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Evolution of Diamination : from Intra- to Intermolecular Version

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List of Abbreviations

Å	:	angstrom(s)
Ac	:	acetyl
Aq	:	aqueous
Ar	:	aryl
Bn	:	benzyl
BOC, Boc	:	<i>tert</i> -butoxycarbonyl
br	:	broad (spectral)
Bu, <i>n</i> -Bu	:	normal (primary) butyl
<i>t</i> -Bu	:	<i>tert</i> -butyl
calcd	:	calculated
cat	:	catalytic
CBZ, Cbz	:	benzyloxycarbonyl
CIF	:	crystallographic information file
compd	:	compound
Cy	:	cyclohexyl
δ	:	Chemical shift in parts per million
d	:	day(s), doublet (spectral)
<i>d</i>	:	density
DCM	:	dichloromethane
DIBALH	:	diisobutylaluminium hydride
DMAP	:	4-(<i>N,N</i> -dimethylamino) pyridine
DMF	:	dimethylformamide
dr	:	diastereomer ratio
EI	:	electron impact
equiv	:	equivalent
er	:	enantiomer ratio
ESI	:	electrospray ionization
Et	:	ethyl
h	:	hour(s)

HPLC	:	high-performance liquid chromatography
HRMS	:	high-resolution mass spectrometry
Hz	:	hertz
IR	:	infrared
<i>J</i>	:	coupling constant
L	:	liter(s)
LAH	:	lithium aluminium hydride
LDA	:	lithium diisopropylamide
μ	:	micro
m	:	multiplet (spectral); milli
M	:	molar (moles per liter)
MALDI	:	matrix-assisted laser desorption ionization
Me	:	methyl
Mes	:	2,4,6-trimethylphenyl (mesityl)
min	:	minute(s)
mmol	:	millimole(s)
mol	:	mole(s)
mp	:	melting point
Ms	:	methylsulfonyl (mesyl)
MS	:	mass spectrometry
N	:	normal (equivalents per liter)
NBS	:	<i>N</i> -bromosuccinimide
NMR	:	nuclear magnetic resonance
Nu	:	nucleophile
Ph	:	phenyl
Piv	:	pivaloyl
ppm	:	part(s) per million
Pr	:	propyl
<i>i</i> -Pr	:	iso-propyl
py	:	pyridine
RCM	:	ring closure metathesis
ROMP	:	ring-opening metathesis polymerisation
rt	:	room temperature
s	:	singlet (spectral)

S _N 1	:	unimolecular nucleophilic substitution
S _N 2	:	bimolecular nucleophilic substitution
t	:	triplet (spectral)
TBDPS	:	<i>tert</i> -butyldiphenylsilyl
TFA	:	trifluoroacetic acid
THF	:	tetrahydrofuran
TMS	:	trimethylsilyl
TLC	:	thin-layer chromatography
Ts	:	<i>para</i> -toluenesulfonyl

Preface:

Diamines are omnipresent in chemistry. We find them in a number of natural products with biological activity and in many important pharmaceutical agents. Even simple diamines and polyamines play key role in natural process. For example 1,4-diaminobutane (**P-1**) (putrescine) was recognised as an important natural polyamine, and together with its derivatives, cadaverine (**P-2**), spermine (**P-3**) and spermidine (**P-4**), became part of a group of substances deeply involved in cell proliferation, in vivo protein synthesis, programmed cell death, tumor prevention and antiviral activities. ^[1, 2]

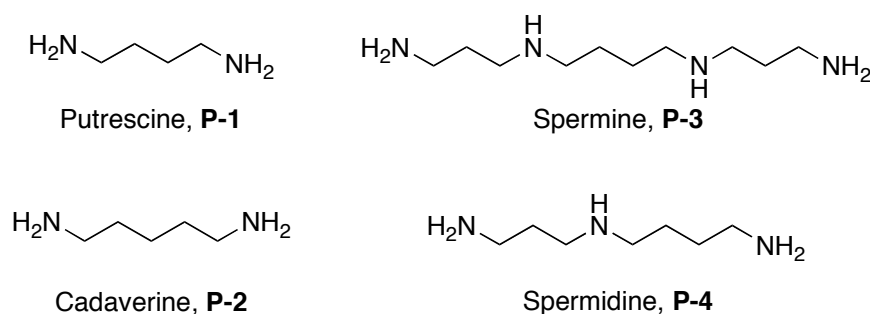


Figure 1. Simple diamines and polyamines with biological activities.

But the importance of diamines extends significantly beyond their role in natural products and pharmaceutical agents since they have also been proven to be invaluable scaffolds for the construction of novel ligands.^[3-9] Chiral diamines, for example, are often used as the control elements in asymmetric synthesis and catalysis. Such compounds are thus an attractive target for the synthetic chemist.

Although the diamination of an alkene seems an obvious route to these structures, far less research has been devoted to it than to the analogous dihydroxylation or aminohydroxylation reactions that are well-established processes in asymmetric synthesis.

In this dissertation we will focus on the development of new approaches to 1,2- and 1,4-diamines, starting with the evolution of the catalytic synthesis of vicinal diamines.

In the following introduction a brief theoretical background will be given on the ubiquity of diamines in nature, their importance to science and modern applications as well as the history of the synthesis of diamines via classical procedures that have been developed.

INTRODUCTION

1. Why such an interest in diamines ?

1.1. On the presence of diamines in Nature

1,2-Diamino carboxylic acids are widely distributed in nature, they can be found either in their native state or as components of more complex products (Figure 2).^[10, 11] Since they do not appear in proteins, they are classified as non-proteinogenic aminoacids. Starting with the simplest members of this family: 2,3-diaminopropionic (L-Dpr, **I-1**) and 2,3-diaminobutanoic (L-Dab, **I-2**) acid, they are found in compositions of antibiotics such as bleomycin,^[12] but have also been isolated from the Murchison meteorite, an extra-terrestrial source. The isolation of **I-1** and **I-2** from this meteorite led to the conclusion that they may have participated in the formation of the peptide nucleic acid material on earth,^[13] which underlines the importance of 1,2-diamines.

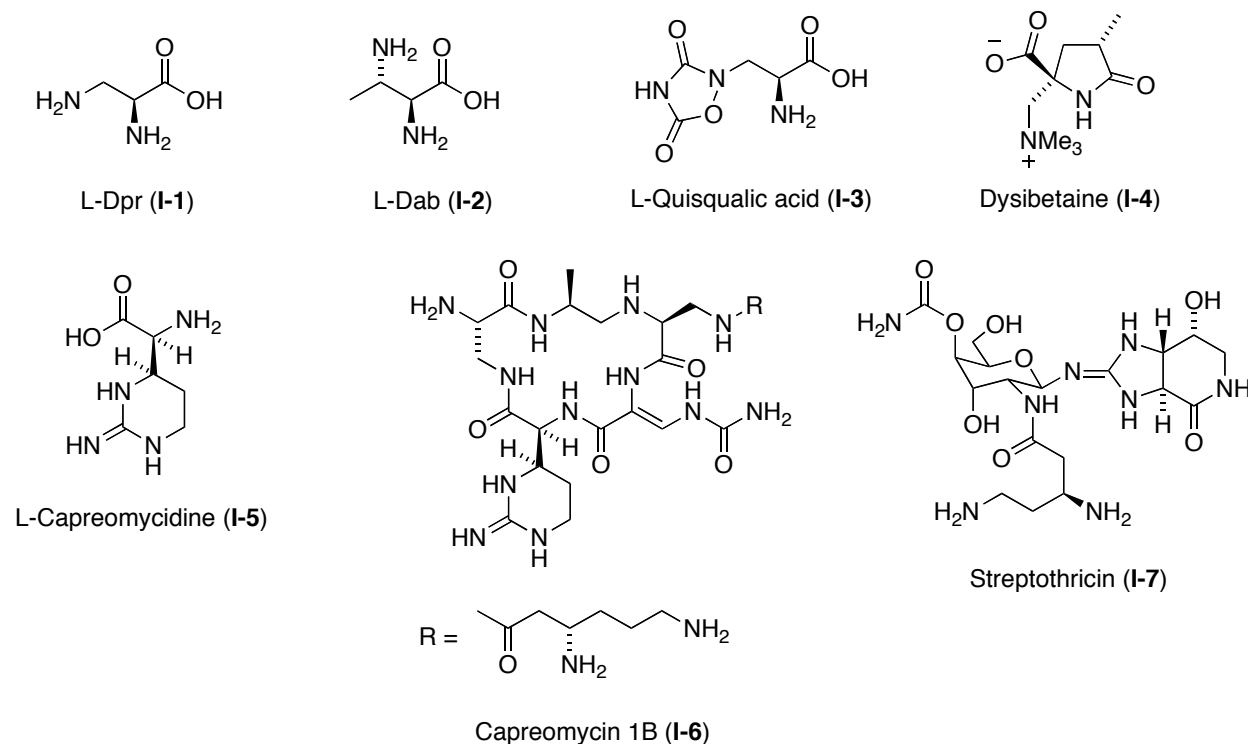


Figure 2. Naturally occurring non-proteinogenic 1,2-diamino acids and their derivatives.

The major interest in 1,2-diamino acids stems from their role as excitatory amino acids (EAA). EAA receptors are widely distributed in the mammalian central nervous system

(CNS) and are directly implicated in such disorders as Alzheimer's disease, epilepsy and parkinsonism^[14] L-quisqualic acid (**I-3**), for example, is a potent agonist of EAA receptors and dysibetaine (**I-4**), an amino acid isolated from a marine sponge, is also a neurotoxin, which may bind to receptors present in the CNS.^[15]

L-Capreomycinidine (**I-5**), is a key structural subunit of capreomycin 1B (**I-6**),^[16] which is a peptide antibiotic for MRD-tuberculosis. Its β -epimer is found in a natural products that inhibit the peptidoglycan biosynthesis of *staphylococcus aureus*.^[17] Another important example is the well known broad spectrum antibiotic streptothricin (**I-7**).^[18]

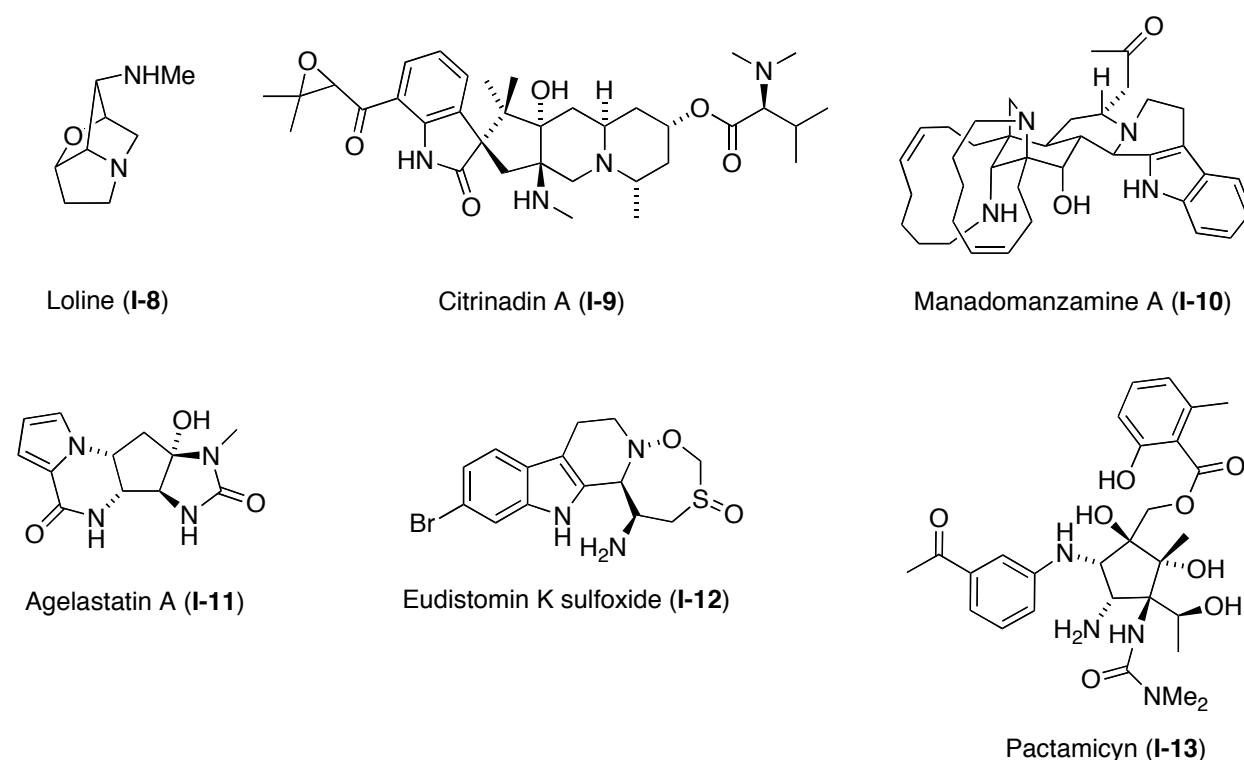


Figure 3. A representative selection of naturally occurring alkaloids that encompass the 1,2-diamine framework.

Leaving the amino acids, many alkaloid natural products contain the diamine motif too, and its presence is often linked to significant biological activity. It goes from simple systems like the pyrrolizidine alkaloid loline (**I-8**),^[19-21] to the pentacycle citrinadin A (**I-9**)^[22, 23] and its derivatives, a group of histamine H3 receptors agonists.^[24] Marine organisms are also a rich source of diamines, including the anti-tuberculosis agent manadomanzamine A (**I-10**),^[25, 26] the antineoplastic agent agelastatin A (**I-11**),^[27, 28] and eudistomin-K sulfoxide (**I-12**),^[29, 30] which acts against both RNA and DNA viruses.

The biological properties of alkaloids explain why they are such interesting challenges in total synthesis. For example, pactamycin (**I-13**) has recently been synthesised^[31] and others including manadomanzamine A (**I-10**), remain unassailed and, as such, offer unique challenges for the development of new diamination methods.

1.2. Diamines in pharmaceutical agents

Diamines are found in a lot of synthetic pharmacological tools, including several clinically approved drugs.^[32] The list includes antiarrhythmics, antidepressant agents, antihypertensives, antipsychotics, analgesics, antianxiety agents, anticancer drugs, antiparasitic agents and can be arbitrarily extended.^[33]

Concerning, for example the anti-microbials, the ethambutol analog SQ109 (**I-14**) can be cited,^[34] it possesses activity against tuberculosis. An to other one, the viral neuraminidase inhibitor oseltamivir (**I-15**),^[35] is employed for the treatment of influenza virus A and B infections.

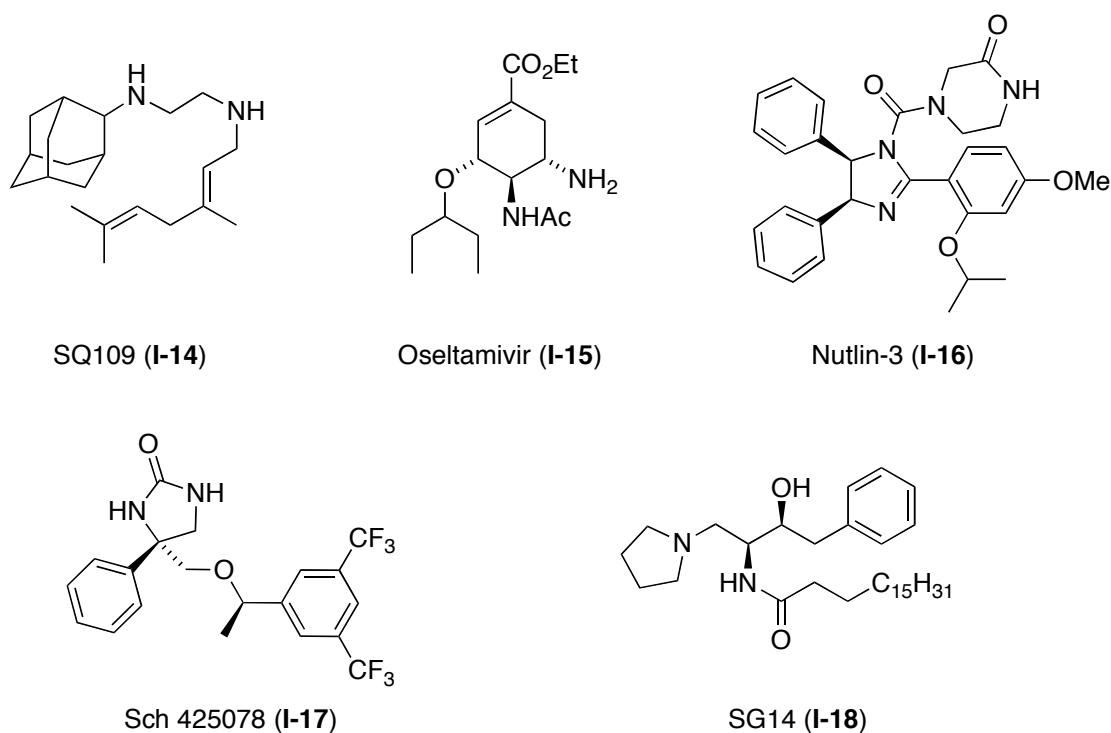


Figure 4. Pharmaceutically active, synthetic and semi-synthetic diamines.

In addition to anti-infectives, we could cite anti-proliferative agents such as the nutlin-3 (**I-16**)^[36] or the anti-emetic agent and NK1-antagonist Sch 425078 (**I-17**)^[37] and much more.

With regards to semi-synthetic pharmaceutical agents, the incorporation of vicinal diamine framework into some natural products has proven to have significant impact on the biological activity of these molecules.^[38] It is for example the case of the 1-amino-1-deoxy sphingoid analog (**I-18**), which is an emerging target for cancer therapeutics.^[39]

Speaking about cancer therapeutics, it should be remarked that diamines complexes with transition metals find unique application in the treatment of cancer. The initial success of “cis-platinum” (**I-19**), founded a whole research area on diamine ligands with anti-tumor properties (Figure 5). Other metals have been found as well to furnish diamine complexes of high pharmacophoric nature. For example, technecium complexes of diamines with attached anti-bodies (**I-20**) have been established as radiopharmaceutical markers, imaging agent and tools for radioactivity delivery. Also copper complexes of recently developed diamine-based ligands (**I-21**) are potential anti-cancer agents since they were found to selectively coordinate DNA strains and cleave them under oxidative conditions. They could emerge as important tools for DNA targeting.^[40]

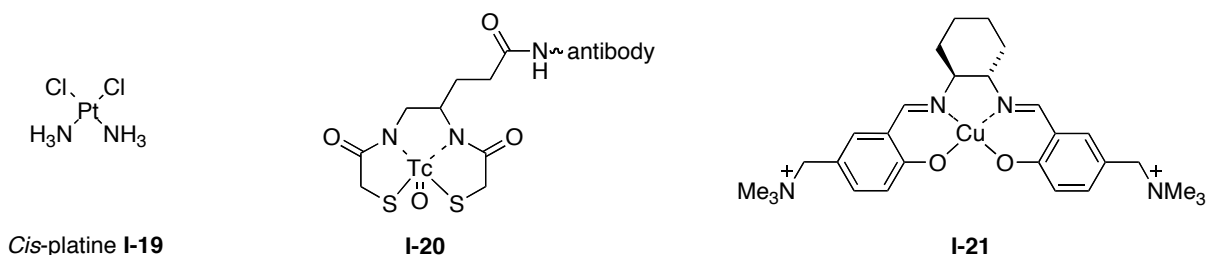


Figure 5. Organometallic clinical agents derived from diamines.

But, as mentioned previously, the importance of diamines is not limited to their role in natural product or pharmaceutical agents. They are also present in the construction of novel metal ligands, in organocatalysts, in chiral reagents and in organic receptors. Although excellent and very detailed reviews on diamines in asymmetric catalysis exist,^[8, 41, 42] a brief overview about the most important catalytic applications should be given in the context of this Thesis.

1.3. Diamines in asymmetric catalysis

1.3.1. *N*-Heterocyclic carbenes

N-Heterocyclic carbenes are mostly derivated from vicinal diamines and have found wide applications in methodology due to their robustness against moisture and air. They have been originally proposed in 1957 by Breslow.^[43] The first isolation of a stable carbene derivative was achieved in 1989 by Bertrand et al^[44, 45] and then in 1991 by Arduengo. The structure of the latter was the first stable *N*-heterocyclic carbene, which was characterised by X-ray analysis.^[46] Since then, these carbenes have emerged as important tools for organometallic chemistry and catalysis (Figure 6).^[47-49] The most famous application of such carbenes remains the metathesis catalysts by Grubbs (**I-22**) and Hoveyda (**I-23**).^[50] In addition, more and more organocatalytic reactions that are catalysed by a carbene itself have been published.^[51, 52]

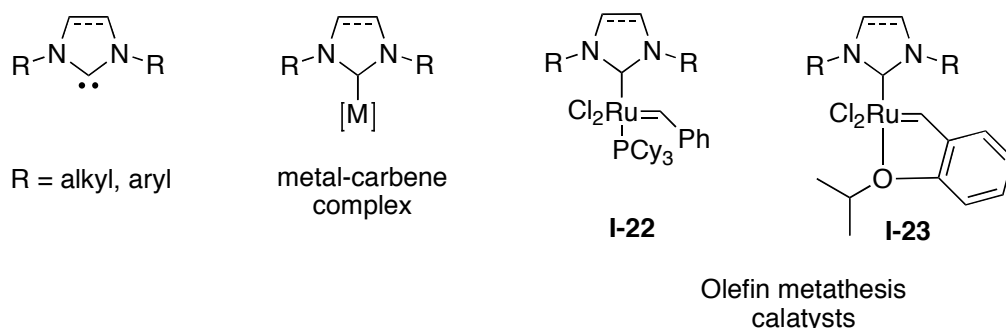


Figure 6. *N*-Heterocyclic carbenes (NHCs) derivated from diamines and some NHC-metal complexes.

1.3.2. Diamines in organocatalysis

(*S*)-Proline (**I-24**), known as the simplest enzyme, is a cornerstone in the field of organocatalysis since its use in the enantioselective intramolecular aldol reaction (Robinson-type annulation) was a crucial event in the history of organocatalytic processes,^[53] being one

of the first examples, where the potential of enantioselective reactions for the synthesis of natural products, even at large scale was demonstrated.^[54]

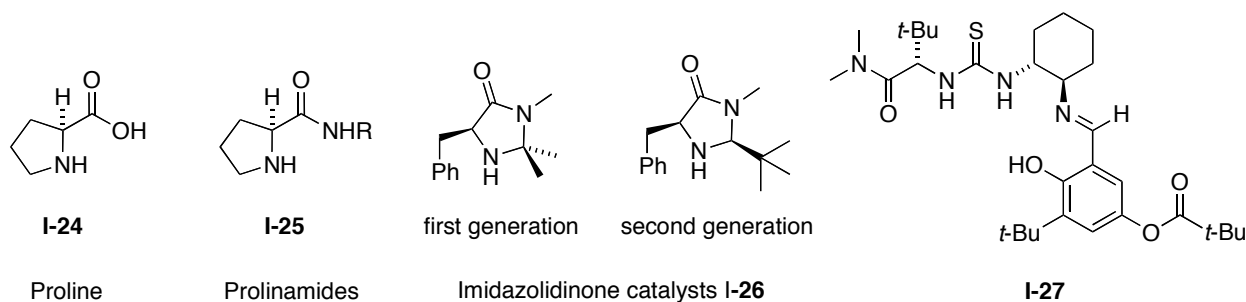
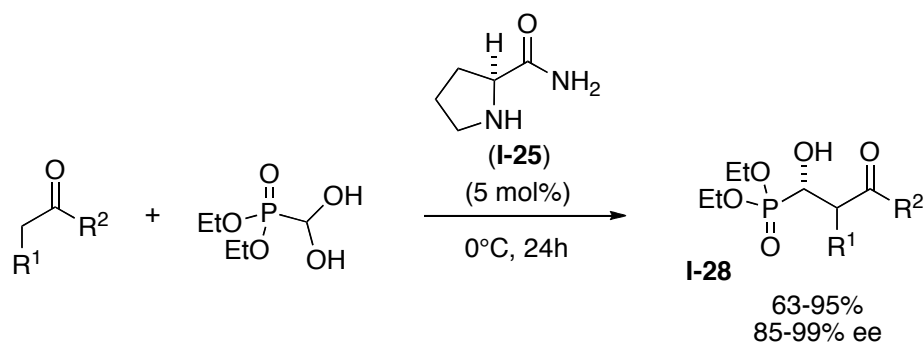


Figure 7. Examples of organocatalysts.

But although (*S*)-proline (**I-24**) (Figure 7) has demonstrated its efficiency in organocatalysis, there are some aspects that can be improved. Those aspects, such as the typical high catalyst loading, excess of source of nucleophile, and long reaction times, are sometimes attributed to the low solubility of catalyst **I-24** in organic media. To overcome these drawbacks and modulate its reactivity some modifications in the structure of (*S*)-proline have been reported, thus improving the activities and conditions.^[55]

The most commonly used group of proline derivatives are prolinamides (**I-25**). The general facts that have made these derivatives useful are: the easy preparation of these starting from (*S*)-proline, the robust amide linkage that provides very stable compounds, which in some cases can be recovered and reused without detrimental effects and finally, the hydrogen of the NH moiety which is sufficiently acidic to activate electrophiles by hydrogen bonding. Even if the simplest prolinamide has shown its efficiency in some reactions, such as the intermolecular aldol reaction between ketones and diethyl formylphosphonate (Scheme 1),^[56] the use of more complex prolinamides and chiral diamines (Figure 7) permitted to broaden the applications of those in organocatalysis.^[55]



Scheme 1. Enantioselective prolinamide catalysed intermolecular aldol reaction.

Besides the importance of diamines in organocatalysis through prolinamides, they also play a crucial role in this field through the imidazolidinone compounds (**I-26**), which are also called MacMillan organocatalysts.^[57] These are suitable catalysts for many asymmetric reactions such as asymmetric Diels-Alder reactions. Finally, another type of diamine that is standing out in organocatalysis over the last decade are the ureas or the thioureas. These catalytically effective (thio)urea derivatives provide explicit double hydrogen-bonding interactions to coordinate and activate H-bond accepting substrates which leads to unprecedented reactivity, which makes them attractive and explains their presence in the market, as for example the Jacobsen's catalyst (**I-27**).^[58]

But the utility of diamines is not limited to organocatalysis. Prolinamide derivatives were for example successfully used as ligands in catalysis, as it is indeed the case for most of the diamines described so far in this work.

1.3.3. Diamines as ligands in metal-catalysed reactions

Diamines are very good ligands for most metals, and a large number of complexes have been reported. For example complexes of cobalt,^[59] copper,^[60] manganese,^[61, 62] palladium,^[63] platinum,^[64] nickel,^[65] titanium,^[66] and lanthanides^[67] can be found in the literature. Concerning the applications of such complexes, they are indeed really extensive. Diamines have shown, since their first use, much success in many important and useful transformations and have become widely studied by many groups.^[5]

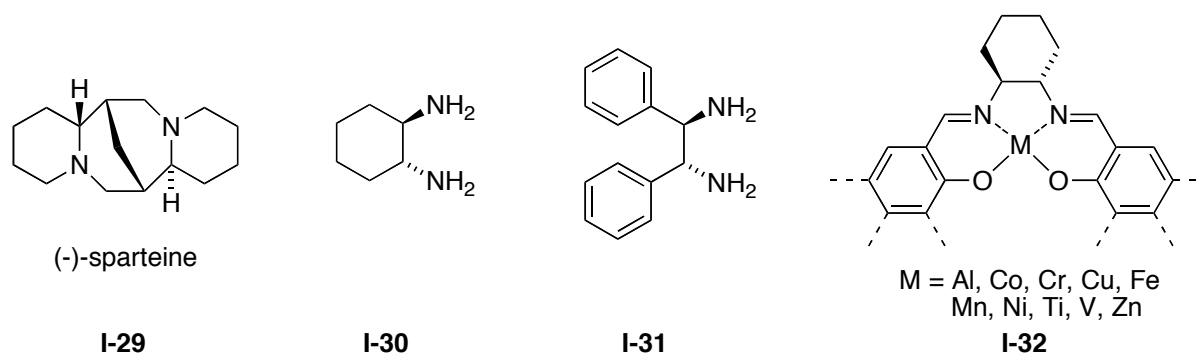
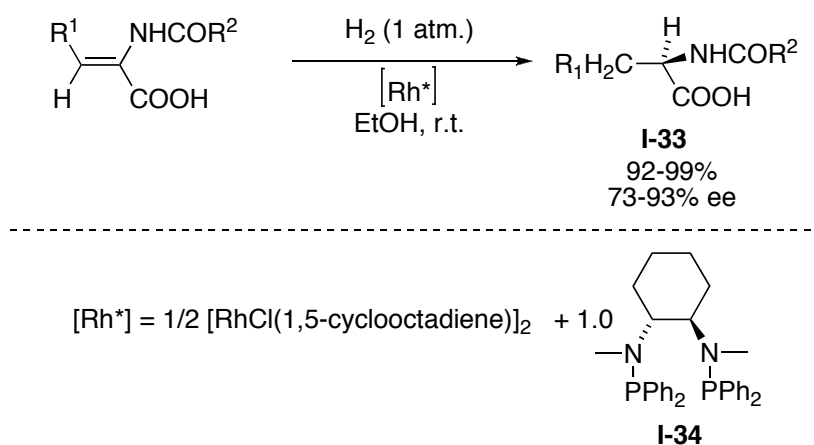


Figure 8. Diamine ligands and metal complexes used in asymmetric synthesis.

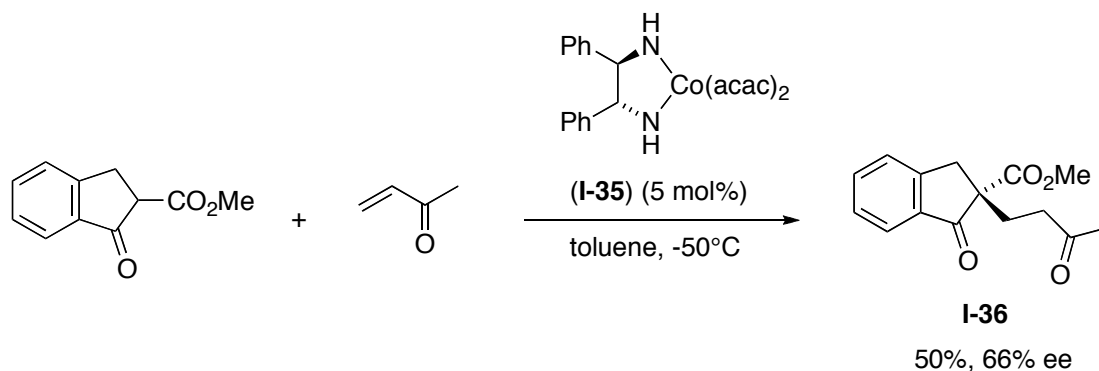
Since the first use of the alkaloid (-)-sparteine (**I-29**) in 1966, a large number of other derivatives have been described that are enantiomerically pure and many of them have been used for asymmetric catalysis. As mentioned previously, prolinamide derivatives and also *trans*-1,2-diamino-cyclohexane (**I-30**) and 1,2-diphenyldiaminoethane (**I-31**) are well-known core structures of diamines (Figure 8) and among the most-often used.

Trans-1,2-diaminocyclohexane (**I-30**) was first reported in 1926 by Wieland and co-workers and is today commercially available at relatively low cost, since it is a component in a by-product generated during the purification of 1,6-hexanediamine, which is used in the manufacture of nylon.^[68] In spite of its ready availability, its utility in asymmetric organic reactions remained unexploited for many years until the studies by Fujita and co-workers^[69] in asymmetric hydrogenation of (*R*)-acyl-aminoacrylic acids (Scheme 2) and by Hanessian and co-workers^[70] in asymmetric C-C bond forming reactions. A vast number of other asymmetric processes based on this chiral motif have been developed since then.



Scheme 2. Asymmetric hydrogenation of (*R*)-acyl-aminoacrylic acids by Fujita et al.

Concerning 1,2-diphenylethylenediamine (**I-31**), one of the first studies on asymmetric conjugate additions to α,β -unsaturated carbonyl compounds (Scheme 3) has been carried out by Brunner et al. using the 1,2-diphenyldiaminoethanecobalt catalyst (**I-35**).^[71]



Scheme 3. Cobalt diamine chelate catalysed enantioselective conjugated addition.

Among these diaminated ligands, the salen type ligands have found wide applications in synthesis in combination with numerous metals (**I-32**). In 1889, Combes prepared the first salen ligand and its Cu complex.^[72] Since then, salen derivatives and their metal complexes have been synthesised and characterised and gradually their value as catalysts has become recognised. The Jacobsen's^[73] and Katsuki's^[74] catalysts (M=Mn) are nowadays the most efficient catalysts available for the enantioselective epoxidation of unfunctionalised (*Z*)-substituted olefins. Vanadium(salen) complexes can also serve for the oxidation of olefins^[75] and cobalt(salen) complexes have found applications in cyclopropanation and epoxide-opening reactions.^[76] Chromium(salen) catalysts are known for their property to catalyse hetero-Diels-Alder reactions.^[77]

After this brief exposition, it appears that this growing field is of prime importance because of the large potential of diamines in many different processes and also because of their large-scale availability and low cost. Since their preparation is of critical importance, synthesis of diamines should now be discussed. We will focus on the diamination of alkenes that offers a particularly direct and efficient means of accessing these compounds. We will try to follow an essentially chronological path, beginning with classical synthesis, then metal-mediated diamination of alkenes under first stoichiometric and then catalytic conditions.

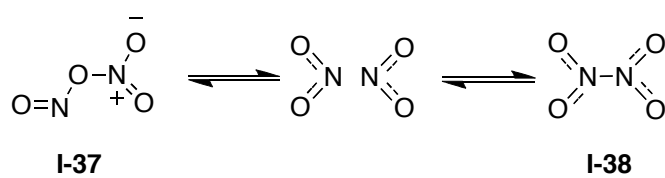
2. Evolution of the synthesis of diamines

2.1. Classical synthesis of diamines

2.1.1. Binary nitrogen oxides

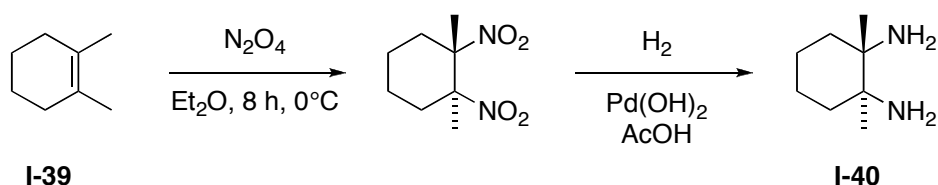
Nitrogen dioxide is the first known reagent used in direct alkene diamination. This diamination process has been studied for over 100 years and has played a historically role in the evolution of organic chemistry.^[78]

Unfortunately this reaction has been limited by several parameters: the instability of the products formed and the equilibrium that exists between dinitrogen tetroxide (**I-37**) and its nitrite isomer (**I-38**) (Scheme 4), which explains the formation of a number of different products.^[79]



Scheme 4. Dynamic equilibria of nitrogen dioxide.

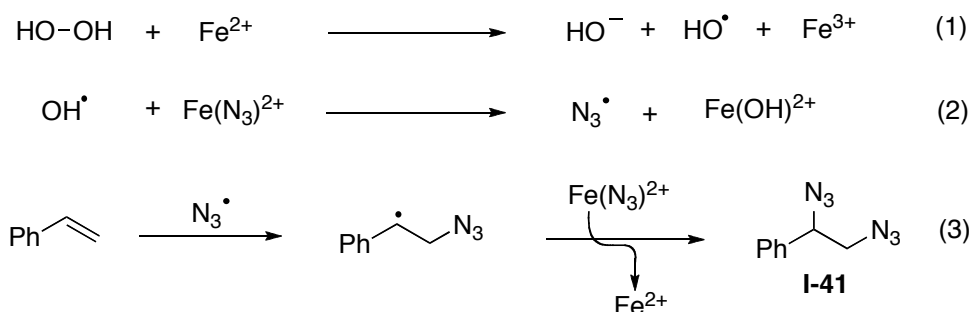
But, despite these disadvantages, this reaction allowed the synthesis of a great number of diamines. For example tetrasubstituted alkenes are suitable substrates for this reaction, since in this case, mainly nitro-nitro compounds are formed and because of this, Jacobsen in 1991 used this process to form the C_2 -symmetric *trans*-1,2-diamine **I-40**^[80] (Scheme 5), starting from the substituted cyclohexene derivative **I-39**.



Scheme 5. Reaction of cyclic tetrasubstituted alkene with N_2O_4 .

2.1.2. Alkene bis-azidation via redox

In 1962, another method of diamination was reported by Minisci et al. They took advantage of the low E_0 (ca. -0.6 V)^[81] of the azide anion (N_3^-) to oxidize it to the corresponding azydil radical (N_3^\bullet). The formed radical is then electrophilic enough to undergo addition to a range of alkenes, and a subsequent addition allows an alkene diazidation under mild conditions.^[82]

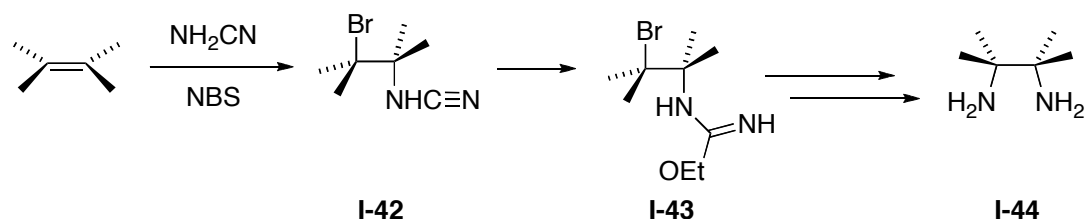


Scheme 6. Ferrous sulfate-mediated diazidation of alkenes.

The reaction between hydrogen peroxide and ferrous sulfate was used to effect the transformation. The mechanism proposed by Minisci is represented in Scheme 6.

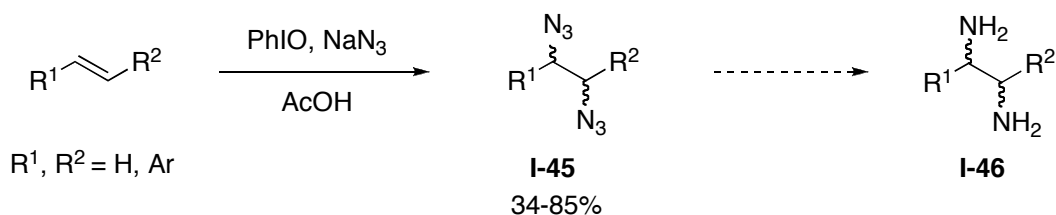
2.1.3 Diamination via hypervalent halogen chemistry

More than twenty years later, in 1984, Kohn et al. developed a synthesis of vicinal diamines from unactivated olefins, cyanamide, and *N*-bromosuccinimide.^[83] Diamination proceeded stereospecifically and permitted access to nitrogen-unsubstituted diamines (**I-44**) through the formation of a bromonium bridge as a first step (Scheme 7).



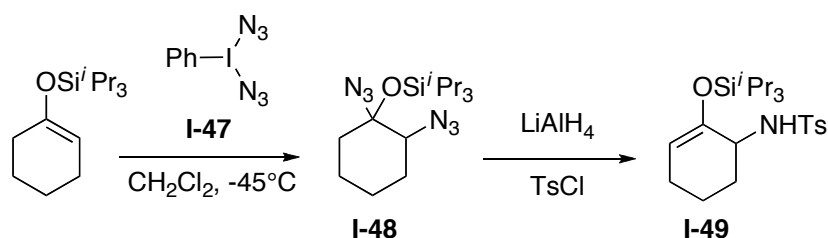
Scheme 7. Diamination developed by Kohn et al.

A few years later, in 1986, Moriarty et al. reported the diazidation using PhIO as oxidant with NaN_3 in AcOH, which allowed a facile diamination with modest to good yields (34-85%).^[84] Unfortunately, the employment of a strong oxidant and the harsh reactions conditions are still not compatible with most functional groups. The diazides **I-45** are obtained as diastereomeric mixtures and subsequent hydrogenation yields the diamines **I-46** (Scheme 8).



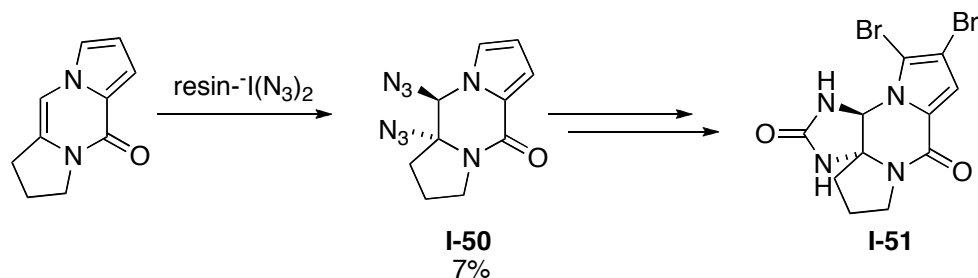
Scheme 8. Stoichiometric diazidation of alkene.

Then, in 1992, the hypervalent iodine(III) compound $\text{PhI(N}_3\text{)}_2$ (**I-47**) used by Magnus et al. allowed the diazidation of trialkylsilyl enol ethers but gave the elimination product **I-49** after reduction with LiAlH_4 (Scheme 9).^[85]



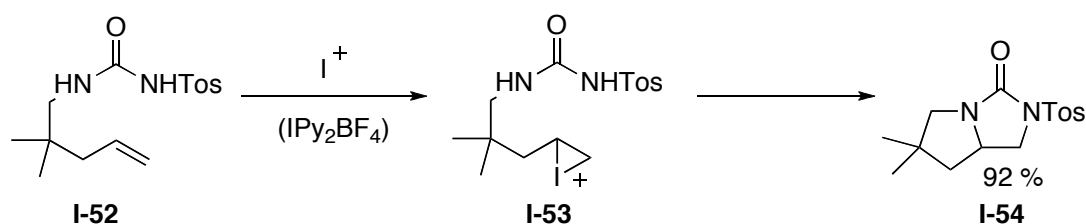
Scheme 9. Diazidation of trialkyl enol ethers.

In 2004, the group of Austin tried the previous method during the total synthesis of (\pm)-dibromophakellstatin (**I-51**)^[86] without success, and found that a treatment with solution-phase hypervalent iodine, by *in-situ* formation of $\text{I(N}_3\text{)}_2$, provided the *syn*-diazide product **I-50** as the major diastereomer (41%) and the *anti*-diazide as a minor diastereomer (7%) (Scheme 10).



Scheme 10. Synthesis of (±)-dibromophakellstatin.

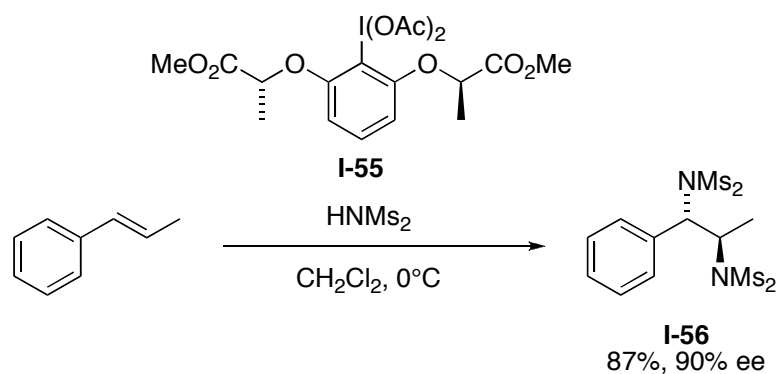
Muñiz et al. went further in 2008 by publishing a one step formation of ureas from alkenes with the use of IPy_2BF_4 (Py = pyridine) (Scheme 11). They decided to apply this reagent to the intramolecular cyclization of ω -alkenylureas **I-52** and after a screening of the conditions obtained the desired products **I-54** with good yields (70-92%).^[87]



Scheme 11. Intramolecular cyclisation of ω -alkenylureas.

Two years later, Wiedenhoefer et al. improved the conditions of this diamination, using the same substrates in combination with NaHCO_3 and NBS (*N*-bromosuccinimide) as oxidant. This procedure allows the formation of the cyclic specie under mild conditions and in toluene at 25°C while 120°C was required before.^[88]

Very recently, great improvements have been made in the field of diamination via hypervalent iodine compounds. Muñiz et al. published in 2011 the enantioselective intermolecular diamination of styrenes using a chiral non-racemic hypervalent iodine compound.^[89] They first observed the diamination of styrene when mixing PhI(OAc)_2 and bistosylimide at room temperature, which already represented a significant advance in the intermolecular diamination of alkenes as it required just two components. Then, they successfully developed an enantioselective version of this reaction by tuning the iodine reagent and using finally the iodine(III) species bearing two lactate groups (**I-55**) (Scheme 12).^[89]



Scheme 12. Enantioselective metal-free diamination of styrenes.

Thanks to these conditions they were able to diaminate more than 60 alkenes with moderate to good yields, and with enantiomeric excesses of up to 99% after recrystallisation.

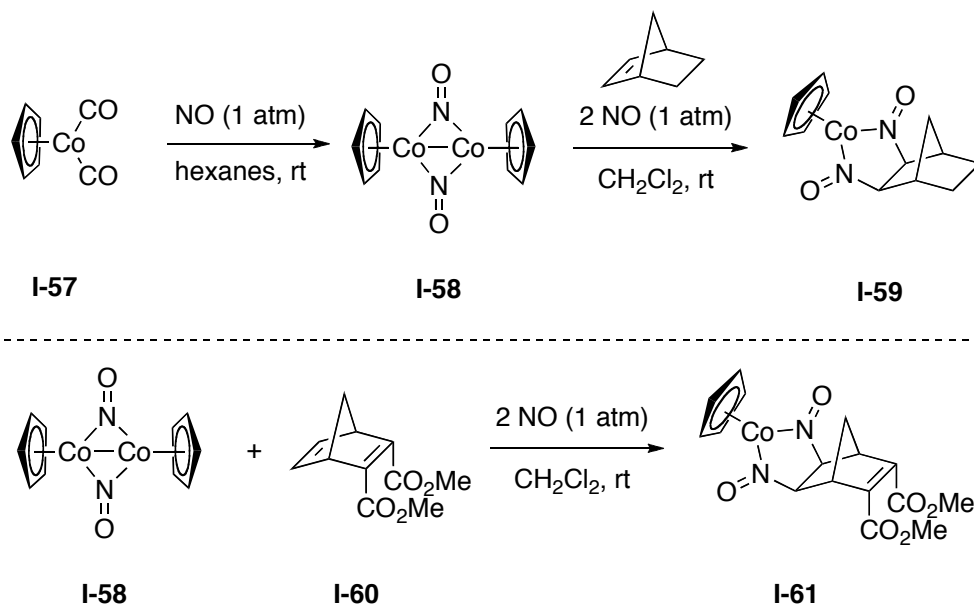
Still one problem remains; the two nitrogen groups that are entering the molecule are equivalent which restrains the use of these diamines in further steps because of the differentiation problem. To overcome this problem, the best-known way to overcome this problem is through the use of metal-catalysis. These reactions can be considered the culmination of a large body of work on stoichiometric metal-mediated diamination reactions.

2.2. Stoichiometric metal-mediated diamination

2.2.1. Through dinitrosoalkane complexes

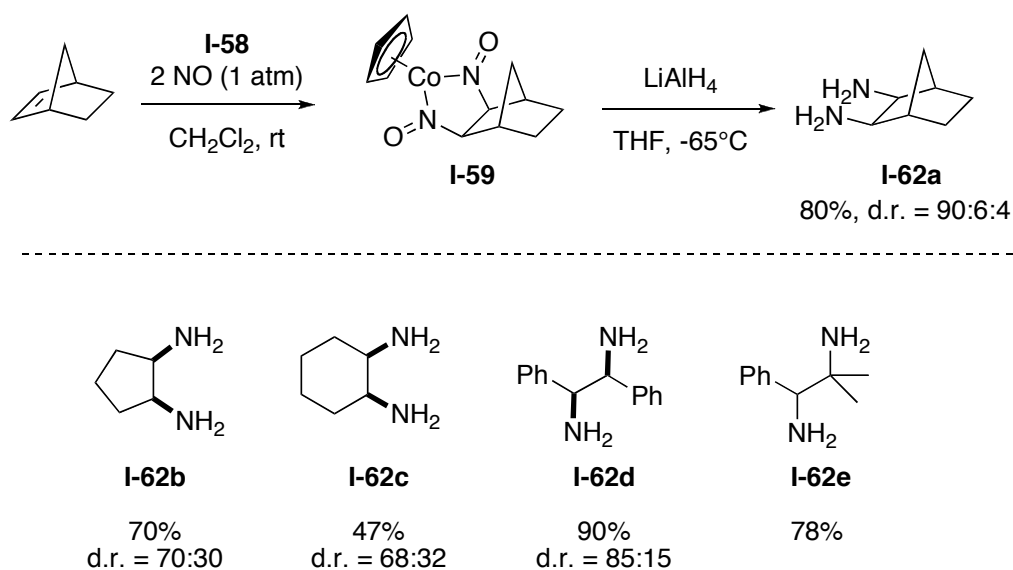
The investigations on metal-mediated direct diamination of alkenes have started in the 1970s. The first direct nitrogen 1,2-difunctionalisation of olefins has been reported by Brunner and Loskot in 1971.^[90] It is a ligand-based reaction of cobalt nitrosyl complex **I-58** with bicyclo[2.2.1]hept-2-enes. First, the cobalt nitrosyl complex is formed via a reaction between cyclopentadienylcobalt dicarbonyl (**I-57**) and nitric oxide (NO). Then this air-stable complex undergoes addition to alkenes to form dinitrosoalkane complexes **I-59** (Scheme 13). Concerning the selectivity of this reaction, it is diastereoselective since only *exo*-complexes are formed; and regioselective since in the case of dienes, such as **I-60**, addition only takes

place at the more electron-rich alkene partner to form in the case of Scheme 13 only compound **I-61**.



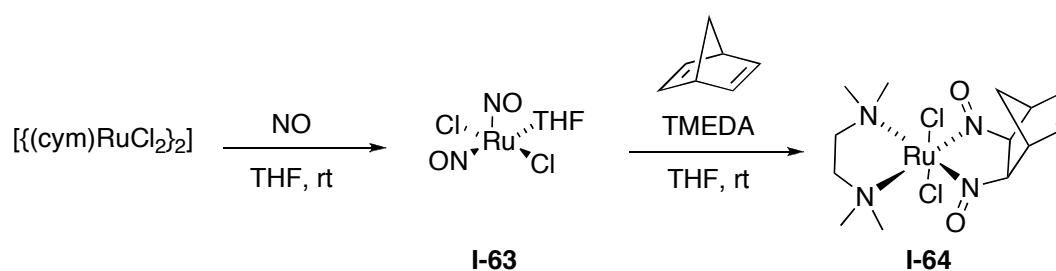
Scheme 13. Generation of cyclopentadienylnitrosylcobalt dimer and its reaction with strained alkenes.^[91]

These observations have subsequently been continued by Bergman et al., who employed this transformation as a method for direct 1,2-diamination of alkenes.^[92] They generated the corresponding 1,2-diamines **I-62** in fair to excellent yields through the *in-situ* reduction of the dinitrosoalkane ligands **I-59** with LiAlH₄ (Scheme 14). Importantly, they also found that this diamination can be stereospecific to di-, tri-, and tetra-substituted aliphatic, linear and cyclic alkenes (Scheme 14).



Scheme 14. Two-step, one-pot 1,2-diamination of alkenes using stoichiometric cobalt complexes.

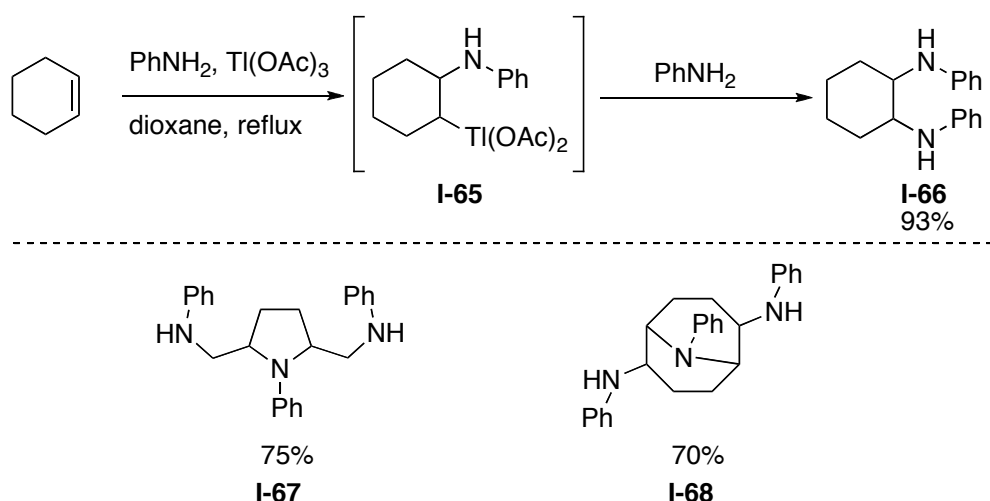
This reaction is still evolving nowadays, since in 2011 Bergman and Toste have reported the alkene bis-nitrosylation through, for the first time, a ruthenium-complex.^[93] They synthesised this dinitrosyl complex **I-63** by the reaction of nitric oxide on $[\{(cym)RuCl_2\}_2]$, and reacted it with strained tetrasubstituted alkenes to obtain the diamine **I-64** (Scheme 15).



Scheme 15. Reaction of alkene with the previously formed dinitrosyl complex $[RuCl_2(NO)_2THF]$.

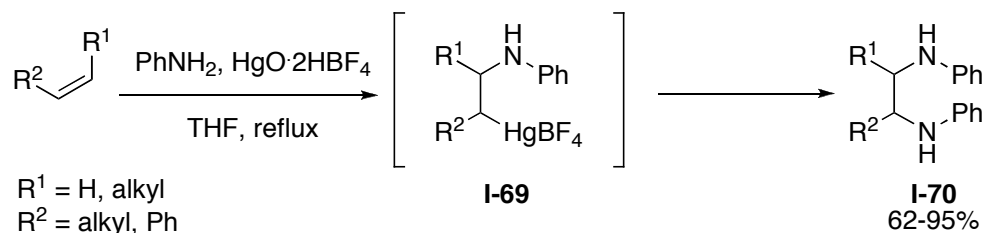
2.2.2. Using thallium and mercury

Dating back to the 1970s, the first direct diamination of alkenes has been reported by Barluenga et al. in 1974.^[94] The reaction is stoichiometric in thallium(III) acetate and allows for the diamination of alkenes in refluxing dioxane. The reaction proceeds via a two-step mechanism consisting of aminothallation (**I-65**, Scheme 16) followed by an amination/reductive dethallation releasing thallium(I) and leading to diamines **I-66** in good yields. It is noteworthy that 1,4-dienes undergo a double addition to form for example the triamines **I-67** and **I-68** as represented in Scheme 16. The major drawbacks of this reaction are first, the limited scope of the reaction, since while primary and secondary aromatic amines participate in this process, primary aliphatic amines fail to react and secondly, the toxicity of the employed metal, especially within its stoichiometric use.



Scheme 16. Addition of aromatic amines to alkenes in the presence of thallium(III) acetate.

Five years later, Barluenga et al. reported a similar approach using mercury(II) salts.^[95, 96] As previously with thallium, they demonstrated that mercury complexes allow for an aminomercuration leading to β -amino alkylmercury(II) salts **I-69**. These mercury salts can then undergo a substitution with several nucleophiles, including amines. The reaction proceeds in good to excellent yields in refluxing THF via, as mentioned, a comparable aminometallation/amination-demetalation sequence (Scheme 17).

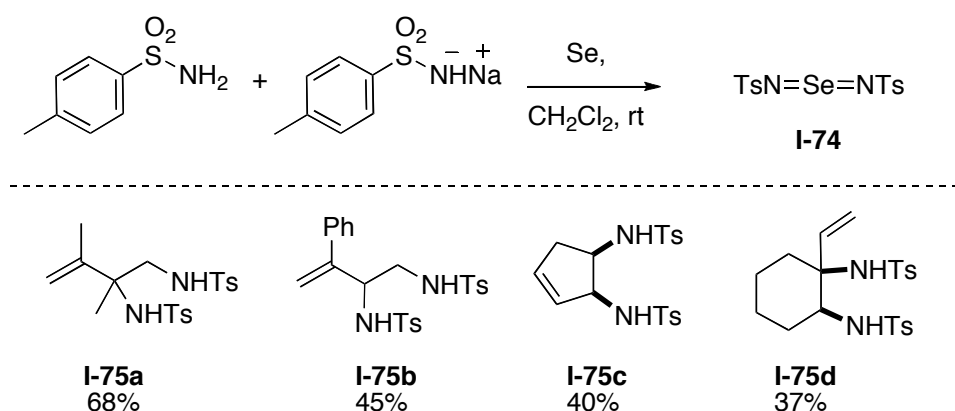


Scheme 17. Mercury-promoted vicinal diamination of olefins.

2.2.3. Stoichiometric palladium(II)-mediated alkene diamination

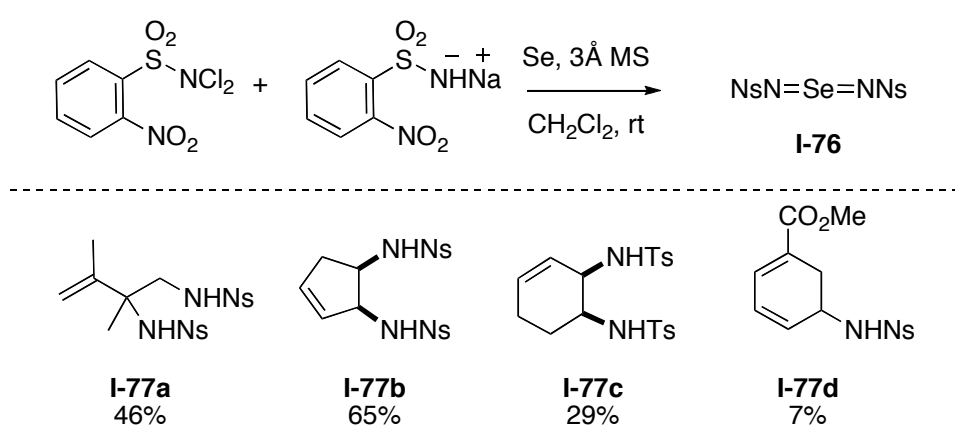
Shortly after the publication of the thallium-mediated diamination, Bäckvall et al. introduced the diamination of alkenes by a stoichiometric amount of palladium under oxidative conditions.^[97, 98] To mediate this one-pot two-step transformation, stoichiometric quantities of *trans*-bis(benzonitrile)dichloropalladium(II) and various strong oxidants, including *m*-CPBA,

undergoes regioselective reaction with cyclic and acyclic 1,3-dienes to generate 1,2-diaminoalkanes **I-75** in low to moderate yields (Scheme 19).



Scheme 19. One-pot 1,2-diamination of 1,3-dienes with the selenium dioxide bis(imide) reagent **I-51**.

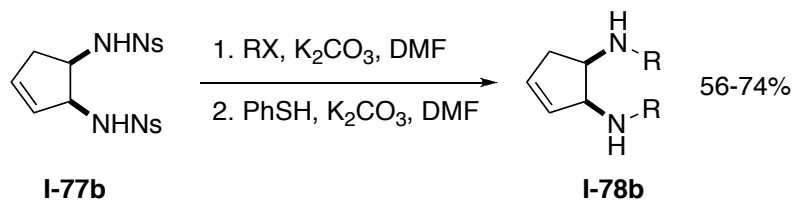
Only one problem remained: the deprotection of the tosyl group, and in order to facilitate the deprotection Sharpless has replaced the tosyl group by a 2-nitro benzenesulfonyl group to form the reagent **I-76** (Scheme 20).^[105] The use of this reagent leads in general to lower diamination yields and it has been observed that electron-withdrawing substituents reduce the reactivity of the dienes. For example, 1,3-cyclohexadiene carboxylate failed to yield the corresponding diamine (**I-77d**) (Scheme 20).



Scheme 20. 1,2-diamination of 1,3-dienes with the modified selenium dioxide bis(imide) reagent.

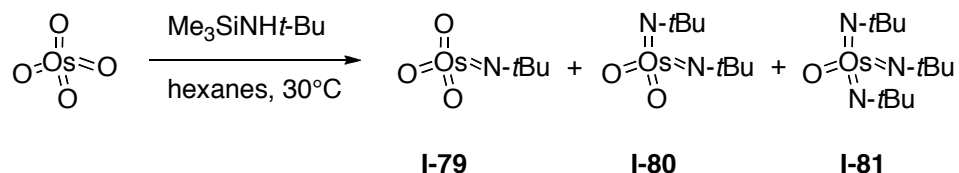
Despite these disadvantages, reagent **I-76** plays a crucial role in the selenium-mediated diamination. Indeed, the deprotection of the formed product **I-77** and then formation of the

corresponding amines **I-78** is really easy (Scheme 21) compared to the tosyl group. For example, deprotection and then *N*-alkylation of **I-77b** is feasible using Fukuyama's conditions,^[106] and provide a route to **I-78b** with moderate to good yields.



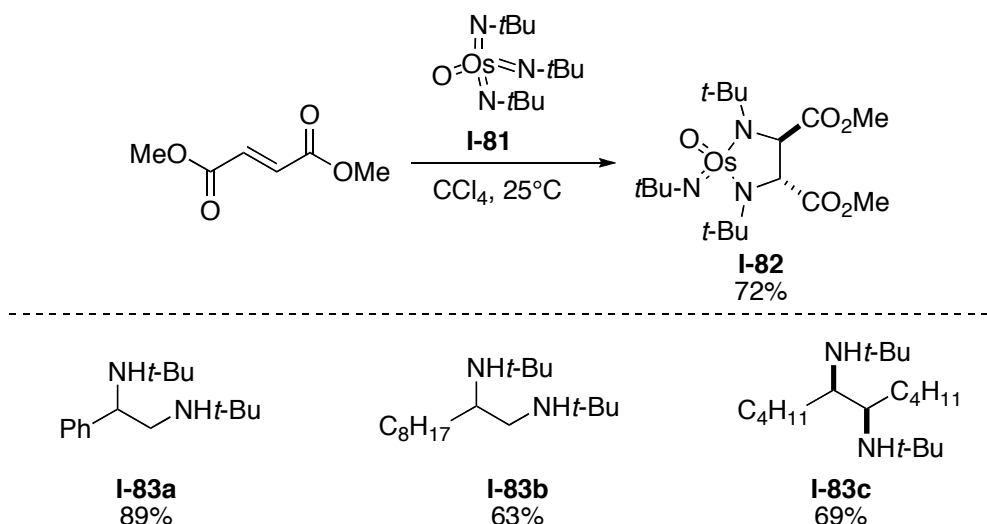
Scheme 21. Deprotection of **I-53** using Fukuyama's conditions.

Sharpless also described the addition of bis- and trisimidoosmium compound (**I-80**, **I-81**) to alkenes.^[107] These imidoosmium(VIII) complexes were first prepared in 1959,^[108] but it was only in 1977 that they were used on alkenes to form 1,2-diamines. These stable reagents are easily prepared by the condensation of amines with osmium tetroxide (Scheme 22). For example, the condensation of *N*-trimethylsilyl-*tert*-butylamine with the osmium complex generates a mixture of compounds **I-79-I-81**, which can subsequently be separated by column.



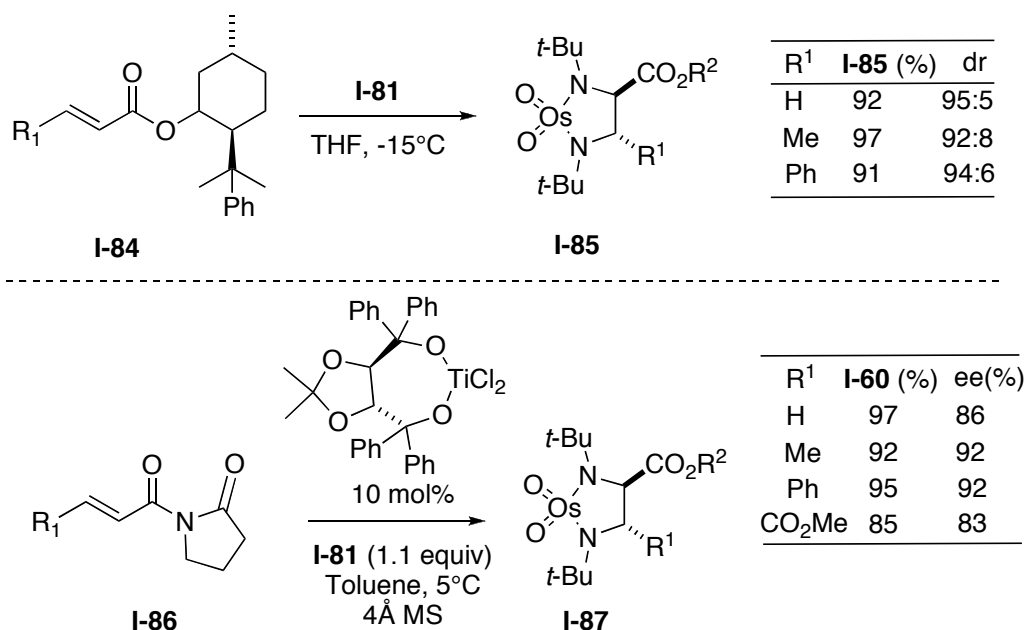
Scheme 22. Preparation of imidoosmium(VIII) complexes from osmium tetroxide.

Sharpless and co-workers have reported the reaction of **I-80** and **I-81** with terminal and disubstituted alkenes (Scheme 23).^[107] The addition leading to the stable diimido complexes **I-82**^[109] is always stereospecific and chemoselective and, after treatment of LiAlH_4 , leads to the corresponding 1,2-di-*tert*-butylamines **I-83**. Concerning the reactivity of the substrate, it is opposite to the selenium-mediated diamination; the introduction of electron-withdrawing groups increases the rate of the reaction, as shown in Scheme 23 for fumarate.



Scheme 23. Stoichiometric diamination of alkenes with oxotris(*tert*-butylimido)osmium(VIII)/ LiAlH_4 .

One of the disadvantages of this osmium chemistry is the stability of the formed osmium imidazolines complexes **I-82**, which blocks the development of a fully catalytic, enantioselective diamination reaction. But during the past decades, Muñiz and co-workers have greatly expanded the work of Sharpless, investigating the mechanism and improving the yield of this method. They have successfully improved the selectivity of the reaction through different strategies allowing the control of the facial addition of the stoichiometric process. One of the examples is the selective diamination of (–)-8-phenylmenthyl acrylate derivatives **I-84** from the *Re*-face with **I-81** (Scheme 24).^[110]

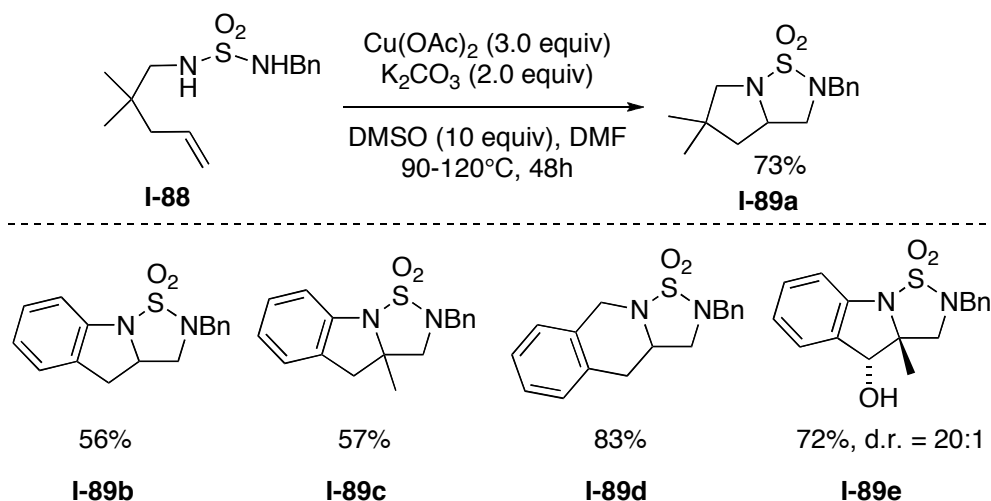


Scheme 24. Diastereo- and enantioselective diamination of electron-deficient alkenes with dioxobis(*tert*-butylimido)osmium(VIII).

A unique enantioselective catalytic variant has been reported in 2006 by Muñiz, employing a titanium(IV) catalyst and the osmium complex **I-81** as the stoichiometric nitrogen source.^[111, 112] In this case the reaction gave rise to the osmium complexes **I-87** with high level of enantioselectivity (Scheme 24). The key of this successful method seems to be the low reactivity of this substrate class **I-86**, which reacts slowly with **I-81**, allowing then the good selectivity.

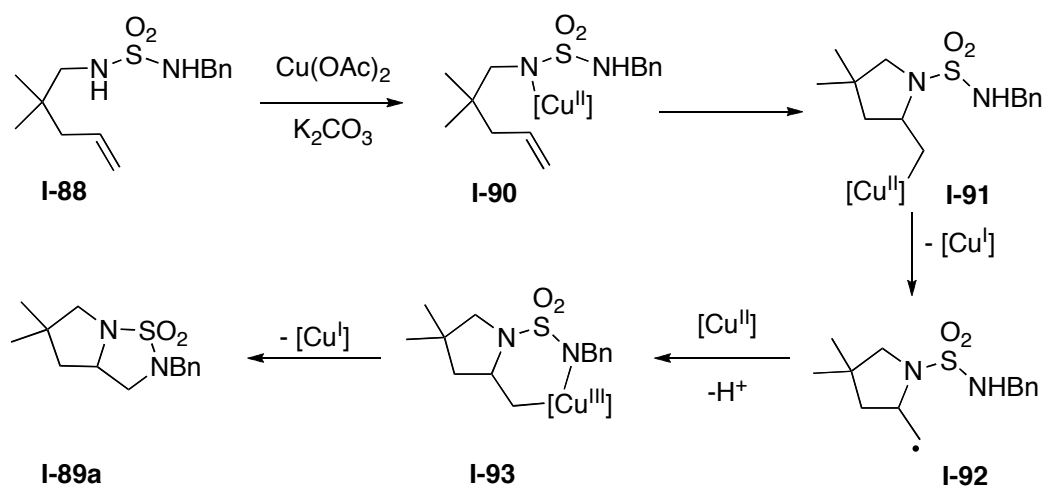
2.2.5. Copper-mediated diamination

Chemler and co-workers have pioneered the copper-mediated and copper catalysis of alkene diamination. They started in 2005, when they reported the intramolecular diamination of γ - and δ -alkenyl-substituted sulfamides. They diaminated substrates such as **I-88**, thanks to the presence of 3.0 equivalents of copper(II) acetate, which allows the formation of the corresponding five- and six-membered sulfamides **I-89** (Scheme 25).^[113] Importantly, this diamination proceeds with complete *exo*-regioselectivity and, for example in the case of product **I-89e**, with a high level of diastereoselectivity.



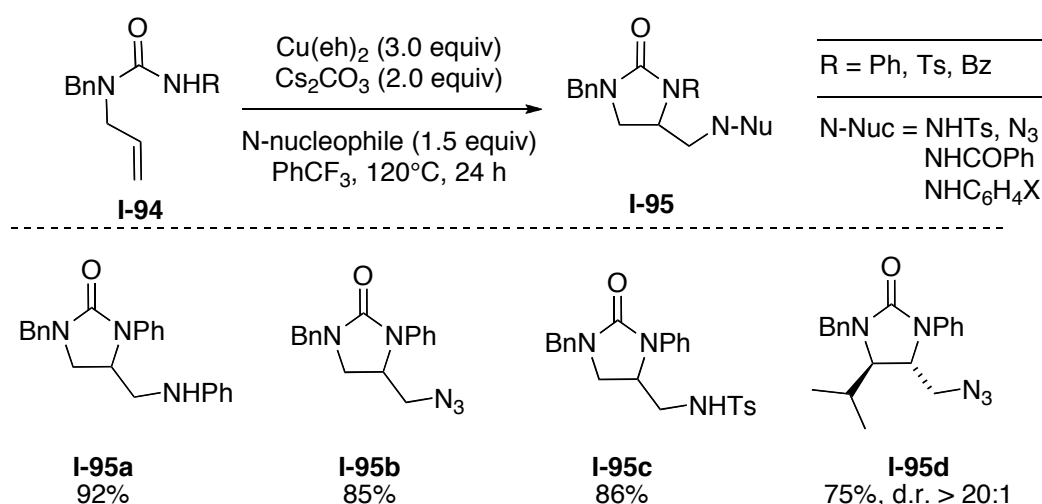
Scheme 25. Copper(II) acetate-promoted intramolecular diamination of δ -alkenyl and γ -alkenyl-substituted sulfamides encompassing 1- and 1,2-substituted terminal alkenes.

Concerning the mechanism, the proposal of Chemler begins with base-assisted ligand exchange between sulfamide **I-88** and copper(II) acetate to form intermediate **I-90** (Scheme 26). Then **I-90** undergoes a *syn*-aminocupration leading to the unstable alkylcopper(II) species **I-91**. This step should be the rate-determining step. It is followed by a subsequent Cu–C bond homolysis giving rise to the radical specie **I-92**. This intermediate reacts with copper acetate again to form the alkylcopper(III) complex **I-93**, which, after a reductive elimination and a concomitant C–N bond formation, would lead to the cyclic sulfamide **I-89a**.



Scheme 26. Proposed mechanism of the copper(II) carboxylate-promoted intramolecular alkene diamination reaction.

Then in 2010, the same group extended the original intra/intramolecular diamination methodology to the intra/intermolecular version. In this work the second C–N bond is provided by external *N*-nucleophiles such as azide, sulfonamides, benzamide and anilines derivatives (Scheme 27).^[114] For example, as represented in Scheme 27, 1-allyl-1-benzyl ureas **I-94** undergo diamination in the presence of [Cu(eh)₂] (eh = 2-ethylhexanoate) with external *N*-nucleophiles such as tosylamide, azide and more, to form 4-substituted imidazolinones **I-95** in good to excellent yields (75-92%).



Scheme 27. Copper(II) 2-ethylhexanoate-promoted intra/intermolecular alkene diamination.

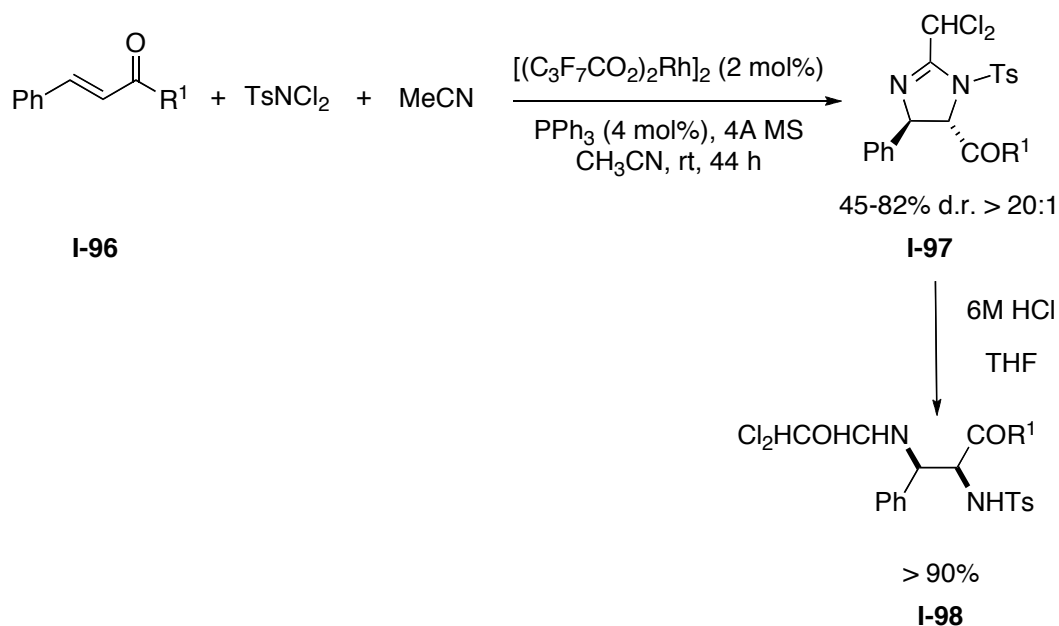
2.3. The metal-catalysed versions of the diamination

Recently, new procedures have been discovered that permit the direct diamination of alkenes and related substrates by catalysis. In the following section, it will be illustrated that these methods have attained astonishing results in terms of yields, regioselectivity and even enantioselectivity.

Since the first catalytic diamination has been made through the use of rhodium complexes, metal-catalysed diamination will be discussed first.

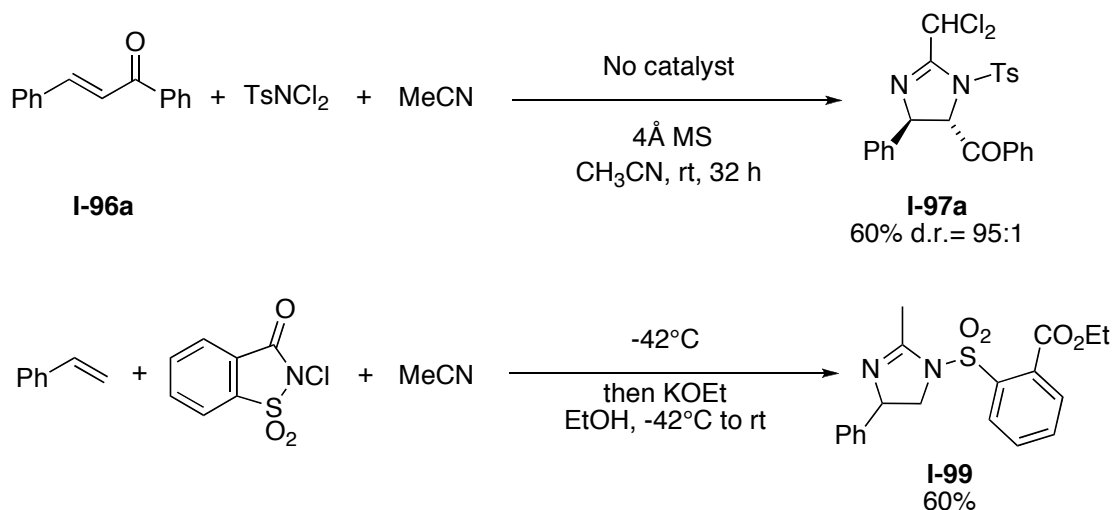
2.3.1. Ritter-type reactions

The first report of catalytic diamination of an alkene goes back to 2001. Li and co-workers reported a this time a reaction that permitted the conversion of α,β -unsaturated ketones **I-96** (and esters) into imidazolines **I-97**. This process works through the use of *N,N*-dichloro-*p*-toluensulfonamide with the rhodium(II) heptafluorobutyrate dimer as the catalyst and in the presence of PPh_3 (Scheme 28).^[115] The mechanism was proposed to start with the aziridination of the double bond by TsNCl_2 and should then be followed by a Ritter-type *syn*-nucleophilic attack by acetonitrile and finish with a subsequent cyclization leading to the *trans*-isomer. A simple hydrolysis of **I-97** afforded the vicinal diamine derivatives **I-98**.



