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New Organogermanium Substrates for Palladium-Catalyzed Cross-Coupling Reactions. Application of Organogermanes towards the Synthesis of Carbon-5 Modified Uridine Analogues

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FLORIDA INTERNATIONAL UNIVERSITY

Miami, Florida

NEW ORGANOGERMANIUM SUBSTRATES FOR PALLADIUM-CATALYZED CROSS-COUPLING REACTIONS. APPLICATION OF ORGANOGERMANES TOWARDS THE SYNTHESIS OF CARBON-5 MODIFIED URIDINE ANALOGUES

A dissertation submitted in partial fulfillment of the
requirements for the degree of
DOCTOR OF PHILOSOPHY
in
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by
Jean-Philippe Pitteloud

2010

To: Dean Kenneth Furton
College of Arts and Sciences

This dissertation, written by Jean-Philippe Pitteloud, and entitled New Organogermanium Substrates for Palladium-Catalyzed Cross-Coupling Reactions. Application of Organogermanes towards the Synthesis of Carbon-5 Modified Uridine Analogues, having been approved in respect to style and intellectual content, is referred to you for judgment.

We have read this dissertation and recommend that it be approved.

David Becker

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Watson Lees

David Lee

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Date of Defense: March 25, 2010

The dissertation of Jean-Philippe Pitteloud is approved.

Dean Kenneth Furton
College of Arts and Sciences

Interim Dean Kevin O’Shea
University Graduate School

Florida International University, 2010

DEDICATION

I dedicate this work to God and my parents for their guidance, support and love. Also to my family and friends for encouraging me to pursue my goal. This could not be possible without you.

ACKNOWLEDGMENTS

I would like to thank my mentor and friend, Professor Stanislaw F. Wnuk for giving me the opportunity to work with him and provide me with valuable lessons on my scientific and personal development. You have been like family to me throughout these years. I also want to thank my lab mates for their support and patience in my good and bad moments; they have also been like family to me. Also, I would like to acknowledge Marcela for her support, especially for her power to calm me down in difficult journeys. Last but not least, I want to show gratitude to the faculty members of the Department of Chemistry and Biochemistry at Florida International University for their support as a Teaching Assistant during the first 3 years of my doctoral studies. To the University Graduate School for the Dissertation Fellowship Award which helped me enormously during my last year as a student.

ABSTRACT OF THE DISSERTATION

NEW ORGANOGERMANIUM SUBSTRATES FOR PD-CATALYZED CROSS-COUPLING REACTIONS. APPLICATION OF ORGANOGERMANES TOWARDS THE SYNTHESIS OF CARBON-5 MODIFIED URIDINE ANALOGUES

by

Jean-Philippe Pitteloud

Florida International University, 2010

Miami, Florida

Professor Stanislaw F. Wnuk, Major Professor

The diverse biological properties exhibited by uridine analogues modified at carbon-5 of the uracil base have attracted special interest to the development of efficient methodologies for their synthesis. This study aimed to evaluate the possible application of vinyl tris(trimethylsilyl)germanes in the synthesis of conjugated 5-modified uridine analogues via Pd-catalyzed cross-coupling reactions. The stereoselective synthesis of 5-[(2-tris(trimethylsilyl)germyl)ethenyl]uridine derivatives was achieved by the radical-mediated hydrogermylation of the protected 5-alkynyluridine precursors with tris(trimethylsilyl)germane [$(TMS)_3GeH$]. The hydrogermylation with Ph_3GeH afforded in addition to the expected 5-vinylgermane, novel 5-(2-triphenylgermyl)acetyl derivatives. Also, the treatment with Me_3GeH provided access to 5-vinylgermane uridine analogues with potential biological applications.

Since the Pd-catalyzed cross-coupling of organogermanes has received much less attention than the couplings involving organostannanes and organosilanes, we were prompted to develop novel organogermane precursors suitable for transfer of aryl and/or alkenyl groups. The allyl(phenyl)germanes were found to transfer allyl groups to aryl iodides in the presence of sodium hydroxide or tetrabutylammonium fluoride (TBAF) via a Heck arylation mechanism. On the other hand, the treatment of allyl(phenyl)germanes with tetracyanoethylene (TCNE) effectively cleaved the Ge-C(allyl) bonds and promoted the transfer of the phenyl groups upon fluoride activation in toluene.

It was discovered that the trichlorophenyl,- dichlorodiphenyl,- and chlorotriphenylgermanes undergo Pd-catalyzed cross-couplings with aryl bromides and iodides in the presence of TBAF in toluene with addition of the measured amount of water. One chloride ligand on the Ge center allows efficient activation by fluoride to promote transfer of one, two or three phenyl groups from the organogermane precursors. The methodology shows that organogermanes can render a coupling efficiency comparable to the more established stannane and silane counterparts. Our coupling methodology (TBAF/moist toluene) was also found to promote the transfer of multiple phenyl groups from analogous chloro(phenyl)silanes and stannanes.

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1. INTRODUCTION

1.1. Nucleosides and nucleotides as targets for antiviral and anticancer therapy

The initial studies on the synthesis of nucleosides and nucleotides were intended to demonstrate the structure of adenosine and other naturally occurring ribo- and deoxyribonucleosides. Further developments have been devised as an opportunity to synthesize nucleoside/nucleotide analogues that might serve as specific inhibitors of enzymes involved in cell metabolism and proliferation. Moreover, the key role of such molecules as building blocks of nucleic acids (DNA and RNA) has promoted the design of many efficient methodologies to create synthetic oligonucleotides of great importance in the elucidation of the human genome, study of DNA-protein interactions, gene modulation, RNA catalysis, and DNA/RNA structure and stability. Although, it remains less costly to obtain the major nucleosides by simple degradation of nucleic acids, decades of efforts have been dedicated to discover more efficient strategies for their total synthesis. Such methodologies led to the preparation of very interesting modified nucleosides, which exhibited wide range anticancer and antiviral activity.[1]

<u>Anticancer nucleoside analogues</u>:

The most common cancer treatments currently in use are based on the inhibition of cell DNA replication and/or interference of its important functions. An important rationale applied on targeting such cellular processes was the fact that most of the cells in adults are in a quiescent state in which replication of its DNA is not in full activity. However, some specific tissues (e.g., hair follicles, gastrointestinal, bone marrow) are always in a replicative state. In addition, since all cells are repairing their often damaged

DNA, exposure to long-term treatments leads to important toxicity levels in cancer patients.[2]

Presently, the U.S. Food and Drug Administration (FDA) has approved around 14 nucleoside-based drugs for the treatment of cancer (Table 1). Noteworthy, this number represents approximately 20% of the drugs in use to treat cancer, and three of these have been approved during the last 6 years.[2] These important events have promoted the investigation of base/sugar-modified nucleosides as novel leads in cancer treatment. In general, many of the purine and pyrimidine antimetabolites share very similar metabolic pathways within the cell but it is the inhibition of certain enzyme(s), which confers them the activity against a particular cancer.

Table 1: FDA approved anticancer purine and pyrimidine nucleoside analogues.[2]

Drug	*Date of approval*
6-mercaptopurine	1953
5-fluorouracil	1962
6-thioguanine	1966
Arabinofuranosylcytosine (cytarabine)	1969
5-fluoro-2'-deoxyuridine (floxuridine)	1970
2'-deoxycoformycin (pentostatin)	1991
Arabinofuranosyl-2-fluoroadenine (fludarabine)	1991
2-chloro-2'-deoxyadenosine (cladribine)	1992
2,2-difluoro-2'-deoxycytidine (gemcitabine)	1996
N^4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine (capecitabine)	1998
5-aza-cytidine (vidaza)	1998
2'-fluoro-2'-deoxyarabinofuranosyl-2-chloroadenine (clofarabine)	2004
O^6-methylarabinofuranosyl guanine (nelarabine)	2005
5-aza-2'-deoxycytidine (decitabine)	2006

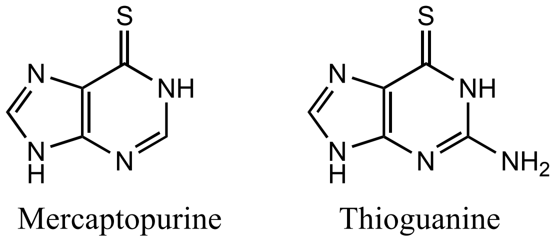
Surprisingly, as noted by some authors[3], “one of the most remarkable features of purine and pyrimidine nucleoside analogues that remain unexplained is how drugs with such similar structural features, share metabolic pathways and elements of their mechanism of action show, such diversity in their clinical activities”. This certainly serves as a driving force for the rational design and synthesis of novel modified nucleoside analogues, looking for the most potent and less toxic anticancer drugs.

In most cases, nucleoside drugs are required as substrates of certain enzymes in order to generate the active metabolite responsible for their biological activity. Phosphoribosyl transferases are responsible for the activation of the three base analogues, mercaptopurine, thioguanine, and fluorouracil, and there are five other enzymes accountable for the first phosphorylation of most of the nucleoside analogues.[4-6] Conversion of the monophosphate nucleoside is followed by a second phosphorylation by the appropiate monophosphate kinases[7] giving the corresponding diphosphate. The last phosphorylating event occurs after the participation of the nucleoside diphosphate kinases. Later, the triphosphate nucleoside analogue usually interacts with the DNA polymerases. There are three modes of interaction between the triphosphate nucleoside and the DNA polymerases: 1) compete with the natural substrate without acting as a substrate; 2) substitute for the natural substrate with a small effect on DNA synthesis; or 3) substitute for the natural substrate and interfere with DNA synthesis by chain termination. Among these three, the latter two have been proposed as the most likely for the interaction of most of the tri-phosphorylated nucleoside drugs with the DNA polymerases. On the other hand, the selectivity and effectiveness of the various approved anticancer drugs can be attributed to 1) how easily the DNA chain is extended after the incorporation of the drug and 2) how easily they may be removed by the proof-reading exonucleases. Some representative examples of nucleoside drugs approved for the treatment of cancer are presented as follows.

a) Thiopurine analogues:

In 1953 the FDA approved 6-mercaptopurine (MP) (Figure 1) as one of the first drugs for the treatment of childhood acute lymphocytic leukemia.[8] Being an analogue of hypoxanthine makes it an excellent substrate for hypoxanthine/guanine phosphoribosyl tranferase. Subsequently, the 6-thio-inosine monophosphate (T-IMP) acts as a substrate of IMP dehydrogenase and is converted to the guanine nucleotide. Therefore, ribonucleotide reductase converts it to the corresponding 6-thio-2'-deoxyguanosine-5'-triphosphate, which is easily incorporated into DNA. Although, its incorporation does not result in the inhibition of DNA polymerase, it is believed to cause important DNA damage accounting for its antitumor activity.

Similarly, thioguanine (TG) is straightforwardly converted to its corresponding nucleotide (T-GMP) by hypoxanthine/guanine phosphoribosyl transferase. The following incorporation of T-GMP into DNA is also suggested to cause DNA damage in analogous fashion to T-IMP.[9] The FDA approved thioguanine (TG) in 1966 as a treatment for myelogenous leukemia.



Mercaptopurine Thioguanine

Figure 1. Thiopurines with anticancer activity.

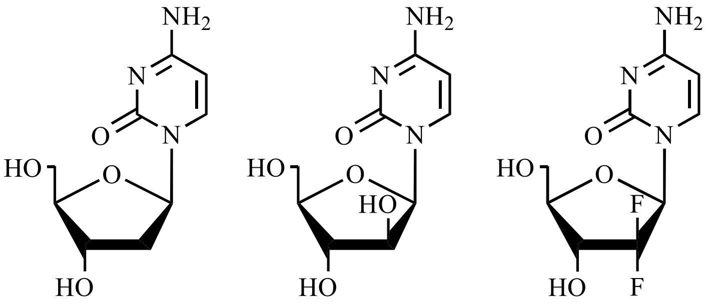
b) Cytidine analogues:

Many deoxynucleoside derivatives have been reported as important anticancer agents. Their clinical use is relatively new and most of them share very similar mechanisms of action based on the inhibition of DNA polymerases and/or ribonucleotide reductase. However, subtle modifications of their structures have resulted in their different properties and unique clinical activities (Figure 2).

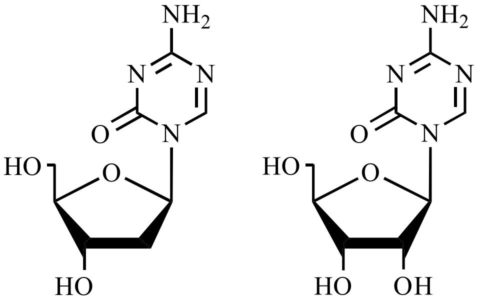
Cytarabine (arabinocytidine, AraC) is a good substrate for deoxycytidine kinase, and its fundamental metabolite inside the cell is its corresponding tri-phosphate AraCTP. After AraCTP incorporation in the 3'-end of the new DNA strand, further elongation is drastically inhibited.[10]

Gemcitabine (2'-difluoro-2'-deoxycytidine, dFdC) is also a good substrate for the DNA polymerases as its tri-phosphorylated analogue dFdC-TP.[11] In contrast to AraC, after its incorporation into DNA, the chain extension is only interrupted after the integration of the next nucleoside. It must be mentioned that a much greater percentage of dFdC-TP was incorporated in internal positions (>90%) compared to araCTP. Moreover, the proof-reading exonucleases associated with DNA polymerase ε were not capable to remove dFdC from the newly damaged DNA, which is not likely the case with araC.[12] Another difference that accounts for the increased potency of Gemcitabine compared to Cytarabine is its ability to inhibit ribonucleotide reductase.[13] Blocking this enzyme results in a considerable reduction of the availability of natural substrates for DNA replication, thus enhancing its anticancer activity. The FDA approved Gemcitabine in 1996 for the treatment of non-small cell lung cancer and pancreatic cancer.

Decitabine (aza-dCyd) and **Vidaza (aza-Cyd)** are both excellent substrates for the successive phosphorylations via deoxycytidine kinase[14-17] and uridine/cytidine kinase to form the aza-dCTP and aza-CTP, respectively. In contrast to Cytarabine and Gemcitabine, aza-dCTP is easily incorporated and extended into the internal positions of the new DNA.[18] Upon its incorporation, inhibition of the methylation of the DNA chain was suggested to be responsible for its observed activity. On the other hand, aza-CTP is a ribonucleotide metabolite, which is readily converted to the corresponding deoxycytidine analogue by ribonucleotide reductase and incorporated into DNA. Although aza-CTP is also integrated into RNA, its antitumor activity is attributed to the inhibition of DNA methyltransferase once present in DNA.



Deoxycytidine AraC Gemcitabine



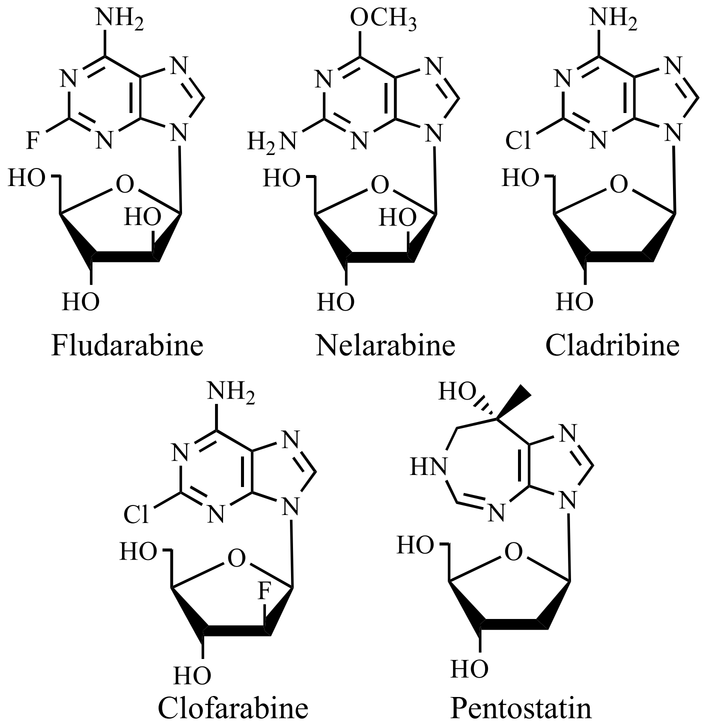
Decitabine Vidaza

Figure 2. Cytidine analogues with anticancer activity.

c) Purine nucleoside analogues:

Since 1991 the FDA has approved five purine deoxynucleosides for their clinical use as anticancer agents (Figure 3).

Fludarabine (F-araA), was approved by the FDA in 1991 for the treatment of chronic lymphocytic leukemia as its monophosphorylated nucleotide F-araAMP.[19,20] The design of F-araA analogue was based on the previous discovery of the effect of substituting the 2-hydrogen atom of adenosine with a halogen, hampering its inactivation by adenosine deaminase.[21,22] **Nelarabine** is a pro-drug of araG approved for the treatment of T-cell malignancies.[23] It is used instead of araG because of the low solubility of the latter. Incorporation of either F-araAMP or araGMP results in the inhibition of the DNA replication by chain termination.[24-26] F-araATP was also reported as a weak inhibitor of ribonucleotide reductase.[27]


Fludarabine Nelarabine Cladribine

Clofarabine Pentostatin

Figure 3. Purine nucleoside analogues with anticancer activity.

Cladribine (Cl-dAdo) is a 2'-deoxyadenosine derivative used for the treatment of hairy-cell leukemia after approval in 1992.[28] It is efficiently converted by the action of deoxycytidine kinase and nucleotide kinase to Cl-dATP, which is an excellent substrate for the DNA polymerases. It is only after the incorporation of three successive Cl-dAdo residues that the DNA replication is stopped.[28] Cladribine is also a more potent inhibitor of ribonucleotide reductase than Fludarabine.[24,28] The presence of the Cl atom at position 2 of the adenine base confers special stability to deamination by adenosine deaminase.

Clofarabine (Cl-F-araA) has almost the same structure as Cladribine with the introduction of a fluorine atom in position 2' of the deoxyribose moiety. It was approved for clinical use against relapsed and refractory pediatric lymphoblastic leukemia in 2004.[29,30] The 2'-fluoro unit confers unique stability to the glycosidic bond in the presence of acids producing very good oral bioavailability. The mechanism of action may be seen as a combination of that described for Fludarabine and Cladribine, resulting in the potent inhibition of both DNA polymerase and ribonucleotide reductase.[24,31,32]

Pentostatin (deoxycoformycin) like Cl-dAdo has also been approved treatment for hairy-cell leukemia since 1991[33,34], but with a different way of action. Pentostatin inhibits adenosine deaminase, causing the accumulation of high levels of dATP, which subsequently inhibits ribonucleotide reductase and further DNA synthesis.

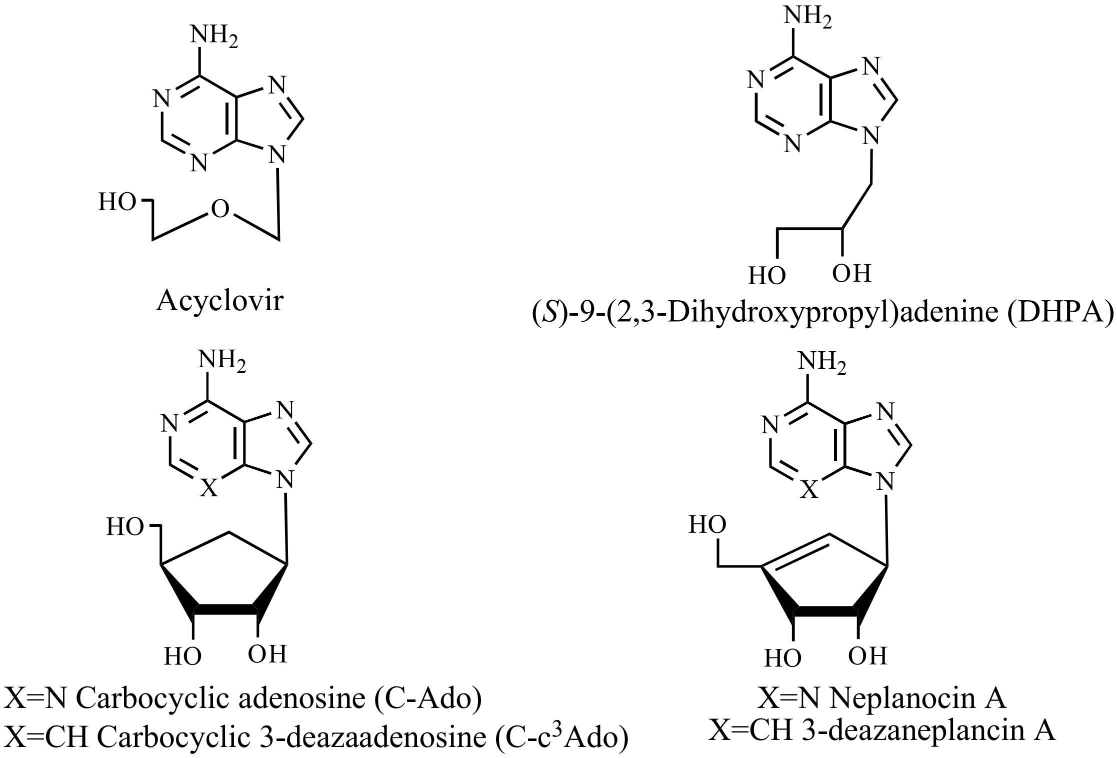
These examples of approved anticancer drugs (figures 1-3) are certainly the product of many years of close collaboration between synthetic organic chemists and biologists. In a similar fashion, such collaboration resulted in the discovery of very important modified nucleosides that exhibit interesting cytotoxic profiles against a wide range of pathogenic viruses in humans (e.g., rhabdoviruses (rabies), filoviruses (Ebola), arenaviruses (Junin, Tacaribe), reoviruses (rota), paramyxoviruses (parainfluenza, measles), retroviruses (HIV), herpesviruses, poxiviruses (variola), etc.). Some examples are presented as follows.

Antiviral nucleoside analogues:

a) Purine nucleoside analogues. Via inhibition of (S)-adenosylhomocysteine hydrolase:

Soon after the discovery of the antiherpes virus properties of **Acyclovir**, **(*S*)-9-(2,3-dihydroxypropyl)adenine (DHPA)** (Figure 4) appeared as broad-spectrum antiviral agent. Specific phosphorylation of the drug by the herpes simplex virus (HSV)-encoded thymidine kinase accounted for the initial metabolism of Acyclovir.[35,36] A similar metabolic pathway was proposed for the alternative DHPA. Many years later, DHPA was demonstrated to be an inhibitor of *S*-adenosylhomocysteine (SAH) hydrolase, which causes accumulation of *S*-adenosylhomocysteine, leading to suppression of the conversion from *S*-adenosylmethionine (SAM) to SAH.[37] This last step is responsible for the methylation (capping) of viral mRNAs, which results in their maturation and further replication.[37]

In the search for other adenosine analogues in which either acyclic or carbocyclic residues have replaced the sugar moiety, **3-deazaadenosine (C-c^{3}Ado)** and **3-deazaneplanocin A** offered interesting profiles. Both analogues were found to be protective to the Ebola virus-infected mouse.[38,39] After finding substantial amounts of interferon in the infected mice, it was suggested that 3-deazaneplanocin A prevents the release of mature mRNAs after inhibiting the capping of viral mRNAs. The resulting accumulated mRNAs promote formation of double-stranded RNA, known to induce production of interferon.



Acyclovir

(*S*)-9-(2,3-Dihydroxypropyl)adenine (DHPA)

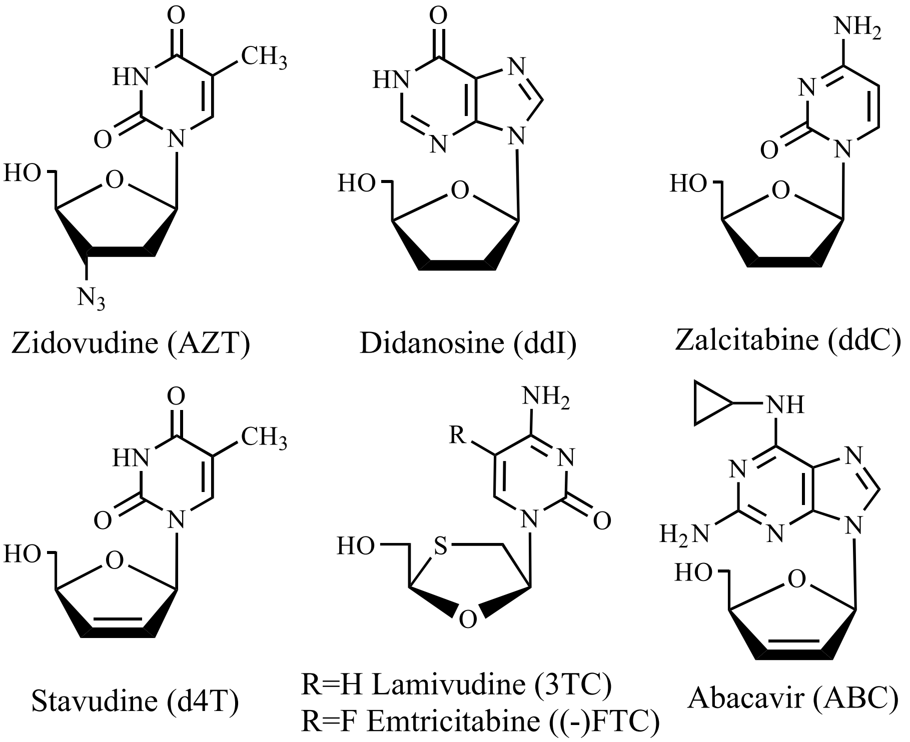
X=N Carbocyclic adenosine (C-Ado)
X=CH Carbocyclic 3-deazaadenosine (C-c^3Ado)

X=N Neplanocin A
X=CH 3-deazaneplancin A

Figure 4. Purine nucleoside analogues with antiviral activity by inhibition of *S*-adenosylhomocysteine (SAH) hydrolase.

b) Purine and pyrimidine nucleoside analogues. Via inhibition of reverse trancriptase (NRTIs):

At the present, seven 2',3'-dideoxynucleoside analogues (ddN) have been approved for the clinical treatment of HIV infections: **zidovudine (AZT)**, **didanosine (ddI)**, **zalcitabine (ddC)**, **stavudine (d4T)**, **lamivudine (3TC)**, **emtricitabine ((-)FTC)**, and **abacavir (ABC)** (Figure 5).[40] They all share the action mechanism first postulated for AZT.[41] Successive phosphorylations result in the formation of the corresponding 5'-triphosphate ddN analogues, which are readily incorporated into DNA by the HIV-encoded reverse transcriptase. The lack of a 3'-hydroxyl group results in the DNA chain termination and subsequent inhibition of the reverse transcription process.



Zidovudine (AZT)

Didanosine (ddI)

Zalcitabine (ddC)

Stavudine (d4T)

R=H Lamivudine (3TC)
R=F Emtricitabine ((-)FTC)

Abacavir (ABC)

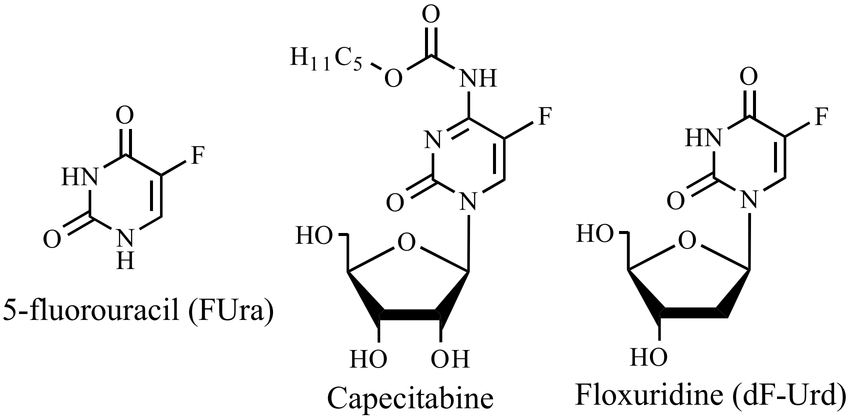
Figure 5. Purine and pyrimidine nucleoside analogues with antiviral activity by inhibition of reverse trancriptase (NRTIs)

1.1.1. 5-Modified pyrimidine nucleosides

1.1.1.1. 5-Fluorouracil (FUra), a potent inhibitor of thymidylate synthase

Approved by the FDA in 1962, fluorouracil or 5-fluorouracil (FUra) may be one of the most important anticancer drugs (Figure 6). Initially, the design of FUra was based on important principles; 1) a fluorine and a hydrogen atom have approximately the same size; 2) a C-F bond is much stronger than a C-H bond; 3) thymidylate synthase substitutes the H5 on uracil base for a methyl group from methylene tetrahydrofolate; and 4) rat hepatoma cells use uracil, but not normal liver cells. Consequently, Heidelberger *et al.* proposed that FUra would selectively kill cancer cells through inhibition of thymidylate synthase.[42] Later on, the proposed hypotheses were confirmed and FUra started to be used in the treatment of colorectal, breast, stomach, and pancreatic cancers.[43]

The metabolic cascade of FUra starts with the conversion of the administered drug (FUra) into the corresponding mono phosphorylated nucleoside analogue (F-UMP) by orotate phosphoribosyl transferase. Subsequently, the corresponding nucleotide kinases convert F-UMP to F-UTP, which acts as a competitive substrate in the synthesis of RNA and promotes the incorporation of high levels of FUra in many different types of RNA. Although the effect of FUra on novel functions of RNA has not been yet elucidated, its incorporation into RNA is suggested to contribute to its high potency.



5-fluorouracil (FUra)

Capecitabine

Floxuridine (dF-Urd)

Figure 6. 5-Fluorouracil (FUra) and its derivatives.

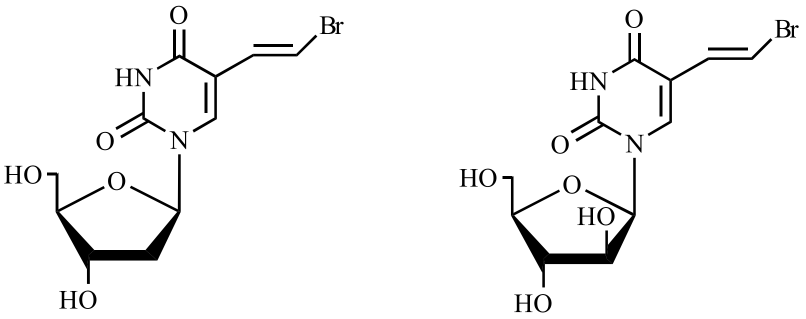
Furthermore, 5-fluorouridine-5'-diphosphate (F-UDP) acts as a substrate for ribonucleotide reductase and is converted to the corresponding F-dUDP by the removal of the 2'-OH group. Action of the nucleoside diphosphate NDP kinase transforms F-UDP into F-UTP, which is readily incorporated into DNA by the DNA polymerases. Recognition of the defective 5-Ura fragment in the new DNA is efficiently performed by uracil glycosylase, resulting in its further removal. The apurinic/apyrimidinic endonuclease I readily identifies the empty site in DNA, causing a single strand break. The DNA repair enzymes finally recognize the broken strand, and trigger the repair and re-synthesis of DNA known to set up a cycle that promotes inhibition of DNA synthesis and cell death. In addition, competition between F-UMP with the natural 2'-deoxyuridine mono-phosphate (dUMP) results in the inhibition of thymidilate synthase because of its inability to remove the fluorine atom. Consequently, the incapacity of thymidilate synthase to produce thymidine triphosphate (TPP) fosters (no competition) the incorporation of F-UTP into DNA with concomitant cell death.[44,45]

In summary, the high potency of FUra as an anticancer drug may be attributed to the symbiotic inhibition of two related metabolic pathways by its corresponding nucleotide derivatives: 1) considerable depression of the availability of TPP for DNA synthesis, and 2) cell death after incorporation of the defective FUra-containing monomer into DNA.

Later on, capecitabine and floxuridine (Figure 6) emerged as effective prodrugs of FUra. The former, administered orally, is converted to FU after three enzymatic steps.[46] Because of the overexpresion of thymidine phosphorylase in tumor tissues, capecitabine is assumed to have increased selectivity compared to FUra. Althugh it is not widely employed, floxuridine readily undergoes a similar coversion to FUra by thymidine phosphorylase.[47]

1.1.1.2. Bromovinyldeoxyuridine (BVDU), an important antiviral drug

Collaborative efforts between the laboratories of Dr. Erick De Clercq (Rega Institute for Medical Research, Belgium) and Dr. Richard Walker (Chemistry Department of the University of Birgminham, U.K.) led to the discovery of [(*E*)-5-(2-bromovinyl)-2'-deoxyuridine] (BVDU), a highly potent antiviral drug with specific activity against herpes simplex virus type 1 (HSV-1) and varicella zoster virus (VZV).[48,49] The unique (*E*)-5-(2-bromovinyl) moiety, attached to carbon 5 in the uracil base, was suggested to be the source of the shown specificity of BVDU, thus promoting the synthesis of congeners containing such a fragment. Among the various BVDU analogues prepared, BVaraU (sorivudine) presented similar activity against HSV-1 and, particularly, VZV (Figure 7).[49]

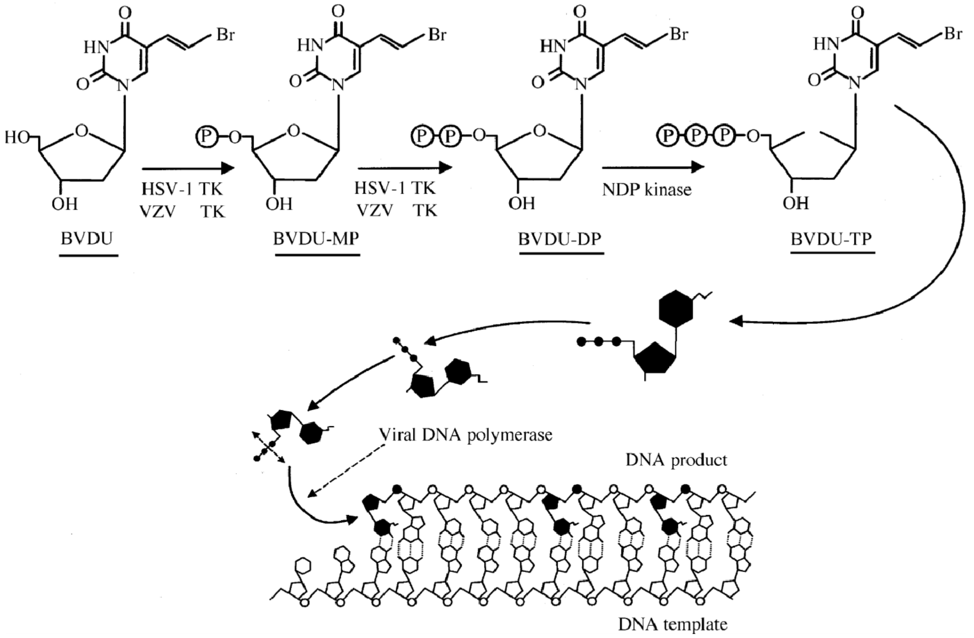


BVDU
[(*E*)-5-(2-bromovinyl)-2'-deoxyuridine]

BVaraU (sorivudine)

Figure 7. (*E*)-5-(2-bromovinyl) containing uridine analogues BVDU and BVaraU. Potent antiviral agents.

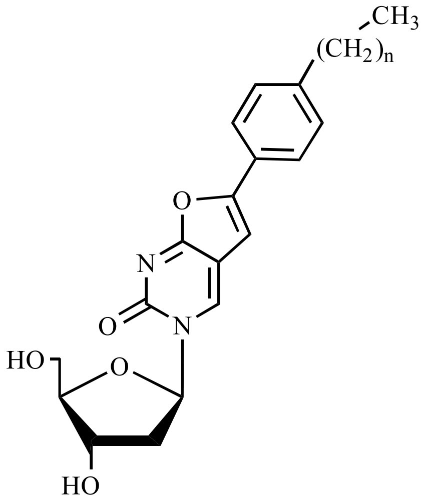
Specific phosphorylation of the nucleoside analogue by the HSV-1 or VZV-encoded thymidine kinase (TK) affords the corresponding 5'-diphosphate (BVDU-DP). A third phosphorylating event, by nucleoside diphosphate kinase (NDP), results in BVDU-TP, which competes with deoxythymidine triphosphate dTPP for the viral DNA polymerase. The efficient incorporation of several BVDU-TP units into the viral DNA renders a structurally and functionally inoperative DNA (Scheme 1).[49] Interestingly, herpes simplex virus type 2 (HSV-2) encoded thymidine kinase (TK) cannot transform the corresponding 5'-monophosphate-BVDU to its 5'-diphosphate, resulting in a decreased activity compared to HSV-1 and VZV. The antiviral activity spectrum of BVDU has been extended to suid herpesvirus type 1 (SHV-1), bovid herpes virus type 1 (BHV-1), simian varicella virus (SVV), herpesvirus saimiri, and herpesvirus platyrrinhae.[50] In comparison with other approved antiviral agents such as acyclovir, valaciclovir, and famciclovir; BVDU can be administered orally at smaller dosage (125 mg) and less frequently (once per day).[51]



Scheme 1: Mechanism of action of BVDU.[49]

On the other hand, BVDU should not be administered to patients under treatment with the 5-fluorouracil (FUra, see section 1.1.1.1). Thymidine phosphorylase converts BVDU to its free base (*E*)-5-(2-bromovinyl)uracil (BVU), which is a potent inhibitor of dehydropyrimidine dehydrogenase (DPD). Similarly, the same enzyme is also in charge of the degradation of 5-fluorouracil.[52]

Recently, bicyclic furo[2,3-*d*]pyrimidine nucleoside analogues (BCNAs) have emerged as a new generation of potent antivirals with activity against varicella zoster virus (VZV).[53,54] Among the BCNAs, Cf 1742 and Cf 1743 (Figure 8) showed high anti-VZV replication activity at subnanomolar concentrations (EC_{50}:0.1-1 nM), which in comparison is about 10-fold lower than for BVDU, and 10,000-fold lower than acyclovir.[55] Although, the mechanism of action of the BCNAs has not been fully resolved, it was proved they inhibit VZV replication as its triphosphorylated derivative BCNA-TP. The latter is suspected to act as a competitive inhibitor/alternate substrate in the viral DNA synthesis.



n=5 Cf 1742
n=4 Cf 1743

Figure 8. Bicyclic furo[2,3-*d*]pyrimidine nucleoside analogues with anti-VZV activity.[55]

In addition, and likely not the case with BVDU, the BCNAs are not substrates for thymidine phosphorylase and thus do not obstruct the catabolism of 5-fluorouracil (FUra).[52] Therefore, BCNAs are the therapy of choice for VZV infections in patients under 5-fluorouracil treatment.

The search for new, therapeutically useful, modified purine and pyrimidine nucleoside analogues has promoted the development of many different approaches for their efficient synthesis. The known versatility, selectivity, and relatively mild reaction conditions necessary for palladium-catalyzed coupling reactions have engendered their application in the synthesis of many important metabolites.[56] Therefore, the second part of this introduction will be focused on a general description of the palladium-catalyzed coupling reaction, emphasizing the new developments and the use of Group 14 metals as well as the role of hypervalent species as reactive intermediates (see 1.2). The third part will review various applications of the palladium-catalyzed coupling reaction in the synthesis of 5-modified pyrimidine nucleoside analogues (see 1.3).

1.2. An overview of the palladium-catalyzed coupling reactions

Many combinations of palladium complexes and organometallic substrates have been successfully employed for the generation of new C-C bonds.[57] The Pd-catalyzed cross-coupling was first studied by Murahashi in the reaction of aryllithiums and vinyl halides (Scheme 2).[58] Later on, Negishi reported efficient coupling of alkenylaluminum, -zinc, and -zirconium reagents with vinyl and aryl halides (Negishi reaction).[59] Reaction of alkenyl copper(I) precursors with alkenyl halides was also reported by Normant.[60] The use of organic tin compounds as coupling precursors was introduced by Migita and Kosugi and extensively followed by Stille (Stille-Migita-Kosugi reaction).[61,62] Suzuki and Miyaura initiated the application of organoboron compounds, which easily undergo cross-coupling after activation with base (Suzuki-Miyaura reaction).[63] Strategies involving the use of organosilanes have been widely exploited in the last decade (Hiyama-Denmark reaction).[64] Terminal alkynes were also found to undergo coupling with halides in the presence of Cu (I) and palladium catalyst (Sonogashira reaction).[65]

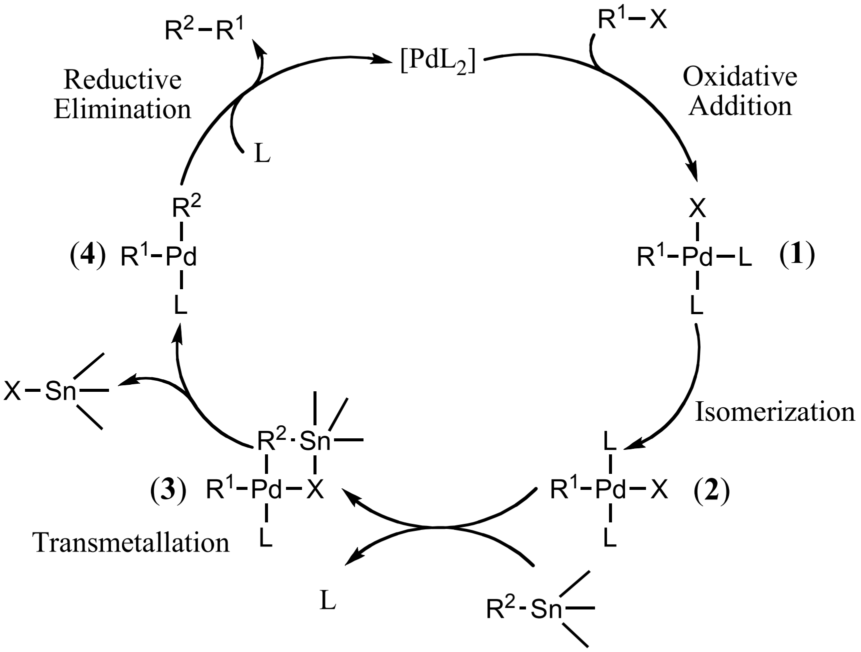
$$\mathrm{R{-}M} + \mathrm{R'{-}X} \xrightarrow{\text{Pd catalyst}} \mathrm{R{-}R'}$$

M= Li (Murahashi)
Al, Zn, Zr (Negishi)
Cu (R=alkenyl, Normant)
Sn (Stille-Migita-Kosugi)
B (Suzuki-Miyaura)
Si (Hiyama-Denmark)
Cu (R=alkynyl, Sonogashira)

X=I, Br, Cl, OTf

Scheme 2. Common organometallic precursors employed in Pd-catalyzed cross-coupling reactions.

The alkenylation of organic electrophiles, also known as the Heck reaction, is often included in the family of coupling process, even though there is no transmetallation step.[66] The cross-coupling reactions may be seen as a very diverse family of processes, in which most of the mechanistic aspects are shared despite the different activation requirements for the organometallic nucleophiles. Important mechanistic information has been mostly obtained from the study of the coupling of organostannanes with organic electrophiles in the presence of palladium and the conclusions extended to other coupling reactions.[67] A general mechanism proposed for the coupling of organostannanes (Scheme 3) consists of an initial oxidative addition of Pd(0) to the corresponding halide to form the *cis*-PdL_2R^1 complex (**1**) followed by fast isomerization to the more stable *trans*-complex (**2**). Transmetallation involving the organometallic nucleophile and the *trans*-complex (**2**) via an associative substitution (S_E2 reaction) give the cyclic intermediate (**3**). Such a complex is assumed to directly afford the *cis*-$PdLR^1R^2$ complex (**4**) from which the cross-coupled product (R^1-R^2) is obtained after reductive elimination of palladium as the reactive PdL_2 complex.[68,69]



Scheme 3. Proposed mechanism for the Stille reaction via a cyclic associative transmetallation.[68,69]

The cyclic associative transmetallation model is applicable to the Stille reaction under the most common conditions consisting of moderately coordinating solvents, palladium complexes with monodentate ligands, and ratios L/Pd >2:1. Investigation of the coupling under different conditions promoted the appearance of different models such as the dissociative and the open associative transmetallation.[70,71]

Because the extensive methodologies developed for the Pd-catalyzed cross-coupling reactions are the subject of numerous excellent reviews,[67] in the next part of the introduction I will concentrate on those aspects of the Pd-catalyzed cross-coupling which are either less developed/understood or have become major subjects of my dissertation.

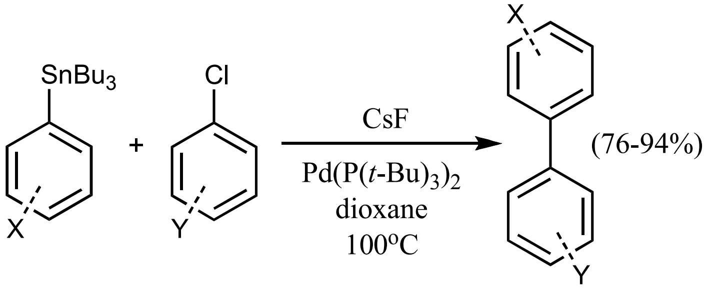
1.2.1. Group 14 metals (Sn, Si, Ge) in Pd-catalyzed cross-coupling reactions

Among all different organometallic reagents efficiently employed in the Pd-catalyzed cross-coupling reactions, organostannanes (Stille-Migita-Kosugi) and organoboranes (Suzuki-Miyaura) have been extensively used due to their reactivity and tolerance to a wide variety of functional groups. Nevertheless, the sensitivity of organoboranes and the toxicity associated with tin-containing byproducts have led to the search for more reliable alternatives. Thus, improvements of Stille-Migita-Kosugi and Hiyama-Denmark reactions have gained special attention in the last decade, as well as the development of new organogermanium coupling partners.

Recent advances on Stille-Migita-Kosugi (Sn) reaction:

Significant advances have been made on the use of more economical and environmentally friendly reaction media when using organotins in Pd-catalyzed cross-coupling reactions. The ability to successfully perform the coupling reaction in aqueous media,[72] supercritical carbon dioxide,[73] and room-temperature ionic liquids (1-butyl-3-methylimidazolium tetrafluoroborate, BMIM BF_4)[74] has notably expanded the scope of the Stille-Migita-Kosugi reaction.

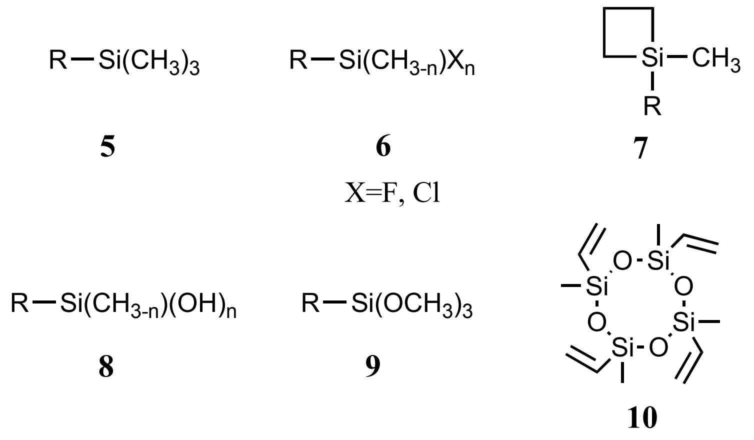
Novel Pd/ligand combinations have increased the reactivity of the less reactive organic bromide and chloride electrophiles (Scheme 4).[75-77] More stable and efficient catalytic systems have been also successfully developed.[78] The fluoride-activated organotins have been used as transmetallating agents, presumably acting via the corresponding hypervalent tin species (see 1.2.1.2).[79-81]



Scheme 4. Coupling of aryltri(butyl)tin with arylchlorides.[77]

Recent advances on the Hiyama-Denmark (Si) reaction:

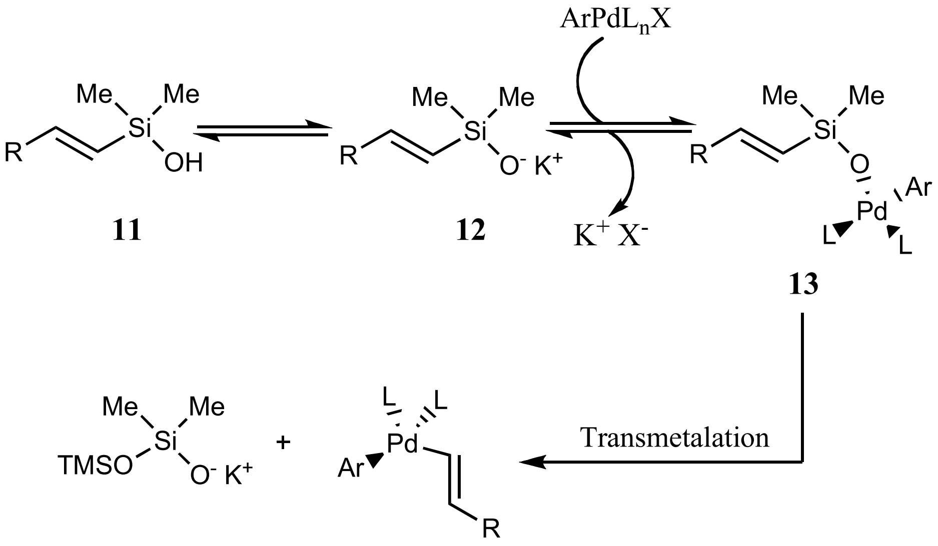
Hiyama *et al.* reported the positive effect of fluoride ion on the nucleophilicity of certain substituents attached to trialkylsilanes **5** (Figure 9) because of the formation of pentavalent silicon species (see 1.2.1.2).[82] However, transfer of alkenyl and allyl groups from the silane was not efficient. In order to overcome this drawback, Hiyama and co-workers[83] found that the presence of an electron-withdrawing ligand on the silicon center efficiently promoted nucleophilic activation by fluoride ions to afford the corresponding pentavalent silicate. Consequently, aryl(halo)silanes **6** were successfully used in the Pd-catalyzed cross-coupling with less reactive arylchlorides.[84,85] As with fluorosilanes, the presence of two chloro ligands was shown to give optimal results. Interestingly, such chloro-substituted silanes were also efficiently activated by hydroxide ions to give the corresponding cross-coupling products from the *in situ* generated silanol.[86]



R=alkyl, aryl, alkenyl or alkynyl

Figure 9. Organosilanes employed in Pd-catalyzed cross-coupling reactions.

