THE UNIVERSITY OF CALGARY

New Desilylations of Phenolic Silanes Using Palladium Catalysts and K_2CO_3/EtOH: Extensions Towards Asymmetric Desymmetrizations

by

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A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTER OF SCIENCE

DEPARTMENT OF CHEMISTRY

CALGARY, ALBERTA

SEPTEMBER, 1997

ABSTRACT

The importance of protecting groups for phenols (particularly TBDMS ethers) in organic synthesis and two new methods for the desilylation of phenolic silanes are discussed. The first method desilylates a variety of phenolic silyl ethers in typically good to excellent yields using 5 mol% $PdCl_2(CH_3CN)_2$ in refluxing wet acetone. The scope and limitations of this method are discussed in detail. The second method desilylates a variety of phenolic silyl ethers in good to excellent yields using 1.1 equivalents of K_2CO_3 in ethanol at 70 °C. Both methods are beneficial since they do not require specialized equipment and are relatively simple, mild and inexpensive procedures. The latter method selectively removes phenolic TBDMS ethers in the presence of alkyl TBDMS ethers.

The asymmetric desymmetrization of meso compounds is a useful strategy in organic chemistry for the preparation of scalemic mixtures. The desymmetrization of *meso*-silylated diols is discussed using palladium catalysts. Initially, achiral palladium catalysts are used to determine what conditions were necessary to effect a mono-desilylation. A variety of chiral phosphine ligands were then coordinated to the palladium catalyst, but it was found that the desilylation reaction was inhibited completely in the presence of these chiral ligands. A variety of other Lewis acid catalysts are tried with silver triflate showing the most promising results.

ACKNOWLEDGMENTS

The author expresses his gratitude to Dr. Brian A. Keay for his supervision, enthusiasm, creativity and perceptiveness both inside and outside the laboratory. The extra effort that he takes to educate and motivate his students was greatly appreciated. Most of all, I would like to thank Dr. Keay for providing me with the opportunity to enroll in graduate studies and join his research group.

The University of Calgary and the Department of Chemistry are acknowledged for their financial support in the form of teaching assistantships and research scholarships.

I am grateful to Dr. Shawn Maddaford, Dr. Ian Hunt, Neil Andersen, and the other past and present members of Dr. Keay's group for their friendship, discussions and helpful suggestions. In particular, I would like to thank Dr. Shawn Maddaford for advice and camaraderie both in and out of the laboratory. I also greatly appreciate Dr. Ian Hunt for his assistance with the kinetic experiments.

I would like to thank the friends that I have met at the University for making my post-secondary education so enjoyable. Most of all, I want to express my gratitude to my wife, Carla, my parents, (Tom and Cathy), my Grandparents, (Vern and Sheila Serl, Ted and Merle Wilson), my brother and sister (Ryan and Stephanie), and my in-laws (John and Barbara Siemens) who over the years have sacrificed so much in order for me to finish my post-secondary education. Thank you!

To my wife and parents.

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Ac	acetyl	DEPT	distortionless enhancement by polarization transfer
aq.	aqueous		
Ar	aryl group	DMF	*N*,*N*-dimethylformamide
ATP	adenosine triphosphate	ee	enantiomeric excess
β	beta	EEL	electric eel acetylcholinesterase
BINAP	2,2'-bis(diphenylphosphino)-1,1`-binaphthyl	Eq.	equation
		equiv.	equivalent
Bn	benzyl	Et	ethyl
bp	boiling point	$Eu(hfc)_3$	tris[3-(heptafluoropropyl hydroxymethylene)-*d*-camphorato] europium (III)
Bu	butyl		
Cbz	benzyloxycarbonyl		
CEH	cytosolic epoxide hydrolase	f'(x)	derivative of some function, f(x)
CHIRAPHOS	bis(diphenylphosphino)-butane	g	gram
dba	dibenzylideneacetone	GC	gas chromatography
DDT	1,1-bis(4-chlorophenyl)-2,2,2-trichloroethane	GC/MS	gas chromatography/mass spectrometry
de	diastereomeric excess	h	hours

HLADH	horse liver alcohol dehydrogenase	*p*	para
		PFL	*Pseudomonas fluorescens* lipase
Hz	hertz		
i	iso	Ph	phenyl
IR	infrared	ppm	parts per million
L	ligand (in Schemes)	Pr	propyl
m	meta	PSL	*Pseudomona cepacia* lipase
M	metal (in Schemes)	PTS	*p*-toluenesulfonic acid
Me	methyl	R	various aryl or alkyl groups
m/z	mass to charge ratio	R*	chiral ligand
MEH	rabbit liver microsomal	r.t.	room temperature
mg	milligram	*t*	tertiary
MHz	megahertz	TBAF	tetrabutylammonium fluoride
min	minutes		
mmol	millimole	TBDMS	*t*-butyldimethylsilyl
mol%	mole percent	TBDPS	*t*-butyldiphenylsilyl
MOM	methoxymethyl	TES	triethylsilyl
mp	melting point	Tf	triflate
NMR	nuclear magnetic resonance	THF	tetrahydrofuran
o	ortho	THP	tetrahydropyran
O	oxygen atom (in text)	TIPS	triisopropylsilyl

TLC	thin layer chromatography
TMS	trimethylsilyl
wt%	weight percent

1 Desilylation of Phenolic *t*-Butyldimethylsilyl Ethers.

1.1 Introduction.

If a reaction in the synthesis of a multifuctionalized target requires selectivity of one reactive site over another, then it is necessary to temporarily block one of the reactive sites. This temporary blocking agent is known in organic synthesis as a protecting group. Many examples of protecting groups have been developed to provide the chemist with a multitude of strategies for organic synthesis. However, in order for a protecting group to fulfill its objective as a temporary blocking agent it must fulfill several requirements: (a) it must provide the protected substrate with a good overall yield, (b) its method(s) of removal should be selective for the particular protecting group, (c) it must provide the deprotected substrate in a good overall yield, and (d) it should not generate new stereogenic centres when formed.[1]

The protection/deprotection protocol of free hydroxyl groups has become commonplace in organic synthesis.[2] As a result, a whole host of hydroxyl protecting groups have been developed. One protecting group that has been widely employed for the protection of both aliphatic and benzylic alcohols is the *t*-butyldimethylsilyl (TBDMS) moiety. It was first reported in 1972 by Corey and Venkateswarlu[3] and has since become the most popular silicon-containing protecting group in organic synthesis.[1] However, the use of TBDMS as a protecting group for phenols has not gained this widespread acceptance. Although removal of the TBDMS ether can be achieved by the

exploitation of the high affinity that silicon has for fluoride ions, (tetra-*n*-butylammonium fluoride (TBAF) is a common desilylating agent),[3,4] this method is limited to the removal of a TBDMS protected phenol since the strong basic fluoride anion often leads to complex mixtures.[5,6] In addition, the use of an aqueous workup can lead to diminished yields of some phenols due to their water solubility.[7]

Although numerous methods have been developed for the removal of the TBDMS group for aliphatic and benzylic systems, only a few methods have been developed for their removal from phenolic systems, and still fewer for their selective removal. While each method has its own merits, they do offer some drawbacks. The following review will present in detail existing methods for the nonselective and selective desilylations of TBDMS phenolic ethers. In the subsequent section, the development of two new methods for the desilylation of TBDMS phenolic ethers are discussed.

1.1.1 Review: Nonselective Desilylations of Phenolic TBDMS Ethers.

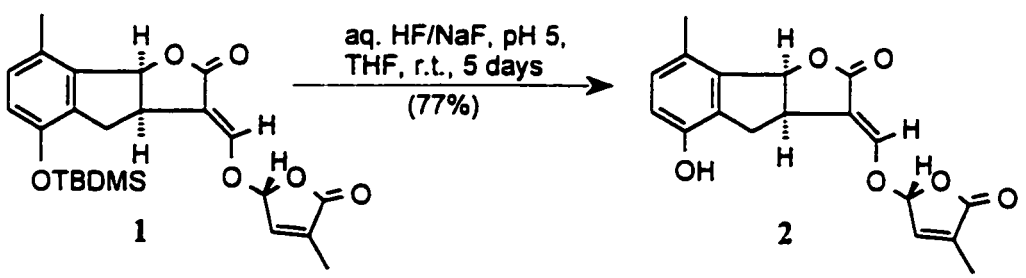
The phenolic hydroxyl group occurs widely in natural products. During the synthesis of natural products containing phenolic hydroxyl groups, it is often necessary to protect the hydroxyl group from unwanted side reactions that may occur with oxidizers, bases, and electrophiles. In addition, the nucleophilic phenoxide ion reacts readily with mild alkylating or acylating agents.[1] According to Greene,[1] the TBDMS protecting group offers protection from many of these reagents.

Although the literature is replete with examples of desilylation of both aliphatic and benzylic TBDMS ethers,[1,5] there are very few methods for the desilylation of

TBDMS protected phenols. The various methods reported for the nonselective desilylation of TBDMS phenolic ethers are outlined below.

In the attempt to synthesize aromatic analogues of strigol (2), a highly potent stimulant in germination of witchweed seed,[8] the removal of TBDMS protecting group was effected with aqueous fluoride at pH 5.[8] Their initial attempt utilized the most common reagent TBAF;[3] however, only complex mixtures were obtained. A second method involved using a mixture of aqueous fluoride buffer (pH 5) in tetrahydrofuran (THF), which effected a clean deprotection (Scheme 1.1). It is the believed that the mechanism proceeds through specific fluoride ion catalysis, since an attempt with an acetate buffer (comparable pH) was ineffectual. While this method does provide the corresponding phenol in good yield, the scope and limitations of the reaction were not reported.

Scheme 1.1



1 2

Sinhababu *et al.*[9] found that the treatment of TBDMS ethers of a variety of phenols and diphenols with potassium fluoride in dimethylformamide (DMF) with catalytic amounts of hydrobromic acid (or 1.2 equivalents of *t*-butyl chloride or *t*-butyl bromide), generated the corresponding phenols or diphenols in high yield (Table 1.1).

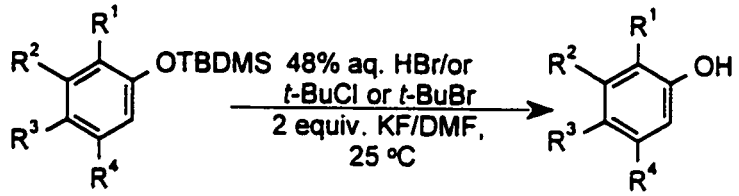
Although the mechanism by which *t*-butyl chloride (or *t*-butyl bromide) catalyzes the desilylation is not entirely known, two proposals were discussed. The first possibility is that *t*-butyl chloride (or *t*-butyl bromide) weakens the O-Si bond through coordination of the incipient *t*-butyl carbocation with oxygen, thereby facilitating attack by fluoride ion at the silicon atom. The second mechanism requires the presence of trace amounts of hydrogen bromide that could potentially be present in the solvent.

In general, the Sinhababu *et al.*[9] method of desilylation is accelerated by the presence of electron-withdrawing groups on the aromatic ring or by the addition of large amounts of hydrobromic acid. This methodology does offer the advantage that the reagents used are inexpensive and readily available. Furthermore, the reaction conditions allow for the regeneration of base-sensitive phenols. However, the use of strong acid does limit the method's range of use since other functional groups in the molecule may not survive the acidic conditions.

Three alternative methods for the desilylation of TBDMS phenol ethers are the use of potassium fluoride with acidic or basic alumina in acetonitrile and the latter with ultrasound (Table 1.2).[10] Despite the presence of the highly basic species associated with KF-Al_2O_3 (i.e. potassium hexafluoroaluminate, potassium hydroxide, potassium aluminate, and potassium carbonate),[11] the most likely mechanism of desilylation involves the nucleophilic attack of fluoride ion at the silicon atom. It is presumed that there is cooperative action of the fluoride ion on the alumina surface which then results in a strong nucleophilic matrix which is not present in KF alone.[10] Although, the method does involve the use of specialized equipment (i.e. an ultrasound bath) the reaction is

beneficial in that the conditions are compatible with sensitive, water-soluble phenols. In addition, partial selectivity of phenolic over benzylic silyl ethers (Table 1.2, entries 2, 5, 6, and 9), and selectivity between TBDMS and 2-(trimethylsilyl)ethoxymethyl (SEM) phenolic ethers have been observed (Table 1.2, entry 8).

Table 1.1 Desilylation of TBDMS Ethers of Phenols.[9]



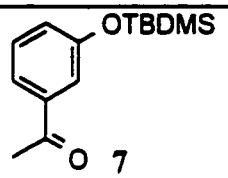
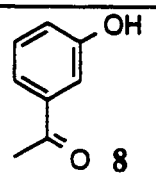
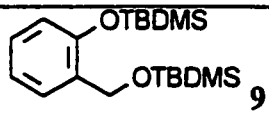
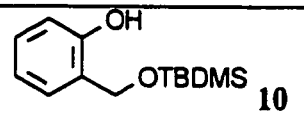
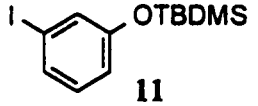
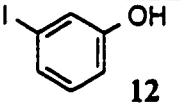
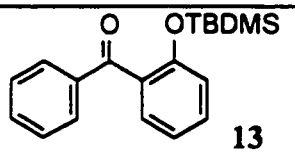
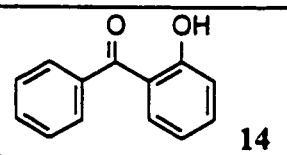
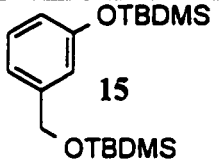
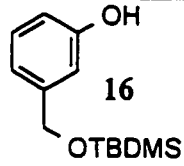
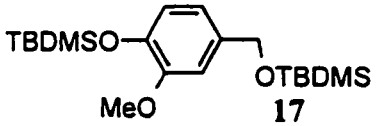
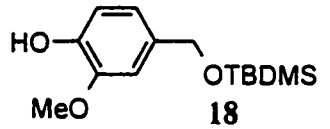
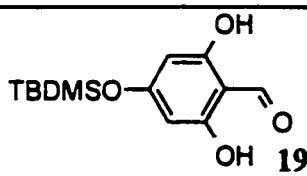
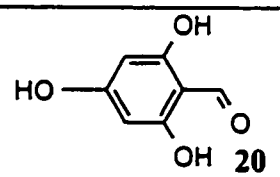
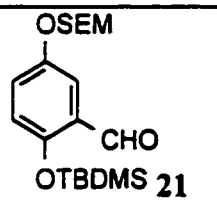
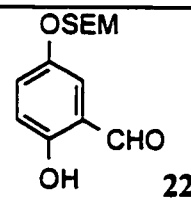
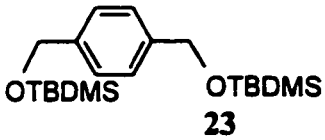
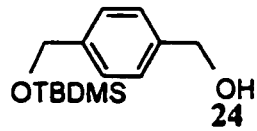
3a $R^1=R^4=H$; $R^2=CHO$; $R^3=F$ — **4a**
3b $R^1=R^2=R^4=H$; $R^3=F$ — **4b**
3c $R^1=F$; $R^2=CHO$; $R^3=R^4=H$ — **4c**
3d $R^1=R^2=R^3=R^4=H$ — **4d**
3e $R^1=OMe$; $R^2=R^3=R^4=H$ — **4e**
3f $R^1=R^3=R^4=H$; $R^2=OMe$ — **4f**
3g $R^1=R^2=R^4=H$; $R^3=OMe$ — **4g**
3h $R^1=R^4=H$; $R^2=R^3=OCH_2Ph$ — **4h**
5a $R^1=R^2=R^3=H$; $R^4=OTBDMS$ — **6a** $R^4=OH$
5b $R^1=F$; $R^2=CHO$; $R^3=H$; $R^4=OTBDMS$ — **6b** $R^4=OH$
5c $R^1=R^4=H$; $R^2=CHO$; $R^3=OTBDMS$ — **6c** $R^3=OH$

Entry	TBDMS Ether	KF (equiv.)	Alkyl or Inorganic Halide (equiv.)	Time (h)	Product (% Yield)
1	**3a**	2	*t*-BuBr (1.2)	24	**4a** (95)
2	**3a**	2	none	24	**4a** (27) + **3a** (70)
3	**3a**	none	*t*-BuBr (1.2)	48	**4a** (20) + **3a** (72)
4	**3a**	2	*t*-BuCl (1.2)	24	**4a** (75) + **3a** (22)
5	**3a**	2	HBr (0.1)	0.5	**4a** (95)
6	**3a**	2	HBr (0.01)	2	**4a** (36) + **3a** (52)
7	**3b**	2	HBr (0.1)	0.5	**4b** (93)
8	**3c**	2	HBr (0.1)	0.5	**4c** (94)
9	**3d**	2	HBr (0.1)	22	**4d** (90)
10	**3d**	2	HBr (0.2)	2	**4d** (90)
11	**3e**	2	HBr (0.3)	2	**4e** (92)
12	**3f**	2	HBr (0.3)	2	**4f** (93)
13	**3g**	2	HBr (0.3)	2	**4g** (96)
14	**3h**	2	HBr (0.2)	6	**4h** (97)
15	**3h**	2	HBr (0.3)	4	**4h** (98)
16	**5a**	2	HBr (0.3)	2	**6a** (91)
17	**5b**	2	HBr (0.1)	1	**6b** (91)
18	**5c**	2	HBr (0.2)	2	**6c** (87)

In addition to the previous example, which used ultrasound to remove phenolic silyl ethers, Varma *et al.*[12] introduced a desilylation method using a domestic microwave

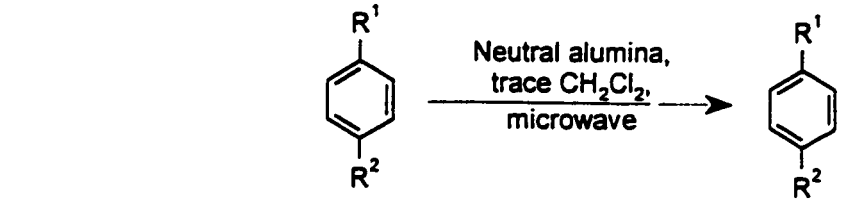
oven. The desilylation occurs on the alumina surface under solvent-free conditions within 10-15 minutes via mild heating (~70-80 °C) using microwave irradiation. Phenols **26**, **28**, and **30** were generated in moderate to good yields (Scheme 1.2). Although this method does not involve an aqueous work up, it does require the use of nonstandard laboratory equipment and is not selective to only TBDMS protected phenols (see **31**→**32** and **33**→**34** in Scheme 1.2). In addition, the deprotection of other functional groups on the solid support has not been investigated.

Table 1.2 Desilylation of TBDMS Ethers Using KF-Al_2O_3 in Acetonitrile.[10]

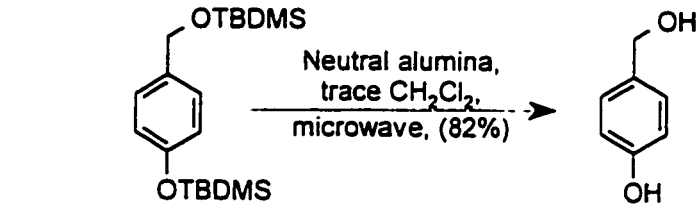
Entry	Reactant	Product	Method[a]	Time (h)	Yield (%)
1	 7	 8	A B	48 0.75	82 81
2	 9	 10	A B	24 0.5	64 78
3	 11	 12	A B	1 0.17	55 55
4	 13	 14	A B C	24 1.5 0.25	72 85 87
5	 15	 16	A B C	4 3 0.25	92 84 86
6	 17	 18	A B C	96 6 4	78 80 73
7	 19	 20	B C	18 1	86 85
8	 21	 22	C	1.5	70
9	 23	 24	C	48	<10

[a] Methods: (A) 3 wt. equiv. KF-Al_2O_3 (acidic), acetonitrile, r.t.; (B) 3 wt. equiv. KF-Al_2O_3 (basic), acetonitrile, r.t.; (C) 3 wt. equiv. KF-Al_2O_3 (basic), acetonitrile, r.t. or 45-55 °C, ultrasound.

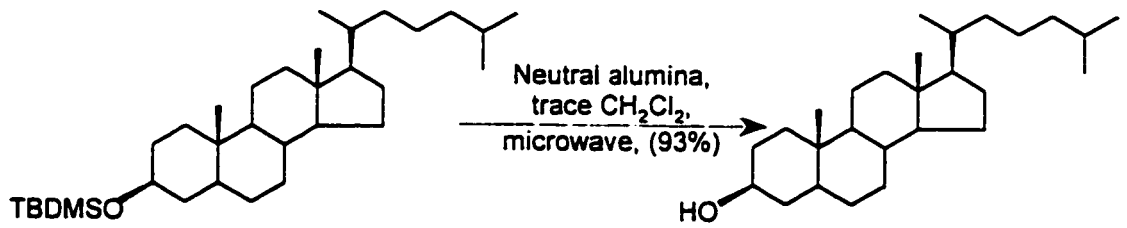
Scheme 1.2



25 $R^1 = (CH_2)_3OTBDMS$, $R^2 = OTBDMS$
26 $R^1 = (CH_2)_3OTBDMS$, $R^2 = OH$, (78%)
27 $R^1 = CHO$, $R^2 = OTBDMS$
28 $R^1 = CHO$, $R^2 = OH$, (91%)
29 $R^1 = COCH_3$, $R^2 = OTBDMS$
30 $R^1 = COCH_3$, $R^2 = OH$, (93%)



31 **32**



33 **34**

1.1.2 Review: Selective Desilylations of Phenolic TBDMS Ethers.

As the complexity of synthetic targets has grown to a more demanding level, the development of new methods for the selective removal of protecting groups has become more important. A recent review on the selective desilylation of a variety of silyl ethers

indicates that some aryl silyl ethers can be cleaved in the presence of alkyl silyl ethers.[2] Work by Davies *et al.*[13] in the measurement of the half-lives of silyl ethers indicated that acidic conditions favor the cleavage of alkyl silyl ethers while basic conditions favor the deprotection of aryl silyl ethers (Table 1.3). The results indicate that potentially 5% NaOH in methanol could be utilized to selectively hydrolyze aryl silyl ethers in the presence of alkyl silyl ethers.[13]

Table 1.3 Half-Lives of Hydrolysis of Alkyl Versus Aryl Silyl Ethers.[13]

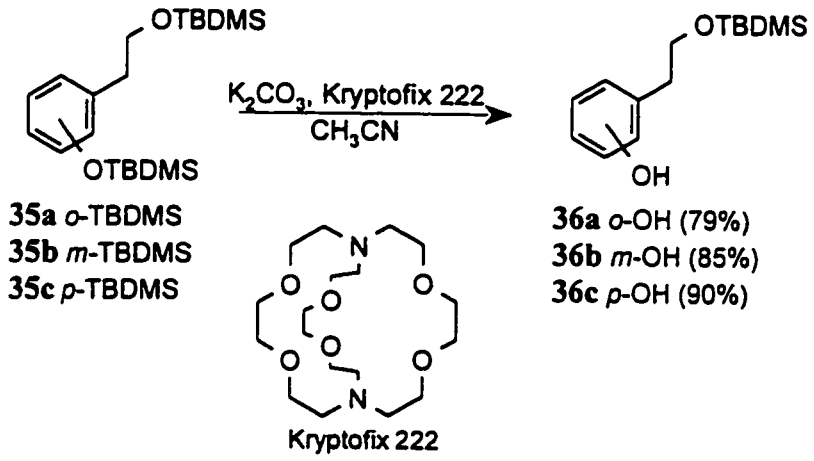
Silyl Ether	R	1% HCl, 95% MeOH	5% NaOH, MeOH
ROTMS	*n*-C_6H_{13}-	≤ 1 min[a]	≤ 1 min[a]
	p-MeC_6H_4-	≤ 1 min[a]	≤ 1 min[a]
ROTBDMS	*n*-C_6H_{13}-	≤ 1 min[a]	NR[b]
	p-MeC_6H_4-	273 min	3.5 min
ROTIPS	*n*-C_6H_{13}-	55 min	NR[b]
	p-MeC_6H_4-	100 h	188 min
ROTBDPS	*n*-C_6H_{13}-	225 min	NR[b]
	p-MeC_6H_4-	100 h	6.5 min

[a] Half-life of 1 min represents the lower limit of sampling technique. [b] No desilylation after 24 h.

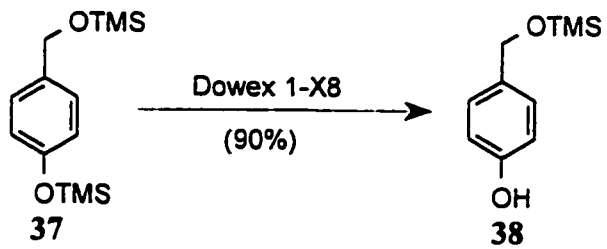
TBDMS phenolic silyl ethers **35a, 35b,** and **35c** were selectively cleaved by treatment with excess K_2CO_3 and Kryptofix 222 (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane) in acetonitrile at 55 °C (Scheme 1.3).[14] Similarly, Kawazoe used a basic ion exchange resin, Dowex, to accomplish selective desilylation

(Scheme 1.4).[15] However, this method is limited to phenolic trimethylsilyl (TMS) ethers, and was not shown to be effective with TBDMS phenolic ethers.

Scheme 1.3

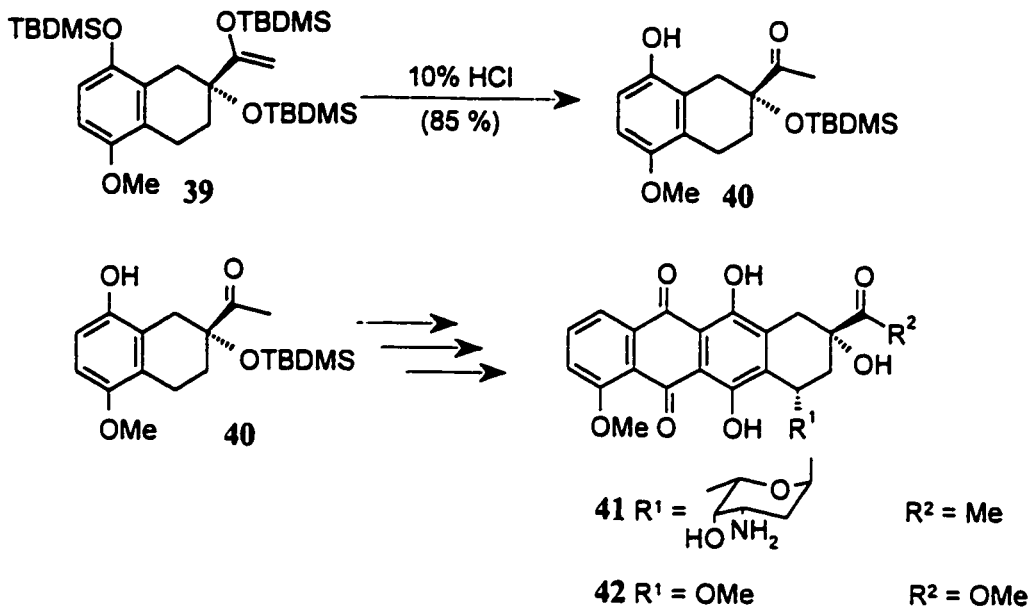


Scheme 1.4



Although Davies *et al.*[13] illustrated that the half-lives of aryl silyl ethers are shorter in basic conditions (Table 1.3), Davis *et al.* have shown that an acidic medium can be used to selectively remove an aryl TBDMS ether in the presence of a tertiary TBDMS ether in the synthesis of daunomycin (**41**) and its 4-demethoxy analogue (**42**) (Scheme 1.5).[16] The addition of 10% HCl to intermediate **39** selectively deprotected the aryl TBDMS ether in the presence of a tertiary TBDMS ether. As expected, the HCl also hydrolyzed the TBDMS silyl enol ether.[1]

Scheme 1.5

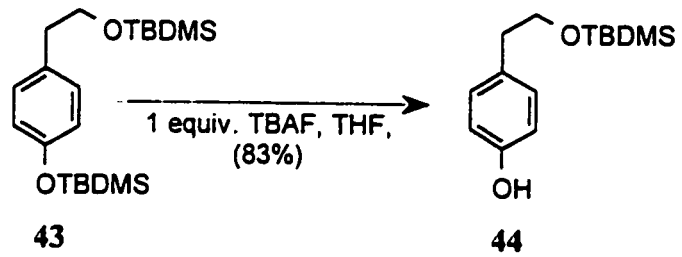


Finally, although the desilylation of aryl TBDMS ethers with TBAF typically gave complex mixtures, the reagent did selectively cleave an aryl TBDMS ether in the presence of alkyl silyl ethers.[17,18] Treatment of aryl TBDMS ether **43** with 1 equivalent of TBAF in THF provided the mono protected phenol **44** in 83% yield (Scheme 1.6).[18] It should be noted that excess TBAF led to complete desilylation of the di-protected material.

The development of new methods for the removal of phenolic TBDMS ethers is necessary since known desilylation techniques typically require either: (a) fluorinated reagents (such as *n*-Bu_4NF/ THF) which can lead to complex mixtures[8], or (b) require the use of specialized equipment[10,12] which may not be available in the laboratory. The next section will present the development of two new methods for the desilylation of TBDMS phenolic silyl ethers. The first method uses catalytic quantities of $PdCl_2(CH_3CN)_2$ in

acetone (Section 1.2) and the second uses K_2CO_3 in ethanol (Section 1.3). Both Sections 1.2 and 1.3 will begin with a short introduction or background to the project, followed by a discussion of the results of each method and some concluding remarks.

Scheme 1.6



43 **44**

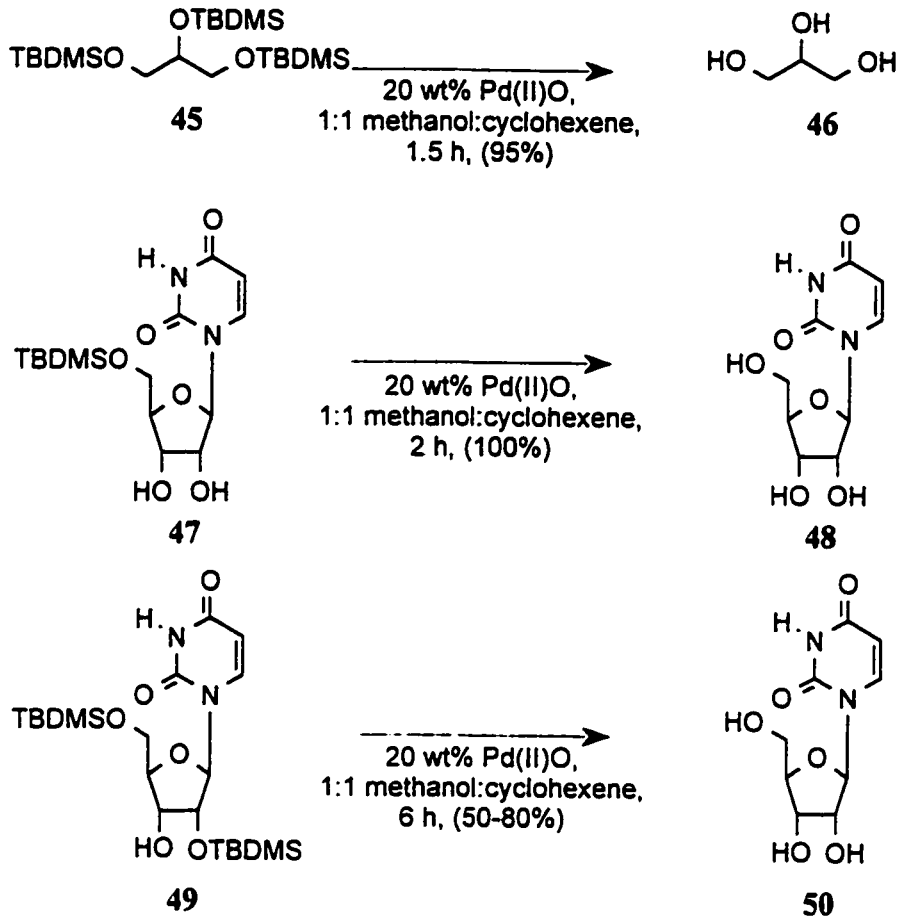
1.2 Desilylation of Phenolic Silyl Ethers Using Palladium Dichloride.

1.2.1 Review: Existing Methods for the Desilylation TBDMS Ethers Using Palladium (II) Catalysts.

The use of palladium (II) catalysts as a reagent for the cleavage of TBDMS ethers has been reported.[19,20,21] However, these desilylation techniques have only been applied to the cleavage of aliphatic or benzylic TBDMS protected hydroxyl groups. This section will review the known methods of desilylation of silyl ethers using palladium catalysts.

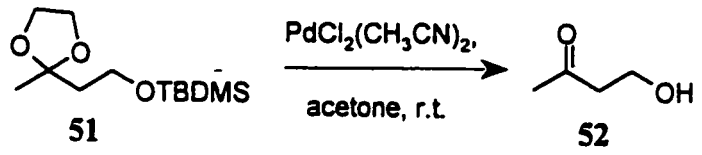
Cormier[19] has developed methodology using a catalytic transfer hydrogenation for the removal of TBDMS ethers. The TBDMS protected alcohol was treated with a catalytic quantity of palladium (II) oxide in a refluxing mixture of methanol and cyclohexene (Scheme 1.7). The main benefit of Cormier's[19] method was that the workup consisted of simple filtration and evaporation of the solvent. The desilylation products **46**, **48**, and **50** were isolated in good to excellent yields.

Scheme 1.7



In a recent report on an acetal/ketal hydrolysis/exchange reaction using catalytic quantities of $PdCl_2(CH_3CN)_2$, Lipshutz *et al.*[20] observed that in addition to the expected loss of the ketyl group, the TBDMS group was also removed in compound **51** (Scheme 1.8). The *t*-butyldiphenylsilyl (TBDPS) protecting group was shown to be inert to the reaction conditions; however, the authors did not explore further the scope and limitations of this reaction.

Scheme 1.8

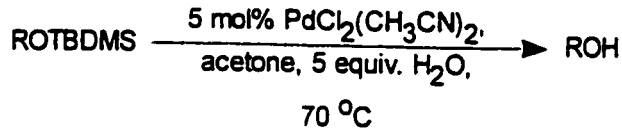


51 52

$PdCl_2(CH_3CN)_2$ has also been developed as an effective reagent for the removal of aliphatic and benzylic TBDMS ethers as part of a new one-pot desilylation/oxidation procedure of TBDMS aliphatic ethers.[21] The scope and limitations of the desilylations of primary and secondary TBDMS ethers were discussed. The optimized desilylation conditions involved refluxing the TBDMS ether in acetone containing 5 equivalents of water, with 5 mol% $PdCl_2(CH_3CN)_2$ (Table 1.4, entries 1-5). The workup for the desilylation procedure was relatively straightforward, and entailed removing the acetone *in vacuo* followed by distillation or flash chromatography of the residual oil. A variety of TBDMS ethers were removed in good to excellent yields.

