Synthetic Studies directed towards Asmarines

Dissertation for the degree of Ph.D.

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to Petra

Acknowledgments

During my studies here at the University of Oslo, I have attended several PhD defences. From this experience I learned that the acknowledgments section is a very important part of the thesis, because most of the future readers will pay attention especially to this section. Therefore, I would like to use this opportunity to encourage everyone who is reading these lines to continue reading through the whole work.

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person I met that possess a samurai sword as well as the driving license for a snow-scooter. "*Get to the choppah!"*

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Uncle Tapio, I will do this in Finnish way. Simply - Thank you. However, I would like to remind you, that you still owe me the lessons of ice-hockey. "*Kultaa Suomelle!"*

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Jindřich Kania
Oslo, February 2013

Summary

The present thesis is focused on the design of synthetic routes towards asmarine analogues. Asmarines are marine natural products isolated from the sponges *Raspalia* sp. The asmarine molecule contains a seven-membered ring fused with a purine core. This tetrahydrodiazepinopurine moiety has previously been constructed for example by ring-closing metathesis (RCM). We were focused on developing this RCM reaction pathway further, in order to introduce a chiral centre to the 7-membered ring.

The attempts to employ chiral allylic amines in the strategy were not successful. However, we managed to achieve the synthesis of the seven-membered ring by a novel synthetic approach employing Ru-catalysed double bond migration and Cu-catalysed C-N coupling. Thus, a new method for double bond migration of *N*-allyl purines was successfully developed, involving the substrate 7-allyl-6-iodo-7*H*-purine and the catalyst $RuClH(CO)(PPh_3)_3$. Furthermore, the possibilities of C-N bond formation between *tert*-butyl allylcarbamate and 7-alkylated 6-halopurines were investigated. Suitable conditions for the coupling were determined using the Goldberg reaction and 6-iodo-7-(prop-1-en-1-yl)-7*H*-purine was successfully coupled with *tert*-butyl allylcarbamate, giving *tert*-butyl allyl(7-(prop-1-en-1-yl)-7*H*-purin-6-yl)carbamate. Finally, the RCM with this intermediate led to the previously known 7,8,9,10-tetrahydro-[1,4]diazepino[1,2,3-gh]purine.

In addition, attention is paid to the synthesis and rearrangement of *N*-allyl to *N*-propenyl purines. There are very few convenient routes to *N*-alkenylpurines in general. Therefore, we have carried out a study on the isomerisation of 9-allyl- and 7-allylpurines. Various *N*-allyl purines were prepared, and base- or transition metal complex promoted isomerisations were explored. Subsequently, this study was extended for substrates bearing additional substitution on the allyl chain. Scope and limitation of the double bond migration methodologies and *E/Z* selectivity is discussed.

Table of contents

List of Abbreviations and symbols

$[a]_D^{20}$	specific rotation
Ac	acetyl
Alloc	allyloxycarbonyl
aq.	aqueous
bd	broad doublet (NMR)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bs	broad singlet (NMR)
Bu	butyl
ºC	degree celsius
calcd.	calculated
cat.	catalyst
CBS	Corey-Bakshi-Shibata
Cbz	Benzyl carbamate
cod	1,5-Cyclooctadiene
comp.	compound
conv.	conversion
Cy	cyclohexyl
δ	delta ppm, chemical shift (NMR)
Δ	heating at reflux
d	doublet (NMR)
dba	Dibenzylideneacetone
DCE	Dichloroethane
DCM	Dichloromethane
dd	doublet of doublet (NMR)
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine (Hünig's base)
DMA	Dimethylacetamide
DMAP	4-*N*,*N*-dimethylaminopyridine

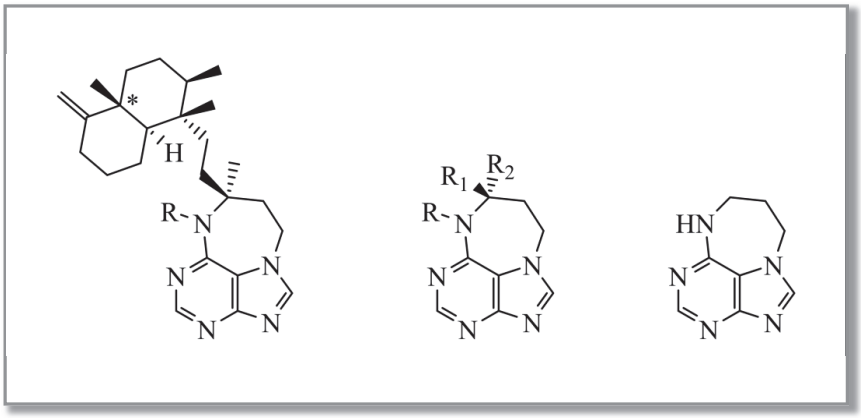
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DNP	2,4-dinitriophenol
E	entgegen
EI	electron impact (MS)
ESI	electrospray (MS)
epi	epimer
Et	ethyl
eq.	equivalent(s)
Fer	ferrocenyl
g	gram
h	hour(s)
^{1}H	proton
Hex	Hexane
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectrometry
Hz	hertz
i-	*iso*
J	coupling constant (NMR)
µL	micro litre
Leu	Leucine
m	multiplet (NMR)
m/z	mass per charge (MS)
M^{+}	molecular ion peak (MS)
Me	methyl
MeCN	Acetonitrile
Mes	mesitylene
mg	milligram
MHz	mega hertz
min	minute(s)
mL	millilitre
mmol	millimole
MOM	methoxymethyl

MS	mass scepctroscopy
mp	melting point
n.d.	not determined
n.r.	no reaction
NMR	nuclear magnetic resonance
PG	protecting group
Ph	phenyl
Phe	Phenylalanine
PMB	*p*-methoxybenzyl
Pr	propyl
Prod.	product
r.t.	room temperature
RCM	ring-closing metathesis
red	reduction
p-	*para*-
S_NAr	Nucleophilic Aromatic Substitution
solv.	solvent
sp.	sponge
subst.	substrate
t	triplet (NMR)
t-	*tert*-
TFA	trifluoroacetic acid
THDAP	10-Hydroxytetrahydro[1,4]diazepino[1,2,3-g,h]purine system
THF	Tetrahydrofurane
TLC	thin layer chromatography
TMPM	trimethoxyphenylmethyl
Ts	tosyl
p-TSAH	*p*-Toluenesulfonic acid
tt	triplet of triplet (NMR)
Val	Valine
Z	zusammen

Graphical abstracts

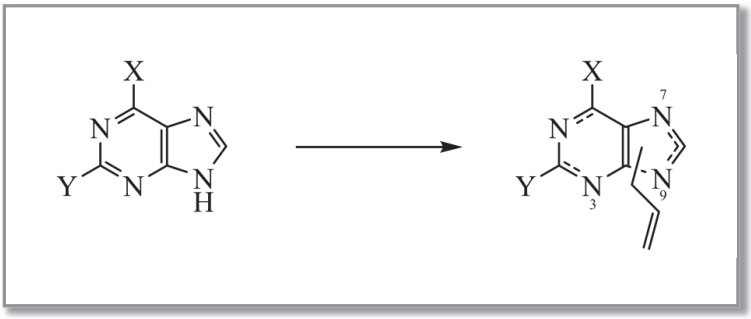
CHAPTER 1

Introduction



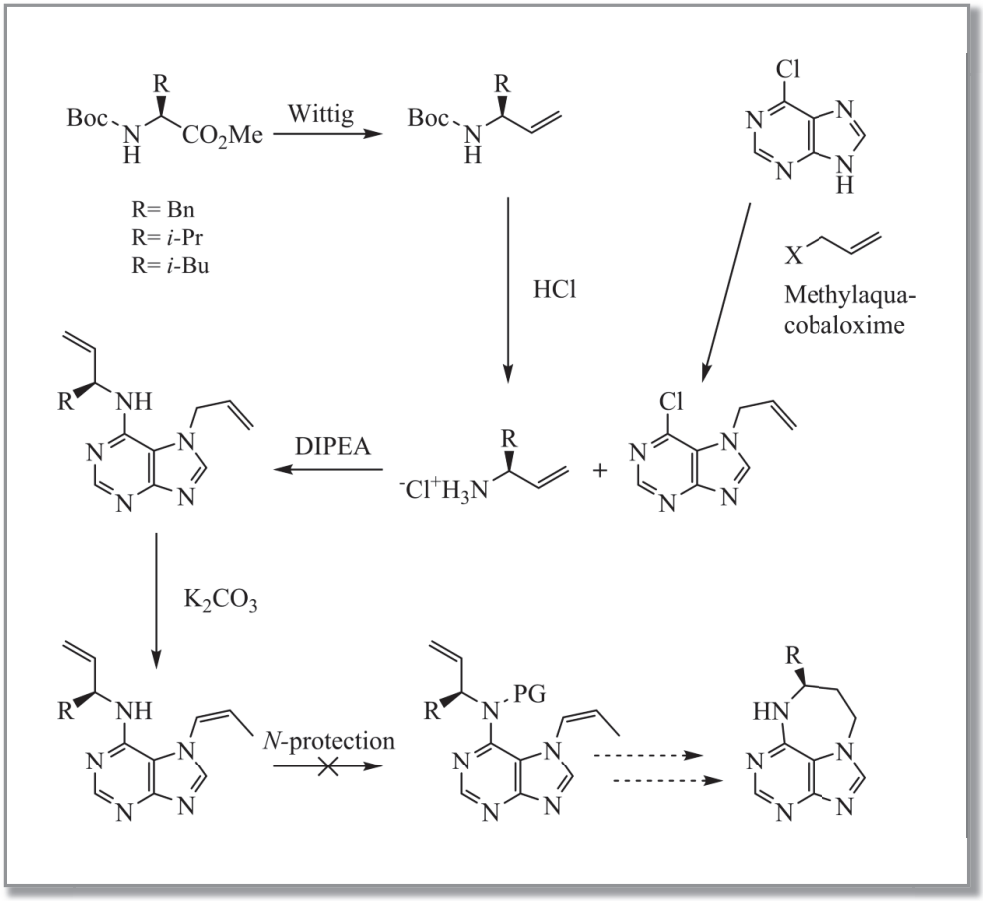
CHAPTER 2

Synthesis of the different *N*-allyl purines



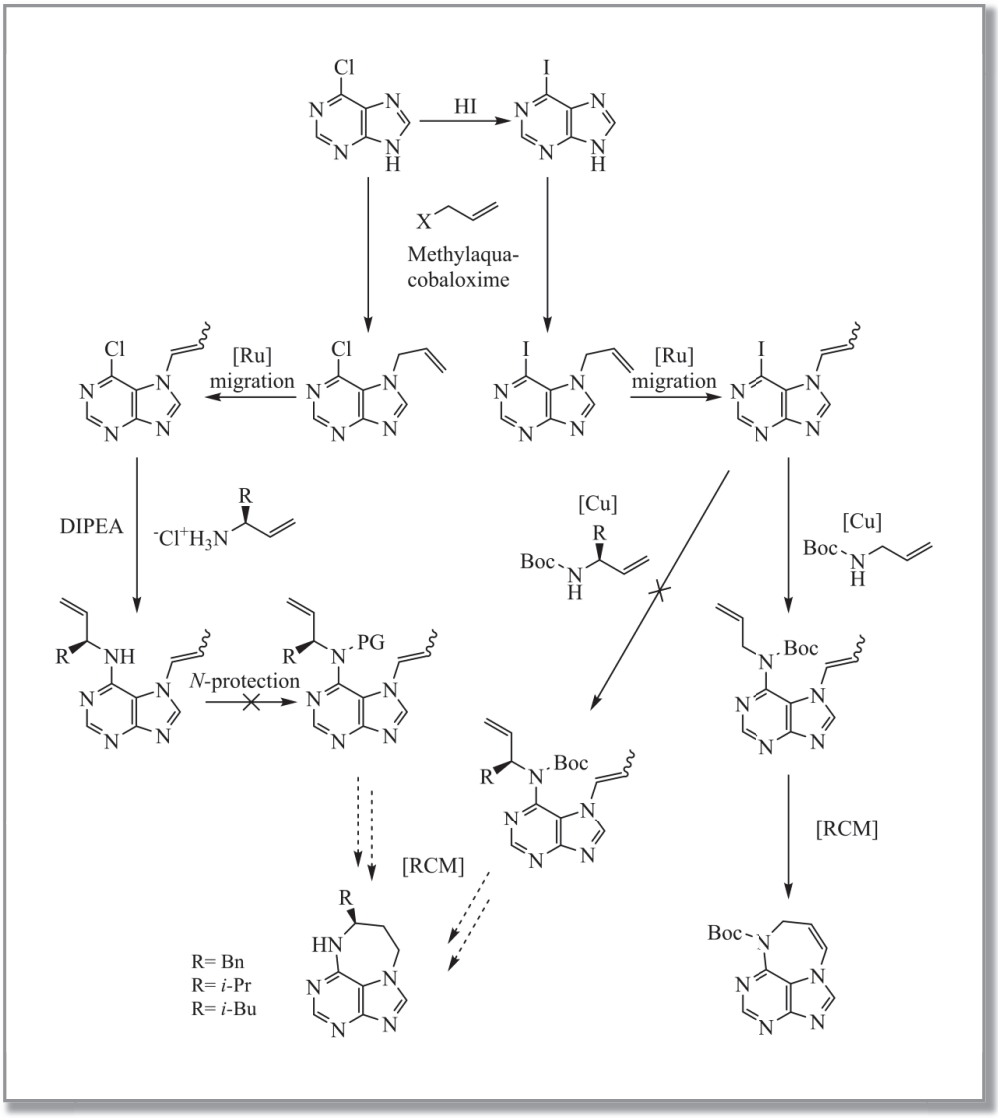
CHAPTER 3

Synthesis towards asmarines starting from *a*-amino acids



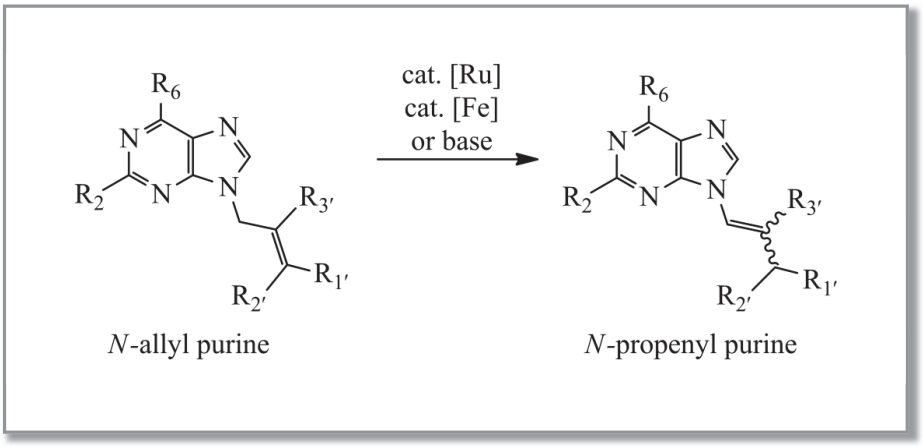
CHAPTER 4

Ru promoted double bond migration and Cu mediated C-N bond formation in the synthesis towards asmarines



CHAPTER 5

Double bond migration in *N*-9 and *N*-7 allyl purines



N-allyl purine

N-propenyl purine

Chapter 1

Synthesis of asmarine analogues

1.1 Marine natural products and bioprospecting

The origin of modern medicine and pharmacology is strongly connected with products from organisms in nature. It is well documented throughout human history, that almost all medications have their origin in natural products from terrestrial organisms such as higher plants being the most traditional source.[1] Nowadays, the share of natural products reaches above one-third of overall drug production.[2,3] For example the hypolipidemic agent atorvastatin (Figure 1.1), which is the analogue of the fungal metabolites,[4] ranked in the 35 best selling pharmaceutical products in 2000, 2001, and 2002.[2] The chemistry of natural products contributes considerably for example in the field of cancer and hypertensive treatment.[2]

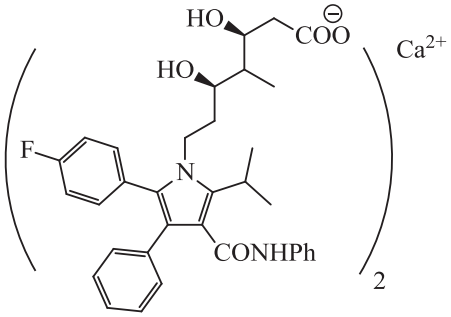


Figure 1.1 Structure of Atorvastatin.[4]

An important trend in the discovery of novel bioactive molecules is the implementation of screening for marine secondary metabolites.[3,5] The marine habitat is a promising reservoir of interesting organisms. In this unique environment, plants, animals and other microorganisms can produce various metabolites, which are structurally different from those found in terrestrial species.[3,6] Interestingly, invertebrates such as marine sponges[7] are known to produce a wide range of compounds for chemical defence.[3] Even though the oceans cover more than 60% of the Earths biosphere, the natural products coming from the seas were somewhat overlooked until recently.[1] The overall interest in marine natural products started approximately 60 years ago with the isolation of spongothymidine and spongouridine (Figure

1.2). Both these sponge-derived nucleosides were obtained from the *Cryptothetia crypta* sponge[8] and possess antiviral activity. This discovery brought the attention to the field of marine natural products bioprospecting.[1,9]

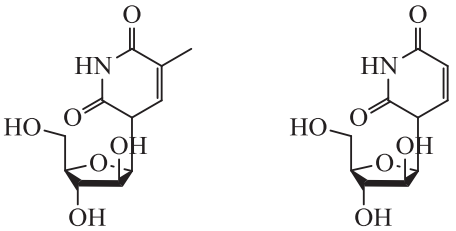


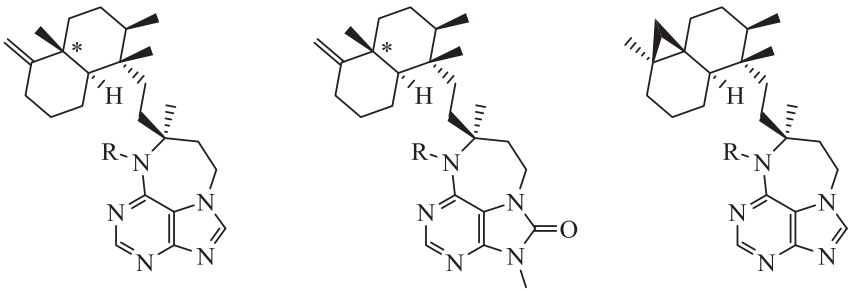
Figure 1.2 Antiviral nucleotides from *Cryptothetia crypta* sponge.

Up to date, the screening for marine natural products has offered more than 14,000 novel and structurally unique compounds with interesting bioactivities.[1,7] However, marine product based analogues reached the level of therapeutic agents to a very little extent.[1] A general problem concerning natural products is the high cost of the time demanding screening process[3] and more importantly, the unavailability of the substances in acceptable amount.[1] A drug production based on the isolation from the marine biomass is not feasible due to the limited availability of the compounds of interest. Moreover, harvesting marine species on a large scale would have a negative impact on the marine ecosystem.[1] Hence, bioprospecting has to be connected with modern synthetic organic chemistry. The development of methods for the synthesis of newly discovered bioactive targets will unlock the possibility to fully investigate the real potential of such substances, if enough material can be produced. Furthermore, preparation of various synthetic analogues of natural products would allow extensive study of structure activity relationship and thereby enhance pharmaceutical effect or address some toxicity issues.[6]

1.2 Asmarines

Asmarines represent a relatively new class of nitrogen-containing metabolites from marine sponges. Currently, eleven different asmarines are reported.[10-13] The first known asmarines A, B and C were isolated from *Raspailia* sp. living in the Red Sea.[10] Later on, the structures of asmarines D, E and F, supplied from the same source, were described.[11] Asmarines G and H were obtained from the Indian ocean species of *Raspailia* sp.[12] The remaining compounds I, J and K were isolated from *Raspailia* sp. located in the Madagascar

area.[13] The asmarine molecules consist of three important structure parts: Particularly the terpenoid moiety which is attached to a diazacycloheptane, and a purine core which is fused with this 7-membered ring in positions C-6 and *N*-7 (Figure 1.3). All known asmarines can be sorted into three categories based on their structural properties. For example the asmarines C-F possess a carbonyl group at C-8 of the purine unit, while a cyclopropane ring in the terpenoid part is a significant structural feature in case of the asmarines I and J.



Asmarine A: R= OH
Asmarine B: R= OH, *epi
Asmarine G: R= OMe
Asmarine H: R= H
Asmarine K: R= H, *epi

Asmarine C: R= H, *epi
Asmarine D: R= H
Asmarine E: R= OMe, *epi
Asmarine F: R= OMe

Asmarine I: R= OH
Asmarine J: R= H

Figure 1.3 Structure of known asmarines.[10-13]

From the biosynthetical point of view, the purine moiety is most probably originating from the adenine molecule.[11] Thus, asmarines could be considered as adenine derivates. On the other hand, the presence of the bicyclic diterpenoid moiety assigns asmarines also to the group of clerodanes.[14] Little is known so far about the bioactivity of these metabolites, however, asmarines A and B possess an interesting selective cytotoxicity to tumor cells.[10] This makes this class of compounds a very attractive target for the development of new pharmaceuticals. Unfortunately, as with all other marine natural products in general, asmarines are only available in very limited amounts. For instance the isolation of the asmarines A and B started with 20 grams of crude collected sponge material. The final amount of the obtained pure metabolites from this material did not exceeded 90 mg.[10] Moreover, asmarines C, D and E, F respectively were isolated as inseparable pairs of compounds.[11] Therefore, an efficient and scalable synthetic route to obtain high amounts of

these natural products or their synthetic analogues is highly desired to allow an enhanced study of the pharmacological potential of this class of substances.[15,16]

1.2.1 Previous work in the field of asmarine analogues synthesis

After the first reports regarding the general structure of asmarines and their cytotoxic properties, there has been a rise in interest in the preparation of these molecules.[17] Regarding the synthesis of the heterocyclic part, the crucial step is the construction of the 10-hydroxytetrahydro[1,4]diazepino[1,2,3-g,h]purine system (THDAP). There are several possibilities for the formation of the bonds **a-e** (Figure 1.4).

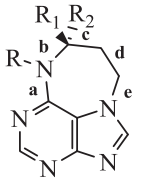
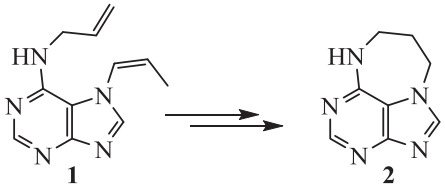


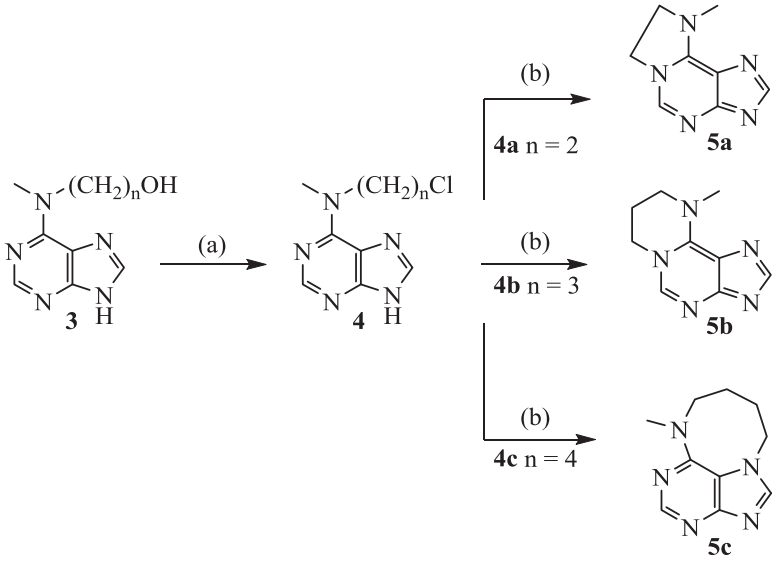
Figure 1.4 THDAP ring and the bonds **a-e** in the general structure of the asmarine.

This thesis will focus on the synthesis of asmarine analogues *via* the formation of bond **d**. We established our study on the basis of recent contribution to the field, wherein the ring-closing metathesis (RCM) was employed as the key step (Scheme 1.1).[18] A detailed discussion regarding this original RCM approach as well as our following investigations of this methodology is presented in Chapter 3 and Chapter 4. The other reported synthetic routes leading to model compounds bearing a 7-membered ring are described below in this chapter.



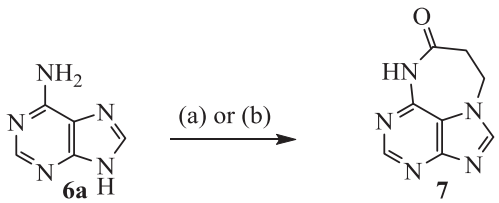
Scheme 1.1 The RCM reaction in the synthesis of the asmarine analogues.

Before the asmarine structure was discovered, there was already a known procedure leading to the tricyclic fused ring system on the adenine molecule (Scheme 1.2). While ethanol and propanol derivates **4a** and **4b** reacted preferably with the *N*-1 position, the cyclisation reaction of the precursor *N*-(4-chlorobutyl)-*N*-methyl-9*H*-purin-6-amine (**4c**) occurred in the position *N*-7 and gave the product **5c** with an 8-membered ring.[19]



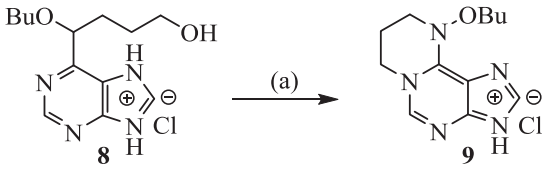
Scheme 1.2 Reagents and conditions: (a) $SOCl_2$, r.t., 3 h; (b) NaH, DMF, r.t., 2 h.[19]

More importantly, the first successful formation of the THDAP ring was achieved during an investigation of the Michael addition with adenine derivates (Scheme 1.3).[20] The reaction of adenine either with acrylic anhydride or vinyl acrylate resulted in the formation of the bonds **b** and **e** in one step. However, this procedure offered only limited yields of the cyclised product **7**.



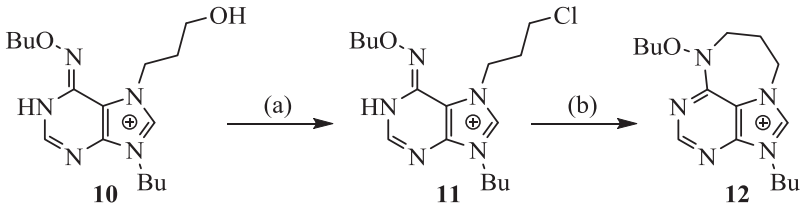
Scheme 1.3 Reagents and conditions: (a) acrylic anhydride, DMSO, 60 ºC, 24 h; vinyl acrylate, DMSO, 60 ºC, 24 h.[20]

The first synthesis directed towards the heterocyclic portion of asmarine molecule was carried out in 2001.[17] In agreement with a previous report,[19] the attempt to form the bond **e** with the propanol precursor **8** resulted in formation of an unwanted species **9** with a 6-membered ring (Scheme 1.4).



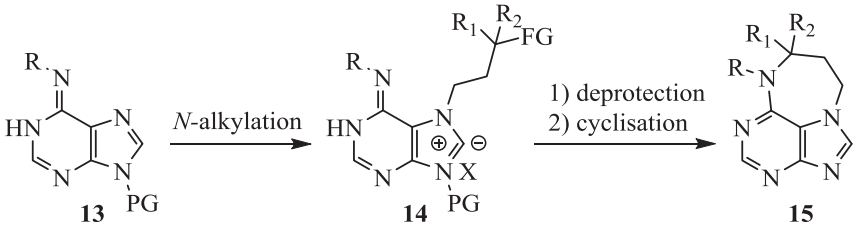
Scheme 1.4 Reagents and conditions: (a) $SOCl_2/CHCl_3$, r.t., 4 h.[17]

Therefore, the *N*-7 alkylated intermediate **10** was chosen as a suitable starting point. The aim to construct bond **b** in the last step of the sequence successfully gave the desired THDAP system (Scheme 1.5).[17]



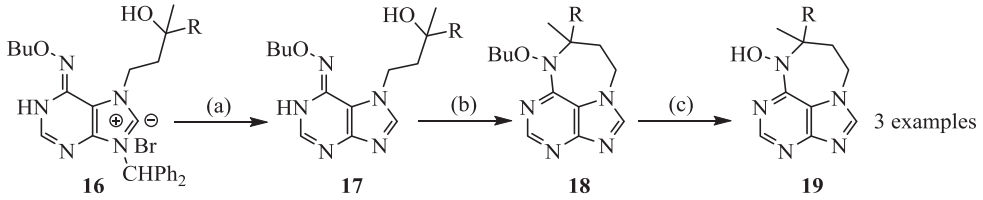
Scheme 1.5 Reagents and conditions: (a) $SOCl_2$, r.t., 1 h; (b) K_2CO_3, DMSO, 60 ºC, 3 days.[17]

Subsequently, this approach was further developed. An important feature of this strategy is the presence of a protecting group in the *N*-9 position. The *N*-9 protection allows the preparation of a suitable *N*-7 alkylated precursor **14** with an appropriate functional group, which could then be available for the following cyclisation (Scheme 1.6). Among the several groups tested, the cyanoethyl group or diphenyl methyl group were found to be the most suitable.[21,22]

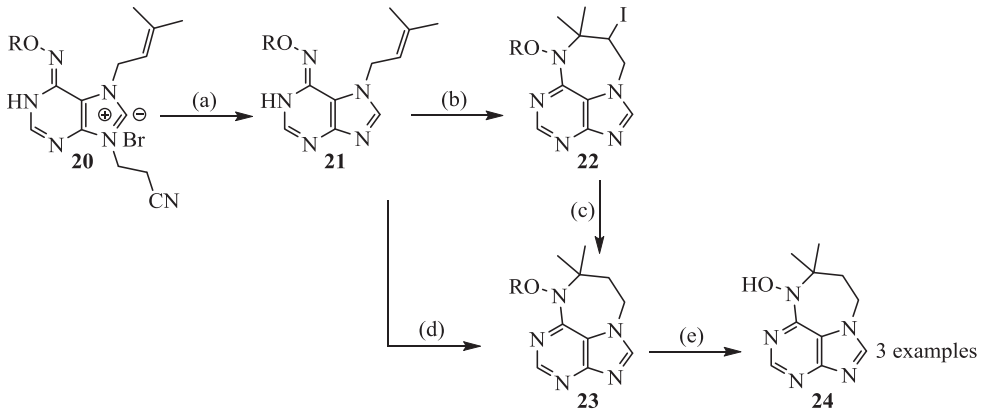


Scheme 1.6 General pathway for the formation of the bond **b** developed by Pappo *et al.*[17,21,22]

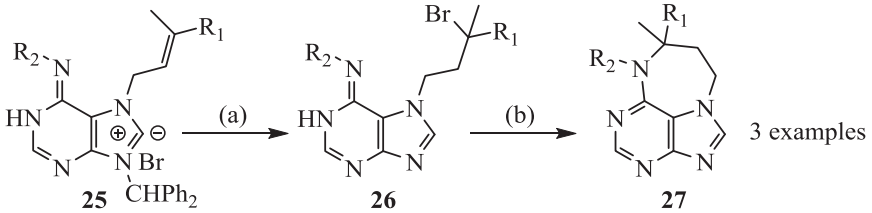
The synthesis of the THDAP system was thereafter also achieved using 4 different cyclisation methods such as the Mitsunobu alkylation (Scheme 1.7),[21,22] the iodocyclisation or aminomercuration (Scheme 1.8),[22] and the acid catalysed cyclisation (Scheme 1.9).[22]



Scheme 1.7 Reagents and conditions: (a) TFA, CH_2Cl_2, r.t., 24 h; (b) DIAD, PPh_3, THF, r.t. to 40 ºC, 24 h; (c) 30% HBr/AcOH, 100 ºC, 3.5 h.[21]

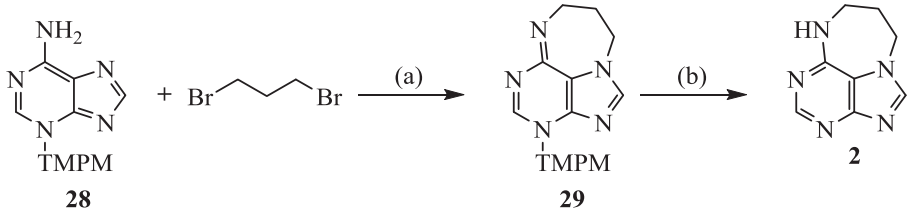


Scheme 1.8 Reagents and conditions: (a) K_2CO_3, MeOH, r.t., 1 h; (b) I_2, $NaHCO_3$, EtOH, r.t., 48 h; (c) Bu_3SnH, THF, Δ, 3 h; (d) 1) $Hg(OAc)_2$, THF, 40 ºC, 24 h, 2) $NaBH_4$/NaOH; (e) 30% HBr/AcOH, 100 °C, 3 h or DDQ, CH_2Cl_2/H_2O, r.t., 4 h.[22]



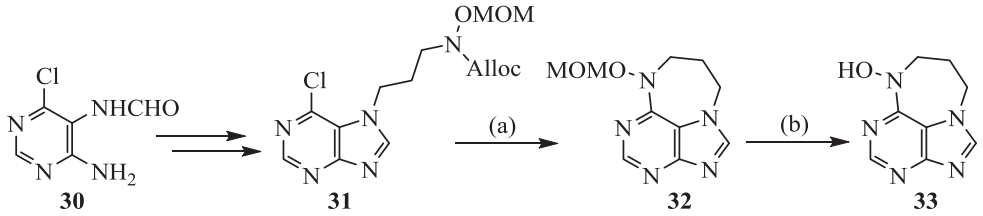
Scheme 1.9 Reagents and conditions: (a) 15% HBr/AcOH, r.t., 12 h; (b) 30% HBr/AcOH, 100 °C, 3 h.[22]

Several novel asmarine analogues were successfully prepared in this fashion. In addition, another derivate was prepared again by the parallel construction of the bonds **b** and **e** (Scheme 1.10). The 3-trimethoxyphenylmethyl group directed the *N*-alkylation with 1,3-dibromopropane to the *N*-7 position, which then resulted in the formation of 7-membered ring system. The cyclised product was deprotected and isolated in high yield.[21]



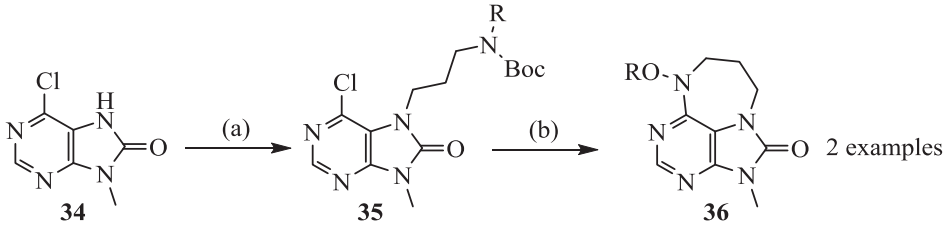
Scheme 1.10 Reagents and conditions: (a) Et_3N, DMA, 80 ºC, 36 h; (b) 30% HBr/AcOH, 100 ºC, 1 h.[21]

So far, no examples regarding the construction of the bond **c** are reported in the literature.[16] In another preliminary study towards the total synthesis of asmarines, the formation of the bond **a** *via* intramolecular C-6 amination was explored (Scheme 1.11). The cyclisation precursor **31** was prepared from the pyrimidine derivate **30** by *N*-alkylation followed by a cyclocondensation. The alloc group was removed from the cyclisation precursor **31** in the presence of 2-ethylhexanoic acid and the catalyst $Pd(PPh_3)_4$. The resulting hydroxylamine intermediate was cyclised under basic conditions. The target product was isolated after deprotection with a good yield.



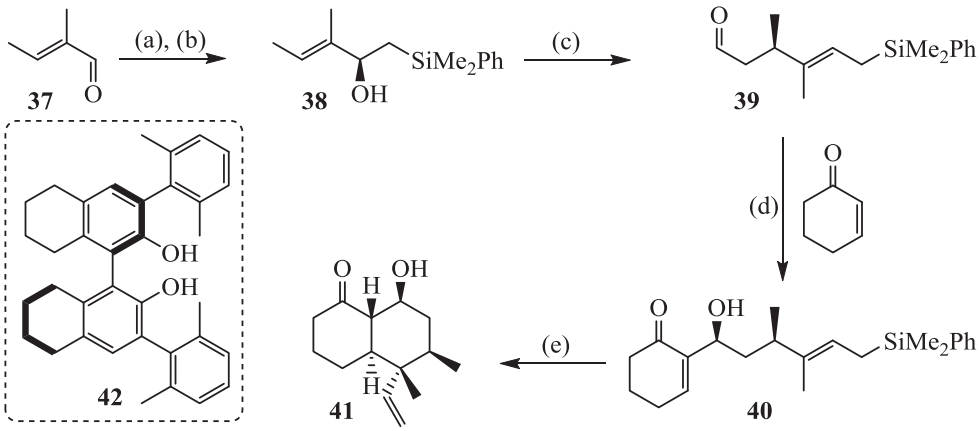
Scheme 1.11 Reagents and conditions: (a) 1) $Pd(PPh_3)_4$, PPh_3, 2-ethylhexanoic acid, CH_2Cl_2/Et_2O, 2) Et_3N, *n*-BuOH; (b) HCl, THF, 55 ºC, 1.5 h.[23]

The deprotection and intramolecular C-6 amination was further employed in the synthesis of analogues **36** with C-8 carbonyl group, related to the asmarines C, D, E and F. Two derivates were prepared from the suitable *N*-7 alkylated 8-oxopurine in this fashion (Scheme 1.12).



Scheme 1.12 Reagents and conditions: (a) alkylbromide, K_2CO_3, *n*-Bu_4NI, DMF, r.t., 22 h; (b) 1) TFA, CH_2Cl_2, 2) Et_3N, *n*-BuOH, Δ, 2 h.[23]

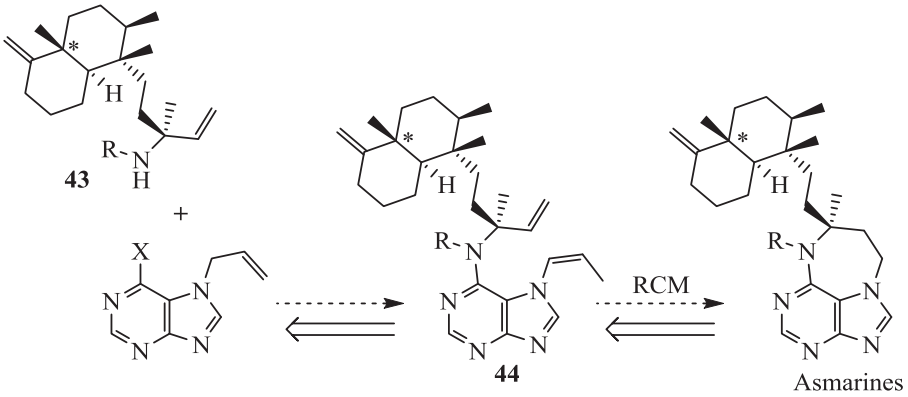
In addition to the reported synthesis of the asmarine heterocyclic core, the construction of the decaline moiety of asmarine A and B was also developed.[14]



Scheme 1.13 (a) 1) $ClMgCH_2SiMe_2Ph$, Et_2O, 0 ºC, 2) o-iodoxybenzoic acid, EtOAc, 76 ºC; (b) (*R*)-Me-CBS-oxaza-borolidine, BH_3, THF, -50 ºC; (c) 1) $Hg(OAc)_2$, $EtOCH{=}CH_2$, 35 ºC 2) SiO_2; (d) cyclohexenone, PEt_3, catalyst **42**; THF, -10 ºC; (e) BF_3OEt_2, CH_2Cl_2, -78 ºC to -10 ºC.[14]

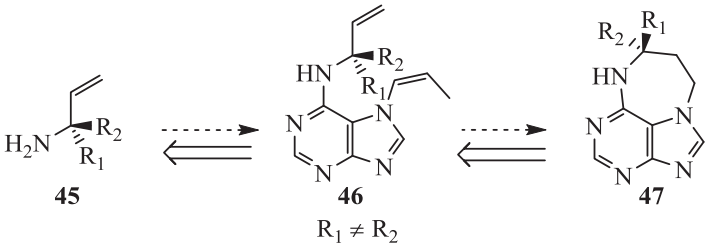
1.2.2 The current project

This work is a part of a larger on-going project towards the asmarines. Up to this date, no total synthesis of the natural asmarines A-K was achieved.[16] The reports related to synthesis of asmarine analogues show so far, that only racemic analogues can be prepared.[15,16] The chiral centre with (*S*)-configuration is a common feature for all the THDAP systems in naturally occurring asmarines, and the construction of this centre still remains a challenge. Moreover, any methods based on the construction of the bond **b** or **c** seems to be less feasible since the cyclisation step would have to be enantioselective. From this point of view, an introduction of the allylic amine intermediate possessing the (*S*)-chiral centre in the α-position seems a promising approach (Scheme 1.14). Subsequently, the target natural product could be obtained by the RCM reaction from this precursor molecule. The RCM might be a very elegant method, since it will not disrupt the stereochemistry during formation of the final THDAP ring.



Scheme 1.14 Retrosynthetic analysis of the possible total synthesis of asmarine.

Therefore, the primary objective of this project was to introduce a chiral centre on the tetrahydrodiazepinopurine moiety using chiral allyl amines (Scheme 1.15).



Scheme 1.15 Chiral allyl amines in the strategy towards asmarine analogues.