In view of the apparent need for the generation of pentavalent silicon species, Denmark *et al.* explored the use of silacyclobutanes (siletanes) **7** as the nuclephilic coupling partners.[87] The use of such strained structures was based on the manifested increase of their Lewis acidity resulting from a change in the coordination geometry (strain-release Lewis acidity) from tetra- to penta-coordinated silicon species.[88] However, further investigations evidenced the formation of silanol and/or siloxanes upon treatment of the corresponding silacyclobutane with TBAF·3H_2O. These products were evaluated as coupling substrates showing reactivity levels comparable to the parent silacyclobutanes.[89] These important discoveries rapidly triggered the study of the Pd-catalyzed cross-coupling of many structurally diverse oxygen-substituted silanes including, silanols **8**, siloxanes **9**, and polysiloxanes **10**.[64] Moreover, alternative use of base and Ag_2O to activate the silanol precursors was demonstrated to be equally effective as the typical fluoride activation.[64,90] Important mechanistic implications arose from the pioneering work by Denmark regarding silanol activation with potassium trimethylsilanolate (TMSOK). Kinetic studies revealed initial pre-equilibrium between the corresponding silanol **11** and a newly formed silanolate **12**. Subsequently, nucleophilic **12** displaces the anionic ligand on Pd generating a reactive Pd-O-Si complex **13**, which can undergo intramolecular transmetallation (see **3** in Scheme 3) without additional activation (Scheme 5).[91]



Scheme 5. Proposed mechanism for silanol activation by TMSOK.[91]

Development of new organogermanium (Ge) reagents for Pd-catalyzed cross-coupling reaction:

The development of organogermanes as valuable reagents for the Pd-catalyzed cross-coupling has been less explored due to the higher cost and the diminished reactivity of germanium precursors compared to their silicon counterparts. The carbagermatranes **14** (Figure 10) were the first examples of labile tetracoordinated germanes to undergo cross-coupling with aryl bromides in the presence of palladium catalyst.[92] Subsequently, the oxagermatranes **15** were reported to be more efficient than the similar carbagermatranes **14** and triethoxygermanes **16**.[93] Internal coordination by the transannular nitrogen was attributed to the reactivity of both germatrane precursors. On the other hand, aryltri(2-furyl)germanes **17**,[94] arylgermanium trichlorides **18**,[95] and their hydrolyzed stable sesquioxides **19**[96] were coupled after treatment with either fluoride ions or NaOH, respectively. Interestingly, fluoride anion failed to promote the coupling of aryltrichlorogermanes **18**.[95]

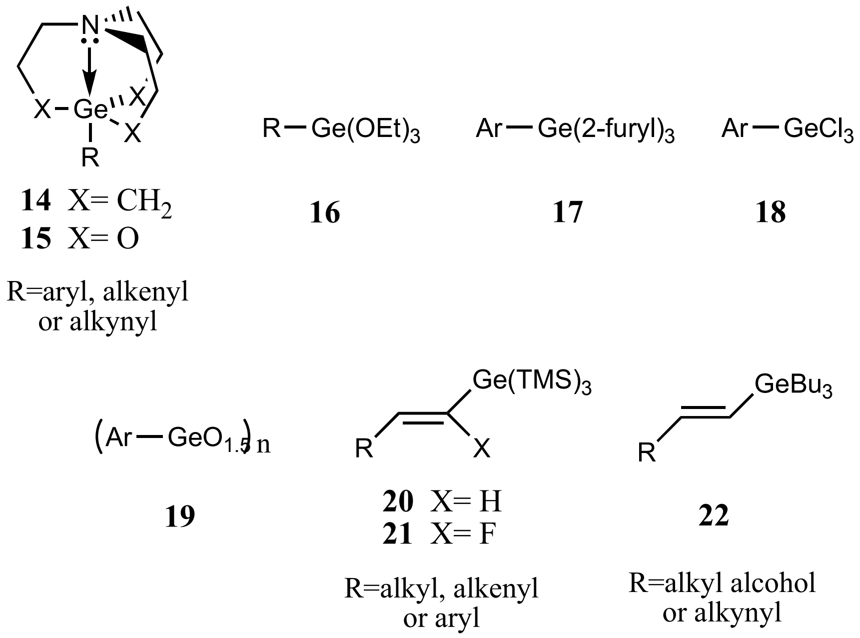


Figure 10. Organogermanes employed in Pd-catalyzed cross-coupling reactions.

The vinyl tris(trimethylsilyl)germanes **20** were also described as efficient precursors in "ligand- and fluoride-free" coupling with halides upon oxidative (H_2O_2) activation.[97] Moreover, the use of their (α-fluoro)vinyl analogues **21** afforded the corresponding fluoroalkenes and fluorodienes.[98] Coupling of vinyltributylgermanes **22** with aryl halides gave preferential access to *Z*-alkenes, although the Heck mechanism was proposed as the major operative pathway.[99]

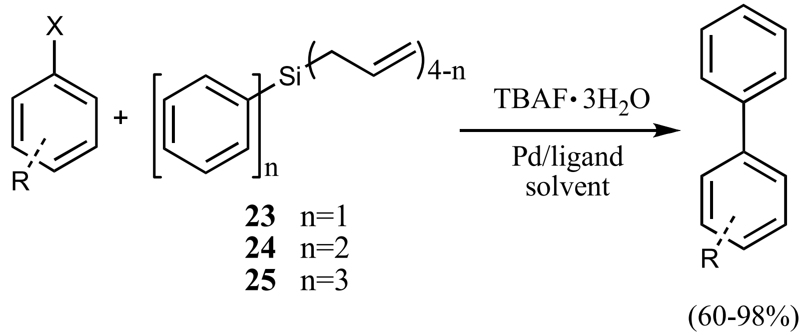
1.2.1.1. Safety-catch precursors

The application of the above-mentioned methodologies is often limited by the apparent lability of the heteroatom-substituted organometals and/or the harsh conditions needed for their *in situ* generation. However, continuous efforts are undertaken to develop novel "safety-catch" silicon and germanium precursors. Silyl hydrides,[100] 2-pyridylsilanes,[101] 2-thienylsilanes,[102] dimethylphenylsilanes,[103] and dimethylbenzylsilanes[104] are successful examples of safety-catch substrates for Hiyama-Denmark coupling. On the other hand, the development of similar germanium precursors has been much less explored. Two of the most recent examples are described below.

Hiyama's allyl(phenyl)silanes:

In 2004 Hiyama and co-workers reported the efficient coupling of aryl halides and the all carbon-substituted triallyl(phenyl)silane **23** (Scheme 6).[105] The design was based on the polarization of the C-Si bond as a result of the *in situ* generation of pentavalent fluorosilicates. Optimization of the reaction conditions revealed that 4 equivalents of tetrabutylammonium fluoride trihydrate ($TBAF \cdot 3H_2O$) were necessary to efficiently promote the coupling reaction of silane **23** with several aryl halides. Supposedly, three equivalents of TBAF cleaved the three allyl substituents to afford trifluorophenylsilane, while the remaining equivalent of fluoride might generate the active pentavalent silicate suspected to undergo transmetallation. Furthermore, the couplings of diallyl(diphenyl)silanes **24**, and allyl(triphenyl)silanes **25** were also performed under similar conditions to afford various biaryls.

The experimental results suggested a clear dependence of the reactivity of the allyl(phenyl)silanes on the number of allyl substituents; $PhSi(allyl)_3$ **23** > $Ph_2Si(allyl)_2$ **24** > $Ph_3Si(allyl)$ **25**. The identity of the active pentacoordinated silicate responsible for transmetallation is not yet well understood. The safety-catch triallyl(phenyl)silane **23** may be seen as a promising alternative to be used in industrial and academic research, even though couplings using **23** and **24** required higher loadings of reagent to be efficient. Attempts to transfer more than one aryl group from **24** and **25** were ineffective supposedly due to the formation of inactive hexacoordinate silicate species.

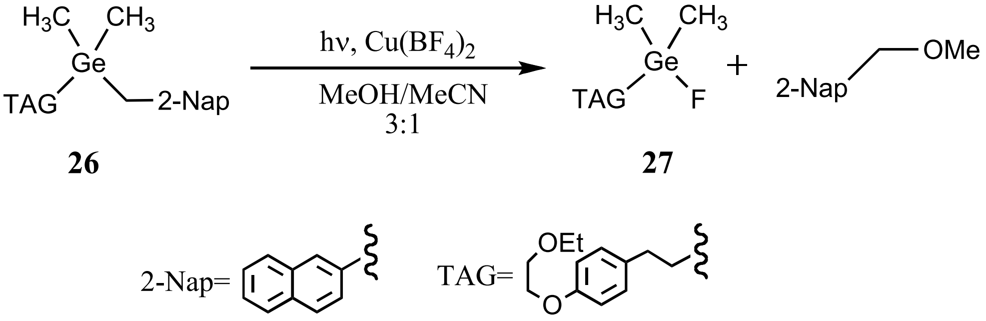


n=1,2 X=Br $PdCl_2/PCy_3$, DMSO-H_2O
n=1,2 X=Cl $[(\eta^3\text{-}C_3H_5)PdCl_2]_2$, THF-$H_2O$
n=3 X=Cl $[(\eta^3\text{-}C_3H_5)PdCl_2]_2$, XPhos, THF-$H_2O$

Scheme 6. Coupling of safety-catch allyl(phenyl)silanes.[105]

Spivey's Bis(2-naphthylmethyl)arylgermanes:

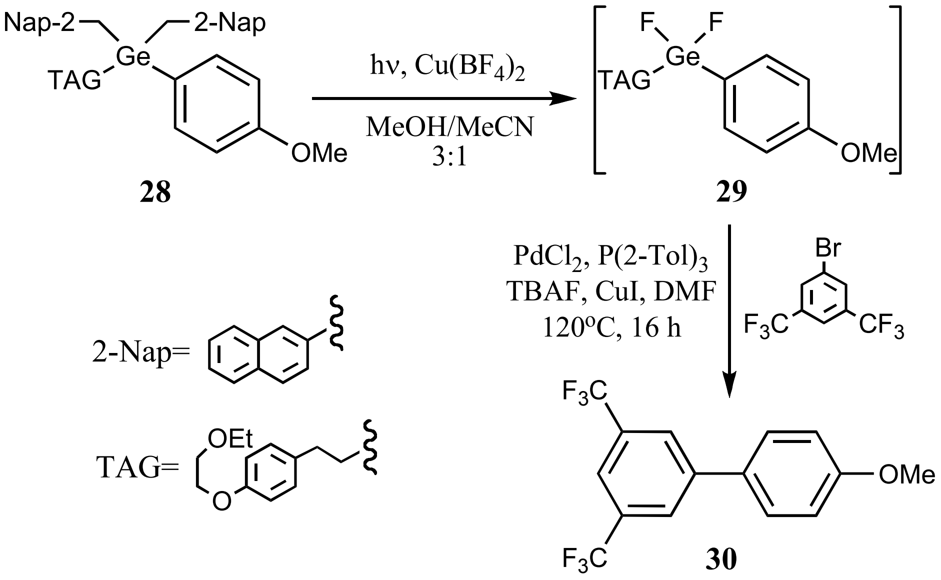
In 2007 Spivey *et al.* developed novel bis(2-naphthylmethyl)arylgermane **28**, highly stable towards bases and nucleophiles and that could be activated photochemically to assist cross-coupling with aryl halides affording biaryls.[106] Also, the possibility for attachment of a phase-tag was successfully explored. On the basis of the assumed necessity for the presence of an electronegative heteroatom on the metallic center in order for it to render hypervalency and be active towards transmetallation, exploratory experiments using arylchlorogermanes and NaOH or KF were performed. They demonstrated that two chlorine ligands were necessary for efficient cross-coupling with aryl bromides. In the search for the most suitable safety-catch germane precursor, extensive and cautious screening established aryldibenzylgermanes as a promising candidate for photochemical activation. However, since the necessary short wavelength (275 nm) employed gave complex mixture of debenzylated products, an alterative group able to absorb light of lower energy was investigated. The replacement of the benzyl group for 2-naphthylmethyl (346 nm) proved to be an excellent choice since irradiation of (2-naphthylmethyl)germane **26** with a high-pressure Hg lamp (125 W) in the presence of $Cu(BF_4)_2 \cdot nH_2O$ afforded the corresponding {2-[4-(2-ethoxyethoxy)phenyl]ethyl}-dimethylfluorogermane **27** [^{19}F NMR δ -196 ppm ("septet", $^{3}J_{F\text{-}H}$ 7 Hz)] (Scheme 7).



Scheme 7. Photooxidative cleavage of (2-naphthylmethyl)germane.[106]

Analogously, treatment of the tagged (4-methoxyphenyl)-bis(naphthalene-2-ylmethyl)germane **28** under the same conditions gave the expected difluorinated intermediate **29** (δ -165 ppm). Subsequent fluoride-promoted Pd-catalyzed coupling of **29** with 3,5-bis(trifluoromethyl)bromobenzene afforded the corresponding biaryl product **30** in 86% yield (Scheme 8).

The same group also reported the scope and limitations of the novel safety-catch bis(2-naphthylmethyl)germane containing a light-fluorous tag. Photooxidation of the bis(2-naphthylmethyl)arylgermanes and subsequent coupling with various arylbromides in the presence of $PdCl_2(MeCN)_2$/$Pd(2\text{-}Tol)_3$, $TBAF \cdot 3H_2O$ and CuI afforded the desired products in moderate to good yields.[107]



Scheme 8. Coupling of safety-catch bis(2-naphthylmethyl)germanes.[106]

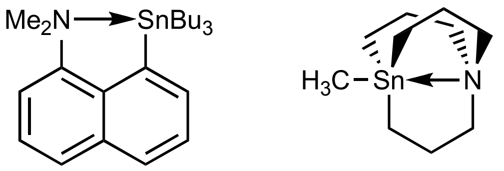
1.2.1.2. Hypervalent species as key reactives intermediates

In the Stille-Migita-Kosugi reaction:

Among all of the features of the Stille-Migita-Kosugi reaction, one of the most important is the ability to efficiently transfer an aryl or a vinyl group from an all-carbon substituted tin center without the need of previous activation. There are, however, a number of reports that show the increased tendency of highly coordinated tin compounds to transfer an alkyl group under mild conditions. As a consequence, many studies have been carried out employing transferable groups on a tin center coordinated to heteroatoms (deactivating group).[108]

a) Hypervalency by internal coordination:

Farina *et al.* reported the exclusive transfer of alkyl ligands from the highly-constrained 1-(dimethylamino)-8-(tributylstannyl)naphthalene **31** (Figure 11).[109] Similar alkyl transfer was promoted by internal coordination of the transannular nitrogen to the tin center in the reaction of methyl-carbastannatranes **32** with aryl bromides in the presence of Pd catalysts.[110] Noteworthy, the formation of a permanent pentacoordinate tin center failed to accelerate the transfer of the aryl substituent from **31**.



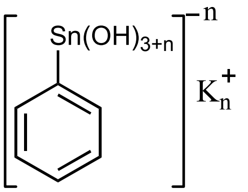
31 **32**

Figure 11. Hypervalent organostannates by internal coordination employed in Pd-catalyzed cross-coupling reactions.

b) Hypervalency by nucleophilic activation:

The Pd-catalyzed cross-coupling of highly deactivated organotin trichlorides upon alkaline aqueous activation was proven to be efficient as well. A pentavalent anionic hydroxotin complex **33** (Figure 12) generated by the basic hydrolysis of the trichlorotin precursor was assumed to be the reactive intermediate.[111,112]

It is well documented that, similar to silicon,[84] tin is fluorophilic. As a consequence, the generation of hypervalent tin species by fluoride activation has also been studied as a plausible way to increase its reactivity towards transmetallation. Fouquet and Rodriguez have described the Pd-catalyzed cross-coupling of the *in situ* generated hypervalent monoorganotin **34** with alkenyl/aryl triflates.[113] The reaction of organic halides with Lappert's stannylene afforded the monoorganotin precursors, which upon TBAF activation produced the reactive complex **34**. The addition of fluoride activated haloorganotin ($ArSnBu_2Cl$) reagents achieved efficient coupling with haloanisole. These results promoted further studies with $(aryl)_nSn(alkyl)_{n-4}$ precursors from which more than one group was efficiently transferred in the presence of TBAF (see section 1.2.1.3).[80]



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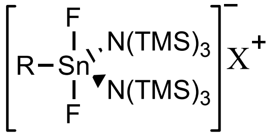

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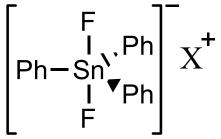
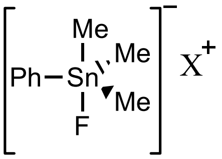


35

For compound **35**: ^{19}F NMR ($CDCl_3$) δ -159.0 ppm
[$^{1}J_{19F\text{-}119Sn}$=1971 Hz, $^{1}J_{19F\text{-}117Sn}$=1887 Hz].[81,114]
For compound **36**: ^{19}F NMR (C_6D_6) δ -144.8 ppm.[115]



36

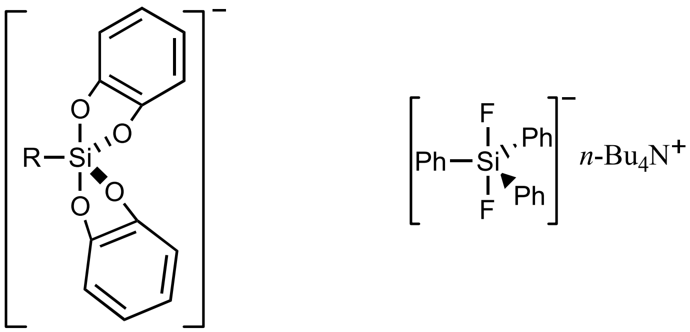
Figure 12. Hypervalent organostannates by nucleophilic activation employed in Pd-catalyzed cross-coupling reactions.

The stable and non-hygroscopic tetrabutylammonium difluorotriphenylstannate **35** was reported as a convenient fluorinating agent in various organic transformations.[114] Moreover, Garcia Martinez *et al.* reported the use of **35** in the Pd-catalyzed cross-coupling with alkenyl and aryl triflates.[81] It was also assumed that the coupling of trimethylphenyltin with arylchlorides in the presence of TBAF occurred via a hypervalent fluorotin intermediate **36.**[115]

<u>In the Hiyama-Denmark reaction</u>:

Since the original reports of Tamao-Kumada[116] and Hiyama,[83] development of Pd-catalyzed cross-coupling reactions employing organosilanes have been driven by the assumed necessity to generate a pentavalent siliconate species. Although there is no irrefutable evidence for the participation of such hypervalent species in the transmetallation step, many reports have accounted for the critical effect of nucleophilic activation of tetracoordinated silanes in coupling reactions.[117,118]

Indirect indication of an activation step is found in the ability of stable, pentavalent siliconates to easily undergo cross-coupling. Hosomi has shown that pentacoordinate cathecolsiliconates **37** (Figure 13) are efficient agents for transferring alkenyl groups to aryl halides and triflates.[119] The unsymmetrical biaryls were formed when aryl triethylammonium bis(cathechol)silicates **38** reacted with aryl and heteroaryl halides/triflates in the presence of TBAF and a suitable Pd/ligand combination.[120] The stable tetrabutylammonium triphenyldifluorosilicate (TBAT) **39**[121,122] has been shown to be a versatile nucleophilic reagent for the transfer of phenyl groups through Pd-catalyzed cross-coupling with aryl halides and allylic alcohol derivatives.[123,124]



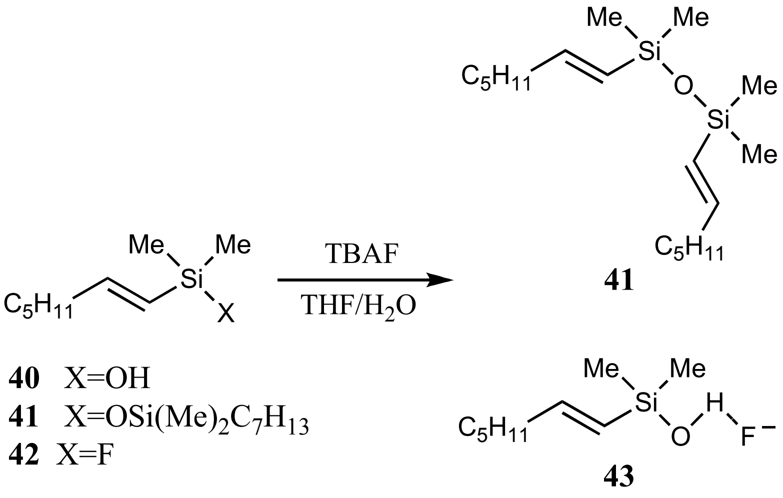
37 R=alkenyl[119]
38 R=aryl[120]

39 TBAT[121,122]

For compound **39**: ^{19}F NMR (DMSO-d_6) δ -96.0 ppm, $^1J_{19\text{F-}29\text{Si}}$= 252 Hz.[121]

Figure 13. Hypervalent siliconates in Pd-catalyzed cross-coupling reactions.

Despite all the progress made on the identification of the possible reactive intermediates involved in the Pd-catalyzed cross-coupling of organosilanes, a clear representation of the reaction mechanism is still lacking. Recent investigations by Denmark's laboratory on the feasible mechanistic pathways and the reaction kinetics have been of extraordinary assistance.[125] Initial efforts were dedicated to establish the identity of the reactive intermediate(s) involved in the coupling of silanols, disiloxanes, and related fluorosilanes upon fluoride activation. Thus, independent synthesis and testing of all three precursors were performed affording coupling products with very similar yields after only 10 minutes. Spectroscopic analysis of the mixtures generated by treatment of representative silanol **40**, disiloxane **41**, or fluorosilane **42** with TBAF (Scheme 9) showed new species assigned to a silanol with a hydrogen-bonded fluorine **43** and the corresponding disiloxane **41**.



40 X=OH
41 X=OSi(Me)$_2$C$_7$H$_{13}$
42 X=F

41

43

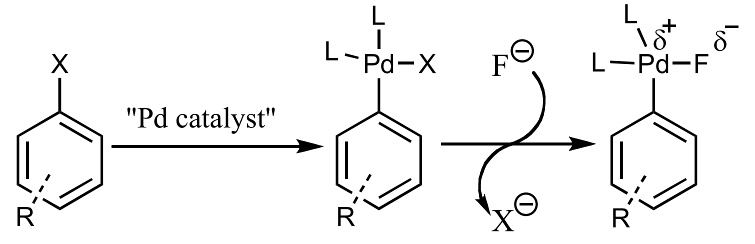
For compound **41**: ^{29}Si NMR (THF-d_8) δ -3.95 ppm

For compound **43**: ^{29}Si NMR (THF-d_8) δ -8.39 ppm
^{19}F NMR (THF-d_8, rt) δ -117.7 ppm
(THF-d_8, -95°C) δ -150.8 ppm

Scheme 9. NMR analysis of alkenylsilane/TBAF mixtures.[125]

These results suggest that the fluoride-promoted coupling of silanol **40**, disiloxane **41**, and fluorosilane **42** is likely to occur via a common mechanism. Furthermore, a meticulous kinetic investigation of the fluoride-promoted coupling of a silanol (e.g., **40**) and 2-iodothiophene suggested that the predominant species exhibited a clear dependence on the concentration of TBAF. Hence, at low concentration of TBAF the corresponding disiloxane **41** was predominant. In contrast, the hydrogen-bonded complex **43** became major at higher loadings of TBAF.

The positive effect of fluoride on the Hiyama-Denmark coupling has also been illustrated in the formation of an aryl-Pd(II)-fluoride complex of type **44** (Scheme 10), expected to be more electrophilic at palladium and hence more reactive towards transmetallation. Nevertheless, aryl-Pd(II)-fluorides have been described to be less reactive than the corresponding iodides, bromides and chlorides.[126]



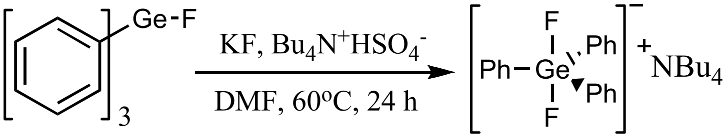
X= I, Br, Cl

44

Scheme 10. Formation of aryl-palladium-fluoride complex.

<u>In the coupling of organogermanes</u>:

With the exception of carbagermatranes **14**[92] (Figure 10, section 1.2.1) and oxagermatranes **15**,[93] in which internal coordination was able to render the Ge center hypervalent, all the other Ge precursors needed activation before the transmetallation step. In general, cleavage/displacement of the existing substituents and formation of hypervalent germanium species by the action of fluoride or hydroxide ions have been assumed to take part in the coupling of tris(2-furyl)germanes **17**,[94] trichlorogermanes **18**,[95] germanium sesquioxides **19**,[96] and tris(trimethylsilyl)germanes **20** and **21**.[97] On the other hand, the addition of fluoride ion to the heteroatom-substituted trialkoxygermanes **16**[93] and difluorogermanes **29**[106] (Scheme 8, section 1.2.1.1) was suggested to produce active pentavalent germanium derivatives. Moreover, the treatment of triphenylgermanium fluoride **45**[127] with KF and tetrabutylammonium hydrogensulphate in DMF resulted in the first synthesis of the pentavalent tetrabutylammonium difluorotriphenylgermanate **46** (Scheme 11).[128] Despite the similarities to its tin and silicon analogues (**35**[114] and **39**[121]), the application of **46** to the Pd-catalyzed cross-coupling reactions has not yet been explored.



45 **46**

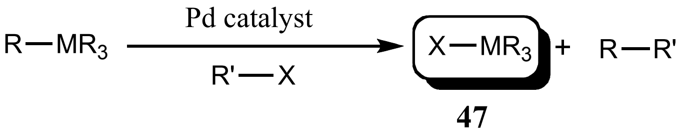
For compound **45**: ^{19}F NMR ($CDCl_3$) δ -202.2 ppm[127]
For compound **46**: ^{19}F NMR (C_6D_6) δ -118.9 ppm.[128]

Scheme 11. Synthesis of tetrabutylammonium difluorotriphenylgermanate.[128]

Although hypervalent germanium species appear to play a critical role in all the above mentioned Pd-catalyzed cross-coupling approaches, clear evidences to prove their presence as reactive intermediates is still lacking.

1.2.1.3. The multi-transfer paradigm

While organostannanes, organosilanes, and organogermanes may carry four carbon substituents on the metallic center, only one group is usually transferred in the Pd-catalyzed cross-coupling reactions due to the deactivating nature of halogen ligands in the haloorganometallic intermediates of type **47** (Scheme 12).[62]

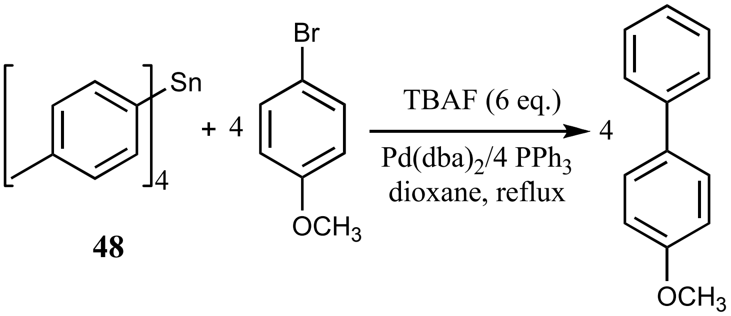


47

M= Sn, Si or Ge
X=Halogen

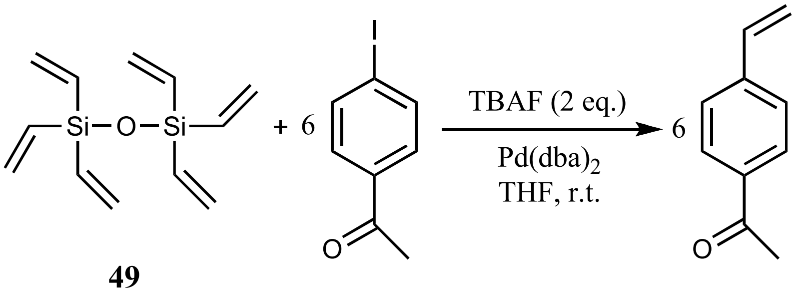
Scheme 12. Pd-catalyzed cross-coupling of tetrasubstituted organometals from Group 14.

Consequently, activation of the residual species derived from each transmetallation step would be required in order to promote multiple transfers from the organometallic precursors. Kosugi and co-workers reported the ability of TBAF to activate tetra(*p*-tolyl)tin **48** for the efficient transfer of all four aryl ligands (Scheme 13).[80] Obvious advantages were derived from this work since less toxic halotin by-products are generated from a sub-stoichiometric amount of organotin precursor employed. Recently, the atom-efficient Pd-catalyzed cross-coupling of tetraphenyltin (Ph_4Sn) with several aryl bromides in the presence of NaOAc in polyethylene glycol (PEG-400) has been developed.[129]



Scheme 13. Coupling of tetra(*p*-tolyl)tin with 4-bromoanisole.[80]

Attempts to promote similar multiple transfers using organosilicon reagents have also been undertaken. However, coupling of diallyl(diphenyl)silane **24** (Scheme 6, section 1.2.1.1) with excess of 4-chloroanisole was shown to occur by transfer of only one phenyl substituent.[105] The formation of inert hexacoordinate silicate species (after the transmetallation of the first phenyl group) was assumed to be impeding a second group transfer. Moreover, coupling of the pre-synthesized tetrabutylammonium triphenyldifluorosilicate **39** (Figure 13, section 1.2.1.2) (1 equiv.) with 4-iodoanisole (1 equiv.) in the presence of TBAF (3 equiv.) indicated that TBAT delivered around 1.25 phenyl groups.[123] However, more convincing evidence for multiple phenyl transfer might be obtained by employing an excess of the aryl halide, but such experiments were lacking. Denmark *et al*. reported the transfer of each vinyl group from the inexpensive hexavinyldisiloxane **49** during the Pd-catalyzed cross-coupling with 4-iodoacetophenone in the presence of TBAF (Scheme 14).[130] The remarkable low cost of the silicon reagents and the non-toxic nature of the corresponding by-products place this methodology in good standing for large scale preparations.



49

Scheme 14. Coupling of hexavinyldisiloxane with 4-iodoacetophenone.[130]

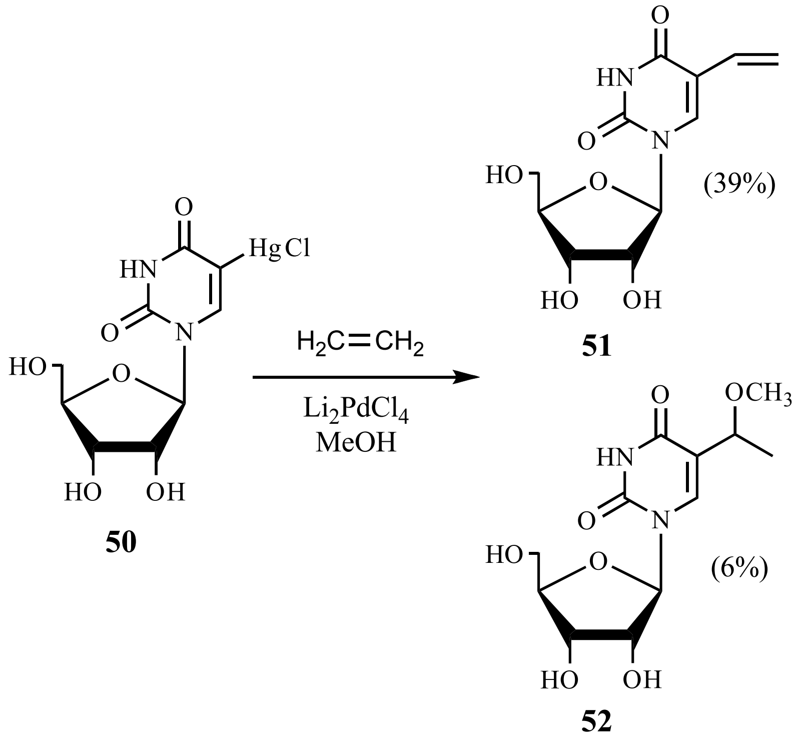
1.3. Pd-catalyzed coupling approaches for the synthesis of 5-modified pyrimidine nucleosides

Although different approaches have been used for the synthesis of base-modified nucleosides, Pd-catalyzed cross-coupling strategies have offered a very convenient alternative.[56] The easy access to 5 and 6 halo-modified pyrimidine nucleosides and 2- and 8-halo purine nucleosides have facilitated their application as substrates for the synthesis of more complex nucleoside/nucleotide scaffolds. Moreover, several 5-halo pyrimidine nucleosides have displayed important biological activity. Among them, 5-iodo-2'-deoxyuridine shows antiviral activity, while 5-fluorouracil[43] and 5-fluoro-2'-deoxyuridine[46] (see FUra and capecitabine in 1.1.1.1) are known for their potent antitumor properties. Several examples describing the application of the Pd-catalyzed cross-coupling to the synthesis of 5-modified pyrimidine nucleosides are presented as follows.

1.3.1. Bergstrom's approach using mercury (Hg) salts by Heck reaction

Bergstrom was first to report the coupling between an alkene and a heterocyclic base[131-133] and comprehensively reviewed the chemistry of the C-5-substituted pyrimidine nucleosides in 1982.[134] The initial application of the Heck reaction in the synthesis of 5-modified nucleoside analogues comprised the application of organopalladium intermediates generated *in situ* from unprotected 5-chloromercuriuridine **50** (Scheme 15). The coupling with ethylene afforded the desired 5-vinyl analogue **51** along with 5-(1-methoxyethyl)-uridine **52** as a minor byproduct.

Later, Bergstrom and others have extended the use of this methodology to prepare C-5 thioether pyrimidine nucleosides,[135] to generate biotin-labeled DNA probes,[136] and to connect iron-EDTA to an oligonucleotide.[137] Other applications of this Pd-coupling approach include the formation of oligomers containing Ru complexes,[138] and the synthesis of nucleoside-peptide conjugates,[139] and the preparation of oligodeoxyribonucleotide methyl thioether probes.[140]

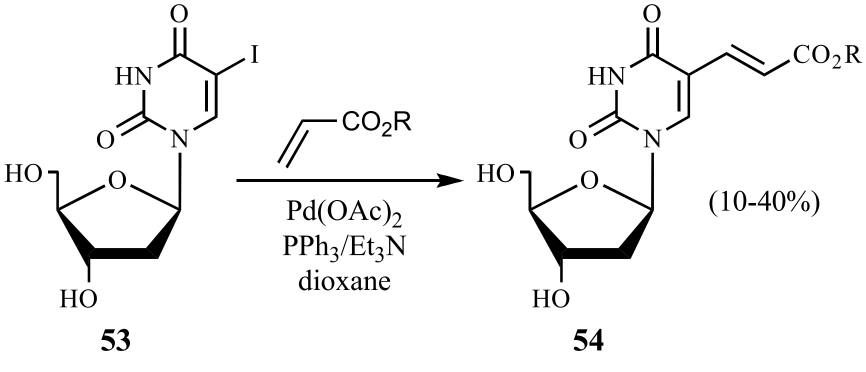


Scheme 15. Coupling of 5-mercuri uridine and ethylene.[131-133]

Whale *et al.* applied the Heck reaction between 5-iodo-2'-deoxyuridine **53** and acrylates to obtain (*E*)-5-(2-carboxyvinyl)uridine **54** (Scheme 16) in poor to moderate yields.[141] Wybotusine, the first tricyclic fluorescent nucleoside isolated from phenylalanine-transfer ribonucleic acids[142,143] was successfully synthesized utilizing the Heck approach.[144]

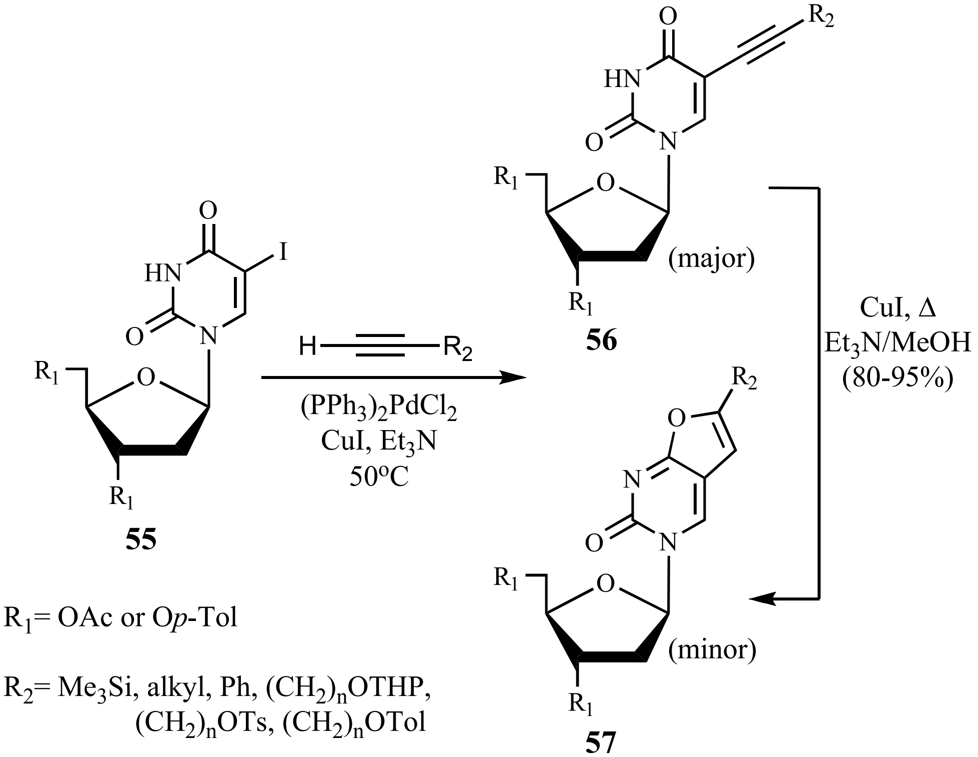
1.3.2. Robins' approach using Sonogashira reaction

Several 5-alkynyl pyrimidine nucleosides **56** have been synthesized employing Pd-catalyzed cross-coupling reactions of the protected 5-iodonucleosides **55** with several terminal alkynes (Scheme 17).[145] Noteworthy, an interesting bicyclic furanopyrimidine byproduct **57** (see BCNAs in 1.1.1.2.) was also reported. Formation of this type of bicyclic furanopyrimidine from (*E*)-5-bromovinyluracil upon base-catalysis was reported by Blackey *et al.* in 1976.[146] Robins and Barr[145,147] described the exclusive synthesis of **57** by treatment of 5-alkynyl uridine analogues **56** with CuI in Et_3N/MeOH at reflux.



R= Et, *n*-Pr, *i*-Pr, *n*-Bu, *s*-Bu, *n*-pentyl, *n*-octyl, benzyl, and others

Scheme 16. Coupling of 5-iodo-2'deoxyuridine with various acrylic esters.[141]

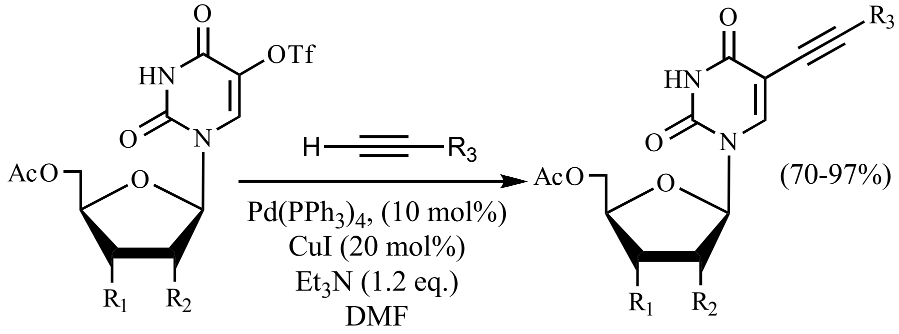


R_1= OAc or O*p*-Tol

R_2= Me_3Si, alkyl, Ph, $(CH_2)_nOTHP$, $(CH_2)_nOTs$, $(CH_2)_nOTol$

Scheme 17. Sonogashira coupling of 5-iodouridine analogues with different terminal acetylenes. Synthesis of furanopyrimidine analogues.[145,147]

Coupling of various protected uridine 5-triflates **58** with alkynes also produced uridine 5-alkynes **59** in high yields (Scheme 18).[148] Higher reaction temperature resulted in an increase of the rate of coupling, while the formation of minor bicyclic byproducts of type **57** (Scheme 17) was considerably inhibited employing DMF. An alternative approach was described employing tandem Sonogashira couplings. Thus, coupling with trimethylsilyl acetylene was followed by a straightforward desilylation and the resulting terminal alkynyl nucleoside analogue was further coupled with various aryl bromides.[148]



58 **59**

R_1=R_2= OAc
R_1= OAc, R_2= H
R_1= OH, R_2=H

R_3= Me_3Si, $HOMe_2C$, Ph, aryl

Scheme 18. Sonogashira coupling of 5-triflate uridine analogues with terminal acetylenes.[148]

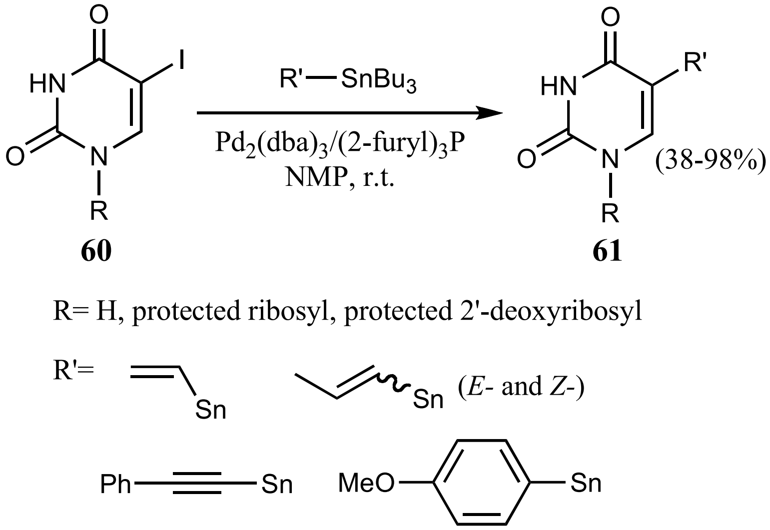
Recently McGuigan *et al.*[53,54] illustrated that furanopyrimidine byproducts displayed significant potency and selectivity against Varicella zoster virus (VZV) (see 1.1.1.2). Meanwhile, imidazo[1,2-*c*]pyrimidin-5(6*H*)-one heterosubstituted analogues were reported to have anti-hepatatis B virus (HBV) activity.[149]

Besides their interesting biological importance, the 5-alkynyl pyrimidine nucleosides have been used as linker arms for the attachment of fluorophores on chainterminating 2',3'-dideoxynucleotides for DNA sequencing experiments.[136,150] Analogues of the anti-HIV drug 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymidine (HEPT) bearing different alkynyl groups of C5 were also prepared employing the Sonogashira coupling reaction.[151]

1.3.3. Approaches using Stille-Migita-Kosugi (Sn) coupling reaction

The high efficiency and mild reaction conditions of the Pd-catalyzed cross-coupling reaction using organotins makes it a very likely alternative for the functionalization of nucleoside analogues. Unfortunately, the high toxicity of tin byproducts has limited its application in their synthesis. The work of Farina and Hauck[152] is a good example in which protected 5-iodouracil/uridine **60** was successfully treated with various vinyl stannanes for the synthesis of 5-substituted uracil/uridine analogues **61** in moderate to excellent yields (Scheme 19). Interestingly, the reaction showed a strong dependence to the type and amount of Pd catalyst used. For example, $(MeCN)_2PdCl_2$ (2 mol %) led to a fast decomposition and 14% yield of product. In contrast, reaction under the same conditions but with $Pd(PPh_3)_4$ gave around 50% conversion. The combination of $Pd_2(dba)_3$/P(2-furyl)$_3$ led to 89% conversion. Presence or absence of protecting groups on the sugar moiety did not affect the reaction outcome.

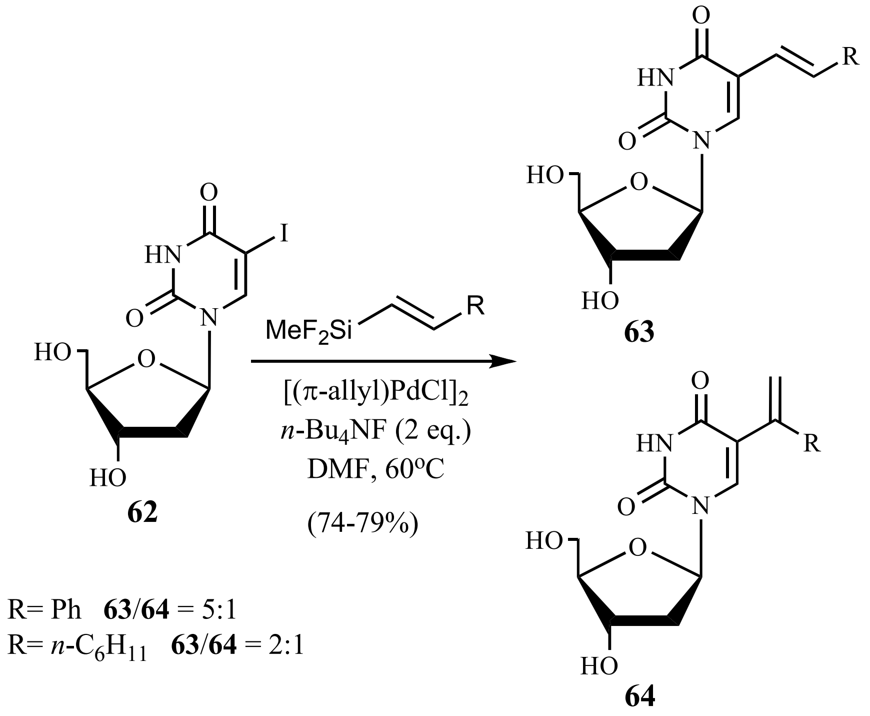
Herdewijn *et al.*[153] reported the coupling of 5-iodo-2'-deoxyuridines with symmetric tetraorganotin compounds under similar conditions. Later on, Rahim *et al.*[154] described couplings with tetra-vinyltins for the synthesis of analogues of the anti-herpes agent 2'-deoxy-4'-thio-5-vinyluridine. A year later, Wiebe and co-workers[155] successfully synthesized (*E*)-5-(2-(trimethylsilyl)vinyl) uridine analogues employing (*E*)-2-(tributylstannyl)-1-(trimethylsilyl)ethene in the presence of catalytic $(PPh_3)_2PdCl_2$ in dry acetonitrile. Uridine analogues were further transformed into the radioactive (*E*)-5-(2-[^{125}I]iodovinyl derivatives for their evaluation as probes for monitoring gene therapy.[155]



Scheme 19. Coupling of 5-iodouracil, uridine, and 2'-deoxyuridine analogues with different unsaturated organotins.[152]

1.3.4. Approach using Hiyama-Denmark (Si) coupling reaction

In 1996, Matsuhashi *et al.*[156] reported the Pd-catalyzed cross-coupling of 5-iodo-2'-deoxyuridine **62** with various vinylfluorosilanes activated by TBAF (Scheme 20). Although, a mixture of isomers **63** and **64** was obtained, the method offers a reliable and less toxic alternative to the organotin approach (see 1.2.1.3) for the preparation of 5-substituted pyrimidine nucleosides.



Scheme 20. Hiyama-Denmark coupling of 5-iodo-2'-deoxyuridine with vinylfluorosilanes.[156]

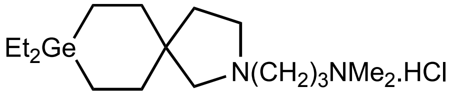
1.4. Biological activity of Germanium-containing compounds

1.4.1. Non-nucleoside derived compounds

Among Group 14 elements, the chemistry and biology of germanium remained unexplored until it was found as a decay product of some nuclear disintegration. In 1962 van der Kerk and co-workers[157] discovered the antifungal properties of triorganogermanium acetates. Later on, the water-soluble carboxyethylgermanium sesquioxide Ge-132 **65** (Figure 14) was synthesized by Asai.[158] In 1994 the first organogermanium pharmaceutical called propagermanium was released in Japan (Serocion®), which displays protection against viruses, immunostimulation, hepatoprotection, and low toxicity. Presently, various organogermanes exhibiting interferon-inducing, hypotensive, neurotropic, antitumor, radioprotective, and immunomodulating properties have been prepared.[159] The most studied organogermanium compounds are germanium sesquioxanes **65** (e.g., 2-carboxyethylgermanium sesquioxide Ge-132; antiviral, immunomodulator, anticancer, hepatoprotective), spirogermanium **66** (2-(3-dimethylaminopropyl)-8,8-diethyl-2-aza-8-germaspiro[4,5]decane; antitumor, antimalarial, antiarthritic), germatranes **67** (antitumor, neurotropic), and germylporphyrines **68** (antitumor). Studies on the biological properties of several organogermane derivatives have been reviewed.[160]

$(GeCH_2CH_2COOH)_2O_3$

65



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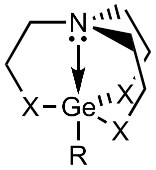

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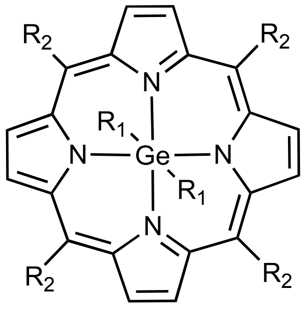
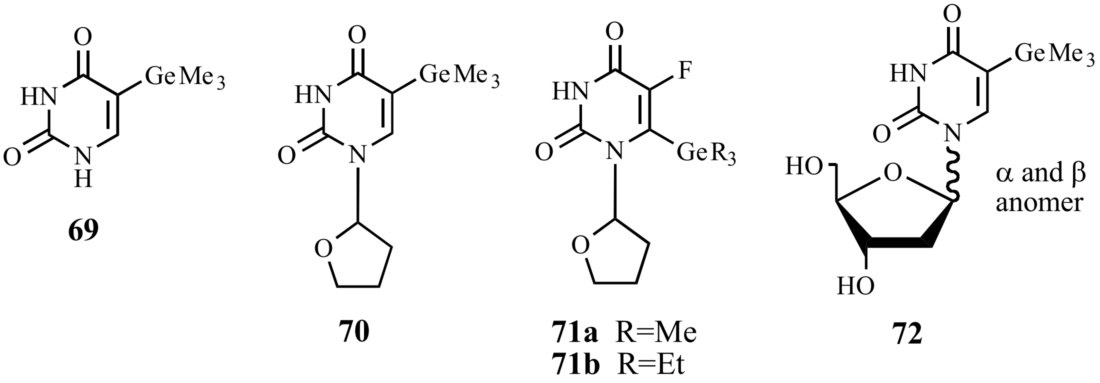


68

Figure 14. Organogermanes with interesting biological activity.

1.4.2. Nucleoside derived compounds

Several heterocyclic derivatives that contain germanium moieties have exhibited interesting biological properties. For example, organogermanium sesquioxanes containing uracil or 5-fluorouracil (5-FUra, see section 1.1.1.1) moieties showed antitumor activity against invasive microcapillary carcinoma (IMC) in mice.[161] Similarly, some germanyl indolyl and furyl amino acid derivatives presented antitumor activity analogous to the potent 5-fluorouracil in sarcoma S-180.[162]



69 **70** **71a** R=Me **71b** R=Et **72**

Figure 15. Nucleoside analogues containing germanium.

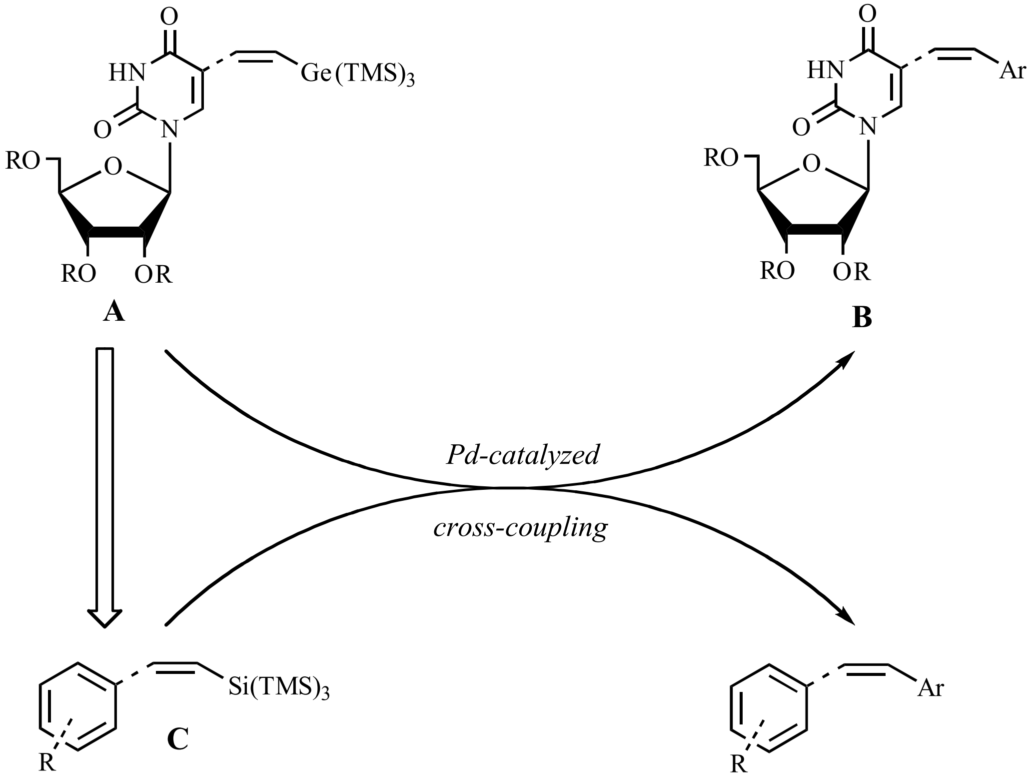
Other modified uracil analogues have also displayed promising pharmaceutical profiles. For example, 5-trimethylgermyluracil **69** and 1-(2-tetrahydrofuryl)-5-trimethylgermyluracil **70** exhibited cytotoxicity to melanoma B16 cells (EC_{50} 32 μg/mL) (Figure 15).[163] Likewise, 1-(2-tetrahydrofuryl)-5-fluoro-6-trimethyl(ethyl)germyluracils **71a-b** have caused inhibition of DNA and RNA biosynthesis in *Frhk* cells by 1.5-2 times more than the renowned antitumor drug Ftorafur.[164] The 5-trimethylgermyl derivatives of 2'-deoxyuridine **72** also showed interesting properties. The *β*-anomer presented weak biological action, however, the corresponding *α*-anomer restrained the replication of herpes simplex virus HSV-1.[165] The *α*-anomer of **72** repressed the incorporation of 2'-deoxyuridine into DNA of hepatoma 22A cells and of thymidine into DNA of cancer ovarian cells as well.

