NANYANG TECHNOLOGICAL UNIVERSITY

PART I: FUNCTIONALIZATIONS OF SILICON-BASED COMPOUNDS

PART II: DISPLACEMENT OF HALOGEN ATOM IN AQUEOUS MEDIA

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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PART I: FUNCTIONALIZATION OF SILICON-BASED COMPOUNDS

PART II: DISPLACEMENT OF HALOGEN ATOM IN AQUEOUS MEDIA

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SUMMARY

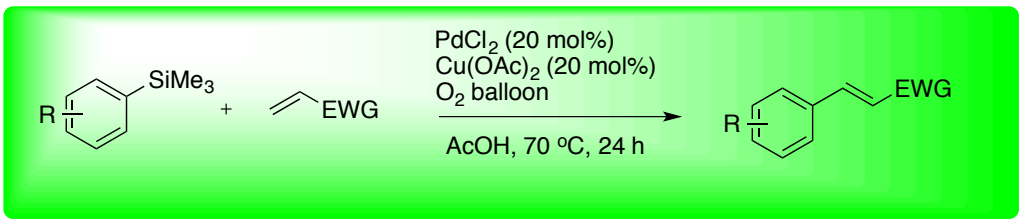
This thesis comprised four chapters in two parts: 1) functionalization of silicon-based compounds; 2) displacement of halogen atoms from simple alkyl halides in aquous media.

I Overview of functionalizations of silicon-based compounds

Chapter 1 reviewed the recent development of functionlization of silicon-based compounds, according to the types of various organosilanes.

II Palladium-catalyzed *ipso*-desilylative coupling of aryl(trimethyl)silanes with alkenes

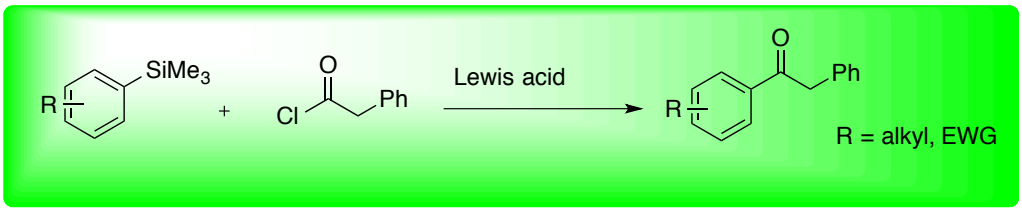
Chapter 2 focused on the recent literature regarding functionalization of aryl(trimethyl)silanes. The results on Pd-catalyzed *ipso*-desilylative coupling of aryl(trimethyl)silanes with electron-deficient alkenes were demonstrated and discussed.



III *ipso*-Desilylative Acylation of Aryl(trimethyl)silanes with Acid Chlorides

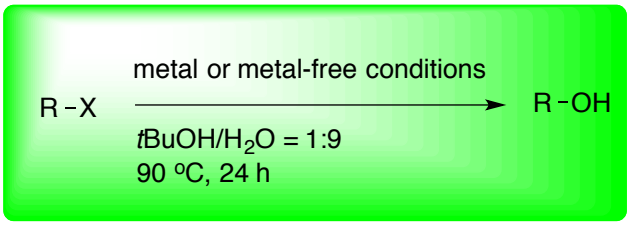
Chpater 3 showed the results for *ipso*-acylation of aryl(trimethyl)silanes with acid chlorides. The TMS group facilitated the transformation in two roles:

a) increase the reactivity of electron-deficient arenes towards electrophiles; b) site selective acylation through stablization of the cation intermediate via silicon β-effect.



IV Displacement of halogen atoms from simple alkyl halides in aqueous media

Chapter 4 discussed a protocol of metal-free and metal-mediated displacement of halogen atoms in aqueous media. Converions of alkyl chlorides were focused and studied.



INDEX OF ABBREVIATIONS

δ	chemical shift
Δ	reflux
ºC	degree centrigrade
Abq	AB quartet
Ac	acetyl
acac	acetoacetonate
Ar	Aryl
AcCl	acetyl chloride
AcOH	acetic acid
Ac_2O	acetic anhydride
Al_2O_3	Aluminium oxide
aq.	aqueous
Bn	benzyl
bs	broad singlet
BuLi	butyl lithium
C	Carbon
Cacld	calculated

Cat. catalytic

$CDCl_3$ deuterated chloroform

CDC cross-dehydrogenative coupling

CF_3 trifluoromethyl

Cp cyclopentadienyl

CH_4 Methane

CH_2Cl_2 Dichoromethane

$CHCl_3$ Chloroform

CCl4 Carbon tetrachloride

cm^{-1} inverse centimeter

COD cyclooctadiene

CuBr copper bromide

CuH copper hydride

d doublet

DABCO 1,4-diazabicyclo[2.2.2]octane

DBU 1,8-diazabicyclo[5.4.0]undec-7-ene

DCM Dichloromethane

dd doublets of doublet

de diastereomeric excess

DCE dichloroethane

DIBAL-H diisobutylaluminum hydride

DMAP 4-(*N,N*-dimethylamino)pyridine

DME 1,2-dimethoxyethane

DMF dimethylformamide

DMP Dess-Martin periodinane

DMSO dimethyl sulfoxide

DoM directed *ortho* metalation

dppf diphenylphosphino ferrocenyl

dq doublets of quartet

dt doublets of triplet

ee enantiomeric excess

EDG electron-donating group

equiv. equivalent

EI electron impact ionization

Et ethyl

ether diethyl ether

Et_3N triethylamine

EtOAc ethyl acetate

EtOH ethanol

EWG electron-withdrawing group

FG Functional group

FTIR Fourier transform infrared spectroscopy

g gram

Gly glycine

h hour

H hydrogen

Hex hexane

HMPA hexamethylphosphoramide

HRMS high-resolution mass spectroscopy

Hz Hertz

IR infrared

i-Pr isopropyl

J coupling constants

kg kilogram

LDA lithium diisopropylamide

M concentration (mol/dm^{-3})

M^+ parent ion peak (mass spectrum)

m multiplet

m-CPBA *meta*-chloroperoxybenzoic acid

Me methyl

MeCN acetonitrile

MeOH methanol

mg milligram

MHz Megahertz

min minute

mmol millimoles

mol moles

MS mass spectrum

Ms methanesulfonyl

M concentration (normality)

NaOAc Sodium Acetate

NCS *N*-chlorosuccinimide

NBS *N*-bromosuccinimide

NIS *N*-Iodosuccinimide

n-Bu *n*-butyl

nmr nuclear magnetic resonance

N.R. no reaction

OTf trifluoromethanesulfonate

Pt Platinum

Pd Pladium

$Pd(PPh_3)_4$ tetrakis(triphenylphosphine)palladium(0)

Pd / C palladium on carbon

Ph phenyl

PMP *p*-methoxyphenyl

PNBA 4-nitrobenzoic acid

ppm parts per million

Py pyridine

q quartet

rt. room temperature

R_f retention factor

s singlet

t triplet

t-Bu *tert*-butyl

t-BuOLi lithium *tert*-butyloxide

td triplets of doublet

TFA trifluoroacetic acid

TfOH triflate acid

Tf_2O triflate anhydride

THF tetrahydrofuran

TLC thin layer chromatography

TMEDA *N*,*N*,*N*',*N*'-tetramethylethylenediamine

TMS Trimethylsilyl

TON turnover number

Ts *p*-toluenesulfonyl

T.S. transition state

vol volume

PART I

CHAPTER 1

Overview of functionalizations of silicon-based compounds

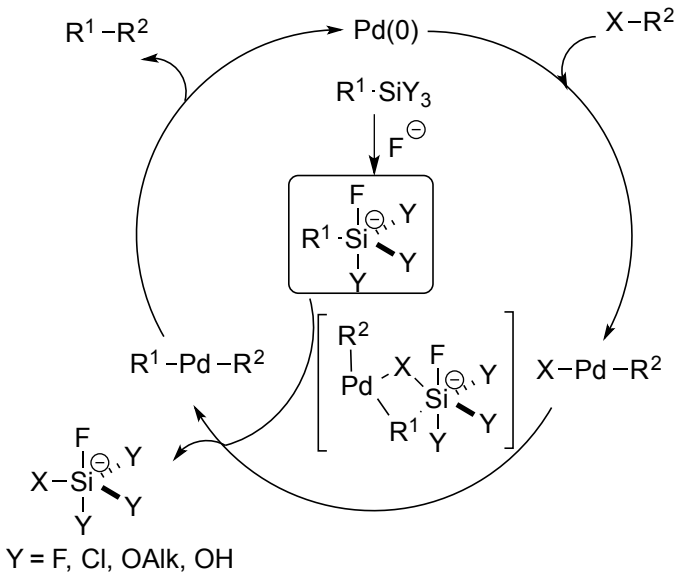
1.1 OVERVIEW OF THE BACKGROUND

Metal-catalyzed cross coupling reactions have attracted great interest over the past few decades, and have been developed and utilized as important strategies in organic synthesis for vast range of pharmaceutical intermediates and materials. Many organometallic coupling partners in the main group have been studied, such as organomagnesium, -zinc, -boron, -tin and -silicon compounds. Among these coupling partners, organosilicon reagents are initially less appreciated and explored due to their lower reactivity. However, a vast range of them is either commercially available or easily accessible, less expensive, extradinary stable and less toxic, therefore silicon-based compounds have been gaining greater attention recently.[1]

During the investigations of organosilicon as coupling partners, efforts have been focused on activation of the weakly polarized carbn-silicon (C-Si) bond. In order to activate and cleave the desired C-Si bond (Scheme 1.1), proper substituents Y on silicon, together with appropriate activators, such as fluoride or hydroxide anion in Hiyama coupling, are found necessary to proceed effective transmetalation from silicon to a transition metal centre.[1f]

Besides the choice of proper activators, the efficiency in the transmetallation key step also relies on the types of organosilicon compounds, for example, tetra-, penta- and hexa-coordinate species. Therefore, searching and making organosilicon reagents, which are easily accessible, highly stable, and leading to smooth functionlization, is the main focus during the investigations.

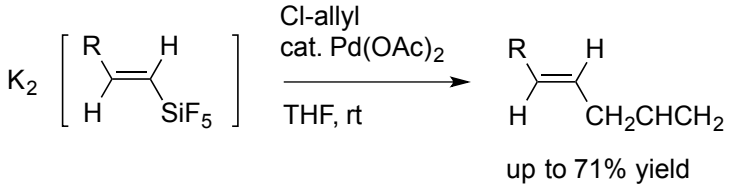
[1] a) Hiyama, T. in *Metal-Catalyzed Cross-Coupling Reactions*, ed. Diederich, F.; Stang, P. J. Wiley-



Scheme 1.1 A general catalytic cycle proposed for silicon cross-coupling reactions by fluoride activation

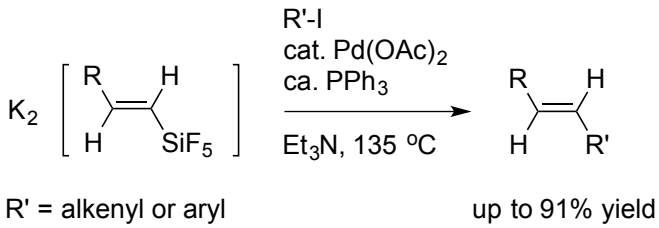
1.2 ORGANO(HALO)SILANES

Hexacoordinate organo(halo)silanes were first reported by Kumada and his coworkers in 1978 (Scheme 1.2).[2] They found that alkenyl(pentafluoro)silicates were potential useful intermediates to couple with allylic electrophiles, with the stereochemistry retained from the reacting potassium pentafluorosilicates. Later, they expanded scope of coupling partners to alkenyl and aryl halides (Scheme 1.3).[3]



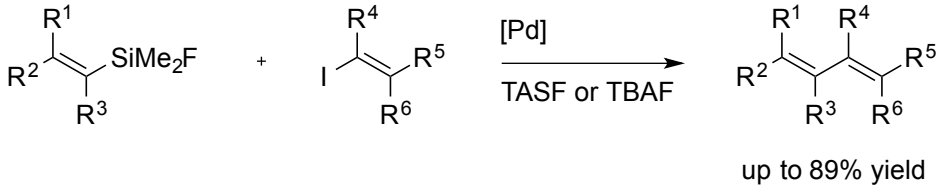
Scheme 1.2 Pd-catalyzed coupling of pentafluorosilicates with allylic halides

[2] Yoshida, J. I.; Tamao, K.; Takahashi, M.; Kumada, M. *Tetrahedron Lett*. **1978**, *19*, 2161.
[3] Yoshida, J.; Tamao, K.; Yamamoto, H.; Kakui, T.; Uchida, T.; Kumada, M. *Organometallics* **1982**, *1*, 542.

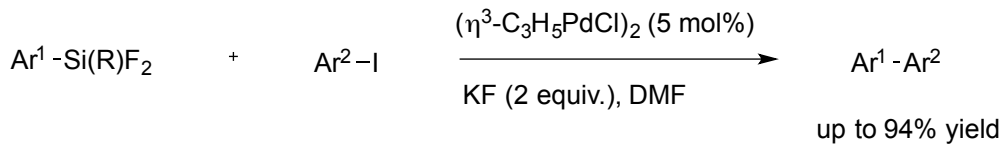


Scheme 1.3 Pd-catalyzed coupling of pentafluorosilicates with alkenyl and aryl halides

In view of practicality, conventional tetracoordinate silicon-based reagents were then more desired and studied, by Hiyama and Hatanaka notebly, and Fu recently. Essential hypervalent silicate intermediate was generated *in situ* from tetracoordinate alkenyl-[4] (Scheme 1.4) and arylsilanes[5] (Scheme 1.5) bearing one or two fluorine atoms. The nucleophilic attack of a fluoride anion to silicon was required to form the pentavalent silicates before transmatalation happened.



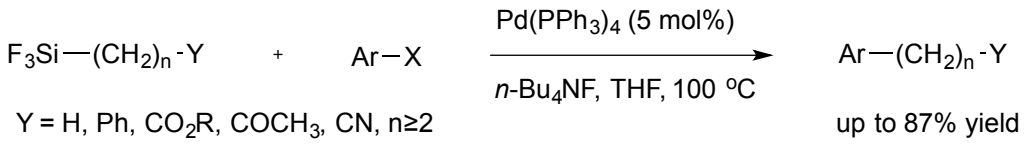
Scheme 1.4 Pd-catalyzed coupling of dimethylfluorosilanes with alkenyl iodides



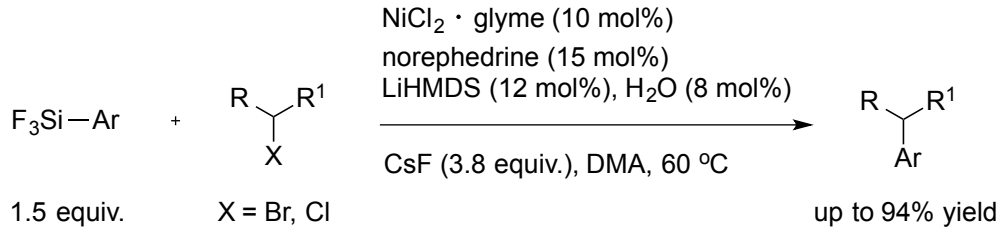
Scheme 1.5 Pd-catalyed coupling of aryl(difluoro)silanes with aryl iodides

[4] Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1989**, *54*, 268. For theoretical study, see: Sugiyama, A.; Ohnishi, Y.; Nakaoka, M.; Nakao, Y.; Sato, H.; Sakaki, S.; Nakao, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 12975.
[5] Hatanaka, Y.; Fukushima, S.; Hiyama, T. *Chem. Lett.* **1989**, 1711.

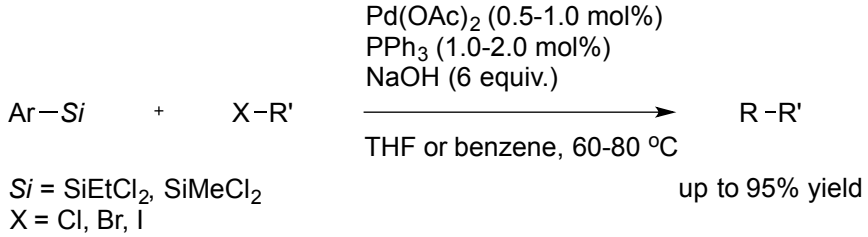
Fluorine substituents were believed to enhance the Lewis acidity of silicon center and stablize the pentacoordinate silicates. Alkyl-[6] (Scheme 1.6) and aryl(trifluoro)silanes[7] (Scheme 1.7) were also tested as alkyl and aryl group transfer reagents, with the protocol of palladium or nickle catalyst. Fluorine atoms could also be replaced by chlorine to give similar electron-withdrawing heteroatom effect.[8] Due to the concern of cost and chemoselectivity casued by fluoride activators, nucleophilic hydroxides were next explored to afford the pentacoordinate silicates (Scheme 1.8).[9]



Scheme 1.6 Pd-catalyzed coupling of alkyl(trifluoro)silanes with aryl iodides



Scheme 1.7 Ni-catalyzed coupling of aryl(trifluoro)silanes with unactivated secondary halides

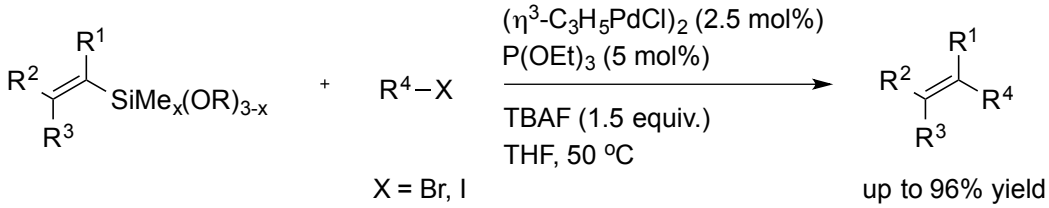


Scheme 1.8 Pd-catalyzed coupling of dichlorosilanes with organic halides

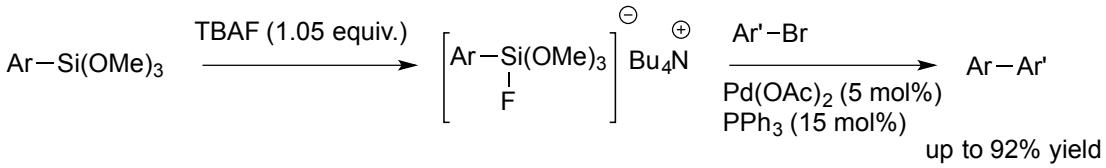
[6] a) Matsuhashi, H.; Kuroboshi, M.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1994**, *35*, 6507; b) Matsuhashi, H.; Asai, S.; Hirabayashi, K.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 437.
[7] Strotman, N. A.; Sommer, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3556.
[8] Hatanaka, Y.; Goda, K.; Okahara, Y.; Hiyama, T. *Tetrahedron* **1994**, *50*, 8301.
[9] Hagiwara, E.; Gouda, K.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1997**, *38*, 439.

1.3 ORGANO(ALKOXY)SILANES

Served as surrogates of halogen atoms, reactions using alkoxy substituents on silicon were first reported by Tamao and Ito[10] (Scheme 1.9). Aryl(trialkoxy)silanes, initially studied by Shibata[11] (Scheme 1.10), were then explored extensively.[12]



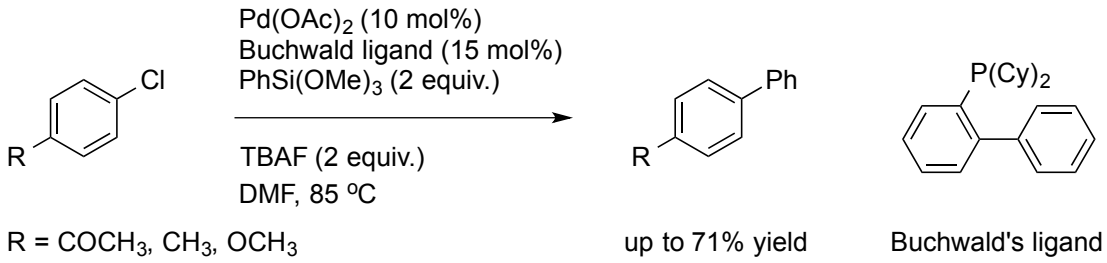
Scheme 1.9 Pd-catalyzed coupling of alkenylalkoxysilanes with C(sp^2)-halides



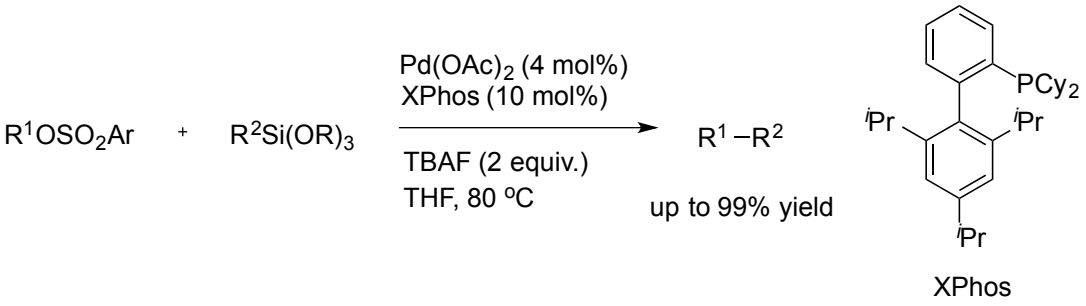
Scheme 1.10 Pd-catalyzed coupling of aryl(trialkoxy)silanes with arylbromides

Recent research in biaryl synthesis, regarding this class of arylsilanes, has involved the application of inexpensive reagents, such as aryl chlorides[13] (Scheme 1.11), tosylates[14] (Scheme 1.12), and mesylates[15]. Nucleophilic hydroxide or TBAB could also be employed as fluoride-free activators.[16]

[10] Tamao, K.; Kobayashi, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 6051.
[11] Shibata, K.; Miyazawa, K.; Goto, Y. *Chem. Commun*. **1997**, 1309.
[12] Handy, C. J.; Manoso, A. S.; McElroy, W. T.; Seganish, W. M.; DeShong, P. *Tetrahedron* **2005**, *61*, 12201.
[13] Mowery, M. E.; DeShong, P. *Org. Lett*. **1999**, *1*, 2137
[14] Zhang, L.; Wu, J. *J. Am. Chem. Soc*. **2008**, *130*, 12250
[15] a) Zhang, L.; Qing, J.; Yang, P. Y.; Wu, J. *Org. Lett*. **2008**, *10*, 4971; b) So, C. M.; Lee, H. W.; Lau, C. P.; Kwong, F. Y. *Org. Lett*. **2009**, *11*, 317.
[16] a) Wolf, C.; Lerebours, R. *Org. Lett*. **2004**, *6*, 1147; b) Alacid, E.; Najera, C. *Adv. Synth. Catal*. **2006**, *348*, 945; c) Gordillo, A.; de Jesus, E.; Lopez-Mardomingo, C. *Org. Lett*. **2006**, *8*, 3517; d) Alacid, E.; Najera, C. *J. Org. Chem*. **2008**, *73*, 2315.

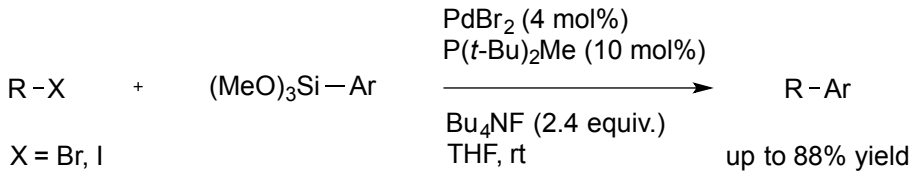


Scheme 1.11 Pd-catalyzed coupling of phenyl(trimethoxy)silane of aryl chlorides



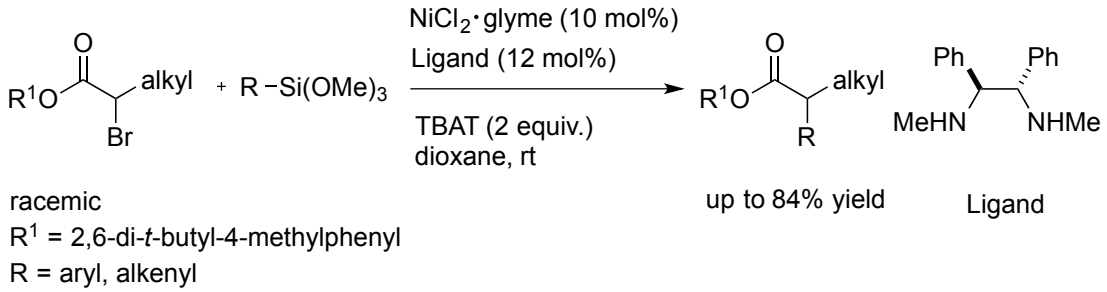
Scheme 1.12 Pd-catalyzed coupling of aryl(trialkoxy)silanes with aryl tosylates

Using aryl(alkoxy)silanes, arylation of primary-[17] (Scheme 1.13), or secondary-alkyl halides[18] (Scheme 1.14), could be performed with the presence of palladium or nickle catalyst respectively. Asymmetric arylation was achieved with the aid of the optically active diamine ligand via dynamic kinetic resolution.



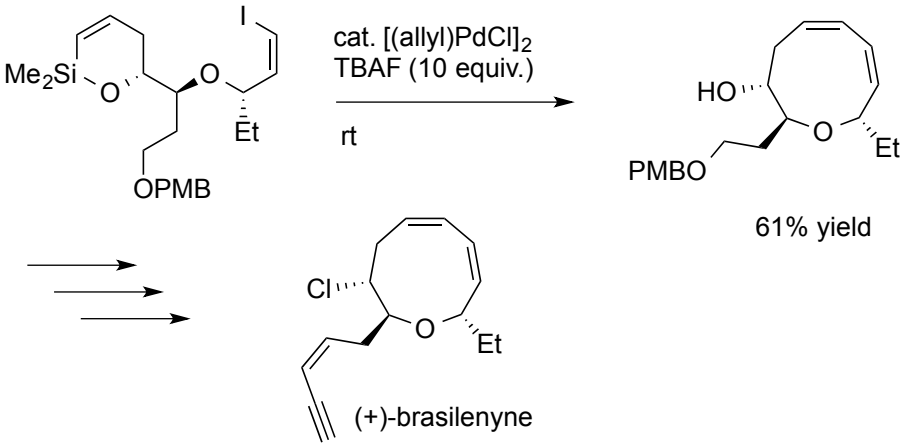
Scheme 1.13 Pd-catalyzed coupling of aryl(triamethoxy)silane with alkyl halides

[17] Lee, J. Y.; Fu, G. C. *J. Am. Chem. Soc*. **2003**, *125*, 5616.
[18] Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc*. **2008**, *130*, 3302.



