α-Trifluoromethylated Carbanion Synthons

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CONSPECTUS

Trifluomethylated organic compounds often have properties that make them suitable for diverse applications, including materials science, agrochemistry, and pharmaceutical industry. But of all the therapeutic drugs currently available, about 10% of them have a partially fluorinated moiety. Thus, a great deal of attention is being paid to the development of reliable methodologies for trifluoromethylation.

Introduction of a trifluoromethyl group into the target molecules mostly relies on either trifluoromethylating reagents or trifluoromethylated synthetic blocks. The chemistry of trifluoromethyl carbanions, nucleophilic trifluoromethylating agents such as the Ruppert−Prakash reagent, and organometallic species has been intensively developed for their important synthetic applications.

But the chemistry of β,β,β-trifluoroethyl carbanions (α-trifluoromethyl carbanions) and organometallic species has remained undeveloped despite their potential usefulness in organic synthesis. The issue needs to be addressed. This Account outlines successful alkylations and useful synthetic applications of α-trifluoromethyl carbanions, such as α-substituted β,β,β-trifluoroethyl, α-trifluoromethylethenyl, trifluoroacetimidoyl, α-trifluoromethyloxiranyl, and related α-trifluoromethylated carbanions.

The strong electron-withdrawing effect of the α-trifluoromethyl group may stabilize the carbanion species electronically. But α-trifluoromethyl carbanions and their corresponding organometallic species mostly release fluoride spontaneously to produce difluoroalkenes. This notorious decomposition of α-trifluoromethylated carbanions and anionoids has hindered the development of these species for organic synthesis. A well-designed device for the generation, stabilization, and acceleration for alkylation of the α-trifluoromethylated carbanions is needed for their synthetic application, as well as stabilization by the electron-withdrawing α-substituent.

The reported α-substituted α-trifluoromethyl carbanions can be roughly categorized into three classes based on their structures. The first category, A, is π-conjugation-stabilized carbanions, which are stabilized by ester, nitro, sulfone, carbonyl, or phenyl groups. α-Substituents of these carbanions can delocalize the negative charges on their π-system with large σ_R electron-withdrawing effects; this prevents accumulation of negative charge on the fluorine atoms.

The second category, B, consists of carbanions with sp^3 orbitals either of highly halogenated carbanions—examples include pentafluoroethyl(trimethyl)fluorosilicate, pentafluoroethyllithium, and α,α-dichloro-β,β,β-trifluoroethylzinc species—or of cyclic structures such as oxiranyl- and aziridinyllithiums. Both of these carbanions are also stabilized since they reduce molecular orbital (MO) overlapping of the carbanion orbital to C−F bond orbitals.

The third category, C, has carbanions with their anion center at the sp^2 orbital, such as α-trifluoromethylated alkenyl carbanions and imidoyl carbanions. These sp^2 orbitals of the carbanion center usually have a small overlap with the C−F bonds of trifluoromethyl groups. The small overlap is able to suppress the E2-type eliminations.

α-Trifluoromethylated carbanions are, in general, unstable. Their stability is largely affected by factors like hybridization of the orbital that accommodates lone pair electrons, the electronic nature of the α-substituents, the degree of covalency in a bond between the carbon and metal, the class of countercation, stabilization by chelation of a metal cation, and so on. The stability, therefore, can be sometimes controlled by tuning these factors adequately so that they can be used for organic synthesis.

The chemistry of α-trifluoromethylated carbanions for organic synthesis has been progressing steadily. However, the simplest trifluoroethyl and trifluoroacetyl carbanions have never been successfully produced and employed for organic synthesis. Elegant generation and synthetic application of these metal species are one of the most attractive and challenging subjects for active investigation in the future.
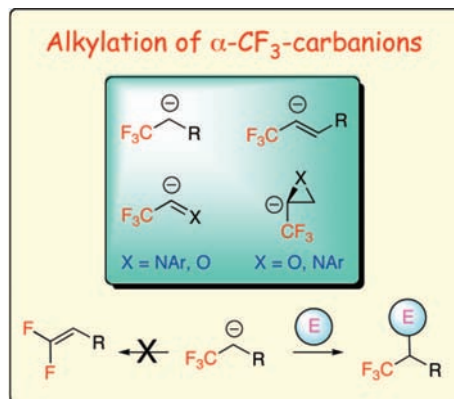
1. Introduction

The chemistry of trifluoromethyl carbanions, nucleophilic trifluoromethylating agents, and organometallic species has been intensively studied due to the importance of these compounds in synthetic applications.[1−4] Meanwhile, the chemistry of β,β,β-trifluoroethyl carbanions (α-trifluoromethyl carbanions) and organometallic species has remained undeveloped, despite the potential utility of these agents in organic synthesis; thus, this issue needs to be addressed. This Account outlines successful alkylations of α-trifluoromethyl carbanions, such as α-substituted β,β,β-trifluoroethyl, α-trifluoromethylethenyl, trifluoroacetimidoyl, α-trifluoromethyloxiranyl, and related α-trifluoromethylated carbanions (Scheme 1).

The strong electron-withdrawing effect of the trifluoromethyl group may stabilize the carbanion species electronically. Such α-trifluoromethyl carbanions and corresponding organometallic species would mostly release fluoride spontaneously to give difluoroalkenes (Scheme 2).[5] This notorious decomposition of α-trifluoromethylated carbanions and anionoids has hindered the development of the species in organic synthesis.[6]

To date, only a few reports of preparations and synthetic utilizations of α-trifluoromethyl carbanions have been published. These compounds are so thermally unstable that they require very low temperature conditions for generation. Some α-trifluoromethyl metal species decompose even at −78 °C; thus, reaction conditions below −100 °C are required.[7] Lewis acidic action of the countercation on the fluorine atom would also promote defluorination. Such action of the cation may cause a negative charge to accumulate on the fluorine,[11] causing the atom to be pulled out. Not only is stabilization by an electron-withdrawing α-substituent necessary, but a well-designed device for generation, stabilization, and acceleration of alkylation of α-trifluoromethylated carbanions is also needed for synthetic applications.

Reported α-substituted α-trifluoromethyl carbanions can roughly be categorized into three classes based on their structures (Scheme 3). The first category consists of π-conjugation-stabilized carbanions (A); these are stabilized by ester,[8−10] nitro,[11] sulfone,[12] carbonyl,[13,14] or phenyl[15] groups. α-Substituents of these carbanions delocalize the negative charges on their π-systems, with large σ_R electron-withdrawing effects that prevent accumulation of negative charge on the fluorine
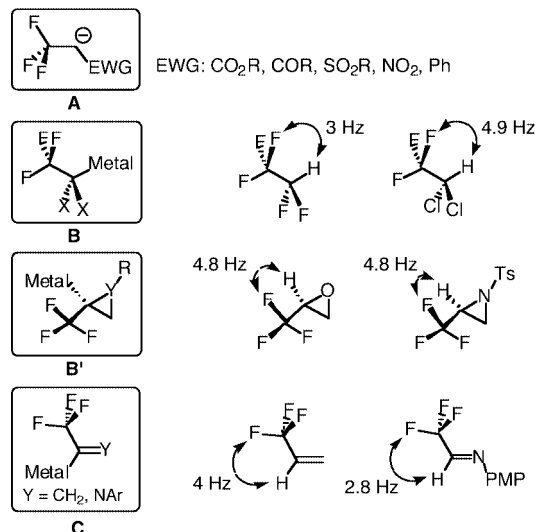
SCHEME 1
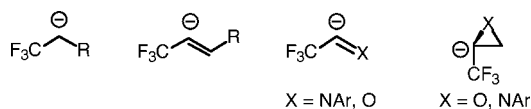
SCHEME 2
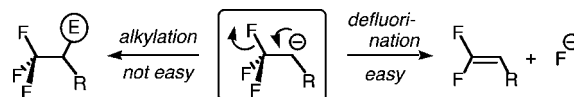
SCHEME 3

atoms. Moreover, some carbanion species are stabilized by association with Pd[10] or Ti metal.[14] The second category (B) contains carbanions with sp^3 orbitals either of highly halogenated carbanions, such as perfluoroalkyllithiums[16,17] and α,α-dichloro-β,β,β-trifluoroethylzinc species,[18,19] or of cyclic structures, such as oxiranyl- and aziridinyllithiums.[20,21] Both of these carbanions are also stabilized, since they reduce molecular orbital (MO) overlapping of the carbanion orbital with C−F bond orbitals. The third category (C) consists of carbanions that have their anion center at the sp^2 orbital and includes the vinyl carbanion[22,23] and imidoyl carbanion.[24−26] The sp^2 orbitals of the carbanion center usually overlap slightly with the C−F bonds of the trifluoromethyl groups, which enables suppression of E2 type eliminations.