Scheme 28. Rhodium-catalysed electrophilic diamination reaction.

Soon afterwards, it was discovered that the combination $\text{FeCl}_3\text{-PPh}_3$, which is less expensive and much easier to handle, was able to catalyse this electrophilic diamination as well and with improved yields and stereoselectivities in many cases (Scheme 29).^[116]



Scheme 29. Ritter-type electrophilic diamination of alkene.

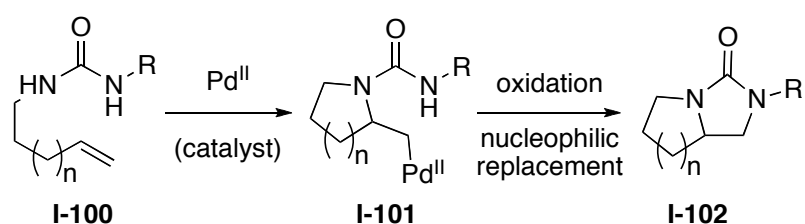
More recently, the same authors have reported other catalysts (CuI–PPh₃ and MnO₂) for this reaction.^[117] It was proposed that the rhodium complex could catalyse the initial aziridination step, but the part played by these catalysts in the reaction remains to be clarified, and even their necessity was questioned by further studies. Indeed, there have been reports of related Ritter-type electrophilic diamination of alkenes^[118] without the use of any metal or catalyst (Scheme 29).^[119, 120]

2.3.2. Metal catalysed intramolecular diamination

In 2005, the research groups of Muñiz and Booker-Milburn reported independently and almost at the same time the first examples of a catalytic diamination of alkenes using, in each case, a unique nitrogen source furnishing both the nitrogen atoms, in other words: the intramolecular fashion. To understand the evolution of the catalytic diamination, the choice of beginning with the intramolecular version should now be explained.

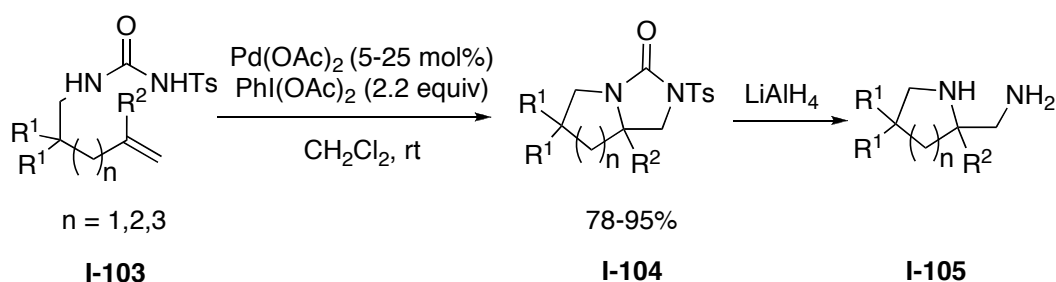
Earlier attempts by Muñiz for diamination catalysis in palladium, again experienced the drawback of metal deactivation by the diamine products. Then it became obvious that, without preventing the product from metal coordination, palladium catalysis would remain inefficient. That is why the initial approach of Muñiz's group went through the use of tethered amides, starting from the assumption that ω -alkenyl-substituted urea molecules **I-100** should undergo cyclization in the presence of an electrophilic palladium(II) catalyst, leading to a

vicinal amino pallada-compound **I-101** (Scheme 30). The formation of the second C-N bond through the replacement of the palladium by the second amino group of the urea under oxidative conditions should then regenerate the palladium(II) catalyst and release the diamination product **I-102** as a cyclic urea, which would not poison the palladium and allow the regeneration of the catalyst. Moreover, intermolecular diamination is entropically disfavoured compared to the intramolecular version. Assembling these ideas explains the choice of intramolecular diamination using tethered amines.



Scheme 30. Intramolecular catalytic diamination of terminal alkenes with ureas using palladium as catalyst.

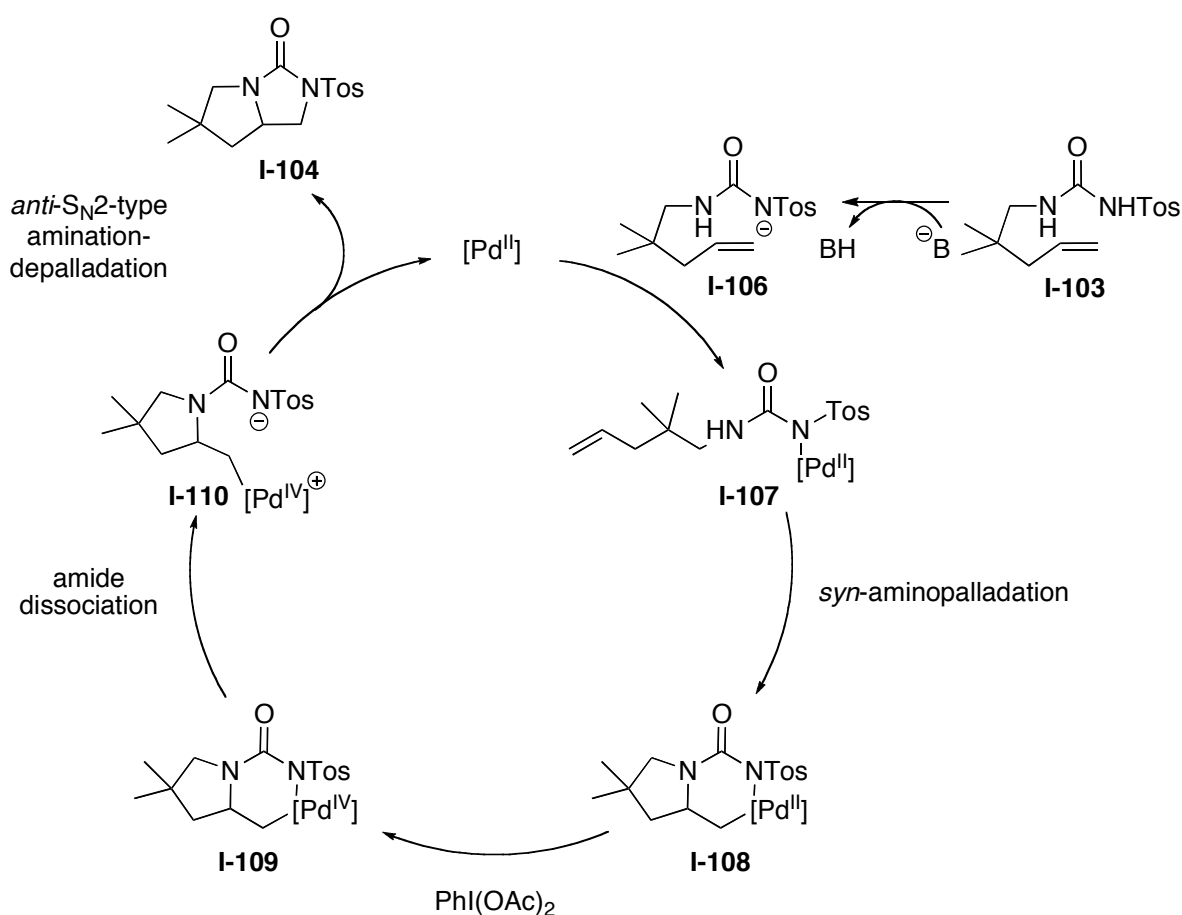
They found that ω -alkenyl-substituted ureas **I-103** formed fused five- to seven-membered rings **I-104** with $\text{Pd}(\text{OAc})_2$ as precatalyst and $\text{PhI}(\text{OAc})_2$ as the oxidant, under mild conditions (CH_2Cl_2 , room temperature).^[121] A simple treatment of the bicyclic products **I-104** with LiAlH_4 gave directly the free diamines **I-105** (Scheme 31). All reactions reached high conversion and no other compounds than the diamination products were observed.



Scheme 31. Intramolecular catalytic diamination of terminal ω -alkenes with ureas.

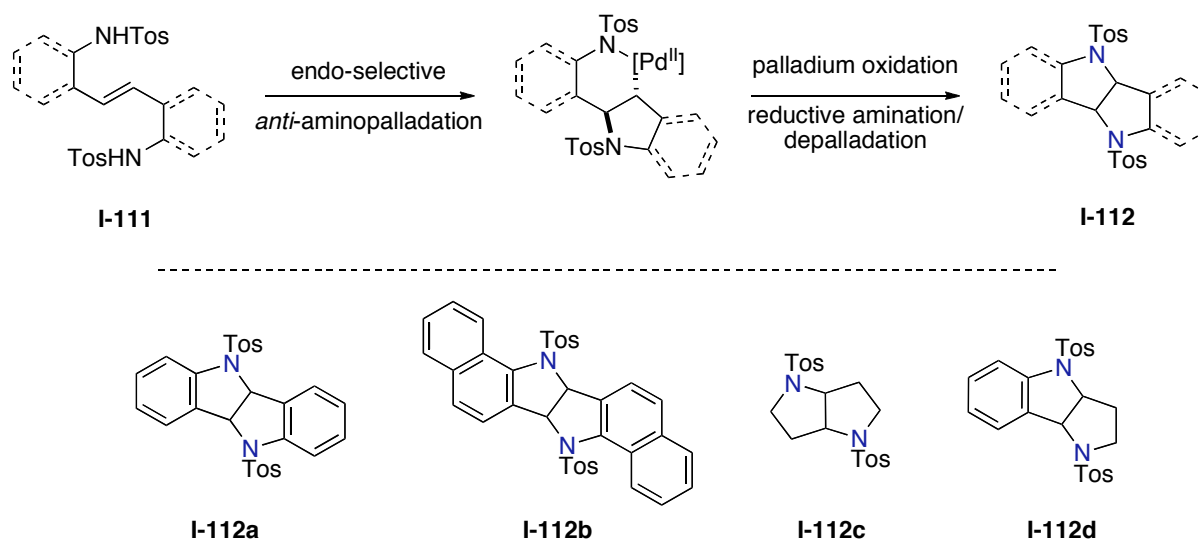
After establishing the optimised conditions, extensive studies led Muñiz to propose a two-step mechanism, which is outlined in Scheme 32. The first step consists in a deprotonation of the urea and then coordination to the palladium leading to **I-107**. This coordination is then followed by *syn*-aminopalladation, the rate-limiting step. The resulting σ -alkylpalladium(II) complex **I-108** undergoes oxidation with iodosobenzenediacetate to palladium(IV)

intermediate **I-109**.^[122, 123] At this stage, dissociation of the urea from the palladium takes place and an intramolecular S_N2 -type displacement, which proceeds with inversion of configuration, forms the second C-N bond and regenerates Pd(II) catalyst. It is noteworthy that while σ -alkylpalladium(II) species **I-108** is susceptible to iodine(III)-mediated oxidation, palladium(II) complex is not.



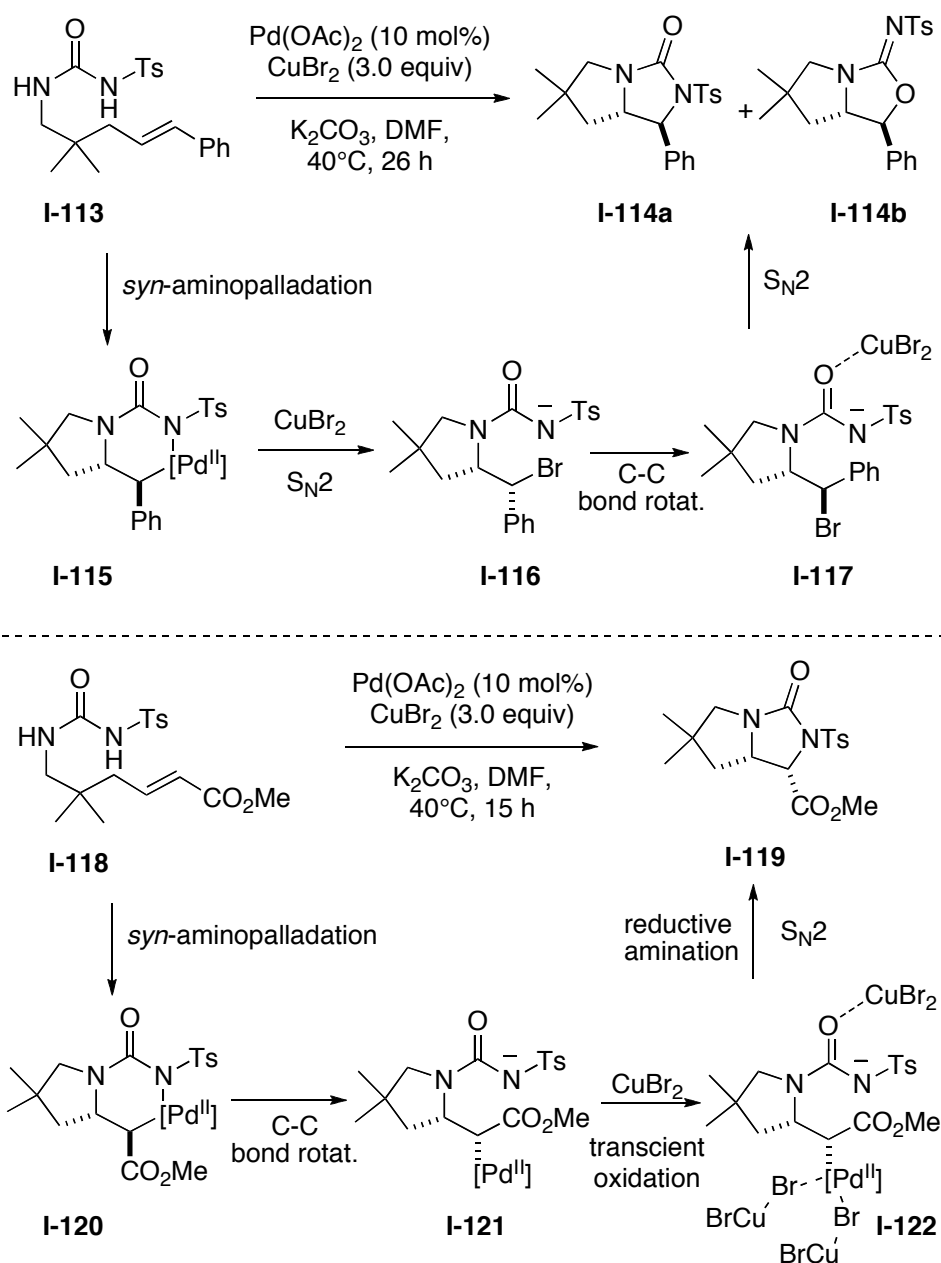
Scheme 32. Proposed mechanism for the Pd(II)-catalysed intramolecular diamination.

While the previous procedure is not working with internal alkenes, Muñiz showed in a following publication that the transfer of two nitrogen atoms is possible for homoallylic sulfonamide substrates such as **I-111**, leading to the formation of bisindolines (**I-112a-b**), bispyrrolidines (**I-112c**), and annulated indolines (**I-112d**) (Scheme 33).^[124] From a mechanistic standpoint the reaction begins with an *endo*-selective *anti*-aminopalladation, followed by a palladium oxidation and then amide dissociation with then an internal displacement leading to the *syn*-diamination product.



Scheme 33. Intramolecular catalytic diamination of internal alkenes with tosylamides.

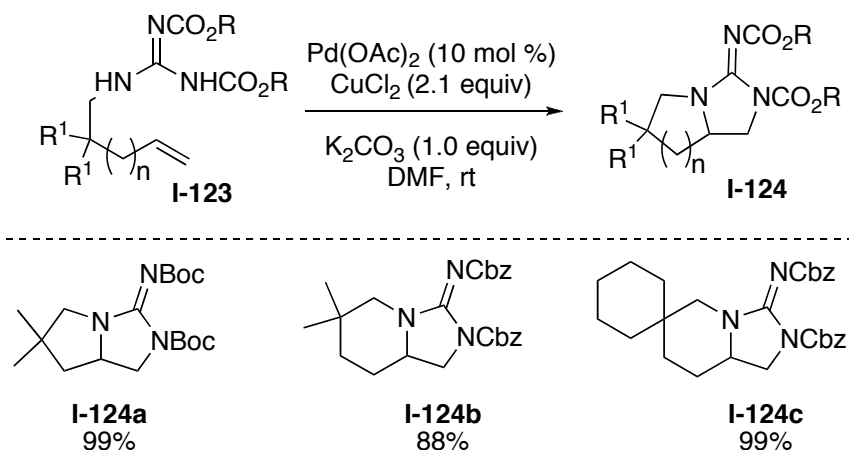
Shortly after, Muñiz and Barluenga have also reported the use of copper(II) salts as terminal oxidants replacing $\text{PhI}(\text{OAc})_2$. One of the advantage of these new conditions is the possibility of diaminating internal alkenes (Scheme 34).^[87] Importantly, the stereochemical outcome of the diaminations done in the presence of copper(II) bromide depends on the nature of the substrate. For example, cyclization of (*E*)-styrene will be different than the one of (*E*)-acrylate. As shown in Scheme 34, cyclisation of (*E*)-styrene derivative (**I-113**) takes place with an overall retention of stereochemistry, while diamination of (*E*)-acrylate (**I-118**) proceeds with inversion (Scheme 34).^[125]



Scheme 34. Stereochemically divergent diamination of non-terminal alkenes and its mechanistic origin.

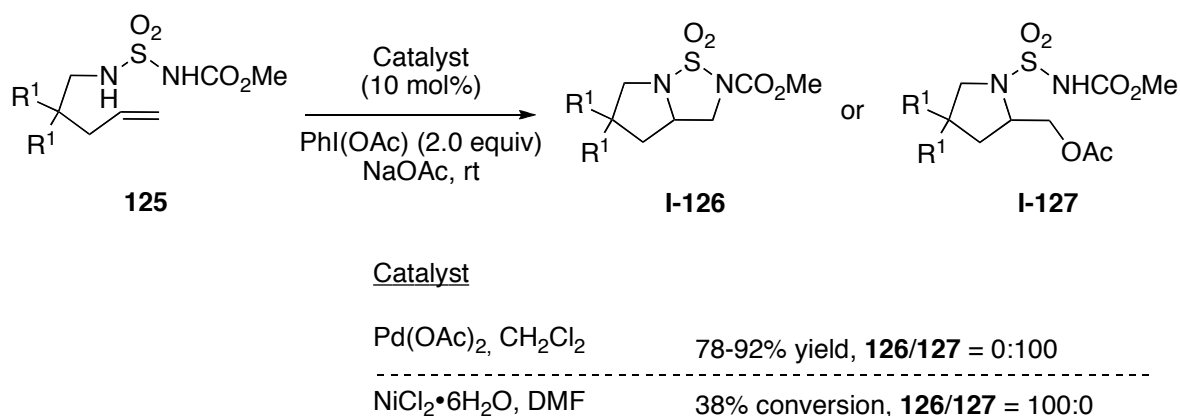
For the example **I-113**, a first *syn*-aminopalladation is proposed, followed by an *anti*-bromination/depalladation, leading to the formation of the alkyl bromide **I-116**. Then a second inversion of configuration takes place through the intramolecular $\text{S}_{\text{N}}2$ -type displacement giving rise to the second bond formation, which is generating both the *anti*-configured urea **I-114a** and isourea **I-114b**. In the case of the acrylate **I-118**, the initial step consists in a *syn*-aminopalladation too, but then formation of the second C–N bond is proposed to take directly place through amide dissociation and oxidatively induced $\text{S}_{\text{N}}2$ ring closure, which consists only in a single inversion of configuration.

An other benefit of the use of copper(II) salts as terminal oxidants is the excellent substrate generality: it has also been employed in the construction of cyclic guanidines (Scheme 35)^[126] allowing the formation of a range of bicyclic products **I-124**. That diamination in this case proceeds with overall *syn*-diastereoselectivity and has been studied by NMR using deuterium labeling.



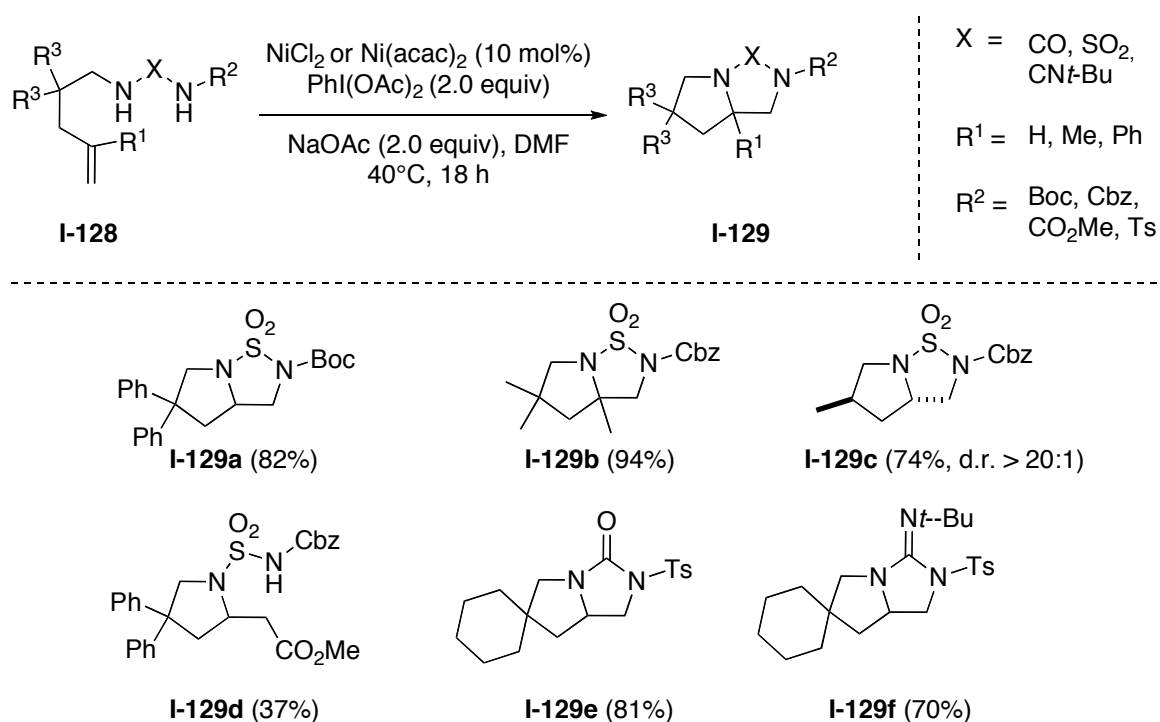
Scheme 35. Direct synthesis of bicyclic guanidines via Pd(II)-catalyzed intramolecular cycloguanidination.

In contrast to the behaviour of ureas and guanidine groups, alkenes that contain terminal sulfamide groups **I-125** failed during this diamination process. Applying the Pd-catalysed conditions to the sulfamides only led to the acyclic aminoacetylation product **I-127**. But, interestingly, the product ratio could be completely inverted in favour of **I-126** when palladium(II) was replaced by nickel(II) salts (Scheme 36).



Scheme 36. Ni(II)-catalysed intramolecular diamination of alkene.

This example represents the first selective C-N bond formation using homogeneous nickel catalysis. In addition to sulfamides, other substrates were tested and the nickel catalysts were also very effective with ureas and guanidines (Scheme 37).^[127] The stereochemistry of the reaction has been studied through deuterium labeling and the analysis revealed that the process is stereospecific with respect to alkene geometry and proceeds with an overall *syn*-stereochemistry. Isolation of product **I-129d** led to the conclusion that the mechanism should start with an initial aminometallation step, but no precise conclusions have been made concerning the overall mechanism of this reaction.

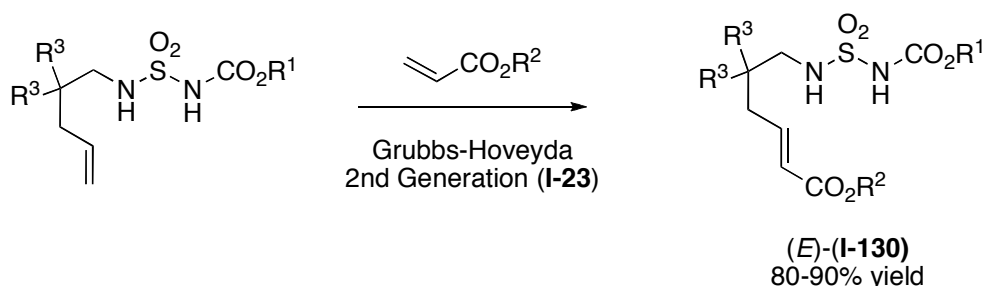


Scheme 37. Nickel(II)-catalysed intramolecular diamination of N- γ -alkenyl sulfamides, ureas, and guanidines.

Despite the large efficiency of this procedure, sulfamides containing internal alkenes failed to undergo diamination in the presence of nickel catalysts. This problem had to be solved since 2,3-diamino carboxylic acid motif represents an interesting nonproteinogenic amino acid, that has attracted attention for its presence in biologically active compounds, and sulfamides are more conveniently accessible than the previously developed ureas and they show a broader potential for structural diversification.

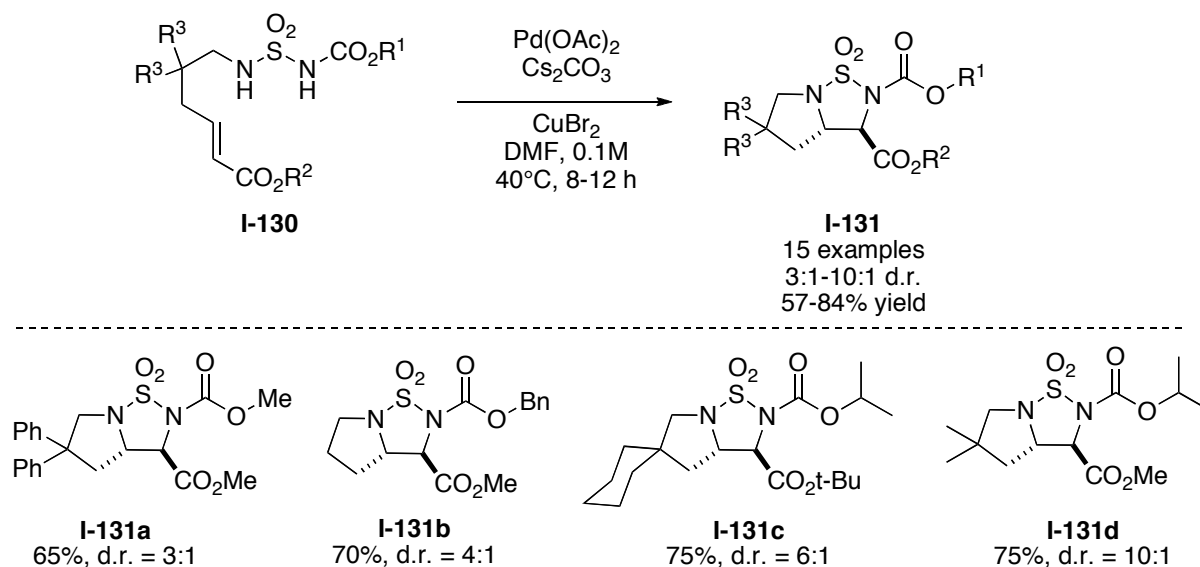
Thus an intermolecular diamination of acrylates using sulfamide groups was recently reported by Muñiz and co-workers.^[128] Starting material **I-130** is available from cross-metathesis

between alkylester-acrylates and previously described ω -alkenyl sulfamide using Grubbs-Hoveyda 2nd generation catalyst **I-23** (Scheme 38).



Scheme 38. Ru-catalysed cross-metathesis to starting material **I-97**.

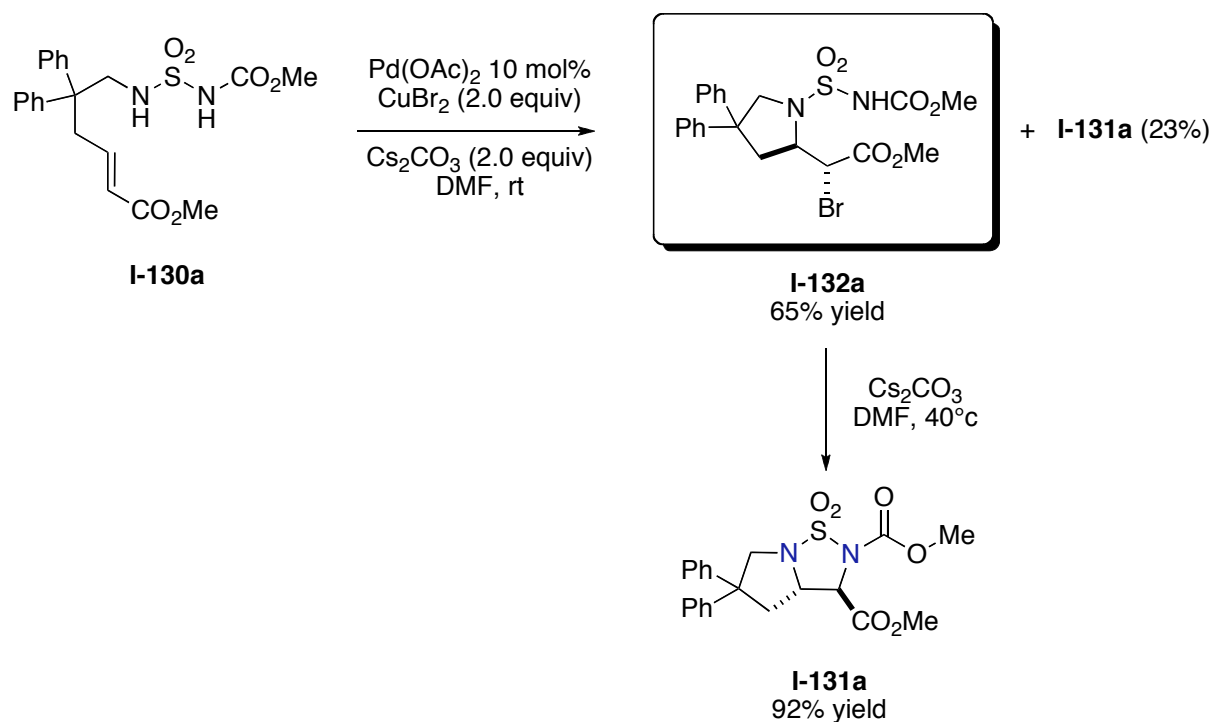
After some experimentations, conditions were found under which diamination reaction of **I-130** proceeded under palladium catalysis with high yield and good diastereoselectivity, using CuBr_2 as oxidant and Cs_2CO_3 as base in DMF at 40°C with 8 to 12 hours of reaction (Scheme 39). The reaction is general for a range of different substrates, with variation of the backbone substituents and both ester groups (Scheme 39).



Scheme 39. Intramolecular palladium(II) catalyzed diamination of acrylates.

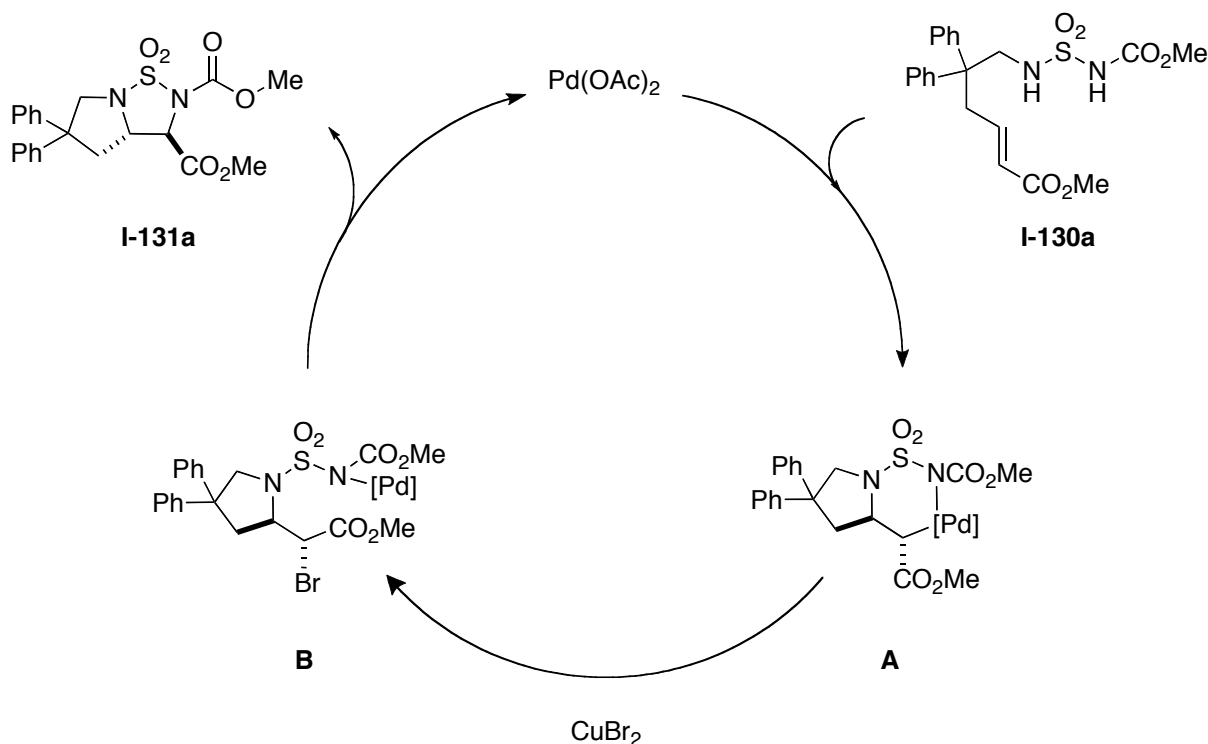
About the mechanism, when **I-130a** was oxidised at room temperature (Scheme 40), the corresponding aminobrominated product **I-132a** was the major product (65% isolated yield)

together with **I-131a** (23%). Treatment of the isolated aminobrominated intermediate **I-132a** with base in DMF gave the expected product **I-131a** as single isomer in 92% isolated yield.



Scheme 40. Aminobrominated intermediate of the intramolecular diamination reaction of **I-130a**.

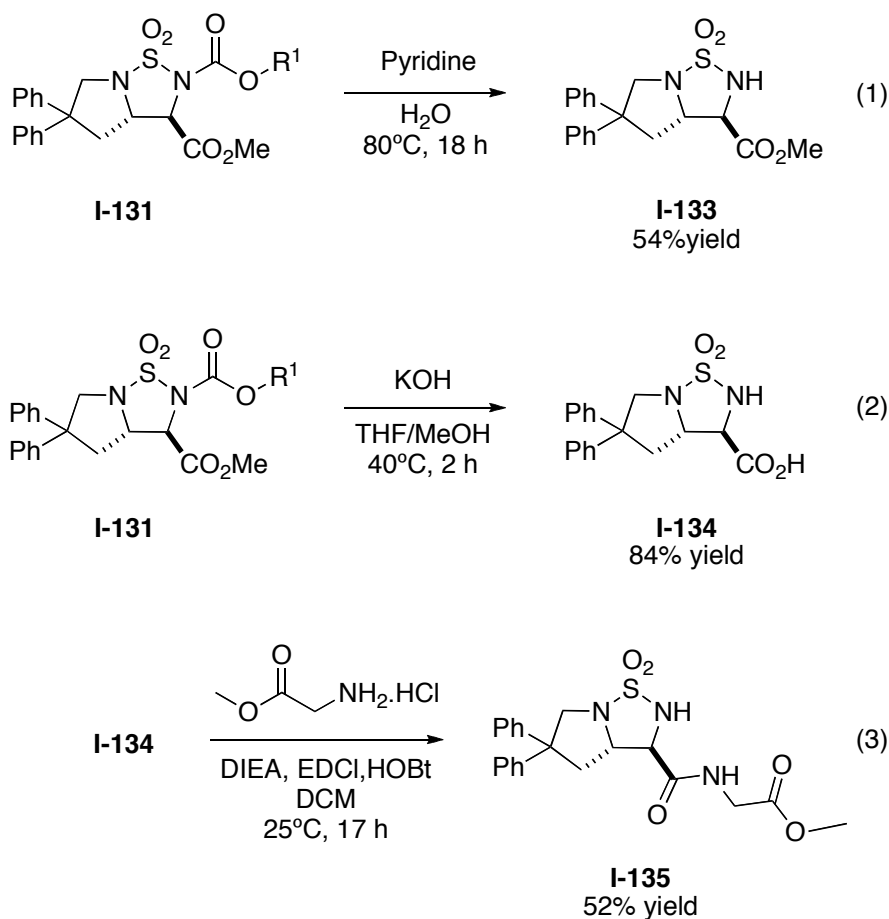
This reaction outcome suggests that the present diamination reaction proceeds through a catalytic cycle beginning by a *syn*-aminopalladation^[129-131] to intermediate **A** (Scheme 41) followed by copper-mediated transient palladium oxidation with concomitant C-Br bond formation (**B**). This latter step proceeds with clean $\text{S}_{\text{N}}2$ chemistry leading to inversion of configuration at carbon. Subsequent C-N bond formation from **B** under second inversion of configuration leads to *anti*-**I-131a**.



Scheme 41. Catalytic cycle for Pd-catalysed diamination of **I-130a**.

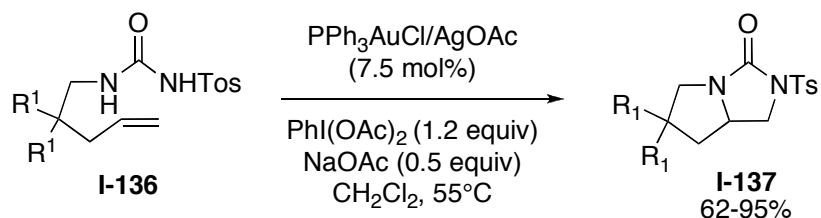
As mentioned before 2,3-diamino carboxylic acids serve as interesting amino acid derivatives, in consequence some general application of products **I-131** in peptide chemistry has been investigated. To this end, it has been found that simple treatment with pyridine in aqueous conditions leads to selective removal of the carbamate groups in compounds **I-131** (Scheme 42, Eq.(1)). Alternatively, use of KOH in THF-methanol solution cleaves both the carbamate and the ester groups of **I-131** to arrive at the free carboxylate **I-134** with intact sulfamate. This aspect should be of interest as it retains the structural rigidity of the *anti*-configured bicyclic system. Coupling of the free acid terminus to glycine methyl ester under standard conditions furnished the coupling product **I-135** in 52 % yield (Scheme 42, Eq.(3)).^[132]

Going further in the process of diamination, intra-inter and inter-intramolecular versions will next be discussed.



Scheme 42. Synthetic transformation of diamination products **I-131**.

In the meantime, in 2009, complementary to the described palladium or nickel-mediated intramolecular diamination, Muñiz and co-workers developed a new diamination methodology using ureas as nitrogen source but, this time, with gold as catalyst (Scheme 43).^[133] This reaction provides diamination product (**I-137**) in good to excellent yields and constitutes one of the rare examples of gold catalysis under oxidative conditions.

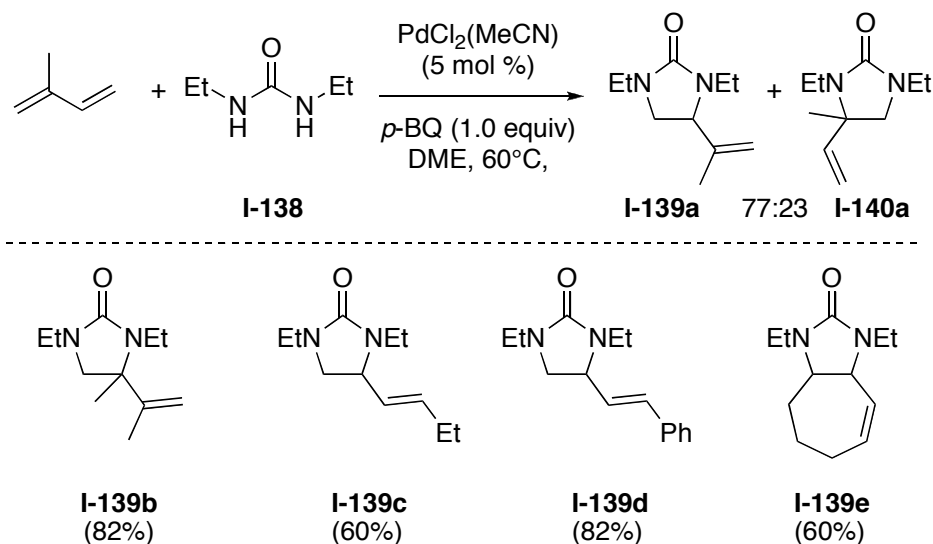


Scheme 43. Gold-catalysed intramolecular diamination.

After a complete study of each step of the mechanism, new pathways for gold-catalysed amination reactions have been proposed. The proposed mechanism begins with an *anti*-aminometallation, followed by an irreversible oxidation of the resulting alkyl gold complex to the corresponding gold(III) complex and terminates with an intramolecular alkyl-nitrogen bond formation that regenerates the gold(I) catalyst and closes the cycle.

2.3.3. Metal catalysed inter-intra and intra-intermolecular diamination

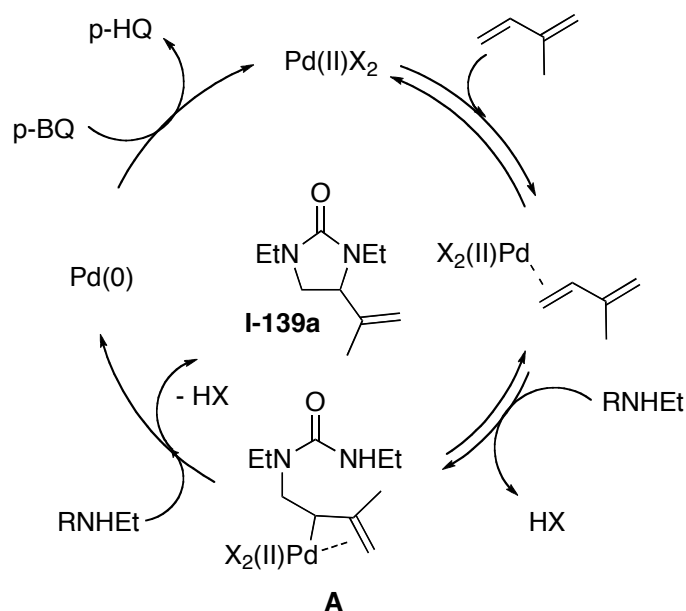
In 2005 Booker-Milburn, Lloyd-Jones and co-workers showed that the inter-intramolecular diamination can be achieved using ureas and Pd(II) as catalyst, but conjugated dienes are required as substrates.^[134] The reaction proceeds through the use of *N,N*-diethylurea (**I-138**) in the presence of catalytic bis(acetonitrile)palladium dichloride and benzoquinone (*p*-BQ), as a stoichiometric oxidant (Scheme 44). Although the diamination of isoprene took place with few regioselectivity, the addition exclusively takes place at the less substituted alkenes with up to 95% regioselectivity in the case of 1-alkyl and aryl-substituted dienes, giving rise to only 1,2-adducts **I-139** (Scheme 44).



Scheme 44. Pd(II)-catalysed inter-intramolecular diamination of conjugated dienes using ureas.

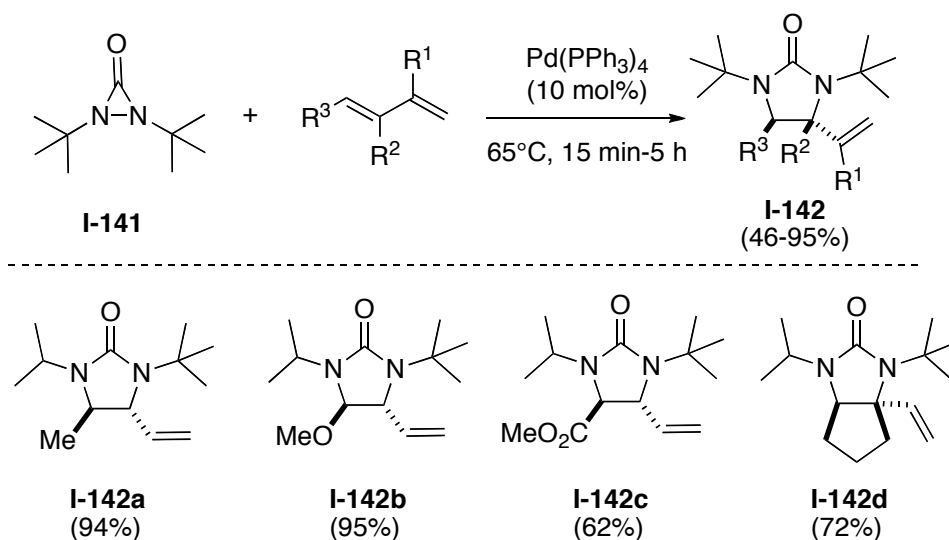
During their investigations, Booker-Milburn and Lloyd-Jones observed that a chloride-bearing Pd(II) was necessary for the success of the reaction and thus proposed the mechanism outlined in Scheme 45. They proposed a first coordination of the alkene to the palladium

followed by an *anti*-aminopalladation, which is generating a η^3 -allyl intermediate **A**. The intermediate **A**, in preference to β -hydride elimination, undergoes an intramolecular displacement of Pd(II) giving rise to the cyclic diamine **I-139a** and at the meantime generates Pd(0), which is then reoxidised by benzoquinone and closes the catalytic cycle.



Scheme 45. Mechanism of Pd(II)-catalyzed diamination of dienes proposed by Booker-Milburn, Lloyd-Jones et al.

Two years later, while ureas and related compounds were emerging as optimal reagents for oxidative metal-catalysed diaminations, Shi and co-workers envisaged a related reagent in the form of a diaziridinone, which might be activated by metal species in their low oxidation state by oxidative addition (Scheme 46). Indeed, strained three-membered cyclic compounds are known to be able to initiate catalytic processes by undergoing an initial oxidative addition with electron-rich transition-metal derivatives. This strategy offers a new diamination process, in which the initial oxidative addition activates the nitrogen atoms of the reagent and avoids the use of an additional oxidant for the metal. This approach of Shi is directly linked to the work of Donohoe^[135] and Yoon^[136] who have, respectively, employed *N*-sulfonyloxycarbamates and *N*-sulfonyl oxaziridines as ‘preoxidised’ nitrogen sources for the oxamination of alkenes. One of the biggest interest of this procedure results in the absence of an external oxidising agent. Thus, di-*tert*-butyldiaziridinone (**I-141**) served as the nitrogen source for a Pd(0)-catalysed diamination of conjugated dienes and trienes (Scheme 46).^[137]

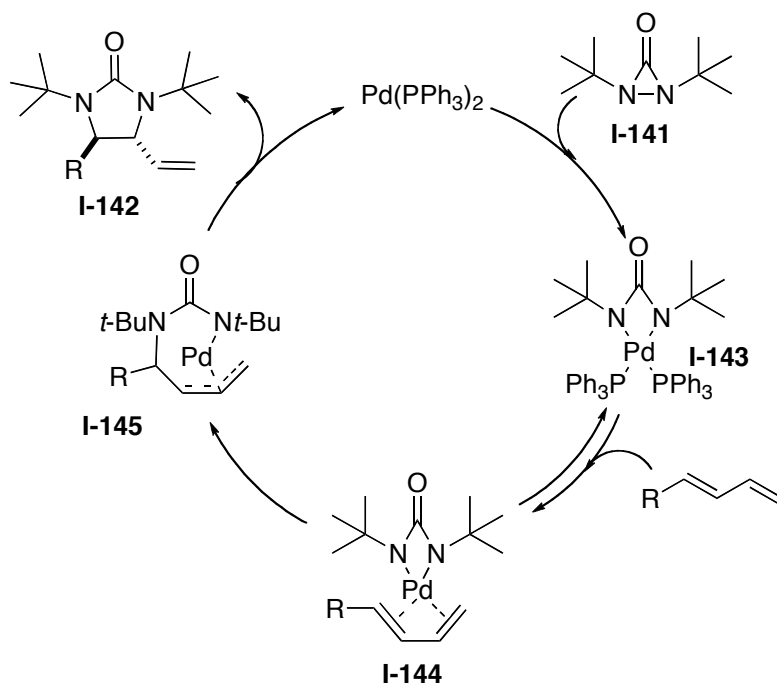


Scheme 46. The Pd(0)-catalysed diamination of conjugated dienes developed by Shi.

Through the use of **I-141** and Pd(PPh₃)₄ as catalyst, a range of substrates undergo diamination to form imidazolidinones **I-142** with moderate to high yield and excellent regioselectivity. Importantly from a synthetic utility standpoint, a simple treatment of **I-142** with strong acids, such as TFA, allows the removal of the *N-tert*-butyl groups and alternatively, a harsher treatment with aqueous acid under reflux conditions affords complete deprotection to the corresponding 1,2-diamines.

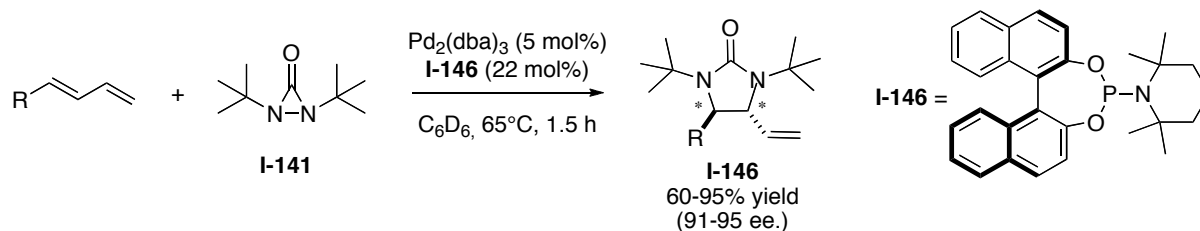
The difference of regioselectivity between the diamination from Booker-Milburn and Lloyd-Jones^[134] and the one observed by Shi imply a different mechanism.

After studying the reaction, Shi has proposed the diamination in this case proceeds through the mechanism outlined in Scheme 47. The first step, which is the rate-determining step, consist in an oxidative insertion of a Pd(0) specie into the N–N bond of **I-141** to form the four-membered Pd(II) complex **I-143**. Then a reversible ligand exchange with conjugated diene forms the complex **I-144**, which undergoes a migratory insertion to give rise to the π -allyl species **I-145**. The last step results in a reductive elimination, leading to the product **I-142** and to the regeneration of the Pd(0) catalyst.



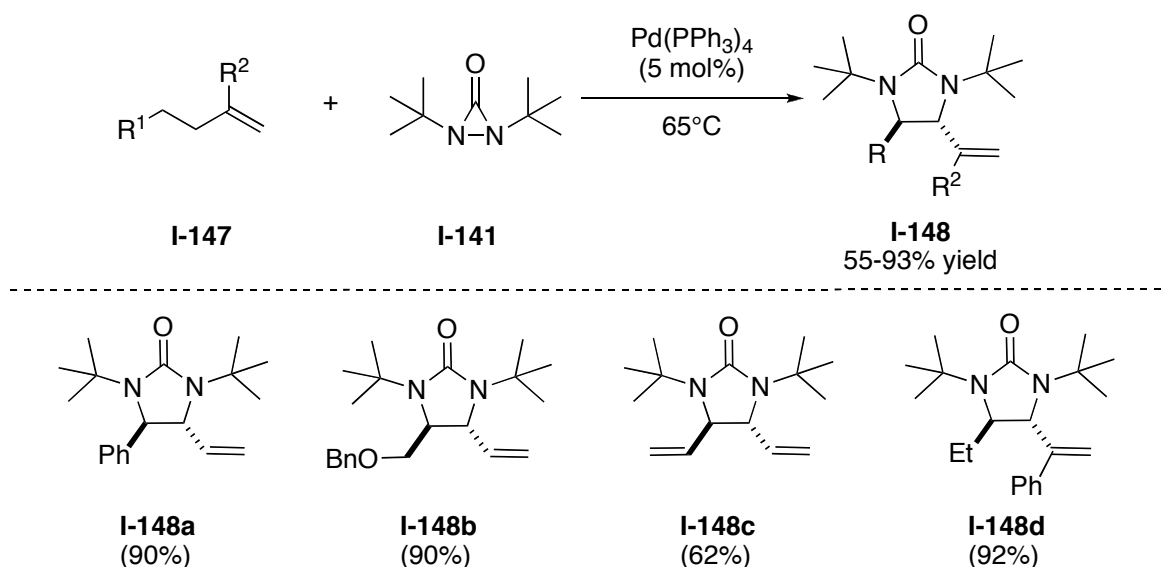
Scheme 47. Proposed catalytic cycle for palladium(0)-catalyzed diamination of 1,3-dienes using di-*tert*-butylidiaziridinone.

The same year, Shi and co-workers have successfully improved their procedure and developed an asymmetric version of this diamination. After the screening the ligand that has given the best enantioselectivity with a range of substrates has been the BINOL-based phosphorous amidite **I-146** (Scheme 48).^[138]



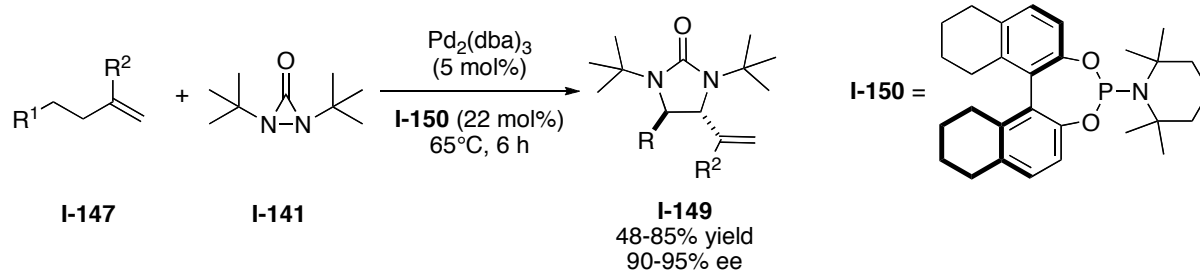
Scheme 48. Asymmetric palladium(0)-catalyzed diamination of conjugated dienes.

Enlarging the procedure, Shi has also found that, in the presence of $\text{Pd}(0)$ and an excess of di-*tert*-butylidiaziridinone (**I-141**), mono-substituted and 1,1-disubstituted alkenes **I-147** give rise to diamination at the allylic and homoallylic positions (Scheme 49). This reaction takes place under solvent free conditions and slow addition of **I-141** and leads to the diaminated products **I-148** in moderate to good yields and complete regio- and stereoselectivity.



Scheme 49. Palladium-catalyzed diamination of terminal alkenes at allylic and homoallylic positions.

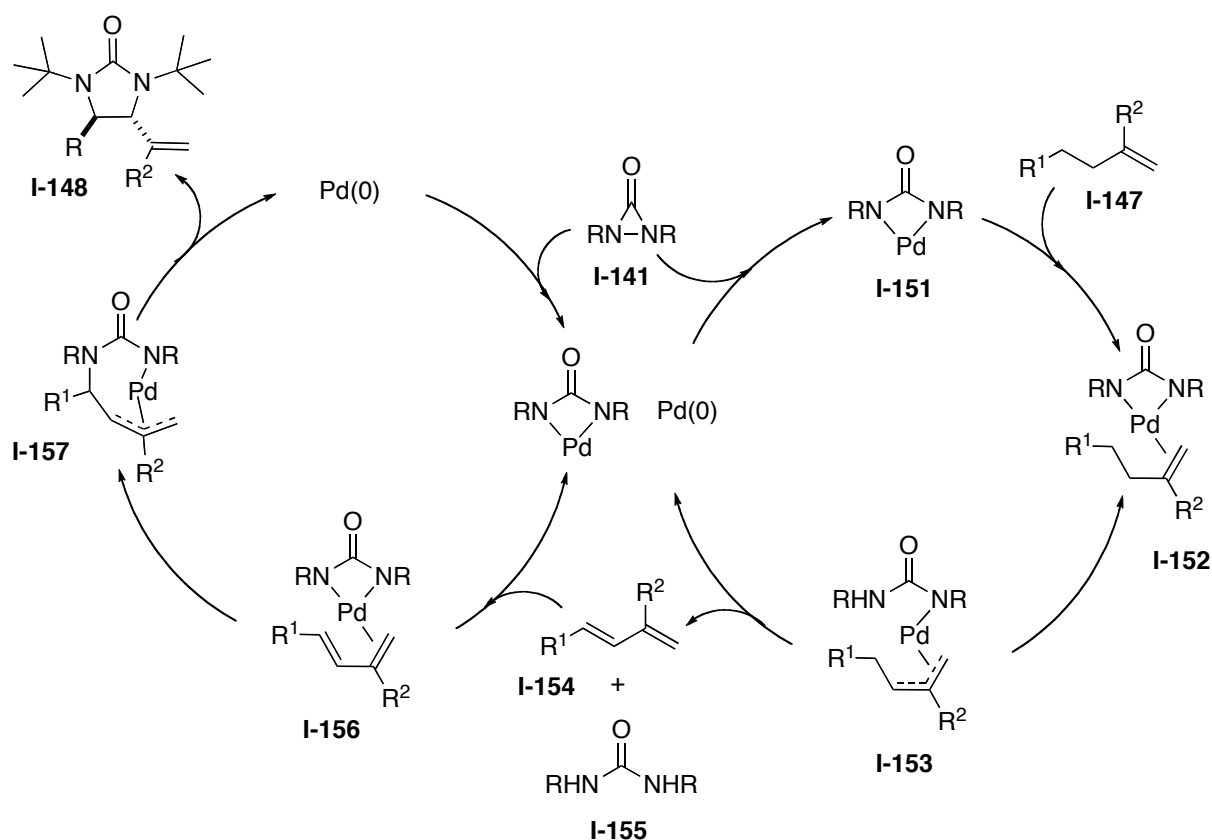
One year later, following the same evolution, Shi has also developed the catalytic asymmetric version of this diamination reaction. In this case, the chiral H_8 -BINOL-derived phosphorus amidite **I-150** in combination with $\text{Pd}_2(\text{dba})_3$ was necessary to obtain a good enantioselectivity (Scheme 50).^[139]



Scheme 50. Palladium-catalyzed asymmetric diamination of terminal alkenes at allylic and homoallylic positions.

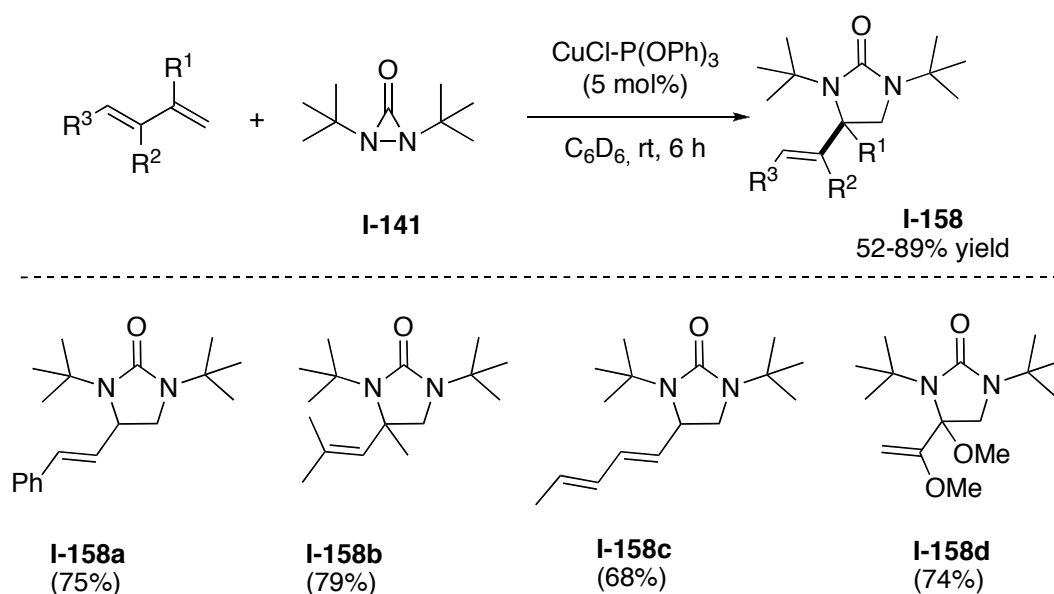
Concerning the mechanism of this transformation, Shi has suggested a catalytic cycle in which diaziridinone **I-141** plays both roles of hydrogen acceptor in the oxidation of alkene **I-147** to the conjugated diene **I-154** and the nitrogen source for the diamination of this *in-situ* formed 1,3-diene (Scheme 51). The mechanism begins with the formation, via oxidative insertion, of **I-151**, which coordinates the alkene **I-147** and allows then the formation of π -allyl complex **I-153** through removal of the allylic hydrogen. A subsequent β -Hydride

elimination from **I-153** regenerates then the Pd(0) catalyst and finally leads to diene **I-154**, which can undergo diamination through the previously discussed mechanism (Scheme 47).



Scheme 51. Proposed catalytic cycle for palladium-catalysed dehydrogenative diamination of terminal alkenes with di-*tert*-butyldiaziridinone.

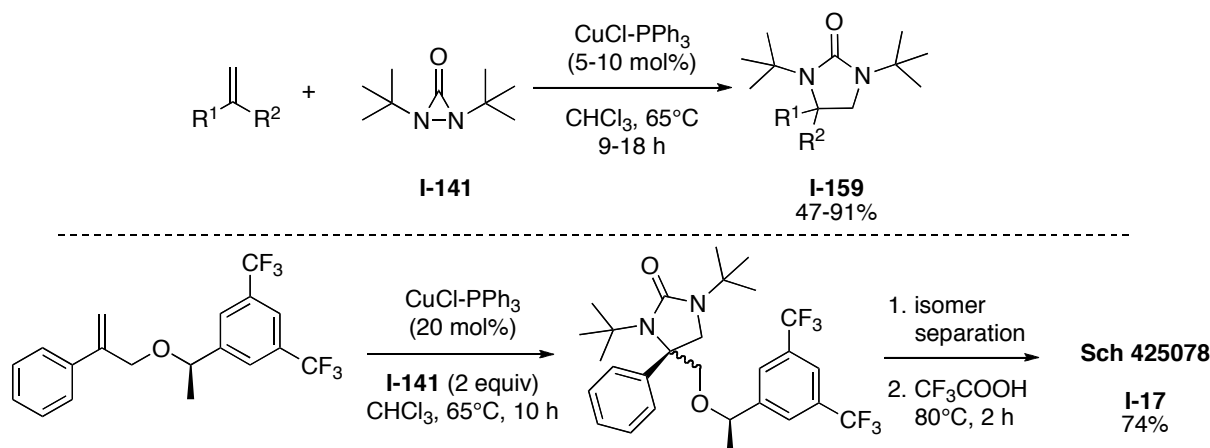
After developing these palladium-catalysed diaminations, Shi has been interested in other metal catalysts, and the same year, in 2007, his group has found that Cu(I) salts were able to catalyse the diamination at the terminal double bond of dienes to give products **I-158** (Scheme 52), providing complementary regioselectivity to the Pd(0)-catalysed diamination product.^[140] Of the various Cu(I) salts and ligands examined, a 1:1 combination of CuCl and P(OPh)₃ was the most effective system (Scheme 52). Using these conditions, diaminations already proceed at room temperature with good to high yields. The switch in the observed regioselectivity of the reactions, going from Pd(0) to Cu(I) catalysts, was ascribed to a change to a different mechanism, which is believed to involve a radical pathway.



Scheme 52. Copper(I)-catalysed terminal diamination of conjugated dienes and trienes.

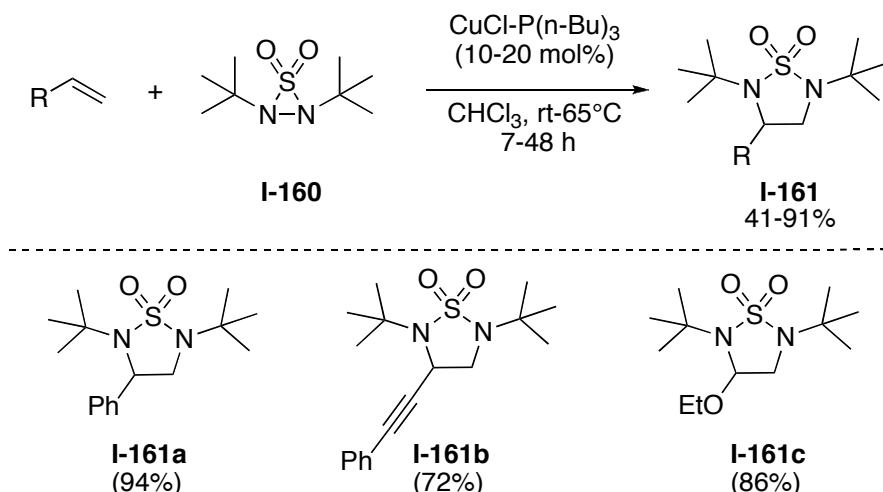
As previously with the palladium-catalysed diamination, Shi successfully developed an asymmetric variant of this process, using this time a combination of CuCl as catalyst and the bisphosphine ligand (R)-DTBM-SEGPHOS.^[141] Under these conditions, conjugated dienes and triene gave the diaminated products with good to high yield and with enantioselectivities between 62 and 74%.

Concerning then the copper-catalysed diamination of alkenes, Shi has found that it was possible to enlarge the scope of the reaction with 1,1-disubstituted olefins that are activated by the presence of an aryl group (Scheme 53).^[142] Importantly, Shi has demonstrated the utility of this procedure via the application of this methodology to the synthesis of the potent NK1-antagonist Sch 425078 (**I-17**).^[142]



Scheme 53. Copper(I)-catalysed diamination of disubstituted terminal alkenes; synthesis of Sch-425078.

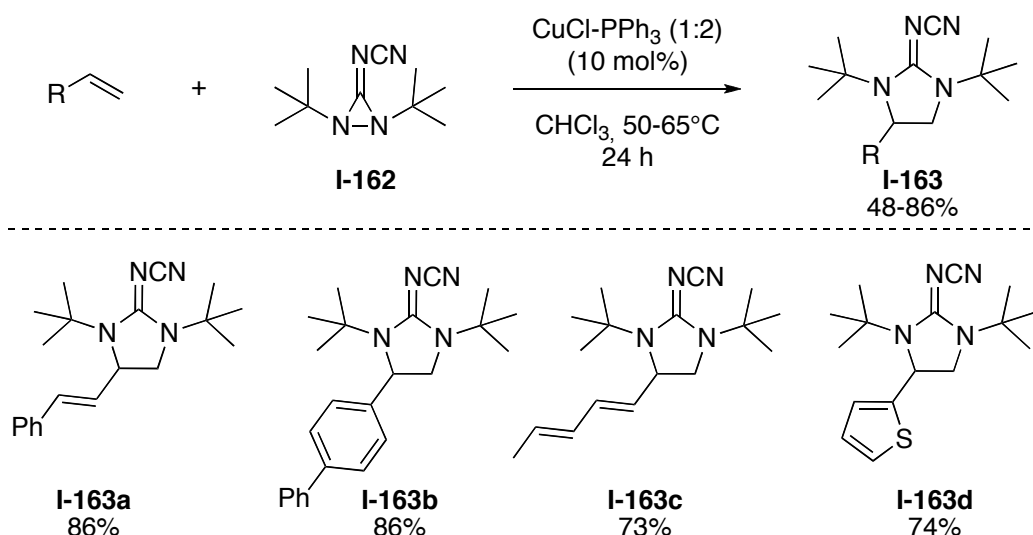
Unfortunately, this copper-catalysed procedure using di-*tert*-butyldiaziridinone **I-141** as nitrogen source does not allow the diamination of monosubstituted terminal olefin, which is always challenging. But, after more experimentations, the diamination was finally reached by replacing **I-141** with di-*tert*-butylthiadiaziridine-1,1-dioxide **I-160** and modifying the copper catalyst, using $\text{CuCl-P}(n\text{-Bu})_3$ instead of $\text{CuCl-P}(\text{OPh})_3$. Thanks to these conditions a range of activated systems, including styrenes, 3-vinylindoles, enynes, and enol ethers can be diaminated in moderate to good yields (41-91%) (Scheme 54).^[143]



Scheme 54. Copper(I)-catalysed intermolecular diamination of activated terminal alkenes with di-*tert*-butyldiaziridinone.

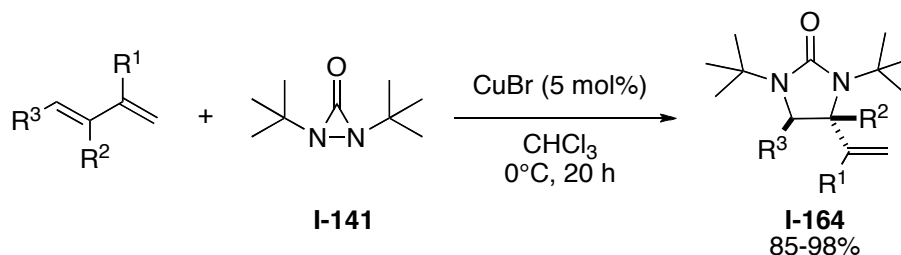
A bit later, Shi and co-workers extended their work to the cycloguanidation of alkenes. They have found that di-*tert*-butyl diaziridinimine **I-162** in the presence of Cu(I)-catalyst, can

undergo diamination at the terminal positions of conjugated dienes, trienes, enynes, and even monosubstituted alkenes to give rise to the products **I-163** in good to excellent yield (Scheme 55).^[144] The deprotection of such products can be done in high yield by simple treatment in acid and then neutralization with NaOH.



Scheme 55. Copper(I)-catalyzed cycloguanidation of alkenes, dienes, and trienes.

Recently, in 2010, Shi has observed that, even in the absence of phosphine ligands, conventional copper(I) salts and in particular the economic CuBr is able to promote alone diene diamination, but with a switch in the regioselectivity leading to the same selectivity than the palladium-catalysed diamination (Scheme 56).^[145] Using again, under these conditions, di-*tert*-butyldiaziridinone **I-141**, diamination is feasible on a range of substrate and leads to imidazolidinones **I-164** in high yield (85-98%).

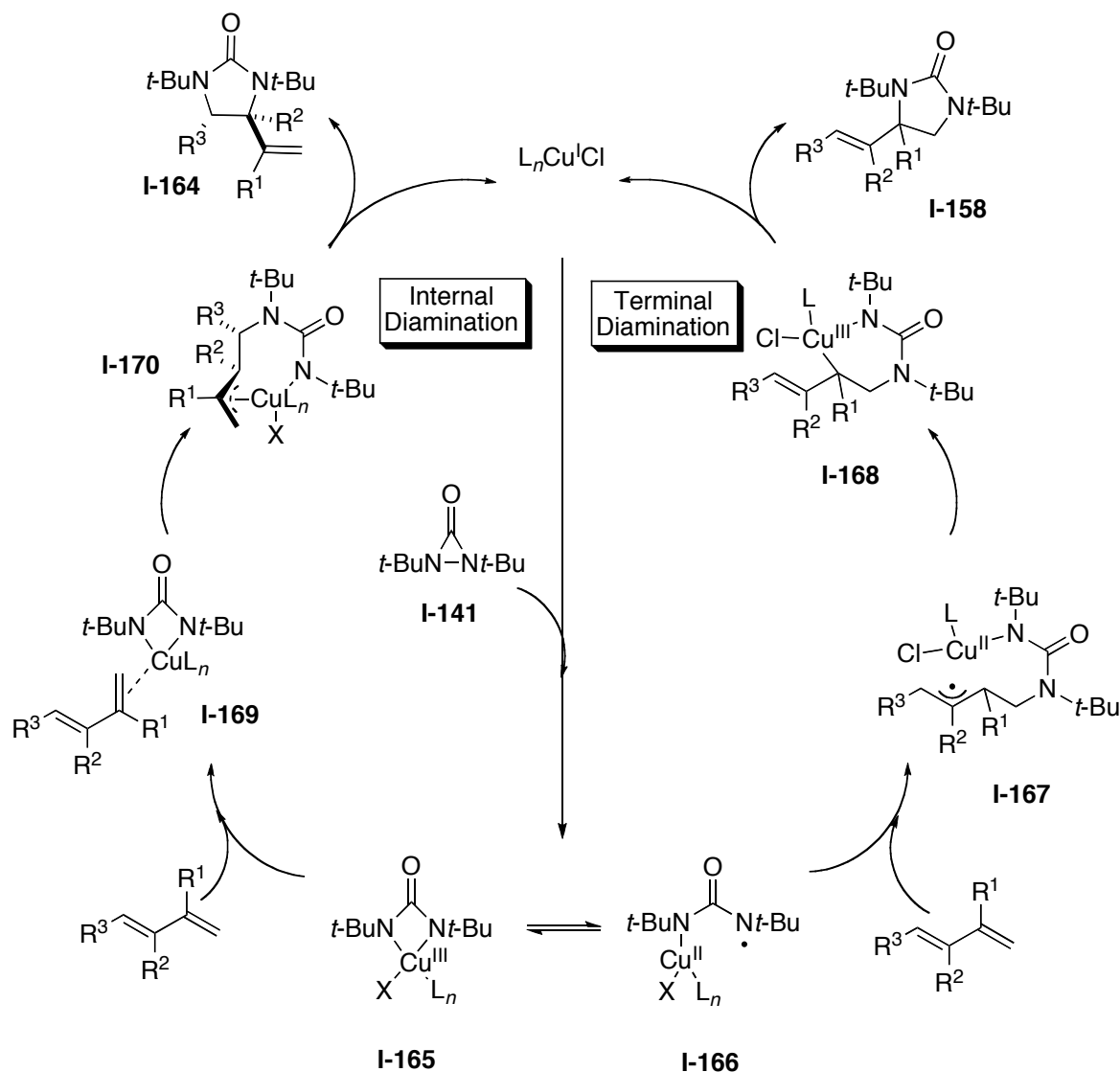


Scheme 56. Copper(I)-catalysed internal diamination of conjugated dienes and trienes.

The difference in regioselectivity observed with the use of CuCl-P(OPh)₃ and CuBr catalysts led to the conclusion that two competing reaction mechanisms exist. The two mechanisms

respectively involving Cu(II) and Cu(III) species (Scheme 57). In both cases, Shi proposed a start from the Cu(I)-mediated cleavage of diaziridinone **I-141** which give rise to Cu(III) complex **I-165** which is itself in equilibrium with the corresponding open-chain Cu(II) amidyl radical **I-166**. Shi proposed that the presence of phosphine ligands favours the formation of **I-166**, which for reason of sterics and stability undergo addition at the terminal position of diene to form the allyl radical **I-167** and/or analog **I-168**. Then the second C-N bond is formed through a reductive elimination and gives rise to the terminal diamination product **I-158**.

In the absence of phosphine ligand the four-membered Cu(III) complex **I-165** is preferentially formed and coordinates the diene to form **I-169**. Then in a similar way to the Pd-catalysed process, migratory insertion of the nitrogen atom to the internal double bond generates the π -allyl species **I-170**. Finally, **I-170** undergoes reductive elimination and gives rise to the internal diamination product **I-164**.



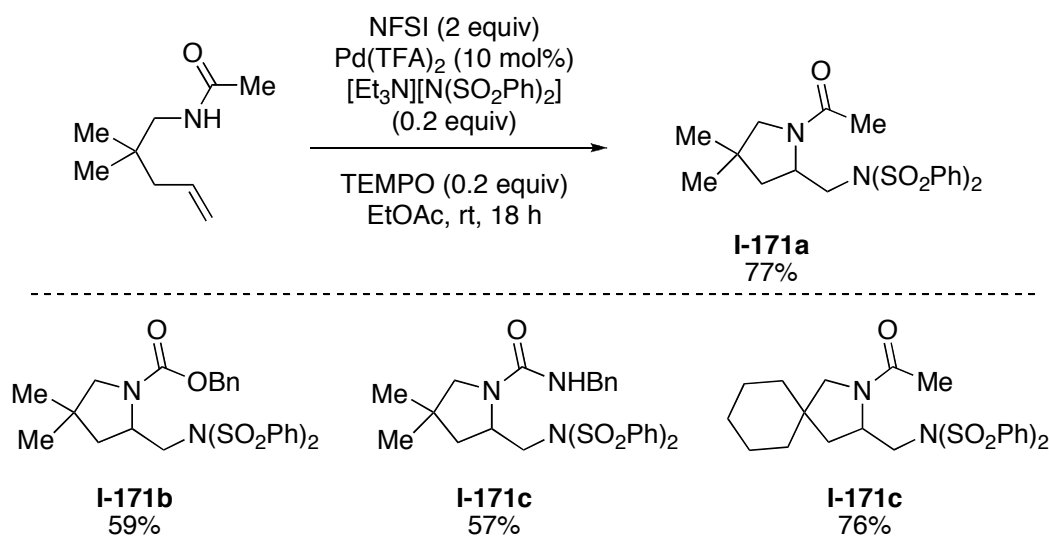
Scheme 57. Proposed dual mechanisms for the copper(I)-catalysed internal and external diamination of conjugated dienes.

Although proceeding through a different mechanism, diaziridinone **I-141** (R = *t*-Bu) has also been used as a dehydrogenating agent in its own right, under copper catalysis.^[146]

After exploring the recent developments of the **inter-intramolecular** metal-catalysed diamination; the **intra-intermolecular** version will now be discussed.

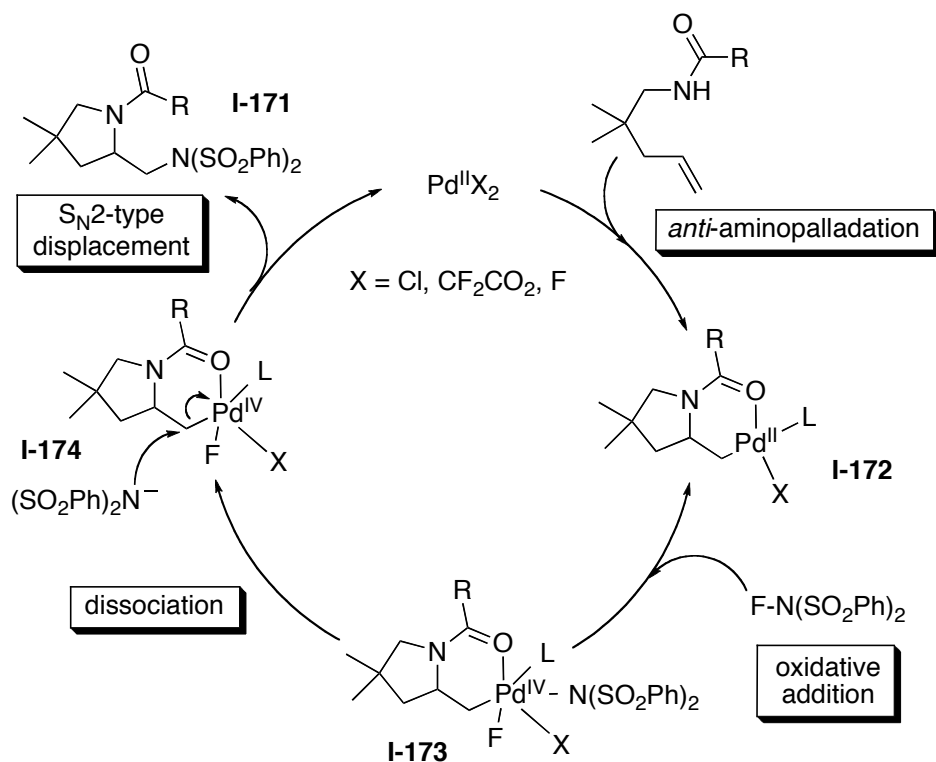
In 2009, Michael and co-workers were the first to report an intra/intermolecular diamination, using *N*-fluoro-bis(phenylsulfonyl)imide (NSFI) as an external nitrogen source (Scheme 58).^[147, 148] The 2-aminomethylpyrrolidine derivatives **I-171** are generated through the presence of NSFI, a catalytic amount of palladium(II) trifluoroacetate, a triethylammonium

benzenesulfonimide additive, and 20 mol% of TEMPO, which serves to prevent alkene isomerization (Scheme 58). This methodology is remarkable because of its generality. Even more important is the fact that the diamination products can be differentially deprotected under relatively mild conditions.