The desilylation technique was shown not to be limited to the cleavage of the TBDMS group (Table 1.5, entries 4, 6 and 7), and did show some selectivity over several protecting groups (Table 1.5, entries 1-3 and 5). In addition to the loss of the TBDMS group, the tetrahydropyran (THP) and acetyl protecting groups were removed in moderate yield. These results illustrated that the TBDMS protecting group can be taken off in the presence of triisopropylsilyl (TIPS), TBDPS, methoxymethyl (MOM) and benzyl protecting groups in good to excellent yields. Although numerous aliphatic examples were reported, the desilylation of aryl silyl ethers was not discussed.

Table 1.4 Desilylation of Primary and Secondary TBDMS Ethers.



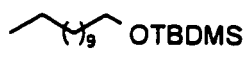
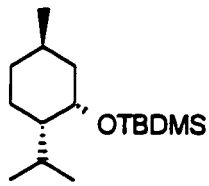
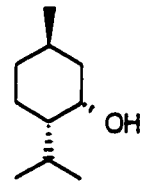
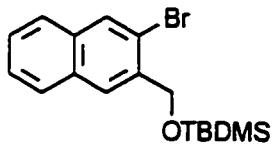
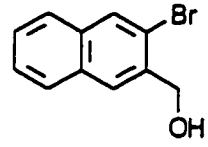
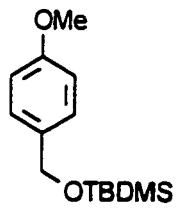
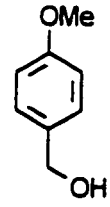
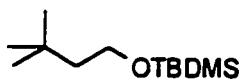
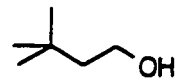
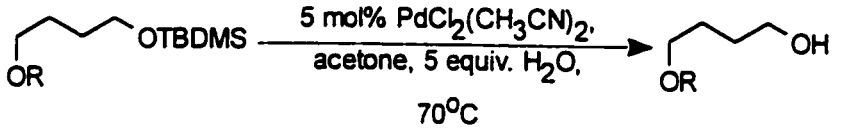
Entry	Starting Material	Time (h)	Product	% Yield[a]
1	 **53**	14	 **54**	91
2	 **55**	14	 **56**	80
3	 **57**	16	 **58**	73
4	 **59**	12	 **60**	82
5	 **61**	18	 **62**	86

Table 1.5 Compatibility of the Optimized Desilylation Conditions with Other Protecting Groups.



Entry	R	% Yield
1	$SiEt_3$	56
2	$Si(i\text{-}Pr)_3$	80
3	$Si(t\text{-}Bu)Ph_2$	81
4	MOM	78[a]
5	Bn	80
6	THP	61[a]
7	Ac	65[a]

[a] Diol present by GC.

1.2.2 Project Objectives.

A major limitation for the removal of TBDMS protected phenols is the sensitivity of the substrates towards the basicity of reagents which can potentially lead to complex mixtures. Whereas three methods for the desilylation of aliphatic TBDMS silyl ethers using catalytic quantities of palladium (II) catalysts have been reported[19,20,21] (Section 1.2.1), the methodology has not been applied to aryl TBDMS protected ethers. Thus, it could be rationalized that the use of mild Lewis acids like palladium (II) catalysts might be effective for the desilylation of TBDMS protected phenols.

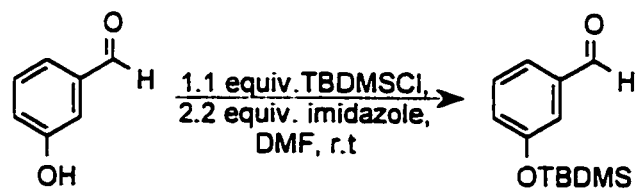
The use of a palladium catalyst may offer two advantages in the removal of a silyl group from a phenolic silyl ether. First, the reaction was performed under relatively mild Lewis acidic conditions and second, the workup of the reaction does not require an

aqueous wash. Higher yields of the corresponding phenols should be possible and perhaps the myth that TBDMS phenolic ethers are difficult to desilylate could be dispelled. Therefore, the development of a potential new method for the removal of TBDMS protected phenols involving catalytic quantities of palladium catalysts was investigated. The results are discussed in the following section.

1.2.3 Scope and Limitations.

It was important to determine if the optimized desilylation conditions for aliphatic silyl ethers could be applied to aryl silyl ethers. Thus, initial studies were done with 3-(*t*-butyldimethylsilyloxy)benzaldehyde (**64**). Once optimized conditions were found for **64**, they would be applied to a variety of other phenolic TBDMS ethers. The protected phenol **64** was produced 98% yield from 3-hydroxybenzaldehyde (**63**), by treatment with *t*-butyldimethylsilyl chloride in DMF containing imidazole (Scheme 1.9).[1] The formation of **64** was confirmed by analyzing the ^{1}H-NMR spectrum.[22]

Scheme 1.9



63 **64**

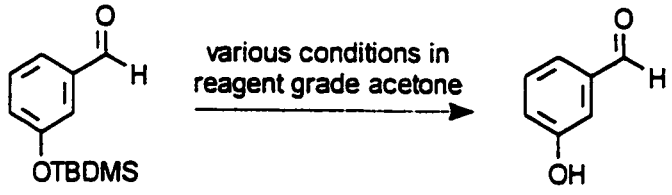
The first attempt to desilylate 3-(*t*-butyldimethylsilyloxy)benzaldehyde (**64**) employed the optimized aliphatic TBDMS ether desilylation conditions. Refluxing a

mixture of **64** with 5 mol% $PdCl_2(CH_3CN)_2$ in reagent grade acetone containing 5 equivalents of water (Table 1.6, entry 1), provided phenol **63** with an isolated 76% yield.

The amount of palladium (II) catalyst was varied to determine its effect on the reaction. The solvent and quantity of water were kept constant while the amount of the palladium (II) catalyst was gradually reduced (entries 1-4). The decrease in palladium (II) catalyst from 5 mol% to 1 mol% (entries 1-3) resulted in a minor lowering of the yield of desilylated product **63**; however, it was noted that the reaction time increased when less $PdCl_2(CH_3CN)_2$ was used (compare entries 1 and 3).

Since there was little or no significant correlation between the reduction in the amount of $PdCl_2(CH_3CN)_2$ and the yield of product **63**, it was proposed that perhaps $PdCl_2(CH_3CN)_2$ was not required for desilylation. It was reasoned that the water may be performing a simple S_N2 displacement of the TBDMS group. This hypothesis was disproved by performing the reaction in the absence of $PdCl_2(CH_3CN)_2$. Only a minor amount of the desilylated product **63** (16%) was detected (entry 4).

Table 1.6 Results from the Desilylation of 3-(*t*-Butyldimethylsilyloxy)benzaldehyde Using a Variety of Conditions.



64 63

Entry	Scale (g)	Catalyst (mol%)	Time (h)	Temp. (°C)[d]	Amount of H_2O	Yield (%)[b]
1	0.350	$PdCl_2(CH_3CN)_2$ (5)	16	75	5 equiv.	76
2	0.300	$PdCl_2(CH_3CN)_2$ (3)	17	75	5 equiv.	76
3	0.313	$PdCl_2(CH_3CN)_2$ (1)	19	75	5 equiv.	74
4	0.260	none	120	75	5 equiv.	16[c]
5	0.150	$Pd(PPh_3)_4$ (5)	19	75	5 equiv.	40
6[e]	0.150	$Pd(PPh_3)_4$ (5)	19	75	5 equiv.	0
7	0.150	$PdCl_2$ (5)	18	75	5 equiv.	70
8	0.303	$PdCl_2(CH_3CN)_2$ (5)	30	75	none	10[c]
9	0.350	$PdCl_2(CH_3CN)_2$ (5)	16	23	5 equiv.	57
10	3.000	$PdCl_2(CH_3CN)_2$ (5)	18	75	5 equiv.	72

[a] Reagent grade acetone purchased from Van Waters and Rogers/Canlab (Edmonton, AB., Canada) was used as solvent. [b] Isolated yields. [c] Decomposition noted. [d] Oil bath temperature. [e] Three attempts performed with these conditions.

Next, the use of a variety of different palladium catalysts was investigated. Although, $Pd(PPh_3)_4$ did initially show a promising result (Table 1.6, entry 5), further attempts with palladium (0) catalysts did not afford product **63** (Table 1.6, entry 6); only starting material was detected. The initial success of the desilylation with $Pd(PPh_3)_4$ in wet acetone was believed to be due to trace amounts of palladium (II), since subsequent reactions were performed from both freshly prepared catalyst[23] and a new bottle of the catalyst. In contrast, ligandless $PdCl_2$ did desilylate TBDMS group to phenol **63** in 70% (Table 1.6, entry 7), indicating the acetonitrile ligands were not necessary for the reaction to proceed.

The reaction temperature and the quantity of water appeared to effect the yield of the product **63**. Performing the reaction at room temperature (~23 °C), resulted in a significant drop in the product yield from 76% to 57% (compare entries 1 and 9 in Table 1.6). Thus, it appeared that the optimum temperature for the desilylation conditions was 75 °C. Similarly, a low yield of 10% was obtained when the desilylation reaction was performed in the absence of water (Table 1.6, entry 8). The reaction also took longer when less water was used (see Section 1.2.4) and the workup became more difficult as the amount of water was increased. Five equivalents of water appeared to provide the optimum amount for the desilylation reaction to occur; however, a kinetic study on the effect of the amount of water on the rate of the reaction was needed to prove or disprove this observation and results from a kinetic study will be discussed in Section 1.2.4.

The optimized conditions for the desilylation of 3-(*t*-butyldimethylsilyloxy)benzaldehyde (**64**) were mixing **64** with 5 mol% $PdCl_2(CH_3CN)_2$

in acetone containing 5 equivalents of water and refluxing the mixture for 16 h. A large scale reaction (Table 1.6 entry 10) was attempted on 3 g of **64** and **63** was obtained in 72% yield. The workup for the desilylation procedures were very simple. The acetone was removed *in vacuo* and the resultant oil was purified by distillation or by flash chromatography.

A variety of silylated phenols (Table 1.7) was prepared by known methods in order to determine the scope and limitations of the desilylation procedure. The silylated phenols were prepared by treatment of the corresponding phenol with *t*-butyldimethylsilyl chloride in DMF, in the presence of imidazole.[1] Silyl ethers **29**, **9**, and **65-77** (odd numbers) were then treated using the optimized desilylation conditions (Table 1.6, entry 1), and the results are listed in Table 1.7.

Some comments are noteworthy. Compounds **29**, **9**, **65-77** (odd numbers) provided their respective phenols in good to excellent yields. Interestingly, **77** gave **78** in poor yield. The steric size of the *t*-butyl groups may be hindering the attack of the silane by water or coordination of the palladium (II) catalyst to the oxygen atom.

A number of functional groups were tolerated during this reaction (Table 1.6 and Table 1.7). The phenolic TBDMS group was removed in the presence of aldehydes, ketones, esters, a bromide, and a nitro group. A silyl ester **69** was also cleaved to its corresponding carboxylic acid **70**. Surprisingly, **73** provided hydroquinone **74** in 79% yield. Oxidation to benzoquinone in the presence of palladium was not observed. Thus, a mild, essentially neutral method for removing TBDMS phenolic ethers has been developed. The reaction is easy to perform, high yielding and appears to be general. The

next step involved determining if TBDMS phenolic ethers could be cleaved in the presence of aliphatic TBDMS ethers.

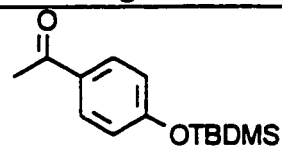
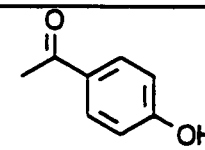
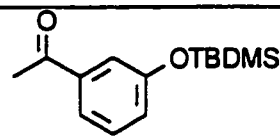
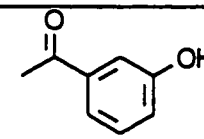
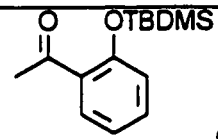
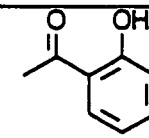
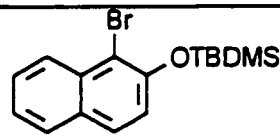
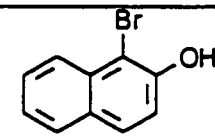
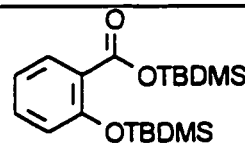
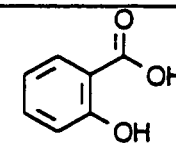
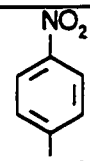
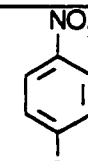
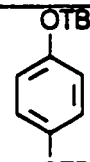
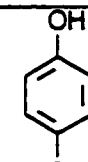
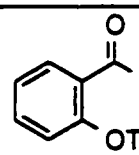
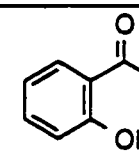
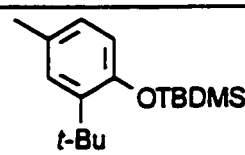
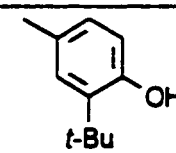
Previous work had shown that aliphatic and benzylic TBDMS ethers can also be cleaved in good to excellent yields with $PdCl_2(CH_3CN)_2$, in reagent grade acetone containing 5 equivalents of water at reflux.[21] Model compound **80**, bearing both a TBDMS protected phenol and a benzylic TBDMS protected alcohol, was prepared to determine if the above desilylation conditions would be selective for the removal of the phenolic TBDMS ether in the presence of benzylic TBDMS ether. Di-TBDMS protected β-estradiol **80** was synthesized from β-estradiol (**79**) using standard conditions (Scheme 1.10).[1] Di-silylated compound **80** was treated with $PdCl_2(CH_3CN)_2$, in reagent grade acetone containing 5 equivalents of water at reflux and produced β-estradiol (**79**) in 86% yield (Scheme 1.10). This experiment confirmed that the optimized conditions would not lend themselves for selectivity between benzylic and phenolic TBDMS ethers.

The success in the development of the desilylation of 3-(*t*-butyldimethylsilyloxy)-benzaldehyde (**64**) using $PdCl_2(CH_3CN)_2$ lead to the investigation of what type of phenolic silyl ether protecting groups could be removed under these conditions. Phenolic silyl ethers **81**, and **83-86** were synthesized according to literature procedures.[1] The phenolic silyl ethers **81**, and **83-86** were treated under the optimum desilylation conditions (Table 1.6, entry 1), and the results are summarized in Table 1.8. In addition to the desilylation of the TBDMS protecting groups, both the TMS and TES protecting groups were removed (Table 1.8, entries 1 and 2); the TIPS and TBDPS phenolic ethers were not cleaved with the optimized conditions (entries 4 and 5). Thus, it should be

possible to selectively remove TMS, TES, and TBDMS protected phenols in the presence of TIPS or TBDPS phenolic ethers.

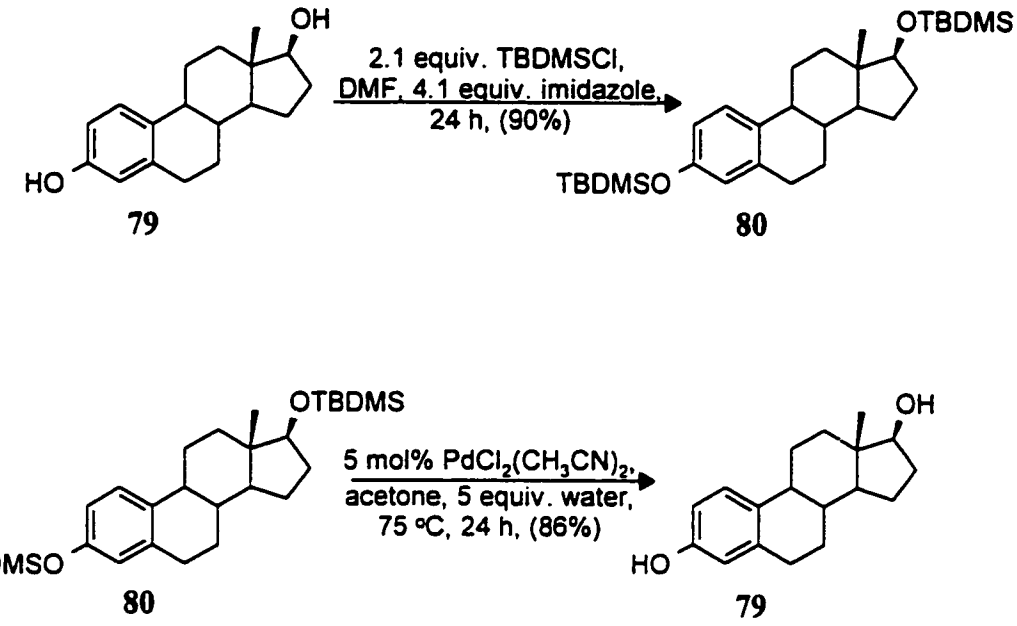
With the scope and limitations of the desilylation conditions thoroughly investigated, the focus shifted to a kinetic study of the desilylation. The next section will discuss a kinetic study on what effect the amount of water has on the rate of the reaction. This will lead to a discussion on a possible mechanism for the desilylation reaction.

Table 1.7 Results from the Desilylation of Various Phenolic Silyl Ethers.

Entry	Starting Material	Time (h)[a]	Product	Yield (%)
1	 **29**	16	 **30**	96
2	 **9**	16	 **8**	88
3	 **65**	14	 **66**	86
4	 **67**	24	 **68**	75
5	 **69**	12	 **70**	88
6	 **71**	19	 **72**	89
7	 **73**	19	 **74**	79
8	 **75**	12	 **76**	92
9	 **77**	48	 **78**	10[b]

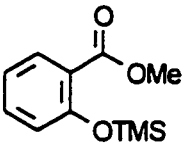
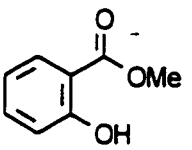
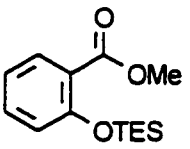
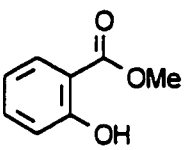
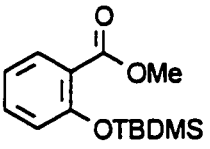
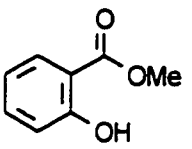
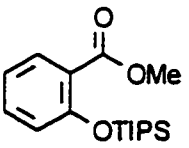
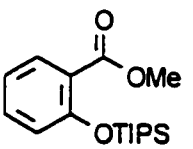
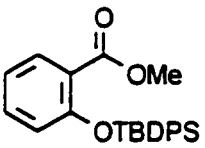
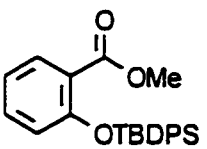
[a] All reactions were performed in reagent grade acetone containing 5 equivalents of water, and 5 mol% $PdCl_2(CH_3CN)_2$ at 75 °C. [b] The remainder was unreacted starting material.

Scheme 1.10



79 80 80 79

Table 1.8 Results of the Desilylation of Silyl Ethers 88, 90-93.

Entry	Starting Material	Time (h)[a]	Product	Isolated Yield (%)
1	 **81**	14	 **82**	93
2	 **83**	14	 **82**	74
3	 **84**	14	 **82**	90
4	 **85**	14	 **85**	no reaction
5	 **86**	14	 **86**	no reaction

[a] All reactions were performed in reagent grade acetone containing 5 equivalents of water, and 5 mol% $PdCl_2(CH_3CN)_2$ at 75 °C.

1.2.4 Kinetic Study: Results and Discussion.

In order to deduce the mechanism of desilylation using $PdCl_2(CH_3CN)_2$, a kinetic study was performed in an attempt to determine the order of the reaction with respect to the concentration of water and phenolic silyl ether.

For a simple chemical reaction (Eq. 1), the rate equation can be expressed as shown in Eq. 2. Experiments can be performed to calculate the value of x and y; i.e. the order of the reaction with respect to A and B.

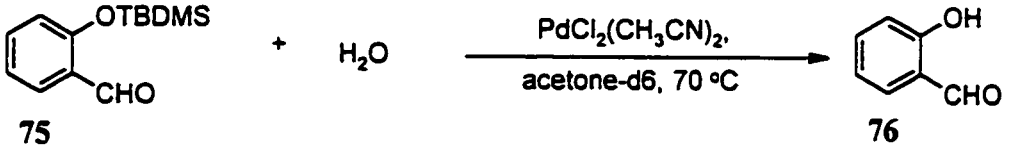
	$A + B \rightarrow C$	Eq. 1
	$Rate = k\,[A]^x\,[B]^y = d[C]/dt$	Eq. 2
where:	k is the rate constant	
	x is the order of reaction with respect to A, and	
	y is the order of reaction with respect to B.	

Using the method of initial rates it is possible to deduce x and y. If the concentration of one species is kept constant (e.g. [B]) while the other ([A]) is varied then a plot of [C] vs. time provides the initial rate of the reaction from the slope of the graph (the slope is measured over "very" short initial time periods) for a given concentration of one species ([B]). The concentration of this species is then varied and the dependence of [C] on time is measured again and plotted as above. Eventually, a number of initial rates for given concentrations of a species is obtained. These data are usually plotted as initial rate vs. $[A]^1$, and if a straight line is obtained, the order of reaction with respect to [A] is

one. If a curve is obtained, the initial rate is plotted vs. $[A]^x$ whereby x is varied until a straight line is obtained, thus providing the order of the reaction with respect to [A]. The above set of experiments and plots are repeated for each species (i.e. [B]) in the chemical reaction, which ultimately leads to the order of the reaction with respect to each reagent.

For the desilylation reaction of phenolic silanes with $PdCl_2$ substrate **75** was chosen (Scheme 1.11) as the formation of product could be easily monitored by ^{1}H-NMR (400 MHz), since the aldehyde protons of **75** and **76** had different chemical shifts in acetone-d_6. Studying the rate of desilylation by NMR also offered some additional advantages. (a) The reaction could be performed in a sealed tube, thus the total volume of liquid was kept constant and the concentration of species did not change over time due to evaporation of solvent. (b) The reaction could be performed at a constant temperature of 70 °C. (c) A workup is not required since the amount of product formed can measured directly from the NMR spectrum. (d) The ratio of starting material to product could be directly measured by integration of the NMR spectrum. (e) The desilylation solvent acetone is readily available as acetone-d_6, thereby reducing the NMR signals due to solvent and simplifying interpretation of the NMR spectrum.

Scheme 1.11



75 **76**

Rate of Formation of **76** = k_1 $[75]^x$ $[H_2O]^y$ Eq. 3

where: k_1 is the rate constant in the presence of $PdCl_2(CH_3CN)_2$

The order of reaction with respect to water was determined first. To a solution of phenolic silyl ether **75** in dry acetone-d_6 (in an NMR tube) was added a freshly prepared solution of $PdCl_2(CH_3CN)_2$ in dry acetone-d_6. An amount of water (0-5 equivalents) was added and the NMR tube was sealed and placed in the NMR probe preheated at 70 °C. The ^{1}H-NMR spectrum was recorded every hour over a period of 4 hours and the molar ratio of **75**:**76** was calculated from integration of the two aldehyde protons. The integration error was estimated to be approximately 10% and this is reflected throughout the calculations. The [**76**] vs. time was plotted and the slope of the line at early times provided the initial rate of reaction for each of the six concentrations of water (Table 1.9).[24]

Table 1.9 Initial Rate Data for the Formation of 76 Using Six Different Concentrations of Water.

Equiv. Water	Initial Rate of Formation of 76[25] (h^{-1})
0	$(1.15 \pm 0.83) \times 10^{-2}$
1	$(1.88 \pm 0.14) \times 10^{-2}$
2	$(2.66 \pm 0.07) \times 10^{-2}$
3	$(4.13 \pm 0.04) \times 10^{-2}$
4	$(7.34 \pm 0.01) \times 10^{-2}$
5	$(1.03 \pm 0.01) \times 10^{-1}$

To determine the order of reaction with respect to water, the initial rate was plotted against the [equivalence of water]^1 (Figure 1.1); however, the data obtained with zero equivalents of water was excluded from the regression (this will be explained later). Although the graph appears curved (linear regression (R) of 0.970), a "best fit analysis" gave an exponential value of 1.06 (Figure 1.2, R = 0.973). This value indicated that the

reaction was essentially first order with respect to water (i.e. Initial Rate = k [75]^{x} [H_2O]^{1}).

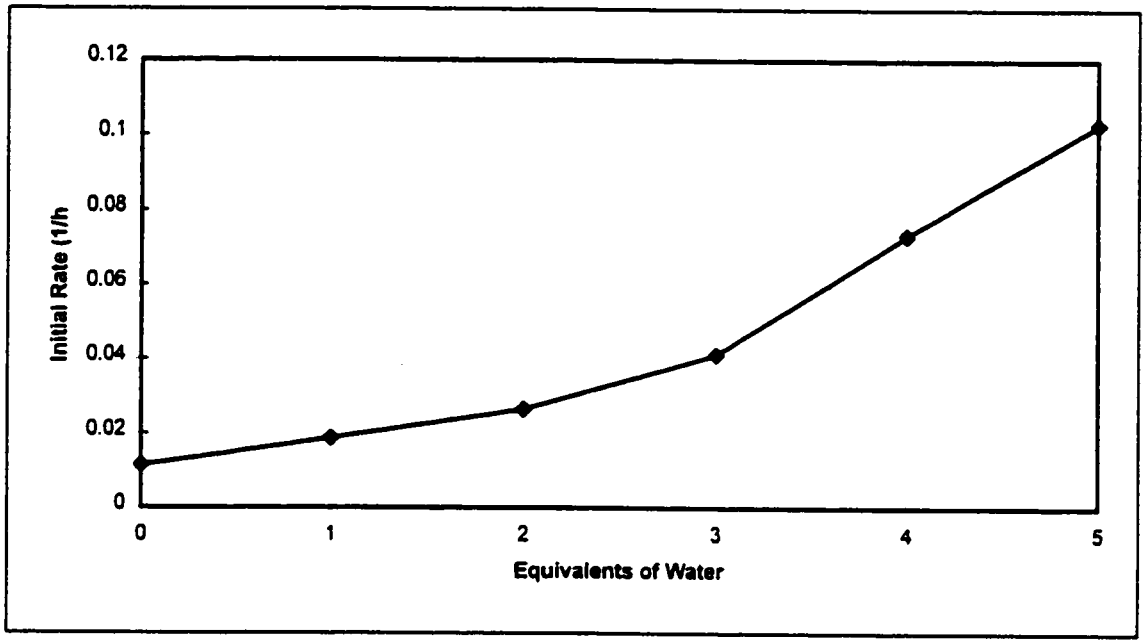


Figure 1.1 Graph of Initial Rate of Formation of 76 vs. [Equivalents of Water]$^{1.00}$ (error bars not shown).

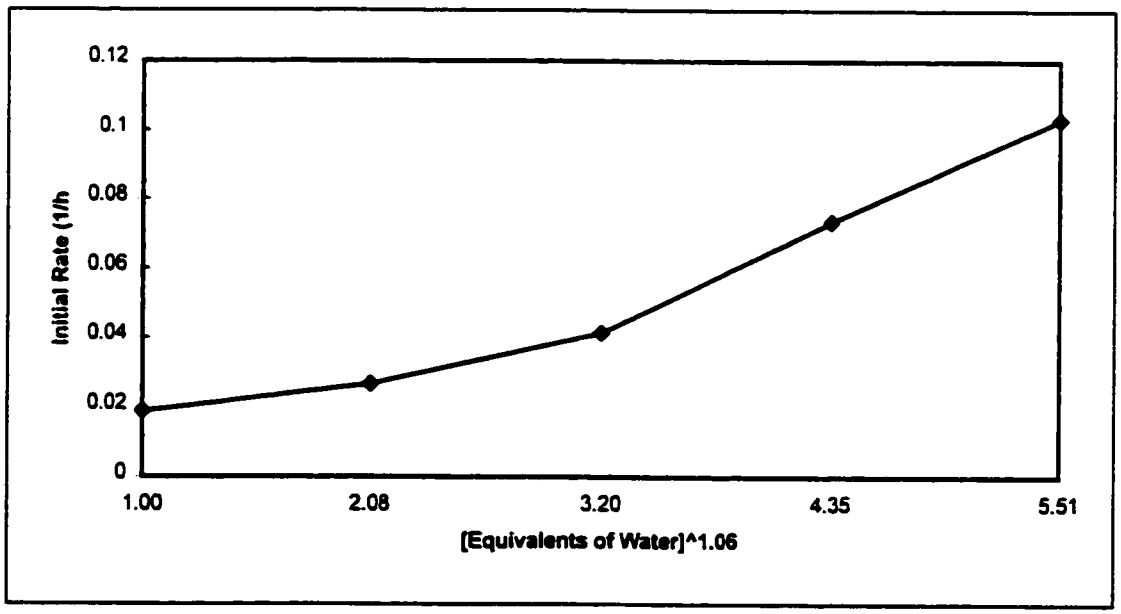


Figure 1.2 Graph of Initial Rate of Formation of 76 vs. [Equivalents of Water]$^{1.06}$ (error bars not shown).

Now that the rate of formation of **76** has been shown to be first order with respect to water, the next goal was to determine the order of reaction with respect to **75**. Closer examination of the data collected in the absence of water indicated that the reaction does proceed without water, but at a slow rate. This observation in conjunction with others (*vide infra*) suggests that the rate expression for the reaction is not as simple as equation 3 (Scheme 1.11). Thus, the order of reaction with respect to **75** was not measured.

Discussion of the Desilylation and Kinetic Results: A Possible Mechanism Unfolds.

Although the rate expression was initially believed to be represented by equation 3 for the desilylation, other experiments suggested the rate expression is more complicated. This conclusion was derived as follows.

(1) In the absence of water, the initial rate of reaction was found to be 1.15×10^{-2} h^{-1}, which is very close to the value obtained when 1 equivalent of water was used (1.88×10^{-2} h^{-1}, Table 1.9). Thus, the reaction proceeded without water and a second term in the rate expression needed to be added to reflect this observation (Eq. 4).

$$\text{Rate} = k_1 [\mathbf{75}]^x [H_2O]^y + k_2 [\mathbf{75}]^z \qquad \text{Eq. 4}$$

where: k_2 is the rate constant in the absence of water and in the presence of $PdCl_2(CH_3CN)_2$

(2) Earlier, it was reported that **64** provided a small amount of **63** (16%) in the absence of $PdCl_2(CH_3CN)_2$ and in the presence of 5 equivalents of water (Table 1.9). There is no reason to suspect that the same could not occur with **75**; therefore, a third term was added to the rate expression (Eq. 5).

$$\text{Rate} = k_1 [75]^x [H_2O]^y + k_2 [75]^z + k_3 [75]^a [H_2O]^b \qquad \text{Eq. 5}$$

where: k_3 is the rate constant in the absence of $PdCl_2(CH_3CN)_2$ and in the presence of water.

(3) During the kinetic measurements an interesting observation was noted. Initially, a stock solution of $PdCl_2(CH_3CN)_2$ dissolved in acetone-d_6 was prepared. The rate of reaction was measured first using 5 equivalents of water and the freshly prepared stock solution (yellow-orange in color). The data were recorded and a second experiment using 4 equivalents of water and the stock solution (now 5 hours old, orange in color) was started. The data indicated that the rate was initially faster than that measured with 5 equivalents of water! This was somewhat confusing so a third experiment was tried using 3 equivalents of water and the stock solution (now 10 hours old and red in color). The initial rate was found to be approximately 6 times that observed when the stock solution was freshly prepared (compare $[(4.13 \pm 0.21) \times 10^{-2}\ h^{-1}]_{\text{fresh catalyst}}$ vs. $[(23.9 \pm 0.12) \times 10^{-2}\ h^{-1}]_{\text{aged catalyst}}$)!

A simple NMR experiment indicated that a change in the catalyst was occurring. $PdCl_2(CH_3CN)_2$ was added to acetone (yellow-orange solution) and stirred at room temperature for 8 hours. The solution (orange) was filtered through glass wool and the acetone removed *in vacuo*. An NMR spectrum was obtained in $CDCl_3$ and compared to the NMR spectrum of $PdCl_2(CH_3CN)_2$ (in $CDCl_3$) (Figure 1.3). The addition of new peaks in the NMR spectrum from the aged catalyst, indicated that a change did occur in the palladium catalyst, presumably by the replacement of one (or both) of the acetonitrile

ligands by acetone (or some other species formed by self-aldol condensations with acetone). Thus, an additional term should be added to the rate expression (Eq. 6).