2. RESEARCH OBJECTIVES

The objective of this dissertation was to develop novel Group 14 (Si, Ge) organometallic substrates for the Pd-catalyzed cross-coupling reaction and evaluate their possible application for the synthesis of 5-modified pyrimidine nucleoside analogues. The rational selection of such targets was based on an extensive review of the methods available in the current literature and the analysis of their advantages, limitations, and possible improvements.

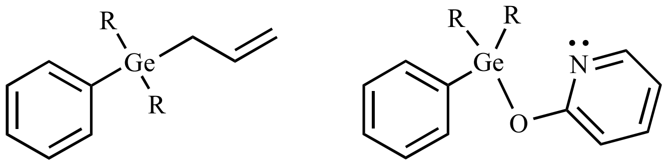
The first targets were novel 5-[(tris(trimethylsilyl)germyl)ethenyl]uridine analogues **A** bearing acyl protections at sugar hydroxyls (Scheme 21). The vinylgermane uridine analogues **A** were designed, in order to explore their application to the synthesis of the highly conjugated pyrimidine nucleosides modified at C5 (**B**) via Pd-catalyzed cross-coupling reactions. The synthesis of *E*- and *Z*-isomers of **A** was envisioned via the stereoselective hydrogermylation of the readily available 5-acetylenic uridine analogues with $(TMS)_3GeH$ in the presence of different radical promoters. The hydrogermylation with other organogermanium hydrides, such as Ph_3GeH or Me_3GeH, was expected to afford novel 5-vinylgermane uridine analogues with interesting biological properties (see section 1.4.2).

In order to optimize the synthesis of 5-modified nucleoside analogues of type **B** through a Pd-catalyzed cross-coupling approach, we initially planned to investigate the less expensive vinyl tris(trimethylsilyl)silane model substrates of type **C** as possible nucleophilic precursors for the cross-coupling with several organic halides (Figure 16). We were especially interested to monitor the progress of the coupling of vinyl tris(trimethylsilyl)silanes **C** using ^{29}Si NMR to acquire additional information about the structure of the possible reactive intermediates.



Scheme 21. Designed Pd-catalyzed cross-coupling of 5-[2-(tris(trimethylsilyl)germyl)-ethenyl]uridine analogues.

The next objective was to develop novel organogermanium substrates capable of transferring the aryl groups from the Ge atom via Pd-catalyzed cross-coupling. We designed allyl(phenyl)germanes **D** (Figure 16), as a bench friendly and stable precursor readily available from inexpensive starting materials, as a possible source of phenyl groups in the cross-coupling reaction with aryl halides in the presence of Pd catalysts. We envisioned that the activation/cleavage of the allyl groups with fluoride or bases would generate *in situ* reactive germanol/germanoxanes and/or their corresponding hypervalent intermediates, which may undergo efficient cross-coupling reactions.



D **E**

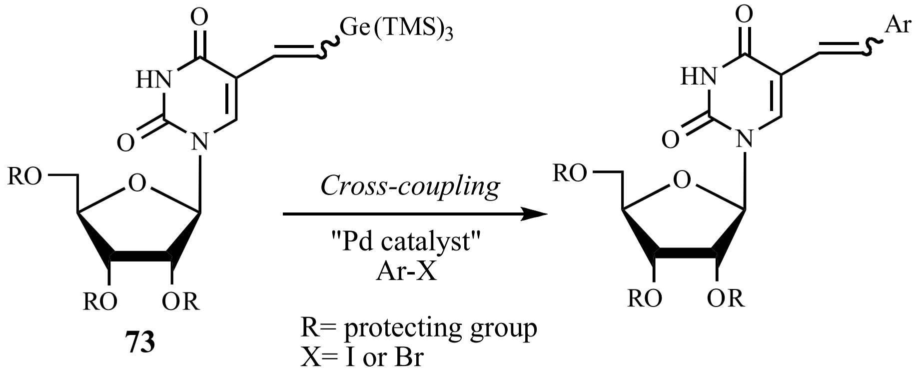
Figure 16. Possible novel Group 14 organometallic substrates for the Pd-catalyzed cross-coupling reaction.

We also designed 2-(dimethyl(aryl)germyloxy)pyridine **E** (Figure 16) as a possible transmetallating partner for the Pd-catalyzed cross-coupling. The rationale behind the design of germanoxanes **E** was the possibility to engage the lone electron pair at nitrogen in the pyridine moiety into an intramolecular coordination that would render the Ge atom hypervalent. Moreover, coordination of the pyridyl group to the Pd-halide complex was envisioned to bring the germanium center into the proximity of the Pd catalyst and promote an efficient intramolecular transmetallation.

The design, synthesis and study of the Pd-catalyzed cross-coupling of organometals **D** and **E** under different reaction conditions (temperature, solvent, catalyst, additives) was expected to provide valuable information about the reactivity of organogermanium species, constructing a platform for valuable comparison with the more established organostannanes and organosilanes.

3. RESULTS AND DISCUSSION

The major interest of the current work was to develop novel Pd-catalyzed cross-coupling methodologies utilizing Group 14 metal (Si, Ge) organometallic precursors and to study their possible application for the synthesis of 5-modified pyrimidine nucleoside analogues. For this reason we started our search encouraged by the results reported by Wang and Wnuk[97,98] on the Pd-catalyzed cross-coupling of vinyl and α-fluorovinyl tris(trimethylsilyl)germanes **20** and **21** with several aryl and alkenyl halides (Figure 10). Consequently, our initial efforts were focused on the efficient synthesis of 5-[2-(tris(trimethylsilyl)germyl)ethenyl]uridine analogues **73** as potential organometallic precursors for the coupling with different aryl halides (Scheme 22).



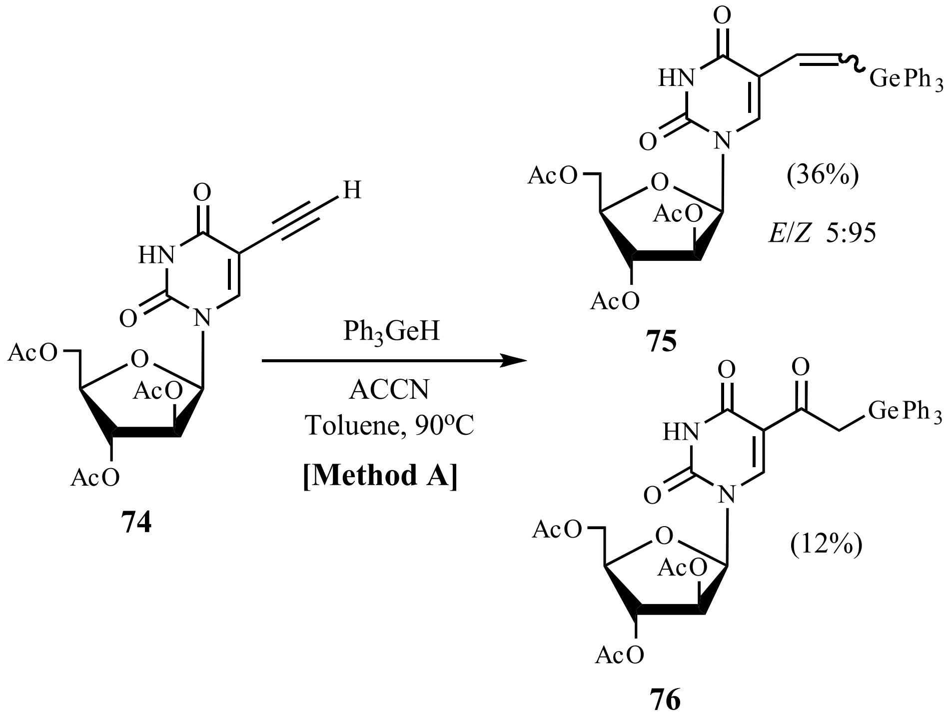
Scheme 22. A possible application of tris(trimethylsilyl)germanes towards the synthesis of 5-modified uridine analogues.

3.1. Synthesis of protected 5-[2-(germyl)ethenyl)]uridine analogues

The increasing interest in vinylmetals as efficient substrates for the Pd-catalyzed cross-coupling reactions have promoted the development of several efficient protocols for the hydrometalation of simple alkyl and aryl acetylenic substrates.[166-169] However, their application to nucleic acid derivatives is often jeopardized by the poor stability of the latter under the commonly employed reaction conditions.

In order to obtain the desired vinyl germanes of type **73** in good yields and with good regio- and stereoselectivity, we screened the available methods using the moderately reactive and inexpensive Ph_3GeH (\$24/g) instead of $(TMS)_3GeH$ (\$90/g). Thus, treatment of 5-ethynyl uridine analogue **74** with Ph_3GeH in the presence of 1,1'-azobis(cyclohexanecarbonitrile) (ACCN) in degassed toluene at 90 ^{o}C (Method A)[166] produced a mixture of *Z*- and *E*-isomers of vinyl germane **75** in 36% yield (*E*/*Z* 5:95, Scheme 23). Nuclear Magnetic Resonance (NMR) spectra were diagnostic in establishing the configuration of *E*-**75** (J=18.8 Hz) and *Z*-**75** (J=13.5 Hz). The formation of the *Z* major isomer is in agreement with expected[166] radical anti-addition to alkynes. Careful column chromatography led also to the separation of a third compound for which we tentatively assigned the structure of **76** (12%), based on a downfield signal (δ -194.03 ppm) typical for ketones in the corresponding ^{13}C NMR analysis.

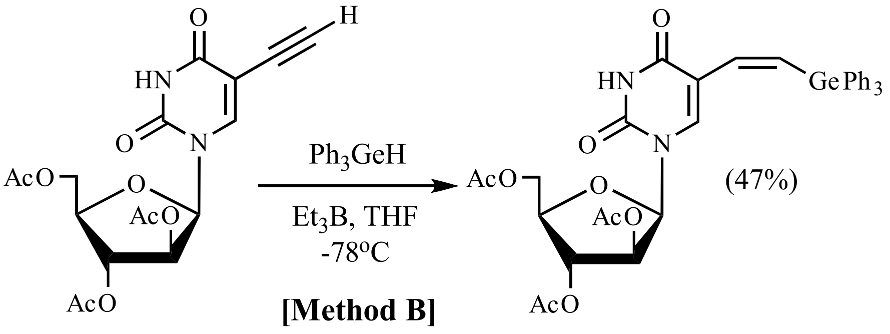
Lewis-acid catalyzed hydrogermylation employing $B(C_6F_5)_3$[168] in CH_2Cl_2 at room temperature proved to be unsuccessful to give the desired product **75** after 24 hours of stirring. Heating, increasing the concentration of $B(C_6F_5)_3$ and prolonged time (48 h, reflux) had minimal effect on the formation of more product. The presence of large quantities of non-consumed starting material as a major spot even after prolonged treatment made this method unlikely to be employed for the synthesis of our target molecules. The $Pd(PPh_3)_4$-catalyzed hydrogermylation[167] of **74** with Ph_3GeH afforded an isomeric mixture of vinylic product **75** (*E*/*Z* 70:30) with the expected preference for the *E*-isomer (based on mechanistic considerations). Also, compound **76** was detected in the reaction mixture.



Scheme 23. Thermal radical hydrogermylation of acetyl-protected 5-ethynylarabinouridine with Ph_3GeH.

3.1.1. Et_3B-induced hydrogermylation of 5-ethynyluridine analogues

Since our previous attempts to obtain 5-(triphenylgermyl)ethenyl uridine analogue **75** resulted in complex mixtures of products, we started the search for a milder and selective hydrogermylation protocol. Thus, the Et_3B promoted radical addition[169] of Ph_3GeH to the terminal acetylenic substrate **74** in THF at -78 °C (Method B) exclusively gave protected (*Z*)-5-(triphenylgermyl)ethenyl uridine **75** in 47% yield (Scheme 24). The *Z*-stereoselectivity of the product under the applied non-equilibrating conditions (-78 °C) was in perfect agreement with the reported results for simpler substrates.[169] Noteworthy, analogous treatment at 0 °C gave **75** along with **76** in a 59:41 ratio (based on ^1H NMR of the purified mixture).

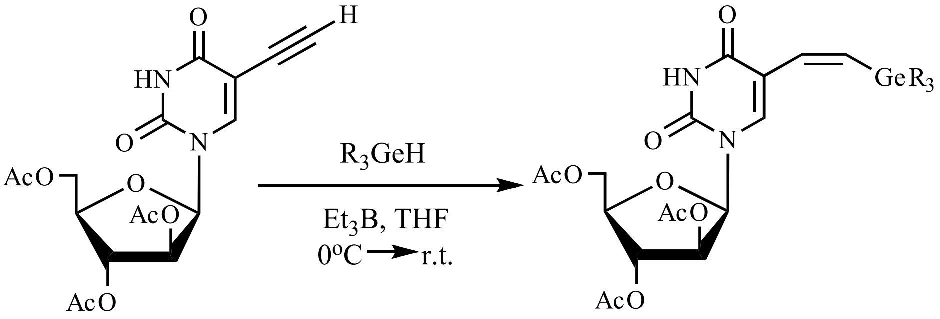


74

75

Scheme 24. Et$_3$B-promoted radical hydrogermylation of 5-alkynylarabinouridine analogues with Ph$_3$GeH.

Because of the interesting biological properties exhibited by some compounds containing germanium (see section 1.4), we also examined the hydrogermylation of **74** with alkyl germanium hydrides. Thus, treatment of **74** with the commercially available trialkyl-substituted germanium hydrides Me_3GeH and Bu_3GeH in the presence of Et_3B failed to form the desired products after 3 hours at -78 ^{o}C. However, increasing the temperature to 0 ^{o}C with progressive warming to room temperature resulted in the formation of the corresponding 5-germanovinylic nucleosides **77** and **78** but in lower yields and with lower stereoselectivity (Scheme 25). The requirement for higher temperatures may be accounted for the lower reactivity of the alkyl-substituted germyl radicals compared to their aryl-substituted counterparts.[169] Since only small amounts (approx. 10-15%) of **74** were recovered, it seems that the reaction temperature may have an impact on the stability of the protected 5-ethynyl nucleoside **74** and/or products **77** and **78** during the radical forming processes.



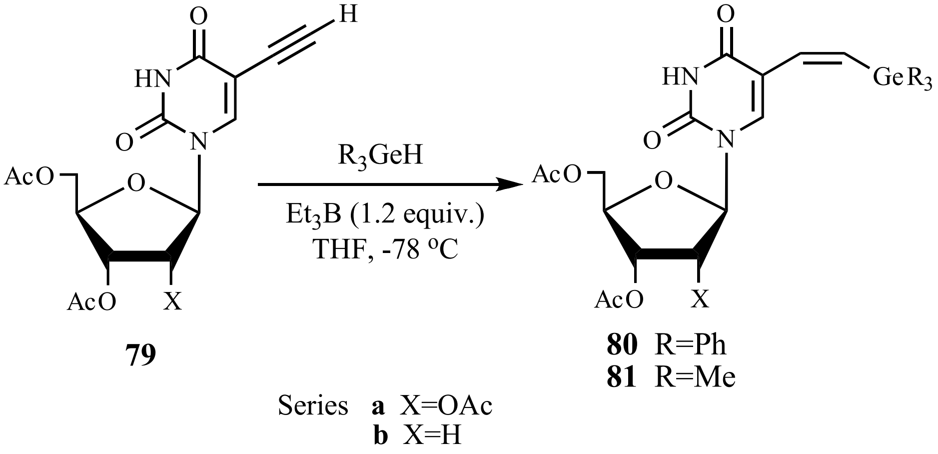
74

77 R=Me (33%, *E*/*Z* 31:69)
78 R= *n*-Bu (14%, *E*/*Z* 6:94)

Scheme 25. Et_3B-promoted radical hydrogermylation of 5-ethynylarabinouridine analogues with Me_3GeH and *n*-Bu_3GeH.

Next, we explored the applicability of the Et_3B promoted hydrogermylation to other pyrimidine nucleoside scaffolds, such as of 2',3',5'-*O*-triacetyl-5-ethynyluridine **79a** and 1-(3,5-*O*-diacetyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-5-ethynyluracil **79b** (Table 2). Thus, treatment of **79a** with Ph_3GeH and Et_3B in anhydrous THF at -78 °C gave ***Z*-80a** selectively as a *trans*-addition product in 50% yield (Table 2, entry 1). Analogous treatment of **79a** with Me_3GeH afforded the corresponding vinylic product **81a** as a mixture of geometric isomers (*E*/*Z* 12:88) but in lower yield (entry 2). Later on, we turned our attention to the preparation of the corresponding 2'-deoxyuridine analogues due to their similarity to the potent antiviral drug BVDU (see section 1.1.1.2). Thus, Et_3B-promoted hydrogermylation of the 3',5'-*O*-diacetyl-2'-deoxy-5-ethynyluridine **79b** with Ph_3GeH (Method B) afforded exclusively ***Z*-80b** in 62% yield (entry 3). In a similar fashion, the treatment of **79b** with Me_3GeH or Et_3B in THF with progressive warming from 0 °C to ambient temperature produced product ***E*/*Z*-81b** with a moderate preference for the kinetic *Z*-isomer (*E*/*Z*, ~23:77) in 46% yield (entry 4).

Table 2. Et_3B-promoted radical hydrogermylation of acetyl-protected 2'-deoxy and 5-ethynyluridine with Ph_3GeH or Me_3GeH.



Entry	Substrate	Product	Conversion (%)[a]	Yield (%)[b]	*E*/*Z* ratio[c]
1	**79a**	**80a**	90	50	0:100
2	**79a**	**81a**	90	13 [d]	12:88
3	**79b**	**80b**	95	62	0:100
4	**79b**	**81b**	90	46 [d]	23:77

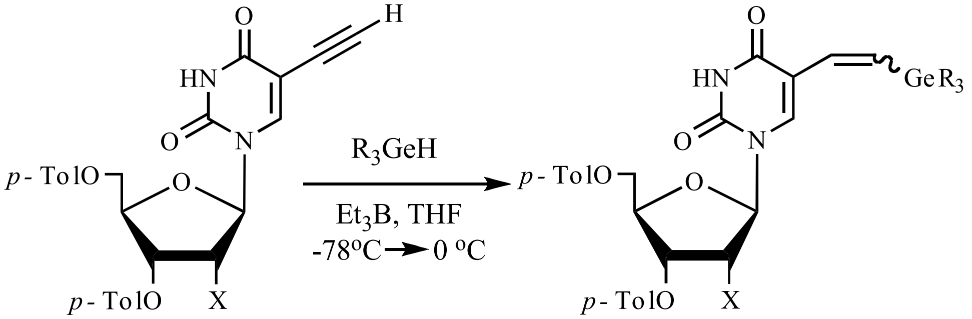
[a] Based on recover starting material. [b] Isolated yield. [c] Determined using coupling constants for *E*- and *Z*-isomer on ^1H NMR. [d] From 0 °C to r.t.

Effect of protecting group: *O*-acetyl vs *O*-toluoyl:

Even though the hydrogermylation of *O*-acetyl protected uridine analogues **74**, **79a**, and **79b** gave the corresponding vinyl germanes in moderate yields; we were interested in exploring the effect of other protecting groups on the outcome of the reaction. Hence, the triethylborane (Et_3B) promoted hydrogermylation of 5-ethynyl-1-(2,3,5-tri-*O*-*p*-toluoyl-*β*-D-ribofuranosyl)uracil **82a** with Ph_3GeH at -78 °C (Method B) showed slow conversion to the desired product. However, progressive warming of the reaction mixture to 0 °C afforded *para*-toluoyl protected ***Z*-83a** in 40% yield (Table 3, entry 1) together with product **85** (13%) (see Figure 17). Similar treatment of **82a** with Me_3GeH gave ***E*/*Z*-84a** (*E*/*Z*~ 45:55) in 37% yield (entry 2). Analogous treatment of the corresponding 2'-deoxy derivative **82b** with Ph_3GeH and Me_3GeH gave products **83b** and

84b in 61% and 30%, respectively (entries 3 and 4). Interestingly, the synthesis of **83b** also required a significant increase of the reaction temperature (from -78 °C to 0 °C) and resulted in the concomitant formation of byproduct **86** (12%) (see Figure 17).

Table 3. Et_3B-promoted radical hydrogermylation of *p*-toluoyl-protected 2'-deoxy and 5-ethynyluridine with Ph_3GeH or Me_3GeH.



82

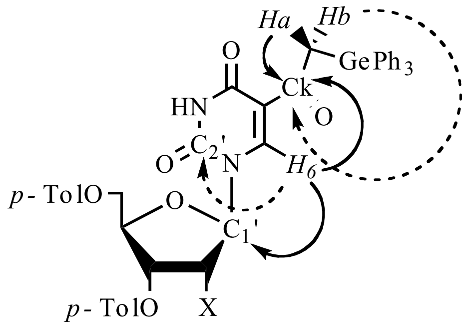
83 R=Ph
84 R=Me

Series **a** X=OTol-*p*
b X=H

Entry	Substrate	Product	Conversion (%)[a]	Yield (%)[b]	*E*/*Z* ratio[c]
1	**82a**	**83a**	90	40	0:100
2	**82a**	**84a**	90	37[d]	45:55
3	**82b**	**83b**	95	61	0:100
4	**82b**	**84b**	85	30[d]	41:59

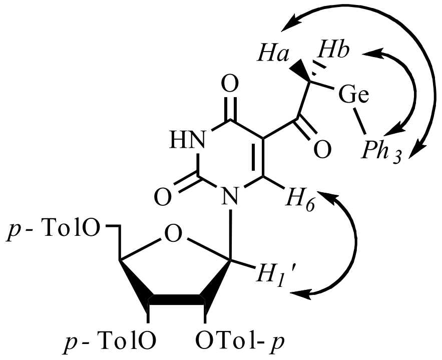
[a] Based on recover starting material. [b] Isolated yield. [c] Determined using coupling constants for *E*- and *Z*-isomer on ^1H NMR. [d] From 0 °C to r.t.

Our results suggested that changing from the base-labile acetyl-protecting group to a more robust *p*-toluoyl group did not result in an appreciable enhancement in the yields or the stereoselectivity. However, the higher reaction temperatures necessary to promote the hydrogermylation of the *para*-toluoyl-protected substrates **82a-b** resulted in the formation of 5-(2-triphenylgermyl)acyl byproducts **85** and **86**, respectively (Figure 17). The tentative structure for the unexpected byproducts **85** and **86** was assigned based on ^1H and ^{13}C NMR analyses. The ^1H NMR spectrum of **85** showed two doublets (J=9.0 Hz) part of an isolated spin-coupling system at δ 3.76 and 3.87 ppm, while the corresponding ^{13}C spectrum displayed a new peak at δ 193.3 ppm characteristic of ketones. The HMBC correlations (Figure 17) and NOE interactions (Figure 18) supported the proposed structures. In addition, ultraviolet spectroscopic analysis of compound **85** revealed a maximum absorption (λ_{max}) at 282 nm, in agreement with the reported values for similar 5-acylated uridine derivatives.[170] Moreover, it was evident that the steric hindrance and/or electronic effects conferred by the phenyl/alkyl germanium hydrides reagents played a decisive role in the yields and stereochemical outcome of the radical additions across the acetylenic moiety (Ph_3GeH vs Me_3GeH).



85 X=OTol-*p*
86 X=H

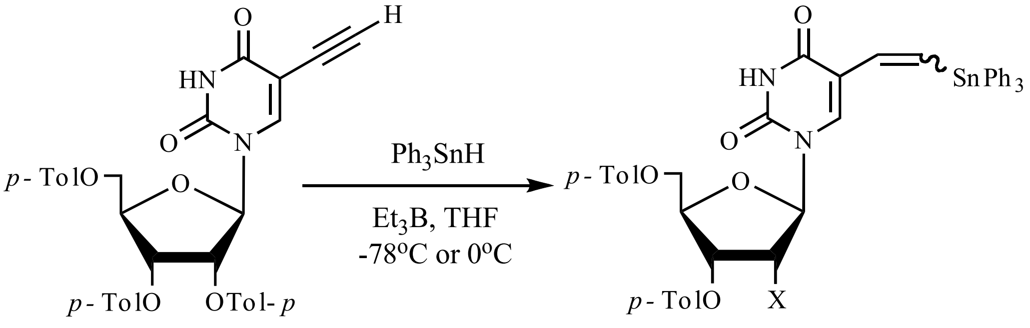
Figure 17. Structure of *p*-toluyl-protected 5-[(2-triphenylgermyl)acetyl]uridine analogues.



85

Figure 18. Important NOE interactions observed for 5-[2-(triphenyl-germyl)acetyl]-2',3',5'-tri-*O*-*p*-toluyluridine.

To correlate the reactivity of the used organometallic hydride (e.g., Ph_3GeH) and the outcome of the hydrometallation reaction, hydrostannylation and hydrosilylation of **82a** with Ph_3SnH and Ph_3SiH in the presence of Et_3B was performed at -78 °C and 0 °C. Interestingly, fast formation of the vinyl stannane ***Z*-87** was achieved at low temperature, while a mixture of geometric isomers was obtained at 0 °C (*E*/*Z*, ~51:49) (Scheme 26). In a sharp contrast, the Et_3B promoted hydrosilylation of **82a** with Ph_3SiH did not proceed at either -78 °C or 0 °C. It seems likely that the generation of the 5-acylated byproducts (e.g. **76**, **85** and **86)** is selective for the use of moderately reactive Ph_3GeH, since no byproduct of this type was detected when more reactive tin analogues, such as Ph_3SnH, were employed.



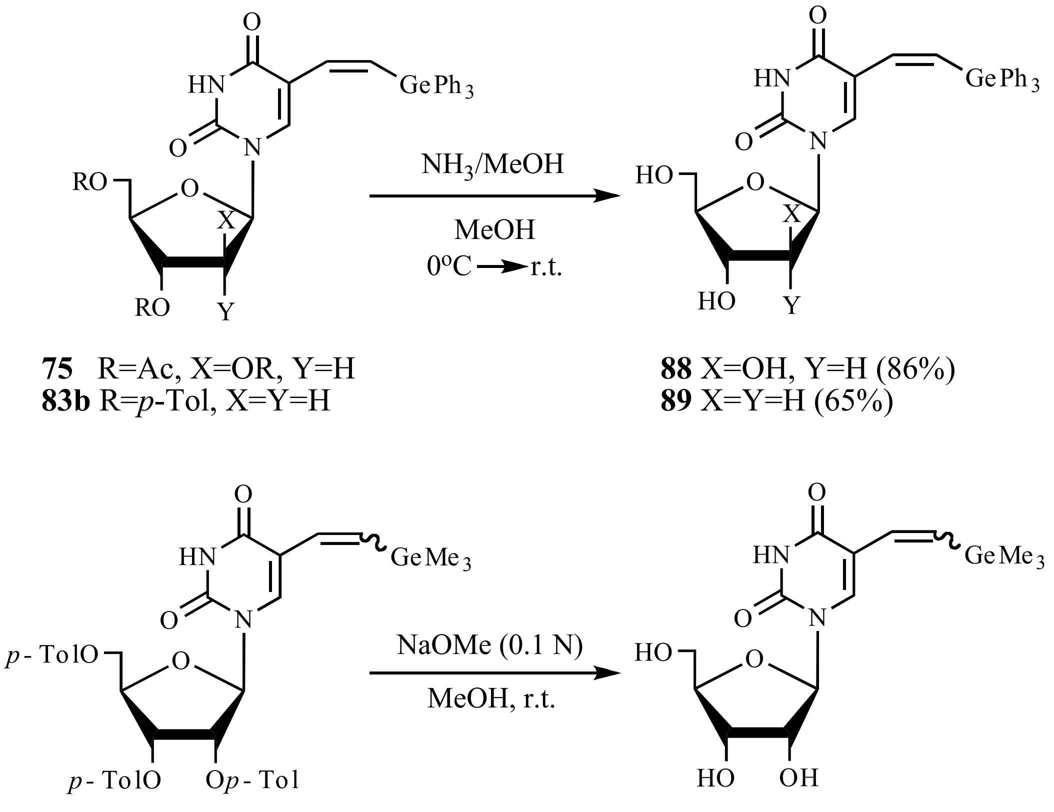
82a

***E*/*Z*-87**

E/*Z* 0:100 at -78°C
E/*Z* 51:49 at 0°C

Scheme 26. Et_3B-promoted radical hydrostannylation of *p*-toluyl-protected 5-ethynyluridine analogues.

The removal of the acetyl and *para*-toluoyl protecting groups was successfully achieved under the typically used basic conditions. Thus, treatment of **75** with a saturated solution of NH_3 in MeOH afforded the deprotected arabino uracil nucleoside **88** in 86% yield (Scheme 27). Analogous treatment of *p*-toluoyl-protected 2'-deoxyuridine analogue **83b** gave deprotected **89** in moderate yield (65%), although, the reaction required longer time to be completed. Treatment of the trimethylgermyl derivative *E*/*Z*-**84a** (*E*/*Z* 45:55) with 0.1N NaOMe in MeOH afforded *E*/*Z*-**90** (*E*/*Z* 42:58) in 71% yield. As described in previous reports,[171] the C(sp^2)-Ge(alkyl)$_3$ and C(sp^2)-Ge(aryl)$_3$ bond seems to be stable under the basic conditions required for the removal of both acetyl and *para*-toluoyl protecting groups. Moreover, the stereochemistry of the protected derivatives remained intact even after prolonged treatment with strongly nucleophilic sodium methoxide.



75 R=Ac, X=OR, Y=H
83b R=*p*-Tol, X=Y=H

88 X=OH, Y=H (86%)
89 X=Y=H (65%)

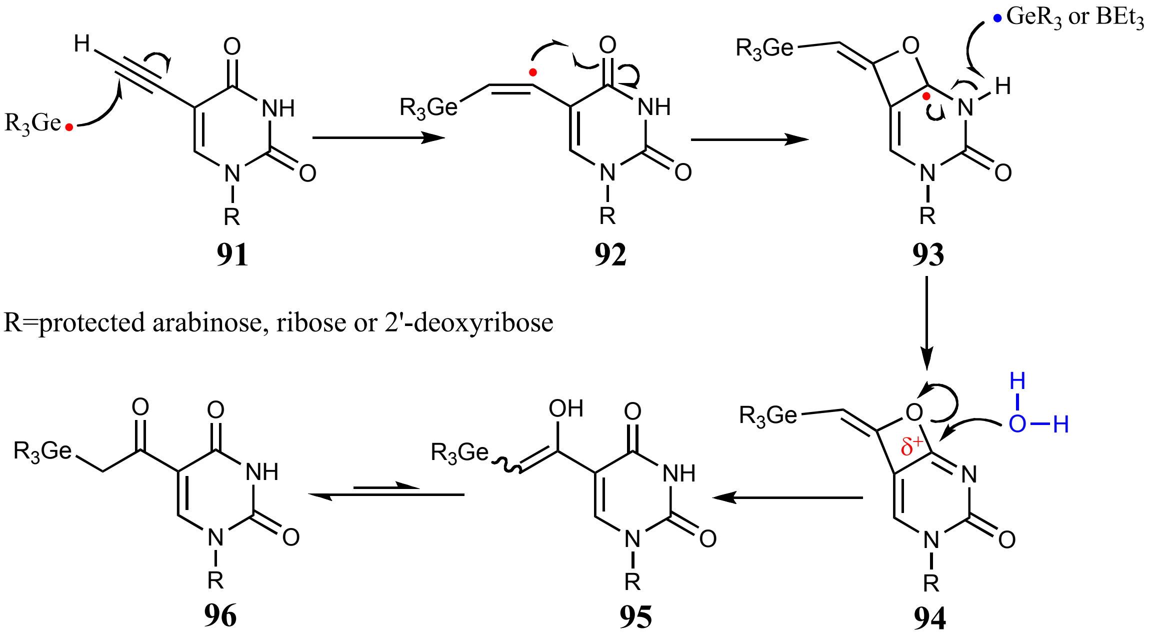
E/*Z*-**84a** (45:55)

E/*Z*-**90** (71%, 42:58)

Scheme 27. Deprotection of acetyl and *p*-toluyl-protected 5-[2-(germyl)ethenyl] uridine analogues.

3.1.2. Investigation on the possible origin of 5-[2-(triphenylgermyl)acetyl]uridine analogues

As described above, the Et_3B promoted hydrogermylation of **74** in the presence of Ph_3GeH at 0 °C produced the desired germanovinylic nucleoside **75** together with the hydrated byproduct **76**. Also, the higher temperature (0 °C vs -78 °C) required for the efficient hydrogermylation of substrates **82a-b** resulted in the formation of small amounts of the unexpected **85** and **86** (Figure 17). Intrigued by this interesting effect of the reaction temperature and the lack of reports on the formation of similar 5-keto products during the hydrogermylation of simpler acetylenes,[169] we have undertaken efforts to examine the origin of **76**, **85** and **86** (Scheme 28).



R=protected arabinose, ribose or 2'-deoxyribose

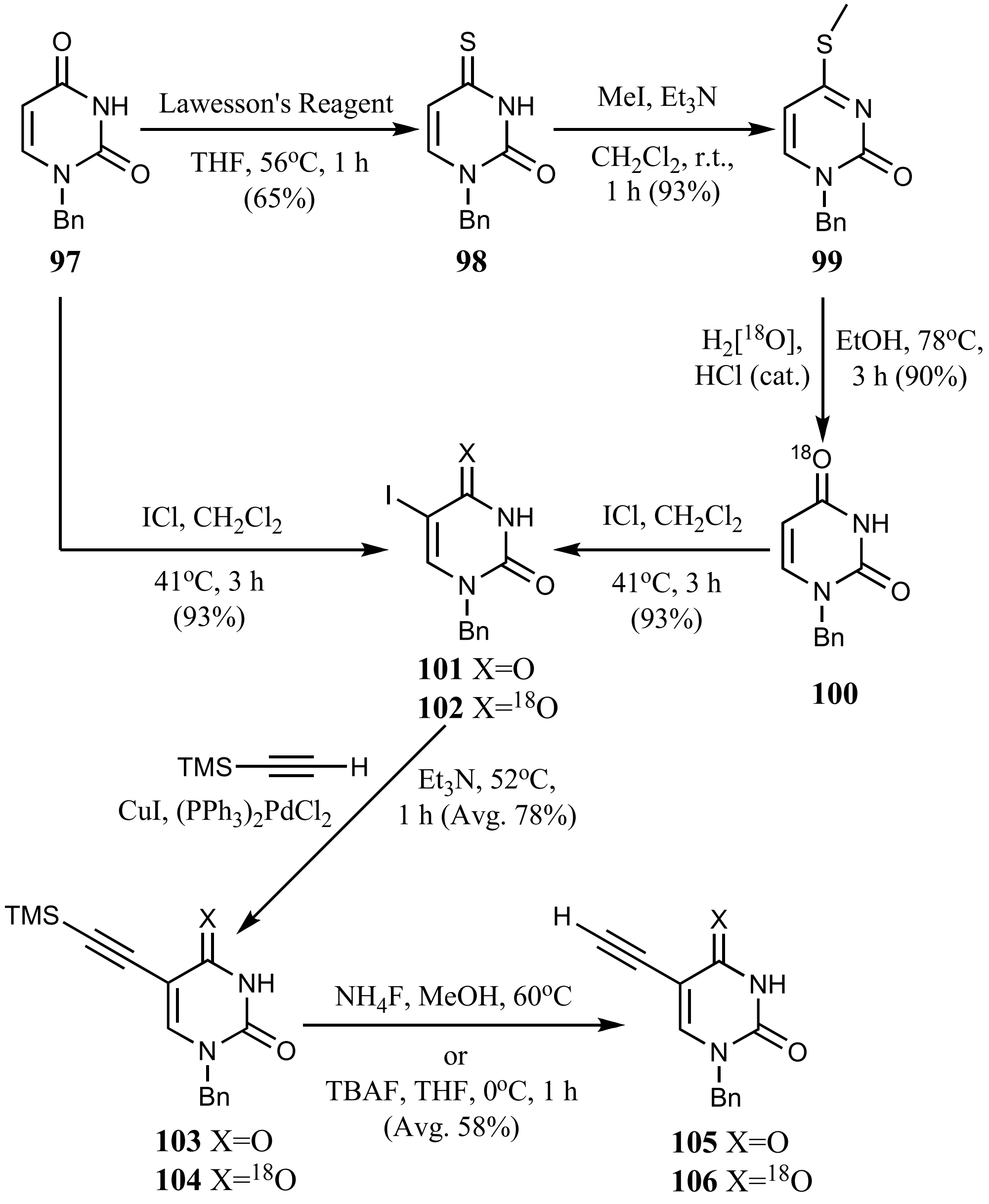
Scheme 28. A working hypothesis for the formation of 5-[2-(triphenylgermyl)acetyl]-uridine derivatives.

In our working hypothesis, an initial attack from the relatively stable triphenylgermyl radical at the acetylenic moiety of **91** would generate a vinylic radical at the carbon α to the uracil base (**92**). Subsequent intramolecular interaction of the newly formed radical with the carbonyl oxygen attached to carbon C4 of the base would result in the formation of an unstable oxy radical intermediate **93**. The rigid planar configuration of the uracil ring facilitates the formation of the bicyclic structure **93**. Rapid re-aromatization caused by the abstraction of the hydrogen at N-3 should lead to a "metastable" intermediate **94** with increased electrophilicity at carbon C4. Consequently, the attack from a water molecule to C4 would lead to a considerable release of strain energy forming the germyl-enol intermediate **95**. A final keto-enolic tautomerization would generate the more stable conjugated α-germylketone **96**. The experiments with

^{18}O-labeled uracil precursor at C4 (**91**) were designed to investigate the formation of the byproduct of type **96** by analysis of the fragments from its mass spectrometry analyses.

3.1.2.1. Synthesis of model compound 1-*N*-benzyl-5-ethynyluracil and its 4-[^{18}O]-labeled analogue

In an attempt to support our proposed pathway for the formation of the keto byproducts **76**, **85**, and **86** (Scheme 28) a model compound 1-*N*-benzyl-5-ethynyluracil **105** and its 4-[^{18}O]-labeled analogue **106** were synthesized. Our strategy was comprised of the synthesis of 1-*N*-benzyluracil **97** by alkylation of freshly prepared 2,4-bis(trimethylsilyloxy)pyrimidine[172] with benzylbromide (Scheme 29).[173] Treatment of **97** with Lawesson's reagent in THF at 56 °C for 1 h gave the corresponding 1-*N*-benzyl-4-thiouracil **98** in 65% yield. *S*-methylation[174] of the purified **98** by treatment with MeI in the presence Et_3N in CH_2Cl_2 led to thioether **99** (93%). The acid-catalyzed hydrolysis[175] of **99** with commercially available $H_2[^{18}O]$ in anhydrous ethanol produced the desired ^{18}O-labeled 1-*N*-benzyluracil analogue **100** in 90% yield. Iodination of **97**, as well as **100**, with a solution of iodine monochloride[176] (1 M in CH_2Cl_2) in dry CH_2Cl_2 afforded 5-iodouracils **101** and **102** in excellent yields (93% avg.). Sonogashira couplings of the 5-iodouracils with (trimethyl)silylethyne in Et_3N resulted in the formation of **103** (80%) and **104** (62%) respectively.

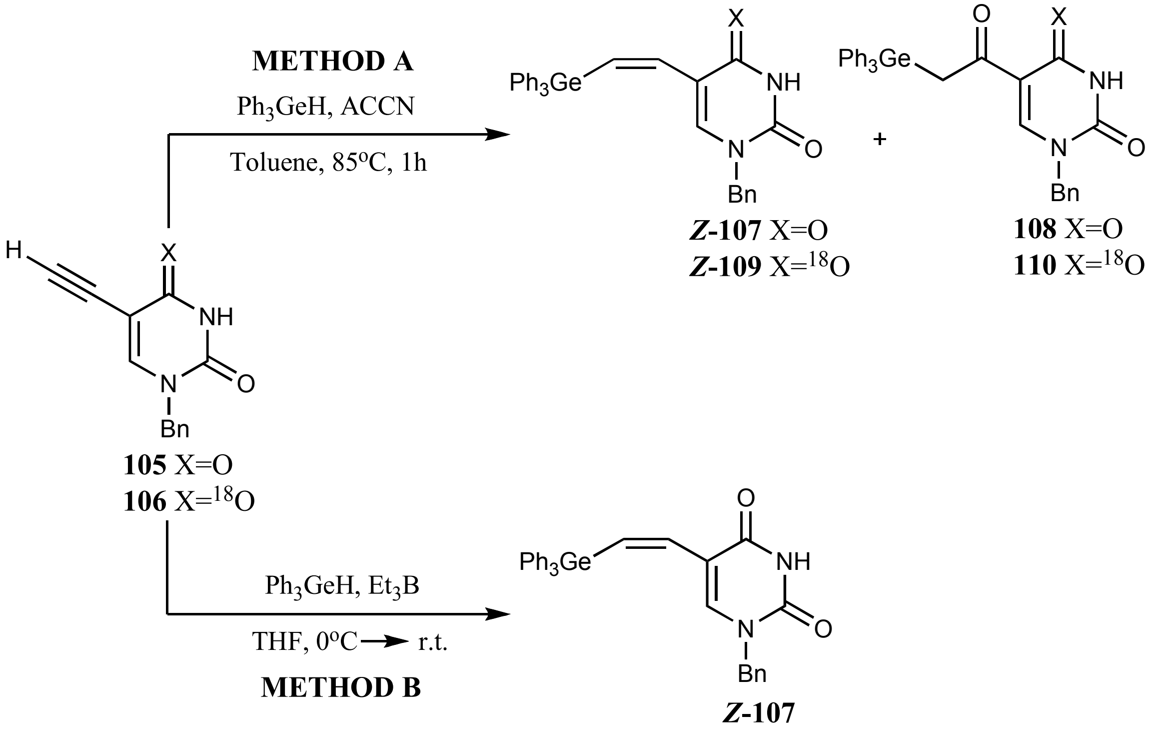


Scheme 29. Synthesis of 1-*N*-benzyl-5-ethynyluracil and its 4-[^{18}O]-labeled analogue.

The fluoride-promoted desilylation with tetrabutylammonium fluoride (TBAF) conveniently furnished products **105** and **106** with moderate to good yields (60% and 58%, respectively). Although the traditional desilylation using TBAF also gave the product **105** (60%) effectively, the treatment with the partially soluble NH_4F/MeOH[177] system offered similar results (57%) and substantially eased the purification from TBAF-derived residues.

3.1.2.2. Hydrogermylation of 1-*N*-benzyl-5-ethynyluracil and its 4-[^{18}O]-labeled analogue

Having synthesized the 5-acetylenic precursors **105** and **106**, the next step was to investigate their hydrogermylation in attempts to obtain 1-*N*-benzyl-5-[2-(triphenylgermyl)acetyl]uracil **108** and its ^{18}O-labeled analogue **110** (Scheme 30). Initial treatment of compound **105** by Method B (Ph_3GeH, Et_3B) at 0 °C resulted only in the isolation of the *trans*-addition product *Z*-**107**.



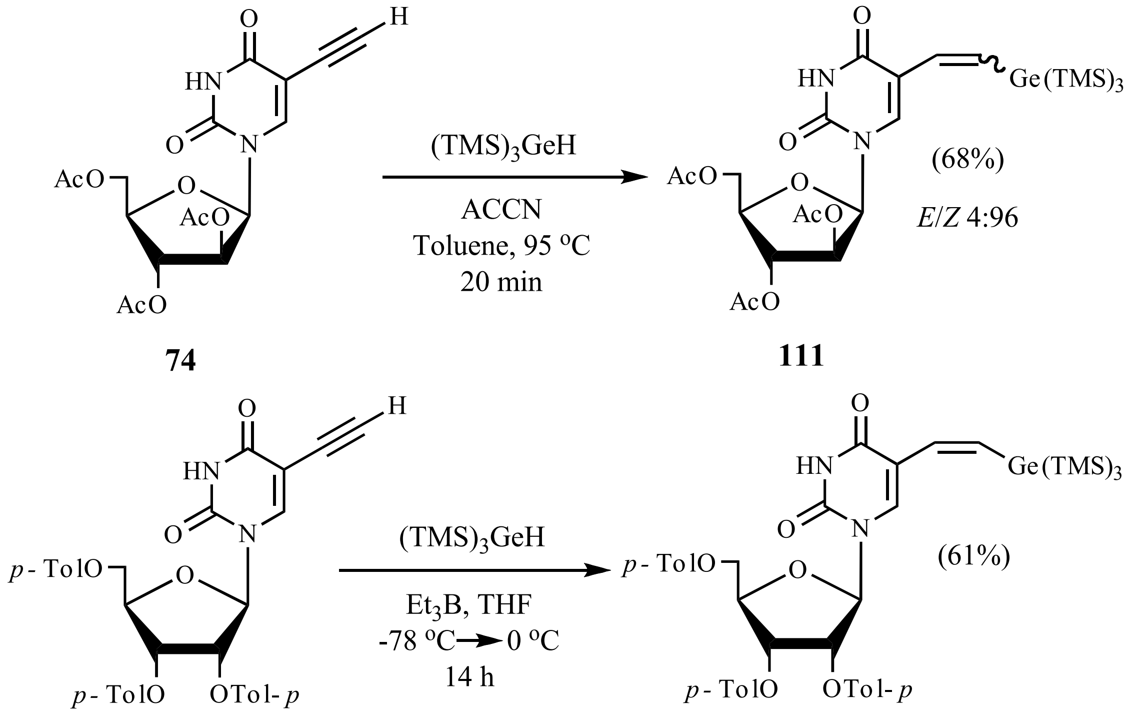
Scheme 30. Hydrogermylation of 1-*N*-benzyl-5-ethynyluracil and its 4-$^{1[8}$O]-labeled analogue.

In contrast, upon thermal radical-generation with ACCN (Method A) a mixture of *Z*-**107** and byproduct **108** was obtained. Careful column chromatography of the mixture yielded a small fraction of **108** with high purity. A similar treatment of the ^{18}O-labeled acetylenic precursor **106** conveniently afforded a small amount of pure **110** after cautious purification from a mixture with *Z*-**109**.

In order to support the pathway proposed for the formation of compounds **76**, **85**, and **86** (see Scheme 28), the isolated uracil compounds **108** and **110** were analyzed by mass spectrometry employing various ionization techniques. Thus, ESI$^+$ analysis of compound **108** showed a peak at *m*/*z* 605 corresponding to the molecular ion $[M+58]^+$. A similar experiment performed on **110** exhibited a signal for *m*/*z* 607 also assigned to $[M+58]^+$. These results indicated the difference of two mass units expected for the analogue containing a heavier isotope of oxygen [^{18}O] in the C5 side chain (see Scheme 28). However, experiments employing electron-impact ionization exhibited the same molecular ion (*m*/*z* 547 for M^+) for both **108** and **110**. Although the fragmentation patterns differed, MS analyses did not lead to any conclusive assignment.

3.1.3. Synthesis of protected 5-[2-(tris(trimethylsilyl)germyl)ethenyl] uridine analogues

Once the conditions for the hydrogermylation of 5-ethynyluridine analogues with several organogermanium hydrides (Ph_3GeH and Me_3GeH) were optimized, hydrogermylation with the more reactive $(Me_3Si)_3GeH$ was also explored in order to develop a convenient synthesis of vinylgermanes **111**/**112**; possible substrates for the Pd-catalyzed cross-coupling reactions. Therefore, treatment of the protected 5-ethynylarabinouridine analogue **74** with $(Me_3Si)_3GeH$ and ACCN in degassed toluene at 95 °C (Method A) efficiently produced the hydrogermylated product **111** (*E*/*Z* 4:96) in 68% yield after 20 minutes (Scheme 31). The increased reactivity of the corresponding hydride and a shorter reaction time may be attributed for the better yield and a higher stereoselectivity of the product with respect to the hydrogermylation with Ph_3GeH under similar conditions (see Scheme 24).



74 **111**

82a **112**

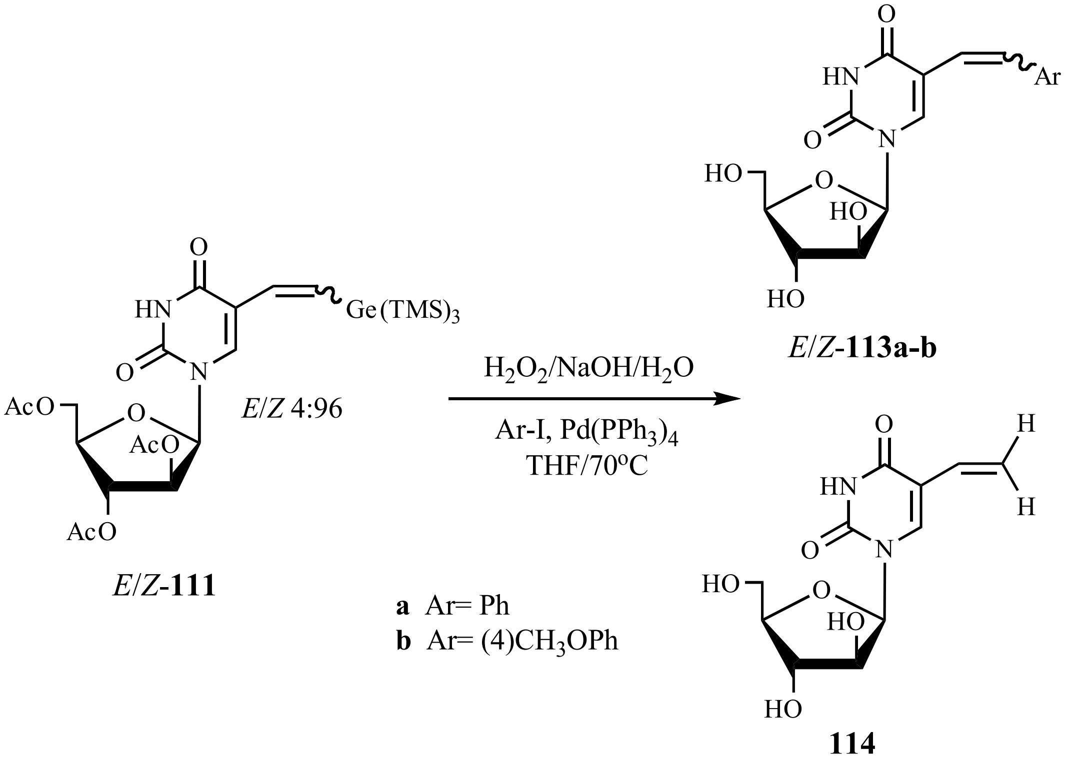
Scheme 31. Synthesis of 5-[2-(tris(trimethylsilyl)germyl)ethenyl]uridine analogues.

Interestingly, treatment of 2',3',5'-tri-*O*-*p*-toluoyl protected **82a** with $(Me_3Si)_3GeH$ in the presence of Et_3B in THF at -78 °C (Method B) for 14 hours also afforded TTMS-germyl vinyl product *Z*-**112** in 61% as a single isomer (^{1}H NMR). Although the vinylgermane product *E*/*Z*-**111** was obtained in much shorter time and slightly higher yield employing thermal conditions (Method A), formation of **112** by Et_3B-induced hydrogermylation (Method B, -78 °C to r.t.) offered a comparable yield and higher stereoselectivity.

