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Novel Approaches for the Synthesis of C-5 Modified Pyrimidine Nucleosides

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NOVEL APPROACHES FOR THE SYNTHESIS OF C-5 MODIFIED PYRIMIDINE NUCLEOSIDES

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in

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by

Yong Liang

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To: Interim Dean Michael R. Heithaus
College of Arts and Sciences

This dissertation, written by Yong Liang, and entitled Novel Approaches for the Synthesis of C-5 Modified Pyrimidine Nucleosides, 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.

Kevin O'Shea

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Date of Defense: November 5, 2014

The dissertation of Yong Liang is approved.

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Florida International University, 2014

DEDICATION

I dedicate this work to my wife Pingping Liang, my parents and sister for their love and support. Without their understanding and encouragement, the completion of this work would not have been possible.

感谢我的家人对我的支持与鼓励，我爱你们!

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ABSTRACT OF THE DISSERTATION

NOVEL APPROACHES FOR THE SYNTHESIS OF C-5 MODIFIED PYRIMIDINE NUCLEOSIDES

by

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Florida International University, 2014

Miami, Florida

Professor Stanislaw F. Wnuk, Major Professor

The antiviral or anticancer activities of C-5 modified pyrimidine nucleoside analogues validate the need for the development of their syntheses. In the first half of this dissertation, I explore the Pd-catalyzed cross-coupling reaction of allylphenylgermanes with aryl halides in the presence of SbF_5/TBAF to give various biaryls by transferring multiple phenyl groups, which has also been applied to the 5-halo pyrimidine nucleosides for the synthesis of 5-aryl derivatives. To avoid the use of organometallic reagents, I developed Pd-catalyzed direct arylation of 5-halo pyrimidine nucleosides. It was discovered that 5-aryl pyrimidine nucleosides could be synthesized by Pd-catalyzed direct arylation of N^3-free 5-halo uracil and uracil nucleosides with simple arenes or heteroaromatics in the presence of TBAF within 1 h. Both N^3-protected and N^3-free uracil and uracil nucleosides could undergo base-promoted Pd-catalyzed direct arylation, but only with electron rich heteroaromatics.

In the second half of this dissertation, 5-acetylenic uracil and uracil nucleosides have been employed to investigate the hydrogermylation, hydrosulfonylation as well as hydroazidation for the synthesis of various functionalized 5-vinyl pyrimidine nucleosides. Hydrogermylation of 5-alkynyl uracil analogues with trialkylgermane or tris(trimethylsilyl)germane hydride gave the corresponding vinyl trialkylgermane, or tris(trimethylsilyl)germane uracil derivatives. During the hydrogermylation with triphenylgermane, besides the vinyl triphenylgermane uracil derivatives,

5-[2-(triphenylgermyl)acetyl]uracil was also isolated and characterized and the origin of the acetyl oxygen was clarified. Tris(trimethylsilyl)germane uracil derivatives were coupled to aryl halides but with decent yield. Iron-mediated regio- and stereoselective hydrosulfonylation of the 5-ethynyl pyrimidine analogues with sulfonyl chloride or sulfonyl hydrazine to give 5-(1-halo-2-tosyl)vinyluracil nucleoside derivatives has been developed. Nucleophilic substitution of the 5-(*β*-halovinyl)sulfonyl nucleosides with various nucleophiles have been performed to give highly functionalized 5-vinyl pyrimidine nucleosides *via* the addition-elimination mechanism. The 5-(*β*-keto)sulfonyluracil derivative has also been synthesized *via* the aerobic difunctionalization of 5-ethynyluracil analogue with sulfinic acid in the presence of catalytic amount of pyridine. Silver catalyzed hydroazidation of protected 2'-deoxy-5-ethynyluridine with $TMSN_3$ in the presence of catalytic amount of water to give 5-(α-azidovinyl)uracil nucleoside derivatives was developed. Strain promoted Click reaction of the 5-(α-azidovinyl)uracil with cyclooctyne provide the corresponding fully conjugated triazole product.

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LIST OF ABBREVIATIONS

5'-araCTP	5'-arabinofuranosylcytosine triphosphate
5-FdU	5-fluoro-2'-deoxyuridine
5-FU	5-fluorouracil
Abs	absorbance
ACCN	1,1'-azobis(cyclohexanecarbonitrile)
Ar	aromatic (NMR)
AZT	3'-Azido-3'-deoxythymidine
β	beta
Bn	benzyl
br	broad (NMR)
BVDU	(*E*)-5-(2-bromovinyl)-2′-deoxyuridine
t-Bu	*tert*-butyl
calcd	calculated (HRMS)
CID	collision-induced dissociation (HRMS)
CMD	concerted metalation-deprotonation
CMV	cytomegalovirus
^{o}C	degrees Celsius
δ	delta
d	doublet (NMR)
DCM	dichloromethane
dCK	deoxycytidine kinase
dCTP	deoxycytidine triphosphate
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide

DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
ESI	electrospray ionization
Et	ethyl
FDA	U.S. Food and Drug Administration
FUra	5-fluorouracil
λ	gamma
g	gram(s)
h	hour(s)
HBV	hepatitis B virus
hENT1	human Equilibrative Nucleoside Transporter 1
HIV	human immunodeficiency virus
HSV	herpes simplex virus
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
J	coupling constant in Hz (NMR)
L	liter(s)
m	milli; multiplet (NMR)
μ	micro
M	moles per liter
MGP	methylgermanium(IV) porphyrin
min	minute(s)
mol	mole(s)
MS	mass spectrometry

m/z	mass to charge ratio (MS)
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NRTI	nucleotide reverse transcriptase inhibitors
NT	nucleoside transporter
p	para
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
$Pd(OAc)_2$	palladium(II) acetate
%	percentage
q	quartet (NMR)
quin	quintet (NMR)
RNA	ribonucleic acid
rt	room temperature
s	second(s); singlet (NMR)
SAR	structure activity relationship
SET	single electron transfer
t	triplet (NMR)
TBAF	tetra-*N*-butylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TEA	triethylamine
THF	tetrahydrofuran
TK	thymidine kinase
TLC	thin layer chromatography
TMS	trimethylsilyl

t_R	retention time (HPLC)
UV-VIS	ultraviolet visible
vs	versus
VV	vaccinia virus
VZV	varicella zoster virus

1. INTRODUCTION

1.1. Activities of purine and pyrimidine nucleosides and nucleotides

It is known that both pyrimidine and purine nucleosides are the basic building blocks for DNA and RNA, which contain the genetic information that is passed from one generation to the next. The sugar linked purine and pyrimidine nucleosides were connected by phosphates to form the backbone for the DNA or RNA, whereas, the different heterobases interact with one and another in a certain pattern *via* hydrogen bond to form the double helix structure for DNA. The sequence of nucleoside bases in DNA is considered as the genetic information, which can be replicated by the DNA polymerase enzyme to RNA with high accuracy. In April 2003, the completion of the human genome sequence was announced.[1]

Natural or synthesized purine and pyrimidine nucleosides are found to possess some important biological activities, which could be applied in biology, biotechnology or pharmaceutical development.[2] With the research development, nucleoside analogues have attracted much more attention because of the wide application in the anticancer and antiviral area.

The active nucleoside analogues of these compounds can be considered as " prodrugs", which need to be activated by normal metabolic process, such as phosphorylation. Both pyrimidine and purine nucleoside analogues are currently used clinically as antimetabolite drugs and share the similar mechanism. They cross into cells with the help of the nucleoside transporter and followed the metabolic pathway to be converted to nucleotide analogues, which could inhibit one or more enzymes that are critical for the DNA synthesis.[3]

1.1.1. Anticancer activity of nucleoside analogues

Until 2014, only 14 nucleoside-based drugs have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of cancer (Table 1).[4] Approximately 10% of the anticancer drugs are nucleoside analogues; six of these drugs were approved during the 1996-2014 and there are more nucleoside analogues in the clinical trial stage. The approval of

nucleosides analogues as anticancer drugs by FDA indicates that synthesis of base/sugar-modified nucleoside analogues is one of the most effective methods for the development of new drugs for cancer.

Table 1. FDA approved anticancer purine and pyrimidine nucleoside analogues

Drug	Catagory	Year
5-aza-2'-deoxycytidine (Decitabine)	2′-Deoxycytidine	2006
O^6-methylarabinofuranosyl guanine (Nelarabine)	Guanosine	2005
5-aza-cytidine (Azacitidine)	2′-Deoxyadenosine	2004
2'-fluoro-2'-deoxyarabinofuranosyl-2-chloroadenine (Clofarabine)	Cytidine	2004
N^4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine (Capecitabine)	Cytidine	1998
2,2-difluoro-2'-deoxycytidine (Gemcitabine)	2′-Deoxycytidine	1996
2-chloro-2'-deoxyadenosine (Cladribine)	2′-Deoxyadenosine	1992
2'-deoxycoformycin (Pentostatin)	Adenosine	1991
Arabinofuranosyl-2-fluoroadenine (Fludarabine)	Purine analogue	1991
5-fluoro-2'-deoxyuridine (Floxuridine)	2′-Deoxyuridine	1970
Arabinofuranosylcytosine (Cytarabine)	Cytidine	1969
6-thioguanine (Lanvis)	Guanine	1966
5-fluorouracil (Adrucil)	Uracil	1962
6-mercaptopurine (Purinethol)	Purine	1953

Taking cytarabine (1-β-D-arabinofuranosylcytosine) as example, it is the anticancer drug in hematological malignanciesone, which is one of the first pyrimidine nucleoside analogs approved in 1969. Cytarabine is transported into the cell with the assistance of human Equilibrative Nucleoside Transporter 1 (hENT1),[5,6] followed by the phosphorylation of deoxycytidine kinase (dCK) and nucleotide kinases to give 5'-arabinofuranosylcytosine triphosphate (5'-araCTP).[7] The anticancer activity of 5'-araCTP is characterized as the inhibitor of DNA polymerase α[8] and incorporation into DNA instead of deoxycytidine triphosphate (dCTP) to interrupt DNA synthesis. 5'-Arabinofuranosylcytosine monophosphate is also able to incorporate into DNA to inhibit the DNA synthesis by preventing the DNA chain extension.[9] However, the biological anticancer

activity could be disabled by cytidine deaminase and cytoplasmic 5'-nucleotidase to give inactive arabinosyluridine.

1.1.2. Antiviral activity of nucleotides analogues

During the past two decades, nucleoside analogues have become reliable antiviral agents in the treatment of different kinds of virus, such as herpes simplex virus (HSV), hepatitis B virus (HBV), human immunodeficiency virus (HIV) and others.[2] Some of the antiviral nucleoside analogues are listed in Table 2.

Table 2. Antiviral properties of purine and pyrimidine nucleoside analogues

Drug	Category	Year
2'-deoxy-2'-fluoro-2'-methyluridine-5'-phosphate (Sofosbuvir)	Thymidine	2013
Tenofovir disoproxil fumarate, mixture of purine analogues (Tenofovir)	Purine	2008
1-2-deoxy-β-L-erythro-pentofuranosylthymine (Telbivudine)	Thymidine	2006
5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (Emtricitabine)	Cytidine	2006
(1*S*,3*R*,4*S*)-4-Hydroxy-3-(hydroxymethyl)-2-methylidenecyclopentylguanosine (Entecavir)	Guanosine	2005
2',3'-didehydro-2',3'-dideoxythymidine (Stavudine)	Thymidine	2001
2',3'-dideoxy-3'-thiacytidine (Lamivudine)	Cytidine	1998
2',3'-didehydro-2',3'-dideoxythymidine (Stavudine)	Thymidine	1994
3'-azido-3'-deoxythymidine (Zidovudine)	Thymidine	1987
2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H*-purin-6-one (Acyclovir)	Guanosine	1982
(*E*)-5-(2-bromovinyl)-2'-deoxyuridine (Brivudine)	Uridine	1980
9-β-D-arabinofuranosyladenine (Vidarabine)	Adenosine	1976
5-ethyl-2'-deoxyuridine (Edoxudine)	Thymidine	1969
5-iodo-2'-deoxyuridine (Idoxuridine)	Uridine	1962

The inhibition mechanism of the antiviral nucleoside analogues is similar to the anticancer agents mentioned above. First of all, the antiviral nucleoside analogues are transported into the cells by the Nucleoside Transporters (NTs), followed by the phosphorylation to give nucleotide analogues. Then, the resulting nucleotides repress the viral reproduction by incorporation into the nascent viral DNA chain which leads to the chain termination. The compound 3'-azido-3'-deoxythymidine (AZT) is the first U.S. government-approved drug for the treatment of HIV,

which is a nucleoside analogue reverse-transcriptase inhibitor (NRTI). It can significantly inhibit the replication of the virus[10] but cannot completely prevent viral replication.[11]

1.2. Biological activities of 5-modified pyrimidine nucleosides

Structure-activity relationship (SAR) studies indicated that the pyrimidine base bearing electron-withdrawing groups or conjugated substitutions at C5 position confer the biological activity of the nucleoside analogues,[4,12-18] such as antiviral,[19-24] anticancer,[4,25] or antibacterial. [26,27]

Examples of pyrimidine nucleoside analogues with modification at C5 position include 5-fluorouracil (**1**, FUra), 5-ethyl-2'-deoxyuridine (**2**, Edoxudine), (*E*)-5-(2-bromovinyl)-2′-deoxyuridine[22,28] (**3**, BVDU), 5-aza-2'-deoxycytidine[4,25] (**4**, Decitabine) and 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (**5**, Emtricitabine) (Figure 1) which have potent antiviral properties. Pronounced cytotoxity and significant antiviral activity have been reported for 1-(β-D-arabinofuranosyl)-5-ethenyluracil[29] and 5-ethynyl-2'-deoxyuridine[30] as well.

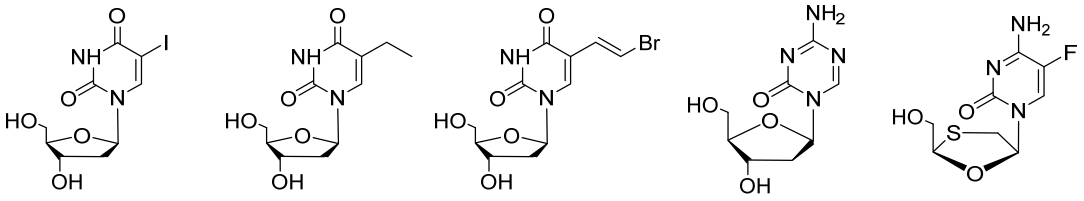


Figure 1.Structure of anticancer/antiviral nucleoside analogues

The 5-iodo-2'-deoxyuridine (**1**, Idoxuridine) is the first antiviral agent topically to treat herpes simplex keratitis. Later on, sugar and/or base modified nucleoside analogues have been synthesized and studied in detail.[4,31] The 5-ethyl-2'-deoxyuridine (**2**, Edoxudine) was the first antiviral nucleoside analogue approved by the FDA in 1969, however it is not currently used clinically. The (*E*)-5-(2-bromovinyl)-2'-deoxyuridine (**3**, BVDU)[28] and bicyclic furanopyrimidine-2-one nucleoside analogues which display remarkable antiviral potency against the varicella zoster virus (VZV),[32] are highly potent and selective antiviral drugs. The 5-aza-2'-deoxycytidine (**4**, Decitabine) was approved by FDA in 2006 for injection for the treatment of

patients with myelodysplastic syndromes (MDS).[33] Emtricitabine (**5**) was approved by FDA in 2006 as well and used for the treatment of HIV infection in adults and children.

It is also worthy to note that the C5-aryl or C5-heteroaryl pyrimidine nucleoside analogues possess intrinsic fluorescence because of the extended conjugation system. These types of pyrimidine nucleoside analogues usually show special fluorescence with the irradiation by UV light, which could be employed as the molecular beacons for detecting the presence of abasic sites of oligonucleotide,[34] determination of the RNA structure,[35] exploring RNA folding and recognition,[36] as well as studing the intramolecular electron transfer[37] or electron injection in to DNA[38,39] and so on.[40,41] Among the 5-arylated pyrimidine nucleoside analogues, the 5-(2-furyl)uridine and 5-(2-thienyl)-2'-deoxyuridine analogues display the strongest florescence, owing to the high conjugation between the electron rich furan or thiophene with the pyrimidine base. Thus they have been incorporated into RNA and DNA fragments using phosphoramidite solid support technology and used as fluorescent probes.[34,36,42,43] The 5-aryl and 5-(2-thienyl) modified 2'-deoxyuridine (or cytidine) triphosphates can also be used as the substrates for DNA polymerases and for DNA staining and electrochemical labels.[44-46]

1.3. Synthesis of the C-5 modified pyrimidine nucleosides via Pd-catalyzed cross-coupling reactions

The transition metal catalyzed cross-coupling reactions have contributed significantly for the synthesis of biaryl compounds. One of the most important transition metal for the cross coupling reactions is the Palladium (Pd). With few exceptions, two different activated components are required. One is the organometallic, alkene (Heck reaction), or alkyne (Sonogashira reaction) and the other is the halides or triflates.

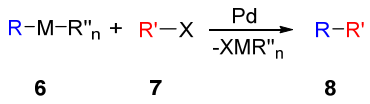
The Pd-catalyzed reaction was first introduced by Dr. Richard Heck in 1970s.[47] Later many Pd-catalyzed cross coupling reactions were published with different substrates, and the methodology became one of the most important methods to build the C-C bond. There are some

reasons for the popularity of the Pd-catalyzed coupling reaction. First of all, the coupling reaction can be carried out under mild conditions, which usually could inhibit the formation of the unwanted byproduct, or in other words, give the desired product in high yield selectively. Second, a wide range of functional groups could be tolerated by the Pd-catalyzed coupling reactions. Addition of ligands usually could increase the yield and decrease the reaction time or temperature by lowering the reaction barrier. Because of the important contribution of the Stille reaction, Heck reaction and Suzuki reaction in the organic synthesis, natural product synthesis or pharmaceutical application, 2010 chemistry Nobel Prize was awarded jointly to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki.[48]

1.3.1. Traditional Pd-catalyzed cross-coupling reactions

1.3.1.1. General consideration

The Pd-catalyzed cross-coupling reactions, such as Suzuki, Hiyama, Stille, Negishi and Kumada reaction, share some common similarity. They all need the organometallic **6** (e.g., B, Si, Sn, Zn, Mg) and aryl halides or pseudohalides **7** for the coupling reaction to work properly (Scheme 1).



Scheme 1. General scheme for Pd-catalyzed cross coupling

The general mechanism for the Pd-catalyzed cross-coupling reaction involves three basic steps (Figure 2). Initially, Pd insert into the sp^2-hybridized C-X bond *via* a concerted three-center intermediate to give intermediate **B**, followed by transmetalation which involve the cleavage of the X-M bond and the formation of the new bond between the carbon of **6** and the palladium center to give intermediate **C**, and reductive elimination to give the coupled product **8** with the regeneration of the palladium catalyst **A**. Oxidative insertion step is usually considered as the rate determining step of the catalytic cycle. The presence of anionic ligands (e.g., OAc) could also

accelerate the oxidative insertion step by the formation of $[Pd(OAc)(PR_3)_n]^-$ to make the palladium more nucleophilic.

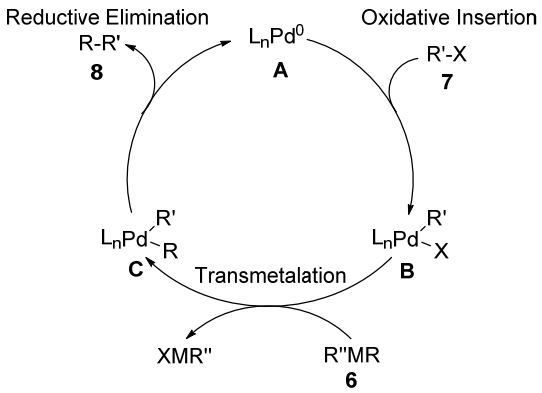


Figure 2. General mechanism for Pd-catalyzed cross-coupling reaction

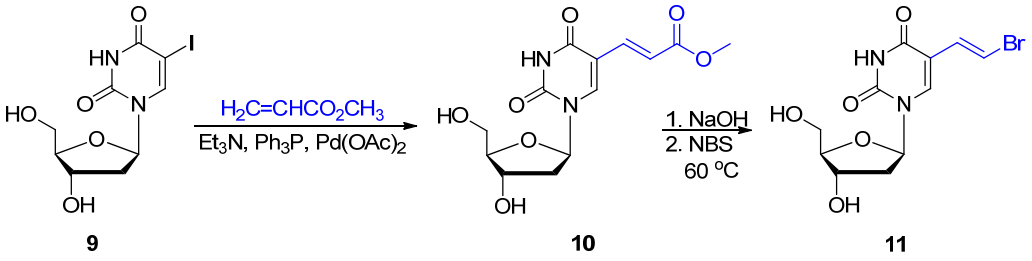
1.3.1.2. Application of the traditional Pd-catalyzed cross-coupling reaction to the synthesis of C-5 modified pyrimidine nucleosides

Since the C-5 modified pyrimidine nucleosides possess important biological activities, the synthesis of these pyrimidine nucleosides have been studied in detail. The Pd-catalyzed cross-coupling reactions, which have developed rapidly during the last 40 years, are one of the most important methodologies used for the formation of new carbon-carbon bond. Thus, 5-aryl pyrimidine nucleosides have been directly synthesized by: i) aromatic photo-substitution of 5-iodouracil nucleoside with poly substituted arenes or *vice versa*,[49-51] ii) Pd-catalyzed coupling reaction employing 5-chloromercuripyrimidine nucleoside,[51,52] or iii) Pd-catalyzed coupling reaction of 5-halopyrimidine nucleosides with organometallic, e.g., organolithium and organozinc compounds, which are required to be freshly prepared,[49] as well as organotin, organosilican and organoboron. [12,30,37,53-60] The synthesis of numerous 5-substituted pyrimidine nucleosides *via* Pd-assisted routes have been reviewed.[12]

Heck Coupling

The Heck reaction[47] can build the C-C bond by coupling of an unsaturated halide (or triflate) with an alkene in the presence of base and palladium catalyst. It could also be employed to

synthesize the C-5 substituted pyrimidine nucleosides.[61] Trans-3-(5-uridylyl)propenoate (**10**), which is an important precursor of BVDU, was first synthesized by Bergstrom[62] with 5-chloromercuriuridine and methyl acrylate in the presence of Li_2PdCl_4 in methanol. Later on, in order to eliminate the toxic mercury, Bergstrom[56] employed the improved Heck condition[63] to synthesize compound **10** in 53% with 5-iodo-2'-deoxyuridine **9**. (*E*)-5-(2-Bromoethenyl)-2-deoxyuridine **11**, one of the most potent anti-herpes simplex virus (HSV) drug, was obtained from **10** by basic hydrolysis followed by decarboxylation and bromination at 60 °C with NBS[64] (Scheme 2).



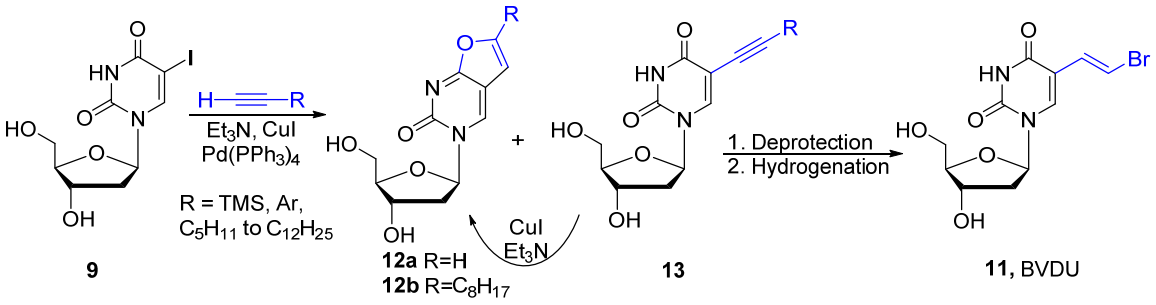
Scheme 2. Synthesis of C-5 modified pyrimidine nucleosides via Heck reaction

Sonogashira Coupling

Sonogashira coupling[65] is a useful tool to synthesize the alkynyl aryl or vinyl derivatives by the reaction of terminal alkynes with aryl or vinyl halides in the presence of Pd catalyst and copper(I) co-catalyst under the amine condition. Even though both 5-alkynyl- and 5-ethynyl- 2'-deoxyuridines have been studied as potent inhibitor of HSV-1, HSV-2, and vaccinia virus (VV), the biological activity is too low to be considered as good antiviral agents.[22,66] The 5-alkynyl pyrimidine nucleosides **13** could be synthesized by the Sonogashira reaction of 5-iodo-2'-deoxyuridine **9** with several of terminal alkynes.[30,67]

Further treatment of **13** with CuI and Et_3N/MeOH at reflux condition gave the bicyclic furanopyrimidine derivative **12**. Surprisingly, the parent bicyclic furanopyrimidine compound **12a** does not possess activity either against HSV-1, HSV-2, cytomegalovirus (CMV), or varicella zoster virus (VZV).[68] However, the long chain bicyclic analogues display surprising and unique

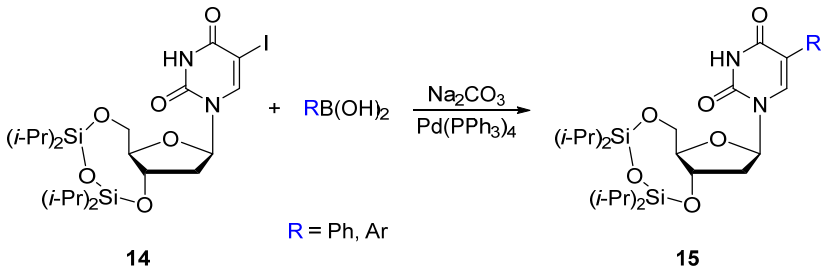
biological profiles, especially for **12b** bearing *n*-octyl group which is more active against VZV than the reference compound acyclovir.[67] When R = TMS, desilylation of **13** with TBAF at 0 °C gave 5-ethynyl pyrimidine analogue, which could be converted to **11** by the selective hydrogenation (Scheme 3).[30]



Scheme 3. Synthesis of C-5 modified pyrimidine nucleosides via Sonogashira reaction

Suzuki Coupling

The Suzuki reaction which couples organoboronic acid and aryl halides in the presence of palladium under basic conditions is another useful tool to build the carbon-carbon bond.[69-71] 5-aryl pyrimidine nucleoside derivatives **15** could be obtained from the reaction of protected 5-iodo pyrimidine substrates **14** with organoboronic acid (Scheme 4).[17,37,54]

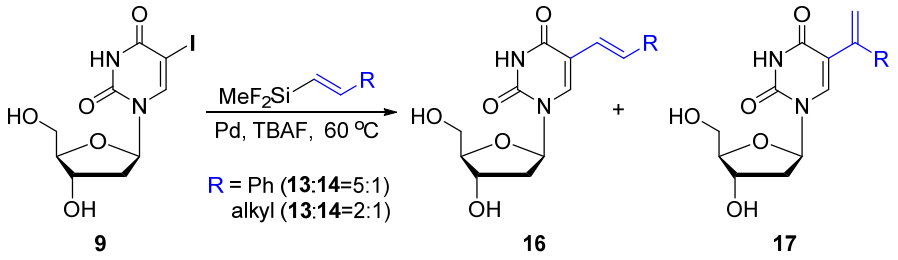


Scheme 4. Synthesis of C-5 modified pyrimidine nucleosides via Suzuki reaction

Hiyama Coupling

Hiyama reaction[72,73] is Pd catalyzed cross-coupling reaction of organosilanes with organic halides, which is promoted by fluoride ion.[74-76] The organofluorosilanes could be used as the starting material directly or generated *in vivo*. C-5 Vinyl modified pyrimidine nucleoside

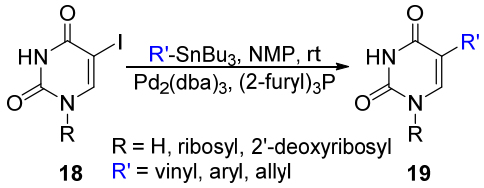
analogues **16** and **17** could be synthesized by the reaction of 5-iodo pyrimidine substrate **9** with fluorovinylsilane[77] in the presence of TBAF at 60 °C (Scheme 5).



Scheme 5. Synthesis of C-5 modified pyrimidine nucleosides via Hiyama reaction

Stille Coupling

Stille reaction,[78,79] which involves the coupling of an organotin compound with organic halides or triflates *via* Pd-catalyzed coupling reaction, is another powerful tool to synthesize the C-5 modified pyrimidine nucleoside derivatives. It could tolerate different type of functional groups existed in the substrates. And various organotin reagents have been utilized for the synthesis of 5-substituted pyrimidine nucleosides **19** (Scheme 6).[57]



Scheme 6. Synthesis of C-5 modified pyrimidine nucleosides via Stille reaction

1.3.2. Direct activation and its application in Pd-catalyzed cross-coupling reactions

With the research in progress, the Pd-catalyzed coupling-reactions can also occur with only one activated substrate under certain conditions (single C-H functionalization); sometimes activation was not required at all (double C-H activation).

Direct arylation of aromatic rings with aryl halides or pseudo halides, which eliminate the usage of organometallic substrates, has been recently established as excellent protocols for the synthesis of biaryls and begun to compete with traditional Pd-catalyzed cross-couplings.[80-85] It has been noted that both intra-[86-88] or intermolecularly[87,89-95] direct arylations can proceed

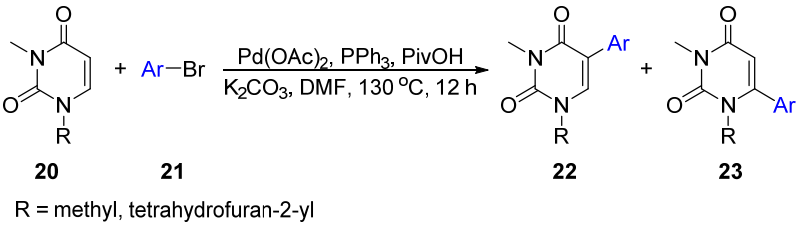
smoothly, especially with electron-rich heteroaromatics.[83] One of the advantages is that either organic halides or organometallic reagents can be substituted by simple arenes as partners in cross-coupling processes. Such approaches are more atom efficiency in terms of sustainable chemistry. Extensive investigations have been made to improve our understanding of how the transition metals catalyze the cleavage and functionalization of the inert C-H bonds effectively. Since Pd is one of the most commonly used transition metal catalyst for the C-H functionalization, I will focus my dissertation on the Pd-catalyzed C-H functionalization.

1.3.2.1. Single C-H functionalzation via Pd-catalyzed cross-coupling reactions

As discussed above the 5-arylated pyrimidine nucleoside could be synthesized by the traditional Pd-catalyzed cross coupling reactions in good yield under the mild condition; however, multistep preparation of pre-activated organometallic substrates is required. Coupling products with toxic organotin residues might be a problem for biological studies as well. Thus, the C-H direct arylation of the pyrimidine nucleosides have been developed as an alternative method to avoid such problems.

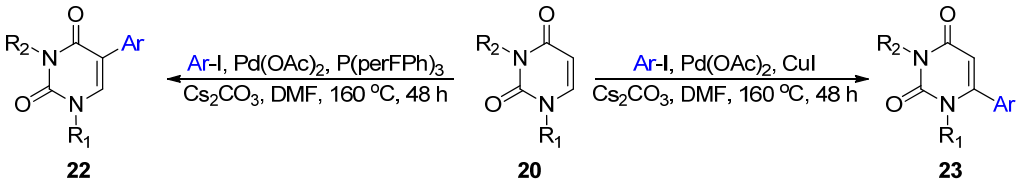
1.3.2.1.1. Direct arylation at C5/C6 position of uracil nucleosides

Kim and coworkers reported that the coupling of 1,3-dimethyluracil **20** with electron rich aryl bromides **21** in the presence of $Pd(OAc)_2$ and Cs_2CO_3 at 130 ^oC for 12 h gave 1,3-dimethyl-5-aryluracil **22** in decent yield (35-79%) along with C6-arylated regioisomer **23** in 0-25 % (Scheme 7).[96] It's the typical selectivity problem observed during the C-H functionalization of uracil base. Moreover, when 1-(tetrahydrofuran-2-yl)-3-benzyluracil was employed as the substrate to mimic the glycosidic bond of the nucleoside, the sever decomposition was observed under the regular coupling condition. Lowering the reaction temperature allowed the isolation of the corresponding product in 55 % with N3 protecting group.



Scheme 7. Direct C-H arylation of uracil analogues with aryl bromide

Hocek and his group found that the 1,3-protected uracil analogues **20** could couple with aryl iodine in the presence of Pd catalyst and cesium carbonate to give the 5-arylated uracil analogues **22**, but with even higher temperature (160 °C) and longer time (48 h) (Scheme 8).[68,69] Interestingly, when the reaction was carried out with addition of CuI as the co-catalyst, the C6 arylated product **23** was obtained as the major isomer but in low yield. If the reaction was carried out without Pd catalyst, **23** was observed as the only product.

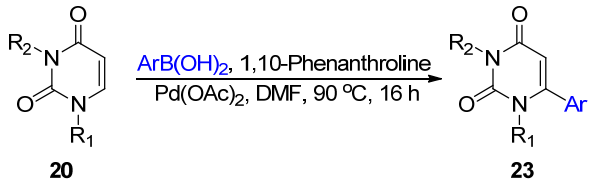


Scheme 8. Catalyst controlled single C-H functionalization of uracil analogues

To obtain the natural uracil analogues, several of protecting groups (e.g., Bn, PMB) need to be installed at N3 position of **20** and later removed under different conditions; some of them were too harsh to give deprotected uracil in good yield. The application of methodology to nucleoside substrates was not discussed at all. It is believed that the coupling precede *via* concerted metalation deprotonation (CMD) mechanism, while the cupper catalyzed condition might proceed with deprotonation-cupration mechanism.

Instead of coupling to aryl halides, 1,3-protected uracil **20** could also couple with boronic acid in the presence of Pd and ligand (1,10-phenanthroline) at 90 °C for 16 h to give 6-aryluracil analogues **23** as the exclusive product (Scheme 9).[97] Interestingly, when the protected uracil analogues **20** coupled with simple arylboronic acid, 6-arylated products **23** were obtained in

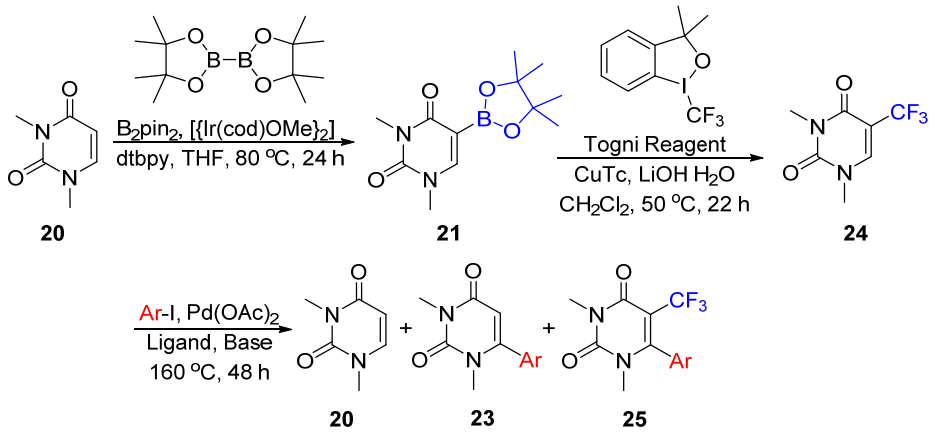
moderate yield exclusively, whereas, when the heteroaromatic boronic acids were employed as the activated component, **20** was recovered unchanged. Similar results were obtained when protected uracil analogues were replaced with free uracil or protected uridine analogues. So, this optimized condition shows some limitations that only work for specific substrates.



Scheme 9. Regioselective C-H arylation of uracil analogues with arylboronic acids

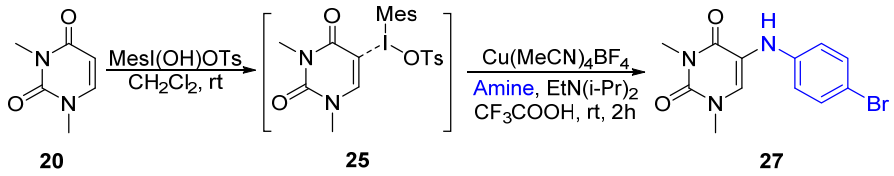
1.3.2.1.2. Other C-H functionalization C5/C6 position of uracil nucleosides

Iridium catalyzed C-H borylation of **20** in the presence of ligand at 80 °C gave unseparable 5-borylated uracil intermediates **21** with 5,6-diborylated uracil analogue. Successive electrophilic trifluoromethylation with Togni reagent yielded 5-trifluoromethyluracil **24** in 21% (Scheme 10). Alternatively, **24** could also be obtained by the selective C-H trifluoromethylation of **20** with $NaSO_2CF_3$ in the presence of *tert*-butyl hydroperoxide.[98] Another C-H direct arylation of **24** with aryl halide gave various products with **20** as the major component. C-6 Arylated products **23** and **25** were only obtained in small quantity due to the instability of the trifluoromethyl group at C-5 position under the basic condition.



Scheme 10. Direct C-H borylation and arylation of 1,3-dimethyluracil

Selective C-H amination product could be synthesized by the coupling of 1,3-dimethyluracil **20** and 4-bromoaniline in the presence of indolyliodonium tosylate (Scheme 11).[99] The iodonium salt intermediate **25** was responsible for the regioselectivity (S_EAr), followed by the amination gave the corresponding product **27** in 65 % yield (Scheme 8).

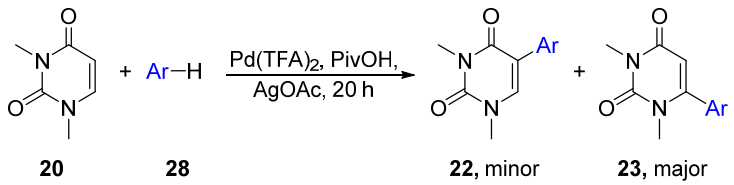


Scheme 11. Direct C-H amination of uracil analogues

1.3.2.2. Double C-H functionalization via Pd-catalyzed cross-coupling reactions

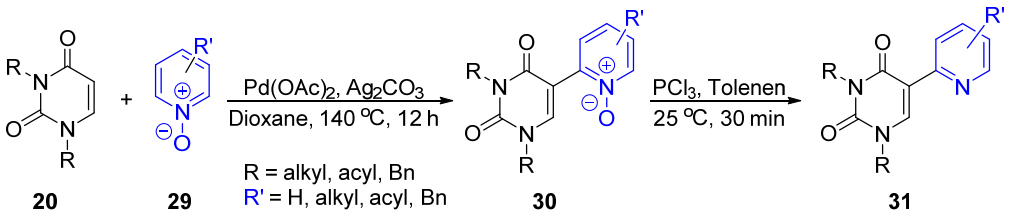
1.3.2.2.1. Direct arylation at C5/C6 position of uracil nucleosides

Double C-H functionalization reactions employ two unfunctionalized components, which could build the C-C bond without the pre-activation of any components. Pd-catalyzed cross-coupling of 1,3-dimethyluracil **20** with arenes **28** in the presence of pivalic acid and silver acetate under the reflux condition gave 1,3-dimethyl-5-aryluracil **22** as the minor product and 1,3-dimethyl-6-aryluracil **23** as the major product (Scheme 12).[96] It is believed that reaction went through a concerted metalation-deprotonation (CMD) processes *via* $Pd^{II}(L)(OPiv)$ species by deprotonation of the more acid hydrogen at C6 of uracil ring, followed by another concert metalation-deprotonation to give the 6-arylated uracil product **23**. Analogously, the C5-C5' and C5-C6' dimer or even C5-C5' and C6-C5' trimer could be synthesized under the similar condition.[100]



Scheme 12. Pd-Catalyzed double C-H functionalization of 1,3-protected uracil analogue

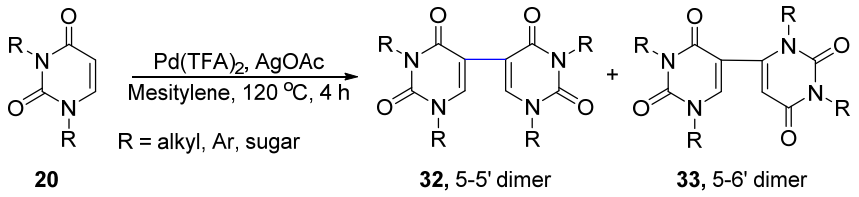
The Pd-catalyzed cross-couplings of unfunctionalized uracil analogues **20** with pyridine-*N*-oxide **29** in presence of $Pd(OAc)_2$ and silver carbonate at 140 °C for 12 h gave C-5 modified uracil product **30** with high regioselectivity and good yield.[101] *N*-oxide analogue **30** was readily reduced by PCl_3/pyridine to give the pyridine derivative **31** (Scheme 13). Comparing to the traditional Pd-catalyzed coupling reaction, the highly selective double C-H functionalization does not need to activate any component of the substrates. It is believed that the electrophilic palladation occurs preferentially at the C-5 position of uracil. Subsequent coordination with pyridine *N*-oxide to give active Pd(II) complex, followed by the reductive elimination to give coupling product **31**.



Scheme 13. Synthesis of 2-uracilyl pyridines via Pd-catalyzed double C-H functionalization

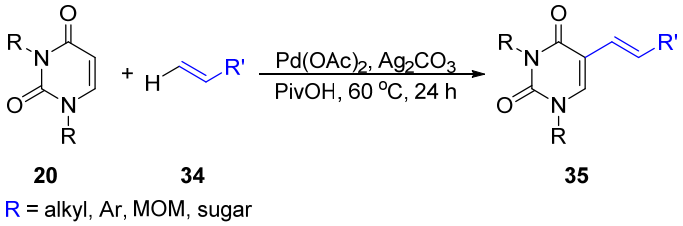
1.3.2.2.2. Other C-H functionalization at C5/C6 position of uracil nucleosides

Fully protected uracil could undergo the self-C-H functionalization to give a mixture of 5-5', 6-6' or 5-6' dimmers in the presence of $Pd(TFA)_2$ and AgOAc (Scheme 14).[100] When the reaction was stirred at 120 °C for 4 h, the 5-5' dimmer **32** was the major regioisomer, whereas, when the reaction was stirred at 80 °C for 16 h, the 5-6' dimmer **33** was the major regioisomer. Interestingly, the reaction of 1,3,5-trimethyluracil or 1,3,6-trimethyluracil did not yield these dimmers under the similar condition. The steric effect of the methyl group either at C5 or C6 position of the uracil base might be responsible for the failure of the reaction. The sugar protected uridine and/or 2'-deoxyuridine analogues also underwent these base-dimmer reactions.



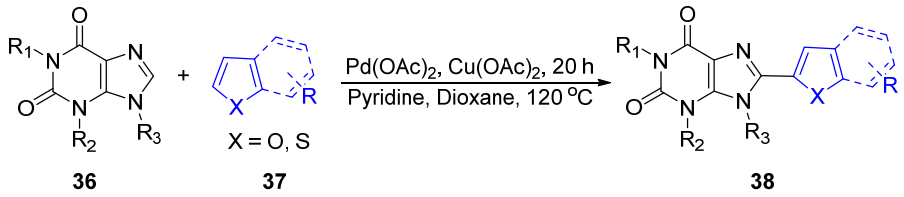
Scheme 14. Synthesis of uracil dimmers via Pd-catalyzed double C-H functionalization

The 5-alkenyl substituted uracil or uracil nucleoside derivatives could also be synthesized *via* the Pd-catalyzed double C-H functionalization.[102] Thus, treatment of 1,3-protected uracil analogues **20** with terminal alkenes **34** in the presence of $Pd(OAc)_2$, Ag_2CO_3 and pivalic acid at 60 °C gave *E*-5-alkenyluracil derivatives **35** with excellent region- and stereoselectivity (Scheme 15). However, it is worth to mention that these coupling conditions were only compatible with the fully protected uracil or uracil nucleosides and no examples of unprotected or N1 or N3 protected uracil were given.



Scheme 15. Synthesis of 5-alkenyl uracil and uracil nucleosides via Pd-catalyzed double C-H activation

The Pd-catalyzed intermolecular oxidative cross coupling of two different heteroaromatic rings to form the unsymmetrical hetero-biaryls has been reported recently by You.[103] The methodology has also been applied to the purine analogues. Thus treatment of 1,3-diethyl xanthine **36** with 2-methylthiophene or furan **37** in the presence of Pd and Cu catalysts gave the bisheteroaromatic products **38** in excellent yield, which indicated the tolerance of free NH group at imidazole ring at purine skeleton (Scheme 16). Thiophene, furan or other fused electron rich heteroaromatics **37** not only couple with purine analogues but also the pyridine *N*-oxide. Thus, the different electron density between the two heteroaromatic components is believed to be the key point for the reactivity and selectivity in the two metalation[104] steps of the catalytic circle.



Scheme 16. Substrate controlled intermolecular double C-H functionalization

It has been proposed that the regioselective electrophilic C-H substitution (S_EAr) with $Pd(OAc)_2$ to give *α*-thienylpalladium(II) intermediate **A** (Figure 3). Followed by the concerted metalation-deprotonation (CMD) process to give the heterocoupling intermediate, which might be the rate determining step. The Cu salt seems to be crucial for the coupling reaction, since, both catalytic efficiency and regioselectivity were dramatically increased with the addition of substoichiometric amount the copper salt.