Scheme 1.14 Ni-catalyzed asymmetic coupling of alkoxysilanes with α-bromo esters

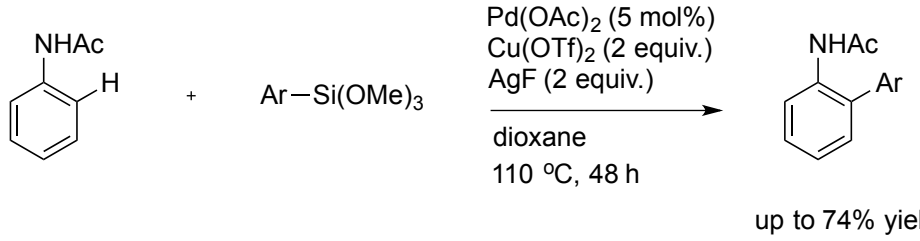
Denmark[19] and coworkers had developed intramolecular cross coupling of alkenyl(alkoxy)silanes via medium-sized ring compounds, which led to successful total sythensis of (+)-brasilenyne (Scheme 1.15).[20]



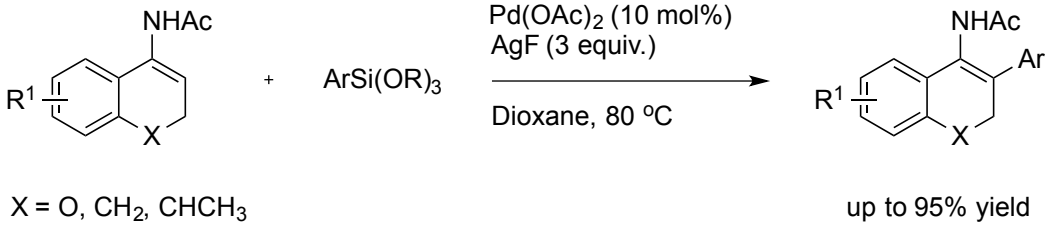
Scheme 1.15 Intramolecular coupling of alkenyl(alkoxy)silane and its application in total synthesis of (+)-brasilenyne

Arylsilanes were also found to couple with other prefunctionlized partners, such as acetanilides[21] (Scheme 1.16), enamides[22] (Scheme 1.17), and heteroarenes[23] (Scheme 1.18).

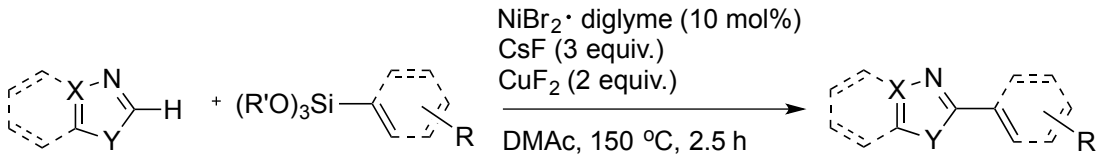
[19] Denmark, S. E.; Yang, S. M. *J. Am. Chem. Soc*. **2002**, *124*, 2102.
[20] a) Denmark, S. E.; Yang, S. M. *J. Am. Chem. Soc*. **2002**, *124*, 15196; b) Denmark, S. E.; Yang, S. M. *J. Am. Chem. Soc*. **2004**, *126*, 12432.
[21] Yang, S. D.; Li, B. J.; Wan, X. B.; Shi, Z. J. *J. Am. Chem. Soc*. **2007**, *129*, 6066.
[22] Zhou, H.; Xu, Y. H.; Chang, W. J.; Loh, T. P. *Angew. Chem., Int. Ed*. **2009**, *48*, 5355.
[23] Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed*. **2010**, *12*, 2202.



Scheme 1.16 Pd-catalyzed coupling of aryl(trimethoxyl)silanes with acetanilides



Scheme 1.17 Pd-catalyzed coupling of aryl(trimethoxyl)silanes with enamides



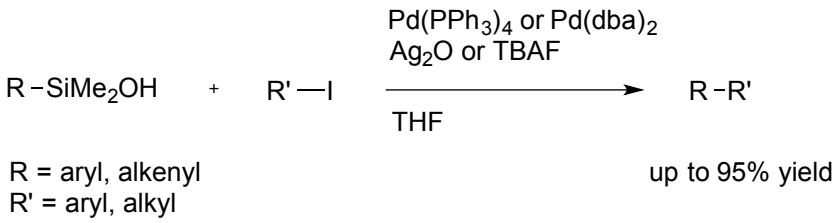
Scheme 1.18 Ni-catalyzed coupling of aryl(trialkoxyl)silanes with heteroarenes

1.4 ORGANOSILANOLS

Organosilanols[24] had gradually developed as a category of reactive and relatively stable organosilicon reagent, and reported by Hiyama[25] and Denmark[26] independently (Scheme 1.19). Denmark and Sweis[27] had studied the mechanism and considered palladium silanolates as key intermediates, which were nucleophilicly

[24] Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res*. **2002**, *35*, 835.
[25] Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett*. **1999**, *1*, 299.
[26] Denmark, S. E.; Wehrli, D. *Org. Lett*. **2000**, *2*, 565.
[27] a) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc*. **2004**, *126*, 4876; b) Denmark, S. E.; Smith, R. C. *J. Am. Chem. Soc*. **2010**, *132*, 1243.

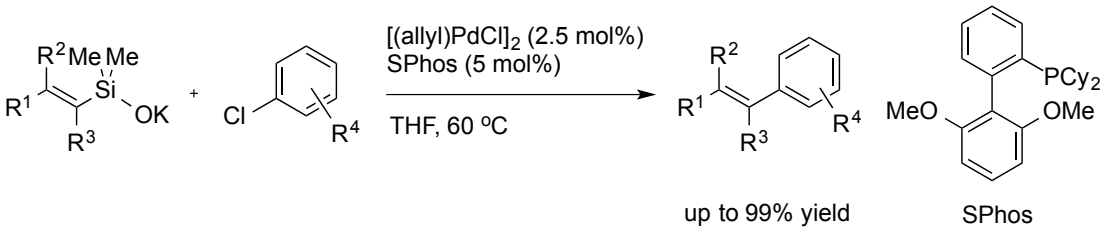
attacked by another silanolate molecule to undergo transmetalation from silicon to palladium.



Scheme 1.19 Pd-catalyzed coupling of silanols with organoiodides

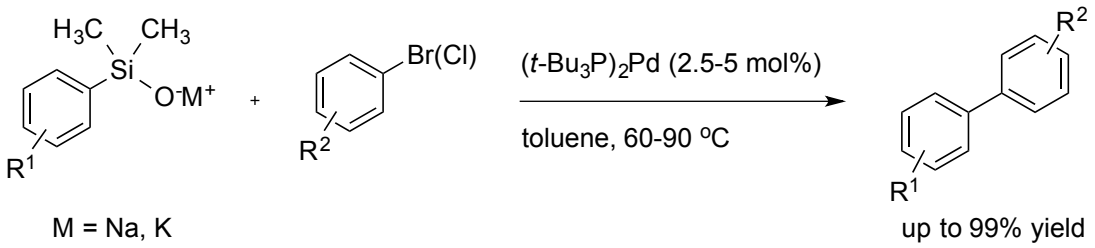
1.5 ORGANOSILANOLATES

Denmark's group then continued to develop preformed organosilanolates via irreversible deprotonation of organosilanols.[28] Advantages of organosilanolates included: easy to handle the bench-stable powder, eliminating to use external bases and suppressing the formation of side products. Various silanoltes, such as alkenyl-[29] (Scheme 1.20), aryl-[30] (Scheme 1.21), heteroaryl-[31] (Scheme 1.22), and crotylsilanolates[32] (Scheme 1.23) could all perform the desired transformations.

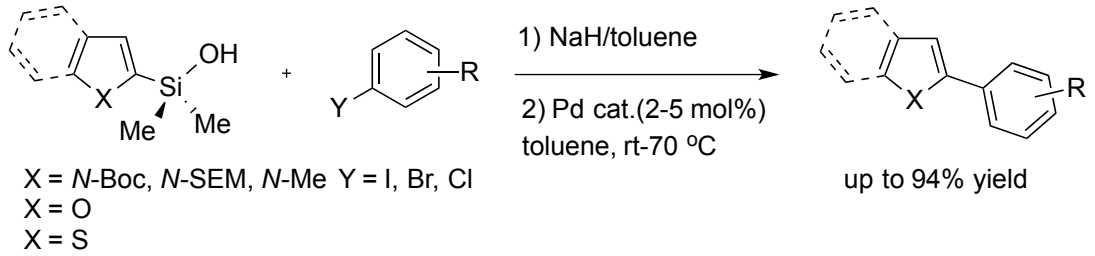


Scheme 1.20 Pd-catalyzed coupling of alkenylsilanolates with aryl chlorides

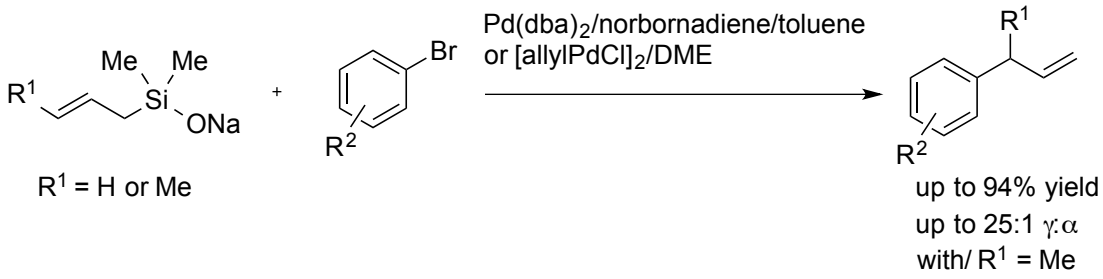
[28] Denmark, S. E.; Baird, J. D. *Chem.-Eur. J.* **2006**, *12*, 4954.
[29] a) Denmark, S. E.; Kallemeyn, J. M. *J. Am. Chem. Soc*. **2006**, *128*, 15958; b) Denmark, S. E.; Butler, C. R. *J. Am. Chem. Soc*. **2008**, *130*, 3690.
[30] a) Denmark, S. E.; Smith, R. C.; Tymonko, S. A. *Tetrahedron* **2007**, *63*, 5730; c) Denmark, S. E.; Smith, R. C.; Chang, W. T. T.; Muhuhi, J. M. *J. Am. Chem. Soc*. **2009**, *131*, 3104.
[31] Denmark, S. E.; Baird, J. D.; Regens, C. S. *J. Org. Chem*. **2008**, *73*, 1440.
[32] a) Hatanaka, Y.; Ebina, Y.; Hiyama, T. *J. Am. Chem. Soc*. **1991**, *113*, 7075; b) Denmark, S. E.; Werner, N. S. *J. Am. Chem. Soc*. **2008**, *130*, 16382; c) Denmark, S. E.; Werner, N. S. *J. Am. Chem. Soc*. **2010**, *132*, 3612.



Scheme 1.21 Pd-catalyzed coupling of arylsilanolates with aryl halides



Scheme 1.22 Pd-catalyzed coupling of heterocyclic silanolates with aryl halides



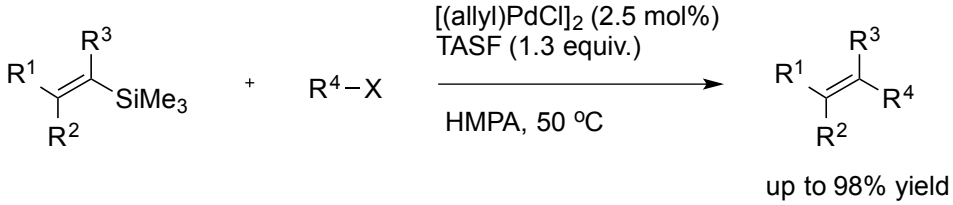
Scheme 1.23 Pd-catalyzed coupling of crotylsilanolates with aryl bromides

1.6 TETRAORGANOSILANES

Based on the results above, installation of one or more electron-withdrawing heteroatoms on silicon center was the key to promote Lewis acidity and reactivity of silanes towards transmetalation. However, in terms of stability and accessibility, tetraorganosilanes were highly desirable and the next hot spot in functionalization of silicon-based compounds.

1.6.1 ALKENYLTRIMETHYLSILANES

Hiyama and Hatanaka, as early as 1988, had reported Pd-catalyzed coupling of alkenyl(trimethyl)silanes with organic halides, but with very limited substrate scope (Scheme 1.24).[33] Alkenyldimethylphenylsilanes, were also studied to couple with acid anhydrides, in the presence of a rhodium catalyst without any activators (Scheme 1.25).[34]



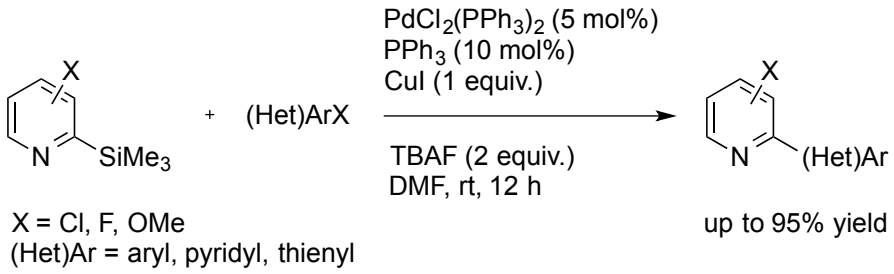
Scheme 1.24 Pd-catalyzed coupling of alkenyl(trimethyl)silanes with organic halides

Scheme 1.25 Rh-catalyzed coupling of alkenyl(trimethyl)silanes with acid anhydrides

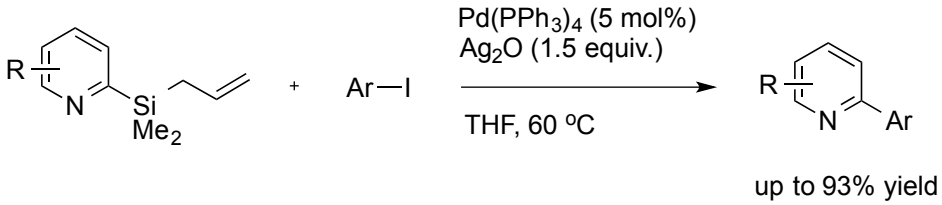
1.6.2 2-PYRIDYLTRIMETHYLSILANES

2-Pyridyl groups have played important roles in directing-group-assisted cross-coupling chemistry, due to their vast presence in pharmaceutical materials. Stable 2-triorgano(2-pyridyl)silanes have been demonstrated to cross couple with aryl iodides with stoichiometric amount of copper[35] (Scheme 1.26) or silver[36] (Scheme 1.27) salts.

[33] Hatanaka, Y.; Hiyama, T. *J. Org. Chem*. **1988**, *53*, 918.
[34] a) Yamane, M.; Uera, K.; Narasaka, K. *Chem. Lett*. **2004**, 424. b) Yamane, M.; Uera, K.; Narasaka, K. *Bull. Chem. Soc. Jpn*. **2005**, *78*, 477
[35] Pierrat, P.; Gros, P.; Fort, Y. *Org. Lett*. **2005**, *7*, 697.
[36] Nokami, T.; Tomida, Y.; Kamei, T.; Itami, K.; Yoshida, J. *Org. Lett*. **2006**, *8*, 729; b) Napier, S.; Marcuccio, S. M.; Tye, H.; Whittaker, M. *Tetrahedron Lett*. **2008**, *49*, 6314.



Scheme 1.26 Pd-catalyzed coupling of pyridyl(trimethyl)silanes with aryl halides



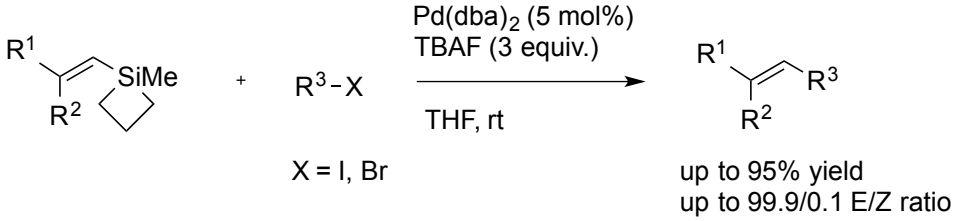
Scheme 1.27 Pd-catalyzed coupling of (2-pyridyl)allyldimethylsilanes with aryl iodides

1.6.3 MASKED SILANOLES

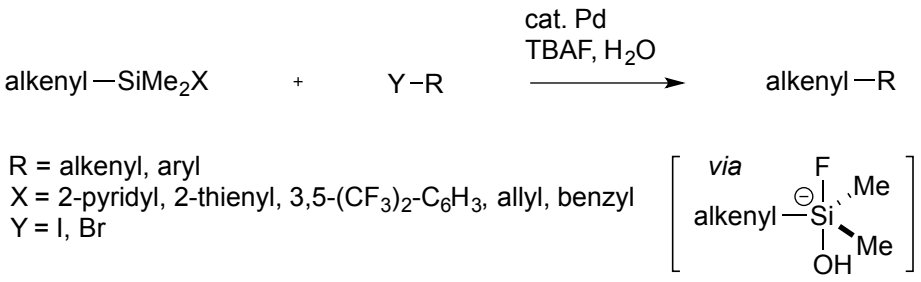
Denmark and coworkers demonstrated alkenylsilacyclobutanes as another feasible tetraorganosilanes to cross couple with aryl halides (Scheme 1.28).[37] It was observed that alkenylsilanol was formed *in situ* from ring opening of the four-membered silicon moiety by nucleophilic attack of fluoride activators.[38] Therefore, some tetraorganosilicon reagents were investigated as "masked silanols or fluorosilanes". Such masking groups include: 2-pyridyl,[39] 2-thienyl,[40] and 3,5-bis(trifluoromethyl)phenyl,[41] benzyl[42] (Scheme 1.29), allyl[43] (Scheme 1.30) groups. Detailed studies revealved that these masking groups were convered to fluoro or

[37] Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc*. **1999**, *121*, 5821.
[38] Denmark, S. E.; Wehrli, D.; Choi, J. Y. *Org. Lett*. **2000**, *2*, 2491.
[39] Itami, K.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc*. **2001**, *123*, 5600.
[40] Hosoi, K.; Nozaki, K.; Hiyama, T. *Chem. Lett*. **2002**, 138.
[41] Katayama, H.; Nagao, M.; Moriguchi, R.; Ozawa, F. *J. Organomet. Chem*. **2003**, *676*, 49.
[42] Trost, B. M.; Machacek, M. R.; Ball, Z. T. *Org. Lett*. **2003**, *5*, 1895.
[43] Sahoo, A. K.; Oda, T.; Nakao, Y.; Hiyama, T. *Adv. Synth. Catal*. **2004**, *346*, 1715.

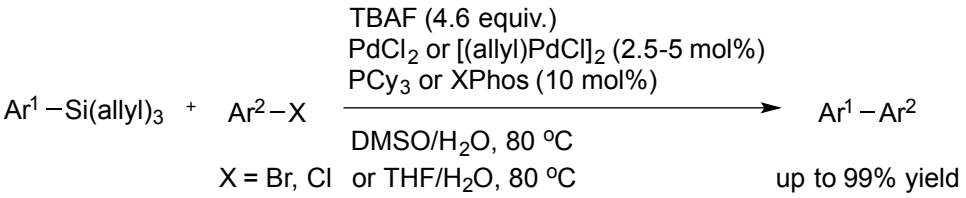
hydroxy group upon attacked by activators, while the resultant Si-F bond was sometimes hydrolyzed by small amount of water comtaminent in TBAF. These masked silanols were stable enough to tolerate many synthetic functionalizations before activated to undergo cross coupling reactions. The phenyl group could also serve as a masking group, with the strong Si-Ph bond cleaved by a strong base (Scheme 1.31).[44]



Scheme 1.28 Pd-catalyzed stereospecific coupling of alkenylsilacyclobutanes

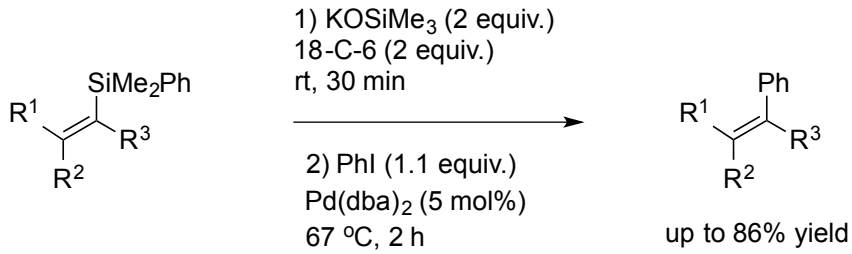


Scheme 1.29 Summary of some masking groups



Scheme 1.30 Pd-catalyzed coupling of aryl(triallyl)silanes with aryl halides

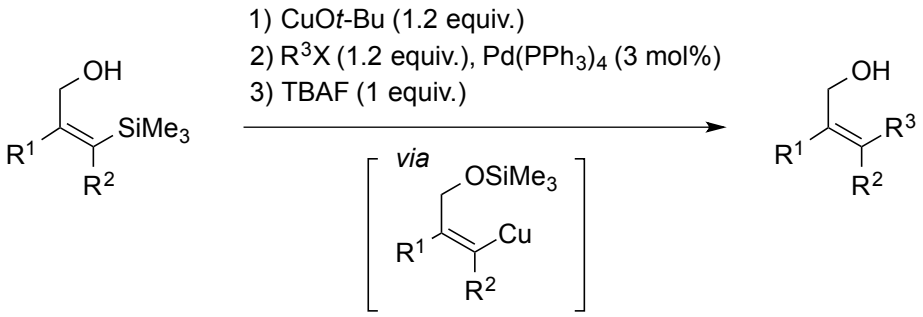
[44] Andereson, J. C.; Munday, R. H. *J. Org. Chem*. **2004**, *69*, 8971.



Scheme 1.31 Pd-catalyzed coupling of vinyldimethylphenylsilanes with iodobenzene

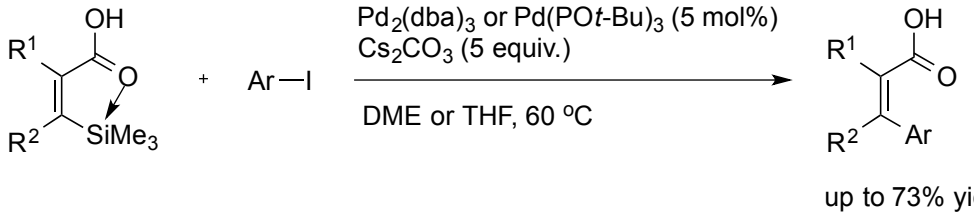
1.6.4 ORGANO[2-(HYDROXYMETHYL)PHENYL]DIMETHYLSILANES

Instead of installing electron-withdrawing heteroatoms on silicon center to promote its Lewis acidity and reactivity, placement of a proper activator at the proximal position could also produce similar results intramolecularly. Takeda and coworkers have shown the transmetalation from alkenyltrimethylsilanes to copper, followed by Pd-catalyzed cross coupling reactions with organic halides, assisted by a proximal hydroxy group (Scheme 1.32).[45] Similar "directing and activating" effect could also be achieved by a nearby carboxylate group (Scheme 1.33).[46]



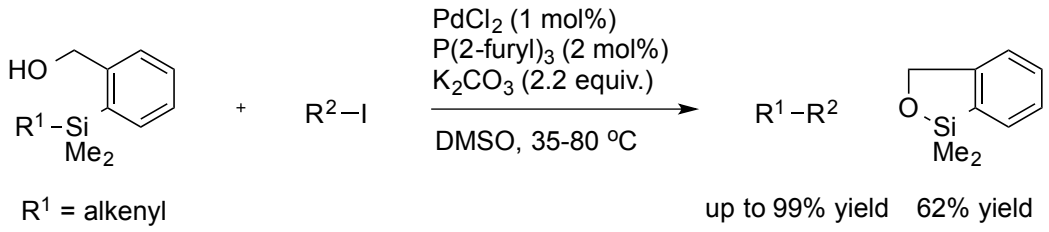
Scheme 1.32 Intramolecular actiation alkenyltrimethylsilanes with the proximal hydroxy group

[45] Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *J. Org. Chem*. **2002**, *67*, 8450.
[46] Shindo, M.; Matsumoto, K.; Shishido, K. *Synlett* **2005**, 176.



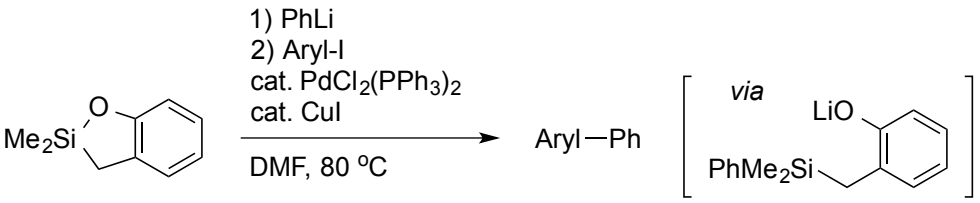
Scheme 1.33 Intramolecular activation of alkenyltrimethylsilanes with the proximal carboxylate group

Inspired by the above two examples, Hiyama and Nakao *et al* designed a series of novel tetraorganosilicon reagents with a [2-(hydroxymethyl)phenyl]dimethylsilane motief (Scheme 1.34).[47] Compared with previous designs, these hydroxy-containing silicon reagents demonstrated excellent chemoselectivity on bond cleavage and presented recyclability after the transferable group involved in the coupling reactions. Wide range of functional groups could be tolerated, including common silyl protecting groups.[48] The recycled oxysilycycle could be further attacked by phenyl lithium base to achieve corresponding aryl transfer (Scheme 1.35).[49]



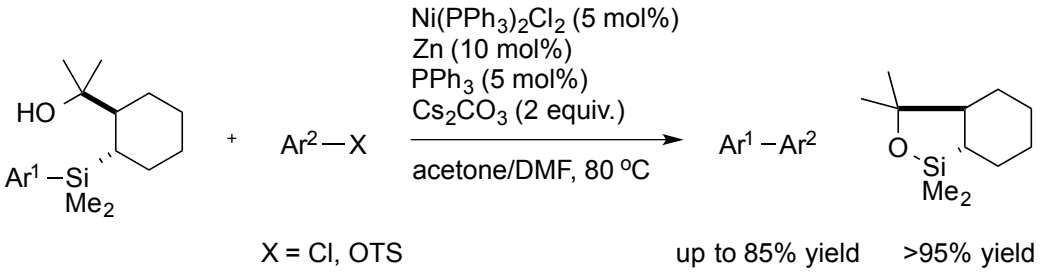
Scheme 1.34 Intramolecular activation of [2-(hydroxymethyl)phenyl]dimethylsilanes

[47] Nakao, Y.; Imanaka, H.; Sahoo, A. K.; Yada, A.; Hiyama, T. *J. Am. Chem. Soc*. **2005**, *127*, 6952.
[48] Nakao, Y.; Imanaka, H.; Chen, J. S.; Yada, A.; Hiyama, T. *J. Organomet. Chem*. **2007**, *692*, 585.
[49] Son, E. C.; Tsuji, H.; Saeki, T.; Tamao, K. *Bull. Chem. Soc. Jpn*. **2006**, *79*, 492.