3.1.4. Pd-catalyzed cross-coupling of 5-[2-(tris(trimethylsilyl)germyl)ethenyl] uridine analogues

The efficient Pd-catalyzed cross-coupling of vinyl tris(trimethylsilyl)germanes **20** and their (α-fluoro)vinyl analogues **21** (see Figure 10, section 1.2.1) proved to be an excellent methodology for the synthesis of substituted alkenes, fluoroalkenes, dienes, and fluorodienes.[97,98] Therefore, we explored the application of this methodology to the synthesis of 5-alkenyluridine analogues. Thus, the Pd-catalyzed coupling [$Pd(PPh_3)_4$] of protected 5-[2-(tris(trimethylsilyl)germyl)ethenyl] uridine analogue *E*/*Z*-**111** (*E*/*Z*, ~4:96) with iodobenzene under oxidative conditions (H_2O_2/NaOH/H_2O/TBAF) yielded the highly conjugated product *E*/*Z*-**113a** in low yields (~15%) as a mixture of geometric isomers (*E*/*Z*, ~89:11) (Scheme 32). Unfortunately, The observed inversion of the stereochemistry (*Z*→*E*) was previously described for the coupling of *Z*-vinyl tris(trimethylsilyl)germanes.[97] As expected, the alkaline conditions required for the coupling effected the removal of the acetyl protecting groups during the reaction. The degermylated 5-vinyl byproduct **114** was also detected in the crude reaction mixture. Moreover, analogous treatment of *E*/*Z*-**111** with 4-iodoanisole resulted in the formation of a complex mixture of *E*/*Z*-**113b** and **114** (**113b**/**114**, ~34:66) in an overall low yield.

It seems that the application of the oxidative conditions necessary for the efficient coupling of vinyl tris(trimethylsilyl)germanes (e.g. **20** and **21**, Figure 10), which also requires a base (NaOH) for the synthesis of more complex nucleoside analogues is hampered by the instability of the acetyl-groups in the ribose of **111**. An alternative approach would require the use of 5-[2-(tris(trimethylsilyl)germyl]uridine analogues bearing base-resistant protecting groups. In addition, the use of a different Pd catalyst/ligand might modulate the reactivity of the corresponding aryl halide leading to a more efficient transmetallation.



Scheme 32. Pd-catalyzed cross-coupling of 5-[2-(tris(trimethylsilyl)germyl)ethenyl]-uridine analogues.

3.2. Novel organosilanes and organogermanes as organometallic substrates for the Pd-catalyzed cross-coupling reaction

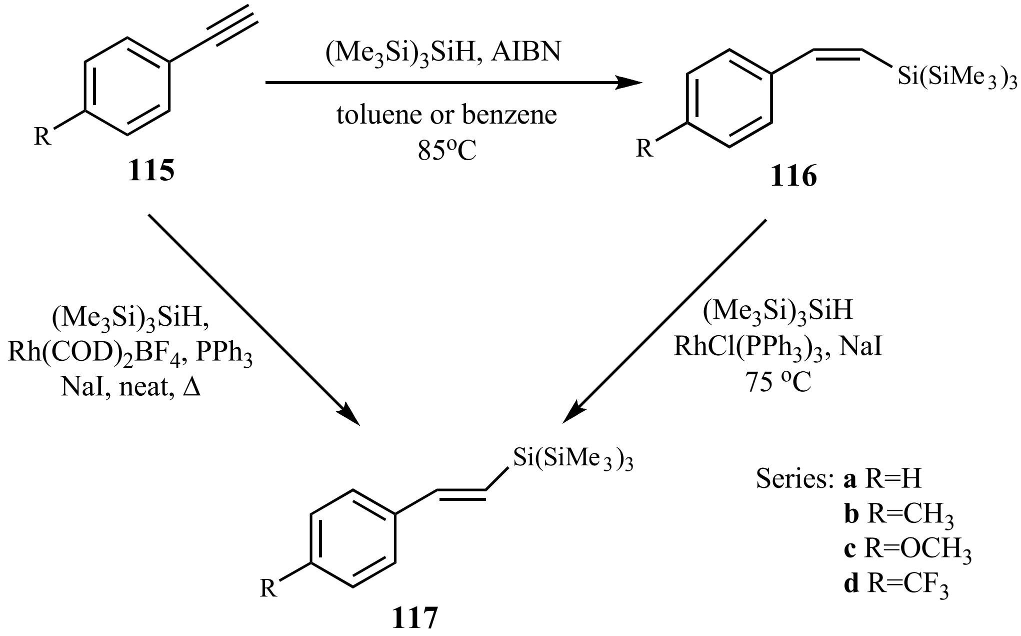
3.2.1 Vinyl tris(trimethylsilyl)silanes: substrates for Hiyama coupling

Encouraged by the reports on the Pd-catalyzed cross-coupling of vinyl tris(trimethylsilyl)germanes **20** and their corresponding (α-fluoro)vinyl analogues **21** (Figure 10), an analogous methodology employing the less expensive vinyl tris(trimethylsilyl)silanes was explored.

3.2.1.1. Synthesis of vinyl tris(trimethylsilyl)silane substrates

The (*Z*)-vinyl tris(trimethylsilyl)silanes (TTMS-silanes) **116a-d** were synthesized in

80-92% yield by the radical-mediated hydrosilylation[178] of the corresponding alkynes **115** with $(TMS)_3SiH$ (Scheme 33). Attempted hydrosilylation of terminal alkynes **115a-c** with $(TMS)_3SiH$ in the presence of $Rh(COD)_2BF_4/PPh_3/NaI$ or $RhCl(PPh_3)_3/NaI$ catalyst systems[179] produced *E* isomers **117a-c** in high yields, however, complete stereoselectivity was not achieved since *Z* isomers **116a-c** were also formed (~5-20%).



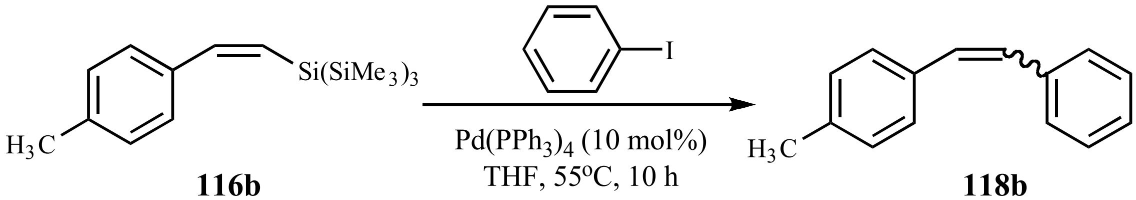
Scheme 33. Stereoselective synthesis of (*E*)- and (*Z*)-vinyl tris(trimethylsilyl)silanes.

For example, hydrosilylation of **115b** gave a **117b**/**116b** (*E/Z,* ~9:1) mixture, which was purified to afford **117b** (82%). Alternative treatment of the (*Z*)-silanes **116a** and **116c** with 0.5 equivalent of $(TMS)_3SiH$ in the presence of Wilkinson's catalyst[179] efficiently effected the isomerization to give the corresponding (*E*)-silanes **117a** (78%) and **117c** (89%). Extended heating (54 h) of **116b** in the presence of $(TMS)_3SiH/RhCl(PPh_3)_3/NaI$ resulted in the quantitative conversion of **116b** into **117b**.

3.2.1.2. Pd-catalyzed cross-coupling of *Z*- and *E*-vinyl tris(trimethylsilyl)silanes

As found previously in the Wnuk laboratory, the presence of peroxide and base are critical for the competent coupling of vinyl tris(trimethylsilanes) **116b,** while fluoride ions seems to only facilitate this conversion (see section 3.2.1.3). See Table 4 for details.

Table 4. Effect of reaction parameters on the cross-coupling of vinyl TTMS-silanes.



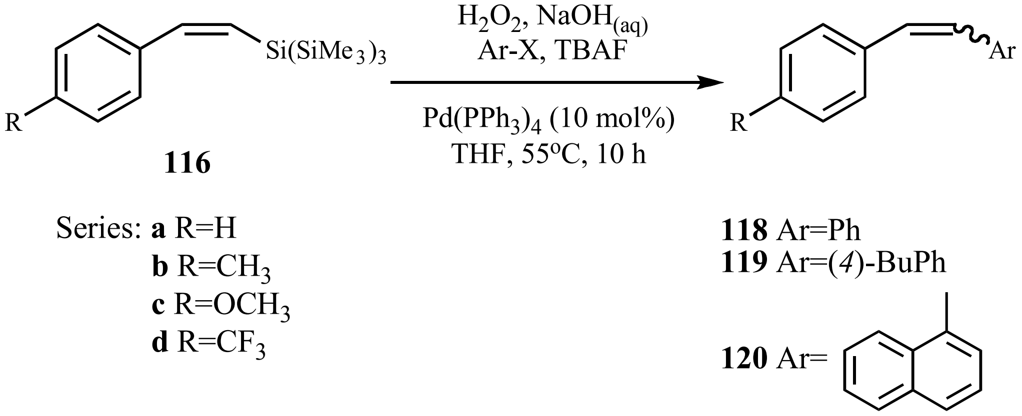
Entry	Peroxide	Base	Fluoride	Yield^a (%)	*E/Z*^{b}
1	none	None	TBAF	$<5^c$	5/95
2	H_2O_2	NaOH	none	$61^{d,e,f}$	15/85
3	H_2O_2	$KOSiMe_3$	none	60	25/75
4	H_2O_2	NaOH	TBAF	90	3/97
5	H_2O_2	$KOSiMe_3$	TBAF	81	2/98
6	H_2O_2	none	TBAF	18^c	67/33
7	none	$KOSiMe_3^g$	TBAF	$<2^c$	n/a
8	H_2O_2	NaOH	NaF	60	40/60
9	H_2O_2	NaOH	CsF	12^c	60/40
10	*t*-BuOOH	KH	none^h	15^c	75/25

^{a} Isolated yields (combined for both isomers of **118b**). Couplings were performed on 0.1 mmol scale of silane (0.03 mM). ^{b} Determined by GC-MS [with internal standard of (*E*)- and (*Z*)-stilbenes] and/or ^{1}H NMR of the crude reaction mixture. ^{c} Based on GC-MS. ^{d} $Pd_2(dba)_3$ also gave **118b** (52%; *E/Z,* 25:75). ^{e} Attempted couplings with H_2O_2 (without NaOH) or with NaOH (without H_2O_2) failed to give **118b**. ^{f} Coupling with bromobenzene instead of iodobenzene gave **118b** (40%; *E/Z,* 20:80). ^{g} Reaction with NaOH instead of $KOSiMe_3$ was also unsuccessful. ^{h} Coupling in the presence of TBAF gave^c **118b** in ~2% yield.

The conditions described above (Table 4, entries 2-5) are general for the coupling of various vinyl TTMS-silanes with several aryl iodides and bromides. Thus, treatment of the conjugated silane (*Z*)-**116a** with H_2O_2/H_2O (30%, 3 equiv.) and NaOH (3 equiv.)/H_2O in THF followed by addition of bromobenzene, $Pd(PPh_3)_4$ and TBAF gave stilbene **118a** (82%; Table 5, entry 1). Similarly, silane (*Z*)-**116b** coupled with iodobenzene and bromobenzene to give *p*-methylstilbene **118b** in 90% and 86% yield, respectively (entries 2 and 3). Less reactive electrophiles such as chlorobenzene and aryl triflate[180] failed to give the desired coupling products (entries 4 and 5). Coupling of (*Z*)-**116b** with 4-butyl-1-iodobenzene and 1-iodonaphthalene efficiently afforded products **119b** and **120b** in moderately good yields (entries 6 and 7). Interestingly, it seems that the substituent on the phenyl ring in (*Z*)-silanes **116a-d** (*p*-MeO, *p*-Me, H, *p*-CF_3) has an effect on the coupling reactions with bromobenzene, since both higher yields (from 70% to 97%) and better stereoselectivity (*E/Z* from 55:45 to 9:91) were obtained as the substituent changed from an electron-withdrawing group to an electron-donating group (entries 1, 3, 8 and 9). The observed higher coupling efficiency of (*Z*)-**116c** with bromobenzene may be attributed to the increased nucleophilicity of the vinylic carbon attached to the Si atom, resulting in faster transmetallation and subsequently better yields and less isomerization.

The (*E*)-TTMS-silanes **117a-c** underwent coupling with aryl halides under the same conditions (H_2O/NaOH/H_2O/TBAF), although with retention of the existing stereochemistry. Thus, coupling of conjugated silanes **117a-c** with aryl iodides and bromides (H_2O_2/NaOH/Pd(0)/TBAF) provided the corresponding products stereoselectively in good to excellent yields (48-90%; Table 6, entries 1-9). The electron-deficient aryl iodides gave to some extent higher yields than the electron rich aryl iodides in the reactions with silane **117a** (entries 1, 3 and 4).

Table 5. Coupling of vinyl (*Z*)-TTMS-silanes.



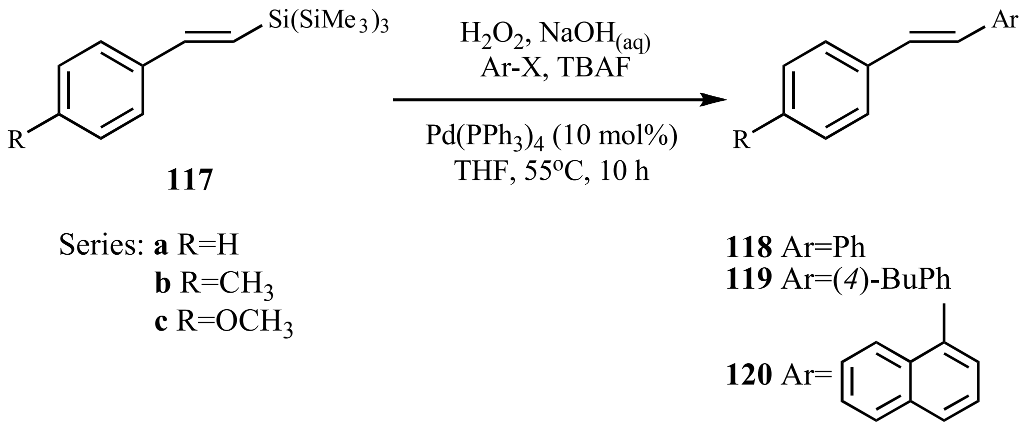
Entry	**Silane**	**Ar-X**	**Product**	**Yield**[a] **(%)**	***E/Z***[b]
1	**116a**	PhBr	**118a**	82	40/60
2	**116b**	PhI	**118b**	90	3/97
3	**116b**	PhBr	**118b**	86	30/70
4	**116b**	PhCl	**118b**	<5[c]	n/a
5	**116b**	PhOTf	**118b**	<5[c]	n/a
6	**116b**	(*4*)BuPhI	**119b**	61	24/76
7	**116b**	1-iodonaphthalene[d]	**120b**	73	15/85
8	**116c**	PhBr	**118c**	97	9/91
9	**116d**	PhBr	**118d**	70	55/45

[a] Isolated yields (combined for the *E/Z* isomers). Couplings were performed on 0.1-1.0 mmol scale of silanes (0.03 mM). $Pd(PPh_3)_4$ (10% mol). [b] Determined by GC-MS and/or ^1H NMR of the crude reaction mixture. [c] GC-MS. [d] Coupling with 1-bromonaphthalene gave **120b** (51%, *E/Z* = 27:73).

3.2.1.3. Coupling experiments without fluoride participation

Even though TBAF promotes couplings of vinyl TTMS-silanes in the presence of H_2O_2/base, it was found that fluoride activation of vinyl TTMS-silanes was not required for the cross-coupling to occur. Hence, oxidative treatment (H_2O_2/NaOH or $KOSiMe_3$) of the conjugated silane (*E*)-**117a** with bromo- and iodobenzene also produced (*E*)-stilbene (Table 7, entries 1 and 2). Other conjugated (*E*)- and (*Z*)-silanes also coupled with the substituted aryl halides (entries 3-7). Again coupling of (*Z*)-silanes occurred with lower stereoselectivity to produce an *E/Z* mixture (entries 4-7). It is noteworthy that TBAF promoted reactions generally gave higher yields and are more stereoselective than the fluoride-free reactions.

Table 6. Coupling of vinyl (*E*)-TTMS-silanes.



117

Series: **a** R=H
b R=CH_3
c R=OCH_3

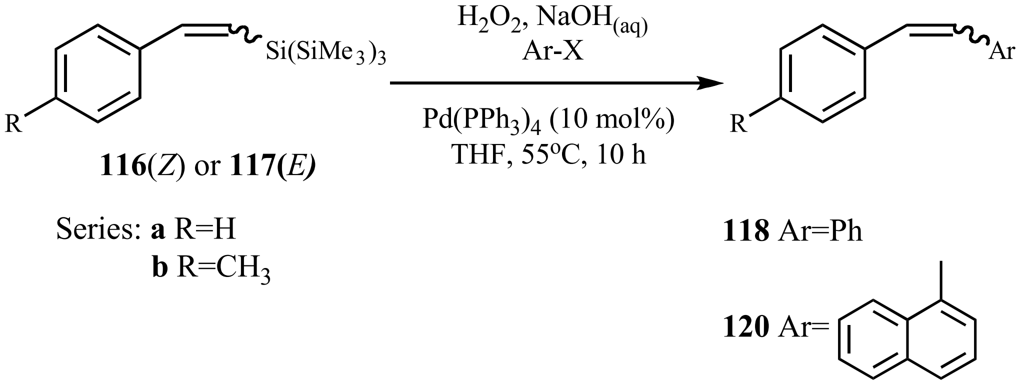
118 Ar=Ph
119 Ar=(*4*)-BuPh
120 Ar=

Entry	Silane	Ar-X	Product[a] (*E*)	Yield[b] (%)
1	**117a**	PhI	**118a**	83
2	**117a**	PhBr	**118a**	67
3	**117a**	(*4*)CH_3OPhI	**118c**	79
4	**117a**	(*4*)CF_3PhI	**118d**	90
5	**117b**	PhI	**118b**	72
6	**117b**	(*4*)BuPhI	**119b**	59
7	**117b**	1-bromonaphthalene	**120b**	48
8	**117b**	1-iodonaphthalene	**120b**	70
9	**117c**	PhBr	**118c**	63

[a] Only *E*-isomers were detected (^1H NMR, GC-MS). Couplings were performed on 0.1-0.5 mmol scale of silanes (0.03 mM). $Pd(PPh_3)_4$ (10% mol).
[b] Isolated yields.

It is also noteworthy that under the oxidative conditions required for the coupling of vinyl TTMS-silanes, the reductive self-coupling of the aryl halides has not been observed for the fluoride promoted reactions (Table 5 and 6) and was only sporadically observed for the fluoride-free reactions (Table 7, entries 2 and 4; 1-3%, GC-MS). Moreover, byproducts resulting from the oxidative homocoupling[18] of the vinyl silanes **116** and **117** have not been observed. Also, although the oxidative conditions employed for generation of the active organosilane species are similar to the ones used in Tamao-Kumada and Fleming oxidation of silanes to alcohols (including vinyl silanes to aldehydes and ketones), which involve cleavage of the C-Si bond,[181] we did not observe conversion of the vinyl silanes **116** and **117** to the corresponding aldehydes. Apparently, Si-Si bond cleavage takes place chemoselectively with the C-Si bond tolerating the relatively mild oxidative conditions required for the cleavage of Si-Si bonds.[182]

Table 7. Fluoride-free coupling of the vinyl TTMS-silanes.



116(*Z*) or **117**(*E*)

Series: **a** R=H
b R=CH_3

118 Ar=Ph

120 Ar=

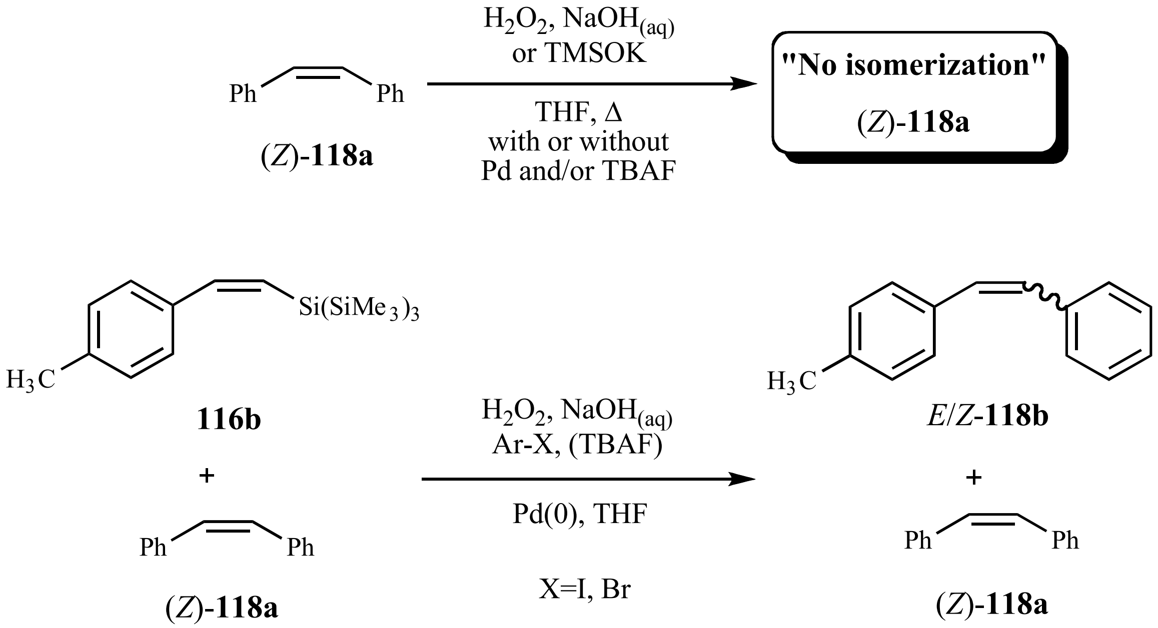
Entry	Silane	Ar-X	Product	Yield[a] (%)	*E/Z*[b]
1	**117a**	PhI	**118a**	75[c]	100/0
2	**117a**	PhBr	**118a**	50	100/0
3	**117b**	1-iodonaphthalene	**120b**	46	100/0
4	**116a**	PhBr	**118a**	55	25/75
5	**116b**	PhI	**118b**	61[d]	15/85
6	**116b**	PhBr	**118b**	40[e]	20/80
7	**116b**	1-bromonaphthalene	**120b**	30	17/83

[a] Isolated yields. Couplings were performed on 0.1 mmol scale of silanes (0.03 mM). $Pd(PPh_3)_4$ (10% mol). [b] Determined by ^1H NMR and/or GC-MS of the crude reaction mixture. [c] With $KOSiMe_3$ instead of NaOH yield was 60% (*E/Z,* 100:0). [d] With $KOSiMe_3$ instead of NaOH yield was 60% (*E/Z,* 25:75). [e] With $KOSiMe_3$ instead of NaOH yield was 48% (*E/Z,* 10:90).

3.2.1.4. Stereochemistry of the coupling with *Z*-vinyl tris(trimethylsilyl)silanes

The lack of stereoselectivity for the coupling of (*Z*)-silanes probably results from the isomerization of silane/Pd intermediate complexes derived from (*Z*)-TTMS-silanes under the coupling conditions. Isomerization[183,184] of the products was excluded based on the following experiments (Scheme 34): (i) no isomerization of the (*Z*)-stilbene **118a** was observed when (*Z*)-**118a** was refluxed in THF in the presence of H_2O_2/NaOH or TMSOK with or without Pd(0) and/or TBAF, (ii) coupling of the 4-methyl-phenyl (*Z*)-silane **116b** under typical conditions [H_2O_2/NaOH/Pd(0)/THF/with or without TBAF] with phenyl iodide or bromide in the presence of 0.25 or 1.0 equiv. of the (*Z*)-stilbene **118a** produced 4-methylstilbene **118b** as the *E/Z* mixture [see Table 5 (entries 2 and 3) and Table 7 (entries 5 and 6)], while isomerization of the (*Z*)-stilbene **118a** into *E* isomer was not observed (GC/MS).

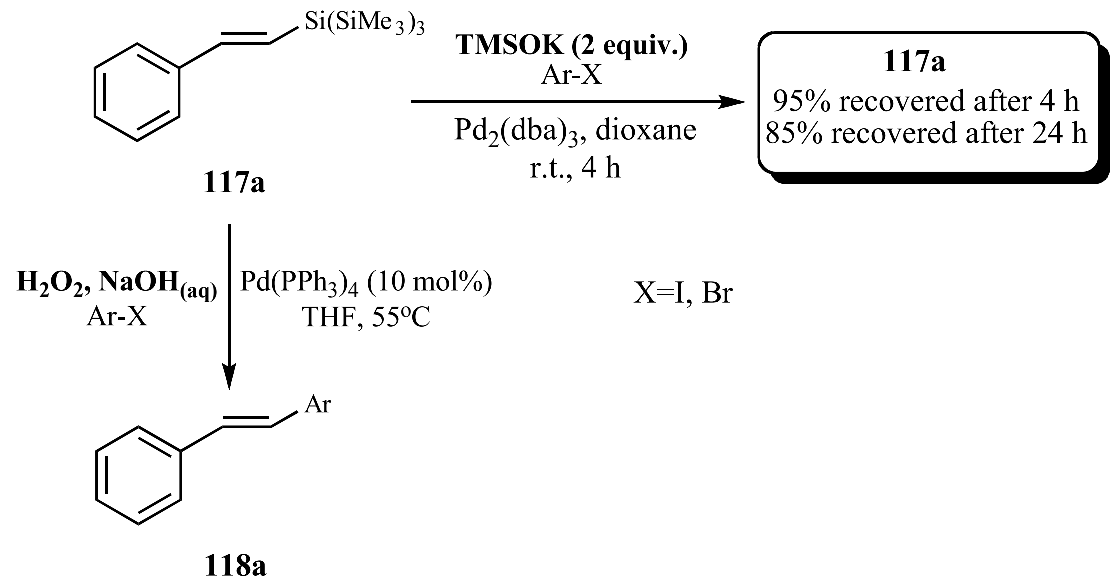
Moreover, a "side-by-side" comparison of the coupling of (*Z*)-**116b** with 1-iodonaphthalene [1 h (30%, *E/Z* 0:100); 3 h (58%, *E/Z* 3:97)] and 1-bromonaphthalene [1 h (22%, *E/Z* 5:95); 3 h (35%, *E/Z* 13:87)] showed that product **120b** is formed at different pace (Table 5, entry 7). It appears that coupling with the aryl iodides is faster and occurs with a higher degree of stereoretention than with the corresponding aryl bromides (see also Table 5, entry 2 *vs.* 3; Table 7, entry 5 *vs.* 6). Longer stirring of the silanes **116** and **117** with H_2O_2/NaOH (45 min. *vs.* 15 min.) prior to the addition of the aryl halide and the catalyst resulted in no improvement of yield or stereoselectivity.



Scheme 34. Study of the inversion of stereochemistry in the coupling of (*Z*)-tris(trimethylsilyl)silanes.

3.2.1.5. Vinyl tris(trimethylsilyl)silanes as "masked silanols". Selective *in situ* generation of reactive intermediates by H_2O_2/NaOH

Denmark and Tymonko have recently utilized substrates bearing two distinct silyl subunits [$RSiMe_2OH$ *vs*. $RSiMe_2Bn$], which required complementary activations (TMSOK *vs*. TBAF) for the construction of unsymmetrical disubstituted 1,4-butadienes.[185] Tris(trimethylsilyl)silanes can also serve as alternative organosilane substrates in Pd-catalyzed couplings. For example, TTMS-silane **117a** remained intact under typical conditions employed in the coupling of dimethylsilanols[185,186] [TMSOK(2 equiv.)/$Pd_2(dba)_3$/dioxane/r.t./4 h] with more than 95% of **117a** being recovered after 4 h and ~85% after 24 h (Scheme 35). This experiment demonstrated that TTMS-silanes could act as masked silanols, which require hydrogen peroxide for activation towards coupling.

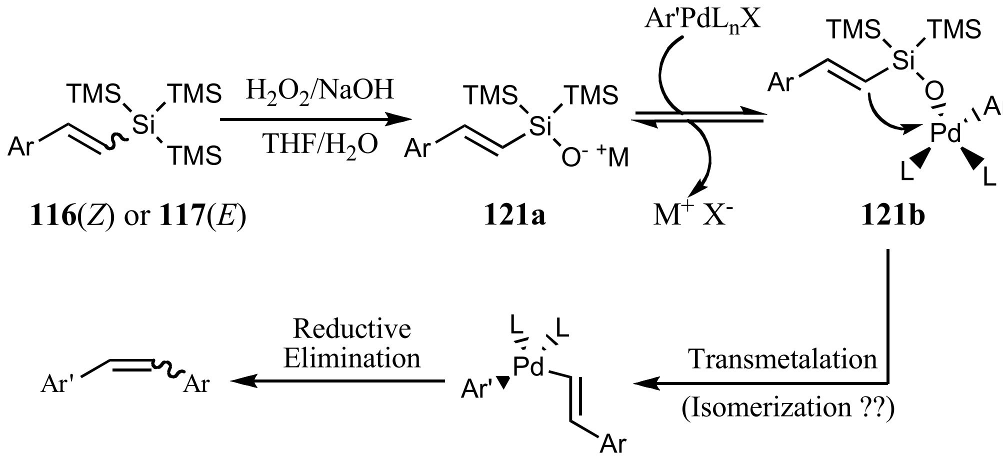


Scheme 35. Possible application of vinyl tris(trimethylsilyl)silanes as "masked silanols".

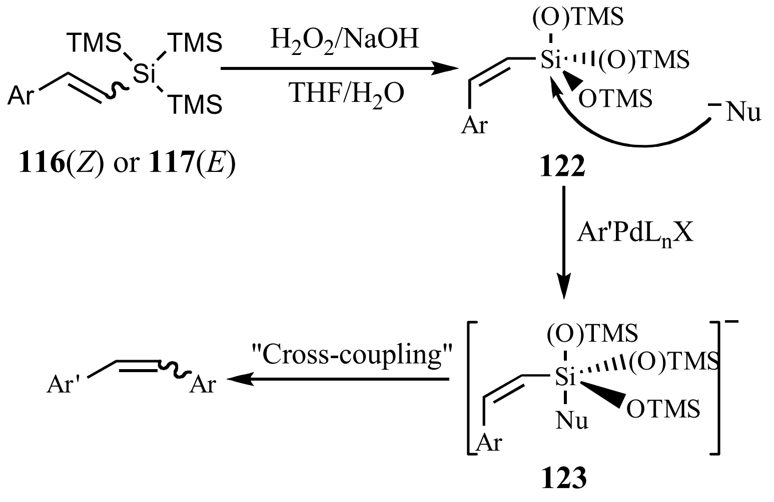
3.2.1.6. Mechanistic implications

We have not yet had the opportunity to systematically investigate the mechanism(s) of the vinyl TTMS-silanes Pd-catalyzed coupling but it appears that hydrogen peroxide might chemoselectively cleave[187] the Si–Si bond(s) to generate silanol species $RSi(OH)_n(SiMe_3)_{3-n}$ (n = 1, 2, or 3). Subsequently, the silanol(s) are converted by the base to a silanolate anion **121a**, which might further follow the coupling mechanism suggested by Denmark *et al.* for the organosilanols which involves the formation of an oxy-palladium intermediate of type **121b**[91] (Scheme 36, see also section 1.2.1).

Alternatively, vinyl TTMS-silanes can be converted by hydrogen peroxide to siloxane species $RSi(OSiMe_3)_n(SiMe_3)_{3-n}$ of type **122** (n = 1, 2, or 3), that can be further transformed to the reactive pentacoordinate species of type **123** (hypervalent silicate anion) by fluoride or base, as suggested by Denmark[125] and DeShong [187] (Scheme 37).



Scheme 36. A plausible mechanism for the coupling of vinyl tris(trimethylsilyl)silanes via formation of silanolate anion by H_2O_2/base.



Scheme 37. A plausibe mechanism for the coupling of vinyl tris(trimethylsilyl)silanes via formation of pentavalent silicate anion by fluoride or base.

In order to obtain additional mechanistic insights, we examined the coupling reaction of **117a** with iodobenzene by ^{29}Si NMR. Thus, treatment of **117a** with hydrogen peroxide (THF-d_8/NaOH/H_2O) resulted in the appearance of new peaks at 9.82, 7.20 and 5.59 ppm (Figure 19), which are characteristic of the species having oxygen attached to silicon,[87,125,182,187] with progressive disappearance of the two distinctive peaks at -85.31 ppm (Si atom attached to *sp*^{2} carbon) and -14.37 pm ($SiMe_3$) for the silicon atoms present in substrate **117a**. Addition of Pd catalyst and phenyl iodide to the resulting mixture resulted in the formation of stilbene (*E)*-**118a**.

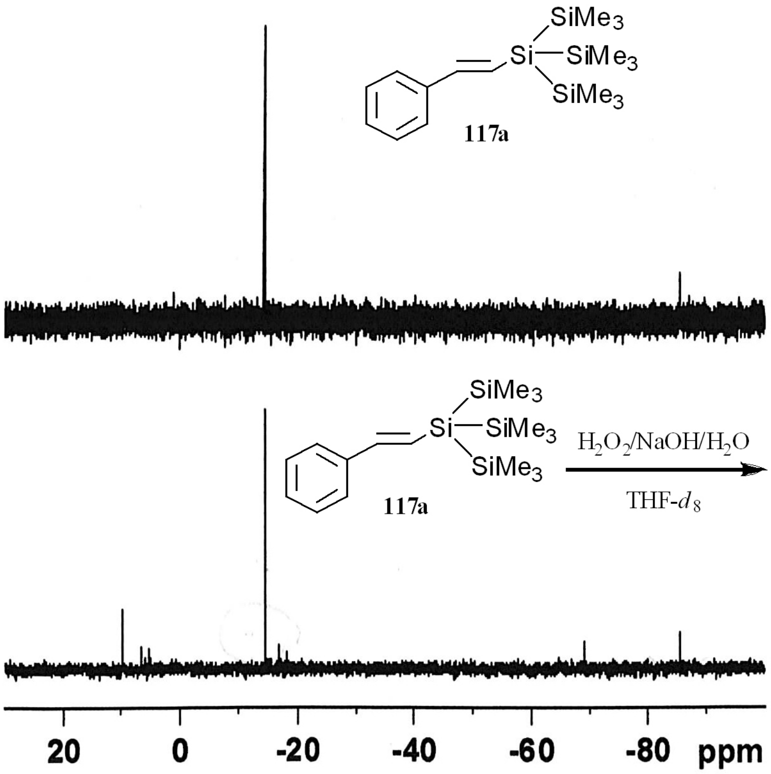
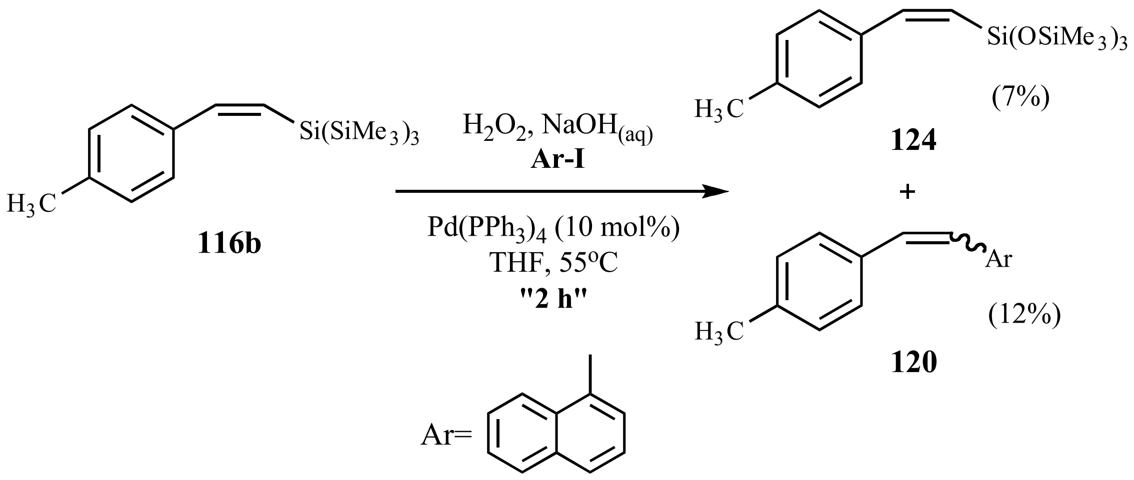


Figure 19. ^{29}Si NMR analysis of the reaction of *(E)*-2-phenyl-1-[tris(trimethylsilyl)-silyl]ethene with $H_2O_2/NaOH_{(aq.)}$ in THF-d_8.

Moreover, when coupling of **116b** with 1-iodonaphthalene under fluoride-free conditions was quenched after 2 h (Scheme 38), the corresponding tris(trimethylsiloxy)silyl compound **124** [(*4*)$CH_3C_6H_4CH{=}CHSi(OSiMe_3)_3$] was isolated in 7% yield in addition to product **120b** (12%).



Scheme 38. The Formation of *(Z)*-2-(4-methylphenyl)-1-[tris(trimethylsiloxy)silyl]-ethene during the coupling with (*Z*)-tris(trimethylsilyl)silanes.

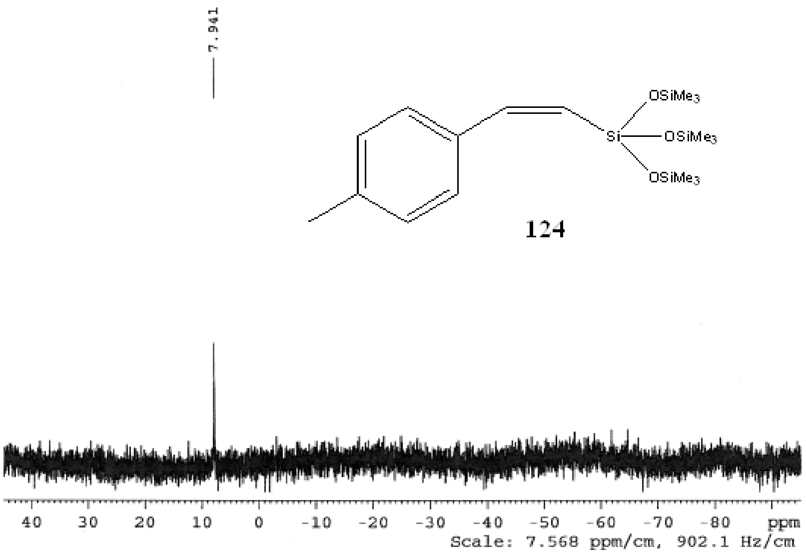
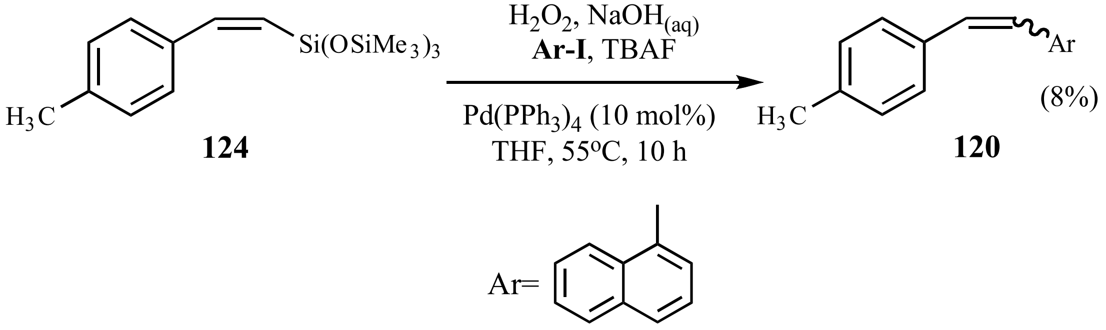


Figure 20. ^{29}Si NMR spectra of *(Z)*-2-(4-Methylphenyl)-1-[tris(trimethylsiloxy)silyl]ethane.

The structure of **124** was assigned based on the HRMS and NMR spectra. The corresponding ^{29}Si NMR spectrum of **124** showed one distinctive peak at δ 7.94 ppm attributable to the three O*Si*Me$_3$ groups from the siloxane moieties (Figure 20), in agreement with values reported for analogous siloxanes[188] (-5 to 20 ppm). The peak for the Si atom attached to the C(sp^2) is hardly detectable at δ -66 ppm. Moreover, subjection of **124** to TBAF promoted coupling with 1-iodonaphthalene (Scheme 39) afforded product **120b** but in low yield (8%; GC/MS).



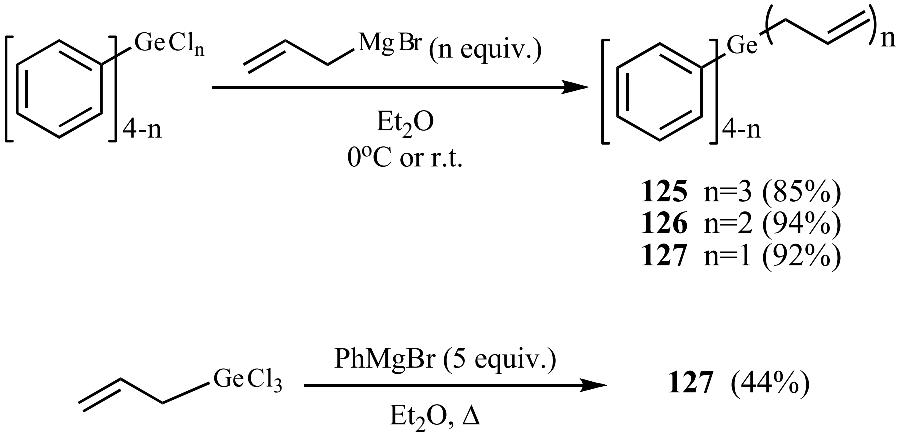
Scheme 39. Pd-catalyzed cross-coupling of *(Z)*-2-(4-methylphenyl)-1-[tris(trimethylsiloxy)silyl]ethene with 1-iodonaphthalene.

3.2.2. Allyl(phenyl)germanes as substrates for the Pd-catalyzed cross-coupling reaction

In an attempt to develop all-carbon substituted germane substrates as possible safety-catch precursors for the Pd-catalyzed cross-coupling, we synthesized allyl(phenyl)germanes (**125-127**) and investigated their ability to transfer the phenyl group from the Ge center. The design of the germanes **125-127** was made based on the reported transfer of the phenyl/aryl group from the moderately reactive allyl(phenyl)silanes **23**[105] and aryl(2-naphthylmethyl)germanes **28**[106] (see section 1.2.1.1).

3.2.2.1. Synthesis of allyl(phenyl)germanes

Treatment of the commercially available trichloro(phenyl)germane with 3 equiv. of allylmagnesium bromide yielded triallyl(phenyl)germane **125** in 85% yield as a "bench" stable compound (Scheme 40). Analogous reaction of the dichloro(diphenyl)germane with allylmagnesium bromide gave diallyl(diphenyl)germane **126** (94%). Treatment of the allyl(trichloro)germane with phenylmagnesium bromide produced allyl(triphenyl)germane **127** (44%). Alternatively, treatment of chloro(triphenyl)germane with allylmagnesium bromide at ambient temperature also afforded germane **127** in 92% yield.



125 n=3 (85%)
126 n=2 (94%)
127 n=1 (92%)

127 (44%)

Scheme 40. Synthesis of allyl(phenyl)germanes.

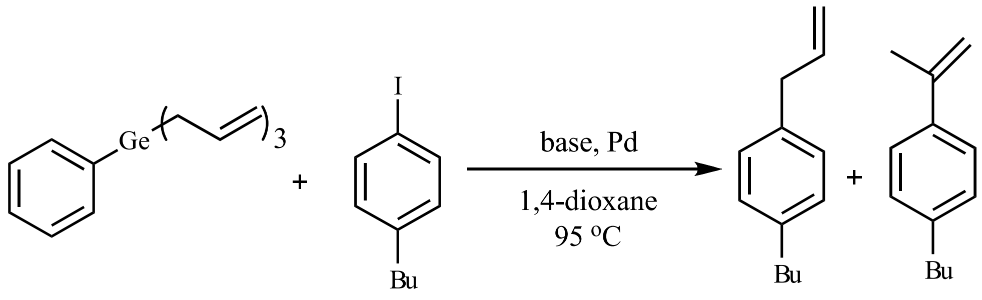
3.2.2.2. Pd-catalyzed cross-coupling of allyl(phenyl)germanes

Allylgermanes have been studied to probe their participation in σ-π C-M hyperconjugation and pπ-dπ bonding.[189] These type of interactions are associated with their enhanced reactivity towards electrophilic reagents.[190] Umpolung reactivity has also been induced and employed for the direct allylation of aromatic substrates (e.g. alternative Friedel-Crafts methodology).[191] Allylgermanes also efficiently participate in addition chemistry and a range of cycloaddition reactions.[192,193] However, the application of allylorganogermanes as substrates for the Pd-catalyzed cross-coupling remained scarcely developed. Consequently, reactions of triallyl(phenyl)germanes **125** under typically employed coupling conditions were explored.

We have attempted to engage triallyl(phenyl)germane **125** in the Pd-catalyzed cross-coupling reactions with aryl iodides employing $PdCl_2$/TBAF/PCy_3/DMSO/H_2O [used for triallyl(phenyl)silanes **23**];[105] or NaOH/H_2O/H_2O_2/$Pd(PPh_3)_4$/THF [utilized for vinyl tris(trimethylsilyl) germanes **20**][97]. However, the transfer of the phenyl group from the germane precursor to yield the corresponding biaryl was not observed. Nevertheless, treatment of **125** with 1-butyl-4-iodobenzene under the conditions employed for the coupling of trichloro(phenyl)germanes **18** [NaOH (8 equiv.)/H_2O/dioxane/$Pd(OAc)_2$][95] afforded 1-allylbenzene product **128a** in 55% yield resulting from the unexpected transfer of the allyl group (Table 8, entry 1). A small amount of the structural isomer **129a** was also detected by GC-MS (**128a/129a**, ~87:13). Based on these results, we turned our attention to examine the effect of NaOH and other reaction parameters (Table 8) on the transfer of the allyl group(s) from triallyl(phenyl)germane **125**.

Thus, treatment of **125** with 1-butyl-4-iodobenzene in the presence of various amounts of NaOH (10 and 12 equiv.) and $Pd(OAc)_2$ in 1,4-dioxane at 95 °C afforded a mixture of regioisomers **128a** and **129a** in up to 78% yield (entries 2 and 3). The combination of NaOH and Pd catalyst proved to be critical for the transfer of allyl groups from **125**, since reactions with only NaOH or $Pd(OAc)_2$ afforded products **128a** and **129a** in much lower yields (entries 4 and 5). Moreover, use of different Pd catalysts also gave the corresponding products with similar yields and regioselectivity (entries 6 and 7). Similar treatment employing Et_3N and TBAF also afforded **128a**/**129a** in moderate yields (entries 8 and 9). Alternative addition of Lewis acid $BF_3{\cdot}Et_2O$ resulted in the formation of **128a** in poor yield (6%, entry 10). The observed results suggested the idea of a Heck type mechanism in which the base plays a crucial role[66] (entry 3 *vs.* 4) and demonstrated that the ratio of isomers **128a/129a** seems to be independent of the conditions employed (entries 3, 4, 5, 8, and 9). It is possible that an easier approach to a less hindered γ position of the allyl substituent on **125** could be accountable for the observed selectivity.

Table 8. Effect of the reaction parameters in the reaction of triallyl-(phenyl)germanes with 1-butyl-4-iodobenzene.



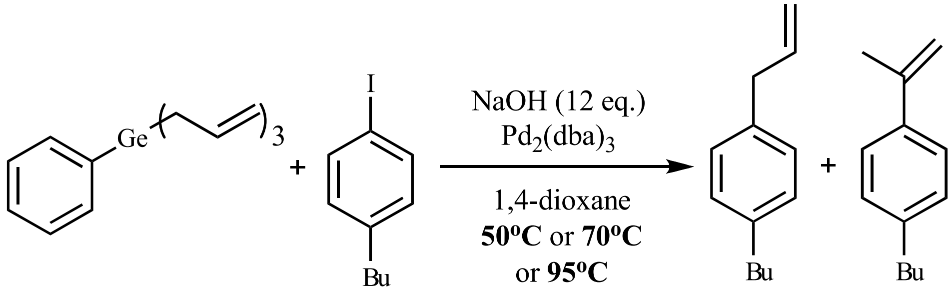
125 **128a** **129a**

Entry	NaOH (equiv.)	Pd	Others	Yield (%)[a]	128a/129a Ratio[b]
1	8	$Pd(OAc)_2$	-	55	87:13
2	10	$Pd(OAc)_2$	-	60	89:11
3	12	$Pd(OAc)_2$	-	78	82:18
4	-	$Pd(OAc)_2$	-	15	94:6
5	12	-	-	16	82:18
6	12	$Pd(PPh_3)_4$	-	78	84:16
7	12	$Pd_2(dba)_3$	-	80	86:14
8	-	$Pd(OAc)_2$	Et_3N	32	83:17
9	-	$Pd(PPh_3)_4$	TBAF	42	82:18
10	-	$Pd(OAc)_2$	$BF_3 \cdot Et_2O$	6	100:0

[a] Determined by GC-MS of the crude reaction mixture using 4-allylanisole as internal standard. [b] Determined based on GC-MS of the crude reaction mixture.

In order to investigate the effect of the temperature on the regioselectivity of the reaction of allylgermane **125** with 1-butyl-4-iodobenzene and $Pd_2(dba)_3$ in 1,4-dioxane (Table 8, entry 7), "side by side" experiments at 50 °C, 70 °C and 95 °C were performed and their outcome monitored by GC-MS (Table 9).

Table 9. Effect of the temperature on the regioselectivity of the reaction of triallyl(phenyl)germane with 1-butyl-4-iodobenzene.



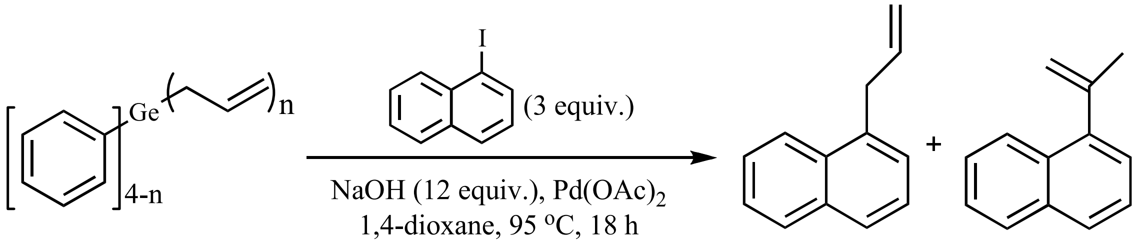
125 **128a** **129a**

	4/5 ratio[a]		
	50°C	70°C	95°C
1 h	90:10	90:10	87:13
3 h	91:9	91:9	87:13
6 h	91:9	91:9	87:13

[a] Determined by GC-MS of the crude reaction mixture.

The presence of both isomeric products **128a** and **129a** after only 1 h heating at 50 °C, 70 °C, or 95 °C implied the lack of correlation between the selectivity and the reaction temperatures. Although faster conversion to products **128a** and **129a** was observed at higher temperatures, the **128a**/**129a** ratios remained constant (~90:10) after prolonged heating.

Since the structure of triallylgermane **125** offers the possibility of transfer of three allyl substituents in the reaction with aryl halides, experiments with 3 equivalents of 1-iodonaphthalene were attempted. Thus, treatment of **125** under the optimized conditions [NaOH(12 equiv.)/dioxane/Pd(OAc)$_2$/95 °C] afforded a mixture of products **128b** and **129b** in 92% yield (**128b**/**129b**, ~87:13, Scheme 41). Similar reactions employing diallyl(diphenyl)germane **126** or allyl(triphenyl)germane **127** with 1-iodonaphthalene (3 equiv.) gave regiosomers **128b** and **129b** in 78% and 38%, respectively. A considerable amount of unchanged aryl halide remained in the reaction mixture.