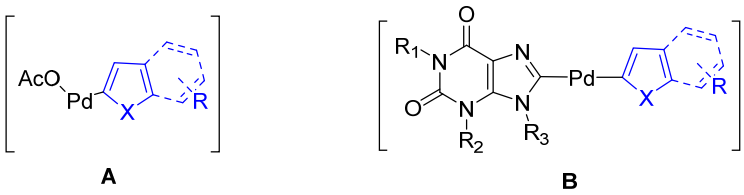
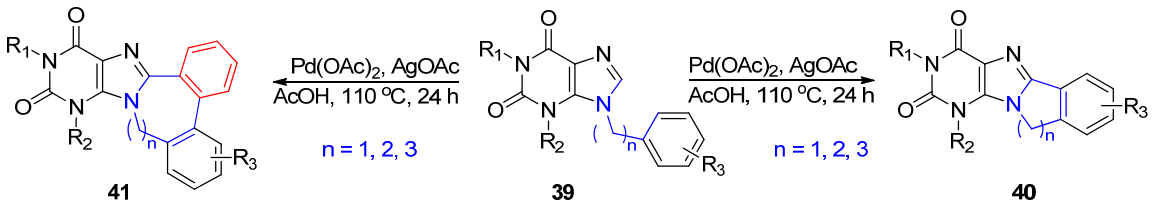


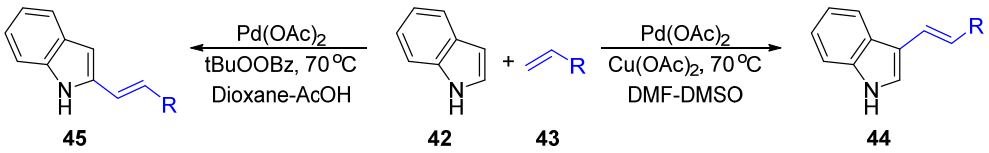
Figure 3. Proposed intermediates for the oxidative double C-H activation

Multi-fused heteroaromatics **40** could also be obtained *via* the intramolecular double C-H activation with benzimidazole or purine analogues **39** in the presence of Pd catalyst and silver salt as the oxidant (Scheme 17).[105] With the addition of iodobenzene, it is possible to construct the seven, eight, or nine member ring bearing two phenyl groups with cooperation of iodobenzene, which is synthetically difficult. However, the double C-H activation was performed in the acidic mediates at 110 °C for 24 h, which will limit the scope of the substrates.



Scheme 17. Substrate controlled intramolecular Pd-catalyzed double C-H functionalization

Catalyst/solvent controlled Pd-catalyzed oxidative heck reaction[106] omit the need for pre-activation of the substrates. According to the reactivity of indole, the palladation and Heck coupling reaction are preferred to take place at the C-3 position.[107] However the reaction site could be changed by the addition of other additives or solvent *via* the migration of the C3-Pd-X bond to the C2-position. Treatment of indole **42** with alkene **43** in the presence of $Pd(OAc)_2$ as catalyst at 70 ^oC yield two different products under the different oxidants and solvents (Scheme 18). When $Cu(OAc)_2$ was used as the oxidant in a mixture of DMF-DMSO, C3-functionalized product **44** was obtained exclusively. However, when *tert*-butyl benzyl peroxide was employed as the reoxidizing agent in the mixture of dioxane and AcOH, the C-H functionalization was directed to the C2 position to give **45**. If the *N*-protected indole was used as the substrate, no alkenylation product was observed at either C2 or C3 position under the similar condition, indicating the crucial role of the free NH moiety.



45 **42** **43** **44**

Scheme 18. Catalyst/solvent controlled alkenylation of indole

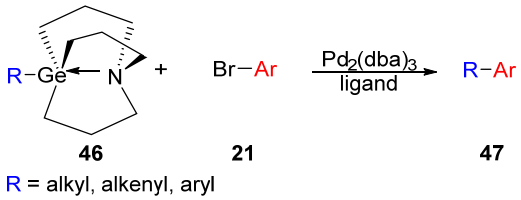
1.4. A short overview of the organogermane chemistry

Even though germanium is located between silicon and tin in the Group IVA in the periodical table, the application of organogermanes to Pd-catalyzed cross couplings has received much less attention comparing to Hiyama (organosilicane) and Stille (organotin) reactions.[76,78,108] Because of the relative high cost and low reactivity of germanium, both the chemistry and biological activity of organogermanium are still under developed so far.

1.4.1. Application of organogermanes to Pd-catalyzed cross-coupling reactions

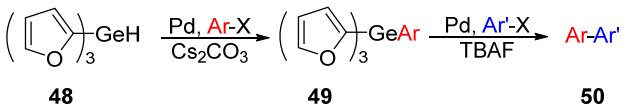
Even though the chemistry[109] of organogermanium compounds could not compete with organosilicon or organotin compounds yet, considerable amount work have been done to the Pd

catalyzed cross-coupling area. Kosugi and coworkers[110] found that Pd-catalyzed cross-coupling of the carbagermatranes **45** with aryl bromides **21** in the presence of ligand yielded corresponding products **47** in excellent yields (Scheme 19). Higher reactivity of the carbagermatrane analogues have been observed toward Stille-type coupling than the corresponding organotributylgermanes.



Scheme 19. Pd-catalyzed cross-coupling of germatrane derivatives 46 with aryl bromides

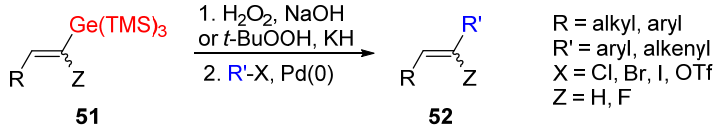
Oshima and coworkers[111] reported the Pd-catalyzed cross-coupling of tri(2-furyl)germane **28** with alkenyl or aryl halides in the presence of base to give aryltri(2-furyl)germane **49** which coupled with another aryl halides in the presence TBAF gave various biaryls (Scheme 20). It has found that the heteroaryl-Ge bond of **49** could be selective cleaved by the TBFA to form $ArGe(OH)_3$ or germanoxanes *in situ*, which are crucial for the coupling to proceed smoothly. Nucleophilic hypervalent organogermanium species, such as $[ArGe(OH)_3F]^-$, was formed by the attack of the excess fluoride ion, followed by the transmetalation and reductive elimination to give biaryls.



Scheme 20. Pd-catalyzed cross-coupling of tri(fur-2-yl)german and tri(fur-2-yl)phenylgerman with aryl halides

Wnuk and coworkers[112,113] noticed that vinyl-$Ge(TMS)_3$ bond of **51** could be selectively cleaved upon the treatment of hydrogen peroxide under the basic condition ($NaOH/H_2O_2$) or *tert*-butyl peroxide (*t*-BuOOH/KH) by generation of the reactive germanol or germanoxane intermediate. Followed by the Pd-catalyzed cross-couplings with alkenyl or aryl halides in the presence of $Pd(PPh_3)_4$ gave the corresponding coupling product **52** (Scheme 21). It is worthy to mention that the *E*-isomer of vinylgermane **51** gave *E*-isomer product only, while Z-isomer of

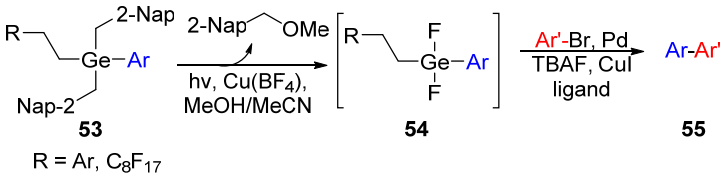
vinylgermane **51** gave a mixture of *E*/*Z* coupling products. The methodology is also applicable to the α-flouro vinylgermane substrates.



51 **52**

Scheme 21. Synthesis of alkenyl arenes via vinyl tris(trimethylsilyl)germanes

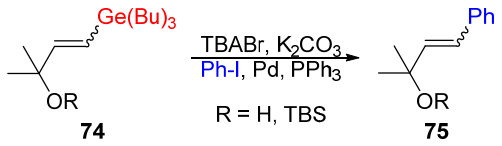
Spivey and coworkers[114,115] found that upon irradiation of bis-(2-naphthylmethyl)arylgermanes **53** with light in the presence of $Cu(BF)_4$ gave difluorogermane intermediate **54** by the elimination of 2 equiv. of 2-naphthylmethlene methyl ether. Followed by the Pd-catalyzed cross-coupling reaction of **54** with aryl bromide in the presence of TBAF gave various biaryls **55** (Scheme 22).



53 **54** **55**

Scheme 22. Photo-induced Pd-catalyzed cross-coupling of bis(2-naphthylmethyl)arylgermens with aryl bromides

Maleczka and coworkers[116] observed that vinyl-$Ge(Bu)_3$ bond of **74** could be cleaved under the base condition, followed by the Pd catalyzed cross-coupling with phenyl iodine to give corresponding products **75** (Scheme 23). It has been stated that the substituents at the allylic position could affect the regio- and stereoselectivity.



74 **75**

Scheme 23. Pd-catalyzed cross-coupling of tri(butyl)vinylgermanes 74 with iodobenzene

1.4.2. Biological activity of the germanium containing compounds

Biological activities[112,113] of organogermanium compounds have been reviewed and a few biologically active germane-modified nucleoside analogues have been developed. Even though

germanium is not considered as the essential element for any living organism, but germanium-containing heterocyclic compounds are usually less toxic than their carbon and silicon analogues,[117] so more and more biological test have been done on organogermanium compounds.[118] Since germanium plays an important role in stimulation of iron consumption and hemoglobin production, dietary germanium supplements became very popular in the 1970s. Later on, the first organogermanium complementary medicine propagermanium (bis(2-carboxyethylgermanium) sesquioxide) showed up in Japan under the trade name Serocion in 1994. Nowadays, there are lots of organogermanium compounds have been synthesized which possess antioxidant,[119,120] antiviral,[121] anti-tumor,[117,122-126] anticancer,[127-129] antiarthritic,[130] antimalarial and immunoregulatory[130] activity and radio protective property.[131]

In 1999, Lukevics and coworkers found that triphenylgermylisoxazoline **58** is a very active antitumor germanium-containing compound (Figure 4).[117] Spirogermanium **59** is also another very important germanium-containing compound which has antitumor,[125] antiarthritic, antimalarial and immunoregulator activity.[128,129,131]

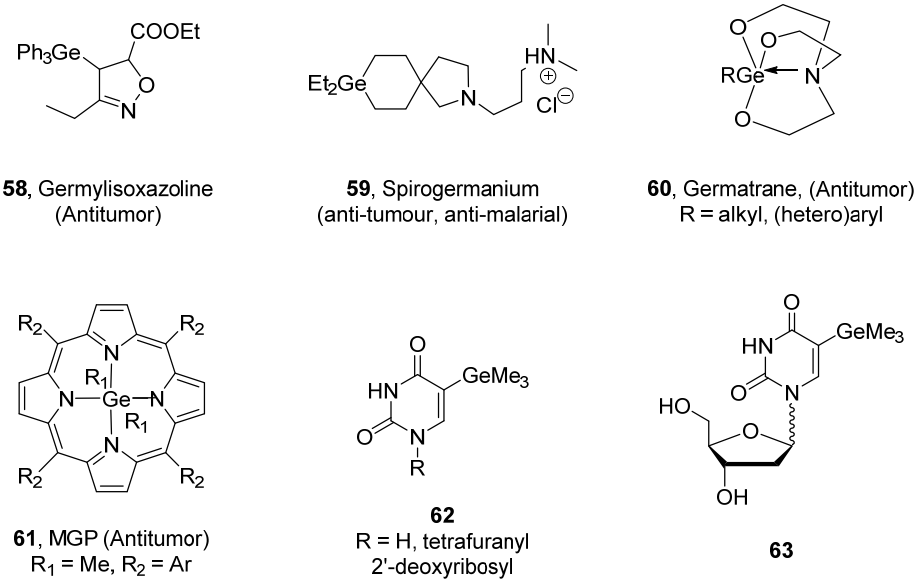


Figure 4. Biological activities of germanium containing compounds

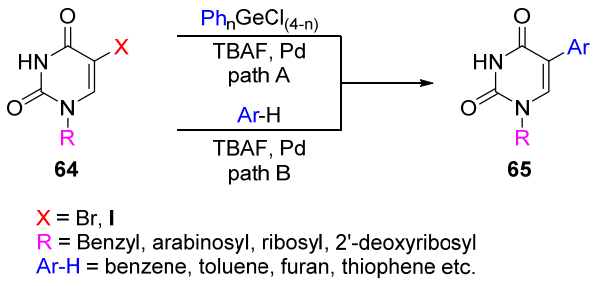
Germatrane **60** also shows the antitumor activity, and its toxicity is depending on the substitution groups which are attached to the germanium atom.[131,132] The antitumor activity of methylgermanium(IV) porphyrin (MGP) **61** was studied by Miyamoto in 1983.[122] The germanium containing nucleoside analogues also shows promising biological activities. The 5-trimethylgermyluracil and 1-(2-tetrahydrofuranyl)-5-trimethylgermyluracil **62** exhibit cytotoxicity to melanoma B16 cells.[133] The α and β anomer of 2'-deoxy-5-trimethylgermyluridine **63**, which is one of the few known examples of germanium-containing nucleoside analogues, display different properties. α-anomer could inhibit the replication of HSV-1 *in vitro* and block incorporation of thymidine and DNA of ovarian cancer cell, while β-anomer does not work as well as the other isomer.[121]

2. RESEARCH OBJECTIVES

The research objectives of this dissertation were to develop novel methods for the preparation of 5-modified pyrimidine nucleosides and to explore their possible applications as biochemical probes.

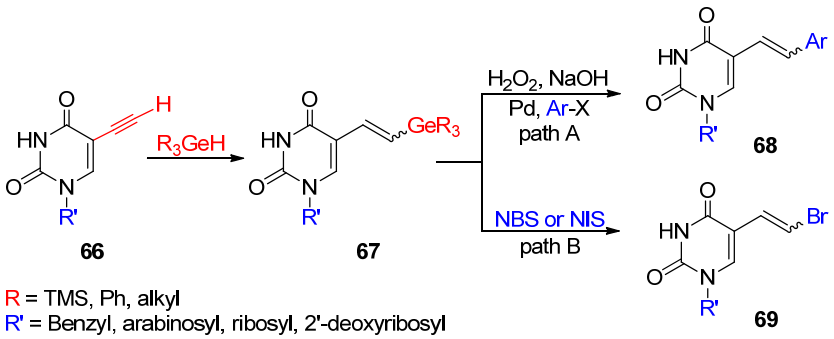
The first objective of this dissertation was to develop a new procedure for the arylation of the uracil nucleosides at C5 *via* Pd catalyzed cross coupling reaction employing organogermanes as nucleophilic coupling substrates. On the basis of our finding[75,134] that transfer of phenyl groups from the phenyl(chloro)germanes to the Pd-activated aryl halides is facilitated by the presence of TBAF, I developed the synthesis of 5-aryluracil nucleosides of type **65** by Pd-catalyzed cross-coupling between arylchlorogermanes and 5-halouracil substrates **64** promoted by TBAF (path A, Scheme 24).

Since the traditional Pd-catalyzed cross-coupling reaction involves the usage of organometallic reagents, in the second objective of my dissertation, I developed a novel methodology for the synthesis of 5-arylated uracil nucleosides of type **65** *via* Pd catalyzed direct arylation of the 5-halouracil substrates **64** with simple arenes or heteroaromatics, which avoids the use of organometallic nucleophiles (path B, Scheme 24). Optimization of direct arylation using various fluoride bases (e.g., CsF, KF or TBAF) or regular bases (e.g., Cs_2CO_3, K_2CO_3 or NaOH) promoters as well as mechanistic considerations would be explored.



Scheme 24. Proposed synthesis of 5-aryl uracil nucleosides by Pd-catalyzed coupling with organogermanes (path A) or direct arylation (path B)

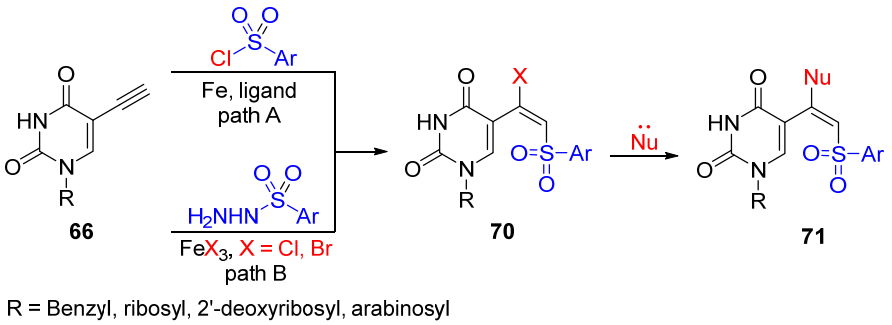
Since hydrogermylations of alkyl or arylalkynes usually give vinylgermanes in good yields, and vinyl tris(trimethylsilyl)germanes are known to be good substrates in the Pd-catalyzed cross-coupling reactions with alkenyl/aryl halides,[112,113] I prepared a series of pyrimidine nucleosides modified at the C-5 position with vinylgermane units. Thus radical hydrogermylation of 5-ethynyluracil nucleosides **66** with alkyl-, aryl- or tris(trimethylsilyl)germane should produce the corresponding 5-modified vinylgermanes **67** (Scheme 25). I investigated the application of the nucleosides for the synthesis of highly conjugated C5 modified pyrimidine nucleoside analogues **68** *via* the Pd catalyzed cross-coupling (path A, Scheme 25). Halodegermylation of **67** with electrophilic halogens (e.g., NBS, NIS) was explored to develop an alternative synthesis of the important 5-halovinyl pyrimidine nucleosides **69** (path B, Scheme 25).



Scheme 25. Proposed synthesis of 5-vinylgermyl uracil nucleosides by hydrogermylation and application to Pd-catalyzed coupling with aryl halides (path A) or halodegermylation (path B)

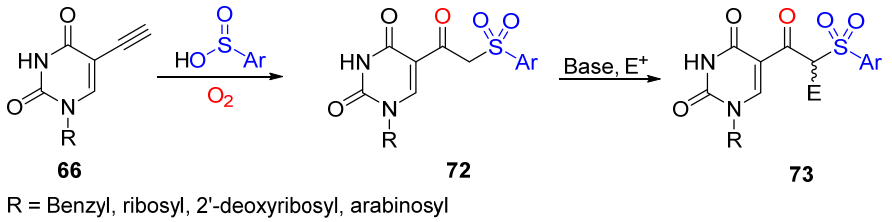
To further investigate the chemistry of 5-ethynyl pyrimidine nucleosides, I synthesized a series of novel 5-(*β*-halo)vinyl sulfonyl analogues **70**. Thus, the synthesis of 5-(*β*-halo)vinyl sulfonyl pyrimidine analogues would be explored *via* Fe(III) mediated regio- and stereoselective hydrosulfonylation of 5-ethynyl analogues **66** with aryl/alkyl sulfonyl chloride in the presence of triphenylphosphine (path A, Scheme 26). Alternatively, iron halide catalyzed hydrosulfonylation with sulfonylhydrazides in the presence of a catalytic amount of *tert*-butyl hydroperoxide (TBHP) would also be explored (path B, Scheme 26). Since, the 5-(*β*-halo)vinyl sulfonyl analogues **70** can serve as an excellent Michael acceptors, e.g., as electrophiles to form covalent adducts with

nucleophile. I studied the addition of typical nucleophiles (e.g., propanethiol, *n*-butylamine) and the corresponding model amino acids (e.g., lysine, cysteine) to these novel 5-modified nucleosides. Kinetics and chemical yields of such Michael addition reaction would be "tuned up" by incorporation of electron donating group (EDG) or electron withdrawing group (EWG) on the aromatic ring of the sulfonyl compounds. I expected that the addition of nucleophiles to such Michael acceptors should occur *via* an addition-elimination reaction with the elimination of halides and formation of the vinyl adducts.



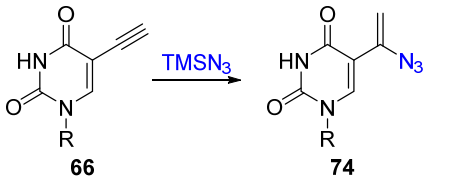
Scheme 26. Proposed synthesis of 5-(β-halo)vinyl sulfonyl pyrimidine nucleosides by hydrosulfonylation of 63 with sulfonyl chloride (path A) or sulfonyl hydrazide (path B) and its application to the nucleophilic substitution

I expect that direct aerobic difunctionalization of 5-ethynyl nucleoside analogues **66** with sulfinic acid in the presence of a catalytic amount of pyridine could serve as an access to the 5-(*β*-keto)sulfonyl pyrimidine nucleoside analogues **72** (Scheme 27). Since the methylene protons adjacent to ketone and sulfonyl groups are quite acidic with pKa around 12, it was envisioned that after deprotonation by base, the corresponding carbon ion could be methylated (e.g., MeI or *S*-Adenosyl methionine) or trapped (e.g., proximal protein electrophiles) by electrophiles to give **73**.



Scheme 27. Proposed synthesis of 5-(β-keto) sulfonyl pyrimidine nucleosides by hydrogermylation of 63 with sulfinic acid and its application to electrophilic substitution

I have also planned to explore the synthesis of 5-(*α*-azido)vinyl pyrimidine nucleosides **42** *via* silver-catalyzed hydroazidation of 5-ethynyl substrates **66** (Scheme 28). Since 5-azido uracil analogues are photo labile, and their application to click chemistry is under development, I am planning to utilize these 5-(*α*-azido)vinyl analogues **74** in copper free click chemistry with the ring strained cyclooctyne to synthesize 5-(*α*-1,2,3-triazol)vinyl pyrimidine nucleosides which could be further incorporated into DNA or RNA as fluorescent probes.



66 **74**

R = Benzyl, ribosyl, 2'-deoxyribosyl, arabinosyl

Scheme 28. Proposed synthesis of 5-(α-azido)vinyl pyrimidine nucleosides by hydroazidation of 63 with $TMSN_3$

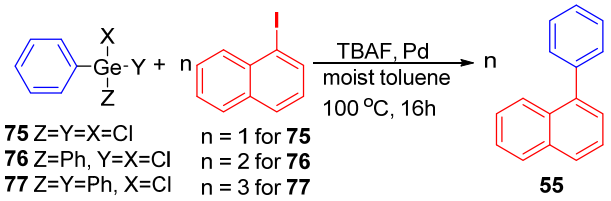
3. RESULTS AND DISCUSSION

3.1. Synthesis of 5-aryluracil nucleosides via Pd-catalyzed cross coupling reactions

3.1.1. Coupling reactions of 5-halouracil nucleosides with chloro(phenyl)germanes

3.1.1.1. Developing a general procedure for transfer of phenyl group(s) from chloro(phenyl)germanes to aryl halides mediated by TBAF

Most recently, we have reported the TBAF-promoted synthesis of biaryls *via* Pd-catalyzed cross coupling of trichloro(phenyl)-, dichloro(diphenyl)-, and chloro(triphenyl)germanes **75-77** with aryl halides in "wet" toluene.[75,134-136] It has been stated that the presence of chloride was necessary for organogermanes to generate the active fluorophenylgermane intermediate *in situ,*[137] which are believed to be the active intermediates in transferring of phenyl groups from Ge atom to Pd-activated aryl halides. Thus coupling of **75** with 1-iodonaphthalene in the presence of $Pd_2(dba)_3$ gave **55** in high yield (Scheme 29). Additional amounts of water have been proven to be necessary for multiple transfers of the phenyl group from the germane center. It has also been shown that the coupling efficiency of arylchlorogermanes is comparable to that of the more developed organotin or organosilane substrates.



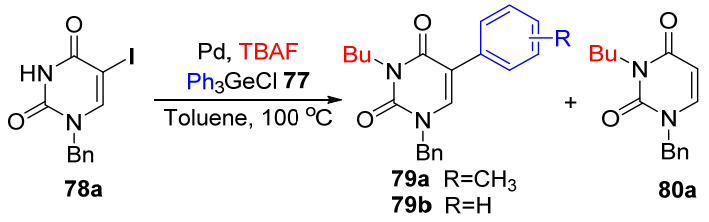
Scheme 29. Synthesis of 1-phenylnaphthalene via chlorophenylgermanes

On the basis of these findings and the available knowledge on the susceptibility of organogermanes toward coupling, it appears that the reaction is promoted either by: (i) intramolecular chelation of a pendant Lewis basic heteroatom which renders the Ge center "permanently" pentavalent[110] or (ii) coordination of a heteroatom activated Ge center with an external Lewis basic ligand (e.g., fluoride, hydroxide, etc.), which is also rendering the Ge center pentavalent. [75,110,115,134] Even though the mechanism of fluoride/base activated Pd-catalyzed cross-

coupling reaction of organogermanes with aryl/alkenyl halides is still unclear, such reactions have been achieved. [75,112,113,134,135]

3.1.1.2. Attempted TBAF-promoted coupling of 1-N-benzyl-5-iodouracil with chloro(pehnyl)germanes in toluene

In order to achieve the first objective of my dissertation, which was synthesis of 5-arylated pyrimidine nucleosides employing 5-halo substrates to couple with organogermanes as the coupling partner, efforts have been taken to develop model coupling between 5-halouracil and chloro(phenyl)germanes, which have been used as the substrates for selective transfer of phenyl groups from the germyl center.[75,112,136,138] Thus, I applied the optimal coupling condition to 5-halo pyrimidine nucleosides for the synthesis of 5-aryl analogues. Treatment of 1-*N*-benzyl-5-iodouracil **78a** with triphenylchlorogermanes **77** in the presence of *tetra*-*N*-butylammonium fluoride (TBAF, 1 M/THF containing 5% of water) and $Pd_2(dba)_3$ catalyst in toluene at 100 °C for 16 h gave 1-*N*-benzyl-3-*N*-butyl-5-phenyluracil **79b** as well as the N^3-butylated reduction product **80a** (Scheme 30).



Scheme 30. TBAF promoted cross-coupling of 5-iodouracil with chloro(triphenyl)germane

However, after careful analysis of GC-MS spectra, it was surprising to find that there is a mixture of 1-*N*-benzyl-3-*N*-butyl-5-(*o,m,p*-methylphenyl)uracil products **79a** which likely derive from the coupling of **78a** with toluene. In order to clarify and simplify the reaction, **78a** was heated in toluene alone in the presence of TBAF and $Pd_2(dba)_3$ at 100 °C for 18 h. As expected, mixture of 5-(*o,m,p*-methylphenyl)uracil products **79a** was obtained in 75 % (combined yield for

all three isomers) along with a small amount of N^3-butylated reduction product **80a**. (See Chapter 3.1.3 for detail discussion)

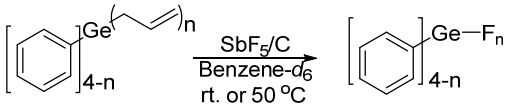
3.1.2. Coupling reactions of 5-halouracil nucleosides with allyl(phenyl)germanes

Although the chemistry of allylgermanes is well established,[139,140] the application of allyl (phenyl)germane to the selective transfer of phenyl groups from a germanyl center by Pd-catalyzed cross-coupling reaction with aryl halides has not been investigated.

3.1.2.1. Developing a general procedure for transfer of phenyl group(s) from allyl(phenyl)germanes to aryl halides mediated by SbF_5/TBAF

3.1.2.1. Optimization for selective transfer of phenyl groups from germane center

On the basis of our experience and literature research, SbF_5 was found to be a suitable reagent to selectively cleave Ge-allyl bonds and to generate reactive germanate species for subsequent transmetalation. Treatment of allyl(phenyl)germanes **83** or **82** with SbF_5 (0.25-0.5 equiv) intercalated in graphite[141] in toluene (0.5-1h, 50 °C) resulted in disappearance of the germane substrates (TLC, ^{1}HNMR). In order to demonstrate that the fluoro(phenyl)germanes are the resulting active intermediates, selective deallylation was carried out in benzene-d_6 at room temperature and 50 ^{o}C side by side (Scheme 31).



81 n = 3
82 n = 2
83 n = 1

84 n = 3
85 n = 2
86 n = 1

Scheme 31. Selective cleavage the allyl-Ge bond of allylphenylgermanes with SbF_5/C

The progress of the reaction was monitored by TLC, which showed the disappearance of the starting material in 1h. The ^{19}F NMR spectra also indicated the formation of fluorogermane intermediates. Reactions with **82** and **83** showed the clean formation of the fluorogermanes Ph_3GeF (s, δ -202.3 ppm; Figure 5; 1 and 2) and Ph_2GeF_2 (2 × s, δ -165.2, and -167.4 ppm; Figure 5; 3 and 4), respectively, with spectroscopic data in agreement with the reported values.[75,115,136]

However, analogous treatment of **81** with SbF_5 gave a cluster of peaks at δ -140.2 to -159.7 ppm (Figure 5; 5 and 6). It is noteworthy that when **81**, **82**, or **83** was treated with TBAF only under the same condition, no Ge-allyl bond cleavage was observed for any of the substrates.

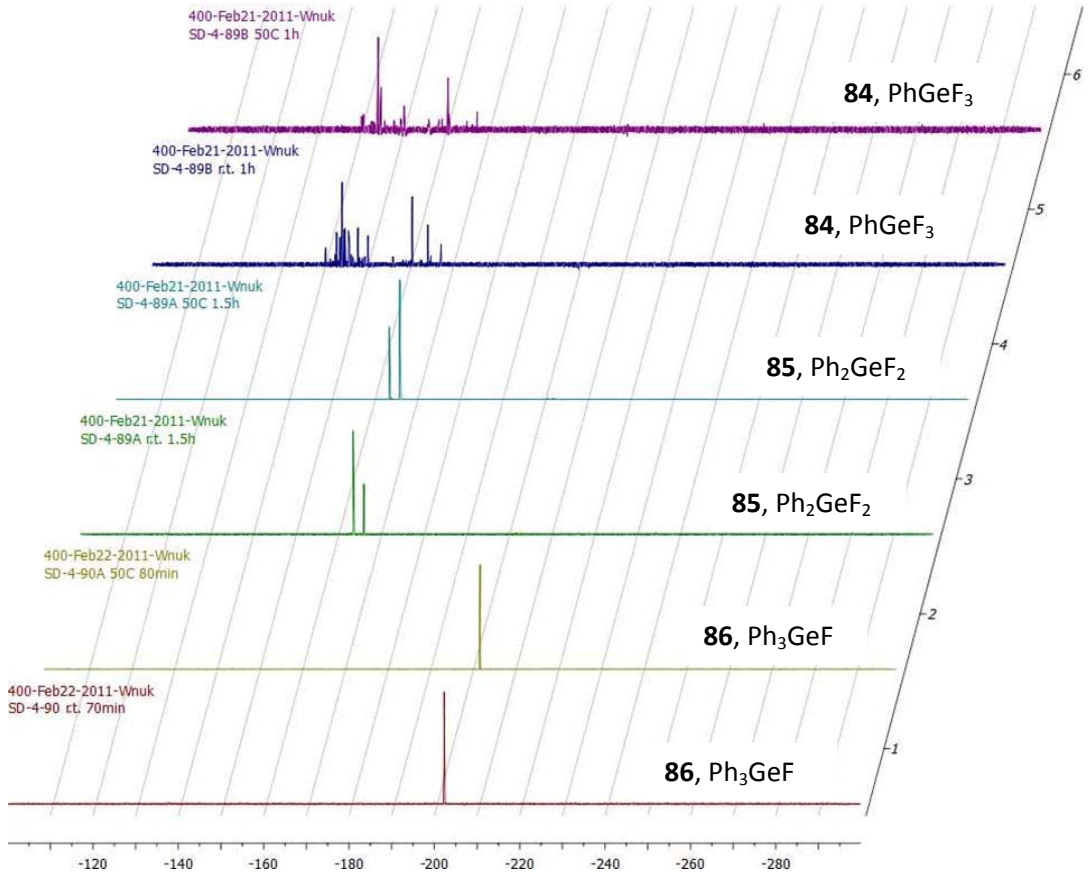
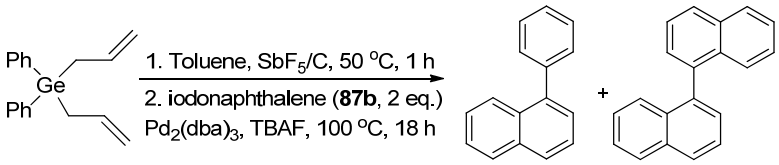


Figure 5. ^{19}F NMR analysis of the allylgermanes cleavage upon treatment of SbF_5/C

Optimizations were performed to find the best coupling condition. Thus, treatment of the fluorogermane generated *in situ* from **82**/SbF_5 with **87b** in TBAF/toluene resulted in transfer of phenyl groups from Ge producing biaryl **88b** in addition to the homocoupling byproduct **89b** (Table 3). Treatment of **82** with SbF_5/C alone, as a fluoride source, failed to give coupling product **88b**. It was found that at least 3 equiv. of TBAF was required to give **88b** in maximum yield (Entries 1-5). The yield was increased dramatically when couplings were carried out with addition of a measured amount of water (~10-30 equiv; Entries 6-8), which was consistent with

the previous finding.[75,134] As expected, two phenyl groups were transferred upon the treatment with the combination of SbF_5/TBAF in moist toluene, which has been shown the TBAF promoted cross-couplings of Ph_2GeCl_2 with aryl halides.[75,134,136] It is worthy to mentioning that the newly developed method here proceeds with the selective cleavage of the allyl-Ge bond of **81-83** with SbF_5 by generation of fluorogermanes **84-86** *in situ*, which allows transfer of phenyl groups, differs from the previous developed protocol that allow selectively transfer of allyl groups from **81-83** upon treatment with base.[135,136] Thus transfer of phenyl or allyl groups from a Ge center could be chemoselective, depending on the activation protocol.

Table 3. Coupling of diallyl(diphenyl)germane 82 with 1-iodonaphthalene 87b promoted by SbF_5



82 **88b** **89b**

Entry	Germane[a]	TBAF[b] (equiv.)	Yield (%)[c, d]	Ratio[d] **88b**:**89b**
1	**82**	1	43	4.4:1
2	**82**	2	53	3.9:1
3	**82**	3	60 (54)	3.8:1
4	**82**	4	47	2.0:1
5	**82**	5	44	1.3:1
6	**82**	3[e]	67 (59)	5.2:1
7	**82**	3[f]	72 (62)	4.5:1
8	**82**	3[g]	68	6.1:1

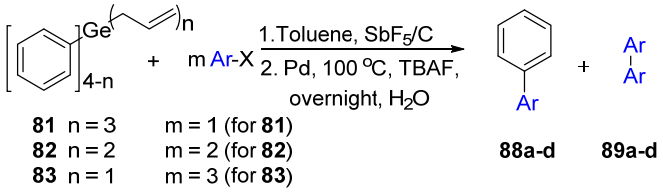
[a] Couplings were performed on 0.14mmol scale of germane **82** (0.04 M) with 2 eqiuv of **87b** and 0.05 equiv of Pd catalyst. [b] Commercial available 1 *M* THF solution containing 5% H_2O. [c] The yield was calculated based upon transferring of two phenyl groups from **82**. Isolated yield in parenthesis. [d] Based on GC-MS of the crude reaction mixture. [e] With the addition of 25 μL of H_2O. [f] With the addition of 50 μL H_2O. [g] With the addition of 75 μL H_2O.

3.1.2.1.2. Extension of the method to other aryl halides

Various biaryls have been synthesized with the optimal conditions and the results are summarized in table 4. Treatment of **81**, **82**, or **83** with SbF_5/C generated active organofluorogermane intermediates *in situ*, followed by subsequent TBAF-promoted Pd-

catalyzed cross-coupling reactions with 1, 2, or 3 equiv. of aryl halides respectively afforded biaryls **88b-88d** in good to excellent yields. Couplings with 1-bromonaphthalene also gave **88b**, but the yield is lower compared to 1-iodonaphthalene **88b**. It is worth mentioning that more than one phenyl groups has been transferred during the cross-coupling reaction and aryl halides bearing electron donating groups (entries 2, 5, and 8) gave better yields and ratios compared to the cases with electron withdrawing groups (entries 3, 6 and 9).

Table 4. Coupling of allyl(phenyl)germanes 81-83 with aryl halides promoted by SbF_5



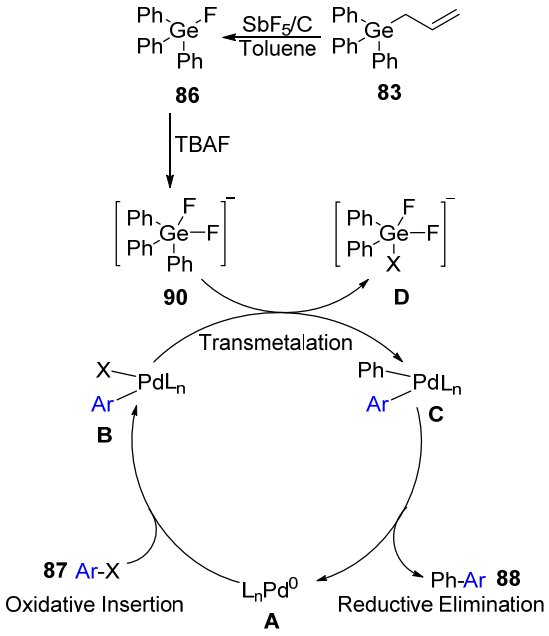
Entry	Germane[a]	Halide	Product	Yield (%)[b]	Ratio **88**:**89**
1	**81**	1-bromonaphthalene	**88e**	45	15:1
2	**81**	(4)CH_3OPhI	**88c**	91	20:1
3	**81**	(4)CF_3PhI	**88d**	49	1.9:1
4	**82**	1-bromonaphthalene	**88b**	73	2.3:1
5	**82**	(4)CH_3OPhI	**88c**	95	1.8:1
6	**82**	(4)CF_3PhI	**88d**	69	1:1
7	**83**	1-bromonaphthalene	**88b**	46	3.3:1
8	**83**	(4)CH_3OPhI	**88c**	104	1.6:1
9	**83**	(4)CF_3PhI	**88d**	75	1:1.5

[a] Couplings were performed on 0.14mmol scale of **81-83** (0.04 M) with 0.05 equiv of $Pd_2(dba)_3$ and 1.0 (for **81**), 2.0 (for **82**), or 3.0 (for **83**) equiv of aryl halides and TBAF/(1M/THF, 3 equiv)/water (50 μL). [b] Based upon transferring of one, two, or three phenyl groups from **81**, **82**, or **83**, respectively. Isolated yield in parenthesis. [c] Determined by GC-MS of the crude reaction mixture.

3.1.2.1.3. Proposed mechanism for the selective transfer of phenyl groups from allyl(phenyl)germanes

Contrary to what has been discovered by a previous group member, that allyl could be selectively transferred under basic conditions in the presence of Palladium to give the allylation product,[136] this methodology allows for the selective transfer of the phenyl group from a Ge center thereby yielding biaryls upon treatment with SbF_5/C and TBAF (Scheme 32). Initially, the

allyl-Ge bond of **83** was selectively cleaved upon treatment with SbF_5 to give fluorophenylgermanes **86** *in situ*, followed by the treatment of TBAF to yield the active pentafluorogermanate intermediates **90**, which were readily coupled with Pd-activated aryl halides **B**. After the transmetalation and reductive elimination, various biaryls **88** were obtained and organogermane **D** will go to the next circle until there is no phenyl group available.

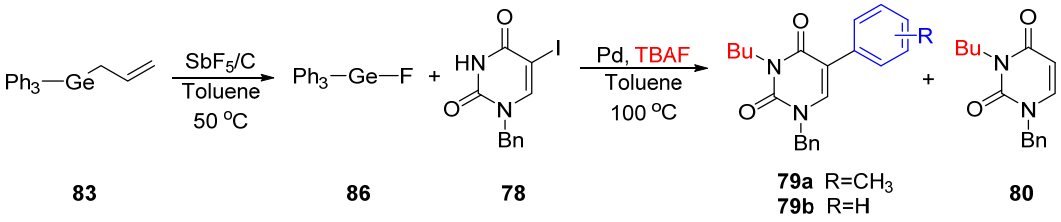


Scheme 32. Proposed mechanism for the SbF_5 promoted transfer of phenyl group from Ge center

3.1.2.2. Attempted SbF_5/TBAF-promoted coupling of 1-N-benzyl-5-iodouracil with allyl(pehnyl)germanes in toluene

In order to further explore the synthesis of 5-arylated pyrimidine nucleosides employing 5-halouracil substrates in coupling reactions with organogermanes, TBAF-promoted Pd-catalyzed cross-coupling reactions of 5-halouracil have also been applied to allyl(phenyl)germanes **81**-**83**. Thus, treatment of allyl(triphenyl)germane **83** with SbF_5/C (0.25 equiv) in toluene at 50 °C for 1 h leads to the formation of active fluoro(phenyl)germane species **86**, which was then followed by the vacuum filtration to give a clear solution that was used directly for the next step (Scheme 33). 1-*N*-benzyl-5-iodouracil **78a**, TBAF (1M/THF), and $Pd_2(dba)_3$ were added to the crude

material from the last step at ambient temperature under nitrogen atmosphere and the resulting brownish mixture was stirred at 100 °C for 18 h. However, no coupling product was observed. Thus, no further studies were performed.



Scheme 33. SbF_5 Mediated Pd-catalyzed cross-coupling of 5-iodouracil 78 with allyl(triphenyl)germane 83

3.1.3. Direct arylation of 5-halouracils and 5-halouracil nucleosides with arenes and heteroarenes

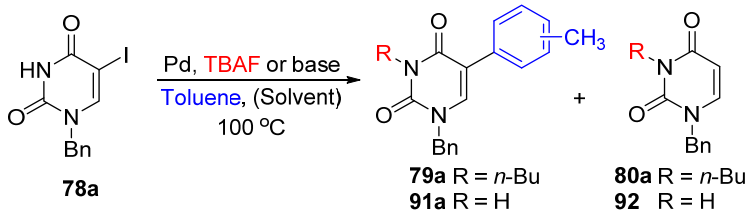
Intrigued by the unexpected result and after reviewing the literature, it was found that direct arylation of the 3-*N* unprotected uracil analogues has not been reported. The currently available methods for direct 5-arylation of the uracil analogues were noted to be either not suitable for the natural (3-*N*-unsubstituted) uracils[142] or caused cleavage of the nucleoside glycosidic bond.[96] Because of the importance of the enolization between the 4-oxo group and the hydrogen at the 3-*N* position in the biology and chemistry of RNA/DNA, as well as in nucleoside-derived drug metabolism, it was deemed of interest to explore the direct arylation of 5-halopyrimidine nucleosides with arenes, which would supplement the well-established Suzuki and Stille approaches.

3.1.3.1. TBAF-Promoted Pd-catalyzed direct arylation of 5-halouracil

To continue with the previous funding (Scheme 30 in Chapter 3.1.1.2), the authentic samples of ***m*-79b**, ***o*-79b** and ***p*-79b** were synthesized *via* Suzuki coupling[54] to elucidate the ratio of the three isomers. By comparing the retention time of each authetic isomer *via* GC and spiking the reaction mixture with the authentic sample, the ratio of *ortho/meta/para* was established as 3:2:1.

In order to eliminate the N^3-butylation during the coupling, the reaction was terminated after 6 h. However, besides an isomeric mixture of **79a**, both N^3-butylated byproducts **80a** and the reduced substrate **92** were also detected as byproducts in the crude reaction mixture (Table 5, entry 1).

Table 5. Effect of the reaction parameters in the direct arylation of 1-*N*-benzyl-5-iodouracil 1a with toluene



Entry	Reagent/solvent[a]	Pd	TBAF (equiv)	Base (2 equiv)	Time (h)	**91a**[b] Yield (%)[c,d]	**92** Yield (%)[d]
1	Toluene	$Pd_2(dba)_3$	7	--	6	45[e]	3
2	Toluene	$Pd_2(dba)_3$	7	--	0.75	75 (71)[f]	5
3	Toluene	$Pd_2(dba)_3$	6	--	1	60	15
4	Toluene	$Pd_2(dba)_3$	5	--	1	48[g]	17
5	Toluene	$Pd_2(dba)_3$	3	--	1	30	8
6	Toluene	$Pd(OAc)_2$	7	--	1	70 (68)[h]	7
7	Toluene/DMF[i]	$Pd_2(dba)_3$	7	--	1	82 (65)	7
8	Toluene/DMF[j]	$Pd_2(dba)_3$	7[k]	--	1	65 (50)[l]	19
9	Toluene/DMA[i]	$Pd_2(dba)_3$	7	--	1	20	10
10	Toluene/dioxane[i]	$Pd_2(dba)_3$	7	--	1	40	46
11	Toluene/DMF[j]	$Pd_2(dba)_3$	--	KF[m]	2	-	11
12	Toluene/DMF[j]	$Pd_2(dba)_3$	--	Cs_2CO_3[n]	2	-	25
13	Toluene/DMF[j]	$Pd(OAc)_2$	--	$KOSiMe_3$	2	-	80 (65)
14	Toluene/DMF[j]	$Pd(OAc)_2$	-	Ag_2CO_3[o]	2	-	17
15	Toluene/DMF/H_2O	$Pd(OAc)_2$	-	K_2CO_3	2	-	23

[a] Couplings were performed on 0.14 mmol scale of **78a** [0.05 M (entries 1-10) or 0.07 M (entries 11-18)] with 0.05 equiv. of Pd catalyst. [b] Mixture of *o/m/p* isomers (3:2:1, GC-MS). [c] Overall yield for *o/m/p* isomers. [d] Determined by GC-MS of the crude reaction mixture. Isolated yield in parenthesis. [e] Also **80a** (35%) was formed. Longer reaction time (18 h) produced **79a** in 85% yield (75% isolated yield as mixture of *o/m/p* isomers; 3.4:2.3:1). [f] 70% yield at 90 °C for 1.5 h. 40% yield at 80 °C for 4 h. [g] 35% with 4 equiv. of TBAF. [h] 69% yield at 90 °C for 1.5 h. [i] 1:1 (v/v). [j] 1:9 (v/v). [k] When neat TBAF·3H_2O (7 equiv.) was used **91a** (67%) and **92** (20%) were produced. [l] 25% yield in 1:20 (v/v; toluene/DMF). [m] Reaction with CsF also did not yield **91a**. [n] Attempts with different equivalents of bases (0.5-4.0) or prolonged reaction time (4 h) were also unsuccessful. [o] Couplings also did not proceed in the presence of Cs_2CO_3 or AgOAc and their combination with pivalic acid.