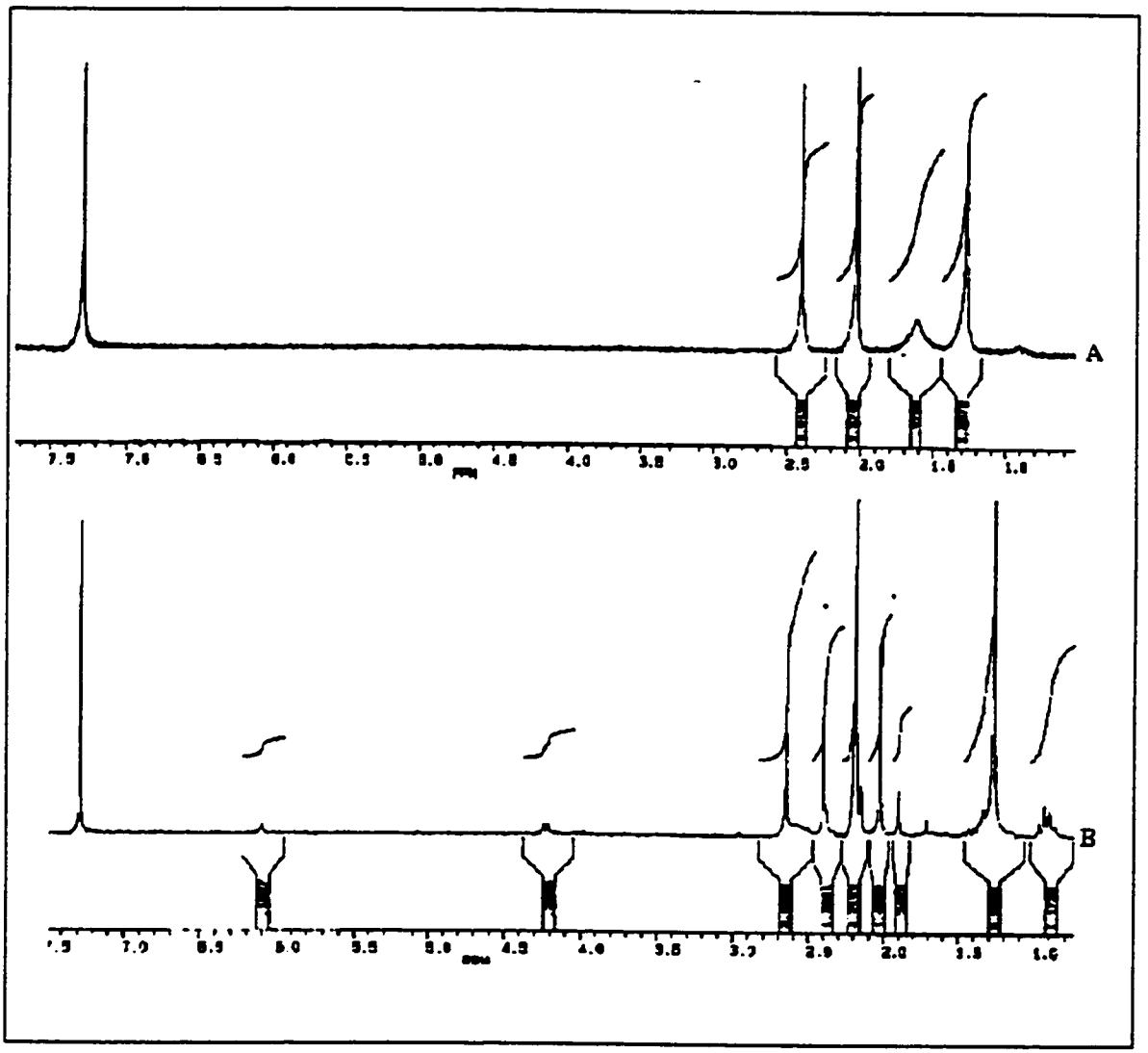


Figure 1.3 ^{1}H-NMR of $PdCl_2(CH_3CN)_2$ (A) and Unknown Palladium Complex (B).

$$\text{Rate} = k_1 [75]^x [H_2O]^y + k_2 [75]^z + k_3 [75]^a [H_2O]^b + k_4 [75]^c [H_2O]^d \quad \text{Eq. 6}$$

where: k_4 is the rate constant in the presence of an altered palladium catalyst.

In addition to the above observation that the acetone appears to be changing the structure of the catalyst, the possibility exists that water could also be reacting with the

$PdCl_2(CH_3CN)_2$. Experiments have not been performed to support this idea; however, if water does alter the catalyst, then the rate expression would become even more complicated.

The above results indicate that rate equation may not be as simple as the one expressed in equation 3. The interpretation of the kinetic data to state explicitly that the order of reaction is one with respect to water; therefore, may be stretching the limit. If, however, the rate constants k_2-k_4 are extremely small compared to k_1, then the latter terms would approach zero and one could argue that the reaction is first order in water. This will be assumed to be true when the mechanism of the reaction is discussed. Nevertheless, more work is required to provide evidence to support (or negate) the above alterations of the rate expression and some suggestions for future experiments are outlined in Section 1.2.6.

A number of mechanisms can be proposed based on the results obtained for this thesis. These will be outlined below.

The desilylation does proceed in the absence of a palladium catalyst when performed in acetone containing 5 equivalents of water. The reaction is slow and low yielding. Presumably, water acted as a Lewis acid and protonated the oxygen atom. Attack by a second molecule of water at the silicon atom results in displacement of the phenol (Eq. 7, Scheme 1.12).

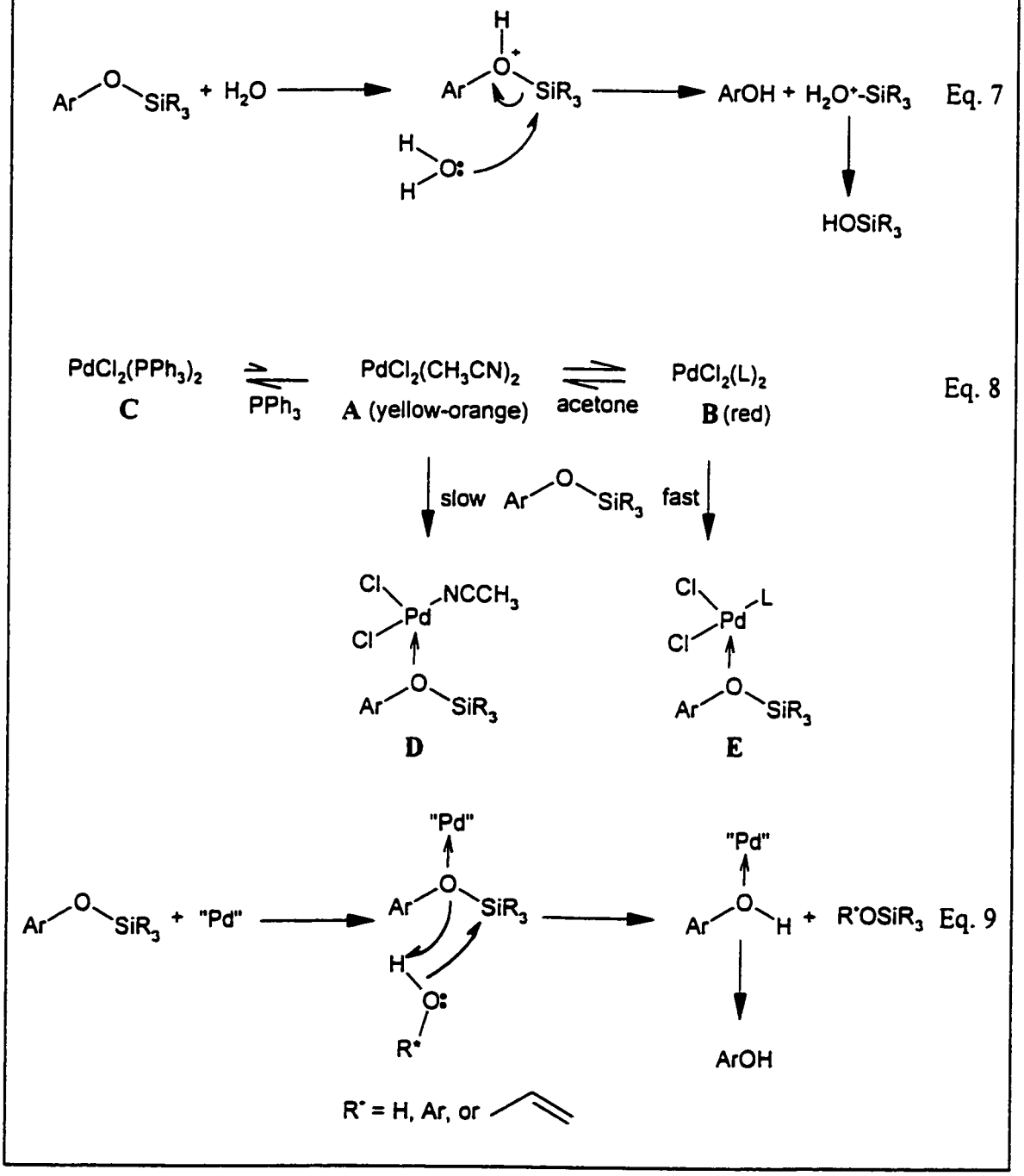
The mechanism of the desilylation in the presence of a palladium catalyst is complicated since it appears that the structure of the palladium catalyst is altered in acetone. In addition, if phosphines are added to the solution, the reaction essentially does

not proceed (observation obtained *vide infra*). Equation 8 illustrates a possible equilibration of the catalyst prior to the desilylation reaction. The lack of a reaction in the presence of phosphine ligands, can be explained on the lowering of the Lewis acidity of the palladium catalyst, due to the presence of the highly basic ligands (i.e. **C** is not an active catalyst). In the presence of $PdCl_2(CH_3CN)_2$, the palladium is somewhat Lewis acidic towards the oxygen atom of the silyl ether, and at early times of the reaction, coordinates to the oxygen atom of the substrate by loss of one acetonitrile ligand to provide **D**. As the desilylation reaction proceeds, the acetone reacts with the $PdCl_2(CH_3CN)_2$ to form a new catalyst **B**, whose structure is not known at this time. Catalyst **B** reacts faster with the silyl ether than the $PdCl_2(CH_3CN)_2$. Presumably, the equilibrium between **A** and **B** is shifted towards **B** in the presence of excess acetone (i.e. the solvent), and this catalyst coordinates to the oxygen atom of the silyl ether faster than **A** (since the ligand(s) is more labile than acetonitrile) and the reaction is accelerated (Eq. 8, Scheme 1.12).

All the remaining mechanisms will involve coordination of a palladium catalyst with the oxygen atom of silyl ether. The catalyst will be designated as "Pd" since its actual structure is not know at this time. The coordination of a catalyst to the oxygen atom results in a weakening of the O-Si bond and attack by a nucleophile at the silicon atom results in the breaking of the O-Si bond. The nucleophile in the absence of water could be either the enol of acetone, or later in the reaction, the phenol (Eq. 9, Scheme 1.12). In the presence of water, it is assumed that the nucleophile is water as the rate of reaction was shown to be first order in water. Although the mechanism is unknown at the

present time, the desilylation of phenolic silyl ethers provides the corresponding phenol in good to excellent yields.

Scheme 1.12



1.2.5 Conclusions.

A simple, inexpensive, neutral procedure for the cleavage of TBDMS phenolic silyl ethers in good to excellent yields has been developed. The desilylation method also has the advantage that it avoids the use of specialized equipment and does not require an aqueous workup.

The reaction temperature, amount of water, and amount of catalyst appears to effect the reaction. As the temperature and amount of water decrease, the yield decreases and reaction time increases. When the amount of catalyst used decreases, longer reaction times are required and the reaction will not proceed without a palladium (II) catalyst.

The scope and limitations using the optimized desilylation conditions indicated that a variety of functional groups (aldehydes, ketones, esters, bromides, and nitro groups) were tolerated; however, a low yield was observed when bulky *ortho* substituents were present. The optimized desilylation conditions were also found to desilylate TMS and TES phenolic ethers, while TIPS or TBDPS protecting groups were tolerated under the reaction conditions.

1.2.6 Future Considerations.

The future direction of this project should be focused on determining the mechanism of the desilylation reaction. In order to begin to understand the mechanism, more kinetic studies are required. These studies could involve determining whether the

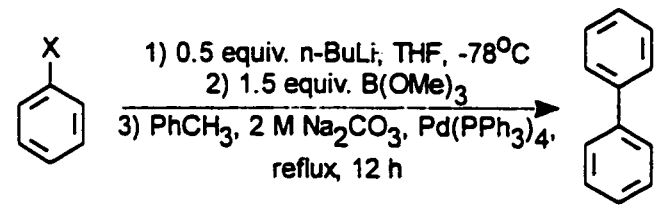
reaction is first or second order in silyl substrate, comparing and contrasting the effects of aging the palladium catalyst, and attempting the same kinetic studies with alkyl silyl ethers. The latter would determine if both phenolic and alkyl silyl ethers proceed with the same mechanism. In addition, if $PM3_{TM}$ calculations were performed, they may indicate whether the palladium was coordinated to the oxygen or the silicon atom, and whether the O-Si or the O-C bond lengths increase. Finally, determining the identity of the "active" and/or the aged catalyst could provide insight into the reaction mechanism.

1.3 Desilylation of Phenolic Silyl Ethers Using Mild Base Conditions.

1.3.1 Background: The Development of a Desilylation of Phenolic Silyl Ethers Using a Mild Base.

The cross-coupling of aryl halides (or triflates) with aryl boronic acids, using palladium catalysts, has been shown to be an effective method for the preparation of biaryls.[26] Recently, Andersen *et al.* have developed a modified *in situ* Suzuki cross-coupling of haloarenes for the preparation of C_2-symmetric biaryls.[27] This involved treating the haloarene with 0.5 equivalents of *n*-BuLi followed by the addition of $B(OMe)_3$. Presumably, this formed a 1:1 molar ratio of haloarene:arylboronate. Subsequent addition of $Pd(PPh_3)_4$ and Na_2CO_3, followed by refluxing the solution provided C_2-symmetric biaryls in good to excellent yields (Table 1.10). In order to further develop the reaction the use of various solvent mixtures were investigated. Eventually, a mixture of 3:3:1 toluene, ethanol, and water provided C_2-symmetric biaryls in good to excellent yields. The modified *in situ* Suzuki cross-coupling conditions tolerated a variety of functional groups, including; esters, ether, amides, acetals, and nitriles. In one example, the TBDPS protecting group was removed (Scheme 1.13). This result led to the question of whether the modified *in situ* Suzuki cross-coupling conditions could be used as a new method for the removal of TBDMS phenolic silyl ethers, using a palladium (0) catalyst instead of a palladium (II) catalyst.

Table 1.10 Initial Results of the *in Situ* Suzuki Coupling Conditions.[27]

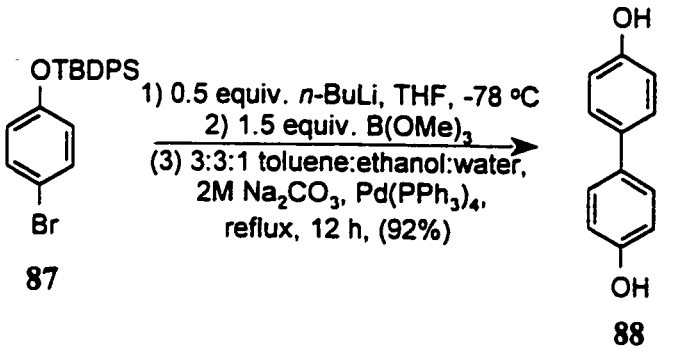


X = Br, I

Entry[a]	Haloarene	Base	Product (% yield)[b]
1	iodobenzene	2 M Na_2CO_3	biphenyl (73)
2	iodobenzene	$Ba(OH)_2$	biphenyl (80)
3	bromobenzene	$Ba(OH)_2$	biphenyl (85)
4	2-bromotoluene	2 M Na_2CO_3	2,2'-dimethyl-biphenyl (40)
5	2-bromoanisole	$Ba(OH)_2$	2,2'-dimethoxy-biphenyl (56)
6	1-iodo-2-methoxy-naphthalene	2 M Na_2CO_3	2,2'-dimethoxy-1,1'-binaphthyl (<10)

[a] Toluene solvent for all entries. [b] Isolated yields.

Scheme 1.13



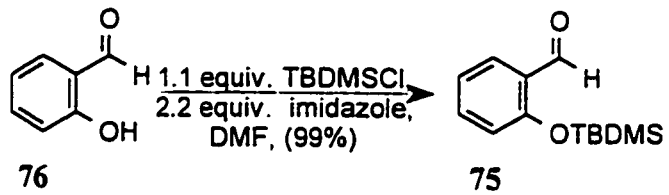
1.3.2 Project Objectives.

Whereas the work by Andersen *et al.*[27] indicated that aryl silyl ethers could potentially be removed under the optimized *in situ* Suzuki cross-coupling conditions (Section 1.3.1), this reaction was not investigated further. Interestingly, the optimized *in situ* Suzuki cross-coupling conditions indicated that $Pd(PPh_3)_4$ may be an active component in the removal of phenolic silyl ethers. This observation was in contrast to the desilylation results obtained earlier, which showed that catalytic amounts of $Pd(PPh_3)_4$ in acetone containing 5 equivalents of water, does not desilylate phenolic silyl ethers. If the desilylation of phenolic silyl ethers proved to be possible with $Pd(PPh_3)_4$, then it may be possible to selectively remove aryl silyl ethers in the presence of aliphatic silyl ethers. Therefore, an investigation was initiated to study the use of the *in situ* Suzuki cross-coupling conditions for the development of a new desilylation reaction. If successful, then the scope and limitations of the new desilylation procedure would be addressed.

1.3.3 Selective Deprotection of Phenolic Silyl Ethers Using Mild Base Conditions.

Initial studies on the optimization of the reaction conditions for the desilylation were performed on *o*-(*t*-butyldimethylsilyloxy)benzaldehyde (**75**) by changing the type and amount of palladium catalyst, base, solvent, and temperature (Table 1.11). *o*-(*t*-Butyldimethylsilyloxy)benzaldehyde (**75**) was produced in 99% yield from 2-hydroxybenzaldehyde (**76**) by treatment with *t*-butyldimethylsilyl chloride in DMF and containing imidazole (Scheme 1.14).[1]

Scheme 1.14



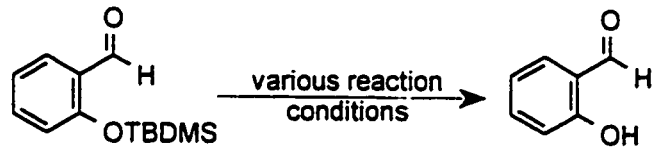
76 **75**

The first attempt to desilylate *o*-(*t*-butyldimethylsilyloxy)benzaldehyde (**75**) employed Andersen's modified *in situ* Suzuki conditions.[27] Compound **75** was treated with 2M Na_2CO_3, and $Pd(PPh_3)_4$ and refluxed in a 3:3:1 mixture of toluene, ethanol, and H_2O. Compound **76** was formed in 80% yield (entry 1, Table 1.11). Since the TBDMS group could be removed under these conditions, it was decided to investigate the reaction by changing the conditions to confirm the necessity of each reagent. To determine whether palladium (0) was necessary for the desilylation, it was removed from the reaction. Compound **76** was formed in 81% yield (Table 1.11, entry 2). This was not unexpected, since palladium (0) catalysts were previously ineffective in the removal of

silyl ethers (Section 1.2.3, Table 1.6, entry 6). Thus, the remaining experiments did not employ a palladium (0) catalyst. The next attempt involved reacting **75** with different bases in order to determine if Na_2CO_3 was the most effective base. Switching bases from a 2 M solution Na_2CO_3 to solid K_2CO_3 resulted in an increase in the overall yield (Table 1.11, entry 3). On the other hand, phenol **76** was obtained in only 5% yield upon removal of the base (Table 1.11, entry 4 and 8). This experiment indicated that the presence of base (K_2CO_3) was necessary for desilylation to occur.

At this point various solvents and temperatures were investigated and the results are summarized in Table 1.11. The removal of toluene from the 3:3:1 ethanol, toluene, and water mixture had no effect on the reaction (compare entry 5 with 3). When the reaction was conducted in refluxing absolute ethanol for 24 h, the yield of the phenol **76** was decreased from 90% to 60% (compare entries 5 and 6). In order to reduce the problems associated with water solubility of some phenols, the amount of water used in the reaction was reduced to only 5 equivalents (entry 7). This had the important impact of raising the overall desilylation yield from 90% to quantitative (compare entries 5 and 7, Table 1.11). Finally, it was determined that the reaction proceeded at room temperature. Stirring a mixture of **75** with 1.1 equivalents of K_2CO_3 in absolute ethanol containing 5 equivalents of water provided a 87% yield of 2-hydroxybenzaldehyde (**76**) after 18 h (entry 9); however, the time for the reaction increased from 12 to 18 hours.

Table 1.11 Desilylation Results Using a Variety of Conditions with 2-(*t*-Butyldimethylsilyloxy)-Benzaldeyde.



75 76

Entry	Scale	Base	Time (h)	Temp. (°C)	Solvent	Amount of H_2O	Yield (%)[a]
1[b]	100 mg	2 M Na_2CO_3	11	75	(3:3:1) ethanol:toluene :water	-	80
2	100 mg	2 M Na_2CO_3	12	75	(3:3:1) ethanol:toluene :water	-	81
3	100 mg	1.1 equiv. K_2CO_3[c]	12	75	(3:3:1) ethanol:toluene :water	-	90
4	100 mg	-	12	75	(3:3:1) ethanol:toluene :water	-	5[d]
5	100 mg	1.1 equiv. K_2CO_3[c]	12	75	(3:1) ethanol:water	-	90
6	100 mg	1.1 equiv. K_2CO_3[c]	24	75	ethanol	none	60[e]
7	100 mg	1.1 equiv. K_2CO_3	12	75	ethanol	5 equiv.	100
8	100 mg	none	120	75	ethanol	5 equiv.	16[e]
9	100 mg	1.1 equiv. K_2CO_3[c]	18	23	ethanol	5 equiv.	87
10	1 g	1.1 equiv. K_2CO_3[c]	12	75	ethanol	5 equiv.	70

[a] Isolated yields. [b] $Pd(PPh_3)_4$ added to reaction mixture. [c] Base added as a solid. [d] Heavy decomposition noted. [e] Unreacted starting material present.

From the above experiments, the optimized conditions for the desilylation of **75** were using 1.1 equivalents of K_2CO_3 in ethanol containing 5 equivalents of water at reflux (Table 1.11, entry 7). The optimized conditions were also used on a large scale reaction. Treatment of 1 gram of 2-(*t*-butyldimethylsilyloxy)benzaldehyde (**75**) (Table 1.11, entry 10), gave a 70% yield of **76** after 12 h. The workup of the reactions were very simple and did not require a wash with water. After TLC or G.C. indicated the silyl group had been removed, the mixture was filtered though Celite and the ethanol removed by a rotoevaporator to leave a residual oil, which was purified by distillation or flash column chromatography followed by distillation.

In order to determine the scope and limitations of the desilylation a variety of silylated phenols and alcohols were prepared as previously described (Scheme 1.9).[1] Silyl ethers **29**, **65**, **89**, **69**, **72**, **91**, **55**, and **61** were obtained in good to excellent yield and subsequently treated using the optimized desilylation conditions (Table 1.11, entry 7). The results are tabulated in Table 1.12.

The results show that a variety of functional groups are stable towards the optimized desilylation conditions (Table 1.11 and Table 1.12). The TBDMS phenolic ethers listed in Table 1.12 and **75** were cleaved in good to excellent yields in the presence of aldehydes, ketones, a bromide, and a nitro group. In addition to the removal of the TBDMS group, silyl esters were also cleaved to the corresponding acid (entry 4). Interestingly, the desilylation reaction rate increased dramatically in the presence of a *para* nitro group (Table 1.12, entry 5).

The selectivity of the optimized reaction conditions was also explored. Benzylic, secondary, and primary silyl ethers were not removed under the optimized desilylation conditions (Table 1.12, entries 6-8). Thus, it appeared that aryl TBDMS silyl ethers could be selectively removed in the presence of aliphatic TBDMS silyl ethers.

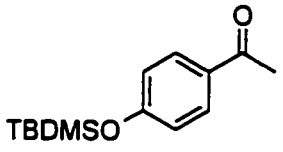
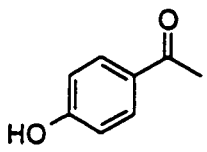
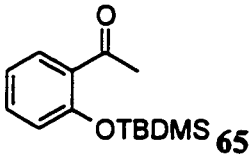
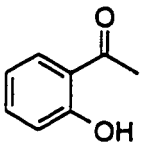
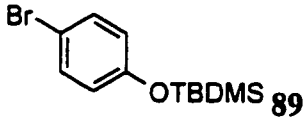
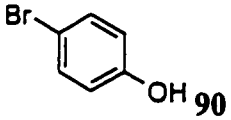
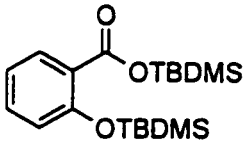
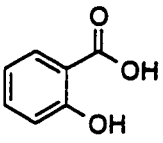
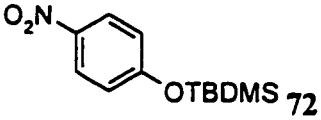
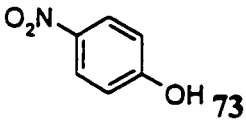
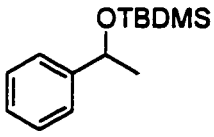
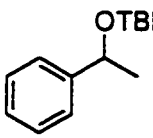
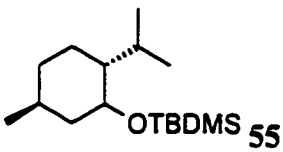
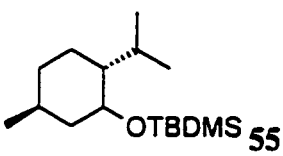
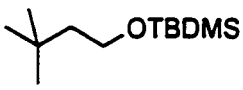
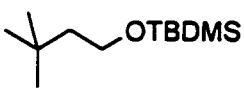
In order to test whether an aryl silyl ether could be selectively removed, the bis-TBDMS silylated β-estradiol was prepared (Scheme 1.15). β-Estradiol (**79**) was treated with 2.2 equivalents of *t*-butyldimethylsilyl chloride in DMF in the presence of imidazole to provide the di-TBDMS protected steroid **80** (Scheme 1.15). The presence of the two TBDMS silanes in steroid **80** was confirmed by examination of the ^{1}H-NMR spectrum (two *t*-butyl singlets) and the mass spectrum (a peak at *m/e* 500). Treatment of steroid **80** with 1.1 equivalents of K_2CO_3 in ethanol containing 5 equivalents of water resulted in selective removal of the aryl TBDMS protecting group over the aliphatic TBDMS protecting group (Scheme 1.15).

For the reasons presented below, the product was identified as steroid **93** by comparison of the ^{1}H-NMR spectra of **79**, **80** and **93**. The ^{1}H-NMR spectrum indicated the presence of only one hydroxyl group. In addition, the chemical shift of H_1 in **80** was similar to that of H_1 in **93**, indicating that the chemical environments were still the same (i.e. the TBDMS group was still present). Carbon atom 1, containing the aliphatic TBDMS silyl ether, is a stereogenic center. Therefore, the methyl groups of the TBDMS silyl ethers on **80** are diastereotopic, and should appear as four singlets in the ^{1}H-NMR spectrum. However, the ^{1}H-NMR spectrum of the di-TBDMS protected steroid **80** shows only three peaks for the four methyl groups, one integrating for two methyl groups and

the other two peaks integrating for one methyl group each. This was expected, since the stereogenic centre was located far away from the TBDMS aryl protected alcohol. Therefore, one peak accounted for both methyl groups of the TBDMS aryl ether. Since steriod **93** also showed two peaks for the methyl groups on the silane in the ^{1}H-NMR spectrum, it was concluded that the TBDMS group remained on the secondary alcohol. Thus, the TBDMS protecting group was **selectively** removed from the aryl hydroxy group.

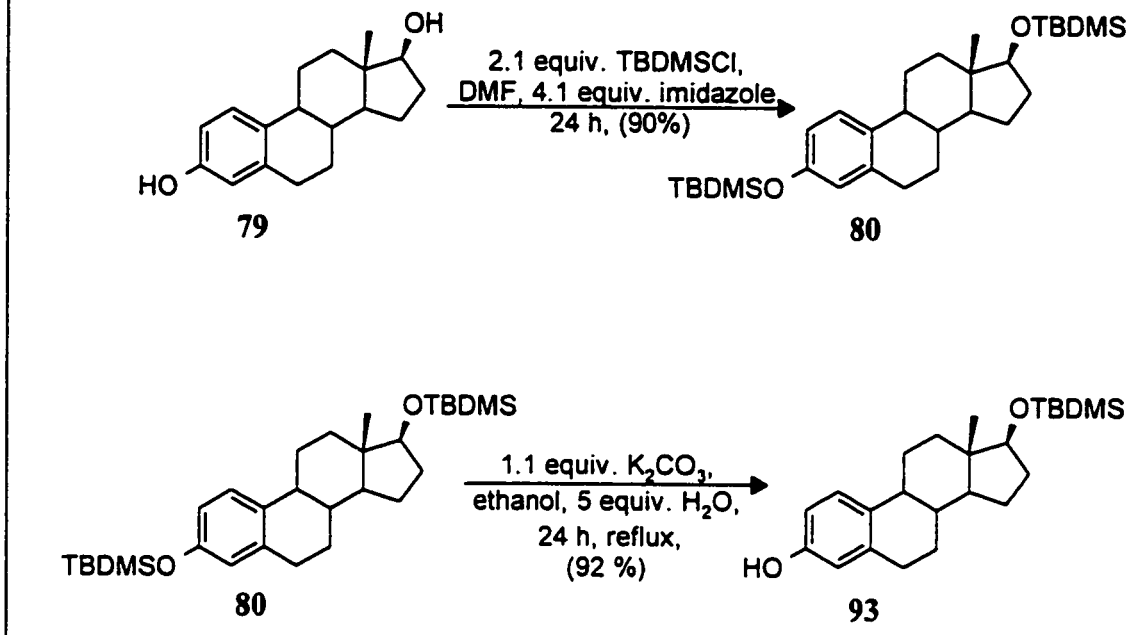
To determine what types of silyl groups could be removed, phenolic silyl ethers **94** and **96-99** were synthesized by previously known methods (Scheme 1.9).[1] Treatment of **94**, and **96-99** with the optimized desilylation conditions (Table 1.11, entry 7) provided phenol **95** in good to excellent yields (Scheme 1.16). Thus, in addition to the removal of a TBDMS group, TMS, TES, TIPS, and TBDPS groups were removed. Interestingly, as the size of the silane increased, the time necessary to complete the reaction increased. This may indicate that the steric size of the silane could be inhibiting attack at the silyl group by a nucleophile (i.e. $^-$OH or $^-$OEt).

Table 1.12 Desilylation Results of Various Silyl Ethers With 1.1 Equivalents of K_2CO_3.

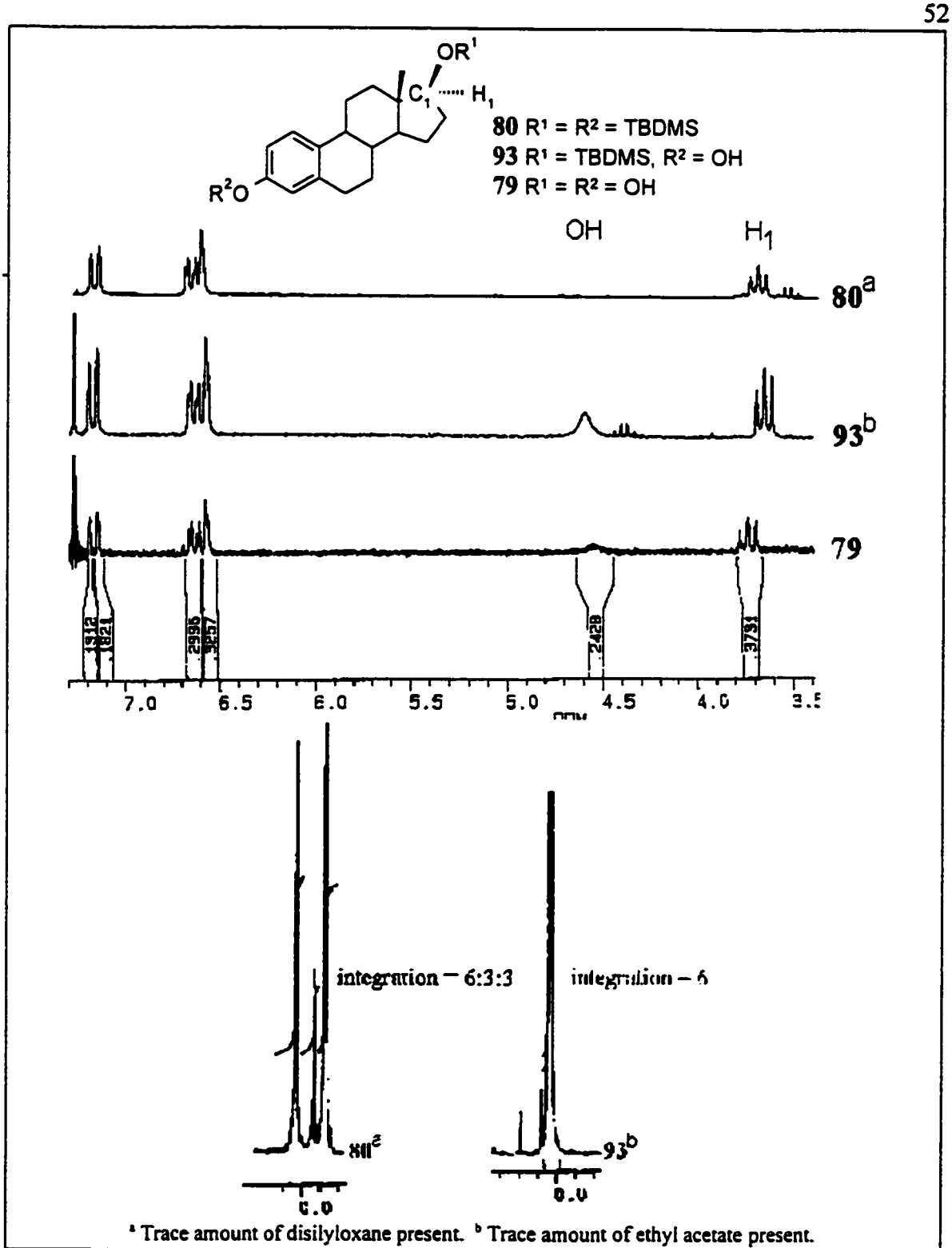
Entry	Starting Material	Time (h)[a]	Product	Yield (%)[b]
1	 **29**	16	 **30**	94
2	 **65**	20	 **66**	81
3	 **89**	24	 **90**	78
4	 **69**	17	 **70**	96
5	 **72**	2	 **73**	98
6	 **91**	24	 **92**	no reaction
7	 **55**	24	 **55**	no reaction
8	 **61**	24	 **61**	no reaction

[a] Reactions performed in ethanol containing 5 equivalents of water at 75 °C. [b] Isolated Yields.

Scheme 1.15



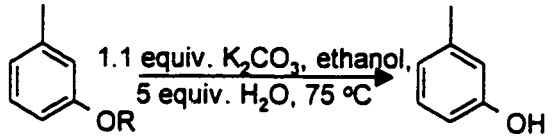
79 **80** **80** **93**



[a] Trace amount of disilyloxane present. [b] Trace amount of ethyl acetate present.

Figure 1.4 Comparison of a Portion of the ^{1}H-NMR Spectra in the Desilylation of Di-TBDMS Protected Estradiol.

Scheme 1.16



94	R = TMS, 10 h	**95**	(100%)
96	R = TES, 10 h	**95**	(99%)
97	R = TBDMS, 12 h	**95**	(98%)
98	R = TIPS, 24 h	**95**	(77%)[a]
99	R = TBDPS, 48 h	**95**	(62%)[a]

[a] Remainder was unreacted starting material.

