2010

Green Chemistry Using Bismuth(III) Salts: Synthesis of Cyclic Acetals and Allylation of Tetrahydropyranyl Ethers and Aldehydes

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Chemistry Research Honors Thesis
Illinois Wesleyan University
April 19, 2010

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Synthesis of Cyclic Acetals and Allylation of Tetrahydropyranyl Ethers and Aldehydes

By

Scott W. Krabbe

A Paper Submitted As Part of The Requirement For Research Honors In Chemistry

Approved:

Professor Ram S. Mohan, Research advisor

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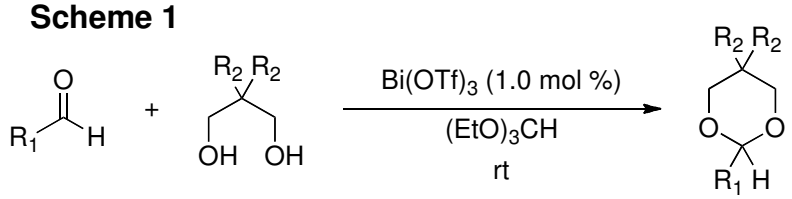
Abstract

Research in our group focuses on environmentally friendly organic synthesis using bismuth compounds. With increasing environmental concerns, the need for environmentally friendly organic synthesis following Green Chemistry principles has assumed increased importance. The *Pollution Prevention Act*, passed in 1990, has been especially important in increasing an interest in Green Chemistry, which is the design and redesign of chemical processes with the goals of improving safety and minimizing environmental impact. Our group focuses on synthetic methodology i.e the transformation of one functional group to another. Such transformations are of special relevance in the pharmaceutical industry where they are used in the manufacture of life saving drugs. Many of the current organic synthesis methods utilize toxic and corrosive catalysts and reagents. In contrast, methods utilizing bismuth(III) salts are environmentally friendly because most bismuth compounds are non-toxic, non-corrosive, and inexpensive..

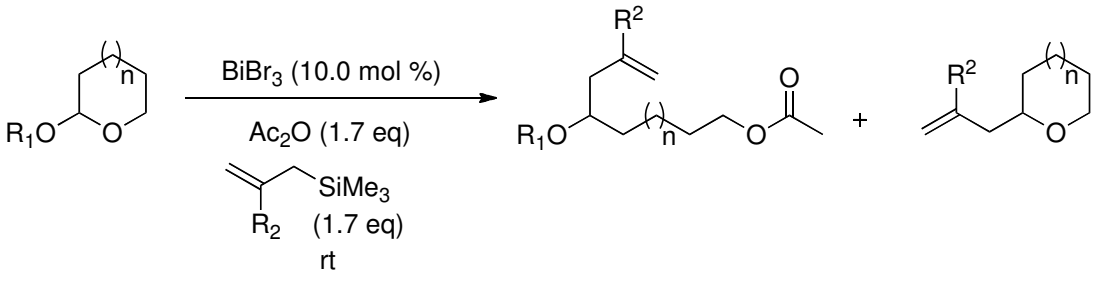
The goal of this project was to utilize bismuth(III) bromide and bismuth(III) triflate as catalysts for the synthesis of cyclic acetals (Scheme 1), the allylation of tetrahydropyranyl and tetrahydrofuranyl ethers (Scheme 2), and the allylation of aldehydes (Scheme 3). All of these processes utilize many Green Chemistry principles such as the use of non-toxic reagents, room temperature reaction conditions and, at times, solvent-free conditions (Schemes 1 and 2).

Summary of Reactions

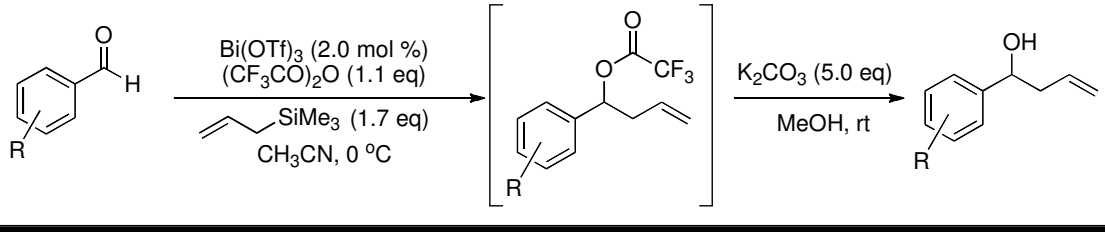
Scheme 1



Scheme 2



Scheme 3



Acknowledgements

First and foremost**,** I would like to thank my research advisor, Dr. Ram Mohan, for all of his support and encouragement over the past three years. Had it not been for his guidance, I would not have had the plethora of excellent opportunities that have become available to me. I am extremely grateful for the countless hours he has spent training me as a scientist and the many opportunities he has given me to attend national meetings. I am also indebted to him for his careful editing of multiple drafts of this dissertation.

I would also like to thank Dr. Brian Brennan, Dr. Rebecca Roesner, and Dr. Zahia Drici for taking their time to be on my thesis committee.

An important thanks goes to the members of the research group over the past few years. First and foremost I would like to thank Jason Bothwell, Maggie Olson, and Long Le for spending some long hours with me over our first summer of research and their continued support throughout our time here at IWU. I am indebted to Jamie Rogers, Kendall Tasche, Jay Christensen, and Herbie Yung for their patience as I followed them around like a lost puppy during my first few months in lab. I would like to thank Dan Podgorski, Veronica Angeles, Paul Sierszulski, Phil Lazarra, Julia Martino, Kyle Beasley, and Matt Berg for making lab an enjoyable place to be as I wrote this thesis. I'd also like to thank Pash DeVore for teaching me how to keep a clean hood and Matt Spafford for his guidance in pursuing research honors.

I would like to thank Cindy Honegger for all her help in the stockroom over the past few years.

A special thanks is in order for my girlfriend, Courtney Gabelhausen, for keeping me sane and always having dinner ready as I spent long hours in lab.

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I. Introduction

A. Green Chemistry Using Bismuth(III) Catalysis

Nearly all aspects of our day-to-day life are affected by chemistry. From the toothpaste we use to brush our teeth to the beds where we lie down to rest, chemistry has played a vital role in bringing it all to be.

A vital aspect of our lives that has been greatly influenced by chemistry is the production of food. In 1898, Sir William Crookes (inventor of the Crookes Tube) warned that, "England and all civilized nations stand in deadly peril" due to an increasing number of people to feed and no viable ways to increase crop yields. Crookes believed that synthetic fertilizer was the answer, and that "it was the chemist who must come to the rescue." Ultimately, two chemists (Fritz Haber and Carl Bosch) invented and industrialized a process, which took the seemingly inert gas, nitrogen (N_2) from the environment and transform it into ammonia (NH_3). Unlike N_2, the 'fixed' nitrogen of NH_3 could be used directly to fertilize crops. This process greatly changed farming practices throughout the world and by 1960, 90 % of the fixed nitrogen used by U.S. farmers came from Haber-Bosch plants. The scale on which the Haber-Bosch process is used today is quite astonishing. The largest plant in the U.S. (Donaldsonville, Louisiana) produces 1.55 million tons of NH_3 annually.[i]

The complete revolution of food production is only one of the untold improvements to human life attributable to chemistry. Numerous innovations in the medical field have also improved our quality of life. Hundreds of synthetic compounds have been discovered and used as antibiotics, antivirals, and as cures for diseases once

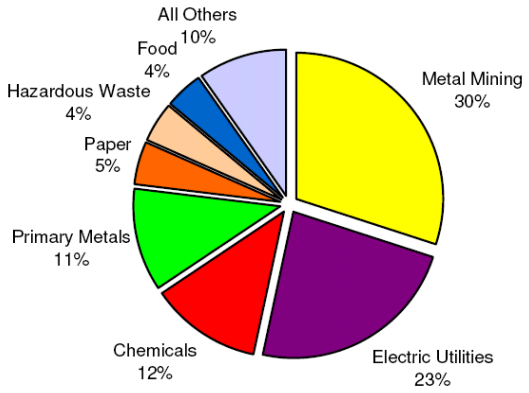
thought incurable. Because of these innovations the average life expectancy has gone up from a mere 47 years[ii] in 1900 to 78 years in 2010.[iii]

Of course, the many benefits of chemistry have come with a cost. "The manufacture, use and disposal of synthetic chemicals" has had a profound impact on "human health and the environment."[2] Unfortunately, the negative effects of our actions are often not always noticed until a major disaster occurs. In December 1984, a malfunctioning tank at a Union Carbide pesticide plant in Bhopal, India released 42 tons of methyl isocyanate and hydrogen cyanide as toxic fumes.[iv] The gas cloud emitted was composed primarily of gases denser than air and thus stayed close to the ground and spread throughout the surrounding communities. The number of people who perished because of this release is estimated to be 8,000-30,000 within the first few days. In addition several hundred thousand people suffered long-term effects. There were many factors that contributed to the problem, but the magnitude of the disaster would have been less if safer chemicals were used in the pesticide production. Safer processes, which did not require the storage of the toxic gas methyl isocyanate, were being used by other companies such as Bayer for the production of Sevin (a wide spectrum carbamate insecticide which controls over 100 species of insects).[v] Sadly, Union Carbide did not use this safer approach because it was not as profitable.

In order to decrease the negative impacts that synthetic chemicals have on human health and the environment, it is important to know which chemicals are being released into the environment. The *Toxic Release Inventory* (TRI), implemented by the United States in 1986 due to outrage over the Union Carbide chemical release and an accident in West Virginia,[vi] keeps track of nearly 650 chemicals released to the environment each

year. In 2008, 12 % of the 3.86 billion pounds of waste released to the environment was classified as chemical (Figure 1).[vii]

Figure 1 TRI Total Disposal for 2008



Knowing the amounts of hundreds of chemicals released to the environment is an excellent resource, but this information does not address the more serious problem. The production and release of toxic chemicals must be avoided whenever possible. The necessary legislation passed in the United States Congress in 1990 as the *Pollution Prevention Act* (PPA). This legislation set forth that the national environmental policy was to prevent waste at its source by "utilizing a variety of methodologies and techniques" to prevent pollution, and thereby obviate the "need for any further treatment or control of chemical substances."[viii] Of course, this proposition is a monumental task, and will require collaboration between several areas of science.

One approach to preventing pollution is to practice *Green Chemistry*. Paul Anastas, currently a professor at Yale University, first coined the term *Green Chemistry* and defined it as "the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products."[2] Pollution prevention is only one aspect of *Green Chemistry*.

The reduction of risk, to both the practicing chemist and anyone else who could be exposed to waste, is the main goal of *Green Chemistry*. Risk is a function of both the hazard of and the exposure to a chemical substance or process (equation 1).

Equation 1: Formulation of Risk

$$\textbf{Risk} = f\,[\textbf{hazard, exposure}]$$

The traditional approach to lowering the risk associated with handling a chemical is to reduce the exposure a person has to chemical in question. Thus with a known level of hazard and a decreased amount of exposure, the level of risk is reduced. Unfortunately, exposure controls only benefits those people who are working directly with the chemicals. The release of a toxic chemical could also affect people downwind or downstream who are not wearing protective clothing. Another drawback of this approach to lowering risk is that exposure control measures can fail. For example no piece of protective clothing is 100 % effective in preventing exposure. In addition, flaws in the protecting gear, equipment failure, and accidental releases during shipping can greatly increase exposure and hence risk. Thus the *Green Chemistry* approach to lowering risk is to reduce the hazards associated with the chemicals and processes used. The reduction of the hazard can be achieved by following the twelve principles of green chemistry, which were first developed by Dr. Anastas.[2]

Principles of Green Chemistry

1. *It is better to prevent waste than to treat or clean up waste after it is formed.*
2. *Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.*

3. *Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.*
4. *Chemical products should be designed to preserve efficacy of function while reducing toxicity.*
5. *The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and, innocuous when used.*
6. *Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.*
7. *A raw material of feedstock should be renewable rather than depleting wherever technically and economically practicable.*
8. *Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.*
9. *Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.*
10. *Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.*
11. *Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.*

12. *Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.*

Unfortunately, scientists and engineers do not yet have the tools and strategies to bring these principles into universal practice. As new chemistry that is focused on green principles is discovered and understood, we move closer to this goal. Even though all of the principles of *Green Chemistry* cannot be applied in all cases at this time, applying even one or two of the principles can make a given process significantly more environmentally friendly.

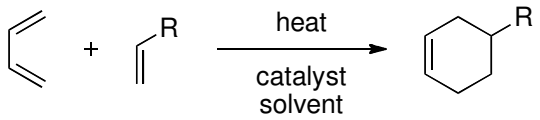
The second *Green Chemistry* principle, atom economy, was pioneered by Barry Trost and is especially relevant to organic synthesis.[ix] Atom economy is a measure of the amount of starting material that is incorporated into the desired product.

$$\textit{Atom Economy} = \frac{\textit{Molecular Weight of Desired Product}}{\textit{Molecular Weight of All Reactants}} \times 100\ \%$$

This metric is not perfect, because the solvents and catalysts required for the synthesis are not taken into account and these contribute significantly to the waste. Even though this metric is flawed, it does provide useful information about the efficiency of a synthesis.

The Diels-Alder cycloaddition,[x] developed by Otto Paul Hermann Diels and Kurt Alder in 1928, is a classic example of a reaction with 100% atom economy (Scheme 1.1). The cyclized product contains all of the atoms present in the two starting materials. The only chemical waste resulting from this classic reaction comes from the use of solvents or catalysts. Remarkably, the Diels-Alder reaction can often be run solvent free without the need for a catalyst.

Scheme 1.1 Diels-Alder Cylcoaddition



Atom economical processes require fewer raw materials and also decrease the amount of waste produced. Thus the chemical industry can often reduce costs by requiring fewer raw materials and spending less on the treatment of potentially hazardous waste products.

The concept of *E* (environmental) factor was introduced by Roger Sheldon in 1992 to assess the impact of chemical processes on the environment.[xi] The *E* factor is defined as the amount of waste associated with a process divided by the amount of the desired product produced.

$$E\ factor = \frac{mass\ of\ waste\ produced}{mass\ of\ product\ produced}$$

Sheldon determined the *E* factor for several different chemical industries (Table 1.1). The *E* factors associated with the production of fine chemicals and pharmaceutical synthesis were much larger than those found for much more efficient industries, such as oil refining and bulk chemical synthesis. The production of large amounts of waste in the pharmaceutical industry is not cost effective and threatens the environment.

Table 1.1 *E* Factors of Selected Chemical Industries

Industry Sector	Product Produced (Tons)	E Factor (Kg waste/kg product)
Oil refining	$10^6 – 10^8$	< 0.1
Bulk chemicals	$10^4 – 10^6$	< 1 – 5
Fine chemicals	$10^2 – 10^4$	5 – 50
Pharmaceuticals	$10 – 10^3$	25 – 100

In order for an industry to reduce the amount of waste they produce, new and greener methods of organic synthesis must be developed and adopted. Research in our laboratory focuses on green chemistry with particular emphasis on environmentally friendly organic methodology. Specifically, we have developed several applications of bismuth(III) compounds as catalysts in organic synthesis.

Bismuth is the 83rd element in the periodic table with a natural abundance in the earth's crust of just 48 parts per billion, making bismuth the 70th most abundant element out of 112 elements. Although bismuth's relative abundance is low compared to many other elements, bismuth compounds are inexpensive because bismuth is a by-product of copper and lead smelting (Table 1.2).

On the periodic table, bismuth neighbors several toxic elements such as antimony, tin, lead and mercury and hence one might expect bismuth to display comparable toxicity. However, bismuth is remarkably non-toxic and has earned itself the status of a "Green" element.[xii] One plausible explanation for the non-toxicity of bismuth is its poor coordinating ability which prevents interaction with many biomolecules.

Table 1.2 Availability of Bismuth(III) Compounds and Comparable Lewis Acids[xiii]

Lewis Acid	Cost/g ($)	Cost/mol ($)
Bismuth Bromide, $BiBr_3$	1.10	491
Bismuth Triflate, $Bi(OTf)_3$	7.61	4993
Bismuth Iodide, BiI_3	2.70	997
Bismuth Chloride, $BiCl_3$	2.34	380
Bismuth Nitrate, $Bi(NO_3)_3$	0.33	108
Bismuth Oxide, Bi_2O_3	0.44	142
Bismuth Oxychloride, BiOCl	0.89	162
Scandium Triflate, $Sc(OTf)_3$	36	17816
Ytterbium Triflate, $Yb(OTf)_3$	36	22391
Trimethylsilyltriflate, TMSOTf	1.90	432
Titanium Tetrachloride, $TiCl_4$	0.13	25

The toxicity of a compound can be measured by determining the lethal dose for 50 % of the population under study (LD_{50}). Mercury(II) chloride, a compound known to be quite toxic, damages sulfur containing amino acids such as cysteine and also accumulates in the liver and kidneys.[xiv] Mercury(II) chloride has an LD_{50} value of 0.001 g/kg, while the relatively non-toxic sodium chloride, common table salt, has an LD_{50} value of 3.8 g/kg. Many bismuth compounds have LD_{50} values even higher than common table salt (Table 1.3). This means that many bismuth compounds are even less toxic than common table salt!

Table 1.3 LD_{50} Values of Selected Bismuth and Related Compounds

Compound	LD_{50} (g/kg)	Species, Route
Sodium chloride, NaCl	3.8	Rat, oral
Mercury chloride, $HgCl_2$	0.001	Rat, oral
Bismuth oxide, Bi_2O_3	5.0	Rat, oral
Bismuth nitrate, $Bi(NO_3)_3$	4.4	Rat, oral
Bismuth oxychloride, BiOCl	22	Rat, oral
Bismuth chloride, $BiCl_3$	3.3	Rat, oral
Indium chloride, $InCl_3$	1.1	Rat, oral
Scandium chloride, $ScCl_3$	3.9	Rat, oral
Cerium chloride, $CeCl_3$	2.1	Rat, oral
Samarium chloride, $SmCl_3$	2.9	Rat, oral
Ytterbium chloride, $YbCl_3$	4.8	Rat, oral

The non-toxicity of bismuth(III) compounds has been taken advantage of by many consumer based industries and bismuth compounds have also found several applications in the medicinal chemistry world (Figure 2).

Figure 2 Bismuth Compounds in Everyday Products

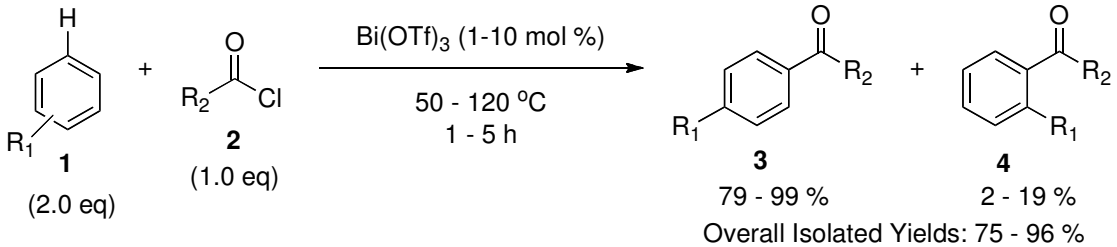
Bismuth subsalicylate is the active ingredient of Pepto-Bismol®, the well-known medication for upset stomach. Bismuthyl chloride, BiOCl is an extremely non-toxic solid

which gives shine to nail polishes. Bismuth subnitrate is used as a wound dressing and as an ointment component for inflamed skin. Bismuth subcitrate is the only known compound active against *Helicobacter pylori*, a bacterium that causes ulcers.[xv] Bismuth is one of two metals, approved by the FDA, for use in shotgun shells for waterfowl hunting. The other approved metal is 'steel' (soft iron), and it does not perform as well as the bismuth containing shells due to its lower density. In this application, bismuth replaces the extremely toxic element lead, which is banned because it was found to contaminate ground water and the pellets were eaten by birds that mistook them for grit.

The electron configuration of bismuth is $[Xe]4f^{14}5d^{10}6s^{2}6p^{3}$. Due to poor shielding of the 4*f* electrons (Lanthanide contraction),[xvi] bismuth(III) compounds exhibit Lewis acidity, a property that has been utilized in organic synthesis. These applications of bismuth compounds have been summarized in excellent reviews.[xvii] The following selected examples are well-known Named Organic Reactions or reactions relevant to this honors project.

The Friedel-Crafts acylation, often promoted by Lewis acids such as aluminum chloride, is an important way to derivatize substituted benzenes. While aluminum chloride is inexpensive, it is required in stoichiometric amounts due to its strong complexation to the arylketone product formed. To circumvent this problem, a bismuth(III) triflate catalyzed method has been developed (Scheme 1.2).[xviii]

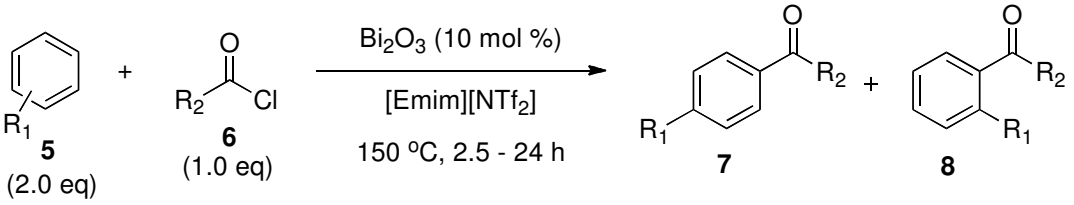
Scheme 1.2



R_1 = OCF_3, OCH_3, CH_3, F, H, Cl
R_2 = Ph, Me, Me_2CH

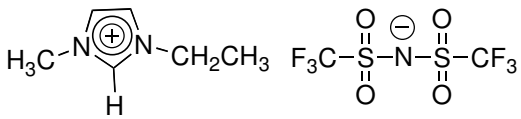
In all cases the major product was a 4-substituted phenone **3**, with the corresponding 2-substituted phenone **4** forming in small amounts. This catalytic method proved useful for the benzoylation of both activated (R_1 = OCF_3, OCH_3, CH_3) and deactivated substrates (R_1 = F, Cl). Friedel-Crafts acylation and benzoylation of aromatic compounds in ionic liquids have been reported by Vaultier (Scheme 1.3).[xix]

Scheme 1.3



R_1 = Ph, CH_3Ph, ClPh
R_2 = Ph ---------- *p*:*o* = 79:19
Me ---------- *p*:*o* = 96:4

Overall Yield: 62 - 91 %



9

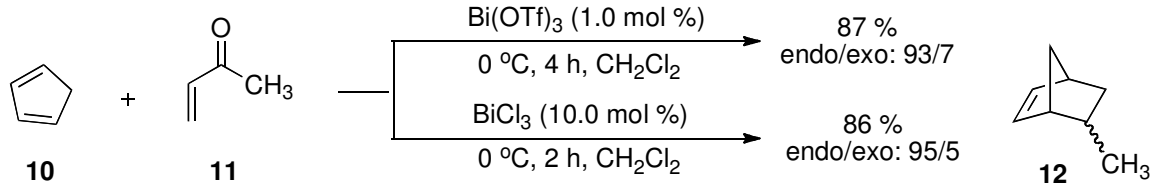
[Emim][NTf_2]

Ionic liquids represent one of the most important alternatives to volatile organic compounds or solvents (VOC).[xx] Although not all ionic liquids are green solvents, their use can greatly reduce the emission and/or combustion risks associated with the use of

many traditional organic solvents. Furthermore, reports of enhanced reaction rates, ease of product recovery, and the ability to recycle the used ionic liquid several times make many ionic liquids a viable alternative to VOCs.