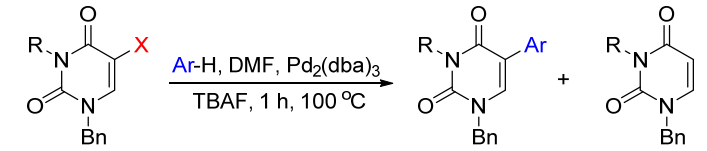
After careful investigation of reaction time and temperature, it is found that the direct arylation of **78a** can be completed in less than one hour (45 min) at 100 °C (entry 2). It is worth

noting that no N^3-butylation was not observed (GC-MS) until 1.5 h at 100 ^oC. Experimental data also showed that the amount of TBAF is crucial for the coupling to proceed smoothly and at least 7 equiv. of TBAF was required to give **91a** in highest yield and with the best **91a** to **92** ratios (entries 2-5). $Pd_2(dba)_3$ was the best catalyst but $Pd(OAc)_2$ also gave **91a** in similar yields compared to other tested Pd catalysts (entry 6). In order to increase the coupling efficiency and lower the ratio of toluene to **78a**, an inert solvent was sought, which is suitable for the direct arylation. Thus, the direct arylation was performed in 1:1 and 1:9 (v/v) mixture of toluene/DMF to give coupling product **91a** in 82 % and 65 % respectively (entries 7 and 8). Replacement of the TBAF/THF solution with the same amount of neat TBAF·$3H_2O$ also gave **91a** with similar yield (entry 8, footnote k). It is noteworthy that each of these fluoride reagents introduced approximately the same amount of water to the reaction mixture and water is known to play multiple roles in enhancing the efficiency of the couplings including the formation of the reactive hydroxypalladium intermediates.[75,136,143,144]Arylation of **78a** with toluene in DMA and dioxane (1:1, v/v) also gave **91a** but in lower yields (entries 9 and 10), whereas, arylation was not successful in mixtures of toluene/THF (1:1; v/v) at reflux, which is probably due to the much lower reaction temperature. Coupling of **78a** with toluene in the presence of either of the fluoride sources, e.g., CsF or KF (2 equiv.), or bases, e.g., Cs_2CO_3, Ag_2CO_3, K_2CO_3, or $KOSiMe_3$, instead of TBAF, did not yield **91a** (entries 11-15). No improvement was observed either by varying the amount or combination of bases, Pd catalysts, and reaction times (entry 12) or by addition of pivalic acid (entry 14). Even though DMF/H_2O (5:1, v/v) was tried as the medium to improve the solubility of inorganic salts, the arylation was still not successful (entry 15).

Determination of the generality of the TBAF-promoted direct arylation in couplings of 5-halouracils **78a** or **78b** with various arenes and heteroaromatics is presented in Table 6. Thus, treatment of 5-iodouracil **78a** with benzene in DMF in the presence of TBAF (7 equiv.) at 100 ^oC for 1 h gave 5-phenyluracil **91b** in 71 % as a single product in addition to a small amount of the

reduced substrate **92** (Table 6, entry 1). Arylation of **78a** with *m*-xylene gave a mixture of the three regioisomers (88%) from which the 2,4-dimethylphenyl isomer **91c** was isolated in 55% yield (entry 2).

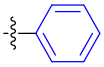
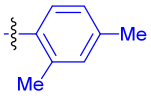
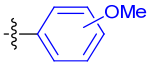
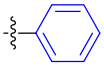
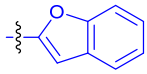
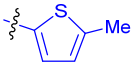
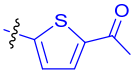
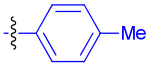
Table 6. Direct arylation of 5-halouracils 78 with and electron-rich arenes and heteroaromatics



78a, R = H, X = **I**
78b, R = H, X = Br
78c, R = Me, X = **I**

91, R = H
93, R = Me

92, R = H
94, R = Me

Entry	Substrate[a]	Product	Ar-	**91** or **93** Yield[b,c] (%)	**92** or **94** Yield[b] (%)
1	**78a**	**91b**		71 (59)	13
2	**78a**	**91c**		88[d] (55)[e]	5
3	**78a**	**91d**		76[f] (68)	21
4	**78b**	**91b**		78[g] (71)	20
5	**78a**	**91e**		95[h,i] (81)	--
6	**78a**	**91f**		72[h,j] (66)	22
7	**78a**	**91g**		97[h] (91)	--
8	**78a**	**91h**		80[h] (70)	2
9	**78a**	**91i**		61[h] (54)	28
10	**78b**	**91e**		91 (85)	--
11	**78c**	**93a**		-	75 (73)
12	**78c**	**93g**		-	59[k]

[a] Couplings were performed on 0.14 mmol scale of **78** (0.07 M) in the presence of 0.05 equiv. of Pd and 7 equiv. of TBAF unless otherwise noted. [b] Determined by GC-MS of the crude reaction mixture. [c] Isolated yield in parenthesis. [d] Overall yield for three possible isomers (ratio, 14:5:1). [e] Yield for 2,4-dimethylphenyl isomer of **91c**. [f] Overall yield for mixture of *o/m/p* (ratio, 4:1:1) isomers. [g] With 14 equiv. of TBAF. [h] With 3.5 equiv. of TBAF. [i] 77% at 90 °C. [j] 47% with benzofuran:**78a** ratio (1.5:1). [k] Coupling with furan instead of thiophene also produced **94** (60%).

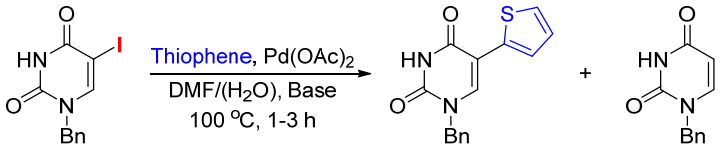
Arylation of **78a** with anisole also gave **91d** as a mixture of *o*/*m*/*p* regioisomers in 76 % (entry 3). As **79b**, the ratio for the *o/m/p* isomers of **91d** was established by comparison with authentic samples prepared by Suzuki coupling.[54] However, coupling of **78a** with arenes bearing electron withdraw group (EWG) either failed (nitrobenzene) or gave the corresponding 5-arylated products in low yields (1,2,3,4,5-pentafluorobenzene, 15%, GC-MS). Analogous treatment of 5-bromouracil **78b**, prepared by bromination of 1-*N*-benzyluracil with 1,3-dibromo-5,5-dimethylhydantoin (DBH) in the presence of TMSOTf,[145] with benzene also proceeded smoothly to give **91b** in 78% yield but 14 equiv. of TBAF was required (entry 4). Compared to the regular arenes, only 3.5 equiv. of TBAF was required for electron rich heteroaromatics to couple efficiently with **78a**. Thus, coupling of **78a** with furan gave 5-(2-furyl)uracil **91e** in 95 % yield as the only isomer (entry 5). Arylation of **78a** with benzo[*b*]furan proceeded in good yield even with only a slight excess of heteroaromatics (benzo[*b*]furan/**78a**, 1.5:1, mol/mol; benzo[*b*]furan/DMF, 1:100, v/v; entry 6). Reaction of **78a** with thiophene gave 5-(2-thienyl)uracil **91g** quantitatively (entry 7), while coupling with 2-substituted thiophenes provided single products **91h** or **91i** in good yield as well (entries 8 and 9). The 5-bromouracil **78b** also coupled efficiently with furan under similar conditions to give **91e** but 14 equiv. of TBAF was required (entry 10). It is worthy to note that TBAF-promoted direct C-H arylation between 3-*N*-methyl-5-iodouracil **78c** and toluene, furan or thiophene only gave the reduced product **94** (entries 11-12).

3.1.3.2. Base promoted Pd-catalyzed direct arylation of 5-halo uracil

Contrary to the unsuccessful coupling of **78a** with simple arenes under the TBAF condition (Table 6, entries 11-18), the π-excessive heteroarenes did couple successfully with 5-iodouracil **78a** in the presence of bases (Table 7). Initially, when **78a** was heated with thiophene (15 equiv.) in DMF at 100 ^{o}C in the presence of $Pd(OAc)_2$ and K_2CO_3 (2 equiv.) for 2 h, only reduced product **92** was obtained (Table 7, entry 1). However, when the reaction was carried out in a mixture of DMF/H_2O (5:1, v/v), product **91g** was obtained in 75% yield (entry 2). Apparently the

increased solubility of K_2CO_3 in the DMF/H_2O mixture changed the outcome of the reaction dramatically. It also has been noted that the solubility of K_2CO_3 is very low in pure organic solvents[146] (e.g., less than 1% of K_2CO_3 was dissolved in DMA after 30 min heating at 120 °C). The yields were only slightly different when 1 or 4 equiv. of K_2CO_3 was used (entry 3).

Table 7. Effect of the reaction parameters in the base-promoted direct arylation of 1-*N*-benzyl-5-iodouracil 78a with thiophene



78a **91g** **92**

Entry	Solvent[a]	Base	Equiv.	T (°C)	Yield **91g** (%)[b,c]	Yield **92** (%)[b]
1	DMF	K_2CO_3	2	100	-	80 (74)
2	DMF/H_2O [d]	K_2CO_3	2	100	75 (60)[e]	20
3	DMF/H_2O	K_2CO_3	1 [f]	100	73 (61)	17
4	DMF/H_2O	NaOH	2	100	16	30
5	DMF/H_2O	CsF	2	100	37	35
6	DMF/H_2O	Ag_2CO_3	2	100	20	8
7	DMF/H_2O	Cs_2CO_3	2	100	61 (53)	32
8	DMF/H_2O	Cs_2CO_3	2	80	53 (41)	8
9	DMF/H_2O	Cs_2CO_3	2	60	13	2
10	DMF	Cs_2CO_3	2	100	76 (65)	11
11	DMF	Cs_2CO_3 [g]	2	100	82 (76)[h]	4

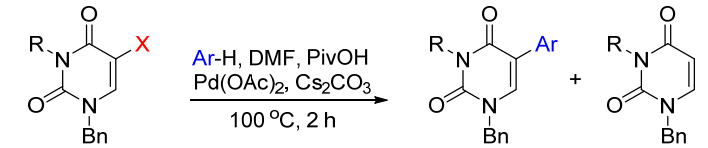
[a] Couplings were performed on 0.14 mmol scale of **78a** (0.05 M) with 0.05 equiv. of $Pd(OAc)_2$. [b] Determined by GC-MS of the crude reaction mixture. [c] Isolated yield in parenthesis. [d] DMF/H_2O (5:1, v/v). [e] $Pd_2(dba)_3$ gave **91g** in 36% isolated yield. [f] 4 equiv. of K_2CO_3 gave **91g** in 50% isolated yield. [g] With addition of PivOH (1.25 equiv.). [h] 80% yield with addition of PivOH (1.25 equiv.) and Ag_2CO_3 (1.0 equiv.).

Direct arylation in the presence of NaOH or CsF or Ag_2CO_3 gave **91g** in low yields (entries 4-6) but proceeded efficiently with Cs_2CO_3 (entry 7). Temperature also plays an important role in the direct arylation. Coupling at 80 °C for 2 h gave **91g** in 53% but with an increased ratio relative to **3** (entry 8), while reaction at 60 °C for 4 h produced **91g** in only 15% (entry 9). Arylation of **78a** in the presence of Cs_2CO_3 in DMF not only increased the yield but also the ratio **91g** to **92** (entry 10), and the result turned out to be even better with the addition of pivalic acid[146] (entry 11).

Generally, direct arylation of **78a** promoted by TBAF gave the best results with $Pd_2(dba)_3$ as the catalyst while base-promoted coupling proceeded more efficiently with $Pd(OAc)_2$.

Other electron-rich heteroarenes have also been coupled to the 5-halouracils *via* the base-promoted C-H direct arylation (Table 8). Coupling of **78a** with furan and thiophene in DMF in the presence of Cs_2CO_3 and PivOH at 100 °C for 2 h gave **91e** and **91g** in 79% and 82%, respectively, in addition to a small amount of reduced product **92** (Table 8, entries 1-2).

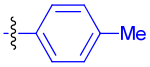
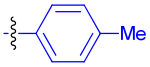
Table 8. Cs_2CO_3 Promoted direct arylation of 5-halouracils 78 with electron-rich heteroaromatics



78a, R = H, X = **I**
78b, R = H, X = Br
78c, R = Me, X = **I**

91, R = H
93, R = Me

92, R = H
94, R = Me

Entry	Substrate [a]	Product	Ar-	**91** or **93** Yield[b,c] (%)	**92** or **94** Yield[b] (%)
1	**78a**	**91e**		79 (73)[d]	12
2	**78a**	**91g**		82 (76)	4
3	**78a**	**91j**		-	11
4	**78b**	**91e**		13	14
5	**78b**	**91g**		16	13
6	**78c**	**93e**		71 (65)	15
7	**78c**	**93g**		70 (62)	15
8	**78a**	**91a**		-	65
9	**78c**	**93a**		-	74

[a] Couplings were performed on 0.14 mmol scale of **78** (0.05 M) with Cs_2CO_3 (2 equiv.), PivOH (1.25 equiv.), and $Pd(OAc)_2$ (0.005 equiv.). [b] Determined by GC-MS of the crude reaction mixture. [c] Isolated yield in parenthesis. [d] Coupling without addition of PivOH gave **91e** in 65% yield.

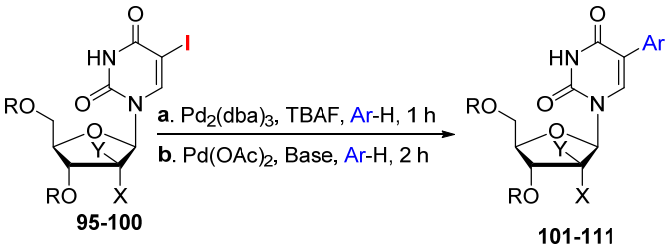
However, coupling was not successful with pyrrole (entry 3). Analogously, **91e** and **91g** could also be obtained in lower yields by the direct arylation of 5-bromouracil **78b** with furan and

thiophene (entries 4 and 5). Surprisingly, contrary to the unsuccessful arylation of **78c** with heteroarenes with TBAF (Table 6, entry 12), the base-promoted arylation of **78c** with furan or thiophene gave coupling products **93e** and **93g** in good yield (entries 6 and 7). However, attempted coupling of the N^3-free **78a** and N^3-protected **78c** uracil substrates with simple arenes, e.g., benzene or toluene, in the presence of Cs_2CO_3 failed to give products (entries 8 and 9).

3.1.3.3. Direct arylation of pyrimidine nucleosides

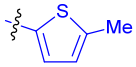
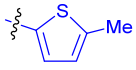
Since our TBAF or base promoted direct arylation methodologies not only avoided the use of toxic organotin substrates[42,43,147] but also worked efficiently with the 3-*N* unprotected uracil substrates,[94,96,142] I will apply them to 5-halopyrimidine nucleosides for the synthesis of 5-arylated uracil nucleosides. Thus, treatment of 2',3',5'-tri-*O*-acetyl-1-(*β*-D-arabinofuranosyl)-5-iodouracil **95** with furan/DMF (1:9, v/v) in the presence of TBAF (3.5 equiv.) and $Pd_2(dba)_3$ afforded 5-(2-furyl)uracil analogue **101** in 61% (Table 9, entry 1). Similarly, the acetyl group protected 2'-deoxy-5-iodouridine **96** was also converted to **102** by coupling with furan (entry 2). Analogous treatment of **97** with furan, thiophene and 2-methylthiophene gave the corresponding products **103**-**105** in moderate yield (entries 3-5). It is obvious that our direct arylation conditions are not only compatible with natural nucleosides but also compatible with the commonly used acyl protection group. Followed by the deacetylation of **101** or **102** with methanolic ammonia at ambient temperature, the corresponding unprotected 5-arylated uracil nucleoside derivatives **106** (92%) and **107** (95%) were obtained. The TBAF-promoted direct arylation has also been applied to the unprotected nucleosides to check compatibility. Thus, subjection of 1-(*β*-D-arabinofuranosyl)-5-iodouracil **98**, 2'-deoxy-5-iodouridine **99**, and 5-iodouridine **100** with furan in the presence of TBAF and Pd-catalyst gave the corresponding 5-(2-furyl)uracil nucleoside analogues **106**-**108** in high yields (entries 6-8).

Table 9. Direct arylation of 5-iodouracil nucleosides with electron-rich heteroaromatics



95-100 **101-111**

Compounds: **95**, **101** X = H, Y = OAc, R = Ac
96, **102** X = H, Y = H, R = Ac
97, **103-105** X = OAc, Y = H, R = Ac
98, **104** X = H, Y = OH, R = H
99, **105** X = H, Y = H, R = H
100, **108-111** X = OH, Y = H, R = H

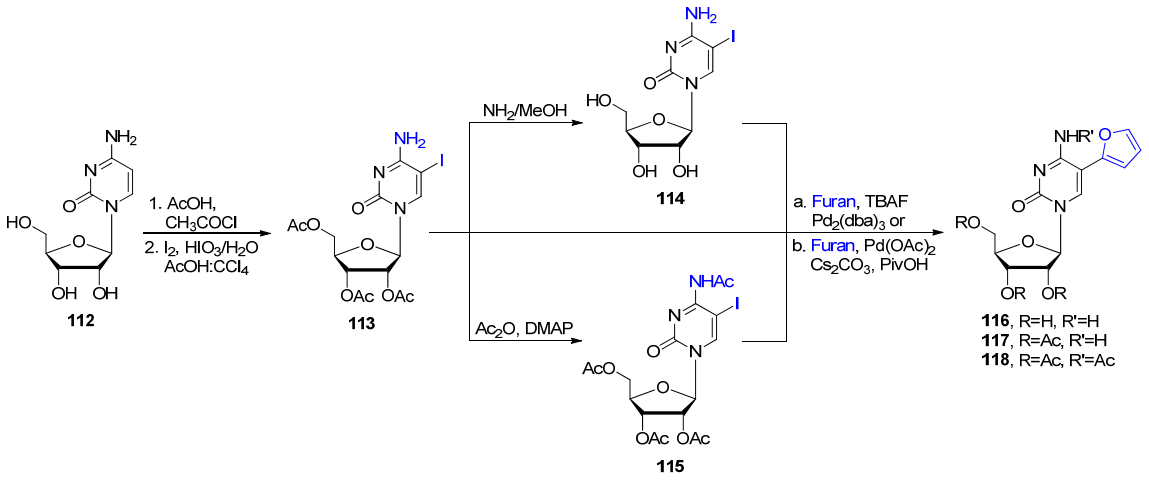
Entry	Substrate [a]	Conditions	Product	Ar-	Yield [b]
1	**95**	a	**101**		61
2	**96**	a	**102**		72
3	**97**	a	**103**		67
4	**97**	a	**104**		63
5	**97**	a	**105**		55
6	**98**	a	**106**		70
7	**99**	a	**107**		73
8	**100**	a	**108**		80[c,d]
9	**100**	a	**109**		98
10	**100**	a	**110**		76
11	**100**	a	**111**		45
12	**100**	b	**108**		23
13	**100**	b	**109**		17

[a] Couplings were performed on 0.14 mmol scale of nucleosides (0.07 M) in the presence of 3.5 equiv. of TBAF and 0.05 equiv. of Pd catalyst. Ratio of Ar-H to substrate nucleosides 15-20:1. [b] Isolated yields. [c] 41% yield with 1.75:1 ratio of furan to **100**. [d] Coupling on 1 mmol scale of **100** gave **105** in 88% yield.

Coupling of **100** proceeded also with only a small excess of furan (1.75 equiv.) affording **108** in 41% isolated yield (entry 8, footnote *c*). The 5-iodouridine **100** coupled efficiently with

thiophene and 2-methylthiophene to give products **109** or **110** (entries 9 and 10). It was found that pyrrole was also able to couple with **100** to give 5-(2-pyrrolyl)uridine **111** in respectable yield (entry 11). This compound can be purified on a silica gel column but is somewhat unstable during storage or upon prolonged exposure to air. Base-promoted C-H direct arylation also works smoothly with natural nucleosides, but the efficiency is not as good as the TBAF methodology. Treatment of **100** with furan or thiophene in the presence of Cs_2CO_3 and Pd catalyst at 100 ^oC for 2 h gave 5-arylated uracil nucleoside derivatives **108** or **109** in 23% and 17% isolated yield (entries 12 and 13). The cleavage of the glycosidic bond was observed during the arylation, which is consistent with the literature report.[96]

In the attempts to expand direct arylation to other pyrimidine systems, the 5-iodocytidine analogues were prepared by the modification of the existing procedure (Scheme 34).[148,149] Stirring of **112** with acetyl chloride in AcOH/$CHCl_3$ (1:1, v/v) at ambient temperature for 40 h gave 2',3',5'-tri-*O*-acetylcytidine in 96%, followed by iodination with I_2/HIO_3 gave **113** in 63%.



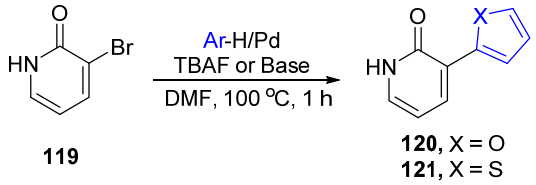
Scheme 34. TBAF or base promoted coupling of 5-iodocytidine analogues with furan

Unfortunately, direct arylation of **113** with furan employing either TBAF or the base protocol was not successful. Alternatively, the acetyl protecting groups of **113** were removed by the treatment with methanolic ammonia to give unprotected cytidine analogue **114**. Acetylation of **113** was also carried out with acetic anhydride to give fully acetyl protected cytidine analogue

115. Both **114** and **115** have been applied to the direct arylation with furan, however, none of these substrates worked successfully in the TBAF or base promoted direct arylation.

3.1.3.4. Scopes and mechanistic consideration

It is important to establish the generality of the direct arylation methodology. Thus the TBAF promoted direct arylation was expanded to other heterocyclic systems, which also have similar tautomerization between the oxo group and the hydrogen at the adjacent nitrogen atom. Treatment of 3-bromo-2-pyridone **119** with furan or thiophene in the presence TBAF and $Pd_2(dba)_3$ without other additives added gave products **120** (41%) and **121** (37%) as well as the unchanged **119** (Scheme 35). Similarly, treatment of **119** with furan in the presence of Cs_2CO_3/PivOH and $Pd(OAc)_2$ gave **120** in 49%. Interestingly, few examples have been reported on the arylation and/or vinylation of the *N*-alkylated 3-halo-2-pyridones at 3 position using Suzuki[150,151] or Stille[152] or Negishi[153] protocols.



Scheme 35. TBAF or base promoted direct arylation of 3-bromo-2-pyridone

On the basis of literature reports and established mechanisms,[80-83,88,146,154] direct arylation of 5-iodouracils is expected to occur *via* either electrophilic aromatic substitution (electrophilic palladation with nucleophilic arenes) or direct proton abstraction (σ-bond metathesis). There is not sufficient data for speculation on the mechanism or the role of TBAF at this moment. However, it is clear that 1-*N*-benzyl-3-*N*-methyl-5-iodouracil (**78c**) did not undergo TBAF-promoted coupling with arenes because of the nonexistence of tautomerization. Thus, it is believed that the C4-alkoxide (enol form of uracil) may participate in the intramolecular processes of hydrogen abstraction *via* a six membered ring as depicted in structures **A** and **B**

(Figure 6). It has also been noted that direct arylation was facilitated by using a Pd-coordinated carboxylate group, which assisted in intramolecular proton abstraction.[146,154]

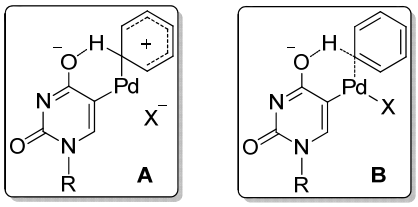
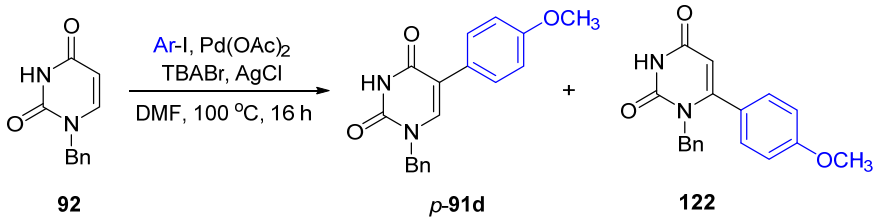


Figure 6. The plausible intermediates for the Pd-catalyzed direct arylation of 5-halouracils: (A) Electrophilic aromatic palladation assisted by C4-alkoxide; (B) Direct proton abstraction assisted by C4-alkoxide.

The TBAF promoted direct C-H arylation methodology has also been applied to 1-*N*-benzyluracil **92** and aryl halides. Thus, treatment of **92** with 4-iodoanisole under the optimal conditions did not give uracil products either at the C5 or the C6 position. However, treatment of **92** with 4-iodoanisole (3 equiv.) in the presence of TBABr/$Pd(OAc)_2$/AgCl[94] produced a mixture of *p*-**91d** (23%) and **122** (33%) in addition to the unchanged **92** (41%, Scheme 36). No further efforts have been made to optimize the conditions for direct C-H arylation of uracil analogues, since Hocek[142,155] and Kim[96] have reported the base-promoted direct C-H arylation of 1,3-*N*-diprotected uracils at C5 and/or C6 position(s) with aryl halides. They found that higher temperature (130-160 ^{o}C) and longer reaction time (12-48 h) are required, which led to the rampant cleavage of the glycosidic bond.[96]



92 *p*-**91d** **122**

Scheme 36. Pd-catalyzed direct C-H arylation of uracil with 4-iodoanisole

3.2. Synthesis of highly functionalized 5-vinyluracil nucleosides from 5-acetylene substrates

3.2.1. Hydrogermylation of 5-ethynyluracil nucleosides

I also investigated the hydrogermylation of the 5-ethynyluracil and uracil nucleosides with germane hydrides with different catalysts. The 5-[2-tris(trimethylsilyl)germanyl]vinyluracil nucleoside analogues have been explored in Pd-catalyst cross-coupling reactions with aryl halides as well as in halodegermylations.

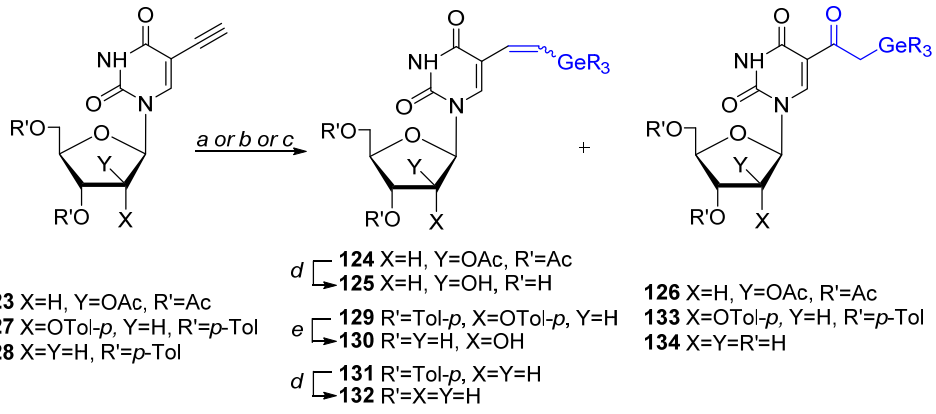
3.2.1.1. Synthesis of 5-[2-(germyl)vinyl]uracil and 5-[2-(triphenylgermyl)acetyl]uracil nucleosides

On the basis of screening of all available methods for hydrogermylation of alkynes, such as Pd(0)-catalyzed,[136,156,157] Lewis acid-promoted,[136,158,159] or radical-mediated[136,160] processes, I have tested for the preparation of 5-[(2-germyl)vinyl]uracil nucleosides **124**. The 1-(2,3,5-tri-*O*-acetyl-*β*-D-arabinofuranosyl)-5-ethenyluracil[161] **123** was subjected to Ph_3GeH in the presence of 1,1'-azobis(cyclohexanecarbonitrile) (ACCN) in toluene at 90 ^oC (Method A) to give the vinyl germanes **124a** as a mixture of regioisomers with the *Z* isomer as the major product *via anti*-addition of the germyl radical to the triple bond (Table 10). The ratio for *E*-**124a** (J = 18.8 Hz) and *Z*-**124a** (J = 13.5 Hz) diastereomers was established as 5:95 by ^1H NMR spectroscopy, which was consistent with the literature report.[160] Surprisingly, careful purification gave another new product, which was assigned (*vide infra*) as 5-[2-(triphenylgermyl)acetyl]uracil nucleoside derivative **126a** (12%; Table 10, entry 1).

Subjection of **123** under the same condition with Ph_3GeH in the absence of ACCN gave **124a** in 60% with a better ratio (*E*/*Z,* 3:97) along with the *β*-keto germyl uracil nucleoside **126a** in 15% (entry 2). Hydrogermylation of **123** with Ph_3GeH in the presence of Et_3B[162] in THF at -78 ^oC (Method B) gave *Z*-vinyl germane **124a** in 55% as the only product (entry 3), while *Z*-**124a** was obtained in 28% at 0 °C as well as **126a**, which was not observed at -78 ^oC (entry 4). Analogous treatment of **123** with Ph_3GeH in the presence of $B(C_6F_5)_3$[159] in CH_2Cl_2 at ambient temperature

gave a trace amount of **124a**. Hydrogermylation[156] of **123** with Ph_3GeH in the presence of $Pd(PPh_3)_4$ in THF gave a mixture of *E*-**124a** and a 5-[1-(triphenylgermyl)ethenyl] regioisomer in 73% with ratio of 3:2 (Method C). The similar regioisomer, which was formed by the addition of a germyl radical to the *α*-carbon, was also observed.[156] It is worthy to note that the *β*-keto germyl uracil nucleoside **126a** was only observed with Method A or Method B at 0 ^oC. Deacetylation of *Z*-**124a** with NH_3/MeOH afforded the 1-(*β*-D-arabinofuranosyl)-5-[2-(triphenylgermyl)acetyl]uracil *Z*-**125a** in 86%. Hydrogermylation of **123** with trimethylgermane hydride (Me_3GeH)[162] by method B at -78 °C did not give **124b**, while it could be obtained in 40% with low stereoselectivity (*E/Z,* 13:87) at ambient temperature (entry 6). Surprisingly, 5-2-(trialkylgermyl)acetyl uracil nucleoside **126b** was not observed at either -78 ^oC or ambient temperature. Hydrogermylation of **123** with $(Me_3Si)_3GeH$ by method A gave 5-2-(TTMS-germyl)ethenyl uracil analogue *Z*-**124c** stereoselectively in 68% in 30 min., but again, *β*-keto germyl uracil nucleoside **126c** was not detected (entry 7). Hydrogermylation of 2',3',5'-tri-*O*-*p*-toluoyl-5-ethynyluridine **127** with Ph_3GeH by Method B (-78 °C→ 0 ^oC) gave **129a** in 40% along with the 5-[2-(triphenylgermyl)acetyl] product **133a** in 13% (entry 8). Analogous treatment of **127** with Me_3GeH by Method B (0 °C→ 25 ^oC) yielded a mixture of stereoisomers **129b** in 41% (*E*/*Z,* 45:55; entry 9). Treatment of **127** with TMS_3GeH by Method B (-78 °C→ 0 ^oC) yielded *Z*-**129c** as the single isomer in 61% (entry 10). Hydrogermylation of 3',5'-di-*O*-*p*-toluoyl-5-ethynyl-2'-deoxyuridine **128** with Ph_3GeH by Method B (-78 °C to 0 °C) gave *Z*-**131a** in 61% along with **134a** in 12% (entry 11).

Table 10. Hydrogermylation of 5-ethynyluracil and related nucleosides with germane hydrides



123 X=H, Y=OAc, R'=Ac
127 X=OTol-*p*, Y=H, R'=*p*-Tol
128 X=Y=H, R'=*p*-Tol

124 X=H, Y=OAc, R'=Ac
125 X=H, Y=OH, R'=H
129 R'=Tol-*p*, X=OTol-*p*, Y=H
130 R'=Y=H, X=OH
131 R'=Tol-*p*, X=Y=H
132 R'=X=Y=H

126 X=H, Y=OAc, R'=Ac
133 X=OTol-*p*, Y=H, R'=*p*-Tol
134 X=Y=R'=H

Compounds **124-134** Series: **a** R = Ph, **b** R = Me, **c** R = $(Me_3Si)_3$
(a) R_3GeH, (ACCN), toluene (THF, DMF), 90 °C;
(b) R_3GeH, Et_3B, THF, -78 °C; (c) $Pd(PPh_3)_4$, THF, rt;
(d) NH_3, MeOH, rt. (e) MeONa/MeOH/r.t.;

Entry	Substrate	Method[a]	Temp (°C)	R_3GeH	Vinyl Germanes			Germyl Ketones	
					Product	Yield[b] (%)	Ratio[b] (*E*/*Z*)	Product	Yield[b] (%)
1	**123**	A	90	Ph_3GeH	**124a**[c]	47	0:100	**126a**	12
2	**123**	A[d]	90	Ph_3GeH	**124a**	60	3:97	**126a**	15
3	**123**	B	-78 → -60	Ph_3GeH	**124a**	55	0:100	-	-
4	**123**	B	0	Ph_3GeH	**124a**	28	0:100	**126a**	19
5	**123**	C	5	Ph_3GeH	**124a**[e]	45	100:0	-	-
6	**123**	B	0 → 25	Me_3GeH	**124b**	40	15:85	-	-
7	**123**	A	0 → 25	$(Me_3Si)_3GeH$	**124c**[f]	68	0:100	-	-
8	**127**	B	-78 → 0	Ph_3GeH	**129a**	40	0:100	**133a**	13
9	**127**	B	0 →25	Me_3GeH	**129b**	41	45:55	-	--
10	**127**	B	-78 → 0	$(Me_3Si)_3GeH$	**129c**	61	0:100	-	-
11	**128**	B	-78 → 0	Ph_3GeH	**131a**	61	0:100	**134a**	12
12	**128**	A[g]	100[h]	Ph_3GeH	**131a**[i]	33	0:100	**134a**	17
13	**128**	B	0→25	Me_3GeH	**131b**	35	40:60	-	-

[a] Method A: R_3GeH/ACCN/toluene/90 or 100 °C; Method B: R_3GeH/Et_3B/THF/-78 or 0 °C; Method C: $Pd(PPh_3)_4$/THF/rt. [b] Isolated yield. [c] Crude reaction mixture (*E*/*Z*-**124a**, 5:95). [d] Without the presence of ACCN. [e] In addition to *E*-**124a** the *α*-addition product was formed as well (~3:2, 73% overall). [f] Crude reaction mixture (*E*/*Z*-**124c**, 4:96). [g] Toluene/THF (20:1, v/v) was used as solvent. [h] Oil-bath. [i] With toluene/DMF/H_2O (20:1:0.1, v/v/v) as solvents *E*-**131a,** *Z*-**131a** and **134a** (~2:2:1, 40% overall) were obtained.

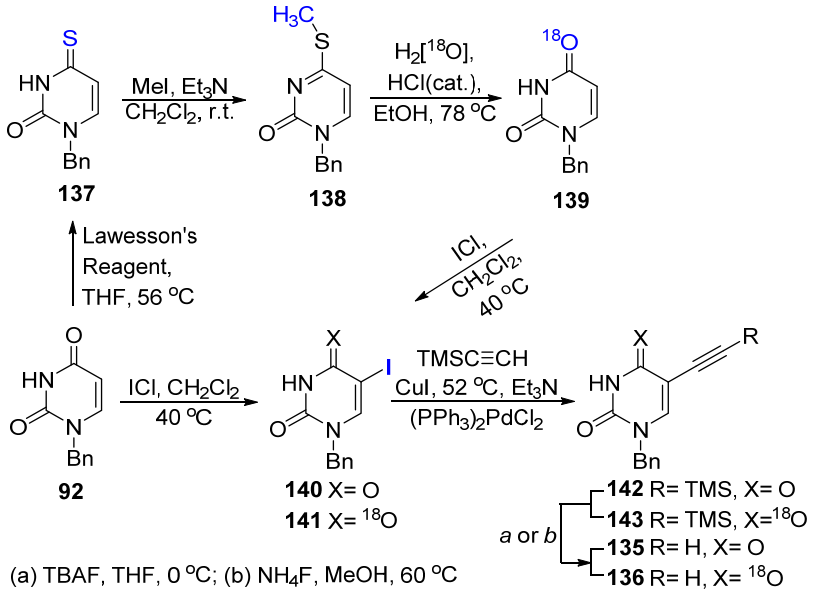
Analogous treatment of **128** with Ph_3GeH by Method A in toluene/THF (20:1, v/v) gave *Z*-**131a** and **134a** (entry 12). Interestingly, analogous hydrogermylation of **128** in toluene/DMF with

addition of a "measured" amount of water (14 equiv.) produced *E/Z*-**131a** (~1:1) and **134a** (entry 12, footnote *i*). Treatment of **128** with Me_3GeH by Method B (0 °C→ 25 °C) gave only *E*/*Z*-**131b** (entry 13) but once again no germyl ketone product was observed. Deprotection of *E*/*Z*-**129b** with MeONa/MeOH gave uridine analogue *E*/*Z*-**130b** in 71%, while deprotection of *Z*-**131a** with NH_3/MeOH yielded 2'-deoxyuridine analogue *Z*-**132a** (65%), confirming the stability[163] of the C(sp^2)-Ge(alkyl)$_3$ and C(sp^2)-Ge(aryl)$_3$ bonds.

It has been stated that hydrogermylation of the alkyl or aryl alkynes gives vinyl germanes in high yields; however, the detection of *β*-germylketones has not been reported yet.[112,160,162,164] Thus, the hydrogermylation of phenylacetylene with Ph_3GeH under the optimal conditions described in Method A and B has been reexamined. No *β*-germylketones were neither observed under such conditions, which is consistent with the literature report. I have also checked the hydrostannylation and hydrosilylation of 5-alkyne nucleoside **127** with Ph_3SnH and Ph_3SiH under the same reaction conditions, but again either 5-[2-(triphenylstannyl,- or silyl)acyl] products of type **129a** were not observed, which suggest the formation of **129a** were exclusive for Ph_3GeH.

Intrigued by this interesting finding, 1-*N*-benzyl-5-ethynyluracil **135** was employed as the model substrate for hydrogermylation to examine the chemistry and mechanism involving the formation of 5-keto pyrimidine nucleosides **126a**, **133a** or **134a**. The ^{18}O-labeled alkyne **136** was also synthesized to elucidate the origin of the acetyl oxygen. The synthesis of **135** and [^{18}O]-**136** was depicted in Scheme 37. Treatment of 1-*N*-benzyluracil **92** with Lawesson's reagent in THF at 56 °C for 1 h gave the 1-*N*-benzyl-4-thiouracil **137** in 65%. *S*-Methylation[165] of the purified **137** by treatment with MeI in the presence Et_3N in CH_2Cl_2 led to the formation of thioether **138** in 93%. The acid-catalyzed hydrolysis[166] of **138** with $H_2[^{18}O]$ (99.2% ^{18}O) in anhydrous EtOH produced desired ^{18}O-labeled 1-*N*-benzyluracil analogue **139** in 90% with 85% of isotopic incorporation, which was calculated on the basis of the corresponding peak intensities in the mass spectra. Iodination of **92**, as well as **139**, with a solution of iodine monochloride[30] (1 M in CH_2Cl_2)

in dry CH_2Cl_2 afforded 5-iodouracils **140** and **141** in excellent yields (93%). Sonogashira couplings of the 5-iodouracils **140** or **141** with trimethylsilylacetylene in Et_3N resulted in the formation of **142** (80%) and **143** (62%) respectively. The fluoride-promoted desilylation with TBAF furnished 5-ethynyluracil **135** and its ^{18}O-labeled **136** in good yields (60% and 58%, respectively). It is noteworthy that desilylation with NH_4F/MeOH[167] offered similar results but substantially eased the purification from TBAF-derived residues.



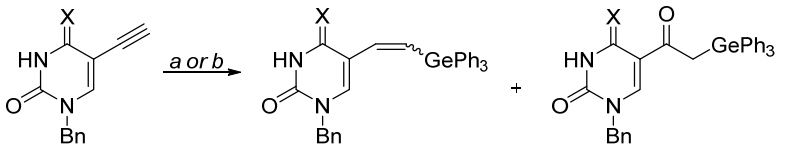
137 138 139 92 **140** X= O **141** X= ^{18}O **142** R= TMS, X= O **143** R= TMS, X= ^{18}O **135** R= H, X= O **136** R= H, X= ^{18}O

Scheme 37. Synthetic route for the preparation of 5-ethynyluracil and ^{18}O-labeled 5-ethynyluracil

Hydrogermylation of **135**[168,169] with Ph_3GeH in the presence of ACCN in toluene at 90 °C for 2 h gave *Z*-vinyl germane **144** in 27% along with 5-[2-(triphenylgermyl)acetyl]uracil **146** in 13% (Table 11, entry 1). Analogously, **135** was subjected to Ph_3GeH in toluene at 100 °C for 10 h in the absence of ACCN to yield Z-**144** and **146** in 34% and 20% yields (entry 2). However, analogous treatment of **135** with Ph_3GeH in "moist" toluene gave *syn*-addition product *E*-**144** in 86% exclusively (entry 3). Hydrogermylation of **135** with Ph_3GeH in the presence of Et_3B/THF at 0 °C produced *Z*-**144** in 52% as the only product (entry 4). Similar treatment of the ^{18}O-labeled alkyne **136** with Ph_3GeH in toluene at 100 °C for 10 h without ACCN afforded *Z*-**145** as

crystalline product in 31% as well as **1147** in 18% (entry 5). On the basis of the mass spectroscopy, the incorporation [^{18}O]-isotopic for both **145** and **147** are the same as the **136**.

Table 11. Hydrogermylation of 1-*N*-benzyl-5-ethynyluracil with triphenylgermane



135 X=O
136 X=^{18}O

144 X=O
145 X=^{18}O

146 X=O
147 X=^{18}O

(a) Ph_3GeH/(ACCN)/toluene/(H_2O)/100 or 85 ^oC;
(b) Ph_3GeH/Et_3B/THF/0 ^oC

Entry	Substrate	Method[a]	Temp (^{o}C)	R_3GeH	Vinyl Germanes			Germyl Ketones	
					Product	Yield[b] (%)	Ratio[b] (*E*/*Z*)	Product	Yield[b] (%)
1	**135**	A	90	Ph_3GeH	**144**	27	0:100	**146**	13
2	**135**	A[c]	100	Ph_3GeH	**144**	34	0:100	**146**	20
3	**135**	A[c,d]	100	Ph_3GeH	**144**	86	100:0	-	-
4	**135**	B	0	Ph_3GeH	**144**	52	0:100	-	-
5	**136**	A	100	Ph_3GeH	**145**	31	0:100	**147**	18

[a] Method A: R_3GeH/ACCN/toluene/90 or 100 ^{o}C. [b] Isolated yield. [c] Without the presence of ACCN. [j] With addition of 25 μL H_2O (14 equiv.).

3.2.2.2. Mechanistic consideration and the origin of 5-acetyl oxygen

The structures of the 5-[(2-triphenylgermyl)acetyl]uracil derivatives were established using NMR spectroscopic data and HRMS analysis. The absence of the vinyl unit for **133a** at the expected downfield region and appearance of two doublets at 3.76 and 3.87 ppm (J = 9.0 Hz) in the ^{1}H NMR spectrum supported the presence of the methylene adjacent to carbonyl and the Ge moiety. The peak at 193.3 ppm in the ^{13}C NMR spectrum of **133a** confirmed the presence of the ketone.

