Part I: Functionalizations of silicon-based compounds. Part II: Displacement of halogen atom in aqueous media

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**NANYANG
TECHNOLOGICAL
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**PART I: FUNCTIONALIZATIONS OF SILICON-
BASED COMPOUNDS**

**PART II: DISPLACEMENT OF HALOGEN ATOM
IN AQUEOUS MEDIA**

XU FENGXIA

**SCHOOL OF PHYSICAL AND MATHEMATICAL
SCIENCES**

2014

**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 aqueous media.

I Overview of functionalizations of silicon-based compounds

Chapter 1 reviewed the recent development of functionalization 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

Chapter 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 stabilization 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. Conversions of alkyl chlorides were focused and studied.

INDEX OF ABBREVIATIONS

δ	chemical shift
Δ	reflux
$^{\circ}\text{C}$	degree centigrade
Abq	AB quartet
Ac	acetyl
acac	acetoacetate
Ar	Aryl
AcCl	acetyl chloride
AcOH	acetic acid
Ac ₂ O	acetic anhydride
Al ₂ O ₃	Aluminium oxide
aq.	aqueous
Bn	benzyl
bs	broad singlet
BuLi	butyl lithium
C	Carbon
Calcd	calculated

Cat. catalytic

CDCl_3 deuterated chloroform

CDC cross-dehydrogenative coupling

CF_3 trifluoromethyl

Cp cyclopentadienyl

CH_4 Methane

CH_2Cl_2 Dichloromethane

CHCl_3 Chloroform

CCl_4 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

Et₃N 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>i</i> -Pr	isopropyl
<i>J</i>	coupling constants
kg	kilogram
LDA	lithium diisopropylamide
M	concentration (mol/dm ⁻³)
M ⁺	parent ion peak (mass spectrum)

m	multiplet
<i>m</i> -CPBA	<i>meta</i> -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	<i>N</i> -chlorosuccinimide
NBS	<i>N</i> -bromosuccinimide
NIS	<i>N</i> -Iodosuccinimide
<i>n</i> -Bu	<i>n</i> -butyl
nmr	nuclear magnetic resonance

N.R.	no reaction
OTf	trifluoromethanesulfonate
Pt	Platinum
Pd	Pladium
$\text{Pd}(\text{PPh}_3)_4$	tetrakis(triphenylphosphine)palladium(0)
Pd / C	palladium on carbon
Ph	phenyl
PMP	<i>p</i> -methoxyphenyl
PNBA	4-nitrobenzoic acid
ppm	parts per million
Py	pyridine
q	quartet
rt.	room temperature
R_f	retention factor
s	singlet
t	triplet
<i>t</i> -Bu	<i>tert</i> -butyl
<i>t</i> -BuOLi	lithium <i>tert</i> -butoxide
td	triplets of doublet

TFA	trifluoroacetic acid
TfOH	triflate acid
Tf ₂ O	triflate anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	Trimethylsilyl
TON	turnover number
Ts	<i>p</i> -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, extraordinary 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 carbon-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 transmetalation 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 notably, and Fu recently. Essential hypervalent silicate intermediate was generated *in situ* from tetracoordinate alkenyl⁴ (Scheme 1.4) and arylsilanes⁵ (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 transmetalation happened.

Scheme 1.4 Pd-catalyzed coupling of dimethylfluorosilanes with alkenyl iodides

Scheme 1.5 Pd-catalyzed 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 stabilize the pentacoordinate silicates. Alkyl-⁶ (Scheme 1.6) and aryl(trifluoro)silanes⁷ (Scheme 1.7) were also tested as alkyl and aryl group transfer reagents, with the protocol of palladium or nickel 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 caused 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 Ito¹⁰ (Scheme 1.9). Aryl(trialkoxy)silanes, initially studied by Shibata¹¹ (Scheme 1.10), were then explored extensively.¹²

