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長岡技術科学大学大学院工学研究科

博士論文

Studies on Novel Transformation of Aromatic Compounds through Reductive Activation of π-Electron System

π電子系の還元的活性化による芳香族化合物の新しい変換法に関する研究

所　　属　材料工学専攻

学籍番号　15343385

氏　　名　鄭素華

指導教員　前川博史

Content

1. General Introduction

1.1 Synthetic Organic Chemistry and Its Background

In our daily life, there are many organic substances around us, such as medicines, pesticides, plastics, and textiles. Since these organic substances are artificially produced, synthetic organic chemistry has become an indispensable research field in our lives. However, conventional synthetic organic reactions sometimes require extreme conditions, for example, high temperature, high pressure or use of harmful reagents.[(1)] The safety and the effects to the natural environment were frequently neglected in old days. The interests in the global warming have been focused and it has become an important issue from the viewpoint of green chemistry how we can efficiently synthesize the target product with a low environmental loading and short processes.[(2)] For the practical synthesis of pharmaceutical drugs and functional materials, *etc.* developing efficient, selective, simple, safe, and environment-friendly methods is strongly required (Figure 1-1).[(3)]

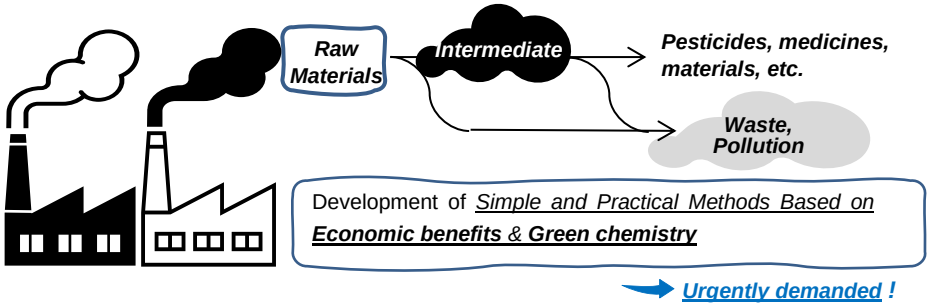


Figure 1-1 Requirement of rationalized processes

The development of reactions such as catalytic reactions and heavy metal-free reactions has been proceeding on the basis of green chemistry in the fields of organometallic chemistry,[(4)] photochemistry,[(5)] electrochemistry,[(6)] asymmetric synthesis,[(7)] redox-type reactions, [(8)] and so on in the recent decade.

1.2 Reductive Coupling Reactions by Electron Transfer

In the redox-type reactions, reductive coupling reactions, so called Umpolung are one of the excellent and sophisticated methods to synthesize various organic compounds.[8]

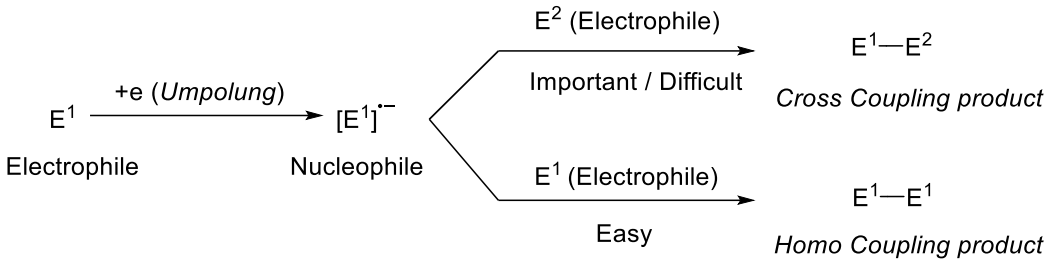
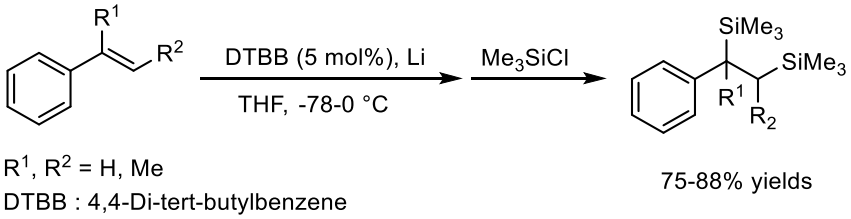


Figure 1-2 Inversion of polarity through electron transfer

A single electron transfer from metal or cathode to a substrate (E^1) generates an anion radical species and the electrophile E^1 is inverted to a nucleophile through Umpolung. When the anion species attacks another molecule of E^1, the homo coupling compound will be formed. On the other hand, when the anion radical species attacks the other type of electrophile (E^2), the cross coupling compound will be synthesized (Figure 1-2). However, the synthesis of cross coupling compounds is difficult in general because more electron-deficient compound will be reduced first, and another molecule of the same compound will be attacked as the electrophile due to the strong electrophilicity.

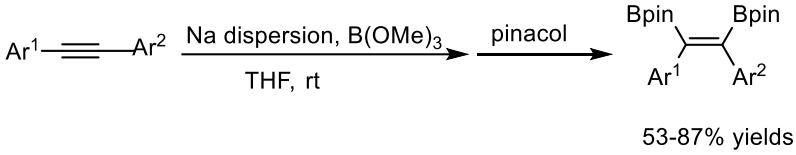
For the reductive coupling, the electron transfer from metal, metal salt, or electrode is applied frequently while hydride reagents as the reducing agent can be used for the synthesis of simply reduced compounds. Alkali metals, especially lithium (Li) and sodium (Na) that have the high ionization potential have been used for long years,[9][10] although alkali metals are usually considered as dangerous metals because of the high risk of explosion or fire.

For example, Yus and coworkers reported the reductive dilithiation of styrenes followed by difunctionalization in THF. Electrophiles such as chlorotrimethylsilane and ketones reacted at the α- and β-position at the same time, and the corresponding products could be isolated in good yields (Scheme 1-1).[9a]



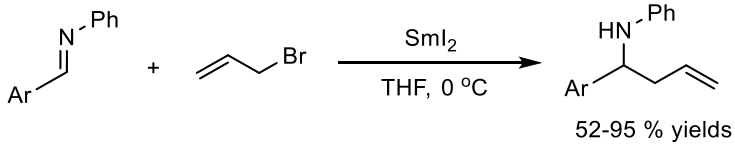
Scheme 1-1 Difunctionalization of styrenes by lithium

Sodium is widely used for reductive coupling reactions.[10] As one example, Yorimitsu and coworkers reported a general method for reductive difunctionalization of alkynes in the presence of trimethoxyborane as an electrophile by sodium (Scheme 1-2).[10a] Besides, sodium metal has been also used for Birch-type reduction that has the great industry application,[10b] and recently, Birch-reduction could be conducted under ammonia-free conditions.[10c]



Scheme 1-2 Reductive difunctionalization of diphenylacetylene by sodium

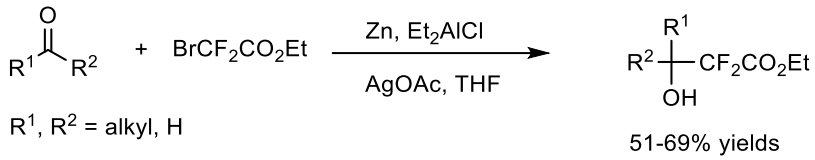
In addition, rare-earth element, samarium (Sm) or its salt (SmI_2) has been also reported as a good electron transfer agent.[11] In 2011, Kim reported an addition reaction of allyl bromide to aldimines to generate aromatic homoallyl amines in good yields by samarium iodide (Scheme 1-3).[11b]



Scheme 1-3 Coupling reaction of aldimines promoted by SmI_2

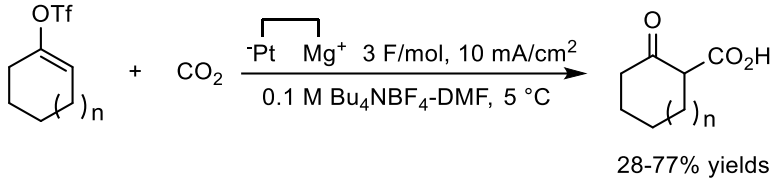
What is more, zinc is also a good reductant for metal-promoted reductive coupling reactions.[12] However, the target compounds by zinc are limited because of its low ionization potential. For example, Curran and coworkers reported selective reductive coupling of aldehydes and ketones with ethyl bromodifluoroacetate by zinc and the access to prepare *α,α*-difluoro-*β*-hydroxy esters

(Scheme 1-4).[12a]



Scheme 1-4 Reduction of aldehydes and ketones by zinc

Electrochemical method is one of the good tools for electron transfer reactions. There are so many reports on the electrochemical coupling reactions.[13] For example, in 1998, Tokuda and coworkers developed the synthesis of *β*-keto carboxylic acids through electrochemical reduction of carbon dioxide (Scheme 1-5).[13a]



Scheme 1-5 Electrochemical reduction of carbon dioxide

1.3 Organic Reactions Promoted by Magnesium Metal

Magnesium is the eighth-most abundant element in the Earth's crust unlike transition metals. (Figure 1-3).[14b]

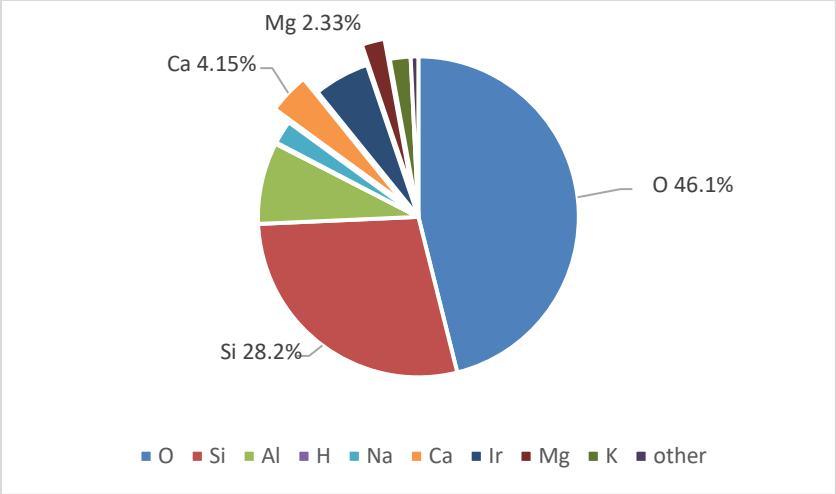
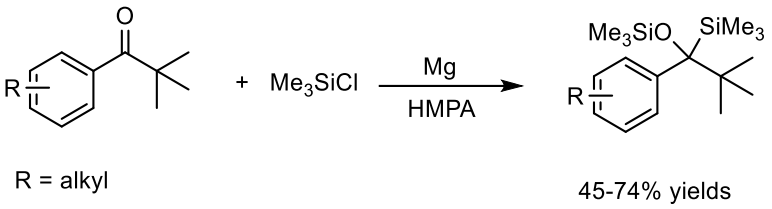


Figure 1-3 Relative abundance of elements in the earth's crust

In synthetic organic chemistry, magnesium is well known as the reagent for Grignard reaction and there are enormous studies on Grignard reactions since the beginning of the last century.[15] There are many advantages such as high reactivity, easy-to-handle, high selectivity, mild reaction conditions, and eco-friendly processes on the use of magnesium.[16] As a reducing agent, pinacol coupling[17] and dehalogenation[18] are main examples of reactions. As mentioned in 1.2, while stronger reducing agents such as alkali metals are dangerous, magnesium that is not a rare metal, is a superior reagent for reduction. Moreover, eco-friendly aprotic polar solvents to stabilize reactive intermediates can be used for reduction and many organic compounds may be targets for the starting material because of the high ionization potential. Some typical reaction patterns developed recently are shown below.

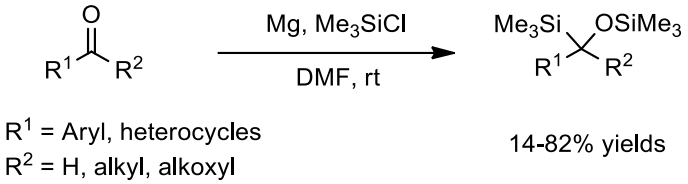
1.3.1 Silylation

Reductive silylation by magnesium was first discovered in the 1970s by Calas and coworkers.[19] Using the Mg/chlorotrimethylsilane/hexamethylphosphoric triamide (HMPA) system, they disclosed a series of silylation of ketones, dienes, enones by magnesium (Scheme 1-6).[19a]



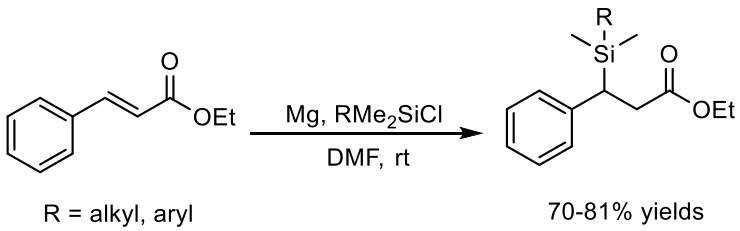
Scheme 1-6 Magnesium-promoted reductive silylation discovered by Calas and coworkers

Later, in the 1990s, Nishiguchi and co-workers re-focused on magnesium and independently discovered several silylation reactions without using the potentially carcinogenic solvent HMPA.[20a] By using *N*, *N*-dimethylformamide (DMF) as the solvent, reductive coupling of aromatic carbonyl compounds with chlorotrimethylsilane at room temperature yielded silylated compounds on the carbonyl carbon atom selectively (Scheme 1-7).[20b]



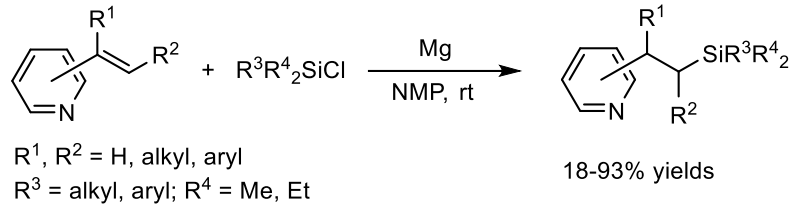
Scheme 1-7 Magnesium-promoted reductive silylation of aromatic carbonyl compounds

On the other hand, magnesium-promoted reductive silylation of ethyl cinnamate was reported by Ghosh and coworkers in 2010 to give *β*-silylated products with various silyl chlorides (Scheme 1-8).[20c]



Scheme 1-8 Reductive silylation of ethyl cinnamates with chlorotrialkylsilanes

In recent years, reductive hydrosilylation of vinylpyridines in *N*-methylpyrrolidone (NMP) was reported, and trimethylsilyl group was selectively introduced to the *β*-position of vinylpyridines in good to excellent yields (Scheme 1-9).[20d]

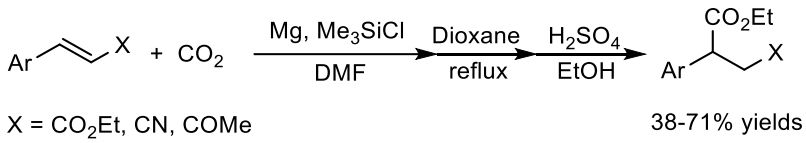


Scheme 1-9 Magnesium-promoted reductive silylation of vinylpyridines

1.3.2 CO_2 Fixation

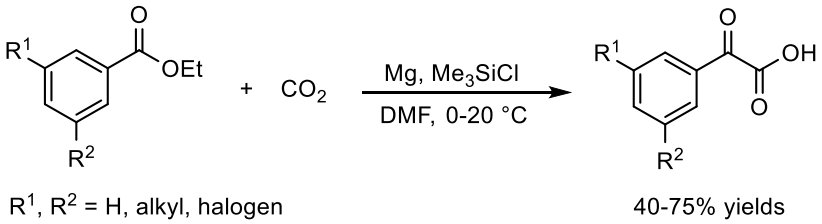
The utilization of carbon dioxide as the carbon source is an important task in synthetic organic chemistry, and so many carbon-carbon bond formation reactions have been reported in the fields of electrochemistry and carbanion chemistry. [21]

As an example, magnesium-promoted reductive carbon dioxide fixation reaction of ethyl cinnamate under the mild reaction conditions was developed in 2011.[22a] The corresponding diethyl 2-phenylsuccinates were synthesized in moderate to good yields with good selectivity through a three-steps protocol (Scheme 1-10).



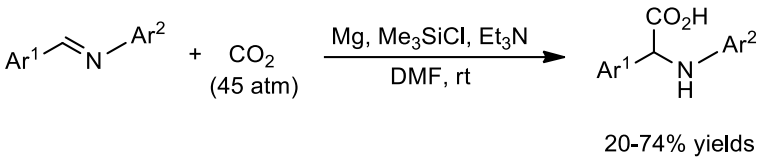
Scheme 1-10 Magnesium-promoted CO_2 fixation of ethyl cinnamates

Additionally, in 2017, a magnesium-promoted reductive carboxylation of ethyl benzoates was reported under the atmospheric pressure.[22b] Carboxylic acids could be obtained directly through carboxylation using carbon dioxide (Scheme 1-11).



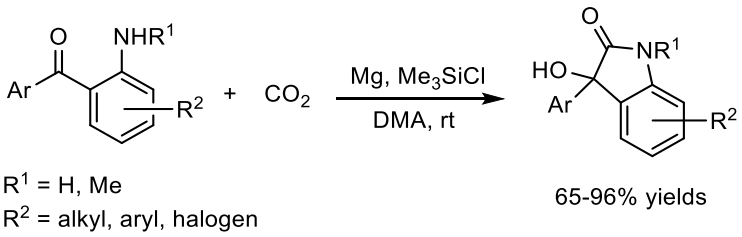
Scheme 1-11 Magnesium-promoted CO_2 fixation of ethyl benzoates

In 2013, Radosevich and coworkers reported the direct synthesis of α-amino acids using carbon dioxide from readily available imines.[22c] A high-pressure reactor is required to introduce the carbon dioxide into imines at room temperature efficiently (Scheme 1-12).



Scheme 1-12 Magnesium-promoted CO_2 fixation of imines

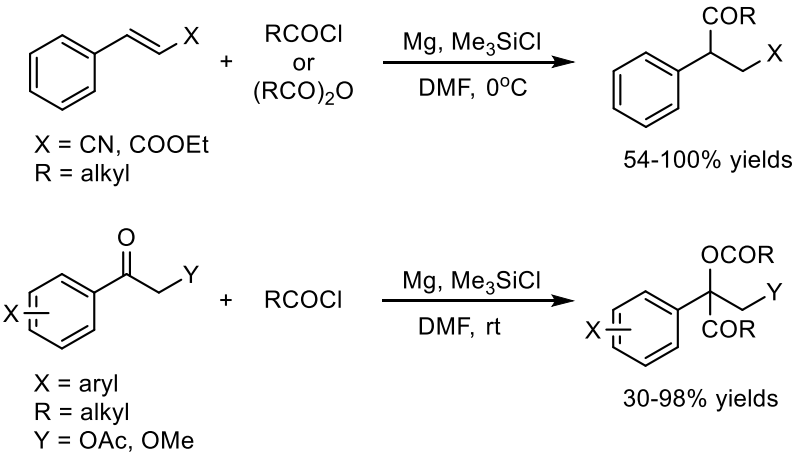
Then in 2016, Hirao and coworkers reported the synthesis of oxindoles via magnesium-promoted reductive coupling of carbon dioxide and 2-aminophenylarylketones in *N*,*N*-dimethylacetamide (DMA) under mild reaction conditions (Scheme 1-13).[22d]



Scheme 1-13 Magnesium-promoted CO_2 fixation of diaryl ketones

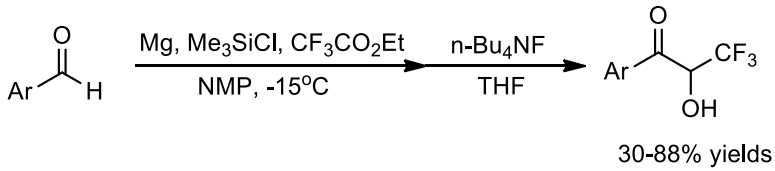
1.3.3 Acylation

The acylation is also one of the important carbon-carbon bond formation reactions and the reductive acylation is an alternative reaction for the reaction of acyl anion equivalent. In 2001, the direct reductive acylation of α,β-unsaturated esters and aromatic ketones has been developed by using magnesium (Scheme 1-14).[23]



Scheme 1-14 Reductive acylation of cinnamic acid derivatives and aromatic ketones

Furthermore, in view of the importance of fluorine-containing organic compounds as pharmaceutical drugs and agrochemicals, trifluoroacetylation of aromatic carbonyl compounds was reported (Scheme 1-15). [24]

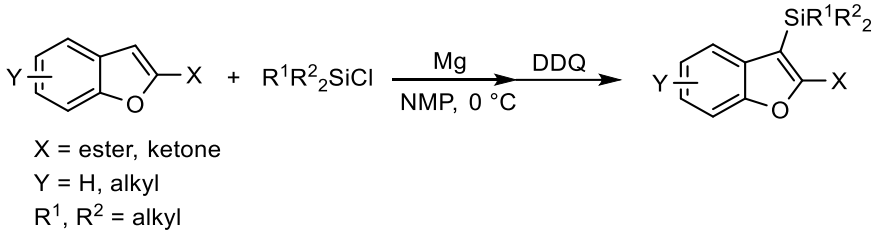


Scheme 1-15 Magnesium-promoted trifluoroacetylation

1.4 Survey of This Thesis

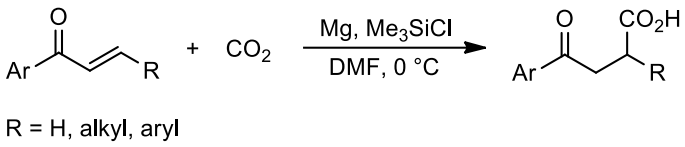
On the basis of the harmless and safe reagent, the high reactivity, the abundance in nature, the eco-friendly and simple process for the sustainable society, I selected magnesium with the higher reduction potential as the reducing agent, and started to find valuable organic compounds that are difficult to obtain using traditional methods.[16] Furthermore, for organic compounds that were impossible to reduce by magnesium, calcium was chosen as a new reducing agent.

In chapter 2, the introduction of the silyl group to 3-position of benzofurans was examined using chlorotrialkylsilane in the presence of magnesium metal in NMP (Scheme 1-16).



Scheme 1-16 Magnesium-promoted reductive 3-silylation of benzofurans

And in chapter 3, the reductive carboxylation of phenyl vinyl ketones in DMF was discussed (Scheme 1-17).



Scheme 1-17 Magnesium-promoted carbon dioxide fixation of phenyl vinyl ketones

Finally, in chapter 4, the reductive silylation of propargyl pivalates and allyl pivalates to yield various propargyl silanes and allyl silanes by eliminating the pivalate group was treated by use of calcium as the reducing agent. (Scheme 1-18).

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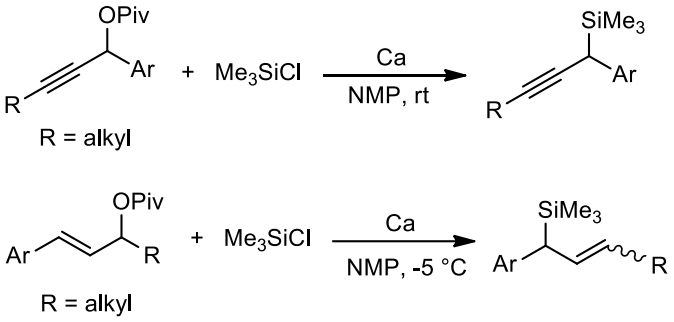

Scheme 1-18 Calcium-promoted silylation of pivalates

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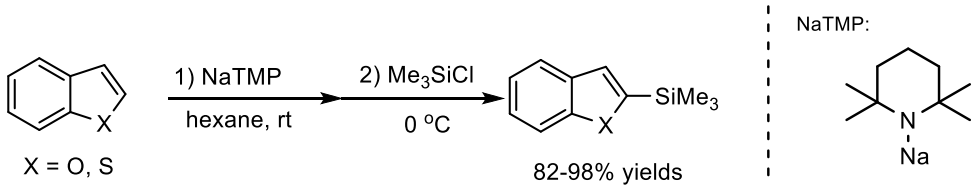
2. Regioselective 3-Silylation via Reductive Coupling of Benzofuran Derivatives with Chlorotrialkylsilane

2.1 Introduction

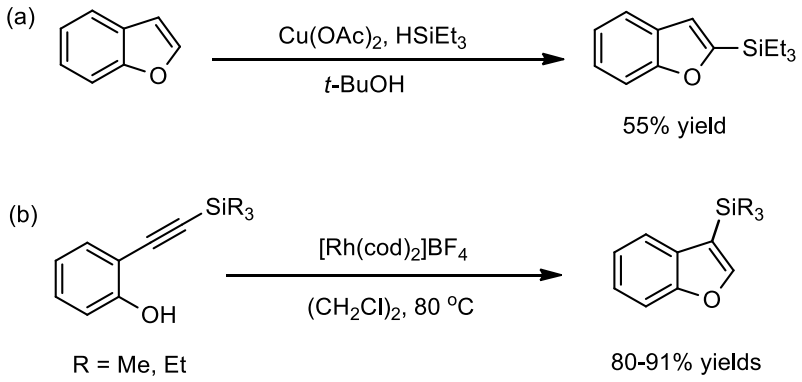
Benzofuran skeleton can be seen in many naturally occurring compounds and attracts chemists , especially medicinal chemists owing to its potent bioactivities.[(1)] Meanwhile, the investigation of aromatic silanes is quite important for molecule syntheses,[(2)] materials science,[(3)] and pharmaceutical discovery as organic fine-chemical intermediates.[(4)]

Herein, silylation of aromatic heterocycles, particularly benzofurans and indoles, has been focused strongly.[(5)] Conventionally, the formation of heteroaromatic carbon-silicon bond at 2-position involves the silylation of aryl organometallic reagents with silicon electrophiles (Scheme 2-1).[(6d)]



Scheme 2-1 Construction of 2-silylated benzofurans or indoles (traditional methods)

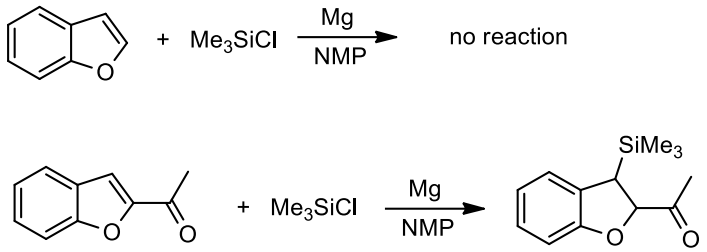
Compared with conventional approaches, most of the recent reports for the preparation of silylated benzofurans are the metal-assisted direct exchange between a hydrogen atom and a silyl group, and the intramolecular cyclization of aromatic alkynylsilanes (Scheme 2-2).[(7-8)]



Scheme 2-2 Construction of 2 or 3-silylated benzofurans or indoles (recent methods)

Although most of these methods are reliable and effective in general, the requirement of rare metal catalysts, hazardous reactants, and harsh reaction conditions sometimes diminish the general application of these tactics. Therefore, the development of new processes to prepare for silylated arenes, especially the less reported 3-silylated benzofurans from easily prepared compounds under mild conditions remains an attractive and important task.

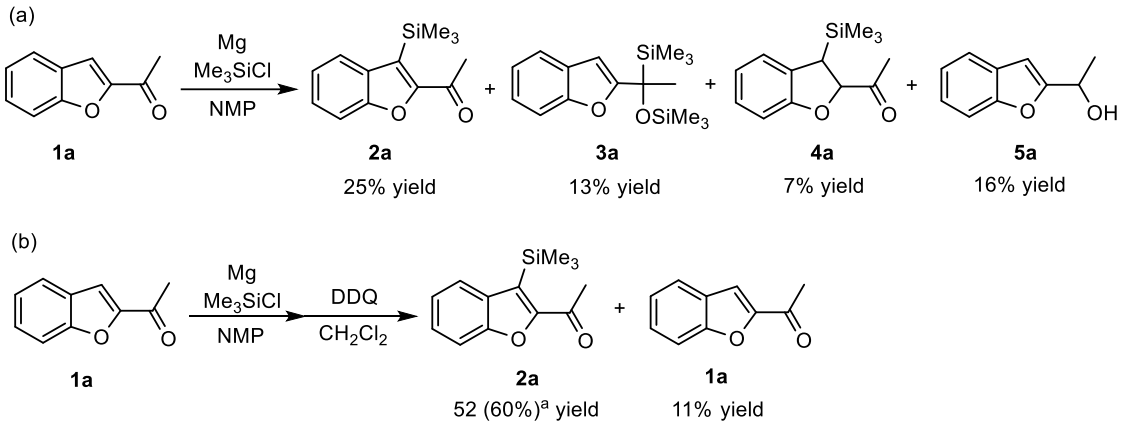
In this research, at first, the direct reduction of benzofuran by magnesium was carried out, however, it was impossible. Then, I selected a benzofuran with an electron-withdrawing group at 2-position and tried the reduction of 2-acetylbenzofurans. The reductive silylation of 2-acetylbenzofuran and the subsequent aromatization by an oxidant led to the efficient formation of 3-silylated benzofuran as the main product (Scheme 2-3).



Scheme 2-3 Construction of 3-silylated benzofuran

2.2 Results and Discussion

Reduction of 2-acetylbenzofuran **1a** was firstly investigated by magnesium turnings in the presence of chlorotrimethylsilane in *N*-methylpyrrolidone (NMP). As a result, 3-silylated benzofuran **2a** was isolated in 25% yield. Meanwhile, di-silylated compound **3a** (13%), reductively silylated compound **4a** (7%) and simply reduced compound of the carbonyl group **5a** (16%) were obtained and considered as side products (Scheme 2-4, a). Considering the air oxidation is insufficient, an oxidative aromatization step with DDQ was added to the reaction process, and as a result, the desired compound **2a** was obtained in 60% GC yield with 11% of the starting material recovered.



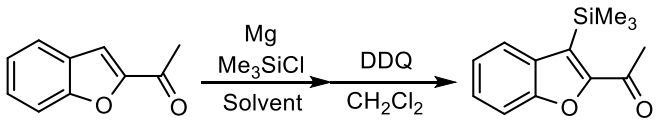
Scheme 2-4 Reductive silylation of 2-acetylbenzofuran by magnesium metal

Reaction Conditions: 1) **1a** (2 mmol), Mg (4 eq.), Me_3SiCl (6 eq.), NMP (15 mL), 3 h, 0 ºC, rt, N_2 atmosphere. 2) DDQ (1 eq.), CH_2Cl_2 (2 mL), 6 h, rt. a) GC yield

Next, I optimized the reaction conditions including solvent effects, solvent volume, reaction temperature, equivalents of reagents and oxidation conditions.

2.2.1 Solvent Effects for the synthesis of 2a

Table 2-1 Solvent effects



1a **2a**

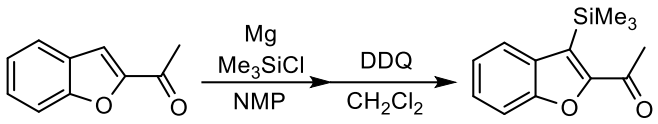
Entry	Solvent	GC Yield (%)
1[a)]	DMI	26
2	DMF	20
3	NMP	60 (52)
4	DMA	40
5	CH_3CN	No Reaction
6	THF	No Reaction

Reaction Conditions: 1) **1a** (2 mmol), Mg (4 eq.), Me_3SiCl (6 eq.), Solvent (15 mL), 3 h, 0 ºC, N_2 atmosphere. 2) DDQ (1 eq.), CH_2Cl_2 (2 mL), 6 h, rt. GC yield was determined using *n*-undecane as the internal standard. Isolated yield was shown in the parenthesis. a) First-step reaction was carried out at room temperature.

First, the solvent effect was studied using 2-acetylbenzofuran **1a** as the standard model in the presence of chlorotrimethylsilane (Table 2-1). As a result, the amide-based aprotic polar solvents, 1,3-dimethyl-2-imidazolidinone (DMI), *N*,*N*-dimethylformamide (DMF), *N*-methyl-2-pyrrolidone (NMP), and *N*,*N*-dimethylacetamide (DMA) gave the desired product probably because of the high stabilizing effects to the reactive intermediates (Entries 1-4), while no reaction occurred in acetonitrile and THF with low-polarity (Entries 5, 6). And among amide-based aprotic polar solvents, NMP gave the best result, and was selected as the optimized solvent.

2.2.2 Effects of the concentration for the synthesis of 2a

Table 2-2 Concentration of substrate



1a **2a**

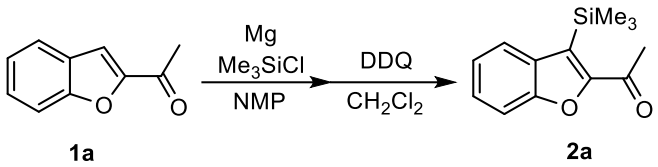
Entry	NMP (mL)	Concentration (mol/L)	GC Yield (%)
1	5	0.40	29
2	15	0.13	60 (52)
3	20	0.10	34
4	25	0.08	33

Reaction Conditions: **1a** (2 mmol), Mg (4 eq.), Me_3SiCl (6 eq.), 0 ºC, NMP (5-25 mL), 3 h, N_2 atmosphere. 2) DDQ (1 eq.), CH_2Cl_2 (2 mL), 6 h, rt. GC yield was determined using *n*-undecane as the internal standard. Isolated yield was shown in the parenthesis.

Subsequently, the substrate concentration was examined (Table 2-2). When the concentration was increased to 0.4 M, the raw material disappeared, however the yield was not improved (Entry 1). On the other hand, the yield of silylated product **2a** was not enhanced under low concentration conditions (Entries 3, 4), because the lower concentration led to the lower probability of collision between molecules, thus resulting in a lower yield of the silylated product. Also, under the conditions of a higher concentration, side reactions were more likely to occur, and the reaction seemed to be more complicated. As a result, 15 mL of NMP (0.13 M) was selected as the optimized reaction condition.

2.2.3 Effects on Reaction Temperature

Table 2-3 Effects on reaction temperature



1a **2a**

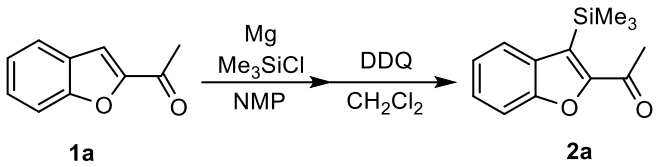
Entry	Reaction Temperature (ºC)	Reaction Time (h)	GC Yield (%)
1	rt	3	48
2	0	3	60 (52)
3	-15	7	31

Reaction Conditions: 1) **1a** (2 mmol), Mg (4 eq.), Me_3SiCl (6 eq.), NMP (15 mL), N_2 atmosphere. 2) DDQ (1 eq.), CH_2Cl_2 (2 mL), 6 h, rt. GC yield was determined using *n*-undecane as the internal standard. Isolated yield was shown in the parenthesis.

Next, the effect on reaction temperature was examined in the range from -15 °C to room temperature (Table 2-3). As a result, **2a** was obtained in 60% yield at 0 °C (Entry 2). The starting material disappeared when the reaction temperature was raised, however the reaction became complicated and the yield of **2a** decreased significantly (Entry 1). In addition, when the reaction was performed at -15 °C, the increase in the solvent's viscosity prevented the collision between **1a** and chlorotrimethylsilane, therefore, the yield of **2a** also decreased (Entry 3).

2.2.4 Optimization on Equivalents of Reagents

Table 2-4 Study on the equivalent of reagents



1a **2a**

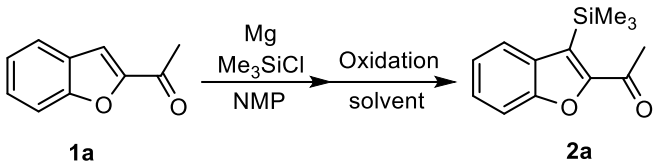
Entry	Mg (eq.)	Me_3SiCl (eq.)	GC Yield (%)
1	2	6	30
2	3	6	43
3	4	6	60 (52)
4	5	6	34
5	4	5	39
6	4	7	47
7	4	8	34

Reaction Conditions: 1) **1a** (2 mmol), Mg (2-5 eq.), Me_3SiCl (5-8 eq.), 0 ºC, NMP (15 mL), 3 h, N_2 atmosphere. 2) DDQ (1 eq.), CH_2Cl_2 (2 mL), 6 h, rt. GC yield was determined using *n*-undecane as the internal standard. Isolated yield was shown in the parenthesis.

Next, the amounts of magnesium and chlorotrimethylsilane were examined (Table 2-4). The yield decreased when 2 equivalents or 3 equivalents of magnesium were used (Entries 1, 2). When the reaction was carried out using 5 equivalents of magnesium, no improvement in yield was observed (Entry 4). Although the amount of chlorotrimethylsilane was increased from 6 equivalents to 7 or 8 equivalents, but the yield was not improved (Entries 6, 7). Moreover, the yield was significantly reduced when 5 equivalents of chlorotrimethylsilane were used (Entry 5). According to the above results, 4 equivalents of magnesium and 6 equivalents of chlorotrimethylsilane were selected as the optimal reaction conditions.

2.2.5 Investigation of Oxidation Conditions

Table 2-5 Study on oxidation conditions



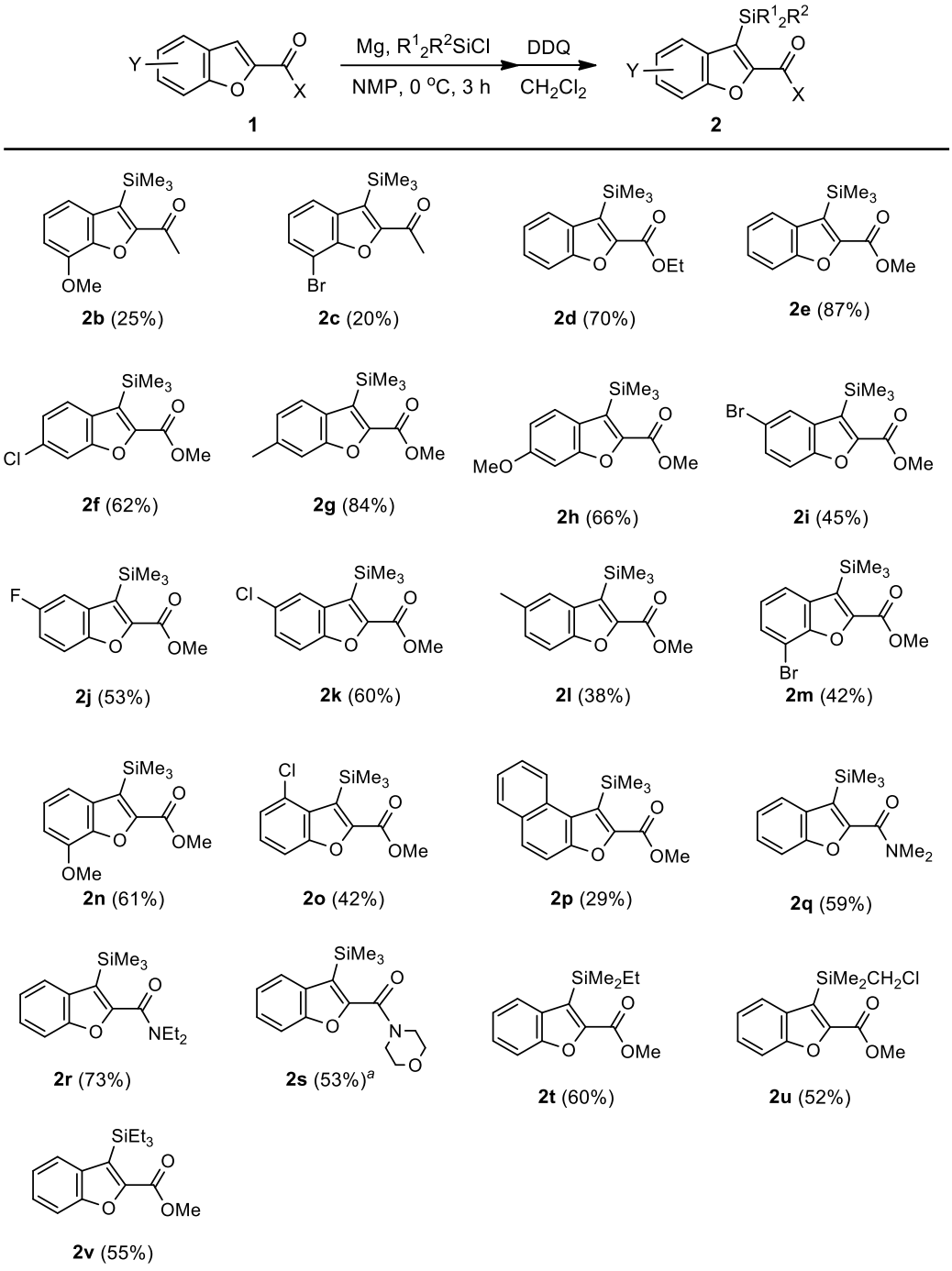
1a **2a**

Entry	Oxidant (eq.)	Solvent (mL)	GC Yield (%)
1	DDQ (0.8)	CH_2Cl_2 (2 mL)	39
2	DDQ (1.0)	CH_2Cl_2 (2 mL)	60 (52)
3	DDQ (1.5)	CH_2Cl_2 (2 mL)	27
4	DDQ (1.0)	CH_2Cl_2 (1 mL)	42
5	DDQ (1.0)	CH_2Cl_2 (5 mL)	48
6	H_2O_2 aq. (1.3 M)	THF (5 mL)	Trace

Reaction Conditions: **1a** (2 mmol), Mg (4 eq.), Me_3SiCl (6 eq.), 0 ºC, NMP (15 mL), 3 h, N_2 atmosphere. 2) Oxidant (0.8-2.0 eq.), solvent (1-5 mL), rt. GC yield was determined using *n*-undecane as the internal standard. Isolated yield was shown in the parenthesis.

Finally, the oxidation conditions at the second step were examined (Table 2-5). First, reducing the amount of DDQ to 0.8 equivalent decreased the yield (Entry 1). When the reaction was carried out using 1.5 equivalents of DDQ, the yield was also significantly reduced (Entry 3). In addition, significant effect was less observed using 1 mL of solvent (Entry 4), and increasing the solvent to 5 mL could not increase the yield (Entry 5). On the other hand, the reaction did not proceed smoothly when hydrogen peroxide solution was used as the oxidizing agent (Entry 6). Finally, 1 equivalent of DDQ and 2 mL of dichloromethane were selected as the optimal reaction conditions.

2.3 Substrate Scope



Scheme 2-5 Substrate scope.

Reaction conditions: **1** (2 mmol), Mg (4 eq.), $R^1_2R^2SiCl$ (6 eq.), 0 ºC, NMP (15 mL), N_2 atmosphere, 3 h; DDQ (1 eq.), CH_2Cl_2 (2 mL), rt, 6 h. Yields are shown in the parentheses. a) At the first step. the reaction mixture was stirred for 20 h.

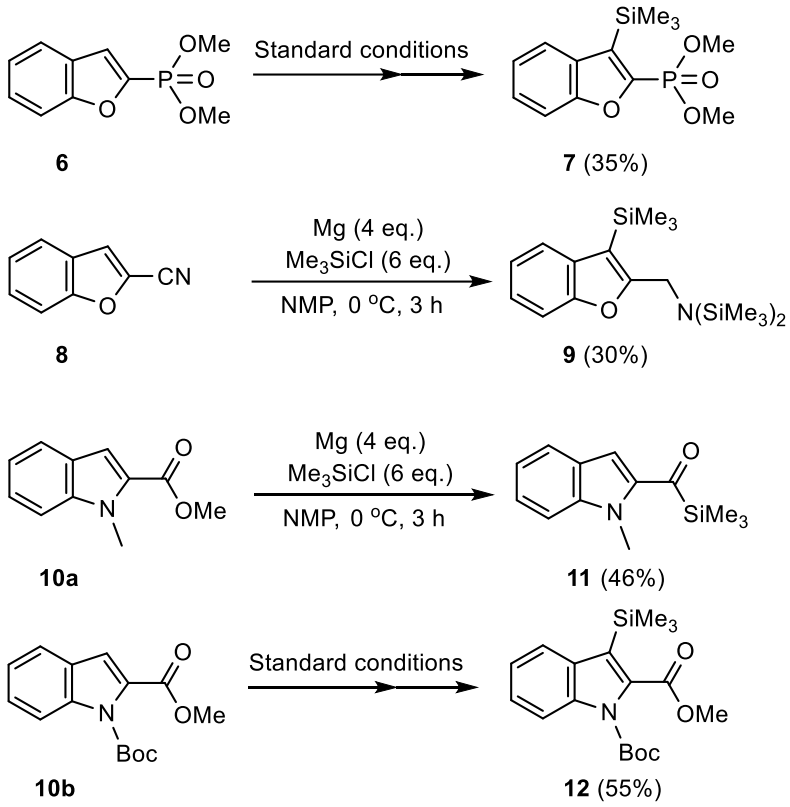
The application of a variety of benzofuran derivatives to this silylation was investigated under the optimal reaction conditions (Scheme 2-5). First, 2-acetylbenzofurans with a methoxy group or a bromine atom at 7-position, provided the products **2b** or **2c** only in 25% and 20% yields, respectively. In these two reactions, the main products were the corresponding dimers. Next, the replacement of the acetyl group with an ester group was tried and a dramatic decrease of byproducts was observed. The yields of **2d** and **2e** were increased to 70% and 87%, respectively.