The (+)ESI-MS analyses of **146** and the ^{18}O-labeled **147** samples produced predominantly the $[M + Na]^+$ ions of **146** and **147**. The collision-induced dissociation (CID) of the $[M - H]^-$ ions did produce ions indicative of the ^{18}O-containing portion of the molecules (Figure 7). Thus, (-)ESI-

MS/MS of the [M - H]$^-$ ion of **146** (*m/z* 547 [^{74}Ge]) showed the most abundant ion cluster containing Ge at *m/z* 504 [^{74}Ge] because of the loss of 43 u (CONH) in addition to *m/z* 158, 200 and 241 fragmentation ions which do not contain Ge. On the other hand (-)ESI-MS/MS of the [M - H]$^-$ ion of [^{18}O]-**147** (*m/z* 549 [^{74}Ge]) showed a cluster at *m/z* 506 [^{74}Ge] in addition to *m/z* 160, 202, and 243 product ions (M + 2 ions relative to **146**). These results indicated that during hydrogermylation the ^{18}O-isotope remained at C4 of the uracil ring and that the 4-carbonyl group did not participate in the reaction pathway leading to the formation of α-(triphenylgermyl)methyl ketones.

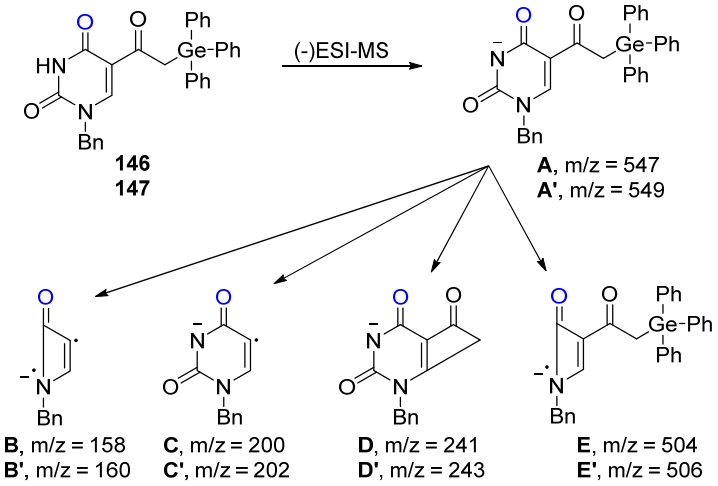
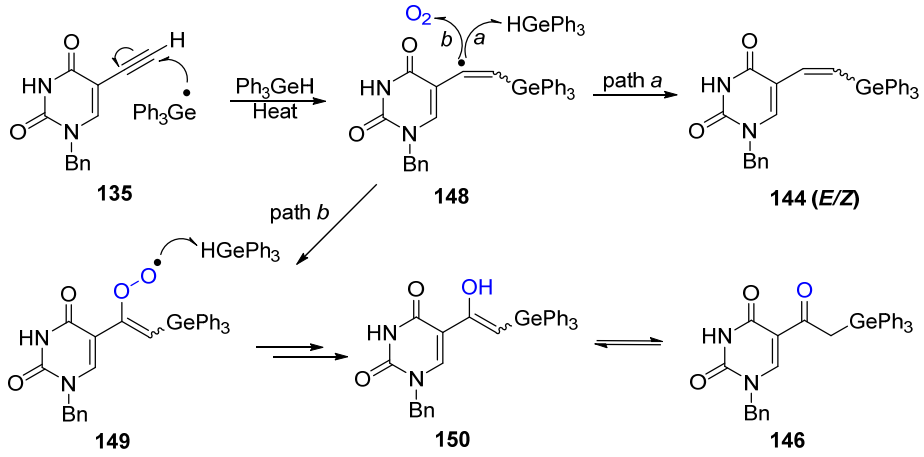


Figure 7. Proposed decomposition route for 5-[2-(triphenylgermyl)acetyl]uracils 146 and 147

On the basis of the experimental results, it is believed that the formation of the 5-[2-(triphenylgermyl)acetyl]uracil products (e.g., **146**) should involve an initial attack of the triphenylgermyl radical at the triple bond of **135** to give a vinylic radical **148** (Scheme 38). Abstraction of hydrogen from triphenylgermane in an *anti* fashion would produce Z-vinyl germane **144** as a major product while the *syn* addition could produce the *E* isomer of **144** (path *a*). Reaction of **148** with residual oxygen present in the reaction mixture might lead to the formation of peroxyl radical **149**,[170] followed by the abstract of hydrogen from Ph_3GeH[171] to give

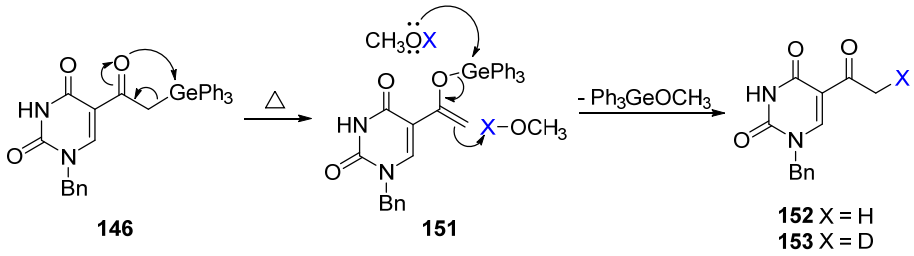
hydroperoxide. The latter can be converted to enol **150**, probably by a radical mechanism, and undergo tautomerization to yield the *β*-germylketone **146** (path *b*).



Scheme 38. A plausible pathway for the formation of 5-[(2-triphenylgermyl)acetyl]uracil 147 during radical addition of Ph_3GeH to 5-acetylenic substrate 135

Efforts have been made to optimize conditions for the preparation **146** in higher yield from the reaction of **135** with Ph_3GeH. Thus, hydrogermylations have been performed varying several experimental parameters. Hydrogermylation of **135** under various condition, such as, Ar *vs* N_2 *vs* aerobic conditions with dry *vs* reagent-grade toluene *vs* "moist" toluene (with the added measured amount of H_2O or D_2O), did not improve the yield of **146**. It is important to note that hydrogermylation of **135** with Ph_3GeH in oxygenated toluene resulted in the recovery of unchanged **135**, which is probably because of the oxygen induced radical termination. I have also attempted the hydrogermylation employing slow addition of Ph_3GeH *via* syringe-pump over 24 hours, but the yield of **146** is not improved. Thus, the optimal conditions for the formation of *β*-germylketones would require very low rate of initiation with very low and nearly constant concentration of Ph_3GeH and oxygen, and then for the germyl radical to react with the terminus of the acetylene group rather than oxygen to give the vinylic radical **148**, which should react with oxygen rather than germane to give **146**.

During recrystallization of **146** from MeOH, the formation of a new product was observed by TLC, which was characterized as 5-acetyl-1-*N*-benzyluracil **152** both spectroscopically and by comparison with an authentic sample of **152** that was independently synthesized by acid-catalyzed hydration[172] of **135**. It has been noticed that (triphenylgermyl)methyl ketone **146** could be converted to the 5-acetyl product **152** quantitatively in MeOH at 65 ^{o}C, which should involve intramolecular thermal isomerization *via* a four-membered ring rearrangement (Scheme 39). Hydrolysis of the resulting *O*-germyl substituted enol **151** led to the formation of the ketone **152**. Analogous thermal rearrangements of the *β*-silylketones into *O*-silyl substituted enols have been noted as well.[173] Heating **146** in either MeOD or MeOH-d_4 gave 1-deuteriomethyl ketone **153** in quantitative yield, which supports the proposed degradation pathway.



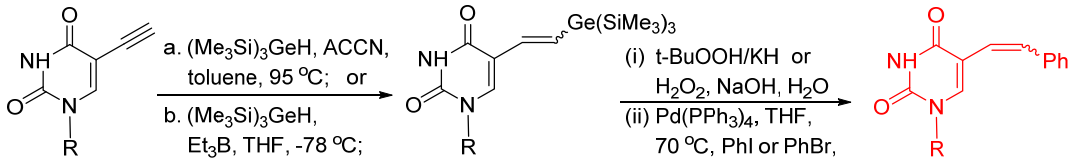
Scheme 39. Proposed route for the thermal degradation of 5-[(2-triphenylgermyl)acetyl]uracil 146 into the 5-acetyl product 152

3.2.1.3. Application of the 5-[2-(germyl)vinyl]uracil to organic synthesis

3.2.1.3.1. Towards Pd-catalyzed cross coupling reaction

The vinyl tris(trimethylsilyl)germanes are known to be good substrates in the Pd-catalyzed cross-coupling reactions with alkenyl/aryl halides.[112,113] Thus, various TTMSGe have been prepared under optimal conditions. Hydrogermylation of **123** with reactive $(Me_3Si)_3GeH$ by Method A gave 5-[2-(tris(trimethylsilyl)germyl)ethenyl]*arabino*-uridine analogue **124c** in 68 % (Scheme 40). Treatment of 2',3',5'-tri-*O*-*p*-toluoyl protected **127** with $(Me_3Si)_3GeH$ by Method B afforded TTMS-germyl vinyl uracil nucleoside product *Z*-**129c** in 61% as a single isomer. Analogously, 1-*N*-benzyl-5-ethynyluracil **135** was converted to *Z*-**154**. The couplings of

synthesized 5-[2-(TTMS-germyl)vinyl]uracil nucleoside derivatives with the aryl halides *via* Pd-catalyzed cross-coupling were performed. However, the attempted Pd-catalyzed [$Pd(PPh_3)_4$] coupling of **124c**, **129c**, or **154** with *β*-bromostyrene as well as aryl iodides or bromides under oxidative aqueous (H_2O_2/NaOH/H_2O) or anhydrous (*t*-BuOOH/KH) conditions in THF[112] gave a complex mixture with the desired coupling products **155** only in 0-15% (GC-MS). Thus, no additional studies were performed.



123 and **124c**: R = 2,3,5-Tri-*O*-acetyl-*β*-D-arabinofuranosyl
127 and **129c**: R = 2,3,5-Tri-*O*-toluoyl-*β*-D-ribofuranosyl
135 and **154**: R = Bn

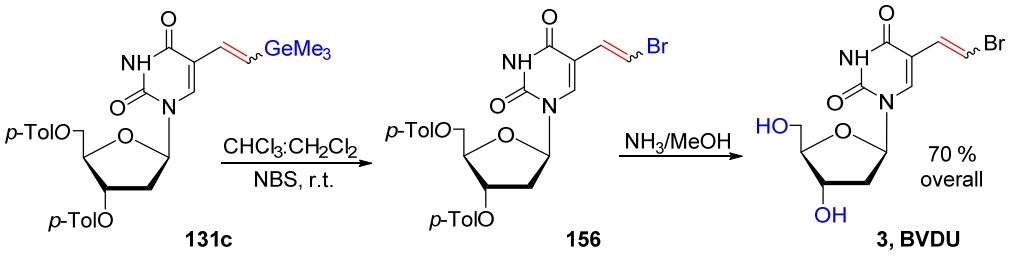
Scheme 40. Hydrogermylation of 5-ethynyluracil and uracil nucleosides 123, 127 and135 with $(Me_3Si)_3GeH$ and attempted Pd-catalyzed cross-coupling of the resulting vinyl germanes with alkenyl or aryl halides

3.2.1.3.2. Radical halodegermylation

It is known that the 5(*E*)-[2-(tributylstannyl)vinyl]uracil nucleosides[174-176] are good substrates for mild and rapid radiohalogenation *via* halodestannylation reactions.[174-177] However, the tendency of 5(*E*)-[2-(tributylstannyl)vinyl]arabinosyl uridine[176] and 5-trimethylstannyl arabinouridine[177] to undergo protiodestannylation was noted. Lindlar hydrogenation of 5-[2-(trimethylsilyl)ethynyl]uracil nucleoside substrates[12,178] gave 5(*Z*)-[2-(trimethylsilyl)vinyl]uracil analogues in good yield, but underwent the solvent-dependent isomerization to give the 5-*E*-isomer analogue as the major component.[179] Halogenative desilylation of 5-*E*-vinyl silane substrates[180] with XeF_2 and metal halides gave 5-(2-halovinyl)uracil products in good yield and short time,[179] and such reactions have been utilized for radioiodination *via* iododesilylations reactions[178,180] Germyldesulfonylation protocols have also been developed for the synthesis of vinyl and (α-fluoro)vinyl germanes.[113] Thus, I carried out the radical halodegermylation of *β*-

TMSGe vinyl uracil substrates with electrophilic halogen as an alternative practical route for the preparation of *β*-halovinyl pyrimidine nucleoside derivatives.

Treatment of 5-[2-(trimethylgermyl)vinyl]uracil nucleoside **131c** (*E/Z*, 40:60) with *N*-bromosuccinimide (NBS) at ambient temperature gave **156** *via* a radical mechanism in high yield, followed by the deprotection with NH_3/MeOH to afford a mixture of 5-(2-bromovinyl)-2'-deoxyuridine **3** in 70% (*E/Z*, ~2:3) with retention of the stereochemistry[159,163,181] (Scheme 41). It indicated the potential application of 5-[2-(trimethylgermyl)vinyl]uracil nucleosides towards the synthesis 5-(2-halovinyl)uracil analogues as well as potential applications to radiolabeling. It is important to note that substitution of the trialkylgermyl group adjacent to an sp[182,183] or sp^2 carbon[181,182] with a halogen proceeded more easily than that of trialkylsilyl substrates and with better stereochemical outcome.



Scheme 41. Radical halodegermylation and deprotection of vinyl trimethylgermane uracil nucleoside with NBS and methanolic ammonia

3.2.2. Iron-mediated regio- and stereoselective hydrosulfonylation of 5-ethynyluracil nucleosides

Vinyl sulfones, which are also known as *α*, *β*-unsaturated sulfones, could be synthesized by a broad variety of traditional synthetic methods, such as the ionic and radical addition to unsaturated alkenes, alkynes and allenes, the addition of sulfonyl-stabilized carbanions to carbonyl substrates, the manipulation of acetylenic sulfones or the use of organometallic reagents.[184,185] As a result of the electron withdrawing property of the sulfonyl group and electron poor nature of their double bond, vinyl sulfones can be treated as excellent Michael acceptors,

which could be attacked by nucleophiles *via* 1,4-addition. Since thiol and amine groups, which are good nucleophiles, naturally present or routinely introduced in most biomolecules, such units could be efficiently installed to the *β*-position of the vinyl sulfones. Thus, on this basis, the 1,4 addition of vinyl sulfones could be employed to synthesize *β*-heterosubstituted vinyl sulfones. Moreover, the sulfonyl moiety can either undergo subsequent functional group transformations or can be easily removed by treatment with Mg or Hg/Na.[186]

Vinyl sulfones also play an important role in the biosciences. These molecules can act as irreversible inhibitors of many types of cysteine proteases through conjugate addition of the thiol group of the active site in the cysteine residue, which is the basis of some modern applications of this chemical function in Proteomics. There are two prominent features for vinyl sulfones: first, it is easy to introduce the vinyl sulfones functional group to proteins or nucleosides and the resulting functionalized reagents or intermediates are stable. Secondly, it is the possibility to carry out the Michael additions in physiological conditions (aqueous media, slightly alkaline pH and room temperature) that preserve the biological function of the proteins in the absence of catalysts and by-products.

Even though there are several reports about the chemical reactivity of vinyl sulfones which allow the functionalization of many organic substrates, the full potential applications of vinyl sulfones are only partially realized. In 2013, Hocek[187] and coworkers reported the interaction between the vinylsulfone modified oligonucleotides/DNA and cysteine or glutathione from protein *via* the Michael addition (Figure 8). The research indicated that the Michael addition modified oligonucleotides/DNA are readily able to couple with cysteine or cysteine-containing peptides/proteins *via* the Michael addition under physiological conditions. The Michael addition modified nucleotides did not interfere with DNA polymerase, and the vinyl sulfone-modified nucleoside triphosphates are still suitable for the primer extension synthesis of modified

oligonucleotides. Thus, vinyl sulfone-modified DNA could communicate with different constructs of p53 protein to form the covalent bond *via* Michael addition.

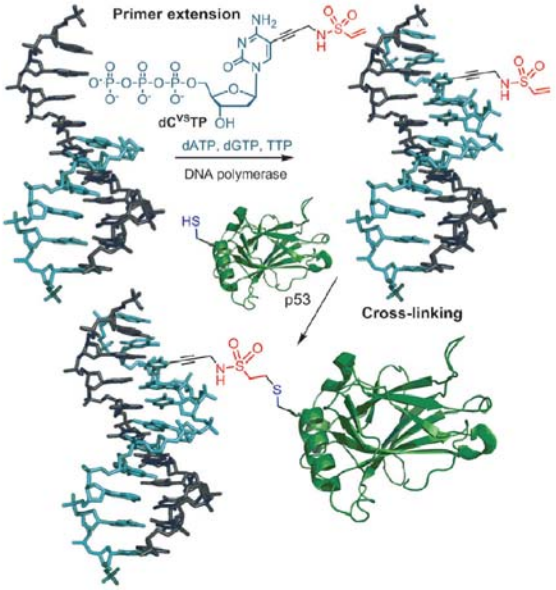
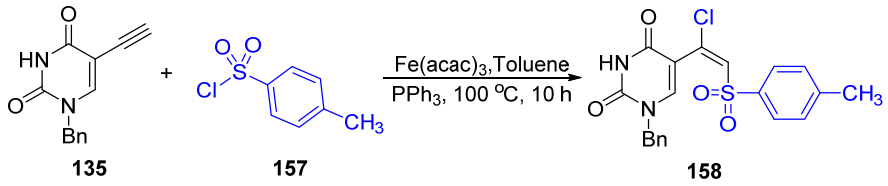


Figure 8. Synthesis of vinylsulfone modified DNA and cross coupling with p53 protein

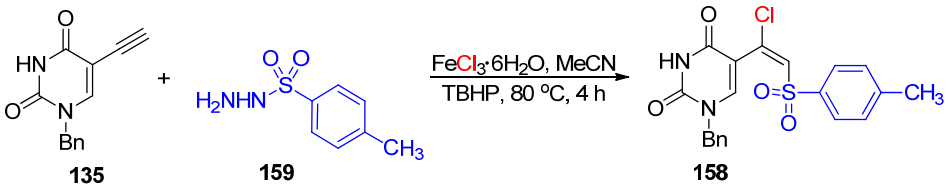
3.2.2.1. Synthesis of 5-(1-chloro-2-tosyl)vinyl uracil nucleosides

My strategy for the synthesis of reactive vinylsulfone modified nucleosides exploit the iron catalyzed regio- and stereoselective radical halosulfonylation[188,189] of 5-ethynyluracil nucleosides with sulfonylhydrazides. Compared to the vinylsulfones, there is an additional halogen atom attached to the *β*-carbon of the vinylsulfones, which makes the *β*-carbon even more prone to be attacked by nucleophiles. Treatment of 1-*N*-benzyl-5-ethynyluracil **135** with sulfonyl chloride **157** in the presence of $Fe(acac)_3$ and triphenylphosphine at 100 ^{o}C for 10 h gave 5-(1-chloro-2-tosyl)vinyl uracil **158** with complete region- and stereoselectivity (Scheme 42), and this process could also tolerate the acetyl protection group. However, the usage of phosphine ligand and relatively harsh reaction conditions limited the application with temperature sensitive substrates. Moreover, only chlorine substituted vinyl sulfones could be obtained by this method. In order to explore other halogenated vinylsulfones and to compare the reactivity of the different 5-(1-chloro-2-tosyl)vinyl uracil analogues, other reaction conditions will be explored.



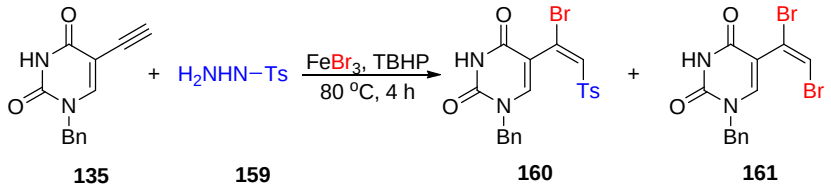
Scheme 42. Synthesis of 5-(1-chloro-2-tosyl)vinyl uracil via hydrosulfonylation of 1-*N*-benzyl-5-ethynyluracil with tosyl chloride

It is known that $FeCl_3$ could act as a chlorine source in some radical sulfonylation reaction.[188,190] Thus, efforts have been made to improve the methodology for hydrosulfonylation of 5-ethynyluracil and uracil nucleosides as well as to achieve the synthesis of bromine substituted *β*-halovinyl sulfones. Thus, treatment of 1-*N*-benzyl-5-ethynyluracil **135** with sulfonylhydrozides **159** in the presence of $FeCl_3$ and TBHP in acetonitrile at 80 °C for 4 h gave 5-(1-chloro-2-tosyl)vinyl uracil **158** in 90% with absolute regio and stereoselectivity (Scheme 43).



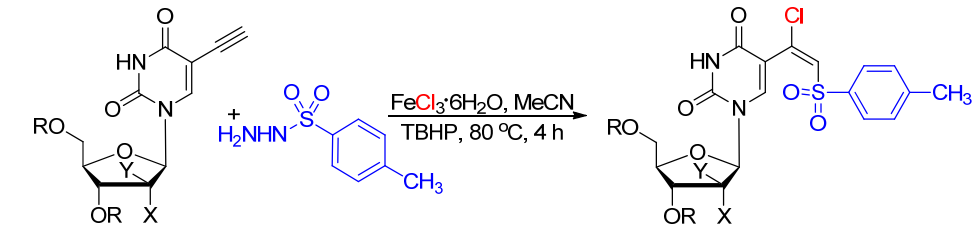
Scheme 43. Synthesis of 5-[(*E*)-(*β*-chloro)vinyl]sulfonyl uracil via hydrosulfonylation of 5-ethynyluracil with tosyl hydrazide in the presence of $FeCl_3$

Similarly, the Fe(III) catalyzed hydrosulfonylation could be also extended to the synthesis of *β*-bromovinyl sulfones *via* addition of $FeBr_3$ as the bromine source. Treatment of 1-*N*-benzyl-5-ethynyluracil **135** with sulfonylhydrozides **159** in the presence of $FeBr_3$ and TBHP in acetonitrile at 80 °C for 4 h gave 5-(1-bromo-2-tosyl)vinyl uracil **160** as well as the dibromo substituted uracil analogue **161** as the byproduct (Scheme 44). It is worth mentioning that the formation of dihalo uracil analogues **161** is specific for $FeBr_3$-promoted hydrosulfonylation and could be inhibited by the increase of the loading of **159**.



Scheme 44. Synthesis of 5-[(*E*)-(*β*-bromo)vinyl]sulfonyl uracil via hydrosulfonylation of 5-ethynyluracil with tosyl hydrazide in the presence of $FeBr_3$

In order to check the generality of the hydrosulfonylation, the methodology was extended to 5-ethynyluracil nucleoside substrates, which share the same nucleobase. Thus, treatment of 2',3',5'-tri-*O*-acetyl-5-ethynyluridine **162**, or 2,3,5-tri-*O*-acetyl-1-(*β*-D-arabinofuranosyl)-5-ethynyluracil **123** with tosyl hydrazide **159** under the optimal conditions gave 5-(1-chloro-2-tosyl)vinyluracil nucleosides **165** and **166** in 68% and 66% respectively (Scheme 45). Analogous treatment of 3',5'-di-*O*-acetyl-5-ethynyl-2'-deoxyuridine **163** with **159** gave the corresponding product **167** in 76%. The hydrosulfonylation is also compatible with the unprotected 5-ethynyluracil nucleosides. Thus, heating of 2'-deoxy-5-ethynyluridine **157** with **159** in the presence of $FeCl_3$ and TBHP gave **168** in 69 %.



Scheme 45. Synthesis of 5-[(*E*)-(*β*-chloro)vinyl]sulfonyl uracil nucleosides via hydrosulfonylation

On the basis of the experimental results and literature reports,[188,189] the proposed mechanism is summarized in Figure 9.

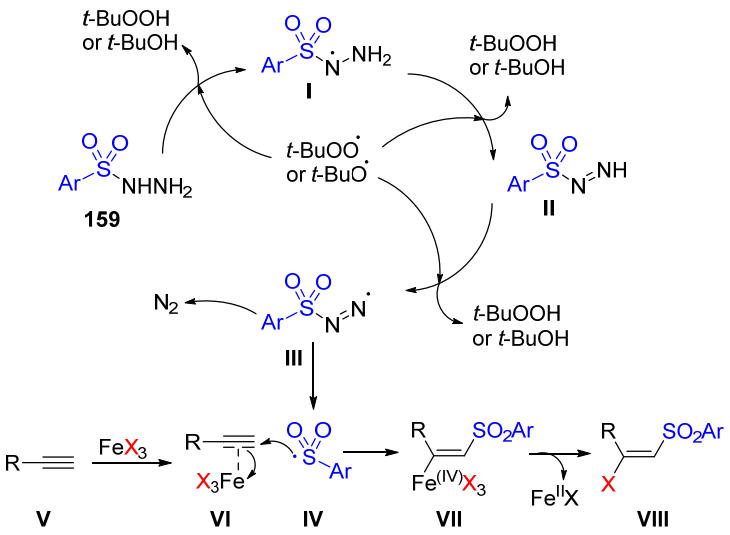


Figure 9.Proposed mechanism for the Fe(III) mediated hydrosulfonylation of 5-ethynyluracil nucleosides

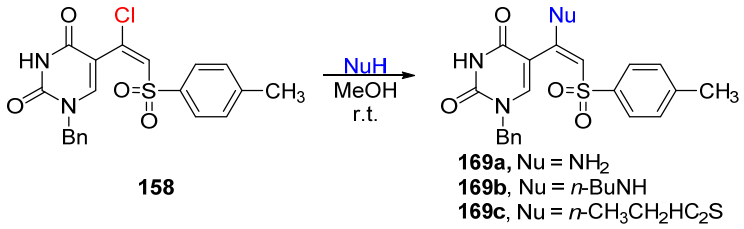
Initially, hydrogen abstraction of sulfonylhydrazides **159** by the tert-butoxyl or tert-butylperoxy radicals, which were generated in situ from an iron-TBHP catalytic circle, gave sulfonylhydrazide radical intermediate **I**, followed by another two hydrogen abstractions to give active sulfonyl radical **IV** with release of N_2. Meanwhile, the 5-ethynyluracil nucleoside **V** is also activated by the iron halides to form the Fe-coordinated alkynes **VI**. Regio- and stereoselective addition of the sulfonyl radical **IV** to the terminal carbon of the Fe-coordinated acetylene intermediate **VI** leads to $Fe^{(IV)}$ intermediate **VII**. Subsequent reductive elimination afforded the (*E*)-*β*-halovinylsulfones **VIII** with the generation of the $Fe^{(II)}$ catalyst.

3.2.2.2. Application of 5-(1-chloro-2-tosyl)vinyl uracil nucleosides to organic synthesis

As it is known that vinyl sulfones are good acceptors for Michael addition reactions, treatment of vinylsulfones with nucleophiles should provide highly functionalized *β*-substituted vinylsulfones. Thus, it is interesting to contemplate what will ensure in such system when the *β*-position is occupied by halogen. Treatment of (*E*)-1-*N*-benzyl-5-(1-chloro-2-tosyl)vinyl uracil **158** with methanolic ammonia in MeOH at room temperature for 2 h led to the formation of a white suspension. Subsequent vacuum filtration gave a white precipitate which was characterized

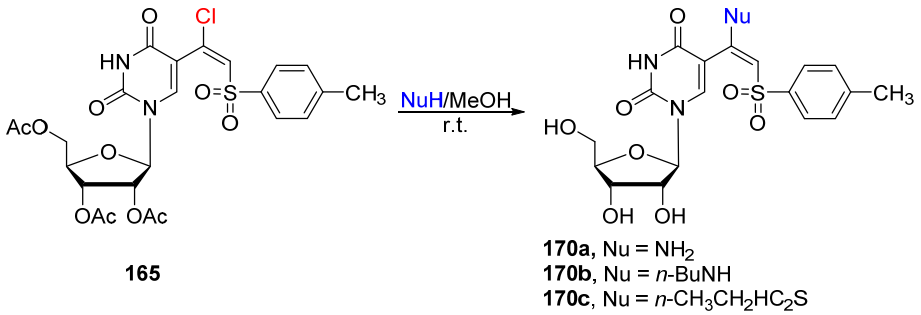
by NMR and HRMS as the (*E*)-1-*N*-benzyl-5-(1-amino-2-tosyl)vinyl uracil **169a** (Scheme 46). It is worthy to note that only one isomer was isolated after the reaction, as the nucleophilic substitution maintained the stereochemical configuration of the starting vinyl sulfonyl substrates.

In order to check the generality of the reaction, **158** was subjected to *n*-butylamine under similar conditions to yield the corresponding product **169b** in quantitative yield in 2 h. However, analogous treatment of **158** with 1-propanethiol only gave unchanged starting substrate after stirring at room temperature for 24 h. Considering the nucleophilicity of the thiol group *vs* the thio anion, a catalytic amount of triethylamine was added as the external base to abstract the hydrogen from the thiol group; surprisingly, the reaction proceeded to completion in 1 h to give **169c** as a single isomer in 99 % yield.



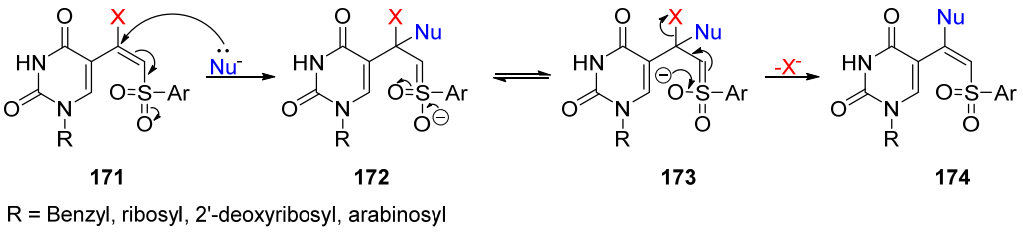
Scheme 46. Nucleophilic substitution of (*E*)-1-*N*-benzyl-5-(1-chloro-2-tosyl)vinyluracil with methanolic ammonia

The stability of the glycosidic bond as well as the protecting group of uracil nucleoside have also been tested. Thus, acetyl protected vinyl sulfonyl uridine **165** was subjected to methanolic ammonia for 48 h and gave 5-(1-amino-2-tosyl)vinyl uridine **170a** as well as small amount of the partial deprotected 5'-*O*-acetyl-5-(1-amino-2-tosylvinyl)uridine (Scheme 47). It is obvious that both deacetylation and nucleophilic substitution took place even in the presence of *n*-butylamine. Similarly, the nucleophilic substitution of **165** with *n*-butylamine and propanethiol (with catalytic amount of Et_3N) gave **170b** and **170c** in respectable yield. The nucleophilic substitution has also been applied to the 5-(1-chloro)vinyl-2'-deoxyuridine derivatives **167** and **168**, which are relative more labile comparing to the ribosyl nucleoside.



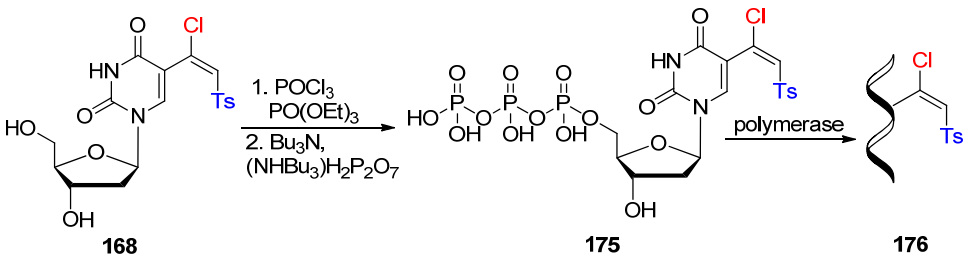
Scheme 47. Synthesis of nucleophile substituted vinyl sulfonyl uracil nucleoside analogues via addition-elimination mechanism

On the basis of the experimental evidence, the nucleophilic substitution is believed to proceed through the addition-elimination mechanism. The proposed mechanism is depicted in Scheme 48. Initially, the nucleophile attacks the *β*-carbon of vinylsulfone **171**, which is partially positive because of the electron withdrawing property of the sulfonyl group as well as the electro-negativity of the halogen, followed by a rearrangement to give intermediate **172**, which tautomerizes to **173**, and ends up as *β*-substituted vinyl sulfone **166** by the elimination of halogen ion.



Scheme 48. Proposed mechanism for the nucleophilic substitution of 5-[(1-halo-2-tosyl)vinyl]uracil and uracil nucleosides

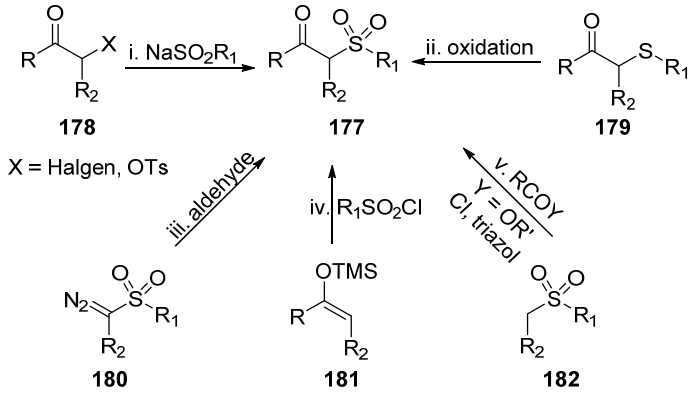
Since the 5-(1-halo-2-tosyl)vinyl uracil nucleosides are excellent substrates for substitution, they could be potentially incorporated into DNA or RNA and employed as a reactive site to study the interaction between oligonucleotide and peptide or protein in biological model systems. With the synthetic method in hand,[191-193] my plan was to convert the 2'-deoxy-5-(1-halo-2-tosyl)vinyl uridine **168** to 5'-triphosphate product **175** by a modified Yoshikawa method, followed by exposure to polymerase to give functionalized nucleotide **176** (Scheme 49).



Scheme 49. Phosphorylation of 2'-deoxy-5-[(1-halo)-2-tosyl]vinyluridine 168 and the synthesis of functionalized nucleotide

3.2.2 Aerobic difunctionalization of 5-ethynyluracil nucleosides

β-Keto sulfones **177** are important synthetic intermediates and some of them have shown biological activity.[194] The summary of the synthetic methods for *β*-keto sulfones is depicted in Scheme 50, which includes i) alkylation of sulfinates with either *α*-halo ketones[195] or *α*-tosyloxy ketones **178**,[196] (ii) oxidation of *β*-thioether ketones **179**,[197] (iii) reactions of diazo sulfones **180** with aldehydes in the presence of $SnCl_2$,[198](iv) ruthenium(II) catalyzed reaction of sulfonyl chlorides with silylenol ethers **181**,[199] and (v) acylation of alkyl sulfones **180**, which could be converted into *β*-keto sulfones by N-Acylbenzotriazoles[200]

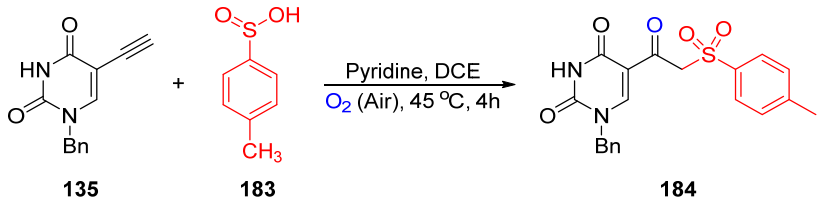


Scheme 50. Reported synthetic route for the preparation of *β*-keto sulfones

3.2.2.1. Synthesis of 5-(β-keto)sulfonyluracil nucleosides

Contrary to the 5-[(1-halo)-2-tosyl]vinyluracil nucleoside derivatives **171**, which are excellent Michael acceptors, 5-(*β*-keto)sulfonyl pyrimidine nucleoside analogues **177** would be good electrophiles after abstraction of a methylene proton with base. They could be synthesized

by direct aerobic difunctionalization of 5-ethynyl uracil nucleoside analogues with sulfinic acid in the presence of a catalytic amount of pyridine. Thus, these two types of 5-modified pyrimidine nucleosides will be excellent substrates for the study of both nucleophilic and electrophilic substitution. Treatment of 1-*N*-benzyl-5-ethynyluracil **135** with *p*-toluyl sufinic acid **183** in the presence of air (oxygen) with a catalytic amount of pyridine at 45 °C for 4h gave the 5-(*β*-keto)sulfonyl uracil derivative **184** in 50% (Scheme 51). Since the sulfinic acid is very easily to be oxidized in air, it is better to synthesize the sulfinic acid just before the hydrosulfonylation.



Scheme 51. Synthesis of 5-[(*β*-keto)sulfonyl]uracil via aerobic difunctionalization of 5-ethynyluracil 135

On the basis of the experimental result and literature reports,[170] a proposed reaction pathway for the synthesis of 5-(*β*-keto)sulfonyl uracil derivatives is depicted in Figure 10. First, pyridine abstract the active hydrogen from sulfinic acid to give sulfinyl anion **I**, followed by the autoxidation with oxygen *via* a single electron transfer (SET) process to afford an oxygencentered radical **II**, which could tautomerize to the more stabilized sulfonyl radical **III**. Subsequently, the terminal carbon of such alkynes is attacked by the sulfonyl radical **III** to produce the reactive vinyl radical **IV**, which could be trapped by dioxygen to give peroxide radical intermediate **V**. Then, peroxide **VII**, which was obtained *via* another single electron transfer and proton transfer successively with sulfinyl anion **I** and pyridinium, undergoes reduction by sulfinic acid to give the *β*-hydroxyvinyl sulfonyl intermediate **VII**. Finally, subsequent tautomerization gave 5-(*β*-keto)sulfonyl uracil derivative **184**.

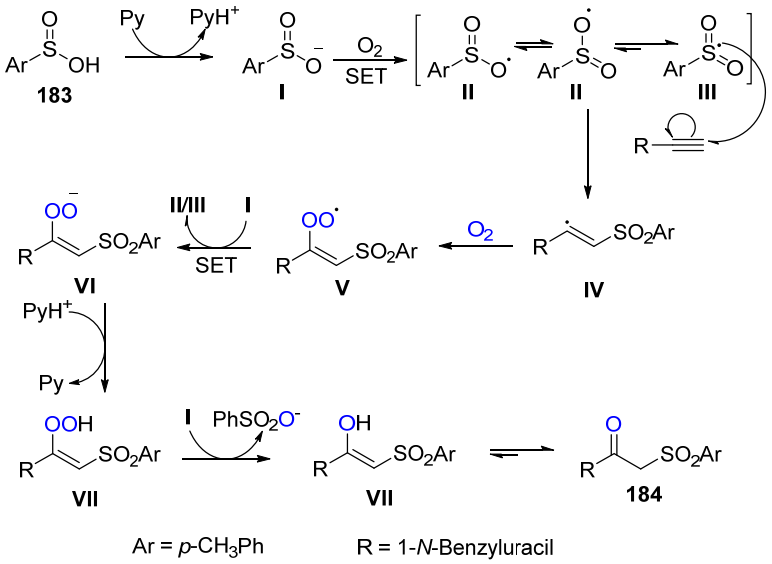
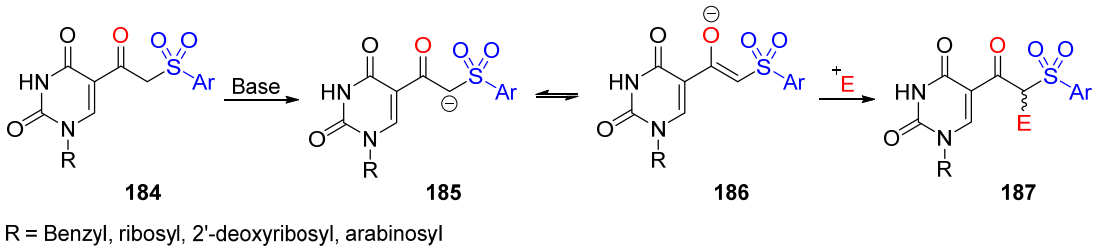


Figure 10. Proposed mechanism for the synthesis of 5-(*β*-keto)sulfonyluracil via aerobic difunctionalization

3.2.2.2. Application of 5-(β-keto)sulfonyluracil nucleosides to organic synthesis

The pK_a of a methylene proton adjacent to a ketone and sulfonyl group is around 12, which is quite acidic. Deprotonation with base should give a stabilized anion **185**, which could act as the nucleophile (Scheme 52). Subsequent addition of an electrophile should provide the highly substituted 5-(*β*-keto)sulfones **187**.



Scheme 52. Proposed mechanism for the electrophilic substitution of 5-[(2-sulfonyl)acetyl]uracil and uracil nucleosides

Thus, treatment of 1-*N*-benzyl-5-[(2-sulfonyl)acetyl]uracil **184** with NaOH at room temperature followed by the addition of benzylbromide gave **188** in 41 % (Scheme 53). In the future, the protocol will be extended to nucleoside substrates as well to functionalized nucleotides.

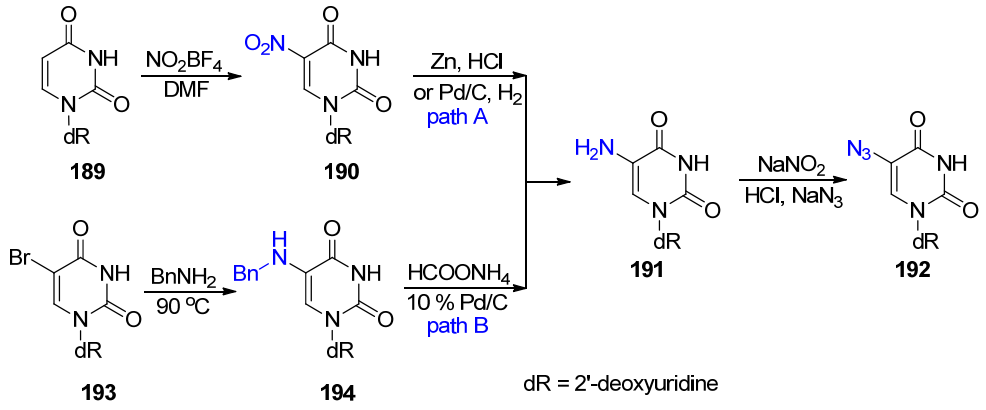
184 188

Scheme 53. Synthesis of 5-[(2-benzyl-2-sulfonyl)acetyl]uracil via the electrophilic substitution

3.2.4 Silver catalyzed hydroazidation of 5-ethynyluracil nucleosides

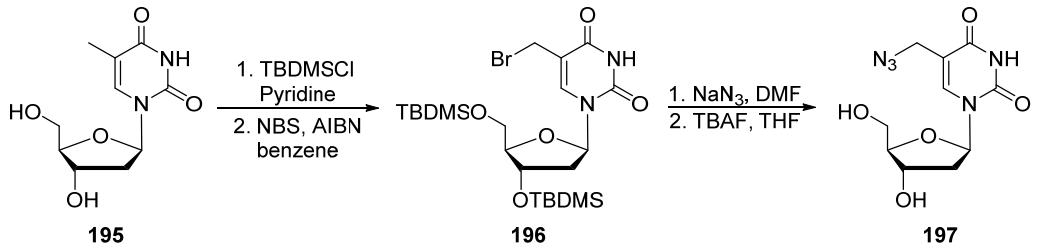
The size of the azido group is extremely small which is favorable for cell permeability, and this feature avoids perturbations. The azide is particularly bioorthogonal, because it is also metabolically stable, and does not naturally exist in cells, so, there are no competing biological side reactions. The incorporation of azido modified nucleoside analogues into living cells can enable sensitive detection of DNA replication through copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC, first generation of click reaction) and strain-promoted azide–alkyne cycloaddition (SPAAC, second generation of click reaction). Since the cyclooctynes are the smallest stable cyclic alkynes which could increases reactivity through ring strain, this high reactivity resulted in the fact that there is no copper catalyst required and that the reaction is quantitative. Thus, cyclooctynes are the best candidate for the click reaction of the azido nucleoside analogues.

The photo-labile 5-azido-2'-deoxyuridine **192** has been synthesized[201-203] *via* preparation and reduction of 5-nitro pyrimidine nucleosides **190**[201,202] (path A, Scheme 54). Due to the inefficiency and tedious preparation of 5-nitrouridine **190**, Clivio and coworkers[203] developed a new approach to synthesize the 5-azido-2'-deoxyuridine **192** in three steps and quantitative yield from the commercially available 5-bromo-2'-deoxyuridine nucleoside **193** *via* a benzylamination reduction sequence (path B, Scheme 54). Since 5-Azido-2'-deoxyuridine **192** is photo-sensitive and has the tendency to decompose when exposed to light (4 h half-life in water[204,205]). It is not surprising that up to seven products were detected, when 5-azido-2'-deoxyuridine **192** was irritated with UV light in water.[205]



Scheme 54. Synthesis of 5-azido-2'-deoxyuridine via two different pathways

In order to overcome the poor chemical stability of 5-azido pyrimidine nucleoside analogues, Luedtke and coworker[204] synthesized 5-(azidomethyl)-2'-deoxyuridine **197**, which is stable in solution at 37 °C, and it gives robust labeling of cellular DNA upon addition of fluorescent alkyne derivatives (Scheme 55). However, the azido group and the pyrimidine ring are isolated by the methylene carbon which is sp^3 hybridized. In other words, the pyrimidine is not conjugated with the 1,2,3-triazole ring that is the formed by the click reaction. As a result, the fluorescent intensity of 5-(azidomethyl)-2'-deoxyuridine **197** might be lower than a derivative whose two aromatic rings are connected by sp^2 hybridized carbons.