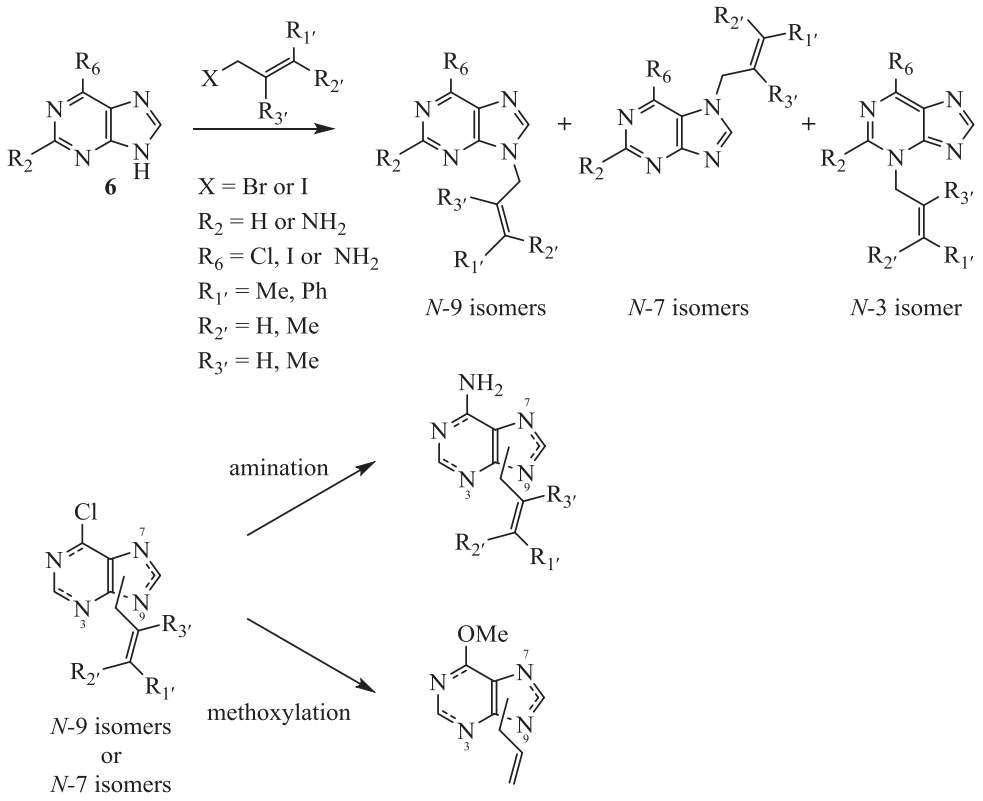
The success of this reaction pathway would open the possibility of a total asmarine synthesis. In addition, the synthetic routes towards the decaline intermediate **43** applicable for this protocol are currently carried out in the Gundersen group at the University of Oslo.

Chapter 2

Synthesis of *N*-allyl purines

2.1 Introduction

Several *N*-7 allyl substituted purines were synthesized as precursors for the asmarine directed synthesis (Chapters 3 and 4). Furthermore, *N*-9 or *N*-7 allylic derivates with substitution on the allyl chain were prepared (Scheme 2.1) to be used as substrates for the study of double bond migration in these systems (Chapter 5).The first part of this chapter gives an overview of the various methods applicable for synthesis of *N*-allyl purines. Typical trends in purine *N*-alkylation are presented herein, as well as the possibilities of regioselective synthesis.

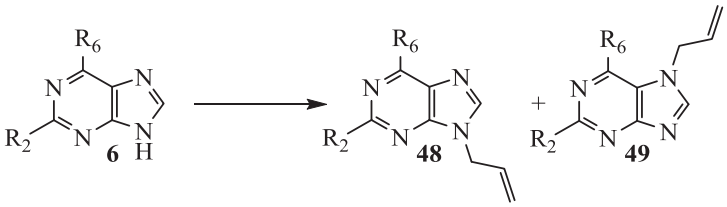


Scheme 2.1 Preparation of various *N*-allyl purines.

2.1.1 Synthesis of *N*-allyl purine by *N*-alkylation

Poor regioselectivity in the *N*-alkylation of purines is a common issue mentioned in the purine chemistry literature.[24-27] The site of *N*-alkylation is dependent on the alkylating reagent and the reaction conditions. Also, the presence and position of other substituents in the molecule is important.[24,25,28,29]

6-Halo-purines, when treated with alkylating agents, give rise to isomeric mixtures of *N*-7 and *N*-9 alkyl purines with the *N*-9 alkyl purine usually obtained in excess.[24,25,30] This phenomenon is caused by the π-electron rich imidazole ring[24] as well as by the electronegative 6-halo substituent. Halogen has a deactivating effect on the pyrimidine moiety, leaving *N*-7 and *N*-9 as the only reactive positions.[31] Dominant formation of the *N*-9 product is due to steric shielding of the *N*-7 position by the C-6 substituent.[29] Typical procedures for the synthesis of *N*-allyl-6-halo-purines (Scheme 2.2) are summarized in Table 2.1. First of all, *N*-allyl-6-halopurines can be obtained in good yields from alkylation with allylhalides under basic conditions (Table 2.1, entries 1-4, 8 and 9).[32-36] Another option is palladium catalysed alkylation using allyl acetate (Table 2.1, entries 5 and 7).[37,38] In addition, Mitsunobu type of allylation with allyl alcohol was also recently reported (Table 2.1, entry 6).[39]



Scheme 2.2 Allylation of different 6-halopurines.

Table 2.1 Conditions for allylation of 6-halopurines

Entry	Subst.	R_2	R_6	Alkyl agent	Conditions	*N*-9 (48) [%][a]	*N*-7 (49) [%][a]
1[32]	**6b**	H	Cl		KOH/Aliquat, r.t.	58	23
2[33]	**6b**	H	Cl		NaH/DMF, r.t.	65	n.d.[b]
3[34]	**6b**	H	Cl		K_2CO_3/DMF, r.t.	67	n.d.
4[35]	**6b**	H	Cl		NaH/DMF, r.t.	60	n.d.[c]
5[37]	**6b**	H	Cl		$Pd(PPh_3)_4$, THF/DMF, 50 ºC	48	32
6[39]	**6b**	H	Cl		DEAD, PPh_3, THF, 70 ºC	78	n.d.
7[38]	**6c**	NH_2	Cl		$Pd(PPh_3)_4$, Cs_2CO_3/DMSO, 45 ºC	18	20
8[35]	**6c**	NH_2	Cl		NaH/MeCN, r.t.	56	n.d.
9[36]	**6d**	H	I		K_2CO_3/MeCN, Δ	77	n.d.

[a]Isolated yields; [b]Not determined; [c]Formed, not isolated.

In the case of 9*H*-purin-6-amine (**6a**), the *N*-alkylation pattern is a complex area. In general it is stated[24-26] that adenines give mainly *N*-3 products, when alkylated under neutral conditions.[40-43] Some of the *N*-9 and *N*-1 alkyl isomers may also be present.[24] Adenines cannot be alkylated in acidic media.[24,25] Regarding the alkylation under basic conditions, *N*-7/*N*-9 regioselective substitution was initially reported.[44-46] The phenomenon of the *N*-7 product formation was later on reinvestigated and found to be a misconception.[47] This misconception was mainly caused in its time by the absence of modern techniques for proper structure elucidation, as well as by the fact, that *N*-3 and *N*-7 isomers show great similarity in physical properties.[24,47] It is now generally accepted, that adenine alkylation under basic conditions gives mainly *N*-9 and *N*-3 alkyl isomers.[24,25] Thus, when adenine is treated with allyl halide in basic solution, a mixture of several different regioisomers is usually obtained, where the 9-alkyl-adenine is the major one followed by the *N*-3 isomer.[32,48] The *N*-7 isomer could be present in the mixture in trace amounts. Several examples of the allylation and the *N*-3 product formation under basic conditions can be found in the literature (Table 2.2).

Table 2.2 Allylation of adenines under basic conditions

Entry	Subst.	Solv.	Alkyl agent	base	*N*-9 [%][a]	*N*-3 [%][a]
1[48]	Adenine **6a**	H_2O	Triallylphosphate	NaOH	31	35
2[32]	Adenine **6a**	Neat		KOH	46	27
3[49]	8-Br-6-(piperidin-1-yl)-9*H*-purine	DMF		K_2CO_3	35	58
4[50]	Adenine **6a**	Ethanol		Na	n.d.[b]	46
5[51]	Adenine **6a**	DMF		K_2CO_3	27	n.d.

[a]Isolated yields; [b]Minor amounts of *N*-9 product formed, removed by crystallisation.

2.1.1.1 Regioselective *N*-7 alkylation

As mentioned above, the *N*-alkylation yields the *N*-7 products only in limited amounts and is not applicable for adenines. Nevertheless, it is possible to access the *N*-7 alkylated purines from the *N*-alkylation with a good yield, when transient protection by methylaquacobaloxime (**50**) is employed. The principle of this method is based on a reversible coordination of the cobaloxime complex **50** to the different nitrogen atoms in the purine ring. The C-6 substituent is blocking the complex from coordinating to the *N*-7 nitrogen. Instead, water from the methylaquacobaloxime is first replaced by the *N*-3 nitrogen of the purine. The complex is further stabilized by an intramolecular hydrogen bond between the hydrogen atom in the *N*-9 position and the oxygen from the cobaloxime. After coordination to *N*-3, the bulk of the cobalt complex is actually blocking the *N*-9 nitrogen, leaving the *N*-7 readily available for the *N*-alkylation step.[52] The resulting complex of cobaloxime with the 6-chloro-9*H*-purine (**6b**) was successfully isolated and characterized by X-ray crystallography (Figure 2.1).[52] The most important advantage of this method is that reasonable yields of 7-substituted products are obtained in a single step. The literature reports show so far, that this procedure was successfully utilised with the reactive organohalides such as allyliodide or 2-bromoacetophenone and 6-halopurines[52-55] or 6-(furan-2-yl)-9*H*-purine.[56]

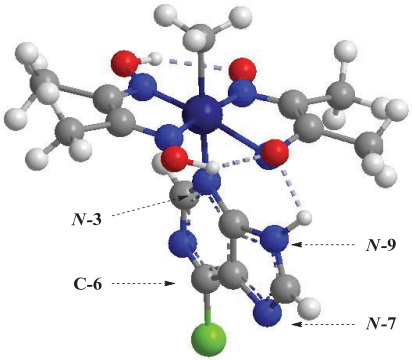
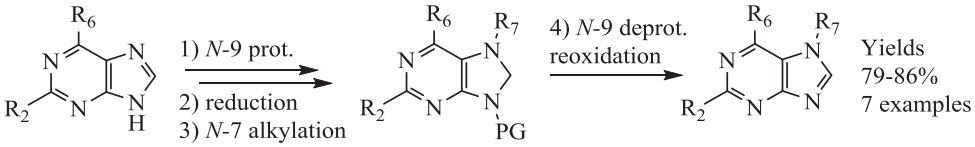


Figure 2.1 Structure of the 1:1 complex of mehylcobaloxime **50** with 6-chloro-9*H*-purine **6b**.[52]

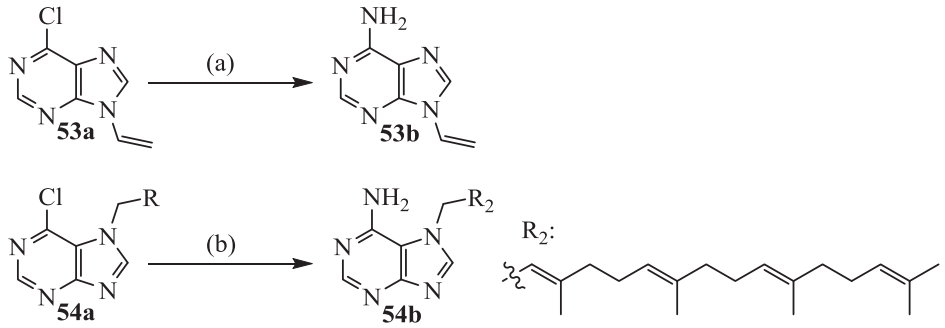
Recently, a new and efficient broad-scope method for the preparation of 7-substituted 6-halopurines has been developed.[57,58] This protocol is based on a sequence of 4 steps starting with the Boc-protection of the *N*-9 nitrogen. The key step of this sequence is the reduction of the imidazole moiety from the *N*-9 protected purine. The reduction converts the *N*-7 position into a secondary amine and allows facile alkylation on this site. The resulting products were re-aromatised and obtained in good overall yield (Scheme 2.3).



Scheme 2.3 7-Substituted purines prepared *via* 7,8-dihydropurines.[57,58]

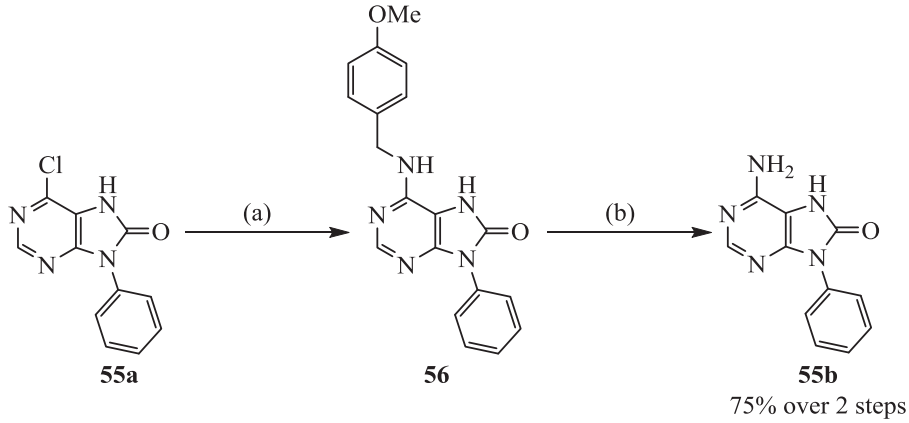
2.1.2 Introduction of the amino group

Halogen atoms in purines can be easily replaced with ammonia and primary or secondary amines.[24,25] For example 6-chloropurine can in this manner be simply converted to adenine.[59] To achieve the amination with ammonia, forcing (*e.g.* sealed tube) conditions are usually required. The amination reaction is typically performed in refluxing alcoholic solution.[24] Literature procedures for the amination, which were applied in the experimental part, are given in Scheme 2.4.[53,60]



Scheme 2.4 Reagents and conditions: (a) NH_3/MeOH, 50 ºC, 15 h;[60] (b) NH_3/*t*-BuOH, 100 ºC, 21 h.[53]

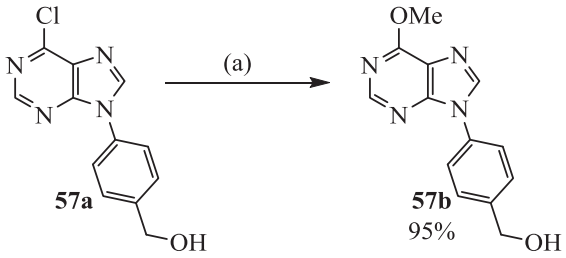
A two step procedure with *p*-methoxybenzylamine could be an alternative method for the introduction of the free amino group.[61] In the first step of the sequence, the chloropurine **55a** is treated with *p*-methoxybenzylamine. The nucleophilic substitution gave the N^6-benzyladenine **56**, which was subjected to debenzylation conditions with TFA. The adenine derivate **55b** was isolated with good overall yield (Scheme 2.5). This approach is useful for substrates, which require a stronger nucleophile than the ammonia for the S_NAr (Nucleophilic Aromatic Substitution) to take place.[61]



Scheme 2.5 Reagents and conditions: (a) *p*-methoxybenzylamine, *n*-BuOH, Δ, 24 h; (b) TFA, 60 ºC, 2 h.[62]

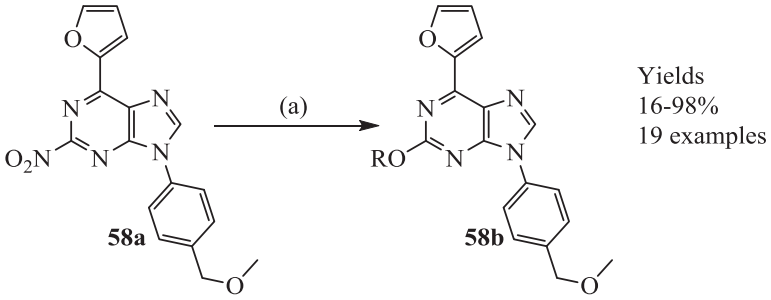
2.1.3 Methoxylation

The methoxylation is usually carried out in a similar fashion to the amination (Section 2.1.2). The methoxy purines are prepared from the corresponding halo analogues *via* halogen replacement. The most typical conditions employ sodium methoxide in alcoholic solution at ambient temperature or heating (Scheme 2.6).[24,63,64]



Scheme 2.6 Reagents and conditions: (a) MeONa, MeOH, Δ, 2 h.

In addition to the standard methoxylation conditions, mild conditions for the introduction of various alkoxy groups were reported (Scheme 2.7).[65] In this particular case, the nitro group from substrate **58a** was replaced by the alkoxy group from the corresponding alcohol by refluxing in the presence of potassium fluoride.

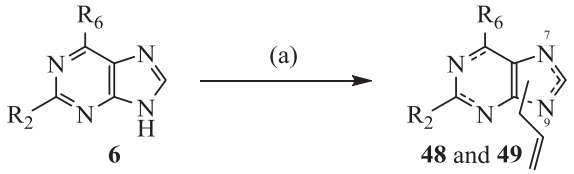


Scheme 2.7 Reagents and conditions: (a) ROH, KF, 50-100 ºC.[65]

2.2 Results and discussion

2.2.1 Allylation under basic conditions

Several *N*-9 and *N*-7 allyl purines were prepared using allyl bromide and potassium carbonate (Scheme 2.8, Table 2.3).[34,66] As expected, with the 6-chloropurine as starting material, the allylation yielded the major *N*-9 isomer **48b** in high excess compared to the *N*-7 allyl purine **49b**. When 6-iodo-9*H*-purine (**6d**) was alkylated, a decrease in formation of the *N*-7 isomer **49d** was observed (Table 2.3, entry 3) as expected based on previous reports.[36,67]



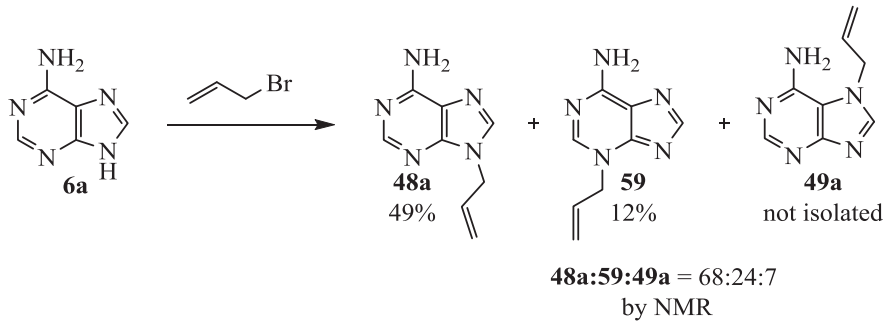
Scheme 2.8 Reagents and conditions: (a) allyl bromide, K_2CO_3, DMF, r.t., 17 h.

Table 2.3 Alkylation of the 6-halogen purines

Entry	Comp. No.	R_6	R_2	Ratio of products[a] *N*-9 (48)	Ratio of products[a] *N*-7 (49)	Yield [%][b] *N*-9 (48)	Yield [%][b] *N*-7 (49)
1	**6b**	Cl	H	71	29	64	22
2	**6c**	Cl	NH_2	80	20	78	14
3	**6d**	I	H	83	17	69	10

[a]Ratio determined by ^{1}H NMR of the crude product; [b]Isolated yield.

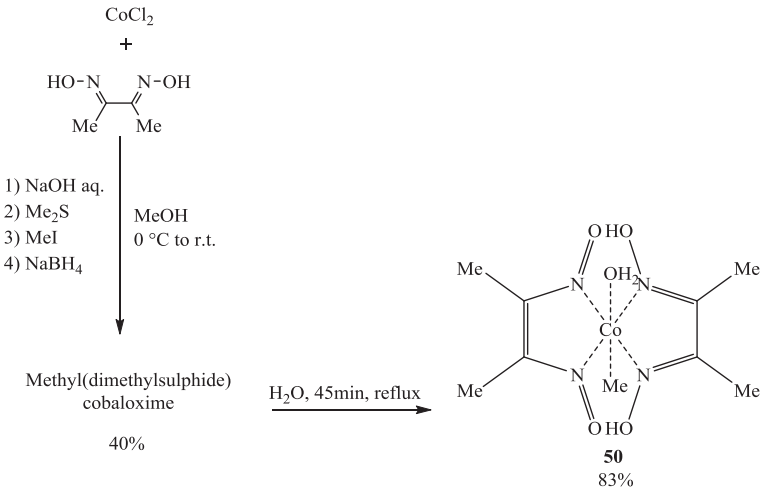
Apart from the *N*-allyl halopurines **48b-d** and **49b-d**, preparation of the 9-allyl-9*H*-purin-6-amine (**48a**) and its *N*-7 analogue **49a** was required for the double bond migration study (Chapter 5). One of the earlier reports[51] on adenine allylation mentions only single *N*-9 product **48a**, but with poor yield. This indicates possible formation of other by-products, which were probably removed during purification and not isolated. In other case it was reported, that when adenine **6a** was treated with allyl bromide and NaH in DMF, a mixture of **48a** and **49a** was obtained. *N*-7 isomer **49a** was removed during flash chromatography.[35] We attempted to reproduce this procedure, in order to investigate whether both the desired products **48a** and **49a** can be obtained from this reaction. We acquired 9-allyl-9*H*-purin-6-amine (**48a**) and 3-allyl-3*H*-purin-6-amine (**59**) instead. The desired *N*-7 isomer (7%) as well as other multiple alkylated products was detected by ^{1}H NMR, but not successfully isolated (Scheme 2.9). Comparable results were achieved when the milder base Cs_2CO_3[68] was used. Since the direct allylation of adenine **6a** did not afford the desired *N*-7 product **49a**, another approach starting from the compound **6b** was chosen (Sections 2.2.4).



Scheme 2.9 Reagents and conditions: (a) NaH, allyl bromide, DMF, r.t., 24 h.

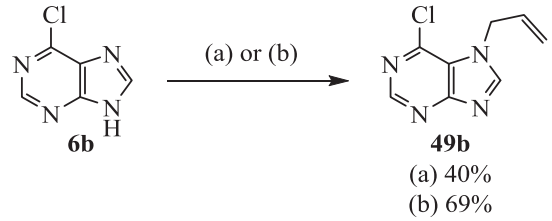
2.2.2 Regioselective *N*-7 alkylation

In the synthesis towards asmarines we were interested in simple methods for the preparation of *N*-7 allyl purines. Among the methods described in section 2.1.1.1, the method proceeding *via* methylaquacobaloxime (**50**) was chosen. The methylaquacobaloxime complex **50** can be easily prepared from commercially available $CoCl_2$ and dimethylglyoxime (Scheme 2.10).[69]



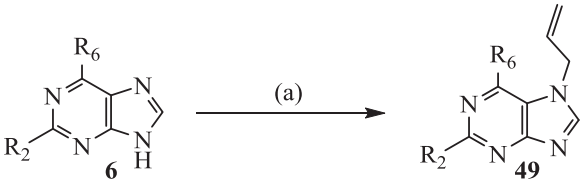
Scheme 2.10 Preparation of the methylaquacobaloxime **50**.

The alkylation of 6-chloro-9*H*-purine (**6b**) as well as 2,6-dichloro-9*H*-purine at *N*-7 by allyl bromide using protection with methylaquacobaloxime has been previously shown.[52] In our case, when allyl bromide was used, we managed to isolate the final product **49b** in 40% yield. The yield of **49b** was improved to 69% when the allyliodide was used instead (Scheme 2.11).



Scheme 2.11 Reagents and conditions: (a) methylaquacobaloxime, allyl bromide, MeCN, r.t. 4 days; (b) methylaquacobaloxime, allyliodide, MeCN, r.t. 4 days.

Compounds **49c** and **49d** were isolated as minor products from the standard alkylation reaction before (Table 2.3, entries 2 and 3). In order to obtain higher amounts of these *N*-*7* alkylated materials, the procedure using methylaquacobaloxime was also applied for the purines **6c** and **6d** (Scheme 2.12), extending the scope of this *N*-7 regiospecific alkylation. The starting material **6c** was fully consumed after 72 h and the undesired *N*-9 product **48c** was not detected using TLC during reaction progress. The product **49c** was purified by repeated column chromatography on silica and further recrystalized from EtOAc. This gave cobaloxime residue free material, as judged by ^{1}H NMR. The final yield of the compound **49c** was increased compared to the standard alkylation conditions, but still deserves further improvement (Table 2.4, entry 2). While attempting to employ 6-iodo-9*H*-purine **6d** in this reaction protocol, we proved that after the cobaloxime is coordinated, a relatively large iodine group in the C-6 position does not prevent successful alkylation. The product 7-allyl-6-iodo-7*H*-purine (**49d**) was isolated in good yield (Table 2.4, entry 3).



Scheme 2.12 Regents and conditions: allyliodide, K_2CO_3, MeCN, r.t.

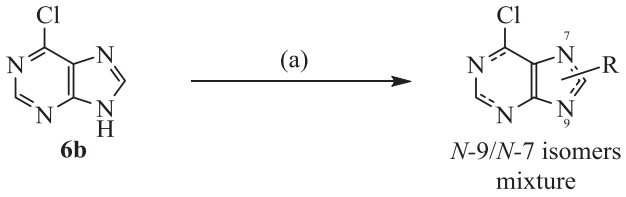
Table 2.4 Regioselective allylation with cobaloxime

Entry	No.	R_6	R_2	Time [h]	Yield [%][a] (49)
1	**6b**	Cl	H	96	69
2	**6c**	Cl	NH_2	72	32
3	**6d**	I	H	120	61

[a]Isolated yield.

2.2.3 Alkylation with substituted allyl and homoallyl halides

The type of the alkyl halide chain has an impact on the regioselectivity of the alkylation (Scheme 2.13, Table 2.5). When allyl bromide was used in the alkylation of purine **6b**, the resulting ratio of the products was in the range of 70:30 for *N*-9 product **48b** and *N*-7 isomer **49b**, respectively (Table 2.3, entry 1). A similar behaviour was observed in the alkylation by C-3 substituted allyl halides (Table 2.5, entries 1-3). A minor change in regioselectivity was observed, when 3-bromo-2-methylprop-1-ene was applied in the reaction. The conversion towards *N*-9 increased to 75%, leading to the *N*-9 regioisomer **62a** in 68% isolated yield (Table 2.5, entry 4). Purines **64** and **65** bearing the homoallylic side chain were observed as minor by-products from the rearrangement reactions (see Section 5.2.4, page 100, Scheme 5.25). These terminal alkenes were not isolated in pure form. Hence, the structure confirmation was based on comparison with ^{1}H NMR spectra of reference compounds, which were synthesized by *N*-alkylation of purines with corresponding homoallylic halides. These reactions showed slightly higher selectivity towards *N*-9 alkylated products (Table 2.5, entries 5 and 6).



Scheme 2.13 Reagents and conditions: (a) alkyl halide (Table 2.5), K_2CO_3, DMF, r.t. 17 h.

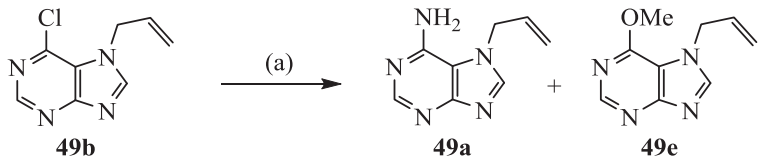
Table 2.5 Alkylation with allyl and homoallyl halides

Entry	Comp. R-Br	Ratio of products[a] *N*-9	*N*-7	Yield [%][b] *N*-9	*N*-7
1		70	30	62, **60a**	29, **61a**
2		70	30	63, **60b**	27, **61b**
3		71	29	68, **60c**	27, **61c**
4		75	25	68, **62a**	23, **63a**
5		80	20	74, **64a**	16, **65a**
6		83	17	73, **64b**	9, **65b**

[a]Ratio determined by ^{1}H NMR of the crude product; [b]Isolated yield.

2.2.4 Amination of 6-chloropurines

For the preparation of 7-allyl-7*H*-purin-6-amine (**49a**), halogen replacement procedures were performed. Initial attempts to introduce the amino group to the C-6 position were carried out by stirring compound **49b** in heated solution of sat. NH_3 in MeOH.[60] Unfortunately, following this procedure offered only a limited overall conversion, very small amount of the desired compound **49a** and a methoxy analogue **49e** as the major product (Scheme 2.14).

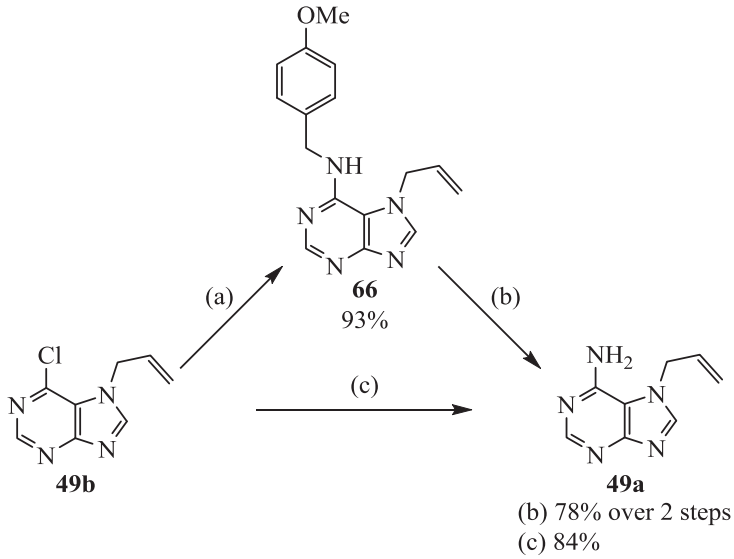


49a:49e:49b = 9:68:23
(by NMR)

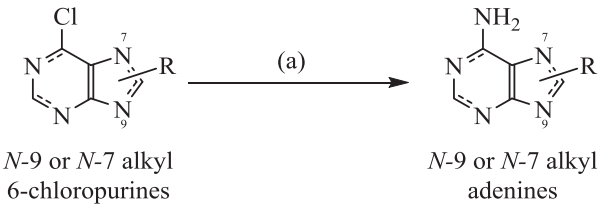
Scheme 2.14 Reagents and conditions: (a) sat. NH_3/MeOH, sealed tube, 50 ºC, 15 h.

After this initial lack of success, the product **49a** was successfully generated in another fashion (Scheme 2.15). The amino group was introduced by a two step procedure, starting with a nucleophilic substitution of **49b** with *p*-methoxybenzylamine. The *p*-methoxybenzyl group from the intermediate **66** was then cleaved off under acidic conditions[70] affording the desired 7-allyl-7*H*-purin-6-amine (**49a**) with a good yield. Another option was to treat the

starting material **49b** with a saturated NH_3/*t*-BuOH solution.[53] The solvent *t*-BuOH was selected to prevent the formation of the unwanted alkoxy products. This particular approach is very convenient, affording full conversion and good yields in a single step (Scheme 2.15). Therefore, this method was chosen as a general method for the synthesis of *N*-allyl adenine analogues (Scheme 2.16, Table 2.6).



Scheme 2.15 Reagents and conditions: (a) *p*-methoxybenzyl amine, DIPEA, *n*-BuOH, Δ, 2 h; (b) TFA, 70 °C, 48 h; (c) sat. NH_3/*t*-BuOH, sealed tube, 120 °C, 21 h.[53]



Scheme 2.16 Reagents and conditions: (a) sat. NH_3/*t*-BuOH, sealed tube, 120 °C, 21 h.[53]

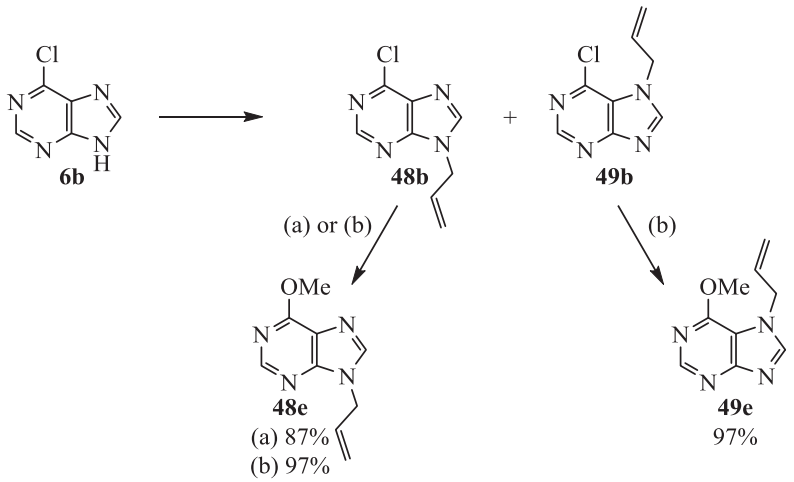
Table 2.6 Amination of 6-chloropurines

Entry	R	Comp. s.m.	Yield [%][a] *N*-9	Entry	R	Comp. s.m.	Yield [%][a] *N*-7
1		**60a**	95, **60d**	**7**		**61a**	97, **61d**
2		**60b**	91, **60e**	**8**		**61b**	77, **61e**
3		**60c**	86, **60f**	**9**		**61c**	80, **61f**
4		**62a**	91, **62b**	**10**		**63a**	87, **63b**
5		**64a**	95, **64c**	**11**		**65a**	95, **65c**
6		**64b**	96, **64d**	**12**		**65b**	44, **65d**

[a]Isolated yield.

2.2.5 Synthesis of *N*-allyl-6-methoxy-purines

To broaden the scope of the double bond rearrangement study on *N*-allyl purines (Chapter 5), substrates bearing a methoxy group in C-6 position were prepared from the corresponding 6-chloro analogues. Two procedures for the C-6 methoxylation were evaluated (Scheme 2.17).



Scheme 2.17 (a) sat. KF/MeOH, Δ, 4 days, 87%; (b) MeONa/MeOH, r.t., 48 h.

First, compound **48b** was stirred with KF in MeOH.[65] The reaction showed unfortunately no detectable progress after 24 h. Minor formation of the desired methoxy product **48e** was observed already after the first 2 hours of the reaction, when the starting material **48b** was refluxed in saturated KF/MeOH solution (Scheme 2.17). However, to reach completion, the reaction required a rather extensive time of 4 days. The best result was obtained when the combination of MeONa in MeOH was used. Most of the material **48b** was consumed within the first 24 h of the reaction at room temperature and full conversion required 48 hours. The desired product **48e** was isolated in good yield and this method was therefore applied for the synthesis of **49e** as well.

2.3 Summary and conclusions

Various *N*-alkyl-6-halopurines were prepared using *N*-alkylation under basic conditions. The *N*-9 alkylated products **48**, **60**, **62** and **64** were isolated as major products. *N*-7 alkylated products **49**, **61**, **63** and **65** were obtained in lower amounts. *N*-allylation of adenine **6a** yielded excess of the 9-allyl-9*H*-purin-6-amine (**48a**) and *N*-3 regioisomer 3-allyl-3*H*-purin-6-amine (**59**). Regarding the *N*-7 regiospecific cobaloxime promoted allylation, the scope of this reaction was extended for the substrates 6-chloro-9*H*-purin-2-amine (**6c**) and 6-iodo-9*H*-purine (**6d**). The *N*-7 products 7-allyl-6-chloro-7*H*-purin-2-amine (**49c**) and 7-allyl-6-iodo-7*H*-purine (**49d**) prepared by regiospecific allylation were obtained in better yields compared to the standard basic allylation. 7-Allyl-7*H*-purin-6-amine (**49a**) was not available by allylation, but prepared *via* amination of the 7-allyl-6-chloro-7*H*-purine (**49b**). *N*-Alkyl adenines **60-65** were obtained in high yields using the same amination method. The 9-allyl-6-methoxy-9*H*-purine (**48e**) and 7-allyl-6-methoxy-7*H*-purine (**49e**) were successfully prepared in high yields from the appropriate 6-chloropurines **48b** and **49b** respectively, employing MeONa in MeOH.

2.4 Experimental

7-Allyl-7*H*-adenine (49a)

7-Allyl-*N*-(4-methoxybenzyl)-7*H*-purin-6-amine **66** (0.910 mmol, 270 mg) was heated in 1 ml of trifuloroacetic acid at 70 ºC for 48 h. The mixture was cooled down and the acid was removed *in vacuo*. The remaining thick sludge of the product was adsorbed on silica and purified by flash chromatography using MeOH:DCM (1:9); yield 135 mg (84%), colourless powder. Data are available in appendix I, compound **3a**.

7-Allyl-6-chloro-7*H*-purin-2-amine (49c)

6-Chloro-9*H*-purin-2-amine (2.38 mmol, 0.404 g) (**6c**) was stirred in dry MeCN (24 mL) under N_2. Methylaquacobaloxime **50** (2.62 mmol, 0.844 g) was added in small portions. After 5 min. K_2CO_3 (2.62 mmol, 0.362 g) was added. The mixture was stirred for another 30 min. Allyliodide (4.76 mmol, 0.435 mL) was injected through septum and the mixture was stirred in the dark for a total of 72 h. The solvent was removed *in vacuo* and the residue transferred to a separatory funnel using CH_2Cl_2 (100 mL) and aq. NaOH (2 M, 100 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (1 x 30 mL), dried with $MgSO_4$, filtered and evaporated *in vacuo.* Product was purified two times by flash chromatography on silica gel using acetone/CH_2Cl_2 (4:6) as eluent. The chromatography was followed by recrystallization from EtOAc in order to obtain the cobaloxime free product; yield 158 mg (32%), yellow crystals. Spectral data were in a good agreement with those reported before.[38]

7-Allyl-*N*-(4-methoxybenzyl)-7*H*-purin-6-amine (66)

7-allyl-6-chloro-7*H*-purine **49b** (1.54 mmol, 300 mg) and DIPEA (3.08 mmol, 0.540 mL) were stirred in *n*-BuOH (8.30 mL) at ambient temperature under N_2 for 5 min. After addition of *p*-methoxybenzylamine (7.7 mmol, 1.0 mL) the reaction mixture was refluxed for 2 h. The mixture was evaporated *in vacuo*. The product was purified by flash chromatography using MeOH/CH_2Cl_2 (1:19); yield 425 mg (93%), off-white powder, mp 156-158 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.76 (s, 3H, OCH_3), 4.63 (d, J = 5.1 Hz, 2H, CH_2'), 4.84 (m, 2H, NCH_2), 4.98 (d, J = 17.2 Hz, 1H, H_A in $=CH_2$), 5.24 (d, J = 10.4 Hz, 1H, H_B in $=CH_2$), 5.38 (t, J = 5.1 Hz, 1H, NH), 5.98-6.07 (m, 1H, CH=), 6.82 (d, J = 8.8 Hz, 2H, =CH in Ph), 7.20 (d, J = 8.4 Hz, 2H, =CH in Ph) 7.77 (s, 1H, H-8), 8.49 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) 44.6 (CH_2'), 49.5 (NCH_2), 55.2 (OCH_3), 111.9 (C-5), 114.0 (Ph), 119.3 ($=CH_2$), 129.1 (Ph), 130.1 (Ph), 133.4 (CH=), 144.5 (C-8), 150.3 (C-6), 153.3 (C-2), 159.0 (Ph), 159.9 (C-4); MS (EI) *m/z* (rel. int.) 295 (46, M^+), 174 (18), 159 (12), 136 (23), 121 (100); HRMS (EI) $C_{16}H_{17}N_5O$ requires 295.1433, found 295.1433.

Chapter 3

Synthesis towards asmarines starting from *α*-amino acids

3.1 Introduction

This chapter focuses on the attempted synthesis of asmarine analogues carrying substituents on the tetrahydrodiazepine ring. In principal, we wanted to explore, whether the 7-membered ring with additional *α*-substituent can be formed *via* RCM reaction. Thus, three asmarine analogues **47** derived from *α*-aminoacids phenylalanine, valine and leucine were designed in order to develop methods, which could be applied in the total synthesis of natural asmarines (Figure 3.1). The position and configuration of the chiral centre of **47** is related to the natural occurring asmarines (Chapter 1, page 3, Figure 1.3).[10,11,71]

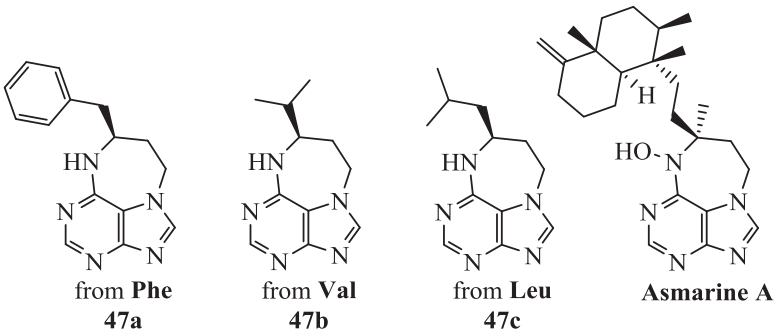
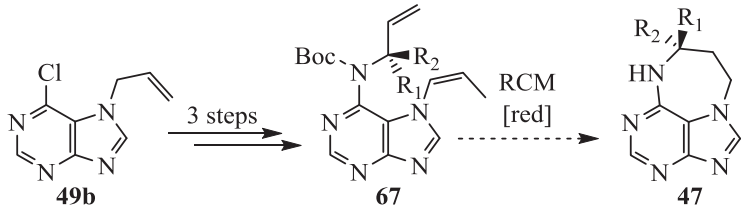


Figure 3.1 Asmarine analogues derived from α-aminoacids.

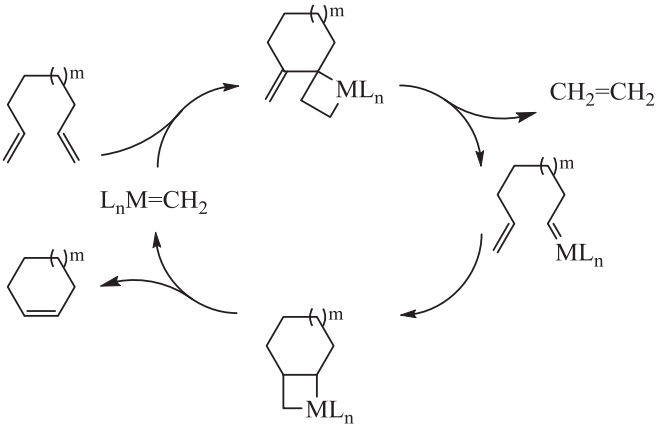
The initial part of this chapter describes the previously reported preparation of the asmarine analogue 7,8,9,10-tetrahydro-[1,4]diazepino[1,2,3-gh]purine **2** using RCM (Scheme 3.1 and Scheme 3.4). This strategy was developed by Vik *et al.*[18] from the Gundersen group. Following the idea of this report, we tried to utilize and to increase the scope of this synthetic pathway in the current study towards new asmarine analogues (see page also 10, Scheme 1.15).



Scheme 3.1 RCM strategy towards asmarine analogues.

3.1.1 Ring closing metathesis

The RCM is a powerful synthetic method for the preparation of cyclic structures *via* carbon-carbon (C-C) bond formation. The new C-C bond is formed by exchange of the alkylidene groups on alkenes. The main advantage of this methodology[72] is the relatively facile preparation of olefin substrates, which are usually more stable than the other precursors for C-C bond formation such as aldehydes, halides or triflates.[73] The conventionally accepted metallacyclobutene mechanism is shown in scheme 3.2.[72,74,75]



Scheme 3.2 Metallacyclobutene mechanism of the ring closing metathesis.

