efficiently converted into

Scheme 2. Nickel-Catalyzed Decarbonylative Cyanation[a,b]



[a]Reaction conditions: acyl chlorides **1** (0.2 mmol), TMSCN (**2**, 0.24 mmol), $Ni(cod)_2$ (0.02 mmol), PPh_3 (0.04 mmol), toluene (1 mL), 110 °C, and 1 h. [b]Isolated yield. [c]150 °C, 1 h. [d]Corresponding carboxylic acid (0.2 mmol) was used. [e]80 °C, 1 h. [f]**1ac** (*E*/*Z* 94:6) was used.

3w in 94% yield. Fused aromatic acyl chlorides (**1x−z**) could be incorporated and gave the corresponding arylnitriles in 80−87% yield at the elevated temperature. It should be noted that heteroatom-containing acyl chlorides also participated in the reaction, furnishing the desired nitriles **3aa** and **3ab** in 99 and 96% yield, respectively. Strikingly, the reaction scope could be readily extended to the synthesis of α,β-unsaturated nitriles (**3ac**). More surprisingly, secondary (**1ad**) and tertiary (**1ae**) alkylated acyl chlorides were proved to be an ideal coupling partner, although primary counterparts were unsuccessful; lauroyl chloride gave only 17% of the corresponding nitrile under standard conditions.

To demonstrate the synthetic utility of the present reaction, the decarbonylative cyanation of biologically active compounds was conducted. Cyanation of probenecid,[26] a carboxylic-acid-containing drug, was viable and gave **3af** in 92% yield (Scheme

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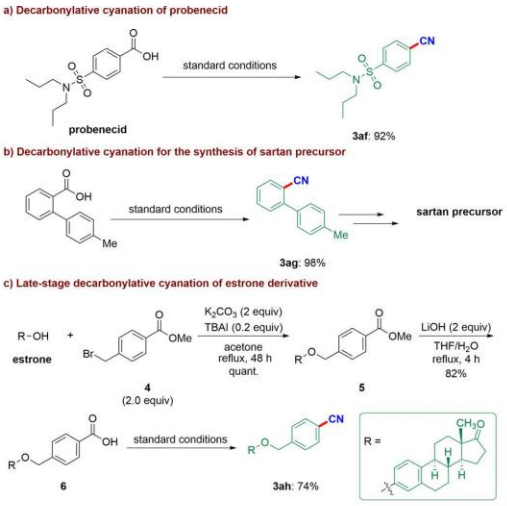
Org. Lett. 2019, 21, 6779−6784

3a). A key intermediate in the synthesis of sartan derivatives,[27] 2-(4-tolyl)benzonitrile (**3ag**), was isolated in 98% yield

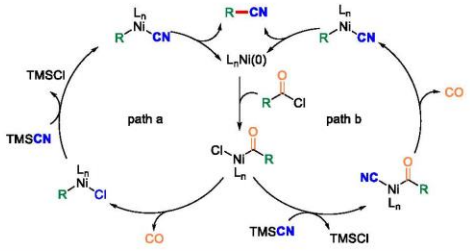
Scheme 3. Synthetic Applications



(Scheme 3b). Besides, we succeeded in the late-stage modification of a bioactive estrone derivative. The etherification of estrone with **4**, followed by the hydrolysis of **5** afforded carboxylic acid **6**. Finally, compound **6** was subjected to decarbonylative cyanation to provide **3ah** in 74% yield (Scheme 3c).