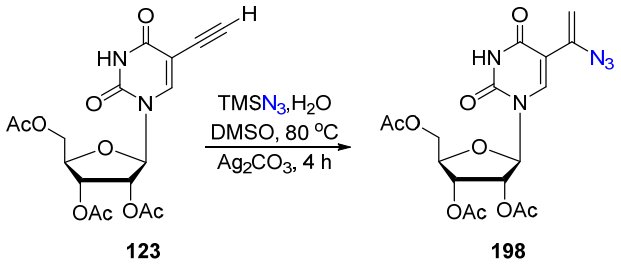


Scheme 55. Synthesis of 5-(azidomethyl)-2'-deoxyuridine from thymidine

3.2.4.1.Synthesis of 5-(α-azidovinyl)uracil nucleosides

Keeping this goal in mind along with careful screening of the literature,[206] I have synthesized the 5-(α-azido)vinyl pyrimidine nucleoside analogues as the substrates for the click reaction. Since the pyrimidine and 1,2,3-triazole ring are conjugated (two aromatics rings are connected by

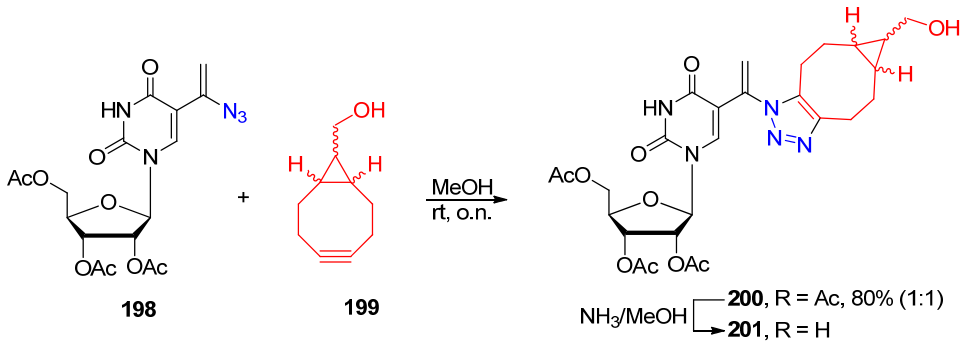
the sp^2 hybridized carbon), it is expected that higher fluorescent intensity will be observed. Treatment of **123** with TMS-N_3 in the presence of silver carbonate with 2 equiv. of H_2O in DMSO at 80 °C for 4 h gave 5-(*α*-azidovinyl)uridine analogue **198**, which is stable at room temperature in MeOH solution (Scheme 56).



Scheme 56. Silver catalyzed hydroazidation of 5-ethynyluridine and click reaction

3.2.4.1. Application of 5-(α-azidovinyl)uracil nucleosides to organic synthesis

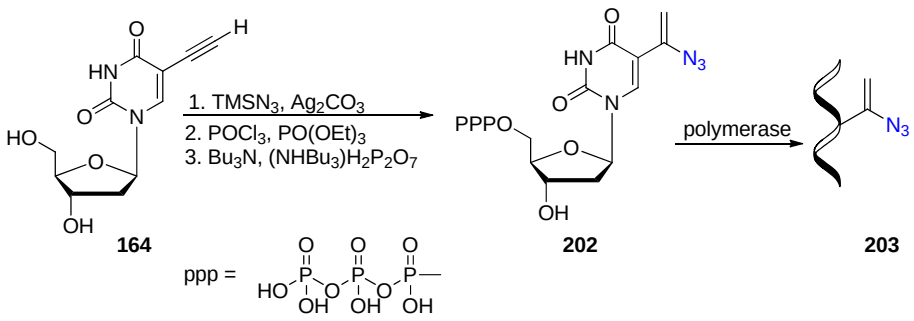
The copper free Click reaction has been performed with acetyl protected 5-(*α*-azido)vinyluridine **198** to check the stability of the azido group. Thus, stirring of **198** with cyclooctyne **199** in MeOH at ambient temperature for 1 h gave the corresponding trizole **200** in 80 % as a mixture of two regio-isomers with ratio of 1:1. Deprotection of **200** with NH_3/MeOH gave **201** in quantitative yield (Scheme 57).



Scheme 57. Strain promoted copper free Click reaction of 5-[(*α*-azido)vinyl]uridine 198 with cyclooctyne 199

It has been noted that clickable oligonucleotides with acetylene residues in the 5-position of pyrimidines (uridine and cytidine) have the tendency to hydrolyze to the acetyl substrates during solid-phase oligonucleotide synthesis and workup conditions.[207] The 5-azido pyrimidine

nucleoside **192** is photo-labile.[204,205] Thus, they are not good substrates for the preparation of base modified oligonucleotides. Even though the 5-methylazido uridine is fairly stable, the azido group and nucleic base are isolated by the methylene group, which will interfere with the conjugation of the system. Thus, it is not the perfect choice as well. Accordingly, it is desirable to synthesize the oligonucleotides with *α*-azidovinyl in the 5-position of pyrimidines. Treatment of 5-ethynyl-2'-deoxyuridine **164** with $TMSN_3$ under the optimal conditions should provide 5-(*α*-azidovinyl)uridine analogues, and subsequent phosphorylation and proton exchange should give **202** (Scheme 58). The 5-(*α*-azido)vinyl functionalized oligonucleotide **203** should be obtained by exposure of **202** to polymerase.



Scheme 58. Proposed route for the synthesis of 5-(*α*-azido)vinyl functionalized nucleotide

4. EXPERIMENTAL SECTION

4.1 General Procedures

^{1}H (Me_4Si) NMR spectra at 400 MHz, ^{13}C (Me_4Si) at 100.6 MHz and ^{19}F (CCl_3F) at 376.4 MHz were determined with solutions in $CDCl_3$. 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 (230-400 mesh) was used for column chromatography. Purity, yields and ratio of the products (crude and/or purified) were established using a GC-MS (EI) system with a mass selective detector [capillary column (30 m × 0.25 mm × 25 μm)] using calibrated standards for products or 2-ethylnaphthalene as internal standard. Mass spectra (MS) was obtained with atmospheric pressure chemical ionization (APCI) technique and HRMS in ESI-TOF mode unless otherwise noted. Tris(dibenzylidene-acetone)dipalladium(0) [$Pd_2(dba)_3$] was purchased from Aldrich-Sigma Co (catalog number: 328774). Germane chlorides are commercially available from Gelest Co., Morrisville, PA, USA.

4.2 Synthesis

1-(Phenyl)naphthalene (55). TBAF (1M/THF, 0.98 mL, 0.98 mmol) was added to a stirred solution of dichlorodiphenylgermane (7**6**; 30.0 μL, 42 mg, 0.14 mmol), 1-iodonaphthalene (45 μL, 78 mg, 0.31 mmol), water (100 μL, 5.7 mmol) and $Pd_2(dba)_3$ (6.5 mg, 0.007 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 15 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 **55** (51 mg, 89%) followed by homocoupling product binaphthlene (6.3 mg, 8%; 16% consumption of 1-iodonaphthalene).

Analogous treatment of trichlorophenylgermane (**75**; 24.0 μL, 35.9 mg, 0.14 mmol) with 1-iodonaphthalene (22.5 μL, 39.1 mg, 0.155 mmol), TBAF (1M/THF, 0.98 mL, 0.98 mmol), water

(100 μL, 5.7 mmol), and $Pd_2(dba)_3$ (6.5 mg, 0.007 mmol) in toluene (3.0 mL) at 100 ^oC (oil bath) for 15 h. gave **55** (27.4 mg, 96%).

Analogous treatment of chlorotriphenylgermane (**77**; 47.5 mg, 0.14 mmol) with 1-iodonaphthalene (67.5 μL, 117 mg, 0.46 mmol), TBAF (1M/THF, 0.98 mL, 0.98 mmol), water (100 μL, 5.7 mmol), and $Pd_2(dba)_3$ (6.5 mg, 0.007 mmol) in toluene (3.0 mL) at 100 ^oC (oil bath) for 15 h. gave **55** (75 mg, 88%).

Triallyl(phenyl)germane (81). In a flame-dried round-bottom flask a solution of trichloro(phenyl)germane (250 mg, 160 μL, 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 ^oC. After 1 h stirring at 0 ^oC the reaction mixture was refluxed (38 ^oC) overnight. The reaction was allowed to cool to room temperature and quenched with NH_4Cl at 0 ^oC. The organic layer was separated and the aqueous layer extracted with Et_2O (2 x 5 mL). The combined extracts was washed (water and brine), dried ($MgSO_4$) and was concentrated *in vacuo*. The residue was chromatographed (hexanes) to give **81** (227 mg, 85%) as clear oil: ^1H 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* 274 (33, M^+ [^{74}Ge]), 151 (100) and (t_R 16.2 min) *m/z* 233 (89, M^+[^{74}Ge]-41), 151 (100). Anal. Calcd for $C_{15}H_{20}Ge$ (272.96): C, 66.00; H, 7.39. Found: C, 65.78; H, 7.44.

Diallyl(diphenyl)germane (82). Treatment of a solution of dichloro(diphenyl)germane (1.0 g, 0.707 μL, 3.359 mmol) in Et_2O (2 mL), as reported for **81**, afforded **82** (980 mg, 94%) as clear oil: ^1H 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^+[^{74}Ge]-41), 227 (29), 151 (80).

Allyl(triphenyl)germane (83). 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 **81,** (mixing at

room temperature instead of 0 °C) afforded **83** (245 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^+[^{74}Ge]-41), 227 (14), 151 (23).

Treatment of a solution of allyltrichlorogermane (855 mg, 560 μL, 3.89 mmol) in Et_2O (2 mL) with phenylmagnesium bromide (4.0 mL, 12 mmol, 3 M solution in Et_2O), following the procedure as described for **81**, gave compound **83** (590 mg, 44%).

1-Phenylnaphthalene (88b). Method A: The antimony (V) fluoride (50 wt % on graphite, 45 mg, 0.105 mmol) was added to a stirring solution of triallyl(phenyl)germane (**81;** 38 mg, 0.14 mmol) in toluene (3.0 mL) at ambient temperature under nitrogen atmosphere in a plastic tube. The resulting mixture was heated at 50 °C (oil bath) for 1.5 h. After cooled down the solution to ambient temperature, the graphite was filtered off and the mother solution was apply to the second step directly. TBAF (1M/THF, 0.42 mL, 0.42 mmol), 1-iodonaphthalene (**87b**; 35 mg, 20 μL, 0.14 mmol), water 25 μL, and $Pd_2(dba)_3$ (6.5 mg, 0.007 mmol) was added to the elute at ambient temperature under nitrogen atmosphere. The resulting brownish mixture was heated at 100℃ (oil bath) for 15 h. The volatiles were evaporated and the residue was partitioned (H_2O/CH_2Cl_2). The organic layer was dried (Na_2SO_4), evaporated and purified by column chromatography (hexane) to give **88b** (13 mg, 45%) followed by **89b** [1.7 mg, 5%, 10% consumption of the iodonaphthalene; GC-MS (t_R 25.02 min) *m/z* 254 (100, M^+)]. Compound **88b** 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^+).

Analogous treatment of **82** (43 mg, 0.14 mmol) and 1-iodonaphthalene (**87b**; 71 mg, 41 μL, 0.28 mmol) with antimony (V) fluoride (50 wt % on graphite, 30 mg, 0.07 mmol) by general method A gave **88b** (35 mg, 62%) and **89b** (8 mg, 11%).

Analogous treatment of **83** (48 mg, 0.14 mmol) and 1-iodonaphthalene (**87b**; 106 mg, 61 μL, 0.42 mmol) antimony (V) fluoride (50 wt % on graphite, 15 mg, 0.035 mmol) by general method A gave **88b** (54 mg, 63%) and **89b** (16.5 mg, 15%).

Analogous treatment **81** (38 mg, 0.14 mmol) with 1-bromonaphthalene (**87e**; 29 mg, 19 μL, 0.14 mmol) by general method A gave **88b** (42%) and **89b** (3%) based on the GC-MS analysis of the crude reaction mixture.

Analogous treatment of **82** (43 mg, 0.14 mmol) and 1-bromonaphthalene (**87e**; 58 mg, 39 μL, 0.28 mmol) with antimony (V) fluoride (50 wt % on graphite, 30 mg, 0.07 mmol) by general method A gave **88b** (34%) and **89b** (15%) based on the GC-MS analysis of the crude reaction mixture.

Analogous treatment of **83** (48 mg, 0.14 mmol) and 1-bromonaphthalene (**87e**; 87 mg, 58 μL, 0.42 mmol) with antimony (V) fluoride (50 wt % on graphite, 15 mg, 0.035 mmol) by general method A gave **87b** (14%) and **88b** (4%) based on the GC-MS analysis of the crude reaction mixture.

1-Phenyl-4-methyloxybenzene (88c). Analogous treatment of **81** (38 mg, 0.14 mmol) with 4-iodoanisole (**87c**; 33mg, 0.14 mmol) by general method A give **88c** (18 mg, 71%) followed by **89c** [1 mg, 3.5%, 7% consumption of the 4-iodoanisole; GC-MS (t_R 20.81 min) *m/z* 214 (100, M^+)]. Compound **88c** 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^+).

Analogous treatment of **82** (43 mg, 0.14 mmol) and 4-iodoanisole (**87c**; 66 mg, 0.28 mmol) with antimony (V) fluoride (50 wt % on graphite, 30 mg, 0.07 mmol) by general method A gave **88c** (45%) and **89c** (16%) based on the GC-MS analysis of the crude reaction mixture.

Analogous treatment of **83** (48 mg, 0.14 mmol) and 4-iodoanisole (**87c**; 98 mg, 0.42 mmol) with antimony (V) fluoride (50 wt % on graphite, 15 mg, 0.035 mmol) by general method A gave **88c** (32%) and **89c** (20%) based on the GC-MS analysis of the crude reaction mixture.

1-Phenyl-4-trifluoromethylbenzene (7d). Analogous treatment of **81** (38 mg, 0.14 mmol) with 4-iodobenzotrifluoride (**87d**; 38 mg, 21 μL, 0.14 mmol) by general method A gave **88d** (13 mg, 41%) followed by **89d** [8.7 mg, 21.5%, 43% consumption of the 4-iodobenzotrifluoride; GC-MS (t_R 13.08 min) *m/z* 290 (100, M^+)]. Compound **88d** had: ^{1}H NMR δ 7.39-7.45 (m, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.61 (d, J = 7.3 Hz, 2H), 7.71 (s, 4H); ^{13}C NMR δ 124.5 (q, $^1J_{C\text{-}F}$ = 271.5 Hz), 125.9 (q, $^3J_{C\text{-}F}$ = 3.6 Hz), 127.4, 127.6, 128.3, 129.1, 129.5 (q, $^2J_{C\text{-}F}$ = 32.7 Hz), 144.9 (q, $^5J_{C\text{-}F}$ = 1.1 Hz); GC-MS (t_R 12.96 min) *m/z* 222 (100, M^+).

Analogous treatment of **82** (43 mg, 0.14 mmol) with 4-iodobenzotrifluoride (**87d**; 76 mg, 41 μL, 0.28 mmol) by general method A gave **88d** (33%) and **89d** (33%) based on the GC-MS analysis of the crude reaction mixture.

Analogous treatment of **83** (35 mg, 0.14 mmol) and 4-iodobenzotrifluoride (**87d**; 114 mg, 61 μL, 0.42 mmol) by general method A gave **88d** (22%) and **89d** (33%) based on the GC-MS analysis of the crude reaction mixture.

1-*N*-Benzyl-3-*N*-methyl-5-iodouracil (78c). Freshly distilled diazomethane solution in ether (10 mL), generated from Diazald (3.0 g, 14.0 mmol), was added dropwise to a stirred solution of **78a**[168] (357 mg, 1.09 mmol) in CH_2Cl_2 (20 mL) at 0 ^{o}C. After 18 h, the volatiles were evaporated to give **78c** (354 mg, 95%) as white powder: ^{1}H NMR δ 3.34 (s, 3H), 4.86 (s, 2H), 7.21-7.30 (m, 5H), 7.57 (s, 1H); ^{13}C NMR δ 29.7, 52.7, 68.0, 128.2, 128.8, 129.3, 135.0, 146.4, 151.5, 160.2; GC-MS (t_R 21.70min.) *m/z* 342 (85, M^+), 91 (100); HRMS calcd for $C_{12}H_{12}IN_2O_2$ $[M + H]^+$ 342.9938, found 342.9935.

1-*N*-Benzyl-5-(2-, 3-, and 4-methylphenyl)uracil (*o/m/p*-91a). **Procedure A**. Toluene (0.2 mL, 173 mg, 1.89 mmol), TBAF (1M/THF solution containing ca 5% wt of water; 980 μL, 0.98

mmol) and $Pd_2(dba)_3$ (6.4 mg, 0.007 mmol) were added to a stirring solution of 1-*N*-benzyl-5-iodouracil[168] (**78a**, 46 mg, 0.14 mmol) in DMF (1.8 mL) under the N_2 atmosphere at ambient temperature. The resulting suspension was stirred for 1 h at 100 ^oC (oil bath). Volatiles were evaporated, and the oily residue was dissolved in EtOAc or MeOH and filtrated through Celite or Whatman GF/A filter paper. The filtrate was partitioned (EtOAc/H_2O). The organic layer was then washed (brine), dried (Na_2SO_4) and evaporated. GC-MS of this material showed peaks at t_R 31.46, 32.38 and 32.70 min. (*m/z* 292, M^+) for the three isomers of **91a** (*ortho/meta/para* with relative intensities of ~3:2:1, respectively). Column chromatography (hexane/EtOAc, 8:2 → 6:4) gave a mixture of *o/m/p*-**91a** (*o/m/p,* 3:2:1; 29 mg, 71% overall yield) followed by **92** (1 mg, 4%). Mixture of *o/m/p*-**91a** had: GC-MS t_R 31.46 (*o*-**91a**), 32.38 (*m*-**91a**) and 32.70 (*p*-**91a**) min. (*m/z* 292, M^+); ^1H NMR δ 2.21 (s, 1.5H, *o*-**91a**), 2.35 (s, 0.5H, *p*-**91a**), 2.36 (s, 1H, *m*-**91a**), 4.97 (s, 1H, *o*-**91a**), 4.985 (s, 0.33H, *p*-**91a**), 4.990 (s, 0.67H, *m*-**91a**), 7.07-7.41 (m, 10H), 8.91 (s, 1H); HRMS calcd for $C_{18}H_{17}N_2O_2$ $[M + H]^+$ 293.1285, found 293.1294.

Attempted purification of the *o/m/p*-**91a** mixture on a long silica gel column (hexane/EtOAc, 8:2 → 7:3) gave partial separation of the *o/m/p* isomers of **91a** but failed to yield single isomers.

***Note**:* Treatment of **78a** (46 mg, 0.14 mmol) with toluene/TBAF/$Pd_2(dba)_3$ in DMF for 18 h at 100 ^oC, as described above (column chromatography; hexane/EtOAc, 98:2 → 95:5) gave mixture of 1-*N*-benzyl-3-*N*-butyl-5-(2-methylphenyl)uracil (*o*-**79a**), 1-*N*-benzyl-3-*N*-butyl-5-(3-methylphenyl)uracil (*m*-**79a**) and 1-*N*-benzyl-3-*N*-butyl-5-(4-methylphenyl)uracil (*p*-**79a**) (36.6 mg, 75% overall yield; *o*-**79a**/*m*-**79a**/*p*-**79a**, 3:2:1): GC-MS t_R 27.29 (*o*-**79a**), 28.27 (*m*-**79a**) and 28.74 (*p*-**79a**) min. (*m/z* 348, M^+); ^1H NMR δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.36 ("sextet", *J* = 7.4 Hz, 2H), 1.67 ("quint", *J* = 7.6, Hz, 2H), 2.18 (s, 1.5H, *o*-**79a**), 2.30 (s, 0.5H, *p*-**79a**), 2.32 (s, 1H, *m*-**79a**), 4.00 ("t", *J* = 7.6 Hz, 2H), 4.94 (s, 1H, *o*-**79a**), 4.95 (s, 0.33H, *p*-**79a**), 4.96 (s, 0.67H, *m*-**79a**), 7.02-7.37 (m, 10H); HRMS calcd for $C_{22}H_{25}N_2O_2$ $[M + H]^+$ 349.1911, found 349.1920.

1-*N*-Benzyl-5-(3-methylphenyl)uracil (*m*-**91a**). *Suzuki Coupling*:[54] 3-Tolylboronic acid (29 mg, 0.21 mmol) and PPh_3 (9 mg, 0.034 mmol) were added to a stirring solution of 1-*N*-benzyl-5-iodouracil (**78a**, 46 mg, 0.14 mmol) in CH_3CN/H_2O (3 mL; v/v, 2:1) under the N_2 atmosphere at ambient temperature, followed by the addition of Na_2CO_3 (22 mg, 0.21 mmol) and $Pd(OAc)_2$ (3 mg, 0.013 mmol). The resulting suspension was stirred for 4 h at 80 ^oC (oil bath). Volatiles were evaporated, and the residue was partitioned between EtOAc and H_2O. The organic layer was then washed (brine), dried (Na_2SO_4) and evaporated. Column chromatography (hexane/EtOAc, 6:4 → 5:5) gave *m*-**91a** (21.7 mg, 53%): ^1H NMR δ 2.38 (s, 3H), 5.01 (s, 2H), 7.16 (dt, J = 6.8, 2.0 Hz, 1H), 7.23-7.29 (m, 2H), 7.30 (t, J = 1.7 Hz, 1H), 7.32 (s, 1H), 7.34-7.46 (m, 5H), 9.35 (s, 1H); ^{13}C NMR δ 21.6, 51.5, 116.1, 125.3, 128.2, 128.5, 128.7, 128.97, 129.01, 129.3, 132.1, 135.4, 138.3, 141.2, 150.9, 162.5; GC-MS (t_R 32.38 min.) *m/z* 292 (85, M^+), 91 (100); HRMS calcd for $C_{18}H_{17}N_2O_2$ $[M + H]^+$ 293.1285, found 293.1293.

1-*N*-Benzyl-5-(4-methylphenyl)uracil (***p*-91a**). *Suzuki Coupling*:[54] Treatment of **78a** (46 mg, 0.14 mmol) with 4-tolylboronic acid (29 mg, 0.21 mmol), as described above for *m*-**91a**, gave *p*-**91a** (20.0 mg, 49%): ^1H NMR δ 2.34 (s, 3H), 4.98 (s, 2H), 7.17 (d, J = 7.9 Hz, 2H), 7.28 (s, 1H), 7.32-7.41 (m, 7H), 9.03 (s, 1H); ^{13}C NMR δ 21.3, 51.5, 115.9, 128.1, 128.2, 128.7, 129.2, 129.3, 129.4, 135.4, 138.2, 140.8, 150.8, 162.4; GC-MS (t_R 32.70 min.) *m/z* 292 (85, M^+), 91 (100); HRMS calcd for $C_{18}H_{17}N_2O_2$ $[M + H]^+$ 293.1285, found 293.1291.

1-*N*-Benzyl-5-phenyluracil (91b). Treatment of **78a** (46 mg, 0.14 mmol) with benzene (0.2 mL, 175 mg, 2.24 mmol) by procedure A gave **91b** (25.3 mg, 59%): ^1H NMR δ 4.99 (s, 2H), 7.32 (s, 1H), 7.33-7.49 (m, 10H), 9.02 (s, 1H); ^{13}C NMR δ 51.6, 115.9, 128.2, 128.3, 128.7, 128.8, 129.4, 132.2, 135.3, 141.2, 150.7, 162.3; GC-MS (t_R 24.52 min.) *m/z* 278 (80, M^+), 91 (100); HRMS calcd for $C_{17}H_{14}N_2NaO_2$ $[M + Na]^+$ 301.0947, found 301.0945.

Analogues treatment of 1-*N*-benzyl-5-bromouracil[208] (**78b**, 39 mg, 0.14 mmol) with benzene (0.2 mL, 175 mg, 2.24 mmol) by procedure A (14 equiv. of TBAF) gave **91b** (27.6 mg, 71%) with spectroscopic data as described above.

1-*N*-Benzyl-5-(2,4-dimethylphenyl)uracil (91c). Treatment of **78a** (46 mg, 0.14 mmol) with *m*-xylene (0.2 mL, 172 mg 1.62 mmol) by procedure A gave the desired product which was recrystallized from hexane/EtOAc to give a single isomer **91c** (23.6 mg, 55%): ^{1}H NMR δ 2.16 (s, 3H), 2.31 (s, 3H), 4.95 (s, 2H), 6.95 (d, J = 8.0 Hz, 1H), 6.99 (br d, J = 8.1 Hz, 1H), 7.05 (s, 1H), 7.11 (s, 1H), 7.30-7.41 (m, 5H), 8.30 (s, 1H); ^{13}C NMR δ 20.1, 21.2, 51.4, 116.5, 126.8, 128.3, 128.7, 128.8, 129.4, 130.5, 131.4, 135.3, 137.6, 138.8, 142.2, 150.8, 161.9; GC-MS (t_R 27.34 min.) *m/z* 306 (70, M^+), 91 (100); HRMS calcd for $C_{19}H_{19}N_2O_2$ $[M + H]^+$ 307.1441, found 307.1442.

GC-MS of the crude reaction mixture showed peaks for three isomers with t_R at 27.34, 27.90 and 28.33 min. with relative intensities of 14:5:1 (*m/z* 306, M^+).

1-*N*-Benzyl-5-(2-,3-,and 4-methoxyphenyl)uracil (*o/m/p*-91d). Treatment of **78a** (46 mg, 0.14 mmol) with anisole (0.2 mL, 199 mg, 1.84 mmol) by procedure A gave **91d** (*o/m/p,* 4:1:1; 29.3 mg, 68%): GC-MS t_R 25.52 (***o*-91d**), 26.68 (***m*-91d**) and 27.31 (***p*-91d**) min. (*m/z* 308, M^+); ^{1}H NMR δ 3.73 (s, 2H, ***o*-91d**), 3.80 (s, 0.5H, ***p*-91d**), 3.81 (s, 0.5H, ***m*-91d**), 4.96 (s, 1.3H, ***o*-91d**), 4.98 (s, 0.7H, ***m,p*-91d**), 6.86-7.34 (m, 10H), 9.01(s, 0.67H, ***o*-91d**) 9.14(s, 0.33H, ***m,p*-91d**); HRMS calcd for $C_{18}H_{17}N_2O_3$ $[M + H]^+$ 309.1234, found 309.1247.

1-*N*-Benzyl-5-(3-methoxyphenyl)uracil (*m*-91d). *Suzuki Coupling*:[54] Treatment of **78a** (46 mg, 0.14 mmol) with 3-methoxyphenylboronic acid (32 mg, 0.21 mmol), as described above for ***m*-91a**, gave ***m*-91d** (22 mg, 51%): ^{1}H NMR δ 3.80 (s, 3H), 4.98 (s, 2H), 6.88 (dd, J = 8.8, 2.5 Hz, 1H), 7.03 ("dt", J = 7.6, 2.0 Hz, 1H), 7.10 ("t", J = 2.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.33-7.40 (m, 6H), 9.33 (s, 1H); ^{13}C NMR δ 51.4, 55.3, 113.6, 114.0, 115.5, 121.4, 128.1, 128.6, 129.2,

129.5, 133.4, 135.2, 141.3, 150.7, 159.6, 162.2; GC-MS (t_R 26.68 min.) *m/z* 308 (75, M^+), 91 (100); HRMS calcd for $C_{18}H_{17}N_2O_3$ $[M + H]^+$ 309.1234, found 309.1238.

1-*N*-Benzyl-5-(4-methoxyphenyl)uracil (***p*-91d**). *Suzuki Coupling*:[54] Treatment of **78a** (46 mg, 0.14 mmol) with 4-methoxyphenylboronic acid (32 mg, 0.21 mmol), as described above for ***m*-91a**, gave ***p*-91d** (23.7 mg, 55%): ^{1}H NMR δ 3.80 (s, 3H), 4.98 (s, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.25 (s, 1H), 7.32-7.39 (m, 7H), 8.64 (s, 1H); ^{13}C NMR δ 51.5, 55.5, 114.2, 115.7, 124.5, 128.2, 128.7, 129.3, 129.5, 135.4, 140.3, 150.8, 159.7, 162.5; GC-MS (t_R 27.31 min.) *m/z* 308 (80, M^+), 91 (100); HRMS calcd for $C_{18}H_{17}N_2O_3$ $[M + H]^+$ 309.1234, found 309.1241.

1-*N*-Benzyl-5-(fur-2-yl)uracil (91e). **Method A**. Treatment of **78a** (46 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure A (3.5 equiv. of TBAF) gave **91e** (29.3 mg, 78%): ^{1}H NMR δ 5.01 (s, 2H), 6.43 (dd, *J* = 3.0, 1.9 Hz, 1H), 7.05 (d, *J* = 3.0 Hz, 1H), 7.28-7.43 (m, 6H), 7.69 (s, 1H), 9.19 (s, 1H); ^{13}C NMR δ 51.9, 107.6, 109.7, 112.1, 128.2, 128.8, 129.3, 135.3, 137.7, 141.3, 145.7, 150.2, 160.4; GC-MS (t_R 27.41 min.) *m/z* 268 (60, M^+), 91 (100); HRMS calcd for $C_{15}H_{13}N_2O_3$ $[M + H]^+$ 269.0921, found 269.0934.

Analogues treatment of **78b** (39 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure A (14 equiv. of TBAF) gave **91e** (31.9 mg, 85%) with spectroscopic data as described above.

Method B. **Procedure B**. Furan (0.2 mL, 187 mg, 2.75 mmol), Cs_2CO_3 (91.2 mg, 0.28 mmol) and $Pd(OAc)_2$ (1.6 mg, 0.007 mmol) were added to a stirring solution of **78a** (46 mg, 0.14 mmol) in DMF (1.8 mL) under the N_2 atmosphere at ambient temperature. The resulting suspension was stirred for 2 h at 100 ^{o}C (oil bath) and after cooling down to ambient temperature was diluted with EtOAc (3 mL). The resulting mixture was vacuum filtered using Whatman GF/A filter paper and the filtrates were evaporated. The oily residue was dissolved in EtOAc and partitioned (EtOAc/H_2O). The organic layer was then washed (brine), dried (Na_2SO_4) and evaporated.

Column chromatography (hexane/EtOAc, 8:2 → 6:4) gave **91e** (24.5 mg, 65% yield) with the spectroscopic data as above and **94** (5 mg, 17%).

Procedure C. Analogous treatment of **78a** (46 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) and Cs_2CO_3 (91.2 mg, 0.28 mmol) in the presence of PivOH (17.9 mg, 0.175 mmol) and $Pd(OAc)_2$ (1.6 mg, 0.007 mmol) by Procedure B gave **91e** (27 mg, 73% yield).

Analogues treatment of **78b** (39 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure B gave **91e** (5 mg, 13% yield) with the spectroscopic data as above.

1-*N*-Benzyl-5-(benzo[*b*]fur-2-yl)uracil (91f). Treatment of **78a** (46 mg, 0.14 mmol) with benzo[*b*]furan (23.1 μL, 24.8 mg, 0.21 mmol) by procedure A (3.5 equiv. of TBAF) gave **91f** (29.4 mg, 66%): ^{1}H NMR δ 5.06 (s, 2H), 7.2 (td, *J* = 7.3, 1.2 Hz, 1H), 7.26 (dt, *J* = 7.3, 1.4 Hz, 1H), 7.37-7.42 (m, 6H), 7.47 (d, *J* = 0.6 Hz, 1H), 7.56 (ddd, *J* = 7.3, 1.5, 0.8 Hz, 1H), 7.95 (s, 1H), 8.67 (s, 1H); ^{13}C NMR δ 52.2, 106.1, 107.0, 110.7, 121.6, 123.3, 124.8, 128.2, 128.9, 129.3, 129.4, 135.1, 139.5, 147.6, 149.9, 153.9, 160.1; HRMS calcd for $C_{19}H_{15}N_2O_3$ $[M + H]^+$ 319.1077, found 319.1081.

1-*N*-Benzyl-5-(thiophen-2-yl)uracil (91g). Method A. Treatment of **78a** (46 mg, 0.14 mmol) with thiophene (0.2 mL, 210 mg, 2.5 mmol) by procedure A (3.5 equiv. of TBAF) gave **91g**[209] (36.2 mg, 91%): ^{1}H NMR (DMSO-d_6) δ 4.98 (s, 2H), 7.06 (dd, *J* = 5.1, 3.7 Hz, 1H), 7.29-7.32 (m, 1H), 7.34-7.37 (m, 4H), 7.44-7.47 (m, 2H), 8.45 (s, 1H), 11.72 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 50.8, 108.1, 122.7, 125.6, 126.4, 127.4, 127.6, 128.6, 133.7, 136.7, 140.9, 149.9, 161.7; HRMS calcd for $C_{15}H_{13}N_2O_2S$ $[M + H]^+$ 285.0692, found 285.0691.

Method B. Analogues treatment of **78a** (46 mg, 0.14 mmol) with thiophene (0.2 mL, 210 mg, 2.5 mmol) by procedure B gave **91g** (30.2 mg, 76% yield) with the spectroscopic data as above.

Analogues treatment of **78b** (39 mg, 0.14 mmol) with thiophene (0.2 mL, 210 mg, 2.5 mmol) by procedure B gave **91g** (6 mg, 16% yield) with the spectroscopic data as above.

1-*N*-Benzyl-5-(5-methylthiophen-2-yl)uracil (91h). Treatment of **78a** (46 mg, 0.14 mmol) with 2-methylthiophene (0.2 mL, 203 mg, 2.1 mmol) by procedure A (3.5 equiv. of TBAF) gave **91h** (29.2 mg, 70%): ^{1}H NMR δ 2.46 (d, *J* = 0.8 Hz, 3H), 4.98 (s, 2H), 6.66 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.15 (d, *J* = 3.6 Hz, 1H), 7.30-7.40 (m, 5H), 7.42 (s, 1H), 9.06 (s, 1H); ^{13}C NMR δ 15.3, 51.7, 110.9, 125.0, 125.5, 128.2, 128.8, 129.4, 130.8, 135.2, 138.2, 140.4, 152.2, 161.4; HRMS calcd for $C_{16}H_{14}N_2O_2SNa$ $[M + Na]^+$ 321.0668, found 321.0674.

1-*N*-Benzyl-5-(5-acetylthiophen-2-yl)uracil (91i). Treatment of **78a** (46 mg, 0.14 mmol) with 2-acetylthiophene (0.2 mL, 234 mg, 2.1 mmol) by procedure A (3.5 equiv. of TBAF) gave **91i** (25 mg, 54%): ^{1}H NMR (DMSO-d_6) δ 2.50 (s, 3H), 4.99 (s, 2H), 7.29-7.34 (m, 1H), 7.37 (d, *J* = 4.3 Hz, 4H), 7.59 (d, *J* = 4.1 Hz, 1H), 7.87 (d, *J* = 4.1 Hz, 1H), 8.76 (s, 1H), 11.89 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 26.4, 51.2, 107.1, 123.0, 127.4, 127.7, 128.6, 133.1, 136.5, 141.9, 142.5, 143.2, 149.7, 161.5, 190.6; GC-MS (t_R 31.00 min.) *m/z* 326 (20, M^+), 91 (100); HRMS calcd for $C_{17}H_{15}N_2O_3S$ $[M + H]^+$ 327.0798, found 327.0801.

1-*N*-Benzyluracil (92). Treatment of **78a** (46 mg, 0.14 mmol) with toluene (0.2 mL, 173 mg, 1.89 mmol) by procedure A [using $KOSiMe_3$ (53.8 mg, 0.42 mmol) instead of TBAF] gave **92**[210] (18.4 mg, 65%): ^{1}H NMR δ 4.92 (s, 1H), 5.70 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.25-7.44 (m, 3H), 9.46 (s, 1H); ^{13}C NMR δ 51.4, 102.8, 128.2, 128.7, 129.3, 135.2, 144.0, 151.3, 163.7; GC-MS (t_R 24.38 min.) *m/z* 202 (35, M^+), 91 (100); HRMS calcd for $C_{11}H_{11}N_2O_2$ $[M + H]^+$ 203.0815, found 203.0817.

1-*N*-Benzyl-3-*N*-methyl-5-(fur-2-yl)uracil (93e). Treatment of **78c** (48 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure B (column chromatography; hexane/EtOAc, 8:2 → 7:3) gave **93e** (19 mg, 48% yield): GC-MS (t_R 17.67 min.) *m/z* 282 (75, M^+), 91 (100); ^{1}H NMR δ 3.45 (s, 3H), 5.03 (s, 2H), 6.45 (dd, *J* = 3.4, 1.8 Hz, 1H), 7.06 (d, *J* = 3.3 Hz, 1H), 7.35 (d, *J* = 5.9 Hz, 1H), 7.33-7.39 (m, 3H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.72 (s, 1H); ^{13}C NMR δ 28.5, 53.0,

106.6, 109.3, 112.0, 128.1, 128.7, 129.3, 135.4, 136.0, 141.2, 146.3, 151.0, 160.2; HRMS calcd for $C_{16}H_{15}N_2O_3$ $[M + H]^+$ 283.1077, found 283.1065.

1-*N*-Benzyl-3-*N*-methyl-5-(thiophen-2-yl)uracil (93g). Treatment of **78c** (48 mg, 0.14 mmol) with thiophene (0.2 mL, 210 mg, 2.5 mmol) by procedure B (column chromatography; hexane/EtOAc, 8:2 → 7:3) gave **93g** (17 mg, 41% yield): GC-MS (t_R 23.66 min.) *m/z* 298 (75, M^+), 91 (100); ^{1}H NMR δ 3.46 (s, 3H), 5.03 (s, 2H), 7.02 (dd, *J* = 5.1, 3.7 Hz, 1H), 7.28 – 7.39 (m, 7H), 7.55 (s, 1H). ^{13}C NMR δ 28.7, 52.8, 109.6, 124.0, 125.8, 126.9, 128.2, 128.8, 129.3, 134.9, 135.3, 137.0, 151.1, 161.4; HRMS calcd for $C_{16}H_{15}N_2O_2S$ $[M + H]^+$ 299.0849, found 299.0852.

1-*N*-benzyl-3-*N*-methyluracil (94). Treatment of **78c** (48 mg, 0.14 mmol) with toluene (0.2 mL, 173 mg, 1.89 mmol) by procedure A (column chromatography; hexane/EtOAc, 6:4 → 4:6) gave **94**[211] (29 mg, 73%): ^{1}H NMR δ 3.36 (s, 3H), 4.94 (s, 2H), 5.75 (d, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 7.9 Hz, 1H), 7.2-7.48 (m, 5H); ^{13}C NMR δ 28.0, 52.4, 102.0, 128.1, 128.6, 129.2, 135.4, 141.7, 152.0, 163.2; GC-MS (t_R 20.49 min.) *m/z* 216 (50, M^+), 91 (100); HRMS calcd for $C_{12}H_{13}N_2O_2$ $[M + H]^+$ 217.0972, found 217.0976.

Analogous treatment (TBAF 3.5 equiv.) of **78c** (48 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure A gave **94**[211] (24 mg, 60%).

1-(2,3,5-Tri-*O*-acetyl-*β*-D-arabinofuranosyl)-5-(fur-2-yl)uracil (101). Treatment (TBAF 3.5 equiv.) of 1-(2,3,5-tri-*O*-acetyl-*β*-D-arabinofuranosyl)-5-iodouracil (**95**, 69.5 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure A (column chromatography; hexane/EtOAc, 6:4 → 5:5) gave **101** (37.3 mg, 61%) as a slightly yellow solid: ^{1}H NMR δ 2.01 (s, 3H), 2.18 (s 3H), 2.19 (s, 3H), 4.24 (dt, *J* = 5.2, 3.9 Hz, 1H), 4.44 (dd, *J* = 12.0, 5.2 Hz, 1H), 4.53 (dd, *J* = 12.0, 4.2 Hz, 1H), 5.22 (dd, *J* = 3.6, 1.7 Hz, 1H), 5.48 (dd, *J* = 4.1, 1.7 Hz, 1H), 6.43 (d, *J* = 4.1 Hz, 1H), 6.49 (dd, *J* = 3.4, 1.8 Hz, 1H), 7.09 (d, *J* = 3.2 Hz, 1H), 7.39 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.97 (s, 1H), 9.39 (s, 1H); ^{13}C NMR δ 20.4, 20.65, 20.68, 62.7, 74.7, 76.5, 80.5, 84.2, 106.6,

109.7, 112.0, 134.1, 141.3, 145.5, 149.0, 159.6, 168.6, 169.6, 170.5; HRMS calcd for $C_{19}H_{21}N_2O_{10}$ $[M + H]^+$ 437.1191, found 437.1176.

3',5'-Di-*O*-acetyl-5-(fur-2-yl)-2'-deoxyuridine (102). Treatment of 3',5'-di-*O*-acetyl-2'-deoxy-5-iodouridine[212] (**96**, 61.3 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure A (column chromatography; hexane/EtOAc, 6:4 → 5:5) gave **102** (38.1 mg, 72%): ^{1}H NMR δ 2.12 (s, 3H), 2.15 (s, 3H), 2.54 (ddd, *J* = 14.4, 6.5, 2.1 Hz, 1H), 2.54 (ddd, *J* = 14.2, 5.6, 1.6 Hz, 1H), 4.31 ("q", *J* = 2.7 Hz, 1H), 4.38-4.39 (m, 2H), 5.28 (dt, *J* = 6.6, 1.7 Hz, 1H), 6.44 (dd, *J* = 6.5, 5.6 Hz, 1H), 6.45 (dd, *J* = 3.4, 1.8 Hz, 1H), 7.08 (d, *J* = 3.2 Hz, 1H), 7.32 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.99 (s, 1H), 9.63 (s, 1H); ^{13}C NMR δ 20.8, 21.0, 38.1, 64.2, 74.6, 82.7, 85.4, 107.9, 109.9, 112.2, 132.5, 141.2, 145.8, 149.6, 160.0, 170.4, 170.5; HRMS calcd for $C_{17}H_{19}N_2O_8$ $[M + H]^+$ 379.1136, found 379.1136.

2',3',5'-Tri-*O*-acetyl-5-(fur-2-yl)uridine (103). Ttreatment of 2',3',5'-tri-*O*-acetyl-5-iodouridine (**97**, 69.5 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure A (column chromatography; hexane/EtOAc, 6:4 → 5:5) gave **103** (40.8 mg, 67%): ^{1}H NMR δ 2.07 (s, 3H), 2.10 (s, 3H), 2.14 (s, 3H), 4.33-4.36 (m, 3H), 5.33-5.44 (m, 2H), 6.16 (d, *J* = 5.6 Hz, 1H), 7.04 (dd, *J* = 5.1, 3.7 Hz, 1H), 7.30 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.42 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.75 (s, 1H), 9.39 (s, 1H); ^{13}C NMR δ 20.5, 20.7, 20.8, 64.6, 70.9, 73.0, 80.6, 86.8, 108.4, 110.2, 112.3, 132.5, 141.3, 145.6, 149.6, 157.8, 169.77, 169.83, 170.4; HRMS calcd for $C_{19}H_{21}N_2O_{10}$ $[M + H]^+$ 437.1191, found 437.1178.

2',3',5'-Tri-*O*-acetyl-5-(thiophen -2-yl)uridine (104). Ttreatment of 2',3',5'-tri-*O*-acetyl-5-iodouridine (**97**, 69.5 mg, 0.14 mmol) with thiophene (0.2 mL, 210 mg, 2.5 mmol) by procedure A (column chromatography; hexane/EtOAc, 6:4 → 5:5) gave **104** (40 mg, 63%): ^{1}H NMR δ 2.07 (s, 3H), 2.10 (s, 3H), 2.14 (s, 3H), 4.33-4.46 (m, 3H), 5.33-5.44 (m, 2H), 6.16 (d, *J* = 5.6 Hz, 1H), 7.04 (dd, *J* = 5.1, 3.7 Hz, 1H), 7.30 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.42 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.75 (s, 1H), 9.39 (s, 1H); ^{13}C NMR δ 20.5, 50.6, 20.8, 63.4, 70.5, 73.0, 80.5, 87.3, 111.3, 125.4, 125.9,

127.3, 133.1, 134.2, 149.6, 160.9, 169.8, 170.3; HRMS calcd for $C_{19}H_{21}N_2O_9S$ $[M + H]^+$ 453.0962, found 453.0966.

2',3',5'-Tri-*O*-acetyl-5-(methylthiophen-2-yl)uridine (105). Ttreatment of 2',3',5'-tri-*O*-acetyl-5-iodouridine (**97**, 69.5 mg, 0.14 mmol) with 2-methylthiophene (0.2 mL, 203 mg, 2.1 mmol) by procedure A (column chromatography; hexane/EtOAc, 6:4 → 5:5) gave **105** (35.9 mg, 55%): ^{1}H NMR δ 2.09 (s, 3H), 2.10 (s, 3H), 2.14 (s, 3H), 2.47 (d, J = 0.7 Hz, 3H), 4.33-4.45 (m, 3H), 5.34-5.40 (m, 2H), 6.16 (d, J = 5.4 Hz, 1H), 6.68 (dd, J = 3.6, 1.1 Hz, 1H), 7.21 (d, J = 3.6 Hz, 1H), 7.65 (s, 1H), 9.18 (s, 1H); ^{13}C NMR δ 15.3, 20.5, 20.7, 20.9, 63.4, 70.5, 72.9, 80.5, 87.2, 111.6, 125.56, 125.57, 130.7, 133.5, 140.6, 149.6, 160.9, 169.76, 169.78, 170.4; HRMS calcd for $C_{20}H_{23}N_2O_9S$ $[M + H]^+$ 467.1119, found 467.1108.

