Contribution

Chemistry of Trifluoroacetimidoyl Halides as Versatile Fluorine-containing Building Blocks

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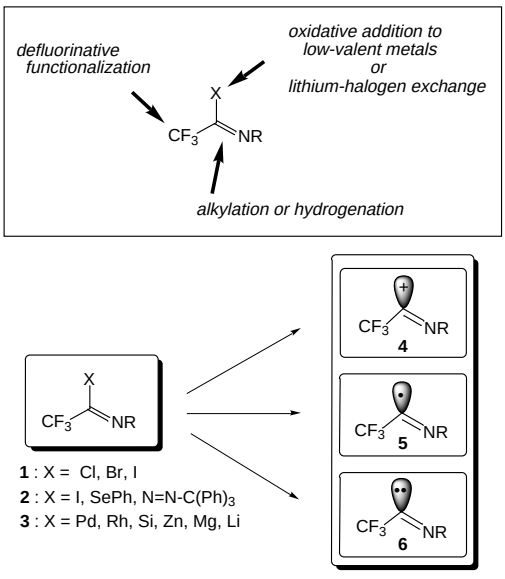
1. Outline of trifluoroacetimidoyl halides

The trifluoromethyl group involved in organic compounds plays important roles as a key functional group in medicine, agricultural chemicals and electronic materials like liquid crystals. Common methods for introducing the trifluoromethyl group (CF_3 group) into organic compounds are categorized into three; 1) the use of building blocks containing CF_3 group, 2) trifluoromethylation by the use of trifluoromethylating agents such as CF_3-TMS, FSO_2CO_2Me, CF_3I, *etc.*, and 3) the transformation of a functional group such as CCl_3 and CO_2H groups to CF_3 group by the use of fluorinating agents such as F_2 and HF. The method 3 is conventionally used for the industrial mass production of CF_3-containing molecules, which are mostly structurally simple and stable molecules. On the other hand, methods 1 and 2 have been used for the structurally complex and valuable CF_3-molecules in small laboratory bases.[1)]

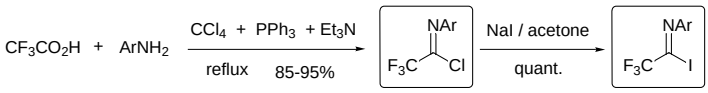
Not many CF_3-containing synthetic blocks are commercially available, therefore it is very important to develop more sophisticated building blocks. They should be synthesized in high yields from easily available starting materials and should contain highly potential functional groups usable for further molecular modification. On this basis, trifluoroacetimidoyl halides are one of the unique and valuable CF_3-containing synthetic building blocks due to the following promising profiles; a) easy one-step synthesis from a very available trifluoroacetic acid in excellent yields, b) relatively stable to be stored, and c) containing highly potential functional groups such as CF_3, imino C=N double bond and halogen (Scheme 1).

(Synthesis)

Imidoyl halides **1** (X: Cl, Br) are synthesized from trifluoroacetic acid in excellent yields (85-95%) as shown in Scheme 2.[2)] It is also possible to use PPh_3Cl_2 instead of carbon tetrachloride (CCl_4) due to the prohibition of its use. In industrial manufacturing, the corresponding trifluoroacetamide can be converted to imidoyl chloride by the use of phosphorus oxychloride.[2c)]



Scheme 1.



Scheme 2.

Imidoyl iodide **1** (X: I) is synthesized quantitatively from the corresponding chloride by the exchange of chlorine for iodine with NaI in acetone. Imidoyl chloride **1** is relatively stable, therefore it is sometimes possible to recover the unreacted **1** by silica gel column chromatography. Trifluoroacetimidoyl halides **1** are hydrolyzed slowly under acidic or neutral conditions, but rapidly under basic conditions. In contrast, nonfluorinated imidoyl halides rapidly react with water to form amides in general. The acid stability arises from the restrained protonation of the imino group by an electron-withdrawing effect of the CF_3-group.

(Reactions)

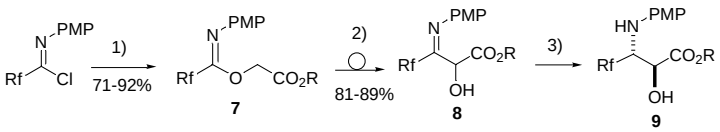
Imidoyl halides **1** have very wide use in various organic reactions; *via* carbocation **4**, radical **5** and carbanion species **6** (Scheme 1). For example, the chloride **1** (X=Cl) can be used for nucleophilic substitution reactions with nucleophiles or acid-catalyzed Friedel-Crafts reactions to convert chlorine to other functional groups. Iodo, seleno and azo-imidoyl compounds **2** produce radical species **5** by photochemical and thermal reactions, which form new carbon-carbon bonds with alkenes, alkynes and aromatic compounds. Imidoyl halide **1** can be converted to the corresponding imidoyl metals **3** by the oxidative addition to low valent transition metals or the halogen-metal exchange reaction, which can also form new carbon-carbon bonds by the electrophilic reactions with electrophiles or the transition metal-catalyzed cross-coupling reactions (Scheme 1).