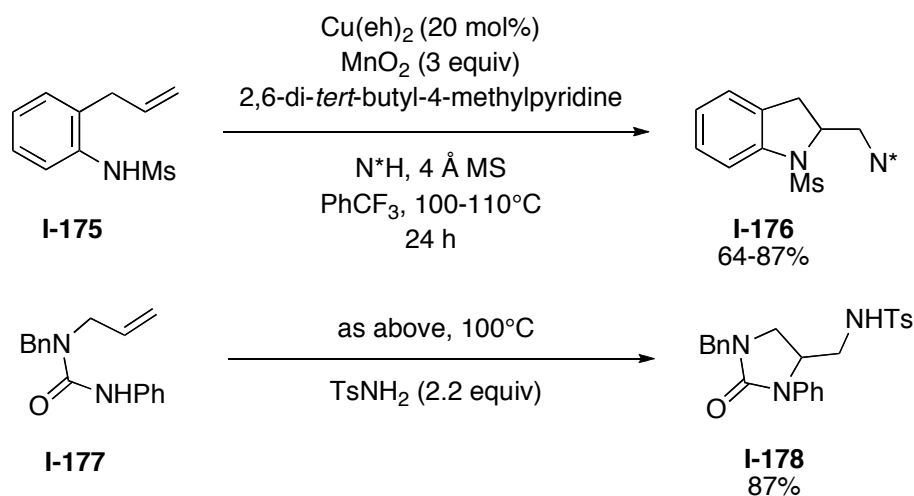
Scheme 58. Palladium-catalysed Intra-Intermolecular diamination.

The mechanistic studies by Michael revealed that the reaction proceeds via an overall *syn*-addition of both nitrogen centers and proposed then the catalytic cycle depicted in Scheme 59.^[147] Michael propose a first *anti*-aminopalladation step leading to Pd(II)-alkyl complex **I-172**. Then Pd(II)-alkyl complex **I-172** undergoes an oxidative addition of NFSI which generates the reactive octahedral-Pd(IV) species **I-173**. Dissociation of benzenesulfonimide takes then place and formation of the second C–N bond occurs through an intermolecular S_N2 displacement. This last step allows the formation of **I-171** and the regeneration of Pd(II). Overall, this work is reminiscent of the stereochemical pathways disclosed by Muñiz in his intramolecular diamination reactions.



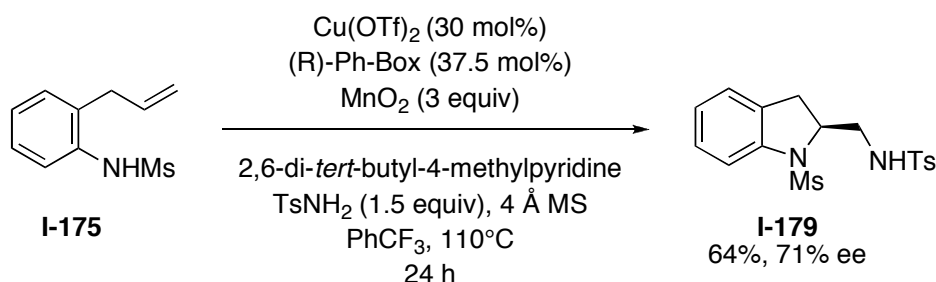
Scheme 59. Proposed catalytic pathway for the palladium-catalysed intra/intermolecular alkene diamination reaction.

One year later, during the improvement of her stoichiometric copper-mediated diamination, Chemler has been able to render the intra/intermolecular alkene diamination reaction catalytic in copper with *N*-sulfonyl-2-allylaniline and *N*-allylurea substrates **I-175** and **I-177** (these are two of the more reactive substrates) using MnO_2 as the stoichiometric oxidant (Scheme 60).^[114]



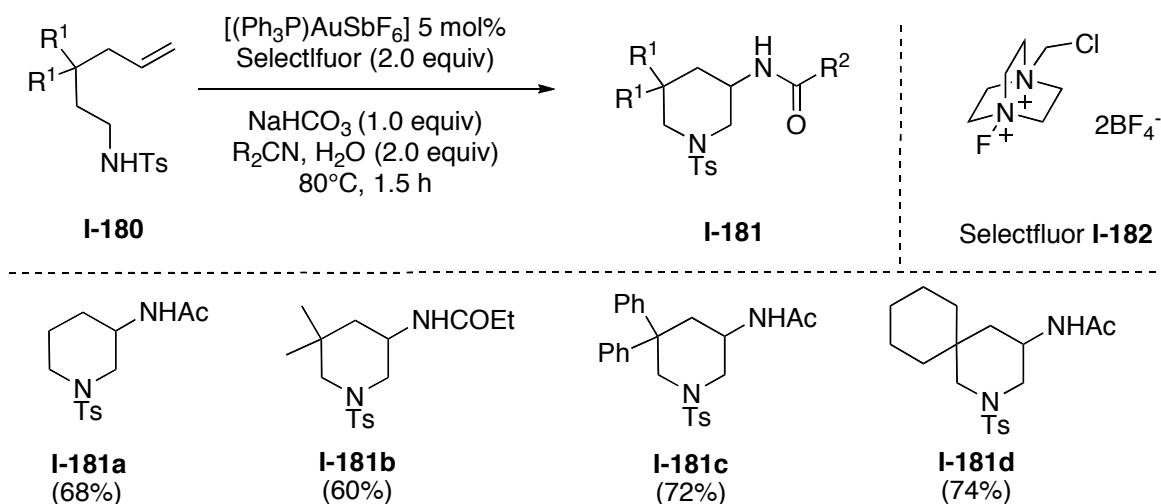
Scheme 60. Copper-catalysed intra/intermolecular diaminations.

The next challenge was then the development of the asymmetric catalysis. To this end, Chemler used the $\text{Cu}(\text{OTf})_2 \cdot (\text{R,R})\text{-Ph-box}$ complex and obtained a promising 64% yield of vicinal diamine **I-179** in 71% ee (Scheme 61). This is the first example of a catalytic enantioselective intramolecular diamination reaction. Unfortunately, this reaction is restricted to few substrates and efforts to further optimise this reaction are apparently ongoing.^[149]



Scheme 61. Asymmetric copper-catalysed intra/intermolecular diaminations.

After palladium in 2009 and copper in 2010, Au(I)/Au(III) catalysis has been extended, in 2011, from the intramolecular^[133] to the intra-intermolecular version by Nevado and de Haro to achieve the intra/intermolecular diamination of N-tosyl-4-pentenyl alkenes **I-180** (Scheme 62).^[150] The *N*-piperidin-3-yl carboxamides **I-181** were formed, in moderate to good yields, through the use of the cationic complex $[(\text{Ph}_3\text{P})\text{AuSbF}_6]$ as catalyst and Selectfluor (**I-182**) as oxidant. External nucleophiles, in this case, are nitriles and the reaction must be considered a Ritter-type amination. Unfortunately, the scope of the reaction is limited to terminal alkene but this method still represents an important alternative to related Pd(II)/Pd(IV)-catalysed processes (Scheme 34).



Scheme 62. Au(I)/Au(III)-catalysed diamination.

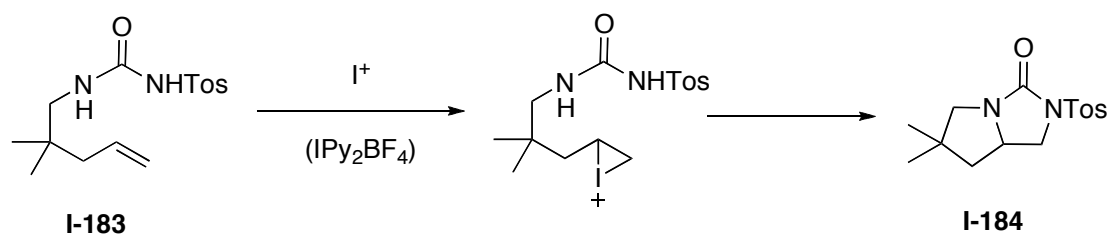
2.4. Main group catalysed diamination

In 2012, Muñiz and co-workers developed a unique catalytic metal-free diamination of alkenes based on bromide catalysis that uses only potassium bromide and sodium chlorite. This unprecedented halide catalysis is of general applicability and proceeds under mild and selective conditions that surpass all conventional metal catalysis in scope.

2.4.1. Introduction

As described previously, in 2005, we initiated a program on catalytic diamination of alkenes using transition metals. We have subsequently developed procedures for intramolecular diamination of simple alkenes that make use of palladium catalysis employing either hypervalent iodine compounds^[121, 123, 151] or copper salts as reoxidant.^[125, 126] A particularly useful protocol is based on the use of homogenous nickel catalysis in combination with iodosobenzene diacetate as oxidant.^[127] Sulfamate groups are employed as nitrogen sources, which are characterized by their convenient way of deprotection to the corresponding free diamines. The groups of Shi and Chemler have contributed interesting copper catalysis for the diamination of alkenes using diaziridinones and related nitrogen sources.

Among our initial developments in this direction, we described a metal-free diamination that made use of the cationic bispyridine iodonium reagent (Scheme 11).^[87]



Scheme 63. Intramolecular cyclisation of π -alkenylureas.

This reaction was further developed by Widenhoefer who introduced N-iodosuccinimide as a suitable promoter for an intramolecular diamination of ureas at room temperature.^[88] Related metal-free intramolecular aminooxygenation reactions of alkenes are also known and are mediated by $\text{PhI}(\text{OAc})_2$ and Lewis or Bronsted acid additives, respectively.^[152-154]

Finally, we have recently contributed an enantioselective metal-free intermolecular diamination using chiral iodine(III) reagents as promoters.^[89]

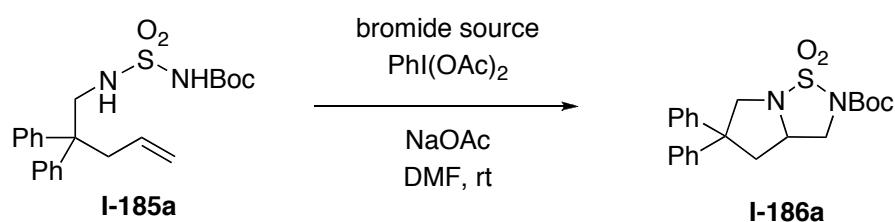
Despite all progress in the area, a reaction *catalytic* in halogen oxidant has remained elusive. Such alternative oxidation protocols that are of higher cost efficiency are obviously desirable. We here describe an approach to this goal employing unique halide catalysis and an economically attractive terminal oxidant.

2.4.2. Results and discussion

Despite its high oxidation potential, iodobenzene diacetate has shown no uncatalyzed background reaction in any of the investigated intramolecular transition metal catalyzed transformations.^[121, 123, 147, 148, 151] When bromide ions are present, however, an intriguing change of reactivity is observed. For example, during the course of its development the use of NiBr_2 in our nickel catalyzed diamination of sulfamides^[127] was found to result in complete conversion at lower temperatures than usually employed in this type of reactions. This change in reactivity was attributed to the formation of halonium ions as the sole promoter for alkene oxidation. Initial experiments showed that this phenomenon was not limited to the use of stoichiometric amounts of halide (NBS) but turned over several cycles, when catalytic amounts of halide and $\text{PhI}(\text{OAc})_2$ as oxidant were used (Table 1). This observation led to the investigation of more economic bromide sources under otherwise unchanged conditions revealing that CuBr_2 , KBr , NBS and $\text{CaBr}_2 \cdot 2\text{H}_2\text{O}$ could be used without any loss in reactivity (Table 1, entries 1-8). The assumption of a diamination catalysed by a Br catalyst is supported

by the observation that the presence of chloride ions does not result in any reactivity, while presence of the easier oxidizable bromide does.

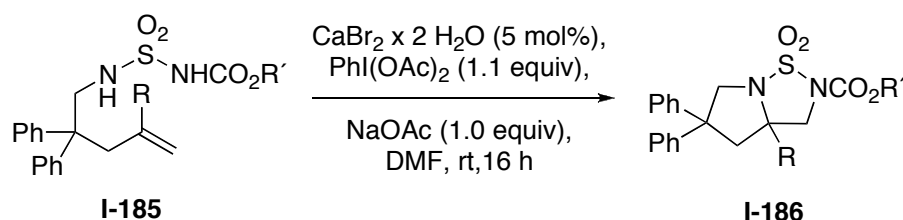
Such an example of a halide catalyzed reaction is rare. Within an important precedence, Sharpless devised a related bromide catalyzed aziridination of olefins with chloramine-T.^[155] The challenge of halide based catalysts usually lies in the easy deactivation of the catalyst as it forms essentially stable bonds to the carbon substrates and is hence easily removed from the catalytic cycle. On the other hand the catalytic use of main group elements may overcome many obstacles of a stoichiometric system, like unselective reactivity that is caused by high reactant concentrations and inhibition by the stoichiometric byproducts of the main group reagents, and thus may result in higher activity and selectivity than stoichiometric reactions.



entry	bromide source	mol%	equiv. of PhI(OAc) ₂	equiv. of base	yield [%]
1	NiBr ₂	10	2	2	99
2	CuBr ₂	10	2	2	99
3	NBS	10	2	2	99
4	NBS	10	1.1	2	99
5	CaBr ₂ x 2H ₂ O	5	1.1	1.0	99
6	CaBr ₂ x 2H ₂ O	10	1.1	0	70
7	CaBr ₂ x 2H ₂ O	5	1.1	1.0	99
8	KBr	10	2	2	99
9	KBr	10	1.1	1.0	99

Table 1. Screening of Br sources. ^aCalculated yields from crude ¹H NMR.

For the mentioned reaction of **I-185a**, the required amount of base could be lowered to 1.0 equiv. without loss of yield, while a total abdication of base led to lowered conversion of 70%. Different solvents were tested in this bromide catalyzed diamination of sulfamides, but only DMF proved viable for this transformation, with all other solvents resulting in either complete inhibition of any reaction or the formation of multiple side products. The optimized conditions, which call for the use of 10 mol% KBr, 1.1 equivalent of oxidant, 1.0 equivalent of NaOAc base and DMF at room temperature, were applied for a number of different substituted sulfamides **I-185a-f** including methyl-, t-butyl- and benzyl carbamates, and 2-substituted olefins (Table 2). All substrates underwent quantitative conversion under the optimized reaction conditions and the cyclic sulfamides **I-186a-f** were isolated in quantitative yield.

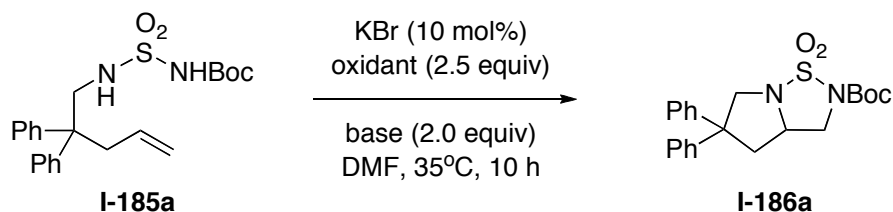


Entry	R =	CO ₂ R' =	product	yield [%] ^a
1	H	Boc		I-186a 95
2	H	CO ₂ Me		I-186b 99
3	H	Cbz		I-186c 99
4	Me	Boc		I-186d 99
5	Me	Cbz		I-186e 97
6	Ph	Cbz		I-186f 99

Table 2. Bromide catalyzed diamination with PhI(OAc)₂ as terminal oxidant. ^aCalculated yields from crude ¹H NMR.

A simple reduction of any remaining oxidant by treatment with aqueous Na₂S₂O₃ solution, extraction and removal of volatile material under reduced pressure readily yielded the diamination products in analytically pure quality. No reactions are observed in the absence of

a bromide source, which concludes a reaction catalytic in Br. Despite the exciting accomplishment of this *first metal-free catalytic* diamination, the present method retains the drawback of a stoichiometric amount of iodosobenzene diacetate. This renders the overall reaction rather cost intensive and requires the disposal of iodobenzene as by-product.

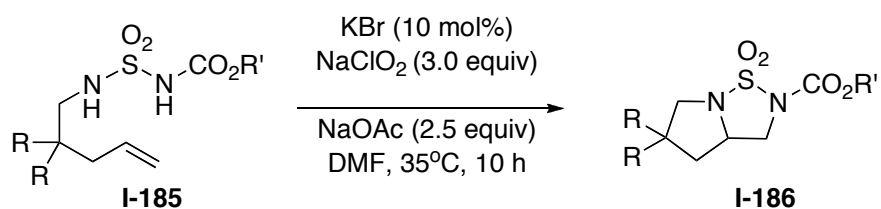


entry	oxidant	base	yield [%] ^a
1	CuBr ₂	Cs ₂ CO ₃	90
2	Cu(NO ₃) ₂	Cs ₂ CO ₃	10
3	MnO ₂	NaOAc	0
4	MnO ₂	no base	0
5	NaOCl	NaOAc	20
6	NaClO ₂	Cs ₂ CO ₃	50
7	NaClO ₂	NaOAc	95

Table 3. Screening of terminal oxidants. ^a Estimated yield from crude ¹H nmr.

As a consequence, screening for a more attractive replacement of this oxidant was undertaken (Table 3). While copper nitrate showed low reactivity, copper bromide led to a surprisingly high conversion (entries 1,2). Still, this reaction produced a metal residue, which was sometimes difficult to remove completely and product batches were still slightly colored due to trace metal contamination. Attempts with manganese dioxide gave no reaction, both in the presence and absence of acetate base (entries 3,4). Some reactivity was encountered with hypochloride (entry 5), and sodium chlorite finally led to a significant reactivity (entries 6, 7). No reaction was observed with sodium chlorite alone in the absence of potassium bromide. Under these conditions, a series of ω-alkenyl sulfamates **I-185** was converted into the corresponding cyclic sulfamates **I-186** (Table 4). This comprises differently substituted

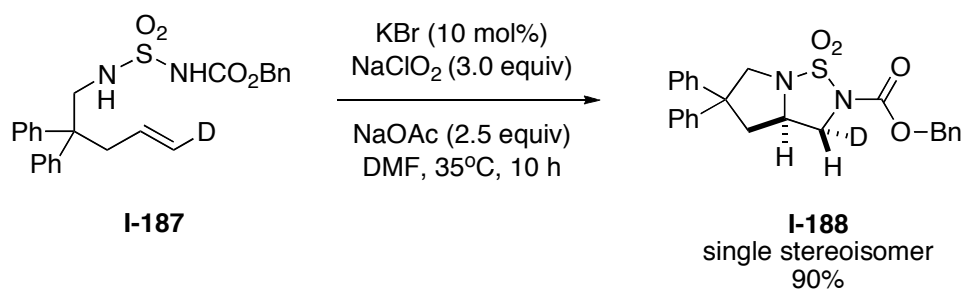
backbones as well as sulfamate carbamoyl groups (entries 1-5). In addition, the simple alkyl chain did also undergo clean diamination and the corresponding product was characterized by X-ray analysis (entry 6). Substituted alkenes showed excellent reactivity as well (entries 7,8). Conversion is quantitative in all cases and isolated yields greatly surpass the ones from related metal catalysis.^[127]



Entry	Starting Material	Product	Yield [%] ^[a]
1	 I-185a	 I-186a	95
2	 I-185b	 I-186b	90
3	 I-185c	 I-186c	97
4	 I-185e	 I-186e	87
5	 I-185f	 I-186f	90
6	 I-185g	 I-186g	85
7	 I-185h	 I-186h	95
8	 I-185i	 I-186i	88

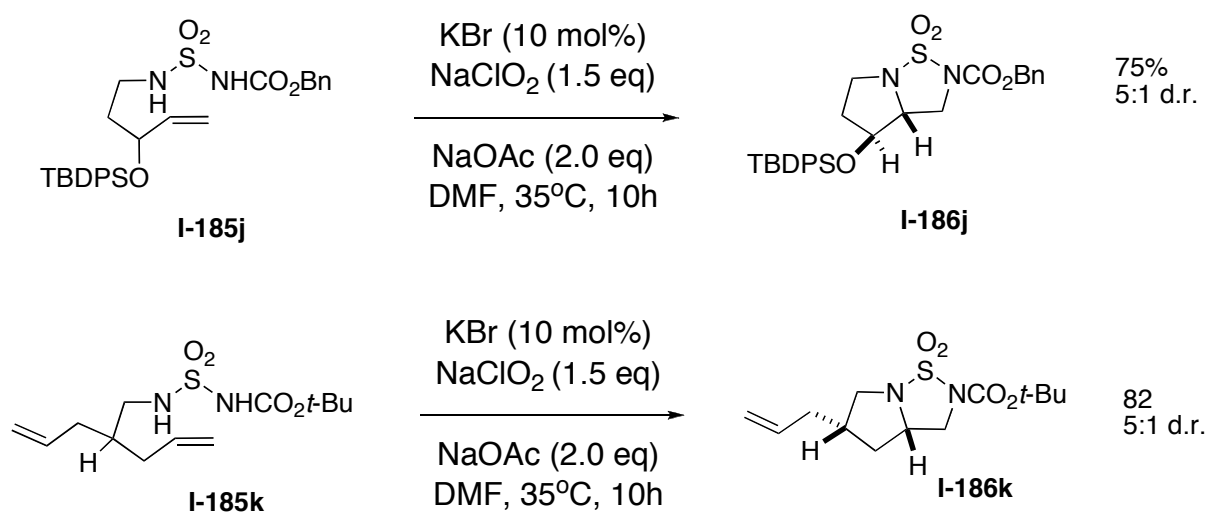
Table 4. Br-catalysed intramolecular diamination of terminal alkenes. ^a Isolated yield after purification.

A stereochemical control experiment confirms that the overall diamination proceeds with stereospecificity regarding the double bond geometry. Hence, when the selectively deuterated substrate **I-187** was submitted to diamination under the metal-free conditions the corresponding product **I-188** was obtained as a single diastereoisomer. Based on previous analysis,^[127] compound **I-188** displays the expected *trans*-configuration.



Scheme 64. Stereochemical control experiment.

Next, starting materials **I-185j** and **I-185k** were investigated (Scheme 65). In both cases, reasonable diastereoselectivity was obtained for the chiral products. For the product **I-186k** and its minor diastereomer **I-186k'** the relative configuration was determined by crystallographic analysis (Figure 9). Note that the second alkene of **I-185k** does remain unfunctionalized under the conditions of Br catalysis. This observation confirms that the present conditions are optimized for the selective intramolecular diamination, but otherwise do not affect free alkenes.



Scheme 65. Diastereoselective metal-free diamination reactions.

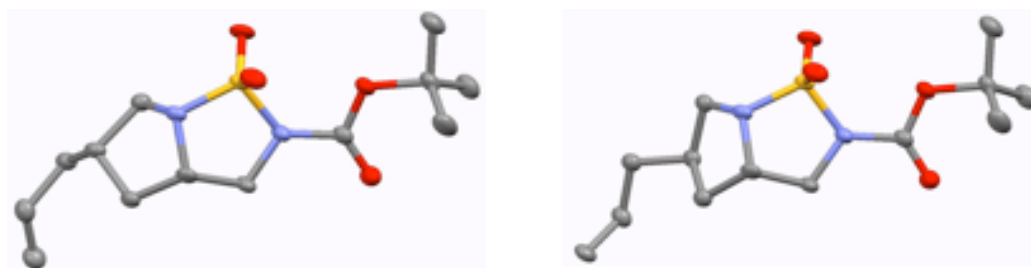


Figure 9. Solid state structures of **186k** (left) and **186k'** (right).

In addition to five-membered ring annelation, the present main group catalysis is also capable of generating the corresponding six-membered ring annelation products **I-190a-c** (Table 5), and the constitution of the products was again secured from solid state analysis of **I-190c**. It is noteworthy that these reactions represent the first examples of diamination of alkenes using sulfamates for six-membered ring annelation, as cyclization of compounds **I-189** does not proceed under the conditions of our earlier nickel catalysis^[127] or in the presence of any other metal catalyst.

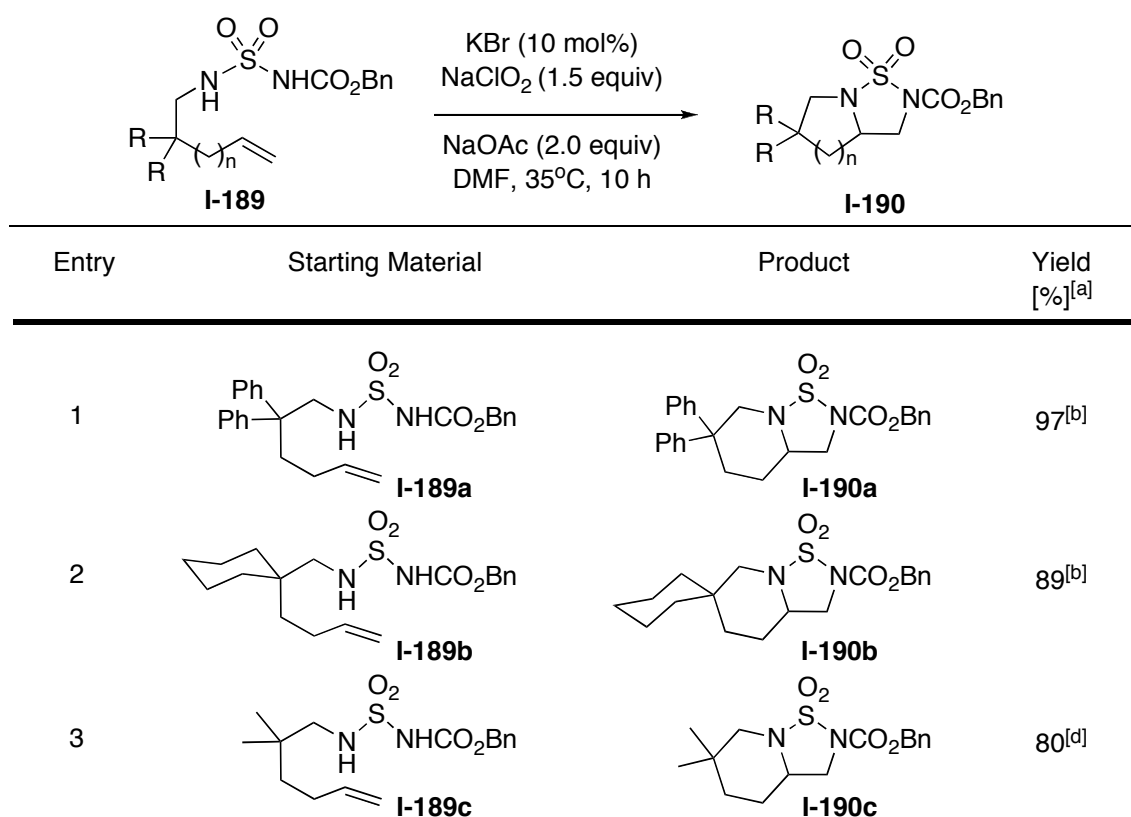


Table 5. Br-catalysed intramolecular diamination leading to six-membered ring annelation. [a] Isolated yield.

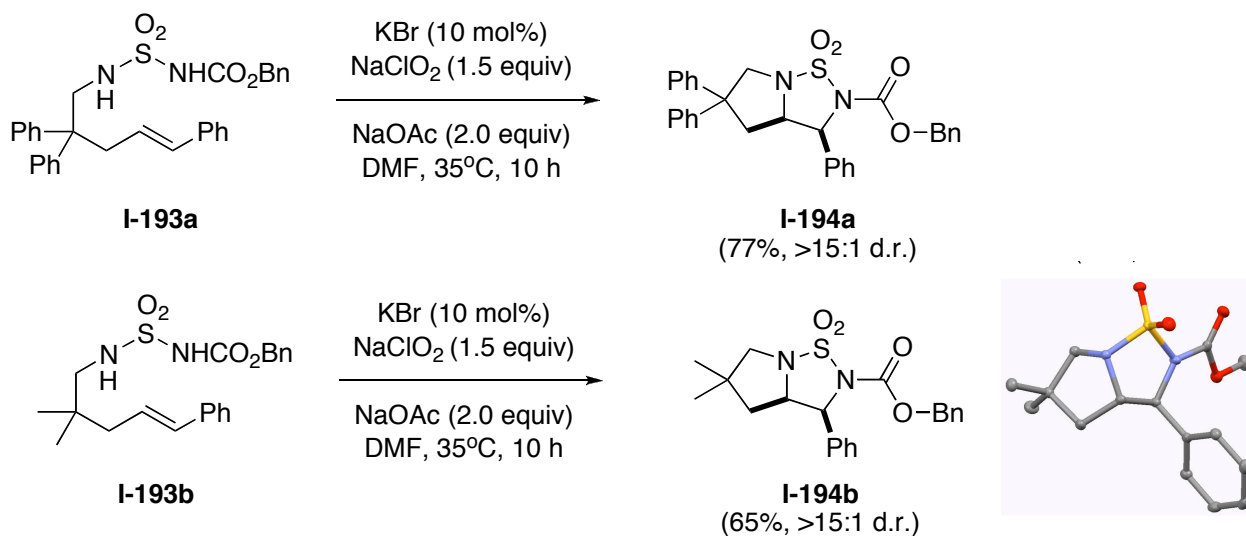
[b] Reaction time 24 h. [c] Reaction time 48 h.

This chemistry also is applicable to ureas. Table 6 displays a representative series of ureas **I-191a-h** that undergo diamination under metal-free conditions. For these cases, it is interesting to see that the reaction proceeds with full chemoselectivity in favor of the diamine product, without any potential aminoxygenation product ever been observed. This is in noteworthy difference to the iodine(III)-mediated intramolecular functionalization of related ureas. Representative examples include various terminal alkenes **I-191a-e** (entries 1-5). Especially interesting is the trichloroacetyl derivative **I-191e**, which does not react under conditions of metal catalysis and which does cyclise under concomitant deprotection to the free urea. Internal alkene **191f** undergoes smooth diamination under conditions that are noteworthy milder than the ones for earlier transformations (entry 6). In addition, six-membered ring annelation is equally efficient (entries 7,8). All these results rival or even surpass related palladium catalysis and the previously described I(py)₂ mediated reactions.

Entry	Startin Material	Product	Yield [%] ^[a]
1	 I-191a	 I-192a	90
2	 I-191b	 I-192b	85
3	 I-191c	 I-192c	92
4	 I-191d	 I-192d	88
5	 I-191e	 I-192e	80
6	 I-191f	 I-192f	91
7	 I-191g	 I-192g	90
8	 I-191h	 I-192h	89

Table 6. Br-catalysed intramolecular diamination using ureas as nitrogen source. [a] Isolated yield.

For subsequent investigation, we limited the substrates to sulfamates as this functional group is more diverse in nature and far easier to manipulate in subsequent steps such as deprotection to the free diamine.



Scheme 66. Diamination of internal alkenes.

Our new metal-free conditions are also compatible with internal alkenes. Scheme 66 shows two examples of the intramolecular diamination of phenyl substituted alkenes. It is remarkable that both products **I-194a,b** are obtained as single diastereoisomers, although the second C-N bond formation requires manipulation of a benzylic position. On the basis of the ^1H nmr coupling constants of $^3J = 7.0$ Hz and 7.4 Hz, respectively, a *trans*-configuration was concluded, which was confirmed by X-ray analysis of product **I-194b**. This result nicely matches the stereochemical outcome from the deuterated alkene **I-187** from Scheme 64.

Finally, a series of acrylates **I-195** were submitted to the metal-free diamination. Again, the expected *trans*-configured products **I-196** were obtained as the major diastereomers (Table 7), although the diastereoselectivities were lower than the ones from the corresponding internal alkenes from Scheme 66. The relative stereochemistry was deduced from comparison with earlier data and from a solid state structure of diamination product **I-196g**.

Entry	Starting Material	Product	d.r.	Yield [%] ^[a]
	<p style="text-align: center;"> $\text{I-195} \xrightarrow[\text{base (2.0 equiv), DMF, 35^\circ\text{C}, 10 h}]{\text{KBr (10 mol\%), oxidant (1.5 equiv)}} \text{I-196}$ </p>			
1	<p style="text-align: center;">I-195a</p>	<p style="text-align: center;">I-196a</p>	4:1	93
2	<p style="text-align: center;">I-195b</p>	<p style="text-align: center;">I-196b</p>	3:1	89
3	<p style="text-align: center;">I-195c</p>	<p style="text-align: center;">I-196c</p>	2:1	70
4	<p style="text-align: center;">I-195d</p>	<p style="text-align: center;">I-196d</p>	4:1	90
5	<p style="text-align: center;">I-195e</p>	<p style="text-align: center;">I-196e</p>	2:5:1	70
6	<p style="text-align: center;">I-195f</p>	<p style="text-align: center;">I-196f</p>	3:1	84
7	<p style="text-align: center;">I-195g</p>	<p style="text-align: center;">I-196g</p>	3:1	83

Table 7. Br-catalysed intramolecular diamination of acrylates. [a] Isolated yield.

Based on the observed reactivity, we propose the following catalytic cycle for the new metal-free diamination with $\text{KBr}/\text{NaClO}_2$ (Figure 10). The reaction starts from bromide, which is originally added in the form of its potassium salt. Oxidation to hypobromite is then accomplished with sodium chlorite, which represents the terminal oxidant.

In the presence of base, this Br^+ species then forms an *N*-brominated carabamoyl group of the sulfamate **A**. Halogenated sulfamates such as **A** are known from synthesis the of thiadiaziridines. In the present case the *N*-Br group oxidises the double bond of the alkene through transition state **B**. The resulting cyclic bromonium ion **C** is consecutively opened by nucleophilic backside attack of sulfamate nitrogen to form the nitrogen heterocycle. The resulting aminobrominated intermediate **D** undergoes an $\text{S}_{\text{N}}2$ reaction, that introduces the second nitrogen, closes the diamine ring to **1** and liberates bromide, which in turn is re-oxidized to close the catalytic cycle. This overall pathway is in full agreement with stereochemical aspects from deuterium labeling and substrates **I-193** and **I-195** containing internal alkenes.

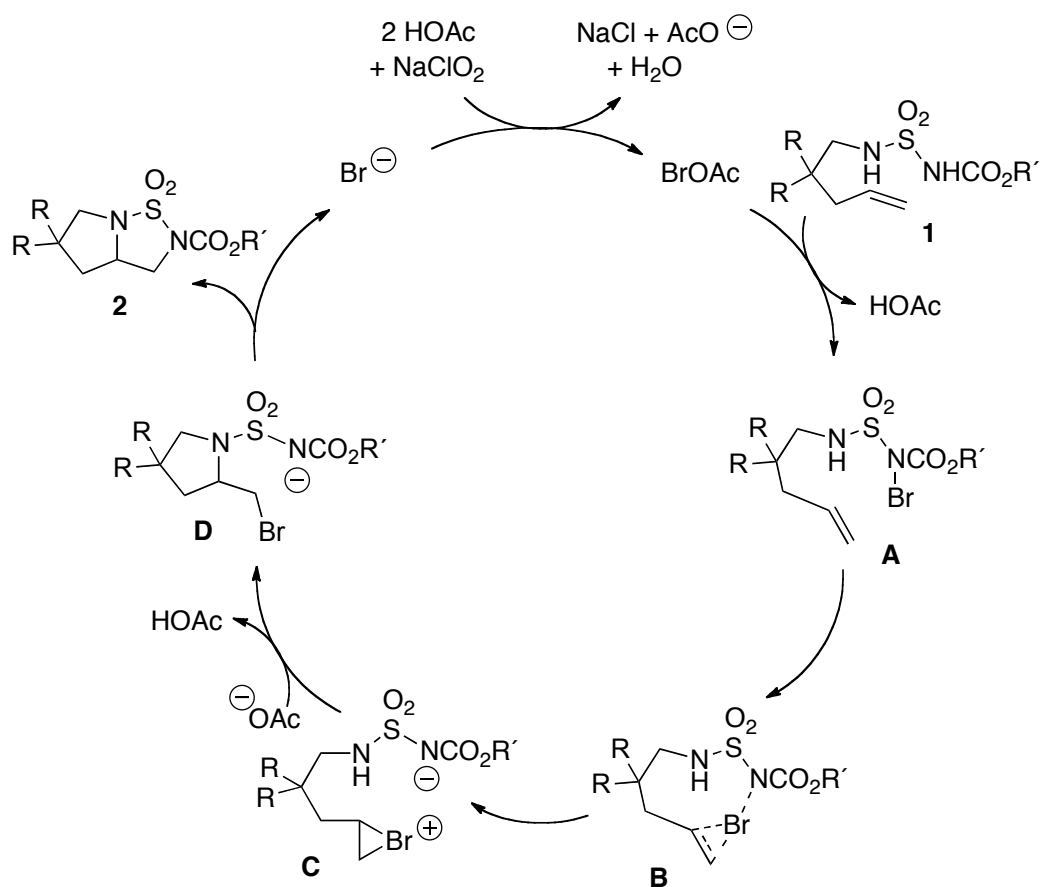
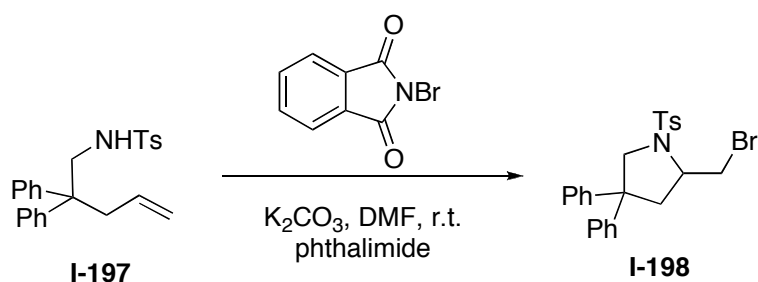


Figure 10. Proposed mechanism for the bromide catalysed diamination.



Scheme 67 . Stoichiometric aminobromination reaction.

The important feature of this cycle consists in the intramolecular reaction pathway for the second C-N bond formation. This step is crucial as it generates bromide and hence allows catalyst regeneration. Such processes might therefore be more difficult for potential intermolecular diamination reactions. For example, cyclization of **I-197** with N-bromophthalimide gives the aminobrominated product **I-198**. In the absence of an intramolecular nitrogen nucleophile and with phthalimide as a weak nucleophile bromide regeneration is essentially prevented. Efforts to overcome this limitation and to provide an intermolecular halide catalysed diamination of alkenes are ongoing.

2.4.3. Conclusions

Overall, we have significantly improved the area of intramolecular diamination of alkenes through the development of a metal-free reaction, which is based on the sole use of a main group catalyst. The reaction can be conducted with a series of terminal oxidants, preferentially with sodium chlorite, which represents a commercially available oxidant.

The present catalyst system bears a broad synthetic potential that should prove useful in the development of alternative oxidation reactions. Investigation along these lines, in particular the application in intermolecular oxidation catalysis is underway.

Results and Discussion

Chapter I: Intermolecular Regioselective 1,2-Diamination of Allylic Ethers

Abstract

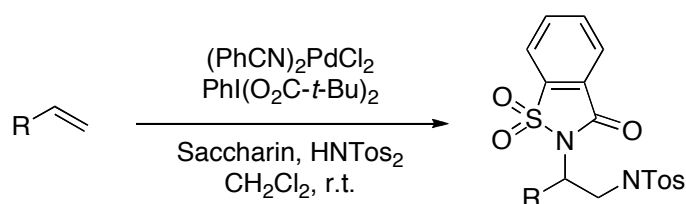
Homogeneous palladium catalysis enables a novel intermolecular regioselective diamination of allylic ethers, which offers a convenient entry into 1,2,3-trisubstituted products. These represent suitable building blocks with differently protected nitrogen atoms for subsequent synthetic application.

Introduction.

The 1,2-diamination of alkenes is an oxidation process to convert carbon-carbon double bonds into vicinal diamine derivatives,^[122, 156, 157] which are of high significance in a variety of areas.^[5, 40, 110, 158]

Recent progress has demonstrated the ability of several transition metals to catalyze this transformation, including palladium,^[87, 121, 123-126, 147, 148] copper,^[114, 142, 143] nickel^[127] and gold.^[133] These reactions share a common concept of intramolecular aminometalation as the initial step and hence give rise to concomitant formation of heterocycles such as pyrrolidines.^[159] In addition to these diamination reactions of non-activated and activated alkenes, Shi has developed elegant sequential δ,γ -C-H activation/diamination reactions of terminal alkenes as well as diamination reactions of 1,3-butadienes.^[134, 137, 160-162]

We recently developed a first strictly intermolecular palladium catalyzed diamination of alkenes (Scheme 68),^[163] using high oxidation state palladium catalysis.^[164]



Scheme 68 . Intermolecular catalyzed-diamination of alkenes.

While quite general for terminal alkenes, we found that allylic ethers do not react under these conditions and are beyond the scope of the reaction. Since allylic ethers can be considered as versatile substrates for alkene oxidation because they lead to an interesting 1,2,3-trifunctionalization, we sought to develop a suitable protocol for this type of substrates. We here report on the regio- and chemoselective intermolecular diamination of allylic ethers and exemplify the utility of the products as versatile building blocks for subsequent organic synthesis.

Results and discussion

At the outset, we took inspiration in the seminal report on intermolecular aminoacetoxylation of allylic ethers by Stahl and Liu.^[165-167] This work demonstrated the versatile combination of phthalimide and a palladium dichloride catalyst to initiate intermolecular aminopalladation. Initial efforts then focused on the exploration of N-fluoro-bis(phenylsulfonyl)imide (NFSI) as a suitable nitrogen source for the second carbon-nitrogen bond instalment.^[147, 148, 168-172]

For the diamination reactions of benzyl allyl ether **1-1a** with phthalimide as nitrogen source and NFSI as oxidant and nitrogen source, a screening of some common palladium salts led only to varyingly low amounts of diamination product (Table 8, entries 1–3). Only palladium bis(hexafluoroacetylacetonate) [Pd(hfacac)₂] as the catalyst precursor was able to induce moderate product formation (entry 4). Under these conditions, phthalimide could also be replaced by saccharin (entry 5). A subsequent screening of solvents revealed that ethyl acetate represented the optimum solvent for the present transformation (entries 5–9). For n-butyl allyl ether **1-1b**, similar reactivity was observed for the two nitrogen sources saccharin and phthalimide, giving rise to products **1-2c** and **1-2d**, respectively (entries 10 and 11).

Entry	R	Y	Pd Catalyst	Solvent	Diamine	Yield %
1	Bn(1-1a)	CO	(MeCN) ₂ PdCl ₂	EtOAc	1-2a	< 10
2	Bn(1-1a)	CO	Pd(OAc) ₂	EtOAc	1-2a	< 10
3	Bn(1-1a)	CO	Pd(O ₂ CCF ₃) ₂	EtOAc	1-2a	15
4	Bn(1-1a)	CO	Pd(hfacac) ₂ ^[a]	EtOAc	1-2a	32
5	Bn(1-1a)	SO ₂		EtOAc	1-2b	37
6	Bn(1-1a)	SO ₂		CH ₂ Cl ₂	1-2b	< 10
7	Bn(1-1a)	SO ₂		MeCN	1-2b	25
8	Bn(1-1a)	SO ₂		acetone	1-2b	28
9	Bn(1-1a)	SO ₂		dioxane	1-2b	< 10
10	n-Bu(1-1b)	SO ₂		EtOAc	1-2c	35
11	n-Bu(1-1b)	CO		EtOAc	1-2d	32
12 ^[b]	n-Bu(1-1b)	CO		EtOAc	1-2d	70

^[a] hfacac = hexafluoroacetylacetonate

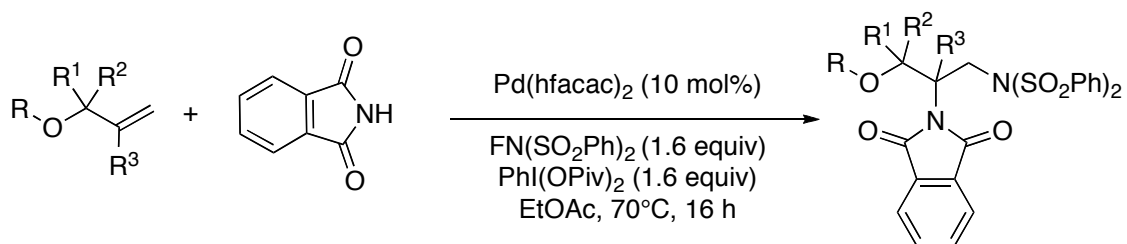
^[b] 2.0 mmol alkene, phthalimide (1.0 mmol), NFSI (1.6 mmol), PhI(OPiv)₂ (1.6 mmol)

Table 8. Palladium-catalyzed diamination of alkenes: optimization of the process.

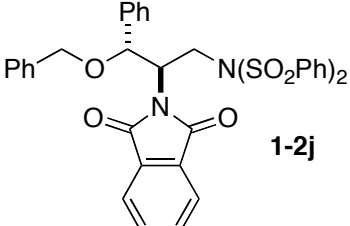
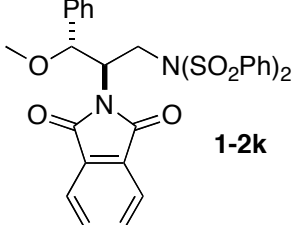
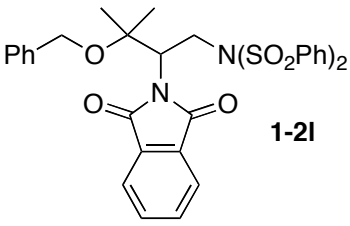
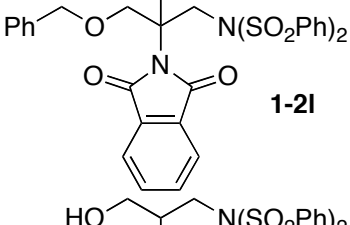
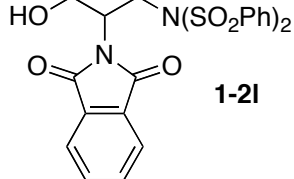
These reactions proceed with complete regioselectivity and no other 1,2-dioxidation products than the diamine derivatives were obtained. However, the reaction suffered from low conversion and yields usually remained below 50%. Finally, addition of iodosobenzene dipivalate to the reaction mixture containing phthalimide and NFSI led to a great improvement in yield and the diamination product **1-2d** could be isolated in 70% yield. Importantly, the corresponding reaction with saccharin does not experience this increase in yield.

This latter procedure was then employed for the synthesis of a series of different diamination products from allylic ethers. Table 9 shows representative examples. Various alkyl allyl ethers undergo clean diamination in 64–72% isolated yield with the expected complete regioselectivity as detected from the crude reaction mixture (entries 1–6). This chemoselectivity over potentially competing aminoxygenation reactions^[164] is noteworthy. A benzoyl-protected allylic substrate was diaminated in 68% yield (entry 7) and two substrates with stereogenic allylic positions gave the corresponding diamination products as single diastereomers (entries 8 and 9). Their relative configuration was assessed by comparison with literature precedents and matches the outcome from the earlier aminoacetoxylation reaction.^[167] A more sterically demanding ether with a gem-disubstituted allylic position still gave selective diamination (entry 10). Benzyl methallyl ether showed an equally reduced reactivity, but again the reaction proceeded with complete regio- and chemoselectivity (entry 11). Internal alkenes were found to be beyond the scope of the reaction. Finally, even free allylic alcohol could be oxidized under the present conditions (entry 12).

Results and discussion



Entry	R	R ¹	R ²	R ³	Diamine	Yield % [a]
1	Bn	H	H	H	 1-2a	72
2	n-Bu	H	H	H	 1-2d	70
3	Me	H	H	H	 1-2e	65
4	Et	H	H	H	 1-2f	64
5	n-Pr	H	H	H	 1-2g	68
6	n-Oct	H	H	H	 1-2h	67
7	PhCO	H	H	H	 1-2i	68

Entry	R	R ¹	R ²	R ³	Diamine	Yield % ^[a]
8	Bn	Ph	H	H	 1-2j	65 ^[b]
9	Me	Ph	H	H	 1-2k	55 ^[b]
10	Bn	Me	Me	H	 1-2l	40
11	Bn	H	H	Me	 1-2i	43
12	H	H	H	Me	 1-2d	32

^[a] Isolated yield after purification

^[b] 100% *de* according to the ¹H NMR spectrum of the reaction crude

Table 9. Palladium-catalyzed intermolecular diamination of allylic ethers.

All products show the expected spectroscopic data in agreement with the depicted structures and the constitution of the diamination products was unambiguously established by an X-ray crystallographic analysis of product **1-2d** (Figure 11).^[173]

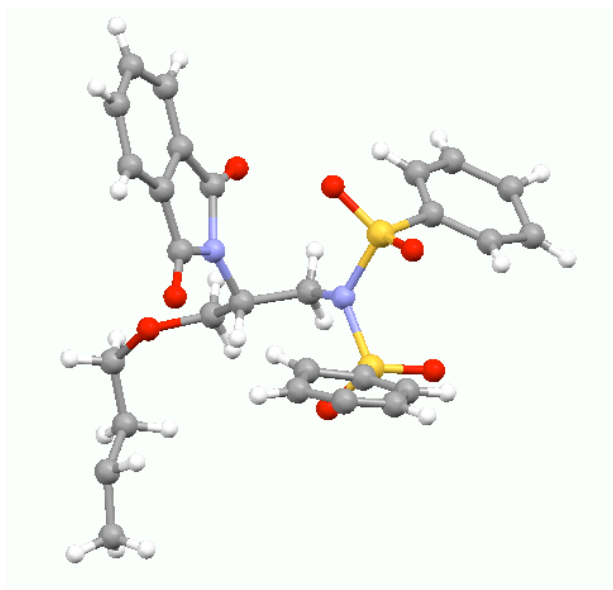
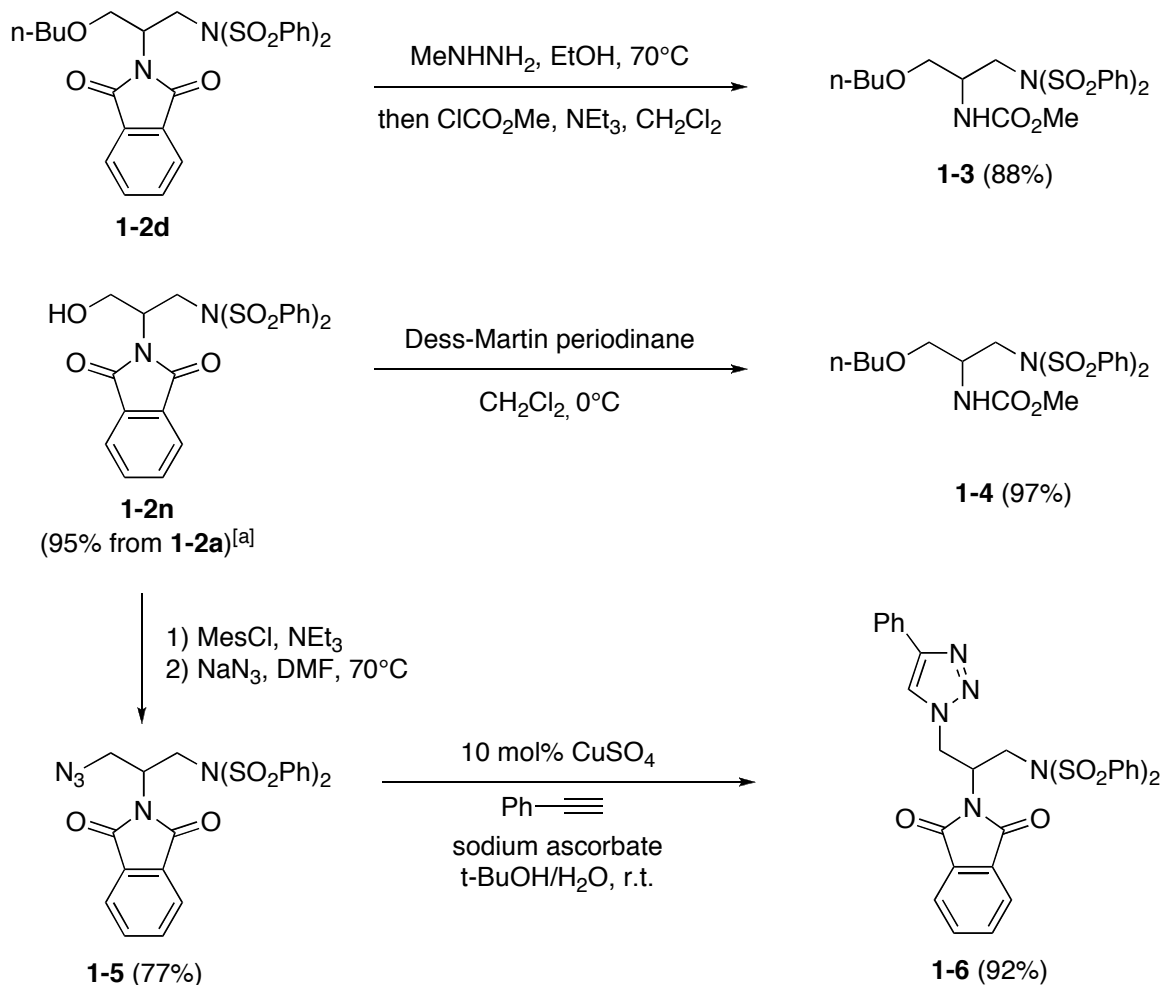


Figure 11. Structure of product **1-2d** in the solid state (N blue, O red, S yellow, C grey).

The synthetic utility of these diamination products as suitable building blocks was investigated within some representative reactions (Scheme 69). In order to allow for further differentiation of the two nitrogen groups, standard treatment of diamination product **1-2d** with methylhydrazine led to clean conversion of the phthalimide group into the free primary amine, which was isolated as the corresponding methyl carbamate **1-3** for the sake of convenient manipulation.

The free alcohol **1-2n** as generated via direct diamination of allylic alcohol can be obtained otherwise via hydrogenolysis of the benzyl ether **1-2a**. By this route, **1-2n** is available in an overall 68% yield from benzyl allyl ether. Again, compound **1-2n** serves as an interesting starting compound for further derivatization. For example, it can selectively be oxidized to the corresponding 2,3-diaminopropionaldehyde **1-4** containing differentiated nitrogen groups. Alternatively, conversion of the free alcohol **1-2n** into the 1,2,3-triaminated azide-containing compound **1-5** proceeds with partial deprotection of the bis-sulfonimide. Compound **1-5** allows for a subsequent cycloaddition process to arrive at the triazole **1-6**, thereby demonstrating that the densely functionalized triamine derivative **1-5** can be successfully employed in “click chemistry”.^[174]



[a] 10 mol% Pd(OH)/C, 1 atm. H₂, EtOAc

Scheme 69. Reactions employing 1,2,3-trifunctionalized diamination products.

Conclusion

In summary, we have realized the catalytic intermolecular diamination of allylic ethers. The reaction employs catalytic amounts of palladium(II) compounds as catalyst source and proceeds with complete regio- selectivity. It represents a significant advance in oxidative 1,2-difunctionalization of alkenes. Work in order to understand the underlying mechanism and the cooperative effect of the two oxidants as well as to extend the intermolecular diamination to internal alkenes is ongoing.

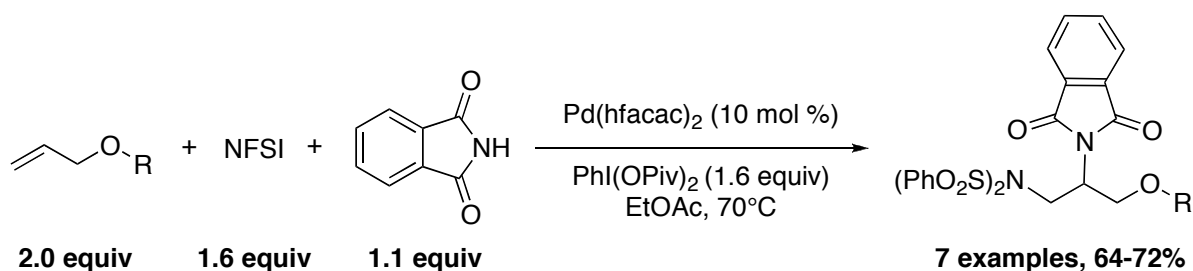
Chapter II: Evolution of the Intermolecular Regioselective 1,2-Diamination of Allylic Ethers

Introduction

Diamination of olefins represents an attractive strategy for the synthesis of vicinal diamines, which are contained in various biologically active compounds as important functional moieties and are widely used in asymmetric synthesis as chiral control elements.^[33, 40, 175] A number of metal-mediated^[92, 94, 95, 98, 107, 111, 113, 176, 177] and -catalyzed diamination reactions have been developed over the last decades.^[87, 115, 116, 121, 123-125, 127, 130, 134, 145, 163, 178-180] In 2010 we reported the first strictly intermolecular palladium catalyzed diamination of alkenes.^[163] Just thereafter, the catalytic intermolecular diamination of allylic ethers^[179] was reported leading to interesting 1,2,3-trifunctionalised compounds that are versatile building blocks for subsequent organic synthesis. However, this procedure required further improvement as two equivalents of allylether and a mixture of two oxidants were necessary. Herein we wish to report an optimized and simplified procedure allowing the diamination of allylic ethers through the use of a limiting amount of one equivalent of alkene and a single terminal oxidant.

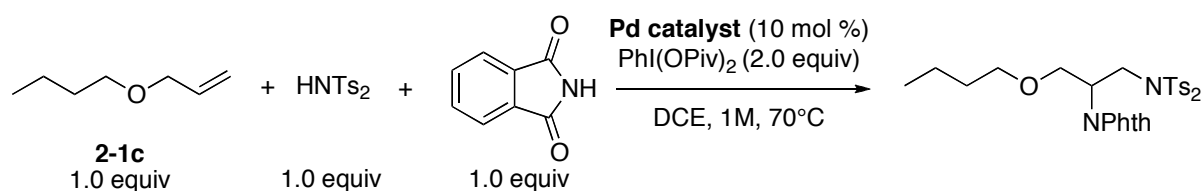
Results and discussion

Starting from the previously established conditions (Scheme 70), the aim of this work was to replace the second oxidant *N*-fluorobenzenesulfonimide (NFSI) by the second amide source HNTs₂ and then to find the best conditions allowing the diamination of allylic ethers to proceed by using only one equivalent of alkene.



Scheme 70. Diamination of allylic ethers using 2.0 equivalents of alkene starting material.^[179]

First, a screening of some common palladium salts (Table 10) led us to the replacement of the special precursor Pd(hfacac)₂ (hfacac = hexafluoroacetylacetonate) (entry 1) by the far more common PdCl₂(PhCN)₂ (entry 4). This result is in agreement with the observations obtained from earlier work on the intermolecular diamination of terminal alkenes.^[163] Next, the impact of some common ligand was studied, and while bathocuproine and neocuproine (entries 6 and 7) inhibit the reaction, phosphines ligands such as dppe or dppf (entries 8 and 9) do almost not affect the yield of the reaction.



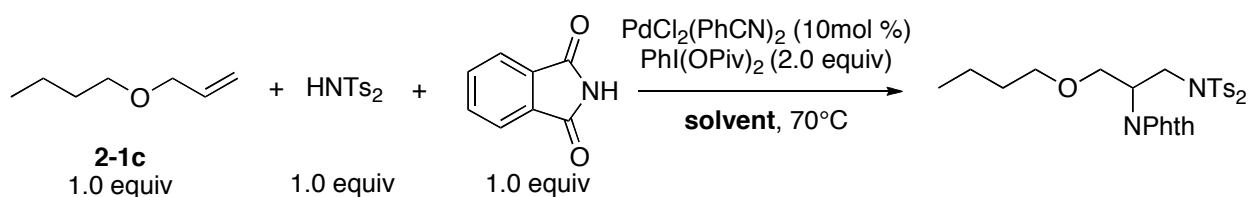
Entry	Catalyst	Ligands	Yield ^a %
1	$\text{Pd}(\text{hfacac})_2$	none	14
2	$\text{Pd}(\text{OAc})_2$	none	27
3	$\text{PdCl}_2(\text{CH}_3\text{CN})_2$	none	28
4	$\text{PdCl}_2(\text{PhCN})_2$	none	33
5	$\text{Pd}(\text{TFA})_2$	none	18
6	$\text{PdCl}_2(\text{PhCN})_2$	Bathocuproine ^b	< 5
7	$\text{PdCl}_2(\text{PhCN})_2$	Neocuproine ^b	< 5
8	$\text{PdCl}_2(\text{PhCN})_2$	bis(diphenylphosphine)ethane ^b	25
9	$\text{PdCl}_2(\text{PhCN})_2$	1,1'- Bis(diphenylphosphino)ferrocene ^b	15
10	none	none	0

^a calculated yield by nmr of the crude reaction with a standard

^b 20mol %

Table 10. Screening of the palladium source and ligands.

A subsequent screening of solvents (Table 11) revealed that DMF (entry 1) and acetonitrile (entry 5) are incompatible with the palladium-catalysed intermolecular diamination while dichloroethane (DCE) (entry 4) represents the solvent of choice. Interestingly, toluene (entry 6) gave unprecedentedly good results, too. Continuing the screening of reaction conditions with DCE (dichloroethane), a screening of different concentrations was carried out (entries 4, 9-11) and the reaction conditions were optimized for an alkene concentration of 0.25M (entry 10). More concentrated solutions suffer of a lack of solubility of the reagents (entry 4,9) and reactivity decreases with more diluted conditions.

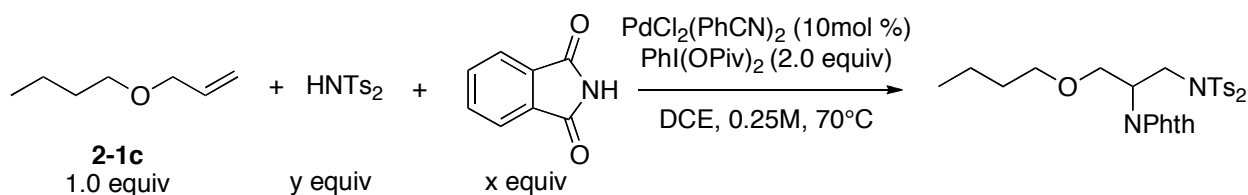


Entry	Solvent	Concentration	Yield ^a %
1	DMF	1M	0
2	EtOAc	1M	31
3	Acetone	1M	26
4	DCE	1M	33
5	Acetonitrile	1M	< 5
6	Toluene	1M	29
7	EtOH	1M	9
8	Dioxane	1M	30
9	DCE	0.5M	36
10	DCE	0.25M	46
11	DCE	0.125M	40

^a calculated yield by nmr of the crude reaction with a standard

Table 11. Screening of the solvent and concentration of the alkene.

Since the present reaction is an intermolecular version of the palladium-catalysed diamination, entropic problems appear and should be solved with a high concentration and/or with an excess of reagents. After analysing the concentrations of the alkene, a study of the equivalent of each nitrogen source (phthalimide and bistosylamide) is necessary to possibly increase the obtained yield (Table 12). The use of 1.2 equivalent of bistosylamide (entry 2) leads to a better yield of 50%. Increasing the number of equivalents of bistosylamide to 1.5 (entry 1) lowers the yield to 40% and a similar behaviour is observed when the number of equivalents of phthalimide surpasses one (entries 4-5). These results may be due to the poor solubility of both reagents under the chosen conditions.

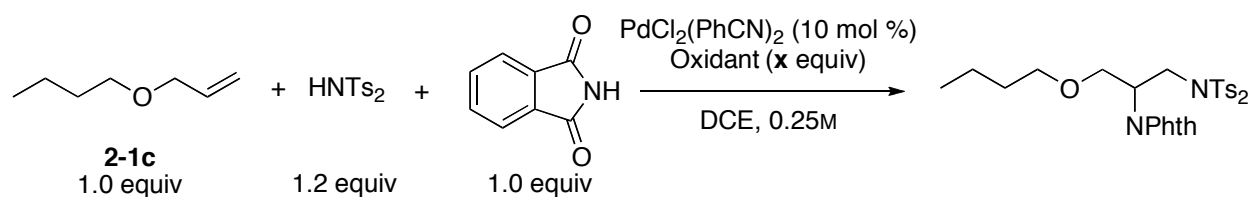


Entry	Amide	Equivalents	Yield ^a %
1	Phthalimide HNTs ₂	x : 1.0 y : 1.5	40
2	Phthalimide HNTs ₂	x : 1.0 y : 1.2	50
3	Phthalimide HNTs ₂	x : 1.0 y : 1.0	46
4	Phthalimide HNTs ₂	x : 1.5 y : 1.0	40
5	Phthalimide HNTs ₂	x : 2.0 y : 1.0	38

^a calculated yield by nmr of the crude reaction with a standard

Table 12. Study of the variation of the equivalent of each nitrogen source.

Finally, different temperatures and variations on the nature and equivalents of the oxidant were tested (Table 13). At room temperature (entry 1) only a few conversion of the alkene is observed, leading to only 17% yield. Raise of the temperature to 40, 60 and then 70°C (entries 2, 3 and 4) leads to better yields reaching a maximum of 50% at 70°C (entry 4). A further increase of the temperature (entry 5) results in a lower yield of 41%, probably linked to the decomposition of the allylic ether. Concerning the oxidant (entries 6-8), iodobenzenediacetate displays a lower reactivity than iodobenzenedipivalate (entry 6) and adding more oxidant in the reaction is only leading to lower yields (entries 7-8). The oxidative property of iodobenzene-dipivalate leads to complete oxidation and decomposition of the alkene after one night at 70°C.

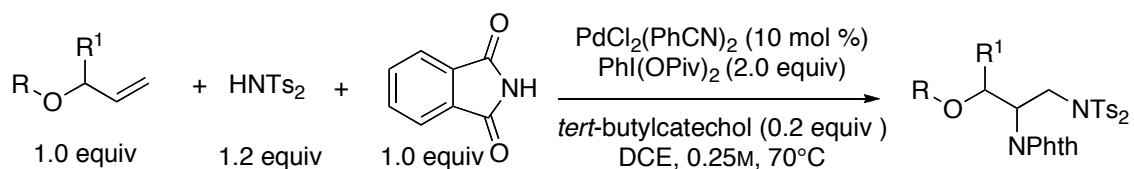


Entry	Oxidant	Temperature °C	Yield ^a %
1	PhI(OPiv) ₂ (2.0 equiv)	rt	17
2	PhI(OPiv) ₂ (2.0 equiv)	40	40
3	PhI(OPiv) ₂ (2.0 equiv)	60	45
4	PhI(OPiv) ₂ (2.0 equiv)	70	50
5	PhI(OPiv) ₂ (2.0 equiv)	80	41
6	PhI(OAc) ₂ (2.0 equiv)	70	45
7	PhI(OPiv) ₂ (2.5 equiv)	70	41
8	PhI(OPiv) ₂ (1.5 equiv)	70	44

^a calculated yield

Table 13. Screening of temperatures of the reaction and variation of the oxidant.

Despite these several screenings, the reaction suffered from relatively low yields that usually remained below 50%. As mentioned previously, the inherent conditions of this intermolecular palladium-catalysed diamination (temperature, oxidative conditions, palladium) favour the decomposition of the allylic ethers during the reaction. To solve this problem, allylic ethers should be stabilized in the reaction medium. Finally, thanks to the addition of 0.2 equivalent of *tert*-butylcatechol, the yield finally increased significantly from 50 to 67%. At this stage, the optimised procedure can now be considered of synthetic value. It was subsequently employed for the synthesis of a series of different diamination products from allylic ethers. Table 14 shows representative examples.



Entry	Allylic Ether	Nitrogen Sources	Product	Yield % ^a
1		2-1a HNPhth HNTs ₂		71
2		2-1b HNPhth HNTs ₂		68
3		2-1c HNPhth HNTs ₂		67
4		2-1c HNPhth HNMs₂		42
5		2-1d HNPhth HNTs ₂		65
6		2-1d HNSucc HNTs ₂		21
7		2-1e HNPhth HNTs ₂		69
8		2-1f HNPhth HNTs ₂		52
9		2-1g HNPhth HNTs ₂		60
10		2-1h HNPhth HNTs ₂	 	39

11		2-1i	HNPhth HNTs ₂		2-2i	57
12		2-1j	HNPhth HNTs ₂		2-2j	42
13		2-1k	HNPhth HNTs ₂		2-2k	52
14		2-1l	HNPhth HNTs ₂		2-2l	50

[a] after chromatographic purification

[b] racemic mixture of two diastereoisomers according to the ¹H NMR spectrum of the reaction crude

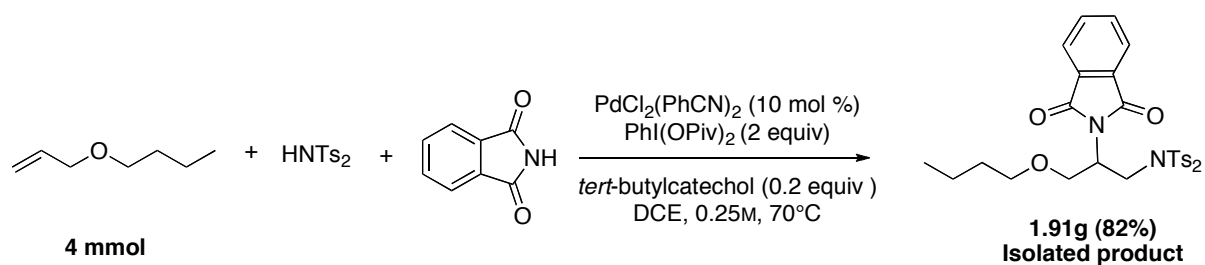
[c] 100% *de* according to the ¹H NMR spectrum of the reaction crude

Table 14. Palladium-catalyzed intermolecular diamination of allylic ethers.

Thanks to the optimised conditions, various simple alkyl allyl ethers undergo clean diamination in 65–71% isolated yield (entries 1–3,5,7). The benzoyl-protected allylic substrate (entry 8) was diaminated in 52% yield. The conditions used are compatible with a large number of chemical functions: ethers, epoxides (entry 9), benzoate (entry 8), molecules containing simple N–O bond (entry 13). A substrate with stereogenic allylic centre gives the corresponding diamination product as single diastereomer (entry 10). Its relative configuration was unambiguously confirmed by X-ray analysis. The reaction is totally regioselective in favour of terminal over internal alkenes (entry 11) and gave the pure product **2-2i** in 57% yield. In general internal alkenes were found to be beyond the scope of the reaction. Interestingly, the amide source can be varied, going for example from bistosylamide to bismesyamide (entry 4), which afforded a product for an easier deprotection, but lowered the yield to 42%. Phthalimide can be replaced, too. Entry 6 shows an example with succinimide that promotes diamination although with only 21% yield. These examples demonstrate that the individual combination of the nitrogen sources can be varied on a case-by-case basis.

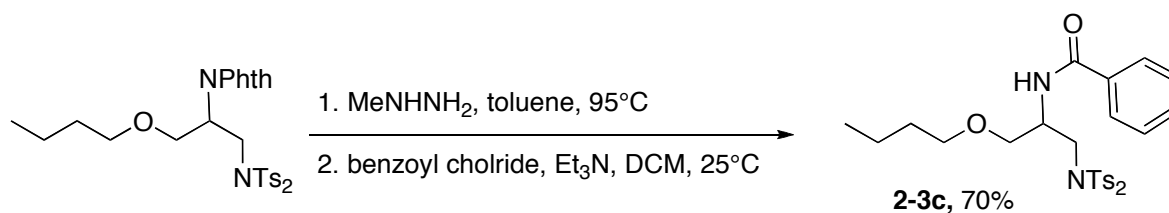
In addition, the reaction can be conveniently conducted on a larger scale (Scheme 71). For example the diamination of **2-1c** with phthalimide and bistosylimide was conducted on a

4mmol scale to provide the corresponding isolated product **2-2c** in a yield of 82%. The improved yield can be explained by the easier purification on a bigger scale.



Scheme 71. Scale-up of the intermolecular palladium-catalysed diamination of allylic ethers.

Importantly, the modifications done on the procedure not only allow for diaminations in moderate to good yields of a number of allylic ethers, starting from only one equivalent of alkene, but are working for simple alkenes too (Table 15).

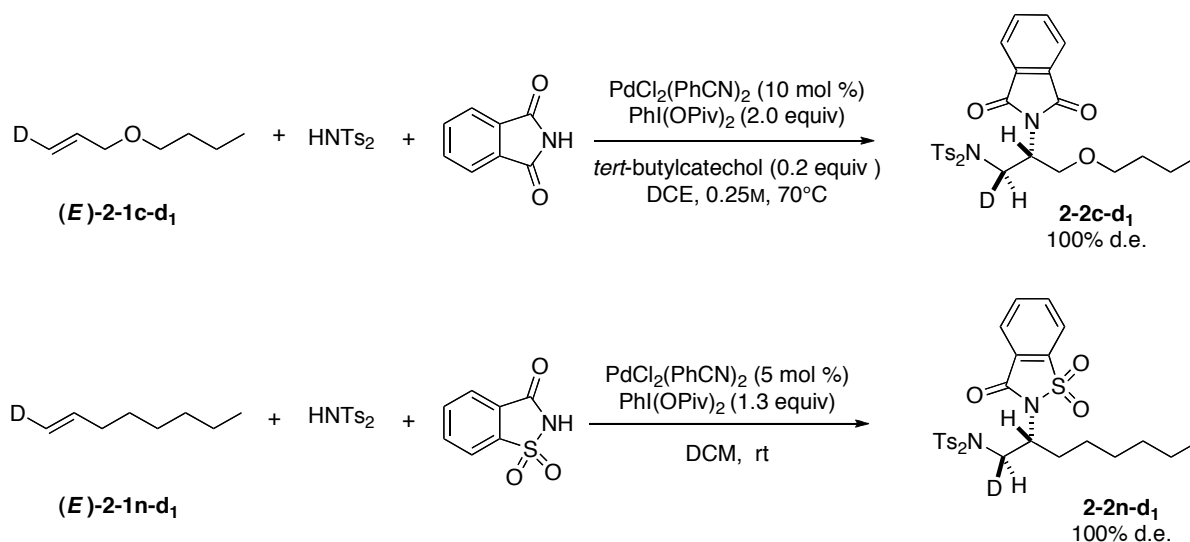


Scheme 72. Selective deprotection of the phthalimide group.

Concerning these synthetic transformations, a first selective deprotection of the nitrogen groups is necessary. To this end a simple treatment of diamination product **2-2c**, for example, with methylhydrazine lead to clean conversion of the phthalimide group into the free primary amine. This primary amine was then further converted to the corresponding benzyl carbamate **2-3c** to allow for a suitable isolation and characterisation (Scheme 72).

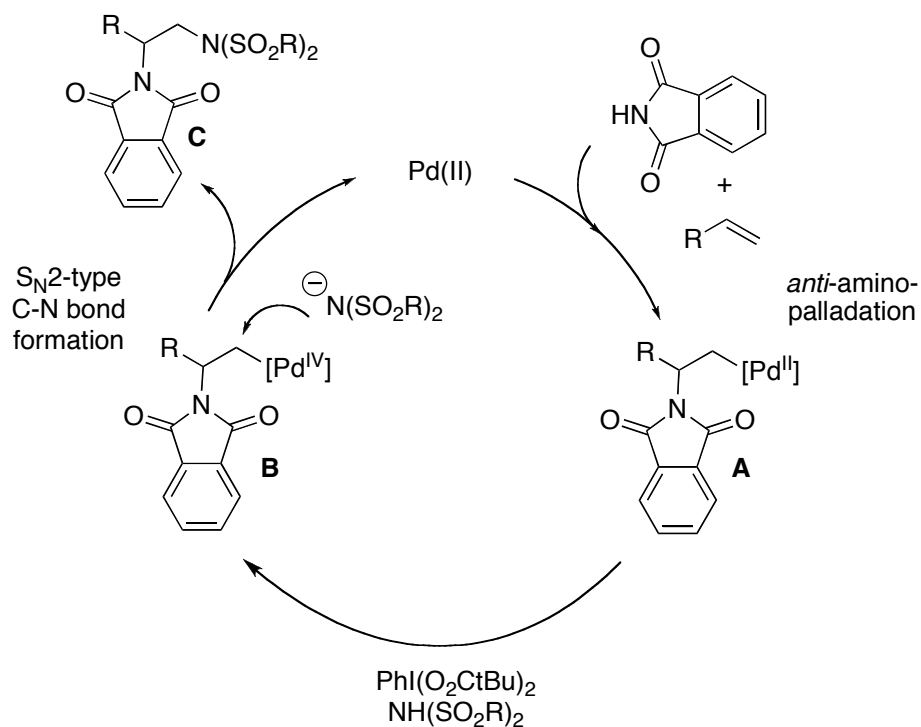
Mechanistic investigations

Investigation on the mechanism was started with deuteration experiments. The deuterated (*E*)-d₁-butylallylether **2-1c-d₁** was used under the previous established conditions of the palladium-catalysed diamination and gave the corresponding diamination product as a single diastereomer. Its relative configuration was assessed by NMR studies and X-Ray analysis and led to the configurations represented on Scheme 73. The same study has been carried out on (*E*)-d₁-octene **2-1n-d₁** applying the conditions described in the publication from our group of 2010^[163] and likewise gave the corresponding diamination product as a single diastereomer. The relative configuration was determined by NMR studies and appeared to be identical to the one from allylic ether (Scheme 73). This observation suggests a related mechanism to be operative in both cases.



Scheme 73. Deuterated experiments and comparison of the selectivities.

Other studies in order to understand the underlying mechanism are still ongoing, but a possible catalytic cycle can already be proposed. The reaction should begin with an *anti*-aminopalladation giving rise to the compound **A**. Iodobenzenedipivalate should oxidize the Pd(II) to Pd(IV) and form intermediate **B**, which can subsequently undergo a $\text{S}_{\text{N}}2$ -type C–N bond formation leading to the final diaminated compound **C**. This step reduces the palladium catalyst back to oxidative state +II and hence closes the overall cycle.



Scheme 74. Proposed catalytic cycle for the intermolecular palladium-catalysed diamination.

The step from **B** to **C** has been the focus of a recent combined theoretical-experimental investigation, which has confirmed the stereochemical pathway in the reductive C-N bond formation from Pd(IV) intermediate.^[181]

Conclusion

In summary, we have realized an optimization and simplification of the procedure allowing the diamination of allylic ethers through the use of only one equivalent of alkene and one oxidant. The reaction employs catalytic amounts of palladium(II) compounds as catalyst source and proceeds with complete regioselectivity in mild conditions compatible with a large number of chemical functions. The scope of the reaction has been enlarged to aliphatic alkenes with moderate to good yields using the more acidic nitrogen source tetrafluorophthalimide. Work in order to understand the overall mechanism is ongoing.