Scheme 1.35 Intramolecular activation of o-hydroxybenzyltrimethylsilanes

With added CuI cocatalyst, aryl groups could also be transferred from the above template.[50] Modified 2-(2-hydroxyprop-2-yl)cyclohexyl motif[51] (Scheme 1.36) with the presence of Ni and Zn as cocatalysts could also afford biaryl synthesis. With allylic or benzylic carbonates, the use of external base could be eliminated Palladium alkoxide was generated from oxidative insertion of the electrophiles, which acted as base to promote transmetalation.[52]



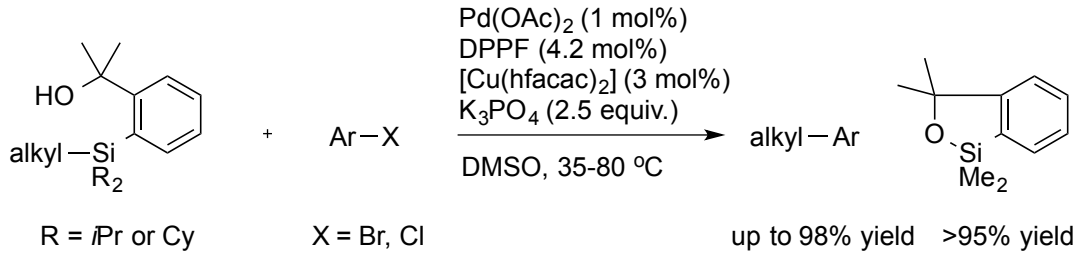
Scheme 1.36 Intramolecular activation of 2-(2-hydroxyprop-2-yl)cyclohexyldimethylsilanes

Similarly, alkyl groups were also able to be transferred by the same reagent design, with the cleavage of strong C(sp^3)-Si bond under fluoride-free conditions

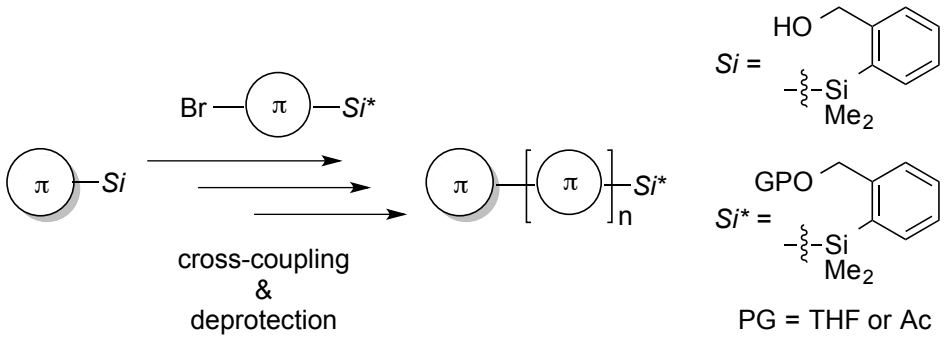
[50] a) Nakao, Y.; Sahoo, A. K.; Yada, A.; Chen, J. S.; Hiyama, T. *Sci. Technol. Adv. Mater*. **2006**, *7*, 536; b) Chen, J. S.; Tanaka, M.; Sahoo, A. K.; Takeda, M.; Yada, A.; Nakao, Y.; Hiyama, T. *Bull. Chem. Soc. Jpn*. **2010**, *83*, 554.
[51] Tang, S.; Takeda, M.; Nakao, Y.; Hiyama, T. *Chem. Commun*. **2011**, *47*, 307.
[52] a) Nakao, Y.; Ebata, S.; Chen, J.; Imanaka, H.; Hiyama, T. *Chem. Lett*. **2007**, *36*, 606; b) Guibe, F.; Saintmleux, Y. *Tetrahedron. Lett*. **1981**, *22*, 3591; c) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem*. **1985**, *50*, 1523.

(Scheme 1.37).[53] In this case, benzylic *gem*-dimethyls were the essential backbone structure to avoid oxidation insertion occurred at the benzylic carbon. Isopropyl groups on silicon were particularly chosen, to allow for discrimination of primary or secondary alkyl groups.

The free hydroxy group in these structure templates was essential for smooth activation of the desired C-Si bond, since *O*-protected substrates gave no coupling reactions. On the other hand, free-hydroxy substrates containing *O*-protected silyl group could then remain intact. Upon *O*-deprotection of the resulted biaryl product, subsequent cross coupling reaction could also proceed. With this silicon-based approch, using various halogenated arylsilanes, oligoarenes could be synthesized by iterative coupling reactions (Scheme 1.38).[54]



Scheme 1.37 Intramolecular activation of C(sp^3)-Si bond



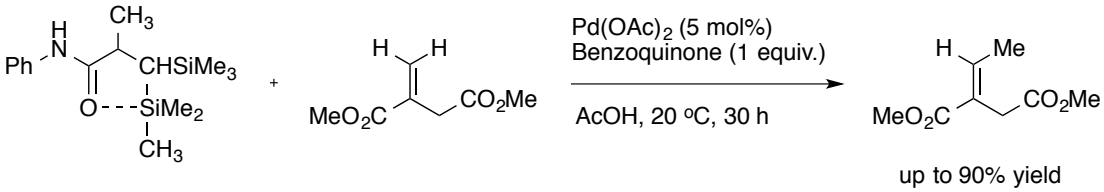
Scheme 1.38 A silicon-based approach to oligoarenes by iterative cross-coupling reactions

[53] Nakao, Y.; Takeda, M.; Matsumoto, T.; Hiyama, T. *Angew. Chem., Int. Ed*. **2010**, *49*, 4447.
[54] Nakao, Y.; Chen, J. S.; Manaka, M.; Hiyama, T. *J. Am. Chem. Soc*. **2007**, *129*, 11694.

1.6.5 TRIMETHYLSILANES

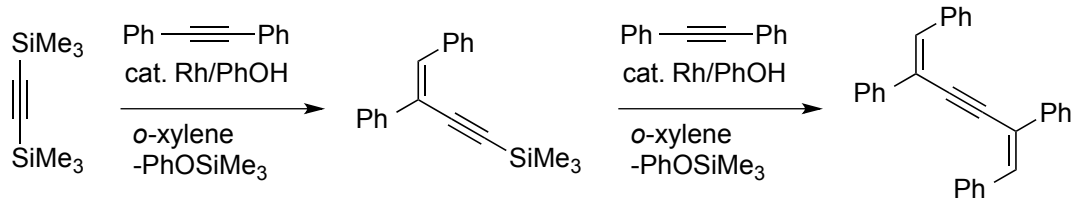
Trimethylsianes were the simplest and idealest tetraorganosilanes in silicon-based chemistry, in terms of their accessibility, stability, and atom economy. Selective cleavage of a defined C-Si bond was achieved, usually through a nearby group with directing and/or coordinating effect.

For alkyltrimethylsilanes, discrimination and activation of C(sp^3)-Si could be performed by the properly aligned amide carbonyl group, and participated in Heck reactions under oxidative conditions, reported by Brown and coworkers (Scheme 1.39).[55]



Scheme 1.39 Amide carbonyl directied intramolecular cleavage of C(sp^3)-Si bond

Bis(trimethylsilyl)acetylene was also reported to couple with diarylacetylenes (Scheme 1.40).[56] Sequential cleavage of alkynl-Si bond was performed by Rh catalyst.



Scheme 1.40 Rh-catalyzed sequential cleavage of alknyl-Si bond

[55] Rauf, W.; Brown, J. M. *Angew. Chem., Int. Ed*. **2008**, *47*, 4228.
[56] Horita, A.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett*. **2008**, *10*, 1751.

Recently, functionalizations of aryltrimethylsilanes have drawn more attention. With activation of C(sp^3)-Si bond, further manipulations could lead to silicon-tethered or linked organic materials, which may possess dramatic different chemical and physicochemical properties. With activation of C(sp^2)-Si bond, the aryl group could be transfer to other reacting/coupling partners.

Our group have been interested in functionalization of aryltrimethylsilanes. More specific background and recent preliminary results found in our lab will be discussed in chapter 2 and 3.

PART I

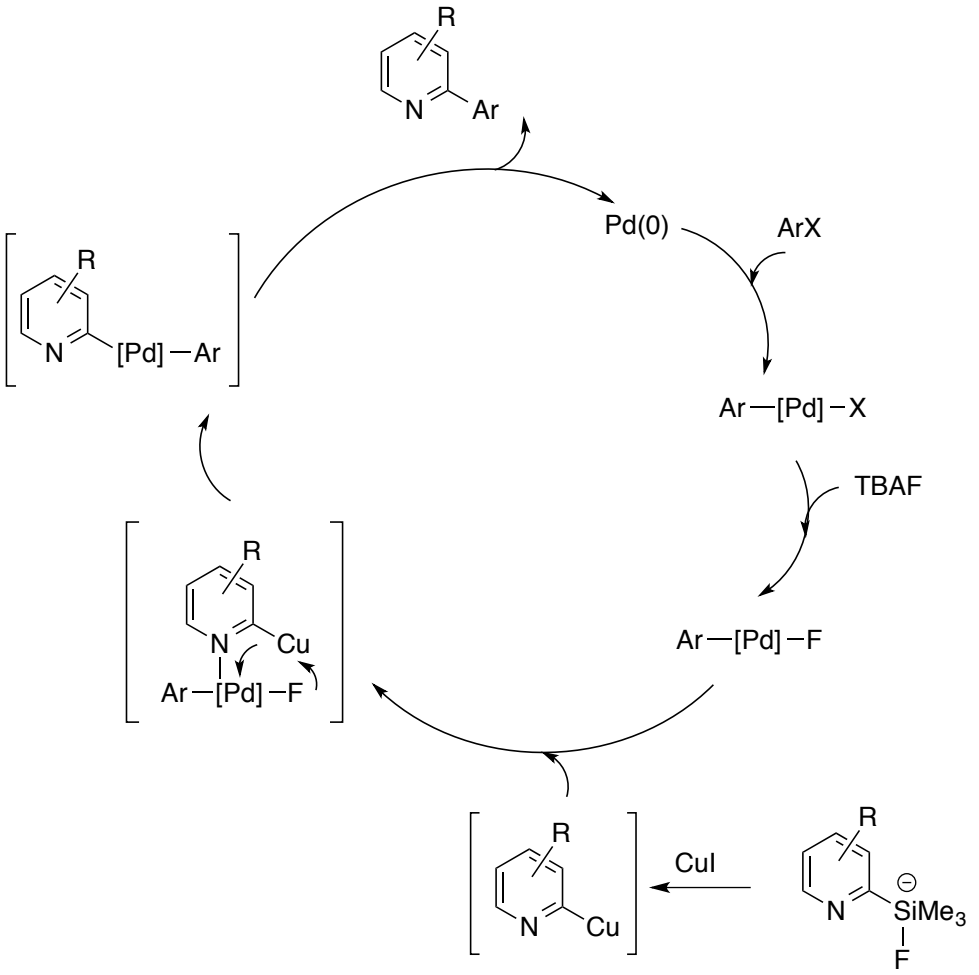
CHAPTER 2

Palladium-catalyzed *ipso*-desilylative coupling of aryl(trimethyl)silanes with alkenes

2.1 INTRODUCTION

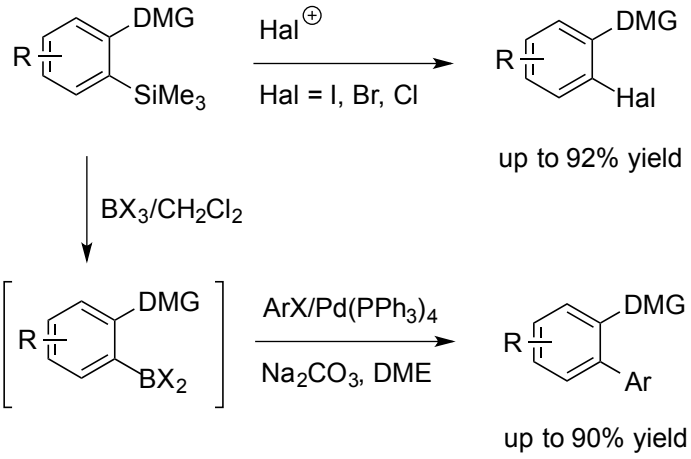
Ary(trimethyl)silanes, as one category of the simplest tetraorganosilanes, are easily accessible and synthesized from arylhalides. To achieve functionalization of aryltrimethylsilanes, selective cleavage of $C(sp^3)$-Si or $C(sp^2)$-Si bond (*ipso*-desilylation) needs to controlled. So far, available methods include: hetero-atom/directing-group assisted coordination of catalyst metal, backbone assisted placement of catalyst metal, and electrophilic desilylative substitution.

For previously discussed 2-pyridyltrimethylsilanes (chapter 1, ref. 35), the nitrogen atom assisted to position palladium center properly in order for transmetalation to occur (Scheme 2.1).



Scheme 2.1 Proposed mechanism for cross coupling of 2-pyridyltrimethylsilanes

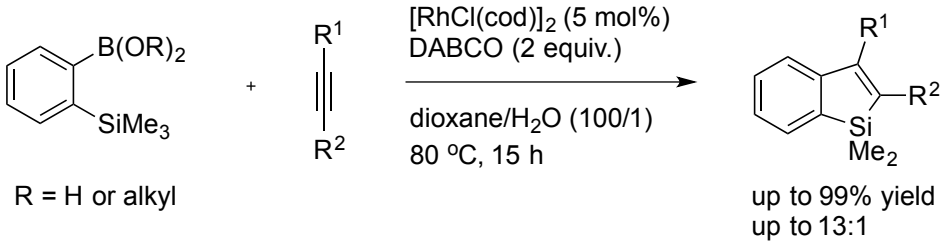
Directing metalation group (DMG) assisted activation of aryl C-Si bond and functionalize it into C-X and C-B bonds were discussed by Snleckus (Scheme 2.2).[1] Sequential *ipso*-borodesilylation followed by Pd-catalyzed arylation allowed the synthesis of diaryl compounds.



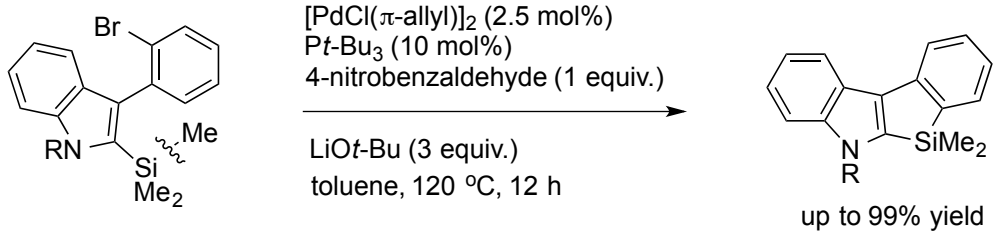
Scheme 2.2 DMG-assisted *ipso*-desilylation of aryltrimethylsilanes

Functionalization of aryltrimethylsilanes through backbone structure assisted placement of a metal catalyst was demonstrated by Chatani[2] (Scheme 2.3), as well as Xi (Scheme 2.4 and 2.5)[3]. A novel process including Rh- or Pd-catalyzed cleavage of C(sp^3)-Si bond followed by intramolecular formation of C(sp^2)-Si bond was described.

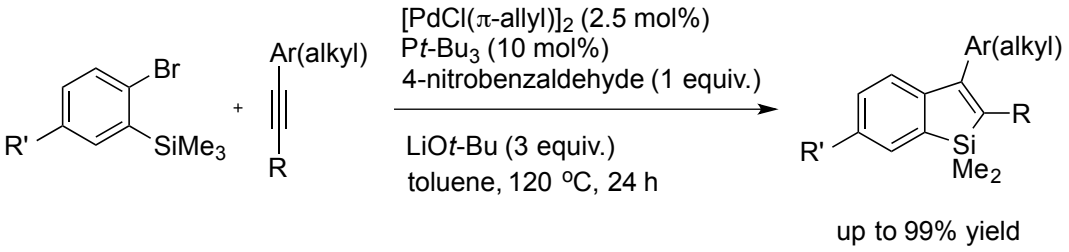
[1] Zhao, Z. -D.; Snleckus, V. *Org. Lett*. **2005**, *7*, 2523.
[2] a) Tobisu, M.; Onoe, M.; Kita, Y.; Chatani, N. J. *Am. Chem. Soc*. **2009**, *131*, 7506; b) Onoe, M.; Baba, K.; Kim, Y.; Kita, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc*. **2012**, *134*, 19477.
[3] a) Liang, Y.; Zhang, S.; Xi, Z. *J. Am. Chem. Soc*. **2011**, *133*, 9204; b) Liang, Y.; Geng, W.; Wei, J.; Xi, Z. *Angew. Chem. Int., Ed*. **2012**, *51*, 1934; c) Luo, Q.; Wang, C.; Li, Y.; Ouyang, K.; Gu, L.; Uchiyama, M.; Xi, Z. *Chem. Sci*. **2011**, *2*, 2271.



Scheme 2.3 Rh-catalyzed coupling of *o*-trimethylsilylphenylboronic acids/esters with alkynes



Scheme 2.4 Pd-catalyzed intramolecular cleavage of $C(sp^3)$-Si and formation of $C(sp^2)$-Si bond

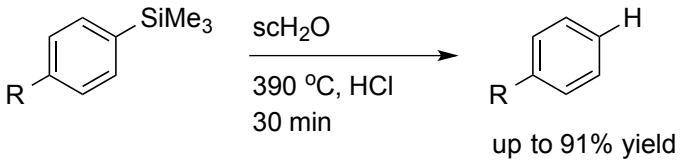


Scheme 2.5 Pd-catalyzed intermolecular coupling of 2-silylaryl bromides with alkynes

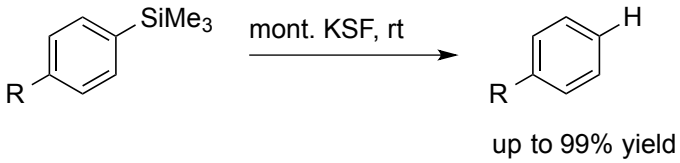
ipso-Desilylative activation of $C(sp^2)$-Si bond in aryltrimethylsilanes without a coordinating heteroatom or an alinged metal catalyst was a great challenge due to their stability and usually required harsh conditions. Supercritical water (Scheme 2.6)[4]

[4] Itami, K.; Terakawa, K.; Yoshida, J.-i.; Kajimoto, O. *J. Am. Chem. Soc*. **2003**, *125*, 6058.

and montmorillonite KSF (Scheme 2.7)[5] were reported to cleave Ar-Si bond. Substitution always happened on the position where silyl group was attached (*ipso*-carbon), which was consistent with usual aromatic electrophilic attack on electrophiles.



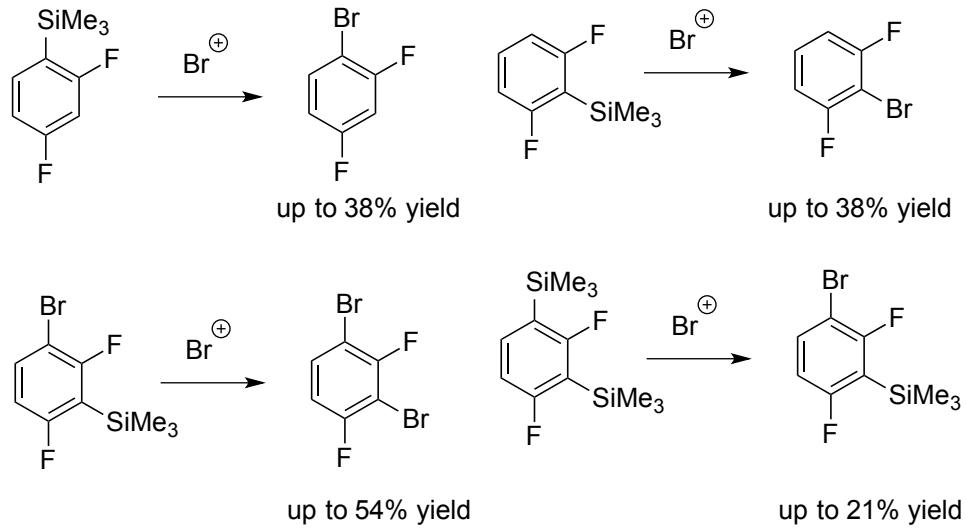
Scheme 2.6 Cleavage of aryl-Si bond by supercritical water



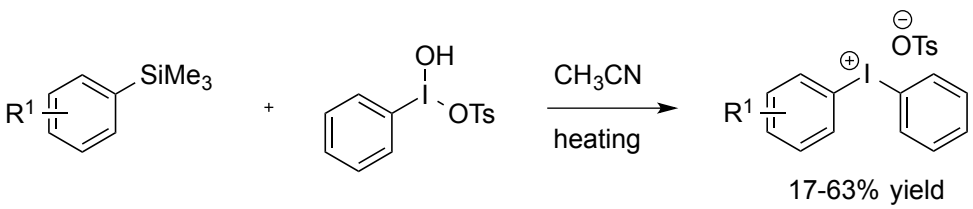
Scheme 2.7 Cleavage of aryl-Si bond by montmorillonite KSF

ipso-Desilylhalogenation of aryltrimethylsilanes was another important transformation. Hashimoto [6] and Eaborn [7] initiated the studies on *ipso*-desilylbromination of aryltrimethylsialnes using Br_2 decades ago, followed by Coe[8] using Br_2/AcOH for fluoroarenes with *para* favored than *ortho* substitution (Scheme 2.8). In 1980, Koser[9] reported the synthesis of diaryliodonium tosylates with aryl C-Si bond cleavage from aryltrimethylsilanes with [hydroxy(tosyloxy)iodo]arenes (Scheme 2.9). Later, silylated arylboroic acids were found as effective substrates for electrophilic ipso-desilyliodination (Scheme 2.10).[10]

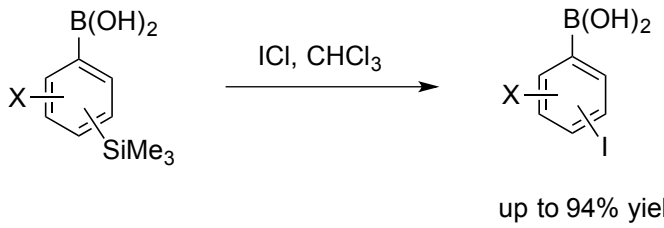
[5] Zafrani, Y.; Gershonov, E.; Columbus, I. *J. Org. Chem*. **2007**, *72*, 7014.
[6] Hashimoto, T. *Yakugaku Zasshi* **1960**, *87*, 528.
[7] Eaborn, C. *J. Organometal. Chem*. **1975**, *100*, 43.
[8] Coe, P. L.; Stuart, A. M.; Moody, D. J. *J. Fluorine Chem*. **1998**, *92*, 27.
[9] Koser, G. F.; Wettach, R. H.; Smith, C. S. *J. Org. Chem*. **1980**, *45*, 1544.
[10] Durka, K.; Górka, J.; Kurach, P.; Luliński, S.; Servatowski, J. *J. Organometal. Chem*. **2010**, *695*, 2635.



Scheme 2.8 *ipso*-Substitution of fluoroaryltrimethylsilanes



Scheme 2.9 *ipso*-Iodination of aryltrimethylsilanes



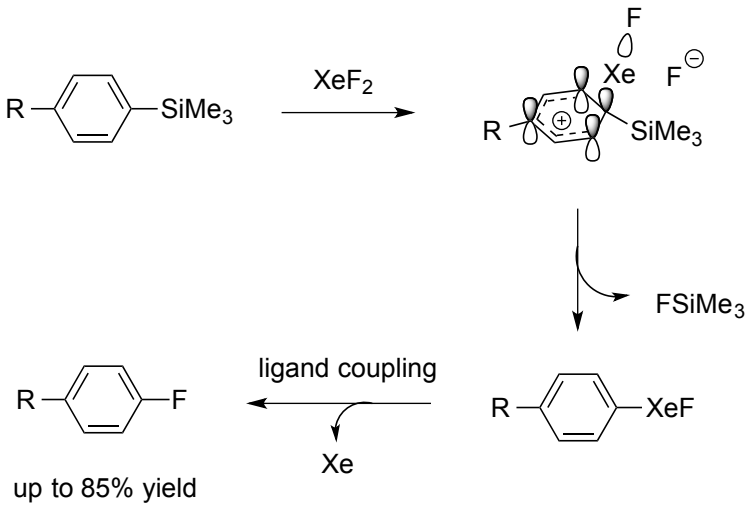
X = F, Cl, Br, CF_3, CN, CHO, OMe, $B(OH)_2$

Scheme 2.10 *ipso*-Iodination of silylated arylboronic acids

ipso-Fluorination of aryltrimethylsilanes using xenon difluoride was reported by Ramsden recently.[11] The cation intermediate could be stablized by both the *β*-

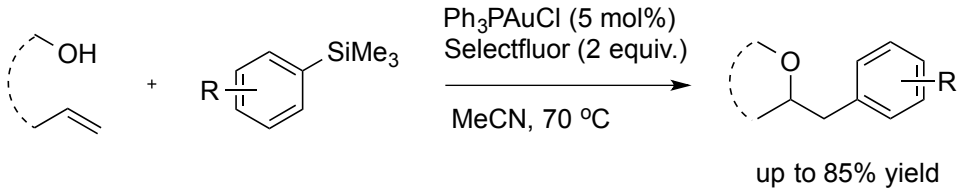
[11] Lothian, A. P.; Ramsden, C. A.; Shaw, M. M.; Smith, R. G. *Tetrahedron* **2011**, *67*, 2788.

effect of TMS group and interaction with the non-bonding molecular orbital from the hypervalent xenon bonds (Scheme 2.11)



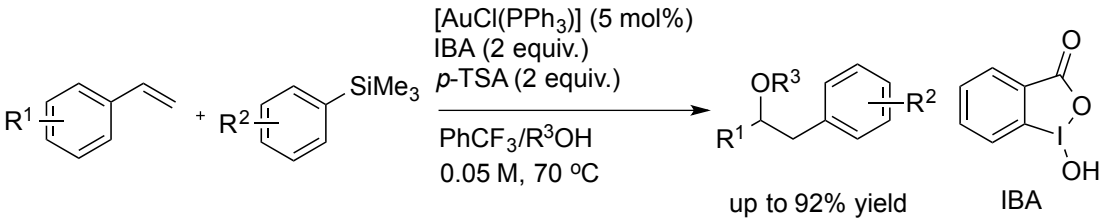
Scheme 2.11 *ipso*-Fluorination of aryltrimethylsilanes

Aryltrimethylsilanes, just like arylboronic acid [12], could also undergo oxyarylation developed by Russell (Scheme 2.12 and 2.13).[13] It was suggested that aryltrimethylsilanes were activated by *in situ* generated fluoride to give Me_3SiF, or by corresponding R^3OH to give trimethylsilyl ether.



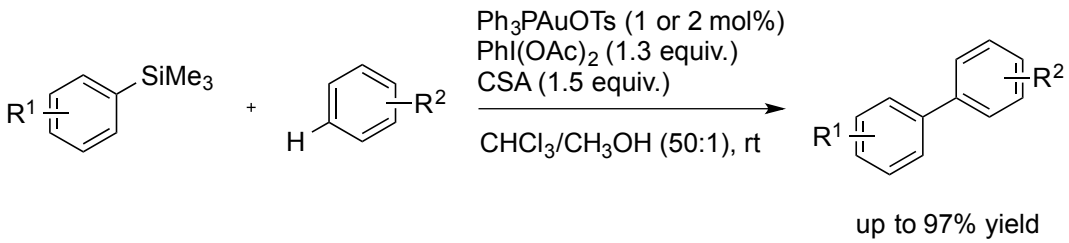
Scheme 2.12 Oxyarylation of olefins using aryltrimethylsilanes by selectfluor

[12] a) Melhado, A. D.; Brenzovich, W. E.; Lackner, A. D.; Toste, F. D. *J. Am. Chem. Soc*. **2010**, *132*, 8885; b) Mankad, N. P.; Toste, F. D. *J. Am. Chem. Soc*. **2010**, *132*, 12859; c) Tkatchouk, E.; Mankad, N. P.; Benitez, D.; Goddard, W. A.; Toste, F. D. *J. Am. Chem. Soc*. **2011**, *133*, 14293.
[13] a) Ball, L. T.; Green, M.; Lloyd-Jones, G. C.; Russell, C. A. *Org. Lett*. **2010**, *12*, 4724; b) Ball, L. T.; Lloyd-Jones, G. C.; Russell, C. A. *Chem. Eur. J*. **2012**, *18*, 2931.