During the past 15 years, the RCM reaction has become a common method in organic synthesis and a number of transition metal catalysts have been developed (Figure 3.2). Catalysts based on ruthenium are commonly used because of their air and moisture stability and tolerance to different functional groups. In addition, ruthenium catalysts **68a-c** can be handled using standard organic techniques.[75,76] For the synthesis of asmarine analogues, we chose the catalyst **68c**, for its ability to close larger rings.[77-79] Suitable alternatives are the Schrock (*e.g.* **69a**, Figure 3.1)[76] molybdenum-based catalysts,[80] which have a broad scope of applications, but possess a much higher sensitivity to air and moisture.[73,74]

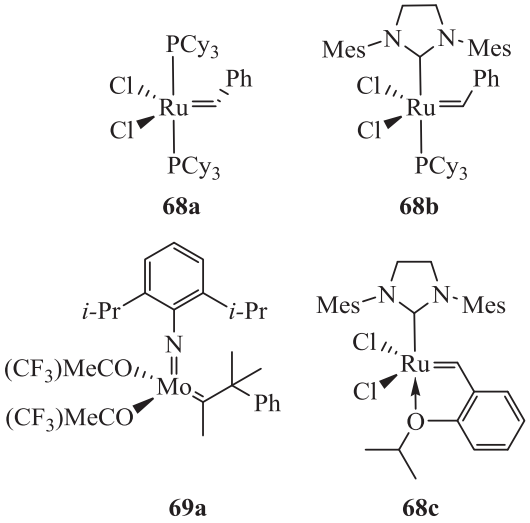
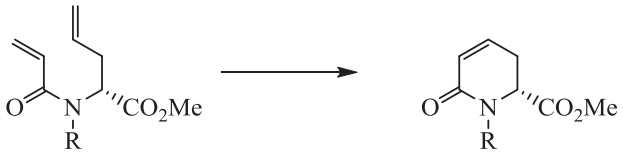


Figure 3.2 Structures of the typical RCM catalysts.

RCM reactions are commonly used for the synthesis of heterocycles or aromatic compounds.[76] Some difficulties were experienced in the cyclisation of amine containing systems. The electron donating properties of the amino group may interfere with the metathesis, if coordination of the amine lone pair to the metal centre is possible.[73,74,81] This complication can be efficiently overcome either by protonation of the amine,[81] or by a protection strategy in order to convert the amine for instance to an amide, carbamate or sulfonamide.[73,74] In some particular cases, the yield of the ring-closed product is strongly dependent on the type of the protecting group (Scheme 3.3).[82,83]



R = H 0%
R = PMB 54%
R = CH_2Fer 18%
R = Boc 93%

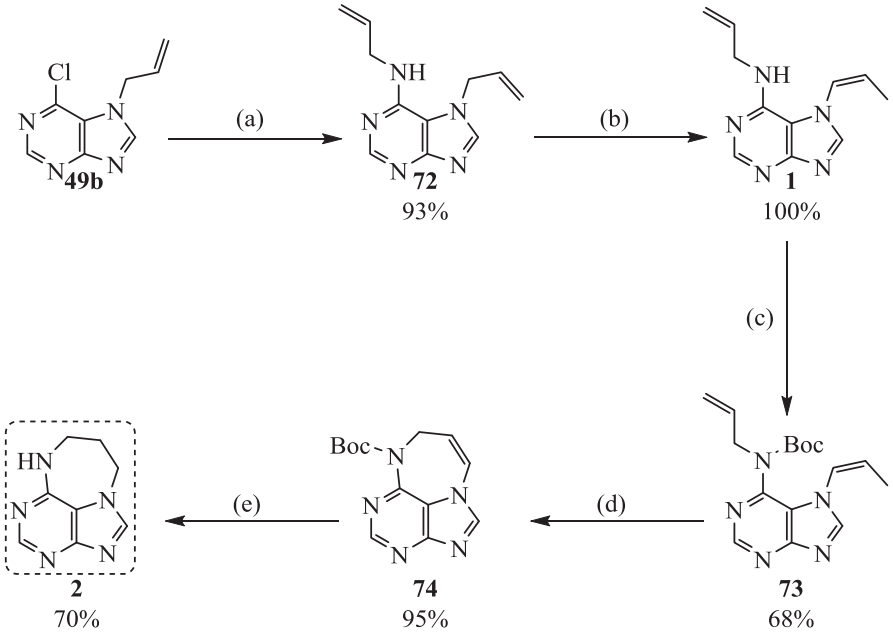
Scheme 3.3 Example of the impact of the protecting group on RCM reaction.[82]

RCM has a broad scope of application for example in the synthesis of natural products, medicinal chemistry or in the field of polymer and material chemistry. Due to the increasing

importance of the RCM in the organic synthesis, the discovery and development of this methodology was awarded with the Nobel Prize in Chemistry in 2005.

3.1.2 Construction of the tetrahydrodiazepinopurine ring system by ring closing metathesis

Herein, an overview regarding the synthesis of the asmarine analogue **2** is presented (Scheme 3.4).[18] In the synthetic route to **2**, there are several interesting synthetic aspects, which will be discussed further in the following chapters. The regiospecific *N*-7 alkylation (Section 2.2.2, page 19) plays a principal role in the reaction route. The target **2** could be considered as *N*-7 alkyl purine. Thus, the easily accessible 7-allyl-6-chloro-7*H*-purine (**49b**) was used as a suitable starting point. Replacing the halogen from **49b** by allyl amine provided a product **72** with two allylic side chains. One of the challenges regarding the formation of the tetrahydrodiazepinopurine ring was the preparation of the *N*-7 propenyl intermediate **1**. Fortunately, an elegant possibility to obtain alkenylpurine **1** was discovered, when compound **72** was refluxed in MeCN in the presence of K_2CO_3. The selective double bond migration on *N*-7 allyl occurred, giving *N*-allyl-7-(prop-1-en-1-yl)-7*H*-purin-6-amine (**1**) as a pure *Z*-isomer in quantitative yield. This discovery opened a unique opportunity to approach the synthesis of the 7-membered ring. The ring closing, when attempted on the free secondary amine **1** was not successful. Consequently, the Boc group was introduced prior to the RCM. The secondary amine **1** showed notably low reactivity under the Boc-protection conditions, nevertheless, the compound **73** was obtained in good yield. The ring-closing of **73** gave the desired intermediate **74** in high yield. The successful RCM was followed by reduction and deprotection of **74** to afford the final asmarine analogue 7,8,9,10-tetrahydro-[1,4]diazepino[1,2,3-gh]purine (**2**) (Scheme 3.4). Alternatively, application of the methyl in place of the Boc group was explored, but ring-closing did not occur. This indicated that the nature of the *N*-protecting group is important for the RCM reaction to take place.

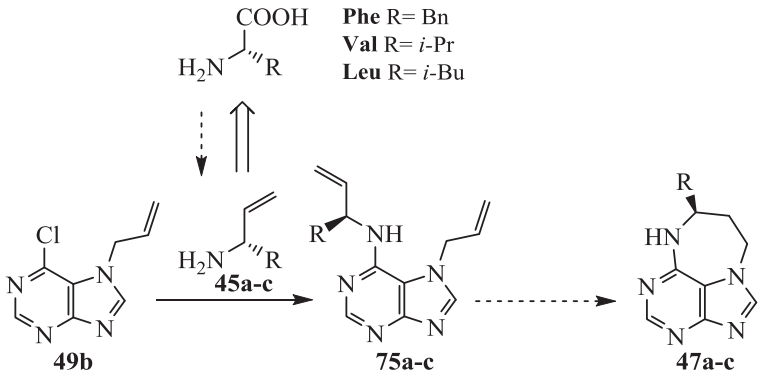


Scheme 3.4 Reagents and conditions: (a) allylamine, pyridine, 100 ºC, 16 h; (b) K_2CO_3, MeCN, Δ, 17 h; (c) $(Boc)_2O$, DMAP, MeCN, r.t., 4 days; (d) Hoveyda-Grubbs II, DCE, Δ, 1.5 h; (e) 1) H_2, Pd/C, EtOAc, 2) HCl/MeOH, r.t., 1 h.[18]

3.2 Results and discussion

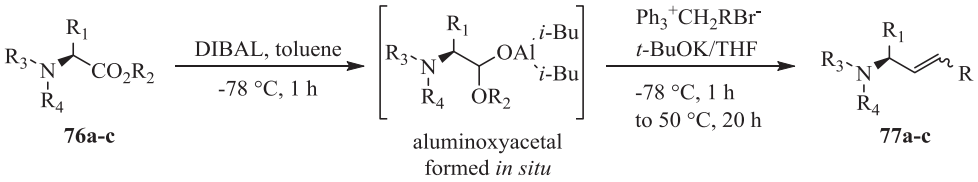
3.2.1 *α*-Amino acids in the synthesis towards asmarines

In order to introduce the substitution to the diazepine ring, the chiral amines **45a-c** derived from *α*-amino acids phenylalanine, valine and leucine had to be synthesized (Scheme 3.5).



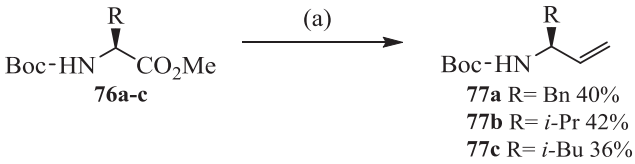
Scheme 3.5 The role of the chiral amines **45a-c** in the synthetic strategy.

The Boc-protected esters of *α*-amino acids were found to be the most suitable, cheap and readily available starting materials. The conversion of the *α*-amino acid esters **76a-c** to the olefins **77a-c** was already reported.[84] This one-pot procedure is based on the reduction of the *N*-Boc-*α*-amino esters with diisobutylaluminium hydride (DIBAL) while avoiding the final product racemization. The resulting aluminoxyacetal formed *in situ* is directly treated with Wittig reagent to afford the desired chiral *N*-protected amines (Scheme 3.6). The fundamental benefit of this procedure is the preservation of the products chiral centre.[84]



Scheme 3.6 Aluminoxyacetal formation in one-pot reduction Wittig olefination procedure.[84]

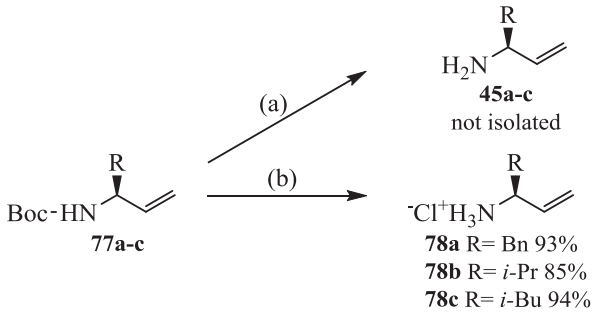
The reaction was carried out following the literature procedure.[84] Initially, the overall yields of **77** were below expectations. According to the procedure, 2 equivalents of the reducing agent DIBAL over 15 minutes were added drop-wise. Increasing the DIBAL addition time to 30 minutes led to yield improvement, however, only moderate amounts of the olefins **77a-c** were eventually isolated (Scheme 3.7). Possible reduction to the corresponding alcohols, difficult detection of the products **77a-c** during flash chromatography or cleavage of the Boc group on silicagel may be the cause of the limited yields. Nevertheless, the *N*-Boc protected olefins **77a-c** were isolated with the optical rotation corresponding to the literature values.[84]



Scheme 3.7 Reagents and conditions: (a) 1) DIBAL, toluene, -78 ºC, 1 h; 2) Ph_3PCH_2Br, *t*-BuOK, THF, -78 ºC 1h to 50 ºC, 20 h.

Having the chiral *N-tert*-butylcarbamantes **77a-c** available, the next step was *N*-Boc deprotection to access the chiral amines **45a-c**, which could be reacted with the purine **49b** (Scheme 3.5). The Boc group should be easily removed under acidic conditions. For this

reason, freshly generated HCl gas was passed through a solution of **77a-c** in MeOH.[18] According to TLC the deprotection was completed in 50 minutes. Despite the promising reaction progress, this method was considered inconvenient. First of all an extensive amount of HCl gas has to be generated prior to the deprotection. The neutralisation of the significant HCl excess in the reaction mixture required an immense amount of saturated $NaHCO_3$ solution. For separation of the resulting inorganic residue and a polar amine **45a-c**, arduous extraction was required to quantitatively transfer the product into the organic phase. In addition to this, due to the volatility, the free amines **45a-c** were difficult to isolate in pure form and in acceptable yield. Subsequently, a more convenient way to achieve deprotection was sought in the literature, wherein the final deprotected products were isolated as ammonium hydrochloride salts.[85] Instead of using the excess of hydrochloride gas, the deprotection was carried out with only 1.7 equivalent of a concentrated (37%) HCl solution, which facilitated the reaction workup. The resulting ammonium salts **78a-c** were obtained in good yields (Scheme 3.8).

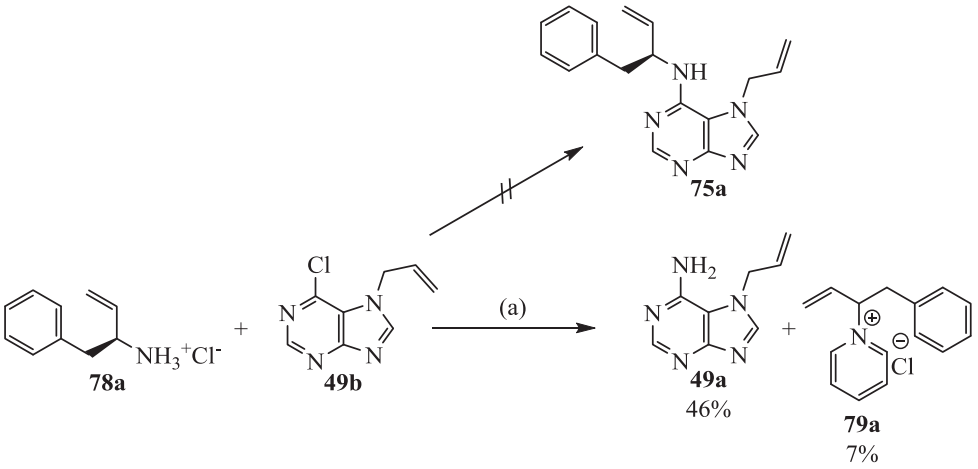


Scheme 3.8 Reagents and conditions: (a) 1) HCl (g), MeOH, 20 min. at 0 ºC then r.t., 30 min 2) sat. $NaHCO_3$; (b) HCl (aq. 37%), Acetone, Δ, 3 h.

3.2.2 Application of the ammonium salts

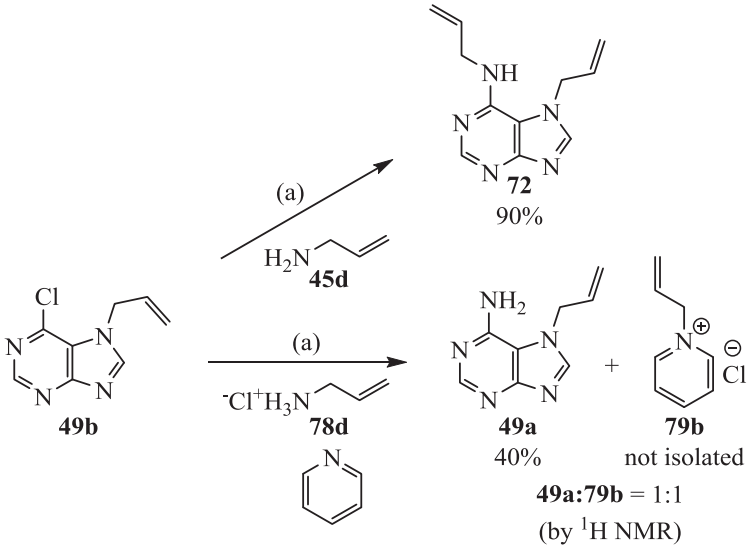
Substitution reactions carried out with ammonium salts and *N*-alkylated 6-chloropurines are occasionally mentioned in the literature.[86,87] The ammonium hydrochloride salt is converted by additional base into the amine *in situ* and the amine is then readily available for the nucleophilic aromatic substitution with the purine. In our particular case, pyridine was used for the reaction of purine **49b** with salt **78a** because pyridine with its basic properties could serve both as a solvent and as the base. The outcome of this reaction was rather surprising. First of all, the desired product **75a** coming from the nucleophilic substitution was neither isolated nor detected during the reaction. Instead, a substantial amount of 7-allyl-7*H*-purin-6-amine (**49a**) was obtained as the major product. Most

importantly, the pyridinium salt **79a** was successfully isolated and characterised (Scheme 3.9).



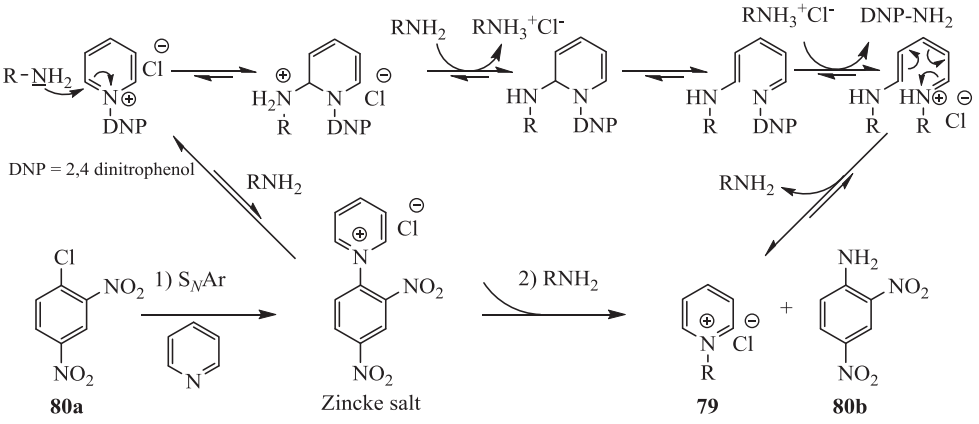
Scheme 3.9 Reagents and conditions: (a) pyridine, 100 ºC, 16 h.

In order to compare this unexpected result to the previous report, where the pyridine was used in similar case,[18] two parallel reactions were carried out. In the first case, material **49b** was treated with 10 equivalents of allylamine (**45d**) in refluxing pyridine, while in the second case, 5 equivalents of allyammonium hydrochloride (**78d**) were used (Scheme 3.10). The equivalents of the allylammonium salt to **49b** were purposefully decreased, to make the procedure more economically acceptable for the future application of the chiral ammonium salts **78a-c**. The reaction of **49b** with allylamine **45d** was easily reproducible and the expected product **72** was isolated in high yield. In contrast to this, when the allyammonium hydrochloride was brought to reaction, only products **49a** and salt **79b** were observed on TLC. The ^{1}H NMR spectra of the crude product indicated formation of salt **79b** in approximately 1:1 relative ratio to the product **49a**. The reaction gave the 7-allyl-7*H*-purin-6-amine (**49a**) in 40% yield. The compound **79b** was not successfully isolated (Scheme 3.10).



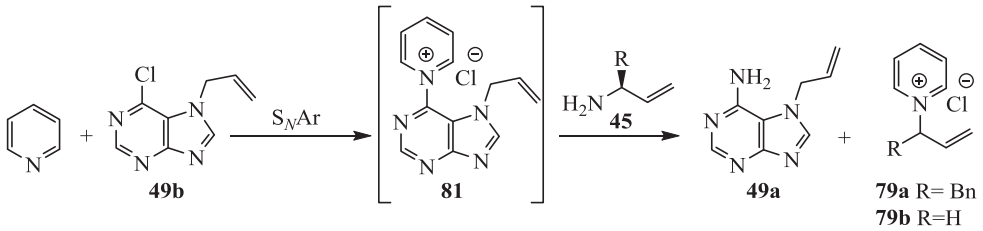
Scheme 3.10 Reagents and conditions: (a) pyridine, 100 ºC, 16 h.

The formation of the pyridinium salts **79** probably corresponds to what was discovered by Zincke *et al.* in early 1900's.[88,89] Zincke reported the formation of the pyridinium salts as well as the following reaction of these salts with amines. Studies of the mechanism revealed, that these reactions occur *via* pyridine ring-opening and reclosure (Scheme 3.11).[90-92] The starting *N*-arylated pyridinium salt (Zincke salt) is obtained by the reaction of pyridine with 2,4-dinitrochlorbenzene (**80a**). When the Zincke salt is exposed to an amine, the amine nitrogen is integrated into the heterocycle and 2,4-dinitroaniline (**80b**) is released. The Zincke reaction is used to synthesize pyridinium salts that cannot be prepared by a direct *N*-functionalization of the pyridine.[93]



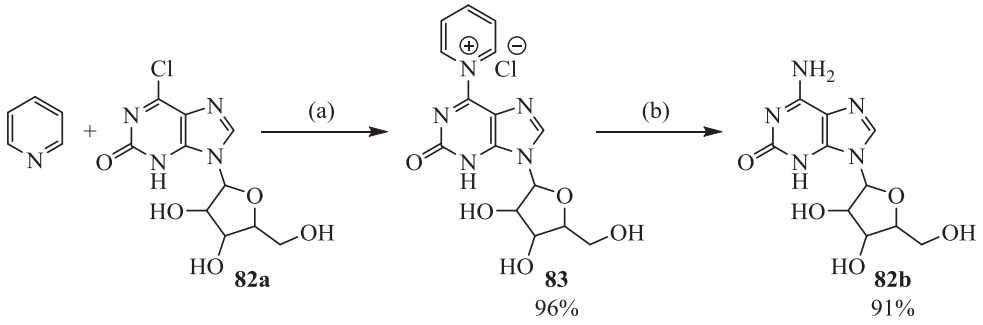
Scheme 3.11 The Zincke reaction.[90,92]

For our particular situation it is possible, that before the allylammonium hydrochloride is neutralised to the amine in pyridine solution, the chloropurine **49b** reacts with the pyridine itself forming the pyridinium salt **81**. Subsequently, this Zincke intermediate reacts with amine **45** which is formed *in situ* during the reaction progress. This gives the product **49a** and the corresponding pyridinium salt **79** (Scheme 3.12).



Scheme 3.12 Possible formation of **49a** and **79** *via* Zincke reaction.

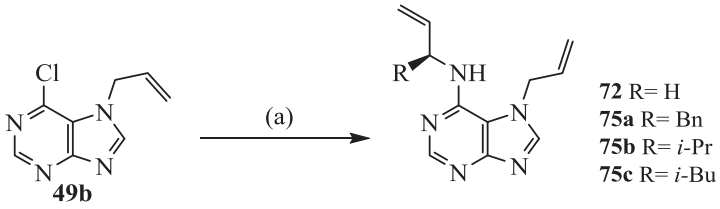
This hypothesis is further supported by two additional facts. First of all, the formation of the pyridinium salts from chloropurines is reported.[94-96] Secondly, a very similar reaction pathway employing the Zincke-type intermediate was utilized for the synthesis of isoguanosine **82b** (Scheme 3.13).[97]



Scheme 3.13 Reagents and conditions: (a) pyridine/water 1:1, 50 ºC, 2 h; (b) aq. NH_3 (32%), 50 ºC, 5 h.[97]

In our case, the formation of the unwanted Zincke intermediate **81** may probably be prevented, if the ammonium salt is treated only with pyridine in the absence of the substrate **49b**, releasing the free amine **45**. After the complete neutralisation, the subsequently added chloropurine **49b** has an opportunity to react with the amine **45** instead of the pyridine. However, we generally decided to exclude pyridine as a solvent of choice in the synthesis of **75a-c**.

The application of another solvent was investigated and *n*-BuOH was chosen (Scheme 3.14). To test the performance of the reaction, model syntheses were carried out. Allylamine or allylammonium chloride (**78d**) was refluxed with **49b** in *n*-BuOH, in the presence of the sterically hindered non-nucleophilic base DIPEA (Table 3.1). The initial results were very promising. Switching from pyridine to *n*-BuOH resulted in an improved reaction progress. The product **72** from the reaction with allyl amine (**45d**) was obtained in high yield after only 2 hours of reaction time (Table 3.1, entry 2). Furthermore, this procedure was also compatible with the allylammonium chloride (**78d**) and the product **72** was isolated in good yield (Table 3.1, entry 3).



Scheme 3.14 Reagents and conditions: (a) see Table 3.1.

Table 3.1 Condensation of amines/ammonium salts with **49b**

Entry	Substrate	Equiv.[a]	Solvent	base	Time [h]	Yield [%][b]	Prod.
1	**45d**	10	Pyridine	-	17	90	**72**
2	**45d**	5	*n*-BuOH	DIPEA	2	97	**72**
3	**78d**	5	*n*-BuOH	DIPEA	2	80	**72**
4	**78a**	1.1	*n*-BuOH	DIPEA	48	92	**75a**
5	**78b**	1.1	*n*-BuOH	DIPEA	48	98	**75b**
6	**78c**	1.1	*n*-BuOH	DIPEA	48	67	**75c**
7	**78c**	3	*n*-BuOH	DIPEA	24	93	**75c**

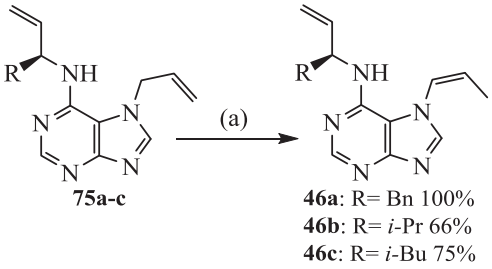
[a] 1 equivalent of **49b** used; [b]Isolated yield.

The previously tested conditions were finally performed with the chiral ammonium salts **78a-c**. Further decrease of the equivalents of **78a-c** relative to **49b** was attempted, which resulted in longer reaction time (Table 3.1, entries 4-6). Under these conditions, the products

75a and **75b** were isolated in high yields. The product **75c** was obtained with better yield, when the equivalents of **78c** were increased from 1.1 to 3 (Table 3.1, entries 6 and 7).

3.2.3 Double bond rearrangement under basic conditions

Compounds **75a-c** were conveniently isomerized to propenylpurines **46a-c** in refluxing MeCN with K_2CO_3 (Scheme 3.15). All the intermediates **75a-c** showed lower reactivity compared to the unsubstituted compound **72**. While the isomerized product **1** was acquired within 17 h (Scheme 3.4), in case of **75a-c**, the reaction required up to 72 h for completion. The *N*-prop-enyl purines **46a-c** were obtained selectively as *Z*-isomers in good yields.



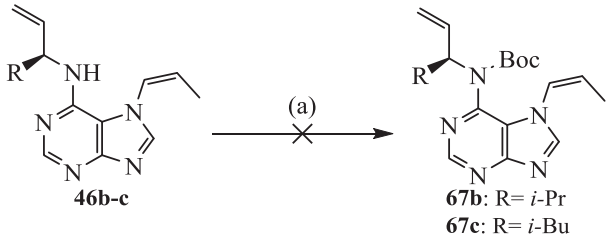
75a-c

46a: R= Bn 100%
46b: R= *i*-Pr 66%
46c: R= *i*-Bu 75%

Scheme 3.15 Reagents and conditions: (a) K_2CO_3, MeCN, Δ, 72 h.

3.2.4 *N*-Protection attempts

The next step in the synthetic sequence was the *N*-Boc protection of compounds **46a-c**. The reduced reactivity of the analogue **1** with $(Boc)_2O$ was already known (Scheme 3.4)[18] and a comparably slow progress was expected also for the reaction with the purines **46a-c**. Unfortunately, the initial attempt to introduce Boc groups to the secondary amines **46b-c**, applying the same conditions as before, gave no product (Scheme 3.16). The starting material **46b** was recovered virtually intact after 4 days (Table 3.2, entry 1). Several other literature conditions for Boc-protection were investigated.[18,98-101] Additional base (Table 3.2, entries 2 and 3), elevated reaction temperature (Table 3.2, entries 4 and 5) or carrying out the reaction with $(Boc)_2O$ in the absence of the solvent (Table 3.2, entries 6 and 7) did not lead to any conversion towards the protected products **67**. In one particular case (Table 3.2, entry 6), 10 molar% of iodine were used as a catalyst for the Boc-protection. It is reported, that iodine in combination with Boc_2O should be compatible with *N*-allylic substrates.[100] Unfortunately, exposing compound **46c** to these conditions lead to formation of several unknown side-products and only 30% of the starting material **46c** was recovered.



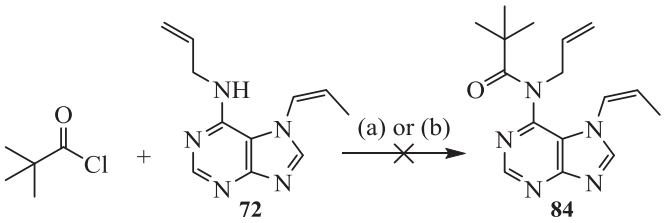
Scheme 3.16 Reagents and conditions: (a) Boc_2O, see Table 3.2.

Table 3.2 Overview of the conditions for *N*-Boc protection of **46b-c**

Entry	s.m.	Solv.	$(Boc)_2O$[a]	Cat/Base	T	Time [h]	rec. [%][b]
1[18]	**46b**	MeCN	4.3	DMAP(1eq.)[18]	r.t.	96	**93**
2[98]	**46b**	DCM	3	DMAP (1eq.)/Et_3N (1eq.)[98]	r.t.	24	**82**
3[98]	**46c**	DCM	3	DMAP (1eq.)/Et_3N (1eq.)[98]	r.t.	24	**93**
4[99]	**46b**	THF	2	DMAP (0.1 eq.)[99]	Δ	24	**70**
5[99]	**46c**	THF	2	DMAP (0.1 eq.)[99]	Δ	24	**80**
6[100]	**46c**	Neat	3.3	I_2 (0.1 eq)[100]	r.t.	72	**30**
7[101]	**46c**	Neat	4.4	DMAP (0.01 eq.)[101]	r.t.	24	**100**

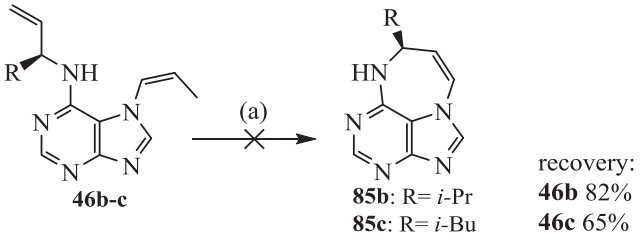
[a]Equivalents of $(Boc)_2O$ to **46**; [b]Recovered starting material.

The additional substitution on the *α*-position in the N^6-allyl chain turned the amines **46b-c** into very challenging substrates. The secondary amine group attached to the electron withdrawing purine is a very poor nucleophile. Moreover, the sterical hindrance of the reaction centre by the *α*-substituents on N^6-allyl chain might cause the overall drop in the reactivity. Realizing the limited reactivity of **46b-c** towards *N*-protection as well as the necessity to introduce a bulky protection group, we investigated the possibility of applying the pivaloyl group. The steric bulk of the pivaloyl protecting group is very similar to the Boc group and its application in RCM is known.[102] Moreover, it can be introduced using the much more reactive pivaloyl chloride. Thus, a model synthesis with **72** and pivaloyl chloride was carried out using a literature procedure[103] (Scheme 3.17). Also in this case, the reaction resulted in no conversion to the desired *N*-alkylated product **84**. Elevated temperature[104] or a continuous addition of the pivaloyl chloride into the reaction mixture did not give any conversion to the *N*-alkylated product **84**.



Scheme 3.17 Reagents and conditions: (a) DMAP, DIPEA, DCM, 0 ºC to r.t., 16 h; (b) DIPEA, DCM, 0 ºC to Δ, 16 h.

One of the main reasons, why the *N*-protecting groups are introduced, is to avoid a poisoning of the ruthenium catalyst by the amine nitrogen from the substrate (Section 3.1.1).[73,74] Resistance of the compounds **46b-c** to any of the attempted protection conditions indicated, that poor nucleophilicity and sterical hindrance of the N^6-nitrogen might prevent this potential poisoning and the desired RCM could take place with unprotected **46b-c**. Regrettably, when the most sterically hindered compounds **46b** or **46c** were brought to the RCM conditions, the ring-closing did not occur even with extended reaction time. The unreacted starting materials **46b** and **46c** were recovered (Scheme 3.18).



Scheme 3.18 Reagents and conditions: (a) Hoveyda-Grubbs II, DCE, Δ, 5 h.

The unsuccessful *N*-protection of the compounds **46b-c** was an unexpected complication in the designed synthetic sequence. From previous experience, the installation of a proper protecting group is the last important step before the key RCM could be approached. Consequently, we decided to change the approach at this point and we tried to obtain *N*-Boc protected intermediates **67a-c** in another fashion. This alternative synthetic strategy, based on a copper catalysed C-N bond formation and ruthenium promoted double bond migration is discussed in the following chapter. However we did not turn away from the *N*-protection investigation completely. The further discussion regarding the employment of the *N*-protection in the synthetic pathway is shown in section 4.2.5, page 64.

3.3 Summary and conclusion

The first attempt towards the synthesis of the asmarine analogues **47a-c**, derived from *α*-amino acids was presented. *N*-Boc protected esters of the *α*-amino acids phenylalanine, valine and leucine were chosen as the starting point. The chiral *N*-Boc protected allylic amines **77a-c** were prepared without racemization and successfully deprotected under acidic conditions. The resulting chiral allylic amines were isolated in high yields as the hydrochloride salts **78a-c**. After initial complications, the chiral allylammonium salts **78a-c** were successfully employed in the synthesis of products **75a-c**. The previously discovered double bond migration under basic conditions was performed with compounds **75a-c**. All corresponding rearranged products **46a-c** were conveniently obtained exclusively as *Z*-isomers in good yields. Unfortunately, all the attempts to introduce a protecting group to the N^6-nitrogen of **46b-c** were not successful. The resistance towards the *N*-protection is probably caused as a combination of a poor nucleophilicity and sterical hindrance of the N^6-nitrogen of the compounds **46**.

3.4 Experimental

The NMR data for purines **72**, **73a-c** and **46a-c** possessing two allylic side chains are presented according to the description in Figure 3.3. The protons from the terminal double bond, which show separate signals in ^{1}H NMR, are presented as H_A in $=CH_2$ and H_B in $=CH_2$ for the *trans* and *cis* proton, respectively.

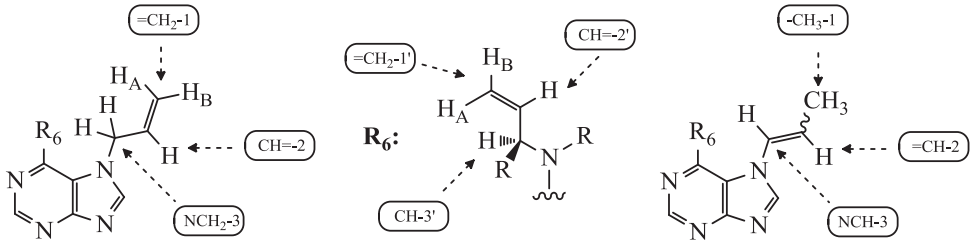


Figure 3.3 Description of the allyl/prop-1-en-3-yl side chain in the NMR spectra.

***(S,Z)-N*-(1-phenylbut-3-en-2-yl)-7-(prop-1-enyl)-7*H*-purin-6-amine (46a)**

(S)-7-allyl-*N*-(1-phenylbut-3-en-2-yl)-7*H*-purin-6-amine **75a** (0.17 mmol, 52 mg) and K_2CO_3 (0.40 mmol, 54 mg) were stirred at reflux in MeCN (3.2 mL) for 72 h under N_2. The reaction mixture was cooled to ambient temperature and filtered. The solvent was removed *in vacuo*

affording the desired product **46a** in quantitative yield; yield 52 mg (100%, *E/Z* = 1<99), yellow oil. *Z*-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53 (dd, J_1 = 7.1 Hz, J_2 = 1.6 Hz, 3H, CH_3-1), 2.94-3.09 (m, 2H, CH_2-4'), 5.01 (bd, *J* = 7.9 Hz, 1H, NH), 5.08 (d, *J* = 17.7 Hz, 1H, H_A in =CH_2-1'), 5.14 (d, *J* = 10.7 Hz, 1H, H_B in =CH_2-1'), 5.23 (m, 1H, CH-3'), 5.90-6.03 (m, 2H, CH=-2' and =CH-2), 6.68 (d, *J* = 7.8 Hz, 1H, NCH-3), 7.14-7.30 (m, 5H, Ph), 7.74 (s, 1H, H-8), 8.52 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.2 (CH_3-1), 40.6 (CH_2-4'), 52.4 (CH-3'), 111.5 (C-5), 115.1 (=CH_2-1'), 122.7 (NCH-3), 126.8, 128.4 and 129.6 (Ph), 132.0 (=CH-2), 136.8 (Ph), 137.8 (CH= 2'), 143.4 (C-8), 150.4 (C-6), 153.7 (C-2), 159.2 (C-4); MS (EI) *m/z* (rel. int.) 305 (9, M^+), 214 (100), 91 (7), 56 (10); HRMS (EI) $C_{18}H_{19}N_5$ requires 305.1640, found 305.1645; $[a]_D^{20}$ = 23 º.

***(S,Z)-N*-(4-methylpent-1-en-3-yl)-7-(prop-1-enyl)-7*H*-purin-6-amine (46b)**

(S)-7-allyl-*N*-(4-methylpent-1-en-3-yl)-7*H*-purin-6-amine (**75b**) (0.450 mmol, 117 mg) and K_2CO_3 (1.03 mmol, 143 mg) were stirred at reflux in MeCN (10 mL) for 72 h under N_2. The reaction mixture was cooled down to ambient temperature and filtered. Solvent was removed *in vacuo*. The residue was purified by flash chromatography using MeOH/CH_2Cl_2 (1:32); yield 81 mg (70%, *E/Z* = 1<99), yellow amorphous solid, mp 93-95 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (d, *J* = 6.8 Hz, 3H, CH*Me*$_2$), 0.90 (d, *J* = 6.8 Hz, 3H, CH*Me*$_2$), 1.69 (dd, J_1 = 7.0 Hz, J_2 = 1.8 Hz, 3H, CH_3-1), 1.93 (m, 1H, C*H*Me$_2$), 4.80 (m, 1H, CH-3'), 5.05-5.19 (m, 3H, =CH_2-1', NH), 5.80 (m, 1H, CH=-2'), 6.20 (m, 1H, =CH-2), 6.90 (dd, J_1 = 7.9 Hz, J_2 = 1.9, 1H, NCH-3) 7.74 (s, 1H, H-8), 8.45 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.3 (CH_3-1), 18.0 (CH*Me*$_2$), 18.4 (CH*Me*$_2$), 31.9 (*C*HMe$_2$), 56.9 (CH-3'), 111.4 (C-5), 115.6 (=CH_2-1'), 123.1 (NCH-3), 132.3 (=CH-2), 136.5 (CH=-2'), 143.3 (C-8), 151.1 (C-6), 153.5 (C-2), 158.8 (C-4); MS (EI) *m/z* (rel. int.) 257 (10, M^+), 242 (16), 214 (100), 200 (10); HRMS (EI) $C_{14}H_{19}N_5$ requires 257.1640, found 257.1633; $[a]_D^{20}$ = 58 º.

***(S,Z)-N*-(5-methylhex-1-en-3-yl)-7-(prop-1-enyl)-7*H*-purin-6-amine (46c)**

(S)-7-allyl-*N*-(5-methylhex-1-en-3-yl)-7*H*-purin-6-amine (**75c**) (0.730 mmol, 198 mg) and K_2CO_3 (1.68 mmol, 232 mg) were stirred at reflux in MeCN (13.5 mL) for 72 h under N_2. The reaction mixture was cooled down to ambient temperature and filtered. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography using MeOH/CH_2Cl_2 (1:49); yield 145 mg (75%, *E/Z* = 1<99), orange amorphous solid, mp 70-73 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (d, *J* = 6.5 Hz, 3H, CH*Me*$_2$), 0.93 (d, *J* = 6.5 Hz, 3H, CH*Me*$_2$), 1.48 (m, 2H, CH_2-4'), 1.61-1.71 (m, 4H, CH_3-1, C*H*Me$_2$), 4.96-5.18 (m, 4H, =CH_2-

1', CH-3', NH), 5.83 (m, 1H, CH=-2'), 6.19 (m, 1H, =CH-2), 6.93 (dd, J_1 = 7.7 Hz, J_2 = 1.8 Hz, 1H, CH-3), 7.78 (s, 1H, H-8), 8.49 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.4 (CH_3-1), 22.5 (CH*Me*$_2$), 22.7 (CH*Me*$_2$), 25.0 (*C*HMe$_2$), 44.4 (CH_2-4'), 50.5 (CH-3'), 111.3 (C-5), 114.7 (=CH_2-1'), 123.0 (NCH-3), 130.5 (=CH-2), 138.7 (CH=-2'), 143.5 (C-8), 150.7 (C-6), 153.4 (C-2), 158.6 (C-4); MS (EI) *m/z* (rel. int.) 271 (13, M^+), 256 (25), 228 (43), 214 (100), 200 (51); HRMS (EI) $C_{15}H_{21}N_5$ requires 271.1797, found 271.1798; $[a]_D^{20}$ = 22 º.

***N*,7-Diallyl-7*H*-purin-6-amine (72)**

Allylamine (12.8 mmol, 1.00 mL) and DIPEA (5.1 mmol, 0.90 mL) were stirred in *n*-BuOH (14 mL) at ambient temperature under N_2 for 1 h prior to use. 7-Allyl-6-chloro-7*H*-purine (**49b**) was added (2.60 mmol, 500 mg) and the reaction mixture was refluxed for 2 h. The mixture was concentrated *in vacuo*. The crude product was purified by flash chromatography using MeOH/CH_2Cl_2 (1:19); yield 540 mg (97%), off-white solid, mp 140-143 °C (Lit[18] 140-143 °C). Spectral data were in a good agreement with those reported before.[18]

***(S)*-7-Allyl-*N*-(1-phenylbut-3-en-2-yl)-7*H*-purin-6-amine (75a)**

(S)-1-phenylbut-3-en-2-aminium chloride **78a** (1.10 mmol, 202 mg) and DIPEA (3.10 mmol, 0.540 mL) were stirred in *n*-BuOH (5.4 mL) at ambient temperature under N_2 for 10 min prior to use. 7-Allyl-6-chloro-7*H*-purine (**49b**) (1.00 mmol, 195 mg) was added and the reaction mixture was refluxed for 48 h. The mixture was evaporated *in vacuo* and the product was purified by flash chromatography using MeOH/CH_2Cl_2 (1:49); yield 280 mg (92%), yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.98 (m, 2H, CH_2-4'), 4.57-4.86 (m, 3H, NCH_2-3, H_A in =CH_2-1), 4.90 (bd, J = 8.63 Hz, 1H, NH), 4.97-5.18 (m, 3H, H_B in =CH_2-1, =CH_2-1'), 5.26 (m, 1H, CH-3'), 5.87 (m, CH=-2, CH=-2'), 7.19 (m, 5H, Ph), 7.79 (s, 1H, H-8), 8.46 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.5 (CH_2-4'), 49.3 (NCH_2-3), 55.4 (CH-3'), 111.9 (C-5), 115.1 (=CH_2-1'), 119.1 (=CH_2-1), 126.7, 128.3 and 129.7 (Ph), 133.0 (CH=-2), 136.9 (Ph), 137.7 (CH=-2'), 144.6 (C-8), 149.8 (C-6) 153.3 (C-2), 160.0 (C-4); MS (EI) *m/z* (rel. int.) 305 (9, M^+), 214 (100), 174 (6), 91 (7); HRMS (EI) $C_{18}H_{19}N_5$ requires 305.1640, found 305.1646; $[a]_D^{20}$ = 45 º.