Chapter III: The First General 1,4-Diamination of Dienes

Introduction

As described at the outset of this thesis, 1,4-diaminobutane (putrescine) and the polyamines derived from it (spermidine and spermine) (Figure 12), are deeply involved in cell proliferation and in vivo protein synthesis.^[1] It has also been shown that the putrescine derivative (*E*)-1,4-diaminobut-2-ene **3-A** and its derivatives are of biological interest and have, for example, important fungicidal activity.^[1, 2]

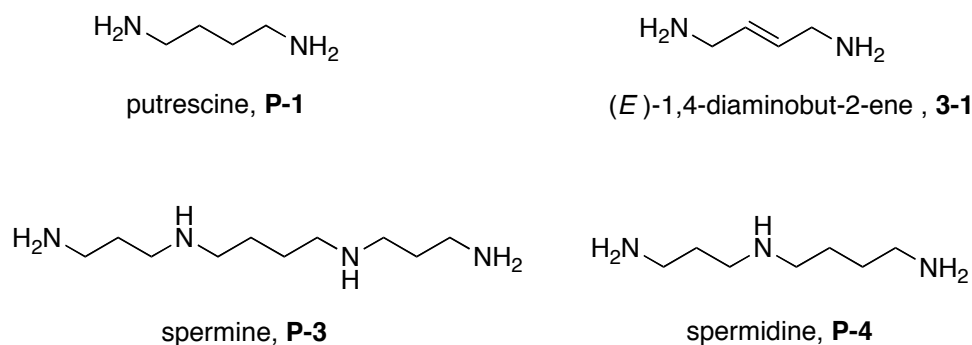


Figure 12. Biologically active molecules: putrescine and its derivatives.

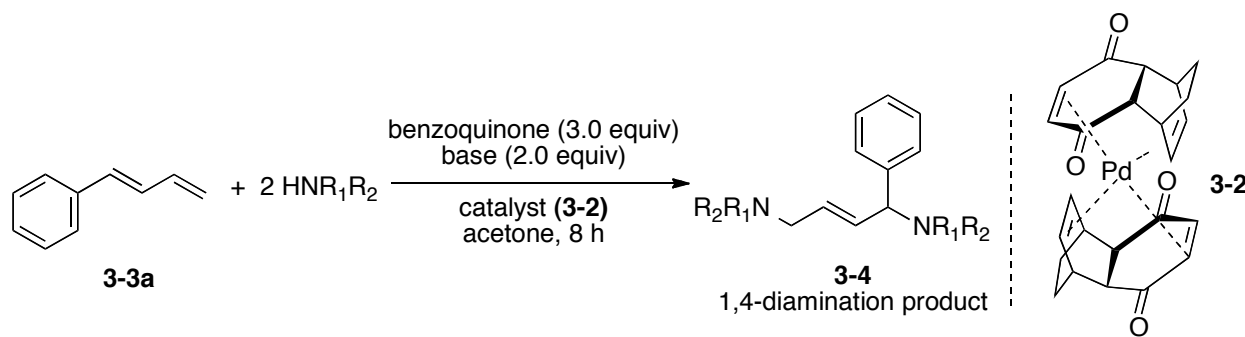
Nevertheless, to the best of our knowledge, few methods have been developed for regio- and stereo- selective 1,4-diamination reaction from conjugated dienes^[101, 182], which constitutes an elegant and direct approach.^[156, 157] Relatively few procedures for 1,2-diamination of simple alkenes are applicable to the 1,4-addition. One of them has recently been published by our laboratory, using an iodine(III) reagent to transform conjugated dienes into diamines.^[183] Although this method has important advantages, as metal free and mild conditions, the reaction is still not sufficiently general, since some of the reagents are only leading to 1,2-diamination instead of the 1,4-oxidation. Thus, a more efficient and general method for the 1,4-diamination is highly desirable.

Some decades ago, Bäckvall developed a regioselective 1,4-oxidation of 1,3-dienes to 1,4-dicarboxy-alk-2-enes using a palladium complex as catalyst.^[101, 182] This work has recently been updated by Buono and Eastgate^[184] who reported additional the mechanistic insight into

this reaction. Within their work, they managed to isolate and characterize the active catalyst (**3-2**) and proposed a revised mechanism in agreement with their observation. Our general approach was to develop a palladium-catalysed 1,4-diamination of conjugated dienes, based on this new knowledge.

Results and discussion

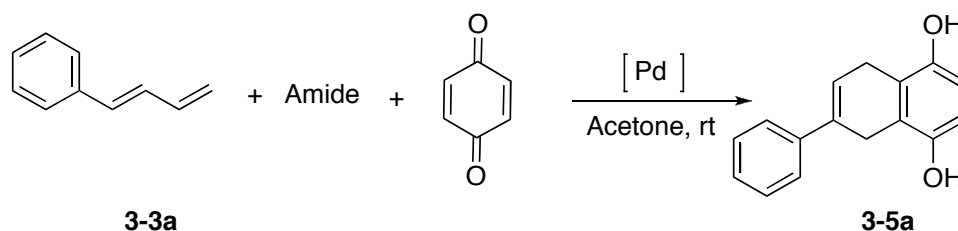
We began by applying the exact conditions of the 1,4-oxidation^[184], using the described active catalyst, various amides like phthalimide, saccharin, bistosylamide or tosylmethylcarbamate with benzoquinone as oxidant in acetone at room temperature (Table 16, entries 1-4).



entry	oxidant	amide	base	solvent	Yield %
1	benzoquinone	NHTsCO ₂ Me	none	acetone	n.o.
2	benzoquinone	saccharin	none	acetone	n.o.
3	benzoquinone	bistosylamide	none	acetone	n.o.
4	benzoquinone	phthalimide	none	acetone	n.o.
5	benzoquinone	phthalimide	Cs ₂ CO ₃	acetone	n.o.
6	benzoquinone	saccharin	Cs₂CO₃	acetone	n.o.
7	CuBr₂	saccharin	Cs ₂ CO ₃	acetone	traces
8	CuBr ₂	phthalimide	K₂CO₃	acetone	n.o.
9	CuBr ₂	saccharin	K ₂ CO ₃	acetone	< 5
10	CuBr ₂	saccharin	K ₂ CO ₃	DMF	6

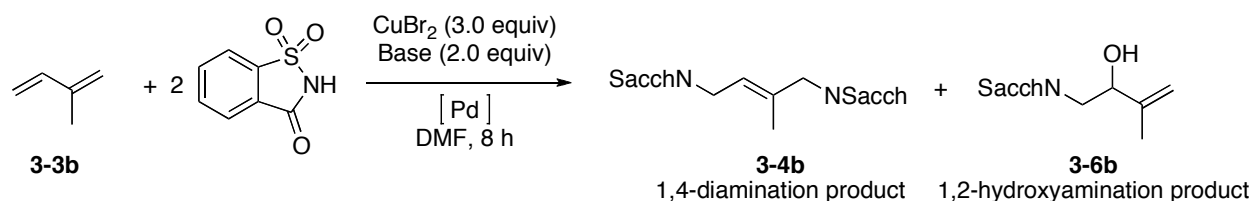
Table 16. Screening of the 1,4-diamination of conjugated dienes.

Since no 1,4-diamination was observed, we decided to test the presence of a base (entries 5–6), unfortunately without any improvement. Using benzoquinone as oxidant only led, in almost quantitative yield, to the Diels-Alder adduct **3-5a** between the oxidant and the diene (Scheme 75). To overcome this problem we decided to replace the oxidant by CuBr_2 (entries 7-10). Finally the use of Copper(II) as oxidant, with palladium and K_2CO_3 as a base in DMF with saccharin appeared to be interesting (entry 10) and resulted in traces of 1,4-diamination.



Scheme 75. Formation of the Diels-Alder adduct **3-5a**.

During the optimisation of the process (Table 17), changing the base to K_3PO_4 allowed to prevent formation of undesired by-products and only 1,4-diaminated and 1,2-hydroxyaminated product were produced (entry 2). Finally, decreasing the amount of water by using an anhydrous base (entry 3) and increasing the temperature to 50°C (entry 5) gave the optimal conditions, leading to good yields. Surprisingly the absence of any palladium catalyst (entry 9) has no consequence on the yield, which explains the constant yields we obtained during the screening of the palladium sources (entry 5-8). Other solvents, bases and concentrations were tested without any positive effect. These mild conditions, compared to the copper-mediated amination developed by Chemler,^[113, 114] and the use of economic reagents, leading to the desired intermolecular 1,4-diamination reaction, motivated us to further investigate this reaction.

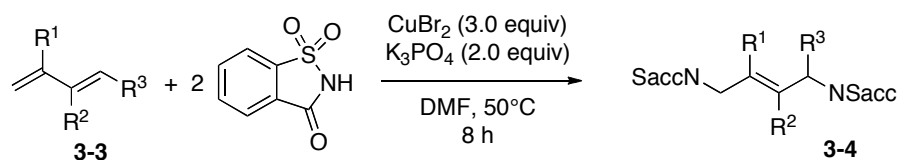


Entry	Base	Temperature °C	Catalyst	Yield %
1	K ₂ CO ₃ .xH ₂ O	25	3-2	6
2	K ₃ PO ₄ .xH ₂ O	25	3-2	32
3	K ₃ PO ₄	25	3-2	64
4	K ₃ PO ₄	35	3-2	72
5	K ₃ PO ₄	50	3-2	87
6	K ₃ PO ₄	50	Pd(hfacac) ₂	84
7	K ₃ PO ₄	50	PdCl ₂ (PhCN) ₂	85
8	K ₃ PO ₄	50	Pd(OAc) ₂	83
9	K ₃ PO ₄	50	none	87

Table 17. Optimisation of the 1,4-diamination reaction

We decided then to test the scope of the reaction, varying the 1,3-diene substrates (Table 18). Examples that gave 1,4-diamination with the iodine(III) chemistry^[183] gave moderate to good yields using CuBr₂ as a promoter (entries 1-3). We were then pleased to observe that (*E*)-buta-1,3-dienylbenzene (entry 6) and its derivatives (entries 7-10), gave good to quantitative yields of intermolecular 1,4-addition. This is an exiting contrast to the case of iodine(III) chemistry, which usually favours the 1,2-addition onto the terminal position leading to the styrene product due to thermodynamic stabilisation.

Results and discussion



Entry	Substrate	Product	Yield ^a %
1	3-3c	3-4c	41
2	3-3b	3-4b	87
3	3-3d	3-4d	60
4	3-3e	3-4e	71
5	3-3f	3-4f	75
6	3-3a	3-4a	75
7	3-3g	3-4g	40
8	3-3h	3-4h	76
9	3-3i	3-4i	72
10	3-3j	3-4j	98

^a isolated yield after purification

Table 18. Intermolecular 1,4-diamination of dienes

All products **3-4a-j** show the expected spectroscopic data that is in full agreement with the described structure. In addition, the structure of the obtained product **3-4a** was confirmed by X-Ray analysis (Figure 13).

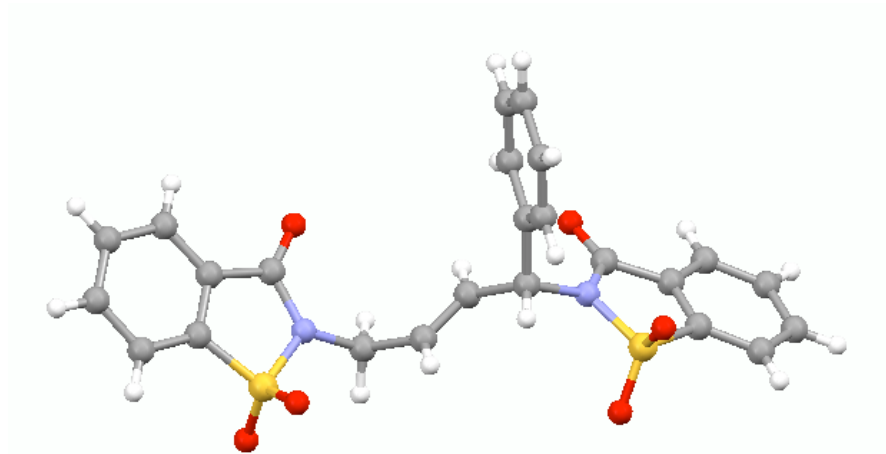
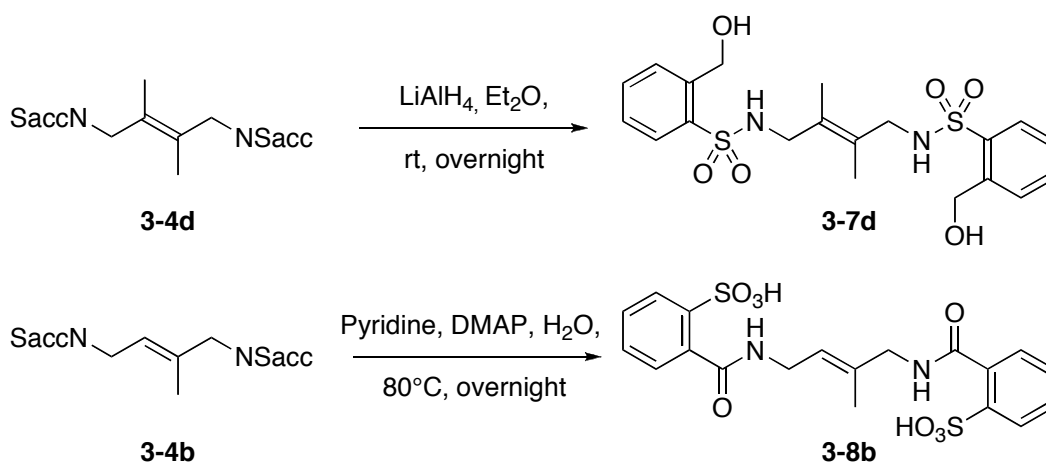


Figure 13. Structure of product **3-2f** in the solid state (N blue, O red, S yellow, C grey).

Unfortunately internal 1,3-dienes gave rise to low or no conversion to 1,4-diamines. During the course of the screening, the only observed by-product was the 1,2-hydroxyaminated diene (Table 17), 1,2-diamination was never observed.

Synthetic transformations

The synthetic utility of these 1,4-diamination products **3-4a-j** as suitable precursor to 1,4-diamine building blocks was investigated within some representative reactions. First, treatment of product **3-4d** with LiAlH_4 leads to the opening of the saccharin ring with a concomitant reduction of the carbonyl group to the alcohol, resulting in product **3-7d** (Scheme 76), which structure was confirmed by X-Ray analysis (Figure 14). Derivatives of **3-7d** are known for their biological properties, as their cytotoxic activity against human tumour cell lines.^[185]



Scheme 76. Synthetic transformations of the 1,4-diamination product.

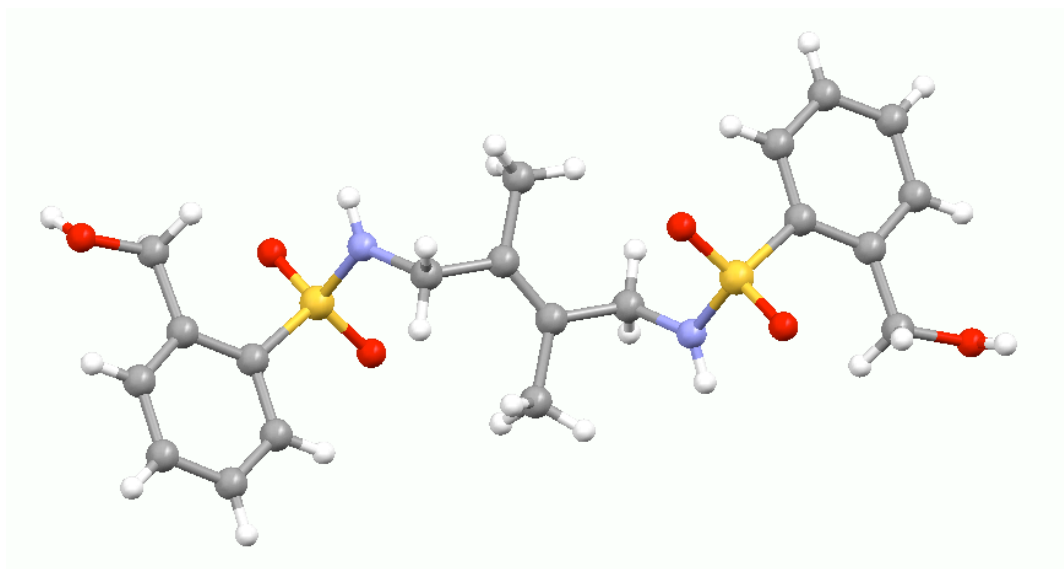


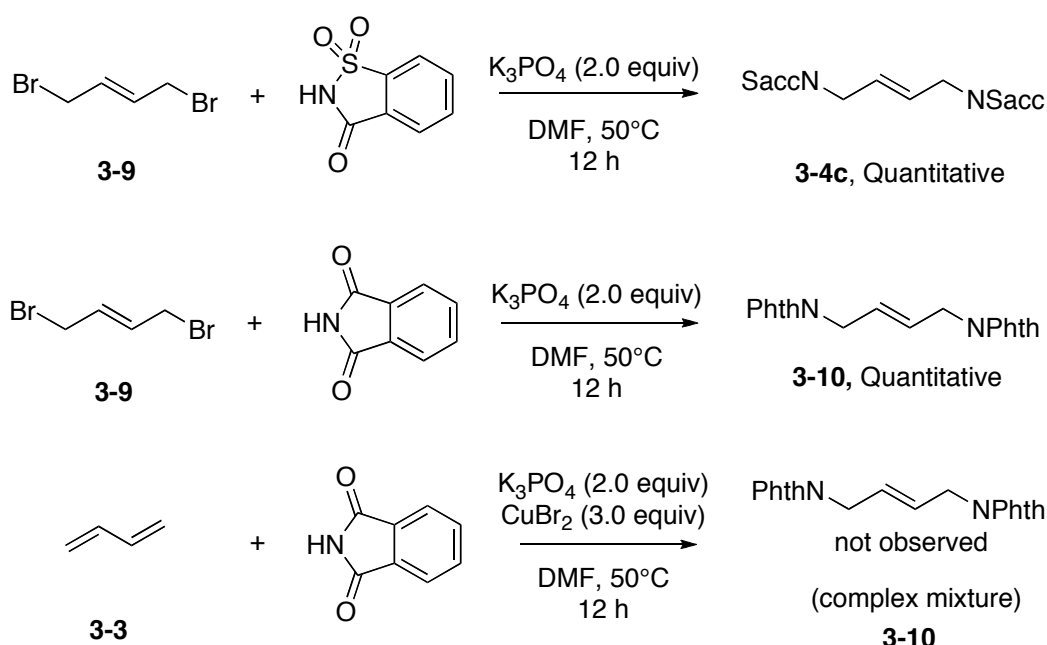
Figure 14. Structure of product **3-7d** in the solid state (N blue, O red, S yellow, C grey).

Compound **3-4b** was treated with DMAP and pyridine in water at 80°C to afford product **3-8b** in a quantitative yield. This method allowed us to open the saccharin ring from the sulfamide side leading to the amide **3-8b**. Derivatives of **3-8b** are recognised for their biologic properties such as their role in probiotic formulations,^[186] or proadhesin or nonadhesin properties.^[187]

The full deprotection of the saccharin to the amine has already been reported in the past, the first one under acidic condition using HCl, the other one through the use of CsF in DMF.^[163]

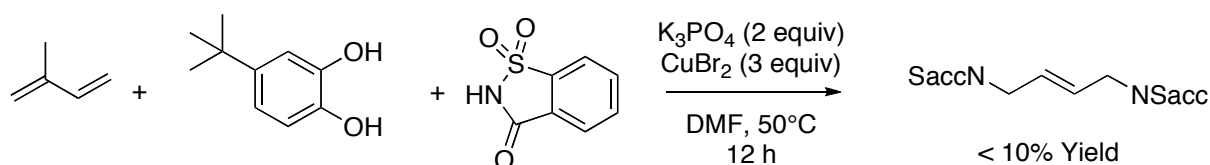
Mechanistic investigations

The initial mechanistic proposal for the 1,4-diamination reaction was a stepwise mechanism beginning with a 1,4-dibromination, followed by two subsequent nucleophilic substitution reaction of the bromides by deprotonated saccharin. Indeed, treatment of dienes by CuBr_2 is known to form the 1,4-dibrominated molecule as major product^[188] and nucleophilic substitution of the bromide by saccharin is also well known too.^[189] Unfortunately, this mechanism could not explain the results observed when phthalimide was used instead of saccharin. If the mechanism starts from a dihalogenation then 1,4-diamination should be possible with phthalimide, too, which is obviously not the case (Scheme 77).



Scheme 77. Control experiments of the 1,4-diamination of dienes.

Another mechanism should then be considered, and since addition of a radical inhibitor (4-*tert*-butylcatechol) significantly lowers the reactivity, a radical pathway maybe consistent.



Scheme 78. Mechanistic investigations of the 1,4-diamination of dienes : effect of a radical inhibitor.

Work in order to understand the underlying mechanism is ongoing.

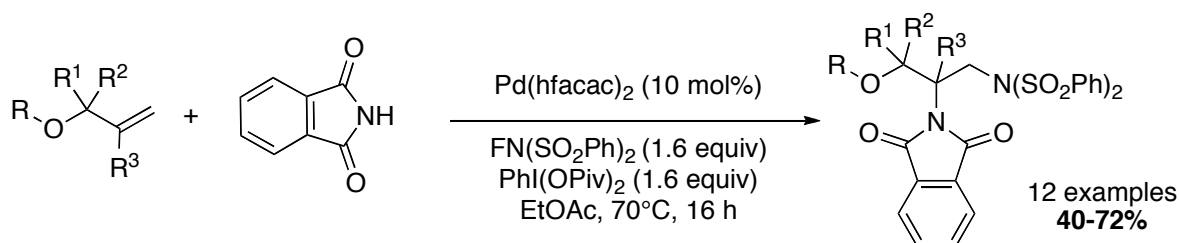
Conclusion

In summary, we have realised the first general intermolecular 1,4-diamination of dienes. The reaction employs economic reagents such as CuBr₂ and saccharin and proceeds with complete regioselectivity under mild conditions. It represents a significant advance in oxidative 1,4-difunctionalization of dienes. Work in order to understand the underlying mechanism as well as to develop further the intermolecular 1,4-diamination to a catalytic amount of copper is ongoing.

Summary and Conclusion

The beginning of this thesis almost coincided with the report of the bromide-catalysed diamination of alkenes, which represented a significant improvement in the area of intramolecular diamination. Thus, it was time to close the chapter of the intramolecular diamination and to follow the evolution of the diamination reaction towards the intermolecular version.

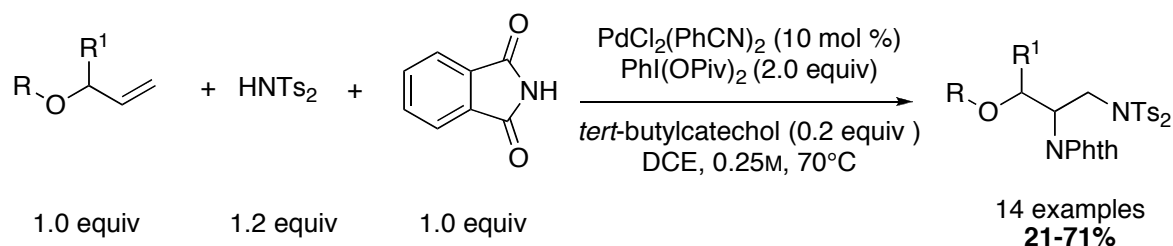
Within this context, the aim of this thesis was first the development of the intermolecular metal-catalysed diamination of allylic ethers. Indeed, allylic ethers are suitable substrates for an elegant synthesis of 1,2,3-trisubstituted products, which form interesting building blocks. A first protocol to carry out this intermolecular reaction has been developed. It works through the use of a catalytic amount of palladium(II), oxidative conditions formed by the presence of two oxidants: NFSI and Iodobenzenedipivalate and phthalimide as nitrogen source and allows the diamination of a large number of allylic ethers in moderate to good yields (Scheme 79).



Scheme 79. First procedure for the palladium-catalysed diamination of allylic ethers.

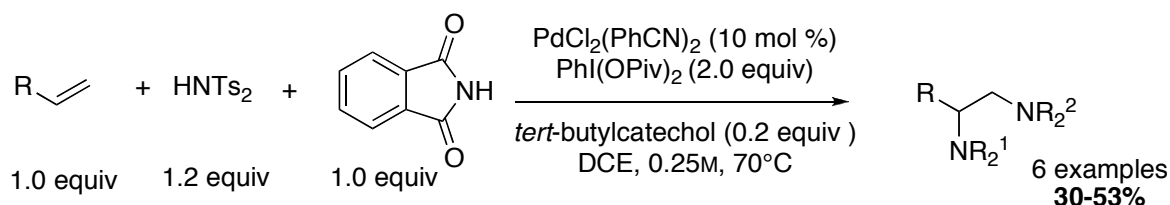
The reaction works under complete regioselectivity and the synthetic utility of the formed products as useful building blocks was investigated within representative reactions.

However, despite the accomplished progresses, this method required further improvements, as two equivalents of allylether and a mixture of two oxidants were necessary. Thus, we optimized and simplified the procedure and finally get the diamination of allylic ethers through the use of only one equivalent of alkene and a single terminal oxidant (Scheme 80).



Scheme 80. Palladium-catalysed diamination of allylic ethers with alkene as limiting agent.

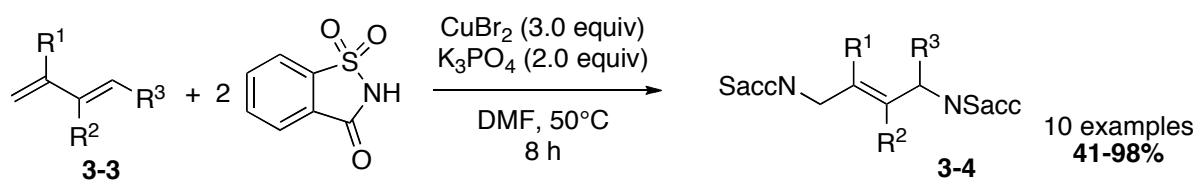
Importantly, under the optimised conditions, not only allylic ethers but aliphatic alkenes too undergo diamination. They can be regioselectively diaminated with phthalimide and bistosylamide as nitrogen sources and, noteworthy, replacing the phthalimide by the more acidic tetrafluorophthalimide allows an improvement of the yields by 20 points (Scheme 81).



Scheme 81. Catalytic diamination of simple alkenes.

These works about intermolecular palladium-catalysed diamination^[163, 179] represent a great improvement of this area. Over three years, the first procedures of intermolecular catalysed diamination have been developed, optimised and extended to several classes of substrates. Studies over the mechanism are still ongoing but a general pathway can already be proposed. The next challenge is now the development of the intermolecular enantioselective catalysed diamination.

In parallel, we get interested in 1,4-diamines, which are biologically active molecules, and developed one of the first general methods of 1,4-diamination through the use of CuBr₂ and Sachharin in the presence of K₃PO₄. This procedure allows the 1,4-diamination of several terminal dienes, including 1,3-dienylbenzene and its derivatives, in good to excellent yields (Scheme 82).



Scheme 82. Copper-mediated 1,4-diamination of terminal dienes

The mild conditions, the economic reagents and the easy isolation of the products render this reaction really attractive. One of the further improvement could be the dimiution of the quantity of CuBr_2 necessary, and why not a catalytic version of this reaction?

Experimental Section

Chapter I: Intermolecular Regioselective 1,2-Diamination of Allylic Ethers

1.1. General

All solvents, reagents and all deuterated solvents were purchased from Aldrich. Column chromatography was performed with silica gel (Merck, type 60, 0.063-0.2 mm). NMR spectra were recorded on a Bruker Avance 300 and Avance 400 MHz spectrometer, respectively. All chemical shifts in NMR experiments are reported as ppm downfield from TMS. The following calibrations were used: CDCl_3 $\delta = 7.26$ and 77.0 ppm, acetone- d_6 $\delta = 2.09$ and 30.6 ppm, respectively. MS (ESI-LCMS) experiments were performed using an Agilent 1100 HPLC with a Bruker micro-TOF instrument (ESI). Unless otherwise stated, a Supelco C8 (5cm x 4.6mm, 5 μm particles) column was used with a linear elution gradient from 100% H_2O (0.5% HCO_2H) to 100% MeCN in 13 min at a flow rate of 0.5 mL/min. Melting points were determined in open capillary tubes on a Büchi Melting point B-545 instrument. MS(EI) and HRMS experiments were performed on a Kratos MS 50 within the service centers at ICIQ.

1.2. General procedure for the palladium-catalyzed intermolecular diamination of alkenes

Procedure A (with saccharine):

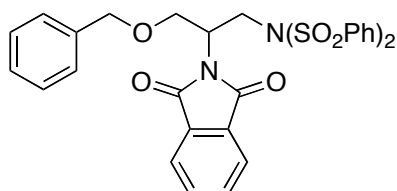
The typical procedure is given for the reaction of benzyl allyl ether with saccharine. $\text{Pd}(\text{hfacac})_2$ (0.028 mmol, 14.5 mg), saccharine (0.4 mmol, 73 mg), *N*-fluorodibenzenesulfonimide (0.64 mmol, 200 mg) and benzyl allyl ether (0.4 mmol, 59 mg) were suspended in 0.4 mL of ethyl acetate (EtOAc) in a pyrex tube. The mixture was heated at 70°C for 12 hours. After cooling, the solution was evaporated under reduced pressure and the crude product was purified by chromatography on silica gel to give diamination product **1-2b** with 37% yield.

Procedure B (with phthalimide):

The typical procedure is given for the reaction of benzyl allyl ether with phthalimide. Pd(hfacac)₂ (0.028 mmol, 14.5 mg), phthalimide (0.4 mmol, 60 mg), PhI(OC(O)*t*-Bu)₂ (0.64 mmol, 260 mg), *N*-fluorodibenzenesulfonimide (0.64 mmol, 200 mg) and benzyl allyl ether (0.8 mmol, 118 mg) were suspended in 0.4 mL of ethyl acetate (EtOAc) in a pyrex tube. The mixture was heated at 70°C for 12 hours. After cooling, the solution was evaporated under reduced pressure and the crude product was purified by chromatography on silica gel to give diamination product **1-2a** with 72% yield.

1.3. Characterization of diamination products

N-[3-(benzyloxy)-2-(1,3-dioxoisindolin-2-yl)propyl]-*N*-(phenylsulfonyl)benzenesulfonamide



1-2a

Obtained as a white solid in 72% yield.

m.p. = 145-146°C.

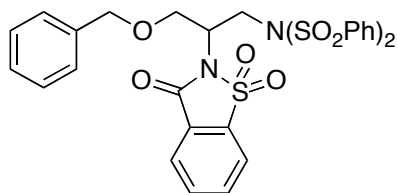
¹H NMR (400 MHz, CDCl₃): δ = 8.08 (d, J = 7.9 Hz, 4H), 7.86 (dd, J = 3.1, 5.4 Hz, 2H), 7.73 (dd, J = 3.0, 5.5 Hz, 2H), 7.66 (t, J = 7.4 Hz, 2H), 7.57 (t, J = 7.8 Hz, 4H), 7.37–7.24 (m, 5H), 5.09–4.96 (m, 1H), 4.58 (d, J = 11.9 Hz, 1H), 4.54 (d, J = 11.9 Hz, 1H), 4.39 (dd, J = 9.2, 15.9 Hz, 1H), 4.13 (dd, J = 2.8, 15.9 Hz, 1H), 3.96–3.83 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): δ = 168.3, 138.7, 137.5, 134.0, 133.8, 131.9, 129.0, 128.6, 128.3, 127.7, 127.6, 123.2, 72.8, 67.1, 50.5, 45.8.

IR ν (cm⁻¹): 3065, 3033, 2902, 2872, 1769, 1706, 1451, 1164, 1025, 717, 548.

HRMS: calcd for C₃₀H₂₆N₂O₇S₂Na: 613.108, found: 613.109.

4-*N*-[3-(benzyloxy)-2-(1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)propyl]-*N*-(phenylsulfonyl)benzenesulfonamide



1-2b

Obtained as a white solid in 37% yield.

m.p. = 73-75°C.

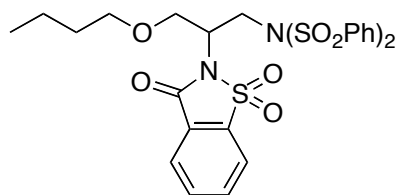
¹H NMR (300 MHz, CDCl₃): δ = 8.02 (d, *J* = 7.6 Hz, 4H), 7.85-7.80 (m, 4H), 7.61 (t, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 8.0 Hz, 4H), 7.37-7.32 (m, 5H), 4.80-4.75 (m, 1H), 4.57 (s, 2H), 4.42 (dd, *J* = 8.4, 16.0 Hz, 1H), 4.27 (dd, *J* = 4.0, 15.6 Hz, 1H), 3.97-3.90 (m, 2H).

¹³C NMR (75 MHz, CDCl₃): δ = 159.4, 138.6, 137.5, 137.3, 134.6, 134.1, 134.0, 129.0, 128.8, 128.3, 127.7, 127.2, 126.9, 125.1, 120.8, 73.0, 67.2, 52.8, 45.81.

IR ν(cm⁻¹): 3063, 2932, 1733, 1450, 1370, 1166, 1083, 758, 546.

HRMS: calcd for C₂₉H₂₆N₂O₈S₃Na: 649.075, found: 649.073.

***N*-[3-butoxy-2-(1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)propyl]-*N*-(phenylsulfonyl)benzenesulfonamide**



1-2c

Obtained as a white solid in 35% yield.

m.p. = 68-69°C.

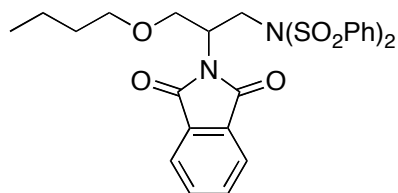
¹H NMR (300 MHz, CDCl₃): δ = 8.02 (d, J = 7.6 Hz, 4H), 7.90-7.81 (m, 4H), 7.64 (t, J = 7.2 Hz, 2H), 7.54 (t, J = 7.6 Hz, 4H), 4.75-4.68 (m, 1H), 4.44 (dd, J = 8.4, 16.0 Hz, 1H), 4.29 (dd, J = 2.8, 15.6 Hz, 1H), 3.95-3.86 (m, 2H), 3.52-3.47 (m, 2H), 1.54-1.61 (m, 2H), 1.36 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ = 159.5, 138.8, 137.4, 134.6, 134.1, 134.0, 129.0, 128.8, 127.3, 125.1, 120.9, 71.1, 67.7, 52.8, 45.9, 31.6, 19.2, 13.9.

IR ν (cm⁻¹): 3069, 2958, 2929, 2872, 1726, 1461, 1448, 1167, 1083, 750, 548.

HRMS: calcd for C₂₆H₂₈N₂O₈S₃Na: 615.091, found: 615.092.

***N*-[3-butoxy-2-(1,3-dioxoisindolin-2-yl)propyl]-*N*-(phenylsulfonyl)benzene-sulfonamide**



1-2d

Obtained as a white solid in 70% yield.

m.p. = 69-70°C.

¹H NMR (300 MHz, CDCl₃): δ = 8.02 (d, *J* = 6.0 Hz, 4H), 7.80-7.78 (m, 2H), 7.65-7.67 (m, 2H), 7.60 (t, *J* = 6.0 Hz, 2H), 7.51 (t, *J* = 6.0 Hz, 4H), 4.93-4.86 (m, 1H), 4.33 (dd, *J* = 9.2, 15.9 Hz, 1H), 4.04 (dd, *J* = 2.8, 15.6 Hz, 1H), 3.77 (d, *J* = 8.0 Hz, 2H), 3.43-3.37 (m, 2H), 1.41-1.47 (m, 2H), 1.26-1.21 (m, 2H), 0.80 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ = 168.4, 138.8, 134.0, 133.9, 131.9, 129.1, 128.6, 123.3, 70.9, 67.7, 50.5, 45.9, 31.6, 19.1, 13.8.

IR ν(cm⁻¹): 2958, 2933, 2871, 1775, 1709, 1448, 1166, 1083, 753, 546.

HRMS: calcd for C₂₇H₂₈N₂O₇S₂Na: 579.124, found: 579.125.

Details concerning the X-ray structure of 1-2d

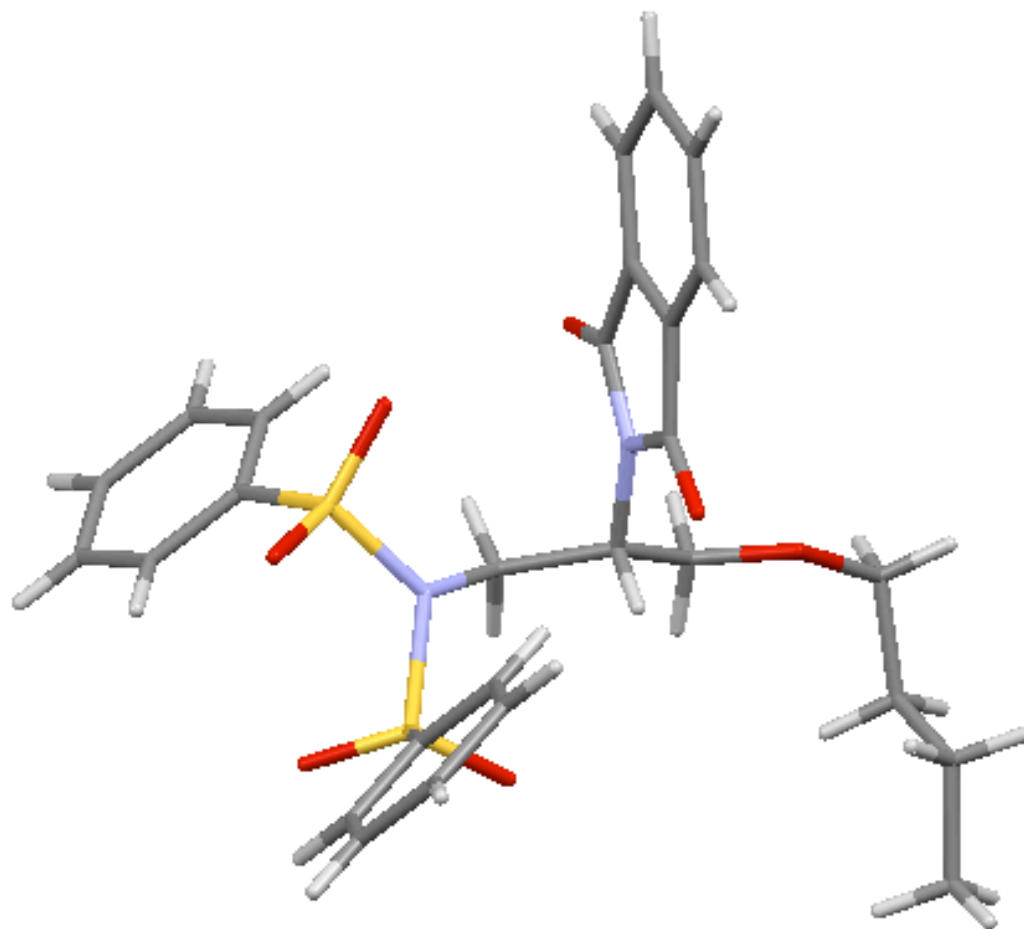
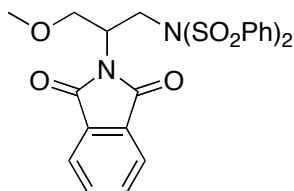


Table 1. Crystal data and structure refinement for compound **1-2d**.

Identification code	JKPn
Empirical formula	C ₅₄ H ₅₆ N ₄ O ₁₄ S ₄
Formula weight	1113.27
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic

Space group	Pn
Unit cell dimensions	a = 8.2570(5) Å $\alpha = 90.00^\circ$. b = 40.475(2) Å $\beta = 98.8700(3)^\circ$. c = 8.2650(5) Å $\gamma = 90.00^\circ$.
Volume	2729.1(3) Å ³
Z	2
Density (calculated)	1.355 Mg/m ³
Absorption coefficient	0.243 mm ⁻¹
F(000)	1168
Crystal size	0.03 x 0.10 x 0.20 mm ³
Theta range for data collection	1.01 to 36.36 °.
Index ranges	-13 ≤ h ≤ 13, -66 ≤ k ≤ 66, -13 ≤ l ≤ 11
Reflections collected	45778
Independent reflections	11907 [R(int) = 0.0614]
Completeness to theta = 36.36 °	0.949 %
Absorption correction	Empirical
Max. and min. transmission	0.98 and 0.80
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	20986 / 181 / 588
Goodness-of-fit on F ²	1.022
Final R indices [I > 2σ(I)]	R1 = 0.0909, wR2 = 0.2380
R indices (all data)	R1 = 0.1482, wR2 = 0.2778
Absolute Structure BASF	x = 0.51
Largest diff. peak and hole	0.467 and -0.613 e.Å ⁻³

***N*-[2-(1,3-dioxisoindolin-2-yl)-3-methoxypropyl]-*N*-(phenylsulfonyl)benzenesulfonamide**



1-2e

Obtained as a white solid in 65% yield.

m.p. = 129-131°C.

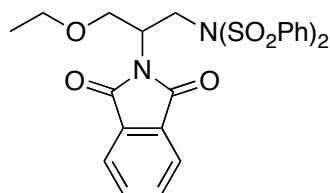
¹H NMR (300 MHz, CDCl₃): δ = 8.04 (d, *J* = 6.0 Hz, 4H), 7.83-7.80 (m, 2H), 7.70-7.67 (m, 2H), 7.64-7.60 (m, 2H), 7.54 (t, *J* = 6.0 Hz, 4H), 4.97-4.88 (m, 1H), 4.31 (dd, *J* = 9.3, 15.9 Hz, 1H), 4.03 (dd, *J* = 3.0, 15.9 Hz, 1H), 3.78-3.68 (m, 2H), 3.31 (s, 3H).

¹³C NMR (75 MHz, CDCl₃): δ = 168.5, 138.7, 134.1, 133.9, 132.0, 129.1, 128.7, 123.3, 69.6, 58.8, 50.3, 45.7.

IR ν(cm⁻¹): 3060, 2927, 1772, 1708, 1369, 1166, 1051, 740, 547.

HRMS: calcd for C₂₄H₂₂N₂O₇S₂Na: 537.076, found: 537.075.

***N*-[2-(1,3-dioxoisindolin-2-yl)-3-ethoxypropyl]-*N*-(phenylsulfonyl)benzene sulfonamide**



1-2f

Obtained as a white solid in 64% yield.

m.p. = 152-153°C.

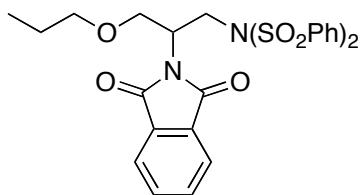
¹H NMR (300 MHz, CDCl₃): δ = 8.03 (d, *J* = 6.0 Hz, 4H), 7.83-7.80 (m, 2H), 7.70-7.67 (m, 2H), 7.65-7.60 (m, 2H), 7.53 (t, *J* = 6.0 Hz, 4H), 4.92-4.88 (m, 1H), 4.32 (dd, *J* = 9.0, 15.9 Hz, 1H), 4.05 (dd, *J* = 2.8, 15.6 Hz, 1H), 3.78 (d, *J* = 7.6 Hz, 2H), 3.49 (q, *J* = 7.2 Hz, 2H), 1.11 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ = 168.5, 138.8, 134.0, 133.9, 132.0, 129.1, 128.7, 123.3, 67.5, 66.4, 50.5, 45.8, 15.1.

IR ν(cm⁻¹): 2975, 2925, 1773, 1708, 1369, 1167, 1085, 754, 547.

HRMS: calcd for C₂₅H₂₄N₂O₇S₂Na: 551.092, found: 551.089.

***N*-[2-(1,3-dioxisoindolin-2-yl)-3-propoxypropyl]-*N*-(phenylsulfonyl)benzene-sulfonamide**



1-2g

Obtained as a white solid in 68% yield.

m.p. = 84-85°C.

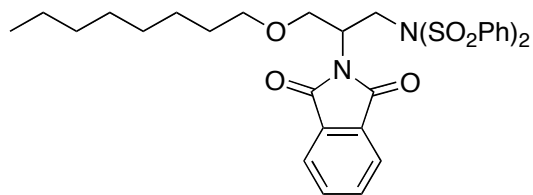
¹H NMR (300 MHz, CDCl₃): δ = 8.04 (d, J = 6.0 Hz, 4H), 7.82-7.80 (m, 2H), 7.70-7.62 (m, 2H), 7.63 (t, J = 6.0 Hz, 2H), 7.54 (t, J = 6.0 Hz, 4H), 4.93-4.86 (m, 1H), 4.32 (dd, J = 9.2, 16.0 Hz, 1H), 4.05 (dd, J = 2.8, 16.0 Hz, 1H), 3.78 (d, J = 7.6 Hz, 2H), 3.41-3.32 (m, 2H), 1.52-1.47 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ = 168.4, 138.8, 134.0, 133.8, 131.9, 129.0, 128.6, 123.2, 72.6, 67.6, 50.4, 45.85, 22.7, 10.4.

IR ν (cm⁻¹): 2963, 2932, 2875, 1774, 1708, 1448, 1369, 1166, 1083, 753, 546.

HRMS: calcd for C₂₆H₂₆N₂O₇S₂Na: 565.107, found: 565.105.

***N*-[2-(1,3-dioxoisindolin-2-yl)-3-(octyloxy)propyl]-*N*-(phenylsulfonyl)-benzenesulfonamide**



1-2h

Obtained as a white solid in 67% yield.

m.p. = 77-79°C.

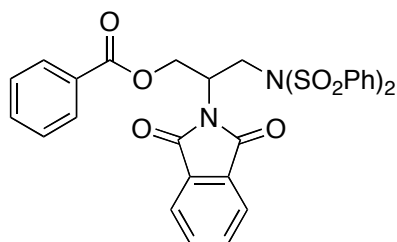
¹H NMR (400 MHz, CDCl₃): δ = 8.09 (d, *J* = 7.5 Hz, 4H), 7.86 (dd, *J* = 3.1, 5.4 Hz, 2H), 7.73 (dd, *J* = 3.0, 5.5 Hz, 2H), 7.70-7.64 (m, 2H), 7.58 (t, *J* = 7.7 Hz, 4H), 4.95-4.87 (m, 1H), 4.36 (dd, *J* = 9.2, 15.8 Hz, 1H), 4.08 (dd, *J* = 2.8, 15.9 Hz, 1H), 3.80-3.78 (m, 2H), 3.47-3.38 (m, 2H), 1.55-1.47 (m, 2H), 1.33-1.29 (m, 4H), 1.23-1.20 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ = 168.4, 138.8, 134.0, 133.8, 131.9, 129.0, 128.6, 123.2, 71.1, 67.6, 50.5, 45.8, 31.7, 29.5, 29.3, 29.2, 26.0, 22.6, 14.0.

IR ν(cm⁻¹): 2926, 2856, 1775, 1708, 1448, 1370, 1167, 1084, 788, 753, 547.

HRMS: calcd for C₃₁H₃₆N₂O₇S₂Na: 635.186, found: 635.185.

2-(1,3-dioxisoindolin-2-yl)-3-[N-(phenylsulfonyl)phenylsulfonamido]-propyl benzoate



1-2i

Obtained as a white solid in 68% yield.

m.p. = 158-159°C.

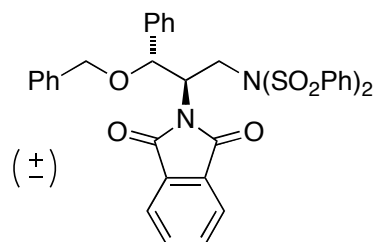
¹H NMR (400 MHz, CDCl₃): δ = 8.11 (d, J = 7.8 Hz, 4H), 8.04 (d, J = 7.6 Hz, 2H), 7.89 (dd, J = 3.1, 5.4 Hz, 2H), 7.75 (dd, J = 3.0, 5.5 Hz, 2H), 7.69 (t, J = 7.4 Hz, 2H), 7.61- 7.55 (m, 5H), 7.45 (t, J = 7.7 Hz, 2H), 5.19-5.12 (m, 1H), 4.77-4.69 (m, 2H), 4.48 (dd, J = 9.1, 15.9 Hz, 1H), 4.26 (dd, J = 2.8, 15.9 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ = 168.2, 165.8, 138.6, 134.1, 134.1, 133.2, 131.8, 129.7, 129.3, 129.1, 128.7, 128.4, 123.5, 62.1, 50.2, 45.5.

IR ν (cm⁻¹): 3065, 2927, 1775, 1710, 1448, 1370, 1267, 1166, 1083, 753, 545.

HRMS: calcd for C₃₀H₂₄N₂O₈S₂Na: 627.087, found: 627.091.

***N*-[3-(benzyloxy)-2-(1,3-dioxisoindolin-2-yl)-3-phenylpropyl]-*N*-
(phenylsulfonyl)benzenesulfonamide**

**1-2j**

Obtained as a white solid in 65% yield.

m.p. = 175-177°C.

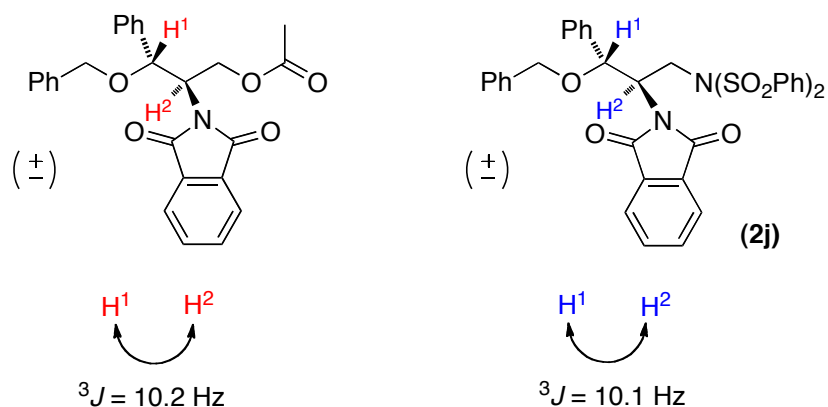
¹H NMR (400 MHz, CDCl₃): δ = 7.81-7.78 (m, 2H), 7.75 (d, *J* = 7.5 Hz, 4H), 7.72-7.69 (m, 2H), 7.46-7.57 (m, 7H), 7.39 (t, *J* = 7.8 Hz, 4H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.03 (t, *J* = 7.4 Hz, 2H), 6.91 (d, *J* = 7.2 Hz, 2H), 5.02 (pseudo dt, *J* = 1.6, 10.5 Hz, 1H), 4.84 (d, *J* = 10.1 Hz, 1H), 4.50 (dd, *J* = 10.5, 15.9 Hz, 1H), 4.32 (d, *J* = 12.1 Hz, 1H), 4.05 (d, *J* = 12.1 Hz, 1H), 3.40 (dd, *J* = 1.6, 15.9 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ = 169.0, 168.1, 138.6, 137.9, 137.7, 133.8, 133.8, 133.7, 132.44, 131.9, 129.1, 129.0, 128.9, 128.6, 128.5, 128.1, 127.5, 127.4, 123.5, 123.0, 77.8, 70.1, 56.4, 45.3.

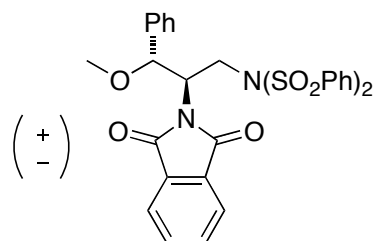
IR ν(cm⁻¹): 2924, 2856, 1772, 1706, 1447, 1376, 1168, 1085, 891, 764, 550.

HRMS: calcd for C₃₆H₃₀N₂O₇S₂Na: 689.139, found: 689.137.

The relative stereochemistry was deduced from a correlation with aminoacetoxylation products obtained Stahl^[167] that were structurally characterized by X-ray. This comparison leads us to the unambiguous conclusion of a relative *trans*-positioning for H¹ and H².



***N*-[3-(benzyloxy)-2-(1,3-dioxisoindolin-2-yl)butyl]-*N*-(phenylsulfonyl)-benzene-sulfonamide**



1-2k

Obtained as a white solid in 55% yield.

m.p. = 172-174°C.

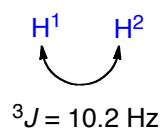
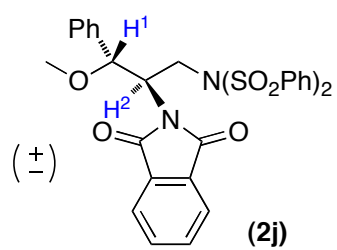
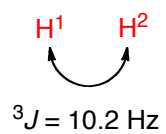
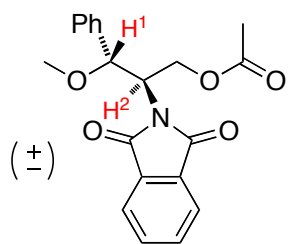
^1H NMR (400 MHz, CDCl_3): δ = 7.88-7.86 (m, 1H), 7.81-7.79 (m, 1H), 7.77-7.71 (m, 6H), 7.55 (t, J = 7.5 Hz, 2H), 7.51-7.46 (m, 5H), 7.41 (t, J = 7.9 Hz, 4H), 4.98 (pseudo dt, J = 1.8, 10.4 Hz, 1H), 4.71 (d, J = 10.2 Hz, 1H), 4.55 (dd, J = 10.5, 16.0 Hz, 1H), 3.44 (dd, J = 1.8, 16.0 Hz, 1H), 3.04 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ = 169.2, 168.1, 138.5, 138.0, 133.9, 133.8, 133.7, 132.4, 131.9, 129.0, 128.9, 128.9, 128.5, 128.4, 123.6, 123.0, 80.3, 56.6, 56.3, 45.5.

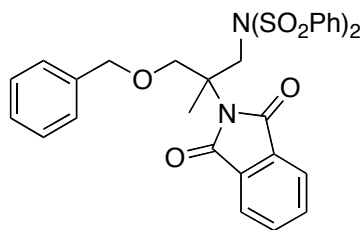
IR $\nu(\text{cm}^{-1})$: 2936, 2827, 1777, 1710, 1446, 1373, 1168, 1085, 765, 548.

HRMS: calcd for $\text{C}_{30}\text{H}_{26}\text{N}_2\text{O}_7\text{S}_2\text{Na}$: 613.108, found: 613.106.

Identical stereochemical assignment as discussed for product **1-2j**:



***N*-[3-(benzyloxy)-2-(1,3-dioxoisindolin-2-yl)-2-methylpropyl]-*N*-(phenylsulfonyl)-benzenesulfonamide**



1-21

Obtained as a white solid in 43% yield.

m.p. = 87-89°C.

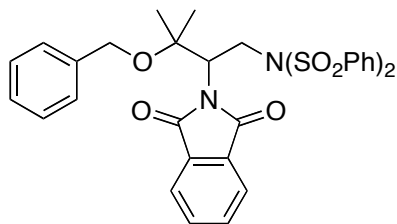
¹H NMR (400 MHz, CDCl₃): δ = 7.93 (dd, *J* = 1.1, 8.5 Hz, 4H), 7.78 (dd, *J* = 3.0, 5.5 Hz, 2H), 7.67 (dd, *J* = 3.0, 5.5 Hz, 2H), 7.66-7.61 (m, 2H), 7.48-7.53 (m, 4H), 7.33-7.19 (m, 5H), 4.60-4.44 (m, 3H), 4.29 (d, *J* = 9.0 Hz, 1H), 4.11 (d, *J* = 16.4 Hz, 1H), 3.67 (d, *J* = 9.0 Hz, 1H), 1.93 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ = 170.1, 138.7, 138.0, 134.0, 133.7, 132.1, 129.0, 128.8, 128.3, 127.6, 127.5, 122.7, 73.1, 72.9, 63.2, 51.0, 21.3.

IR ν(cm⁻¹): 3067, 2923, 2852, 1740, 1713, 1448, 1369, 1161, 1082, 742, 682, 546.

HRMS: calcd for C₃₁H₂₈N₂O₇S₂Na: 627.124, found: 627.123.

***N*-(3-(benzyloxy)-2-(1,3-dioxoisindolin-2-yl)-3-methylbutyl)-*N*-(phenylsulfonyl)-benzenesulfonamide**



1-2m

Obtained as a white solid in 40% yield.

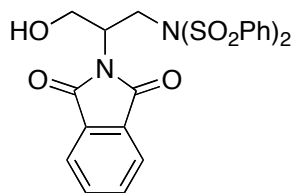
¹H NMR (400 MHz, CDCl₃): δ = 8.01-7.97 (m, 4H), 7.88-7.85 (m, 1H), 7.82-7.78 (m, 1H), 7.71-7.67 (m, 2H), 7.59 (t, J = 7.5 Hz, 2H), 7.48 (t, J = 7.8 Hz, 4H), 7.39 (d, J = 7.2 Hz, 2H), 7.30 (t, J = 7.4 Hz, 2H), 7.24 (d, J = 7.3 Hz, 1H), 4.89 (dd, J = 1.0, 9.9 Hz, 1H), 4.75 (dd, J = 10.0, 15.8 Hz, 1H), 4.63 (d, J = 11.2 Hz, 1H), 4.59 (d, J = 11.4 Hz, 1H), 4.28 (dd, J = 1.1, 15.8 Hz, 1H), 1.47 (s, 3H), 1.39 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ = 169.0, 168.9, 139.2, 138.8, 134.0, 133.8, 133.6, 132.57, 131.2, 128.9, 128.6, 128.1, 127.1, 127.0, 123.4, 123.1, 77.6, 63.9, 58.4, 44.6, 23.6, 23.5.

IR ν (cm⁻¹): 3064, 2976, 2932, 2872, 1775, 1710, 1448, 1369, 1165, 1083, 806, 718, 547.

HRMS: calcd for C₃₂H₃₀N₂O₇S₂Na: 641.139, found: 641.137.

***N*-[2-(1,3-dioxisoindolin-2-yl)-3-hydroxypropyl]-*N*-(phenylsulfonyl)-benzenesulfonamide**



1-2n

Obtained as a white solid in 68% yield.

m.p. = 146-148°C.

¹H NMR (400 MHz, acetone-*d*₆): δ = 7.99 (d, J = 8.3 Hz, 4H), 7.87 (s, 4H), 7.79-7.72 (m, 2H), 7.64 (t, J = 7.8 Hz, 4H), 4.94-4.87 (m, 1H), 4.42 (dd, J = 9.3, 15.9 Hz, 1H), 4.16 (dd, J = 2.7, 16.0 Hz, 1H), 4.05-4.02 (m, 1H), 3.99-3.90 (m, 1H).

¹³C NMR (101 MHz, acetone-*d*₆): δ = 169.9, 140.6, 135.9, 135.7, 133.8, 130.9, 130.0, 124.6, 61.2, 55.7, 47.8.

IR ν (cm⁻¹): 3436, 3067, 2945, 1767, 1687, 1447, 1370, 1167, 1083, 784, 752, 544.

HRMS: calcd for C₂₃H₂₀N₂O₇S₂Na: 523.061, found: 523.062.

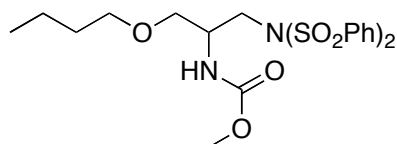
1.4. Synthetic transformations

1.4.1 Procedure for the hydrogenation of (1-2a) to (1-2n).

A stirred solution of **1-2a** (2.0 mmol, 1.2 g) and 10% Pd(OH)₂/C (150 mg) in EtOAc (5 mL), was hydrogenated at 1 atm and room temperature overnight. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane) giving **1-2n** with 95% yield. Analytical data matches the one from the independent synthesis using direct diamination as reported above.

1.4.2 Protocol for phthalimide deprotection

Methyl-(1-butoxy-3-[N-(phenylsulfonyl)phenylsulfonamido]propan-2-yl)- carbamate



1-3

To a solution of the diamination product **1-2d** (100 mg, 0.18 mmol) in EtOH (2 mL) was added methylhydrazine (19 μ L, 0.36 mmol) and stirred at 70°C overnight. Then the solution was concentrated under reduced pressure and water and EtOAc was added, organic layer was separated and the aqueous layer was extracted twice with EtOAc (10 mL). The combined organic layer was washed with NH₄Cl (10 mL) and brine (10 mL), dried with anhydrous MgSO₄, filtered and concentrated under reduced pressure to a yellow coloured crude product. This crude product was then dissolved in CH₂Cl₂ (2 mL) at 0°C, triethylamine (26 μ L, 0.19 mmol) was added and then methylchloroformate (19 μ L, 0.24 mmol) was added dropwise to the stirred solution. After overnight stirring, the solution was concentrated under reduced pressure. Then water and EtOAc was added, organic layer was separated and the aqueous layer was extracted twice with EtOAc (10 mL). The combined organic layer was washed with NH₄Cl solution (10 mL) and brine (10 mL), dried with anhydrous MgSO₄, filtered and

concentrated under reduced pressure. The crude product was then purified over silica gel column (EtOAc/hexane) to furnish title compound **1-3** (76 mg, 88 %) as a white solid.

m.p. = 78-80°C.

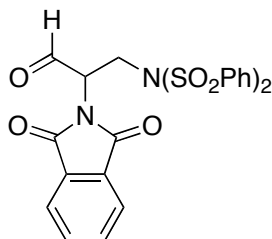
¹H NMR (400 MHz, CDCl₃): δ = 8.04 (d, J = 7.6 Hz, 4H), 7.66 (t, J = 7.4 Hz, 2H), 7.55 (t, J = 7.7 Hz, 4H), 5.32 (d, J = 7.6 Hz, 1H), 4.19 (br s, 1H), 3.91 (dd, J = 4.3, 15.5 Hz, 1H), 3.79 (dd, J = 10.1, 15.4 Hz, 1H), 3.59 (s, 3H), 3.46-3.43 (m, 4H), 1.53-1.50 (m, 2H), 1.37-1.33 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ = 156.4, 139.3, 134.0, 129.1, 128.4, 71.3, 70.2, 52.1, 49.9, 48.7, 31.6, 19.3, 13.9.

IR ν (cm⁻¹): 3277, 3054, 2986, 2960, 1723, 1515, 1448, 1374, 1169, 1083, 895, 731, 703, 584, 551.

HRMS: calcd for C₂₁H₂₈N₂O₇S₂Na: 507.124, found: 507.123.

1.4.3 Procedure for aldehyde formation

***N*-[2-(1,3-dioxisoindolin-2-yl)-3-oxopropyl]-*N*-(phenylsulfonyl)benzene- sulfonamide****1-4**

To a solution of the alcohol (**1-2n**) (100 mg, 0.2 mmol) in CH₂Cl₂ (2 mL) at 0 °C was added Dess–Martin periodinane (91 mg, 0.22 mmol). The resulting cloudy white solution was stirred for 30 min, before warming to room temperature. After a further 3 h at room temperature, the mixture was filtered through celite. The filtrate was concentrated under reduced pressure to a white solide. Purification by column chromatography (Et₂O/hexane) afforded the title compound **1-4** in 97% yield.

m.p. = 97-99°C.

¹H NMR (400 MHz, CDCl₃): δ = 9.58 (s, 1H), 7.92 (d, *J* = 7.7 Hz, 4H), 7.87 (dd, *J* = 3.0, 5.5 Hz, 2H), 7.73 (dd, *J* = 3.1, 5.4 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 2H), 7.50 (t, *J* = 7.8 Hz, 4H), 5.17 (dd, *J* = 2.4, 9.5 Hz, 1H), 4.56 (dd, *J* = 2.4, 16.3 Hz, 1H), 4.20 (dd, *J* = 9.6, 16.3 Hz, 1H).

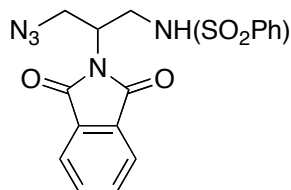
¹³C NMR (101 MHz, CDCl₃): δ = 194.3, 167.7, 138.2, 134.4, 134.3, 131.8, 129.2, 128.67, 123.8, 58.3, 44.8.

IR ν(cm⁻¹): 3065, 2961, 2852, 1777, 1711, 1448, 1370, 1165, 1083, 792, 754, 545.

HRMS: calcd for C₂₃H₁₈N₂O₇S₂Na(MeOH) : 553.072, found: 552.974.

1.4.4 Formation of the azide compound

***N*-[3-azido-2-(1,3-dioxisoindolin-2-yl)propyl]benzenesulfonamide**



1-5

To a stirred solution of the starting material **1-2n** (1.0 equiv, 0.1 mmol) in dry CH₂Cl₂ (1 mL) triethylamine (1.1 equiv, 0.11 mmol) was added and cooled to 0 °C. Then methanesulfonyl chloride (1.1 equiv, 0.11 mmol) was added to the solution and stirred for two hours. After consumption of the starting material, the solvent was evaporated and the solid was dissolved in DMF (1 mL). NaN₃ (3.5 equiv, 0.35 mmol) was added, and the solution was heated at 90°C overnight. The solution was cooled to room temperature and diluted with diethyl ether and water. The organic phase was dried and concentrated. The crude product was purified by column chromatography to furnish the title compound **1-5** (404 mg, 77%) as a waxy solid.

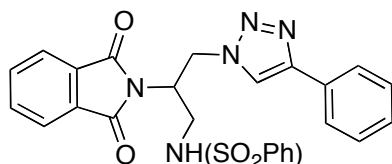
¹H NMR (400 MHz, CDCl₃): δ = 7.88-7.82 (m, 4H), 7.79 (dd, *J* = 3.1, 5.4 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 2H), 5.13 (dd, *J* = 5.6, 7.5 Hz, 1H), 4.53-4.49 (m, 1H), 3.91 (dd, *J* = 8.9, 12.6 Hz, 1H), 3.72 (dd, *J* = 5.9, 12.7 Hz, 1H), 3.69-3.62 (m, 1H), 3.40-3.34 (m, 1H).

¹³C NMR (126 MHz, CDCl₃): δ = 168.3, 139.7, 134.4, 132.8, 131.5, 129.2, 126.9, 123.7, 50.4, 49.8, 42.9.

IR ν(cm⁻¹): 3285, 2925, 2854, 2104, 1775, 1708, 1447, 1377, 1160, 1092, 754, 721, 583.

HRMS: calcd for C₁₇H₁₅N₅O₄SNa: 408.074, found: 408.074.

1.4.5 Protocol for the click reaction

***N*-[2-(1,3-dioxisoindolin-2-yl)-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propyl]benzenesulfonamide****1-6**

The azide product **1-5** (52 mg, 0.1 mmol), phenylacetylene (0.11 mmol), copper (II) sulfate (9 mg, 0.05 mmol), and sodium ascorbate (20 mg, 0.1 mmol) were mixed in *tert*-butyl alcohol/water (1:1; 0.5 mL) and stirred at room temperature overnight. The solution was then cooled to 0°C, and the precipitate was filtrated. The white solid was purified over silica gel column (EtOAc/hexane) to furnish the titled compound **1-6** (92%) as a white solid.

m.p. = 208-210°C.

¹H NMR (400 MHz, acetone-*d*₆): δ = 8.41 (s, 1H), 7.89-7.80 (m, 8H), 7.66-7.55 (m, 3H), 7.45-7.40 (m, 2H), 7.36-7.30 (m, 1H), 7.10 (t, J = 6.6 Hz, 1H), 5.13 (dd, J = 9.7, 14.1 Hz, 1H), 5.01 (dd, J = 4.9, 14.1 Hz, 1H), 4.94-4.88 (m, 1H), 3.80 (ddd, J = 6.3, 9.1, 13.9 Hz, 1H), 3.63 (ddd, J = 5.3, 7.1, 13.8 Hz, 1H).

¹³C NMR (101 MHz, acetone-*d*₆): δ = 169.4, 148.7, 142.4, 135.9, 134.1, 133.4, 132.8, 130.8, 130.3, 129.4, 128.4, 127.0, 124.7, 122.7, 53.9, 50.0, 43.5.

IR ν (cm⁻¹): 3277, 3061, 3027, 2349, 1775, 1701, 1464, 1445, 1382, 1158, 1088, 759, 717, 587.

HRMS: calcd for C₂₅H₂₁N₅O₄SNa : 510.121, found: 510.121.

Chapter II: Evolution of the Intermolecular Regioselective 1,2-Diamination of Allylic Ethers

2.1 General

All solvents, reagents and all deuterated solvents were purchased from Aldrich and TCI. Column chromatography was performed with silica gel (Merck, type 60, 0.063-0.2 mm). NMR spectra were recorded on a Bruker Avance 400 MHz or 500 MHz spectrometer, respectively. All chemical shifts in NMR experiments were reported as ppm downfield from TMS. The following calibrations were used: CDCl_3 $\delta = 7.26$ and 77.0 ppm, $\text{DMSO-}d_6$ $\delta = 2.50$ and 39.52 ppm. MS (ESI-LCMS) experiments were performed using an Agilent 1100 HPLC with a Bruker micro-TOF instrument (ESI). Unless otherwise stated, a Supelco C8 (5 cm x 4.6 mm, 5 μm particles) column was used with a linear elution gradient from 100% H_2O (0.5% HCO_2H) to 100% MeCN in 13 min at a flow rate of 0.5 mL/min. MS (EI) and HRMS experiments were performed on a Kratos MS 50 within the service centers at ICIQ. Melting points were determined in a Büchi Melting Point B-540 apparatus. IR spectra were taken in a Bruker Alpha instrument in the solid state.

2.2. General procedure for the synthesis of 1,2-diamines

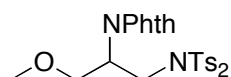
A Pyrex tube equipped with a stirrer bar is charged with 0.059 mg phthalimide (0.4 mmol, 1.0 equiv), 15 mg bis(benzonitrile)palladiumdichloride (0.04 mmol, 10%) in 0.5 mL of absolute dichloromethane and the solution is stirred at 70 °C for 1h. Then, 156 mg bistosylamide (0.48 mmol, 1.2 equiv), 325 mg iodosobenzene dipivalate (0.80 mmol, 2.0 equiv) and a previously prepared solution of 0.40 mmol of alkene with 14 mg of 4-*tert*-butylcatechol (0.08 mmol, 20%) are added. The resulting solution is sealed and stirred at 70°C for 8 h. After cooling down to room temperature, the solution was washed with a 2% solution of KOH (5 mL) and extracted with CH_2Cl_2 (4 x 10 mL). The organic phases were combined, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by chromatography (silica gel, neutralized with *n*-hexane/ Et_3N (3%) and then *n*-hexane/ethyl acetate, 3/1, v/v) to give the pure diaminated product.

2.3. Scale up of the diamination reaction

A Pyrex tube equipped with a stirrer bar is charged with 0.59 g phthalimide (4.0 mmol, 1.0 equiv), 0.15 g bis(benzonitrile)palladiumdichloride (0.04 mmol, 10%) in 5.0 mL of absolute dichloromethane and the solution is stirred at 70°C for 1h. Then, 1.56 g bistosylamide (4.8 mmol, 1.2 equiv), 3.25 g iodosobenzene dipivalate (8.0 mmol, 2.0 equiv) and a previously prepared solution of butyl allyl ether 0.46 g (4.0 mmol, 1 equiv) with 0.14 g of 4-*tert*-butylcatechol (0.8 mmol, 20%) are added. The resulting solution is sealed and stirred at 70°C for 8h. After cooling down to room temperature, the solution was washed with a 2% solution of KOH (5 mL) and extracted with CH₂Cl₂ (4 x 10 mL). The organic phases were combined, dried over Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by chromatography (silica gel, neutralized with *n*-hexane/Et₃N (3%) and then *n*-hexane/ethyl acetate, 3/1, v/v) to give the pure diaminated product in 82% yield.

2.4. Characterization of the diamination products

N-(2-(1,3-Dioxoisindolin-2-yl)-3-methoxypropyl)-4-methyl-*N*-tosylbenzene sulfonamide



2-2a

Obtained as a white solid in 67% yield.

m.p.: 113-115°C.

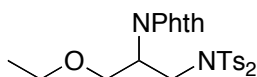
¹H NMR (400 MHz, CDCl₃): δ = 7.94 (d, *J* = 8.4 Hz, 4H), 7.84 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 4H), 5.02–4.89 (m, 1H), 4.29 (dd, *J* = 15.8, 9.1 Hz, 1H), 4.01 (dd, *J* = 15.8, 2.9 Hz, 1H), 3.82 (dd, *J* = 10.1, 8.7 Hz, 1H), 3.72 (dd, *J* = 10.1, 6.6 Hz, 1H), 3.34 (s, 3H), 2.45 (s, 6H).

^{13}C NMR (125 MHz, CDCl_3): δ = 168.5, 145.1, 135.9, 133.8, 132.0, 129.7, 128.8, 128.2, 123.3, 69.6, 58.8, 50.4, 45.5, 21.7.

IR $\nu(\text{cm}^{-1})$: 2925, 1954, 1771, 1596, 1491, 1342, 1306, 1121, 1084, 1059, 806, 786, 702, 596, 477.

HRMS: calcd for $\text{C}_{26}\text{H}_{29}\text{N}_2\text{O}_7\text{S}_2\text{Na}$: 565.1079, found: 565.1074.

***N*-(2-(1,3-Dioxoisindolin-2-yl)-3-ethoxypropyl)-4-methyl-*N*-tosylbenzene sulfonamide**



2-2b

Obtained as a white solid in 68% yield.

m.p.: 63-64°C.

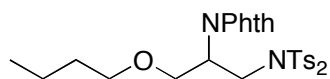
^1H NMR (500 MHz, CDCl_3): δ = 7.93 (d, J = 8.4 Hz, 4H), 7.84 (dd, J = 5.5, 3.0 Hz, 2H), 7.71 (dd, J = 5.5, 3.0 Hz, 2H), 7.34 (d, J = 8.2 Hz, 4H), 5.02–4.89 (m, 1H), 4.30 (dd, J = 15.8, 9.2 Hz, 1H), 4.03 (dd, J = 15.8, 2.8 Hz, 1H), 3.88–3.67 (m, 2H), 3.54–3.47 (m, 2H), 2.45 (s, 6H), 1.13 (t, J = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3): δ = 168.5, 145.1, 135.9, 133.8, 132.0, 129.6, 128.8, 123.2, 67.5, 66.3, 50.6, 45.6, 21.7, 15.0.

IR $\nu(\text{cm}^{-1})$: 3063, 2926, 1774, 1708, 1595, 1493, 1367, 1162, 1117, 933, 811, 784, 718, 660, 545.

HRMS: calcd for $\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}_7\text{S}_2\text{Na}$: 579.1236, found: 579.1218.

***N*-(3-Butoxy-2-(1,3-dioxoisindolin-2-yl)propyl)-4-methyl-*N*-tosylbenzene sulfonamide**



2-2c

Obtained as a white solid in 71% yield.

m.p.: 60-61°C

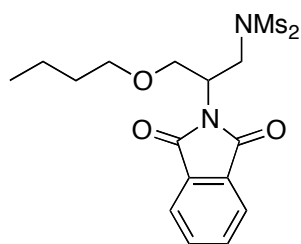
¹H NMR (500 MHz, CDCl₃): δ = 7.93 (d, *J* = 8.3 Hz, 4H), 7.83 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.69 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 4H), 5.10–4.86 (m, 1H), 4.31 (dd, *J* = 15.8, 9.1 Hz, 1H), 4.03 (dd, *J* = 15.8, 2.9 Hz, 1H), 3.86–3.74 (m, 2H), 3.52–3.32 (m, 2H), 2.43 (s, 6H), 1.51–1.42 (m, 2H), 1.32–1.19 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 168.5, 145.1, 135.9, 134.3, 133.8, 132.6, 132.0, 129.6, 128.7, 123.6, 123.2, 70.8, 67.7, 50.6, 45.7, 31.6, 21.7, 19.1, 13.8.

IR ν(cm⁻¹): 2959, 2932, 2871, 1710.

HRMS: calcd for C₂₉H₃₂N₂O₇S₂Na: 607.1549, found: 607.1563.

***N*-(3-Butoxy-2-(1,3-dioxoisindolin-2-yl)propyl)-*N*-(methylsulfonyl)methanesulfonamide**



2-2c'

Obtained as a white solid in 42% yield.

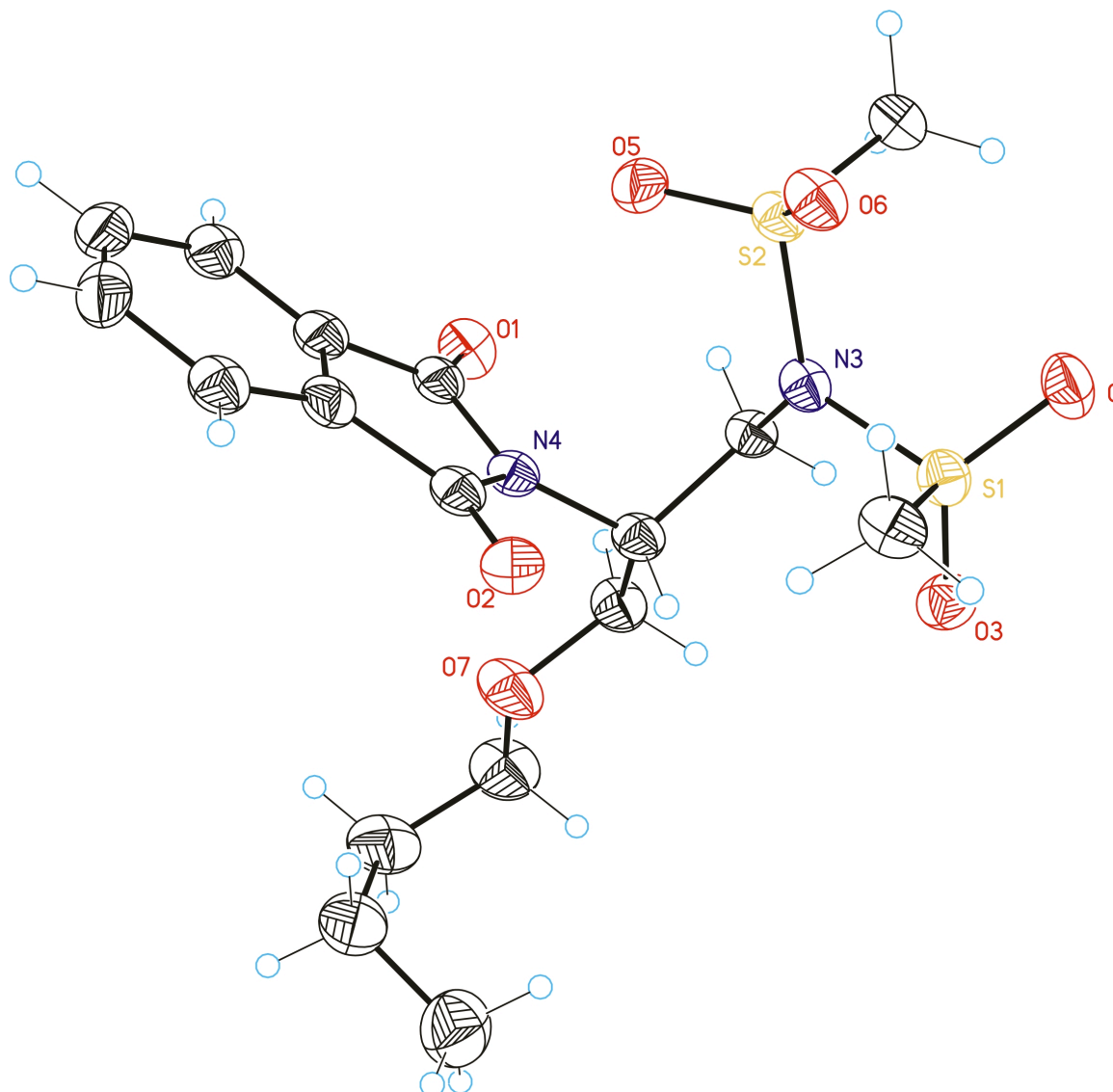
m.p.: 73-75 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.86 (dd, J = 5.4, 3.0 Hz, 2H), 7.74 (dd, J = 5.5, 3.0 Hz, 2H), 4.81–4.67 (m, 1H), 4.24 (dd, J = 15.1, 10.0 Hz, 1H), 4.15 (dd, J = 15.1, 2.7 Hz, 1H), 3.90 (dd, J = 7.6, 3.0 Hz, 2H), 3.48 (d, J = 6.5 Hz, 1H), 3.40 (d, J = 6.1 Hz, 1H), 3.33 (s, 6H), 1.56–1.46 (m, 2H), 1.35–1.21 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 168.7, 134.1, 131.8, 123.4, 71.0, 67.3, 50.63, 46.4, 43.2, 31.5, 19.1, 13.8.

