PART 1: SYNTHESIS AND APPLICATION OF RECYCLABLE REAGENT AND CATALYST

PART 2: SYNTHESIS OF A TRISACCHARIDE UNIT FROM *K. PNEUMONIAE* K-2044

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Declaration Page

I hereby declare that this thesis is my original work and it has been written by me in its entirety, under the supervision of A/P Lam Yulin, (in the laboratory S5-03-19/03), Chemistry Department, National University of Singapore, between 2009 and 2013.

I have duly acknowledged all the sources of information which have been used in the thesis.

This thesis has also not been submitted for any degree in any university previously.

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Tables of Contents

SUMMARY

This thesis is composed of two parts: Synthesis and applications of recyclable reagents and catalyst (part 1); synthesis of trisaccharide unit of *K. pneumoniae*.

Part 1 consists of two projects which includes (i) the synthesis and application of a recyclable polymer-supported oxidant (Davis reagent) and (ii) the synthesis and application of a recyclable fluorous-tagged Pd catalyst.

In the first project we have demonstrated that the oxidation of (i) alkenes, (ii) silyl enol ethers, (iii) pyridines and (iv) rearrangement of tetrahydrobenzimidazole could be achieved with the polymer-supported Davis reagent in high yields and short reaction time. In the second project, we have shown the use of fluorous-tagged oxime palladacycle as a catalyst in carbon-carbon cross-coupling reaction such as (i) Suzuki–Miyaura reaction, (ii) Sonogashira reaction, (ii) Stille reaction, (iii) Heck reaction and (iv) Kumada reaction.

Part 2 of the thesis focuses on the synthesis of a trisaccharide unit of a Capsular Polysaccharide (CPS) from *K. pneumoniae* NTUH-K2044.

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

List of Abbreviations

δ	Chemical shift
Ac	Acetyl
ACN	Acetonitrile
Ac_2O	Acetic anhydride
AIBN	Azobisisobutyronitrile
Bn	Benzyl
BAIB	Bisacetoxyiodobenzene
$(CD_3)_2CO$	Deuterated acetone
CD_3OD	Deuterated methanol
$CDCl_3$	Deuterated chloroform
CuI	Copper iodide
CsF	Cesium fluoride
CSA	Camphorsulfonic acid
Cy_2NMe	Dicyclohexylmethylamine
DMAc	Dimethylacetamide
d	Doublet
dd	Doublet of doublet
dt	Doublet of triplet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-dimethylaminopyridine

DMF	Dimethylforamide
DMSO	Dimethylsulfoxide
EA	Ethyl acetate
EI	Electronic ionization
Eq	Equivalent
ESI	Electron spray ionisation
Et	Ethyl
Et_2O	Ethyl ether
EtOH	Ethanol
FT-IR	Fourier transform infrared spectroscopy
F-SPE	Fluorous Solid Phase Extraction
HCl	Hydrochloric acid
ICP-OES	Inductively coupled plasma atomic emission spectroscopy
KBr	Potassium bromide
KOH	Potassium hydroxide
KHMDS	Potassium bis(trimethylsilyl)amide
M	Molar
MeOH	Methanol
m	Multiplet
Me	Methyl
m-CPBA	meta-chloroperoxybenzoic acid
M.W	Microwave
MS	Molecular sieve

Nap	Methylnaphthanlene
NIS	*N*-Iodosuccinimide
NMR	Nuclear magnetic resonance
PPh_3	Triphenylphosphine
PPTS	Pyridinium *p*-toluenesulfonate
Ph	Phenyl
s	Singlet
SO_2Cl	Sulfuryl chloride
t	Triplet
TBAA	Tetrabutylammonium acetate
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
td	Triplet of doublet
*t*BuOK	Potassium *tert*-butoxide
TEA	Triethylamine
TFA	Trifluoroacetic acid
TMSCl	Trimethylsilyl chloride
TMS	Tetramethylsilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TsOH	*p*-Toluenesulfonic acid

List of Publications

1. Susanto, W., Lam, Y., *Tetrahedron*, **2011**, 67, 8353-8359.
2. Susanto, W., Chu, C. Y., Ang, W. J., Chou, T. C., Lo, L. C., Lam, Y., *Green Chem*., **2012**, 14, 77-80.
3. Susanto, W., Chu, C. Y., Ang, W. J., Chou, T. C., Lo, L. C., Lam, Y., *J. Org. Chem*., **2012**, 77, 2729-2742.

Chapter 1: Introduction

1.1 Green Chemistry

In 1991, a special program was commenced by the US Environmental Protection Agency (EPA) to implement sustainable development in chemistry and chemical technology by industry, academia and government; the term green chemistry was first brought up by P. T. Anastas. The start of green chemistry is usually considered a response to the need to ease the damage done to the environment by man-made materials and the processes used to manufacture them. Green chemistry incorporates an alternative that reduces the threats to public health and environment during the synthesis, purification and the application of chemical substances. Numerous examples of large-scale process chemistry and chemical engineering have showcased the development of green chemistry.[1] Through the development of combinatorial chemistry, there has been the introduction of various new tools with the potential for green chemistry applications.[2] The development of solid-supported chemicals and soluble-polymer support for solution-phase synthesis facilitate the significant reduction in the amount of solvent used for product purification through a chromatography-free technique. This also enchances sample analysis capability.[3] Fluorous chemistry also has a good potential to be an excellent technique for green chemistry applications. Fluorous technologies has been broadly applied in different fields such as homogeneous catalysis,[4] high-throughput synthesis of small molecules,[5] separation of biomolecules,[6] enzymatic catalysis, and green chemistry.[7]

Green chemistry also incorporates atom economy in its framework in designing or improving materials, products, processes and systems. Atom economy (atom efficiency) describes the efficiency of a chemical process in terms of the atoms involved, where in an ideal case, the amount of starting materials would all be converted to the desired products and no atom is wasted. However, in common chemical reactions a byproduct would usually result in addition to the desired product. As it is a significant goal of green chemistry to maximize efficiency of the reactants and minimize waste, the byproduct must either have other use (i.e. recyclability) or be eliminated. In the case of using a polymer support or fluorous technologies, the byproduct at the end of reaction could be recycled or recovered, respectively, achieving atom efficiency.

1.2 Functionalized Polymer for Green Chemistry Application

In the present context, functionalized polymer is a synthetic macromolecule where chemically or physically bound reactive functional groups can be employed as reagents, protecting groups, catalysts, etc. which is used in stoichiometric quantities in order to attain the chemical modification of an added substrate (Figure 1-1).

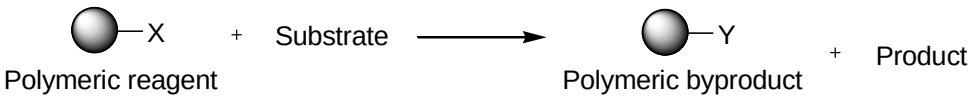

Figure 1-1. Polymeric reagent in a chemical reaction.

Chemical reagents that are covalently bonded to polymeric carriers are generally more useful than those physically adsorbed since, in the latter system, the components tend to dissociate upon usage and they are therefore unsuitable for column or repeated use. In the former system, the polymeric byproducts as shown in Figure 1-1 would remain attached to the polymer, which can then be removed with just simple filtration techniques. Depending on the chemistry involved, the polymer could be regenerated and recycled. Some examples of such a system are the polymeric phosphine reagent that is used in a Wittig reaction[8-13] or the use of polymeric peroxide reagent in the epoxidation of alkenes or the oxidation of thioethers[14-17]. Currently, there are three established methods to incorporate active functional groups into polymer chains. The first method would be through a direct polymerization and copolymerization of monomers containing the desired functional groups. Alternatively, a chemical modification of a preformed polymer could also be used. The last method would be the combination of both.

The majority of synthetic macromolecules used as supports are vinyl addition polymers. Styrene-based polymers are by far the most important support due to its advantage of being relatively chemically inert but readily funtionalized, as compared with methacrylate and acrylamide-based systems which are more susceptible to chemical degradation. These monomers are usually polymerized through a free radical process.[18,19]

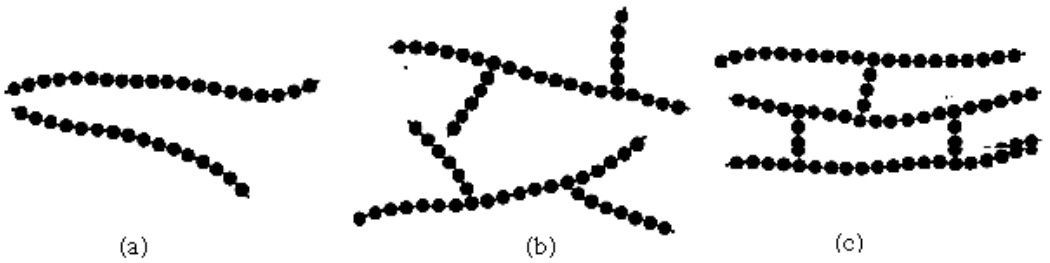

Figure 1-2. Synthetic macromolecular structure (a) linear (b) branched (c) cross-linked.

Vinyl polymers can be synthesized as a linear species (Figure 1-2a) that can be solvated in a suitable solvent resulting in a molecular solution, or an alternatively branched species (Figure 1-2b), which is commonly known as resin, where it remains macroscopically insoluble even though it is readily being solvated by a suitable solvent. Vinyl monomer could also be copolymerized with divinyl monomers which would result in an infinite cross-linked network (Figure 1-2c), which would swell in a thermodynamically compatible solvent instead of dissolution to form isotropic solutions due to their infinite molecular weight.

In general, immobilization of the reagents in solid support involve the use of an insoluble or semi-soluble polymeric resin, which is usually a functionalized divinylbenzene(DVB)-cross-linked polystyrene. Other organic or inorganic scaffolds such as glass beads, silica, alumina, cellulose, zeolites, graphite and clays have also been developed. In the case of functionalized divinylbenzene(DVB)-cross-linked polystyrene, the bound reagents remain largely accessible within the support matrix to both solvent and to the solution-

dissolved reactants. The degree of cross-linking of the resin and the conditions used during the preparation of the resins, determines the extent of swelling or solvation of the functionalized polymeric supports; low degree of cross-linking of DVB (1-2%) has greater swelling ability as compared to a higher cross-linked resin (>5%). The ease of manipulating a resin is crucial in the degree of success in its application as a reagent or catalyst.

The use of soluble polymer-supported reagents has also gained much attention as an alternative to traditional solid supports. Such reagents combine advantages from both solid and solution phase reactions in a single flask or platform.

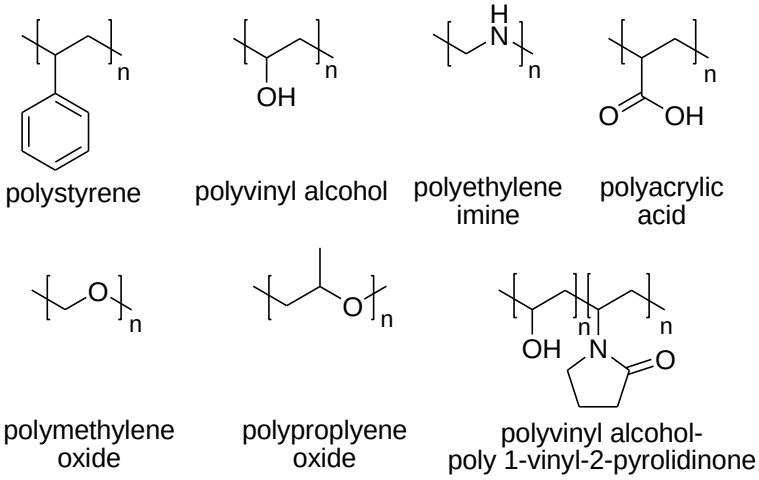

Figure 1-3. Soluble polymer support used in liquid-phase synthesis.

In order for a polymer to be a soluble support, it needs to (1) exhibit high solubilizing power to solubilize organic molecular entities with low solubility to allow the development of general methodology that is independent of the

physicochemical properties of target molecules, (2) have an easy anchoring point for the organic moieties and (3) be robust enough to withstand the reaction conditions. Most soluble supports are made up of hydrocarbon or alkyl ether backbone structures that are stable under normal reaction conditions (Figure 1-3).

There should also be a compromise between loading capacity and solubilizing ability provided by the soluble polymer support, which is crucial in cases where there would be complications by the neighbouring anchoring sites. Loading capacity is termed as a measure of the number of attachment of organic moieties per gram of polymer (mmol g^{-1}). In general, as the loading capacity of the polymer support increases, the solubilizing ability of the polymer-organic moiety conjugate would decrease.

The method used for separating soluble polymer support from the reaction mixture is slightly different as compared to solid phase support. Firstly, the homogeneous polymer reaction would need to be diluted with an appropriate solvent so as to induce precipitation of the support, prior to the isolation the polymer through filtration. Some soluble polymers could also be recrystallized to minimize the inclusion of impurities during precipitation, to achieve adequate recovery and purity.[20]

Over the years, there has been a drive for the development for rapid and sensitive methods for molecular structural analysis of support-bound species.[21-25] These

includes different approaches such as a destructive or nondestructive on-bead analysis to determine the degree of substitution or functionalization of a polymer. FT-IR is an example of nondestructive method by monitoring the appearance or disappearance of certain functional group (Figure 1.4). Elemental analysis is a traditional method used for destructive on-bead analysis, which is an accurate quantitative technique. It is a valuable technique if the reaction involves the loss or introduction of heteroatoms such as N, S, P or halogens. Loading level of a functional group could also be determined through this method (e.g the displacement of chloride from the Merrifield resin).

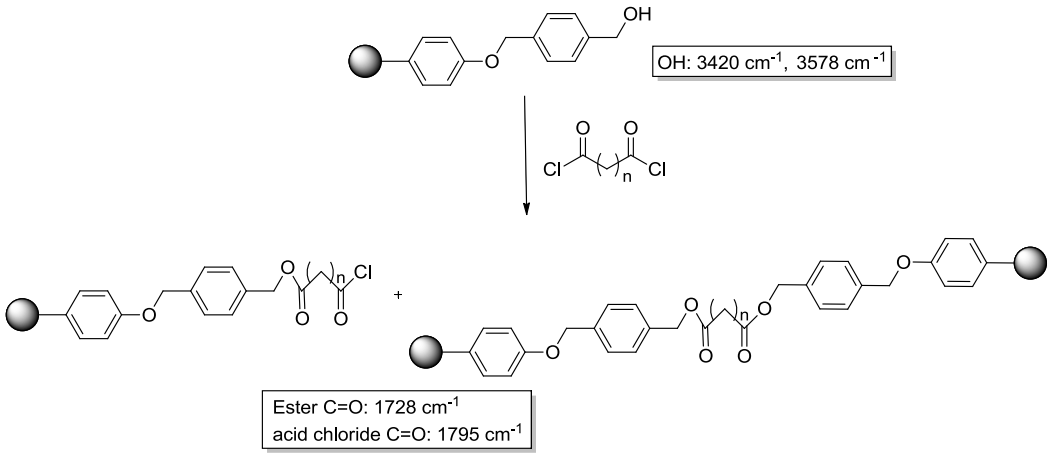

Figure 1-4. Investigation of site-site interactions using FT-IR microspectroscopy.

Depending on the nature of polymer and the chemical modification involved, nuclear magnetic resonance (NMR) spectroscopy[32] could also be used for nondestructive, qualitative and quantitative analysis. Unfortunately, heavily cross-linked polymers could not be prepared to be applied in normal solution phase NMR techniques. Thus solid phase NMR spectroscopy would be required through

the use of high resolution magic angle spinning (HR-MAS), cross-polarization (CP) and single pulse excitation (SPE) techniques. However the quality and resolution of the spectra obtained is still inferior as compared with a solution phase spectra.

As mentioned earlier, the most important advantage in using a functionalized polymer as a reagent or catalyst is the simplification of product work-up such as simple filtration procedures and solvent evaporation to isolate the desired products, eliminating the need for complex chromatographic techniques. This is particularly useful in reactions where traditional phase reagents produce by-products that are hard to remove even through conventional purification. Through the fast and anhydrous work-up that supported reagents permit, it also improves the success of isolating products that are not stable to the exposure of water or silica gel. In most cases, the supported reagents are used in stoichiometric excess to rapidly push the reaction to completion, thus resulting in lesser impurities. An example to showcase the advantages mentioned is through the use of polymer-supported triphenylphosphine, which allows the convenient separation of both excess reagents used and by-products (Figure 1-5).[33-35]

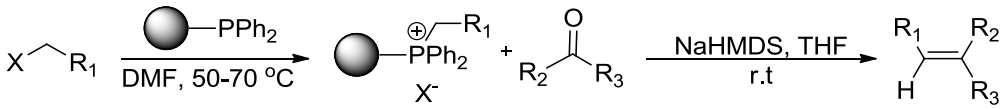

Figure 1-5. Use of polymer-supported triphenylphosphine in Wittig reaction.

Another attractive aspect of supported reagents is the immobilization of toxic or hazardous reagents and its by-products, thus allowing for easy handling and increased general safety. This situation is also aptly shown in the conversion of amides to thioamides by the elimination of toxic sulfur by-product, making the reaction desirable on a larger scale or in multiparallel arrays (Figure 1-6).[36]

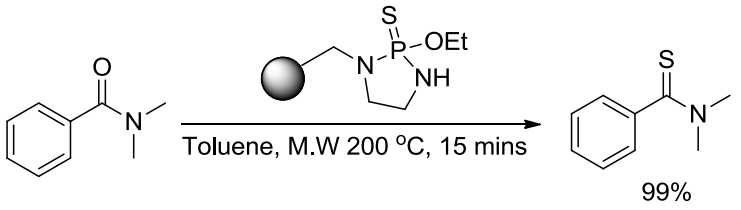

Figure 1-6. Polymer-supported thionating reagent.

1.3 Fluorous Technologies for Green Chemistry Applications

In recent years, there have been extensive studies on the application of fluorous chemistry in green chemistry, due to the ease of product separation from the reaction mixture. The term fluorous is analogues to the term aqueous, which means it dissolves in fluorocarbon solvents, which reflects a simple 'like dissolves like' effect. Fluoroalkyl moieties are often abbreviated $(CH_2)_mR_{fn}$, where the quantity and length of the perfluoroalkyl segment determines the molecules degree of solubility in the fluorous liquid phase. Hence, a new phase of phase-tag-based separation techniques was developed from the solvophobicity of aqueous and organic solvents. The early development of the techniques was exploited on biphasic catalysis[37] where the reaction is carried out at high temperature followed

by the biphasic separation of the fluorous catalyst at a low temperature (Figure 1-7).

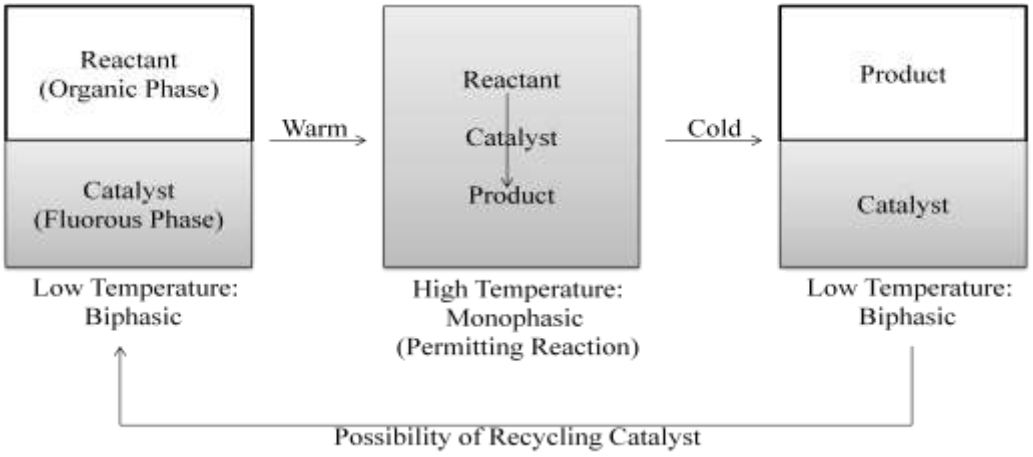

Figure 1-7. Recovery sequence through biphasic techniques applied to a fluorous catalyst.

Through this novel idea, it paved a way for biphasic recycling system in large-scale process chemistry applications. At present, there are numerous fluorous solvents that are commercially available; the most common solvent for fluorous chemistry is perfluorohexane (C_6F_{14}) or FC-72.

The aforementioned techniques could not be translated to "light fluorous" catalysts that have less than 60% fluorine content for a good partition coefficiency in fluorous solvents. On top of that, fluorous solvents have disputed toxicological properties[38] and are environmentally persistent[39], which is in conflict with the idea of green chemistry. In order to address these problems, a new avenue for the development of "light fluorous" chemistry has opened up. The use of short

perfluorocarbon chains such as $-C_8F_{17}$ or $-C_6F_{13}$ are extensive in "light fluorous" chemistry so as to reduce the fluorine content in the molecule. A primary technique to separate light fluorous compounds is through the use of fluorous silica gel containing a $-C_8F_{17}$ as the stationary phase, called fluorous solid-phase extraction (F-SPE).[40] Due to their solvophobic and fluorophilic natures, the fluorous molecules would be initially retained in fluorous silica gel cartridges when eluted with a fluorophobic solvent such as THF : H_2O (80 : 20). After the non-fluorous molecules have flowed through the fluorous silica gel cartridge, the fluorous compound would then be eluted out with the use stronger solvent such as MeOH or THF (Figure 1-8). Through this separation technique, the use of fluorous solvents in the reaction and separation steps could be eliminated as the reactions could be performed in common organic solvents. Thus, synthetic efficiency could be increased and the amount of solvents used for compound purification in column chromatography is reduced.[41] Another added advantage is that with a fluorous catalyst, it could be recovered easily and recycled for a few runs, which is an important principle of green chemistry.[42]

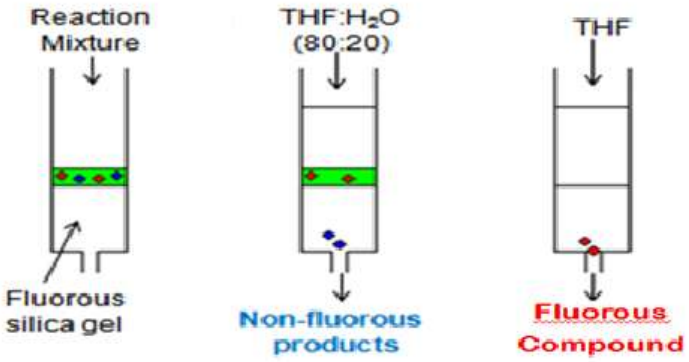

Figure 1-8. General Procedure for F-SPE.

Due to widespread practice of combinatorial chemistry, the application of combinatorial chemistry to drug development has fueled the need to synthesize large amount of compounds with high purity in a short amount of time. In most cases, obtaining the desired product from the reaction mixture would be the bottleneck. Hence, the use of fluorous technologies in synthetic organic chemistry allows a significant reduction in the amount of time required during the purification stage. One example would be the use of heavy fluorous phosphine in carrying out Wittig reactions with stabilized ylides as shown by Sinou and coworkers,[43] where the crude reaction mixture was subjected to liquid/liquid/liquid extraction with D-100 fluorous solvent (Figure 1-9).

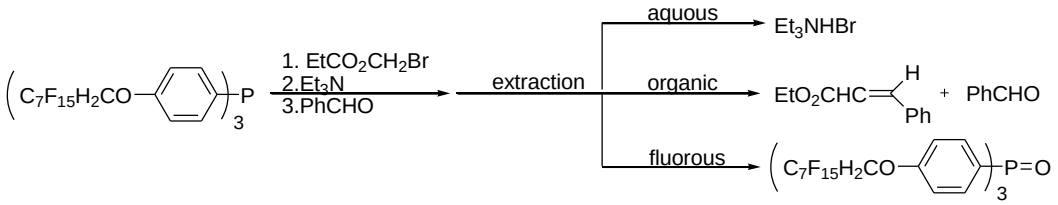

Figure 1-9. Wittig reaction with heavy fluorous phosphine.

Gladysz and coworkers have also shown the advantage in using fluorous reagents through the use of fluorous diacetoxy-iodo-arenes for the oxidation of hydroquinones to quinones.[44] In this reaction, perfluoromethylcyclohexane (PFCM) was added into the reaction mixture to achieve a biphasic layer to obtain the desired product (Figure 1-10).

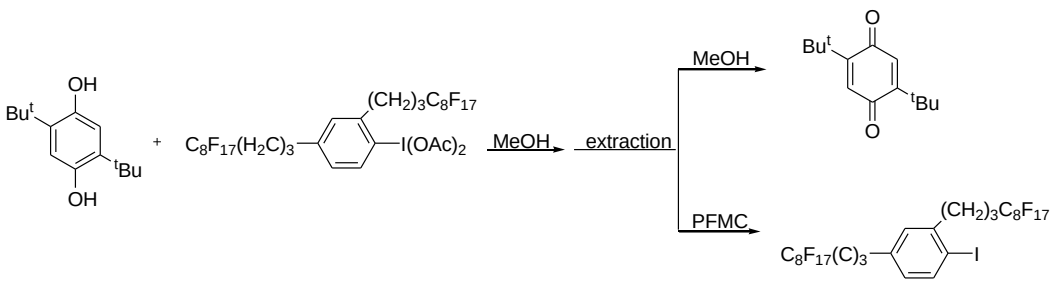

Figure 1-10. Oxidation using fluorous hypervalent iodine reagent.

Betzemeier and Knochel have also demonstrated the use of perfluoro-labelled catalysts in Negishi reactions that could be easily separated from the desired organic product through liquid/liquid extraction (Figure 1-11).[45] It was shown that the perfluoro-labelled catalyst could be reused up to four times yielding the desired products in excellent yields.

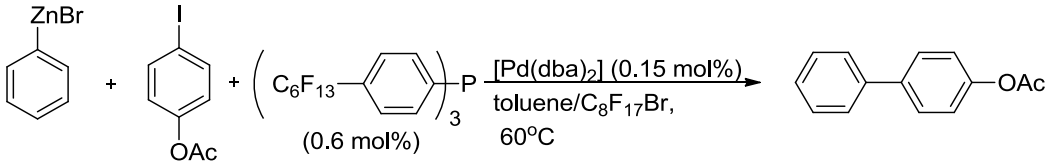

Figure 1-11. Negishi coupling reaction with the use of perfluoro-labelled catalyst.

1.4 Introduction to Microwave-Assisted Organic Synthesis (MAOS)

In the electromagnetic spectrum, the microwave radiation region is located between infrared radiation and radio waves. Microwaves have wavelengths ranging from approximately 1 mm to 30 cm, corresponding to frequencies between 3-30 GHz. High-speed synthesis with microwaves has attracted a considerable amount of attention in recent years[46] as it not only reduces chemical

reaction times from hours to minutes, but it is also known to reduce side reactions, increase yields, and improve reproducibility. Thus research groups in industry and academic labs are using MAOS for rapid optimization of reactions, for the efficient synthesis of new chemical entities, and for discovering and probing new chemical reactivity.

Conventional form of heating is dependent on the convection currents and the thermal conductivity of various materials thus resulting in a rather slow and inefficient method for transferring energy into a reaction mixture. This therefore often results in the temperature of the reaction vessel being higher than that of the reaction mixture. In contrast, microwave irradiation produces efficient internal heating by direct coupling of microwave energy with the molecules that are present in the reaction mixture.[47,48] However the reaction vessels employed in microwave chemistry are made out of essentially microwave transparent materials such as glass or Teflon, hence only the reaction mixture gets heated but not the vessel. Microwave-enhanced chemistry is based on the efficient heating of materials by "microwave dielectric heating" effects. This phenomenon is dependent on the ability of a specific material (solvent or reagent) to absorb microwave energy and convert it into heat. Microwaves are electromagnetic waves which consist of an electric and magnetic field component. For most practical purposes, it is the electric component[49] of the electromagnetic field that is of higher importance through a main mechanism that is called dipolar polarization and ionic conduction. In the presence of an applied electric field from

microwave, the dipole will align in the applied electric field. As the applied field oscillates, this dipole will attempt to realign with the alternating electric field. Field energy is transferred to the matrix and electrical energy is converted into kinetic or thermal energy and ultimately into heat due to molecular friction and dielectric loss.[47,48,50] As such, gases could not be heated under microwave irradiation because the distance between the rotating molecules is too great.

Coupling the speed of microwave-assisted chemistry with the convenient separation of fluorinated tags or polymer-supported reagents provides the potential to reduce the amount of time needed for the reaction and product separation in modern high throughput applications.[51] Another benefit would also be the potential possibility of recycling the expensive ligands and metal catalyst used.

1.5 Objectives of Our Studies

The trend towards green chemistry is increasing and it is a powerful tool that researchers must use to evaluate the environmental impact. Tremendous efforts are being made to make a chemical process more "green" through variables such as increasing chemical yield, safety in handling chemicals and ease of product workup and purification. Hence the objective of our studies is to synthesize a polymer-supported Davis reagent that is able to be used in various oxidation reactions and recycled over multiple runs. On top of that we also aim to synthesize a fluorous-tagged catalyst which could be used in the commonly

known cross-coupling reactions and recovered easily to be used in subsequent runs.

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Chapter 2: Oxidation Reaction Using Polymer-Supported 2-Benzenesulfonyl-3-(4-nitrophenyl)oxaziridine

2.1 Introduction

Advances in the use of polymers in organic synthesis[1-3] have led to the development of improved technologies for the preparation of chemical libraries. In particular, the use of polymer-supported reagents[4-6] in what is commonly referred to as polymer-assisted organic synthesis is an attractive technique that combines the advantages of solid-phase chemistry with those of solution-phase synthesis. In this technique, a polymer-bound reagent is added to a substrate in solution to effect a chemical transformation. At the end of the reaction, the polymer-bound spent reagent can be separated via filtration, thus simplifying product purification. Furthermore, since both the substrate and product are in solution during the reaction, conventional solution-phase analytical techniques, such as thin-layer chromatography, can be employed for reaction monitoring. The versatility of this methodology facilitates the process of library synthesis and has been the main stimulus for the recent growth of interest in polymer-supported reagents and catalysts.

To date, various polymer-supported variants of commonly used reagents have been prepared and employed in numerous synthetic strategies.[3, 7-10] Amongst them, a number of oxidants, such as IBX,[11] trimethylamine *N*-oxide,[12] dichromate,[13] and Swern oxidants[14,15] have been developed. Recently, our group has reported the

synthesis of a soluble polymer-supported 2-phenylsulfonyloxaziridine (Davis reagent) **2-1** (Fig. 2-1) and its application to the oxidation of sulfides, selenides, amines, phosphines, and enolates.[16] Although polymer **2-1** effected clean and selective oxidation with high yields and simple workup, it was not thermally stable and could only be applied to reactions at ambient or low temperatures. To address the need of some oxidation reactions that occur much slower and require prolong heating for useful yields, we sought to develop a more stable form of polymer **2-2**.

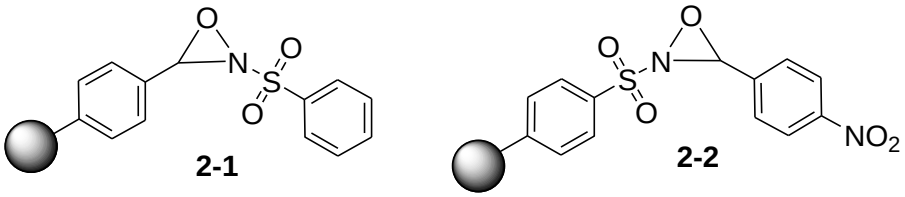
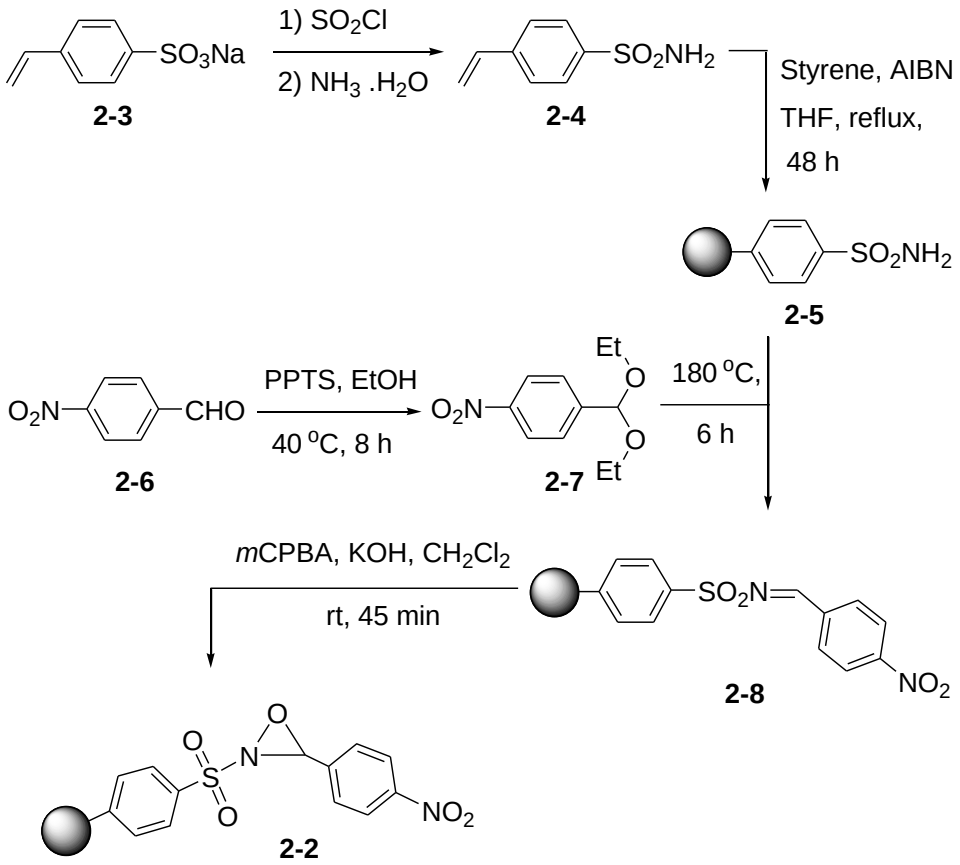


Figure 2-1. Polymer-supported 2-phenylsulfonyloxaziridines.

Davis and Sheppard had earlier reported the use of a thermally more stable 2-(phenylsulfonyl)-3-(*p*-nitrophenyl)oxaziridine for the oxidation of silyl enol ethers.[17,18] We reasoned that a polymer-supported version of this reagent would provide a thermally stable, neutral, aprotic, and mild polymer-supported oxidant that could contribute to a simpler and more convenient oxidative process. Hence we herein present the synthesis of soluble polymer-supported 2-benzenesulfonyl-3-(*p*-nitrophenyl)oxaziridine **2-2** and its application in the oxidation of various substrate types.

2.2 Synthesis of Polymer 2-2

The synthesis of polymer **2-2** (Scheme 2-1) began with the conversion of the sodium salt of 4-styrenesulfonic acid **2-3** to 4-vinylbenzenesulfonamide **2-4**. This was accomplished by first treating **2-3** with thionyl chloride to form the sulfonyl chloride, which was then reacted with ammonium hydroxide to provide **2-4**.



Scheme 2-1. Synthesis of polymer **2**.

Polymerization of **2-4** with styrene using standard AIBN initiated radical polymerization afforded polymer **2-5** whose formation was amenable to KBr FTIR analysis (i.e., the appearance of primary sulfonamide bands at 3392 and

3269 cm^{-1}). From elemental analysis data, the loading level of polymer **2-5** was calculated to be 1.20 mmol/g. This is consistent with the loading level of polymer **2-5** (~1.2 mmol/g) determined via gel permeation chromatography (molecular weight of polymer **2-5**=26,093) and ^{1}H NMR spectroscopy.

Following the synthesis of polymer **2-5**, we initially attempted to directly condense it with 4-nitrobenzaldehyde **2-6** to obtain polymer **2-8**. Jennings and Lovely[19] have shown that addition of $TiCl_4$ to a mixture of aromatic aldehyde, sulfonamide, and triethylamine in CH_2Cl_2 gave the *N*-sulfonylimine after ca. 30 min at 0 °C. However, when the procedure was applied to **2-6** and polymer **2-5**, the reaction had to be carried out under reflux in order for the reaction to proceed (entry 1, Table 2-1). Polymer **2-8** that precipitated from cold hexane was an impure product (as shown in the ^{1}H NMR spectrum) and attempts to purify it proved difficult as the product surprisingly underwent hydrolysis when washed with cold methanol. This could be attributed to the presence of a Lewis acid in a protic solvent, which causes the imine nitrogen to become protonated, thus resulting in hydrolysis. Attempts to use other Lewis acids, such as TFAA,[20] $FeCl_3$,[21] and $Ti(OEt)_4$[22] gave very low loading levels of the product or no reaction at all (entries 2, 4, and 5, Table 1). To circumvent this problem, we converted **2-6** to 1-(diethyloxymethyl)-4-nitrobenzene **2-7**, which was then reacted neat with polymer **2-5** at 180 °C to provide polymer **2-8**.[23] To prevent the hydrolysis of polymer **2-8**, ethanol that formed as a by-product was distilled off

immediately. This procedure gave a 78% conversion and the polymer **2-8** obtained was stable even when it was precipitated from cold methanol.

Table 2-1. Synthesis of polymer **2-8** from polymer **2-5** and 4-nitrobenzaldehyde **2-6** or 1-(diethyloxymethyl)-4-nitrobenzene **2-7**

Entry	Conditions	Reaction time (h)	% Conversion[a]
1	$TiCl_4$, TEA, CH_2Cl_2, **2-6**, reflux	6	75
2	$FeCl_3$, EtOH, **2-6**, rt	24	-
3[b]	Amberlyst 15, **2-6**, toluene, reflux	24	25
4	TFAA, **2-6**, CH_2Cl_2, reflux	24	30
5	$Ti(OEt)_4$, CH_2Cl_2, **2-6**, reflux	24	25
6	**2-7**, 180 ^oC	6	78

[a] Determined by comparing the loading of polymer **2-5** with the loading of polymer **2-8**. Loading of polymer **2-5** was determined by elemental analysis whilst loading of polymer **2-8** was determined by ^1H NMR

[b] Ref. 24

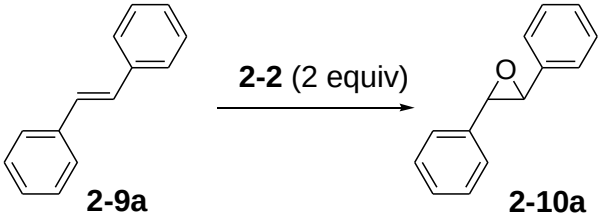
Polymer **2-8** was subsequently oxidized with *m*-CPBA in the presence of KOH to polymer **2-2** (Scheme 2-1). Through ^1H NMR spectroscopic analysis of polymer **2-2** and elemental analysis, the loading of polymer **2-2** was determined to be ~1.00 mmol/g.

2.3 Oxidation of Alkenes and Silyl Enol Ethers

Like peracids, 2-sulfonyloxaziridines epoxidize alkenes in a *syn* stereospecific manner.[25] However, compared to the peracids, oxidation with 2-benzenesulfonyl-3-(*p*-nitrophenyl)oxaziridine occurs much more slowly and a typical reaction

requires 3–12 h of heating at 60 °C.[26] With polymer **2-2** in our hands, we proceeded to examine such reactions using *trans*-stilbene **2-9a**. As observed in solution-phase epoxidation, reaction of **2-9a** with polymer **2-2** provided an observable change in color from an initial yellow solution to an intense yellow solution and with 1.25 equiv of polymer **2-2**, the yield of **2-10a** was 50% (entry 1, Table 2-2). To optimize the reaction, we varied the amount of polymer **2-2**, the solvent and reaction condition. The best yield was obtained when the reaction was carried out in CH_2Cl_2 under microwave irradiation for 15 min (entry 5,Table 2-2).