125 n=3
126 n=2
127 n=1

128b **129b**

from **125** (92%-**128b**/**129b**, 87:13)
from **126** (78%-**128b**/**129b**, 89:11)
from **127** (38%-**128b**/**129b**, 92:8)

Scheme 41. Transfer equivalency of allyl(phenyl)germanes.

Since the overall yield for the couplings was less than 100% (based on allylgermanes **125-127** as limiting reagents), it seems likely that only one allyl group from each of the germanes (**125-127**) participates in the reaction. However, the increase in the number of available allyl moieties affects the yields in a proportional fashion [from germane **125**→(92%), **126**→(78%), and **127**→(38%)]. Also, the increased steric hindrance conferred by replacing allyl groups with bulkier phenyl substituents (**125**→**126**→**127**) promoted a slight enhancement in the corresponding isomeric ratios. Moreover, the reactions of allylgermanes **125**, **126**, or **127** with only 1 equivalent of 1-butyl-4-iodobenzene and 1-iodonaphthalene showed a similar proportional decrease of the yields of isomeric products **128a-b** and **129a-b** from triallyl(phenyl)germane (**125**) to allyl(triphenyl)germane (**127**) (Table 10, entries 1-3 and 7-9). Alternative use of $Pd_2(dba)_3$ afforded the products **128a-b** and **129a-b** in higher yields, albeit the regioselectivity was not improved (entry 1 *vs* 4, 2 *vs* 5, 3 *vs* 6).

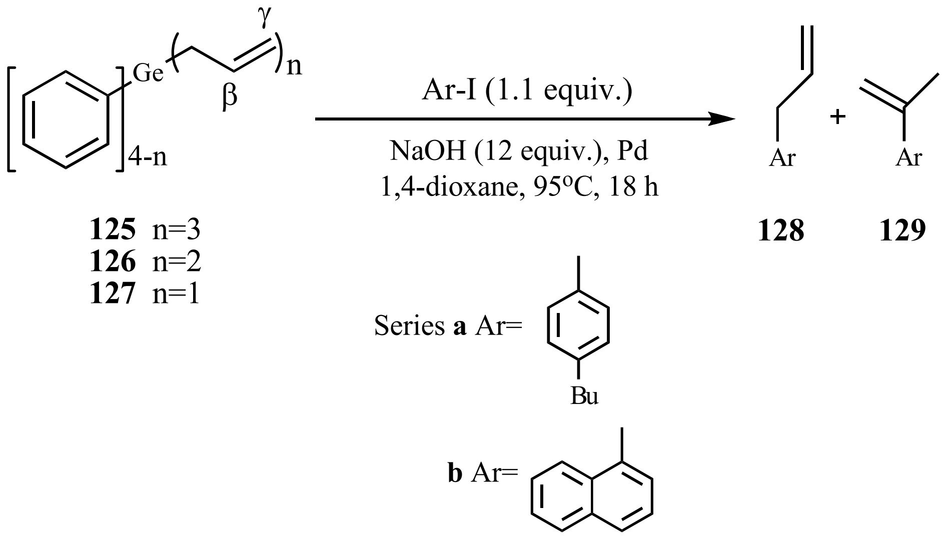
Interestingly, the reactions with the bulkier 1-iodonaphthalene showed a significant enhancement in the regioselectivity compared with similar reactions with 1-butyl-4-iodobenzene (entry 1 *vs* 7, 4 *vs* 10).

It seems feasible that the formation of products **128** and **129** from allyl(phenyl)germanes **125-127** in the presence of NaOH and Pd catalyst might follow a Heck arylation mechanism (Scheme 42). Allylgermatranes[93] and allyltrimethylsilanes[194] have been reported to undergo Heck reaction with aryl halides under similar conditions.

In our proposed mechanism (Scheme 42), addition of the aryl-Pd complex **130a** to the double bond on the allylgermane (**125-127**) would lead to the formation of the π-bound complex **130b**. Addition of the aryl group to the double bond might take place either on the terminal (**131a**) or on the internal (**131b**) carbon (pathways A and B) leading to the formation of isomeric products **128** and **129**. In pathway A, the intermediate **131a** would undergo an iodide-promoted intramolecular degermylation yielding 1-allylbenzene product **128**. In pathway B, a β-hydrogen elimination would occur on **131b**, producing an internally arylated allylgermane π-bound to Pd(H)(I) (**132**). Insertion of this alkene into the Pd-H bond would afford the complex **133**, which will eleminate R_3GeI and Pd(0) to give product **129**.

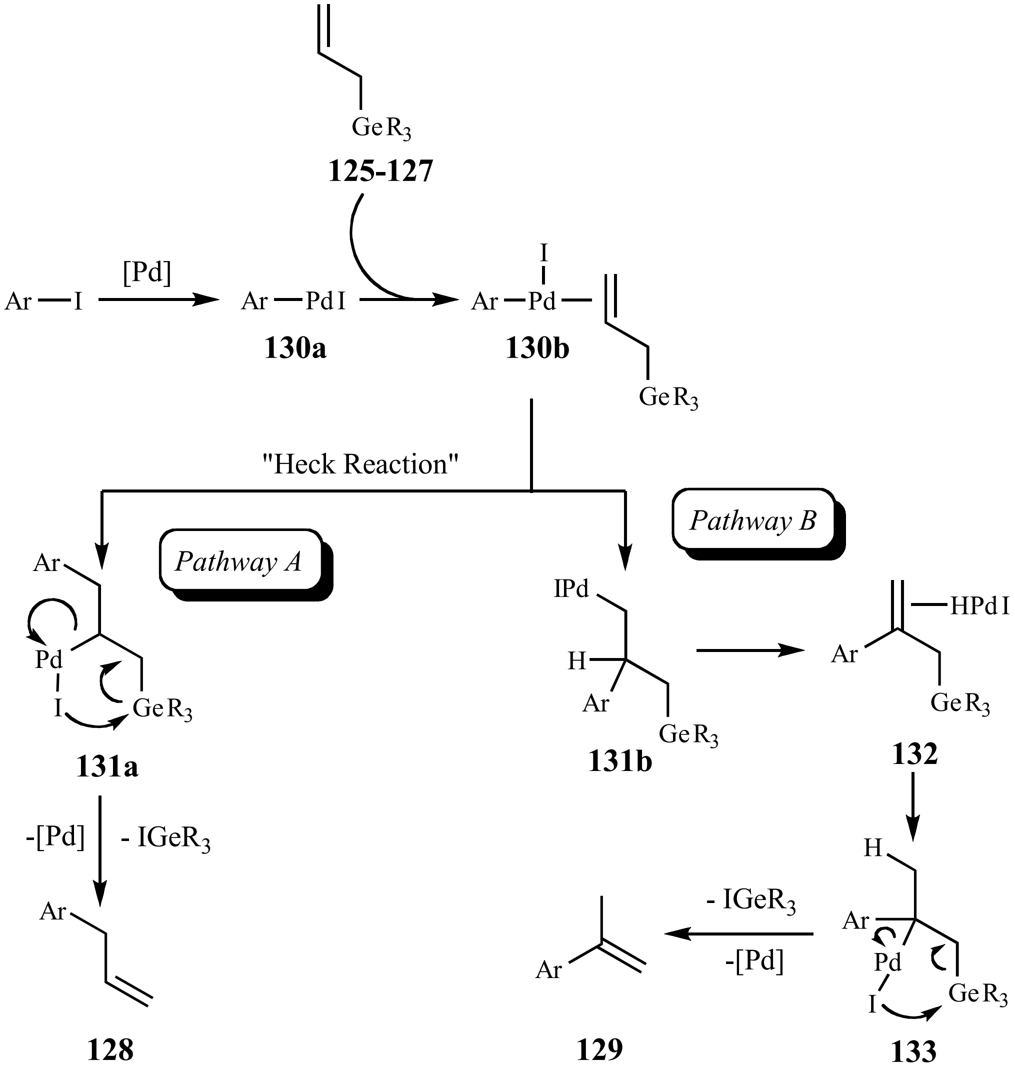
Although the described Heck arylation of allylgermanes (**125-127**) in the presence of NaOH displayed less efficiency than other available methodologies,[195] a careful investigation of the proposed mechanism would advance the usually limited knowledge about the reactivity of organogermanium species. However, the development of a convenient strategy for the selective cleavage of the Ge-allyl bond in germanes **125-127** was still our main objective.

Table 10. Reaction of allyl(phenyl)germanes with 1-butyl-4-iodobenzene and 1-iodonaphthalene.



Entry	Germane	Pd	Products	Yield (%)[a]	128/129 Ratios[b]
1	**125**	$Pd(OAc)_2$	**128a/129a**	78	82:18
2	**126**	$Pd(OAc)_2$	**128a/129a**	47	82:18
3	**127**	$Pd(OAc)_2$	**128a/129a**	32	86:14
4	**125**	$Pd_2(dba)_3$	**128a/129a**	80	86:14
5	**126**	$Pd_2(dba)_3$	**128a/129a**	55	85:15
6	**127**	$Pd_2(dba)_3$	**128a/129a**	33	85:15
7	**125**	$Pd(OAc)_2$	**128b/129b**	73	91:9
8	**126**	$Pd(OAc)_2$	**128b/129b**	51	90:10
9	**127**	$Pd(OAc)_2$	**128b/129b**	29	91:9
10	**125**	$Pd_2(dba)_3$	**128b/129b**	88	91:9
11	**126**	$Pd_2(dba)_3$	**128b/129b**	69	92:8
12	**127**	$Pd_2(dba)_3$	**128b/129b**	40	93:7

[a] Determined by GC-MS of the crude reaction mixture using 4-allylanisole as internal standard. [b] Determined GC-MS of the crude reaction mixture.

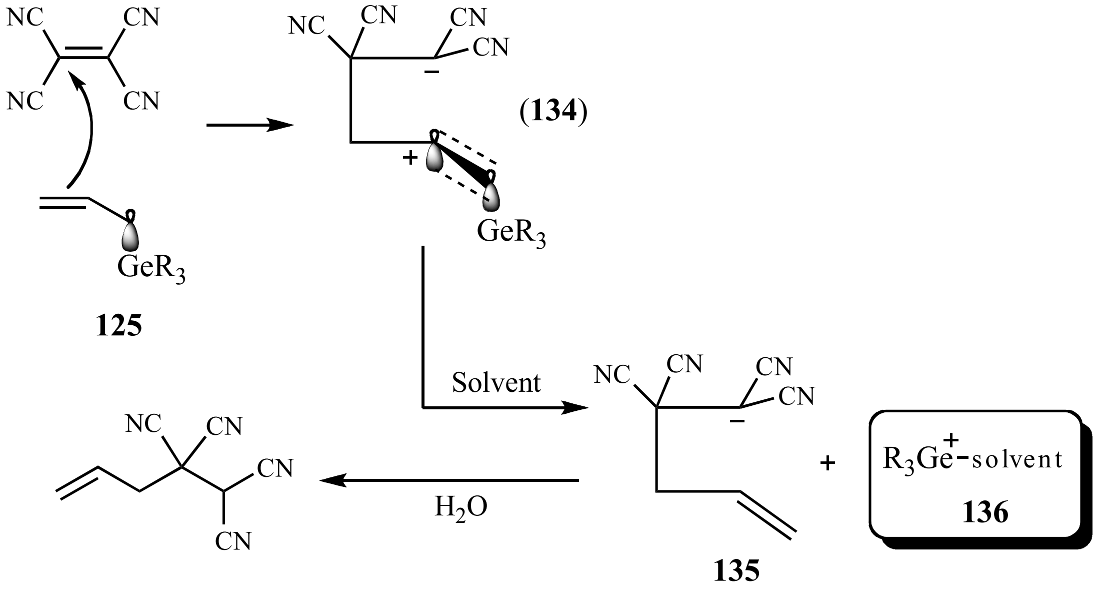


Scheme 42. A plausible mechanism for the Heck arylation of allyl(phenyl)germanes.

3.2.2.3. Treatment of allyl(triphenyl)germane with TCNE. Possible transfer of the phenyl group

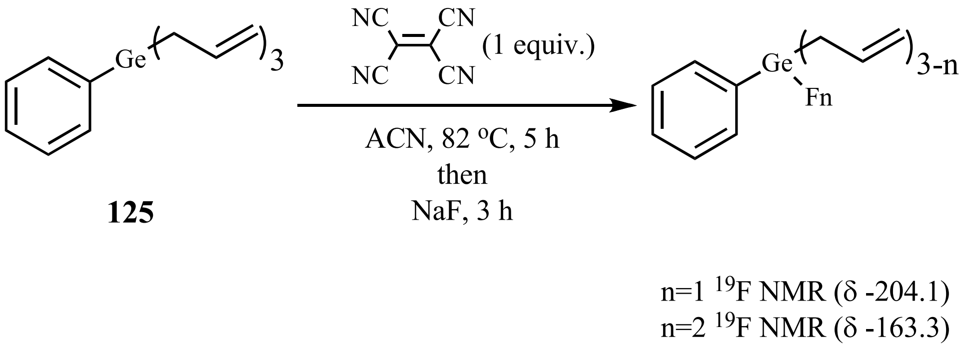
During our study of the Pd-catalyzed cross-coupling of allyl(phenyl)germanes **125-127**, the coupling of photochemically activated (2-naphthylmethyl)germanes **28** (see Scheme 8) with different aryl halides was reported.[106] The photooxidation of **28** in the presence of $Cu(BF_4)_2$ resulted in the selective cleavage of Ge-C(2-naphthylmethyl) bonds and formation of reactive arylfluorogermanes **29** which subsequently underwent transmetallation.

On this basis, the reaction of allyl(triphenyl)germane **3** with the strong oxidizing agent tetracyanoethylene[196] (TCNE) was envisioned as a possible route to reactive halo- or hydroxogermanes known to be active in the Pd-catalyzed cross-coupling reactions.[93-97] Thus, treatment of triallyl(phenyl)germane **125** with TCNE in refluxing acetonitrile for 7 h resulted in the complete consumption of starting allylgermanes, as shown by TLC analysis of the crude reaction mixture. Presumably, the Ge-C(allyl) bond of **125** was cleaved following a similar pathway to that proposed for the reaction of allyltrimethylsilanes with TCNE (Scheme 43).[196] In a first step, the electron-accepting TCNE would promote the interaction with the π-system of **125**, generating zwitterionic complex **134**, stabilized by σ-π hyperconjugation with the Ge-C bond. Subsequent solvation of the Ge center would promote the formation of the R_3Ge^+–solvent adduct **136** and an anionic cyano-contaning compound **135**.



Scheme 43. A tentative mechanism for the reaction of allylgermanes with tetracyanoethylene.

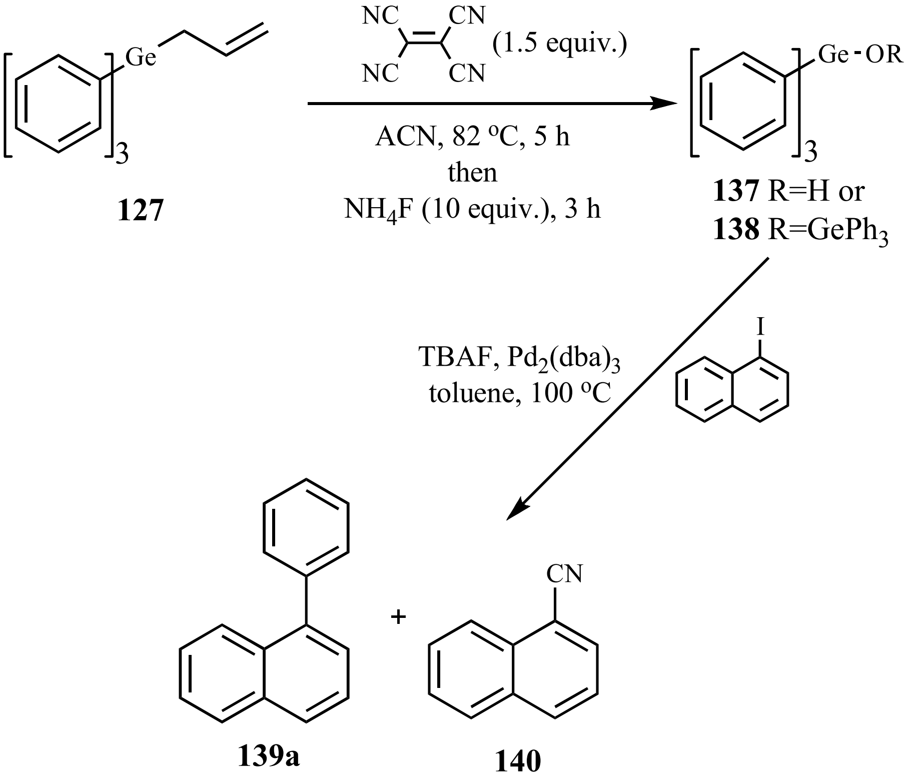
Based on the pathway described above (Scheme 43), we explored the synthesis of reactive fluorogermanes by quenching *in situ* the generated solvated R_3Ge^+ ion **136** [from the reaction of allylgermane **125** and TCNE (1 equiv.)] with fluoride ions (e.g. NaF). The ^{19}F NMR spectrum of the crude reaction mixture displayed two peaks at δ -204.1 and δ -163.3 ppm (Scheme 44), characteristic for organogermanes bearing 1 and 2 fluorine atoms.[106] In agreement with the observed results, ^1H NMR confirmed the presence of the residual Ge-C(allyl) bonds. The attempted separation of the resulting fluorogermanes from an intense colored reaction mixture was not successful due to their instability on silica gel. Experiments employing excess of TCNE followed by addition of the more soluble TBAF, as a fluoride source, did not produce an analogous signal in the corresponding ^{19}F NMR spectrum.



Scheme 44. Reaction of triallyl(phenyl)germane with TCNE and NaF.

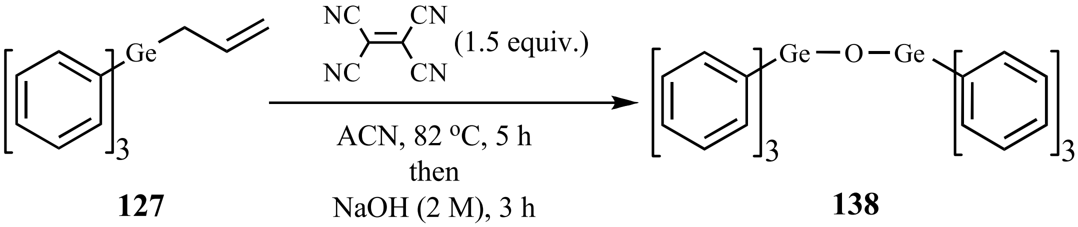
In an attempt to promote the cleavage of all the Ge-C(allyl) bonds in the organogermanium precursor (to avoid competition between allyl and aryl group transfers), analogous experiments were initially performed employing allyl(triphenyl)germane **127**. Thus, treatment of **127** with TCNE (1.5 equiv.) in refluxing acetonitrile for 4 h (total disappearance of **127** on TLC) followed by addition of TBAF (1.5 equiv.) afforded a green-colored reaction mixture. However, ^{19}F NMR of the decolorized (charcoal) crude reaction exhibited only a small signal for the monofluorinated germane Ph_3GeF (δ -201.9 ppm). It seems likely that solvation of the fluoride ions by the polar acetonitrile precluded the efficient fluorination of the R_3Ge^+–solvent adduct.

Analogous reaction of **127** employing excess of the inexpensive NH_4F (10 equiv.) as the fluoride source failed to generate the desired Ph_3GeF (Scheme 45). However, analysis of the crude reaction mixture by ^1H NMR and GC-MS suggested the presence of an oxy germane of type Ph_3GeOR (**137**, R=H or **138**, R=$GePh_3$). Subsequent treatment of the non-purified crude with TBAF (7 equiv.), 1-iodonaphthalene, and $Pd_2(dba)_3$ in toluene at 100 ^oC (see section 3.2.3.1) afforded an equal mixture of the desired biaryl product **139a**, 1-cyanonaphthalene **140**, and unreacted aryl halide. Since the reaction of TCNE with 1-iodonaphthalene in the presence of $Pd_2(dba)_3$ failed to produce 1-cyanonaphthalene, the cyano-containing byproducts generated from the treatment of **127** with TCNE (see Scheme 43) might be accounted forby the formation of unexpected **140**. The 1-cyanonaphthalene could be formed via Pd-catalyzed transfer of the cyano group or via nucleophilic aromatic substitution.



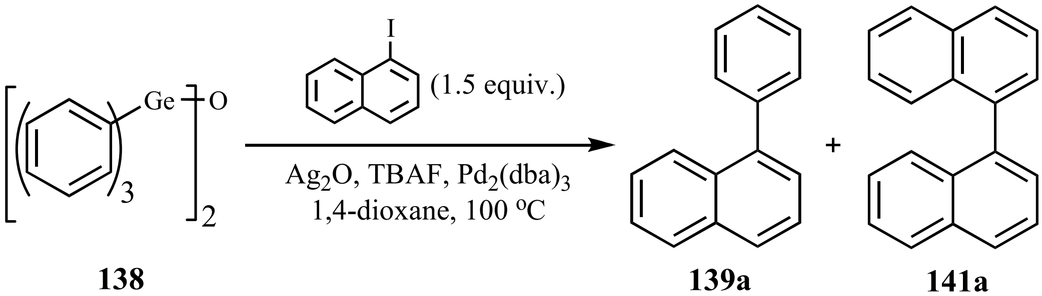
Scheme 45. Reaction of allyl(triphenyl)germane with TCNE and NH_4F followed by coupling with 1-iodonaphthalene.

On the basis of the results described above, the synthesis of oxo-germanium species of type **137**/**138** was attempted by replacing the fluoride sources with NaOH. The strong alkaline conditions were anticipated to perform a dual role: *i*) hydrolyze the corresponding Ph_3Ge^+–solvent adduct (see Scheme 43) to produce oxo-germanes **137**/**138**; and *ii*) hydrolyze the residual cyano-byproducts to the water-soluble carboxylate salts. As predicted, treatment of allylgermane **127** with TCNE in refluxing acetonitrile for 7 h, followed by addition of a 2 M NaOH solution afforded hexaphenyldigermoxane **138** as a crystalline solid (Scheme 46). The identity of **138** was confirmed by comparison of the spectroscopic data and meting point (179-181 °C, uncorrected) with commercially available $(Ph_3Ge)_2O$ (m.p. 181 °C).



Scheme 46. Reaction of allyl(triphenyl)germane with TCNE and NaOH. Formation of hexaphenyldigermoxane.

Next, we explored the ability of digermoxane **138** to participate in the Pd-catalyzed cross-coupling reactions under the conditions applied for the coupling of analogous diaryl(dimethyl)disiloxanes [Ag_2O/$Pd(PPh_3)_4$/TBAF/THF][197]. Thus, treatment of **138** with 1-iodonaphthalene (3 equiv.), Ag_2O, $Pd_2(dba)_3$, and TBAF in 1,4-dioxane at 100 °C afforded 1-phenylnaphthalene **139a** (54%) along with the reductive homocoupling byproduct **141a** (**139a**/**141a**, ~59:41) (Scheme 47). The yield was determined by GC-MS using 2-ethylnaphthalene as internal standard [internal response factor (IRF=0.703)], while the **139a**/**141a** ratio was calculated based on GC-MS of the crude reaction mixture. Moreover, treatment of **138** with 1-iodonaphthalene in toluene as solvent afforded **139a** in better yields (95%, organogermane as limiting reagent) and better **139a**/**141a** ratio (61:39).



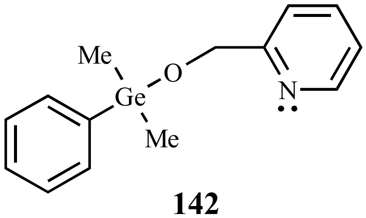
Scheme 47. Coupling of hexaphenyldigermoxane and 1-iodonaphthalene.

Although digermoxane **138** bears 6 phenyl groups among its two Ge centers, the obtained results suggested that presumably only one phenyl group is transferred from **138** in the Pd-catalyzed coupling with 1-iodonaphthalene. It seems that the development of the first methodology able to promote multi-transfers from an organogermanium precursor is still a very ambitious challenge. Additional implications regarding the participation of **138** in the Pd-catalyzed cross-coupling reaction will be discussed later.

Further efforts to efficiently engage digermoxane **138** in the coupling with aryl halides were undertaken employing the conditions described for the reaction of arylgermanium sesquioxides **19**[96] (see Figure 10 in section 1.2.1) with various aryl halides in the presence of base. However, treatment of **138** with 1-iodonaphthalene (3 equiv.) in the presence of aqueous NaOH and $Pd_2(dba)_3$ in 1,4-dioxane (100 ^{o}C) failed to efficiently produce biaryl **139a** (<5%).

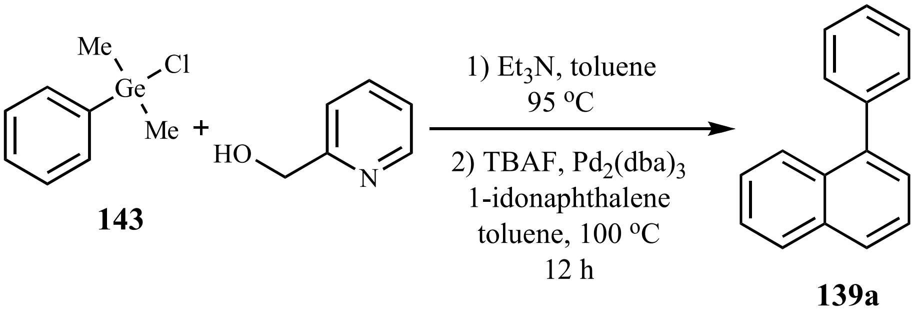
3.2.3. Arylchlorogermanes/TBAF/”moist” toluene. A promising combination for Pd-catalyzed germyl-Stille cross coupling

Given our interest in developing new organogermanium substrates for the Pd-catalyzed cross-coupling reaction, the synthesis of novel 2-(dimethyl(phenyl)germyloxy)pyridine **142** (Figure 21) was undertaken. Thus, treatment of the commercially available chloro(dimethyl)phenylgermane **143** with 2-(hydroxymethyl)pyridine in the presence of Et_3N (or other bases) in ethanol/reflux or toluene at 95 ^{o}C failed to afford the desired product **142**, but instead gave unchanged 2-(hydroxymethyl)pyridine and some unidentified byproducts. Nevertheless, treatment of **143** with 2-(hydroxymethyl)pyridine followed by the addition of TBAF (1.5 equiv.), 1-iodonaphthalene, and $Pd_2(dba)_3$ to the reaction mixture and stirring at 95 ^{o}C overnight afforded coupling product **139a** (detected by GC-MS) (Scheme 48). A subsequent reaction of germane **143** with 1-iodonaphthalene under similar conditions [TBAF/$Pd_2(dba)_3$/toluene/95 °C] without 2-(hydroxymethyl)-pyridine and Et_3N also afforded biaryl product **139a**, suggesting that the coupling was likely to happen through a reactive organogermane derived from chlorogermane **143**.



142

Figure 21. Structure of 2-(dimethyl(phenyl)germyloxy)pyridine.

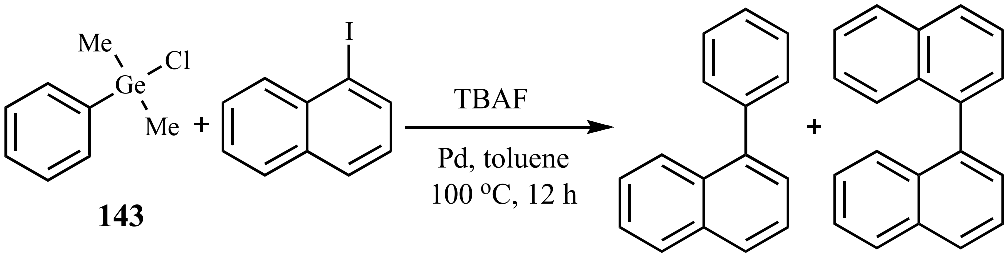


Scheme 48. Tandem alkoxylation/Pd-catalyzed coupling of chloro(dimethyl)phenylgermane and 1-iodonaphthalene.

3.2.3.1. Pd-catalyzed cross-coupling of chlorophenylgermanes

Motivated by the results with chloro(dimethyl)phenylgermane (**143**), optimization of the reaction parameters was performed. Thus, treatment of $PhGeMe_2Cl$ **143** with 1-iodonaphthalene in the presence of TBAF and tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] in toluene gave cross-coupling product **139a** in addition to the binaphthyl homocoupling byproduct **141a** (Table 11). The amount of TBAF was found to be crucial for the successful coupling (entries 1-5). At least 4 equiv. of TBAF were required to produce **139a** in maximum yield. Other Pd catalysts afforded **139a** in lower yields and a decreased ratio of **139a** to **141a** (entries 6-7). Replacing 1M TBAF/THF solution with neat TBAF·3H_2O also gave product **139a** (entry 8). Coupling in the presence of Me_4NF, CsF or NH_4F instead of TBAF failed to produce **139a**. The reaction also proceeded successfully at 80 °C (80%; 10:1) and 110 °C (93%; 10:1) as well as at reflux in benzene (90%; 10:1), requiring 12 h for the best results (entry 4).

Table 11. Effect of various reaction parameters on the efficiency of cross-coupling of chloro(dimethyl)phenylgermane with 1-iodonaphthalene.[a]



143 **139a** **141a**

Entry	Pd	TBAF[b]	139a [yield(%)][c]	139a/141a ratio[c]
1	$Pd_2(dba)_3$	1.0	19	1:1
2	$Pd_2(dba)_3$	2.0	61	9:1
3	$Pd_2(dba)_3$	3.0	79	17:1
4	$Pd_2(dba)_3$	4.0	93[d,e]	20:1
5	$Pd_2(dba)_3$	5.0	94	12:1
6	$Pd(OAc)_2$	4.0	58	5:2
7	$Pd(PPh_3)_4$	4.0	5	2:1
8	$Pd_2(dba)_3$	4.0[f]	70	6:1

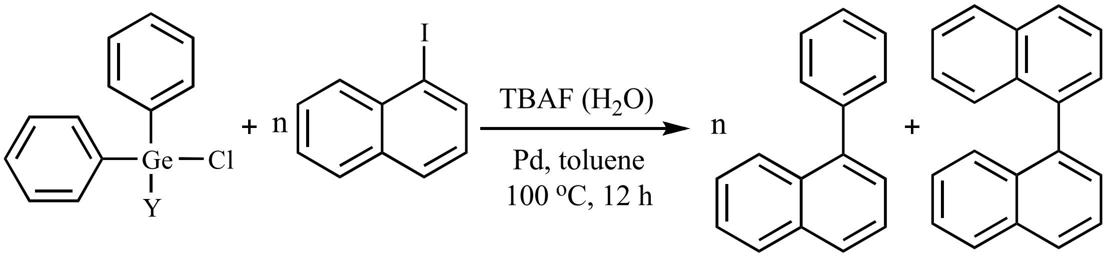
[a] Couplings were performed on 0.14 mmol scale of **143** (0.04 M) with 1.1 equiv of iodonaphthalene and 0.09 equiv of Pd catalyst. [b] Commercial 1M THF solution containing 5% of water, unless otherwise noted. [c] Determined by GC-MS of the crude reaction mixture. [d] Isolated yield. [e] After 4 h, 49% (8:1); 8 h, 78% (15:1). [f] With TBAF·3H_2O.

Toluene was the obvious solvent choice since attempts in DMSO (5%, 110 °C) or THF at reflux (0%) or dioxane at reflux (59%; 3:1) failed or afforded **139a** in lower yields. Higher yield for the coupling in dioxane than in THF may be attributable to the increased temperature of the reaction as well the difference in dielectric constant [7.58 for THF as compared to dioxane (2.21) and toluene (2.15)].[120] Bases such as NaOH [Pd(OAc)$_2$; dioxane/H_2O, 2:1] or KOSiMe$_3$ [Pd$_2$(dba)$_3$, toluene)], instead of TBAF, failed or were less efficient in promoting couplings.

3.2.3.2. Effect of added water on the coupling of chloro(phenyl)germanes with 1-iodonaphthalene

In order to examine the effect of additional chloro ligands on the Ge center, couplings of dichloro(diphenyl)germane **144** or chloro(triphenyl)germane **145** with iodonaphthalene were performed. Thus, treatment of **144** with 1.1 equiv. of iodide and TBAF (7 equiv.) gave **139a** (Table 12, entry 1). Coupling of **144** with 2.2 equiv of iodonaphthalene also resulted in total consumption of iodide to afford **139a** and **141a** (entry 2). Interestingly, couplings in toluene with addition of the *measured* amount of water (1 M TBAF/THF//H_2O; ~1:5 M/M) gave a higher yield of **139a** with a superior ratio of **139a**/**141a** (entries 3 *vs* 1 and 4 *vs* 2). An investigation of the coupling reactions with different amounts of water, revealed that addition of 100 μL of H_2O (~40 equiv.) gave optimal yields (entry 10). Two phenyl groups were efficiently transferred in the presence of excess iodide with the average efficiency of 89% (entry 4; yield is based upon two phenyl groups transferring from the chlorogermane reagent **144**). It is worth noting that halides are often used in couplings as limiting reagents to reduce formation of homocoupling byproducts and the yields are based on the halide components unlike herein.

Table 12. Cross-coupling of dichloro(diphenyl)germane and chloro(triphenyl)germane with 1-iodonaphthalene promoted by TBAF and TBAF/H_2O.



144 Y=Cl
145 Y=Ph

n=2 (for **144**)
n=3 (for **145**)

139a **141a**

Entry	germane	R-X (equiv.)	method[a]	139a [yield(%)][b]	139a/141a ratio
1	**144**	1.1	A	32[c] (30)	2.7:1
2	**144**	2.2	A	58 (55)	2.2:1
3	**144**	1.1	B	45 (42)	23:1
4	**144**	2.2	B	91 (89)	10:1
5	**145**	1.1	A	13[d] (12)	1:1.4
6	**145**	2.2	A	37 (35)	2:1
7	**145**	3.3	A	40 (39)	1.2:1
8	**145**	1.1	B	18 (17)	2.5:1
9	**145**	2.2	B	60 (60)	9:1
10	**145**	3.3	B	95[e] (88)	13:1

[a] Method A: Couplings were performed on 0.14 mmol scale of germane (0.04 M) with $Pd_2(dba)_3$ (0.09 equiv) and 7 equiv of TBAF (1M/THF). Method B: as in Method A with addition of H_2O (100 μL). [b] Based upon transferring two phenyl groups from **144** or three phenyl groups from **145**. Determined by GC-MS of the crude reaction mixture (isolated yields in parenthesis). [c] 26% and 31% with 6 and 8 equiv. of TBAF. [d] 11% and 14% with 6 and 8 equiv of TBAF. [e] 57% (3.8:1) with 50 μL H_2O; 82% (7:1) with 150 μL H_2O.

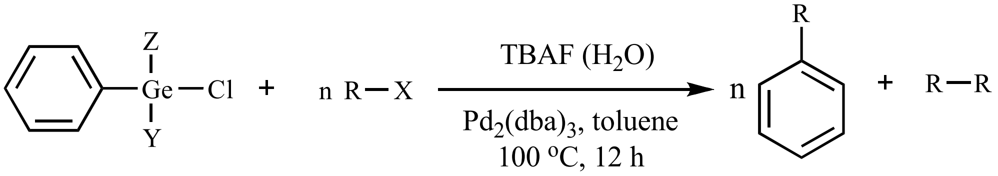
We were very fortunate to find that the couplings of chloro(triphenyl)germane **145** with 1.1, 2.2 or 3.3 equiv of iodonaphthalene proceeded with efficient transfer of up to three phenyl groups to give **139a** (entries 5-10). Again, yields and **139a**/**141a** ratios increased when wet toluene was used. Atom-efficient Stille cross-couplings of Ar_4Sn with aryl halides (**48**, Scheme 13, section 1.2.1.3), where all four substituents on tin participate in the carbon-carbon bond formation, are known.[80,129] Also, vinylpolysiloxanes (**49**, Scheme 14, section 1.2.1.3) were shown to transfer each of their vinyl groups during Pd-catalyzed couplings with aryl and alkenyl iodides in the presence of TBAF.[130] However, attempts to induce multiple transfer of the phenyl group during fluoride-promoted couplings of $(\text{allyl})_X\text{Ph}_{4-X}\text{Si}$ (x = 1 or 2) with aryl halides failed (**23** and **24**, Scheme 6, section 1.2.1.1).[105]

It is viable that the germanium species with extra halogen ligands formed after each transmetallation cycle is rendered more reactive to efficiently transfer a second or third phenyl group from the Ge atom. Water might play multiple roles in enhancing the efficiency of the couplings as was found with organosilanes, including the formation of the reactive hydroxypalladium intermediates.[91,125,198] For example, the hydration level of Cs_2CO_3 and CsOH were found to be a decisive factor during the coupling of the aryl(dimethyl)silanols with aryl halides.[199] Also, Denmark and Sweis showed that water was a critical additive in the fluoride promoted reaction of alkenylsilanols with phenyl nonaflate.[200] In addition, the fluorination of the bulky chlorogermanes may be accelerated by the addition of water as was reported for hindered chlorosilanes.[201]

Couplings of **144** or **145** with other aryl, alkenyl, and heterocyclic iodides and bromides (using 2.2 or 3.3 equiv of halides, respectively) promoted by TBAF/H_2O are presented in Table 13 (entries 1-14)**.** Reactions of germanes **144** or **145** with reactive 4-iodoacetophenone produced **139d** in low yields in addition to large quantities of the reductive homocoupling byproduct **141d**. However, coupling of the less reactive 4-bromoacetophenone at higher temperature (115 °C) resulted in better yields and improved **139d**/**141d** ratios (entries 5 *vs* 4 and 12 *vs* 11). Treatment of $PhGeCl_3$ **146** with halides and TBAF/toluene or wet toluene also afforded coupling products **7** (entry 15-22), although it has been reported that fluoride ion did not promote the couplings of $PhGeCl_3$

with aryl halides.[95] It appears that reactivity of the chlorogermanes increases with the number of halogen ligands on the Ge center (**145 < 144 < 146**). As expected,[94] coupling attempts with Ph_4Ge failed, and thus emphasize the need for at least one labile heteroatom ligand at the Ge center. The necessity of two halogen ligands had been proposed for nucleophilic activation by F^- or OH^- ions.[106]

Table 13. Cross-coupling of chloro(phenyl)germanes with halides.[a]



144 Y=Cl, Z=Ph n=2 (for **144**)
145 Y=Z=Ph n=3 (for **145**)
146 Y=Z=Cl n=1 (for **146**)

139a-f **141a-f**

Entry	germane	R-X	Product	yield (%)[b]	139/141 ratio
1	**144**	1-Bromonaphthalene[c]	**139a**	54 (48)	7.2:1
2	**144**	(*4*)CH_3OPhI	**139b**	86[d] (85)	9.8:1
3	**144**	(*3*)CF_3PhI	**139c**	70 (68)	3.4:1
4	**144**	(*4*)CH_3COPhI	**139d**	12 (10)	3:2
5	**144**	(*4*)$CH_3COPhBr$	**139d**	26[d] (21)	99:1
6	**144**	PhCH=CHBr	**139e**	8[e,g] (5)	1:3
7	**144**	2-Iodo-5-Me-thiophene	**139f**	13[e] (6)	2:3
8	**145**	1-Bromonaphthalene	**139**[a]	24	1.4:1
9	**145**	(*4*)CH_3OPhI	**139b**	48[f] (40)	4:1
10	**145**	(*3*)CF_3PhI	**139c**	48	3:2
11	**145**	(*4*)CH_3COPhI	**139d**	3	1:20
12	**145**	(*4*)$CH_3COPhBr$	**139d**	24[d]	1:1
13	**145**	PhCH=CHBr	**139e**	3[g]	1:8
14	**145**	2-Iodo-5-Me-thiophene	**139f**	3[g]	2:3
15	**146**	1-Iodonaphthalene	**139a**	99[h] (96)	35:1
16	**146**	1-Bromonaphthalene	**139a**	90[g] (82)	99:1
17	**146**	(*4*)CH_3OPhI	**139b**	88[g] (80)	10:1
18	**146**	(*3*)CF_3PhI	**139c**	93 (87)	9:1
19	**146**	(*4*)CH_3COPhI	**139d**	99 (88)	99:1
20	**146**	(*4*)$CH_3COPhBr$	**139d**	91	99:1
21	**146**	PhCH=CHBr	**139e**	30[e,g] (28)	3:1
22	**146**	2-Iodo-5-Me-thiophene	**139f**	48[e,g] (35)	3:2

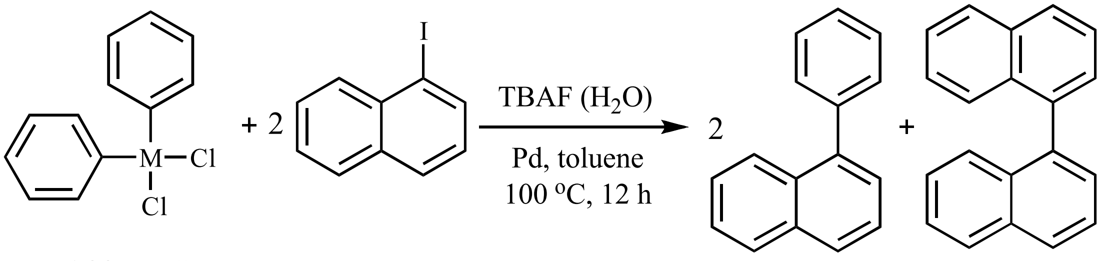
[a] Couplings were performed on 0.14 mmol scale of germanes (0.04 M) with 0.09 equiv of Pd catalyst, 1.1 (**146**), 2.2 (**144**) or 3.3 (**145**) equiv of halides and TBAF/(1 M/THF, 7 equiv)/water (100 μL). [b] Based upon transferring of one, two or three phenyl groups from **146**, **144** or **145**, respectively. Determined by GC-MS of the crude reaction mixture (isolated yields in parenthesis). [c] Coupling with 1-chloronaphthalene failed. [d] 115 °C. [e] Biphenyl was also produced (~25-50%). [f] 28 h. [g] Without H_2O. [h] 88% (81%, 19:1) without H_2O.

3.2.3.3. Comparison with chloro(phenyl)stannanes and chloro(phenyl)silanes

Since organostannanes and organosilanes have been known to display much higher reactivity towards the Pd-catalyzed cross-coupling and reports in literature on the ability of chlorosilanes to undergo coupling were inconsistent, we performed a comparative study of the coupling efficiency of chloro(phenyl)-germanes, -silanes, and –stannanes under our conditions [TBAF/ "moist" toluene]. In order to establish reaction protocols, couplings of dichloro(diphenyl)germane **144**, -silane **147**, and -stannane **148** with 1-iodonaphthalene (2 equiv.) in the presence of $Pd_2(dba)_3$ were attempted under different conditions and the results summarized in Table 14.

We found that coupling with dichloro(diphenyl)germane **144** required heating at 100 °C for 15 h to afford biaryl **139a** in good yields (86%; based on the transfer of two phenyl groups, 172% total yield of 1-phenylnaphthalene). Analogous reaction conditions promoted the coupling of dichloro(diphenyl)silane **147** (93%) and dichloro(diphenyl)stannane **148** (99%) after only 5 h and 2 h respectively (Table 14, entry 4). The reaction of **144**, **147**, and **148** at lower temperature (60 °C and 80 °C) indicated a higher reactivity of organostannane **147** with respect to its silicon and germanium counterparts (entry 4, footnotes). Moreover, the smaller amounts of TBAF required for the efficient coupling of **148** or **147** with 1-iodonaphthalene in toluene also indicated a faster activation of stannanes or silanes towards transmetallation. Additional experiments utilizing an alternative fluoride source (entry 5) and different solvents (entries 6 and 7) supported the described observations. Noteworthy, the coupling of silane **147** under our optimized conditions constitutes the first example of the cross-coupling of halosilanes from which every phenyl groups has been transferred.

Table 14. Comparison of the couplings of dichloro(diphenyl)-germane, -silane, and -stannane with 1-iodonaphthalene.



144 M=Ge
147 M=Si
148 M=Sn

139a

141a

Entry	**TBAF** [b]	**From 144 (15 h)**		**From 147 (5 h)**		**From 148 (2h)**	
		139a Yield (%)[c]	**139a/141a ratio**[d]	**139a Yield (%)**[c]	**139a/141a ratio** [d]	**139a Yield (%)**[c]	**139a/141a ratio** [d]
1	1.0	--	--	--	--	14	99:1
2	3.0	7	20:1	3	1:0	63	99:1
3	5.0	34	17:1	72	20:1	93	99:1
4	7.0	86 [e]	10:1	93 [f]	10:1	99 [g]	99:1
5	7.0 [h]	80	4:1	95	33:1	96	99:1
6	7.0 [i]	48	6:1	56	2:1	95	Pure
7	7.0 [j]	94	20:1	81	19:1	97	Pure

[a] Couplings were performed on 0.14 mmol scale of organometallics (0.04 M) with 2.0 equiv. of 1-iodonaphthalene and 0.05 equiv. of Pd catalyst. [b] Commercial 1M THF solution containing 5% H_2O, unless otherwise noted. [c] Based upon transferring two phenyl groups from **144**, **147-148**. Determined by GC-MS of the crude reaction mixture. [d] Molar ratio. [e] At 60 °C (19%, 10:1) and at 80 °C (43%, 4:1). [f] At 60 °C (43%, 30:1) and at 80 °C (91%, 15:1). [g] At 60 °C (87%, pure) and at 80 °C (94%, pure). [h] TBAF·$3H_2O$. [i] THF (60 °C). [j] Dioxane (80 °C).

3.2.3.4. Mechanistic implications

During the optimization of the cross-coupling reactions between **143** ($PhMe_2GeCl$) and 1-iodonaphthalene (Table 11) it became obvious that the coupling outcome strongly depended on TBAF/organogermane ratios. TBAF most likely facilitates the coupling by generating the more reactive hypervalent fluorogermanium species and the reactivity of these hypervalent Ge species could be superior in toluene due to weak solvation. Hypervalent (fluoro pentacoordinated) tin[81,114,115] and silicon[121-123,202] species has been established as active intermediates in Pd-catalyzed coupling reactions (see section 1.2.1.2).

In order to get insight about the role hypervalent germanium species play in the coupling of chlorogermanes **143-146**, we have studied their interaction with TBAF. Initial experiments were conducted using chloro(dimethyl)phenylgermane **143**. Thus, mixing of **143** (32.2 mg, 0.15 mmol) and TBAF (1.5 equiv. 1 M solution in THF) in benzene-d_6 at room temperature resulted in the substitution of the chlorine ligand by the fluoride ion and formation of $PhMe_2GeF$. The observed septet centered at -194.6 ppm (^{19}F NMR) with the coupling to six equivalent protons of the two methyl groups ($^3J_{F\text{-}H}$ ~ 6.0 Hz, spectrum *a*, Figure 22) had a chemical shift in agreement with the literature value (-196.0) for the analogous fluorodimethylgermane.[106,127] Heating the sample at 50 °C for 3 h resulted in broadening of the signal at -194.6 ppm and appearance of a major broad peak centered at -150.8 ppm suggesting an equilibrium between $PhMe_2GeF$ and $PhMe_2GeF(X)^-$ (X=Cl or OH) species (spectrum *b*). The pentavalent difluorogermanate $Ph(Me)_2GeF_2^-$ appeared as a minor peak at -126.4 (septet, $^3J_{F\text{-}H}$ ~5.8 Hz) is agreement with reported chemical shift for the analogous hypervalent difluorotriphenylgermana **46**[128] (see Scheme 11, section 1.2.1.2). Overnight heating resulted both in the additional broadening of the peaks at -150.8 ppm and -194.3 ppm and in increasing intensity of signal(s) at -126.4 ppm (spectrum *c*). Washing the sample with D_2O resulted in the reappearance of the septet at -194.3 ppm [$PhMe_2GeF$] as the sole signal (spectrum *d*).

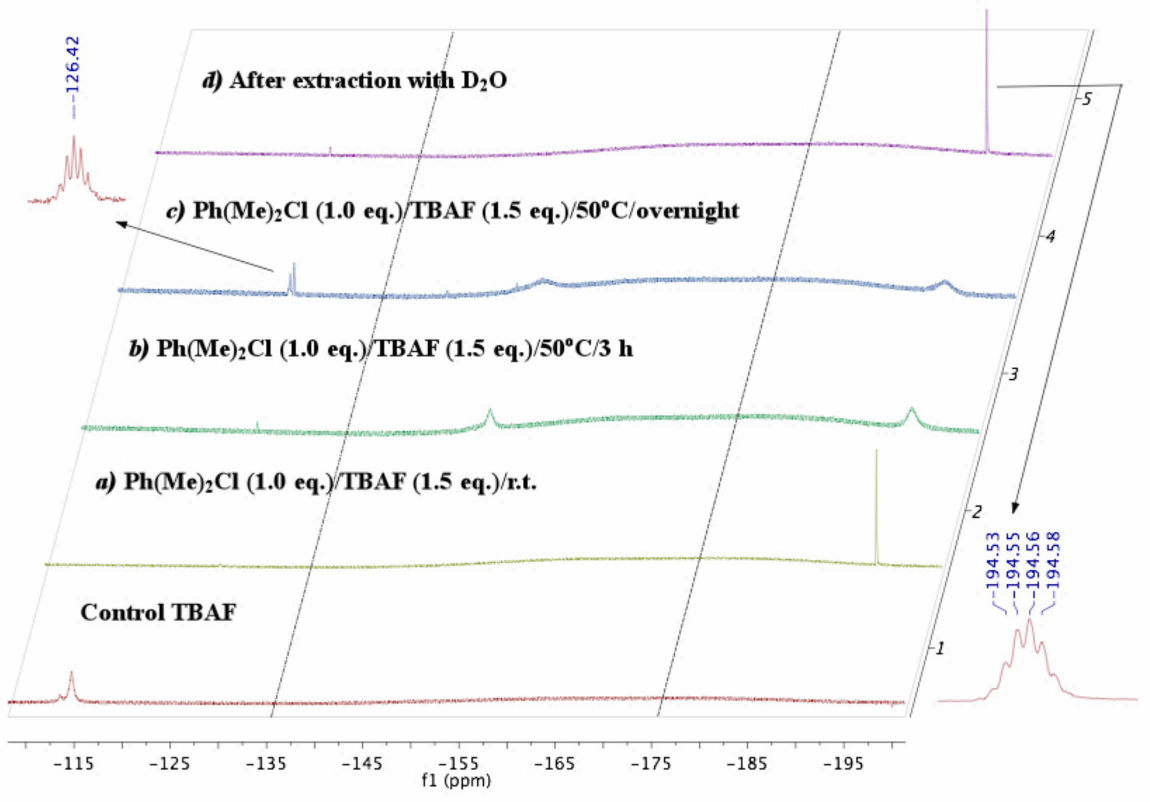


Figure 22. ^{19}F NMR analyses of the reaction of chloro(dimethyl)phenylgermane with TBAF in benzene-d_6.