The reduction of various benzofurans derivatives substituted by a methyl group, a methoxy group, or a halogen atom was then studied, and the reactions proceeded smoothly under the optimal reaction conditions, to afford the target products **2f** to **2o** in 38% to 84% yields. A naphthofuran could also be tolerated to afford **2p** in 29% yield under the optimized conditions.

Furthermore, the reaction of the electron-withdrawing group at 2-position was also examined, and the starting materials could be extended to carboxamides. The products **2q-2s** could be synthesized in moderate to good yields.

Finally, this method could also be applied to other more silylating reagents. The silyl groups like ethyldimethylsilyl, chloromethyldimethylsilyl and triethylsilyl groups were regioselectively introduced into the 3-position of benzofurans in moderate yields (**2t-2v**).

2.4 Effects on other Electron-Withdrawing Groups and Heterocycles



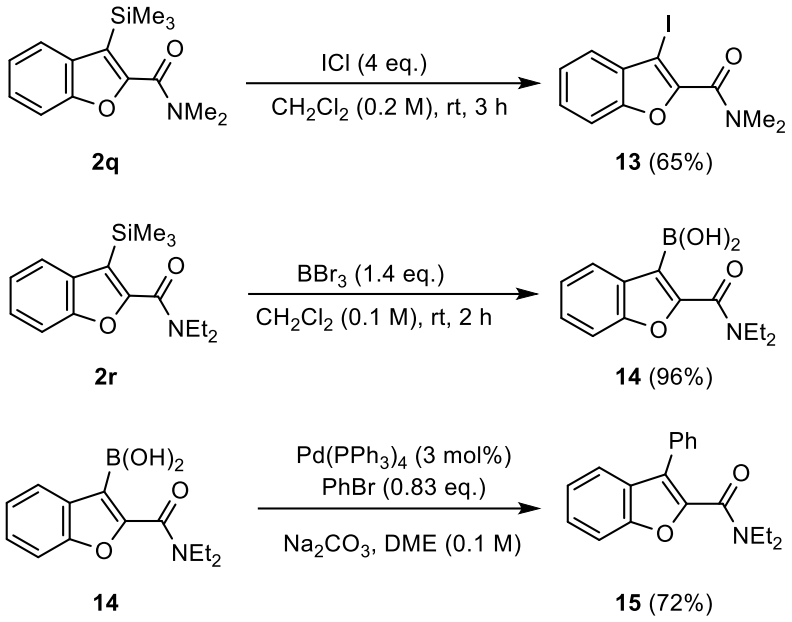
Scheme 2-6 Effects on other electron-withdrawing groups and indoles

To demonstrate the utility of this reaction, derivatives with other electron-withdrawing groups at 2-position of benzofuran and indole derivatives were investigated.

As shown in Scheme 2-6, the silylation of a derivative with a dimethylphosphono group acetate **6** and 2-cyanobenzofuran **8** under the optimal reaction conditions, gave the corresponding 3-silylated product **7** in 35% yield and an unexpected tri-silylated product **9** in 30% yield.

Additionally, the reaction of *N*-tert-botoxycarbonyl indole **10b** gave a good result, while the reaction of *N*-methyl indole **10a** afforded acylsilane **11** only in 46% yield.[(9)] The difference of electron density of the aromatic ring, especially the five-membered ring may explain these observation.[(10)]

2.5 Synthetic Usability

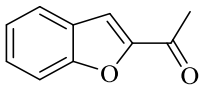
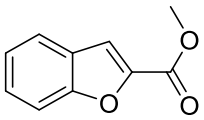
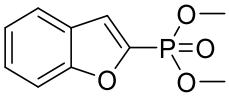
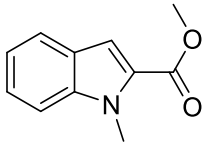


Scheme 2-7 Synthetic usability

Next, the synthetic applicability of products **2q** and **2r** was investigated (Scheme 2-7). As a result, the substrate **2q** could be converted into *N*,*N*-dimethyl-3-iodobenzofuran-2-carboxamide **13** by addition of 4 equivalents ICl at room temperature and the substrate **2r** was also quantitatively converted into boronic acid **14** which was considered as an effective reagent for Suzuki-Miyaura coupling reactions. The palladium-catalyzed coupling reaction of boronic acid **14** with bromobenzene was carried out to give a biaryl compound **15** in 72% yield. The structure of benzofuran-2-carboxamides like **15** sometimes show the bioactivity on anti-inflammatory, analgesic, and anti-pyretic effect.[(11)] Moreover, the simple route from arylsilane **2** to biaryl compounds may be used to synthesize a variety of potential drug candidates.

2.6 Reduction Potentials

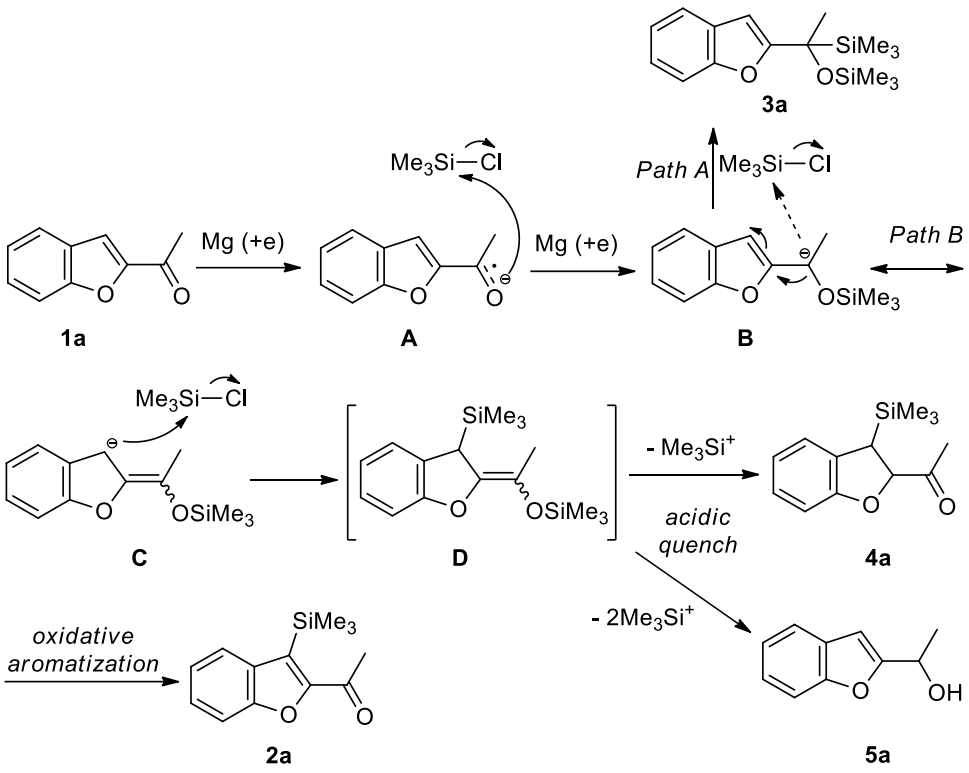
Table 2-6 Reduction potentials of substrates

Entry	Substrate	Reduction Potential (V vs. Ag/AgCl)
1	 **1a**	-1.75 V
2	 **1e**	-2.08 V
3	 **6**	-2.43 V
4	 **10a**	-2.24 V
5	Me_3SiCl	No significant peak (-3.00 to 0 V)

Working Electrode: Pt; Counter Electrode: Pt; Reference Electrode: Ag/AgCl; Solvent: NMP (10 mL); Supporting Electrolyte: 0.1M *n*-Bu_4NClO_4; Scan Rate: 0.2 Vs^{-1}

Reduction potentials for some substrates were measured by cyclic voltammetry (CV) and the results are listed in Table 2-6. As a result, the reduction potentials of the substrates benzofuran **1a** and **1e** showed peaks at -1.75 V and -2.08 V, respectively. No reduction peak of chlorotrimethylsilane was observed in the range of -3.00 to 0 V. It is considered that this reaction is started by one electron transfer from magnesium to benzofuran **1**.

2.7 Plausible Reaction Mechanism



Scheme 2-8 Reaction mechanism

Based on the previous results, the plausible reaction mechanism is summarized in Scheme 2-8. At first, a single electron transfer from magnesium to 2-acetylbenzofuran **1a** gives an anion radical species **A**. The anion radical species **A** will react with chlorotrimethylsilane to yield an anionic species **B** followed by the second electron transfer from magnesium immediately. In pathway A, the anionic intermediate **B** is then attacked directly by chlorotrimethylsilane, yielding a side product **3a** disilylated at the carbonyl group. After DDQ oxidation, the byproduct **3a** and simply reduced compound **5a** will be converted into the starting material **1a**. Meanwhile, **C** attacks chlorotrimethylsilane on the 3-position of the benzofuran ring via resonance with the furan ring, yielding intermediate **D** in pathway **B**. The hydrolysis of **D** provides compounds **4a** and **5a**, while the final product **2a** will be generated after aromatization of **4a** by an oxidant without elimination of the silyl group at the 3-position of **2a**.

2.8. Experimental Section

2.8.1 General Information

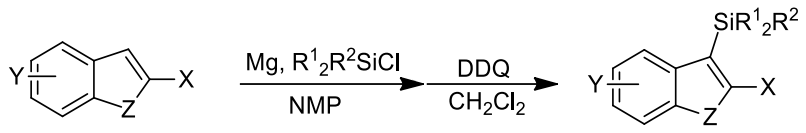
Materials

All reactions were performed under an atmosphere of nitrogen unless stated otherwise. Unless otherwise noted. All reagents were purchased from TCI, Sigma-Aldrich, Nacalai tesque, Wako, Kanto Chemical, Alfa Aesar, and SynQuest, and were used without further purification. Magnesium for Grignard reagent is commercially available and was used with no pre-treatment. Solvents were distilled under reduced pressure by standard procedures. Acetonitrile of super dehydrated grade was bought from Wako Pure Chemical Industries, Ltd. without further treatment. THF was freshly distilled from sodium/benzophenone. Chlorotrimethylsilane was simply distilled before use.

Analysis Instruments

Cyclic voltammograms were measured by ALS-600. Melting points were performed on a Yanaco MP-500D or a MP-J3 instrument and were uncorrected. NMR spectra (^{1}H, ^{13}C, ^{19}F) were recorded on a JEOL JNM AL-400 (400 MHz) spectrometer. Chemical shifts (δ) in parts per million (ppm) were reported relative to the residual signal of chloroform (7.26 ppm), and coupling constants were reported in hertz (Hz). Carbon chemical shifts were referenced to the carbon signal of $CDCl_3$ at 77.0 ppm. Fluorine chemical shifts were referenced to the signal of CF_3CO_2H at -76.50 ppm. Signal Multiplicity was shown as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). IR spectra were obtained on a JASCO 470Plus FTIR spectrometer, and peaks were reported in wavenumber (cm^{-1}). MS spectra were recorded on a Shimadzu GCMS-QP2010plus, a JEOL JMS-600H or a JMS-T200GC spectrometer. TLC was performed on Merck pre-coated plates (silica gel 60 F_{254}, Art 5715, 0.25 mm). Column chromatography was performed using neutral silica gel (60N, spherical, 63-210 mesh, Kanto Chemical).

2.8.2 General Procedure for Silylation of Benzofuran Derivatives



1, 6, 10 **2, 7, 11, 12**

In a round-bottom flask, a mixture of magnesium turnings (194 mg, 8 mmol, 4 eq.), chlorotrimethylsilane (1.52 mL, 12 mmol, 6 eq.) and NMP (5 mL) was stirred for 30 min at room temperature under nitrogen atmosphere. Then, to the mixture was added a solution of benzofuran or indole (2 mmol) in NMP (10 mL). After stirring for 3 h at room temperature, the reaction mixture was poured into 50 mL of 1 M sulfuric acid and products were extracted with diethyl ether (30 mL × 3). The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, and then concentrated in vacuo. The crude products were transferred into another round-bottom flask, and a dichloromethane (2 mL) solution of DDQ (454 mg, 2 mmol, 1 eq.) was added. The mixture was stirred for 6 h at room temperature. The reaction mixture was quenched by 50 mL of 1 M sodium hydroxide solution and the product was extracted with diethyl ether (30 mL × 3). The combined organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentration in vacuo, the final product was purified by flash column chromatography.

*1-[3-(Trimethylsilyl)benzofuran-2-yl]ethanone (**2a**).*

52% yield (242 mg), hexane / ethyl acetate = 5:1, R_f = 0.7. White solid, mp 98.7-101.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.90 (1H, d, *J* = 8.3 Hz), 7.57 (1H, d, *J* = 8.3 Hz), 7.45 (1H, t, *J* = 8.3 Hz), 7.28 (1H, t, *J* = 8.3 Hz), 2.66 (3H, s), 0.45 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 190.9, 156.9, 155.1, 132.3, 127.3, 124.7, 123.3, 122.2, 112.0, 27.5, -0.2. IR (KBr): 3098, 2957, 2902, 1681, 1521 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{16}O_2Si$ 232.0914; found 232.0935.

*[1-(Benzofuran-2-yl)-1-(trimethylsilyloxy)ethyl]trimethylsilane (**3a**).*

13% yield (77 mg), hexane / ethyl acetate = 5:1, R_f = 0.8. Colorless oil. ^{1}H NMR (400 MHz,

$CDCl_3$) δ (ppm): 7.50 (1H, d, *J* = 8.0 Hz), 7.42 (1H, d, *J* = 8.0 Hz), 7.21-7.18 (2H, m), 6.40 (1H, s), 1.68 (3H, s), 0.05 (9H, s), 0.03 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.1, 154.6, 129.0, 122.9, 122.4, 120.2, 110.8, 100.6, 69.1, 22.6, 2.2, -4.1. IR (neat): 3066, 2958, 2900, 2869, 1577, 1569, 1455, 1250 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{16}H_{26}O_2Si_2$ 306.1471; found 306.1495.

*1-[3-(Trimethylsilyl)-2,3-dihydrobenzofuran-2-yl]ethanone (**4a**).*

7% yield (34 mg), hexane / ethyl acetate = 5:1, R_f = 0.75. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.13-7.08 (2H, m), 6.88-6.86 (2H, m), 5.17 (1H, d, *J* = 9.9 Hz), 3.06 (1H, d, *J* = 9.9 Hz), 2.23 (3H, s) , 0.11 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 209.0, 158.8, 129.5, 127.3, 124.0, 121.1, 109.5, 89.8, 35.7, 28.1, -1.3. IR (neat): 3070, 2956, 2926, 2903, 2856, 1715, 1522 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{18}O_2Si$ 234.1076; found 234.1063.

*1-(Benzofuran-2-yl)ethanol (**5a**).* Known compound.[(12)]

16% yield (53 mg), hexane / ethyl acetate = 5:1, R_f = 0.2. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.57 (1H, d, *J* = 8.0 Hz), 7.50 (1H, d, *J* = 8.0 Hz), 7.31 (1H, t, *J* = 8.0 Hz), 7.26 (1H, t, *J* = 8.0 Hz), 6.61 (1H, s), 5.02 (1H, q, *J* = 6.8 Hz), 3.09 (1H, broad, s), 1.65 (3H, d, *J* = 6.8 Hz).

*1-[7-Methoxy-3-(trimethylsilyl)benzofuran-2-yl]ethanone (**2b**).*

25% yield (133 mg), hexane / ethyl acetate = 5:1, R_f = 0.3. Pale yellow solid, mp 117.1-118.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.47 (1H, d, *J* = 8.0 Hz), 7.19 (1H, t, *J* = 8.0 Hz), 6.93 (1H, d, *J* = 8.0 Hz), 4.03 (3H, s), 2.69 (3H, s), 0.44 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 190.8, 157.0, 145.9, 144.8, 134.0, 123.8, 122.5, 116.6, 108.6, 56.1, 27.5, -0.2. IR (KBr): 3080, 3046, 3002, 2958, 2898, 1683, 1580 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{18}O_3Si$ 262.1025; found 262.1015.

*1-[7-Bromo-3-(trimethylsilyl)benzofuran-2-yl]ethanone (**2c**).*

20% yield (124 mg), hexane / ethyl acetate = 5:1, R_f = 0.6. Pale yellow solid, mp 85.0-86.5 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.83 (1H, d, *J* = 7.8 Hz), 7.61 (1H, d, *J* = 7.8 Hz), 7.16 (1H, t, *J* = 7.8 Hz), 2.70 (3H, s), 0.44 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 190.8, 157.0, 152.3, 133.5, 130.1, 124.5, 123.8, 123.1, 104.7, 27.5, -0.3. IR (KBr): 3075, 3041, 2999, 2956, 2899, 1685, 1521 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{15}O_2SiBr$ 310.0025; found 310.0003.

*Ethyl 3-(trimethylsilyl)benzofuran-2-carboxylate (**2d**).*

70% yield (368 mg), hexane / ethyl acetate = 5:1, R_f = 0.6. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.86 (1H, d, *J* = 8.0 Hz), 7.60 (1H, d, *J* = 8.0 Hz), 7.41 (1H, t, *J* = 8.0 Hz), 7.26 (1H, t, *J* = 8.0 Hz), 4.47 (2H, q, *J* = 7.2 Hz), 1.45 (3H, t, *J* = 7.2 Hz), 0.48 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.3, 155.2, 149.7, 132.0, 127.0, 124.2, 123.8, 123.1, 112.1, 61.5, 14.3, 0.3. IR (neat): 3051, 2984, 2954, 2901, 1717, 1538 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{18}O_3Si$ 262.1025; found 262.1010.

*Methyl 3-(trimethylsilyl)benzofuran-2-carboxylate (**2e**).*

87% yield (431 mg), hexane / ethyl acetate = 5:1, R_f = 0.5. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.87 (1H, d, *J* = 8.0 Hz), 7.59 (1H, d, *J* = 8.0 Hz), 7.41 (1H, t, *J* = 8.0 Hz), 7.26 (1H, t, *J* = 8.0 Hz), 3.99 (3H, s), 0.49 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.4, 155.1, 149.2, 131.8, 127.0, 124.2, 124.1, 123.1, 112.0, 52.0, 0.1. IR (neat): 3033, 2952, 2900, 2844, 1724, 1538 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{16}O_3Si$ 248.0869; found 248.0868.

*Methyl 6-chloro-3-(trimethylsilyl)benzofuran-2-carboxylate (**2f**).*

62% yield (350 mg), hexane / ethyl acetate = 5:1, R_f = 0.5. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.75 (1H, d, *J* = 8.5 Hz), 7.56 (1H, s), 7.23 (1H, d, *J* = 8.5 Hz), 3.98 (3H, s), 0.46 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.2, 155.3, 149.8, 133.0, 130.5, 124.7, 124.13, 124.08, 112.4, 52.2, 0.0. IR (neat): 3085, 2953, 2926, 2902, 2855, 1725, 1538 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{15}O_3SiCl$ 282.0479; found 282.0458.

*Methyl 6-methyl-3-(trimethylsilyl)benzofuran-2-carboxylate (**2g**).*

84% yield (442 mg), hexane / ethyl acetate = 5:1, R_f = 0.6. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.73 (1H, d, *J* = 7.6 Hz), 7.38 (1H, s), 7.09 (1H, d, *J* = 7.6 Hz), 3.98 (3H, s), 2.48 (3H, s), 0.47 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.6, 155.7, 148.7, 137.8, 129.5, 124.9, 124.4, 123.6, 112.0, 52.1, 21.8, 0.1. IR (neat): 3088, 3024, 2952, 2900, 2854, 1716, 1538 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{18}O_3Si$ 262.1025; found 262.1049.

*Methyl 6-methoxy-3-(trimethylsilyl)benzofuran-2-carboxylate (**2h**).*

66% yield (365 mg), hexane / ethyl acetate = 5:1, R_f = 0.5. Pale yellow solid, mp 72.2-74.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.71 (1H, d, *J* = 7.7 Hz), 7.07 (1H, s), 6.90 (1H, d, *J* = 7.7 Hz), 3.97 (3H, s), 3.86 (3H, s), 0.45 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.5, 160.1, 156.6, 148.5, 125.3, 124.8, 124.5, 113.2, 95.4, 55.6, 52.0, 0.1. IR (KBr): 3087, 3018, 2995, 2953, 2899, 2837, 1713, 1616 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{18}O_4Si$ 278.0974; found 278.0981.

*Methyl 5-bromo-3-(trimethylsilyl)benzofuran-2-carboxylate (**2i**).*

45% yield (291 mg), hexane / ethyl acetate = 5:1, R_f = 0.5. White solid, mp 42.0-44.3 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.96 (1H, s), 7.50 (1H, d, *J* = 9.0 Hz), 7.44 (1H, d, *J* = 9.0 Hz), 3.98 (3H, s), 0.46 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.2, 153.9, 150.2, 133.8, 130.1, 126.7, 123.6, 116.4, 113.5, 52.3, 0.1. IR (KBr): 3097, 3076, 3029, 2951, 2907, 2841, 1721, 1538 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{15}O_3SiBr$ 325.9974; found 325.9978.

*Methyl 5-fluoro-3-(trimethylsilyl)benzofuran-2-carboxylate (**2j**).*

53% yield (282 mg), hexane / ethyl acetate = 5:1, R_f = 0.5. Yellow solid, mp 43.1-44.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.54-7.49 (2H, m), 7.18-7.13 (1H, m), 3.99 (3H, s), 0.46 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.3, 159.2 (d, $^1J_{CF}$ = 237.7 Hz), 151.5, 150.8, 132.6 (d, $^3J_{CF}$ = 11.0 Hz), 124.2, 115.3 (d, $^2J_{CF}$ = 26.1 Hz), 112.7 (d, $^3J_{CF}$ = 10.0 Hz), 109.4 (d, $^2J_{CF}$ =

30.1 Hz), 52.3, 0.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -119.54 (m). IR (KBr): 3107, 3049, 3014, 2963, 2908, 2849, 1716, 1584 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{15}O_3FSi$ 266.0775; found 266.0770.

*Methyl 5-chloro-3-(trimethylsilyl)benzofuran-2-carboxylate (**2k**).*

60% yield (338 mg), hexane / ethyl acetate = 5:1, R_f = 0.6. Pale yellow solid, mp 103.8-104.7 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.82 (1H, s), 7.51 (1H, d, *J* = 8.8 Hz), 7.39 (1H, d, *J* = 8.8 Hz), 3.99 (3H, s), 0.47 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.3, 153.6, 150.4, 133.2, 128.9, 127.5, 123.7, 113.5, 113.1, 52.3, 0.1. IR (KBr): 3098, 3075, 3004, 2955, 2909, 2848, 1721, 1537 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{15}O_3SiCl$ 282.0479; found 282.0480.

*Methyl 5-methyl-3-(trimethylsilyl)benzofuran-2-carboxylate (**2l**).*

38% yield (198 mg), hexane / ethyl acetate = 5:1, R_f = 0.5. Pale yellow solid, mp 87.0-88.8 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.63 (1H, s), 7.47 (1H, d, *J* = 8.5 Hz), 7.24 (1H, d, *J* = 8.5 Hz), 3.98 (3H, s), 2.45 (3H, s), 0.47 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.6, 153.7, 149.3, 132.7, 132.0, 128.6, 124.0, 123.8, 111.6, 52.1, 21.5, 0.2. IR (KBr): 3070, 3034, 2954, 2919, 2861, 1718, 1533 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{18}O_3Si$ 262.1025; found 262.1049.

*Methyl 7-bromo-3-(trimethylsilyl)benzofuran-2-carboxylate (**2m**).*

42% yield (274 mg), hexane / ethyl acetate = 5:1, R_f = 0.6. White solid, mp 91.2-93.5 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.80 (1H, d, *J* = 7.9 Hz), 7.59 (1H, d, *J* = 7.9 Hz), 7.15 (1H, t, *J* = 7.9 Hz), 3.99 (3H, s), 0.47 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.3, 152.5, 149.8, 133.0, 129.9, 125.1, 124.4, 123.3, 104.6, 52.3, 0.1. IR (KBr): 3068, 2997, 2951, 2907, 2842, 1720, 1538 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{15}O_3SiBr$ 325.9974; found 325.9985.

*Methyl 7-methoxy-3-(trimethylsilyl)benzofuran-2-carboxylate (**2n**).*

61% yield (341 mg), hexane / ethyl acetate = 5:1, R_f = 0.4. Yellow solid, mp 74.0-75.7 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43 (1H, d, *J* = 8.1 Hz), 7.19 (1H, t, *J* = 8.1 Hz), 6.91 (1H, d,

J = 8.1 Hz), 4.01 (3H, s), 3.97 (3H, s), 0.47 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.5, 149.4, 145.9, 144.9, 133.5, 124.5, 123.7, 116.0, 108.2, 55.9, 52.1, 0.1. IR (KBr): 3104, 3027, 3006, 2981, 2947, 2898, 2837, 1721, 1542 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{18}O_4Si$ 278.0969; found 278.0994.

*Methyl 4-chloro-3-(trimethylsilyl)benzofuran-2-carboxylate (**2o**).*

42% yield (236 mg), hexane / ethyl acetate = 5:1, R_f = 0.5. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.48 (1H, d, *J* = 7.2 Hz), 7.34-7.29 (2H, m), 3.96 (3H, s), 0.47 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 161.3, 155.6, 150.7, 130.6, 128.3, 127.1, 124.8, 120.2, 110.5, 52.7, 1.7. IR (neat): 3024, 2952, 2928, 2901, 2855, 1736, 1530 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{15}O_3SiCl$ 282.0479; found 282.0458.

*Methyl 3-(trimethylsilyl)naphtho[2,1-b]furan-2-carboxylate (**2p**).*

29% yield (174 mg), hexane / ethyl acetate = 5:1, R_f = 0.8. White solid, mp 80.2-82.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.37 (1H, d, *J* = 7.8 Hz), 7.96 (1H, d, *J* = 7.8 Hz), 7.86 (1H, d, *J* = 7.8 Hz), 7.71 (1H, d, *J* = 7.8 Hz), 7.62 (1H, t, *J* = 7.8 Hz), 7.52 (1H, t, *J* = 7.8 Hz), 4.01 (3H, s), 0.57 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 161.1, 153.4, 149.3, 131.2, 129.3, 129.10, 129.05, 127.0, 126.1, 125.9, 124.7, 123.1, 112.5, 52.4, 1.4. IR (KBr): 3055, 2988, 2951, 2926, 2854, 1732, 1531 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{17}H_{18}O_3Si$ 298.1025; found 298.1030.

*N,N-Dimethyl-3-(trimethylsilyl)benzofuran-2-carboxamide (**2q**).*

59% yield (307 mg), hexane / ethyl acetate = 5:1, R_f = 0.5. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.72 (1H, d, *J* = 7.9 Hz), 7.51 (1H, d, *J* = 7.9 Hz), 7.34 (1H, t, *J* = 7.9 Hz), 7.26 (1H, t, *J* = 7.9 Hz), 3.08 (6H, broad, s), 0.39 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.3, 154.4, 153.5, 131.7, 125.1, 123.0, 122.8, 115.2, 111.4, 38.3, 35.2, -0.4. IR (neat): 3066, 2953, 2928, 2900, 2856, 1652, 1583, 1444 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{19}NO_2Si$ 261.1185; found 261.1178.

*N,N-Diethyl-3-(trimethylsilyl)benzofuran-2-carboxamide (**2r**).*

73% yield (422 mg), hexane / ethyl acetate = 5:1, R_f = 0.5. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.72 (1H, d, *J* = 7.8 Hz), 7.50 (1H, d, *J* = 7.8 Hz), 7.33 (1H, t, *J* = 7.8 Hz), 7.26 (1H, t, *J* = 7.8 Hz), 3.56 (2H, q, *J* = 7.1 Hz), 3.31 (2H, q, *J* = 7.1 Hz), 1.29-1.21 (6H, m), 0.41 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.7, 154.3, 154.2, 131.8, 124.9, 122.9, 122.8, 114.8, 111.4, 43.0, 39.8, 14.3, 12.5, -0.4. IR (KBr): 3068, 2963, 2899, 1645, 1428 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{16}H_{23}NO_2Si$ 289.1498; found 289.1526.

*Morpholino-4-yl-[3-(trimethylsilyl)benzofuran-2-yl]methanone (**2s**).*

53% yield (322 mg), hexane / ethyl acetate = 3:2, R_f = 0.6. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.71 (1H, d, *J* = 7.6 Hz), 7.48 (1H, d, *J* = 7.6 Hz), 7.32 (1H, t, *J* = 7.6 Hz), 7.24 (1H, t, *J* = 7.6 Hz), 3.78-3.75 (4H, m), 3.65-3.63 (2H, m), 3.47-3.45 (2H, m), 0.40 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 161.8, 154.2, 152.8, 131.5, 125.3, 123.1, 122.9, 116.6, 111.4, 66.9, 66.6, 47.3, 42.6, -0.3. IR (neat): 3067, 2961, 2899, 2855, 1647, 1430 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{16}H_{21}NO_3Si$ 303.1291; found 303.1277.

*Methyl 3-(ethyldimethylsilyl)benzofuran-2-carboxylate (**2t**).*

60% yield (313 mg), hexane / ethyl acetate = 5:1, R_f = 0.3. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.87 (1H, d, *J* = 7.6 Hz), 7.60 (1H, d, *J* = 7.6 Hz), 7.43 (1H, t, *J* = 7.6 Hz), 7.28 (1H, t, *J* = 7.6 Hz), 3.99 (3H, s), 1.01-0.96 (5H, m), 0.47 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.6, 155.2, 149.3, 132.2, 127.1, 124.3, 123.5, 123.2, 112.1, 52.2, 7.49, 7.47, -2.1. IR (neat): 3088, 3051, 3030, 2953, 2910, 2874, 2844, 1724, 1535 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{18}O_3Si$ 262.1025; found 262.1052.

*Methyl 3-[(chloromethyl)dimethylsilyl]benzofuran-2-carboxylate (**2u**).*

52% yield (292 mg), hexane / ethyl acetate = 5:1, R_f = 0.3. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.84 (1H, d, *J* = 7.9 Hz), 7.61 (1H, d, *J* = 7.9 Hz), 7.46 (1H, t, *J* = 7.9 Hz), 7.31 (1H, t, *J* = 7.9 Hz), 4.01 (3H, s), 3.25 (2H, s), 0.62 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.5,

155.3, 149.8, 131.6, 127.5, 124.0, 123.6, 121.1, 112.2, 52.5, 30.2, -2.9. IR (neat): 3049, 3031, 2955, 2926, 2849, 1719, 1540 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{15}O_3SiCl$ 282.0479; found 282.0505.

*Methyl 3-(triethylsilyl)benzofuran-2-carboxylate (**2v**).*

55% yield (317 mg), hexane / ethyl acetate = 5:1, R_f = 0.5. Yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.74 (1H, d, *J* = 7.8 Hz), 7.49 (1H, d, *J* = 7.8 Hz), 7.31 (1H, t, *J* = 7.8 Hz), 7.16 (1H, t, *J* = 7.8 Hz), 3.87 (3H, s), 0.95-0.85 (15H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.7, 155.2, 149.5, 132.6, 127.1, 124.4, 123.2, 121.7, 112.0, 52.2, 7.6, 3.8. IR (neat): 3051, 3031, 2954, 2910, 2875, 2733, 1724, 1533 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{16}H_{22}O_3Si$ 290.1338; found 290.1327.

*Dimethyl 3-(trimethylsilyl)benzofuran-2-yl phosphonate (**7**).*

35% yield (210 mg), hexane / ethyl acetate = 3:2, R_f = 0.3. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.84 (1H, d, *J* = 7.7 Hz), 7.57 (1H, d, *J* = 7.7 Hz), 7.38 (1H, t, *J* = 7.7 Hz), 7.26 (1H, t, *J* = 7.7 Hz), 3.83 (6H, d, $^3J_{HP}$ = 11.5 Hz), 0.52 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 156.4 (d, $^3J_{CP}$ = 11.6 Hz), 148.8 (d, $^1J_{CP}$ = 238.3 Hz), 131.3 (d, $^3J_{CP}$ = 14.9 Hz), 128.0 (d, $^2J_{CP}$ = 31.4 Hz), 126.4, 123.7, 123.0, 111.7, 53.0 (d, $^2J_{CP}$ = 6.0 Hz), 0.6. ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm): 8.37. IR (neat): 3066, 2954, 2926, 2853, 1249, 1033 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{19}O_4SiP$ 298.0790; found 298.0788.

*N,N,3-Tris(trimethylsilyl)-2-benzofuranmethanamine (**9**).*

30% yield (216 mg), hexane / ethyl acetate = 5:1, R_f = 0.6. Yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.24 (1H, d, *J* = 8.0 Hz), 7.19 (1H, t, *J* = 8.0 Hz), 6,94 (1H, t, *J* = 8.0 Hz), 6.90 (1H, d, *J* = 8.0 Hz), 3.92 (2H, s), 0.24 (9H, s), 0.19 (18H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.7, 158.7, 128.0, 125.4, 124.7, 122.3, 121.3, 109.3, 33.3, 3.1, -0.7. IR (neat): 3078, 3037, 2954, 2900, 1644, 1606, 1479, 1463 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{18}H_{33}NOSi_3$ 363.1870; found 363.1857.

*1-Methyl-2-(trimethylsilyl)carbonyl 1H-indole (**11**).*

46% yield (213 mg), hexane / ethyl acetate = 5:1, R_f = 0.5. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.76 (1H, d, *J* = 7.3 Hz), 7.43-7.36 (3H, m), 7.18 (1H, t, *J* = 7.3 Hz), 4.07 (3H, s), 0.46 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 226.8, 139.3, 139.2, 126.2, 126.1, 123.0, 120.5, 114.4, 110.3, 32.0, -1.3. IR (neat): 3126, 3059, 2956, 2900, 1613, 1580 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{17}NOSi$ 231.1074; found 231.1091.

*1-(1,1-Dimethylethyl) 2-methyl 3-(trimethylsilyl)-1H-indole-1,2-dicarboxylate (**12**).*

55% yield (379 mg), hexane / ethyl acetate = 5:1, R_f = 0.7. White solid, mp 62.6-64.0 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.16 (1H, d, *J* = 7.9 Hz), 7.73 (1H, d, *J* = 7.9 Hz), 7.37 (1H, t, *J* = 7.9 Hz), 7.26 (1H, t, *J* = 7.9 Hz), 3.93 (3H, s), 1.64 (9H, s), 0.40 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.8, 148.9, 136.2, 135.5, 132.8, 125.2, 122.9, 122.6, 117.6, 115.2, 84.7, 52.2, 27.8, -0.2. IR (KBr): 3096, 3074, 3050, 3006, 2981, 2959, 2903, 1743, 1732, 1524 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{18}H_{25}NO_4Si$ 347.1553; found 347.1580.

*3-Iodo-N,N-dimethylbenzofuran-2-carboxamide (**13**).*

65% yield (205 mg), hexane / ethyl acetate = 5:1, R_f = 0.3. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.41-7.32 (3H, m), 7.26 (1H, t, *J* = 7.2 Hz), 3.08 (3H, s), 3.07 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.7, 153.5, 147.9, 130.2, 127.0, 123.9, 122.3, 111.6, 68.0, 38.3, 35.4. IR (neat): (cm^{-1}): 3061, 3016, 2929, 2865, 1652, 1444 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{11}H_{10}NO_2I$ 314.9757; found 314.9751.

*2-(Diethylaminocarbonyl)-3-benzofuranboronic acid (**14**).*

96% yield (250 mg), hexane / ethyl acetate = 5:1, R_f = 0.2. White solid, mp 123.7-124.4 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.28 (2H, s), 8.27 (1H, d, *J* = 7.2 Hz), 7.49 (1H, d, *J* = 7.2 Hz), 7.41 (1H, t, *J* = 7.2 Hz), 7.33 (1H, t, *J* = 7.2 Hz), 3.77-3.48 (4H, m), 1.51-1.10 (6H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.8, 153.9, 153.7, 130.9, 126.6, 125.2, 123.8, 110.9, 44.1, 42.5,

14.6, 12.5. IR (neat): 3303, 2984, 2943, 2909, 2880, 2830, 2764, 1593, 1560, 1479, 1452, 1313, 1303 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{16}BNO_4$ 261.1172; found 261.1155.

*N,N-Diethyl-3-phenylbenzofuran-2-carboxamide (**15**).*

72% yield (88 mg), hexane / ethyl acetate = 5:1, R_f = 0.3. Yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.75 (1H, d, *J* = 7.4 Hz), 7.62 (2H, d, *J* = 7.4 Hz), 7.56 (1H, d, *J* = 7.4 Hz), 7.47 (2H, t, *J* = 7.4 Hz), 7.41 (1H, t, *J* = 7.4 Hz), 7.39 (1H, t, *J* = 7.4 Hz), 7.32 (1H, t, *J* = 7.4 Hz), 3.53 (2H, q, *J* = 7.1 Hz), 3.17 (2H, q, *J* = 7.1 Hz), 1.20 (3H, t, *J* = 7.1 Hz), 0.92 (3H, t, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 161.9, 154.2, 144.7, 131.0, 128.81, 128.77, 128.0, 127.0, 125.7, 123.4, 120.9, 120.5, 111.9, 43.0, 39.5, 14.0, 12.4. IR (neat): 3060, 2976, 2935, 2874, 1639, 1446 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{19}H_{19}NO_2$ 293.1416; found 293.1438.

2.9 References

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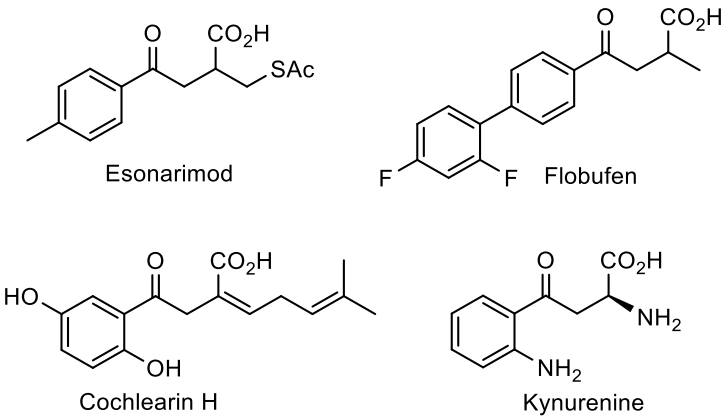
3. Magnesium-Promoted Reductive Carboxylation of Phenyl Vinyl Ketones: A Facile Synthesis of γ-Keto Carboxylic Acids

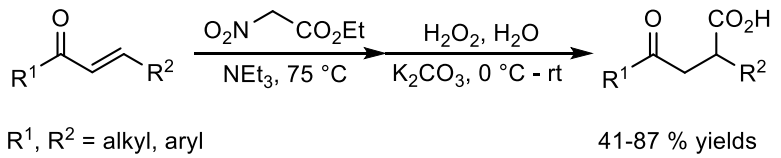
3.1 Introduction

The derivatives of γ-keto carboxylic acid derived from natural compounds sometimes have excellent biological and medicinal properties (Scheme 3-1).[(1)]



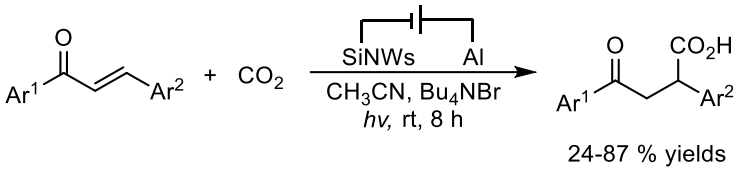
Scheme 3-1 Representative pharmaceuticals and natural ingredients bearing γ-keto carboxylic acid motifs

In addition, γ-keto carboxylic acid motif is also a key synthetic intermediate in organic synthesis,[(2)] and owing to its prominence in both synthetic chemistry and medicinal chemistry, a variety of effective methods to synthesize γ-keto carboxylic acids have been developed to date.[(3)] As one example, Cossío and coworkers reported a synthetic two-stage protocol from enones to γ-keto carboxylic acid through Michael addition and the subsequent Nef oxidation in 2010 (Scheme 3-2).[(3a)] The desired products γ-keto carboxylic acids could be obtained from the two-step strategy in 47-87% yields.



Scheme 3-2 Synthesis of γ-keto carboxylic acids through Michael addition and Nef oxidation

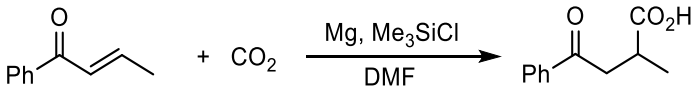
On the other hand, as a renewable and environmentally friendly C1 source that has been studied for a long time,[4] carbon dioxide has been also used to generate γ-keto carboxylic acids through direct carboxylation. For example, a carbon dioxide fixation to chalcone derivatives through a photo-electrochemical method was reported by Wang and Zhang's group in 2020 (Scheme 3-3).[3b]



Scheme 3-3 Photoelectrochemical CO_2 fixation to synthesize γ-keto carboxylic acids

Generally, the strategies for γ-keto carboxylic acids are quite useful, however, they also have some disadvantages. For example, these approaches are frequently impractical due to the need for special equipment or reactors, as well as the limitation of substrates. Therefore, development of more practical methods for γ-keto carboxylic acids from simple and readily accessible compounds under mild reaction conditions has been strongly required.

There are some reports on the magnesium-promoted reductive carbon dioxide fixation of aromatic conjugated compounds.[5] However, there is no reductive carboxylation of aliphatic enone structure by magnesium. In this research, the direct carboxylation of phenyl vinyl ketones to synthesize γ-keto carboxylic acids was examined in DMF using the well-developed Mg/Me_3SiCl system. As a result, the desired products, γ-keto carboxylic acids were selectively synthesized in moderate to good yields. The benzoyl group was intact under the reduction conditions, and the carboxylation only occurred on the γ-carbon position (Scheme 3-4).

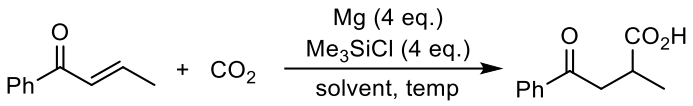


Scheme 3-4 Magnesium-promoted CO_2 fixation of phenyl vinyl ketones

3.2 Results and Discussion

3.2.1 Investigation of Solvent Effects and Reaction Temperature

Table 3-1 Optimizing the reaction conditions (solvent and temperature)



1a **2a**

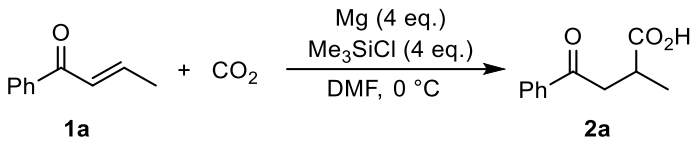
Entry	Temp (°C)	Solvent	Volume (mL)	Concentration (M)	Yield (%)
1	rt	DMF	7	0.14	53
2	0	DMF	7	0.14	83
3	-10	DMF	7	0.14	71
4	0	NMP	7	0.14	52
5	0	DMA	7	0.14	69
6	0	THF	7	0.14	No Reaction
7	0	CH_3CN	7	0.14	No Reaction
8	0	DMF	4	0.25	63
9	0	DMF	10	0.10	70

Reaction conditions: **1a** (1 mmol), Me_3SiCl (4 eq.), Mg (4 eq.), CO_2 balloon (1 atmosphere), solvent (4-10 mL), 1 h.

Initially, reduction of phenyl vinyl ketone **1a** by magnesium metal under carbon dioxide atmosphere was investigated in *N*,*N*-dimethylformamide (DMF) at 25 °C in the presence of chlorotrimethylsilane, and the desired carboxylic acid **2a** was obtained in 53% yield (Entry 1). Then, the examination of the temperature suggested that 0 °C was the appropriate reaction temperature (83% yield, Entry 2). In the screening several commonly used organic solvents, a diminish in yields of carboxylic acid **2a** was obtained in amide solvents, *N*-methyl-2-pyrrolidone (NMP) and *N*,*N*-dimethylacetamide (DMA) (Entries 4, 5). Meanwhile, no reduction of **1a** was observed in THF and acetonitrile (Entries 6, 7). In addition, the examination of the substrate concentration showed that 0.14 M (1 mmol / 7 mL) was the optimum concentration (Entries 8, 9).

3.2.2 Effects of Dropping Rate and CO_2 Bubbling Time

Table 3-2 Optimizing the reaction conditions (dropping rate and CO_2 bubbling time)



Entry	Dropping time (min)	Dropping rate (mL/min)[a)]	CO_2 Bubbling Time (h)	Yield (%)
1	1	3	0.5	74
2	1	3	1	73
3	1	3	No Bubbling	67
4	10	0.30	0.5	83
5	20	0.15	0.5	75
6	0	No Dropping	0.5	70

Reaction conditions: **1a** (1 mmol), Me_3SiCl (4 eq.), Mg (4 eq.), DMF (7 mL), CO_2 balloon (1 atmosphere), 0 °C, 1 h. a) To the flask containing Mg (4 eq.), Me_3SiCl (4 eq.) and DMF (4 mL) in a CO_2 atmosphere, **1a** in DMF (3 mL) was added dropwise using a dropping funnel.