Let us evaluate the extent of overlap of the carbanion orbitals with the C−F bond orbitals, which could be roughly estimated by $^3J_{F-H}$ couplings of the parent protonated compounds by ^{1}H NMR spectroscopy. The overlap of the carbanion orbital with the C−F bonds is not the sole factor that determines the fate of α-trifluoromethylated carbanions; however, it should be an important product-determining factor. The $^3J_{F-H}$ coupling constant of trifluoroethanol derivatives like ether and tosylate, which experience spontaneous defluorination when lithiated at the α-carbon, is in the range of 8−10 Hz.[27,28] The $^3J_{F-H}$ coupling constant of pentafluoroethane (protonated form of B) is 3 Hz,[27] that of 1,1-dichloro-2,2,2-trifluoroethane (B) is 4.9 Hz,[28] that of 2,3-epoxy-1,1,1-trifluoro-
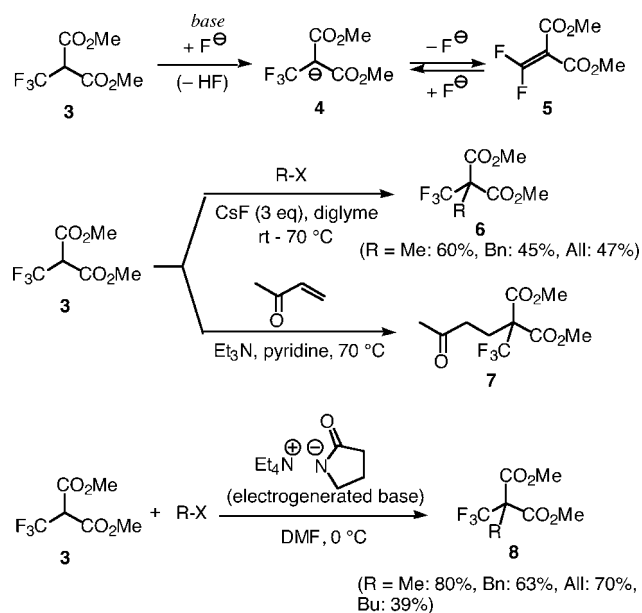
SCHEME 4
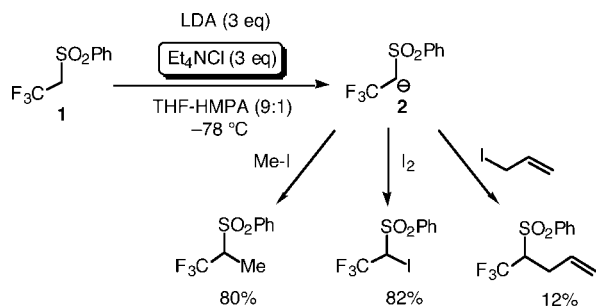
ropropane (protonated form of B') is 4.8 Hz,[29] that of N-tosyl-2-trifluoromethylaziridine (B') is 4.8 Hz,[21] that of trifluoropropene (protonated form of C) is 4 Hz,[27] and that of imine (C) is 2.8 Hz.[30] These small $^3J_{F-H}$ coupling constants ($^1/_3$–$^1/_2$ the value of the coupling constant of 2,2,2-trifluoroethanol) of the parents of the anionoids suggest a smaller overlapping of the orbitals of C−F bond to that of the anion (Scheme 3).

2.1. α-Trifluoromethyl Carbanions Stabilized by Electron-Withdrawing Groups. Despite scientific importance and synthetic utility, alkylations of α-trifluoromethylated carbanions have been successful only in a small number of cases. Lithiation of heteroatom-substituted 2,2,2-trifluoroethanes (CF_3CH_2R; R = OPh, OR, OTs, SPh, Cl, or F) results in defluorination, yielding gem-difluoroalkenes, $F_2C=CHR$.[31] In contrast, 1-phenylsulfonyl-2,2,2-trifluoroethyl carbanion (generated by LDA/THF-HMPA), which is strongly stabilized by a $PhSO_2$ group, reacts with some electrophiles (MeI, I_2, and allyl iodide) (Scheme 4).[12] Furthermore, the quaternary ammonium cation was found to be more effective than the lithium cation in stabilization of the carbanion **2**.

Ishikawa demonstrated an alkylation of dimethyl trifluoromethylmalonate **3** with an excess of CsF. During the transformation, the fluoride addition to difluoromethylenemalonate **5** maintains a moderate concentration of α-trifluoromethylated carbanion **4**, which undergoes alkylation and Michael addition (Scheme 5).[8] Independently, Fuchigami reported an efficient alkylation of trifluoromethylmalonate **3** using an electrogenerated base (EGB), a tetraethylammonium amide of pyrrolidone (Scheme 5).[9] So far, the replacement of the alkaline metal ion with tetraalkylammonium ion weakens the metal−fluorine interaction, thus stabilizing the anion and enhancing alkylation.

Another effective alkylation of the methylene carbon bearing CF_3 group relies on stabilized enolate chemistry. In general, metal enolates are synthetically important in C−C bond-forming reactions. However, α-CF_3 metal enolates are unstable and difficult to prepare because of the facile β-fluoride elimi-
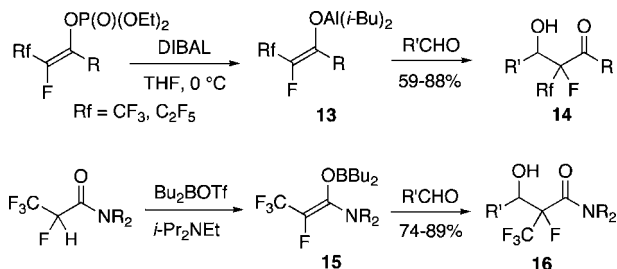
## SCHEME 5

SCHEME 6
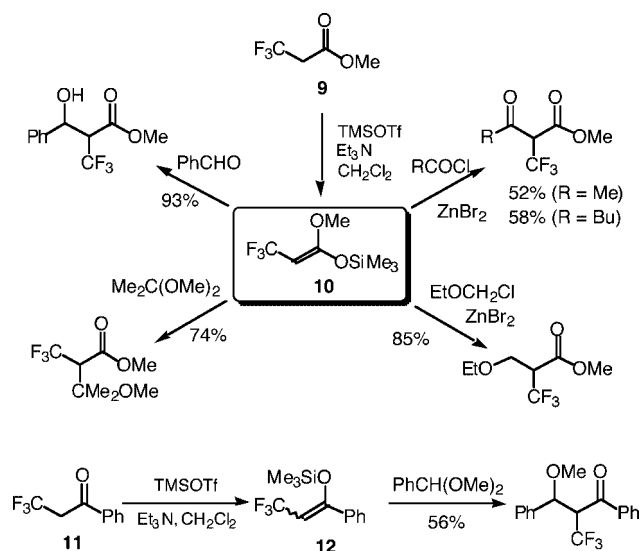
nation. To overcome difficulties, the choice of metals for stabilization of the enolates is essential. Silyl enolate **10** of methyl 3,3,3-trifluoropropionate (with TMSOTf/Et₃N) is alkylated at α-carbon either by aldol reactions or by Lewis acid-mediated alkylation (Scheme 6).[32] A similar alkylation of silyl enol ether **12** of 3,3,3-trifluoropropiophenone **11**, *in situ* generated with acetals, is known.[33]