Table 2-2. Epoxidation of *trans*-stilbene **2-9a** by polymer **2-2**



2-9a **2-10a**

Entry	Solvent	Reaction conditions	Yield[a] (%)
1	CH_2Cl_2	Reflux, 4 h	50[b]
2	CH_2Cl_2	Reflux, 4 h	73[c]
3	CH_2Cl_2	Reflux, 4 h	88
4	CH_2Cl_2	MW, 100 ^oC, 5 mins	42
5	CH_2Cl_2	MW, 100 ^oC, 15 mins	93
6	THF	MW, 100 ^oC, 15 mins	87
7	$CHCl_3$	MW, 100 ^oC, 15 mins	90
8	Toluene	MW, 100 ^oC, 15 mins	67

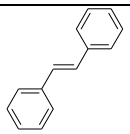
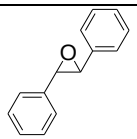
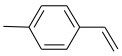
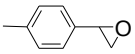
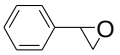
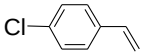
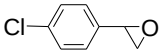
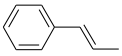
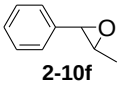
[a] Isolated yield.

[b] Using 1.25 equiv of polymer **2-2**.

[c] Using 1.5 equiv of polymer **2-2**.

To demonstrate the applicability of polymer **2-2** in the oxidation of alkenes, five other substrates were tested using the optimized reaction condition and good yields were obtained for all cases (Table 2-3). This shows that polymer **2-2** is able to oxidize alkenes in good yields and in a much shorter reaction time.

Table 2-3. Epoxidation of alkenes using **2-2**

Entry	Substrate	Products	Yield (%)[a]
1	 **2-9a**	 **2-10a**	93 (70[b], 58[c])
2	 **2-9b**	 **2-10b**	79
3	 **2-9c**	 **2-10c**	85
4	 **2-9d**	 **2-10d**	75
5	 **2-9e**	 **2-10e**	72
6	 **2-9f**	 **2-10f**	88 (70[b])

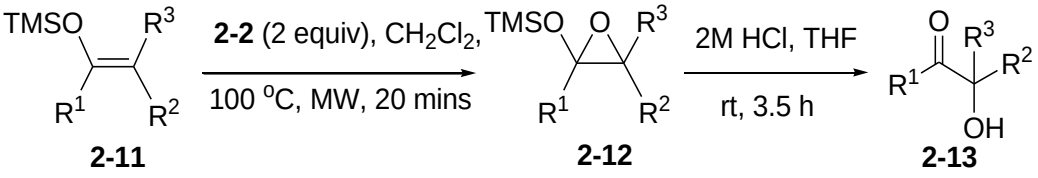
[a] Yield of isolated product.

[b] Solution-phase reaction yield using 2-(phenylsulfonyl)-3-(*p*-nitrophenyl)oxaziridine (2 equiv), $CHCl_3$, 60 °C, 12 h (Ref. 25).

[c] Using polymer **2-1** (2 equiv), MW, 100 °C, CH_2Cl_2. Reaction was incomplete.

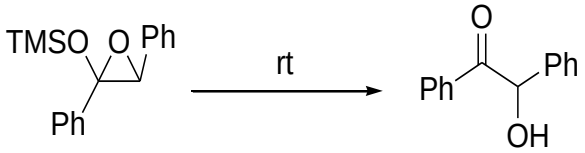
Encouraged by these results, we further explored the use of polymer **2-2** in the oxidation of silyl enol ethers **2-11** (Scheme 2-2). Under microwave irradiation at 100 °C, the oxidation was completed in 20 min and the α-silyl epoxide **2-12** that formed was isolated in quantitative yield. Compound **2-12** was then further treated with 2M HCl (Table 2-4) to afford the corresponding α-hydroxy ketone in good yield (Table 2-5).

Scheme 2-2. Synthesis of α -hydroxy ketone from silyl enol ether.



2-11 **2-12** **2-13**

Table 2-4. Conversion of **2-12** to **2-13**.



2-12a **2-13a**

Entry	Solvent	Reaction conditions	Yield[a] (%)
1	wet EtOAc	DDQ, 5 h[b]	67[c]
2	THF	2M HCl, 3.5 h	93
3	THF	5% HCl, 7 h[d]	76[e]
4	THF	Bu_4NF, 2 h	56[c]

[a] Isolated yield.

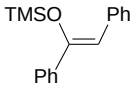
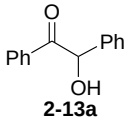
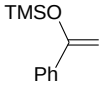
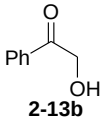
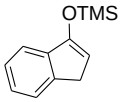
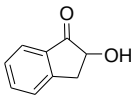
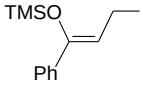
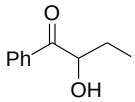
[b] Ref. 26.

[c] Over-oxidation of benzoin observed.

[d] Ref. 17.

[e] TLC showed incomplete reaction.

Table 2-5. Oxidation of silyl enol ether using **2-2**.

Entry	Substrate	Products	Yield (%)[a, b]
1	 **2-11a**	 **2-13a**	96
2	 **2-11b**	 **2-13b**	83
3	 **2-11c**	 **2-13c**	89
4	 **2-11d**	 **2-13d**	92

[a] Isolated yield.

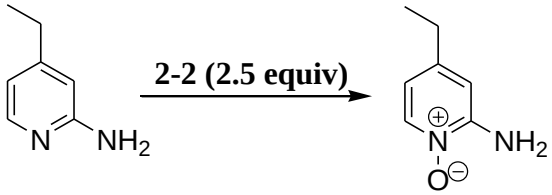
[b] Purity of product ≥95%.

2.4 Oxidation of Pyridine

Pyridine *N*-oxide derivatives are compounds of growing importance as there has been increasing interest in them as chiral controllers for asymmetric synthesis[27] as well as inhibitors to the human immunodeficiency virus (HIV),[28] human SARS, and feline infectious peritonitis coronavirus.[29] These *N*-oxides are typically prepared by oxidation of pyridines with hydrogen peroxide, peracids, sodium perborate or sodium percarbonate in the presence of catalysts.[30-35] To carry out the oxidation in a more environmentally friendly manner, various polymer-supported catalysts and solid-state oxidative processes have been developed.[36-38] However the shortcomings of these methods are the requirement of higher

temperatures or catalyst loading and long reaction times. To our knowledge, there are no earlier reports on the oxidation of pyridines with polymer-supported 2-phenylsulfonyloxaziridines. Hence in this work, we have investigated the performance of polymer **2-2** on such an oxidative reaction.

Table 2-6. Oxidation of 4-ethyl-pyridin-2-ylamine **2-14a** with **2-2**



2-14a **2-15a**

Entry	Solvent	Reaction conditions	Yield[a] (%)
1	CH_2Cl_2	rt, 4 h	93
2	CH_2Cl_2	MW, 60 °C, 25 mins	98
3	CH_2Cl_2	MW, 100 °C, 2 mins	99
4	THF	MW, 100 °C, 25 mins	89
5	$CHCl_3$	MW, 100 °C, 7 mins	96
6	CH_2Cl_2	MW, 100 °C, 14 mins	96[b]

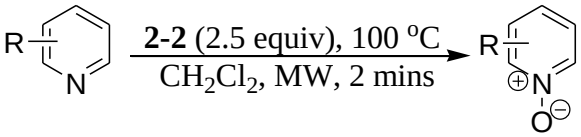
[a] Isolated yield.

[b] Using 1.2 equiv of **2-2**.

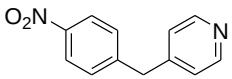
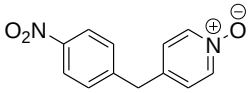
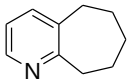
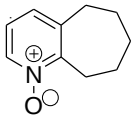
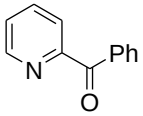
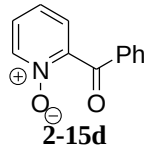
4-Ethyl-pyridin-2-ylamine **2-14a** was used as a model substrate in the oxidation to the corresponding *N*-oxide with polymer **2-2** (2.5 equiv) employing the optimized conditions obtained by varying solvent and reaction conditions (Table 2-6). Under microwave irradiation at 100 °C, oxidation of **2-14a** was completed in 2 min and

4-ethyl-pyridin-2-ylamine *N*-oxide **2-15a** was obtained in quantitative yield (entry 3, Table 2-6). Application of this reaction condition to other pyridine analogs also resulted in good yields (Table 2-7).

Table 2-7. Oxidation of pyridines with **2-2**



2-14a **2-15a**

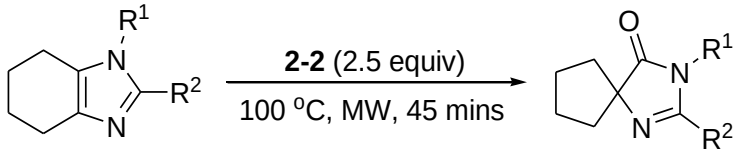
Entry	Substrate	Product	Yield[a] (%)
1	 **2-14b**	 **2-15b**	92
2	 **2-14c**	 **2-15c**	91
3	 **2-14d**	 **2-15d**	82

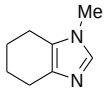
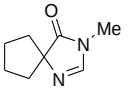
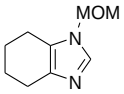
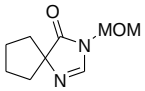
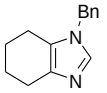
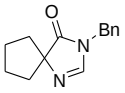
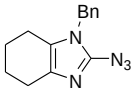
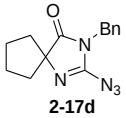
[a] Isolated yield.

2.5 Oxidative Rearrangement

Our group has earlier[16] reported the rearrangement of tetrahydrobenzimidazoles to the corresponding 5-imidazolone using polymer **2-1**.

Table 2-8. Oxidation rearrangement of tetrahydrobenzimidazole **2-16** using **2-2**



Entry	Substrate	Products	Yield (%)[a]
1	 **2-16a**	 **2-17a**	85 (82[b],61[c])
2	 **2-16b**	 **2-17b**	63 (50[d])
3	 **2-16c**	 **2-17c**	85 (80[b], 62[c], 21[e])
4	 **2-16d**	 **2-17d**	77 (70[f])

[a] Isolated yield.

[b]Solution-phase oxidative rearrangement using 2-benzenesulfonyl-3-phenyloxaziridine (2 equiv), $CHCl_3$ at room temperature for 4 h (Ref. 39).

[c] Isolated yield when the oxidative rearrangement was carried out with polymer **2-1** (2 equiv) at room temperature for 24 h.

[d]Solution-phase oxidative rearrangement using 2-benzenesulfonyl-3-phenyloxaziridine (2 equiv), $CHCl_3$ at 35 °C for 24 h[39].

[e] Isolated yield when the oxidative rearrangement was carried out with polymer **2-1** (2.5 equiv), 100 °C, MW, 45 min.

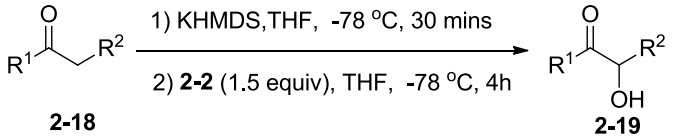
[f]Solution-phase oxidative rearrangement using 2-(phenylsulfonyl)-3-(*p*-nitrophenyl)oxaziridine (2 equiv), $CHCl_3$ at 35 °C for 24 h[39].

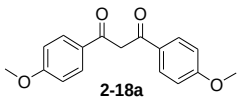
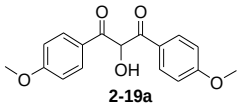
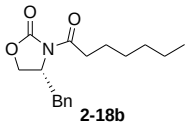
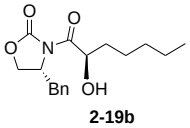
Since polymer **2-1** was not thermally stable, the rearrangement reaction had to be carried out at room temperature, which required 24 h to complete and provided the product in moderate yields (61–62%). To determine if the rearrangement would proceed more favorably at higher temperatures, we applied polymer **2-2** to the reaction. To begin, 1-methyl-4,5,6,7-tetrahydro-1*H*-benzimidazole **2-16a** was dissolved in CH_2Cl_2 and treated with polymer **2-2** (2 equiv) under reflux for 6 h. To our delight, this gave **2-17a** in 82% yield. Subsequently, we explored the reaction under microwave irradiation and found that at 100 °C, the reaction was completed within 45 min providing **2-17a** in 85% yield. Applying this reaction condition to other analogs of **2-16** also resulted in good yields of the oxidative rearranged product (Table 2-8).

2.6 Oxidation of Enolates

α-Hydroxy carbonyl moieties are key structural units in various natural products and are useful auxiliaries in chemical synthesis. In our earlier studies, we have demonstrated that enolates could be oxidized by polymer **2-1** (1.5 equiv) at -78 ^{o}C to α-hydroxy ketones. To explore the applicability of polymer **2-2** for reactions at low temperatures, we examined the oxidation of enolate **2-20a** at -78 ^{o}C and obtained the α-hydroxy ketone **2-21a** in very good yield (entry 1, Table 10). Furthermore the enolate oxidation with chiral imide **2-20b** occurred diastereoselectively to give isomer **2-21b** only. With polymer **2-2**, no overoxidation of the alcohol functional group was observed for both substrates.

Table 2-9. Enolate and enamine oxidation with **2-2**.



Entry	Substrate	Products	Yield (%)[a]
1	 2-18a	 2-19a	93
2	 2-18b	 2-19b	86 (87[b])

[a] Isolated yield.

[b] Isolated yield when the oxidation was carried out with polymer **2-1**

2.7 Oxidation of Sulfides and Phosphines

Partial oxidation of sulfides results in the formation of sulfoxides which are valuable synthons in organic synthesis. Davis and co-workers had earlier reported that N-phenylsulfonyloxaziridine is able to quantitatively and selectively oxidize sulfides to sulfoxides.[40] Our group have also shown that polymer **2-1** is capable of oxidizing sulfides to sulfoxides in excellent yields. Since polymer **2-1** was not thermally stable, the oxidation had to be carried out at room temperature and required 7 h to complete. To demonstrate the applicability of polymer **2-2** in such oxidations, we initially examined the oxidation of diphenyl sulfide **2--20a** at room temperature and this provided diphenyl sulfoxide **2-21a** in 99% yield (entry 1. Table 2-10), which was comparable to the yield obtained with polymer **2-1**.

Table 2-10. Oxidation of diphenyl sulfide **2-20a**.

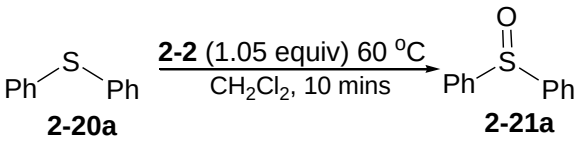
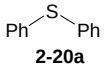
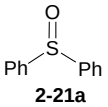
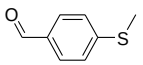
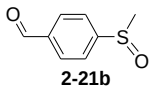
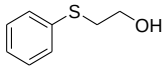
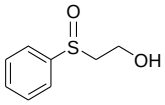
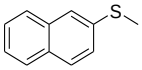
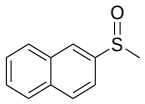
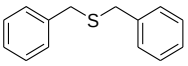
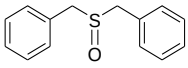
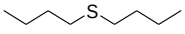
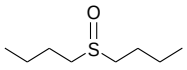
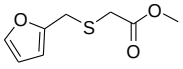
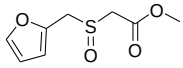


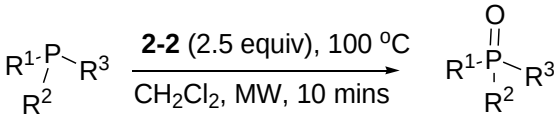
Table 2-11. Oxidation of sulfides using **2-2**

Entry	Substrate	Products	Yield (%)[a]
1	 **2-20a**	 **2-21a**	99 (98[b])
2	 **2-20b**	 **2-21b**	97 (94[b])
3	 **2-20c**	 **2-21c**	98
4	 **2-20d**	 **2-21d**	95 (96[b])
5	 **2-20e**	 **2-21e**	99 (99[b])
6	 **2-20f**	 **2-21f**	98 (97[b])
7	 **2-20g**	 **2-21g**	97 (95[b])

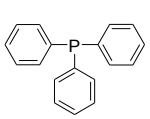
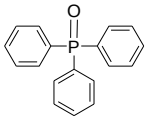
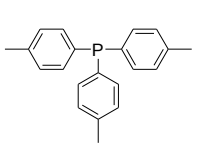
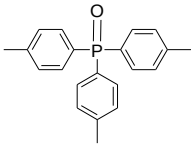
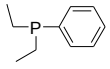
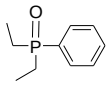
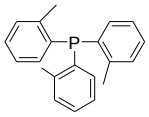
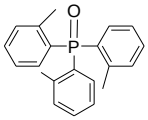
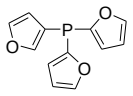
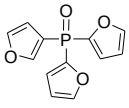
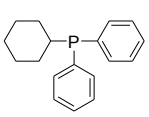
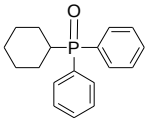
[a] Isolated yield.

[b] Isolated yield when the oxidation was carried out with polymer **2-1**

Table 2-12. Oxidation of phosphines using **2-2**.



2-22 **2-23**

Entry	Substrate	Products	Yield (%)[a]
1	 **2-22a**	 **2-23a**	99 (99[b])
2	 **2-22b**	 **2-23b**	99 (99[b])
3	 **2-22c**	 **2-23c**	95 (96[b])
4	 **2-22d**	 **2-23d**	99 (98[b])
5	 **2-22e**	 **2-23e**	99 (99[b])
6	 **2-22f**	 **2-23f**	94 (95[b])

[a] Isolated yield.

[b] Isolated yield when the oxidation was carried out with polymer **2-1**

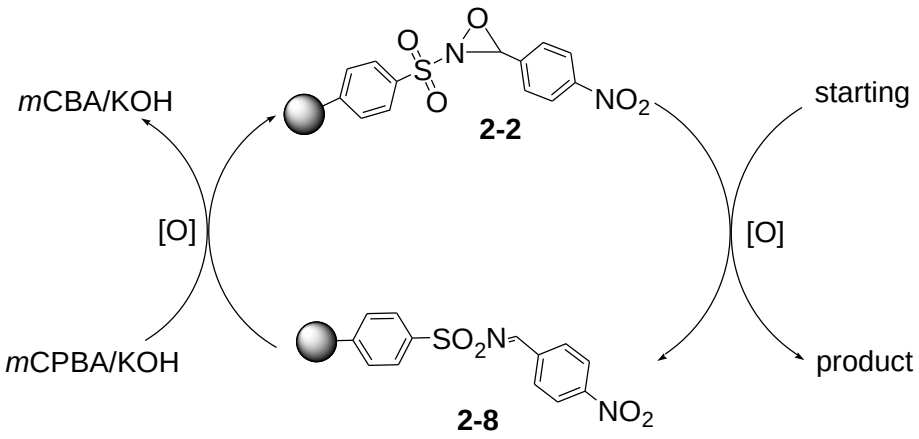
Since polymer **2-2** was thermally stable, we next explored the effects of microwave irradiation on the reaction. To our delight, we found that with 1.05 equiv of polymer **2-2** and at 60 ^{o}C, the reaction was completed in 10 min (entry 6, Table 2-10). To demonstrate the generality of this optimized condition, we carried

out the oxidation on various sulfides which essentially gave excellent yields in all cases (Table 2-11).

Similarly, we have also employed polymer **2-2** to the oxidation of phosphines. Previously, we have shown that triphenylphosphine **2-22a** was oxidized at room temperature by polymer **2-1** (5 equiv) within 1 h to yield triphenylphosphine oxide **2-23a** in 99% yield. When the same reaction was performed with polymer **2-2**, **2-23a** was obtained in similar yield but the reaction required 3 h to complete. We rationalized that the presence of heat could shorten the reaction time and also reduce the amount of polymer **2-2** used. Incidentally, we found that when the oxidation was carried out with 2.5 equiv of polymer **2-2** under microwave irradiation at 100 ^{o}C, the reaction time shortened to 10 min and **2-23a** was obtained in quantitative yield (entry 1, Table 2-12). Various other phosphines were examined and very good yields were obtained in all cases (Table 2-12).

2.8 Recycling of 2-2

The reduced product of the oxygen transfer reaction with polymer **2-2** is polymer **2-8** (Scheme 2-3). To regenerate the oxidant, the spent polymer was reoxidized with *m*-CPBA/KOH.



Scheme 2-3 Recycling of polymer **2-2**.

Table 2-13. Recycling versus oxidative activity of **2-2**

Recycling	Yield[a] (%)
2-9a → (**2-2** (2 equiv), MW, 100 °C, 15 min) → **2-10a**	
Initial	93
1st	93
2nd	91
3rd	90
4th	89
5th	86
2-20a → (**2-2** (1.05 equiv), CH_2Cl_2, MW, 60°C, 10 min) → **2-21a**	
Initial	99
1st	98
2nd	95
3rd	96
4th	93
5th	90

Recycling	Yield[a] (%)
2-22a → (**2-2** (2.5 equiv), 100 °C, CH_2Cl_2, MW, 10 min) → **2-23a**	
Initial	99
1st	99
2nd	97
3rd	96
4th	93
5th	92
2-16c → (**2-2** (2.5 equiv), 100 °C, MW, 45 min) → **2-17c**	
Initial	85
1st	83
2nd	82
3rd	80
4th	79

[a] Isolated yield.

With careful repetitive regeneration of consumed **2-2**, the loading levels could be restored to 0.8–1.0 mmol/g. To determine the oxidative activity of regenerated **2-2**, different oxidative reactions were performed to demonstrate the recycling possibility. Gratifyingly, the regenerated **2-2** was indistinguishable from polymer **2-2** and showed only a slow decline in oxidative activity after multiple recovery steps (Table 2-13).

2.9 Conclusion

In summary, we have developed a thermally stable polymer-supported oxidant **2-2**, which can be applied to reactions that occurred at elevated temperatures. With polymer **2-2**, the microwave-assisted reactions at elevated temperatures generally required much shorter reaction times and gave excellent to good yields of the desired product. Polymer **2-2** was proven to be a potent oxidant, effecting clean and selective oxidation of alkenes, silyl enol ethers, pyridines, sulfides and phosphines. It also enables tetrahydrobenzimidazoles to be oxidatively rearranged in an efficient manner to the spiro fused 5-imidazolones. Polymer **2-2** is also able to perfom chemoselective reaction of sulfide and phosphines in the presence of an alkene functional group at room temperature. Previous works by Davis and his co-workers have shown that 2-benzenesulfonyl-3-(4-nitrophenyl)oxaziridine could not be used to facilitate enantioselective oxidation reactions. Hence, a second-generation of the polymer-supported Davis reagent could be synthesized with the use of [(8,8-dihalocamphoryl)sulfonyl]oxaziridine for the synthesis of

enantiomerically enriched α-hydroxy carbonyl compounds, sulfoxides, selenoxides and epoxides.[42]

2.10 Experimental

2.10.1 General

All chemical reagents were obtained from Aldrich, Merck, Lancaster or Fluka and used without further purification. Moisture-sensitive reactions were carried out under nitrogen with commercially obtained anhydrous solvents. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (Merck silica gel 60, F_{254}) and visualized with UV light or stained with the Dragendorff-Munier and Hanessian stain. Flash column chromatography was performed with silica (Merck, 230–400 mesh). NMR spectra (^{1}H and ^{13}C) were recorded at 298 K on a Bruker ACF300, DPX300 or AMX500 Fourier Transform spectrometers. Chemical shifts are expressed in terms of δ parts per million (ppm) relative to the internal standard tetramethylsilane (TMS). Mass spectra were performed on Finnigan TSQ 7000 for EI normal mode or Finnigan MAT 95XL-T spectrometer under EI, ESI, and FAB techniques. All infrared (IR) spectra were recorded on a Bio-Rad FTS 165 spectrometer. All isolated products are of ≥95% purity (by ^{1}H NMR). Microwave reactions were performed on the Biotage Initiator™ microwave synthesizer.

2.10.2 Synthesis of 4-Vinylbenzenesulfonamide (2-4)

To an ice-cooled solution of the sodium salt of 4-styrenesulfonic acid **2-3** (10.3 g, 50 mmol) in dimethylformamide (DMF) (83 mL) under a nitrogen atmosphere was added thionyl chloride (30 mL, 413 mmol). The reaction mixture was stirred for 6 h and then left in the fridge overnight. The solution was slowly poured into ice-water (150 mL) and extracted with ether (70 mL×3). The combined washing was dried with $MgSO_4$ and concentrated to give the intermediate product, a sulfonyl chloride, which was then reacted with aqueous ammonium hydroxide (180 mL) for 2 h. Thereafter, the reaction mixture was extracted with ether and the combined ether extract was dried with $MgSO_4$ and concentrated to give **2-4** as a white solid. Yield: 4.53 g (60%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.88 (s, 2H), 5.43 (d, 1H, J = 10.7 Hz), 5.88 (d, 1H,J = 17.7 Hz), 6.75 (dd, 1H, J = 10.7 and 17.7 Hz), 7.52 (d, 2H, J = 8.2 Hz), 7.87 (d, 2H, J = 8.2 Hz). ^{13}C NMR (acetone-d_6, 125 MHz) δ 115.9, 126.0, 126.1, 135.2, 140.6, 142.9. HRMS (EI): m/z=183.0354, calcd for $C_8H_9O_2NS$: 183.0354.

2.10.3 Synthesis of Polymer-Supported Benzenesulfonylamide (2-5)

To a mixture of styrene (0.34 mL, 3 mmol) and **2-4** (0.091 g, 0.5 mmol) in tetrahydrofuran (THF) (10 mL) was added AIBN (0.0025 g, 0.015 mmol). The reaction mixture was purged with argon for 30 min and then heated to reflux for 48 h. Thereafter, the reaction mixture was concentrated and the resulting residue was dissolved in THF (1 mL) and added slowly into vigorously stirred hexane (10 mL). The resulting suspension that formed was filtered by suction filtration

and washed with cold methanol to afford polymer **2-5** as a white powder. Yield: 0.267 g (80%). Loading calculated from elemental analysis data: 1.30 mmol/g; ^{1}H NMR ($CDCl_3$, 500 MHz) δ1.43 – 1.84 (m, H_2O+–CH_2CH–), 6.58 – 7.60 (m, 40H, ArH). IR (KBr) v=3078, 3059, 2921, 2850, 1492, 1452, 1338, 1163 cm^{-1}.

2.10.4 Synthesis of 1-(Diethoxymethyl)-4-nitrobenzene (2-7)

Pyridinium *p*-toluenesulfonate (PPTS) (0.025 g, 0.1 mmol) was added to a solution of 4-nitrobenzaldehyde **2-6** (0.151 g, 1 mmol) in ethanol (10 mL). The solution mixture was heated for 12 h at 40 °C and then poured into brine solution and extracted with ethyl acetate (3×5 mL). The combined organic extract was then dried over $MgSO_4$, concentrated, and purified by flash column chromatography using 1:9 (EtOAc/hexane) system to give **2-7** as a yellow liquid (R_f=0.32). Yield: 0.192 g (85%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, 6H, J = 7.0 Hz), 3.57 (m, 2H), 5.56 (s, 1H), 7.65 (d, 2H, J = 8.8 Hz), 8.20 (d, 2H, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.1, 61.3, 100.1, 123.4, 127.7, 146.1, 147.9. HRMS (EI): m/z=225.1000, calcd for $C_{11}H_{15}O_4N$: 225.1001.

2.10.5 Synthesis of Polymer-Supported *N*-Benzenesulfonamide-*p*-nitro-benzylidene (2-8)

1-(Diethoxymethyl)-4-nitrobenzene **2-7** (1.54 g, 6.83 mmol) and polymer-supported benzenesulfonamide **2-5** (8.45 g, 6.5 mmol) were added into a 100-mL single-necked round-bottomed flask equipped with short-path distilling head. The reaction mixture was heated at 180 °C in an oil bath until all the ethanol had

ceased distilling over (~6 h). After which, the reaction mixture was placed under high vacuum and cooled to room temperature. The crude solid product obtained was dissolved in CH_2Cl_2 (8 mL) and precipitated by slow addition into ice-cold CH_3OH (25 mL). The suspension was then filtered by suction filtration to afford polymer **2-8** as a yellow solid. Yield: 75–80%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.41 – 1.77 (m, H_2O+–CH_2CH–), 6.55 – 8.32 (m, 40H, ArH), 9.13 (s, 1H, CH). IR (KBr) v=3082, 3060, 2923, 1595, 1527, 1346, 1162 cm^{-1}.

2.10.6 Synthesis of Polymer-Supported 2-Benzenesulfonyl-3-(*p*-nitrophenyl)oxaziridine (2-2)

Polymer **2-8** (0.51 g, 0.5 mmol) was added to a white suspension of *m*-CPBA (70–75% purity, 0.216 g, 1.25 mmol) and powdered KOH (0.093 g, 1.65 mmol) in 5 mL of CH_2Cl_2 (previously prepared and stirred for 30 min at room temperature) and stirred for another 45 min. The reaction mixture was then filtered though Celite and the filter cake was washed with CH_2Cl_2 (10 mL×3). The combined filtrate and washings were concentrated to a small volume (~3 mL) and added slowly into vigorously stirred ice-cold CH_3OH (25 mL). The resulting suspension was filtered by suction filtration and dried in high vacuum to afford polymer **2-2** as a pale yellow powder; yield: 95–98%. Loading calcd by ^{1}H NMR spectroscopy: 1.00 mmol/g and elemental analysis: 1.04 mmol/g. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.43 – 1.84 (m, H_2O+–CH_2CH–), 5.57 (s, 1H, CH), 6.57 –

8.25 (m, 40H, ArH); IR (KBr): *v*=3061, 3024, 2920, 2850, 1604, 1490, 1444, 1354, 1174, 1083, 1022 cm^{-1}.

2.10.7 General Procedure for Alkene Oxidation by Polymer 2-2

Polymer **2-2** (0.6 mmol (based on the oxidizing equivalent)) was added to a solution of the respective alkene **2-9** (0.3 mmol) in dry CH_2Cl_2 (1.5 mL) placed in a sealed microwave vessel. The reaction mixture was microwave irradiated (with the heating program starting at 150 W) at 100 °C for 15 min. When the reaction is completed, the polymer-supported reagent was precipitated with ice-cold CH_3OH (25 mL) and filtered through filter paper. The filter cake was then washed with ice-cold CH_3OH (3×10 mL). The combined filtrate and washing was concentrated to 2–3 mL and filtered through a Miniart® single use syringe filter (pore size 0.2 μm) to remove any residual polymer. The filtrate was concentrated and purified using simple flash column chromatography to afford **2-10**.

2, 3-Diphenyloxirane (2-10a)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39 - 7.34 (m, 10H), 3.57 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.1, 128.5, 128.3, 125.4, 62.8. HRMS (EI) calcd. for $C_{14}H_{12}O$: 196.0888, found: 196.0879.

2-*p*-Tolyloxirane (2-10b)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.18 - 7.14 (m, 4H), 3.83 (q, 1H, J = 1.2 Hz), 3.12 (q, 1H, *J* = 1.2 Hz), 2.79 (q, 1H, *J* = 2.5 Hz), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 125

MHz): δ 137.9, 134.5, 129.1, 125.4, 52.3, 51.0, 21.1. HRMS (EI) calcd. for $C_9H_{10}O$: 134.0732, found: 134.0733.

9-Oxa-bicyclo[6.1.0]nonane (2-10c)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.88 - 2.14 (m, 2H), 2.13 - 1.63 (m, 2H), 1.61 - 1.38 (m, 8H), 1.30-1.22 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 55.5, 26.5, 26.2, 25.5. HRMS (EI) calcd. for $C_8H_{14}O$: 125.1330, found: 125.1326.

2-Phenyloxirane (2-10d)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37 - 7.27 (m, 5H), 3.86 (t, 1H, *J* = 3.7 Hz), 3.15 (q, 2H, *J* = 1.1 Hz), 2.80 (q, 2H, *J* = 2.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.6, 128.5, 128.5, 128.2, 125.5, 52.4, 51.2. HRMS (EI) calcd. for C_8H_8O: 120.0575, found: 120.0573.

2-(4-Chlorophenyl)oxirane (2-10e)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.18 - 7.07 (m, 4H), 3.74 (q, 1H, *J* = 2.5 Hz), 3.05 (q, 1H, *J* = 3.7 Hz), 2.66 (q, 2H, *J* = 2.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.8, 134.5, 129.7, 128.2, 125.4, 123.7, 51.6, 51.1. HRMS (EI) calcd. for C_8H_7OCl: 154.0185, found: 154.0184.

2-Methyl-3-phenyloxirane (2-10f)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.27 - 7.17 (m, 5H), 3.49 (d, 1H, *J* = 1.9 Hz), 2.96 (q, 1H, *J* = 3.1 Hz), 1.37 (d, 3H, *J* = 5.6 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ

137.7, 128.4, 128.0, 125.5, 59.5, 59.0, 17.8. HRMS (EI) calcd. for $C_9H_{10}O$: 134.1751, found: 134.1749.

2.9.8 Preparation of Silyl Enol Ether 2-11

The compound was synthesized according to a literature procedure.[43]

(Z)-(1,2-Diphenylvinyloxy)trimethylsilane (2-11a)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71 - 7.18 (m, 10H), 6.17 (s, 1H), 0.1 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.9, 139.6, 136.6, 128.6, 128.1, 128.0, 126.1, 126.0, 110.5, 0.6. HRMS (FAB) calcd. for $C_{17}H_{20}OSi$: 268.1278, found: 268.1291.

Trimethyl(1-phenylvinyloxy)silane (2-11b)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69 - 7.67 (m, 2H), 7.41 - 7.34 (m, 3H), 4.99 (d, 1H, *J* = 1.2 Hz), 4.51 (s, 1H), 0.35 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 155.6, 137.5, 128.1, 128.0, 125.1, 91.0, 0.1. HRMS (FAB) calcd. for $C_{11}H_{15}OSi$: 191.0892, found: 191.0894.

(3H-Inden-1-yloxy)trimethylsilane (2-11c)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.28 - 7.09 (m, 4H), 5.32 (br s, 1H), 3.16 (d, 2H, *J* = 1.9 Hz), 0.1 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.5, 142.6, 141.7, 125.9, 125.1, 123.7, 118.1, 106.1, 33.9, 0. HRMS (FAB) calcd. for $C_{12}H_{16}OSi$: 204.0965, found: 204.0968.

(Z)-Trimethyl(pent-2-en-2-yloxy)silane (2-11d)

^{1}H NMR (MeOD, 500 MHz): δ 7.46 - 7.22 (m, 5H), 5.25 (t, 1H, *J* = 7.5 Hz), 4.86 (s, 1H), 2.22 - 2.18 (m, 2H), 1.04 (t, 3H, *J* = 7.6 Hz), 0.1 (s, 9H). ^{13}C NMR (MeOD, 75 MHz): δ 149.9, 140.5, 129.0, 128.4, 126.3, 113.8, 20.5, 14.5, 0.5. HRMS (FAB) calcd. for $C_{13}H_{20}OSi$: 220.1278, found: 220.1271.

2.10.9 General Procedure for Silyl Enol Ether Oxidation by Polymer 2-2

Polymer **2-2** (0.6 mmol (based on the oxidizing equivalent)) was added to a solution of the respective silyl enol ether **2-11** (0.3 mmol) in dry CH_2Cl_2 (1.5 mL) placed in a sealed microwave vessel. The reaction mixture was then microwave irradiated (with the heating program starting at 150 W) at 100 °C for 20 min. When the reaction was completed, the polymer-supported reagent was precipitated with ice-cold CH_3OH (25 mL) and filtered through a filter paper. The filter cake was then washed with ice-cold CH_3OH (3×10 mL). The combined filtrate and washing was concentrated to 2–3 mL and filtered through a Miniart® single use syringe filter (pore size 0.2 μm) to remove any residual polymer. The filtrate was concentrated to dryness to afford the respective epoxide **2-12**. The compound **2-12** was then stirred in a mixture of 2 M of HCl (3 mL) and THF (5 mL) and the hydrolysis reaction was monitored using TLC. When the reaction was completed, the reaction mixture was diluted with EtOAc and the aqueous phase was extracted with EtOAc (5 mL). The combined organic extract was washed with brine, dried over $MgSO_4$, filtered, concentrated, and

purified by a simple flash column chromatography to afford the α-alcohol carbonyl compound **2-13**.

2-Hydroxy-1,2-diphenylethanone (2-13a)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.80 - 7.79 (m, 2H), 7.41-7.29 (m, 1H), 7.25 - 7.13 (m, 7H), 5.84 (s, 1H), 4.48 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.9, 138.9, 133.8, 133.4, 129.0, 128.6, 128.5, 127.7, 76.1. HRMS (EI) calcd. for $C_{14}H_{12}O_2$: 212.0837, found: 212.0845.

2-Hydroxy-1-phenylethanone (2-13b)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.93 - 7.90 (m, 2H), 7.65 - 7.47 (m, 3H), 4.87 (s, 1H), 3.61 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.3, 134.2, 133.3, 128.9, 127.6, 65.3. HRMS (EI) calcd. for $C_8H_8O_2$: 136.0524, found: 136.0518.

2-Hydroxy-2,3-dihydroinden-1-one (2-13c)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.75 - 7.37 (m, 4H), 4.54 (dd, 1H, *J* = 5.1 & 7.6 Hz), 3.56 (dd, 1H, *J* = 8.2 & 16.4 Hz), 3.01 (dd, 1H, *J* = 5.1 & 16.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 206.5, 150.9, 135.8, 134.0, 127.9, 126.7, 124.4, 74.2, 35.1. HRMS (EI) calcd. for $C_9H_8O_2$: 148.0524, found: 148.0521.

2-Hydroxy-2,3-dihydroinden-1-one (2-13d)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.91 - 7.90 (m, 2H), 7.62-7.48 (m, 3H), 5.05 (dd, 1H, *J* = 3.8 & 6.9 Hz), 3.72 (br s, 1H), 1.97-1.91 (m, 1H), 1.63-1.58 (m, 1H), 0.93

(t, 3H, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 202.0, 133.8, 133.7, 128.8, 128.4, 73.9, 28.7, 8.8. HRMS (EI) calcd. for $C_{10}H_{11}O_2$: 163.0759, found: 163.0740.

2.10.10 General Procedure for the Oxidation of Pyridines by Polymer 2-2

Polymer **2-2** (0.75 mmol (based on the oxidizing equivalent)) was added to a solution of the respective pyridine **2-14** (0.3 mmol) in dry CH_2Cl_2 (1.5 mL) placed in a sealed microwave vessel. The reaction mixture was then microwave irradiated (with the heating program starting at 150 W) at 100 °C for 2 min. When the reaction was completed, the polymer-supported reagent was precipitated with ice-cold CH_3OH (25 mL) and filtered through a filter paper. The filter cake was then washed with ice-cold CH_3OH (3×10 mL). The combined filtrate and washing was concentrated to 2–3 mL and filtered through a Miniart® single use syringe filter (pore size 0.2 μm) to remove any residual polymer. The filtrate was concentrated to dryness to afford the respective compound **2-15**.

4-Ethylpyridine N-oxide-2-amine (2-15a)

^{1}H NMR (D_3COD, 500 MHz): δ 7.99 (d, J = 6.9 Hz, 1H), 6.93 (s, 1H), 6.73 (d, J = 6.9 Hz, 1H), 6.73 (d, J = 1.9 Hz, 1H), 2.67 (q, J = 7.6 Hz, 2H), 1.24 (t, J = 7.6 Hz, 3H) ^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.29, 129.27, 126.92, 114.57, 112.56, 29.17, 13.79. HRMS (EI) calcd. for $C_7H_{10}ON_2$: 138.0793, found: 138.0793.

4-(4-Nitrobenzyl)pyridine N-oxide (2-15b)

^{1}H NMR (D_3COD, 500 MHz): δ 8.26 (d, *J* = 6.9 Hz, 2H), 8.17 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 6.9 Hz, 2H), 4.20 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.49, 147.80, 144.85, 140.41, 131.39, 128.58, 125.10, 40.60. HRMS (EI) calcd. for $C_{12}H_{10}O_3N_2$: 230.0691, found: 230.0690.

6,7,8,9-Tetrahydro-5H-cyclohepta[b]pyridine-oxide (2-15c)

^{1}H NMR (D_3COD, 500 MHz): δ 8.19 (d, *J* = 5.7 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.24 (m, 1H), 3.39 (m, 2H), 2.92 (m, 2H), 1.91 (m, 2H), 1.69 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 155.61, 144.89, 138.54, 131.33, 124.45, 35.55, 32.87, 28.30, 27.22, 26.13. HRMS (EI) calcd. for $C_7H_{10}ON_2$: 163.0997, found: 163.0994.