2. Reactions of trifluoroacetimidoyl halides with nucleophilic reagents

2.1. The reactions with oxygen nucleophiles

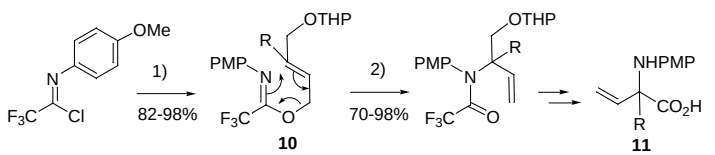
Since the imino carbon of imidoyl chloride **1** has high electrophilicity, the reaction with alcohols easily occurs with a base catalyst under mild conditions and produces the corresponding imidates **7** and **10** in good yields (Scheme 3 and 4).

Each of imidates **7** [3] and **10** [4] can be used for the synthesis of fluorinated amino acid derivatives through rearrangement. The driving force of these rearrangements arises from higher thermodynamic stability of the corresponding amides than the starting imidates. Imidoyl chloride **1** reacts with diazoalcohol **12** to produce the amide **13** (Scheme 5).[5] The carbene intermediate generated from **13** is attacked by amido carbonyl oxygen intramolecularly, followed by the rearrangement to form **14**. The rearrangement is highly substituent dependent. For example, the trichloroacetamide **15** is converted to **16** by the 1,2-shift of the aryl group. In the overall transformation (Scheme 5), the hydroxyl group at C-3 of **12** shifts to C-2 of **14** *via* the imidate-amide rearrangement.



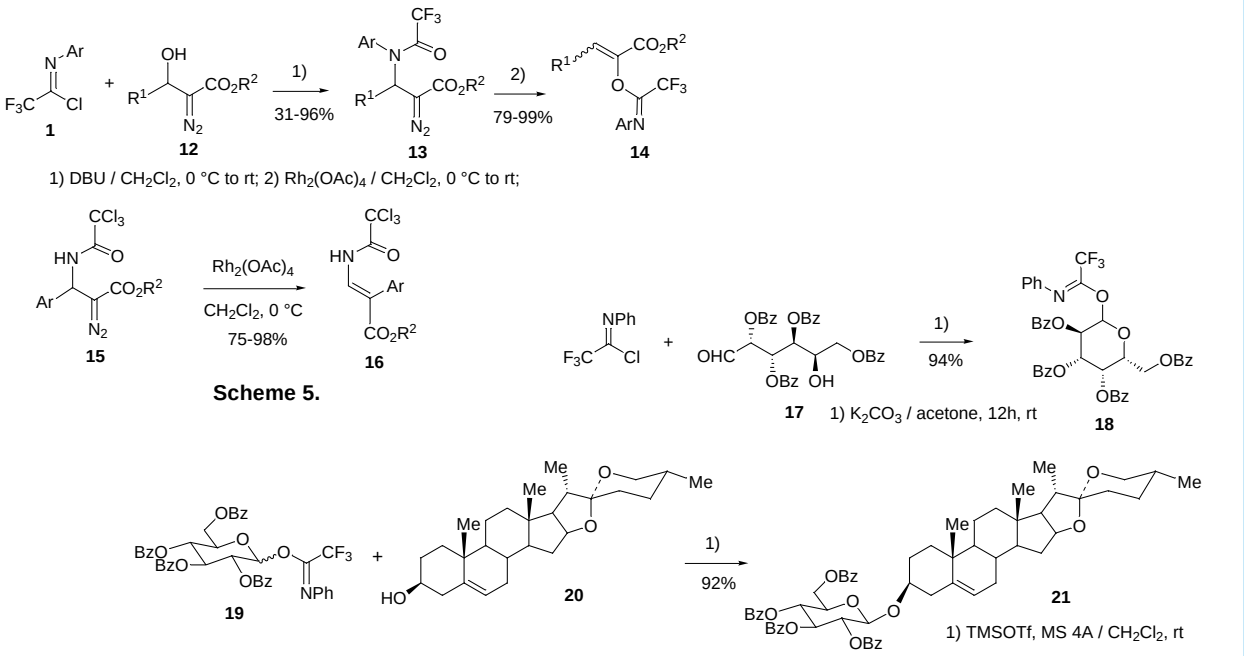
1) $HOCH_2CO_2R$, Et_3N / benzene, 50 °C, 5 h; 2) LiTMP / DME-THF, -105 → -70 °C;
3) $NaBH_4$, $ZnCl_2$ / i-PrOH-THF Rf = CF_3, $CClF_2$, C_3F_7

Scheme 3.