To date, reaction sequences for transition-metal-catalyzed decarbonylative couplings are still under debate. Two possible reaction pathways for the present reaction are shown in Scheme 4. In both pathways, the initial oxidative addition of

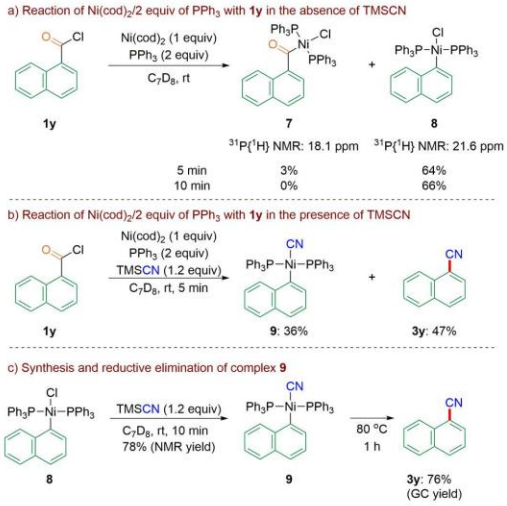
Scheme 4. Two Possible Reaction Pathways



acyl chloride to Ni(0) forms an acyl(chloro)nickel(II) species,[28] and the final reductive elimination affords the product. In path a, CO elimination takes place prior to transmetalation with TMSCN, which was supported by Shi[29] and Sanford.[30] They conducted stoichiometric reactions to isolate acyl(halogeno)nickel(II) complexes, leading to a smooth decarbonylation process. In addition, theoretical calculations performed by Szostak also illustrated that the acylpalladium species is prone to decarbonylation.[31] Alternatively, path b involves the reaction sequences of the transmetalation of the acyl(chloro)nickel(II) complex with TMSCN prior to decarbonylation. Ritter[24] also showed experimental evidence for supporting path b by isolation of the intermediate complexes in the Pd-catalyzed decarbonylative difluoromethylation. Furthermore, Itami,[32] Rueping,[33] and Schoenebeck[34] performed density functional theory (DFT) calculations in which a lower energy barrier is required for a smooth decarbonylation of the intermediates than for transmetalation.

To clarify which pathway in Scheme 4 is more favorable, we carried out some stoichiometric reactions. Initially, the reaction of $Ni(cod)_2$ and 2 equiv of PPh_3 with 1-naphthoyl chloride (**1y**) in C_7D_8 was monitored by the $^{31}P\{^1H\}$ NMR measurements at room temperature (Scheme 5a). After 5

Scheme 5. Mechanistic Studies Using PPh_3 as the Ligand



min, a singlet at δ 18.1 assigned to acyl(chloro)nickel(II) complex **7** was observed in only 3% yield, which completely disappeared after 10 min, whereas 64% of aryl(chloro)nickel(II) complex **8** (δ 21.6) and 33% of $Ni(CO)_2(PPh_3)_2$ (δ 32.9) were detected. This result suggests that both oxidative addition and subsequent decarbonylation can readily occur due to a weak coordination ability of PPh_3, which possesses an open coordination site to accept the carbonyl ligand.

Given that no reaction took place between **1y** and TMSCN, we performed the identical reaction in the presence of TMSCN at room temperature (Scheme 5b). After 5 min, complex **9** was detected in 36% NMR yield, along with the formation of **3y** in 47% yield, suggesting that the rates of both transmetalation and decarbonylation are faster than that of reductive elimination, leading to the product **3y**.

Alternatively, complex **9** was prepared by the reaction of the once prepared complex **8**, derived from the reaction of $Ni(cod)_2$, 2 equiv of PPh_3, and **1y**, with TMSCN. Heating the toluene solution of complex **9** to 80 °C for 1 h smoothly afforded **3y** in 76% yield through reductive elimination (Scheme 5c). When the same reaction was conducted in the presence of 2 equiv of PPh_3, the yield of the product **3y** was dropped to 50%. These results strongly support the notion that the reductive elimination takes place by ligand dissociation to