The Diels-Alder reaction is one of the best ways to construct a six-membered ring. Lewis acids, such as aluminum chloride, commonly catalyze the Diels-Alder reaction. Although aluminum chloride is frequently used to catalyze the Diels-Alder reaction, it is quite corrosive and often leads to polymerization of the diene substrates. Thus there has been interest in developing new and milder methods to catalyze the Diels-Alder reaction. Bismuth(III) triflate and bismuth(III) chloride have been reported to efficiently catalyze the Diels-Alder reaction, and each showed higher catalytic activity than scandium, titanium and ytterbium based catalysts (Scheme 1.4).[xxi]

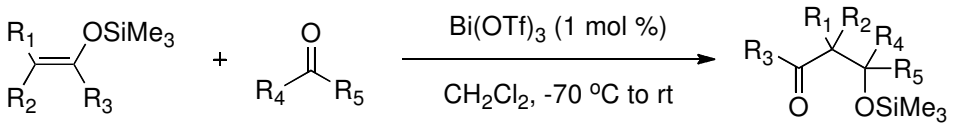
Scheme 1.4



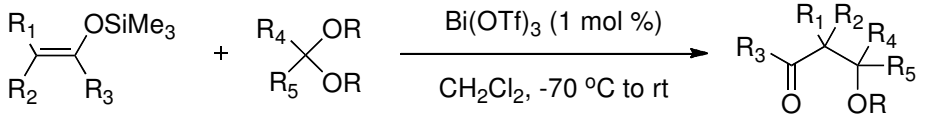
10 **11** **12**

The Mukaiyama Aldol reaction is considered to be one of the most important carbon-carbon bond forming reactions in organic synthesis.[xxii] Bismuth(III) salts have been extensively studied as catalysts for the Mukaiyama Aldol reaction and several efficient methods have been developed. Le Roux and co-workers have reported the bismuth(III) triflate catalyzed addition of silyl enol ethers to a variety of ketones, aldehydes, and acetals to give the corresponding β-hydroxy **15** (Scheme 1.5) and alkoxycarbonyl **18** compounds (Scheme 1.6).[xxiii]

Scheme 1.5

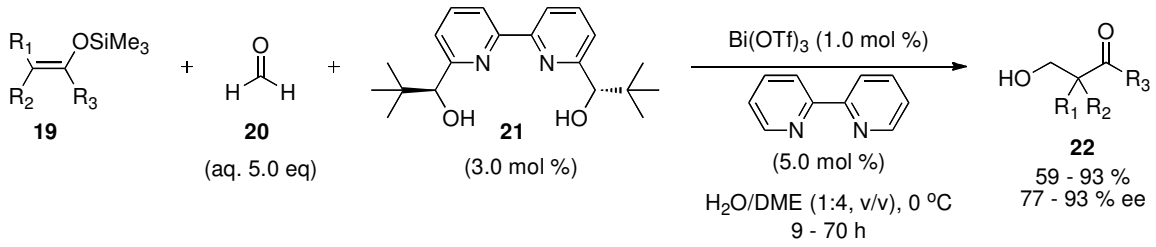


Scheme 1.6



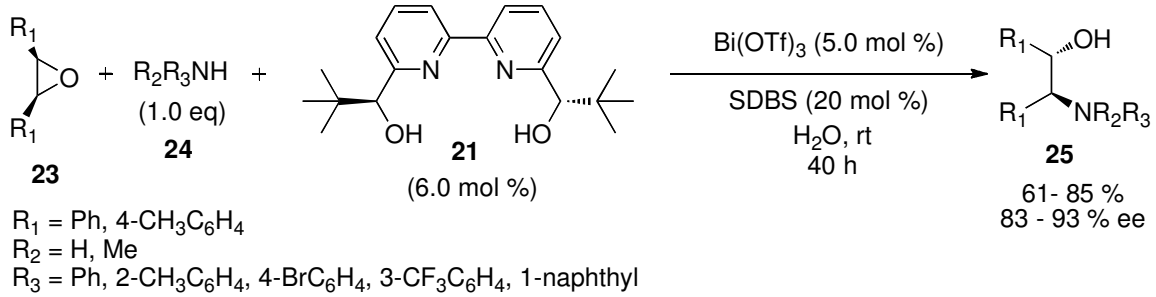
The Mukaiyama Aldol reaction is one of only a few reactions in which a chiral bismuth complex has been utilized to form products enantioselectively (Scheme 1.7).[xxiv]

Scheme 1.7

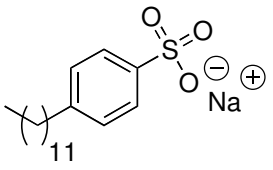


Kobayashi and co-workers reported the reaction of formaldehyde **20** with a variety of silyl enol ethers **19** to give the corresponding β-hydroxycarbonyl products **22** in moderate to high yields with good enantioselectivity. Using the same chiral bipyridine catalyst Kobayashi also developed an asymmetric ring-opening of *meso*-epoxides **23** by aromatic amines **24** to give β-amino alcohols **25** in good yields with high enantioselectivity (Scheme 1.8).[xxv]

Scheme 1.8



R_1 = Ph, 4-$CH_3C_6H_4$
R_2 = H, Me
R_3 = Ph, 2-$CH_3C_6H_4$, 4-BrC_6H_4, 3-$CF_3C_6H_4$, 1-naphthyl



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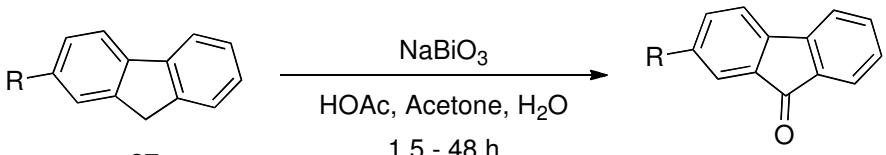
Sodium Dodecybenzenesulfonate (SDBS)

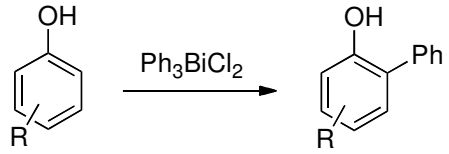
In addition to the +3 oxidation state, bismuth can also exist in the +5 oxidation state. Bismuth(V) compounds, such as sodium bismuthate and triphenylbismuth(V) dichloride, are commonly used as oxidizing agents. Sodium bismuthate has been utilized for the benzylic oxidation of aromatic compounds (Scheme 1.9).[xxvi]

Scheme 1.9



Triphenylbismuth(V) dichloride has been used for the oxidative phenylation of phenols (Scheme 1.10).[xxvii]

Scheme 1.10



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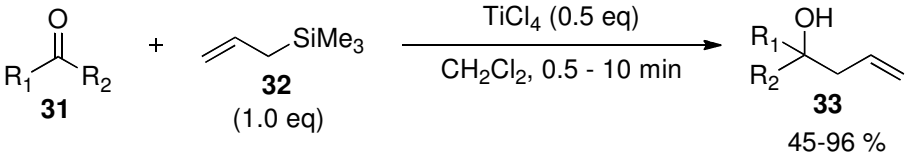
R = Electron Donating

B. Literature Review

Hosomi-Sakurai Allylation of Aldehydes

The formation of carbon-carbon bonds is one of the most important transformations in organic chemistry and is especially important in the synthesis of natural products and pharmaceuticals. Several methods have been developed for the formation of carbon-carbon bonds including Friedel-Crafts acylation[xxviii] and alkylation,[xxix] Suzuki Cross-Coupling,[xxx] Olefin Metathesis,[xxxi] Michael addition,[xxxii] and the Diels-Alder cyclization.[10] Another important reaction for the formation of carbon-carbon bonds is the Hosomi-Sakurai reaction, which involves the allylation of carbonyl compounds and acetals. Hosomi and Sakurai first reported the allylation of aldehydes and ketones promoted by titanium tetrachloride to yield homoallyl alcohols (Scheme 1.11).[xxxiii]

Scheme 1.11



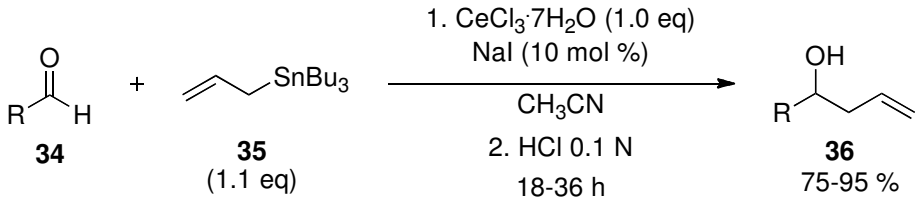
31 **32** (1.0 eq) **33** 45-96 %

R_1 = $CH_3(CH_2)_2$, $(CH_3)_2CH$, $Ph(CH_2)_2$, Ph, CH_3
R_2 = H, CH_3,

Following the report by Hosomi and Sakurai , many other methods have been reported for the allylation of aldehydes and ketones to give homoallyl alcohols. The

promoters and catalysts used for these carbon-carbon bond forming reactions include $Yb(OTf)_3$ (with one equivalent of benzoic acid),[xxxiv] $Sc(OTf)_3$,[xxxv] $YbCl_3$,[xxxvi] I_2,[xxxvii] $FeCl_3$,[xxxviii] $AlCl_3$,[xxxix] $CeCl_3 \bullet 7H_2O$-NaI (Scheme 1.12),[xl] $PtCl_2(PPh_3)_2$,[xli] and $PdCl_2(PPh_3)_2$.[41] Several of these methods utilize the highly toxic compound allyltributyltin **35** as the allyl source group. Furthermore, many of these catalysts such as $PtCl_2(PPh_3)_2$ are rather expensive.

Scheme 1.12

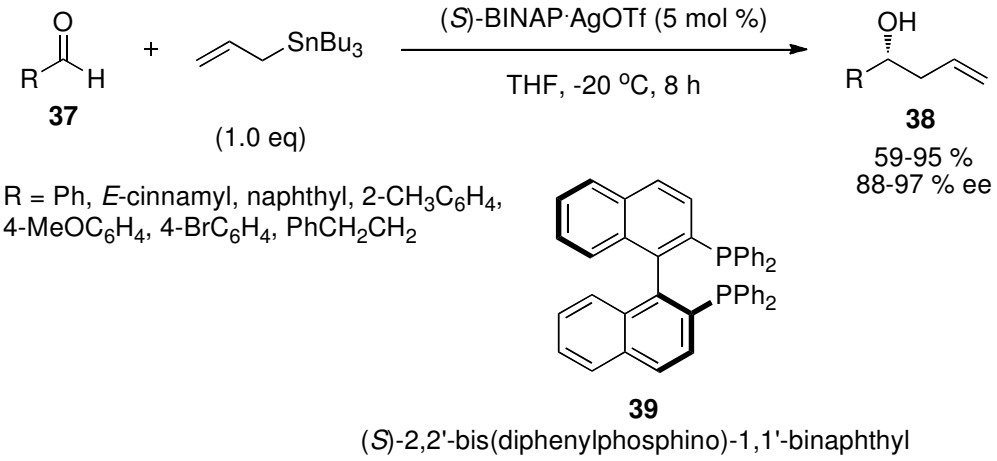


34 **35** (1.1 eq) **36** 75-95 %

R = 4-$CF_3C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-$CH_3C_6H_4$, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, $PhCH_2CH_2$, $CH_3(CH_2)_7$,

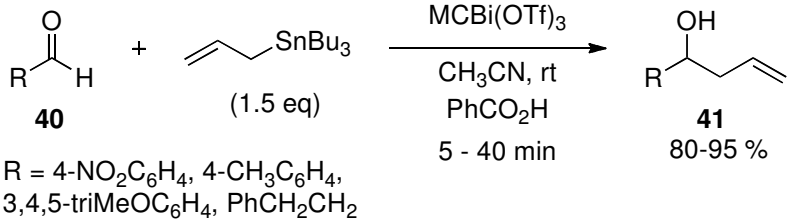
The control of stereochemistry is often important in the course of a total synthesis. Because a chiral center is formed during the Hosomi-Sakurai reaction, an enantioselective transformation would be potentially useful. Several enantioselective Hosomi-Sakurai type reactions have been reported using catalysts and promoters such as BINAP-Ag(OTf) (Scheme 1.13),[xlii] Ti(O-*i*-Pr),[xliii] Aryl *t*-butyl sulfoxides,[xliv] and PM-BOX-ZnI_2 (phosphinoylmethylbisoxazoline).[xlv]

Scheme 1.13



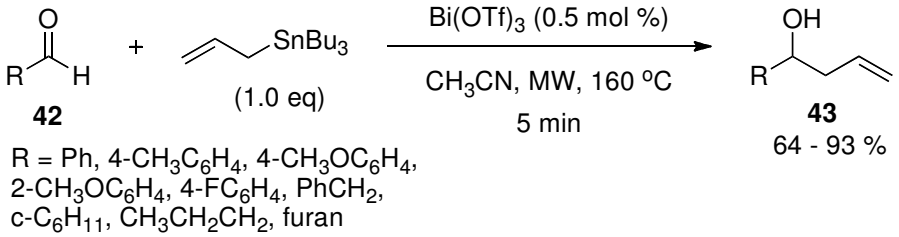
Our continued interest in bismuth(III) salts as catalysts in organic synthesis prompted us to investigate the Hosomi-Sakurai reaction using a Bi(III) catalyst. Bismuth(III) triflate has been reported as a mild and efficient catalyst for the allylation of aldehydes, but the reported methods require microwave reactors or difficult preparation of the catalyst. In the first example, a recoverable and reusable polymer encapsulated $Bi(OTf)_3$ [$MCBi(OTf)_3$] catalyst is used for the allylation of aldehydes by allyltributlystannane (Scheme 1.14).[xlvi]

Scheme 1.14



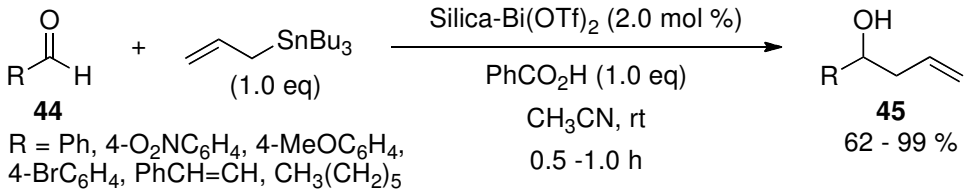
The report indicates that the polymer based catalyst is easy to prepare, but efforts in our group by previous group members to reproduce the published procedure were unsuccessful. A similar system, using $Bi(OTf)_3$ as the catalyst, utilizes microwave irradiation to allylate aldehydes with allylstannane (Scheme 1.15).[xlvii]

Scheme 1.15



Bismuth sulfonate immobilized on silica gel has also been reported for the allylation of aldehydes using allyltributlystannane (Scheme 1.16).[xlviii]

Scheme 1.16



44

R = Ph, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$, 4-BrC_6H_4, PhCH=CH, $CH_3(CH_2)_5$

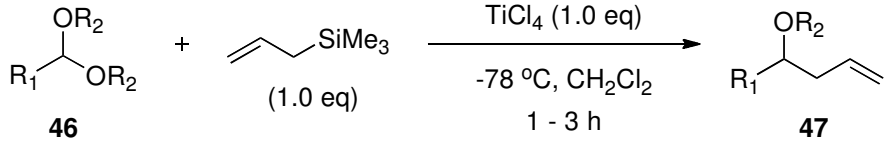
45

62 - 99 %

Unfortunately, all of these methods use toxic allylstannanes as the allyl source group, and thus a more environmentally friendly method is highly desirable.

In addition to the allylation of aldehydes and ketones, Hosomi and Sakurai also reported the allylation of acyclic acetals to give homoallyl ethers (Scheme 1.17).[xlix]

Scheme 1.17



46

R_1 = Ph, $PhCH_2CH_2$, $BrCH_2$, $(CH_3)_2$, $CH_3(CH_2)_3$

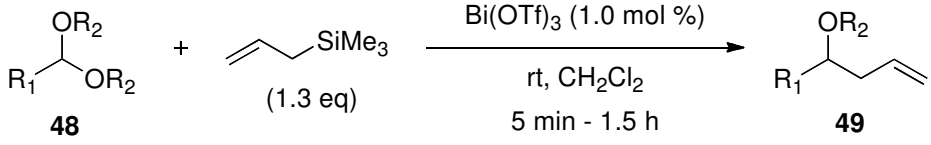
R_2 = Me, Et

47

24-98 %

Following their report, many different catalysts and promoters have been utilized for the synthesis of homoallyl ethers via allylation of acyclic acetals. Two such catalysts, bismuth(III) triflate[l] (Scheme 1.18) and iron(III) tosylate,[li] (Scheme 1.19) were reported by our group.

Scheme 1.18



48

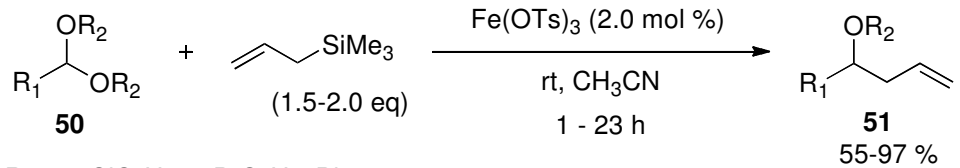
R_1 = 4-ClC_6H_4, 3-BrC_6H_4, Ph, cinnamyl, $PhCH_2$, $CH_3(CH_2)_5$

R_2 = Me, Et

49

69-96 %

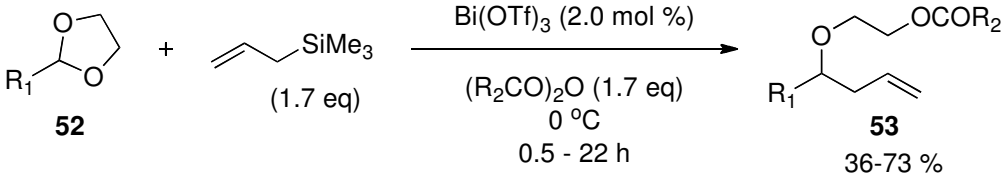
Scheme 1.19



R_1 = 4-ClC_6H_4, 3-BrC_6H_4, Ph,
4-$MeOC_6H_4$, $PhCH_2$, $CH_3(CH_2)_{10}$
R_2 = Me, Et

In contrast to acylic acetals, cyclic acetals have received less attention as allylation substrates. Cyclic acetals are usually employed as acid-labile protecting groups in organic synthesis,[lii] but they can also be converted into useful functional groups in the course of a synthesis. The allylation of 1,3-dioxolanes promoted by $TiCl_4$,[liii] $AlCl_3$,[53] $SnCl_4$,[53] $BF_3{\cdot}Et_2O$,[liv] TMSOTf,[53,lv] and $Sn(OTf)_2$[lvi] has been reported but many of these methods required stoichiometric loading of toxic or corrosive promoters. We recently reported a bismuth(III) triflate catalyzed allylation of 1,3-dioxolanes which avoids the stoichiometric loading of toxic or corrosive promoters and utilizes a less toxic and commercially available allyl source, allyltrimethylsilane (Scheme 1.20).[lvii]

Scheme 1.20

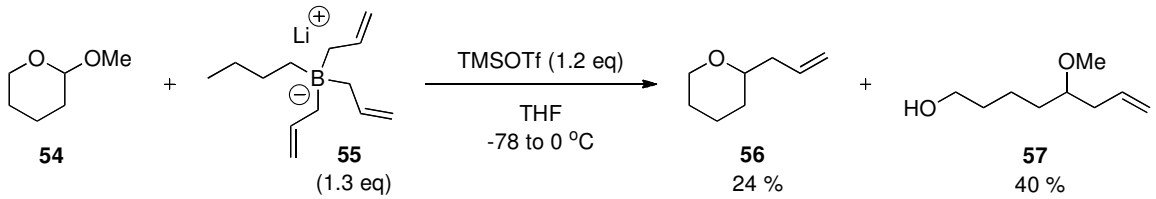


R_1 = 2-BrC_6H_4, 4-ClC_6H_4, 4-$CH_3C_6H_4$. $PhCH_2$, $CH_3(CH_2)_8$
R_2 = CH_3, ^{i}Pr, ^{t}Bu

The allylation of tetrahydropyranyl ethers, common protecting groups for alcohols and phenols,[52] has also received scant attention in the literature. THP ethers are stable to aqueous base but they are readily cleaved under acidic conditions. Since THP ethers are basically acetals (the term ether being a misnomer), the allylation of a THP ether should

yield a highly functionalized alcohol product. To the best of our knowledge, there are only two reported THP ether allylations to give open-chain alcohol products. Hunter and coworkers report the trimethylsilyl triflate promoted allylation of 2-methoxytetrahydropyran **54** with lithium *n*-butyltriallylborate **55** as the allyl source (Scheme 1.21).[55]

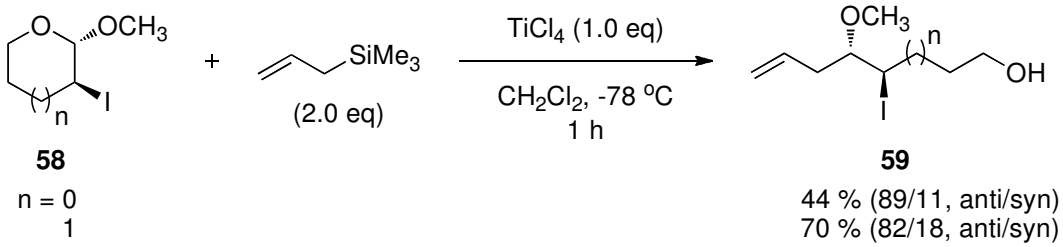
Scheme 1.21



They report a 40 % yield of the open-chain alcohol product **57** and a 24 % yield of 2-allyltetrahydro-2*H*-pyran **56**. The need for stoichiometric loading of the highly corrosive trimethylsilyl triflate, and lack of commercial availability of the allyl source, lithium *n*-butyltriallylborate detract from the synthetic utility of this method.

Maeda and coworkers report the allylation of 3-iodo-2-methoxytetrahydro-2*H*-pyran and 3-iodo-2-methoxytetrahydro-2*H*-furan **58** by allyltrimethylsilane promoted by titanium(IV) tetrachloride.[lviii] In both cases the open-chain alcohol **59** is obtained as the major product (Scheme 1.22).

Scheme 1.22



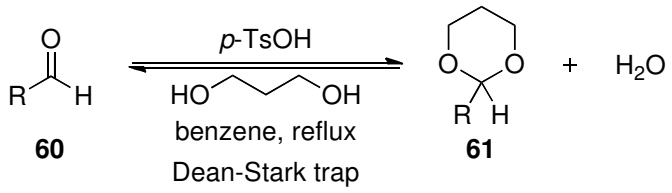
The lack of a highly catalytic, widely applicable, and environmentally friendly method for the allylation of THP and THF ethers and our previous success with acetal allylation prompted us to investigate a bismuth(III) bromide catalyzed allylation of THP and THF ethers.

II. Results and Discussion

A. Bismuth(III) Triflate Catalyzed Synthesis of Cyclic Acetals

Cyclic acetals (dioxolanes and dioxanes) are widely used protecting groups for aldehydes and ketones in organic synthesis.[52] A common literature method for the synthesis of these acetals utilizes the highly corrosive *p*-toluenesulfonic acid as a catalyst and requires the use of a Dean-Stark trap for azeotropic removal of water, a by-product of the reaction (Scheme 2.1).[52]

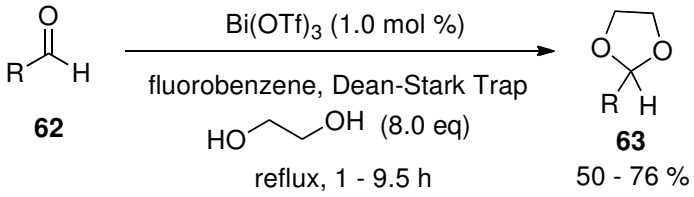
Scheme 2.1



If water is not removed using a Dean-Stark trap, the reactions attain an equilibrium between aldehyde and desired dioxane. If this equilibrium is not pushed towards product, a low yield of the desired cyclic acetal can result. Although this method is widely used, it has several drawbacks. The catalyst, *p*-toluenesulfonic acid, is highly corrosive and the solvent, benzene, is a known carcinogen. In addition, the use of a Dean-Stark trap is practical only on gram scale reactions, and is thus not conducive to microscale organic synthesis.

Many new methods have been developed to eliminate some of the problems associated with this common literature method.[52] One such method, developed in our group, is the bismuth(III) triflate catalyzed synthesis of dioxolanes (Scheme 2.2).[lix]

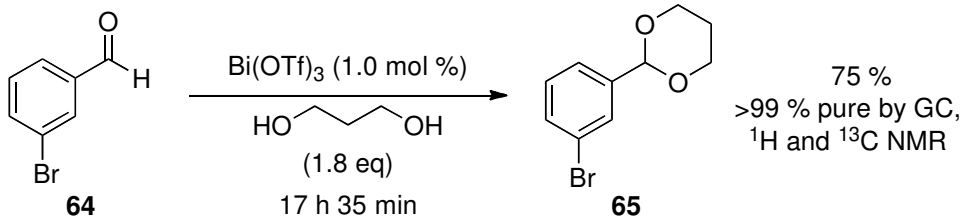
Scheme 2.2



This method utilizes a safer solvent, fluorobenzene, in place of carcinogenic benzene and uses bismuth(III) triflate as a catalyst in place of the corrosive *p*-toluenesulfonic acid. Although this method shows significant improvement over the common literature method, it still requires the use of a Dean-Stark trap and harsh refluxing conditions for water removal. Due to our continued interest in *Green Chemistry* and the use of bismuth(III) salts as catalysts, we set out to develop a method that does not require the Dean-Stark trap or elevated temperatures, but still utilizes bismuth(III) triflate as a catalyst and safer solvents when necessary. We also sought high purity of the crude products, so that purification via flash chromatography on silica gel would not be necessary.

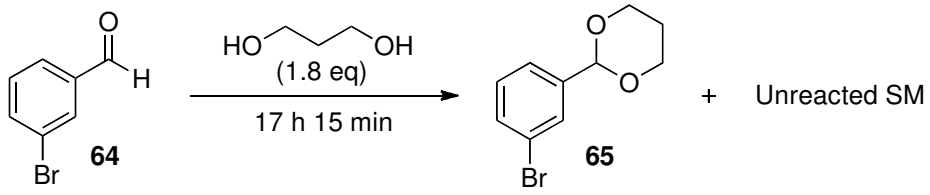
Our preliminary results were quite promising. In the presence of 1.0 mol % bismuth(III) triflate and 1.8 equivalents of 1,3-propanediol, 3-bromobenzaldehyde **64** underwent smooth protection to give the desired dioxane in moderate yield with excellent purity (Scheme 2.3).

Scheme 2.3



In order to confirm that bismuth(III) triflate was necessary for the reaction, a control reaction was performed. The aldehyde and diol were stirred in the absence of bismuth(III) triflate. In the absence of catalyst only 9 % conversion to the product was observed over the same time period (Scheme 2.4).

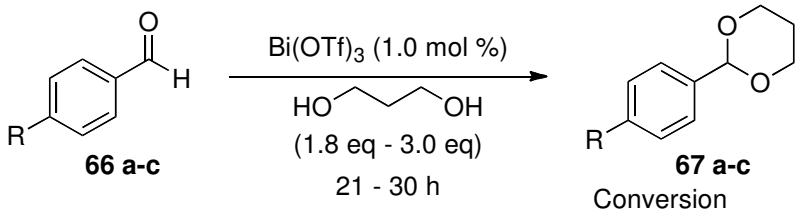
Scheme 2.4



9 % Conversion by GC and ^{1}H NMR

With these promising results in hand we applied the reaction conditions to a variety of different aldehydes. Although these conditions gave a pure dioxane product from 3-bromobenzaldehyde, aromatic aldehydes with electron donating groups gave less satisfactory results (Scheme 2.5). Poor conversion to the desired 1,3-dioxanes was observed.

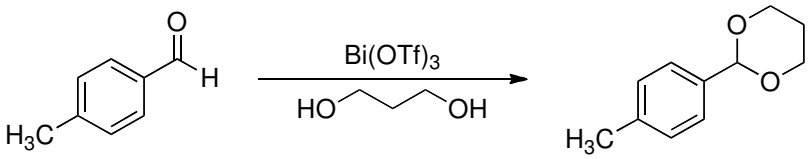
Scheme 2.5



a R = 4-CH_3..... 84 %
b R = 4-OH..... 70 %
c R = 4-$OSiMe_2{}^tBu$..... 55 %

We sought to optimize the reaction by altering several variables—increased catalyst loading, increased equivalents of diol and use of solvent—none of these changes gave the desired percent conversions. (Table 2.1).

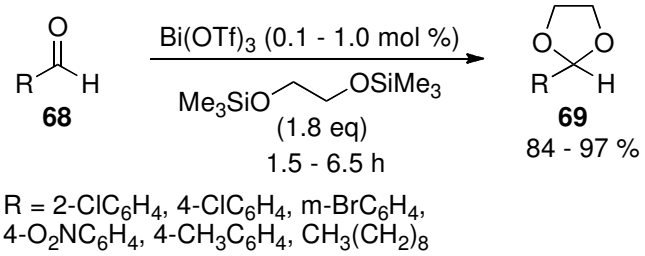
Table 2.1



Diol (eq)	$Bi(OTf)_3$ (mol %)	Solvent	Time (h)	Conversion (%)
1.8	1.0	neat	21	84
1.8	5.0	neat	23	93
3.6	1.0	neat	4	90
1.8	1.0	toluene	19	85

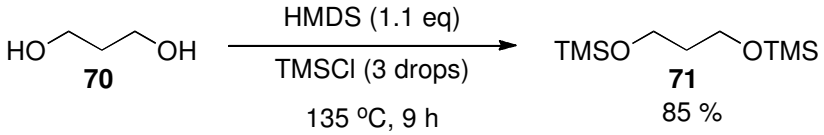
Two different approaches were then taken to increase the conversion of the aldehyde to the desired 1,3-dioxane. One of the many literature methods for synthesizing 1,3-dioxolanes, which avoids the use of a Dean-Stark trap, utilizes 1,2-bis(trimethylsilyloxy)ethane instead of a diol.[lx] When this bis silyl compound is used, an unfavorable equilibrium is not observed and the desired 1,3-dioxolane is obtained in good yield. Previous work in our group on the bismuth(III) triflate catalyzed synthesis of 1,3-dioxolanes using the commercially available 1,2-bis(trimethylsilyloxy)ethane has shown that this procedure is a viable alternative to the synthesis of 1,3-dioxolanes using a Dean-Stark trap (Scheme 2.6). The crude 1,3-dioxolane products obtained by this method contained silyl by-products which had to be removed by silica gel chromatography.

Scheme 2.6

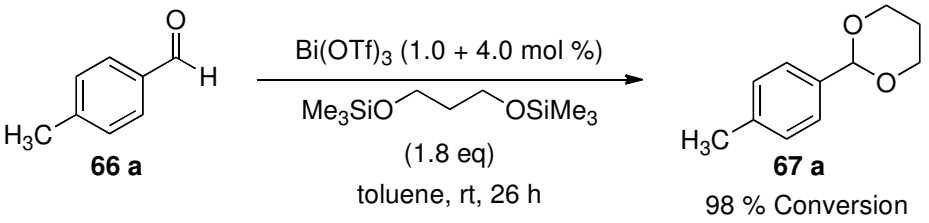


We sought to apply this methodology to the synthesis of dioxanes by using 1,3-bis(trimethylsilyloxy)propane **71**. Since 1,3-bis(trimethylsilyloxy)propane is not commercially available, we synthesized it following a literature procedure[lxi] (Scheme 2.7) and investigated its utility in the synthesis of 1,3-dioxanes (Scheme 2.8).