1-(*β*-D-Arabinofuranosyl)-5-(fur-2-yl)uracil (106). Method A. Treatment of 1-(*β*-D-arabinofuranosyl)-5-iodouracil[213] (**98**, 52 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure A (column chromatography; CH_2Cl_2/MeOH, 15:1 → 10:1) gave **106** (30.5 mg, 70%) as off-white solid. The analytical sample was obtained by precipitation from minimum amount of MeOH:CH_2Cl_2 (1:1, v/v) with hexane: ^{1}H NMR (DMSO-d_6) δ 3.60 (dt, J = 10.3, 5.0 Hz, 1H), 3.68 (dt, J = 10.3, 5.1 Hz, 1H), 3.78 ("q", J = 4.6 Hz, 1H), 3.97 (dd, J = 7.3, 3.8 Hz, 1H), 4.04 (dt, J = 7.8, 3.9 Hz, 1H), 5.09 (t, J = 5.2 Hz, 1H), 5.51 (d, J = 4.4 Hz, 1H), 5.64 (d, J = 5.0 Hz, 1H), 6.07 (d, J = 4.3 Hz, 1H), 6.52 (dd, J = 3.3, 1.9 Hz, 1H), 6.85 (dd, J = 3.3, 0.5 Hz, 1H), 7.63 (dd, J = 1.8, 0.7 Hz, 1H), 8.07 (s, 1H), 11.65 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 60.7, 75.3, 75.6, 84.8, 85.3, 104.0, 107.6, 111.5, 136.5, 141.4, 146.5, 149.4, 160.2. HRMS calcd for $C_{13}H_{15}N_2O_7$ $[M + H]^+$ 311.0784, found 311.0811.

Method B. Compound **101** (43.6 mg, 0.10 mmol) was dissolved in NH_3/MeOH (3 mL) at 0 ^{o}C (ice bath), and the resulting solution was stirred overnight. Volatiles were removed under the reduced pressure and the residue was column chromatographed (CH_2Cl_2/MeOH, 15:1 → 10:1) to give **106** (27.9 mg, 90%) with the spectroscopic data as above.

5-(Fur-2-yl)-2'-deoxyuridine (107). Method A. Treatment of 2'-deoxy-5-iodourdine[212] (**99**, 49.6 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure A (column chromatography; CH_2Cl_2/MeOH, 15:1 → 10:1) gave **107** (30.1 mg, 73%) as yellow solid: ^{1}H NMR (DMSO-d_6) δ 2.18 (dd, J = 6.6, 4.8 Hz, 2H), 3.61 (dd, J = 8.8, 5.0 Hz, 2H), 3.84 (q, J = 3.3 Hz, 1H), 4.28 ("quint", J = 4.0 Hz, 1H), 5.08 (t, J = 4.8 Hz, 1H), 5.27 (d, J = 4.2 Hz, 1H), 6.22 (t, J = 6.7 Hz, 1H), 6.52 (dd, J = 3.3, 1.8 Hz, 1H), 6.85 (dd, J = 3.3, 0.5 Hz, 1H), 7.61 (dd, J = 1.8, 0.7 Hz, 1H), 8.33 (s, 1H), 11.62 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 40.1, 61.1, 70.4, 84.7, 87.6, 105.6, 107.8, 111.5, 134.6, 141.5, 146.4, 149.4, 160.1. HRMS calcd for $C_{13}H_{13}N_2O_6$ $[M - H]^-$ 293.0779, found 293.0788.

Method B. Treatment of **102** (38 mg, 0.10 mmol) with NH_3/MeOH, as described for **106** (Method B), gave **107** (26 mg, 90%) with the spectroscopic data as above.

5-(Fur-2-yl)uridine (108). Method A. Treatment of 5-iodouridine[212] (**100**, 52 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure A (column chromatography; CH_2Cl_2/MeOH, 15:1 → 10:1) gave **108** (34.7 mg, 80%) as off-white solid. Precipitation of **108** from MeOH:CH_2Cl_2 (1:1, v/v) solution with hexane gave analytical sample of **108**: UV (MeOH) λ_{max} = 314 nm; ^{1}H NMR (DMSO-d_6) δ 3.60 (ddd, J = 11.9, 4.6, 2.9 Hz, 1 H), 3.68 (ddd, J = 11.9, 4.7, 2.9 Hz, 1H), 3.90 ("q", J = 3.2 Hz, 1H), 4.02 ("q", J = 4.5 Hz, 1H), 4.12 ("q", J = 5.1 Hz, 1H), 5.11 (d, J = 5.0 Hz, 1H), 5.21 (t, J = 4.7 Hz, 1H), 5.43 (d, J = 5.5 Hz, 1H), 5.87 (d, J = 5.1 Hz, 1H), 6.52 (dd, J = 3.3, 1.8 Hz, 1H), 6.86 (dd, J = 3.3, 0.6 Hz, 1H), 7.60 (dd, J = 1.8, 0.7 Hz, 1H), 8.42 (s, 1H), 11.64 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 60.6, 69.9, 74.0, 85.0, 88.2, 105.7, 108.0, 111.6, 134.9, 141.6, 146.4, 149.7, 160.1; HRMS calcd for $C_{13}H_{13}N_2O_7$ $[M - H]^-$ 309.0728, found 309.0734.

Analogous treatment of **100** (310 mg, 1.0 mmol) with furan (1.1 mL, 1.03 g, 15 mmol) by procedure A gave **108** (273 mg, 88%).

Method B. Treatment of **100** (52 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure B (column chromatography; CH_2Cl_2/MeOH, 15:1 → 10:1) gave **108** (10 mg, 23% yield) with the spectroscopic data as above.

5-(Thiophen-2-yl)uridine (109). Method A. Treatment of 5-iodouridine (**100**, 52 mg, 0.14 mmol) with thiophene (0.2 mL, 210 mg, 2.5 mmol) by procedure A (column chromatography; CH_2Cl_2/MeOH, 15:1 → 10:1) gave **109** (44.7 mg, 98%) as off-white solid. Precipitation of **109** from MeOH:CH_2Cl_2 (1:1, v/v) solution with hexane gave analytical sample of **109**: UV (MeOH) λ_{max} = 318 nm; ^{1}H NMR (DMSO-d_6) δ 3.64 (ddd, *J* = 12.0, 4.4, 2.3 Hz, 1H), 3.76 (ddd, *J* = 12.0, 4.7, 2.8 Hz, 1H), 3.92 (dt, *J* = 4.8, 2.7 Hz, 1H), 4.06 ("q", *J* = 5.1 Hz, 1H), 4.13 ("q", *J* = 4.8 Hz, 1H), 5.09 (d, *J* = 5.5 Hz, 1H), 5.42 (t, *J* = 4.6 Hz, 1H), 5.46 (d, *J* = 5.3 Hz, 1H), 5.84 (d, *J* = 4.2 Hz, 1H), 7.05 (dd, *J* = 5.1, 3.7 Hz, 1H), 7.40 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.46 (dd, *J* = 5.1, 1.1 Hz, 1H), 8.65 (s, 1H), 11.69 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 60.2, 69.4, 74.3, 84.7, 88.7, 108.3, 122.5, 125.7, 126.4, 133.9, 135.7, 149.6, 161.3; HRMS calcd for $C_{13}H_{14}N_2NaO_6S$ $[M + Na]^+$ 349.0465, found 349.0465.

Method B. Treatment of **100** (52 mg, 0.14 mmol) with thiophene (0.2 mL, 210 mg, 2.5 mmol) by procedure B (column chromatography; CH_2Cl_2/MeOH, 15:1 → 10:1) gave **109** (8 mg, 17% yield) with the spectroscopic data as above.

5-(5-Methylthiophen-2-yl)uridine (110). Treatment of 5-iodouridine (**100**, 52 mg, 0.14 mmol) with 2-methylthiophene (0.2 mL, 203 mg, 2.1 mmol) by procedure A (column chromatography; CH_2Cl_2/MeOH, 15:1 → 10:1) gave **110** (36.5 mg, 76%) as off-white solid. Precipitation of **110** from MeOH:CH_2Cl_2 (1:1, v/v) solution with hexane gave analytical sample of **110**: ^{1}H NMR (DMSO-d_6) δ 2.42 (s, 3H), 3.63 (ddd, *J* = 12.0, 4.4, 2.3 Hz, 1H), 3.74 (ddd, *J* = 12.0, 4.6, 2.8 Hz, 1H), 3.91 ("dt", *J* = 4.8, 2.4 Hz, 1H), 4.05 ("q", *J* = 5.0 Hz, 1H), 4.11 ("q", *J* = 4.8 Hz, 1H), 5.08 (d, *J* = 5.4 Hz, 1H), 5.38 (t, *J* = 4.6 Hz, 1H), 5.44 (d, *J* = 5.4 Hz, 1H), 5.83 (d, *J* = 4.4 Hz, 1H), 6.72 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.19 (d, *J* = 3.6 Hz, 1H), 8.53 (s, 1H), 11.63 (s, 1H);

^{13}C NMR (DMSO-d_6) δ 14.7, 60.2, 69.4, 74.2, 84.7, 88.6, 108.6, 122.6, 124.7, 131.5, 134.9, 138.8, 149.5, 161.3; HRMS calcd for $C_{14}H_{17}N_2O_6S$ $[M + H]^+$ 341.0802, found 341.0803.

5-(Pyrrol-2-yl)uridine (111). Treatment of 5-iodouridine (**100**, 52 mg, 0.14 mmol) with pyrrole (0.2 mL, 193 mg, 2.88 mmol) by procedure A [reaction was carried out in a flask covered in aluminum foil under N_2 atmosphere; column chromatography (CH_2Cl_2/MeOH, 15:1 → 10:1)] gave **111** (19.4 mg, 45%) as brownish amorphous powder. This material is stable when stored in refrigerator under the inert condition for at least 1 month: ^{1}H NMR (DMSO-d_6) δ 3.60 (ddd, J = 12.0, 4.4, 3.3 Hz, 1H), 3.70 (ddd, J = 11.8, 4.6, 3.5 Hz, 1H), 3.87 ("q", J = 3.5 Hz, 1H), 4.03 ("q", J = 4.7 Hz, 1H), 4.14 ("q", J = 5.2 Hz, 1H), 5.10 (d, J = 5.2 Hz, 1H), 5.27 (t, J = 4.8 Hz, 1H), 5.42 (d, J = 5.6 Hz, 1H), 5.83 (d, J = 5.1 Hz, 1H), 6.03 (dd, J = 5.8, 2.6 Hz, 1H), 6.39 (dd, J = 4.5, 2.7 Hz, 1H), 6.76 (dd, J = 4.1, 2.5 Hz, 1H), 8.22 (s, 1H), 10.85 (s, 1H), 11.54 (bs, 1H); ^{13}C NMR (DMSO-d_6) δ 60.6, 69.6, 73.6, 84.7, 88.2, 105.5, 107.2, 108.0, 118.2, 123.8, 133.6, 149.7, 162.0; HRMS calcd for $C_{13}H_{16}N_3O_6$ $[M + H]^+$ 310.1034, found 310.1034.

2',3',5'-Tri-*O*-acetylcytidine hydrochloride. Cytidine (**112**, 486 mg, 2 mmol) was dissolved in the mixture of $CH_3COOH/CHCl_3$ (9 mL, 1:2, v/v), followed by the addition of acetyl chloride (0.6 mL). The resulting clear solution was stirred at ambient temperature for 40h. Volatiles was removed under the reduced pressure and the oily residue was column chromatographed ($CHCl_3$:MeOH = 9:1) to give product **112** as white precipitate (776 mg, 96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.05 (s, 3H), 2.06 (s, 3H), 2.07 (s, 3H), 4.18-4.37 (m, 3H), 5.32 (t, J = 6.0 Hz, 1H), 5.48 (dd, J = 6.1, 4.4 Hz, 1H), 5.90 (d, J = 4.3 Hz, 1H), 6.20 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 7.8 Hz, 1H), 8.70 (s, 1H), 9.70 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 20.27, 20.31, 20.6, 62.8, 69.4, 72.4, 79.3, 89.2, 94.8, 144.7, 148.1, 160.6, 169.3, 170.1.

2',3',5'-Tri-*O*-acetyl-5-iodocytidine (113). 2',3',5'-Tri-*O*-acetylcytidine hydrochloride (405 mg, 1 mmol) was dissolved in the mixture of CCl_4/CH_3COOH (8 mL, 1:1, v/v), followed by the addition of I_2 (152 mg, 0.6 mmol) and HIO_3 (153 mg, 0.87 mmol). The resulting red solution was

stirred at 40 ^{o}C for 12 h. After cool down to ambient temperature, reaction mixture was washed with water and saturated $NaHCO_3$. The color of iodine was reduced with 5% of $NaHSO_3$, and the organic was dried over the Na_2SO_4. Volatiles was removed under the reduced pressure and the residue was column chromatographed ($CHCl_3$:MeOH = 95:5) to give product **113** as white precipitate (361 mg, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.05 (s, 3H), 2.06 (s, 3H), 2.07 (s, 3H), 4.13-4.27 (m, 2H), 4.27-4.37 (m, 1H), 5.30-5.39 (m, 1H), 5.45 (dd, *J* = 6.4, 4.4 Hz, 1H), 5.80 (d, *J* = 4.3 Hz, 1H), 6.83 (s, 1H), 8.04 (s, 1H), 8.07 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 20.3, 20.7, 48.6, 57.8, 63.0, 69.7, 72.5, 78.9, 98.8, 148.6, 153.6, 164.1, 169.4, 170.0.

3-(Fur-2-yl)pyridin-2(1*H*)-one (120). Method A. Treatment of **119** (24.36 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure A (14 equiv. of TBAF) gave **120** (7 mg, 31%) followed by **119** (11 mg, 45%). Compound **120** had: UV (MeOH) λ_{max} = 332 nm; ^{1}H NMR (CD_3CN) δ 6.33 (t, *J* = 6.9 Hz, 1H), 6.53 (dd, *J* = 3.3, 1.8 Hz, 1H), 7.27-7.29 (m, 2H), 7.54 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.89 (dd, *J* = 7.1, 2.0 Hz, 1H), 10.33 (s, 1H); ^{13}C NMR (CD_3CN) δ 106.5, 111.1, 112.7, 122.2, 133.7, 134.6, 143.0, 150.4, 160.2; HRMS calcd for $C_9H_8NO_2$ $[M + H]^+$ 162.0550, found 162.0553.

Method B. Treatment of **119** (24.36 mg, 0.14 mmol) with furan (0.2 mL, 187 mg, 2.75 mmol) by procedure B gave **120** (15.3 mg, 68% yield) with the spectroscopic data as above.

3-(Thiophen-2-yl)pyridin-2(1*H*)-one (121). Treatment of **119** (24.36 mg, 0.14 mmol) with thiophene (0.2 mL, 210 mg, 2.5 mmol) by procedure A (14 equiv. of TBAF) gave **121** (7 mg, 27%) followed by **119** (12 mg, 49%). Compound **22** had: UV (MeOH) λ_{max} = 346 nm; ^{1}H NMR (CD_3CN) δ 6.32 (dd, *J* = 7.0, 6.6 Hz, 1H), 7.09 (dd, *J* = 5.1, 3.8 Hz, 1H), 7.28 (dd, *J* = 6.5, 1.9 Hz, 1H), 7.40 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.67 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.97 (dd, *J* = 7.1, 1.9 Hz, 1H), 9.98 (s, 1H); ^{13}C NMR (CD_3CN) δ 105.4, 123.6, 126.2, 126.4, 128.2, 129.2, 132.4, 134.5, 159.6; HRMS calcd for C_9H_8NOS $[M + H]^+$ 178.0321, found 178.0320.

1-*N*-Benzyl-6-(4-methoxyphenyl)uracil (122). AgCl (60 mg, 0.42 mmol), $Pd(OAc)_2$ (3.2 mg, 0.014 mmol) and tetrabutylammonium bromide (TBABr, 67.7 mg, 0.21 mmol) were added to a stirred solution of 1-*N*-benzyluracil[210] (**92**, 28.3 mg, 0.14 mmol) and 4-iodoanisole (98.3 mg, 0.42 mmol) in DMSO (1 mL) under the N_2 atmosphere at ambient temperature. The resulting suspension was stirred for 16 h at 100 ^oC (oil bath). Volatiles were evaporated, and the oily residue was dissolved in EtOAc and filtrated through Whatman GF/A filter paper. The filtrate was column chromatographed (hexane/EtOAc, 5:5 → 4:6) to give *p*-**91d** (10 mg, 23%) and **122** (14 mg, 33%) followed by **92** (12 mg, 41%). Compound **23** had: ^1H NMR δ 3.84 (s, 1H), 4.96 (s, 1H), 5.65 (s, 1H), 6.87 (d, J = 8.6 Hz, 1H), 6.90-6.95 (m, 1H), 7.08 (d, J = 8.5 Hz, 1H), 7.19-7.26 (m, 1H), 9.73 (s, 1H); ^{13}C NMR δ 48.6, 55.5, 104.1, 114.2, 125.3, 127.0, 127.7, 128.7, 129.5, 136.5, 152.3, 157.3, 161.0, 163.1; GC-MS (t_R 24.77 min.) *m/z* 308 (70, M^+), 91 (100); HRMS calcd for $C_{18}H_{17}N_2O_3$ $[M + H]^+$ 309.1234, found 309.1229.

1-(2,3,5-Tri-*O*-acetyl-β-D-arabinofuranosyl)-5-(*E/Z*)-[2-(triphenylgermyl)ethenyl]uracil (124a) and 1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-5-[2-(triphenylgermyl)acetyl]uracil (126a). Method A. *ACCN-induced hydrogermylation***.** Nucleoside **123**[161] (50 mg, 0.13 mmol) was added to freshly distilled toluene (6 mL) and the suspension was stirred and degassed with N_2 for 30 min. The mixture was then pre-heated at 80 °C and Ph_3GeH (50 mg, 0.16 mmol) was added followed by ACCN (4 mg, 0.02 mmol). The temperature was increased to 90 °C and the solution was stirred until **123** was completely consumed (TLC; 14 h). The volatiles were removed in vacuo and the oily residue was chromatographed (hexane/EtOAc, 2:3) to give a separable mixture of *Z*-**124a** (43 mg, 47%) and **126a** (10.5 mg, 12%). Compound *Z*-**124a** had: ^1H NMR δ 1.99 (s, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 3.70 (dd, J = 13.7, 7.7 Hz, 1H), 3.91-3.98 (m, 2H), 4.97 (dd, J = 3.2, 2.0 Hz, 1H), 5.27 (dd, J = 4.1, 1.9 Hz, 1H), 5.71 (d, J = 4.1 Hz, 1H), 6.56 (d, J = 13.5 Hz, 1H), 7.08 (d, J = 1.0 Hz, 1H), 7.36 (m, 10H), 7.52 (m, 6H), 8.30 (br. s, 1H); ^{13}C NMR δ 20.4, 20.6, 20.7, 62.3, 74.6, 76.1, 79.8, 84.4, 113.4, 128.4, 129.1, 131.7, 134.8, 136.38, 136.41, 138.2,

148.6, 161.3, 168.5, 169.4, 170.2; MS *m/z* 701 (100, MH^+, ^{74}Ge), 699 (71, MH^+, ^{72}Ge) 698 (51, MH^+, ^{70}Ge); Anal. Calcd for $C_{35}H_{34}GeN_2O_9$ (699.29): C, 60.11; H, 4.90; N, 4.01. Found: C, 59.63; H, 4.92; N, 4.00.

^1H NMR of the crude reaction mixture showed also a presence (~5%) of the *E*-**124a** with the characteristic peaks at δ 6.31 (d, *J* = 4.0 Hz, H1'), 6.69 (d, *J* = 18.8 Hz, CH).

Compound **126a** had: ^1H NMR δ 1.90 (s, 3H), 2.14 (s, 3H), 2.15 (s, 3H), 3.48 (d, *J* = 9.3 Hz, 1H), 4.16-4.19 (m, 1H), 4.17 (d, *J* = 9.3 Hz, 1H), 4.33 (dd, *J* = 12.1, 4.5 Hz, 1H), 4.44 (dd, *J* = 12.1, 4.9 Hz, 1H), 5.12 (dd, *J* = 3.3, 1.6 Hz, 1H), 5.33 (dd, *J* = 4.1, 1.6 Hz, 1H), 6.23 (d, *J* = 4.1 Hz, 1H), 7.21-7.37 (m, 9H), 7.50-7.55 (m, 6H), 8.08 (s, 1H), 8.49 (br. s, 1H); ^{13}C NMR δ 20.4, 20.7, 20.8, 33.0, 62.4, 74.6, 76.6, 80.8, 83.9, 113.3, 128.4, 129.5, 135.1, 135.3, 146.6, 148.8, 160.4, 168.8, 169.6, 170.8, 194.2; HRMS calcd for $C_{35}H_{34}{}^{74}GeN_2NaO_{10}$ $[M + Na]^+$ 739.1323, found 739.1311.

Treatment of **123** (100 mg, 0.26 mmol) and Ph_3GeH (94 mg, 0.30 mmol) in toluene without ACCN (85 °C, 14 h; column chromatography (50 → 60% EtOAc/hexane) gave *E/Z*-**124a** (110 mg, 60%; *E/Z,* 3:97) and **126a** (26 mg, 15%).

Method B. *Et_3B-induced hydrogermylation.* A solution of Et_3B in THF (1M; 140 μL, 0.14 mmol) was added to a stirred solution of **123** (50 mg, 0.127 mmol) and Ph_3GeH (43 mg, 0.14 mmol) in dry THF (5 mL) at -78 °C placed in a screw-capped glass tube. The resulting mixture was stirred for 3 hours at -78 °C until TLC showed appearance of a less polar spot. The reaction mixture was slowly warmed up to -60 °C and was stirred for another 1.5 h. The volatiles were evaporated and the resulting oil was column chromatographed (hexane/EtOAc, 2:3) to give *Z*-**124a** (49 mg, 55%).

Treatment of **123** (49 mg, 0.12 mmol) with Ph_3GeH (42 mg, 0.14 mmol) by Method B (0 °C/6 h) gave a mixture of *Z*-**124a** and **126a** (39 mg, ~46%; **124a**/**126a**, ~59:41, ^1H NMR). Recrystallization (hexane/Et_2O) gave *Z*-**124a** as a white powder (22 mg, 25% from **123**).

Method C. *Pd-catalyzed hydrogermylation.* Ph_3GeH (59 mg, 0.2 mmol) and $Pd(PPh_3)_4$ (8 mg, 0.08) was added to stirred suspension of **123** (70 mg, 0.18 mmol) in THF (3 mL) in a flamed dried round bottle flask at ambient temperature under N_2. After 5 h, the volatiles were evaporated *in vacuo* and the resulting oil was column chromatographed (hexane/EtOAc, 1:1) to give inseparable mixture of the *E*-isomer of **124** and the corresponding regioisomer resulting from the addition to α-carbon (90 mg, 73%; *E*-**124**/α-addition product, 3:2; ^{1}H NMR;): MS (ESI) *m*/*z* 701 (100, MH^+, ^{74}Ge), 699 (70, MH^+, ^{72}Ge), 697 (50, MH^+, ^{70}Ge). Compound *E*-**124a** had: ^{1}H NMR δ 1.88 (s, 3H), 1.98 (s, 3H), 2.14 (s, 3H), 4.23 (m, 2H), 4.35-4.39 (m, 1H), 5.09 (dd, *J*= 3.4, 1.5 Hz, 1H), 5.43 (dd, *J*= 3.9, 1.5 Hz, 1H), 6.31 (d, *J*= 4.0 Hz, 1H), 6.69 (d, *J*= 18.8 Hz, 1H), 7.60 (s, 1H), 7.33-7.40 (m, 10H), 7.51-7.55 (m, 6H), 9.29 (br. s, 1H). The α-addition product 1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-5-[1-(triphenylgermyl)ethenyl] uracil had: ^{1}H NMR δ 1.80 (s, 3H), 2.07 (s, 3H), 2.11 (s, 3H), 4.00-4.23 (m, 2H), 4.45-4.49 (m, 1H), 4.98 (dd, *J*= 3.5, 1.9 Hz, 1H), 5.35 (dd, *J*= 4.1, 1.5 Hz, 1H), 5.72 (d, *J*= 2.0 Hz, 1H), 6.17 (d, *J*= 4.1 Hz, 1H), 6.41 (d, *J*= 2.0 Hz, 1H), 7.33-7.40 (m, 9H), 7.42 (s, 1H), 7.51-7.55 (m, 6H), 8.98 (br. s, 1H).

1-(2,3,5-Tri-*O*-acetyl-β-D-arabinofuranosyl)-5-(*E*/*Z*)-[2-(trimethylgermyl)ethenyl]uracil (124b). Nucleoside **123** (50 mg, 0.13 mmol) was treated with Me_3GeH (30 mg, 29.6 μL, 0.25 mmol) in dry THF (5 mL) as described in Method B (with injection of Me_3GeH into the reaction mixture *via* syringe and progressive warming from 0 °C to ambient temperature) for 14 h. The volatiles were removed under reduced pressure and the residue was column chromatographed (hexane/EtOAc, 2:3) to give *E*/*Z*-**124b** (27 mg, 40%; *E*/*Z,* 13:87). ^{1}H NMR δ 0.26 (s, 7.83H), 0.28 (s, 1.17H), 2.02 (s, 3H), 2.12 (s, 2.61H), 2.15 (s, 0.39H), 2.16 (s, 2.61H), 2.17 (s, 0.39H), 4.19-4.25 (m, 1H), 4.34 (dd, *J*= 11.9, 6.2 Hz, 0.87H), 4.37-4.45 (m, 0.13H), 4.44 (dd, *J*= 11.9, 4.2 Hz, 0.87H), 4.52 (dd, *J*= 11.9, 6.2 Hz, 0.13H), 5.11 (dd, *J*= 3.8, 1.4 Hz, 0.87H), 5.15 (dd, *J*= 3.4, 1.6 Hz, 0.13H), 5.44-5.48 (m, 1H), 6.10 (d, *J*= 13.8 Hz, 0.87H), 6.24 (d, *J*= 3.8 Hz, 0.87H), 6.33 (d, *J*= 4.0 Hz, 0.13H), 6.60 (d, *J*= 18.9 Hz, 0.13H), 6.80 (d, *J*= 19.0 Hz, 0.13H), 6.98 (dd, *J*

= 13.8, 1.0 Hz, 0.87H), 7.45 (d, *J*= 1.0 Hz, 0.87, 1H), 7.59 (s, 0.13H), 8.97 (br. s, 0.13H), 9.09 (br. s, 0.87H); ^{13}C NMR δ -1.7, -0.2, 20.5, 20.6, 20.8, 20.87, 20.92, 62.7, 63.2, 74.7, 74.8, 76.4, 76.5, 80.4, 80.8, 84.6, 112.9, 114.2, 132.1, 133.6, 134.3, 136.1, 136.4, 137.6, 149.2, 149.6, 161.8, 162.2, 168.6, 168.7, 169.7, 169.8, 170.5; HRMS calcd for $C_{20}H_{28}{}^{74}GeNaN_2O_9$ $[M + Na]^+$ 537.0899, found 537.0888.

1-(2,3,5-Tri-*O*-acetyl-*β*-D-arabinofuranosyl)-5-(*Z*)-[2-(tris(trimethylsilyl)germyl)ethenyl] uracil (124c). Nitrogen gas was bubbled through a heterogeneous mixture of **123** (127 mg, 0.32 mmol) in dry toluene (10 mL) for 30 min. The suspension was pre-heated up to 90 °C (~5 min) and $(Me_3Si)_3GeH$ (115 mg, 123 μL, 0.39 mmol) was added *via* syringe in one portion followed by ACCN (8 mg, 0.04 mmol) dissolved in degassed toluene (1 mL). The solution was heated at 95 ^{o}C over 30 min as TLC revealed total consumption of **123**. The mixture was cooled down to ambient temperature. Volatiles were evaporated and the residue was column chromatographed (hexane/EtOAc, 3:2) to give *Z*-**124c** (152 mg, 68%): ^{1}H NMR δ 0.20 (s, 27H), 2.01 (s, 3H), 2.10 (s, 3H), 2.14 (s, 3H), 4.17-4.24 (m, 1H), 4.34 (dd, *J*= 12.0, 5.5 Hz, 1H), 4.38 (dd, *J*= 12.0, 5.2 Hz, 1H), 5.14 (dd, *J*= 3.8, 1.6 Hz, 1H), 5.47 (dd, *J*= 3.8, 1.7 Hz, 1H), 6.16 (d, *J*= 3.9 Hz, 1H), 6.28 (d, *J*= 13.5 Hz, 1H), 6.90 (dd, *J*= 13.5, 1.4 Hz, 1H), 7.29 (d, *J*= 1.4 Hz,1H), 8.27 (br. s, 1H); ^{13}C NMR δ 1.95, 20.7, 20.9, 21.0, 63.1, 75.0, 76.5, 80.7, 85.4, 116.1, 133.9, 134.1, 136.2, 149.6, 162.0, 168.9, 169.7, 170.6; HRMS calcd for $C_{26}H_{47}{}^{74}GeN_2O_9Si_3$ $[M + H]^+$ 689.1801, found 689.1798.

^{1}H NMR of the crude reaction mixture showed 4:96 mixture of *E/Z* isomers of **124c**. The *E*-**124c** had the characteristic peaks on the ^{1}H NMR spectrum at: δ 6.36 (d, *J*= 3.5 Hz, H1'), 6.63 (d, *J*= 18.7 Hz, CH), 6.86 (d, *J*= 18.5 Hz, CH).

1-(*β*-D-Arabinofuranosyl)-5-(*Z*)-[2-(triphenylgermyl)ethenyl]uracil (125a). A saturated solution of $MeOH/NH_3$ (2 mL) was added to a suspension of *Z*-**124a** (40.0 mg, 0.057 mmol) in

MeOH (2 mL) 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. Volatiles were evaporated under vacuum and the residue was column chromatographed (EtOAc/MeOH, 98:2) to give *Z*-**125a** (28.2 mg, 86%). ^{1}H NMR (MeOH-d_4) δ 3.28 (dd, *J* = 11.3, 4.0 Hz, 1H), 3.37 (dd, *J* = 11.3, 5.6 Hz, 1H), 3.76 (ddd, *J* = 5.8, 4.1, 2.1 Hz, 1H), 3.98-4.02 (m, 2H), 5.59 (d, *J* = 3.3 Hz, 1H), 6.50 (d, *J* = 13.2 Hz, 1H), 7.30 (d, *J* = 13.3 Hz, 1H), 7.35 (m, 10H), 7.51 (m, 6H); ^{13}C NMR (MeOH-d_4) δ 62.6, 76.6, 78.4, 87.0, 88.3, 113.8, 129.3, 130.0, 131.5, 136.0, 138.2, 139.9, 140.7, 151.3, 165.0; HRMS calcd for $C_{29}H_{28}{}^{74}GeNaN_2O_6$ $[M + Na]^+$ 597.1051, found 597.1076. Anal. Calcd for $C_{29}H_{28}GeN_2O_6$• CH_3OH•H_2O (623.24): C, 57.81; H, 5.50; N, 4.49. Found: C, 57.84; H, 5.41; N, 4.69.

5-Ethynyl-2',3',5'-tri-*O*-*p*-toluoyluridine (127). The *p*-toluoyl chloride (86 µL, 101 mg, 0.65 mmol) was added to a stirred solution of 5-ethynyluridine[214] (50 mg, 0.19 mmol) in the dry pyridine (5 mL). After 24 h, the volatiles were evaporated and the residue was partitioned between $NaHCO_3$/H_2O//$CHCl_3$. The organic layer was washed with diluted HCl/H_2O, $NaHCO_3$/H_2O, brine, and was dried ($MgSO_4$), and evaporated. The residue was column chromatographed (hexane/EtOAc, 7:3 → 6:4) to give **127** (85 mg, 73%): ^{1}H NMR δ 2.40 (s, 3H), 2.44 (s, 6H, 2 x Me), 2.94 (s, 1H), 4.69-4.76 (m, 2H), 4.78-4.84 (m, 1H), 5.70 ("t", *J* = 6.0 Hz, 1H), 5.84 (dd, *J* = 5.9, 3.6 Hz, 1H, H3), 6.37 (d, *J* = 6.1 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.81 (s, 1H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.91 (d, *J* = 8.2 Hz, 2H), 8.02 (d, *J* = 8.2 Hz, 2H), 8.18 (s, 1H); ^{13}C NMR δ 21.8, 21.9, 63.8, 71.5, 73.76, 73.77, 81.4, 82.5, 87.9, 100.6, 125.7, 126.1, 126.5, 129.4, 129.5, 129.7, 129.9, 130.1, 130.2, 143.2, 144.6, 144.8, 144.9, 148.8, 160.6, 165.4, 165.5, 166.3; HRMS calcd for $C_{35}H_{31}N_2O_9$ $[M + H]^+$ 623.2024, found 623.2033.

5-(*Z*)-[2-(Triphenylgermyl)ethenyl]-2',3',5'-tri-*O*-*p*-toluoyluridine (129a) and 5-[2-(triphenylgermyl)acetyl]-2',3',5'-tri-*O*-*p*-toluoyluridine (133a). Nucleoside **127** (49 mg, 0.08

mmol; prepared by treatment of 5-ethynyluridine[214] with *para*-toluoyl chloride in pyridine as described in SI) was treated with Ph_3GeH (26 mg, 0.085 mmol) in dry THF (5 mL) as described in Method B. After 6 h at -78 °C, TLC revealed slow progression towards product. The reaction mixture was slowly warmed to 0 °C until TLC showed approximately 95% consumption of the substrate **127** (~24 h). The volatiles were removed under vacuum and the residue was column chromatographed (hexane/EtOAc, 1:1) to give a separable mixture of *Z*-**129a** (29 mg, 40%) and **133a** (10 mg, 13%). Compound *Z*-**129a** had: ^{1}H NMR δ 2.40 (s, 6H), 2.42 (s, 3H), 4.34 (dd, *J*= 12.2, 5.4 Hz, 1H), 4.40 (dd, *J*= 12.2, 3.4 Hz, 1H), 4.47 (ddd, *J*= 5.8, 5.4, 3.5 Hz, 1H), 5.38 (dd, *J* = 6.2, 4.5 Hz, 1H), 5.51 ("t", *J* = 6.0 Hz, 1H), 5.52 (d, *J*= 4.4 Hz, 1H), 6.50 (d, *J* = 13.6 Hz, 1H), 7.11 (d, *J* = 0.9 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.22 (dd, *J*= 13.5, 0.9 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.31-7.36 (m, 9H), 7.50-7.55 (m, 6H), 7.80 (d, *J* = 8.2 Hz, 4H), 7.96 (d, *J* = 8.2 Hz, 2H), 8.09 (br. s, 1H); ^{13}C NMR δ 21.67, 21.69, 21.72, 63.5, 70.5, 73.6, 79.9, 89.8, 115.0, 125.9, 126.0, 126.7, 128.5, 129.1, 129.2, 129.3, 129.7, 129.8, 129.9, 131.4, 134.7, 136.6, 137.0, 138.2, 144.2, 144.4, 144.5, 148.8, 161.4, 165.0, 165.1, 166.1; HRMS calcd for $C_{53}H_{46}{}^{74}GeN_2NaO_9$ $[M + Na]^+$ 951.2307, found 951.2315.

Compound **133a** had: UV (MeOH) λ_{max} = 282 nm; ^{1}H NMR δ 2.35 (s, 3H), 2.40 (s, 3H), 2.42 (s, 3H), 3.76 (d, *J*= 9.0 Hz, 1H), 3.87 (d, *J*= 9.0 Hz, 1H), 4.67-4.75 (m, 3H), 5.66 (dd, *J*= 5.9, 5.1 Hz, 1H), 5.83 ("t", *J* = 5.7 Hz, 1H), 6.01 (d, *J*= 5.0 Hz, 1H), 7.16-7.22 (m, 6H), 7.31-7.36 (m, 9H), 7.50-7.55 (m, 6H), 7.83 (d, *J*= 8.2 Hz, 2H), 7.87 (d, *J*= 8.2 Hz, 2H), 8.02 (d, *J* = 8.2 Hz, 2H), 8.05 (s, 1H); ^{13}C NMR δ 21.7, 33.0, 63.5, 71.0, 73.9, 80.9, 90.4, 113.7, 125.7, 126.0, 126.6, 128.2, 129.21, 129.24, 129.3, 129.4, 129.8, 129.9, 135.0, 135.1, 144.1, 144.5, 144.7, 146.6, 148.5, 160.2, 165.19, 165.21, 166.3, 193.3; HRMS calcd for $C_{53}H_{47}{}^{74}GeN_2O_{10}$ $[M + H]^+$ 945.2437, found 945.2456.

5-(*E*/*Z*)-[2-(Trimethylgermyl)ethenyl]-2',3',5'-tri-*O*-*p*-toluoyluridine (129b). Nucleoside **127** (50.0 mg, 0.08 mmol) was treated with Me_3GeH (19.0 mg, 18.8 μL 0.16 mmol) in dry THF

(5 mL) as described in 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 evaporated and the oily residue was column chromatographed (hexane/EtOAc, 3:2) to give *E*/*Z*-**129b** (24.5 mg, 41%; *E*/*Z,* 45:55). ^{1}H NMR δ 0.12 (s, 4.05H), 0.20 (s, 4.95H), 2.40, 2.43, 2.44 (singlets, 9H), 4.68-4.82 (m, 3H), 5.72 ("t", *J* = 6.0 Hz, 0.55H), 5.78 ("t", *J* = 6.3 Hz, 0.45H), 5.82 (dd, *J* = 6.1, 3.9 Hz, 0.55H), 5.88 (dd, *J* = 5.8, 2.8 Hz, 0.45H), 5.98 (d, *J* = 13.7 Hz, 0.55H), 6.34 (d, *J*= 5.9 Hz, 0.55H), 6.37 (d, *J* = 19.0 Hz, 0.45H), 6.50 (d, *J*= 6.8 Hz, 0.45H), 6.69 (d, *J*= 19.0 Hz, 0.45H), 6.72 (dd, *J*= 13.7, 1.0 Hz, 0.55H), 7.16-7.32 (m, 6H), 7.34 (d, *J* = 1.0 Hz, 0.55H), 7.54 (s, 0.45H), 7.83-8.04 (m, 6H), 8.24 (br. s, 0.45H), 8.27 (br. s, 0.55H); ^{13}C NMR δ -2.0, -0.2, 21.7, 63.7, 64.2, 71.1, 71.5, 73.45, 73.53, 80.7, 81.0, 86.9, 88.0, 114.4, 116.0, 125.65, 125.70, 125.96, 125.97, 126.3, 126.5, 129.24, 129.25, 129.29, 129.4, 129.6, 129.71, 129.73, 129.88, 129.9, 129.95, 130.0, 131.8, 134.1, 134.4, 135.1, 135.8, 138.7, 144.3, 144.5, 144.57, 144.63, 144.64, 144.7, 149.3, 149.7, 161.3, 161.7, 165.3, 165.35, 165.38, 165.5, 166.1; MS (ESI$^+$) *m*/*z* 765 (100, MNa^+, ^{74}Ge), 763 (71, MNa^+, ^{72}Ge), 762 (52 MNa^+, ^{70}Ge); Anal. Calcd for $C_{38}H_{40}GeN_2O_9 \bullet H_2O$ (759.39): C, 60.10; H, 5.57; N, 3.69. Found: C, 60.39; H, 5.38; N, 3.87.

5-(*E*/*Z*)-[2-(Trimethylgermyl)ethenyl]uridine (130b). A 0.1 N solution of MeONa in anhydrous MeOH (2 mL) was added to **129b** (18.8 mg, 0.025 mmol; *E*/*Z*, ~45:55) and the resulting mixture stirred for 6 h. An additional portion of 0.1N MeONa/MeOH was added (0.75 mL) and stirring was continued until the substrate **129b** was consumed (TLC). The reaction mixture was carefully neutralized by addition of Dowex 50WX2-200(H^+) to pH ~6.2. The mixture was filtered, and the resin washed with MeOH. The combined filtrate was evaporated under reduced pressure and the residue partitioned between Et_2O/H_2O. The organic layer was extensively washed with water. The combined aqueous layer was evaporated to yield *E*/*Z*-**130b** (7 mg, 71%; *E*/*Z*, ~40:60): ^{1}H NMR (D_2O) δ 0.27 (s, 5.4H), 0.32 (s, 3.6H), 3.84-3.91 (m, 1H), 3.95 (dd, *J*= 12.7, 2.7 Hz, 0.6H), 4.05 (dd, *J*= 12.9, 2.4 Hz, 0.4H), 4.18-4.24 (m, 1H), 4.29 ("t", *J* =

5.0 Hz, 0.6H), 4.34 ("t", *J* = 5.7 Hz, 0.4H), 4.39-4.44 (m, 1H), 6.00 (d, *J*= 3.8 Hz, 0.4H), 6.05 (d, *J*= 5.3 Hz, 0.6H), 6.36 (d, *J*= 13.6 Hz, 0.6H), 6.70 (d, *J*= 19.0 Hz, 0.4H), 6.83 (d, *J* =19.0 Hz, 0.4H), 6.93 (d, *J* =13.6 Hz, 0.6H), 7.77 (s, 0.6H), 8.20 (s, 0.4H); ^{13}C NMR (MeOH-d_4) δ -2.9, -1.2, 60.1, 61.0, 68.9, 69.8, 73.7, 74.1, 84.0, 84.7, 88.8, 89.7, 113.8, 115.7, 132.1, 134.1, 134.7, 137.6, 137.8, 140.8, 151.1, 151.6, 164.6, 165.3; HRMS calcd for $C_{14}H_{23}{}^{74}GeN_2O_6$ $[M + H]^+$ 389.0762, found 389.0775.

1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-*β*-D-*erythro*-pentofuranosyl)-5-(*Z*)-[2-(triphenylgermyl) ethenyl]uracil (131a) and 1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-*β*-D-*erythro*-pentofuranosyl)-5-[2-(triphenylgermyl)acetyl]uracil (134a). Nucleoside **128**[178] (44 mg, 0.09 mmol) was treated with Ph_3GeH (30 mg, 0.1 mmol) in dry THF (5 mL) as described in Method B. After 6 h at -78 °C TLC revealed slow progression towards product. Thus, the reaction mixture was slowly warmed to 0 °C until TLC showed approximately 95% consumption of the starting **128**. The volatiles were evaporated under vacuum and the residue was column chromatographed (hexane/EtOAc, 3:2) to give a separable mixture of *Z*-**131a** (43 mg, 61%) and **134a** (9 mg, 12%). Compound *Z*-**131a** had: ^{1}H NMR δ 1.68 (ddd, *J*= 14.9, 8.1, 7.0 Hz, 1H), 2.31 (ddd, *J*= 14.5, 5.7, 1.8 Hz, 1H), 2.41 (s, 3H), 2.45 (s, 3H), 4.16 (dd, *J*= 11.1, 3.5 Hz, 1H), 4.26-4.30 (m, 1H), 4.32 (dd, *J*= 11.1, 5.0 Hz, 1H), 5.15 ("dt", *J*= 6.8, 1.8 Hz, 1H), 5.84 (dd, *J*= 8.1, 5.7 Hz, 1H), 6.51 (d, *J*= 13.5 Hz, 1H), 7.11 (d, *J*= 1.0 Hz, 1H), 7.21-7.27 (m, 5H), 7.36-7.40 (m, 9H), 7.52-7.56 (m, 6H), 7.88 (d, *J*= 8.2 Hz, 2H), 7.91 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR δ 21.68, 21.72, 37.3, 63.9, 74.5, 82.3, 85.5, 114.8, 126.4, 126.7, 128.5, 129.2, 129.25, 129.28, 129.6, 129.8, 131.0, 134.8, 135.6, 136.6, 138.8, 144.2, 144.5, 149.3, 161.7, 165.8, 166.0; HRMS calcd for $C_{45}H_{41}{}^{74}GeN_2O_7$ $[M + H]^+$ 795.2120, found 795.2131.

Compound **134a** had: ^{1}H NMR δ 2.18-2.27 (m, 1H), 2.36 (s, 3H), 2.45 (s, 3H), 2.64 (ddd, *J*= 14.3, 5.7, 1.8 Hz, 1H), 3.81 (d, *J*= 9.1 Hz, 1H), 3.85 (d, *J*= 9.1 Hz, 1H), 4.53-4.60 (m, 2H), 4.74-4.80 (m, 1H), 5.54 ("d", *J* = 6.6 Hz, 1H), 6.16 (dd, *J*= 8.3, 5.7 Hz, 1H), 7.16 (d, *J*= 8.0 Hz, 2H),

7.28 (d, *J* = 8.1 Hz, 2H), 7.32-7.39 (m, 9H), 7.53-7.57 (m, 6H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.95 (d, *J* = 8.2 Hz, 2H), 8.15 (s, 1H); ^{13}C NMR δ 21.70, 21.73, 32.8, 38.4, 63.8, 74.5, 83.2, 86.2, 113.6, 126.3, 126.6, 128.2, 129.25, 129.28, 129.3, 129.8, 135.1, 135.2, 144.1, 144.5, 145.2, 148.8, 160.3, 165.8, 166.2, 193.5; HRMS calcd for $C_{45}H_{41}{}^{74}GeN_2O_8$ $[M + H]^+$ 811.2075, found 811.2063.