1.3.4 Conclusions.

A simple, inexpensive, **selective** (at least for TBDMS), mild procedure for the desilylation of phenolic silyl ethers in good to excellent yields has been developed. The procedure uses only conventional laboratory equipment and reagents and avoids an aqueous workup. Changing the base from Na_2CO_3 to K_2CO_3 resulted in an increased yield of the desilylated phenol. The optimized desilylation conditions were 1.1 equivalents K_2CO_3, in ethanol with 5 equivalents of water at reflux. The mild reaction conditions are tolerated by a variety of functional groups (aldehydes, ketones, bromides, and nitro groups) and the rate of the reaction decreases as the size of the groups on the silane increase.

1.4 Overall Conclusions.

In conclusion, two new methods for the desilylation of phenolic TBDMS ethers have been developed. Method one, 5 mol% $PdCl_2(CH_3CN)_2$ in acetone containing 5 equivalents of water, was shown to desilylate a variety of phenolic silyl ethers in typically good to excellent yields. Method two, 1.1 equivalents of K_2CO_3 in ethanol containing 5 equivalents of water, also showed that a variety of phenolic silyl ethers could be desilylated in good to excellent yields. Both methods are beneficial in that they do not require specialized equipment and are relatively simple, mild and inexpensive procedures. In addition, method two has the added advantage in that it was shown to be **selective** (at least for TBDMS) for phenolic silyl ethers.

2 The Development of a One-Step Asymmetric Desilylation/Desymmetrization of TBDMS Protected Diols 213 and 214 and Glycerol (46).

With the success of the palladium (II) catalyzed aliphatic and phenolic desilylation of TBDMS ethers, described in Chapter 1, an intriguing idea emerged: could bis-TBDMS protected diols having C_s symmetry be asymmetrically desymmetrized using palladium (II) catalysts with chiral ligands? A search of the literature revealed that this strategy had not been reported. Therefore, a series of experiments was designed to test the possibility of this idea, and these results will be discussed. This chapter will begin by outlining the importance of various methods for performing asymmetric syntheses. A review illustrating several examples of both enzymatic and non-enzymatic desymmetrization of molecules containing a plane of symmetry will follow, along with the project goals. Finally, a summary of the studies done towards the development of an asymmetric desilylation/desymmetrization method using chiral palladium (II) catalysts will be presented.

2.1 Introduction.

Natural products have been isolated for many years, leading to a large catalogue of organic and inorganic compounds. Some of the compounds that have been isolated are enantiomerically pure (or enantiopure). If an optically active natural product can be isolated in large quantities and is relatively cheap to obtain, then it can be classed as part

of the "chiral pool"[28], otherwise the enantiomerically pure compound must be synthesized.

The majority of natural products isolated are chiral compounds. The synthesis of chiral compounds from achiral compounds (molecules which are superimposible with their mirror image) is termed asymmetric synthesis. The following sections will explain the importance of, and describe various reported strategies toward, asymmetric synthesis, define desymmetrization, and finally, present an overview of the literature in which asymmetric desymmetrizations have been reported.

2.1.1 Importance of Asymmetric Synthesis.

The preparation of enantiomerically pure compounds has received considerable attention in organic synthesis. Organic chemists seek to produce enantiomerically pure compounds not only for the challenge, but also because we now recognize the significance chirality plays in biological pathways.[29] The classical example whereby the chirality of the molecule led to extremely different biological responses, is that involving thalidomide (Figure 2.1). Thalidomide was marketed as a racemic mixture for pregnant women as a sedative and anti-nausea agent. Unfortunately, the (-)-(*S*)-enantiomer of thalidomide (**100**) possessed a teratogenic side effect. Children born to women who had been administered the drug, had a higher incidence of disfigurements than those children born to women who did not use the drug. As a result of both the thalidomide case and the realization that the chirality of a molecule can lead to extremely different biological

responses, the Food and Drug Administration now requires a drug to pass extensive clinical trials of both individual enantiomers and the racemate before the drug can be marketed.

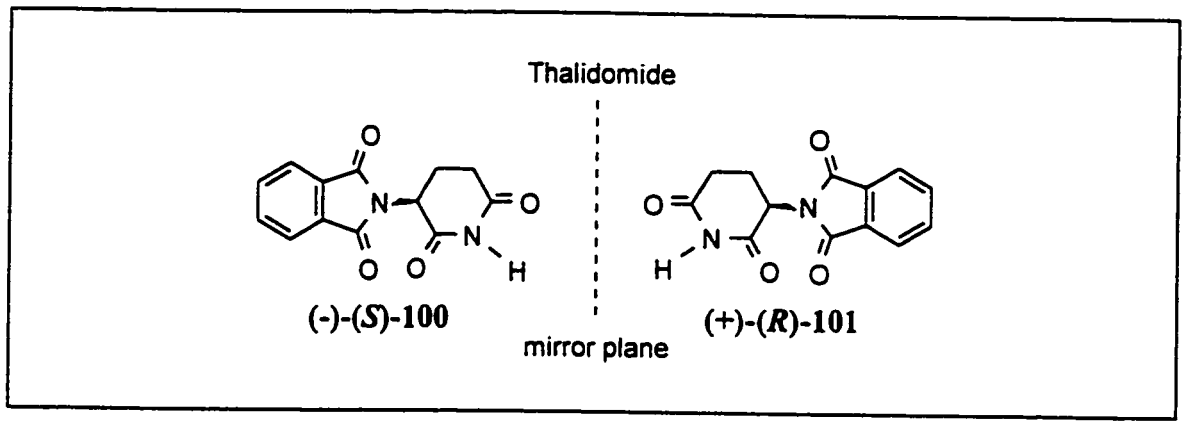


Figure 2.1 Enantiomers of Thalidomide

2.1.2 Methods for the Production of Enantiopure Compounds.

The preparation (and separation of racemates) of enantiomerically pure compounds has become a unique and significant challenge in both the theory and practice of synthetic organic chemistry.[30] The next paragraphs will briefly review the five known methods of generating enantioenriched or enantiopure compounds. The reader should be made aware that these are not distinct divisions and in some instances a combination of two different methods is required.

(1) Resolution:

Involves placing a scalemic (enriched in one enantiomer) or racemic mixture in a chiral environment which results in the formation of diastereomers or diastereotopic interactions. A separation of the isomers is then required (e.g. selective recrystalization

of one diastereomer or separation using GC or HPLC columns). There are three types of resolutions: kinetic, thermodynamic, and racemic. Diastereotopic interactions are important for kinetic and thermodynamic resolutions, while racemate resolution is the separation of enantiomers by the formation of either diastereomers or diastereotopic interactions which have different physical properties. After separation of the diastereomers the chiral group is removed.

(2) Chiral templates[31] (a.k.a. "chiral pool"):

Involves the generation of a new, optically pure product using the stereogenic centre(s) of previously synthesized or isolated chiral molecules. Starting compounds used in this manner are commonly from the "chiral pool". The absolute stereochemistry of the stereogenic centre(s) in the template can be inverted, maintained or destroyed in order to synthesize the desired enantiopure product.

(3) Metal, Reagent or Catalyst Bound Auxiliaries:

Involves the use of a chiral ligand(s) bound to a catalyst, reagent or metal, which is involved in the transition state of a reaction, thereby creating diastereotopic interactions which lead to the product(s) being formed enantioselectively.

(4) Substrate Bound Chiral Auxiliaries:

Involves covalently attaching a chiral auxiliary to the prochiral substrate which then influences the stereochemical outcome of a reaction. This influence results in the formation of diastereomers. Removal of the chiral auxiliary then results in the product being enantioenriched.

(5) Biological systems:

Involves the generation of a new, optically pure product using enzymes. The reactions are usually highly stereo-, chemo- and regiospecific under mild conditions leading to optically pure compounds.[32]

There are many examples in the literature[33] that illustrate the usefulness of the above five methods for the preparation of enantiopure or enantioriched products. For the purpose of this thesis, examples of 3, 4 and 5 involving the asymmetric desymmetrization of bi-functionalized compounds will be reviewed.

2.1.3 Definition of Desymmetrization.

The challenge of developing enantiomerically pure compounds is increased by the endeavor to develop high yielding and selective asymmetric syntheses. In order to perform an enantioselective conversion of an achiral substrate into a chiral, nonracemic product, a selective differentiation of enantiotopic faces or groups of the substrate in question must occur. A powerful strategy for preparing enantiomerically pure compounds is by the asymmetric desymmetrization of *meso*-compounds.

Desymmetrization can be simply defined as the systematic removal of elements of symmetry.[34] There are several methods in which symmetry elements can be removed. The first method is by distortion of the compound (Figure 2.2). Bicyclo[2.2.2]octane (**102**) is desymmetrized from the point group $\mathbf{D_{3h}}$ to $\mathbf{D_3}$ (removal of planes of symmetry), by twisting the compound in to its skewed form **103**. A second method of

desymmetrization entails substitution onto the symmetrical lattice framework (Scheme 2.1).[34] In this example of desymmetrization (Scheme 2.1), compound **105** looses its plane of symmetry when one of the ligands (X in this case) is substituted with a different ligand (R). The result is two compounds **104** and **106** which are enantiomers.

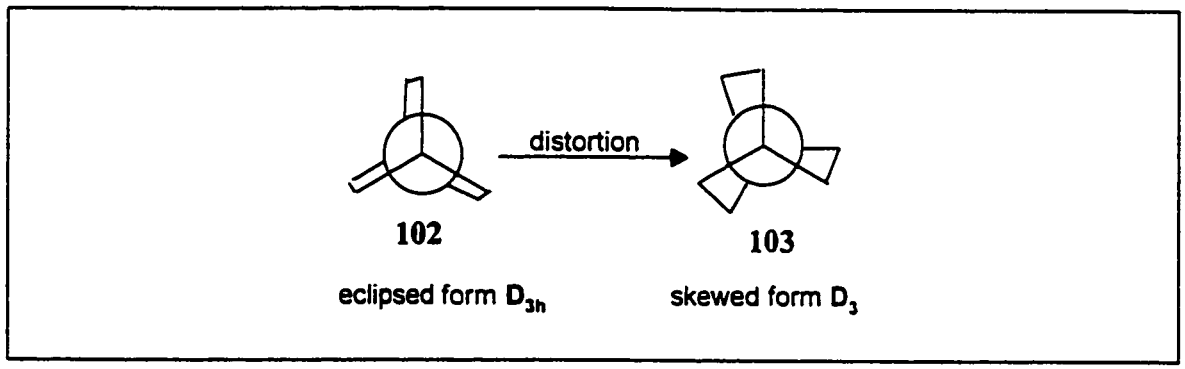
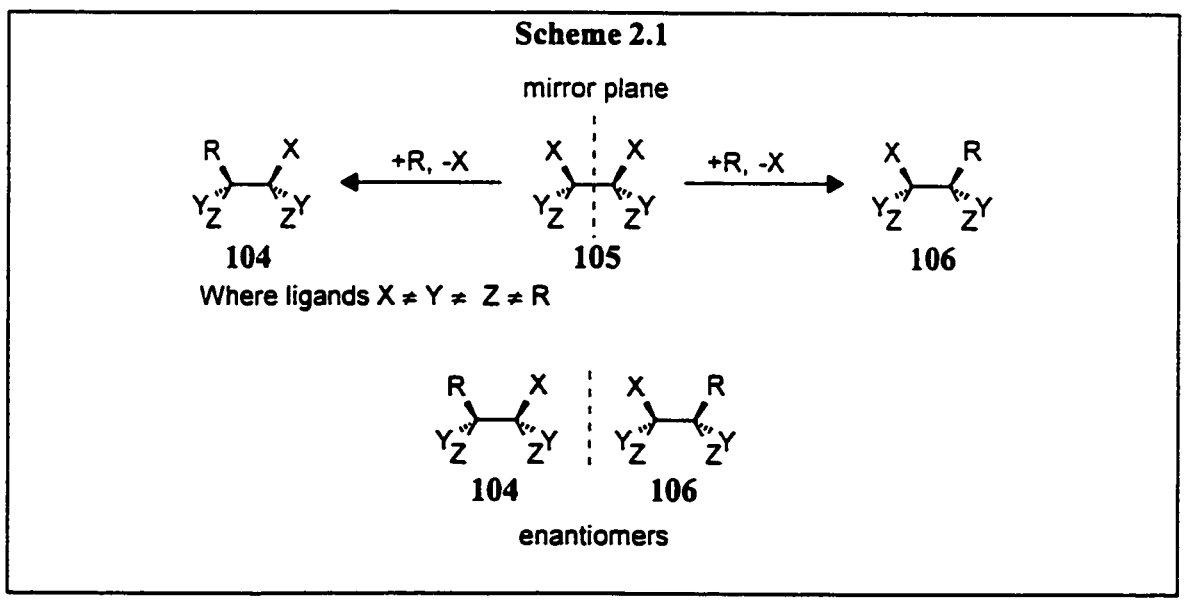


Figure 2.2 Newman Projection of the Desymmetrization of Bicyclo[2.2.2]octane (102) by Distortion.



As the need for enantiomerically pure compounds increases, new methods and strategies for asymmetric synthesis are being developed. The asymmetric desymmetrization of *meso*-compounds is a strategy that can (and has) led to the

preparation of non-racemic compounds. The next sections will describe known methods for the asymmetric desymmetrization of molecules possessing a plane of symmetry by both enzymatic and non-enzymatic methods. Due to length restrictions on the thesis, an exhaustive review on this subject is not possible. Instead, the reader is referred to excellent reviews in the literature.[33,45]

2.1.4 An Abbreviated Review: Selected Enzyme Mediated Asymmetric Desymmetrizations.

Enzymes have been utilized for centuries in industrial and medical applications with some of the most common applications involving fermenting of alcohol, curdling of cheese, and leavening of bread. Since these humble beginnings, more than 3,000 enzymes have been cataloged and several hundred can be purchased commercially.[35]

The attraction for using enzymes is that a variety of transformations of various substrates can be performed using only catalytic quantities of the enzyme. Enzymes are classified into six main groups: (1) Oxidoreductases; (2) Transferases; (3) Hydrolases; (4) Lyases; (5) Isomerases; and (6) Ligases. Enzymes in groups 1-4 are most commonly employed for organic transformations.

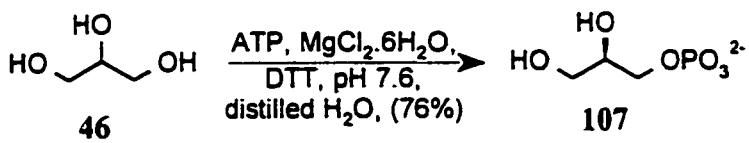
More importantly, enzymes are also capable of differentiating enantiotopic groups in prochiral compounds, and for this reason the enzymatic approach to the asymmetric desymmetrization of *meso*-compounds has become very common. The following section will describe some selected enzymatic asymmetric desymmetrizations of (1) acyclic and (2) cyclic C_s symmetric compounds.

(1) Acyclic *meso*-compounds

An important intermediate in the synthesis of phospholipids, L-glycerol-3-phosphate (**107**), can be prepared by desymmetrization of glycerol (**46**). Whiteside *et al.* have developed a simple, regioselective, one-step procedure for the desymmetrization of **46** into phophorylated glycerol **107**.[36] Although the enantiopurity of the phophorylated glycerol **107**, prepared by treatment of **46** with ATP, was not reported by the authors, the method does illustrate the ability of an enzyme to selectively react at one center over another (Scheme 2.2).

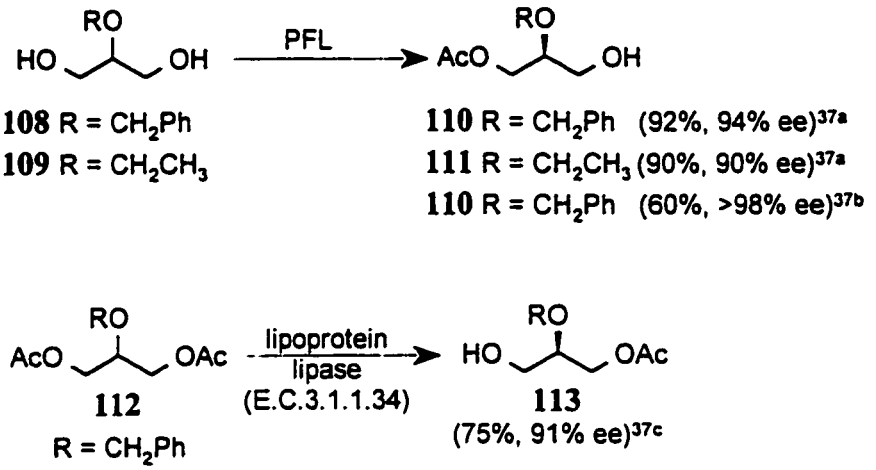
Alternative approaches for the asymmetric desymmetrization of glycerol derivatives using hydrolytic enzymes have been studied. For example, compounds **108**, **109** and **112** yield desymmetrized products **110**, **111** and **113** respectively, with moderate to excellent yields and good to excellent enantiopurity (Scheme 2.3).[37] Although the methods illustrated in Scheme 2.3 desymmetrize glycerol derivatives enantioselectively, they require further synthetic steps in order to produce phophorylated glycerol **107**.

Scheme 2.2



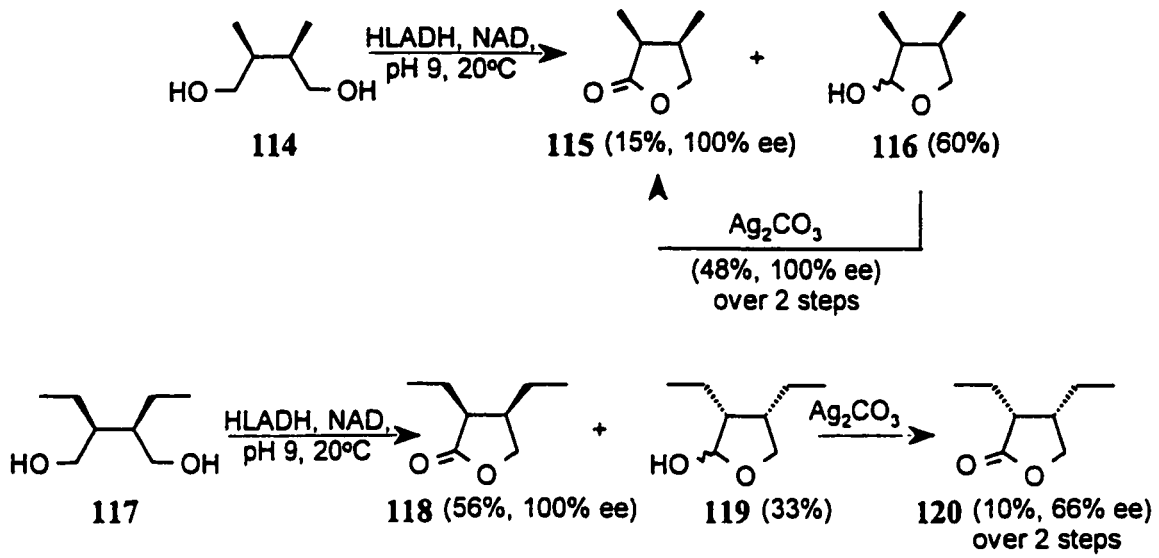
46 **107**

Scheme 2.3



The asymmetric desymmetrization of *meso*-2,3-disubstituted butane-1,4-diols **114** and **117** have also been achieved using enzymatic mediated syntheses. Jones and co-workers stereoselectively oxidized 2,3-dimethyl- and 2,3-diethyl-1,4-butanediol (**114** and **117**) to a mixture of cyclic hemiacetals (**116** and **119**) and lactones (**115** and **118**) with horse liver alcohol dehydrogenase (HLADH). The cyclic intermediates **116** and **119** were treated *in situ* with Ag_2CO_3 to provide the corresponding lactones **115** and **120** in low to moderate chemical yields with moderate to excellent enantiomeric excess (Scheme 2.4).[38]

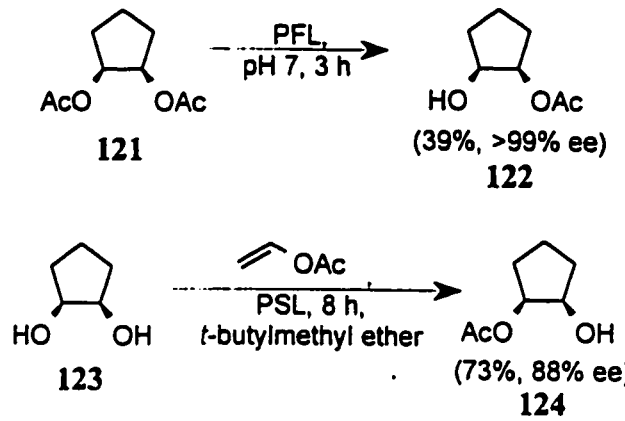
Scheme 2.4



2) Cyclic *meso*-compounds

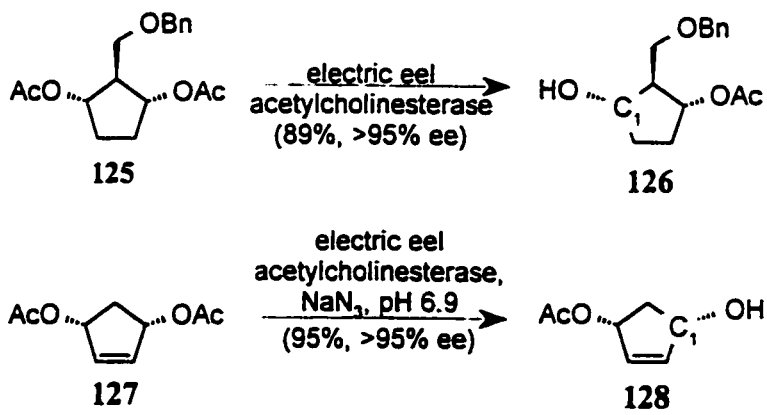
Meso-cyclopentanediols have played an important role in the development of chemoenzymatic syntheses of prostaglandins, prostacyclins, and many other natural products.[35] The hydrolysis of *cis*-1,2-diacetoxycyclopentane (**121**) by treatment with *Pseudomonas fluorescens* lipase (PFL) afforded the corresponding monoacetate **122** with an ee of 99% (Scheme 2.5).[39] Another example involved the esterfication of *cis*-cyclopentanediol **123**, which occurred with *Pseudomonas cepacia* lipase (PSL) providing **124**. This reaction provides **124** in a higher chemical yield but at the cost of a lower optical purity.[40]

Scheme 2.5



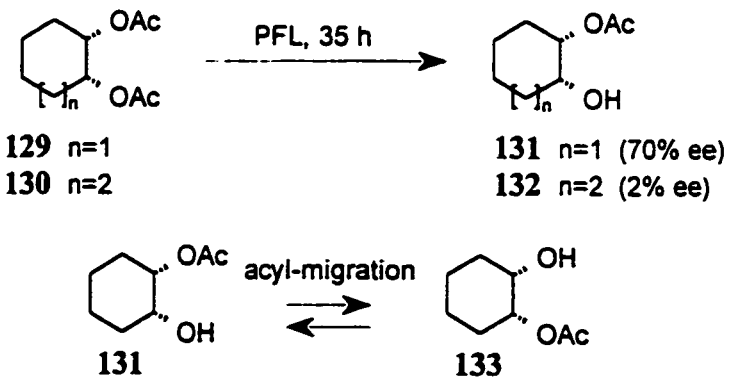
Griffith and Danishefsky used a chemoenzymatic synthesis in the preparation of chitinase inhibitors.[41] Utilizing the action of electric eel acetylcholinesterase (EEL) on *meso*-diester **125**, alcohol **126** was prepared in 89% yield with >95% enantiomeric excess (Scheme 2.6). A similar reaction with **127** provided **128** having the opposite absolute stereochemistry at C_1 to that in **126**.[42] This example illustrates that slight changes in the substrate structure can lead to dramatic changes in the stereochemistry of the products when using enzymes.

Scheme 2.6

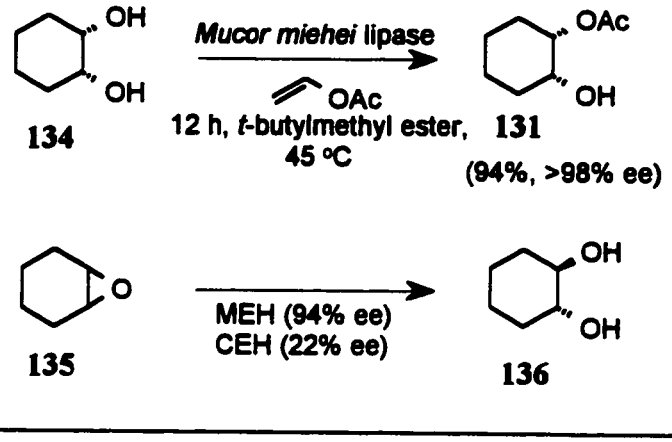


The desymmetrization of *meso*-cyclohexanols by enzymes has been shown to be synthetically useful. Unlike the previous example with *meso*-cyclopentanols (Scheme 2.5), PFL was less efficient for desymmetrization of *meso*-cyclohexanediols and cycloheptanediols (see **131→133** in Scheme 2.7).[39] The lower selectivity and optical purity was attributed to an unwanted enzyme-catalyzed acyl-migration, thereby reducing the enantioenrichment (Scheme 2.7). This effect was even more pronounced for *vic*-cycloheptanediols (2% ee, see **130→132**). Interestingly, Nicolosi *et al.* managed to desymmetrize *meso*-cyclohexanediol **134** using Lipozyme® (*Mucor miehei* lipase) to provide monoacetate **131** in excellent chemical yield and optical purity (Scheme 2.8).[40] Another method to avoid the unwanted enzyme-catalyzed acyl-migration used an epoxide hydrolase to open cyclohexene oxides. (*R*,*R*)-Cyclohexane-*trans*-1,2-diol (**136**) was formed by epoxide opening of **135** using rabbit liver microsomal (MEH) and cytosolic epoxide hydrolase (CEH) (Scheme 2.8).[43]

Scheme 2.7



Scheme 2.8



2.1.5 An Abbreviated Review: Selected Non-Enzyme Desymmetrizations Involving Symmetrical Bi-functional Compounds.

The following section will discuss some non-enzymatic methods for the desymmetrization of compounds containing symmetry, with emphasis on molecules containing a plane of symmetry, into non-racemic products. The desymmetrization of *meso*-compounds or symmetrical bi-fuctionalized compounds has been shown to be a very attractive method for the construction of asymmetric intermediates for natural product synthesis.[44] As previously mentioned in the introduction, chemical substitution can be used for the removal of symmetry elements (Scheme 2.1).[45]

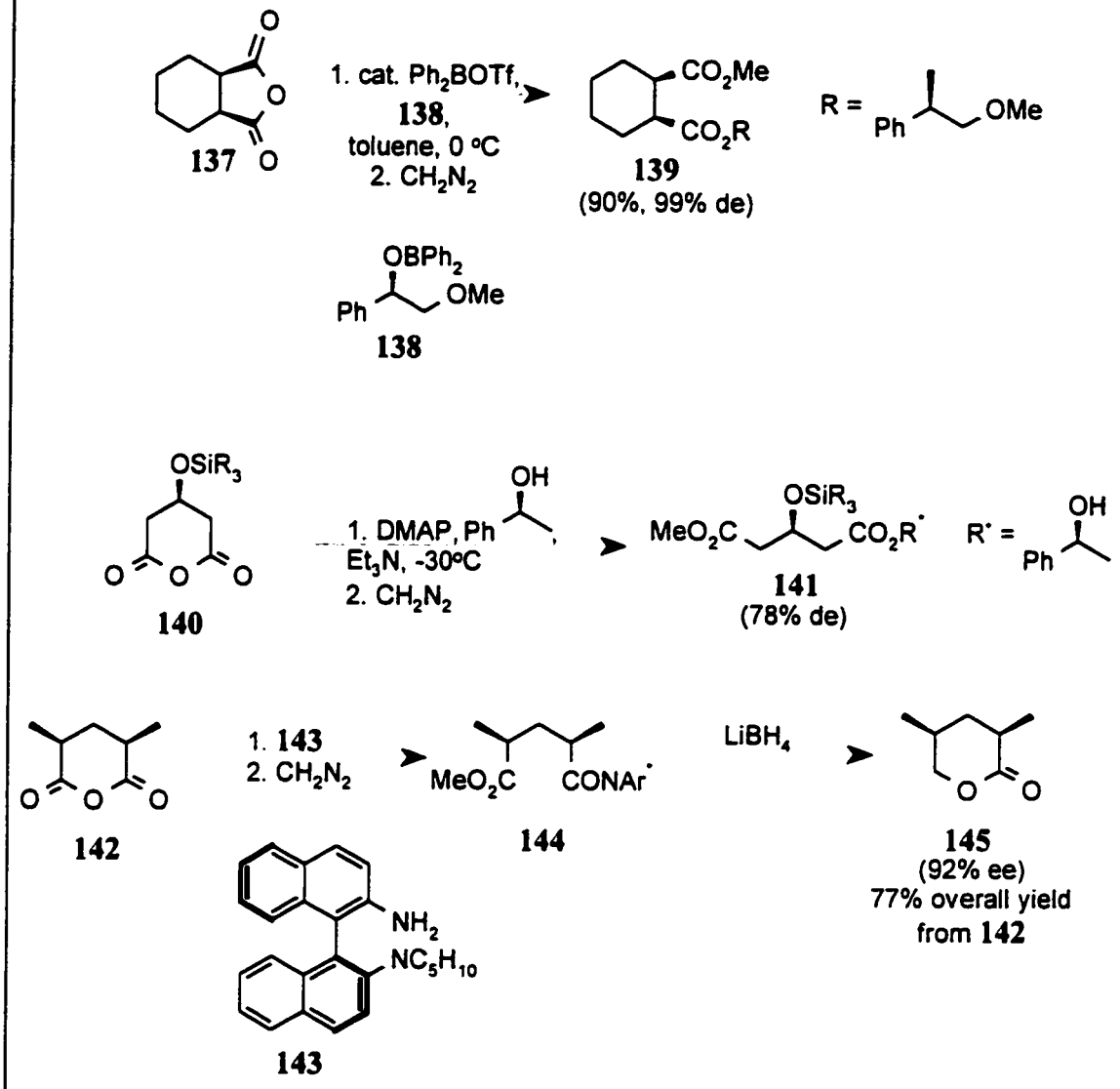
(1) Carbonyl Containing Compounds

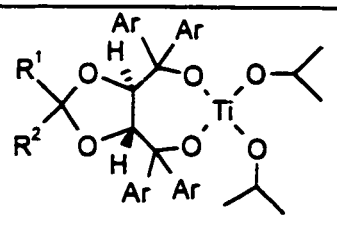
The synthesis of diesters is important for the preparation of natural products.[46] One method for the synthesis of chiral diesters involves an enantiotopic, catalytic ring opening of symmetrical anhydrides. The ring opening of symmetrical anhydrides with

either homochiral alcohols or amines is one of the most common methods.[47] This strategy of generating enantioenriched compounds can be defined as asymmetric method 3 for example one and asymmetric method 2 for examples two and three (Scheme 2.9). The first two examples describe methods of anhydride ring opening involving the use of homochiral alcohols (Scheme 2.9). Diesters **139** and **141** were produced with high diastereomeric excess when anhydrides **137** and **140** were treated with homochiral alcohols. The third example illustrates an alternative approach. In this case, the asymmetric desymmetrization of anhydride **142** to ester amide **144** was performed by anhydride ring opening with a homochiral amine (Scheme 2.9). Further reduction of **144** with $LiBH_4$ provided **145** with a 92% ee.

The generation of enantioenriched or enantiopure acid esters (Scheme 2.10) is an example of asymmetric method 3: metal, reagent or catalyst bound auxiliaries. Seebach and co-workers described the synthesis of acid ester derivatives by the reaction of anhydrides with isopropanol, using catalytic quantities of chiral Lewis acids such as the diisopropoxytitanium TADDOLates (**146-149**) (Figure 2.3).[46] Monocyclic, bicyclic, and tricyclic anhydrides **150**, **152**, and **154** were shown to yield acid esters with high enantiopurity (Scheme 2.10). The only limitation was when a methyl substituent was in the β-position to the carbonyl groups. Compound **156** only provided a moderate 3:1 enantiomeric ratio.