Scheme 2.7



Scheme 2.8

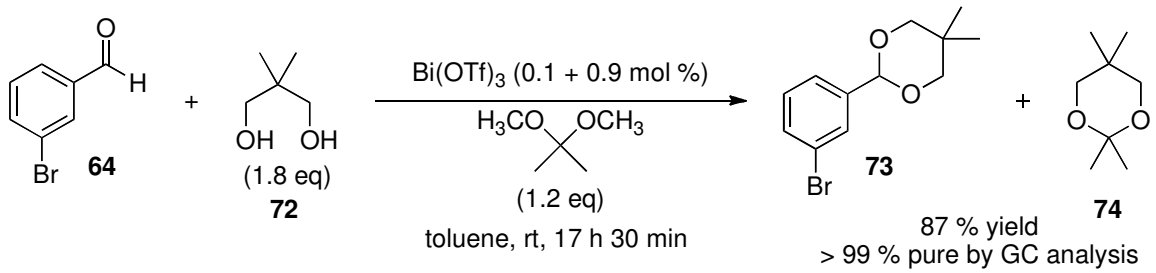


Although the initial result was promising, the need for 5.0 mol% catalyst loading, the lack of commercial availability of the bis silyl compound, and the need to purify the product detracted from this procedure. Because of these drawbacks we continued to investigate the use of 1,3-propane diol in the synthesis of 1,3-dioxanes.

While the conversions with 1,3-propane diol were relatively good, even without removal of water, they were not sufficiently high (> 98%) to make the procedure synthetically useful. We reasoned that the addition of a water scavenger was likely to

boost the conversions to an acceptable level. Two different water scavengers were used and both gave promising preliminary results. A commonly used water scavenger in the synthesis of acetals is 2,2-dimethoxypropane. When 3-bromobenzaldehyde was subjected to our acetalization conditions in the presence of 2,2-dimethoxypropane, the desired dioxane was obtained in good yield with high purity by GC analysis. Further analysis of the product by ^{1}H and ^{13}C NMR spectroscopy showed the formation of the desired 1,3-dioxane **73** along with an impurity which was identified as 2,2,5,5-tetramethyl-1,3-dioxane **74** (Scheme 2.9).

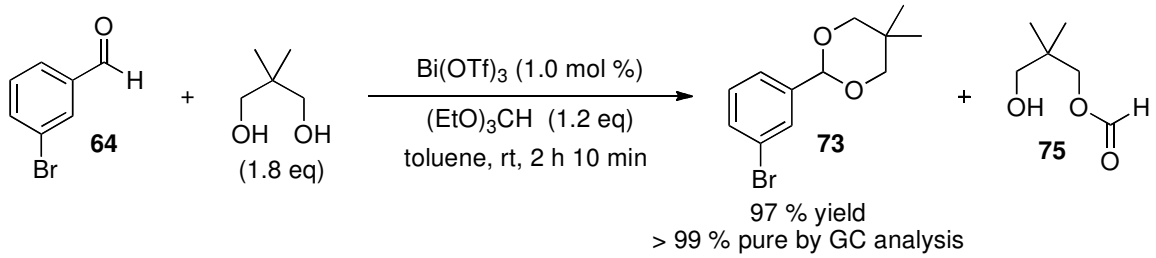
Scheme 2.9



This impurity was not volatile enough to be removed on rotary evaporator and could only be removed by chromatography on silica gel. Because we sought a method in which the crude products were sufficiently pure (> 98%), this method was not further investigated.

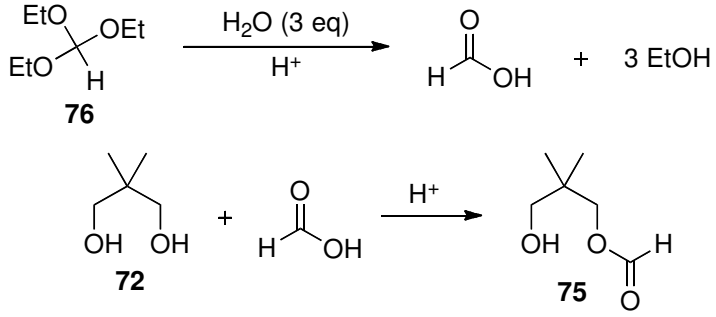
Another water scavenger, triethyl orthoformate, is also widely used in the synthesis of acetals, specifically acyclic ethyl acetals. When 3-bromobenzaldehyde was subjected to the acetalization conditions in the presence of triethyl orthoformate, the desired dioxane **73** was obtained in good yield and high purity (99 %). However characterization by ^{1}H and ^{13}C NMR spectroscopy revealed that the crude product also contained 3-hydroxy-2,2-dimethylpropyl formate **75** as an impurity (Scheme 2.10).

Scheme 2.10



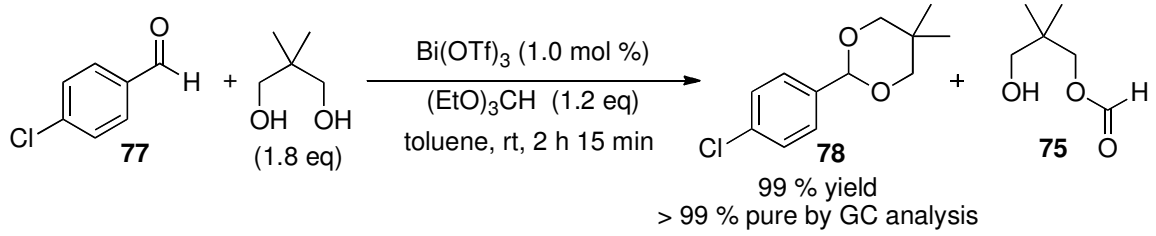
This ester was formed from the reaction of 2,2-dimethyl-1,3-propanediol **72** and formic acid. Formic acid is generated by the reaction of triethyl orthoformate **76** with three equivalents of water (Scheme 2.11).

Scheme 2.11



This impurity was also observed as a by-product in the acetalization reaction of 4-chlorobenzaldehyde under the same conditions (Scheme 2.12).

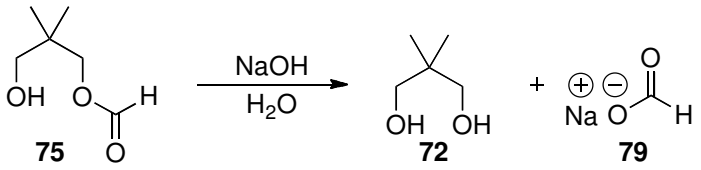
Scheme 2.12



Since, apart from this impurity, the reactions gave satisfactory conversions and purity, we sought to develop a work-up procedure to remove 3-hydroxy-2,2-dimethylpropyl formate **75** from the desired product. Because the by-product was an

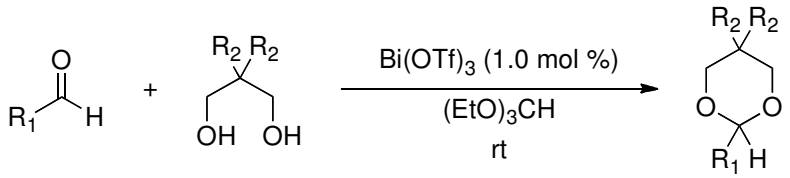
ester and its corresponding hydrolysis products (2,2-dimethylpropanediol and formate) are water soluble, we incorporated a basic hydrolysis step, using 2 M NaOH, into the normal work-up. Upon completion of the reaction 2 M NaOH was added to hydrolyze the ester by-product (Scheme 2.13).

Scheme 2.13



With this additional step in the work-up, the desired 1,3-dioxane products were obtained in good yields with satisfactory purity (Table 2.2) without the need for purification by silica gel chromatography. The reactions in which 1,3-propanediol was utilized as the diol, a homogeneous mixture resulted, even without a solvent, because the diol was a liquid. The reactions in which 2,2-dimethyl-1,3-propanediol, a solid, was utilized toluene was added to give a homogeneous reaction solution.

Table 2.2 $Bi(OTf)_3$ catalyzed synthesis of dioxanes



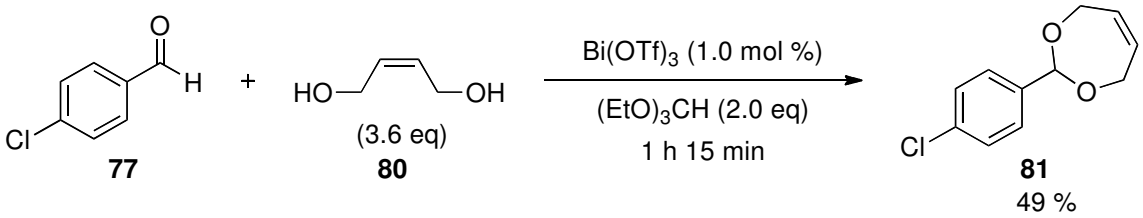
R_1	R_2	Diol (eq)	$(EtO)_3CH$ (eq)	t	Yield (%)[a]
$CH_3(CH_2)_7CH_2$	H	2.3	0.3	9 h 15 min	93[b]
4-ClC_6H_4	H	1.8	1.0	3 h 20 min	90
4-$CH_3C_6H_4$	H	1.8	1.0	25 h 20 min[c]	79
2-BrC_6H_4	H	1.8	1.0	2 h 35 min	78[d]

R_1	R_2	Diol (eq)	$(EtO)_3CH$ (eq)	t	Yield (%)[a]
4-$CH_3OC_6H_4$	CH_3	1.8	1.2	23 h 30 min	93
4-ClC_6H_4	CH_3	1.2	0.3	4 h	83
$CH_3(CH_2)_7CH_2$	CH_3	1.8	0.3	1 h 40 min	95[b]
4-$CH_3C_6H_4$	CH_3	1.8	0.3	6 h 15 min	87
4-^{t}BuMe$_2$SiOC_6H_4	CH_3	2.4	1.0	71 h	57

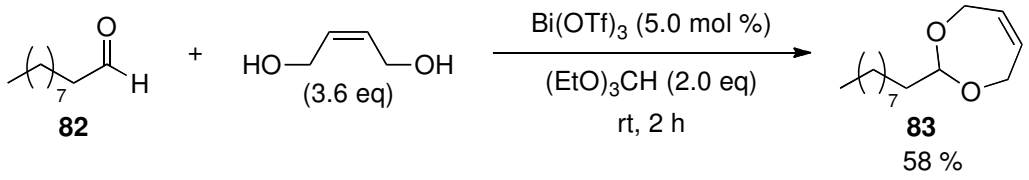
[a] $\geq$ 95 % pure by GC, ^{1}H and ^{13}C NMR; [b] 5.0 mol % $Bi(OTf)_3$; [c] time not optimized; [d] purified by flash chromatography on SiO_2;

This method was also applicable to the synthesis of 1,3-dioxepines **81** and **83** arising from the use of *cis*-2-butene-1,4-diol **80** (Schemes 2.14 and 2.15).

Scheme 2.14



Scheme 2.15

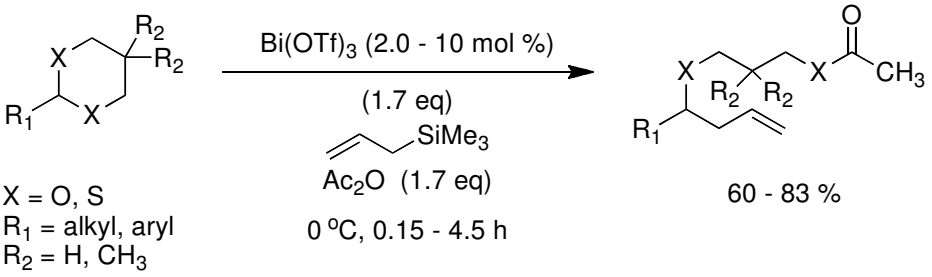


In both these cases the crude product contained unreacted aldehyde and diol which was removed by silica gel chromatography. Although 1,3-dioxepines are normally not used as protecting groups for aldehydes, they can be quite useful synthetically as illustrated below.

B. Bismuth(III) Triflate Catalyzed Allylation and Subsequent Hydrolysis of Dioxepines

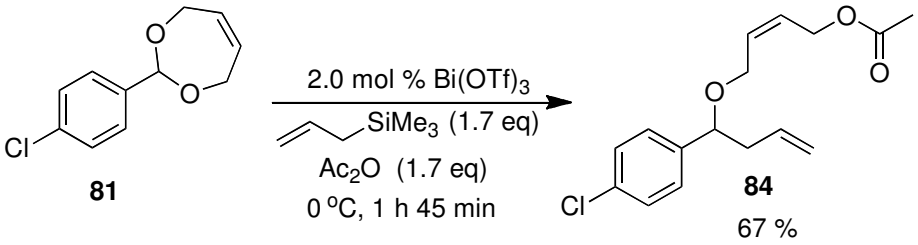
As discussed previously, the bismuth(III) triflate catalyzed allylation of 1,3-dioxolanes gives rise to synthetically useful compounds with functional groups amenable to further transformation.[57] Previous work in the group extended this acetal allylation methodology to the allylation of 1,3-dioxanes and 1,3-dithianes to give similarly useful compounds (Scheme 2.16).

Scheme 2.16

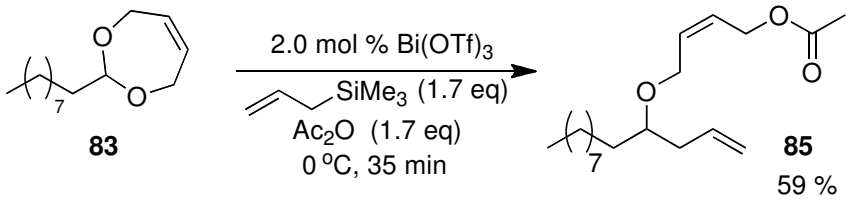


In order to further expand the scope of this allylation we attempted the allylation with 1,3-dioxepines (Schemes 2.17 and 2.18).

Scheme 2.17

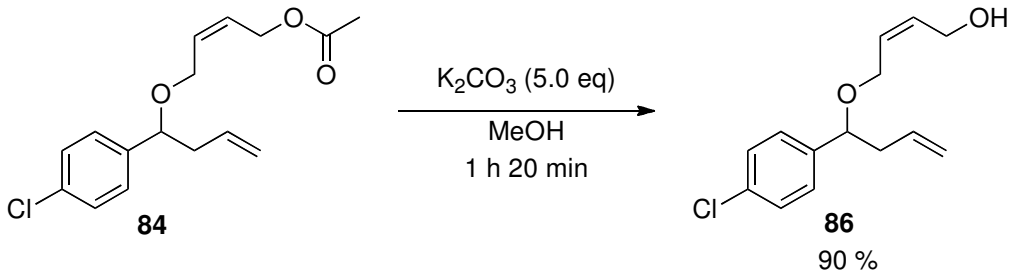


Scheme 2.18

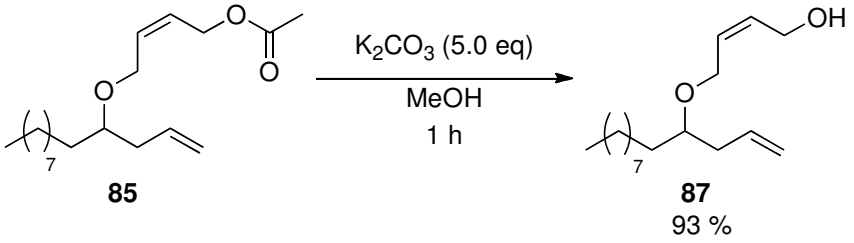


These allylations proceeded smoothly under the mild and solvent free conditions to give the desired ester products in good yields following purification by flash chromatography on silica gel. The ester products obtained were hydrolyzed using standard conditions, thus allowing easy synthesis of alcohols (Schemes 2.19 and 2.20).[52]

Scheme 2.19



Scheme 2.20

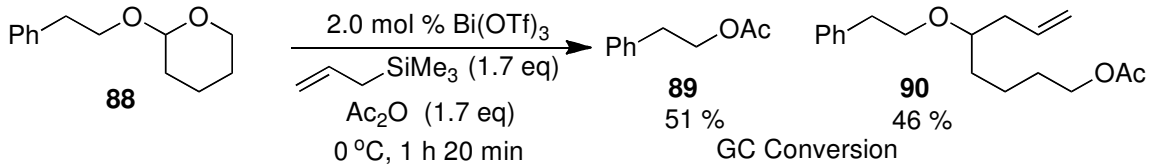


These hydrolysis reactions proceeded smoothly, and following purification of the crude products on silica gel, the desired alcohol products were obtained in high yield.

C. Bismuth(III) Bromide Catalyzed Allylation of Tetrahydropyranyl and Tetrahydrofuranyl Ethers

Tetrahydropyranyl (THP) and tetrahydrofuranyl (THF) ethers are useful protecting groups for alcohols and phenols in organic synthesis.[52] Although they are referred to as ethers, examination of their structure reveals they are actually acetals. In light of our recent success in the allylation of cyclic acetals such as dioxolanes, dioxanes, and dioxepines, and the lack of an analogous reaction in the literature with THF and THP ethers, we were prompted to investigate the bismuth(III) triflate catalyzed allylation of THP and THF ethers. When 2-phenethoxytetrahydro-2*H*-pyran **88** was subjected to the allylation conditions, a mixture of phenethyl acetate **89** and the desired open chain ester **90** was obtained (Scheme 2.21). The direct conversion of THP ethers to their corresponding acetates has been reported using acetic anhydride and bismuth(III) salts.[lxii]

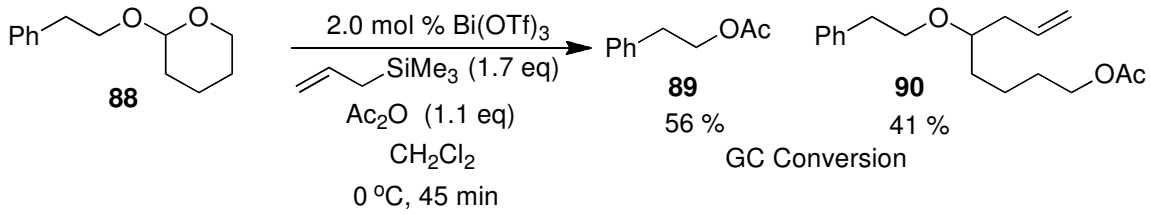
Scheme 2.21



Although this result was discouraging due to the large amount of phenethyl acetate, we were optimistic that optimization of the reaction conditions could maximize the amount of desired product while minimizing the formation of unwanted side products.

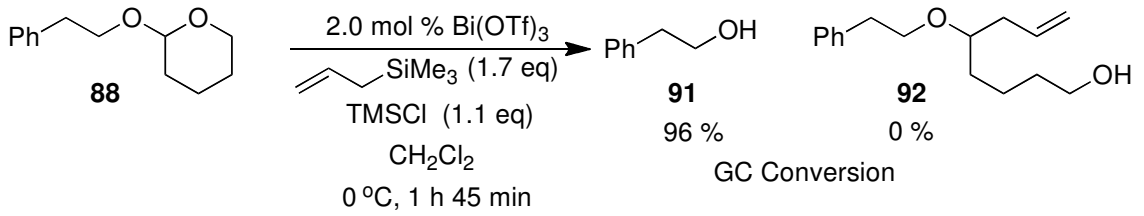
Dichloromethane has been previously reported as a suitable solvent for the bismuth triflate catalyzed allylation of acylic acetals using allyltrimethylsilane as the allyl source.[50] This report prompted us to investigate the allylation of 2-phenethoxytetrahydro-2*H*-pyran **88** in dry dichloromethane (Scheme 2.22).

Scheme 2.22



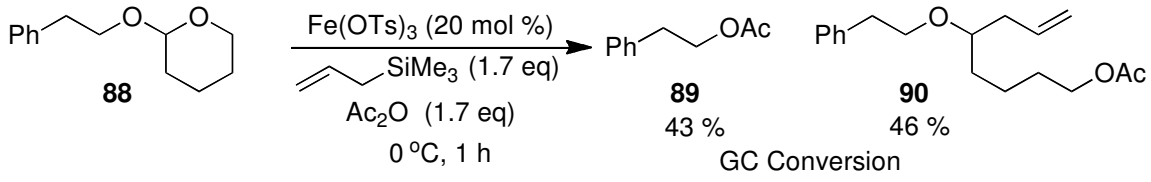
Unfortunately, an increase in the amount of the desired open chain product **90** was not observed. We then investigated the use of trimethylsilyl chloride to trap the putative alkoxide intermediate instead of acetic anhydride (Scheme 2.23). Following aqueous work-up we expected to isolate the open chain alcohol **92**.

Scheme 2.23



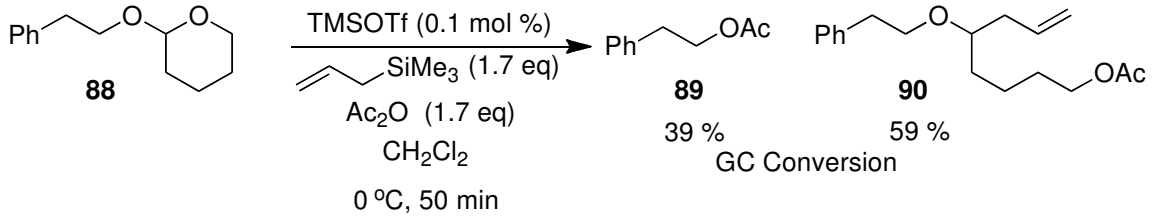
GC analysis of the crude product revealed that the major product was phenethyl alcohol **91**, arising from allylation of the THP ring and expulsion of the 2-phenylethoxy moiety. As a result of these unsatisfactory results we screened some other catalysts known to promote allylation. Iron(III) tosylate has been shown to catalyze the allylation of acyclic acetals.[lxiii] When 2-phenethoxytetrahydro-2*H*-pyran **88** was submitted to the allylation conditions in the presence of iron(III) tosylate, the results were again not promising. (Scheme 2.24).

Scheme 2.24



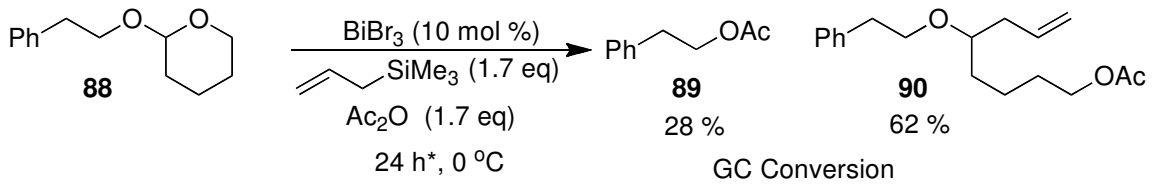
GC analysis of the crude product revealed a nearly one to one mixture of the desired open chain product **90** and phenethyl acetate **89**. Further reactions with iron(III) tosylate were not conducted. As discussed previously trimethylsilyl triflate (TMSOTf) has been reported as a catalyst for the allylation of 2-methoxytetrahydropyran using lithium *n*-butyltriallylborate as the allyl source.[55] When 2-phenethoxytetrahydro-2*H*-pyran **88** was submitted to allylation conditions in the presence of catalytic trimethylsilyl triflate more satisfactory results were obtained than in the previous studies (Scheme 2.25).

Scheme 2.25



GC analysis of the crude reaction mixture indicated 59 % of the desired open chain product **90** and 39 % phenethyl acetate **89**. Although higher conversion to the desired product was achieved, trimethylsilyl triflate is extremely corrosive and is not ideal given our *Green Chemistry* goals. At this point we investigated bismuth(III) bromide, a non-toxic and non-corrosive salt, as a catalyst for the allylation of THP ethers. To our delight, when 2-phenethoxytetrahydro-2*H*-pyran **88** was submitted to allylation conditions in the presence of catalytic bismuth(III) bromide conversion to the open chain product **90** was greater than with any of the previous catalysts (Scheme 2.26).

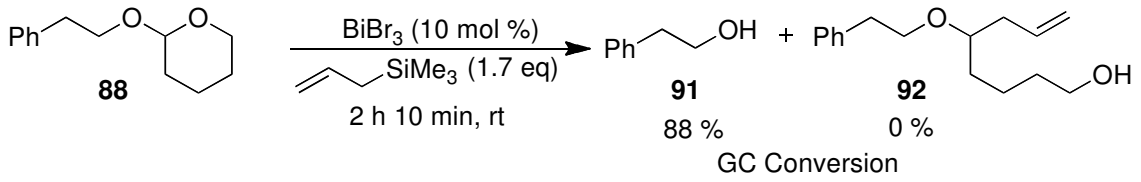
Scheme 2.26



*time not optimized

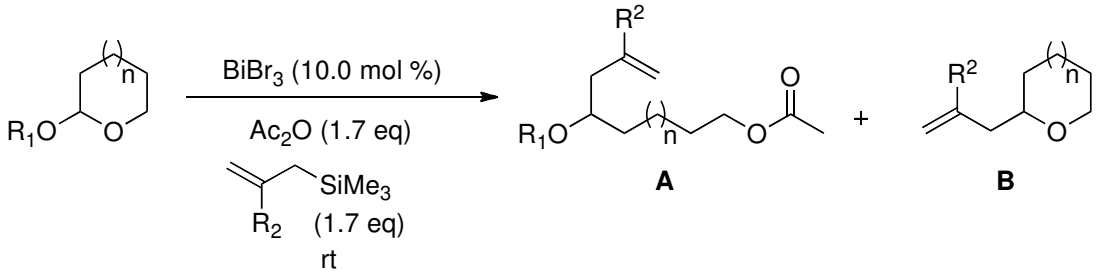
With these promising results we investigated the need for acetic anhydride to capture the putative alkoxide intermediate. When 2-phenethoxytetrahydro-2*H*-pyran **88** was submitted to allylation conditions in the absence of acetic anhydride none of the expected open chain alcohol product **92** was observed (Scheme 2.27).

Scheme 2.27



Instead, GC analysis of the crude reaction mixture showed formation of mostly phenethyl alcohol **91**. This product most likely arises from allylation of the THP ring and expulsion of the 2-phenylethoxy group. After establishing the need for acetic anhydride, we optimized reaction temperature. With the optimized conditions in hand (10 mol % bismuth(III) bromide, 1.7 equivalents of acetic anhydride, and 1.7 equivalents of allyltrimethylsilane at room temperature) a variety of THP and THF ethers were submitted to allylation. After obtaining consistently moderate yields of the desired open chain product it was realized that another product, 2-allyltetrahydro-2*H*-pyran, was being formed in significant amounts. We had initially missed detection of this rather volatile compound by GC analysis because the solvent and this compound had the same retention time. By modifying the GC conditions, we were able to detect 2-allyltetrahydro-2*H*-pyran by GC and hence quantify its amount in the reaction. In many cases a pure sample of 2-allyltetrahydro-2*H*-pyran was isolated by column chromatography and characterized spectroscopically. The results of this project are summarized in Table 2.3.