Phenyl(pyridin-2-yl-oxide)methanone (2-15d)

^{1}H NMR (D_3COD, 500 MHz): δ 8.35 (br s, 1H), 7.79 (m, 2H), 7.64 (m, 4H), 7.53 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.27, 148.32, 141.14, 136.44, 135.54, 130.40, 130.30, 130.08, 129.06, 126.99. HRMS (EI) calcd. for $C_7H_{10}ON_2$: 199.0633, found: 199.0632.

2.10.11 Preparation of Tetrahydrobenzimidazole 2-16

Compound **16** was synthesized according to a literature procedure.[39]

1-Methyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole (2-16a)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.26 (s, 1H), 3.45 (s, 3H), 2.56 - 2.44 (m, 4H), 1.80 - 1.73 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 136.5, 135.3, 125.7, 32.0, 30.6, 29.5, 24.1, 23.1, 22.8, 20.1, 13.9. HRMS (ESI) calcd. for $C_8H_{12}N_2$: 136.1000, found: 136.1000.

1-(Methoxymethyl)-4,5,6,7-tetrahydro-1H-benzo[d]imidazole (2-16b)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44 (s, 1H), 5.10 (s, 2H), 3.25 (s, 3H), 2.60 - 2.53 (m, 4H), 1.84 - 1.78 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.6, 135.8, 75.5, 55.6, 29.6, 24.1, 23.2, 22.8, 20.3. HRMS (ESI) calcd. for $C_9H_{14}ON_2$: 166.1106, found: 166.1107.

1-Benzyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole (2-16c)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40 (s, 1H), 7.34 - 7.07 (m, 5H), 4.98 (s, 2H), 2.61-2.60 (br d, 2H), 2.34 (br s, 2H), 1.77 - 1.75 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.1, 136.4, 135.3, 128.8, 127.8, 126.8, 125.7, 48.4, 24.2, 23.2, 22.9, 20.5. HRMS (ESI) calcd. for $C_{14}H_{16}N_2$: 212.1313, found: 212.1316.

2-Azido-1-benzyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole (16d)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.22 - 6.98 (m, 5H), 4.70 (s, 2H), 2.44 - 2.43 (br d, 2H), 2.22 (br s, 1H), 1.66-1.64 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.0, 136.2, 134.3, 128.6, 127.5, 126.5, 124.7, 45.9, 23.9, 22.9, 22.5, 20.5. HRMS (ESI) calcd. for $C_{14}H_{15}N_5$: 253.1327, found: 253.1316.

2.10.12 General Procedure for Oxidative Rearrangement by 2-2

Polymer **2-2** (0.75 mmol) was added to a solution of the tetrahydrobenzimidazole **2-16** (0.3 mmol) in dry CH_2Cl_2 (2.0 mL) placed in a sealed-tube microwave vessel. The reaction mixture was microwave irradiated (with the heating program starting at 150 W) at 100 °C for 45 min. When the reaction was completed, the polymer-supported reagent was precipitated with cold methanol (25 mL) and filtered through filter paper. The filter cake was washed with cold methanol (3×10 mL) and the combined filtrate and washings was concentrated to 2–3 mL and filtered through a Miniart® single use syringe filter (pore size 0.2 μm) to remove any residual polymer. The filtrate was concentrated and purified by a simple flash column chromatography to give **2-17**.

3-Methyl-1,3-diazaspiro[4.4]non-1-en-4-one (2-17a)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55 (s, 1H), 3.07 (s, 3H), 1.96 - 1.90 (m, 6H), 1.77 - 1.74 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 185.5, 152.1, 77.6, 37.2, 27.3, 25.7. HRMS (ESI) calcd. for $C_8H_{12}ON_2$: 152.0950, found: 152.0954.

3-Methoxymethyl-1,3-diazaspiro[4.4]non-1-en-4-one (2-17b)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70 (s, 1H), 4.81 (s, 2H), 3.29 (s, 3H), 1.98 - 1.79 (m, 8H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 185.2, 150.5, 78.0, 71.7, 56.5, 37.3, 25.8. HRMS (ESI) calcd. for $C_9H_{14}O_2N_2$: 182.1055, found: 182.1056.

3-Benzyl-1,3-diazaspiro[4.4]non-1-en-4-one (2-17c)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46 (s, 1H), 7.29 - 7.14 (m, 5H), 4.56 (s, 2H), 1.95 - 1.71 (m, 8H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 185.0, 151.0, 135.6, 129.0, 128.1, 127.5, 77.8, 44.5, 37.2, 25.8. HRMS (ESI) calcd. for $C_{14}H_{16}ON_2$: 228.1263, found: 228.1257.

2-Azido-3-Benzyl-1,3-diazaspiro[4.4]non-1-en-4-one (2-17d)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46 - 7.31 (m, 5H), 4.97 (s, 2H), 2.35 - 2.03 (m, 8H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.9, 156.6, 134.0, 129.0, 128.7, 128.7, 74.4, 45.4, 37.4, 25.3. HRMS (ESI) calcd. for $C_{14}H_{15}ON_5$: 269.1277, found: 269.1274.

2.10.13 General Procedure for the Oxidation of Enolates by Polymer 2-2

To a solution of KHMDS (60 mL, 0.5 M in THF, 0.3 mmol) in THF (15 mL) was added compound **2-18** (0.2 mmol) under argon in dry argon at -78^{o}C. After stirring the reaction mixture at -78^{o}C for 30 min, polymer **2-2** (0.3 mmol) in THF (5 mL) was added in one portion. The reaction was monitor by TLC and was observed to be completed within 4 h. The reaction was quenched with 0.5 mL saturated aqueous NH_4Cl solution and concentrated to 1-2 mL. Ice-cold methanol (20 mL) was then added and the suspension that formed was filtered through a filter paper and the filter cake was washed with cold methanol (3 x 10 mL). The combined filtrate and washings was concentrated to 2-3 mL and filtered through a Miniart® single use syringe filter (pore size 0.2 μm) to remove any residual

polymer. The filtrate was concentrated and purified by a simple flash column chromatography to give **2-19**.

2-Hydroxy-1,3-bis-(4-methoxy-phenyl)-propane-1,3-done (2-19a)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.99 (d, 4H), 6.92 (d, 4H), 5.96 (s, 1H), 4.70 (s, 1H), 3.85 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ194.0, 164.3, 132.7, 131.7, 114.0, 78.7, 55.4. HRMS (ESI) calcd. for $C_{17}H_{16}O_5$: 300.0998, found: 300.0997.

(R)-4-Benzyl-3-((R)-2-hydroxyheptanoyl)oxazolidin-2-one (2-19b)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35 - 7.20 (m, 5H), 6.69 - 6.64 (m, 1H), 4.29 - 4.22 (m, 2H), 3.45 (s, 1H), 3.31 (dd, *J* = 3.2 Hz, *J* = 13.2 Hz), 2.84 (dd, *J* = 9.5 Hz, *J* = 13.2 Hz, 1H), 1.82-1.78 (m, 1H), 1.62-1.51 (m, 3H), 1.36-1.26 (m, 4H), 0.89 (t, 3H) ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.4, 153.4, 135.3, 129.4, 128.9, 127.3, 66.1, 55.1, 37.9, 35.5, 31.5, . HRMS (ESI) calcd. for $C_{14}H_{15}ON_5$: 305.1627, found: 305.1628.

2.10.14 General Procedure for Sulfide Oxidation by 2-2

Polymer **2-2** (0.32 mmol) was added to a solution of the respective sulfide **2-20** (0.3 mmol) in dry CH_2Cl_2 (1.5 mL) placed in a sealed-tube microwave vessel. The reaction mixture was then microwave irradiated at 60 ^{o}C for 10 min. When the reaction was completed, the polymer-supported reagent was precipitated with cold methanol (25 mL) and filtered through filter paper. The filter cake was then washed with cold methanol (3 x 10 mL). The combined filtrate and washing was

concentrated to 2-3 mL and filtered through a Miniart® single use syringe filter (pore size 0.2 µm) to remove any residual polymer. The filtrate was concentrated to dryness to afford the respective sulfoxide **2-21**.

1-(Phenylsulfinyl)benzene (2-21a)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.64 - 7.40 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.4, 130.9, 129.2, 124.6. HRMS (EI) calcd. for $C_{12}H_{10}OS$: 202.0452, found: 202.0451.

4-(Methylsulfinyl)benzaldehyde (2-21b)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.0 (s, 1H), 8.03 (d, 2H, *J* = 8.2 Hz), 7.81 (d, 2H, *J* = 8.2 Hz), 2.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.0, 152.5, 138.1, 130.3, 124.1, 43.8. HRMS (EI) calcd. for $C_8H_8O_2S$: 168.0245, found: 168.0240.

2-(Phenylsulfinyl)ethanol (2-21c)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.65 - 7.49 (m, 5H), 4.19 - 3.99 (m, 1H), 3.20 - 3.14 (m, 1H), 2.90-2.86 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.0, 131.2, 129.4, 123.9, 58.1, 57.1. HRMS (EI) calcd. for $C_8H_{10}O_2S$: 170.0402, found: 170.0399.

2-(Methylsulfinyl)naphthalene (2-21d)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.21 (s, 1H), 8.00 - 7.57 (m, 5H), 2.79 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.7, 134.4, 132.9, 129.5, 128.5, 128.0, 127.7, 127.3, 124.0, 119.4, 43.7. HRMS (EI) calcd. for $C_{11}H_{10}O_2S$: 190.0452, found: 190.0448.

1-(Benzylsulfinylmethyl)benzene (2-21e)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41 - 7.28 (m, 10H), 3.95 - 3.85 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 130.1, 128.9, 128.3, 57.2. HRMS (EI) calcd. for $C_{14}H_{14}OS$: 230.0765, found: 230.0765.

1-(Butylsulfinyl)butane (2-21f)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.67 - 2.60 (m, 4H), 1.73 - 1.70 (m, 4H), 1.50 - 1.42 (m, 4H), 0.93 (t, 6H, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 52.0, 24.5, 22.0, 13.5. HRMS (EI) calcd. for C_8H_8OS: 162.1078, found: 162.1077.

Methyl 2-(furan-2-ylmethylsulfinyl)acetate (2-21g)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43 (d, 1H, *J* = 1.8 Hz), 6.45-6.38 (m, 2H), 4.30-4.17 (m, 2H), 3.77 (s, 3H), 3.68-3.55 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.5, 143.8, 143.2, 112.0, 111.2, 54.2, 52.8, 50.6. HRMS (ESI) calcd. for $C_8H_{10}O_4S$: 202.0300, found: 202.0302.

2.10.15 General Procedure for Phosphine Oxidation by 2-2

Polymer **2-2** (0.75 mmol) was added to a solution of the respective phosphine **2-22** (0.3) in dry CH_2Cl_2 (1.5 ml) placed in a sealed-tube microwave vessel. The reaction mixture was then microwave irradiated at 100 ^oC for 10 min. When the reaction was completed, the polymer-supported reagent was precipitated with cold methanol (25 mL) and filtered through filter paper. The filter cake was washed with cold methanol (3 x 10 mL) and the combined filtrate and washings was concentrated to 2-3 mL and filtered through a Miniart® single use syringe filter (pore size 0.2 µm) to remove any residual polymer. The filtrate was concentrated to dryness to afford the respective phosphine oxide **2-23**.

Triphenylphosphine oxide (2-23a)

^1H NMR ($CDCl_3$, 300 MHz): δ 7.70 - 7.43 (m, 15H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 133.1, 132.0, 131.9, 131.8, 131.8, 131.7, 128.5, 128.3. ^{31}P NMR ($CDCl_3$, 202 Hz): δ 29.6. HRMS (ESI) calcd. for $C_{18}H_{14}OP$: 277.0782, found: 277.0780.

Tri(*p*-tolyl)phosphine oxide (2-23b)

^1H NMR ($CDCl_3$, 300 MHz): δ 7.56 - 7.22 (m, 12H), 2.39 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.1, 142.1, 132.0, 131.9, 130.0, 129.2, 129.1, 129.0, 21.5. ^{31}P NMR ($CDCl_3$, 202 Hz): δ 30.0. HRMS (ESI) calcd. for $C_{21}H_{20}OP$: 319.1252, found: 319.1251.

Diethyl(phenyl)phosphine oxide (2-23c)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.69 - 7.42 (m, 5H), 2.06 - 1.77 (m, 4H), 1.14 - 1.03 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 132.1, 131.5, 131.4, 130.9, 130.5, 130.3, 128.6, 128.4, 22.6, 21.6, 5.4, 5.3. ^{31}P NMR ($CDCl_3$, 202 Hz): δ 44.6. HRMS (ESI) calcd. for $C_{10}H_{15}OP$: 182.0861, found: 182.0856.

Tri(*o*-tolyl)phosphine oxide (2-23d)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.46 - 7.05 (m, 12H), 2.47 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.5, 143.4, 133.0, 132.8, 132.5, 132.1, 131.9, 130.8, 129.5, 125.5, 125.4, 21.9, 21.9. ^{31}P NMR ($CDCl_3$, 202 Hz): δ 38.4. HRMS (ESI) calcd. for $C_{21}H_{20}OP$: 319.1252, found: 319.1250.

Trifuran-2-ylphosphine oxide (2-23e)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.73 - 6.54 (m, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.9, 148.8, 144.9, 123.6, 123.3, 111.1, 110.9. ^{31}P NMR ($CDCl_3$, 202 Hz): δ -11.1. HRMS (ESI) calcd. for $C_{12}H_9O_4P$: 248.0238, found: 248.0236.

Cyclohexyldiphenylphosphine oxide (2-23f)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.80 - 7.45 (m, 10H), 1.80 - 1.23 (m, 11H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 132.5, 132.2, 131.4, 131.3, 131.0, 130.9, 128.8, 128.5, 128.4, 126.3, 37.6, 36.6, 26.4, 26.2, 25.7, 24.7, 24.7. ^{31}P NMR ($CDCl_3$, 202 Hz): δ 35.3. HRMS (ESI) calcd. for $C_{18}H_{20}OP$: 283.1252, found: 283.1251.

2.10.16 General Procedure for the Regeneration of Polymer-Supported 2-Benzenesulfonyl-3-(*p*-nitrophenyl)oxaziridine 2-2

To a solution of *m*-CPBA (70–75% purity, 0.216 g, 1.25 mmol) in CH_2Cl_2 (5 mL) was added powdered KOH (0.093 g, 1.65 mmol) and the resulting suspension was stirred at room temperature for 30 min. Thereafter, the spent polymer (0.5 mmol) was added and the mixture was stirred at room temperature for an additional 45 min. After this, the reaction mixture was filtered though Celite and the filter cake was washed with CH_2Cl_2(10 mL×3). The combined filtrate and washings were concentrated to a small volume (~3 mL) and added slowly into vigorously stirred ice-cold CH_3OH (25 mL). The resulting suspension was filtered by suction filtration and dried in high vacuum to afford polymer **2-2**.

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Chapter 3: Fluorous Oxime Palladacycle: A Precatalyst for Carbon−Carbon Coupling Reactions in Aqueous and Organic Medium

3.1 Introduction

Palladium-catalyzed carbon–carbon bond-forming reactions are one of the most important tools in the synthesis of symmetric and asymmetric biaryls, having found applications in the preparation of a wide spectrum of organic chemicals, materials, and natural products.[1] Over the decades, various homogeneous catalytic systems have been developed for this transformation.[2] This includes the start of the field on palladacycles as catalysts for cross-coupling reactions in 1995 when Herrmann and Beller reported that the application of cyclopalladated tri-*o*-tolylphosphane for the Pd-catalyzed Heck[3] and Suzuki[4] coupling reactions provided unparalleled turnover numbers (TONs). Since then, a wide variety of nitrogen, oxygen, phosphorus, and sulfur palladacycles with high TONs have been developed for different C–C and C-heteroatom-coupling reactions.[5]

Although homogeneous catalysts generally have a higher activity and selectivity as compared to heterogeneous catalysts, difficulties in separation and recovery of the catalyst and contamination of the products with traces of the heavy metals are common problems encountered which restrict their applications in certain industries.[6] To circumvent this problem, various new strategies for transition-metal catalysis have been developed.[7] One of these strategies involves the development of fluorous-tagged catalyst.[7e-7g] Attaching fluorous groups, such as

perfluorooctyl ($-C_8F_{17}$) groups to organic molecules eases the separation of the catalyst from the reaction products. In addition, fluorous tags are inert to chemical reactions and have little effect on the reactivity of the parent molecule as the electron-withdrawing fluorines are insulated from the reactive site of the parent molecule via methylene segments alone or methyl segments with heteroatoms or phenyl rings. Today, there are basically two types of fluorous catalysts. In fluorous biphasic catalysis, the catalyst contains >60% fluorine by molecular weight so as to provide good liquid/liquid separation between the organic and perfluorocarbon solvent. However the prohibitive cost of the perfluorocarbon solvents makes such catalysis impractical for industrial purposes. An alternative method involves "light fluorous" catalysts where the fluorine content is <50% by molecular weight.[7g] These catalysts can be used in conventional organic solvents, recovered and recycled by fluorous solid-phase extraction (F-SPE) with fluorous silica.[8] However, these methods of catalysis are typically conducted in perfluorocarbon solvents.[9] From the environmentally benign viewpoint, the use of water as a solvent in transition-metal catalysis offers many advantages.[10] Although various catalytic systems in aqueous solutions have been developed,[11] very few examples of fluorous palladium-based catalysis in aqueous media have been reported.[12] In 2008, a recyclable polymer-supported fluorous catalyst (Amberlyst A-21-Pd$(OPf)_2$, 1 mol% Pd) was shown to promote the Sonogashira reaction in water at 80 °C in 1–18 h (Pd leaching: 3.6–11.6 ppm) [12a] and recently, recyclable fluoro silica gel-supported perfluoro-tagged palladium nanoparticles (0.1 mol% Pd) were used to catalyze the Suzuki–Miyaura reaction in water at 100

°C in 8–12 h (Pd leaching: <10 ppm).[12b] In 2009, Theberge *et al.* have also reported a fluorous–aqueous biphasic Suzuki–Miyaura coupling in droplets at room temperature in 0.75–8 h (Pd leaching: <0.5 ppm).[12c]

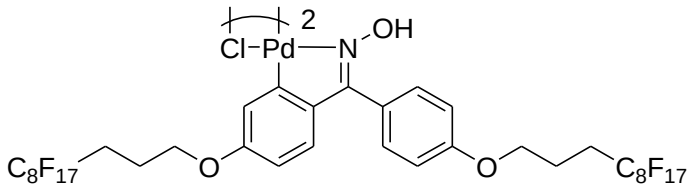


Figure 3-1. Oxime-derived fluorous-tagged palladacycle **3-1**.

Oxime-derived palladacycle was chosen due to several advantages[13] such as the slow release of zerovalent palladium, Pd(0) into the catalytic cycle thus suppressing the inactivation processes from nucleation and growth of large Pd(0) metal. They are also thermally stable and insensitive to air and moisture. Another added advantage is that phosphines are not involved in the reaction thus oxidation of the phosphines to its oxide and removal from the catalytic cycle is not a problem. The temperature-dependent solubility of the solid palladacycle **3-1** in common organic solvents eliminates the use of expensive and potentially toxic fluorous solvents as reaction medium. With the -C_8F_{17} fluorous tags at both ends of the molecule, palladacycle **3-1** incorporates the benefit of a heterogeneous catalyst such as the ease of separation from the reaction products through the use of F-SPE due to its classification as a "light fluorous" molecule (50% fluorine content by molecular weight)[14].

Apart from its advantage in the ease of separation, reaction conditions for solution phase synthesis can also be used directly for fluorous synthesis. Table 3-2 compares conventional solution phase and solid phase synthesis with fluorous synthesis which shows that the latter synthetic methodology exhibits a combination of the advantages of both solution and solid phase synthesis.

Table 3-2. Comparison of conventional solution phase, solid phase and fluorous synthesis[15].

	Solution phase	Solid phase	Fluorous
Intermediate analysis	√		√
Ease of scale-up	√		√
Ease of purification		√	√
Use of excess reagents		√	√
Mixture synthesis		√	√
Potential for automation		√	√

3.2 Synthesis of Fluorous-Tagged Oxime Palladacycle

Palladacycle **3-1** was prepared by treating 4,4'-dihydroxybenzophenone **3-2** with allyl bromide at room temperature for a day to give the allyl ether **3-3** in quantitative yield. Compound **3-3** was then reacted with perfluorooctyl iodide ($C_8F_{17}I$) in the presence of azobisisobutyronitrile (AIBN) in a radical reaction to give compound **3-4** in 74% yield. Removal of the iodide in compound **3-4** was carried out using tributyltin hydride (Bu_3SnH) and AIBN in dichloroethane at

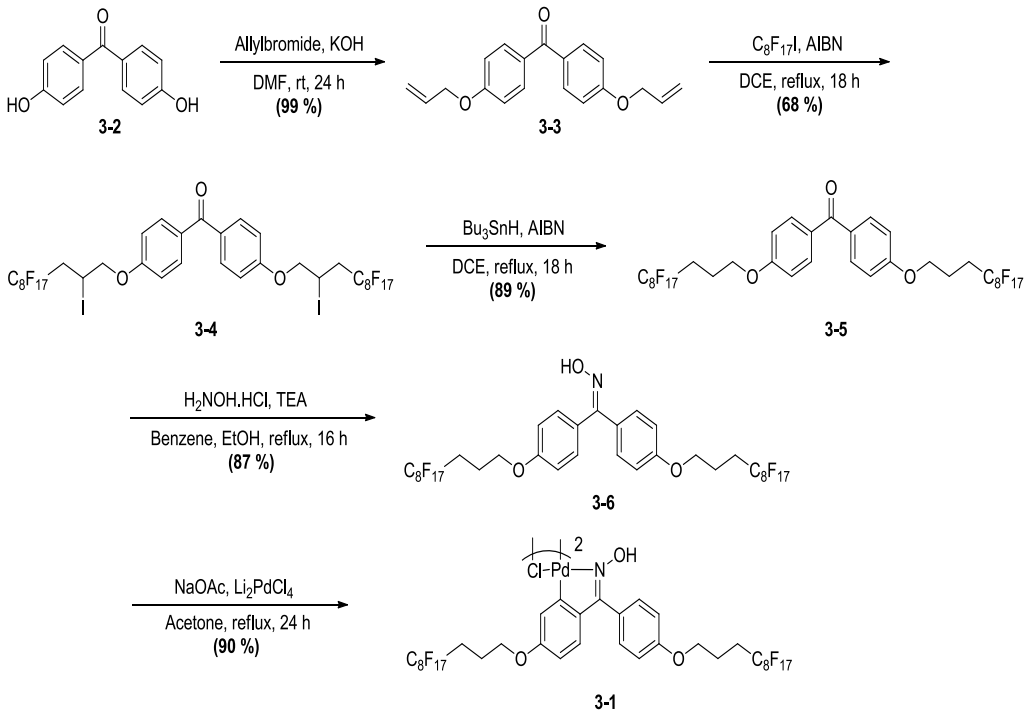
refluxing temperature to give compound **3-5** in 89% yield. Subsequent condensation of **3-5** with hydroxylamine hydrochloride ($H_2NOH{\cdot}HCl$) gave oxime **3-6** (87% yield) which in turn was treated with tetrachlorolithiumpalladate (Li_2PdCl_4) in the presence of a base to produce palladacycle **3-1**.

Table 3-2. Optimization of the synthesis of palladacycle **3-1**

Entry	Temp	Solvent	Time	Yield
1	rt	CH_3OH	7	30
2	rt	THF	6	53
3	rt	acetone	6	92
4	reflux	acetone	1	90

[a] isolated yield.

For the synthesis of palladacycle **3-1**, we had initially used the reaction conditions reported by Alacid and N´ajera.[25] However, formation of Pd black was observed during the reaction and palladacycle **3-1** was obtained in low yield (Table 3-2, entry 1). This could be attributed to the insolubility of compound **3-6** in methanol. In order to optimize the reaction, we varied the solvent and reaction time and found that the best result was obtained in acetone. However at room temperature, the reaction required 6 days to complete. This long reaction time could be due to the poor solubility of sodium acetate in acetone. Hence, we carried out the reaction under reflux and indeed, the reaction time was shortened to 1 day and palladacycle **3-1** was obtained in 90% yield (Table 3-2, entry 4).



Scheme 3-1. Synthesis of palladacycle 3-1

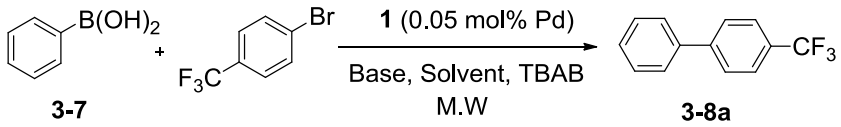
3.3 Suzuki-Miyaura Reaction

Palladium-catalyzed cross-coupling reaction of aryl halides and arylboronic acids is a very versatile and widely used methodology for the construction of biaryls which are important building blocks in natural products, pharmacophores, and functional materials.[16]

Initial assessment of the catalytic activity of palladacycle **3-1** (0.05 mol% Pd) was conducted using the Suzuki–Miyaura reaction between phenylboronic acid **3-7** and 4-bromobenzotrifluoride with K_2CO_3 as the base, water as the solvent, TBAB as an additive and undermicrowave irradiation at 140 °C. The use of TBAB, as an additive in all our coupling reactions, helps in stabilizing the active Pd species and

prevents it from agglomerating to form the inactive Pd black, known as the Jeffery's approach.[17] Another reason for the use of TBAB is that it can act as a phase-transfer catalyst, thus increasing the rate of reaction. The reaction proceeded efficiently to give the biphenyl product **3-8a** in 98% yield within 2 min (Table 3-3, entry 1). It is worth noting that other solvent systems, including THF which is commonly used for the homogeneous palladium-catalyzed Suzuki–Miyaura reaction, gave lower yields of the product (Table 3-3, entries 3–6). These results indicate that the presence of hydroxide ion is essential in the Suzuki mechanism, acting as a ligand rather than a base. Thus, the use of carbonate in water facilities the formation of hydroxide ions which facilitates the formation of the reactive species, *trans*-[Pd(Ar)(OH)$(L)_2$], in the rate-determining transmetallation step.[18]

Table 3-3. Optimization of the Suzuki-Miyaura reaction.



3-7 3-8a

Entry	Temp (^{o}C)	Base	Solvent	Time (min)	Yield (%)[a]
1	140	K_2CO_3	H_2O	2	98
2	140	K_2CO_3	H_2O[b]	4.5	98[b]
3	140	K_2CO_3	THF	2	58
4	140	K_2CO_3	THF/H_2O[c]	3	69
5	140	K_2CO_3	DMF/H_2O[c]	2	92
6	140	K_2CO_3	CH_3OH/H_2O[c]	2	88
7	140	KOH	H_2O	3	83
8	140	Cy_2NMe	H_2O	5	83
9	100	K_2CO_3	H_2O	20	79[d]
10	170	K_2CO_3	H_2O	0.25	89
11	140	K_2CO_3	H_2O	2	0[e]
12	140	K_2CO_3	H_2O	2	17[f]

[a] isolated yield.

[b] precatalyst loading of 0.005 mol% Pd.

[c] ratio of organic solvent to water is 3:1.

[d] yield obtained when the experiment was carried out under conventional heating.

[e] addition of 1 drop of mercury.

[f] addition of 0.5 equivalent of CS_2 (per metal atom).

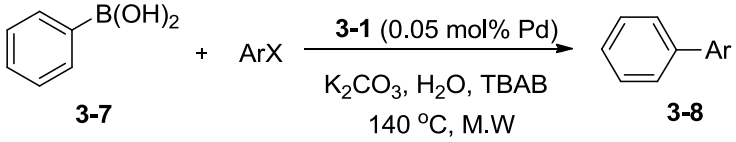
We next examined the effects of the bases on the reaction. Two inorganic bases (K_2CO_3 and KOH) and an organic base (Cy_2NMe) were investigated, and K_2CO_3 was found to be the most effective base for the reaction (Table 3-3, entries 1, 7–8). The use of KOH as a base resulted in a lower yield as compared to K_2CO_3 (Table 3-3, entries 2 and 7). These observation is in accordance that hydroxide ion plays

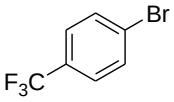
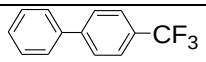
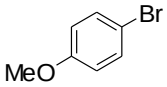
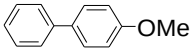
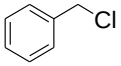
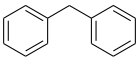
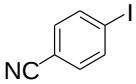
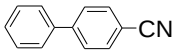
an antagonistic role in the Suzuki reaction mechanism.[18] As KOH salt are easily dissociated into hydroxide ions in presence of water, it could easily react with the arylboronic acid to form the inactive arylboronate. On top of that, the presence of counter ion K^+ in the reaction system would also coordinate with the active $[Pd(Ar)(OH)(L)_2]$, thus retarding the transmetallation step. The reaction temperature was also varied and the experimental data obtained (Table 3-3, entries 1, 9–10) indicated that although the reaction completed more rapidly under microwave irradiation conditions, raising the temperature to 170 °C resulted in a lower yield of the product. Finally, we tried to reduce the precatalyst loading to 0.005 mol% Pd. This afforded **3-8a** in 98% yield (corresponding to 2×10^4 TON) and the reaction time was only slightly longer than the reaction with 0.05 mol% Pd (Table 3-3, entries 1 and 2). However, when 0.005 mol% Pd was applied to the cross-coupling of **3-7** with benzyl chloride under microwave irradiation at 140 °C, the reaction required nearly an hour to complete. Thus, a pre-catalyst loading of 0.05 mol% Pd was used for the remaining Suzuki–Miyaura reactions with palladacycle **3-1** (Table 3-4).

To determine the catalytically active species in the reaction, we carried out the mercury drop test and another test using sub-stoichiometric amounts of CS_2. Results from both tests (Table 3-3, entries 11 and 12) strongly suggest that the palladium nanoparticles are the catalytic species in the reaction. A comparison of palladacycle **3-1** with its polymer-supported analog showed that the Suzuki–Miyaura reaction with palladacycle **3-1** occurred more rapidly and gave a higher

yield of the product (Table 3-4, entries 2–3). It was also gratifying to note that our reaction protocol could be applied successfully to the synthesis of diarylmethanes (Table 3-4, entry 3), as such syntheses have been reported to be difficult using various homogeneous palladium catalyst systems[19] and was only recently made more accessible *via* palladium–phosphine catalysts.[20]

Table 3-4. Suzuki-Miyaura reaction of arylboronic acid with different aryl and benzyl halides.



Entry	ArX	Time (min)	Product (Yield[a])
1		2	 **3-8a** (98%)
2		6 (2½ h[b])	 **3-8b** (99%, 82%[b])
3		3.5 (1 h[c])	 **3-8c** (92%, 86%[c])
4		2	 **3-8d** (93%)

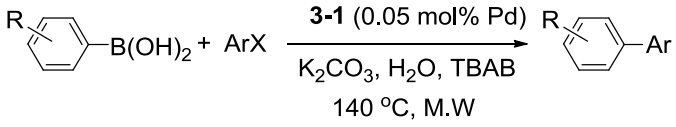
[a] isolated yield.

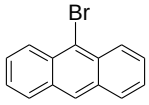
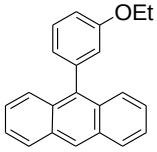
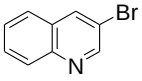
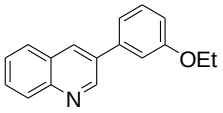
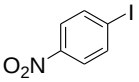
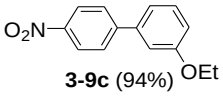
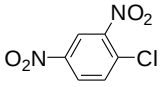
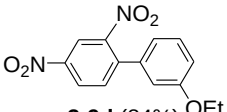
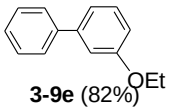
[b]using polymer-supported oxime-based palladacycle[21]: 0.1 mol% Pd, K_2CO_3, H_2O, 100 °C

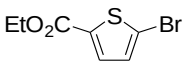
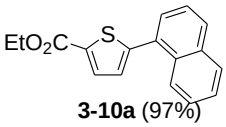
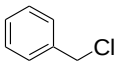
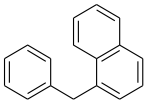
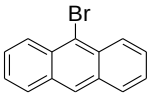
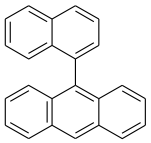
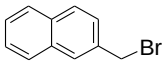
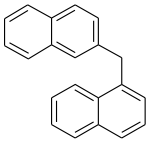
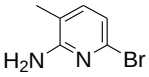
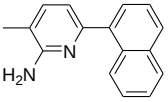
[c]using polymer-supported oxime-based palladacycle[21]: 0.1 mol% Pd, KOH, TBAB, acetone-H_2O (3:2), 50 °C

To investigate the general usefulness of palladacycle **3-1** for the Suzuki−Miyaura reaction, we extended our studies to different combinations of halides and boronic acids (Tables 3-5 and 3-6). Another use of TBAB as an additive in the reaction is that it is known to help in the slow oxidative addition step of the mechanism by activating the Pd(0), especially for deactivated arylbromide and activated arylchloride (Table 3-4, entries 1 and 3).

Table 3-5. Suzuki-Miyaura reaction of arylboronic acids with various aryl and benzyl halides



Entry	ArX	R	Time (min)	Product (Yield[a])
1		3-OEt	5	 **3-9a** (89%)
2		3-OEt	5	 **3-9b** (92%)
3		3-OEt	2	 **3-9c** (94%)
4		3-OEt	10	 **3-9d** (84%)
5		3-OEt	12	 **3-9e** (82%)

6		C_4H_4[b]	7	 **3-10a** (97%)
7		C_4H_4[b]	13	 **3-10b** (89%)[c]
8		C_4H_4[b]	12	 **3-10c** (97%)
9		C_4H_4[b]	7	 **3-10d** (95%)
10		C_4H_4[b]	18	 **3-10e** (93%)

[a] isolated yield.

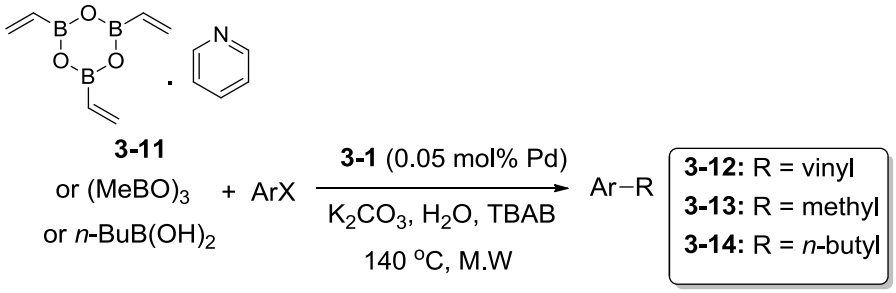
[b] refers to 1-naphthylboronic acid.

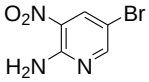
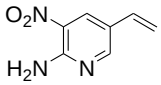
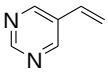
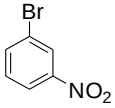
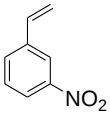
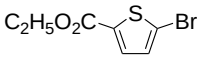
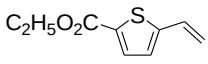
[c] use of TBAB is crucial for good conversion to **3-10b**. TBAB is known to be a phase-transfer catalyst and it also stabilizes the Pd nanoparticles so as to avoid aggregation.[24]

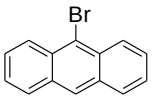
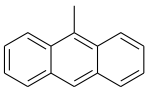
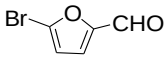
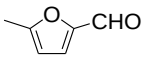
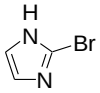
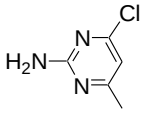
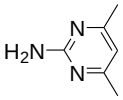
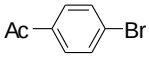
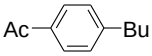
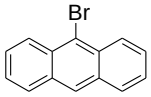
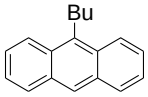
Under the optimized reaction conditions, good to excellent yields of the desired products were achieved in all cases. It was also gratifying to note that our reaction protocol could be applied successfully to aryl chlorides (Table 3-5, entries 4 and 5) as only few recyclable catalytic systems are known to promote the Suzuki−Miyaura reaction of chloroarenes in water.[22]

Since styrene derivatives are often used as key building blocks in the polymer industry and also for fine chemical synthesis,[24] we proceeded to examine the synthesis of styrene compounds using palladacycle **3-1** and trivinylboroxine-pyridine complex **3-11** as the representative vinylating agent.

Table 3-6. Suzuki-Miyaura reaction of trivinylboroxine-pyridine complex **3-11**, trimethylboroxine or butylboronic acid with various aryl and benzyl halides



Entry	ArX	Time (min)	Product (Yield[a])
1		12	 **3-12a** (99%)
2		7	 **3-12b** (95%)
3		15	 **3-12c** (86%)
4		11	 **3-12d** (93%)

5		12	 **3-13a** (97%, 82%[b])
6		16	 **3-13b** (82%)
7		25	 **3-13c** (93%)
8		38	 **3-13d** (85%)
9		7 (2h[c])	 **3-14a** (93%, 51%)[c]
10		6	 **3-14b** (82%)

[a] isolated yield.

[b] Using 4.5 equiv of methylboronic acid instead of 1.5 equiv of TMB

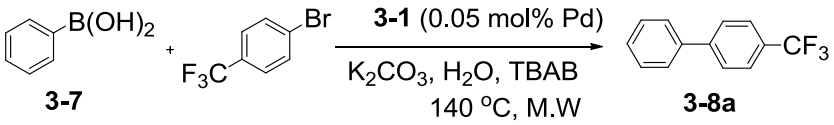
[c] using polymer-supported oxime-based palladacycle[25]: 1 mol% Pd, K_2CO_3, H_2O. TBAB, 100 ^oC.

Treatment of **3-11** with various aryl halides under the optimized reaction condition provided the styrene derivatives in good yields (Table 3-6, entries 1−4), indicating that palladacycle **3-1** is an efficient precatalyst for the installation of a terminal vinyl group. Besides $Csp^2–Csp^2$ bond formation, we have also applied palladacycle **3-1** to the formation of $Csp^2–Csp^3$ bonds through the cross-coupling between aromatic or heteroaryl halides with trimethylboroxine (TMB) or butylboronic acid (Table 3-6, entries 5−10). In our initial studies, we had

attempted to methylate the aromatic ring by cross-coupling aryl bromides with methylboronic acid and palladacycle **3-1** under the optimized reaction conditions. However, with methylboronic acid (1.5 equiv), the reaction proceeded sluggishly and the yield of the desired product obtained was much lower as compared to the yield obtained when the same equivalence of TMB was used. Increasing the amount of methylboronic acid used resulted in a higher yield of the desired product (Table 3-6, entry 5). Since TMB gave a better yield of the desired product and is also a cheaper reagent than methylboronic acid, it was used as the methylating agent for our Suzuki-Miyaura reaction.

Next, we investigated the possibility of recovering and reusing palladacycle **3-1**. 4-Bromobenzotrifluoride and **3-7** were used for the model study under the optimized reaction conditions. The recycling experiments were carried out over 5 runs and the time taken for the reaction to reach completion was 2–7 min to produce **3-8a** in 92–98% yields (Table 3-7). In addition, ICP-OES analysis of Pd leaching in the crude product was very low (0.023–0.033 ppm over 5 cycles). It is worth noting that the amount of palladium leaching is much much lower than that observed for the polymer-supported oxime-based palladacycle analog (14.4–20.2 ppm over 7 cycles)[25] and the three earlier reported fluorous Pd-catalysts which were applied to the cross-coupling reactions in aqueous media (*vide supra*).[13]

Table 3-7. Recycling of palladacycle **3-1** in Suzuki-Miyaura coupling reaction.



Cycle	Time (min)	Yield (%)[a]	Pd leaching (ppm)[b]	Recovered **3-1** (wt%)
1	2	98	0.031	90
2	3	96	0.033	93
3	4	95	0.027	91
4	6	95	0.023	89
5	7	92	0.027	88

[a] isolated yield.

[b] determined by ICP-OES of the crude product.

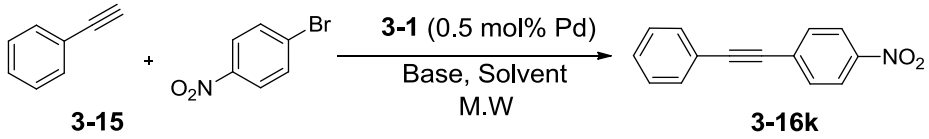
3.4 Sonogashira Reaction.