Scheme 2.9





146 ($R^1 = R^2 = CH_3$, Ar = β-$C_{10}H_7$)

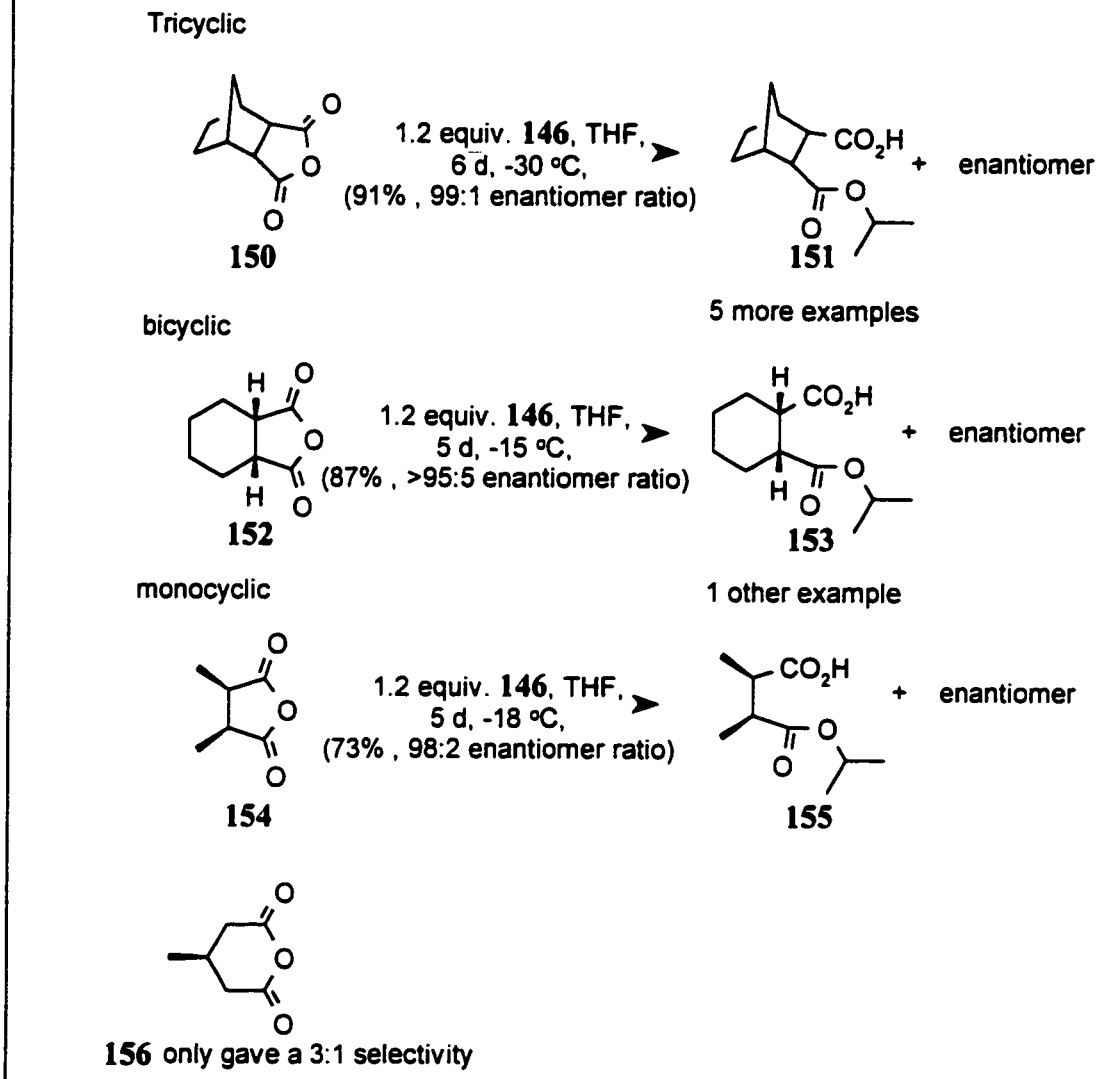
147 ($R^1 = R^2$ = Ar = C_6H_5)

148 ($R^1 = R^2 = CH_3$, Ar = C_6H_5)

149 (R^1 = Ar = C_6H_5, R^2 = H)

Figure 2.3 Diisopropoxytitanium TADDOLates Used by Seebach *et al.*[46]

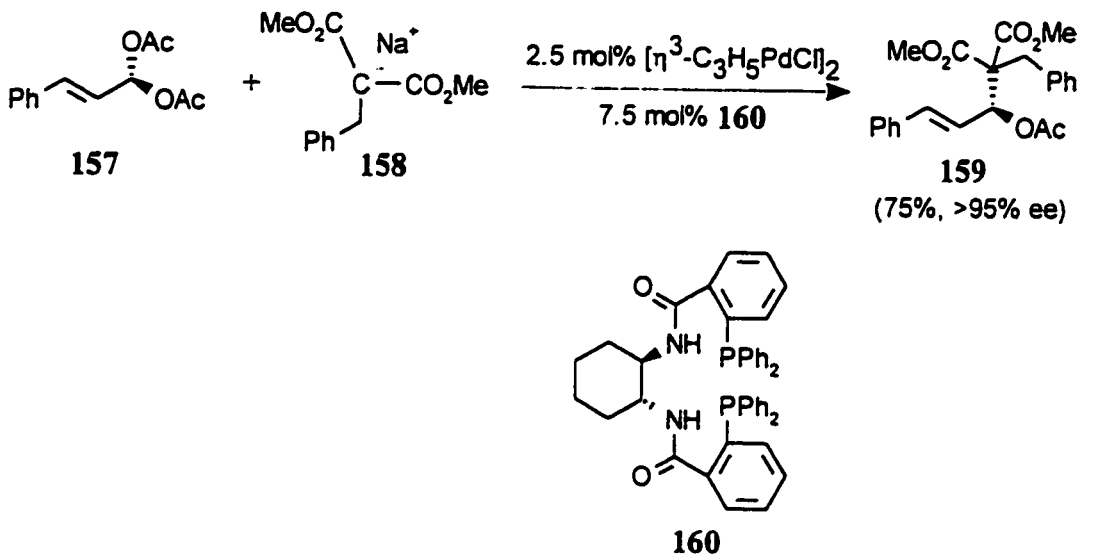
Scheme 2.10



Trost and co-workers have shown numerous examples of asymmetric desymmetrization reactions employing chiral catalysts.[18] The following work by Trost and co-workers is an example of desymmetrization by substitution. The reaction proceeds via a nucleophilic displacement of an acetoxy group. The achiral *gem*-dicarboxylate **157** was converted to the monoalkylated product **159** in 75% yield with

>95% ee when treated with palladium (II) catalyst, in the presence of chiral ligand **160** (Scheme 2.11).[48a]

Scheme 2.11



(2) *meso*-Diols

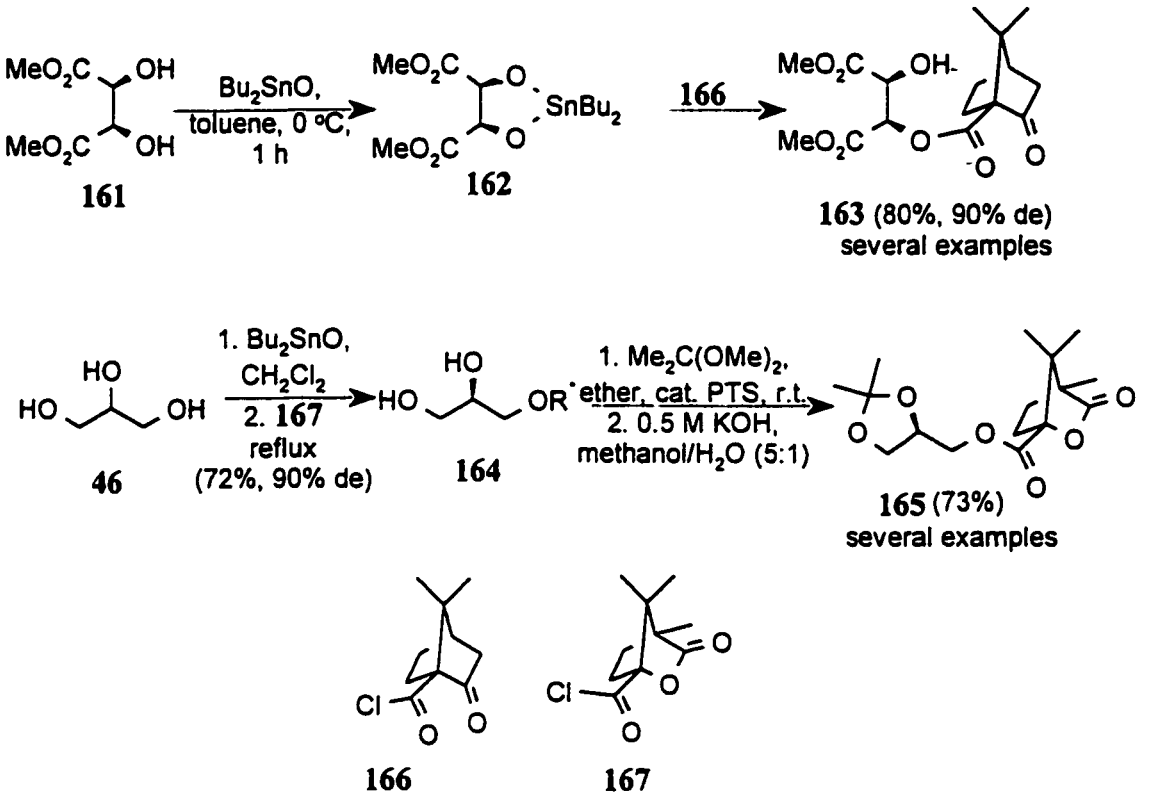
The asymmetric desymmetrization of *meso*-diols has been shown to be important in synthetic chemistry.[49] Such desymmetrization techniques have included the use of homochiral amines,[50] acyl halides,[51] dibutylstannylene acetals,[52] monoalkoxide sodium salts,[53] nucleophilic attack on spiroacetals[54] or benzylidene-type acetals,[55] palladium-mediated syntheses,[48e,48f,56] and monoacylation under acidic conditions.[49] The following examples will consider several of the above methods with emphasis on examples that illustrate asymmetric syntheses via methods 3 and 4.

The acylation of a *meso*-diol using chiral acyl halides affords monoacyl derivatives in moderate to good enantiomeric excess.[57] Treatment of *meso*-diol **161**[51a] or

glycerol (**46**)[51b] with dibutyltin oxide, followed by the addition of one equivalent of homochiral acyl halide **166** (or **167**), afforded the monoacyl derivatives **163** and **165** in high diastereomer excess (Scheme 2.12). Although these examples are examples of asymmetric method 3, the next paragraph illustrates that a combination of two asymmetric methods is sometimes required: resolution and substrate bound chiral auxiliaries.

Prostaglandin precursors (+)-**172** and (-)-**174** were prepared by the desymmetrization of *cis*-2-cyclopentene-1,4-diol (**168**) (Scheme 2.13).[58] *cis*-2-Cyclopentene-1,4-diol (**168**) was treated with one equivalent of homochiral acyl halide **173** and the subsequent mixture was separated to give **169a** and **169b**. Compounds **169a** and **169b** were then converted into (+)-**172** and (-)-**174** respectively.

Scheme 2.12



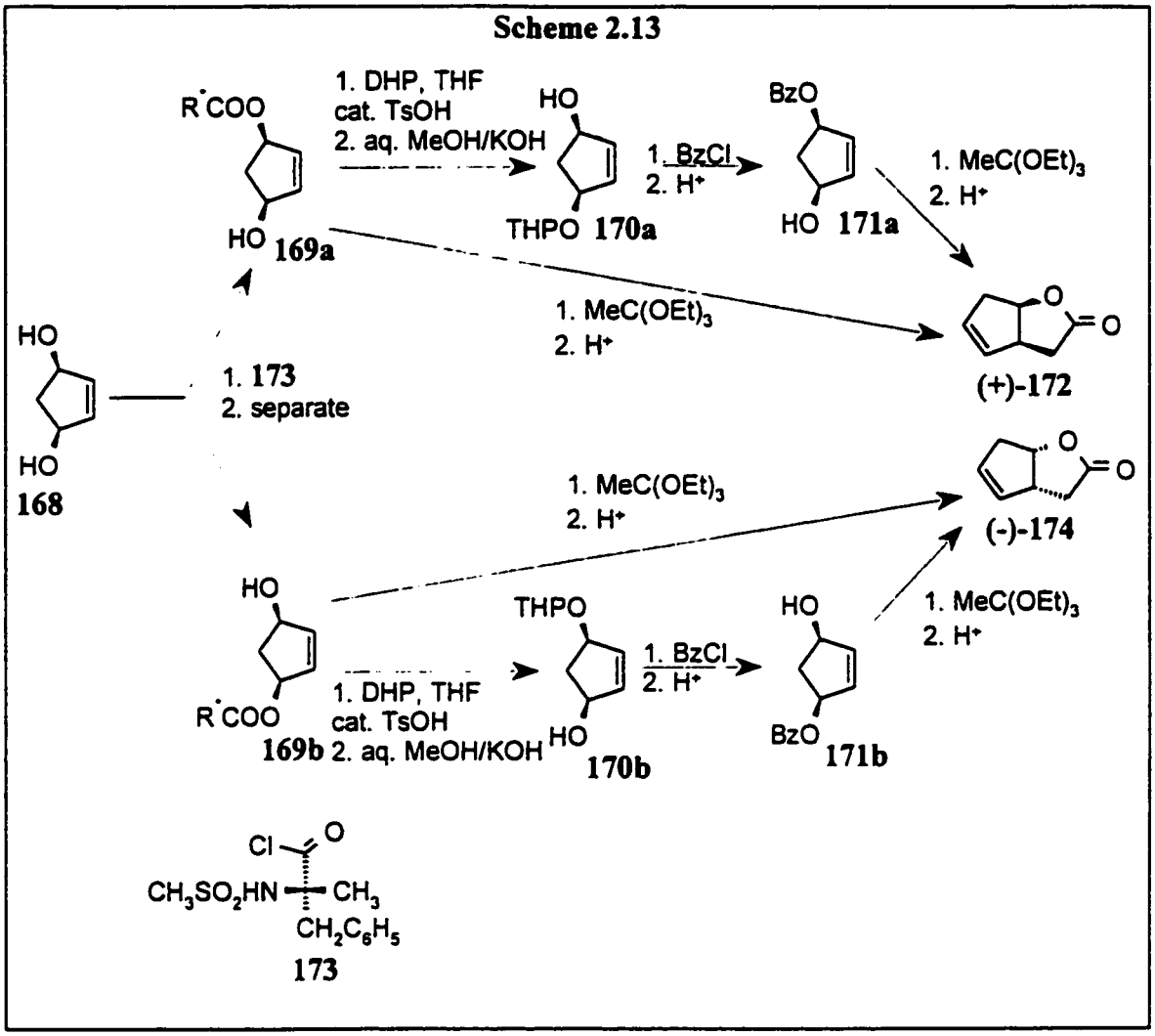
46 **164** **165** (73%) several examples

163 (80%, 90% de) several examples

161 **162**

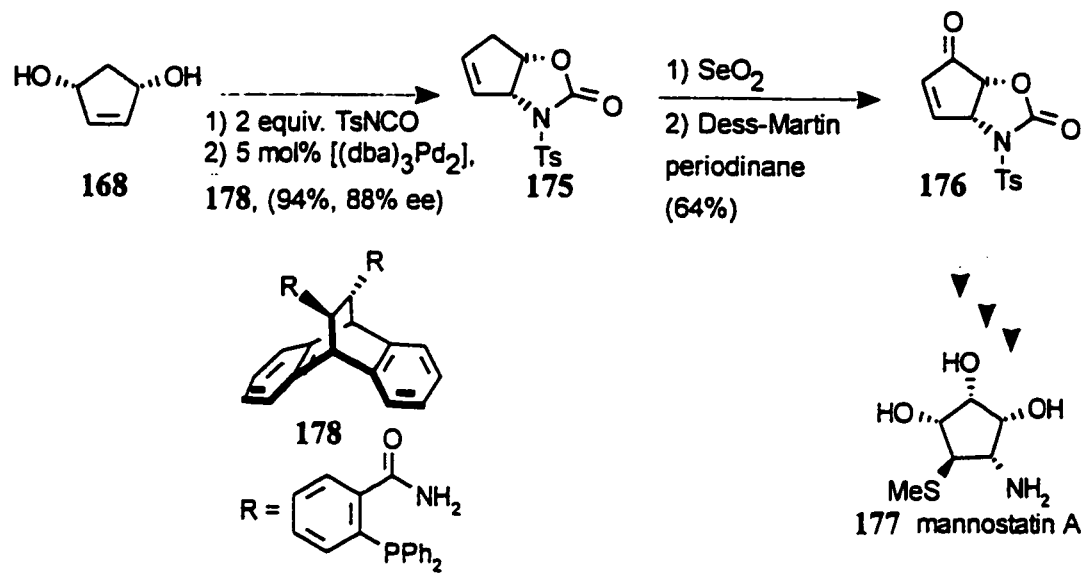
166 **167**

Scheme 2.13



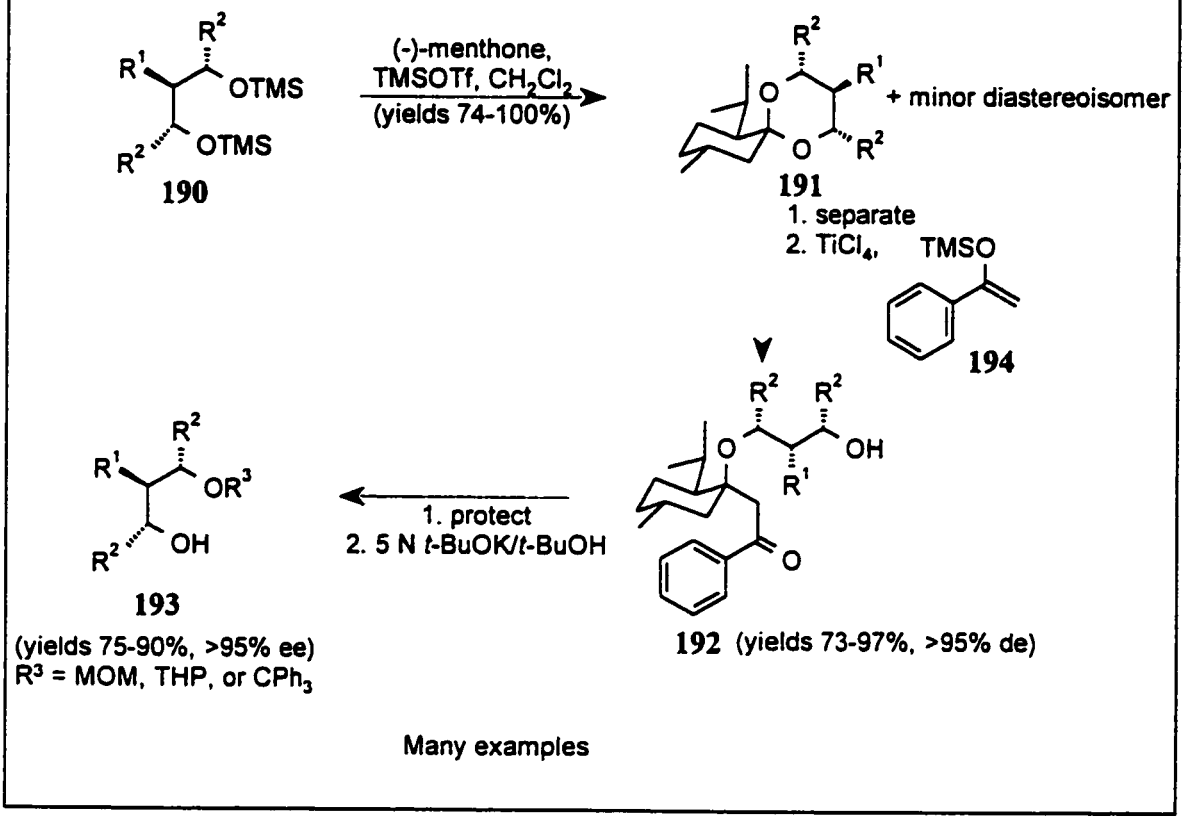
The first step in the synthesis of mannostatin A (**177**) utilized the desymmetrization of *meso*-2-cyclopentene-1,4-diol (**168**) (Scheme 2.14).[48e] The synthesis of the intermediate **176** began with the palladium-catalyzed ionization/cyclization of **168** in the presence of chiral ligand **178** to afford oxazolidinone **175**. Oxidation of oxazolidinone **175** with 5 equivalents selenium dioxide in refluxing diglyme, afforded ketone **176** which was subsequently converted into mannostatin A (**177**).

Scheme 2.14



The final example of a non-enzyme mediated desymmetrization is the only one (to the best of the author's knowledge) which resulted in a desymmetrization of 1,2-, 1,3-, and 1,4-diols initially protected with silyl ethers. A spiroketal **191** is produced when **190** is treated with (-)-menthone (Scheme 2.15).[54] Both of the oxygen atoms in **191** are now diastereotopic. Ring opening of the spiroketal with **194**, at the less hindered equatorial C-O bond upon the addition of $TiCl_4$ provided **192** with de's >95%. Protection of the hydroxyl group in **192** (as a MOM, THP or CPh_3), followed by base induced removal of the menthone derivative, led to compounds like **193** with >95% ee. The reader should note that although this method initially involved a symmetrical bis-silyl ether, the desymmetrization step occurred in the second step (**191** →**192**) and did not involve the enantioselective removal of one of the TMS groups.

Scheme 2.15



2.1.6 Summary.

The examples illustrated in this review for both enzymatic and non-enzymatic methods show that symmetrical bi-functionalized compounds can be asymmetrically desymmetrized generally with good to high yields and optical purity. When enzymes are used to perform the desymmetrizations, products are typically prepared in high enantiomeric excess. However, enzymatic methods can be limited by two factors: (1) the presence of certain functionalities can affect the reaction with enzymes, and (2) enzymatic methods are often performed in aqueous media; therefore, the low solubility of

the organic substrate can be problematic.[59] Typically, the non-enzymatic production of enantiopure compounds involves the use of asymmetric strategies 1 to 4 (or a combination thereof) and can produce enantioriched compounds in high enantiomeric excess. In addition, non-enzymatic methods are beneficial, since the reactions are typically performed in organic media. Therefore the solubility of the organic substrate is not problematic.

It is worth noting that while selective deprotections of silyl ethers are known,[2] a direct, one-step procedure for the asymmetric desilylation/desymmetrization of *meso*-silyl ethers has not been reported. The next section describes the project goals in the development of a palladium (II) catalyzed asymmetric desilylation/desymmetrization of *meso*-TBDMS ethers.

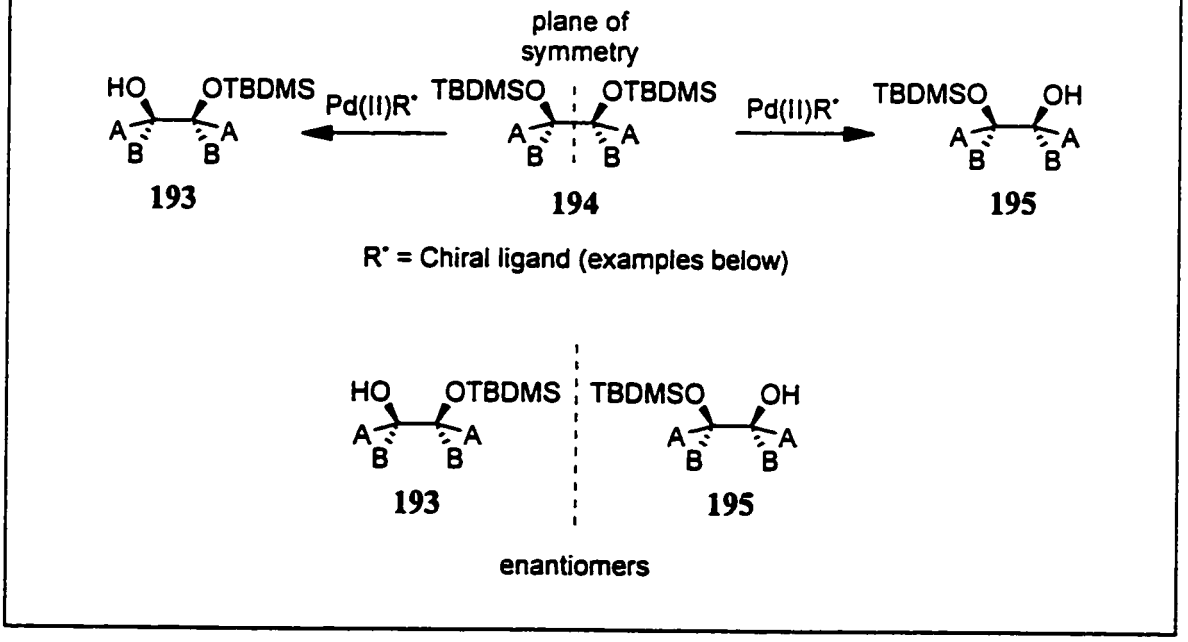
2.2 Project Objectives.

The synthesis of enantiomerically pure compounds has long been of great interest in Dr. Keay's research laboratory, as well as numerous other organic chemists. One potential and intriguing idea for the synthesis of enantiomerically pure compounds was the asymmetric desymmetrization of TBDMS protected *meso*-diols. Dr. Keay's group has reported that $PdCl_2$ can be used to desilylate TBDMS silyl ethers,[7,21] thus an extension would be to attempt to desymmetrize TBDMS protected *meso*-diols using $PdCl_2$ in the presence of a chiral ligand. A review of the literature indicated that although TBDMS protected diols can be selectively deprotected (i.e. aryl verses aliphatic bis-TBDMS

ethers or 1° verses 2° bis-TBDMS ethers),[2] the asymmetric desilylation/desymmetrization of TBDMS protected diols had not been reported.

This project involved investigating whether the treatment of di-TBDMS protected symmetrical-diols with catalytic quantities of palladium (II) catalyst coordinated with chiral ligands, would provide the corresponding mono-TBDMS compound enantioselectively (**194→193** or **195**) (Scheme 2.16). First, the project would involve the development of optimized reaction conditions for the removal of only one TBDMS group. Initial experiments would begin by changing the optimized aliphatic TBDMS ether desilylation conditions (i.e. 5 mol% $PdCl_2(CH_3CN)_2$ in reagent grade acetone containing 5 equivalents of water (Chapter 1)) sequentially. If this study was not successful, then alternative methods would be explored and developed.

Scheme 2.16



If successful conditions were found for the removal of only one TBDMS group, then the scope and limitations of the reaction would be explored. This would require altering the reaction conditions, such as: solvents, temperature, palladium (II) catalysts, using various chiral ligands such as **196-200** (Figure 2.4), and various diols such as **201-205, 123, 168** and **134** (Figure 2.5). The ultimate plan was to use this method to create chiral molecules (eg. **207**) which can be used to synthesize natural products such as prostagladins and carbovir (**209**) (Scheme 2.17), or possibly to synthesize diols containing axial chirality (**211**→**210** or **212**) (Scheme 2.17) which could be used as chiral auxiliaries.

The next two sections will discuss the results obtained in the attempt to desymmetrize *meso*-TBDMS protected diols and tri-silylated glycerol **45** using palladium (II) complexes. This will be followed by conclusions and suggestions for future work.

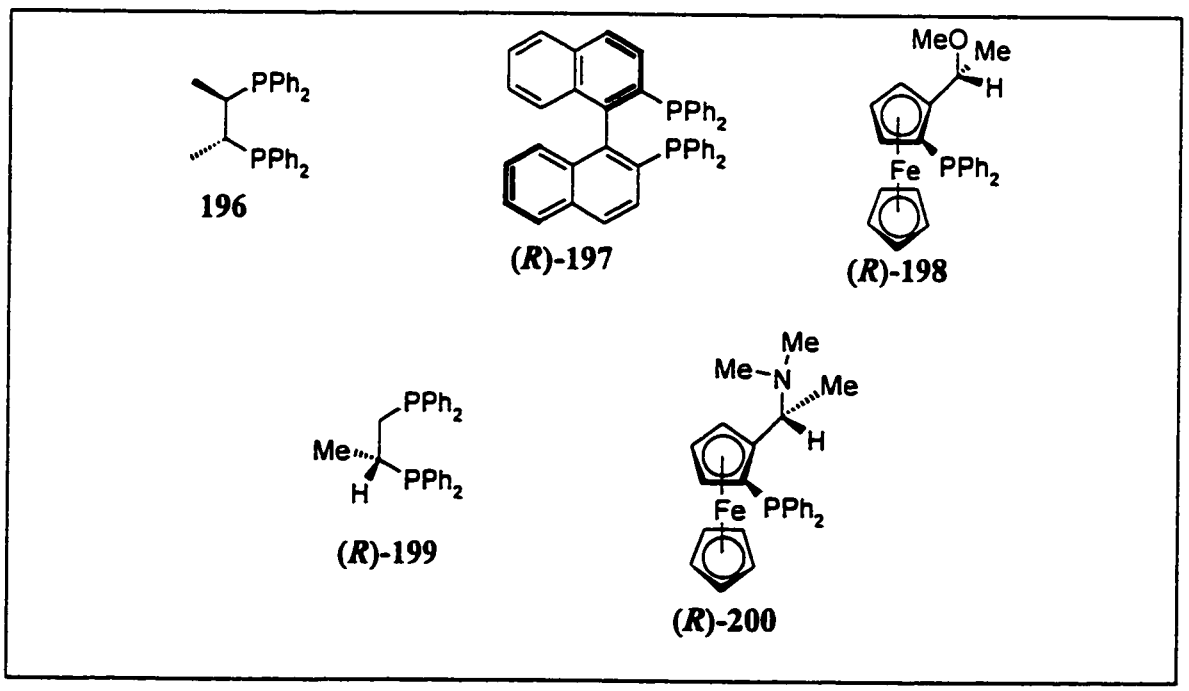


Figure 2.4 Potential Chial Ligands for Desilylation/Desymmetrization Attempts.

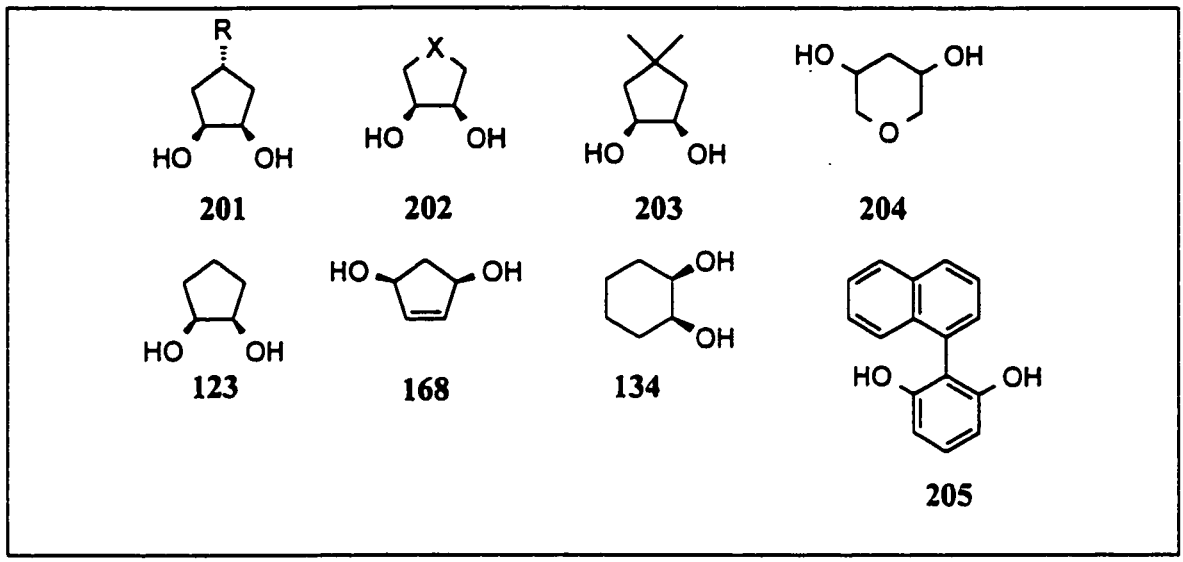
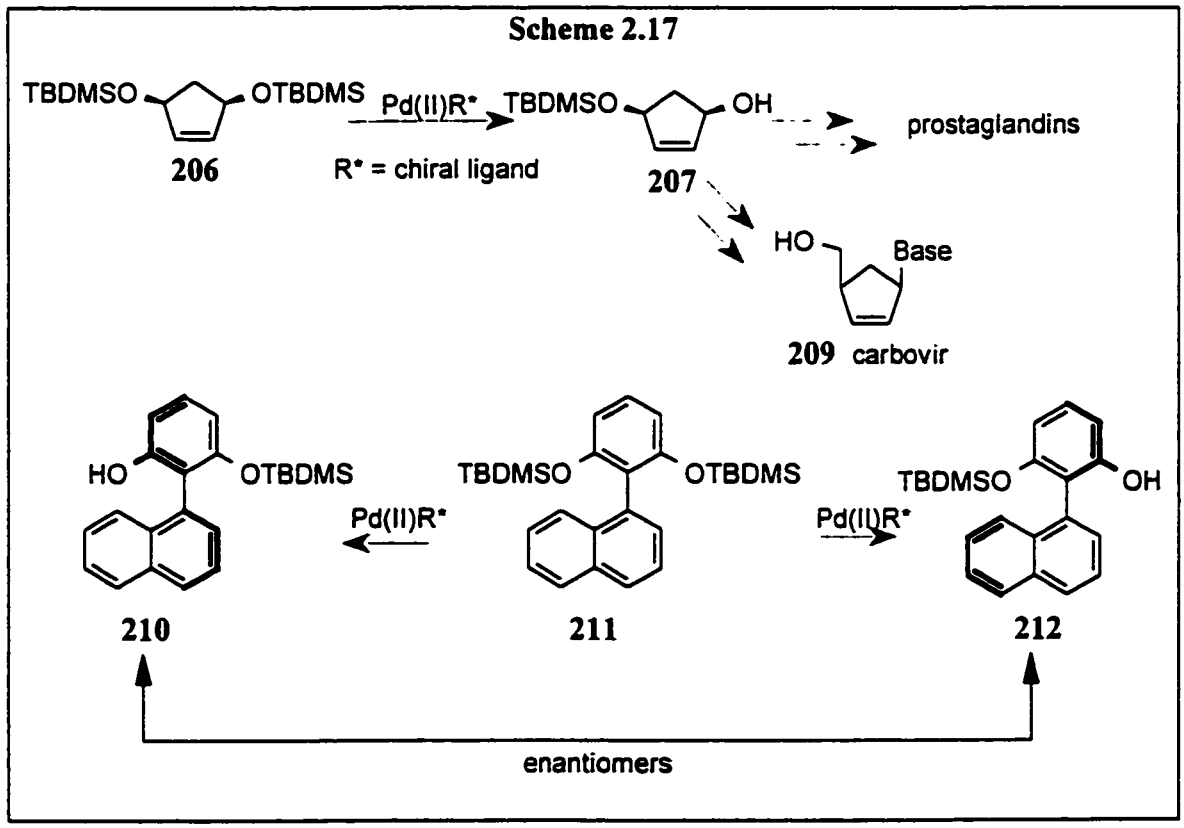


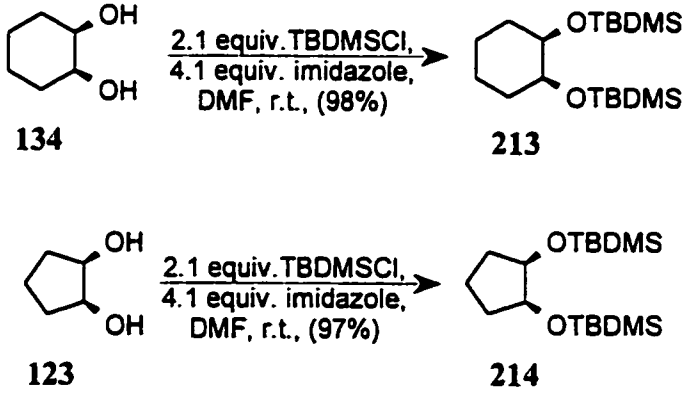
Figure 2.5 Potential symmetrical-diols.