Scheme 2.13 Oxyarylation of olefins using aryltrimethylsilanes by alcohol

Aryltrimethylsilanes were also found applicable and valuable in direct biaryl synthesis recently. Lloyd-Jones and Russell discovered the gold-catalyzed site-selective arylation of aromatic compounds with aryltrimethylsilanes (Scheme 2.14).[14] The site-selectivity and substrate reactivity were predictable according to the electrophilic aromatic substitution principle. Low yields and poor selectivity were observed for electron-deficient (hetero)arenes, such as fluorobenzene and pyridine, with aryltrimethylsilanes acting as electrophiles. Similarly, aryltrimethylsilanes with electron-donating substituents, such as methyl group, afforded the biaryl product at lower yield.

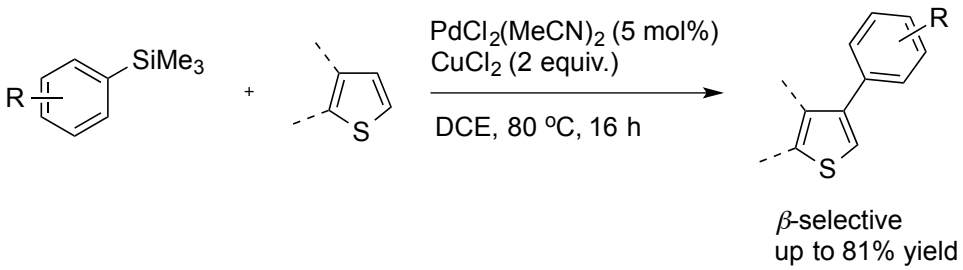


Scheme 2.14 Au-catalyzed direct arylation of arenes with aryltrimethylsilanes

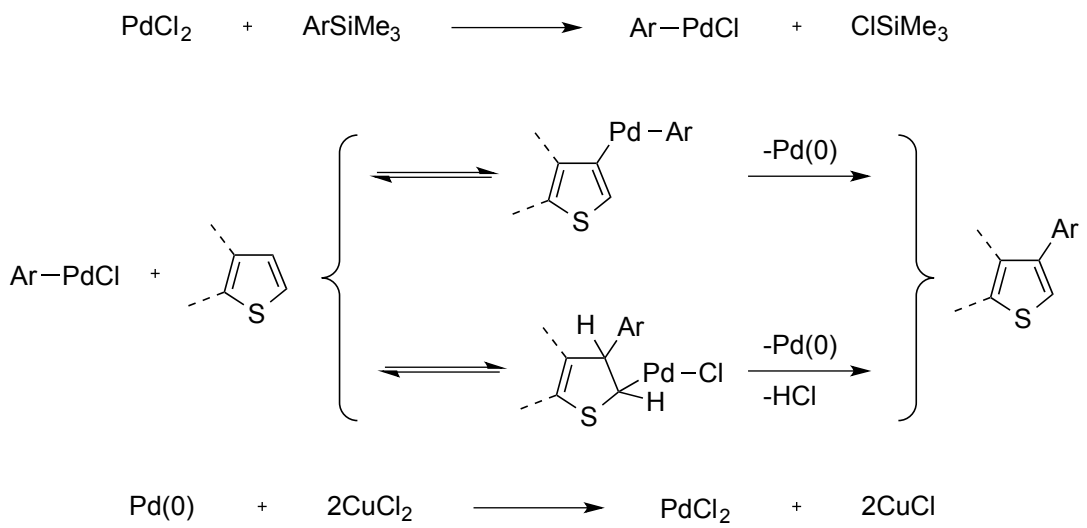
At the same time, Oi[15] described Pd-catalyzed *β*-selective arylation of thiophenes and benzothiophenes with aryltrimethylsilanes (Scheme 2.15). Mechanism studies (Scheme 2.16) suggested that transmetalation of aryltrimethylsilanes

[14] Ball, L. T.; Lloyd-Jones, G. C.; Russell, C. A. *Science*, **2012**, *337*, 1644.
[15] Funaki, K.; Sato, T.; Oi, S. *Org. Lett*. **2012**, *14*, 6186.

generated the arylpalladium intermediate which exhibiting an electrophilic character. Therefore, electron-rich thiophenes afforded better yields than electron-deficient ones.



Scheme 2.15 Arylation of thiophenes with aryltrimethylsilanes



Scheme 2.16 Plausible mechanism about arylation of thiophenes with aryltrimethylsilanes

2.2 PALLADIUM-CATALYZED *IPSO*-DESILYLATIVE COUPLING OF ARYL(TRIMETHYL)SILANES WITH ELECTRON-DEFICIENT ALKENES

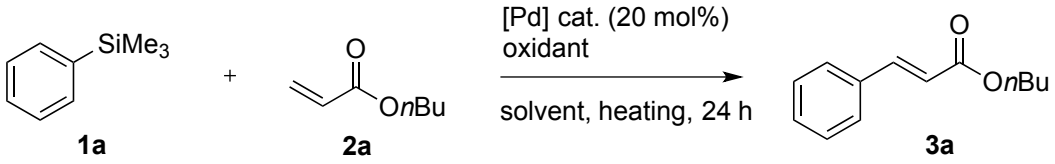
Inspired by the above work, we aim to develop a fluoride-free protocol to functionalize aryltrimethylsilanes and transform them into other useful organic compounds. Based on the recent research progress regarding olefin-olefin coupling in our group[16], we chose alkene as the other coupling parner to investigate on how to connect it with aryltrimethylsilane.

Phenyl(trimethyl)silane (**1a**) and *n*-butyl acrylate (**1b**) were chosen as the model study to optimize the reaction conditions (Table 2.1). We started to apply $PdCl_2$ (20 mol%) as the catalyst and $Cu(OAc)_2$ (1 equiv.) as the oxidant to screen commonly used solvents. The desired coupling product was only observed and successfully isolated at 10% yield in AcOH as the solvent (entry 2). DMF, DMSO and toluene could not give the positive results (entries 8-10). With DCE or 1,4-dixoane as the solvent, unknown side-products formed and were inseparable from the desired product (entries 11 and 12).

Besides $Cu(OAc)_2$, other common oxidants were also tried, such as 1,4-benzoquinone (BQ), air and molecular oxygen (entries 1, 4 and 5). Combination of 1 atm of oxygen together with 0.2 equiv. of $Cu(OAc)_2$, the isolated yield could be increased to 50% (entry 5). A satisfactory yield of 70% could be achieved by further increasing the temperature from 50 to 70 ^{o}C (entry 6). The control experiment without $PdCl_2$ was tested, and no product formed as expected (entry 7).

[16] a) Xu, Y. H.; Lu, J.; Loh, T. P. *J. Am. Chem. Soc*. **2009**, *131*, 1372; b) Wen, Z. -K.; Xu, Y. -H.; Loh, T. -P. *Chem. Eur. J*. **2012**, *18*, 13284.

Table 2.1: Optimization of reaction conditions for activation of phenyl C-Si bond[a]



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

Entry	Solvent	Oxidant	Catalyst	Yield (%)
1	AcOH	1,4-benzoquinone	$PdCl_2$	28
2	AcOH	$Cu(OAc)_2$	$PdCl_2$	10
3	AcOH	$Cu(OAc)_2$	$Pd(OAc)_2$	<5
4[b]	AcOH	$Cu(OAc)_2/O_2$	$PdCl_2$	13
5[b,c]	AcOH	$Cu(OAc)_2/O_2$	$PdCl_2$	50
6[b,d]	AcOH	$Cu(OAc)_2/O_2$	$PdCl_2$	70
7	AcOH	$Cu(OAc)_2$	None	0
8	DMF	$Cu(OAc)_2$	$PdCl_2$	0
9	DMSO	$Cu(OAc)_2$	$PdCl_2$	0
10	Toluene	$Cu(OAc)_2$	$PdCl_2$	<5
11[e]	DCE	$Cu(OAc)_2$	$PdCl_2$	13
12[e]	1,4-Dioxane	$Cu(OAc)_2$	$PdCl_2$	10

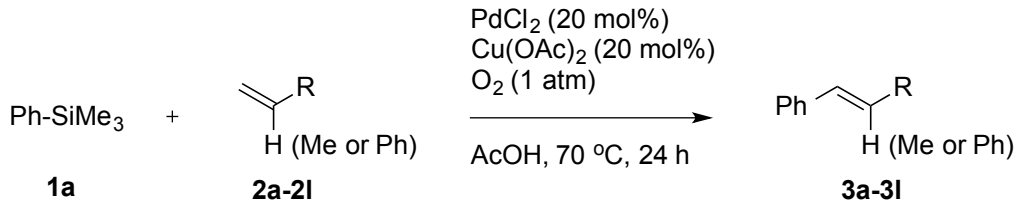
[a] Reactions were run with phenyl(trimethyl)silane (1 equiv.), *n*-butyl acrylate (2 equiv.), Pd catlayst (20 mol%), oxidant (1 equiv.) at 50 °C for 24 h unless specifically stated. Isolated yield were determined after column purification. [b] $Cu(OAc)_2$ (20 mol%) and of O_2 (oxygen balloon) were applied. [c] Reaction was run for 48 h. [d] Reaction was run at 70 °C. [e] An unknown side-product was formed and inseparable from the desired product.

With this optimized condition, we proceeded to screen various alkenes (Table 2.2). *n*-Butyl, *t*-butyl and methyl acrylate gave similar satifactory yields above 70% (entries 1-3). Phenylvinylsulfone also underwent the coupling reaction smoothly,

giving 60% yield (entry 4). For the styrene series, generally, substrates with electron-withdrawing substituents afforded the desired product at better yields than those with electron-donating ones (entries 5-8). *m*-Nitro and *para*- chlorostyrene afforded the corresponding products at 74% and 62% yield, respectively; while para-methyl and para-methoxystyrene gave the desired products at lower yields. 1,1-Disubstituted electron poor alkenes, such as methyl methacrylate, gave slightly lower yield (57%, entry 9) than methyl acrylate (72%, entry 3). Other weakly electron-poor 1,1-di-substituted alkenes reacted slugishly under this protocol (entries 10-11). Unfortunately, electron neutral alkene did not react under the optimized conditions (entry 12). Thus this protocol worked better with conjugated electron-deficient alkenes than other electron normal or rich alkenes.

Next, we proceeded to screen different aryl(trimethyl)silanes using *n*-butylacrylate with the optimized conditions (Table 2.3). After testing a series of aryl(trimethyl)silanes, we found that alkyl, electron-donating or weekly electron-withdrawing substituents *para* or *meta* to $SiMe_3$, such as *t*-butyl, methoxy, fluoro group, did not affect the yields significantly (60%-70%, entries 1-7). Lower yields were obtained for **1h** and **1i** (45% and 30% respectively, entries 8-9). Strongly electron-withdrawing group like CF_3 greatly decreased the reactivity and only affored the product at 13% yield (entry 10). From the comparison of 2- and 1-naphthyltrimethylsilanes **1l** and **1k**, this reaction was very sensitive with the steric hinderance, thus only trace amount of desired product was observed for **1k** (entries 10 and 12). 2-(Trimethylsilyl)pyridine **1l** as a representative heteroaryl(trimethyl)silane was also tried, however no desired product could be obtained (entry 12).

Table 2.2 Pd (II)-catlayzed phenyl(trimethyl)silane coupling with various alkenes



1a **2a-2l** **3a-3l**

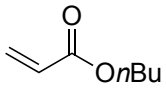
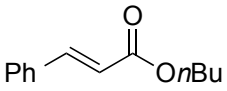
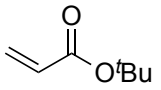
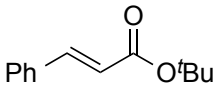
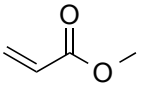
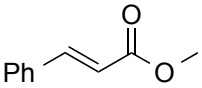
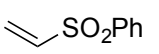
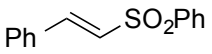
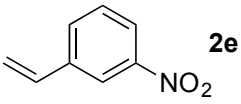
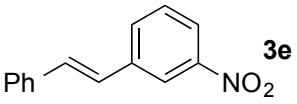
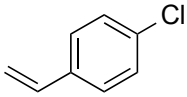
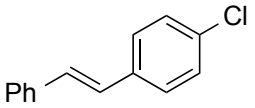
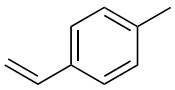
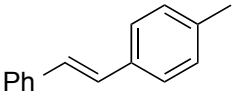
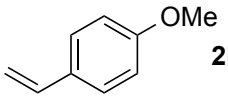
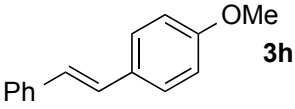
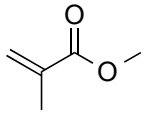
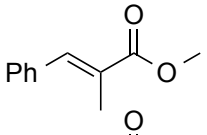
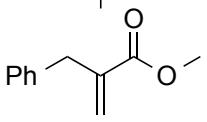
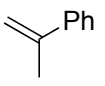
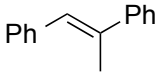
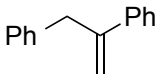
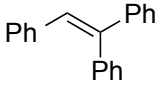
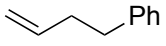
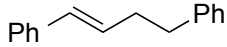
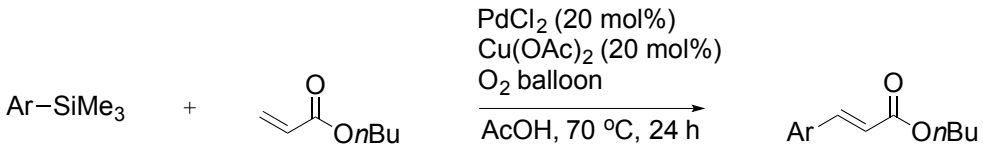
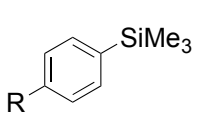
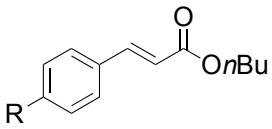
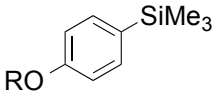
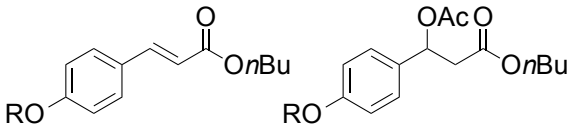
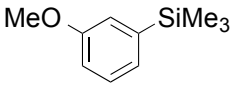
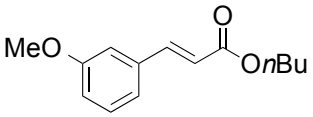
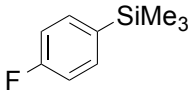
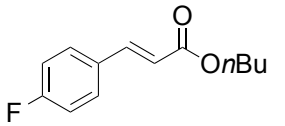
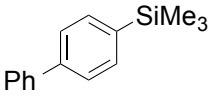
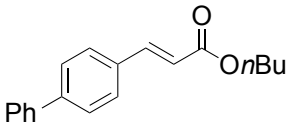
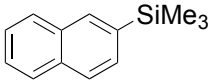
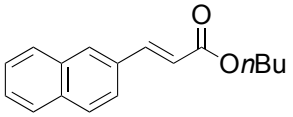
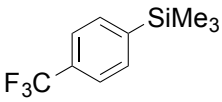
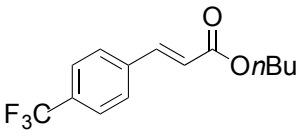
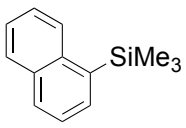
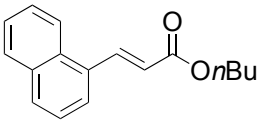
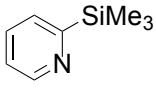
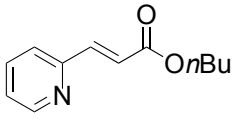
Entry	Alkenes	Product	Yield (%)
1	 **2a**	 **3a**	70
2	 **2b**	 **3b**	70
3	 **2c**	 **3c**	72
4	 **2d**	 **3d**	60
5	 **2e**	 **3e**	74
6	 **2f**	 **3f**	62
7	 **2g**	 **3g**	38
8	 **2h**	 **3h**	25
9	 **2i**	 **3i**  **3i'**	57 (1:1)
10	 **2j**	 **3j**  **3j'**	12 (1:1)
11	 **2k**	 **3k**	26
12	 **2l**	 **3l**	0

Table 2.3 Pd(II)-catlayzed aryl(trimethyl)silanes coupling with *n*-butylacrylate

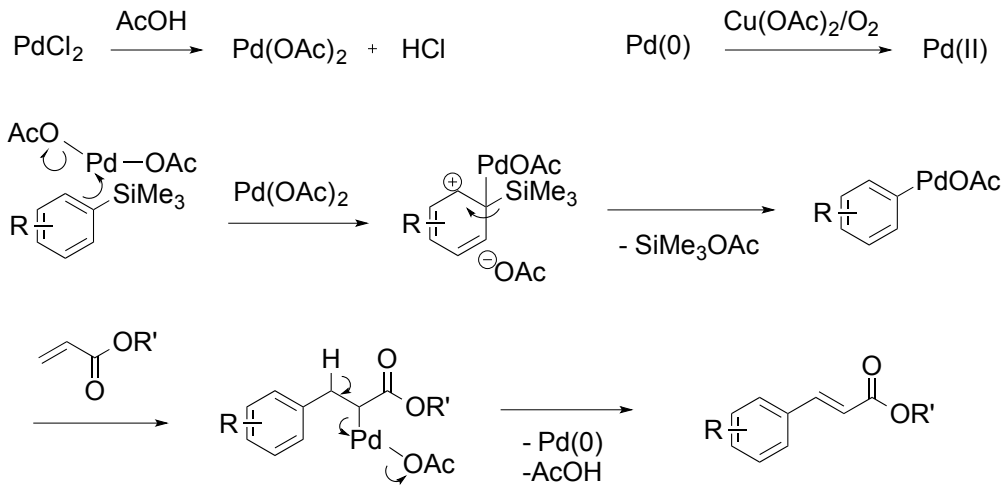


1a-1h **2a** **4a-4h**

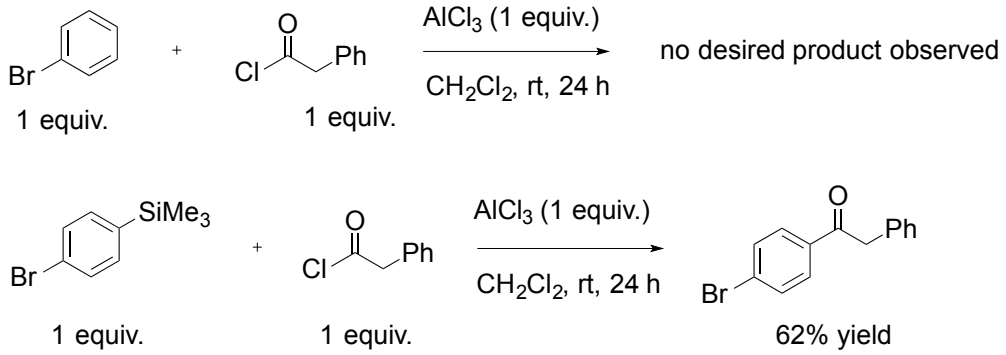
Entry	Ar-SiMe$_3$		Product		Yield (%)
					
1	R = H	**1a**	R = H	**4a**	70
2	R = Me	**1b**	R = Me	**4b**	64
3	R = *t*Bu	**1c**	R = *t*Bu	**4c**	68
					
4	R = OMe	**1d**	R = OMe	**4d** and **4d'**	69 (**4d**:**4d'** = 1:1)
5	R = OPh	**1e**	R = OPh	**4e** and **4e'**	65 (**4e**:**4e'** = 8:3)
6		**1f**		**4f**	64
7		**1g**		**4g**	60
8		**1h**		**4h**	45
9		**1i**		**4i**	30
10		**1j**		**4j**	13
11		**1k**		**4k**	trace
12		**1l**		**4l**	trace

Based on the above results that this reaction went well with electron rich aryl(trimethyl)silanes but sluggishly with electron deficient ones, we proposed that the reaction might undergo Friedal Crafts transmatalation assisted with silicon *β*-cation stabilization effect, followed by re-aromatization via the drop of Me_3SiOAc and *β*-H elimination to afford the Heck-type product (Scheme 2.17).

Scheme 2.17 Plausible mechanism



Scheme 2.18 Comparison the reactivity towards Friedel-Crafts reaction between bromobenzene and (4-bromophenyl)trimethylsilanes



To demonstrate the stablization effect of $SiMe_3$ group, two control Friedel-Crafts acylation reactions were run (Scheme 2.18). At the same reaction conditions, simple bromobenzene was not reactive enough to undergo the Friedal Crafts

acylation. However, with the aid of $SiMe_3$ group, the substrate reactivity was greatly enhanced and achieve the desired product at 62% yield.

2.3 CONCLUSION

In summary, we have developed a fluoride and hydroxide-free protocol for Pd-catalyzed activation of aryl C-Si bond in tetraorganosilanes with electron-deficient alkenes through Frideal Crafts transmetalation. The aryl C-Si bond in both electron rich and weakly poor arene substituents could be cleaved and couple with butylacrylate at satisfactory yields.

2.4 EXPERIMENTAL

General methods

All alkenes, trimethylphenylsilane, and solvents that were commercially available, were used directly without further purification. All copper acetate, benzoquinone and palladium catalysts were purchased from chemical companies and used directly without further purifications. Commercially unavailable aryltrimethylsilanes were synthesized according to the following methioned procedure.

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with acidic solution of ceric molybdate. Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.

Infrared spectra were recorded on a Bio-Rad FTS 165 FTIR spectrometer. The oil samples were examined under neat conditions. High Resolution Mass (HRMS) spectra were obtained using Finnigan MAT95XP GC/HRMS (Thermo Electron Corporation).

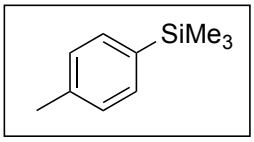
Proton nuclear magnetic resonance spectra (1H NMR) were recorded on a Bruker Avance DPX 300, Bruker AMX 400 or 500 spectrophotometer ($CDCl_3$ as solvent). Chemical shifts for 1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ

7.2600, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (13C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet).

General procedure for the synthesis of aryltrimethylsilanes

To an oven drid 100 mL round bottom flask, 50 mL anhydrous THF and corresponding arylhalide (5 mmol, 1 equiv.) were added and cooled to – 78 ^{o}C with stirring and nitrogen protected. Then, *n*BuLi (5.5 mmol, 1.1 equiv.) was added to the mixture slowly. After 30 min, trimethylchlorosilane (6 mmol, 1.2 equiv.) was added dropwise. While the reaction mixture warmed to room temperature over 1 h, saturated NH_4Cl was added, followed by extraction with ethyl acetate three times. The combined organic layers were washed with saturated brine and dried over Na_2SO_4, and concentrated under vacuo. The residue was purified by silica gel column chromatography using diethyl ether/hexane (5:95) as eluant to afford the desired aryltrimethylsilane.

Characterization data for aryltrimethylsilanes



Trimethyl(*p*-tolyl)silane (1b):[17] The title compound was synthesized from 1-bromo-

[17] Hevesi, L.; Dehon, M.; Crutzen, R.; Lazarescu-Grigore, A. *J. Org. Chem*. **1997**, *62*, 2011.

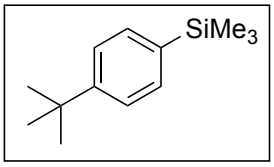
4-methylbenzene according to the general procedure (colorless oil, 92% yield);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.18 (d, *J* = 6.9 Hz, 2H), 2.34 (s, 3H), 0.26 (s, 9H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6, 136.8, 133.4, 128.6, 21.5, -1.0 ppm;

HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{10}H_{17}Si$: 165.1100, found: 165.1105;

FTIR (NaCl, neat): ν 2955.0, 1604.8, 1247.9, 1107.0, 839.0, 798.5, 754.2 cm^{-1}.



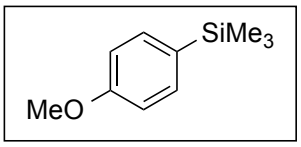
(4-(*tert*-Butyl)phenyl)trimethylsilane (1c):[11] The title compound was synthesized from 1-bromo-4-(*tert*-butyl)benzene according to the general procedure (white solid, 94% yield, mp = 77 ^{o}C);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 7.3 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 1.32 (s, 9H), 0.26 (s, 9H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 136.9, 133.3, 124.7, 34.6, 31.3, -1.0 ppm;

HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{13}H_{23}Si$: 207.1569, found: 207.1576;

FTIR (NaCl, neat): ν 1599.0, 1247.9, 1087.6, 837.1cm^{-1}.



(4-Methoxyphenyl)trimethylsilane (1d):[17] The title compound was synthesized from 1-bromo-4-methoxybenzene according to the general procedure (colorless oil, 90% yield);

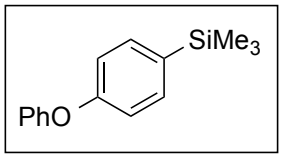
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 8.1 Hz, 2H), 3.70

(s, 3H), 0.15 (s, 9H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 134.7, 131.3, 113.5, 55.0, -0.9 ppm;

HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{10}H_{17}OSi$: 181.1049, found: 181.1057;

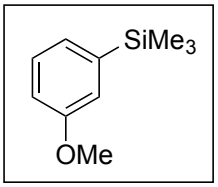
FTIR (NaCl, neat): ν 2953.0, 2835.4, 1595.1, 1502.6, 1276.9, 1247.9, 1182.4, 1111.0, 1033.9, 839.0 cm^{-1}.



(4-Phenoxyphenyl)trimethylsilane (1e):[18] The title compound was synthesized from 1-bromo-4-phenoxybenzene according to the general procedure (colorless oil, 85% yield);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, *J* = 7.80 Hz, 0.92Hz, 2H), 7.30 (td, *J* = 7.44 Hz, 1.4Hz, 2H), 7.03 (t, *J* = 7.38 Hz, 1H), 7.01 (d, *J* = 7.88 Hz, 2H), 6.98 (d, *J* = 8.68 Hz, 2H), 0.26 (s, 9H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 156.9, 134.9, 134.4, 129.8, 123.4, 119.2, 118.0, -0.9 ppm.

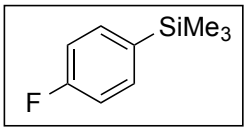


(3-Methoxyphenyl)trimethylsilane (1f):[19] The title compound was synthesized from 1-iodo-3-methoxybenzene according to the general procedure (colorless oil, 67% yield);

[18] Eaborn, C.; Sperry, J. A. *J. Chem. Soc*. **1961**, 4923.
[19] Al-Hassan, M. I.; Al-Najjar, I. M.; Al-Oraify, I. M. *Magn. Res. Chem*. **1989**, *27*, 1112.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (t, *J* = 7.68 Hz, 1H), 7.10 (d, *J* = 7.20 Hz, 1H), 7.06 (d, *J* = 2.6 Hz, 1H), 6.89 (dt, *J* = 8.24, 1.36 Hz, 1H), 3.82 (s, 3H), 0.26 (s, 9H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 142.2, 129.0, 125.6, 119.0, 113.8, 55.1, -1.1 ppm.



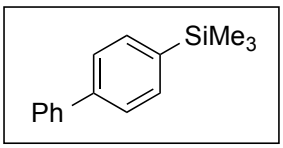
(4-Fluorophenyl)trimethylsilane (1g):[11] The title compound was synthesized from 1-fluoro-4-iodobenzene according to the general procedure (colorless oil, 96% yield);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (t, *J* = 6.8 Hz, 2H), 6.93 (t, *J* = 8.4 Hz, 2H), 0.15 (s, 9H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6 (d, *J* = 246.0 Hz), 135.9 (d, *J* = 3.7 Hz), 135.2 (d, *J* = 7.2 Hz), 114.9 (d, *J* = 19.4 Hz), -1.0 ppm;

HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_9H_{14}SiF$: 169.0849, found: 169.0855;

FTIR (NaCl, neat): ν 2956.9, 1591.3, 1498.7, 1261.5, 1249.9, 1232.5, 1163.1, 1105.2, 850.6, 756.1 cm^{-1}.