The Sonogashira reaction is a common reaction used for the formation of biarylacetylenes. In recent years, active research in green chemistry has resulted in numerous reports on the use of water as a cosolvent and/or the use of catalysts containing water-soluble ligands for this reaction.[27] However Sonogashira reactions in neat water and in the absence of additives[28] are rare and often low-yielding because of the poor solubility or instability of the catalysts and coupling reagents in aqueous medium.[29] Attempts to use copper-free sonogashira of coupling was also made in order to surpress the undersired formation of Glaser-type oxidative homocoupling.[30]

Attempts to carry out the Sonogashira coupling of *p*-nitrophenyl bromide and phenylacetylene **3-15** with palladacycle **3-1** (0.05 mol% Pd) and different bases

under microwave irradiation at 140 °C resulted in a sluggish reaction (Table 3-8, entries 1, 3–5). Hence the precatalyst loading was increased to 0.5 mol% Pd and the best yield was obtained when pyrrolidine was used as the base (Table 3-8, entries 1–5). In the Sonogashira reaction, pyrrolidine not only act as a base but also a ligand to the active Pd(0), which facilitates the oxidative addition step.[31,34] Next, we varied the solvent and found that water proved to be the best solvent (Table 3-8, entries 5–9). These results were gratifying as Sonogashira coupling reactions in neat water and in the absence of additives[28] are rare and low yielding because of the poor solubility or instability of the catalysts and coupling reagents in aqueous media.[32] Mechanistic studies of the copper-free version of the Sonogashira coupling have shown that the polarity and hydrogen bonding ability of the solvents are important in accelerating the reaction by stabilizing the ionic intermediates of the catalytic cycle.[34] For our experiments into the Sonogashira coupling reaction in aqueous media, we had initially used undegassed water for the reaction. The presence of oxygen in the reaction mixture resulted in the homocoupled product of **3-17c** being formed as a side-product, as the oxygen may reoxidize the Pd(0) back to Pd(II), which in turn may catalyze homocoupling.[33] To circumvent this problem, we tried degassed water and found that not only was the homocoupled product absent but the reaction time was also reduced.

Table 3-8**.** Optimization of the Sonogashira reaction.



3-15 **3-16k**

Entry	Temp (^{o}C)	Base	Solvent	Time (min)	Yield (%)[a]
1	140	K_2CO_3	NMP	5	53 (21[b])
2	140	TEA	NMP	5.5	45
3	140	TBAA	NMP	9	82 (30[b])
4	140	TBAF	NMP	15	63 (22[b])
5	140	Pyrrolidine	NMP	6	89 (35[b])
6	140	Pyrrolidine	DMF	5	89
7	140	Pyrrolidine	ACN	6.5	81
8	140	Pyrrolidine	THF	7	85
9	140	Pyrrolidine	H_2O	6	93[c]
10	90	Pyrrolidine	H_2O	100	69[d]
11	140	Pyrrolidine	H_2O[e]	3.5	95

[a] isolated yield

[b] 0.05mol% of Pd (incomplete reaction even after 2 h in 140 ^{o}C in M.W)

[c] presence of homocoupled **3-15** (10%)

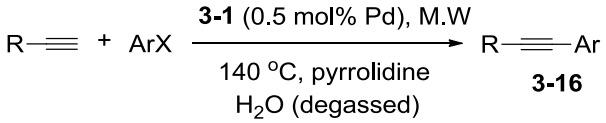
[d] yield obtained when the experiment was carried out under conventional heating.

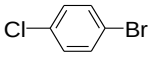
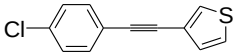
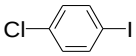
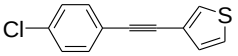
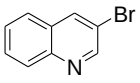
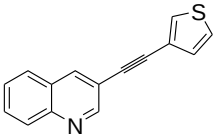
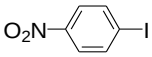
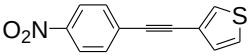
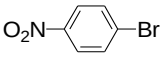
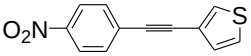
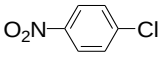
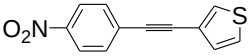
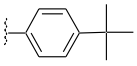
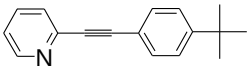
[e] degassed water

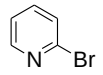
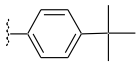
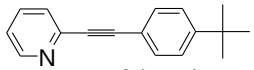
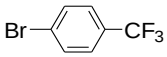
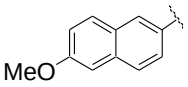
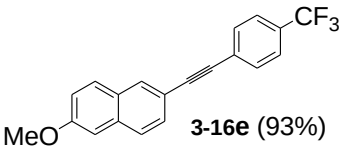
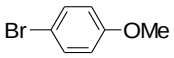
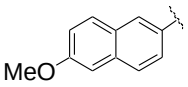
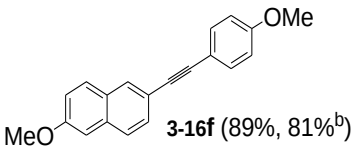
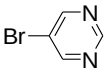
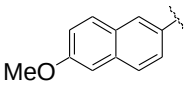
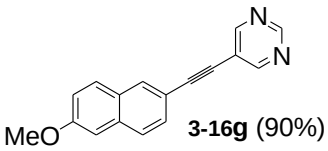
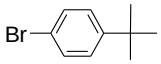
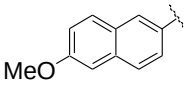
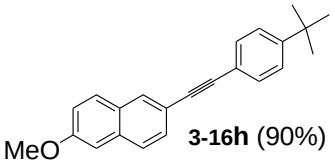
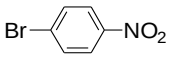
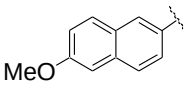
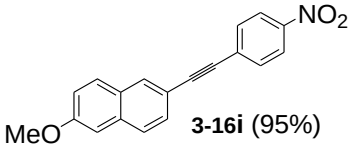
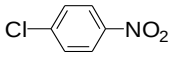
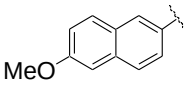
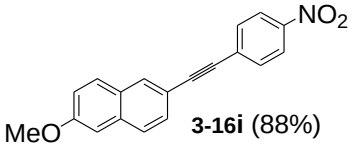
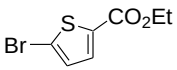
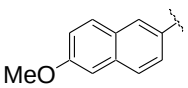
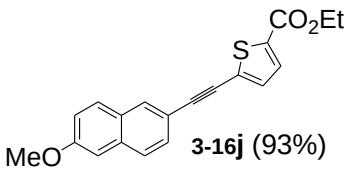
To demonstrate the versatility of palladacycle **3-1** for copper-free Sonogashira coupling reactions, we applied the optimized reaction conditions to other terminal alkynes and aryl halides which also gave good yields of the desired product (Table 3-9). The results obtained show that good reactivity was preserved in both

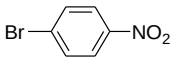
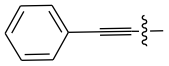
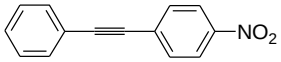
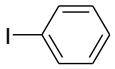
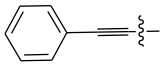
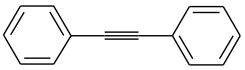
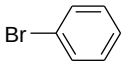
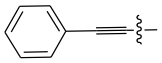
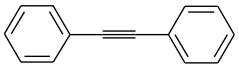
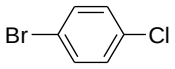
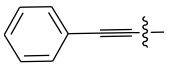
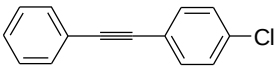
activated and nonactivated aryl halides, indicating that palladacycle **3-1** is an efficient precatalyst for the Sonogashira coupling reaction in aqueous medium.

Table 3-9. Sonogashira reaction using palladacycle **3-1**



Entry	ArX	R	Time (min)	Product (Yield[a])
1			15	 **3-16a** (88%)
2			8	 **3-16a** (95%)
3			30	 **3-16b** (87%)
4			12	 **3-16c** (92%)
5			15	 **3-16c** (90%)
6			27	 **3-16c** (87%)
7			10	 **3-16d** (93%)

8			12	 **3-16d** (88%)
9			6	 **3-16e** (93%)
10			8 (4 h)[b]	 **3-16f** (89%, 81%[b])
11			12	 **3-16g** (90%)
12			7	 **3-16h** (90%)
13			8	 **3-16i** (95%)
14			15	 **3-16i** (88%)
15			7	 **3-16j** (93%)

16			2	 **3-16k** (93%)
17			7	 **3-16l** (96%, 90%[c])
18			14	 **3-16l** (88%, 87%[c])
19			12	 **3-16m** (86%, 73%[c])

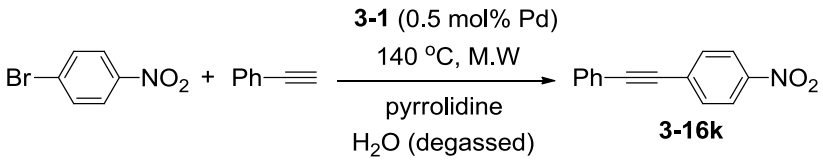
[a] isolated yield.

[b] using pincer complexes of palladium: Pd cat (100 ppm), K_3PO_4, ethylene glycol, 140 ^oC.[32]

[c] Ref. 35.

We have also investigated the possibility of recovering and recycling palladacycle **3-1** from the Sonogashira reaction. 4-Nitrobromobenzene and phenylacetylene were used for the model reaction under the optimized reaction conditions. In this regard, we found that over 5 runs, the time taken for the reaction to complete was 5−12 min, and compound **3-16k** was obtained in 89−93% yields (Table 3-10). In addition, ICP-OES analysis of the crude product indicated that the Pd content was very low (0.063−0.073 ppm over 5 cycles). To our knowledge, this leaching concentration is significantly lower than the amounts determined for the recyclable Pd catalysts reported earlier for the Sonogashira reaction.[26,36]

Table 3-10. Recycling of palladacycle **3-1** in the Sonogashira reaction



Cycle	Time (min)	Yield (%)[a]	Pd leaching (ppm)[b]	Recovered **1** (wt%)[c]
1	5	93	0.067	93
2	7	93	0.063	90
3	8	91	0.065	92
4	12	89	0.069	90
5	12	89	0.073	89

[a] isolated yield.

[b] determined by ICP-OES of the crude product.

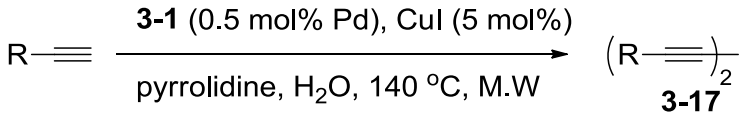
[c] recovered from running through F-SPE

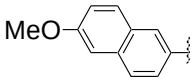
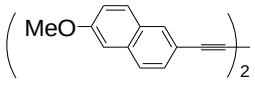
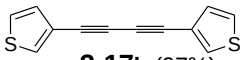
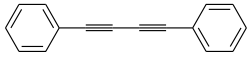
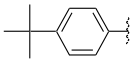
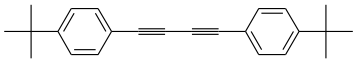
3.5 Homocoupling Reaction of Terminal Alkynes

During the optimization of the Sonogashira reaction with phenylacetylene and various aryl halides, we found that a significant amount of the homocoupled product was formed as a side-product when undegassed water was used as the solvent. This prompted us to explore the use of palladacycle **3-1** as a precatalyst for such Glaser-type homocoupling reactions. In our initial experimentation, we used undegassed water and the optimized reaction condition for the Sonogashira reaction. However, this provided the homocoupled product in moderate yield (Table 3-11, entry 1). Addition of CuI as a co-catalyst not only increased the yield but also slightly reduced the reaction time. This is because CuI could aid in the formation of an activated species through its reaction with the terminal alkyne.[37]

To demonstrate the generality of this reaction condition, we carried out the homocoupling reaction on other terminal alkynes which essentially gave quantitative yields for all cases (Table 3-11, entries 2−4).

Table 3-11. Glaser-type oxidative homocoupling using palladacycle **3-1**



Entry	R	Time (min)	Product (Yield[a])
1		15 (19[b])	 **3-17a** (88%, 68%[b])
2		12	 **3-17b** (97%)
3		8 (10 h)[c]	 **3-17c** (99%, 90%[c])
4		10 (8 h)[d]	 **3-17d** (97%, 90%[d])

[a] isolated yield.

[b] in the absence of co-catalyst CuI.

[c] using mesoporous Pd-MCM-48: Pd catalyst (0.6 mol%), ethanol, refluxed.[38]

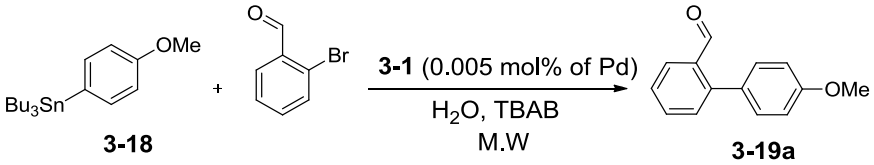
[d] using mesoporous $PdCl_2(PPh_3)_2$ in ionic liquid: Pd catalyst (2 mol%), piperidine, 25 °C.[39]

3.6 Stille Coupling

The Stille coupling reaction is a versatile C−C bond-forming reaction between stannanes and halides because of its tolerance toward most functional groups and

also because the organotin reagents are easy to make and are very stable to oxygen and moisture. In our initial studies, palladacycle **3-1** (0.05 mol% Pd) was added to tributyl(4-methoxyphenyl)stannane **3-18**[40] and *o*-bromobenzaldehyde in different solvents (Table 3-12, entries 1–4).

Table 3-12. Optimization of the Stille reaction.



3-18 **3-19a**

Entry	Temp (^{o}C)	Solvent	Time (min)	Yield (%)[a]
1	140	DMF[b]	25	67
2	140	THF[b]	45	71
3	140	ACN[b]	35	72
4	140	H_2O[b]	28	86
5	170	H_2O[b]	21	77
6	140	H_2O[c]	2	91
7	140	H_2O	2	89
8	100	H_2O	2.5	92
9	100	H_2O	30	76[d]

[a] isolated yield

[b] 0.05mol% of Pd without the presence of TBAB

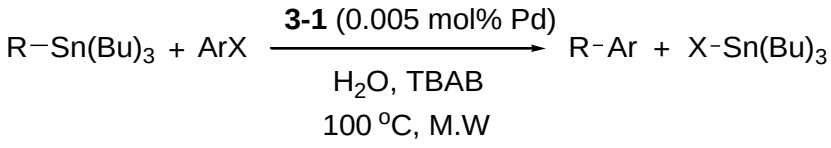
[c] 0.05mol% of Pd in the presence of 0.5 eq. of TBAB

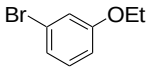
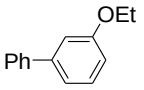
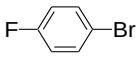
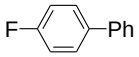
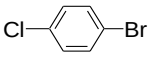
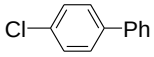
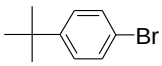
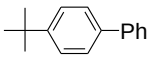
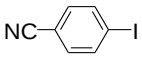
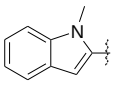
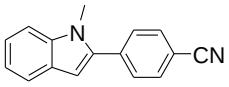
[d] yield obtained when the experiment was carried out under conventional heating.

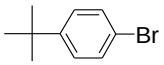
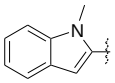
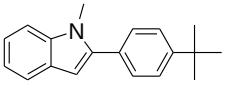
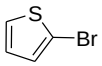
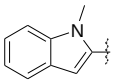
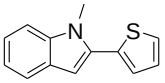
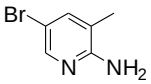
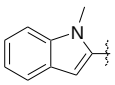
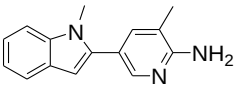
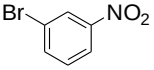
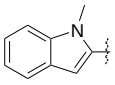
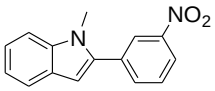
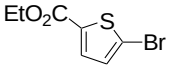
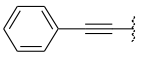
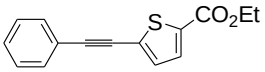
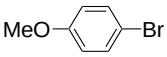
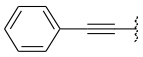
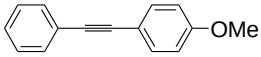
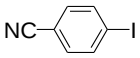
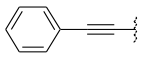
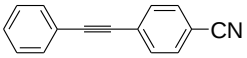
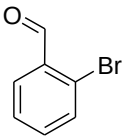
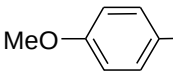
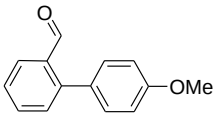
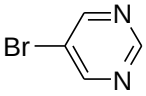
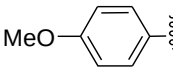
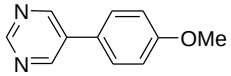
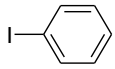
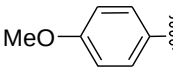
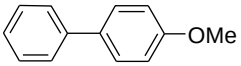
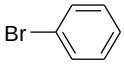
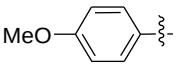
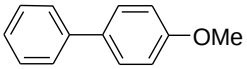
The best yield was obtained when water was used as the reaction solvent but the reaction time was 28 min. To reduce the reaction time, we tried increasing the

reaction temperature but this gave a poorer yield of the desired product. Thus we introduced TBAB as an additive and this resulted in a higher yield (91%) and a significant reduction in reaction time (2 min) (Table 3-12, entry 6). This could be rationalized that the nitrogen atom of TBAB could also enhance the nucleophilicity of organostannanes[43a], on top of being a phase-transfer reagent. Another reason for the faster and higher yield obtained upon the addition of TBAB would be the stabilizing effect of bromide ion on the anionic Pd(0) species.[43b]

Table 3-13. Stille coupling reaction using palladacycle **3-1**



Entry	ArX	R	Time (min)	Product (Yield[a])
1		C_6H_5	4.5	 **3-19a** (90%)
2		C_6H_5	1	 **3-19b** (93%)
3		C_6H_5	1.5 (18 h)[b]	 **3-19c** (88%, 74%[b])
4		C_6H_5	2 (8 h)[c]	 **3-19d** (92%. 91%[c])
5			0.75	 **3-19e** (97%)

6			3	 **3-19f** (88%)
7			6	 **3-19g** (88%)
8			6	 **3-19h** (90%)
9			1.5	 **3-19i** (95%)
10			5	 **3-19j** (87%)
11			3.5 (24 h)[d]	 **3-19k** (83%, 75%[d])
12			0.58	 **3-19l** (92%)
13			2	 **3-19m** (94%)
14			10	 **3-19n** (81%)
15			1.5	 **3-19o** (93%)
16			4	 **3-19o** (89%)

[a] isolated yield.

[b] Pd cat (5 mol%), dioxane, reflux.[42]

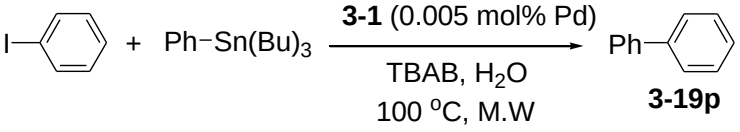
[c] Pd cat, CsF, dioxane, rt→100 °C.[43c]

[d] Pd cat (0.5 mol%), DMF/H_2O (9:1), 80 °C.[44]

Further experimentation showed that the reaction proceeded equally well at a lower temperature (100 °C) and precatalyst loading (0.005 mol% Pd), giving the product in both a comparable yield and reaction time (Table 3-12, entry 8).

To survey the scope of this reaction, we herein conducted the reaction using other organostannanes and aryl halides (Table 3-13). To our delight, the reactions occurred with ease leading to only the cross-coupled product for all cases, indicating that palladacycle **3-1** was generally suitable for CuI-free Stille couplings in water (CuI was demonstrated to accelerate the coupling reaction[42]). This could be rationalized that there is no neutral ligand released, during the oxidation of Pd(0) to *trans*-$PdArXL_2$, the actual species that undergoes transmetalation.

Table 3-14. Recycling of palladacycle **3-1** in the Stille reaction



Cycle	Time (min)	Yield (%)[a]	Pd leaching (ppm)[b]	Recovered **3-1** (wt%)[c]
1	0.75	99	0.52	95
2	0.75	99	0.58	96
3	0.75	98	0.56	93

4	0.75	99	0.58	93
5	0.8	97	0.57	91

[a] isolated yield.

[b] determined by ICP-OES of the crude product.

[c] recovered from running through F-SPE

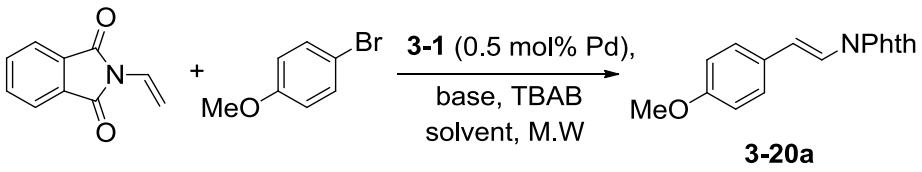
To address the recyclability of palladacycle **3-1** in the Stille reaction, the leaching of the active Pd species in solution was examined for the coupling reaction of tributyl(phenyl)stannane with iodobenzene under the optimized reaction conditions. The results obtained were gratifying as the yields over five runs were quantitative and the time required for the reaction to go to completion remained short (Table 3-14). In addition, the Pd leaching was also very low.

3.7 Heck Reaction

Previous studies on homogeneous catalysis have shown that palladacycles, despite their high catalytic activities,[45] are not stable under the Heck reaction conditions and undergo decomposition via olefin insertion into the C−Pd bond followed by Pd(II) to Pd(0) reduction.[46] To facilitate recovery and reuse, supported palladacycles, such as the polymer-supported cyclopalladated Milstein-type imine complex (the immobilized palladacycle was reported to have completely lost its activity in the third run)[47] and the palladated Kaiser oxime resin,[48] were developed. Since palladacycle **3-1** has been shown to be an efficient precatalyst for the Suzuki−Miyaura, Sonogashira, Glaser-type, and Stille coupling reactions,

from a practical point of view, it was important to study the scope of this palladacycle as a precatalyst in the Heck reaction.

Table 3-15. Optimization of the Heck reaction



3-20a

Entry	Temp (^{o}C)	Base	Solvent	Time (min)	Yield (%)[a]
1	160	Cy_2NMe	DMF	30	79
2	170	Cy_2NMe	DMF	20	87[b]
3	180	Cy_2NMe	DMF	10	72
4	170	TEA	DMF	20	65
5	170	Cs_2CO_3	DMF	20	0
6	120	Cy_2NMe	CH_2Cl_2	150	10
7	140	Cy_2NMe	THF	25	72
8	170	Cy_2NMe	CH_3CN	20	72
9	170	Cy_2NMe	H_2O	20	0

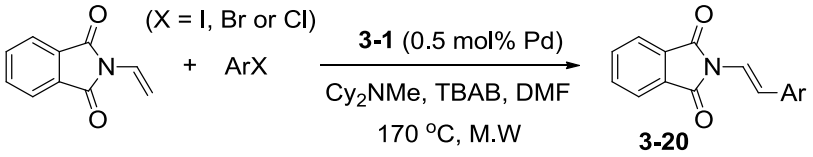
[a] isolated yield. *E*/*Z* regioisomeric ratio is >98/2.

[b] Using palladacycle **3-1** (2.5 mol% Pd), the isolated yield was 72%.

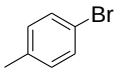
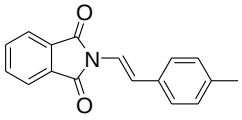
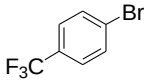
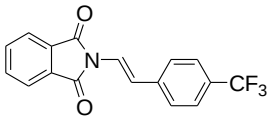
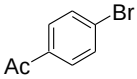
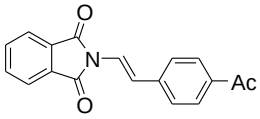
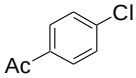
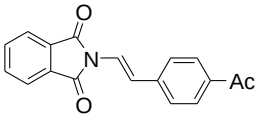
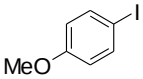
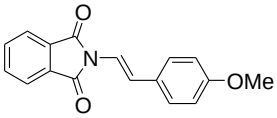
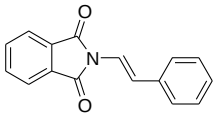
In our initial studies, the Heck reaction was performed using N-vinylphthalimide and 4-methoxybromobenzene with Cy_2NMe as base, TBAB as additive, palladacycle **3-1** (0.5 mol% Pd) as precatalyst, DMF as solvent, and under

microwave irradiation at 160 °C. This gave the E-configuration product **3-20a** in 79% yield (Table 3-15, entry 1). The coupling occurred through a neutral mechanism which gave only the β-N-vinlyphtalimide product. The addition of TBAB in Heck reaction, can serve as promoters to increase the rates of some steps of the catalytic cycle, for instance, the oxidative addition resulting from the increase of electron density on Pd atom due to the formation of more electron-rich anionic Pd(0) species.[49] It can also act as a stabilizing additive to increase the lifetime of underligated Pd(0) species to match slower oxidative addition rates with less reactive substrates, by entering the coordination shell of underligated palladium and form either more stable neutral complexes to impose a Coulombic barrier for collisions and formation of clusters further growing into metal particles.[50] Increasing the reaction temperature to 170 and 180 °C resulted in a shortening of the reaction time (Table 3-15, entries 2−3) however it also resulted in a lower yield.

Table 3-16. Heck reaction of *N*-vinylphthalimide with various aryl halides



3-20

Entry	ArX	Time (min)	Product (Yield[a])
1		20	 **3-20b** (81%)
2		15	 **3-20c** (98%)
3		25 (14 h[b])	 **3-20d** (91%, 68%[b])
4		25 (20[c], 24 h[d])	 **3-20d** (87%, 73%[c], 32%[d])
5		8 (6 h[b], 3 h[d])	 **3-20a** (84%, 79%[b], 83%[d])
6		3 (14 h[b])	 **3-20e** (93%, 86%[b])

[a] isolated yield. E/Z regioisomeric ratio is >98/2.

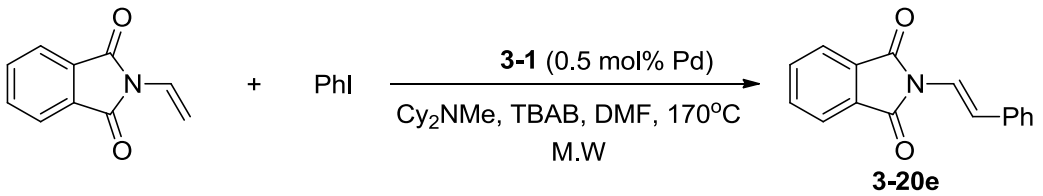
[b] Polymer-supported reaction condition: Cy_2NMe, TBAB, DMF, 120 °C.[51]

[c] Solution-phase reaction condition: Cy_2NMe, TBAB, DMF, M.W, 140 °C.[51]

[d] Solution-phase reaction condition: Cy_2NMe, TBAB, DMF, 140 °C.[51]

Since the product yield was higher at 170 °C, this reaction temperature was used in our subsequent studies. Next, we investigated the effects of bases on the reaction. In addition to Cy_2NMe, TEA and Cs_2CO_3 were examined (Table 3-15, entries 2, 4, and 5), and Cy_2NMe was found to be the most effective base for the reaction. The similarity of structure between methyl(dicyclohexyl)amine and phosphanes led us to hypothesize that the similarly shaped amine bases may function in the same role as the phosphane ligands often employed in Heck reactions. Methyl(dicyclohexyl)amine are closer in shape to triphenylphosphane than the usual bases in Heck reactions, triethylamine, which have a more spherical shape, which could explain the lower yield obtained (Table 3-15, entry 2 and 4). The faster rate of reaction observed with the uses methyl(dicyclohexyl)amine as base might be due to a more rapid conversion of an intermediate $[L_2Pd(HX)]$ complex (L = methyl(dicyclohexyl)amine) since the base which is needed to remove HX is already bound to the palladium.[52] The zero conversion obtained when Cs_2CO_3 was used as a base could be attributed to the insolubility of the base in DMF. Whereas, the use of soluble amine as base would result in a faster HX elimination, which explains the high yield obtained when compared with inorganic base.[53]

Table 3-17. Recycling experiments: Heck reaction of N-vinylphthalimide with iodobenzene.



3-20e

Cycle	Time (min)	Yield (%)[a]	Pd leaching (ppm)[b]	Recovered **3-1**[d] (wt %)
1	3 (14h)[c]	93 (86)[c]	0.24 (0.35)[c]	70
2	10 (24h)[c]	93 (72)[c]	0.24 (0.35)[c]	75
3	20 (24h)[c]	92 (46)[c]	0.18 (0.47)[c]	60
4	30	90	< 0.1	51

[a] Isolated yield.

[b] determined by ICP-OES of the crude product.

[c] Data within parentheses are the results obtained from Polymer-supported reaction condition[26]: Cy_2NMe, TBAB, DMF at 120 °C.

[d] Recovered via F-SPE.

Solvent was also varied and the experimental data obtained (Table 3-15, entries 2 and 6−9) indicated that the reaction proceeded most efficiently in DMF, which is the commonly used solvent in Heck reaction. Using the optimized reaction conditions, we extended the Heck reaction to both activated and deactivated aryl halides, which gave good to excellent yields of the desired product (Table 3-16). Comparison of palladacycle **3-1** with its polymer-supported and solution-phase analogues also showed that the Heck reaction with palladacycle **3-1** gave a higher yield of the product (Table 3-16, entries 3−6). Palladacycle catalyst **3-1** can also

be applied to low reactivity arylchloride to give a comparable yield and time like arylbromide (Table 3-16, entries 3 and 4), as arylchloride are known to have slow oxidative addition (rate determining step) onto the Pd(0), resulting in a slower rate.

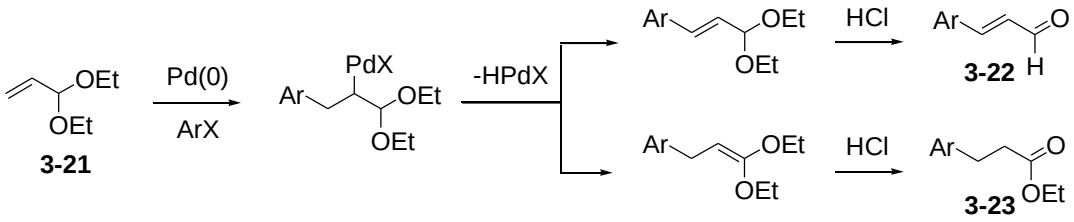
Recycling experiments for the Heck reaction were performed using iodobenzene, N-vinylphthalimide under the optimized reaction conditions. From the results obtained (Table 3-17), the reaction gave **3-20e** in good yields: 93% in 3 min in the first run to 90% in 30 min in the fourth run. These values are higher than those obtained via polymer-supported palladacycle[27] and with palladacycle **3-1**, no drastic decrease in the product yield was observed.

Pd leaching was observed in the crude product but the amount of Pd leached was lower than that from the polymer-supported palladacycle[27] (Table 3-17, entries 1−3). The increase in reaction time and lower amount of palladacycle **3-1** recovered could be due to the formation of the palladium black in the reaction at elevated temperature.

Encouraged by the results obtained from the Heck reaction between N-vinylphthalimide and the aryl halides, we proceeded to explore other coupling partners for this reaction. Previous works by Cacchi and co-workers[54] have shown that under appropriate reaction conditions and with $Pd(OAc)_2$ as catalyst, cinnamaldehydes **3-22** (Cacchi condition) and ethyl 3-arylpropionates **3-23** (Heck

condition) could be prepared from acrolein diethyl acetal **3-21** using the Heck reaction (Scheme 3-2).

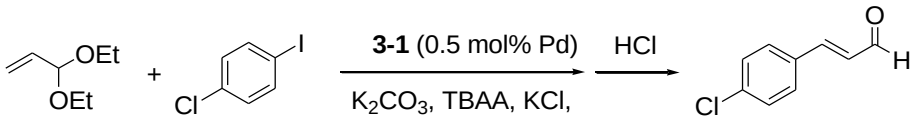
Scheme 3-2. Synthesis of cinnamaldehydes and ethyl 3-arylpropionates using the Heck reaction



In our study, we initially carried out the reaction with **3-21** and 4-chloroiodobenzene employing the Cacchi condition (K_2CO_3 as base, tetra-n-butylammonium acetate (TBAA) and KCl as additives at 120 °C) with palladacycle **3-1** (0.5 mol% of Pd) as pre-catalyst. By varying the solvent, we found that the best yield for cinnamaldehyde **3-22a** was obtained when DMAc was used as the solvent (Table 3-18, entries 2, 5, and 7). Performing the reaction under microwave irradiation although gave **3-22a** in a similar yield, but the reaction time was very much shorter and selectivity was high (**3-22a**: **3-23a** = 97:3). Application of these reaction conditions to other aryl halides also proceeded well providing cinnamaldehyde **3-22** in good yields and high selectivity (Table 3-19, entries 1 and 2). For the synthesis of ethyl 3-arylpropionates **3-23**, total switch in selectivity was observed by changing the base from K_2CO_3 to Cy_2NMe and using DMAc/H_2O as solvent. This could be attributed to the similarity in shape of Cy_2NMe and triphenylphosphine which

leads to the ease of its coordination with [Pd(HX)].[55a] This results in the removal of HX to form the ammonium salt, which hydrolyzes the ketene acetal into an ester.[55b] In addition, ethyl 3-arylpropionates **3-23** were obtained in good yields (Table 3-19, entries 3−6). Depending on the reaction conditions, the selectivity of the reaction toward the aldehyde **3-22** or the ester **3-23** could be easily explained through the formation of different active Pd species. Under the Cacchi condition, the active Pd species formed favours the formation of anionic palladium species $[L_2Pd(0)Cl]^-$ due to the presence of stoichiometric amount of KCl, whereas in the normal Heck reaction, a neutral Pd active species that is coordinated by two ligands or solvent is involved in the initial phase of the catalytic cycle, as reported by Jutand *et. al.*[56] Internal rotation along the ArCH-CH(Pd)CHR bond that is usually reported in the Heck mechanism is prevented due to the additional strong interaction between the Pd(II) centre and the aromatic ring. This factor allows the *syn* β-hydrogen elimination to mainly occur via the proton *gem* to the diacetal thus yielding the ester **3-22**. Such interactions would be restricted where anionic Pd(II) complexes (Cacchi condition) were involved due to the initial formation of the pentacoordinated $[Pd(II)L_2ArXCl]^-$ by the oxidative addition of the aryl halide, as a consequence the formation of the aldehyde would be predominant.

Table 3-18. Optimization of the Heck coupling of **3-21** with 4-chloroiodobenzene



3-21 **3-22a**

Entry	Temp (^{o}C)	Solvent	Time (s)	Yield (%)[a]
1	120	DMAc	15 min[b] (3 h[c])	82[b] (85[c])
2	120	DMAc	60	87
3	150	DMAc	10	41
4	170	DMAc	5	77
5	120	DMF	60	31
6	120	DMAc/H_2O[d]	90	39
7	100	CH_3CN	90	37

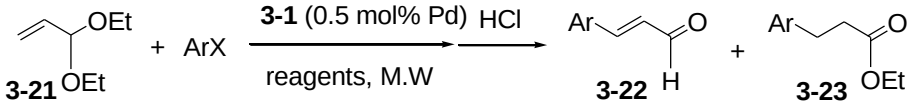
[a] isolated yield.

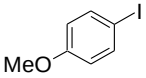
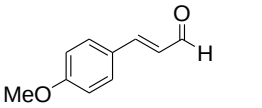
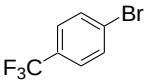
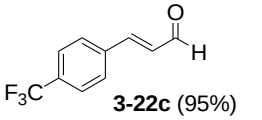
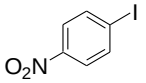
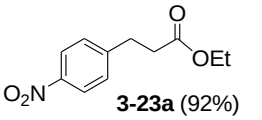
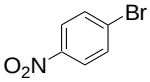
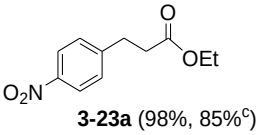
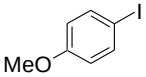
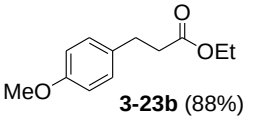
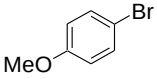
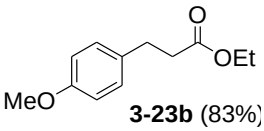
[b] with oil bath heating.

[c] polymer-supported reaction condition: Pd catalyst, K_2CO_3, TBAA, KCl, DMAc, 120 ^{o}C.[57]

[d] DMAc:H_2O = 4:1.

Table 3-19. Chemoselective synthesis of **3-22** and **3-23** using Heck reaction of **3-21** and various aryl halides



Entry	ArX	Time (min)	Reagents[a]	Isomer ratio (**3-22**:**3-23**)	Product (Yield[b])
1		7 (3 h[c])	A	100:0	 **3-22b** (85%, 91%[c])
2		10	A	91:9	 **3-22c** (95%)
3		4	B	0:100	 **3-23a** (92%)
4		15 (3 h[c])	B	0:100	 **3-23a** (98%, 85%[c])
5		8	B	0:100	 **3-23b** (88%)
6		14	B	0:100	 **3-23b** (83%)

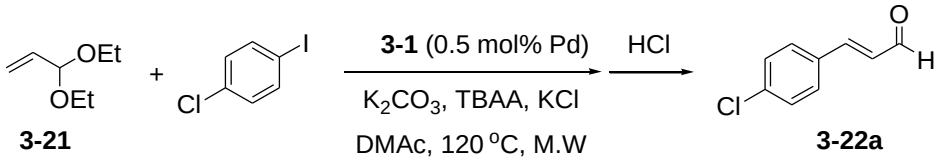
[a] A: **1** (0.5 mol% Pd), K_2CO_3, TBAA, KCl, DMAc; B: **1** (0.5 mol% Pd), Cy_2NMe, TBAB, DMAc/H_2O.

[b] isolated yield.

[c] polymer-supported reaction condition: Pd catalyst, K_2CO_3, TBAA, KCl, DMAc, 120 ^oC.[57]

For studying the recovery and reuse of palladacycle **3-1** in the Heck reaction, the experiments were performed using **3-21** and 4-chloroiodobenzene under the optimized reaction conditions. The palladacycle **3-1** recovered from each run (Table 3-20) was lower than the amount recovered from the Suzuki−Miyaura, Sonogashira, and Stille reactions. We postulate that the agglomeration of Pd particles during the reaction could be due to strong dehalogenation rate of arylhalide (under Cacchi condition). It is nevertheless worth noting that the recovered palladacycle **3-1** showed high activity under the reaction condition and the amount of Pd leached into the solution of crude product is significantly lower than that observed from the polymer-supported palladacycle.[57]

Table 3-20. Recycling of palladacycle **3-1** in the Heck reaction



3-21 **3-22a**

Cycle	Time (min)	Yield (%)[a]	Pd leaching (ppm)[b]	Recovered **3-1** (wt%)[d]
1	1 (2.5 h)	92 (96)[c]	0.067 (0.51)[c]	84
2	3 (3.5 h)	91 (90)[c]	0.076 (0.56)[c]	82
3	6 (5.5 h)	87 (92)[c]	0.048 (0.63)[c]	65
4	10 (9 h)	85 (90)[c]	0.004	63
5	22 (14 h)	82 (84)[c]	0.023	63

[a] isolated yield.

[b] determined by ICP-OES of the crude product.

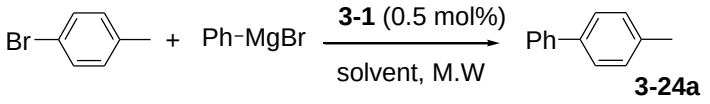
[c]Data within parentheses are the results obtained from polymer-supported reaction condition.[57]

[d] recovered from running through F-SPE

3.8 Kumada Cross-Coupling Reaction

The Kumada cross-coupling reaction is commonly used in the industrial-scale production of styrene derivatives as it provides an economical C−C bond-forming transformation through the direct coupling between Grignard reagents and alkyl, vinyl or aryl halides.