Note: Treatment of **128** (50 mg, 0.10 mmol) with Ph_3GeH (36 mg, 0.12 mmol) in toluene (4 mL) as described in Method A [DMF (0.2 mL) and water (25 μL, 25 mg, 1.4 mmol) were added to the pre-heated reaction mixture] gave partially separated *E*-**131a** (13 mg, 16%), **134a** (6.5 mg, 8%) and *Z*-**131a** (13 mg, 16%). Compound *E*-**131a** had characteristic peaks for *trans* vinylic protons at δ 6.63 (d, *J* = 18.8 Hz, 1H) and within the envelope of aromatic protons at δ 7.20-7.50 (Cosy).

1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-*β*-D-*erythro*-pentofuranosyl)-5-(*E*/*Z*)-[2-(trimethylgermyl) ethenyl]uracil (131b). Nucleoside **128**[178] (45.0 mg, 0.092 mmol) was treated with Me_3GeH (21.8 mg, 21.6 μL, 0.18 mmol) in dry THF (5 mL) as described in 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 evaporated under vacuum and the residue was column chromatographed (hexane/EtOAc, 1:1) to give *E*/*Z*-**131b** (16.5 mg, 35%; *E*/*Z,* 40:60): ^{1}H NMR δ 0.14 (s, 3.6H), 0.21 (s, 5.4H), 2.25-2.34 (m, 1H), 2.42, 2.43, 2.45 (singlets, 6H), 2.78 (ddd, *J* = 14.2, 5.5, 1.6 Hz, 0.6H), 2.80 (ddd, *J* = 14.3, 5.1, 1.2 Hz, 0.4H), 4.56-4.61 (m, 1H), 4.65 (dd, *J* = 12.2, 3.2 Hz, 0.6H), 4.73-4.77 (m, 0.8H), 4.75 (dd, *J* = 12.2, 3.8 Hz, 0.6H), 4.59 ("dt", *J* = 4.9, 1.9 Hz, 0.6H), 4.63 ("d", *J* = 6.4 Hz, 0.4H), 6.00 (d, *J* = 13.7 Hz, 0.6H), 6.40 (dd, *J* = 8.7, 5.4 Hz, 0.6H), 6.41 (d, *J* = 19.2 Hz, 0.4H), 6.46 (d, *J* = 8.9, 5.2 Hz, 0.4H), 6.72 (d, *J* = 19.0 Hz, 0.4H), 6.78 (dd, *J* = 13.7, 1.0 Hz, 0.6H), 7.22-7.32 (m, 4H), 7.48 (d, *J* = 1.0 Hz, 0.6H), 7.67 (s, 0.4H), 7.85-7.99 (m, 4H), 8.51 (br. s, 0.4H), 8.57 (br. s, 0.6H); ^{13}C NMR δ -2.0, -0.2, 21.70, 21.73, 38.5, 64.1, 64.4, 74.7, 75.0, 82.9, 83.1, 85.6, 113.9, 115.4, 126.3, 126.4, 126.5, 129.30, 129.34, 129.50, 129.54 129.6, 129.8,

131.9, 133.9, 134.2, 134.9, 135.1, 138.3, 144.4, 144.5, 144.6, 149.2, 149.7, 161.5, 161.9, 166.0, 166.1; HRMS calcd for $C_{30}H_{34}{}^{74}GeN_2NaO_7$ $[M + Na]^+$ 631.1470, found 631.1482.

Note. Treatment of **131b** (*E*/*Z,* 40:60; 12 mg; 0.02 mmol;) with NBS (5 mg, 0.028 mmol) in $CHCl_3/CH_2Cl_2$ (1:1.5, v/v; 2.5 mL) for 6 h at 0 ^oC (ice-bath) followed by deprotections with NH_3/MeOH (0 ^oC to ambient temperature, 12 h) gave give *E* and *Z* 5-(2-bromovinyl)-2'-deoxyuridine (2:3, 70% overall from **131b**) with data as reported.[64,215]

1-(β-D-*Erythro*-pentofuranosyl)-5-(*Z*)-[2-(triphenylgermyl)ethenyl]uracil (132a). A saturated solution of MeOH/NH_3 (2 mL) was added to a suspension of *Z*-**131a** (33 mg, 0.042 mmol) in MeOH (2 mL) and the resulting mixture was stirred for 20 h at ambient temperature. An additional portion of MeOH/NH_3 solution (1 mL) was added and the solution was stirred for 48 h at ambient temperature. The volatiles were evaporated and the residue was column chromatographed (dry method, EtOAc) to give *Z*-**132a** (15 mg, 65%): ^{1}H NMR (MeOH-d_4) δ 1.44 (ddd, *J* = 14.2, 7.9, 6.6 Hz, 1H), 1.87 (ddd, *J* = 13.6, 5.9, 2.7 Hz, 1H), 3.38 ("d", *J* = 4.4 Hz, 2H), 3.70 ("q", *J* = 3.8 Hz, 1H), 3.97 (ddd, *J* = 6.0, 3.3, 2.8 Hz, 1H), 5.81 (dd, *J* = 8.0, 6.0 Hz, 1H), 6.52 (d, *J* = 13.3 Hz, 1H), 7.28 (d, *J* = 1.1Hz, 1H), 7.31 (dd, *J* = 13.3, 1.1 Hz, 1H), 7.36-7.41 (m, 9H), 7.49-7.54 (m, 6H); ^{13}C NMR (MeOH-d_4) δ 40.3, 63.0, 72.3, 86.3, 88.6, 115.8, 129.5, 130.2, 131.8, 135.9, 138.1, 138.2, 140.8, 151.6, 164.7; MS (ESI$^+$) *m*/*z* 581 (100, MNa^+, ^{74}Ge), 579 (70, MNa^+, ^{70}Ge), 577 (49, MNa^+, ^{70}Ge); Anal. Calcd for $C_{29}H_{28}GeN_2O_5$ (557.18): C, 62.51; H, 5.07; N, 5.03. Found: C, 62.14; H, 5.28; N, 4.86.

1-*N*-Benzyluracil (92). In a flame-dried 100 mL round-bottomed flask uracil (1.8 g, 16.0 mmol) was suspended in 1,1,1,3,3,3-hexamethyldisilazane (HMDS; 20 mL) and stirred for 10 min under nitrogen. Trimethylsilyl chloride (687 mg, 800 μL, 6.33 mmol) was added *via* syringe and the resulting mixture was refluxed (125 °C, oil bath) for 2 h until it became a clear solution. Volatiles were evaporated in vacuum and the resulting white solid was dissolved in 1,2-dichloroethane (70 mL). Benzyl bromide (3.29 g, 2.29 mL, 19.25 mmol) followed by I_2 (100 mg,

0.39 mmol) were added and the resulting orange solution was refluxed for 5 h. Volatiles were evaporated and the brownish solidified residue was washed with small amount of cold MeOH (2 × 2 mL). The resulting orange solid was recrystallized from EtOH to give **92** (2.75 g, 75%; two crops) as a white solid with data identical as reported:[210] ^{1}H NMR δ 4.92 (s, 2 H, CH_2), 5.70 (dd, $^3J_{5\text{-}6}$ = 7.9 Hz, 1 H, H5), 7.15 (d, $^3J_{6\text{-}5}$ = 7.9 Hz, 1 H, H6), 7.27-7.41 (m, 5 H, Ph). GC-MS (t_R 21.90 min) *m*/*z* 202 (27, M^+), 200 (<1), 91 (100).

1-*N*-Benzyl-4-thiouracil (137). Compound **92** (501 mg, 2.48 mmol) was placed in a flamed-dry round-bottomed flask under a N_2 atmosphere and dissolved in dry THF (40 mL). Dried Lawesson's reagent (1.02 g, 2.52 mmol) was added and the resulting suspension was heated at 56 °C for about 1 h until TLC showed ~95% consumption of the substrate **92**. Volatiles were evaporated and the residue was partitioned between $NaHCO_3$ and EtOAc. The organic phase was washed with brine and was dried over anhydrous Na_2SO_4. Column chromatography (hexanes/EtOAc, 3:2) gave **137**[216] (315 mg, 65%) as a yellowish solid: ^{1}H NMR δ 4.92 (s, 2 H, CH_2), 6.36 (d, $^3J_{5\text{-}6}$ = 7.5 Hz, 1 H, H5), 6.98 (d, $^3J_{6\text{-}5}$ = 7.5 Hz, 1 H, H6), 7.28-7.33 (m, 2 H, Ph), 7.34-7.43 (m, 3 H, Ph), 9.86 (br. s, 1 H, NH). ^{13}C NMR δ 51.9, 113.5, 128.3, 128.9, 129.3, 134.4, 138.6, 148.4, 189.8. GC-MS (t_R 27.26 min.) *m*/*z* 218 (39, M^+), 91 (100).

1-Benzyl-4-(methylthio)-2(1*H*)-pyrimidinone (138). Freshly distilled Et_3N (146 mg, 203 μL, 1.44 mmol) was added to a stirred solution of **137** (314.8 mg, 1.44 mmol) in dry CH_2Cl_2 (42 mL) at ambient temperature under N_2. After 10 min, methyl iodide (410 mg, 180 μL, 2.89 mmol) was added *via* syringe and the reaction vessel was covered with aluminum foil. After 1.5 h, the volatiles were evaporated and the residue was dissolved in CH_2Cl_2 and was washed with H_2O (2×). The organic layer was dried (Na_2SO_4) and was evaporated to give **138**[217] (320 mg, 93%): ^{1}H NMR δ 2.57 (s, 3 H, Me), 5.04 (s, 2 H, CH_2), 6.16 (d, $^3J_{5\text{-}6}$ = 6.8 Hz, 1 H, H5), 7.22 (d, $^3J_{6\text{-}5}$ = 6.8

Hz, 1 H, H6), 7.29-7.40 (m, 5 H, Ph); ^{13}C NMR δ 12.9, 52.9, 103.8, 128.5, 128.5, 129.1, 135.4, 143.1, 154.9, 177.7. GC-MS (t_R 24.39 min.) *m*/*z* 232 (44, M^+), 91 (100).

4-[^{18}O]-1-*N*-benzyluracil (139). Compound **137** (248 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 mg, 250 μL, 12.5 mmol, 99.2% ^{18}O) was added *via* syringe followed by three drops of concentrated HCl and the mixture was refluxed until TLC showed consumption of the all substrate **138**. The volatiles were evaporated and the residue was partitioned between $CHCl_3$ and $NaHCO_3$ solution. The organic layer was washed with brine, dried ($MgSO_4$), evaporated and the residue was column chromatographed (hexanes/EtOAc, 2:3) to give **139** (197 mg, 90%) as a puffy white powder with data identical to the reported above for **92**; except for GC-MS (t_R 21.91 min) *m*/*z* 204 (22, M^+), 202 (3.3, M-2), 91 (100). The $^{18}O/^{16}O$ ratio in **6** (85:15) was calculated from the peak intensities at *m*/*z* 204 and 202.

1-*N*-Benzyl-5-iodouracil (140). Iodine monochloride (ICl; 361 mg, 2.22 mmol) was added to a stirred solution of **92** (297.6 mg, 1.47 mmol) in dry CH_2Cl_2 (30 mL) at ambient temperature under N_2. The resulting red-wine solution was refluxed until TLC showed complete consumption of **92**. 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), dried (Na_2SO_4) and was evaporated to give crude **140** as a slightly yellow solid. Washing of this material with small amount of cold MeOH (3 × 2 mL) yielded **140**[168] (446 mg, 93%) as white powder: ^{1}H NMR δ 4.92 (s, 2 H, CH_2), 7.28-7.32 (m, 2 H, Ph), 7.35-7.44 (m, 3 H, Ph), 7.59 (s, 1 H, H6), 8.42 (br. s, 1 H, NH); ^{13}C NMR δ 51.6, 68.2, 128.1, 128.9, 129.3, 134.6, 148.3, 150.4, 159.9. GC-MS (t_R 25.90 min.) *m*/*z* 328 (30, M^+), 91 (100), with no peak at *m*/*z* 326 $(M-2)^+$.

4-[^{18}O]-1-*N*-benzyl-5-iodouracil (141). Treatment of **139** (257 mg, 1.26 mmol) with ICl (310 mg, 1.9 mmol), as described for **140**, afforded **141** (394 mg, 95%) as a white powder with data identical to that reported above for **140**, except for GC-MS (t_R 25.90 min.) *m*/*z* 330 (24, M^+),

328 (5, M-2), 91 (100). The $^{18}O/^{16}O$ ratio in **141** (83:17) was calculated from peak intensities at *m*/*z* 330 and 328.

1-*N*-Benzyl-5-[(trimethylsilyl)ethynyl]uracil (142). Compound **140** (602 mg, 1.83 mmol) was suspended in freshly distilled Et_3N (56 mL) and the mixture degassed for 1 h. Trimethylsilylacetylene (723 mg, 1.04 mL, 7.36 mmol) was added followed by $(PPh_3)_2PdCl_2$ (30 mg, 0.043 mmol) and CuI (22 mg, 0.12 mmol). The resulting mixture was then heated at 50 °C until TLC showed consumption of the substrate **140**. Volatiles were evaporated and the brownish residue was chromatographed (CH_2Cl_2/EtOAc, 10:1) to give **142**[169] (438 mg, 80%) as a off white powder: ^1H NMR δ 0.21 (s, 9 H, Me_3), 4.92 (s, 2 H, CH_2), 7.28-7.32 (m, 2 H, Ph), 7.35-7.43 (m, 3 H, Ph), 7.47 (s, 1 H, H6), 8.35 (br. s, 1 H, NH); ^{13}C NMR δ -0.2 (Me), 51.7 (CH_2), 94.8, 100.1, 100.6, 128.1, 128.9, 129.3, 134.6, 147.1, 149.7, 161.0. GC-MS (t_R 26.68 min.) *m*/*z* 298 (29, M^+), 283 (29, M-15), 91 (100), with no peak at *m*/*z* 296 $(M-2)^+$.

4-[^{18}O]-1-*N*-Benzyl-5-[(trimethylsilyl)ethynyl]uracil (143). Treatment of **141** (388 mg, 1.18 mmol), as described for **142**, gave **143** (218 mg, 62%) as a off white powder with data identical to that reported above for **142**, except for GC-MS (t_R 26.67 min.) *m*/*z* 300 (23, M^+), 298 (4, M-2), 285 (23, M-15), 91 (100). The $^{18}O/^{16}O$ ratio in **143** (14:86) was calculated from the peak intensities at *m*/*z* 300 and 298.

1-*N*-Benzyl-5-ethynyluracil (135). Procedure A. TBAF (1 M/THF; 1.88 mL, 1.88 mmol,) was added *via* syringe to a stirred solution of **142** (560 mg, 1.88 mmol) in dry THF (32 mL) at 0 ^oC (ice-bath). After 1 h, the volatiles were evaporated and the oily yellowish residue was dissolved in $CHCl_3$ (30 mL) and successively washed with saturated $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and was column chromatographed (CH_2Cl_2/EtOAc, 5:1) to give **135**[169] (390 mg, 92%) as white powder: UV (MeOH) max 292 nm (ε 12 600), min 251 (ε 2000); ^1H NMR (DMSO-d_6) δ 4.15 (s, 1 H, C≡CH), 4.92 (s, 2 H, CH_2), 7.35-7.42 (m, 5 H, Ph), 8.31 (s, 1 H, H6), 11.71 (br. s, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 50.8 (CH_2), 76.1, 83.7, 97.2, 127.5, 127.8,

128.6, 136.4, 149.5, 150.0, 162.1. GC-MS (t_R 26.63 min) *m*/*z* 226 (19, M^+), 91 (100), no peak at *m*/*z* 224 $(M-2)^+$; HRMS calcd for $C_{13}H_{11}N_2O_2$ $[M + H]^+$ 227.0815, found 227.0805.

Procedure B. NH_4F (1.05 g, 28.1 mmol) was added to a stirred solution of **142** (645 mg, 2.16 mmol) in MeOH (25 mL) and the resulting suspension was refluxed until TLC showed total consumption of **142** (10 h). The reaction mixture was allowed to cool down to ambient temperature and was filtered off. The mother liquor was evaporated and the residue was column chromatographed ($CHCl_3$) to afford **135** (330 mg, 67%).

4-[^{18}O]-1-*N*-Benzyl-5-ethynyluracil (136). Treatment of **143** (209 mg, 0.70 mmol) by Procedure A gave **136** (123 mg, 78%) as a white powder with data identical to the reported above for **135**, except for GC-MS (t_R 26.73 min) *m*/*z*, 228 (16, M^+), 226 (3, M-2), 91 (100). The $^{18}O/^{16}O$ ratio in **136** (14:86) was calculated from the peak intensities at *m*/*z* 228 and 226. HRMS calcd for $C_{13}H_{11}N_2O^{18}O$ $[M + H]^+$ 229.0857, found 229.0848.

1-*N*-Benzyl-5-(*Z*)-[2-(triphenylgermyl)ethenyl]uracil (144). Alkyne **135**[168,169] (50 mg, 0.22 mmol) was dissolved in dry THF (5 mL) and the resulting solution was stirred for 20 min under N_2 at 0 °C in a screw-capped glass tube. Ph_3GeH (73 mg, 0.24 mmol) and Et_3B (1M/THF 265 uL, 0.265 mmol,) were added and the resulting solution was stirred at 0 °C for 7 h. The volatiles were evaporated and the resulting bright-yellow liquid was column chromatographed (hexane/EtOAc, 1:1) to give *Z*-**144** (61 mg, 52%) as a white powder: M.p. 202-204 °C (MeOH); UV (MeOH) max 296 nm (ε 11 000), min 255 (ε 3500); ^{1}H NMR δ 4.03 (s, 2H), 6.30 (d, *J* = 13.5 Hz, 1H), 6.69 ("d", *J* = 7.0 Hz, 2H), 6.84 (s, 1H), 7.09 ("t", *J* = 7.5 Hz, 2H), 7.16 ("t", *J* = 7.1 Hz, 1H), 7.23-7.35 (m, 10H), 7.37-7.46 (m, 6H), 8.51 (br. s, 1H); ^{13}C NMR δ 51.2, 113.7, 128.3, 128.3, 128.4, 128.8, 129.1, 129.5, 134.8, 135.0, 136.7, 138.7, 141.0, 150.1, 162.4; HRMS calcd for $C_{31}H_{26}{}^{74}GeN_2NaO_2$ $[M + Na]^+$ 555.1105, found 555.1113.

1-*N*-Benzyl-5-(*E*)-[2-(triphenylgermyl)ethenyl]uracil (144). Ph_3GeH (118.6 mg, 0.38 mmol) and H_2O (25 μL, 25 mg, 1.4 mmol) were added to a stirred solution of **135** (80 mg, 0.35

mmol) in toluene (5 mL) at ambient temperature. The resulting mixture was heated 100 ^{o}C (oil-bath) for 12 h and was cooled down to ambient temperature. The volatiles were removed in vacuo and the resulting oily residue was column chromatographed (CH_2Cl_2/EtOAc, 10:1) to give *E*-**144** (126 mg, 86%) as white solid. Recrystallization from MeOH gave white crystals: M.p. 185-186 ^{o}C; UV (MeOH) max 300 nm (ε 13 900), 251 nm (ε 15 500), min 272 (ε 7100); ^{1}H NMR δ 4.92 (s, 2H), 6.56 (d, *J* = 18.7 Hz, 1H), 7.21 (s, 1H), 7.28-7.30 (m, 2H), 7.33 (d, *J* = 18.7 Hz, 1H), 7.35-7.39 (m, 12H), 7.49-7.51 (m, 6H), 8.78 (br. s, 1H); ^{13}C NMR δ 51.5, 113.8, 127.2, 127.9, 128.3, 128.6, 129.1, 129.2, 135.1, 135.2, 136.1, 136.9, 141.7, 150.1, 161.8; HRMS calcd for $C_{31}H_{26}{}^{74}GeN_2NaO_2$ $[M + Na]^+$ 555.1105, found 555.1111. Anal. Calcd for $C_{31}H_{26}GeN_2O_2$ (531.19): C, 70.09; H, 4.93; N, 5.27. Found: C, 69.82; H, 4.64; N, 5.35.

1-*N*-Benzyl-5-[2-(triphenylgermyl)acetyl]uracil (146). Alkyne **135** (50 mg, 0.22 mmol) was suspended in dry toluene (5 mL) and the suspension was degassed with N_2 for 45 min at ambient temperature in a screw-capped glass tube. Ph_3GeH (73 mg, 0.24 mmol) and ACCN (10 mg, 0.041 mmol) were added and the suspension was heated at 85 °C for 2 h (TLC showed approximately 80% consumption of **135**). The volatiles were evaporated under vacuum and the resulting yellow oil was slowly column chromatographed (hexane/EtOAc, 3:2) to give **146** (15 mg, 13%) followed by *Z*-**144** (31 mg, 27%): The compound **146** was recrystallized from warm MeOH to give colorless crystals: M.p. 205-207 ^{o}C; UV (MeOH) max 294 nm (ε 10 600), min 255 (ε 3800); ^{1}H NMR δ 3.81 (s, 2H), 4.77 (s, 2H), 7.24-7.40 (m, 14H), 7.48-7.54 (m, 6H), 7.79 (br. s, 1H), 7.85 (s, 1H); ^{13}C NMR δ 33.1, 52.4, 113.3, 128.3, 128.5, 129.1, 129.3, 129.5, 134.5, 135.2, 135.3, 149.7, 149.9, 160.7, 194.3; HRMS calcd for $C_{31}H_{26}{}^{74}GeN_2NaO_3$ $[M + Na]^+$ 571.1054, found 571.1068; Anal. Calcd for $C_{31}H_{26}GeN_2O_3$ (547.2): C, 68.04; H, 4.79; N, 5.12. Found: C, 68.26; H, 4.60; N, 4.81.

Analogous treatment of **135** (40 mg, 0.18 mmol) with Ph_3GeH (59 mg, 0.20 mmol) without ACCN [100 °C (oil-bath)/10 h] gave an oily residue that was column chromatographed (CH_2Cl_2/EtOAc, 10:1) to give **146** (19 mg, 20%) as a white powder and *Z*-**144** (33 mg, 34%).

1-*N*-Benzyl-5-acetyluracil (152). Procedure A. A solution of **146** (15 mg, 0.03 mmol) in CH_3OH (3 mL) was heated for 12 h at 65 ^oC (oil-bath). Volatiles were evaporated and the residue was column chromatographed (CH_2Cl_2/EtOAc, 2:1) to give **152**[218] (6.5 mg, 95%) as a white powder: UV (MeOH) max 290 nm (ε 12 200), 226 nm (ε 8100), min 249 (ε 1400); ^1H NMR δ 2.61 (s, 3H), 5.01 (s, 2H), 7.33-7.41 (m, 5H), 8.28 (s, 1H), 8.59 (br. s, 1H); ^{13}C NMR δ 30.6, 52.5, 112.8, 128.3, 129.0, 129.3, 134.3, 150.2, 150.6, 161.2, 193.9. GC-MS (t_R 26.87 min) *m*/*z* 244 (20, M^+), 91 (100); HRMS calcd for $C_{13}H_{12}N_2NaO_3$ $[M + Na]^+$ 267.0740, found 267.0739.

Procedure B. H_2SO_4 (0.5 M; 7 mL) was added dropwise to a stirred solution of **135** (100 mg, 0.44 mmol) in THF (5 mL) at ambient temperature and the resulting mixture was heated at 70 ^oC (oil-bath) for 7 h. CH_2Cl_2 (15 mL) was added to the cooled down reaction mixture and the separated organic layer was washed with saturated $NaHCO_3$, brine, and was dried over anhydrous Na_2SO_4. Volatiles were evaporated and the residue was column chromatographed (CH_2Cl_2/EtOAc, 2:1) to give **152** (95 mg, 88%) with data as reported above.

1-*N*-Benzyl-5-(2-deuterioacetyl)uracil (153). Treatment [18 h, 65 ^oC (oil-bath)] of **146** (10 mg, 0.02 mmol) as described above for **152** (Procedure A) using MeOD or MeOH-d_4 instead of MeOH gave **153** (4.2 mg, 94%): GC-MS (t_R 26.87 min) *m*/*z* 245 (20, M^+), 91 (100). ^1H NMR spectrum of **153** corresponded to this of the above **152** with 1/3 reduction of the integrated intensity for the signal from methyl group at 2.61 ppm.

(*E*)-1-*N*-benzyl-5-(1-chloro-2-tosylvinyl)uracil (158). Method A: $Fe(acac)_3$ (3 mg, 0.01 mmol), Ph_3P (3 mg, 0.01 mmol) and tosylchloride **157** (29 mg, 0.15 mmol) was added to a stirring solution of 1-*N*-benzyl-5-ethynyluracil **135** (22.6 mg, 0.1 mmol) in 2 mL toluene at ambient temperature. The resulting solution was stirred at 100 ^oC (oil bath) for 16 h. Volatiles

were removed under the reduced pressure and the residue was chromatographed (Hexane : EtOAc = 1:1) to give **158** (24.8 mg, 60 %) as white solid. Compound **158** had:^{1}H NMR δ 2.23 (s, 3H), 4.82 (s, 2H), 6.70 (s, 1H), 7.09 (d, *J* = 8.1 Hz, 2H), 7.32-7.18 (m, 5H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.42 (s, 1H), 8.99 (s, 1H); ^{13}C NMR δ 21.8, 52.4, 108.9, 128.0, 128.7, 129.1, 129.4, 130.1, 134.2, 134.5, 136.7, 139.7, 145.4, 145.8, 150.1, 159.6; HRMS calcd for $C_{20}H_{18}ClN_2O_4S$ $[M + H]^+$ 417.0670, found 417.0664.

Method B: $FeCl_3 \cdot 6H_2O$ (108 mg, 0.4 mmol), TBHP (80 μL, 0.4 mmol; 5-6 M in Hexane) and tosylhydrazide **159** (52.2 mg, 0.28 mmol) was added to a stirring solution of 1-*N*-benzyl-5-ethynyluracil **135** (45.2 mg, 0.2 mmol) in 2 mL CH_3CN at ambient temperature. The resulting solution was stirred at 80 ^{o}C (oil bath) for 4.5 h. Volatiles were removed under the reduced pressure and the residue was chromatographed (Hexane:EtOAc = 1:1) to give **158** (64.9 mg, 65 %) as white solid with the same spectroscopic data as above.

(*E*)-1-*N*-benzyl-5-(1-bromo-2-tosylvinyl)uracil (160) and 1-*N*-benzyl-5-(1,2-dibromovinyl)uracil (161) $FeBr_3$ (118.2 mg, 0.4 mmol) and TBHP (80 μL, 0.4 mmol; 5-6 M in Hexane) and tosylhydrazide **159** (149.1 mg, 0..8 mmol) was added to a stirring solution of 1-*N*-benzyl-5-ethynyluracil **135** (45.2 mg, 0.2 mmol) in 2 mL CH_3CN at ambient temperature. The resulting solution was stirred at 80 ^{o}C (oil bath) for 4.5 h. volatiles were removed under the reduced pressure and the residue was chromatographed to give **160** (37.8 mg, 41 %) as well as 1-*N*-benzyl-5-(1,2-dibromovinyl)uracil **161** (8.2 mg, 12%). Compound **160** had ^{1}H NMR δ 2.40 (s, 3H), 4.99 (s, 2H), 7.09 (s, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.40-7.45 (m, 5H), 7.58 (s, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 9.29 (s, 1H); ^{13}C NMR δ 21.8, 52.4, 110.4, 128.0, 128.6, 128.7, 129.1, 129.4, 130.1, 134.5, 136.6, 137.8, 145.1, 145.4, 150.2, 159.6.

Compound **161** had ^{1}H NMR δ 4.69 (s, 2H), 6.54 (s, 1H), 6.99 (s, 1H), 7.04-7.13 (m, 5H), 8.93 (s, 1H); ^{13}C NMR δ 51.9, 109.0, 112.1, 112.5, 128.3, 129.0, 129.4, 134.6, 145.3, 150.4, 159.7.

2,3,5-Tri-*O*-acetyl-5-(1-chloro-2-tosylvinyl)uracil (165). $FeCl_3 \cdot 6H_2O$ (108 mg, 0.4 mmol), TBHP (80 μL, 0.4 mmol; 5-6 M in Hexane) and tosylhydrazide **159** (52.2 mg, 0.28 mmol) was added to a stirring solution of 2,3,5-tri-*O*-acetyl-5-ethynyluridine **162** (78.9 mg, 0.2 mmol) in 2 mL CH_3CN at ambient temperature. The resulting solution was stirred at 80 ^oC (oil bath) for 4.5 h. After cooled down to room temperature, volatiles were removed under the reduced pressure and the residue was chromatographed (Hexane : EtOAc = 1:1 → 4:6) to give **165** (80 mg, 68%) as white solid. ^1H NMR δ 2.12 (s, 3H), 2.14 (s, 3H), 2.18 (s, 3H), 2.42 (s, 3H), 4.37-4.47 (m, 3H), 5.36-5.41 (m, 1H), 5.44 (t, *J* = 5.5 Hz, 1H), 6.10 (d, *J* = 5.3 Hz, 1H), 6.94 (s, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.82 (s, 1H), 8.63 (s, 1H); ^{13}C NMR δ 20.6, 20.7, 21.0, 21.8, 63.2, 70.4, 73.4, 80.7, 88.0, 109.4, 128.1, 130.2, 135.3, 136.7, 139.6, 141.6, 145.5, 149.2, 159.6, 169.6, 169.7, 170.5; HRMS calcd for $C_{24}H_{25}ClN_2NaO_{11}S$ $[M + Na]^+$ 607.0760, found 607.0755.

2,3,5-Tri-*O*-acetyl-1-(*β*-D-arabinofuranosyl)-5-(1-chloro-2-tosylvinyl)uracil (166). $FeCl_3 \cdot 6H_2O$ (108 mg, 0.4 mmol), TBHP (80 μL, 0.4 mmol; 5-6 M in Hexane) and tosylhydrazide **159** (52.2 mg, 0.28 mmol) was added to a stirring solution of 2,3,5-tri-*O*-acetyl-1-(*β*-D-arabinofuranosyl)-5-ethynyluracil **123** (78.9 mg, 0.2 mmol) in 2 mL CH_3CN at ambient temperature. The resulting solution was stirred at 80 ^oC (oil bath) for 4.5 h. After cooled down to room temperature, volatiles were removed under the reduced pressure and the residue was chromatographed (Hexane : EtOAc = 1:1 → 4:6) to give **166** (77 mg, 66%) as white solid. ^1H NMR δ 2.11 (s, 3H). 2.15 (s, 6H), 2.41 (s, 3H), 4.22-4.28 (m, 1H), 4.41 (dd, *J* = 4.2, 12.0 Hz, 1H), 4.48 (dd, *J* = 6.3, 12.0 Hz, 1H), 5.13 (dd, *J* =1.3, 2.7 Hz, 1H), 5.45 (dd, *J* = 1.5, 4.0 Hz, 1H), 6.30 (d, *J* = 4.0 Hz, 1H), 6.84 (s, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.80 (s, 1H), 9.36 (s, 1H); ^{13}C NMR δ 20.8, 20.9, 21.8, 62.6, 74.3, 76.5, 81.3, 85.0, 109.8, 128.1, 130.2, 134.2, 136.7, 138.5, 141.5, 145.5, 149.1, 159.3, 169.2, 169.7, 180.8; HRMS calcd for $C_{24}H_{26}ClN_2O_{11}S$ $[M + H]^+$ 585.0940, found 585.0918.

3,5-Di-*O*-acetyl-5-(1-chloro-2-tosylvinyl)uridine (167). $FeCl_3 \cdot 6H_2O$ (540 mg, 2 mmol), TBHP (400 μL, 2 mmol; 5-6 M in Hexane) and tosylhydrazide **159** (372 mg, 2 mmol) was added to a stirring solution of 3,5-di-*O*-acetyl-2'-deoxy-5-ethynyluridine **163** (336 mg, 1 mmol) in 6 mL CH_3CN at ambient temperature. The resulting solution was stirred at 80 ^oC (oil bath) for 4.5 h. After cooled down to room temperature, volatiles were removed under the reduced pressure and the residue was chromatographed (Hexane : EtOAc = 1:1 → 4:6) to give **167** (400 mg, 76%) as white solid. ^1H NMR δ 2.12 (s, 3H), 2.16 (s, 3H), 2.27-2.37 (m, 1H), 2.42 (s, 3H), 2.58 (ddd, *J* = 1.7, 5.5, 14.3 Hz, 1H), 4.30-4.35 (m, 2H), 4.46 (td, *J* = 2.3, 5.0 Hz, 1H), 5.27 (d, *J* = 6.4 Hz, 1H), 6.35 (dd, *J* = 5.5, 8.5 Hz, 1H), 6.89 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.88 (s, 1H), 8.83 (s, 1H); ^{13}C NMR δ 21.02, 21.04, 21.8, 28.8, 38.2, 64.0, 74.4, 83.1, 85.7, 109.2, 127.9, 130.2, 134.7, 136.7, 139.9, 141.5, 145.6, 149.3, 158.9, 170.5, 170.6; HRMS calcd for $C_{22}H_{24}ClN_2O_9S$ $[M + H]^+$ 527.0886, found 527.0863.

2'-deoxyl-5-(1-chloro-2-tosylvinyl)uracil (168). $FeCl_3 \cdot 6H_2O$ (108 mg, 0.4 mmol), TBHP (80 μL, 0.4 mmol; 5-6 M in Hexane) and tosylhydrazide **159** (52.2 mg, 0.28 mmol) was added to a stirring solution of 5-ethynyl-2'-deoxyuridine **164** (50.5 mg, 0.2 mmol) in 2 mL CH_3CN at ambient temperature. The resulting solution was stirred at 80 ^oC (oil bath) for 4.5 h. After cooled down to room temperature, volatiles were removed under the reduced pressure and the residue was chromatographed ($CHCl_3$: MeOH= 9:1 → 85:15) to give **168** (60.8 mg, 69%) as white solid. ^1H NMR MeOD-d_6 δ 2.25-2.34 (m, 1H), 2.38 (ddd, *J* = 13.4, 6.0, 4.1 Hz, 1H), 2.45 (s, 3H), 3.78 (dd, *J* = 12.0, 3.5 Hz, 1H), 3.84 (dd, *J* = 12.0, 2.9 Hz, 1H), 3.99 (dd, *J* = 6.3, 3.0 Hz, 1H), 4.37-4.53(m, 1H), 6.31 (t, *J* = 6.4 Hz, 1H), 7.23 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 2H), 7.69 (d, *J* = 7.8 Hz, 2H), 8.31 (s, 1H); ^{13}C NMR MeOD-d_6 δ 21.6, 41.8, 62.7, 72.0, 87.0, 89.3, 109.7, 129.1, 131.0, 136.0, 138.3, 142.0, 143.9, 146.8, 151.3, 161.6; HRMS calcd for $C_{18}H_{19}ClN_2NaO_7S$ $[M + Na]^+$ 465.0494, found 465.0493.

(*E*)-5-(1-amino-2-tosylvinyl)-1-*N*-benzyluracil (169a). (*E*)-1-*N*-benzyl-5-(1-chloro-2-tosylvinyl)uracil **158** (41.6 mg, 0.1 mmol) was dissolved in NH_3/MeOH (3 mL) at 0 ^oC (ice bath). After kept stirring for 24 h, volatiles was removed under the reduced pressure and the residue was dried under the high vacuum pump to give (*E*)-1-*N*-benzyl-5-(1-(butylamino)-2-tosylvinyl)uracil **169a** (27 mg, 67%) as white solid. UV (MeOH) λ_{max} = 272 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.37 (s, 3H), 4.92 (s, 2H), 5.26 (s, 1H), 7.08 (s, 2H), 7.28-7.36 (m, 7H), 7.75 (d, *J* = 8.2 Hz, 2H), 8.35 (s, 1H); ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ 2.35 (s, 3H), 4.90 (s, 2H), 5.24 (s, 1H), 7.28-7.36 (m, 7H), 7.73 (d, *J* = 8.2 Hz, 2H), 8.28 (s, 1H); ^{13}C NMR (101 MHz, DMSO) δ 21.2, 51.6, 106.9, 125.7, 127.6, 128.1, 128.9, 129.8, 136.5, 142.3, 142.9, 157.1, 150.0, 150.7, 162.3; HRMS calcd for $C_{20}H_{19}N_3NaO_4S$ $[M + Na]^+$ 420.0994, found 420.0939.

(*E*)-1-*N*-benzyl-5-[1-(*n*-butylamino)-2-tosylvinyl]uracil (169b). *n*-Butylamine (100μL, 1 mmol) was added to a stirring solution of (*E*)-1-*N*-benzyl-5-(1-chloro-2-tosylvinyl)uracil **158** (41.6 mg, 0.1 mmol) in 3 mL of MeOH at ambient temperature. After kept stirring for 2 h, white precipitates showed up. The solid was collected by vacuum filtrated, wash with cold MeOH and dried under the high vacuum pump to give 1-*N*-benzyl-5-[1-(butylamino)-2-tosylvinyl]uracil **169b** (32 mg, 71%)as a mixture of two regioisomers with ratio 15:85 (*Z*:*E*). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.75 (t, *J* = 7.3 Hz, 0.45H), 0.85 (d, *J* = 7.3 Hz, 2.55H), 1.08-1.14 (m, 0.3H), 1.26-1.36 (m, 2H), 1.42-1.47 (m, 1.7H), 2.33 (s, 2.55H), 2.33 (s, .45H), 2.89 (dd, *J* = 6.8,12.0 Hz, 1.7H), 2.96 (dd, *J* = 6.6, 13.1 Hz, 0.3H), 4.87 (s, 1.7H), 4.91 (s, 0.3H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.24-7.42 (m, 6), 7.47 (d, *J* = 8.2 Hz, 2H), 7.67 (s, 1H), 11.41 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 13.7, 19.7, 20.9, 42.8, 50.7, 93.0, 125.6, 125.8, 127.3, 127.5, 127.7, 128.5, 128.6, 129.1, 129.5, 136.7, 141.4, 143.2, 150.6, 161.4; HRMS calcd for $C_{24}H_{28}N_3O_4S$ $[M + H]^+$ 454.1795, found 454.1793.

(*E*)-1-*N*-Benzyl-5-(1-(propylthio)-2-tosylvinyl)uracil (169c). *n*-Propylthiol (90μL, 1 mmol) and Et_3N (279 μL, 20 mmol) were added to a stirring solution of (*E*)-1-*N*-benzyl-5-(1-chloro-2-

tosylvinyl)uracil **158** (41.6 mg, 0.1 mmol) in 3 mL of MeOH at ambient temperature. After the reaction mixture was kept stirring for 2 h, white precipitates showed up. The solid was collected by vacuum filtrated, wash with cold MeOH and dried under the high vacuum pump to give 1-*N*-benzyl-5-[1-(propylthio)-2-tosylvinyl]uracil **169c** (28.1 mg, 62 %) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.92 (t, J = 7.3 Hz, 3H), 1.50-1.59 (m, 2H), 2.38 (s, 3H), 2.80 (t, J = 7.2 Hz, 3H), 4.92 (s, 2H), 6.48 (s, 1H), 7.31-7.41 (m, 7H), 7.60 (d, J = 8.3 Hz, 2H), 7.86 (s, 1H), 11.56 (s, 1H); ^{13}C NMR (101 MHz, DMSO) δ 13.2, 20.6, 21.1, 33.6, 50.6, 108.9, 122.0, 127.1, 127.4, 127.8, 128.6, 129.5, 136.7, 138.8, 143.68, 143.73, 147.6, 150.4, 160.7; HRMS calcd for $C_{23}H_{25}N_2O_4S_2$ $[M + H]^+$ 457.1250, found 457.1229.

1-*N*-benzyl-5-(2-tosylacetyl)uracil (184). Fresh prepared sulfinic acid **183** (156 mg, 1.0 mmol) was added to a stirring solution of 1-*N*-benzyl-5-ethynyluracil **135** (45.2 mg, 0.2 mmol) in 1,2-dichloroethane (DCE, 2 mL) at ambient temperature. A balloon filled with oxygen was connected to the flask, followed by the addition of pyridine (66 μL, 64.9 mg, 0.82 mmol). The resulting solution was stirred at 45 ^{o}C for 4h. Then the reaction mixture was cooled down to room temperature and volatiles were removed under the reduced pressure. The oily residue was column chromatographed (Hexane : EtOAc = 1:1) to give **184** (39.8 mg, 50 %) as white solid. ^{1}H NMR δ 2.42 (s, 3H), 4.98 ("s", 4H), 7.29 (d, J = 8.0 Hz, 2H), 7.34-7.31 (m, 2H), 7.45-7.37 (m, 3H), 7.79 (d, J = 8.3 Hz, 2H), 8.23 (s, 1H), 8.46 (s, 1H); ^{13}C NMR δ 21.8, 52.9, 65.4, 112.0, 128.58, 128.61, 129.4, 129.6, 129.9, 133.9, 137.0, 145.3, 149.6, 151.7, 160.5, 183.8; HRMS calcd for $C_{20}H_{19}N_2O_5S$ $[M + H]^+$ 399.1009, found 399.1017.

1-*N*-benzyl-5-(2-benzyl-2-tosylacetyl)uracil (188). Sodium hydroxide (8 mg, 0.2 mmol) was added to a stirring solution of 1-*N*-benzyl-5-(2-tosylacetyl)uracil **184** (20 mg, 0.05 mmol) in MeOH (2 mL) at ambient temperature. After stirring for 5 min, benzyl bromide (9.4 mg, 6.5 μL, 0.055 mmol) was injected to the clear solution via the syringe. The resulting solution was stirred

at ambient temperature for 16 h. Volatiles were removed under the reduced pressure and the residue was dissolved in EtOAc (5 mL) and washed with 5 % HCl solution, saturated $NaHCO_3$ and brine. The volatiles was removed under the reduced pressure and the residue was column chromatographed (Hexane : EtOAc = 6:4) to give **188** (10 mg, 50 %) as white solid. Compound **188** Had ^{1}H NMR δ 2.41 (s, 3H), 3.14 (dd, *J* = 3.5, 13.9 Hz, 1H), 3.44 (dd, *J* = 11.6, 13.9 Hz, 1H), 4.91 (d, *J* = 14.7 Hz, 1H), 4.95 (d, *J* = 14.7 Hz, 1H), 6.57 (dd, *J* = 3.5, 11.2 Hz, 1H), 7.03-7.05 (m, 2H), 7.09-7.15 (m, 3H), 7.26-7.30 (m, 4H), 7.38-7.41 (m, 3H), 7.80 (d, *J* = 8.3 Hz, 2H), 8.17 (s, 1H), 8.83 (s, 1H); ^{13}C NMR δ 21.8, 32.7, 52.9, 71.4, 112.6, 126.9, 128.6, 128.7, 129.0, 129.3, 129.4, 129.5, 129.9, 133.9, 135.3, 136.2, 145.4, 149.6, 151.6, 161.0, 187.0; HRMS calcd for $C_{27}H_{25}N_2O_5S$ $[M + H]^+$ 489.1479, found 489.1458.

2,3,5-Tri-*O*-acetyl-5-(*α*-azido)vinyl uridine (198). $TMSN_3$ (46 mg, 0.4 mmol) and H_2O (7 μL, 0.4 mmol) were added to a stirring solution of 2,3,5-tri-*O*-acetyl-5-ethynyl uridine **135** (78.7 mg, 0.2 mmol) in 2 mL of DMSO at ambient temperature. Followed by the addition of Ag_2CO_3 (5.5 mg, 0.02 mmol), the suspension was heated and stirred at 80 ^{o}C for 1.5 h. After cooled down to roon temperature, the volatiles were removed under the reduced pressure and oily residue was dilute with EtOAc, washed with H_2O, and brine. Organic layer was dried over anhydrous Na_2SO_4 and column chromatographied (Hexan:EtOAc = 1:1) to give white solid **198** (47 mg, 54%). ^{1}H NMR δ 2.08 (s, 3H), 2.13 (s, 3H), 2.18 (s, 3H), 4.21-4.47 (m, 3H), 5.09 (d, *J* = 2.2 Hz, 1H), 5.22-5.42 (m, 2H), 6.12 (d, *J* = 5.8 Hz, 1H), 6.37 (d, *J* = 2.2 Hz, 1H), 7.76 (s, 1H), 9.57 (s, 1H); ^{13}C NMR 20.50, 20.56, 20.65, 63.5, 70.1, 72.9, 80.5, 87.1, 102.5, 113.7, 137.2, 146.2, 149.6, 160.5, 169.81, 169.83, 170.7; HRMS calcd for $C_{17}H_{19}N_5NaO_9$ $[M + Na]^+$ 460.1075, found 460.1062.