1) n-BuLi / allylic alcohols / THF, -78 °C; 2) benzene, rt

Scheme 4.



Scheme 5.

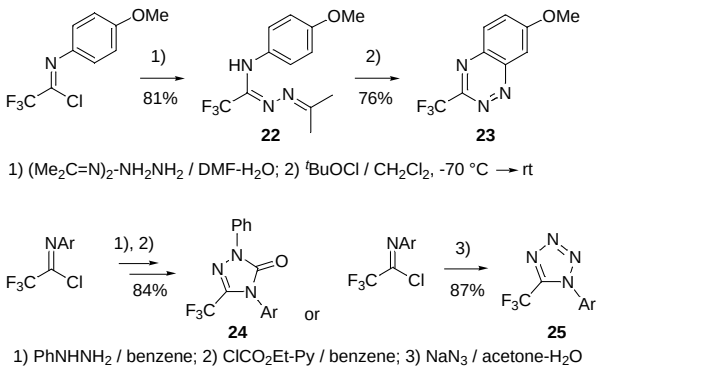
Scheme 6.

Since Yu *et al* reported that trifluoroacetimidate **19** is a novel glycosyl donor due to its high reactivity with alcohols and the good leaving ability of the trifluoroacetimidoyl group under Lewis acid-catalyzed conditions,[6b] the trifluoroacetimidate **19** has been often used for the glycosylation reaction.[6] The reaction of trifluoroacetimidates (glycosyl donor) with alcohols (glycosyl acceptor) occurs smoothly under mild conditions in high yields as shown in Scheme 6.

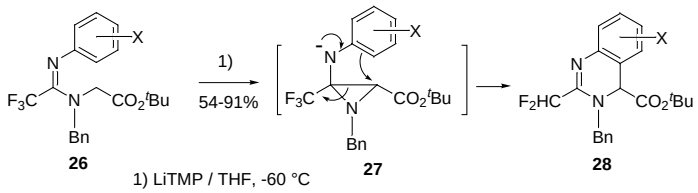
2.2. Reaction with nitrogen nucleophiles

Chlorine of the imidoyl chloride **1** can be replaced smoothly with nitrogen nucleophiles to give various iminoamides, which are transformed into useful trifluoromethyl nitrogen heterocycles. Some synthetic applications such as oxidative cyclization of **22** with *t*-BuOCl to CF_3-benzotriazine **23**,[7] reaction with phenylhydrazine followed by condensation-cyclization to the CF_3-triazole **24**, and cyclization *via* imidoyl azide to the CF_3-tetrazole **25**[8] are shown in Scheme 7. The difluoromethyl quinazoline **28** is synthesized by the successive cyclization-defluorination sequence *via* aziridine intermediate **27** starting from imidamide **26** (Scheme 8).[9]

Scheme 7.



Scheme 8.

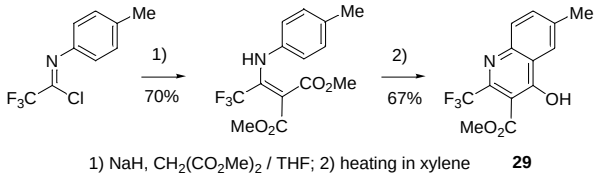


2.3. Reaction with carbon nucleophiles

Imidoyl chloride **1** can also react with carbon nucleophiles, therefore it is often used for the part of CF_3-containing compounds. Examples of the syntheses of 2-CF_3-substituted quinolone carboxylic acid **29**[10] and both diastereoisomers of 2-thio-3-aminobutanoic ester **30**[11] are shown in Schemes 9 and 10, respectively.

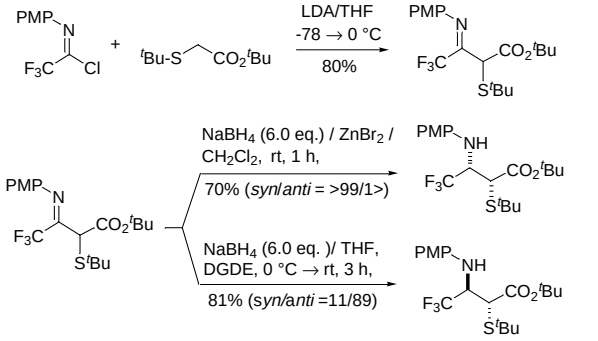
Fustero *et al* have synthesized an optically pure cyclic amino acid **36** *via* the reaction of difluoroimidoyl chloride **31** with optical active sulfoxide **32**, followed by the diastereoselective reduction of imino group using the sulfinyl group as a chiral auxiliary. A ring-closing metathesis reaction with Grubbs' catalyst derived β,β-difluoro cyclic amino acid **36** (Scheme 11).[12] The related 5- and 6-membered β,β-difluoro cyclic amino acids have been synthesized from the corresponding fluorinated imidoyl chlorides.[13] The same methods can be applied to the synthesis of trifluoro, difluoro and chlorodifluoro alanines **37** (Scheme 12).[14]