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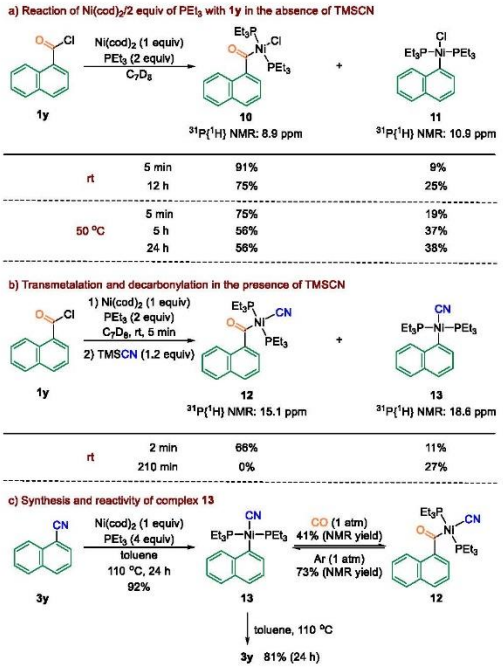
Org. Lett. 2019, 21, 6779−6784

form a three-coordinate complex rather than proceeding from a four-coordinate intermediate.

To verify the effect of the phosphine ligands, we conducted the identical stoichiometric reactions using PEt_3 (Scheme 6a).

Scheme 6. Mechanistic Studies Using PEt_3 as the Ligand



Similarly, the oxidative addition of **1y** to nickel was completed at room temperature within 5 min, and acyl(chloro)nickel(II) complex **10** was observed in 91% yield, along with aryl(chloro)nickel(II) complex **11** in 9% yield. Although this solution was kept for 12 h, 75% of complex **10** still remained intact. The same reaction was conducted at 50 °C, but no further decarbonylation occurred, even after 24 h. These results indicate the presence of an equilibrium between **10** and **11** and relatively unfavorable decarbonylation from **10** rather than **7**. To our delight, acyl(chloro)nickel complex **10** could be isolated in 45% yield, and its structure was unambiguously determined by X-ray analysis (Figure 1a).

Next, we investigated the reaction of the Ni(0) precursor with **1y** in the presence of TMSCN (Scheme 6b). The mixture of $Ni(cod)_2$, 2 equiv of PEt_3, and **1y** in C_7D_8 was stirred at room temperature for 5 min. Upon the addition of TMSCN, complex **10** was converted to produce complex **12** immediately in 66% yield. Complex **12** was then gradually converted to complex **13** in 27% yield via decarbonylation over 210 min, albeit with other unidentified major products bearing two PEt_3 ligands (22% combined yields). Besides, an insoluble solid was observed at the bottom of an NMR tube. With the results shown in Scheme 6a,b in hand, we concluded that transmetalation with TMSCN is faster than decarbonylation with a PEt_3 ligand.

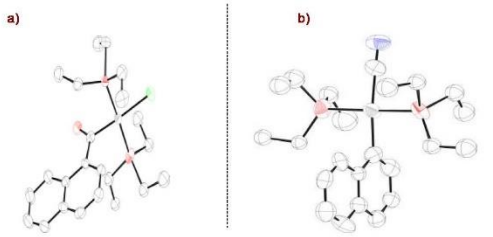
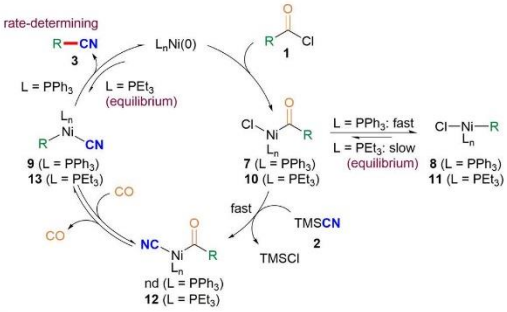


Figure 1. X-ray crystal structure of complexes (a) **10** and (b) **13**. ORTEP drawings with atoms at 50% probability. Hydrogen atoms are omitted for clarity. A PEt_3 ligand was treated as disordered.

Complex **13** could also be synthesized by oxidative addition of **3y** to $Ni(cod)_2$/4 PEt_3 in 92% NMR yield (Scheme 6c).[35] Upon heating complex **13** at 110 °C for 24 h, reductive elimination product **3y** was obtained in 81% yield. Although this observation is inconsistent with the result that a catalytic reaction did not proceed when PEt_3 was employed, no CO-coordinated Ni-complex was detected at all. Due to the robustness of the aryl(cyano)nickel(II) complex **13**, its X-ray analysis was successful (Figure 1b). Treatment of the toluene solution of complex **13** with CO gas in a balloon, complex **12** was detected in 41% NMR yield, along with the remaining complex **13** in 36% yield, while upon the replacement of CO with Ar, complex **13** was recovered in 73% NMR yield, indicating that a decarbonylation process is reversible.