2.3 Results and Discussion: Desymmetrization of Cyclic *Meso*-diols.

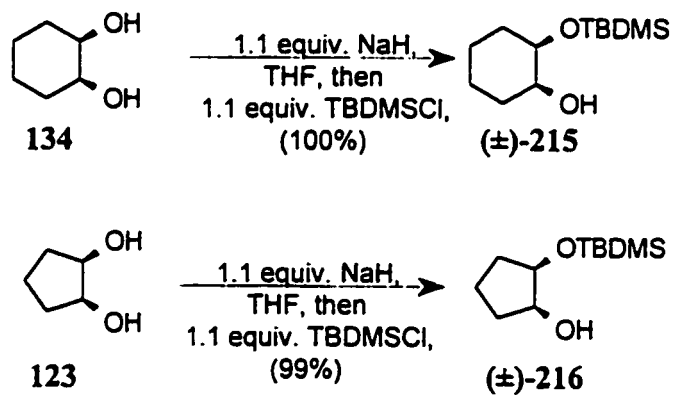
It was important to determine if the optimized desilylation conditions for aliphatic silyl ethers, stated in Section 1.2.1, could be applied to the asymmetric desymmetrization of *meso*-di-protected diol, i.e. the selective removal of only one TBDMS group. Initial studies were performed on *cis*-1,2-di(*t*-butyldimethylsilyloxy)cyclohexane (**213**) and *cis*-1,2-di(*t*-butyldimethylsilyloxy)cyclopentane (**214**). If conditions for the removal of one TBDMS group were found for **213** and **214**, reactions in the presence of chiral ligands would be tried to develop an enantioselective variant of this reaction. The protected cyclodiols **213** and **214** were produced in 98% and 97% respectively, from *cis*-1,2-cyclohexanediol (**134**) and *cis*-1,2-cyclopropanediol (**123**) by treatment with *t*-butyldimethylsilyl chloride in DMF containing imidazole (Scheme 2.18).[1] The formation of disilylated products **213** and **214** was confirmed by analyzing a variety of spectral data.

Scheme 2.18



In order to be able to determine the % ee's when chiral additives were to be used, racemic mono-TBDMS compounds (±)-**215** and (±)-**216** were synthesized. *Meso*-diols **134** and **123** were added to a suspension of NaH in THF.[60] After stirring the reaction several minutes, *t*-butyldimethylsilyl chloride was added to produce the corresponding mono-TBDMS protected compounds (±)-**215** and (±)-**216** (Scheme 2.19). The formation of the mono-silylated products **215** and **216** was confirmed by analyzing a variety of spectral data (refer to experimental for more details).

Scheme 2.19

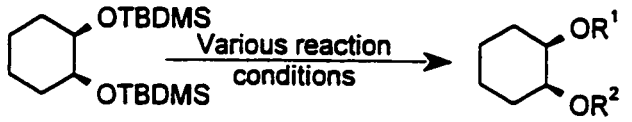


The first attempt to desymmetrize **213** and **214** employed the optimized aliphatic TBDMS ether desilylation conditions: 5 mol% $PdCl_2(CH_3CN)_2$ in reagent grade acetone containing 5 equivalents of water. This was performed to determine if a palladium (II) catalyst would selectively remove one TBDMS protecting group before the second TBDMS group was removed. Treatment of compound **213** with 5 mol% $PdCl_2(CH_3CN)_2$ in reagent grade acetone containing 5 equivalents of water provided a mixture of diol **134** as the major product (80% yield), and a small amount of monosilylated compound **215** (20% yield) (Table 2.1, entry 1). This result indicated that the removal of the first

TBDMS group may be the rate-determining step, since the yield of diol **135** was greater than the monosilylated compound **215**. In contrast, when compound **214** was treated under the above desilylation conditions, diol **123** was produced quantitatively (Table 2.1, entry 1).

Work focused on developing conditions to increase the yield of **215** and **216**. Results for the desilylation of aliphatic TBDMS ethers (Chapter 1, Section 1.2.1) indicated that a decrease in temperature or the amount of water, resulted in a decrease in the rate of reaction (albeit with a reduction in yield). Therefore, the next attempts involved lowering the temperature and/or amount of water. As the temperature was decreased from room temperature to -78 °C, the yield of the mono-TBDMS protected 6-membered ring **215** increased from 20% to 25% (Table 2.1, compare entries 1 and 2). Interestingly, no mono-TBDMS protected 5-membered ring **216** was observed (Table 2.2, entry 2). When the amount of water was reduced from 5 equivalents to 1 equivalent, the yield of the mono-TBDMS protected 6-membered **215** ring increased to 39%, and only trace amounts of diol **134** was detected (Table 2.1, entry 3). Treating **213** with $PdCl_2(CH_3CN)_2$, in dry acetone with 1 equivalent of water at -78 °C, yielded 40% of mono-TBDMS protected 6-membered ring **215** (Table 2.1, entry 4). Unfortunately, lowering the temperature and quantity of water had no effect on the di-TBDMS protected 5-membered ring **214** and only diol **123** was isolated (Table 2.2, entry 3).

Table 2.1 Desymmetrization of *cis*-1,2- Di(*t*-butyldimethylsilyloxy)cyclohexane (213) with Acetone as Solvent.



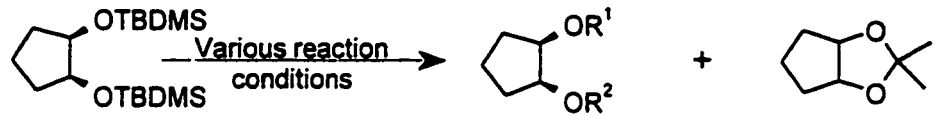
213

134 $R^1 = R^2 = H$
215 R^1 = TBDMS, R^2 = H
or R^1 = H, R^2 = TBDMS

Entry[a]	Equiv. H_2O	Catalyst (5 mol%)	Ligand (see Fig. 2.4)	Temp. (°C)	Time (h)	Product (% Yield)
1	5	$PdCl_2(CH_3CN)_2$	-	23	24	**134** (80) **215** (20)
2	5	$PdCl_2(CH_3CN)_2$	-	-78	48	**134** (25) **215** (25)
3	1	$PdCl_2(CH_3CN)_2$	-	23	19	**215** (39)[c]
4	1	$PdCl_2(CH_3CN)_2$	-	-78	20	**215** (40)[c]
5	5	$PdCl_2$	**199**	23	18	N.R.[b]
6	5	$PdCl_2$	**196**	23	18	N.R.[b]
7[d]	1	$PdCl_2(PPh_3)_2$	-	23	22	N.R.[b]
8[d]	1	$PdCl_2(PPh_3)_2$	-	75	22	N.R.[b]

[a] Acetone used as solvent in all reactions except when stated. [b] No reaction detected.
[c] Recovered starting material and trace amounts of **134**. [d] 1:1 Acetone:DMF mixture

Table 2.2 Desymmetrization of *cis*-1,2- Di(*t*-butyldimethylsilyloxy)cyclopentane (214) with Acetone as Solvent.



214 **123** $R^1 = R^2 = H$ **217**

216 R^1 = TBDMS, R^2 = H or R^1 = H, R^2 = TBDMS

Entry[a]	Equiv. H_2O	Catalyst (5 mol%)	Ligand (see Fig. 2.4)	Temp. (°C)	Time (h)	Product (% Yield)
1	5	$PdCl_2(CH_3CN)_2$	-	23	24	**123** (100)
2	5	$PdCl_2(CH_3CN)_2$	-	-78	24	**123** (100)
3	1	$PdCl_2(CH_3CN)_2$	-	-78	20	**123** (100)
4	1	$PdCl_2(CH_3CN)_2$	PPh_3	23	16	N.R.[b]
5	5	$PdCl_2(CH_3CN)_2$	PPh_3	23	20	N.R.[b]
6	5	$PdCl_2(PPh_3)_2$	-	23	15.5	N.R.[b]
7	1	$PdCl_2$	**197**	23	21	N.R.[b]
8	1	$PdCl_2$	**198**	23	20	**217** (86) **216** (3)
9	1	$PdCl_2$	**198**	23	19	N.R.[b]
10	1	$PdCl_2$	**200**	23	19	N.R.[b]
11	1	$PdCl_2$	**196**	23	23	N.R.[b]
12	1	$PdCl_2$	-	23	16	**216** (24)[c]
13[d]	5	$PdCl_2(PPh_3)_2$	-	23	19	N.R.[b]
14[d]	5	$PdCl_2$	**197**	23	19	N.R.[b]

[a] Acetone used as solvent in all reactions except when stated. [b] No reaction detected.
[c] Products **123** and **217** were also present by GC analysis but not isolated. [d] Acetonitrile used as solvent.

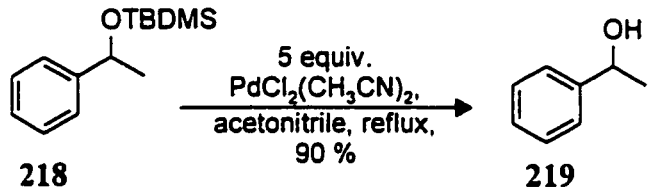
Although **215** was only produced in 40% yield, attention was diverted to trying various palladium catalysts with and without chiral ligands. Palladium (II) catalysts for all reaction systems in Sections 2.3 and 2.4 were either prepared *in situ* or added as a solid to the reaction mixture. Treatment of *meso*-compound **214** with 1 and 5 equivalents of water in the presence of $PdCl_2(CH_3CN)_2$ and 10 mol% PPh_3 in HPLC grade acetone

only provided starting material (Table 2.2, entry 4 and 5). When the catalyst $PdCl_2(PPh_3)_2$ (purchased from Aldrich) was used, no reaction was observed (Table 2.2, entry 6). Attempts with palladium (II) chloride in the presence of chiral ligands **196-200** were also performed (Table 2.1, entries 5 and 6; Table 2.2, 7-11). In all cases except one (Table 2.2, entry 8), no reaction was observed and only starting material was recovered. In the one case, although only 3% of the mono-desilylated product **216** was formed, an excellent yield of the unexpected acetonide **217** (86%) was obtained (Table 2.2, entry 8). Unfortunately, the mono-desilylated product **216** was proven to be racemic by examining the ^{1}H-NMR spectra in the presence of the chiral shift reagent $Eu(hfc)_3$. Further attempts to desymmetrize compounds **214** in the presence of the chiral ligand **198** (Table 2.2, entry 9) provided only starting material. It was therefore postulated that the chiral palladium (II) species was not the active species present in solution for entry 8 of Table 2.2, and that possibly trace amounts of $PdCl_2$ resulted in the desilylation. This result was confirmed when treatment of compound **214** in acetone containing 1 equivalent of water in the presence of $PdCl_2$ yielded 24% of mono-desilylated product **216** (Table 2.2, entry 12). The side products **123** and **217** were also observed by GC but were not isolated.

Toms *et al.* observed that benzylic TBDMS ether **218** could be desilylated in acetonitrile in the presence of 5 mol% $PdCl_2(CH_3CN)_2$ (Scheme 2.20).[61] Although acetonitrile has been reported to give inconsistent desilylation results,[61] two attempts to desymmetrize *meso*-TBDMS ether **214** were tried using acetonitrile as solvent. Unfortunately, only starting material was recovered (Table 2.2, entries 13 and 14). Attempts were also performed using the 1:1 acetone:DMF mixture, which had been

reported to desilylate TBDMS aliphatic ethers,[21] with the following modification: $PdCl_2(PPh_3)_2$ was used instead of $PdCl_2(CH_3CN)_2$. Again, no desilylation occurred even after refluxing, and only starting material **213** was detected (Table 2.1, entries 7 and 8).

Scheme 2.20

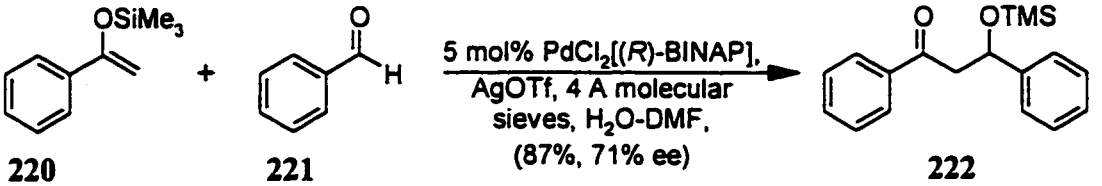


218 **219**

With the disappointing initial results, new routes were explored for the asymetric desymmetrization of *meso*-TBDMS protected diols **213** and **214**. A literature search revealed two desilylation procedures that could be modified for the asymmetric desymmetrization reaction.

Shibasaki[62] reported a catalytic asymmetric aldol reaction between **220** and **221** via a chiral palladium (II) enolate in wet DMF (Scheme 2.21). Compound **222** was isolated in 87% yield and 71% ee. Thus, it was postulated that the palladium (II) catalyst developed in Shibasaki's report may be a more reactive Lewis acid and therefore should be tried for the asymmetric desilylation/desymmetrization (Table 2.3).

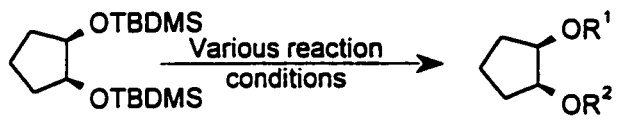
Scheme 2.21



220 **221** **222**

Initial desymmetrization attempts were performed under the conditions described by Shibasaki and co-workers[62] (see arrow, Scheme 2.21), and the results are listed in Table 2.3. The palladium species generated under these conditions, according to the report by Shibasaki, should be either the cationic palladium complex, [PdCl(phosphine ligand)(DMF)]$^+$[OH]$^-$, or its covalent complex, PdCl(OH)(phosphine ligand). In all the experiments tried, no mono-desilylated compound **216** was obtained. Some of the experimental condition changes were: raising the temperature from room temperature to 75 °C (Table 2.3, compare entries 2 and 3), varying the ligands (Table 2.3, entries 1, 2, and 4), and varying the solvent conditions from DMF to an acetone:DMF mixture (Table 2.3, compare entries 2 and 5).

Table 2.3 Desymmetrization Attempts Using DMF Solvent Systems.



214

123 $R^1 = R^2 = H$
216 R^1 = TBDMS, $R^2 = H$ or $R^1 = H$, R^2 = TBDMS

Entry[a]	Equiv. H_2O	Catalyst (5 mol%)	Ligand	Temp. (°C)	Time (h)	% Yield
1	5	PdClOH	**196**	23	24	N.R.[b]
2	5	PdClOH	**197**	23	24	N.R.[b]
3	5	PdClOH	**197**	75	24	N.R.[b]
4	5	PdClOH	PPh_3	75	24	N.R.[b]
5[c]	1	PdClOH	**197**	23	20	N.R.[b]

[a] DMF used as solvent in all reactions except where stated. [b] No reaction detected. [c] 1:1 Acetone:DMF mixture.

As previously illustrated in Section 1.2.1, Cormier reported that TBDMS ethers can be desilylated with palladium (II) oxide in a cyclohexene:MeOH mixture to provide

the corresponding alcohol.[19] Compounds **213** and **214** were treated with this solvent system in the presence of a variety of palladium (II) complexes and the results are listed in Tables 2.4 and 2.5.

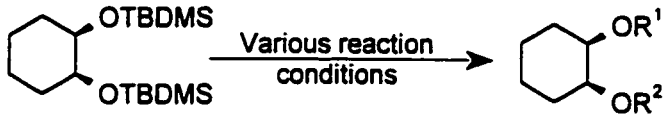
Initial attempts proved to be somewhat rewarding. Although treatment of compound **213** with cyclohexene:MeOH in the presence of 5 mol% $PdCl_2(PPh_3)_2$ at room temperature (~23 °C) did not proceed (Table 2.4, entry 1), reacting compound **214** under the same conditions produced compound **216** in 4% yield (Table 2.5, entry 1). Raising the temperature of the reaction to 65 °C resulted in an increase of the yield of **216** from 4% to 50% (Table 2.5, compare entries 1 and 2), but did not result in desilylation of compound **213** (Table 2.4, compare entries 1 and 2).

Further studies showed that the cyclohexene:MeOH solvent mixture in conjunction with a palladium (II) complex was required for the reaction to proceed. These results are reported in Table 2.5. Removal of either cyclohexene or MeOH from the reaction mixture resulted in no desilylation (entries 3 and 4). Compound **214** was also treated with $PdCl_2(PPh_3)_2$ in MeOH containing 5 equivalents of water with no effect; only starting material was recovered (entry 5). Finally, no desilylation was observed when compound **214** was stirred at 65 °C in cyclohexene:MeOH without a palladium (II) catalyst present (entry 6).

Different chiral palladium (II) compounds were tried next. The reactions were generally performed at room temperature (~23 °C) and not at reflux, since lower temperatures typically provided more of the mono-silylated compound (i.e. **215** or **216**). Treatment of compounds **213** and **214** with cyclohexene:MeOH in the presence of 5

mol% $PdCl_2$ and chiral ligands (**197**, **199** and **200**) in general gave no reaction (Table 2.4, entry 3; Table 2.5, entries 7-9). Desilylation also did not occur when compound **213** was treated with Shibaski's catalyst in Cormer's solvent conditions (cyclohexene:MeOH) (Table 2.4, entry 4), or when acetone was substituted for methanol (Table 2.4, entry 10). However, when **196** was used as the chiral ligand a mixture of products was obtained. Compound **213** provided diol **134** (5%) and mono-TBDMS ether **215** (11%) (Table 2.4, entry 5), while compound **214** provided diol **123** (30%) and mono-TBDMS ether **216** (37%) (Table 2.5, entry 11). The mixtures also contained unreacted starting material. Performing the reaction at 65 °C resulted in an increase in the yield of **215** yield from 11% to 33% (Table 2.4, compare entries 5 and 6), but only diol **123** was formed with **214** (Table 2.5, compare entries 11 and 12). Unfortunately, the mono-desilylated products **215** and **216** from Table 2.4 (entries 5 and 6) and Table 2.5 (entry 11) were proven to be racemic by ^{1}H-NMR when run in the presence of chiral shift reagent $Eu(hfc)_3$.

Table 2.4 New Attempts in the Desymmetrization of *cis*-1,2- Di(*t*-butyldimethylsilyloxy)cyclohexane (213).



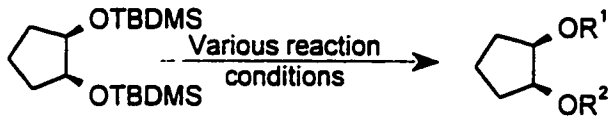
213

134 $R^1 = R^2 = H$
215 R^1 = TBDMS, $R^2 = H$
or $R^1 = H$, R^2 = TBDMS

Entry	Solvent	Catalyst (5 mol%)	Ligand	Temp. (°C)	Time (h)	Product (% Yield)
1	cyclohexene, MeOH	$PdCl_2(PPh_3)_2$	-	23	22	N.R.[a]
2	cyclohexene, MeOH	$PdCl_2(PPh_3)_2$	-	65	22	N.R.[a]
3	cyclohexene, MeOH	$PdCl_2$	**199**	23	18	N.R.[a]
4[d]	cyclohexene, MeOH	PdClOH	**196**	23	18	N.R.[a]
5	cyclohexene, MeOH	$PdCl_2$	**196**	23	20	**215** (11) **134** (5)
6	cyclohexene, MeOH	$PdCl_2$	**196**	75	19	**215** (33) **134** (25)

[a] No reaction detected. [b] Trace amount of DMF present.

Table 2.5 New Attempts in the Desymmetrization of *cis*-1,2- Di(*t*-butyldimethylsilyloxy)cyclopentane (214).



214

123 $R^1 = R^2 = H$
216 R^1 = TBDMS, $R^2 = H$
or $R^1 = H$, R^2 = TBDMS

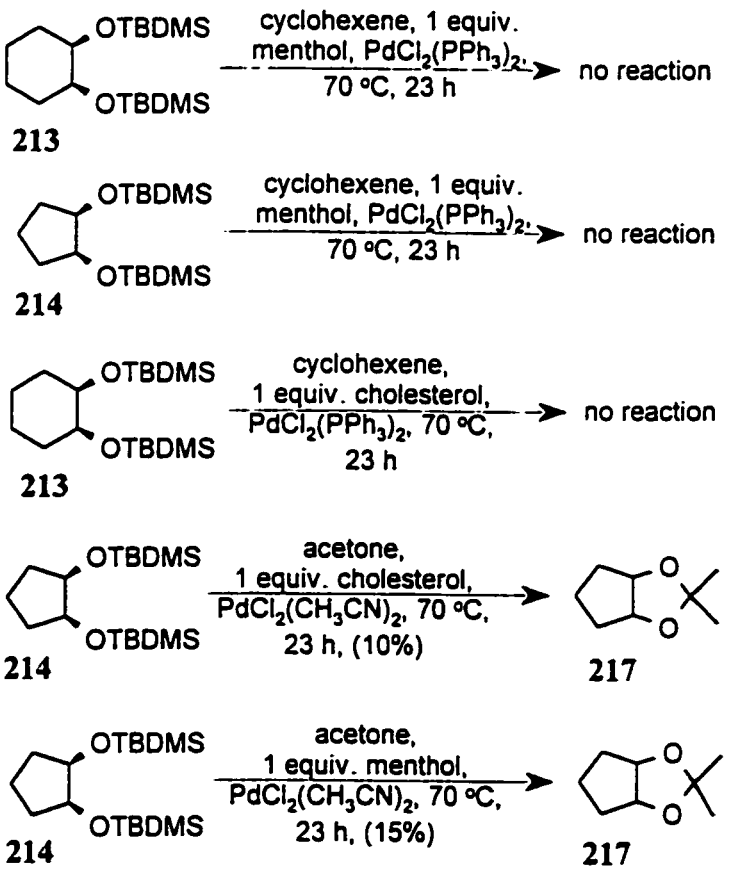
Entry	Solvent	Catalyst.	Ligand	Temp. (°C)	Time (h)	Product (% Yield)
1	cyclohexene, MeOH	$PdCl_2(PPh_3)_2$	-	23	15.5	**216** (4)
2	cyclohexene, MeOH	$PdCl_2(PPh_3)_2$	-	65	7	**216** (50)
3	MeOH	$PdCl_2(PPh_3)_2$	-	70	21	N.R.[a]
4	cyclohexene	$PdCl_2(PPh_3)_2$	-	65	18	N.R.[a]
5	MeOH, H_2O	$PdCl_2(PPh_3)_2$	-	65	19	N.R.[a]
6	cyclohexene, MeOH	-	-	65	18	N.R.[a]
7	cyclohexene, MeOH	$PdCl_2$	**197**	23	20	N.R.[a]
8	cyclohexene, MeOH	$PdCl_2$	**200**	23	17	N.R.[a]
9	cyclohexene, MeOH	$PdCl_2$	**200**	23	18	N.R.[a]
10	Acetone, cyclohexene	$PdCl_2(PPh_3)_2$	-	65	20	N.R.[a]
11	cyclohexene, MeOH	$PdCl_2$	**196**	23	23	**216** (37) **123** (30)
12	cyclohexene, MeOH	$PdCl_2$	**196**	75	17	**123** (99)

[a] No reaction detected.

The final attempts to desymmetrize *meso*-TBDMS ethers **213** and **214** involved an attempt at an asymmetric induction and the results are shown in Scheme 2.22. The chiral

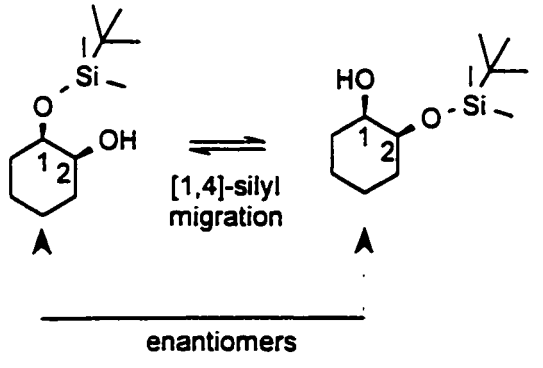
alcohols menthol and cholesterol were used in place of the methanol or water. No reaction occurred when compounds **213** and **214** were treated with cyclohexene containing 1 equivalent of menthol in the presence of $PdCl_2(PPh_3)_2$, or when compound **213** was treated with cyclohexene containing 1 equivalent of cholesterol (Scheme 2.22). However, acetonide **217** was produced, albeit in poor yield, when compound **214** was treated with acetone containing 1 equivalent menthol or cholesterol in the presence of $PdCl_2(CH_3CN)_2$.

Scheme 2.22



The unsuccessful results (i.e. no enantiomeric enrichment) obtained for the asymmetric desymmetrization of compounds **213** and **214** could be attributed to a intramolecular [1,4] O→O silyl migration[63] or in the absence of a silyl migration, poor asymmetric induction due to unfavorable coordination of the chiral auxiliary to the palladium catalyst. Since successful asymmetric aldol reactions have been reported by Shibasaki using palladium (II) catalysts in the presence of chiral auxiliaries, the 0% ee could be due to the intramolecular [1,4] O→O silyl migration of the TBDMS ether from the oxygen atom at C-1, to the oxygen atom at C-2, providing a racemic mixture (Scheme 2.23). In retrospect, the initial choice of using 1,2-*meso*-diols **123** and **134** was not the best. Instead, *meso*-diols that have a structure and/or geometry which limits and/or hinders intramolecular silyl migrations should have been tried (see Future Work, Section 2.2.5).

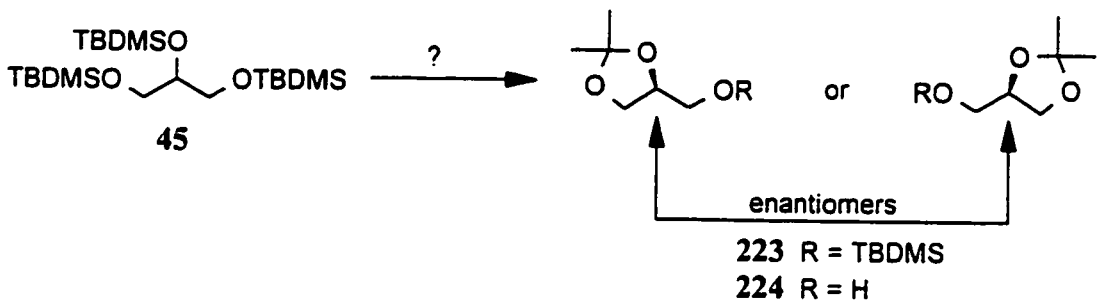
Scheme 2.23



The formation of acetonide **217** (Scheme 2.22), coupled with the result in Table 2.2 (entry 8), led to the following idea. If an asymmetric desymmetrization of 1,2-*meso*-diols was not possible due to intramolecular [1,4] O→O silyl migration, then perhaps a

tri-silylated compound, such as tri-silylated glycerol **45**, could be asymmetrically desymmetrized by the removal of two silyl groups and the formation of an acetonide (Scheme 2.24). If **223** or **224** were formed, then silyl migrations could not occur and hopefully, **223** and **224** would be formed in high yields and % ee. The following paragraphs will describe attempts to desymmetrize tri-silylated glycerol **45**.

Scheme 2.24



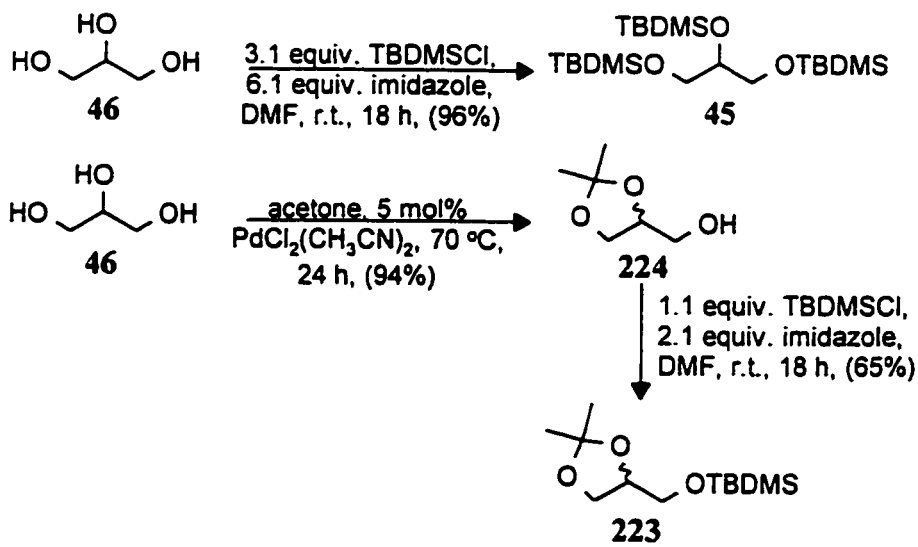
45

223 R = TBDMS
224 R = H

2.4 Results and Discussion: Desymmetrization of Tri-silylated Glycerol 45.

Tri-silylated glycerol **45** was synthesized in quantitative yield from glycerol (**46**) by treatment with *t*-butyldimethylsilyl chloride in DMF containing imidazole (Scheme 2.25). In order to be able to determine the % ee's, racemic acetonides **223** and **224** were also synthesized. Glycerol (**46**) was treated with dry acetone in the presence of 5 mol% $PdCl_2(CH_3CN)_2$ at 70 °C to produce compound **224** in 94% yield (Scheme 2.25). Treatment of **224** with *t*-butyldimethylsilyl chloride in DMF containing imidazole provided the mono-TBDMS protected product **223** (65% yield) (Scheme 2.25). The formation of products **45**, **223** and **224** were confirmed by analysis of a variety of spectral data.

Scheme 2.25



The initial attempt to desymmetrize tri-TBDMS silyl ether **45** involved a modification of the optimized aliphatic TBDMS ether desilylation conditions: 5 mol%

$PdCl_2(CH_3CN)_2$ in reagent grade acetone containing 5 equivalents of water. The modification involved using anhydrous conditions in order to limit the possibility of hydrolysis of the acetonide group. Treating compound **45** with 5 mol% $PdCl_2(CH_3CN)_2$ in freshly distilled acetone provided 86% yield of acetonide **223** (Table 2.6, entry 1).

This initial positive result led to an investigation with various palladium (II) dichloride complexes containing either achiral (PPh_3) or chiral ligands **197**, **199**, and **200** (Figure 2.4). In addition, the effect of solvent on the yield of the reaction was studied. Unfortunately, when the palladium catalyst was complexed with a ligand containing a phosphine group, only starting material **45** was detected (Table 2.6, entries 2-8). Increasing the temperature of the reaction to 75 °C had no effect, and once again only starting material was detected (Table 2.6, compare entries 6 and 7). Only starting material was found when the ligands were changed from PPh_3 to the less basic $AsPh_3$ ligand, even after warming to 70 °C (Table 2.6, compare entries 2 and 9). No reaction occurred when compound **45** was treated with 5 mol% $PdCl_2(PPh_3)_2$ in a variety of different solvents (acetonitrile, propionitrile, THF, and DMF) containing 1.1 equivalents of acetone (Table 2.6, entries 10-13). Since the initial attempts to asymmetrically desymmetrize compound **45** failed, new methods for desilylation/desymmetrization were investigated.

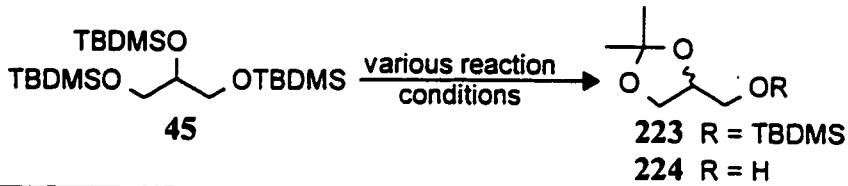
The above discouraging results indicated that a more reactive palladium (II) complex may be needed in order for the reaction to proceed. Treatment of compound **45** with $PdBr_2(PPh_3)_2$ provided only starting material (Table 2.6, entry 14). On the advice of fellow colleagues, cationic palladium complexes were tried. $PdCl_2(PPh_3)_2$ was treated

with 1 equivalent $AgBF_4$ or 2 equivalents of AgOTf in an attempt to produce the $[PdCl(PPh_3)_2]^+BF_4^-$ or $[Pd(PPh_3)_2]^{+2}[OTf]^{-2}$ cationic complexes *in situ*. The palladium complex was then added to a mixture containing compound **45** and freshly distilled acetone. When palladium complex $[PdCl(PPh_3)_2]^+BF_4^-$ was added only starting material **45** was detected (Table 2.6, entry 15); however, $[Pd(PPh_3)_2]^{+2}[OTf]^{-2}$ produced **223** in 80% yield (Table 2.6, entry 16). Interestingly, further attempts with $[Pd(PPh_3)_2]^{-2}[OTf]^{-2}$ resulted in no acetonide **223** formation (Table 2.6, entry 17).

This result presented the possibility that trace amounts of AgOTf and not $[Pd(PPh_3)_2]^{+2}[OTf]^{-2}$ were the active Lewis acid in the reaction. Tri-silylated compound **45** was treated with AgOTf in acetone at room temperature and produced acetonide **223** in 95% yield (Table 2.6, entry 18). This experiment confirmed that AgOTf was most probably the active species for the formation of **223** and this may require further investigation.

Since the use of a palladium (II) dichloride complex with chiral ligands appeared no longer worth pursuing, new approaches for the asymmetric desymmetrization of tri-silylated compound **45** were studied. Two methods considered were asymmetric induction and the use of different Lewis acids.

Table 2.6 Desymmetrization of Tri-silylated Glycerol 45.



45

223 R = TBDMS
224 R = H

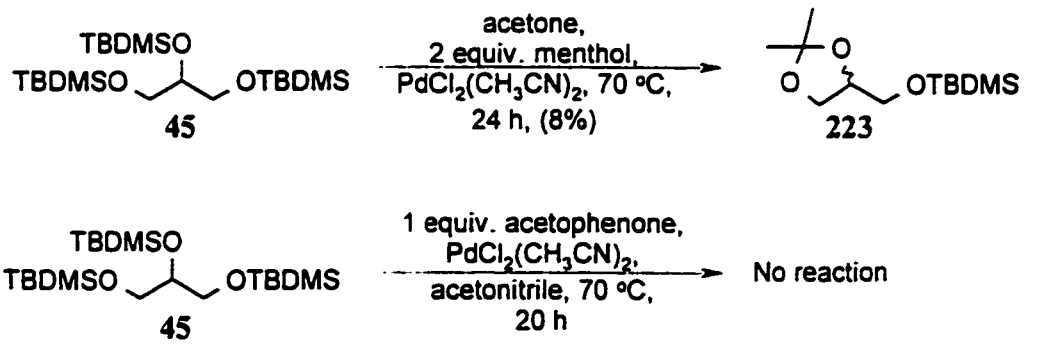
Entry	Solvent	Catalyst.	Ligand	Temp. (°C)	Time (h)	Product (% Yield)
1	acetone	$PdCl_2(CH_3CN)_2$	-	23	26	**223** (86)
2	acetone	$PdCl_2(PPh_3)_2$	-	23	26	N.R.[a]
3	acetone	$PdCl_2$	**197**	23	18	N.R.[a]
4	acetone	$PdCl_2$	**199**	23	22	N.R.[a]
5[c]	acetone	PdClOH	**200**	23	26	N.R.[a]
6	acetone	$PdCl_2$	**200**	23	25	N.R.[a]
7	acetone	$PdCl_2$	**200**	75	25	N.R.[a]
8	acetone	$PdCl_2(PFu_3)_2$	-	23	22	N.R.[a]
9	acetone	$PdCl_2(AsPh_3)_2$	-	23-70	20 20	N.R.[a]
10	acetone: acetonitrile	$PdCl_2(PPh_3)_2$	-	23	18	N.R.[a]
11	acetone: propionitrile	$PdCl_2(PPh_3)_2$	-	23	18	N.R.[a]
12	acetone: THF	$PdCl_2(PPh_3)_2$	-	23	48	N.R.[a]
13	acetone:DMF	$PdCl_2(PPh_3)_2$	-	23	18	N.R.[a]
14	acetone	$PdBr_2(PPh_3)_2$	-	23	23	N.R.[a]
15	acetone	$[PdCl(PPh_3)_2]^+$	-	23	23	N.R.[a]
16	acetone:DMF	$[Pd(PPh_3)_2]^{+2}$	-	23	18	**223** (80)
17	acetone:DMF	$[Pd(PPh_3)_2]^{+2}$	-	23	24	N.R.[a]
18	acetone	AgOTf	-	23	23	**223** (95)

[a] No reaction detected. [c] Trace amount of DMF.