Moreover, alkylations using enolates **13**[34] and **15**[35] were reported by Ishihara and Kuroboshi (Scheme 7). Recently, Mikami succeeded in generation of Ti-enolates of α-CF_3 ketones, in addition to their applications to stereoselective aldol reactions (Scheme 8).[14,36] In contrast to possible defluorinative interactions of fluorine with the lithium ion in Li-
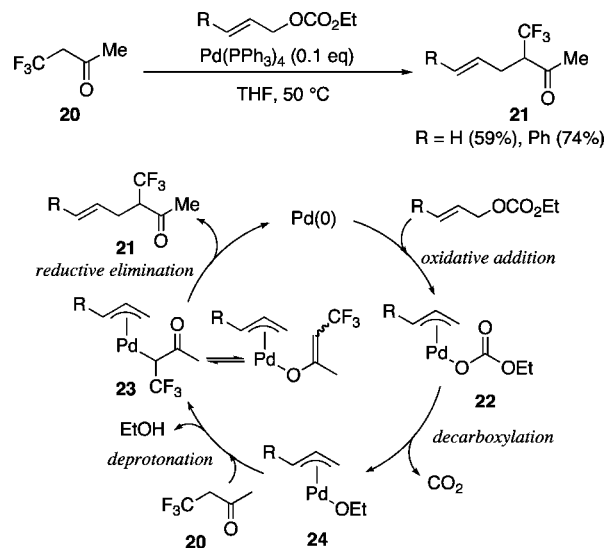
SCHEME 7

SCHEME 8
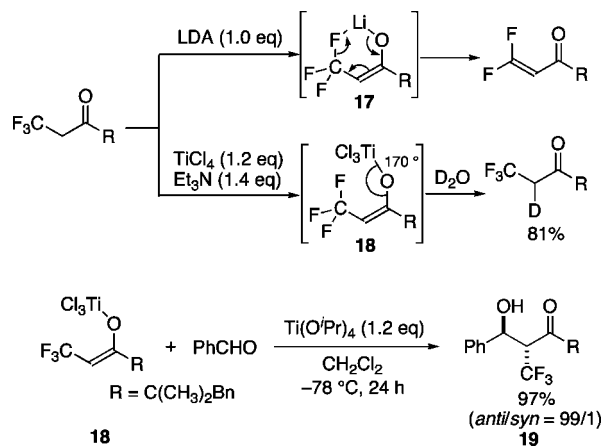
enolate **17**, titanium enolate **18** is stable against defluorination due to the linear aligned structure of C−O−Ti, which makes a possible interaction of fluorine with titanium weak.

A catalytic transformation involving Pd-enolate of α-CF$_3$ ketone was accomplished. With a catalytic amount of Pd(PPh$_3$)$_4$, 4,4,4-trifluorobutan-2-one **20** reacts with various allylic carbonates to give α-allylated ketones **21** in good yields (Scheme 9).[10] Interestingly, the α-allylation reactions proceed smoothly under neutral conditions; the π-allyl palladium alkoxide intermediate **24** could abstract the α-proton of the ketone **20** effectively, loading to palladium enolate **23**.

2.2. Perfluoroalkyl Organometallics. The highly hydrophobic nature of the perfluoroalkylated molecules may favorably alter *in vivo* transport rates and stability of a drug. Nucleophilic introduction of perfluoroalkyl groups is one of the most effective and popular methods for the synthesis of perfluoroalkylated compounds. However, (2,2,2-trifluoroethyl)-lithiums and the corresponding Grignard reagents are not synthetically useful due to their rapid decomposition. However, there is an obvious increase in the stability of the (perfluoroalkyl)lithium reagent.[37−39]

Gassman reported reactions of (pentafluoroethyl)lithium with carbonyl compounds (Scheme 10).[16] Pentafluoroethyl iodide undergoes a halogen−metal exchange reaction with
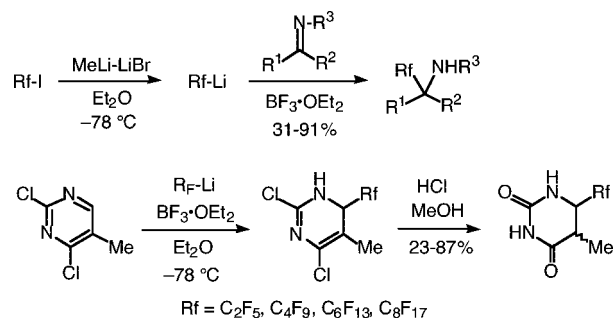
SCHEME 9

R = H (59%), Ph (74%)

SCHEME 10

SCHEME 11

Rf = C$_2$F$_5$, C$_4$F$_9$, C$_6$F$_{13}$, C$_8$F$_{17}$
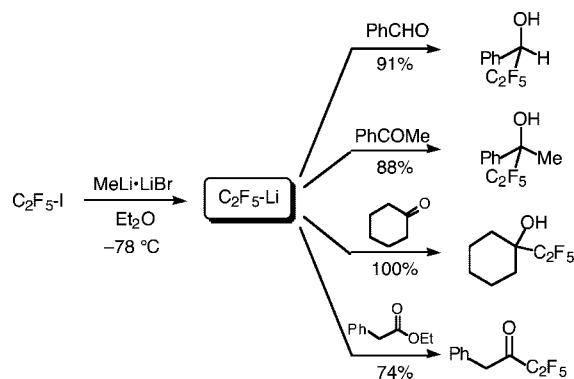
MeLi at −78 °C in the presence of carbonyl compounds, without addition of methyllithium.[40]

Uno reported reactions of (perfluoroalkyl)lithiums, prepared via halogen−metal exchange, with carbon−nitrogen double bonds in the presence of BF$_3$·OEt$_2$ catalyst (Scheme 11).[17,41] N-Heterocycles, such as quinolines, isoquinolines, and pyrimidines, react smoothly with (perfluoroalkyl)lithiums, giving the corresponding adducts (Scheme 11).[42]