Table 2.3 Bismuth(III) bromide catalyzed allylation of THP and THF ethers



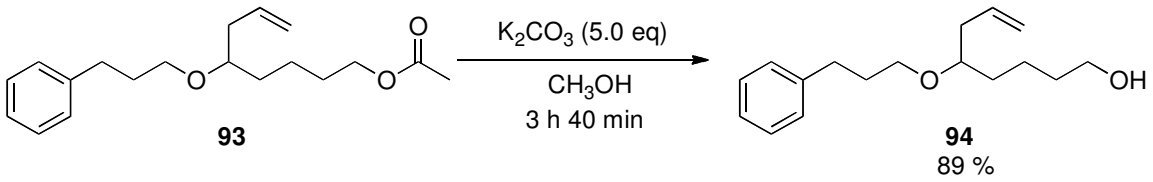
R_1 =	R_2 =	n =	t =	Yield **A**[a] (%)	Yield **B**[b] (%)
$CH_3(CH_2)_4$	H	1	1 h 45 min	54	-
$CH_3(CH_2)_4$	CH_3	1	1 h 35 min	35	-
cyclohexyl-	H	1	1 h 30 min	44	-
$CH_3(CH_2)_6$	H	1	2 h 35 min	62	-
$CH_3(CH_2)_6$	H	0	2 h 10 min	21	-
$BrCH_2(CH_2)$	H	1	1 h 30 min	45	27
$HC{\equiv}C(CH_2)_2$	H	1	1 h 30 min	43	30
Me	H	1	1 h	58	24
Me	CH_3	1	1 h 30 min	30	55
$PhCH_2(CH_2)_2$	H	1	2 h 15 min	49	31[c]
$PhCH_2(CH_2)_2$	H	0	1 h 30 min	25	-
CH_3CH_2	H	0	20 h 25 min[d]	40	-

[a] The reaction mixture was loaded onto a silica gel column and the products were isolated by flash chromatography; products $\geq$ 97 % pure by GC, ^{1}H and ^{13}C NMR. [b] Isolated yields with purity $\geq$ 98 % as determined by GC, ^{1}H and ^{13}C NMR; those not shown were obtained as a mixture with the acetate of starting material. [c] Yield of 3-phenylpropyl acetate. [d] Reaction time not optimized.

This methodology provides access to highly functionalized esters in a mild, one pot, solvent-free method from readily available THP and THF ethers. Hydrolysis of the

resulting ester yields a synthetically useful alcohol amenable to further transformations (Scheme 2.28).

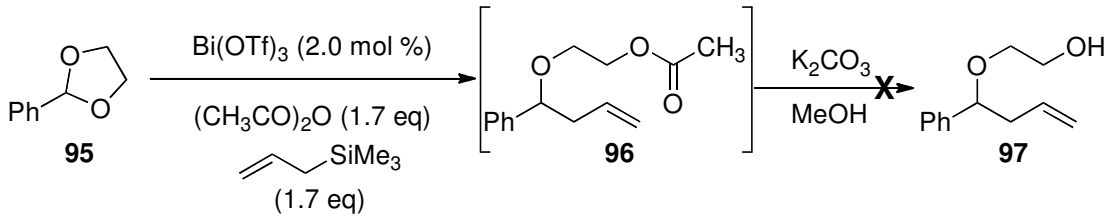
Scheme 2.28



D. One-Pot Bismuth(III) Triflate Catalyzed Allylation of 1,3-Dioxolanes

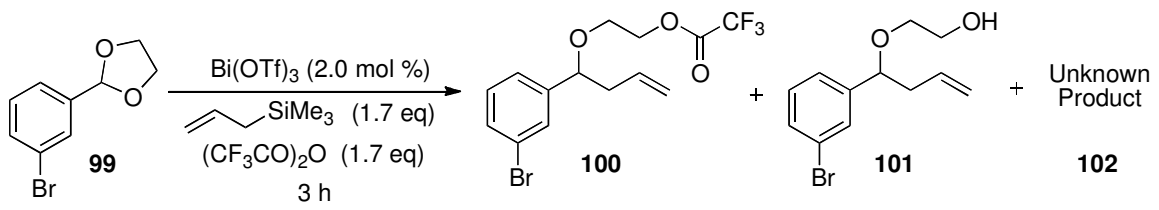
Our success with the bismuth(III) triflate catalyzed allylation of 1,3-dioxolanes to give highly functionalized esters prompted us to investigate a one-pot method for the synthesis of highly functionalized alcohols. Although the *in situ* hydrolysis of the acetate **96** generated by our published procedure should give alcohol **97**, this reaction was unsuccessful with 2-phenyl-1,3-dioxolane (Scheme 2.29).[57]

Scheme 2.29



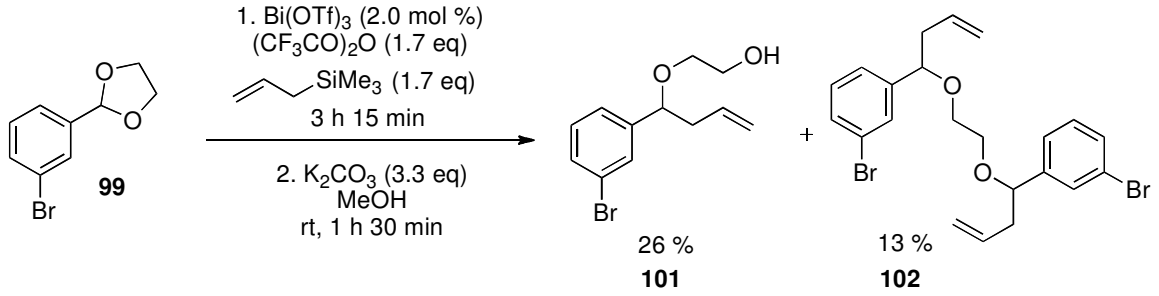
We reasoned that a more reactive ester, such as the trifluoroacetic ester, might be prone to *in situ* hydrolysis and hence likely to give the desired alcohol product. We first attempted the bismuth(III) triflate catalyzed allylation as reported but replaced acetic anhydride with trifluoroacetic anhydride (Scheme 2.30).

Scheme 2.30



Analysis of the crude products showed a mixture of the desired alcohol **101**, trifluoroacetate **100**, and an unknown product **102**. This mixture was then subjected to hydrolysis with potassium carbonate in methanol in an attempt to cleave the trifluoroacetate. The crude product, following hydrolysis, contained a mixture of the desired alcohol **101** and the same unknown **102**. In order to elucidate the structure of this unknown product, the reaction was repeated on a larger scale and a one-pot hydrolysis procedure was employed (Scheme 2.31).

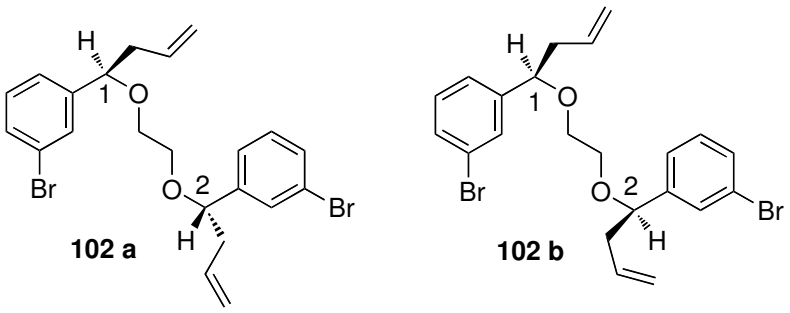
Scheme 2.31



This one-pot procedure successfully yielded the desired alcohol product **101**, but ^{1}H and ^{13}C NMR, IR, COSY, and HETCOR spectra provided evidence for the presence of a dimeric product **102** that was obtained in a significant yield following column chromatography. The absence of an OH and carbonyl stretch in the IR spectrum and a ^{13}C NMR spectrum that was similar to compound **101** suggested that the unknown might be a dimer. The ^{13}C spectrum contained two sets of very closely separated peaks (δ 68.2, 68.3, 81.5, 81.6), suggesting the presence of a pair of diastereomers. These diastereomers

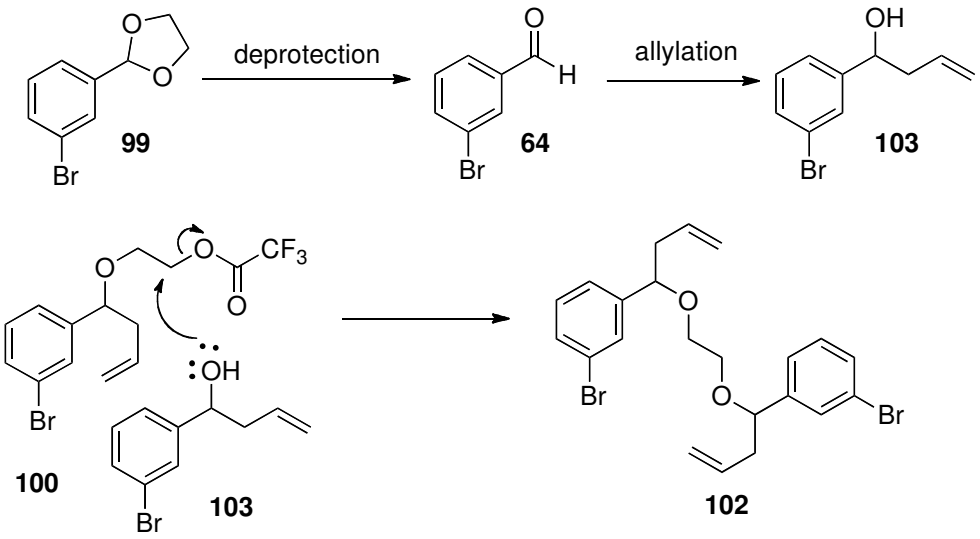
could give slightly different signals in the ^{13}C NMR spectrum, and we believe the presence of both diastereomers **102a** and **102b** gives rise to the observed signals (Scheme 2.32).

Scheme 2.32



We proposed that the dimeric product could arise from reaction of a homoallyl alcohol **103** (which itself would arise from allylation of the aldehyde **64** resulting from deprotection of the starting dioxolane **99** under the reaction conditions[lxiv]) and the trifluoroacetate product **100** (Scheme 2.33).

Scheme 2.33



Although this discovery meant that a one-pot procedure for the allylation of 1,3-dioxolanes to give alcohol products directly was not likely to be fruitful, examination of

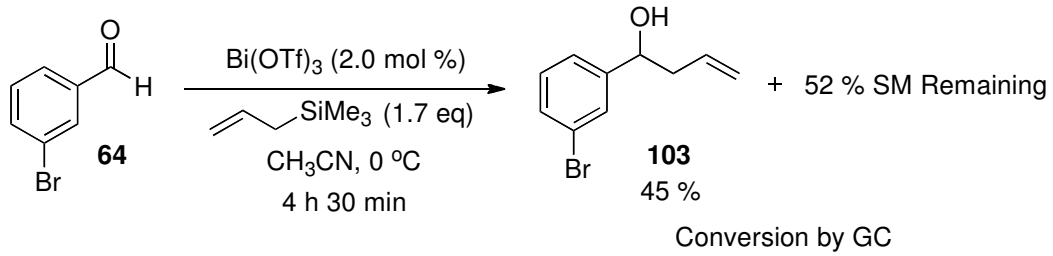
the proposed intermediate **103** suggested that aldehydes could be allylated directly using a similar procedure. As discussed previously bismuth(III) triflate has been used to catalyze the allylation of aldehydes using the highly toxic allyltributyl tin as the allyl group source.[46,47,48] However, the bismuth(III) triflate catalyzed allylation of aldehydes using the less toxic allyltrimethylsilane as the allyl source has not been reported in the literature.

E. Bismuth(III) Triflate Catalyzed Allylation of Aldehydes to Yield Homoallyl Alcohols

Following the discovery that bismuth triflate catalyzes the allylation of aldehydes using allyltrimethylsilane, we explored this reaction further. The effect of solvents, varying the equivalents of trifluoroacetic anhydride, equivalents of allyltrimethylsilane, and catalyst loading were all investigated not only to find the conditions which gave the highest conversion to product, but also conditions that followed *Green Chemistry* principles. Following these studies we found that the optimal conditions to be the use of 1.1 equivalents of trifluoroacetic anhydride in acetonitrile as the solvent.[lxv] A catalyst loading of only 2.0 mol % was sufficient to catalyze these allylations in short reaction times.

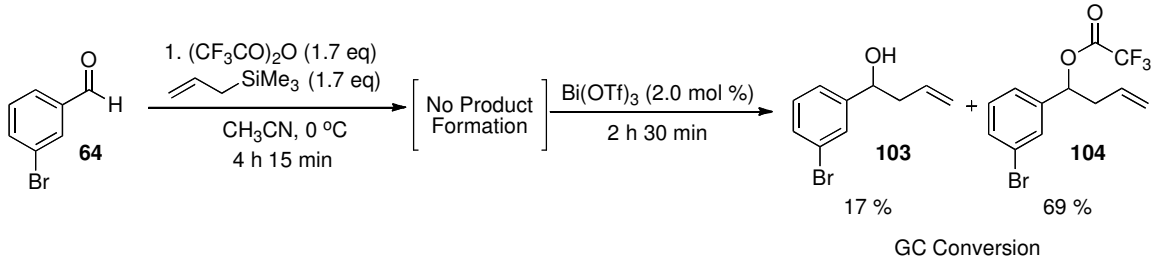
In the absence of trifluoroacetic anhydride, conversion to the desired homoallyl alcohol **103** does not go to completion (Scheme 2.34).

Scheme 2.34



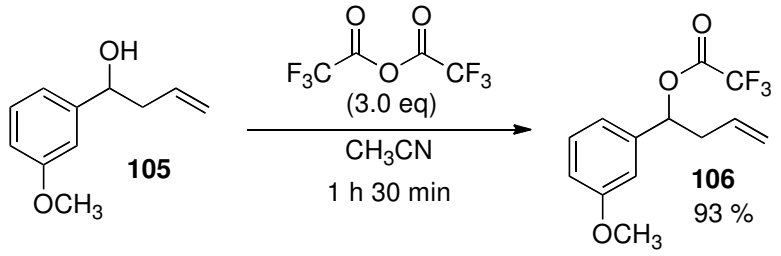
In the absence of bismuth(III) triflate no conversion to the homoallyltrifluoroacetate **105** or alcohol **104** is observed. If the catalyst is then added to the reaction mixture, the starting material is consumed and the expected products are observed (Scheme 2.35).

Scheme 2.35



Because the trifluoracetates are relatively unstable and are likely to be cleaved on silica gel, their presence as an intermediate was confirmed by matching the GC retention time of an authentic sample of trifluoroacetate **106** with the chromatograph obtained by real time analysis of the allylation 3-methoxybenzaldehyde. An authentic sample of **106** was synthesized as shown in scheme 2.36.

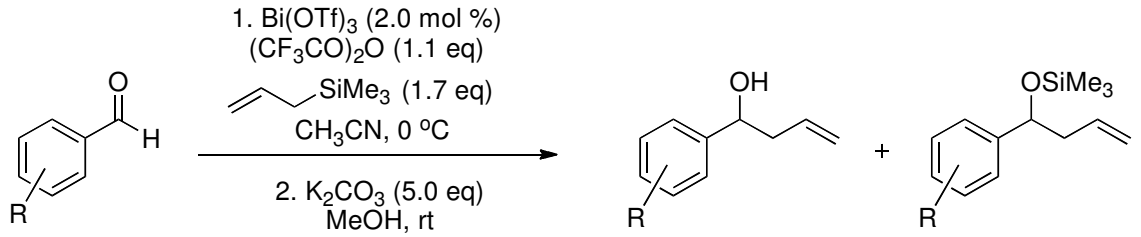
Scheme 2.36



After removal of the solvent and excess trifluoroacetic anhydride (b.p. 39.5 – 40 °C), homoallyl trifluoroacetate **106** was characterized by IR, ^{1}H and ^{13}C NMR spectroscopy.

The developed method was then applied to a variety of benzaldehydes (Table 2.4). In several cases, despite the basic hydrolysis conditions, the trimethylsilyl ether of the homoallyl alcohol was isolated in small quantities.

Table 2.4 Bismuth(III) triflate catalyzed allylation of aldehydes

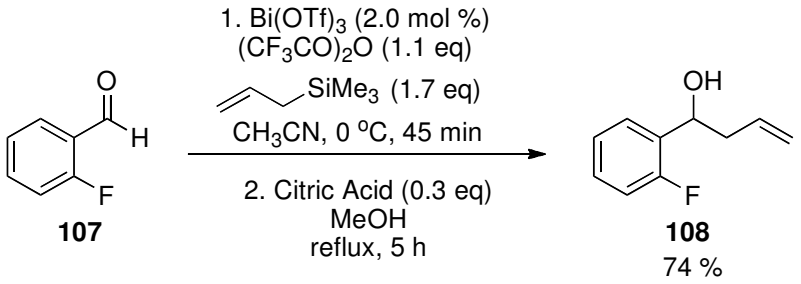


R =	t_1	t_2	Yield (%)[a]	Yield of TMS ether (Purity: %)[b]
p-CH_3	20 min	1 h 30 min	56	-
p-Br	1 h 10 min	1 h 45 min	86	-
o-F	30 min	55 min	63	18 % (88)
m-OCH_3	45 min	1 h	76	4 % (99)
m-CH_3	1 h15 min	45 min	61	-

[a] Products were purified by flash chromatography on silica gel and purity $\geq$ 98 % as determined by GC, ^{1}H and ^{13}C NMR. [b]As determined by GC.

Because the trimethylsilyl ether of the desired product was observed, even after basic hydrolysis in several cases, we reasoned that acidic hydrolysis might be a better alternative to cleave both the trimethylsilyl ether and the trifluoroacetate to maximize the yield of the desired homoallyl alcohol product. Hydrolysis with citric acid in methanol afforded the homoallyl alcohol **108** (Scheme 2.37).

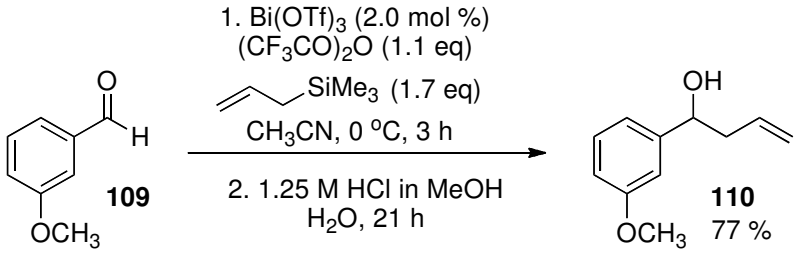
Scheme 2.37



107 **108** 74 %

Although the trimethylsilyl ether was cleaved at room temperature, cleavage of the trifluoroacetate required refluxing conditions. Since these rather harsh conditions are unlikely to be compatible with sensitive functional groups, a milder hydrolysis method was sought. The use of hydrochloric acid in methanol gave the cleavage of both the trimethylsilyl ether and trifluoroacetate at room temperature (Scheme 2.38).

Scheme 2.38

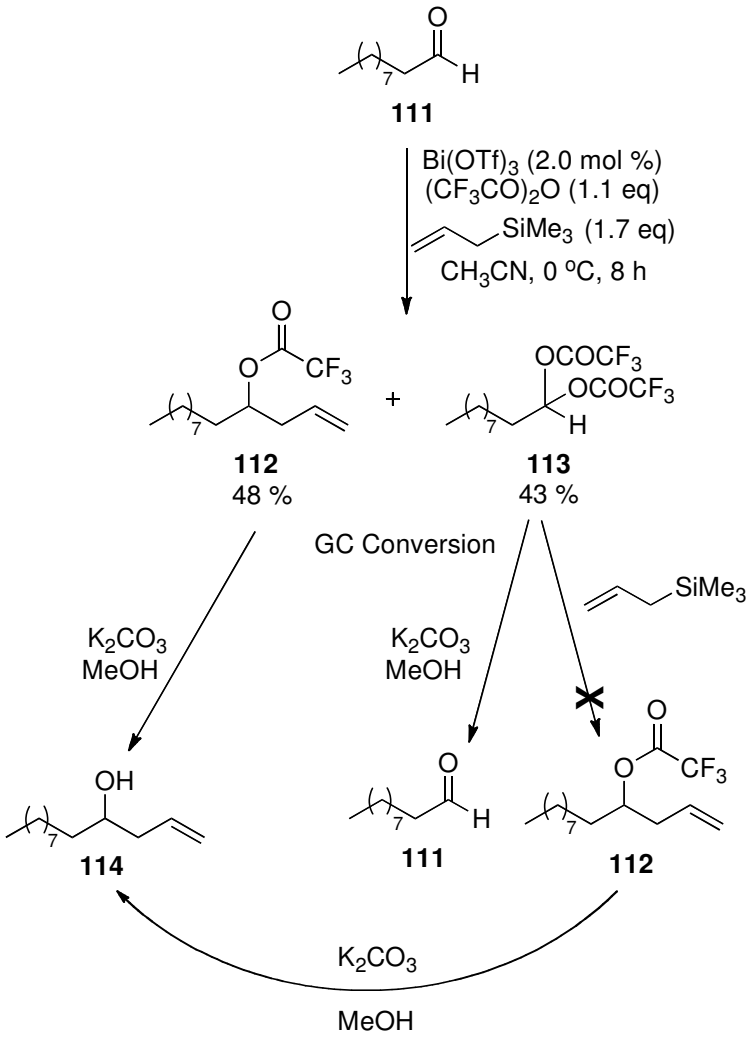


109 **110** 77 %

Attempts to expand this methodology to the allylation of alkyl aldehydes such as decanal **111** have been unsuccessful. Although rapid formation of the desired homoallyl trifluoroacetate **112** is observed, the aldehyde is also converted to its corresponding

acylal **113** which, under these reaction conditions, did not undergo allylation (Scheme 2.39). If the acylal **113** underwent allylation, the homoallyltrifluoroacetate **112** obtained could be hydrolyzed to give the desired homoallyl alcohol **114**.

Scheme 2.39



Following basic hydrolysis, the acylal **113** is cleaved to regenerate decanal **111** and the trifluoroacetate is cleaved to give the desired homoallyl alcohol **114**. Future work needs to be done to optimize the reaction conditions for aliphatic aldehydes.

III. Conclusions

(1) A robust method for the synthesis of cyclic acetals (dioxanes and dioxepines), has been developed using bismuth(III) triflate as a catalyst. Low catalyst loading, crude products of high purity, and no need for the Dean-Stark trap make this an attractive procedure.

(2) There has been little precedent in the literature for the allylation of tetrahydropyranyl and tetrahydrofuranyl ethers, so the bismuth(III) bromide catalyzed method provides new access to highly functionalized esters and alcohols.

(3) The bismuth(III) triflate catalyzed allylation of aldehydes provides access to homoallyl alcohols in a one-pot method while avoiding the use of toxic tin reagents.

(4) The use of non-toxic, non-corrosive, and inexpensive bismuth(III) triflate and bismuth(III) bromide as catalysts make these procedures attractive from a Green Chemistry prospective.

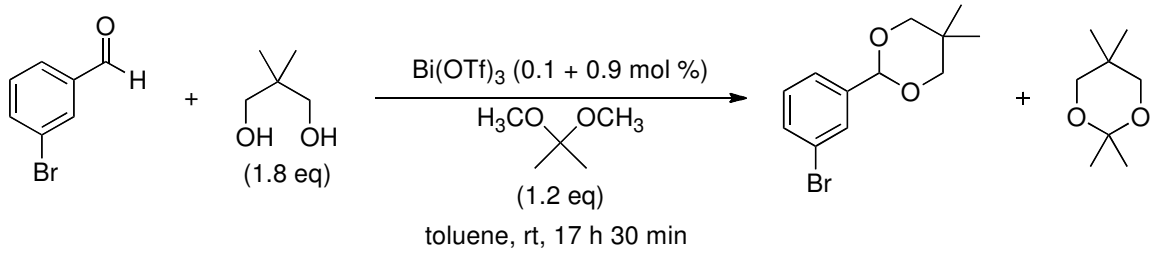
VI. Experimental

A. General Experimental

Bismuth(III) triflate was purchased from Lancaster and bismuth(III) bromide was purchased from the Aldrich Chemical Company. Each bismuth compound was stored under vacuum prior to use. The diols, anhydrides, and substituted benzaldehydes were purchased from Aldrich, Acros, or Fisher, stored at room temperature, and used as received. Decanal was distilled prior to use. Methallyltrimethylsilane and allyltrimethylsilane were purchased from Acros or Aldrich, stored at 0 °C and used as received. All solvents, water scavengers and bases were purchased and used as received. Tetrahydropyranyl and tetrahydrofuranyl ethers were synthesized by a bismuth(III) triflate catalyzed method previously developed in our group and stored room temperature prior to use.[lxvi] Reaction progress was followed by gas chromatography (Varian CP-3800 capillary GC, 30 m silica packed column with diameter of 0.25 mm) and/or TLC. Products were analyzed on a JEOL NMR spectrometer at 270 MHz (^{1}H) or 67.5 MHz (^{13}C) in $CDCl_3$ as the solvent unless otherwise mentioned. Flash chromatography was performed on Merck silica gel (230-400 Mesh).[lxvii] TLC was performed on aluminum-backed or glass-backed silica gel plates and spots were visualized under UV light and staining with 2,4-dinitrophenylhydrazine or spraying with phosphomolybdic acid followed by heating. IR spectra were recorded on a Thermo Scientific Nicolet iS10 spectrometer. Product purity was also checked by GC analysis.

A. Synthesis of Cyclic Acetals

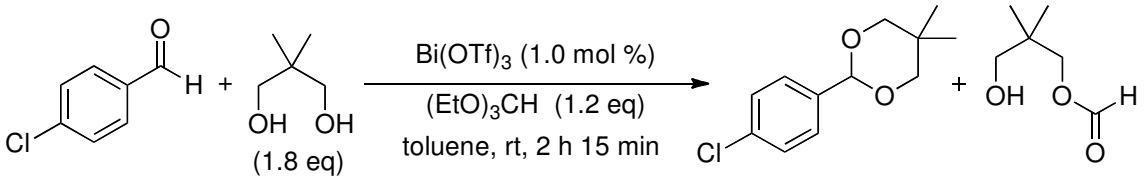
Synthesis of 2-(3-bromophenyl)-5,5-dimethyl-1,3-dioxane[lxviii] (swk1137)



A solution of 3-bromobenzaldehyde (0.250 g, 1.35 mmol), 2,2-dimethyl-1,3-propanediol (0.253 g, 2.43 mmol, 1.8 eq), and 2,2-dimethoxypropane (0.169 g, 0.20 mL, 1.62 mmol, 1.2 eq) in toluene (2.5 mL) was stirred at rt as bismuth(III) triflate (0.9 mg, 0.001 mmol, 0.10 mol %) was added. The reaction was followed by GC analysis. After 4 h 35 min additional bismuth triflate (8.0 mg, 0.012 mmol, 0.9 mmol %) was added to the reaction solution. After 17 h 30 min the reaction solution was diluted with EtOAc (20 mL) and washed with aqueous saturated $NaHCO_3$ (15 mL), H_2O (2 x 20 mL) and aqueous saturated NaCl (15 mL). The organic layer was dried (Na_2SO_4) and concentrated on a rotary evaporator to yield 0.319 g (87 %) of a cloudy white liquid. (GC analysis of the crude product was misleading and showed the crude to be > 99 % pure). ^{1}H NMR and ^{13}C NMR spectra showed presence of desired dioxane product and 2,2,5,5-tetramethyl-1,3-dioxane.[lxix] ^{1}H NMR (desired product) δ 0.80 (s, 3 H), 1.29 (s, 3 H), 3.61-3.79 (doublet of doublets, J = 11.0, 27.2 Hz, 4 H), 5.35 (s, 1 H), 7.18-7.27 (m, 1 H), 7.42 (m, 2 H), 7.70 (s, 1 H). ^{1}H NMR (2,2,5,5-tetramethyl-1,3-dioxane) δ 0.98 (s, 6 H), 1.43 (s, 6 H), 3.35 (s), (s, 4 H); ^{13}C NMR (10 peaks) δ: 21.7, 22.9, 30.1, 77.5, 100.5, 122.49, 125.00, 129.50, 129.97, 131.97, 140.78. ^{13}C NMR (2,2,5,5-tetramethyl-1,3-dioxane, 5

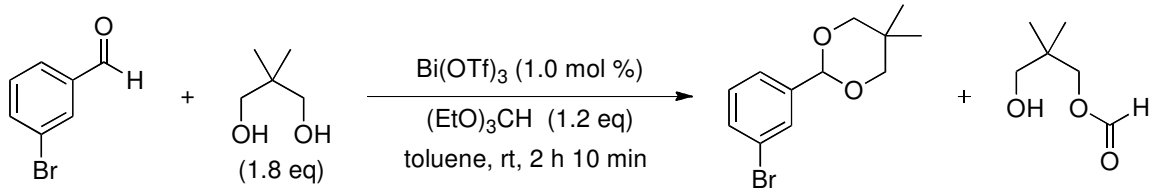
peaks) δ 21.4, 22.5, 30.1, 70.5, 97.6. The crude product was not purified because we desired a method which gives pure products without the need for purification.