Next, dropping rate and carbon dioxide bubbling time were changed to get the optimized conditions (Table 3-2). According to the previous study of my laboratory, it is necessary to introduce carbon dioxide to the solvent to exclude nitrogen gas before starting the reaction. And in this research, the appropriate bubbling time was 0.5 h (Entry 1), and the results also indicated that the bubbling time was not the critical factor to affect the product yield. Next, the dropping rate was investigated, and it was found that the best addition time of starting material **1a** was 10 minutes (Entry 4).

3.2.3 Examination on Equivalents of Reagents

Table 3-3 Optimizing the reaction conditions (equivalents of reagents)

1a **2a**

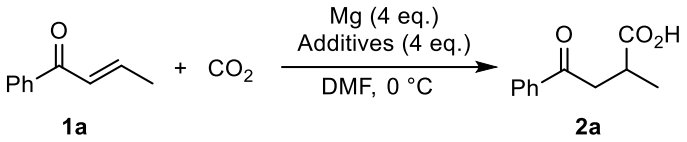
Entry	Me_3SiCl (eq.)	Mg (eq.)	Yield (%)
1	0	4	no reaction
2	3	4	78
3	4	4	83
4	5	4	80
5	4	0	no reaction
6	4	3	79
7	4	5	75

Reaction conditions: **1a** (1 mmol), Me_3SiCl (0-5 eq.), Mg (0-5 eq.), DMF (7 mL), CO_2 balloon (1 atmosphere), 0 °C, 1 h.

Subsequently, the amounts of magnesium and chlorotrimethylsilane were examined (Table 3-3). No reaction occurred in the absence of chlorotrimethylsilane, and the yield slightly decreased when 3 equivalents or 5 equivalents of chlorotrimethylsilane were used (Entries 2, 4). When the amount of magnesium was changed from 4 equivalents to 3 or 5 equivalents, the yield was not improved (Entries 6, 7). Moreover, no reaction occurred when no magnesium was added (Entry 5). Therefore, the use of 4 equivalents of magnesium and 4 equivalents of chlorotrimethylsilane was adopted as the optimal reaction conditions.

3.2.4 Effects on Reaction Time and Additives

Table 3-4 Optimizing the reaction conditions (reaction time and additives)



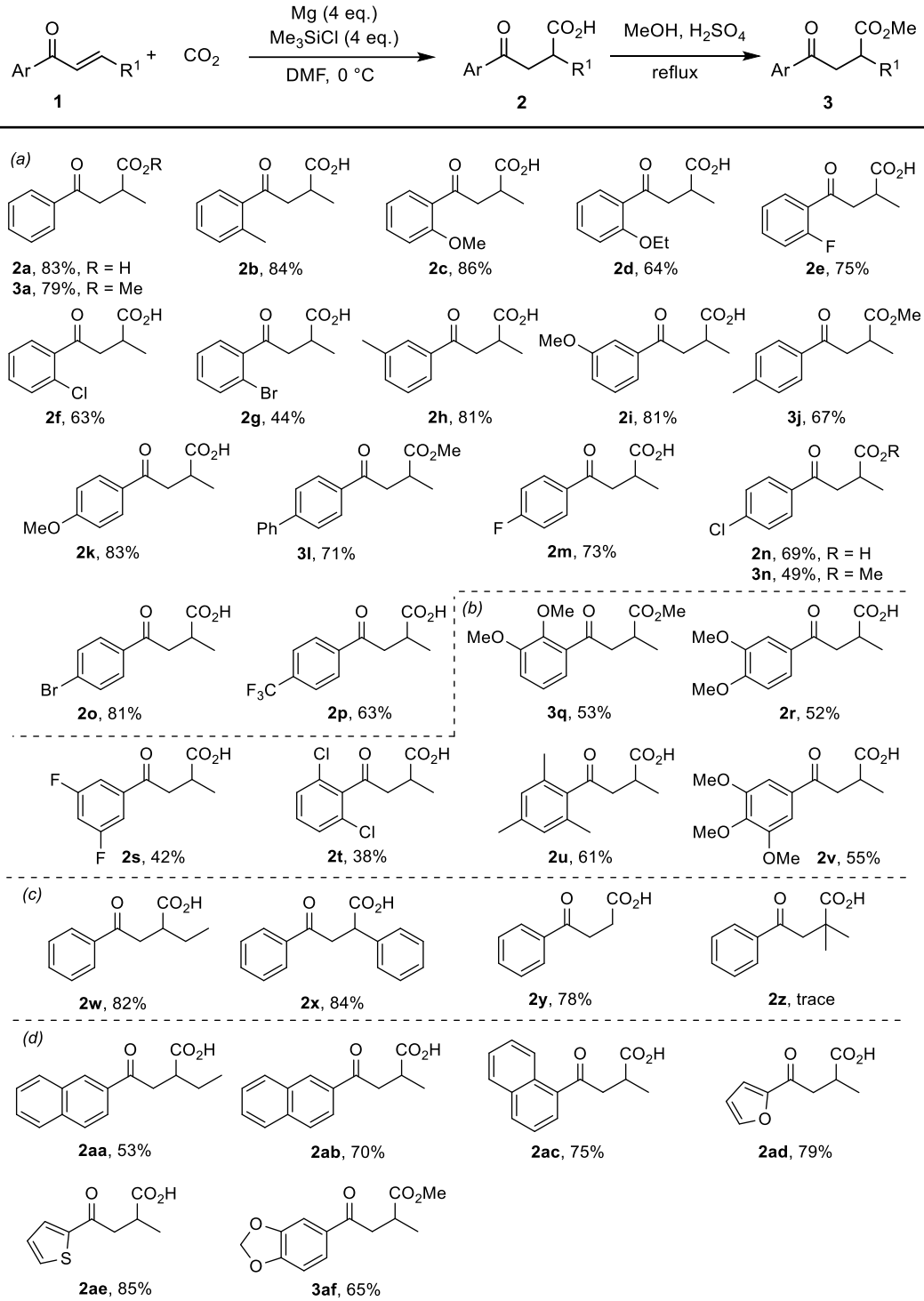
1a **2a**

Entry	Reaction Time (h)	Additives	Yield (%)
1	0.5	Me_3SiCl	81
2	1	Me_3SiCl	83
3	3	Me_3SiCl	68
4	1	Me_2SiCl_2	72
5	1	Et_3SiCl	46
6	1	$PhMe_2SiCl$	54

Reaction conditions: **1a** (1 mmol), additives (4 eq.), Mg (4 eq.), DMF (7 mL), CO_2 balloon (1 atmosphere), 0 °C.

The reaction time and additive effects were also studied (Table 3-4). It was found that the reaction time of 1 h was appropriate for this carboxylation. And as anticipated, shorter reaction time gave a slightly low yield (Entry 1). Additionally, longer the reaction time also gave no benefit for this carboxylation reaction (Entry 3). Besides, the additives are necessary for the activation of the magnesium metal, and the better additive was Me_3SiCl. Other activating agents, including Me_2SiCl_2, Et_3SiCl, and $PhMe_2SiCl$, led to a slight decrease in yields (Entries 4-6).

3.3 Substrate Scope



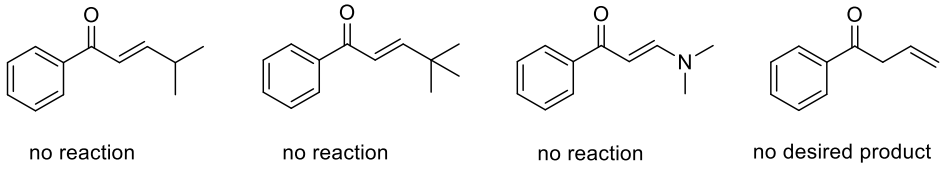
Scheme 3-5 Substrate scope. Reaction conditions: 1) **1** (1 mmol), Me_3SiCl (4 eq.), Mg (4 eq.), DMF (7 mL), 0 °C, CO_2 balloon (1 atmosphere), 1 h. 2) Crude product of **2** without purification, MeOH (0.1 M, 10 mL), concentrated H_2SO_4 (0.5 mL), reflux, 1 h.

Under the optimum reaction conditions, reduction of a series of phenyl vinyl ketone derivatives **1** was investigated and the results are shown in Scheme 3-5. Firstly, a variety of phenyl vinyl ketones with a less substituent on the benzene ring were studied (Scheme 3-5, a). The scope of electron-donating groups such as a methyl, a methoxy, or an ethoxy group at *ortho*-, *meta*- or *para*-position afforded the corresponding carboxylic acids **2b**, **2c**, **2d**, **2h**, **2i**, **2k** in 64-86% yields. Furthermore, substrates with a halogen atom or a strong electron-withdrawing trifluoromethyl group were tolerated to give products **2e**, **2f**, **2g**, **2m**, **2n**, **2o**, **2p** in 44-81% yields. Several carboxylic acids **2** were converted to the corresponding esters **3** in the presence of methanol and concentrated sulfuric acid under reflux to separate the desired products effectively. and esters **3a**, **3j**, **3l**, **3n** were synthesized in 79%, 67%, 71%, 49% yields, respectively. The product **3l** is the derivative of the non-steroidal anti-inflammatory drug metbufen.[(6)]

Secondly, carboxylation of di- or tri-substituted phenyl vinyl ketones **1** was also tolerated under standard reaction conditions to give the desired products in diminished yields (Scheme 3-5, b). Specifically, 2,3-dimethoxyphenyl and 3,4-dimethoxyphenyl derivatives were transformed into **3q** and **2r** in 53% and 52% yields, respectively. While substrates bearing fluorine atoms and chlorine atoms afforded target products **2s** and **2t** in 42% and 38% yields, respectively. The reaction of tri-substituted substrates was compatible with this carboxylation to produce carboxylic acids **2u** and **2v** in 61% and 55% yields, respectively.

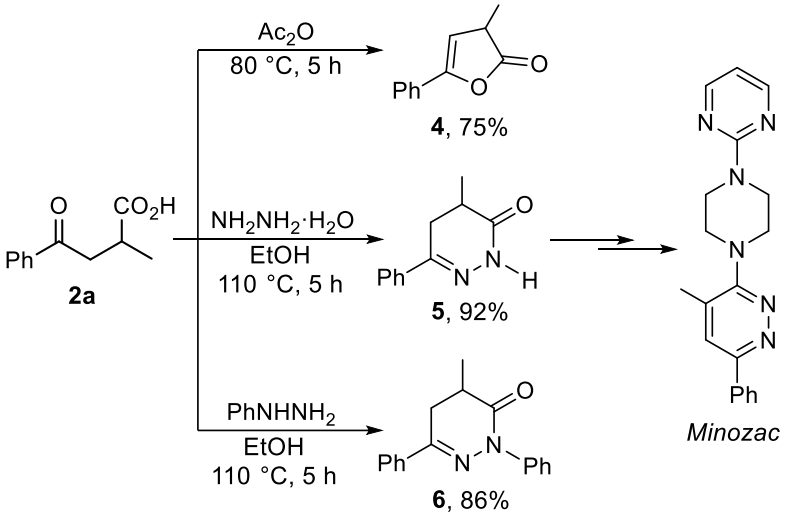
The replacement of the methyl group to an ethyl group or a phenyl group gave **2w** and **2x** in excellent yields. The reaction was also worked well with terminal alkene to generate **2y** in 78% yield (Scheme 3-5, c). The substrate with two methyl groups at the terminal carbon atom gave no desired product **2z**. Unfortunately, the substrates with a bulky *iso*-propyl group, a *tert*-butyl group, or a dimethylamino group as R^1 was unsuccessful (Scheme 3-6).

Finally, naphthyl, 2-furyl, and 2-thienyl derivatives were also examined to afford the corresponding carboxylic acids **2aa**-**2ae** and ester **3af** in good yields (Scheme 3-5, d).



Scheme 3-6 Unsuccessfully examples

3.4 Synthetic Usability

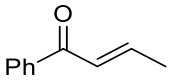
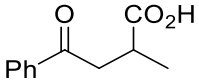


Scheme 3-7 Application of carboxylic acid **2a** to synthesis of heterocyclic compounds

The synthetic usability of carboxylic acids **2** was demonstrated by some cyclization reactions of **2a** to give cyclic compounds **4**, **5**, and **6** in excellent yields (Scheme 3-7). Firstly, carboxylic acid **2a** was treated with acetic anhydride for 5 h at 80 °C to give lactone **4** in 75% yield.[7a] The cyclic compound **5**, the crucial intermediate to produce the active pharmaceutical ingredient Minozac, was obtained via the reaction between carboxylic acid **2a** and hydrazine monohydrate in 92% yield.[7b] Finally, under the same reaction conditions, carboxylic acid **2a** was converted into the similar product **6** to the compound **5** in 86% yield.

3.5 Reduction Potentials

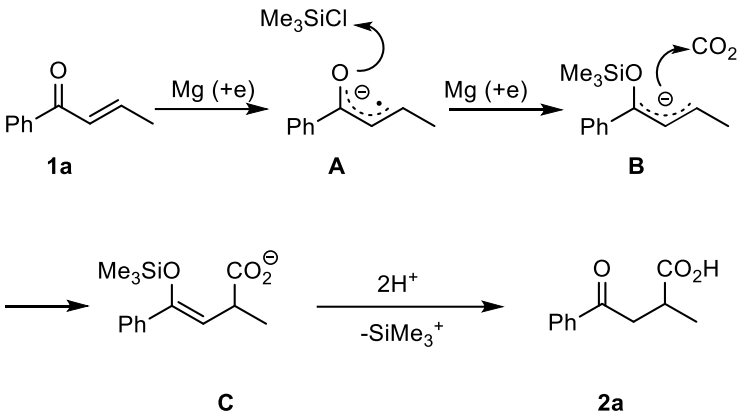
Table 3-5 Reduction potential of substrates

Entry	Substrates		Reduction Potential (V vs. Ag/AgCl)
1		**1a**	-1.66 V
2	Me_3SiCl		no significant peak (-3.00 ~ 0 V)
3		**2a**	-2.30 V

Working electrode: Pt, counter electrode: Pt, reference electrode: Ag/AgCl, solvent: DMF (10 mL), supporting electrolyte: 1% nBu$_4$NClO$_4$, scan rate: 0.1 Vs^{-1}

The reduction potentials of some substrates were measured by cyclic voltammetry (CV), and the results are shown in Table 3-5. The reduction potential of the substrate phenyl vinyl ketone **1a** was recorded at -1.66 V. No reduction peak of chlorotrimethylsilane was observed in the range of -3.00 to 0 V. And the reduction potential of product **2a** was recorded at -2.30 V. Therefore, it is considered that this reaction is initiated by single electron transfer from magnesium to phenyl vinyl ketone **1a**.

3.6 Plausible Reaction Mechanism



Scheme 3-8 Plausible reaction mechanism of carboxylation

A plausible reaction mechanism for the formation of carboxylic acid **2a** was shown in Scheme 3-8. Firstly, phenyl vinyl ketone **1a** is converted to an anion radical species **A** through a single electron transfer from magnesium. The active species **A** attacks chlorotrimethylsilane to yield an anionic species **B** after the immediate second electron transfer from magnesium. Then, an attack of anionic species **B** to carbon dioxide will furnish the stable anion **C**. The anionic intermediate **C** will be coordinated with magnesium cation or a trimethylsilyl cation in the reaction mixture. Finally, the product **2a** may be formed through the hydrolysis of the intermediate **C**.

3.7. Experimental Section

3.7.1 General Information

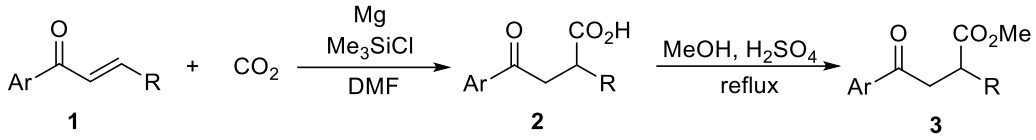
Materials

All reactions were performed under an atmosphere of carbon dioxide unless stated otherwise. Unless otherwise noted. All reagents were purchased from TCI, Sigma-Aldrich, Nacalai tesque, Wako, Kanto Chemical, Alfa Aesar, and SynQuest, and were used without further purification. Magnesium for Grignard reagent is commercially available and was used with no pre-treatment. Solvents were distilled under reduced pressure by standard procedures. Acetonitrile of super dehydrated grade was bought from Wako Pure Chemical Industries, Ltd. without further treatment. THF was freshly distilled from sodium/benzophenone. Chlorotrimethylsilane was simply distilled before use.

Analysis Instruments

Cyclic voltammograms were measured by ALS-600. Melting points were performed on a Yanaco MP-500D or a MP-J3 instrument and were uncorrected. NMR spectra (^{1}H, ^{13}C, ^{19}F) were recorded on a JEOL JNM AL-400 (400 MHz) spectrometer. Chemical shifts (δ) in parts per million (ppm) were reported relative to the residual signal of chloroform (7.26 ppm), and coupling constants were reported in hertz (Hz). Carbon chemical shifts were referenced to the carbon signal of $CDCl_3$ at 77.0 ppm. Fluorine chemical shifts were referenced to the signal of CF_3CO_2H at -76.50 ppm. Signal Multiplicity was shown as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). IR spectra were obtained on a JASCO 470Plus FTIR spectrometer, and peaks were reported in wavenumber (cm^{-1}). MS spectra were recorded on a Shimadzu GCMS-QP2010plus or a JMS-T200GC spectrometer. TLC was performed on Merck pre-coated plates (silica gel 60 F_{254}, Art 5715, 0.25 mm). Column chromatography was performed using neutral silica gel (60N, spherical, 63-210 mesh, Kanto Chemical).

3.7.2 General Procedure for Carboxylation of Phenyl Vinyl Ketones



To an oven-dried flask containing magnesium turnings (4 mmol, 4 eq.) was in a CO_2 atmosphere, chlorotrimethylsilane (4 mmol, 4 eq.) in dry DMF (4 mL) was added. The reaction mixture was then stirred for 0.5 h at room temperature. Next, phenyl vinyl ketones **1** (1 mmol, 1 eq.) in dry DMF (3 mL) was added dropwise, and the reaction mixture was stirred at 0 °C. After consuming starting material (usually 1 h, monitored by TLC), the reaction mixture was carefully poured into a beaker containing 50 mL of 0.25 M hydrochloric acid solution. The product was extracted with diethyl ether (30 mL ×3), the combined organic layer was in sequence washed with water (50 mL), brine (50 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. Finally, the desired product carboxylic acids **2** was purified by column chromatography (hexane / ethyl acetate = 1 : 1).

For the synthesis of ester product **3**, the crude product obtained in the previous stage was directly subjected to a flask containing methanol (0.1 M, 10 mL) and concentrated sulfuric acid (0.5 mL). The reaction was stirred at reflux for 1 h and then quenched with water (30 mL). The product was extracted with diethyl ether (30 mL ×3), the combined organic layer was washed with brine (50 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The desired products **3** was purified by column chromatography (hexane / ethyl acetate = 30 : 1).

*2-Methyl-4-oxo-4-phenyl butanoic acid (**2a**).* Known compound.[8]

83% yield (160 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.97 (2H, d, J = 7.4 Hz), 7.57 (1H, t, J = 7.4 Hz), 7.46 (2H, t, J = 7.6 Hz), 3.48 (1H, dd, J = 17.8, 7.8 Hz), 3.20-3.12 (1H, m), 3.05 (1H, dd, J = 17.8, 5.4 Hz), 1.32 (3H, d, J = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 197.8, 181.9, 136.5, 133.3, 128.6, 128.0, 41.7, 34.8, 17.1.

*Methyl 2-methyl-4-oxo-4-phenyl butanoate (**3a**).* Known compound.[9]

79% yield (163 mg), hexane / ethyl acetate = 6 : 1, R_f = 0.7. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.97 (2H, d, *J* = 7.6 Hz), 7.57 (1H, t, *J* = 7.6 Hz), 7.46 (2H, t, *J* = 7.6 Hz), 3.70 (3H, s), 3.49 (1H, dd, *J* = 17.5, 7.8 Hz), 3.18-3.10 (1H, m), 3.03 (1H, dd, *J* = 17.5, 5.6 Hz), 1.28 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 198.0, 176.4, 136.7, 133.2, 128.6, 128.0, 51.9, 42.0, 34.9, 17.3.

*2-Methyl-4-oxo-4-(2-methylphenyl) butanoic acid (**2b**).* Known compound.[10]

84% yield (173 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.68 (1H, d, *J* = 7.6 Hz), 7.38 (1H, t, *J* = 7.6 Hz), 7.28-7.23 (2H, m), 3.40 (1H, dd, *J* = 17.8, 8.0 Hz), 3.19-3.10 (1H, m), 2.97 (1H, dd, *J* = 17.8, 5.2 Hz), 2.49 (3H, s), 1.31 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 201.8, 182.1, 138.3, 137.3, 132.0, 131.5, 128.5, 125.7, 44.5, 35.0, 21.3, 17.0.

*4-(2-Methoxyphenyl)-2-methyl-4-oxo butanoic acid (**2c**).*

86% yield (191 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid, mp 92.8-94.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.75 (1H, d, *J* = 7.8 Hz), 7.46 (1H, t, *J* = 7.8 Hz), 6.99 (1H, t, *J* = 7.8 Hz), 6.96 (1H, d, *J* = 7.8 Hz), 3.91 (3H, s), 3.45 (1H, dd, *J* = 19.6, 9.1 Hz), 3.14-3.08 (2H, m), 1.27 (3H, d, *J* = 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 199.7, 182.4, 158.8, 133.8, 130.5, 127.4, 120.6, 111.5, 55.4, 47.1, 35.1, 16.9. IR (KBr): 3304, 3077, 3032, 2981, 2942, 2900, 1704, 1664, 1598 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{12}H_{14}O_4$ 222.0887; found 222.0899.

*4-(2-Ehoxyphenyl)-2-methyl-4-oxo butanoic acid (**2d**).*

64% yield (151 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid, mp 135.8-136.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.73 (1H, d, *J* = 7.8 Hz), 7.43 (1H, t, *J* = 7.8 Hz), 6.97 (1H, t, *J* = 7.8 Hz), 6.92 (1H, d, *J* = 7.8 Hz), 4.13 (2H, q, *J* = 7.1 Hz), 3.48 (1H, dd, *J* = 17.9, 7.4 Hz), 3.19-3.06 (2H, m), 1.48 (3H, t, *J* = 7.1 Hz), 1.27 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 199.9, 182.4, 158.2, 133.7, 130.5, 127.5, 120.5, 112.3, 64.1, 47.3, 35.1, 16.9, 14.7. IR

(KBr): 3305, 3077, 3042, 2978, 2934, 2904, 1705, 1662, 1594 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{16}O_4$ 236.1043; found 236.1047.

*4-(2-Fluorophenyl)-2-methyl-4-oxo butanoic acid (**2e**).* Known compound.[10]

75% yield (158 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.02 (1H, bs), 7.87 (1H, t, *J* = 7.6 Hz), 7.54-7.48 (1H, m), 7.21 (1H, t, *J* = 7.6 Hz), 7.15-7.10 (1H, m), 3.48-3.41 (1H, m), 3.16-3.04 (2H, m), 1.30 (3H, d, *J* = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 196.1, 182.0, 162.1 (d, $^1J_{CF}$ = 254.0 Hz), 134.7 (d, $^3J_{CF}$ = 9.0 Hz), 130.7, 125.1 (d, $^2J_{CF}$ = 12.0 Hz), 124.5 (d, $^3J_{CF}$ = 3.0 Hz), 116.6 (d, $^2J_{CF}$ = 23.0 Hz), 46.6, 34.8, 17.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -109.01 (m).

*4-(2-Chlorophenyl)-2-methyl-4-oxo butanoic acid (**2f**).*

63% yield (142 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid, mp 85.2-87.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.21 (1H, bs), 7.51 (1H, d, *J* = 8.0 Hz), 7.41-7.35 (2H, m), 7.31 (1H, t, *J* = 8.0 Hz), 3.40 (1H, dd, *J* = 17.8, 7.8 Hz), 3.20-3.11 (1H, m), 3.05 (1H, dd, *J* = 17.8, 5.5 Hz), 1.31 (3H, d, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 200.8, 181.8, 138.7, 131.9, 130.9, 130.5, 129.1, 126.9, 45.8, 35.1, 16.8. IR (KBr): 3379, 3074, 3022, 2975, 2940, 2883, 1706, 1699, 1591 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{11}H_{11}O_3Cl$ 226.0391; found 226.0395.

*4-(2-Bromophenyl)-2-methyl-4-oxo butanoic acid (**2g**).*

44% yield (119 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid, mp 80.2-81.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.57 (1H, bs), 7.54 (1H, d, *J* = 7.8 Hz), 7.39 (1H, d, *J* = 7.8 Hz), 7.31 (1H, t, *J* = 7.8 Hz), 7.24 (1H, t, *J* = 7.8 Hz), 3.32 (1H, dd, *J* = 17.8, 7.8 Hz), 3.15-3.07 (1H, m), 2.98 (1H, dd, *J* = 17.8, 5.5 Hz), 1.27 (3H, d, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 201.6, 181.8, 141.0, 133.7, 131.7, 128.7, 127.4, 118.6, 45.5, 35.0, 16.8. IR (KBr): 3381, 3042, 2975, 2939, 2909, 2886, 1712, 1703, 1588 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{11}H_{11}O_3Br$ 269.9886; found 269.9897.

*2-methyl-4-oxo-4-(3-methylphenyl) butanoic acid (**2h**).* Known compound.[10]

81% yield (167 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.77 (1H, s), 7.76 (1H, d, *J* = 8.8 Hz), 7.39-7.33 (2H, m), 3.46 (1H, dd, *J* = 17.8, 7.6 Hz), 3.20-3.11 (1H, m), 3.05 (1H, dd, *J* = 17.8, 5.6 Hz), 2.41 (3H, s), 1.32 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 198.0, 181.9, 138.4, 136.5, 134.0, 128.6, 128.5, 125.3, 41.7, 34.8, 21.3, 17.1.

*4-(3-Methoxyphenyl)-2-methyl-4-oxo butanoic acid (**2i**).* Known compound.[10]

81% yield (180 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.55 (1H, d, *J* = 7.8 Hz), 7.49 (1H, s), 7.37 (1H, t, *J* = 7.8 Hz), 7.12 (1H, d, *J* = 7.8 Hz), 3.85 (3H, s), 3.46 (1H, dd, *J* = 17.6, 7.7 Hz), 3.19-3.11 (1H, m), 3.05 (1H, dd, *J* = 17.6, 5.4 Hz), 1.32 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 197.7, 181.7, 159.8, 137.8, 129.6, 120.7, 119.9, 112.1, 55.4, 41.8, 34.8, 17.0.

*Methyl 2-methyl-4-oxo-4-(4-methylphenyl) butanoate (**3j**).* Known compound.[11]

67% yield (147 mg), hexane / ethyl acetate = 6 : 1, R_f = 0.7. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.84 (2H, d, *J* = 7.9 Hz), 7.23 (2H, d, *J* = 7.9 Hz), 3.67 (3H, s), 3.43 (1H, dd, *J* = 17.5, 7.8 Hz), 3.15-3.06 (1H, m), 2.98 (1H, dd, *J* = 17.5, 5.6 Hz), 2.38 (3H, s), 1.25 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 197.5, 176.3, 143.8, 134.2, 129.2, 128.0, 51.7, 41.7, 34.8, 21.5, 17.2.

*4-(4-Methoxyphenyl)-2-methyl-4-oxo butanoic acid (**2k**).* Known compound.[12]

83% yield (184 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.94 (2H, d, *J* = 8.6 Hz), 6.92 (2H, d, *J* = 8.6 Hz), 3.86 (3H, s), 3.41 (1H, dd, *J* = 17.5, 7.6 Hz), 3.16-3.09 (1H, m), 3.01 (1H, dd, *J* = 17.5, 5.6 Hz), 1.30 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 196.4, 181.9, 163.6, 130.3, 129.6, 127.5, 55.4, 41.3, 34.8, 17.1.

*Methyl 4-([1,1'-biphenyl]-4-yl)-2-methyl-4-oxobutanoate (**3l**).*

71% yield (200 mg), hexane / ethyl acetate = 6 : 1, R_f = 0.7. White solid, mp 87.2-88.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.04 (2H, d, *J* = 8.4 Hz), 7.69 (2H, d, *J* = 8.4 Hz), 7.63 (2H, d, *J* = 7.3 Hz), 7.47 (2H, t, *J* = 7.3 Hz), 7.40 (1H, t, *J* = 7.3 Hz), 3.72 (3H, s), 3.52 (1H, dd, *J* = 17.5, 7.8 Hz), 3.21-3.12 (1H, m), 3.06 (1H, dd, *J* = 17.5, 5.4 Hz), 1.30 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 197.6, 176.4, 145.9, 139.8, 135.4, 128.9, 128.6, 128.2, 127.23, 127.22, 51.9, 42.0, 34.9, 17.3. IR (KBr): 3439, 3339, 3084, 3054, 3028, 2984, 2951, 2912, 2878, 2846, 1731, 1679, 1605 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{18}H_{18}O_3$ 282.1251; found 282.1258.

*4-(4-Fluorophenyl)-2-methyl-4-oxo butanoic acid (**2m**).* Known compound.[12]

73% yield (153 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.06 (1H, bs), 7.99 (2H, dd, *J* = 8.6, 5.5 Hz), 7.12 (2H, dd, $J_1 = J_2$ = 8.6 Hz), 3.44 (1H, dd, *J* = 17.8, 8.0 Hz), 3.18-3.09 (1H, m), 2.98 (1H, dd, *J* = 17.8, 5.2 Hz), 1.31 (3H, d, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 196.2, 182.1, 165.8 (d, $^1J_{CF}$ = 255.0 Hz), 132.9 (d, $^4J_{CF}$ = 4.0 Hz), 130.7 (d, $^3J_{CF}$ = 9.0 Hz), 115.7 (d, $^2J_{CF}$ = 22.0 Hz), 41.6, 34.8, 17.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -104.99 (m).

*4-(4-Chlorophenyl)-2-methyl-4-oxo butanoic acid (**2n**).* Known compound.[12]

69% yield (156 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.90 (2H, d, *J* = 8.3 Hz), 7.43 (2H, d, *J* = 8.3 Hz), 3.44 (1H, dd, *J* = 17.8, 8.0 Hz), 3.19-3.10 (1H, m), 3.00 (1H, dd, *J* = 17.8, 5.4 Hz), 1.32 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 196.6, 181.6, 139.8, 134.8, 129.4, 128.9, 41.6, 34.7, 17.1.

*Methyl 4-(4-Chlorophenyl)-2-methyl-4-oxo butanoate (**3n**).* Known compound.[13]

49% yield (118 mg), hexane / ethyl acetate = 6 : 1, R_f = 0.7. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.85 (2H, d, *J* = 8.5 Hz), 7.38 (2H, d, *J* = 8.5 Hz), 3.64 (3H, s), 3.40 (1H, dd, *J* = 17.7, 8.0 Hz), 3.12-3.03 (1H, m), 2.92 (1H, dd, *J* = 17.7, 5.4 Hz), 1.23 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 196.8, 176.2, 139.6, 135.0, 129.4, 128.9, 51.9, 41.9, 34.8, 17.2.

*4-(4-Bromophenyl)-2-methyl-4-oxo butanoic acid (**2o**).* Known compound.[12]

81% yield (219 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.81 (2H, d, *J* = 8.4 Hz), 7.59 (2H, d, *J* = 8.4 Hz), 3.43 (1H, dd, *J* = 17.8, 7.8 Hz), 3.18-3.10 (1H, m), 2.99 (1H, dd, *J* = 17.8, 5.4 Hz), 1.31 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 196.8, 181.8, 135.2, 131.9, 129.5, 128.5, 41.6, 34.8, 17.0.

*2-methyl-4-oxo-4-(4-trifluoromethylphenyl) butanoic acid (**2p**).* Known compound.[10]

63% yield (164 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.06 (2H, d, *J* = 8.2 Hz), 7.73 (2H, t, *J* = 8.2 Hz), 3.50 (1H, dd, *J* = 17.8, 8.0 Hz), 3.22-3.13 (1H, m), 3.05 (1H, dd, *J* = 17.8, 5.2 Hz), 1.34 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 196.9, 181.7, 139.2, 134.6 (q, $^2J_{CF}$ = 32.0 Hz), 128.4, 125.7 (d, $^3J_{CF}$ = 3.0 Hz), 123.6 (q, $^1J_{CF}$ = 272.0 Hz), 41.9, 34.8, 17.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -63.33 (s).

*Methyl 4-(2,3-dimethoxyphenyl)-2-methyl-4-oxobutanoate (**3q**).*

53% yield (141 mg), hexane / ethyl acetate = 6 : 1, R_f = 0.7. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.14 (1H, d, *J* = 7.5 Hz), 7.05 (1H, t, *J* = 7.5 Hz), 7.01 (1H, d, *J* = 7.5 Hz), 3.88 (3H, s), 3.86 (3H, s), 3.66 (3H, s), 3.45-3.38 (1H, m), 3.10-3.00 (2H, m), 1.22 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 200.5, 176.2, 152.9, 148.2, 133.4, 123.9, 120.6, 115.7, 61.2, 55.9, 51.6, 46.6, 34.9, 17.0. IR (neat): 3075, 2974, 2950, 2880, 2839, 1737, 1680, 1580 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{18}O_5$ 266.1149; found 266.1165.

*4-(3,4-Dimethoxyphenyl)-2-methyl-4-oxo butanoic acid (**2r**).* Known compound.[14]

52% yield (131 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.59 (1H, d, *J* = 8.4 Hz), 7.52 (1H, s), 6.88 (1H, d, *J* = 8.4 Hz), 3.94 (3H, s), 3.92 (3H, s), 3.43 (1H, dd, *J* = 17.5, 7.8 Hz), 3.18-3.10 (1H, m), 3.03 (1H, dd, *J* = 17.5, 5.5 Hz), 1.31 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 196.5, 181.8, 153.4, 149.0, 129.7, 122.7, 110.1, 110.0, 56.1, 55.9, 41.2, 34.9, 17.1.

*4-(3,5-Difluorophenyl)-2-methyl-4-oxo butanoic acid (**2s**).*

42% yield (96 mg), hexane / ethyl acetate = 5 : 1, R_f = 0.7. Pale yellow solid, mp 98.4-99.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.47-7.44 (2H, m), 7.05-6.99 (1H, m), 3.42 (1H, dd, *J* = 18.0, 8.0 Hz), 3.19-3.10 (1H, m), 2.97 (1H, dd, *J* = 18.0, 5.1 Hz), 1.33 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.3, 181.6, 163.0 (dd, $^1J_{CF}$ = 250.0, 11.0 Hz), 139.3, 110.0 (dd, $^2J_{CF}$ = 19.0, 7.0 Hz), 108.6 (t, $^2J_{CF}$ = 25.0 Hz), 41.8, 34.7, 17.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -90.40 (m). IR (KBr): 3348, 3086, 2982, 2931, 2886, 2764, 2674, 1699, 1690, 1598 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{11}H_{10}O_3F_2$ 228.0593; found 228.0606.

*4-(2,6-Dichlorophenyl)-2-methyl-4-oxo butanoic acid (**2t**).*

38% yield (99 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid, mp 109.9-112.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.98 (1H, bs), 7.27-7.19 (3H, m), 3.28 (1H, dd, *J* = 19.0, 6.1 Hz), 3.15-3.07 (1H, m), 2.95 (1H, dd, *J* = 19.0, 6.5 Hz), 1.30 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 199.7, 181.6, 139.0, 130.7, 130.5, 128.1, 46.4, 34.1, 16.7. IR (KBr): 3409, 3083, 2987, 2939, 1727, 1708, 1582 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{11}H_{10}O_3Cl_2$ 260.0002; found 260.0021.

*2-Methyl-4-(2,4,6-trimethylphenyl)-4-oxo butanoic acid (**2u**).*

61% yield (143 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid, mp 100.0-101.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.83 (2H, s), 3.21-3.09 (2H, m), 2.83 (1H, dd, *J* = 18.5, 4.6 Hz), 2.28 (3H, s), 2.20 (6H, s), 1.33 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 208.0, 181.9, 138.6, 138.5, 132.7, 128.5, 47.8, 34.2, 21.0, 18.9, 16.9. IR (KBr): 3380, 2979, 2939, 2913, 2763, 2658, 1714, 1700, 1612 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{18}O_3$ 234.1251; found 234.1264.

*2-Methyl-4-oxo-4-(3,4,5-trimethoxyphenyl) butanoic acid (**2v**).*

55% yield (155 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid, mp 120.2-121.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.03 (1H, bs), 7.19 (2H, s), 3.87 (9H, s), 3.41 (1H, dd, *J* =

17.7, 7.7 Hz), 3.15-3.06 (1H, m), 3.01-2.91 (1H, m), 1.28 (3H, d, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 196.6, 181.5, 152.9, 142.6, 131.6, 105.4, 60.8, 56.2, 41.4, 34.8, 17.0. IR (KBr): 3347, 3091, 2975, 2943, 2907, 2830, 1703, 16832, 1587 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{18}O_6$ 282.1098; found 282.1114.

*2-Ethyl-4-oxo-4-phenyl butanoic acid (**2w**).* Known compound.[15]

82% yield (169 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.35 (1H, bs), 7.96 (2H, d, J = 7.7 Hz), 7.56 (1H, t, J = 7.7 Hz), 7.45 (2H, t, J = 7.7 Hz), 3.45 (1H, dd, J = 18.9, 9.6 Hz), 3.09-3.01 (2H, m), 1.81-1.66 (2H, m), 1.01 (3H, t, J = 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 198.0, 181.6, 136.5, 133.2, 128.6, 128.0, 41.5, 39.6, 24.9, 11.5.

*4-Oxo-2,4-diphenyl butanoic acid (**2x**).* Known compound.[3a]

84% yield (214 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.80 (1H, bs), 7.97 (2H, d, J = 7.4 Hz), 7.56 (1H, t, J = 7.4 Hz), 7.45 (2H, t, J = 7.4 Hz), 7.39-7.34 (4H, m), 7.32-7.28 (1H, m), 4.33 (1H, dd, J = 10.0, 4.2 Hz), 3.91 (1H, td, J = 18.0, 10.0 Hz), 3.30 (1H, dd, J = 18.0, 4.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 197.3, 179.1, 137.6, 136.2, 133.3, 128.9, 128.6, 128.1, 128.0, 127.7, 46.3, 42.2.

*3-Benzoylpropanoic acid (**2y**).* Known compound.[16]

78% yield (139 mg), hexane / ethyl acetate = 3 : 1, R_f = 0.2. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.58 (1H, bs), 7.98 (2H, d, J = 7.4 Hz), 7.57 (1H, t, J = 7.4 Hz), 7.46 (2H, t, J = 7.4 Hz), 3.31 (2H, t, J = 6.6 Hz), 2.81 (2H, t, J = 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 197.8, 178.8, 136.3, 133.3, 128.6, 128.0, 33.1, 28.0.

*2-Ethyl-4-(2-naphthalenyl)-4-oxo butanoic acid (**2aa**).*

53% yield (136 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid, mp 110.5-112.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.49 (1H, s), 8.03 (1H, d, J = 8.2 Hz), 7.96 (1H, d, J = 8.2 Hz),

7.89 (1H, d, *J* = 8.2 Hz), 7.88 (1H, d, *J* = 8.2 Hz), 7.62-7.53 (2H, m), 3.60 (1H, dd, *J* = 17.8, 8.8 Hz), 3.21 (1H, dd, *J* = 17.8, 4.9 Hz), 3.14-3.07 (1H, m), 1.89-1.70 (2H, m), 1.05 (3H, t, *J* = 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 198.0, 180.9, 135.7, 133.9, 132.5, 129.8, 129.6, 128.50, 128.47, 127.8, 126.8, 123.8, 41.6, 39.7, 25.0, 11.6. IR (KBr): 3328, 3062, 2984, 2949, 2922, 2780, 2679, 2611, 1704, 1673, 1626 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{16}H_{16}O_3$ 256.1094; found 256.1105.

*2-Methyl-4-(2-naphthalenyl)-4-oxo butanoic acid (**2ab**).* Known compound.[12]

70% yield (169 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.49 (1H, s), 8.03 (1H, d, *J* = 8.0 Hz), 7.96 (1H, d, *J* = 8.0 Hz), 7.89 (1H, d, *J* = 8.0 Hz), 7.87 (1H, d, *J* = 8.0 Hz), 7.60 (1H, t, *J* = 8.0 Hz), 7.55 (1H, t, *J* = 8.0 Hz), 3.62 (1H, dd, *J* = 16.8, 6.8 Hz), 3.28-3.17 (2H, m), 1.37 (3H, d, *J* = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 197.8, 181.7, 135.7, 133.9, 132.5, 129.8, 129.6, 128.54, 128.49, 127.8, 126.8, 123.7, 41.8, 34.9, 17.1.

*2-Methyl-4-(1-naphthalenyl)-4-oxo butanoic acid (**2ac**).* Known compound.[10]

75% yield (182 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid, mp 114.1-114.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.24 (1H, bs), 8.63 (1H, d, *J* = 8.0 Hz), 7.98 (1H, d, *J* = 8.0 Hz), 7.91 (1H, d, *J* = 8.0 Hz), 7.86 (1H, d, *J* = 8.0 Hz), 7.58 (1H, t, *J* = 8.0 Hz), 7.52 (1H, t, *J* = 8.0 Hz), 7.47 (1H, t, *J* = 8.0 Hz), 3.57 (1H, dd, *J* = 17.8, 8.0 Hz), 3.30-3.22 (1H, m), 3.11 (1H, dd, *J* = 17.8, 5.2 Hz), 1.37 (3H, d, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 201.9, 182.3, 135.3, 133.9, 132.8, 130.0, 128.3, 127.9, 127.7, 126.4, 125.7, 124.3, 44.9, 35.2, 16.9.

*4-(2-furyl)-2-methyl-4-oxo butanoic acid (**2ad**).* Known compound.[8]

79% yield (144 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.44 (1H, bs), 7.57 (1H, s), 7.20 (1H, d, *J* = 2.6 Hz), 6.52 (1H, d, *J* = 2.6 Hz), 3.31 (1H, dd, *J* = 17.4, 7.7 Hz), 3.16-3.08 (1H, m), 2.91 (1H, dd, *J* = 17.4, 5.8 Hz), 1.28 (3H, d, *J*

= 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 187.0, 181.7, 152.4, 146.4, 117.2, 112.3, 41.2, 34.4, 16.9.

*2-methyl-4-oxo-4-(2-thiophenyl)butanoic acid (**2ae**).* Known compound.[8]

85% yield (168 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.2. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.75 (1H, d, *J* = 4.2 Hz), 7.65 (1H, d, *J* = 4.2 Hz), 7.13 (1H, t, *J* = 4.2 Hz), 3.40 (1H, dd, *J* = 17.3, 7.6 Hz), 3.20-3.11 (1H, m), 3.00 (1H, dd, *J* = 17.3, 5.8 Hz), 1.31 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 190.7, 181.6, 143.7, 133.8, 132.1, 128.1, 42.1, 34.8, 17.0.

*Methyl 4-(benzo[d][1,3]dioxol-5-yl)-2-methyl-4-oxobutanoate (**3af**).*

65% yield (163 mg), hexane / ethyl acetate = 6 : 1, R_f = 0.7. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.54 (1H, d, *J* = 8.0 Hz), 7.40 (1H, s), 6.81 (1H, d, *J* = 8.0 Hz), 6.01 (2H, s), 3.67 (3H, s), 3.37 (1H, dd, *J* = 17.4, 7.9 Hz), 3.12-3.03 (1H, m), 2.92 (1H, dd, *J* = 17.4, 5.5 Hz), 1.24 (3H, d, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.9, 176.4, 151.8, 148.1, 131.5, 124.2, 107.77, 107.75, 101.8, 51.8, 41.7, 34.9, 17.2. IR (neat): 3079, 2976, 2953, 2908, 1734, 1678, 1604 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{14}O_5$ 250.0836; found 250.0825.

*3-Methyl-5-phenyl furan-2(3H)-one (**4**).* Known compound.[17]

75% yield (131 mg), hexane / ethyl acetate = 6 : 1, R_f = 0.4. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.60 (2H, d, *J* = 8.0 Hz), 7.42-7.35 (3H, m), 5.82 (1H, d, *J* = 4.0 Hz), 3.49 (1H, qd, *J* = 8.0, 4.0 Hz), 1.44 (3H, t, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 179.3, 152.5, 129.5, 128.6, 128.4, 124.7, 104.1, 40.3, 15.8.

*4-Methyl-6-phenyl-4,5-dihydropyridazin-3(2H)-one (**5**).* Known compound.[18]

92% yield (173 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.5. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.98 (1H, s), 7.74-7.71 (2H, m), 7.44-7.38 (3H, m), 3.14-3.04 (1H, m), 2.70-

2.57 (2H, m), 1.32 (3H, d, J = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 170.8, 150.8, 135.7, 129.7, 128.6, 125.8, 30.9, 30.3, 15.1.