(*S*)-7-allyl-*N*-(4-methylpent-1-en-3-yl)-7*H*-purin-6-amine (75b)

Ammonium chloride **78b** (1.10 mmol, 150 mg) and DIPEA (3.10 mmol, 500 μl) were stirred in *n*-BuOH (5.4 mL) at ambient temperature under N_2 for 1 h prior to use. 7-Allyl-6-chloro-7*H*-purine (**49b**) (1.00 mmol, 195 mg) was added and reaction mixture was refluxed for 48 h. The mixture was evaporated *in vacuo* and purified by flash chromatography using

MeOH/CH_2Cl_2 (1:19); yield 194 mg (98%), beige solid, mp 115-117 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (d, *J* = 6.8 Hz, 3H, CH*Me*$_2$), 0.92 (d, *J* = 6.8 Hz, 3H, CH*Me*$_2$), 1.84-2.00 (m, 1H, C*H*Me$_2$), 4.84 (m, 1H, CH-3'), 4.91 (m, 2H, NCH_2-3), 5.00 (bd, *J* = 8.8 Hz, 1H, NH), 5.09 (m, 2H, =CH_2-1'), 5.18 (dt, J_1 = 17.4, J_2 = 2.0 Hz, 1H, H_A in =CH_2-1), 5.44 (dt, J_1 = 10.5, J_2 = 1.8 Hz, 1H, H_B in =CH_2-1), 5.81 (m, 1H, CH=-2'), 6.16 (m, 1H, CH=-2), 7.83 (s, 1H, H-8), 8.44 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.3 (CH*Me*$_2$), 18.5 (CH*Me*$_2$), 31.9 (*C*HMe$_2$), 49.4 (NCH_2-3), 57.2 (CH-3'), 111.9 (C-5), 115.7 (=CH_2-1'), 119.2 (=CH_2-1), 133.3 (CH=-2), 136.5 (CH=-2'), 144.6 (C-8), 150.4 (C-6), 153.4 (C-2), 160.1 (C-4); MS (EI) *m/z* (rel. int.) 257 (12, M^+), 242 (23), 214 (100), 200 (15), 174 (13), 56 (9), 41 (13); HRMS (EI) $C_{14}H_{19}N_5$ requires 257.1640, found 257.1645; $[a]_D^{20}$ = 55 º.

***(S)*-7-Allyl-*N*-(5-methylhex-1-en-3-yl)-7*H*-purin-6-amine (75c)**

(S)-5-methylhex-1-en-3-aminium chloride **78c** (2.90 mmol, 427 mg) and DIPEA (6.62 mmol, 1.13 mL) were stirred in *n*-BuOH (25 mL) at ambient temperature under N_2 for 1 h prior to use. 7-Allyl-6-chloro-7*H*-purine (**49b**) (0.82 mmol, 160 mg) was added and the reaction mixture was refluxed for 24 h. The mixture was concentrated *in vacuo*. The crude product was purified by flash chromatography using MeOH/CH_2Cl_2 (1:49); yield 207 mg (93%), yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (d, *J* = 6.5 Hz, 3H, CH*Me*$_2$), 0.86 (d, *J* = 6.5 Hz, 3H, CH*Me*$_2$), 1.39 (m, 2H, CH_2-4'), 1.62 (m, 1H, C*H*Me$_2$), 4.85-5.17 (m, 7H, CH-3', =CH_2-1', NCH_2-3, NH, H_A in =CH_2-1) 5.36 (dt, J_1 = 10.5 Hz, J_2 = 2.0 Hz, 1H, H_B in =CH_2-1), 5.77 (m, 1H, CH=-2'), 6.05 (m. 1H, CH=-2), 7.80 (s, 1H, H-8), 8.39 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3 (CH*Me*$_2$), 22.1 (CH*Me*$_2$), 24.7 (*C*HMe$_2$), 44.3 (CH_2-4'), 49.4 (NCH_2-3), 50.5 (CH-3'), 111.7 (C-5), 114.3 (=CH_2-1'), 119.0 (=CH_2-1), 133.5 (CH=-2), 138.7 (CH=-2'), 144.6 (C-8), 150.2 (C-6), 153.1 (C-2), 159.4 (C-4); MS (EI) *m/z* (rel. int.) 271 (6, M^+), 256 (27), 228 (44), 214 (100), 200 (54), 174 (18).); HRMS (EI) $C_{15}H_{21}N_5$ requires 271.1797, found 271.1794; $[a]_D^{20}$ = 26 º.

1-(1-Phenylbut-3-en-2-yl)pyridin-1-ium chloride (79a)

7-Allyl-6-chloro-7*H*-purine (**49b**) (0.25 mmol, 49 mg) was refluxed in pyridine (3.0 mL) with *(S)*-1-Phenylbut-3-en-2-aminium chloride **78a** (1.14 mmol, 282 mg) for 20 h. The mixture was concentrated *in vacuo*. The crude products were separated by flash chromatography on silica using MeOH/CH_2Cl_2 (1:9); yield 23 mg, (7%), off-white solid, mp 203 °C decomp. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.41-3.59 (m, 2H, CH_2-1), 5.50 (m, 2H, =CH_2-4), 5.92 (dt, J_1 = 9.1 Hz, J_2 = 6.4 Hz, 1H, NCH-2), 6.33-6.44 (m, 1H, CH=-3), 7.15-7.25 (m, 5H, Ph), 8.13

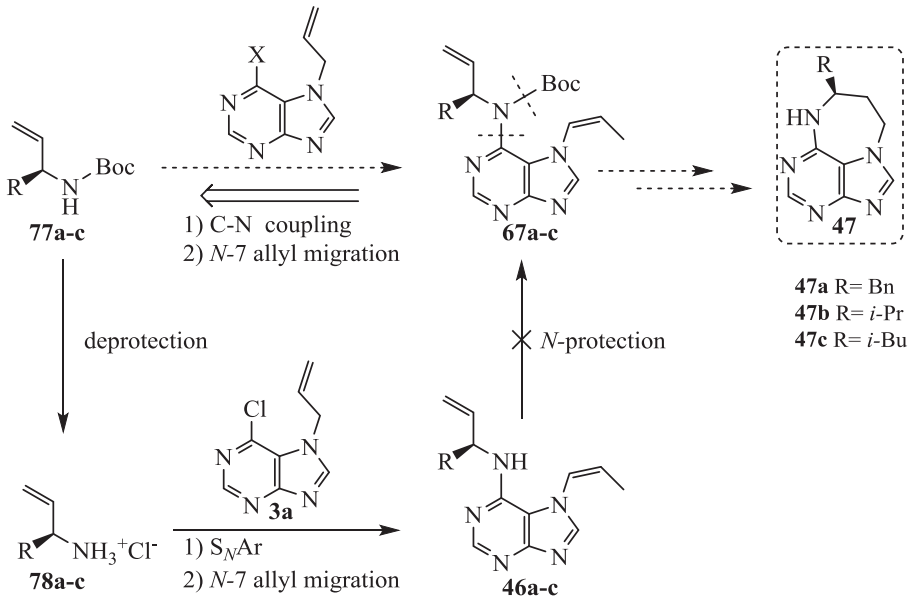
(dd, J_1 = 7.7 Hz, J_2 = 6.5 Hz, 2H, H-3 + H-5), 8.58 (tt, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1H, H-4), 9.25 (dd, J_1 = 6.5 Hz, J_2 = 1.3 Hz, H-2 + H-6); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 38.4 (CH_2-1), 72.8 (NCH-2), 121.3 (=CH_2-4), 126.5 (Ph), 127.8 (C-3+C-5), 128.00 and 128.5 (Ph), 133.9 (CH=-3), 134.9 (Ph), 143.2 (C-2+C-6), 145.8 (C-4); MS (ESI) *m/z* (rel. int.) 210 $[M+1]^+$; HRMS (EI) $C_{15}H_{16}N$ requires 210.1277, found 210.1277.

Chapter 4

Ruthenium promoted double bond migration and copper mediated C-N bond formation in the synthesis towards asmarines

4.1 Introduction

Facing serious problems with the *N*-Boc protection (Section 3.2.4, page 38), we had to redesign the initial reaction pathway. The Boc group of intermediate **77a-c** was removed in the second step of the original strategy in order to allow a nucleophilic substitution with the 6-chloropurine **49b**. Unfortunately, later in the sequence we encountered difficulties trying to reintroduce the Boc group to obtain the product **67a-c** (Scheme 4.1). Therefore, another strategy employing carbon-nitrogen (C-N) bond formation was explored. The primary objective of this alternative approach was to investigate, whether the C-N bond between a suitable halopurine and the carbamates **77a-c** could be formed directly, without previous Boc-deprotection (Scheme 4.1). To complete this reaction pathway leading to the RCM precursor **67**, conditions for *N*-7 allyl rearrangement were investigated.

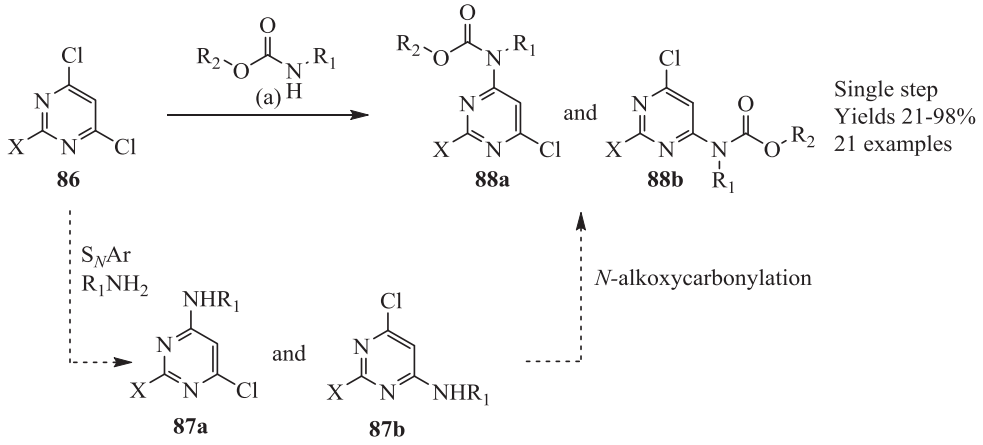


Scheme 4.1 Strategies towards the *N*-Boc protected products **67a-c**.

4.1.1 Methods for C-N bond formation

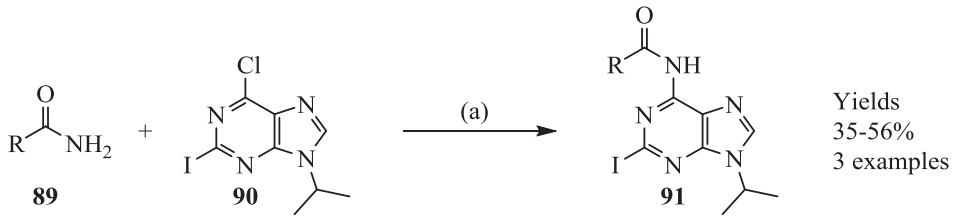
4.1.1.1 Nucleophilic substitution with *N*-sodium carbamates

Formation of the C-N bond using *N*-protected amines can be achieved in a relatively facile manner. There are examples known, wherein Boc-protected amines are taking part in nucleophilic substitutions *via* *N*-sodium carbamate formation.[105,106] The apparent benefit of this method was demonstrated in the synthesis of *N*-alkoxyaminopyridines **88**.[107] The typical synthetic procedure consists of two steps, starting with the treatment of an appropriate chloropyrimidine with a free amine. After S_NAr, the *N*-alkoxycarbonylation should take place. In contrast to this, taking advantage of the *N*-sodium carbamate formation, the whole process can be covered in single step with good yield of the final products (Scheme 4.2).[107,108]



Scheme 4.2 Reagents and conditions: (a) NaH, DMF, r.t., 0.5 to 22 h.[107]

Interestingly, this method was successfully employed in amidation of 6-halopurines **90** (Scheme 4.3).[109]



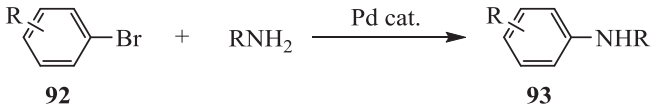
Scheme 4.3 Reagents and conditions: (a) NaH, DMF, 0 ºC to r.t., 2 to 4 h.[109]

Despite the advantages, there is an apparent general limitation of this type of S_NAr. The substrate leaving group has to be present either in α or γ position on an appropriate *N*-

heterocyclic core or on an aromatic ring in *ortho* or *para* position relative to the electron withdrawing group.[110] Nevertheless, considering the similarity of this approach with the aim of our investigation, we decided to examine this strategy (Section 4.2.1).

4.1.1.2 Hartwig-Buchwald coupling

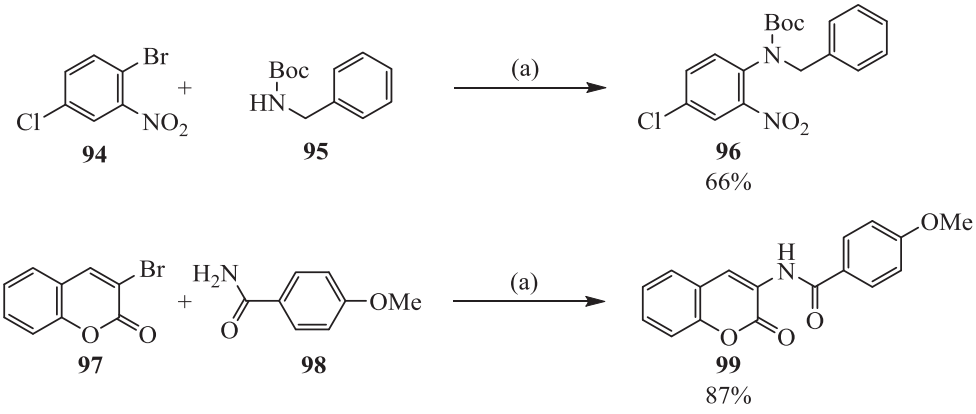
One of the sophisticated methods for C-N bond formation is the palladium catalysed hetero cross-coupling, which was developed by Hartwig and Buchwald. This method was originally designed for the coupling of primary amines with aromatic bromides **92** (Scheme 4.4).[111,112]



92 **93**

Scheme 4.4 Aryl bromides in the Hartwig-Buchwald coupling with amines.

The scope if this reaction was later on extended, hence the Hartwig-Buchwald coupling is now commonly performed with a broad range of amines or anilines and aryl halides. This coupling is manly suitable for electron poor aryl halides.[112] In our particular case, we were interested in this type of reactions since the application of various amides or carbamates in Hartwig-Buchwald coupling is known (Scheme 4.5).[110,113-115]

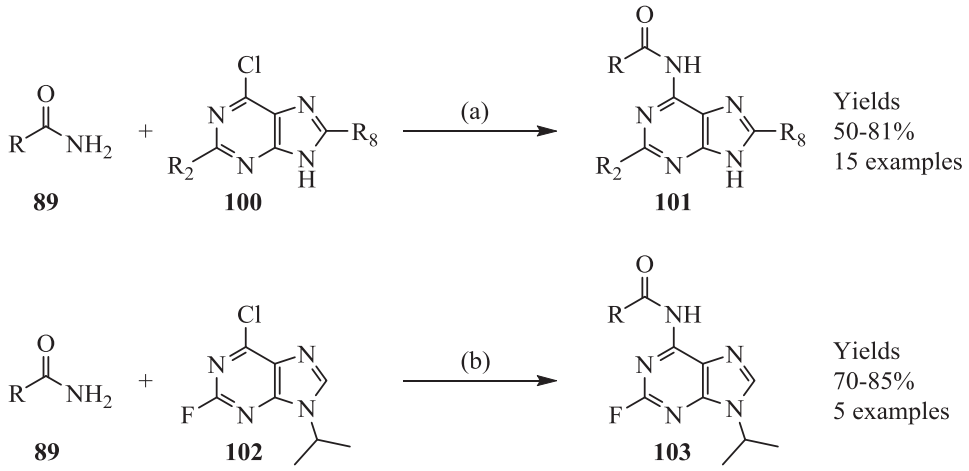


94 **95** **96** 66%

97 **98** **99** 87%

Scheme 4.5 Reagents and conditions: (a) $Pd(OAc)_2$, Xanthphos, Cs_2CO_3, dioxane, 110 ºC, 20 h.[110,115]

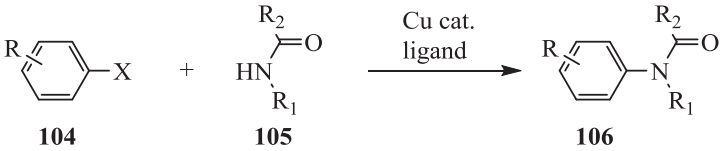
Most importantly, the Pd catalysed amidation found its application in purine chemistry. Several *N*-9 unprotected 6-halopurines **100**[116,117] or *N*-alkyl 6-halopurines **102**[109,116] were successfully employed in this Hartwig-Buchwald protocol.



Scheme 4.6 Reagents and conditions: (a) $Pd_3(dba)_2$, Xanthphos, Cs_2CO_3, dioxane, 130 ºC, 8 to 24 h;[116] (b) $Pd_3(dba)_2$, Xanthphos, Cs_2CO_3, dioxane, 100 ºC, 1 h.[109]

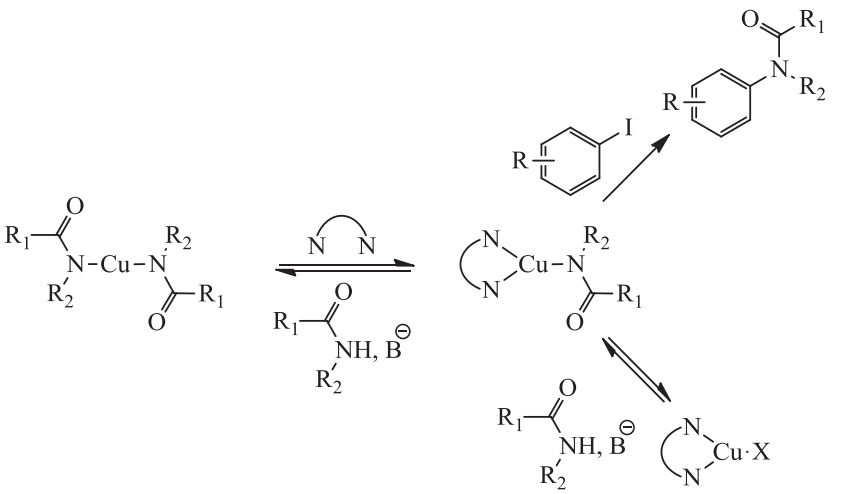
4.1.1.3 Goldberg reaction

For the substrates which are incompatible with the Hartwig-Buchwald coupling, the Goldberg reaction[118] is usually a suitable alternative.[119] The Goldberg reaction is a copper catalysed amidation of aryl or heteroaryl halides (Scheme 4.7).[118] The original application of this method was rather limited due to the requirement of elevated reaction temperatures and large amounts of copper reagents. On top of that, the copper coupling occurred only in polar solvents, giving moderate yields.[119,120]



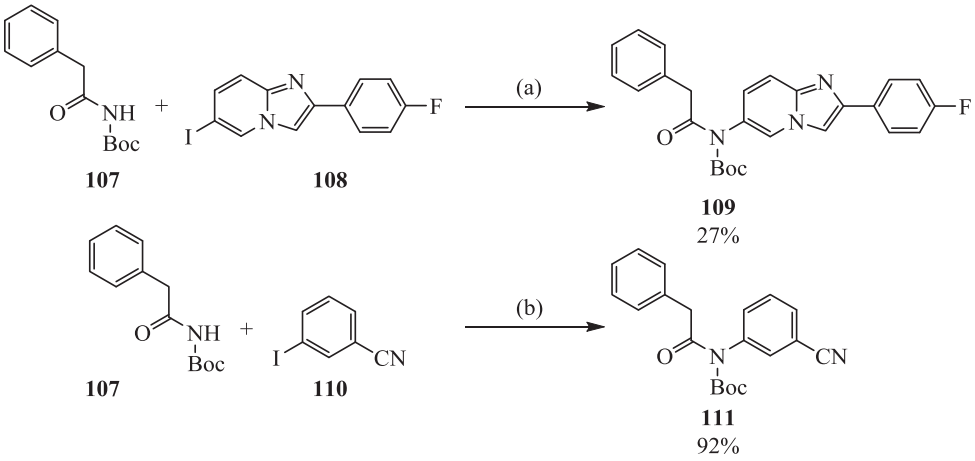
Scheme 4.7 Copper catalysed amidation of aryl halides.

Recent development of suitable ligand systems (Scheme 4.8) facilitated the reaction conditions and thus opened a broad employment of the Goldberg reaction in organic synthesis.[119-122] The most important advantage of this method is its wide application with different amides and electron rich aryl halides. Moreover, the reaction is carried out with inexpensive catalysts such as copper salts.



Scheme 4.8 Chelating ligands in the Goldberg reaction.[122]

The *tert*-butyl carbamates can be problematic substrates in some cases.[123] However, the amidation using Boc-protected amines is reported (Scheme 4.9).[119,123] The Goldberg reaction was successfully utilised in our synthetic strategy (Section 4.2.2).

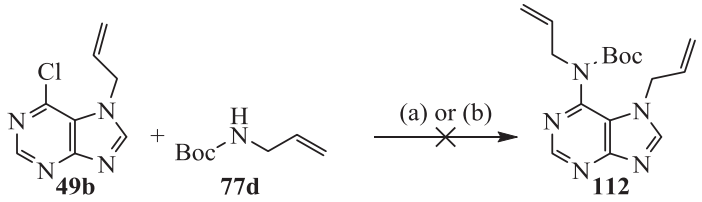


Scheme 4.9 Reagents and conditions: (a) CuI, N^1,N^2-dimethylethane-1,2-diamine, K_2CO_3, toluene, 110 ºC, 20 h;[123] (b) CuI, (1*S*,2*S*)-cyclohexane-1,2-diamine, K_3PO_4, toluene, 110 ºC, 25 h.[119]

4.2 Results and discussion

4.2.1 Attempts for the application of *N*-sodium carbamate

Initially, a method for establishing the C-N bond *via* *N*-sodium carbamate was explored (Scheme 4.10). Model reactions using **49b** and *tert*-butyl allylcarbamate were carried out following literature procedures. *tert*-Butyl allylcarbamate was stirred with NaH in dry DMF for 1 hour[107,108] prior to addition of 7-allyl-6-chloro-*7H*-purine (**49b**). Formation of hydrogen gas in the reaction mixture indicated successful generation of the *N*-sodium allyl carbamate. Purine **49b** was subsequently added at -25 ºC and the reaction was allowed to warm up to ambient temperature. Regrettably, no product was observed after 24 h and 50% of the starting **49b** was recovered (Scheme 4.10). Based on another report,[106] the solution of *N*-sodium carbamate was prepared in THF at 0 ºC. Subsequently, the purine **3a** was added and the reaction was allowed to proceed at ambient temperature. This attempt resulted in the degradation of the substrate **49b** after 4 h, as judged by TLC. Unfortunately, the chloropurine **49b** does not seem to be compatible with the reaction conditions. Since no conversion towards desired *N*-Boc protected product **112** was achieved by deprotonation of *tert*-butyl allylcarbamate 7**7d** we had to focus on the investigation of the hetero cross couplings.



Scheme 4.10 Regents and conditions: (a) NaH, DMF, -25 ºC to r.t., 24 h;[108] (b) NaH, THF, 0 ºC to r.t., 4 h.

4.2.2 Investigation of the transition metal catalysed C-N bond formation

The Pd catalysed Hartwing-Buchwald and Cu promoted Goldberg reaction conditions were examined. The ligands used in the reactions are depicted in Figure 4.1.

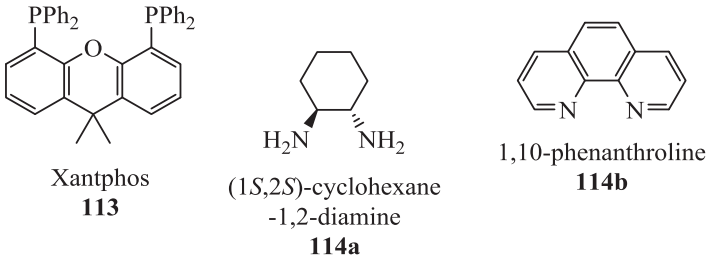
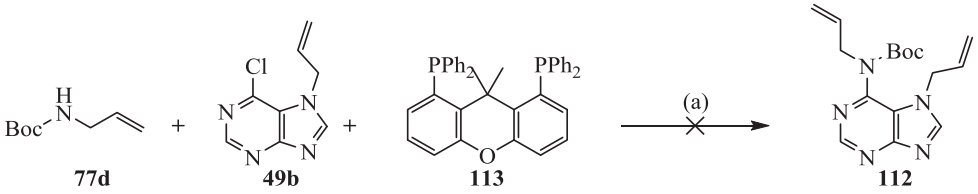


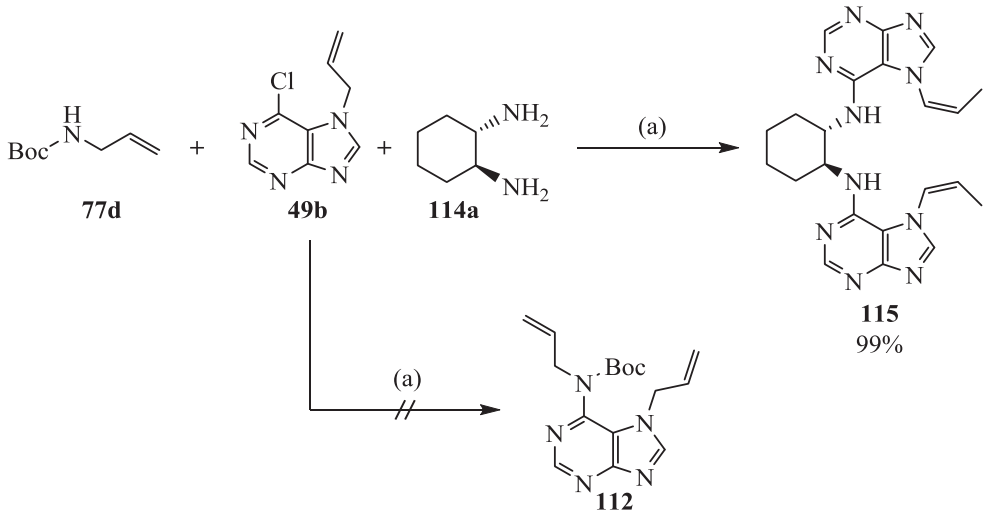
Figure 4.1 Ligands used in C-N coupling reactions.

First we attempted the coupling of 7-allyl-6-chloro-7*H*-purine (**49b**) and carbamate **77d** under Hartwig-Buchwald conditions, using $Pd(Ac)_2$ and the ligand **113**[110,115] (Scheme 4.11). This reaction did not lead to any observable conversion and we switched our attention to the copper mediated coupling reactions.



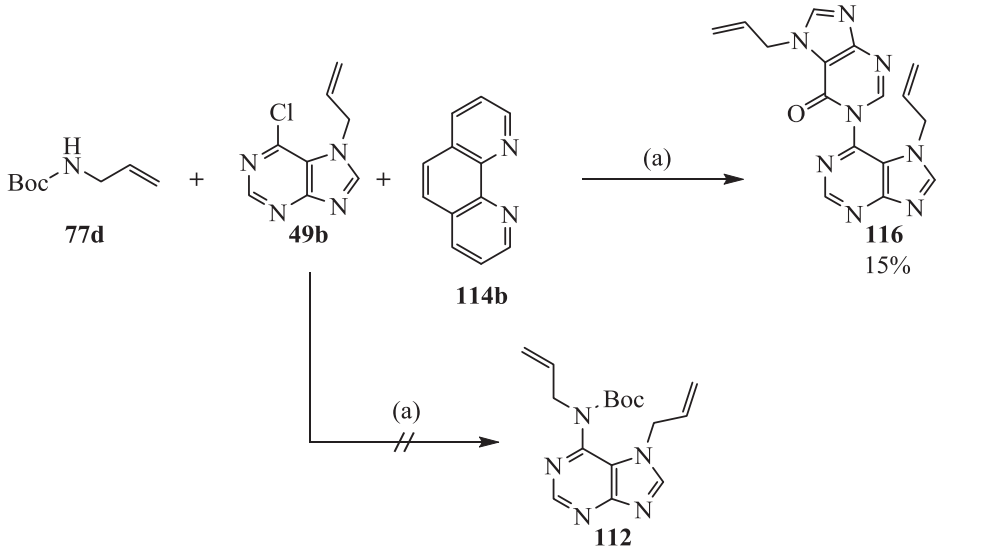
Scheme 4.11 Reagents and conditions: $Pd(Ac)_2$, Cs_2CO_3, dioxane, 110 ºC, 24 h.

Unfortunately, the initial results from the copper mediated Goldberg reaction were also not promising. In the beginning of our investigation, we tried to follow the literature procedures for the amidation of various aryl iodides, wherein a ligand (1*S*,2*S*)-cyclohexane-1,2-diamine (**114a**) was used.[119,121,124] These coupling conditions were applied to 7-allyl-6-chloro-7*H*-purine (**49b**) (Scheme 4.12 and Scheme 4.13) to explore, whether the reactivity of **49b** can be comparable to the reactivity of the reported aryl iodides. Regrettably, the ligand **114a**, present in reaction mixture, reacted completely with the chloropurine **49b** by S_NAr and the hetero cross-coupling did not take place. In addition, the substitution was followed by migration of the double bond on the 7-allyl side chain. The reaction yielded 99% of the dimer **115** (Scheme 4.12).



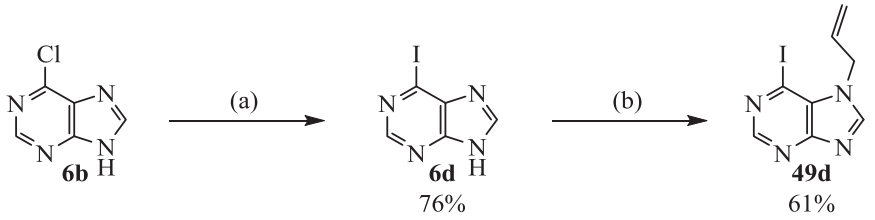
Scheme 4.12 Reagents and conditions: CuI, K_3PO_4, dioxane, 110 ºC sealed tube, 24 h.

The coupling reaction was also attempted with the non-nucleophilic ligand 1,10-phenanthroline (**114b**).[121,125] The desired C-N coupling did not take place here either. Instead, an unexpected side reaction leading to the by-product **116** occurred (Scheme 4.13). The minor formation of **116** could be explained by presence of moisture in the reaction mixture. The desired product **112** was not observed and 37% of the starting **49b** was recovered.



Scheme 4.13 Reagents and conditions: CuI, Cs_2CO_3, dioxane, 110 ºC sealed tube, 24 h.

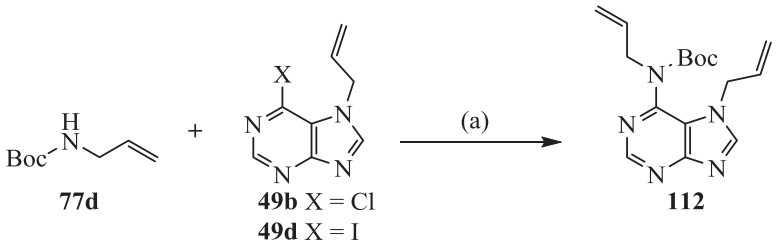
Since the chloropurine **49b** showed no reactivity in the attempted copper coupling reactions, we tried to explore, whether the coupling will take place if the chlorine in the C-6 position of the substrate will be replaced by iodine. For this reason, a suitable approach to obtain the iodo analogue **49d** was investigated (Scheme 4.14). Iodination of chloropurines is usually performed with hydroiodic acid (47%) or with combination of hydroiodic acid and potassium or sodium iodide. This halogen exchange procedure is reported both with alkyl purines,[126,127] as well as with free purine bases.[128] In our particular case the allyl chain in **49b** cannot be preserved under the iodination conditions. Thus, the starting 6-iodo-9*H*-purine (**6d**) had to be synthesized first. A treatment of chloropurine **6b** with hydroiodic acid[128] gave high yield of the iodopurine **6d** (Scheme 4.14). The product **49d** was subsequently obtained in good yield from the regioselective allylation of **6d** (Scheme 4.14, see also Section 2.2.2, page 20).



Scheme 4.14 Reagents and conditions: HI (47%), 0 ºC, 3 h; (b) methylaquacobaloxime, allyliodide, MeCN, r.t., 120 h.

Having decent amounts of iodopurine **49d** readily available, we were focused on the investigation of the Cu mediated C-N coupling. A series of test scale reactions were prepared and the conversion towards **112** was monitored by ^{1}H NMR (Scheme 4.15, Table 4.1). Performing the coupling with compound **49d** led to the formation of product **112** for the first time. Unfortunately, the unwanted dimer **116** was also initially detected (Table 4.1, entries 1-4). Setting up the reaction under the inert atmosphere of a glovebox prevented a further occurrence of by-product **116**. Moreover, additional improvement of the reaction progress was achieved by refluxing in THF in place of dioxane (Table 4.1, entries 4-6). A notable complication in this reaction procedure is the separation of substrate **49d** and product **112**. Both compounds possess very similar R_f values, thus purification by column chromatography was fairly difficult and the product was not isolated pure from the initial experiments (Table 4.1, entry 1-5). Finally, when using a slow gradient elution, the product **112** was obtained in a pure form and acceptable yield (Table 4.1, entry 6). Higher conversion in this case helped to

facilitate the purification. In conjunction with previous attempts, C-N coupling did not take place with chloropurine **49b** (Table 4.1, entry 7).



Scheme 4.15 Reagents and conditions: (a) CuI, 1,10-phenanthroline; for solvents, temperature and time (see Table 4.1).

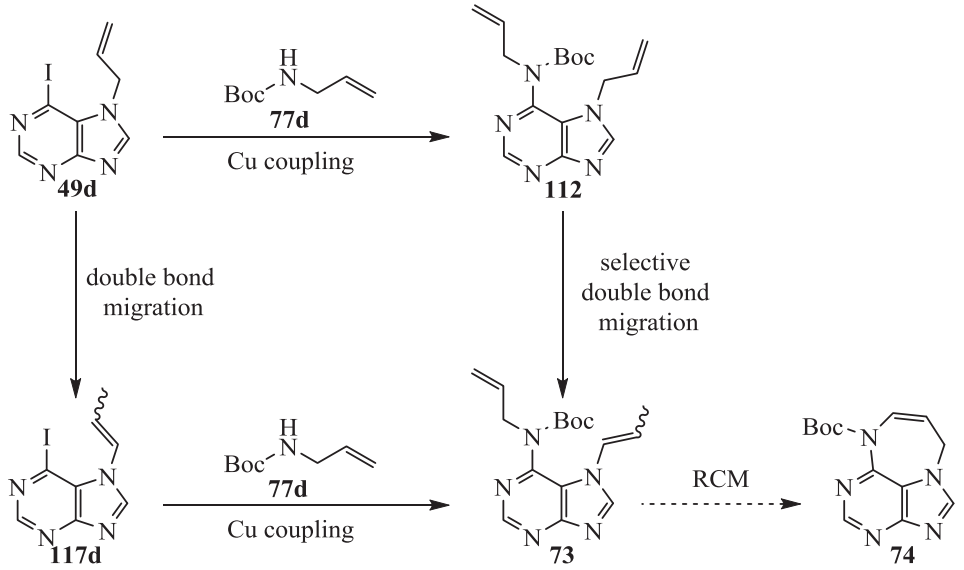
Table 4.1 Cu coupling with halo-purines **49d** and **49b**

Entry	Subs.	solvent	T [°C]	time [h]	Conversion [%][a] 112	116	
1	**49d**	dioxane	110 °C	24	20	30	sealed tube
2	**49d**	dioxane	r.t. to 80 °C	55	35	7	sealed tube
3	**49d**	THF	70 °C	4	15	3	sealed tube
4	**49d**	THF	Δ	16	60	8	
5	**49d**	THF	Δ	24	45	n.d.[b]	
6	**49d**	THF	Δ	48	60	n.d.	Yield 56%
7	**49b**	THF	Δ	48	n.d.	n.d.	

[a]Determined by ^{1}H NMR of the crude product; [b]Not detected.

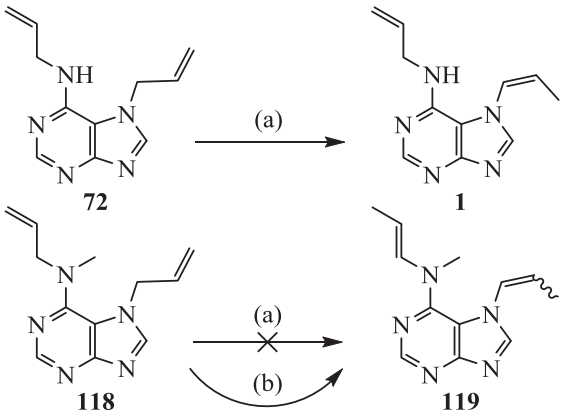
4.2.3 Development of the method for the double bond migration

To obtain the 7-membered ring by RCM, a double bond migration has to be employed in the synthetic sequence (see Chapter 3). Due to the successful finding of suitable C-N coupling conditions (Section 4.2.2), there are two possible pathways towards the RCM precursor **73** (Scheme 4.16). First of all, we wanted to examine, whether the coupling product **112** could be rearranged to the desired product **73**. In this particular case the isomerisation has to be regioselective, taking place on the *N*-7 allyl chain only. Another possibility is to rearrange the 6-iodopurne **49d** prior to copper coupling. 7-Allyl-6-iodo-7*H*-purine (**49d**) possess only one allyl side chain, thus no selective rearrangement would be required. Both synthetic routes were investigated.



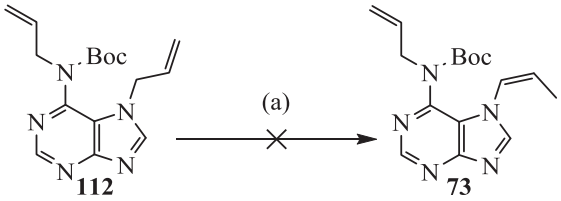
Scheme 4.16 Two possible reaction pathways towards the RCM precursor **73** employing a sequence of C-N coupling and double bond migration.

The primary research was focused on a rearrangement of the *N*-Boc protected compound **112** under basic conditions (Scheme 4.18, Table 4.2). From previous experience[18] it was known, that 7-allyl-purines **72** and **75a-c** bearing a free -NH group on C-6 can be selectively isomerised to corresponding 7-(propen-1-yl) purines using K_2CO_3 in refluxing MeCN (Section 3.2.3, page 38, Scheme 3.15). Importantly, when the proton from the secondary amine (*Z*)-*N*-allyl-7-(prop-1-en-1-yl)-7*H*-purin-6-amine (**72**) was replaced by a methyl group, a considerable decrease of the isomerisation was noted earlier (Scheme 4.17).[18]



Scheme 4.17 Reagents and conditions: (a) K_2CO_3, MeCN, Δ; (b) K_2CO_3, *n*-BuOH, Δ.[18]

The same decrease in reactivity was observed for the rearrangement of the *N*-Boc protected compound **112**. Inorganic carbonates or phosphates as well as elevated reaction temperatures were used, but the migration did not occur (Table 4.2, entries 1-4). We also tried to achieve the rearrangement of **112** using the strong base *t*-BuOK.[129] This reaction resulted in partial decomposition of **112** (Table 4.2, entry 5). Substrate **112** also showed limited stability when exposed to sodium hydride either at reflux or at ambient temperature (Table 4.2, entries 6 and 7).



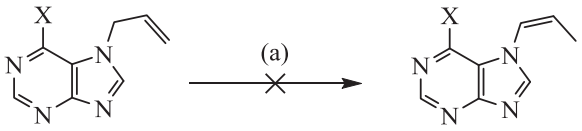
112 **73**

Scheme 4.18 Reagents and conditions: (a) see Table 4.2.

Table 4.2 attempts for base promoted rearrangement of **112**

Entry	solvent	base	T	time [h]	recovered 112 [%]
1	MeCN	K_2CO_3	Δ	24	99
2	MeCN	K_3PO_4	Δ	24	99
3	dioxane	K_3PO_4	Δ	24	99
4	dioxane	Cs_2CO_3	Δ	24	99
5	MeCN	*t*-BuOK	Δ	24	70
6	MeCN	NaH	r.t. to Δ	3,5	0
7	MeCN	NaH	r.t.	24	50

In summary, no base promoted migration of the *N*-7 allylic double bond was observed for the *N*-Boc protected compound **112**. Therefore our attention switched to the investigation of how the rearrangement of 6-iodopurine **49d** could be achieved. However, the treatment of **49b** or **49d** with various bases did not lead to the migration of the double bond (Scheme 4.19).

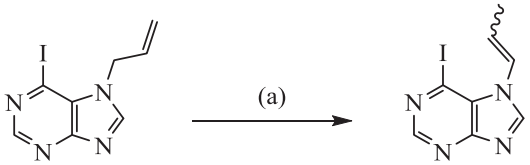


49b X = Cl
49d X = I

117b X = Cl
117d X = I

Scheme 4.19 Reagents and conditions: K_2CO_3, Cs_2CO_3 or K_3PO_4, MeCN, Δ, 24 h.

We then turned to an alternative strategy and chose to study transition metal induced rearrangements.[130] There are few known examples, describing the metal induced rearrangement of the *N*-allyl group in aromatic compounds and nitrogen containing heterocycles.[131-136] However, application of this method on the *N*-allyl purines was not reported so far. Consequently, we chose to explore the rearrangement of **49d** (Scheme 4.20) with catalyst $RuClH(CO)(PPh_3)_3$.[137,138] This particular Ru catalyst was chosen for its known ability to rearrange *N*-allyl group attached to the endocyclic nitrogen.[134,139-141]



49d **117d**

Scheme 4.20 Reagents and conditions: see Table 4.3.

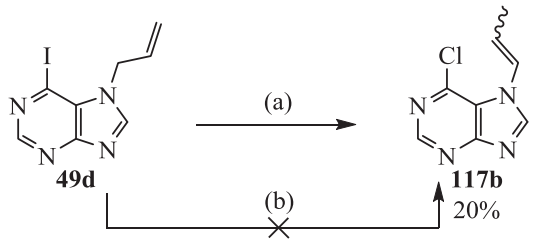
Initial attempts to migrate the *N*-allyl double bond in compound **49d** were carried out in refluxing toluene.[134] Limited solubility of **49d** in toluene caused very low conversion as well as partial substrate decomposition (Table 4.3, entries 1-3). Switching the solvents to either THF or DCM resolved the solubility problem. Upon these conditions, the rearrangement took place. Nevertheless, the reaction was still somewhat sluggish, giving approximately 10% conversion towards the desired intermediate **117d** (Table 4.3, entries 4-6).