Diastereoselective reduction of the enamine **38**, which is synthesized from chiral oxazoline **39** and imidoyl chlorides, provides β-amino acid derivatives **40**. This method gave optically pure β-amino acids **42** (Scheme 13).[15]



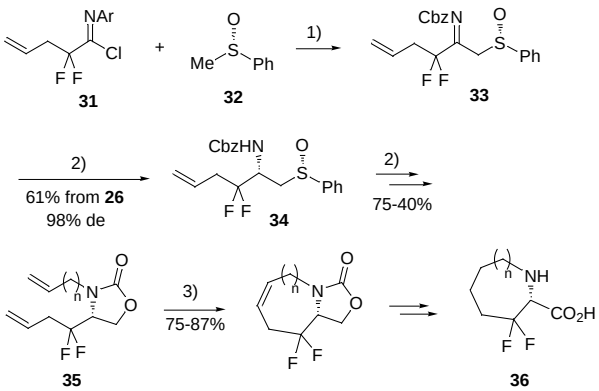
1) NaH, $CH_2(CO_2Me)_2$ / THF; 2) heating in xylene **29**

Scheme 9.



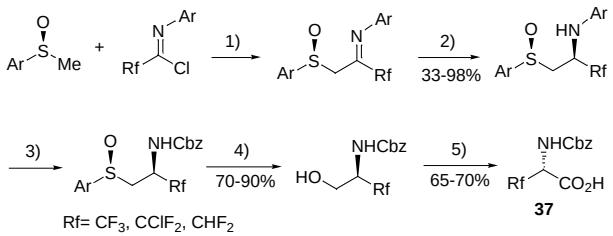
1) CAN, H_2NNH_2; 2) aq HCl / MeOH **30**

Scheme 10.



1) (i) LDA / THF, -78 °C, (ii) Bu_4NBH_4 THF-MeOH, -70 °C, (iii) CAN / MeCN-H_2O, (iv) $ClCO_2Bn$, K_2CO_3; 2) (i) TFA, (ii) K_2CO_3, (iii) $NaBH_4$, (iv) BzOH, DCC, DMAP, (v) CH_2=CH$(CH_2)_n$Br, NaH, DMF; 3) Grubbs' RCM.

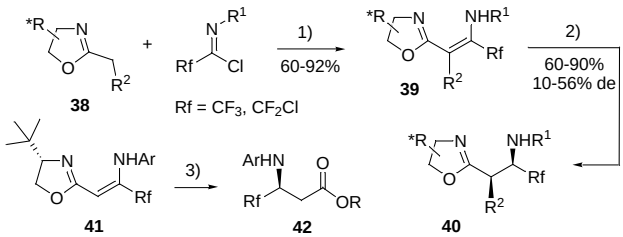
Scheme 11.



Rf= CF_3, $CCIF_2$, CHF_2

1) LDA (2.0 eq.), THF, -78 °C; 2) Bu_4NBH_4 / MeOH, -70 °C; 3) (i) CAN, MeCN / H_2O, rt, (ii) $ClCO_2Bn$ / dioxane, 50% aq. K_2CO_3; 4) (i) TFAA / MeCN, *s*-collidine, 0 °C, (ii) 10% K_2CO_3, (iii) $NaBH_4$, H_2O; 5) RuO_2•xH_2O / $NaIO_4$, acetone / H_2O, rt.

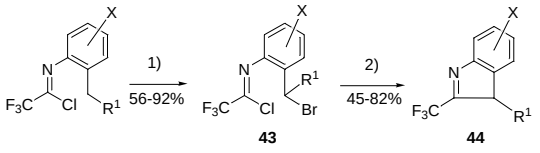
Scheme 12.



Rf = CF_3, CF_2Cl

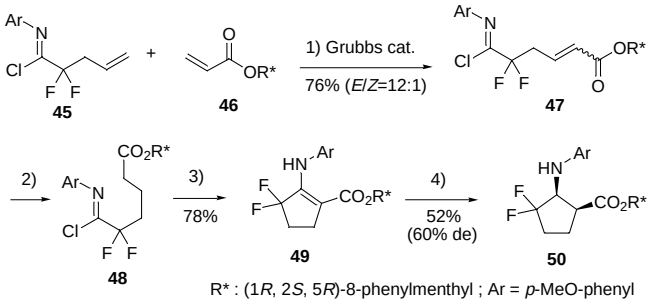
1) LDA / THF, -78 °C, 2-8 h; 2) $NaBH_4$, ZnI_2 / CH_2Cl_2, rt or H_2, Pd/C, MeOH, rt; 3) (i)1*N* HCl, heat, (ii) ROH / HCl.