*4-Methyl-2,6-diphenyl-4,5-dihydropyridazin-3(2H)-one (**6**).*

86% yield (227 mg), hexane / ethyl acetate = 1 : 1, R_f = 0.3. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.80-7.76 (2H, m), 7.57 (2H, d, J = 8.0 Hz), 7.43-7.37 (5H, m), 7.24 (1H, t, J = 8.0 Hz), 3.20-3.12 (1H, m), 2.82-2.74 (2H, m), 1.35 (3H, d, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.7, 151.2, 141.4, 135.8, 129.9, 128.6, 128.4, 126.4, 126.0, 124.9, 32.3, 30.5, 15.5. IR (neat): 3061, 2969, 2932, 2874, 1686, 1491 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{17}H_{16}N_2O$ 264.1257; found 264.1261.

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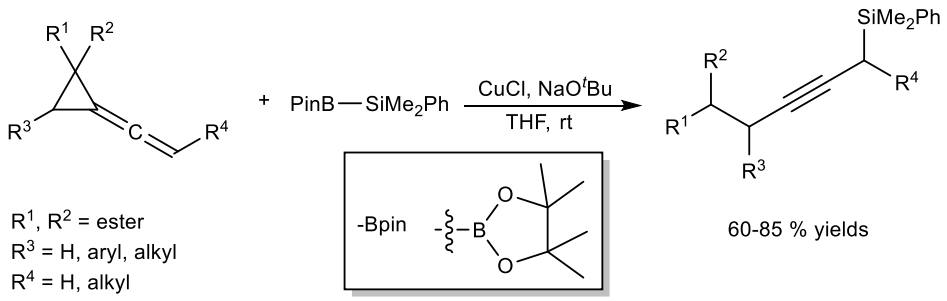
4. Regioselective Silylations of Propargyl and Allyl Pivalates through Ca-Promoted Reductive Carbon-Oxygen Bond Cleavage

4.1 Introduction

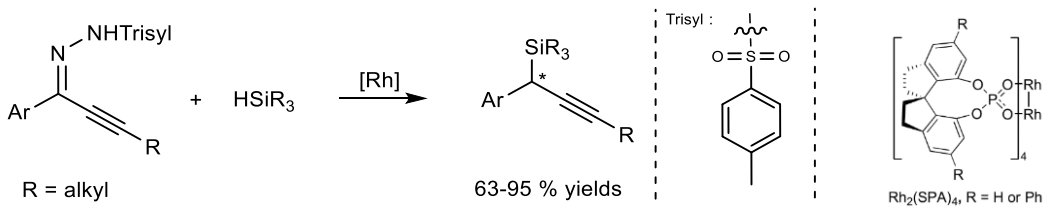
Organosilicon compounds are one of the important intermediates in the synthesis of natural products, medicines, and functional materials as mentioned in chapter 2.[1] The development of new methods for synthesizing organosilicon compounds has been continued for a long time.[2]

As two series of organosilicon compounds, propargyl silanes and allyl silanes are very important synthetic intermediates in organic chemistry.[3] lots of investigation on synthetic methods and transformations have been reported. For example, Chen and coworkers reported the formation of propargyl silanes under mild conditions from vinylidene cyclopropanes. However, the starting materials are not easily accessible, multi-steps are usually required to synthesize the starting materials (Scheme 4-1).[4]



Scheme 4-1 Synthesis of propargyl silanes from vinylidene cyclopropanes

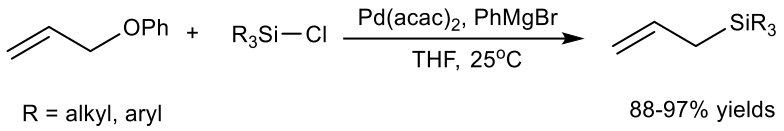
Recently, Zhu and coworkers demonstrated a method for synthesizing chiral propargylsilanes from alkynyl sulfonylhydrazones through alkynylcarbene insertions into Si-H bonds utilizing rhodium catalysts (Scheme 4-2).[5]



Scheme 4-2 Synthesis of propargyl silanes from alkynyl sulfonylhydrazones

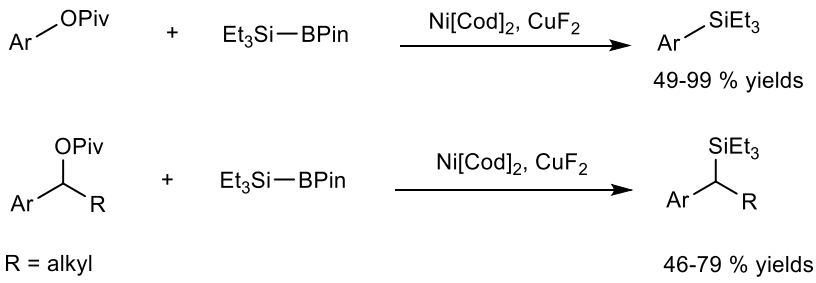
According to these two reports, the development of more practical and general routes to propargylsilanes that use readily available feedstocks remains an attractive goal.

In addition, compared with propargyl silanes, the development of a mild and efficient method for the synthesis of allylsilanes have been used extensively over many years. [(6)] The traditional synthetic methods usually require catalyst reagents such as palladium[(7)] or copper[(8)] and so on with multiple steps. The direct coupling of silyl groups with alkenes to produce allylsilanes offers a step-efficient and atom-economical synthetic tool. For example, Terao and Kambe reported the synthesis of allylsilanes from allylic ethers in the presence of chlorotrialkylsilanes using palladium catalysts (Scheme 4-3). [(7a)]



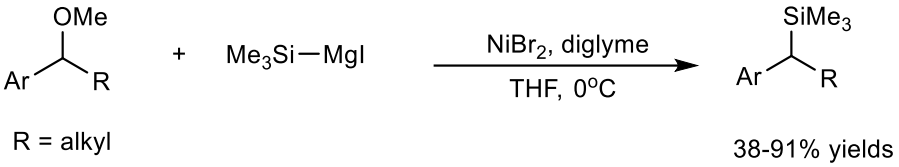
Scheme 4-3 Pd-catalyzed silylation of allylic ethers

On the other hand, benzylic ethers and esters have been widely used as alternatives to organic halides in recent years due to their availability and simplicity of handling.[(9)] And in the synthesis of organosilanes using less reactive C-O electrophiles, Martin and coworkers published the Ni/Cu catalyzed silylation of benzyl and aryl pivalates using silylboranes (Scheme 4-4).[(10)]



Scheme 4-4 Ni/Cu-catalyzed silylations of benzyl/aryl pivalates through C-O cleavage

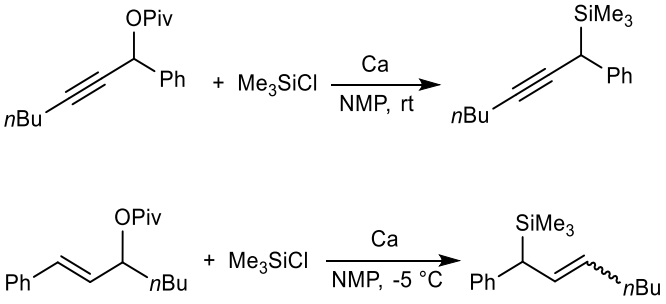
In addition, Rasappan and coworkers reported the construction of a series of benzylsilanes through carbon-oxygen cleavage catalyzed by nickel (Scheme 4-5).[(11)]



Scheme 4-5 Synthesis of benzylsilanes through C-O cleavage

What is more, alkaline earth metals as a practical electron transfer agent have been demonstrated by previous research.[12] Even though the electron transfer reaction promoted by magnesium has been widely reported, calcium-promoted reductive reaction has not been documented up to now.

In this work, a method to synthesize propargylsilanes and allylsilanes from propargyl pivalates and allyl pivalates using calcium under reduction conditions was studied (Scheme 4-6).

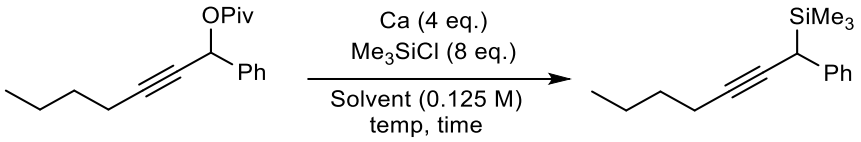


Scheme 4-6 Calcium-promoted silylations of propargyl and allyl pivalates

4.2 Results and Discussion

4.2.1 Investigation on Reaction Temperature, Time and Solvent Effects

Table 4-1 Optimizing the reaction conditions (temperature, time and solvent)



1a **2a**

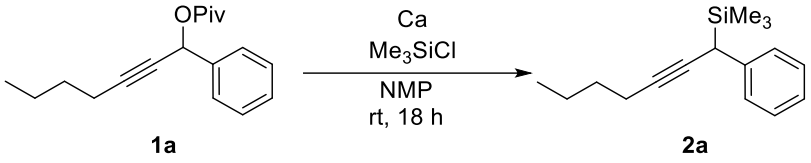
Entry	Temp (°C)	Time (h)	Solvent	Yield (%)
1	25 (rt)	24	NMP	61
2	0	24	NMP	37
3	25	12	NMP	47
4	25	18	NMP	65
5	25	48	NMP	57
6	25	18	DMF	5
7	25	18	DMI	10
8	25	18	DMA	25
9	25	18	THF	No Reaction
10	25	18	CH_3CN	-
11	25	18	DMSO	No Reaction

Reaction conditions: **1a** (1 mmol), Ca (4 eq.), Me_3SiCl (8 eq.) in solvent (0.125 M, 8 mL) in a nitrogen atmosphere.

First, investigation of the effects of the reaction temperature was carried out, and it was found that room temperature was appropriate for this calcium-promoted silylation reaction (Entry 1). Next, the reaction time was examined. The yield of this reaction decreased when the reaction time was shortened to 12 hours (Entry 3). Extending the reaction time to 48 hours could not increase the yield (Entry 5). As a result, the optimal reaction time was 18 hours (Entry 4). Then, a series of common organic solvents were used and the reactions occurred in DMF, DMI, and DMA, albeit in lower yields (Entries 6-8); and no reaction occurred in THF and DMSO (Entries 9, 11). Finally, NMP was selected as the solvent for further research.

4.2.2 Effects of Concentration and Equivalents of Reagents

Table 4-2 Optimizing the concentration and equivalents



1a **2a**

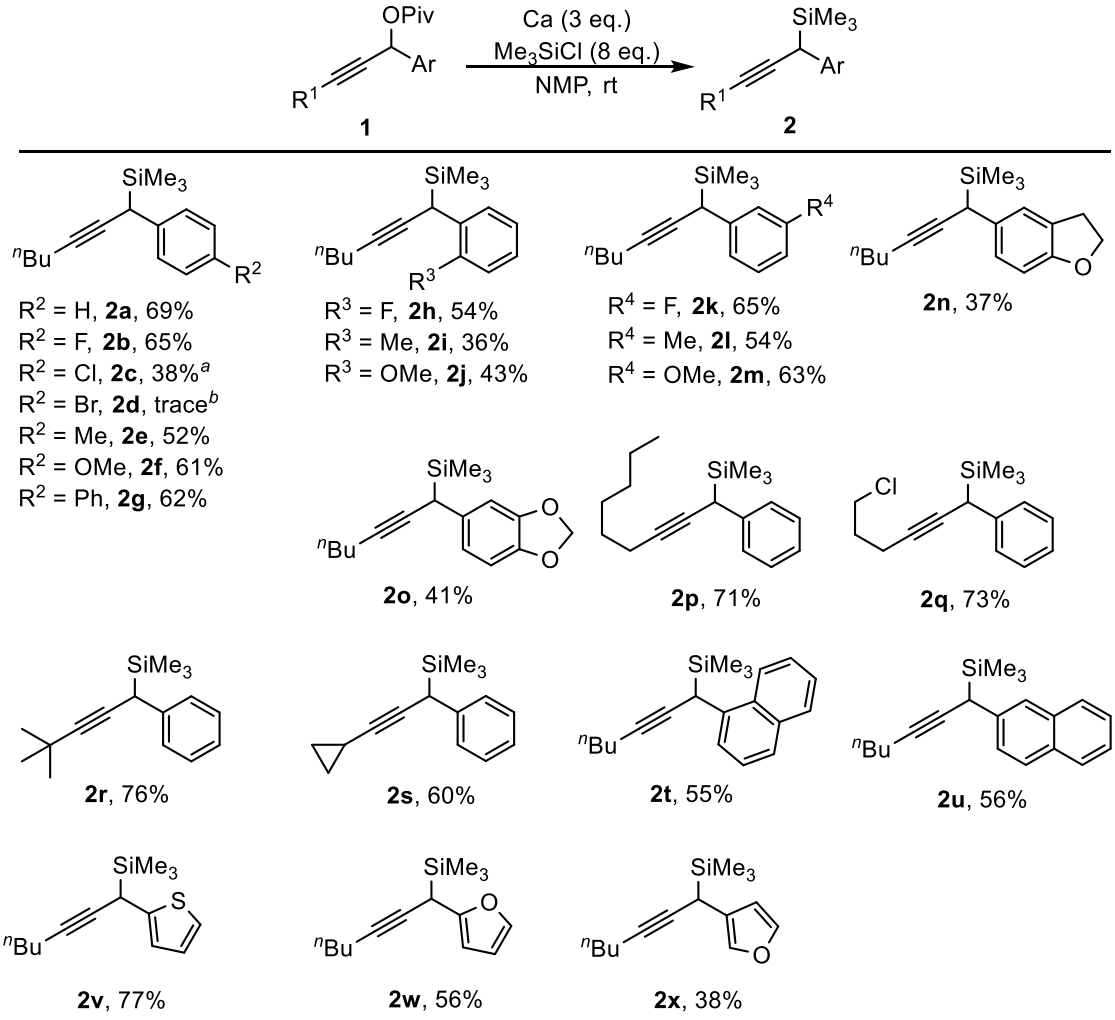
Entry	Concentration (M)	Ca (eq.)	Me_3SiCl (eq.)	Yield (%)
1	0.250	4	8	53
2	0.125	4	8	65
3	0.067	4	8	55
4	0.125	0	8	No Reaction
5	0.125	2	8	37
6	0.125	3	8	69
7	0.125	5	8	59
8	0.125	3	6	59
9	0.125	3	7	65
10	0.125	3	9	56

Reaction conditions: **1a** (1 mmol), Ca (0-5 eq.), Me_3SiCl (6-9 eq.), NMP (0.067-0.250 M, 4-15 mL) at nitrogen atmosphere.

Subsequently, the examination of the concentration effects was carried out, and the best yield was obtained when the solvent concentration was 0.125 M (Entry 2). The quantity of calcium and chlorotrimethylsilane were next examined. Specifically, no reaction occurred when no calcium granules was added to the reaction (Entry 4), and about the amount of calcium, the addition of 3 equivalents gave the best yield (Entries 5-7). For the number of silylating agents ranging from 6 to 9 equivalents, not many effects was observed in yields (Entries 8-10). As a result, the use of 3 equivalents of calcium and 8 equivalents of chlorotrimethylsilane is the best conditions for the reaction (Entry 6).

4.3 Substrate Scope

4.3.1 Reaction of Propargyl Pivalates



Scheme 4-7 Substrate scope of propargyl pivalates.

Reaction conditions: **1** (1 mmol), Ca (3 eq.), and Me_3SiCl (8 eq.) in NMP (0.125 M, 8 mL) under nitrogen atmosphere. Isolated yield after flash column chromatography. a) **2a** was isolated in 28% yield as a byproduct. b) **2a** was isolated in 64% yield as a by-product.

The substrate scope of propargyl pivalates **1** under the optimal reaction conditions was investigated (Scheme 4-7). Reactions of substrates with a chlorine atom at the *para*-position of phenyl ring gave the desired product **2c** in 38% yield, meanwhile, the product **2a** after the elimination of chlorine atom was obtained in 28% yield. Unfortunately, the reaction of **1d** afforded the same compound **2a** in 64% yield due to the elimination of the bromine atom. Pleasingly, the

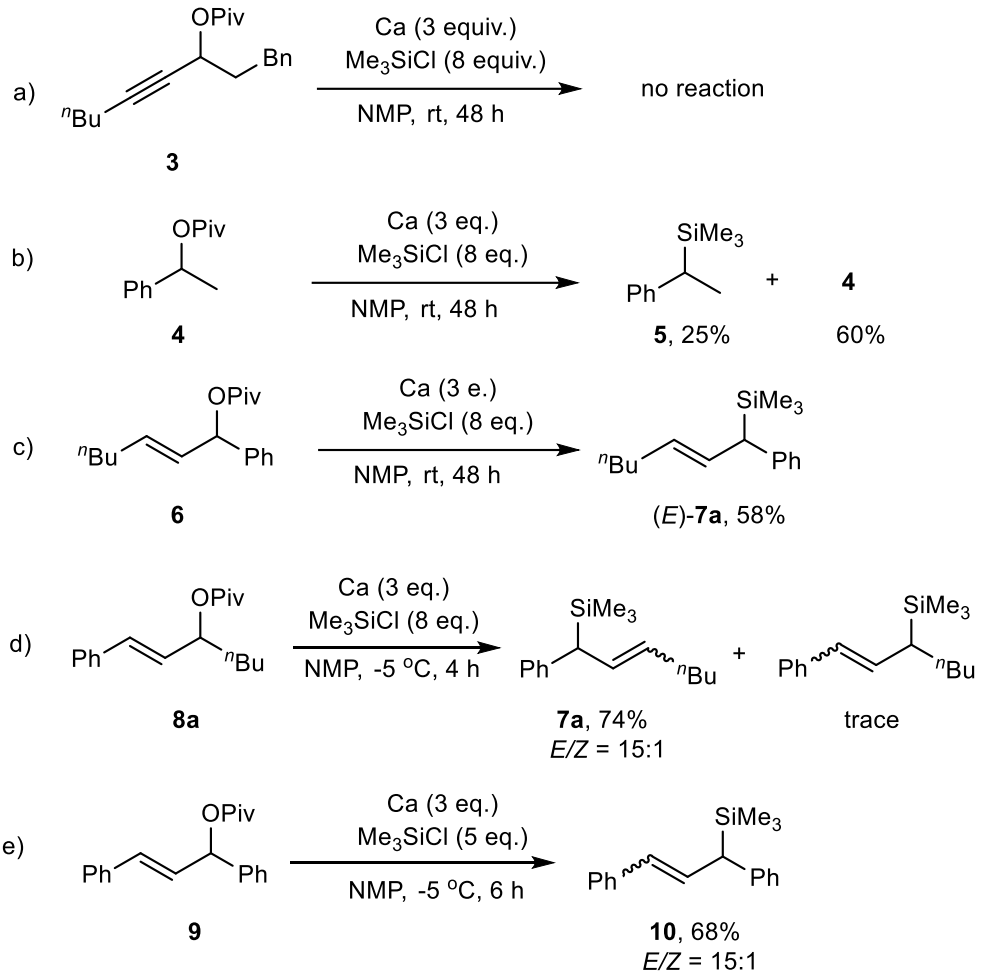
fluorine atom survived the under the reduction conditions and furnished the desired product propargyl silane **2b** in 65% yield.

Propargyl pivalates **1** bearing electron-donating groups such as a methyl and a methoxy group on the phenyl ring were suitable to afford the desired products **2e** and **2f** in acceptable yields. Moreover, 4-biphenyl substrate also underwent this reaction smoothly to give the corresponding product **2g** in 62% yield. Besides, the substrates bearing a fluorine atom or an electron-donating group at the *ortho*-position, which might hinder the silylation at the benzylic position, gave silanes **2h**, **2i**, and **2j** in 36-54% yields. The reactions were feasible with *meta*-substituted substrates and afforded the corresponding products **2k**, **2l** and **2m** in 64%, 54% and 63% yields, respectively.

The reaction of fused bicyclic substrates such as dihydrobenzofuran and benzodioxole rings were also tolerated, albeit in lower yields (**2n**, **2o**). In addition to the various substituents on the phenyl ring, the effects of alkyl group (R^1) were examined. Propargyl pivalate **1p**, which has a longer linear carbon chain, was capable under the same reaction conditions to deliver silane **2p** in 71% yield. The chlorine atom of the 2-chloroethyl group was insensitive to the reduction condition and furnished the propargyl silane **2q** in 73% yield. Notably, the steric hindrance effect of alkyl groups (R^1), such as the *tert*-butyl group and cyclopentyl group was not shown in this reaction and the reaction delivered the corresponding silanes **2r** and **2s** in good yields.

Finally, the substrate scope to diverse aromatic rings was examined. Propargyl pivalates bearing naphthyl groups (**1t**, **1u**), 2-thienyl group (**1v**) and furyl groups (**1w**, **1x**) were also tolerated to furnish the corresponding propargyl silanes **2t**-**2x** in moderate to good yields.

4.3.2 Reaction of Various Pivalates

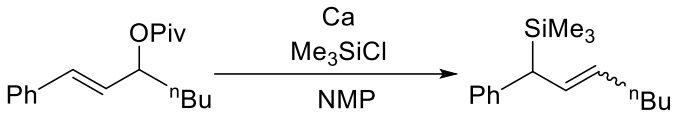


Scheme 4-8 Reductive silylations of various pivalates

To extend the present methodology, further trial to various pivalates was carried out (Scheme 4-8). No conversion of pivalate **3** was observed and the reaction of pivalate **4** afforded the corresponding silane **5** in only 25% yield accompanying with 60% recovery of the starting material. Allyl pivalates **6** could undergo reductive silylation to afford allyl silane **7a** (*E* isomer) in 58% yield. Notably, the reaction of allyl pivalate **8a** gave the same product as the reaction of pivalate **6a**, indicating that an allylic rearrangement process was involved in the reaction of pivalate **8a**. Similarly, the reaction of pivalate **9** afforded allyl silane **10** in 68% yield.

4.3.3 Study on Reaction Temperature and Equivalent of Reagents for Allyl Pivalate

Table 4-3 Optimizing the reaction conditions



8a **7a**

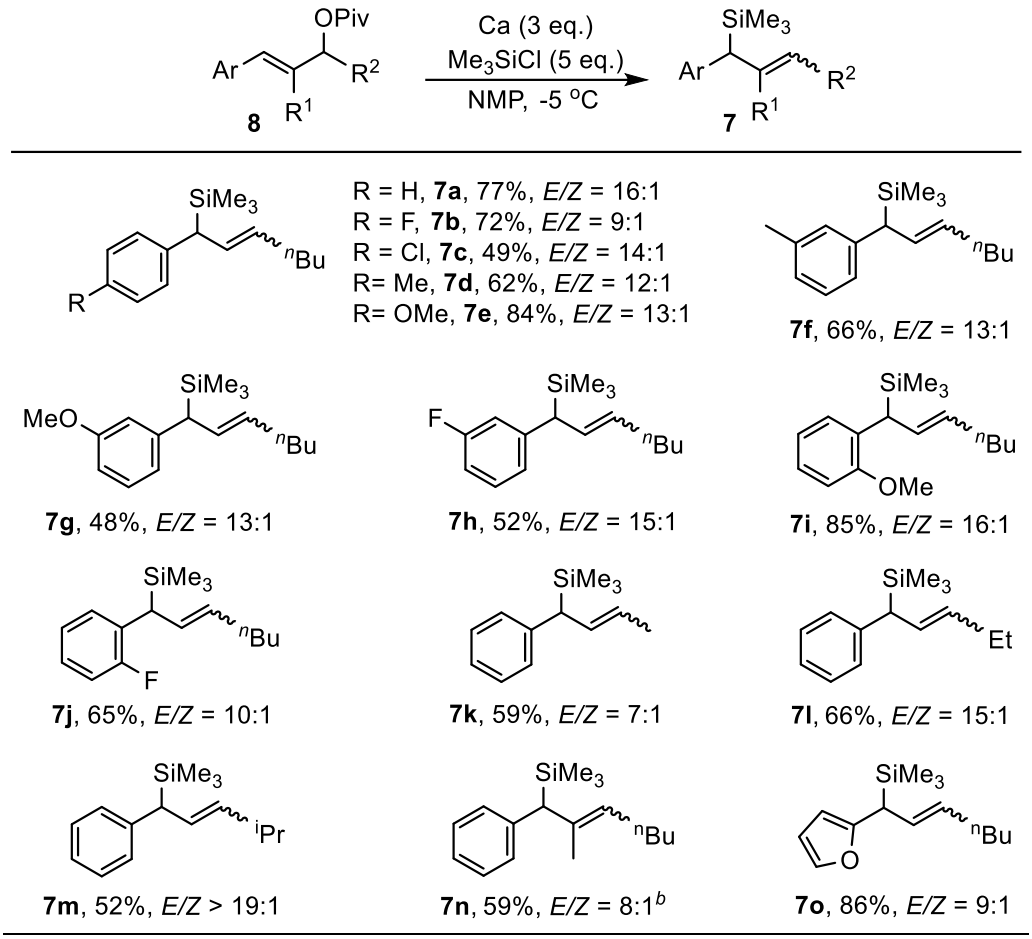
Entry	Temp (°C)	Me_3SiCl (eq.)	Ca (eq.)	Time (h)	Yield (%)	E/Z ratio[a]
1	rt	8	3	18	27	-
2	rt	8	3	6	49	-
3	0	8	3	3	55	-
4	-5	8	3	4	74	14 : 1
5	-10	8	3	6	68	-
6	-5	6	3	4	74	15 : 1
7	-5	5	3	4	77	16 : 1
8	-5	4	3	4	72	14 : 1
9	-5	3	3	4	63	16 : 1
10	-5	5	0	7	No Reaction	-
11	-5	5	1	7	62[b]	12 : 1
12	-5	5	2	6	73	12 : 1
13	-5	5	4	4	77	17 : 1

Reaction conditions: **8a** (1 mmol), Ca (0-4 eq.), Me_3SiCl (3-8 eq.) in NMP (0.125 M, 8 mL) at nitrogen atmosphere. a) *E/Z* ratio was determined by GC. b) 8% of starting materials **8a** was recovered.

From the result of scheme 4-5 (c), the optimization conditions for the synthesis of allylsilane **7a** were investigated. First, it was found that the lower reaction temperature gave a positive effect on the yield (Entries 1-5). Second, increasing or decreasing the amount of chlorotrimethylsilane has no significant effect on the results (Entries 6-9). Third, the amount of calcium was also examined, and the results showed that only 1 equivalent of calcium worked well, albeit gave a little lower

yield of product **7a** (Entry 11). On the other hand, increasing the amount of calcium to 4 equivalents did not improve the outcome of allylsilane **7a** (Entry 13). Finally, according to these results, Entry 7 was selected as the optimal reaction conditions.

4.3.4 Reaction of Allyl Pivalates



Scheme 4-9 Reductive silylations of allyl pivalates.

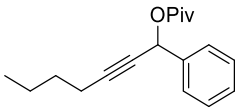
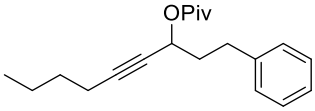
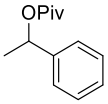
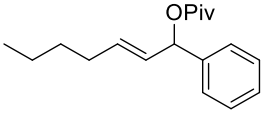
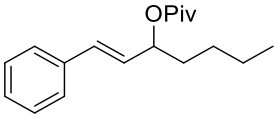
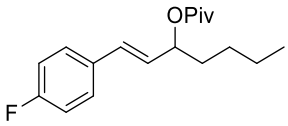
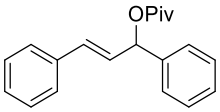
Reaction conditions: **8** (1 mmol), Ca (3 eq.), Me_3SiCl (5 eq.) in NMP (0.125 M, 8 mL) under nitrogen atmosphere at −5 °C. The configuration of the major isomer was determined by NOE analysis.

The substrate scope of allylsilanes **7** was studied (Scheme 4-9). Firstly, various allyl pivalates bearing a halogen atom were tolerated to furnish the corresponding allylsilanes **7b**, **7c**, **7h**, and **7j** in moderate to good yields. Allyl silanes with a methyl or a methoxy substituent at *ortho*-, *meta*- and *para*-positions of phenyl rings **7d**-**7g** and **7i** were also obtained in 48-85% yields.

Besides, the *n*-butyl group (R^2) could be replaced with diverse alkyl groups such as methyl, ethyl, and isopropyl groups to afford allyl silanes **7k**-**7m** in 52-66% yields. Notably, pivalate with a methyl group **8n** could be also converted to allyl silane **7n** in 59% yield, albeit in a little low *E*/*Z* ratio. Moreover, the replacement of the phenyl ring to a furyl ring was also capable, and the desired product **7o** was obtained in 86% yield. The *E*/*Z* ratios were determined by gas chromatography. And in all cases, the major isomers are *E*-isomers, which could be confirmed by the coupling constant value between two alkenyl protons (value at around ~15.0 Hz).

4.4 Reduction Potentials

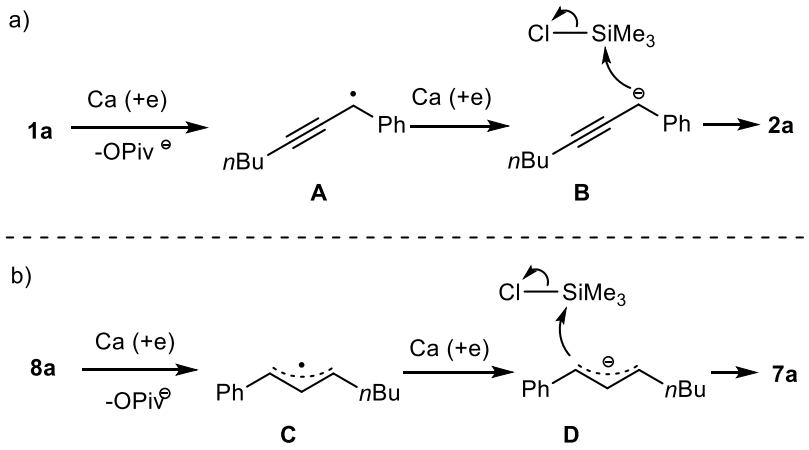
Table 4-4 Reduction Potential of Reagents

Entry	Substrate		Reduction Potential (V vs. Ag/AgCl)
1		**1a**	-2.57 V
2		**3**	No Significant Peak (-3.50 ~ 0 V)
3		**4**	-2.93 V
4		**6**	-2.52 V
5		**8a**	-2.53 V
6		**8b**	-2.50 V
7		**9**	-2.41 V
8	Me_3SiCl		No Significant Peak (-3.50 ~ 0 V)

Working electrode: Pt, counter electrode: Pt, reference electrode: Ag/AgCl, solvent: NMP (10 mL), supporting electrolyte: 1% nBu$_4$NClO$_4$, scan rate: 0.1 Vs^{-1}.

The reduction potential of the reagents was measured (Table 4-4). No significant reduction peak of pivalate **3** ranging from 0 to -3.50 V was found, while the reduction potentials of pivalates **1a**, **4**, **6**, **8a**, **8b** and **9** were recorded at -2.57 V, -2.93 V, -2.52 V, -2.53 V, -2.50 V and -2.41 V, respectively. Therefore, according to the results in scheme 4-5, it can be confirmed that pivalate **3** was inert to the negative reduction potential, and the reductive coupling reactions by calcium in NMP may be possible in the more positive range than -2.93 V.

4.5 Plausible Reaction Mechanism



Scheme 4-10 Reaction mechanism

A plausible mechanistic pathway is shown in scheme 4-10 based on the above results. Under the reduction conditions, radicals **A** and **C** are generated from the starting materials by direct elimination of the pivalate group. The benzylic position of intermediate **A** is stabilized, and an additional electron transfer from calcium instantly transforms **A** into anion **B** which is conjugated to both the acetylenic group and the aromatic ring. Alternatively, after the second electron transfer from calcium, an allylic anion **D** is formed from the radical species **C** and silylation occurs at the more stable site. Finally, products **2a** and **7a** were formed by the silylation of intermediate **B** or **D** with chlorotrimethylsilane, respectively.

4.6. Experimental Section

4.6.1 General Information

Materials

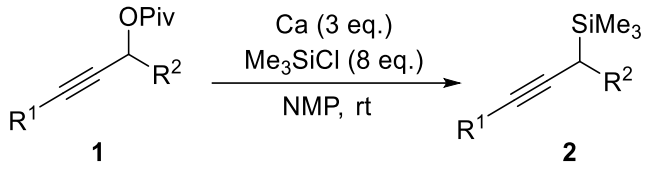
All reactions were performed under an atmosphere of nitrogen unless stated otherwise. Unless otherwise noted. All reagents were purchased from TCI, Sigma-Aldrich, Nacalai tesque, Wako, Kanto Chemical, Alfa Aesar, and SynQuest, and were used without further purification. Calcium is commercially available and was used with no pre-treatment. Solvents were distilled under reduced pressure by standard procedures. Acetonitrile of super dehydrated grade was bought from Wako Pure Chemical Industries, Ltd. without further treatment. THF was freshly distilled from sodium/benzophenone. Chlorotrimethylsilane was simply distilled before use.

Analysis Instruments

Cyclic voltammograms were measured by ALS-600. Melting points were performed on a Yanaco MP-500D or a MP-J3 instrument and were uncorrected. NMR spectra (^{1}H, ^{13}C, ^{19}F) were recorded on a JEOL JNM AL-400 (400 MHz) spectrometer. Chemical shifts (δ) in parts per million (ppm) were reported relative to the residual signal of chloroform (7.26 ppm), and coupling constants were reported in hertz (Hz). Carbon chemical shifts were referenced to the carbon signal of $CDCl_3$ at 77.0 ppm. Fluorine chemical shifts were referenced to the signal of CF_3CO_2H at -76.50 ppm. Signal Multiplicity was shown as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), m (multiplet). IR spectra were obtained on a JASCO 470Plus FTIR spectrometer, and peaks were reported in wavenumber (cm^{-1}). MS spectra were recorded on a Shimadzu GCMS-QP2010plus or a JMS-T200GC spectrometer. TLC was performed on Merck pre-coated plates (silica gel 60 F_{254}, Art 5715, 0.25 mm). Column chromatography was performed using neutral silica gel (60N, spherical, 63-210 mesh, Kanto Chemical).

4.6.2 General Procedure for Reductive Silylations of Propargyl and Allyl Pivalates

General procedure for synthesis of propargylsilanes



In an oven-dried round-bottom flask, a mixture of calcium granules (9 mesh, 120 mg, 3 mmol, 3 eq.), chlorotrimethylsilane (1.01 mL, 8 mmol, 8 eq.) and NMP (3 mL) was stirred for 30 min at room temperature under nitrogen atmosphere. Then, to the mixture was added a solution of propargyl pivalates **1** (1 mmol) in NMP (5 mL) within 30 min. After the consumption of propargyl pivalate (usually 18 h to 24 h, monitored by TLC/iodine staining), the reaction mixture was quenched by 30 mL of saturated sodium bicarbonate and 10 mL of diethyl ether at 0 °C. The mixture was allowed to stir for 20 min and extracted with diethyl ether (30 mL × 3). The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, and then concentrated under vacuum. The crude products were purified by flash column chromatography to afford the corresponding propargylsilanes **2**.

Silane **5** from pivalate **4** and allyl silane **7a** from pivalate **6** were conducted under the same procedure.

*(1-phenylhept-2-yn-1-yl)trimethylsilane (**2a**).*

69% yield (169 mg), R_f = 0.5, hexane. Colorless oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.27 (t, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 7.6 Hz, 2H), 7.13 (t, *J* = 7.6 Hz, 1H), 3.12 (t, *J* = 2.8 Hz, 1H), 2.30 (td, *J* = 6.8 Hz, 2.8 Hz, 2H), 1.59-1.45 (m, 4H), 0.96 (t, *J* = 6.8 Hz, 3H), 0.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 140.2, 128.0, 127.0, 124.8, 82.8, 79.5, 31.5, 29.4, 22.0, 18.7, 13.6, -3.3. IR (neat): 3082, 3061, 3025, 2958, 2932, 2220, 1598, 1494, 1248, 1068, 842, 700 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{24}Si$ 244.1642, found 244.1631.

*(1-(4-Fuorophenyl)hept-2-yn-1-yl)trimethylsilane (**2b**).*

65% yield (171 mg), R_f = 0.5, hexane. Colorless oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.13 (dd, *J* = 8.8 Hz, 5.6 Hz, 2H), 6.95 (dd, *J* = 8.8 Hz, 8.8 Hz, 2H), 3.07 (t, *J* = 2.4 Hz, 1H), 2.28 (td, *J* = 6.8 Hz, 2.4 Hz, 2H), 1.57-1.42 (m, 4H), 0.94 (t, *J* = 6.8 Hz, 3H), 0.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.8 (d, $^1J_{CF}$ = 242.7 Hz), 135.8 (d, $^4J_{CF}$ = 3.0 Hz), 128.1 (d, $^3J_{CF}$ = 8.0 Hz), 114.8 (d, $^2J_{CF}$ = 21.1 Hz), 83.1, 79.5, 31.5, 28.7, 22.0, 18.7, 13.6, -3.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -119.28 (m). IR (neat): 3066, 3034, 2959, 2933, 2246, 1506, 1249, 1223, 1157, 909, 843, 734 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{23}FSi$ 262.1548, found 262.1533.

*(1-(4-Chlorophenyl)hept-2-yn-1-yl)trimethylsilane (**2c**).*

38% yield (107 mg), R_f = 0.4, hexane. Pale yellow oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.22 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 3.07 (t, *J* = 2.2 Hz, 1H), 2.27 (td, *J* = 6.8 Hz, 2.2 Hz, 2H), 1.56-1.41 (m, 4H), 0.93 (t, *J* = 6.8 Hz, 3H), 0.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.9, 130.5, 128.2, 128.1, 83.4, 79.1, 31.4, 29.0, 22.0, 18.7, 13.6, -3.4. IR (neat): 3080, 3026, 2959, 2933, 2873, 2205, 1591, 1489, 1249, 1092, 1014, 845 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{23}SiCl$ 278.1252, found 278.1246.

*(1-(4-Methylphenyl)hept-2-yn-1-yl)trimethylsilane (**2e**).*

52% yield (134 mg), R_f = 0.45, hexane. Colorless oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.09-7.07 (m, 4H), 3.07 (t, *J* = 2.4 Hz, 1H), 2.32 (s, 3H), 2.29 (td, *J* = 6.8 Hz, 2.4 Hz, 2H), 1.57-1.45 (m, 4H), 0.95 (t, *J* = 6.8 Hz, 3H), 0.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 137.0, 134.2, 128.7, 126.9, 82.7, 79.8, 31.5, 28.9, 22.0, 20.9, 18.7, 13.6, -3.3. IR (neat): 3087, 3048, 3020, 2957, 2931, 2862, 2218, 1510, 1247, 1080, 843 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{26}Si$ 258.1798, found 258.1789.

*(1-(4-Methoxyphenyl)hept-2-yn-1-yl)trimethylsilane (**2f**).*

61% yield (167 mg), R_f = 0.3, hexane / ethyl acetate (80 : 1). Pale yellow oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.09 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 3.78 (s, 3H), 3.02 (t, *J* = 2.4 Hz, 1H), 2.26 (td, *J* = 6.8 Hz, 2.4 Hz, 2H), 1.56-1.39 (m, 4H), 0.93 (t, *J* = 6.8 Hz, 3H), 0.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 157.2, 132.1, 127.8, 113.6, 82.7, 79.9, 55.3, 31.5, 28.3, 22.0, 18.7, 13.6, -3.3. IR (neat): 3032, 3002, 2959, 2934, 2873, 2253, 1508, 1248, 908, 843, 734 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{26}OSi$ 274.1747, found 274.1736.

*(1-([1,1'-Biphenyl]-4-yl)hept-2-yn-1-yl)trimethylsilane (**2g**).*

62% yield (198 mg), R_f = 0.35, hexane. Pale yellow oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.62 (d, *J* = 7.2 Hz, 2H), 7.53 (d, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 7.2 Hz, 2H), 3.18 (t, *J* = 2.4 Hz, 1H), 2.33 (td, *J* = 7.0 Hz, 2.4 Hz, 2H), 1.62-1.47 (m, 4H), 0.98 (t, *J* = 7.0 Hz, 3H), 0.10 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 141.1, 139.5, 137.8, 128.7, 127.4, 126.9 (×2, overlap), 126.7, 83.0, 79.5, 31.5, 29.2, 22.0, 18.7, 13.6, -3.2. IR (neat): 3079, 3058, 3028, 2957, 2931, 2872, 2217, 1487, 1248, 1076, 908, 847 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{22}H_{28}Si$ 320.1955, found 320.1966.

*(1-(2-Fluorophenyl)hept-2-yn-1-yl)trimethylsilane (**2h**).*

54% yield (142 mg), R_f = 0.6, hexane. Colorless oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.45-7.41 (m, 1H), 7.11-7.08 (m, 2H), 6.99-6.94 (m, 1H), 3.49 (t, *J* = 2.6 Hz, 1H), 2.28 (td, *J* = 7.2 Hz, 2.6 Hz, 2H), 1.58-1.42 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H), 0.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 159.1 (d, $^1J_{CF}$ = 243.7 Hz), 128.9 (d, $^3J_{CF}$ = 4.2 Hz), 127.7 (d, $^2J_{CF}$ = 15.0 Hz), 126.2 (d, $^3J_{CF}$ = 8.0 Hz), 123.9 (d, $^4J_{CF}$ = 3.3 Hz), 114.7 (d, $^2J_{CF}$ = 22.1 Hz), 82.5, 78.8, 31.5, 22.0, 21.6, 18.7, 13.6, -3.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -118.09 (m). IR (neat): 3066, 3040, 2959, 2933, 2873, 2219, 1584, 1488, 1455, 1250, 1228, 1077, 843, 753 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{23}FSi$ 262.1548, found 262.1528.

*(1-(2-Methylphenyl)hept-2-yn-1-yl)trimethylsilane (**2i**).*

36% yield (92 mg), R_f = 0.5, hexane. Colorless oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.41 (d, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.05 (t, *J* = 8.0 Hz, 1H), 3.36 (t, *J* = 2.0 Hz, 1H), 2.28 (td, *J* = 6.8 Hz, 2.0 Hz, 2H), 2.25 (s, 3H), 1.59-1.42 (m, 4H), 0.96 (t, *J* = 6.8 Hz, 3H), 0.08 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.9, 133.7, 130.0, 127.5, 125.9, 124.8, 81.6, 80.5, 31.5, 24.9, 22.0, 20.1, 18.7, 13.6, -3.0. IR (neat): 3063, 3019, 2957, 2931, 2872, 2218, 1485, 1461, 1248, 841, 743 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{26}Si$ 258.1798, found 258.1790.

*(1-(2-Methoxyphenyl)hept-2-yn-1-yl)trimethylsilane (**2j**).*

43% yield (119 mg), R_f = 0.3, hexane / ethyl acetate (80 : 1). Colorless oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40 (d, *J* = 7.8 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.93 (t, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 3.76 (s, 3H), 3.66 (t, *J* = 2.6 Hz, 1H), 2.26 (td, *J* = 7.2 Hz, 2.6 Hz, 2H), 1.57-1.42 (m, 4H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.01 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 155.3, 129.0, 128.0, 125.6, 120.4, 109.6, 81.8, 80.2, 54.9, 31.6, 22.0, 21.4, 18.7, 13.6, -3.2. IR (neat): 3062, 3027, 2957, 2933, 2873, 2219, 1490, 1242, 842, 750 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{26}OSi$ 274.1747, found 274.1743.

*(1-(3-Fluorophenyl)hept-2-yn-1-yl)trimethylsilane (**2k**).*

65% yield (169 mg), R_f = 0.5, hexane. Colorless oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.23-7.17 (m, 1H), 6.95-6.91 (m, 2H), 6.81 (t, *J* = 8.6 Hz, 1H), 3.11 (t, *J* = 2.4 Hz, 1H), 2.28 (td, *J* = 7.2 Hz, 2.4 Hz, 2H), 1.56-1.43 (m, 4H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.9 (d, $^1J_{CF}$ = 243.7 Hz), 143.2 (d, $^3J_{CF}$ = 7.4 Hz), 129.3 (d, $^3J_{CF}$ = 8.3 Hz), 122.6 (d, $^4J_{CF}$ = 3.3 Hz), 113.8 (d, $^2J_{CF}$ = 22.4 Hz), 111.7 (d, $^2J_{CF}$ = 21.5 Hz), 83.5, 78.9, 31.4, 29.6, 22.0, 18.7, 13.6, -3.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -114.07 (m). IR (neat): 3061, 3036, 2959, 2933, 2873, 2219, 1612, 1588, 1484, 1444, 1249, 842 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{23}FSi$ 262.1548, found 262.1543.

*(1-(3-Methylphenyl)hept-2-yn-1-yl)trimethylsilane (**2l**).*

54% yield (139 mg), R_f = 0.5, hexane. Colorless oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.14 (t, *J* = 7.6 Hz, 1H), 7.00 (s, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 3.06 (t, *J* = 2.6 Hz, 1H), 2.33 (s, 3H), 2.28 (td, *J* = 7.2 Hz, 2.6 Hz, 2H), 1.58-1.42 (m, 4H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 140.1, 137.5, 127.9, 127.7, 125.6, 124.2, 82.8, 79.7, 31.5, 29.3, 22.0, 21.5, 18.7, 13.6, -3.2. IR (neat): 3055, 3021, 2958, 2931, 2862, 2220, 1605, 1587, 1486, 1248, 1077, 842, 701 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{26}Si$ 258.1798, found 258.1800.