Table 4.3 Rearrangement screening with $RuClH(CO)(PPh_3)_3$

Entry	Solv.	cat. [%]	T [°C]	Time [h]	Conv. [%][a]	Note
1	Toluene	5%	120	2	6	
2	Toluene	5%	120	24	n.d	Decomposition
3	Toluene	5%	Δ	24	16	Partial decomposition
4	THF	5%	76	24	~10	
5	DCM	5%	Δ	24	~10	
6	THF	5%	76	72	~10	
7	DCE	5%	Δ	12	30	Chlorination
8	DCE	5%	110	24	16	Partial decomposition, Chlorination
9	DCE	5%	Δ	24	50	Chlorination, 20% yield of **117b**
10	DCE	10%	Δ	72	50	Chlorination
11	dioxane	5%	Δ	72	n.d.	Decomposition

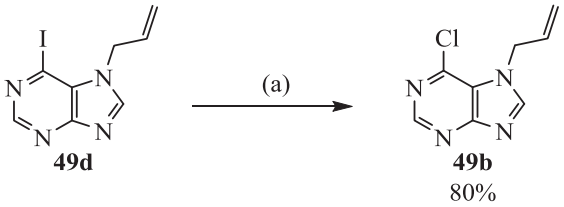
[a]Determined by ^{1}H NMR of the crude product.

When the reaction was carried out in DCE, the isomerisation progress was slightly higher (Table 4.3, entries 7-10). However, an unexpected phenomenon was also observed. The combination of $RuClH(CO)(PPh_3)_3$ in DCE caused unwanted halogen exchange of the 6-iodine from iododopurine **49d** forming the undesired 6-chloro-7-(prop-1-en-1-yl)-7*H*-purine (**117b**) (Scheme 4.21). Even though $RuClH(CO)(PPh_3)_3$ contains a chloride atom, the catalyst cannot be the only source of chlorination. The product **117b** was isolated in 20% yield, which exceeded the stoichiometric amount of the catalyst in the reaction mixture (Scheme 4.21, Table 4.3, entry 9). When **49d** was refluxed in DCE in absence of the catalyst, the chlorination did not take place. Therefore the catalyst itself was identified as the chlorination initiator with DCE as a chlorine source.



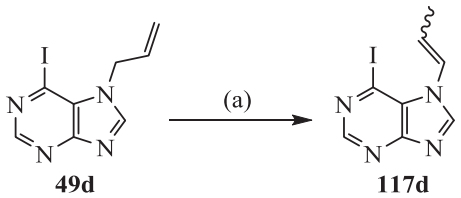
Scheme 4.21 Reagents and conditions: (a) $RuClH(CO)(PPh_3)_3$, DCE, Δ, 24h; (b) DCE Δ, 24 h.

Several successful rearrangements of allylic double bonds with the Grubbs II catalyst are reported.[142-144] Hence, we also tried to achieve the rearrangement of **49d** using this catalyst. However, no rearrangement was observed, and the halogen exchange occurred almost exclusively (Scheme 4.22). This generally excluded halogenated solvents from consideration.



Scheme 4.22 Reagents and conditions: (a) Grubbs II, DCE, Δ, 24h.

We then tried to perform the rearrangement in refluxing dioxane (Table 4.3, entry 11). Following the reaction by TLC indicated promising progress within the first 48 h of the reaction. Regrettably, after 72 h, before the reaction could reach completion, decomposition of **49d** occurred. Considering the sluggish reaction performance, we decided to explore, whether the reaction process could be more efficient under microwave irradiation conditions. We prepared a set of experiments in test scale and followed the reaction progress by ^{1}H NMR (Scheme 4.23, Table 4.4) no products were isolated.



Scheme 4.23 Reagents and conditions: see Table 4.4, microwave irradiation, dioxane.

The results presented in Table 4.3 indicated, that successful migration takes place only at elevated temperature. Thus, we first performed screening for the optimal reaction temperature

(Table 4.4, entries 1-5). As starting point we chose the reaction temperature close to the boiling point of dioxane (Table 4.4, entry 1), 1 hour reaction time and 5% catalyst loading. The reaction temperature was raised by 10 ºC for each entry. The most promising conversion was achieved at 130 °C. Additional increase of the reaction temperature up to 140 °C did not lead to further improvement. At this point, we decided to increase the catalyst loading to 10%, which resulted in 90% conversion (Table 4.4, entry 6). The last step was to extend the reaction time up to 3 hours, which gave slightly higher conversion as well (Table 4.4, entry 7).

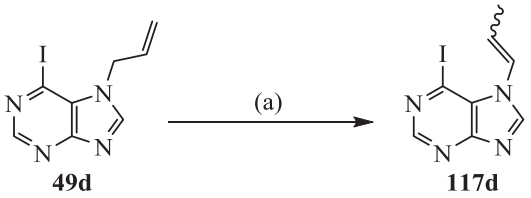
Table 4.4 Microwave assisted catalytic double bond migration of **49d** by $RuClH(CO)(PPh_3)_3$

Entry	cat. [%]	Time [h]	T [°C]	Conv. [%][a]
1	5	1	100	24
2	5	1	110	24
3	5	1	120	46
4	5	1	130	75
5	5	1	140	60
6	10	1	130	90
7	10	3	130	93

[a]Determined by ^{1}H NMR of the crude product.

Based on these results, the suitable reaction temperature, time and catalyst concentration were determined. The experiment was successfully reproduced on a preparative scale and the desired rearranged product **117d** was isolated with high yield as a 50:50 mixture of *E/Z* isomers (Scheme 4.24, Table 4.5, entry 1). Taking into consideration that the rearrangement is taking place at around 130 ºC, we also attempted this reaction in refluxing xylenes. To our delight, the isomerisation occurred with the same efficiency. This allowed us to perform the migration using convenient standard techniques without microwave irradiation (Table 4.5, entry 2). Overall, there is one minor drawback as the rearrangement was always followed by minor halogen exchange. As mentioned before, this is caused by the catalyst itself, resulting in contamination of the final product **117d** by 10% of the unwanted chloro analog **117b**. When we tried to decrease the catalyst loading to 5%, the conversion dropped noticeably (Table 4.5, entry 3). An alternative chlorine free catalyst, $RhH(CO)(PPh_3)_3$ was also employed on this substrate, but the conversion to the propenylpurine **117d** was only 8%

(Table 4.5, entry 4). On the other hand, despite the chlorination, the rearrangement was performed on a preparative scale with satisfactory results (Table 4.5, entries 1 and 2). Therefore, we decided to move forward and finally employ this method in the synthetic pathway.



49d **117d**

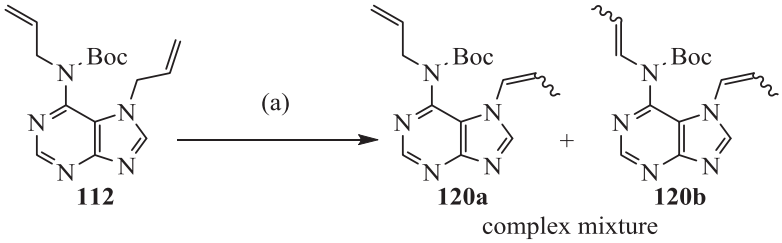
Scheme 4.24 Reagents and conditions: (a) see Table 4.5.

Table 4.5 Conditions for rearrangement of **49d**

Entry	Catalyst	Conditions	Conv. [%][a]	Yield [%][b]
1	10% $RuClH(CO)(PPh_3)_3$	dioxane, microwave, 130 ºC, 3h	95	74[c]
2	10% $RuClH(CO)(PPh_3)_3$	xylenes, Δ, 3h	90	73[c]
3	5% $RuClH(CO)(PPh_3)_3$	xylenes, Δ, 3h	68	n.d.
4	10% $RhH(CO)(PPh_3)_3$	xylenes, Δ, 3h	8	n.d.

[a]Determined by ^{1}H NMR of the crude product; [b]Isolated yield; [c]Calculated yield of **117d**, was isolated together with minor amounts of **117b**.

The designed isomerisation conditions were also applied on the *N*-Boc protected **112**. Treatment of **112** with $RuClH(CO)(PPh_3)_3$ gave no selective rearrangement and low conversion. Both *N*-allylic double bonds were isomerized giving a complex mixture of rearranged isomers, which were not successfully separated (Scheme 4.25).



112 **120a** **120b**

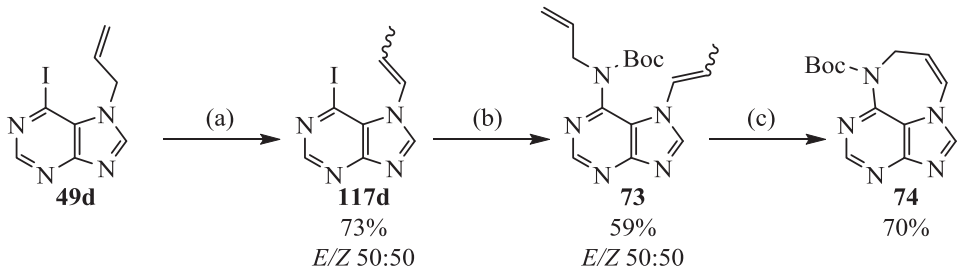
complex mixture

Scheme 4.25 Reagents and conditions: (a) 10% $RuClH(CO)(PPh_3)_3$, xylenes, Δ, 3 h.

The general rearrangement of *N*-allyl purines was further investigated. The background of the rearrangement methodology, mechanisms as well as the scope and limitation study with *N*-allyl purines is discussed in the following chapter.

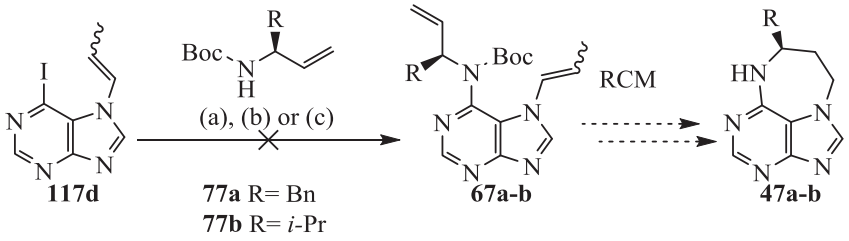
4.2.4 Application of the double bond migration and C-N coupling in the synthesis towards asmarines

After designing the conditions for *N*-allyllic double bond isomerisation and C-N bond formation, we decided to approach the model synthesis with *tert*-butyl allylcarbamate (**77d**) (Scheme 4.26). Compound **49d** was rearranged to **117d**. Intermediate **117d** containing 10% of the chloro-analogue **117b** was then subjected to coupling reaction with *tert*-butyl allylcarbamate (**77d**). This reaction gave good yield of product **73** as a 50:50 mixture of *E/Z* isomers. The unwanted chloro analogue **117b** does not take part in the C-N coupling and was separated from the product **73** using flash chromatography. The RCM with **73** led to the previously reported[18] asmarine analog **74**. While only the *Z*-isomer of **73** was employed in previous synthesis,[18] the important outcome of this experiment is that both *E*- and *Z*-isomers underwent the RCM successfully, yielding product **74**.



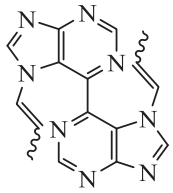
Scheme 4.26 Reagents and conditions: (a) 10% $RuClH(CO)(PPh_3)_3$, xylenes, Δ, 3h; (b) allylcarbamate **77d**, CuI, 1,10-phenanthroline, Cs_2CO_3, dioxane, Δ, 2 days; (c) 5% Hoveyda-Grubbs II, DCE, Δ, 1.5 h.

Regrettably, when we tried to introduce the *α*-substituted *tert*-butyl allyl carbamates **77a-b** (Scheme 4.27), the results were not satisfactory. Using more substituted carbamates **77**, the copper mediated coupling with **117d** did to take place and side reactions started to occur instead. The coupling did probably not occur due to the sterical hindrance caused by additional *α*-substitution on amides **77a-b**. As experienced before, the reactivity in coupling can drop significantly with increasing sterical hindrance of the coupling partners.[119]



Scheme 4.27 (a) CuI, 1,10-phenanthroline, Cs_2CO_3, dioxane, Δ, 24 h; (b) CuI, 1,10-phenanthroline, K_3PO_4, dioxane, Δ, 24 h, (c) CuI, 1,10-phenanthroline, K_3PO_4, DMF, Δ, 24 h.

tert-Butyl allyl carbamates **77a-b** showed reasonable stability upon the given conditions and were recovered from the reaction mixture in the range of 70-80%. In contrast to this, substrate **117d** formed a mixture of unwanted by-products. The MS ESI spectra analysis revealed that trace amounts of the desired product **67a** were formed. The dimer **116** was also observed. Importantly, the most intensive molecular ion observed in the MS ESI spectra corresponded to the probable product **121** (Figure 4.2). This homocoupled product **121** could be formed by a copper mediated Ullman reaction.[145] The Ullmann reaction can become a competitive process, when the rate of the C-N coupling is too slow.[110] In addition, similar dimerisation of the 6-iodo purines using copper catalyst was reported recently.[36]



121

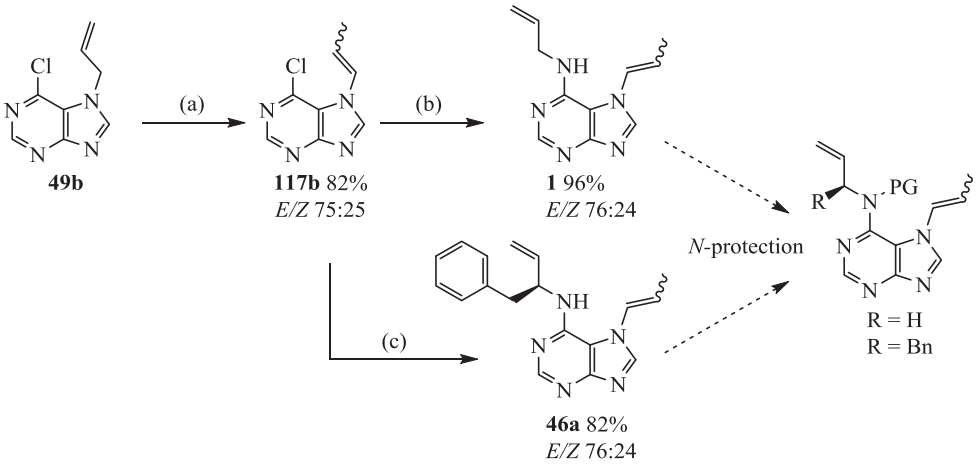
Figure 4.2 Possible product from Ulmann reaction with **117d.**

In order to initiate the coupling, we increased the reaction temperature using reflux in DMF.[120,146] Nevertheless, no coupling occurred and a complex mixture of by-products was formed. The desired product **67a** was not observed in this case.

4.2.5 *N*-protection experiments

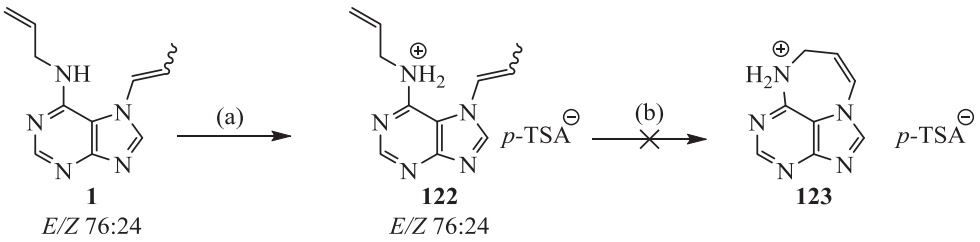
Realizing that the C-N bond formation cannot easily be achieved in the fashion described above, we decided to investigate the *N*-protection possibility once more. Taking advantage of the previously developed double bond migration, we prepared the *E/Z*-isomers of 6-chloro-7-(prop-1-en-1-yl)-7*H*-purine (**117b**). Subsequently, intermediate **117b** was treated with allylamine **45d** or the ammonium salt **78a**. This allowed easy access to the *N*-

propenyl purines **1** and **46a**, with no need to perform time demanding K_2CO_3 promoted isomerisation (Section 3.2.3, page 38). Both products were obtained as *E/Z*-isomers in good overall yield (Scheme 4.28).



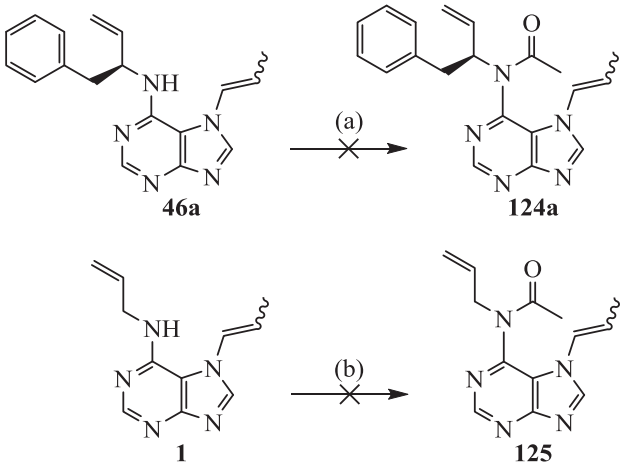
Scheme 4.28 Reagents and conditions: (a) 10% $RuClH(CO)(PPh_3)_3$, xylenes, Δ, 3h; (b) allyl amine (**45d**), DIPEA, *n*-BuOH, Δ, 2 h; (c) allyl ammonium salt **78a**, DIPEA, *n*-BuOH, Δ, 48 h.

At first we investigated, if the secondary amine **1** can be protected *via* protonation with *p*-toluenesulfonic acid. The resulting salt could then be cyclised under RCM conditions. Successful olefin metathesis with amines which were protected in this manner is known.[81] The salt of **1** and *p*-TsOH was successfully formed as judged by ^{1}H NMR. Nevertheless, when the resulting salt **122** was subjected to RCM conditions, no cyclised product **123** was observed even after 24 h (Scheme 4.29).



Scheme 4.29 Reagents and conditions: (a) anhydrous *p*-TSAH, DCM, 30 min;[81] (b) 5% Hoveyda-Grubbs II, DCE, Δ, 24 h.

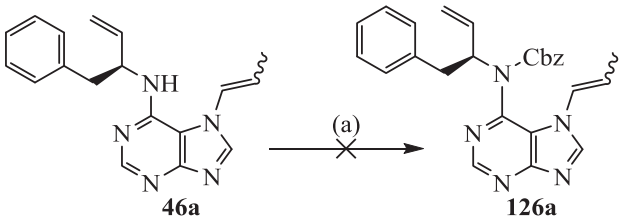
In view of the previous application of acetyl as the protecting group in the RCM,[147,148] the conversion of the secondary amines into acetamides was also considered. Formation of the acetamide could prevent coordination of the N^6-nitrogen to the metathesis catalyst and RCM could take place (see also Section 3.1.1, page 28). *N*-Propenyl purine **1** was *N*-protected earlier using Boc anhydride (see Section 3.1.2, page 30). Hence, we decided to use the acetic anhydride. Once again we had to face the inactivity of the secondary amine **46a**. No conversion to acetamide **125** was achieved following the literature conditions,[149] even after extended reaction time (Scheme 4.30). Furthermore, the conditions which were used for the protection of **1** with Boc anhydride,[18] were attempted using acetic anhydride instead. This attempt resulted in no visible conversion (Scheme 4.30).



Scheme 4.30 Reagents and conditions: (a) acetic anhydride, 5% DMAP, pyridine;[149] (b) acetic anhydride, 1eq. DMAP, pyridine.[18]

We furthermore evaluated the application of the benzyl carbamate (Cbz) protecting group. The Cbz group is often employed for amine protection prior to RCM.[83,150-152] Compared to the Boc group, the Cbz group is less bulky, which could facilitate its introduction to the sterically hindered amines **1** and **46a**. Moreover, it is usually introduced using benzyl chloroformate, which might be more reactive with the secondary amine **1** or **46a** than Boc_2O. Several literature conditions were investigated, but no promising outcome was achieved in any of the experiments (Scheme 4.31, Table 4.6). Test reactions with triethylamine and DMAP[153] (Table 4.6, entry 1) or with a stronger base (NaH)[154] (Table 4.6, entry 2) did not show any visible progress as judged by TLC and the starting material **46a** was

recovered to major extent. Using Na_2CO_3 in aqueous MeOH[155] led to a complex mixture of products. No traces of the desired intermediate **126a** were observed (Table 4.6, entry 3).



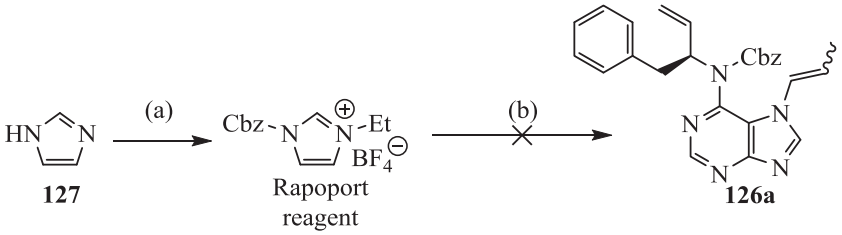
Scheme 4.31 Reagents and conditions: (a) benzylchloroformate, see Table 4.6.

Table 4.6 *N*-protection attempts with benzyl chloroformate

Entry	Solv.	Cbz-Cl[a]	Cat/Base	T	Time [h]	rec [%][b]
1[153]	DMF	2	DMAP/ Et_3N	r.t.	48	67
2[154]	DMF	1.1	NaH	0 ºC to r.t.	17	60
3[155]	MeOH/H_2O	1.2	Na_2CO_3	r.t.	1.5	n.d.[c]

[a]Equivalents of benzylchloroformate, [b]Recovered starting material,[c]Complex products mixture formed.

Since the *N*-protection was not successful with benzyl chloroformate, an additional approach for Cbz group introduction was attempted. The Rapoport reagent[156] is used for the Cbz-protection of exocyclic amines in *N*-heterocycles.[156,157] The reagent is easily prepared from commercially available chemicals, starting with the reaction of imidazole with benzylchloroformate. The *N*-Cbz-imidazole is then treated with triethyloxonium tetrafluoroborate, and the resulting solution of Rapoport reagent is used as prepared for the amine protection (Scheme 4.32).[156] Regrettably, when **46a** was reacted with the Rapoport reagent, the outcome was far from our expectations. On one hand we managed to overcome the limited reactivity of **46a**, since some progress of the reaction was finally observable by TLC. On the other hand, the reaction offered only a complex mixture of products.



Scheme 4.32 Reagents and conditions: (a) 1) benzylchloroformate, toluene, 0 ºC to r.t., 17 h, 2) Et_3OBF_4, DCM, 0 ºC to r.t., 2 h; (b) compound **46a**, MeCN, r.t., 72 h.

The MS ESI spectra of the crude products indicated that decarboxylation of the Rapoport reagent occurred during the reaction. However, no traces of the desired protected product **126a** were detected. Based on MS ESI data we assumed the structures of two possible products **128a** and **129** (Figure 4.3). These were contaminated by an excess of the Rapoport reagent and were not successfully obtained in a pure form, even after repeated column chromatography.

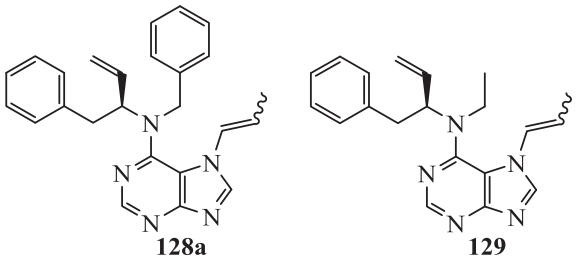
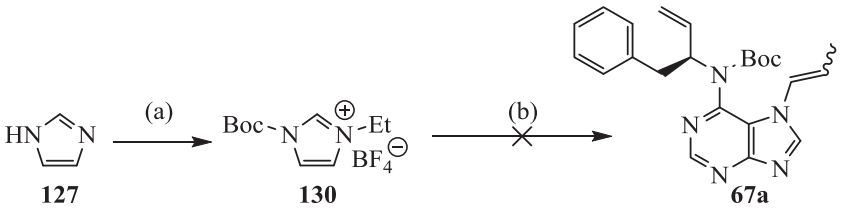


Figure 4.3 The possible outcome from the treatment of **46a** with Rapoport reagent.

The Boc group can be introduced in similar fashion like the Cbz group using an imidazolium salt.[158] The reagent was prepared in the same way like the Rapoport reagent from imidazole and triethyloxonium tetrafluoroborate (Scheme 4.33).[156]



Scheme 4.33 Reagents and conditions: 1) Boc_2O, toluene, 0 ºC to r.t., 17 h, 2) Et_3OBF_4, DCM, 0 ºC to r.t., 2 h; (b) compound **46a**, MeCN, r.t., 72 h.

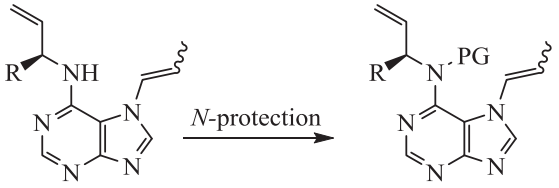
This reagent showed much lower reactivity towards **46a** compared to the Rapoport reagent. No conversion was seen and thus, preparation of the *N*-protected RCM precursor **67a** in this fashion was not successful.

4.3 Conclusion

A synthetic approach towards the asmarine analogues **47a-c** (Scheme 4.1) was presented. The possibilities of employing double bond migration and C-N bond formation were investigated. From the initial copper catalysed C-N coupling experiments performed with purines it was observed, that the C-N coupling does not occur with 7-allyl-6-chloro-7*H*-purine (**49b**). Thus, the conditions for copper mediated C-N coupling were tested and finally determined for the iododerivate **49d**. The coupling gave the *tert*-butyl allyl(7-allyl-7*H*-purin-6-yl)carbamate (**112**) in satisfactory yield. Another obstacle in the reaction pathway was successfully overcome, when the rearrangement of *N*-allyl purine **49d** using $RuClH(CO)(PPh_3)_3$ was explored. The development of conditions for the *N*-allyl purine rearrangement opened the application of this method in the asmarine analogues synthesis. Moreover, it also offered a unique opportunity for further investigation of the isomerisation in this system, as discussed in Chapter 5. The previously tested Ru mediated double bond migration and copper catalysed coupling were successfully applied in the synthesis of *tert*-butyl allyl(7-(prop-1-en-1-yl)-7*H*-purin-6-yl)carbamate (**73**). Most importantly, the metathesis reaction performed with the mixture of *E/Z*-isomers of this precursor gave the previously known[18] asmarine analogue *tert*-butyl [1,4]diazepino[1,2,3-gh]purine-10(9*H*)-carboxylate (**74**) in good yield. Regrettably, the C-N coupling was not achieved using the target *α*-substituted *N*-allyl carbamates **77a-c**. Hence the *N*-protection had to be further explored. Regarding the *N*-protection of compounds **1** and **46a**, several approaches were attempted. The amine protection *via* protonation, introduction of acetyl, Cbz and Boc groups or application of the Rapoport reagents were not successful in any of the experiments. The limited reactivity as well as sterical hindrance of the secondary amines **1** and **46a** probably prevented successful formation of the *N*-protected RCM intermediates in those experiments. The successful synthesis of the target asmarine analogues **47a-c** was not achieved. Further strategies towards asmarine total synthesis are currently under investigation in the Gundersen group at the University of Oslo.

4.4 Future prospects

There are two apparent complications in our synthetic strategy: the RCM does not take place without the *N*-protection and there are difficulties to accomplish the *N*-protection itself. Even though we tried several different approaches to avoid these obstacles, there are always alternative ways which could be investigated in the future.



46a R =Bn
46b R =*i*-Pr
46c R =*i*-Bn

67a-c PG = Boc
124a-c PG = Ac
126a-c PG = Cbz
128a-c PG = Bn

Scheme 4.34 *N*-protection prior to RCM.

First of all, regarding the introduction of different protecting groups (Scheme 4.34), there are several alternative reagents[159] for each protecting group which can be employed (Figure 4.4).

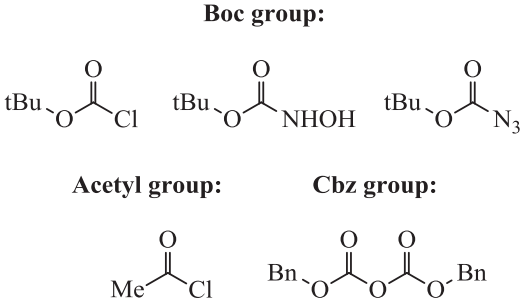
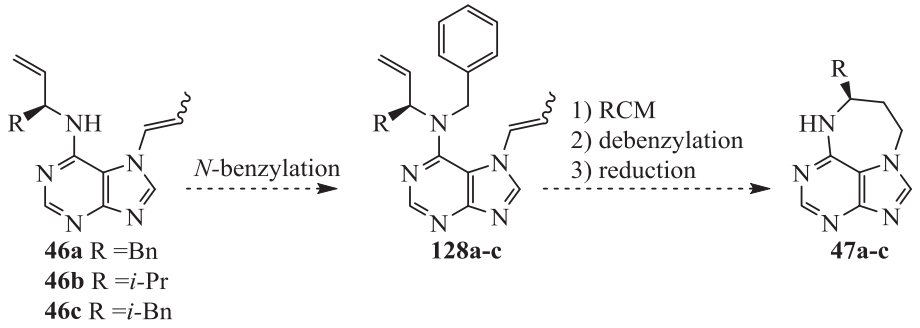


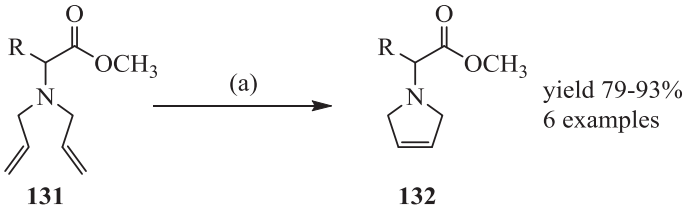
Figure 4.4 Examples of alternative reagents for the introduction of various protecting groups.

In addition, at the last stage of our investigation we realized that that the unexpected product **35** with the N^6-benzyl group was observed in the experiments with the Rapoport reagent. This compound was neither isolated in a pure form nor in acceptable amount (see Figure 4.3). However, the benzylation should be further explored (Scheme 4.35) since there are numerous reports[82,83,152,160] describing the benzyl as a suitable protecting group for the RCM. Moreover, the ring-closing of a benzyl protected allyl amine intermediates, leading to 7-membered rings, is known as well.[161-163]



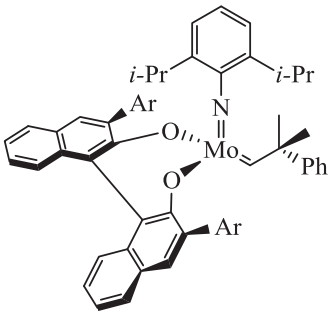
Scheme 4.35 Application of the benzyl as a protecting group in the synthesis.

Should the RCM reaction not lead to the formation of the desired products even after successful installation of the *N*-protection group, performing the RCM in the presence of a Lewis acid could be considered. The beneficial effect of the Lewis acids on the progress of the RCM was demonstrated in the synthesis of pyrrolidines (Scheme 4.36).[164]



Scheme 4.36 Reagents and conditions: (a) *e.g.* $Ti(O\textit{i}\text{-}Pr)_4$, Ru-catalyst, CH_2Cl_2, 40 ºC.[164]

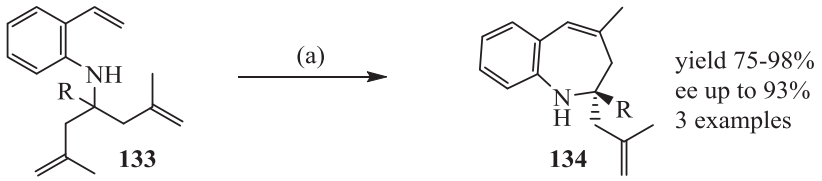
In our investigation, based on the previous success,[18] we tried to employ the Ru-based Hoveyda-Grubbs II catalyst. However, the constantly evolving field of the RCM methodology offers also other alternatives such as catalysts based on Molybdenum[80] (Figure 4.5).



69b Ar = 2,4,6-$Me_3C_6H_2$
69c Ar = 2,4,6-$(\textit{i}\text{-}Pr)_3C_6H_2$

Figure 4.5 Molybdenium based catalyst[165]

Interestingly, the catalysts **69b** and **69c** were employed in the synthesis of a 7-membered ring, which is very similar to our case (Scheme 4.37).[165] Most importantly, the ring-closing step readily occurred with the unprotected secondary amine **134** with high yields. Thus, the application of the various Schrock type catalysts could be investigated.



133 **134**

Scheme 4.37 Reagents and conditions: (a) catalyst **69b** or **69c**, benzene, 55 ºC, 3 to 24 h.

4.5 Experimental

***(E/Z)-N*-allyl-7-(prop-1-enyl)-7*H*-purin-6-amine (1)**

Allylamine (**45d**) (6.35 mmol, 0.480 mL) and DIPEA (2.54 mmol, 0.440 mL) were stirred in *n*-BuOH (6.9 mL) at ambient temperature under N_2 and 6-chloro-7-(prop-1-en-1-yl)-7*H*-purine (**117b**) (1.27 mmol, 247 mg, *E/Z* = 75:25) was added. The reaction mixture was refluxed for 2 h. The mixture was evaporated *in vacuo* and purified by flash chromatography using MeOH/CH_2Cl_2 (1:49); yield 231 mg (96%, *E/Z* = 75:25), yellow solid. *Z*-isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.70 (dd, J_1 = 7.0 Hz, J_2 = 1.8 Hz, 3H, CH_3-1), 4.21 (tt, J_1 = 5.6 Hz, J_2 = 1.5 Hz, 2H, CH_2-3'), 5.17 (m, 3H, =CH_2-1' + NH), 5.95 (m, 1H, CH=-2'), 6.16 (m, 1H, =CH-2), 6.90 (dd, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H, NCH-3), 7.78 (s, 1H, H-8), 8.51 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.4 (CH_3-1), 43.1 (CH_2-3'), 111.5 (C-5), 116.6 (=CH_2-1'), 122.9 (NCH-3), 131.6 (=CH-2), 134.1 (CH=-2'), 143.6 (C-8), 150.9 (C-6), 153.4 (C-2), 158.9 (C-4); *E*-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.96 (dd, J_1 = 7.1 Hz, J_2 = 1.3 Hz, 3H, CH_3-1), 4.22-4.28 (m, 2H, CH_2-3'), 5.15-5.27 (m, 3H, =CH_2-1' + NH), 5.93-6.05 (m, 1H, CH=-2'), 6.07-6.21 (m, 1H, =CH-2), 6.97 (dd, J_1 = 13.6 Hz, J_2 = 1.9 Hz, 1H, NCH-3), 7.88 (s, 1H, H-8), 8.53 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.2 (CH_3-1), 43.2 (CH_2-3'), 111.0 (C-5), 116.6 (=CH_2-1'), 123.2 (NCH-3), 128.9 (=CH-2), 134.2 (CH=-2'), 143.4 (C-8), 150.7 (C-6), 153.3 (C-2), 159.1 (C-4); MS (EI) *m/z* (rel. int.) 215/216 (96/20, M^+), 200 (100), 187 (10), 174 (17), 159 (29), 147 (8), 135 (12), 120 (11), 93 (6), 80 (9), 68 (8), 56 (20), 41 (48) and 28 (18); HRMS (EI) $C_{18}H_{19}N_5$ requires 215.1171, found 215.1163.

***(S,E/Z)*-*N*-(1-phenylbut-3-en-2-yl)-7-(prop-1-enyl)-7*H*-purin-6-amine (46a)**

(S)-1-phenylbut-3-en-2-aminium chloride (**78a**) (3.82 mmol, 702 mg) and DIPEA (10.7 mmol, 1.8 mL) were stirred in *n*-BuOH (19 mL) at ambient temperature under N_2 for 10 min prior to use. Subsequently, 6-chloro-7-(prop-1-en-1-yl)-7*H*-purine (**117b**) (3.47 mmol, 675 mg, *E/Z* = 75:25) was added and the reaction mixture was refluxed for 48 h. The solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography using MeOH/CH_2Cl_2 (1:49); yield 78 mg (82%, *E/Z* = 75:25), yellow solid. *Z*-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53 (dd, J_1 = 7.1 Hz, J_2 = 1.6 Hz, 3H, CH_3-1), 2.94-3.09 (m, 2H, CH_2-4'), 5.01 (bd, *J* = 7.9 Hz, 1H, NH), 5.08 (d, *J* = 17.7 Hz, 1H, H_A in =CH_2-1'), 5.14 (d, *J* = 10.7 Hz, 1H, H_B in =CH_2-1'), 5.23 (m, 1H, CH-3'), 5.90-6.03 (m, 2H, CH=-2' and =CH-2), 6.68 (d, *J* = 7.8 Hz, 1H, NCH-3), 7.14-7.30 (m, 5H, Ph), 7.74 (s, 1H, H-8), 8.52 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.2 (CH_3-1), 40.6 (CH_2-4'), 52.4 (CH-3'), 111.5 (C-5), 115.1 (=CH_2-1'), 122.7 (NCH-3), 126.8, 128.4 and 129.6 (Ph), 132.0 (=CH-2), 136.8 (Ph), 137.8 (CH= 2'), 143.4 (C-8), 150.4 (C-6), 153.7 (C-2), 159.2 (C-4); *E*-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78 (dd, J_1 = 7.1 Hz, J_2 = 1.6 Hz, 3H, CH_3-1), 3.00-3.12 (m, 2H, CH_2-4'), 4.80 (bd, *J* = 8.0 Hz, 1H, NH), 5.09 (d, *J* = 17.8 Hz, 1H, H_A in =CH_2-1'), 5.15 (d, *J* = 10.5 Hz, 1H, H_B in =CH_2-1'), 5.29 (m, 1H, CH-3'), 5.85-6.03 (m, 2H, CH=-2', =CH-2), 6.67 (d, *J* = 13.8 Hz, 1H, NCH-3), 7.14-7.30 (m, 5H, Ph), 7.82 (s, 1H, H-8), 8.52 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.1 (CH_3-1), 41.0 (CH_2-4'), 52.3 (CH-3'), 110.9 (C-5), 115.0 (=CH_2-1'), 123.0 (NCH-3), 127.0 and 128.4 (Ph), 129.0 (=CH-2), 129.6 and 136.8 (Ph), 137.8 (CH=-2'), 143.3 (C-8), 150.1 (C-6), 153.6 (C-2), 159.5 (C-4); MS (EI) *m/z* (rel. int.) 305 (9, M^+), 214 (100), 91 (7), 56 (10); HRMS (EI) $C_{18}H_{19}N_5$ requires 305.1640, found 305.1645.

7-allyl-6-chloro-7*H*-purine (49b)

7-Allyl-6-iodo-7*H*-purine (**49d**) (0.17 mmol, 100 mg) and the catalyst Grubbs II (8.5×10^{-3} mmol, 7.00 mg) were added to the oven-dried reaction vessel. The vessel was sealed with a septum and DCE (3 mL) was injected. Subsequently, the septum was replaced by condenser and the reaction was refluxed for 24 h. The mixture was filtered through a silica gel pad using 10 mL of EtOAc as the eluent. The solvent was removed *in vacuo* and the residue was purified by flash chromatography using gradient elution with MeOH/CH_2Cl_2 (1:20 to 1:19); yield 36 mg (80%), pale yellow solid. The spectral data were in good agreement with those reported before.[52]

***(E/Z)-tert*-Butyl allyl(7-(prop-1-enyl)-7*H*-purin-6-yl)carbamate (73)**

A resealable tube was charged with a solid reagents, *tert*-butyl allylcarbamate (**77d**) (0.700 mmol, 110 mg), Cs_2CO_3 (0.490 mmol, 160 mg) and CuI (1.7×10^{-2} mmol, 3.3 mg, 5 mol%). Tube was evacuated and backfilled with Ar. 1,10-Phenanthroline (3.5×10^{-2} mmol, 6.3 mg, 10 mol%), 6-iodo-7-(prop-1-en-1-yl)-7*H*-purine (**117d**) (0.35 mmol, 100 mg, *E/Z* = 45:55) and dioxane (2.1 mL) were added. The tube was sealed and the reaction mixture was stirred at 110 °C for 48 h. The mixture was filtered through a pad of silica using 15 mL MeOH/CH_2Cl_2 (1:9) as the eluent. Solvents were removed *in vacuo* and the remaining crude product was purified using flash chromatography on silica with MeOH/CH_2Cl_2 (1:99); yield 66 mg (59%, *E/Z* = 45:55), yellow oil. *Z*-isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s, 9H, *t*-Bu), 1.60 (d, *J* = 6.1 Hz, 3H, CH_3-1), 4.44 (d, *J* = 5.8 Hz, 2H, CH_2-3'), 5.15 (m, 2H, =CH_2-1'), 5.78-5.92 (m, 2H, =CH-2, CH=-2'), 6.71 (d, *J* = 8.07 Hz, 1H, NCH-3), 8.07 (H-8), 8.88 (H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.3 (CH_3-1), 28.0 (CH_3 in *t*-Bu), 50.8 (CH_2-3'), 82.4 (C in *t*-Bu), 118.4 (=CH_2-1'), 120.4 (C-5), 126.7 (NCH-3), 128.4 (=CH-2), 134.0 (CH=-2'), 147.7 (C-8 and C-6), 152.5 (C-2), 153.6 (C=O), 162.2 (C-4); *E*-isomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.43 (br s, 9H, *t*-Bu), 1.87 (d, *J* = 6.9 Hz, 3H, CH_3-1), 4.54 (d, *J* = 5.8 Hz, 2H, CH_2-3'), 5.14-5.21 (m, 2H, =CH_2-1'), 5.89-6.02 (m, 2H, =CH-2, CH=-2'), 6.83 (d, *J* = 13.3 Hz, 1H, NCH-3), 8.26 (H-8), 8.92 (H-2); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.1 (CH_3-1), 28.1 (CH_3 in *t*-Bu), 50.7 (CH_2-3'), 82.3 (C in *t*-Bu), 118.1 (=CH_2-1'), 122.1 (C-5), 123.3 (NCH-3 and =CH-2), 133.5 (CH=-2'), 146.2 (C-8), 147.4 (C-6), 152.8 (C-2), 152.8 (C=O), 162.6 (C-4); MS (EI) *m/z* (rel. int.) 315 (38, M^+), 259 (83), 242 (18), 214 (30), 200 (47), 174 (23), 57 (100); HRMS (EI) $C_{16}H_{21}N_5O_2$ requires 315.1695, found 315.1689.