Scheme 13.



1) NBS, BPO / CCl_4, reflux; 2) Mg / THF

Scheme 14.



R* : (1*R*, 2*S*, 5*R*)-8-phenylmenthyl ; Ar = *p*-MeO-phenyl

1) [($IMesH_2$)(PCy_3)Cl_2Ru=CHPh] (5 mol %); 2) H_2/Pd/C; 3) LDA / THF; 4) HCO_2NH_4 Pd / C (10%)/EtOH, microwave, 100 °C / 45 min.

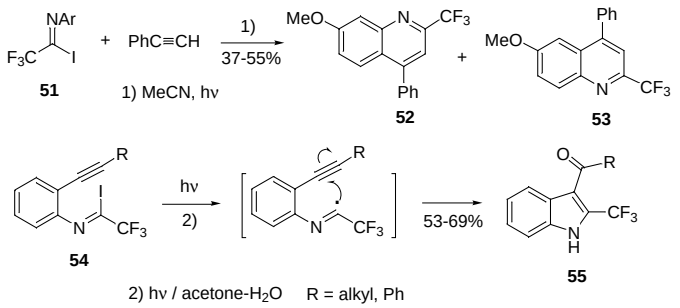
Scheme 15.

2.4. Intramolecular reactions with carbon nucleophiles

The intramolecular reaction of the imidoyl moiety with carbon nucleophiles has been used for the synthesis of nitrogen heterocycles. Bromine at the benzyl position of imidoyl chlorides **43** reacts chemoselectively with magnesium even in the presence of aromatic C-Cl bond, then intramolecular substitution follows to produce 2-CF_3-indole derivative **44** (Scheme 14).[16] Hydrogenation of **47** followed by intramolecular alkylation produces β-amino-α,β-unsaturated cyclic ester **49**. The compound **47** is synthesized from difluoroimidoyl chloride **45** and chiral acrylate **46**. Diastereoselective hydrogenation of **49** produces 5-membered cyclic amino acid **50** in a moderate de (Scheme 15).[17]

3. Radical reaction of trifluoroacetimidoyl halides and the related compounds

When the functional group X of the trifluoroacetimidoyl derivatives **2** is iodine, selenium or azo functional groups, the corresponding radical **5** is produced by photo-irradiation or heating, which triggers the radical reaction with alkenes and alkynes. Scheme 16 shows both intra-molecular and intermolecular reactions. Photoreaction of **51** with phenylacetylene produces a mixture of isomers **52** and **53**. Attack of the vinyl radical intermediate at the ipso position and the breaking of C-N bond of the spiro ring followed by the 1,2-migration lead to compound **52**. On the other hand, the breaking of C-C bond followed by the 1,2-migration lead to another compound **53**.[18b] 3-Ketoindole **55** is produced by the photolysis of **54**. The intramolecular carbo-iodination to a triple bond *via* the imidoyl radical intermediate and the subsequent hydrolytic transformation of iodoalkylidene moiety to an acyl group results in 3-ketoindole **55** as a final product.[18a]



2) hν / acetone-H_2O R = alkyl, Ph

Scheme 16.

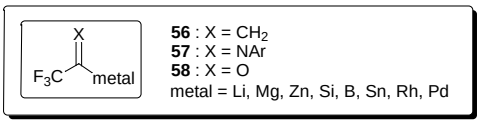
4. Reactions with trifluoroacetimidoyl metals

Trifluoroacetimidoyl metals **57** are potentially applicable for a variety of syntheses of trifluoromethyl nitrogen compounds *via* the metal-based C-C bond formations. Three active species **56**, **57**, and **58** are available with various X shown in Scheme 17. Many reports have been already published especially about isopropenyl metals **56**.[19] On the other hand, trifluoroacetyl metals **58** are very unstable and only trifluoroacetyl palladium species has been employed for organic synthesis.[20] The chemistry of trifluoroacetimidoyl metals **57** has been extensively explored in our group. In this account, the chemistries of the trifluoroacetimidoyl metals **57**, their preparation, properties, reactions, and synthetic applications are described.

The stability of the imidoyl metals **57** is primarily dependent on the degree of the covalency of the carbon-metal bond. The smaller difference of electronegativities between carbon and metal gives higher stability (Figure 1). For example, Pd species are stable even at 130 °C for a long time. Meanwhile, lithium species have to be kept at a temperature lower than at least –60 °C, although the lithium species are most reactive as carbanions.