*(1-(2-Methoxyphenyl)hept-2-yn-1-yl)trimethylsilane (**2m**).*

63% yield (172 mg), R_f = 0.3, hexane / ethyl acetate (80 : 1). Pale yellow oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.17 (t, *J* = 8.0 Hz, 1H), 6.79 (s, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 3.80 (s, 3H), 3.09 (t, *J* = 2.4 Hz, 1H), 2.28 (td, *J* = 7.2 Hz, 2.4 Hz, 2H), 1.58-1.45 (m, 4H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 159.5, 141.9, 128.9, 119.7, 112.8, 110.3, 83.0, 79.5, 55.1, 31.5, 29.6, 22.0, 18.7, 13.6, -3.2. IR (neat): 3051, 2998, 2957, 2933, 2873, 2834, 2221, 1598, 1582, 1486, 1466, 1436, 1248, 1155, 1051, 842, 697 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{26}OSi$ 274.1747, found 274.1750.

*(1-(2,3-Dihydrobenzofuran-5-yl)hept-2-yn-1-yl)trimethylsilane (**2n**).*

37% yield (106 mg), R_f = 0.4, hexane / ethyl acetate (80 : 1). Pale yellow oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.02 (s, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 4.53 (t, *J* = 8.5 Hz, 2H), 3.18 (t, *J* = 8.5 Hz, 2H), 3.01 (t, *J* = 2.6 Hz, 1H), 2.26 (td, *J* = 7.0 Hz, 2.6 Hz, 2H), 1.54-1.41 (m, 4H), 0.93 (t, *J* = 7.0 Hz, 3H), 0.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 157.1, 132.0, 126.7, 126.4, 123.3, 108.7, 82.6, 80.1, 71.1, 31.5, 30.0, 28.5, 22.0, 18.7, 13.6, -3.3. IR (neat): 3049, 3014, 2957, 2930, 2873, 2859, 2250, 1612, 1490, 1474, 1247, 985, 841 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{18}H_{26}OSi$ 286.1747, found 286.1759.

*(1-(Benzo[d][1,3]dioxol-5-yl)hept-2-yn-1-yl)trimethylsilane (**2o**).*

41% yield (118 mg), R_f = 0.25, hexane / ethyl acetate (80 : 1). Pale yellow oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.73 (d, *J* = 8.0 Hz, 1H), 6.70 (s, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 5.91 (s, 2H), 3.01 (t, *J* = 2.6 Hz, 1H), 2.26 (td, *J* = 7.2 Hz, 2.6 Hz, 2H), 1.56-1.42 (m, 4H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 147.4, 145.0, 134.1, 119.6, 107.9, 107.7, 100.7, 83.0, 79.7, 31.5, 29.0, 22.0, 18.7, 13.6, -3.2. IR (neat): 3070, 2958, 2932, 2873, 2775, 2219, 1610, 1503, 1486, 1441, 1247, 1229, 1041, 842 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{24}O_2Si$ 288.1540, found 288.1545.

*(1-Phenylnon-2-yn-1-yl)trimethylsilane (**2p**).*

71% yield (193 mg), R_f = 0.5, hexane. Pale yellow oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.32 (t, *J* = 7.2 Hz, 2H), 7.25 (d, *J* = 7.2 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 3.16 (t, *J* = 2.4 Hz, 1H), 2.34 (td, *J* = 6.8 Hz, 2.4 Hz, 2H), 1.61 (quint, *J* = 6.8 Hz, 2H), 1.51 (sext, *J* = 6.8 Hz, 2H), 1.41-1.36 (m, 4H), 0.97 (t, *J* = 6.8 Hz, 3H), 0.10 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 140.2, 128.0, 127.0, 124.9, 83.0, 79.6, 31.4, 29.5, 29.4, 28.6, 22.6, 19.0, 14.1, -3.3. IR (neat): 3061, 3025, 2956, 2930, 2858, 2203, 1600, 1494, 1451, 1248, 1068, 844, 699 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{18}H_{28}Si$ 272.1955, found 272.1949.

*(6-Chloro-1-phenylhex-2-yn-1-yl)trimethylsilane (**2q**).*

73% yield (193 mg), R_f = 0.3, hexane. Pale yellow oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.26 (t, *J* = 7.8 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 7.12 (t, *J* = 7.8 Hz, 1H), 3.70 (t, *J* = 6.6 Hz, 2H), 3.10 (t, *J* = 2.6 Hz, 1H), 2.48 (td, *J* = 6.6 Hz, 2.6 Hz, 2H), 1.99 (quint, *J* = 6.6 Hz, 2H), 0.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.8, 128.1, 126.9, 125.0, 81.0, 80.6, 43.8, 32.0, 29.4, 16.5, -3.3. IR (neat): 3082, 3061, 3025, 2959, 2912, 2871, 2221, 1598, 1493, 1451, 1248, 844, 700 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{15}H_{21}SiCl$ 264.1096, found 264.1084.

*(4,4-Dimethyl-1-phenylpent-2-yn-1-yl)trimethylsilane (**2r**).* Known compound.[3a]

76% yield (186 mg), R_f = 0.45, hexane. Colorless oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.33 (t, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 7.8 Hz, 1H), 3.16 (s, 1H), 1.36 (s, 9H), 0.12 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 140.2, 128.0, 126.9, 124.8, 92.2, 78.1, 31.5, 29.2, 27.7, -3.3. IR (neat): 3083, 3062, 3025, 2966, 2927, 2227, 1598, 1494, 1451, 1248, 844 (cm^{-1}). MS (EI) m/z: 244 $[M]^+$.

*(3-Cyclopropyl-1-phenylprop-2-yn-1-yl)trimethylsilane (**2s**).*

60% yield (136 mg), R_f = 0.5, hexane. Pale yellow oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.19 (t, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 7.05 (t, *J* = 7.8 Hz, 1H), 3.01 (d, *J* = 2.0 Hz, 1H), 1.28-1.21 (m, 1H), 0.71-0.67 (m, 2H), 0.61-0.58 (m, 2H), -0.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 140.1, 128.0, 126.9, 124.9, 86.2, 75.0, 29.4, 8.4, 8.3, -0.1, -3.3. IR (neat): 3061, 3023, 2959, 2898, 2863, 2225, 1598, 1492, 1451, 1248, 1069, 843, 700 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{15}H_{20}Si$ 228.1329, found 228.1321.

*(1-(Naphthalen-1-yl)hept-2-yn-1-yl)trimethylsilane (**2t**).*

55% yield (161 mg), R_f = 0.45, hexane. Pale yellow oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.94 (t, *J* = 8.0 Hz, 1H), 7.85-7.83 (m, 1H), 7.65 (t, *J* = 8.0 Hz, 2H), 7.48-7.43 (m, 3H), 4.01 (t, *J* = 2.4 Hz, 1H), 2.33 (td, *J* = 7.4 Hz, 2.4 Hz, 2H), 1.60-1.48 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.8, 133.8, 130.7, 128.8, 125.53, 125.49, 125.2, 125.1, 124.7, 123.7, 82.7, 80.4, 31.5, 24.7, 22.0, 18.8, 13.6, -2.6. IR (neat): 3059, 3047, 3010, 2957, 2931, 2222, 1595, 1576, 1509, 1465, 1394, 1248, 1068, 841, 776 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{20}H_{26}Si$ 294.1798, found 294.1798.

*(1-(Naphthalen-2-yl)hept-2-yn-1-yl)trimethylsilane (**2u**).*

56% yield (164 mg), R_f = 0.4, hexane. Pale yellow oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.79 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.64 (s, 1H), 7.44 (t, *J* = 8.4 Hz, 1H), 7.39 (t, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 3.28 (t, *J* = 2.4 Hz, 1H), 2.33 (td, *J* = 7.2 Hz, 2.4 Hz, 2H), 1.61-1.45 (m, 4H), 0.97 (t, *J*

= 7.4 Hz, 3H), 0.08 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.0, 133.6, 131.6, 127.5, 127.42, 127.35, 126.4, 125.8, 124.7, 124.6, 83.2, 79.6, 31.5, 29.7, 22.0, 18.8, 13.6, -3.2. IR (neat): 3055, 3028, 2957, 2931, 2860, 2218, 1600, 1507, 1247, 1082, 841 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{20}H_{26}Si$ 294.1798, found 294.1824.

*(1-(Thiophen-2-yl)hept-2-yn-1-yl)trimethylsilane (**2v**).*

77% yield (192 mg), R_f = 0.4, hexane. Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.04 (dd, *J* = 5.1 Hz, 1.2 Hz, 1H), 6.91 (dd, *J* = 5.1 Hz, 3.2 Hz, 1H), 6.75 (td, *J* = 3.2 Hz, 1.2 Hz, 1H), 3.37 (t, *J* = 2.6 Hz, 1H), 2.27 (td, *J* = 7.2 Hz, 2.6 Hz, 2H), 1.57-1.43 (m, 4H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.11 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 144.0, 126.6, 122.4, 121.7, 83.0, 79.2, 31.3, 24.6, 21.9, 18.6, 13.6, -3.2. IR (neat): 3106, 3069, 2958, 2932, 2873, 2861, 2222, 1526, 1436, 1249, 1084, 843, 688 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{14}H_{22}SiS$ 250.1206, found 250.1225.

*(1-(Furan-2-yl)hept-2-yn-1-yl)trimethylsilane (**2w**).*

56% yield (132 mg), R_f = 0.4, hexane. Pale yellow oil, quickly turns to yellow in contact with air. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.26-7.25 (m, 1H), 6.29-6.28 (m, 1H), 6.03 (d, *J* = 2.8 Hz, 1H), 3.16 (t, *J* = 2.6 Hz, 1H), 2.23 (td, *J* = 7.0 Hz, 2.6 Hz, 2H), 1.54-1.39 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H), 0.09 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 154.4, 140.5, 110.4, 103.9, 82.3, 76.9, 31.3, 22.9, 21.9, 18.6, 13.6, -3.0. IR (neat): 3117, 2959, 2933, 2873, 2862, 2247, 1585, 1503, 1250, 1006, 910, 845, 734 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{14}H_{22}OSi$ 234.1434, found 234.1417.

*(1-(Furan-3-yl)hept-2-yn-1-yl)trimethylsilane (**2x**).*

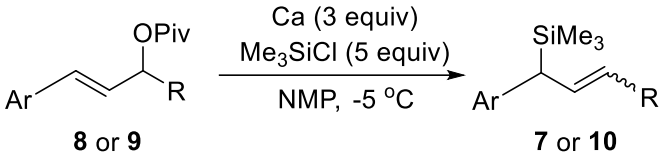
38% yield (89 mg), R_f = 0.5, hexane. Orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.31 (s, 1H), 7.22 (d, *J* = 1.5 Hz, 1H), 6.23 (d, *J* = 1.5 Hz, 1H), 2.87 (t, *J* = 2.2 Hz, 1H), 2.22 (td, *J* = 7.2 Hz, 2.2 Hz, 2H), 1.52-1.38 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H), 0.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 142.5, 138.2, 113.5, 110.6, 81.7, 79.1, 31.4, 21.9, 18.7, 18.6, 13.6, -3.3. IR (neat):

3151, 2960, 2934, 2874, 2254, 1250, 909, 844, 733 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{14}H_{22}OSi$ 234.1434, found 234.1426.

*Trimethyl(1-phenylethyl)silane (**5**).* Known compound.[13]

25% yield (45 mg), R_f = 0.7, hexane. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.25 (t, *J* = 7.6 Hz, 2H), 7.12-7.05 (m, 3H), 2.18 (q, *J* = 7.6 Hz, 1H), 1.38 (d, *J* = 7.6 Hz, 3H), -0.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 146.0, 128.0, 127.0, 124.2, 29.8, 14.8, -3.3. MS (EI) m/z: 178 $[M]^+$.

General procedure for synthesis of allylsilanes



8 or **9** **7** or **10**

In an oven-dried round-bottom flask, a mixture of calcium granules (9 mesh, 120 mg, 3 mmol, 3 eq.), chlorotrimethylsilane (0.63 mL, 5 mmol, 5 eq.) and NMP (3 mL) was stirred for 30 min at room temperature under nitrogen atmosphere. Then, the mixture was cooled to -5 °C and to the mixture was added a solution of pivalates **8** or **9** (1 mmol) in NMP (5 mL) within 30 min. After the consumption of starting materials (usually 4 h to 6 h, monitored by TLC/iodine staining), the reaction mixture was quenched by 30 mL of saturated sodium bicarbonate and 10 mL of diethyl ether at -5 °C. The mixture was then extracted with diethyl ether (30 mL × 3). The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, and then concentrated under vacuum. The crude products were purified by flash column chromatography to afford the corresponding allylsilanes.

*Trimethyl(1-phenylhept-2-en-1-yl)silane (**7a**).* Known compound.[(14)]

77% yield (189 mg), *E/Z* = 16 : 1, R_f = 0.7, hexane. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 7.25 (t, *J* = 7.6 Hz, 2H), 7.11-7.06 (m, 3H), 5.78 (dd, *J* = 15.2 Hz, 9.6 Hz, 1H), 5.40 (dt, *J* = 15.2 Hz, 6.7 Hz, 1H), 2.89 (d, *J* = 9.6 Hz, 1H), 2.05 (q, *J* = 6.7 Hz, 2H), 1.37-1.31 (m, 4H), 0.90 (t, *J* = 6.7 Hz, 3H), -0.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 143.2, 129.2, 129.0, 128.2, 127.1, 124.4, 42.8, 32.5, 32.1, 22.2, 13.9, -3.0. MS (EI) m/z: 246 $[M]^+$.

*(1-(4-Fluorophenyl)hept-2-en-1-yl)trimethylsilane (**7b**).*

72% yield (190 mg), *E/Z* = 9 : 1, R_f = 0.6, hexane. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 7.01 (dd, *J* = 8.7 Hz, 5.5 Hz, 2H), 6.94 (dd, *J* = 8.7 Hz, 8.7 Hz, 2H), 5.72 (dd, *J* = 14.9 Hz, 9.9 Hz, 1H), 5.40 (dt, *J* = 14.9 Hz, 6.8 Hz, 1H), 2.87 (d, *J* = 9.9 Hz, 1H), 2.05 (q, *J* = 6.8 Hz, 2H), 1.39-1.30 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H), -0.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 160.4 (d, $^1J_{CF}$ = 240.7 Hz), 138.8, 129.5, 128.9, 128.2 (d, $^3J_{CF}$ = 7.0

Hz), 114.9 (d, $^2J_{CF}$ = 21.1 Hz), 41.8, 32.5, 32.0, 22.2, 13.9, -3.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) -119.86 (m). IR (neat): 3107, 3037, 2957, 2927, 2873, 2859, 1654, 1604, 1507, 1248, 1231, 1158, 966, 870, 841 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{25}FSi$ 264.1704, found 264.1683.

*(1-(4-Chlorophenyl)hept-2-en-1-yl)trimethylsilane (**7c**).*

49% yield (137 mg), *E/Z* = 14 : 1, R_f = 0.65, hexane. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 7.21 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 8.3 Hz, 2H), 5.71 (dd, *J* = 15.0 Hz, 9.8 Hz, 1H), 5.40 (dt, *J* = 15.0 Hz, 6.6 Hz, 1H), 2.86 (d, *J* = 9.8 Hz, 1H), 2.04 (q, *J* = 6.6 Hz, 2H), 1.36-1.32 (m, 4H), 0.90 (t, *J* = 6.6 Hz, 3H), -0.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 141.8, 129.8, 128.44, 128.40, 128.32, 128.26, 42.2, 32.5, 32.0, 22.2, 13.9, -3.1. IR (neat): 3081, 3024, 2957, 2926, 2872, 2858, 1654, 1596, 1490, 1248, 1093, 1013, 966, 866, 843 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{25}ClSi$ 280.1409, found 280.1409.

*(1-(4-Methylphenyl)hept-2-en-1-yl)trimethylsilane (**7d**).*

62% yield (160 mg), *E/Z* = 12 : 1, R_f = 0.5, hexane. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 7.07 (d, *J* = 7.9 Hz, 2H), 6.97 (d, *J* = 7.9 Hz, 2H), 5.76 (dd, *J* = 15.1 Hz, 10.0 Hz, 1H), 5.39 (dt, *J* = 15.1 Hz, 6.7 Hz, 1H), 2.85 (d, *J* = 10.0 Hz, 1H), 2.31 (s, 3H), 2.05 (q, *J* = 6.7 Hz, 2H), 1.38-1.30 (m, 4H), 0.90 (t, *J* = 6.7 Hz, 3H), -0.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 140.1, 133.6, 129.3, 129.0, 128.9, 127.0, 42.2, 32.5, 32.1, 22.2, 20.9, 13.9, -3.0. IR (neat): 3088, 3046, 3020, 2956, 2925, 2859, 1654, 1613, 1511, 1247, 965, 840 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{28}Si$ 260.1955, found 260.1970.

*(1-(4-Methoxyphenyl)hept-2-en-1-yl)trimethylsilane (**7e**).*

84% yield (231 mg), *E/Z* = 13 : 1, R_f = 0.5, hexane / ethyl acetate (50 : 1). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 6.99 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.73 (dd, *J* = 15.1 Hz, 9.7 Hz, 1H), 5.37 (dt, *J* = 15.1 Hz, 7.1 Hz, 1H), 3.78 (s, 3H), 2.82 (d, *J* = 9.7 Hz, 1H), 2.04 (q, *J* = 7.1 Hz, 2H), 1.36-1.31 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H), -0.05 (s, 9H). ^{13}C NMR

(100 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 156.7, 135.2, 129.4, 129.0, 127.9, 113.7, 55.2, 41.5, 32.5, 32.1, 22.2, 13.9, -3.0. IR (neat): 3096, 2998, 2956, 2923, 2872, 1654, 1610, 1581, 1508, 1465, 1298, 1246, 1179, 1039, 965, 869, 840 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{28}OSi$ 276.1904, found 276.1899.

*(1-(3-Methylphenyl)hept-2-en-1-yl)trimethylsilane (**7f**).*

66% yield (172 mg), *E/Z* = 13 : 1, R_f = 0.55, hexane. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 7.15 (t, *J* = 7.7 Hz, 1H), 6.92-6.87 (m, 3H), 5.78 (dd, *J* = 14.9 Hz, 10.0 Hz, 1H), 5.40 (dt, *J* = 14.9 Hz, 6.9 Hz, 1H), 2.86 (d, *J* = 10.0 Hz, 1H), 2.33 (s, 3H), 2.06 (q, *J* = 6.9 Hz, 2H), 1.40-1.31 (m, 4H), 0.91 (t, *J* = 6.9 Hz, 3H), -0.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 143.1, 137.6, 129.14, 129.10, 128.0, 127.9, 125.1, 124.2, 42.7, 32.5, 32.1, 22.2, 21.5, 13.9, -3.0. IR (neat): 3098, 3021, 2956, 2926, 2859, 1654, 1604, 1586, 1487, 1248, 1092, 964, 840, 703 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{28}Si$ 260.1955, found 260.1969.

*(1-(3-Methoxyphenyl)hept-2-en-1-yl)trimethylsilane (**7g**).*

48% yield (132 mg), *E/Z* = 13 : 1, R_f = 0.4, hexane / ethyl acetate (30 : 1). Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 7.17 (t, *J* = 7.8 Hz, 1H), 6.68-6.64 (m, 3H), 5.76 (dd, *J* = 15.1 Hz, 10.0 Hz, 1H), 5.40 (dt, *J* = 15.1 Hz, 7.0 Hz, 1H), 3.80 (s, 3H), 2.87 (d, *J* = 10.0 Hz, 1H), 2.05 (q, *J* = 7.0 Hz, 2H), 1.39-1.31 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H), -0.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 159.5, 144.9, 129.3, 129.0, 128.9, 119.7, 113.1, 109.5, 55.0, 42.9, 32.5, 32.0, 22.2, 13.9, -2.9. IR (neat): 3099, 3019, 2957, 2929, 2872, 1654, 1601, 1585, 1488, 1259, 1149, 1052, 968, 839 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{28}OSi$ 276.1904, found 276.1917.

*(1-(3-Fluorophenyl)hept-2-en-1-yl)trimethylsilane (**7h**).*

52% yield (136 mg), *E/Z* = 15 : 1, R_f = 0.6, hexane. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 7.22-7.16 (m, 1H), 6.84-6.76 (m, 3H), 5.72 (dd, *J* = 15.0 Hz, 10.0 Hz, 1H), 5.41 (dt, *J* = 15.0 Hz, 6.8 Hz, 1H), 2.90 (d, *J* = 10.0 Hz, 1H), 2.05 (q, *J* = 6.8 Hz, 2H), 1.39-1.30

(m, 4H), 0.90 (t, J = 6.8 Hz, 3H), -0.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 162.9 (d, $^1J_{CF}$ = 244.1 Hz), 146.1 (d, $^3J_{CF}$ = 7.4 Hz), 129.8, 129.5 (d, $^3J_{CF}$ = 9.1 Hz), 128.2, 122.8 (d, $^4J_{CF}$ = 2.5 Hz), 113.7 (d, $^2J_{CF}$ = 21.5 Hz), 111.1 (d, $^2J_{CF}$ = 20.7 Hz), 42.8, 32.5, 32.0, 22.2, 13.9, -3.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) -114.02 (m). IR (neat): 3078, 3018, 2958, 2927, 2873, 2859, 1654, 1615, 1588, 1486, 1249, 1138, 966, 839 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{25}FSi$ 264.1704, found 264.1709.

*(1-(2-Methoxyphenyl)hept-2-en-1-yl)trimethylsilane (**7i**).*

85% yield (234 mg), *E/Z* = 16 : 1, R_f = 0.55, hexane / ethyl acetate (50 : 1). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 7.12 (d, J = 7.7 Hz, 1H), 7.08 (t, J = 7.7 Hz, 1H), 6.90 (t, J = 7.7 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 5.79 (dd, J = 15.1 Hz, 10.0 Hz, 1H), 5.41 (dt, J = 15.1 Hz, 7.1 Hz, 1H), 3.79 (s, 3H), 3.44 (d, J = 10.0 Hz, 1H), 2.04 (q, J = 7.1 Hz, 2H), 1.37-1.33 (m, 4H), 0.90 (t, J = 7.1 Hz, 3H), -0.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 155.7, 131.8, 129.1, 129.0, 127.3, 125.0, 120.4, 110.1, 55.0, 34.1, 32.5, 32.1, 22.2, 13.9, -2.9. IR (neat): 3061, 3027, 2956, 2926, 2872, 1654, 1596, 1465, 1241, 1033, 837, 749 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{28}OSi$ 276.1904, found 276.1929.

*(1-(2-Fluorophenyl)hept-2-en-1-yl)trimethylsilane (**7j**).*

65% yield (171 mg), *E/Z* = 10 : 1, R_f = 0.6, hexane. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 7.19-7.14 (m, 1H), 7.08-7.05 (m, 2H), 7.02-6.97 (m, 1H), 5.78 (dd, J = 14.9 Hz, 10.0 Hz, 1H), 5.45 (dt, J = 14.9 Hz, 6.8 Hz, 1H), 3.28 (d, J = 10.0 Hz, 1H), 2.06 (q, J = 6.8 Hz, 2H), 1.38-1.32 (m, 4H), 0.91 (t, J = 6.8 Hz, 3H), -0.01 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 159.6 (d, $^1J_{CF}$ = 242.5 Hz), 132.5, 130.1, 128.2 (d, $^3J_{CF}$ = 5.0 Hz), 127.7, 125.5 (d, $^2J_{CF}$ = 8.3 Hz), 123.8 (d, $^3J_{CF}$ = 3.3 Hz), 115.2 (d, $^2J_{CF}$ = 23.2 Hz), 34.3, 32.5, 32.0, 22.2, 13.9, -3.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) -117.31 (m). IR (neat): 3064, 3033, 2957, 2927, 2873, 2858, 1654, 1610, 1582, 1488, 1454, 1249, 1227, 1092, 966, 839, 752 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{25}FSi$ 264.1704, found 264.1724.

*Trimethyl(1-phenylbut-2-en-1-yl)silane (**7k**).* Known compound.[15]

59% yield (120 mg), *E/Z* = 7 : 1, R_f = 0.45, hexane. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37-7.26 (m, 3H), 7.14-7.09 (m, 2H), 6.38-6.22 (m, 2H, *Z*-isomer), 5.84 (dd, *J* = 15.1 Hz, 10.0 Hz, 1H, *E*-isomer), 5.45 (dt, *J* = 15.1 Hz, 6.1 Hz, 1H, *E*-isomer), 3.33 (d, *J* = 11.5 Hz, 1H, *Z*-isomer), 2.92 (d, *J* = 10.0 Hz, 1H, *E*-isomer), 1.74 (d, *J* = 6.1 Hz, 3H, *E*-isomer), 1.22 (d, *J* = 7.3 Hz, 3H, *Z*-isomer), 0.06 (s, 9H, *Z*-isomer), 0.01 (s, 9H, *E*-isomer). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): (*E*,*Z*-mixture) 143.2, 130.2, 129.6, 128.4, 128.2, 127.1, 126.2, 125.6, 124.4, 123.5, 121.7, 42.8, 37.3, 18.1, 13.5, -3.0, -3.4. MS (EI) m/z: 204 $[M]^+$.

*Trimethyl(1-phenylpent-2-en-1-yl)silane (**7l**).*

66% yield (144 mg), *E/Z* = 15 : 1, R_f = 0.45, hexane. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 7.30-7.20 (m, 3H), 7.08 (d, *J* = 8.3 Hz, 2H), 5.79 (dd, *J* = 15.1 Hz, 10.0 Hz, 1H), 5.46 (dt, *J* = 15.1 Hz, 7.4 Hz, 1H), 2.90 (d, *J* = 10.0 Hz, 1H), 2.07 (quint, *J* = 7.4 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H), -0.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 143.2, 130.8, 128.2, 128.0, 127.1, 124.4, 42.7, 25.9, 14.3, -3.0. IR (neat): 3082, 3061, 3024, 2961, 2931, 2897, 2872, 1654, 1599, 1494, 1451, 1248, 965, 865, 842, 699 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{14}H_{22}Si$ 218.1485, found 218.1496.

*Trimethyl(4-methyl-1-phenylpent-2-en-1-yl)silane (**7m**).* Known compound.[14]

52% yield (120 mg), *E/Z* > 19 : 1, R_f = 0.55, hexane. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.27 (t, *J* = 7.6 Hz, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 2H), 5.76 (dd, *J* = 15.0 Hz, 10.0 Hz, 1H), 5.39 (dd, *J* = 15.0 Hz, 6.6 Hz, 1H), 2.90 (d, *J* = 10.0 Hz, 1H), 2.39-2.28 (m, 1H), 1.03 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), -0.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 143.2, 136.4, 128.2, 127.1, 125.9, 124.3, 42.6, 31.4, 23.0, 22.9, -3.0. MS (EI) m/z: 232 $[M]^+$.

*Trimethyl(2-methyl-1-phenylhept-2-en-1-yl)silane (**7n**).*

59% yield (153 mg), *E/Z* = 8 : 1, R_f = 0.5, hexane. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 7.26-7.22 (m, 2H), 7.15-7.13 (m, 3H), 5.33 (d, *J* = 7.2 Hz, 1H), 2.76 (s, 1H), 2.06 (q, *J* = 7.2 Hz, 2H), 1.59 (s, 3H), 1.39-1.34 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H), 0.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 142.7, 135.4, 128.7, 127.9, 126.7, 124.8, 48.6, 32.2, 28.1, 22.4, 18.2, 14.0, -1.3. IR (neat): 3082, 3061, 3025, 2957, 2927, 2872, 2857, 1654, 1599, 1494, 1451, 1249, 837, 699 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{28}Si$ 260.1955, found 260.1944.

*(1-(2-Furyl)hept-2-en-1-yl)trimethylsilane (**7o**).*

86% yield (202 mg), *E/Z* = 9 : 1, R_f = 0.5, hexane. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 7.28 (d, *J* = 2.5 Hz, 1H), 6.28 (t, *J* = 2.5 Hz, 1H), 5.87 (d, *J* = 2.5 Hz, 1H), 5.56 (dd, *J* = 15.2 Hz, 9.4 Hz, 1H), 5.39 (dt, *J* = 15.2 Hz, 8.8 Hz, 1H), 2.99 (d, *J* = 8.8 Hz, 1H), 2.04 (q, *J* = 6.8 Hz, 2H), 1.37-1.30 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H), 0.01 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 157.0, 140.1, 129.7, 126.7, 110.1, 103.2, 35.5, 32.4, 32.0, 22.2, 13.9, -2.8. IR (neat): 3115, 3018, 2957, 2925, 2872, 2853, 1656, 1582, 1503, 1248, 1008, 968, 841 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{14}H_{24}OSi$ 236.1591, found 236.1603.

*(1,3-Diphenylallyl)trimethylsilane (**10**).* Known compound.[16]

68% yield (181 mg), *E/Z* = 15 : 1, R_f = 0.45, hexane. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 7.39 (d, *J* = 7.2 Hz, 2H), 7.34-7.30 (m, 4H), 7.23-7.14 (m, 4H), 6.64 (dd, *J* = 15.8 Hz, 10.0 Hz, 1H), 6.40 (d, *J* = 15.8 Hz, 1H), 3.17 (d, *J* = 10.0 Hz, 1H), 0.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 142.3, 138.2, 130.5, 128.5, 128.4, 128.1, 127.2, 126.6, 125.9, 124.7, 43.8, -2.8. MS (EI) m/z: 266 $[M]^+$.

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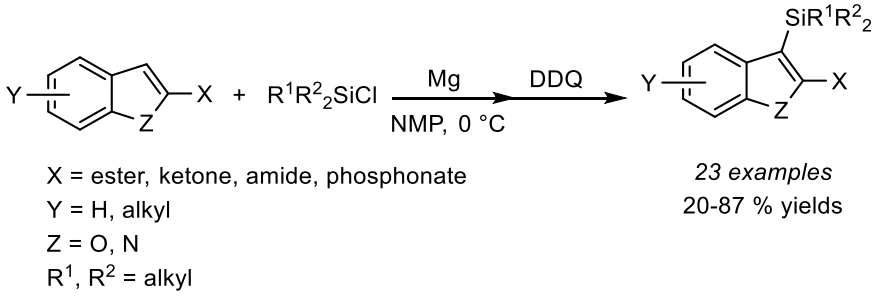
5. Conclusion

In this thesis, three types of coupling reactions by electron transfer from magnesium or calcium to π-electron systems were developed: (1) Selective 3-silylation of benzofuran derivatives; (2) Carboxylation of phenyl vinyl ketones; (3) Silylation of propargyl pivalates or allyl pivalates through C-O bond cleavage .

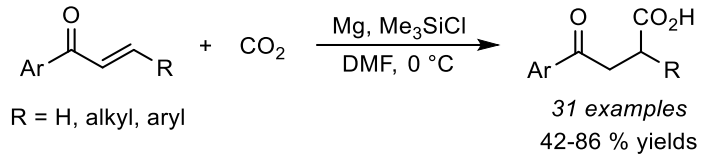
(1) For the synthesis of benzofurans derivatives in chapter 2, magnesium-promoted silylation of readily available benzofurans and the subsequent oxidative rearomatization by DDQ gave the selective formation of 3-silylated benzofurans. Application of various substituents was investigated to give 23 examples of corresponding products in 20-87% yields under mild reaction conditions with wide substrate scope (Scheme 5-1). Moreover, the silyl group introduced on the five-membered ring by the reductive coupling could survive with no elimination throughout the oxidation process. It was also clarified that this silylation could be extended to indole derivatives. The silylated heteroaromatic skeletons are useful as intermediates in organic synthesis, and the practical utility was also demonstrated by several transformation reactions.



Scheme 5-1 Magnesium-promoted reductive 3-silylation of benzofurans

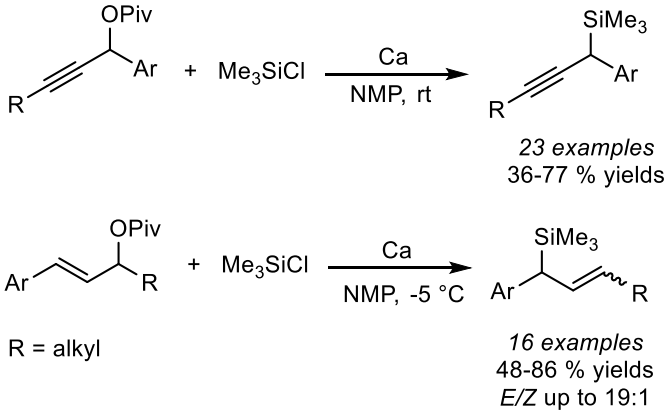
(2) In the synthesis of carboxylic acids in chapter 3, reductive carboxylation of easily prepared phenyl vinyl ketones under the atmosphere of carbon dioxide led to the selective formation of γ-keto carboxylic acids. The reaction is characterized by the carbon-carbon bond formation of carbon dioxide as a carbon source and using easily handling magnesium as the reducing agent under mild reaction conditions. This protocol showed wide substrate scope and provided a useful and convenient alternative to access biological important γ-keto carboxylic acids in moderate to good yields (42-86%). The carboxylation of di- or tri- substituted phenyl vinyl ketones was also compatible under the standard conditions in moderate yields. 31 examples were obtained by this

method showed that good functional tolerance (Scheme 5-2).



Scheme 5-2 Magnesium-promoted CO_2 fixation of phenyl vinyl ketones

(3) In addition, the calcium-promoted reductive silylation of propargyl pivalates and allyl pivalates gave various propargyl silanes and allyl silanes in good yields with high selectivity via C-O bond cleavage strategy. In this research, the pivalate was cleavage under the reduction conditions using calcium, which is the first example of using this metal in reductive coupling reactions (Scheme 5-3).



Scheme 5-3 Calcium-promoted reductive silylations of propargyl and allyl pivalates

Magnesium and calcium were used as the easily handling reducing agent and various types of transformation reactions were developed through the activation of π-electron systems including aromatic groups. These reactions will strongly contribute to the field of organic fine-chemicals intermediate synthesis, especially C1-chemistry and organosilane chemistry.

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Suhua Zheng

Nagaoka University of Technology

List of Publications

1. S. Zheng, T. Zhang, H. Maekawa, "Mg-Promoted Reductive Carboxylation of Aryl Vinyl Ketones: Synthesis of γ-Keto Carboxylic Acids" *The Journal of Organic Chemistry*, **2022**, *87*, 7342-7349.
2. T. Zhang, S. Zheng, T. Kobayashi, H. Maekawa, "Regioselective Silylations of Propargyl and Allyl Pivalates through Ca-Promoted Reductive C(sp^3)-O Bond Cleavage." *Organic Letters*, **2021**, *23*, 7129-7133.
3. S. Zheng, T. Zhang, H. Maekawa, "Reductive 3-Silylation of Benzofuran Derivatives via Coupling Reaction with Chlorotrialkylsilane." *The Journal of Organic Chemistry*, **2020**, *85*, 13965-13972.
4. T. Zhang, Y. Shimizu, K. Shimizu, M. Abe, S. Zheng, H. Maekawa, "Selective Introduction of Trifluoroacetyl Group to β- and δ-Position of Aromatic Conjugated Esters: Facile Synthesis of Fluorine-Containing Keto Esters." *Asian Journal of Organic Chemistry*, **2019**, *8*, 344-347.

Participated Conferences

1. S. Zheng, T. Zhang, H. Maekawa, “Synthesis of *gamma*-Keto Carboxylic Acids by Mg-Promoted Reductive CO_2 Fixation of Propenyl Ketones.” *The international Chemical Congress of Pacific Basin Societies* 2021 (Pacifichem 2021), Dec 19, 2021.
2. S. Zheng, T. Zhang, H. Maekawa, “Mg-Promoted Reductive CO_2 Fixation of Propenyl Ketones.” *The 101st CSJ Annual Meeting*, Mar 21, 2021.
3. 鄭素華、張田原、前川博史、マグネシウム還元法による 2 位に電子求引基を有するベンゾフラン類のシリル化反応、第 78 回有機合成化学協会関東支部シンポジウム、2019/12/01.
4. 鄭素華、張田原、前川博史、1-ベンゾフラン-2-カルボン酸メチル類のマグネシウム還元シリル化反応、日本化学会第 99 回春季年会、2019/03/16.
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Reductive 3-Silylation of Benzofuran Derivatives via Coupling Reaction with Chlorotrialkylsilane

Suhua Zheng, Tianyuan Zhang, and Hirofumi Maekawa*

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ABSTRACT: Reductive silylation of benzofurans with an electron-withdrawing group by a magnesium metal and the subsequent oxidative rearomatization by DDQ gave the selective formation of less reported 3-silylated benzofurans in moderate to good yields under mild reaction conditions with wide substituent scope. The silyl group introduced on the five-membered ring by the reductive coupling could survive with no elimination throughout the oxidation process. The silylated heteroaromatic skeleton is useful as an intermediate in organic synthesis, and its practical utility was also demonstrated by several transformation reactions.

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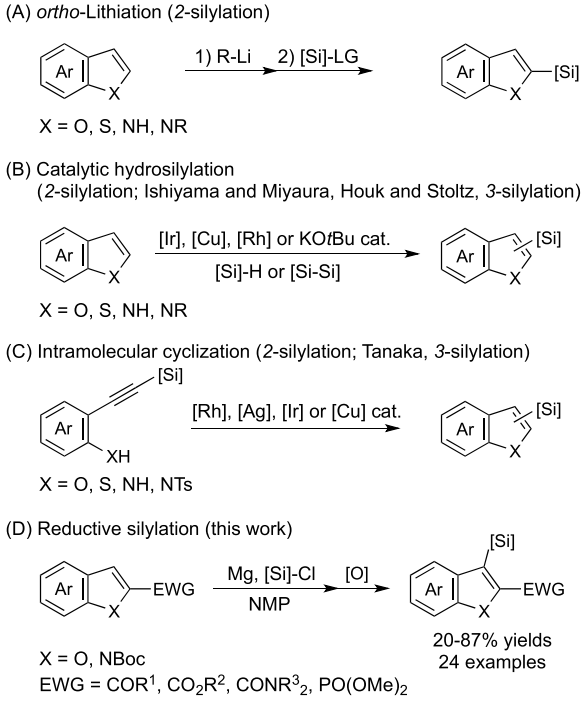
INTRODUCTION

A benzofuran structure can be frequently seen in the skeleton of naturally occurring compounds and has been focused by medicinal chemists and pharmacologists due to its potent bioactivities.[1] Silylated compounds such as vinylsilanes, allylsilanes, and arylsilanes are of particular importance as useful intermediates in the field of organic syntheses,[2] materials science,[3] and medicinal chemistry[4] because they behave as superior nucleophiles. From these backgrounds, extensive attention has been paid to the introduction of silyl groups into heteroaromatics, especially benzofurans and indoles to construct novel bioactive groups of compounds.[5] Conventionally, 2-silylation of heteroaromatics can be easily achieved by a reaction with an organometallic reagent followed by the electrophilic attack of chlorotrialkylsilanes (Scheme 1A).[6] In comparison with traditional methods, many of the recent synthetic approaches to silylated benzofurans are investigated such as the catalytic direct silylation by C−H activation (Scheme 1B)[7] and the intramolecular cyclization of alkynylsilanes (Scheme 1C).[8] These processes are generally useful and reliable; however, the main products in almost all of the reactions are 2-silylated benzofuran derivatives except for some examples[7a,8d] and the reactions sometimes demand hazardous reactants or the troublesome preparation of starting materials. Therefore, the development of new strategies toward the silylation of heteroaromatics, especially the less reported 3-silylated benzofurans[7a,8d] or indoles[7b] from simple feedstocks under mild reaction conditions still remains an attractive and vital task.

We have previously developed a series of magnesium-promoted silylation of electron-deficient aromatic alkenes or alkynes under mild reaction conditions.[9] However, the reductive silylation of benzofuran or indole was not achieved due to their high stability and more negative reduction potentials.[10] In this study, 2-acetylbenzofuran was first selected as the benchmark substrate, and the reductive silylation to the

Scheme 1. (A−D) Scope of Silylation of Benzofuran and Analogues



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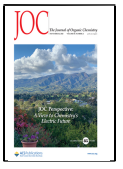

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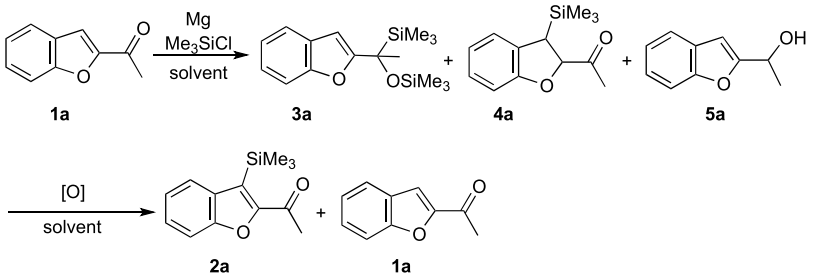
Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	temp (°C)	[O] conditions	yield of **2a** (%)
1	NMP	25	air oxidation	(25)[b]
2	NMP	25	DDQ/CH_2Cl_2	48
3	NMP	−15	DDQ/CH_2Cl_2	31
4	NMP	0	DDQ/CH_2Cl_2	60 (52)[c]
5	DMI	25	DDQ/CH_2Cl_2	26
6	DMF	0	DDQ/CH_2Cl_2	20
7	DMA	0	DDQ/CH_2Cl_2	40
8	THF	0	DDQ/CH_2Cl_2	no reaction
9	NMP	0	DDQ/CH_2Cl_2	29[d]
10	NMP	0	DDQ/CH_2Cl_2	33[e]

[a]Reaction conditions: (1) **1a** (2 mmol), Mg (4 equiv), Me_3SiCl (6 equiv), solvent (15 mL, 0.13 M), N_2 atmosphere, and 3 h. (2) DDQ (1 equiv), CH_2Cl_2 (1 M, 2 mL), 25 °C, and 6 h. Yields were determined by gas chromatography using *n*-undecane as the internal standard. Isolated yields are shown in the parentheses. [b]Air oxidation for 24 h instead of DDQ oxidation afforded a mixture of **2a** (25%), **3a** (13%), **4a** (7%), **5a** (16%), and **1a** (10%). [c]Starting material **1a** was reproduced in 11% yield. [d]NMP (5 mL, 0.40 M) was used. [e]NMP (25 mL, 0.08 M) was used. See the Supporting Information for detailed optimization on equivalents of reagents.

five-membered ring was investigated. As a result, the reductive coupling of benzofuran derivatives with chlorotrimethylsilane followed by the subsequent oxidative aromatization allowed the efficient delivery of the corresponding benzofurans silylated at the 3-position as the main product (Scheme 1D).

RESULTS AND DISCUSSION

Our study was initiated by reduction of 2-acetylbenzofuran **1a** with magnesium turnings in the presence of chlorotrimethylsilane in *N*-methylpyrrolidone (NMP), and the desired product, 3-silylated benzofuran **2a**, was obtained in 25% yield after air oxidation, accompanying with the disilylated compound of the carbonyl group **3a** (13%), 3-silylated dihydrobenzofuran **4a** (7%), and simply reduced product of the carbonyl group **5a** (16%) as the side products (Table 1, entry 1). Oxidative aromatization facilitated by addition of DDQ (see the Supporting Information for detailed optimization) and investigation on the reaction temperature gave the desired product **2a** at 0 °C in 60% yield with only a small amount of the starting material (Table 1, entry 4), while reactions at −15 °C or room temperature gave slightly lower yields (Table 1, entries 2 and 3). Then, extensive screening of the solvent effect suggested the requirement of the aprotic polar solvent for the coupling, and NMP was found to be the best solvent (Table 1, entries 4−8). On the other hand, the investigation of the substrate concentration showed no improvement on yields (Table 1, entries 9 and 10).

Under the optimized reaction conditions, the substrate scope and generality of this reaction were carefully screened (Scheme 2). First, substitution by a methoxy group or a bromine atom at the 7-position of 2-acetylbenzofurans showed undesired reaction efficiency, and the target product **2b** or **2c** was obtained in only 25 and 20% yields, respectively, with a much amount of dimers and recovery of the starting material. Pleasingly, the replacement of the acetyl group to an ester group led to a dramatic decrease of side products and the yields of **2d** and **2e** were enhanced to 70 and 87%, respectively. A range of benzofurans, with a methyl group, a methoxy group, or a halogen atom, were well compatible with this reductive coupling under the optimal reaction conditions, which allowed the efficient transformation into 3-silylated benzofurans **2f** to **2o** in 38 to 84% yields. A naphthofuran ring was also tolerated under the standard conditions, albeit in diminished yields (**2p**). Furthermore, the scope of the electron-withdrawing group at the 2-position was extended to carboxamides, which allowed the facile synthesis of products **2q**−**2s** in moderate to good yields. In addition, this protocol can also be extended to other silylating agents, and silyl groups such as ethyldimethylsilyl, chloromethyldimethylsilyl, and triethylsilyl groups were selectively introduced to the 3-position of benzofurans in moderate yields (**2t**−**2v**, respectively).