Scheme 1.9 Pd-catalyzed coupling of alkenylalkoxysilanes with C(sp²)-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 chlorides¹³ (Scheme 1.11), tosylates¹⁴ (Scheme 1.12), and mesylates¹⁵. 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.; Segansh, 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 halides¹⁸ (Scheme 1.14), could be performed with the presence of palladium or nickel 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 asymmetric coupling of alkoxy silanes with α -bromo esters

Denmark¹⁹ and coworkers had developed intramolecular cross coupling of alkenyl(alkoxy)silanes via medium-sized ring compounds, which led to successful total synthesis 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 prefunctionalized partners, such as acetanilides²¹ (Scheme 1.16), enamides²² (Scheme 1.17), and heteroarenes²³ (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

Organosilanols²⁴ had gradually developed as a category of reactive and relatively stable organosilicon reagent, and reported by Hiyama²⁵ and Denmark²⁶ independently (Scheme 1.19). Denmark and Sweis²⁷ had studied the mechanism and considered palladium silanolates as key intermediates, which were nucleophilically

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 organiodides

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 silanolates, such as alkenyl-²⁹ (Scheme 1.20), aryl-³⁰ (Scheme 1.21), heteroaryl-³¹ (Scheme 1.22), and crotylsilanolates³² (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 arylsilanates with aryl halides

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

Scheme 1.23 Pd-catalyzed coupling of crotylsilanates 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 copper³⁵ (Scheme 1.26) or silver³⁶ (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 benzyl⁴² (Scheme 1.29), allyl⁴³ (Scheme 1.30) groups. Detailed studies revealed that these masking groups were converted 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 contaminant 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 vinyl dimethylphenylsilanes 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 activation of 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 motif (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 oxysilyl cycle 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 motif⁵¹ (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(sp³)-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 approach, using various halogenated arylsilanes, oligoarenes could be synthesized by iterative coupling reactions (Scheme 1.38).⁵⁴

Scheme 1.37 Intramolecular activation of C(sp³)-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

Trimethylsilylanes were the simplest and ideal 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 alkyltrimethylsilylanes, discrimination and activation of C(sp³)-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 directed intramolecular cleavage of C(sp³)-Si bond

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

Scheme 1.40 Rh-catalyzed sequential cleavage of alkynyl-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(sp³)-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(sp²)-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(sp³)-Si or C(sp²)-Si bond (*ipso*-desilylation) needs to be 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 Chatani² (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(sp³)-Si bond followed by intramolecular formation of C(sp²)-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(sp³)-Si and formation of C(sp²)-Si bond

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

ipso-Desilylative activation of C(sp²)-Si bond in aryltrimethylsilanes without a coordinating heteroatom or an aligned 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. Hashimoto⁶ and Eaborn⁷ initiated the studies on *ipso*-desilylbromination of aryltrimethylsilanes using Br₂ decades ago, followed by Coe⁸ using Br₂/AcOH for fluoroarenes with *para* favored than *ortho* substitution (Scheme 2.8). In 1980, Koser⁹ reported the synthesis of diaryliodonium tosylates with aryl C-Si bond cleavage from aryltrimethylsilanes with [hydroxy(tosyloxy)iodo]arenes (Scheme 2.9). Later, silylated arylboronic 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

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 stabilized 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 acid¹², 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 Me₃SiF, or by corresponding R³OH 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, Oi¹⁵ 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 group¹⁶, we chose alkene as the other coupling partner 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 PdCl₂ (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-dioxane 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 °C (entry 6). The control experiment without PdCl₂ 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

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 catalyst (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 O₂ (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 satisfactory 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-disubstituted alkenes reacted sluggishly 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 weakly electron-withdrawing substituents *para* or *meta* to SiMe₃, 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 CF₃ greatly decreased the reactivity and only afforded 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)-catalyzed phenyl(trimethyl)silane coupling with various alkenes