IR ν (cm⁻¹): 3015, 2958, 2933, 2871, 1707.

HRMS: calcd for C₁₇H₂₄N₂O₇S₂Na: 455.0923, found: 455.0929.

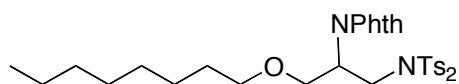
Details concerning the X-ray structure of 2-2c'.Table 1. Crystal data and structure refinement for **2-2c'**.

Identification code	CCDC 885867
Empirical formula	C ₁₇ H ₂₄ N ₂ O ₇ S ₂
Formula weight	432.50
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic

Experimental Section

Space group	P-1
Unit cell dimensions	a = 6.7342(18) Å α = 102.131(9) °. b = 10.136(3) Å β = 91.641(8) °. c = 15.489(4) Å γ = 94.043(9) °.
Volume	1030.0(5) Å ³
Z	2
Density (calculated)	1.395 Mg/m ³
Absorption coefficient	0.299 mm ⁻¹
F(000)	456
Crystal size	0.30 x 0.15 x 0.05 mm ³
Theta range for data collection	1.35 to 27.49 °.
Index ranges	-8 ≤ h ≤ 8, -13 ≤ k ≤ 12, -19 ≤ l ≤ 20
Reflections collected	7716
Independent reflections	4303 [R(int) = 0.0413]
Completeness to theta = 27.49 °	0.909 %
Absorption correction	Empirical
Max. and min. transmission	0.9611 and 0.9158
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	4303 / 6 / 256
Goodness-of-fit on F ²	0.911
Final R indices [I > 2σ(I)]	R1 = 0.0616, wR2 = 0.1547
R indices (all data)	R1 = 0.0972, wR2 = 0.1820
Largest diff. peak and hole	0.619 and -0.593 e.Å ⁻³

***N*-(2-(1,3-Dioxoisindolin-2-yl)-3-(octyloxy)propyl)-4-methyl-*N*-tosylbenzene
sulfonamide**



2-2d

Obtained as a white solid in 65% yield.

m.p.: 55-57°C.

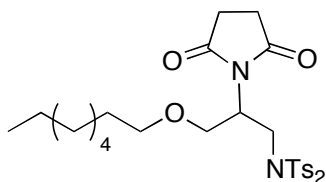
¹H NMR (500 MHz, CDCl₃): δ = 7.94 (d, *J* = 8.4 Hz, 4H), 7.84 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 4H), 4.99–4.90 (m, 1H), 4.31 (dd, *J* = 15.8, 9.1 Hz, 1H), 4.02 (dd, *J* = 15.8, 2.9 Hz, 1H), 3.86–3.73 (m, 2H), 3.49–3.32 (m, 2H), 2.44 (s, 6H), 1.53–1.40 (m, 2H), 1.22–1.11 (m, 10H), 0.87 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 168.5, 145.1, 135.9, 134.3, 133.8, 132.7, 132.0, 129.6, 128.7, 123.6, 123.2, 71.1, 67.6, 50.6, 45.7, 31.8, 29.5, 29.3, 29.2, 26.0, 22.6, 21.7, 14.1.

IR ν(cm⁻¹): 3065, 2925, 2075, 1774, 1596, 1493, 1334, 1188, 1084, 932, 874, 785, 595, 527.

HRMS: calcd for C₃₃H₄₀N₂O₇S₂Na: 663.2175, found: 663.2184.

***N*-(2-(2,5-Dioxopyrrolidin-1-yl)-3-(octyloxy)propyl)-4-methyl-*N*-tosylbenzenesulfonamide**



2-2d'

Obtained as a white solid in 21% yield.

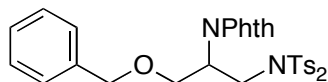
¹H NMR (500 MHz, CDCl₃): δ = 7.94 (d, J = 8.4 Hz, 4H), 7.38 (d, J = 8.3 Hz, 4H), 4.86–4.70 (m, 1H), 4.10 (dd, J = 15.8, 9.7 Hz, 1H), 3.89 (dd, J = 15.8, 2.2 Hz, 1H), 3.81–3.58 (m, 2H), 3.54–3.29 (m, 2H), 2.85–2.57 (m, 4H), 2.47 (s, 6H), 1.54 (dq, J = 13.6, 6.4 Hz, 2H), 1.37–1.08 (m, 10H), 0.89 (t, J = 6.9 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 178.1, 145.2, 135.6, 129.7, 128.9, 71.1, 66.9, 51.1, 43.9, 31.8, 29.6, 29.4, 29.3, 28.1, 26.0, 22.7, 21.7, 14.1.

IR ν (cm⁻¹): 2930, 2860, 1730, 1620.

HRMS: calcd for C₂₆H₃₄N₂O₇S₂Na: 573.1705, found: 573.1710.

***N*-(3-(Benzyloxy)-2-(1,3-dioxoisindolin-2-yl)propyl)-4-methyl-*N*-tosylbenzene
sulfonamide**



2-2e

Obtained as a white solid in 69% yield.

m.p.: 59-60°C.

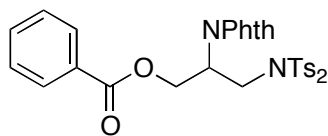
¹H NMR (500 MHz, CDCl₃): δ = 7.93 (d, J = 8.4 Hz, 4H), 7.84 (dd, J = 5.5, 3.0 Hz, 2H), 7.71 (dd, J = 5.5, 3.0 Hz, 2H), 7.33 (d, J = 8.2 Hz, 4H), 7.30–7.24 (m, 5H), 5.08–4.99 (m, 1H), 4.55 (d, J = 11.9 Hz, 1H), 4.51 (d, J = 11.9 Hz, 1H), 4.32 (dd, J = 15.9, 9.2 Hz, 1H), 4.05 (dd, J = 15.9, 2.8 Hz, 1H), 3.87 (d, J = 7.6 Hz, 2H), 2.44 (s, 6H).

¹³C NMR (125 MHz, CDCl₃): δ = 168.5, 145.2, 137.6, 135.8, 133.9, 131.9, 129.7, 129.6, 128.8, 128.7, 128.4, 127.7, 127.6, 123.3, 72.8, 67.2, 50.6, 45.6, 21.8.

IR ν (cm⁻¹): 2869, 1708, 1595, 1367, 1163, 1083, 1052, 812, 785, 718, 660, 545.

HRMS: calcd for C₃₂H₃₀N₂O₇S₂Na: 641.1392, found: 641.1417.

2-(1,3-Dioxoisindolin-2-yl)-3-(4-methyl-N-tosylphenylsulfonamido)propyl benzoate



2-2f

Obtained as a white solid in 52% yield.

m.p.: 91-93°C.

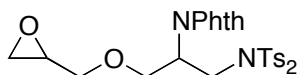
¹H NMR (400 MHz, CDCl₃): δ = 8.05–7.98 (m, 2H), 7.96 (d, J = 8.3 Hz, 4H), 7.86 (dd, J = 5.5, 3.1 Hz, 2H), 7.72 (dd, J = 5.5, 3.0 Hz, 2H), 7.60–7.51 (m, 1H), 7.45–7.38 (m, 2H), 7.35 (d, J = 8.3 Hz, 4H), 5.21–5.06 (m, 1H), 4.77–4.58 (m, 2H), 4.42 (dd, J = 15.9, 9.0 Hz, 1H), 4.20 (dd, J = 15.9, 3.0 Hz, 1H), 2.44 (s, 6H).

¹³C NMR (125 MHz, CDCl₃): δ = 168.2, 165.8, 145.3, 135.7, 134.1, 133.2, 131.8, 129.8, 129.7, 129.4, 128.78, 128.4, 123.5, 62.2, 50.3, 45.3, 21.7.

IR ν (cm⁻¹): 3065, 3034, 2962, 2924, 1710, 1597.

HRMS: calcd for C₃₂H₂₈N₂O₈S₂Na: 655.1185, found: 655.1206.

***N*-(2-(1,3-Dioxoisindolin-2-yl)-3-(oxiran-2-ylmethoxy)propyl)-4-methyl-*N*-tosylbenzenesulfonamide**



2-2g

Obtained as a white solid in 60% yield.

m.p.: 77-79°C.

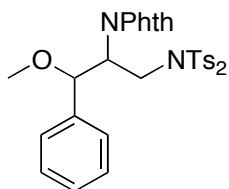
¹H NMR (500 MHz, CDCl₃): δ = 7.93 (d, J = 8.4 Hz, 4H), 7.84 (dd, J = 5.5, 3.0 Hz, 2H), 7.71 (dd, J = 5.5, 3.0 Hz, 2H), 7.34 (d, J = 8.2 Hz, 4H), 5.01–4.90 (m, 1H), 4.30 (ddd, J = 15.8, 9.1, 1.3 Hz, 1H), 4.03 (ddd, J = 15.8, 7.0, 2.9 Hz, 1H), 3.93 (ddd, J = 10.2, 7.7, 3.6 Hz, 1H), 3.86 (ddd, J = 10.2, 7.7, 5.2 Hz, 1H), 3.75 (ddd, J = 11.5, 2.9, 1.9 Hz, 1H), 3.41 (ddd, J = 11.5, 5.7, 1.4 Hz, 1H), 3.13–3.04 (m, 1H), 2.74 (td, J = 5.1, 4.2 Hz, 1H), 2.58 (ddd, J = 13.7, 5.0, 2.7 Hz, 1H), 2.44 (s, 6H).

¹³C NMR (125 MHz, CDCl₃): δ = 168.4, 145.2, 135.8, 133.9, 131.9, 129.7, 128.8, 123.3, 71.4, 68.3, 50.6, 50.5, 45.5, 44.1, 21.7.

IR ν (cm⁻¹): 3058, 2924, 1774, 1596, 1493, 1351, 1188, 1154, 811, 758, 594, 481, 405.

HRMS: calcd for C₂₈H₂₈N₂O₈S₂Na: 607.1185, found: 607.1158.

***N*-(2-(1,3-Dioxoisindolin-2-yl)-3-methoxy-4-phenylbutyl)-4-methyl-*N*-tosylbenzenesulfonamide**



2-2h

Obtained as a white solid in 39% yield.

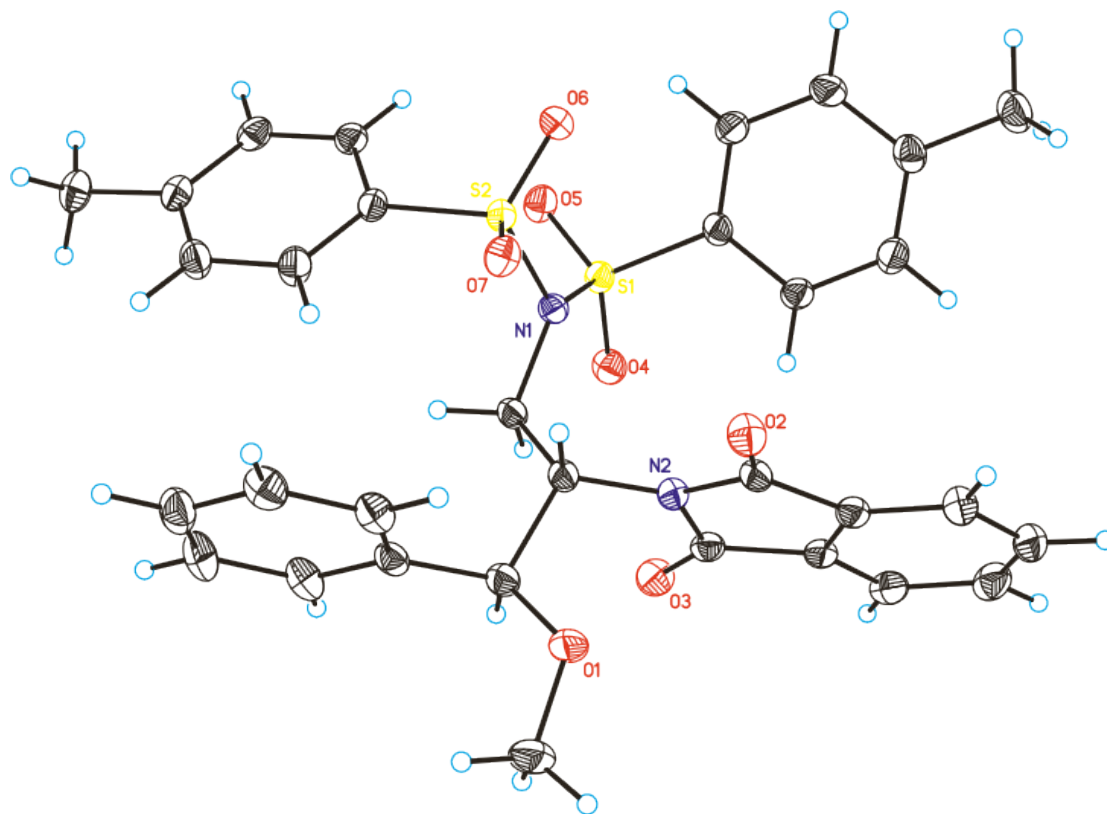
m.p.: 208-210°C.

¹H NMR (500 MHz, CDCl₃): δ = 7.93–7.86 (m, 1H), 7.85–7.78 (m, 1H), 7.76–7.68 (m, 2H), 7.62 (d, *J* = 8.3 Hz, 4H), 7.53–7.41 (m, 5H), 7.17 (d, *J* = 8.1 Hz, 4H), 5.02 (pseudo td, *J* = 10.4, 1.9 Hz, 1H), 4.71 (d, *J* = 10.4 Hz, 1H), 4.53 (dd, *J* = 16.0, 10.6 Hz, 1H), 3.40 (dd, *J* = 16.0, 1.9 Hz, 1H), 3.03 (s, 3H), 2.38 (s, 6H).

¹³C NMR (125 MHz, CDCl₃): δ = 169.2, 168.1, 144.8, 137.9, 135.6, 133.8, 133.7, 132.4, 131.9, 129.5, 128.9, 128.8, 128.5, 128.5, 123.5, 122.9, 80.3, 56.6, 56.3, 45.4, 21.7.

IR ν(cm⁻¹): 2853, 1723, 1593, 1375, 1162, 1024, 783, 718, 548.

HRMS: calcd for C₃₂H₃₀N₂O₇S₂Na: 641.1392, found: 641.1409.

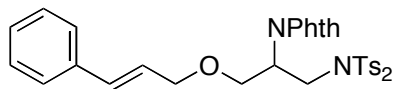
Details concerning the X-ray structure of 2-2b
Table 1. Crystal data and structure refinement for **2-2h**.

Identification code	CCDC 885869	
Empirical formula	C ₃₂ H ₃₀ N ₂ O ₇ S ₂	
Formula weight	618.70	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 14.8817(12) Å	a = 90.00 °.
	b = 10.2424(8) Å	b = 96.174(2) °.
	c = 19.3931(15) Å	g = 90.00 °.
Volume	2938.8(4) Å ³	

Experimental Section

Z	4
Density (calculated)	1.398 Mg/m ³
Absorption coefficient	0.234 mm ⁻¹
F(000)	1296
Crystal size	0.20 x 0.15 x 0.10 mm ³
Theta range for data collection	2.11 to 30.07 °.
Index ranges	-20 ≤ h ≤ 20 , -14 ≤ k ≤ 13 , -25 ≤ l ≤ 25
Reflections collected	33006
Independent reflections	7536 [R(int) = 0.0251]
Completeness to theta = 30.07 °	0.873 %
Absorption correction	Empirical
Max. and min. transmission	0.9770 and 0.9547
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	7536 / 0 / 391
Goodness-of-fit on F ²	1.031
Final R indices [I > 2σ(I)]	R1 = 0.0379 , wR2 = 0.0998
R indices (all data)	R1 = 0.0422 , wR2 = 0.1033
Largest diff. peak and hole	0.447 and -0.393 e.Å ⁻³

(E)-N-(3-(Cinnamyloxy)-2-(1,3-dioxoisindolin-2-yl)propyl)-4-methyl-N-tosylbenzenesulfonamide



2-2i

Obtained as a white solid in 57% yield.

m.p.: 100-102°C.

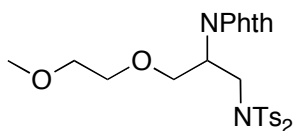
¹H NMR (500 MHz, CDCl₃): δ = 7.94 (d, J = 8.4 Hz, 4H), 7.83 (dd, J = 5.5, 3.0 Hz, 2H), 7.70 (dd, J = 5.5, 3.0 Hz, 2H), 7.40–7.26 (m, 9H), 6.57 (d, J = 15.9 Hz, 1H), 6.20 (dt, J = 15.9, 6.0 Hz, 1H), 5.09–4.88 (m, 1H), 4.32 (dd, J = 15.8, 9.1 Hz, 1H), 4.19–4.13 (m, 2H), 4.05 (dd, J = 15.9, 2.9 Hz, 1H), 3.94–3.80 (m, 2H), 2.43 (s, 6H).

¹³C NMR (125 MHz, CDCl₃): δ = 168.5, 145.1, 136.6, 135.9, 133.8, 132.7, 132.0, 129.7, 128.8, 128.5, 127.7, 126.5, 125.4, 123.3, 71.4, 67.1, 50.7, 45.6, 21.7.

IR ν (cm⁻¹): 2923, 1774, 1710, 1369, 1188, 1121, 719, 660, 548.

HRMS: calcd for C₃₄H₃₂N₂O₇S₂Na: 667.1549, found: 667.1554.

***N*-(2-(1,3-Dioxoisindolin-2-yl)-3-(2-methoxyethoxy)propyl)-4-methyl-*N*-tosylbenzenesulfonamide**



2-2j

Obtained as a white solid in 42% yield.

m.p.: 69-72°C.

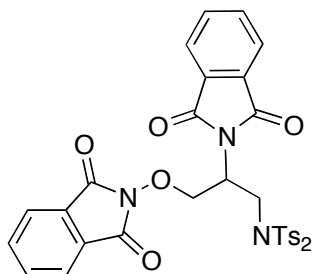
¹H NMR (400 MHz, CDCl₃): δ = 7.92 (d, J = 8.4 Hz, 4H), 7.82 (dd, J = 5.5, 3.1 Hz, 2H), 7.70 (dd, J = 5.5, 3.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 4H), 5.05–4.87 (m, 1H), 4.30 (dd, J = 15.9, 9.1 Hz, 1H), 4.01 (dd, J = 15.9, 2.8 Hz, 1H), 3.88 (d, J = 7.7 Hz, 2H), 3.70–3.54 (m, 2H), 3.52–3.41 (m, 2H), 3.28 (s, 3H), 2.43 (s, 6H).

¹³C NMR (125 MHz, CDCl₃): δ = 168.4, 145.1, 135.9, 133.8, 132.0, 129.6, 128.7, 123.2, 71.8, 70.2, 68.3, 58.9, 50.4, 45.5, 21.7.

IR ν (cm⁻¹): 2922, 2876, 1774, 1708, 1596, 1367, 1189, 1083, 864, 811, 718, 660, 545.

HRMS: calcd for C₂₈H₃₀N₂O₈S₂Na: 609.1341, found: 609.1347.

***N*-[2-(1,3-Dioxoisindolin-2-yl)-3-((1,3-dioxoisindolin-2-yl)oxy)propyl]-4-methyl-*N*-tosylbenzenesulfonamide**



2-2k

Obtained as a white solid in 52% yield.

m.p.: 156-158°C.

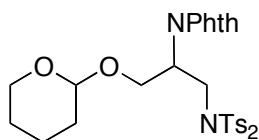
¹H NMR (500 MHz, CDCl₃): δ = 7.95 (d, J = 8.4 Hz, 4H), 7.88 (dd, J = 5.5, 3.0 Hz, 2H), 7.80 (dd, J = 5.6, 3.0 Hz, 2H), 7.76–7.71 (m, 4H), 7.35 (d, J = 8.2 Hz, 4H), 5.14 (tdd, J = 8.4, 6.7, 3.6 Hz, 1H), 4.67-4.66 (m, 2H), 4.31 (dd, J = 15.8, 8.7 Hz, 1H), 4.21 (dd, J = 15.9, 3.7 Hz, 1H), 2.45 (s, 6H).

¹³C NMR (125 MHz, CDCl₃): δ = 163.1, 145.4, 135.9, 134.7, 134.6, 134.1, 132.2, 129.9, 129.8, 128.9, 128.4, 123.8, 123.7, 123.5, 75.5, 49.4, 45.8, 21.9.

IR ν (cm⁻¹): 2926, 1777, 1732, 1369, 1164, 1082, 1018, 876, 813, 700, 661, 548.

HRMS: calcd for C₃₃H₂₇N₃O₉S₂Na: 696.1086, found: 696.1111.

***N*-(2-(1,3-Dioxoisindolin-2-yl)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)propyl)-4-methyl-*N*-tosylbenzenesulfonamide**



2-21

Obtained as a yellow solid in 50% yield.

m.p.: 65-67°C.

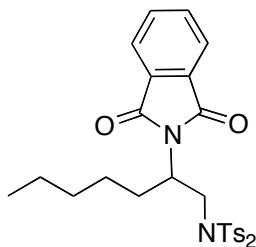
¹H NMR (500 MHz, CDCl₃): δ = 7.91 (dd, J = 8.4, 4.9 Hz, 4H), 7.83-7.80 (m, 2H), 7.687 (dd, J = 5.4, 3.0 Hz, 2H), 7.31 (dd, J = 8.4, 1.9 Hz, 4H), 4.94-4.87 (m, 1H), 4.61-4.59 (m, 1H), 4.31 (ddd, J = 15.8, 9.3, 3.1 Hz, 1H), 4.12-3.98 (m, 2H), 3.84-3.73 (m, 2H), 3.64 (ddd, J = 11.5, 9.0, 2.9 Hz, 1H), 3.51-3.38 (m, 1H), 2.45-2.43 (m, 1H), 2.42 (s, 6H), 1.67-1.61 (m, 2H), 1.52-1.47 (m, 2H).

¹³C NMR (125 MHz, CDCl₃): δ = 168.6, 145.2, 136.1, 133.9, 132.2, 129.8, 128.9, 123.3, 98.4, 64.4, 62.1, 51.1, 45.8, 30.4, 25.4, 21.8, 19.2.

IR ν (cm⁻¹): 2943, 2871, 1774, 1709, 1596, 1369, 1031, 812, 786, 661, 547.

HRMS: calcd for C₃₀H₃₂N₂O₈S₂Na: 635.1498, found: 635.1520.

***N*-(2-(1,3-Dioxoisindolin-2-yl)heptyl)-4-methyl-*N*-tosylbenzenesulfonamide**



2-2m

Obtained as a white solid in 34% yield.

m.p. = 108-112°C.

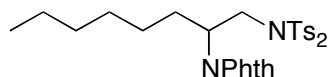
¹H NMR (400 MHz, CDCl₃): δ = 7.91 (d, J = 8.0 Hz, 4H), 7.81 (dd, J = 5.2, 2.8 Hz, 2H), 7.68 (dd, J = 5.2, 2.8 Hz, 2H), 7.32 (d, J = 8.0 Hz, 4H), 4.72-4.61 (m, 1H), 4.26 (dd, J = 15.6, 9.2 Hz, 1H), 3.87 (dd, J = 15.6, 2.4 Hz, 1H), 2.43 (s, 6H), 2.07-1.96 (m, 1H), 1.75-1.64 (m, 1H), 1.31-1.20 (m, 6H), 0.83 (t, J = 6.6 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 168.7, 145.0, 135.9, 133.8, 132.0, 129.6, 128.8, 123.2, 51.7, 48.2, 31.2, 30.0, 25.8, 22.4, 21.7, 13.9.

IR ν (cm⁻¹): 2926, 2858, 2360, 1772, 1708, 1596, 1466, 1367, 1308, 1237, 1187, 1164, 1084, 1017, 909, 813, 787, 718, 662.

HRMS: calcd for C₂₉H₃₂N₂O₆S₂Na: 591.1599, found: 591.1604.

***N*-(2-(1,3-Dioxoisindolin-2-yl)octyl)-4-methyl-*N*-tosylbenzenesulfonamide**



2-2n

Obtained as a white solid in 30% yield

m.p.: 58-59°C.

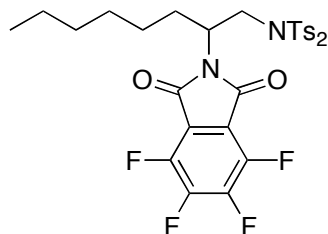
¹H NMR (400 MHz, CDCl₃): δ = 7.92 (d, J = 8.2 Hz, 4H), 7.81 (dd, J = 5.5, 3.0 Hz, 2H), 7.68 (dd, J = 5.5, 3.1 Hz, 2H), 7.33 (d, J = 8.0 Hz, 4H), 4.66 (tdd, J = 10.0, 5.5, 2.6 Hz, 1H), 4.26 (dd, J = 15.8, 9.4 Hz, 1H), 3.87 (dd, J = 15.8, 2.3 Hz, 1H), 2.43 (s, 6H), 2.05-1.97 (m, 1H), 1.74-1.67 (m, 1H), 1.28-1.18 (m, 8H), 0.83 (t, J = 7.0 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 168.8, 145.2, 136.0, 133.9, 129.7, 128.9, 123.3, 100.1, 51.8, 48.3, 31.7, 30.2, 28.9, 26.3, 22.6, 21.8, 14.1.

IR ν (cm⁻¹): 2956, 2927, 2858, 1773, 1708.

HRMS: calcd for C₃₀H₃₄N₂NaO₆S₂: 605.1756, found: 605.1786.

4-Methyl-*N*-(2-(4,5,6,7-tetrafluoro-1,3-dioxisoindolin-2-yl)octyl)-*N*-tosylbenzenesulfonamide



2-2n'

Obtained as a white solid in 53% yield

m.p.: 65-66°C.

¹H NMR (400 MHz, CDCl₃): δ = 7.89 (d, *J* = 8.4 Hz, 4H), 7.37 (d, *J* = 8.0 Hz, 4H), 4.60 (tdd, *J* = 10.0, 5.7, 2.3 Hz, 1H), 4.10 (dd, *J* = 16.1, 10.0 Hz, 1H), 3.83 (dd, *J* = 16.0, 2.2 Hz, 1H), 2.46 (s, 1H), 2.02-1.93 (m, 1H), 1.74-1.67 (m, 1H), 1.29-1.21 (m, 8H), 0.85 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 163.1, 146 (*J*_{C-F} = 15.5 Hz), 145.5, 144.7 (*J*_{C-F} = 13.2 Hz), 143.6 (*J*_{C-F} = 15.2 Hz), 142.1 (*J*_{C-F} = 12.3 Hz), 135.5, 129.8, 129.1, 113.9, 52.8, 47.4, 31.6, 29.8, 28.8, 26.2, 22.6, 22.6, 21.8, 14.1.

¹⁹F NMR (376 MHz, CDCl₃): δ = -136.0, -136.9, -143.2.

IR ν(cm⁻¹): 2956, 2929, 2860, 1720.

HRMS: calcd for C₃₀H₃₀F₄N₂NaO₆S₂: 677.1379, found: 677.1409.

Details concerning the X-ray structure of 2-2n'

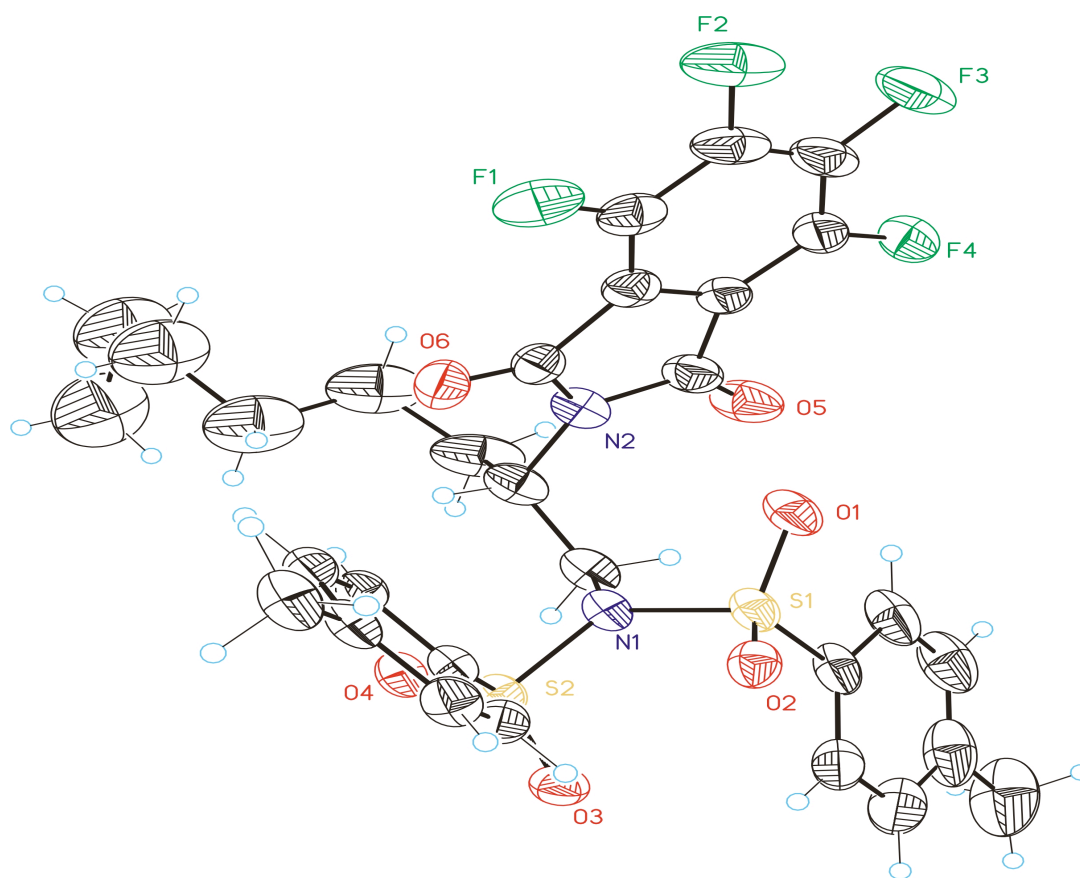
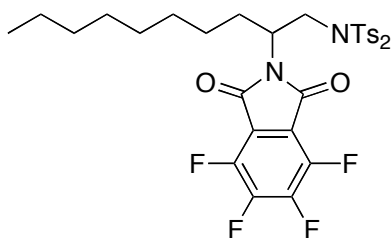


Table 1. Crystal data and structure refinement for 2-2n'.

Identification code	CCDC 885870	
Empirical formula	C ₃₀ H ₃₀ F ₄ N ₂ O ₆ S ₂	
Formula weight	654.68	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 10.4389(7) Å	$\alpha = 90.00^\circ$.
	b = 16.6742(11) Å	$\beta = 98.870(3)^\circ$.

	$c = 17.6450(11) \text{ \AA}$	$\gamma = 90.00^\circ$
Volume	3034.6(3) \AA^3	
Z	4	
Density (calculated)	1.433 Mg/m^3	
Absorption coefficient	0.246 mm^{-1}	
F(000)	1360	
Crystal size	0.25 x 0.10 x 0.03 mm^3	
Theta range for data collection	1.69 to 26.43 $^\circ$.	
Index ranges	$-13 \leq h \leq 13$, $-20 \leq k \leq 20$, $-22 \leq l \leq 22$	
Reflections collected	55068	
Independent reflections	6227 [R(int) = 0.0524]	
Completeness to theta =26.43 $^\circ$	0.997 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9927 and 0.9410	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6227 / 156 / 419	
Goodness-of-fit on F^2	1.020	
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0572 , wR2 = 0.1558	
R indices (all data)	R1 = 0.0821 , wR2 = 0.1843	
Largest diff. peak and hole	1.089 and -0.540 e.\AA^{-3}	

4-Methyl-*N*-(2-(4,5,6,7-tetrafluoro-1,3-dioxoisindolin-2-yl)decyl)-*N*-tosylbenzenesulfonamide



2-2o

Obtained as a yellow wax in 50% yield

¹H NMR (400 MHz, CDCl₃): δ = 7.93-7.88 (m, 4H), 7.37-7.33 (m, 4H), 4.60 (tdd, J = 9.9, 5.7, 2.1 Hz, 1H), 4.09 (dd, J = 16.0, 9.9 Hz, 1H), 3.82 (dd, J = 16.0, 2.2 Hz, 1H), 2.47 (s, 3H), 2.45 (s, 3H), 1.27-1.22 (m, 14H), 0.86 (t, J = 6.9 Hz, 3H).

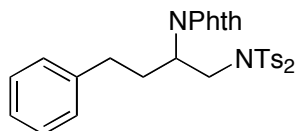
¹³C NMR (125 MHz, CDCl₃): δ = 117.9, 145.5, 145.0, 137.0, 135.5, 129.8, 129.7, 129.0, 128.6, 52.8, 47.4, 32.0, 29.8, 29.5, 29.1, 27.2, 26.3, 22.8, 21.8, 14.2.

¹⁹F NMR (376 MHz, CDCl₃): δ = -143.2.

IR ν (cm⁻¹): 2955, 2926, 2856, 1721.

HRMS: calcd for C₃₂H₃₄F₄N₂NaO₆S₂: 705.1692, found: 705.1718.

***N*-(2-(1,3-Dioxoisindolin-2-yl)-4-phenylbutyl)-4-methyl-*N*-tosylbenzenesulfonamide**



2-2q

Obtained as a white solid in 32% yield

m.p.: 75-78°C.

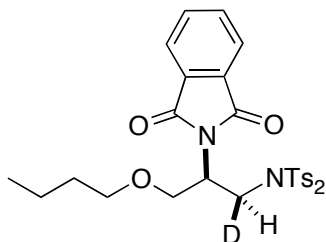
¹H NMR (400 MHz, CDCl₃): δ = 7.91 (d, J = 8.1 Hz, 4H), 7.78 (dd, J = 5.4, 3.0 Hz, 2H), 7.66 (dd, J = 5.5, 3.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 4H), 7.18 (t, J = 7.5 Hz, 2H), 7.11 (d, J = 7.6 Hz, 2H), 7.07 (t, J = 7.4 Hz, 1H), 4.79-4.73 (m, 1H), 4.29 (dd, J = 15.8, 9.4 Hz, 1H), 3.92 (dd, J = 15.8, 2.5 Hz, 1H), 2.67 (ddd, J = 15.0, 9.3, 6.0 Hz, 1H), 2.57 (ddd, J = 14.3, 9.2, 6.6 Hz, 1H), 2.48-2.39 (m, 1H), 2.43 (s, 6H), 2.06 (ddt, J = 14.4, 10.4, 5.6 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃): δ = 168.7, 145.2, 140.5, 135.9, 133.8, 132.0, 129.7, 128.9, 128.3, 126.0, 123.2, 51.8, 48.3, 32.8, 31.4, 21.8.

IR ν (cm⁻¹): 3063, 3029, 2924, 2858, 1707.

HRMS: calcd for C₃₂H₃₀N₂NaO₆S₂: 625.1443, found: 625.1469.

***N*-(3-Butoxy-2-(1,3-dioxoisindolin-2-yl)propyl)-4-methyl-*N*-tosylbenzene sulfonamide**



2-2c-d₁

Obtained as a white solid in 69 % yield.

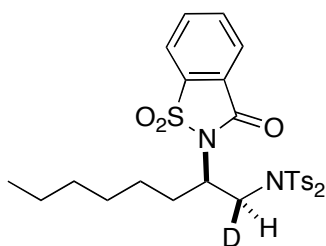
¹H NMR (500 MHz, CDCl₃): δ = 7.91 (d, J = 8.4 Hz, 4H), 7.82 (dd, J = 5.4, 3.0 Hz, 2H), 7.69 (dd, J = 5.4, 3.0 Hz, 2H), 7.32 (d, J = 8.6 Hz, 4H), 4.90 (ddd, J = 8.3, 7.1, 2.8 Hz, 1H), 3.98 (d, J = 2.8 Hz, 1H), 3.81-3.73 (m, 2H), 3.45-3.35 (m, 2H), 1.48-1.41 (m, 2H), 1.29-1.21 (m, 2H), 0.81 (t, J = 7.4 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 168.6, 145.2, 136.1, 133.9, 132.2, 129.8, 128.9, 123.4, 70.9, 67.9, 50.7, 31.7, 21.8, 19.3, 13.9.

IR ν (cm⁻¹): 3065, 3033, 2902, 2872, 1769, 1706, 1451, 1164, 1025, 717.

HRMS: calcd for C₂₉H₃₁DN₂O₇S₂Na: 608.1611, found: 608.1611.

***N*-(2-(1,3-Dioxoisindolin-2-yl)octyl)-4-methyl-*N*-tosylbenzenesulfonamide**



2-2n-d₁

Obtained as a white solid in 32% yield.

¹H NMR (500 MHz, CDCl₃): δ = 8.03 (d, J = 6.9 Hz, 1H), 7.92 (d, J = 8.1 Hz, 4H), 7.88-7.79 (m, 3H), 7.33 (d, J = 8.1 Hz, 4H), 4.43-4.38 (m, 1H), 4.03 (d, J = 4.2 Hz, 1H), 3.15 (q, J = 7.3 Hz, 1H), 2.15-2.07 (m, 2H), 1.80-1.73 (m, 2H), 1.26-1.19 (m, 6H), 0.80 (t, J = 7.1 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 159.5, 145.3, 137.5, 136.0, 134.6, 134.3, 130.0, 129.7, 129.1, 128.3, 127.6, 125.1, 120.9, 54.6, 31.7, 29.7, 28.9, 26.4, 22.7, 21.8, 14.2.

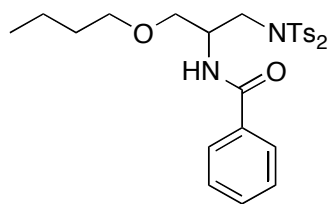
IR ν (cm⁻¹): 3069, 2955, 2928, 2858, 1728, 1614, 1377, 1337, 1166, 1060, 663, 551.

HRMS: calcd for C₂₉H₃₃DN₂O₇S₃Na: 642.1489, found: 642.1509.

Protocol for phthalimide deprotection.

The diamination product **2-2c** (0.21 g, 0.36 mmol) was dissolved in toluene (5 mL) and MeNH₂NH₂ (0.095 mL, 1.80 mmol) was added dropwise. The mixture was stirred 1h at 25 °C and then was heated at 95 °C for 12h. After cooling down to 25 °C and the solvent was removed under reduced pressure. This crude product was then dissolved in CH₂Cl₂ (4 mL) at 0°C, triethylamine (0.078 mL, 0.56 mmol) was added and then benzoyl chloride (0.43 mL, 3.7 mmol) was added drop to drop to the stirred solution. After overnight stirring at 25 °C, the solution was concentrated under reduced pressure. Then water and CH₂Cl₂ was added, organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3x). The combined organic layer was washed with NH₄Cl solution and brine, dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (silicagel, *n*-hexane/EtOAc, 3/1, v/v) to obtain **2-3c** (170 mg, 70 %) as a white solid.

***N*-(1-butoxy-3-(4-methyl-*N*-tosylphenylsulfonamido)propan-2-yl)benzamide**



2-3c

Obtained as a white solid in 70% yield.

m.p. = 158-160 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.93 (d, J = 8.3 Hz, 4H), 7.73 (dd, J = 7.1, 1.8 Hz, 2H), 7.50-7.46 (m, 1H), 7.42-7.38 (m, 2H), 7.28 (d, J = 8.1 Hz, 4H), 7.05 (d, J = 7.8 Hz, 1H), 4.64 (ddq, J = 11.7, 7.9, 4.2 Hz, 1H), 4.05 (dd, J = 15.5, 4.6 Hz, 1H), 3.94 (dd, J = 15.5, 11.1 Hz, 1H), 3.63-3.57 (m, 2H), 3.48-3.41 (m, 2H), 2.38 (s, 6H), 1.58-1.51 (m, 2H), 1.42-1.33 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 167.2, 145.3, 136.3, 134.1, 131.5, 129.9, 128.5, 128.4, 127.1, 71.4, 70.1, 48.6, 48.5, 31.9, 21.7, 19.4, 14.0.

IR ν (cm⁻¹): 3379, 2958, 2929, 2872, 2859, 1641.

HRMS: calcd for C₂₈H₃₄N₂O₆S₂Na: 558.1858 found: (ENVIADO)

Chapter III: The First General 1,4-Diamination of Dienes

3.1. General

All solvents, reagents and all deuterated solvents were purchased from Aldrich. Column chromatography was performed with silica gel (Merck, type 60, 0.063-0.2 mm). NMR spectra were recorded on a Bruker Avance 300 and Avance 400 MHz spectrometer, respectively. All chemical shifts in NMR experiments are reported as ppm downfield from TMS. The following calibrations were used: CDCl₃ δ = 7.26 and 77.0 ppm, acetone-d₆ δ = 2.09 and 30.6 ppm, respectively. MS (ESI-LCMS) experiments were performed using an Agilent 1100 HPLC with a Bruker micro-TOF-instrument (ESI). Unless otherwise stated, a Supelco C8 (5cm x 4.6mm, 5 μ m particles) column was used with a linear elution gradient from 100%

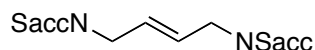
H₂O (0.5% HCO₂H) to 100% MeCN in 13 min at a flow rate of 0.5 mL/min. Melting points were determined in open capillary tubes on a Büchi Melting point B-545 instrument. MS(EI) and HRMS experiments were performed on a Kratos MS 50 within the service centers at ICIQ.

3.2. General procedure for the intermolecular 1,4-diamination of dienes

In a flame dried Schlenk tube flushed with nitrogen, 268 mg (1.2 mmol, 3.0 equiv) of CuBr₂, 170 mg (0.8 mmol, 2.0 equiv) of K₃PO₄ and 147 mg (0.8 mmol, 2.0 equiv) of saccharin were dissolved in 2.0 mL of DMF, then 1.0 equiv of diene was added. After stirring for 12 hours at 50°C the reaction mixture was cooled to room temperature and 10 mL of water were added. The aqueous-layer was extracted with 5 x 7 mL of dichloromethane, and the combined organic layers dried on Na₂SO₄, and evaporated under reduced pressure. The crude product was purified by chromatography on neutralized (with a 3% Et₃N solution in *n*-hexane) silica gel column to give the pure 1-4 diamination product.

3.3. Characterization of diamination products

(*E*)-2,2'-(but-2-ene-1,4-diyl)bis(benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide)



3-4c

Obtained as a white solid in 41% yield.

m.p. = 246-248°C.

¹H NMR (300 MHz, acetone-*d*₆): δ = 8.21-7.99 (m, 8H), 6.08-6.02 (m, 2H), 4.41 (dd, *J* = 3.0, 1.2 Hz, 4H).

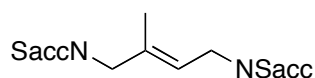
¹³C NMR (126 MHz, acetone-*d*₆): δ = 158.3, 137.9, 135.5, 134.8, 127.7, 127.0, 125.0, 121.1, 39.3.

IR ν(cm⁻¹): 3093, 2872, 1715, 1592, 1433, 1332, 1264, 1186, 1131, 898, 735, 583, 390.

Nominal Mass: 441.0

HRMS: calcd for C₁₈H₁₄N₂O₆S₂Na: 441.0191, found: 441.0188.

(*E*)-2,2'-(2-methylbut-2-ene-1,4-diyl)bis(benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide)



3-4b

Obtained as a white solid in 87% yield.

m.p. = 159-163°C.

¹H NMR (400 MHz, CDCl₃): δ = 7.98-7.81 (m, 8H), 5.85 (t, *J* = 7.2 Hz, 1H), 4.47 (d, *J* = 7.2 Hz, 2H), 4.37 (s, 2H), 1.97 (s, 3H).

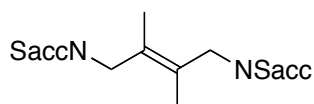
¹³C NMR (101 MHz, CDCl₃): δ = 158.9, 158.5, 137.8, 137.8, 135.1, 134.8, 134.7, 134.3, 134.2, 127.4, 127.2, 125.3, 125.2, 121.9, 121.0, 120.9, 45.8, 36.4, 14.4.

IR ν(cm⁻¹): 3120, 2901, 1717, 1592, 1463, 1430, 1331, 1301, 1253, 1181, 1162, 753, 674, 580, 507.

Nominal Mass: 455.0.

HRMS: calcd for C₁₉H₁₆N₂O₆S₂Na: 455.0347, found: 455.0346.

(*E*)-2,2'-(2,3-dimethylbut-2-ene-1,4-diyl)bis(benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide)



3-4d

Obtained as a white solid in 60% yield.

m.p. = 199-202°C.

¹H NMR (500 MHz, CDCl₃): δ = 8.12-8.07 (m, 2H), 7.98-7.83 (m, 6H), 4.53 (s, 4H), 2.03 (s, 6H).

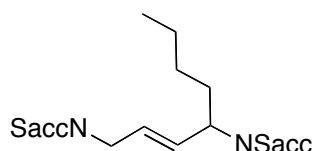
¹³C NMR (101 MHz, CDCl₃): δ = 159.2, 137.8, 134.7, 134.3, 128.3, 127.3, 125.2, 120.9, 41.9, 16.2.

IR $\nu(\text{cm}^{-1})$: 1722, 1591, 1458, 1426, 1328, 1311, 1257, 1181, 982, 960, 753, 672, 581, 530, 509, 425.

Nominal Mass: 469.1.

HRMS: calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_6\text{S}_2\text{Na}$: 469.0504, found: 469.0509.

(E)-2,2'-(oct-2-ene-1,4-diyl)bis(benzo[d]isothiazol-3(2H)-one 1,1-dioxide)



3-4e

Obtained as a white solid in 71% yield.

m.p. = 227-230°C.

^1H NMR (500 MHz, CDCl_3): δ = 8.09-8.03 (m, 2H), 7.95-7.80 (m, 6H), 6.32 (dd, J = 15.4, 8.2 Hz, 1H), 6.00 (dt, J = 15.4, 6.4 Hz, 1H), 4.71 (q, J = 7.8 Hz, 1H), 4.44 (dd, J = 15.9, 5.8 Hz, 1H), 4.38 (dd, J = 15.9, 6.8 Hz, 1H), 2.29-2.14 (m, 1H), 2.09-1.97 (m, 1H), 1.44-1.33 (m, 4H), 0.90 (t, J = 6.9 Hz, 3H).

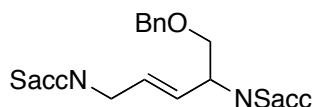
^{13}C NMR (126 MHz, CDCl_3): δ = 158.5, 158.5, 137.8, 137.7, 134.8, 134.6, 134.3, 134.2, 132.2, 127.3, 127.3, 127.1, 125.3, 125.1, 121.0, 120.7, 55.9, 40.1, 31.5, 28.5, 22.1, 13.9.

IR $\nu(\text{cm}^{-1})$: 2956, 2926, 1722, 1629, 1590, 1181, 1132, 1114, 1017, 747, 636, 585, 507.

Nominal Mass: 497.0.

HRMS: calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_6\text{S}_2\text{Na}$: 497.0817, found: 497.0795.

(E)-2,2'-(5-(benzyloxy)pent-2-ene-1,4-diyl)bis(benzo[d]isothiazol-3(2H)-one 1,1-dioxide)



3-4f

Obtained as a white solid in 75% yield.

m.p. = 181-185°C.

¹H NMR (400 MHz, acetone-d₆): δ = 8.20-7.99 (m, 8H), 7.38-7.33 (m, 2H), 7.31-7.23 (m, 3H), 6.34 (dd, J = 15.5, 7.3 Hz, 1H), 6.16 (dt, J = 15.5, 5.9 Hz, 1H), 5.09 (m, 1H), 4.66 (d, J = 11.9 Hz, 1H), 4.59 (d, J = 11.9 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H), 4.20 (dd, J = 10.2, 8.3 Hz, 1H), 3.95 (dd, J = 10.2, 6.3 Hz, 1H).

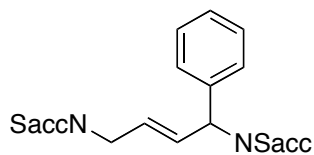
¹³C NMR (101 MHz, acetone-d₆): δ = 158.2, 158.0, 138.1, 137.6, 137.5, 135.2, 135.2, 134.6, 134.5, 128.4, 127.9, 127.8, 127.2, 127.1, 126.7, 126.6, 124.8, 124.7, 120.8, 120.7, 72.2, 68.47, 53.9, 39.2.

IR ν (cm⁻¹): 3063, 1735, 1608, 1482, 1332, 1254, 1181, 991, 921, 753, 690, 581, 530, 507.

Nominal Mass: 561.1.

HRMS: calcd for C₂₆H₂₂N₂O₇S₂Na: 561.0766, found: 561.0776.

(E)-2,2'-(1-phenylbut-2-ene-1,4-diyl)bis(benzo[d]isothiazol-3(2H)-one 1,1-dioxide)



3-4a

Obtained as a white solid in 75% yield.

m.p. = 179-181°C.

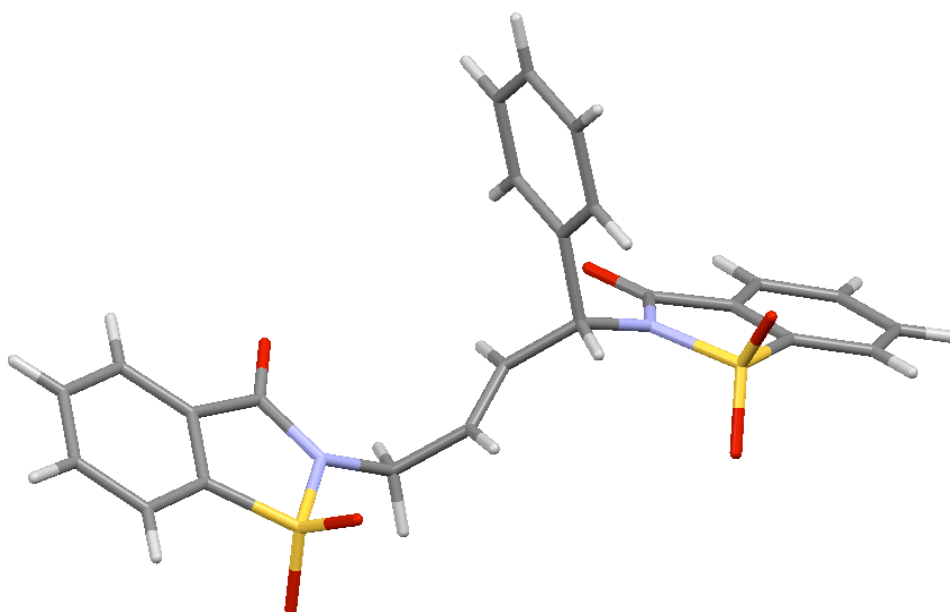
¹H NMR (400 MHz, CDCl₃): δ = 8.13-8.09 (m, 1H), 8.06-8.02 (m, 1H), 7.98-7.81 (m, 6H), 7.60-7.57 (m, 2H), 7.43-7.31 (m, 3H), 6.75 (dd, J = 15.4, 7.7 Hz, 1H), 6.10 (dt, J = 15.4, 6.2 Hz, 1H), 5.91 (d, J = 7.7 Hz, 1H), 4.55-4.51 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): δ = 158.5, 158.1, 137.8, 136.1, 134.8, 134.7, 134.3, 134.2, 129.9, 130.0, 128.6, 128.5, 128.3, 128.0, 127.3, 127.1, 125.3, 125.2, 121.0, 120.9, 57.7, 39.9.

IR ν (cm⁻¹): 3065, 3047, 1736, 1713, 1335, 1290, 1252, 1178, 745.

Nominal Mass: 517.0.

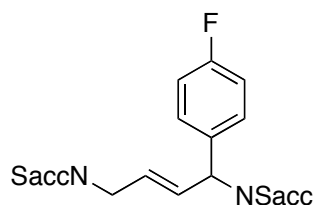
HRMS: calcd for C₂₄H₁₈N₂O₆S₂Na: 517.0530, found: 517.0529.

Details concerning the X-ray structure of 3-4a
Table 1. Crystal data and structure refinement for **3-4a**.

Identification code	mo_JK654_1_0m	
Empirical formula	C ₂₄ H ₁₈ N ₂ O ₆ S ₂	
Formula weight	494.52	
Temperature	100(2) K	
Wavelength	0.71073 \approx	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.1904(7) \approx	$\alpha = 99.279(3)^\circ$
	b = 8.4426(8) \approx	$\beta = 95.164(3)^\circ$
	c = 18.4191(18) \approx	$\gamma = 98.188(3)^\circ$
Volume	1084.93(18) \approx^3	
Z	2	
Density (calculated)	1.514 Mg/m ³	
Absorption coefficient	0.292 mm ⁻¹	
F(000)	512	
Crystal size	0.10 x 0.10 x 0.01 mm ³	
Theta range for data collection	2.26 to 29.96 $^\circ$	

Index ranges	-9 <=h<=9 , -11 <=k<=11 , -25 <=l<=25
Reflections collected	5494
Independent reflections	4160 [R(int) = 0.0319]
Completeness to theta =29.96 °	0.873 %
Absorption correction	Empirical
Max. and min. transmission	0.9971 and 0.9714
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	5494 / 0 / 307
Goodness-of-fit on F ²	1.023
Final R indices [I>2sigma(I)]	R1 = 0.0531 , wR2 = 0.1332
R indices (all data)	R1 = 0.0778 , wR2 = 0.1457
Largest diff. peak and hole	1.180 and -0.683 e. ^{≈-3}

(E)-2,2'-(1-(4-fluorophenyl)but-2-ene-1,4-diyl)bis(benzo[d]isothiazol-3(2H)-one 1,1-dioxide)



3-4g

Obtained as a white solid in 40% yield.

m.p. = 194-197°C.

¹H NMR (400 MHz, CDCl₃): δ = 8.11-8.06 (m, 1H), 8.04-7.99 (m, 1H), 7.96-7.80 (m, 6H), 7.59-7.51 (m, 2H), 7.10-7.02 (m, 2H), 6.68 (dd, *J* = 15.4, 7.5 Hz, 1H), 6.05 (dt, *J* = 15.4, 6.2 Hz, 1H), 5.86 (d, *J* = 7.5 Hz, 1H), 4.57-4.44 (m, 2H).

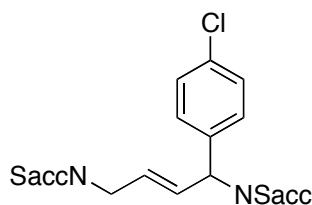
¹³C NMR (101 MHz, CDCl₃): δ = 158.5, 158.1, 137.8, 137.7, 134.8, 134.3, 134.3, 131.9, 130.1, 130.0, 129.8, 128.6, 127.3, 127.0, 125.3, 125.2, 121.0, 120.9, 115.6, 115.4, 57.0, 39.9.

IR ν (cm⁻¹): 1720, 1603, 1509, 1458, 1332, 1289, 1233, 1179, 986, 921, 750, 674, 582, 543, 526, 418.

Nominal Mass: 535.0.

HRMS: calcd for C₂₄H₁₇FN₂O₆S₂Na: 535.0410, found: 535.0408 .

(E)-2,2'-(1-(4-chlorophenyl)but-2-ene-1,4-diyl)bis(benzo[d]isothiazol-3(2H)-one 1,1-dioxide)



3-4h

Obtained as a white solid in 76% yield.

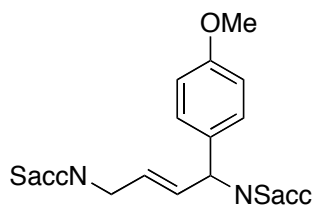
m.p. = 184-186°C.

¹H NMR (400 MHz, CDCl₃): δ = 8.10-8.06 (m, 1H), 8.04-7.98 (m, 1H), 7.98-7.78 (m, 6H), 7.54-7.46 (m, 2H), 7.38-7.30 (m, 2H), 6.67 (dd, J = 15.4, 7.7 Hz, 1H), 6.06 (dt, J = 15.4, 6.2 Hz, 1H), 5.84 (d, J = 7.7 Hz, 2H), 4.58-4.42 (m, 2H).

Nominal Mass: 551.0.

HRMS: calcd for C₂₄H₁₇ClN₂O₆S₂Na: 551.0114, found: 551.0100.

(E)-2,2'-(1-(4-methoxyphenyl)but-2-ene-1,4-diyl)bis(benzo[d]isothiazol-3(2H)-one 1,1-dioxide)



3-4i

Obtained as a white solid in 72% yield.

m.p. = 184-187°C.

¹H NMR (500 MHz, CDCl₃): δ = 8.09-8.06 (m, 1H), 8.02-7.99 (m, 1H), 7.95-7.78 (m, 6H), 7.53-7.48 (m, 2H), 6.92-6.88 (m, 2H), 6.70 (dd, J = 15.4, 7.5 Hz, 1H), 6.04 (dt, J = 15.4, 6.3 Hz, 1H), 5.87 (d, J = 7.5 Hz, 1H), 4.55-4.45 (m, 2H), 3.80 (s, 3H).

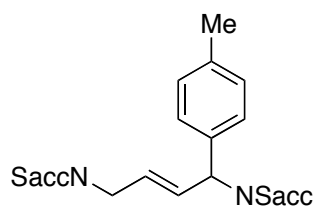
¹³C NMR (101 MHz, CDCl₃): δ = 159.5, 158.5, 158.1, 137.8, 134.8, 134.7, 134.3, 134.2, 130.3, 129.6, 128.0, 127.9, 127.8, 127.3, 127.1, 125.3, 125.1, 121.0, 120.8, 113.9, 57.4, 55.2, 40.0.

IR ν (cm⁻¹): 1730, 1649, 1605, 1574, 1511, 1461, 1333, 1289, 1246, 1178, 988, 919, 748, 674, 580, 528, 417.

Nominal Mass: 547.1.

HRMS: calcd for C₂₅H₂₀N₂O₇S₂Na: 547.0610, found: 547.0619.

(E)-2,2'-(1-(*p*-tolyl)but-2-ene-1,4-diyl)bis(benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide)



3-4j

Obtained as a white solid in 98% yield.

m.p. = 173-174°C.

¹H NMR (500 MHz, CDCl₃): δ = 8.06-8.04 (m, 1H), 7.99-7.97 (m, 1H), 7.92-7.76 (m, 6H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.69 (dd, *J* = 15.4, 7.6 Hz, 1H), 6.03 (dt, *J* = 15.4, 6.3 Hz, 1H), 5.84 (d, *J* = 7.6 Hz, 1H), 4.53-4.42 (m, 2H), 2.31 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ = 158.4, 158.1, 138.1, 137.8, 134.7, 134.6, 134.3, 134.2, 133.0, 130.2, 129.3, 129.3, 128.2, 128.0, 127.3, 127.1, 125.2, 125.1, 120.9, 120.8, 57.6, 39.9, 21.1.

IR ν(cm⁻¹): 1731, 1591, 1509, 1456, 1335, 1291, 1227, 1177, 960, 926, 750, 674, 579, 531, 508, 419.

Nominal Mass: 531.1.

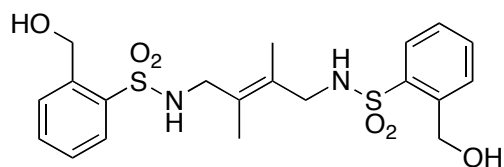
HRMS: calcd for C₂₅H₂₀N₂O₆S₂Na: 531.0660, found: 531.0650.

3.3 Synthetic transformations

3.3.1 Procedure for the saccharin ring-opening of 3-4d to 3-7d.

A flame-dried Schlenk-flask was set under inert gas atmosphere, equipped with a stirrer bar and charged with LiAlH₄ (17 mg, 0.44 mmol) and abs. Et₂O (5 mL). The suspension was stirred and, cooled to 0°C. The diamination product **3-4d** (100 mg, 0.22 mmol) was added slowly to the suspension. Upon complete addition the mixture was stirred overnight at r.t. The mixture was cooled to 0°C and the remaining LiAlH₄ was carefully quenched by addition of small amounts of water. The mixture was dried by addition of MgSO₄, filtered and concentrated under reduced pressure to yield the pure product **3-7d**.

(*E*)-*N,N'*-(2,3-dimethylbut-2-ene-1,4-diyl)bis(2-(hydroxymethyl)benzenesulfon amide)



3-7d

Obtained as a white solid in 90% yield.

m.p. = 175-177°C.

¹H NMR (400 MHz, CD₃OD): δ = 7.93 (dd, *J* = 7.9, 1.4 Hz, 2H), 7.80 (dd, *J* = 7.6, 1.2 Hz, 2H), 7.69 (td, *J* = 7.6, 1.4 Hz, 2H), 7.51 (td, *J* = 7.7, 1.4 Hz, 2H), 5.06 (s, 4H), 3.44 (s, 4H), 1.55 (s, 6H).

¹³C NMR (101 MHz, CD₃OD): δ = 140.1, 137.3, 132.5, 128.8, 128.6, 128.5, 127.0, 60.9, 45.1, 15.2.

IR ν(cm⁻¹): 3271, 2915, 2864, 1445, 1409, 1319, 1151, 1117, 1022, 874, 822, 756, 707, 552, 481.

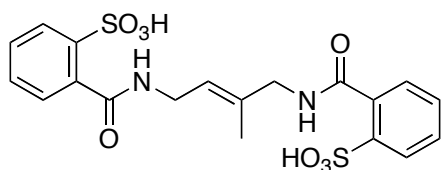
Nominal Mass: 453.1.

HRMS: calcd for $C_{20}H_{25}N_2O_6S$: 453.1160, found: 453.1170.

3.3.1 Procedure for the saccharin ring-opening of 3-4d to 3-7d.

A solution of product **3-4d** (100 mg, 0.21 mmol) in 2.0 mL of pyridine and 2 mL of H₂O with dimethylpyridine (12 mg, 0.10 mmol) was heated at 80°C for 18 h. The reaction was then cooled to rt and all volatiles were removed under reduced pressure. The residue was dissolved in 5 mL of H₂O and the solution was adjusted to an alkaline pH at 10 by addition of solution of NaOH (2M) and extracted with 3 x 5 mL of CH₂Cl₂. The pH of the aqueous solution was adjusted to 2 and then solution was concentrated under reduced pressure to afford the pure product as a white solid. (79% yield).

(E)-2,2'-(2-methylbut-2-ene-1,4-diyl)bis(azanediyl)bis(oxomethylene)dibenzenesulfonic acid



3-8b

Obtained as a white solid in 79% yield.

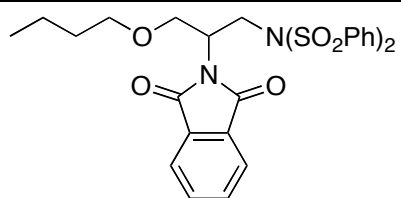
¹H NMR (400 MHz, CD₃OD): δ = 8.07-7.99 (m, 2H), 7.95-7.89 (m, 2H), 7.78-7.73 (m, 4H), 5.06 (s, 1H), 3.56 (d, *J* = 7.7, 1.4 Hz, 2H), 3.42 (s, 2H).

¹³C NMR (101 MHz, CD₃OD): δ = 136.7, 133.8, 133.6, 133.4, 132.3, 132.2, 131.7, 131.4, 130.4, 123.7, 51.4, 41.8, 14.3.

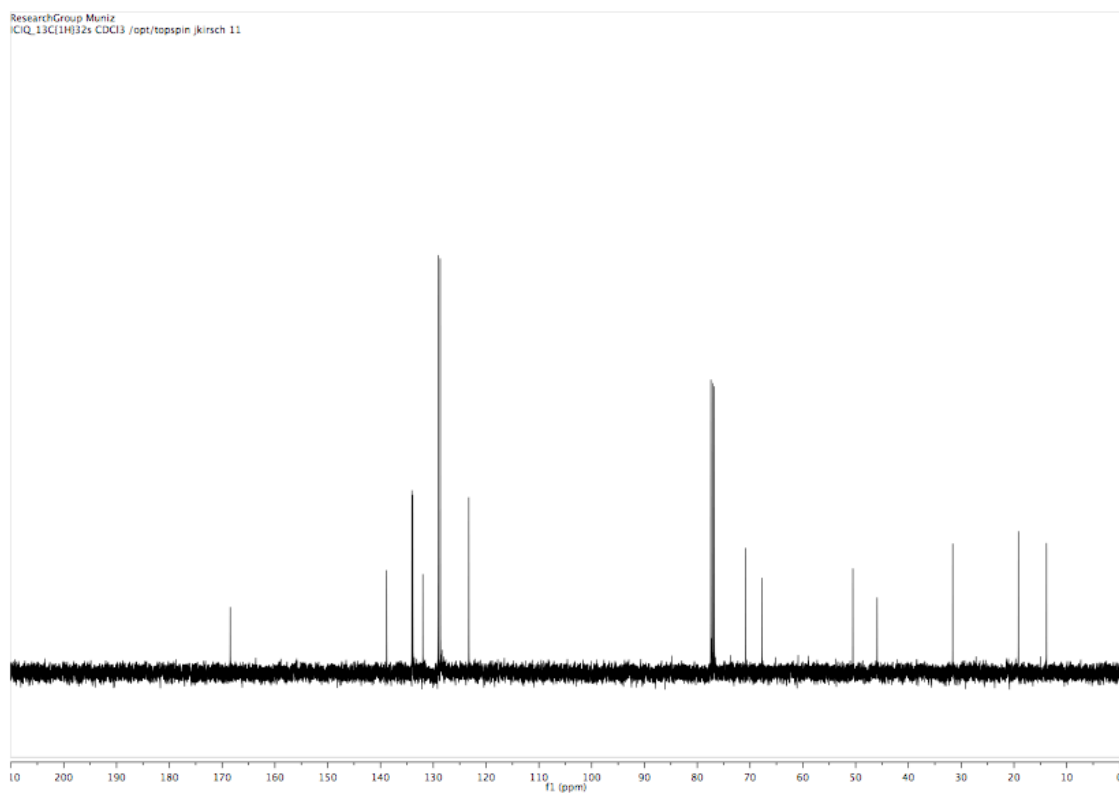
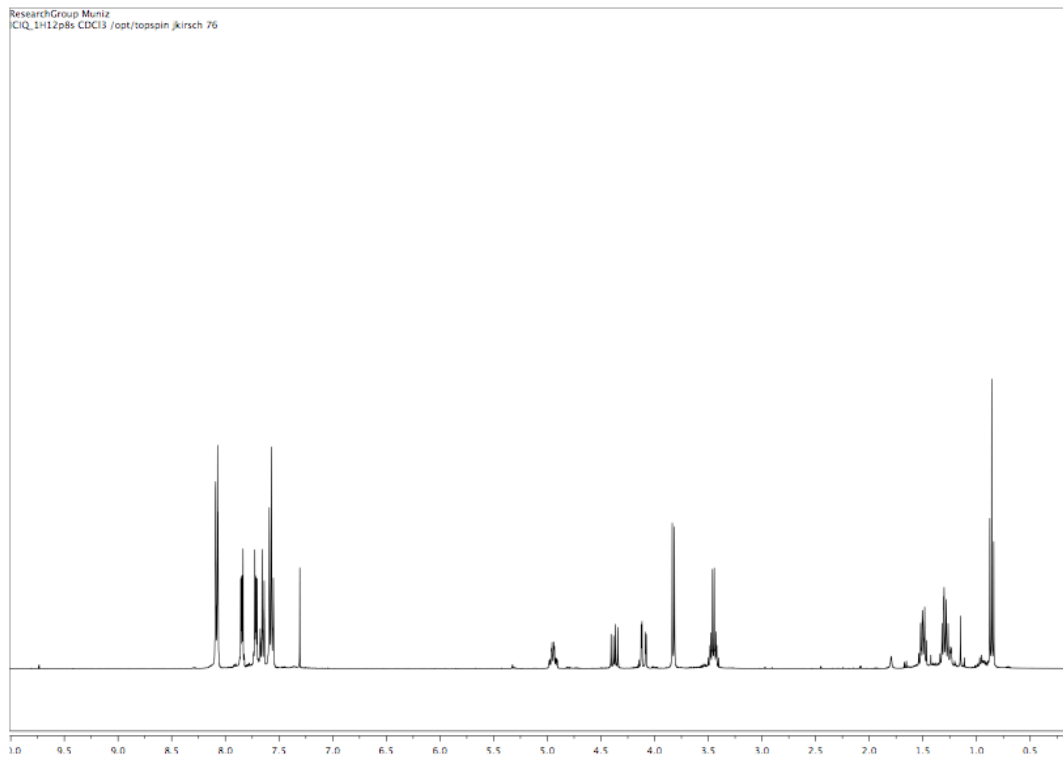
IR ν(cm⁻¹): 3271, 2915, 2864, 1445, 1409, 1319, 1151, 1117, 1022, 874, 822, 756, 707, 552, 481.