SCHEME 12

SCHEME 13

a) C_2F_5I, MeLi·LiBr, Et_2O (49%), (b) 50% H_2SO_4, MeOH (92%).
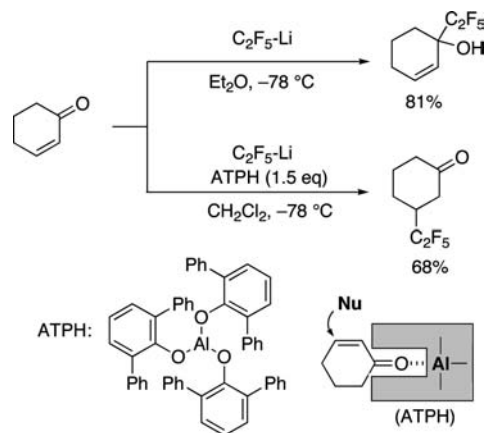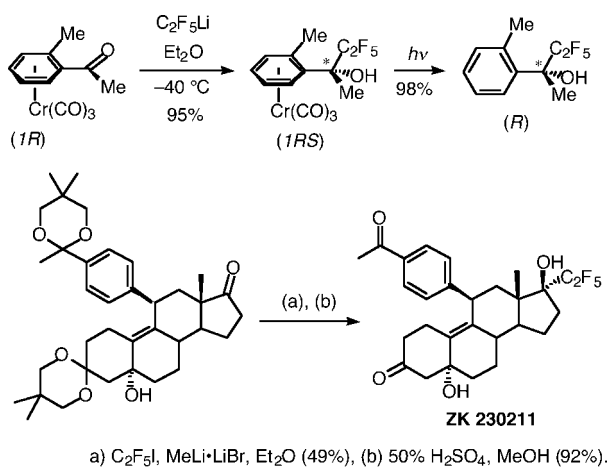
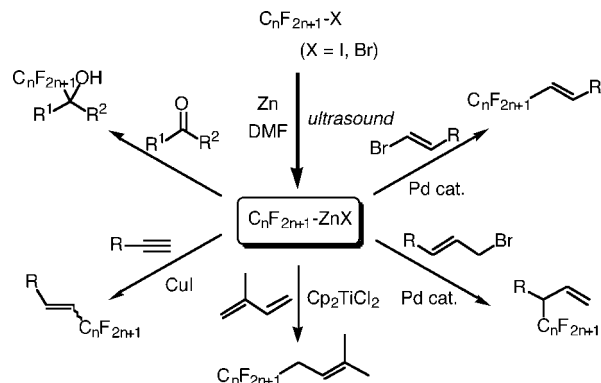**SCHEME 14**

SCHEME 15

There have been several reports on regioselective (Scheme 12)[43] and stereoselective (Scheme 13)[44] nucleophilic pentafluoroethylations.

Perfluoroalkylzinc reagents are more stable than the corresponding lithium or magnesium reagents. The zinc reagents were prepared from perfluoroisopropyl iodide with metallic zinc.[45] The reactions with acyl fluorides or acid anhydrides gave perfluoroalkyl ketones.[46] With ultrasonic irradiation, (perfluoroalkyl)zinc reagents undergo Pd-catalyzed perfluoroalkylation of allyl, vinyl, and aryl halides, alkynes, and dienes, affording perfluoroalkylated compounds (Scheme 14).[47]

Thermal stability of perfluoroalkyl agents (R_F-M) depends on the kind of metal present (M). Intuitively, a large degree of covalency of carbon−metal bonds (M is a less electropositive element) and a low degree of orbital overlap of carbon−metal with carbon−fluorine bonds (M is a heavier or higher period element) increase the thermal stability of R_F-M. Other examples of thermally stable (perfluoroalkyl)metal (Ca,[48] Mn,[49] Ag,[49] and Sn[50]) species are known.
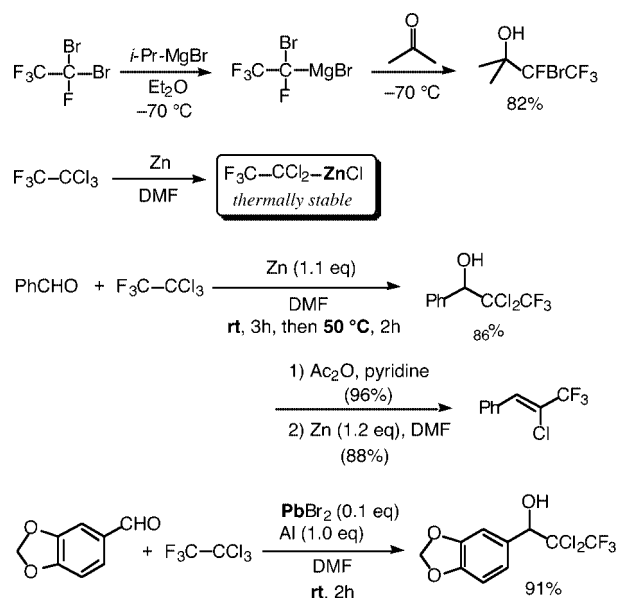
In addition to perfluoroalkyl iodides, fluorohalogeno-ethanes CF_3CXYZ (X = F, Cl, Br; Y, Z = Cl, Br) undergo metal−halogen exchange with alkyl- or arylmagnesium halides at low temperatures to yield organometallic compounds $CF_3CXYMgX$, although they are not reactive enough at such low temperatures.[18] Fujita and Hiyama were able to generate a thermally stable CF_3CCl_2ZnCl from CCl_3CF_3 and Zn powder. At room temperature, addition of CF_3CCl_2ZnCl[19] and CF_3CCl_2PbCl[51] with various aldehydes and ketones afforded adducts in high yields (Scheme 15).

2.3. β-Fluoroalkyl- and Perfluoroalkylsilanes. A large number of organosilicon compounds are utilized in organic synthesis. In general, organosilicon compounds are considerably stable and easy to handle. Meanwhile, in the presence of fluoride as an initiator, they act as metal-free carbanion sources via pentavalent silicate intermediates for nucleophilic alkylation (Scheme 16).

SCHEME 16

Metal-Free Carbanion Equivalent
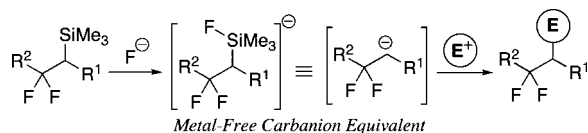
SCHEME 17
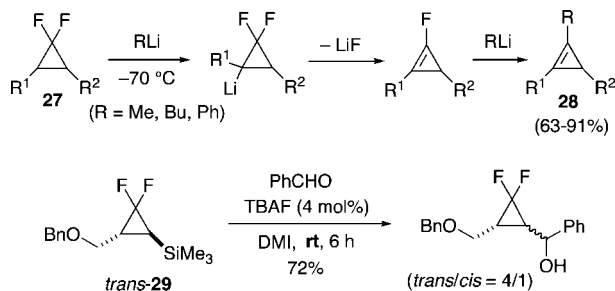
In many cases, pentavalent fluorosilicates are thermally stable intermediates, which survive at higher temperatures. Taguchi reported the generation of β-fluoroalkyl carbanions. It is known that the deprotonation reaction of difluorocyclopropanes **27** by alkyllithium (RLi) proceeds rapidly, while the resultant anions having lithium as a counterion are so unstable, even at low temperatures, that the products **28** form through β-elimination of LiF (Scheme 17).[52] In contrast, silyl-substituted difluorocyclopropanes **29** react with a variety of aldehydes without defluorination. With a catalytic amount of TBAF, the reactions proceed at room temperature to yield the corresponding cyclopropylcarbinols.[53]
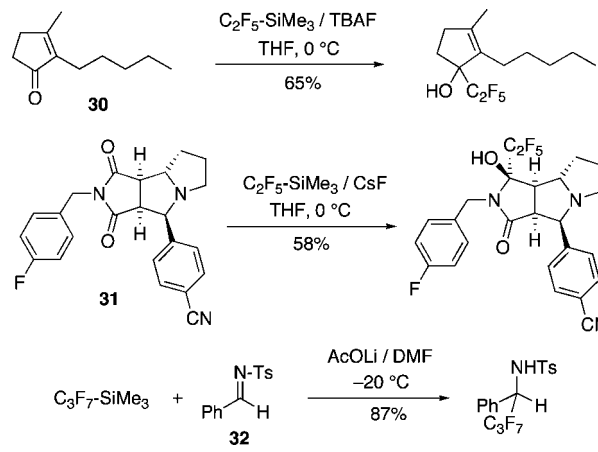
Interestingly, perfluoroalkylsilanes (Ruppert−Prakash reagent, R_F-SiMe$_3$)[54] are useful compounds as perfluoroalkyl anion sources for introduction of perfluoroalkyl groups into various organic compounds. Perfluoroalkylsilanes have been used for formation of not only C−C bonds with ketones **30**,[55] amide **31**,[56] imines **32**[57] (Scheme 18), and aryl iodides **33**[58] (Scheme 19) but also carbon−heteroatom bonds with sulfur and nitrogen reagents[59] (Scheme 20), phosphites,[60] and borate[61] (Scheme 21).