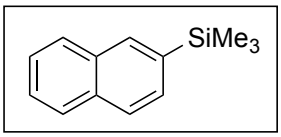
[1,1'-Biphenyl]-4-yltrimethylsilane (1h):[20] The title compound was synthesized from 4-bromo-1,1'-biphenyl according to the general procedure (white solid, 77% yield, mp = 55 ^{o}C);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.57 (m, 6H), 7.44 (tt, *J* = 7.76 Hz, 1.8 Hz, 2H),

[20] Curtis, M. D.; Allred, A. L. *J. Am. Chem. Soc*. **1965**, *87*, 2554.

7.34 (tt, *J* = 7.36 Hz, 1.22 Hz, 1H), 0.30 (s, 9H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.6, 141.2, 139.2, 133.8, 128.8, 127.3, 127.2, 126.5, -1.1 ppm.



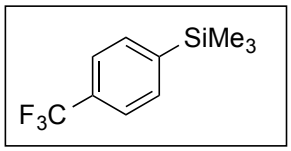
Trimethyl(naphthalen-2-yl)silane (1i):[21] The title compound was synthesized from 2-bromonaphthalene according to the general procedure (colorless oil, 85% yield);

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.84-7.78 (m, 3H), 7.59 (d, *J* = 8.2 Hz, 1H), 7.48-7.44 (m, 2H), 0.34 (s, 9H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 133.8, 133.7, 133.0, 129.8, 128.0, 127.7, 127.0, 126.2, 125.9, -1.0 ppm;

HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{13}H_{17}Si$: 201.1100, found: 201.1096;

FTIR (NaCl, neat): ν 3051.4, 2953.0, 1498.6, 1325.1, 1247.9, 1085.9, 866.0, 837.1, 754.2 cm^{-1}.

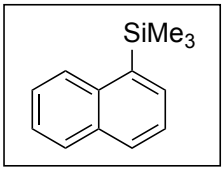


Trimethyl(4-(trifluoromethyl)phenyl)silane (1j):[21] The title compound was synthesized from 1-bromo-4-(trifluoromethyl)benzene according to the general procedure (colorless oil, 82% yield);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.88 Hz, 2H), 7.58 (d, *J* = 8.12 Hz, 2H), 0.29 (s, 9H);

[21] Tobisu, M.; Kita, Y.; Chatani, N. *J. Am. Chem. Soc*. **2006**, *128*, 8152.

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5, 133.6, 130.9 (q, *J* = 31.92 Hz), 124.4 (q, *J* = 270.34 Hz), 124.3 (q, *J* = 3.78 Hz), -1.3 ppm.



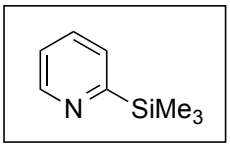
Trimethyl(naphthalen-1-yl)silane (1k):[21] The title compound was synthesized from 1-bromonaphthalene according to the general procedure (colorless oil, 72% yield);

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 7.5 Hz, 1H), 7.85-7.83 (m, 2H), 7.68 (d, *J* = 6.4 Hz, 1H), 7.51-7.41 (m, 3H), 0.34 (s, 9H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 136.9, 133.4, 133.2, 129.7, 129.1, 128.1, 125.6, 125.3, 125.1, -0.3 ppm;

HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{13}H_{17}Si$: 201.1100, found: 201.1089;

FTIR (NaCl, neat): ν 3055.2, 2955.0, 2897.1, 1589.3, 1504.5, 1249.9, 983.7, 854.5, 794.7 cm^{-1}.



2-(Trimethylsilyl)pyridine (1l): The title compound was synthesized from 2-iodopyridine according to the general procedure (brown yellow oil, 62% yield);

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (dd, *J* = 3.76 Hz, 1.08 Hz, 1H), 7.52 (td, *J* = 7.56 Hz, 1.72 Hz, 2H), 7.46 (dt, *J* = 2.32 Hz, 1.12 Hz, 1H), 7.12 (ddd, J = 7.56 Hz, 4.88 Hz, 1.44 Hz, 1H), 0.28 (s, 9H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 150.0, 133.8, 128.6, 122.6, -1.9 ppm;

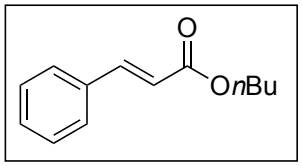
HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_8H_{14}NSi$: 152.0896, found: 152.0891;

FTIR (NaCl, neat): ν 3400.5, 3064.9, 2955.0, 1573.9, 1417.7, 1247.9, 1138.0, 841.0 cm^{-1}.

General procedure for the *ipso*-desilylative coupling of aryltrimethylsilanes with alkenes

To an oven drid 10 mL round bottom flask, Pd catalyst (0.06 mmol, 20 mol%), $Cu(OAc)_2$ (0.06 mmol, 20 mol%), aryl(trimethyl)silane (0.3 mmol, 1 equiv.), alkene (0.6 mmol, 2 equiv.), solvent (3 mL) were added and the mixture was stirred at 70 ^oC with O_2 balloon for 24 h. After cooled down, 15 mL of saturated $NaHCO_3$ was added followed by extraction with ethyl acetate three times. The combined organic layers were washed with saturated brine and dried over Na_2SO_4, and concentrated under vacuo. The residue was purified by silica gel column chromatography using diethyl ether/hexane (10:90) as eluant to afford the desired product.

Characterization data for the *ipso*-desilylative coupling products



Butyl cinnamate (3a, 4a):[22] pale yellow oil, 70% yield;

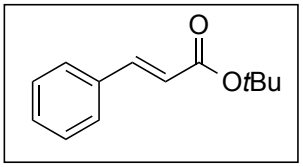
^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 16.00 Hz, 1H), 7.66-7.52 (m, 2H), 7.39-7.37 (m, 3H), 6.44 (d, *J* = 16.00 Hz, 1H), 4.21 (t, *J* = 6.00 Hz, 2H), 1.73-1.65 (m, 2H), 1.49-1.40 (m, 2H) 0.97 (t, *J* = 8.00 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 144.6, 134.5, 130.2, 128.9, 128.1, 118.3, 64.5, 30.8, 19.2, 13.8 ppm;

HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{13}H_{17}O_2$: 205.1229, found: 205.1231;

[22] Wu, S.; Ma, H. -C.; Jia, X. -J.; Zhong, Y. -M.; Lei, Z. -Q. *Tetrahedron* **2011**, *67*, 250.

FTIR (NaCl, neat): ν 3003.2, 2976.2, 2931.8, 1707.0, 1637.6, 1577.8, 1448.5, 1329.0, 1207.4, 1149.6, 979.8, 871.8, 767.7 cm^{-1}.



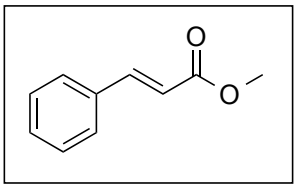
***tert*-Butyl cinnamate (3b):**[22] pale yellow oil, 70% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 16.00 Hz, 1H), 7.51-7.49 (m, 2H), 7.37-7.35 (m, 3H), 6.37 (d, *J* = 16.00 Hz, 1H), 1.54 (s, 9H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 143.5, 134.7, 129.9, 128.8, 127.9, 120.2, 80.5, 28.2 ppm;

HRMS (ESI, m/z): $[M+Na]^+$, calcd. for $C_{13}H_{16}O_2Na$: 227.1048, found: 227.1059;

FTIR (NaCl, neat): ν 2960.7, 2872.0, 1714.7, 1635.6, 1606.7, 1464.0, 1309.7, 1269.2, 1170.8, 983.7, 827.5 cm^{-1}.



Methyl cinnamate (3c):[23] white solid, 72% yield;

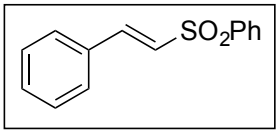
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 16.0 Hz, 1H), 7.54-7.51 (m, 2H), 7.40-7.37 (m, 3H), 6.44 (d, *J* = 16.0 Hz, 1H), 3.81 (s, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 144.9, 134.4, 130.3, 128.9, 128.1, 117.8, 51.7 ppm;

HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{10}H_{11}O_2$: 163.0759, found: 163.0763;

[23] Zhang, Z. -H.; Wang, Z. -Y. *J. Org. Chem*. **2006**, *71*, 7485.

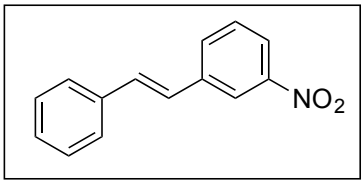
FTIR (NaCl, neat): ν 3408.2, 2947.2, 1714.7, 1637.6, 1452.4, 1315.5, 1170.8, 983.7, 773.5 cm^{-1}.



(*E*)-(2-(Phenylsulfonyl)vinyl)benzene (3d):[24] pale yellow solid, 60% yield, mp = 75 ^{o}C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 7.26 Hz, 2H), 7.71 (d, *J* = 15.96 Hz, 1H), 7.63 (t, *J* = 7.36 Hz, 1H), 7.56 (t, *J* = 7.16 Hz, 2H), 7.48-7.50 (m, 2H), 7.39-7.42 (m, 3H), 6.91 (d, *J* = 16.00 Hz, 1H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.9, 141.1, 133.9, 132.7, 131.7, 129.8, 129.5, 129.0, 128.1, 127.7 ppm.



(*E*)-1-Nitro-3-styrylbenzene (3e):[25] yellow crystal, 74% yield, mp = 106 ^{o}C;

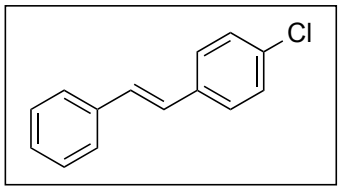
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 8.08 (dd, *J* = 7.52 Hz, 1.44 Hz, 1H), 7.78 (d, *J* = 8.00 Hz, 1H), 7.54-7.48 (m, 3H), 7.39 (t, *J* = 7.48 Hz, 2H), 7.32 (d, *J* = 7.32 Hz, 1H), 7.22 (d, *J* = 16.36 Hz, 1H), 7.11 (d, *J* = 16.32 Hz, 1H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 139.1, 136.3, 132.2, 131.7, 129.5, 128.8, 128.5, 126.8, 126.1, 122.0, 120.9 ppm;

HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{14}H_{12}NO_2$: 226.0868, found: 226.0869;

FTIR (NaCl, neat): ν 3412.1, 2725.4, 1535.3, 1350.2, 966.3, 806.3 cm^{-1}.

[24] Cardillo, G.; Savoia, D.; Umani-Ronchi, A. *Sythesis* **1975**, 453.
[25] Leng, Y. -T.; Yang, F.; Wei, K.; Wu, Y. -J. *Tetrahedron* **2010**, *66*, 1244.



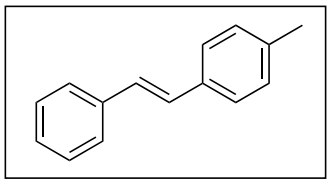
(*E*)-1-Chloro-4-styrylbenzene (3f):[25] white solid, 62% yield, mp = 128 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.68 Hz, 2H), 7.41 (d, *J* = 8.44 Hz, 2H), 7.34 (t, *J* = 7.72 Hz, 2H), 7.30 (d, *J* = 8.48 Hz, 2H), 7.27-7.23 (m, 1H), 7.04-7.03 (m, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 135.8, 133.2, 129.3, 128.8, 128.7, 127.9, 127.7, 127.4, 126.6 ppm;

HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{14}H_{12}Cl$: 215.0628, found: 215.0618;

FTIR (NaCl, neat): ν 3439.1, 1643.4, 966.3, 817.8 cm^{-1}.



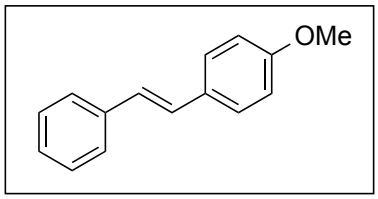
(*E*)-1-Methyl-4-styrylbenzene (3g):[25] white solid, 38% yield, mp = 120 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.52 (m, 2H), 7.41 (d, *J* = 8.10 Hz, 2H), 7.33-7.37 (m, 2H), 7.22-7.26 (m, 1H), 7.17 (d, *J* = 8.16 Hz, 2H), 7.11 (d, *J* = 16.00 Hz, 1H), 7.05 (d, *J* = 15.96 Hz, 1H), 2.35 (s, 3H), ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 134.6, 129.4, 128.9, 127.7, 127.5, 126.4, 126.3, 21.2 ppm;

HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{15}H_{15}$: 195.1174, found: 195.1170;

FTIR (NaCl, neat): ν 3429.4, 2358.9, 1263.4, 960.6, 802.4, 744.5 cm^{-1}.



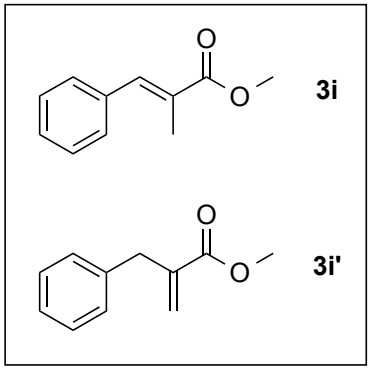
(*E*)-1-Methoxy-4-styrylbenzene (3h):[25] white solid, 25% yield, mp = 134 ^{o}C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.44 (m, 4H), 7.34 (t, *J* = 7.64 Hz, 2H), 7.24 (d, *J* = 7.48 Hz, 1H), 7.07 (d, *J* = 16.28 Hz, 1H), 6.97 (d, *J* = 16.32 Hz, 1H), 6.90 (d, *J* = 6.72 Hz, 2H), 3.83 (s, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 137.7, 130.2, 128.7, 128.2, 127.7, 127.2, 126.6, 126.3, 114.2, 55.3 ppm;

HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{15}H_{15}O$: 211.1123, found: 211.1116;

FTIR (NaCl, neat): ν 2922.2, 1602.9, 1510.3, 1462.0, 1377.2, 1249.9, 1030.0, 968.3 cm^{-1}.



Products **3i** and **3i'** were inseperable by flash column purification, the combined yield was 57% with **3i**/**3i'** around 1:1

(*E*)-Methyl 2-methyl-3-phenylacrylate (3i):[25] yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 1.53 Hz, 1H), 7.28-7.40 (m, 5H), 3.80 (s, 3H), 2.11 (d, *J* = 1.56 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 139.1, 135.9, 129.6, 128.5, 128.4, 128.3, 52.3,

14.4 ppm;

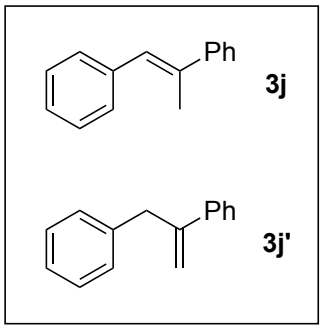
Methyl 2-benzylacrylate (3i'):[26] yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.38 (m, 2H), 7.33-7.25 (m, 3H), 6.65 (d, *J* = 16.00 Hz, 1H), 6.32–6.24 (m, 1H), 4.73–3.72 (m, 2H), 2.09 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 136.3, 134.3, 128.6, 128.2, 126.7, 123.2, 65.1, 21 ppm;

HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{11}H_{13}O_2$: 177.0916, found: 177.0920;

FTIR (NaCl, neat): ν 3412.1, 2949.2, 1712.8, 1631.8, 1492.9, 1435.0, 1257.6, 1203.6, 1116.8, 765.7, 704.0 cm^{-1}.



Products **3j** and **3j'** were inseperable by flash column purification, the combined yield was 12% with **3j**/**3j'** around 1:1

(*E*)-Prop-1-ene-1,2-diyldibenzene (3j):[22] colorless oil;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.53 (m, 2H), 7.45-7.43 (m, 2H), 7.38-7.35 (m, 4H), 7.31-7.30 (m, 2H), 6.85 (s, 1H), 4.53 (s, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 140.8, 139.5, 128.9, 128.3, 128.2, 127.4, 125.9, 17.5 ppm;

Prop-2-ene-1,2-diyldibenzene (3j'):[27] colorless oil;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.53 (m, 2H), 7.41-7.30 (m, 7H), 7.29-7.24 (m,

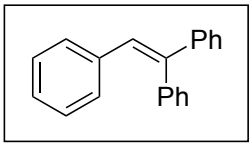
[26] Mi, X.; Huang, M. -M.; Guo, H.; Wu, Y. -J. *Tetrahedron* **2013**, *69*, 5123.
[27] Alacid, E.; Nájera, C. *Org. Lett*. **2008**, *10*, 5011.

1H), 5.60 (ddd, *J* = 2.12, 1.23, 0.65 Hz, 1H), 5.11 (dt, *J* = 2.43, 1.22, 0.85 Hz, 1H), 3.93 (t, *J* = 1.38 Hz, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 140.8, 139.5, 129.0, 128.4, 128.3, 127.5, 126.2, 114.6, 41.7 ppm;

HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{15}H_{15}$: 195.1174, found: 195.1175;

FTIR (NaCl, neat): ν 3431.4, 3024.4, 1600.9, 1494.8, 1263.4, 756.1, 696.3 cm^{-1}.



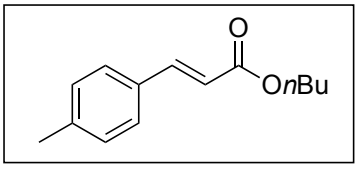
Ethene-1,1,2-triyltribenzene (3k):[26] pale yellow oil, 26% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.27 (m, 8H), 7.25-7.19 (m, 2H), 7.15-7.09 (m, 3H), 7.03 (d, *J* = 7.92 Hz, 2H), 6.97 (s, 1H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 142.6, 140.4, 137.4, 130.4, 129.6, 128.6, 128.22, 128.19, 128.0, 127.6, 127.5, 127.4, 126.8 ppm;

HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{20}H_{17}$: 257.1330, found: 257.1342;

FTIR (NaCl, neat): ν 3417.9, 3022.5, 1597.1, 1489.1, 1442.8, 1076.3, 1028.1, 758.0, 694.4 cm^{-1}.



(*E*)-Butyl-3-(*p*-tolyl)acrylate (4b):[28] yellow oil, 64% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 16.00 Hz, 1H), 7.42 (d, *J* = 7.84 Hz, 2H), 7.18 (d, *J* = 7.80 Hz, 2H), 6.39 (d, *J* = 16.00 Hz, 1H), 4.20 (t, *J* = 6.68 Hz, 2H), 2.37

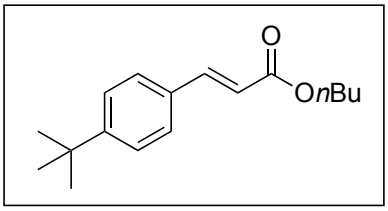
[28] Okubo, K.; Shirai, M.; Yokoyama, C. *Tetrahedron Lett*. **2002**, *43*, 7115.

(s, 3H), 1.71-1.65 (m, 2H), 1.47-1.41 (m, 2H), 0.96 (t, *J* = 7.36 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 144.6, 140.6, 131.8, 129.6, 128.1, 117.2, 64.4, 30.8, 21.5, 19.2, 13.8 ppm;

HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{11}H_{13}O_2$: 177.0916, found: 177.0916;

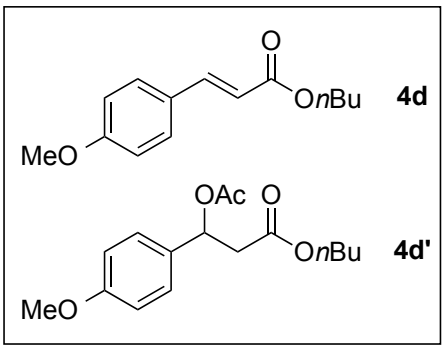
FTIR (NaCl, neat): ν 3410.2, 2958.9, 2872.0, 1712.8, 1637.6, 1608.6, 1514.1, 1309.7, 1168.9, 814.0 cm^{-1}.



(*E*)-Butyl-3-(4-(*tert*-butyl)phenyl)acrylate (4c):[26] yellow oil, 68% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 15.96 Hz, 1H), 7.47 (d, *J* = 8.36 Hz, 2H), 7.40 (d, *J* = 8.43 Hz, 2H), 6.41 (d, *J* = 16.00 Hz, 1H), 4.21 (t, *J* = 6.70 Hz, 2H), 1.73-1.66 (m, 2H), 1.47-1.41 (m, 2H), 1.35 (s, 9H), 0.97 (t, *J* = 7.38 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 153.8, 144.5, 131.7, 127.9, 125.9, 117.4, 64.4, 34.9, 31.2, 30.8, 19.2, 13.8 ppm;



(*E*)-Butyl-3-(4-methoxyphenyl)acrylate (4d):[26] colorless oil, 36% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 15.96 Hz, 1H), 7.47 (d, *J* = 8.56 Hz, 2H), 6.90 (d, *J* = 8.52 Hz, 2H), 6.31 (d, *J* = 15.96 Hz, 1H), 4.19 (t, *J* = 6.64 Hz, 2H), 3.83

(s, 3H), 1.72-1.65 (m, 2H), 1.48-1.39 (m, 2H), 0.96 (t, *J* = 7.34 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 161.3, 144.2, 129.7, 127.2, 115.8, 114.3, 64.3, 55.3, 30.8, 19.2, 13.8 ppm;

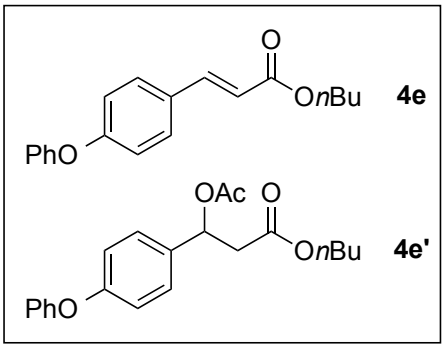
HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{11}H_{13}O_3$: 193.0865, found: 193.0857;

FTIR (NaCl, neat): ν 3410.2, 2958.8, 1708.9, 1633.7, 1602.9, 1512.2, 1251.8, 1168.9 cm^{-1}.

Butyl-3-acetoxy-3-(4-methoxyphenyl)propanoate (4d'); colorless oil, 33% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.72 Hz, 2H), 6.87 (d, *J* = 8.72 Hz, 2H), 6.12 (dd, *J* = 8.76 Hz, 5.56 Hz, 1H), 4.06 (t, *J* = 6.60 Hz, 2H), 3.79 (s, 3H), 2.97 (dd, *J* = 15.56 Hz, 8.84 Hz, 1H), 2.74 (dd, *J* = 15.52 Hz, 5.56 Hz, 1H), 2.03 (s, 3H), 1.60-1.53 (m, 2H), 1.37-1.28 (m, 2H), 0.91 (t, *J* = 7.38 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 169.8, 159.6, 128.1, 113.9, 71.9, 64.6, 55.3, 41.3, 30.6, 21.1, 19.0, 13.6 ppm;



(*E*)-Butyl-3-(4-phenoxyphenyl)acrylate (4e): colorless oil, 40% yield;

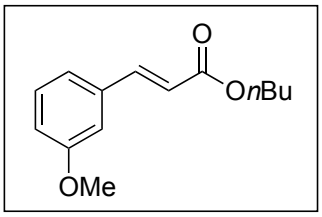
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 16.00 Hz, 1H), 7.48 (dt, *J* = 11.24 Hz, 4.76 Hz, 2H), 7.39-7.34 (m, 2H), 7.15 (tt, *J* = 7.42 Hz, 1.00 Hz, 1H), 7.04 (dq, *J* = 8.68 Hz, 0.88 Hz, 2H), 6.98 (dt, *J* = 8.68 Hz, 2.26 Hz, 2H), 6.35 (d, *J* = 15.96 Hz, 1H), 4.20 (t, *J* = 6.68 Hz, 2H), 1.72-1.65 (m, 2H), 1.46-1.41 (m, 2H), 0.96 (t, *J* = 7.38 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 159.4, 156.2, 143.8, 129.9, 129.7, 129.3, 124.1, 119.7, 118.4, 117.0, 64.4, 30.8, 19.2, 13.8 ppm;

Butyl-3-acetoxy-3-(4-phenoxyphenyl)propanoate (4e'): colorless oil, 33% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.32 (m, 4H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.01 (dq, *J* = 8.72 Hz, 1.59 Hz, 2H), 6.96 (dt, *J* = 8.68 Hz, 2.40 Hz, 2H), 6.15 (dd, *J* = 8.84 Hz, 5.52 Hz, 1H), 4.08 (td, *J* = 6.70 Hz, 0.84 Hz, 2H), 2.97 (dd, *J* = 15.64 Hz, 8.84 Hz, 1H), 2.76 (dd, *J* = 15.60 Hz, 5.48 Hz, 1H), 2.05 (s, 3H), 1.61-1.54 (m, 2H), 1.37-1.29 (m, 2H), 0.92 (t, *J* = 7.38 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 157.5, 156.8, 133.9, 129.8, 128.2, 123.6, 119.3, 118.6, 71.8, 64.7, 41.4, 30.6, 21.1, 19.0, 13.7 ppm;

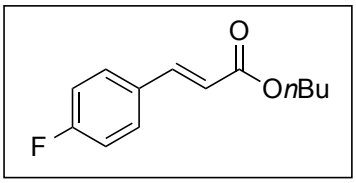


Butyl-(*E*)-3-(3-methoxyphenyl)acrylate (4f):[29] yellow oil, 64% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 15.96 Hz, 1H), 7.29 (t, *J* = 7.92 Hz, 1H), 7.12 (d, *J* = 7.48 Hz, 1H), 7.05 (d, *J* = 1.64 Hz, 1H), 6.93 (dd, *J* = 8.20 Hz, 2.40 Hz, 1H), 6.43 (d, *J* = 16.00 Hz, 1H), 4.21 (t, *J* = 6.68 Hz, 2H), 3.83 (s, 3H), 1.73-1.66 (m, 2H), 1.49-1.39 (m, 2H), 0.97 (t, *J* = 7.36 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 159.9, 144.5, 135.8, 129.8, 120.7, 118.6, 116.1, 112.9, 64.4, 55.3, 30.8, 19.2, 13.7 ppm;

[29] Yang, C.; Nolan, S. P. *Synlett* **2001**, *10*, 1539.



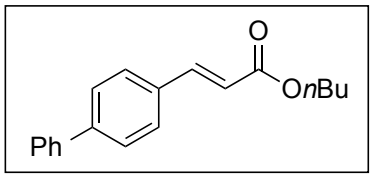
(*E*)-Butyl-3-(4-fluorophenyl)acrylate (4g):[30] yellow oil, 60% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 16.00 Hz, 1H), 7.51 (dd, *J* = 8.36 Hz, 5.60 Hz, 2H), 7.07 (t, *J* = 8.58 Hz, 2H), 6.36 (d, *J* = 16.00 Hz, 1H), 4.21 (t, *J* = 6.68 Hz, 2H), 1.71-1.65 (m, 2H), 1.47-1.41 (m, 2H), 0.97 (t, *J* = 7.38 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 163.9 (d, *J* = 249.75 Hz), 143.2, 130.7 (d, *J* = 3.43 Hz), 129.9 (d, *J* = 8.36 Hz), 118.1 (d, *J* = 2.21 Hz), 116.0 (d, *J* = 21.73 Hz), 64.5, 30.8, 19.2, 13.7 ppm;

HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{10}H_{10}O_2F$: 181.0665, found: 188.0674;

FTIR (NaCl, neat): ν 2960.7, 2873.9, 1718.6, 1639.5, 1600.9, 1510.3, 1465.9, 1415.8, 1313.5, 1176.6, 981.8, 831.3cm^{-1}.