Table 3-21. Optimization of the Kumada cross-coupling reaction



3-24a

Entry	Temp (^{o}C)	Solvent	Time (min)	Yield (%)[a]
1	140	DMAc	1	53
2	140	CH_2Cl_2	1	76
3	140	THF	1	97
4	140	EtOEt	1	62
5	rt[b]	THF	8 h	53
6	reflux[b]	THF	3 h	69
7	100	THF	1 (30 min[c])	96 (93[c])
8	100[d]	THF	1.5	95
9	100[e]	THF	5	40

[a] isolated yield.

[b] experiment was carried out not under M.W. condition

[c] experiment was carried out not under M.W. condition: $Pd(OAc)_2$ (1 mol%), toluene, rt.[58]

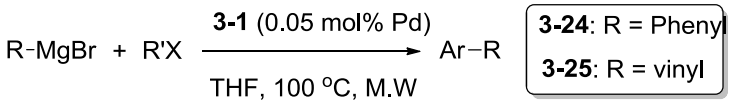
[d] Using palladacycle **3-1** (0.05 mol% Pd).

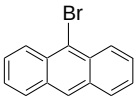
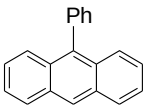
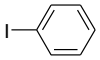
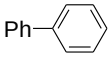
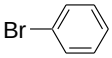
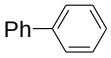
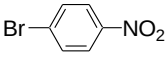
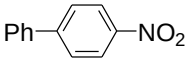
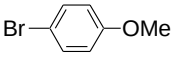
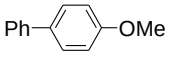
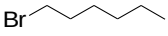
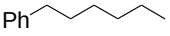
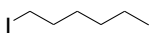
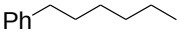
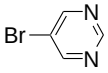
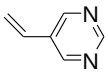
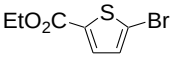
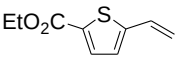
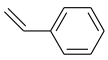
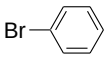
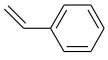
[e] Using palladacycle **3-1** (0.005 mol% Pd).

Herein we report for the first time the use of an oxime-based palladacycle to catalyze the Kumada cross-coupling reaction. Initial studies of the Kumada cross-coupling reaction between phenylmagnesium bromide (1 M) in THF and 4-bromotoluene in DMAc under microwave irradiation at 140 °C afforded 4-methylbiphenyl **3-24a** in only 53% yield. By screening through various solvents (Table 3-21, entries 1−4), we found that THF gave the best result, providing **3-24a** in 97% yield within 1 min. Next we varied the reaction temperature and the experimental data obtained indicated that comparable yield and reaction time could be achieved at 100 °C (Table 3-21, entries 5−7). Finally, we explored the possibility of reducing the pre-catalyst loading to 0.05 mol % Pd. This afforded **3-24a** in 95% yield within a similar reaction time (Table 3-21, entry 8). However, further reduction of the precatalyst loading to 0.005 mol% Pd drastically decreased the product yield (Table 3-21, entry 9). Thus a pre-catalyst loading of 0.05 mol % Pd was used for our subsequent experiments.

With the optimized reaction condition, we extended the reaction to different combinations of Grignard reagents and halides which afforded good yields of the desired product (Table 3-22). Finally to determine the stability of palladacycle **3-1** under the Kumada crosscoupling reaction conditions, we carried out the recycling experiment using bromobenzene and phenylmagnesium bromide for the model study (Table 3-23).

Table 3-22. Kumada cross-coupling reaction using palladacycle **3-1**



Entry	R'X	Time (min)	Product (Yield[a])
1		10	 **3-24b** (90%)
2		0.5 (8 h)[b]	 **3-19q** (98%, 90%[b])
3		2 (20 h)[c]	 **3-19q** (95%, 85%[c])
4		10	 **3-24c** (88%)
5		7	 **3-24d** (76%)
6		12	 **3-24e** (79%)
7		5	 **3-24e** (85%)
8		10	 **3-12b** (88%)
9		6	 **3-12d** (82%)
10		0.75	 **3-25** (86%)
11		1	 **3-25** (86%)

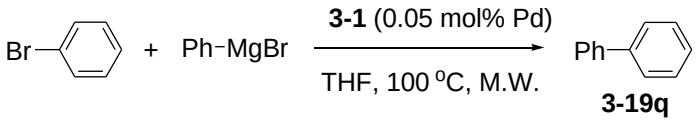
[a] isolated yield.

[b] Using nanosized MCM-41-supported palladium bipyridyl complext (0.05 mol% Pd), THF, 50 °C.[60]

[c] Using silica-supported phosphine Pd(0) complex (1 mol% Pd), THF, 65 °C.[61]

Palladacycle **3-1** could be reused over 4 runs with yields ranging from 91 to 63%. The decreasing yield could be attributed to the very small amounts of Pd black formed during the reaction and the comparatively higher Pd leaching. However this amount of Pd leaching is within the purity required for active pharmaceutical ingredients (2−20 ppm).[59]

Table 3-23. Recycling of palladacycle **3-1** in the Kumada cross-coupling reaction



3-19q

Cycle	Time (min)	Yield (%)[a]	Pd leaching (ppm)[b]	Recovered **1** (wt%)[c]
1	2	91	0.87	90
2	3.5	83	0.88	88
3	4.5	72	0.88	86
4	5	63	0.84	81

[a] isolated yield.

[b] determined by ICP-OES of the crude product.

[c] recovered from running through F-SPE

3.9 Conclusion

In summary, a fluorous oxime-based palladacycle **3-1** was synthesized and we have demonstrated that palladacycle **3-1** is a very versatile and efficient precatalyst which can be used in a wide variety of cross-coupling reactions (Suzuki-Miyaura, Sonogashira, Stille, Heck and Kumada), both in organic and

aqueous media. Palladacycle **3-1** could be used under microwave irradiation at high temperatures which significantly shortened the reaction time The stability of palladacycle **3-1** is also remarkable and it could be reused four to five times without significant loss of activity. The amount of Pd leaching was also very low.

3.10 Experimental Sections

All chemical reagents purchased were used without further purification. Moisture-sensitive reactions were carried out under nitrogen with commercially obtained anhydrous solvents. Analytical thin-layer chromatography (TLC) was carried out on precoated F254 silica plates and visualized with UV light or stained with the Dragendorff−Munier and Hanessian stain. Column chromatography was performed with silica (230−400 mesh). NMR spectra (^{1}H and ^{13}C) were recorded at 298 K. Chemical shifts are expressed in terms of δ (ppm) relative to the internal standard tetramethylsilane (TMS). Mass spectra were performed under EI mode. Microwave reactions were performed on the Biotage InitiatorTM microwave synthesizer in quartz pressure tubes.

3.10.1 Bis(4-(allyloxy)phenyl)-methanone (3-3)

To a solution of 4,4′-dihydroxybenzophenone (5.0 g, 23.3 mmol) in DMF (50 mL) were added KOH (6.5 g, 116.7 mmol) and allyl bromide (5.1 mL, 58.4 mmol). The reaction mixture was stirred at room temperature for 24 h, quenched with H_2O (10 mL), and consecutively washed with EtOAc (100 mL × 3). The organic layers were combined, washed with brine (50 mL × 3), dried over anhydrous

$MgSO_4$, filtered, and concentrated. The desired product **3-3** (6.77 g, 99%) was obtained as a white crystal after purification by column chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, 8H, *J* = 8.9 Hz), 6.96 (d, 8H, *J* = 8.9 Hz), 6.06 (m, 2H), 5.44, (dd, 2H, *J*1 = 17.1 Hz, *J*2 = 1.3 Hz), 5.32 (dd, 2H, *J*1 = 10.7 Hz, *J*2 = 1.3 Hz), 4.61 (d, 4 H, *J* = 5.1 Hz). ^{13}C NMR (125 MHz, CDCl3): δ 194.3, 161.8, 132.6, 132.1, 130.8, 118.1, 114.1, 68.8. HRMS (EI): calcd for $C_{19}H_{18}O_3$ 294.1256, found 294.1259.

3.10.2 Bis(4-(perfluorooctyl-2-iodopropoxy)phenyl)methanone (3-4)

Compound **3-3** (0.59 g, 2.0 mmol) was dissolved in dichloroethane (1.2 mL), and $C_8F_{17}I$ (1.3 mL, 4.8 mmol) and AIBN (65.6 mg, 0.4 mmol) were added. The reaction flask was equipped with a condenser, and the apparatus was purged and filled with Ar, stirred at 85 °C for 18 h, and then concentrated to dryness. The desired product **3-4** (2.06 g, 74%) was obtained as a pale yellow solid after purification by column chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, 8H, *J* = 8.9 Hz), 6.98 (d, 8H, *J* = 8.9 Hz), 4.56 (q, 2H, J = 6.4 Hz), 4.38 (q, 2H, *J* = 5.0 Hz), 4.28 (q, 2H, *J* = 6.4 Hz), 3.23 − 3.12 (m, 2H), 2.91 − 2.79 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.1, 160.8, 132.3, 131.7, 114.3, 72.7, 37.9 (t, *J* = 21.0 Hz), 12.1. ^{19}F NMR (282 MHz, $CDCl_3$): δ −80.71 (t, 6F, *J* = 10.3 Hz), −113.16 to −113.59 (m, 4F), −121.49 to −121.83 (d, 12F), −122.63 (s, 4F), −123.39 (s, 4F), −126.04 (s, 4F). HRMS (ESI): calcd for $C_{35}H_{18}O_3F_{34}I_2Na$ (M + Na) 1408.8692, found 1408.8695.

3.10.3 Bis(4-(perfluorooctylpropoxy)phenyl)methanone (3-5)

Compound **3-4** (20.8 g, 15.0 mmol) was dissolved in dichloroethane (80 mL), and Bu_3SnH (10.5 mL, 39.0 mmol) and AIBN (0.49 mg, 3.0 mmol) were added. The reaction flask was equipped with a condenser, and the apparatus was purged and filled with Ar. The reaction mixture was stirred at 85 °C for 18 h and then concentrated to dryness. The desired product **3-5** (15.19 g, 89%) was obtained as a white solid after purification by column chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, 8H, *J* = 8.8 Hz), 6.96 (d, 8H, *J* = 8.8 Hz), 4.13 (t, 4H, *J* = 6.3 Hz), 2.39 − 2.29 (m, 4H), 2.18 − 2.13 (m, 4H). ^{13}C NMR (125 MHz, 50 °C, $CDCl_3$): δ 194.1, 161.9, 132.2, 131.4, 114.1, 66.7, 28.1 (t, *J* = 21.9 Hz), 20.7. ^{19}F NMR (282 MHz, $CDCl_3$): δ −81.60 (t, 6F, *J* = 10.3 Hz), −114.73 (t, 4F, *J* = 14.4 Hz), −122.22 to −122.43 (d, 12F), −123.25 (s, 4F), −123.98 (s, 4F), −126.71 (s, 4F). HRMS (ESI): calcd for $C_{35}H_{20}O_3F_{34}Na$ (M + Na) 1157.0763, found 1157.0762.

3.10.4 Bis(4-(perfluorooctylpropoxy)phenyl)methanone Oxime (3-6)

To a solution of compound **3-5** (1.26 g, 1.11 mmol) and triethylamine (1.7 mL, 12.5 mmol) in anhydrous EtOH (10.0 mL) and benzene (15.0 mL) was added hydroxylamine hydrochloride (575 mg, 8.28 mmol). The mixture was refluxed with a Dean−Stark apparatus for 16 h and then concentrated to dryness. Citric acid (5%) was added, and the resulting mixture was extracted with EtOAc. The organic phase was washed consecutively with 5% citric acid, 5% $NaHCO_3$, H_2O, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The desired

product **3-6** (1.11 g, 87%) was obtained as a white solid after purification by column chromatography. ^{1}H NMR (500 MHz, acetone-d_6): δ 10.09 (s, 1H), 7.39 (d, 2H, *J* = 8.8 Hz), 7.33 (d, 2H, *J* = 8.8 Hz), 7.04 (d, 4H, *J* = 8.8 Hz), 6.93 (d, 4H, *J* = 8.8 Hz), 4.22 (t, 2H, *J* = 6.3 Hz), 4.17 (t, 2H, *J* = 5.7 Hz), 2.57 − 2.42 (m, 4H), 2.19 − 2.11 (m, 4H). ^{13}C NMR (125 MHz, acetone-d_6): δ 160.3, 159.7, 155.2, 132.8, 131.8, 131.3, 129.8, 127.1, 115.0, 114.7, 67.1, 67.1, 66.5, 28.5− 28.1 (m), 21.3. ^{19}F NMR (282 MHz, $CDCl_3$): δ −80.72 (t, 6F, J = 10.3 Hz), −114.4 to −114.32 (d, 4F), −121.67 to −121.87 (d, 12F), −122.66 (s, 4F), −123.36 (s, 4F), −126.05 (s, 4F). HRMS (ESI): calcd for $C_{35}H_{22}O_3F_{34}N$ (M + H) 1150.1055; found 1150.1051.

3.10.5 Palladacycle (3-1)

To a suspension of oxime **3-6** (2.3 g, 2.0 mmol) in acetone (26 mL) were added anhydrous sodium acetate (0.165 g, 2.0 mmol) and Li_2PdCl_4 (0.524 g, 2.0 mmol). The mixture was stirred under reflux for 1 day, after which water (10 mL) was added and the precipitate which formed was filtered off and dried under reduced pressure over P_2O_5 to give the desired product **3-1** (2.33 g, 90%) as a brown solid. ^{1}H NMR (500 MHz, acetone-d_6): δ 10.9 (s, 1H), 7.49 (d, 1H, *J* = 2.5 Hz), 7.42 (d, 4H, *J* = 8.85 Hz), 7.12 (d, 4H, *J* = 8.85 Hz), 6.59 (d, 1H, *J* = 8.15 Hz), 6.49, 6.48 (dd, 1H, *J*1 = 8.2 Hz, *J*2 = 2.5 Hz), 4.27 (t, 2H, *J* = 6.3 Hz), 4.09 (t, 2H, *J* = 6.3 Hz), 2.57 − 2.41 (m, 4H), 2.19 − 2.07 (m, 4H). ^{13}C NMR (125 MHz, acetone-d_6): δ 163.7, 160.5, 158.0, 155.0, 137.4, 131.4, 128.0, 123.3, 121.8, 119.9, 115.1, 110.0, 67.3, 66.8, 55.4, 31.7, 28.6−28.0 (m), 21.2. ^{19}F NMR (282 MHz, $CDCl_3$): δ

−81.64 (t, 6F, J = 10.3 Hz), −114.72 (t, 4F, J = 12.4 Hz), −122.22 to −122.43 (d, 12F), −123.25 (s, 4F), −123.95 (s, 4F), −126.71 (s, 4F). IR (KBr): v = 3429, 2961, 2762, 1578, 1246, 1206, 1025 cm^{-1}. MALDI HR: calcd for $C_{35}H_{18}O_3F_{34}NPd$ (M−H) 1287.9545, found 1287.9540.

3.10.6 General Procedure for the Suzuki−Miyaura Reaction of Boronic Acids and Various Halides under Microwave Heating.

To a suspension of aryl halide (0.50 mmol), boronic acid/boroxine (0.75 mmol), TBAB (0.161 g, 0.50 mmol), palladacycle **3-1** (0.05 mol% Pd), and water (1.0 mL) in a pressure tube was added a 2 M solution of K_2CO_3 (0.5 mL). The reaction mixture was microwave irradiated (with the heating program starting at 150 W) at 140 °C, and the reaction was monitored by TLC. When the reaction has completed, the reaction mixture was cooled to room temperature, poured into EtOAc (20 mL), and washed successively with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was then purified by column chromatography. On the basis of the ^1H NMR, the purities of compounds were determined to be ≥96%.

4-(Trifluoromethyl)-biphenyl (3-8a)

^1H NMR ($CDCl_3$, 500 MHz): δ 7.71 (s, 4H), 7.62 (d, 1H, *J* = 7.6 Hz), 7.51 - 7.47 (m, 2H), 7.44 - 7.41 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.7, 139.7, 129.3 (q, *J* = 32.3 Hz), 129.0, 128.2, 127.6, 127.4, 127.3, 125.6 (q, J = 3.2 Hz), 124.3 (q, *J* = 272.1 Hz). HRMS (EI) calcd. for $C_{13}H_9F_3$: 222.0656, found: 222.06557.

4-(Methoxy)-biphenyl (3-8b)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.66 - 7.60 (m, 4H), 7.52 - 7.47 (m, 2H), 7.41 - 7.36 (m, 1H), 7.06 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 140.7, 133.7, 128.7, 128.1, 126.7, 126.6, 114.1, 55.2. HRMS (EI) calcd. for $C_{13}H_{12}O$: 184.0888, found: 184.0884.

Diphenylmethane (3-8c)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44 - 7.41 (m, 4H), 7.35 - 7.33 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 141.1, 128.9, 128.4, 126.0, 41.9. HRMS (EI) calcd. for $C_{13}H_{12}$: 168.0939, found: 168.0932.

4-(Nitrile)-biphenyl (3-8d)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.23 - 8.21 (m, 2H), 7.67 - 7.65 (m, 2H), 7.57 - 7.55 (m, 2H), 7.40 - 7.38 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.5, 139.0, 132.5, 129.0, 128.6, 127.6, 127.1, 118.8, 110.8. HRMS (EI) calcd. for $C_{13}H_9N$: 179.0735, found: 179.0731.

10-(3-Ethoxyphenyl)anthracene (3-9a)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.51 (s, 1H), 8.07 (d, 2H, *J* = 8.5 Hz), 7.78 (d, 2H, *J* = 14.1 Hz), 7.55 − 7.47 (m, 3H), 7.42 − 7.37 (m, 2H), 7.13 − 7.05 (m, 3H), 4.10 (q, 2H, *J* = 7.0 Hz), 1.47 (t, 3H, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 140.1, 136.9, 131.3, 130.1, 129.3, 128.3, 126.9, 126.4, 125.3, 125.1, 123.5, 117.1, 113.8, 63.4, 14.8. HRMS (EI): calcd for $C_{22}H_{18}O$ 298.1358, found 298.1357.

3-(3-Ethoxyphenyl)quinoline (3-9b)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.07 (s, 1H), 8.16 (s, 1H), 8.03 (d, 1H, *J* = 8.2 Hz), 7.74 (d, 1H, *J* = 7.9 Hz), 7.63 - 7.57 (m, 1H), 7.47 - 7.42 (m, 1H), 7.32 - 7.28 (m, 1H), 7.17 - 7.12 (m, 1H), 6.86 - 6.83 (m, 1H), 4.00 (q, 2H, J = 7.0 Hz), 1.35 (t, 3H, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.5, 149.8, 147.3, 139.2, 133.6, 133.1, 130.1, 129.3, 129.1, 127.9, 126.9, 119.6, 113.8, 63.5, 14.8. HRMS (EI) calcd. for $C_{17}H_{15}ON$: 249.1154, found: 249.1151.

3-Ethoxy-4′-nitrobiphenyl (3-9c)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.28 (d, 2H, *J* = 8.9 Hz), 7.72 (d, 2H, *J* = 8.8 Hz), 7.41 - 7.38 (m, 1H), 7.20 - 7.14 (m, 2H), 6.97 (d, 1H, *J* = 8.2 Hz), 4.11 (q, 2H, *J* = 7.0 Hz), 1.46 (t, 3H, *J* = 6.9Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.3, 149.1, 146.8, 142.1, 136.3, 133.1, 130.2, 126.3, 119.8, 119.5, 115.4, 114.0, 63.7, 14.7. HRMS (EI) calcd. for $C_{14}H_{13}O_3N$: 243.0895, found: 243.0893.

3-Ethoxy-2′,4′-dinitrobiphenyl (3-9d)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.68 (s, 1H), 8.45 (d, 1H, *J* = 8.5 Hz), 7.68 (d, 1H, *J* = 8.5 Hz), 7.39 - 7.34 (m, 1H), 7.01 - 6.98 (m, 1H), 6.89 - 6.84 (m, 2H), 4.05 (q, 2H, *J* = 7.0 Hz), 1.43 (t, 3H, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.3, 149.1, 146.8, 142.1, 136.3, 133.1, 130.2, 126.3, 119.8, 119.5, 115.4, 114.0, 63.7, 14.7. HRMS (EI) calcd. for $C_{14}H_{12}O_5N_2$: 288.0746, found: 288.0743.

3-Ethoxybiphenyl (3-9e)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.64 (d, 1H, *J* = 8.2 Hz), 7.49 − 7.41 (m, 2H), 7.39 − 7.37 (m, 2H), 7.23 − 7.18 (m, 2H), 6.95 − 6.92 (m, 1H), 4.13 (q, 2H, *J* = 6.9 Hz), 1.49 (t, 3H, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.3, 142.7, 141.1, 129.7, 128.7, 127.3, 127.1, 119.5, 113.5, 113.2, 63.4, 14.9. HRMS (EI): calcd for $C_{14}H_{14}O$ 198.1045, found 198.1046.

Ethyl-5-(Naphthalen-1-yl)thiophene-2-carboxylate (3-10a)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.18 (d, 1H, *J* = 2.6 Hz), 7.92 − 7.87 (m, 3H), 7.59 − 7.49 (m, 4H), 7.24 (d, 1H, *J* = 3.8 Hz), 4.41 (q, 2H, *J* = 7.0 Hz), 1.42 (t, 3H, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.3, 149.0, 133.8, 133.7, 133.4, 131.4, 131.4, 129.3, 128.4, 128.2, 128.0, 126.8, 126.2, 125.3, 125.2, 61.2, 14.4. HRMS (EI): calcd for $C_{17}H_{14}O_2S$ 282.0715, found 282.0714.

1-Benzylnaphthalene (3-10b)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.73 − 7.66 (m, 3H), 7.57 − 7.55 (m, 1H), 7.38 − 7.11 (m, 8H), 4.06 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 141.0, 138.6, 133.6, 132.0, 129.0, 128.5, 128.1, 127.6, 127.6, 127.5, 127.1, 126.1, 126.0, 125.3, 42.1. HRMS (EI): calcd for $C_{17}H_{14}$ 218.1096, found 218.1093.

10-(Naphthalen-1-yl)anthracene (3-10c)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.51 (s, 1H), 8.02 − 7.91 (m, 4H), 7.62 − 7.59 (m, 2H), 7.45 − 7.31 (m, 4H), 6.99 (d, 1H, *J* = 8.9 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz):

δ 136.5, 134.9, 133.7, 133.5, 131.4, 131.0, 129.1, 128.4, 128.2, 128.1, 126.9, 126.9, 126.5, 126.2, 125.9, 125.5, 125.5, 125.2. HRMS (EI): calcd for $C_{24}H$= 304.1252, found 304.1255.

Naphthalen-1-yl(naphthalen-2-yl)methane (3-10d)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.07 (d, 1H, J = 8.2 Hz), 7.90 − 7.72 (m, 5H), 7.63 (s, 1H), 7.51 − 7.35 (m, 4H), 4.62 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.1, 136.5, 133.9, 133.6, 132.1, 132.1, 128.6, 128.0, 127.8, 127.6, 127.5, 127.4, 127.4, 127.2, 127.0, 126.0, 125.9, 125.8, 125.6, 125.5, 125.3, 39.2. HRMS (EI): calcd for $C_{21}H_{16}$ 268.1252, found 268.1255.

3-Methyl-6-(naphthalen-1-ylmethyl)pyridin-2-amine (3-10e)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.15 − 8.13 (m, 1H), 7.91 − 7.87 (m, 2H), 7.57 − 7.47 (m, 4H), 5.59 (s, 2H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.2, 167.5, 163.0, 136.7, 133.8, 130.5, 129.5, 128.3, 126.8, 126.5, 126.0, 125.4, 125.1, 111.8, 24.0. HRMS (EI): calcd for $C_{17}H_{16}N_2$ 248.1313, found 248.1312.

3-Nitro-5-vinylpyridin-2-amine (3-12a)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.44 (s, 1H), 8.41 (s, 1H), 6.61 (dd, 1H, *J* = 17.7 Hz and 11.4 Hz), 5.71 (d, 1H, *J* = 17.7 Hz), 5.29 (d, 1H, *J* = 11.4 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.9, 152.6, 131.4, 131.3, 128.0, 124.4, 114.6. HRMS (EI): calcd for $C_7H_7O_2N_3$ 165.0538, found 165.0534.

5-Vinylpyrimidine (3-12b)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.10 (s, 1H), 8.76 (s, 1H), 6.66 (dd, 1H, *J* = 17.7 Hz and 11.4 Hz), 5.93 (d, 1H, *J* = 17.7 Hz), 5.51 (d, 1H, *J* = 11.4 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.6, 154.2, 130.9, 130.1, 118.6. HRMS (EI): calcd for $C_6H_6N_2$ 106.0531, found 106.0536.

1-Nitro-3-vinylbenzene (3-12c)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (s, 1H), 8.12 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 6.79 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.92 (d, *J* = 17.6 Hz, 1H), 5.47 (d, *J* = 10.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.61, 139.27, 134.74, 132.02, 129.41, 122.38, 120.85, 117.04. HRMS (EI): calcd for $C_8H_7NO_2$ 149.0477, found 149.0475.

Ethyl-5-vinylthiophene-2-carboxylate (3-12d)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.64 (d, 1H, *J* = 3.8 Hz), 6.95 (d, 1H, *J* = 3.8 Hz), 6.77 (dd, 1H, *J* = 17 Hz and 10.7 Hz), 5.71 (d, 1H, *J* = 17 Hz), 5.29 (d, 1H, *J* = 10.7 Hz), 4.34 (q, 2H, *J* = 7.0 Hz), 1.47 (t, 3H, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.2, 149.3, 133.6, 132.1, 129.5, 116.3, 61.1, 14.3. HRMS (EI): calcd for $C_9H_{10}O_2S$ 182.0402, found 182.0407.

9-Methylanthracene (3-13a)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.36 − 8.31 (m, 3H), 8.04 − 8.02 (m, 2H), 7.56 − 7.49 (m, 4H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.5, 130.1, 129.0,

128.1, 125.3, 125.2, 124.8, 124.6, 13.9. HRMS (EI): calcd for $C_{15}H_{12}$ 192.0939, found 192.0942.

5-Methylfuran-2-carbaldehyde (3-13b)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.40 (s, 1H), 7.08 (d, 1H, *J* = 3.8 Hz), 6.15 (d, 1H, *J* = 4.5 Hz), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.6, 159.5, 151.7, 123.5, 109.3, 13.7. HRMS (EI): calcd for $C_6H_6O_2$ 110.0368, found 110.0367.

2-Methyl-1H-imidazole (3-13c)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 12.44 (s, 1H), 6.97 (s, 2H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.6, 121.2, 13.7. HRMS (EI): calcd for $C_4H_6N_2$ 82.0531, found 82.0532.

4,6-Dimethylpyrimidin-2-amine (3-13d)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.27 (s, 1H), 5.68 (s, 2H), 2.20 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.5, 163.0, 110.1, 23.4. HRMS (EI): calcd for $C_6H_9N_3$ 123.0796, found 123.0797.

1-(4-Butylphenyl)ethanone (3-14a)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.80 (d, 2H, *J* = 8.2 Hz), 7.19 (d, 2H, *J* = 8.2 Hz), 2.60 (t, 2H, *J* = 7.6 Hz), 2.51 (s, 3H), 1.58 − 1.52 (m, 2H), 1.33 − 1.27 (m, 2H), 0.86 (t, 3H, *J* = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 197.8, 148.8, 134.9,

128.6, 128.4,35.7, 33.2, 26.5, 22.3, 13.9. HRMS (EI): calcd for $C_{12}H_{16}O$ 176.1201, found 176.1203.

10-Butylanthracene (3-14b)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.36 − 8.31 (m, 3H), 8.03 − 8.02 (m, 2H), 7.54 − 7.46 (m, 4H), 3.64 (t, 2H, *J* = 8.2 Hz), 1.88 − 1.82 (m, 2H), 1.68 − 1.60 (m, 2H), 1.07 (t, 3H, *J* = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 135.4, 131.6, 129.5, 129.2, 128.6, 128.1, 125.3, 124.5, 33.5, 27.8, 23.4, 14.1. HRMS (EI): calcd for $C_{18}H_{18}$ 234.1409, found 234.1410.

3.10.7 General Procedure for the Sonogashira Cross-Coupling Reactions Between Terminal Alkynes with Various Aryl Halides under Microwave Heating.

To a suspension of aryl halide (0.50 mmol), phenylacetylene (0.75 mmol), pyrrolidine (0.161 g, 0.25 mmol), and palladacycle **3-1** (0.05 mol% Pd) in a pressure tube was added 1 mL of degassed water. The reaction mixture was microwave irradiated (with the heating program starting at 150 W) at 140°C, and the reaction was monitored by TLC. When the reaction was complete, the reaction mixture was cooled to room temperature, poured into ether (20 mL), and washed successively with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was then purified by column chromatography. On the basis of the ^{1}H NMR, the purities of compounds were determined to be ≥96%.

3-(2-(4-Chlorophenyl)ethynyl)thiophene (3-16a)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 − 7.50 (m, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.34 − 7.24 (m, 3H), 7.19 (d, *J* = 5.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 134.2, 132.7, 130.5, 129.8, 128.9, 128.7, 125.5, 122.0, 87.8, 85.4. HRMS (EI): calcd for $C_{12}H_7ClS$ 217.9957, found 217.9955.

3-(2-(Thiophene-3-yl)ethynyl)quinoline (3-16b)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.99 (d, *J* = 2.0 Hz, 1H), 8.28 (d, *J* = 1.8 Hz, 1H), 8.10 (d, *J* = 8.3 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.73 − 7.68 (m, 1H), 7.63−7.53 (m, 2H), 7.35 − 7.33 (m, 1H), 7.28 − 7.23 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 152.0, 146.8, 138.1, 130.0, 129.8, 129.4, 129.4, 127.6, 127.3, 125.6, 121.7, 117.4, 88.9, 87.8, 86.2. HRMS (EI): calcd for $C_{15}H_9SN$ 235.0456, found 235.0455.

3-(2-(4-Nitrophenyl)ethynyl)thiophene (3-16c)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.8 Hz, 2H), 7.67 − 7.59 (m, 3H), 7.34 (dd, *J* = 5.0, 2.8 Hz, 1H), 7.22 (d, *J* = 5.1 Hz, 1H), 1.55 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 147.0, 132.1, 130.3, 130.1, 129.7, 125.8, 123.6, 121.2, 89.9, 87.2. HRMS (EI): calcd for $C_{12}H_7SNO_2$ 229.0197, found 229.0197.

2-(2-(4-tert-Butylphenyl)ethynyl)pyridine (3-16d)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.60 (d, *J* = 5.1, 1H), 7.67 − 7.50 (m, 3H), 7.39 − 7.37 (m, 2H), 7.22 - 7.19 (m, 1H), 1.32 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ

152.3, 150.0, 143.7, 136.0, 131.8, 127.0, 125.4, 122.5, 119.2, 89.5, 88.1, 34.8, 31.1. HRMS (EI): calcd for $C_{17}H_{17}N$ 235.1361, found 235.1361.

2-Methoxy-6-(2-(4-(trifluoromethyl)phenyl)ethynyl)naphthalene (3-16e)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.74 − 7.55 (m, 7H), 7.19 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.6, 134.4, 131.7, 131.7, 129.9, 129.6, 129.4, 128.8, 128.5, 127.4, 126.9, 125.3, 125.3, 125.2, 125.2, 125.1, 122.9, 119.6, 117.4, 105.9, 92.5, 87.7, 55.3. HRMS (EI): calcd for $C_{20}H_{13}F_3O$ 326.0918, found 326.0914.

2-Methoxy-6-(2-(4-methoxyphenyl)ethynyl)naphthalene (3-16f)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.70 (t, *J* = 8.9 Hz, 2H), 7.52 (ddd, *J* = 8.8, 7.6, 1.7 Hz, 3H), 7.16 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 3.93 (s, 3H), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.5, 158.2, 134.0, 133.0, 130.9, 129.3, 129.0, 128.6, 126.8, 119.3, 118.5, 115.6, 114.0, 105.9, 89.0, 88.6, 55.3, 55.3. HRMS (EI): calcd for $C_{20}H_{16}O_2$ 288.1150, found 288.1151.

5-(2-(6-Methoxynaphthalen-2-yl)ethynyl)pyrimidine (3-16g)

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.14 (s, 1H), 8.87 (s, 1H), 8.00 (s, 1H), 7.72 (dd, *J* = 8.7, 2.3 Hz, 2H), 7.53 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.18 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.12 (d, *J* = 2.1 Hz, 1H), 3.92 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.8,

158.5, 156.5, 134.7, 131.9, 129.5, 128.6, 128.3, 127.0, 120.1, 119.7, 116.5, 105.9, 97.1, 55.3. HRMS (EI): calcd for $C_{17}H_{12}N_2O$ 260.0950, found 260.0950.

2-(2-(4-tert-Butylphenyl)ethynyl)-6-methoxynaphthalene (3-16h)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.71 (t, *J* = 9.2 Hz, 2H), 7.59 − 7.46 (m, 3H), 7.44 − 7.37 (m, 2H), 7.17 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.12 (d, *J* = 2.3 Hz, 1H), 3.93 (s, 3H), 1.35 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.2, 151.4, 134.0, 131.3, 131.1, 129.3, 129.1, 128.5, 126.8, 125.3, 120.4, 119.3, 118.4, 89.3, 89.2, 55.3, 34.8, 31.2. HRMS (EI): calcd for $C_{23}H_{22}O$: 314.1671, found 314.1670.

2-Methoxy-6-(2-(4-nitrophenyl)ethynyl)naphthalene (3-16i)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.7 Hz, 2H), 8.00 (s, 1H), 7.72 (dd, *J* = 8.7, 4.1 Hz, 2H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.54 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.19 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.12 (d, *J* = 2.3 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.7, 146.7, 134.6, 132.1, 132.0, 130.4, 129.4, 128.7, 128.3, 127.0, 123.6, 119.7, 116.8, 105.9, 95.6, 87.3, 55.3. HRMS (EI): calcd for $C_{19}H_{13}NO_3$ 303.0895, found 303.0890.

Ethyl 5-(2-(6-Methoxynaphthalen-2-yl)ethynyl)thiophene-2-carboxylate (3-16j)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.70 (dd, *J* = 10.6, 6.0 Hz, 3H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 3.8 Hz, 1H), 7.17 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.11 (d, *J* = 1.7 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.92 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 161.6, 158.6, 134.5, 134.1, 133.1, 131.9, 131.6, 130.1, 129.4, 128.5, 128.4, 127.0, 119.6, 117.0, 105.9, 96.3, 81.8, 61.3, 55.3, 14.3. HRMS (EI): calcd for $C_{20}H_{16}O_3S$ 336.0820, found 336.0818.

1-Nitro-4-(2-phenylethynyl)benzene (3-16k)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H), 7.64−7.53 (m, 2H), 7.52− 7.35 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.9, 132.2, 131.8, 130.2, 129.2, 128.5, 123.6, 122.0, 94.7, 87.5. HRMS (EI): calcd for $C_{14}H_9NO_2$ 223.0633, found 223.0630.

1,2-Diphenylethyne (3-16l)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.57 - 7.56 (m, 2H), 7.45 - 7.32 (m, 8H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.6, 128.5, 128.4, 121.9, 96.9, 88.6. HRMS (EI) calcd. for $C_{14}H_{10}$: 178.0783, found: 178.0781.

1-Chloro-4-(2-phenylethynyl)benzene (3-16m)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.51 - 7.55 (m, 2H), 7.46 (d, 2H, *J* = 1.9 Hz), 7.38 - 7.32 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 134.2, 132.8, 131.6, 128.7, 128.5, 128.4, 122.9, 121.8, 90.3, 88.2. HRMS (EI) calcd. for $C_{14}H_9Cl$: 212.0393, found: 212.0392.

3.10.8 General Procedure for Glaser-Type Oxidative Homocoupling under Microwave Heating.

To a suspension of the respective terminal alkyne (0.25 mmol), pyrrolidine (0.041 mL, 0.5 mmol), palladacycle **3-1** (0.05 mol% Pd), and CuI (5 mol %) in a pressure tube was added water (1 mL). The reaction mixture was microwave irradiated (with the heating program starting at 150 W) at 140 °C, and the reaction was monitored by TLC. When the reaction has completed, the reaction mixture was cooled to room temperature, poured into ether (20 mL), and washed successively with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was then purified by column chromatography. On the basis of the ^{1}H NMR, the purities of compounds were determined to be ≥96%.

1,4-Bis(6-methoxynaphthalen-2-yl)buta-1,3-diyne (3-17a)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (s, 2H), 7.70 (dd, *J* = 12.5, 8.7 Hz, 4H), 7.52 (dd, *J* = 8.5, 1.4 Hz, 2H), 7.18 − 7.11 (m, 4H), 3.94 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.8, 134.6, 132.8, 129.4, 129.2, 128.4, 127.0, 119.6, 119.1, 105.9, 82.2, 73.9, 55.4. HRMS (EI): calcd for $C_{26}H_{18}O_2$ 362.1307, found 362.1307.

3-(4-(Thiophene-3-yl)buta-1,3-diynyl)thiophene (3-17b)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 − 7.57 (m, 2H), 7.28 (dd, *J* = 5.0, 2.9 Hz, 2H), 7.17 (dd, *J* = 5.0, 1.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.2, 130.2,

125.6, 120.9, 76.5, 73.5. HRMS (EI): calcd for $C_{12}H_6S_2$ 213.9911, found 213.9908.

1,4-Diphenylbuta-1,3-diyne (3-17c)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 − 7.50 (m, 4H), 7.41 − 7.31 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 132.5, 129.2, 128.4, 121.8, 81.5, 73.9, 31.1. HRMS (EI): calcd for $C_{16}H_{10}$ 202.0783, found 202.0779.

1,4-Bis(4-tert-butylphenyl)buta-1,3-diyne (3-17d)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.3 Hz, 4H), 7.36 (d, *J* = 8.5 Hz, 4H), 1.33 (s, 18H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.1, 131.9, 125.3, 119.1, 83.8, 76.4, 34.8, 31.1. HRMS (EI): calcd for $C_{24}H_{26}$ 314.2035, found 314.2033.

3.10.9 General Procedure for the Stille Cross-Coupling Reaction between Organostannanes with Aryl Halides under Microwave Heating.

To a suspension of aryl halide (0.50 mmol), boronic acid (0.75 mmol), TBAB (0.161 g, 0.25 mmol), and palladacycle **3-1** (0.005 mol % Pd) in a pressure tube was added 1 mL of degassed water. The reaction mixture was microwave irradiated (with the heating program starting at 150 W) at 100 °C, and the reaction was monitored by TLC. When the reaction has completed, the reaction mixture was cooled to room temperature, poured into ether (20 mL), and washed successively with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was then purified by

column chromatography. On the basis of the ^{1}H NMR, the purities of compounds were determined to be ≥96%.

3-Ethoxybiphenyl (3-19a)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 8.0 Hz, 2H), 7.27 − 7.19 (m, 2H), 6.96 (dd, *J* = 8.2, 2.4 Hz, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 1.52 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 142.7, 141.1, 129.7, 128.7, 127.3, 127.1, 119.5, 113.5, 113.2, 63.4, 14.9. HRMS (EI): calcd for $C_{14}H_{14}O$ 198.1045, found 198.1041.

4-Fluorobiphenyl (3-19b)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 − 7.52 (m, 3H), 7.52 − 7.41 (m, 13H), 7.39 − 7.29 (m, 2H), 7.17 − 7.10 (m, 2H). ^{13}C NMR (125MHz, $CDCl_3$): δ 136.5, 128.8, 128.7, 128.6, 128.2, 127.9, 127.2, 127.0, 115.7, 115.5. HRMS (EI): calcd for $C_{12}H_9F$ 172.0688, found 172.0687.

4-Chlorobiphenyl (3-19c)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 − 7.46, (m, 3H), 7.44 − 7.42 (m, 4H), 7.39 − 7.33 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.5, 132.7, 128.9, 128.9, 128.4, 127.9, 127.6, 127.0. HRMS (EI): calcd for $C_{12}H_9Cl$ 188.0393, found 188.0390.

4-tert-Butylbiphenyl (3-19d)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 − 7.59 (m, 2H), 7.56 − 7.54 (m, 2H), 7.49 − 7.42 (m, 4H), 7.34 − 7.33 (m, 1H), 1.41 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.2, 141.0, 138.3, 136.8, 128.7, 127.0, 127.0, 126.8, 125.7, 31.3, 15.3. HRMS (EI): calcd for $C_{16}H_{18}$: 210.1409, found 210.1409.