A similar treatment of chlorotriphenylgermane **145** (68 mg, 0.20 mmol) with TBAF in benzene-d_6 gave comparable pattern of peaks as that of **143**. As expected, reactions of di- and trichlorogermanes **144** and **146** with TBAF led to more complex mixtures. Nevertheless, treatment of dichlorogermane **144** produced difluorinated tetravalent germane Ph_2GeF_2 showing a signal -163.88 ppm in agreement with the value reported by Spivey for analogous difluoride.[106]

To correlate ease of formation, spectroscopic characteristics, and reactivities in the fluoride-promoted couplings of the hypervalent germanium species with those of the corresponding silanes and stannanes, reactions of the fluoride ion with chloro(triphenyl)silane **149** and chloro(triphenyl)stannane **150** in benzene-d_6 were also explored. Thus, heating of chlorostannane **150** (71.1 mg, 0.18 mmol) with TBAF (1.5 equiv.) resulted in the appearance on ^{19}F NMR spectra of two singlets at -158.6 and -159.5 ppm accompanied by F-Sn satellite signals (spectrum *a*, Figure 23). Further addition of TBAF (1.5 equiv.) resulted in the formation of difluorotriphenylstannate **35** which resonated as a sharp singlet at -160.5 ppm with satellite peaks ($^1J_{^{19}F-^{119}Sn}$=2034.2 Hz, $^1J_{^{19}F-^{117}Sn}$=1940.2 Hz) in close agreement with the reported values for the isolated **35**[114] (spectrum *b*). Treatment of chlorosilane **149** with TBAF (1.5 equiv.) produced a broad peak for Ph_3SiF Although only slow equilibration between Ph_3Si-F[201] at -168.39 ppm which exists in equilibrium with $Ph_3SiF_2^-$ **39** (-94.5 ppm) (spectrum *c*). The characteristic signal[121] for the pentavalent complex **39** was, however, clearly observed with 3 equiv. of TBAF after additional heating [δ -94.6 ppm ($^1J_{^{19}F-^{29}Si}$=255.1 Hz) and -95.3 ppm ($^1J_{^{19}F-^{29}Si}$=255.1 Hz)] (spectrum *d*). In contrast, chlorogermane **145**, under similar conditions, produced only a small amount of the pentavalent intermediate **151** (-154.7 ppm) in equilibrium with the monofluorinated tetravalent compound **45** (-201.6 ppm, spectrum *e*, see section 1.2.1.2). An additional portion of TBAF and prolonged heating resulted in further broadening of the signal(s) but also in dissapearance of the signal from **45** (spectrum *f*). It appears that Ph_3SnCl is more susceptible than its silicon and germanium counterparts to form the reactive pentavalent complex **35**, even at low concentrations of fluoride ions. On the other hand, the silicon analogue **149**, although it requires higher concentration of TBAF to afford the corresponding pentavalent complex **39** than the tin counterpart, is more prone to form hypervalent species than the analogous organogermane precursor. Since substrates **144**, **147**, and **148** undergo coupling under similar conditions (sovent/TBAF; Table 14) but require divergent reaction conditions (time/temperature), these results might suggest that differences in their coupling efficiencies might be related to their ability to generate reactive hypervalent intermediates upon fluoride activation.

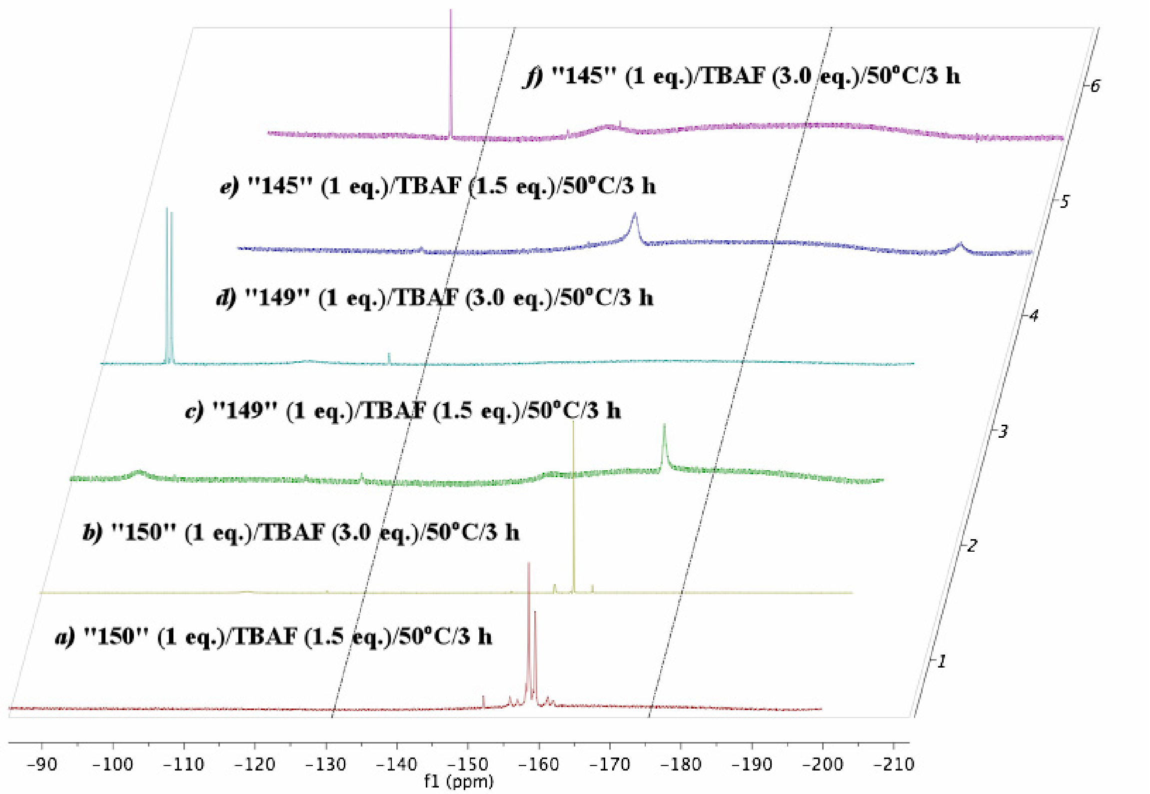
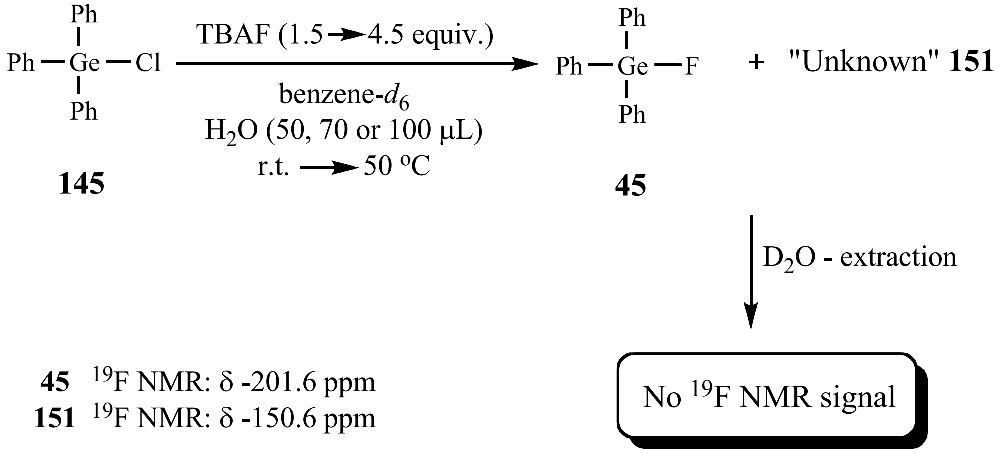


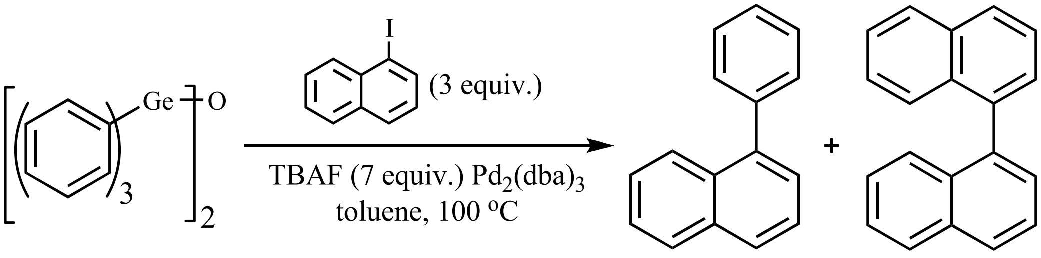
Figure 23. ^{19}F NMR analysis of the reaction of chloro(triphenyl)germane, silane, and stannane with TBAF in benzene-d_6.

To investigate the effect of the addition of water on the coupling of chlorotriphenylgermane **145** (68 mg, 0.20 mmol) with TBAF (1.5 equiv) in benzene-d_6 (2 mL) in the presence of various amounts of water (25, 50, and 100 μL) were analyzed by ^{19}F NMR (Scheme 49). It seems that increasing the amount of water resulted in the faster formation of sharper and higher peak at -202.5 ppm for Ph_3GeF (**45**; r.t. and 1.5 equiv. TBAF). Interestingly, fluorination of the bulky chlorosilanes has been reported to be accelerated by the addition of water.[201] Heating of the reaction mixture at 50 °C produced also the hypervalent germanium compound **151** (-154.8 ppm) matching the results from the analogous experiments without additional water added (Figure 23, spectrum *e*). Overnight stirring with 4.5 equiv. of TBAF and extraction of the benzene slution with D_2O, resulted in the disappearance of the ^{19}F signals. It is likely that the putative hypervalent germanium species **151**, generated during the study, were hydrolyzed and/or transformed into triphenylgermanol **137** or hexaphenyldigermoxane **138** derivatives.



Scheme 49. ^{19}F NMR study of the effect of added water in the reaction of chloro(triphenyl)germane with TBAF.

To establish the role of digermoxane **138** in the coupling of chlorogermane **145** in toluene, the reaction of **138** with 1-iodonaphthalene was attempted under our optimized conditions (Table 11). Thus, treatment of **138** with 1-iodonaphthalene (3 equiv.) in the presence of TBAF (7 equiv.) and $Pd_2(dba)_3$ in toluene afforded biaryl product **139a** in 68% yield (Scheme 50; the yield was determined by GC-MS using 2-ethylnaphthalene as internal standard and **138** as limiting reagent) in addition to homocoupling byproduct. Analogous coupling of **138** with 3 or 6 equiv. of 1-iodonaphthalene also afforded **139a** (with total yields not exceeding the theoretical 100% yield which would indicate multiple transfer of phenyl group from **138**). All attempts of changing the reaction conditions between **138** and 1-iodonaphthalene (e.g. wet toluene, THF or 1,4-dioxane at reflux as solvents, and Ag_2O/TBAF and NaOH as base) failed or give **139a** in lower yield. It seems that **138** although might be formed during the coupling of chlorogermane **145**, and can contribute to the overall yield of the cross-coupling, it is not formed on a major reaction pathway but rather on a deactivation pathway.

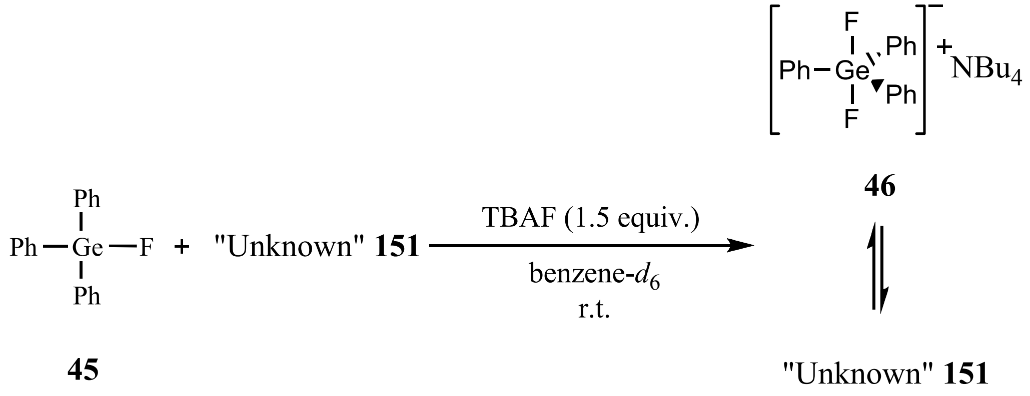


138 **139a** **141a**

Scheme 50. Coupling of hexaphenyldigermoxane and 1-iodonaphthalene.

To confirm the structure of the postulated intermediates generated during the reaction of chloro(triphenyl)germane **145** with TBAF, and to study their role in the fluoride-promoted coupling with halide in “moist” toluene, the independent synthesis of fluoro(triphenyl)germane **45** was undertaken. Thus, treatment of **145** with tetramethylammonium fluoride[127] (Me_4NF) in dry CH_2Cl_2 at reflux afforded **45** (-201.9 ppm; see Scheme 11, section 1.2.1.2) along with the unknown compound **151** (-145.8ppm, Scheme 51). Moreover, slow conversion of **45** to **151** was observed when the stability of **45** was monitored by ^{19}F NMR during different periods of time. Nevertheless, treatment of the isolated sample of **45**/**151** (~3:1, ^{19}F NMR) with TBAF (1.5 equiv.) in benzene-d_6 at room temperature resulted in the complete dissapearance of the signal at -

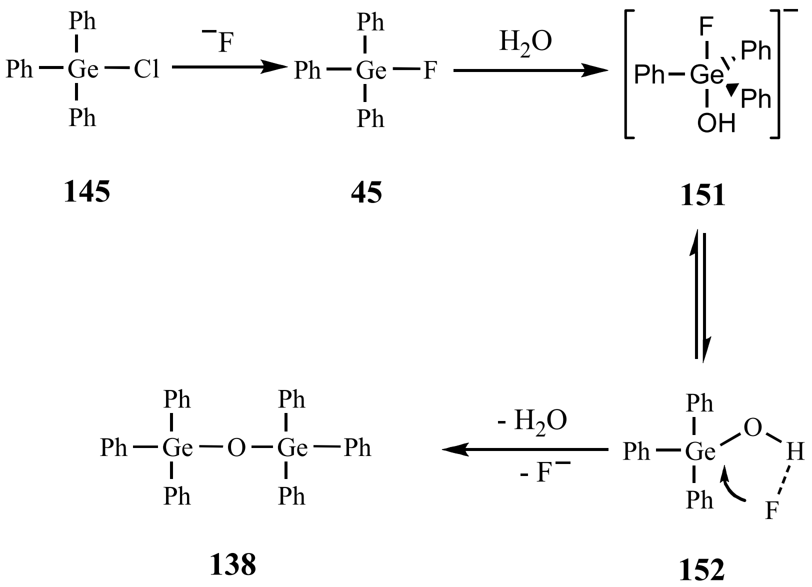
201.9 ppm (**45**), broadening of the signal at -145.8 ppm (**151**) and appearance of a new broad signal around -117.0 ppm. These results might suggest that the unknown species **151** are in equilibrium with the corresponding hypervalent difluorogermanate species **46** (δ ~ -117 ppm; see Scheme 11, section 1.2.1.2).[128]



45 ^{19}F NMR: δ -201.6 ppm
46 ^{19}F NMR: around δ -117 ppm
151 ^{19}F NMR: δ -150.6 ppm

Scheme 51. ^{19}F NMR study of the effect TBAF to a mixture of fluoro(triphenyl)germane and unknown compound **151**.

Based on our results, we propose that the coupling of chloro(triphenyl)germane **145** occurs via the formation of fluoro(triphenyl)germane **46** which generates unknown compound **151** upon hydrolysis. The hydrolysis of compound **46** could be accelerated by the presence of water either from TBAF (~5% in 1 M/THF solution) or from the *measured* amount added (Table 12). If the aryl-Pd complex(es) is not present in the reaction mixture in sufficient amount (e.g. with less reactive aryl bromides or chlorides), two molecules of the unknown **151** could condense eliminating fluoride and water to afford less reactive hexaphenyldigermoxane **138**. Therefore, the structure of the unknown intermediate **151** has been proposed as a reactive pentavalent fluoro(hydroxo)triphenylgermanate which would be in equilibrium with a hydrogen-bonded germanol **152** (Scheme 52). It is worth pointing out that similar reactive intermediates have been proposed by Denmark as reactive intermediates during the coupling of vinyl silanols promoted by fluoride ions.[125]



Scheme 52. Proposed pathway for the activation of chloro(triphenyl)germane with TBAF.

4. EXPERIMENTAL SECTION

4.1. General procedures

The ^1H (Me_4Si, 400 MHz), ^{13}C (Me_4Si, 100.6 MHz), and ^{19}F (CCl_3F, 376.4 MHz) NMR spectra were determined in $CDCl_3$ unless otherwise stated. Mass spectra (MS) were obtained by atmospheric pressure chemical ionization (APCI) or electro-spray ionization (ESI) techniques. Reagent grade chemicals were used and solvents were dried using a solvent purification system. TLC was performed on Merck kieselgel 60-F_{254} and products were detected with 254 nm light or by development of color with I_2. Merck kieselgel 60 (130-400 mesh) was used for column chromatography. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Purity and identity of the products (crude and/or purified) were also established using a Hewlett-Packard (HP) GC/MS (EI) system with a HP 5973 mass selective detector [capillary column HP-5MS (30 m x 0.25 mm)] or a reverse phase (RP)-HPLC/MS (APCI) system (C_{18} column).

4.2 Synthesis

1-(2,3,5-Tri-*O*-acetyl-*β*-D-arabinofuranosyl)-5-[(*Z*)-2-(triphenylgermyl)ethenyl]-uracil (*Z*-75).

Method A. Thermally-induced radical hydrogermylation of the protected 5-ethynyluridine analogues. In a round-bottomed flask, the starting material **74** (50 mg, 0.13 mmol) was added to freshly distilled toluene (6 mL) and the suspension was stirred and degassed with N_2 for 40 min. The mixture was then pre-heated at 80 °C and Ph_3GeH (50 mg, 0.16 mmol) was added followed by 1,1'-azobis(cyclohexanecarbonitrile) (4 mg, 0.02 mmol). The temperature was increased to 90 °C and the solution was stirred until **74** was completely consumed (TLC). The volatiles were removed in vacuo and the oily residue was chromatographed (hexanes/EtOAc, 2:3) to give a separable mixture of *Z*-**75** (31.5 mg, 36%) and **76** (10.5 mg, 12%). ^{1}H NMR δ 1.99 (s, 3H, Ac-*Me*), 2.09 (s, 3H, Ac-*Me*), 2.11 (s, 3H, Ac-*Me*), 3.70 (dd, $^{2}J_{H5''-H5'}$=13.7 Hz, $^{3}J_{H5''-H4'}$=7.7 Hz, 1H, H5''), 3.91-3.98 (m, 2H, H4' and H5'), 4.97 (dd, $^{3}J_{H3'-H4'}$=3.2 Hz, $^{3}J_{H3'-H2'}$=2.0 Hz, 1H, H3'), 5.27 (dd, $^{3}J_{H2'-H1'}$=4.1 Hz, $^{3}J_{H2'-H3'}$=1.9 Hz, 1H, H2'), 5.71 (d, $^{3}J_{H1'-H2'}$=4.1 Hz, 1H, H1'), 6.56 (d, $^{3}J_{V1-V2}$=13.5 Hz, 1H, vinyl 1), 7.08 (d, $^{4}J_{H6-V2}$=1.0 Hz, 1H, H6), 7.36 (m, 10H, GePh_3 + vinyl 2), 7.52 (m, 6H, GePh_3), 8.30 (br. s, 1H, NH). ^{13}C NMR δ 20.38, 20.65, 20.72 (Ac-*Me*), 62.31 (C5'), 74.57 (C2'), 76.10 (C3'), 79.82 (C4'), 84.37 (C1'), 113.39 (C5), 128.35 (GePh_3 x 6), 129.11 (GePh_3 x 3), 131.67 (vinyl 1), 134.80 (GePh_3 x 6), 136.39 (C6), 136.44 (GePh_3 Q x 3), 138.20 (vinyl 2), 148.57 (C2), 161.28 (C4), 168.45, 169.36, 170.24 (Ac-*C*=*O*). MS (APCI^{+}) *m*/*z* 700.9 [MH]$^{+}$ based on ^{74}Ge.

Method B. Et_3B-induced radical hydrogermylation of 5-ethynyl protected uridine analogues. Placed in a screw-capped glass tube, a 1M solution of Et_3B in THF (140 μL, 0.14 mmol) was added to a solution of **74** (50.0 mg, 0.127 mmol) and Ph_3GeH (43.0 mg, 0.14 mmol) in dry THF (5 mL) at -78 °C. The resulting solution was stirred for 3 hours at -78 °C and TLC analysis showed appearance of a less polar spot and remaining **74**. The reaction mixture was slowly warmed up to -60 °C and was stirred for another 1.5 h. The volatiles were removed under vacuum and the resulting crude was chromatographed (hexanes/EtOAc, 2:3) to give *Z*-**75** (42.0 mg, 47%), with identical data to the reported above.

Treatment of **74** (49.0 mg, 0.12 mmol) with Ph_3GeH (42.0 mg, 0.14 mmol) by Method B at 0 °C for 6 h gave an unseparable mixture of **75** and **76** (39.0 mg; **75**/**76**

~59:41 based on ^{1}H NMR of the mixture). Recrystallyzation from a hexane/Et_2O mixture gave **75** as a white powder (23.0 mg, 26%).

1-(2,3,5-Tri-*O*-acetyl-*β*-D-arabinofuranosyl)-5-[2-(triphenylgermyl)acetyl]uracil (76). ^{1}H NMR δ 1.92 (s, 3H, Ac-*Me*), 2.150 (s, 3H, Ac-*Me*), 2.154 (s, 3H, Ac-*Me*), 3.48 (d, $^3J_{H8a\text{-}H8b}$=9.3 Hz, 1H, H8a), 4.19 (d, $^3J_{H8b\text{-}H8a}$=9.3 Hz, 1H, H8b), 4.16-4.21 (m, 1H, H4'), 4.36 (dd, $^2J_{H5''\text{-}H5'}$=12.1 Hz, $^3J_{H5''\text{-}H4'}$=4.7 Hz, 1H, H5''), 4.46 (dd, $^2J_{H5'\text{-}H5''}$=12.1 Hz, $^3J_{H5'\text{-}H4'}$=4.9 Hz, 1H, H5'), 5.14 (dd, $^3J_{H3'\text{-}H4'}$=3.4 Hz, $^3J_{H3'\text{-}H2'}$=1.6 Hz, 1H, H3'), 5.35 (dd, $^3J_{H2'\text{-}H4'}$=4.1 Hz, $^3J_{H2'\text{-}H3'}$=1.6 Hz, 1H, H2'), 6.24 (d, $^3J_{H1'\text{-}H2'}$=4.1 Hz, 1H, H1'), 7.32-7.42 (m, 2.25H, Ge*Ph*$_3$), 7.50-7.57 (m, 1.5H, Ge*Ph*$_3$), 8.10 (s, 1H, H6), 8.49 (bs, 1H, NH). ^{13}C NMR δ 20.26, 20.60, 20.62 (Ac-*Me*), 32.84 (C8), 62.26 (C5'), 74.43 (C2'), 76.42 (C3'), 80.64 (C4'), 83.77 (C1'), 113.20 (C5), 128.23 (Ge*Ph*$_3$ x6), 129.35 (Ge*Ph*$_3$ x 3), 135.00 (Ge*Ph*$_3$ x 6), 135.11 (Ge*Ph*$_3$ Q x 3), 146.07 (C2), 148.33 (C6), 159.92 (C4), 168.64, 169.46, 170.66 (Ac-*Me*), 194.03 (C7-ketone). MS (APCI$^+$) *m*/*z* 716.9 (MH$^+$ for **76**, 33%) based on ^{74}Ge.

1-(2,3,5-Tri-*O*-acetyl-*β*-D-arabinofuranosyl)-5-[(*E*/*Z*)-2-(trimethylgermyl)ethenyl]-uracil (*E*/*Z*-77). A solution of **74** (49.6 mg, 0.126 mmol) and Me_3GeH (29.9 mg, 29.6 μL, 0.252 mmol) in dry THF (5 mL) was treated according to Method B (with injection of Me_3GeH into the reaction mixture via syringe and progressive warming from 0 °C to 25 °C) for 8 h. The volatiles were removed under reduced pressure and the residue was chromatographed (hexanes/EtOAc, 2:3) to give *E*/*Z*-**77** (22.0 mg, 33%, *E*/*Z* 39:61). ^{1}H NMR δ 0.26 (s, 5.5H, Ge*Me*$_3$-*Z*), 0.28 (s, 3.5H, Ge*Me*$_3$-*E*), 2.02 (s, 3H, Ac-*Me E*+*Z*), 2.12 (s, 1.83H, Ac-*Me*-*Z*), 2.15 (s, 1.17H, Ac-*Me*-*E*), 2.16 (s, 1.83H, Ac-*Me*-*Z*), 2.17 (s, 1.17H, Ac-*Me-E*), 4.19-4.25 (m, 1H, H4'-*E*+*Z*), 4.34 (dd, $^2J_{\mathrm{H5''-H5'}}$=11.9 Hz, $^3J_{\mathrm{H5''-H4'}}$=6.2 Hz, 0.61H, H5''-*Z*), 4.37-4.45 (m, 0.39H, H5''-*E*), 4.44 (dd, $^2J_{\mathrm{H5'-H5''}}$=11.9 Hz, $^3J_{\mathrm{H5'-H4'}}$=4.2 Hz, 0.61H, H-5'*Z*), 4.52 (dd, $^2J_{\mathrm{H5'-H5''}}$=11.9 Hz, $^3J_{\mathrm{H5'-H4'}}$=6.2 Hz, 0.39H, H5'-*E*), 5.11 (dd, $^3J_{\mathrm{H3'-H4'}}$=3.8 Hz, $^3J_{\mathrm{H3'-H2'}}$=1.4 Hz, 0.61H, H3'-*Z*), 5.15 (dd, $^3J_{\mathrm{H3'-H4'}}$=3.4 Hz, $^3J_{\mathrm{H3'-H2'}}$=1.6 Hz, 0.39H, H3'-*E*), 5.44-5.48 (m, 1H, H2'-*E*+*Z*), 6.10 (d, $^3J_{\mathrm{V1-V2}}$=13.8 Hz, 0.61H, vinyl 1-*Z*), 6.24 (d, $^3J_{\mathrm{H1'-H2'}}$=3.8 Hz, 0.61H, H1'-*Z*), 6.33 (d, $^3J_{\mathrm{H1'-H2'}}$=4.0 Hz, 0.39H, H1'-*E*), 6.60 (d, $^3J_{\mathrm{V1-V2}}$=18.9 Hz, 0.39H, vinyl 1-*E*), 6.80 (d, $^3J_{\mathrm{V2-V1}}$=19.0 Hz, 0.39H, vinyl 2-*E*), 6.98 (dd, $^3J_{\mathrm{V2-V1}}$=13.8 Hz, $^4J_{\mathrm{V2-H6}}$=0.9 Hz, 0.61H, vinyl 2-*Z*), 7.45 (d, $^4J_{\mathrm{H6-V2}}$=0.8 Hz, 0.61H, H6-*Z*), 7.59 (s, 0.39H, H6-*E*), 8.97 (br. s, 0.39H, NH-*E*), 9.09 (br. s, 0.61H, NH-*Z*). ^{13}C NMR δ -1.70 (GeMe_3-*E*), -0.23 (GeMe_3-*Z*), 20.53, 20.59, 20.79, 20.87, 20.92 (Ac-*Me*), 62.67 (C5'-*E*), 63.16 (C5'-*Z*), 74.69 (C2'-*E*), 74.76 (C2'-*Z*), 76.44 (C3'-*E*), 76.49 (C3'-*Z*), 80.43 (C4'-*Z*), 80.76 (C4'-*E*), 84.55 (C1'-*E*+*Z*), 112.90 (C5-*E*), 114.19 (C5-*Z*), 132.14 (vinyl 1-*E*), 133.62 (vinyl 2-*E*), 134.30 (vinyl 2-*Z*), 136.10 (C6-*Z*), 136.36 (C6-*E*), 137.55 (vinyl 1-*Z*), 149.18 (C2-*E*), 149.56 (C2-*Z*), 161.81 (C4-*E*), 162.17 (C4-*Z*), 168.63, 168.73, 169.69, 169.78, 170.50 (Ac-*C*=*O*). MS (APCI$^+$) *m*/*z* 514.9 [MH]$^+$ based on ^{74}Ge.

1-(2,3,5-Tri-*O*-acetyl-*β*-D-arabinofuranosyl)-5-*Z*-[2-(tributyl-germyl)ethenyl]uracil (*E*/*Z*-78). A solution of **74** (50.0 mg, 0.13 mmol) and $\mathrm{Bu_3GeH}$ (63.7 mg, 69.5 μL, 0.26 mmol) in dry THF (5 mL) was treated according to Method B (with stirring at 0 °C and progressively warming to ambient temperature) for 18 h (TLC showed approximately 85% consumption of **74**, based on comparison with new spots). The volatiles were removed under vacuum and the oily residue was chromatographed (hexanes/EtOAc, 2:3) to give a mixture of *E*/*Z*-**78** (11.0 mg, *E*/*Z*~6:94). ^{1}H NMR δ 0.88-1.00 (m, 15H, GeBu_3), 1.25-1.40 (m, 12H, GeBu_3), 2.02 (s, 3H, Ac-*Me-Z*), 2.12 (s, 3H, Ac-*Me-Z*), 2.16 (s, 3H, Ac-*Me*-*Z*), 4.19-4.25 (m, 1H, H4'-*Z*), 4.34 (dd, $^{2}J_{\text{H5''-H5'}}$=11.8 Hz, $^{3}J_{\text{H5'-H4'}}$=6.0 Hz, 1H, H5"-*Z*), 4.44 (dd, $^{2}J_{\text{H5'-H5''}}$=11.8 Hz, $^{3}J_{\text{H5'-H4'}}$=5.0 Hz, 1H, H5'-*Z*), 5.12 (dd, $^{3}J_{\text{H3'-H4'}}$=3.8 Hz, $^{3}J_{\text{H3'-H2'}}$=1.5 Hz, 1H, H3'-*Z*), 5.46 (dd, $^{3}J_{\text{H2'-H1'}}$=3.8 Hz, $^{3}J_{\text{H2'-H3'}}$=1.6 Hz, 1H, H2'-*Z*), 6.07 (d, $^{3}J_{\text{V1-V2}}$=14.0 Hz, 1H, vinyl 1-*Z*), 6.24 (d, $^{3}J_{\text{H1'-H2'}}$=3.8 Hz, 1H, H1'-*Z*), 6.59 (d, $^{3}J_{\text{V1-V2}}$=19.1 Hz, 0.05H, vinyl 1-*E*), 6.76 (d, $^{3}J_{\text{V2-V1}}$=19.1 Hz, 0.06H, vinyl 2-*E*), 7.02 (dd, $^{3}J_{\text{V2-V1}}$=14.0 Hz, $^{4}J_{\text{V2-H6}}$=1.0 Hz, 1H, vinyl 2-*Z*), 7.42 (d, $^{4}J_{\text{H6-V2}}$=0.9 Hz, 1H, H6-*Z*), 8.54 (br. s, 1H, NH-*Z*). ^{13}C NMR δ 13.72 (Ge*Bu*$_3$), 14.15 (Ge*Bu*$_3$), 20.40 (Ac-*Me*), 20.65 (Ac-*Me*), 20.68 (Ac-*Me*), 26.41 (Ge*Bu*$_3$), 27.39 (Ge*Bu*$_3$), 62.92 (C5'), 74.68 (C2'), 76.39 (C3'), 80.22 (C4'), 84.50 (C1'), 114.44 (C5), 134.70 (vinyl 2), 135.27 (vinyl 1), 135.50 (C6), 149.28 (C2), 161.72 (C4), 168.56, 169.46, 170.27 (Ac-*C*=*O*). MS (APCI$^+$) *m*/*z* 641.0 [MH]$^+$ based on ^{74}Ge.

2',3',5'-Tri-*O*-acetyl-5-[(*Z*)-2-(triphenylgermyl)ethenyl]uridine (*Z*-80a). A solution of **79a** (89.7 mg, 0.228 mmol), Ph$_3$GeH (76.3 mg, 0.25 mmol) in dry THF (8 mL) was treated according to Method B for 6 h. The volatiles were removed under vacuum and the residue was chromatographed (hexanes/EtOAc, 3:7) to give *Z*-**80a** (64.2 mg, 50%). ^{1}H NMR δ 2.055 (s, 3H, Ac-*Me*), 2.060 (s, 3H, Ac-*Me*), 2.09 (s, 3H, Ac-*Me*), 3.95 ("d", *J*=4.3 Hz, 2H, H5'/5"), 4.05-4.10 (m, 1H, H4'), 4.98 ("t", $^{3}J_{\text{Avg}}$=6.1 Hz, 1H, H3'), 5.02 (dd, $^{3}J_{\text{H2'-H3'}}$=6.1 Hz, $^{3}J_{\text{H2'-H1'}}$=3.9 Hz, 1H, H2'), 5.26 (d, $^{3}J_{\text{H1'-H2'}}$=3.8 Hz, 1H, H1'), 6.56 (d, $^{3}J_{\text{V1-V2}}$=13.6 Hz, 1H, vinyl 1), 7.01 (d, $^{4}J_{\text{H6-V2}}$=0.9 Hz, 1H, H6), 7.31 (dd, $^{3}J_{\text{V2-V1}}$=13.6 Hz, $^{4}J_{\text{V2-H6}}$=0.8 Hz, 1H, vinyl 2), 7.32-7.39 (m, 9H, Ge*Ph*$_3$), 7.48-7.54 (m, 6H, Ge*Ph*$_3$), 8.00 (br. s, 1H, NH). ^{13}C NMR δ 20.37, 20.38, 20.75 (Ac-*Me*), 62.75 (C5'), 69.39 (C3'), 72.85 (C2'), 79.23 (C4'), 89.29 (C1'), 114.92 (C5), 128.49 (Ge*Ph*$_3$ x 6), 129.17 (Ge*Ph*$_3$ x 3), 131.45 (vinyl 1), 134.72 (Ge*Ph*$_3$ x 6), 136.44 (C6), 136.53 (Ge*Ph*$_3$ Q x 3), 138.60

(vinyl 2), 149.08 (C2), 161.71 (C4), 169.12, 169.21, 170.14 (Ac-*C*=*O*). MS (ESI$^+$) *m*/*z* 701.0 [MH]$^+$ based on ^{74}Ge.

1-(2-Deoxy-3,5-di-*O*-acetyl-β-D-*erythro*-pentofuranosyl)-5-[(*Z*)-2-(triphenylgermyl)-ethenyl]uracil (*Z*-80b). A solution of **79b** (43.5 mg, 0.129 mmol) and Ph_3GeH (43.4 mg, 0.142 mmol) in dry THF (5 mL) was treated according to Method B for 6 h. The volatiles were removed under vacuum and the residue was chromatographed (hexanes/EtOAc, 3:7) to give *Z*-**80b** (24.3 mg, 46%). ^{1}H NMR δ 1.40 (“dt”, $^2J_{H2''-H2'}$=15.0 Hz, $^3J_{Avg}$=7.5 Hz, 1H, H2''), 2.02 (ddd, $^2J_{H2'-H2''}$=14.2 Hz, $^3J_{H2'-H1'}$=5.8 Hz, $^3J_{H2'-H3'}$=2.0 Hz, 1H, H2'), 2.05 (s, 3H, Ac-*Me*), 2.06 (s, 3H, Ac-*Me*), 3.84 (dd, $^2J_{H5''-H5'}$=11.8 Hz, $^3J_{H5''-H4'}$=5.9 Hz, 1H, H5''), 3.89 (dd, $^2J_{H5'-H5''}$=11.9 Hz, $^3J_{H5'-H4'}$=4.5 Hz, 1H, H5'), 3.93-3.97 (m, 1H, H4'), 4.75 (“dt”, ^3J=7.1 Hz, ^3J=2.6 Hz, 1H, H3'), 5.72 (dd, $^3J_{H1'-H2''}$=8.3 Hz, $^3J_{H1'-H2'}$=5.8 Hz, 1H, H1'), 6.53 (d, $^3J_{V1-V2}$=13.5 Hz, 1H, vinyl 1), 7.00 (s, 1H, H6), 7.33-7.40 (m, 10H, GePh_3 + vinyl 2), 7.50-7.56 (m, 6H, GePh_3), 8.90 (br. s, 1H, NH). ^{13}C NMR δ 20.76, 20.85 (Ac-*Me*), 36.53 (C2'), 63.48 (C5'), 73.76 (C3'), 81.76 (C4'), 85.12 (C1'), 114.82 (C5), 128.52 (GePh_3 x 6), 129.25 (GePh_3 x 3), 130.84 (vinyl 1), 134.71 (GePh_3 x 6), 135.55 (GePh_3 Q x 3), 136.54 (C6), 138.97 (vinyl 2), 149.39 (C2), 161.81 (C4), 170.11, 170.22 (Ac-*C*=*O*). MS (ESI$^+$) *m*/*z* 643.0 [MH]$^+$ based on ^{74}Ge.

2',3',5'-Tri-*O*-acetyl-5-[(*E*/*Z*)-2-(trimethylgermyl)ethenyl]uridine (*E*/*Z*-81a). A solution of **79a** (99.8 mg, 0.25 mmol) and Me_3GeH (35.3 mg, 35.0 μL, 0.30 mmol) in dry THF (8 mL) was treated according to Method B (with injection of Me_3GeH into the reaction mixture via syringe at 0 °C) for 7 h. The volatiles were removed under vacuum and the oily residue was chromatographed (hexanes/EtOAc, 3:7) to give *E*/*Z*-**81b** (15.7 mg, 13%, *E*/*Z* 12:88). ^{1}H NMR δ 0.21 (s, 9H, GeMe_3-*Z*), 0.25 (s, 1.17H, GeMe_3-*E*), 2.09

(s, 3H, Ac-*Me-Z*), 2.10 (s, 3H, Ac-*Me-Z*), 2.13 (s, 3H, Ac-*Me-Z*), 4.30-4.41 (m, 3H, H4' and H5'/H5"), 5.29-5.36 (m, 2H, H2' and H3'), 6.06 (d, $^{3}J_{\mathrm{H1'-H2'}}$=3.8 Hz, 1H, H1'-*Z*), 6.12 (d, $^{3}J_{\mathrm{V1-V2}}$=13.6 Hz, vinyl 1-*Z*), 6.55 (d, $^{3}J_{\mathrm{V1-V2}}$=19.0 Hz, 0.13H, vinyl 1-*E*), 6.75 (d, $^{3}J_{\mathrm{V2-V1}}$=19.0 Hz, 0.13H, vinyl 2-*E*), 6.92 (dd, $^{3}J_{\mathrm{V2-V1}}$=13.7 Hz, $^{4}J_{\mathrm{V2-H6}}$=1.2 Hz, 1H, vinyl 2-*Z*), 7.28 (d, $^{4}J_{\mathrm{H6-V2}}$=1.0 Hz, 1H, H6-*Z*), 7.44 (s, 0.13H, H6-*E*), 8.68 (br. s, 0.13H, NH-*E*), 8.74 (br. s, 1H, NH-*Z*). ^{13}C NMR δ -1.70 (Ge*Me*$_3$-*E*), -0.05 (Ge*Me*$_3$-*Z*), 20.51, 20.63, 20.96 (Ac-*Me-Z*), 63.16 (C5'-*Z*), 70.14, 72.87 (C2' and C3'-*Z*), 80.11 (C4'-*Z*), 87.55 (C1'-*Z*), 116.14 (C5-*Z*), 134.80 (vinyl 2-*Z*), 135.39 (C6-*Z*), 138.88 (vinyl 1-*Z*), 149.99 (C2-*Z*), 161.99 (C4-*Z*), 169.63, 169.71, 170.23 (Ac-*C*=*O*-*Z*).

1-(2-Deoxy-3,5-di-*O*-acetyl-*β*-D-*erythro*-pentofuranosyl)-5-[(*E*/*Z*)-2-(trimethylgermyl)ethenyl]uracil (*E*/*Z*-81b). A solution of **79b** (43.5 mg, 0.13 mmol) and Me$_3$GeH (30.9 mg, 30.6 μL, 0.26 mmol) in dry THF (5 mL) was treated according to Method B (with injection of Me$_3$GeH into the reaction mixture via syringe at 0 $^{\circ}$C) for 7 h. The volatiles were removed in under vacuum and the oily residue was chromatographed (hexanes/EtOAc, 2:3) to give *E*/*Z*-**81b** (24.3 mg, 46%, *E*/*Z* 23:77). ^{1}H NMR δ 0.22 (s, 6.93H, Ge*Me$_3$*-*Z*), 0.25 (s, 2.07H, Ge*Me$_3$*-*E*), 2.04-2.24 (m, 10H, Ac-*Me*-*E*/*Z* + H2"-*E*/*Z*), 2.49-2.57 (m, 1H, H2'-*E*/*Z*), 4.25-4.30 (m, 1H, H4'-*E*/*Z*), 4.28-4.44 (m, 1H, H5'/5"-*E*/*Z*), 5.18-5.26 (m, 1H, H3'-*E*/*Z*), 6.12 (d, $^{3}J_{\mathrm{V1-V2}}$=13.6 Hz, 0.77H, vinyl 1-*Z*), 6.27 (dd, ^{3}J=8.6 Hz, ^{3}J=5.7 Hz, 0.77H, H1'-*Z*), 6.30-6.35 (m, 0.23H, H1'-*E*), 6.56 (d, $^{3}J_{\mathrm{V1-V2}}$=18.8 Hz, 0.23H, vinyl 1-*E*), 6.76 (d, $^{3}J_{\mathrm{V2-V1}}$=19.0 Hz, 0.23H, vinyl 2-*E*), 6.93 (dd, $^{3}J_{\mathrm{V2-V1}}$=13.7 Hz, $^{4}J_{\mathrm{V2-H6}}$=1.0 Hz, 0.77H, vinyl 2-*Z*), 7.39 (d, $^{4}J_{\mathrm{H6-V2}}$=0.9 Hz, 0.77H, H6-*Z*), 7.56 (s, 0.23H, H6-*E*), 8.22 (br. s, 0.23H, NH-*E*), 8.26 (br. s, 0.77H, NH-*Z*). ^{13}C NMR δ -1.83 (Ge*Me$_3$*-*E*), -0.18 (Ge*Me$_3$*-*Z*), 20.83 (Ac-*Me-Z*), 20.89 (Ac-*Me-Z*), 38.03 (C2'-*Z*), 63.75 (C5'-*Z*), 73.88 (C3'-*Z*), 82.23 (C4'-*Z*), 85.25 (C1'-*Z*), 115.47 (C5-*Z*), 134.66 (vinyl 2-*Z*), 134.95 (C6-*Z*), 138.39 (vinyl 1-*Z*), 149.63 (C2-*Z*), 161.76 (C4-*Z*), 170.14 (Ac-*C*=*O*-*Z*), 170.33 (Ac-*C*=*O*-*Z*).

5-[(*Z*)-2-(Triphenylgermyl)ethenyl]-2',3',5'-tri-*O*-*p*-toluoyl-uridine (*Z*-83a). A solution of **82a** (49.0 mg, 0.079 mmol) and Ph$_3$GeH (26.0 mg, 0.085 mmol) in dry THF (5 mL) was treated according to Method B. After 6 h at -78 °C TLC analysis revealed slow progression towards product. Hence, the reaction mixture was slowly warmed to 0 °C until TLC reveal approximately 95% consumption of the starting **82a** relative to the possible product. The volatiles were removed under vacuum and the residue was chromatographed (hexanes/EtOAc, 1:1) to give a separable mixture of *Z*-**83a** (29.0 mg, 40%) and **85** (10 mg, 13%). Compound *Z*-**83a** had: ^{1}H NMR δ 2.40 (s, 6H, *p*-Tol-*Me*), 2.42 (s, 3H, *p*-Tol-*Me*), 4.34 (dd, $^{2}J_{\text{H5''-H5'}}$=12.2 Hz, $^{3}J_{\text{H5''-H4'}}$=5.4 Hz, 1H, H5''), 4.40 (dd, $^{2}J_{\text{H5'-H5''}}$=12.2 Hz, $^{3}J_{\text{H5'-H4'}}$=3.4 Hz, 1H, H5'), 4.47 (ddd, $^{3}J_{\text{H4'-H3'}}$=5.8 Hz, $^{3}J_{\text{H4'-H5''}}$=5.4 Hz, $^{3}J_{\text{H4'-H5'}}$=3.5 Hz, 1H, H4'), 5.38 (dd, $^{3}J_{\text{H2'-H3'}}$=6.2 Hz, $^{3}J_{\text{H2'-H1''}}$=4.5 Hz, 1H, H2'), 5.51 (“t”, $^{3}J_{\text{Avg}}$=6.0 Hz, 1H, H3'), 5.52 (d, $^{3}J_{\text{H1'-H2'}}$=4.4 Hz, 1H, H1'), 6.50 (d, $^{3}J_{\text{V1-V2}}$=13.6 Hz, 1H, vinyl 1), 7.11 (d, $^{4}J_{\text{H6-V2}}$=0.8 Hz, 1H, H6), 7.16 (d, $^{3}J_{\text{o-m}}$=8.1 Hz, 2H, *p*-Tol-*H*), 7.19 (d, $^{3}J_{\text{o-m}}$=8.0 Hz, 2H, *p*-Tol-*H*), 7.22 (dd, $^{3}J_{\text{V2-V1}}$=13.5 Hz, $^{4}J_{\text{V2-H6}}$=1.0 Hz, 1H, vinyl 2), 7.24 (d, $^{3}J_{\text{o-m}}$=8.0 Hz, 2H, *p*-Tol-*H*), 7.31-7.36 (m, 9H, Ge*Ph*$_3$), 7.50-7.55 (m, 6H, Ge*Ph*$_3$), 7.80 (d, $^{3}J_{\text{o-m}}$=8.2 Hz, 4H, *p*-Tol-*H*), 7.96 (d, $^{3}J_{\text{o-m}}$=8.2 Hz, 2H, *p*-Tol-*H*), 8.09 (br. s, 1H, NH). ^{13}C NMR δ 21.67, 21.69, 21.73 (*p*-Tol-*Me*), 63.54 (C5'), 70.51 (C3'), 73.59 (C2'), 79.91 (C4'), 89.76 (C1'), 114.99 (C5), 125.90 (*p*-Tol-*Q*), 125.98 (*p*-Tol-*Q*), 126.67 (*p*-Tol-*Q*), 128.47 (Ge*Ph*$_3$ x 6), 129.13 (Ge*Ph*$_3$ x3 + *p*-Tol-*CH*), 129.21 (*p*-Tol-*CH*), 129.29 (*p*-Tol-*CH*), 129.75 (*p*-Tol-*CH*), 129.82 (*p*-Tol-*CH*), 129.91 (*p*-Tol-*CH*), 131.42 (vinyl

1), 134.74 (GePh_3 x 6), 136.61 (GePh_3 Q x 3), 136.96 (C6), 138.23 (vinyl 2), 144.19 (*p*-Tol-*Q*), 144.36 (*p*-Tol-*Q*), 144.52 (*p*-Tol-*Q*), 148.84 (C2), 161.38 (C4), 164.97, 165.07, 166.08 (*p*-Tol-*C*=*O*). MS (ESI$^+$) *m*/*z* 951.2 $[M+Na]^+$ based on ^{74}Ge.

5-[2-(Triphenylgermyl)acetyl]-2',3',5'-tri-*O*-*p*-toluoyl-uridine (85). ^{1}H NMR δ 2.35 (s, 3H, *p*-Tol-*Me*), 2.40 (s, 3H, *p*-Tol-*Me*), 2.42 (s, 3H, *p*-Tol-*Me*), 3.76 (d, $^2J_{\mathrm{H8a\text{-}H8b}}$=9.0 Hz, 1H, H8a), 3.87 (d, $^2J_{\mathrm{H8b\text{-}H8a}}$=9.0 Hz, 1H, H8b), 4.67-4.75 (m, 3H, H4' and H5'/5"), 5.66 (dd, $^3J_{\mathrm{H2'\text{-}H3'}}$=5.9 Hz, $^3J_{\mathrm{H2'\text{-}H1'}}$=5.1 Hz, 1H, H2'), 5.83 (“t”, $^3J_{\mathrm{Avg}}$=5.7 Hz, 1H, H3'), 6.01 (d, $^3J_{\mathrm{H1'\text{-}H2'}}$=5.0 Hz, 1H, H1'), 7.16-7.22 (m, 6H, *p*-Tol-*H*), 7.31-7.36 (m, 9H, GePh_3), 7.50-7.55 (m, 6H, GePh_3), 7.83 (d, $^3J_{\mathrm{o\text{-}m}}$= 8.2 Hz, 2H, *p*-Tol-*H*), 7.87 (d, $^3J_{\mathrm{o\text{-}m}}$= 8.2 Hz, 2H, *p*-Tol-*H*), 8.02 (d, $^3J_{\mathrm{o\text{-}m}}$= 8.2 Hz, 2H, *p*-Tol-*H*), 8.05 (s, 1H, H6). ^{13}C NMR δ 21.72 (*p*-Tol-*Me* x3), 32.95 (C8), 63.50 (C5'), 70.95 (C3'), 73.89 (C2'), 80.89 (C4'), 90.35 (C1'), 113.69 (C5), 125.66, 125.96, 126.58 (*p*-Tol-*Q*), 128.21 (GePh_3 x 6), 129.21, 129.24, 129.27 (*p*-Tol-*CH*), 129.36 (GePh_3 x 3), 129.86 (*p*-Tol-*CH*), 129.92 (*p*-Tol-*CH* x2), 135.04 (GePh_3 x 6), 135.09 (GePh_3 Q x 3), 144.06, 144.50, 144.69 (*p*-Tol-*Q*), 146.56 (C6), 148.51 (C2), 160.17 (C4), 165.19, 165.21, 166.25 (*p*-Tol-*C*=*O*), 193.32 (C7-ketone). Qualitative UV/Vis (MeOH) λ_{max}=282 nm. MS (ESI$^+$) *m*/*z* 945.0 $[M+H]^+$ based on ^{74}Ge.

1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-*β*-D-*erythro*-pentofuranosyl)-5-[(*Z*)-2-(triphenylgermyl)ethenyl]uracil (*Z*-83b). A solution of **82b** (44.0 mg, 0.09 mmol) and Ph_3GeH (30.0 mg, 0.099 mmol) in dry THF (5 mL) was treated according to Method B. After 6 h at -78 °C TLC analysis revealed slow progression towards product. Thus, the reaction mixture was slowly warmed to 0 °C until TLC reveal approximately 95% consumption of the starting **82b** relative to the possible product. The volatiles were removed under vacuum and the residue was chromatographed (hexanes/EtOAc, 3:2) to give a separable mixture of *Z*-**83b** (43.0 mg, 61%) and **86** (9 mg, 12%). Compound *Z*-**83b** had: ^{1}H NMR δ 1.68 (ddd, $^{2}J_{\mathrm{H2''-H2'}}$=14.9 Hz, $^{3}J_{\mathrm{H2''-H1'}}$=8.1 Hz, $^{3}J_{\mathrm{H2''-H3'}}$=7.0 Hz, 1H, H2"), 2.31 (ddd, $^{2}J_{\mathrm{H2'-H2''}}$=14.5 Hz, $^{3}J_{\mathrm{H2'-H1'}}$=5.7 Hz, $^{3}J_{\mathrm{H2'-H3'}}$=1.8 Hz, 1H, H2'), 2.41 (s, 3H, *p*-Tol-*Me*), 2.45 (s, 3H, *p*-Tol-*Me*), 4.16 (dd, $^{2}J_{\mathrm{H5''-H5'}}$=11.1 Hz, $^{3}J_{\mathrm{H5''-H4'}}$=3.5 Hz, 1H, H5"), 4.26-4.30 (m, 1H, H4'), 4.32 (dd, $^{2}J_{\mathrm{H5'-H5''}}$=11.1 Hz, $^{3}J_{\mathrm{H5'-H4'}}$=5.0 Hz, 1H, H5'), 5.20 ("dt", $^{3}J_{\mathrm{H3'-H2''}}$=6.8 Hz, $^{3}J_{\mathrm{H3'-H2'}}$=1.8 Hz, $^{3}J_{\mathrm{H3'-H4'}}$=1.8 Hz, 1H, H3'), 5.85 (dd, $^{3}J_{\mathrm{H1'-H2''}}$=8.3 Hz, $^{3}J_{\mathrm{H1'-H2'}}$=5.8 Hz, 1H, H1'), 6.51 (d, $^{3}J_{\mathrm{V1-V2}}$=13.5 Hz, 1H, vinyl 1), 7.11 (d, $^{4}J_{\mathrm{H6-V2}}$=0.9 Hz, 1H, H6), 7.21-7.27 (m, 5H, *p*-Tol-*H* + vinyl 2), 7.36-7.40 (m, 9H, Ge*Ph*$_3$), 7.52-7.56 (m, 6H, Ge*Ph*$_3$), 7.88 (d, $^{3}J_{\mathrm{o-m}}$=8.2 Hz, 2H, *p*-Tol-*H*), 7.91 (d, $^{3}J_{\mathrm{o-m}}$=8.2 Hz, 2H, *p*-Tol-*H*). ^{13}C NMR δ 21.68 (*p*-Tol-*Me*), 21.72 (*p*-Tol-*Me*), 37.27 (C2'), 63.87 (C5'), 74.47 (C3'), 82.32 (C4'), 85.49 (C1'), 114.78 (C5), 126.35 (*p*-Tol-*Q*), 126.71 (*p*-Tol-*Q*), 128.50 (Ge*Ph*$_3$ x 6), 129.21 (Ge*Ph*$_3$ x 3), 129.26, 129.28, 129.63, 129.80 (*p*-Tol-*CH* x 2), 130.96 (vinyl 1), 134.75 (Ge*Ph*$_3$ x 6), 135.62 (C6), 136.62 (Ge*Ph*$_3$ Q x 3), 138.83 (vinyl 2), 144.24 (*p*-Tol-*Q*), 144.46 (*p*-Tol-*Q*), 149.33 (C2), 161.73 (C4), 165.80 (*p*-Tol-*C*=*O*), 166.00 (*p*-Tol-*C*=*O*). MS (APCI^{+}) *m*/*z* 794.9 [MH]$^{+}$ based on ^{74}Ge.