Imidoyl lithium **59** is formed *in situ* by the exchange reaction of iodine with lithium on treating **1** with butyl lithium, and it immediately reacts with nucleophiles to produce **60**. At above –60 °C, unstable lithium species **59** dimerizes *via* carbene intermediate **61** (Scheme 18).[21] The corresponding zinc species generated with Zn-Al in DMF at room temperature is more stable than lithium species and smoothly reacts with electrophiles (Scheme 19).[22]

Imidoyl magnesium is generated by the reaction of imidoyl chloride **1** with magnesium in the presence of TMS-Cl in THF. The magnesium species is relatively stable to be handled at 0 °C. Selective silylation of **1** on the imino carbon at –70 °C gives imidoyl silane **62** in about 70% yield (Scheme 20).[23] Interestingly, the reaction at 0 °C gives the double silylation product **63** in good yields. The successive magnesium-promoted C-Cl and C-F bond activations proceed leading to the formation of **63**.[24] This bis-silylated enamine **63** has three reaction sites; nitrogen, C-1 and C-2. The stepwise activation of nitrogen and then C-1 with KF provides **64**. Meanwhile, the activation of nitrogen with Lewis acid and then C-1 with KF gives **65**. The Lewis acid-catalyzed alkylation of **63** on C-2 with benzaldehyde produces **66a**. Then, the benzoate **66b** is transformed to a precursor **68b** of 4-hydroxy-3,3-difluoro-2-aminobutanoic acid (Scheme 20, 21).[24] Fluoride ion-catalyzed desilylative allylation on amino nitrogen and aza-Claisen rearrangement of **69** gives difluoro compounds **70**, **71**, and **72** (Scheme 21).[25]



Scheme 17.

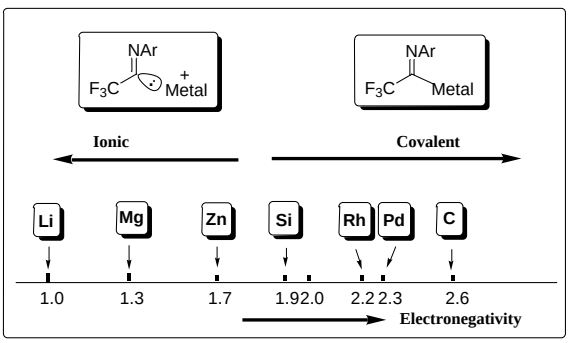
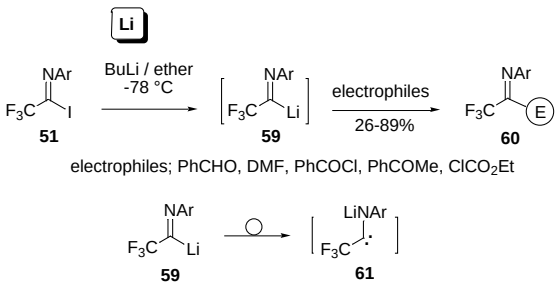
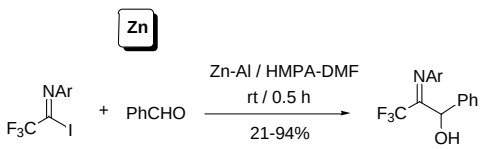


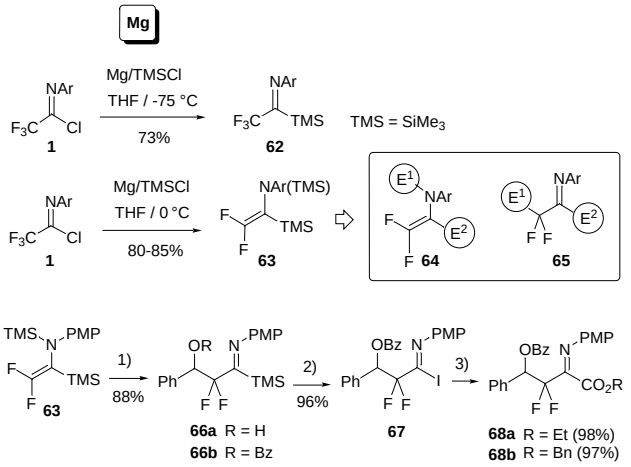
Figure 1. Ionic Charactoer of Carbon-Metal Bond in Trifluoroacetimidoyl Metal



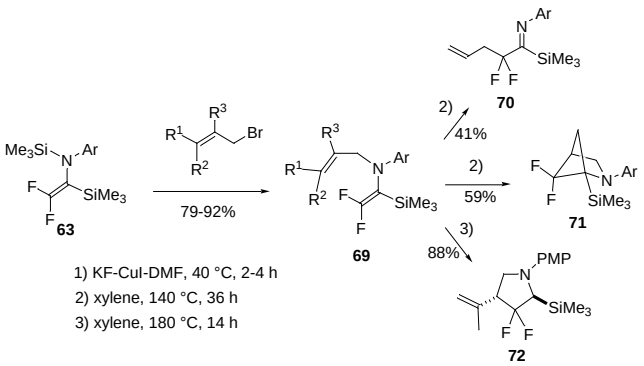
Scheme 18.