***tert*-Butyl allyl(7-allyl-7*H*-purin-6-yl)carbamate (112)**

The reaction vessel was charged with a solid reagents, *tert*-butyl allylcarbamate **77d** (1.00 mmol, 157 mg), Cs_2CO_3 (0.700 mmol, 228 mg), CuI (2.6×10^{-2} mmol, 5.0 mg, 5 mol%) 1,10-phenanthroline (5.5×10^{-2} mmol, 10.0 mg, 10 mol%) and 7-allyl-6-iodo-7*H*-purine (**49d**) (0.500 mmol, 143 mg) under inert atmosphere of glovebox. THF (3.0 mL) was injected through the septum. The heterogeneous reaction mixture was refluxed for 48 h. The mixture was filtered through a pad of silica eluting with 10 mL of MeOH/CH_2Cl_2 (1:9). The solvent was removed *in vacuo*. The crude product was purified using flash chromatography on silica with gradient elution by MeOH/CH_2Cl_2 (1:99 to 1:32); yield 89 mg (56%). Spectral data were in a good agreement with those reported before.[18]

***(1S,2S)*-N^1,N^2-bis(7-(*(E)*-prop-1-enyl)-7*H*-purin-6-yl)cyclohexane-1,2-diamine (115)**

The solid reagents CuI (4.2 x 10^{-2} mmol, 0.70 mg), allylcarbamate **77d** (0.42 mmol, 66 mg), K_3PO_4 (0.840 mmol, 178 mg) and 7-Allyl-6-chloro-7*H*-purine (**49b**) (0.5 mmol, 100 mg) were charged in oven-dried reaction tube under inert atmosphere of glovebox. *trans*-1,2-Cyklohexanediamine (4.2 x 10^{-2} mmol, 5.0 µl, 10 mol%) and dioxane (0.5 mL) were injected through the resealable cap. The product was isolated using flash chromatography on silica with MeOH/CH_2Cl_2 (1:9); yield 16 mg (99%), yellow solid, mp 113-120 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.27-1.37 (m, 8H, 2x CH_3-1 and cyclohexyl), 1.54 (m, 2H, cyclohexyl), 1.74 (m, 2H, cyclohexyl), 2.05 (d, J = 13.2 Hz, 2H, cyclohexyl), 4.41 (m, 2H, 2x NCH-cyclohexyl), 5.87 (m, 2H, 2x =CH-2), 6.20 (d, J = 7.3 Hz, 2H, 2x NH), 6.88 (dd, J_1 = 8.0 Hz, J_2 = 1.9 Hz, 2H, 2x NCH=-3), 8.11 (s, 2H, 2x H-8), 8.32 (s, 2H, 2x H-2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 11.6 (CH_3-1), 24.6 (CH_2-cyclohexyl), 31.8 (CH_2-cyclohexyl), 53.4 (CH-cyclohexyl), 110.4 (C-5), 122.8 (NCH=-3), 127.6 (=CH-2), 144.5 (C-8), 150.5 (C-6), 152.4 (C-2), 158.5 (C-4); MS (EI) *m/z* (rel. int.) 430 (44, M^+), 255 (100), 226 (24), 215 (14), 200 (15), 176 (54); HRMS (EI) $C_{22}H_{26}N_{10}$ requires 430.2342 found 430.2333.

1-[7-(Prop-2-en-1-yl)-7*H*-purin-6-yl]-7-propyl-6,7-dihydro-1*H*-purin-6-one (116)

The oven-dried reaction ampoule was charged with a solid reagents 7-Allyl-6-chloro-7*H*-purine (**49b**) (0.500 mmol, 100 mg), allylcarbamate **77d** (0.60 mmol, 94 mg), Cs_2CO_3 (0.700 mmol, 228 mg), CuI (2.5 x 10^{-2} mmol, 5.0 mg, 1 mol%) and 1,10-phenanthroline (5.5 x 10^{-2} mmol, 10.0 mg, 10 mol%) under inert atmosphere of glovebox. Dioxane (1.0 ml) was injected through a resealable cap. The cap was closed and the reaction proceeded at 110 °C for 24 h. The crude reaction mixture was filtered through a pad of silica using EtOAc. The solvent was removed *in vacuo*. The product was isolated using flash chromatography on silica with MeOH/CH_2Cl_2 (1:20); yield 31 mg (15%), yellow solid, mp 209-212 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.63-4.79 (m, 3H, NCH_2-3', H_A in =CH_2-1'), 4.94-5.10 (m, 3H, H_B in =CH_2-1', NCH_2-3), 5.16 (d, J = 17.1 Hz, 1H, H_A in =CH_2-1), 5.29 (d, J = 10.2 Hz, 1H, H_B in =CH_2-1), 5.69 (m, 1H, CH=-2'), 6.03 (m, 1H, CH=-2). 7.97 (s, 1H, H-8), 8.19 (s, 1H, H-2), 8.30 (s, 1H, H-8'), 9.09 (s, 1H, H-2'); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 49.4 (NCH_2-3), 49.5 (NCH_2-3'), 114.2 (C-5), 119.2 (=CH_2-1), 119.3 (=CH_2-1'), 121.2 (C-5'), 131.2 (CH=-2), 132.2 (CH=-2'), 141.1 (C-6'), 144.4 (C-8), 145.3 (C-2), 149.9 (C-8'), 152.8 (C-2'), 153.8 (C-6), 157.5 (C-4), 163.9 (C-4'); MS (EI) *m/z* (rel. int.) 334 (100, M^+), 333 (30), 319 (6), 306 (8), 215 (19), 199 (6), 176 (6), 160 (11); HRMS (EI) $C_{16}H_{14}N_8O$ requires 334.1291 found 344.1288.

6-Chloro-7-(prop-1-en-1-yl)-7*H*-purine (117b)

7-Allyl-6-iodo-7*H*-purine (**49d**) (0.35 mmol, 100 mg) and catalyst $RuClH(CO)(PPh_3)_3$ (1.7 x 10^{-3} mmol, 17.0 mg) were added to the oven-dried reaction vessel. The vessel was sealed with a septum and DCE (6.00 mL) was injected. The septum was replaced by condenser and the reaction was refluxed for 24 h. The heterogeneous mixture was filtered through a silica gel pad using 10 mL of EtOAc as the eluent. The solvent was removed *in vacuo* and the residue was purified by flash chromatography using gradient elution with $MeOH/CH_2Cl_2$ (1:20 to 1:19); yield 36 mg (20%), pale yellow solid. For data see Appendix I. compound **5c**

6-Iodo-7-(prop-1-en-1-yl)-7*H*-purine (117d)

Microwave assisted double bond migration with $RuClH(CO)(PPh_3)_3$

A 0.5-2 mL vial was oven-dried prior to use and cooled down under inert atmosphere of Ar. 7-Allyl-6-iodo-7*H*-purine (**49d**) (0.17 mmol, 50 mg) and catalyst $RuClH(CO)(PPh_3)_3$ (1.7 x 10^{-2} mmol, 17 mg) were added. Vial was sealed with a cap with septum and dioxane (3 mL) was injected. The reaction proceeded in microwave reactor for 3 h at 130 °C. The reaction mixture was filtered through a silica gel pad using 10 mL of EtOAc as the eluent. The solvent was removed *in vacuo* and the residue was purified by flash chromatography using gradient elution with $MeOH/CH_2Cl_2$ (1:20 to 1:19); yield 36 mg (72%, contained 10% of Chloro-analog **117b**), pale yellow solid. For data see Appendix I. compound **5e**.

***(E/Z)*-*N*-allyl-7-(prop-1-enyl)-7*H*-purin-6-amommonium 4-methylbenzene-1-sulfonate (122)**

A solution of anhydrous *p*-toluenesulfonic acid (0.46 mmol, 80 mg) in CH_2Cl_2 (1.53 mL) was added to a stirred solution of compound **1** (0.46 mmol, 100 mg) in CH_2Cl_2 (1.53 mL) at room temperature. After stirring for 10 min, the turbid mixture became clear. The solvent was removed *in vacuo* and the resulting salt was dried under reduced pressure; yield 180 mg (100%), yellow oil. *Z*-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.56 (d, J = 6.8 Hz, 3H, CH_3-1), 2.33 (s, 3H, OCH_3), 4.33-4.35 (m, 2H, CH_2-3'), 5.09 (d, J = 10.2 Hz, 1H, H_B in $=CH_2$-1'), 5.19 (d, J = 17.2 Hz, 1H, CH_A in $=CH_2$-1'), 5.83-5.93 (m, 1H, CH=-2'), 6.20 (m, 1H, =CH-2), 7.15 (d, J = 7.8 Hz, Ph), 7.32 (d, J = 7.8 Hz, 1H, NCH-3), 7.77 (d, J = 7.9 Hz, Ph), 7.88 (s, 1H, H-8), 8.17 (br s, 1H, NH), 8.54 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.3 (CH_3-1), 21.3 (OCH_3), 44.3 (CH_2-3'), 111.3 (C-5), 118.0 ($=CH_2$-1'), 122.1 (NCH-3), 125.9 and 128.9 (Ph), 132.5 (CH=-2'), 132.6 (=CH-2), 140.3 and 141.9 (Ph), 144.7 (C-8), 146.6 (C-2), 147.8 (C-4), 152.0 (C-6); *E*-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.88 (d, J = 6.6 Hz, 3H,

CH_3-1), 2.33 (s, 3H, OCH_3), 4.31-4.33 (m, 2H, CH_2-3'), 5.09 (d, J = 10.2 Hz, 1H, H_B in =CH_2-1'), 5.19 (d, J = 17.2 Hz, 1H, CH_A in =CH_2-1'), 5.83-5.93 (m, 1H, CH=-2'), 6.05-6.11 (m, 1H, =CH-2), 7.15 (d, J = 7.8 Hz, Ph), 7.50 (d, J = 13.4 Hz, 1H, NCH-3), 7.77 (d, J = 7.9 Hz, Ph), 7.97 (s, 1H, H-8), 8.44 (br s, 1H, NH), 8.50 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.1 (CH_3-1), 21.3 (OCH_3), 44.4 (CH_2-3'), 110.7 (C-5), 117.9 (=CH_2-1'), 122.6 (NCH-3), 125.9 and 128.9 (Ph), 130.8 (=CH-2), 132.4 (CH=-2'), 140.3 and 141.9 (Ph), 144.7 (C-8), 146.3 (C-2), 148.0 (C-4), 151.9 (C-6); MS (ESI) *m/z* (rel. int.) 216 $[M+H]^+$, 171 $[M+H]^+$.

***tert*-Butyl 1*H*-imidazole-1-carboxylate (130)**

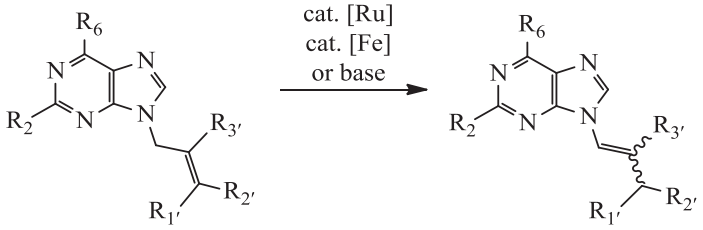
Imidazole (14.7 mmol, 1.00 g) was stirred in 15 mL of CH_2Cl_2 at room temperature, until completely dissolved. A solution of Boc_2O (20.6 mmol, 4.5 g) in 5 mL of CH_2Cl_2 was added dropwise. The mixture was stirred for 15 h and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with EtOAc/Hex (1:6); yield 1.96 g (79%), colourless crystals, mp 44-46 °C (Lit[166] 42-45 °C). Spectral data were in a good agreement with those reported before.[166]

Chapter 5

Rearrangement of *N*-allyl purines

5.1 Introduction

During the course of our work on studying synthetic routes towards asmarines (Chapter 3 and Chapter 4), we investigated conditions for the rearrangement of the asmarine intermediates **49b**, **49d** and **75a-c**. These preliminary results offered a unique possibility for the synthesis of *N*-alkenyl purines. Since there are in general very few convenient synthetic routes to *N*-alkenyl purines, we decided to carry out a further exploration of this methodology. Herein, we focused on base- or transition metal complex promoted isomerisations (Scheme 5.1). Even though the more thermodynamically stable *E*-isomers of propenyl purines were expected as major products, some of the base promoted rearrangements occurred with a surprisingly high *Z*-selectivity. The synthesis of starting materials for this study is described in Chapter 2.

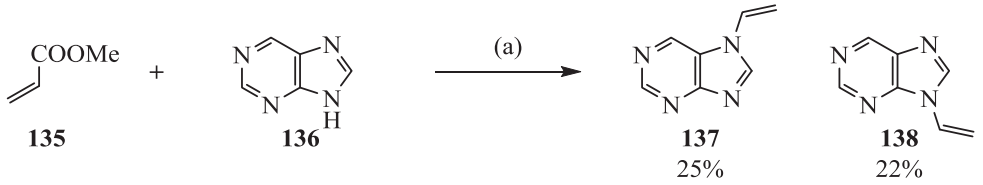


N-9 allyl purine *N*-9 propenyl purine

Scheme 5.1 Example of the rearrangement of the *N*-9 allyl purine.

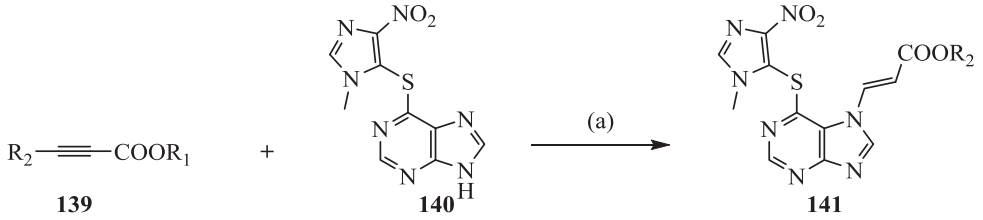
5.1.1 Alkenyl purines

Alkenyl purines are seldom reported in the literature and in general not easy to synthesize. For instance, the vinyl purines can be obtained as a mixture of *N*-7 and *N*-9 isomer by vinylation of purines with $Hg(OAc)_2$ (Scheme 5.2).[167,168]



Scheme 5.2 Reagents and conditions: (a) $Hg(AcO)_2$, H_2SO_4/EtOAc, 40 ºC, 3 to 4 days.

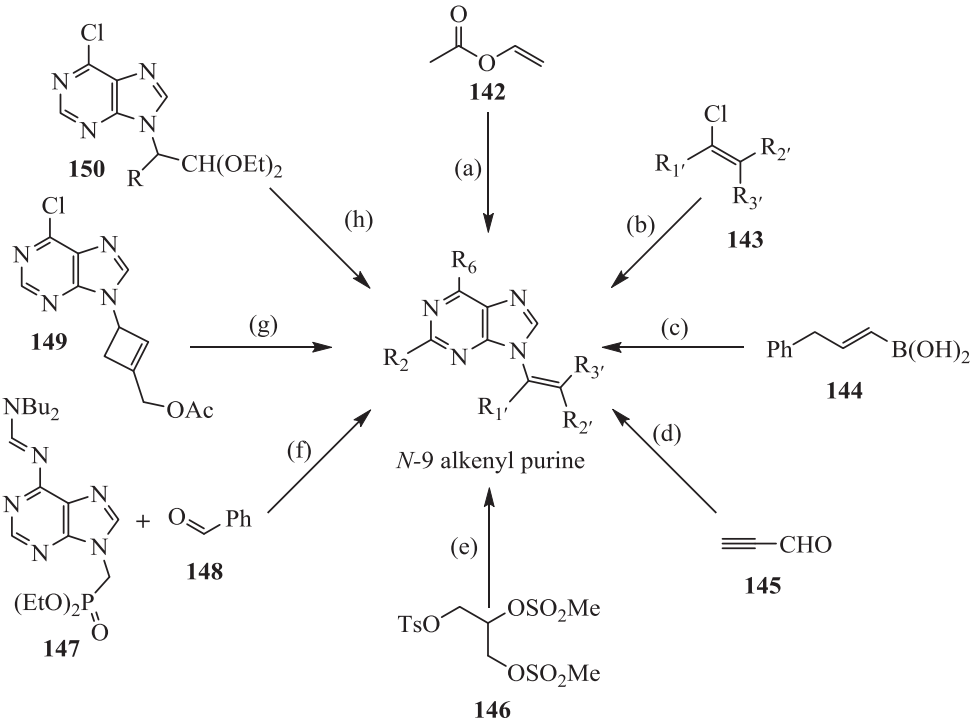
Furthermore, it was recently reported, that the *N*-7 alkenylated purines can be isolated as the only product from the reaction of acetylene carboxylates in the presence of PPh_3 (Scheme 5.3).[169]



Scheme 5.3 Reagents and condition: (a) 1) PPh_3, CH_2Cl_2, -15 ºC to r.t., 15 min; 2) K_2HPO_4, 90 ºC, 1 h.[169]

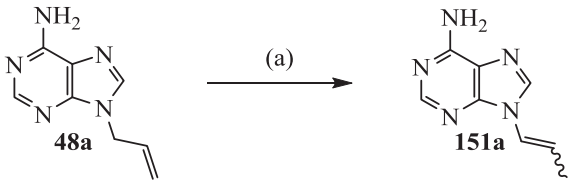
In addition, 7-propenyl purine can be quantitavely obtained by selective *N*-7 allyl rearrangement of N^6,*N*-7-diallyladenine **72** as we demonstrated previously (Section 3.1.2 page 30 and ref. 18)

Regarding the formation of *N*-9 alkenyl purines, more examples can be found in the literature. Apart from the reaction with vinyl acetate and Hg salts,[168] the vinylation can be achieved with di- or tetrachloro ethene in HMPA.[170] More convenient procedures employ Cu-promoted alkenylation with boronic acids[171] or Michael addition with activated alkynes.[172-174] Furthermore, the alkenyl purines can be synthesised by tandem *N*-alkylation/elimination methods,[175-177] or by Horner-Wadsworth-Emmons reactions.[178,179] In addition, the ring opening of 9-(cyclobutenyl)purines, or reactions of 9-(2,2-diethoxyethyl)purines with malonic acid leading to the *N*-alkenyl formation is known.[180] The literature examples of the *N*-9 alkenyl purines syntheses are given in the Scheme 5.4**.**



Scheme 5.4 Reagents and conditions: (a) $Hg(AcO)_2$;[168] (b) base, HMPA;[170] (c) $Cu(OAc)_2$;[171] (d) Et_3N;[172] (e) CH_3COOH;[177] (f) NaH;[178] (g) liq. NH_3/EtOH;[181] (h) malonic acid.[180]

Most importantly, the alkenyl purines can be prepared by migration of the allylic double bond in the presence of *t*-BuOK.[129,182] The first synthesis of alkenyl purines *via* double bond migration was reported by in 1965.[129]

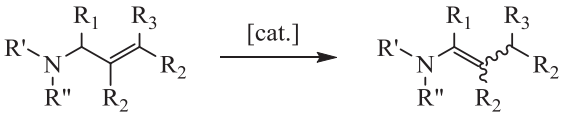


Scheme 5.5 Reagents and conditions: (a) *t*-BuOK, DMSO, 100 ºC, 20 min.[129]

The biological activities of several *N*-9 alkenyl purines were investigated and the compounds displayed anticancer-[172,183] and antiviral- properties[177,182-184] or kinase inhibiting activities.[179,185]

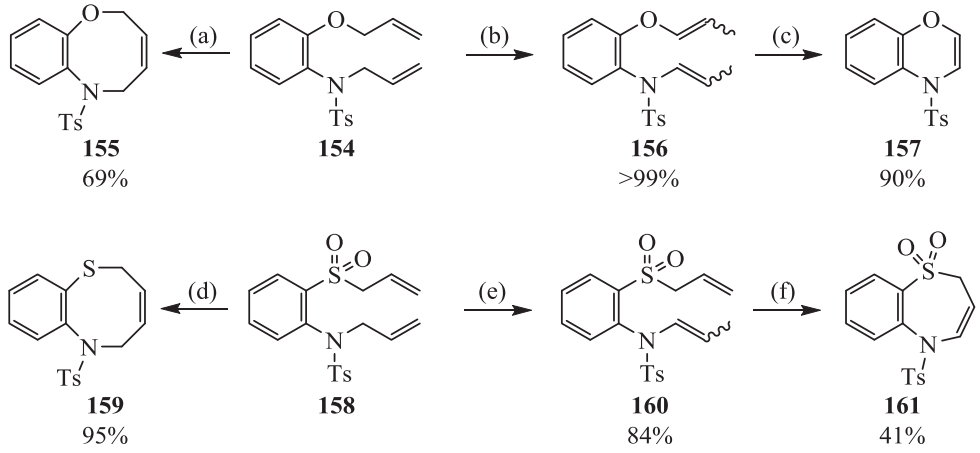
5.1.2 Double bond migration in *N*-allyl systems

Isomerisation of *N*-allyl groups is the important example of reactions in allylic systems. Various allylic intermediates (*e.g.* amines, imines, amides, imides, *N*-allyl protected heterocycles) can be easily converted to the corresponding *N*-(1-propenyl) or more generally *N*-vinyl products in this fashion (Scheme 5.6).[130]



Scheme 5.6 Double bond migration of the *N*-allyl group.

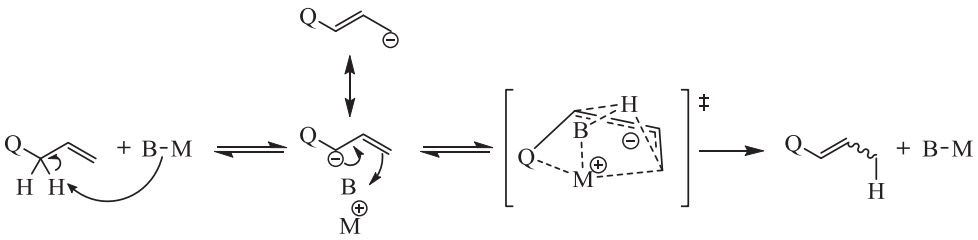
In general, the double bond rearrangement can be induced by various classes of reagents[130,186] such as acids (*e.g.* H_2SO_4, $HClO_4$), bases (*e.g.* KOH, NaOMe, *t*-BuOK), metals on support (Pd/C, Rh/C, Ru/C) and transition metal complexes (*e.g.* $RuClH(CO)(PPh_3)_3$, $RuCl_2(PPh_3)_3$, $RhH(CO)(PPh_3)_3$ and $Fe(CO)_5$. The application of the rearrangement methodology includes preparation of amino acid derivatives,[131] formation of the precursors for the cycloaddition reactions,[139,140] removal of the *N*-allyl protecting group[129,134,141,186] or synthesis of the nucleoside analogues.[132] One of the interesting examples is the synthesis of various heterocycles employing a tandem sequence of migration followed by the RCM (Scheme 5.7).[187,188]



Scheme 5.7 Reagents and conditions: (a) Grubbs II, toluene, r.t., 5 h; (b) $RuClH(CO)(PPh_3)_3$, toluene, 95 ºC, 2 h; (c) Grubbs II, toluene, 45 ºC, 2,5 h; (d) Grubbs II, $CHCl_3$, r.t., 24 h, then 45 ºC, 24 h; (e) $RuClH(CO)(PPh_3)_3$, toluene, 105 ºC, 24 h; (f) Grubbs II, toluene, 50 ºC, 24 h, r.t. then further Grubbs II, 80 ºC, 24 h.[187]

5.1.2.1 Reaction mechanism of the base promoted rearrangement

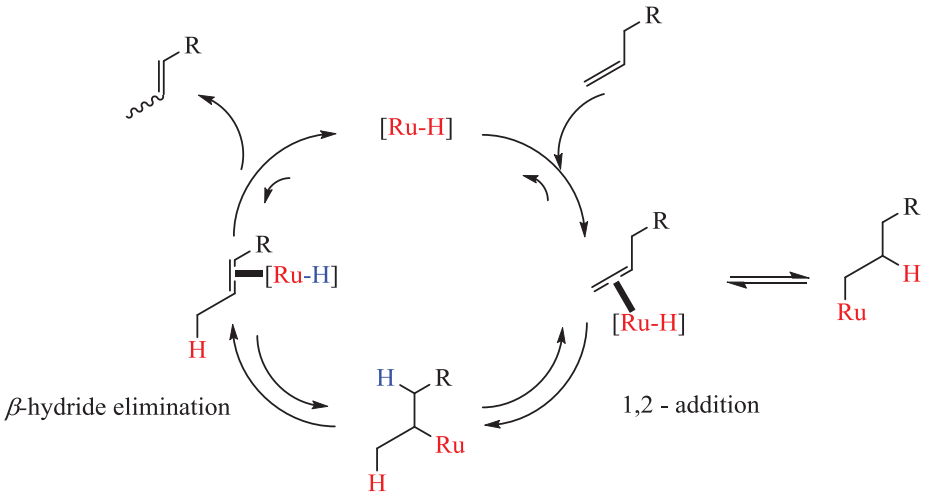
The mechanistic studies of the base promoted allylic rearrangement were reported earlier with various allylic substrates such as but-3-en-2-ylbenzene,[189] substituted pent-1-enes,[190] allyl ethers,[191,192] or *cis*-but-2-ene.[193] It has been commonly established,[194] that the base promoted rearrangement occurs *via* a carbanion formation.[189-193] The deprotonation on the C-1' of the allyl leads to the π-allyl anion which is stabilised by the base, especially when the *Q*-group is a heteroatom with an electron lone pair available for interaction with the cation species (Scheme 5.8).[191,192] The proton abstracted from the C-1' is then transferred to the carbon C-3'.[191,193]



Scheme 5.8 Base promoted double bond migration *via* π-allylic anion.

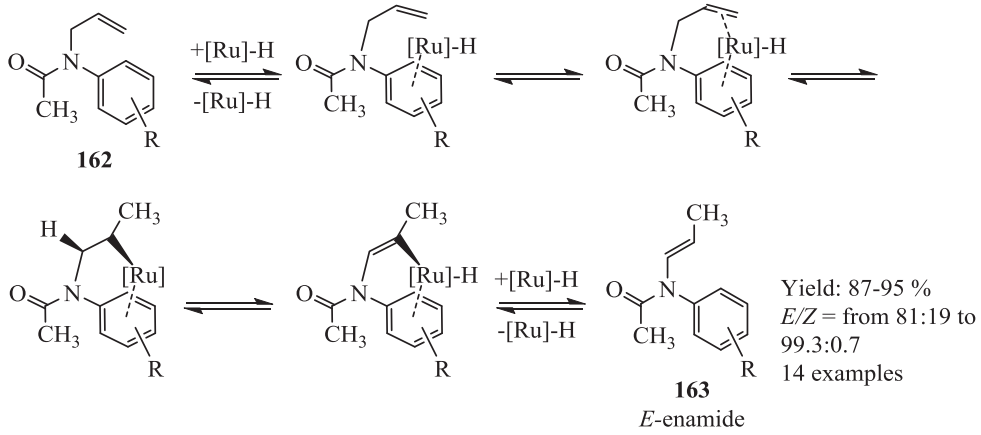
5.1.2.2 Mechanism of the rearrangement with transition metal hydrides

The isomerisation of *N*-allyl purines was studied with $RuClH(CO)(PPh_3)_3$, which belongs to the group of metal hydride catalysts. The rearrangement promoted by this type of catalyst occurs *via* a hydride addition-elimination mechanism.[186,195] In the initial phase of the catalyst cycle, the metal hydride coordinates to the π-electrons of the allyl group. The coordination is then followed by 1,2-addition on the double bond. The metal alkyl intermediate may then, by β-hydrogen elimination, form either the desired rearranged product or revert to the original metal coordinated olefin (Scheme 5.9).[186]



Scheme 5.9 Hydride addition-elimination mechanism of the allyl rearrangement.

The Ru or Rh mediated rearrangements are usually *Z*-selective.[137,138,196,197] Nonetheless, if an aromatic ring is present in the molecule, *E*-selectivity is observed instead. The *β*-hydride elimination is considered to be the key step for the *E*-selectivity. The transition state proposed for this phenomenon showes that the *E*-stereoselectivity originates from the coordination of the Ru atom to the aromatic ring (Scheme 5.10).[137,138,196,197] This hypothesis was supported by theoretical calculations.[138,196] In our case, high *E*-selectivity of the double bond migration of *N*-allyl purines with $RuHCl(CO)(PPh_3)_3$ was also observed.



162

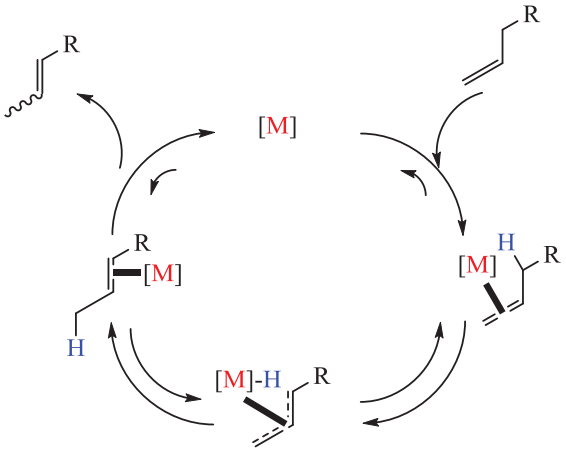
163
E-enamide

Scheme 5.10 The coordination of the Ru atom with the aryl substituent as a possible reason for the *E*-selectivity of $RuClH(CO)(PPh_3)_3$ mediated rearrangement with aromatic substrates.[138]

Various transition metal hydrido-complexes such as ($HCo(CO)_4$), ($RuClH(CO)(PPh_3)_3$) or ($PtH(ClO_4)(PPh_3)_3$) belong to the class of catalysts that rearranges allyl groups according to the addition-elimination mechanism.[186]

5.1.2.3 *π*-Allyl hydride mechanism

In contrast to transition metal hydride promoted rearrangements, isomerisation induced by non-hydrido complexes of Fe or Ir occurs *via* a *π*-allyl hydride mechanism.[186,193,198] The 1,2-addition does not occur in the course of this mechanism. Instead, the catalyst forms a *π*-allyl hydride complex *in situ*.[192,198-200] The hydride is then directly migrated *via* 1,3-hydrogen shift from the C-1' to C-3' through this metal complex intermediate (Scheme 5.11).

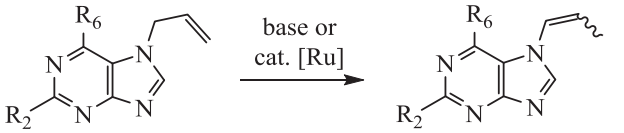


Scheme 5.11 π-allyl hydrido mechanism.

Typical examples of non-hydrido complexes, isomerising olefins according to the π-allyl hydrido mechanism are $Fe(CO)_5$, $Fe_3(CO)_{12}$ or complexes of palladium, such as $PdCl_2(PhCN)_2$ and the cationic iridium complexes $Ir(cod)(PMePh_2)_2^+$ PF_6^- or BF_4^-.[186] The possible advantage of the rearrangement by a π-allyl hydrido mechanism was investigated for the rearrangement of 2-methylallyl purines (Section 5.2.3)

5.2 Results and discussion

5.2.1 Rearrangement of 7-allyl purines



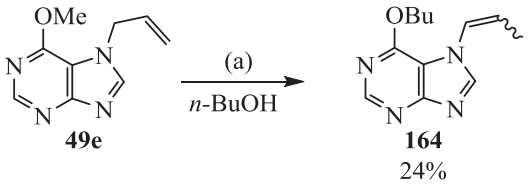
49a R_2 = H, R_6 = NH_2
72 R_2 = H, R_6 = NH-allyl
49b R_2 = H, R_6 = Cl
49c R_2 = NH_2, R_6 = Cl
49d R_2 = H, R_6 = I
49e R_2 = H, R_6 = OMe

117a R_2 = H, R_6 = NH_2
1 R_2 = H, R_6 = NH-allyl
117b R_2 = H, R_6 = Cl
117c R_2 = NH_2, R_6 = Cl
117d R_2 = H, R_6 = I
117e R_2 = H, R_6 = OMe

Scheme 5.12 Rearrangement of 7-allyl purines.

A very convenient rearrangement method was discovered, when the compound *N*,7-diallyl-7*H*-purin-6-amine (**72**) was isomerised under very mild basic conditions, giving the

corresponding rearranged product (*Z*)-*N*-allyl-7-(prop-1-en-1-yl)-7*H*-purin-6-amine (**1**) in quantitative yield.[18] In general, this type of rearrangement is a rather special phenomenon and this was the first known synthesis of a 7-propenyl purine. Furthermore, the migration in this case takes place regioselectively on the *N*-7 allyl chain while the N^6-allyl remains intact. Above all, the most surprising feature of this isomerisation is the complete *Z*-selectivity. In the current study towards asmarines, we slightly extended the scope of this reaction for the substrates **75a-c**. The corresponding products **46a-c** were obtained in high yield again exclusively as the *Z*-isomers (see page 31, Scheme 3.4 and page 38, Scheme 3.15). Subsequently, we performed further investigations of this type of double bond migration using 7-allyl purines with various substituents in the C-2 and C-6 position (Scheme 5.12, Table 5.1). First of all, to evaluate the importance of the base for this reaction, we refluxed adenine **49a** in MeCN in the absence of the K_2CO_3. As expected, the rearrangement did not occur (Table 5.1, entry 1). We then applied the K_2CO_3 mediated rearrangement with all the designed substrates. Surprisingly, the rearrangement occurred only with the adenine type of derivates **49a** and **72** (Table 5.1, entries 2 - 4), while other 7-allylpurines remained unchanged under given conditions. In the case of methoxypurine **49e**, solvents with higher boiling point such as chlorobenzene or dioxane were employed with no success. Consequently, we refluxed compound **49e** in *n*-BuOH. In this particular case some migration was achieved, but also with an additional replacement of the methoxy group caused by *n*-BuOH (Table 5.1, entry 9, Scheme 5.13).



49e **164** 24%

Scheme 5.13 Reagents and conditions: (a) K_2CO_3, *n*-BuOH, Δ, 4 days.

When *t*-BuOK[129] was used for the reaction with adenine **49a**, the reaction went to completion after 20 minutes at ambient temperature. In contrast to the *Z*-selectivity with K_2CO_3, the product **117a** was obtained with the majority of *E*-isomer (Table 5.1, entry 3).

Table 5.1 Base promoted rearrangement of the 7-allylpurines

Entry	Subst.	R_2	R_6	Method	Time [h]	Conv. [%][a]	*E/Z*[a]	Yield [%][b]
1	**49a**	H	NH_2	MeCN, Δ	96	n.r.	–	–
2	**49a**	H	NH_2	A[c]	96	90	>1:99	53, **117a**
3	**49a**	H	NH_2	B[d]	0.30	98	69:31	84, **117a**
4	**72**	H	NH-allyl	A	17	100	>1:99	100, **1**[e]
5	**49b**	H	Cl	A	24	n.r.	–	–
6	**49c**	NH_2	Cl	A	96	n.r.	–	–
7	**49d**	H	I	A	24	n.r.	_	_
8	**49e**	H	OMe	A	24	n.r.[f]	–	–
9	**49e**	H	OMe	A[g]	96	–[h]	–	–

[a]From ^{1}H NMR of the crude product, after 24 h if otherwise not stated; [b]Isolated yield; [c]Method A: K_2CO_3, MeCN, Δ; [d]Method B: *t*-BuOK, DMSO, r.t.; [e]Taken from reference 18; [f]Also n.r. in dioxane, Δ or Ph-Cl, Δ; [g]*n*-BuOH as solvent; [h]Double bond migration took place, but the MeO-group was also partly exchanged with *n*-BuO-group (Scheme 5.13).

It can be summarised from these results, that only the purines with a free amino groups were successfully rearranged using the mild base (K_2CO_3) in MeCN. Subsequently, 7-allyl purines were subjected to the previously designed isomerisation conditions with $RuClH(CO)(PPh_3)_3$ in refluxing xylenes (see also Section 4.2.3, page 55). In general, the Ru promoted isomerisation occurred with all the *N*-7 allyl analogues (Table 5.2) and the rearranged products were isolated in good yields. In the case of compound **49a** the isomerisation required an extended reaction time. The product **117a** was, despite the good conversion, isolated only in moderate yield, which was caused by a challenging separation of **117a** from the starting material **49a** by column chromatography (Table 5.2, entry 1). Low conversion was observed in the rearrangement of *N*,7-diallyl-7*H*-purin-6-amine (**72**). The two allyl chains from the substrate **72** are in close vicinity and probably prevented the proper addition of the relatively bulky $RuClH(CO)(PPh_3)_3$ catalyst to the double bond. This may have caused the slow progress of the reaction. Regrettably, the product from this reaction was not isolated pure

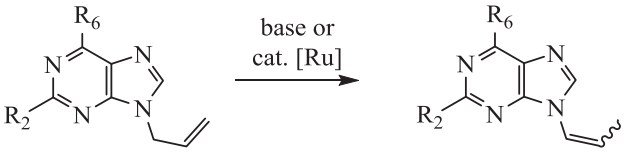
(Table 5.2, entry 2). The isomerisation of 9-allyl-6-iodo-9*H*-purine (**49d**) was followed by a minor halogen exchange (Table 5.2, entry 5), as discussed previously (see Section 4.2.3, page 58).

Table 5.2 Rearrangement of the 7-allylpurines with $RuClH(CO)(PPh_3)_3$

Entry	Subst.	R_2	R_6	Method	Time [h]	Conv. [%][a]	*E/Z*[a]	Yield [%][b]
1	**49a**	H	NH_2	C[c]	24	80	38:62	38, **117a**
2	**72**	H	NH-allyl	C	24	40	28:72	–[d]
3	**49b**	H	Cl	C	3	99	75:25	76, **117b**
4	**49c**	NH_2	Cl	C	3	89	74:26	78, **117c**
5	**49d**	H	I	C	3	90	50:50	73, **117d**[e]
6	**49e**	H	OMe	C	3	97	81:19	87, **117e**

[a]From ^{1}H NMR of the crude product, after 24 h if otherwise not stated; [b]Isolated yield. [c]$RuClH(CO)(PPh_3)_3$, xylenes, Δ; [d]Not isolated in pure form; [e]Calculated yield of **49d**, was isolated together with minor amounts of **49b**.

5.2.2 Rearrangement of 9-allyl purines



48a R_2 = H, R_6 = NH_2
165 R_2 = H, R_6 = NH-allyl
48b R_2 = H, R_6 = Cl
48c R_2 = NH_2, R_6 = Cl
48d R_2 = H, R_6 = I
48e R_2 = H, R_6 = OMe

151a R_2 = H, R_6 = NH_2
166 R_2 = H, R_6 = NH-allyl
151b R_2 = H, R_6 = Cl
151c R_2 = NH_2, R_6 = Cl
151d R_2 = H, R_6 = I
151e R_2 = H, R_6 = OMe

Scheme 5.14 Rearrangement of 9-allyl purines.

In the first report regarding the formation of *N*-propenyl purines, the *N*-9 allyl adenine **48a** was isomerised using *t*-BuOK in DMSO at 100 ºC.[129] Since no *E/Z* selectivity was mentioned, we decided to examine this procedure. The method proved to be easily reproducible giving the *E*-isomer **151a** as the major product (Table 5.3 entry 1). Furthermore, we found that the reaction is equally efficient at ambient temperature (Table 5.3, entry 2).

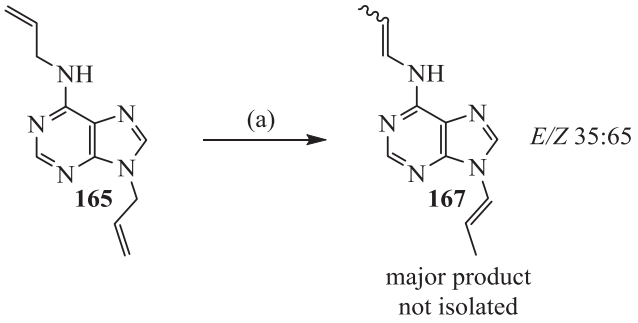
When *t*-BuOK was exchanged with K_2CO_3, the rearrangement was significantly slower, leading to only 40% conversion after 8 days (Table 5.3, entry 3). In contrast to the efficient method with *t*-BuOK, none of the *N*-9 allylpurines were rearranged using K_2CO_3 in refluxing MeCN. Based on the previous report,[18] we therefore performed the reaction with substrates **48a**, **165** and **48e** in refluxing *n*-BuOH instead of MeCN. This brought satisfactory results with adenines **48a** and **165**. The rearrangement was *Z*-selective, although to a much lower extent (Table 5.3, entry 5 and 7) compared to 7-allylpurines (see Table 5.1). Interestingly, only the *N*-9 allyl chain was isomerised in the case of the substrate **165**. In a similar manner like before, the methoxy group from the substrate **48e** was replaced by the butoxy group when **48e** was treated with K_2CO_3 in *n*-BuOH (Table 5.3, entry 13). 6-Chloro purine **48b** is not compatible with *t*-BuOK and a complex mixture of products was formed (Table 5.3, entry 9).

Table 5.3 Base promoted rearrangement of the 9-allylpurines

Entry	Subst.	R_2	R_6	Method[a]	Time [h]	Conv. [%][b]	*E/Z*[b]	Yield [%][c]
1	**48a**	H	NH_2	B[d]	0.30	>99	95:5	92, **151a**[e]
2	**48a**	H	NH_2	B	0.30	>99	93:7	93, **151a**
3	**48a**	H	NH_2	A[d]	8 days	40	16:84	_
4	**48a**	H	NH_2	A	96	n.r.	–	–
5	**48a**	H	NH_2	A[f]	96	92	37:63	69, **151a**
6	**165**	H	NH-allyl	A	96	n.r.	–	–
7	**165**	H	NH-allyl	A[f]	48	90	35:65	89, **166**
8	**48b**	H	Cl	A	24	n.r.	–	–
9	**48b**	H	Cl	B	0.30	_[g]	_	_
10	**48c**	NH_2	Cl	A	24	n.r.	–	–
11	**48d**	H	I	A	24	n.r.	–	–
12	**48e**	H	OMe	A	24	n.r.[h]	–	–
13	**48e**	H	OMe	A[f]	96	–[i]	–	–

[a]Methods A and B are defined in Table 5.1; [b]From ^{1}H NMR of the crude product; [c]Isolated yield; [d]performed at 100 ^oC; [e]performed according to ref. 51; [f]*n*-BuOH as solvent; [g]A complex mixture formed, chloride exchanged with *t*-BuO; [h]Also n.r. in dioxane, Δ or Ph-Cl, Δ; [i]Double bond migration took place, but the methoxy group was also partly exchanged with butoxy.

All the 9-allyl purines were readily isomerised to 9-propenyl purines, when exposed to catalytic amounts of $RuClH(CO)(PPh_3)_3$ (Table 5.4). The range of the *E*-selectivity (83-86%) was slightly higher than for the corresponding *N*-7 isomers. When the *N*,9-diallyl-9*H*-purin-6-amine (**165**) was treated with the Ru catalyst, both allyl chains were rearranged as judged from the ^{1}H NMR of the crude product (Table 5.4, entry 2). Nevertheless, limited stability of the probable product **167** did not allow a successful isolation (Scheme 5.15).



Scheme 5.15 Reagents and conditions: (a) cat. $RuClH(CO)(PPh_3)_3$, xylenes, Δ, 3 h.