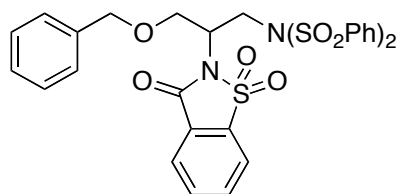
Reproduction of selected NMR spectra

Chapter I: Intermolecular Regioselective 1,2-Diamination of Allylic Ethers

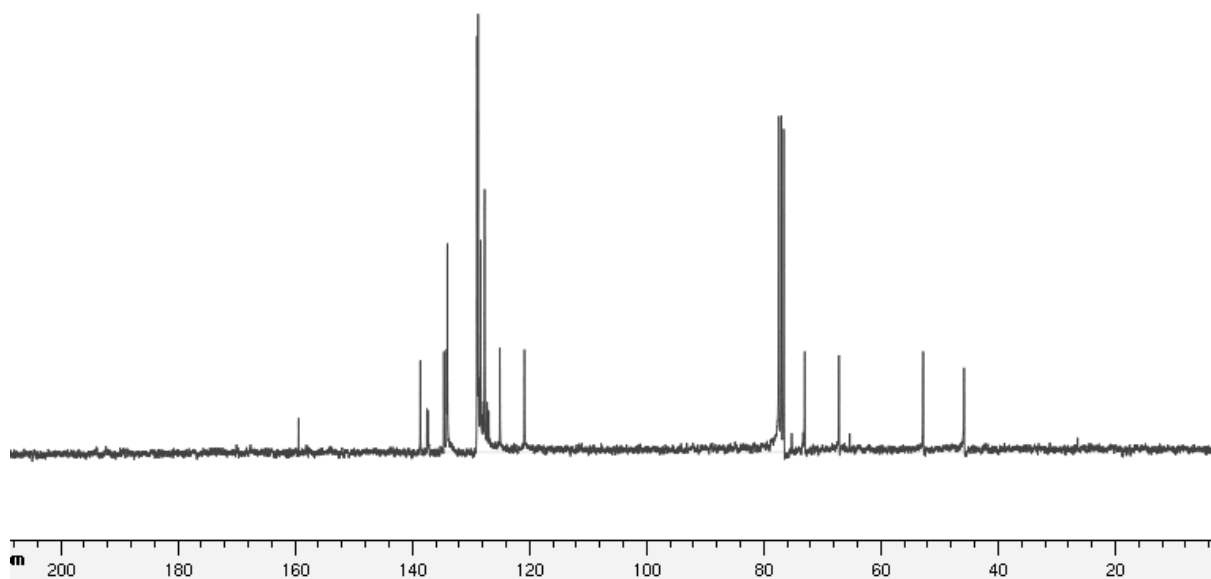
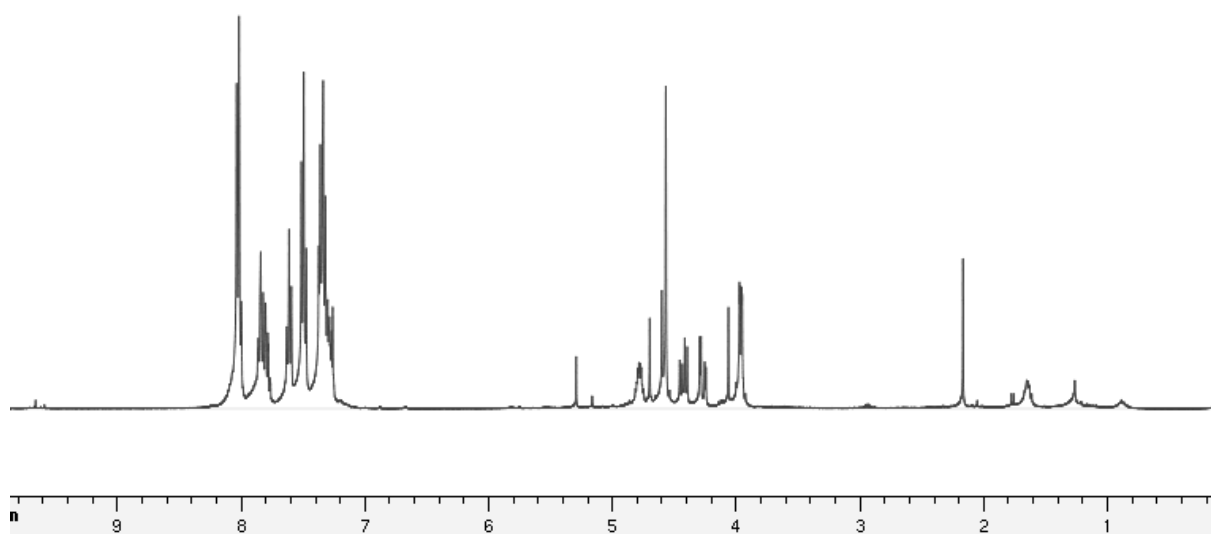


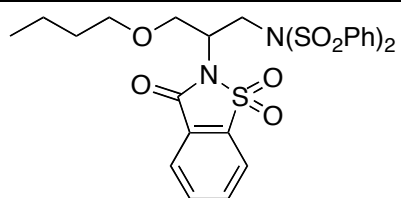
1-2a



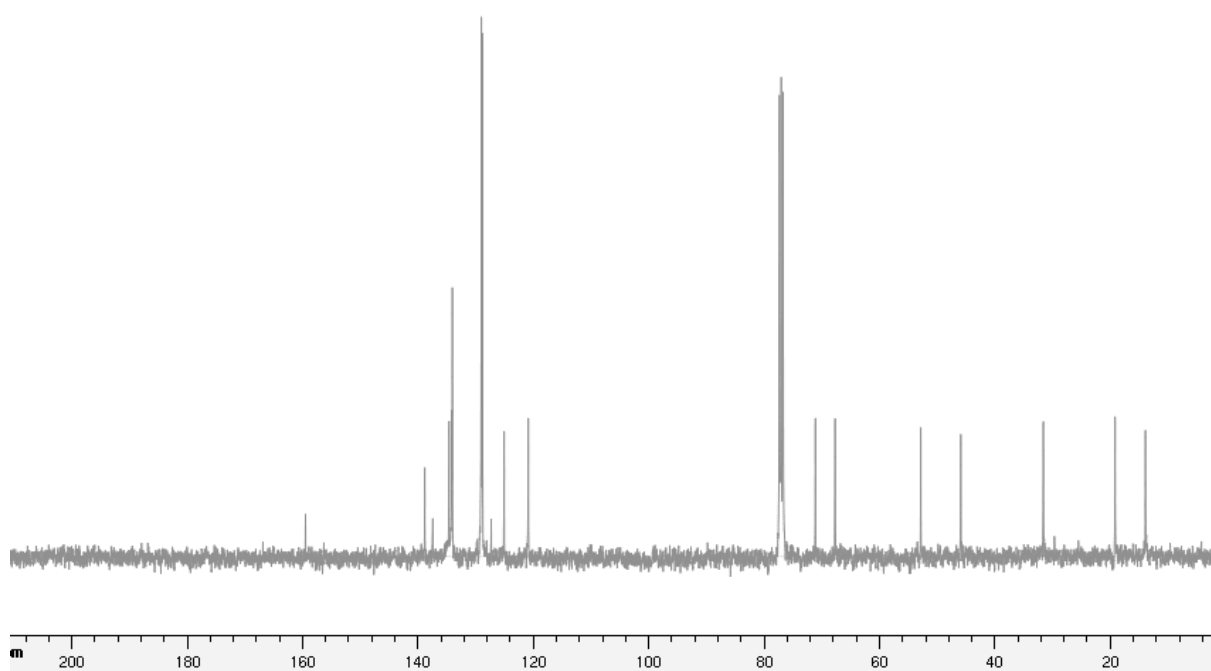
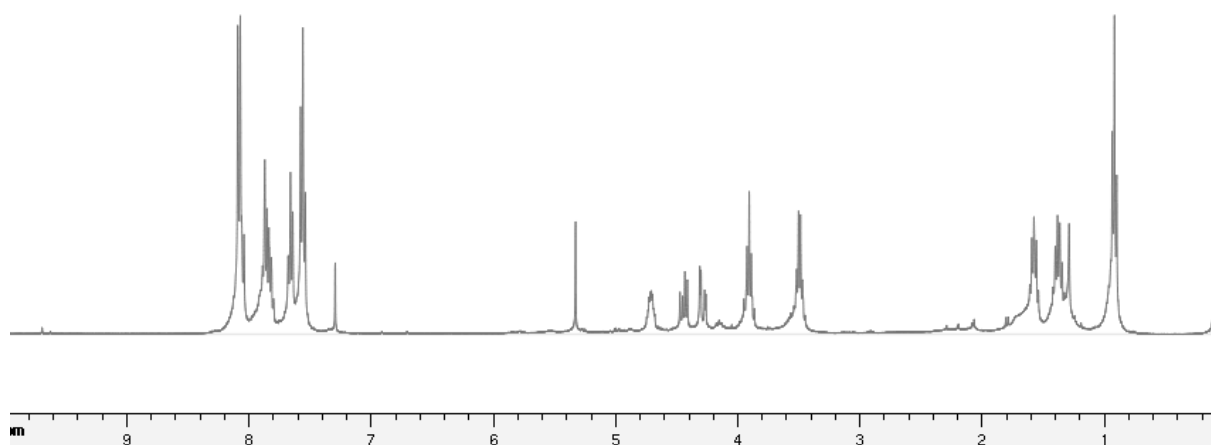


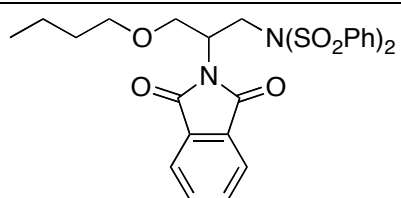
1-2b



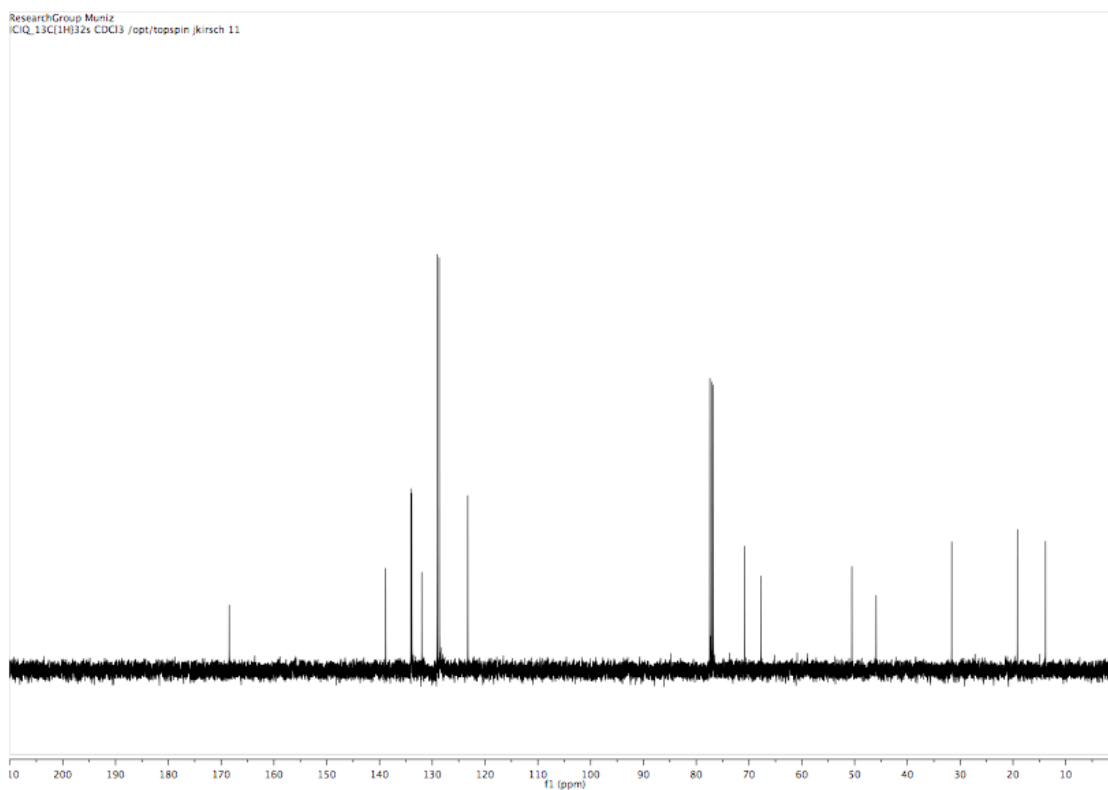
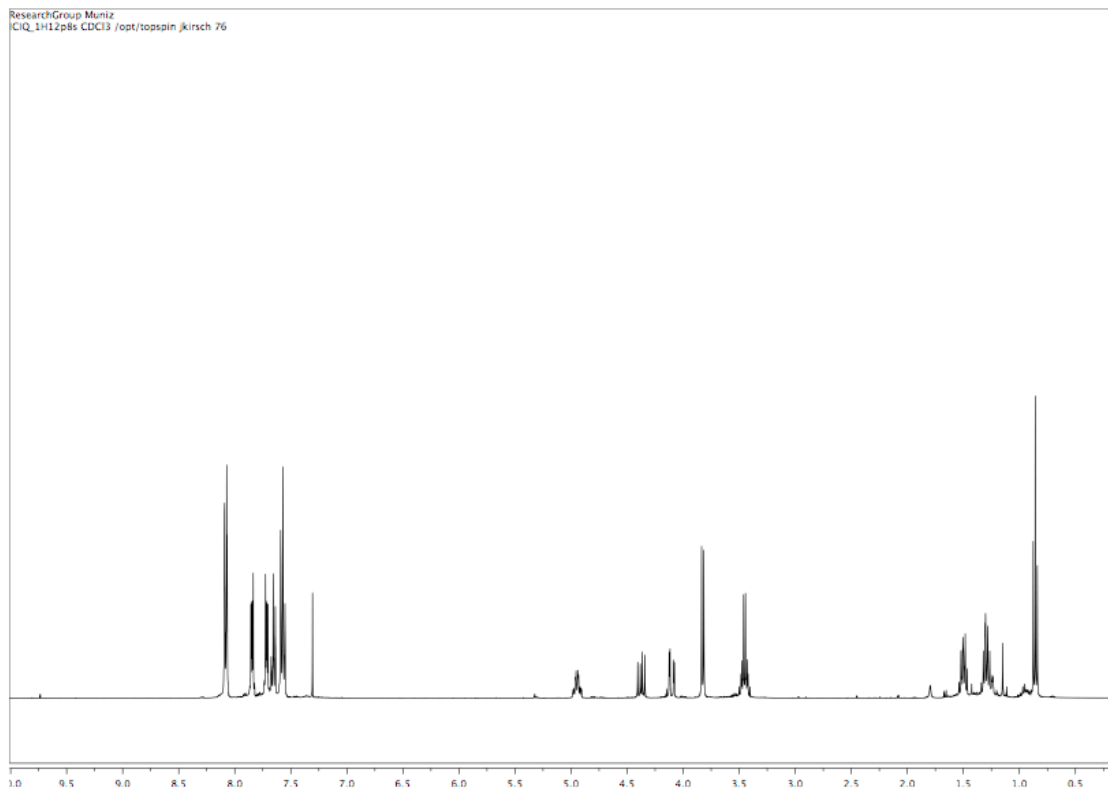


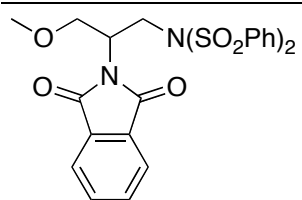
1-2c



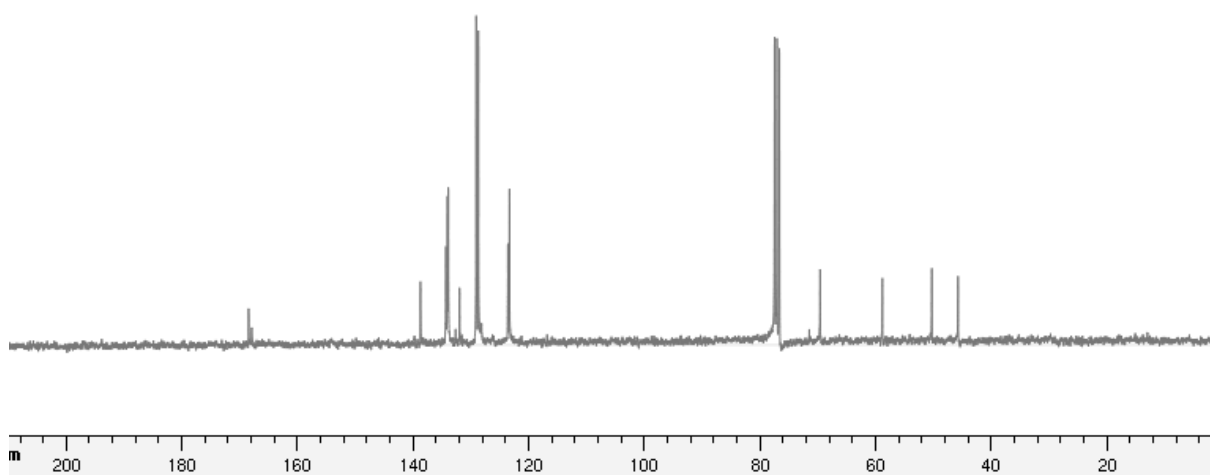
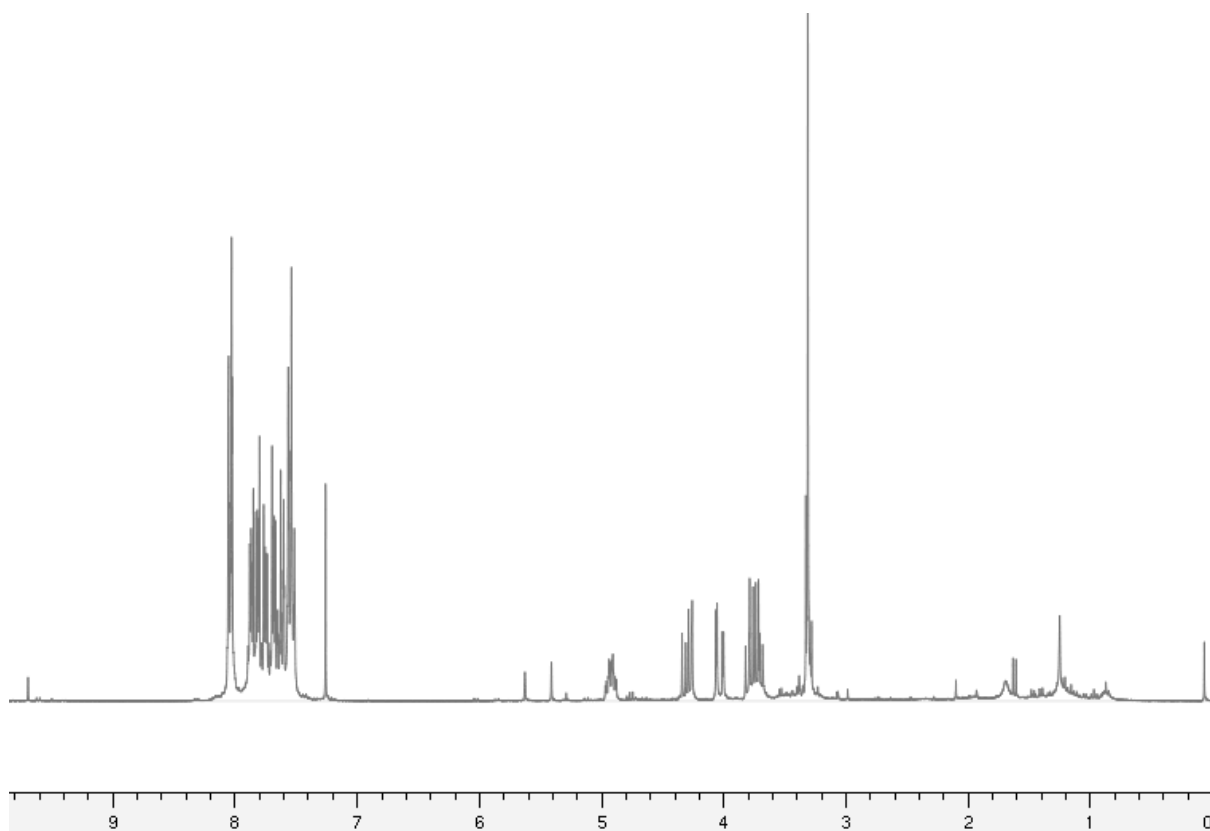


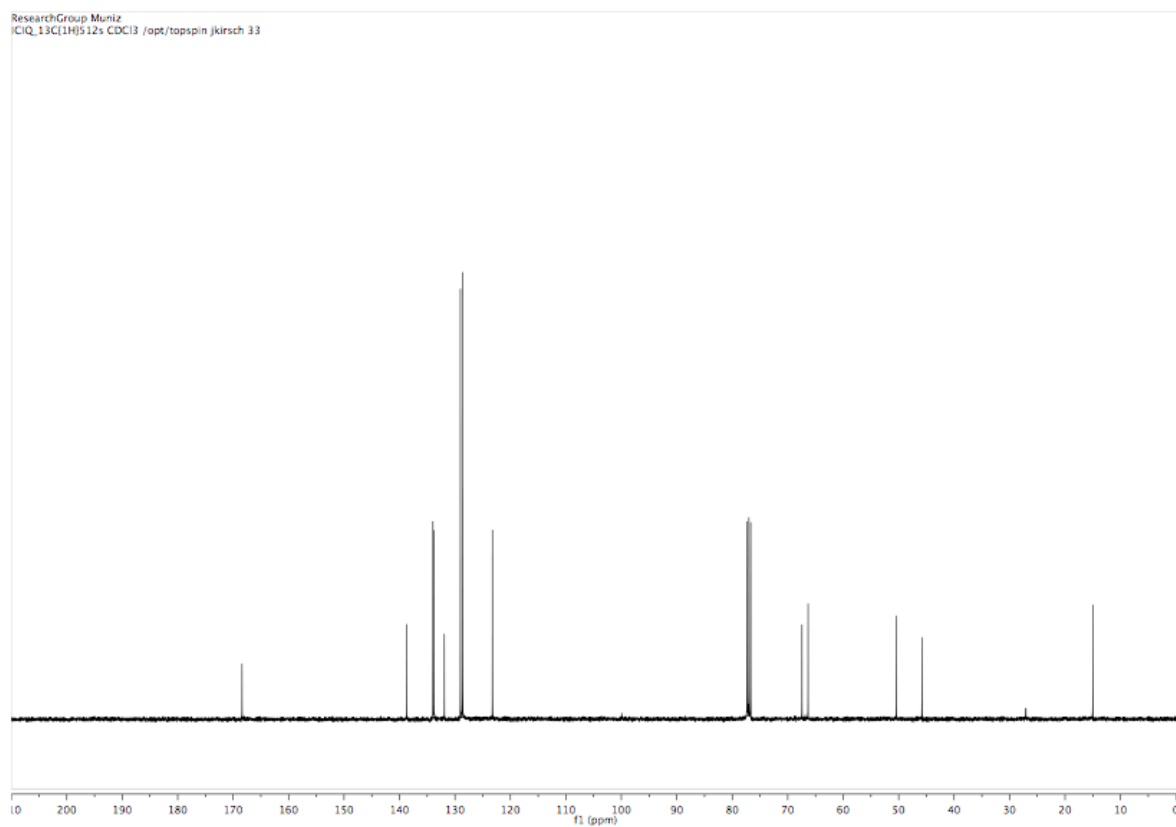
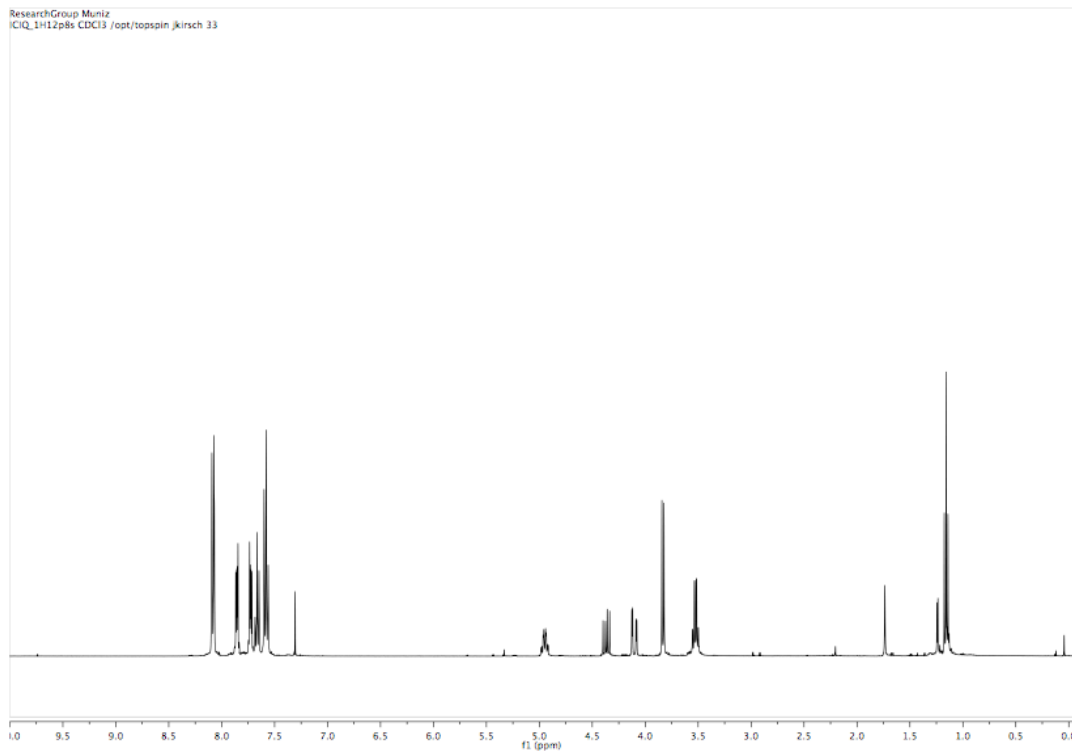
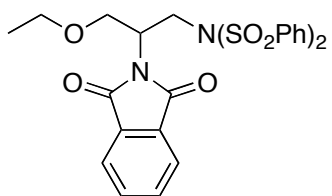
1-2d

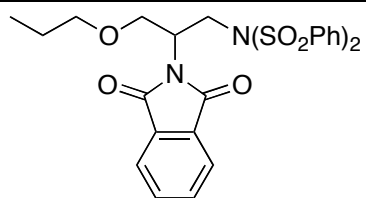




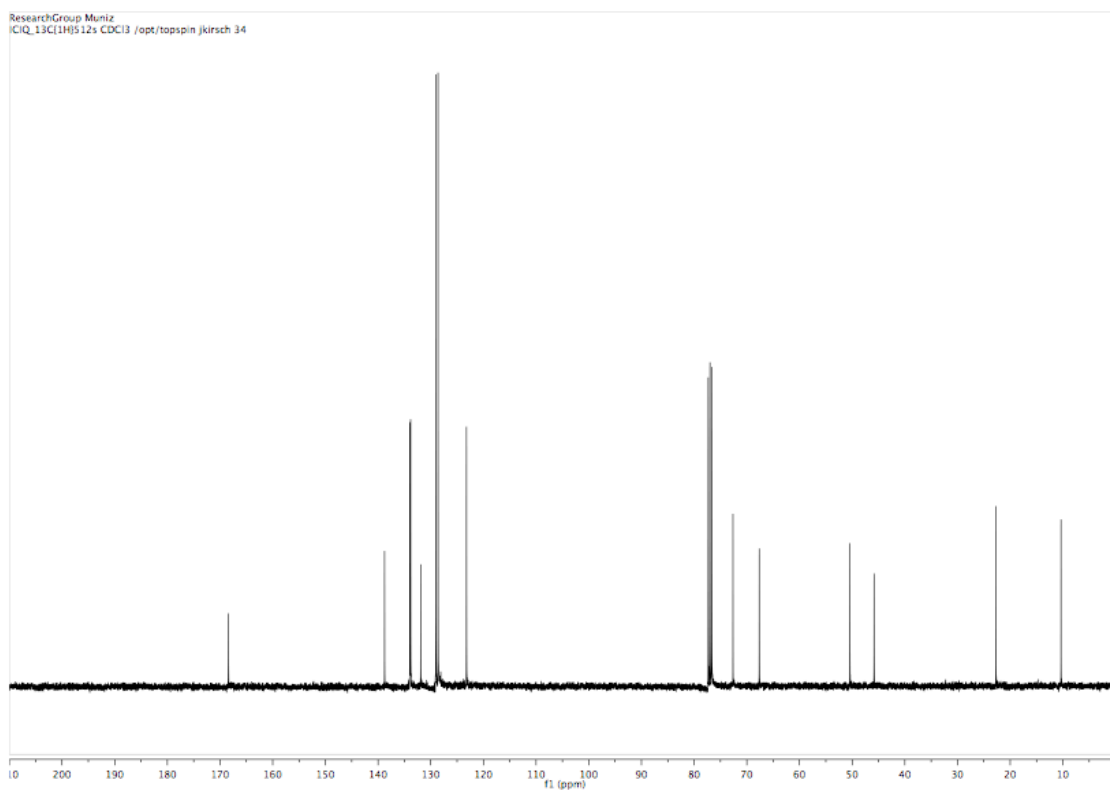
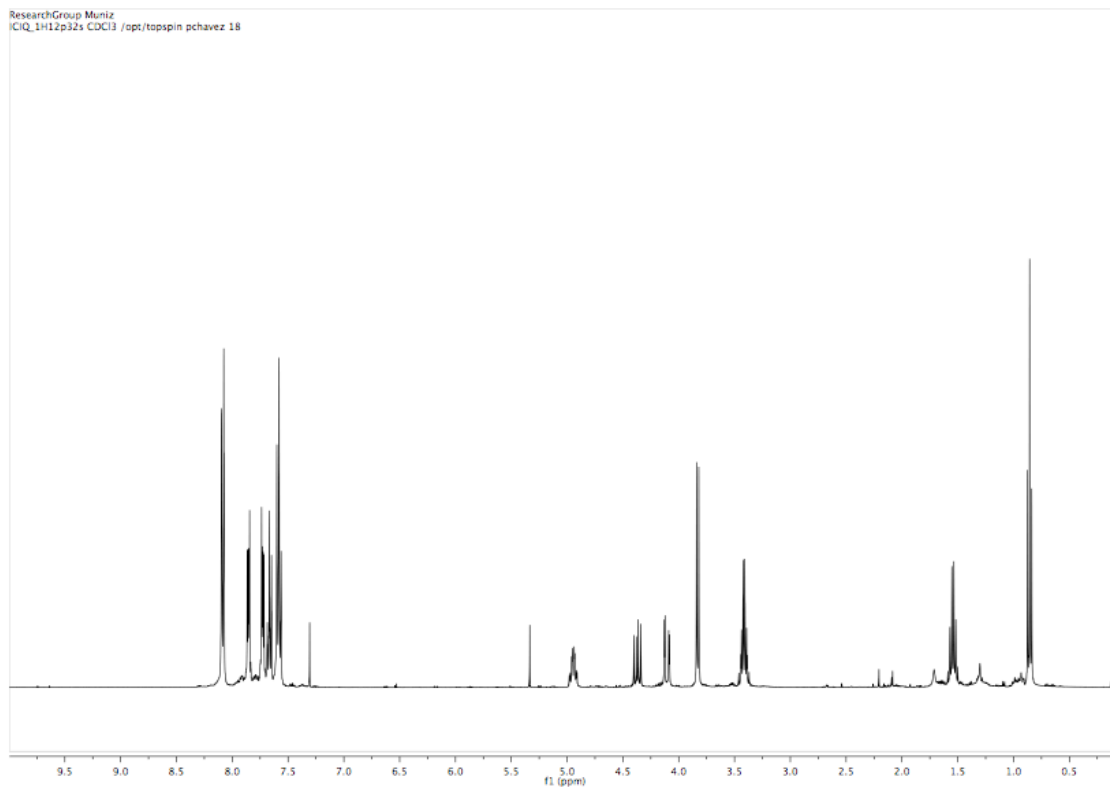
1-2e



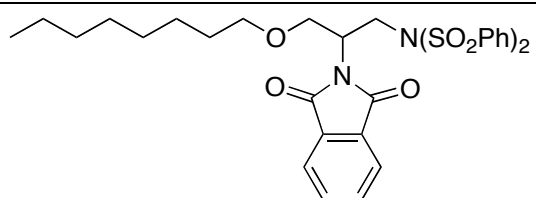




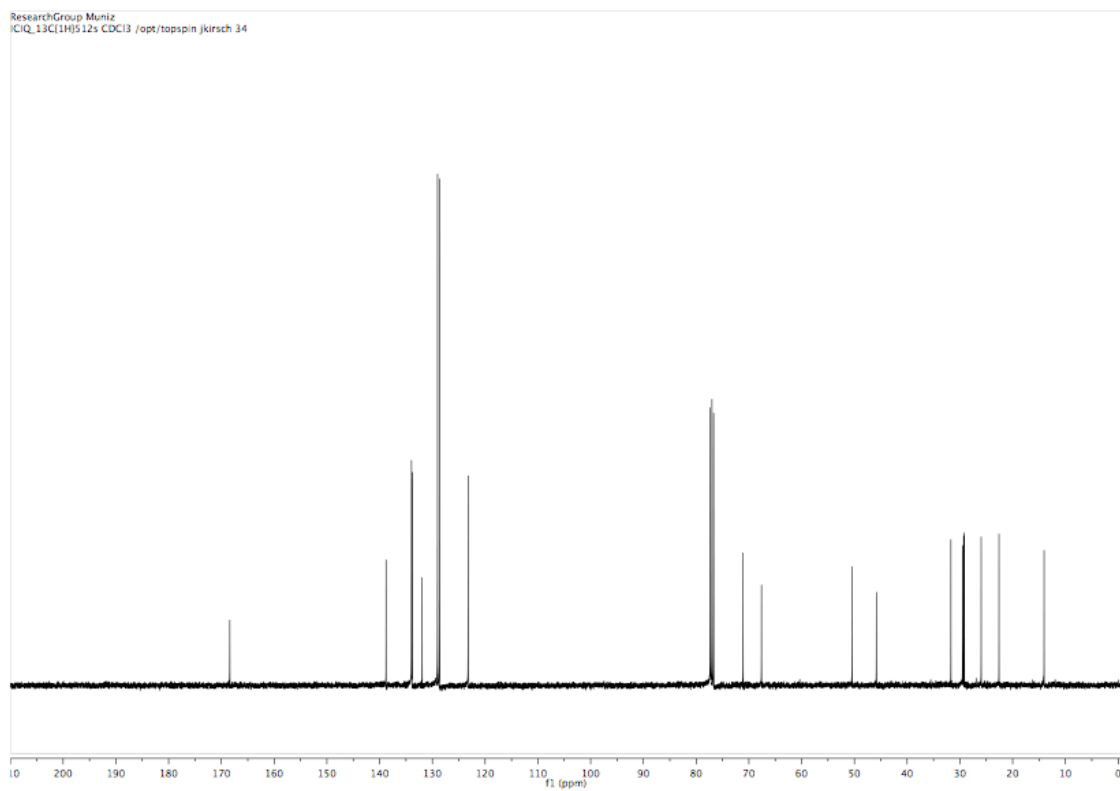
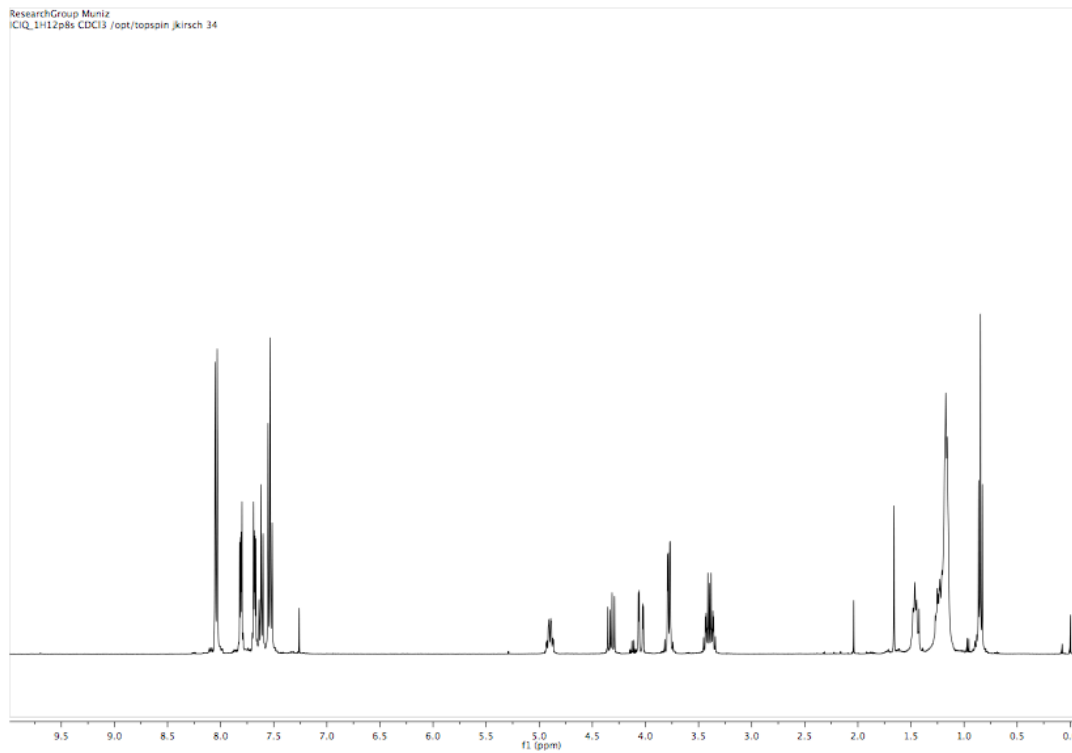
1-2g

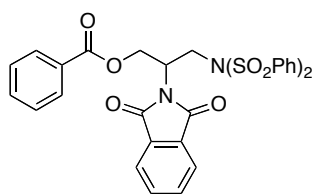


Reproduction of selected NMR spectra

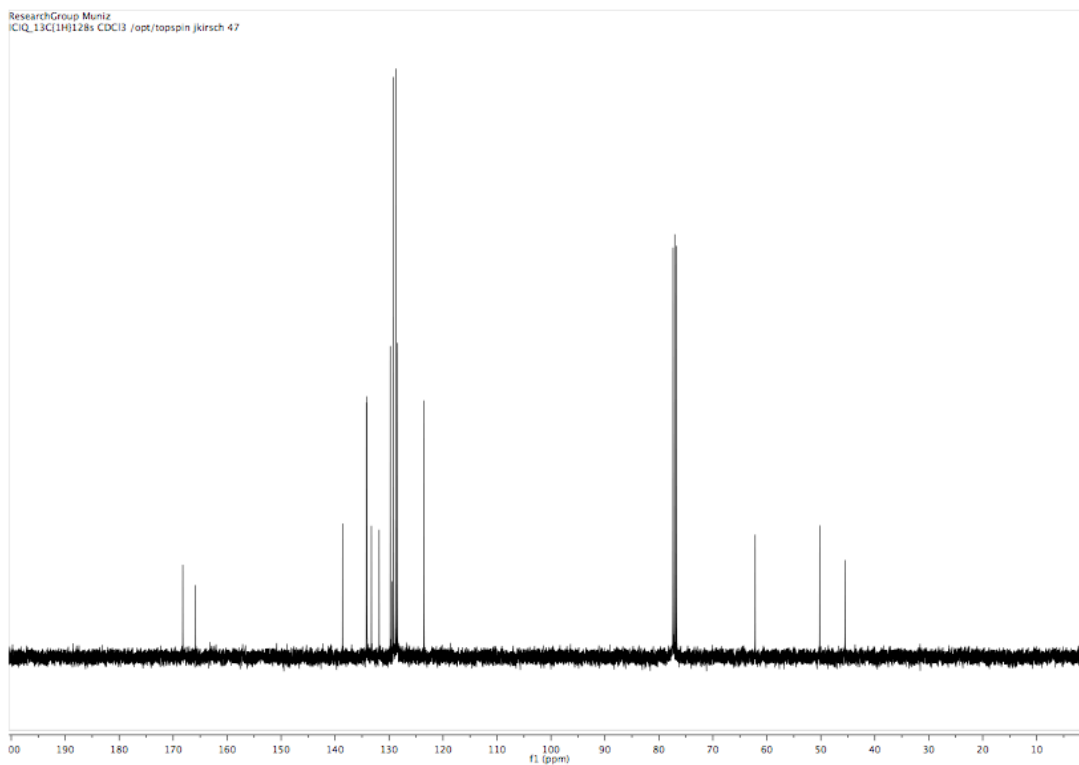
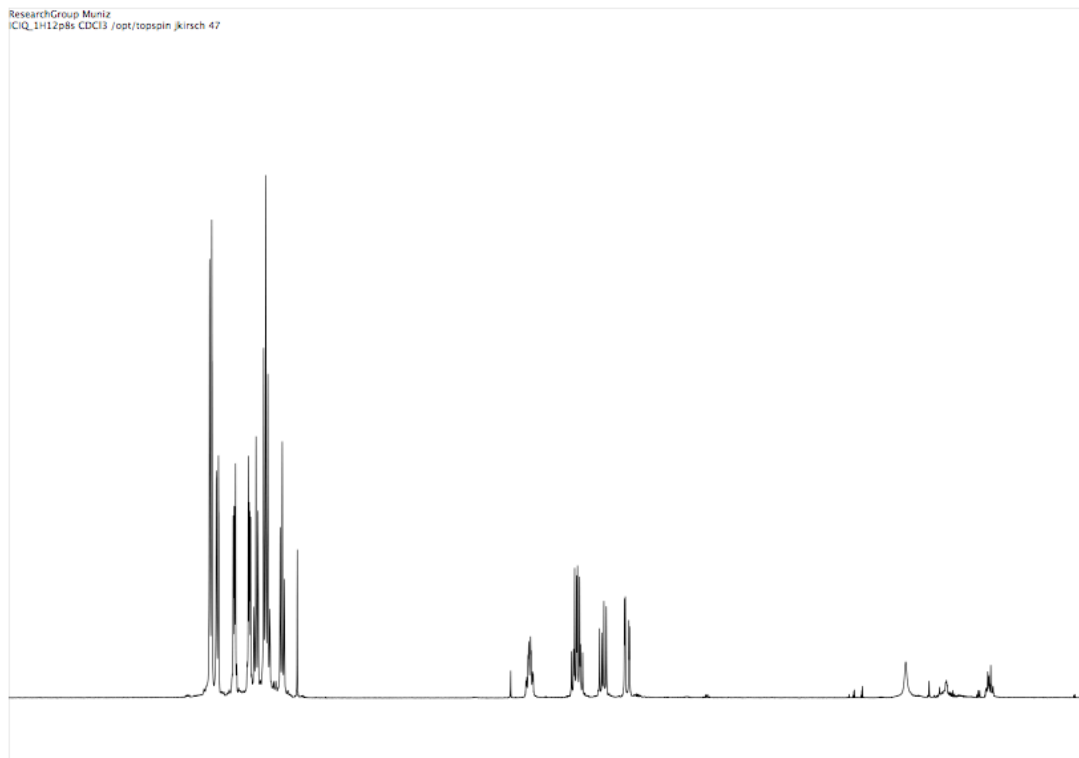


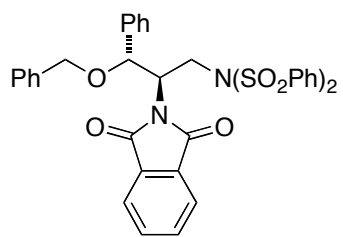
1-2h



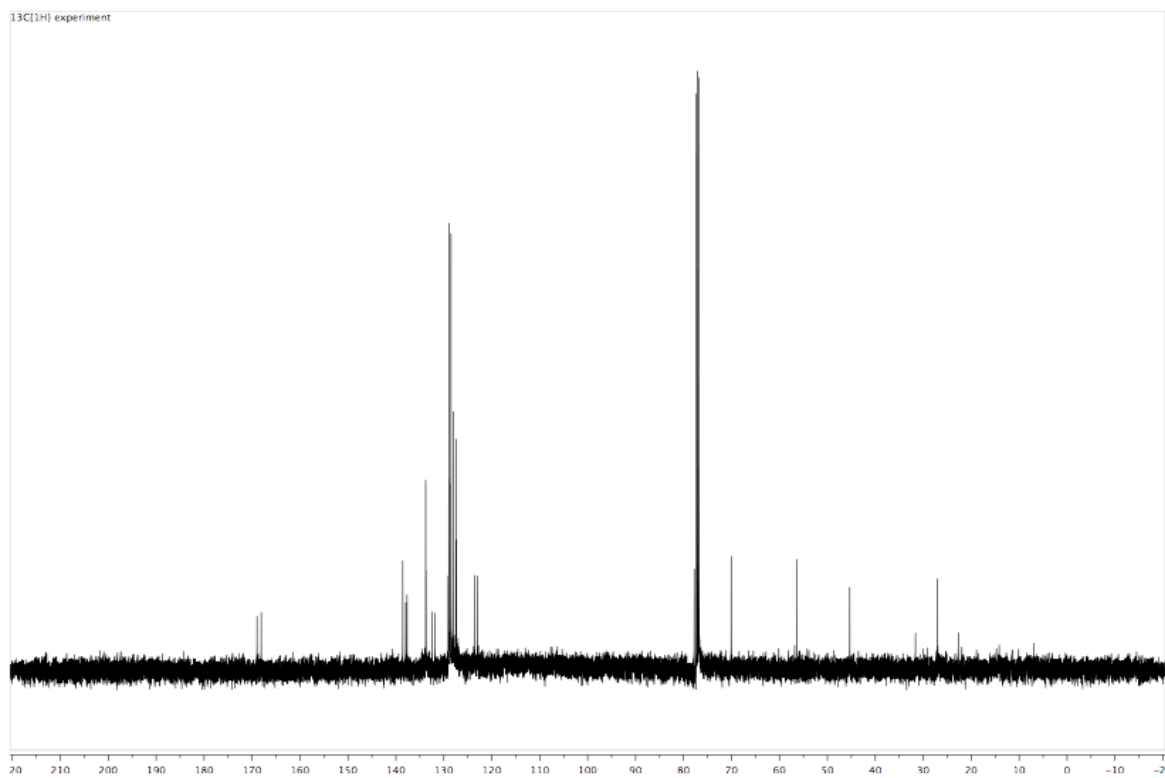
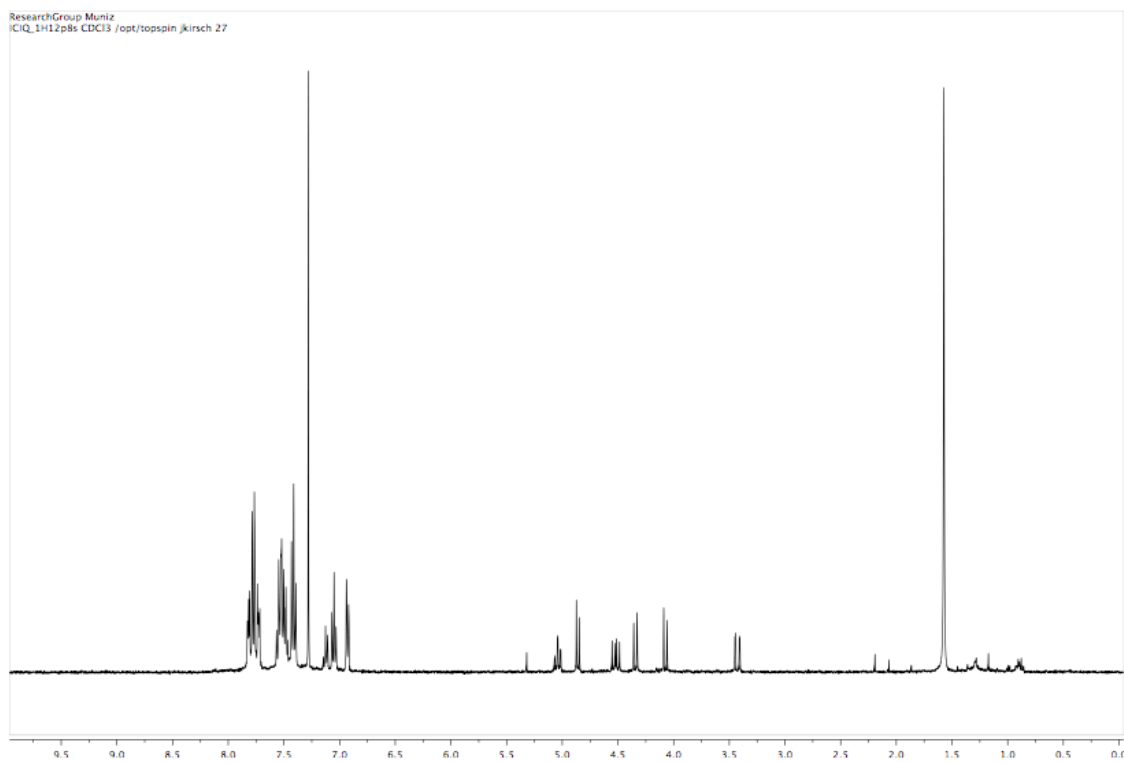


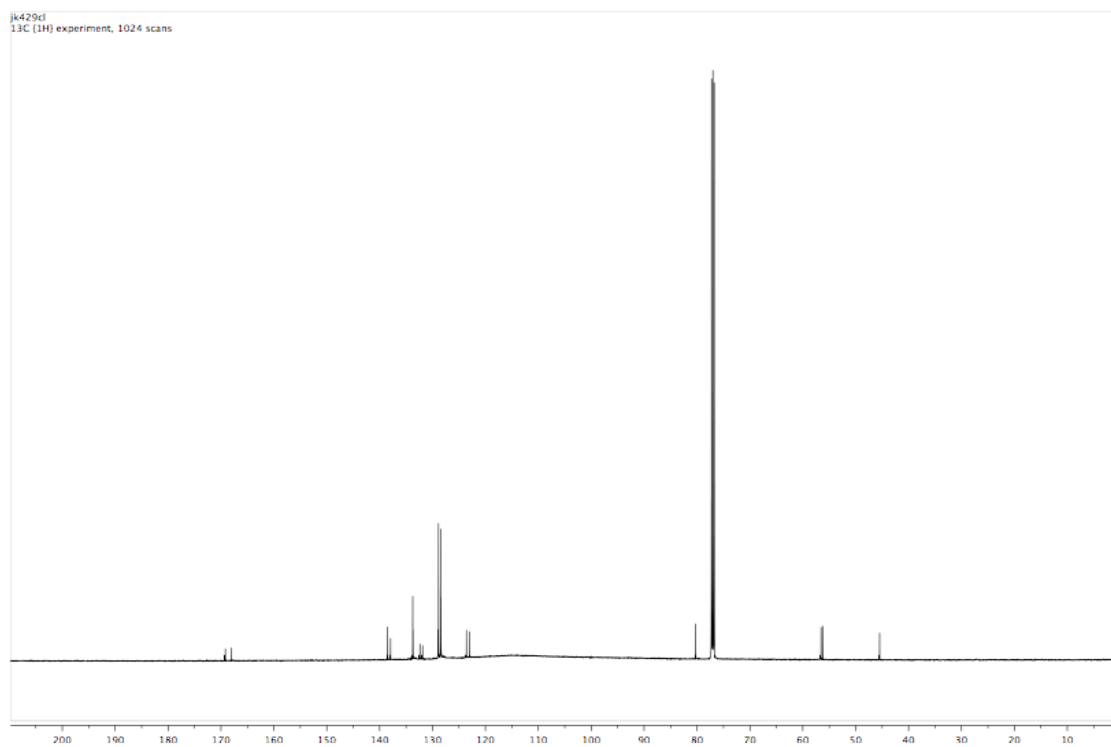
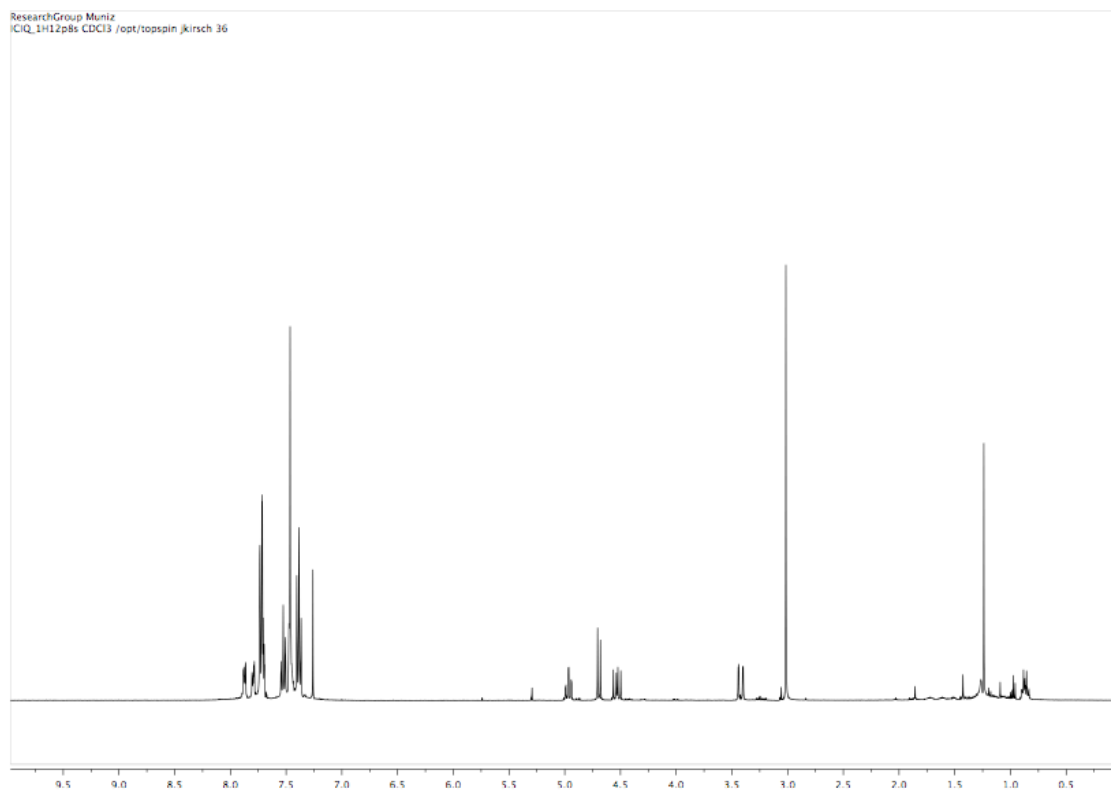
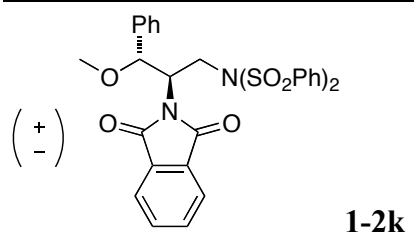
1-2i

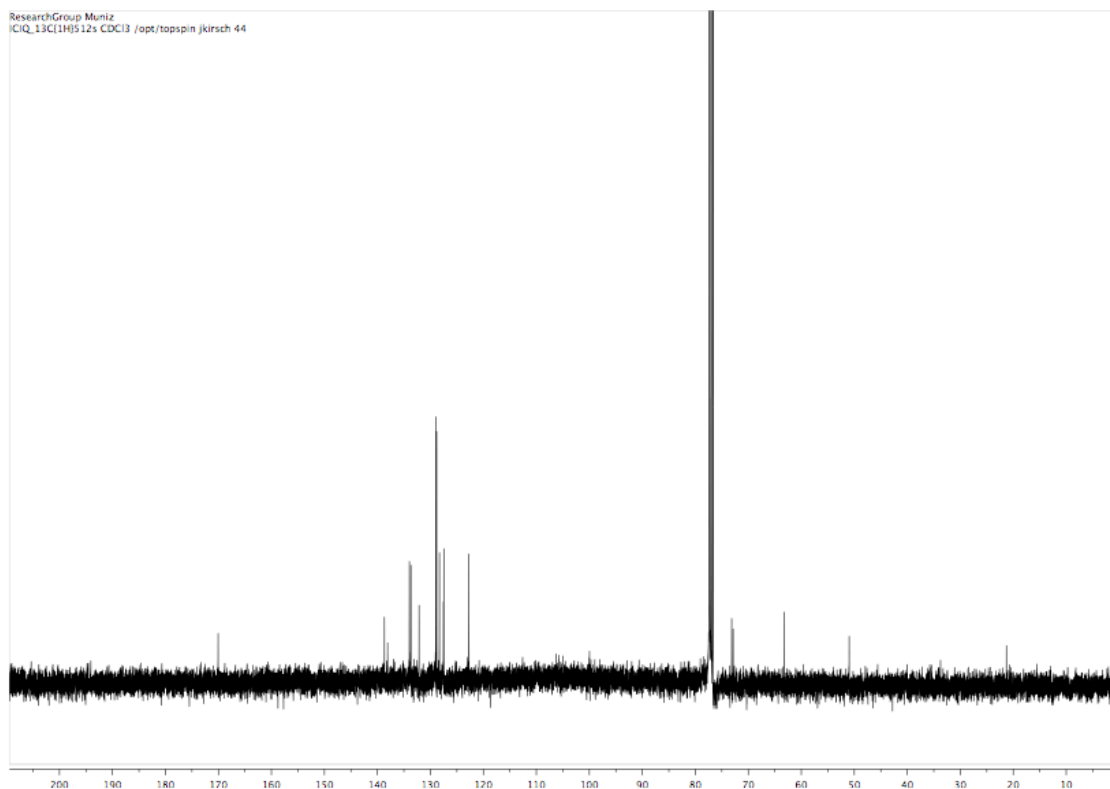
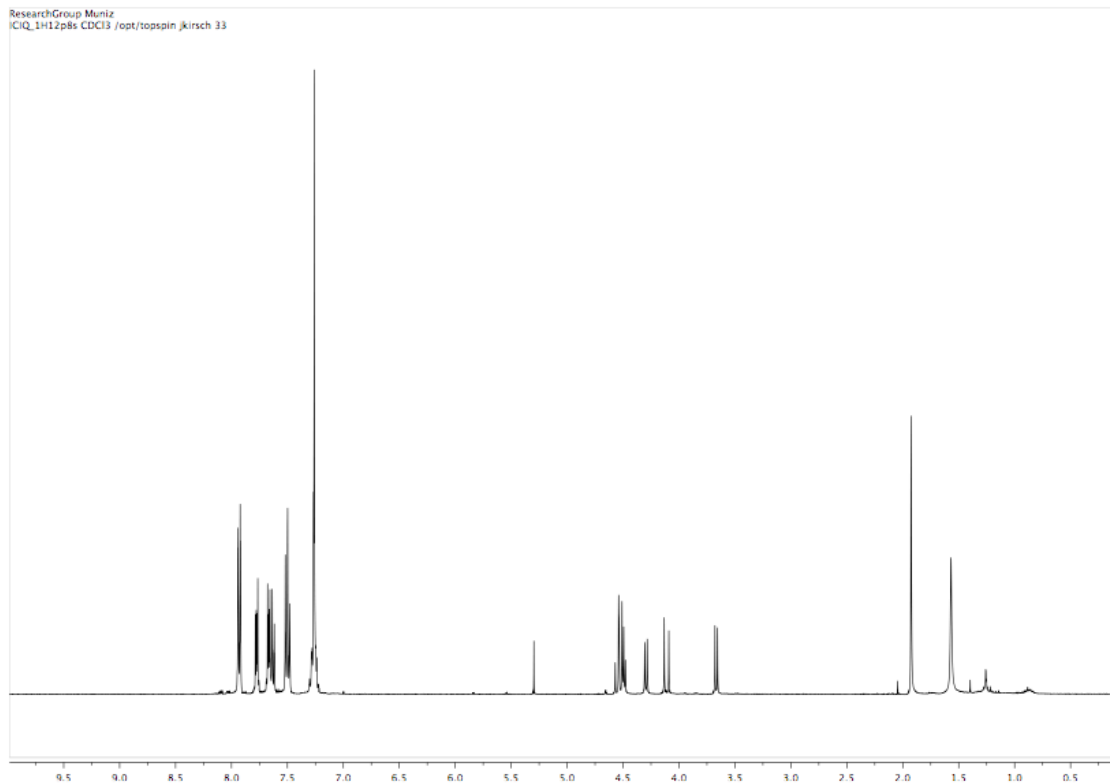
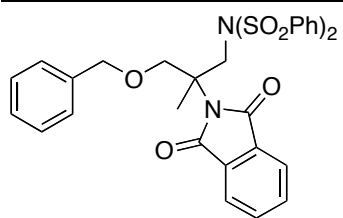


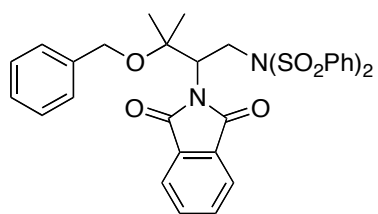


1-2j

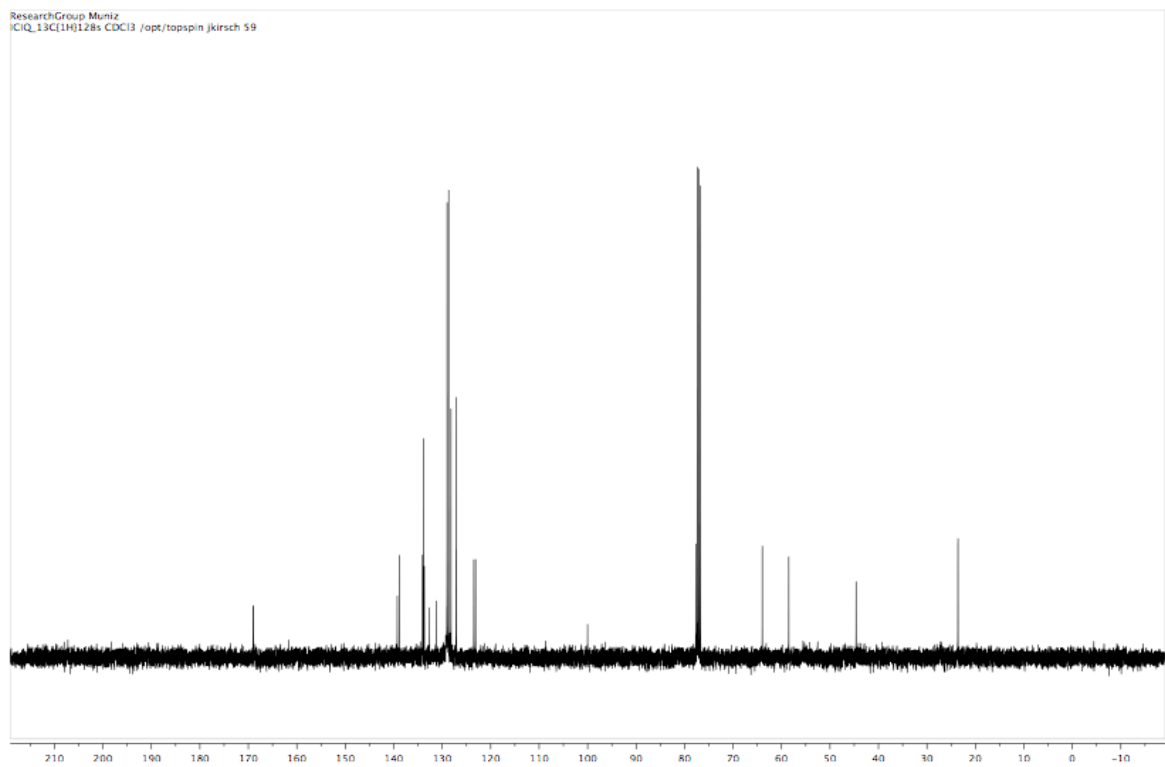
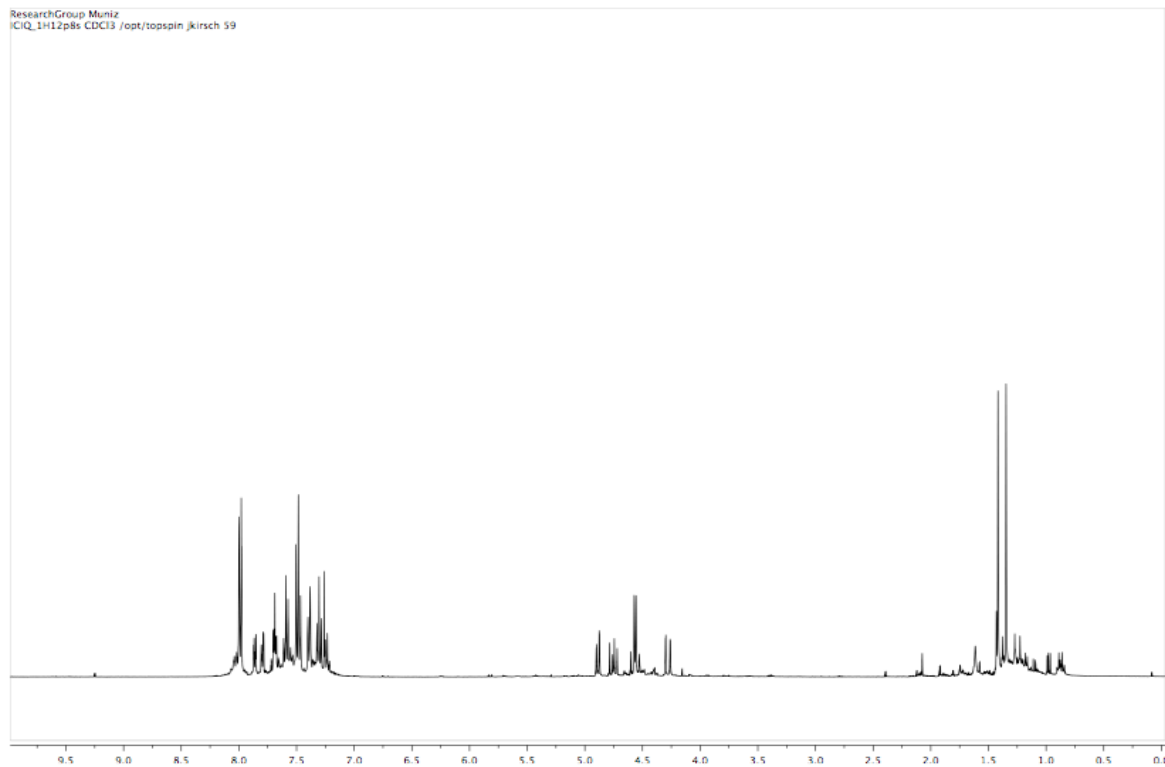


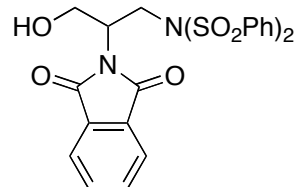




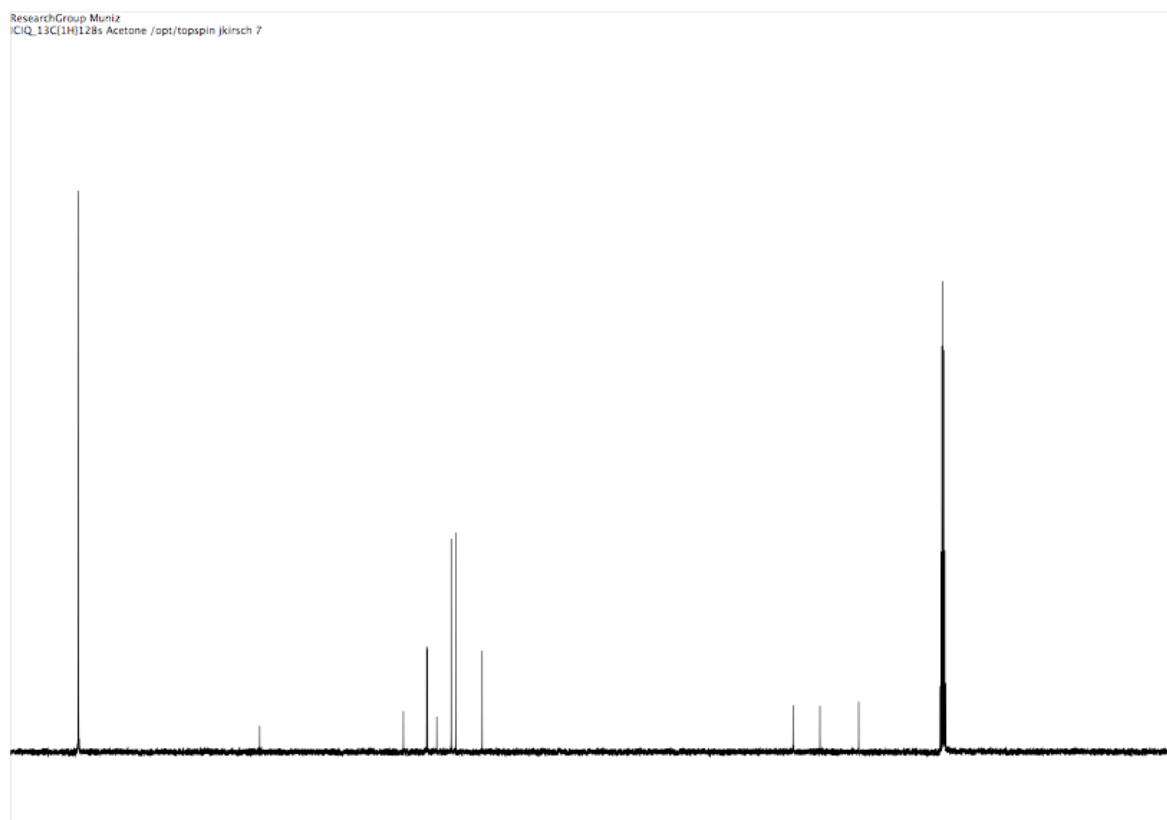
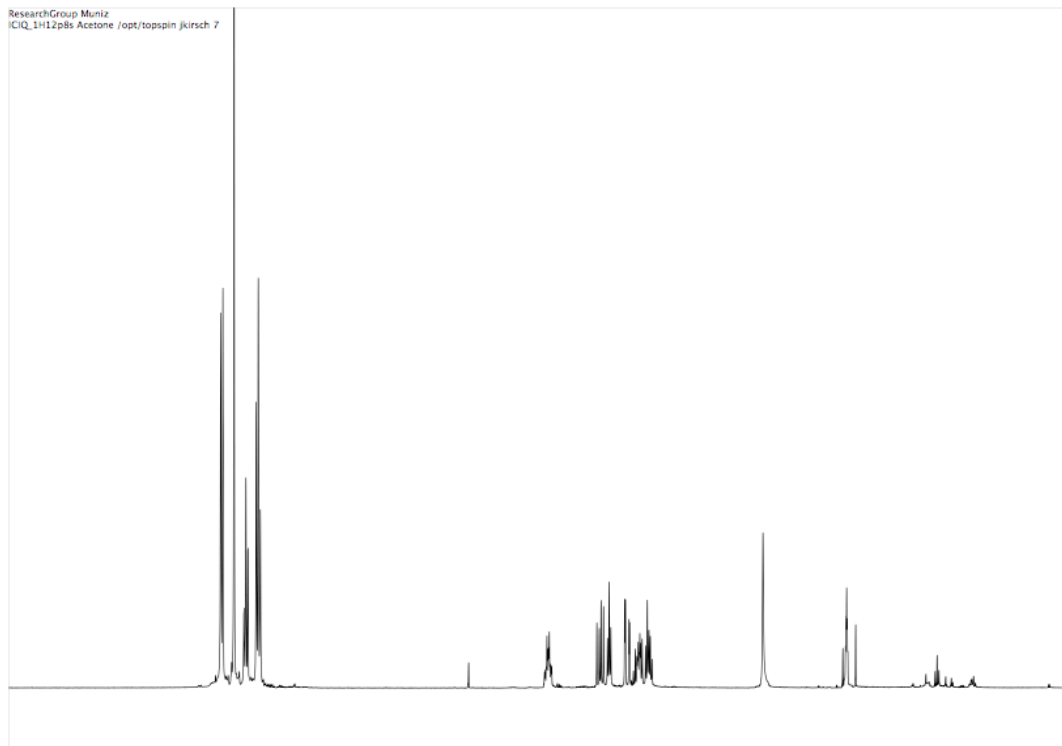


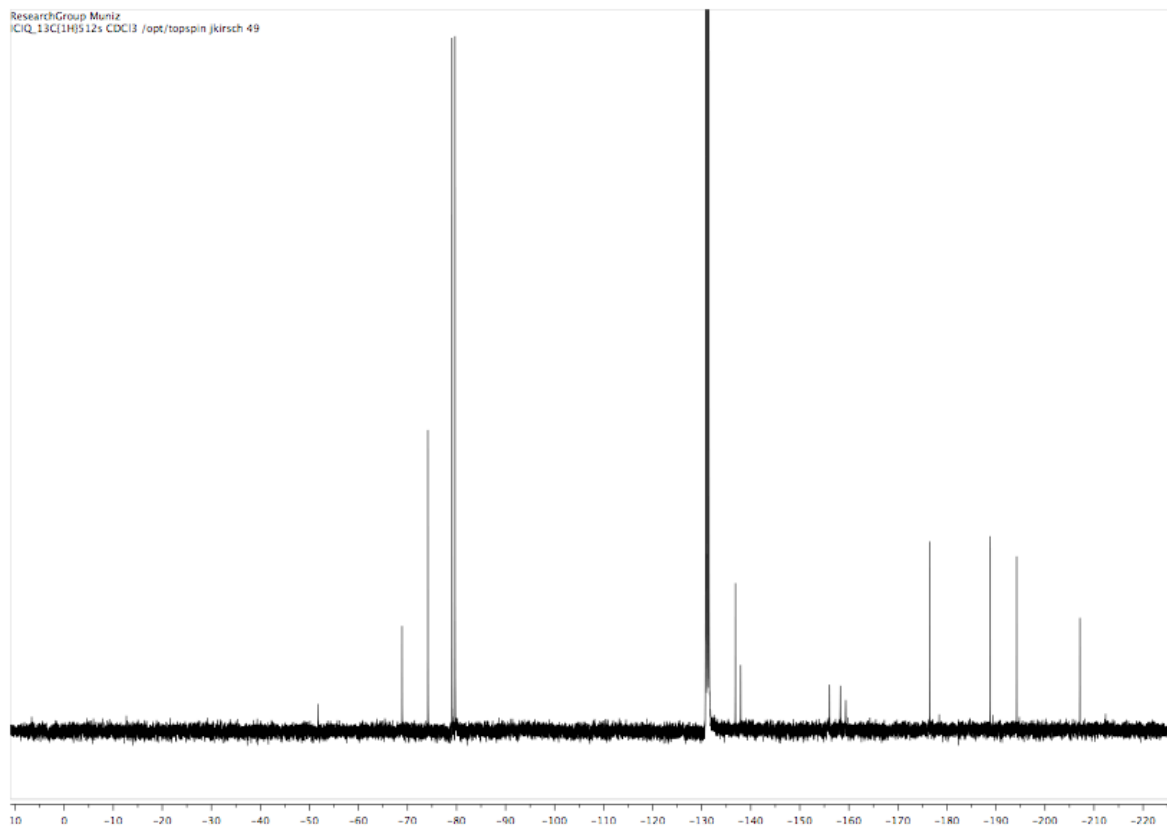
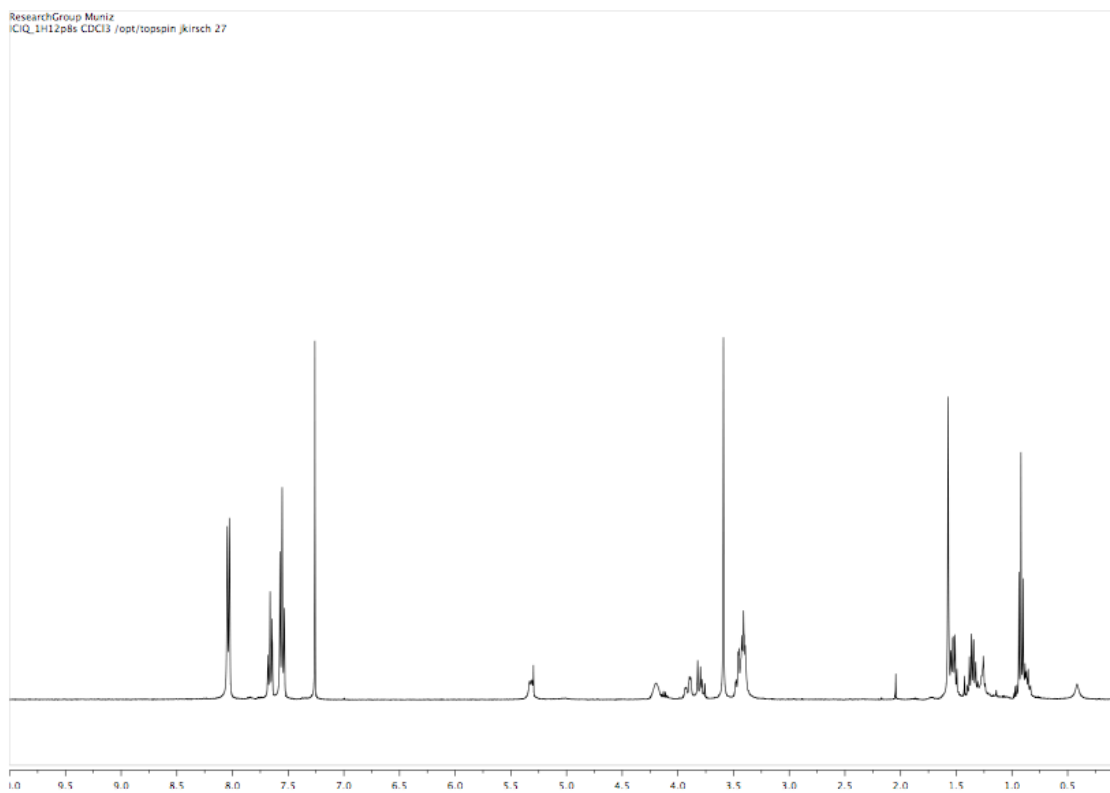
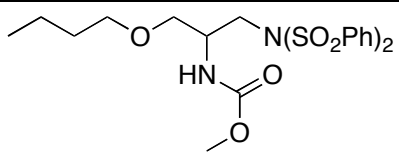
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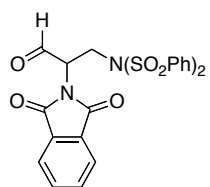




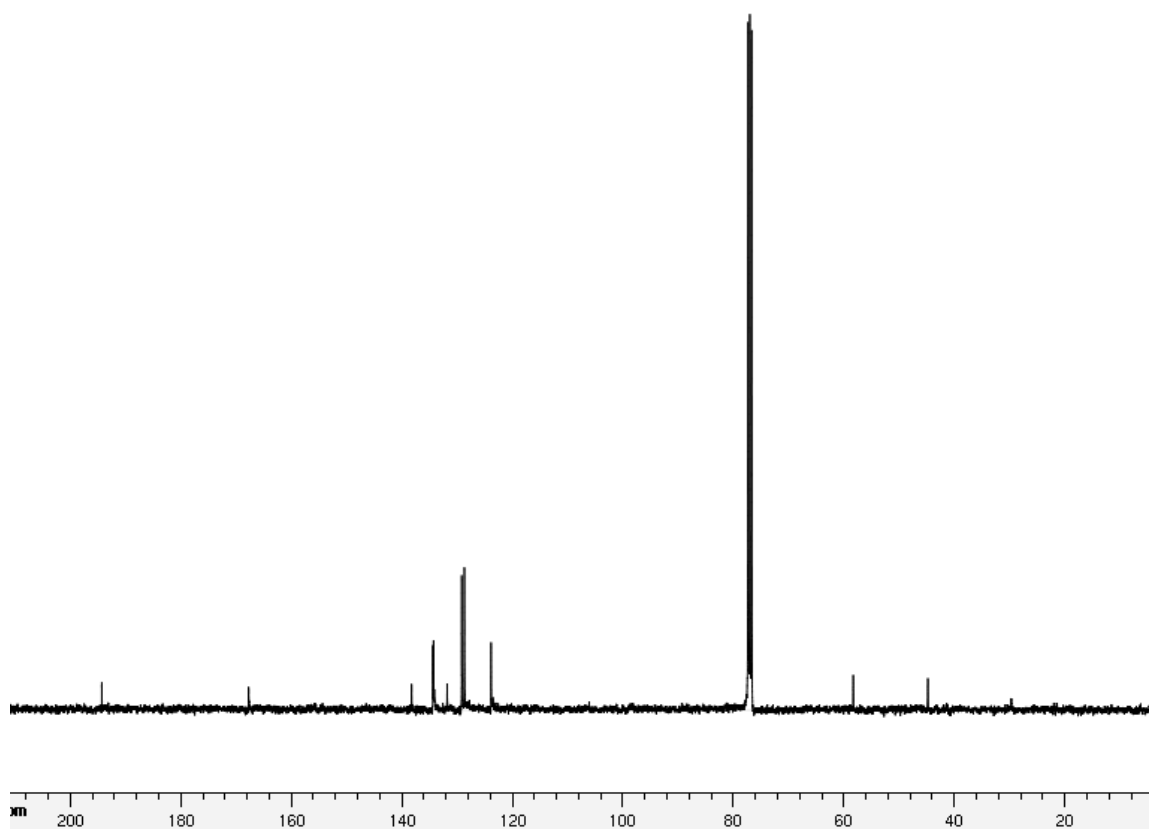
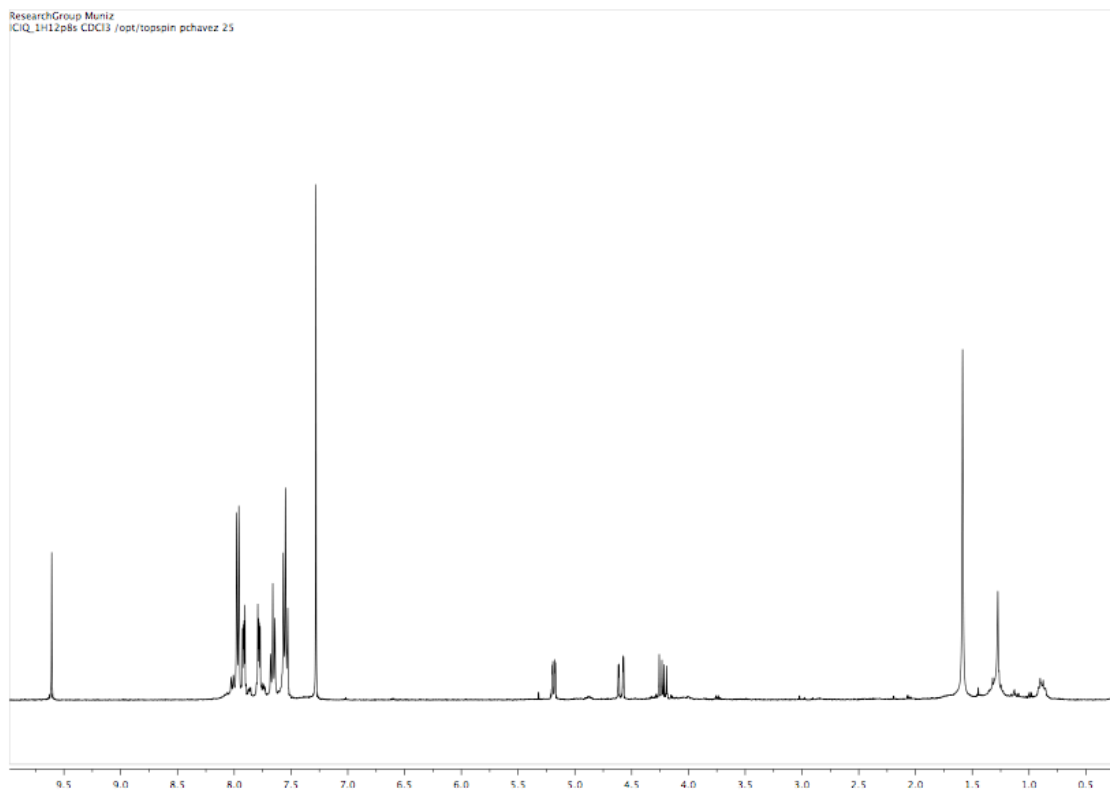
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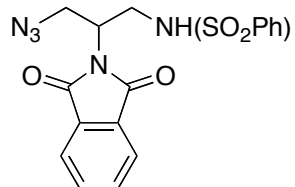




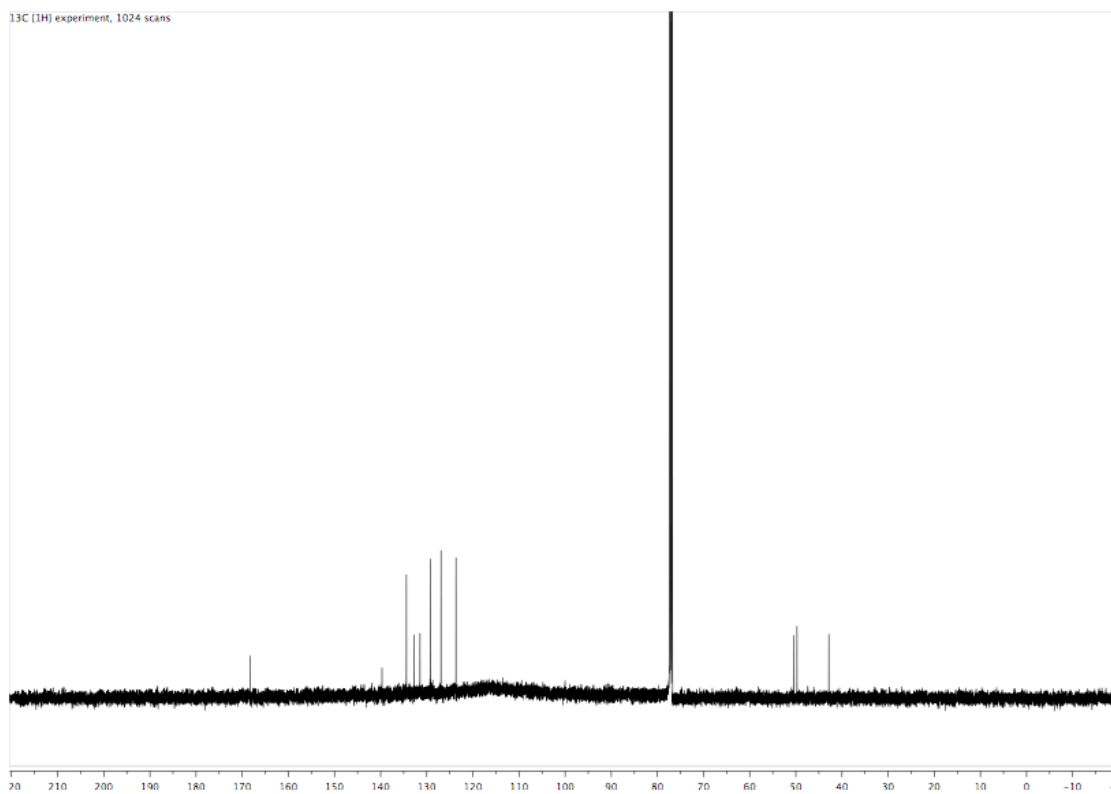
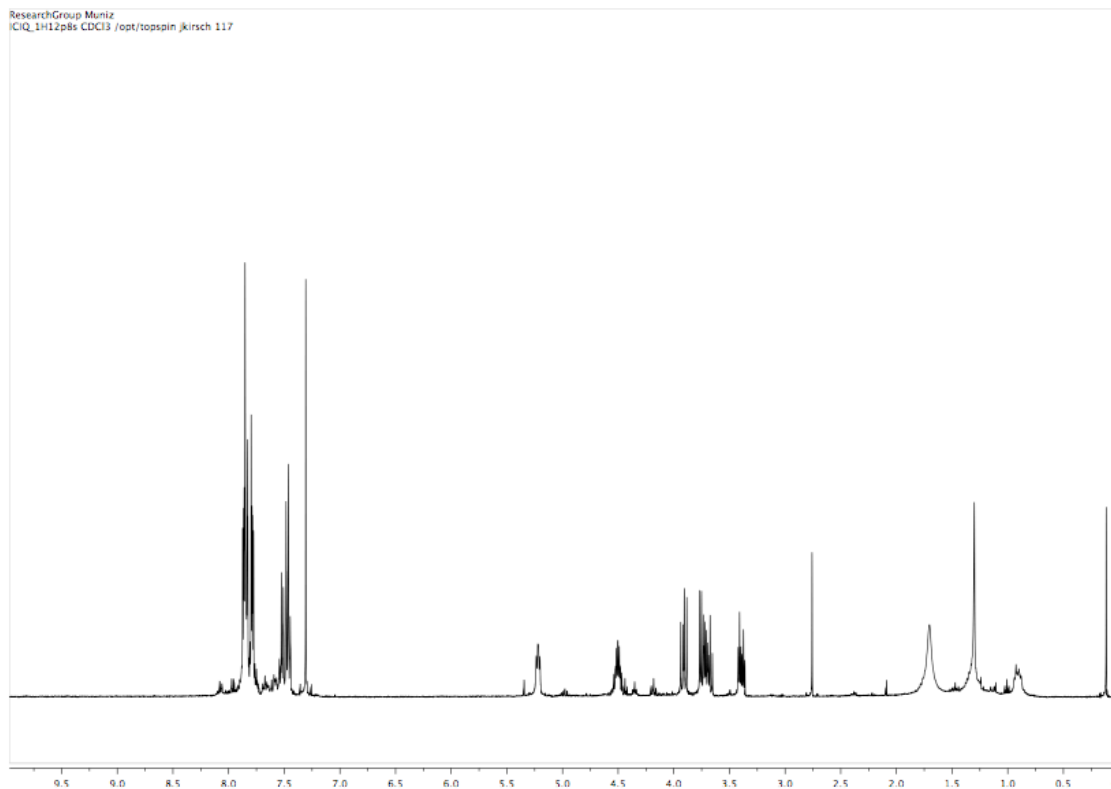