4-(1-Methyl-1H-indol-2-yl)benzonitrile (3-19e)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.8 Hz, 1H), 7.36 − 7.28 (m, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 6.67 (s, 1H), 3.78 (s, 3H).). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.2, 139.0, 137.2, 132.3, 129.4, 127.6, 122.7, 120.9, 120.3, 118.7, 111.1, 109.8, 103.5, 31.4. HRMS (EI): calcd for $C_{16}H_{12}N_2$ 232.1000, found 232.1007.

2-(4-tert-Butylphenyl)-1-methyl-1H-indole (3-19f)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.64 (d, *J* = 7.6 Hz, 1H), 7.51 − 7.45 (m, 4H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.25 − 7.23 (m, 1H), 7.15 − 7.13 (m, 1H), 6.55 (s, 1H), 3.79 (s, 3H), 1.39 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.9, 141.6, 138.3, 129.9, 129.0, 128.0, 125.4, 121.5, 120.3, 119.7, 109.5, 101.3, 34.7, 31.3, 31.2. HRMS (EI): calcd for $C_{19}H_{21}N$ 263.1674, found 263.1677.

1-Methyl-2-(thiophene-2-yl)-1H-indole (3-19g)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.5 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.31(d, *J* = 8.3 Hz, 1H), 7.23 − 7.20 (m, 2H), 7.12 − 7.06 (m, 2H), 6.64 (s, 1H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.3, 134.1, 133.9, 127.6, 127.6,

126.7, 126.1, 122.0, 120.5, 120.0, 109.5, 102.7, 31.0. HRMS (EI): calcd for $C_{13}H_{11}NS$ 213.1612, found 213.1619.

3-Methyl-5-(1-methyl-1H-indol-2-yl)pyridin-2-amine (3-19h)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.43 (s, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.26 − 7.22 (m, 1H), 7.22 − 7.12 (m, 1H), 6.50 (s, 1H), 4.60 (br s, 2H), 3.72 (s, 3H), 2.21 (s, 3H) . ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.7, 145.9, 138.8, 138.6, 138.1, 127.9, 121.5, 120.2, 120.0, 119.6, 116.2, 109.5, 101.1, 30.9, 17.1. HRMS (EI): calcd for $C_{15}H_{15}N_3$ 237.1266, found 237.1265.

1-Methyl-2-(3-nitrophenyl)-1H-indole (3-19i)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (t, *J* = 1.8 Hz, 1H), 8.31 − 8.25 (m, 1H), 7.89 − 7.87 (m, 1H), 7.73 − 7.65 (m, 2H), 7.46 − 7.20 (m, 3H), 6.72 (s, 1H), 3.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.3, 138.7, 138.6, 134.9, 134.5, 129.5, 127.6, 123.7, 122.6, 122.4, 120.9, 120.3, 109.8, 103.2, 31.3. HRMS (EI): calcd for $C_{15}H_{12}N_2O_2$ 252.0899, found 252.0895.

Ethyl 5-(2-Phenylethynyl)thiophene-2-carboxylate (3-19j)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 4.0 Hz, 1H), 7.56 − 7.50 (m, 2H), 7.47 − 7.32 (m, 3H), 7.21 (d, *J* = 3.9 Hz, 1H), 4.35 (q, *J* = 7.0 Hz, 2H), 1.38 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.5, 134.3, 133.4, 133.0, 131.5, 130.8, 129.0, 128.4, 122.2, 95.5, 82.0, 61.4, 14.3. HRMS (EI): calcd for $C_{15}H_{12}SO_2$ 256.0558, found 256.0555.

1-Methoxy-4-(2-phenylethynyl)benzene (3-19k)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 − 7.49 (m, 2H), 7.47 (d, *J* = 8.8 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.6, 131.4, 128.3, 127.9, 123.6, 115.4, 114.0, 55.3. HRMS (EI): calcd for $C_{15}H_{12}O$ 208.0888, found 208.0887.

4-(2-Phenylethynyl)benzonitrile (3-19l)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 − 7.58 (m, 4H), 7.56 − 7.54 (m, 2H), 7.40 − 7.38 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 132.0, 132.0, 131.8, 129.1, 128.5, 128.2, 122.2, 118.5, 111.4, 93.8, 87.7. HRMS (EI): calcd for $C_{15}H_9N$ 203.0735, found 203.0733.

4'-Methoxybiphenyl-2-carbaldehyde (3-19m)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.99 (s, 1H), 8.01 - 7.99 (m, 1H), 7.63 - 7.60 (m, 1H), 7.47 - 7.42 (m, 2H), 7.32 - 7.29 (m, 2H), 7.02 - 6.99 (m, 2H), 3.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.6, 159.6, 145.6, 133.7, 133.5, 131.2, 130.7, 129.9, 127.5, 127.3, 113.9, 55.3. HRMS (EI) calcd. for $C_{14}H_{12}O_2$: 212.0837, found: 212.0838.

5-(4-Methoxyphenyl)pyrimidine (3-19n)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.14 (s, 1H), 8.90 (s, 2H), 7.51 (d, 2H, *J* = 8.9 Hz), 7.03 (d, 2H, *J* = 8.9 Hz), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.4,

156.8, 154.4, 133.9, 128.1, 126.5, 114.9, 55.4. HRMS (EI) calcd. for $C_{11}H_{10}ON_2$: 186.0793, found: 186.0794.

4'-Methoxybiphenyl (3-19o)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.57 - 7.53 (m, 4H), 7.44 - 7.41 (m, 2H), 7.33 - 7.30 (m, 1H), 7.00 - 6.98 (m, 2H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.1, 140.8, 133.7, 128.7, 128.1, 126.7, 126.6, 114.2, 55.3. HRMS (EI) calcd. for $C_{13}H_{12}O$: 184.0888 found: 184.0887.

Biphenyl (3-19p)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 − 7.63 (m, 4H), 7.49 − 7.46 (m, 4H), 7.40 − 7.37 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.2, 128.7, 127.2, 127.1. HRMS (EI): calcd for $C_{12}H_{10}$ 154.0783, found 154.0785.

3.10.10 General Procedure for the Synthesis of (E)-N-Styrylphthalimides (3-20) via the Heck Reaction and under Microwave Heating.

A mixture of the respective aryl halide (0.51 mmol), N-vinylphthalimide (87.0 mg, 0.50 mmol), Cy_2NMe (0.16 mL, 0.75 mmol), TBAB (161 mg, 0.50 mmol), and the palladacycle **3-1** (0.5 mol% Pd) in DMF (0.75 mL) was placed in a pressure tube. The reaction mixture was microwave irradiated (with the heating program starting at 150 W) at 170 °C, and the reaction was monitored by TLC. When the reaction was complete, the mixture was cooled to room temperature and concentrated to dryness. The crude product was separated from the palladacycle

3-1 using F-SPE,[8] and the desired E-product **3-20** was purified by column chromatography. On the basis of the ^{1}H NMR, the purities of compounds were determined to be ≥96%.

(E)-2-(4-Methoxystyryl)isoindoline-1,3-dione (3-20a)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 − 7.88 (m, 2 H), 7.76 − 7.73 (m, 2 H), 7.60 (d, 1H, *J* = 15.1 Hz), 7.41 (d, *J* = 8.7 Hz, 1H), 7.23 (d, *J* = 15.1 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 1H), 3.83 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 159.3, 134.4, 131.7, 128.5, 127.4, 123.6, 120.1, 115.9, 114.2, 55.3. HRMS (EI): calcd for $C_{17}H_{13}O_3N$ 279.0895, found 279.0896.

(E)-2-(4-Methylstyryl)isoindoline-1,3-dione (3-20b)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 − 7.88 (m, 2 H), 7.77 − 7.74 (m, 2 H), 7.62 (d, *J* = 15.1 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 2 H), 7.32 (d, *J* = 15.1 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2 H), 2.36 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 137.5, 134.5, 133.0, 131.7, 129.4, 126.1, 123.6, 120.3, 116.8, 21.2. HRMS (EI): calcd for $C_{17}H_{13}O_2N$ 263.0946, found 263.0949.

(E)-2-[4-(Trifluoromethyl)styryl]isoindoline-1,3-dione (3-20c)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 − 7.90 (m, 2 H), 7.79 − 7.77 (m, 2 H), 7.68 (d, *J* = 15.15 Hz, 1H), 7.59 (d, 2H, *J* = 8.85 Hz), 7.55 (d, 2H, *J* = 8.85 Hz), 7.43 (d, *J* = 15.15 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 139.7, 134.7, 131.6,

129.5, 126.3, 125.7 (q, J = 0.91 Hz), 123.8, 119.5, 118.4. HRMS (EI): calcd for $C_{17}H_{10}O_2NF_3$ 317.0664, found 317.0667.

(E)-2-(4-Acetylstyryl)isoindoline-1,3-dione (3-20d)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 − 7.90 (m, 4 H), 7.79 − 7.76 (m, 2 H), 7.69 (d, *J* = 15.1 Hz, 1 H), 7.54 (d, *J* = 8.4 Hz, 2 H), 7.46 (d, 1 H, *J* = 15.1 Hz), 2.60 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.4, 166.2, 140.9, 135.9, 134.7, 131.5, 128.9, 126.1, 123.8, 119.6, 118.6, 26.6. HRMS (EI): calcd for $C_{18}H_{13}O_3N$ 291.0895, found 291.0899.

(E)-2-Styrylisoindoline-1,3-dione (3-20e)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91−7.88 (m, 2 H), 7.77−7.74 (m, 2 H), 7.65 (d, J = 15.1 Hz, 1 H), 7.47 (d, J = 7.38 Hz, 2 H), 7.38 - 7.33 (m, 3 H), 7.28−7.23 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.4, 136.0, 134.5, 131.7, 128.7, 127.6, 126.2, 123.6, 120.3, 117.6. HRMS (EI): calcd for $C_{16}H_{11}O_2N$ 249.0790, found 249.0795.

3.10.11 General Procedure for the Synthesis of Cinnamaldehydes (3-22) under Microwave Heating.

A suspension of the respective aryl halide (0.25 mmol), acrolein diethyl acetal (0.06 mL, 0.38 mmol), K_2CO_3 (51.8 mg, 0.38 mmol), TBAA (151 mg, 0.50 mmol), KCl (18.8 mg, 0.25 mmol), and palladacycle **1** (0.5 mol% Pd) in DMAc (1 mL) was placed in a pressure tube. The reaction mixture was microwave

irradiated (with the heating program starting at 150 W) at 120 °C, and the reaction was monitored by TLC. When the reaction has completed, the reaction mixture was cooled to room temperature, and an aqueous solution of HCl (2 M, 2.5 mL) was added slowly. The mixture was stirred at room temperature for 10 min, poured into EtOAc (5 mL), and then washed successively with HCl (2 M, 5 mL) and H_2O (2 × 5 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was separated from the palladacycle 1 using F-SPE and the desired cinnamaldehyde **3-22** was purified by column chromatography. On the basis of the ^{1}H NMR, the purities of compounds were determined to be ≥96%.

4-Chlorocinnamaldehyde (3-22a)

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.70 (d, *J* = 7.6 Hz, 1 H), 7.50 (d, *J* = 8.8 Hz, 2 H), 7.41 (d, *J* = 8.8 Hz, 2 H), 7.43 (d, *J* = 15.8 Hz, 1 H), 6.69 (dd, *J*1 = 15.8 Hz, *J*2 = 7.6 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.3, 151.0, 137.3, 132.5, 129.6, 129.4, 129.0. HRMS (EI): calcd for C_9H_7OCl 166.0185, found 166.0182.

4-Methoxycinnamaldehyde (3-22b)

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.65 (d, *J* = 7.6 Hz, 1 H), 7.50(d, *J* = 8.8 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 7.42 (d, *J* = 15.8 Hz, 1 H), 6.61 (dd, *J*1 = 15.8Hz, *J*2 = 7.6 Hz, 1 H), 3.86 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6, 152.6, 162.2, 130.3, 126.8, 114.6, 126.6, 55.4. HRMS (EI): calcd for $C_{10}H_{10}O_2$ 162.0681, found 162.0681.

4-(Trifluoromethyl)cinnamaldehyde (3-22c)

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.74 (d, *J* = 7.6 Hz, 1 H), 7.72 − 7.64 (m, 4 H), 7.50 (d, *J* = 15.8 Hz, 1 H), 6.77 (dd, *J*1 = 15.8 Hz, *J*2 = 7.6 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.1, 150.2, 137.3, 132.6 (q, J = 32.1 Hz), 130.5, 126.0 (q, J = 3.7 Hz), 123.7 (q, J = 272.2 Hz), 128.3. HRMS (EI): calcd for $C_{10}H_7OF_3$ 200.0449, found 200.0446.

3.10.12 General Procedure for the Synthesis of Ethyl 3-Arylpropionates (3-23) under Microwave Heating.

A solution of the respective aryl halide (0.25 mmol), acrolein diethyl acetal (0.06 mL, 0.38 mmol), Cy_2NMe (0.08 mL, 0.38 mmol), TBAB (80.5 mg, 0.25 mmol), and palladacycle **3-1** (0.5 mol% Pd) in DMAc (1 mL) and water (0.25 mL) was placed in a pressure tube. The reaction mixture was microwave irradiated (with the heating program starting at 150 W) at 120 °C, and the reaction was monitored by TLC. When the reaction has completed, the reaction mixture was cooled to room temperature, poured into EtOAc (5 mL), and washed successively with HCl (2 M, 2 × 5 mL) and H_2O (5 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was separated from the palladacycle **3-1** using F-SPE, and the desired ethyl 3-arylpropanoate **3-22** was purified by column chromatography. On the basis of the ^{1}H NMR, the purities of compounds were determined to be ≥96%.

Ethyl 3-(4-Nitrophenyl)propanoate (3-23a)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.6 Hz, 2 H), 7.35 (d, *J* = 8.6 Hz, 2 H), 4.10 (q, *J* = 7.1 Hz, 2 H), 3.04 (t, *J* = 7.4 Hz, 2 H), 2.65 (t, *J* = 7.6 Hz, 2 H), 1.21 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 148.3, 146.6, 129.2, 123.6, 60.6, 35.0, 30.6, 14.1. HRMS (EI): calcd for $C_{11}H_{13}O_4N$ 223.0845, found 223.0846.

Ethyl 3-(4-Methoxyphenyl)propanoate (3-23b)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.12 (q, *J* = 7.3 Hz, 2H), 2.91 (t, *J* = 7.7 Hz, 2H), 2.58 (t, *J* = 7.7 Hz, 2H), 1.24 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.1, 158.2, 132.3, 129.3, 113.9, 60.7, 55.2, 36.3, 30.1, 14.1. HRMS (EI): calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1097.

3.10.13 General Procedure for the Kumada Cross-Coupling between Grignard Reagents with Various Halides under Microwave Heating.

To a solution of the respective halide (0.25 mmol) and anhydrous THF (1 mL) in a pressure tube was added palladacycle **3-1** (0.05 mol% Pd) followed by 1 M Grignard reagent in THF (0.3 mL). The reaction mixture was microwave irradiated (with the heating program starting at 150 W) at 100 °C, and the reaction was monitored by TLC. When the reaction has completed, the reaction mixture was cooled to room temperature, poured into EtOAc (20 mL), and washed successively with water (3 × 10 mL). The organic layer was dried over anhydrous

$MgSO_4$, filtered, and concentrated. The crude product obtained was purified by column chromatography. On the basis of the ^1H NMR, the purities of compounds were determined to be ≥96%.

4-Methylbiphenyl (3-24a)

^1H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, J = 8.2 Hz, 2H), 7.50−7.44 (m, 2H), 7.42−7.36 (m, 2H), 7.06 (d, J = 8.2 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.2, 136.7, 131.2, 130.8, 128.7, 127.2, 127.1, 119.0, 20.5. HRMS (EI): calcd for $C_{13}H_{12}$ 168.0939, found 168.0937.

10-Phenylanthracene (3-24b)

^1H NMR (500 MHz, $CDCl_3$): δ 8.53 (s, 1H), 8.08 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.8 Hz, 2H), 7.68 − 7.54 (m, 2H), 7.53 − 7.46 (m, 4H), 7.41 − 7.36 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.7, 137.0, 131.3, 131.2, 130.2, 128.3, 128.3, 127.4, 126.8, 126.5, 125.3, 125.0. HRMS (EI): calcd for $C_{20}H_{14}$ 254.1096, found 254.1093.

4-Nitrobiphenyl (3-24c)

^1H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, J = 8.8 Hz, 2H), 7.36 − 7.32 (m, 2H), 7.08 − 7.00 (m, 1H), 6.98 (d, J = 8.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.3, 142.3, 132.1, 129.4, 121.6, 118.9, 118.2, 112.5. HRMS (EI): calcd for $C_{12}H_9O_2N$ 199.0633, found 199.0632.

4-Methoxybiphenyl (3-24d)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.66 − 7.60 (m, 4H), 7.52 − 7.47 (m, 2H), 7.41 − 7.36 (m, 1H), 7.06 (d, 2H, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.1, 140.7, 133.7, 128.7, 128.1, 126.7, 126.6, 114.1, 55.2. HRMS (EI): calcd for $C_{13}H_{12}O$ 184.0888, found 184.0884.

Hexylbenzene (3-24e)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.28 − 7.24 (m, 2H), 7.14 − 7.12 (m, 3H), 2.63 (t, J = 7.6 Hz, 2H), 1.61 (m, 2H), 1.35 − 1.31 (m, 6H), 0.89 (t, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.1, 128.4, 128.2, 125.6, 36.2, 31.9, 31.5, 29.1, 22.7, 14.1. HRMS (EI): calcd for $C_{12}H_{18}$ 162.1409, found 162.1407.

Styrene (3-25)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, J = 7.9 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.30 (t, J = 7.4 Hz, 0H), 6.78 (dd, J = 17.6, 10.9 Hz, 0H), 5.80 (d, J = 17.6 Hz, 1H), 5.30 (d, J = 10.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.6, 136.9, 128.5,127.8, 126.2, 113.8. HRMS (EI): calcd for C_8H_8 104.0626, found 104.0626.

3.10.14 General Procedure for the Recycling Experiment Using F-SPE.

The reaction mixture was first diluted with THF/H_2O = 8:2 and loaded into F-SPE fluorous silica. The crude product was eluted using THF/H_2O = 8:2 as eluent, and the palladacycle **3-1** was subsequently eluted with THF, concentrated, dried, and used for another run. For elemental analysis of Pd leaching, a solution of the

crude product was concentrated and analyzed by ICP-OES. The crude product was then concentrated followed by diluting it with EtOAc (20 mL) and washed with water (10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was then purified by column chromatography.

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Chapter 4: Synthesis of a Trisaccharide Unit of CPS from *Klebsiella Pneumoniae*

4.1 Introduction

Monosaccharide is a term that covers a fairly well-defined group of aliphatic polyhydroxy aldehydes (aldose) and ketones (ketose) having four to nine carbon atoms in their backbone chain that have a molecular formula of $C_n(H_2O)_n$ (hence the name of carbohydrate – hydrates of carbon). The carbon atom of a monosaccharide is numbered in a way that the carbonyl carbon is given the lowest possible number (Figure 4-1). There are two groups that carbohydrate could be divided into, which have different chemical and physical properties. The first group would be the monosaccharides that could not be broken down further into smaller subunits upon treatment with aqueous acid. Another group would be the complex saccharides which consist of oligosaccharides and polysaccharides, which are formed by two or more monosaccharides through glycosidic bonds. Derivatives of carbohydrate could also be formed by the replacement of one or more hydroxyl groups with amino, thiol or similar heteroatomic groups.

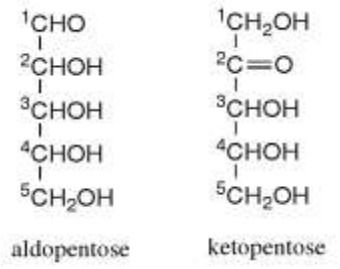


Figure 4-1. Numbering of carbon atoms in aldose and ketose.

4.2 The Anomeric Effects

Anomeric effec is a stereoelectronic effect that describes the tendency of heteroatomic substituents adjacent to a heteroatom within acyclohexane ring to prefer the axial orientation instead of the less hindered equatorial orientation that would be expected from steric considerations. This is the result of dipole-dipole interactions and stereoelectronic effects. The two nonbonding electron pairs on the endocyclic sp^3 hybridized oxygen atom (C-O-C) form a dipole that points in the exocyclic direction whereas, the polarized bond between the anomeric carbon and the exocyclic heteroatom (C-Y) attached to it forms another dipole (Figure 4-2). The interaction of these two dipoles is unfavourable in the $^4C_1$ conformation of the β-D-glucopyranose anomers due to the almost parallel direction, resulting in high dipole-dipole interaction. However in the α-D-anomers, these two dipoles point away from each other resulting in small dipole-dipole repulsions. According to stereoelectronic interpretation, the nonbonding electrons of the endocyclic oxygen atom, which is axially oriented are synperiplanar to the antibonding orbital of the anomeric substituent when the ring is in the α configuration. This effect allows the two orbitals to mix and form $n \rightarrow \sigma^*$ interaction, which would shorten the C-O-C1 bond and lengthen the C1-Y bond (Figure 4-3, alpha-anomer). However, this effects occur only when the anomeric C-X bond is axially oriented, where the $^4C_1$ conformation of the α-D-anomers and the $^1C_4$ conformation of the β-D-anomers. The conformational equilibrium of the α-D-anomers is also strongly solvent dependent, where solvents with low dielectric constants would result in a higher proportional axially substituted conformer.[1] On top of that, electron

withdrawing ability of the anomeric substituent would affect the axial preference[2] and in general, a more electron-negative anomeric substituent exhibits a stronger preference for an anxial orientation.

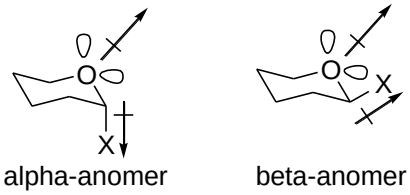


Figure 4-2. Dipole moments of α- and β-anomers.

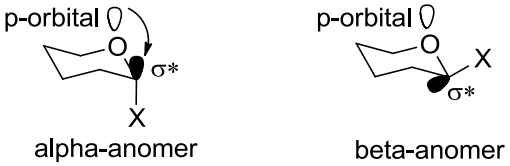


Figure 4-3. Orientation of *p* and σ* orbitals of α- and β-anomers.

The term exo-anomeric effect was described as an orientational effect of the aglycon part which demonstrates similar properties. The nonbonding electrons of the anomeric oxygen atom could occupy different positions due to the rotation around the C1-O(exo) bond (Figure 4-4). Through the Newman projection of three rotamers, it is evident that in rotamers "b" and "c", the nonbonding orbitals can overlap the σ* orbital of the O(endo)-C1 bond but such overlap is not possible in rotamer "a". Rotamer "c", which is antiperiplanar to the C1-H bond is energetically unfavourable due to the relatively bulky R substituent is placed

directly under the plane of the pyranose ring in the α-D-anomers, unlike rotamer "b".

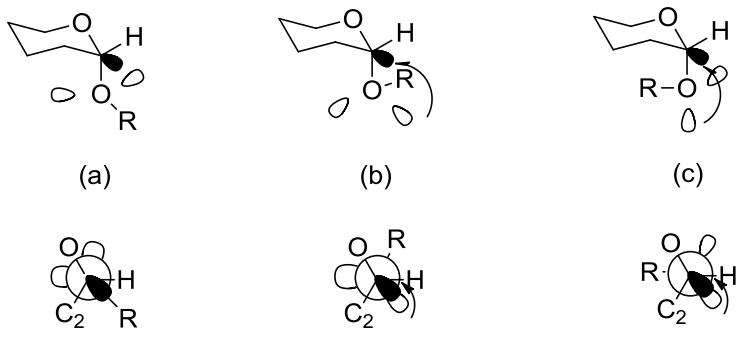


Figure 4-4. Three C1-O_{exo} rotamers of α-D-anomers and the Newman projections.

4.3 Protecting Group Strategies for Carbohydrates

Protecting group strategies are particularly important in carbohydrate chemistry due to the presence of a large number of functional groups, which are mostly hydroxyl groups. Thus it is necessary to have regioselective protecting strategies in order for other functionalities to be reacted selectively which sometimes can be quite laborious. It is also relatively hard to predict how all the protecting group would affect outcomes of the reactions (e.g stereochemistry of anomeric carbon). The protecting groups used in carbohydrate chemistry are essentially the same as those used in other areas of organic chemistry. The only difference is that carbohydrate chemistry requires an immense amount of protecting groups and the constant need for regioselectivity. There are various books which have been written on protecting group strategies in organic chemistry.[3-7] Despite the complexities of the aforementioned, there are general synthetic strategies for most

of the sugar molecules with the use of some well-proven protecting groups to achieve regioselectivity.

4.3.1 Acyl Protecting Groups

The formation of O-acetate is one of the classical protecting groups used in carbohydrate chemistry, due to its ease in preparation and deprotection.[2,6,8] Moreover, with a fully acylated saccharide, the transformation of the anomeric centre could be achieved easily through an orthogonal reaction. Acyl group could be easily cleaved under basic condition (i.e. cat. NaOMe in MeOH) but it is relatively stable under acidic conditions (Figure 4-5).[9]

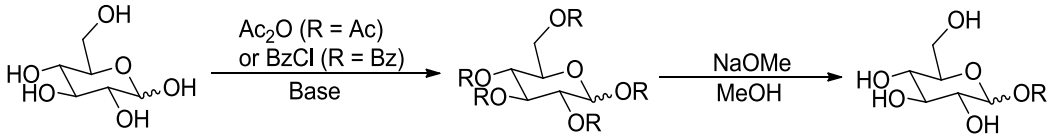


Figure 4-5. Protection and deprotection of acyl group on glucose molecule.

Another benefit of using acyl group is that it can be selectively removed by tuning their reactivity based on steric and electronic effects. For example, the rate of saponification of some ester occurs in the following order: trichloroacetate < chloroacetate < acetate[6], hence making it possible to selectively remove chloroacetate in the presence of benzoate (Figure 4-6). Another benefit of an acyl group is that it can be regio- and chemoselectively introduced and removed by enzymes.[10-12]

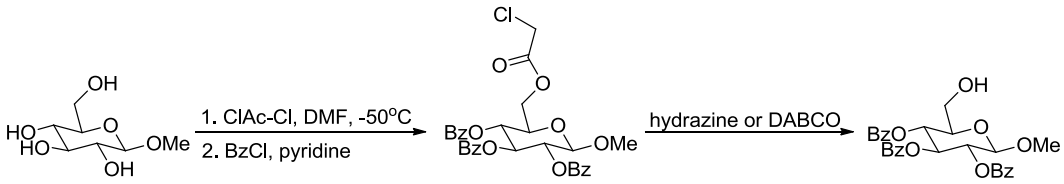


Figure 4-6. Selective deprotection of chloroacetate in the presence of benzoyl groups.

4.3.2 Ether Protecting Groups

Ethers like benzyl and allyl are amongst the most common protecting group and are a perfect set of orthogonal protecting groups to acyl protecting group (Figure 4-7).[13a] The ether group is generally stable under basic conditions, thus allowing the selective deprotection of acyl group (Figure 4-8). On top of that, there are also conditions that would selectively deprotect the ether group in the presence of the acyl moiety, such as hydrogenolysis of benzyl ether (Figure 4-8).

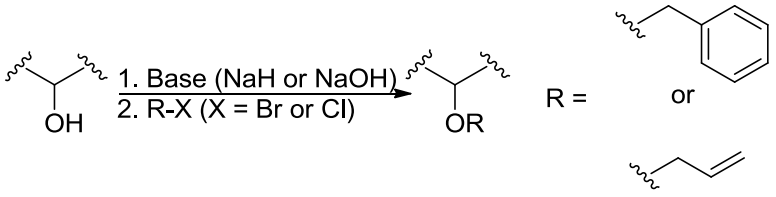


Figure 4-7. Formation of ether protecting groups.

The ether group can be introduced by reductive cleavage of the acetal group (Section 4.3.3) thus offering highly flexible protecting group strategies for carbohydrates. Another advantage of using ether protecting groups would be its effect in modulating the reactivity of the molecule. For example the C-4 position

of a glucoside would become more nucleophilic with the presence of benzyl ether at the C-3 position.[13b]

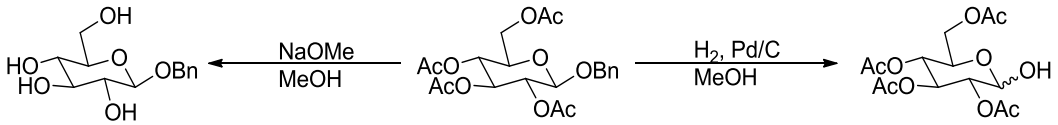


Figure 4-8. Selective deprotection of acyl and benzyl protecting group.

4.3.3 Acetal Protecting Groups

The most commonly used acetal protecting groups for diol in carbohydrate synthesis are benzylidene and isopropylidene.[14,15] Acetal protecting groups are usually introduced through the condensation of sugar molecules with an aldehyde or ketone or through transacetalation in the presence of an acid catalyst (Figure 4-9).[16] The hydrolysis of the acetals can be achieved under mild acid conditions or by hydrogenation in the case of benzylidene (Figure 4-10). Benzylidene can also be partially hydrolysed under appropriate conditions, as mentioned earlier in section 4.3.2 (Figure 4-10).

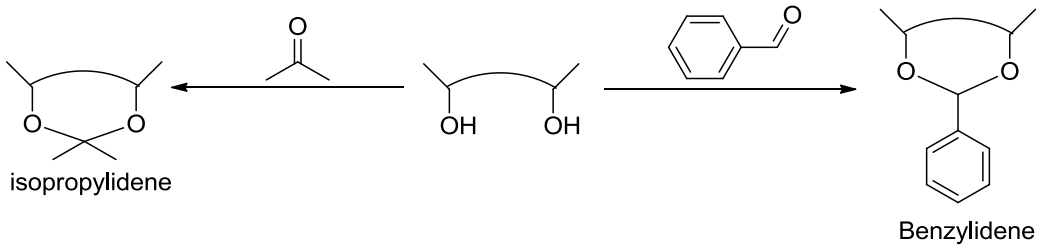


Figure 4-9. Acetal protecting group of diols.

Benzylidene and isopropylidene acetals are not able to selectively protect *trans* diols in sugar molecules. Thus to circumvent the problem, other derivatives such as dispiroketal (Dispoke) and cyclohexane-1,2-diacetal (CDA) are used instead (Figure 4-11).[17,18,19] These functional groups are compatible with other protecting groups such as TBDMS, Bn, PMB and acyl groups.

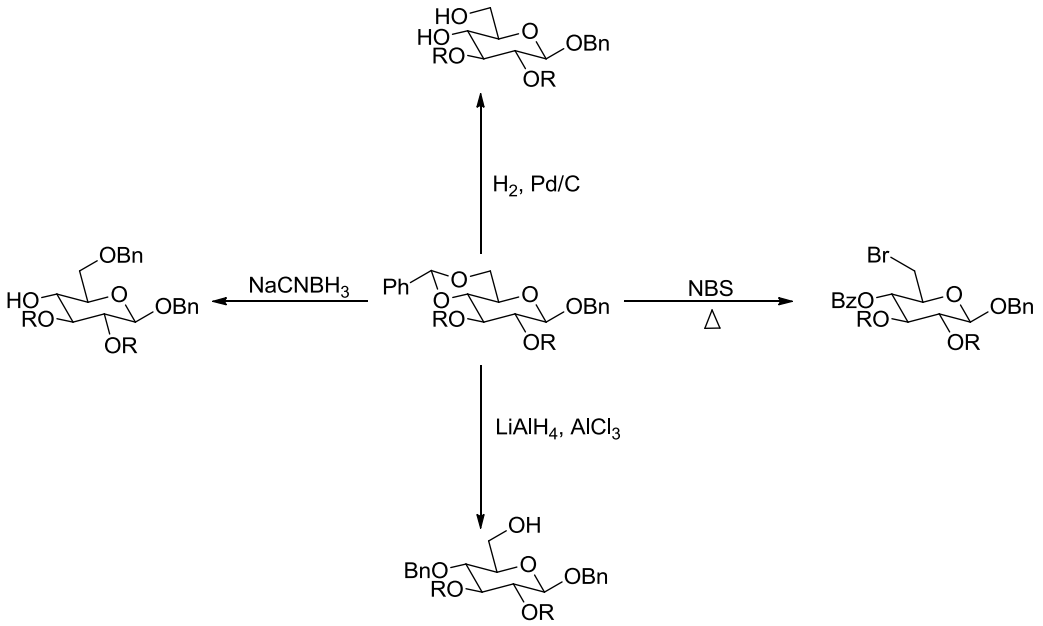


Figure 4-10. Selective ring opening of benzylidene protecting group.

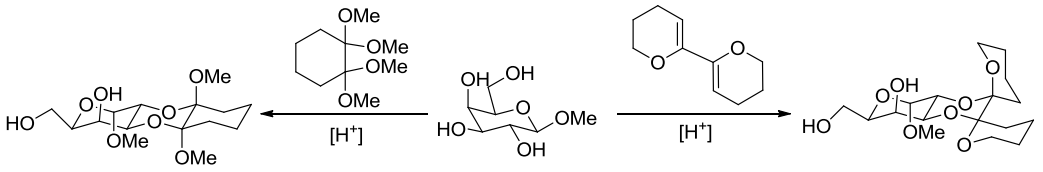


Figure 4-11. Selective protection of trans-diol in carboydrates.

4.4 Glycosylation Methods

The majority of carbohydrates found in nature do not occur in their free form, but the individual sugar molecule is linked to other types of sugar molecules through

a glycosidic bond. The commonly found glycosidic bonds in nature are the O-glycoside, S-glycoside and N-glycoside, amongst which the O-glycosidic linkage is the most abundant and important (Figure 4-12). Glycosylation plays a crucial role in carbohydrate chemistry for several reasons. There is a rapid increase in awareness of the role played by oligosaccharides in biology. It is also apparent to scientists that glycoconjugates provide an array of additional biological functions. Some of these functions include the control of the half-life of proteins, modulation of protein function, presentation of target structures for micro-organisms, toxins and antibodies, etc.[20,21] However, these advances are traditionally dependent on the progress of structural studies of these biomolecules. Thus saccharide sequences would need to be available to scientists in substantial amount in order to study the characteristics interaction between the carbohydrate and the receptor on the cell in more detail. Unfortunately, the isolation of the desired oligosaccharides from natural product is still a cumbersome process. Chemical syntheses is a major tool that researchers can exploit for the advancement in glycobiology, and an essential part of the chemical synthesis is the formation of glycosidic bonds present in oligosaccharides or polymeric structures.

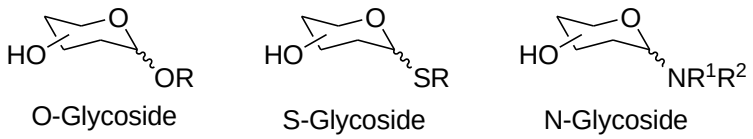


Figure 4-12. O-, S-, N-glycosides.

In most cases, the first step involves the formation of a temporary glycosidic bond at the anomeric which allows various chemical transformation at other positions to be carried out, as the substituent on the anomeric carbon is the most reactive among the other functional groups present in the monosaccharide. By protecting the anomeric carbon, it also eliminates the problem of equilibration of the free sugars into different anomeric configurations and ring sizes.

Ever since the pioneering work on glycoside syntheses by Michael[22], Fischer[23,24], Koenigs and Knoor[25], there has been a significant array of effective promoters in the formation of glycosyl donors (Figure 4-13).[26-29] Nonetheless, the formation of a glycosidic bond is not an easy feat and a general method that carbohydrate chemist can rely on is still lacking. This is due to the many unpredictable elements in the reaction, such as the stability of glycosyl donors, anomeric stereoselectivity or acceptor reactivity and the yield of the glycosylation steps. The stereochemical outcome of the reaction also depends on a variety of factors such as solvents, participating groups, temperature, etc. Reactivity of acceptor is typically inversely correlated with 1,2-cis stereoselectivity, in which the stronger the nucleophile, the faster the reaction thus stereochemical control is more diffucult. The general rule states that glycosylation of more reactive primary alcohol gives poorer stereoselectivity as compared to a secondary alcohol.[30] However, study done by Cid *et. al.* have shown that factors governing the stereochemical outcome by glycosyl donor is difficult to predict and glycosyl donor always play a major role.[31] Fortunately, it is not all trial and error in sugar

synthesis. A careful analysis of previously accomplished syntheses of similar structure would help the carbohydrate chemist reduce the number of unknown parameters.

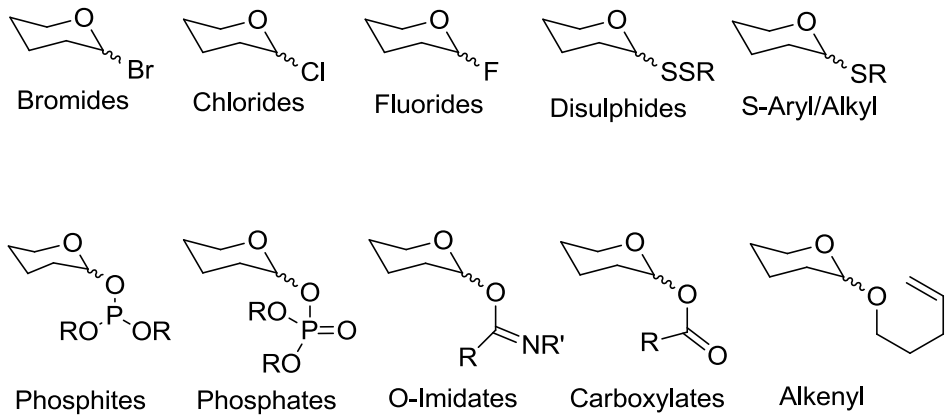


Figure 4-13. Examples of different glycosyl donors.

4.4.1 Trichloroacetimidate Method

The trichloroacetimidate method was developed by R. R. Schmidt and co-workers and it has been employed in numerous oligosaccharide syntheses. Anomeric oxygen atom of glycosyl trichloroacetimidates is a good leaving group, where it is derivatized with a group that is easily removed, which makes them a good glycosyl donor. Often glycosyl trichloroacetimidate are stable and they can be stored for months at low temperature. They can be activated by commonly used Lewis acid catalysts such as $BF_3.EtO_2$ and TMSOTf in an inert solvent such as DCM or acetonitrile. The amount of Lewis acid added vary from case to case, where in most cases a diluted solution of TMSOTf in dry DCM is sufficient for the reaction to complete. However, in cases where orthoesters are formed as an

intermediate, repeated additions of of the Lewis acid are required. The high reactivity of gylcosyl trichloroacetimidates can also lead to side reactions or rearrangement of the donor before reacting with the gylcosyl acceptor which has no donor activity (Figure 4-14). In order to improve the yield and stereocontrol of the reaction, an 'inverse gylcosylation' method is usually employed, where the gylcosyl acceptor and the catalyst are first dissolved prior to the addition of the gylcosyl donor.

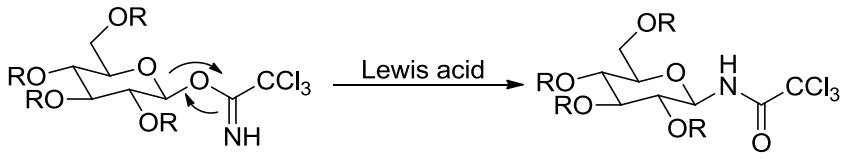


Figure 4-14. Rearrangement of gylcosyl trichloroacetimidate.

In the trichloroacetimidate method, neighbouring group participation at C-2 is usually the dominating effect in anomeric stereocontrol which would be elaborated in the section 4.4.3. When there is no participating group involved, a S_n^2-type reaction can be carried out with the use of non-polar solvents at low temperature in the presence of a mild Lewis acid catalyst ($BF_3.EtO_2$). On the other hand, the use of strong Lewis acid catalysts (TMSOTf or TfOH) at higher temperature and polar solvent would result in the formation of the thermodynamically more stable glycosylation products.