Synthesis of 2-(4-chlorophenyl)-5,5-dimethyl-1,3-dioxane[lxx] (swk1145)



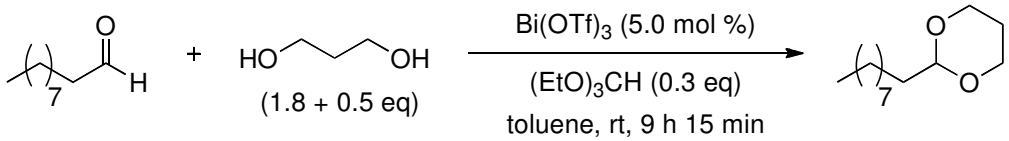
A mixture of 4-chlorobenzaldehyde (0.250 g, 1.78 mmol), 2,2-dimethyl-1,3-propanediol (0.333 g, 3.20 mmol, 1.8 eq), and triethyl orthoformate (0.316 g, 0.355 mL, 2.13 mmol, 1.2 eq) in toluene (2.5 mL) was stirred at rt as bismuth(III) triflate (11.7 mg, 0.018 mmol, 1.0 mol %) was added. Upon addition of the catalyst a clear solution resulted. The reaction was followed by GC analysis. After 2 h 15 min the reaction mixture was diluted with EtOAc (20 mL) and washed with aqueous saturated $NaHCO_3$ (20 mL), H_2O (2 x 20 mL) and aqueous saturated NaCl (15 mL). The organic layer was dried (Na_2SO_4) and concentrated on a rotary evaporator to yield 0.401 g (99 %) of a white solid (GC analysis of the crude product was misleading and showed the crude to be >99 %). ^{1}H NMR and ^{13}C NMR spectra showed a mixture of desired dioxane and 3-hydroxy-2,2-dimethylpropyl formate (6.5:1). ^{1}H NMR (desired product) δ 0.78 (s, 3 H), 1.27 (s, 3 H), 3.61-3.77 (doublet of doublets, J = 10.9, 24.5 Hz, 4 H), 5.34 (s, 1 H), 7.32-7.45 (doublet of doublets, J = 8.7 Hz, 20.0 Hz, 4 H); ^{1}H NMR (3-hydroxy-2,2-dimethylpropyl formate) δ 0.91 (s, 6 H), 1.95 (broad s, 1 H), 3.30 (s, 2 H), 4.00 (s, 2 H), 8.09 (s, 1 H); ^{13}C NMR (desired product, 9 peaks) δ 21.7, 22.9, 30.1, 77.5, 100.8, 127.5, 128.3, 134.5, 137.0; ^{13}C NMR (3-hydroxy-2,2-dimethylpropyl formate, 5 peaks) δ 21.3, 36.0, 68.0, 68.8, 161.3.

Synthesis of 2-(3-bromophenyl)-5,5-dimethyl-1,3-dioxane[68] (swk1147)



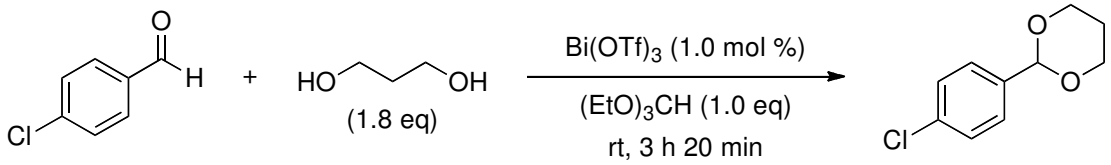
A solution of 3-bromobenzaldehyde (0.250 g, 1.35 mmol), 2,2-dimethyl-1,3-propanediol (0.253 g, 2.43 mmol, 1.8 eq), and triethyl orthoformate (0.240 g, 0.27 mL, 1.62 mmol, 1.2 eq) in toluene (2.5 mL) was stirred at rt as bismuth(III) triflate (8.7 mg, 0.014 mmol, 1.0 mol %) was added. The reaction was followed by GC analysis. After 2 h 10 min the reaction mixture was diluted with EtOAc (20 mL) and washed with aqueous saturated $NaHCO_3$ (15 mL), H_2O (2 x 20 mL) and aqueous saturated NaCl (15 mL). The organic layer was dried (Na_2SO_4) and concentrated on a rotary evaporator to yield 0.355 g (97 %) of a white solid (99 % pure by GC analysis). ^{1}H NMR and ^{13}C NMR spectra showed presence of desired dioxane and 3-hydroxy-2,2-dimethylpropyl formate (6.7:1). ^{1}H NMR (desired product) δ 0.77 (s, 3 H), 1.27 (s, 3 H), 3.59-3.77 (doublet of doublets, J = 10.8, 26.9 Hz, 4 H), 5.33 (s, 1 H), 7.19-7.25 (m, 1 H), 7.40-7.47 (m, 2 H), 7.68 (m, 1 H); ^{1}H NMR (3-hydroxy-2,2-dimethylpropyl formate) δ 0.90 (s, 6 H), 3.28 (s, 2 H), 3.99 (s, 2 H), 8.08 (s, 1 H); ^{13}C NMR (desired product, 11 peaks) δ 21.7, 22.9, 30.0, 77.4, 100.4, 122.2, 124.7, 129.2, 129.7, 131.7, 140.5; ^{13}C NMR (3-hydroxy-2,2-dimethylpropyl formate, 5 peaks) δ 21.1, 36.0, 67.8, 68.7, 161.3.

Synthesis of 2-nonyl-1,3-dioxane[lxxi] (swk1169)



A solution of decanal (2.00 g, 12.8 mmol), 1,3-propanediol (1.753 g, 1.67 mL, 23.04 mmol, 1.8 eq), and triethyl orthoformate (0.569 g, 0.64 mL, 3.84 mmol, 0.3 eq) in toluene (20 mL) was stirred at rt as bismuth(III) triflate (419.9 mg, 0.640 mmol, 5.0 mol %) was added. The reaction was followed by GC analysis. After 8 h 30 min additional 1,3-propanediol (0.487 g, 0.462 mL, 6.400 mmol, 0.5 eq) was added to the reaction solution. After 9 h 15 min aqueous 2 M NaOH (10 mL) was added to the reaction solution and the resulting mixture was stirred vigorously for 5 min. The reaction mixture was extracted with ethyl ether (50 mL + 15 mL). The combined organic layers were washed with H_2O (2 x 30 mL) and aqueous saturated NaCl (20 mL), dried ($MgSO_4$), and concentrated on a rotary evaporator to yield 2.544 g (93 %) of a clear liquid (96 % pure by GC analysis). ^{1}H NMR δ 0.80-0.85 (t, 3 H, *J* = 6.5 Hz), 1.12-1.35 (m, 16 H), 1.49-1.57 (m, 2 H), 1.93-2.10 (m, 1 H), 3.66-3.74 (triplet of doublets, 2 H), 4.01-4.07 (doublet of doublets, *J* = 12.4, 22.5 Hz, 2 H), 4.43-4.47 (t, 1 H, *J* = 5. 1 Hz); ^{13}C NMR (10 peaks) δ 14.0, 22.6, 23.9, 25.8, 29.2, 29.4, 31.8, 35.2, 66.8, 102.4.

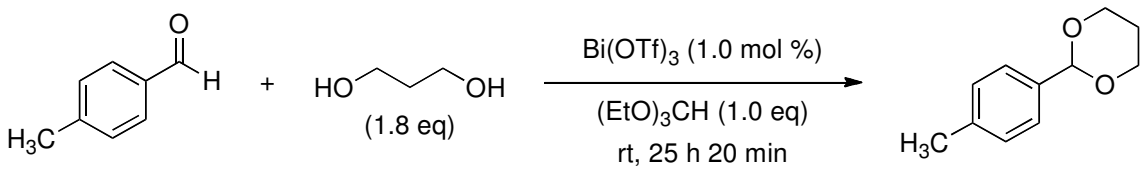
Synthesis of 2-(4-chlorophenyl)-1,3-dioxane[lxxii] (swk2013)



A homogeneous mixture of 4-chlorobenzaldehyde (1.000 g, 7.114 mmol), 1,3-propanediol (0.974 g, 0.93 mL, 12.8 mmol, 1.8 eq), and triethyl orthoformate (1.054 g, 1.19 mL, 7.114 mmol, 1.0 eq) was stirred at rt as bismuth(III) triflate (46.7 mg, 0.071 mmol, 1.0 mol %) was added. The reaction was followed by GC analysis. After 3 h 20 min, aqueous 2 M NaOH (10 mL) was added to the reaction mixture and stirred for 10 min. The mixture was extracted with ethyl ether (2 x 30 mL). The combined organic

layers were washed with H_2O (2 x 30 mL) and aqueous saturated NaCl (20 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator to yield 1.273 g (90 %) of a white solid (>99 % pure by GC analysis). ^{1}H NMR δ 1.41-1.46 (m, 1 H), 2.11-2.29 (m, 1 H), 3.92-4.02 (m, 2 H), 4.22-4.26 (doublet of doublets, *J* = 4.9, 5.7 Hz, 2 H), 5.46 (s, 1 H), 7.30-7.42 (doublet of doublets, *J* = 8.5, 15.8 Hz, 4 H); ^{13}C NMR (7 peaks) δ 25.7, 67.4, 100.8, 127.5, 128.4, 134.5, 137.2.

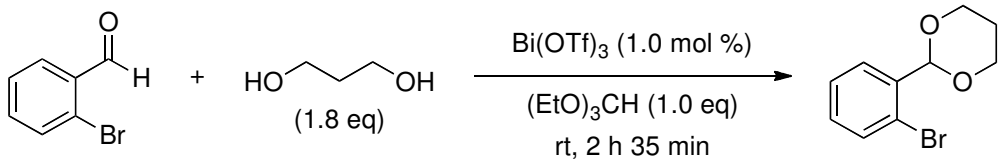
Synthesis of 2-(*p*-tolyl)-1,3-dioxane[lxxiii] (swk2015)



A homogeneous mixture of 4-tolualdehyde (2.00 g, 16.6 mmol), 1,3-propanediol (2.279 g, 2.17 mL, 29.96 mmol, 1.8 eq), and triethyl orthoformate (2.467 g, 2.77 mL, 16.64 mmol, 1.0 eq) was stirred at rt as bismuth(III) triflate (109.2 mg, 0.166 mmol, 1.0 mol %) was added. Upon addition of the catalyst the reaction mixture became slightly warm. The reaction was followed by GC analysis. After 25 h 20 min, aqueous 2 M NaOH (25 mL) was added to the reaction mixture and stirred for 10 min. The reaction mixture was then extracted with ethyl ether (50 mL + 25 mL). The combined organic layers were washed with a mixture of aqueous saturated $NaHSO_3$/ ethanol (59/41, v/v, 2 x 30 mL), H_2O (2 x 30 mL) and aqueous saturated NaCl (20 mL). The organic layer was dried (Na_2SO_4) and concentrated on a rotary evaporator to yield 2.33 g (79 %) of a clear liquid (95 % pure by GC analysis) that solidified to a wet, white solid under house vacuum. ^{1}H NMR and ^{13}C NMR showed presence of product and starting material (93:7). ^{1}H NMR δ 1.39-1.44 (d, 1 H, *J* = 13.3 Hz), 2.11-2.31 (m, 1 H), 2.35 (s, 3 H), 3.93-4.02 (triplet of

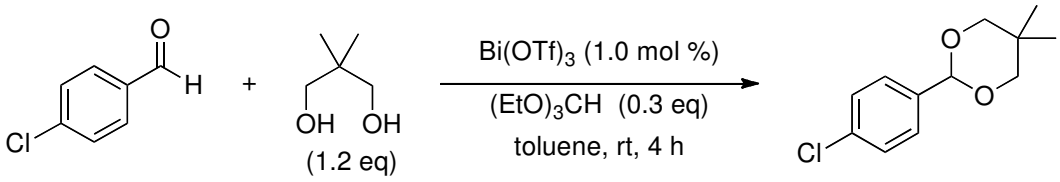
doublets, 2 H), 4.23-4.28 (doublet of doublets, J = 5.1, 5.7 Hz, 2 H), 5.48 (s, 1 H), 7.16-7.40 (doublet of doublets, J = 8.2, 47.5 Hz, 4 H); ^{13}C NMR (8 peaks) δ 21.1, 25.6, 67.2, 101.5, 125.7, 128.7, 135.8, 138.3.

Synthesis of 2-(2-bromophenyl)-1,3-dioxane[lxxiv] (swk2025)



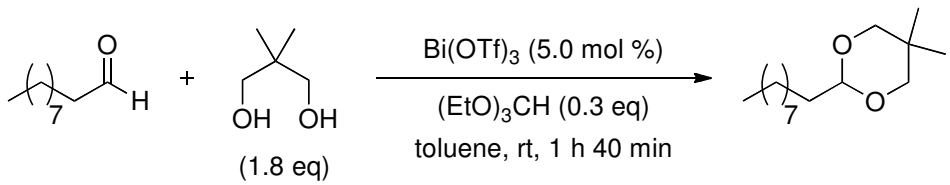
A homogeneous mixture of 2-bromobenzaldehyde (2.00 g, 10.8 mmol), 1,3-propanediol (1.481 g, 1.41 mL, 19.46 mmol, 1.8 eq), and triethyl orthoformate (1.602 g, 1.80 mL, 10.81 mmol, 1.0 eq) was stirred at rt as bismuth(III) triflate (70.9 mg, 0.108 mmol, 1.0 mol %) was added. After addition of the catalyst the reaction mixture became slightly warm. The reaction was followed by GC analysis. After 2 h 35 min, aqueous 2 M NaOH (20 mL) was added to the reaction mixture and stirred for 10 min. The mixture was extracted with ethyl ether (60 mL + 20 mL). The combined organic layers were washed with H_2O (2 x 40 mL), aqueous saturated NaCl (20 mL), dried ($MgSO_4$), and concentrated on a rotary evaporator to yield 2.61 g of a clear liquid. A portion of the crude product (2.48 g) was filtered through silica gel (70 g, EtOAc/heptane, 15/85, v/v). Forty fractions (8 mL) were collected. Fractions 26-36 were combined to yield 2.05 g, (78 %) of a white solid (>99 % pure by GC analysis). ^{1}H NMR δ 1.41-1.46 (d, 1 H, J = 13.3 Hz), 2.16-2.34 (m, 1 H), 3.97-4.05 (triplet of doublets, 2 H), 4.23-4.29 (doublet of doublets, J = 5.1, 5.9 Hz, 2 H), 5.76 (s, 1 H), 7.16-7.21 (triplet of doublets, 1 H), 7.31-7.36 (t, 1 H, J = 7.3 Hz), 7.51-7.54 (d, 1 H, J = 7.9 Hz), 7.68-7.70 (doublet of doublets, J = 1.7, 6.2 Hz, 1 H); ^{13}C NMR (9 peaks) δ 25.6, 67.5, 100.8, 122.2, 127.4, 128.0, 130.2, 132.5, 137.4.

Synthesis of 2-(4-chlorophenyl)-5,5-dimethyl-1,3-dioxane[70] (swk1175)



A solution of 4-chlorobenzaldehyde (1.00 g, 7.12 mmol,), 2,2-dimethyl-1,3-propanediol (1.334 g, 12.81 mmol, 1.8 eq), and triethyl orthoformate (0.316 g, 0.36 mL, 2.13 mmol, 0.3 eq) in toluene (2.5 mL) was stirred at rt as bismuth(III) triflate (46.7 mg, 0.071 mmol, 1.0 mol %) was added. The reaction was followed by GC analysis. After 4 h, aqueous 2 M NaOH (10 mL) was added to the reaction solution and stirred vigorously for 5 min. The resulting mixture was extracted with ethyl ether (2 x 15 mL). The combined organic layers were washed with H_2O (2 x 25 mL), aqueous saturated NaCl (20 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator to yield 1.342 g (83 %) of a white solid (>99 % pure by GC analysis). ^{1}H NMR δ 0.79 (s, 3 H), 1.28 (s, 3 H), 3.61-3.78 (doublet of doublets, J = 11.0, 24.5 Hz, 4 H), 5.35 (s, 1 H), 7.32-7.46 (doublet of doublets, J = 8.5, 20.3 Hz, 4 H); ^{13}C NMR (9 peaks) δ 21.8, 22.9, 30.1, 77.5, 100.8, 127.6, 128.3, 134.5, 137.0.

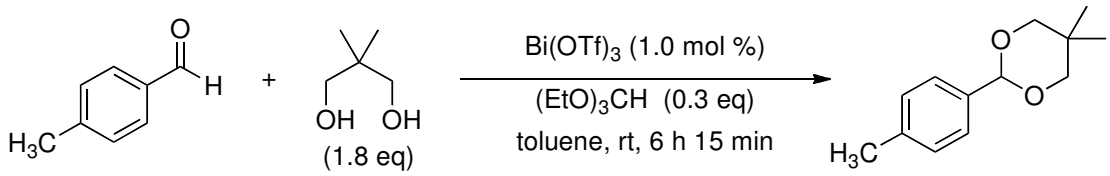
Synthesis of 5,5-dimethyl-2-nonyl-1,3-dioxane[lxxv] (swk1181)



A solution of decanal (1.00 g, 6.40 mmol), 2,2-dimethyl-1,3-propanediol (1.20 g, 11.5 mmol, 1.8 eq), and triethylorthoformate (0.285 g, 0.32 mL, 1.92 mmol, 0.3 eq) in toluene (10 mL) was stirred at rt as bismuth(III) triflate (210.0 mg, 0.320 mmol, 5.0 mol %) was

added. The reaction was followed by GC analysis. After 1 h 40 min, aqueous 2 M NaOH (10 mL) was added to the solution and the resulting mixture was stirred vigorously for 10 min. The mixture was extracted with ethyl ether (2 x 25 mL). The combined organic layers were washed with H_2O (2 x 20 mL), aqueous saturated NaCl (15 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator to yield 1.466 g (95 %) of a clear liquid (98 % pure by GC analysis). ^{1}H NMR δ 0.66 (s, 3 H), 0.80-0.85 (t, 3 H, *J* = 6.7 Hz), 1.14 (s, 3 H), 1.17-1.38 (m, 16 H), 3.35-3.60 (doublet of doublets, *J* = 10.8, 39.1 Hz, 4 H), 4.33-4.37 (t, 1 H, *J* = 5.1 Hz); ^{13}C NMR (12 peaks) δ 14.0, 21.8, 22.6, 22.9, 23.9, 29.3, 29.5, 30.1, 31.8, 34.9, 77.1, 102.2.

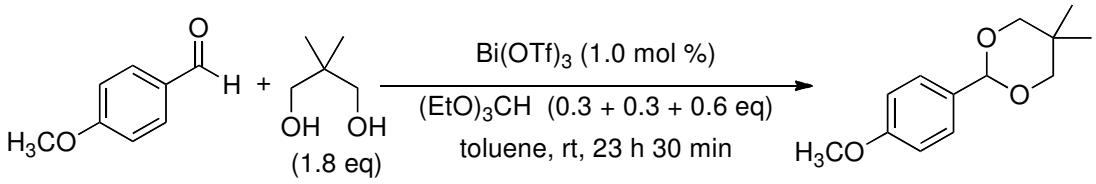
Synthesis of 5,5-dimethyl-2-(*p*-tolyl)-1,3-dioxane[70] (swk1185)



A solution of 4-tolualdehyde (3.00 g, 25.0 mmol), 2,2-dimethyl-1,3-propanediol (4.681 g, 44.94 mmol, 1.8 eq), and triethyl orthoformate (1.110 g, 1.25 mL, 7.460 mmol, 0.3 eq) in toluene (30 mL) was stirred at rt as bismuth(III) triflate (16.4 mg, 0.025 mmol, 0.1 mol %) was added. The reaction was followed by GC analysis. After 6 h 15 min, aqueous 2 M NaOH (15 mL) was added to the reaction solution and stirred vigorously for 10 min. The mixture was extracted with ether (50 mL + 15 mL). The combined organic layers were washed with H_2O (2 x 20 mL), aqueous saturated NaCl (15 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator to yield 4.47g (87 %) of a white solid (97 % pure by GC analysis). ^{1}H NMR δ 0.81 (s, 3 H), 1.32 (s, 3 H), 2.37 (s, 3 H), 3.63-3.80 (doublet of doublets, *J* = 10.9, 23.7 Hz, 4 H), 5.38 (s, 1 H), 7.19-7.44 (doublet of doublets, *J* = 8.0,

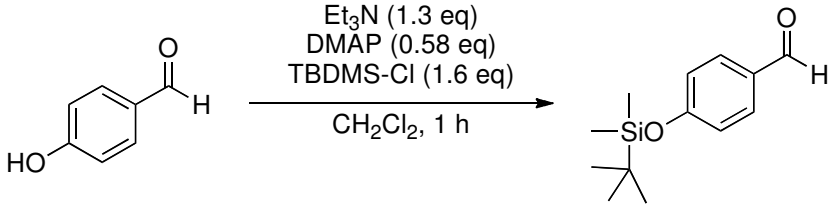
52.7 Hz, 4 H); ^{13}C NMR (10 peaks) δ 21.2, 21.8, 22.9, 30.1, 77.5, 101.7, 125.9, 128.8, 135.6, 138.4.

Synthesis of 2-(4-methoxyphenyl)-5,5-dimethyl-1,3-dioxane[70] (swk1187)



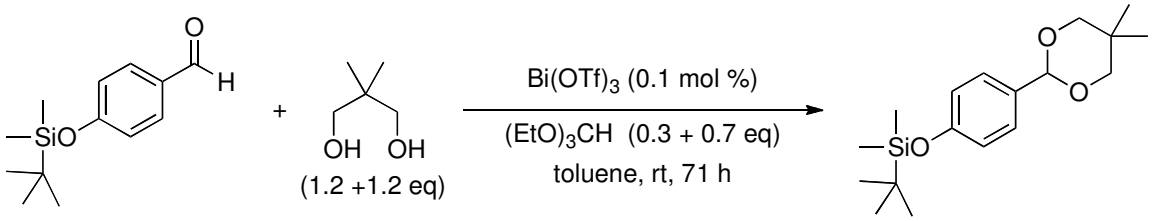
A solution of 4-methoxybenzaldehyde (3.00 g, 22.0 mmol), 2,2-dimethyl-1,3-propanediol (4.131 g, 39.66 mmol, 1.8 eq) and triethyl orthoformate (0.980 g, 1.11 mL, 6.61 mmol, 0.3 eq) in toluene (30 mL) was stirred at rt as bismuth(III) triflate (144.6 mg, 0.220 mmol, 1.0 mol %) was added. The reaction was followed by GC analysis. After 6 h 10 min additional triethyl orthoformate (1.11 mL, 0.980 g, 6.61 mmol, 0.3 eq) was added to the reaction solution. After 7 h 20 min additional triethyl orthoformate (2.20 mL, 1.959 g, 13.22 mmol, 0.6 eq) was added to the reaction solution. After 23 h 30 min, aqueous 2 M NaOH (15 mL) was added to the reaction solution and stirred vigorously for 10 min. The mixture was extracted with ethyl ether (50 mL + 20 mL). The combined organic layers were washed with H_2O (2 x 30 mL), aqueous saturated NaCl (20 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator to yield 4.54 g (93 %) of a white solid (>99 % pure by GC analysis). ^{1}H NMR δ 0.78 (s, 3 H), 1.29 (s, 3 H), 3.60-3.78 (doublet of doublets, J = 12.4, 22.5 Hz, 4 H), 4.78 (s, 3 H), 5.34 (s, 1 H), 6.87-7.45 (doublet of doublets, J = 8.7, 138.2 Hz, 4 H); ^{13}C NMR (10 peaks) δ 21.8, 22.9, 30.0, 55.1, 77.5, 101.5, 113.5, 127.3, 131.0, 159.8.

Synthesis of 4-((*tert*-butyldimethylsilyl)oxy)benzaldehyde[lxxvi] (swk1075)



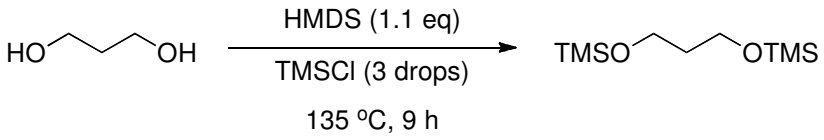
A solution of 4-hydroxybenzaldehyde (5.00 g, 40.9 mmol) in dichloromethane (50 mL) was stirred at 0 °C under N_2 as triethylamine (5.39 g, 7.42 mL, 53.2 mmol, 1.3 eq), 4-dimethylaminopyridine (2.901 g, 23.75 mmol, 0.58 eq), and *tert*-butyldimethylsilyl chloride (9.874 g, 65.51 mmol, 1.6 eq) were added. The ice bath was not maintained. The reaction was followed by GC analysis. After 1 h the reaction mixture was diluted with dichloromethane (60 mL) and washed with H_2O (4 x 15 mL), aqueous 2 M NaOH (20 mL), and aqueous saturated NaCl (20 mL). The organic phase was concentrated on a rotary evaporator to yield 12.18 g of a pale yellow colored liquid (93 % pure by GC analysis). The crude product was purified in two portions. Portion 1: A six-gram portion of the crude product was filtered through silica gel (120 g, EtOAc/heptane, 15/85, v/v) Forty fractions (20 mL) were collected. Fractions 8-30 were combined to yield 3.79 g (79 %) of a clear liquid (>99 % pure by GC analysis). Portion 2: A six-gram portion of the crude product was filtered through silica gel (120 g, EtOAc/heptane, 15/85, v/v). Forty fractions (20 mL) were collected. Fractions 2-27 were combined to yield 3.81 g (81 %) of a clear liquid (>99 % pure by GC analysis). ^{1}H NMR δ 0.23 (s, 6 H), 0.98 (s, 9 H), 6.91-7.79 (doublet of doublets, J = 8.5, 219.8 Hz, 4 H), 9.87 (s, 1 H); ^{13}C NMR (8 peaks) δ -4.5, 18.1, 25.4, 120.4, 130.3, 131.8, 161.4, 190.7. Overall yield: 7.6 g (78.5 %)

Synthesis of *tert*-butyl(4-(5,5-dimethyl-1,3-dioxane-2-yl)pheoxy)-dimethylsilane (swk1191)



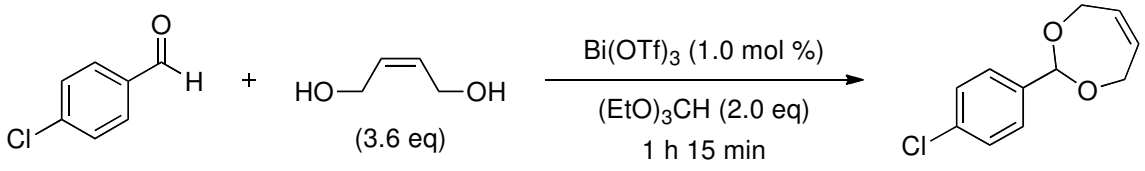
A solution of 4-(*tert*-buyldimethylsilyloxy)benzaldehyde (0.20 g, 0.85 mmol), 2,2-dimethyl-1,3-propanediol (0.106 g, 1.02 mmol, 1.2 eq), and triethyl orthoformate (0.038 g, 0.04 mL, 0.25 mmol, 0.3 eq) in toluene (2.0 mL) was stirred at rt as bismuth(III) triflate (0.6 mg, 0.001 mmol, 0.1 mol %) was added. The reaction was followed by GC analysis. After 5 h 35 min additional 2,2-dimethyl-1,3-propanediol (0.106 g, 1.015 mmol, 1.2 eq) and triethyl orthoformate (0.10 mL, 0.09 g, 0.592 mmol, 0.7 eq) were added to the reaction solution. After 71 h 20 min, aqueous 2 M NaOH (5 mL) was added to the reaction solution and stirred vigorously for 10 min. The mixture was extracted with ethyl ether (2 x 20 mL). The combined organic layers were washed with H_2O (2 x 20 mL), aqueous saturated NaCl (15 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator to yield 0.155 g (57 %) of a white solid (94 % pure by GC analysis). ^{1}H NMR δ 0.15 (s, 6 H), 0.78 (s, 3 H), 0.98 (s, 9 H), 1.28 (s, 3 H), 3.60-3.77 (doublet of doublets, *J* = 11.0, 22.5 Hz, 4 H), 5.32 (s, 1 H), 6.80-7.37 (doublet of doublets, *J* = 8.5, 137.7 Hz, 4 H); ^{13}C NMR (12 peaks) δ -4.5, 18.2, 21.9, 23.1, 25.7, 30.2, 77.7, 101.8, 120.0, 127.3, 131.6, 156.2.