To increase the utility of this reaction, we next switched our attention to the investigation of benzofurans with other types of electron-withdrawing groups and indole derivatives. As shown in Scheme 3, under the designated reaction conditions, silylation of dimethyl phosphonate **6** gave the 3-silylated product **7** in 35% yield, while 2-cyanobenzofuran **8** was transformed into an unpredicted tris-silylated product **9** in 30% yield. Furthermore, the reaction of Boc-protected indole **10b** also gave a positive result, while the reaction of *N*-methylindole **10a** gave aroylsilane **11** in 46% yield.[11] The contrast results of indoles may be explained by the difference of electron density of the five-membered ring,[12] which will be referred to the reaction mechanism.

The synthetic usability of the products **2q** and **2r** was demonstrated in Scheme 4.[2b] First, the substrate **2q** was converted into an *ipso*-substitution product, 2-acetyl-3-iodobenzofuran **13**, by addition of 4 equiv of ICl at ambient temperature, and the substrate **2r** was also transformed into

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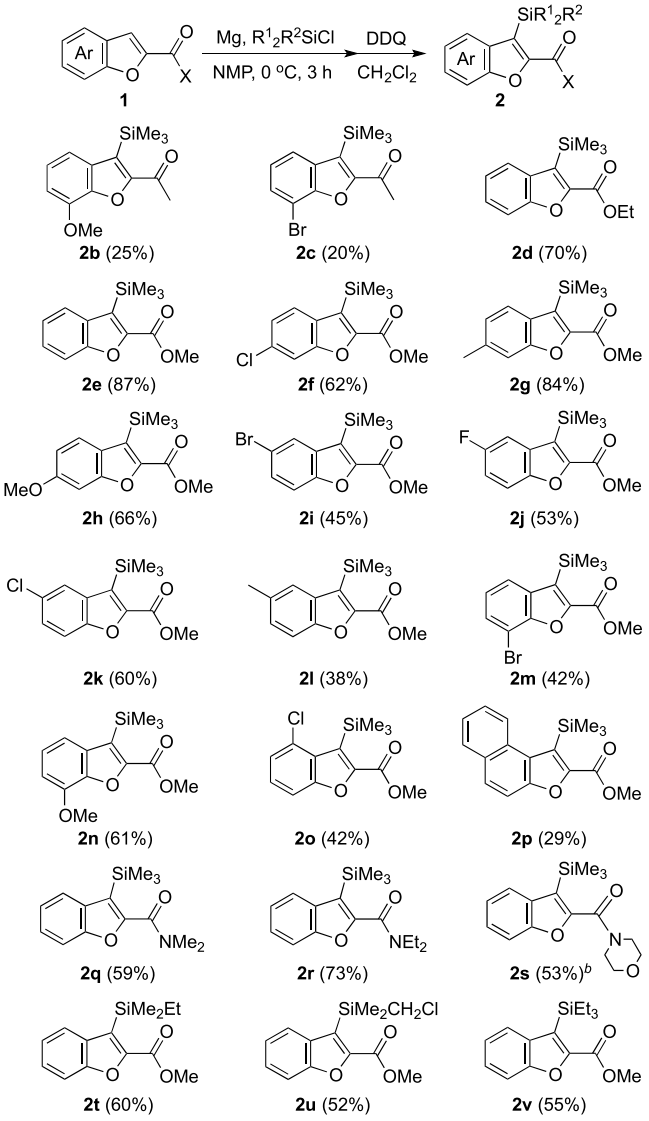
Scheme 2. Scope of the Reductive Silylation of Benzofuran Derivatives[a]

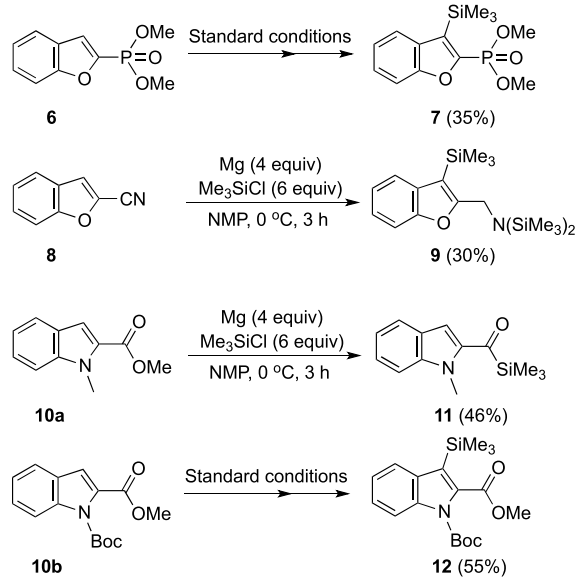


[a]Reaction conditions: substrate **1** (2 mmol), Mg (4 equiv), silylating agent (6 equiv), NMP (15 mL, 0.13 M), N_2 atmosphere, and 3 h; DDQ (1 equiv), CH_2Cl_2 (2 mL, 1 M), 25 °C, and 6 h. Yields are shown in the parentheses. [b]At the first step, the reaction mixture was stirred for 20 h.

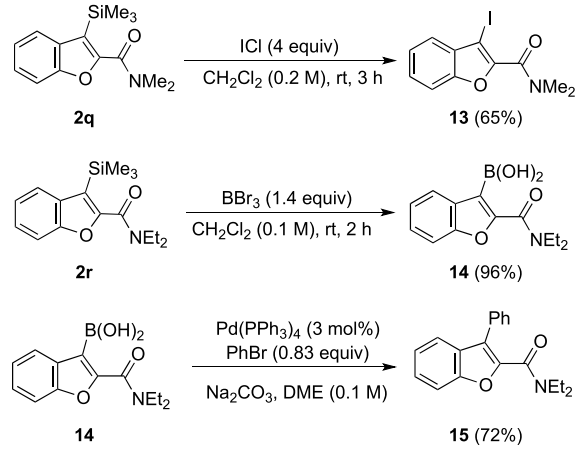
boronic acid **14**, quantitatively. Boronic acid **14** is regarded as a good reagent for Suzuki−Miyaura coupling reactions, and in fact, the palladium-catalyzed coupling of **14** with bromobenzene afforded a biaryl compound **15** in 72% yield. Benzofuran-2-carboxamides including biaryl compounds like **15** were reported to have the bioactive potential on anti-inflammatory, analgesic, and antipyretic activities,[13] and these two-step reactions from arylsilane **2** to biaryl compounds may be dedicated to the synthesis of a series of potential drug candidates.

Finally, to gain insight into the reaction mechanism, several control experiments were executed (Scheme 5). No reaction was observed without magnesium in the presence of chlorotrimethylsilane; then, zinc turnings, which had the lower reducibility than magnesium, were applied to this coupling instead of magnesium, and a mixture of pinacol

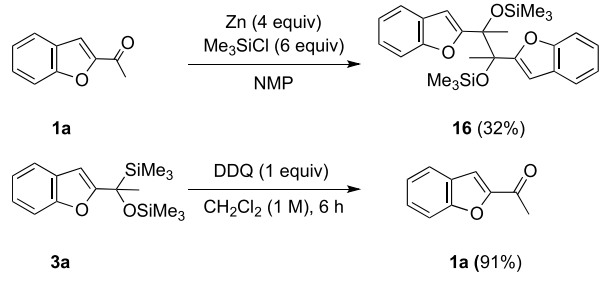
Scheme 3. Reactions of Benzofurans with Other Electron-Withdrawing Groups and Indole Derivatives



Scheme 4. Synthetic Applications of 3-Silylated Benzofurans



Scheme 5. Mechanistic Studies



isomer **16** was obtained in 32% yield with no detection of the C-silylated product. On the basis of this result, it was rationalized that the conjugation system including the carbonyl group could be easily reduced by the single electron transfer from the metal. Furthermore, DDQ oxidation of the isolated disilylated compound **3a** under the same reaction conditions afforded the starting material **1a** and this result suggested that the crude reaction mixture composed of **3a**, **4a**, and **5a** would be convergent to a mixture of **2a** and the starting material **1a** by DDQ oxidation (see Table 1). In addition, it is remarkable

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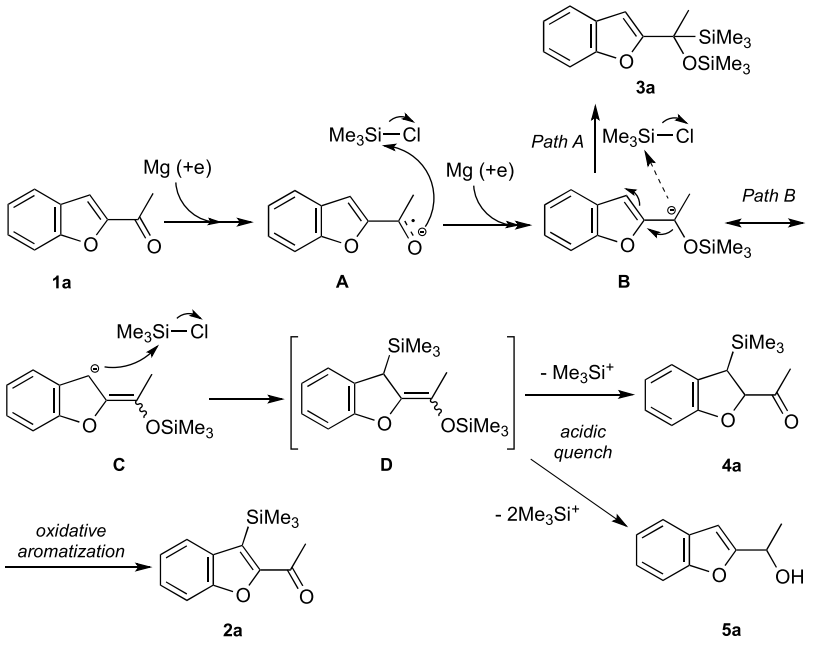
Scheme 6. Proposed Reaction Mechanism



that the silyl group on the five-membered ring of **4a** survived during DDQ oxidation, while the silyl group of **3a** on a carbon atom of the side chain had been completely removed.

Based on the above observations and previous research,[14] a plausible reaction mechanism on the formation of **2a** is descripted in Scheme 6. Initially, a single electron transfer from the magnesium metal to 2-acetylbenzofuran **1a** affords an anion radical species **A**, which will attack chlorotrimethylsilane to give **B** after the second electron transfer from magnesium. Then, a direct attack of the anionic intermediate **B** to chlorotrimethylsilane will furnish a side product **3a** disilylated at the carbonyl group through pathway A. The compound **3a** and simply reduced product **5a** will be transformed into the starting material **1a** after DDQ oxidation. Meanwhile, in pathway B, the attack of **C** through the resonance with the furan ring to chlorotrimethylsilane occurs on the 3-position of the benzofuran ring to yield intermediate **D**. The compounds **4a** and **5a** may be formed through the hydrolysis of **D**, and the oxidative aromatization of **4a** will give the product **2a** with no elimination of the silyl group from the 3-position.

CONCLUSIONS

In conclusion, magnesium-promoted reductive silylation of benzofurans and Boc-protected indoles with an electron-withdrawing group at the 2-position and the subsequent oxidative aromatization led to the selective formation of the corresponding 3-silylated products. It is noteworthy that the oxidative aromatization proceeded without elimination of the introduced silyl group and this two-step silylation has a broad functional group tolerance. The reaction is characterized by a simple process, mild reaction conditions, easily available silylating agent, and use of an Earth-abundant metal. Selectively prepared silylated heteroaromatics were also proved to be promising intermediates for the synthesis of natural products and pharmaceutical drugs by some transformation reactions.

EXPERIMENTAL SECTION

General Information. All commercially available chemicals were used without further purification, unless otherwise noted. All solvents were distilled by standard techniques prior to use. Chlorotrialkylsilanes were simply distilled before use. All starting materials except **1o**[15] are known compounds, and they were synthesized according to the procedures from the literature studies, **1a−1c**,[16] **1d−1n**,[17] **1p**,[17] **1q−1s**,[18] **6**,[19] **8**,[20] **10a**,[21] and **10b**.[22] ^{1}H NMR, ^{13}C{^{1}H} NMR, ^{19}F NMR, and ^{31}P{^{1}H} NMR spectra were measured on a JEOL JNM AL-400 (400 MHz) spectrometer at 20 °C. Proton chemical shifts were expressed in parts per million (ppm) downfield from the residual signal of chloroform (7.26 ppm). Carbon chemical shifts were referenced to the carbon signal of the solvent at 77.0 ppm ($CDCl_3$). Fluorine chemical shifts were referenced to the external fluorine signal of trifluoroacetic acid at −76.50 ppm. A phosphorus chemical shift was referenced to the external phosphorus signal of triphenylphosphine at −5.65 ppm. Infrared (IR) spectra were recorded on a JASCO 470Plus FTIR spectrometer. A low mass spectrum was recorded on a Shimadzu GCMS-QP2010 spectrometer (quadrupole, EI). High-resolution mass spectra were recorded on a JEOL JMS-600H spectrometer (double-focusing, EI), and spectra of **2a**, **2n**, and **11** were recorded on a JEOL JMS-T200GC spectrometer (TOF, EI). Melting point determinations were performed using a Yanaco MP-J3 instrument and are uncorrected. Cyclic voltammograms were measured with an ALS model 600.

General Procedure for 3-Silylation of Benzofurans and Indoles. In a round-bottom flask, a mixture of magnesium (194 mg, 8 mmol, 4 equiv), chlorotrimethylsilane (1.52 mL, 12 mmol, 6 equiv), and NMP (5 mL) was stirred for 30 min at room temperature under a nitrogen atmosphere. Then, to the mixture was added a solution of benzofuran or indole (2 mmol) in NMP (10 mL). After stirring for 3 h at room temperature, the reaction mixture was poured into 50 mL of 1 M sulfuric acid and products were extracted with diethyl ether (30 mL × 3). The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, and then concentrated *in vacuo*. The crude products were transferred into another round-bottom flask, and a dichloromethane (2 mL) solution of DDQ (454 mg, 2 mmol, 1 equiv) was added. The mixture was stirred for 6 h at room temperature. The reaction mixture was quenched by 50 mL of 1 M sodium hydroxide solution, and the product was extracted with diethyl ether (30 mL × 3). The combined organic layer was washed with brine and dried over anhydrous magnesium sulfate. After

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concentration *in vacuo*, the final product was purified by flash column chromatography.

1-[3-(Trimethylsilyl)benzofuran-2-yl]ethanone (**2a**). 52% yield (242 mg); hexane/ethyl acetate = 5:1; R_f = 0.7; white solid; mp 98.7−101.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.90 (1H, d, J = 8.3 Hz), 7.57 (1H, d, J = 8.3 Hz), 7.45 (1H, t, J = 8.3 Hz), 7.28 (1H, t, J = 8.3 Hz), 2.66 (3H, s), 0.45 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 190.9, 156.9, 155.1, 132.3, 127.3, 124.7, 123.3, 122.2, 112.0, 27.5, −0.2. IR (KBr): 3098, 2957, 2902, 1681, 1521 (cm^{-1}). HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{13}H_{16}O_2Si$, 232.0914; found, 232.0935.

[1-(Benzofuran-2-yl)-1-(trimethylsilyloxy)ethyl]trimethylsilane (**3a**). 13% yield (77 mg); hexane/ethyl acetate = 5:1; R_f = 0.8; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.50 (1H, d, J = 8.0 Hz), 7.42 (1H, d, J = 8.0 Hz), 7.21−7.18 (2H, m), 6.40 (1H, s), 1.68 (3H, s), 0.05 (9H, s), 0.03 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 164.1, 154.6, 129.0, 122.9, 122.4, 120.2, 110.8, 100.6, 69.1, 22.6, 2.2, −4.1. IR (neat): 3066, 2958, 2900, 2869, 1577, 1569, 1455, 1250 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{16}H_{26}O_2Si_2$, 306.1471; found, 306.1495.

1-[3-(Trimethylsilyl)-2,3-dihydrobenzofuran-2-yl]ethanone (**4a**). 7% yield (34 mg); hexane/ethyl acetate = 5:1; R_f = 0.75; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.13−7.08 (2H, m), 6.88−6.86 (2H, m), 5.17 (1H, d, J = 9.9 Hz), 3.06 (1H, d, J = 9.9 Hz), 2.23 (3H, s), 0.11 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 209.0, 158.8, 129.5, 127.3, 124.0, 121.1, 109.5, 89.8, 35.7, 28.1, −1.3. IR (neat): 3070, 2956, 2926, 2903, 2856, 1715, 1522 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{18}O_2Si$, 234.1076; found, 234.1063.

1-(Benzofuran-2-yl)ethanol (**5a**). 16% yield (53 mg); known compounds;[23] hexane/ethyl acetate = 5:1; R_f = 0.2; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.57 (1H, d, J = 8.0 Hz), 7.50 (1H, d, J = 8.0 Hz), 7.31 (1H, t, J = 8.0 Hz), 7.26 (1H, t, J = 8.0 Hz), 6.61 (1H, s), 5.02 (1H, q, J = 6.8 Hz), 3.09 (1H, broad, s), 1.65 (3H, d, J = 6.8 Hz). MS (EI) m/z: $[M]^+$ 162.

1-[7-Methoxy-3-(trimethylsilyl)benzofuran-2-yl]ethanone (**2b**). 25% yield (133 mg); hexane/ethyl acetate = 5:1; R_f = 0.3; pale yellow solid; mp 117.1−118.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.47 (1H, d, J = 8.0 Hz), 7.19 (1H, t, J = 8.0 Hz), 6.93 (1H, d, J = 8.0 Hz), 4.03 (3H, s), 2.69 (3H, s), 0.44 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 190.8, 157.0, 145.9, 144.8, 134.0, 123.8, 122.5, 116.6, 108.6, 56.1, 27.5, −0.2. IR (KBr): 3080, 3046, 3002, 2958, 2898, 1683, 1580 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{18}O_3Si$, 262.1025; found, 262.1015.

1-[7-Bromo-3-(trimethylsilyl)benzofuran-2-yl]ethanone (**2c**). 20% yield (124 mg); hexane/ethyl acetate = 5:1; R_f = 0.6; pale yellow solid; mp 85.0−86.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.83 (1H, d, J = 7.8 Hz), 7.61 (1H, d, J = 7.8 Hz), 7.16 (1H, t, J = 7.8 Hz), 2.70 (3H, s), 0.44 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 190.8, 157.0, 152.3, 133.5, 130.1, 124.5, 123.8, 123.1, 104.7, 27.5, −0.3. IR (KBr): 3075, 3041, 2999, 2956, 2899, 1685, 1521 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{15}O_2SiBr$, 310.0025; found, 310.0003.

Ethyl 3-(Trimethylsilyl)benzofuran-2-carboxylate (**2d**). 70% yield (368 mg); hexane/ethyl acetate = 5:1; R_f = 0.6; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.86 (1H, d, J = 8.0 Hz), 7.60 (1H, d, J = 8.0 Hz), 7.41 (1H, t, J = 8.0 Hz), 7.26 (1H, t, J = 8.0 Hz), 4.47 (2H, q, J = 7.2 Hz), 1.45 (3H, t, J = 7.2 Hz), 0.48 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 160.3, 155.2, 149.7, 132.0, 127.0, 124.2, 123.8, 123.1, 112.1, 61.5, 14.3, 0.3. IR (neat): 3051, 2984, 2954, 2901, 1717, 1538 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{18}O_3Si$, 262.1025; found, 262.1010.

Methyl 3-(Trimethylsilyl)benzofuran-2-carboxylate (**2e**). 87% yield (431 mg); hexane/ethyl acetate = 5:1; R_f = 0.5; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.87 (1H, d, J = 8.0 Hz), 7.59 (1H, d, J = 8.0 Hz), 7.41 (1H, t, J = 8.0 Hz), 7.26 (1H, t, J = 8.0 Hz), 3.99 (3H, s), 0.49 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 160.4, 155.1, 149.2, 131.8, 127.0, 124.2, 124.1, 123.1, 112.0, 52.0, 0.1. IR (neat): 3033, 2952, 2900, 2844, 1724, 1538 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{16}O_3Si$, 248.0869; found, 248.0868.

Methyl 6-Chloro-3-(trimethylsilyl)benzofuran-2-carboxylate (**2f**). 62% yield (350 mg); hexane/ethyl acetate = 5:1; R_f = 0.5; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.75 (1H, d, J = 8.5 Hz), 7.56 (1H, s), 7.23 (1H, d, J = 8.5 Hz), 3.98 (3H, s), 0.46 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 160.2, 155.3, 149.8, 133.0, 130.5, 124.7, 124.13, 124.08, 112.4, 52.2, 0.0. IR (neat): 3085, 2953, 2926, 2902, 2855, 1725, 1538 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{15}O_3SiCl$, 282.0479; found, 282.0458.

Methyl 6-Methyl-3-(trimethylsilyl)benzofuran-2-carboxylate (**2g**). 84% yield (442 mg); hexane/ethyl acetate = 5:1; R_f = 0.6; yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.73 (1H, d, J = 7.6 Hz), 7.38 (1H, s), 7.09 (1H, d, J = 7.6 Hz), 3.98 (3H, s), 2.48 (3H, s), 0.47 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 160.6, 155.7, 148.7, 137.8, 129.5, 124.9, 124.4, 123.6, 112.0, 52.1, 21.8, 0.1. IR (neat): 3088, 3024, 2952, 2900, 2854, 1716, 1538 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{18}O_3Si$, 262.1025; found, 262.1049.

Methyl 6-Methoxy-3-(trimethylsilyl)benzofuran-2-carboxylate (**2h**). 66% yield (365 mg); hexane/ethyl acetate = 5:1; R_f = 0.5; pale yellow solid; mp 72.2−74.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.71 (1H, d, J = 7.7 Hz), 7.07 (1H, s), 6.90 (1H, d, J = 7.7 Hz), 3.97 (3H, s), 3.86 (3H, s), 0.45 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 160.5, 160.1, 156.6, 148.5, 125.3, 124.8, 124.5, 113.2, 95.4, 55.6, 52.0, 0.1. IR (KBr): 3087, 3018, 2995, 2953, 2899, 2837, 1713, 1616 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{18}O_4Si$, 278.0974; found, 278.0981.

Methyl 5-Bromo-3-(trimethylsilyl)benzofuran-2-carboxylate (**2i**). 45% yield (291 mg); hexane/ethyl acetate = 5:1; R_f = 0.5; white solid; mp 42.0−44.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.96 (1H, s), 7.50 (1H, d, J = 9.0 Hz), 7.44 (1H, d, J = 9.0 Hz), 3.98 (3H, s), 0.46 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 160.2, 153.9, 150.2, 133.8, 130.1, 126.7, 123.6, 116.4, 113.5, 52.3, 0.1. IR (KBr): 3097, 3076, 3029, 2951, 2907, 2841, 1721, 1538 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{15}O_3SiBr$, 325.9974; found, 325.9978.

Methyl 5-Fluoro-3-(trimethylsilyl)benzofuran-2-carboxylate (**2j**). 53% yield (282 mg); hexane/ethyl acetate = 5:1; R_f = 0.5; yellow solid; mp 43.1−44.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.54−7.49 (2H, m), 7.18−7.13 (1H, m), 3.99 (3H, s), 0.46 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 160.3, 159.2 (d, $^1J_{CF}$ = 237.7 Hz), 151.5, 150.8, 132.6 (d, $^3J_{CF}$ = 11.0 Hz), 124.2, 115.3 (d, $^2J_{CF}$ = 26.1 Hz), 112.7 (d, $^3J_{CF}$ = 10.0 Hz), 109.4 (d, $^2J_{CF}$ = 30.1 Hz), 52.3, 0.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): −119.54 (m). IR (KBr): 3107, 3049, 3014, 2963, 2908, 2849, 1716, 1584 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{15}O_3FSi$, 266.0775; found, 266.0770.

Methyl 5-Chloro-3-(trimethylsilyl)benzofuran-2-carboxylate (**2k**). 60% yield (338 mg); hexane/ethyl acetate = 5:1; R_f = 0.6; pale yellow solid; mp 103.8−104.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.82 (1H, s), 7.51 (1H, d, J = 8.8 Hz), 7.39 (1H, d, J = 8.8 Hz), 3.99 (3H, s), 0.47 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 160.3, 153.6, 150.4, 133.2, 128.9, 127.5, 123.7, 113.5, 113.1, 52.3, 0.1. IR (KBr): 3098, 3075, 3004, 2955, 2909, 2848, 1721, 1537 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{15}O_3SiCl$, 282.0479; found, 282.0480.

Methyl 5-Methyl-3-(trimethylsilyl)benzofuran-2-carboxylate (**2l**). 38% yield (198 mg); hexane/ethyl acetate = 5:1; R_f = 0.5; pale yellow solid; mp 87.0−88.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.63 (1H, s), 7.47 (1H, d, J = 8.5 Hz), 7.24 (1H, d, J = 8.5 Hz), 3.98 (3H, s), 2.45 (3H, s), 0.47 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 160.6, 153.7, 149.3, 132.7, 132.0, 128.6, 124.0, 123.8, 111.6, 52.1, 21.5, 0.2. IR (KBr): 3070, 3034, 2954, 2919, 2861, 1718, 1533 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{18}O_3Si$, 262.1025; found, 262.1049.

Methyl 7-Bromo-3-(trimethylsilyl)benzofuran-2-carboxylate (**2m**). 42% yield (274 mg); hexane/ethyl acetate = 5:1; R_f = 0.6; white solid; mp 91.2−93.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.80 (1H, d, J = 7.9 Hz), 7.59 (1H, d, J = 7.9 Hz), 7.15 (1H, t, J = 7.9 Hz), 3.99 (3H, s), 0.47 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 160.3, 152.5, 149.8, 133.0, 129.9, 125.1, 124.4, 123.3, 104.6, 52.3, 0.1. IR (KBr): 3068, 2997, 2951, 2907, 2842, 1720,

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1538 (cm^{-1}). HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{13}H_{15}O_3SiBr$, 325.9974; found, 325.9985.

*Methyl 7-Methoxy-3-(trimethylsilyl)benzofuran-2-carboxylate (**2n**).* 61% yield (341 mg); hexane/ethyl acetate = 5:1; R_f = 0.4; yellow solid; mp 74.0−75.7 °C. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43 (1H, d, *J* = 8.1 Hz), 7.19 (1H, t, *J* = 8.1 Hz), 6.91 (1H, d, *J* = 8.1 Hz), 4.01 (3H, s), 3.97 (3H, s), 0.47 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 160.5, 149.4, 145.9, 144.9, 133.5, 124.5, 123.7, 116.0, 108.2, 55.9, 52.1, 0.1. IR (KBr): 3104, 3027, 3006, 2981, 2947, 2898, 2837, 1721, 1542 (cm^{-1}). HRMS (EI-TOF) *m/z*: $[M]^+$ calcd for $C_{14}H_{18}O_4Si$, 278.0969; found, 278.0994.

*Methyl 4-Chloro-3-(trimethylsilyl)benzofuran-2-carboxylate (**2o**).* 42% yield (236 mg); hexane/ethyl acetate = 5:1; R_f = 0.5; pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.48 (1H, d, *J* = 7.2 Hz), 7.34−7.29 (2H, m), 3.96 (3H, s), 0.47 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 161.3, 155.6, 150.7, 130.6, 128.3, 127.1, 124.8, 120.2, 110.5, 52.7, 1.7. IR (neat): 3024, 2952, 2928, 2901, 2855, 1736, 1530 (cm^{-1}). HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{13}H_{15}O_3SiCl$, 282.0479; found, 282.0458.

*Methyl 3-(Trimethylsilyl)naphtho[2,1-b]furan-2-carboxylate (**2p**).* 29% yield (174 mg); hexane/ethyl acetate = 5:1; R_f = 0.8; white solid; mp 80.2−82.6 °C. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.37 (1H, d, *J* = 7.8 Hz), 7.96 (1H, d, *J* = 7.8 Hz), 7.86 (1H, d, *J* = 7.8 Hz), 7.71 (1H, d, *J* = 7.8 Hz), 7.62 (1H, t, *J* = 7.8 Hz), 7.52 (1H, t, *J* = 7.8 Hz), 4.01 (3H, s), 0.57 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 161.1, 153.4, 149.3, 131.2, 129.3, 129.10, 129.05, 127.0, 126.1, 125.9, 124.7, 123.1, 112.5, 52.4, 1.4. IR (KBr): 3055, 2988, 2951, 2926, 2854, 1732, 1531 (cm^{-1}). HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{17}H_{18}O_3Si$, 298.1025; found, 298.1030.

*N,N-Dimethyl-3-(trimethylsilyl)benzofuran-2-carboxamide (**2q**).* 59% yield (307 mg); hexane/ethyl acetate = 5:1; R_f = 0.5; pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.72 (1H, d, *J* = 7.9 Hz), 7.51 (1H, d, *J* = 7.9 Hz), 7.34 (1H, t, *J* = 7.9 Hz), 7.26 (1H, t, *J* = 7.9 Hz), 3.08 (6H, broad, s), 0.39 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 163.3, 154.4, 153.5, 131.7, 125.1, 123.0, 122.8, 115.2, 111.4, 38.3, 35.2, −0.4. IR (neat): 3066, 2953, 2928, 2900, 2856, 1652, 1583, 1444 (cm^{-1}). HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{14}H_{19}NO_2Si$, 261.1185; found, 261.1178.

*N,N-Diethyl-3-(trimethylsilyl)benzofuran-2-carboxamide (**2r**).* 73% yield (422 mg); hexane/ethyl acetate = 5:1; R_f = 0.5; yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.72 (1H, d, *J* = 7.8 Hz), 7.50 (1H, d, *J* = 7.8 Hz), 7.33 (1H, t, *J* = 7.8 Hz), 7.26 (1H, t, *J* = 7.8 Hz), 3.56 (2H, q, *J* = 7.1 Hz), 3.31 (2H, q, *J* = 7.1 Hz), 1.29−1.21 (6H, m), 0.41 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 162.7, 154.3, 154.2, 131.8, 124.9, 122.9, 122.8, 114.8, 111.4, 43.0, 39.8, 14.3, 12.5, −0.4. IR (KBr): 3068, 2963, 2899, 1645, 1428 (cm^{-1}). HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{16}H_{23}NO_2Si$, 289.1498; found, 289.1526.

*Morpholino-4-yl-[3-(trimethylsilyl)benzofuran-2-yl]methanone (**2s**).* 53% yield (322 mg); hexane/ethyl acetate = 3:2; R_f = 0.6; pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.71 (1H, d, *J* = 7.6 Hz), 7.48 (1H, d, *J* = 7.6 Hz), 7.32 (1H, t, *J* = 7.6 Hz), 7.24 (1H, t, *J* = 7.6 Hz), 3.78−3.75 (4H, m), 3.65−3.63 (2H, m), 3.47−3.45 (2H, m), 0.40 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 161.8, 154.2, 152.8, 131.5, 125.3, 123.1, 122.9, 116.6, 111.4, 66.9, 66.6, 47.3, 42.6, −0.3. IR (neat): 3067, 2961, 2899, 2855, 1647, 1430 (cm^{-1}). HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{16}H_{21}NO_3Si$, 303.1291; found, 303.1277.

*Methyl 3-(Ethyldimethylsilyl)benzofuran-2-carboxylate (**2t**).* 60% yield (313 mg); hexane/ethyl acetate = 5:1; R_f = 0.3; colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.87 (1H, d, *J* = 7.6 Hz), 7.60 (1H, d, *J* = 7.6 Hz), 7.43 (1H, t, *J* = 7.6 Hz), 7.28 (1H, t, *J* = 7.6 Hz), 3.99 (3H, s), 1.01−0.96 (5H, m), 0.47 (6H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 160.6, 155.2, 149.3, 132.2, 127.1, 124.3, 123.5, 123.2, 112.1, 52.2, 7.49, 7.47, −2.1. IR (neat): 3088, 3051, 3030, 2953, 2910, 2874, 2844, 1724, 1535 (cm^{-1}). HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{14}H_{18}O_3Si$, 262.1025; found, 262.1052.

*Methyl 3-[(Chloromethyl)dimethylsilyl]benzofuran-2-carboxylate (**2u**).* 52% yield (292 mg); hexane/ethyl acetate = 5:1; R_f = 0.3; yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.84 (1H, d, *J* = 7.9 Hz), 7.61 (1H, d, *J* = 7.9 Hz), 7.46 (1H, t, *J* = 7.9 Hz), 7.31 (1H, t, *J* = 7.9 Hz), 4.01 (3H, s), 3.25 (2H, s), 0.62 (6H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 160.5, 155.3, 149.8, 131.6, 127.5, 124.0, 123.6, 121.1, 112.2, 52.5, 30.2, −2.9. IR (neat): 3049, 3031, 2955, 2926, 2849, 1719, 1540 (cm^{-1}). HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{13}H_{15}O_3SiCl$, 282.0479; found, 282.0505.

*Methyl 3-(Triethylsilyl)benzofuran-2-carboxylate (**2v**).* 55% yield (317 mg); hexane/ethyl acetate = 5:1; R_f = 0.5; yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.74 (1H, d, *J* = 7.8 Hz), 7.49 (1H, d, *J* = 7.8 Hz), 7.31 (1H, t, *J* = 7.8 Hz), 7.16 (1H, t, *J* = 7.8 Hz), 3.87 (3H, s), 0.95−0.85 (15H, m). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 160.7, 155.2, 149.5, 132.6, 127.1, 124.4, 123.2, 121.7, 112.0, 52.2, 7.6, 3.8. IR (neat): 3051, 3031, 2954, 2910, 2875, 2733, 1724, 1533 (cm^{-1}). HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{16}H_{22}O_3Si$, 290.1338; found, 290.1327.

*Dimethyl 3-(Trimethylsilyl)benzofuran-2-yl Phosphonate (**7**).* 35% yield (210 mg); hexane/ethyl acetate = 3:2; R_f = 0.3; colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.84 (1H, d, *J* = 7.7 Hz), 7.57 (1H, d, *J* = 7.7 Hz), 7.38 (1H, t, *J* = 7.7 Hz), 7.26 (1H, t, *J* = 7.7 Hz), 3.83 (6H, d, $^3J_{HP}$ = 11.5 Hz), 0.52 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 156.4 (d, $^3J_{CP}$ = 11.6 Hz), 148.8 (d, $^1J_{CP}$ = 238.3 Hz), 131.3 (d, $^3J_{CP}$ = 14.9 Hz), 128.0 (d, $^2J_{CP}$ = 31.4 Hz), 126.4, 123.7, 123.0, 111.7, 53.0 (d, $^2J_{CP}$ = 6.0 Hz), 0.6. $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ (ppm): 8.37. IR (neat): 3066, 2954, 2926, 2853, 1249, 1033 (cm^{-1}). HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{13}H_{19}O_4SiP$, 298.0790; found, 298.0788.

*N,N,3-Tris(trimethylsilyl)-2-benzofuranmethanamine (**9**).* 30% yield (216 mg); hexane/ethyl acetate = 5:1; R_f = 0.6; yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.24 (1H, d, *J* = 8.0 Hz), 7.19 (1H, t, *J* = 8.0 Hz), 6.94 (1H, t, *J* = 8.0 Hz), 6.90 (1H, d, *J* = 8.0 Hz), 3.92 (2H, s), 0.24 (9H, s), 0.19 (18H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 164.7, 158.7, 128.0, 125.4, 124.7, 122.3, 121.3, 109.3, 33.3, 3.1, −0.7. IR (neat): 3078, 3037, 2954, 2900, 1644, 1606, 1479, 1463 (cm^{-1}). HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{18}H_{33}NOSi_3$, 363.1870; found, 363.1857.

*1-Methyl-2-(trimethylsilyl)carbonyl 1H-Indole (**11**).* 46% yield (213 mg); hexane/ethyl acetate = 5:1; R_f = 0.5; yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.76 (1H, d, *J* = 7.3 Hz), 7.43−7.36 (3H, m), 7.18 (1H, t, *J* = 7.3 Hz), 4.07 (3H, s), 0.46 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 226.8, 139.3, 139.2, 126.2, 126.1, 123.0, 120.5, 114.4, 110.3, 32.0, −1.3. IR (neat): 3126, 3059, 2956, 2900, 1613, 1580 (cm^{-1}). HRMS (EI-TOF) *m/z*: $[M]^+$ calcd for $C_{13}H_{17}NOSi$, 231.1074; found, 231.1091.

*1-(1,1-Dimethylethyl) 2-Methyl 3-(Trimethylsilyl)-1H-indole-1,2-dicarboxylate (**12**).* 55% yield (379 mg); hexane/ethyl acetate = 5:1; R_f = 0.7; white solid; mp 62.6−64.0 °C. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.16 (1H, d, *J* = 7.9 Hz), 7.73 (1H, d, *J* = 7.9 Hz), 7.37 (1H, t, *J* = 7.9 Hz), 7.26 (1H, t, *J* = 7.9 Hz), 3.93 (3H, s), 1.64 (9H, s), 0.40 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 164.8, 148.9, 136.2, 135.5, 132.8, 125.2, 122.9, 122.6, 117.6, 115.2, 84.7, 52.2, 27.8, −0.2. IR (KBr): 3096, 3074, 3050, 3006, 2981, 2959, 2903, 1743, 1732, 1524 (cm^{-1}). HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{18}H_{25}NO_4Si$, 347.1553; found, 347.1580.

*3-Iodo-N,N-dimethylbenzofuran-2-carboxamide (**13**).* 65% yield (205 mg); hexane/ethyl acetate = 5:1; R_f = 0.3; yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.41−7.32 (3H, m), 7.26 (1H, t, *J* = 7.2 Hz), 3.08 (3H, s), 3.07 (3H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 160.7, 153.5, 147.9, 130.2, 127.0, 123.9, 122.3, 111.6, 68.0, 38.3, 35.4. IR (neat): 3061, 3016, 2929, 2865, 1652, 1444 (cm^{-1}). HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{11}H_{10}NO_2I$, 314.9757; found, 314.9751.

*2-(Diethylaminocarbonyl)-3-benzofuranboronic Acid (**14**).* 96% yield (250 mg); hexane/ethyl acetate = 5:1; R_f = 0.2; white solid; mp 123.7−124.4 °C. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.28 (2H, s), 8.27 (1H, d, *J* = 7.2 Hz), 7.49 (1H, d, *J* = 7.2 Hz), 7.41 (1H, t, *J* = 7.2 Hz), 7.33 (1H, t, *J* = 7.2 Hz), 3.77−3.48 (4H, m), 1.51−1.10 (6H, m). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 162.8, 153.9, 153.7, 130.9, 126.6, 125.2, 123.8, 110.9, 44.1, 42.5, 14.6, 12.5. IR (neat): 3303, 2984, 2943, 2909, 2880, 2830, 2764, 1593, 1560, 1479, 1452,

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1313, 1303 (cm^{-1}). HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{13}H_{16}BNO_4$, 261.1172; found, 261.1155.

*N,N-Diethyl-3-phenylbenzofuran-2-carboxamide (**15**).* 72% yield (88 mg); hexane/ethyl acetate = 5:1; R_f = 0.3; yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.75 (1H, d, *J* = 7.4 Hz), 7.62 (2H, d, *J* = 7.4 Hz), 7.56 (1H, d, *J* = 7.4 Hz), 7.47 (2H, t, *J* = 7.4 Hz), 7.41 (1H, t, *J* = 7.4 Hz), 7.39 (1H, t, *J* = 7.4 Hz), 7.32 (1H, t, *J* = 7.4 Hz), 3.53 (2H, q, *J* = 7.1 Hz), 3.17 (2H, q, *J* = 7.1 Hz), 1.20 (3H, t, *J* = 7.1 Hz), 0.92 (3H, t, *J* = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 161.9, 154.2, 144.7, 131.0, 128.81, 128.77, 128.0, 127.0, 125.7, 123.4, 120.9, 120.5, 111.9, 43.0, 39.5, 14.0, 12.4. IR (neat): 3060, 2976, 2935, 2874, 1639, 1446 (cm^{-1}). HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{19}H_{19}NO_2$, 293.1416; found, 293.1438.

*4,5-Di(benzofuran-2-yl)-2,2,4,5,7,7-hexamethyl-3,6-dioxa-2,7-disilaoctane (**16**).* 32% yield (151 mg); meso/dl = 1:1; hexane/ethyl acetate = 5:1; R_f = 0.6; colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66 (1H, d, *J* = 7.6 Hz), 7.58−7.54 (2H, m), 7.37−7.30 (2H, m), 7.26−7.25 (3H, m), 6.73 (1H, s), 6.53 (1H, s), 1.89 (3H, s), 1.77 (3H, s), 0.21 (9H, s), 0.08 (9H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 161.6, 160.9, 154.6, 154.3, 128.5, 128.4, 123.4, 123.3, 122.4, 122.2, 120.7, 120.6, 111.0, 110.9, 104.3, 104.2, 79.9, 79.6, 22.8, 22.3, 2.0, 1.8. IR (neat): 3116, 3085, 3066, 3035, 2993, 2956, 2899, 2862, 1580, 1455 (cm^{-1}). HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{26}H_{34}O_4Si_2$, 466.1996; found, 466.1948.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01995.

Copies of ^1H NMR spectrum for **5a**; ^1H NMR spectra and $^{13}C\{^1H\}$ NMR spectra for **1o**, **2a**−**2v**, **3a**, **4a**, **7**, **9**, and **11**−**16**; ^{19}F NMR spectrum for **2j**; $^{31}P\{^1H\}$ NMR spectrum for **7**; and DEPT-135 spectrum for **9** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Hirofumi Maekawa − *Department of Materials Science and Technology, Nagaoka University of Technology, Nagaoka, Niigata 940-2188, Japan;* orcid.org/0000-0002-8192-8518; Email: maekawa@vos.nagaokaut.ac.jp

Authors

Suhua Zheng − *Department of Materials Science and Technology, Nagaoka University of Technology, Nagaoka, Niigata 940-2188, Japan*

Tianyuan Zhang − *Department of Materials Science and Technology, Nagaoka University of Technology, Nagaoka, Niigata 940-2188, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c01995

Notes

The authors declare no competing financial interest.

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(15) Characterization data of methyl 4-chlorobenzofuran-2-carboxylate (**1o**): 55% yield (231 mg); hexane/ethyl acetate = 5:1; R_f = 0.3; white solid; mp 78.5−79.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.56 (1H, s), 7.44 (1H, d, J = 8.0 Hz), 7.32 (1H, t, J = 8.0 Hz), 7.22 (1H, d, J = 8.0 Hz), 3.94 (3H, s). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 159.4, 155.7, 145.7, 128.1, 127.7, 126.6, 123.6, 112.2, 110.8, 52.5. IR (KBr): 3131, 3097, 3079, 3040, 2964, 2927, 2852, 1719, 1575 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{10}H_7O_3Cl$, 210.0084; found, 210.0087.

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Magnesium-Promoted Reductive Carboxylation of Aryl Vinyl Ketones: Synthesis of γ-Keto Carboxylic Acids

Suhua Zheng, Tianyuan Zhang, and Hirofumi Maekawa*

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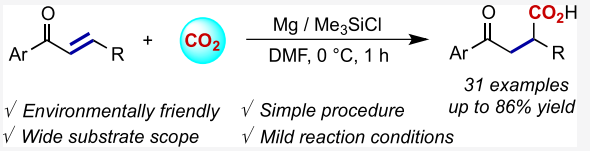
ABSTRACT: Direct reductive carboxylation of easily prepared aryl vinyl ketones under the atmosphere of carbon dioxide led to the selective formation of γ-keto carboxylic acids in 38−86% yields. The reaction is characterized by the carbon−carbon bond formation of carbon dioxide at the β-position of enone, with the use of magnesium turnings that can be easily handled as the reducing agent and the eco-friendly reaction conditions such as no pressuring, no lower or higher reaction temperature, and short reaction time. This protocol showed a wide substrate scope and provided a useful and convenient alternative to access biologically important γ-keto carboxylic acids.



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INTRODUCTION

Derivatives of γ-keto carboxylic acids are one kind of the key intermediates in organic synthesis[1] and are also widely found in natural products as ingredients sometimes with excellent biological and medicinal properties (Scheme 1a).[2] Owing to their prominence, numerous strategies for the efficient synthesis of γ-keto carboxylic acids have been developed to date in the field of both synthetic chemistry and medicinal chemistry.[3] For example, Cossio and co-workers reported a two-stage protocol to synthesize γ-keto carboxylic acid from enones through Michael addition and the subsequent Nef oxidation in 2010 (Scheme 1b).[3b] Besides, carbon dioxide has been studied as a less harmful and potential C1 source for a long time,[4] and the preparation of γ-keto carboxylic acids has also been reported through direct carboxylation.[5] However, the synthetic methods of γ-keto carboxylic acids were only limited to electrochemical carboxylation reactions and photo-induced carboxylation reactions to the best of our knowledge. As a recent example, Wang and Zhang's group disclosed the carboxylation of chalcone derivatives through a photo-electrochemical method using carbon dioxide as the carbon source in 2020 (Scheme 1c).[5a] In general, most of these preparative methods for γ-keto carboxylic acids are useful, while they are also suffering from some drawbacks, which include the requirement for special equipment and the limitation on substrate scope. Therefore, a more practical and facile protocol to access γ-keto carboxylic acids from easily prepared starting materials under mild reaction conditions is still required and remains one of the challenging research themes.