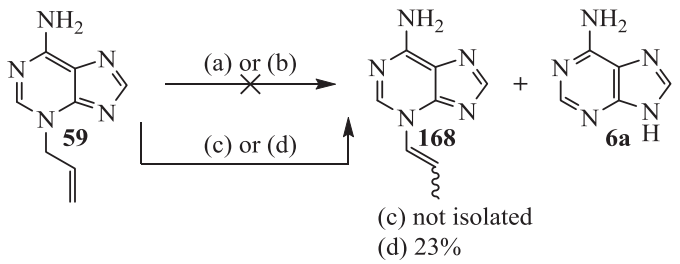
When the iodide **48d** was reacted with $RuClH(CO)(PPh_3)_3$, a minor halogen exchange occurred (Table 5.4, entry 5). Apart from the product **167**, all the other *N*-9 propenyl purines were obtained in good yields (Table 5.4).

Table 5.4 Rearrangement of the 9-allylpurines with $RuClH(CO)(PPh_3)_3$

Entry	Subst.	R_2	R_6	Method[a]	Time [h]	Conv. [%][b]	*E/Z*[b]	Yield [%][c]
1	**48a**	H	NH_2	C	3	98	86:14	84, **151a**
2	**165**	H	NH-allyl	C	3	>99[d]	–[d]	–[d]
3	**48b**	H	Cl	C	3	97	86:14	85, **151b**
4	**48c**	NH_2	Cl	C	3	97	83:17	76, **151c**
5	**48d**	H	I	C	3	95	84:16	77, **151d**[e]
6	**48e**	H	OMe	C	3	97	83:17	86, **151e**

[a]Method C is defined in Table 5.2; [b]From ^{1}H NMR of the crude product; [c]Isolated yield; [d]NMR indicated that compound **167** (*E/Z* 35:65) was formed, but the compound was not isolated in pure form; [e]Calculated yield of **48d**, was isolated together with minor amounts of **48b**.

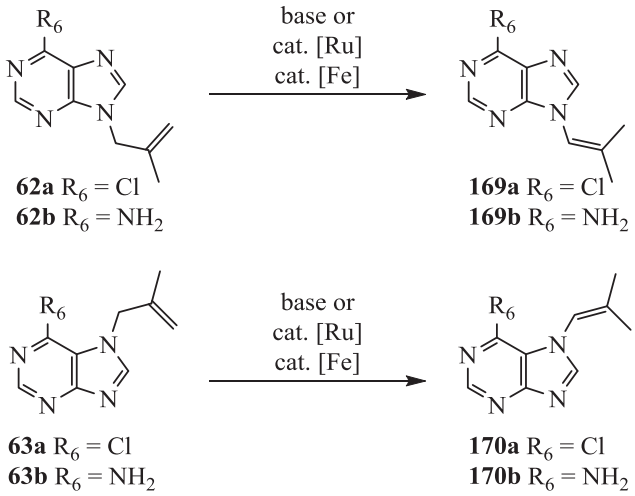
In addition, we investigated the rearrangement of 3-allyl-3*H*-purin-6-amine **59** (Scheme 5.16). This substrate seems to be generally less suitable for the rearrangement, and the reaction with K_2CO_3 in MeCN did not give any isomerisation. To our surprise, the Ru promoted rearrangement did not occur to any extent either with this substrate. When the adenine **59** was treated with K_2CO_3 in refluxing *n*-BuOH, a significant deallylation was observed after 24 hours. The ratio between product **168**, substrate **59** and adenine **6a** was determined by ^{1}H NMR to be 49:25:26. Finally, the rearrangement using *t*-BuOK in DMSO gave the product **168** as a predominant *E*-isomer (*E/Z* 85:15) although in limited yield.



Scheme 5.16 Reagents and conditions: (a) K_2CO_3, MeCN, Δ, 24 h; (b) cat. $RuClH(CO)(PPh_3)_3$, xylenes, Δ, 3 h; (c) K_2CO_3, *n*-BuOH, Δ, 24 h; (d) *t*-BuOK, DMSO, 100 ºC, 20 min.

5.2.3 Substitution on allyl C-2' position

After investigating of the rearrangement with purines bearing the simple *N*-7 and *N*-9 allyl group, we moved forward to purines with an additional substitution on the *N*-allyl chain. In the first place, we explored the influence of the methyl group on the double bond migration using 2-methylallyl derivates (Scheme 5.17).



Scheme 5.17 Example of the rearrangement with *N*-2-methylallyl purine.

The tendency to undergo the rearrangement was initially tested under basic conditions (Table 5.5). No rearrangement was observed with the 6-chlorosubstrates (Table 5.5, entries 1 and 4). In the case of the adenine substrates **62b** and **63b**, the base promoted rearrangement led to the desired products. The *N*-7 allyladenine **63b** was conveniently isomerised with K_2CO_3 in refluxing MeCN, giving high yield of the product **170b**. Nevertheless, for the rearrangement of the corresponding *N*-9 isomer, more forcing conditions were required. Even though the isomerisation was carried out under microwave irradiation, the conversion only reached 50% after 16 hours (Table 5.5, entry 6). Refluxing the compound **62b** in *n*-BuOH gave a comparable result (Table 5.5, entry 7). Regrettably, the product and the starting material were not successfully separated. The most efficient method for the 2-methylallyl adenines **62b** and **63b** was the application of *t*-BuOK. First of all, using the literature conditions,[129] we rearranged the adenine **62b** in DMSO at 100 ºC (Table 5.5, entry 8). Moreover, the reaction was also performed with the same efficiency at ambient temperature. The substrates **62b** and **63b** were converted almost quantitatively to the corresponding products**.** The products **169b** and **170b** were obtained with high yield (Table 5.5, entries 3 and 9).

Table 5.5 Base promoted rearrangement of the 2-methyl-allylpurines

Entry	Subst.	R_6	Method[a]	Time [h]	Conv. [%][b]	Yield [%][c]
1	**63a**	Cl	A	24	n.r.	_
2	**63b**	NH_2	A	48	94	90, **170b**
3	**63b**	NH_2	B	0.30	92	74, **170b**
4	**62a**	Cl	A	48	n.r.	_
5	**62b**	NH_2	A	48	n.r.	_
6	**62b**	NH_2	A[d]	16	50	_
7	**62b**	NH_2	A[e]	72	43	_
8	**62b**	NH_2	B[f]	0.30	93	90, **169b**
9	**62b**	NH_2	B	0.30	93	87, **169b**

[a]Methods A and B are defined in Table 5.1; [b]From ^{1}H NMR of the crude product; [c]Isolated yield; [d]200 °C, microwave cond.; [e]*n*-BuOH as solvent; [f]Performed at 100 °C.

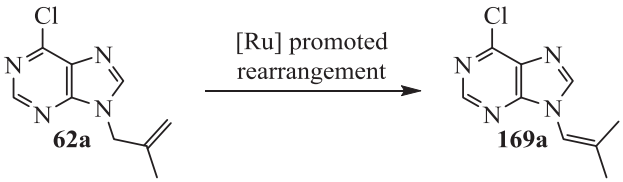
Application of $RuClH(CO)(PPh_3)_3$ was much less efficient. Almost no migration was observed with all of the substrates under standard conditions (Table 5.6) even with extended reaction time. In addition, the almost identical polarity of the starting material and the product did not allow successful separation by column chromatography or by recrystallisation in any of the cases.

Table 5.6 2-methylallyl purines under standard conditions with $RuClH(CO)(PPh_3)_3$

Entry	Subst.	R_6	Method[a]	Time [h]	Conv. [%][b]	Yield [%][c]
1	**63a**	Cl	C	3	n.r.	_
2	**63a**	Cl	C	24	6	_
3	**63b**	NH_2	C	24	n.r.	_
4	**62a**	Cl	C	48	21	_
5	**62b**	NH_2	C	24	11	–
6	**62b**	NH_2	C	48	6	_

[a]Method C is defined in Table 5.2; [b]From ^{1}H NMR of the crude product; [c]Isolated yield.

After this lack of success using the standard Ru promoted procedure, we tried to adjust the rearrangement conditions for 2-methylallyl chloropurines **62a** and **63a**, which could not be rearranged using *t*-BuOK. We performed a set of test reactions with the 6-chloro purine **62a** (Scheme 5.18, Table 5.7). Initially, we attempted to improve the conversion using the microwave irradiation (Table 5.7, entry 1). Nonetheless, even increasing the reaction temperature up to 175 ºC did not give any significant improvement of the process (Table 5.7, entries 2-4). Thus, the catalyst loading was increased (Table 5.7, entry 5) or the reaction was carried out with a continuous addition of the catalyst over 96 hours (Table 5.7, entry 6). Regrettably, in both cases the reactions did not bring about satisfactory results.



Scheme 5.18 Reagents and conditions: see Table 5.7.

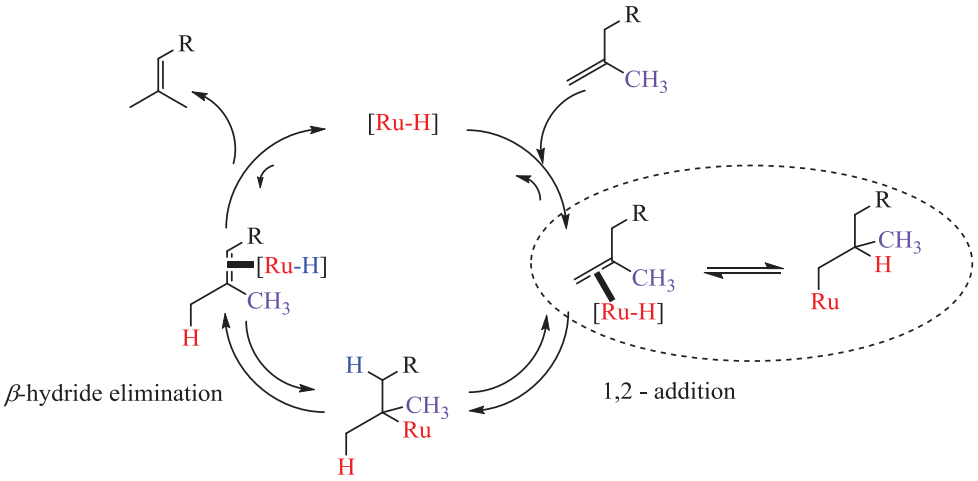
Table 5.7 Attempts for the improvement of the isomerisation of **62a** with $RuClH(CO)(PPh_3)_3$

Entry	Ru catalyst loading [%]	solvent	Temp. [ºC]	Time [h]	Conv. [%][a] to 169a
1	10	dioxane	130[b]	3	9
2	10	dioxane	150 to 160[b,c]	5	8
3	10	dioxane	175[b]	3,5	10
4	10	xylenes	175	24	10
5	20	xylenes	Δ	96	44
6	30[d]	xylenes	Δ	96	36

[a]From ^{1}H NMR of the crude product; [b]Microwave irradiation used; [c]3 h at 150 ºC and 2 h at 160 ºC; [d]Started with 5% catalyst loading, 5% catalyst was added every 16 hours.

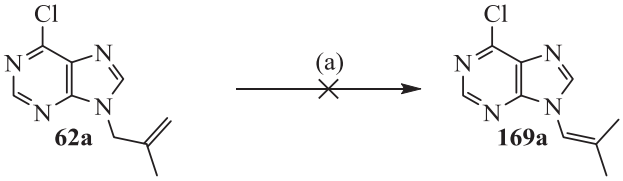
A possible answer for the significant drop in the reactivity of 2-methyl allyl substrates could be found in the rearrangement mechanism (Scheme 5.19). The crucial point of the Ru-hydride addition-elimination mechanism is the 1,2-addition step (Section 5.1.2.2). For the

rearrangement to take place, the ruthenium catalyst needs to be attached to the C-2' position. However, in the case of the 2-methyl allyl group, this C-2' position is occupied by the methyl group, which would complicate this addition. For this reason, the catalyst is most probably adding to the less hindered carbon C-3' instead. If the catalyst is added to the C-3', the catalytic cycle will lead back to the starting 2-methylallyl group after the *β*-hydride elimination, which in turn would explain a low overall conversion.



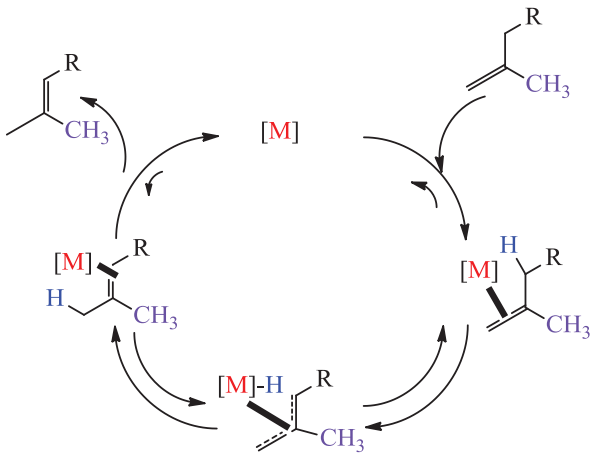
Scheme 5.19 C-2' substituted allyl group in the hydride mechanism.

Facing severe problems with the Ru mediated migration we decided to explore other possible alternatives. Exchanging the ruthenium with the similar rhodium catalyst did not lead to any isomerisation (Scheme 5.20). We then switched our attention to the rearrangement carried out with $Fe(CO)_5$.



Scheme 5.20 Reagents and conditions: (a) cat. $RhH(CO)(PPh_3)_3$, xylenes, Δ, 24 h.

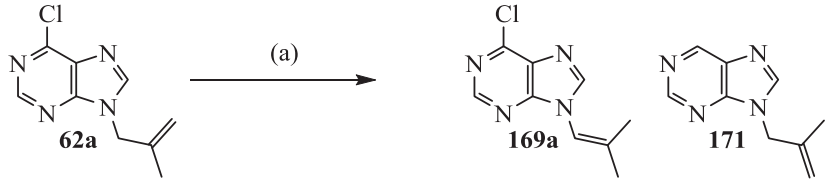
This reagent was considered since the isomerisation with $Fe(CO)_5$ takes place *via* the *π*-allyl hydride mechanism[198] (Section 5.1.2.3). Ideally, the methyl group on the carbon C-2' should not interfere with the reaction progress (Scheme 5.21). Furthermore, a similar case of rearrangement of the 2-methylallyl group is reported in the literature.[131,200]



Scheme 5.21 Possible π-allyl hydrido mechanism for the rearrangement of the 2-methyl allyl group.

Several test reactions were carried out with the chloropurine **62a**. Following the literature procedure, we started with 0.2 or 1 equivalent of $Fe(CO)_5$ (Table 5.8, entries 1 and 2) in refluxing xylenes.[131,200] Despite the low conversion, we also observed that a notable amount of $Fe(CO)_5$ is evaporated from the reaction mixture during reflux. Due to the volatility of $Fe(CO)_5$ we decided to perform the reaction in a sealed tube. When the reaction mixture was heated at 140 ºC for 24 hours, the desired product **169a** was detected by ^{1}H NMR (Table 5.8, entry 4). The progress was further improved with longer reaction time or by increasing the amount of $Fe(CO)_5$ in the reaction mixture (Table 5.8, entries 5 and 7). Unfortunately, when we further raised the loading of $Fe(CO)_5$, a partial reductive dehalogenation of **62a** to **171** was observed (Table 5.8, entry 6). Reductive dehalogenation using $Fe(CO)_5$ is known, but usually takes place only in protic solvents.[201-203] The formation of the reduced product **171** was not prevented using dry and degassed solvents and working under the inert atmosphere of a glovebox. Furthermore we realised, that while varying different parameters of the procedure (Table 5.8, entries 5 and 7-12), the outcome of the reaction was very similar. The conversion to the product **169a** varied from 42-65%. We deducted two possible reasons for this low conversion. Either the catalyst is thermally unstable, which was suggested before,[192] or the reaction reaches an equilibrium between the starting material and the rearranged product. $Fe(CO)_5$ is also known to be photosensitive, however, running the reaction in the dark did not lead to any significant improvement (Table 5.8, entry 11). Subsequently, a simple experiment was performed to investigate the reason for the limited conversion. A mixture of purine **62a**

and **169a** was used as a starting material. This forced the reaction to progress further (Table 5.8, entry 12) and also indicated, that the reason of the low conversion is actually the thermal stability of $Fe(CO)_5$ and not the establishment of an equilibrium in the reaction. At this point we simply carried out the reaction with continuous addition of fresh $Fe(CO)_5$ over 24 hours. Finally, the isomerisation gave appreciable conversion and the desired product was successfully isolated in reasonable yield (Table 5.8, entry 13).



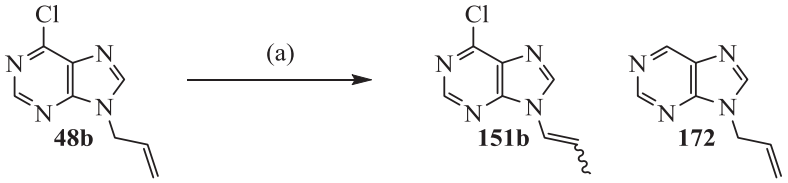
Scheme 5.22 Reagents and conditions: (a) $Fe(CO)_5$, see Table 5.8.

Table 5.8 Screening for the rearrangement conditions with $Fe(CO)_5$

Entry	Eq. $Fe(CO)_5$	T [°C][a]	Time [h]	Conversion [%][b] 62a	169a	171	Yield[c] [%]169a
1	0.2	Δ	24	87	13	_	_
2	1	Δ	24	65	35	_	_
3	1	100	24	100	_	_	_
4	1	140	24	75	25	_	_
5	1	140	48	58	42	_	_
6	2	120	24	88	4	8	_
7	2	140	24	45	55	_	_
8	4	140	24	39	58	3	_
9	2	140	48	41	55	4	_
10	2	150	24	43	57	8	16
11	2	140[d]	24	52	45	3	_
12[e]	2	140	24	22	65	13	_
13	4[f]	140	24	23	71	6	48

[a]Sealed tube used if not stated otherwise; [b]From ^{1}H NMR of the crude product; [c]Isolated yield; [d]Performed in the dark; [e]Started with 42:58 mixture of **62a** to **169a**; [f]0.5 eq. was added every 6 hours.

To compare the reactivity, we also performed the $Fe(CO)_5$ mediated rearrangement using the allylic purine **48b** with an unsubstituted allyl chain (Table 5.9, Scheme 5.23). The isomerisation with the *N*-allyl purine **48b** occurred more readily. The product **151b** was obtained in high yield with 2 eq. of $Fe(CO)_5$ after 3 hours. Thus, the continuous addition of $Fe(CO)_5$ was not required in this case. Further increase of the reaction time up to 24 h gave a slightly higher conversion as well as improved yield (Table 5.9, entry 2). This rearrangement gave the *E*-isomer of **151b** in high excess. Minor traces of the reduced starting material **172** were also observed.



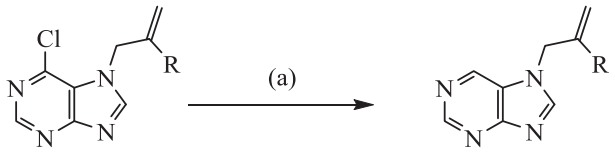
Scheme 5.23 Reagents and conditions: (a) $Fe(CO)_5$, see Table 5.9.

Table 5.9 Double bond migration of **48b** with $Fe(CO)_5$

Entry	Eq. $Fe(CO)_5$	T [°C][a]	Time [h]	Conversion [%][b]			Yield [%][c]
				48b	151b	172	151b
1	2	140 °C	3	8	91	1	88, *E/Z* 85:15
2	2	140 °C	24	3	95	2	93, *E/Z* 87:13

[a]Sealed tube; [b]From ^{1}H NMR of the crude product; [c]Isolated yield.

When we treated the *N*-7 isomers **49b** and **63a** with $Fe(CO)_5$, the outcome was somewhat surprising. The rearrangement did not occur and only a reduction of the starting material was observed (Scheme 5.24). The hydride species formed *in situ* from $Fe(CO)_5$ (Scheme 5.11 and Scheme 5.21) probably reacted with the chloride in the C-6 position. Both dechlorinated products **173** and **174** were successfully isolated and characterised (Table 5.10). The increased tendency of the *N*-7 purines to undergo reductive dehalogenation compared to *N*-9 isomers, was noted before in a study of Negishi couplings.[66]



49b R = H
63a R = Me

173 R = H
174 R = Me

Scheme 5.24 Reagents and conditions: (a) $Fe(CO)_5$, see Table 5.10.

Table 5.10 Reductive dehalogenation of *N*-7 allyl purines with $Fe(CO)_5$

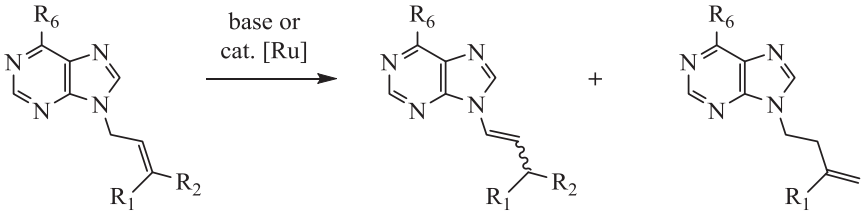
Entry	Subst.	R	Eq. $Fe(CO)_5$	T [°C][a]	Time [h]	Conversion [%][b]			Yield[c] [%]
						s.m.	migr.	Red.	
1	**49b**	H	2	140	3	70	_	30	25, **173**
2	**63a**	Me	2	140	24	33	_	66	32, **174**

[a]Sealed tube; [b]From ^{1}H NMR of the crude product; [c]Isolated yield.

In summary, the application of $Fe(CO)_5$ does not seem to be suitable for the 6-chloro-*N*-7 allyl purines, while the corresponding *N*-9 isomers **48b** and **62a** were successfully rearranged by this method and the products were obtained in good yields.

5.2.4 Substitution on allyl C-3' position

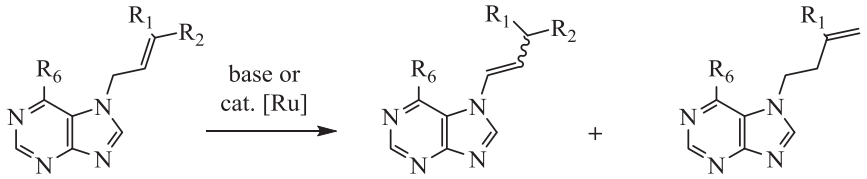
N-allyl C-3' substituted purines was the last class of substrates, we investigated in the isomerisation study. In most of the cases, the use of Ru or the base promoted rearrangement of the C-3' substituted allyl purines lead to a mixture of the desired *N*-propenyl purines and the purines bearing *N*-homoallylic side chain (Scheme 5.25). Generally, isolating the *N*-propenyl products was appreciably easier compared to the C-2' substituted analogues and so even in cases with low conversion, the products **175** and **176** were isolated in pure form.



60a R_1 = H, R_2 = Me, R_6 = Cl
60d R_1 = H, R_2 = Me, R_6 = NH_2
60b R_1 = R_2 = Me, R_6 = Cl
60e R_1 = R_2 = Me, R_6 = NH_2
60c R_1 = H, R_2 = Ph, R_6 = Cl
60f R_1 = H, R_2 = Ph, R_6 = NH_2

175a R_1 = H, R_2 = Me, R_6 = Cl
175d R_1 = H, R_2 = Me, R_6 = NH_2
175b R_1 = R_2 = Me, R_6 = Cl
175e R_1 = R_2 = Me, R_6 = NH_2
175c R_1 = H, R_2 = Ph, R_6 = Cl
175f R_1 = H, R_2 = Ph, R_6 = NH_2

64a R_1 = H, R_6 = Cl
64c R_1 = H, R_6 = NH_2
64b R_1 = Me, R_6 = Cl
64d R_1 = Me, R_6 = NH_2



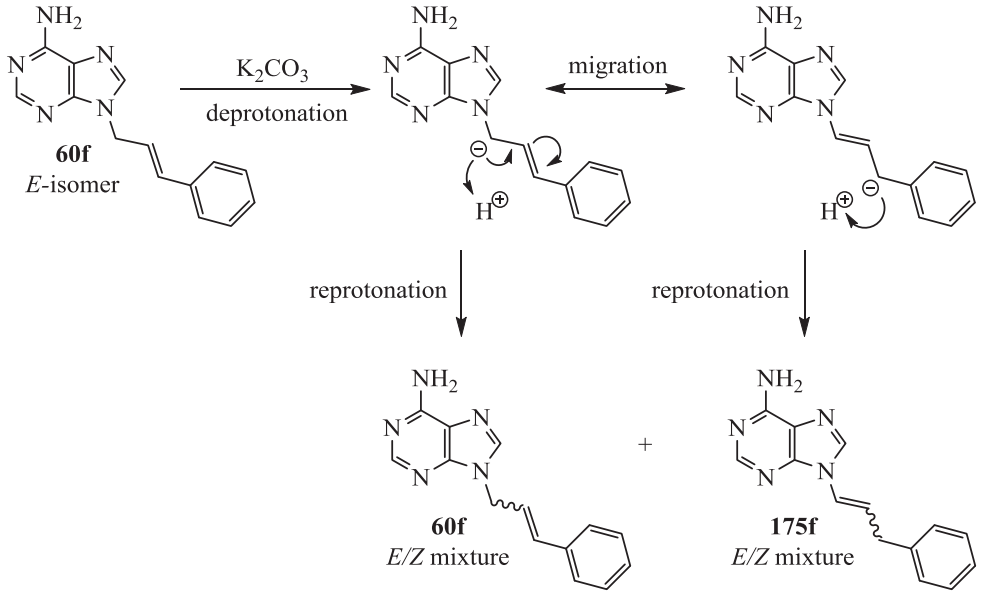
61a R_1 = H, R_2 = Me, R_6 = Cl
61d R_1 = H, R_2 = Me, R_6 = NH_2
61b R_1 = R_2 = Me, R_6 = Cl
61e R_1 = R_2 = Me, R_6 = NH_2
61c R_1 = H, R_2 = Ph, R_6 = Cl
61f R_1 = H, R_2 = Ph, R_6 = NH_2

176a R_1 = H, R_2 = Me, R_6 = Cl
176d R_1 = H, R_2 = Me, R_6 = NH_2
176b R_1 = R_2 = Me, R_6 = Cl
176e R_1 = R_2 = Me, R_6 = NH_2
176c R_1 = H, R_2 = Ph, R_6 = Cl
176f R_1 = H, R_2 = Ph, R_6 = NH_2

65a R_1 = H, R_6 = Cl
65c R_1 = H, R_6 = NH_2
65b R_1 = Me, R_6 = Cl
65d R_1 = Me, R_6 = NH_2

Scheme 5.25 The rearrangement with C-3' substituted allylpurines.

All the substrates did not react at all under the mild basic conditions with K_2CO_3 in MeCN (data not shown). The adenine derivates which cannot undergo nucleophilic substitution were also treated with K_2CO_3 in refluxing *n*-BuOH (Table 5.11). The rearrangement occurred only in the case of substrate **60f**. Despite the low conversion, the product **176f** was successfully isolated (Table 5.11, entry 13). Interestingly, even though we started the reaction with **60f** as a pure *E*-isomer, the starting material was recovered as a 96:4 *E/Z* mixture (Table 5.11, entry 13). This indicates that the deprotonation by K_2CO_3 took place, but was not followed by the migration to any significant extent (Scheme 5.26).



Scheme 5.26 Possible explanation of the *E/Z* isomerisation of the compound **60f**.

We then approached more forcing conditions with *t*-BuOK in DMSO at room temperature, which gave generally less than 20% conversion for the compounds **61d**, **61e**, **61f**, **60d**, **60e** and **60f**. Most importantly, the deallylation leading to adenine **6a** was observed in all of the cases. If the reaction mixture was heated to 100 ºC, the deallylation occurred almost quantitatively within 20 minutes. The isomerisation of the substrates **61d** and **60d** occurred with higher *Z*-selectivity (Table 5.11, entries 2 and 9). The substrates **61e** and **60e** were rearranged only to the homoallylic analogues **65d** and **64d** (Table 5.11, entry 5 and 12). The fact that the *N*-alkenyl products **176e** and **175e** were not observed in this case gives an indication, that after the deprotonation at CH_2 the rearrangement did not occur and the deallylation took place instead. When the deprotonation took place on the other side of the double bond, the terminal alkenes could be formed (Table 5.11, entries 2, 5, 9 and 12). In connection with this, the highest degree of allyl chain cleavage was observed with the cinnamylaldehyde **61f** and **60f**, which can only be deprotonated at CH_2 (Table 5.11, entry 7 and 14). In the case of *t*-BuOK mediated rearrangement of **61d** and **60d**, the formation of the terminal alkenes was also detected by ^{1}H NMR of the crude product mixture (Table 5.11, entries 2 and 9). In general, the terminal alkenes **64** and **65** were not obtained in pure form and were identified by a comparison with the spectral data of the reference compounds. The

reference compounds were prepared by *N*-alkylation with the corresponding homoallylic halides (Section 2.2.3, page 22).

Table 5.11 C-3' substituted allylpurines under basic conditions

Entry	Starting material	R_1	R_2	R_6	Method[a]	Time [h]	Conversion [%][b] 60 or 61	175 or 176	64 or 65	6a[c]	Yield [%] 175 or 176 (*E*/*Z*)[d]	*E*/*Z* recovered 60 or 61
1	**61d**	H	Me	NH_2	A[e]	24	>99	n.d.[f]	n.d.	n.d.	–	>99:1
2	**61d**	H	Me	NH_2	B	0.30	83	13	1	3	12 (34:66)	>99:1
3	**61e**	Me	Me	NH_2	A[e]	72	>99	n.d.	n.d.	n.d.	–	–
4	**61e**	Me	Me	NH_2	A[g]	7	54	n.d.	n.d.	46	–	–
5	**61e**	Me	Me	NH_2	B	0.30	94	n.d.	5	1	–	–
6	**61f**	H	Ph	NH_2	A[e]	24	>99	n.d.	–	n.d.	–	>99:1
7	**61f**	H	Ph	NH_2	B	0.30	78	2	–	20	– (>99:1)	>99:1
8	**60d**	H	Me	NH_2	A[e]	72	>99	n.d.	n.d.	n.d.	–	>99:1
9	**60d**	H	Me	NH_2	B	0.30	79	16	1	4	9 (54:46)[h]	>99:1
10	**60e**	Me	Me	NH_2	A[e]	72	>99	n.d.	n.d.	n.d.	–	–
11	**60e**	Me	Me	NH_2	A[g]	3	>99	n.d.	n.d.	n.d.	–	–
12	**60e**	Me	Me	NH_2	B	0.30	71	n.d.	18	11	–	–
13	**60f**	H	Ph	NH_2	A[e]	72	89	11	–	n.d.	10 (80:20)	96:4
14	**60f**	H	Ph	NH_2	B	0.30	54	n.d.	–	46	–	>99:1

[a]Methods A and B are defined in Table 5.1; [b]From ^{1}H NMR of the crude product; [c]Formation of adenine **6a**; [d]Isolated yield; [e]*n*-BuOH as solvent; [f]not detected; [g]200 °C, microwave cond.;[h]Ratio from ^{1}H NMR of the crude product 40:60.

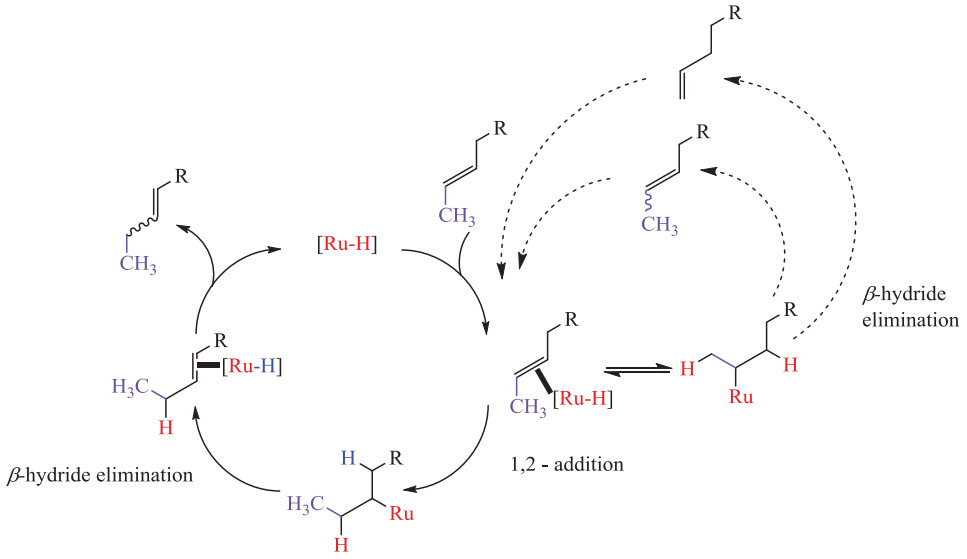
All the C-3' substituted allylpurines were slightly more reactive compared to the substrates with 2-methylallyl purines, when treated with $RuClH(CO)(PPh_3)_3$. On the other hand, the conversion was still much lower compared to the substrates **48** and **49** with unsubstituted allyl moiety. Generally, all the rearrangements gave the *N*-propenyl purines as major products with high *E*-selectivity. The terminal alkenes, when possible to form, were also observed. In addition, the isomerisation of the starting material from the *E*-isomer to *Z*-isomer occurred.

Table 5.12 C-3' substituted allylpurines with $RuClH(CO)(PPh_3)_3$

Entry	Starting material	R_1	R_2	R_6	Method[a]	Time [h]	Conversion [%][b]			Yield [%] 175 or 176 (*E*/*Z*)[c]	*E*/*Z* recovered 60 or 61
							60 or 61	175 or 176	64 or 65		
1	**61a**	H	Me	Cl	C	24	58	32	11	28 (85:15)	79:21
2	**61d**	H	Me	NH_2	C	24	75	22	3	20 (67:33)	88:12
3	**61b**	Me	Me	Cl	C	24	>99	n.d.	n.d.	–	–
4	**61e**	Me	Me	NH_2	C	24	>99	n.d.	n.d.	–	–
5	**61c**	H	Ph	Cl	C	24	91	9	–	– (>99:1)	95:5
6	**61f**	H	Ph	NH_2	C	24	>99	n.d.	–	–	>99:1
7	**60a**	H	Me	Cl	C	24	47	46	7	42 (90:10)	79:21
8	**60d**	H	Me	NH_2	C	24	47	48	5	35 (>99:1)[d]	84:16
9	**60b**	Me	Me	Cl	C	24	82	8	10	– (>99:1)	–
10	**60e**	Me	Me	NH_2	C	24	93	3	4	– (>99:1)	–
11	**60c**	H	Ph	Cl	C	24	87	13	–	– (>99:1)	97:3
12	**60f**	H	Ph	NH_2	C	48	88	12	–	9 (>99:1)	97:3

[a]Method C is defined in Table 5.2; [b]From ^{1}H NMR of the crude product; [c]Isolated yield; [d]Ratio from ^{1}H NMR of the crude product 87:13.

The low reactivity of the C-3' substituted substrates could once again be explained by the hydride addition-elimination mechanism.[186] For the simple, unsubstituted *N*-allyl, there are only two possible outcomes from the 1,2-addition step. Either the Ru catalyst is attached to the C-2', which leads to the desired *N*-propenyl group formation, or the Ru catalyst is connected to the C-3' and then the *β*-hydride elimination will direct the reaction back to the original *N*-allyl group (see Scheme 5.9). In contrast to this, if an additional substituent (*e.g.* methyl group) is present in the C-3' and the Ru is attached to the C-3' position as well, the *β*-hydride elimination can also lead to the formation of *N*-homoallyl group. Most importantly, all the isomers have a possibility to enter the catalytic cycle again. Thus, a mixture of several different isomers could be expected as the outcome of this type of reaction.



Scheme 5.27 Possible outcome from the Ru mediated rearrangement of the C-3' substituted allyl group.

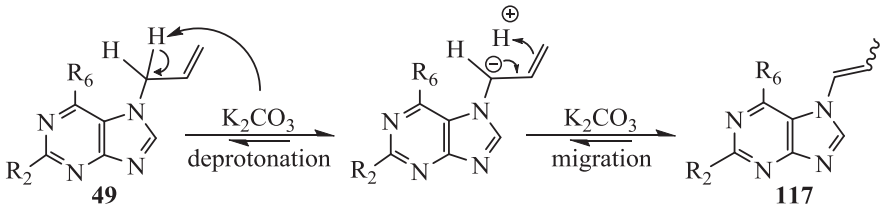
5.3 Summary and conclusions

The rearrangement of *N*-allyl purines under basic conditions was explored. Only *N*-7-allyl adenines were successfully rearranged by K_2CO_3 in refluxing MeCN. This K_2CO_3 rearrangement occurred with a remarkably high *Z*-selectivity. Most of the other substrates were unreactive with K_2CO_3 or required solvents with higher boiling point for the rearrangement to take place. The cleavage of the allyl chain and formation of homoallyl derivates was observed, when certain substituted allylpurines were treated with strong base (*t*-BuOK).

The $RuClH(CO)(PPh_3)_3$ catalysed isomerisation of precursors with a simple *N*-allyl chain was found to be a suitable method for the synthesis of *N*-propenyl purines. The Ru promoted rearrangements occurred with high *E*-selectivity. The efficiency of the rearrangement with $RuClH(CO)(PPh_3)_3$ significantly dropped with increasing substitution pattern around the allylic double bond. The reasons for the limited reactivity of the purines with 2-methyl allyl and C-3' substituted allyls were proposed based on the hydride addition-elimination mechanism. In the case of the rearrangement of the C-3' substituted substrates, the *E*- to *Z*-isomerisation of the starting material itself as well as the formation of homoallyl purines was observed. For the 2-methyl-allyl purines an alternative method employing $Fe(CO)_5$ was successfully explored.

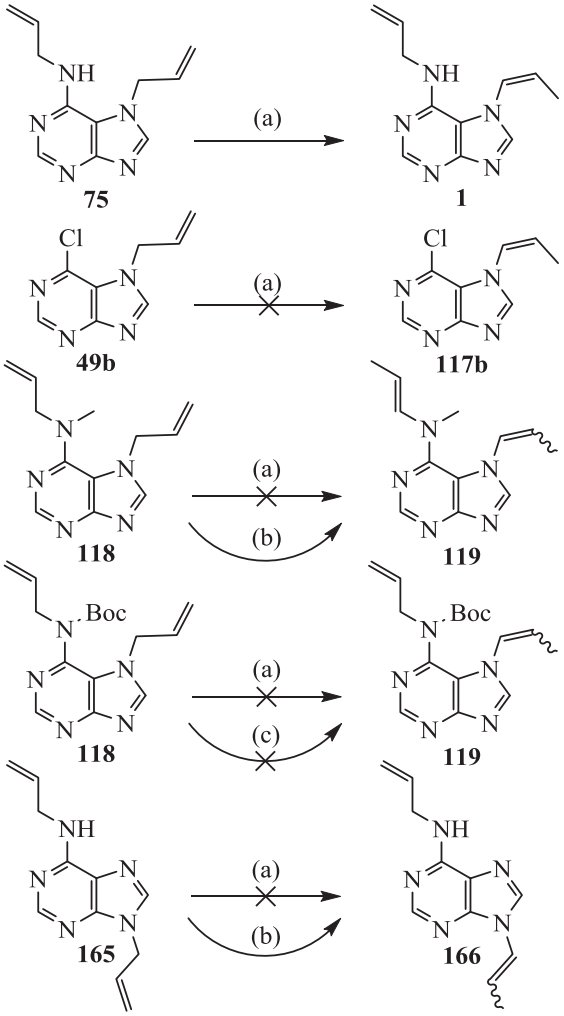
5.4 Future prospects

The complete *Z*-selectivity in the K_2CO_3 mediated rearrangement of compounds **72** and **75a-c** is a very interesting feature (see page 31, Scheme 3.4 and page 38, Scheme 3.15) since the *Z*-isomers are generally regarded as the less thermodynamically stable products. A similar example of *N*-allyl rearrangement is not reported in the literature. Bearing in mind that base promoted allylic rearrangements occurs *via* carbanion formation (Section 5.1.2.1), we can assume that the whole process has to start with deprotonation of the CH_2 group in the C-1' position (Scheme 5.28).



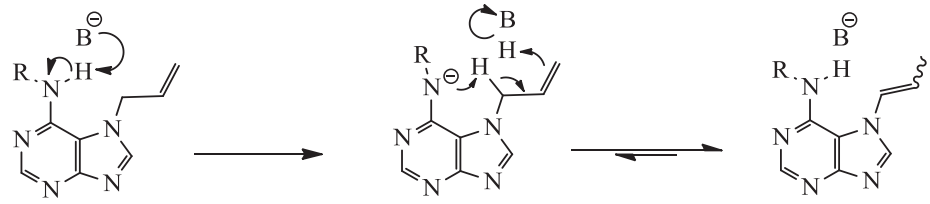
Scheme 5.28 Deprotonation by K_2CO_3 in *N*-7 allyl purine **49**.

Thus, performing the reaction with chloro purine **49b**, bearing the electronegative chlorine atom in the C-6 position, should lead to the isomerisation as well. However, the reaction did not take place at all in this case (Scheme 5.29). In opposition to this, considering the remaining results presented in the Table 5.1, the rearrangement occurs readily when an electron donating primary and secondary amino group is present in the C-6 position. Therefore it seems that this kind of isomerisation is specific only for the 7-allyl adenines with exchangeable NH protons. On top of that, replacing the exchangeable proton in the 6-NHR group with methyl or Boc group leads to a drop in the reactivity in K_2CO_3 mediated isomerisations. This was observed in the case of compound **118**[18] and **112** (Section 4.2.3, page 57). The corresponding *N*-9 isomers were also rearranged using K_2CO_3 but in this case the reaction required higher temperatures and the *E/Z* selectivity dropped significantly (Scheme 5.29).



Scheme 5.29 Reagents and conditions: (a) K_2CO_3, MeCN, Δ; (b) K_2CO_3, *n*-BuOH, Δ, (c) see Table 4.2 page 57.

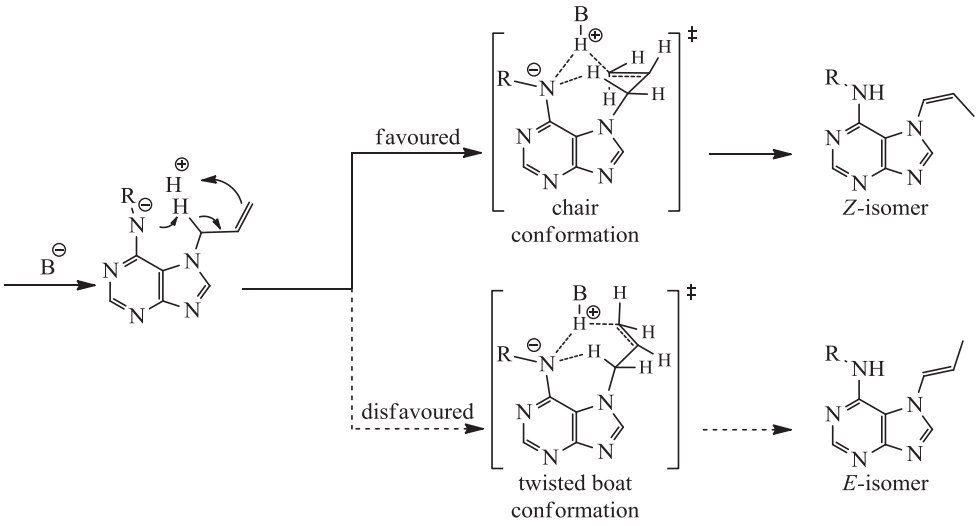
Therefore, the rearrangement in the case of 7-allyl adenines could be facilitated by the presence of the 6-NHR group.