Synthesis of 1,3-*bis*(trimethylsiloxy)propane from 1,3-propanediol[61] (swk1107)



A mixture of 1,3-propanediol (0.8320 g, 0.79 mL, 10.93 mmol) and hexamethyldisilazane (2.00 g, 2.58 mL, 12.39 mmol, 1.1 eq) was stirred at rt as chlorotrimethylsilane (3 drops) was added slowly. Addition of chlorotrimethylsilane caused the evolution of white fumes and a white solid formed in the reaction mixture. The reaction mixture was heated to 135 °C using an oil bath. After 3 h 25 min the reaction mixture was cooled to rt. After 5 h additional 1,3-propanediol (3.00 mL, 3.159 g, 41.52 mmol), hexamethyldisilazane (7.594 g, 9.81 mL, 47.05 mmol, 1.1 eq), and chlorotrimethylsilane (1 drop) was added to the reaction mixture. The reaction mixture was again heated to 135 °C using an oil bath. Vigorous gas evolution was observed. After 9 h the reaction mixture was cooled to rt and the crude mixture was purified using Kugelrohr distillation (15 mmHg, house vacuum, 110 °C) to yield 9.789 g of a colorless liquid (85 %). ^{1}H NMR δ 0.07 (s, 18 H), 1.68-1.73 (pentet, 2 H), 3.60-3.65 (t, 4 H, J = 6.3 Hz); ^{13}C NMR (3 peaks) δ -0.6, 35.5, 59.1.

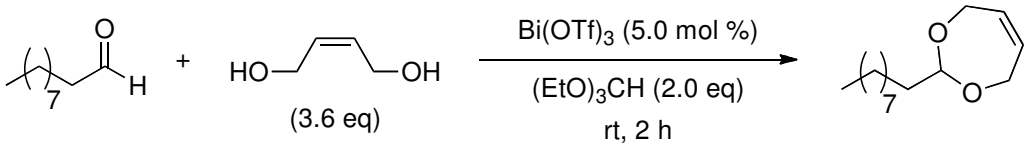
Synthesis of 2-(4-chlorophenyl)-4,7-dihydro-1,3-dioxepine[lxxvii] (swk2171)



A mixture of 4-chlorobenzaldehyde (3.00 g, 21.3 mmol), *cis*-2-butene-1,4-diol (6.33 g, 6.77 mL, 76.8 mmol, 3.6 eq), and triethyl orthoformate (7.108 g, 6.33 mL, 42.7 mmol, 2.0 eq) was stirred at rt as bismuth(III) triflate (140.0 mg, 0.213 mmol, 1.0 mol %) was

added. The reaction was followed by GC analysis. After 1 h 15 min, aqueous 2 M NaOH (50 mL) was added to the reaction mixture and stirred vigorously for 15 min. The mixture was extracted twice with ethyl ether (2 x 75 mL). The combined organic layers were washed with H_2O (5 x 40 mL), aqueous saturated NaCl (35 mL), dried ($MgSO_4$) and concentrated on a rotary evaporator to yield 5.66 g of a slightly yellow colored solid. The crude product was filtered through silica gel (200 g, EtOAc/heptane, 10/90, v/v). Following a prefraction (175 mL), forty fractions (20 mL) were collected. Fractions 21-25 were combined to yield 2.19 g (49 %) of a white solid (>99 % pure by GC analysis). ^{1}H NMR δ 4.20-4.39 (m, 4 H), 5.75-5.76 (t, 2 H, *J* = 1.9 Hz), 5.80 (s, 1 H), 7.30-7.48 (doublet of doublets, *J* = 8.4, 25.7 Hz, 4 H); ^{13}C NMR (7 peaks) δ 64.5, 11.4, 127.9, 128.3, 129.8, 134.2, 137.4.

Synthesis of 2-nonyl-4,7-dihydro-1,3-dioxepine (swk2179)

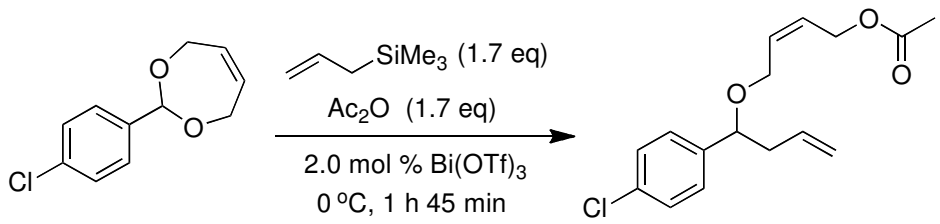


A mixture of decanal (3.00 g, 19.2 mmol), *cis*-2-butene-1,4-diol (6.089 g, 5.68 mL, 69.11 mmol, 3.6 eq), and triethyl orthoformate (5.690 g, 6.39 mL, 38.40 mmol, 2.0 eq) was stirred at rt as bismuth(III) triflate (629.9 mg, 0.960 mmol, 5.0 mol %) was added. The reaction was followed by GC analysis. After 2 h, aqueous 2 M NaOH (75 mL) was added to the reaction mixture and stirred vigorously for 15 min. The resulting mixture was extracted with ethyl ether (2 x 100 mL). The combined organic layers were washed with H_2O (4 x 50 mL), aqueous saturated NaCl (30 mL), dried ($MgSO_4$), and concentrated on a rotary evaporator to yield 4.50 g of a clear, yellow colored liquid. The crude product was filtered through silica gel (200 g, EtOAc/heptane, 5/95, v/v).

Following a prefraction (225 mL), forty-five fractions (20 mL) were collected. Fractions 19-36 were combined to yield 2.53 g (58 %) of a slightly cloudy liquid (>99 % pure by GC analysis). ^{1}H NMR δ 0.82-0.87 (t, 3 H, *J* = 6.7 Hz), 1.21-1.37 (m, 14 H), 1.58-1.66 (m, 2 H), 4.10-4.39 (m, 4 H), 4.71-4.75 (t, 1 H, *J* = 5.8 Hz), 5.68-5.71 (t, 2 H, *J* = 1.7 Hz); ^{13}C NMR (12 peaks) δ 14.1, 22.6, 24.8, 29.3, 29.4, 29.48, 29.53, 31.9, 33.5, 65.0, 104.5, 129.8.

C. Allylation and Subsequent Hydrolysis of Dioxepines

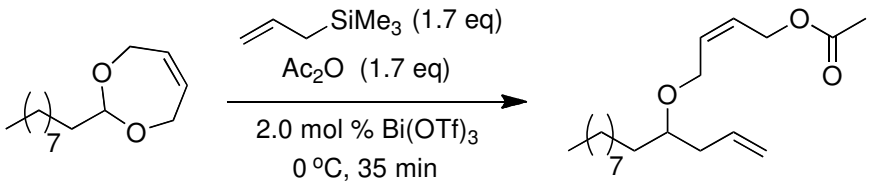
Allylation of 2-(4-chlorophenyl)-4,7-dihydro-1,3-dioxepine (swk2173)



A mixture of 2-(4-chlorophenyl)-4,7-dihydro-1,3-dioxepine (1.835 g, 8.710 mmol), allyltrimethylsilane (1.692 g, 2.353 mL, 14.81 mmol, 1.7 eq), and acetic anhydride (1.512 g, 1.40 mL, 14.8 mmol, 1.7 eq) was stirred at 0 °C under N_2 in a flame-dried three-neck round bottom flask as bismuth(III) triflate (114. 3 mg, 0.174 mmol, 2.0 mol %) was added. The bismuth triflate immediately dissolved and the reaction turned light brown. The reaction was followed by GC analysis. After 1 h 45 min the reaction mixture was filtered through silica gel (250 g, EtOAc/ heptane, 10/90, v/v). Following a prefraction (250 mL), one hundred and forty-one fractions were collected. Fractions 84-117 were combined to yield 1.72 g (67 %) of a clear, pale yellow liquid product (>99 % pure by GC analysis). ^{1}H NMR: δ 2.02 (s, 3 H), 2.30-2.59 (m, 2 H), 3.84-3.97 (m, 2 H), 4.24-4.29 (t, 1 H, *J* = 6.67 Hz), 4.49-4.52 (d, 2 H, *J* = 5.94 Hz), 4.98-5.04 (m, 2 H), 5.60-5.78 (m, 3 H), 7.19-7.25 (m, 2 H), 7.28-7.32 (m, 2 H); ^{13}C NMR (14 peaks) δ 21.0, 42.5, 60.4,

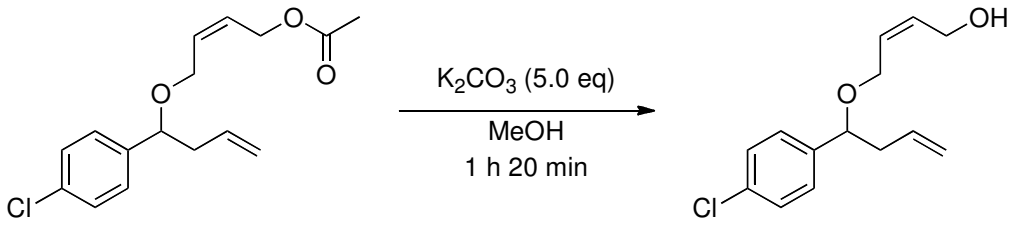
64.3, 81.0, 117.5, 126.7, 128.2, 128.7, 130.7, 133.5, 134.3, 140.2, 170.8. HRMS-CI (*m/z*): M^+ calculated for $C_{16}H_{20}O_3Cl$, 295.1101; found, 295.1094.

Allylation of 2-nonyl-4,7-dihydro-1,3-dioxepine (swk2185)



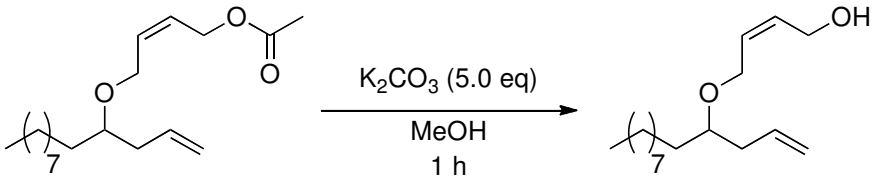
A mixture of 2-nonyl-4,7-dihydro-1,3-dioxepine (1.00 g, 4.42 mmol), allyltrimethylsilane (0.858 g, 1.19 mL, 7.51 mmol, 1.7 eq) and acetic anhydride (0.710 g, 0.767 mL, 7.51 mmol, 1.7 eq) was stirred at 0 °C under N_2 in a flame-dried three-neck round bottom flask as bismuth(III) triflate (58.0 mg, 0.088 mmol, 2.0 mol %) was added. The reaction mixture immediately turned black. The reaction was followed by GC analysis. After 35 min the reaction mixture was filtered through silica gel (125 g, EtOAc/ heptane, 5/95, v/v). Following a prefraction (130 mL), one hundred and ten fractions were collected. Fractions 51-96 were combined to yield 0.807 g (59 %) of a clear, yellow colored liquid product (>99 % pure by GC analysis). ^{1}H NMR: δ 0.82-0.87 (t, 3 H, *J* = 6.68 Hz), 1.22-1.45 (m, 16 H), 2.02 (s, 3 H), 2.21-2.25 (t, 2 H, *J* = 6.55 Hz), 3.25-3.34 (pentet, 1 H), 3.99-4.14 (m, 2 H), 4.59-4.61 (d, 2 H, *J* = 6.18 Hz), 4.99-5.07 (m, 2 H), 5.57-5.86 (m, 3 H); ^{13}C (19 peaks) δ 14.2, 21.0, 22.7, 25.4, 29.4, 29.6, 29.7, 29.8, 32.0, 33.9, 38.4, 60.4, 64.5, 79.0, 116.9, 125.9, 131.7, 135.0, 170.8. HRMS-CI (*m/z*): M^+ calculated for $C_{19}H_{35}O_3$, 311.2586; found, 311.2586.

Hydrolysis of 4-(1-(4-chlorophenyl)but-3-enyloxy)but-2-enyl acetate (swk2187)



A solution of 4-(1-(4-chlorophenyl)but-3-enyloxy)but-2-enyl acetate (0.500 g, 1.70 mmol) in methanol (5.0 mL) was stirred at rt as anhydrous K_2CO_3 (1.172 g, 8.481 mmol, 5.0 eq) was added. The reaction was followed by GC analysis. After 1 h 20 min the mixture was diluted with ether (75 mL). The inorganic solids were removed by suction filtration. The resulting cloudy filtrate was washed with H_2O (2 x 40 mL) and aqueous saturated NaCl (15 mL). The organic layer was dried ($MgSO_4$) and concentrated on a rotary evaporator to yield 0.413 g (96 %) of a clear, pale yellow colored liquid product. The crude product was filtered through silica gel (30 g, EtOAc/ heptane, 30/70, v/v). Following a prefraction (40 mL), thirty-six fractions were collected. Fractions 10-28 were combined to yield 0.386 g (90 %) of a clear, colorless liquid product (>99 % pure by GC analysis). ^{1}H NMR δ 2.29-2.57 (m, 2 H), 2.67-2.73 (broad doublet, 1 H, J = 15.3 Hz), 3.78-3.91 (m, 2 H), 4.00-4.03 (d, 2 H, J = 6.18 Hz), 4.24-4.29 (t, 1 H, J = 6.68 Hz), 4.96-5.02 (m, 2 H), 5.56-5.77 (m, 3 H), 7.18-7.21 (d, 2 H, J = 8.42 Hz), 7.27-7.30 (d, 2 H, J = 8.40 Hz); ^{13}C (12 peaks) δ 42.5, 58.5, 64.3, 80.9, 117.6, 128.0, 128.2, 128.7, 132.5, 133.5, 134.2, 140.1. HRMS-CI (*m/z*): M^+ calculated for $C_{14}H_{18}O_2Cl$, 253.09953; found 253.09928.

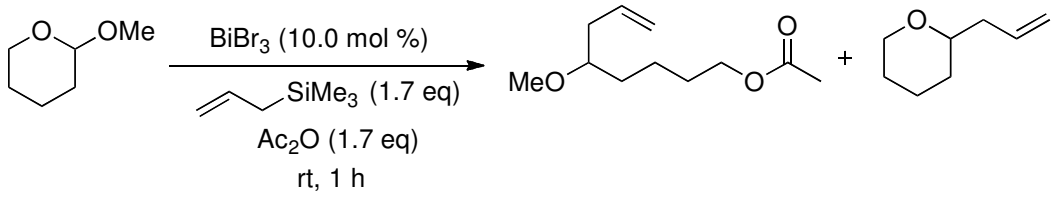
Hydrolysis of 4-(tridec-1-en-4-yloxy)but-2-enyl acetate (swk2189)



A solution of 4-(tridec-1-en-4-yloxy)but-2-enyl acetate (0.500 g, 1.16 mmol) in methanol (5.0 mL) was stirred at rt as anhydrous K_2CO_3 (1.113 g, 8.052 mmol, 5.0 eq) was added. Reaction progress was followed by GC analysis. After 1 h the reaction mixture was diluted with ether (75 mL) and the inorganic solids were removed by suction filtration. The cloudy filtrate was washed with H_2O (2 x 40 mL) and aqueous saturated NaCl (15 mL). The organic layer was dried ($MgSO_4$) and concentrated on a rotary evaporator to yield 0.438 g of a clear, yellow liquid. The crude product was filtered through silica gel (30 g, EtOAc/ heptane, 30/70, v/v). Following a prefraction (30 mL), twenty-eight fractions were collected. Fractions 5-18 were combined to yield 0.401 g (93 %) of a clear, colorless liquid (>99 % pure by GC analysis). ^{1}H NMR δ 0.82-0.86 (t, 3 H, J = 6.55 Hz), 1.23 (broad s, 14 H), 1.29-1.45 (m, 2 H), 2.21-2.26 (m, 2 H), 2.56 (s, 1 H), 3.27-3.36 (pentet, 1 H), 3.96-4.10 (m, 2 H), 4.13-4.15 (m, 2 H), 5.00-5.08 (m, 2 H), 5.60-5.85 (m, 3 H); ^{13}C NMR (17 peaks) δ 14.2, 22.7, 25.4, 29.4, 29.65, 29.67, 29.8, 32.0, 33.8, 38.3, 58.6, 64.6, 79.2, 117.1, 128.8, 131.9, 134.9. HRMS-CI (*m/z*): M^+ calculated for $C_{17}H_{33}O_2$, 269.2481; found 269.2479.

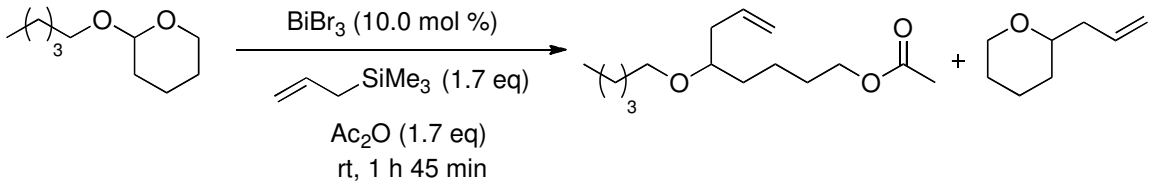
D. Allylation of Tetrahydropyranyl and Tetrahydrofuranyl Ethers

Allylation of 2-methoxytetrahydropyran (swk3043)



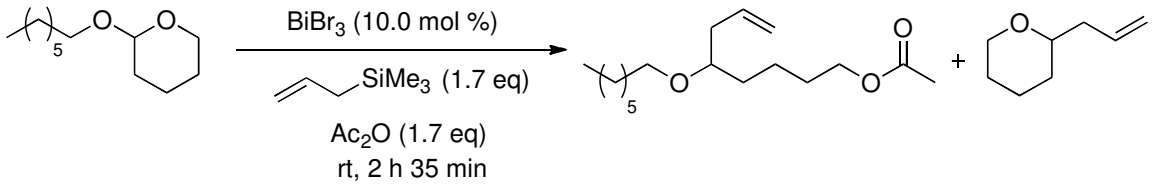
A homogeneous mixture of 2-methoxytetrahydropyran (1.000 g, 8.609 mmol), allyltrimethylsilane (2.33 mL, 1.67 g, 14.6 mmol, 1.7 eq), and acetic anhydride (1.38 mL, 1.49 g, 14.6 mmol, 1.7 eq) was stirred at rt under N_2 as bismuth(III) bromide (386.3 mg, 0.861 mmol, 10.0 mol %) was added. The bismuth(III) bromide dissolved and the reaction mixture became slightly warm and turned yellow. The reaction was followed by GC analysis. After 1 h the reaction mixture was filtered through silica gel (50 g, EtOAc/pentane, 4/96, v/v). Following a prefraction (210 mL, 2/98, v/v), eighty fractions (8 mL) were collected. Fractions 17-36 were combined to yield 0.261 g of a very pale yellow liquid that was determined to be 2-allyltetrahydro-2*H*-pyran[lxxviii] (96 % pure by GC analysis). Fractions 37-75 were combined to yield 1.000 g (58 %) of the ester as a clear liquid (99 % pure by GC analysis). ^{1}H NMR δ 1.25-1.63 (m, 6 H), 2.00 (s, 3 H), 2.13-2.30 (m, 2 H), 3.12-3.19 (pentet, 1 H), 3.30 (s, 3 H), 3.99-4.04 (t, 2 H, J = 6.5 Hz), 5.00-5.06 (m, 2 H), 5.68-5.83 (m, 1 H); ^{13}C NMR (11 peaks) δ 20.9, 21.6, 28.6, 32.9, 37.6, 56.5, 64.4, 80.1, 116.9, 134.6, 171.1. IR ν_{max} 2937, 1738, 1641 cm^{-1}. HRMS-CI (*m/z*): M^+ calculated for $C_{11}H_{21}O_3$, 201.14908; found, 201.14888.

Allylation of 2-(pentyloxy)tetrahydro-2*H*-pyran (swk3049)



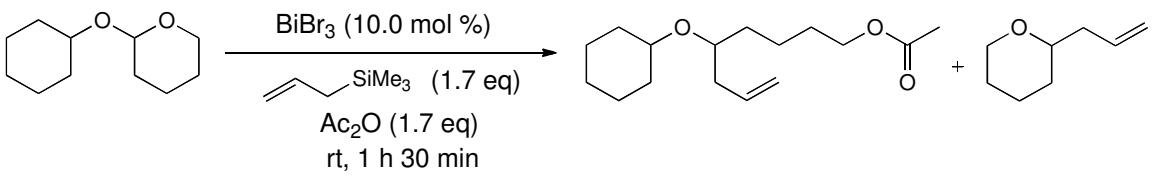
A homogeneous mixture of 2-(pentyloxy)tetrahydro-2*H*-pyran (1.000 g, 5.809 mmol), allyltrimethylsilane (1.128 g, 1.57 mL, 9.875 mmol, 1.7 eq), and acetic anhydride (1.008 g, 0.93 mL, 9.875 mmol, 1.7 eq) was stirred at rt under N_2 as bismuth(III) bromide (260.6 mg, 0.581 mmol, 10.0 mol %) was added. The bismuth(III) bromide dissolved and the reaction mixture became slightly warm and turned yellow. The reaction was followed by GC analysis. After 1 h 45 min the reaction mixture was filtered through silica gel (50 g, EtOAc/ pentane, 2/98, v/v). Following a prefraction (25 mL), eighty fractions (8 mL) were collected. Fractions 13-28 were combined to yield 0.236 g of a clear liquid that was determined to be a mixture of several products including 2-allyltetrahydro-2*H*-pyran.[78] Fractions 31-75 were combined to yield 0.796 g (54 %) of the ester as a clear liquid (>99 % pure by GC analysis). ^{1}H NMR δ 0.83-0.88 (m, 3 H), 1.21-1.64 (m, 12 H), 2.00 (s, 3 H), 2.12-2.29 (m, 2 H), 3.18-3.27 (pentet, 1 H), 3.27-3.49 (m, 2 H), 3.99-4.04 (t, 2 H, J = 6.6 Hz), 4.98-5.05 (m, 2 H), 5.69-5.85 (m, 1 H); ^{13}C NMR (15 peaks) δ 14.0, 20.9, 21.8, 22.5, 28.3, 28.6, 29.8, 33.5, 38.3, 64.4, 69.1, 78.7, 116.7, 135.0, 171.1. IR ν_{max} 2933, 1739, 1641 cm^{-1}. HRMS-CI (*m/z*): M^+ calculated for $C_{15}H_{29}O_3$, 257.2117; found, 257.2111.

Allylation of 2-(heptyloxy)tetrahydro-2*H*-pyran (swk3005)



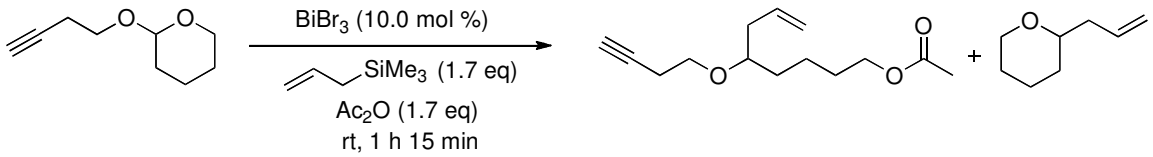
A homogenous mixture of 2-(heptyloxy)tetrahydro-2*H*-pyran (0.300 g, 1.50 mmol), allyltrimethylsilane (0.291 g, 0.40 mL, 2.55 mmol, 1.7 eq), and acetic anhydride (0.260 g, 0.24 mL, 2.55 mmol, 1.7 eq) was stirred at rt under N_2 as bismuth(III) bromide (67.2 mg, 0.150 mmol, 10 mol %) was added. The bismuth(III) bromide dissolved and the reaction mixture turned slightly yellow. The reaction was followed by GC analysis. After 2 h 35 min the reaction mixture was filtered through silica gel (25 g, EtOAc/ heptane, 240 mL of 1/99, then 5/95, v/v). Seventy fractions (8 mL) were collected. Fractions 17-21 were combined to yield 80.3 mg of a clear liquid that was determined to be 2-allyltetrahydro-2*H*-pyran[78] by ^{1}H NMR spectroscopy. Fractions 45-64 were also combined to yield 0.263 g (62 %) of the ester as a clear liquid (>99 % pure by GC analysis). ^{1}H NMR δ 0.86 (t, 3 H, J = 6.5 Hz), 1.22-1.36 (m, 8 H), 1.40-1.66 (m, 8 H), 2.02 (s, 3 H), 2.14-2.32 (m, 2 H), 3.20-3.29 (pentet, 1 H), 3.29-3.51 (m, 2 H), 4.01-4.06 (t, 2 H, J = 6.5 Hz), 5.00-5.08 (m, 2 H), 5.71-5.86 (m, 1 H); ^{13}C NMR (17 peaks) δ 14.1, 21.0, 21.9, 22.6, 26.2, 28.6, 29.1, 30.1, 31.8, 33.5, 38.4, 64.5, 69.2, 78.7, 116.7, 135.0, 171.2. IR ν_{max} 2928, 1741, 1641 cm^{-1}. HRMS-CI (*m/z*): M^+ calculated for $C_{17}H_{33}O_3$, 285.2430; found, 285.2431.