Magnesium is a promising reducing agent, which is abundant in the earth, eco-friendly, and less harmful, and we have reported many types of reductive coupling reactions by magnesium metal.[6] Carboxylation of aromatic conjugated compounds using carbon dioxide through magnesium-promoted reduction was studied by other groups and us.[7] In this study, magnesium-promoted reductive carboxylation of easily available aryl vinyl ketones in the presence of carbon dioxide under mild reaction conditions was carried out to give a variety of γ-keto carboxylic acids with a wide substrate scope in one step (Scheme 1d).

RESULTS AND DISCUSSION

We commenced our investigations on carboxylation of aryl vinyl ketone **1a** in the presence of magnesium turnings and chlorotrimethylsilane in *N*,*N*-dimethylformamide (DMF) at 25 °C in a carbon dioxide atmosphere, to give the desired carboxylic acid **2a** in 53% yield (Table 1, entry 1). Then, we investigated the temperature effects and found that the optimal reaction temperature was 0 °C (83% yield, entry 2). Encouraged by this result, we next carefully screened several typical organic solvents instead (entries 4−7). Specifically, a reduction in the yield of carboxylic acid **2a** was observed in other amide solvents including *N*-methyl-2-pyrrolidone (NMP) and *N*,*N*-dimethylacetamide (entries 4 and 5), while no reaction occurred in tetrahydrofuran (THF) and acetonitrile (entries 6 and 7). On the other hand, the investigation of the substrate concentration suggested that the appropriate solvent concentration was 0.14 M (1 mmol/7 mL), and the other conditions could not enhance the yields (entries 8 and 9). In addition, we also studied factors including equivalents of reagents, reaction time, and additive effects, and no improvement in yields was observed (Tables S1−S4, see the Supporting Information for details).

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Scheme 1. Backgrounds on γ-Keto Carboxylic Acid Motifs and the Synthetic Strategies

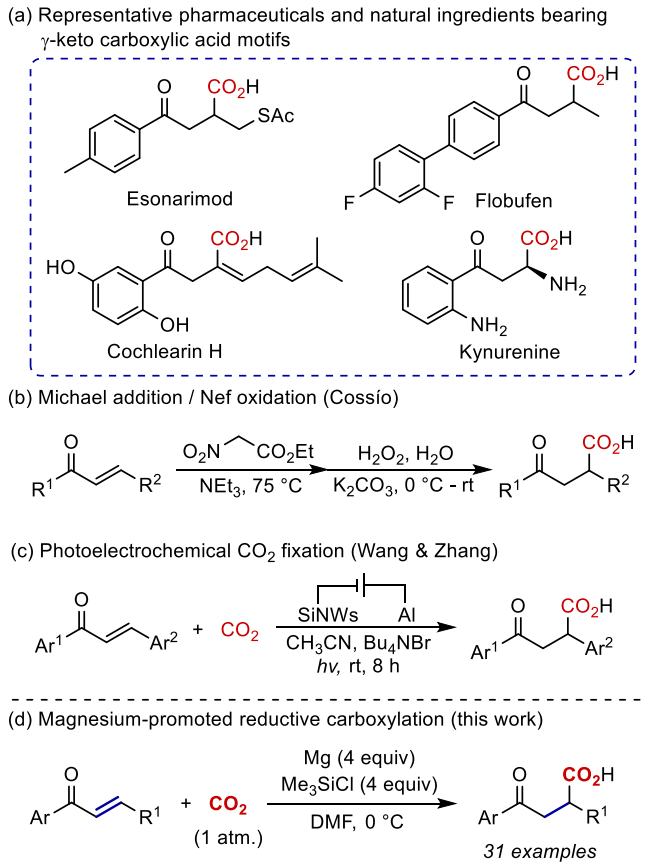
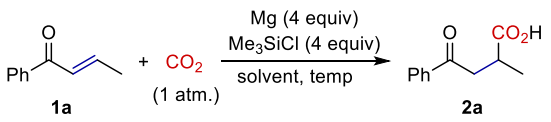


Table 1. Optimization of the Reaction Conditions[a]



entry	temp (°C)	solvent	conc (M)/solvent volume	yield of 2a (%)
1	25	DMF	0.14 M/7 mL	53
2	0	DMF	0.14 M/7 mL	**83**
3	−10	DMF	0.14 M/7 mL	71
4	0	NMP	0.14 M/7 mL	52
5	0	DMA	0.14 M/7 mL	69
6	0	THF	0.14 M/7 mL	no reaction
7	0	CH_3CN	0.14 M/7 mL	no reaction
8	0	DMF	0.25 M/4 mL	63
9	0	DMF	0.10 M/10 mL	70

[a]Reaction conditions: **1a** (1 mmol), Me_3SiCl (4 equiv), Mg (4 equiv), CO_2 balloon (1 atm), solvent (0.10−0.25 M, 4−10 mL), 1 h.

We next explored the substrate scope concerning various aryl vinyl ketone derivatives **1** under the optimal reaction conditions, and the results are summarized in Scheme 2. First, a series of aryl vinyl ketones with various electron-deficient and electron-donating substituents on the benzene ring were investigated (Scheme 2a). In general, an electron-donating group, methyl, methoxy, or ethoxy group at ortho-, meta-, and para-positions worked well to give the corresponding carboxylic acids **2b**, **2c**, **2d**, **2h**, **2i**, and **2k** in 64−86% yields. Besides, both slightly electron-withdrawing halogen atoms and strong electron-withdrawing trifluoromethyl groups were tolerated to afford **2e**, **2f**, **2g**, **2m**, **2n**, **2o**, and **2p** in 44−81% yields. To isolate the desired products efficiently, the carboxylic acids **2** were transformed into the corresponding esters **3** under the typical esterification conditions, and the esters **3a**, **3j**, **3l**, and **3n** were obtained in 79, 67, 71, and 49% yields, respectively. Second, the carboxylation of multi-substituted aryl vinyl ketones **1** also proceeded smoothly to furnish the desired products, albeit in slightly lower yields (Scheme 2b). For example, 2,3-dimethoxy- and 3,4-dimethoxyphenyl derivatives gave **3q** and **2r** in 53 and 52% yields, respectively, while 3,5-difluoro- and 2,6-dichlorophenyl derivatives afforded the corresponding carboxylic acids **2s** and **2t** in 42 and 38% yields, respectively. Pleasingly, the reactions of trisubstituted substrates worked well to deliver **2u** and **2v** in 61 and 55% yields, respectively. To our delight, the R^1 group of the starting materials **1** could be replaced with ethyl group **2w** and phenyl group **2x**, and the reaction was also compatible with terminal alkenes to afford **2y** in 78% yield (Scheme 2c). Unfortunately, further investigation of the R^1 substituents such as bulky iso-propyl group, tert-butyl group, and dimethylamino group was not successful (Table S6, see the Supporting Information for details), and a compound with dimethyl groups on the β-carbon atom gave a trace of **2z** due to the crowded structure. This protocol was also compatible with aromatic rings such as naphthyl, 2-furyl, and 2-thienyl rings (Scheme 2d). Moreover, the desired carboxylic acids **2aa**−**2ae** and ester **3af** were obtained in satisfactory yields. Some γ-keto carboxylic acids or their esters are used as pharmaceutical drugs, for instance, the product **3l** prepared by our method is a derivative of metbufen, a non-steroidal anti-inflammatory drug.[8] The reaction of alkyl vinyl ketone **1ag** did not proceed under our optimized reaction conditions. Finally, a gram scale synthesis of **2a** was carried out and **2a** was obtained in a satisfactory 76% yield.

To demonstrate the utility of γ-keto carboxylic acids **2** as effective synthetic intermediates, we conducted several cyclization reactions of **2a** to afford cyclic compounds **4**, **5**, and **6** in good yields (Scheme 3). Treatment of **2a** with acetic anhydride at 80 °C for 5 h led to the formation of lactone **4** in 75% yield.[9] Cyclization of carboxylic acid **2a** in the presence of a hydrazine monohydrate gave a compound **5**, the key intermediate for an active pharmaceutical ingredient Minozac,[10] in excellent yield. Similarly, the cyclization of carboxylic acid **2a** with phenylhydrazine at the same reaction conditions also provided a biologically interesting compound **6** in 86% yield.

We next measured the reduction potentials of compounds **1a**, **2a**, together with chlorotrimethylsilane in DMF, to analyze the reaction mechanism (Table S5, see the Supporting Information for details). The reduction peaks (E_{red}) of **1a** and **2a** were recorded at −1.66 and −2.30 V, respectively, while chlorotrimethylsilane showed no significant peak. From this measurement result, the starting material **1a** can be easily reduced by magnesium[11] to initiate the reaction, and a plausible reaction mechanism is proposed in Scheme 4. Initially, a single electron transfer from magnesium metal to aryl vinyl ketone **1a** will give an anion radical species **A**, which reacts with chlorotrimethylsilane and receives the second electron from magnesium immediately to yield an anionic species **B**. Next, **B** attacks a carbon dioxide molecule to afford an intermediate **C**. The intermediate anion **C** will be

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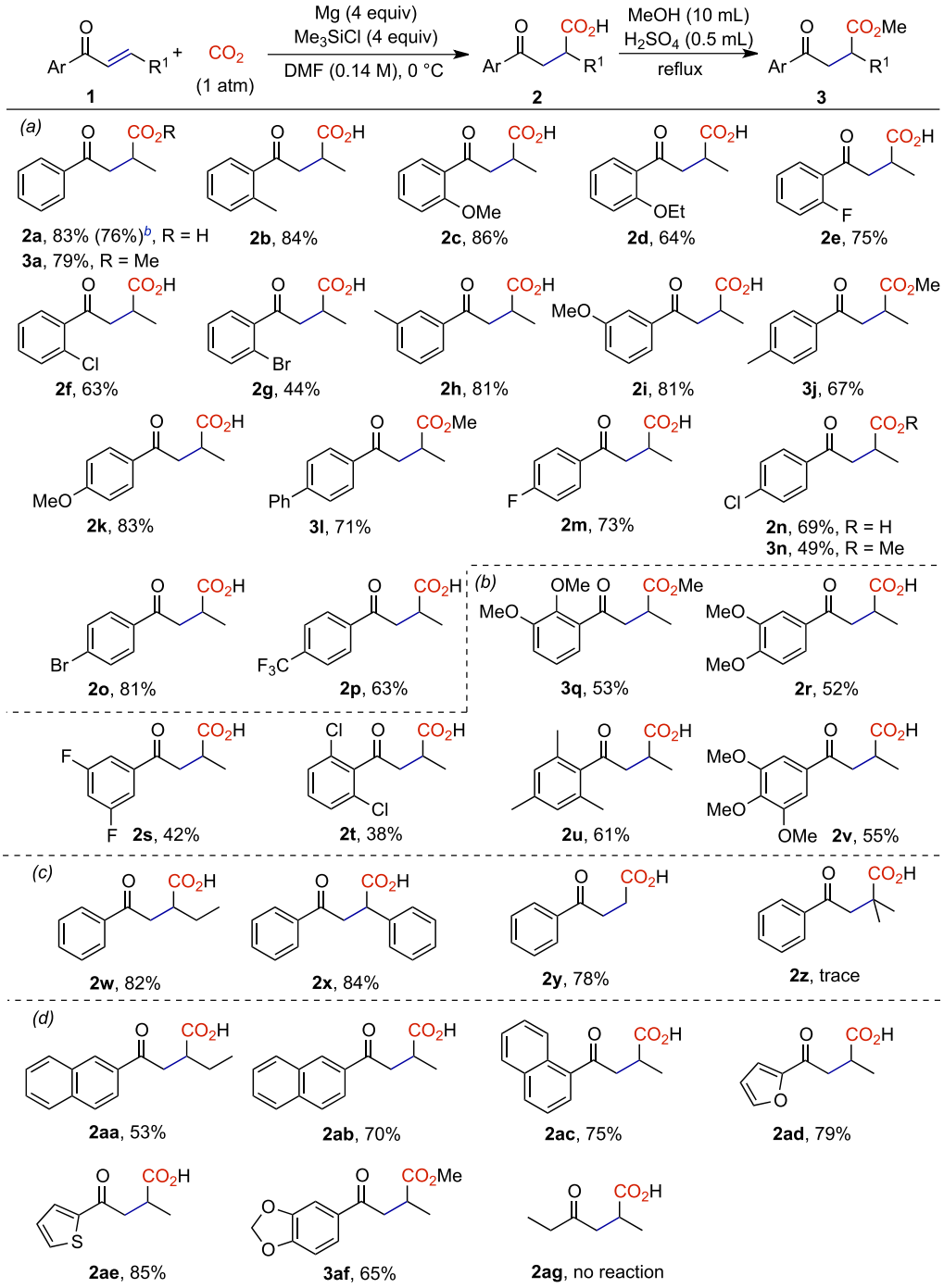
Scheme 2. Reductive Carboxylation of Aryl Vinyl Ketones 1: Scope[a]



[a]Reaction conditions: (1) **1** (1 mmol), Me_3SiCl (4 equiv), Mg (4 equiv), DMF (0.14 M, 7 mL), 0 °C, 1 h, CO_2 balloon (1 atm). (2) Crude product **2** was used without purification, MeOH (0.1 M, 10 mL), conc H_2SO_4 (0.5 mL), reflux, 1 h. [b]Reaction on a 7 mmol (1.020 g) scale.

coordinated with a trimethylsilyl cation or magnesium cation in situ, and finally, the product **2a** will be generated at the quenching stage after the hydrolysis of the anion **C**. Therefore, the reduction of **2a** did not occur and the selective carboxylation might be achieved in high yields.

CONCLUSIONS

In this study, a convenient method for the preparation of γ-keto carboxylic acids from easily prepared aryl vinyl ketones and carbon dioxide as a carbon source was developed with the aid of an eco-friendly magnesium metal as a reducing agent. A variety of γ-keto carboxylic acids with a wide substrate scope were synthesized in good to excellent yields under mild reaction conditions. Further study on efficient carboxylation under mild reaction conditions using carbon dioxide is underway in our laboratory.

EXPERIMENTAL SECTION

General Information. All solvents were distilled by standard techniques and pre-treated with CO_2 bubbling for 0.5 h prior to use. Chlorotrimethylsilane was simply distilled before use. All starting

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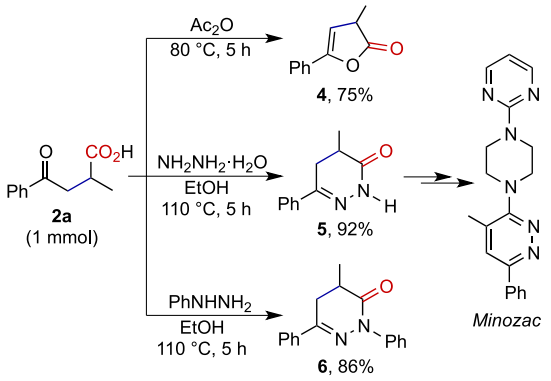
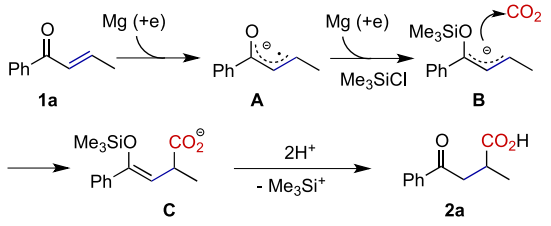
Scheme 3. Some Reactions of Carboxylic Acid 2a and Synthesis of a Key Intermediate for Minozac



Scheme 4. Plausible Reaction Mechanism



materials except **1d**, **1q**, **1s**, **1t**, **1v**, and **1aa** are known compounds, and they were synthesized according to the procedures from the literature.[12] ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a JEOL JNM AL-400 (400 MHz) spectrometer at 20 °C. Proton chemical shifts were expressed in parts per million (ppm) downfield from the residual signal of chloroform (7.26 ppm). Carbon chemical shifts were referenced to the carbon signal of the solvent at 77.0 ppm ($CDCl_3$). Fluorine chemical shifts were referenced to the external fluorine signal of trifluoroacetic acid at −76.50 ppm. Infrared (IR) spectra were recorded on a JASCO 470Plus Fourier transform infrared spectrometer. Mass spectra were recorded on a JEOL JMS-T200GC (TOF) spectrometer in electron impact (EI) mode. Melting point determinations were performed by using a Yanaco MP-J3 instrument and were uncorrected. Cyclic voltammograms were measured with an ALS model 600.

(E)-1-(2-Ethoxyphenyl)but-2-en-1-one (**1d**). 69% yield (1.31 g, 10 mmol scale), hexane/ethyl acetate = 5:1, R_f = 0.7. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49 (1H, d, J = 7.8 Hz), 7.38 (1H, t, J = 7.8 Hz), 6.96 (1H, t, J = 7.8 Hz), 6.91 (1H, d, J = 7.8 Hz), 6.84 (1H, qd, J = 15.4, 6.6 Hz), 6.74 (1H, d, J = 15.4 Hz), 4.07 (2H, q, J = 7.0 Hz), 1.91 (3H, d, J = 6.6 Hz), 1.39 (3H, t, J = 7.0 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 193.4, 157.2, 143.2, 132.4, 132.3, 130.0, 129.2, 120.4, 112.4, 64.1, 18.2, 14.6. IR (neat): 3072, 3034, 2980, 2937, 2912, 2888, 1654, 1618, 1597 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{12}H_{14}O_2$, 190.0988; found, 190.1000.

(E)-1-(2,3-Dimethoxyphenyl)but-2-en-1-one (**1q**). 82% yield (1.69 g, 10 mmol scale), hexane/ethyl acetate = 5:1, R_f = 0.7. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.06 (1H, t, J = 7.8 Hz), 6.98 (1H, d, J = 7.8 Hz), 6.97 (1H, d, J = 7.8 Hz), 6.79 (1H, qd, J = 15.6, 6.8 Hz), 6.59 (1H, d, J = 15.6 Hz), 3.86 (3H, s), 3.79 (3H, s), 1.91 (3H, d, J = 6.8 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 194.0, 152.8, 147.4, 145.6, 134.4, 132.3, 124.0, 120.6, 114.6, 61.7, 55.9, 18.3. IR (neat): 3285, 3074, 3000, 2969, 2939, 2919, 2875, 2838, 1653, 1619, 1579 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{12}H_{14}O_3$, 206.0938; found, 206.0950.

(E)-1-(3,5-Difluorophenyl)but-2-en-1-one (**1s**). 59% yield (1.07 g, 10 mmol scale), hexane/ethyl acetate = 5:1, R_f = 0.7. Pale yellow solid, mp 37.2−38.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36−7.30 (2H, m), 7.04 (1H, qd, J = 15.4, 6.8 Hz), 6.93−6.87 (1H, m), 6.74 (1H, d, J = 15.4 Hz), 1.93 (3H, d, J = 6.8 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 187.4, 162.8 (dd, $^1J_{CF}$ = 250.4, 12.3 Hz), 146.6, 140.7 (t, $^3J_{CF}$ = 8.2 Hz), 126.3, 111.0 (dd, $^2J_{CF}$ = 19.0, 7.4 Hz), 107.5 (t, $^2J_{CF}$ = 25.6 Hz), 18.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ (ppm) −82.82 (m). IR (KBr): 3091, 3074, 2991, 2957, 2926, 1676, 1616, 1605 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{10}H_8OF_2$, 182.0538; found, 182.0548.

(E)-1-(2,6-Dichlorophenyl)but-2-en-1-one (**1t**). 56% yield (1.20 g, 10 mmol scale), hexane/ethyl acetate = 5:1, R_f = 0.7. Pale yellow solid, mp 35.2−37.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.27−7.19 (3H, m), 6.53 (1H, qd, J = 15.8, 6.8 Hz), 6.28 (1H, d, J = 15.8 Hz), 1.90 (3H, d, J = 6.8 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 192.6, 149.3, 137.7, 132.0, 131.4, 130.4, 127.9, 18.6. IR (KBr): 3080, 3034, 3017, 2977, 2940, 2912, 1664, 1639, 1586, 1560 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{10}H_8OCl_2$, 213.9947; found, 213.9961.

(E)-1-(3,4,5-Trimethoxyphenyl)but-2-en-1-one (**1v**). 78% yield (1.84 g, 10 mmol scale), hexane/ethyl acetate = 5:1, R_f = 0.7. White solid, mp 66.8−69.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.11 (2H, s), 7.03−6.95 (1H, m), 6.82 (1H, d, J = 15.1 Hz), 3.83 (9H, s), 1.91 (3H, d, J = 6.8 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 188.8, 152.8, 144.5, 142.0, 132.8, 126.7, 105.7, 60.6, 56.0, 18.3. IR (KBr): 3011, 2951, 2937, 2913, 2838, 1667, 1619, 1583 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{16}O_4$, 236.1043; found, 236.1037.

(E)-1-(Naphthalen-2-yl)pent-2-en-1-one (**1aa**). 85% yield (1.76 g, 10 mmol scale), hexane/ethyl acetate = 10:1, R_f = 0.5. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.49 (1H, s), 8.08 (1H, d, J = 7.7 Hz), 7.99 (1H, d, J = 7.7 Hz), 7.93 (1H, d, J = 7.7 Hz), 7.90 (1H, d, J = 7.7 Hz), 7.64−7.55 (2H, m), 7.24 (1H, td, J = 15.5, 6.3 Hz), 7.09 (1H, d, J = 15.5 Hz), 2.46−2.38 (2H, m), 1.22 (3H, t, J = 7.4 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 190.5, 151.0, 135.3, 135.2, 132.4, 129.8, 129.3, 128.3, 128.1, 127.6, 126.5, 124.9, 124.4, 25.8, 12.3. IR (neat): 3059, 2967, 2934, 2874, 1667, 1653, 1616 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{15}H_{14}O$, 210.1039; found, 210.1029.

General Procedure for Reductive Carboxylation of Aryl Vinyl Ketones 1. To an oven-dried flask containing magnesium turnings (4 mmol, 4 equiv) in a CO_2 atmosphere, chlorotrimethylsilane (4 mmol, 4 equiv) in dry DMF (4 mL) was added. The reaction mixture was then stirred for 0.5 h at room temperature. Next, aryl vinyl ketones **1** (1 mmol, 1 equiv) in dry DMF (3 mL) was added dropwise, and the reaction mixture was stirred at 0 °C. After consuming the starting material (usually 1 h, monitored by thin-layer chromatography), the reaction mixture was carefully poured into a beaker containing 50 mL of 0.25 M hydrochloric acid solution. The product was extracted with diethyl ether (30 mL × 3), and the combined organic layer was in sequence washed with water (50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. Finally, the desired carboxylic acid **2** was purified by column chromatography (hexane/ethyl acetate = 1:1). For the synthesis of ester **3**, the crude product obtained in the previous stage was directly subjected to a flask containing methanol (0.1 M, 10 mL) and concentrated sulfuric acid (0.5 mL). The reaction mixture was stirred at reflux for 1 h and then quenched with water (30 mL). The product was extracted with diethyl ether (30 mL × 3), and the combined organic layer was washed with brine (50 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The desired product **3** was purified by column chromatography (hexane/ethyl acetate = 30:1).

2-Methyl-4-oxo-4-phenylbutanoic Acid (**2a**). Known compound.[3e] 83% yield (160 mg) on 1 mmol scale; 76% (1.020 g) on 7 mmol scale, hexane/ethyl acetate = 1:1, R_f = 0.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.97 (2H, d, J = 7.4 Hz), 7.57 (1H, t, J = 7.4 Hz), 7.46 (2H, t, J = 7.4 Hz), 3.48 (1H, dd, J = 17.8, 7.8 Hz), 3.20−3.12 (1H, m), 3.05 (1H, dd, J = 17.8, 5.4 Hz), 1.32 (3H, d, J = 7.3 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 197.8, 181.9, 136.5, 133.3, 128.6, 128.0, 41.7, 34.8, 17.1. LRMS (EI) m/z: 192 $[M]^+$.

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*Methyl 2-Methyl-4-oxo-4-phenylbutanoate (**3a**).* Known compound.[3c] 79% yield (163 mg), hexane/ethyl acetate = 6:1, R_f = 0.7. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.97 (2H, d, J = 7.6 Hz), 7.57 (1H, t, J = 7.6 Hz), 7.46 (2H, t, J = 7.6 Hz), 3.70 (3H, s), 3.49 (1H, dd, J = 17.5, 7.8 Hz), 3.18−3.10 (1H, m), 3.03 (1H, dd, J = 17.5, 5.6 Hz), 1.28 (3H, d, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 198.0, 176.4, 136.7, 133.2, 128.6, 128.0, 51.9, 42.0, 34.9, 17.3. LRMS (EI) m/z: 206 $[M]^+$.

*2-Methyl-4-(2-methylphenyl)-4-oxobutanoic Acid (**2b**).* Known compound.[3g] 84% yield (173 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.68 (1H, d, J = 7.6 Hz), 7.38 (1H, t, J = 7.6 Hz), 7.28−7.23 (2H, m), 3.40 (1H, dd, J = 17.8, 8.0 Hz), 3.19−3.10 (1H, m), 2.97 (1H, dd, J = 17.8, 5.2 Hz), 2.49 (3H, s), 1.31 (3H, d, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 201.8, 182.1, 138.3, 137.3, 132.0, 131.5, 128.5, 125.7, 44.5, 35.0, 21.3, 17.0. LRMS (EI) m/z: 206 $[M]^+$.

*4-(2-Methoxyphenyl)-2-methyl-4-oxobutanoic Acid (**2c**).* 86% yield (191 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. White solid, mp 92.8−94.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.75 (1H, d, J = 7.8 Hz), 7.46 (1H, t, J = 7.8 Hz), 6.99 (1H, t, J = 7.8 Hz), 6.96 (1H, d, J = 7.8 Hz), 3.91 (3H, s), 3.45 (1H, dd, J = 19.6, 9.1 Hz), 3.14−3.08 (2H, m), 1.27 (3H, d, J = 6.6 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 199.7, 182.4, 158.8, 133.8, 130.5, 127.4, 120.6, 111.5, 55.4, 47.1, 35.1, 16.9. IR (KBr): 3304, 3077, 3032, 2981, 2942, 2900, 1704, 1664, 1598 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{12}H_{14}O_4$, 222.0887; found, 222.0899.

*4-(2-Ethoxyphenyl)-2-methyl-4-oxobutanoic Acid (**2d**).* 64% yield (151 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. White solid, mp 135.8−136.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.73 (1H, d, J = 7.8 Hz), 7.43 (1H, t, J = 7.8 Hz), 6.97 (1H, t, J = 7.8 Hz), 6.92 (1H, d, J = 7.8 Hz), 4.13 (2H, q, J = 7.1 Hz), 3.48 (1H, dd, J = 17.9, 7.4 Hz), 3.19−3.06 (2H, m), 1.48 (3H, t, J = 7.1 Hz), 1.27 (3H, d, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 199.9, 182.4, 158.2, 133.7, 130.5, 127.5, 120.5, 112.3, 64.1, 47.3, 35.1, 16.9, 14.7. IR (KBr): 3305, 3077, 3042, 2978, 2934, 2904, 1705, 1662, 1594 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{16}O_4$, 236.1043; found, 236.1047.

*4-(2-Fluorophenyl)-2-methyl-4-oxobutanoic Acid (**2e**).* Known compound.[3g] 75% yield (158 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.02 (1H, bs), 7.87 (1H, t, J = 7.6 Hz), 7.54−7.48 (1H, m), 7.21 (1H, t, J = 7.6 Hz), 7.15−7.10 (1H, m), 3.48−3.41 (1H, m), 3.16−3.04 (2H, m), 1.30 (3H, d, J = 6.8 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 196.1, 182.0, 162.1 (d, $^1J_{CF}$ = 254.0 Hz), 134.7 (d, $^3J_{CF}$ = 9.0 Hz), 130.7, 125.1 (d, $^2J_{CF}$ = 12.0 Hz), 124.5 (d, $^3J_{CF}$ = 3.0 Hz), 116.6 (d, $^2J_{CF}$ = 23.0 Hz), 46.6, 34.8, 17.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ (ppm) −109.01 (m). LRMS (EI) m/z: 210 $[M]^+$.

*4-(2-Chlorophenyl)-2-methyl-4-oxobutanoic Acid (**2f**).* 63% yield (142 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. White solid, mp 85.2−87.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.21 (1H, bs), 7.51 (1H, d, J = 8.0 Hz), 7.41−7.35 (2H, m), 7.31 (1H, t, J = 8.0 Hz), 3.40 (1H, dd, J = 17.8, 7.8 Hz), 3.20−3.11 (1H, m), 3.05 (1H, dd, J = 17.8, 5.5 Hz), 1.31 (3H, d, J = 7.3 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 200.8, 181.8, 138.7, 131.9, 130.9, 130.5, 129.1, 126.9, 45.8, 35.1, 16.8. IR (KBr): 3379, 3074, 3022, 2975, 2940, 2883, 1706, 1699, 1591 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{11}H_{11}O_3Cl$, 226.0391; found, 226.0395.

*4-(2-Bromophenyl)-2-methyl-4-oxobutanoic Acid (**2g**).* 44% yield (119 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. White solid, mp 80.2−81.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.57 (1H, bs), 7.54 (1H, d, J = 7.8 Hz), 7.39 (1H, d, J = 7.8 Hz), 7.31 (1H, t, J = 7.8 Hz), 7.24 (1H, t, J = 7.8 Hz), 3.32 (1H, dd, J = 17.8, 7.8 Hz), 3.15−3.07 (1H, m), 2.98 (1H, dd, J = 17.8, 5.5 Hz), 1.27 (3H, d, J = 7.3 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 201.6, 181.8, 141.0, 133.7, 131.7, 128.7, 127.4, 118.6, 45.5, 35.0, 16.8. IR (KBr): 3381, 3042, 2975, 2939, 2909, 2886, 1712, 1703, 1588 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{11}H_{11}O_3Br$, 269.9886; found, 269.9897.

*2-Methyl-4-(3-methylphenyl)-4-Oxobutanoic Acid (**2h**).* Known compound.[3g] 81% yield (167 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.77 (1H, s), 7.76 (1H, d, J = 8.8 Hz), 7.39−7.33 (2H, m), 3.46 (1H, dd, J = 17.8, 7.6 Hz), 3.20−3.11 (1H, m), 3.05 (1H, dd, J = 17.8, 5.6 Hz), 2.41 (3H, s), 1.32 (3H, d, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 198.0, 181.9, 138.4, 136.5, 134.0, 128.6, 128.5, 125.3, 41.7, 34.8, 21.3, 17.1. LRMS (EI) m/z: 206 $[M]^+$.

*4-(3-Methoxyphenyl)-2-methyl-4-oxobutanoic Acid (**2i**).* Known compound.[3g] 81% yield (180 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.55 (1H, d, J = 7.8 Hz), 7.49 (1H, s), 7.37 (1H, t, J = 7.8 Hz), 7.12 (1H, d, J = 7.8 Hz), 3.85 (3H, s), 3.46 (1H, dd, J = 17.6, 7.7 Hz), 3.19−3.11 (1H, m), 3.05 (1H, dd, J = 17.6, 5.4 Hz), 1.32 (3H, d, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 197.7, 181.7, 159.8, 137.8, 129.6, 120.7, 119.9, 112.1, 55.4, 41.8, 34.8, 17.0. LRMS (EI) m/z: 222 $[M]^+$.

*Methyl 2-Methyl-4-(4-methylphenyl)-4-oxobutanoate (**3j**).* Known compound.[13] 67% yield (147 mg), hexane/ethyl acetate = 6:1, R_f = 0.7. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.84 (2H, d, J = 7.9 Hz), 7.23 (2H, d, J = 7.9 Hz), 3.67 (3H, s), 3.43 (1H, dd, J = 17.5, 7.8 Hz), 3.15−3.06 (1H, m), 2.98 (1H, dd, J = 17.5, 5.6 Hz), 2.38 (3H, s), 1.25 (3H, d, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 197.5, 176.3, 143.8, 134.2, 129.2, 128.0, 51.7, 41.7, 34.8, 21.5, 17.2. LRMS (EI) m/z: 220 $[M]^+$.

*4-(4-Methoxyphenyl)-2-methyl-4-oxobutanoic Acid (**2k**).* Known compound.[3f] 83% yield (184 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.94 (2H, d, J = 8.6 Hz), 6.92 (2H, d, J = 8.6 Hz), 3.86 (3H, s), 3.41 (1H, dd, J = 17.5, 7.6 Hz), 3.16−3.09 (1H, m), 3.01 (1H, dd, J = 17.5, 5.6 Hz), 1.30 (3H, d, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 196.4, 181.9, 163.6, 130.3, 129.6, 127.5, 55.4, 41.3, 34.8, 17.1. LRMS (EI) m/z: 222 $[M]^+$.

*Methyl 4-(biphenyl-4-yl)-2-methyl-4-oxobutanoate (**3l**).* 71% yield (200 mg), hexane/ethyl acetate = 6:1, R_f = 0.7. White solid, mp 87.2−88.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.04 (2H, d, J = 8.4 Hz), 7.69 (2H, d, J = 8.4 Hz), 7.63 (2H, d, J = 7.3 Hz), 7.47 (2H, t, J = 7.3 Hz), 7.40 (1H, t, J = 7.3 Hz), 3.72 (3H, s), 3.52 (1H, dd, J = 17.5, 7.8 Hz), 3.21−3.12 (1H, m), 3.06 (1H, dd, J = 17.5, 5.4 Hz), 1.30 (3H, d, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 197.6, 176.4, 145.9, 139.8, 135.4, 128.9, 128.6, 128.2, 127.23, 127.22, 51.9, 42.0, 34.9, 17.3. IR (KBr): 3439, 3339, 3084, 3054, 3028, 2984, 2951, 2912, 2878, 2846, 1731, 1679, 1605 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{18}H_{18}O_3$, 282.1251; found, 282.1258.

*4-(4-Fluorophenyl)-2-methyl-4-oxobutanoic Acid (**2m**).* Known compound.[3f] 73% yield (153 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 11.06 (1H, bs), 7.99 (2H, dd, J = 8.6, 5.5 Hz), 7.12 (2H, dd, J_1 = J_2 = 8.6 Hz), 3.44 (1H, dd, J = 17.8, 8.0 Hz), 3.18−3.09 (1H, m), 3.00 (1H, dd, J = 17.8, 5.2 Hz), 1.31 (3H, d, J = 7.3 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 196.2, 182.1, 165.8 (d, $^1J_{CF}$ = 255.0 Hz), 132.9 (d, $^4J_{CF}$ = 4.0 Hz), 130.7 (d, $^3J_{CF}$ = 9.0 Hz), 115.7 (d, $^2J_{CF}$ = 22.0 Hz), 41.6, 34.8, 17.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ (ppm) −104.99 (m). LRMS (EI) m/z: 210 $[M]^+$.

*4-(4-Chlorophenyl)-2-methyl-4-oxobutanoic Acid (**2n**).* Known compound.[3f] 69% yield (156 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.90 (2H, d, J = 8.3 Hz), 7.43 (2H, d, J = 8.3 Hz), 3.44 (1H, dd, J = 17.8, 8.0 Hz), 3.19−3.10 (1H, m), 3.00 (1H, dd, J = 17.8, 5.4 Hz), 1.32 (3H, d, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 196.6, 181.6, 139.8, 134.8, 129.4, 128.9, 41.6, 34.7, 17.1. LRMS (EI) m/z: 226 $[M]^+$.

*Methyl 4-(4-Chlorophenyl)-2-methyl-4-oxobutanoate (**3n**).* Known compound.[14] 49% yield (118 mg), hexane/ethyl acetate = 6:1, R_f = 0.7. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.85 (2H, d, J = 8.5 Hz), 7.38 (2H, d, J = 8.5 Hz), 3.64 (3H, s), 3.40 (1H, dd, J = 17.7, 8.0 Hz), 3.12−3.03 (1H, m), 2.92 (1H, dd, J = 17.7, 5.4 Hz), 1.23 (3H, d, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 196.8, 176.2, 139.6, 135.0, 129.4, 128.9, 51.9, 41.9, 34.8, 17.2. LRMS (EI) m/z: 240 $[M]^+$.

*4-(4-Bromophenyl)-2-methyl-4-oxobutanoic Acid (**2o**).* Known compound.[3f] 81% yield (219 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.81 (2H, d, J = 8.4 Hz), 7.59 (2H, d, J = 8.4 Hz), 3.43 (1H, dd, J = 17.8, 7.8 Hz), 3.18−3.10

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(1H, m), 2.99 (1H, dd, J = 17.8, 5.4 Hz), 1.31 (3H, d, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm): 196.8, 181.8, 135.2, 131.9, 129.5, 128.5, 41.6, 34.8, 17.0. LRMS (EI) m/z: 270 $[M]^+$.

*2-Methyl-4-oxo-4-(4-trifluoromethylphenyl)butanoic Acid (**2p**).* Known compound.[3g] 63% yield (164 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.06 (2H, d, J = 8.2 Hz), 7.73 (2H, d, J = 8.2 Hz), 3.50 (1H, dd, J = 17.8, 8.0 Hz), 3.22−3.13 (1H, m), 3.05 (1H, dd, J = 17.8, 5.2 Hz), 1.34 (3H, d, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 196.9, 181.7, 139.2, 134.6 (q, $^2J_{CF}$ = 32.0 Hz), 128.4, 125.7 (d, $^3J_{CF}$ = 3.0 Hz), 123.6 (q, $^1J_{CF}$ = 272.0 Hz), 41.9, 34.8, 17.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ (ppm) −63.33 (s). LRMS (EI) m/z: 260 $[M]^+$.

*Methyl 4-(2,3-dimethoxyphenyl)-2-methyl-4-oxobutanoate (**3q**).* 53% yield (141 mg), hexane/ethyl acetate = 6:1, R_f = 0.7, Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.14 (1H, d, J = 7.5 Hz), 7.05 (1H, t, J = 7.5 Hz), 7.01 (1H, d, J = 7.5 Hz), 3.88 (3H, s), 3.86 (3H, s), 3.66 (3H, s), 3.45−3.38 (1H, m), 3.10−3.00 (2H, m), 1.22 (3H, d, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 200.5, 176.2, 152.9, 148.2, 133.4, 123.9, 120.6, 115.7, 61.2, 55.9, 51.6, 46.6, 34.9, 17.0. IR (neat): 3075, 2974, 2950, 2880, 2839, 1737, 1680, 1580 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{18}O_5$, 266.1149; found, 266.1165.

*4-(3,4-Dimethoxyphenyl)-2-methyl-4-oxobutanoic Acid (**2r**).* Known compound.[15] 52% yield (131 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.59 (1H, d, J = 8.4 Hz), 7.52 (1H, s), 6.88 (1H, d, J = 8.4 Hz), 3.94 (3H, s), 3.92 (3H, s), 3.43 (1H, dd, J = 17.5, 7.8 Hz), 3.18−3.10 (1H, m), 3.03 (1H, dd, J = 17.5, 5.5 Hz), 1.31 (3H, d, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 196.5, 181.8, 153.4, 149.0, 129.7, 122.7, 110.1, 110.0, 56.1, 55.9, 41.2, 34.9, 17.1. LRMS (EI) m/z: 252 $[M]^+$.

*4-(3,5-Difluorophenyl)-2-methyl-4-oxobutanoic Acid (**2s**).* 42% yield (96 mg), hexane/ethyl acetate = 5:1, R_f = 0.7, Pale yellow solid, mp 98.4−99.5 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.47−7.44 (2H, m), 7.05−6.99 (1H, m), 3.42 (1H, dd, J = 18.0, 8.0 Hz), 3.19−3.10 (1H, m), 2.97 (1H, dd, J = 18.0, 5.1 Hz), 1.33 (3H, d, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 195.3, 181.6, 163.0 (dd, $^1J_{CF}$ = 250.0, $^3J_{CF}$ = 11.0 Hz), 139.3, 110.0 (dd, $^2J_{CF}$ = 19.0, $^4J_{CF}$ = 7.0 Hz), 108.6 (t, $^2J_{CF}$ = 25.0 Hz), 41.8, 34.7, 17.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ (ppm) −90.40 (m). IR (KBr): 3348, 3086, 2982, 2931, 2886, 2764, 2674, 1699, 1690, 1598 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{11}H_{10}O_3F_2$, 228.0593; found, 228.0606.

*4-(2,6-Dichlorophenyl)-2-methyl-4-oxobutanoic Acid (**2t**).* 38% yield (99 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. White solid, mp 109.9−112.1 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.98 (1H, bs), 7.27−7.19 (3H, m), 3.28 (1H, dd, J = 19.0, 6.1 Hz), 3.15−3.07 (1H, m), 2.95 (1H, dd, J = 19.0, 6.5 Hz), 1.30 (3H, d, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 199.7, 181.6, 139.0, 130.7, 130.5, 128.1, 46.4, 34.1, 16.7. IR (KBr): 3409, 3083, 2987, 2939, 1727, 1708, 1582 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{11}H_{10}O_3Cl_2$, 260.0002; found, 260.0021.

*2-Methyl-4-oxo-4-(2,4,6-trimethylphenyl)butanoic Acid (**2u**).* 61% yield (143 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. White solid, mp 100.0−101.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.83 (2H, s), 3.21−3.09 (2H, m), 2.83 (1H, dd, J = 18.5, 4.6 Hz), 2.28 (3H, s), 2.20 (6H, s), 1.33 (3H, d, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 208.0, 181.9, 138.6, 138.5, 132.7, 128.5, 47.8, 34.2, 21.0, 18.9, 16.9. IR (KBr): 3380, 2979, 2939, 2913, 2763, 2658, 1714, 1700, 1612 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{18}O_3$, 234.1251; found, 234.1264.

*2-Methyl-4-oxo-4-(3,4,5-trimethoxyphenyl)butanoic Acid (**2v**).* 55% yield (155 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. White solid, mp 120.2−121.5 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.03 (1H, bs), 7.19 (2H, s), 3.87 (9H, s), 3.41 (1H, dd, J = 17.7, 7.7 Hz), 3.15−3.06 (1H, m), 3.01−2.91 (1H, m), 1.28 (3H, d, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 196.6, 181.5, 152.9, 142.6, 131.6, 105.4, 60.8, 56.2, 41.4, 34.8, 17.0. IR (KBr): 3347, 3091, 2975, 2943, 2907, 2830, 1703, 1683, 1587 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{18}O_6$, 282.1098; found, 282.1114.

*2-Ethyl-4-oxo-4-phenylbutanoic Acid (**2w**).* Known compound.[16] 82% yield (169 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 11.35 (1H, bs), 7.96 (2H, d, J = 7.7 Hz), 7.56 (1H, t, J = 7.7 Hz), 7.45 (2H, t, J = 7.7 Hz), 3.45 (1H, dd, J = 18.9, 9.6 Hz), 3.09−3.01 (2H, m), 1.81−1.66 (2H, m), 1.01 (3H, t, J = 7.4 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 198.0, 181.6, 136.5, 133.2, 128.6, 128.0, 41.5, 39.6, 24.9, 11.5. LRMS (EI) m/z: 206 $[M]^+$.

*4-Oxo-2,4-diphenylbutanoic Acid (**2x**).* Known compound.[3b] 84% yield (214 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.80 (1H, bs), 7.97 (2H, d, J = 7.4 Hz), 7.56 (1H, t, J = 7.4 Hz), 7.45 (2H, t, J = 7.4 Hz), 7.39−7.28 (5H, m), 4.33 (1H, dd, J = 10.0, 4.2 Hz), 3.91 (1H, td, J = 18.0, 10.0 Hz), 3.30 (1H, dd, J = 18.0, 4.2 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 197.3, 179.1, 137.6, 136.2, 133.3, 128.9, 128.6, 128.1, 128.0, 127.7, 46.3, 42.2. LRMS (EI) m/z: 254 $[M]^+$.

*4-Oxo-4-phenylbutanoic Acid (**2y**).* Known compound.[17] 78% yield (139 mg), hexane/ethyl acetate = 3:1, R_f = 0.2. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.58 (1H, bs), 7.98 (2H, d, J = 7.4 Hz), 7.57 (1H, t, J = 7.4 Hz), 7.46 (2H, t, J = 7.4 Hz), 3.31 (2H, t, J = 6.6 Hz), 2.81 (2H, t, J = 6.6 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 197.8, 178.8, 136.3, 133.3, 128.6, 128.0, 33.1, 28.0. LRMS (EI) m/z: 178 $[M]^+$.

*2-Ethyl-4-(naphthalen-2-yl)-4-oxobutanoic Acid (**2aa**).* 53% yield (136 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. White solid, mp 110.5−112.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.49 (1H, s), 8.03 (1H, d, J = 8.2 Hz), 7.96 (1H, d, J = 8.2 Hz), 7.89 (1H, d, J = 8.2 Hz), 7.87 (1H, d, J = 8.2 Hz), 7.62−7.53 (2H, m), 3.60 (1H, dd, J = 17.8, 8.8 Hz), 3.21 (1H, dd, J = 17.8, 4.9 Hz), 3.14−3.07 (1H, m), 1.89−1.70 (2H, m), 1.05 (3H, t, J = 7.4 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 198.0, 180.9, 135.7, 133.9, 132.5, 129.8, 129.6, 128.50, 128.47, 127.8, 126.8, 123.8, 41.6, 39.7, 25.0, 11.6. IR (KBr): 3328, 3062, 2984, 2949, 2922, 2780, 2679, 2611, 1704, 1673, 1626 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{16}H_{16}O_3$, 256.1094; found, 256.1105.