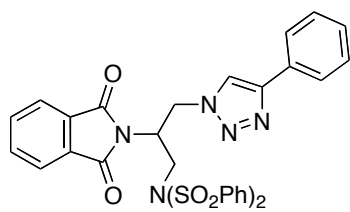
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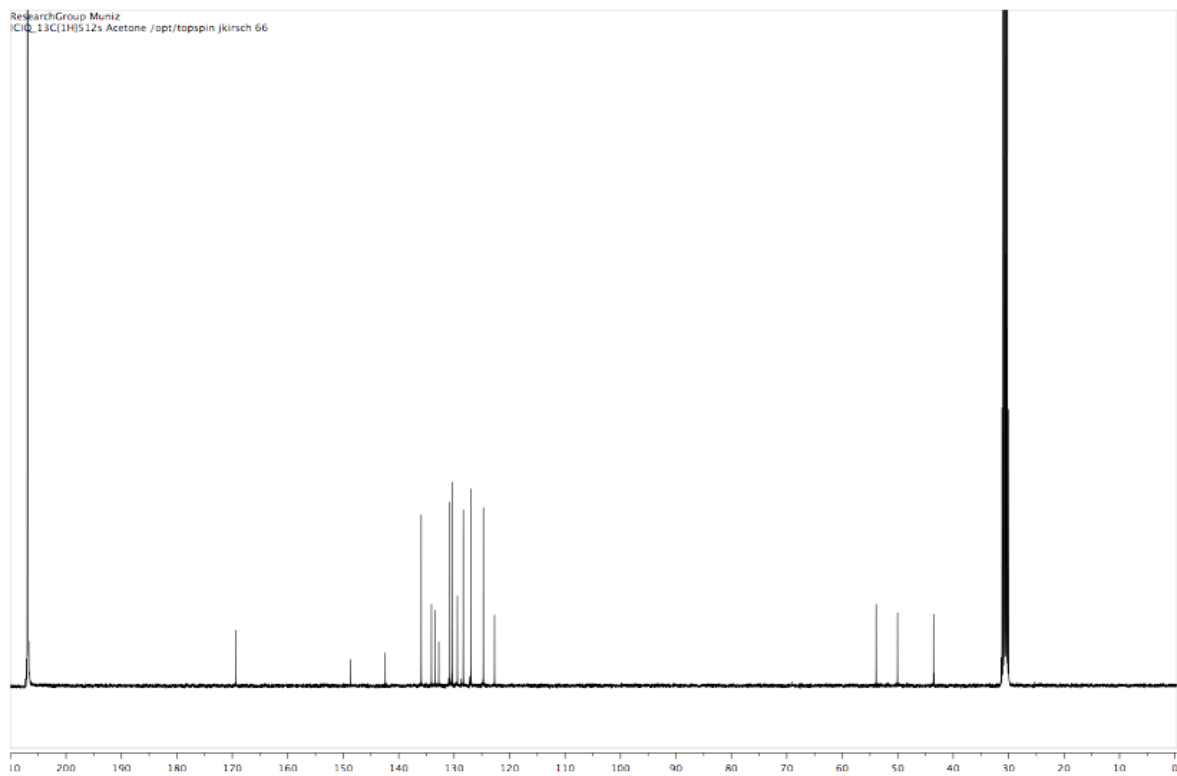
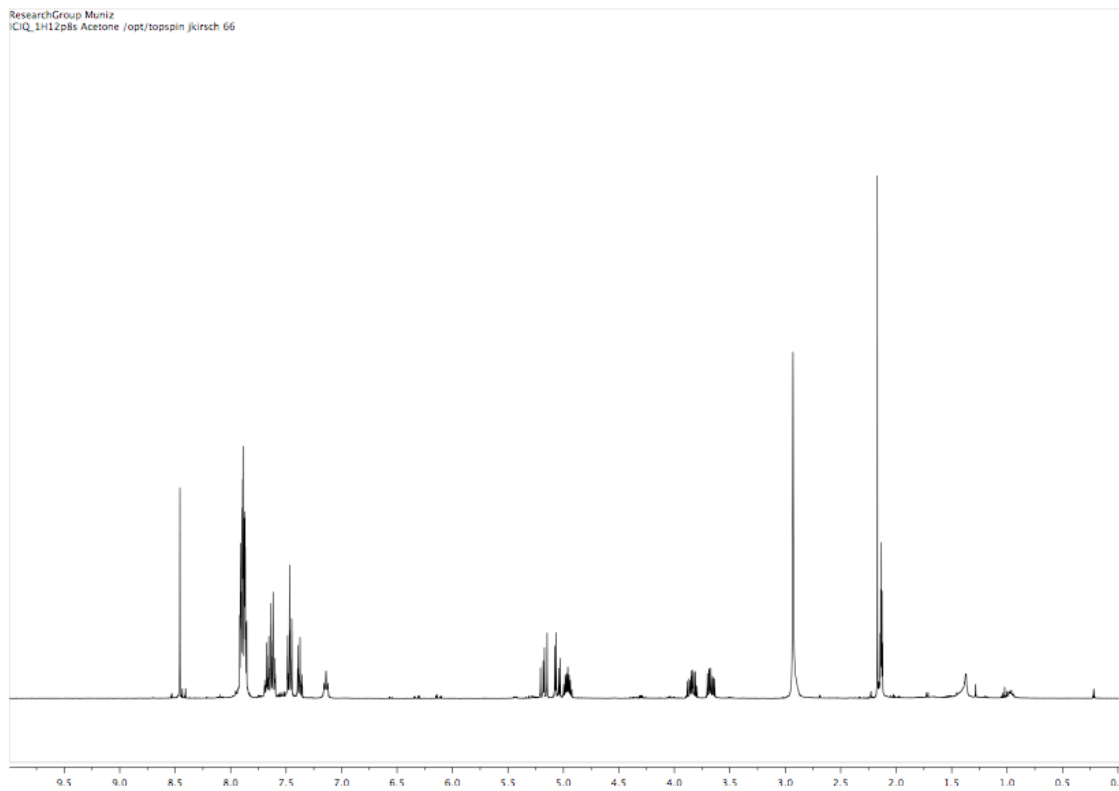


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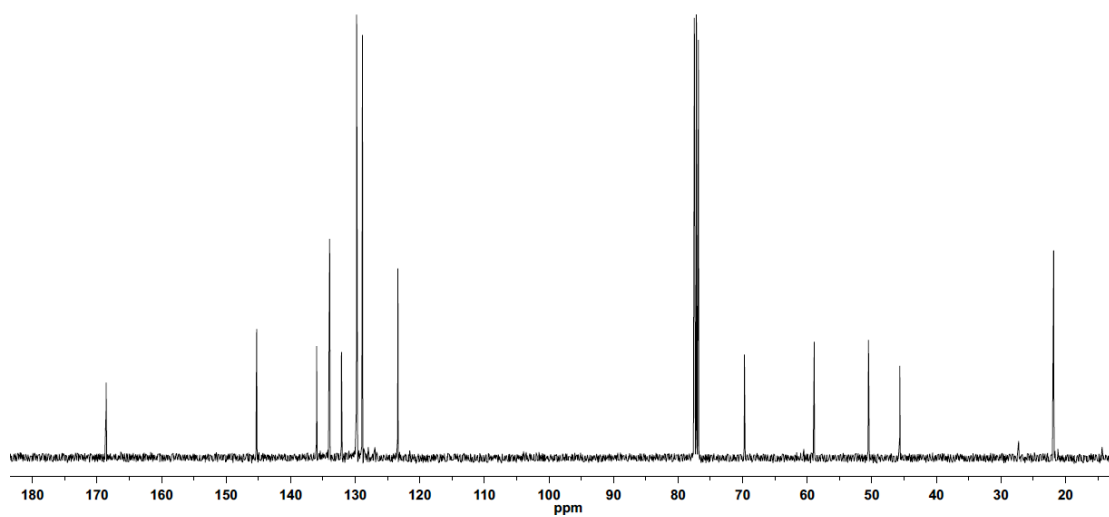
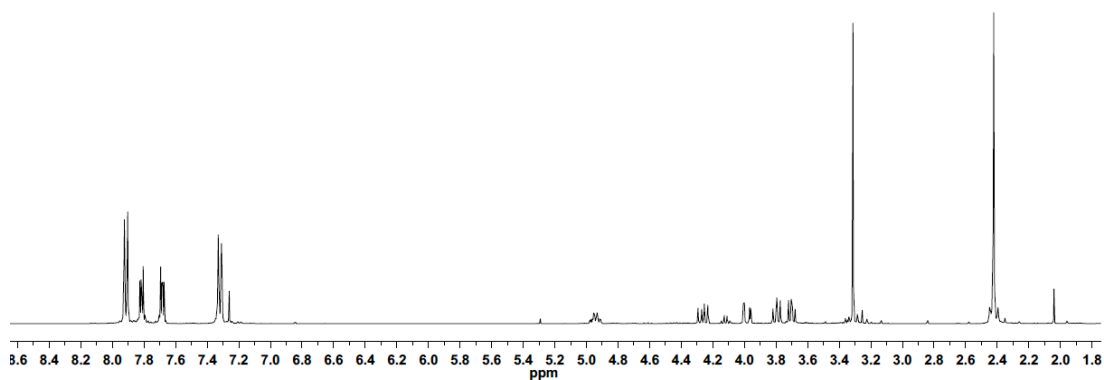
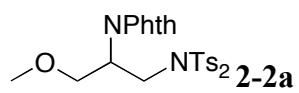


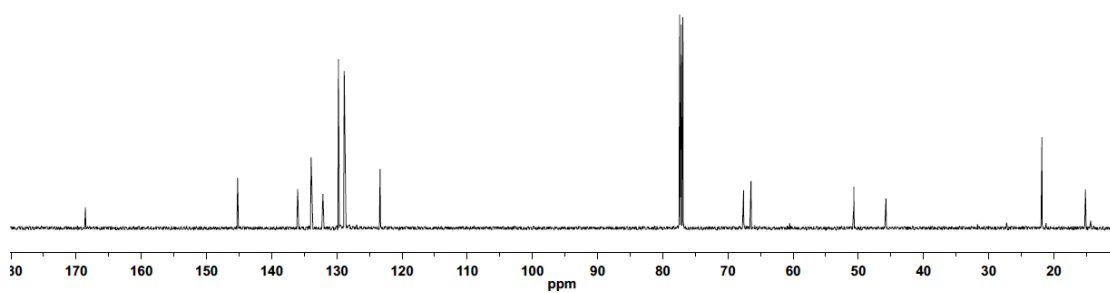
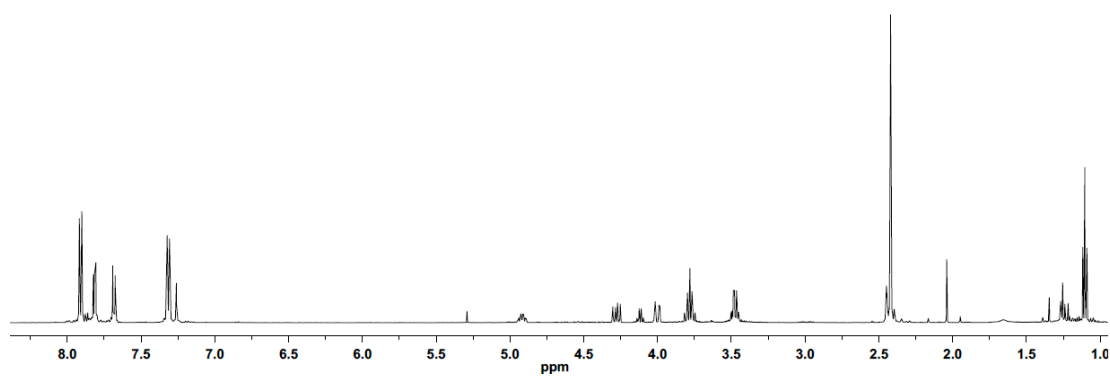
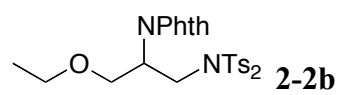


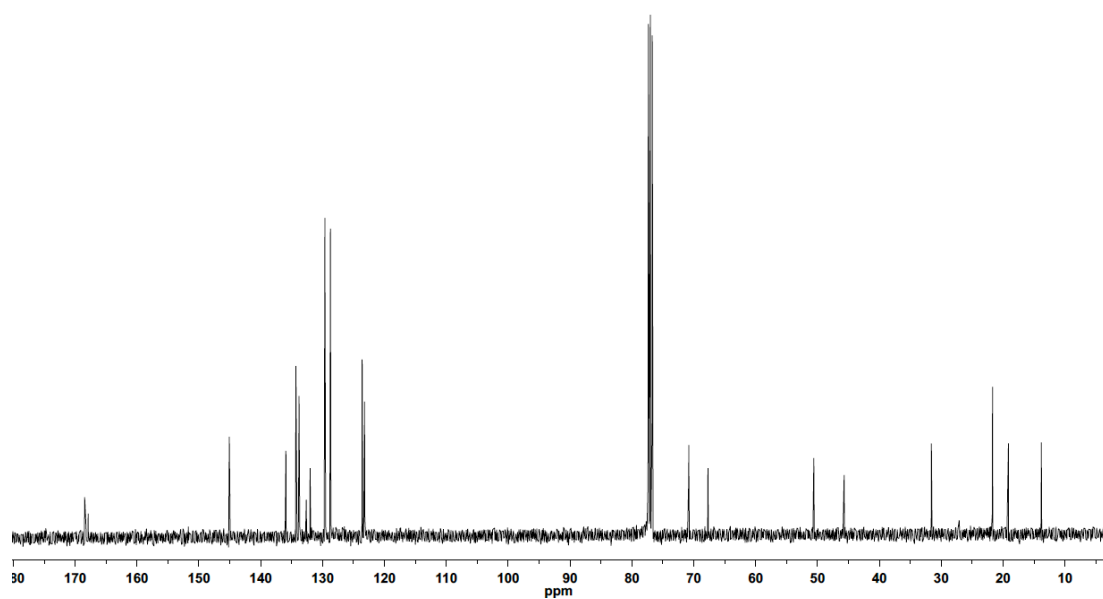
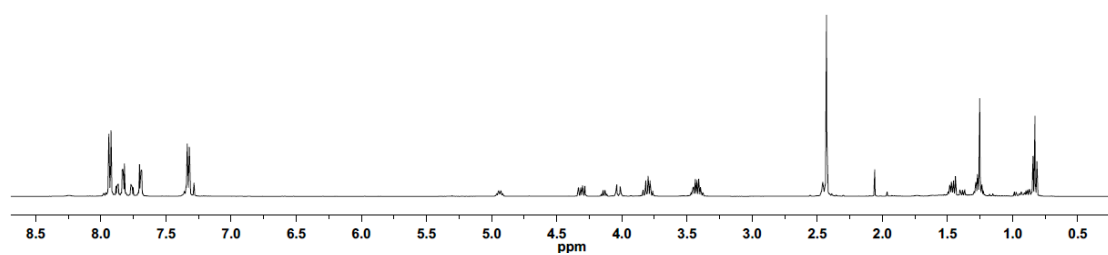
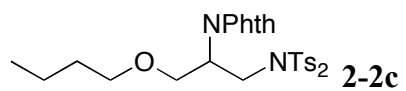
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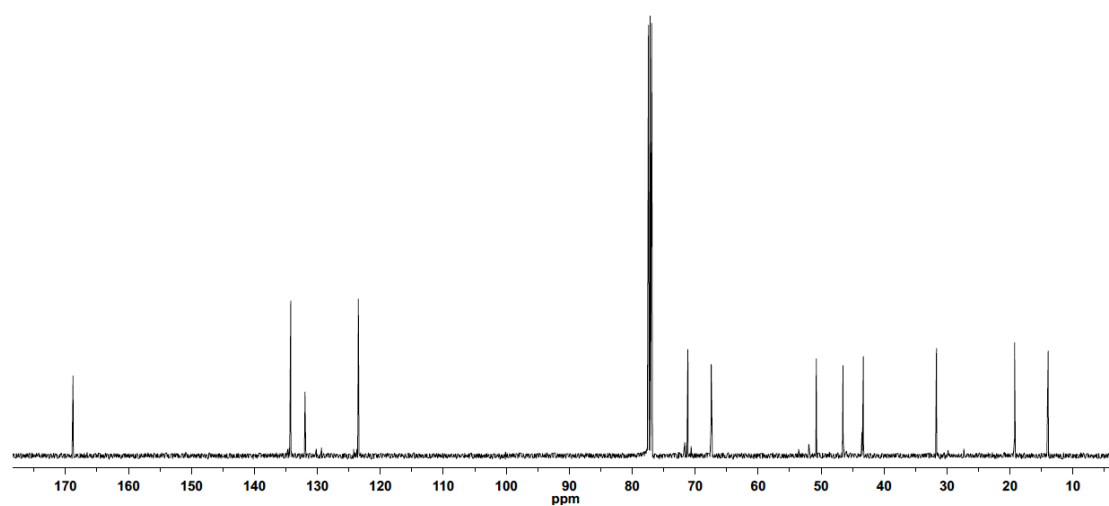
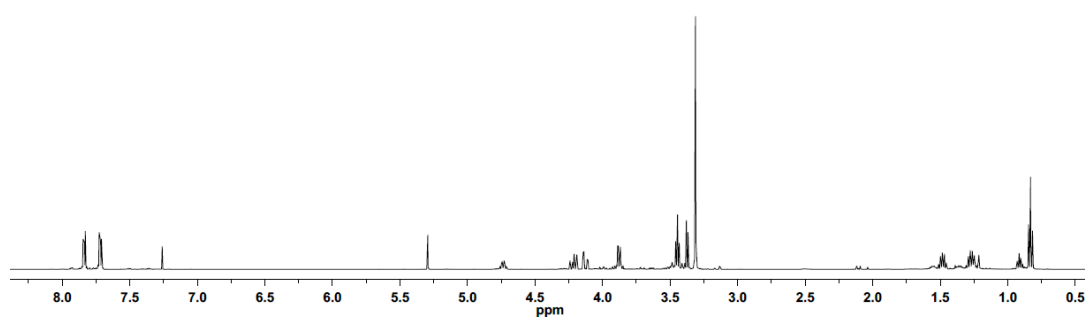
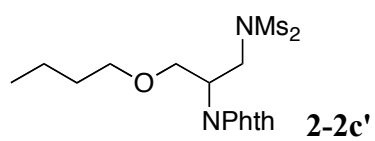


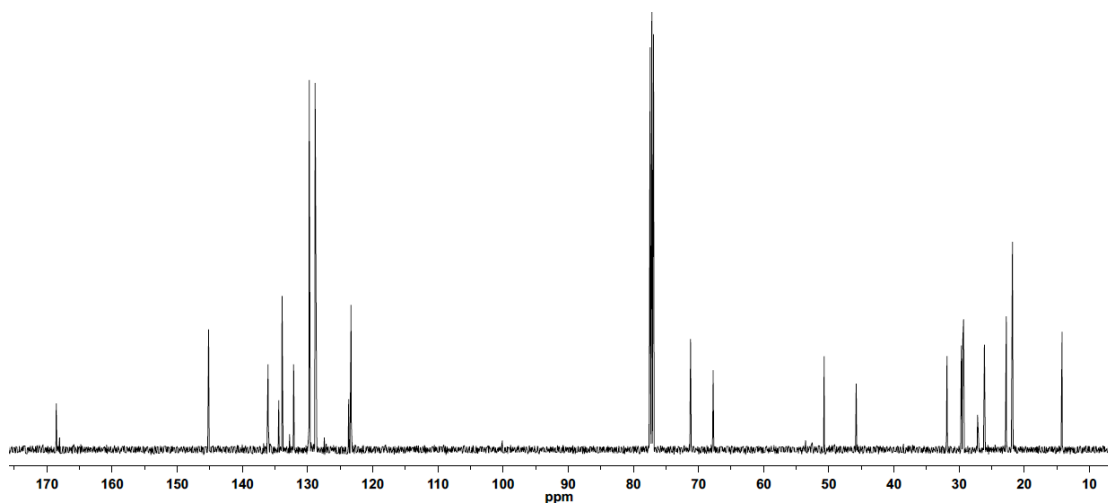
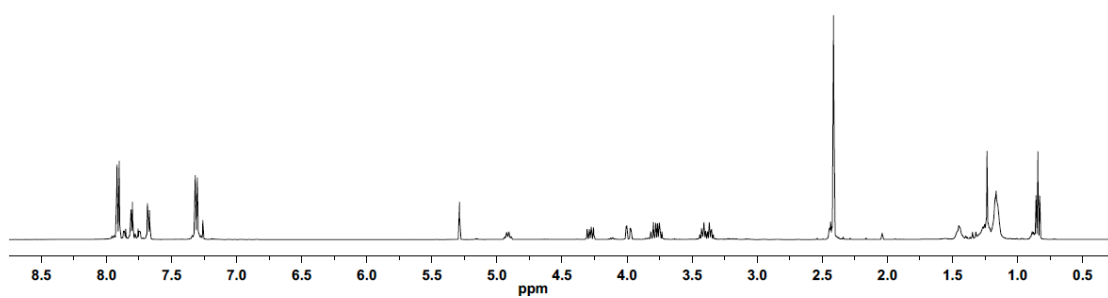
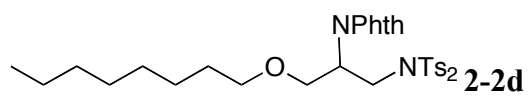
Chapter II: Evolution of the Intermolecular Regioselective 1,2-Diamination of Allylic Ethers

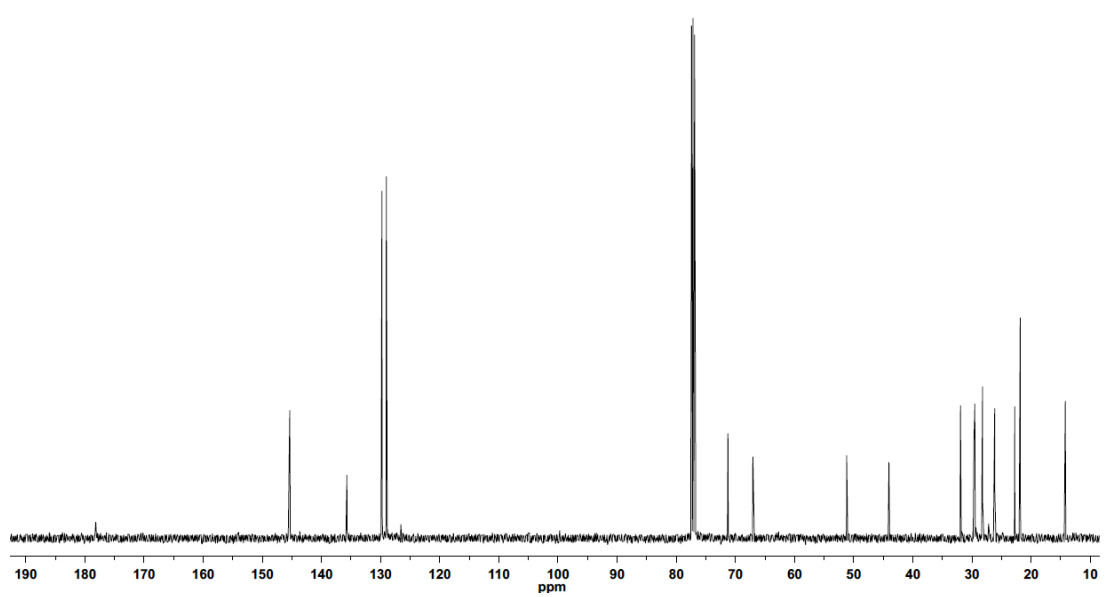
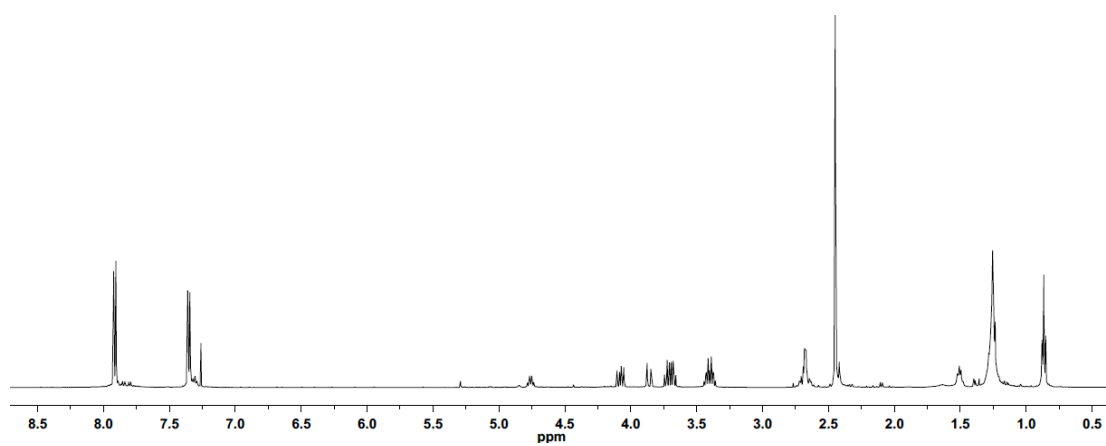
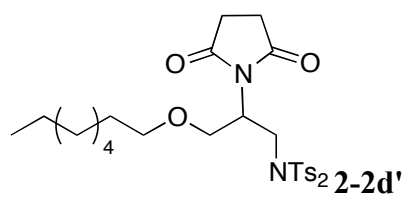


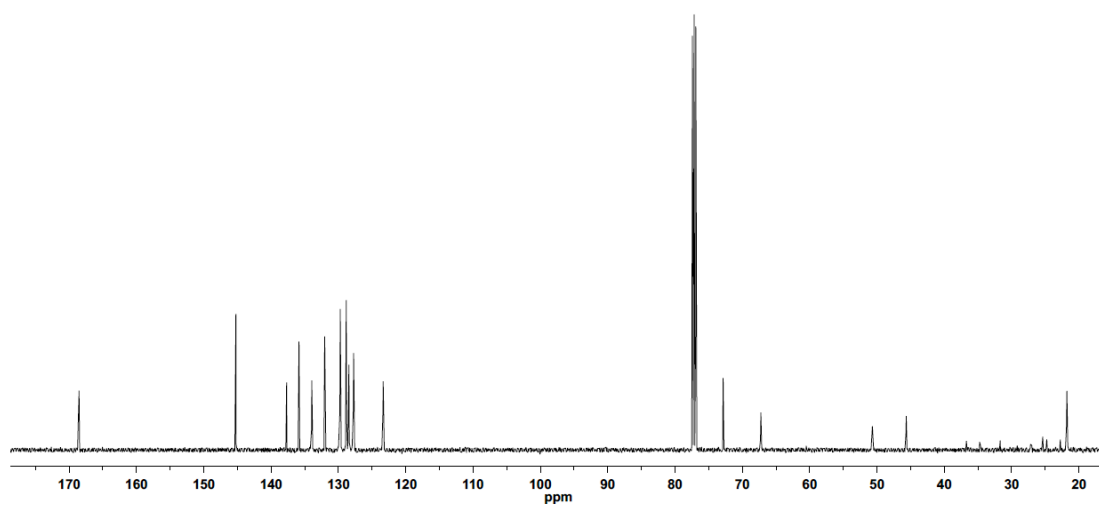
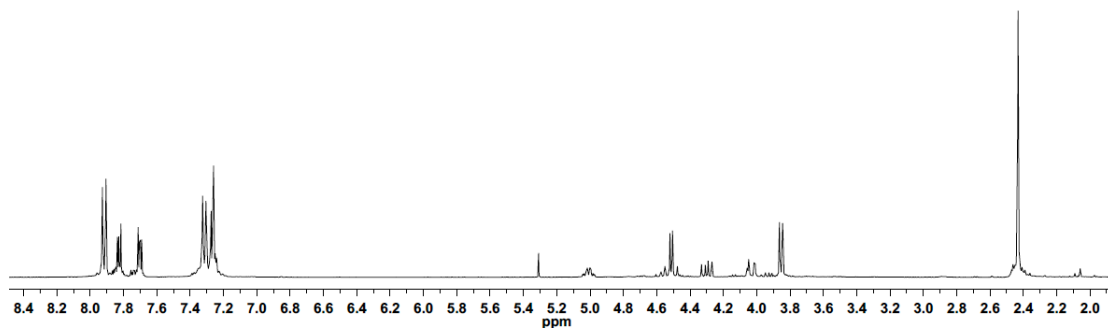
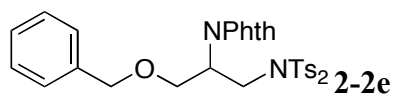


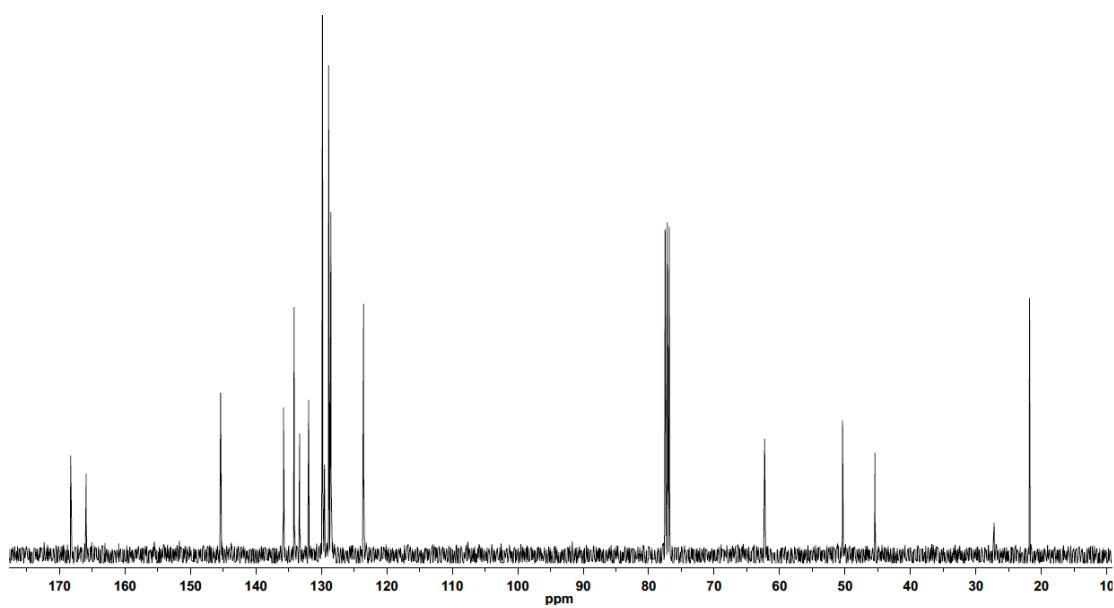
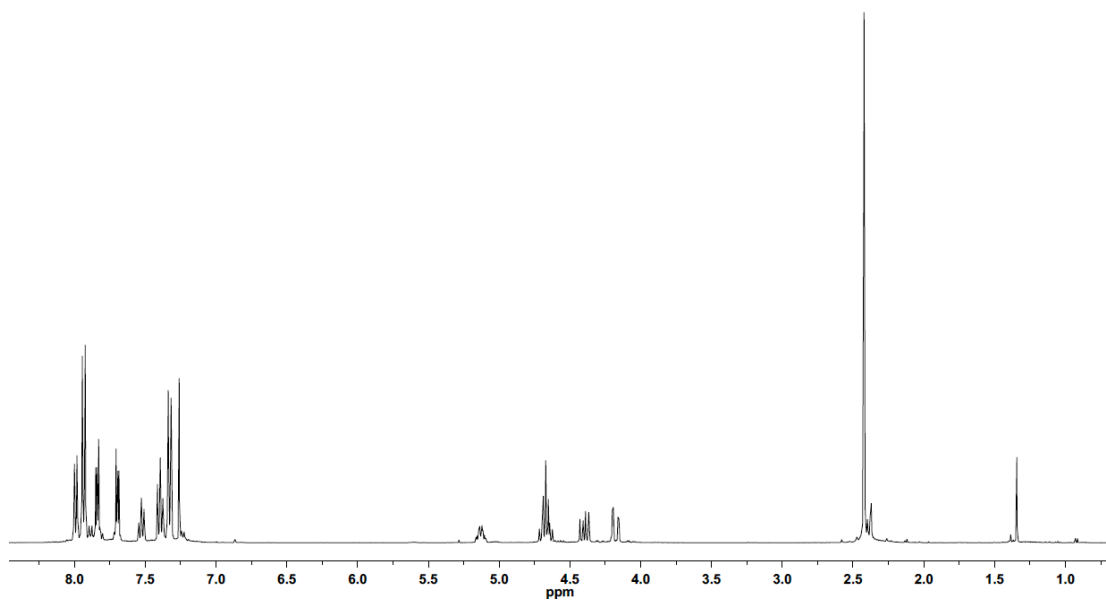
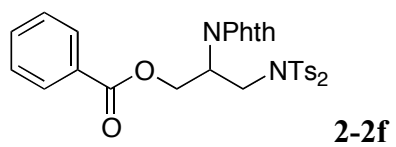


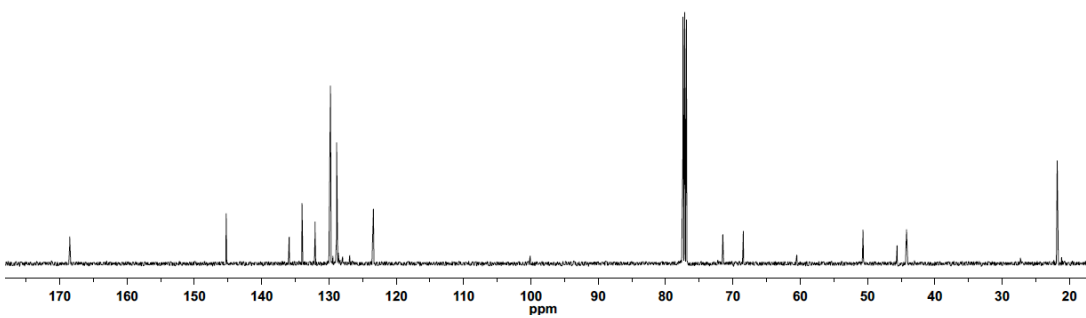
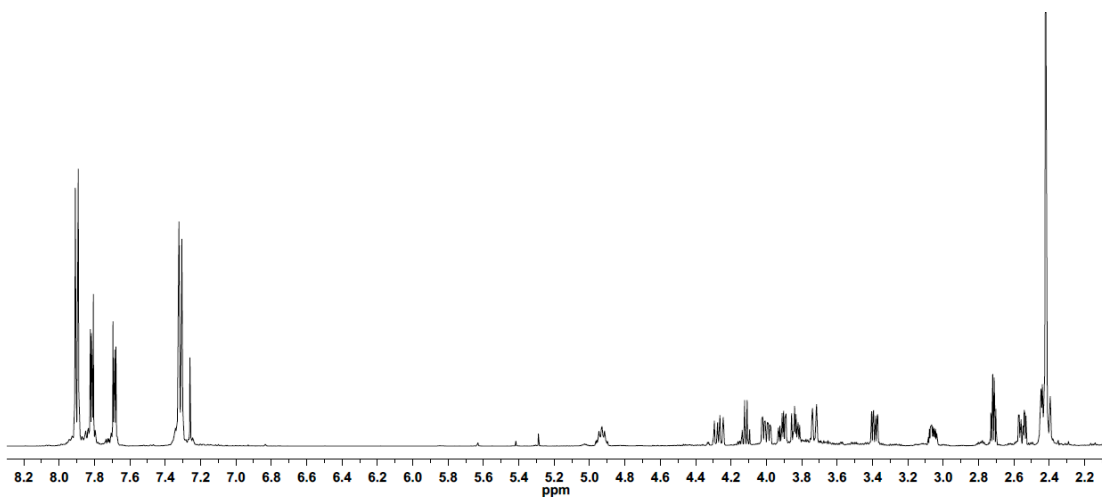
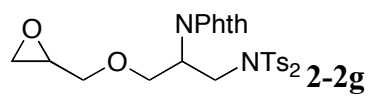


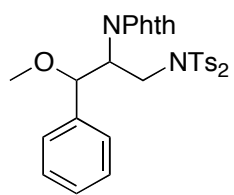




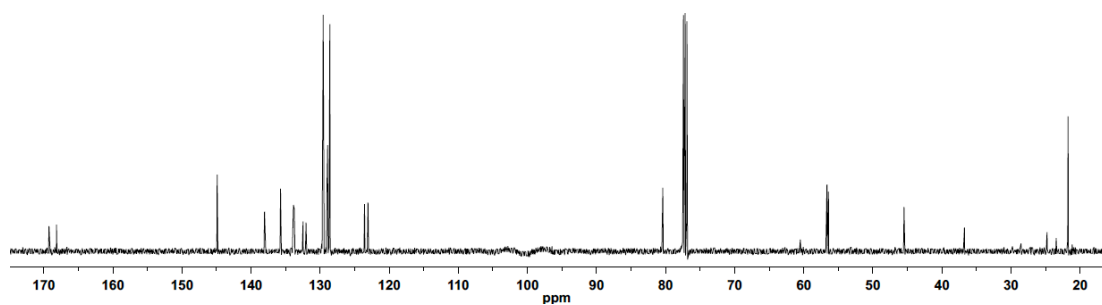
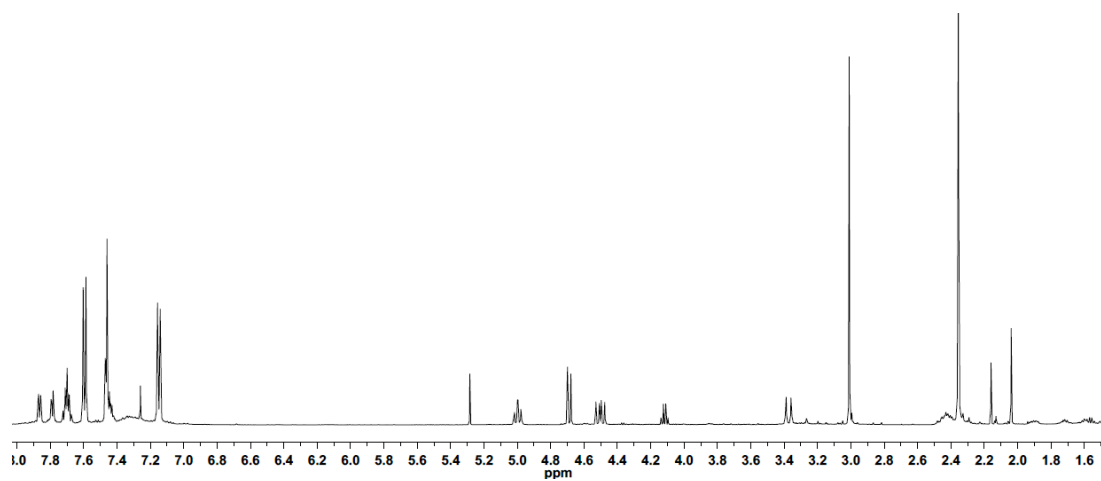


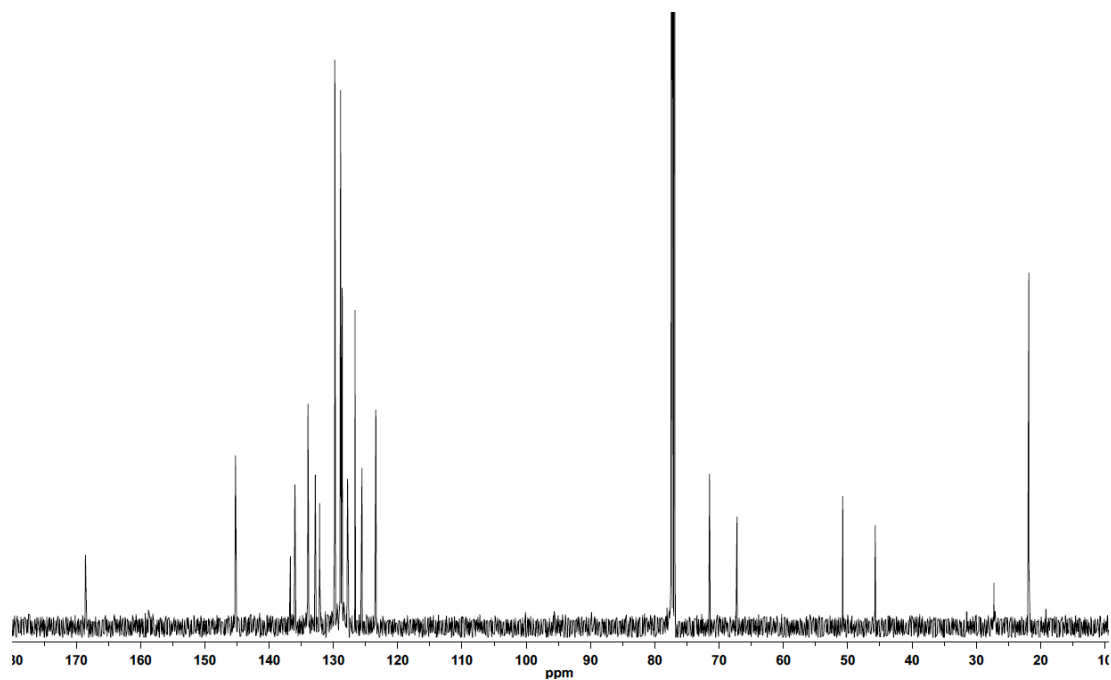
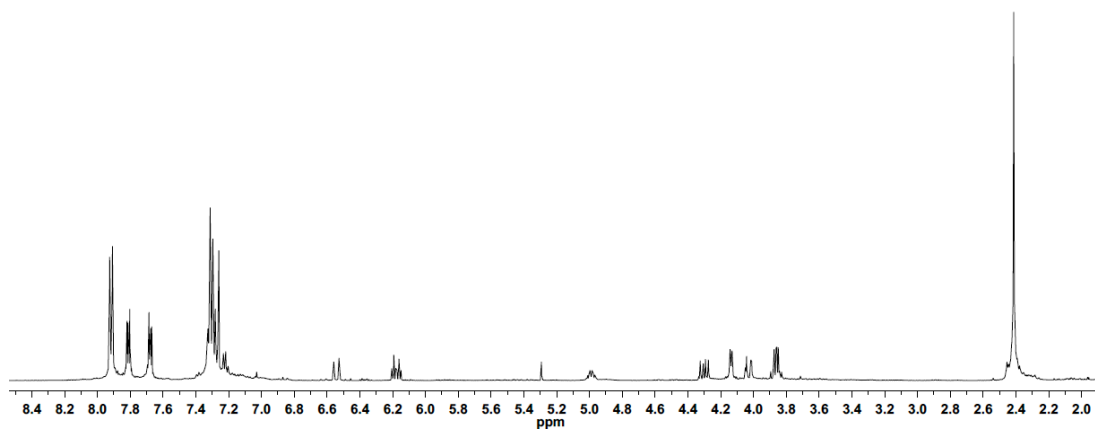
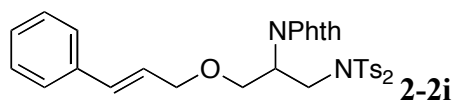


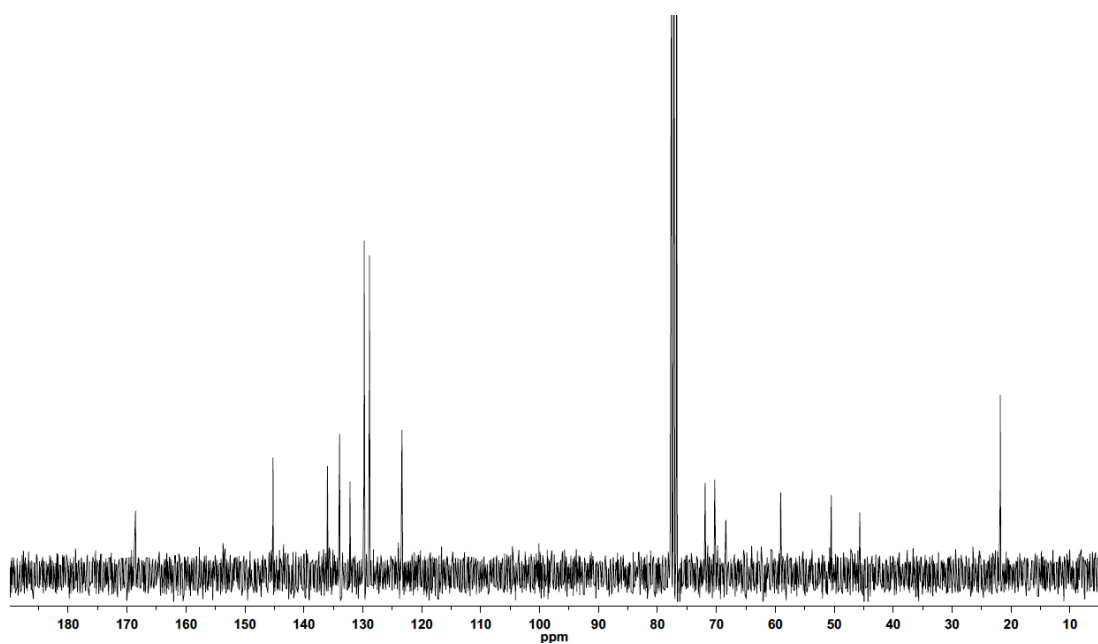
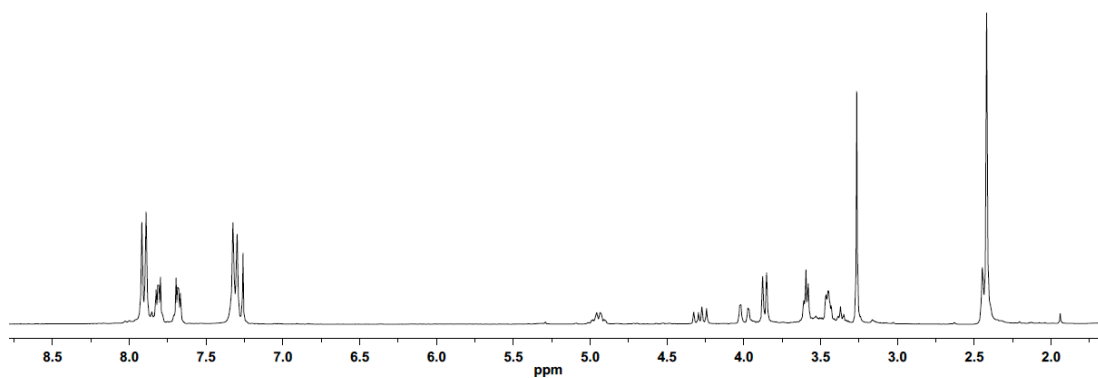
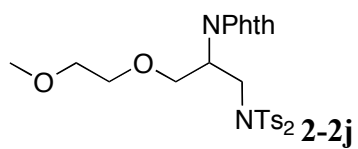


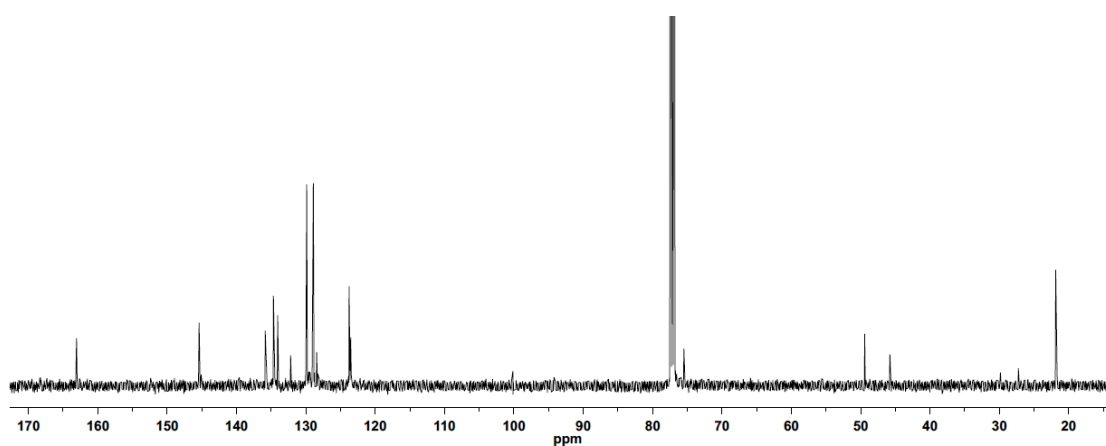
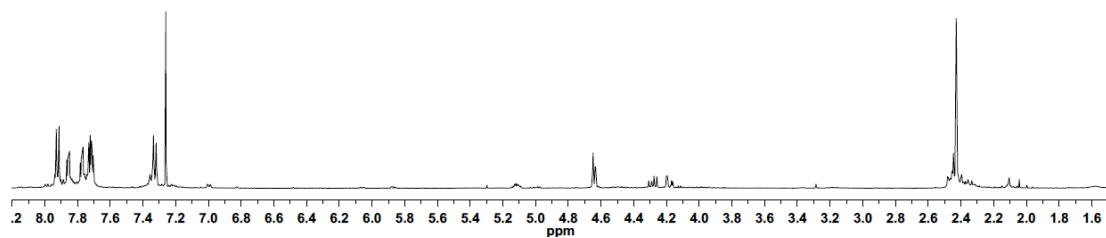
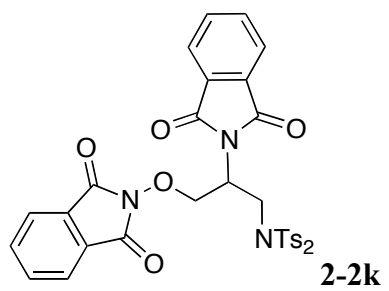


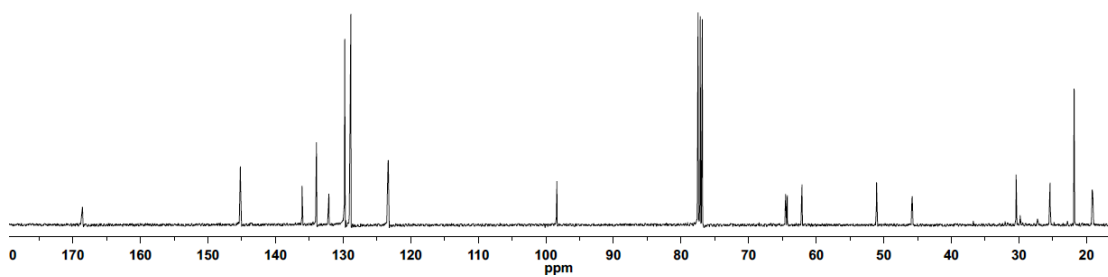
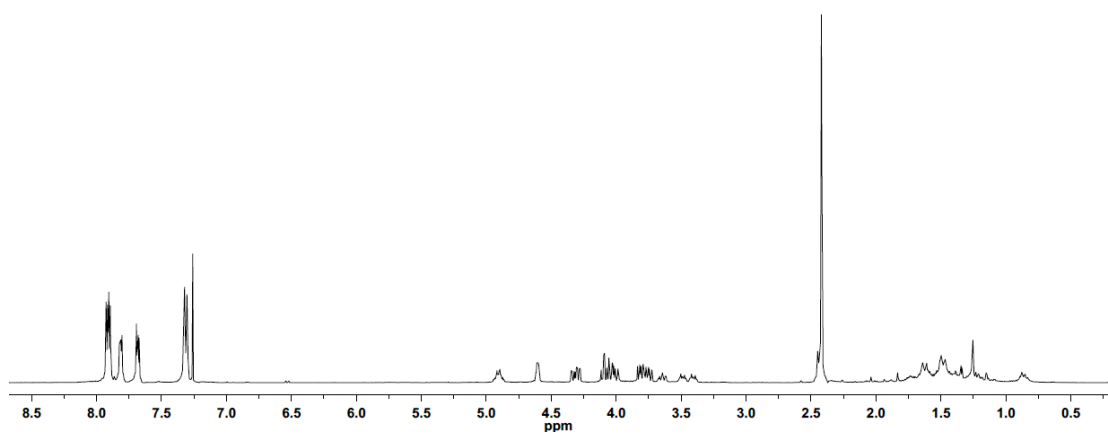
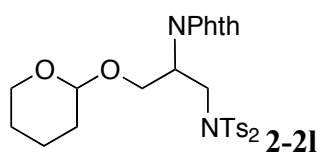
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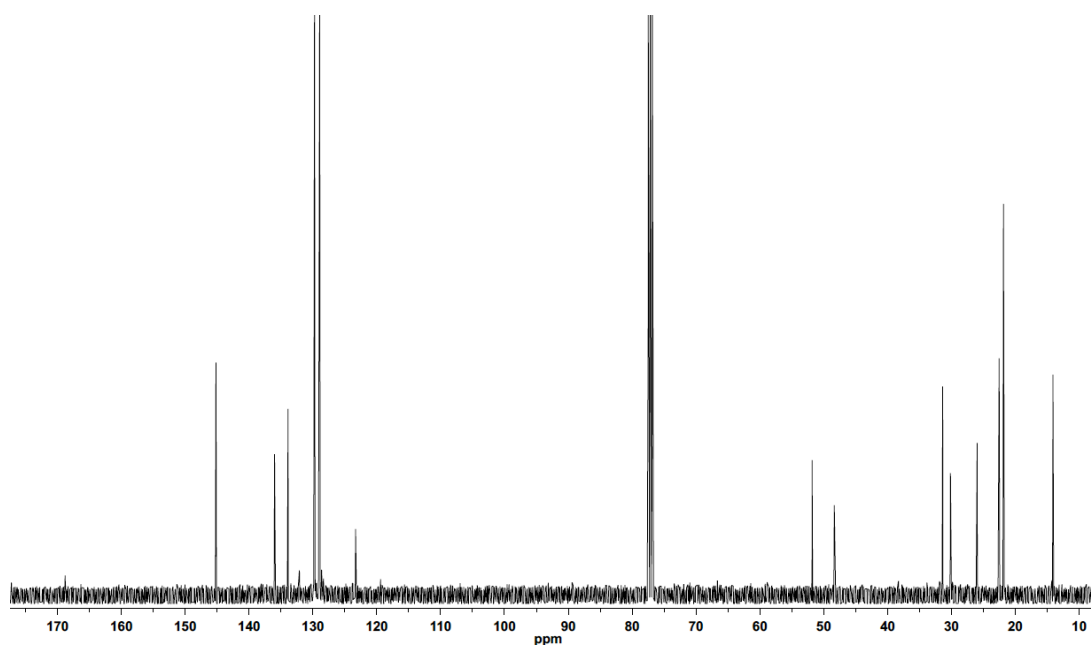
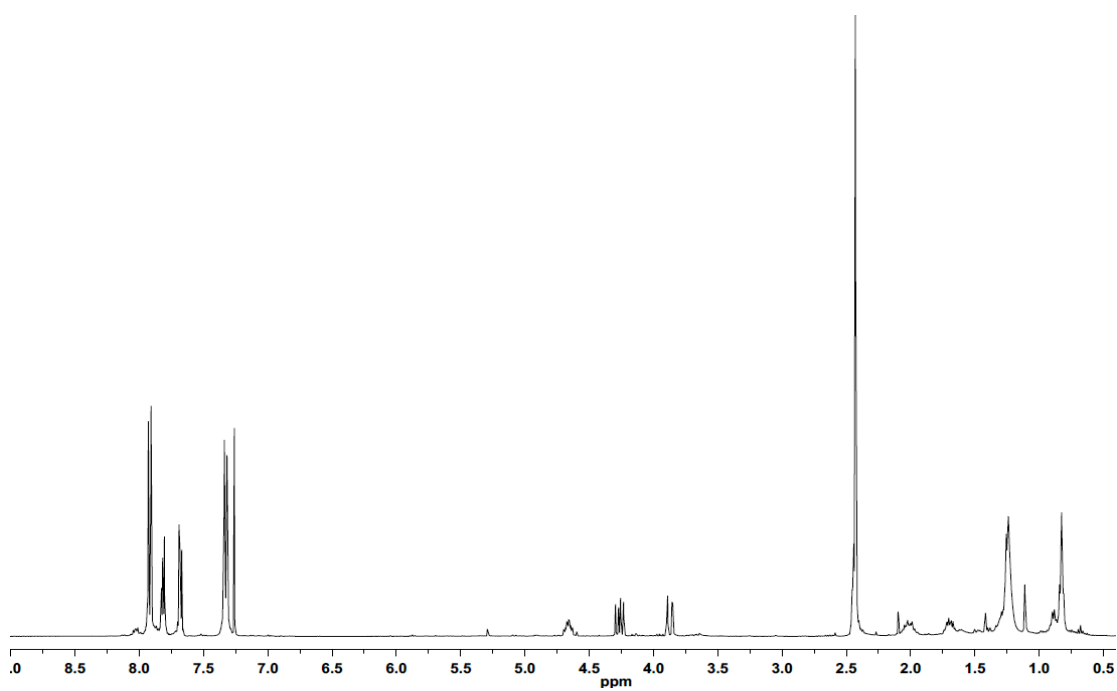
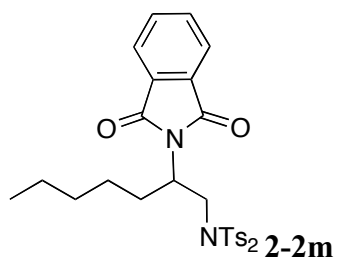




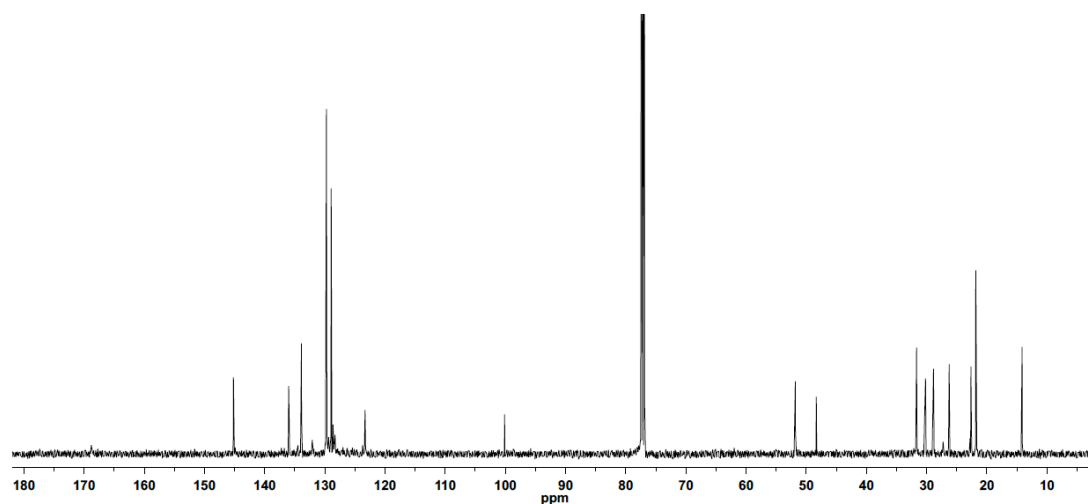
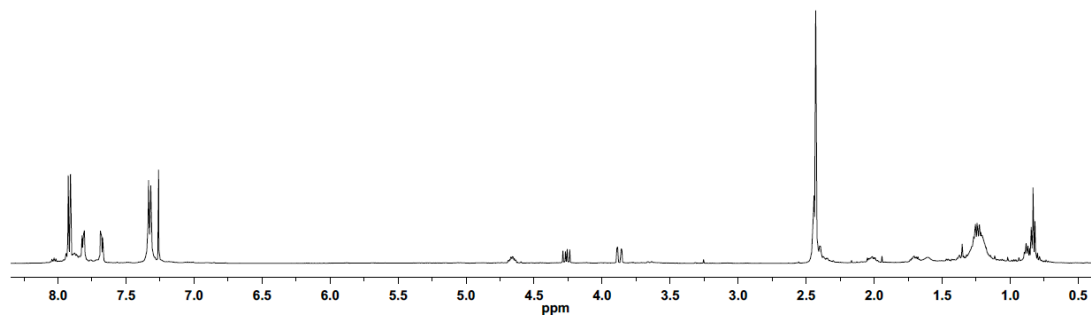
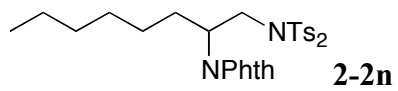


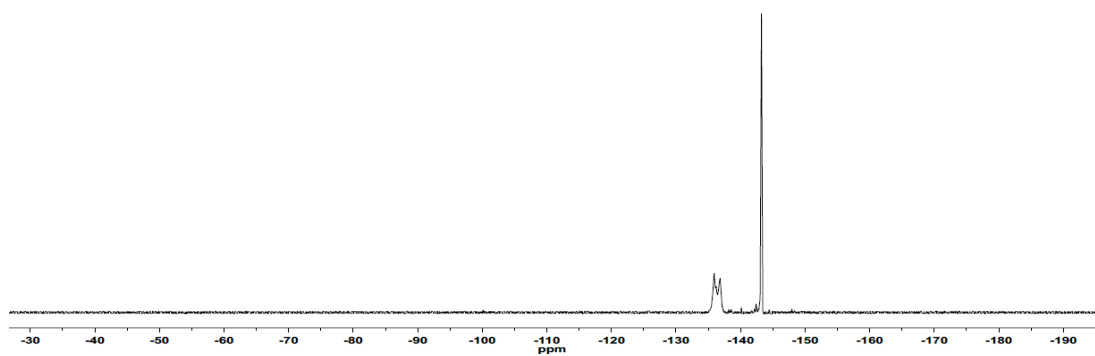
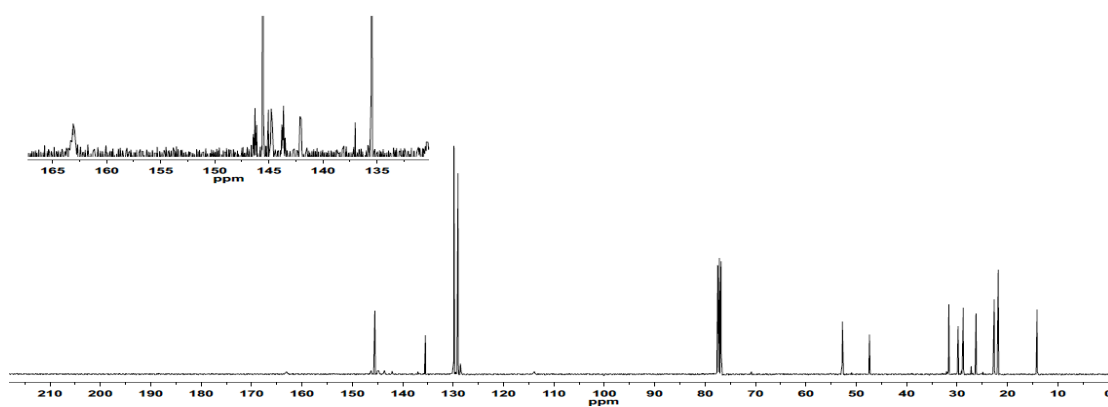
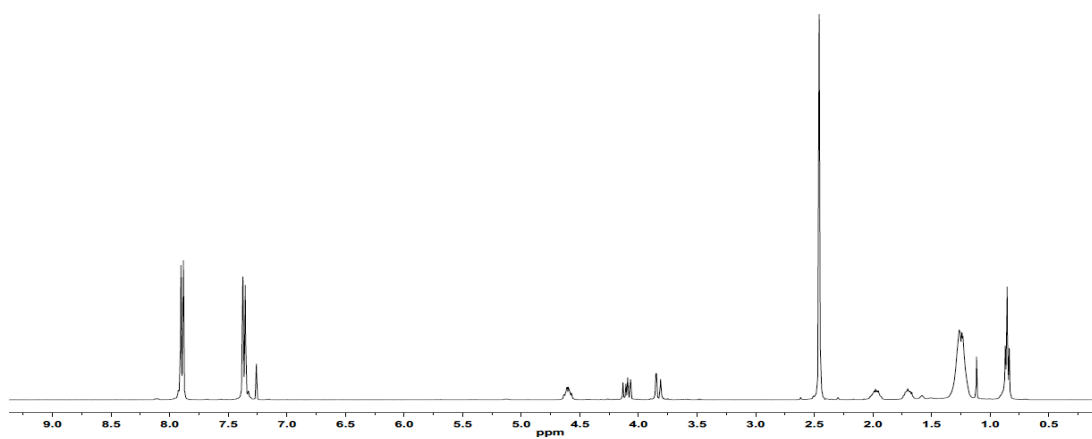
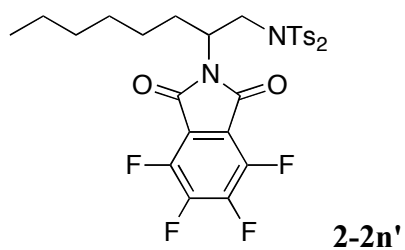


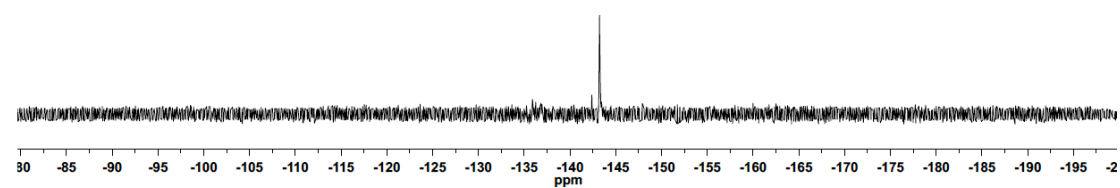
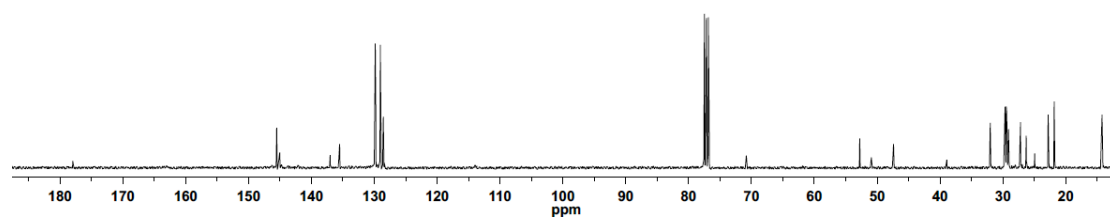
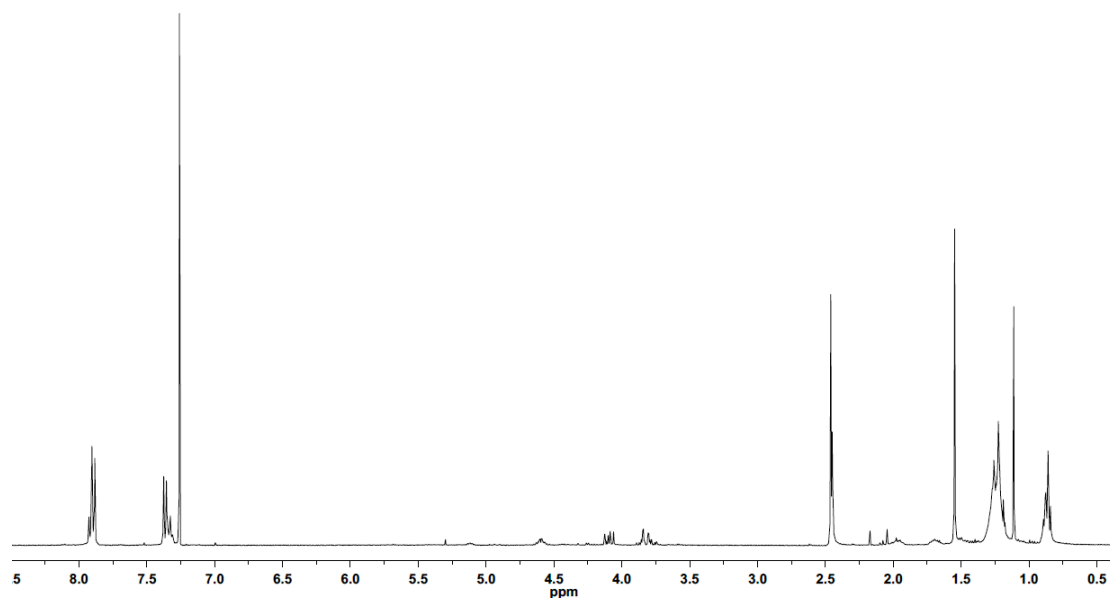
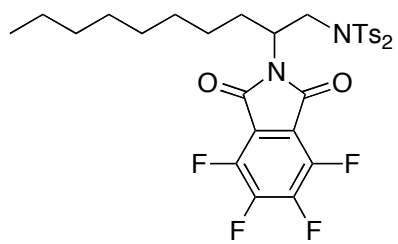


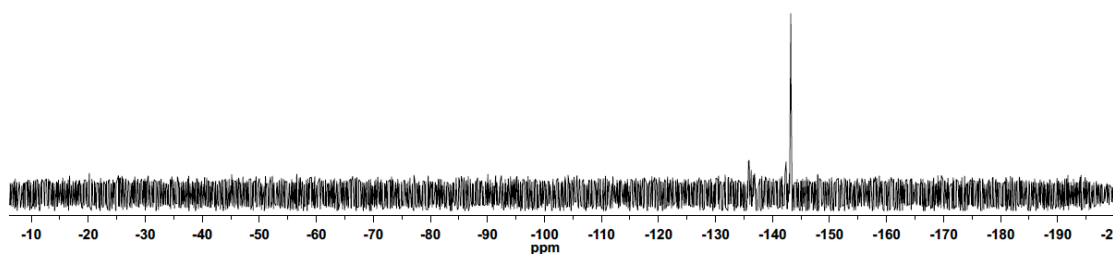
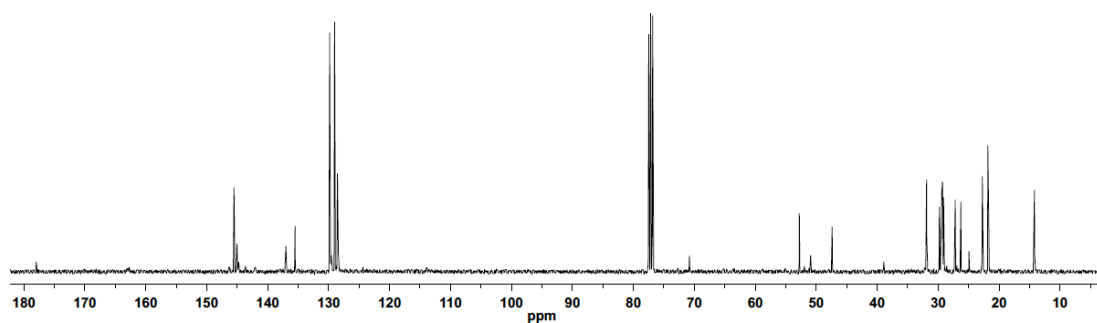
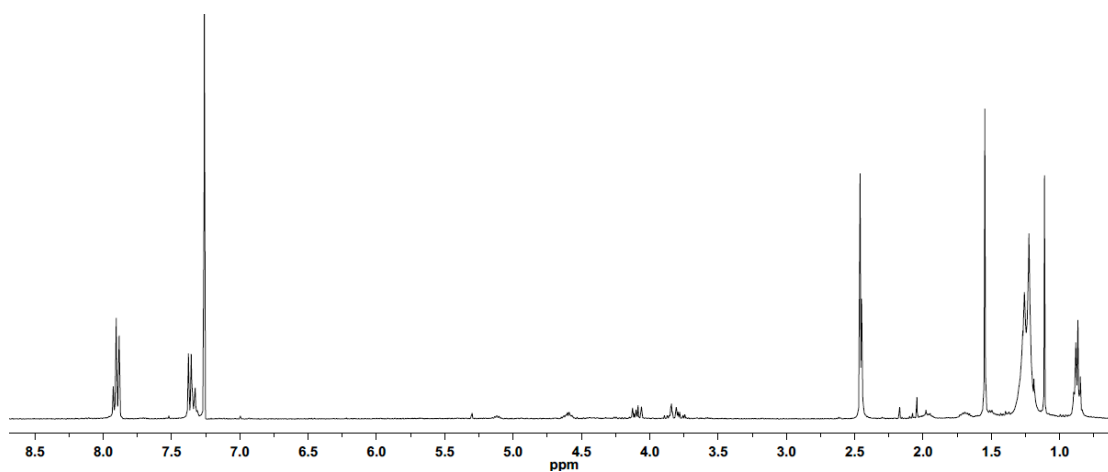
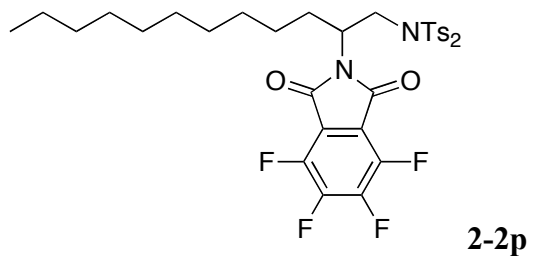


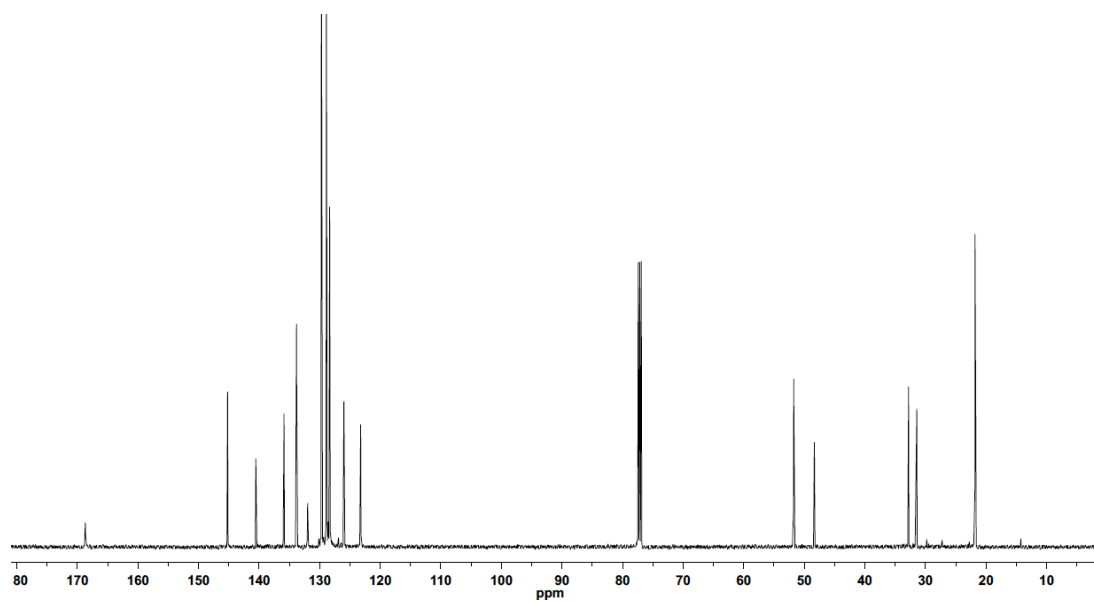
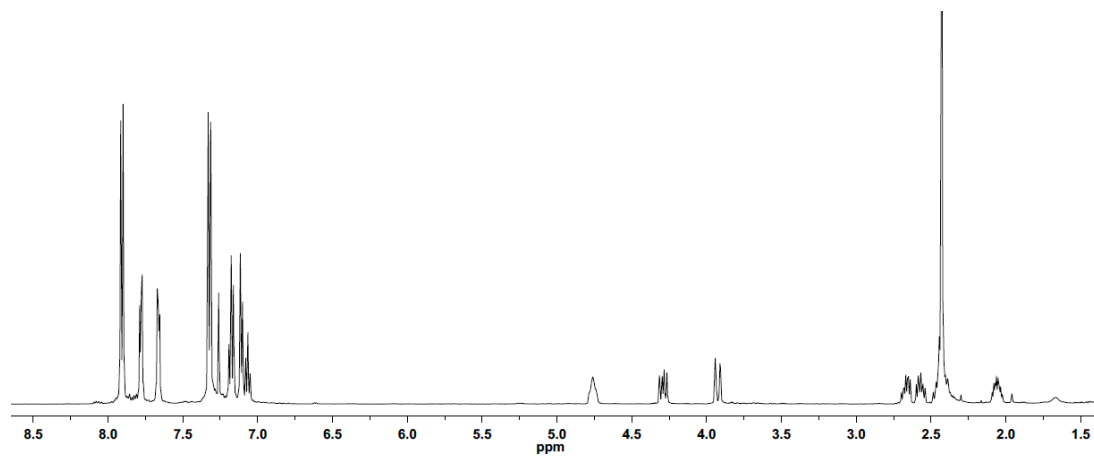
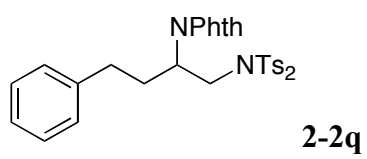
Reproduction of selected NMR spectra