To ascertain whether asymmetric induction was possible for the desymmetrization of **45**, two reactions were attempted. Since compound **214** formed acetonide **217** when treated with acetone containing 1 equivalent menthol in the presence of $PdCl_2(CH_3CN)_2$ (Scheme 2.22), a similar attempt was tried by treating compound **45** with the same reaction conditions (Scheme 2.26). Product **223** was formed in 8% yield, but was proven to be racemic by ^{1}H-NMR using chiral shift reagent $Eu(hfc)_3$.

The second strategy for asymmetric induction involved replacing acetone with a ketone containing a stereogenic centre in the molecule. In order to test this hypothesis acetophenone was used initially to determine if ketalization was possible. If ketalization was successful, then a variety of ketones containing stereogenic centres could tried. Acetonitrile was chosen as solvent since Toms[61] did observe desilylation of **218** in acetonitrile (Scheme 2.20). However, no ketalization occurred when acetophenone was used as a model (Scheme 2.26).

Scheme 2.26

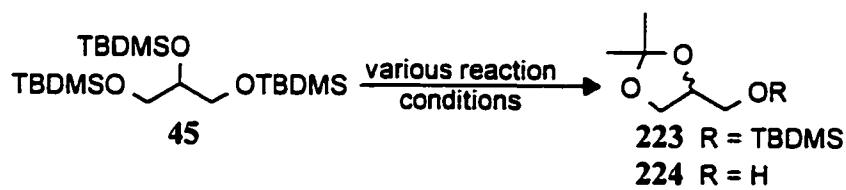


Since palladium (II) dichloride does not appear to be an effective Lewis acid for the asymmetric desymmetrization of **45** in the presence of phosphine ligands and in the

absence of acetone, other Lewis acids were used. Acetonide **223** did not form at room temperature or at 70 °C when $ZnCl_2$ was used as the Lewis acid (Table 2.7, entries 1 and 2), and $ZnBr_2$ showed similar results (Table 2.7, entries 3 and 4).

While this thesis was being written, Yamamoto *et al.* reported that AgOTf can be used in conjunction with (*S*)-BINAP to provide **226** in 88% yield in 96% ee (Scheme 2.27).[64] Since ketalization does occur with AgOTf (Table 2.6, entry 18) it may be possible to desymmetrize compound **45** with phosphine ligands in the reaction mixture (e.g. PPh_3). In a recent desymmetrization attempt, compound **45** was treated with AgOTf and triphenylphosphine in freshly distilled acetone at room temperature for 3 days. Compound **223** was formed in 54% yield (Table 2.7, entry 5). This result may indicate that asymmetric desymmetrization will be possible if AgOTf is used in the presence of chiral ligands (e.g. (*S*)-BINAP (**227**)). Although this is very positive result, due to time constraints no further reactions have been performed on this system.

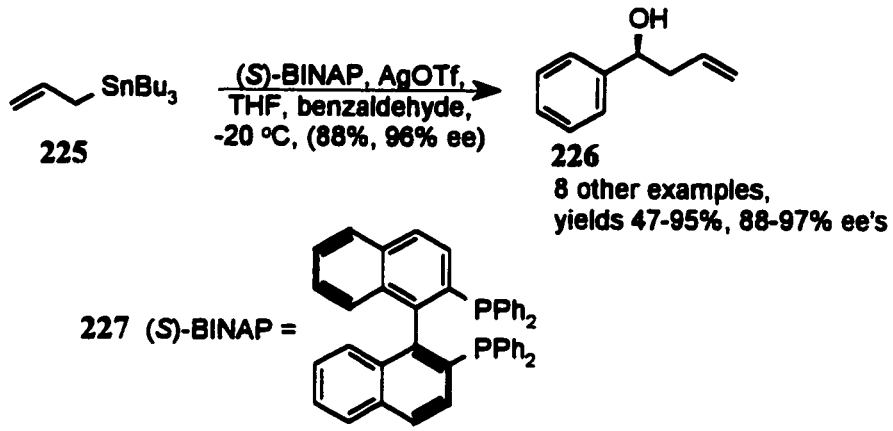
Table 2.7 Attempts to Desymmetrize Tri-silylated Glycerol (45) with Different Lewis Acids.



Entry	Solvent	Catalyst	Ligand	Temp. (°C)	Time (h)	Product (% Yield)
1	acetone	5 mol% $ZnCl_2$	-	23	48	N.R.[a]
2	acetone	5 mol% $ZnCl_2$	-	70	20	N.R.[a]
3	acetone	5 mol% $ZnBr_2$	-	r.t.	20	N.R.[a]
4	acetone	5 mol% $ZnBr_2$	-	70	19	N.R.[a]
5	acetone	AgOTf	PPh_3	23	3 d	**223** (54)[b]

[a] No reaction detected. [b] Yield not optimized

Scheme 2.27



2.5 Conclusions.

The synthesis of enantiomerically pure compounds **215**, **216**, and **223** was not possible using the methods tried to date. In some examples, however, desymmetrization was possible and compounds **215**, **216**, and **223** were formed as racemic mixtures. The best results for the desymmetrization of *meso*-compounds **213** and **214** were obtained when **213** and **214** were treated with $PdCl_2$(CHIRAPHOS) in a cyclohexene:MeOH solvent. Unfortunately, the product was shown to be racemic. The low enantioselectivity may be due to an intramolecular [1,4] O→O migration. The lack of success in asymmetric desymmetrization of *meso*-compounds **213** and **214** and tri-silylated glycerol **45** may also be attributed to palladium (II) dichloride being a weaker Lewis acid in the

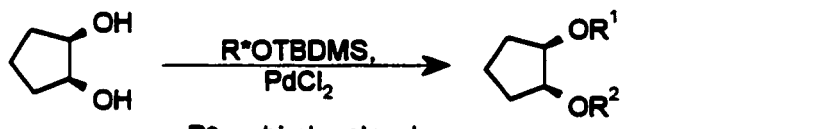
presence of phosphine ligands. Several other Lewis acids were used in the desymmetrization reaction and the most successful result was with the desymmetrization of tri-silylated glycerol **45**. In this case, acetonide **223** was formed in 54% yield when AgOTf was used as the Lewis Acid **in the presence of a phosphine ligand**. Thus, further work using AgOTf with chiral phosphines must be explored. Some ideas are presented in the next section.

2.6 Future Work.

The are several directions that this project could take. The following paragraphs outline where this project could and should proceed:

(1) Instead of attempting an asymmetric induction to desilylate/desymmetrize *meso*-TBDMS ethers **213** and **214**, the reaction could be reversed and diols **134** and **123** could be **silylated**/desymmetrized by asymmetric induction from a TBDMS silyl ether containing a chiral centre. In this case a chiral TBDMS protected ether could be added to the symmetrical diol (Scheme 2.28).

Scheme 2.28



123 R* = chiral molecule **216** R^1 = TBDMS, R^2 = H or R^1 = H, R^2 = TBDMS

(2) Reactions should be done to determine if the intramolecular TBDMS silyl migration was occurring in compounds **215** and **216**. This could be investigated by attempting to desilylate other *meso*-diols (Figure 2.6) where intramolecular silyl migrations should not occur because the structure and/or geometry of the compound prohibit an intramolecular silyl migration.

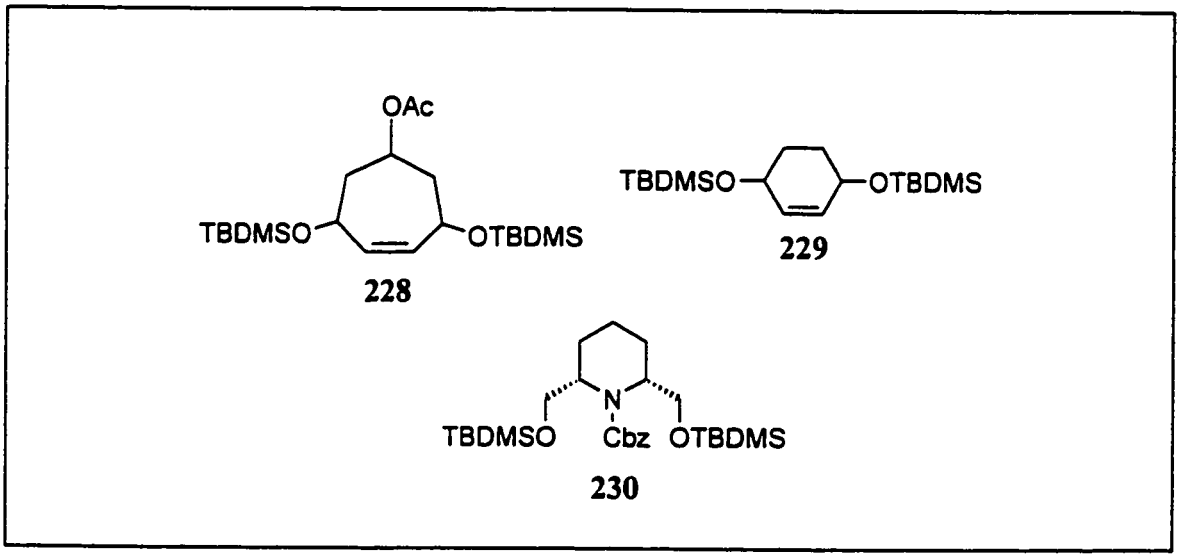
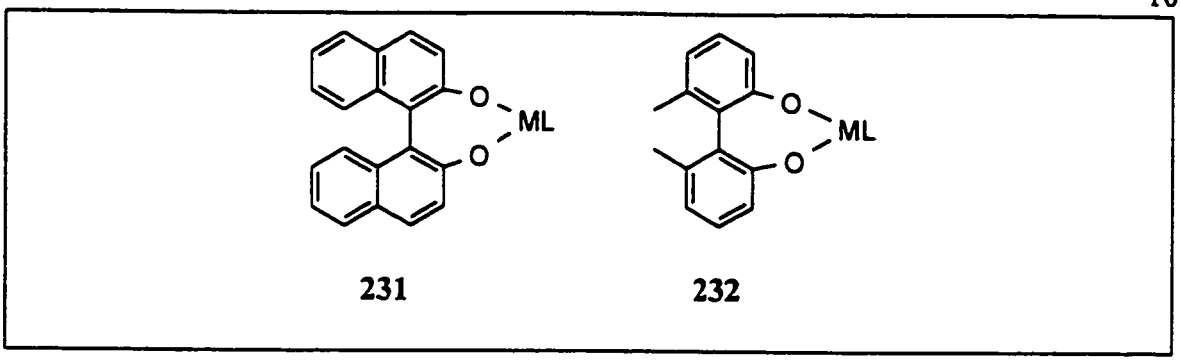


Figure 2.6 Potential *meso*-Diols that May Not Undergo Silyl Migration.

(3) Investigate further the reaction of compound **45** with AgOTf in the presence of chiral phosphine ligands, since the model study with AgOTf and PPh_3 did provide acetonide **221** in 54% yield.

(4) Finally, the desilylation of TBDMS groups has been observed when treated with $LiAlH_4$.[65] Perhaps an asymmetric reduction using aluminium complexes with C_2-symmetric biaryl diols (**231**[66] and **233**[67]) could be used to reduce the O-Si bond and produce enantiomerically pure compounds (Figure 2.7). All of these project continuations are intriguing, but time constraints prevented further study for this thesis.



231 232

Figure 2.7 Examples of Ligands Used for the Asymmetric Reduction of Ketones.[68]

3 Experimental Methods.

3.1 General methods.

Solvents and reagents were purchased in anhydrous form or were purified by standard methods[69] where necessary. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl, while methylene chloride (CH_2Cl_2) was freshly distilled from calcium hydride. Both solvents (THF and CH_2Cl_2) were distilled immediately before use. Acetone (HPLC grade), acetonitrile, diethyl ether, *N*,*N*-dimethylformamide (DMF), ethanol (HPLC grade) and methanol were purchased as anhydrous solvents in Sure/Seal® bottles from the Aldrich Chemical Company. Acetone (HPLC grade) was further dried by distilling from anhydrous $CaSO_4$ onto 4 Å molecular sieves and stored under nitrogen in dried Sure/Seal® bottles. Reagent grade acetone was purchased from Van Waters and Rogers/Canlab (Edmonton, AB., Canada). Propionitrile and cyclohexene (99+%) were dried over calcium hydride, distilled, and stored under nitrogen in dried Sure/Seal® bottles. TBDMS, TES, TIPS, and TBDPS chlorides were distilled before use. All alcohols used in this thesis were purchased from Aldrich Chemical Company and were distilled before use.[70,71]

All glassware, stir bars, and metal syringe needles employed in anhydrous reactions were oven dried (120 °C) for at least 2 hours. Reaction vessels were cooled to room temperature under a stream of nitrogen, while glass syringes and metal syringe needles were cooled in a desiccator containing Drierite® and purged with nitrogen prior to

use. Moisture or oxygen sensitive reactions were performed under a nitrogen atmosphere.

The following cooling baths[72] were used to maintain sub-ambient temperatures: liquid nitrogen-ethyl acetate (-85 °C), dry ice-acetone (-78 °C), and dry ice-acetonitrile (-41 °C).

Aluminium-backed silica gel plates purchased from E. Merck (0.2 mm silica gel 60, F_{252}) were used for thin layer chromatography (TLC). The plates were visualized with an ultraviolet lamp (254 nm or 366 nm) and/or by heating with a hot air gun after immersion a developing solution (118.4g $(NH_4)_8Mo_7O_{24}\cdot 4H_2O$, 200 mL concentrated H_2SO_4, and 2 L deionized water). Flash column chromatography was performed using 230-400 mesh silica gel (E. Merck), according to the method of Still *et al.*[73] Radial plate chromatography was accomplished with a Chromatotron (Harrison Research, Model 7924T) with the plates loaded with 1, 2, or 4 mm of silica gel (EM Science silica gel 60 PF_{254} with gypsum binder). Solvent systems used for TLC or chromatography as the liquid phase were various ratios of hexanes and ethyl acetate, and are listed with the following format: volume of hexanes:volume of ethyl acetate.

Analytical gas liquid chromatography (GC) was performed on a Shimadzu GC-9A gas chromatography equipped with a flame ionization detector using a 25 m x O.53 mm (i.d.) x 3 μm (film thickness) 007 Series Methyl Silicone (Quadrex Corporation) fused silica column. Chiral phase gas liquid chromatography was attempted on the same instrument using 25 m x 0.33 mm (i.d.) x 3 μm (film thickness) Cybex-B (Scientific Glass Engineering) fused silica column. Helium was used as carrier gas in both cases.

All compounds were named according to the IUPAC rules. Melting points were determined on all solids purified by column chromatography using an Electrothermal® melting point apparatus and are uncorrected. Boiling points recorded are uncorrected and refer to air-bath temperature measured with a Kugelrohr short path distillation apparatus.

The infrared spectra were recorded on a Mattson Model Series 4030 FT-IR spectrophotometer. Liquid samples were placed as thin films (neat) between NaCl plates. Solid samples were positioned between NaCl plates by addition of one or two drops of a solvent (Et_2O, $CDCl_3$, or $CHCl_3$) of the solid onto one of the plates at which time the solvent was evaporated producing a thin solid layer. The other NaCl plate was then placed on the thin solid layer. Main absorptions are listed in wavenumbers followed by the assignment in parentheses.

Nuclear magnetic resonance spectra were obtained on either a Bruker ACE-200 (^{1}H-200 MHz, ^{13}C-50 MHz) or a Bruker AM-400 (^{1}H-400 MHz, ^{13}C-100 MHz) spectrometer. Deuteriochloroform, unless otherwise stated, was used as the solvent and the ^{1}H-NMR spectra were referenced to the ^{1}H resonance of residual chloroform (δ 7.27), while ^{13}C-NMR spectra were referenced to the centre line of the ^{13}C-NMR resonance of deuteriochloroform (δ 77.0). ^{1}H-NMR spectra are listed in the following format: chemical shift (in ppm), (multiplicity, number of protons, coupling constant(s) (Hz), assignment). The following abbreviations are used to describe the multiplicities: br=broad, s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet. ^{13}C-NMR spectra are listed with the following format: chemical shift (in ppm), methyl (CH_3), methylene (CH_2), methine (CH), quaternary carbon (C), as determined by DEPT experiments,

assignment. In cases where the assignment of signals was ambiguous, the signals and assignments are grouped together. The numbering of atoms in the compounds to allow for the assignment of spectra may differ from the numbering to name the compound according to IUPAC nomenclature.

Low resolution mass spectra were either obtained using a Hewlett Packard 5890 Series II gas chromatograph interfaced to a Hewlett Packard 5971A mass selective detector or acquired by Mrs. Q. Wu (University of Calgary) using a VG-7070 spectrometer. The data was listed using the following format: mass (*m/z*), (relative intensity, assignment). Low resolution mass spectra using chemical ionization (NH_3 was the carrier gas) were recorded by Mrs. D. Fox (University of Calgary) on a Kratos MS-80 spectrometer. Elemental analyses were also performed by Mrs. D. Fox using a Control Equipment Corporation 440 Elemental Analyzer.

3.2 General Experimental Procedures.

3.2.1 General Procedure 1: The Preparation of a Silyl Protected Aryl or Aliphatic Alcohol.

The silylation reactions were performed as described by Corey *et al.*[3] To a solution of the silyl chloride (2.2 mmol) and imidazole (4.4 mmol) in freshly distilled DMF (10 mL) stirred at room temperature in a round bottom flask was added either the aryl or aliphatic alcohol (1.8 mmol). The reaction mixture was stirred at room

temperature under N_2 until analysis by TLC indicated the reaction was complete (typically 16 hours). 5% HCl (10 mL) was then added to quench the reaction. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), and dried over anhydrous Na_2SO_4. The solution was filtered to remove the drying agent, and the solvent was removed *in vacuo* to provide the crude silyl protected product. Purification was effected by flash column chromatography and/or distillation.

3.2.2 General Procedure 2: The Selective Preparation of a TBDMS Protected Aliphatic Alcohol.

The silylation reactions were performed as described by McDougal *et al.*[74] The diol (0.36 mmol) was dissolved with THF (1 mL) and then added dropwise to a suspension of NaH (0.40 mmol) in THF (5 mL) in a round bottom flask. After stirring the reaction for 5-10 minutes, *t*-butyldimethylsilyl chloride (0.40 mmol) was added to the solution. The reaction was stirred at room temperature, under N_2, until TLC indicated the reaction was complete (typically 16 hours). Water (3 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (2 x 10 mL) and the combined organic layers were dried with anhydrous Na_2SO_4. The drying agent was removed by filtration, and the solvent was removed *in vacuo* to provide the crude mono silylated product. Purification was effected by flash chromatography and/or distillation.

3.2.3 General Procedure 3: The Desilylation of a Phenolic Silyl Ether Using Palladium Dichloride.

To a solution of the TBDMS protected phenol (1.0 mmol) in acetone (1.25 mL) containing water (5.0 mmol), in a round bottom flask equipped with a reflux condenser, was added $PdCl_2(CH_3CN)_2$ (0.05 mmol). The reaction was heated at reflux, with stirring under N_2, until analysis by TLC or GC indicated the reaction was complete (typically 16 hours). The reaction was cooled to room temperature, filtered through Celite, and the acetone and water removed *in vacuo* to give the corresponding phenol. Purification was effected by distillation or by flash column chromatography followed by distillation.

3.2.4 General Procedure 4: A Kinetic Study in the Desilylation of Compound 75 Using Palladium Dichloride.

To an NMR tube was added a solution of compound **75** (6.3×10^{-2} mmol) dissolved in acetone-d_6 (0.5 mL) containing 0, 1, 2, 3, 4 or 5 equivalents of water, followed by the addition of a freshly prepared solution of $PdCl_2(CH_3CN)_2$ (50 μL, 3.2×10^{-3} mmol) dissolved in acetone-d_6 (see next paragraph for preparation of catalyst). Upon addition of the palladium catalyst the NMR tube was quickly cooled in a liquid N_2 bath and flame sealed. The reaction was then heated to 70 °C in the 400 MHz NMR spectrometer and analyzed by ^{1}H-NMR spectra at regular 1 hour intervals for four hours. Integration of the aldehyde proton for both starting material **75** and product **76** was

determined. Then, a plot of concentration (molar ratio based on integration) vs. time was created for each of the six different equivalents of water (see Table 3.1 for the slope and linear regression). Finally, the initial rates (slope) from each of these graphs were plotted verses equivalents of water to find the order of the reaction with respect to water.

A freshly prepared solution of $PdCl_2(CH_3CN)_2$ was made prior to each kinetic run attempt. In order to hopefully achieve a homogeneous mixture of $PdCl_2(CH_3CN)_2$ (20 mg, 7.7×10^{-2} mmol) was dissolved in acetone-d_6 (1 mL) in a 1 mL volumetric flask. Then an aliquot of the solution (831 μL, 7.7×10^{-2} mmol/mL) was dissolved in acetone-d_6 and brought to volume in a 1 mL volumetric flask to provide a yellow/orange solution (6.4×10^{-2} mmol/mL). An aliquot of this solution was immediately used for the above procedure. It should be noted that on prolonged standing the palladium (II) solution changed from yellow/orange→red/brown.

Table 3.1 Results from Kinetic Sample Runs.

Equiv. Water	Initial Rate of Reaction[25] (h^{-1})	Linear Regression
0	$(1.15 \pm 0.83) \times 10^{-2}$	0.999
1	$(1.88 \pm 0.14) \times 10^{-2}$	0.992
2	$(2.66 \pm 0.07) \times 10^{-2}$	0.997
3	$(4.13 \pm 0.04) \times 10^{-2}$	0.991
4	$(7.34 \pm 0.01) \times 10^{-2}$	0.995
5	$(1.03 \pm 0.01) \times 10^{-1}$	0.986

Method used for the calculation of error:

The error in NMR integration is assumed to be 10 % therefore:

$$\Delta y \cong f'(x)$$

where Δy is the error in concentration of **75**, and x is the number obtained NMR integration multiplied by 10%.

$$f'(x) = \lim_{(h\to 0)} \frac{((x+h)/(1+(x+h))-(x/(1+h))}{h}$$

$$= \lim_{(h\to 0)} \frac{h}{h(1+x+h)(1+x)}$$

$$= 1/(1+x)^2$$

$$\text{Therefore } \Delta y = 1/(1+x)^2$$

The error measurements were then plotted as error bars on the concentration (**75**) vs. time graphs and the error in initial rate was approximated to be the largest error of concentration calculated.

3.2.5 General Procedure 5: The Desilylation of a Phenolic Silyl Ether Using Mild Base Conditions.

To a solution of the TBDMS protected phenol (0.4 mmol) and absolute ethanol (2 mL) containing water (2.1 mmol), in a round bottom flask equipped with a reflux condenser, was added K_2CO_3 (2 mL). The reaction was heated at refluxed with stirring until analysis by TLC or GC indicated the reaction was complete (2-24 hours). The reaction was cooled to room temperature, filtered through Celite, and the ethanol and

water removed *in vacuo* to give the corresponding phenol. Purification was effected by distillation or by flash column chromatography followed by distillation.

3.2.6 General Procedure 6: Desilylation/Desymmetrization Using Palladium (II) Catalysts.

To a solution of either compound **45**, **123**, or **134** (0.2 mmol) in solvent (see Table 3.2 for solvent systems and amount used) containing 0, 1 or 5 equivalents of water (0, 0.2, or 1.0 mmol), in a round bottom flask, was added the palladium (II) catalyst (0.01 mmol). The reaction was heated at reflux, cooled to -78 °C (equipped with a reflux condenser), or left at room temperature with stirring until analysis by TLC or GC indicated the reaction was complete (typically over night). The reaction was cooled or warmed to room temperature, filtered through Celite, and the solvent and water removed *in vacuo* to give the corresponding diol, mono-TBDMS protect alcohol or the acetonide. Purification was effected by distillation or by flash column chromatography followed by distillation.

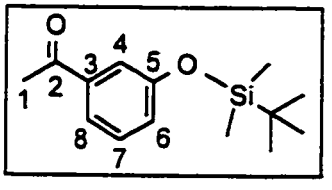
Table 3.2 Solvent Systems Used.

Entry	Solvent 1	Solvent 2
1	acetone (2.5 mL)	-
2	acetone (1.25 mL)	DMF (1.25 mL)
3	acetonitrile (2.5 mL)	-
4	DMF (2.5 mL)	-
5	cyclohexene (1.25 mL)	MeOH (1.25 mL)
6	cyclohexene (2.5 mL)	-
7	MeOH (2.5 mL)	-
8	acetone (1.25 mL)	cyclohexene (1.25 mL)
9	acetone (1.25 mL)	acetonitrile (1.25 mL)
10	acetone (1.25 mL)	propionitrile (1.25 mL)
11	acetone (1.25 mL)	THF (1.25 mL)

3.3 Experimental Procedures Pertaining to Chapter 1.

All silyl ethers presented in chapter one were prepared from known alcohols and desilylation of the silyl ether led to the corresponding known alcohols. For this reason, the characterization of the alcohols will not be reported in this section. However, the reader should be aware that in order to establish that the desired known alcohols had been formed ^{1}H-NMR (and typically mass spectra) was collected and then compared to ^{1}H-NMR (and typically mass spectra) of the purchased pure alcohols.

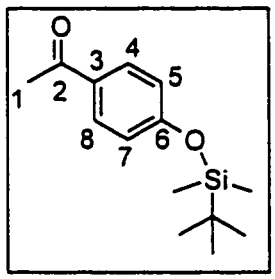
1-(3-{[1-(*t*-Butyl)-1,1-dimethylsilyl]oxy}phenyl)-1-ethanone (9)



General procedure 1 was used to convert phenol **8** (0.12 g, 0.89 mmol) to TBDMS protected phenol **9** (0.20 g, 0.79 mmol) in 89% yield following purification by flash column chromatography (9:1). bp 83-90 °C/0.1 Torr; IR 1691 (C=O), 926 (Si-O) cm^{-1}; ^{1}H-NMR

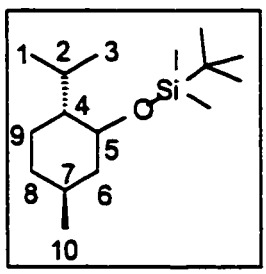
(200 MHz) 0.21 (s, 6H, $Si(CH_3)_2$), 0.99 (s, 9H, $C(CH_3)_3$), 2.56 (s, 3H, H-1), 7.30 (m, 4H, H-4, H-6, H-7, and H-8); ^{13}C-NMR (100 MHz) -4.5 (2 x CH_3), 18.1 (C), 25.6 (3 x CH_3), 26.6 (CH_3), 119.4 (CH), 121.5 (CH), 124.9 (CH), 129.5 (CH), 138.5 (C), 155.8 (C), 197.8 (C); Mass spectrum 250 (15, M^+), 197 (100, $[M-C_4H_9]$); Exact mass calc'd for $C_{14}H_{22}O_2Si$: 250.1389. Found: 250.1390.

1-(4-{[1-(*t*-Butyl)-1,1-dimethylsilyl]oxy}phenyl)-1-ethanone (29)



General procedure 1 was used to convert phenol **30** (0.35 g, 2.57 mmol) to TBDMS protected phenol **29** (0.57 g, 2.29 mmol) in 89.1% yield following purification by bulb-to-bulb distillation. Compound **29** was a clear colorless liquid. bp 85-90 °C/0.12 Torr; IR 1710 (C=O), 923 (Si-O) cm^{-1}; ^{1}H-NMR (200 MHz) 0.24 (s, 6H, $Si(CH_3)_2$), 1.00 (9H, s, $C(CH_3)_3$), 2.56 (s, 3H, H-1), 6.86 (d, 2H, H-4 and H-8), 7.88 (d, 2H, H-5 and H-7); ^{13}C-NMR (50 MHz) -4.4 (2 x CH_3), 18.2 (C), 25.5 (3 x CH_3), 26.3 (CH_3), 119.8 (2 x CH), 120.8 (C), 130.4 (2 x CH), 160.2 (C), 196.8 (C); Mass spectrum 250 (100, M^+); Exact mass calc'd for $C_{14}H_{22}O_2Si$: 250.1389. Found: 250.1371.

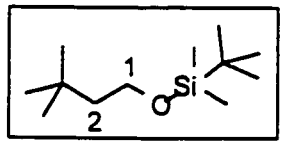
1-(*t*-Butyl)-1,1-dimethylsilyl (2-isopropyl-5-methylcyclohexyl) ether (55)



General procedure 1 was used to convert menthol (1.68 g, 10.72 mmol) to silyl ether **55** (2.48 g, 9.18 mmol) in 85.6% yield following purification by flash column chromatography (20:1) and

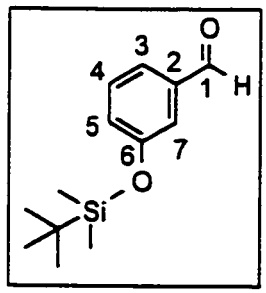
bulb-to-bulb distillation under reduced pressure. Compound **55** was a clear, colorless liquid. bp 85-90 °C/0.08 Torr; ^{1}H-NMR (200 MHz) 0.07 and 0.08 (2s, 6H, $Si(CH_3)_2$), 0.86 (9H, s, $C(CH_3)_3$), 1.20 (m, 17H, H-1, H-3, H-4, H-6, H-7, H-8, H-9, and H-10), 1.97 (br d, 1H, H-4), 2.16 (m, 1H, H-2), 3.41 (td, 1H, H-5). The ^{1}H-NMR spectrum was in good agreement with the literature.[75]

1-(*t*-Butyl)-1,1-dimethylsilyl (3,3-dimethylbutyl) ether (61)



General procedure 1 was used to convert 3,3-dimethyl-1-butanol (0.20 g, 1.96 mmol) to silyl ether **61** (0.423 g, 1.95 mmol) in 99.8% yield following purification by bulb-to-bulb distillation under reduced pressure. Compound **61** was a clear, colorless liquid. bp 45-50 °C/0.12 Torr; IR 2926 (H-C (sp^3)), 1094 (Si-O) cm^{-1}; ^{1}H-NMR (200 MHz) 0.06 (s, 6H, $Si(CH_3)_2$), 0.90 (2S, 18H, 2 x $C(CH_3)_3$), 1.48 (t, 2H, H-2), 3.68 (t, 2H, H-1); ^{13}C-NMR (50 MHz) -5.3 (2 x CH_3), 18.3 (C), 26.0 (3 x CH_3), 29.7 (C), 29.8 (3 x CH_3), 46.4 (CH_2), 60.4 (CH_2); Mass spectrum 159 (39, [M-C_4H_9]); Exact mass cal'd for $C_8H_{19}OSi$ [M-C_4H_9]: 159.1205. Found: 159.1214.

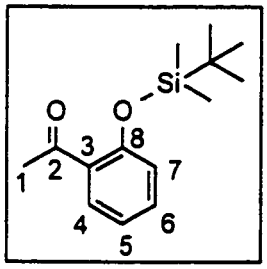
3-{[1-(*t*-Butyl)-1,1-dimethylsilyl]oxy}benzaldehyde (64)



General procedure 1 was used to convert phenol **63** (0.21 g, 1.72 mmol) to TBDMS protected phenol **64** (0.40, 1.68 mmol) in 98.0% yield following purification bulb-to-bulb distillation under reduced pressure. Compound **64** was a clear colorless liquid. bp 80-85 °C/0.08 Torr; ^{1}H-NMR (200 MHz) 0.26 (s, 6H, $Si(CH_3)_2$), 0.98 (s, 9H, $C(CH_3)_3$), 6.80

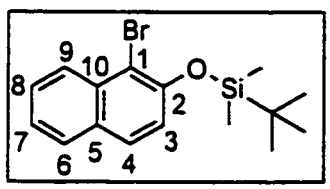
(dd, 1H, $J_{5,4}$=7.9 Hz, $J_{5,3}$=1.1 Hz H-5), 7.00 (m, 1H, H-4), 7.43 (m, 1H, H-3), 7.79 (dd, 1H, J=1.9 Hz, J=7.5Hz, H-7), 10.43 (s, 1H, H-1). The ^{1}H-NMR spectrum was in good agreement with the literature.[76]

1-(2-{[1-(*t*-Butyl)-1,1-dimethylsilyl]oxy}phenyl)-1-ethanone (65)



General procedure 1 was used to convert phenol **66** (0.10 g, 0.73 mmol) to TBDMS silyl ether **65** (0.14 g, 0.57 mmol) in 77.8% yield following purification by radial chromatography (50:1) provided a pure sample of **65**. Compound **65** was a clear colorless liquid. bp 80-85°C/0.1 Torr; IR 1686 (C=O), 910 (Si-O) cm^{-1}; ^{1}H-NMR (200 MHz) 0.27 (s, 6H, $Si(CH_3)_2$), 1.00 (s, 9H, $C(CH_3)_3$), 2.61 (s, 3H, H-1), 6.88 (dd, 1H, $J_{7,6}$=9.2 Hz, $J_{7,5}$=0.9 Hz, H-7), 6.99 (dt, 1H, $J_{6,7}$=$J_{6,5}$=7.7 Hz, $J_{6,4}$=1.0 Hz, H-6), 7.35 (m, 1H, H-5), 7.60 (dd, 1H, $J_{4,5}$=7.7 Hz, $J_{4,6}$=1.8 Hz, H-4); ^{13}C-NMR (50 MHz) -4.0 (2 x CH_3), 18.4 (C), 25.8 (3 x CH_3), 31.3 (CH_3), 120.2 (CH), 121.1 (CH), 129.9 (CH), 132.8 (CH), 154 (C), 200.9 (C); Mass spectrum 235 (2, [M-CH_3]), 193 (100, [M-C_4H_9]); Exact mass cal'd for $C_{13}H_{19}O_2Si$ [M-CH_3]: 235.1154. Found: 235.1157.