4.4.2 Thioglycosides Method

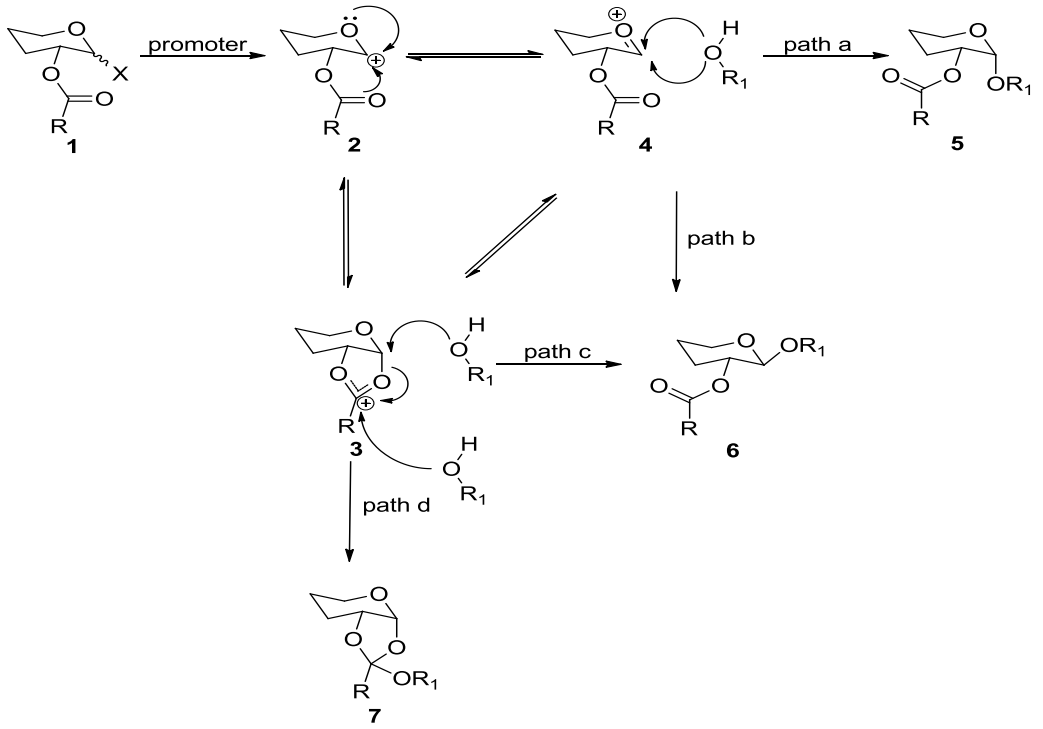
Thiogylcosides are often a common choice for the synthesis of oligosaccharides due to its versatility to be a glycosyl donor by itself and directly converted to other type of gylcosyl donors or by a two-step procedure. Importantly, their long shelf lives and able to tolerate very diverse chemical manipulations, unlike glycosyl trichloroacetimidate or glycosyl bromides during deacylation reaction. Thus, the use of thioglycosides allows protecting group exchange plausible. Furthermore, thioglycosides are also inert under several glycosylation conditions (absence of thiophilic promoter), allowing it to be a glycosyl acceptor in the formation of oligosaccharide.

Participating group at C-2 of they glycosyl acceptor plays an important role in the anomeric control in glycosidation of thioglycosides (Section 4.4.3), which lead in the formation of 1,2-trans glycosides. In cases of a non-participating group such as benzyl ether at C-2, it would result in a mixture of anomers depending on the nature of solvents. In general, the use of low polarity solvent would increase α-selectivity by surpressing the formation of oxocarbenium ions. For example, diethyl ether is known to increase α-anomeric selectivity, presumably through the formation of β-diethyl-oxonium ion intermediate due to steric reason. Furthermore, it has been shown that glycosyl donor : acceptor ratio, presence of molecular sieve and iodomium ion plays a major role on the stereochemistry of glycosylation products.[32] Mechanistic studies have shown that thioglycosides can undergo *in situ* anomerization in the presence iodonium ion catalysts, in which it

could be surpressed through the use of bulky leaving group.[33] It has been proposed that this anomerization process is important for the stereochemical outcome of gylcosylations.

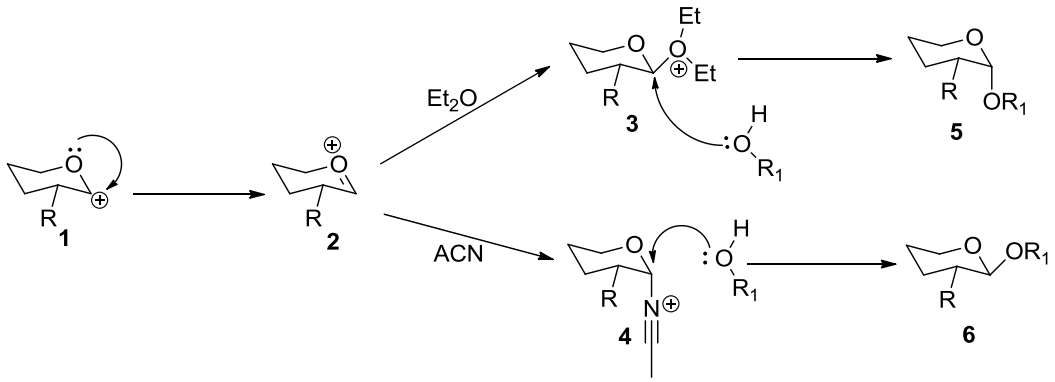
4.4.3 Stereochemical Aspects of Glycoside Bond Formation

Stereoselectivity control at the anomeric carbon is an important aspect of the glycosylation reactions. The stereoselectivity in the formation of O-glycoside is strongly dependent on the neighbouring glycosyl donor. In general, the presence of an acyloxy group at C-2 directs the formation of *trans* linked O-glycosidic bond. As shown in Scheme 4-1, the presence of an ester functional group would allow the formation of acyloxonium ion **3** readily from the initial oxocarbenium ion **2**. Thus hydroxyl nucleophile can only approach from the top face of the ring to form the *trans*-glycoside **6** with the regeneration of acyloxy group. In some cases, the formation of cis-glycosides **5** is also possible even with a C-2 neighboring group participation, especially in unreactive substrates (Scheme 4-1, path a). The formation of orthoester **7** (Scheme 4-1, path d) can be limited with the use of slightly acidic glycosylation condition. Some of the commonly used participating groups are O-acetyl, O-benzyl and O-trichloroacetate.



Scheme 4-1. Synthesis of 1,2-trans glycosidic linkage with a neighbouring group participation.

The stereoselectivity of glycosylation reaction without a participating group at C-2 is largely dependent on the nature of the solvent used in the reaction. Solvents that are of low polarity such as ether-type tend to enhance the formation of cis-glycoside **5**, which is rationalized through the formation of equatorial oxonium ion type intermediate **3** (Scheme 4-2). Hence, the hydroxyl nucleophile would need to approach the bottom face of the ring to form the cis-glycoside. On the contrary, nitrile-type solvents such as acetonitrile favour the formation of trans-glycoside **6** (Scheme 4-2).



Scheme 4-2. Participation of solvent in glycosylation reaction.

The structure of glycosyl donors together with the choice of promoter and solvent play a major role in the determination of stereoselectivity. Other factors such as temperature, concentration, the sequence of addition of the reactants and pressure also play a part in determining the stereoselectivity of glycosylation. There are various reviews that have a detailed discussion on the effects of the aforementioned factors.[34-36]

4.5 *Klebsiella pneumonia* (*K. pneumoniae*)

Pneumonia and urinary tract infections are usually caused by an opportunistic pathogen in the Enterobacteriaceae family called *K. pneumoniae*. During the past few decades, the emergence of a new type of invasive disease caused by *K. pneumoniae* which results in primary pyrogenic liver abscess (PLA)[3] in patients without biliary tract diseases or other intra-abdominal infections[37-40] has surfaced in Taiwan, Korea, North America and Europe. In 1990s a large percentage of emerging disease cases in Taiwan involving diabetic middle-aged men with metastatic complications, most notably endophtalmitis due to *K. pneumoniae* liver

abscess (KLA). Hepatobiliary malignancy and other newly diagnosed malignancy have been detected in about 50% of patients who have risk factors for non-*K. pneumonia* liver abscess in non-diabetic patients; the remainder are dibetes mellitus, which could be a pre-disposing factor.[41-44] Interestingly, such a unique epidemiologic change has a geographic difference and has been restricted to some Asian countries.[45] For the last decade, *K. pneumoniae* has been reported as the most common microorganism causing pyrogenic liver abscess in Korea.[46]

Capsular polysaccharide (CPS, which is the K antigen) and lipopolysaccharide (LPS, which is the O antigen) are the two key surface components that are crucial for the virulence of *K. pneumonia*.[47,48] It had been shown that through Toll-like receptor 4 (TLR4), PLA *K. pneumoniae* capsular polysaccharide (CPS) is able to induce secretion of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) by macrophages.[49] To date, *K. pneumoniae* has caused higher reported incidence of pyrogenic liver abscess and even splenic abscess compared to other bacteria. The knowledge of how *K. pneumoniae* expresses virulence genes at the appropriate time during systemic infection, and how it survives and replicates within the host while resisting the innate immune system, nitrous oxide oxidation, and antimicrobial factors is still superficial and the active components of (PLA) *K. pneumoniae* in stimulating cytokine expression in macrophages are still unknown.[50,51]

Earlier studies revealed that rats which are actively immunized with purified CPS appeared to be protected against the lethal pneumonia caused by *K. pneumonia*,[52,53] indicating that CPS could be an important component for the prevention of pneumonia. It was also found that *K. pneumoniae* require the mucoviscosity of CPS from a liver abscess strain for bacterial virulence.[54,55] Hence, understanding the complete structure of CPS of PLA *K. pneumoniae* is important in determining clinical manifestations, and it was shown to consist of repeating units of the trisaccharide (→3)-β-D-Glc-(1→4)-[2,3-(*S*)-pyruvate]-β-D-GlcA-(1→4)-α-L-Fuc-(1→) and has the unusual feature of extensive pyruvation of glucuronic acid and acetylation of C_2-OH or C_3-OH, but not both hydroxyl group of fucose.[56] Previous studies of meningococcal CPS have shown that the *O*-acetyl group provides an epitope of misdirected immunogenicity enabling escape from immune surveillance.[57] Hence, it is speculated that it could be a similar case in the PLA *K. pneumoniae* CPS, resulting in a less functionally active antibodies. Studies have also shown that the O-pyruvation is a vital group for immunological activities and it has the potential in influencing the host-pathogen interaction at several levels.[49]

Computer modeling sites in mouse TLR4 interacting with a short fragment (Glc-Fuc-GlcA-Glc) of PLA *K. pneumoniae* CPS allows a better understanding of interaction between the CPS moiety and TLR4.[57-59] The modeling suggested that there are hydrogen bond interactions between the carboxylate anion of the pyruvate and the guanidinium group of Arg-90 in TLR4; the carbonyl group at

C_3-OH of the fucose acetal substituent also shows hydrogen bond interaction with the acetyl group between the hydroxyl group of tyrosine Tyr-102 in TLR4, and between the main chain amide-NH group of serine Ser-120 and the carbonyl group of proline (Pro-118) and glucose. There are also apparent interactions between leucine Leu-94 and the CH_3 of the acetyl group of fucose, between glucose and Phe-121 and between Phe-121 and the CH_3 of the pyruvate acetal substituent of glucuronic acid. Ionic interactions may play the major role in the binding of the oligosaccharide with TLR4 as deacetylated and depyruvylated oligosaccharides seem to be deficient in the binding of TLR4 (Figure 4-15).[49] Thus, suggesting that acetyl group on fucose and the carboxylate anion of the pyruvate acetal substituent on glucuronic acid, of PLA *K. pneumoniae* CPS may interact with TLR4 and trigger the signal to transit. Previous studies have shown that anti-CPS monoclonal antibody (clone 10F8G4) is able to kill liver abscess *K. pneumoniae* and also protect mice from magA *K. pneumoniae*-induced death.[60] To determine if shorter chains of CPS would retain the immunomodulatory properties, we have enzymatically digested CPS into shorter fragments and showed that the oligosaccharides are able to stimulate macrophages to release cytokines. However enzymatic digestion only provided 6- to 21-mers, but not trisaccharide **4-1**. To determine the minimal length required for CPS to demonstrate its immunomodulatory properties and to better understand the molecular basis of the bacterium-host interactions in liver abscess formation, we decided to synthesize short fragments of CPS.

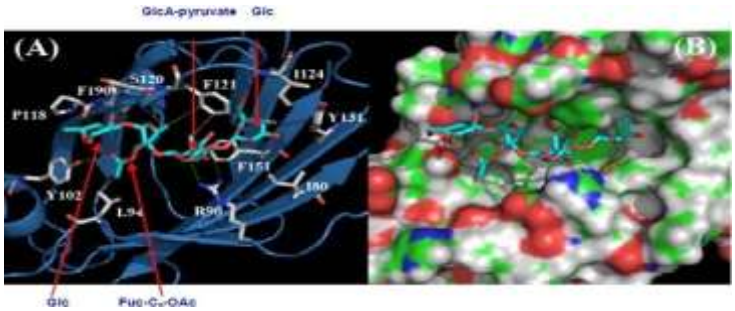
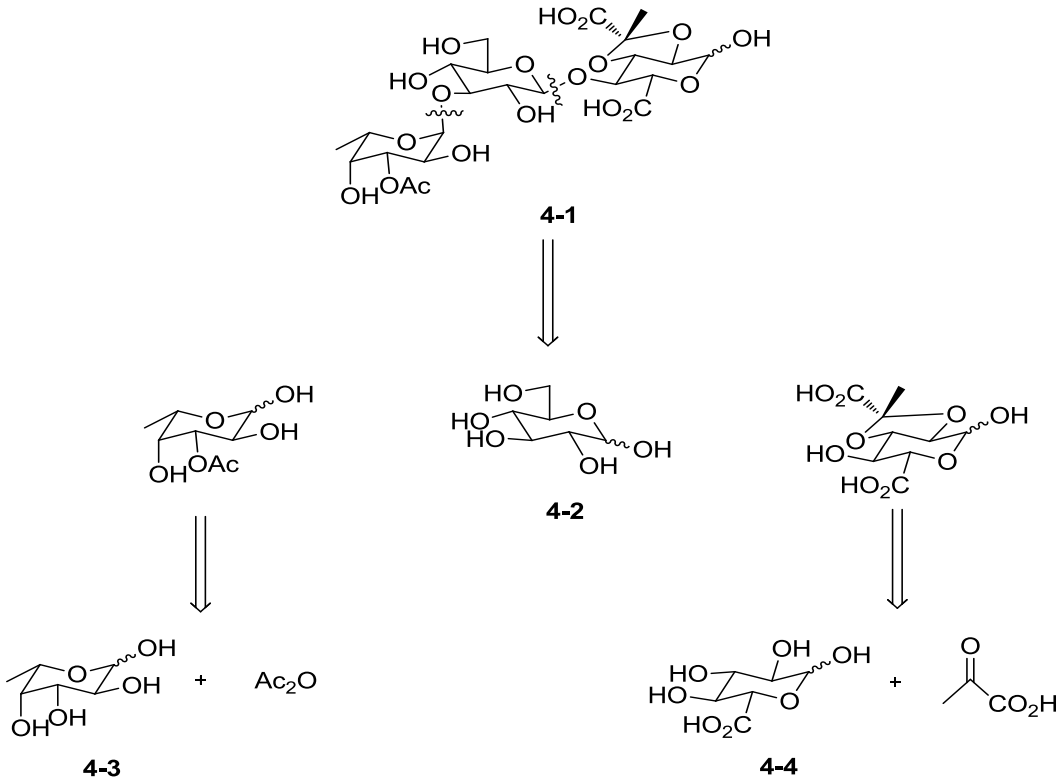


Figure 4-15. Interaction between the CPS moiety and TLR4.[49]

4.6 Synthesis of Trisaccharide Unit (Fuc-Glu-GluA)

A retrosynthetic analysis of trisaccharide **4-1** is depicted in Scheme 4-3. The key synthetic consideration is the control of anomeric stereochemistry during the respective glycosylation reactions with or without the participation of the protecting group at C-2.



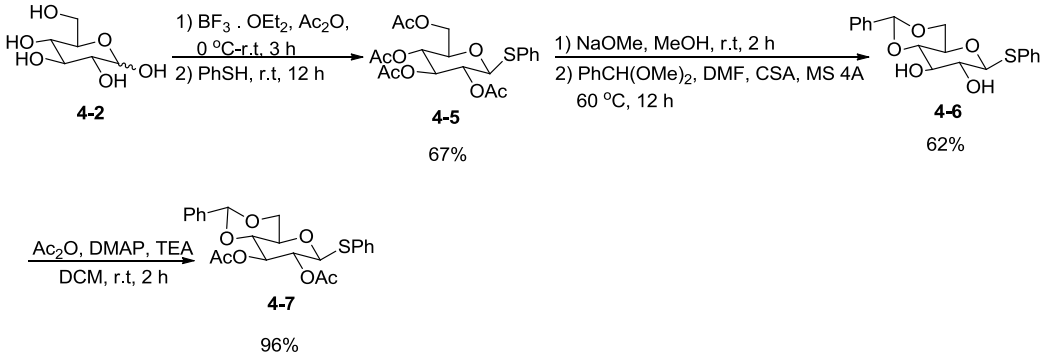
Scheme 4-3. Retrosynthesis of building block **4-1**.

Furthermore, it was envisaged that all the hydroxyl groups in the saccharides would be protected with benzyl groups prior to the final global deprotection step by catalytic hydrogenation which would allow access to the deprotected trisaccharide. On the basis of these considerations, three building blocks **4-2 – 4-4** were designed, with the consideration of the O-acetyl and O-pyruvate on the fucose and glucuronic acid, respectively.

4.6.1 Synthesis of Glucose Fragment

The synthesis of glucose fragment was achieved in 3 steps (Scheme 4-4). Thioglycoside **4-5** was prepared from D-glucose in a one pot reaction, which was initially reacted with acetic anhydride in the presence of boron trifluoride etherate

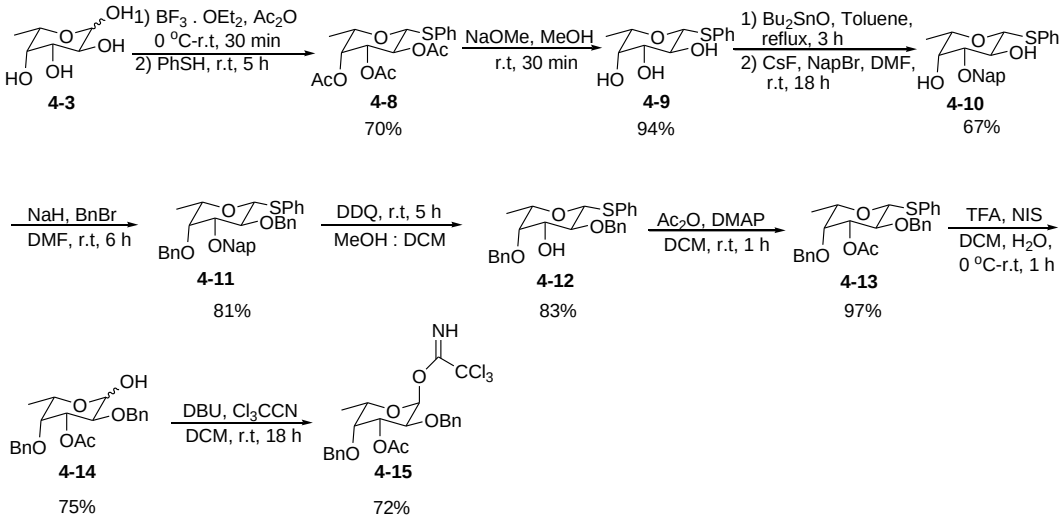
followed by reacting it with thiophenol at room temperature. The reason for using thioglucoside is due to its stability in the subsequent protection and deprotection methods employed. With a few grams of the acetylated thioglycoside **4-5** in hand, we proceeded with the deprotection of the acetates in the presence of catalytic base, NaOMe, in methanol. Upon complete deacetylation, the reaction mixture was further reacted with benzaldehyde dimethyl acetal in the presence of CSA to form compound **4-6**. Following that, we would need a directing group at C-2 of compound **4-6**, thus we decided to use an acetate protecting group as it would allow us to obtain the β-anomer upon glycosylation with the glucuronic acid fragment and also due to the ease in the deprotection of acetate which would thus give a clean reaction. Therefore, we treated compound **4-6** with acetic anhydride in the presence of a base which gave compound **4-7** in very good yield. Compound **4-7** would be glycosylated to the glucuronic acid fragment **4-26**. Another reason for the use of thioglucoside is due to the presence of a participating group at C-2 of the glycosyl donor which would give us primarily the desired stereoselective β-anomer product upon glycosylation with the glucuronic fragment.



Scheme 4-4. Synthesis of glucose fragment.

4.6.2 Synthesis of Fucose Fragment

The synthesis of the fucose fragment **4-15** is shown in Scheme 4-5. The synthesis of compound **4-11** has been reported before by Szábo et al.[61] With compound **4-11** in hand, we proceeded with the deprotection of methylnaphthalene group with DDQ to obtain compound **4-12**. As mentioned earlier, the presence of an acetyl at the C-3 or C-2 position is crucial. Thus we further reacted the free alcohol group at C-3 with acetic anhydride in the presence of a base to obtain compound **4-13**. Based on our previous experience, the glycosylation of fucose proceeded better with trichloroacetimide as compared to thiophenol. As with the use of the S-fucoside, we also observed the formation of the β conformer but not with trichloroacetimide as the leaving group. Hence, we decided to cleave the anomeric thiophenol protecting group with NIS and TfOH in the presence of water to give the free anomeric carbon in fucose **4-14**. Following that, the final fucose fragment **4-14** is then reacted with DBU and excess trichloroacetonitrile in DCM to give compound **4-15**, which is ready for glycosylation. The reason for the use of trichloroacetimidate for the glycosylation is due to its ability in forming the thermodynamically more stable desired product with the use of stronger Lewis acid catalyst such as TMSOTf at higher temperature (Section 4.4.1)., as compared to thioglycoside which would give a mixture of anomers in the absence of C-2 participating group.



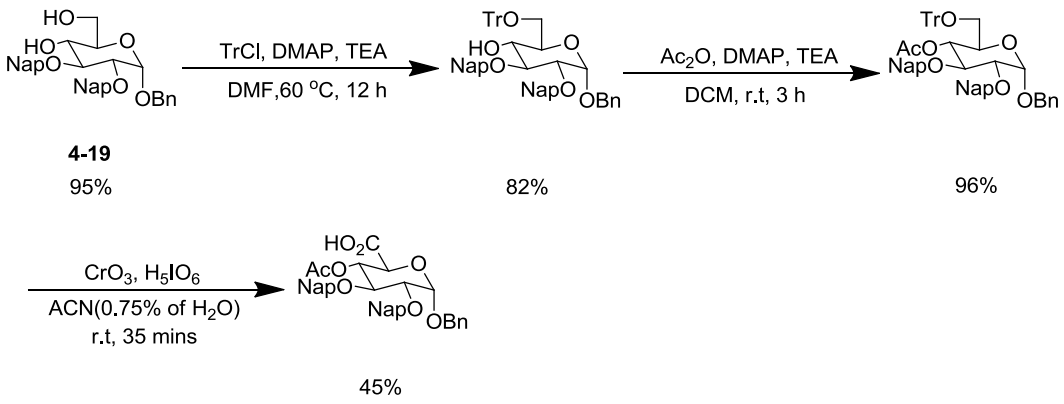
Scheme 4-5. Synthesis of fucose fragment.

4.6.3 Synthesis of Glucuronic Acid Fragment

The synthesis of the glucuronic acid started from D-glucose (Scheme 4-7) where it was first reacted with benzyl alcohol in the presence of *p*-TsOH as an acid catalyst to form compound **4-16**. We were not able to determine the ratio of α and β conformer that is formed at this step, therefore we proceeded to use both anomers in the formation of benzylidene to give compound **4-17**. With the formation of compound **4-17** we were able to determine the ratio of α and β to be 1.5:1 respectively. Following that, C-2 and C-3 of the carbohydrate molecule would need to be protected prior to the oxidation of the primary alcohol at C-6. 2-(Bromomethyl)naphthalene was use as a protecting group for the diol in the presence of a strong base, NaH, in DMF.

Compound **4-18** was then treated with acid in the presence of water in order to cleave the acid labile benzylidene group to give compound **4-19** under microwave

conditions. The O-glucoside **4-19** was then oxidized to give the glucuronic acid. Our initial attempt was to protect the primary alcohol at C-6 with trityl group followed by the protection of C-4 with acetyl group (Scheme 4-6). With the protection of the alcohol groups in glucose, we then treated the compound with CrO_3 in the presence of 2.5 equivalent of H_5IO_6 to form the glucuronic acid (Scheme 4-6). However, we could only obtain a yield of ~45% for this oxidation reaction, which is not economical knowing that there are many more steps ahead. Thus we decided to try TEMPO as our oxidant to form the glucuronic acid fragment. To our delight, we not only managed to oxidize the primary alcohol selectively without protecting the C-4 and C-6 but it also gave a higher yield. On top of that, we were able to effect one pot protection for the carboxylic acid group upon the oxidation of the primary alcohol to give compound **4-20**.



Scheme 4-6. Initial route for the synthesis of glucuronic acid fragment.

We then continue to protect the C-4 of compound **4-20** with an acetyl group prior to the deprotection of the methylnaphthalene group, in order to attach the

pyruvate group at the C-2 and C-3 position, to give compound **4-22**. Initial attempts to form the acetal directly with the use of methyl pyruvate were not successful even with different conventional lewis acids for cis-diol, such as TMSOTf[62], SO_2Cl_2-TfOH[63], methyl triflate (MT)[64], dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST)[65], or nitroso tetrafluoroborate ($NOBF_4$)[66], BF_3 . OEt_2[67] (Figure 4-16).

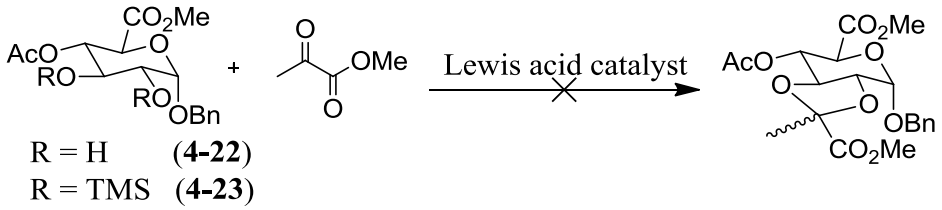
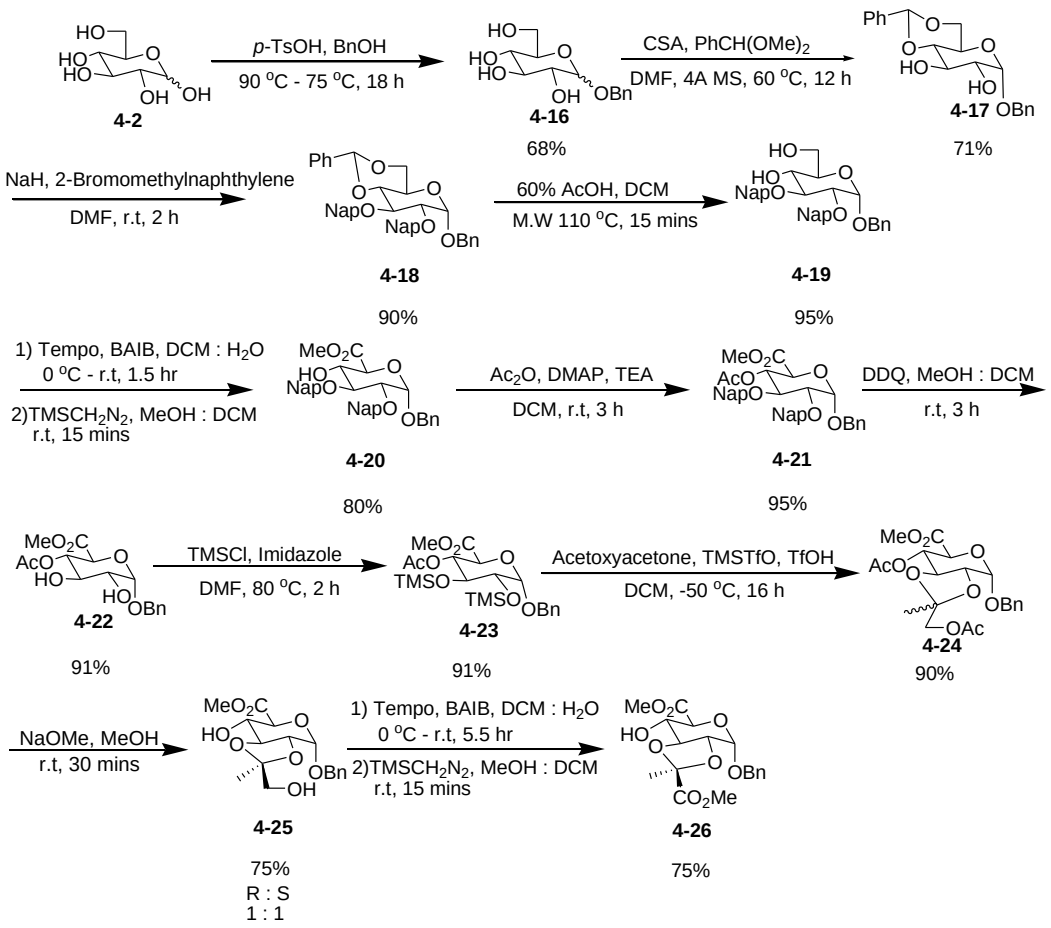


Figure 4-16. Acetal formation on glucuronic acid with methyl pyruvate

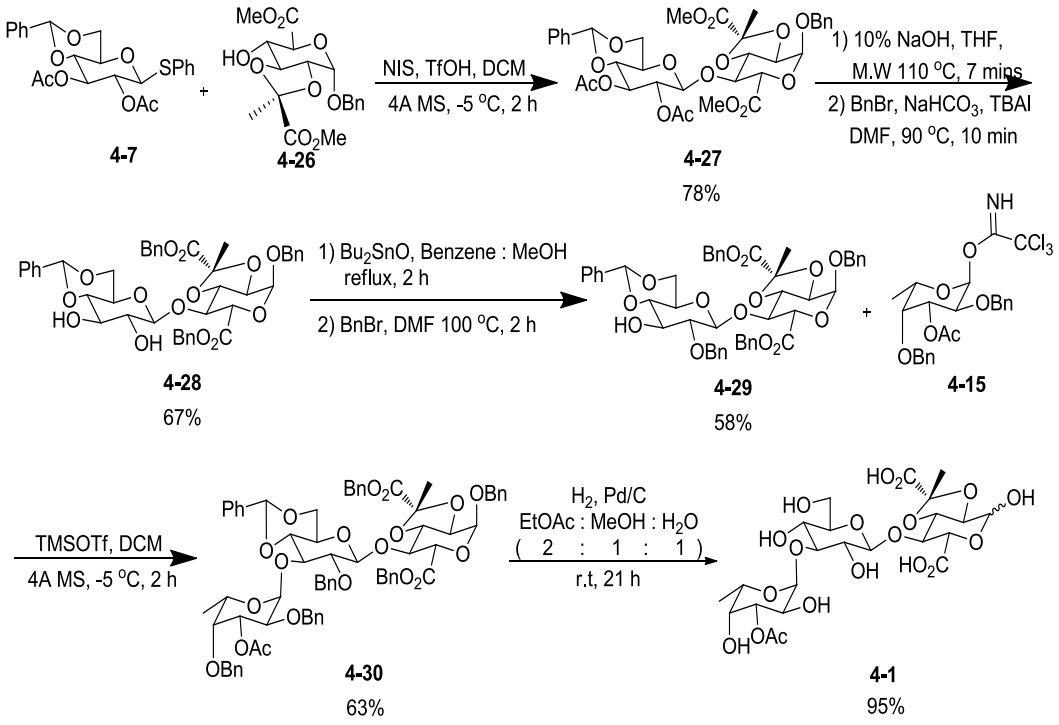
With little success on the direct pyruvation onto the trans-diol, we decided to use acetoxyacetone as a precursor. On top of that, we decided to make the oxygen at position C-2 and C-3 more activated by protecting it with a silyl group (Scheme 4-7, compound **4-23**). With the following changes, we were able to form the acetal at C-2 and C-3 in very good yield (Scheme 4-7, compound **4-24**). Both acetate protecting groups in compound **4-24** would then be removed for the glycosylation at position C-4 and also the oxidation of the primary alcohol to give the pyruvated compound **4-26**.



Scheme 4-7. Synthesis of glucuronic acid fragment.

With the individual carbohydrate fragments ready for glycosylation, we then proceeded on to synthesize the trisaccharide unit (Scheme 4-8). Compound **4-7** and compound **4-26** were glycosylated to form the disaccharide **4-27** in good selectivity and yield. As mentioned earlier, the acetal directing group at C-2 position of compound **4-7** allows us to obtain only the β-conformer of the disaccharide. After obtaining the disaccharide **4-27**, the ester functional groups were then hydrolyzed and replaced with benzyl ester functional group on the glucuronic acid in view of the final global deprotection step. Compound **4-28** was then selectively protected at the C-2 position of the glucose fragment with the use

of dibutyltin oxide to give the monobenzylated compound **4-29**. The protected trisaccharide unit **4-30** was obtained through the glycosylation of disaccharide **4-29** with the protected fucose fragment **4-15** to give good stereoselectivity of only the α-anomer. Initial attempt to glycosylate disaccharide **4-29** directly with S-fucoside **4-13** did not result in good stereoselectivity as we obtained α and β anomer of compound **4-30** in a ratio of 3:1.



Scheme 4-8. Synthesis of trisaccharide from the individual carbohydrate fragment.

With the trisaccharide synthesized, global deprotection of the benzyl group was performed with the use of Pd/C in the presence of hydrogen gas to give the target compound **4-1** in very good yield. The rationale to use 3 different solvents was due to the insolubility of trisaccharide **4-30** in polar protic solvent and also the insolubility of the final compound **4-1** in most organic solvents.

4.7 Conclusion

We achieved the first synthesis of a trisaccharide unit which represents the core structure of a CPS from the liver abscess strain *K. pneumoniae*. A series of efficient synthetic transformations involved three building blocks **4-7**, **4-15**, **4-26** which were eventually glycosylated into trisaccharide **4-1**. The overall efficiency of the assembly process benefited from a set of properly selected protecting groups. Complete stereoselectivity for each glycosylation was also ensured through the selection of blocking groups by virtue of orthogonality, participating effect, and, importantly, reactivity and tuning effects on the glycosylating agents. We are in the midst of making different sequence of analogues which will be important tools to establish a structure-activity relationship and their effects on the immunomodulation activities. Such biological effects are currently being explored by our collaborator.

4.8 Experimental

4.8.1 General

All chemical reagents were obtained from Aldrich, Merck, Lancaster or Fluka and used without further purification. Moisture-sensitive reactions were carried out under nitrogen with commercially obtained anhydrous solvents. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (Merck silica gel 60, F_{254}) and visualized with UV light or stained with the 10% sulphuric acid in ethanol stain. Flash column chromatography was performed with silica (Merck, 230–400 mesh). NMR spectra (^{1}H and ^{13}C) were recorded at 298 K on a Bruker

ACF300, DPX300 or AMX500 Fourier Transform spectrometers. Chemical shifts are expressed in terms of δ parts per million (ppm) relative to the internal standard tetramethylsilane (TMS). Mass spectra were performed on Finnigan TSQ 7000 for EI normal mode or Finnigan MAT 95XL-T spectrometer under EI, ESI, and FAB techniques. All infrared (IR) spectra were recorded on a Bio-Rad FTS 165 spectrometer. All isolated products are of ≥95% purity (by ^{1}H NMR). Microwave reactions were performed on the Biotage Initiator™ microwave synthesizer.

4.8.2 2,3,4,6-tetra-O-Acetly-1-thio-β-glucopyranoside (4-5)

To a mixture a D-glucose (5 g, 27.8 mmol) in acetic anhydride (13.4 ml, 141.7 mmol) was cooled to 0 ^{o}C using an ice-bath with continous stirring prior to the dropwise addition of $BF_3.Et_2O$ (10.3 ml, 41.7 mmol). After complete addition of $BF_3.Et_2O$, the reaction was allowed to stir at r.t for 3 h. Upon completion of the reaction (checked by TLC) thiophenol (44 ml, 43.3 mmol) was then added and the reaction mixture was stirred for another 12 h. The reaction was quenched by addition of aq $NaHCO_3$ and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the crude product by column chromatography on silica gel using hexane–EtOAc (2:1) as the eluent furnished the pure compound **4-5** in 67%. ^{1}H NMR (CD_3OD, 300 MHz) δ 5.18 (t, 1H, J = 9.3 Hz), 5.02 - 4.89 (m, 2H), 4.67 (d, 1H, J = 10.2 Hz), 4.17 - 4.13 (m, 2H), 3.71 - 3.66 (m, 1H), 2.03 (s, 3H), 2.02 (s, 3H), 1.96 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (CD_3OD, 75 MHz) δ 139.1,

134.3, 133.5, 129.9, 129.0, 128.8, 127.5, 102.9, 89.8, 81.9, 76.1, 74.4, 71.7, 69.6. HRMS (ESI) calcd for $C_{20}H_{24}O_9SNa$: 463.1033, found 463.1028 $(M+Na)^+$.

4.8.3 4,6-O-Benzylidene-1-thio-glucopyranoside (4-6)

To a solution of compound **4-5** (1.8 g, 4.1 mmol) in MeOH (24 ml) was added NaOMe (0.011 g, 0.21 mmol) and the reaction mixture was stirred for 2 h. Thereafter, the reaction was quenched with the addition of Amberlyst 15. The mixture was then filtered and concentrated under reduced pressure. To a solution of crude reaction mixture in DMF (14 ml) was added dimethoxytoluene (1.26 ml, 8.4 mmol), CSA (0.097 g, 0.42 mmol) and 4Å MS and the reaction mixture was stirred for 12 h at 60 ^oC. Upon completion of the reaction (based on TLC), the reaction mixture was diluted with EtOAc and washed with water. The aqueous layer was extracted with EtOAc (x3). The organic layer is then washed with brine (x3), dried with Na_2SO_4, and concentrated under reduced pressure. Purification of the crude product by column chromatography on silica gel using hexane–EtOAc (1.5:1) as the eluent furnished the pure compound **4-6** in 62%. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.62 - 7.37 (m, 10H), 5.63 (s, 1H), 4.78 (d, 1H, J = 10.1 Hz), 4.34 (dd, 1H, J = 5.1, 10.7 Hz), 3.81 (t, 1H, J = 10.1 Hz), 3.74 (t, 1H J = 8.5 Hz), 3.54 - 3.49 (m, 1H), 3.40 - 3.36 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.2, 169.9, 169.1, 169.0, 132.9, 131.4, 128.8, 128.7, 128.2, 85.4, 75.5, 73.7, 69.7, 68.0, 61.9, 20.5, 20.4. HRMS (ESI) calcd for $C_{19}H_{20}O_5SNa$: 383.0924, found 383.0919 $(M+Na)^+$.

4.8.4 2,3-O-Acetyl-4,6-O-benzylidene-1-thio-glucopyranoside (4-7)

To a solution of compound **4-6** (0.1 g, 0.28 mmol) in CH_2Cl_2 (4 ml) was added TEA (0.2 ml, 1.39 mmol) followed by DMAP (6.7 mg, 0.055 mmol) and acetic anhydride (79 µl, 0.83 mmol). The reaction mixture was stirred for 2 h at r.t. Upon completion of the reaction (checked by TLC), the reaction was quenched with $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with water, dried with Na_2SO_4, and concentrated under reduced pressure. Purification of the crude product by column chromatography on silica gel using hexane–EtOAc (5:1) as the eluent furnished the pure compound **4-7** in 96%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.33 (m, 10H), 5.52 (s, 1H), 5.37 (t, *J* = 9.4 Hz, 1H), 5.03 (t, *J* = 9.5 Hz, 1H), 4.84 (d, *J* = 10.1 Hz, 1H), 4.42 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.82 (t, *J* = 10.3 Hz, 1H), 3.69 (t, *J* = 9.5 Hz, 1H), 3.65-3.58 (m, 1H), 2.13 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.1, 129.0, 128.0, 125.9, 101.4, 86.52, 78.0, 72.8, 70.8, 70.4, 68.3, 20.8, 20.8. HRMS (ESI) calcd for $C_{23}H_{24}O_7S$: 444.1243, found 444.1239 $(M)^+$.