*2-Methyl-4-(naphthalen-2-yl)-4-oxobutanoic Acid (**2ab**).* Known compound.[3f] 70% yield (169 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.49 (1H, s), 8.03 (1H, d, J = 8.0 Hz), 7.96 (1H, d, J = 8.0 Hz), 7.89 (1H, d, J = 8.0 Hz), 7.87 (1H, d, J = 8.0 Hz), 7.60 (1H, t, J = 8.0 Hz), 7.55 (1H, t, J = 8.0 Hz), 3.62 (1H, dd, J = 16.8, 6.8 Hz), 3.28−3.17 (2H, m), 1.37 (3H, d, J = 6.8 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 197.8, 181.7, 135.7, 133.9, 132.5, 129.8, 129.6, 128.54, 128.49, 127.8, 126.8, 123.7, 41.8, 34.9, 17.1. LRMS (EI) m/z: 242 $[M]^+$.

*2-Methyl-4-(naphthalen-1-yl)-4-oxobutanoic Acid (**2ac**).* Known compound.[3g] 75% yield (182 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. White solid, mp 114.1−114.9 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 11.24 (1H, bs), 8.63 (1H, d, J = 8.0 Hz), 7.98 (1H, d, J = 8.0 Hz), 7.91 (1H, d, J = 8.0 Hz), 7.86 (1H, d, J = 8.0 Hz), 7.58 (1H, t, J = 8.0 Hz), 7.52 (1H, t, J = 8.0 Hz), 7.48 (1H, t, J = 8.0 Hz), 3.57 (1H, dd, J = 17.8, 8.0 Hz), 3.30−3.22 (1H, m), 3.11 (1H, dd, J = 17.8, 5.2 Hz), 1.37 (3H, d, J = 7.2 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 201.9, 182.0, 135.4, 133.9, 132.8, 130.1, 128.4, 128.0, 127.7, 126.5, 125.8, 124.3, 45.0, 35.2, 17.0. LRMS (EI) m/z: 242 $[M]^+$.

*4-(2-Furyl)-2-methyl-4-oxobutanoic Acid (**2ad**).* Known compound.[3e] 79% yield (144 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.44 (1H, bs), 7.57 (1H, s), 7.20 (1H, d, J = 2.6 Hz), 6.52 (1H, d, J = 2.6 Hz), 3.31 (1H, dd, J = 17.4, 7.7 Hz), 3.16−3.08 (1H, m), 2.91 (1H, dd, J = 17.4, 5.8 Hz), 1.28 (3H, d, J = 7.2 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 187.0, 181.7, 152.4, 146.4, 117.2, 112.3, 41.2, 34.4, 16.9. LRMS (EI) m/z: 182 $[M]^+$.

*2-Methyl-4-oxo-4-(2-thiophenyl)butanoic Acid (**2ae**).* Known compound.[3e] 85% yield (168 mg), hexane/ethyl acetate = 1:1, R_f = 0.2. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.75 (1H, d, J = 4.2 Hz), 7.65 (1H, d, J = 4.2 Hz), 7.13 (1H, t, J = 4.2 Hz), 3.40 (1H, dd, J = 17.3, 7.6 Hz), 3.20−3.11 (1H, m), 3.00 (1H, dd, J = 17.3, 5.8 Hz), 1.31 (3H, d, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 190.7, 181.6, 143.7, 133.8, 132.1, 128.1, 42.1, 34.8, 17.0. LRMS (EI) m/z: 198 $[M]^+$.

*Methyl 4-(1,3-dioxaindan-5-yl)-2-methyl-4-oxobutanoate (**3af**).* 65% yield (163 mg), hexane/ethyl acetate = 6:1, R_f = 0.7, Colorless

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oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.54 (1H, d, J = 8.0 Hz), 7.40 (1H, s), 6.81 (1H, d, J = 8.0 Hz), 6.01 (2H, s), 3.67 (3H, s), 3.37 (1H, dd, J = 17.4, 7.9 Hz), 3.12−3.03 (1H, m), 2.92 (1H, dd, J = 17.4, 5.5 Hz), 1.24 (3H, d, J = 7.3 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 195.9, 176.4, 151.8, 148.1, 131.5, 124.2, 107.77, 107.75, 101.8, 51.8, 41.7, 34.9, 17.2. IR (neat): 3079, 2976, 2953, 2908, 1734, 1678, 1604 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{14}O_5$, 250.0836; found, 250.0825.

*3-Methyl-5-phenylfuran-2(3H)-one (**4**).* Known compound.[18] 75% yield (131 mg), hexane/ethyl acetate = 6:1, R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 (2H, d, J = 8.0 Hz), 7.42−7.35 (3H, m), 5.82 (1H, d, J = 4.0 Hz), 3.49 (1H, qd, J = 8.0, 4.0 Hz), 1.44 (3H, d, J = 8.0 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 179.3, 152.5, 129.5, 128.6, 128.4, 124.7, 104.1, 40.3, 15.8. LRMS (EI) m/z: 174 $[M]^+$.

*4-Methyl-6-phenyl-4,5-dihydropyridazin-3(2H)-one (**5**).* Known compound.[10] 92% yield (173 mg), hexane/ethyl acetate = 1:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.98 (1H, s), 7.74−7.71 (2H, m), 7.44−7.38 (3H, m), 3.14−3.04 (1H, m), 2.70−2.57 (2H, m), 1.32 (3H, d, J = 7.0 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm): 170.8, 150.8, 135.7, 129.7, 128.6, 125.8, 30.9, 30.3, 15.1. LRMS (EI) m/z: 188 $[M]^+$.

*4-Methyl-2,6-diphenyl-4,5-dihydropyridazin-3(2H)-one (**6**).* Carboxylic acid **2a** (0.232 g, 1 mmol) and phenylhydrazine (0.108 g, 1 mmol) were suspended in 95% ethanol (0.1 M, 10 mL). The mixture was refluxed at 110 °C for 5 h. Then, the solvent was removed under reduced pressure and the residue was treated with water (30 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layer was washed with brine and concentrated under reduced pressure. The final product was purified by column chromatography. 86% yield (227 mg), hexane/ethyl acetate = 1:1, R_f = 0.3. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.80−7.76 (2H, m), 7.57 (2H, d, J = 8.0 Hz), 7.43−7.37 (5H, m), 7.24 (1H, t, J = 8.0 Hz), 3.20−3.12 (1H, m), 2.82−2.74 (2H, m), 1.35 (3H, d, J = 8.0 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 168.7, 151.2, 141.4, 135.8, 129.9, 128.6, 128.4, 126.4, 126.0, 124.9, 32.3, 30.5, 15.5. IR (neat): 3061, 2969, 2932, 2874, 1686, 1491 (cm^{-1}). HRMS (EI) m/z: $[M]^+$ calcd for $C_{17}H_{16}N_2O$, 264.1257; found, 264.1261.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c00557.

Copies of NMR spectra of unknown starting materials and products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Hirofumi Maekawa − *Department of Materials Science and Technology, Nagaoka University of Technology, Nagaoka 940-2188, Japan*; orcid.org/0000-0002-8192-8518; Email: maekawa@vos.nagaokaut.ac.jp

Authors

Suhua Zheng − *Department of Materials Science and Technology, Nagaoka University of Technology, Nagaoka 940-2188, Japan*

Tianyuan Zhang − *Department of Materials Science and Technology, Nagaoka University of Technology, Nagaoka 940-2188, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.2c00557

Notes

The authors declare no competing financial interest.

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Regioselective Silylations of Propargyl and Allyl Pivalates through Ca-Promoted Reductive C(sp^3)−O Bond Cleavage

Tianyuan Zhang, Suhua Zheng, Taro Kobayashi, and Hirofumi Maekawa*

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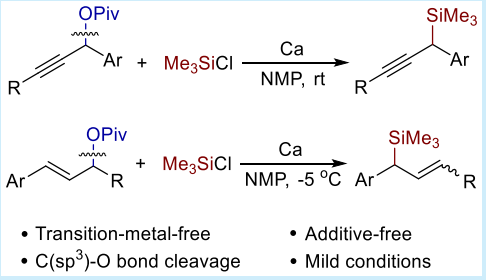
ABSTRACT: A practical protocol for the regioselective preparation of 3-phenylpropargylsilanes and 3-phenylallylsilanes in yields of 36−77 and 48−86%, respectively, from readily accessible 3-phenylpropargyl and 1-phenylallyl pivalates was developed through reductive C(sp^3)−O bond cleavage. This method represents the first example of the direct application of vastly abundant calcium granules to a reductive coupling reaction. A broad range of propargylsilanes and allylsilanes are simply prepared using easy-to-handle pivalates and chlorotrimethylsilane under mild catalyst-free and additive-free conditions.



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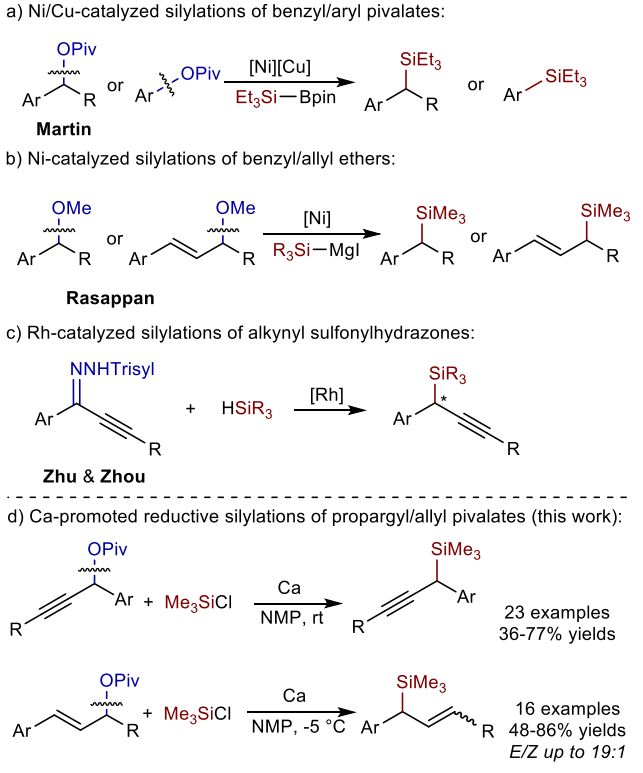
Benzylic esters, benzylic ethers, and their analogues are versatile and potent C(sp^3)−O electrophiles,[1] and their availability and ease of handling have led to their use as alternatives to halides in arylation,[2] alkylation,[3] borylation,[4] and stannylation[5] chemistry in recent years. On the other hand, organosilicon compounds are extremely important organic fine chemical intermediates for the synthesis of natural products,[6] drugs,[7] and functional materials.[8] Therefore, much effort has been devoted to developing various strategies for the syntheses of organosilicon compounds in recent decades;[9] however, less-reactive C(sp^3)−O electrophiles have been sparsely used in this regard. In 2014, Martin et al.[10a] reported the Ni/Cu-catalyzed silylations of benzyl and aryl pivalates using silylboranes (Scheme 1a). In addition to this pioneering work, in 2021, Rasappan et al.[10b] reported the construction of a series of benzylsilanes and allylsilanes through C(sp^3)−OMe cleavage catalyzed by nickel (Scheme 1b). While silylations of alcohols and their derivatives using nucleophilic silicon reagents are well-documented,[11] the development of simple silylation strategies using more common electrophilic silylating agents through C(sp^3)−O bond cleavage remains challenging.

Propargylsilanes are vital intermediates in organic synthesis, with intensive investigations into transformations[12] and synthetic tactics[13] reported in the past few decades. While propargylsilanes are not readily available, they can be prepared by transforming propargylsilane derivatives or under harsh reaction conditions in multiple steps using highly flammable *tert*-butyllithium or toxic copper(I) cyanide.[12a,13a−d] In 2019, Chen and co-workers reported an efficient method for delivering propargylsilanes from vinylidenecyclopropanes;[13e] however, the starting materials for this process are not straightforward, and the use of complicated reagents and multi-step reactions, including functional group protection and deprotection, are required. Very recently, the group of Zhu and

Scheme 1. Silylations through C−O Bond Cleavage and the Syntheses of Propargylsilanes and Allylsilanes: Background



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Zhou disclosed a synthetic pathway to chiral propargylsilanes from alkynyl sulfonylhydrazones through alkynylcarbene insertions into Si−H bonds using rhodium catalysts (Scheme 1c).[13f] These latest reports also suggest that the development of other more practical and general routes to propargylsilanes that use readily available feedstocks remains an attractive goal.

Furthermore, the selective preparation of propargylsilanes and allylsilanes bearing aromatic rings at their 3 positions has not yet been sufficiently resolved. For instance, the direct silylation of 1-phenylpropene, 3-phenylpropene, or their derivatives usually gives 1-phenylallylsilane or a mixture of 1-phenylallylsilane and 3-phenylallylsilane, with the exception of a few cases[14] in which the formation of the conjugated product is favored.

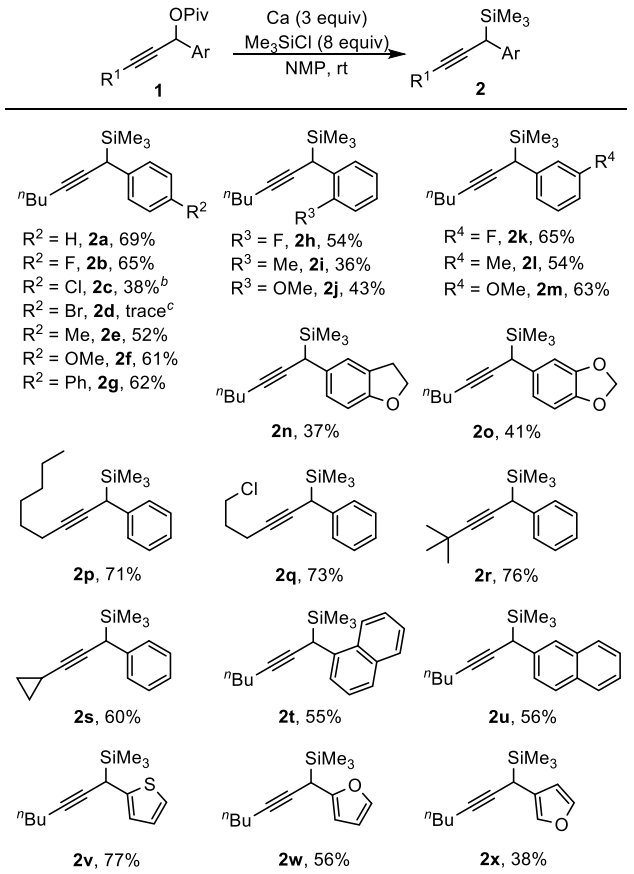
With our continuing interest in the synthesis of valuable organosilicon compounds,[15] we present our efforts toward the syntheses of 3-phenylpropargylsilanes and 3-phenylallylsilanes[16] from readily accessible pivalates through calcium-promoted C(sp^3)−O bond cleavage (Scheme 1d).

In the previous research, reductive coupling reactions involving metals or metal salts, such as magnesium,[17] sodium,[18] and samarium iodide,[19] have been well-documented by many groups, including ours. However, despite its vast abundance in the Earth's crust, eco-friendliness, and commercial availability, the use of calcium in organic processes has been limited to a few areas, including calcium-catalyzed transformations,[20] heavy Grignard reagents,[21] and simple Birch-type reductions in liquid ammonia.[22] To the best of our knowledge, the behavior of calcium metal as a promoter of organic transformations has not been investigated to date, most likely as a result of the lack of effective methods for surface activation. Considering the reduction potential of calcium, we herein report the first example of the direct use of calcium metal as a promising alternative to dangerous alkali or rare earth metals in reductive coupling reactions.

Our initial study into the reductive silylation of propargyl pivalate **1a** in the presence of calcium granules (4 equiv, 9 mesh, particle size of 2 mm) and chlorotrimethylsilane proceeded in *N*-methyl-2-pyrrolidone (NMP) smoothly at ambient temperature to furnish propargylsilane **2a** in 61% yield with no isomerization of the acetylenic group (Table S1 of the Supporting Information). A dramatic decrease in the yield was observed when the reaction was conducted at 0 °C. Screening of the reaction time revealed that all starting materials were completely consumed after 18 h, and prolonging the reaction time resulted in a decrease in the yield. We next investigated the effect of the solvent, with frequently used amide solvents, such as *N*,*N*-dimethylformamide (DMF), *N*,*N*′-dimethylimidazolidinone (DMI), and *N*,*N*-dimethylacetamide (DMA); however, no improvement in the yield was observed. Notably, no reaction was observed in tetrahydrofuran (THF) or dimethyl sulfoxide (DMSO), whereas the desired product was not formed when the reaction was carried out in acetonitrile. On the other hand, no reduction proceeded in the absence of calcium granules, and a lower amount of calcium granules (3 equiv) gave the best product yield (69%) accompanying a small amount of byproducts (Table S2 of the Supporting Information). A parallel reaction using propargyl acetate exhibited the same reaction efficiency as propargyl pivalate **1a**. Finally, we examined the effects of additives, of which none improved the outcome (Table S3 of the Supporting Information).

The substrate scope was examined under the optimized reaction conditions using pivalates **1** (Scheme 2). The reaction

Scheme 2. Reductive Silylations of Pivalates 1: Scope[a]



[a]Reaction conditions: propargyl pivalate **1** (1 mmol), calcium (3 equiv), and Me_3SiCl (8 equiv) in NMP (0.125 M, 8 mL) under N_2, with the isolated yield after flash column chromatography. [b]Product **2a** was isolated in 28% yield as a byproduct. [c]Product **2a** was isolated in 64% yield as a byproduct.

of substrate **1c** bearing a chlorine atom at the *para* position of the benzene ring gave the desired product **2c** in 38% yield, accompanied by product **2a** in 28% yield through the elimination of the chlorine atom. Unfortunately, the *para*-brominated derivative **1d** afforded product **2a** in 64% yield through the analogous elimination of the bromine atom. Pleasingly, a fluorine atom at the *para* position survived under the same reaction conditions, and the desired propargylsilane **2b** was obtained in 65% yield. Propargyl pivalates bearing electron-donating groups, such as methyl and methoxy, on their benzene rings afforded products **2e** and **2f** in good yields. Moreover, a *para*-biphenyl derivative also underwent this reaction smoothly to give the corresponding product **2g** in 62% yield. In addition, the substrate bearing a fluorine atom or an electron-donating group at the *ortho* position, which is expected to provide steric hindrance during silylation at the benzylic position, gave the corresponding silane **2h**, **2i**, or **2j** in 36−54% yield. The reactions were feasible with *meta*-substituted substrates, with products **2k**, **2l**, and **2m** obtained in yields of 65, 54, and 63%, respectively. Fused bicyclic substrates, including dihydrobenzofuran and benzodioxole rings, were also tolerated, albeit with products obtained in

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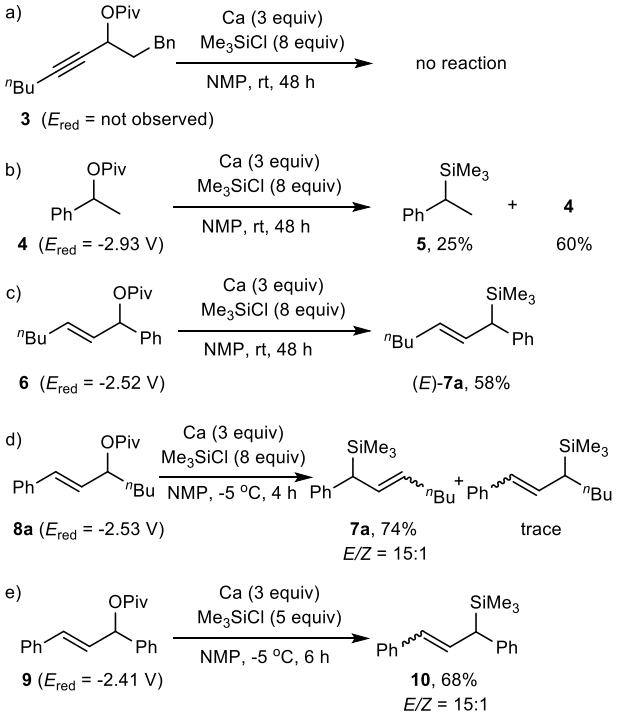
lower yields. In addition to various substituents on the benzene ring, the effect of the alkyl group (R^1) was further studied. Propargyl pivalate **1p**, with a long linear carbon chain, reacted under the same reaction conditions to deliver silane **2p** in 71% yield. To our delight, the 2-chloropropyl group in pivalate **1q** was found to be insensitive to the reduction conditions, furnishing propargylsilane **2q** in 73% yield with no elimination of the chlorine atom.

The bulky *tert*-butyl group (R^1) did not lead to lower reactivity, and the cyclopropyl group did not undergo ring opening to give the corresponding silanes **2r** and **2s**. Finally, the substrate scope was extended to include diverse aromatic rings. Propargyl pivalates bearing naphthyl (**1t** and **1u**), thienyl (**1v**), and furyl (**1w** and **1x**) groups were also tolerated, with the corresponding propargylsilanes **2t**−**2x** furnished in moderate to good yields.

To further extend the present methodology, we switched our attention to various pivalates (Scheme 3). Pivalate **3** devoid of

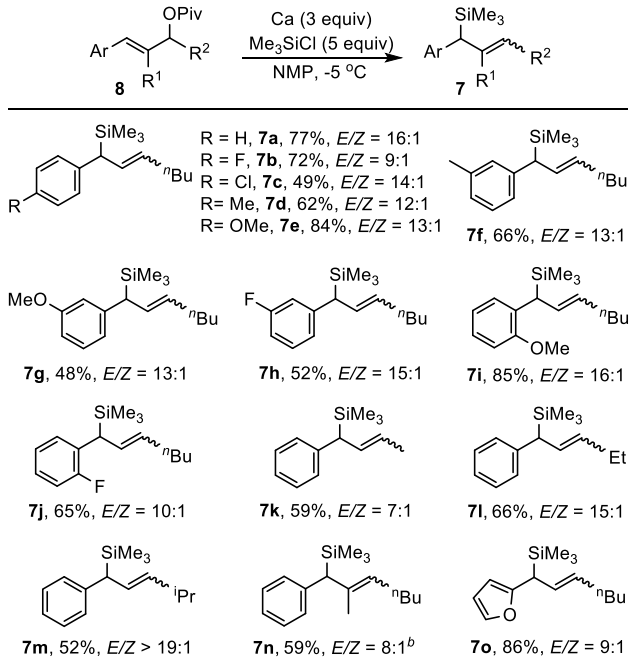
Scheme 3. Reductive Silylations of Various Pivalates



an aromatic ring on the geminal carbon atom did not react under the same reduction conditions, and pivalate **4** devoid of an alkynyl or alkenyl group afforded the corresponding product, trimethyl(1-phenylethyl)silane **5**, in only 25% yield, with 60% of the starting material recovered. Allyl pivalate **6** underwent reductive silylation to afford allylsilane **7a** (*E* isomer) in 58% yield. Notably, the reaction of allyl pivalate **8a** gave the same product as pivalate **6**, which indicates that pivalate **8a** undergoes allylic rearrangement.[11] Similarly, pivalate **9** reacted to afford allylsilane **10** in 68% yield. The results of the reactions of pivalates **8a** and **9** suggest that allylic rearrangement led to a lower *E*/*Z* product selectivity. The reduction potentials of several representative starting materials were measured to understand the differences in the results obtained. Pivalate **3** exhibited no significant reduction peak (E_{red}) in the range from 0 to −3.50 V (versus Ag/AgCl), while the reduction potentials of pivalates **4**, **6**, **8a**, and **9** were recorded to be −2.93, −2.52, −2.53, and −2.41 V, respectively. As suggested in our previous report,[15b] pivalate **3** is reductively silylated inefficiently as a result of its negative reduction potential, and the border for reductive coupling reactions using calcium in NMP is likely to be more positive than −2.93 V.

Encouraged by these results, the substrate scope of allylsilanes **7** was studied next under slightly modified conditions (Scheme 4; see the Supporting Information for

Scheme 4. Silylations of Allyl Pivalates 8: Scope[a]



[a]Reaction conditions: allyl pivalate **8** (1 mmol), calcium (3 equiv), Me_3SiCl (5 equiv) in NMP (0.125 M, 8 mL) under N_2 at −5 °C, with the isolated yield after flash column chromatography. [b]The configuration of the major isomer was determined by nuclear Overhauser effect (NOE) analysis.

reaction optimization details). Various allylsilanes bearing halides were tolerated to give the corresponding allylsilanes **7b**, **7c**, **7h**, and **7j** in moderate to good yields. Allylsilanes with methyl or methoxy substituents at the *ortho*, *meta*, and *para* positions of their benzene rings also reacted well, providing products **7d**−**7g** and **7i** in yields of 48−85%. In addition, a diverse range of alkyl groups R^2 were tolerated, including methyl, ethyl, and isopropyl, to construct allylsilanes **7k**−**7m** in yields of 52−66%. Notably, pivalate **8n** was also converted to allylsilane **7n** in 59% yield, albeit with a low *E*/*Z* ratio. Moreover, replacement of the benzene ring with a furyl ring successfully led to the desired product **7o** in 86% yield. *E*/*Z* ratios were determined by gas chromatography, with the *E* isomer determined to be the major isomer in each case, as confirmed by the ^1H nuclear magnetic resonance (NMR) coupling constant between each pair of alkenyl protons (∼15.0 Hz for each major isomer).

On the basis of the above results and our previous investigations, plausible mechanistic pathways for the formation of propargylsilane **2a** and allylsilane **7a** are proposed in Scheme 5. Radicals **A** and **C** are formed from the starting materials through the direct elimination of the pivalate group under reduction conditions. Intermediate **A** is stabilized at the benzylic position and is immediately transformed into anion **B**

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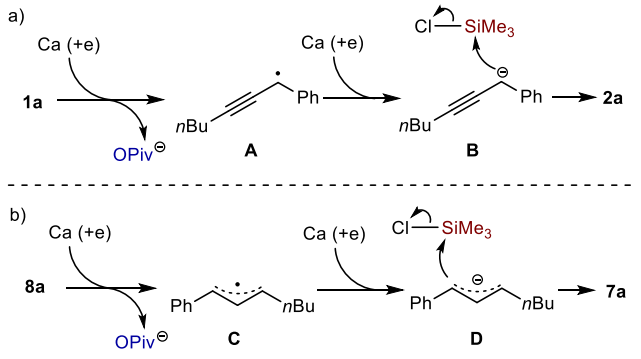
Scheme 5. Plausible Mechanism



through the transfer of a second electron from calcium. Intermediate **B** is conjugated to both the aromatic ring and the acetylenic group. In contrast, radical intermediate **C** exists as an allylic radical, with silylation occurring at the more stable position after the second electron transfer from calcium. Finally, reductive silylation of intermediate **B** or **D** with chlorotrimethylsilane results in the formation of product **2a** or **7a**, respectively.

In conclusion, we developed a practical protocol that accesses useful propargylsilanes and allylsilanes from propargyl and allyl pivalates through benzylic C−O bond cleavage promoted by electron transfer from calcium. Readily accessible starting materials, ease of handling, and catalyst-free, additive-free, and mild reaction conditions that afford products in good yields are the major advantages of this method over other synthetic methods. In addition, these reactions represent the first examples of the direct use of calcium granules in reductive coupling reactions. The reported outcomes reveal that calcium is an attractive and low-cost alternative to noble transition metals and highlight its use in reductive coupling reactions. Investigations into the use of calcium granules in additional reductive coupling reactions are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02532.

Experimental procedures, compound characterization data, copies of NMR spectra, and reaction setup (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Hirofumi Maekawa − *Department of Materials Science and Technology, Nagaoka University of Technology, Nagaoka, Niigata 940-2188, Japan;* orcid.org/0000-0002-8192-8518; Email: maekawa@vos.nagaokaut.ac.jp

Authors

Tianyuan Zhang − *Department of Materials Science and Technology, Nagaoka University of Technology, Nagaoka, Niigata 940-2188, Japan*

Suhua Zheng − *Department of Materials Science and Technology, Nagaoka University of Technology, Nagaoka, Niigata 940-2188, Japan*

Taro Kobayashi − *Department of Materials Science and Technology, Nagaoka University of Technology, Nagaoka, Niigata 940-2188, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c02532

Notes

The authors declare no competing financial interest.

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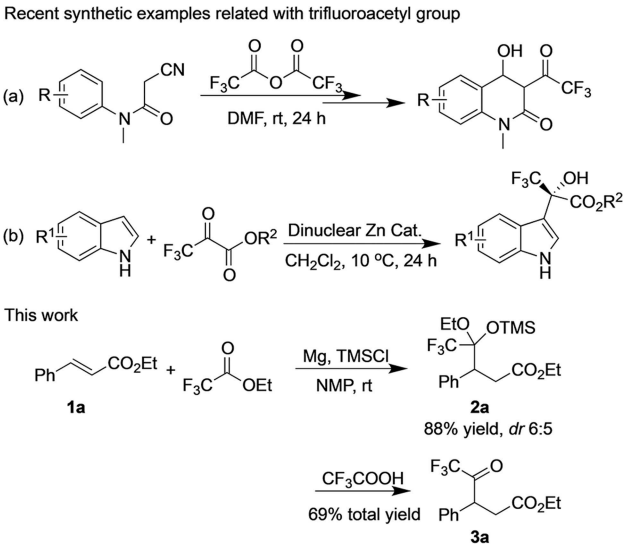
Selective Introduction of Trifluoroacetyl Group to β- and δ-Position of Aromatic Conjugated Esters: Facile Synthesis of Fluorine-containing Keto Esters

Tianyuan Zhang, Yuhei Shimizu, Kazuyuki Shimizu, Mitsuhiro Abe, Suhua Zheng, and Hirofumi Maekawa*[a]

Abstract: An approach to trifluoroacetylation of aromatic conjugated esters successfully led to the efficient and selective introduction of trifluoroacetyl group to the electron-deficient β- or δ-carbon atom of ester under mild reaction conditions by magnesium-promoted reduction, followed by deacetalization with trifluoroacetic acid in moderate to good yields. A variety of fluorinated keto esters derived from ethyl cinnamates and β, γ- or γ-, δ-unsaturated fluorinated keto esters from aromatic dienoesters with a longer conjugation system were synthesized through this simple methodology utilizing ethyl trifluoroacetate as a fluorine-containing carbon source.

Introduction

Significance of partially fluorinated organic compounds has been increasing in the fields of medicinal science and material science because of their unique properties in chemistry and biology.[1] Direct formation of a carbon-fluorine bond or trifluoromethylation by typical reagents such as the XtalFluor reagents or Togni reagents has been focused as conventional synthetic strategies of partially fluorinated organic compounds.[2] Recently, increasing attention has also been paid to novel synthetic methods of partially fluorinated organic compounds from cross-coupling reactions of one substrate with one fluorine-containing component bearing a trifluoroacetyl group.[3] For instance, Kobayashi and co-workers developed a cross-coupling reaction of cyanoacetanilides with trifluoroacetic anhydride as a fluorine-containing source to afford trifluoroacetylquinoline moieties in good yields (Scheme 1, a).[4] Yang and Wang disclosed an asymmetric Friedel-Crafts alkylation of indoles with trifluoropyruvic acid ester as a fluorine-containing carbon block using a dinuclear zinc complex catalyst (Scheme 1, b).[5] We also developed synthetic methods of partially fluorinated compounds by ethyl trifluoroacetate as a fluorinated carbon source.[6] Recently, we reported a simple two-step protocol to synthesize 4-trifluoromethylcyclopentenones and 2-trifluoromethylfurans from the reductive cross-coupling reaction of conjugated ynones with ethyl trifluoroacetate.[7]



Scheme 1. Synthesis of partially fluorinated organic compounds by reagents containing a trifluoroacetyl group.

Cinnamic acid esters and their analogs have been widely used in perfumery products, cosmetics and pharmaceutical industries.[8] Our attention to ethyl cinnamate as a substrate led to magnesium-induced reductive acylation by acid chloride or acid anhydride and electroreductive silylation by chlorotrimethylsilane at the β-position of ester in DMF in high yield.[9] In our recent work, we disclosed the magnesium-promoted reduction of ethyl cinnamates in the presence of carbon dioxide to afford the corresponding diethyl phenylsuccinates as single products in good yields after decarboxylation and esterification.[10] In connection with our recent interest in the synthesis of partially fluorinated compounds,[6] we commenced our study of the cross-coupling reaction of ethyl cinnamate **1a** with ethyl trifluoroacetate. As predicted, an acetal of β-trifluoroacetylated compound **2a** from ethyl cinnamate **1a** was obtained successfully in NMP. The acetal was directly converted to the corresponding fluorinated keto ester **3a** through deacetalization by trifluoroacetic acid (Scheme 1, this work).

[a] *Dr. T. Zhang, Y. Shimizu, K. Shimizu, M. Abe, S. Zheng, Prof. Dr. H. Maekawa*
Department of Materials Science and Technology, Nagaoka University of Technology,
1603-1, Kamitomioka-cho, Nagaoka, Niigata 940-2188, Japan
E-mail: maekawa@vos.nagaokaut.ac.jp

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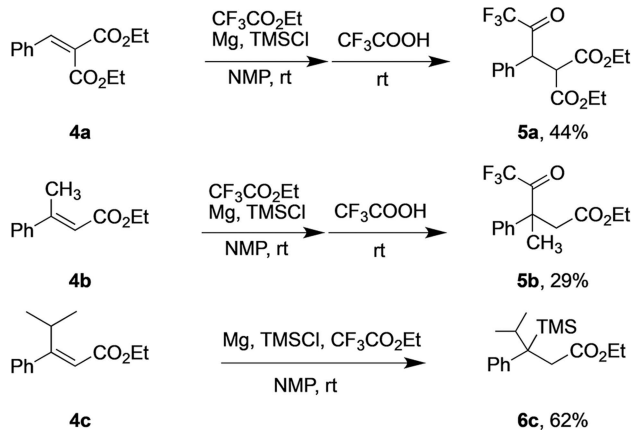
Results and Discussion

After an extensive screening of equivalents of components, solvents, reaction temperature, and deacetalization reagents, trifluoroacetylation step[11] and deacetalization step[12] were successfully realized and direct approach from **1a** to trifluoroacetylated products **3a** was explored from view of efficient synthesis (see Supporting information, Table S1).[13] Through this two-step sequence, fluorinated keto esters **3a** was selectively synthesized in 69% total isolated yield with no purification of intermediate **2a**.

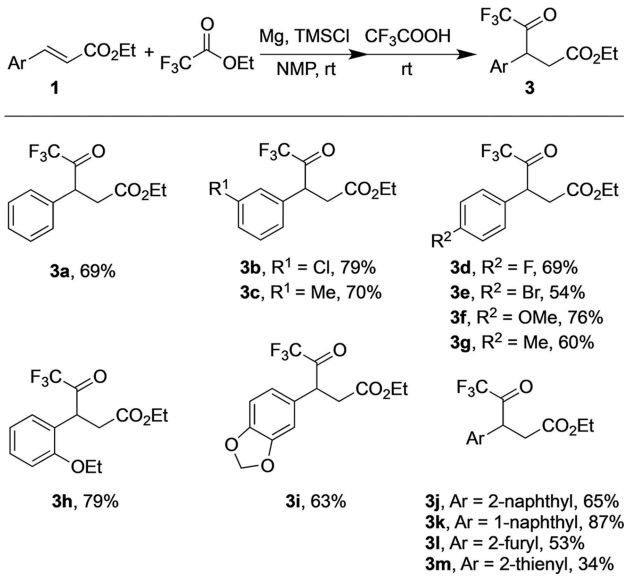
With the optimized conditions in hand, [14] we next examined the synthetic scope of the trifluoroacetylation to ethyl cinnamate derivatives **1** (Scheme 2). No special effect of mono substituent on the benzene ring was found and the desired products **3a**–**3h** were obtained in 54~79% yields. It should be also noted that disubstituted benzene ring with 3, 4-methylenedioxy group exhibited the similar reactivity to afford the desired product **3i** in 63% yield. Application of naphthyl groups to the aromatic ring has also been investigated and the yields of the corresponding fluorinated keto esters **3j** and **3k** were 65% and 87%, respectively. The reaction of heteroaromatic derivatives such as furyl and thienyl groups also gave moderate yields of **3l** and **3m** under slightly modified reaction conditions.

The substituent on the carbon atoms of the alkene is also important in the coupling reaction and diethyl benzylidenemalonate **4a** was converted to the corresponding product **5a** in 44% yield, while diminished yield of **5b** (29% yield) was observed when the β-hydrogen atom was replaced by a methyl group (Scheme 3). As predicted, the trifluoroacetylation did not proceed in case of the substitution by a more bulky isopropyl group at the β-position, instead, β-silylated compound **6c** was obtained in 62% yield. [9b]

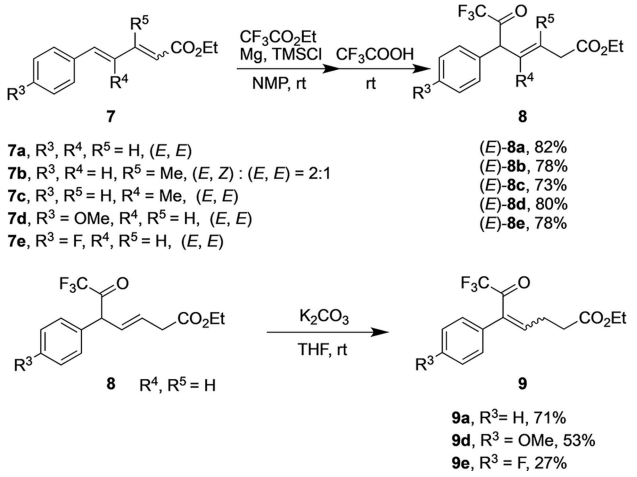
From the results of ethyl cinnamate derivatives shown above, we challenged selective introduction of a trifluoroacetyl group to longer conjugated system. Diene derivatives **7** prepared by known methods[15] were reduced by magnesium metal as well and non-conjugated compounds with a trifluoroacetyl group at the δ-position of the ester group **8** were solely synthesized in high yields under similar reaction conditions (Scheme 4, see Supporting information, Table S2). In addition to the regioselectivity, products **8** were selectively formed as *E*-isomers and the structures of **8b** and **8c** were confirmed by the measurement of NOE relationship around the olefinic proton and the protons of methyl group. As a result, it was proved that a methyl group on the olefin carbon atom and a substituent on the aromatic ring did not show any significant effects to the yield and the regioselectivity in the trifluoroacetylation of dienoesters. After the treatment of esters **8** with potassium carbonate in THF, the olefinic group moved to the neighboring position to give conjugated ketones **9**. The selective transposition was not observed when a stronger or weaker base was used instead of potassium carbonate (see Supporting information, Table S3). Single isomers of **9** were obtained although the configuration could not be confirmed.[16]



Scheme 3. Reductive coupling reaction of ethyl cinnamates with a substituent on the alkene.



Scheme 2. Synthesis of trifluoroacetylated compounds **3** from ethyl cinnamates **1**.



Scheme 4. Application of trifluoroacetylation to aromatic dienoesters **7** with a longer conjugation system.

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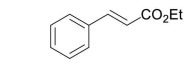
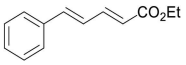
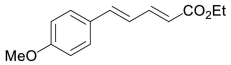
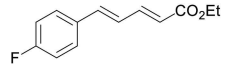
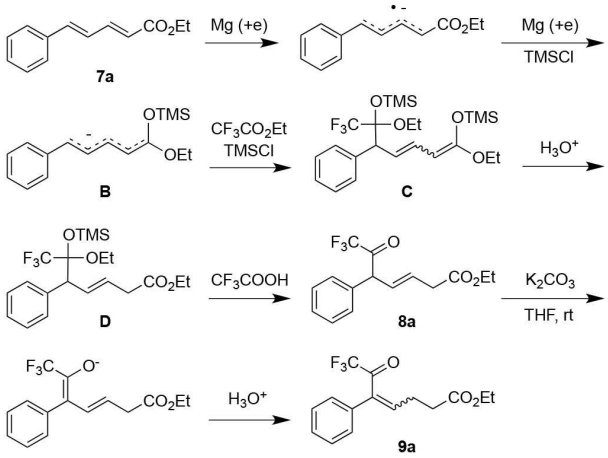
Table 1. Reduction potential of substrates.[a]

Entry	Substrates		Reduction Potential (V vs. Ag/AgCl)
1		**1a**	−1.82
2		**7a**	−1.60
3		**7d**	−1.69
4		**7e**	−1.60
5	CF_3CO_2Et		−2.47
6	TMSCl		No wave (0 ~ −3.0)

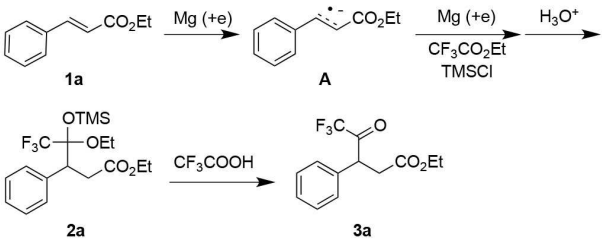
[a] Working electrode: Pt, Counter electrode: Pt, Reference electrode: Ag/AgCl, Solvent: NMP, Supporting electrolyte: 1% *n*-Bu_4NClO_4, Scan rate: 0.2 $V s^{-1}$.



Scheme 6. Proposed reaction mechanism for trifluoroacetylation of dienoester **7a** and olefinic transposition of **8a**.

The reduction potential of some starting materials, ethyl trifluoroacetate and chlorotrimethylsilane was measured by cyclic voltammetry, and the results are summarized in Table 1. The reduction potential of **1a** and **7a** is −1.82 V and −1.60 V, respectively, which is more positive than that of ethyl trifluoroacetate. These results indicated that the reaction would be initiated by a single electron transfer from magnesium metal to conjugated ester **1a** and **7a**.

A plausible reaction mechanism for trifluoroacetylation of ethyl cinnamate is shown in Scheme 5. A single electron



Scheme 5. Proposed reaction mechanism for trifluoroacetylation of ethyl cinnamate.

transfer from magnesium metal to ethyl cinnamate **1a** affords an anion radical species **A**, which is then attacked by the electrophiles, ethyl trifluoroacetate and chlorotrimethylsilane, followed by the second electron transfer to give an acetal of the corresponding β-trifluoroacetylated compound **2a**. Fluorinated keto ester **3a** is formed after deacetalization of the intermediate **2a** by treatment with trifluoroacetic acid. On the basis of the reaction mechanism for ethyl cinnamate shown in Scheme 5, a mechanism of trifluoroacetylation of dienoester **7a** and isomerization of **8a** to **9a** is proposed in Scheme 6.

A single electron transfer from magnesium metal to **7a** will form an anion radical species which is subjected to the attack by chlorotrimethylsilane and the second electron transfer to give an anionic species **B**. The regioselective coupling reaction of **B** with ethyl trifluoroacetate at the benzylic position, followed by the attack of chlorotrimethylsilane, leads to the formation of **C**. Intermediate **C** cannot further obtain electrons from magnesium due to its much more negative reduction potential. Hydrolysis of **C** will afford the unconjugated compound **D** just like formation of **2a** from **1a**. Treatment of **D** with trifluoroacetic acid hydrolyzes the acetal structure of **D** to give the compound **8a**. With the aid of potassium carbonate, the abstraction of a proton from the benzylic position results in the transposition of the olefinic group of **8a** to the neighboring position to afford the conjugated ketone **9a**.

Conclusions

An efficient method for the synthesis of β- or δ-trifluoroacetylated esters was explored by magnesium-promoted reduction of aromatic conjugated esters under mild reaction conditions, followed by deacetalization with trifluoroacetic acid. The protocol demonstrated in this paper allows a simple and selective introduction of a trifluoroacetyl group onto the electron-deficient β- or δ-carbon atom of conjugated esters in good yields by use of ethyl trifluoroacetate as a fluorine-containing carbon source. Further studies on synthesis of partially fluorinated organic compounds are currently underway in our laboratory.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

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Keywords: Electron transfer · Ethyl cinnamate · Ethyl trifluoroacetate · Magnesium · Trifluoroacetylation

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[11] Our previous results on reductive acylation reactions by magnesium metal indicated that acylation required strong acylating agents such as acid chlorides or acid anhydrides.[9a] However, ethyl trifluoroacetate was the best reagent for magnesium-promoted trifluoroacetylation[6b] and trifluoroacetylation demands the excess amount of ethyl trifluoroacetate, which will be a weaker electrophile than chlorotrimethylsilane added as an essential activating agent for magnesium in the reaction.[6]

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[13] Methyl silyl acetal of the trifluoroacetyl group is stable enough during the work-up process and sometimes resists hydrolysis due to the electron-withdrawing effect of the trifluoromethyl group.[6b]

[14] Reaction conditions for trifluoroacetylation; ethyl cinnamates **1** (5 mmol), ethyl trifluoroacetate (10 equiv), Mg (2 equiv), TMSCl (4 equiv), NMP (30 mL), rt, N_2 atmosphere. For deacetalization; trifluoroacetic acid (10 mL), 0 °C.

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[16] Our trial to confirm the configuration of **9** by NOE measurements failed because the important proton signals were not fully separated.

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