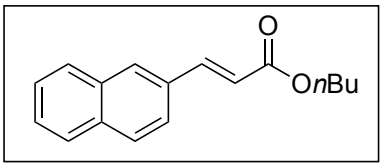


Butyl-(*E*)-3-([1,1'-biphenyl]-4-yl)acrylate (4h):[31] white solid, 45% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 16.00 Hz, 1H), 7.61-7.58 (m, 6H), 7.44 (t, *J* = 7.48 Hz, 2H), 7.36 (t, *J* = 7.36 Hz, 1H), 6.47 (d, *J* = 16.00 Hz, 1H), 4.22 (t, *J* = 6.68 Hz, 2H), 1.74-1.66 (m, 2H), 1.49-1.40 (m, 2H), 0.97 (t, J = 7.38 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 144.1, 143.0, 140.2, 133.4, 128.9, 128.5, 127.8, 127.5, 127.0, 118.1, 64.4, 30.8, 19.2, 13.8 ppm;

[30] Zhou, X. -Y.; Luo, J. -Y.; Liu, J.; Peng, S. -M.; Deng, G. -J. *Org. Lett*. **2011**, *13*, 1432.
[31] Mino, T.; Shirae, Y.; Sasai, Y.; Sakamoto, M.; Fujita, T. *J. Org. Chem*. **2006**, *71*, 6834.



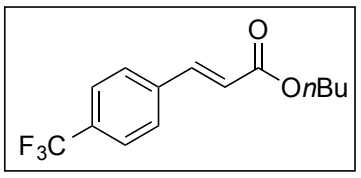
(*E*)-Butyl-3-(naphthalen-2-yl)acrylate (4i):[30] yellow oil, 30% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.87-7.83 (m, 4H), 7.67 (dd, *J* = 8.6 Hz, 1.52 Hz, 1H), 7.54-7.49 (m, 2H), 6.56 (d, *J* = 15.92 Hz, 1H), 4.24 (t, *J* = 6.68 Hz, 2H), 1.75-1.68 (m, 2H), 1.51-1.42 (m, 2H), 0.99 (t, *J* = 7.38 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 144.6, 134.2, 133.3, 132.0, 129.9, 128.7, 127.8, 127.2, 126.7, 123.5, 118.6, 64.5, 30.8, 19.2, 13.8 ppm;

HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{17}H_{19}O_2$: 255.1385,found: 255.1382;

FTIR (NaCl, neat): ν 3442.9, 1712.8, 1633.7, 1292.3, 1257.2, 1170.8 cm^{-1}.



Butyl-(*E*)-3-(4-(trifluoromethyl)phenyl)acrylate (4j):[26] pale yellow oil, 13% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 16.00 Hz, 1H), 7.66-7.61 (m, 4H), 6.51 (d, *J* = 16.00 Hz, 1H), 4.23 (t, *J* = 6.68 Hz, 2H), 1.74-1.67 (m, 2H), 1.49-1.39 (m, 2H), 0.97 (t, *J* = 7.40 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 142.7, 137.9 (d, *J* = 1.01 Hz), 131.7 (q, *J* = 32.41 Hz), 123.9 (q, *J* = 270.43 Hz), 128.2, 125.9 (q, *J* = 3.77 Hz), 120.9, 64.7, 30.7, 19.2, 13.7 ppm.

PART I

CHAPTER 3

ipso-Desilylative Acylation of Aryl(trimethyl)silanes with Acid Chlorides

3.1 INTRODUCTION

From the control experiments in previous chapter, we found that the TMS group could significantly increase the reactivity of aromatic compounds towards electrophilic substitution, with site of attack selective on *ipso*-carbon. Based on these results, we envisioned that aryltrimethylsianes were feasible substrates for selective *ipso*-desilylative Friedel-Crafts (FC) acylation, especially for electron-deficient arenes.

As we know, classical FC acylation required more or as reactive as halobenzenes. Traditional methods generally employed quantitative amount of Lewis acid, such as $ZnCl_2$, $AlCl_3$, $TiCl_4$, $SnCl_4$, $FeCl_3$, or strong protic acids, such as HF and H_2SO_4, which may evolve hazadous gas HCl and large volumes of waste.[1] Morden methods focused on "green revolution" and exploration of new efficient catalysts.[2]

However, low reactivity for electron-deficient arenes limited the substrate scope, and selectivity of FC reactions normally followed the aromatic electrophilic substitution principle. *para*-Acylation was usually prefered than *ortho*-position due to steric hinderance for electron rich arenes, and *meta*-acylation for electron poor arenes.[3] Therefore site-selective FC acylation of both electron rich and deficient arenes was desired for synthesis of multifuctional arenes.

With the hint from chapter 2, we continued to investigate the functionalizations of aryltrimethylsilanes, and discussed the preliminary results of *ipso*-desilylative acylation of aryltrimethylsilanes with acid chlorides in this chapter.

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[1] a) Grucarevic, S.; Merz, V. *Chem. Ber*. **1873**, *6*, 60; b) Gore, P. H. *Aromatic Ketone Synthesis in Friedel-Crafts and Related Reactions*; Olah, G. A., Ed.; John Wiley & Sons Inc.; London, 1964; Vol III, Part 1, p 1; c) Olah, G. A. *Friedel-Crafts Chemistry*; Wiley: New York, 1973; d) Ross, J.; Xiao, J. *Green Chem*. **2002**, *4*, 129; e) Sartori, G.; Maggi, R. *Chem. Rev*. **2006**, *106*, 1077; f) Sartori, G.; Maggi, R. *Advances in Friedel-Crafts Acylation Reactions Catalytic and Green Processes*, CRC Press Taylor & Francis Group, 2010.

[2] a) Sheldon, R. A.; Downing, R. S. *Appl. Catal. A: Gen*. **1999**, *189*, 163; b) Anastas, P. T.; Bartlett, L. B.; Kirchhoff, M. M.; Williamson, T. C. *Catal. Today* **2000**, *55*, 11.

[3] Sharghi, H.; Jokar, M.; Doroodmand, M. M. Khalifeh, R. *Adv. Synth. Catal*. **2010**, *352*, 3031.

3.2 *IPSO*-DESILYLATIVE ACYLATION OF ARYL(TRIMETHYL)SILANES WITH ACID CHLORIDES

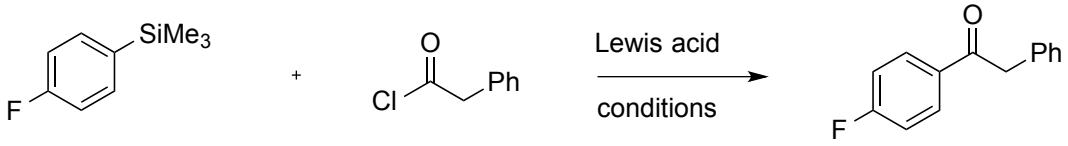
With the aim of developing a protocol for FC acylation of electron-deficient aryltrimethylsilanes, (4-fluorophenyl)trimethylsilane (**1a**) and 2-phenylacetyl chloride (**b**) were chosen as the model study to optimize the reaction conditions (Table 3.1).

Knowing that 1 equiv. of $AlCl_3$ could afford FC acylation for (4-bromophenyl)trimethylsilane at 62% yield from chapter 2, we applied the same condition for **1a** and **2**, and the desired product **3a** was isolated at 24% yield (entry 1). Increasing the concentration to make the reaction as nearly to "solvent less or free", 48% yield was obtained with 15 equiv. of DCM used (entry 2).

With the hope to make the FC acylation catalytic, we then screened some common Lewis acids with 0.5 equiv of loading. Unfortunately, no desired product was obtained at room temperature after 3 hours (entries 3-10) for other metal salts, except for $AlCl_3$ giving 35% yield at room temperature and 43% yield at 40 ^oC. Nonetheless, the use of 1 equiv. of $AlCl_3$ gave rise to the desired product at 65% (entries 13-14). A satisfactory yield of 84% was obtained when applying a superstoichiometric amount of Lewis acid (entry 16). Further increase of $AlCl_3$ loading, higher temperature or less solvent could not produce better results (entries 15, 17-20).

With this optimized condition, we proceeded to test other substrates, especially electron-deficient aryltrimethylsilanes (Table 3.2). Due to time constraint, only those listed substrates were screened.

Table 3.1: Optimization of reaction condition for *ipso*-desilylative acylation

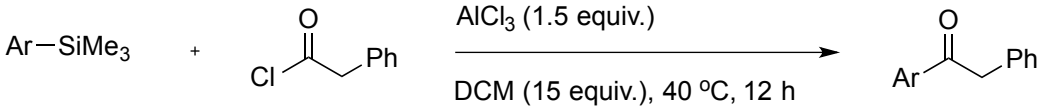


1a (1 equiv.) **2** (1 equiv.) **3a**

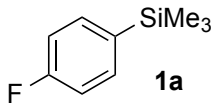
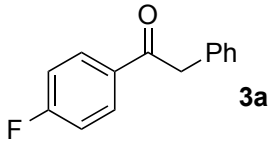
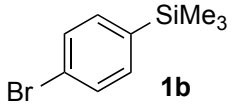
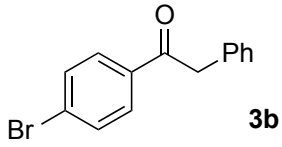
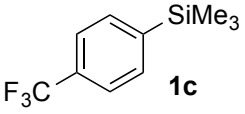
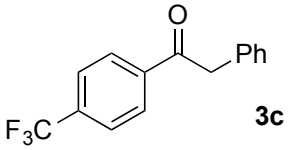
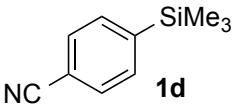
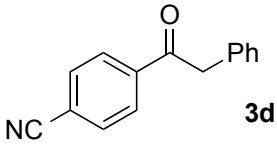
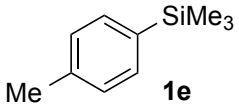
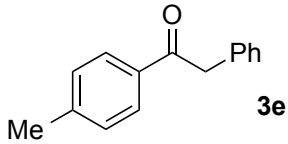
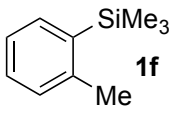
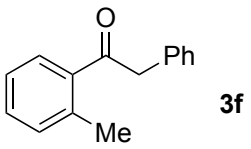
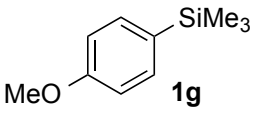
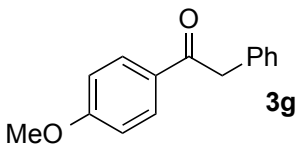
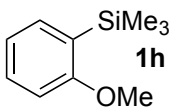
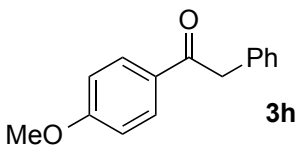
Entry	Lewis Acid (equiv.)	Solvent (equiv.)	Temp. (^oC)	Time (h)	Yield (%)
1	$AlCl_3$ (1)	DCM (2 mL)	rt	3	24
2	$AlCl_3$ (1)	DCM (15)	rt	3	48
3	$InBr_3$ (0.5)	DCM (15)	rt	3	N.A.
4	$In(OTf)_3$ (0.5)	DCM (15)	rt	3	N.A.
5	$Cu(OTf)_3$ (0.5)	DCM (15)	rt	3	N.A.
6	ZnO (0.5)	DCM (15)	rt	3	N.A.
7	$FeCl_3$ (0.5)	DCM (15)	rt	3	N.A.
8	$Fe(acac)_3$ (0.5)	DCM (15)	rt	3	N.A.
9	$ZnFe_2O_4$ (0.5)	DCM (15)	rt	3	N.A.
10	$ZnBr_2$ (0.5)	DCM (15)	rt	3	N.A.
11	$AlCl_3$ (0.5)	DCM (15)	rt	3	35
12	$AlCl_3$ (0.5)	DCM (15)	40	3	43
13	$AlCl_3$ (1)	DCM (15)	40	3	65
14	$AlCl_3$ (1)	DCM (15)	40	12	64
15	$AlCl_3$ (1)	DCE (15)	70	12	46
16	$AlCl_3$ (1.5)	DCM (15)	40	12	84
17	$AlCl_3$ (1.5)	DCM (10)	40	12	messy
18	$AlCl_3$ (1.5)	DCM (5)	40	12	messy
19[a]	$AlCl_3$ (2)	DCM (15)	40	12	23
20[a]	$AlCl_3$ (2)	DCM (15)	40	12	79

[a] 2 equiv. of acid chloride was applied.

Table 3.2: Screening of aryl(trimethyl)silanes for ipso-desilylative acylation

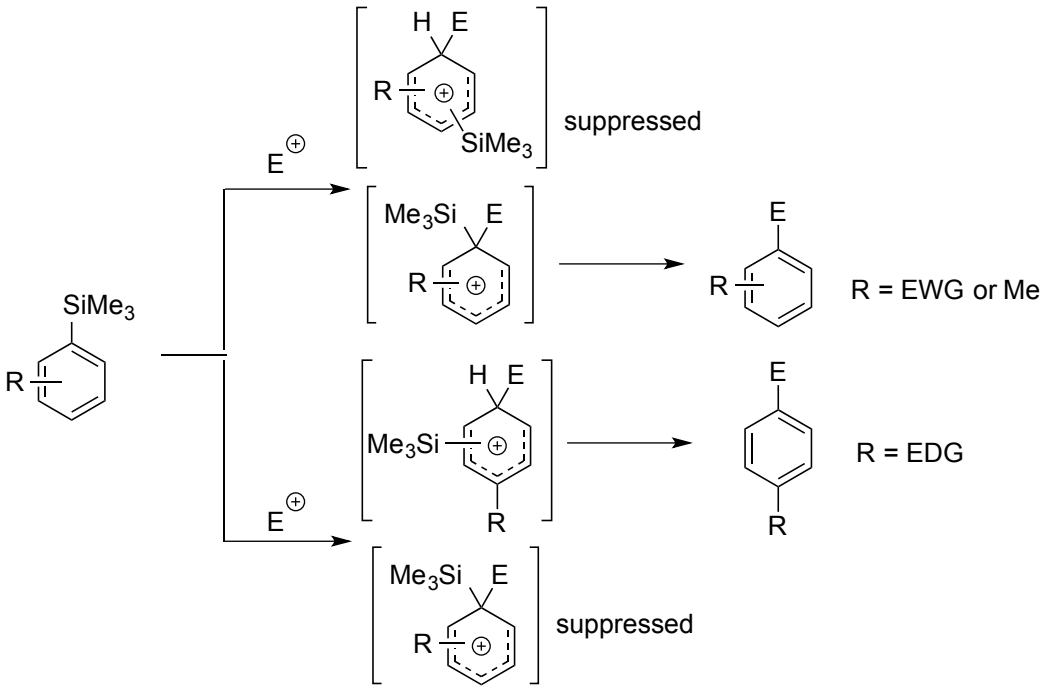


1a-1h (1 equiv.) **2** (1 equiv.) **3a-3h**

Entry	Ar-$SiMe_3$	Product	Yield (%)
1	 **1a**	 **3a**	84
2	 **1b**	 **3b**	86
3	 **1c**	 **3c**	18
4	 **1d**	 **3d**	<5
5	 **1e**	 **3e**	65
6	 **1f**	 **3f**	77
7	 **1g**	 **3g**	72
8	 **1h**	 **3h**	68

4-Fluoro and 4-bromo(trimethylphenyl)silanes gave excellent yields of 84% and 86% (entries 1-2). With strong electron-withdrawing group, 4-trifluoromethyl afforded the desired product at much lower yield of 18% (entry 3). For 4-cyano(trimethylphenyl)silanes, only less than 5% NMR yield was observed, which might be the cause of instability of CN group under the reaction conditions. Notably, TMS group controlled over the methyl group on the site selectivity, to produce *ipso*-desilyl acylation products from *para*- and *ortho*-methyl(trimethylphenyl)silanes at 65% and 77% yields respectively (entries 5-6). As expected, aryltrimethylsilanes with strong donating substituents such as *para* and *ortho*-methoxy groups underwent Friedel-Crafts acylation only at the positions governed by methoxy rather than TMS group (72% and 68% yield, entries 7-8).

Scheme 3.1 Electrophilic desilyl substitutions of aryltrimethylsilanes



The mechanism of this reaction was straightforward as shown (Scheme 3.1). Aryltrimethylsilanes with substituents less and as electron-donating ability than

methyl group, *ipso*-desilylative acylation occurred. The cation intermediate was stablized by *β*-effect of TMS group. The competing dehydro-acylation pathway was supressed. However, aryltrimethylsilanes with substituents more or as electron-donating ability than methoxy group, FC-acylation was controlled by the more powerful substituent, with TMS group dropped at the reaction conditions.

3.3 CONCLUSION

In summary, we have demonstrated a protocol for site-selective *ipso*-desilylative acylation of aryltrimethylsilanes, especially for electron deficient aryltriemthylsilanes. With electron-withdrawing or methyl substituents, acylation occurred at *ipso* position. With more electron-donating substituents, FC acylation proceeded at the site controlled by the substituent, with desilylation happened at the given reaction conditions.

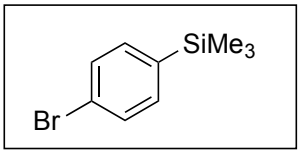
3.4 EXPERIMENTAL

All the Lewis acids used were commercially available. Solvents were dried through distillation and molecular seives or purchased from Sigma Aldrich. Aryltrimethylsilanes that appeared in chapter 2 were used directly. Additional aryltrimethylsilanes were synthesized according to the procedure below, unless otherwise stated.

General procedure for the synthesis of aryltrimethylsilanes

To an oven drid 100 mL round bottom flask, 50 mL anhydrous THF and corresponding arylhalide (5 mmol, 1 equiv.) were added and cooled to – 78 ^{o}C with stirring and nitrogen protected. Then, *n*BuLi (5.5 mmol, 1.1 equiv.) was added to the mixture slowly. After 30 min, trimethylchlorosilane (6 mmol, 1.2 equiv.) was added dropwise. While the reaction mixture warmed to room temperature over 1 h, saturated NH_4Cl was added, followed by extraction with ethyl acetate three times. The combined organic layers were washed with saturated brine and dried over Na_2SO_4, and concentrated under vacuo. The residue was purified by silica gel column chromatography using diethyl ether/hexane (5:95) as eluant to afford the desired aryltrimethylsilane.

Characterization data for aryltrimethylsilanes

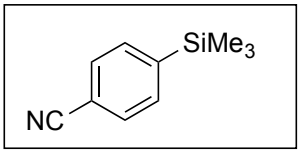


(4-Bromophenyl)trimethylsilane (1b):[4] The title compound was synthesized from 1,4-dibromobenzene according to the literature cited (colorless oil, 32% yield);

[4] Tobisu, M.; Onoe, M.; Kita, Y.; Chatani, N. *J. Am. Chem. Soc*. **2009**, *131*, 7506.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.12 Hz, 1H), 7.44 (d, *J* = 7.56 Hz, 1H), 7.27 (t, *J* = 7.28 Hz, 1H), 7.19 (t, *J* = 8.00 Hz, 1H), 0.38 (s, 9H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.1, 136.1, 132.7, 130.7, 130.6, 126.4, -0.6 ppm.



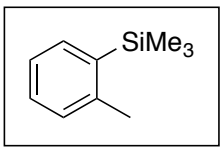
4-(Trimethylsilyl)benzonitrile (1d):[5] The title compound was synthesized from 4-iodobenzonitrile according to method A (colorless oil, 68% yield);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (s, 4H), 0.29 (s, 9H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 133.8, 130.9, 119.0, 112.3, -1.5 ppm;

HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{10}H_{14}NSi$: 176.0896 , found: 176.0892;

FTIR (NaCl, neat): ν 2959, 2228, 1380, 1251, 1100, 835, 726 cm^{-1}.

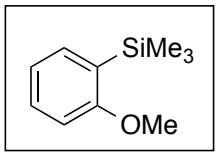


Trimethyl(*o*-tolyl)silane (1f):[6] The title compound was synthesized from 1-bromo-2-methylbenzene according to method A (colorless oil, 89% yield);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.00 Hz, 1H), 7.24-7.22 (m, 1H), 7.16-7.12 (m, 2H), 2.44 (s, 3H), 0.30 (s, 9H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 138.4, 134.3, 129.7, 129.2, 124.9, 23.0, -0.1 ppm.

[5] Van Walree, C. A.; Lauteslager, X. Y.; van Wageningen, A. M. A.; Zwikker, J. W.; Jenneskens, L. W. *J. Organomel. Chem*. **1995**, *496*, 117.
[6] Ball, L. T.; Green, M.; Lloyd-Jones, G. C.; Russell, C. A. *Org Lett*. **2010**, *12*, 4724.



(2-Methoxyphenyl)trimethylsilane (1h):[7] The title compound was synthesized from 1-bromo-2-methoxybenzene according to method A (colorless oil, 73% yield);

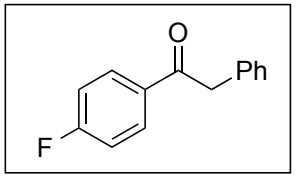
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.31 (m, 2H), 6.96-6.92 (m, 1H), 6.83 (d, *J* = 8.20 Hz, 1H), 3.80 (s, 3H), 0.26 (s, 9H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 135.0, 130.7, 127.9, 120.4, 109.5, 55.0, -0.93 ppm.

General procedure for the *ipso*-desilylative acylation of aryltrimethylsilanes with acid chlorides

To an oven drid 4 mL sample vial, $AlCl_3$ (72 mg, 1.5 equiv.), aryl(trimethyl)silane (0.3 mmol, 1 equiv.), acid chloride (0.3 mmol, 1 equiv.), DCM (0.3 mL, 15 equiv.) were added and the mixture were stirred at 40 ^{o}C for 12 h. After reaction was complete, 15 mL of saturated $NaHCO_3$ was added followed by extraction with ethyl acetate three times. The combined organic layers were washed with saturated brine and dried over Na_2SO_4, and concentrated under vacuo. The residue was purified by silica gel column chromatography using ethyl acetate/hexane (10:90) as eluant to afford the desired product.

Characterization data for *ipso*-desilylative acylation products

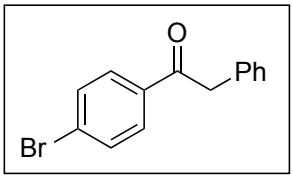


[7] McNeill, E.; Barder, T. E.; Buchwald, S. L. *Org. Lett*. **2007**, *9*, 3785.

1-(4-Fluorophenyl)-2-phenylethan-1-one (3a):[8] white solid, 84% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04-8.00 (m, 2H), 7.34-7.30 (m, 2H), 7.26-7.23 (m, 3H), 7.13-7.08 (m, 3H), 4.25 (s, 2H) ppm;

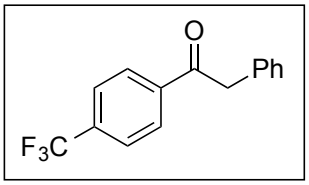
^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0, 165.7 (d, J = 253.46 Hz), 134.3, 133.0 (d, J = 2.83 Hz), 131.3 (d, J = 9.3 Hz), 129.4, 128.7, 127.0, 115.7 (d, J = 21.85 Hz), 45.5 ppm.



1-(4-Bromophenyl)-2-phenylethan-1-one (3b):[8] white solid, % yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87-7.83 (m, 2H), 7.59-7.55 (m, 2H), 7.33-7.30 (m, 2H), 7.26-7.23 (m, 3H), 4.23 (s, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 135.2, 134.1, 131.9, 130.1, 129.4, 128.7, 128.3, 127.0, 45.5 ppm.

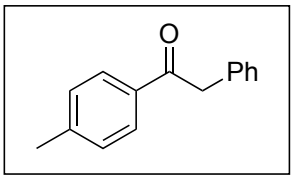


2-Phenyl-1-(4-(trifluoromethyl)phenyl)ethan-1-one (3c):[9] white solid, 18% yield;

^{1}H NMR (400 MHz, $CDCl_3$): 8.12(d, J = 8.44 Hz, 2H), 7.72 (d, J = 8.56 Hz, 2H), 7.36-7.26 (m, 5H), 4.32 (s, 2H) δ ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 139.2, 134.4 (q, J = 32.6 Hz), 133.8, 129.2, 129.0, 128.8, 127.2, 125.8 (q, J = 3.84 Hz), 123.6 (q, J = 273.6 Hz), 45.9 ppm.

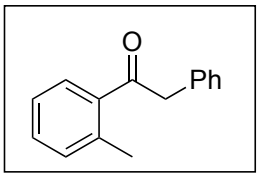
[8] Kim, S. -H.; Rieke, R. D. *J. Org. Chem*. **1998**, *63*, 6766.
[9] Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc*. **2006**, *128*, 14800.



2-phenyl-1-(*p*-tolyl)ethan-1-one (3e):[10] white solid, 65% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.20 Hz, 2H), 7.31 (t, *J* = 7.32 Hz, 2H), 7.26-7.23 (m, 5H), 4.25 (s, 2H), 2.39 (s, 3H) ppm;

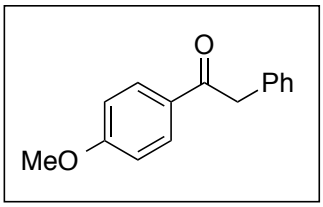
^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 144.0, 134.8, 134.1, 129.4, 129.3, 128.8, 128.6, 126.8, 45.4, 21.6 ppm.



2-phenyl-1-(*o*-tolyl)ethan-1-one (3f):[11] yellow solid, 77% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 7.60 Hz, 2H), 7.37-7.29 (m, 3H), 7.25-7.21 (m, 5H), 4.20 (s, 2H), 2.43 (s, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.4, 138.5, 137.6, 134.5, 132.0, 131.3, 129.5, 128.6, 126.9, 125.6, 48.4, 21.3 ppm.



1-(4-Methoxyphenyl)-2-phenylethan-1-one(3g and **3h):**[10] white solid, 68-72% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8.84 Hz, 2H), 7.32-7.23 (m, 5H), 6.91 (d,

[10] Zhao, B. -W.; Lu, X. -Y. *Org. Lett*. **2006**, *8*, 5987.
[11] Anstead, G. M.; Peterson, C. S.; Pinney, K. G.; Wilson, S. R.; Katzenellenbogen, J. A. *J. Med. Chem*. **1990**, *33*, 2726.

J = 8.84 Hz, 2H), 4.22 (s, 2H), 3.83 (s, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 163.5, 134.8, 130.9, 129.4, 129.6, 128.7, 126.7, 113.5, 55.5, 45.2 ppm.