R = H, alkyl

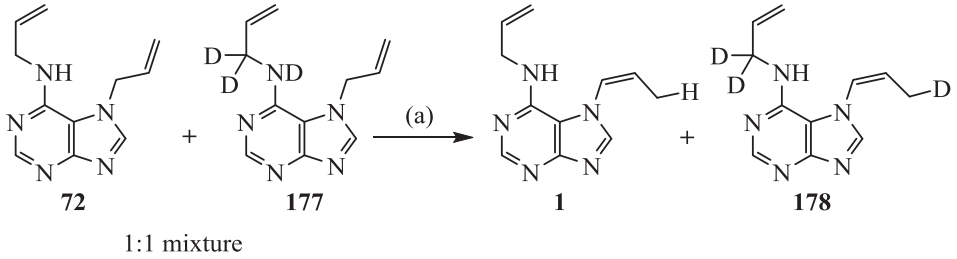
Scheme 5.30 Possible facilitation of the K_2CO_3 rearrangement by 6-NHR group.

This hypothesis offers an explanation of the increased reactivity of the *N*-7 allyl adenines in the reaction with mild K_2CO_3. However, the significantly high *Z*-selectivity still needs to be explained. The fact that only one single *Z*-isomer was obtained from this rearrangement indicates, that the reaction occurs in a way which prevents a formation of the *E*-isomer. If we accept that the interaction of the amino group with protons from the *N*-7 allyl C-1' group is the cause of the intramolecular rearrangement, then this rearrangement could occur *via* two possible 6-membered cyclic transition states. The twisted boat conformation of the transition state would lead to the *E*-isomer. More importantly, if the transition state has a chair conformation, the outcome of the reaction will be the *Z*-isomer, which was observed in our case. Hence this theory could be investigated for example by theoretical calculations.



Scheme 5.31 Proposed 6-membered cyclic transition state for the K_2CO_3 mediated rearrangement of 7-allyl adenines.

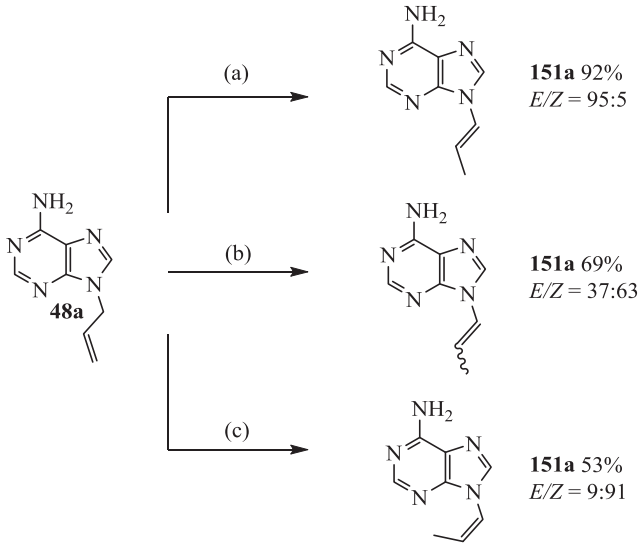
In addition, a deuterium labeled experiment could be performed in order to have more insight into this system (Scheme 5.32).



Scheme 5.32 Reagents and conditions: (a) K_2CO_3, MeCN, Δ.

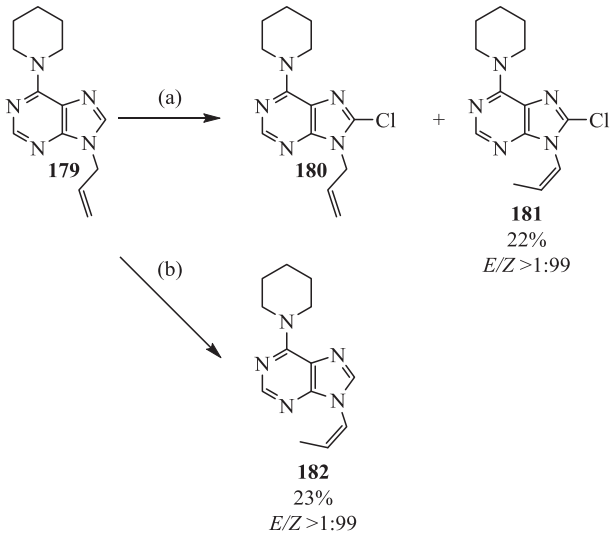
Performing the experiment with compound **72** and deuterium labeled isomer **177** in a 1:1 mixture would reveal, whether we are dealing with the intramolecular isomerisation or not. Moreover, if the C-6 amino group interacts with the *N*-7 allyl chain and the rearrangement takes place *via* the proposed 6-membered cyclic mechanism, the deuterium should be introduced to the C-3' position of the *N*-propenyl chain in the product **178**. Both **1** and **177** should then be easily distinguishable by ^{1}H NMR of the crude products. The evaluation of the proposed hypothesis would be a suitable starting point for a following study in the field of *N*-allyl isomerisations.

Furthermore, a broad scope of base mediated isomerisation conditions was explored *e.g.* with 9-allyl-9*H*-purin-6-amine (**48a**) (Table 5.3, page 89). When the adenine **48a** was refluxed with K_2CO_3 in *n*-BuOH for 3 days, the expected product **151a** was obtained as a mixture of *E/Z* isomers. Using *t*-BuOK in DMSO at 100 °C or at room temperature resulted in a high yield of product **151a**, which was formed almost exclusively as the *E*-isomer. In addition, in the course of a recent study on functionalization of the purine 8-position *via* 8-purinyl anions[204] it was reported, that treating **48a** with LDA at -78 °C in THF resulted in a formation of the product **151a** as well, but with high *Z*-selectivity in this case (Scheme 5.33).



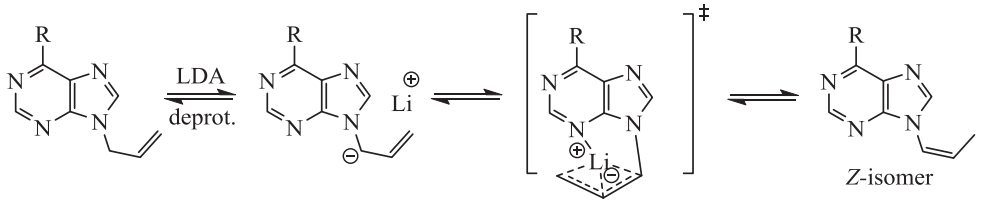
Scheme 5.33 Reagents and condition: (a) *t*-BuOK, DMSO, 100 °C, 20 min.; (b) K_2CO_2, *n*-BuOH, Δ, 4 days; (c) 5eq. LDA, THF, -78 °C, 1 h.

A similar outcome from reaction was observed when the 9-allyl-6-(piperidin-1-yl)-9*H*-purine was treated with LDA.[205] The deprotonation took place in *N*-allyl as well as in the C-8 position and the rearranged product was obtained as pure *Z*-isomer (Scheme 5.34).



Scheme 5.34 Reagents and conditions: (a) 1) LDA, THF, -78 °C, 1 h, 2) C_2Cl_6, -78 °C, 15 min.; (b) 1) LDA, THF, -78 °C, 1 h, 2) NH_4Cl, -78 °C, 1 h.

The low reaction temperature indicates a kinetic control of the process and the high *Z*-selectivity in this case could be explained again by possible π-allylic carbanion formation. Theoretical calculations showed a possible intermediate with the lithium atom coordinated to the allylic moiety and stabilized further by coordination to the nitrogen *N*-3 of the purine.[205] This Similarly high *Z*-selectivity of the LDA induced rearrangement was reported in a study of isomerisation of allyl ethers.[206]



Scheme 5.35 Rearrangement of the 9-allyl purines by LDA *via* π-allylic anion as a possible explanation of the *Z*-selectivity.

In summary, the examples discussed above illustrate that *E/Z* selectivity of the isomerisation could potentially be controlled. Nevertheless, the general guidelines for the *E/Z* selectivity cannot yet be concluded, since too many variable parameters in the reaction conditions were used so far. Hence, the future study of *N*-allyl purines could be focused on the influence of different bases, solvents as well as temperatures on the *E/Z* selectivity of the *N*-allyl rearrangement.

5.5 Experimental

6-Butoxy-7-(prop-1-en-1-yl)-7*H*-purine (164)

K_2CO_3 (2.24 mmol, 310 mg) and 7-allyl-6-methoxy-7*H*-purine **49e** (0.45 mmol, 85 mg) were stirred in refluxing *n*-BuOH for 4 days. The mixture was cooled down and filtered. The solvent was removed *in vacuo* and the product was isolated using flash chromatography on silica gel with gradient elution by MeOH/CH_2Cl_2 (1:32 to 1:16); yield 29 mg (24%), yellow solid. *Z*-isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, J = 7.3 Hz, 3H, CH_3 in Bu), 1.41-1.50 (m, 2H, CH_2 in Bu), 1.76-1.84 (m, 5H, CH_2 in Bu and CH_3-1), 4.51 (t, J = 6.6 Hz, 2H, OCH_2), 5.71-5.81 (m, 1H, =CH-2), 6.92 (dd, J_1 = 8.6 Hz, J_2 = 1.8 Hz, 1H, NCH-3), 8.06 (s, 1H, H-8), 8.59 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.6 (CH_3-1), 13.7 (CH_3 in Bu), 19.2 (CH_2 in Bu), 30.2 (CH_2 in Bu), 66.8 (OCH_2), 112.6 (C-5), 122.2 (=CH-2), 123.1 (NCH-3), 144.7 (C-8), 152.5 (C-2), 157.4 (C-6), 161.1 (C-4); *E*-isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (t, J = 7.2 Hz, 3H, CH_3 in Bu), 1.41-1.50 (m, 2H, CH_2 in Bu), 1.76-1.88 (m, 5H, CH_2

in Bu and CH_3-1), 4.54 (t, J = 6.6 Hz, 2H, OCH_2), 5.95-6.06 (m, 1H, =CH-2), 7.09 (dd, J_1 = 14.2 Hz, J_2 = 1.8 Hz, 1H, NCH-3), 8.19 (s, 1H, H-8), 8.57 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7 (CH_3 in Bu), 15.1 (CH_3-1), 19.2 (CH_2 in Bu), 30.7 (CH_2 in Bu), 66.8 (OCH_2), 111.9 (C-5), 118.9 (=CH-2), 123.6 (NCH-3), 142.2 (C-8), 152.3 (C-2), 157.2 (C-6), 161.4 (C-4); MS (EI) *m/z* (rel. int.) 232 (23, M^+), 202 (6), 189 (6), 176 (100), 149 (22); HRMS (EI) $C_{12}H_{16}N_4O$ requires 232.1324, found 232.1322.

7-Allyl-7*H*-purine (173)

The reaction tube was charged with $FeCO_5$ (0.51 mmol, 66 µL) and 7-Allyl-6-chloro-7*H*-purine (**49b**) (0.26 mmol, 50 mg) under inert atmosphere of glovebox. Xylenes (2.1 ml) were injected through septum on resealable cap. The cap was closed and the mixture was stirred at 138 ºC for 24 h. The resulting thick mixture was filtered through a silica pad using 15 mL MeOH/CH_2Cl_2 (1:9) as the eluent. The filtrate was concentrated *in vacuo*. The final product was isolated using flash chromatography on silica with MeOH/CH_2Cl_2 (1:9); yield 10 mg (25%), beige solid, mp 71-72 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.88 (d, J = 5.8 Hz, 2H, NCH_2), 5.31 (d, J = 17.0 Hz, 1H, H_A in =CH_2), 5.31 (d, J = 10.5 Hz, 1H, H_B in =CH_2), 6.02 (m, 1H, CH=), 8.21 (s, 1H, H-8), 8.93 (s, 1H, H-6), 9.14 (H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.6 (NCH_2), 120.5 (=CH_2), 125.3 (C-5), 130.6 (CH=), 140.2 (C-6), 147.8 (C-8), 153.4 (C-2), 161.0 (C-4); MS (EI) *m/z* (rel. int.) 160 (100, M^+), 133 (14), 160 (11), 79 (6); HRMS (EI) $C_8H_8N_4$ requires 160.0749, found 160.0751.

7-(2-Methylallyl)-7*H*-purine (174)

6-Chloro-7-(2-methylallyl)-7*H*-purine (**63a**) (0.24 mmol, 50 mg) and $FeCO_5$ (0.48 mmol, 64 µL) were added to the reaction tube under inert atmosphere of glovebox. Xylenes (1.9 ml) were added through septum on resealable cap. The cap was sealed and the mixture was stirred at 138 ºC for 24 h. The resulting thick solution was filtered through a silica pad using 15 mL MeOH/CH_2Cl_2 (1:9) as the eluent. The filtrate was concentrated *in vacuo*. The final product was isolated using flash chromatography on silica with MeOH/CH_2Cl_2 (1:9); yield 14 mg (32%), beige solid, mp 95-97 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70 (s, 3H, CH_3), 4.78 (s, 2H, NCH_2), 4.93 (s, 1H, H_A in =CH_2), 5.09 (s, 1H, H_B in =CH_2), 8.19 (s, 1H, H-8), 8.91 (s, 1H, H-6), 9.13 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.6 (CH_3), 52.4 (NCH_2), 115.7 (=CH_2), 125.4 (C-5), 138.4 (C(CH_2)CH_3), 140.3 (C-6), 148.1 (C-8), 153.4 (C-2), 160.9 (C-4); MS (EI) *m/z* (rel. int.) 174 (100, M^+), 159 (24), 133 (20), 120 (9), 106 (11); HRMS (EI) $C_9H_{10}N_4$ requires 174.0905, found 174.0902.

References:

(1) Proksch, P.; Edrada-Ebel, R.; Ebel, R. *Marine Drugs* **2003**, *1*, 5.

(2) Butler, M. S. *J. Nat. Prod.* **2004**, *67*, 2141.

(3) Costantino, V.; Fattorusso, E.; Menna, M.; Taglialatela-Scafati, O. *Curr. Med. Chem.* **2004**, *11*, 1671.

(4) Roth, B. D. *Prog. Med. Chem.* **2002**, *40*, 1.

(5) Demain, A. L.; Vaishnav, P. *Microb Biotechnol* **2011**, *4*, 687.

(6) Schumacher, M.; Kelkel, M.; Dicato, M.; Diederich, M. *Molecules* **2011**, *16*, 5629.

(7) Blunt, J. W.; Copp, B. R.; Hu, W. P.; Munro, M. H.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2009**, *26*, 170.

(8) Bergmann, W.; Feeney, R. J. *J. Org. Chem.* **1951**, *16*, 981.

(9) Hamann, M. T.; Hill, R.; Roggo, S. *Chimia* **2007**, *61*, 313.

(10) Yosief, T.; Rudi, A.; Stein, Z.; Goldberg, I.; Gravalos, G. M. D.; Schleyer, M.; Kashman, Y. *Tetrahedron Lett.* **1998**, *39*, 3323.

(11) Yosief, T.; Rudi, A.; Kashman, Y. *J. Nat. Prod.* **2000**, *63*, 299.

(12) Rudi, A.; Shalom, H.; Schleyer, M.; Benayahu, Y.; Kashman, Y. *J. Nat. Prod.* **2004**, *67*, 106.

(13) Rudi, A.; Aknin, M.; Gaydou, E.; Kashman, Y. *J. Nat. Prod.* **2004**, *67*, 1932.

(14) Rodgen, S. A.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 4929.

(15) Gordaliza, M. *Mar Drugs* **2009**, *7*, 833.

(16) Gundersen, L.-L. *Phytochem. Rev.* **2012**.

(17) Pappo, D.; Rudi, A.; Kashman, Y. *Tetrahedron Lett.* **2001**, *42*, 5941.

(18) Vik, A.; Gundersen, L.-L. *Tetrahedron Lett.* **2007**, *48*, 1931.

(19) Griengl, H.; Hayden, W.; Plessing, A. *J. Heterocycl. Chem.* **1984**, *21*, 333.

(20) Brahme, N. M.; Smith, W. T. *J. Heterocycl. Chem.* **1985**, *22*, 109.

(21) Pappo, D.; Kashman, Y. *Tetrahedron* **2003**, *59*, 6493.

(22) Pappo, D.; Shimony, S.; Kashman, Y. *J. Org. Chem.* **2005**, *70*, 199.

(23) Ohba, M.; Tashiro, T. *Heterocycles* **2002**, *57*, 1235.

(24) Lister, J. H. *The Chemistry of Heterocyclic Compounds, Fused Pyrimidines: The Purines*; Part 2, Volume 24 ed.; Wiley-Interscience, 1971; Vol. 24.

(25) Hurst, D. T. *Introduction to the Chemistry and Biochemistry of Pyrimidines, Purines and Pteridines*; John Wiley & Sons Ltd, 1980.

(26) Joule, J. A.; Mills, K. *Heterocyclic chemistry*; 4th ed.; Blackwell Publishing: Tunbgridge Wells, Kent, 2000.

(27) Eicher, T.; Hauptmann, S. *The chemistry of heterocycles: structure, reactions, synteses, and applications*; 2nd, Completely Revised, and Enlarged Edition ed.; Wiley-VCH, 2003.

(28) Rasmussen, M.; Chan, J. H.-S. *Aust. J. Chem.* **1975**, *28*, 1031.

(29) Geen, G. R.; Grinter, T. J.; Kincey, P. M.; Jarvest, R. L. *Tetrahedron* **1990**, *46*, 6903.

(30) Montgomery, J. A.; Temple, C. *J. Am. Chem. Soc.* **1961**, *83*, 630.

(31) Rasmussen, M.; Hope, J. M. *Aust. J. Chem.* **1982**, *35*, 525.

(32) Platzer, N.; Galons, H.; Bensald, Y.; Miocque, M.; Bram, G. *Tetrahedron* **1987**, *43*, 2101.

(33) Latxague, L.; Thibon, J.; Guillot, C.; Moreau, S.; Deleris, G. *Tetrahedron Lett.* **1994**, *35*, 5869.

(34) Gundersen, L.-L. *Acta Chem. Scand.* **1996**, *50*, 58.

(35) Thibon, J.; Latxague, L.; Deleris, G. *J. Org. Chem.* **1997**, *62*, 4635.

(36) Tobrman, T.; Štěpnička, P.; Císařová, I.; Dvořák, D. *Eur. J. Org. Chem.* **2008**, *2008*, 2167.

(37) Amblard, F.; Nolan, S. P.; Gillaizeau, I.; Agrofoglio, L. A. *Tetrahedron Lett.* **2003**, *44*, 9177.

(38) Gundersen, L.-L.; Benneche, T.; Rise, F.; Gogoll, A.; Undheim, K.; Wang, D.-N.; Christensen, S. B. *Acta Chem. Scand.* **1992**, *46*, 761.

(39) Lu, W.; Sengupta, S.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. *J. Org. Chem.* **2007**, *72*, 5012.

(40) Jones, J. W.; Robins, R. K. *J. Am. Chem. Soc.* **1962**, *84*, 1914.

(41) Pal, B. C. *Biochemistry* **1962**, *1*, 558.

(42) Montgomery, J.; Thomas, J. *J. Heterocycl. Chem.* **1964**, *1*, 115.

(43) Fujii, T.; Walker, G. C.; Leonard, N. J. *J. Med. Chem.* **1979**, *22*, 125.

(44) Baker, B. R.; Schaub, R. E.; Joseph, J. P. *J. Org. Chem.* **1954**, *19*, 638.

(45) Baker, B. R.; Joseph, J. P.; Schaub, R. E.; Williams, J. H. *J. Org. Chem.* **1954**, *19*, 1780.

(46) Blackburn, G. M.; Johnson, A. W. *J. Chem. Soc.* **1960**, 4347.

(47) Townsend, L. B.; Robins, R. K.; Loeppky, R. N.; Leonard, N. J. *J. Am. Chem. Soc.* **1964**, *86*, 5320.

(48) Tanabe, T.; Yamauchi, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 259.
(49) Litinas, K. E.; Thalassitis, A. *Tetrahedron Lett.* **2010**, *51*, 6451.
(50) Leonard, N. J.; Deyrup, J. A. *J. Am. Chem. Soc.* **1962**, *84*, 2148.
(51) Montgomery, J.; Thomas, J. *J. Org. Chem.* **1965**, *30*, 3235.
(52) Dalby, C.; Bleaksdale, C.; Clegg, W.; Elsegood, M. R. J.; Golding, B. T.; Griffin, R. J. *Angew. Chem., Int. Ed. Engl.* **1993**, *105*, 1822.
(53) Vik, A.; Hedner, E.; Charnock, C.; Tangen, L. W.; Samuelsen, O.; Larsson, R.; Bohlin, L.; Gundersen, L.-L. *Bioorg. Med. Chem.* **2007**, *15*, 4016.
(54) Buehler, S.; Schollmeyer, D.; Hauser, D.; Laufer, S.; Peifer, C. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2007**, *63*, O4646.
(55) Peifer, C.; Buhler, S.; Hauser, D.; Kinkel, K.; Totzke, F.; Schachtele, C.; Laufer, S. *Eur. J. Med. Chem.* **2009**, *44*, 1788.
(56) Read, M. L.; Krapp, A.; Miranda, P. O.; Gundersen, L.-L. *Tetrahedron* **2012**, *68*, 1869.
(57) Kotek, V.; Chudikova, N.; Tobrman, T.; Dvorak, D. *Org. Lett.* **2010**, *12*, 5724.
(58) Kotek, V.; Tobrman, T.; Dvořák, D. *Synthesis* **2012**, *44*, 610.
(59) Bendich, A.; Russell, P. J.; Fox, J. J. *J. Am. Chem. Soc.* **1954**, *76*, 6073.
(60) Wang, Y. H., Wei-Sheng; Sundaramoorthi, Rajeswari; Zhu, Xioatian; Thomas, R. Matthew; Shakespeare, William C.; Dalgarno, David C.; Sawyer, Tomi K. In *PCT Int. Appl. 68 pp. Patent 2007 CODEN:PIXXD2*; C07F 9/6512 (2006.01) ed. 2007; Vol. WO 2007021937 A2.
(61) Siah, H.-S. M.; Gundersen, L.-L. *Synth. Commun.* **2012**, In press.
(62) Siah, H. S.; Gorbitz, C. H.; Gundersen, L.-L. *J. Heterocycl. Chem.* **2011**, *48*, 1375.
(63) García-Mera, X.; Alonso, N.; Caamaño, O.; Fernández, F.; Morales, M.; Rodríguez-Borges, J.; De Clercq, E. *Synthesis* **2008**, *2008*, 1845.
(64) Aguado, L.; Thibaut, H. J.; Priego, E. M.; Jimeno, M. L.; Camarasa, M. J.; Neyts, J.; Perez-Perez, M. J. *J. Med. Chem.* **2010**, *53*, 316.
(65) Braendvang, M.; Gundersen, L.-L. *Bioorg. Med. Chem.* **2007**, *15*, 7144.
(66) Gundersen, L.-L.; Bakkestuen, A. K.; Aasen, A. J.; Overås, H.; Rise, F. *Tetrahedron* **1994**, *50*, 9743.
(67) Okamura, T.; Kikuchi, T.; Fukushi, K.; Irie, T. *J. Med. Chem.* **2009**, *52*, 7284.
(68) Zhang, L.; Fan, J.; Vu, K.; Hong, K.; Le Brazidec, J. Y.; Shi, J.; Biamonte, M.; Busch, D. J.; Lough, R. E.; Grecko, R.; Ran, Y.; Sensintaffar, J. L.; Kamal, A.;

Lundgren, K.; Burrows, F. J.; Mansfield, R.; Timony, G. A.; Ulm, E. H.; Kasibhatla, S. R.; Boehm, M. F. *J. Med. Chem.* **2006**, *49*, 5352.

(69) Schrauzer, G. *Inorg. Synth.* **1968**, *11*, 61.

(70) Crey-Desbiolles, C.; Kotera, M. *Bioorg. Med. Chem.* **2006**, *14*, 1935.

(71) Rudi, A.; Aknin, M.; Gaydou, E.; Kashman, Y. *J. Nat. Prod.* **2004**, *67*, 1932.

(72) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH, 2003; Vol. 1.

(73) Compain, P. *Adv. Synth. Catal.* **2007**, *349*, 1829.

(74) Phillips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999**, *32*, 75.

(75) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117.

(76) van Otterlo, W. A.; de Koning, C. B. *Chem Rev* **2009**, *109*, 3743.

(77) Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P. D.; Greene, B.; Yusuff, N.; Wood, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16300.

(78) Ettari, R.; Micale, N. *J. Organomet. Chem.* **2007**, *692*, 3574.

(79) Wang, H. *Tetrahedron* **2009**, *65*, 6291.

(80) Schrock, R. R.; Czekelius, C. *Adv. Synth. Catal.* **2007**, *349*, 55.

(81) Woodward, C. P.; Spiccia, N. D.; Jackson, W. R.; Robinson, A. J. *Chem. Commun. (Cambridge, U. K.)* **2011**, *47*, 779.

(82) Rutjes, F. P. J. T.; Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677.

(83) Maier, M. E.; Lapeva, T. *Synlett* **1998**, *1998*, 891.

(84) Zhong-Yong Wei, E. E. K. *Synthesis* **1994**, 1463.

(85) Albeck, A.; Persky, R. *J. Org. Chem.* **1994**, *59*, 653.

(86) Kanie, K.; Mizuno, K.; Kuroboshi, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1973.

(87) Cosyn, L.; Gao, Z.-G.; Van Rompaey, P.; Lu, C.; Van Calenbergh, S. *Bioorg. Med. Chem.* **2006**, *14*, 1403.

(88) Zincke, T. *Liebigs Ann. Chem.* **1904**, *330*, 361.

(89) Zincke, T.; Heuser, G.; Moller, W. *Liebigs Ann. Chem.* **1904**, *333*, 296.

(90) Marvell, E. N.; Caple, G.; Shahidi, T. *J. Am. Chem. Soc.* **1970**, *92*, 5641.

(91) Ise, N.; Okubo, T.; Kitano, H.; Kunugi, S. *J. Am. Chem. Soc.* **1975**, *97*, 2882.

(92) Kunugi, S.; Okubo, T.; Ise, N. *J. Am. Chem. Soc.* **1976**, *98*, 2282.

(93) Vanderwal, C. D. *J. Org. Chem.* **2011**, *76*, 9555.

(94) Bredereck, H.; Christmann, O.; Graudums, I.; Koser, W. *Angew. Chem.* **1960** *72*, 708.

(95) Skalski, B.; Wenska, G.; Gdaniec, Z.; Adamiak, R. W. *Tetrahedron* **1993**, *49*, 5859.

(96) Schmidt, A.; Kindermann, M. K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2379.

(97) De Napoli, L.; Montesarchio, D.; Piccialli, G.; Santacroce, C.; Varra, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 15.

(98) Crich, D.; Suk, D. H.; Hao, X. L. *Tetrahedron* **2002**, *58*, 5789.

(99) Ishibashi, K.; Tsue, H.; Takahashi, H.; Tamura, R. *Tetrahedron: Asymmetry* **2009**, *20*, 375.

(100) Varala, R.; Nuvula, S.; Adapa, S. R. *J. Org. Chem.* **2006**, *71*, 8283.

(101) Raju, M.; Maeorg, S.; Tsubrik, O.; Maeorg, U. *Arkivoc* **2009**, *2009*, 291.

(102) Appukkuttan, P.; Dehaen, W.; Van der Eycken, E. *Chemistry* **2007**, *13*, 6452.

(103) Cornella, J.; Lu, P.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506.

(104) Bao, C.; Gan, Q.; Kauffmann, B.; Jiang, H.; Huc, I. *Chemistry* **2009**, *15*, 11530.

(105) Krein, D. M.; Lowary, T. L. *J. Org. Chem.* **2002**, *67*, 4965.

(106) Kuo, G.-H.; DeAngelis, A.; Emanuel, S.; Wang, A.; Zhang, Y.; Connolly, P. J.; Chen, X.; Gruninger, R. H.; Rugg, C.; Fuentes-Pesquera, A.; Middleton, S. A.; Jolliffe, L.; Murray, W. *J. Med. Chem.* **2005**, *48*, 4535.

(107) Montebugnoli, D.; Bravo, P.; Corradi, E.; Dettori, G.; Mioskowski, C.; Volonterio, A.; Wagner, A.; Zanda, M. *Tetrahedron* **2002**, *58*, 2147.

(108) Zanda, M.; Talaga, P.; Wagner, A.; Moiskowski, C. *Tetrahedron Lett.* **2000**, *41*, 1757.

(109) Piguel, S.; Legraverend, M. *J. Org. Chem.* **2007**, *72*, 7026.

(110) Tasler, S.; Mies, J.; Lang, M. *Adv. Synth. Catal.* **2007**, *349*, 2286.

(111) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805.

(112) G. Frost, C.; Mendonca, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2615.

(113) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575.

(114) Dallas, A. S.; Gothelf, K. V. *J. Org. Chem.* **2005**, *70*, 3321.

(115) Audisio, D.; Messaoudi, S.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. *Tetrahedron Lett.* **2007**, *48*, 6928.

(116) Ibrahim, N.; Mouawad, L.; Legraverend, M. *Eur. J. Med. Chem.* **2010**, *45*, 3389.

(117) Ibrahim, N.; Legraverend, M. *J. Comb. Chem.* **2009**, *11*, 658.

(118) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(119) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

(120) Deng, W.; Wang, Y.-F.; Zou, Y.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2004**, *45*, 2311.

(121) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.

(122) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120.

(123) Enguehard-Gueiffier, C.; Thery, I.; Gueiffier, A.; Buchwald, S. L. *Tetrahedron* **2006**, *62*, 6042.

(124) Crawford, K. R.; Padwa, A. *Tetrahedron Lett.* **2002**, *43*, 7365.

(125) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973.

(126) Tumkevicius, S.; Masevicius, V. *Synthesis* **2007**, *2007*, 3815.

(127) Tanji, K.-I.; Higashino, T. *Chem. Pharm. Bull.* **1988**, *36*, 1935.

(128) Elion, G. B.; Hitchings, G. H. *J. Am. Chem. Soc.* **1956**, *78*, 3508.

(129) Montgomery, J.; Thomas, H. J. *J. Org. Chem.* **1965**, *30*, 3235.

(130) Krompiec, S.; Krompiec, M.; Penczek, R.; Ignasiak, H. *Coord. Chem. Rev.* **2008**, *252*, 1819.

(131) Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139.

(132) Delogu, G.; Faedda, G.; Gladiali, S. *J. Organomet. Chem.* **1984**, *268*, 167.

(133) Krompiec, S.; Suwinsky, J. *Pol. J. Chem.* **1990**, *64*, 505.

(134) Kamijo, S.; Huo, Z.; Jin, T.; Kanazawa, C.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 6389.

(135) Alcaide, B.; Almendros, P.; Alonso, J. M. *Chemistry* **2006**, *12*, 2874.

(136) Dhami, A.; Mahon, M. F.; Lloyd, M. D.; Threadgill, M. D. *Tetrahedron* **2009**, *65*, 4751.

(137) Krompiec, S.; Pigulla, M.; Szczepankiewicz, W.; Bieg, T.; Kuznik, N.; Leszczynska-Sejda, K.; Kubicki, M.; Borowiak, T. *Tetrahedron Lett.* **2001**, *42*, 7095.

(138) Krompiec, S.; Pigulla, M.; Bieg, T.; Szczepankiewicz, W.; Kuznik, N.; Krompiec, M.; Kubicki, M. *J. Mol. Catal. A: Chem.* **2002**, *189*, 169.

(139) Krompiec, S.; Bujak, P.; Szczepankiewicz, W. *Tetrahedron Lett.* **2008**, *49*, 6071.

(140) Bujak, P.; Krompiec, S.; Malarz, J.; Krompiec, M.; Filapek, M.; Danikiewicz, W.; Kania, M.; Gębarowska, K.; Grudzka, I. *Tetrahedron* **2010**, *66*, 5972.

(141) Im, G. Y.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2010**, *132*, 17933.

(142) Cadot, C.; Dalko, P. I.; Cossy, J. *Tetrahedron Lett.* **2002**, *43*, 1839.

(143) Hanessian, S.; Giroux, S.; Larsson, A. *Org. Lett.* **2006**, *8*, 5481.

(144) Smith, A. B., 3rd; Kurti, L.; Davulcu, A. H.; Cho, Y. S.; Ohmoto, K. *J. Org. Chem.* **2007**, *72*, 4611.

(145) Ullmann, F.; Ullmann *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382.

(146) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803.

(147) Rosillo, M.; Dominguez, G.; Casarrubios, L.; Amador, U.; Perez-Castells, J. *J. Org. Chem.* **2004**, *69*, 2084.

(148) Efskind, J.; Römming, C.; Undheim, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2697.

(149) Lopez, M. D.; Quijano, M. L.; Sanchez, A.; Nogueras, M. *J. Heterocycl. Chem.* **2001**, *38*, 727.

(150) Gille, S.; Ferry, A.; Billard, T.; Langlois, B. R. *J. Org. Chem.* **2003**, *68*, 8932.

(151) Kamal, A.; Shaik, A. A.; Sandbhor, M.; Malik, M. S.; Azeeza, S. *Tetrahedron: Asymmetry* **2006**, *17*, 2876.

(152) Lahiri, R.; Kokatla, H. P.; Vankar, Y. D. *Tetrahedron Lett.* **2011**, *52*, 781.

(153) Koh, Y. H.; Shim, J. H.; Girardet, J. L.; Hong, Z. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5261.

(154) Peifer, M.; De Giacomo, F.; Schandl, M.; Vasella, A. *Helv. Chim. Acta* **2009**, *92*, 1134.

(155) Bell, M. G.; Gernert, D. L.; Grese, T. A.; Belvo, M. D.; Borromeo, P. S.; Kelley, S. A.; Kennedy, J. H.; Kolis, S. P.; Lander, P. A.; Richey, R.; Sharp, V. S.; Stephenson, G. A.; Williams, J. D.; Yu, H.; Zimmerman, K. M.; Steinberg, M. I.; Jadhav, P. K. *J. Med. Chem.* **2007**, *50*, 6443.

(156) Watkins, B. E.; Kiely, J. S.; Rapoport, H. *J. Am. Chem. Soc.* **1982**, *104*, 5702.

(157) Liu, F.; Austin, D. J. *Org. Lett.* **2001**, *3*, 2273.

(158) Grapsas, I.; Mobashery, S. *1-(t-Butoxycarbonyl)imidazole e-EROS Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd. Chichester, UK, 2001.

(159) *e-EROS Encyclopedia of Reagents for Organic Synthesis*; by John Wiley & Sons, Ltd. All rights reserved., 2010.

(160) Theeraladanon, C.; Arisawa, M.; Nishida, A.; Nakagawa, M. *Tetrahedron* **2004**, *60*, 3017.

(161) Clavier, H.; Caijo, F.; Borré, E.; Rix, D.; Boeda, F.; Nolan, S. P.; Mauduit, M. *Eur. J. Org. Chem.* **2009**, *2009*, 4254.

(162) Vo Thanh, G.; Loupy, A. *Tetrahedron Lett.* **2003**, *44*, 9091.

(163) Ascic, E.; Le Quement, S. T.; Ishoey, M.; Daugaard, M.; Nielsen, T. E. *ACS Comb. Sci.* **2012**, *14*, 253.

(164) Yang, Q.; Xiao, W. J.; Yu, Z. *Org. Lett.* **2005**, *7*, 871.

(165) Dolman, S. J.; Schrock, R. R.; Hoveyda, A. H. *Org. Lett.* **2003**, *5*, 4899.

(166) Sharma, G. V. M.; Reddy, J. J.; Lakshmi, P. S.; Krishna, P. R. *Tetrahedron Lett.* **2004**, *45*, 6963.

(167) Takemoto, K.; Kawakubo, F.; Kondo, K. *Makromol. Chem.* **1971**, *148*, 131.

(168) Pitha, J. *J. Org. Chem.* **1975**, *40*, 3296.

(169) Farshadi, A.; Ramazani, A.; Mahyari, A. T.; Khoobi, M.; Ahmadi, Y.; Nasrabadi, F. Z. *Phosphorus, Sulfur Silicon Relat. Elem.* **2010**, *185*, 2489.

(170) Joshi, R. V.; Xu, Z.-Q.; Ksebati, M. B.; Kessel, D.; Corbett, T. H.; Drach, J. C.; Zemlicka, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1089.

(171) Jacobsen, M. F.; Knudsen, M. M.; Gothelf, K. V. *J. Org. Chem.* **2006**, *71*, 9183.

(172) Johnson, F.; Pillai, K. M. R.; Grollman, A. P.; Tseng, L.; Takeshita, M. *J. Med. Chem.* **1984**, *27*, 954.

(173) Lazrek, H. B.; Khaider, H.; Rochdi, A.; Barascut, J. L.; Imbach, J. L. *Tetrahedron Lett.* **1996**, *37*, 4701.

(174) Lazrek, H. B.; Rochdi, A.; Khaider, H.; Barascut, J. L.; Imbach, J. L.; Balzarini, J.; Witvrouw, M.; Pannecouque, C.; De Clercq, E. *Tetrahedron* **1998**, *54*, 3807.

(175) Jokić, M.; Škarić, V. *Tetrahedron Lett.* **1994**, *35*, 2937.

(176) Ciapetti, P.; Taddei, M. *Tetrahedron* **1998**, *54*, 11305.

(177) Ivanov, A. V.; Andronova, V. L.; Galegov, G. A.; Jasko, M. V. *Russ. J. Bioorg. Chem.* **2005**, *31*, 58.

(178) Boesen, T.; Madsen, C.; Henriksen, U.; Dahl, O. *J. Chem. Soc., Perkin Trans.1* **2000**, 2015.

(179) Huang, W. S.; Zhu, X.; Wang, Y.; Azam, M.; Wen, D.; Sundaramoorthi, R.; Thomas, R. M.; Liu, S.; Banda, G.; Lentini, S. P.; Das, S.; Xu, Q.; Keats, J.; Wang, F.; Wardwell, S.; Ning, Y.; Snodgrass, J. T.; Broudy, M. I.; Russian, K.; Daley, G. Q.; Iuliucci, J.; Dalgarno, D. C.; Clackson, T.; Sawyer, T. K.; Shakespeare, W. C. *J. Med. Chem.* **2009**, *52*, 4743.

(180) Doláková, P.; Masojídková, M.; Holý, A. *Nucleosides, Nucleotides Nucleic Acids* **2003**, *22*, 2145.

(181) Gharbaoui, T.; Legraverend, M.; Bisagni, E. *Tetrahedron Lett.* **1992**, *33*, 7141.

(182) Phadtare, S.; Zemlicka, J. *Tetrahedron Lett.* **1990**, *31*, 43.

(183) Phadtare, S.; Kessel, D.; Corbett, T. H.; Renis, H. E.; Court, B. E.; Zemlicka, J. *J. Med. Chem.* **1991**, *34*, 421.

(184) Ryu, K.; Kim, N. D.; Choi, S. I.; Han, C. K.; Yoon, J. H.; No, K. T.; Kim, K. H.; Seong, B. L. *Bioorg. Med. Chem.* **2009**, *17*, 2975.

(185) Wang, Y.; Shakespeare, W. C.; Huang, W. S.; Sundaramoorthi, R.; Lentini, S.; Das, S.; Liu, S.; Banda, G.; Wen, D.; Zhu, X.; Xu, Q.; Keats, J.; Wang, F.; Wardwell, S.; Ning, Y.; Snodgrass, J. T.; Broudy, M. I.; Russian, K.; Dalgarno, D.; Clackson, T.; Sawyer, T. K. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4907.

(186) Guibé, F. *Tetrahedron* **1997**, *53*, 13509.

(187) van Otterlo, W. A. L.; Morgans, G. L.; Khanye, S. D.; Aderibigbe, B. A. A.; Michael, J. P.; Billing, D. G. *Tetrahedron Lett.* **2004**, *45*, 9171.

(188) Yadav, D. B.; Morgans, G. L.; Aderibigbe, B. A.; Madeley, L. G.; Fernandes, M. A.; Michael, J. P.; de Koning, C. B.; van Otterlo, W. A. L. *Tetrahedron* **2011**, *67*, 2991.

(189) Cram, D. J.; Uyeda, R. T. *J. Am. Chem. Soc.* **1962**, *84*, 4358.

(190) Bank, S.; Rowe, C. A.; Schriesheim, A. *J. Am. Chem. Soc.* **1963**, *85*, 2115.

(191) Price, C. C.; Snyder, W. H. *J. Am. Chem. Soc.* **1961**, *83*, 1773.

(192) Hubert, A. J.; Georis, A.; Warin, R.; Teyssié, P. *J. Chem. Soc., Perkin Trans. 2* **1972**, 366.

(193) Yokoyama, S.-y.; Tanaka, K.-i.; Haneda, H. *J. Chem. Soc., Chem. Commun.* **1982**, 820.

(194) Cram, D., J. *Fundamentals of Carbanion Chemistry*; Academic Press, Inc., New York: New York, 1965.

(195) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev. (Washington, DC, U. S.)* **1998**, *98*, 2599.

(196) Krompiec, S.; Pigulla, M.; Krompiec, M.; Marciniec, B.; Chadyniak, D. *J. Mol. Catal. A: Chem.* **2005**, *237*, 17.

(197) Krompiec, S.; Kuźnik, N.; Krompiec, M.; Penczek, R.; Mrzigod, J.; Tórz, A. *J. Mol. Catal. A: Chem.* **2006**, *253*, 132.

(198) Hendrix, W. T.; Cowherd, F. G.; von Rosenberg, J. L. *Chem. Commun.* **1968**, 97.

(199) Murdoch, H.; Weiss, E. *Helv. Chim. Acta* **1963**, *46*, 1588.

(200) Sergeyev, S.; Hesse, M. *Synlett* **2002**, 1313.

(201) Usieli, V.; Gronowitz, S.; Andersson, I. *J. Organomet. Chem.* **1979**, *165*, 357.

(202) Hashiba, S.; Fuchigami, T.; Nonaka, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2424.

(203) Brunet, J.-J.; Taillefer, M. *J. Organomet. Chem.* **1988**, *348*, C5.

(204) Lim, F. S. P. *Functionalization of the purine 8-position via 8-purinyl anions; scopes and limitations with respect to substituents at N9*; Universitetet i Oslo: Oslo, 2011.

(205) Marzouk, V. H. R.; Hennum, M.; Gundersen, L.-L. *manuscript under preparation*.

(206) Su, C.; Williard, P. G. *Org. Lett.* **2010**, *12*, 5378.

Appendix 1