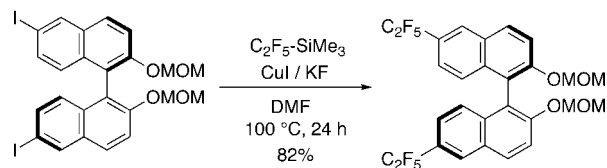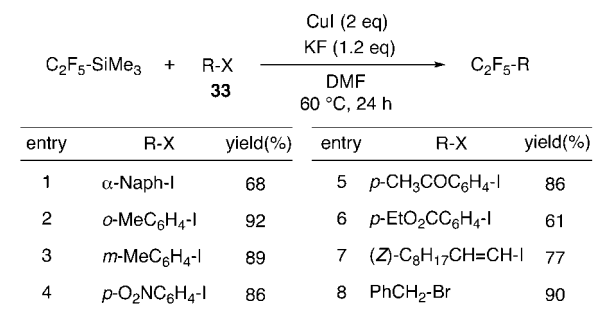## 3. Oxiranyl and Aziridinyl Anions

Besides ring openings,[62] the anion **36** of the epoxide **34** and the anion **37** of the aziridine **35** could be generated regioselectively, as well as stereospecifically, on the ring carbons attached to the trifluoromethyl group (Scheme 22).[21,63] Negative charges of these anions would be delocalized by overlapping of the sp^3 anion center orbital to lone pair orbitals on the ring oxygen.[63]

The oxiranyl anion **36** from 2,3-epoxy-1,1,1-trifluoropropane **34** with *n*-BuLi was found to be thermally unstable.[7,20]

SCHEME 18

SCHEME 19

entry	R-X	yield(%)	entry	R-X	yield(%)
1	α-Naph-I	68	5	*p*-CH$_3$COC$_6$H$_4$-I	86
2	*o*-MeC$_6$H$_4$-I	92	6	*p*-EtO$_2$CC$_6$H$_4$-I	61
3	*m*-MeC$_6$H$_4$-I	89	7	(*Z*)-C$_8$H$_{17}$CH=CH-I	77
4	*p*-O$_2$NC$_6$H$_4$-I	86	8	PhCH$_2$-Br	90

SCHEME 20
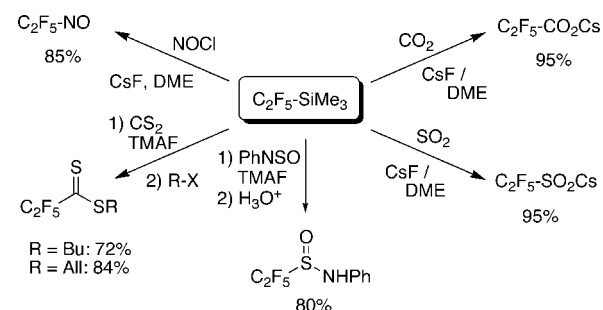
Its generation and reaction should be undertaken below −100 °C. Reaction at higher temperatures (−40 °C) resulted in decomposition (via defluorinations). However, the anion reacted at −100 °C with a variety of electrophiles to give optically active 2-substituted 2-trifluoromethyl oxiranes **40**, with retention of its configuration (Scheme 23).

Generation of the aziridinyl anion **37** was affected by N-substituents. The aziridine, with a strong electron-withdrawing N-tosyl substituent, was converted to the anion **37** with

SCHEME 21

SCHEME 22

SCHEME 23

SCHEME 24

molecules. They are mostly generated from the corresponding halides by halogen−metal exchange or oxidative addition of the halides to low-valent metals. The stability of these sp² hybridized metal species is highly dependent on the following: (1) the electronegativity difference between the carbon and the heteroatom (X in **42−44**), (2) the electronegativity difference between carbon and metal, and (3) the affinity of the metal to the fluorine of the trifluoromethyl group [bond strength for metal−F = Li−F 138, Mg−F 110, and Zn−F 88 kcal/mol]. Thus, ethenyl metals **42** 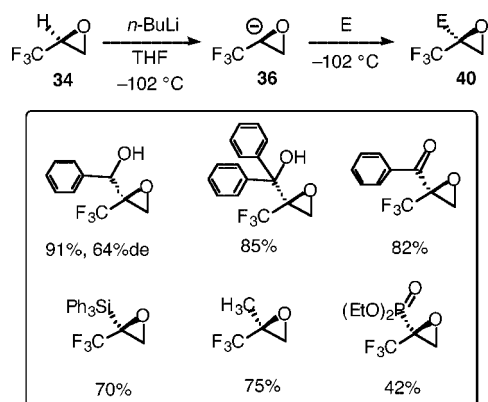are most stable, and acetyl metals **44** are least stable (stability order, metal−C=C > metal−C=NR > metal−C=O). The following is a brief summary of the generation, stability, reactivity, and synthetic applications of the α-trifluoromethylated sp²-hybridized metal species **42**, **43**, and **44** (Scheme 25).

SCHEME 25

4.1. α-Trifluoromethylethenyl Metals. α-Trifluoromethylethenyl metals **42** (metal = Li, Mg, Zn, B, Si, Sn, and Pd) have been investigated. Their stability is dependent on the degree of metal−carbon bond covalency (electronegativity of Li, Mg, Zn, Si, Sn, B, Rh, and Pd = 0.98, 1.31, 1.65, 1.90, 1.96, 2.04, 2.20, and 2.28, respectively) and also on the affinity of the metal to fluorine. The lithium species **46** is generated by bromine−lithium exchange of 2-bromo-3,3,3-trifluoropropene **45** with *n*-BuLi in hexane at below −90 °C and can be trapped with carbonyl compounds (32−51% yield).[64] However, the lithium species **46** is extremely unstable even at around at −90 °C, due to the strong affinity of lithium to fluorine and also due to the strong ionic nature of the lithium−carbon bond. Thus, it undergoes defluorination rap-
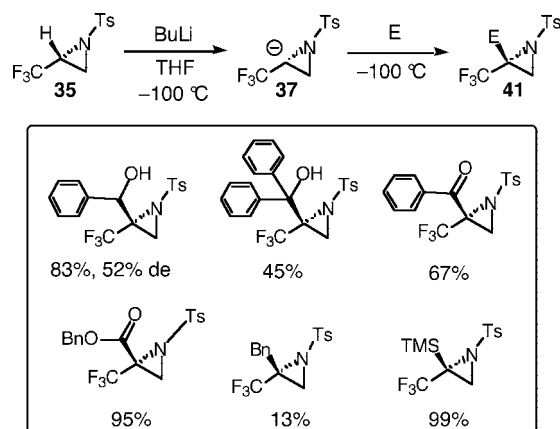
n-BuLi. The anion could react with a variety of electrophiles in good yields (Scheme 24). The aziridinyl anion is also thermally unstable, so these reactions should be conducted below −100 °C.[21]

The aziridines with *N-o*-anisyl and *N-p*-anisyl substituents, which could π-conjugate to the nitrogen atom, were converted to the anion by *sec*-BuLi (*n*-BuLi failed to deprotonate of **35**). However, generation of anion from *N*-benzyl-2-trifluoromethylaziridine with *sec*-BuLi was unsuccessful. Thus, the trifluoromethyl group alone would not be enough to generate and stabilize the α-trifluoromethylaziridinyl anions.