1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-*β*-D-*erythro*-pentofuranosyl)-5-[2-(triphenylgermyl)acetyl]uracil (86). ^{1}H NMR δ 2.18-2.27 (m, 1H, H-2"), 2.36 (s, 3H, *p*-Tol-*Me*), 2.45 (s, 3H, *p*-Tol-*Me*), 2.64 (ddd, $^{2}J_{\mathrm{H2'-H2''}}$=14.3 Hz, $^{3}J_{\mathrm{H2'-H1'}}$=5.7 Hz, $^{3}J_{\mathrm{H2'-H3'}}$=1.8 Hz, 1H, H2'), 3.81 (d, $^{2}J_{\mathrm{H8a-H8b}}$=9.1 Hz, 1H, H8a), 3.85 (d, $^{2}J_{\mathrm{H8b-H8a}}$=9.1 Hz, 1H, H8b), 4.53-4.60 (m, 2H, H4' and H5"), 4.74-4.80 (m, 1H, H5'), 5.54 ("d", ^{3}J=6.6 Hz, 1H, H3'), 6.16 (dd, $^{3}J_{\mathrm{H1'-H2''}}$=8.3 Hz, $^{3}J_{\mathrm{H1'-H2'}}$=5.7 Hz, 1H, H1'), 7.16 (d, $^{3}J_{\mathrm{o-m}}$=8.0 Hz, 2H, *p*-Tol-*H*), 7.28 (d, $^{3}J_{\mathrm{o-m}}$= 8.1 Hz, *p*-Tol-*H*), 7.32-7.39 (m, 9H, Ge*Ph*$_3$), 7.53-7.57 (m, 6H, Ge*Ph*$_3$), 7.94 (d, $^{3}J_{\mathrm{o-m}}$=

8.2 Hz, 2H, *p*-Tol-*H*), 7.95 (d, $^3J_{\text{o-m}}$= 8.2 Hz, 2H, *p*-Tol-*H*), 8.15 (br. s, 1H, C6). ^{13}C NMR δ 21.71, 21.73 (*p*-Tol-*Me*), 32.80 (C8), 38.42 (C2'), 63.76 (C5'), 74.52 (C3'), 83.19 (C4'), 86.15 (C1'), 113.58 (C5), 126.30, 126.58 (*p*-Tol-*Q*), 128.20 (GePh_3 x 6), 129.25 (*p*-Tol-*CH*), 129.28 (*p*-Tol-*CH*), 129.32 (GePh_3 x 3), 129.82 (*p*-Tol-*CH* x2), 135.06 (GePh_3 x 6), 135.24 (GePh_3 Q x 3), 144.12 (*p*-Tol-*Q*), 144.55 (*p*-Tol-*Q*), 145.17 (C6), 148.76 (C-2), 160.26 (C-4), 165.82 (*p*-Tol-*C=O*), 166.19 (*p*-Tol-*C=O*), 193.48 (C7-ketone). MS (ESI$^+$) *m*/*z* 810.9 [MH]$^+$ based on ^{74}Ge.

5-[(*E*/*Z*)-2-(Trimethylgermyl)ethenyl]-2',3',5'-tri-*O*-*p*-toluoyl-uridine (*E*/*Z*-84a). A solution of **82a** (50.0 mg, 0.08 mmol) and Me_3GeH (19.0 mg, 18.8 μL 0.16 mmol) in dry THF (5 mL) was treated according to Method B (with injection of Me_3GeH into the reaction mixture via syringe and progressive warming from 0 °C to 25 °C) for 10 h. The volatiles were removed under reduced pressure and the oily residue was chromatographed (hexanes/EtOAc, 3:2) to give *E*/*Z*-**84a** (22.0 mg, 37%, *E*/*Z* 45:55). ^{1}H NMR δ 0.12 (s, 4.05H, GeMe_3-*E*), 0.20 (s, 4.95H, GeMe_3-*Z*), 2.40, 2.43, 2.44 (singlets, 9H, *p*-Tol-*Me*-*E*/*Z*), 4.68-4.82 (m, 3H, H4' and H5'/5"-*E*/*Z*), 5.72 ("t", $^3J_{\text{Avg}}$=6.0 Hz, 0.55H, H2'-*Z*), 5.78 ("t", $^3J_{\text{Avg}}$=6.3 Hz, 0.45H, H2'-*E*), 5.82 (dd, ^3J=6.1 Hz, ^3J=3.9 Hz, 0.55H, H3'-*Z*), 5.88 (dd, ^3J=5.8 Hz, ^3J=2.8 Hz, 0.45H, H3'-*E*), 5.98 (d, $^3J_{\text{V1-V2}}$=13.7 Hz, 0.55H, vinyl 1-*Z*), 6.34 (d, $^3J_{\text{H1'-H2'}}$=5.9 Hz, 0.55H, H1'-*Z*), 6.37 (d, $^3J_{\text{V1-V2}}$=19.0 Hz, 0.45H, vinyl 1-*E*), 6.50 (d, $^3J_{\text{H1'-H2'}}$= 6.8 Hz, 0.45H, H1'-*E*), 6.69 (d, $^3J_{\text{V2-V1}}$=19.0 Hz, 0.45H, vinyl 2-*E*), 6.72 (dd, $^3J_{\text{V2-V1}}$=13.7 Hz, $^4J_{\text{V2-H6}}$=1.0 Hz, 0.55H, vinyl 2-*Z*), 7.16-7.32 (m, 6H, *p*-Tol-*H*, set of doublets collapsed), 7.34 (d, $^4J_{\text{H6-V2}}$=1.0 Hz, 0.55H, H6-*Z*), 7.54 (s, 0.45H, H6-*E*), 7.83, 7.86, 7.89, 7.91, 7.96, 8.04 (doublets, $^3J_{\text{o-m}}$=8.2 Hz, 6H, *p*-Tol-*H*), 8.24 (br. s, 0.45H, NH-*E*), 8.27 (br. s, 0.55H, NH-*Z*). ^{13}C NMR δ -2.02 (GeMe_3-*E*), -0.17

(Ge*Me*$_3$-*Z*), 21.71 (*p*-Tol-*Me-E*/*Z*), 63.72 (C5'-*Z*), 64.19 (C5'-*E*), 71.08 (C3'-*Z*), 71.47 (C3'-*E*), 73.45 (C2'-*E*), 73.54 (C2'-*Z*), 80.73 (C4'-*Z*), 81.05 (C4'-*E*), 86.87 (C1'-*E*), 88.04 (C1'-*Z*), 114.42 (C5-*E*), 115.95 (C5-*Z*), 125.65, 125.70, 125.96, 125.97, 126.27, 126.48 (*p*-Tol-*Q*-*E*/*Z*), 129.23, 129.25, 129.29, 129.39, 129.63, 129.71, 129.73, 129.886, 129.89, 129.95, 130.00 (*p*-Tol-*CH*-*E*/*Z*), 131.77 (vinyl 2-*E*), 134.06 (vinyl 2-*Z*), 134.43 (vinyl 1-*E*), 135.14 (C6-*E*), 135.78 (C6-*Z*), 138.68 (vinyl 1-*Z*), 144.29, 144.54, 144.57, 144.62, 144.64, 144.66 (*p*-Tol-*Q*-*E*/*Z*), 149.30, 149.66 (C2-*E*+*Z*), 161.34, 161.72 (C4-*E*+*Z*), 165.28, 165.36, 165.39, 165.48, 166.11 (*p*-Tol-*C*=*O*). MS (ESI$^+$) *m*/*z* 765.1 [M + Na]$^+$ based on ^{74}Ge.

1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-*β*-D-*erythro*-pentofuranosyl)-5-[(*E*/*Z*)-2-(trimethylgermyl)ethenyl]uracil (*E*/*Z*-84b). A solution of **82b** (45.0 mg, 0.092 mmol) and Me$_3$GeH (21.8 mg, 21.6 μL, 0.18 mmol) in dry THF (5 mL) was treated according to Method B (with injection of Me$_3$GeH into the reaction mixture via syringe and progressive warming from 0 °C to 25 °C) for 10 h. The volatiles were removed in under vacuum and the residue was chromatographed (hexanes/EtOAc, 1:1) to give *E*/*Z*-**84b** (14.2 mg, 30%, *E*/*Z* 41:59). ^{1}H NMR δ 0.14 (s, 3.69H, Ge*Me*$_3$-*E*), 0.21 (s, 5.31H, Ge*Me*$_3$-*Z*), 2.25-2.34 (m, 1H, H2''-*E*/*Z*), 2.42, 2.43, 2.45 (singlets, 6H, *p*-Tol-*Me*-*E*/*Z*), 2.78 (ddd, $^2J_{H2''-H2'}$=14.2 Hz, $^3J_{H2''-H1'}$=5.5 Hz, $^3J_{H2''-H3'}$=1.6 Hz, 0.59H, H2'-*Z*), 2.80 (ddd, $^2J_{H2'-H2''}$=14.3 Hz, $^3J_{H2'-H1'}$=5.1 Hz, $^3J_{H2'-H3'}$=1.2 Hz, 0.41H, H2'-*E*), 4.56-4.61 (m, 1H, H4'-*E*/*Z*), 4.65 (dd, $^2J_{H5''-H5'}$=12.2 Hz, $^3J_{H5''-H4'}$=3.2 Hz, 0.59H, H5''-*Z*), 4.73-4.77 (m, 0.82H, H5'/5''-*E*), 4.75 (dd, $^2J_{H5'-H5''}$=12.2 Hz, $^3J_{H5'-H4'}$=3.8 Hz, 0.59H, H5'-*Z*), 4.59 (“dt”, ^3J=4.9 Hz, ^3J=1.9 Hz, 0.59H, H3'-*Z*), 4.63 (“d”, ^3J=6.4 Hz, 0.41H, H3'-*E*), 6.00 (d, $^3J_{V1-V2}$=13.7 Hz, 0.59H, vinyl 1-*Z*), 6.40 (dd, $^3J_{H1'-H2''}$=8.7 Hz, $^3J_{H1'-H2'}$=5.4 Hz, 0.59H, H1'-*Z*), 6.41 (d, $^3J_{V1-V2}$=19.2 Hz, 0.41H, vinyl 1-*E*), 6.46 (d, $^{3}J_{\mathrm{H1'-H2''}}$=8.9 Hz, $^{3}J_{\mathrm{H1'-H2'}}$=5.2 Hz, 0.41H, H1'-*E*), 6.72 (d, $^{3}J_{\mathrm{V2-V1}}$=19.0 Hz, 0.41H, vinyl 2-*E*), 6.78 (dd, $^{3}J_{\mathrm{V2-V1}}$=13.7 Hz, $^{4}J_{\mathrm{V2-H6}}$=0.9 Hz, 0.59H, vinyl 2-*Z*), 7.22-7.32 (m, 4H, *p*-Tol-*H*-*E*/*Z*), 7.48 (d, $^{4}J_{\mathrm{H6-V2}}$=1.0 Hz, 0.59H, H6-*Z*), 7.67 (s, 0.41H, H6-*E*), 7.85-7.99 (m, 4H, *p*-Tol-*H*-*E*/*Z*), 8.51 (br. s, 0.41H, NH-*E*), 8.57 (br. s, 0.59H, NH-*Z*). ^{13}C NMR δ -1.99 (Ge*Me*$_3$-*E*), -0.20 (Ge*Me*$_3$-*Z*), 21.70, 21.74 (*p*-Tol-*Me*-*E*/*Z*), 38.51 (C2'-*E*/*Z*), 64.06 (C5'-*Z*), 64.39 (C5'-*E*), 74.65 (C3'-*Z*), 74.94 (C3'-*E*), 82.94 (C4'-*Z*), 83.14 (C4'-*E*), 85.59 (C1'-*E*/*Z*), 113.85 (C5-*E*), 115.37 (C5-*Z*), 126.27, 126.39, 126.50 (*p*-Tol-*Q*-*E*/*Z*), 129.30, 129.34, 129.50, 129.55, 129.61, 129.83 (*p*-Tol-*H*-*E*/*Z*), 131.93 (vinyl 2-*E*), 133.93 (vinyl 1-*E*), 134.18 (vinyl 2-*Z*), 134.86 (C6-*E*), 135.08 (C6-*Z*), 138.27 (vinyl 1-*Z*), 144.35, 144.53, 144.59 (*p*-Tol-*Q*-*E*/*Z*), 149.20 (C2-*E*), 149.66 (C2-*Z*), 161.53 (C4-*E*), 161.88 (C4-*Z*), 165.97, 166.04 (*p*-Tol-*C*=*O*-*E*/*Z*). MS (ESI^{+}) *m*/*z* 631.0 [M + Na]$^{+}$ based on ^{74}Ge.

5-[(*Z*)-2-(Triphenylstannyl)ethenyl]-2',3',5'-tri-*O*-*p*-toluoyl-uridine (*Z*-87). A solution of **82a** (41.0 mg, 0.066 mmol) and Ph$_3$SnH (26.0 mg, 0.074 mmol) in dry THF (4.5 mL) was treated according to Method B. After 6 h, the volatiles were removed under vacuum and the residue was chromatographed (hexanes/EtOAc, 1:1) to give *Z*-**87** (20.0 mg, 31%). ^{1}H NMR δ 2.37 (s, 3H, *p*-Tol-*Me*), 2.42 (s, 6H, *p*-Tol-*Me*), 4.53 (dd, $^{2}J_{\mathrm{H5''-H5'}}$=12.2 Hz, $^{3}J_{\mathrm{H5''-H4'}}$=4.0 Hz, 1H, H5''), 4.62 (“q”, $^{3}J_{\mathrm{Avg}}$=3.7 Hz, 1H, H4'), 4.71 (dd, $^{2}J_{\mathrm{H5'-H5''}}$=12.2 Hz, $^{3}J_{\mathrm{H5'-H4'}}$=2.8 Hz, 1H, H5'), 5.62 (“t”, $^{3}J_{\mathrm{Avg}}$=5.8 Hz, 1H, H2'), 5.77 (dd, $^{3}J_{\mathrm{H3'-H2'}}$=5.9 Hz, $^{3}J_{\mathrm{H3'-H4'}}$=4.7 Hz, 1H, H3'), 5.92 (d, $^{3}J_{\mathrm{H1'-H2'}}$=5.5 Hz, 1H, H1'), 6.43 (d, $^{3}J_{\mathrm{V1-V2}}$=13.9 Hz, 1H, vinyl 1), 6.87 (dd, $^{3}J_{\mathrm{V2-V1}}$=14.1 Hz, 1H, vinyl 2), 7.20 (d, $^{3}J_{\mathrm{o-m}}$=8.1 Hz, 4H, *p*-Tol-*H*), 7.25-7.35 (m, 12H, *p*-Tol-*H* + Sn*Ph*$_3$ + H6), 7.52-7.57 (m, 6H, Sn*Ph*$_3$), 7.84 (d, $^{3}J_{\mathrm{o-m}}$=8.4 Hz, 2H, *p*-Tol-*H*), 7.86 (d, $^{3}J_{\mathrm{o-m}}$=8.4 Hz, 2H, *p*-Tol-*H*), 8.01 (d, $^{3}J_{\mathrm{o-m}}$=8.2 Hz, 2H, *p*-Tol-

H). ^{13}C NMR δ 21.64, 21.72, 21.74 (*p*-Tol-*Me*), 63.53 (C5'), 71.06 (C3'), 73.71 (C2'), 80.68 (C4'), 88.52 (C1'), 115.17 (C5), 125.77 (*p*-Tol-*Q*), 125.97 (*p*-Tol-*Q*), 126.49 (*p*-Tol-*Q*), 128.39 (SnPh_3 x 6), 128.64 (SnPh_3 x 3) 129.23, 129.26, 129.52, 129.74, 129.87, 129.97 (*p*-Tol-*CH*), 133.90 (vinyl 1), 136.84 (SnPh_3 x 6), 138.02 (C6), 139.45 (vinyl 2), 140.42 (SnPh_3 Q x 3), 144.55 (*p*-Tol-*Q* x2), 144.66 (*p*-Tol-*Q*), 148.52 (C2), 161.65 (C4), 165.20, 165.31, 166.08 (*p*-Tol-*C=O*). MS (ESI$^+$) *m*/*z* 896.7 [M-77]$^+$ based on ^{120}Sn.

1-(*β*-D-Arabinofuranosyl)-5-[(*Z*)-2-(triphenylgermyl)ethenyl]uracil (*Z*-88). A saturated solution of MeOH/NH_3 was added to a suspension of *Z*-**75** (40.0 mg, 0.057 mmol) in MeOH (2 mL) was added and the reaction mixture stirred for 6 h at 0 °C. An additional portion of MeOH/NH_3 solution (1 mL) was then added and the solution was stirred overnight at ambient temperature. The mixture was concentrated under vacuum and the residue was chromatographed (dry method; EtOAc/MeOH, 98:2) to give *Z*-**88** (28.2 mg, 86%). ^{1}H NMR (MeOH-d_4) δ 3.28 (dd, $^2J_{H5''-H5'}$=11.3 Hz, $^3J_{H5'-H4'}$=4.0 Hz, 1H, H5''), 3.37 (dd, $^2J_{H5'-H5''}$=11.3 Hz, $^3J_{H5'-H4'}$=5.6 Hz, 1H, H5'), 3.76 (ddd, $^3J_{H4'-H5'}$=5.8 Hz, $^3J_{H4'-H5''}$=4.1 Hz, $^3J_{H4'-H3'}$=2.1 Hz, 1H, H4'), 3.98-4.02 (m, 2H, H2' and H3'), 5.59 (d, $^3J_{H1'-H2'}$=3.3 Hz, 1H, H1'), 6.50 (d, $^3J_{V1-V2}$=13.2 Hz, 1H, vinyl 1), 7.30 (dd, $^3J_{V2-V1}$=13.3 Hz, $^4J_{V2-H6}$=1.2 Hz, 1H, vinyl 2), 7.35 (m, 10H, GePh_3 and H6), 7.51 (m, 6H, GePh_3). ^{13}C NMR (MeOH-d_4) δ 62.56 (C5'), 76.64 and 78.44 (C2' and C3'), 86.95 (C4'), 88.31 (C1'), 113.75 (C5), 129.34 (GePh_3 x 6), 130.01 (GePh_3 x 3), 131.49 (vinyl 1), 136.03 (GePh_3 x 6), 138.15 (GePh_3 Q x 3), 139.92 (C6), 140.71 (vinyl 2), 151.31 (C2), 173.03 (C4). MS (APCI$^+$) *m*/*z* 574.8 [MH]$^+$ based on ^{74}Ge.

1-(*β*-D-*erythro*-Pentofuranosyl)-5-[(*Z*)-2-(triphenylgermyl)-ethenyl]uracil (*Z*-89). A saturated solution of MeOH/NH_3 (2 mL) was added to a suspension of **83b** (33 mg, 0.042

mmol) in MeOH (2 mL) and the reaction mixture stirred for 20 h at ambient temperature. An additional portion of MeOH/NH$_3$ solution (1 mL) was added and the solution stirred for 48 h at ambient temperature. The mixture was concentrated under vacuum and the residue chromatographed (dry method, EtOAc) to give *Z*-**89** (15.0 mg, 65%). ^{1}H NMR (MeOH-d_4) δ 1.44 (ddd, $^2J_{H2''-H2'}$=14.2 Hz, $^3J_{H2''-H1'}$=7.9 Hz, $^3J_{H2''-H3'}$=6.6 Hz, 1H, H2''), 1.87 (ddd, $^2J_{H2'-H2''}$=13.6 Hz, $^3J_{H2'-H1'}$=5.9 Hz, $^3J_{H2'-H3'}$=2.7 Hz, 1H, H2'), 3.38 ("d", J_{Avg}=4.4 Hz, 2H, H5' and H5''), 3.70 ("quartet", $^3J_{Avg}$=3.8 Hz, 1H, H4'), 3.97 (ddd, $^3J_{H3'-H2''}$=6.0 Hz, $^3J_{H3'-H4'}$=3.3 Hz, $^3J_{H3'-H2'}$=2.8 Hz, 1H, H3'), 5.81 (dd, $^3J_{H1'-H2''}$=8.0 Hz, $^3J_{H1'-H2'}$=6.0 Hz, 1H, H1'), 6.52 (d, $^3J_{V1-V2}$=13.3 Hz, 1H, vinyl 1), 7.28 (d, $^4J_{H6-V2}$=0.9 Hz, H6), 7.31 (dd, $^3J_{V2-V1}$=13.3 Hz, $^4J_{V2-H6}$=1.1 Hz, 1H, vinyl 2), 7.36-7.41 (m, 9H, Ge*Ph*$_3$), 7.49-7.54 (m, 6H, Ge*Ph*$_3$). ^{13}C NMR (MeOH-d_4) δ 40.34 (C2'), 63.01 (C5'), 72.33 (C3'), 86.27 (C1'), 88.55 (C4'), 115.85 (C5), 129.54 (Ge*Ph*$_3$ x 6), 130.22 (Ge*Ph*$_3$ x 3), 131.78 (vinyl 1), 135.89 (Ge*Ph*$_3$ x 6), 138.08 (Ge*Ph*$_3$ Q x 3), 138.19 (C6), 140.79 (vinyl 2), 151.55 (C2), 164.66 (C4). MS (ESI$^+$) *m/z* 581.1 [M+Na]$^+$ based on ^{74}Ge.

5-[(*E*/*Z*)-2-(Trimethylgermyl)ethenyl]uridine (*E*/*Z*-90). A 0.1 N solution of sodium methoxide in anhydrous MeOH (2 mL) was added to *E*/*Z*-**84a** (18.8 mg, 0.025 mmol; *E*/*Z*, ~45:55) and the mixture stirred for 6 h. An additional portion of 0.1N NaOMe/MeOH solution was added (0.75 mL) and the solution stirred until the starting *E*/*Z*-**84a** was completely consumed. The reaction mixture was carefully neutralized by addition of DOWEX 50WX2-200(H$^+$) until moistened pH paper indicated pH~6.2. The mixture was filtered, and the resin washed with fresh MeOH. The combined filtrate was evaporated under reduced pressure and the residue partitioned between Et$_2$O and H$_2$O. The organic layer was extensively washed with water. The combined aqueous layers were evaporated under vacuum to yield *E*/*Z*-**90** (7.0 mg, 71%; *E*/*Z*, ~42:58). ^{1}H NMR (MeOH-d_4) δ 0.27 (s, 5.22H, Ge*Me*$_3$-*Z*), 0.32 (s, 3.78H, Ge*Me*$_3$-*E*), 3.84-3.91 (m, 1H, H5''-*E*/*Z*), 3.95 (dd, $^{2}J_{\mathrm{H5'-H5''}}$=12.7 Hz, $^{3}J_{\mathrm{H5'-H4'}}$=2.7 Hz, 0.58H, H5'-*Z*), 4.05 (dd, $^{2}J_{\mathrm{H5'-H5''}}$=12.9 Hz, $^{3}J_{\mathrm{H5'-H4'}}$=2.4 Hz, 0.42H, H5'-*E*), 4.18-4.24 (m, 1H, H4'-*E*/*Z*), 4.29 (“t”, $^{3}J_{\mathrm{Avg}}$=5.0 Hz, 0.58H, H3'-*Z*), 4.34 (“t”, $^{3}J_{\mathrm{Avg}}$=5.7 Hz, 0.42H, H3'-*E*), 4.39-4.44 (m,1H, H2'-*E*/*Z*), 6.00 (d, $^{3}J_{\mathrm{H1'-H2'}}$=3.8 Hz, 0.42H, H1'-*E*), 6.05 (d, $^{3}J_{\mathrm{H1'-H2'}}$=5.3 Hz, 0.58H, H1'-*Z*), 6.36 (d, $^{3}J_{\mathrm{V1-V2}}$=13.6 Hz, 0.58H, vinyl 1-*Z*), 6.70 (d, $^{3}J_{\mathrm{V1-V2}}$=19.0 Hz, 0.42H, vinyl 1-*E*), 6.83 (d, $^{3}J_{\mathrm{V2-V1}}$=19.0 Hz, 0.42H, vinyl 2-*E*), 6.93 (d, $^{3}J_{\mathrm{V2-V1}}$=13.6 Hz, 0.58H, vinyl 2-*Z*), 7.77 (s, 0.58H, H6-*Z*), 8.20 (s, 0.42H, H6-*E*). ^{13}C NMR (MeOH-d_4) δ -2.89 (Ge*Me*$_3$-*E*), -1.17 (Ge*Me*$_3$-*Z*), 60.14 (C5'-*E*), 60.98 (C5-*Z*), 68.90 (C3'-*E*), 69.83 (C3'-*Z*), 73.70 (C2'-*Z*), 74.13 (C2'-*E*), 83.98 (C4'-*E*), 84.72 (C4'-*Z*), 88.83 (C1'-*E*), 89.72 (C1'-*Z*), 113.75 (C5-*E*), 115.68 (C5-*Z*), 132.07 (vinyl 1-*E*), 134.11 (vinyl 2-*Z*), 134.67 (vinyl 2-*E*), 137.60 (C6-*E*), 137.83 (C6-*Z*), 140.81 (vinyl 1-*Z*), 151.07 (C2-*E*), 151.64 (C2-*Z*), 164.60 (C4-*E*), 165.34 (C4-*Z*).

1-*N*-Benzyluracil (97). In a flame-dried 100 mL round-bottomed flask uracil (1.7960 g, 16.02 mmol) was suspended in 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (20 mL) and stirred for 10 min under nitrogen. Trimethylsilyl chloride (687.2 mg, 800 μL, 6.33 mmol) was added via syringe and the resulting mixture refluxed (125 °C, oil bath) for 2 h until it became a clear solution. While still hot, the mixture was filtered by gravity and washed with fresh 1,2-dichloroethane (1,2-DCE) (25 mL). The liquid and washings were collected in a dried 250 mL round-bottomed flask and concentrated in vacuo to give a white solid. The solid was dissolved in fresh 1,2-DCE (72 mL) and benzyl bromide (3.29 g, 2.29 mL, 19.25 mmol) was added followed by I_2 (100 mg, 0.39 mmol). The resulting orange solution was then refluxed (92 °C) until TLC analysis revealed no additional progress. The hot solution was filtered by gravity and the filtrate washed two times with 1,2-DCE. The mother liquor was concentrated and thoroughly dried under vacuum to give an orange solid. Recrystallization from EtOH gave **97** as a white solid (2.10 g, 65%) with data identical as reported.[173] ^{1}H NMR δ 4.92 (s, 2H, Ph-C*H*$_2$), 5.70 (dd, $^3J_{\text{H5-H6}}$=7.9 Hz, $^4J_{\text{H5-NH}}$=2.2 Hz, 1H, H5), 7.15 (d, $^3J_{\text{H6-H5}}$=7.9 Hz, 1H, H6), 7.27-7.41 (m, 5H, *Ph*). GC-MS (t_R 21.90 min) *m*/*z* 202 (27, M$^+$), 200 (<1), 91 (100).

1-*N*-Benzyl-4-thiouracil (98). Compound **97** (501.1 mg, 2.48 mmol) was placed in a flamed-dry round-bottomed flask under a N_2 atmosphere and dissolved in dry THF (44 mL). Previously dried Lawesson's reagent (1.02 g, 2.52 mmol) was added and the resulting suspension heated at 56 °C for about 1 h until TLC showed ~95% consumption of the substrate **97**. The volume of solvent was reduced to half and the solution washed with a saturated solution of $NaHCO_3$ and partitioned with EtOAc. The organic phase was washed with H_2O two times and dried over anhydrous Na_2SO_4. After removal of the volatiles the resulting crude was chromatographed (hexanes/EtOAc, 3:2) to give **98** (315.0 mg, 65%) as yellow oil of a sufficient purity to be used directly in next step. ^{1}H NMR δ 4.92 (s, 2H, Ph-C*H*$_2$), 6.36 (d, $^3J_{\text{H5-H6}}$=7.5 Hz, 1H, H5), 6.98 (d, $^3J_{\text{H6-H5}}$=7.5 Hz, 1H, H6), 7.28-7.33 (m, 2H, *Ph*), 7.34-7.43 (m, 3H, *Ph*), 9.86 (br. s, 1H, NH). ^{13}C NMR δ 51.87 (Ph-*C*H$_2$), 113.49 (C5), 128.25, 128.89, 129.30 (*Ph*), 134.40 (*Ph-Q*), 138.63 (C6), 148.42 (C2), 189.75 (C4).

1-Benzyl-4-(methylthio)-2(1*H*)-pyrimidinone (99). Compound **98** (314.8 mg, 1.44 mmol) was dissolved in dry CH_2Cl_2 (42 mL) and mixed with freshly distilled Et_3N (146.2 mg, 203 μL, 1.44 mmol). The resulting yellow solution was stirred for 10 min under N_2

and methyl iodide (410.4 mg, 180 μL, 2.89 mmol) was added via syringe. The reaction vessel was covered with aluminum foil and stirred at room temperature for 1.5 h. The volatiles were removed under vacuum and the crude dissolved in CH_2Cl_2 and washed two times with H_2O. The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness to give **99** (320.0 mg, 93%). ^{1}H NMR δ 2.57 (s, 3H, S-*Me*), 5.04 (s, 2H, Ph-C*H*$_2$), 6.16 (d, $^3J_{H5\text{-}H6}$=6.8 Hz, 1H, H5), 7.22 (d, $^3J_{H6\text{-}H5}$=6.8 Hz, 1H, H6), 7.29-7.40 (m, 5H, *Ph*). ^{13}C NMR δ 12.85 (S-*Me*), 52.94 (Ph-*C*H$_2$), 103.78 (C5), 128.48, 128.49, 129.09 (*Ph*), 135.39 (*Ph-Q*), 143.05 (C6), 154.93 (C2), 177.69 (C4). GC-MS (t_R 24.39 min.) *m*/*z* 232 (44, M$^+$), 91 (100).

4-[^{18}O]-1-*N*-benzyluracil (100). Compound **99** (248.5 mg, 1.07 mmol) was suspended in anhydrous absolute EtOH (6 mL) and stirred at room temperature for 5 min in a screw-capped glass tube. Isotope enriched $H_2[^{18}O]$ (277.0 mg, 250.0 μL, 12.5 mmol, 99.2% ^{18}O) was added via syringe followed by three drops of concentrated HCl and the mixture was heated at 78°C until TLC showed complete conversion to a spot with identical *Rf* as compound **97**. The volatiles were removed under vacuum and the residue was dissolved in $CHCl_3$ and was washed successively with a saturated solution of $NaHCO_3$ and H_2O. The volatiles were evaporated and the residue was chromatographed (hexanes/EtOAc, 2:3) to give **100** (197 mg, 90 %) as a puffy white powder with data identical to the reported above for **97**, except for GC-MS (t_R 21.91 min) *m*/*z* 204 (22, M$^+$), 202 (4.4, M-2), 91 (100). [^{16}O/^{18}O ratio, ~15:85; based on comparison of the peak intensities at *m*/*z* 202 (M$^+$, **97**) and *m*/*z* 204 (M$^+$, **100**)].

1-*N*-Benzyl-5-iodouracil (101). In a round-bottomed flask **97** (297.6 mg, 1.47 mmol) was dissolved in dry CH_2Cl_2 (30 mL) and stirred under N_2 until the solution became clear. Iodine monochloride (ICl) (361.0 mg, 2.22 mmol) was added and the resulting red-wine solution refluxed (41 °C) until TLC showed complete consumption of **97**. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and decolorized with the minimum amount of 2% $NaHSO_3$ aqueous solution. The organic phase was washed with H_2O (20 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent gave compound **101** (446.4 mg, 93%) as a slightly yellow solid. ^{1}H NMR δ 4.92 (s, 2H, Ph-CH_2), 7.28-7.32 (m, 2H, *Ph*), 7.35-7.44 (m, 3H, *Ph*), 7.59 (s, 1H, H6), 8.42 (br. s, 1H, NH). ^{13}C NMR δ 51.59 (Ph-CH_2), 68.22 (C5), 128.13, 128.91, 129.33 (*Ph*), 134.61 (*Ph-Q*), 148.26 (C6), 150.42 (C2), 159.93 (C4). GC-MS (t_R 25.90 min.) *m*/*z* 328 (30, M$^+$), 91 (100), no peak at *m*/*z* 326 (M-2)$^+$.

4-[^{18}O]-1-*N*-benzyl-5-iodouracil (102). Treatment of **100** (256.8 mg, 1.26 mmol) with iodine monochloride (ICl) (310.0 mg, 1.91 mmol) as described for **101**, afforded compound **102** (393.6 mg, 95%) as a slightly yellow solid with data identical to that reported above for **101**, except for GC-MS (t_R 25.90 min.) *m*/*z* 330 (24, M$^+$), 328 (5, M-2), 91 (100). [^{16}O/^{18}O ratio, ~17:83; based on comparison of the peak intensities at *m*/*z* 328 (M$^+$, **101**) and *m*/*z* 330 (M$^+$, **102**)].

1-*N*-Benzyl-5-((trimethylsilyl)ethynyl)uracil (103). Compound **101** (602.0 mg, 1.83 mmol) was suspended in freshly distilled Et_3N (56 mL) and the mixture degassed for 1 h. Trimethylsilylacetylene (723.0 mg, 1.04 mL, 7.36 mmol) was added to the suspension followed by $(PPh_3)_2PdCl_2$ (30 mg, 0.043 mmol) and CuI (22 mg, 0.12 mmol). The mixture was then heated at 50 °C until TLC confirmed total consumption of the starting **101**. All the volatiles were removed under vacuum and the brown residue was chromatographed (hexanes/EtOAc, 1:1) to give **103** (438.0 mg, 80%) as a pale-yellow solid. ^{1}H NMR δ 0.21 (s, 9H, Si*Me*$_3$), 4.92 (s, 2H, Ph-*CH*$_2$), 7.28-7.32 (m, 2H, *Ph*), 7.35-7.43 (m, 3H, *Ph*), 7.47 (s, 1H, H6), 8.35 (br. s, 1H, NH). ^{13}C NMR δ -0.18 (Si*Me*$_3$), 51.72 (Ph-*CH*$_2$), 94.78, 100.14, 100.61 (C5, *C≡C*), 128.09, 128.85, 129.29 (*Ph*), 134.62 (*Ph-Q*), 147.06 (C6), 149.74 (C2), 161.01 (C4). GC-MS (t_R 26.68 min.) *m*/*z* 298 (29, M$^+$), 283 (29, M-15), 91 (100), no peak at *m*/*z* 296 (M-2)$^+$.

4-[^{18}O]-1-*N*-Benzyl-5-((trimethylsilyl)ethynyl)uracil (104). Treatment of **102** (388.0 mg, 1.18 mmol) as described for **103** gave compound **104** (218.0 mg, 62%) as a pale-yellow solid with data identical to that reported above for **103**, except for GC-MS (t_R 26.67 min.) *m*/*z* 300 (23, M$^+$), 298 (4, M-2), 285 (23, M-15), 91 (100). [^{16}O/^{18}O ratio, ~14:86; based on comparison of the peak intensities at *m*/*z* 298 (M$^+$, **103**) and *m*/*z* 300 (M$^+$, **104**)].

1-*N*-Benzyl-5-ethynyluracil (105). Procedure A. Compound **103** (560.0 mg, 1.88 mmol) was dissolved in dry THF (32 mL) and the clear solution stirred at 0 °C for about 20 min. Tetrabutylammonium fluoride (1.88 mL, 1.88 mmol, 1 M in THF) was added via syringe and the solution stirred for one hour at 0 °C. The solvent was removed under reduced pressure and the resulting yellow crude dissolved in $CHCl_3$ (30 mL) and successively washed with saturated $NaHCO_3$ and H_2O. After drying the organic phase over anhydrous Na_2SO_4 the oily residue was chromatographed (CH_2Cl_2/EtOAc, 7:3) to give compound **105** (252.5 mg, 60%) containing a little impurity associated to tetrabutylammonium fluoride. ^{1}H NMR δ 3.18 (s, 1H, C≡C*H*), 4.93 (s, 2H, Ph-*CH*$_2$), 7.27-7.44 (m, 5H, *Ph*), 7.49 (s, 1H, H6), 8.44 (br. s, 1H, NH). ^{13}C NMR δ 51.76 (Ph-*CH*$_2$), 74.20, 82.40, 99.37 (C5, *C*≡*C*H), 128.20, 128.95, 129.34 (*Ph*), 134.39 (*Ph-Q*), 147.35 (C6), 149.67 (C2), 161.18 (C4). GC-MS (t_R 24.11 min) *m*/*z* 226 (19, M^+), 91 (100), no peak at *m*/*z* 224 $(M-2)^+$. HRMS calcd for $C_{13}H_{11}N_2O_2$ (MH^+) 227.08205. Found 227.08191.

Procedure B. Compound **103** (645.0 mg, 2.16 mmol) was suspended in MeOH (15 mL) and ammonium fluoride (1.04 g, 28.08 mmol) added. The resulting heterogeneous mixture was refluxed (60 °C) until TLC confirmed the total consumption of the starting **103**. The reaction mixture was allowed to cool down to ambient temperature and filtered by gravity to removed undissolved NH_4F. The volatiles were evaporated and the residue chromatographed (dry method, $CHCl_3$) to afford **105** (281.0 mg, 57%) as a white solid.

4-[^{18}O]-1-*N*-Benzyl-5-ethynyluracil (106). Treatment of **103** (209.0 mg, 0.70 mmol) as described in Procedure A, afforded compound **106** (91.5 mg, 58%) as a white powder with data identical to the reported above for **105**, except for GC-MS (t_R 24.12 min) *m*/*z*, 228 (16, M^+), 226 (3, M-2), 91 (100). [$^{16}O/^{18}O$ ratio, ~14:86; based on comparison of the peak intensities at *m*/*z* 226 (M^+, **105**) and *m*/*z* 228 (M^+, **106**)]. HRMS calcd for $C_{13}H_{11}N_2O^{18}O$ (MH^+) 229.08630. Found 229.08594.

(*Z*)-1-*N*-Benzyl-5-(2-(triphenylgermyl)ethenyl)uracil (*Z*-107). In a screw-capped glass tube **105** (49.7 mg, 0.22 mmol) was dissolved in dry THF (5 mL) and stirred for 20 min under N_2 at 0 °C. Triphenylgermanium hydride (73.0 mg, 0.24 mmol) and Et_3B (265 uL, 0.265 mmol, 1M in THF) were added and the solution stirred at 0 °C for 7 h (Method B). The volatiles were removed under reduced pressure and the resulting bright-yellow liquid chromatographed (hexanes/EtOAc, 1:1) to give *Z*-**107** (54.1 mg, 46%). ^{1}H NMR δ 4.03 (s, 2H, Ph-CH_2), 6.30 (d, $^3J_{V1-V2}$=13.5 Hz, 1H, vinyl 1), 6.69 (“d”, $^3J_{o-m}$=7.0 Hz, Ph-*H*-ortho), 6.84 (s, 1H, H6), 7.09 (“t”, $^3J_{m-o/p}$=7.5 Hz, Ph-*H*-meta), 7.16 (“t”, $^3J_{p-m}$=7.1 Hz, Ph-*H*-para), 7.23-7.35 (m, 10H, Ge*Ph*$_3$ + vinyl 2), 7.37-7.46 (m, 6H, Ge*Ph*$_3$), 8.51 (br. s, 1H, NH). ^{13}C NMR δ 51.21 (Ph-*CH*$_2$), 113.71 (C5), 128.27 (Ph-*C*H-ortho), 128.30 (vinyl 1), 128.44 (Ph-*C*H-para), 128.76 (Ge*Ph*$_3$ x6), 129.03 (Ph-*C*H-meta), 129.47 (Ge*Ph*$_3$ x 3), 134.78 (Ge*Ph*$_3$ x 6), 135.02 (Ph-*Q*), 136.65 (Ge*Ph*$_3$ Q x 3), 138.74 (vinyl 2), 141.03 (C6), 150.18 (C2), 162.53 (C4).

1-*N*-Benzyl-5-(2-(triphenylgermyl)acetyl)uracil (108). In a screw-capped glass tube **105** (50.0 mg, 0.22 mmol) was suspended in dry toluene (5 mL) and the mixture degassed using N$_2$ for 50 min. Triphenylgermanium hydride (73.0 mg, 0.24 mmol) and 1,1'-azobis(cyclohexanecarbonitrile) (catalytic amount) were added and the suspension heated at 85 °C for 2 h (TLC showed approximately 80% consumption of **105** relative to a new higher moving spot). The volatiles were evaporated under vacuum and the resulting yellow oil slowly chromatographed (hexanes/EtOAc, 3:2) to give two fractions. The first fraction contained **108** (3.5 mg, 3%) while the second gave an inseparable mixture of **108** and *Z*-**107** (28.2 mg). Compound **108** had: ^{1}H NMR δ 3.81 (s, 2H, H8), 4.77 (s, 2H, Ph-*CH*$_2$), 7.24-7.40 (m, 14H, Ge*Ph*$_3$ + Ph-*H*), 7.48-7.54 (m, 6H, Ge*Ph*$_3$), 7.79 (br. s, 1H, NH), 7.85 (s, 1H, H6). ^{13}C NMR δ 33.11 (C8), 52.38 (Ph-*C*H$_2$), 113.30 (C5), 128.30 (Ge*Ph*$_3$ x 6), 128.46 (Ph-*C*H-ortho), 129.09 (Ph-*C*H-para), 129.34 (Ph-*C*H-meta), 129.45 (Ge*Ph*$_3$ x 3), 134.51 (Ph-*Q*), 135.15 (Ge*Ph*$_3$ x 6), 135.29 (Ge*Ph*$_3$ Q x 3), 149.70 (C2), 149.88 (C6), 160.68 (C4), 194.30 (C7-ketone). MS (ESI$^+$) *m*/*z* 605.0 [M+58]$^+$; MS (EI) 547.0 (85, M$^+$), 469.0 (24), 305.0 (100).

4-[^{18}O]-1-*N*-Benzyl-5-(2-(triphenylgermyl)acetyl)uracil (110). Treatment of **106** (44.5 mg, 0.20 mmol) as described for **108**, afforded two fractions after chromatography (hexanes/EtOAc, 3:2). The first fraction contained **110** (3.3 mg, 3%) while the second consists of a mixture of **110** and *Z*-**109** (25.3 mg). Both compounds *Z*-**109** and byproduct **110** showed identical NMR data as reported above for the unlabeled analogues *Z*-**107** and **108**. However, for compound **110**; MS (ESI$^+$) *m*/*z* 607.0 [M+58] and MS (EI) *m*/*z* 547.1 (9, M$^+$), 457.1 (28), 305.0 (100).

1-(2,3,5-Tri-*O*-acetyl-*β*-D-arabinofuranosyl)-5-[(*E*/*Z*)-2-(tris(trimethylsilyl)germyl)-ethenyl]uracil (*E*/*Z*-111). A flame-dried 3 neck round-bottomed flask was charged with dry and degassed toluene (10 mL) circulating N_2. The compound **74** (127.0 mg, 0.322 mmol) was transferred into the flask and the resulting heterogeneous mixture was stirred and degassed for additional 30 min. The suspension was pre-heated up to 90 ^oC and just when all the solid was dissolved, tris(trimethylsilyl)germane (TMS)GeH (115.3 mg, 123 μL, 0.39 mmol) was added via syringe in one portion and fast. A catalytic amount of 1,1'-azobis(cyclohexanecarbonitrile) was dissolved in degassed toluene (1 mL) and transferred to the reaction mixture. The solution was refluxed over 20 min and TLC revealed total consumption of **74**. The mixture was immediately allowed to stabilize at room temperature and concentrated under reduced pressure. The residue was chromatographed (hexanes/EtOAc, 3:2) to give *E*/*Z*-**111** (152.0 mg, 68%, *E*/*Z* 4:96). ^{1}H NMR δ 0.20 (s, 25.92H, Ge(*TMS*)$_3$-*Z*), 0.24 (s, 1.08H, Ge(*TMS*)$_3$-*E*), 2.01 (s, 2.88H, Ac-*Me*-*Z*), 2.10 (s, 2.88H, Ac-*Me*-*Z*), 2.11 (s, 0.12H, Ac-*Me*-*E*), 2.13 (s, 0.12H, Ac-*Me*-*E*), 2.14 (s, 2.88H, Ac-*Me*-*Z*), 2.16 (s, 0.12H, Ac-*Me*-*E*), 4.17-4.24 (m, 1H, H4'-*E*/*Z*), 4.32-4.40 (m, 0.04H, H5''-*E*), 4.34 (dd, $^2J_{H5''\text{-}H5'}$=12.0 Hz, $^3J_{H5''\text{-}H4'}$=5.5 Hz, 0.96H, H5''-*Z*), 4.38 (dd, $^2J_{H5'\text{-}H5''}$=12.0 Hz, $^3J_{H5'\text{-}H4'}$=5.2 Hz, 0.96H, H5'-*Z*), 4.58 (dd, $^2J_{H5'\text{-}H5''}$=11.9 Hz, $^3J_{H5'\text{-}H4'}$=7.3 Hz, 0.04H, H5'-*E*), 5.07 (dd, ^3J=1.8 Hz, ^3J=0.6 Hz, 0.04H, H3'-*E*), 5.14 (dd, $^3J_{H3'\text{-}H4'}$=3.8 Hz, $^3J_{H3'\text{-}H2'}$=1.6 Hz, 0.96H, H3'-*Z*), 5.40 (dd, $^3J_{H2'\text{-}H1'}$=3.5 Hz, $^3J_{H2'\text{-}H3'}$=1.0 Hz, 0.04H, H2'-*E*), 5.47 (dd, $^{3}J_{\mathrm{H2'-H1'}}$=3.8 Hz, $^{3}J_{\mathrm{H2'-H3'}}$=1.7 Hz, 0.96H, H2'-*Z*), 6.16 (d, $^{3}J_{\mathrm{H1'-H2'}}$=3.9 Hz, 0.96H, H1'-*Z*), 6.28 (d, $^{3}J_{\mathrm{V1-V2}}$=13.5 Hz, 0.96H, vinyl 1-*Z*), 6.36 (d, $^{3}J_{\mathrm{H1'-H2'}}$=3.5 Hz, 0.04H, H1'-*E*), 6.63 (d, $^{3}J_{\mathrm{V1-V2}}$=18.7 Hz, 0.04H, vinyl 1-*E*), 6.86 (d, $^{3}J_{\mathrm{V2-V1}}$=18.5 Hz, 0.04H, vinyl 2-*E*), 6.90 (dd, $^{3}J_{\mathrm{V2-V1}}$=13.5 Hz, $^{4}J_{\mathrm{V2-H6}}$=1.4 Hz, 0.96H, vinyl 2-*Z*), 7.29 (d, $^{4}J_{\mathrm{H6-V2}}$=1.4 Hz, 0.96H, H6-*Z*), 7.52 (s, 0.04H, H6-*E*), 9.00 (br. s, 1H, NH-*Z*). ^{13}C NMR δ 1.73 (Ge(*TMS*)$_3$-*E*), 1.95 (Ge(*TMS*)$_3$-*Z*), 20.66, 20.88, 20.96 (Ac-*CH$_3$*-*Z*), 63.07 (C5'-*Z*), 74.95 (C2'-*Z*), 76.46 (C3'-*Z*), 80.71 (C4'-*Z*), 85.40 (C1'-*Z*), 116.09 (C5-*Z*), 133.88 (vinyl 2-*Z*), 134.11 (vinyl 1-*Z*), 136.20 (C6-*Z*), 149.59 (C2-*Z*), 161.95 (C4-*Z*), 168.86, 169.71, 170.56 (Ac-*C*=*O*). MS (APCI$^+$) *m*/*z* 688.9 [MH]$^+$ based on ^{74}Ge.

5-[(*Z*)-2-(tris(trimethylsilyl)germyl)ethenyl]-2',3',5'-tri-*O*-*p*-toluoyl-uridine (*Z*-112). A solution of **82a** (38.0 mg, 0.061 mmol) and (Me$_3$Si)$_3$GeH (21.6 mg, 23 μL, 0.074 mmol) in dry THF (4 mL) was treated according to Method B (with progressive warming from -78 °C to 0 °C) for 6 h. The volatiles were removed under vacuum and the oily residue was chromatographed (hexanes/EtOAc, 3:2) to give *Z*-**112** (27.5 mg, 61%). ^{1}H NMR δ 0.16 (s, 27H, Ge(*TMS*)$_3$), 2.39 (s, 6H, *p*-Tol-*Me*), 2.40 (s, 3H, *p*-Tol-*Me*), 4.62 (dd, $^{2}J_{\mathrm{H5''-H5'}}$=11.5 Hz, $^{3}J_{\mathrm{H5''-H4'}}$=4.7 Hz, 1H, H5''), 4.65-4.71 (m, 1H, H4'), 4.73 (dd, $^{2}J_{\mathrm{H5'-H5''}}$=11.5 Hz, $^{3}J_{\mathrm{H5'-H4'}}$=3.0 Hz, 1H, H5'), 5.90-5.96 (m, 3H, H1'/H2'/H3'), 6.17 (d, $^{3}J_{\mathrm{V1-V2}}$=13.5 Hz, 1H, vinyl 1), 6.79 (dd, $^{3}J_{\mathrm{V2-V1}}$=13.5 Hz, $^{4}J_{\mathrm{V2-H6}}$=1.1 Hz, 1H, vinyl 2), 7.14 (d, $^{3}J_{\mathrm{o-m}}$=7.6 Hz, 2H, *p*-Tol-*H*), 7.17 (d, $^{3}J_{\mathrm{o-m}}$=7.6 Hz, 2H, *p*-Tol-*H*), 7.19-7.24 (m, 3H, *p*-Tol-*H* + H6), 7.82 (d, $^{3}J_{\mathrm{o-m}}$=8.2 Hz, 4H, *p*-Tol-*H*), 7.93 (d, $^{3}J_{\mathrm{o-m}}$=8.2 Hz, 2H, *p*-Tol-*H*). ^{13}C NMR δ 1.93 (Ge(*TMS*)$_3$), 21.84, 21.85 (*p*-Tol-*Me*), 63.84 (C5'), 71.11 and 74.17 (C2' and C3'), 80.59 (C4'), 92.15 (C1'), 116.92 (C5), 126.07, 126.23, 126.87 (*p*-Tol-*Q*), 129.28, 129.36, 129.93, 129.98, 130.04 (*p*-Tol-*C*H), 132.77 (vinyl 1), 133.78 (vinyl 2), 137.46 (C6), 144.20, 144.47, 144.66 (*p*-Tol-*Q*), 149.55 (C2), 162.14 (C4), 165.33, 165.39, 166.30 (*p*-Tol-*C*=*O*). MS (ESI$^+$) *m/z* 939.1 [M+Na]$^+$ based on ^{74}Ge.