$ \begin{array}{c} \text{Ph-SiMe}_3 + \begin{array}{c} \text{R} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{H (Me or Ph)} \end{array} \\ \text{1a} \qquad \qquad \text{2a-2l} \end{array} \xrightarrow[\text{AcOH, 70 } ^\circ\text{C, 24 h}]{\begin{array}{c} \text{PdCl}_2 \text{ (20 mol\%)} \\ \text{Cu(OAc)}_2 \text{ (20 mol\%)} \\ \text{O}_2 \text{ (1 atm)} \end{array}} \begin{array}{c} \text{Ph} \text{---} \text{CH} \text{=C} \text{---} \text{R} \\ \text{H (Me or Ph)} \end{array} $			
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)-catalyzed aryl(trimethyl)silanes coupling with *n*-butylacrylate

$\text{Ar-SiMe}_3 + \text{CH}_2=\text{CH-C(=O)OnBu} \xrightarrow[\text{AcOH, 70 } ^\circ\text{C, 24 h}]{\text{PdCl}_2 \text{ (20 mol\%)} \\ \text{Cu(OAc)}_2 \text{ (20 mol\%)} \\ \text{O}_2 \text{ balloon}}$		$\text{Ar-CH=CH-C(=O)OnBu}$	
1a-1h		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 = <i>t</i> Bu 1c	R = <i>t</i> 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 Friedel Crafts transmetalation 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 stabilization 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 Friedel Crafts

acylation. However, with the aid of SiMe₃ 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 (^{13}C 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 dried 100 mL round bottom flask, 50 mL anhydrous THF and corresponding arylhalide (5 mmol, 1 equiv.) were added and cooled to $-78\text{ }^{\circ}\text{C}$ 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);

^1H 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): $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{10}\text{H}_{17}\text{Si}$: 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 °C);

^1H 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): $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{13}\text{H}_{23}\text{Si}$: 207.1569, found: 207.1576;

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

^1H 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): $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{10}\text{H}_{17}\text{OSi}$: 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);

^1H NMR (400 MHz, CDCl_3): δ 7.46 (dd, $J = 7.80$ Hz, 0.92 Hz, 2H), 7.30 (td, $J = 7.44$ Hz, 1.4 Hz, 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.

^1H 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);

^1H 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): $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_9\text{H}_{14}\text{SiF}$: 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 °C);

^1H 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);

^1H 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): $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{13}\text{H}_{17}\text{Si}$: 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);

^1H 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);

^1H 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): $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{13}\text{H}_{17}\text{Si}$: 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);

^1H 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): $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_8\text{H}_{14}\text{NSi}$: 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 dried 10 mL round bottom flask, Pd catalyst (0.06 mmol, 20 mol%), $\text{Cu}(\text{OAc})_2$ (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 °C 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): $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{13}\text{H}_{17}\text{O}_2$: 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;

^1H 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): $[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_2\text{Na}$: 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;

^1H 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): $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{10}\text{H}_{11}\text{O}_2$: 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)vinylbenzene (3d):²⁴ pale yellow solid, 60% yield, mp = 75 °C;

¹H NMR (400 MHz, CDCl₃): 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;

¹³C NMR (100 MHz, CDCl₃): 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 °C;

¹H NMR (400 MHz, CDCl₃): 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;

¹³C NMR (100 MHz, CDCl₃): 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 C₁₄H₁₂NO₂: 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. *Synthesis* **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;

¹H NMR (400 MHz, CDCl₃): 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;

¹³C NMR (100 MHz, CDCl₃): 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 C₁₄H₁₂Cl: 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;

¹H NMR (400 MHz, CDCl₃): 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;

¹³C NMR (100 MHz, CDCl₃): 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 C₁₅H₁₅: 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 °C;

¹H NMR (400 MHz, CDCl₃): 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;

¹³C NMR (100 MHz, CDCl₃): 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 C₁₅H₁₅O: 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 inseparable 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;

¹H NMR (400 MHz, CDCl₃): 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;

¹³C NMR (100 MHz, CDCl₃): 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;

¹H NMR (400 MHz, CDCl₃): 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);

¹³C NMR (100 MHz, CDCl₃): 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 C₁₁H₁₃O₂: 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 inseparable by flash column purification, the combined yield was 12% with **3j/3j'** around 1:1