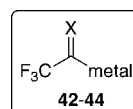# 4. α-Trifluoromethylethenyl Metals and Their Related Metal Species

α-Trifluoromethylethenyl metals **42** and the related trifluoroacetimidoyl- (**43**) and trifluoroacetyl- (**44**) metals have been employed for the preparation of trifluoromethylated organic

idly, resulting in the formation of 1,1-difluoropropadiene **47**.[65] Some results obtained on reacting **45** with *n*-BuLi at low temperature for 15 min are listed in Scheme 26, which indicates that about 70% of ethenyl-lithium **46** undergoes defluorination at −78 °C.[66] The corresponding lithium species **49** of 2-bromopentafluoropropene **48** is also generated in a similar manner (Scheme 26).[67]

SCHEME 26

| | −78 °C / 15 min | 20% | 54% | 17% |
| | −96 °C / 15 min | 31% | 11% | 58% |
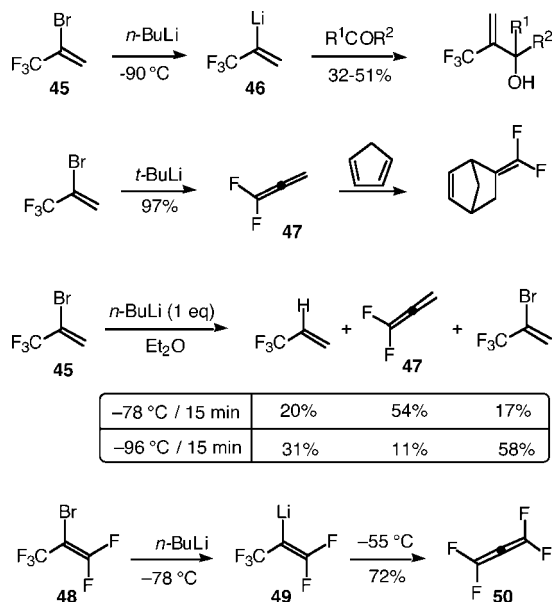
Bromide **45** reacts with magnesium metal smoothly at 0 °C to form the Grignard reagent **51**, which spontaneously reacts with meth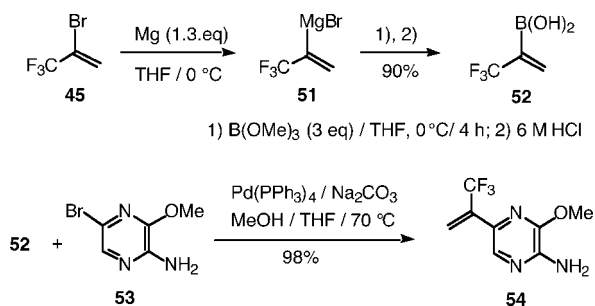yl boronate under Barbier conditions, affording trifluoromethylethenyl boronic acid (**52**).[23] The boronic acid **52** is useful for Pd-catalyzed cross-coupling with highly functionalized heteroaromatic bromide **53** (Scheme 27).[23]

SCHEME 27

The corresponding zinc species is more stable than the lithium and magnesium reagents, and thus is generated by the oxidative addition of **45** to Zn(Ag) in the presence of TMEDA (in THF at 60 °C for 6 h, 93%). It can be stored at room temperature over months or heated at 70 °C for a prolonged time in the absence of air and moisture.[68] It is less nucleophilic

SCHEME 28
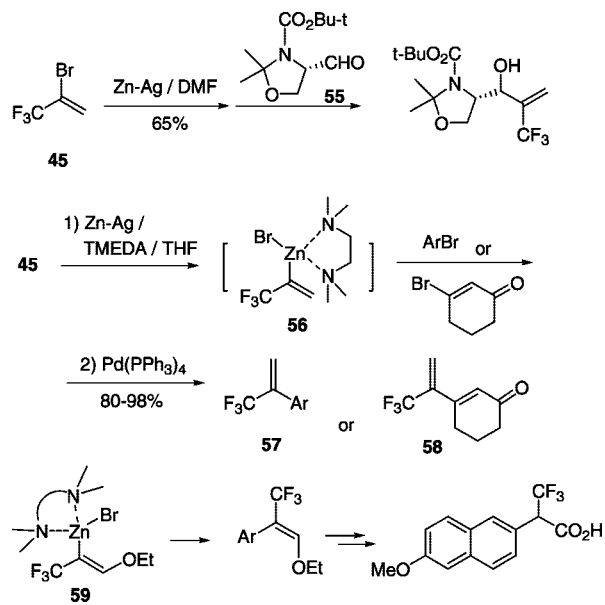
SCHEME 29
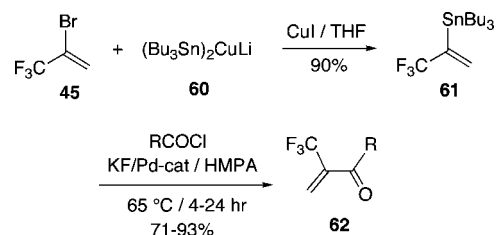
than the lithium species and thus reacts with the formyl group of **55** chemoselectively[69] and with carbon dioxide to give trifluoromethacrylic acid.[70] The zinc reagent **56** is stabilized by chelation with TMEDA in THF. It undergoes palladium-catalyzed cross-coupling with aryl or alkenyl bromides and alkenyltriflate, providing α-trifluoromethylstyrenes **57** and β-trifluoroisopropenylcyclohexenone **58**.[68] The cross-coupling of 2-bromo-6-methoxynaphthalene with the ethoxylated zinc reagent **59** provides a precursor of trifluoromethylnaproxen (Scheme 28).[71]

Trifluoromethylethenyl-stannane **61** is successfully prepared by the stannylcupration of the bromide **45** with bis-(stannyl)copper lithium **60**, where the stannyl group is incorporated into C2 rather than C1, although most of nucleophiles preferentially attack C1 of **45**. Vinylstannane **61** reacts with a variety of acyl halides under Pd-catalyzed cross-coupling conditions in the presence of CuI, affording α-trifluoromethyl-α,β-unsaturated ketones **62**,[72] whereas the corresponding zinc reagent does not (Scheme 29).

The trifluoroisopropenyl-palladium reagent **63** is readily generated by the reaction of the bromide **45** with PdCl$_2$, and it subsequently undergoes carbon−carbon bond formation

SCHEME 30
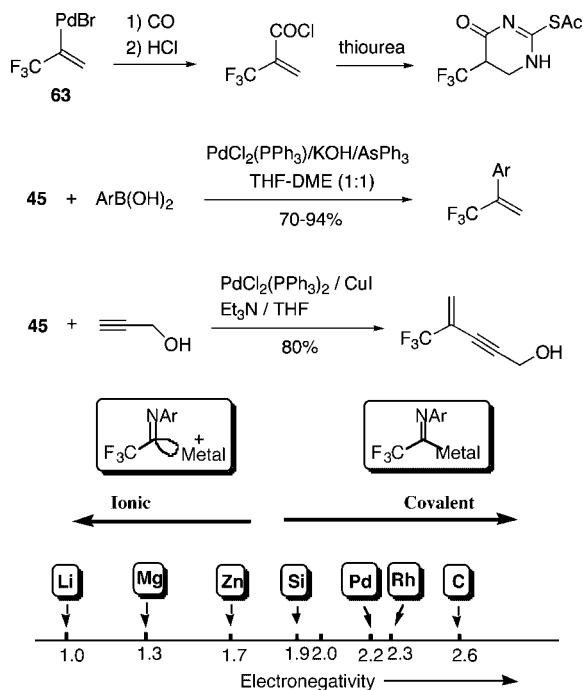
FIGURE 1. Ionic character of the carbon−metal bond in trifluoroacetimidoyl metals.

with carbon monoxide,[73] aryl and alkenyl boronic acids,[74] and terminal alkynes under Sonogashira conditions (Scheme 30).[75]

4.2. Trifluoroacetimidoyl Metals. The stability and the reactivity of trifluoroacetimidoyl metals are also remarkably dependent on the ionic nature of the carbon−metal bond, which is closely related to the electronegativity difference between carbon and the metals. Figure 1 illustrates the ionic character of the carbon−metal bond in trifluoroacetimidoyl metals. The lithium species is the least stable, so it must be generated and handled at temperatures below −60 °C; meanwhile, the palladium and rhodium species can be handled at over 100 °C for prolonged times.