***(Z)*-2-(4-Methylphenyl)-1-[tris(trimethylsilyl)silyl]ethene (116b). Method C (Radical hydrosilylation of alkynes).** $(Me_3Si)_3SiH$ (0.31 mL, 248 mg, 1 mmol) was added in one portion via a syringe to a degassed solution of **115b** (0.13 mL, 116 mg, 1 mmol) in dry benzene (3 mL) at ambient temperature under N_2 atmosphere. The AIBN (83.8 mg, 0.50 mmol) was then added and the resulting solution was heated (oil bath, 85 °C) for 3 h or until the alkyne was consumed (GC). The volatiles were evaporated in vacuo and the oily residue was flash chromatographed (hexanes) on silica gel to give **116b** (336 mg, 92%) as a colorless oil: ^{1}H NMR δ 0.16 (s, 27H), 2.37 (s, 3H), 5.82 (d, *J*=14.5 Hz, 1H), 7.16 (d, *J*=7.8 Hz, 2H), 7.22 (d, *J*=7.8 Hz, 2H), 7.40 (d, *J*=14.5 Hz, 1H); ^{13}C NMR δ 1.4, 21.3, 123.1, 128.1, 129.0, 137.1, 137.8, 146.6; ^{29}Si NMR d -88.33 [s, *Si*$(SiMe_3)_3$], -11.67 [s, Si(*Si*$Me_3)_3$]; GC-MS: (t_R 22.12 min) *m/z* 364 (6, M$^+$), 174 (100). HRMS Calcd for $C_{18}H_{36}Si_4$ (M$^+$): 364.1894. Found: 364.1896.

***(Z)*-2-(4-Methoxyphenyl)-1-[tris(trimethylsilyl)silyl]ethene (116c).** Treatment of **115c** (0.13 mL, 136 mg, 1 mmol) with $(Me_3Si)_3SiH$ (0.31 mL, 248 mg, 1.0 mmol) and AIBN (84 mg, 0.5 mmol) by method C gave **116c** (308 mg, 81%) as a colorless oil: ^{1}H NMR δ 0.17 (s, 27H), 3.84 (s, 3H), 5.80 (d, *J*=14.4 Hz, 1H), 6.87 (d, *J*=8.7 Hz, 2H), 7.33 (d, *J*=8.7 Hz, 2H), 7.38 (d, *J*=14.4 Hz, 1H); ^{13}C NMR δ 1.4, 55.5, 113.8, 121.9, 129.4, 133.5, 146.1, 159.1; MS *m/z* 380 (10, M$^+$), 174 (100). Anal. Calcd for $C_{18}H_{36}OSi_4$ (380.82): C, 56.77; H, 9.53. Found: C, 56.37; H, 9.78.

***(Z)*-2-(4-Trifluoromethylphenyl)-1-[tris(trimethylsilyl)silyl]ethene (116d).** Treatment of **115d** (0.16 mL, 170 mg, 1 mmol) with $(Me_3Si)_3SiH$ (0.31 mL, 248 mg, 1 mmol) and

AIBN (84 mg, 0.50 mmol) by method C gave **116d** (334 mg, 80%) as a colorless oil: ^{1}H NMR δ 0.16 (s, 27H), 6.09 (d, *J*=14.6 Hz, 1H), 7.45 (d, *J*=14.6 Hz, 1H), 7.47 (d, *J*=8.2 Hz, 2H), 7.60 (d, *J*=8.2 Hz, 2H); ^{13}C NMR δ 1.35, 124.37 (q, *J*=272.0 Hz), 125.40 (q, *J*=3.8 Hz), 128.15, 128.36, 129.35 (q, *J*=32.6 Hz), 144.24, 144.98; ^{19}F NMR δ -62.45 (s); MS *m/z* 418 (3, M$^+$), 174 (100). Anal. Calcd for $C_{18}H_{33}F_3Si_4$ (418.79): C, 51.62; H, 7.94. Found: C, 51.58; H, 8.15.

***(E)*-2-Phenyl-1-[tris(trimethylsilyl)silyl]ethene (117a).** The vinyl silane (*Z*)-**116a**[178] (350 mg, 1 mmol), $(Me_3Si)_3SiH$ (0.15 mL, 124 mg, 0.5 mmol), $Rh(COD)_2BF_4$ (40.7 mg, 0.1 mmol), PPh_3 (52.5 mg, 0.2 mmol) and NaI (22.5 mg, 0.15 mmol) were placed into a screw-capped glass tube. The reaction mixture was heated with stirring at 60 °C for 18 h. The volatiles were evaporated and the residue [GC-MS: **117a**/**116a** (*E/Z,* 88:12; t_R 21.04 min, *Z*, t_R 21.33 min, *E*) *m/z* 350 (10, M$^+$), 174 (100)] was chromatographed (hexanes) to give **117a**[178,203] (273 mg, 78%): ^{1}H NMR δ 0.19 (s, 27H), 6.47 (d, *J*=18.8 Hz, 1H), 6.91 (d, *J*=18.8 Hz, 1H), 7.23 (t, *J*=7.2 Hz, 1H), 7.33 (t, *J*=7.3 Hz, 2H), 7.39 (d, *J*=7.3 Hz, 2H); ^{29}Si NMR (THF-d_8) δ -85.30 [s, *Si*$(SiMe_3)_3$], -14.34 [s, Si(*Si*$Me_3)_3$]. HRMS Calcd for $C_{17}H_{34}Si_4$ (M$^+$): 350.1738. Found: 350.1741.

***(E)*-2-(4-Methylphenyl)-1-[tris(trimethylsilyl)silyl]ethene (117b).** Alkyne **115b** (116 mg, 0.127 mL, 1.0 mmol), $Rh(COD)_2BF_4$ (40.7 mg, 0.1 mmol), PPh_3 (52.5 mg, 0.2 mmol), NaI (22.5 mg, 0.15 mmol)] and $(Me_3Si)_3SiH$ (0.37 mL, 297 mg, 1.2 mmol) were placed under nitrogen in a screw-capped glass tube and the resulting mixture was heated with stirring at 60 °C for 20 h. The volatiles were evaporated and the residue [GC-MS: **117b**/**116b** (*E/Z*, 9:1); t_R 22.12 min, *Z*; 22.39 min, *E*] was chromatographed (hexanes) to give **117b** (298 mg, 82%): ^{1}H NMR δ 0.19 (s, 27H), 2.36 (s, 3H), 6.39 (d, *J*=18.8 Hz, 1H), 6.83 (d, *J*=18.8 Hz, 1H), 7.16 (d, *J*=7.9 Hz, 2H), 7.24 (d, *J*=7.8 Hz, 2H); ^{13}C NMR δ 1.1, 21.4, 121.4, 126.1, 129.4, 136.6, 137.5, 145.5; ^{29}Si NMR d -83.41 [s, *Si*(SiMe$_3$)$_3$], -12.49 [s, Si(*Si*Me$_3$)$_3$]; GC-MS: (t_R 22.39 min) *m/z* 364 (10, M$^+$), 174 (100). HRMS Calcd for $C_{18}H_{36}Si_4$ (M$^+$): 364.1894. Found: 364.1898.

The vinyl silane (*Z*)-**116b** (1.06 g, 2.92 mmol), (MeSi)$_3$SiH (0.435 mL, 342 mg, 1.375 mmol), RhCl(PPh$_3$)$_3$ (112 mg, 0.275 mmol) and NaI (61.6 mg, 0.42 mmol) were place into a screw-capped glass tube. The reaction mixture was heated with stirring at 75 °C for 54 h. The volatiles were evaporated and the residue [GC-MS: **117b**/**116b** (*E/Z*, 99.5:0.5)] was chromatographed (hexanes) to give **117b** (987 mg, 93%) as colorless oil.

***(E)*-2-(4-Methoxyphenyl)-1-[tris(trimethylsilyl)silyl]ethene (117c).** The vinyl silane (*Z*)-**116c** (381 mg, 1 mmol), (Me$_3$Si)$_3$SiH (0.15 mL, 124 mg, 0.5 mmol), Rh(COD)$_2$BF$_4$ (40.7 mg, 0.1 mmol), PPh$_3$ (52.5 mg, 0.2 mmol) and NaI (22.5 mg, 0.15 mmol) were placed into a screw-capped glass tube. The reaction mixture was heated with stirring at 60 °C for 18 h. The volatiles were evaporated and the residue [GC-MS: **117c**/**116c** (*E/Z,* 92:8; t_R 22.02 min, *Z*, t_R 22.34 min, *E*) *m/z* 380 (15, M$^+$), 174 (100)] was chromatographed (hexanes) to give **117c** (338 mg, 89%): ^{1}H NMR δ 0.25 (s, 27H), 3.84 (s, 3H), 6.29 (d, *J*=18.8 Hz, 1H), 6.87 (d, *J*=18.8 Hz, 1H), 6.89 (d, *J*=8.8 Hz, 2H), 7.35 (d, *J*=8.8 Hz, 2H); ^{13}C NMR δ 1.0, 55.4, 114.0, 119.6, 127.2, 132.4, 145.0, 159.3. AP-ESI-HRMS Calcd for $C_{18}H_{36}ONaSi_4$ (MNa$^+$): 403.1735. Found: 403.1739.

(*E*)-1,2-Diphenylethene (118a). Method D (Pd-catalyzed cross-coupling of vinyl TTMS-silanes with NaOH as base). A solution of NaOH (60 mg, 1.5 mmol) and H_2O_2 (30% solution, 0.15 mL, 1.5 mmol) in deionized H_2O (1.5 mL) were added to a stirred solution of **117a** (175 mg, 0.5 mmol) in THF (15 mL) at ambient temperature. After 15 min, iodobenzene (84 μL, 153 mg, 0.75 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) and tetrabutylammonium fluoride (1M/THF, 1.5 mL, 1.5 mmol) were added and the resulting brownish mixture was heated at 55 °C (oil bath) for 10 h. The volatiles were evaporated and the residue was partitioned ($H_2O/CHCl_3$). The aliquot of the organic layer was subjected to GC-MS and/or ^{1}H NMR analysis in order to establish the overall stereochemistry. The organic layer was dried ($MgSO_4$), evaporated and chromatographed (hexanes) to give (*E*)-**118a** (74 mg, 83%) with data identical to commercial sample: GC-MS (t_R 17.9 min, *E*) *m/z* 180 (100, M^+).

Treatment of **117a** (35 mg, 0.10 mmol) with bromobenzene (16 μL, 23.6 mg, 0.15 mmol) by method D gave (*E*)-**118** (12 mg, 67%).

Analogous treatment of **117a** (35 mg, 0.10 mmol) with iodobenzene (17 μL, 31 mg, 0.15 mmol) by method D (without TBAF) gave (*E*)-**118a** (13.5 mg, 75%).

Analogous treatment of **117a** (35 mg, 0.10 mmol) with bromobenzene (16 μL, 23.6 mg, 0.15 mmol) by method D (without TBAF) gave (*E*)-**118a** (9 mg, 50%). Also, biphenyl (1%; e.g., 2% consumption of bromobenzene) was detected: GC-MS (t_R 11.3 min) *m/z* 154 (100, M^+).

Method E (Pd-catalyzed cross-coupling of TTMS-silanes with $KOSiMe_3$ as base). $KOSiMe_3$ (38.5 mg, 0.3 mmol) and H_2O_2 (30% solution, 31 μL, 0.30 mmol) were added to a stirred solution of **117a** (35 mg, 0.10 mmol) in THF (3 mL) at ambient temperature. After 20 min, iodobenzene (17 μL, 31 mg, 0.15 mmol) and $Pd(PPh_3)_4$ (11 mg, 0.01 mmol) were added and the resulting mixture was heated at 55 °C (oil bath) for 10 h. Aqueous work-up and purification as described in method D gave (*E*)-**118a** (11 mg, 60%).

(*E/Z*)-1,2-Diphenylethene (118a). Treatment of **116a**[178] (35 mg, 0.10 mmol) with bromobenzene (16 µL, 23.6 mg, 0.15 mmol) by method D gave **118a** (*E/Z*, 40:60; 15 mg, 82%) with data identical to commercial sample: GC-MS (t_R 15.1 min, Z; t_R 17.9 min, *E*) *m/z* 180 (100, M^+). HRMS Calcd for $C_{14}H_{13}$ (MH^+): 181.1073. Found: 181.1079.

Analogous treatment of **116a** (35 mg, 0.10 mmol) with bromobenzene (16 µL, 23.6 mg, 0.15 mmol) by method D (without TBAF) gave **118a** (*E/Z*, 25:75; 10 mg, 55%). Also, biphenyl (3%; e.g. 6% consumption of bromobenzene) was detected (GC-MS).

(*E*)-1-(4-Methylphenyl)-2-phenylethene (118b). Treatment of **117b** (36.5 mg, 0.10 mmol) with iodobenzene (17 µL, 31 mg, 0.15 mmol) by method D gave (*E*)-**118b** (14 mg, 72%) with data as reported:[23] ^{1}H NMR δ 2.22 (s, 3H), 6.92 (d, *J*=18.1 Hz, 1H), 6.98 (d, *J*=18.1 Hz, 1H), 7.03 (d, *J*=7.9 Hz, 2H), 7.13 (t, *J*=7.3 Hz, 1H), 7.22 (t, *J*=7.4 Hz, 2H), 7.30 (d, *J*=8.1 Hz, 2H), 7.39 (d, *J*=7.9 Hz, 2H), GC-MS (t_R 19.6 min) *m/z* 194 (100, M^+).

(*E/Z*)-1-(4-Methylphenyl)-2-phenylethene (118b). Treatment of **116b** (364 mg, 1.0 mmol) with iodobenzene (0.17 mL, 306 mg, 1.5 mmol) by method D gave **118b**[204] (*E/Z*, 3:97; 175 mg, 90%): GC-MS (t_R 16.8 min, *Z*; t_R 19.6 min, *E*) *m/z* 194 (100, M^+). HRMS Calcd for $C_{15}H_{15}$ (MH^+): 195.1174. Found: 195.1179. (*Z*)-**118b** had: ^{1}H NMR δ 2.20 (s, 3H), 6.43 (s, 2H), 6.92 (d, *J*=7.9 Hz, 2H), 7.03 (d, *J*=7.9 Hz, 2H), 7.11-7.20 (m, 5H).

Treatment of **116b** (36.5 mg, 0.10 mmol) with bromobenzene (16 µL, 23.6 mg, 0.15 mmol) by method D gave **118b** (*E/Z*, 30:70; 17 mg, 86%).

Analogous treatment of **116b** (36.5 mg, 0.10 mmol) with iodobenzene (17 µL, 31 mg, 0.15 mmol) by method D (without TBAF) gave **118b** (*E/Z*, 15:85; 12 mg, 61%). Identical coupling with bromobenzene (0.15 mmol) gave **118b** (*E/Z*, 20:80; 8 mg, 40%).

Treatment of **116b** (36.5 mg, 0.10 mmol) with iodobenzene (17 µL, 31 mg, 0.15 mmol) by method E gave **118b** (*E/Z*, 25:75; 11.6 mg, 60%). Identical coupling with bromobenzene (0.15 mmol) gave **118b** (*E/Z*, 10:90; 9 mg, 48%).

Analogous treatment of **116b** (36.5 mg, 0.10 mmol) with iodobenzene (17 µL, 31 mg, 0.15 mmol) by method E [with addition of TBAF (0.3 mmol) as described in method D] gave **118b** (*E/Z*, 2:98; 15.7 mg, 81%).

Analogous treatment of **116b** (36.5 mg, 0.10 mmol) with iodobenzene by method D [using aqueous NaF (12.6 mg, 0.3 mmol) instead of TBAF] gave **118b** (*E/Z*, 40:60; 11.6 mg, 60%).

Analogous treatment of **116b** (36.5 mg, 0.10 mmol) with iodobenzene by method D [using $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol) instead of $Pd(PPh_3)_4$ and without addition of TBAF] gave **118b** (*E/Z*, 25:75; 10 mg, 52%).

(*E*)-1-(4-Methoxyphenyl)-2-phenylethene (118c). Treatment of **117a** (35 mg, 0.10 mmol) with 4-methoxyiodobenzene (35 mg, 0.15 mmol) by method D gave (*E*)-**118c**[204] (14 mg, 79%): ^{1}H NMR δ 3.84 (s, 3H), 6.90 (d, *J*=8.2 Hz, 2H), 6.98 (d, *J*=16.4 Hz, 1H), 7.07 (d, *J*=16.4 Hz, 1H), 7.24 (t, *J*=7.3 Hz, 1H), 7.34 (t, *J*=7.9 Hz, 2H), 7.44-7.51 (m, 4H); ^{13}C NMR δ 55.3, 114.1, 126.2, 126.6, 127.2, 127.7, 128.2, 128.6, 130.1, 137.6, 159.2; MS *m*/*z* 210 (100, M^+).

Treatment of **117c** (35 mg, 0.10 mmol) with bromobenzene (16 µL, 23.6 mg, 0.15 mmol) by method D gave (*E*)-**118c** (13 mg, 63%).

(*E/Z*)-1-(4-Methoxyphenyl)-2-phenylethene (118c). Treatment of **116c** (38 mg, 0.10 mmol) with bromobenzene (16 µL, 23.6 mg, 0.15 mmol) by method D gave *E*/*Z*-**118c**[204] (*E/Z*, 9:91; 20 mg, 97%): GC-MS (t_R 19.0 min, Z; t_R 21.6 min, *E*) *m*/*z* 210 (100, M^+).

HRMS Calcd for $C_{15}H_{14}O$ (M^+ + H): 211.1123. Found: 211.1124. (*Z*)-**118c** had: ^{1}H NMR δ 3.81 (s, 3H), 6.50 ("s", 2H), 6.79 (d, *J*=8.4 Hz, 2H), 7.20-7.31 (m, 7H); ^{13}C NMR δ 55.6, 114.0, 127.3, 128.6, 129.2, 129.2, 130.1, 130.2, 130.6, 138.0, 159.1.

(*E*)-1-(4-Trifluoromethylphenyl)-2-phenylethene (118d). Treatment of **117a** (35 mg, 0.10 mmol) with 4-iodo-*α,α,α*-trifluorotoluene (22 μL, 41 mg, 0.15 mmol) by method D gave (*E*)-**118d**[205] (22.3 mg, 90%): ^{1}H NMR δ 7.12 (d, *J*=16.3 Hz, 1H), 7.22 (d, *J*=16.3 Hz, 1H), 7.31 (t, *J*=7.3 Hz, 1H), 7.39 (t, *J*=7.3 Hz, 2H), 7.34 (d, *J*=7.3 Hz, 2H), 7.61 (br. s, 4H); ^{19}F NMR δ -62.90 (s); MS *m/z* 248 (100, M^+).

(*E/Z*)-1-(4-Trifluoromethylphenyl)-2-phenylethene (118d). Treatment of **116d** (42 mg, 0.10 mmol) with bromobenzene (16 μL, 23.6 mg, 0.15 mmol) by method D gave *E*/*Z*-**118d**[205] (*E/Z*, 55:45; 17 mg, 70%). HRMS Calcd for $C_{15}H_{11}F_3$ (M^+ + H): 249.0891. Found: 249.0883. (*Z*)-**118d** had: ^{1}H NMR δ 6.62 (d, *J*=12.3 Hz, 1H), 6.75 (d, *J*=12.3 Hz, 1H), 7.20-7.35 (m, 5H), 7.41 (d, *J*=7.8 Hz, 2H), 7.50 (d, *J*=7.8 Hz, 2H); ^{19}F NMR δ-62.98 (s); MS *m/z* 248 (100, M^+).

***(E)*-1-(4-*n*-Butylphenyl)-2-(4-methylphenyl)ethene (119b).** Treatment of **117b** (50 mg, 0.14 mmol) with 4-*n*-butyl-1-iodobenzene (36 mL, 54 mg, 0.21 mmol) by method D gave (*E*)-**119b** (20 mg, 59%): ^{1}H NMR δ 0.97 (t, *J*=7.3 Hz, 3H), 1.40 (sextet, *J*=7.4 Hz, 2H), 1.60-1.68 (m, 2H), 2.39 (s, 3H), 2.65 (t, *J*=7.7 Hz, 2H), 7.08 (s, 2H), 7.19 and 7.20 (2 × d, *J*=8.2 Hz, 2H), 7.43 and 7.45 (2 × d, *J*=8.2 Hz, 2H); ^{13}C NMR δ 13.9, 21.2, 22.4, 33.6, 35.4, 126.3, 127.71, 127.72, 128.7, 129.4, 134.8, 135.0, 137.3, 142.4; GC-MS (t_R 24.3 min) *m/z* 250 (70, M^+), 207 (100). HRMS Calcd for $C_{19}H_{22}$ (M^+): 250.1721. Found: 250.1728.

***(E/Z)*-1-(4-*n*-Butylphenyl)-2-(methylphenyl)ethene (119b).** Treatment of **116b** (52 mg, 0.14 mmol) with 4-*n*-butyl-1-iodobenzene (36 mL, 56 mg, 0.21 mmol) by method D gave *E*/*Z*-**119b** (*E/Z*, 24:76; 22 mg, 61%): GC-MS (t_R 21.5 min, *Z*; 24.3 min, *E*) *m/z* 250 (70, M^+), 207 (100). (*Z*)-**119b** had: ^1H NMR δ 0.94 (t, *J*=7.3 Hz, 3H), 1.37 (sextet, *J*=7.5 Hz, 2H), 1.57-1.65 (m, 2H), 2.34 (s, 3H), 2.59 (t, *J*=7.8 Hz, 2H), 6.55 (s, 2H), 7.06 (d, *J*=8.1 Hz, 4H), 7.17-7.22 (m, 4H); ^{13}C NMR δ 14.0, 21.3, 22.4, 33.5, 35.4, 128.2, 128.7, 128.8, 128.9, 129.49, 129.58, 134.5, 134.7, 136.2, 141.3. HRMS Calcd for $C_{19}H_{22}$ (M^+): 250.1721. Found: 250.1728.

***(E)*-1-(4-Methylphenyl)-2-(naphtha-1-yl)ethene (120b).** Treatment of **117b** (35 mg, 0.096 mmol) with 1-iodonaphthalene (22 mL, 37 mg, 0.14 mmol) by method D gave (*E*)-**120b**[206] (16 mg, 70%): ^1H NMR δ 2.42 (s, 3H), 7.16 (d, *J*=16.0 Hz, 1H), 7.25 (d, *J*=8.0 Hz, 2H), 7.50-7.60 (m, 5H), 7.77 (d, *J*=7.2 Hz, 1H), 7.82 (d, *J*=8.2 Hz, 1H), 7.87 (d, *J*=15.9 Hz, 1H), 7.90 (d, *J*=7.5 Hz, 1H), 8.26 (d, *J*=8.0 Hz, 1H); ^{13}C NMR δ 21.3, 123.5, 123.8, 124.8, 125.7, 125.8, 126.0, 126.6, 127.9, 128.6, 129.5, 131.4, 131.7, 133.8, 134.9, 135.2, 137.7; GC-MS (t_R 25.8 min) *m/z* 244 (98, M^+), 229 (100). HRMS Calcd for $C_{19}H_{16}$ (M^+): 244.1252. Found: 244.1253.

Analogous treatment of **117b** (55 mg, 0.15 mmol) with 1-iodonaphthalene (33 mL, 58 mg, 0.22 mmol) by method D (without TBAF) gave (*E*)-**120b** (17 mg, 46%).

Analogous treatment of **117b** (55 mg, 0.15 mmol) with 1-bromonaphthalene (31 mL, 46 mg, 0.22 mmol) by method D gave (*E*)-**120b** (18 mg, 48%).

(*E/Z*)-1-(4-Methylphenyl)-2-(naphtha-1-yl)ethene (120b). Treatment of **116b** (50 mg, 0.14 mmol) with 1-iodonaphthalene (31 mL, 52 mg, 0.21 mmol) by method D gave *E*/*Z*-**120b**[206] (*E/Z*, 15:85; 25 mg, 73%): GC-MS (t_R 23.1 min, *Z*; 25.8 min, *E*) *m/z* 244 (98,

M^+), 229 (100). (*Z*)-**120b** had: ^{1}H NMR δ 2.26 (s, 3H), 6.83 (d, *J*=12.2 Hz, 1H), 6.92 (d, *J*=8.1 Hz, 2H), 7.01 (d, *J*=8.1 Hz, 2H), 7.03 (d, *J*=12.2 Hz, 1H), 7.35-7.42 (m, 2H), 7.48-7.55 (m, 2H), 7.80 (d, *J*=7.7 Hz, 1H), 7.88-7.92 (m, 1H), 8.09-8.14 (m, 1H); ^{13}C NMR δ 21.2, 125.0, 125.6, 125.9, 126.0, 126.4, 127.4, 127.6, 128.4, 128.8, 129.0, 131.6, 131.9, 133.7, 133.9, 135.6, 136.9. HRMS Calcd for $C_{19}H_{16}$ (M^+): 244.1252. Found: 244.1253.

Analogous treatment of **116b** (41 mg, 0.11 mmol) with 1-bromonaphthalene (24 mL, 35 mg, 0.17 mmol) by method D gave *E*/*Z*-**120b** (*E/Z,* 27:73; 14 mg, 51%).

Analogous treatment of **116b** (41 mg, 0.11 mmol) with 1-bromonaphthalene (24 mL, 35 mg, 0.17 mmol) by method D (without TBAF) gave *E*/*Z*-**120b** (*E/Z,* 17:83; 8 mg, 30%).

***(Z)*-2-(4-Methylphenyl)-1-[tris(trimethylsiloxy)silyl]ethene (124).** Treatment of **116b** (50 mg, 0.14 mmol) with 1-iodonaphtalene (22 mL, 35 mg, 0.14 mmol) by method D [without TBAF, 2 h, NaOH (5 equiv.)] and column chromatography (hexanes) gave **124** (4 mg, 7%) and *E*/*Z*-**120b** (*E/Z,* 7:93; 4 mg, 12%). Compound **124** had: ^{1}H NMR δ 0.07 (br s, 27H), 2.36 (s, 3H), 5.50 (d, *J*=15.5 Hz, 1H), 7.12 (d, *J*=7.9 Hz, 2H), 7.21 (d, *J*=15.5 Hz, 1H) 7.44 (d, *J*=8.0 Hz, 2H); ^{29}Si NMR δ -66.0 [s, *Si*($OSiMe_3)_3$], 7.94 [s, Si(O*Si*$Me_3)_3$]; GC-MS (t_R 17.60 min) *m/z* 412 (6, M^+), 175 (100); HRMS Calcd for $C_{18}H_{37}O_3Si_4$ (MH^+): 413.1814. Found: 413.1823.

Triallyl(phenyl)germane (125). In a flame-dried round-bottom flask a solution of trichloro(phenyl)germane (250 mg, 160 mL, 0.976 mmol) in Et_2O (2 mL) was treated with allylmagnesium bromide (3.1 mL, 3.12 mmol, 1 M solution in Et_2O) added dropwise for 20 min at 0 °C. After 1 h stirring at 0 °C the reaction mixture was refluxed (38 °C) overnight. The reaction was allowed to cool to room temperature and quenched with NH_4Cl at 0 °C. The organic layer was separated and the aqueous layer extracted with Et_2O (2x5 mL). The combined extracts were washed with water and brine and dried over anhydrous $MgSO_4$. The crude mixture was concentrated in vacuo and chromatographed (hexanes) to give **125** (227 mg, 85%) as clear oil. ^{1}H NMR δ 2.04 (d, *J*=8.3 Hz, 6H), 4.89 (d, *J*=10.0 Hz, 3H), 4.95 (d, *J*=16.9 Hz, 3H), 5.88 (m, 3H), 7.38 (m, 3H), 7.47 (m, 2H). ^{13}C NMR δ 19.54, 113.67, 127.99, 128.74, 133.87, 134.84, 137.95. GC-MS (t_R 19.1 min) *m/z* 273 (33, M^+), 151 (100); (t_R 16.2 min) *m/z* 233 (89, M^+-41), 151 (100).

Diallyl(diphenyl)germane (126). Treatment of a solution of dichloro(diphenyl)germane (1.0 g, 0.707 mL, 3.359 mmol) in Et_2O (2 mL) as reported for **125** afforded compound **126** (980 mg, 94%) as clear oil. ^{1}H NMR δ 2.27 (dt, *J*=8.3, 1.0 Hz, 4H), 4.90 (dq, *J*=9.2 Hz, 1.7 Hz, 2H), 4.95 (d, *J*=16.9 Hz, 2H), 5.90 (m, 2H), 7.39 (m, 6H), 7.49 (m, 4H). ^{13}C NMR δ 20.08, 114.12, 128.08, 128.90, 134.48, 134.62, 137.12. GC-MS (t_R 22.3 min) *m/z* 269 (100, M^+-41), 227 (29), 151 (80).

Allyl(triphenyl)germane (127). Treatment of a solution of chloro(triphenyl)germane (260.0 mg, 0.77 mmol) in Et_2O (2 mL) with allylmagnesium bromide as reported for **125** (mixing at room temperature instead of 0 °C) afforded compound **127** (245.0 mg, 92%) as white solid. ^{1}H NMR δ 2.52 (d, *J*=8.1 Hz, 2H), 4.90 (dq, *J*=10.0 Hz, 1.0 Hz, 1H), 5.00 (dq, *J*=16.9 Hz, 1.6 Hz, 1H), 5.95 (m, 1H), 7.40 (m, 9H), 7.51 (m, 6H). ^{13}C NMR δ 21.24, 114.50, 128.18, 129.02, 134.53, 135.02, 136.55. GC-MS (t_R 24.5 min) *m/z* 305 (100, M^+-41), 227 (14), 151 (23).

Treatment of a solution of allyltrichlorogermane (855 mg, 560 mL, 3.886 mmol) in Et_2O (2 mL) with phenylmagnesium bromide (4.0 mL, 4.02 mmol, 3 M solution in

Et_2O) following the procedure described above for **125** gave compound **127** (590 mg, 44%).

1-Allyl-4-butylbenzene (128a). 1-butyl-4-iodobenzene (45.1 mg, 29.4 μL, 0.174 mmol) was added to a solution of tris(allyl)phenylgermane **125** (43.0 mg, 0.16 mmol) and 2 M NaOH (1.0 mL, 2.0 mmol) in 1,4-dioxane (5 mL). The reaction mixture was stirred for 15 min at ambient temperature and $Pd(OAc)_2$ (5 mg, 0.022 mmol) was added. The reaction mixture was heated at 95 ^{o}C for 16 h. The resulting mixture was quenched with 20 mL of water and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvent evaporated under reduced pressure. Purification of the crude by column chromatography (hexanes) gave an unseparable mixture of **128a** and **129a** (17 mg, 60%, 88:12; based on ^{1}H NMR). GC-MS: (t_R 11.9 min, **128a**; t_R 12.7 min, **129a**) *m/z* 175 (M+1, 7), 174 (M^+, 44), 131 (100), 117 (55), 91 (42). ^{1}H NMR δ 0.95 (t, *J*=7.4 Hz, 2.64H), 0.96 (t, *J*=7.3 Hz, 0.36H), 1.38 (sextet, 2H), 1.58-1.64 (m, 2H), 2.17 (s, 0.36H), 2.61 (t, *J*=7.8 Hz, 1.76H), 2.63 (t, *J*=7.7 Hz, 0.24H), 3.39 (d, *J*=6.8 Hz, 1.76H), 5.06 (m, 0.12H), 5.08 (dq, *J*=10.3 Hz, 1.0 Hz, 0.88H), 5.11 (dq, *J*=17.0 Hz, 1.7 Hz, 0.88H), 5.36-5.38 (m, 0.12H), 5.99 (ddt, *J*=16.9 Hz, 10.1 Hz, 6.7 Hz, 1H), 7.11-7.15 (m, 4H), 7.17 (d, *J*=8.2 Hz, 0.24H), 7.42 (d, *J*=8.2 Hz, 0.24H).

1-Allylnaphthalene (128b). 1-iodonaphthalene (43.8 mg, 25.2 μL, 0.17 mmol) was added to a solution of tris(allyl)phenylgermane **125** (42.8 mg, 0.16 mmol) and 2 M NaOH (1.0 mL, 2.0 mmol) in 1,4-dioxane (5 mL). The reaction mixture was stirred for 15 min at ambient temperature and $Pd(OAc)_2$ (5 mg, 0.022 mmol) was added. The reaction mixture was heated at 95 ^{o}C for 16 h. The resulting mixture was quenched with 20 mL of water and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvent evaporated under reduced pressure. Purification of the crude by column chromatography (hexanes) gave an unseparable mixture of **128b** and **129b** (18 mg, 67%, 90:10; based on ^{1}H NMR). GC-MS: (t_R 13.4 min, **129b**; t_R 14.3 min, **128b**) *m/z* 169 (M+1, 14), 168 (M^+, 100), 167 (M-1, 89), 153 (M-15, 91), 141 (26). ^{1}H NMR δ 2.2 (s, 0.3H), 3.83 (d, *J*=6.3 Hz, 1.8H), 5.08-5.12 (m, 0.1H), 5.09-5.15 (m, 1.8H), 5.40-5.44 (m, 0.1H), 6.14 (ddt, *J*=16.8 Hz, 10.1 Hz, 6.7 Hz, 0.9H), 7.30-7.38 (m, 1H), 7.47-7.56 (m, 3H), 7.72-7.78 (m, 1H), 7.83-7.89 (m, 1H), 8.02-8.08 (m, 1H).

Hexaphenyldigermoxanes (138). Tetracyanoethylene (41.4 mg, mmol) was added to a stirred solution of allyl(triphenyl)germane **127** (99.5 mg, 0.29 mmol) in acetonitrile (8 mL) under nitrogen atmosphere. The resulting mixture was heated at 82 °C until TLC analysis showed complete consumption of the starting germane **127**. An aqueous solution of NaOH (3 mL, 1 M solution) was added and the resulting brown solution stirred for additional 3 h at 82 °C. The mixture was concentrated under vacuum and the reaction mixture partitioned between EtOAc and H_2O to give a brown solid which yielded a white solid (55.0 mg, 61%; m.p. 180 °C, uncorrected) after washing with MeOH. ^{1}H NMR δ 7.24-7.31 (m, 6H), 7.37 (tt, *J*=7.6 Hz, 1.2 Hz, 3H), 7.43-7.49 (m, 6H). ^{13}C NMR δ 128.0, 129.37, 134.42, 137.54.

1-Phenylnaphthalene (139a). TBAF (1M/THF, 0.56 mL, 0.56 mmol) was added to a stirred solution of chlorodimethyl(phenyl)germane (**143;** 30.0 mL, 30 mg, 0.14 mmol), 1-iodonaphthalene (22.5 μL, 39 mg, 0.16 mmol) and $Pd_2(dba)_3$ (6 mg, 0.013 mmol) in toluene (3.0 mL) at ambient temperature under nitrogen atmosphere. The resulting brownish mixture was heated at 100 °C (oil bath) for 12 h. The volatiles were evaporated and the residue was partitioned (H_2O/CH_2Cl_2). The organic layer was dried ($MgSO_4$), evaporated and purified by column chromatography (hexane) to give **139a**[207] (26.6 mg, 93%) followed by **141a**[207] [1.7 mg, 4%, 8% consumption of the iodonaphthalene; GC-MS (t_R 25.02 min) *m/z* 254 (100, M^+)]. Compound **139a** had: ^{1}H NMR δ 7.41-7.58 (m, 9H), 7.89 (d, *J*=8.2Hz, 1H), 7.91-7.96 (m, 2H) ; ^{13}C NMR δ 125.5, 125.9, 126.15, 126.18, 127.1, 127.4, 127.8, 128.4, 130.2, 131.8, 134.0, 140.4, 140.9; GC-MS (t_R 19.87 min) *m/z* 204 (100, M^+).

Method F (Pd-catalyzed cross-coupling of chloro(phenyl)germanes with TBAF). TBAF (1M/THF, 0.98 mL, 0.98 mmol) was added to a stirred solution of dichlorodiphenylgermane (**144**; 30.0 mL, 42 mg, 0.14 mmol), 1-iodonaphthalene (22.5 µL, 39 mg, 0.16 mmol) and $Pd_2(dba)_3$ (6 mg, 0.013 mmol) in toluene (3.0 mL) at ambient temperature under nitrogen atmosphere. The resulting brownish mixture was heated at 100 °C (oil bath) for 12 h. The volatiles were evaporated and the residue was partitioned (H_2O/CH_2Cl_2). The organic layer was dried ($MgSO_4$), evaporated and purified by column chromatography (hexane) to give **139a** (17.1 mg, 30%) followed by **141a** (8.0 mg, 20%).

Treatment of **144** (30.0 mL, 42 mg, 0.14 mmol) with iodonaphthalene (45 µL, 78 mg, 0.31 mmol) by Method F gave **139a** (31.1 mg, 55%) and **141a** (17.6 mg, 22%).

Treatment of chlorotriphenylgermane (**145**; 47.5 mg, 0.14 mmol) with iodonaphthalene (22.5 µL, 39 mg, 0.16 mmol) by Method F gave **139a** (10.0 mg, 12%) and **141a** (17.4 mg, 43%).

Treatment of **145** (47.5 mg, 0.14 mmol) with iodonaphthalene (45 µL, 78 mg, 0.31 mmol) by Method F gave **139a** (30.0 mg, 35%) and **141a** (18.7 mg, 24%).

Treatment of **145** (47.5 mg, 0.14 mmol) with iodonaphthalene (67.5 µL, 117 mg, 0.46 mmol) by Method F gave **139a** (33.7 mg, 39%) and **141a** (35.0 mg, 30%).

Treatment of **145** (47.5 mg, 0.14 mmol) with bromonaphthalene (70 μL, 99 mg, 0.46 mmol) by Method F gave **139a** (24%) and **141a** (15%) based on GC/MS analysis of the crude reaction mixture.

Treatment of **146** (24.0 mL, 35.9 mg, 0.14 mmol) with iodonaphthalene (22.5 μL, 39 mg, 0.16 mmol) by Method F gave **139a** (23.1 mg, 81%) and **141a** (1.5 mg, 4%).

Treatment of **146** (24.0 mL, 35.9 mg, 0.14 mmol) with bromonaphthalene (22.3 μL, 33 mg, 0.16 mmol) by Method F gave **139a** (23.4 mg, 82%).

Method G (Pd-catalyzed cross-coupling of chloro(phenyl)germanes with TBAF and added water). TBAF (1M/THF, 0.98 mL, 0.98 mmol) was added to a stirred solution of **144** (30.0 mL, 42 mg, 0.14 mmol), 1-iodonaphthalene (22.5 μL, 39 mg, 0.16 mmol), water (100 μL, 5.7 mmol) and $Pd_2(dba)_3$ (6 mg, 0.013 mmol) in toluene (3.0 mL) at ambient temperature under nitrogen atmosphere. The resulting brownish mixture was heated at 100 ^{o}C (oil bath) for 12 h. The volatiles were evaporated and the residue was partitioned (H_2O/CH_2Cl_2). The organic layer was dried ($MgSO_4$), evaporated and purified by column chromatography (hexane) to give **139a** (24.0 mg, 42%) followed by **141a** (1.3 mg, 3%).

Treatment of **144** (30.0 mL, 42 mg, 0.14 mmol) with iodonaphtalene (45 μL, 78 mg, 0.31 mmol) by Method G gave **139a** (50.8 mg, 89%) and **141a** (6.3 mg, 8%).

Treatment of **144** (30.0 mL, 42 mg, 0.14 mmol) with bromonaphthalene (45 μL, 66 mg, 0.31 mmol) by Method G [H_2O; 30 μL, 1.7 mmol] gave **139a** (27.0 mg, 48%) and **141a** (4.5 mg, 6%).

Treatment of **145** (47.5 mg, 0.14 mmol) with iodonaphthalene (22.5 μL, 39 mg, 0.16 mmol) by Method G gave **139a** (14.3 mg, 17%) and **141a** (7.1 mg, 18%).

Treatment of **145** (47.5 mg, 0.14 mmol) with iodonaphthalene (45 μL, 78 mg, 0.31 mmol) by Method G gave **139a** (51.1 mg, 60%) and **141a** (7.0 mg, 9%).

Treatment of **145** (47.5 mg, 0.14 mmol) with iodonaphthalene (67.5 μL, 117 mg, 0.46 mmol) by Method G gave **139a** (75.0 mg, 88%) and **141a** (7.0 mg, 6%).

Treatment of **146** (24.0 mL, 35.9 mg, 0.14 mmol) with iodonaphthalene (22.5 μL, 39 mg, 0.16 mmol) by Method G gave **139a** (27.4 mg, 96%) and **141a** (1.0 mg, 2.5%).

4-Phenylanisole (139b). Treatment of **144** (30.0 mL, 30 mg, 0.14 mmol) with 4-iodoanisole (60.0 mL, 60 mg, 0.31 mmol) by Method G at 115 °C gave **139b**[80] (43.8 mg, 85%) followed by **141b**[207] [5.2 mg, 8%, GC-MS (t_R 20.81 min) *m/z* 214 (100, M^+)]. Compound **139b** had: ^{1}H NMR δ 3.86 (s, 3H), 7.98 (d, *J*=7.8 Hz, 2H), 7.31 (t, *J*=7.8 Hz, 1H), 7.42 (t, *J*=8.6 Hz, 2H), 7.50-7.58 (m, 4H); ^{13}C NMR δ 55.5, 114.4, 126.8, 126.9, 128.3, 128.9, 134.0, 141.0, 159.3; GC-MS (t_R 17.41 min) *m/z* 184 (100, M^+).

3-(Trifluoromethyl)biphenyl (139c). Treatment of **144** (30.0 mL, 42 mg, 0.14 mmol) with 1-iodo-3-(trifluoromethyl)benzene (44.6 mL, 84.8 mg, 0.31 mmol) by Method G gave **139c** (42.0 mg, 68%) followed by **141c**[208] [16.0 mg, 18%; GC-MS (t_R 12.58 min) *m/z* 290 (100, M^+)]. Compound **139c** had: ^{1}H NMR δ 7.38-7.64 (m, 7H), 7.78 (d, *J*=7.4 Hz, 1H), 7.85 (br. s, 1H); ^{13}C NMR δ 124.07 (q, ^3J=3.2 Hz), 124.11 (q, ^3J=3.2 Hz), 124.4 (q, ^1J=272.2 Hz), 127.4, 128.2, 129.2, 129.4, 130.6, 131.3 (q, ^2J=32.5 Hz), 134.0, 142.2; GC-MS (t_R 12.84 min) *m/z* 222 (100, M^+).

4-Acetylbiphenyl (139d). Treatment of **144** (30.0 mL, 42 mg, 0.14 mmol) with 4-iodoacetophenone (75.8 mg, 0.31 mmol) by Method G gave **139d** (5.5 mg, 10%) followed by **141d**[209] [4.5 mg, 6%; GC-MS (t_R 24.80 min) *m/z* 238 (30, M^+)]. Compound **139d** had: ^{1}H NMR δ 2.64 (s, 3H), 7.41 (t, *J*=7.2 Hz, 1H), 7.48 (t, *J*=7.7 Hz, 2H), 7.63 (d, *J*=6.7 Hz, 2H), 7.69 (d, *J*=7.2 Hz, 2H), 8.04 (d, *J*=8.4 Hz, 2H); ^{13}C NMR δ 26.8, 127.35, 127.4, 128.4, 129.0, 129.1, 136.0, 140.0, 145.9, 197.9; GC-MS (t_R 19.41 min) *m/z* 196 (45, M$^+$).

(*E*)-1,2-Diphenylethene (139e). Treatment of **144** (30.0 mL, 42 mg, 0.14 mmol) with β-bromostyrene (*E/Z,* ~85:15; 40.0 mL, 105 mg, 0.31 mmol) by Method F gave **139e**[210] (2.5 mg, 5%), **141e** [8.6 mg, 13%; GC-MS (t_R 22.02 min) *m/z* 206 (100, M$^+$)] and biphenyl[207] [5.4 mg, 50%; GC-MS (t_R 12.89 min) *m/z* 154 (100, M$^+$)]. Compound **139e** had: ^{1}H NMR δ 7.14 (s, 2H), 7.29 (tt, *J*=7.3 Hz, 1.5 Hz, 2H), 7.39 (t, *J*=8.0 Hz, 4H), 7.54 (d, *J*=7.2 Hz, 4H); ^{13}C NMR δ 126.7, 127.8, 128.8, 128.9, 137.5; GC-MS (t_R 17.93 min) *m/z* 180 (100, M$^+$).

2-Methyl-5-phenylthiophene (139f). Treatment of **144** (30.0 mL, 42 mg, 0.14 mmol) with 2-iodo-5-methylthiophene (37 mL, 70 mg, 0.31 mmol) by Method G gave **139f**[211] (3.0 mg, 6%), **141f**[212] [5.0 mg, 8%; GC-MS (t_R 16.74 min) *m/z* 194 (100, M$^+$)] and biphenyl[207] [5.4 mg, 25%; GC-MS (t_R 12.89 min) *m/z* 154 (100, M$^+$)]. Compound **139f** had: ^{1}H NMR δ 2.52 (s, 3H), 6.74 (dd, *J*=3.5 Hz, 0.8 Hz, 1H), 7.12 (d, *J*=3.5 Hz, 1H), 7.21-7.28(m, 1H), 7.36 (t, *J*=8.0 Hz, 2H), 7.56 (d, *J*=8.0 Hz, 2H); ^{13}C NMR δ 15.6, 123.0, 125.7, 126.3 127.1, 128.9, 134.9, 139.6, 142.2; GC-MS (t_R 15.03 min) *m/z* 174 (100, M$^+$).

5. CONCLUSION

The stereoselective synthesis of novel 2',3',5'-tri-*O*-acetyl and 2',3',5'-*O*-*p*-toluoyl protected 5-[2-(tris(trimethylsilyl)germyl)ethenyl]uridine analogues was achieved via radical-promoted hydrogermylation of 5-alkynyl substrates with tris(trimethylsilyl)germane (TTMS-germane). These novel uridine analogues modified at carbon-5 were efficiently prepared using both thermally-induced radical addition (Method A) and Et_3B-promoted hydrogermylation (Method B) with similar yields. The hydrogermylation with the bulky TTMS-germane using Et_3B, as a low-temperature radical initiator, occurred stereoselectively via *anti* addition yielding exclusively the *Z*-vinylgermane. On the other hand, the use of thermal radical initiation utilizing 1,1'-azobis(cyclohexanecarbonitrile) (ACCN) gave predominantly the *Z*-isomer (*E*/*Z*, ~4:96). The preference for the *anti*-addition of radicals to terminal alkynes by Et_3B-promoted hydrogermylation was also confirmed when 5-alkynyl uridine analogues were treated with less-reactive organogermanium hydrides, such as Ph_3GeH, Me_3GeH, and Bu_3GeH. The stereoselectivity for the kinetic *Z*-isomer was found to increase when bulkier germyl hydrides [Me_3GeH (*E*/*Z*, ~40:60), Bu_3GeH (*E*/*Z*, ~6:94), Ph_3GeH (pure *Z*)] were employed. Also, the hydrogermylation showed better yields when more reactive aryl-substituted germanes (~40-60%) were utilized instead of alkyl-substituted germyl hydrides (~30-45%).

During the hydrogermylation of several 5-ethynyluridine precursors with Ph_3GeH at higher temperatures (0 ^{o}C *vs* -78 ^{o}C) in addition to the desired vinylgermane product, an unexpected byproduct which was tentatively assigned as a 5-[2-(triphenylgermyl)acetyl]uridine analogue was also observed. In order to investigate the formation of such 5-(α-germyl)acetyl uridine derivatives, the ^{18}O-labeled 4-[^{18}O]-1-*N*-5-ethynylbenzyluracil was synthesized from the 5-iodouracil precursor using established procedures. The hydrogermylation of the ^{18}O-labeled 5-ethynyluracil with Ph_3GeH employing thermal-radical initiation (Method A) also gave the corresponding ^{18}O-labeled 5-(α-germyl)acetyl uracil derivative.

We demonstrated that conjugated and non-conjugated vinyl tris(trimethylsilyl)silanes undergo Pd-catalyzed cross-coupling with aryl iodides and bromides under aqueous oxidative conditions in the presence of sodium hydroxide with or without fluoride activation. Contrary to (*E*)-silanes, which undergo coupling with retention of stereochemistry, coupling of (*Z*)-silanes occurred with lower stereoselectivity giving an *E/Z* mixture of products. The best stereoselectivity was achieved when either aryl iodides or electron-rich TTMS-silanes were used. Under the oxidative coupling conditions neither reductive self-coupling of the halides nor oxidative homocoupling of the vinyl TTMS-silanes were observed. The tris(trimethylsilyl)silanes remained intact under typical conditions employed in the coupling of dimethylsilanols (bases such as $KOSiMe_3$), thus making stable and readily accessible vinyl TTMS-silanes alternative substrates ("masked" silanols) for the Hiyama coupling. Hydrogen peroxide is assumed to chemoselectively cleave Si–Si bond(s) generating active silanol/siloxane species that undergo coupling in the presence of base. The silanol/siloxane intermediates were observed when the progress of the reaction of vinyl TTMS-silanes with H_2O_2/base was monitored by ^{29}Si NMR. The (*Z*)-2-(4-methylphenyl)-1-[tris(trimethylsiloxy)silyl]ethene was isolated from the coupling reaction mixture and characterized by spectroscopic techniques, supporting the proposed oxygen insertion in the presence of such oxidative coupling conditions.

The ability of novel allyl(phenyl)germanes to transfer the phenyl groups via Pd-catalyzed cross-coupling with aryl iodides was explored in the presence of fluoride ions, base, or a base/H_2O_2 combination. However, instead of the formation of expected biaryls, the transfer of the allyl groups from the germane precursor was observed using aqueous NaOH and several Pd catalysts. A Heck arylation mechanism was proposed based on the formation of regioisomeric mixtures of allylated products. In order to force the transfer of the phenyl groups from the allyl(phenyl)germanes precursors, the selective cleavage of the Ge-C(allyl) bond was explored by treatment with tetracyanoethylene (TCNE). A one-pot cleavage/hydrolysis sequence afforded hexaphenyldigermoxane which was able to undergo Pd-cross-coupling with 1-iodonaphthalene in the presence of fluoride ions.

We have demonstrated that arylchlorogermanes undergo Pd-catalyzed cross-couplings with aryl halides in the presence of TBAF in wet toluene to afford biaryl products. One chloride ligand on Ge center allows efficient activation by fluoride to promote transfer of up to three aryl groups from germane. The methodology shows that organogermanes can render a coupling efficiency comparable to the more established stannane and silane counterparts. Our coupling methodology (TBAF/”moist” toluene) was also found to promote transfer of multiple phenyl groups from analogous chloro(phenyl)silanes and chloro(phenyl)stannanes. The study of the activation of chloro(phenyl)germanes with TBAF by ^{19}F NMR led to the observation of typical peaks for tetravalent monofluorogermanes (δ -204 ppm) and difluorogermanes (δ -163 ppm), as well as, other signals tentatively assigned to pentavalent fluorogermanates around δ -148 ppm and δ -120 ppm.

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Dissertation title: "New organogermanium substrates for Pd-catayzed cross-coupling reactions. Application of organogermanes towards the synthesis of carbon-5 modified uridine analogues".
Advisor: Professor Stanislaw F. Wnuk.

B.S., Chemistry, May 2005, Universidad Simon Bolivar, Caracas, Venezuela.
Thesis title: "Synthesis of Coronarin C, a labdane-type diterpene isolated from *Hedychium coronarium*".
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Experience

Student Researcher, Sep. 2004-Jan. 2005, Natural Products Synthesis Laboratory. Chemistry Center. Venezuelan Institute for Scientific Research, I.V.I.C, Altos de Pipe, Venezuela.
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Publications

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Presentations

Wnuk, S. F.; Sobczak, A. J.; Malladi, A.; Sacasa, P. R.; Pitteloud, J-P. “*S*-adenosylhomocysteine vs. *S*-ribosylhomocysteinase (LuxS): Similarities and differences between two enzymes”, Abstracts of Papers, 237th ACS National Meeting, Salt Lake City, UT. United States, Mar. 22-26, 2009.

Restrepo, J. A.; Sacasa, P. R.; Pitteloud, J-P.; Wnuk, S. F. “Application of germyldesulfonylation reactions in nucleoside chemistry”, Abstracts of Papers, 235th ACS National Meeting, New Orleans, LA. United States, Apr. 6-10, 2008.

Pitteloud, J-P.; Wnuk, S. F., “Studies toward cross-coupling reactions with organogermanes”. 14th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis, Nara, Japan, Aug. 2-6, 2007.

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