On the basis of our experimental studies, we propose the mechanism of the present reaction (Scheme 7). Initially, the

Scheme 7. Proposed Mechanism



oxidative addition of acyl chlorides **1** to Ni(0) generates the acyl(chloro)nickel(II) intermediate **7** (L = PPh_3) or **10** (L = PEt_3). In the absence of **2**, the reaction rate of the decarbonylation of complex **7** leading to **8** is much faster than that of the conversion of complex **10** to **11**, whereas in the presence of **2**, although both transmetalation and decarbonylation are too fast to detect in the PPh_3 system, the transmetalation of acyl(chloro)nickel(II) **10** takes place to produce complex **12** prior to decarbonylation, forming complex **13** in the PEt_3 system. The fact that the lifetime of complex **9** was observed to some extent suggests that reductive elimination might be a rate-determining step in the catalytic cycle, although other possibilities such as the CO loss to regenerate the active Ni(0) catalyst cannot be ruled out.

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In summary, we have developed the decarbonylative cyanation of easily available acyl chlorides under nickel catalysis. This reaction can readily transform diverse acyl chlorides into nitriles with a broad substrate scope and functional group tolerance. Detailed mechanistic studies clarified the sequences of the reaction in the catalytic cycle. The utilization of a weaker coordinating PPh_3 ligand is crucial to facilitate both decarbonylation and reductive elimination steps.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02398.

Experimental procedures, characterization of new compounds, and spectroscopic data (PDF)

Accession Codes

CCDC 1909903−1909904 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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Presentation

1) Methoxylation of Aroyl Fluorides with Tris(2,4,6-trimethoxyphenyl)phosphine via Carbon-Fluorine and Carbon-Oxygen Bond Cleavages under Metal-Free Conditions
Xiu Wang, Zhenhua Wang, Yasushi Nishihara
The 98th CSJ Annual Meeting 2018 (2018.3.20-23/Nihon University, Funabashi Campus, Funabashi, Japan)

2) Nickel-Catalyzed Decarbonylative Silylation of Aroyl Fluorides
Xiu Wang, Zhenhua Wang, Li Liu, Yasushi Nishihara
The 99th CSJ Annual Meeting 2019 (2019.3.16-19/Konan University, Okamoto Campus, Kobe, Japan)

Other Presentation

1) Methoxylation of Aroyl Fluorides with Cyclopentyl Methyl Ether Mediated by Tetrabutylammonium difluorotriphenylsilicate (TBAT)
Zhenhua Wang, Xiu Wang, Yasushi Nishihara
The 98th CSJ Annual Meeting 2018 (2018.3.20-23/Nihon University, Funabashi Campus, Funabashi, Japan)

2) Nickel-Catalyzed Decarbonylative Borylation of Aroyl Fluorides
Zhenhua Wang, Xiu Wang, Yasushi Nishihara
65th Symposium on Organometallic Chemistry 2019 (2019.9.19-21/Doshisha University, Imadegawa Campus, Kyoto, Japan)

3) Nickel-Catalyzed Decarbonylative Cyanation of Acid Chlorides
Zhenhua Wang, Xiu Wang, Yasushi Nishihara
The 99th CSJ Annual Meeting 2019 (2019.3.16-19/Konan University, Okamoto Campus, Kobe, Japan)

4) Nickel-Catalyzed Decarbonylative Transformations of Acyl Halides

Yasushi Nishihara, Yasuhiro Okuda, Zhenhua Wang, Xiu Wang, Li Liu, and Yasuyuki Ura

The 20th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (2019,7.21-25/Heidelberg, Germany)

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