4.2.1. Trifluoroacetimidoyl Lithium, Magnesium, And Zinc Reagents. The trifluoroacetimidoyl lithium species **65** is generated readily by a lithium−iodine exchange reaction of iodide **64** at −70 °C and can be trapped with electrophiles (Scheme 31). The major side reaction of the reagent at temperatures above −60 °C is migration of lithium to imino-nitrogen from imino-carbon to generate a carbene-type intermediate **66**, which readily undergoes dimerization.[24,25] The driving force for the exclusive migration of lithium in **65** would arise from the polar nature of the carbon−nitrogen bond and the strong affinity of the lithium cation to the imino nitrogen, since lithium in trifluoromethylethenyl lithium does not migrate to the β-carbon. In order to avoid the unfavor-

SCHEME 31
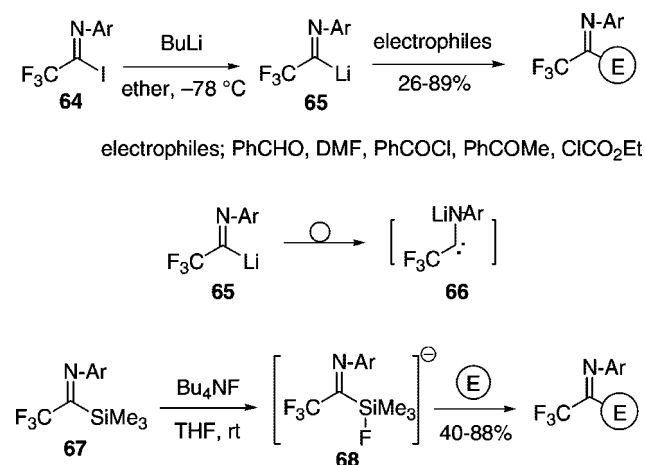
able lithium migration and to generate the more stable trifluoroacetimidoyl carbanion equivalent, fluoride promoted desilylation and alkylation of trifluoroacetimidoyl silane **67** via fluorosilicate **68**, the corresponding carbanion equivalent, has been devised (Scheme 31).[26]

The trifluoroacetimidoyl silane **67** is prepared via the magnesium reagent **70** by the reaction of trifluoroacetimidoyl chloride with metal magnesium at −73 °C.[76] In contrast to the instability of lithium species, alkylation via the silane **67** can be conducted even at 50 °C. Interestingly, the reaction of **69** with magnesium at 0 °C activates both carbon−chlorine and carbon−fluorine bonds successively, affording the doubly silylated products **71**, which are synthetic precursors both for **72** and **73**. One of the synthetic applications of **71** is shown in Scheme 32.[77] This double silylation of **69** via **67** is easily understood by the fact that trifluoromethyl imines **74** undergo Mg-promoted defluorinative silylation leading to **75** (Scheme 33).[78]

The corresponding zinc species is more stable than the lithium species. It can be generated by the oxidative addition of **69** to metal zinc (Zn/Al) at room temperature and can be alkylated with electrophiles.[79]

4.2.2. Trifluoroacetimidoyl Palladium and Rhodium Reagents. The trifluoroacetimidoyl palladium species **77** is easily generated by the oxidative addition of trifluoroacetimidoyl halides **76** (halogen = I, Br, or Cl) to zerovalent palladium (Scheme 34). Trifluoroacetimidoyl iodide **76** (X = I) is a favorable substrate for the palladation since it reacts rapidly with Pd(0), but the corresponding chloride **76** (X = Cl) is also usable under reaction conditions lacking any nucleophiles. For example, alcoholysis (replacement of halogen in **76** with alkoxy group of alcohol) and palladation are competitive in carboalkoxylation of **76**, where alcoholysis is much faster for the chloride **76** (X = Cl) than palladation. Meanwhile, palla-

SCHEME 32
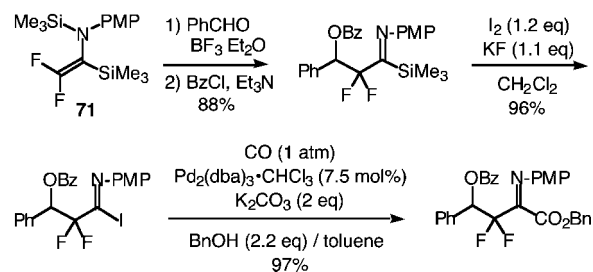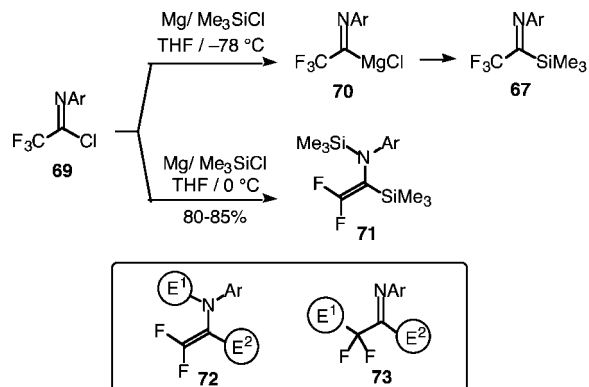
SCHEME 33
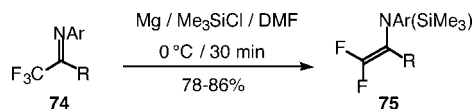
dation is much faster for the iodide **76** (X = I), which is a favorable substrate for the carboalkoxylation (Scheme 34).[80] Even *tert*-butoxycarbonylation of **76** (X = I) is successful when DMF or DMI is used as a solvent.[81] The Heck−Mizoroki reaction with alkenes and the Sonogashira reaction with alkynes provide alkenyl imines **78** and alkynyl imines **79** at room temperature, respectively.[82] The palladium species **77** is stable enough to be handled at higher temperatures. Under a CO atmosphere, the palladium catalyst promotes homocoupling of **76** (X = I) at 60 °C, providing trifluoromethylated diimines **81** (Scheme 34).[83]

Palladium-catalyzed intramolecular chloro-imination of an alkyne is a unique reaction where both chlorine and an imidoyl moiety are incorporated into a carbon−carbon triple bond simultaneously (Scheme 35). The chloride **83** is usable for the construction of functionalized quinolines, **84**, where 4-chlorine and 3-hydrogen can be further functionalized for quinolonecarboxylic acids **85** (Scheme 35).[84]