Scheme 19.

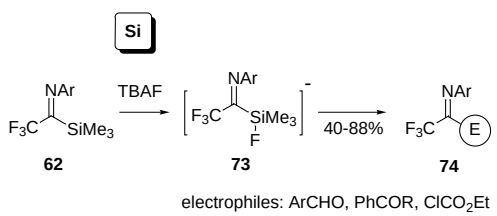


Scheme 20.



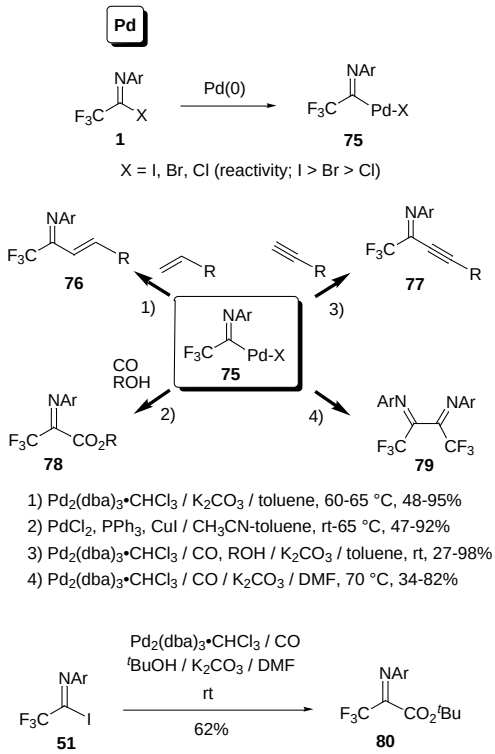
Scheme 21.

The fluoride ion-catalyzed desilylation of **62** can generate the penta-valent silicate intermediate **73**, an imidoyl carbanion equivalent which is much more stable than the lithium species and can be handled and alkylated even at 50 °C to give **74** (Scheme 22).[26] Therefore, the imidoyl silane **62** is useful for the reaction with the less reactive electrophiles.



Scheme 22.

Palladium species **75** can be generated from any imidoyl halides (X = I, Br, Cl). However, oxidative addition of the halide to low valent palladium is rate-determining so that iodo imidoyl is the most useful for the reaction where the oxidative addition and nucleophilic substitution of the imidoyl halide with nucleophiles in the reaction solution are competitive, and in particular the nucleophilic reaction is faster than the oxidative addition. Imidoyl palladium species **75** is used for various C-C bond formations and synthetic applications as shown in Schemes 23 and 24. Both the Heck-Mizorogi reaction with 1-alkenes and the Sonogashira reaction with alkynes are very successful for the preparations of ene-imines and yne-imines, respectively.[27] Pd-catalyzed carboalkoxylation of **1** (X=I) with primary alcohols such as benzyl and ethyl alcohols provides 3,3,3-trifluoro-2-iminopropanoates in excellent yields, which are good precursors for trifluoroalanine.[28] It is noteworthy that even *tert*-butyl ester **78** (R=*t*-Bu) can be prepared in 60-70% yields in DMF or DMI as solvents.[29] In the absence of nucleophiles which trap the palladium species, α-diimines **79** are formed *via* dimerization of **75** (Scheme 23).[30]

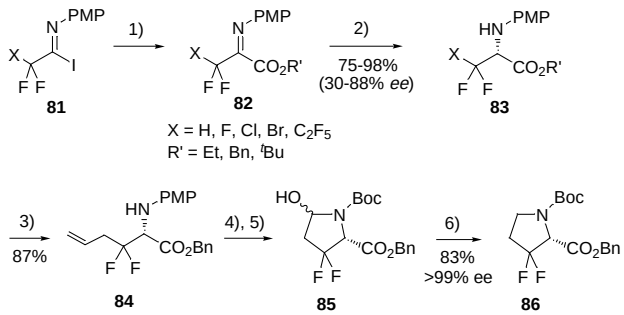


Scheme 23.