PART II

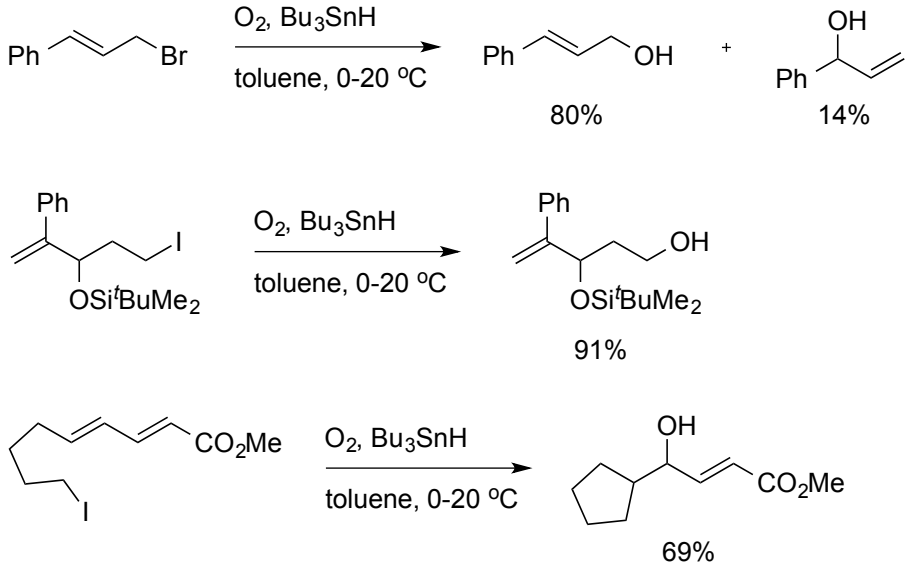
CHAPTER 4

Displacement of halogen atoms from simple alkyl halides in aqueous media

4.1 INTRODUCTION

Conversion of halogen atom into hydroxy group is a less appreciated transformation in organic synthesis. Generally, hydrolysis of activated halides, such as benzyl and allyl halides can be performed by water or hydroxide ions.[1] However, it is more challenging to displace halogen atoms from simple alkylhalides, and there are fewer methods and reviews to provide relative mild contidions.[2] Available methodologies include a two-step procedure: nucleophilic substitution to form acetate or formate, followed by hydrolysis of the ester group.[3] Alternative approach is more direct and efficient via a free-radical pathway.

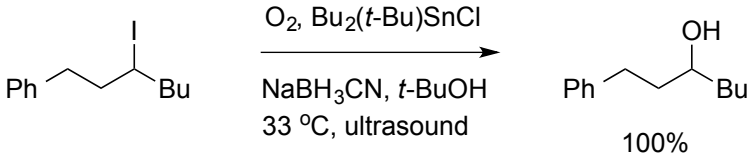
Nakamura reported the first free-radical transformation from C-X bond to C-O bond (Scheme 4.1).[4] The substrate scope was limited to iodides and activated bromides.



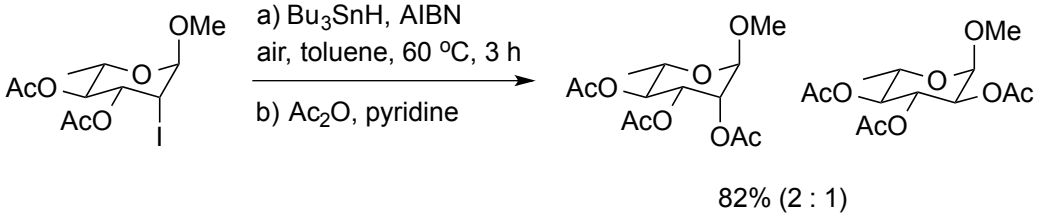
Scheme 4.1 Sn-initiated radical oxygenation of organic halides

[1] Larock, R. C. *Comprehensive Organic Transformation*; VCH Publishers Inc.: New York, **1989**, 481.
[2] a) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, **1992**; p370. b) Mitsunobo, O. In *Synthesis of Alcohols and Ethers*, In *Comprehensive Organic Synthesis*, Vol. 6; Trost, B. M.; Fleming, I.; Eds.; Pergamon Press: Oxford, **1993**, 2.
[3] a) Alexander, J.; Renyer, M. L.; Veerapanane, H. *Synth. Commun*. **1995**, *25*, 3875; b) Ruddick, C. L.; Hodge, P.; Houghton, M. P. *Synthesis* **1996**, 1359; c) Abad, A.; Agullo, C.; Cunat, A. C.; Navarro, I. *Synthesis* **2005**, 3355.
[4] Nakamura, E.; Inubushi, T.; Aoki, S.; Machii, D. *J. Am. Chem. Soc*. **1991**, *113*, 8980.

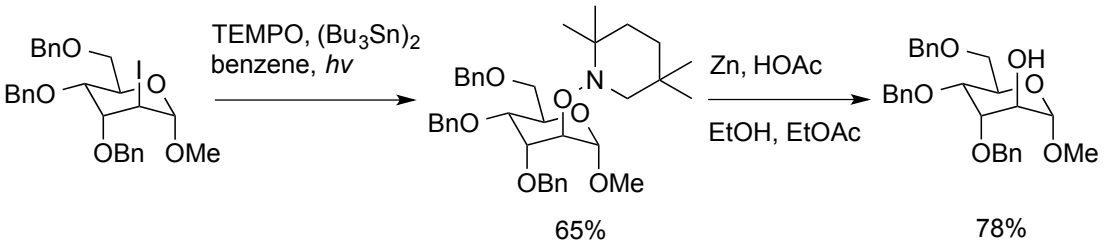
Later, catalytic version of Bu_2(*t*-Bu)SnCl with stoichiometric $NaBH_3CN$ under ultrasonic irradiation was reported by the same group (Scheme 4.2).[5] More hindered substrates, such as 2-deoxy-2-iodo hexopyranosides that was incompatible with the conventional nucleophilic substituion, was reported by Prandi[6] using Bu_2(*t*-Bu)SnCl (Scheme 4.3) and Rys[7] using TEMPO and Zn (Scheme 4.4), respectively.



Scheme 4.2 Sn-catalyzed oxygenation of organic halides



Scheme 4.3 Oxygenation of 2-deoxy-2-iodo hexopyranosides

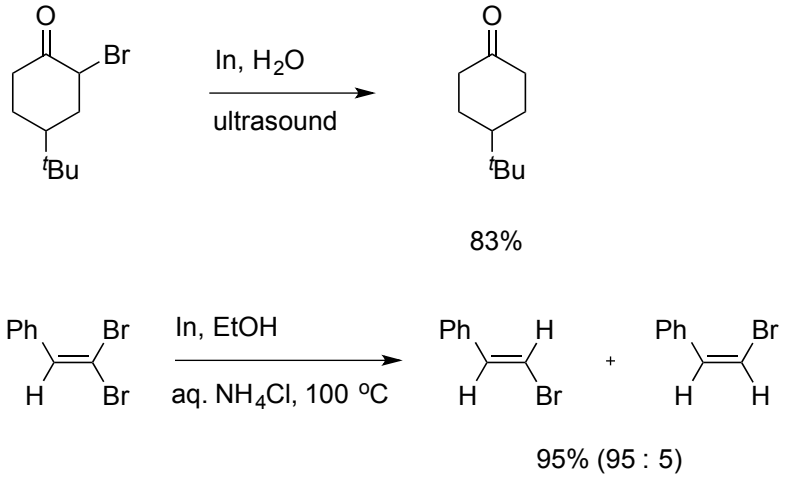


Scheme 4.4 Oxygenation of 2-deoxy-2-iodo hexopyranosides with TEMPO and Zn

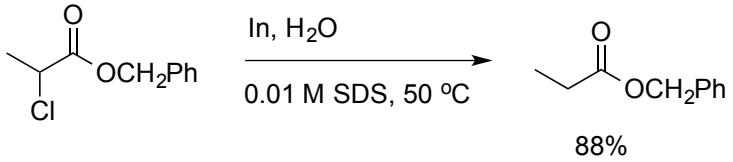
[5] a) Sawamura, M.; Kawaguchi, Y.; Sato, K.; Nakamura, E. *Chem. Lett*. **1997**, 705; b) Sawamura, M.; Kawaguchi, Y.; Nakamura, E. *Synlett*. **1997**, 801.
[6] Moutel, S.; Prandi, J. *Tetrahedron Lett*. **1994**, *35*, 8163.
[7] Barrett, A. G. M.; Rys, D. J. *J. Chem. Soc., Chem. Commun*. **1994**, 837.

Indium chemistry has found vast applications in organic synthesis[8]. Indium-mediated transformations in aqueous media have also attracted particular attention recently. Ranu reported the first systematic study about indium-assisted dehalogenations (Scheme 4.5).[9]

Various α-bromo and α-iodocarbonyl compounds were reduced in water under ultrasound. However, simple alkyl and aryl halides were untouched with this condition. Later, Ranu expanded this method to aryl-substituted gem-dibromides to give (*E*)-vinyl bromides selectively. Heteroarene such as thiophene- and furan-substituted *gem*-dibromides were not tolerated.



Scheme 4.5 Indium-mediated reductions of α-halocarbonyl compounds and aryl-substituted *gem*-dibromides

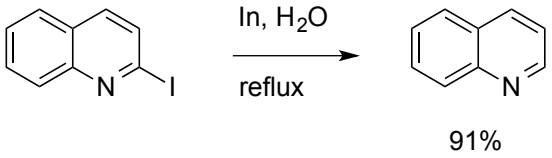


Scheme 4.6 Indium-mediated reductions of α-chlorocarbonyl compounds

[8] Shen, Z.-L.; Wang, S.-Y.; Chok, Y.-K.; Xu, Y.-H.; Loh, T.-P. *Chem. Rov*. **2013**, *113*, 271.
[9] a) Ranus, B. C.; Dutta, P.; Sarkar, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1139; b) Ranus, B.; Samanta, S.; Guchhait, S. K. *J. Org. Chem*. **2001**, *66*, 4120.

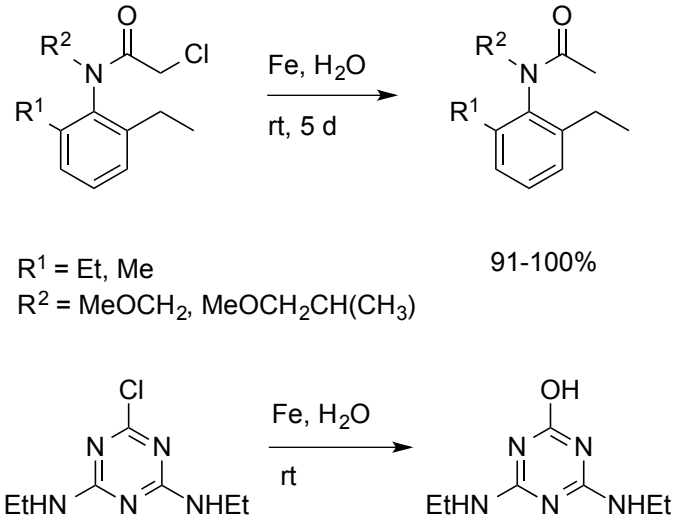
Kim also studied the dehalogenations of α-carbonyl compounds, especially α-chlorocarbonyls using micellar solutions to enhance the reactivity (Scheme 4.6).[10]

Notably, dehalogenation of C(sp^2)-X bond could also be achieved by indium metal in water. However, only heteroaryl halides demonstrated satisfactory reactivity compared with normal aromatic halides (Scheme 4.7).[11]



Scheme 4.7 Indium-mediated reductions of iodoheteroaromatics

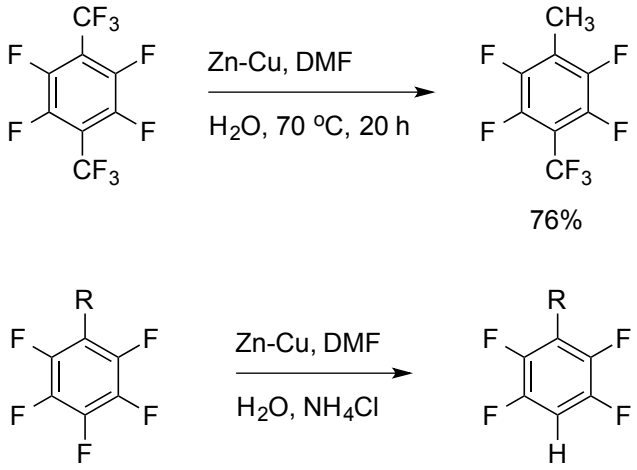
Besides indium, granular iron metal was also found effective in the reductive dechlorination of herbicides in water, such as alachlor, metolachlor and atrazine (Scheme 4.8).[12]



Scheme 4.8 Iron-mediated reductions of herbicides

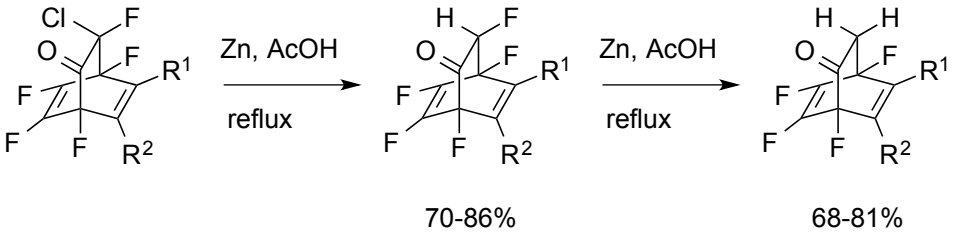
[10] Park, L.; Keum, G.; Kang, S. B.; Kim, K. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4462.
[11] Hirasawa, N.; Takahashi, Y.; Fukuda, E.; Sugimoto, O.; Tanji, K. *Tetrahedron Lett*. **2008**, *49*, 1492.
[12] a) Eykholt, G. R.; Davenport, D. T. *Environ. Sci. Technol*. **1998**, *32*, 1482; b) Monson, S. J.; Ma, L.; Cassada, D. A.; Spalding, R. F. *Anal. Chim. Acta* **1998**, *373*, 153.

Apart from indium and iron, zerovalent zinc also exhibited strong reducing ability.[13] Zinc-mediated dehalogenation of carbon tetrachloride was also studied by several groups.[14] In addition, selective defluorination of perfluoroarenes could also be performed by Zn-Cu-DMF-H2O protocol under mild conditions (Scheme 4.9).[15]



Scheme 4.9 Zinc-mediated selective defluorination of perfluorenes

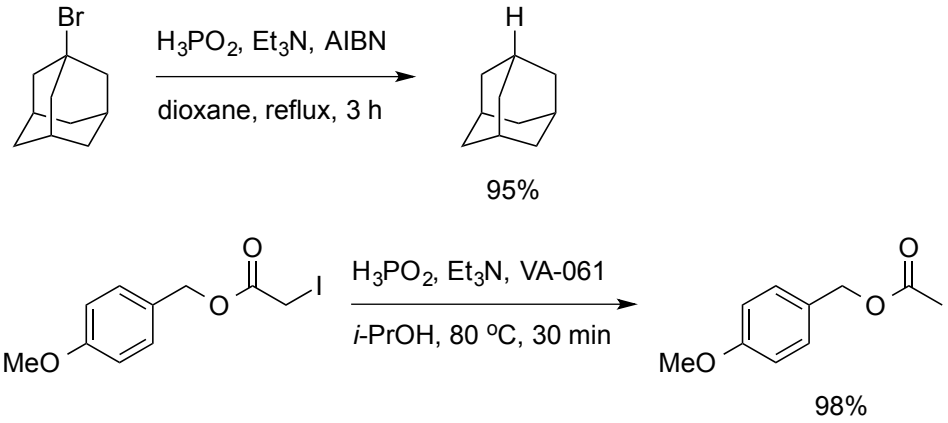
Zinc was also applied for dehalogenations in organic synthesis reported by Kobrina (Scheme 4.10). [16] Selective dechlorination of 8-chloro-1,2,3,4,8-pentafluorobicyclo[2.2.2]octa-2,5-dienones with zinc in acetic acid, followed by successive defluorination at the 8-position was demonstrated as example.



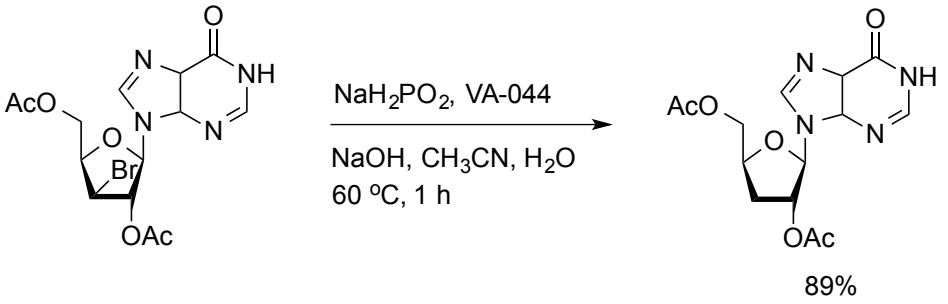
Scheme 4.10 Zinc-mediated selective and successive dehalogenations

[13] Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev*. **2002**, *102*, 4009.
[14] a) Warren, K. D.; Arnold, R. G.; Bishop, T. L.; Lindholm, L. C.; Betterton, E. A. *J. Hazard. Mater*. **1995**, *41*, 217; b) Boronina, T.; Klabunde, K. J.; Sergeev, G. B. *Environ. Sci. Technol*. **1995**, *29*, 1511; c) Boronina, T.; Lagadic, I.; Sergeev, G. B.; Klabunde, K. J. *Environ. Sci. Technol*. **1998**, *32*, 2614.
[15] a) Krasnov, V. I.; Platonov, V. E.; Beregovaya, I. V.; Shchegoleva, L. N. *Tetrahedron* **1997**, *53*, 1797; b) Krasnov, V. I.; Platonov, V. E. *Russ. J. Org. Chem*. **2001**, *37*, 517.
[16] Bogachev, A. A.; Kobrina, L. S. *J. Fluorine Chem*. **1998**, *92*, 33.

Metal-free conditions with the presence of hypophosphorous acid or its salts were developed and reported first by Barton for effective radical dehalogenations and deoxygenation (Scheme 4.11).[17] Izawa continued to study hypophosphorous sodium salts to afford the debromination of nucleosides in aqueous media (Scheme 4.12).[18]



Scheme 4.11 H_3PO_2-mediated dehalogentaions under metal free conditions

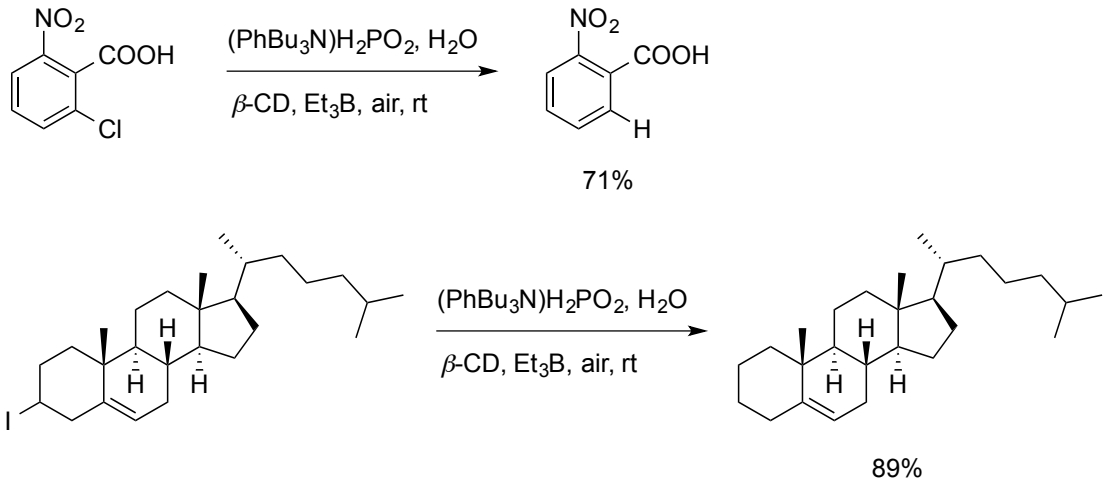


Scheme 4.12 NaH_2PO_2-mediated debrominations in aqueous media

Recently, tetrasubstituted ammonium hypophosphite was discovered as both an efficient reducing agent and a surfactant with β-cclodextrin adopted as the

[17] a) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett*. **1992**, *33*, 5709; b) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *J. Org. Chem*. **1993**, *53*, 6838; c) Nambu, H.; Alinejad, A. H.; Hata, K.; Fujioka, H.; Kita, Y. *Tetrahedron Lett*. **2004**, *45*, 8927.
[18] Takamastu, S.; Katayama, S.; Hirose, N.; Naito, M.; Izawa, K. *Tetrahedron Lett*. **2001**, *42*, 7605.

molecular reactor (Scheme 4.13).[19] Ary and alkyl halides were tolerated under this condition.



Scheme 4.13 Radical dehalogenation in aqueous *β*-CD molecular reactor

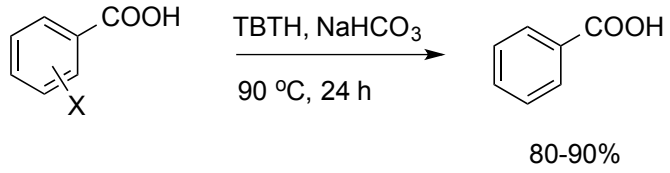
Metal hydrides were another category of radical reducing agents that were frequently used in dehalogenations, such as tri-butyltin hydride (TBTH)[20] developed by Maitra (Scheme 4.14), diarylsilanes [21] by Yokoyama (Scheme 4.15) and $(Me_3Si)_3SiH$[22] by Chatgilialoglu (Scheme 4.16).

TBTH was ultilized together with some necessary detergents such as sodium dedecyl sulfate (SDS), triton-X-100 or cetyltrimethylammonium bromide, which helped to solubilize TBTH and those substrates with low solubitily in water. Halogenative carboxylic acids could be dehalogenated by TBTH only with the presence of $NaHCO_3$ as the base.

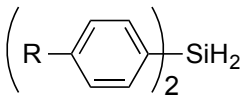
Diarylsilanes, made soluble in water by hydrophilic side chains containing ether or hydroxyl group, could dehalogenate alkyl and aryl halides in aqueous media with the presence of triethylborane and air.

[19] Johnson, A. E.; Perchyonok, V. T. *Curr. Org. Chem*. **2009**, *13*, 914.
[20] a) Maitra, U.; Sarma, K. D. *Tetrahedron Lett*. **1994**, *35*, 7861; b) Sarma, K. D.; Maitra, U. *Tetrahedron* **1998**, *54*, 4965.
[21] Yamazaki, O.; Togo, H.; Nogami, G.; Yokoyama, M. *Bull. Chem. Soc. Jpn*. **1997**, 2519.
[22] Postigo, A.; Kopsov, S.; Ferreri, C.; Chatgilialoglu, C. *Org Lett*. **2007**, *9*, 5159

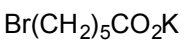
$(Me_3Si)_3SiH$ was able to dehalogenate substrates both hydrophilic and hydrophobic in aqueous media. This protocol contained substrates, silane and initiator (ACCN) at 100 ^oC, with added amphiphilic thiol for those water-soluble substrates.



Scheme 4.14 TBTH-mediated dehalogenation in aqueous medium



R = $O(CH_2)_2O(CH_2)_2OMe$, $O(CH_2)_2OH$, $OCH_2CH(OH)CH_2OH$



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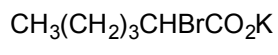

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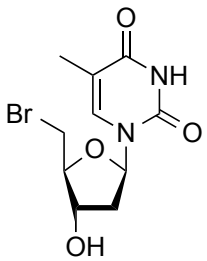

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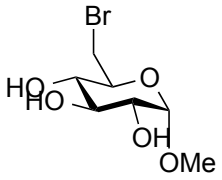
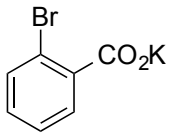


88%



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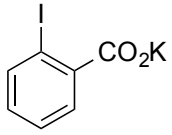
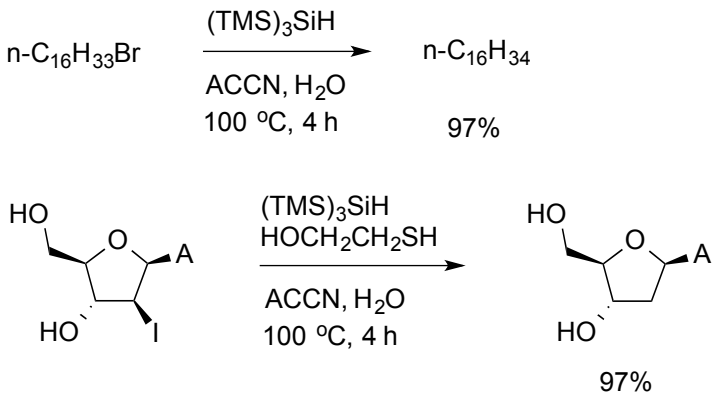


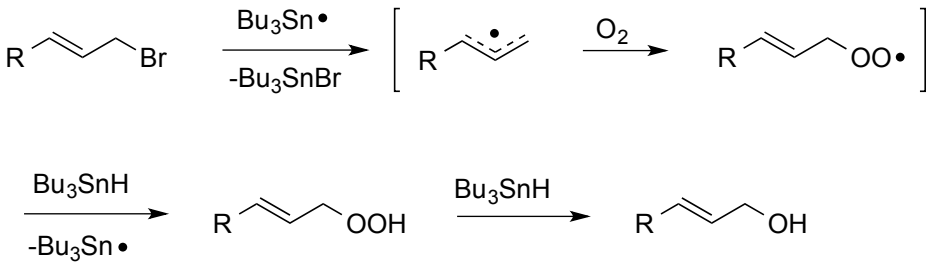
97%

Scheme 4.15 Diarylsilanes-mediated dehalogenation in water



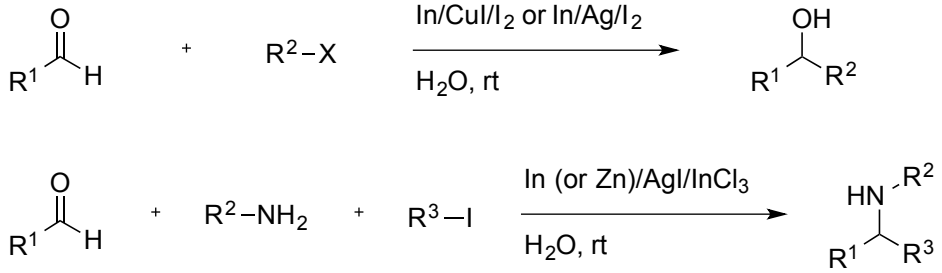
Scheme 4.16 $(TMS)_3SiH$-mediated dehalogenation in water

Considering the above methodologies for displacement of halogen atoms, we were particular interested in transforming halides to alcohols, which might provide more synthetic values than hydrodehalogenations. However, available methods using tin reagents[4-7] were limited in applications due to usage of toxic reagents, water-intolerence and limited substrate scope (only alkyl iodides and activated alkyl bromides) (Scheme 4.17). Therefore a new radical method is highly desirable, which can convert simple alkyl halides into alcohols in aqueous media.



Scheme 4.17 Reductive oxygenation of allylic bromides

Combining years of studies and devotions in studying indium chemistry in our group and previous research (our group[8, 23] and others[24]) on indium or zine mediated Barbier-type addition via single electron transfer (Scheme 4.18), we envisioned that transformations from simple alkyl halides to alcohols in aqueous media may be achieved with the presence of indium, which might provide more insights and applications in treatment of industrial halogenated wastes.



Scheme 4.18 Indium and zinc mediated Barbier-type addition

Preliminary studies and results in our group demonstrated that the system including indium, sodium hypophosphoric salt and alkyl halides in water/^{t}BuOH (1:1) at 60 ^{o}C with air bubbling was able to give corresponding alcohols at moderate to satisfactory yields. However, this condition worked better for secondary and tertiary alkyl bromides and iodides (Table 4.1).[25] Only one example of tertiary chloride was presented in the table with 34% yield. Therefore, in this chapter, we focused on displacing chloride atom from simple alkylchlorides in aqueous media.