Allylation of 2-(cyclohexyloxy)tetrahydro-2*H*-pyran (swk3057)



A homogeneous mixture of 2-(cyclohexyloxy)tetrahydro-2*H*-pyran (0.447 g, 2.45 mmol), allyltrimethylsilane (0.471 g, 0.66 mL, 4.12 mmol, 1.7 eq), and acetic anhydride (0.421 g, 0.39 mL, 4.12 mmol, 1.7 eq) was stirred at rt under N_2 as bismuth(III) bromide (108.9 mg, 0.243 mmol, 10.0 mol %) was added. The bismuth(III) bromide dissolved and the reaction mixture became slightly warm and turned yellow. The reaction was followed by GC analysis. After 1 h 30 min the reaction mixture was filtered through silica gel (20 g, EtOAc/ pentane, 2/98, v/v). Following a prefraction (15 mL), fifty fractions (8 mL) were collected. Fractions 3-10 were combined to yield 0.103 g of a clear liquid that was determined to be a mixture of several products (72 % 2-allyltetrahydro-2*H*-pyran[78]) by GC analysis. Fractions 23-41 were combined to yield 0.286 g (44 %) of the ester as a clear liquid (>99% pure by GC analysis). ^{1}H NMR δ 1.15-1.90 (m, 16 H), 2.00 (s, 3 H), 2.16-2.21 (triplet of doublets, 2 H), 3.18-3.17 (m, 1 H), 3.30-3.39 (pentet, 1 H), 3.99-4.04 (t, 2 H, J = 6.5 Hz), 4.98-5.04 (m, 2 H), 5.70-5.86 (m, 1 H); ^{13}C NMR (16 peaks) δ 20.9, 22.0, 24.36, 24.44, 25.7, 28.7, 32.8, 33.4, 34.2, 39.5, 64.5, 75.9, 76.0, 116.6, 135.2, 171.1. IR ν_{max} 2930, 1739, 1640 cm^{-1}. HRMS-CI (*m/z*): M^+ calculated for $C_{16}H_{29}O_3$, 269.2117; found, 269.2120.

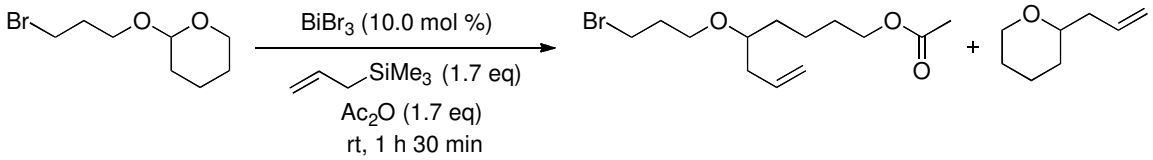
Allylation of 2-(but-3-ynyloxy)tetrahydro-2*H*-pyran (swk3055)



A homogeneous mixture of 2-(but-3-ynyloxy)tetrahydro-2*H*-pyran (1.000 g, 6.485 mmol), allyltrimethylsilane (1.260 g, 1.75 mL, 11.02 mmol, 1.7 eq), and acetic anhydride (1.125 g, 1.04 mL, 11.02 mmol, 1.7 eq) was stirred at rt under N_2 as bismuth(III) bromide (291.0 mg, 0.649, 10.0 mol %) was added. The bismuth(III) bromide dissolved and the

reaction mixture became slightly warm and turned yellow. The reaction was followed by GC analysis. After 1 h 15 min the reaction mixture was filtered through silica gel (50 g, EtOAc/ pentane, 190 mL of 2/98 then 4/96, v/v). Seventy fractions (8 mL) were collected. Fractions 8-18 were combined to yield 0.247 g of 2-allyltetrahydro-2*H*-pyran[78] (>99 % by GC analysis). ^{1}H NMR δ 1.22-1.63 (m, 5 H), 1.77-1.83 (m, 1 H), 2.11-2.32 (m, 2 H), 3.26-3.46 (m, 2 H), 3.94-4.00 (m, 1 H), 5.01-5.11 (m, 2 H), 5.74-5.90 (m, 1 H); ^{13}C NMR (8 peaks) δ 23.4, 26.0, 31.4, 41.0, 68.5, 77.3, 116.5, 135.0. Fractions 39-60 were also combined to yield 0.659 g (43 %) of the ester as a clear oil (>99% pure ester product by GC analysis). ^{1}H NMR δ 1.30-1.66 (m, 6 H), 1.94-1.96 (t, 1 H, J = 2.6 Hz), 2.03 (s, 3 H), 2.16-2.33 (m, 2 H), 2.39-2.45 (m, 2 H), 3.28-3.36 (pentet, 1 H), 3.47-3.66 (m, 2 H), 4.01-4.06 (t, 2 H, J = 6.6 Hz), 5.02-5.09 (m, 2 H), 5.72-5.87 (m, 1 H); ^{13}C NMR (14 peaks) δ 20.0, 20.8, 21.7, 28.5, 33.3, 38.2, 64.3, 67.0, 69.1, 79.0, 81.3, 116.9, 134.5, 170.9. IR ν_{max} 3298, 2939, 1736, 1641 cm^{-1}. HRMS-CI (*m/z*): M$^+$ calculated for C$_{14}$H$_{23}$O$_3$, 239.1647; found, 239.1646.

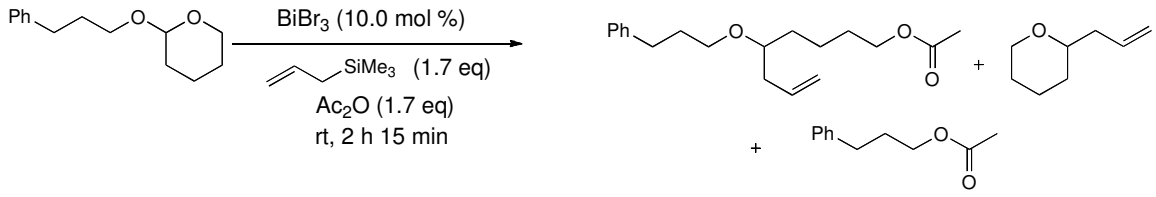
Allylation of 2-(3-bromopropoxy)tetrahydro-2*H*-pyran (swk3033)



A homogenous mixture of 2-(3-bromopropoxy)tetrahydro-2*H*-pyran (0.500 g, 2.24 mmol), allyltrimethylsilane (0.435 g, 0.61 mL, 3.81 mmol, 1.7 eq), and acetic anhydride (0.389 g, 0.36 mL, 3.81 mmol, 1.7 eq) was stirred at rt under N_2 as bismuth(III) bromide (100.6 mg, 0.224 mmol, 10.0 mol %) was added. The bismuth(III) bromide dissolved and the reaction mixture turned yellow. The reaction was followed by GC analysis. After 1 h 30 min the reaction mixture was filtered through silica gel (25 g, EtOAc/

pentane, 1/99 [290 mL], then 2/98, v/v). Sixty-five fractions (8 mL) were collected. Fractions 17-27 were combined to yield 77.2 mg of 2-allyltetrahydro-2*H*-pyran[78] as a clear liquid (97 % by GC analysis). Fractions 46-58 were also combined to yield 0.307 g (45 %) of the ester as a clear liquid (>99 % pure by GC analysis). ^{1}H NMR δ 1.18-1.52 (m, 4 H), 1.56-1.66 (m, 2 H), 2.03 (s, 3 H), 2.00-2.09 (m, 1 H), 2.21-2.26 (m, 2 H), 3.25-3.33 (pentet, 1 H), 3.45-3.64 (m, 2 H), 3.50 (t, 2 H, *J* = 6.5 Hz), 4.04 (t, 2 H, *J* = 6.7 Hz), 5.02-5.09 (m, 2 H), 5.70-5.5.86 (m, 1 H); ^{13}C NMR (13 peaks) δ 21.0, 21.8, 28.6, 30.9, 33.1, 33.4, 38.2, 64.4, 66.0, 79.0, 117.0, 134.7, 171.2. IR ν_{max} 2939, 1736, 1640 cm^{-1}. HRMS-CI (*m/z*): M^+ calculated for $C_{13}H_{24}O_3Br$, 307.0909; found, 307.0910.

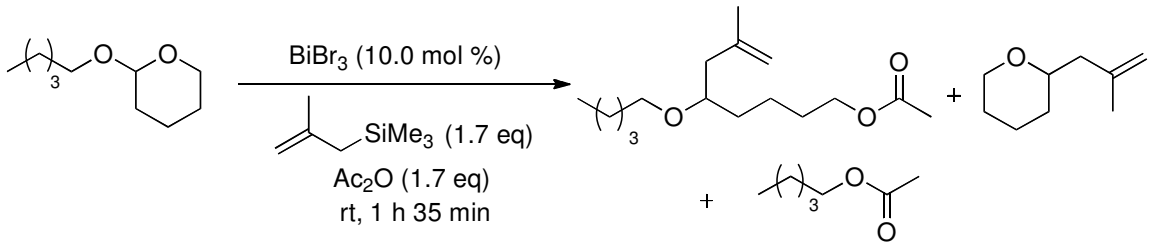
Allylation of 2-(3-phenylpropoxy)tetrahydro-2*H*-pyran (swk3041)



A homogenous mixture of 2-(3-phenylpropoxy)tetrahydro-2*H*-pyran (1.000 g, 4.539 mmol), allyltrimethylsilane (0.882 g, 1.23 mL, 7.72 mmol, 1.7 eq), and acetic anhydride (0.788 g, 0.73 mL, 7.72 mmol, 1.7 eq) was stirred at rt under N_2 as bismuth(III) bromide (203.7 mg, 0.454 mmol, 10.0 mol %) was added. The bismuth(III) bromide dissolved and the reaction mixture became slightly warm. The reaction was followed by GC analysis. After 2 h 15 min the reaction mixture was filtered through silica gel (50 g, EtOAc/ pentane, 2/98, v/v). Following a prefraction (35 mL), one-hundred twenty fractions (8 mL) were collected. Fractions 11-24 were combined to yield 0.166 g of a clear liquid mixture of 2-allyltetrahydro-2*H*-pyran[78] (88 %) and 3-phenylpropyl acetate (11 %) by GC analysis. Fractions 32-51 were combined to yield 0.250 g of a clear liquid

that was determined to be 3-phenylpropyl acetate by GC analysis and ^{1}H NMR. Fractions 52-103 were combined to yield 0.672 g (49 %) of the ester as a clear liquid (>99 % pure by GC analysis). ^{1}H NMR δ 1.30-1.55 (m, 4 H), 1.58-1.67 (m, 2 H), 1.82-1.92 (m, 2 H), 2.02 (s, 3 H), 2.17-2.34 (m, 2 H), 2.66-2.72 (t, 2 H, *J* = 7.7 Hz), 3.23-3.31 (pentet, 1 H), 3.34-3.55 (m, 2 H), 4.03-4.08 (t, 2 H, *J* = 6.5 Hz), 5.02-5.10 (m, 2 H), 5.73-5.89 (m, 2 H); ^{13}C NMR (17 peaks) δ 21.0, 21.9, 28.6, 31.7, 32.4, 33.5, 38.3, 64.5, 68.1, 78.8, 116.8, 125.7, 128.2, 128.4, 134.9, 142.0, 171.1. IR ν_{max} 2938, 1737, 1640 cm^{-1}. HRMS-CI (*m/z*): M^+ calculated for $C_{19}H_{29}O_3$, 305.21168; found, 305.21146.

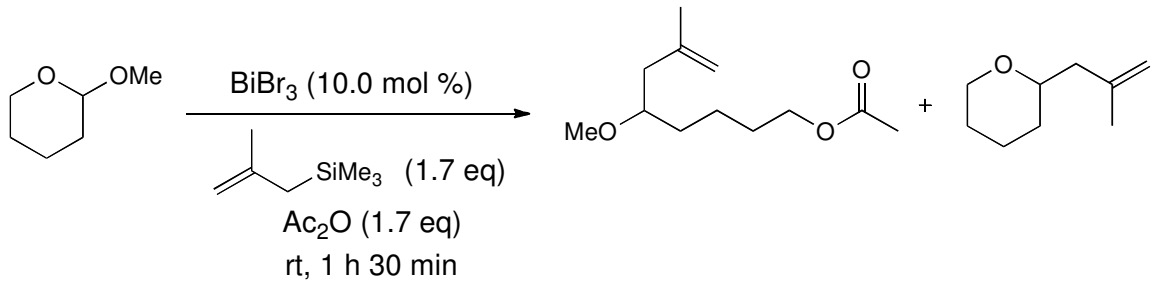
Methallylation of 2-(pentyloxy)tetrahydro-2*H*-pyran (swk3063)



A homogeneous mixture of 2-(pentyloxy)tetrahydro-2*H*-pyran (0.500 g 2.90 mmol), methallyltrimethylsilane (0.633 g, 0.87 mL, 4.94 mmol, 1.7 eq), and acetic anhydride (0.504 g, 0.47 mL, 4.94 mmol, 1.7 eq) was stirred at rt under N_2 as bismuth(III) bromide (130.3 mg, 0.290 mmol, 10.0 mol %) was added. The bismuth(III) bromide dissolved and the reaction mixture became slightly warm and turned yellow. The reaction was followed by GC analysis. After 1 h 35 min the reaction mixture was filtered through silica gel (25 g, EtOAc/ pentane, 2/98, v,v). Following a prefraction (35 mL), forty-five fractions (8 mL) were collected. Fractions 3-14 were combined to yield 0.281 g of a clear liquid mixture of 2-(2-methallyl)tetrahydro-2*H*-pyran[lxxix] (62 %) and pentyl acetate (34 %) by GC analysis and ^{1}H NMR. Fractions 19-38 were combined to yield 0.273 g

(35 %) of the ester as a clear liquid (>99 % pure by GC analysis). ^{1}H NMR δ 0.84-0.89 (m, 3 H), 1.22-1.65 (m, 12 H), 1.72 (s, 3 H), 2.01 (s, 3 H), 2.05-2.30 (doublet of quartets, 2 H), 3.32-3.49 (m, 3 H), 4.00-4.05 (t, 2 H, J = 6.5 Hz), 4.69-4.74 (double of multiplets, 2 H); ^{13}C NMR (16 peaks) δ 14.2, 21.0, 21.8, 22.5, 22.9, 28.4, 28.7, 29.8, 33.6, 42.6, 64.5, 69.1, 77.7, 112.5, 143.0, 171.2. IR ν_{max} 2933, 1740, 1646 cm^{-1}. HRMS-CI (*m/z*): M$^+$ calculated for $C_{16}H_{31}O_3$, 271.2273; found, 271.2274.

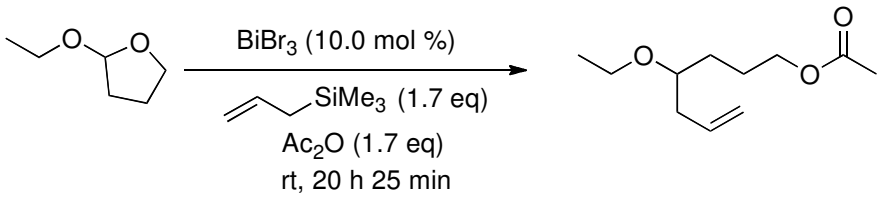
Methallylation of 2-methoxytetrahydropyran (swk3067)



A homogeneous mixture of 2-methoxytetrahydropyran (0.500 g, 4.30 mmol), methallyltrimethylsilane (0.939 g, 1.29 mL, 7.32 mmol, 1.7 eq), and acetic anhydride (0.747 g, 0.69 mL, 7.32 mmol, 1.7 eq) was stirred at rt under N_2 as bismuth(III) bromide (193.1 mg, 0.430 mmol, 10.0 mol %) was added. The bismuth(III) bromide dissolved and the reaction mixture became slightly warm and turned yellow. The reaction was followed by GC analysis. After 1 h 30 min the reaction mixture was filtered through silica gel (25 g, EtOAc/ pentane, 2/98, v/v). Following a prefraction (40 mL), seventy fractions (8 mL) were collected. Fractions 1-10 were combined to yield 0.329 g of 2-(2-methallyl)tetrahydro-2*H*-pyran[79] (99 % by GC analysis) as a clear liquid. ^{1}H NMR δ 1.14-1.27 (m, 1 H), 1.35-1.60 (m, 4 H), 1.70 (s, 3 H), 1.74-1.80 (m, 1 H), 2.01-2.27 (doublet of quartets, 2 H), 3.33-3.44 (m, 2 H), 3.92-3.97 (doublet of multiplets, 1 H), 4.70-4.75 (doublet of multiplets, 2 H); ^{13}C NMR (9 peaks) δ 22.5, 23.5, 26.0, 31.7, 45.0,

68.5, 75.8, 112.2, 142.6. Fractions 29-60 were combined to yield 0.275 g (30 %) of the ester as a clear liquid (98 % by GC analysis). ^{1}H NMR δ 1.30-1.50 (m, 4 H), 1.55-1.66 (m, 2 H), 1.72 (s, 3 H), 2.02 (s, 3 H), 2.03-2.31 (doublet of quartets, 2 H), 3.25-3.33 (m, 1 H), 3.31 (s, 3 H), 4.01-4.05 (t, 2 H, J = 6.5 Hz), 4.70-4.76 (doublet of multiplets, 2 H); ^{13}C NMR (12 peaks) δ 21.0, 21.6, 22.8, 28.7, 33.1, 42.0, 56.5, 64.5, 79.1, 112.5, 142.8, 171.2. IR ν_{max} 2936, 1738, 1646 cm^{-1}. HRMS-CI (*m/z*): M^{+} calculated for $C_{12}H_{23}O_3$, 215.1647; found, 215.1643.

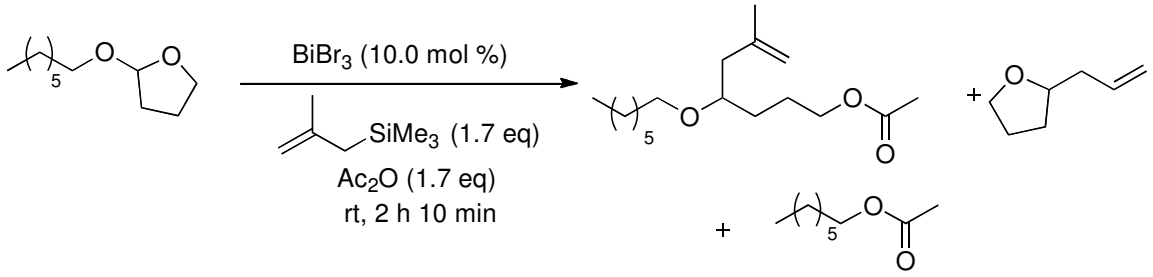
Allylation of 2-ethoxytetrahydrofuran (swk2129)



A homogeneous mixture of 2-ethxoytetrahydrofuran (1.00 g, 8.61 mmol), allyltrimethylsilane (1.673 g, 2.33 mL, 14.6 mmol, 1.7 eq), and acetic anhydride (1.494 g, 1.38 mL, 14.6 mmol, 1.7 eq) was stirred at rt under N_2 in a flame-dried round bottom flask as bismuth(III) bromide (386.3 mg, 0.861 mmol, 10.0 mol %) was added. The reaction was followed by GC analysis. After 20 h 25 min aqueous 10 % Na_2CO_3 (25 mL) was added to the reaction solution and stirred vigorously for 15 min. The resulting mixture was extracted with ethyl acetate (2 x 35 mL). The combined organic layers were washed with aqueous saturated NaCl (15 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator to yield 1.19 g of a clear liquid. The crude product was filtered through silica gel (120 g, EtOAc/heptane, 5/95 [75 mL], 15/85, v/v). Following a prefraction (50 mL), eighty fractions (8 mL) were collected. Fractions 34-54 were combined to yield 0.68 g (40 %) of a clear liquid (97 % pure by GC analysis). ^{1}H NMR δ 1.10-1.15 (t, 3 H,

J = 7.0 Hz), 1.37-1.80 (m, 4 H), 1.98 (s, 3 H), 2.11-2.29 (m, 2 H), 3.21-3.29 (pentet, 1 H), 3.32-3.57 (m, 2 H), 3.98-4.03 (t, 2 H, *J* = 6.5 Hz), 4.97-5.04 (m, 2 H), 5.67-5.82 (m, 1 H); ^{13}C NMR (11 peaks) δ 15.4, 20.9, 24.6, 30.2, 38.3, 64.2, 64.5, 78.2, 116.8, 134.7, 171.0.

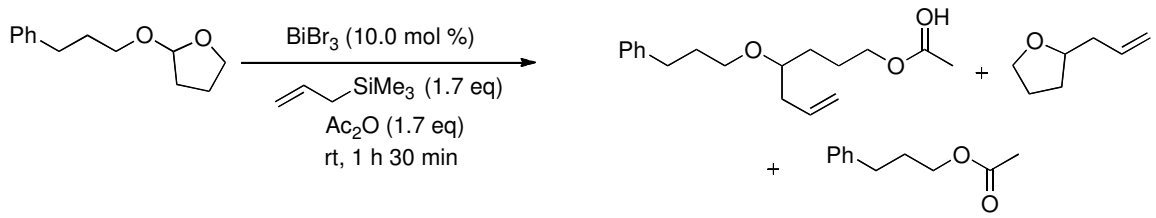
Allylation of 2-(heptyloxy)tetrahydrofuran (swk3061)



A homogeneous mixture of 2-(heptyloxy)tetrahydrofuran (0.500 g, 2.68 mmol), allyltrimethylsilane (0.521 g, 0.73 mL, 4.56 mmol, 1.7 eq), and acetic anhydride (0.466 g, 0.43 mL, 4.56 mmol, 1.7 eq) was stirred at rt under N_2 as bismuth(III) bromide (120.4 mg, 0.268 mmol, 10.0 mol %) was added. The bismuth(III) bromide dissolved and the reaction mixture became slightly warm and turned yellow. The reaction was followed by GC analysis. After 2 h 10 min the reaction mixture was filtered through silica gel (25 g, EtOAc/ pentane, 2/98, v/v). Following a prefraction (50 mL), thirty fractions (8 mL) were collected. Fractions 3-8 were combined to yield 0.112 g of a clear liquid that was determined to be 81 % heptyl acetate by GC analysis and ^{1}H NMR. Fractions 9-13 were combined to yield 75.0 mg of 2-allyltetrahydro-2*H*-furan[lxxx] (87 % by GC analysis and ^{1}H NMR) as a clear liquid. Fractions 14-20 were combined to yield 0.155 g (21 %) of the ester as a clear liquid (98 % by GC analysis). ^{1}H NMR δ 0.83-0.88 (m, 3 H), 1.18-1.36 (m, 8 H), 1.43-1.80 (m, 6 H), 2.02 (s, 3 H), 2.15-2.33 (m, 2 H), 3.21-3.37 (m, 2 H), 3.43-3.49 (m, 1 H), 4.02-4.06 (t, 2 H, *J* = 6.5 Hz), 5.01-5.08 (m, 2 H), 5.71-5.83 (m, 1 H); ^{13}C NMR (16 peaks) δ 14.1, 21.0, 22.6, 24.7, 26.2, 29.1, 30.1, 30.2, 31.8, 38.3, 64.6, 69.1,

78.4, 116.9, 134.8, 171.2. IR ν_{max} 2928, 1740, 1641 cm^{-1}. HRMS-CI (*m/z*): M^+ calculated for $C_{16}H_{31}O_3$, 271.2273; found, 271.2267.

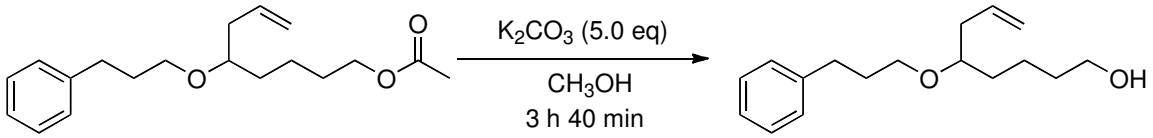
Allylation of 2-(3-phenylpropoxy)tetrahydrofuran (swk3065)



A homogeneous mixture of 2-(3-phenylpropoxy)tetrahydrofuran (0.500 g, 2.42 mmol), allyltrimethylsilane (0.471 g, 0.66 mL, 4.12 mmol, 1.7 eq), and acetic anhydride (0.421 g, 0.39 mL, 4.12 mmol, 1.7 eq) was stirred at rt under N_2 as bismuth(III) bromide (108.8 mg, 0.242 mmol, 10.0 mol %) was added. The bismuth(III) bromide dissolved and the reaction mixture became slightly warm and turned yellow. The reaction was followed by GC analysis. After 1 h 30 min the reaction mixture was filtered through silica gel (25 g, EtOAc/ pentane, 2/98, v/v). Fifty-five fractions (8 mL) were collected. Fractions 13-17 were combined to yield 85.7 mg of a clear liquid that was determined to contain 2-allyltetrahydro-2*H*-furan[80] (63 %) and several unidentified products by GC analysis and ^{1}H NMR. Fractions 18-32 were combined to yield 0.141 g of a clear liquid which contained 3-phenylpropoxy acetate (85 % by GC analysis and ^{1}H NMR) and a few unidentified impurities. Fractions 33-48 were combined to yield 0.175 g (25 %) of the ester as a clear liquid (>99 % pure by GC analysis). ^{1}H NMR δ 1.47-1.92 (m, 6 H), 2.03 (s, 3 H), 2.17-2.35 (m, 2 H), 2.65-2.71 (t, 2 H, *J* = 7.8 Hz), 3.25-3.33 (pentet, 1 H), 3.33-3.55 (doublet of multiplets, 2 H), 4.03-4.08 (t, 2 H, *J* = 6.5 Hz), 5.03-5.10 (m, 2 H), 5.73-5.85 (m, 2 H), 7.14-7.30 (m, 5 H); ^{13}C NMR (16 peaks) δ 21.0, 24.7, 30.2, 31.7, 34.4, 38.3, 64.6, 68.2, 78.5, 117.0, 125.7, 128.3, 128.4, 134.7, 142.0, 171.2. IR ν_{max} 2936,

1737, 1640 cm^{-1}. HRMS-CI (*m/z*): M^+ calculated for $C_{18}H_{27}O_3$, 291.1960; found, 291.1957.

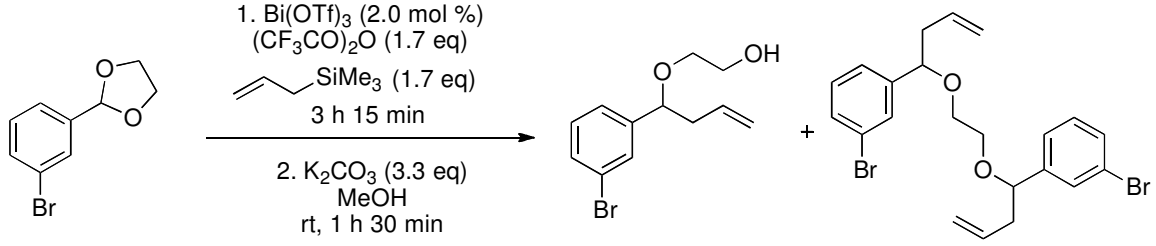
Hydrolysis of 5-(3-phenylpropoxy)oct-7-enyl acetate (swk3045)



A solution of 5-(3-phenylpropoxy)oct-7-enyl acetate (0.25 g, 0.82 mmol) in methanol (0.5 mL) was stirred at rt as anhydrous K_2CO_3 (0.568 g, 4.11 mmol, 5.0 eq) was added. The reaction was followed by GC analysis. After 3 h 40 min ether (25 mL) was added to the reaction mixture and the inorganic solids were removed by suction filtration. The filtrate was washed with aqueous saturated NaCl (20 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator to yield 0.199 g of a clear oil. The crude product was filtered through silica gel (10 g, EtOAc/ heptane, 30/70, v/v). Fifteen fractions (8 mL) were collected. Fractions 5-9 were combined to yield 0.192 g (89 %) of the alcohol as a clear oil (>99 % pure by GC analysis). ^{1}H NMR δ 1.30-1.62 (broad m, 7 H), 1.82-1.92 (m, 2 H), 2.27-2.34 (m, 2 H), 2.66-2.71 (t, 2 H, J = 7.7 Hz), 3.23-3.32 (pentet, 1 H), 3.35-3.54 (m, 2 H), 3.61-3.65 (t, 2 H, J = 5.3 Hz), 5.03-5.10 (m, 2 H), 5.74-5.87 (m, 1 H), 7.14-7.30 (m, 5 H); ^{13}C NMR (15 peaks) δ 21.6, 31.7, 32.4, 32.7, 33.7, 38.3, 62.8, 68.1, 79.0, 116.8, 125.7, 128.2, 128.4, 135.0, 142.0. IR ν_{max} 3370, 2934, 1640 cm^{-1}. HRMS-CI (*m/z*): M^+ calculated for $C_{17}H_{27}O_2$, 263.2011; found, 263.2012.