(E)-Prop-1-ene-1,2-diyl dibenzene (3j):²² colorless oil;

¹H NMR (400 MHz, CDCl₃): 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;

¹³C NMR (100 MHz, CDCl₃): 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-diyl dibenzene (3j'):²⁷ colorless oil;

¹H NMR (400 MHz, CDCl₃): 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): $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{15}\text{H}_{15}$: 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;

^1H 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): $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{20}\text{H}_{17}$: 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;

^1H 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): $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{11}\text{H}_{13}\text{O}_2$: 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;

^1H 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;

^1H 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): $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{11}\text{H}_{13}\text{O}_3$: 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;

^1H 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;

^1H 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;

^1H 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;

^1H 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;

¹H NMR (400 MHz, CDCl₃): 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;

¹³C NMR (100 MHz, CDCl₃): 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 C₁₀H₁₀O₂F: 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, 831.3 cm⁻¹.

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

¹H NMR (400 MHz, CDCl₃): 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;

¹³C NMR (100 MHz, CDCl₃) 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;

¹H NMR (400 MHz, CDCl₃): 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;

¹³C NMR (100 MHz, CDCl₃): 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 C₁₇H₁₉O₂: 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;

¹H NMR (400 MHz, CDCl₃): 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;

¹³C NMR (100 MHz, CDCl₃): 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 aryltrimethylsilanes 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 ZnCl₂, AlCl₃, TiCl₄, SnCl₄, FeCl₃, or strong protic acids, such as HF and H₂SO₄, which may evolve hazardous gas HCl and large volumes of waste.¹ Modern 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 preferred 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 multifunctional 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.

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 °C. 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

Entry	Lewis Acid (equiv.)	Solvent (equiv.)	Temp. (°C)	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 ₂ O 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

$\text{Ar-SiMe}_3 + \text{Cl-C(=O)-CH}_2\text{-Ph} \xrightarrow[\text{DCM (15 equiv.), 40 }^\circ\text{C, 12 h}]{\text{AlCl}_3 \text{ (1.5 equiv.)}} \text{Ar-C(=O)-CH}_2\text{-Ph}$			
	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 stabilized by β -effect of TMS group. The competing dehydro-acylation pathway was suppressed. 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 aryltrimethylsilanes. 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 sieves 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 dried 100 mL round bottom flask, 50 mL anhydrous THF and corresponding arylhalide (5 mmol, 1 equiv.) were added and cooled to -78°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.

^1H 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);

^1H 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): $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{10}\text{H}_{14}\text{NSi}$: 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);

^1H 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. Organomet. 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);

¹H NMR (400 MHz, CDCl₃): 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;

¹³C NMR (100 MHz, CDCl₃): 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 dried 4 mL sample vial, AlCl₃ (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 °C for 12 h. After reaction was complete, 15 mL of saturated NaHCO₃ was added followed by extraction with ethyl acetate three times. The combined organic layers were washed with saturated brine and dried over Na₂SO₄, 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;

¹H NMR (400 MHz, CDCl₃): 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;

¹³C NMR (100 MHz, CDCl₃): 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;

¹H NMR (400 MHz, CDCl₃): 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;

¹³C NMR (100 MHz, CDCl₃): 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;

¹H NMR (400 MHz, CDCl₃): 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;

¹³C NMR (100 MHz, CDCl₃): 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;

¹H NMR (400 MHz, CDCl₃): 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;

¹³C NMR (100 MHz, CDCl₃): 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;

¹H NMR (400 MHz, CDCl₃): 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;

¹³C NMR (100 MHz, CDCl₃): 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;

¹H NMR (400 MHz, CDCl₃): 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 conditions.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 $\text{Bu}_2(t\text{-Bu})\text{SnCl}$ 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 substitution, was reported by Prandi⁶ using $\text{Bu}_2(t\text{-Bu})\text{SnCl}$ (Scheme 4.3) and Rys⁷ 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 synthesis⁸. 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. Rev.* **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.

chlorocarbonyls using micellar solutions to enhance the reactivity (Scheme 4.6).¹⁰

compared with normal aromatic halides (Scheme 4.7).¹¹

Scheme 4.7 Indium-mediated reductions of iodoheteroaromatics

(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. I* **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 perfluoroarenes

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 dehalogenations 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 -cyclodextrin 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**, 58, 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-butylin hydride (TBTH)²⁰ developed by Maitra (Scheme 4.14), diarylsilanes²¹ by Yokoyama (Scheme 4.15) and $(\text{Me}_3\text{Si})_3\text{SiH}$ ²² by Chatgililoglu (Scheme 4.16).