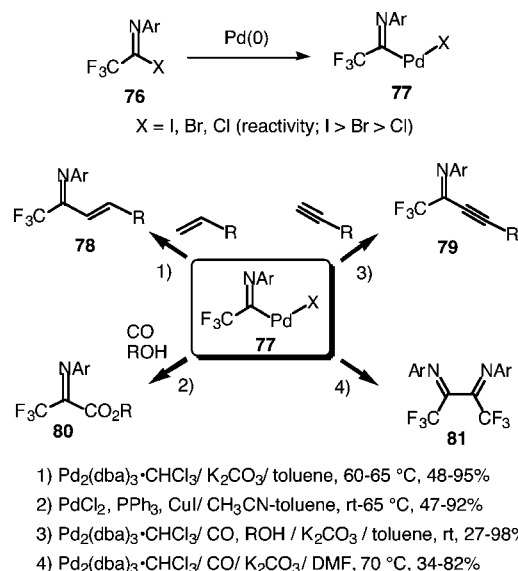The rhodium catalyst activates the carbon−chlorine bond of imidoyl chlorides **86** and then induces carbo-rhodation to the triple bond of alkynes, followed by ring closure via carbon−carbon bond formation leading to 2-trifluorometh-

SCHEME 34

1) Pd₂(dba)₃•CHCl₃/ K₂CO₃/ toluene, 60-65 °C, 48-95%
2) PdCl₂, PPh₃, CuI/ CH₃CN-toluene, rt-65 °C, 47-92%
3) Pd₂(dba)₃•CHCl₃/ CO, ROH / K₂CO₃ / toluene, rt, 27-98%
4) Pd₂(dba)₃•CHCl₃/ CO/ K₂CO₃/ DMF, 70 °C, 34-82%

SCHEME 35

Rf = CF₃, CHF₂, C₃F₇

1) Pd₂(dba)₃ / BINAP/ AcONa
  / toluene, 30 °C, 5 h,
  74 - 88%
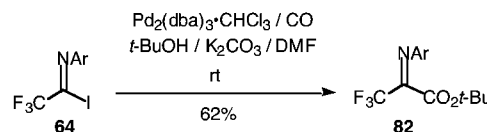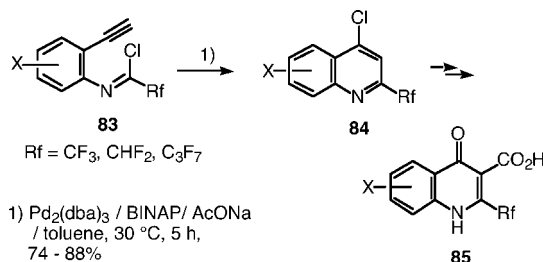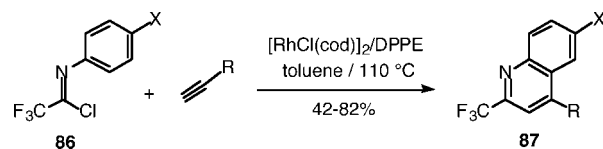
SCHEME 36

ylquinolines **87** (Scheme 36).[85] The rhodium species seems to be stable enough for prolonged heating at 110 °C.

4.3. Trifluoroacetyl Metals. Due to the greater polarity of the carbonyl group compared with the corresponding imino and ethenyl groups, trifluoroacetyl metals are extremely unstable, so very few of them have been successfully employed for organic synthesis. No successful synthetic work on trifluoroacetyl lithium, magnesium, and zinc species has been reported. Less ionic, that is, more covalent, carbon−metal bonds would be needed for synthetically feasible trifluoroacetyl metals. So far, palladium and rhodium species have been studied.

SCHEME 37
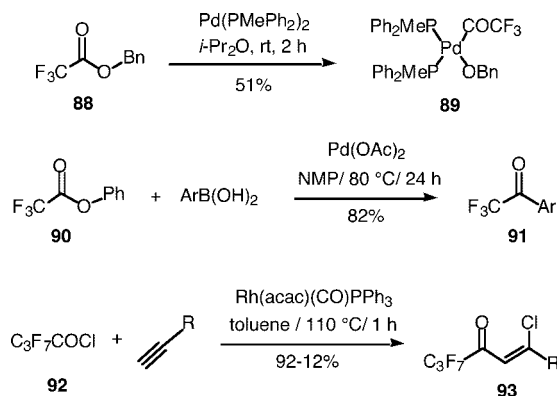
The trifluoroacetyl palladium species is prepared from benzyl trifluoroacetate and is isolated as a phosphine complex, **89**.[86] Phenyl trifluoroacetate undergoes palladium-catalyzed cross-coupling with arene boronic acid (Scheme 37).[87] The oxidative addition of **88** occurs at the bond between acetyl carbon and benzyloxy oxygen, rather than between the benzyl carbon and trifluoroacetoxy oxygen. Rhodium-catalyzed chloro-perfluoroacylation of terminal alkynes provides β-chloro-α,β-unsaturated ketones **93** in reasonable yields, where no decarbonylation from $C_3F_7CORhCl$ is observed.[88]

5. Conclusion

α-Trifluoromethylated carbanions are, in general, unstable. Their stability is greatly affected by several factors, such as hybridization of the orbital that accommodates lone pair electrons, the electronic nature of the α-substituents, the degree of covalency in a bond between the carbon and metal, the class of countercation, stabilization by chelation of a metal cation, and others. Therefore, stability can be controlled by tuning these factors appropriately.

The study of the chemistry of α-trifluoromethylated carbanions for organic synthesis has been progressing steadily. However, the simplest trifluoroethyl and trifluoroacetyl carbanions have never been successfully generated. Elegant generation and synthetic applications of these metal species are one of the attractive and challenging subjects for active investigation in the future.

BIOGRAPHICAL INFORMATION

Kenji Uneyama was born in 1941. He obtained his Doctor of Technology under the direction of Prof. Oae while studying the chemistry of divalent sulfur-stabilized carbanions at the Osaka City University in 1969. He became a Lecturer at the Okayama University in 1969, an Associate Professor in 1970, and a full Professor in 1984. He spent one year (1972−1973) at The Ohio State University as a postdoctoral fellow to study electrochemi-

cal molecular transformation of small aza-ring compounds with Prof. Gassman. He has been a visiting professor at the University of Paris (Chatenay-Malabry) and the University of Valencia. He served as the vice chair for the editorial board of *Chemistry Letters* and *Bulletin of the Chemical Society of Japan* and has been a member of the editorial board of *Journal of Fluorine Chemistry*. He had enjoyed research on the synthesis of natural products and electrochemical molecular transformation in Prof. Torii's group in Okayama for 14 years. Since 1985, he has been involved in the study of organofluorine chemistry, which focuses on the synthetic methodology of organic fluorine compounds and covers particularly the chemistry of trifluoroacetimidoyl halides and C−F bond activation for synthetic chemistry. He has received the Award of the Society of Synthetic Organic Chemistry, Japan, and the ACS Award for Creative Work in Fluorine Chemistry.

Toshimasa Katagiri was born in 1960. He received his Doctor of Science degree in 1988 under the direction of Prof. Maruyama at Kyoto University. During 1988−1990, he carried out postdoctoral work on the Mechanism of the Grignard reaction. Then, he joined Nippon Mining Company (Japan Energy Corporation), where he first studied organofluorine chemistry. Since 1995, he has been a Lecturer and then an Associate Professor at the Okayama University (Uneyama's group). His research interest is the reaction and synthesis of organofluorine compounds, their properties, and their utilization in nanoarchtectures and new nanofunctions of the fluorinated tunnel micropores.

Hideki Amii was born in 1968. He received his Doctoral degree in 1996 under the direction of Prof. Ito. During 1996−2003, he worked as Research Associate at the Okayama University (Uneyama's group). He carried out postdocotral work in France with Dr. Bertrand at Université Paul Sabatier during 2000−2001. He was the recipient of Inoue Research Award for Young Scientists (1998), the Otsuka Award in Synthetic Organic Chemistry, Japan (1998), and the Chemical Society of Japan Award for Young Chemists (2002). In 2003, he was appointed to Associate Professor at Kobe University. His research interest is currently in the synthesis of organofluorine compounds by the use of metal reagents.

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