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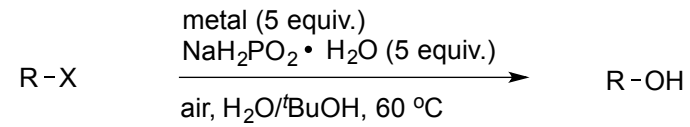
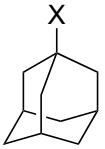
[23] a) Tan, K. T.; Chng, S. S.; Cheng, H. S.; Loh, T. P. *J. Am. Chem. Soc*. **2003**, *125*, 2958; b) Loh, T. P.; Li, X. R. *Angew. Chem., Int. Ed*. **1997**, *36*, 980; c) Shen, Z. L.; Loh, T. P. *Org. Lett*. **2007**, *9*, 5413; d) Shen, Z. L.; Cheong, H. L.; Loh, T. P. *Chem.-Eur. J*. **2008**, *14*, 1875; e) Shen, Z. L.; Yeo, Y. L.; Loh, T. P. *J. Org. Chem*. **2008**, *73*, 3922; f) Shen, Z. L.; Cheong, H. L.; Loh, T. P. *Tetrahedron Lett*. **2009**, *50*, 1051; g) Yang, Y. S.; Shen, Z. L.; Loh, T. P. *Org. Lett*. **2009**, *11*, 1209; for reviews, see h) Loh, T. P. In *Science of Synthesis*; Yamamoto, H. Ed.; Georg Thieme Verlag: Stuttgart, New York, **2004**, pp 413; i) Loh, T. P.; Chua, G. L. *Chem. Commun*. **2006**, 2739.

[24] a) Keh, C. C. K.; Wei, C. M.; Li, C. J. *J. Am. Chem. Soc*. **2003**, *125*, 4062; for reviews, see b) Herrerías, C. I.; Yao, X. Q.; Li, Z. P.; Li, C. J. *Chem. Rev*. **2007**, *107*, 2546; c) Li, C. J. *Chem. Rev*. **2005**, *105*, 3095; d) Li, C. J. *Chem. Rev*. **1993**, *93*, 2023; e) Miyabe, H.; Naito, T. *Org. Biomol. Chem*. **2004**, *2*, 1267.

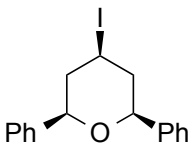
[25] Dr. Zhou Hai's thesis, **2011**, chapter 2.

Table 4.1 Preliminary results on aerobic aqueous conversion of alkyl halides to alcohols





X = I 54%
X = Br 75%
X = Cl 34%



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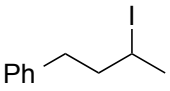

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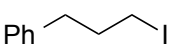

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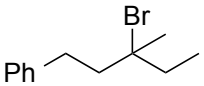
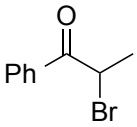


46%



47%

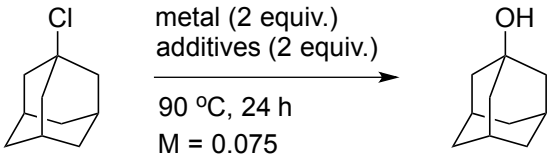
4.2 DISPLACEMENT OF HALOGEN ATOMS FROM SIMPLE ALKYLHALIDES IN AQUEOUS MEDIA

With the aim of developing a protocol that showed potential for treatment of industrial halogenated wastes, we hope to enable the transformations workable in aqueous media with at least 90% of water by volume. 1-Chloroadamantane was chosen as the model to optimize the reaction conditions (Table 4.2).

First, we tried to use H_2O_2 (30 wt.% in water), a stronger radical source than air. At 70 ^oC, screened four solvents gave similar results, with *t*BuOH and DME at slightly better yields (entries 1-4). With increasing the temperature to 90 ^oC, the yields were generally higher. Varing the volume ratio of organic solvent/water until 90% of H_2O as the aqueous media, the desired product was obtained at 69% yield (entries 5-9).

Molecular oxygen is the most favorable radical source and more desired than peroxides. Therefore, we tried to replace 30% H_2O_2 with an O_2 balloon installed on the vial cap. It was gratifying that the reaction worked best in 90% of water to give quantitative yield at 99% (entries 10-13). Control experiments were also run, and it was surprising to find that indium, additives and even oxygen balloon were not necessary for this transformation, with 67% yield obtained as the background reaction in 100% water as the aqueous media (entries 14-17).

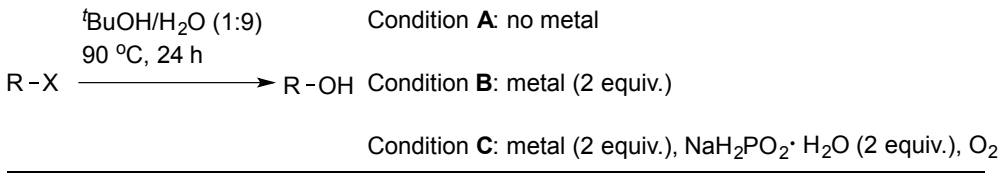
Table 4.2 Optimization of reaction conditions

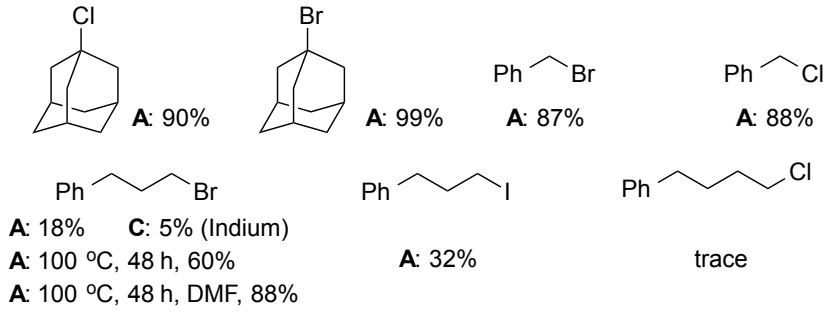


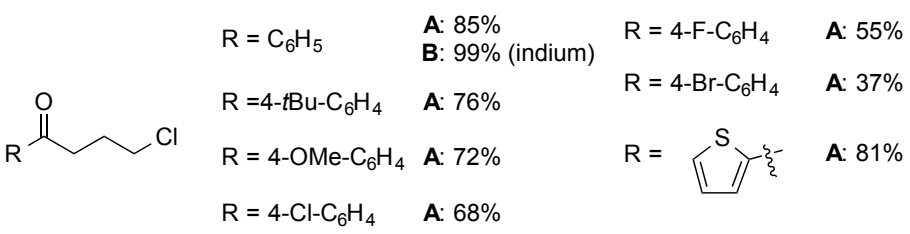
Entry	Metal	Solvent	Additives	Remarks	Yield (%)
1[a]	In	H_2O_2/*t*BuOH (5:5)	$NaH_2PO_2 \cdot H_2O$	30% H_2O_2	58
2[a]	In	H_2O_2/DME (5:5)	$NaH_2PO_2 \cdot H_2O$	30% H_2O_2	56
3[a]	In	H_2O_2/DMSO (5:5)	$NaH_2PO_2 \cdot H_2O$	30% H_2O_2	43
4[a]	In	H_2O_2/1,4-dioxane (5:5)	$NaH_2PO_2 \cdot H_2O$	30% H_2O_2	48
5	In	H_2O_2/*t*BuOH (5:5)	$NaH_2PO_2 \cdot H_2O$	30% H_2O_2	60
6	In	H_2O_2/DME (5:5)	$NaH_2PO_2 \cdot H_2O$	30% H_2O_2	82
7	In	H_2O_2/DME/H_2O (4:4:2)	$NaH_2PO_2 \cdot H_2O$	30% H_2O_2	75
8	In	H_2O_2/DME/H_2O (3:1:6)	$NaH_2PO_2 \cdot H_2O$	30% H_2O_2	64
9	In	H_2O_2/DME/H_2O (1:1:8)	$NaH_2PO_2 \cdot H_2O$	30% H_2O_2	69
10	In	*t*BuOH/H_2O (5:5)	$NaH_2PO_2 \cdot H_2O$	O_2 balloon	82
11	In	DME/H_2O (5:5)	$NaH_2PO_2 \cdot H_2O$	O_2 balloon	79
12	In	*t*BuOH/H_2O (3:7)	$NaH_2PO_2 \cdot H_2O$	O_2 balloon	63
13	In	*t*BuOH/H_2O (1:9)	$NaH_2PO_2 \cdot H_2O$	O_2 balloon	99
14	In	*t*BuOH/H_2O (1:9)	$NaH_2PO_2 \cdot H_2O$	capped	96
15	In	*t*BuOH/H_2O (1:9)	none	capped	84
16	none	*t*BuOH/H_2O (1:9)	none	capped	90
17	none	Only H_2O	none	capped	67

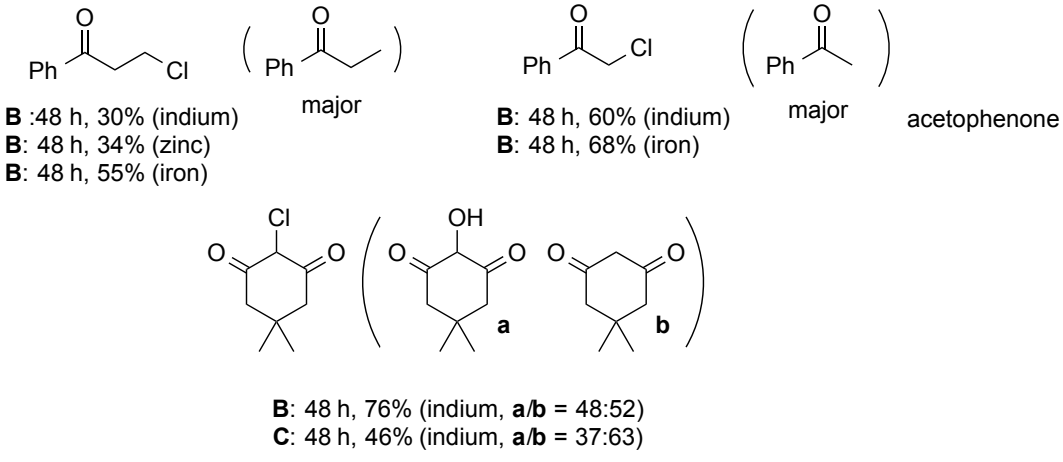
[a] Reactions were run at 70 °C.

Table 4.3: Screening of alkyl halides for oxydehalogenation





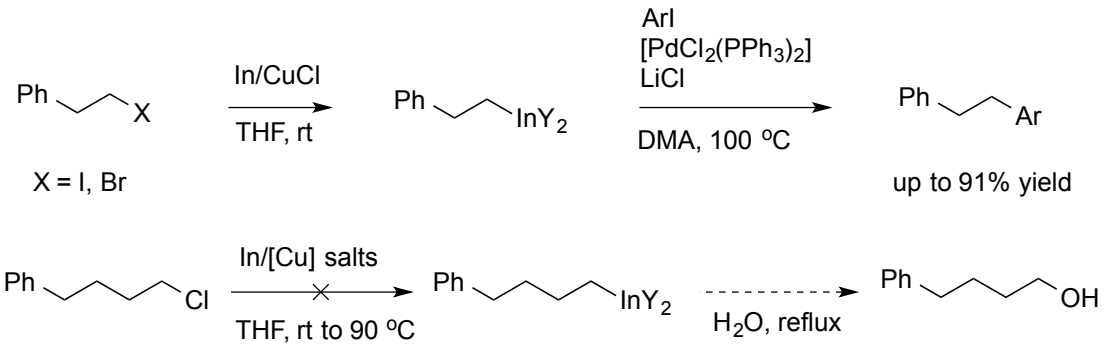




Next, we screen the above selected alkyl halides with both metal and metal-free conditions and the results were summarized (Table 4.3). Tertiary chlorides and bromides, such as 1-chloroadamantane and 1-bromoadamantane, converted to its alcohol product at nearly quantitave yield under metal free condition **A**. Similarly, reactive primary alkyl halides, such as benzyl chloride and benzy bromide could also

easily transform to benzy alcohol at 88% and 87% yield respectively under condition **A**. Unactivated primary alkyl bromide, (3-bromopropyl)benzene as an example, gave best yield of 88% under **A** at 100 ^{o}C for 48 h. However, (3-iodopropyl)benzene as a representative unactivated primary alkyl iodide, only afforded the alcohol product at 32% yield.

Scheme 4.19 Hydrolysis of primary alkyl chlorides



Unfortunately, unactivated primary alkyl chloride was still a great challenge, with only trace of the desired product observed from the crude ^{1}H NMR. Other methods[26] were also tested (Scheme 4.19), with the hope to react alkyl chlorides with indium to form alkyl indium complex intermediate before hydrolysized to correspounding alcohol. However, the formation of the desired alkyl indium complex from alkyl chlorides instead of alkyl iodides and bromides was rather difficult, despite various copper salts with elevated temperature were tried.

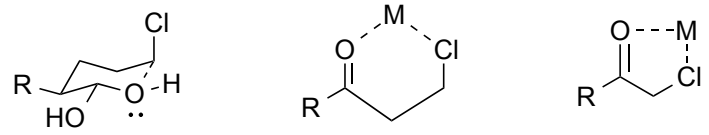
Notebly, with an added carbonyl functional group to primary alkyl chlorides, hydrolysis could occur at moderate to satisfacotry yields. A serious of 4-chloro-1-arylbutan-1-one species worked best under metal free condition **A**, giving up to 85%

[26] a) Shen, Z. -L.; Goh, K. K. K.; Cheong, H. -L.; Wong, C. H. A.; Lai, Y. -C.; Yang, Y. -S.; Loh, T. -P. *J. Am. Chem. Soc*. **2010**, *132*, 15852; b) Shen, Z. -L.; Lai, Y. -C.; Wong, C. H. A.; Goh, K. K. K.; Yang, Y. -S.; Cheong, H. -L.; Loh, T. -P. *Org. Lett*. **2011**, *13*, 422; c) Shen, Z. -L.; Goh, K. K. K.; Wong, C. H. A.; Yang, Y. -S.; Lai, Y. -C.; Cheong, H. -L.; Loh, T. -P. *Chem. Commun*. **2011**, *47*, 4778; d) Shen, Z. -L.; Goh, K. K. K.; Yang, Y. -S.; Lai, Y. -C.; Wong, C. H. A.; Cheong, H. -L.; Loh, T. -P. *Angew. Chem., Int. Ed*. **2011**, *50*, 511.

yield of its oxydehalogenation product. Electron-withdrawing substituents, such as 4-fluoro, 4-chloro and 4-bromo on the phenyl rings resulted in lower yields of 37-68%. 4-Chloro-1-(thiophen-2-yl)butan-1-one as an example containing heteroaryl group was also tested and gave satisfacotry yield of 81%.

Reducing the number of carbons between carbonyl and chloride atom, 3-chloro-1-phenylbutan-1-one afforded the hydrodehalogenation product at lower yields of 30-55% under condition **B**, where Fe was the better metal choice. 2-Chloro-1-phenylethan-1-one also converted to acetophenone preferentially with 60% (indium) and 68% yield (iron) under condition **B**. 2-Chloro-5,5-dimethylcyclohexane-1,3-dione was hydrolyzed to both oxydehalogenative and hydrodehalogenative products at 46-76% yield with varied ratios under condition **B** and **C**.

Scheme 4.20



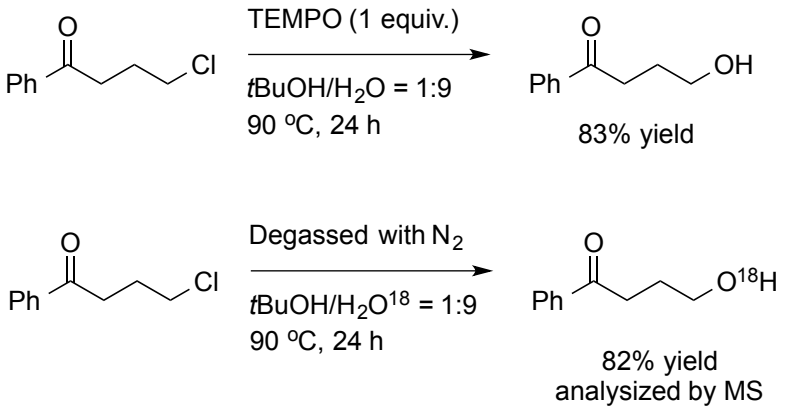
metal free condition **A** condition **B** and **C**

The carbonyl in 4-chloro-1-arylbutan-1-one might be attacked by incoming H_2O to form the acetal. The axial lone pair of electrons of the hydroxyl group could hyperconjugate with the anti-bonding orbital of C-Cl bond, which helped to lengthen and weaken the C-Cl bond so as to facilitate the displacement of chlorine atom. The added metal in 3- and 2-chloro-1-phenylbutan-1-one would chelate the carbonyl group and chlorine atom in a six or five member ring transition state (Scheme 4.20). This might also explain why metal was necessary in the later cases.

To further understand the mechanism for carbonyl-assisted hydrolysis of alkyl chlorides, two following experiments were run (Scheme 4.21). With the addition of 1

equiv. of TEMPO, the desired product was still obtained at 83% yield, which indicated that radicals were not involved in the key step. When deuterated water (H_2O^{18}) was used as the solvent, after proper degassing with nitrogen, O^{18} was incoperated in the resulted product, which was confirmed by mass spectroscopy analysis.

Scheme 4.21 Two control experiments to understand the mechanism



Other alkyl halides, such as secondary alkyl bromides and chlorides, allylic bromides and chlorides, were also screened. So far, satisfactory yields of these transformations were not obtained yet.

4.3 CONCLUSION AND FUTURE WORK

In summary, we have developed a protocol for metal-free and metal-mediated displacement of halogen atom from alkyl halides in aqueous media with above 90% of water by volume. Tertiary halides, benzyl halides, and carbonyl containing alkyl chlorides could be converted to their corresponding alcohols at satisfactory to good yields. Primary alkyl bromide and iodide could also afford moderate to satisfactory yield.

Conversion of unactivated primary alkyl chlorides was still a great challenge, together with unactivated secondary alkyl bromides and chlorides. Development of effective conditions was in progress in our group.

Further expanding the scope of alkyl halides to tetrahalides, such as carbon tetrabromides and carbon tetrachlorides was also extensively studied in our group, with the evolement of CO_2 as the product.

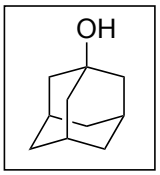
With continuing research on displacement of halogen atoms in aqueous media, we hope to apply this strategy to treatment of industrial halogenated wastes in the future.

4.4 EXPERIMENTAL

General procedure for hydrolysis of alkyl halides

To an oven drid 8 mL sample vial, alkyl halide (0.3 mmol, 1 equiv.), with/without metal (0.6 mmol, 2 equiv.), ^{t}BuOH (0.4 mL), and H_2O (3.6 mL) were added and stirred at 90 ^{o}C for 24 h. After the reaction was complete, extract the mixture with ethyl acetate three times. The combined organic layers were washed with saturated brine and dried over Na_2SO_4, and concentrated under vacuo. The residue was purified by silica gel column chromatography using ethyl acetate/hexane (20:80) as eluant to afford the desired product.

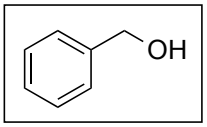
Characterization data for products



1-Adamantanol: [CAS. 768-95-6]; 99% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13 (s, 3H), 1.71-1.70 (m, 6H), 1.65-1.56 (m, 6H), 1.42 (br, 1H) ppm;

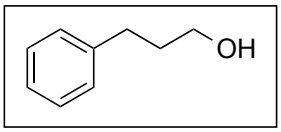
^{13}C NMR (100 MHz, $CDCl_3$): δ 68.2, 45.4, 36.1, 30.7 ppm;



Phenylmethanol: [CAS. 100-51-6]; 87% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.23 (m, 5H), 4.62 (s, 2H), 2.26 (br, 1H) ppm;

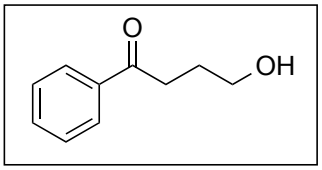
^{13}C NMR (100 MHz, $CDCl_3$): δ 140.8, 128.5, 127.6, 127.0, 65.2 ppm;



3-phenylpropan-1-ol: [CAS. 122-97-4]; pale yellow oil, % yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.24 (m, 2H), 7.20-7.17 (m, 3H), 3.66 (t, *J* = 6.44 Hz, 2H), 2.70 (t, *J* = 7.72 Hz, 2H), 1.93-1.85 (m, 2H), 1.52 (br, 1H) ppm;

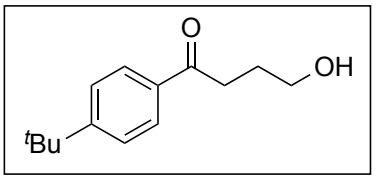
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 128.42, 128.39, 125.9, 62.3, 34.2, 32.1 ppm;



4-hydroxy-1-phenylbutan-1-one:[27] colorless oil, 71-85% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 4.00, 2H), 7.53 (t, *J* = 4.00 Hz, 1H), 7.45-7.42 (t, *J* = 6.00 Hz, 2H), 3.72 (t, *J* = 6.00 Hz, 2H), 3.11 (t, *J* = 6.00 Hz, 2H), 2.40 (br, 1H), 2.03-1.96 (m, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.6, 136.8, 133.1, 128.5, 128.0, 62.1, 35.2, 26.9 ppm;

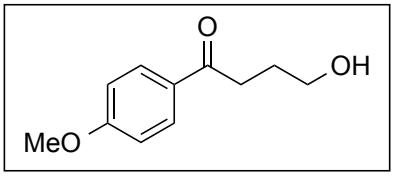


1-(4-(*tert*-butyl)phenyl)-4-hydroxybutan-1-one:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.00 Hz, 2H), 7.47 (d, *J* = 8.00 Hz, 2H), 3.74 (t, *J* = 6.00 Hz, 2H), 3.11 (t, *J* = 6.00 Hz, 2H), 2.14 (br, 1H), 2.04-1.98 (m, 2H), 1.34 (s, 9H) ppm;

[27] Fuji, K.; Usami, Y.; Kiryu, Y.; Node, M. *Synthesis* **1992**, *9*, 852.

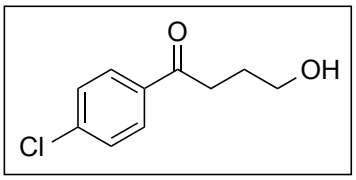
^{13}C NMR (100 MHz, $CDCl_3$): δ 200.4, 156.9, 134.3, 128.1, 125.7, 62.4, 35.2, 35.1, 31.1, 27.0 ppm;



4-hydroxy-1-(4-methoxyphenyl)butan-1-one:[27] 72% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.00 Hz, 2H), 6.92 (d, *J* = 8.00 Hz, 2H), 3.85 (s, 3H), 3.72 (t, *J* = 6.00 Hz, 2H), 3.07 (t, *J* = 6.00 Hz, 2H), 2.28 (br, 1H), 2.02-1.95 (m, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 199.3, 163.5, 130.4, 129.9, 113.7, 62.3, 55.4, 35.0, 27.1 ppm;

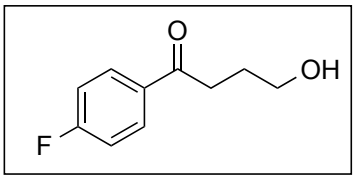


1-(4-chlorophenyl)-4-hydroxybutan-1-one:[28] 68% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 4.00 Hz, 2H), 7.44 (d, *J* = 4.00 Hz, 2H), 3.74 (t, *J* = 8.00 Hz, 2H), 3.10 (t, *J* = 8.00 Hz, 2H), 2.04-1.98 (m, 2H), 1.93 (br, 1H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 199.3, 139.6, 135.2, 129.5, 128.9, 62.1, 35.2, 26.8 ppm;

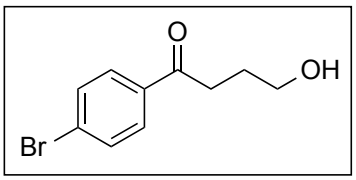
[28] Fujioka, H.; Komatsu, H.; Miyoshi, A.; Murai, K.; Kita, Y. *Tetrahedron Lett*. **2011**, *52*, 973.



1-(4-fluorophenyl)-4-hydroxybutan-1-one: 55% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02-7.99 (m, 2H), 7.13 (t, *J* = 8.00 Hz, 2H), 3.74 (t, *J* = 6.00 Hz, 2H), 3.11 (t, *J* = 6.00 Hz, 2H), 2.05-1.98 (m, 2H), 1.87 (br, 1H) ppm;

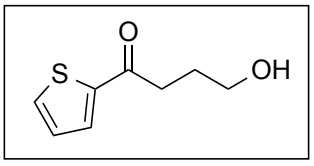
^{13}C NMR (100 MHz, $CDCl_3$): δ 199.0, 165.8 (d, *J* = 252.99 Hz), 133.3, 130.7 (d, *J* = 9.28 Hz), 115.7 (d, *J* = 21.70 Hz), 62.2, 35.2, 26.9 ppm;



1-(4-bromophenyl)-4-hydroxybutan-1-one: 37% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.00, 2H), 7.60 (t, *J* = 8.00 Hz, 2H), 3.74 (t, *J* = 6.00 Hz, 2H), 3.09 (t, *J* = 6.00 Hz, 2H), 2.04-1.98 (m, 2H), 1.93 (br, 1H) ppm;

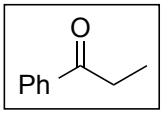
^{13}C NMR (100 MHz, $CDCl_3$): δ 199.4, 135.6, 131.9, 129.6, 128.3, 62.2, 35.2, 26.8 ppm;



4-hydroxy-1-(thiophen-2-yl)butan-1-one: 81% yield;

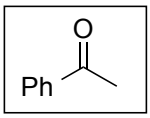
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 4.00, 1H), 7.62 (d, *J* = 4.00 Hz, 1H), 7.12 (t, J = 4.00 Hz, 1H), 3.72 (t, *J* = 6.00 Hz, 2H), 3.06 (t, *J* = 6.00 Hz, 2H), 2.19 (br, 1H), 2.03-1.97 (m, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5, 144.1, 133.7, 132.1, 128.1, 62.1, 36.0, 27.2 ppm;



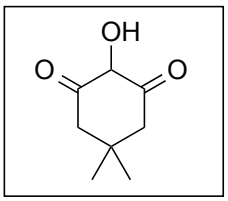
Propiophenone: [CAS. 93-55-0]; 30-55% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98-7.96 (m, 2H), 7.58-7.53 (m, 1H), 7.48-7.43 (m, 2H), 3.01 (q, J = 7.24 Hz, 2H), 1.23 (t, J = 7.26 Hz, 3H) ppm.



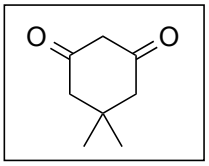
Acetophenone: [CAS. 98-86-2]; 60-68% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ



2-Hydroxy-5,5-dimethylcyclohexane-1,3-dione: 33% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.49 (s, 1H), 2.26 (s, 4H), 1.09 (s, 6H) ppm.



5,5-Dimethylcyclohexane-1,3-dione: [CAS. 126-81-8]; 43% yield;

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.34 (s, 2H), 2.53 (s, 4H), 1.04 (s, 6H) ppm.

List of Publications

1. Xu, F. -X.; Loh, T. -P. *ipso*-Desilylative functionalizations of aryl(trimethyl)silanes *manuscript in preparation*
2. Xu, F. -X.; Yin, B.; Zhou, H.; Loh, T. -P. Displacement of halogen atoms in aquous media *manuscript in preparation*