Optically pure β,β-difluoroproline **86** is synthesized from bromodifluoroacetimidoyl iodide **81** (Scheme 24).[31] Ester **82** is prepared from imidoyl iodide **81** under Pd catalyzed carboalkoxylation conditions and its imino group is subjected to asymmetric hydrogenation under $Pd(OCOCF_3)_2$ catalyst in trifluoroethanol[32] to produce **83** with 88% ee.[32] The radical allylation of **83** and enantiomeric enrichment of **84** by recrystallization followed by ozonolysis, dehydration and then hydrogenation of **85** lead to the synthesis of enantiomerically pure proline **86**.[31]

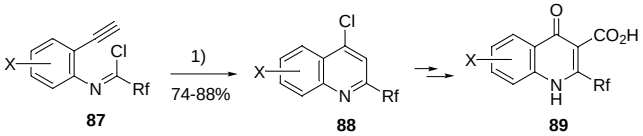
A halogen atom of imidoyl halides **1** is not incorporated into products obtained in so far as these examined reactions (Scheme 23). However, incorporation of both an imidoyl moiety and a halogen atom into a product would increase its additional synthetic value. Scheme 25 shows an example in which both a halogen atom and an imidoyl moiety can be utilized effectively for the synthesis.[33] A chlorine atom at the 4-position of the quinoline ring is useful for the construction of quinolone carboxylic acid **89**.

Scheme 24.



1) $Pd_2(dba)_3$•$CHCl_3$ (Pd: 0.10 eq.), CO (1 atm), R'OH, K_2CO_3, toluene or DMF, DMI, rt; 2) $Pd(OCOCF_3)_2$, (*R*)-BINAP, H_2 (100 atm), CF_3CH_2OH, rt, 24h; 3) $AllylSnBu_3$, AIBN / toluene; 4) (i) CAN / MeCN-H_2O, (ii) CbzCl / $NaHCO_3$ (84%); 5) O_3 / CH_2Cl_2 (90%); 6) (i) PPh_3Cl_2 / DMF, (ii) $RhCl(PPh_3)$-H_2

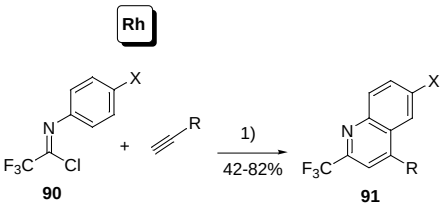
Scheme 25.



Rf = CF_3, CHF_2, C_3F_7; X = H, F, CO_2Et

1) $Pd_2(dba)_3$ / BINAP/ AcONa / toluene, 30 °C, 5 h,

Rhodium catalyst also activates imidoyl chloride **90**. Introduction of alkyne at the ortho position of an *N*-aryl ring and imidoyl carbon *via* imidoyl rhodium species gives the quinoline ring **91**. Reactions with various alkynes construct substituted quinoline skeletons effectively (Scheme 26).[34)]



1) $[RhCl(cod)]_2$ / DPPE, toluene / 110 °C

R	Yield(%)	regio[a]
C_6H_{13}	68	94:6
$SiMe_3$	82	95:5
$C_2H_4SiMe_2{}^tBu$	46	99:1
CH_2SiMe_2Ph	52	95:5
Ph	42	99:1
$CH(OMe)_2$	70	99:1
CO_2Et	70	29:71

[a] regioisomer ratio

Scheme 26.

5. Conclusion

Nowadays, about ten percent of the drugs currently commercialized involve the fluorine atom or a fluorinated functionality which markedly enhances their biological activity. Fluorinated compounds thus have been receiving great attention. However, one of the biggest problems in the synthetic organic fluorine chemistry is a lesser availability of the starting fluorinated compounds usable for the target molecules. On this basis, synthetic organic chemists are responsible for developing versatile fluoroorganic synthetic blocks which can be supplied by the conventional reactions of highly available starting substrates such as trifluoroacetic acid, for example. Trifluoroacetimidoyl halides are such useful and reliable compounds which justify the requirement for the synthetic organic fluorine chemistry. They are prepared by one step reaction of trifluoroacetic acid in an excellent yield under very conventional conditions. The imidoyl halides **1** provide us versatile reactivity as the imidoyl carbocation, radical and carbanion species, in particular imidoyl metals, all of which are reliable for the organic synthesis and will be used more in future.

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Kenji Uneyama was born in Osaka, Japan in 1941. He studied chemistry at the Department of Applied Chemistry, Osaka City University, where he received Bs. Eng., in 1964, Ms. Eng. in 1966, and Dr. Engineering in 1969. His professional academic career started as a lecturer at the Department of Applied Chemistry, Okayama University in 1969, where he was promoted to an associate professor in 1970, and to a professor in 1984. He has been a visiting professor at the Univ. of Paris (Chatenay-Malabry) and the Univ. of Valencia. He served as the vice chair for the editorial board of *Chem. Lett.* and *Bull. Chem. Soc. Jpn.* and has been the member of the editorial board of *J. Fluorine Chem.* Since 1985, he has been involved in study on organofluorine chemistry, which focuses on the synthetic methodology of organic fluorine compounds and covers particularly the chemistry of trifluoroacetimidoyl halides and the C-F bond activation for synthetic chemistry. He has received Award of the Society of Synthetic Organic Chemistry, Japan 1997 and ACS Award for Creative Work in Fluorine Chemistry 2007.