E. Allylation of 1,3-Dioxolanes

Allylation of 2-(3-bromophenyl)-1,3-dioxolane (swk3099)

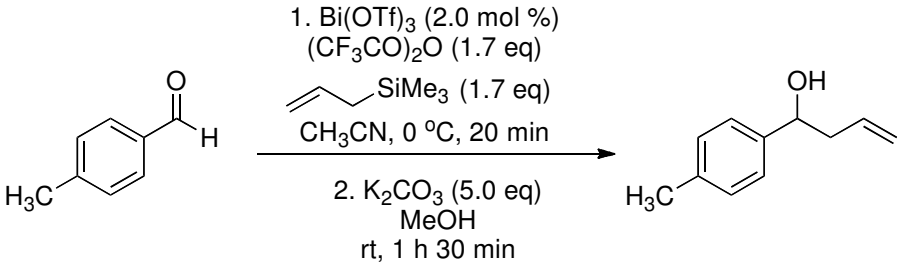


A homogeneous mixture of 2-(3-bromophenyl)-1,3-dioxolane (1.00 g, 4.37 mmol), allyltrimethylsilane (0.848 g, 1.18 mL, 7.42 mmol, 1.7 eq), and trifluoroacetic anhydride (1.559 g, 1.03 mL, 7.42 mmol, 1.7 eq) was stirred at rt under N_2 as bismuth(III) triflate (57.3 mg, 0.087 mmol, 2.0 mol %) was added. The reaction was followed by GC analysis. After 4 h, the reaction mixture was taken up in methanol (10 mL) and anhydrous K_2CO_3 (2.00 g, 14.5 mmol, 3.3 eq) was slowly added. Effervescence was observed and after an additional 1 h 30 min the reaction mixture was diluted with methanol (15 mL) and the inorganic solids were removed by suction filtration. The filtrate was concentrated on a rotary evaporator and the resulting residue was taken up in EtOAc (40 mL), washed with aqueous saturated NaCl (25 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator to yield 1.313 g of a clear, pale yellow liquid. A portion of the crude product (1.00 g) was filtered through silica gel (50 g, EtOAc/heptane, 10/90 [130 mL including 50 mL prefraction], 20/80 [80 mL], 30/70 thereafter, v/v). Fractions (8 mL) 3-5 were combined to yield 0.277 g of a clear liquid. ^{1}H and ^{13}C NMR, COSY, HETCOR, and DEPT spectra of this clear liquid were consistent with the dimeric product shown. IR spectrum of this clear liquid showed no alcohol peak. ^{1}H NMR δ 2.31-2.60 (m, 4 H), 3.37-3.48 (m, 4 H), 4.24-4.29 (t, 2 H, *J* =

6.7 Hz), 5.00-5.06 (m, 4 H), 5.67-5.82 (m, 2 H), 7.18-7.44 (m, 8 H); ^{13}C NMR (13 peaks) δ 42.5, 68.2, 68.3, 81.5, 81.6, 117.2, 122.5, 125.3, 129.7, 129.9, 130.6, 134.3, 144.5. Fractions 21-26 were combined to yield 0.3077 g (26 %) of a clear liquid (>99 % pure by GC analysis). ^{1}H and ^{13}C NMR, COSY, HETCOR, and DEPT spectra of this clear liquid were consistent with the alcohol product. ^{1}H NMR δ 2.24 (broad s, 1 H), 2.32-2.59 (m, 2 H), 3.30-3.48 (m, 2 H), 3.66-3.70 (t, 2 H, J = 4.7 Hz), 4.23-4.28 (m, 1 H), 5.01-5.08 (m, 2 H), 5.66-5.81 (m, 1 H),7.19-7.42 (m, 4 H); ^{13}C NMR (12 peaks) δ 42.3, 61.8, 70.1, 81.6, 117.6, 122.5, 125.1, 129.6, 130.0, 130.7, 134.1, 144.1. IR ν_{max} 3402, 2863, 1642 cm^{-1}. HRMS-CI (*m/z*): M^{+} calculated for $C_{17}H_{27}O_2$, 271.03336; found, 271.03380.

F. Allylation of Aldehydes to Yield Homoallyl Alcohols

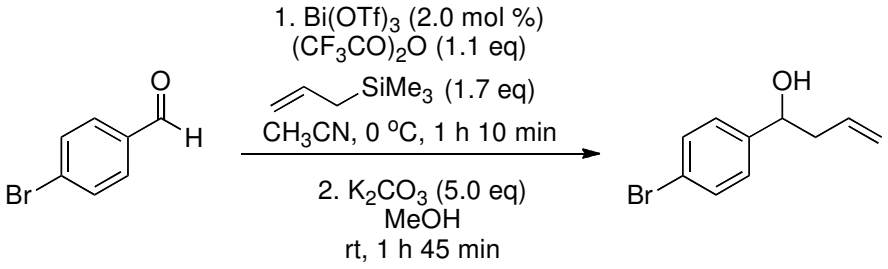
Allylation of 4-tolualdehyde[lxxxi] (swk3111)



A solution of 4-tolualdehyde (0.500 g, 4.16 mmol), allyltrimethylsilane (0.808 g, 1.12 mL, 7.08 mmol, 1.7 eq), and trifluoroacetic anhydride (1.49 g, 0.98 mL, 7.08 mmol, 1.7 eq) in anhydrous CH_3CN (5.0 mL) was stirred at 0 °C under N_2 as bismuth(III) triflate (54.6 mg, 0.083 mmol, 2.0 mol %) was added. The bismuth(III) triflate dissolved and the reaction solution turned bright yellow. The reaction was followed by GC analysis. After 40 min anhydrous K_2CO_3 (2.88 g, 20.8 mmol, 5.0 eq) and methanol (2.0 mL) was added to the reaction solution. Effervescence was observed. After 1 h 10 min additional methanol (1.0 mL) was added to the reaction mixture. After 2 h 50 min the reaction

mixture was diluted with EtOAc (20 mL) and the inorganic solids were removed by suction filtration. The filtrate was concentrated on rotary evaporator, and the resulting residue was taken up in EtOAc (20 mL), washed with aqueous saturated NaCl (10 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator to yield 0.738 g of a yellow-orange colored oil. The crude product was filtered through silica gel (50 g, EtOAc/heptane, 10/90, v/v). Fractions (8 mL) 17-36 were combined to yield 0.376 g (56 %) of a clear pale yellow liquid (98 % pure by GC analysis). ^{1}H NMR δ 1.94-1.95 (d, 1 H, *J* = 3.2 Hz), 2.33 (s, 3 H), 2.47-2.52 (m, 2 H), 4.67-4.73 (m, 1 H), 5.11-5.18 (m, 2 H), 5.72-5.85 (m, 1 H), 7.13-7.26 (doublet of doublets, *J* = 8.2, 16.8 Hz, 4 H); ^{13}C NMR (9 peaks) δ 21.0, 43.6, 73.1, 118.0, 125.7, 129.0, 134.5, 137.1, 140.9. IR ν_{max} 3364, 2922, 1640 cm^{-1}.

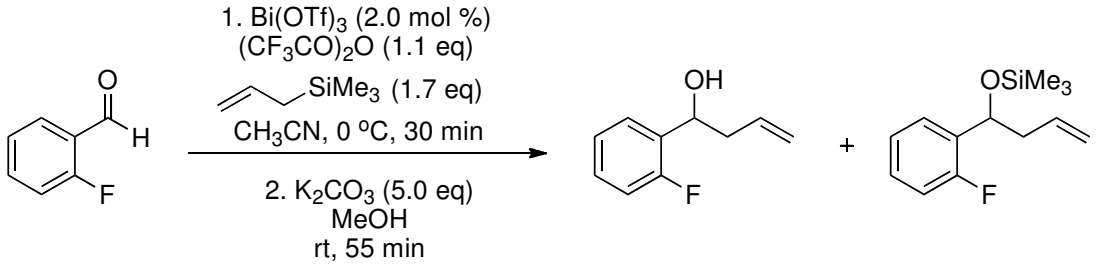
Allylation of 4-bromobenzaldehyde[lxxxii] (swk3165)



A solution of 4-bromobenzaldehyde (1.000 g, 5.405 mmol), allyltrimethylsilane (1.05 g, 1.46 mL, 9.19 mmol, 1.7 eq), and trifluoroacetic anhydride (1.25 g, 0.83 mL, 5.95 mmol, 1.1 eq) in anhydrous CH_3CN (5.4 mL) was stirred at 0 °C under N_2 as bismuth(III) triflate (70.9 mg, 0.108 mmol, 2.0 mol %) was added. The bismuth(III) triflate dissolved and the reaction solution turned pale yellow. The reaction was followed by GC analysis. After 1 h 10 min anhydrous K_2CO_3 (3.73 g, 27.0 mmol, 5.0 eq) and methanol (10.0 mL) was added to the reaction solution. Effervescence was observed and the resulting mixture

turned bright orange in color. After 2 h 55 min the reaction mixture was diluted with EtOAc (40 mL) and the inorganic solids were removed by suction filtration. The filtrate was concentrated on rotary evaporator, and the resulting residue was partitioned between EtOAc (30 mL) and aqueous saturated NH_4Cl (10 mL). The organic layer was washed with aqueous saturated NaCl (10 mL), dried (Na_2SO_4), and concentrated on rotary evaporator to yield 1.396 g of a bright yellow colored oil. The crude product was filtered through silica gel (70 g, EtOAc/heptane, 15/85, v/v). Following a prefraction (50 mL), fifty fractions (8 mL) were collected. Fractions 29-49 were combined to yield 1.058 g (86 %) of a pale yellow oil (99 % pure by GC analysis). ^{1}H NMR δ 2.38-2.45 (m, 2 H), 2.48 (s, 1 H), 4.60-4.64 (t, 1 H, *J* = 6.4 Hz), 5.09-5.14 (m, 2 H), 5.63-5.81 (m, 1 H), 7.15-7.18 (d, 2 H, *J* = 8.4 Hz), 7.42-7.45 (d, 2 H, *J* = 8.4 Hz); ^{13}C NMR (8 peaks) δ 43.6, 72.5, 118.6, 121.1, 127.5, 131.3, 133.8, 142.7. IR ν_{max} 3357, 1641 cm^{-1}

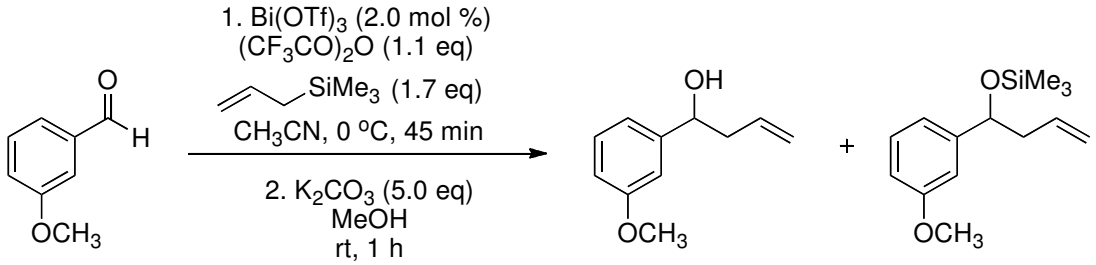
Allylation of 2-fluorobenzaldehyde[lxxxiii] (swk3173)



A solution of 2-fluorobenzaldehyde (1.000 g, 8.057 mmol), allyltrimethylsilane (1.565 g, 2.18 mL, 13.70 mmol, 1.7 eq), and trifluoroacetic anhydride (1.861 g, 1.23 mL, 8.863 mmol, 1.1 eq) in anhydrous CH_3CN (8.1 mL) was stirred at 0 °C under N_2 as bismuth(III) triflate (105.7 mg, 0.161 mmol, 2.0 mol %) was added. The bismuth(III) triflate dissolved and the reaction solution turned pale yellow. The reaction was followed by GC analysis. After 30 min anhydrous K_2CO_3 (3.73 g, 27.0 mmol, 5.0 eq) and methanol (10.0

mL) was added to the reaction solution. Effervescence was observed and the resulting mixture turned bright orange-red in color. The reaction mixture slowly turned bright yellow over 30 min. After 1 h 25 min the reaction mixture was diluted with EtOAc (30 mL) and the inorganic solids were removed by suction filtration using Celite. The filtrate was concentrated on a rotary evaporator and the resulting residue was partitioned between EtOAc (30 mL) and H_2O (10 mL). The organic layer was washed with aqueous saturated NaCl (10 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator to yield 1.527 g of a clear yellow-orange oil. The crude product was filtered through silica gel (70 g, EtOAc/heptane, 15/85, v/v). Following a prefraction (50 mL), thirty-nine fractions were collected. Fractions 8-14 were combined to yield 0.356 g of a clear, yellow colored oil (88 % pure trimethylsilylether by GC analysis). ^{1}H and ^{13}C NMR spectra of the yellow colored oil indicated the presence of the trimethylsilylether shown and some unidentified impurities. Fractions 21-36 were combined to yield 0.845 g (63 %) of a clear, yellow colored oil (>99 % pure homoallyl alcohol by GC analysis). ^{1}H NMR δ 2.41-2.60 (m, 3 H), 5.01-5.05 (m, 1 H), 5.10-5.16 (m, 2 H), 5.72-5.87 (m, 1 H), 6.96-7.27 (m, 3 H), 7.42-7.48 (m, 1 H); ^{13}C NMR (16 peaks) δ 42.5, 67.1, 114.9-115.3 (J = 21.7 Hz), 118.5, 124.08-124.13 (J = 3.1 Hz), 127.12-127.19 (J = 4.6 Hz), 128.6-128.8 (J = 8.2 Hz), 130.7-130.8 (J = 12.9 Hz), 134.0, 157.8-161.4 (J = 243.9 Hz). IR ν_{max} 3358, 1641 cm^{-1}.

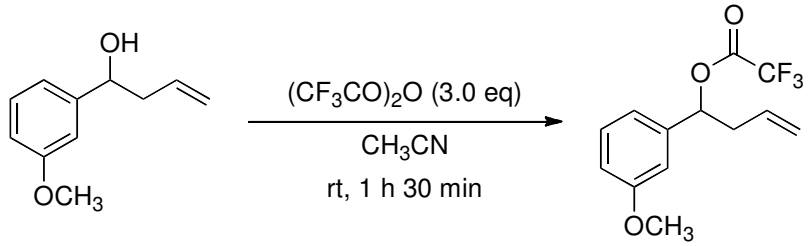
Allylation of 3-methoxybenzaldehyde[81] (swk3183)



A solution of 3-methoxybenzaldehyde (1.000 g, 7.345 mmol), allyltrimethylsilane (1.43 g, 1.98 mL, 12.5 mmol, 1.7 eq), and trifluoroacetic anhydride (1.70 g, 1.12 mL, 8.08 mmol, 1.1 eq) in anhydrous CH_3CN (7.5 mL) was stirred at 0 °C under N_2 as bismuth(III) triflate (96.4 mg, 0.147 mmol, 2.0 mol %) was added. The bismuth(III) triflate dissolved and the reaction solution turned pale yellow. The reaction was followed by GC analysis. After 45 min anhydrous K_2CO_3 (5.075 g, 36.72 mmol, 5.0 eq) and methanol (10.0 mL) was added to the reaction solution. Effervescence was observed and the resulting mixture turned bright yellow. After 1 h 45 min the reaction mixture was diluted with EtOAc (20 mL) and the inorganic solids were removed by suction filtration using Celite. The filtrate was concentrated on a rotary evaporator and the resulting residue was partitioned between EtOAc (40 mL) and H_2O (15 mL). The aqueous layer was extracted again with EtOAc (15 mL). The combined organic layers were washed with aqueous saturated NaCl (15 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator to yield 1.475 g of a slightly cloudy, yellow-orange liquid. The crude product was filtered through silica gel (60 g, EtOAc/heptane, 20/80, v/v). Following a prefraction (50 mL), forty-eight fractions (8 mL) were collected. Fractions 7-9 were combined to yield 70.1 mg (4 %) of a clear liquid (> 99 % pure trimethylsilyl ether by GC analysis). ^{1}H NMR δ 0.03 (s, 9 H), 2.31-2.51 (m, 2 H), 3.80 (s, 3 H), 4.60-4.65 (t, 1 H, J = 6.3 Hz), 4.99-5.05 (m, 2 H), 5.68-5.83

(m, 1H), 6.74-6.87 (m, 3 H), 7.18-7.23 (t, 1 H, J = 7.7 Hz); ^{13}C NMR (12 peaks) δ 0.1, 45.0, 55.1, 74.8, 111.3, 112.4, 116.8, 118.3, 129.0, 135.3, 146.6, 159.5. IR ν_{max} 2954, 1641, 837 cm^{-1}. Fractions 23-46 were combined to yield 1.000 g (76 %) of a clear, pale yellow liquid (98 % pure homoallyl alcohol by GC analysis). ^{1}H NMR δ 2.44-2.50 (m, 3 H), 3.78 (s, 3 H), 4.63-4.68 (t, 1 H, J = 6.4 Hz), 5.09-5.16 (m, 2 H), 5.71-5.86 (m, 1 H), 6.78-6.81 (m, 1 H), 6.89-6.91 (m, 2 H), 7.21-7.27 (m, 1 H); ^{13}C NMR (10 peaks) δ 43.6, 55.0, 73.1, 111.2, 112.8, 118.04, 129.2, 134.4, 145.6, 159.5. IR ν_{max} 3404, 2937, 1641 cm^{-1}.

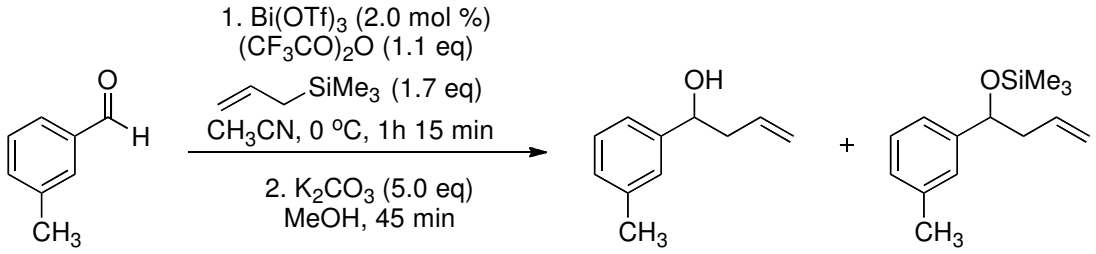
Synthesis of 1-(3-methoxyphenyl)but-3-en-1-yl 2,2,2-trifluoroacetate (swk4006)



A solution of 1-(3-methoxyphenyl)but-3-en-1-ol (0.050 g, 0.28 mmol) in anhydrous CH_3CN (0.25 mL) was stirred at rt under N_2 as trifluoroacetic anhydride (0.18 g, 0.12 mL, 0.84 mmol, 3.0 eq) was added. The reaction solution became slightly warm and turned yellow. The reaction was followed by GC analysis. After 1 h 30 min the reaction mixture was concentrated on a rotary evaporator and under high-vacuum to yield 0.071 g (93 %) of a clear, yellow colored liquid (90 % pure by GC analysis). ^{1}H and ^{13}C NMR spectra of this liquid showed the trifluoroacetate product in high purity. ^{1}H NMR δ 2.60-2.81 (m, 2 H), 3.81 (s, 3 H), 5.11-5.17 (m, 2 H), 5.62-5.77 (m, 1 H), 5.87-5.92 (m, 1 H), 6.87-6.95 (m, 3 H), 7.26-7.33 (m, 1 H); ^{13}C NMR (19 peaks) δ 40.4, 55.2, 79.5, 108.2-120.8 (q, J = 283.9 Hz), 112.2, 114.1, 118.7, 119.3, 129.9, 131.8, 139.1, 155.7-157.6 (q, J

= 42.3 Hz), 159.8. IR ν_{max} 1781, 1640 cm^{-1}. GC retention time of pure sample: 4.78 min; GC retention time of suspected trifluoractetate intermediate prior to hydrolysis in swk3183: 4.76 min.

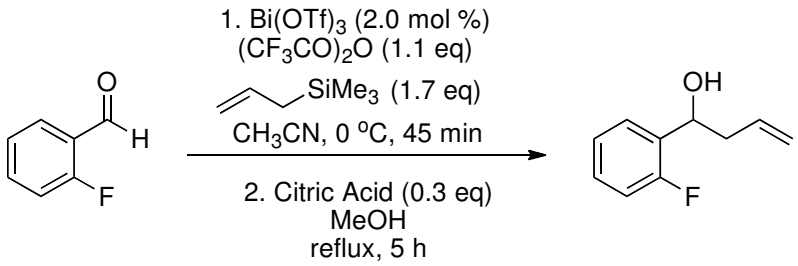
Allylation of 3-tolualdehyde[38] (swk3185)



A solution of 3-tolualdehyde (1.000 g, 8.323 mmol), allyltrimethylsilane (1.62 g, 2.25 mL, 14.2 mmol, 1.7 eq), and trifluoroacetic anhydride (1.92 g, 1.27 mL, 90.2 mmol, 1.1 eq) in anhydrous CH_3CN (8.5 mL) was stirred at 0 °C under N_2 as bismuth(III) triflate (109.2 mg, 0.167 mmol, 2.0 mol %) was added. The bismuth(III) triflate dissolved and the reaction solution turned pale yellow. The reaction was followed by GC analysis. After 1 h 15 min the reaction mixture was concentrated on a rotary evaporator and the resulting residue was taken up in methanol (10 mL). Anhydrous K_2CO_3 (5.752 g, 41.62 mmol, 5.0 eq) was added to this solution resulting in effervescence. The reaction mixture acquired a dull yellow color which slowly changed to light brown. After 1 h the reaction mixture was diluted with EtOAc (20 mL) and the inorganic solids were removed by suction filtration using Celite. The filtrate was concentrated on a rotary evaporator and the resulting residue was taken up in EtOAc (40 mL) and washed with H_2O (15 mL), aqueous saturated NaCl (15 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator to yield 1.410 g of a cloudy, dark orange-brown liquid. The crude product was filtered through silica gel (60 g, EtOAc/heptane, 15/85, v/v). Following a prefraction (50 mL),

forty-eight fractions (8 mL) were collected. Fractions 19-35 were combined to yield 0.820 g (61 %) of a clear oil (99 % homoallyl alcohol by GC analysis). ^{1}H NMR δ 2.38 (s, 3 H), 2.48-2.55 (m, 3 H), 4.63-4.68 (t, 1 H, J = 6.5 Hz), 5.13-5.19 (m, 2 H), 5.74-5.90 (m, 1 H), 7.10-7.28 (m, 4 H); ^{13}C NMR (11 peaks) δ 21.3, 43.6, 73.2, 117.9, 122.8, 126.4, 128.07, 128.10, 134.5, 137.8, 143.8. IR ν_{max} 3361, 2922, 1640 cm^{-1}.

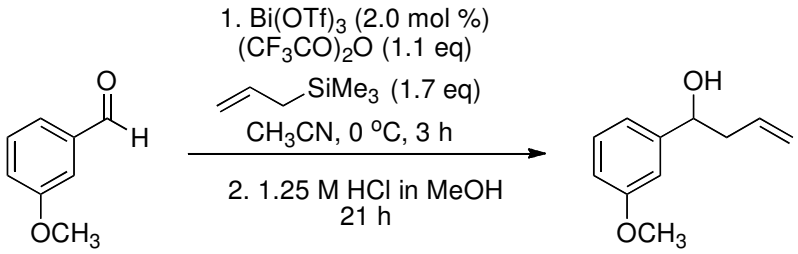
Allylation of 2-fluorobenzaldehyde[83] (swk3187)



A solution of 2-fluorobenzaldehyde (1.000 g, 8.057 mmol), allyltrimethylsilane (1.57 g, 2.18 mL, 13.7 mmol, 1.7 eq), and trifluoroacetic anhydride (1.86 g, 1.23 mL, 8.86 mmol, 1.1 eq) in anhydrous CH_3CN (8.1 mL) was stirred at 0 °C under N_2 as bismuth(III) triflate (105.7 mg, 0.161 mmol, 2.0 mol %) was added. The bismuth(III) triflate dissolved and the reaction solution turned pale yellow. The reaction was followed by GC analysis. After 45 min the reaction solution was concentrated on a rotary evaporator and the resulting residue was taken up in methanol (10 mL). Citric acid (0.464 g, 2.42 mmol, 0.3 eq) was added to this solution and the reaction mixture was stirred at rt for 16 h 35 min and was then heated to reflux. After 5 h the reaction mixture was cooled and concentrated on a rotary evaporator. The residue was taken up in EtOAc (50 mL) and washed with aqueous saturated $NaHCO_3$ (15 mL). The aqueous layer was extracted again with EtOAc (15 mL). The combined organic layers were washed with aqueous saturated NaCl (10 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator to yield

1.638 g of a clear, pale yellow oil. The crude product was filtered through silica gel (70 g, EtOAc/heptane, 15/85, v/v). Following a prefraction (50 mL), forty-eight fractions (8 mL) were collected. Fractions 22-38 were combined to yield 0.988 g (74 %) of a clear, colorless liquid (>99 % pure by GC analysis). ^{1}H and ^{13}C NMR spectra were consistent with those obtained previously for this homoallyl alcohol (swk3173).

Allylation of 3-methoxybenzaldehyde[81] (swk3189)



A solution of 3-anisaldehyde (0.250 g, 1.836 mmol), allyltrimethylsilane (0.357 g, 0.50 mL, 3.12 mmol, 1.7 eq), and trifluoroacetic anhydride (0.424 g, 0.28 mL, 2.02 mmol, 1.1 eq) in anhydrous CH_3CN (2.0 mL) was stirred at 0 °C under N_2 as bismuth(III) triflate (24.1 mg, 0.037 mmol, 2.0 mol %) was added. The bismuth(III) triflate dissolved and the reaction solution turned yellow. The reaction was followed by GC analysis. After 3 h the reaction solution was concentrated on a rotary evaporator and the resulting residue was taken up in methanol (1.0 mL). Hydrochloric acid (1.25 M) in methanol (5.0 mL) was added to the reaction solution and stirred at rt. After 2 h, H_2O (1.0 mL) was added to the reaction solution. After 21 h the reaction mixture was concentrated on a rotary evaporator and the resulting residue was taken up in EtOAc (20 mL). This solution was washed with aqueous saturated $NaHCO_3$ (10 mL), aqueous saturated NaCl (5 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator to yield 0.324 g of a clear, yellow liquid. The crude product was filtered through silica gel (15 g, EtOAc/heptane, 20/80,

v/v). Twenty fractions (8 mL) were collected. Fractions 8-16 were combined to yield 0.229 g (77 %) of a clear liquid with very pale yellow color (98 % pure by GC analysis). ^{1}H and ^{13}C NMR spectra were consistent with those previously reported for this compound (swk3183).

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