2,3,5-Tri-*O*-acetyl-5-{*α*-[(5aR,6R,6aS)-1,4,5,5a,6,6a,7,8-octahydrocyclopropa[5,6] cycloocta[1,2-*d*][1,2,3]triazol-6-yl]methanol}vinyl uridine (200). (1R,8S,9S)-Bicyclo[6.1.0]non-4-yn-9-ylmethanol **199** (9.6 mg, 0.064 mmol) was added to a solution of 2,3,5-Tri-O-acetyl-5-(*α*-azido)vinyl uridine **198** (28 mg, 0.064 mmol) in 2 mL of MeOH at ambient

temperature. The resulting clear solution was stirred for 8 h and the volatiles were removed under the reduced pressure to give clear oily residue. Followed column chromatography ($CHCl_3$ → $CHCl_3$: MeOH =100 → 95:5) gave corresponding product **200** as a mixture of two regioisomers as a white solid (80%, 30 mg, 0.051 mmol). ^{1}H NMR δ 0.99-1.12 (m, 2H), 1.17-1.22 (m, 1H), 1.48-1.60 (m, 2H), 2.067-2.073 (d, 3H), 2.10 (s, 3H), 2.137-2.142 (d, 3H), 2.22-2.29 (m, 2H), 2.61-2.67 (m, 1H), 2.87-2.94 (m, 2H), 3.17-3.22 (m, 1H), 3.68-3.74 (m, 2H), 4.13-4.15 (m, 1H), 4.16-4.27 (m, 2H), 5.23-5.26 (m, 2H), 5.51 (s, 1H), 5.78 (d, *J* = 4.5 Hz, 1H), 5.81 (d, *J* = 4.9 Hz, 1H), 6.55 (d, *J* = 4.0 Hz, 1H), 6.95 (d, 1H), 9.38 (s, 1H); ^{13}C NMR δ 14.2, 19.8, 19.92, 19.94, 20.1, 20.5, 20.6, 21.0, 21.5, 21.6, 22.4, 22.5, 22.6, 22.77, 22.81, 23.5, 25.9, 26.0, 31.7, 53.6, 59.79, 59.81, 63.17, 63.20, 70.5, 73.0, 73.1, 80.4, 89.2, 89.6, 110.9, 111.0, 119.7, 119.8, 134.0, 135.1, 135.2, 139.1, 138.3, 144.7, 144.8, 149.0, 149.1, 160.4, 169.68, 169.69, 169.8, 169.9, 170.60, 170.62; HRMS calcd for $C_{27}H_{34}N_5O_{10}$ $[M + H]^+$ 588.2300, found 588.2312.

5-{*α*-[(5aR,6R,6aS)-1,4,5,5a,6,6a,7,8-octahydrocyclopropa[5,6]cycloocta[1,2-*d*][1,2,3]triazol-6-yl]methanol}vinyl uridine (201). Compound **200** (30.6 mg, 0.05 mmol) was dissolved in NH_3/MeOH (3 mL) at 0 °C (ice bath), and the resulting solution was stirred overnight. Volatiles were removed under the reduced pressure and the residue was column chromatographed ($CHCl_3$:MeOH, 9:1→ 8:2) to give **201** (15 mg, 64%) as white solid. UV (MeOH) λ_{max} = 283 nm; ^{1}H NMR (DMSO-d_6) δ 0.84-0.89 (m, 2H), 0.94-1.00 (m, 1H), 1.49-1.58 (m, 2H), 2.02-2.11 (d, 2H), 2.55-2.61 (m, 1H), 2.80-2.84 (m, 2H), 3.00-3.05 (m, 1H), 3.37-3.41 (m, 1H), 3.46-3.48 (m, 2H), 3.78-3.81 (m, 2H), 3.84-3.90 (m, 1H), 4.32 (t, *J* = 4.59 Hz, 1H), 4.84 (dt, *J* = 5.25, 8.38 Hz, 1H), 5.11 (s, 1H), 5.38 (s, 1H), 5.44 (d, *J* = 4.41 Hz, 1H), 5.75-5.77 (m, 1H), 6.27-6.31 (m, 1H), 7.34-7.43 (m, 1H), 11.65 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 18.61, 18.64, 18.7, 18.9, 20.85, 20.90, 21.3, 21.8, 22.5, 22.87, 22.97, 25.5, 25.6, 48.6, 54.9, 57.35, 57.38, 60.97, 61.03, 69.95, 69.99, 74.03, 85.0, 88.2, 88.4, 109.7, 116.3, 116.4, 134.3, 134.4, 135.3, 135.4,

138.89, 138.92, 143.59, 143.63, 149.69, 149.71, 160.8, 141.5; HRMS calcd for $C_{21}H_{27}N_5NaO_7$ [M + Na]$^+$ 484.1803, found 484.1810.

5. CONCLUSION

I have developed a method for efficient transfer of one, two, or three phenyl groups from chloro(phenyl)germanes to the Pd catalyzed aryl halides to give the access to various biaryls. These cross-coupling reactions were mediated by TBAF and facilitated by adding of measured amount of water in toluene as solvent. The TBAF promoted Pd-catalyzed cross-coupling of organogermanes have been attempted to extend to the 5-halo pyrimidine nucleoside analogues for the synthesis of 5-aryl derivatives by transfer of phenyl groups from the germane center. However, during the coupling of 5-halo uracil with chloro(phenyl)germanes in toluene, in addition to the desired 5-phenyluracil product (formed in small quantity), an unexpected mixture of 5-(*o,m,p*-methylphenyl)uracil has been observed as the major product. In order to investigate the formation of such unexpected 5-aryluracil derivatives, which were formed by direct activation of toluene (simple arene) without necessary of using organometallic component, I have further studied the reaction of 1-*N*-benzyl-5-iodouracil with regular arenes.

To further apply the organogermane substrates to cross-coupling reaction with 5-halouracil, I have also developed a method to selective transfer of phenyl group(s) from allyl(phenyl)germanes in Pd catalyzed cross-coupling processes. I have shown that selective cleavage of allyl-Ge bond upon treatment with SbF_5/C can serve as an alternative method for the generation of active coupling species fluoro(phenyl)germanes in situ, followed by the Pd-catalyzed cross-coupling with aryl halides in the presence of TBAF gave various biaryls.

I have demonstrated that TBAF-mediated Pd-catalyzed direct arylation of 5-halouracil and uracil nucleosides with simple arenes (e.g., benzene, toluene, and anisole) and electron rich heteroarenes (e.g., furan, thiophene, and pyrrole) in DMF undergoes smoothly to give 5-arylated analogues in high to excellent yields. This methodology has been extended to other enolizable heterocyclic systems, such as 3-bromo-2-pyridone. Similarly, the base-promoted Pd-catalyzed

direct arylation of 5-halouracils also proceeds with the π-excessive heteroarenes in the presence of pivalic acid.

It is worth to mention that the TBAF-promoted direct C-H arylation protocol developed here differs from the existing routes to 5-aryluracils as outlined below. First, our protocol eliminates organometallic precursors required in Suzuki, Hiyama or Stille couplings. Secondly, no ligands or any other additives are required for the direct arylation to proceed smoothly. Thirdly, it is efficient with a variety of uracils and uracil nucleosides, which are important and the basis of the DNA or RNA. In addition, the protocol does not induce glycosidic bond cleavage, avoiding a major drawback with other methodologies.

In my research efforts to study the chemistry of 5-ethynyl pyrimidine nucleosides, I have shown that the trialkyl or triphenylgermanes add across a triple bond of 5-acetylene pyrimidine *via* radical or thermal hydrogermylation. Interestingly, *Z*-vinylgermanyl products were obtained exclusively in good yields at elevated temperature; while, the *E* isomers are formed exclusively with the addition of "measured" amount of water. During the hydrogermylation of 5-ethynyluracil nucleosides with triphenylgermane in toluene, unexpected 5-[2-(triphenylgermyl)acetyl]uracil nucleosides were isolated up to 20 % along with the desired vinylgermane products. The 4-[^{18}O]-1-*N*-benzyl-5-ethynyluracil was synthesized to clarify the formation of the unexpected *β*-germyl ketone as well as confirming the origin of the oxygen in the 5-acetyl moiety. A plausible mechanism had been proposed for the formation of the unexpected *β*-germyl ketone on the basis of literature, NMR spectroscopy and HRMS fragmentation analysis, which indicates that the origin of the oxygen atom in the 5-acetyl moiety is from the residual oxygen in the reaction solution. Interestingly, thermodegradation of the *β*-ketogermyl uracil analogues in MeOH give 5-acetyluracil nucleosides in quantitative yield *via* hydrolysis of the *O*-germyl substituted enols. Bromodegermylation of the 5-[(trimethyl)vinyl]germyl substrates with NBS produced 5-(2-bromovinyl) analogues with the

retention of the stereochemistry in high yields. However, Pd-catalyzed cross-coupling reaction of 5-[(trimethyl)vinyl]germyl substrates with aryl halides gave corresponding products in only 10-30%.

I have also demonstrated that hydrosulfonylation of 5-ethynyluracil nucleoside analogues with either sulfinic acid or sulfonylhydrazide in the presence of iron catalyst give 5-(*β*-halo)vinyl sulfonyl uracil nucleoside analogues in moderate to high yield. It is worth mentioning that only 5-*E*-(*β*-chloro)vinyl sulfonyl products are obtained when the reactions were performed in the presence of $FeCl_3$. Moreover, when the reactions are carried out in the presence of $FeBr_3$, a mixture of *E*/*Z* isomers is obtained with the ratio of 15:85 as well as the 5-(*α*, *β*-dibromo)vinyl substrate in small quantity. I have showed the 5-(*β*-halo)vinyl sulfonyl analogues can serve as excellent Michael acceptors and various of nucleophiles (e.g., *n*-butylamine, propanethiol, ammonia) have been added across the double to give the corresponding *β*-substituted vinylsulfones in high yields. Triethylamine was required as a catalyst for the addition of thiol due to the week nucleophilicity. Similarly, 1-*N*-benzyl-5-(2-sulfonylketo)uracil has been synthesized *via* the direct aerobic difunctionalization of 5-ethynyl substrate with sulfinic acid in the presence of pyridine in moderate yield. I have also demonstrated that hydroazidation of the acetyl protected 5-ethynyluridine with $TMSN_3$ in the presence of silver salt and catalytic amount of water produced novel 5-(*α*-azido)vinyluridine derivatives. Comparing to the light sensitive 5-azidouridine with half-life of 4 h in the 3% DMSO/water solution, the 5-(*α*-azido)vinyluridine turned out to be fairly stable. These 5-(*α*-azido)vinyluridine analogues have been showed to be an excellent substrates for the strain-promoted click reaction with cyclooctyne to provide novel 5-(*α*-1,2,3-triazole)vinyluridine as a possible fluorescence probe.

REFERENCES

(1) In *Nucleic Acids in Chemistry and Biology*; 3rd ed.; Blackburn, G. M., Gait, M. J., Loakes, D., Williams, D. M., Eds.; The Royal Society of Chemistry: 2006, p 1-12.

(2) Ahmadian, M.; Bergstrom, D. E. In *Modified Nucleosides: in Biochemistry, Biotechnology and Medicine*; Herdewijn, P., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: 2008, p 249-276.

(3) Damaraju, V. L.; Damaraju, S.; Young, J. D.; Baldwin, S. A.; Mackey, J.; Sawyer, M. B.; Cass, C. E. *Oncogene* **2003**, *22*, 7524-7536.

(4) Parker, W. B. *Chem. Rev.* **2009**, *109*, 2880-2893.

(5) Wiley, J. S.; Jones, S. P.; Sawyer, W. H. *Eur. J. Cancer Clin. Oncol.* **1983**, *19*, 1067-1074.

(6) Galmarini, C. M.; Thomas, X.; Calvo, F.; Rousselot, P.; Rabilloud, M.; El Jaffari, A.; Cros, E.; Dumontet, C. *Br. J. Haematol.* **2002**, *117*, 860-868.

(7) Owens, J. K.; Shewach, D. S.; Ullman, B.; Mitchell, B. S. *Cancer Res.* **1992**, *52*, 2389-2393.

(8) Heinemann, V.; Hertel, L. W.; Grindey, G. B.; Plunkett, W. *Cancer Res.* **1988**, *48*, 4024-4031.

(9) Fram, R. J.; Egan, E. M.; Kufe, D. W. *Leuk. Res.* **1982**, *7*, 243-249.

(10) Wright, K. *Nature* **1986**, *323*, 283.

(11) Jeffries, D. J. *BMJ* **1989**, *298*, 1132-1133.

(12) Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, *103*, 1875-1916.

(13) Goodchild, J.; Porter, R. A.; Raper, R. H.; Sim, I. S.; Upton, R. M.; Viney, J.; Wadsworth, H. J. *J. Med. Chem.* **1983**, *26*, 1252-1257.

(14) Regan, C. F.; Guo, Z.; Chen, Y.; Huang, C. Q.; Chen, M.; Jiang, W.; Rueter, J. K.; Coon, T.; Chen, C.; Saunders, J.; Brown, M. S.; Betz, S. F.; Struthers, R. S.; Yang, C.; Wen, J.; Madan, A.; Zhu, Y.-F. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4503-4507.

(15) Chen, C.; Wu, D.; Guo, Z.; Xie, Q.; Reinhart, G. J.; Madan, A.; Wen, J.; Chen, T.; Huang, C. Q.; Chen, M.; Chen, Y.; Tucci, F. C.; Rowbottom, M.; Pontillo, J.; Zhu, Y.-F.; Wade, W.; Saunders, J.; Bozigian, H.; Struthers, R. S. *J. Med. Chem.* **2008**, *51*, 7478-7485.

(16) Medda, F.; Russell, R. J. M.; Higgins, M.; McCarthy, A. R.; Campbell, J.; Slawin, A. M. Z.; Lane, D. P.; Lain, S.; Westwood, N. J. *J. Med. Chem.* **2009**, *52*, 2673-2682.

(17) Crisp, G. T.; Macolino, V. *Synth. Commun.* **1990**, *20*, 413-422.

(18) Machida, H.; Sakata, S. In *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K., Baker, D. C., Eds.; Plenum Press: New York, 1993, p 245-264.

(19) Jordheim, L. P.; Durantel, D.; Zoulim, F.; Dumontet, C. *Nat. Rev. Drug Discov.* **2013**, *12*, 447-464.

(20) Horwitz, J. P.; Chua, J.; Noel, M. *J. Org. Chem.* **1964**, *29*, 2076-2078.

(21) Ostertag, W.; Roesler, G.; Krieg, C. J.; Kind, J.; Cole, T.; Crozier, T.; Gaedicke, G.; Steinheider, G.; Kluge, N.; Dube, S. *Proc. Natl. Acad. Sci. USA* **1974**, *71*, 4980-4985.

(22) Clercq, E. D.; Descamps, J.; De Somer, P.; Barr, P. J.; Jones, A. S.; Walker, R. T. *Proc. Natl. Acad. Sci. USA* **1979**, *76*, 2947-2951.

(23) Suzutani, T.; Machida, H.; Sakuma, T.; Azuma, M. *Antimicrob. Agents Chemother.* **1988**, *32*, 1547-1551.

(24) Machida, H.; Sakata, S.; Kuninaka, A.; Yoshino, H. *Antimicrob. Agents Chemother.* **1981**, *20*, 47-52.

(25) Kantarjian, H. M.; O'Brien, S.; Cortes, J.; Giles, F. J.; Faderl, S.; Issa, J.-P.; Garcia-Manero, G.; Rios, M. B.; Shan, J.; Andreeff, M.; Keating, M.; Talpaz, M. *Cancer* **2003**, *98*, 522-528.

(26) Krim, J.; Grunewald, C.; Taourirte, M.; Engels, J. W. *Bioorg. Med. Chem.* **2012**, *20*, 480-486.

(27) Elwell, L. P.; Ferone, R.; Freeman, G. A.; Fyfe, J. A.; Hill, J. A.; Ray, P. H.; Richards, C. A.; Singer, S. C.; Knick, V. B.; Rideout, J. L. *Antimicrob. Agents Chemother.* **1987**, *31*, 274-280.

(28) De Clercq, E.; Descamps, J.; De Somer, P.; Barr, P. J.; Jones, A. S.; Walker, R. T. *Proc. Natl. Acad. Sci. USA* **1979**, *76*, 2947-2951.

(29) Machida, H.; Kuninaka, A.; Yoshino, H.; Ikeda, K.; Mizuno, Y. *Antimicrob. Agents Chemother.* **1980**, *17*, 1030-1031.

(30) Robins, M. J.; Barr, P. J. *J. Org. Chem.* **1983**, *48*, 1854-1862.

(31) De Clercq, E. *J. Med. Chem.* **2009**, *53*, 1438-1450.

(32) McGuigan, C.; Barucki, H.; Blewett, S.; Carangio, A.; Erichsen, J. T.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **2000**, *43*, 4993-4997.

(33) http://www.cancer.gov/cancertopics/druginfo/fda-decitabine

(34) Noé, M. S.; Sinkeldam, R. W.; Tor, Y. *J. Org. Chem.* **2013**, *78*, 8123-8128.

(35) Piton, N.; Mu, Y.; Stock, G.; Prisner, T. F.; Schiemann, O.; Engels, J. W. *Nucleic Acids Res.* **2007**, *35*, 3128-3143.

(36) Srivatsan, S. G.; Tor, Y. *Tetrahedron* **2007**, *63*, 3601-3607.

(37) Amann, N.; Wagenknecht, H.-A. *Synlett* **2002**, *5*, 687-691.

(38) Amann, N.; Pandurski, E.; Fiebig, T.; Wagenknecht, H.-A. *Chem. Eur. J.* **2002**, *8*, 4877-4883.

(39) Amann, N.; Pandurski, E.; Fiebig, T.; Wagenknecht, H.-A. *Angew. Chem. Int. Ed.* **2002**, *41*, 2978-2980.

(40) Greco, N. J.; Sinkeldam, R. W.; Tor, Y. *Org. Lett.* **2009**, *11*, 1115-1118.

(41) Sinkeldam, R. W.; Greco, N. J.; Tor, Y. *Chem. Rev.* **2010**, *110*, 2579-2619.

(42) Greco, N. J.; Tor, Y. *J. Am. Chem. Soc.* **2005**, *127*, 10784-10785.

(43) Srivatsan, S. G.; Tor, Y. *J. Am. Chem. Soc.* **2007**, *129*, 2044-2053.

(44) Hocek, M.; Fojta, M. *Org. Biomol. Chem.* **2008**, *6*, 2233-2241.

(45) Cahová, H.; Havran, L.; Brázdilová, P.; Pivoňková, H.; Pohl, R.; Fojta, M.; Hocek, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 2059-2062.

(46) Raindlová, V.; Pohl, R.; Šanda, M.; Hocek, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 1064-1066.

(47) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320-2322.

(48) The Nobel Prize in Chemistry Announcement. http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/#

(49) Al-Razzak, L. A.; Schwepler, D.; Decedue, C. J.; Balzarini, J.; De Clercq, E.; Mertes, M. P. *J. Med. Chem.* **1987**, *30*, 409-419.

(50) Al-razzak, L.; Hassan, M. E.; Mertes, M. P. *Nucleos. Nucleot.* **1983**, *2*, 243-248.

(51) Bigge, C. F.; Mertes, M. P. *J. Org. Chem.* **1981**, *46*, 1994-1997.

(52) Chang, G.; Mertes, M. P. *J. Org. Chem.* **1987**, *52*, 3625-3631.

(53) Western, E. C.; Daft, J. R.; Johnson, E. M.; Gannett, P. M.; Shaughnessy, K. H. *J. Org. Chem.* **2003**, *68*, 6767-6774.

(54) Fresneau, N.; Hiebel, M.-A.; Agrofoglio, L.; Berteina-Raboin, S. *Molecules* **2012**, *17*, 14409-14417.

(55) Ruth, J. L.; Bergstrom, D. E. *J. Org. Chem.* **1978**, *43*, 2870-2876.

(56) Bergstrom, D. E.; Ogawa, M. K. *J. Am. Chem. Soc.* **1978**, *100*, 8106-8112.

(57) Farina, V.; Hauck, S. I. *Synlett* **1991**, *1991*, 157-159.

(58) Herdewijn, P.; Kerremans, L.; Wigerinck, P.; Vandendriessche, F.; Van Aerschot, A. *Tetrahedron Lett.* **1991**, *32*, 4397-4400.

(59) Gutierrez, A. J.; Terhorst, T. J.; Matteucci, M. D.; Froehler, B. C. *J. Am. Chem. Soc.* **1994**, *116*, 5540-5544.

(60) Peyron, C.; Benhida, R.; Bories, C.; Loiseau, P. M. *Bioorg. Chem.* **2005**, *33*, 439-447.

(61) Bergstrom, D. E. *Nucleos. Nucleot.* **1982**, *1*, 1-34.

(62) Bergstrom, D. E.; Ruth, J. L. *J. Am. Chem. Soc.* **1976**, *98*, 1587-1589.

(63) Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 1133-1136.

(64) Jones, A. S.; Verhelst, G.; Walker, R. T. *Tetrahedron Lett.* **1979**, *20*, 4415-4418.

(65) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467-4470.

(66) De Clercq, E.; Descamps, J.; Verhelst, G.; Walker, R. T.; Jones, A. S.; Torrence, P. F.; Shugar, D. *J. Infect. Dis.* **1980**, *141*, 563-574.

(67) McGuigan, C.; Yarnold, C. J.; Jones, G.; Velázquez, S.; Barucki, H.; Brancale, A.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **1999**, *42*, 4479-4484.

(68) Kumar, R.; Wiebe, L. I.; Knaus, E. E. *Can. J. Chem.* **1996**, *74*, 1609-1615.

(69) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437-3440.

(70) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866-867.

(71) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513-519.

(72) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918-920.

(73) Denmark, S. E.; Regens, C. S. *Acc. Chem. Res.* **2008**, *41*, 1486-1499.

(74) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, *12*, 845-853.

(75) Pitteloud, J.-P.; Zhang, Z.-T.; Liang, Y.; Cabrera, L.; Wnuk, S. F. *J. Org. Chem.* **2010**, *75*, 8199-8212.

(76) Denmark, S. E.; Sweis, R. F. In *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH Verlag GmbH: 2008, p 163-216.

(77) Matsuhashi, H.; Hatanaka, Y.; Kuroboshi, M.; Hiyama, T. *Heterocycles* **1996**, *42*, 375-384.

(78) Mitchell, T. N. In *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH Verlag GmbH: 2008, p 125-161.

(79) Stille, J. K. *Angew. Chem. Int. Ed.* **1986**, *25*, 508-524.

(80) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174-238.

(81) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrich. Chim. Acta* **2007**, *40*, 35-41.

(82) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792-9826.

(83) Fagnou, K. *Top. Curr. Chem.* **2010**, *292*, 35-56.

(84) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

(85) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359-1470.

(86) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186-9187.

(87) Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578-7584.

(88) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066-1067.

(89) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020-18021.

(90) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330-7331.

(91) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748-11749.

(92) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Org. Chem.* **2012**, *77*, 658-668.

(93) Yan, T.; Chen, L.; Bruneau, C.; Dixneuf, P. H.; Doucet, H. *J. Org. Chem.* **2013**, *78*, 4177-4183.

(94) Cheng, C.; Shih, Y.-C.; Chen, H.-T.; Chien, T.-C. *Tetrahedron* **2013**, *69*, 1387-1396.

(95) Liu, X.-W.; Shi, J.-L.; Yan, J.-X.; Wei, J.-B.; Peng, K.; Dai, L.; Li, C.-G.; Wang, B.-Q.; Shi, Z.-J. *Org. Lett.* **2013**, *15*, 5774-5777.

(96) Kim, K. H.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2011**, *52*, 6228-6233.

(97) Mondal, B.; Hazra, S.; Roy, B. *Tetrahedron Lett.* **2014**, *55*, 1077-1081.

(98) Ćerňová, M.; Pohl, R.; Klepetářová, B.; Hocek, M. *Heterocycles* **2014**, *89*, 1159-1171.

(99) Sokolovs, I.; Lubriks, D.; Suna, E. *J. Am. Chem. Soc.* **2014**, *136*, 6920-6928.

(100) Kim, K. H.; Lee, H. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2012**, *53*, 1323-1327.

(101)Kianmehr, E.; Rezaeefard, M.; Rezazadeh Khalkhali, M.; Khan, K. M. *RSC Advances* **2014**, *4*, 13764-13767.

(102) Yu, Y.-Y.; Georg, G. I. *Chem. Commun.* **2013**, *49*, 3694-3696.

(103) Xi, P.; Yang, F.; Qin, S.; Zhao, D.; Lan, J.; Gao, G.; Hu, C.; You, J. *J. Am. Chem. Soc.* **2010**, *132*, 1822-1824.

(104) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172-1175.

(105)Meng, G.; Niu, H.-Y.; Qu, G.-R.; Fossey, J. S.; Li, J.-P.; Guo, H.-M. *Chem. Commun.* **2012**, *48*, 9601-9603.

(106) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 3125-3129.

(107) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097-2100.

(108) Köhler, K.; Wussow, K.; Wirth, A. S. In *Palladium-Catalyzed Coupling Reactions*; Wiley-VCH Verlag GmbH & Co. KGaA: 2013, p 1-30.

(109) *The Chemistry of Organic Germanium, Tin and Lead Compounds*; Patai, S.; Rappoport, Z., Eds.; John Wiley & Sons: Chichester, UK, 1995; Vol. 1 & 2002; Vol 2.

(110) Kosugi, M.; Tanji, T.; Tanaka, Y.; Yoshida, A.; Fugami, K.; Kameyama, M.; Migita, T. *J. Organomet. Chem.* **1996**, *508*, 255-257.

(111) Nakamura, T.; Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 3165-3167.

(112) Wang, Z.; Wnuk, S. F. *J. Org. Chem.* **2005**, *70*, 3281-3284.

(113) Wnuk, S. F.; Garcia, P. I.; Wang, Z. *Org. Lett.* **2004**, *6*, 2047-2049.

(114) Spivey, A. C.; Tseng, C.-C.; Hannah, J. P.; Gripton, C. J. G.; de Fraine, P.; Parr, N. J.; Scicinski, J. J. *Chem. Commun.* **2007**, 2926-2928.

(115)Spivey, A. C.; Gripton, C. J. G.; Hannah, J. P.; Tseng, C.-C.; de, F. P.; Parr, N. J.; Scicinski, J. J. *Appl. Organomet. Chem.* **2007**, *21*, 572-589.

(116) Torres, N. M.; Lavis, J. M.; Maleczka Jr, R. E. *Tetrahedron Lett.* **2009**, *50*, 4407-4410.

(117) Lukevics, E.; Arsenyan, P.; Germane, S.; Shestakova, I. *Appl. Organomet. Chem.* **1999**, *13*, 795-798.

(118) Lukevics, E.; Ignatovich, L. In *Metallotherapeutic Drugs and Metal-Based Diagnostic Agents*; Gielen, M., Tiekink, E. R. T., Eds. 2005, p 279-295.

(119) Yao, S.; Jiang, J.; Yang, P.; Cai, J. *Bull. Korean Chem. Soc.* **2012**, *33*, 1121-1122.

(120) Jiang, J.; Yao, S.; Cai, H.-H.; Yang, P.-H.; Cai, J. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5727-5732.

(121) Mel'nik, S. l.; Bakhmedova, A. A.; Nedorezova, T. P.; Iartseva, I. V.; Zhukova, O. S.; Dobrynin, Y. V.; Preobrazhenskaya, M. N.; Kolesnikov, S. P.; Li, V. Y. *Bioorg. Khim.* **1985**, *11*, 1248-1252.

(122) Miyamoto, T. K.; Sugita, N.; Matsumoto, Y.; Sasaki, Y.; Konno, M. *Chem. Lett.* **1983**, *12*, 1695-1698.

(123) Li, F.; Zhang, Z.; Gao, H. *Met.-Based Drugs* **1996**, *3*, 241-242.

(124) Yang, F.; Jin, H.; Pi, J.; Jiang, J.-h.; Liu, L.; Bai, H.-h.; Yang, P.-h.; Cai, J.-Y. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5544-5551.

(125) Shangguan, G. Q.; Huang, L. L.; Qu, X. G. *Chin. Chem. Lett.* **2007**, *18*, 1347-1350.

(126) Li, J.; Zhai, F.; Wang, X.; Li, E.; Zhang, S.; Zhang, Q.; Du, X. *Polyhedron* **2008**, *27*, 1150-1154.

(127) Lukevics, E.; Ignatovich, L.; Shestakova, I. *Appl. Organomet. Chem.* **2003**, *17*, 898-905.

(128) Mirabelli, C. K.; Badger, A. M.; Sung, C. P.; Hillegass, L.; Sung, C. M.; Johnson, R. K.; Picker, D.; Schwartz, D.; Dorman, J.; Martellucci, S. *Anticancer Drug Des.* **1989**, *3*, 231-242.

(129) Slavik, M.; Blanc, O.; Davis, J. *Invest. New Drugs* **1983**, *1*, 225-234.

(130)DiMartino, M. J.; Lee, J. C.; Badger, A. M.; Muirhead, K. A.; Mirabelli, C. K.; Hanna, N. *J. Pharmacol. Exp. Ther.* **1986**, *236*, 103-110.

(131) Lukevics, E.; Ignatovich, L. *Appl. Organomet. Chem.* **1992**, *6*, 113-126.

(132) Menchikov, L. G.; Ignatenko, M. A. *Pharm. Chem. J.* **2013**, *46*, 635-638.

(133) Trushule, M.; Kupche, É.; Augustane, I.; Verovskii, N. V.; Lukevits, É.; Baumane, L.; Gavar, R.; Stradyn, Y. *Chem. Heterocycl. Compd.* **1991**, *27*, 1358-1364.

(134) Zhang, Z.-T.; Pitteloud, J.-P.; Cabrera, L.; Liang, Y.; Toribio, M.; Wnuk, S. F. *Org. Lett.* **2010**, *12*, 816-819.

(135) Pitteloud, J.-P.; Liang, Y.; Wnuk, S. F. *Chem. Lett.* **2011**, *40*, 967-969.

(136) Pitteloud, J.-P., Florida International University, 2011.

(137) Prince, P. D.; Sean McGrady, G.; Steed, J. W. *New J. Chem.* **2002**, *26*, 457-461.

(138) Liang, Y.; Pitteloud, J.-P.; Wnuk, S. F. *J. Org. Chem.* **2013**.

(139)Akiyama, T. In *Main Group Metals in Organic Synthesis*; Yamamoto, H., Oshima, K., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, p 593-619.

(140) Spivey, A. C.; Diaper, C. M. *Sci. Syn.* **2003**, *5*, 181-188.

(141) Corriu, R. J. P.; Fernandez, J. M.; Guerin, C. *J. Organomet. Chem.* **1980**, *192*, 347-352.

(142) Čerňová, M.; Čerňa, I.; Pohl, R.; Hocek, M. *J. Org. Chem.* **2011**, *76*, 5309-5319.

(143) Spivey, A. C.; Gripton, C. J. G.; Hannah, J. P. *Curr. Org. Synth.* **2004**, *1*, 211-226.

(144) Denmark, S. E.; Sweis, R. F.; Wehrli, D. *J. Am. Chem. Soc.* **2004**, *126*, 4865-4875.

(145) Rayala, R.; Wnuk, S. F. *Tetrahedron Lett.* **2012**, *53*, 3333-3336.

(146) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496-16497.

(147) Wicke, L.; Engels, J. W. *Bioconjugate Chem.* **2012**, *23*, 627-642.

(148) Kobayashi, Y.; Yamamoto, K.; Asai, T.; Nakano, M.; Kumadaki, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, *0*, 2755-2761.

(149) Bobek, M.; Kavai, I.; Sharma, R. A.; Grill, S.; Dutschman, G.; Cheng, Y. C. *J. Med. Chem.* **1987**, *30*, 2154-2157.

(150) Conreaux, D.; Bossharth, E.; Monteiro, N.; Desbordes, P.; Vors, J.-P.; Balme, G. *Org. Lett.* **2007**, *9*, 271-274.

(151) Bengtsson, C.; Almqvist, F. *J. Org. Chem.* **2009**, *75*, 972-975.

(152) Singh, B. K.; Cavalluzzo, C.; De Maeyer, M.; Debyser, Z.; Parmar, V. S.; Van der Eycken, E. *Eur. J. Org. Chem.* **2009**, *27*, 4589-4592.

(153) Shimizu, H.; Manabe, K. *Tetrahedron Lett.* **2006**, *47*, 5927-5931.

(154) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754-8756.

(155) Čerňová, M.; Pohl, R.; Hocek, M. *Eur. J. Org. Chem.* **2009**, *22*, 3698-3701.

(156) Ichinose, Y.; Oda, H.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3468-3470.

(157) Kinoshita, H.; Nakamura, T.; Kakiya, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 2521-2524.

(158) Nozaki, K.; Ichinose, Y.; Wakamatsu, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2268-2272.

(159) Schwier, T.; Gevorgyan, V. *Org. Lett.* **2005**, *7*, 5191-5194.

(160) Bernardoni, S.; Lucarini, M.; Pedulli, G. F.; Valgimigli, L.; Gevorgyan, V.; Chatgilialoglu, C. *J. Org. Chem.* **1997**, *62*, 8009-8014.

(161) Sharma, R. A.; Kavai, I.; Hughes, R. G.; Bobek, M. *J. Med. Chem.* **1984**, *27*, 410-412.

(162) Ichinose, Y.; Nozaki, K.; Wakamatsu, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 3709-3712.

(163) Wnuk, S. F.; Sacasa, P. R.; Restrepo, J. *Nucleos. Nucleot. Nucl.* **2009**, *28*, 537-549.

(164) David-Quillot, F.; Thiery, V.; Abarbri, M.; Thibonnet, J.; Besson, T.; Duchene, A. *Main Group Met. Chem.* **2007**, *30*, 235-244.

(165) Brancale, A.; McGuigan, C.; Algain, B.; Savy, P.; Benhida, R.; Fourrey, J.-L.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2507-2510.

(166) Thurber, T. C.; Townsend, L. B. *J. Org. Chem.* **1976**, *41*, 1041-1051.

(167) Zhang, W.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177-1180.

(168) Prachayasittikul, S.; Sornsongkhram, N.; Pingaew, R.; Worachartcheewan, A.; Ruchirawat, S.; Prachayasittikul, V. *Molecules* **2009**, *14*, 2768-2779.

(169) Fahrig, R.; Eger, K.; Fuehrer, M.; Heinze, N.; Klemm, M.; Heinrich, J.-C. US, 2009; Vol. 0166096 A1.

(170) Lu, Q.; Zhang, J.; Zhao, G.; Qi, Y.; Wang, H.; Lei, A. *J. Am. Chem. Soc.* **2013**, *135*, 11481-11484.

(171) Chatgilialoglu, C.; Timokhin, V. I.; Zaborovskiy, A. B.; Lutsyk, D. S.; Prystansky, R. E. *J. Chem. Soc., Perkin Trans. 2* **2000**, 577-582.

(172) Barr, P. J.; Chananont, P.; Hamor, T. A.; Jones, A. S.; O'Leary, M. K.; Walker, R. T. *Tetrahedron* **1980**, *36*, 1269-1273.

(173) Lutsenko, I. F.; I. Baukov, Y.; Dudukina, O. V.; Kramarova, E. N. *J. Organomet. Chem.* **1968**, *11*, 35-48.

(174) Dougan, H.; Rennie, B. A.; Lyster, D. M.; Sacks, S. L. *Appl. Radiat. Isot.* **1994**, *45*, 795-801.

(175) Yu, C.-S.; Oberdorfer, F. *Synlett* **2000**, 86-88.

(176) Yu, C.-S.; Wu, C.-H.; Chiang, L.-W.; Wang, R.-T.; Wang, H.-Y.; Yeh, C.-H.; Lin, K.-I. *Chem. Lett.* **2005**, *34*, 1390-1391.

(177) Yu, C.-S.; Chiang, L.-W.; Wu, C.-H.; Wang, R.-T.; Chen, S.-W.; Wang, H.-Y.; Yeh, C.-H. *Nucl. Med. Biol.* **2006**, *33*, 367-370.

(178) Robins, M. J.; Manfredini, S.; Wood, S. G.; Wanklin, R. J.; Rennie, B. A.; Sacks, S. L. *J. Med. Chem.* **1991**, *34*, 2275-2280.

(179) Robins, M. J.; Manfredini, S. *Tetrahedron Lett.* **1990**, *31*, 5633-5636.

(180) Morin, K. W.; Atrazheva, E. D.; Knaus, E. E.; Wiebe, L. I. *J. Med. Chem.* **1997**, *40*, 2184-2190.

(181) Oda, H.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 3221-3224.

(182) Oda, H.; Oshima, K.; Nozaki, H. *Chem. Lett.* **1985**, 53-56.

(183) Cai, C.; Vasella, A. *Helv. Chim. Acta* **1996**, *79*, 255-268.

(184) Forristal, I. *J. Sulfur Chem.* **2005**, *26*, 163-185.

(185) Meadows, D. C.; Gervay-Hague, J. *Med. Res. Rev.* **2006**, *26*, 793-814.

(186) Nájera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547-10658.

(187) Dadová, J.; Orság, P.; Pohl, R.; Brázdová, M.; Fojta, M.; Hocek, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 10515-10518.

(188) Li, X.; Shi, X.; Fang, M.; Xu, X. *J. Org. Chem.* **2013**, *78*, 9499-9504.

(189) Zeng, X.; Ilies, L.; Nakamura, E. *Org. Lett.* **2012**, *14*, 954-956.

(190) Taniguchi, T.; Fujii, T.; Ishibashi, H. *J. Org. Chem.* **2010**, *75*, 8126-8132.

(191) MacPherson, I. S.; Temme, J. S.; Habeshian, S.; Felczak, K.; Pankiewicz, K.; Hedstrom, L.; Krauss, I. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 11238-11242.

(192) Macíčková-Cahová, H.; Pohl, R.; Hocek, M. *ChemBioChem* **2011**, *12*, 431-438.

(193) Borsenberger, V.; Kukwikila, M.; Howorka, S. *Org. Biomol. Chem.* **2009**, *7*, 3826-3835.

(194) Wolf, W. M. *J. Mol. Struct.* **1999**, *474*, 113-124.

(195) Wildeman, J.; Van Leusen, A. M. *Synthesis* **1979**, *9*, 733-734.

(196) Xie, Y.-Y.; Chen, Z.-C. *Synth. Commun.* **2001**, *31*, 3145-3149.

(197) Fan, A.-L.; Cao, S.; Zhang, Z. *J. Heterocycl. Chem.* **1997**, *34*, 1657-1660.

(198) Holmquist, C. R.; Roskamp, E. J. *Tetrahedron Lett.* **1992**, *33*, 1131-1134.

(199) Kamigata, N.; Udodaira, K.; Shimizu, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, *5*, 783-786.

(200) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Wang, M. *J. Org. Chem.* **2003**, *68*, 1443-1446.

(201)Rechtin, T. M.; Black, M. E.; Mao, F.; Lewis, M. L.; Drake, R. R. *J. Biol. Chem.* **1995**, *270*, 7055-7060.

(202) Evans, R. K.; Haley, B. E. *Biochemistry* **1987**, *26*, 269-276.

(203) Gourdain, S.; Petermann, C.; Harakat, D.; Clivio, P. *Nucleos. Nucleot. Nucl.* **2010**, *29*, 542-546.

(204) Neef, A. B.; Luedtke, N. W. *ChemBioChem* **2014**, *15*, 789-793.

(205) Gourdain, S.; Martinez, A.; Petermann, C.; Harakat, D.; Clivio, P. *J. Org. Chem.* **2009**, *74*, 6885-6887.

(206) Liu, Z.; Liao, P.; Bi, X. *Org. Lett.* **2014**, *16*, 3668-3671.

(207) Ingale, S. A.; Mei, H.; Leonard, P.; Seela, F. *J. Org. Chem.* **2013**, *78*, 11271-11282.

(208) Shelke, S. A.; Sigurdsson, S. T. *Angew. Chem. Int. Ed.* **2010**, *49*, 7984-7986.

(209) Balaji, V. N. I.; Prasanna, M. D.; Samiron, P.; Singh, S. K.; PCT/IN2007/000157: 2009, p 30pp., Cont.-in-part of Appl. No. PCT/IN2007/000157.

(210) Malik, V.; Singh, P.; Kumar, S. *Tetrahedron* **2005**, *61*, 4009-4014.

(211) Sako, M.; Hirota, K.; Maki, Y. *Tetrahedron* **1983**, *39*, 3919-3921.

(212) Asakura, J.; Robins, M. J. *J. Org. Chem.* **1990**, *55*, 4928-4933.

(213) Schinazi, R. F.; Chen, M. S.; Prusoff, W. H. *J. Med. Chem.* **1979**, *22*, 1273-1277.

(214) Barr, P. J.; Jones, A. S.; Serafinowski, P.; Walker, R. T. *J. Chem. Soc., Perkin Trans. 1* **1978**, *10*, 1263-1267.

(215) Jones, A. S.; Rahim, S. G.; Walker, R. T.; De Clercq, E. *J. Med. Chem.* **1981**, *24*, 759-760.

(216) Baker, B. R.; Kelley, J. L. *J. Med. Chem.* **1970**, *13*, 461-467.

(217) Doub, L.; Krolls, U.; Vandenbelt, J. M.; Fisher, M. W. *J. Med. Chem.* **1970**, *13*, 242-246.

(218) Nair, V.; Chi, G.; Uchil, V. R. USA, 2007; Vol. WO 2007/106450 A2.

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Zhu, M.-L.; Zhang, Z.-T.; Xue, D.; Hua, H.-L.; Liang, Y.; Wnuk, S. F. Synthesis of 1-amino-5,6-diaryl-3-cyano-1*H*-pyridin-2-ones and 6,7-diaryl-4-cyano-3-hydroxy-1*H*-[1,2]diazepines from isoflavones. *Helv. Chim. Acta. 2014, 97, 561-568.*

Adhikary, A.; Kumar, A.; Heizer, A. N.; Palmer, B. J.; Pottiboyina, V.; Liang, Y.; Wnuk, S. F. Hydroxyl ion addition to one-electron oxidized thymine: Unimolecular interconversion of C5 to C6 OH-adducts. *J. Am. Chem. Soc.* 2013, *135*, 3121-3135.

Liang, Y.; Gloudeman, J.; Akinniyi, O.; Wnuk, S. F. TBAF-promoted Pd-catalyzed direct arylation of 5-iodouracil nucleosides. *247th ACS National Meeting & Exposition*, Dallas, TX, United States, 2014, March 16-20.

Liang, Y.; Pitteloud, J.-P.; Herrandez, E.; Wnuk, S. F. Unexpected hydrogermylaytion of 5-ethynyluracil nucleosides: Mechanistic consideration. *89th Florida Annual Meeting and Exposition* (FAME), Tampa, FL, United States, 2013, May 9-11.

Liang, Y.; Pitteloud, J.-P.; Wnuk, S. F. Hydrogermylation of 5-ethynyluracil nucleosides: Formation of 5-(2-germylvinyl)uracil and 5-(2-germylacetyl)uracil nucleosides. *J. Org. Chem.* 2013, *78*, 5761-5767.

Liang, Y.; Pitteloud, J.-P.; Wnuk, S. F. Conversion of 5-ethynyluracil nucleosides to 5-(2-germylvinyl) and 5-(2-germylacetyl)uracil nucleosides *via* hydrogermylation. *245th ACS National Meeting & Exposition*, New Orleans, LA, United States, 2013, April 7-11.

Liang, Y.; Pitteloud, J.-P.; Wnuk, S. F. Chemoselective transfer of allyl or phenyl group from allyl(phenyl)germanes in Pd-catalyzed reactions with aryl halides. *243rd ACS National Meeting & Exposition*, San Diego, CA, United States, 2012 March 25-29, 600.

Liang, Y.; Zhang, Z.-T.; The synthesis of diphenylpyrazole[3,4-*b*]pyridine compound and single crystal structure analysis. *CCS 6th national organic chemistry conference*. 2009, *6*, 60.

Zhu, M.; Zhang, Z.; Xue, D.; Qiao, J.; Liang, Y.; Wnuk, S. F. Synthesis of 5,6-diarylpyridin-2(1*H*)-ones from isoflavones. *Chin. J. Chem. 2013, 31,* 1027-1032.

Pitteloud, J.-P.; Liang, Y.; Wnuk, S. F. Chemoselective transfer of allyl or phenyl group from allyl(phenyl)germanes in Pd-catalyzed reactions with aryl halides. *Chem. Lett.* 2011, *40*, 967-969.

Zhang, Z.-T.; Ma, Y.-Q.; Liang, Y.; Xue, D.; He, Q.. An efficient one-pot synthesis of diarylpyrazolo[1,5-a]pyrimidine from isoflavones. *J. Heterocyclic Chem.* 2011, *48*, 279-285.

Pitteloud, J.-P.; Zhang, Z.-T.; Liang, Y.; Cabrera, L.; Wnuk, S. F. Fluoride-promoted cross-coupling of chloro(mono-, di-, or triphenyl)germanes with aryl halides in "moist" toluene. Multiple transfer of the phenyl group from organogermane substrates and comparison of the coupling efficiencies of chloro(phenyl)germanes with their corresponding stannane and silane counterparts. *J. Org. Chem.* 2010, 75, 8199-8212.

Zhang, Z.-T.; Pitteloud, J.-P.; Cabrera, L.; Liang, Y.; Toribio, M.; Wnuk, S. F., Arylchlorogermanes/TBAF/"moist" toluene: A promising combination for Pd-catalyzed germyl-stille cross-coupling. *Org. lett.* 2010, *12*, 816-819.

Zhang, Z.-T.; Liang, Y.; Ma, Y.-Q.; Xue, D.; Yang, J.-L. A one-step synthesis of diarylpyrazolo[3,4-b]pyridines from isoflavones. *J. Comb. Chem.* 2010*, 12*, 600-603.

Zhang, X.-L.; Zhang, Z.-T.; Liang, Y. Synthesis and single crystal X-ray structure of $[Na(H_2O)_2(C_{18}H_{15}O_6SO_3)]_2$. *J. Chem. Crystallogr.* 2008, *38*, 861-865.