TBTH was utilized 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 solubility 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.; Chatgililoglu, C. *Org Lett.* **2007**, *9*, 5159

$(\text{Me}_3\text{Si})_3\text{SiH}$ was able to dehalogenate substrates both hydrophilic and hydrophobic in aqueous media. This protocol contained substrates, silane and initiator (ACCN) at 100 °C, with added amphiphilic thiol for those water-soluble substrates.

Scheme 4.14 TBTH-mediated dehalogenation in aqueous medium

R = $\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OMe}$, $\text{O}(\text{CH}_2)_2\text{OH}$, $\text{OCH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$

99%

97%

42%

88%

23%

97%

Scheme 4.15 Diarylsilanes-mediated dehalogenation in water

Scheme 4.16 $(\text{TMS})_3\text{SiH}$ -mediated dehalogenation in water

Considering the above methodologies for displacement of halogen atoms, we were particularly interested in transforming halides to alcohols, which might provide more synthetic values than hydrodehalogenations. However, available methods using tin reagents⁴⁻⁷ were limited in applications due to usage of toxic reagents, water-intolerance 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 others²⁴) on indium or zinc 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/^tBuOH (1:1) at 60 °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.

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) Herrerias, 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

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 °C, screened four solvents gave similar results, with *t*BuOH and DME at slightly better yields (entries 1-4). With increasing the temperature to 90 °C, the yields were generally higher. Varying 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 ₂ O ₂ / <i>t</i> BuOH (5:5)	NaH ₂ PO ₂ ·H ₂ O	30% H ₂ O ₂	58
2 ^a	In	H ₂ O ₂ /DME (5:5)	NaH ₂ PO ₂ ·H ₂ O	30% H ₂ O ₂	56
3 ^a	In	H ₂ O ₂ /DMSO (5:5)	NaH ₂ PO ₂ ·H ₂ O	30% H ₂ O ₂	43
4 ^a	In	H ₂ O ₂ /1,4-dioxane (5:5)	NaH ₂ PO ₂ ·H ₂ O	30% H ₂ O ₂	48
5	In	H ₂ O ₂ / <i>t</i> BuOH (5:5)	NaH ₂ PO ₂ ·H ₂ O	30% H ₂ O ₂	60
6	In	H ₂ O ₂ /DME (5:5)	NaH ₂ PO ₂ ·H ₂ O	30% H ₂ O ₂	82
7	In	H ₂ O ₂ /DME/H ₂ O (4:4:2)	NaH ₂ PO ₂ ·H ₂ O	30% H ₂ O ₂	75
8	In	H ₂ O ₂ /DME/H ₂ O (3:1:6)	NaH ₂ PO ₂ ·H ₂ O	30% H ₂ O ₂	64
9	In	H ₂ O ₂ /DME/H ₂ O (1:1:8)	NaH ₂ PO ₂ ·H ₂ O	30% H ₂ O ₂	69
10	In	<i>t</i> BuOH/H ₂ O (5:5)	NaH ₂ PO ₂ ·H ₂ O	O ₂ balloon	82
11	In	DME/H ₂ O (5:5)	NaH ₂ PO ₂ ·H ₂ O	O ₂ balloon	79
12	In	<i>t</i> BuOH/H ₂ O (3:7)	NaH ₂ PO ₂ ·H ₂ O	O ₂ balloon	63
13	In	<i>t</i> BuOH/H ₂ O (1:9)	NaH ₂ PO ₂ ·H ₂ O	O ₂ balloon	99
14	In	<i>t</i> BuOH/H ₂ O (1:9)	NaH ₂ PO ₂ ·H ₂ O	capped	96
15	In	<i>t</i> BuOH/H ₂ O (1:9)	none	capped	84
16	none	<i>t</i> BuOH/H ₂ O (1:9)	none	capped	90
17	none	Only H ₂ O	none	capped	67

^a Reactions were run at 70 °C.