4.8.5 2,3,4,-tetra-O-Acetly-1-thio-β-L-fucopyranoside (4-8)

To a mixture a D-fucose (1 g, 6.1 mmol) in acetic anhydride (2.4 ml, 25 mmol) was cooled to 0 ^{o}C using an ice-bath with continous stirring prior to the dropwise addition of $BF_3.Et_2O$ (2.3 ml, 9.1 mmol). After complete addition of $BF_3.Et_2O$, the reaction mixture was allowed to stir at r.t for 10 min. Upon completion of the reaction (checked by TLC), thiophenol (0.97 ml, 9.5 mmol) was added and the reaction mixture was stirred for another 5 h. The reaction was quenched by

addition of aq $NaHCO_3$ and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water, dried with Na_2SO_4, and concentrated under reduced pressure. Purification of the crude product by column chromatography on silica gel using hexane–EtOAc (3:1) as the eluent furnished the pure compound **4-8** in 70%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.43 - 7.42 (m, 2H), 7.42 – 7.20 (m, 3H), 5.16 (d, *J* = 8.2 Hz, 1H), 5.11 (t, *J* = 9.5 Hz, 1H), 4.98 (dd, *J* = 3.15, 10.1 Hz, 1H), 4.65 (d, *J* = 10.1 Hz, 1H), 3.78 - 3.74 (m, 1H), 2.04 (s, 3H), 1.99 (s, 3H), 1.88 (s, 3H), 1.14 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.5, 170.0, 169.4, 132.9, 132.3, 128.8, 127.9, 86.2, 73.1, 72.4, 70.3, 67.3, 20.8, 20.6, 20.6, 16.4. HRMS (ESI) calcd for $C_{18}H_{22}O_7SNa$: 405.4984, found 405.4986 $(M+Na)^+$.

4.8.6 1-Thio-β-L-fucopyranoside (4-9)

To a solution of **4-8** (1.57 g, 4.1 mmol) in MeOH (24 ml) was added NaOMe (0.011 g, 0.21 mmol). The reaction was then stirred for 30 min prior to the addition of Amberlyst 15 to quench the reaction. The organic layer was concentrated under reduced pressure. Purification of the crude product by column chromatography on silica gel using DCM–acetone (3:1) as the eluent furnished the pure compound **4-9** (yield=94%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50 - 7.47 (m, 2H), 7.26 - 7.20 (m, 3H), 5.07 (d, *J* = 4.6 Hz, 1H), 4.64 (br s, 1H), 4.58 (d, *J* = 10.1 Hz, 1H), 4.04 (d, *J* = 5.0 Hz), 3.82 (br s, 2H), 3.67 (br s, 1H), 3.59 - 3.52 (m, 1H), 1.26 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.6, 131.5, 128.8, 127.3, 88.5, 75.2, 74.6, 71.7, 69.6, 16.6. HRMS (ESI) calcd for $C_{12}H_{16}O_4SNa$: 279.0667, found 279.0663 $(M+Na)^+$.

4.8.7 3-O-Methylnapthalene-1-thio-β-L-fucopyranoside (4-10)

Starting material **4-9** (0.72 g, 2.1 mmol) and Bu_2SnO (0.67 g, 2.7 mmol) was suspended in dry toluene (17 mL) and then refluxed for three hours under a Dean–Stark apparatus. After which, CsF (0.62 g, 4.2 mmol) was added to the solution and following an additional 10 min of refluxing, the solvent was evaporated to dryness in vacuo. The residue was redissolved in dry DMF (14 mL) and the alkylating agent (0.92 g, 4.2 mmol) was added. The reaction mixture was then stirred for 18 h. Thereafter, the reaction mixture was diluted with DCM, the precipitating salts were filtered through a pad of Celite, and the filtrate was extracted with water and saturated NaCl solution, dried and evaporated. Purification of the crude product by column chromatography on silica gel using Hexane-EtOAc (6:1) as the eluent furnished the pure compound **4-9** (yield=94%). ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.73 – 7.77 (m, 4H), 7.52 – 7.40 (m, 5H), 7.23 – 7.21 (m, 3H), 4.81 (s, 2H), 4.41 (d, *J* = 10 Hz, 1H), 3.76 - 3.72 (m, 2H), 3.47 - 3.38 (m, 2H), 2.69 (s, 1H), 2.39 (s, 1H), 1.29 (d, *J* = 6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75MHz) δ (ppm): 135.1, 133.0, 132.4, 132.2, 128.8, 128.3, 127.8, 127.7, 127.6, 126.7, 126.1, 126.0, 125.7, 88.3, 81.5, 74.5, 72.0, 69.2, 68.7, 16.6. HRMS (ESI) calcd for $C_{23}H_{24}O_4SNa$: 419.1288, found 419.1293 $(M+Na)^+$.

4.8.8 2,4-O-Benzyl-3-O-methylnapthalene-1-thio-β-L-fucopyranoside (4-11)

The starting material **4-10** (0.15 g, 0.33 mmol) was dissolved in dry DMF (0.49 mL). NaH (0.22 g, 5.3 mmol) was then added carefully to the mixture followed by the addition of benzylbromide (0.63 g, 5.3 mmol). The reaction mixture was

stirred for 6 h and then diluted with EtOAc and washed with water. The aqueous layer was extracted with EtOAc (x3). The organic layer is then washed with brine (x3), dried with Na_2SO_4, and concentrated under reduced pressure. Purification of the crude product by column chromatography on silica gel using hexane-EtOAc (9:1) as the eluent furnished the pure compound **4-11** in 81% yield. ^{1}H NMR ($CDCl_3$, 500MHz) δ 7.97 – 7.77 (m, 4H), 7.69 – 7.63 (m, 2H), 7.53 – 7.26 (m, 18H), 5.12 (d, *J* = 11.4 Hz, 1H), 4.95 (d, *J* = 3.2 Hz, 1H), 4.91 (d, *J* = 10.8 Hz, 1H), 4.85 (d, *J* = 10.1 Hz, 1H), 4.78 (d, *J* = 11.4 Hz, 1H), 4.69 (d, *J* = 9.5 Hz, 1H), 4.62 (s, 1H), 4.05 (t, *J* = 9.5 Hz, 1H), 3.72 - 3.70 (m, 2H), 3.59 - 3.56 (m, 1H), 1.34 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125MHz) δ 138.7, 138.3, 135.8, 134.3, 133.2, 132.9, 131.4, 128.7, 128.3, 128.3, 128.1, 127.8, 127.8, 127.7, 127.6, 127.5, 127.4, 126.9, 126.2, 126.1, 125.9, 125.6, 87.5, 84.3, 77.3, 76.7, 75.5, 74.6, 74.6, 72.8, 72.0, 17.2. HRMS (ESI) calcd for $C_{37}H_{36}O_4S$: 576.2334, found 576.2339 $(M)^+$.

4.8.9 2,4-O-Benzyl-1-thio-β-L-fucopyranoside (4-12)

To a solution of **4-11** (2.3 g, 3.9 mmol) in MeOH (8.7 ml) and DCM (34 ml) was added DDQ (1.3 g, 5.8 mmol). The reaction mixture was stirred for 5 h prior to the addition of aqueous saturated $Na_2S_2O_3$ to quench the reaction. After which, the reaction mixture was diluted with EtOAc and aqueous saturated $NaHCO_3$, and extracted with EtOAc (x3). The organic layer was washed with brine (x3). The organic layer was then dried with Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by column chromatography on silica

gel using hexane–EtOAc (7:1) as the eluent furnished the pure compound **4-12** (yield=83%). ^{1}H NMR ($CDCl_3$, 500MHz) δ 7.97 – 7.77 (m, 4H), 7.65 – 7.63 (m, 2H), 7.42 – 7.27 (m, 13H), 4.94 (d, *J* = 10.7 Hz, 1H), 4.83 (d, *J* = 11.4 Hz, 1H), 4.78 (d, *J* = 11.4 Hz, 1H), 4.69 (d, *J* = 11.4 Hz, 1H), 4.62 (d, *J* = 8.9 Hz, 1H), 3.74 - 3.70 (m, 2H), 3.63 - 3.62 (m, 2H), 2.32 (s, 1H), 1.37 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125MHz) δ 138.4, 138.2, 134.3, 131.3, 128.8, 128.4, 128.3, 128.3, 127.9, 127.8, 127.7, 127.0, 87.1, 79.2, 77.9, 76.0, 75.4, 75.1, 74.7, 17.2. HRMS (ESI) calcd for $C_{26}H_{28}O_4SNa$: 459.1606, found 459.1620 $(M+Na)^+$.

4.8.10 3-O-Acetyl-2,4-O-benzyl-1-thio-β-L-fucopyranoside (4-13)

To a solution of **4-12** (1.4 g, 3.2 mmol) in DCM (64 ml) was added DMAP (0.12 g, 0.96 mmol) followed by the addition of Ac_2O (1.58 ml, 17 mmol). The reaction mixture was then stirred for 1 h prior to the addition of aqueous saturated $NaHCO_3$ to quench the reaction. Thereafter, the aqueous layer with DCM (x3) and the organic layer was washed with brine (x3), dried with Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by column chromatography on silica gel using hexane–EtOAc (6:1) as the eluent furnished the pure compound **4-13** (yield=97%). ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.49 – 7.52 (m, 2H), 7.30 – 7.14 (m, 13H), 4.86 (dd, *J* = 2.9, 9.6 Hz, 1H), 4.75 (d, *J* = 11.1 Hz, 1H), 4.61 - 4.54 (m, 3H), 4.48 (d, *J* = 11.1 Hz, 1H), 3.66 (d, *J* = 2.6 Hz, 1H), 1.82 (s, 3H), 1.21 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75MHz) δ 170.4, 138.1, 133.9, 131.5, 128.8, 128.3, 128.0, 127.8, 127.7, 127.1, 87.4, 75.3, 75.2, 75.0, 74.3,

20.9, 17.0. HRMS (ESI) calcd for $C_{28}H_{30}O_5SNa$: 501.1706, found 501.1700 $(M+Na)^+$.

4.8.11 3-O-Acetyl-2,4-O-benzyl-L-fucopyranoside (4-14)

To a vigorously stirred solution of **4-13** (0.89 g, 1.8 mmol) in DCM (18 mL) and H_2O (01.8 mL) was added NIS (0.42 g, 1.8 mmol) and TFA (0.14 ml, 1.8 mmol) at 0 ^oC. After 1 h, TLC analysis showed complete consumption of the starting material. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ and washed with saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel using hexane–EtOAc (5:1→1:2) as the eluent furnished the pure compound **4-14** (yield=75%). ^1H NMR ($CDCl_3$, 300MHz) δ 7.25 – 7.16 (m, 10H), 5.20 - 5.14 (m, 1H), 4.80 - 4.76 (m, 1H), 4.58 - 4.46 (m, 4H), 4.12 - 4.08 (m, 1H), 3.91 - 3.89 (m, 1H), 3.64 - 3.48 (m, 2H), 1.86 - 1.82 (d, 3H), 1.11 - 1.05 (m, 3H). ^{13}C NMR ($CDCl_3$, 75MHz) δ 170.5, 170.5, 138.4, 137.9, 137.8, 137.7, 128.3, 128.2, 128.1, 128.0, 128.0, 127.7, 127.7, 127.4, 97.4, 90.3, 78.1, 77.8, 75.4, 75.3, 74.4, 73.9, 72.8, 72.7, 70.3, 65.9, 20.8, 20.7, 16.5, 16.3. HRMS (ESI) calcd for $C_{22}H_{26}O_6SNa$: 409.1627, found 409.1630 $(M+Na)^+$.

4.8.12 3-O-Acetyl-2,4-O-benzyl-1-trichloroacetimide-L-fucopyranoside (4-15)

To a vigorously stirred solution of **4-14** (0.1 g, 0.26 mmol) in DCM (1.4 ml) was added Cl_3CCN (0.26 ml, 2.6 mmol) and DBU (51 µl, 0.34 mmol). After 18 h,

when TLC analysis showed complete consumption of the starting material, the reaction mixture was concentrated in vacuo. Purification of the crude product by column chromatography on pre-treated silica gel with TEA using hexane–EtOAc (3:1) with 1% TEA as the eluant furnished the pure compound **4-15** (yield=72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.42 – 7.24 (m, 10H), 6.54 (d, *J* = 3.5 Hz, 1H), 5.33 (dd, *J* = 10.6, 3.0 Hz, 1H), 4.67 (m, 4H), 4.30 – 4.19 (m, 2H), 3.91 (d, *J* = 2.6 Hz, 1H), 2.01 (s, 3H), 1.22 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 161.2, 137.9, 137.7, 128.3, 128.2, 128.0, 127.8, 127.6, 127.5, 94.7, 91.2, 77.6, 75.6, 72.7, 72.7, 68.8, 20.9, 16.4. HRMS (ESI) calcd for $C_{24}H_{26}Cl_3O_6NNa$: 552.0723, found 552.0729 $(M+Na)^+$.

4.8.13 1-O-Benzyl-D-glucopyranoside (4-16)

To a mixture of D-glucose (5 g, 27.8 mmol) and *p*-TsOH (0.53 g, 2.78 mmol) was added BnOH (13.6 ml, 130.6 mmol). The mixture was then heated to 90 ^{o}C and stirred until D-glucose dissolved to give a slightly yellow solution. The reaction mixture was then stirred at 75 ^{o}C for 18 h and then cooled to r.t. Purification of the crude product by column chromatography using hexane-EtOAc (2:1) followed by DCM-EtOH (8:1→6:1) as the eluant furnished the pure compound **4-16** (yield=68%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.36 – 7.19 (m, 5H), 4.88 - 4.86 (m, 1H), 4.63 – 4.58 (m, 1H), 4.33 - 4.28 (m, 1H), 3.86 - 3.83 (m, 1H), 3.66 - 3.64 (m, 1H), 3.33 - 3.20 (m, 4H). HRMS (ESI) calcd for $C_{13}H_{18}O_6Na$: 293.1001, found 293.1010 $(M+Na)^+$.

4.8.14 4,6-O-Benzylidene-1-O-benzyl-D-glucopyranoside (4-17)

To a solution of glucoside **4-16** (6.12 g, 22.7 mmol) in DMF (47.5 ml) was added CSA (0.526 g, 2.27 mmol) followed by dimethoxytoluene (6.8 ml, 45.3 mmol) and 4Å MS (10.9 g). The mixture was then heated to 60 ^{o}C and stirred for 12 h. Thereafter, the reaction was then cooled to r.t and filtered. The filtrate was then diluted with EtOAc and washed with water. The aqueous layer was extracted with EtOAc (x3). The combined organic layer was washed with brine (x3), dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel using hexane–EtOAc (1.5:1→1:1) as the eluent furnished the pure compound **4-17** (yield=71%) with the following ratio of α:β (1.5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.49 (m, 2H), 7.37 - 7.35 (m, 8H), 5.50 (s, 1H), 4.95 (d, *J* = 3.8 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.21 (dd, *J* = 5.1, 10.7 Hz, 1H), 3.92 (t, *J* = 9.5 Hz, 1H), 3.86 - 3.81 (m, 1H), 3.69 (t, *J* = 10.7 Hz, 1H), 3.59 (dd, *J* = 3.8, 9.5 Hz, 1H), 3.46 (t, *J* = 9.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0, 136.7, 129.1, 128.5, 128.2, 128.1, 126.3, 101.8, 98.1, 80.9, 72.7, 71.5, 70.0, 68.8, 62.6. HRMS (ESI) calcd for $C_{20}H_{24}O_6Na$: 381.1314, found 381.1320 $(M+Na)^+$.

4.8.15 4,6-O-Benzylidene-2,3-O-methylnapthalene-1-O-benzyl-α-D-glucopyranoside (4-18)

To a solution of glucoside **4-17** (1.2 g, 3.3 mmol) in DMF (14 ml) was added NaH (0.32 g, 8.0 mmol) in portions followed by the addition of 2-bromomethylnapthalene (1.8 g, 8.0 mmol). The mixture was then stirred for 2 h at

r.t. After which, the reaction mixture was diluted with EtOAc and washed with water. The aqueous layer is then extracted with EtOAc (x3), and the combined organic layer was then washed with brine (x3). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel using hexane–EtOAc (12:1 → 10:1) as the eluent furnished the pure compound **4-18** (yield=90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.79 (m, 8H), 7.68 - 7.45 (m, 16H), 5.69 (s, 1H), 5.28 (d, *J* = 3.8 Hz, 1H), 5.19 (d, *J* = 12.0 Hz, 1H), 5.05 - 5.02 (m, 2H), 4.92 - 4.87 (m, 2H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.39 - 4.34 (m, 2H), 4.12 - 4.07 (m, 1H), 3.84 - 3.78 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 136.9, 136.3, 135.5, 133.2, 133.1, 128.8, 128.3, 128.2, 128.1, 128.1, 127.9, 127.8, 127.6, 127.5, 126.6, 126.4, 126.0, 126.0, 126.0, 125.8, 125.8, 125.7, 125.6, 101.2, 96.5, 82.1, 79.2, 78.6, 75.2, 73.3, 69.2, 68.9, 62.6. HRMS (ESI) calcd for $C_{42}H_{38}O_6Na$: 638.2668, found 638.2660 $(M+Na)^+$.

4.8.16 2,3-O-Methylnapthalene-1-O-benzyl-α-D-glucopyranoside (4-19)

To a solution of glucoside **4-18** (0.64 g, 1 mmol) in DCM (0.5 ml) was added 60% AcOH (0.5 ml). The mixture was microwaved at 110 ^{o}C for 15 min and then concentrated in vacuo. Purification of the crude product by column chromatography on silica gel using DCM followed by hexane–EtOAc (2:1) as the eluent furnished the pure compound **4-19** (yield=95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.74 (m, 8H), 7.52 - 7.36 (m, 11H), 5.24 (d, *J* = 12.0 Hz, 1H), 4.98 (d, *J* = 12.0 Hz, 1H), 4.92 (d, *J* = 3.2 Hz, 1H), 4.81 - 4.74 (m, 3H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.01 (t, *J* = 9.5 Hz, 1H), 3.77 - 3.60 (m, 5H), 2.97 (br s, 1H), 2.33

(br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 136.2, 135.4, 133.3, 133.1, 132.9, 132.9, 128.4, 128.2, 128.2, 128.1, 127.9, 127.8, 127.6, 127.6, 126.6, 126.4, 126.1, 126.0, 126.0, 125.8, 125.7, 125.7, 95.5, 81.3, 79.7, 75.3, 72.7, 71.1, 70.3, 69.1, 62.1. HRMS (ESI) calcd for $C_{35}H_{34}O_6Na$: 573.2253, found 573.2259 $(M+Na)^+$.

4.8.17 2,3-O-Methylnapthalene-1-O-benzyl-α-D-glucuronate methyl (4-20)

To a solution of glucoside **4-19** (2.82 g, 5.12 mmol) in DCM (51.2 ml) and water (25.6 ml) at 0 ^oC was added BAIB (4.13 g, 12.8 mmol) and TEMPO (0.16 g, 1.02 mmol). The mixture was stirred for 30 min at 0 ^oC before it was warmed up to r.t and stirred for another 1 h. The reaction mixture was quenched with 10% aqueous $Na_2S_2O_3$ and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product was then dissolved in DCM (25.1 ml) and MeOH (12.6 ml) followed by the dropwise addition of $TMSCH_2N_2$ (5.2 ml, 10.3 mmol) at r.t. The reaction mixture was then stirred at r.t for 15 min before AcOH was added dropwise to quench the reaction. The mixture is then diluted with DCM and then washed with $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel using hexane–EtOAc (2:1) as the eluent furnished the pure compound **4-20** (yield=80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.70 (m, 8H), 7.51 - 7.34 (m, 11H), 5.11 (d, *J* = 12.0 Hz, 1H), 5.02 (d, *J* = 12.0 Hz, 1H), 4.97 (d, *J* = 3.2 Hz, 1H), 4.85 - 4.73 (m, 2H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.27 (d, *J* = 9.5 Hz, 1H), 4.01 (t, *J* = 9.5 Hz, 1H), 3.88 (t, *J* = 9.5 Hz, 1H), 3.79 (s, 3H),

3.65 (dd, *J* = 3.8, 9.5 Hz, 1H), 3.05 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 136.8, 136.1, 135.3, 133.3, 133.2, 133.0, 133.0, 128.5, 128.3, 128.2, 128.0, 127.9, 127.9, 127.7, 127.6, 126.8, 126.5, 126.1, 126.0, 126.0, 125.9, 125.8, 125.8, 96.1, 80.3, 78.4, 75.4, 73.3, 71.9, 70.9, 69.7, 52.6. HRMS (ESI) calcd for $C_{36}H_{34}O_7Na$: 601.2202, found 601.2210 $(M+Na)^+$.

4.8.18 4-O-Acetyl-2,3-O-methylnapthalene-1-O-benzyl-α-D-glucuronate methyl (4-21)

To a solution of glucoside **4-20** (1.33 g, 2.3 mmol) in DCM (25 ml) at r.t was added DMAP (0.028 g, 0.23 mmol), Ac_2O (0.33 ml, 3.45 mmol) and TEA (0.96 ml, 6.9 mmol).The mixture was then stirred for 3 h. The reaction was quenched with MeOH and washed with saturated aqueous $NaHCO_3$. The aqueous layer was then extracted with DCM (x3) and the combined organic layer was then washed with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel using hexane–EtOAc (3:1) as the eluent furnished the pure compound **4-21** (yield=95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 – 7.67 (m, 8H), 7.67 – 7.25 (m, 11H), 5.44 – 5.25 (m, 1H), 5.20 – 4.89 (m, 5H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 6.6 Hz, 1H), 3.99 (d, *J* = 9.8 Hz, 1H), 3.94 – 3.45 (m, 5H), 1.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 167.9, 136.8, 135.5, 135.4, 133.1, 133.1, 132.9, 132.8, 128.4, 127.9, 127.8, 127.8, 127.5, 126.7, 126.3, 126.0, 125.9, 125.9, 125.8, 125.7, 102.1, 81.2, 80.9, 75.1, 74.8, 72.7, 71.2, 71.1, 52.6, 20.5. HRMS (ESI) calcd for $C_{38}H_{36}O_8Na$: 643.2308, found 643.2315 $(M+Na)^+$.

4.8.19 4-O-Acetyl-1-O-benzyl-α-D-glucuronate methyl (4-22)

To a solution of glucoside **4-21** (1.38 g, 2.22 mmol) in DCM (20 ml) and MeOH (5 ml) at r.t was added DDQ (1.52 g, 6.67 mmol).The mixture was then stirred for 3 h prior to the addition of aqueous saturated $Na_2S_2O_3$ to quench the reaction. The reaction mixture was then diluted with EtOAc and aqueous saturated $NaHCO_3$, and extracted with EtOAc (x3). The organic layer was washed with brine (x3), dried with Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by column chromatography on silica gel using hexane–EtOAc (2:1) as the eluent furnished the pure compound **4-22** (yield=91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.24 (m, 5H), 5.03 (d, *J* = 4.0 Hz, 1H), 4.93 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.39 (d, *J* = 7.7 Hz, 1H), 3.90 (d, *J* = 9.8 Hz, 1H), 3.74 (d, *J* = 7.8 Hz, 3H), 3.66 (t, *J* = 9.2 Hz, 1H), 3.58 – 3.47 (m, 1H), 3.27 (s, 2H), 2.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 167.9, 136.6, 128.5, 128.2, 128.1, 101.3, 73.8, 73.5, 72.9, 71.6, 71.3, 52.7, 20.7. HRMS (ESI) calcd for $C_{16}H_{20}O_8Na$: 363.1056, found 363.1063 $(M+Na)^+$.

4.8.20 4-O-Acetyl-2,3-O-trimethylsilane-1-O-benzyl-α-D-glucuronate methyl (4-23)

To a solution of compound **4-22** (0.6 g, 1.76 mmol) in DMF (1.4 ml) was added imidazole (1.19 g, 17.5 mmol) and TMSCl (1.11 ml, 8.76 mmol). The reaction mixture was stirred at 80 ^{o}C for 2 h. Thereafter, the reaction was cooled to r.t, diluted with EtOAc and washed with water. The aqueous layer was extracted with EtOAc (x3), and the combined organic layer was washed with brine (x3), dried

with Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by column chromatography on silica gel using hexane–EtOAc (10:1) as the eluent furnished the pure compound **4-23** (yield=91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 5H), 4.95 – 4.84 (m, 2H), 4.75 (d, *J* = 12.5 Hz, 1H), 4.57 (d, *J* = 12.5 Hz, 1H), 4.23 (d, *J* = 10.1 Hz, 1H), 4.02 (t, *J* = 8.9 Hz, 1H), 3.72 (d, *J* = 4.8 Hz, 3H), 3.61 (dd, *J* = 9.0, 3.6 Hz, 1H), 2.06 (s, 3H), 0.11 (s, 9H), 0.03 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 169.0, 136.9, 128.3, 128.1, 127.9, 98.1, 72.7, 72.4, 71.8, 69.8, 69.0, 52.6, 20.8, 0.6, 0.0. HRMS (ESI) calcd for $C_{22}H_{36}O_8Si_2Na$: 507.1846, found 507.1857 $(M+Na)^+$.

4.8.21 4-O-Acetyl-2,3-O-acetoxyacetal-1-O-benzyl-α-D-glucuronate methyl (4-24)

To a solution of compound **4-23** (0.22 g, 0.45 mmol) in DCM (0.44 ml) was added acetoxyacetone (0.15 ml, 1.8 mmol) and 4Å MS (0.2 g). The mixture was allowed to stir at r.t for 1 h. Thereafter, the reaction mixture was then cooled to -50 ^{o}C prior to the addition of TMSOTf (32.6 µl, 0.18 mmol) and TfOH (0.797 µl, 0.00902 mmol) in DCM (0.42 ml). The reaction mixture was the allowed to stir for another 16 h before TEA (0.1 ml) was added to quench the reaction. The reaction mixture was then diluted with EtOAc and washed with brine. The aqueous layer was extracted with EtOAc (x3) and the combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel using hexane–EtOAc (5:1→3:1→1.5:1) as the eluent furnished the pure compound **4-24** (yield=90%). ^{1}H NMR (500 MHz,

$CDCl_3$) δ 7.47 – 7.24 (m, 10H), 5.41-5.39 (m, 1H), 5.32-5.28 (m, 1H), 5.22 – 5.12 (m, 1H), 5.09-5.06 (m, 1H), 4.81-4.78 (m, 1H), 4.70-4.65 (m, 1H), 4.35-4.21 (m, 1H), 4.13-4.03 (m, 2H), 3.96-3.93 (m, 1H), 3.77-3.69 (m, 1H), 2.09-1.95 (m, 3H), 1.83-1.82 (m, 3H), 1.46=1.42 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 169.6, 167.9, 136.7, 136.6, 134.8, 128.9, 128.7, 128.6, 128.6, 128.5, 128.1, 128.1, 127.9, 127.8, 109.8, 109.7, 96.8, 96.7, 76.1, 75.3, 74.5, 73.5, 71.8, 71.5, 70.8, 70.8, 70.2, 70.1, 67.9, 66.7, 66.4, 22.6, 22.4, 20.9, 20.7, 20.6. HRMS (ESI) calcd for $C_{21}H_{26}O_{10}Na$: 461.1424, found 461.1433 $(M+Na)^+$.

4.8.22 2,3-O-(S)-Propanolacetal-1-O-benzyl-α-D-glucuronate methyl (4-25)

To a solution of **4-24** (0.16 g, 0.368 mmol) in MeOH (1.4 ml) was added NaOMe (0.0079 g, 0.147 mmol). The reaction mixture was stirred for 10 min prior to the addition of Amberlyst 15 to quench the reaction. The organic layer was filtered and concentrated under reduced pressure. Purification of the crude product by column chromatography on silica gel using DCM–EtOAc (20:1) with 1% TEA as the eluent furnished the pure compound **4-25** (yield=75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.26 (m, 6H), 5.38 (d, *J* = 3.0 Hz, 1H), 5.30 (s, 1H), 4.84 (d, *J* = 12.1 Hz, 1H), 4.69 (d, *J* = 12.1 Hz, 1H), 4.29 (t, *J* = 9.7 Hz, 1H), 4.10 (t, *J* = 9.5 Hz, 1H), 4.00 (d, *J* = 9.2 Hz, 1H), 3.84 (s, 3H), 3.69 – 3.54 (m, 3H), 1.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 136.6, 128.6, 128.1, 127.6, 111.5, 96.9, 76.6, 75.1, 72.3, 72.0, 70.5, 67.0, 52.9, 22.3. HRMS (ESI) calcd for $C_{17}H_{22}O_8Na$: 377.1212, found 377.1216 $(M+Na)^+$.

4.8.23 2,3-O-(S)-Methylpyruvate-1-O-benzyl-α-D-glucuronate methyl (4-26)

To a solution of glucoside **4-25** (0.113 g, 0.319 mmol) in DCM (3.2 ml) and water (1.6 ml) at 0 ^{o}C was added BAIB (0.257 g, 0.798 mmol) and TEMPO (0.01 g, 0.0638 mmol). The mixture was then stirred for 30 min before it was warmed up to r.t and stirred for another 5 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product was then dissolved in DCM (1.6 ml) and MeOH (0.8 ml) followed by the dropwise addition of $TMSCH_2N_2$ (0.32 ml, 0.638 mmol) at r.t. The reaction mixture was stirred at r.t for 15 min before AcOH was added dropwise to quench the reaction. The mixture is then diluted with DCM and then washed with $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel using hexane–EtOAc (2:1) as the eluent furnished the pure compound **4-26** (yield=80%). ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 7.76 – 7.04 (m, 6H), 5.38 (d, *J* = 2.9 Hz, 1H), 4.84 (d, J=12.6, 1H), 4.69 (d, J=12 Hz, 1H), 4.34 (t, *J* = 9.7 Hz, 1H), 4.11 (t, J = 5.0 Hz, 1H), 3.98 (d, J = 5.0 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.60 (dd, *J* = 9.7, 2.9 Hz, 1H), 1.60 (s, 3H). ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 169.5, 169.2, 137.6, 128.3, 127.5, 127.3, 96.8, 78.2, 75.4, 73.3, 71.7, 69.6, 51.6, 22.1, 22.1. HRMS (ESI) calcd for $C_{18}H_{22}O_9Na$: 405.1162, found 405.1161 $(M+Na)^+$.

4.8.24 Building Block 4-27

To a solution of thioglucoside **4-7** (0.12 g, 0.27 mmol) and compound **4-26** (98.6 mg, 0.258 mmol) in DCM (3 ml) was added NIS (0.097 g, 0.435 mmol) with 4Å MS (0.6 g). The mixture was allowed to stir at r.t for 1 h. Thereafter, the reaction mixture was cooled to -5 ^{o}C prior to the addition of TfOH (14.4 µl, 0.163 mmol) in DCM (1 ml). The reaction mixture was then stirred for another 1 h before TEA (0.1 ml) was added to quench the reaction. The reaction mixture was then diluted with EtOAc and washed with aqueous saturated $Na_2S_2O_3$ followed by brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel using hexane–EtOAc (2:1) as the eluent furnished the pure compound **4-27** (yield=78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.29 (m, 10H), 5.48 (s, 1H), 5.33 (d, *J* = 3.2 Hz, 1H), 5.29 (t, *J* = 9.5 Hz, 1H), 5.15 (d, *J* = 12.1 Hz, 1H), 5.00 – 4.93 (m, 1H), 4.77 (d, *J* = 12.3 Hz, 1H), 4.71 (d, *J* = 7.9 Hz, 1H), 4.67 (d, *J* = 12.3 Hz, 1H), 4.47 (t, *J* = 9.7 Hz, 1H), 4.36 – 4.19 (m, 2H), 4.05 (d, *J* = 9.3 Hz, 1H), 3.70 (d, *J* = 19.2 Hz, 2H), 3.58 (dd, *J* = 9.7, 2.8 Hz, 1H), 3.43 (td, *J* = 9.8, 5.0 Hz, 1H), 2.07 (d, *J* = 7.9 Hz, 6H), 1.63 (d, *J* = 35.1 Hz, 7H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 169.6, 168.4, 168.3, 136.9, 136.5, 135.3, 135.0, 128.7, 128.7, 128.6, 128.5, 128.2, 128.2, 127.9, 127.8, 127.6, 126.1, 106.5, 101.4, 100.2, 96.3, 78.8, 78.1, 76.6, 75.4, 72.1, 71.9, 71.3, 70.4, 68.4, 67.6, 67.1, 66.4, 22.6, 20.5. HRMS (ESI) calcd for $C_{35}H_{40}O_{16}Na$: 739.2214, found 739.2216 $(M+Na)^{+}$.

4.8.25 Building Block 4-28

To a solution of disaccharide **4-27** (0.101 g, 0.141 mmol) in THF (1 ml) was added 10% NaOH (1 ml). The reaction mixture was then microwave at 110 ^{o}C for 7 min. The reaction mixture was then cooled to 0 ^{o}C in an ice-bath prior to the dropwise addition of 1 M HCl until the solution is pH~2. The reaction mixture was then extracted diluted with EtOAc (x3) and the organic layer was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product was then dissolved in DMF (1.4 ml) and $NaHCO_3$ (0.0712 g, 0.848 mmol) was added to the mixture followed by TBAI (0.0261 g, 0.0706 mmol) and BnBr (50.5 µl, 0.424 mmol). The reaction was heated to 90 ^{o}C and allowed to stir for 10 min. Thereafter, the reaction mixture was cooled to r.t., diluted with water and extracted with EtOAc (x3). The organic layer was washed with brine (x3), dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel using hexane–EtOAc (1.5:1) as the eluent furnished the pure compound **4-28** (yield=67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.47 (m, 2H), 7.4 – 7.08 (m, 18H), 5.49 (s, 1H), 5.37 (d, *J* = 3.0 Hz, 1H), 5.28 – 5.16 (m, 4H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.43 (d, *J* = 7.8 Hz, 1H), 4.24 – 4.06 (m, 4H), 3.85 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.72 (m, 2H), 3.50 (t, *J* = 9.3 Hz, 1H), 3.43 (t, *J* = 8.1 Hz, 1H), 3.32 (m, 1H), 1.67 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 168.5, 136.9, 136.3, 135.2, 134.9, 129.2, 128.7, 128.6, 128.5, 128.5, 128.5, 128.3, 128.1, 127.9, 127.9, 126.3, 106.5, 102.6, 101.8, 96.3, 80.2, 78.1, 77.3, 77.0, 76.8, 76.6, 75.2, 74.1, 73.0, 71.2,

70.5, 68.4, 67.6, 67.3, 66.6, 22.4. HRMS (ESI) calcd for $C_{43}H_{44}O_{14}Na$: 807.2629, found 807.2633 $(M+Na)^+$.

4.8.26 Building Block 4-29

To a solution of disaccharide **4-28** (58.3 mg, 0.0743 mmol) in benzene (0.44 ml) and MeOH (44 µl) was added Bu_2SnO (22.1 mg, 0.0891 mmol) and refluxed for 2 h. Thereafter, the reaction mixture was concentrated in vacuo and the crude mixture was dissolved in DMF (0.12 ml) followed by the addition of BnBr (41.2 µl, 0.347 mmol) in 3 portions at every 40 min interval while maintaining the temperature at 100 ^oC. The reaction mixture was then allowed to cool to r.t., diluted with water and extracted with EtOAc (x3). The organic layer was washed with brine (x3), dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel using hexane–EtOAc (4:1→3:1) as the eluent furnished the pure compound **4-29** (yield=58%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.10 (m, 25H), 5.50 (s, 1H), 5.33 (d, *J* = 2.9 Hz, 1H), 5.24 – 5.17 (m, 5H), 4.91 (d, *J* = 11.8 Hz, 1H), 4.82 (d, *J* = 11.8 Hz, 2H), 4.76 (d, *J* = 12.3 Hz, 1H), 4.66 (d, *J* = 12.1 Hz, 2H), 4.49 – 4.45 (m, 2H), 4.25 (t, *J* = 9.5 Hz, 1H), 4.21- 4.10 (m, 4H), 3.70 – 3.54 (m, 5H), 1.63 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 168.4, 138.4, 137.4, 136.3, 135.3, 134.9, 128.9, 128.7, 128.6, 128.5, 128.5, 128.5, 128.3, 128.2, 128.2, 128.0, 128.0, 127.9, 127.8, 127.7, 127.6, 126.3, 126.0, 106.5, 102.6, 101.2, 96.4, 81.0, 80.1, 78.0, 75.34 74.5, 74.3, 71.3, 70.4, 68.5, 67.5, 67.1, 66.6, 22.6. HRMS (ESI) calcd for $C_{50}H_{50}O_{14}Na$: 897.3098, found 897.3096 $(M+Na)^+$.

4.8.27 Building Block 4-30

To a solution of trichloroacetimidate **4-15** (12.3 mg, 0.0232 mmol) and disaccharide **4-29** (7.8 mg, 0.00892 mmol) in DCM (0.1 ml) was added with 4Å MS (0.1 g). The mixture was stirred at r.t for 15 min, then cooled to -5 ^{o}C. TMSOTf (0.134 µl, 0.000731 mmol) in DCM (0.1 ml) was added and the reaction mixture was allowed to stir for another 1 h. Thereafter TEA (0.01 ml) was added to quench the reaction. The reaction mixture was then filtered, dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel using hexane–EtOAc (3:1→2:1) as the eluent furnished the pure trisaccharide **4-30** (yield=63%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.39 (m, 2H), 7.36 – 7.27 (m, 19H), 7.25 – 7.16 (m, 13H), 7.07 – 7.05 (m, 1H), 5.49 (s, 1H), 5.46 (d, *J* = 3.6 Hz, 1H), 5.33 (d, *J* = 2.9 Hz, 1H), 5.30 – 5.24 (m, 3H), 5.18 (s, 2H), 4.86 (d, *J* = 12.1 Hz, 1H), 4.80 (d, *J* = 12.1 Hz, 1H), 4.66 (d, *J* = 12.1 Hz, 1H), 4.55 (d, *J* = 12.5 Hz, 1H), 4.52 – 4.44 (m, 3H), 4.41 (d, J = 8.3 Hz, 1H), 4.39 – 4.29 (m, 3H), 4.25 – 4.22 (m, 2H), 4.20 – 4.09 (m, 3H), 3.91 (dd, *J* = 10.7, 3.6 Hz, 1H), 3.85 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.72 – 3.65 (m, 3H), 3.65 – 3.58 (m, 1H), 3.56 (m, 1H), 1.91 (s, 1H), 1.32 (s, 1H), 0.67 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 169.1, 168.5, 138.2, 138.1, 138.0, 137.3, 136.4, 135.2, 134.6, 129.0, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.9, 127.6, 127.4, 127.3, 127.3, 126.6, 126.4, 106.6, 102.0, 97.3, 96.4, 96.0, 79.5, 79.4, 78.9, 76.3, 75.8, 75.5, 73.5, 73.1, 72.8, 72.0, 71.1, 71.0, 70.5, 68.6, 68.1, 67.2, 65.7, 63.2, 60.4, 21.9, 21.0, 15.6. HRMS (ESI) calcd for $C_{73}H_{77}O_{19}Na$: 1265.4735, found 1265.4726 $(M+Na)^{+}$.

4.8.28 Trisaccharide 4-1

Trisaccharide **4-30** (33 mg, 0.0266 mmol) was dissolved in EtOAc (0.6 ml), MeOH (0.3 ml) and H_2O (0.3 ml) (that has been bubbled with H_2 gas for 15 min) followed by the addition of 10% Pd/C (0.1 g) and stirred at r.t for 21 h. The reaction was then filtered through a short pad of Celite, washed with reaction solvent of EtOAc:MeOH:$H_2$0 (2:1:1) as eluent and concentrated in vacuo to furnish the pure trisaccharide **4-1** (yield=95%). ^{1}H NMR (500 MHz, D_2O) δ 5.45 (s, 1H), 5.28 – 5.08 (m, 2H), 4.99 (d, *J* = 6.0 Hz, 1H), 4.68 – 4.57 (m, 2H), 4.48 – 4.38 (m, 2H), 4.36 – 4.23 (m, 2H), 4.15 (d, *J* = 7.5 Hz, 2H), 4.07 – 3.87 (m, 3H), 3.81 – 3.70 (m, 4H), 3.72 – 3.60 (m, 4H), 3.55 – 3.39 (m, 4H), 2.19 (s, 3H), 1.59 (s, 3H), 1.26 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 107.4, 101.0, 89.8, 77.6, 77.1, 75.9, 74.4, 73.7, 73.4, 73.0, 69.8, 69.3, 66.6, 61.7, 60.5, 60.1, 22.4, 20.5, 15.4. HRMS (ESI) calcd for $C_{23}H_{33}O_{19}$: 613.1622, found 613.1610 $(M-1)^+$.

4.9 References

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