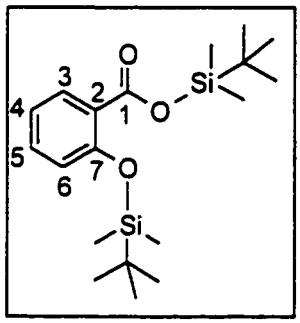
1-Bromo-2-naphthyl [1-(*t*-butyl)-1,1-dimethylsilyl] ether (67)



General procedure 1 was used to convert 1-bromo-2-napthol **68** (0.05 g, 0.24 mmol) to TBDMS protected phenol **67** (0.08 g, 0.23 mmol) in 92.7% yield following purification by flash column chromatography (9:1) and distillation under reduced pressure.

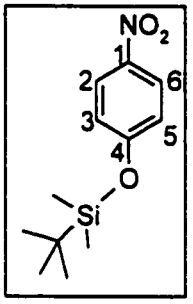
Compound **67** was a clear colorless liquid. bp 110-120 °C/0.06 Torr; ^{1}H-NMR (200 MHz) 0.31 (s, 6H, $Si(CH_3)_2$), 1.10 (9H, s, $C(CH_3)_3$), 7.15 (d, 1H, H-6), 7.39 (t, 1H, H-8), 7.56 (t, 1H, H-8), 7.67 (d, 1H, H-9), 7.79 (d, 1H, H-4), 8.24 (d, 1H, H-3). The ^{1}H-NMR spectrum was in good agreement with the literature.[75]

1-(*t*-Butyl)-1,1-dimethylsilyl 2-{[1-(*t*-butyl)-1,1-dimethylsilyl]oxy}benzoate (69)



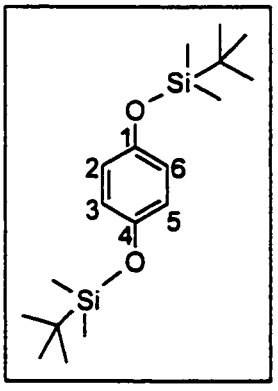
General procedure 2 was used to convert phenol **70** (0.12 g, 0.87 mmol) to TBDMS protected phenol **69** (0.32 g, 0.86 mmol) in 99.4% yield following purification by bulb-to-bulb distillation under reduced pressure. Compound **69** was a clear colorless liquid. bp 85-90 °C/0.1 Torr; IR 1686 (C=O), 909 (Si-O) cm^{-1}; ^{1}H-NMR (200 MHz) 0.23 (s, 6H, $Si(CH3)_2$), 0.38 (s, 6H, $Si(CH_3)_3$), 1.02 (s, 9H, $C(CH_3)_3$), 1.03 (s, 9H, $C(CH_3)_3$), 6.95 (m, 2H, H-6 and H-5), 7.35 (dt, 1H, $J_{4,3}=J_{4,5}=8.1$ Hz, $J_{4,6}=1.0$ Hz, H-4), (dd, 1H, $J_{3,4}=7.7$ Hz, $J_{3,5}=1.8$ Hz, H-3); ^{13}C-NMR (50 MHz) -4.3 and -4.5 (2 x CH_3), 17.8 (C), 18.4 (C), 25.6 (3 x CH_3), 25.8 (3 x CH_3), 120.7 (CH), 121.6 (CH), 124.1 (C), 131.5 (CH), 132.8 (CH), 155.8 (C), 208.4 (C); Mass spectrum 351 (3, [M-CH_3]), 309 (100, [M-C_4H_9]); Exact mass calc'd for $C_{19}H_{21}O_3Si$ [M-C_4H_9]: 309.1342. Found 309.1306.

4-Nitrophenyl [1-(*t*-butyl)-1,1-dimethylsilyl] ether (71)



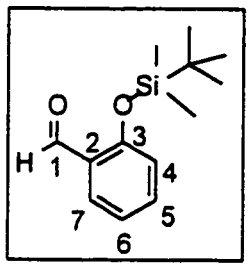
General procedure 1 was used to convert phenol **72** (0.11 g, 0.79 mmol) to TBDMS protected phenol **71** (0.16 g, 0.62 mmol) in 78.0% yield following purification bulb-to-bulb distillation under reduced pressure. Compound **71** was a yellow/orange solid. mp 45-46 °C; bp 90-95 °C/0.1 Torr (literature[77] mp 34 °C); IR 1348 (N-O), 910 (Si-O) cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6) 0.64 (s, 6H, $Si(CH_3)_2$), 1.35 (s, 9H, $C(CH_3)_3$), 7.31 (d, 2H, H-3 and H-5), 8.20 (d, 2H, H-2 and H-6); ^{13}C-NMR (50 MHz) -4.5 (2 x CH_3), 18.1 (C), 25.5 (3 x CH_3), 115.7 (CH), 120.1 (CH), 125.1 (CH), 126.1 (CH), 141.8 (C), 162.6 (C); Mass spectrum 253 (26, M^+), 196 (100, $[M-C_4H_9]$).

***t*-Butyl(4-{[1-(*t*-butyl)-1,1-dimethylsilyl]oxy}phenoxy)dimethylsilane (73)**



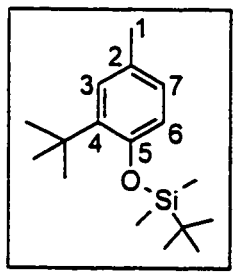
General procedure 2 was used to convert phenol **74** (0.20 g, 1.82 mmol) to TBDMS protected phenol **73** (0.52 g, 1.52 mmol) in 80.0% yield following purification by distillation under reduced pressure. Compound **73** was a white solid. mp 45-46 °C; ^{1}H-NMR (200 MHz) 0.15 (s, 12H, 2 x $Si(CH_3)_2$), 0.96 (s, 18H, 2 x $C(CH_3)_3$), 6.68 (s, 4H, H-2, H-3, H-5, and H-6). The ^{1}H-NMR spectrum was in good agreement with the literature.[78]

2-{[1-(*t*-Butyl)-1,1-dimethylsilyl]oxy}benzaldehyde (75)



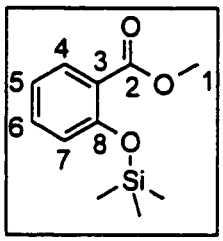
General procedure 1 was used to convert phenol **76** (0.41 g, 3.35 mmol) to TBDMS protected phenol **75** (0.79 g, 3.32 mmol) in 98.9% yield following purification by flash column chromatography (9:1) and distillation under reduced pressure. Compound **75** was a clear colorless liquid. bp 80-90 °C/0.1 Torr; ^{1}H-NMR (200 MHz) 0.25 (s, 6H, $Si(CH_3)_2$), 1.00 (s, 9H, $C(CH_3)_3$), 6.95 (m, 2H, H-5 and H-6), 7.45 (m, 1H, H-4), 7.32 (m, 1H, H-7), 10.45 (s, 1H, H-1). The ^{1}H-NMR spectrum was in good agreement with the literature.[79]

1-(*t*-Butyl)-1,1-dimethylsilyl [2-(*t*-butyl)-4-methylphenyl] ether (77)



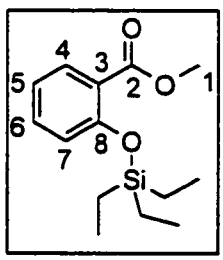
General procedure 1 was used to convert phenol **76** (0.05 g, 0.33 mmol) to provide TBDMS protected phenol **77** (0.07 g, 0.24 mmol) in 80.4% yield, based on 92% of starting material after purification by radial chromatography (20:1). Since, **76** was contaminated with a small amount of impurity (^{1}H-NMR, m, 7.45 ppm and disilyloxane) only IR, ^{1}H-NMR, and MS were used to confirm the desired product had formed. Compound **77** was a clear yellow liquid. bp 85-95 °C/0.1 Torr; IR 890 (Si-O) cm^{-1}; ^{1}H-NMR (200 MHz) 0.36 (s, 6H, $Si(CH_3)_2$), 1.08 (s, 9H, $C(CH_3)_3$), 1.42 (s, 9H, $C(CH_3)_3$), 2.31 (s, 3H, H-1), 6.60 (s, 1H, H-3), 6.94 (m, 1H, H-7), 7.14 (m, 1H, H-6); Mass Spectrum 278 (25, M^+), 221 (100, $[M-C_4H_9]$).

Methyl 2-[(1,1,1-trimethylsily)oxy]benzoate (81)



General procedure 1 was used to convert phenol **82** (0.10 g, 0.67 mmol) to TMS protected phenol **81** (0.15 g, 0.65 mmol) in 97.1% yield following purification by bulb-to-bulb distillation under reduced pressure. Compound **81** was a clear colorless liquid. bp 45-50 °C/0.1 Torr (literature[80] 83.2 °C/ 1.5 mm); IR 1715 (C=O), 930 (Si-O) cm^{-1} (literature[81] 1715 (C=O), 935 (Si-O) cm^{-1}); ^{1}H-NMR (200 MHz) 0.27 (s, 9H, $Si(CH_3)_3$), 3.87 (s, 3H, H-1), 6.89 (m, 2H, H-7 and H-6), 7.36 (dt, 1H, $J_{5,6}=J_{5,4}=9.8$ Hz, $J_{5,7}=1.8$ Hz, H-5), 7.80 (dd, 1H, $J_{4,5}=7.8$ Hz, $J_{4,6}=1.8$ Hz, H-4).

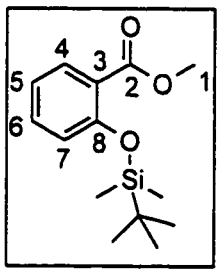
Methyl 2-[(1,1,1-triethylsilyl)oxy]benzoate (83)



General procedure 1 was used to convert phenol **82** (0.20 g, 1.31 mmol) to TES protected phenol **83** (0.31 g, 1.16 mmol) in 88.6% yield following purification by bulb-to-bulb distillation under reduced pressure. Compound **83** was a clear colorless liquid. bp 70-80 °C/0.1 Torr (literature[82] 122-123 °C/.5 Torr); IR 1717 (C=O), 912 (Si-O) cm^{-1}; ^{1}H-NMR (200 MHz) 0.8 (m, 9H, 3 x CH_3), 1.05 (m, 6H, 3 x $SiCH_2$), 3.88 (s, 3H, H-1), 6.87 (dd, 1H, $J_{4,5}=8.2$ Hz, $J_{4,6}=1.1$ Hz, H-4), 6.98 (dt, 1H, $J_{5,4}=J_{5,6}=8.5$ Hz, $J_{5,7}=1.1$ Hz, H-5), 7.35 (dt, 1H, $J_{6,5}=J_{6,7}=8.5$ Hz, $J_{6,4}=1.8$ Hz, H-6), 7.78 (dd, 1H, $J_{7,6}=7.7$ Hz, $J_{7,5}=1.8$ Hz, H-7); ^{13}C-NMR (50 MHz) 5.1 (3 x CH_2), 6.5 (3 x CH_3), 51.6 (CH_3), 120.8 (CH), 121.0 (C), 122.6

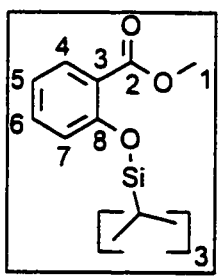
(CH), 131.5 (CH), 133.0 (CH), 155.3 (C), 167.0 (C); Mass spectrum 237 (100, [M-C_2H_5]).

Methyl 2-{[1-(*t*-butyl)-1,1-dimethylsilyl]oxy}benzoate (84)



General procedure 1 was used to convert phenol **82** (0.20 g, 1.31 mmol) to TBDMS silyl ether **84** (0.31 g, 1.18 mmol) in 89.7% yield following purification by distillation under reduced pressure. Compound **84** was a clear colorless liquid. bp 80-90 °C/0.1 Torr; ^{1}H-NMR (200 MHz) 0.19 (s, 6H, $Si(CH_3)_2$), 0.99 (s, 9H, $C(CH_3)_3$), 3.84 (s, 3H, H-1), 6.85 (dd, 1H, $J_{3,4}$=8.3, $J_{3,5}$=1.0 Hz, H-4), 6.95 (dt, 1H, $J_{4,3}$=$J_{4,5}$=7.5 Hz, $J_{4,6}$=0.8 Hz, H_4), 7.32 (m, 1H, H-5), 7.75 (dd, 1H, $J_{6,5}$=7.8 Hz, $J_{6,4}$=0.8 Hz, H-6). The ^{1}H-NMR spectrum was in good agreement with the literature.[83]

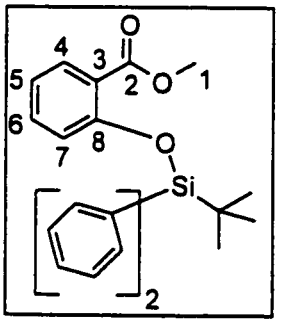
Methyl 2-[(1,1,1-triisopropylsilyl)oxy]benzoate (85)



General procedure 1 was used to convert phenol **81** (0.20 g, 1.31 mmol) to TIPS silyl ether **85** (0.36 g, 1.16 mmol) in 87.9% yield following purification by flash column chromatography (9:1) and distillation under reduced pressure. Compound **85** was a clear colorless liquid. bp 87-90/0.1 Torr; IR 1735 (C=O), 919 (Si-O) cm^{-1}; ^{1}H-NMR (200 MHz) 1.15 (d, 6H, 6 x CH_3), 1.32 (septet, 1H, $Si(CH)_3$), 3.88 (s, 3H, H-1), 7.00 (overlapping m and dd, 2H, H-5 and H-6), 7.73 (dd, 1H, $J_{4,5}$=5.8 Hz, $J_{4,6}$=1.9 Hz, H-4), 7.33 (dt, 1H, $J_{5,4}$=$J_{5,6}$=5.6 Hz, $J_{5,7}$=1.9 Hz, H-5); ^{13}C-NMR (100 MHz) 13.0 (3 x CH), 17.9

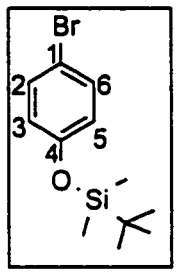
(6 x CH_3), 51.7 (CH_3), 120.3 (CH), 120.4 (CH), 122.6 (C), 131.5 (CH), 132.8 (CH), 155.4 (C), 167.5 (C); Mass spectrum 265 (100, [M-C_3H_7]); Exact mass cal'd for $C_{14}H_{21}O_3Si$ [M-C_3H_7]: 265.1260. Found: 265.1250.

Methyl 2-{[1-(*t*-butyl)-1,1-diphenylsilyl]oxy}benzoate (86)



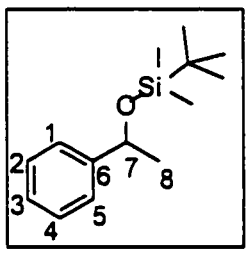
General procedure 1 was used to convert phenol **82** (0.20 g, 1.31 mmol) to give TBDPS silyl ether **86** (0.46 g, 1.19 mmol) as a clear colorless liquid 90.3% yield following purification by flash column chromatography (20:1) and distillation under reduced pressure. The product was contaminated with disilyloxane which could not fully be removed. bp 110-115 °C/0.1 Torr; IR 1730 (C=O), 919 (Si-O) cm^{-1}; ^{1}H-NMR (400 MHz) 1.14 (s, 9H, $C(CH_3)_3$), 3.93 (s, 3H, H-1), 6.52 (brd, 1H, Ar-H); 6.91 (brt, 1H, Ar-H); 7.05 (brt, 1H, Ar-H), 7.40 (m, 7H, 7 x Ar-H), 7.75 (m, 4H, 4 x Ar-H); ^{13}C-NMR (100 MHz) 19.5 (C), 26.2 (3 x CH_3), 51.9 (CH_3), 120.5 (CH), 120.6 (CH), 122.3 (C), 127.7 (CH), 127.8 (3 x CH), 129.6 (CH), 129.9 (2 x CH), 131.4 (CH), 132.3 (CH), 132.5 (2 x C), 34.8 (CH), 135.4 (2 x CH), 154.8 (C), 167.5 (C); Mass spectrum 390 (4, M^+), 333 (100, [M-C_4H_9]).

4-Bromophenyl [1-(*t*-butyl)-1,1-dimethylsilyl] ether (89)



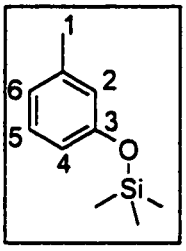
General procedure 1 was used to convert phenol **90** (0.16 g, 0.97 mmol) to TBDMS protected phenol **89** (0.24 g, 0.88 mmol) in 87.6% yield following purification by bulb-to-bulb distillation under reduced pressure. Compound **89** was a clear colorless liquid. bp 65-70/0.1 Torr; ^{1}H-NMR (200 MHz) 0.19 (s, 6H, $Si(CH_3)_2$), 0.98 (9H, s, $C(CH_3)_3$), 6.72 (dd, 2H, $J_{5,6}=J_{3,2}=2.8$ Hz, H-3 and H-5), 7.32 (dd, 2H, $J_{6,5}=J_{2,3}=2.8$ Hz, H-2 and H-6). The ^{1}H-NMR spectrum was in good agreement with the literature.[84]

1-(*t*-Butyl)-1,1-dimethylsilyl (1-phenylethyl) ether (91)



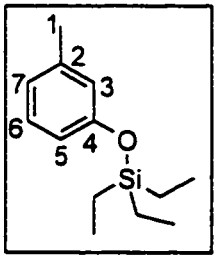
General procedure 1 was used to convert 1 phenyl-1-ethanol (2.04 g, 18.21 mmol) to silyl ether **91** (3.41 g, 16.38 mmol) in 90% yield following purification by flash column chromatography (50:1) and distillation under reduced pressure. Compound **91** was a clear, colorless liquid. bp 90-100 °C/0.08 Torr; ^{1}H-NMR (200 MHz) 0.03 and 0.05 (2s, 6H, $Si(CH_3)_2$), 0.10 (9H, s, $C(CH_3)_3$), 1.40 (d, 3H, $J_{8,7}=6.4$ Hz, H-8), 4.86 (q, 1H, $J_{7,8}=6.4$ Hz, H-7), 7.29 (m, 5H, H-1, H-2, H-3, H-4, and H-5). The ^{1}H-NMR spectrum was in good agreement with the literature.[75]

3-Methylphenyl (1,1,1-trimethylsilyl) ether (94)



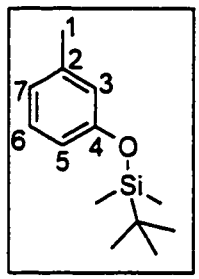
General procedure 1 was used to convert phenol **95** (0.25 g, 2.3 mol) to TMS protected phenol **94** (0.41 g, 2.3 mmol) in 100% yield following purification by bulb-to-bulb distillation. Compound **94** was a clear, colorless liquid. bp 47-50 °C/0.12 Torr (literature[85] 53-53.5 °C/1 mm); ^{1}H-NMR (200 MHz) 0.27 (s, 6H, $Si(CH_3)_3$), 2.31 (s, 3H, H-1), 6.80 (m, 4H, H-2, H-4, H-5, and H-6), ^{13}C-NMR (50 MHz) 0.1 (3 x CH_3), 22.1 (CH_3), 117.1 (CH), 120.5 (CH), 122.0 (CH), 128.8 (CH) 138.7 (C), 155.1 (C). The ^{13}C-NMR spectrum was in good agreement with the literature.[86]

3-Methylphenyl (1,1,1-triethylsilyl) ether (96)



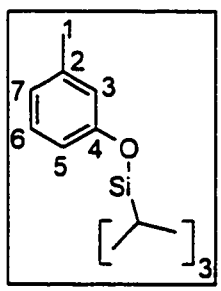
General procedure 1 was used to convert phenol **95** (0.20 g, 1.85 mmol) to TES protected phenol **96** (0.37 g, 1.65 mmol) in 89.3% yield following purification by bulb-to-bulb distillation under reduced pressure. Compound **96** was a clear colorless liquid. bp 61-63 °C/0.15 Torr; ^{1}H-NMR (200 MHz) 0.79 (q, 6H, $Si(CH_2)_3$), 1.04 (t, 9H, 3 x CH_3), 2.33 (s, 3H, H-1), 6.71 (brm, 2H, Ar-H), 6.79 (brd, 1H, Ar-H), 7.15 (t, 1H, Ar-H). The ^{1}H-NMR spectrum was in good agreement with the literature[87]

1-(*t*-Butyl)-1,1-dimethylsilyl (3-methylphenyl) ether (97)



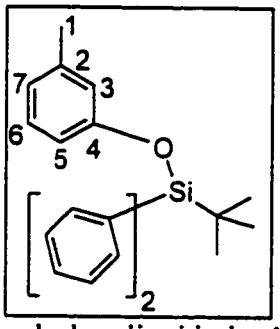
General procedure 1 was used to convert phenol **95** (.20 g, 1.85 mmol) to TBDMS silyl ether **97** (0.40 g, 1.81) in 98.1% yield following purification by bulb-to-bulb distillation under reduced pressure. Compound **97** was a clear colorless liquid. bp 80-85 °C/0.1 Torr (literature[88] 101 °C/760 mm); ^{1}H-NMR (200 MHz) 0.10 (s, 6H, $Si(CH_3)_2$), 0.78 (s, 9H, $C(CH_3)_3$), 2.20 (s, 3H, H-1), 7.00 (m, 4H, H-3, H-5, H-6, and H-7). The ^{1}H-NMR spectrum was in good agreement with the literature.[88]

3-Methylphenyl (1,1,1-triisopropylsilyl) ether (98)



General procedure 1 was used to convert phenol **95** (0.20 g, 1.85 mmol) to TIPS silyl ether **98** (0.34 g, 1.29) in 69.7% yield following purification by bulb-to-bulb distillation under reduced pressure. Compound **98** was a clear colorless liquid. bp 87-90/0.1 Torr; IR 883 (Si-O) cm^{-1}; ^{1}H-NMR (200 MHz) 1.15 (d, 18H, 3 x CH_3), 1.32 (septet, 3H, 3 x SiCH), 3.88 (s, 3H, H-1), 7.00 (m, 2H, H-5 and H-6), 7.73 (dd, 1H, $J_{7,6}$=5.8 Hz, $J_{7,5}$=1.9 Hz, H-7), 7.33 (m, 1H, H-3); ^{13}C-NMR (50 MHz) 12.7 (CH), 17.9 (6 x CH_3), 21.3 (CH_3), 116.7 (CH), 120.7 (CH), 121.8 (CH), 129.0 (CH), 139.2 (C), 156.0 (C); Mass Spectrum 265 (100, [M-C_3H_7]); Exact mass calc'd for $C_{17}H_{28}O_3Si$ [M-C_3H_7]: 265.1260. Found 265.1250.

1-(*t*-Butyl)-1,1-diphenylsilyl (3-methylphenyl) ether (99)

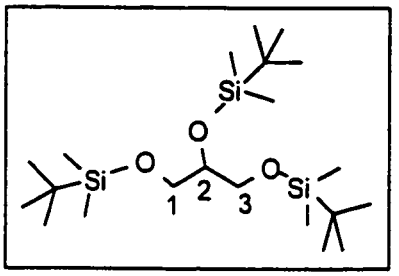


General procedure 1 was used to convert phenol **95** (0.13 g, 1.16 mmol) to TBDPS silyl ether **99** (0.37g, 1.06 mmol) in 91.3% yield following purification by flash column chromatography (9:1) and distillation under reduced pressure. Compound **99** was a clear colorless liquid. bp 125-130 °C/0.18 Torr; IR 836 (Si-O) cm^{-1}; ^{1}H-NMR (400 MHz) 1.15 (s, 9H, $C(CH_3)_3$), 2.23 (s, 3H, H-1), (brd, 1H, Ar-H), (brd, 2H, 2 x Ar-H), 6.97 (t, 1H, Ar-H), 7.44 (m, 6H, Ar-H), 7.76 (m, 4H, Ar-H); ^{13}C-NMR (100 MHz) 19.5 (C), 21.3 (CH_3), 26.5 (3 x CH_3), 116.6 (CH), 120.5 (CH), 121.8 (CH), 127.7 (2 x CH), 128.8 (CH), 129.6 (CH), 129.8 (3 x CH), 133.1 (2 x C), 135.5 (2 x CH), 139.2 (C), 155.5 (C); Mass spectrum 346 (3, M^+), 289 (100, $[M-C_4H_9]$); Exact mass calc'd for $C_{23}H_{26}Si$: 346.1753. Found 346.1743.

3.4 Experimental Procedures Pertaining to Chapter 2.

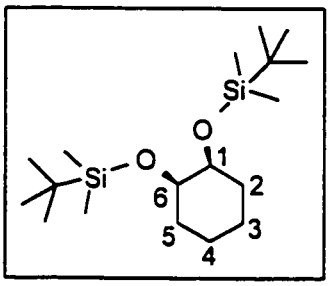
Since the route to an one-step asymmetric desilylation/desymmetrization was not successful, several of the compounds presented in this section were not fully characterized. In several cases, only sufficient spectral data (usually a ^{1}H-NMR and mass spectra) were collected to establish that the desired compound had been formed, unless otherwise stated.

1-(*t*-Butyl)-1,1-dimethylsilyl {2,3-di[1-(*t*-butyl)-1,1-dimethylsilyl]propyl} ether (45)



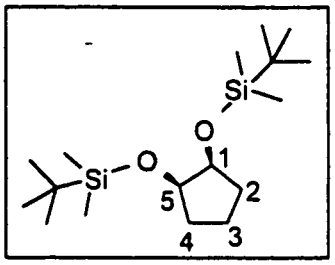
General procedure 1 was used to convert glycerol (**46**) (1.2 g, 13.0 mmol) to TBDMS silyl ether **45** (4.8 g, 12.4 mmol) in 96.1% yield following purification by bulb-to-bulb distillation under reduced pressure. Compound **45** was a white solid. mp 47-50 °C (literature[89] 53-55 °C); ^{1}H-NMR (200 MHz) 0.19 (s, 18H, 3 x $Si(CH_3)_2$), 1.00 (s, 18H, 3 x $C(CH_3)_3$), 3.65 (m, 5H, H-1, H-2, and H-3). The ^{1}H-NMR spectrum was in good agreement with the literature.[89]

***t*-Butyl[(*cis*-2-{[1-(*t*-butyl)-1,1-dimethylsilyl]oxy}cyclohexyl)oxy]dimethylsilane (213)**



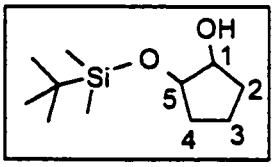
General procedure 1 was used to convert diol **134** (0.32 g, 2.75 mmol) to TBDMS silyl ether **213** (0.84 g, 2.45 mmol) in 88.8% yield following purification by bulb-to-bulb distillation under reduced pressure. Compound **213** was a clear color liquid. bp 85-90 °C/0.1 Torr; IR 1717 836 (Si-O) cm^{-1}; ^{1}H-NMR (200 MHz) 0.05 and 0.06 (d, 6H, 2 x $Si(CH_3)_2$), 0.90 (s, 18H, 2 x $C(CH_3)_3$), 1.5 (brm, 8H, H-2, H-3, H-4, and H-5), 3.65 (brd, 2H, H-1 and H-6); ^{13}C-NMR (50 MHz) -4.5 (2 x CH_3), 18.3 (2 x C), 25.7 (2 x CH_2), 26.0 (6 x CH_3), 31.2 (2 x CH_2), 72.8 (2 x CH); Mass spectrum 273 (100, $[M-C_4H_9]$); Exact mass calc'd for $C_{13}H_{29}O_2Si_2$ $[M-C_4H_9]$: 273.1706. Found 273.1680.

t-Butyl[(*cis*-2-{[1-(*t*-butyl)-1,1-dimethylsilyl]oxy}cyclopentyl)oxy]dimethylsilane (214)



General procedure 1 was used to convert **123** (0.34 g, 3.31 mmol) to **214** (0.94 g, 2.85 mmol) in 86% yield following purification by bulb-to-bulb distillation under reduced pressure. Compound **214** was a clear colorless liquid. bp 70-75 °C/0.1 Torr; IR 836 (Si-O) cm^{-1}; ^{1}H-NMR (200 MHz) 0.05 (s, 12H, $Si(CH_3)_2$), 0.90 (s, 18H, $C(CH_3)_3$), 1.63 (m, 6H, H-2, H-3, and H-4), 3.78 (m, 2H, H-1 and H-5); ^{13}C-NMR (50 MHz) -4.7 and -4.5 (2 x CH_3), 18.3 (2 x C), 19.2 (2 x CH_2), 26.0 (6 x CH_3), 30.5 (CH_2), 75.6 (2 x CH); Mass spectrum 273 (100, [M-C_4H_9]); Exact mass calc'd for $C_{13}H_{29}O_2Si_2$ [M-C_4H_9]: 273.1706. Found 273.1680.

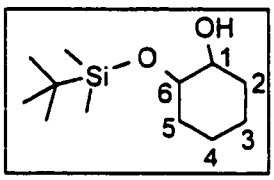
2-{[1-(*t*-Butyl)-1,1-dimethylsilyl]oxy}-1-cyclopentanol (216)



(A) General procedure 2 was used to convert **123** (0.04 g, 0.40 mmol) to mono TBDMS silyl ether **216** (0.09 g, 0.40 mmol) in 99.0% yield following purification by bulb-to-bulb distillation under reduced pressure. Compound **216** was a clear colorless liquid. bp 70-80°C/0.1 Torr; ^{1}H-NMR (200 MHz) 0.09 (s, 6H, $Si(CH_3)_3$), 0.90 (s, 9H, $C(CH_3)_3$), 1.75 (brm, 6H, H-2, H-3, and H-4), 2.47 (brs, 1H, OH), 3.90 (m, 1H, H-5), 4.05 (m, 1H, H-1); Mass spectrum 159 (41, [M-C_4H_9]).

(B) General procedure 6, with an cyclohexene:MeOH solvent mixture (Table 3.2, entry 5) in the presence of 5 mol% $PdCl_2$ was used to convert **214** (0.10 g, 0.30 mmol) to mono TBDMS silyl ether **216** (0.02g, 0.11 mmol) in 37% yield following purification radial chromatography (20:1) (see Table 2.5, entry 11 for reaction time and temperature). Compound **216** was a clear colorless liquid.

2-{[1-(*t*-Butyl)-1,1-dimethylsilyl]oxy}-1-cyclohexanol (215)



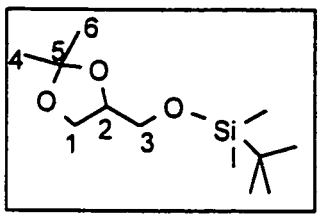
(A) General procedure 2 was used to convert diol **134** (0.10 g, 0.86 mmol) to TBDMS silyl ether **215** (0.20 g, 0.86 mmol) in 100% yield following purification by bulb-to-bulb distillation under reduced pressure. Compound **215** was a clear colorless liquid. bp 70-75 °C/.1 Torr; ^{1}H-NMR (200 MHz); ^{1}H-NMR (200 MHz) 0.08 (s, 12H, 2 x $Si(CH_3)_2$), 0.90 (s, 18H, 2 x $C(CH_3)$), 1.50 (brm, 8H, H-2, H-3, H-4, and H-5), 3.66 (m, 1H, H-6), 3.77 (m, 1H, H-1); Mass spectrum 173 (34, $[M-C_4H_9]$).

(B) General procedure 6, with an acetone as solvent (Table 3.2, entry 1) containing 1 equivalent of water, and in the presence of 5 mol% $PdCl_2(CH_3CN)_2$ was used to convert **214** (0.10 g, 0.29 mmol) to mono TBDMS silyl ether **216** (0.03 g, 0.12 mmol) in 40.0% yield following purification radial chromatography (20:1) (see Table 2.1, entry 4 for time and temperature). Compound **216** was a clear colorless liquid.

(C) General procedure 6, with an cyclohexene:MeOH solvent mixture (Table 3.2, entry 5) in the presence of 5 mol% $PdCl_2$ was used to convert **213** (0.09 g, 0.26 mmol) to mono TBDMS silyl ether **215** (0.02 g, 0.09 mmol) in 32.6% yield following purification

radial chromatography (20:1) (see Table 2.4, entry 6 for reaction time and temperature). Compound **215** was a clear colorless liquid.

1-(*t*-Butyl)-1,1-dimethylsilyl [(2,2-dimethyl-1,3-dioxolan-4-yl)methyl] ether (223)



(A) General procedure 1 was used to convert acetonide **224** (0.05g, 0.38 mmol) to TBDMS silyl ether **223** (0.06 g, 0.25 mmol) in 65.4% yield following purification radial chromatography (20:1). bp 100-110 °C/(aspirator), (literature bp 165-170 °C/760 Torr); ^{1}H-NMR (200 MHz) 0.26 (s, 6H, $Si(CH_3)_2$), 1.12 (s, 9H, $C(CH_3)_3$), 1.46 and 1.48 (2s, 6H, H-4 and H-6), 3.98 (m, 5H, H-1, H-2, and H-3). The ^{1}H-NMR spectrum was in good agreement with the literature.[90]

(B) General procedure 6, with dry acetone as solvent (Table 3.2, entry 1) in the presence of 10 mol% AgOTf was used to convert **45** (0.43 g, 0.99 mmol) to acetonide **223** (0.23 g, 0.94 mmol) in 95.2% yield following purification by radial chromatography (20:1) (see Table 2.6, entry 18 for time and temperature). In addition, when **45** (0.05 g, 0.11 mmol) was treated under similar reaction conditions as above and in the presence of 10 mol% PPh_3 (Table 2.7, entry 5), **223** (0.02 mg, 0.06 mmol) was obtained in 53.6% yield following purification by radial chromatography (20:1). Compound **223** was a clear colorless liquid.

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22 Since the silylation of alcohols is straight forward, each individual reaction will not be discussed in detail and the reader can refer to the experimental section for further details.

23 The $Pd(PPh_3)_4$ catalyst was prepared by S. Kalivoda.

24 Each individual reaction trial data will not be discussed in detail and the reader can refer to the experimental section for further details.

25 The reader should be aware that for simplification the unit h^{-1} was used for initial rate. In order to convert the initial rate unit from h^{-1} to M s^{-1} multiply the initial rate by the constant 3.5×10^{-5} M h s^{-1}.

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