Table 4.3: Screening of alkyl halides for oxydehalogenation

$\text{R-X} \xrightarrow[\text{90 } ^\circ\text{C, 24 h}]{\text{tBuOH/H}_2\text{O (1:9)}} \text{R-OH}$		Condition A : no metal
		Condition B : metal (2 equiv.)
		Condition C : metal (2 equiv.), $\text{NaH}_2\text{PO}_2 \cdot \text{H}_2\text{O}$ (2 equiv.), O_2
<hr/>
A : 90%
		A : 99%

		A : 87%

		A : 88%
A : 18% C : 5% (indium)
A : 100 $^\circ\text{C}$, 48 h, 60%		A : 32%
A : 100 $^\circ\text{C}$, 48 h, DMF, 88%		trace
<hr/>
$\text{R} = \text{C}_6\text{H}_5$	A : 85% B : 99% (indium)
	$\text{R} = 4\text{-tBu-C}_6\text{H}_4$	A : 76%
	$\text{R} = 4\text{-OMe-C}_6\text{H}_4$	A : 72%
	$\text{R} = 4\text{-Cl-C}_6\text{H}_4$	A : 68%
	$\text{R} = 4\text{-F-C}_6\text{H}_4$	A : 55%
	$\text{R} = 4\text{-Br-C}_6\text{H}_4$	A : 37%
	$\text{R} = $	A : 81%
<hr/>
B : 48 h, 30% (indium)
B : 48 h, 34% (zinc)		
B : 48 h, 55% (iron)		
	major
B : 48 h, 60% (indium)
B : 48 h, 68% (iron)		
	major	acetophenone
<hr/>

	a b	
	B : 48 h, 76% (indium, a/b = 48:52)	
	C : 48 h, 46% (indium, a/b = 37:63)	

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 quantitative yield under metal free condition **A**. Similarly, reactive primary alkyl halides, such as benzyl chloride and benzyl 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 °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 ^1H NMR. Other methods²⁶ were also tested (Scheme 4.19), with the hope to react alkyl chlorides with indium to form alkyl indium complex intermediate before hydrolyzed to corresponding 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.

Notably, with an added carbonyl functional group to primary alkyl chlorides, hydrolysis could occur at moderate to satisfactory yields. A series 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 satisfactory 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

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 incorporated 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 evolution of CO₂ 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 dried 8 mL sample vial, alkyl halide (0.3 mmol, 1 equiv.), with/without metal (0.6 mmol, 2 equiv.), ^tBuOH (0.4 mL), and H₂O (3.6 mL) were added and stirred at 90 °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 Na₂SO₄, 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;

¹H NMR (400 MHz, CDCl₃): δ 2.13 (s, 3H), 1.71-1.70 (m, 6H), 1.65-1.56 (m, 6H), 1.42 (br, 1H) ppm;

¹³C NMR (100 MHz, CDCl₃): δ 68.2, 45.4, 36.1, 30.7 ppm;

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

¹H NMR (400 MHz, CDCl₃): δ 7.36-7.23 (m, 5H), 4.62 (s, 2H), 2.26 (br, 1H) ppm;

¹³C NMR (100 MHz, CDCl₃): δ 140.8, 128.5, 127.6, 127.0, 65.2 ppm;

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

^1H 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;

^1H 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:

^1H 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 Fujii, 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;

^1H 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;

^1H 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;

^1H 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;

^1H 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;

^1H 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;

^1H 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;

^1H NMR (400 MHz, CDCl_3): δ

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

^1H 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;

^1H 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 aqueous media *manuscript in preparation*