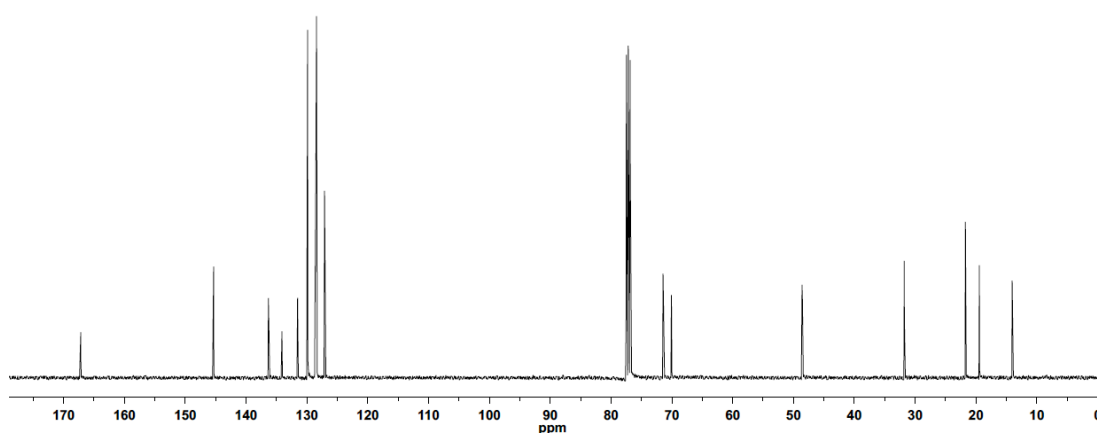
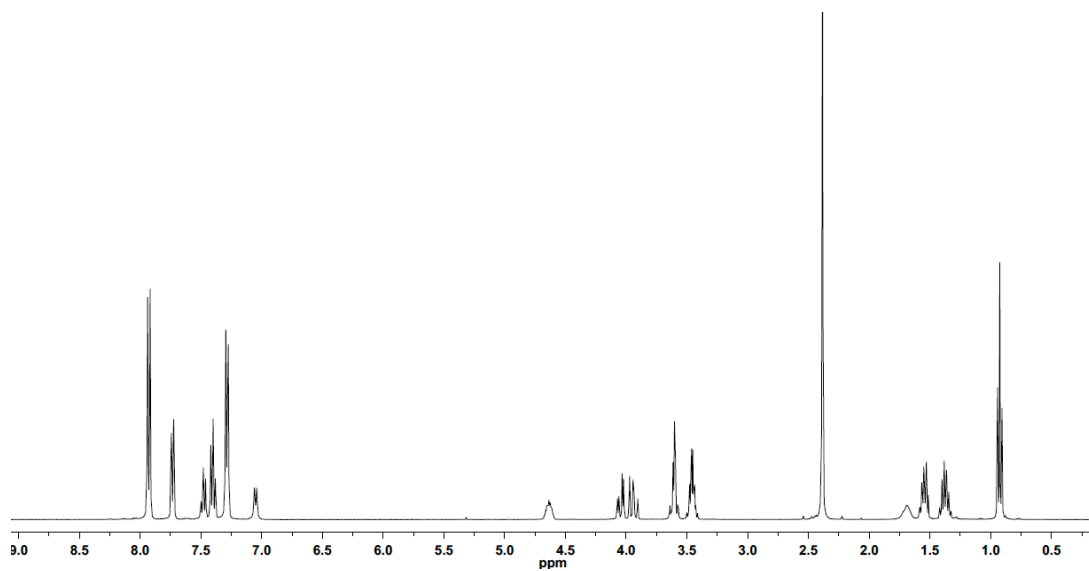
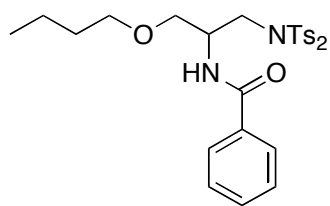


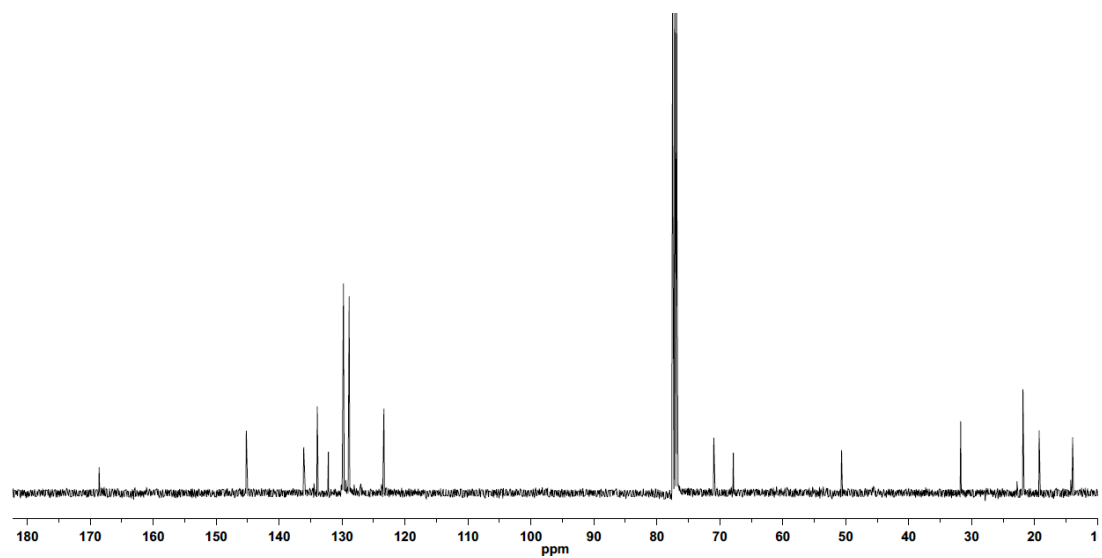
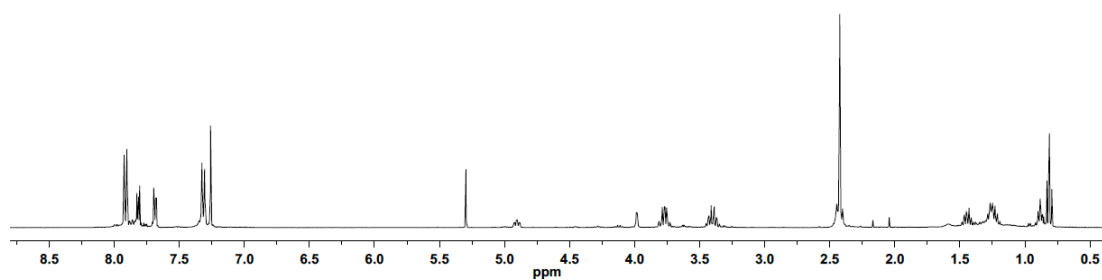
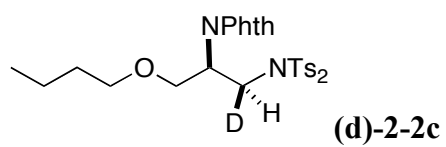


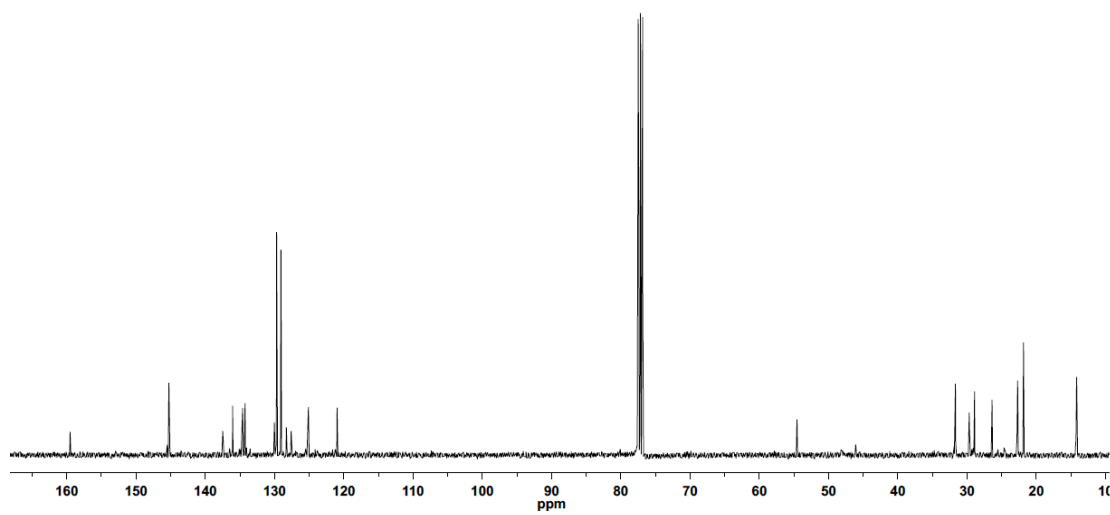
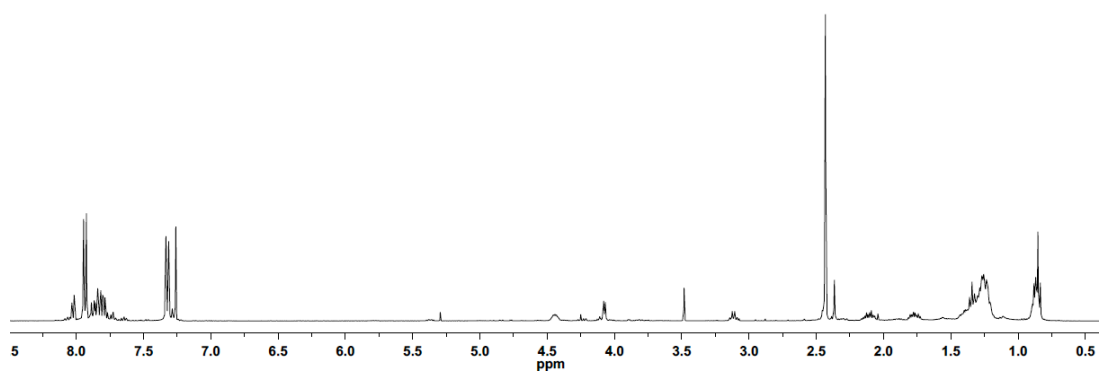
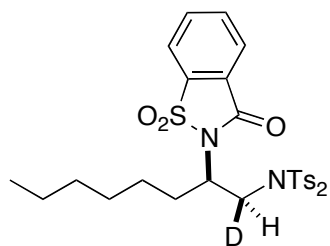




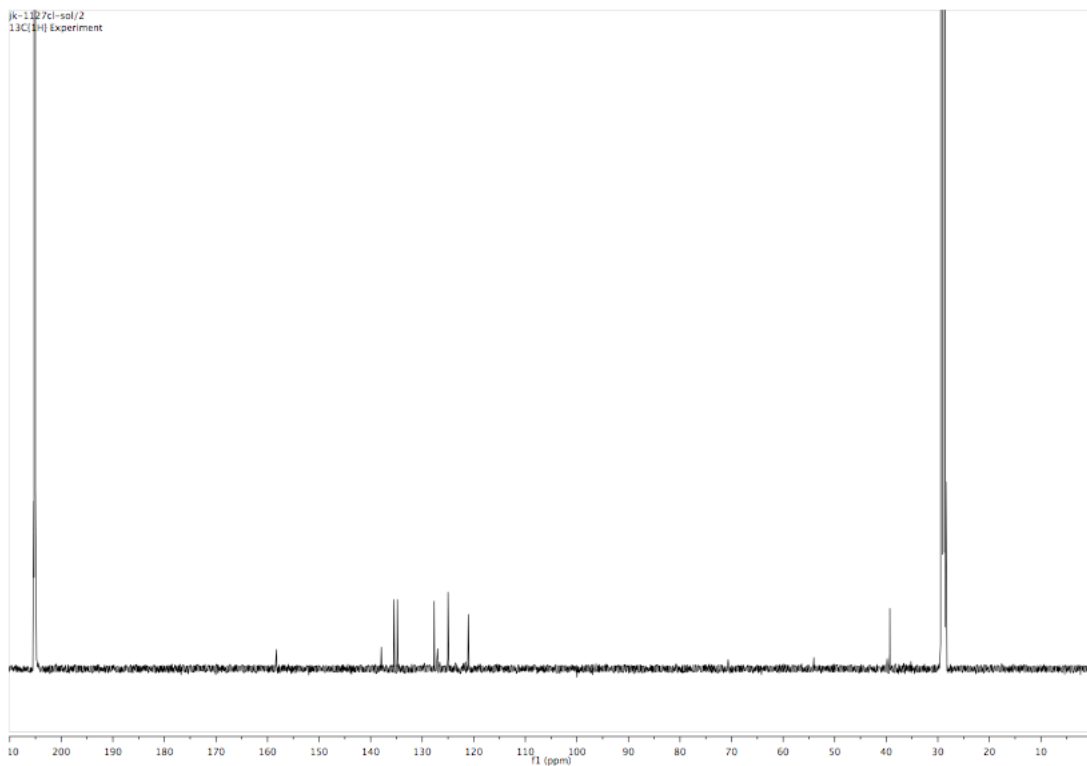
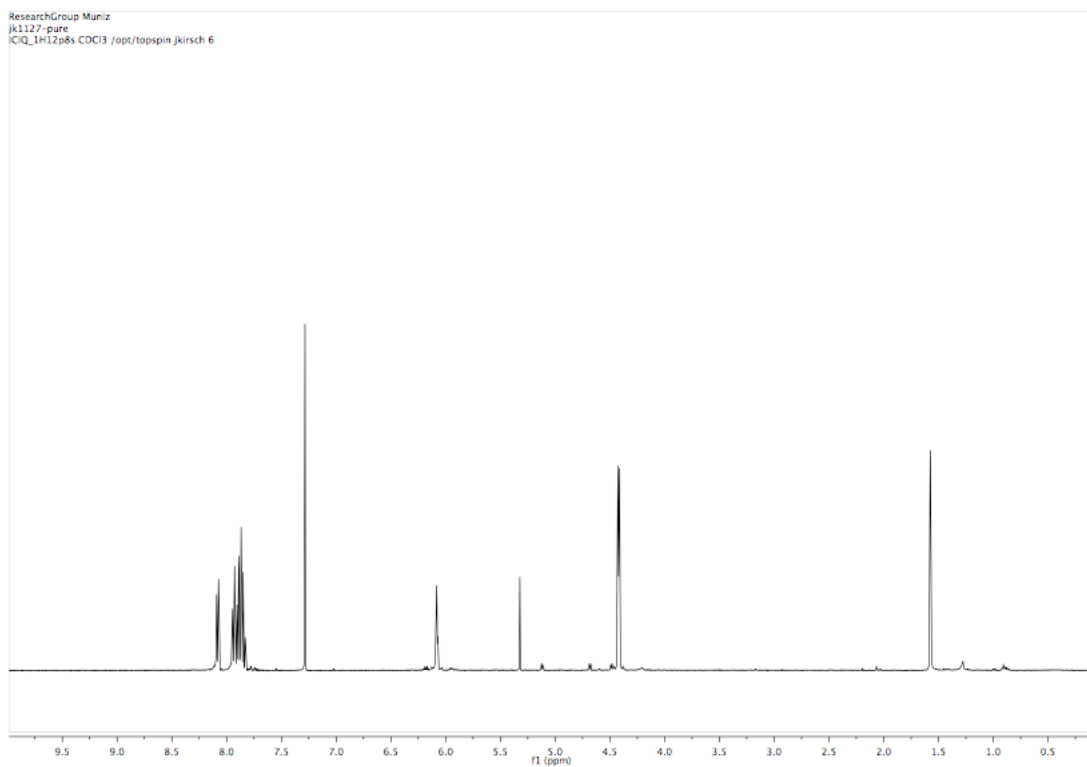
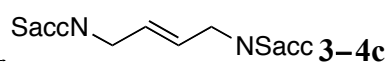


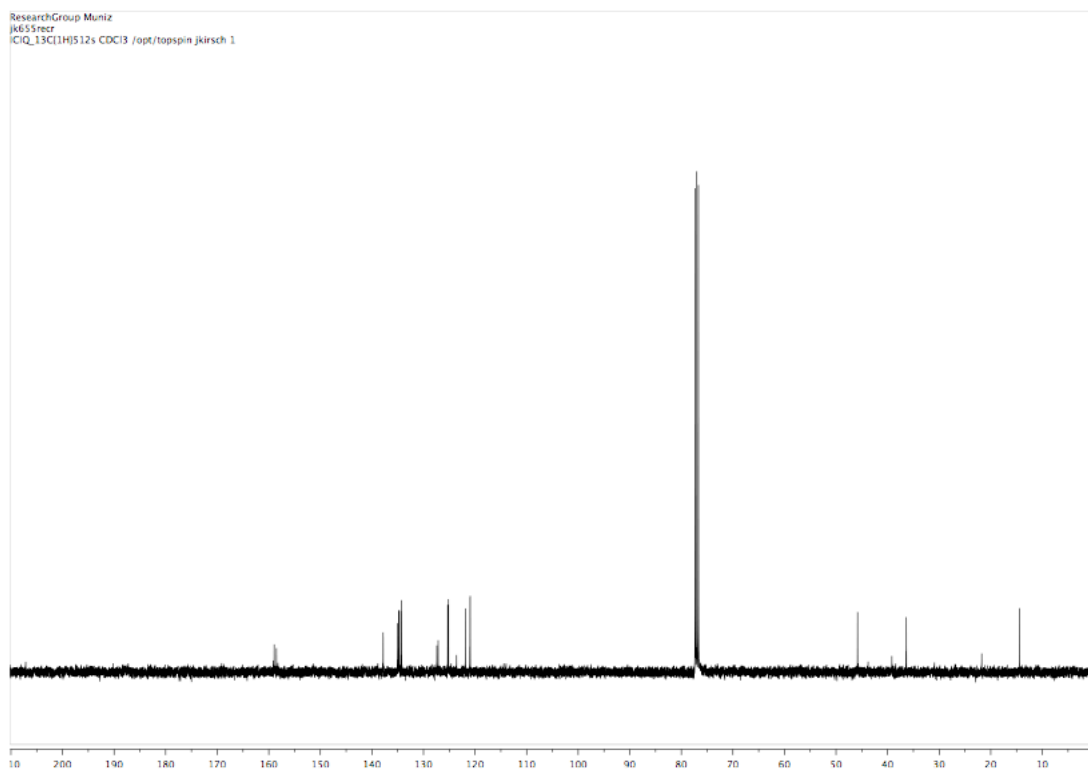
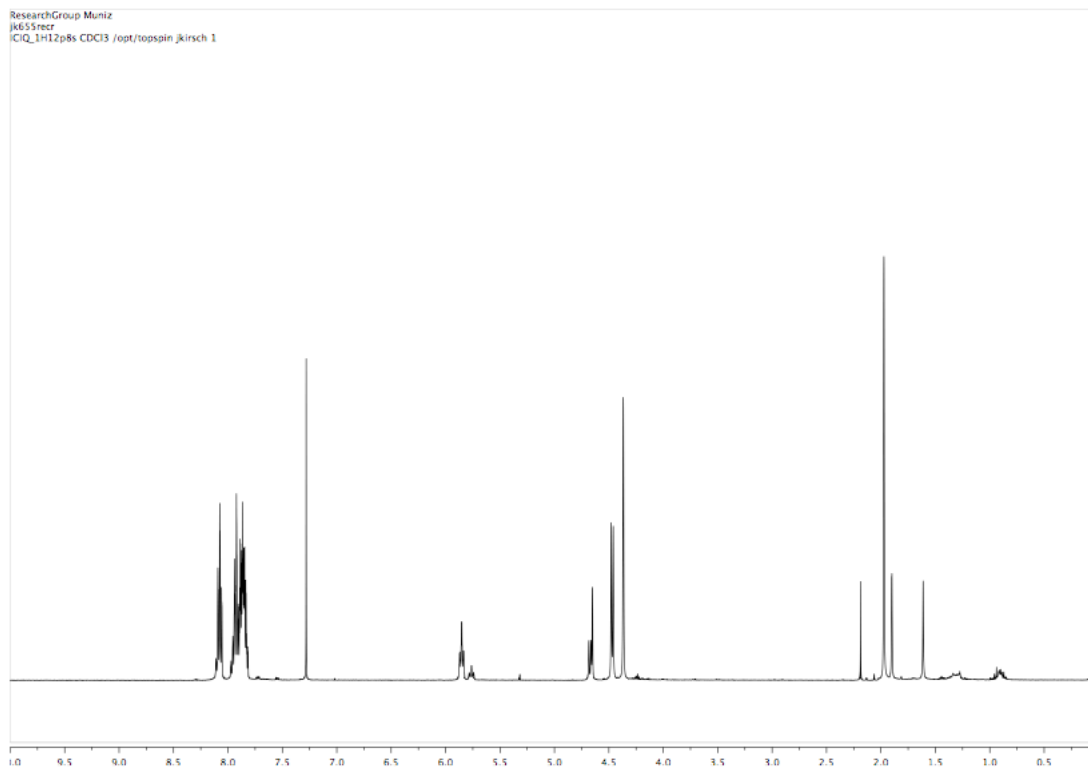
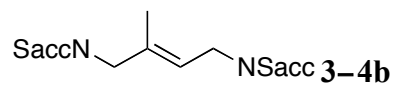


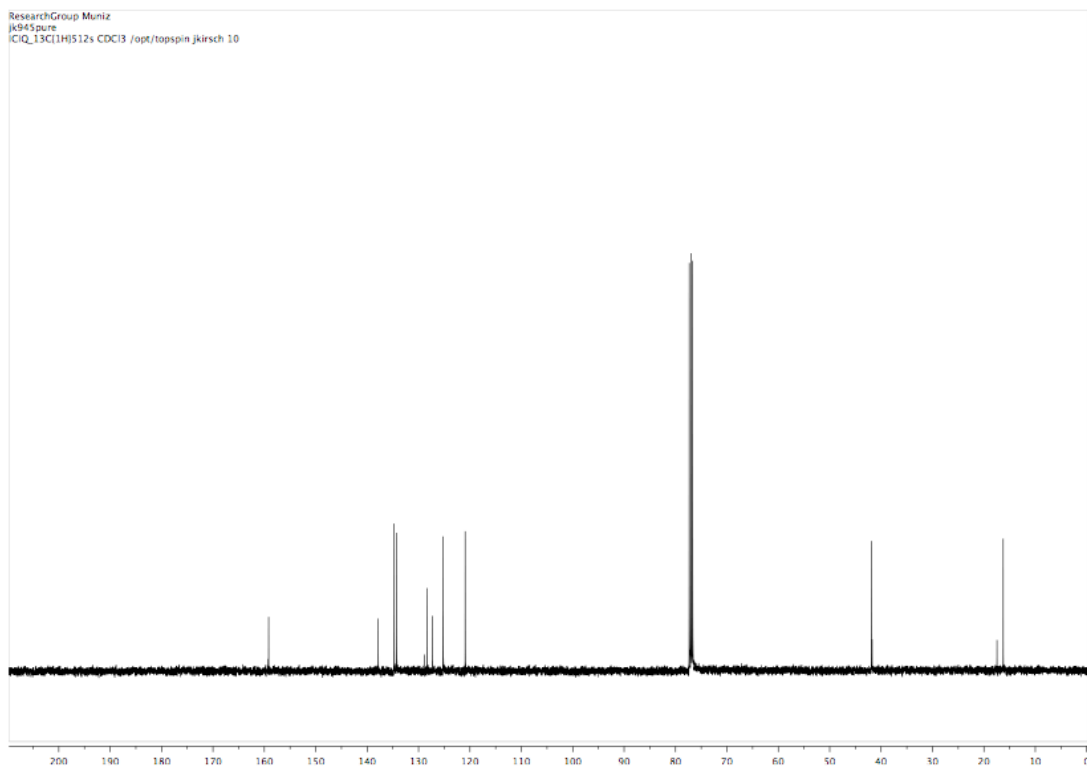
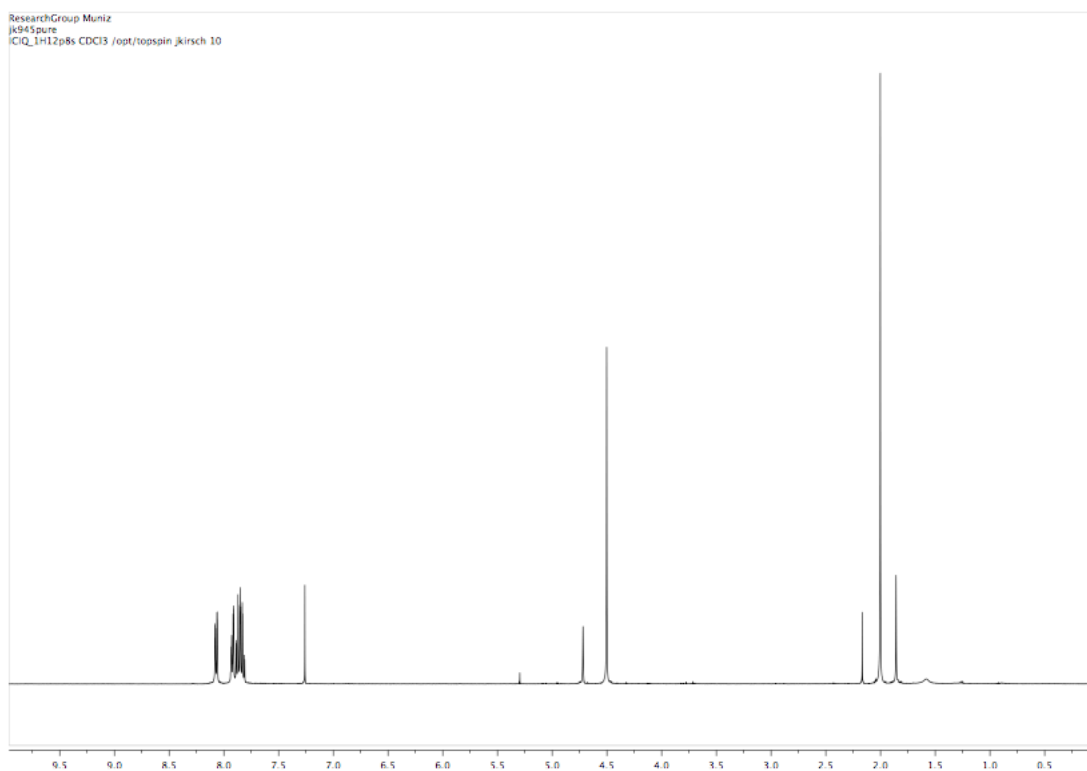
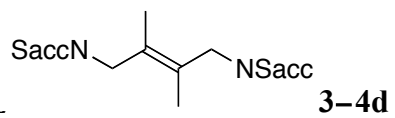


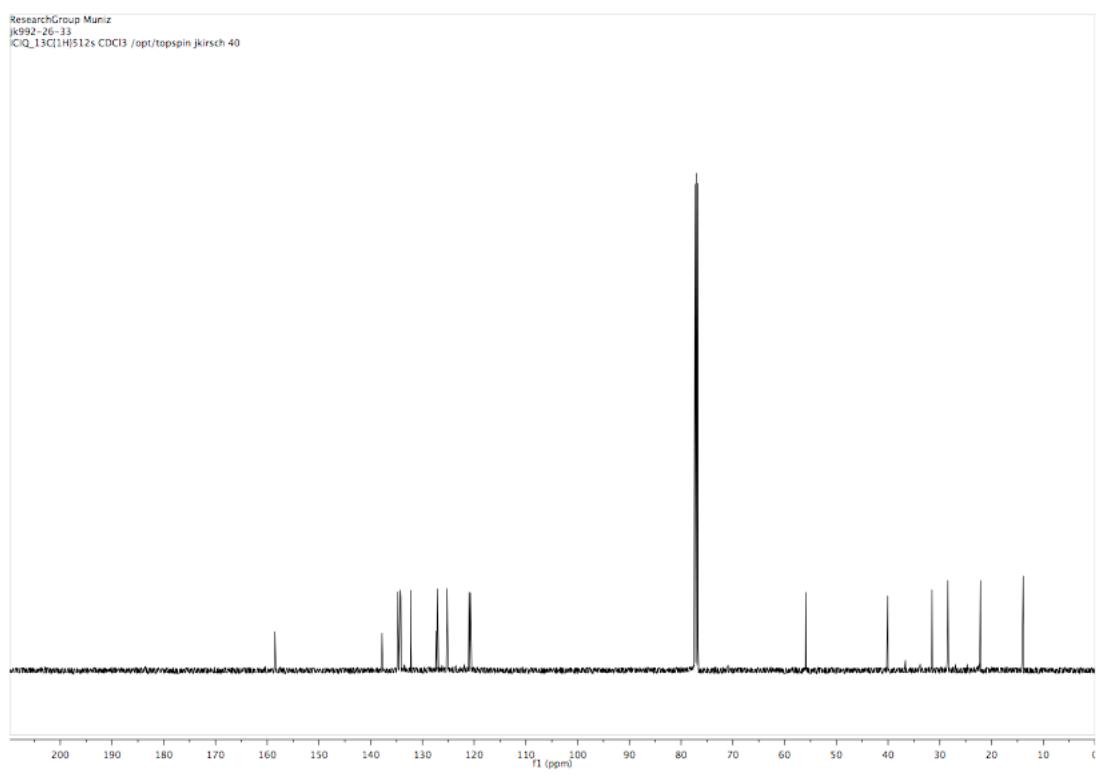
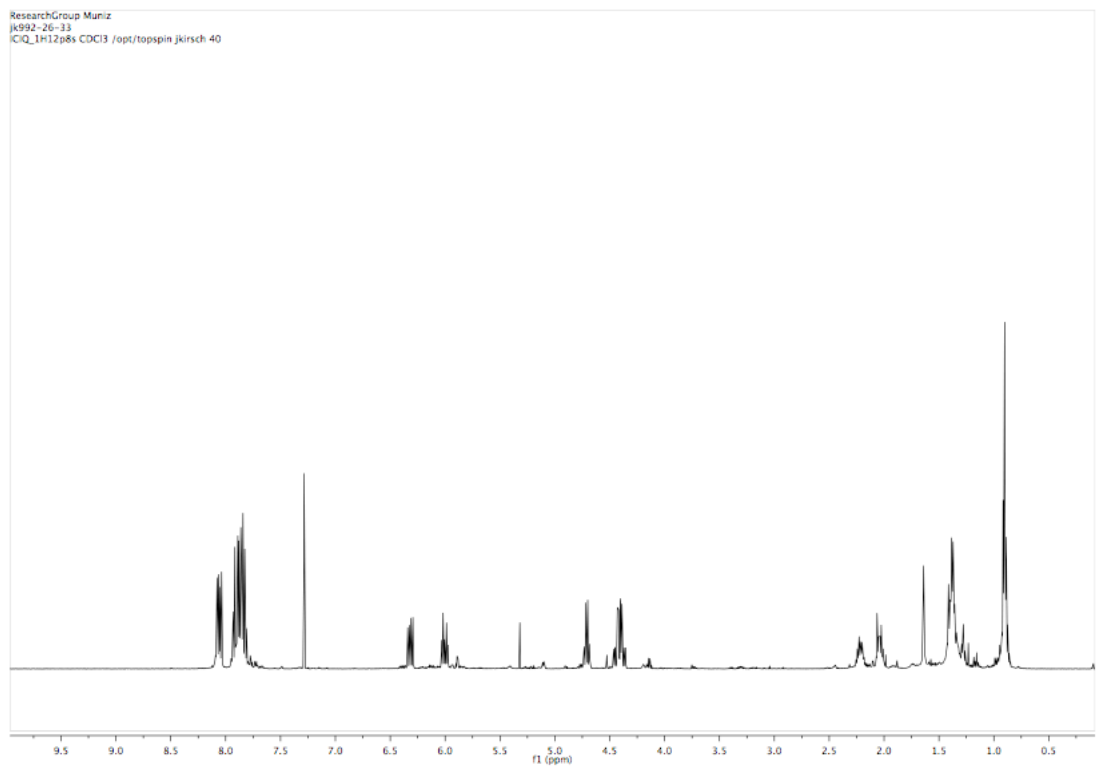
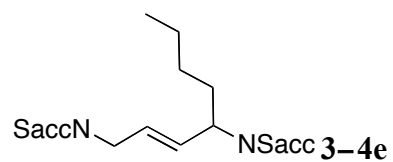


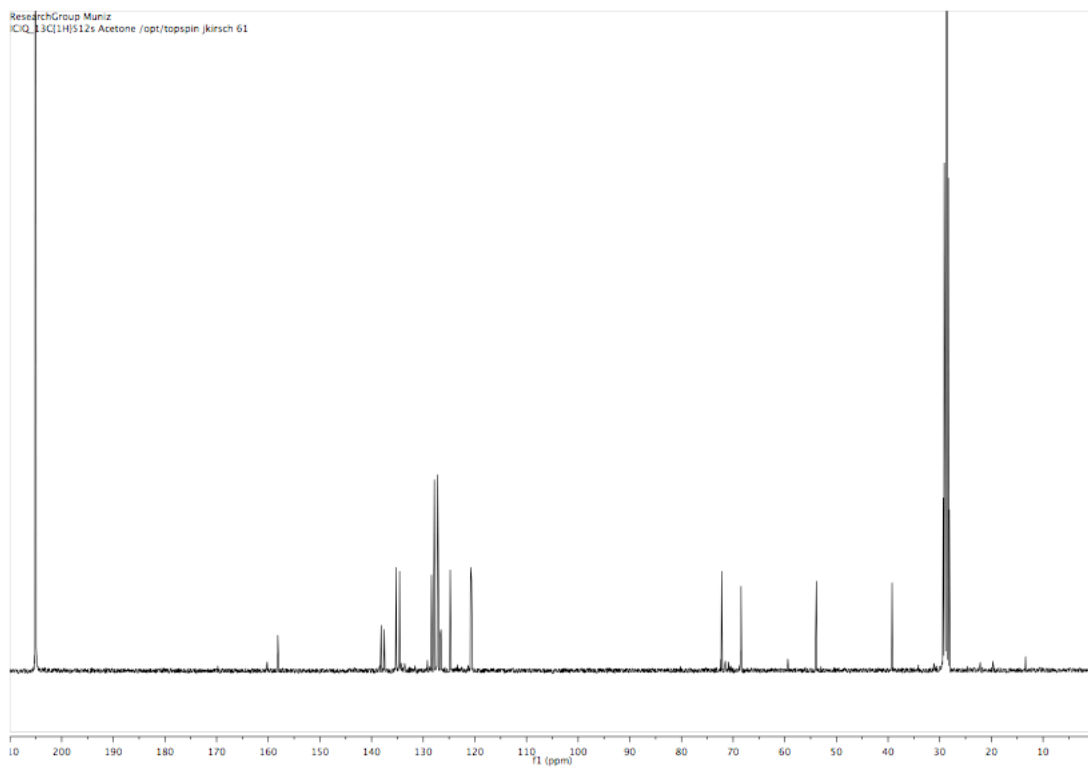
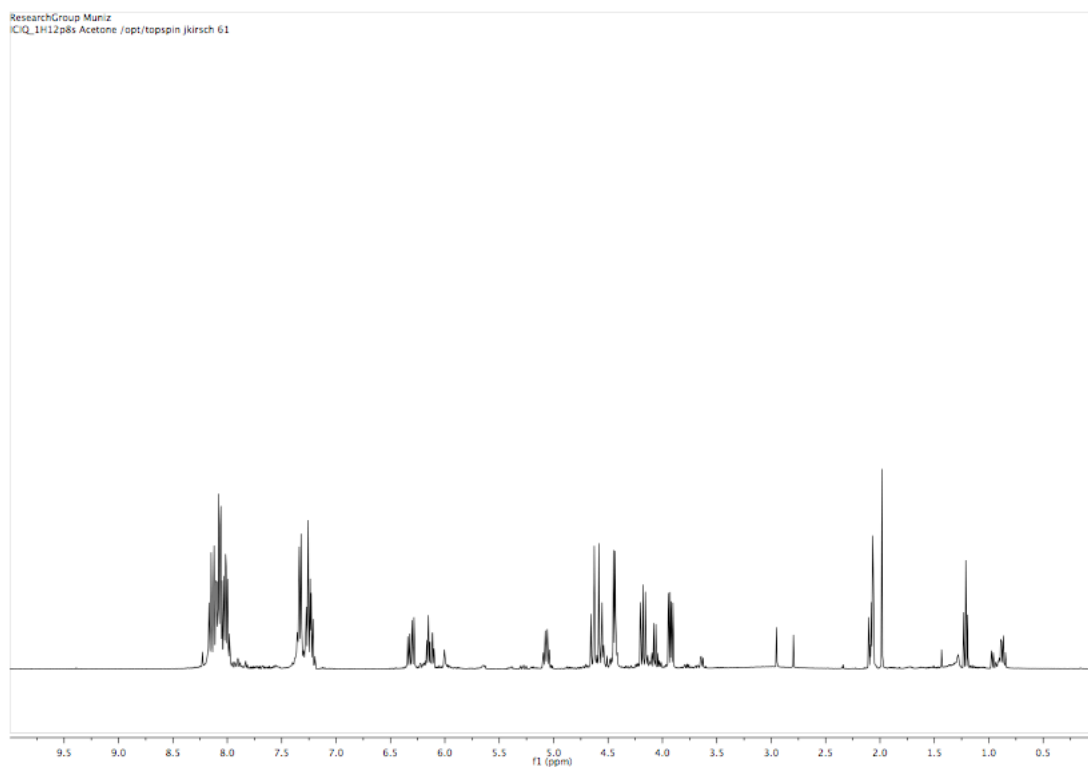
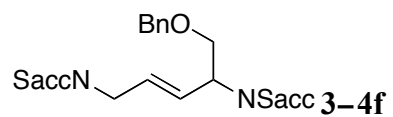
Chapter III: The First General 1,4-Diamination of Dienes

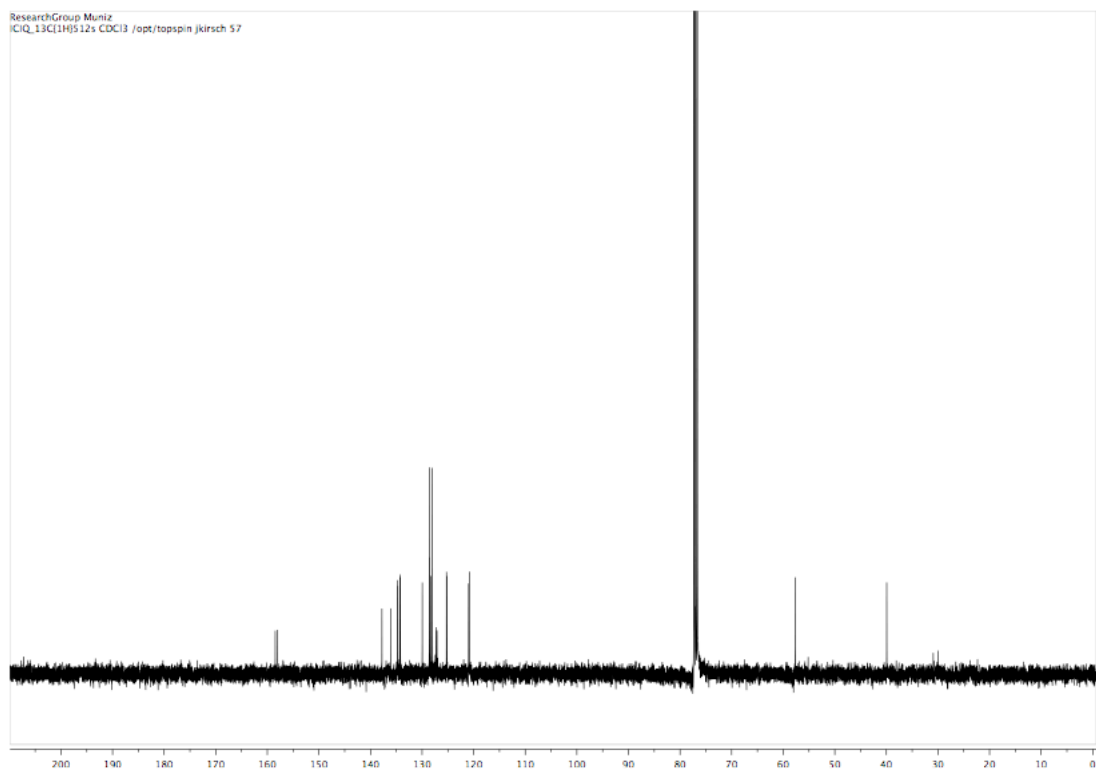
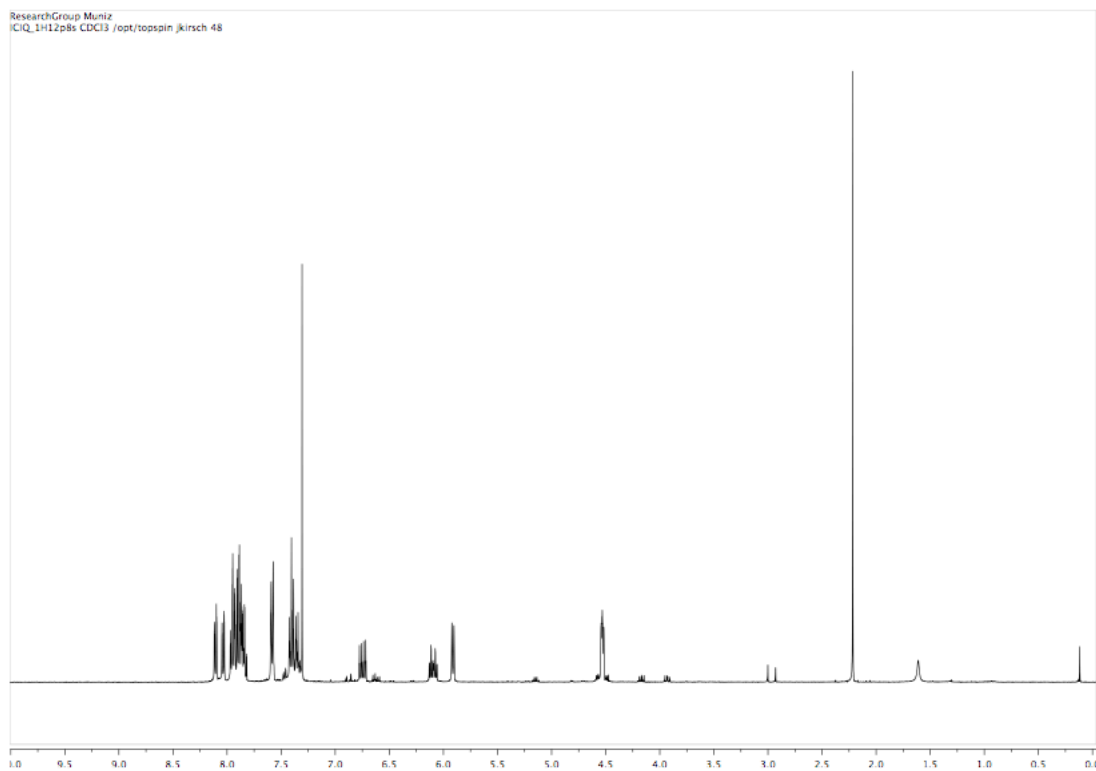
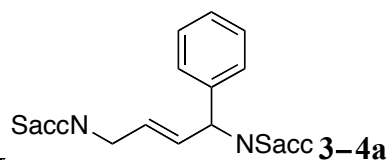


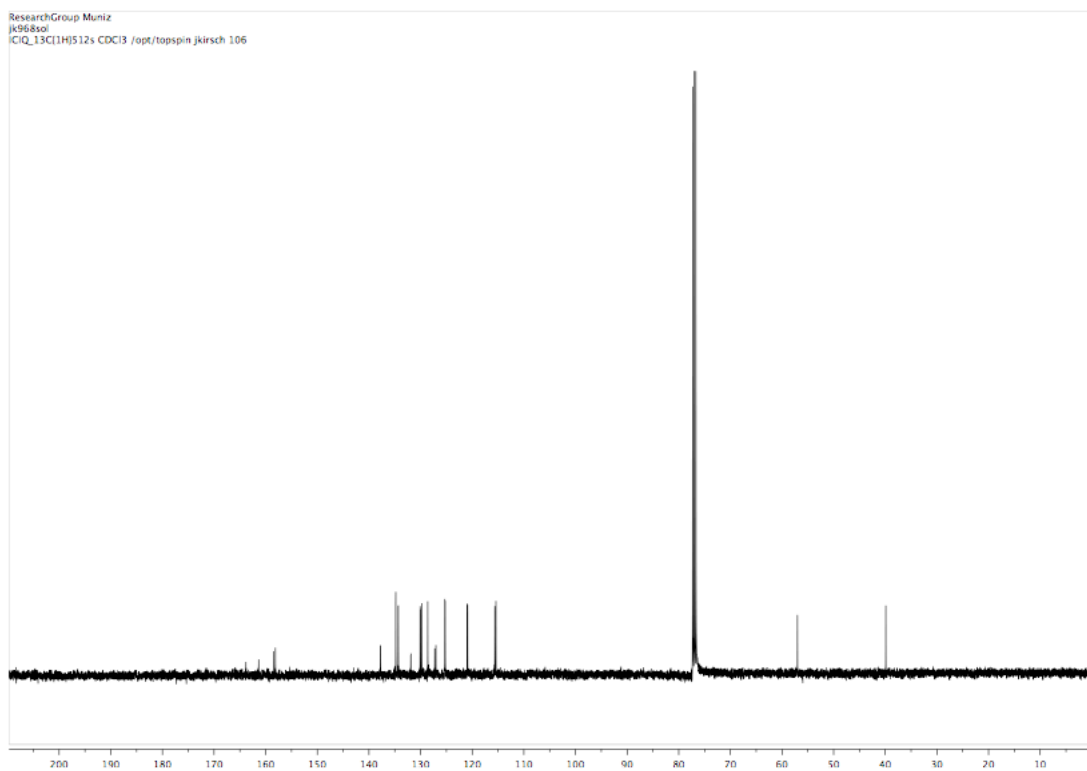
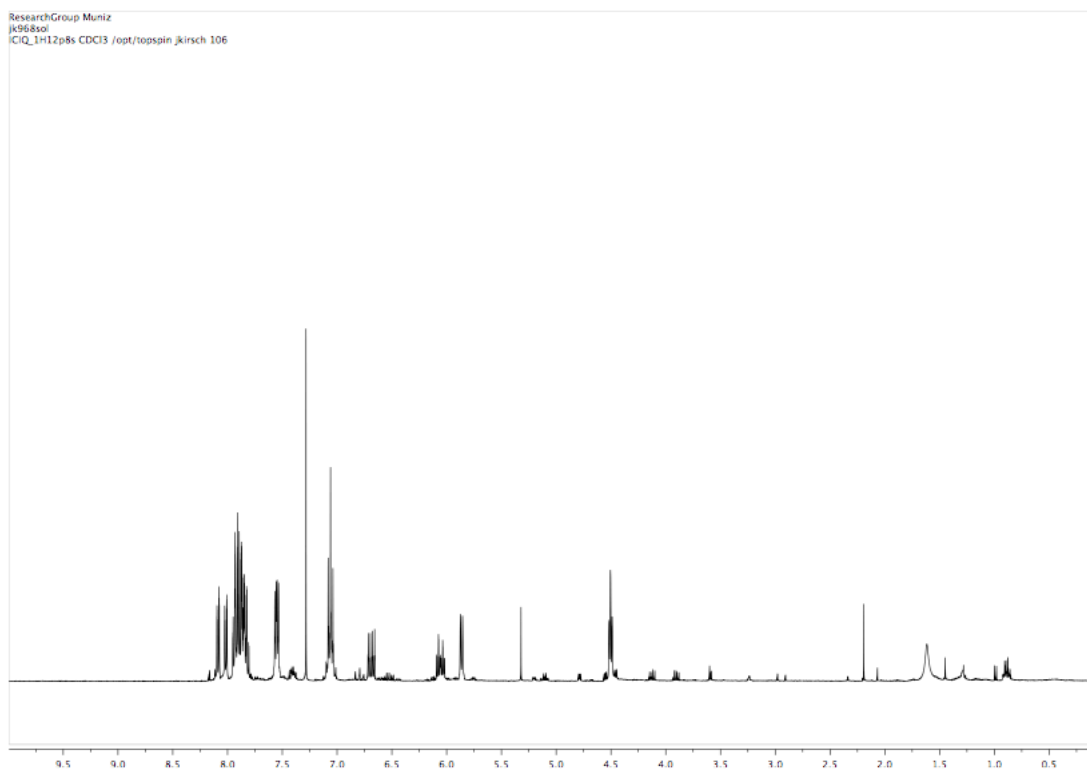
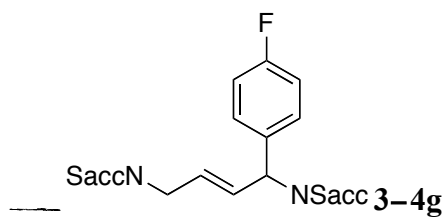


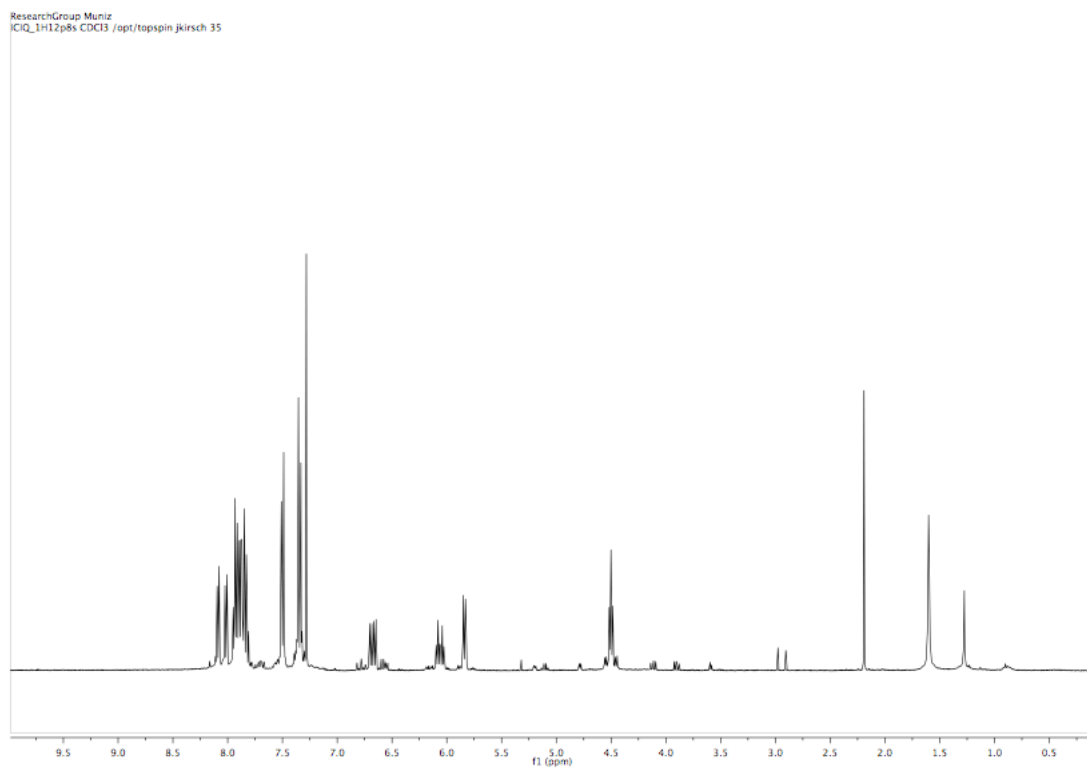
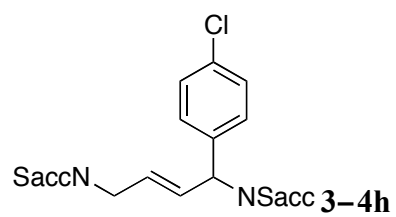


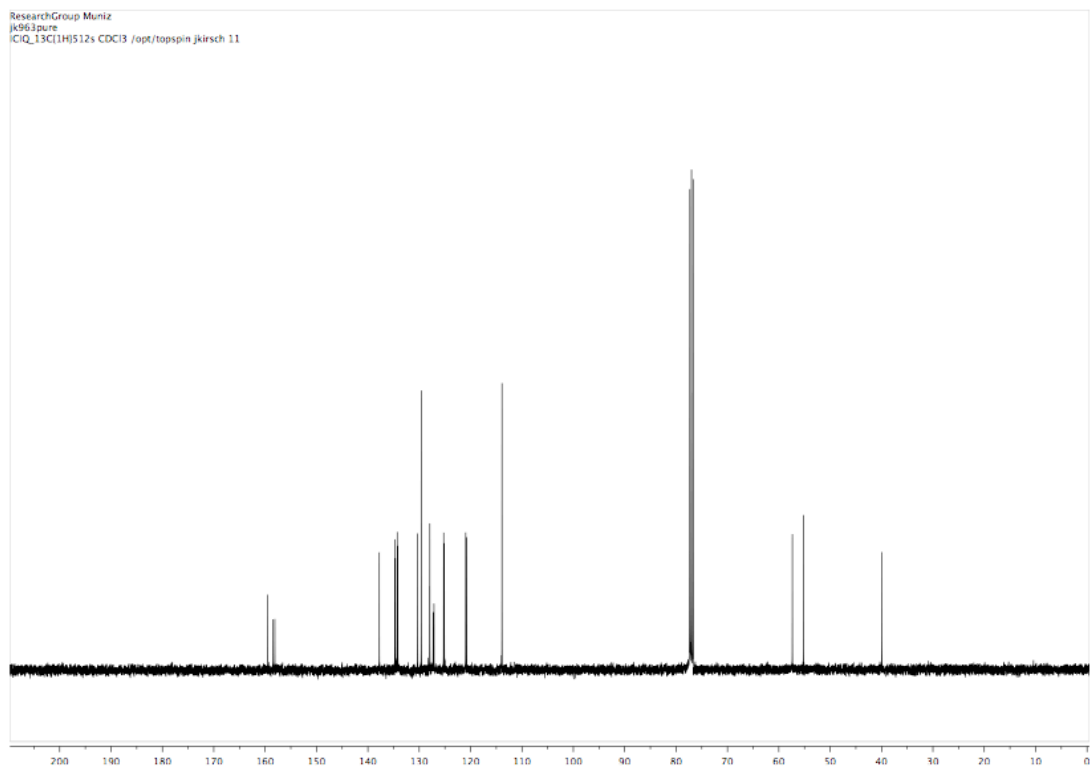
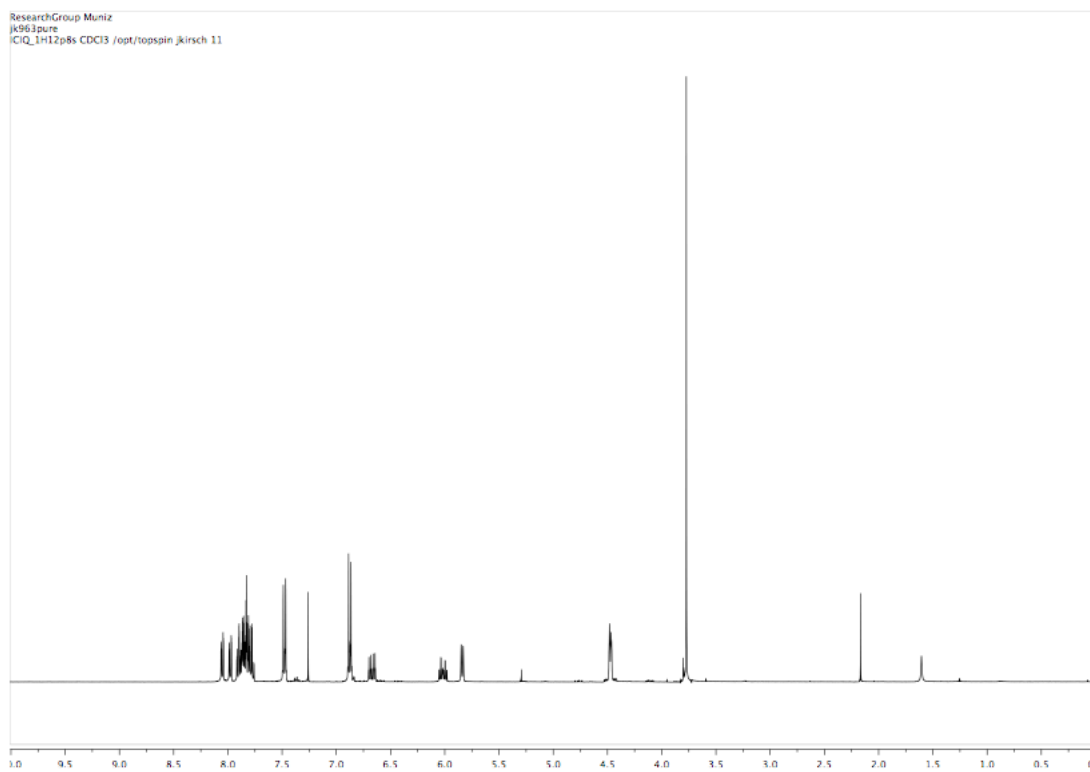
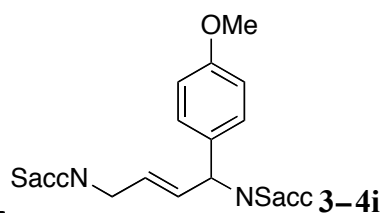


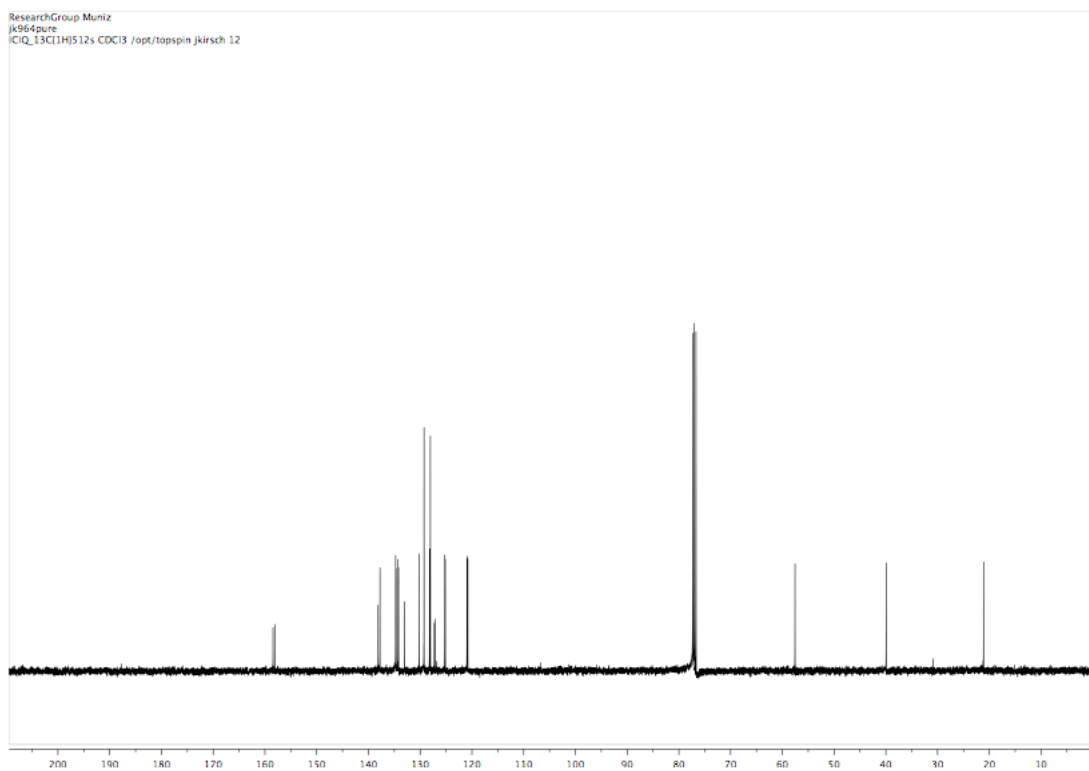
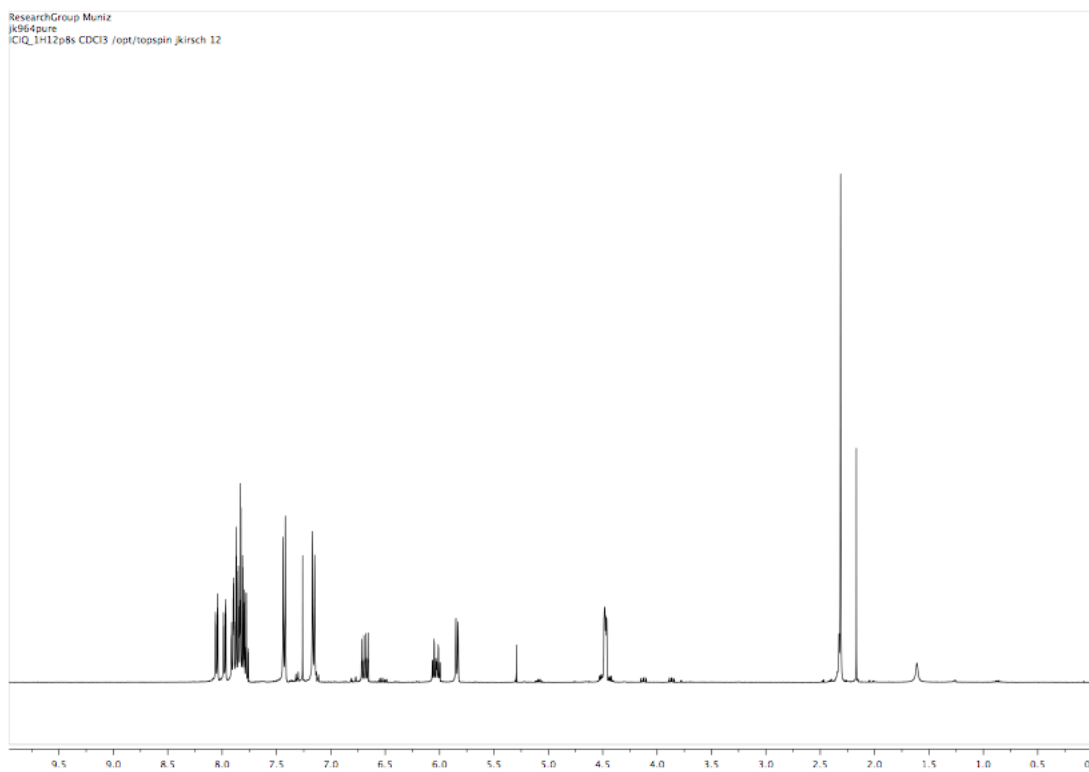
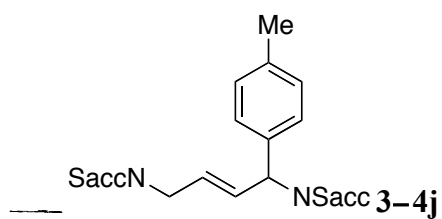


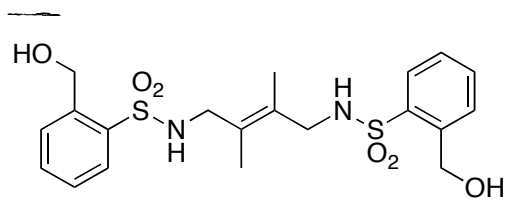




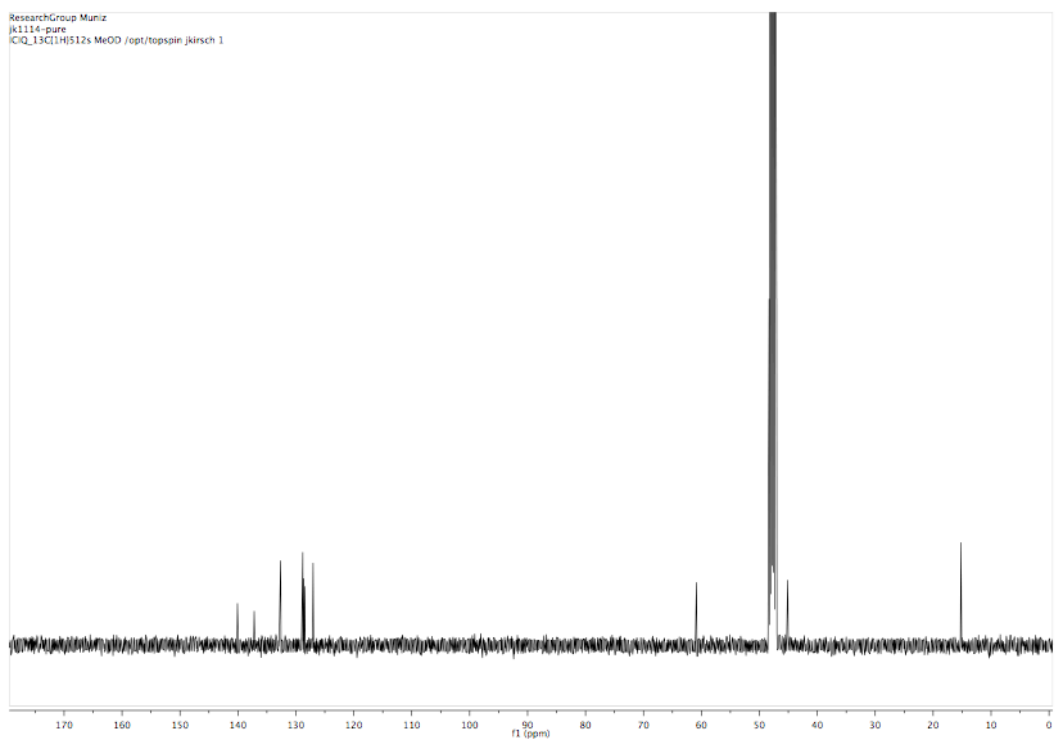
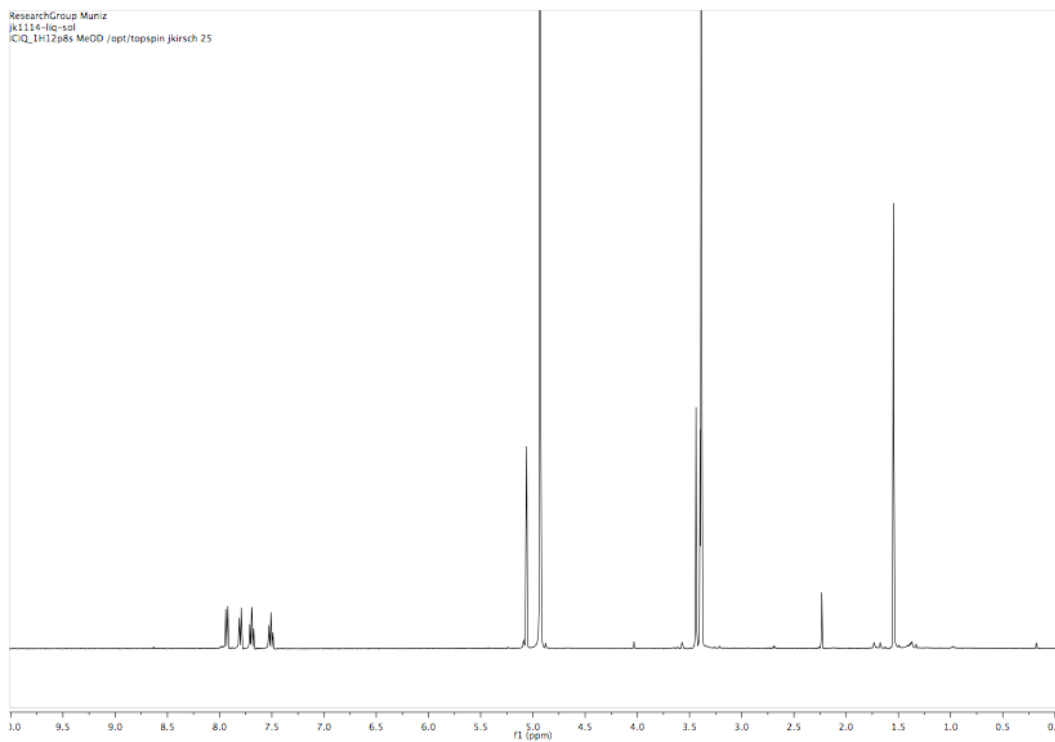


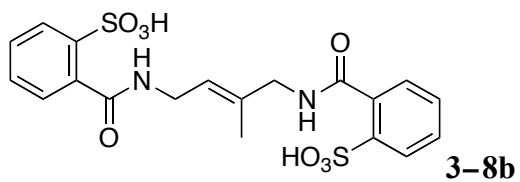




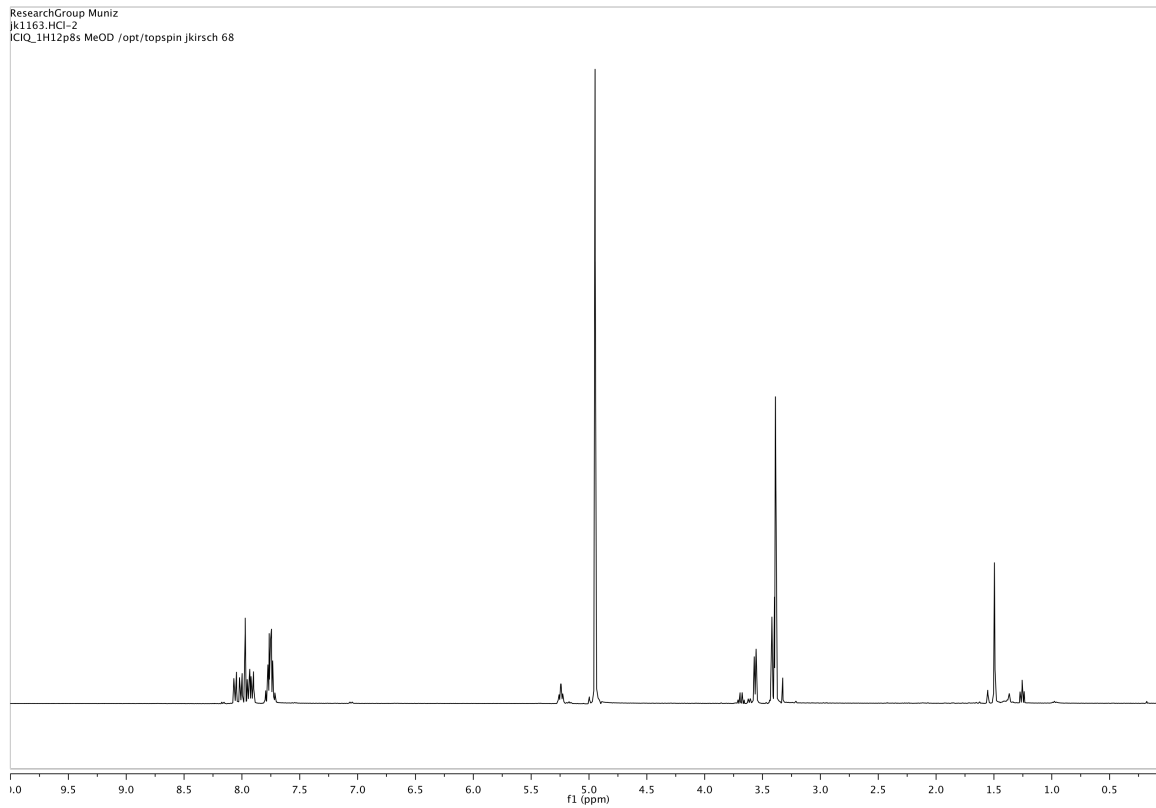


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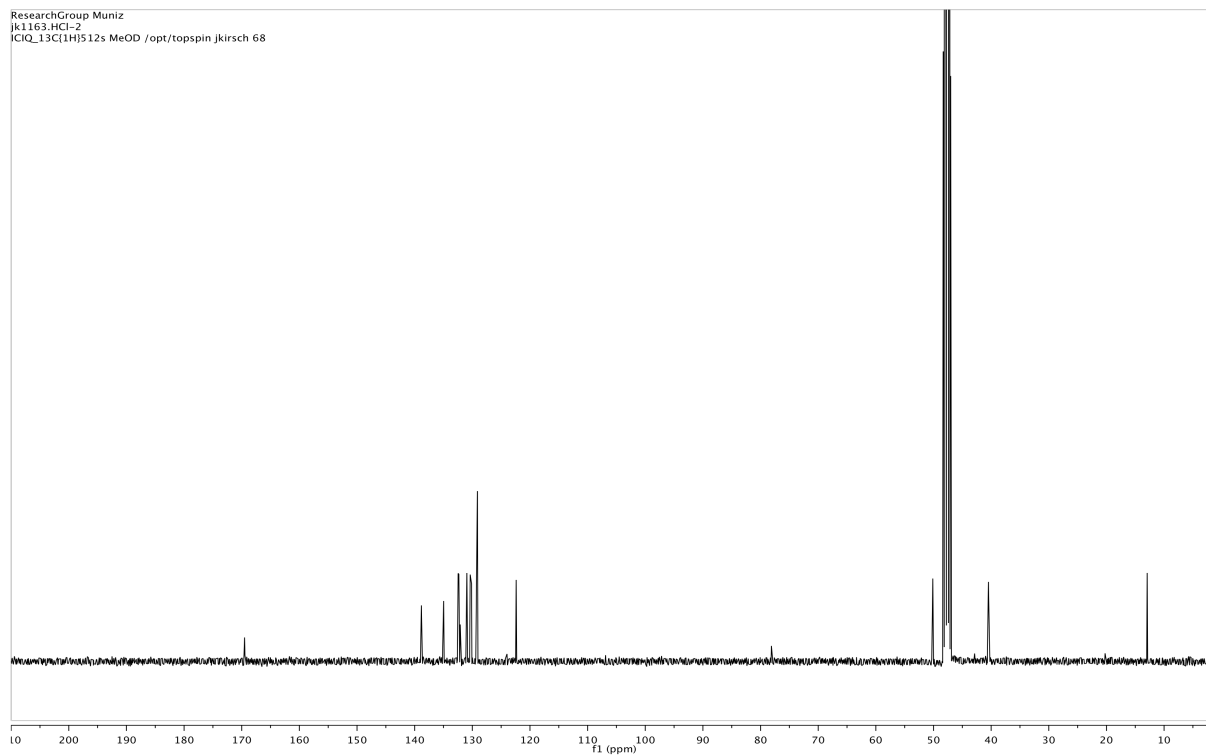




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Curriculum Vitae

PhD – Student

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EDUCATION :

2009-2012 : PhD under the Co-direction of Prof. Dr. Kilian Muñiz ICIQ (Institut Català d'Investigació Química) - Tarragona – Spain and Dr. Pierre Braunstein UDS - France. Working on Homogeneous Catalysis.
2008-2009 : Master 2 of Molecular and Supramolecular Chemistry - Université De Strasbourg. (France)
2007-2008 : Chemistry Agregation – ULP - **Accepted.**
2006-2007 : Chemistry Agregation (competitive examination to be a teacher) - ENS LYON - Eligible.
2005-2006 : Master 1 of Molecular and Supramolecular Chemistry - ULP.
2004-2005 : Licence 3 of Chemistry - ULP (Université Louis Pasteur - France).
2002-2004 : Preparation for national competitive entrance exams to leading French "grandes écoles", specializing in chemistry and physics.- Lycée Fabert – Metz. Eligible to the “Concours Communs Polytechniques”.
2001-2002 : Bachelor in Science. Speciality: Mathématiques – Lycée Teyssier – Bitche (Moselle - France).

RESEARCH TRAINING

2005 – 2007 Internship with Dr. Pierre Braunstein at University Louis Pasteur, Strasbourg, France, working on Organometallic Complexes (18 months).

POSTER PRESENTATION

“Palladium Catalysed Intermolecular 1,2-diamination of Alkenes”

J.Kirsch, P. Chávez, A. Iglesias, E. Perez, K. Muñiz, 2nd China-Spain Bilateral Symposium on Catalysis, ICIQ, Tarragona. November 22-24, 2010

“Transition Metal-Catalysed Oxidative 1,2-Diamination of Alkenes“

J.Kirsch, P. Chávez, A. Iglesias, E. Perez, K. Muñiz, XXXIII Reunion Bienal De La RSEQ – Valencia. July 25-28, 2011.

PUBLICATIONS

1. "Intermolecular Regioselective 1,2-Diamination of Allylic Ethers."

Muñiz K., **Kirsch J.**, Chávez P. *Adv. Synth. Catal.* **2011**, 353, 689.

2. "Intramolecular Diamination of Acrylic Ester Using Sulfamates as Nitrogen Source."

Chávez P., Streuff J., **Kirsch J.**, Muñiz K. *J. Org. Chem.*, **2012**, 77, 1922.

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4. "General Palladium-Catalysed Intermolecular Diamination."

J. Kirsch, C. Martinez, K. Muñiz, *submitted*.

5. " NHC Gold(III) Triflimidate Complexes. "

B. Jacques, **J. Kirsch**, P. de Frémont, P. Braunstein, *submitted*.

REFERENCES

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Résumé

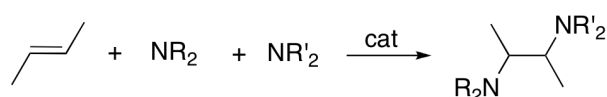
Introduction :

La conversion directe d'alcènes en 1,2-diamines vicinales représente un vrai défi dans le monde de la chimie. En effet les diamines constituent un groupement fonctionnel présent dans de nombreux produits naturels, dans des molécules d'intérêt pharmaceutique et biologique, ainsi que dans de nombreux complexes métalliques et catalyseurs.

L'omniprésence de ce groupement fonctionnel explique aisément l'intérêt qui lui est porté, ainsi que les nombreux travaux de recherche qui lui sont consacrés, dont celui développé au cours de ma thèse.

Objectif :

L'objectif de ma thèse est donc le développement de nouvelles réactions catalytiques d'oxydation directe des alcènes en composés diaminés :



Il s'agit donc de déterminer des conditions de réaction permettant la mise en place de cette réaction, puis d'étudier la régiosélectivité ainsi que la stéréosélectivité de la formation de ces diamines ainsi que les mécanismes de ces réactions.

Mais avant de débiter les recherches sur la version intermoléculaire de la diamination, nous nous sommes attachés à finir tout d'abord en grande partie la version intramoléculaire.

1.) Point de départ : la fin de la diamination intramoléculaire

1.1) Avancement des recherches du Laboratoire avant ma thèse

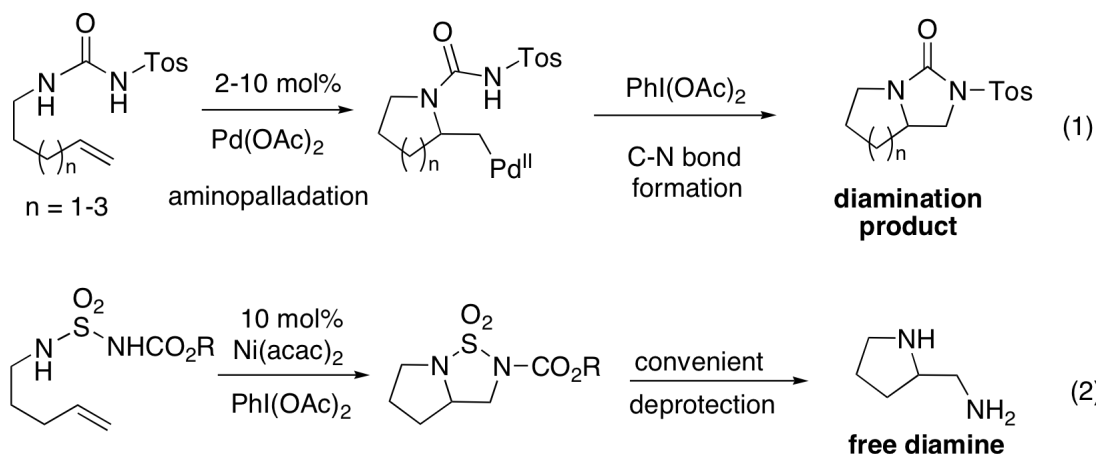
Le développement de la diamination est basé sur de nombreux travaux antérieurs stipulant que cette réaction fonctionne mais au prix de l'utilisation stœchiométrique de métaux, ceci pouvant s'expliquer par :

- un potentiel de réoxydation excessif (Thallium)
- un problème de régénération du catalyseur dû à la chélation des diamines formées (Palladium, Osmium).

Pour contrecarrer ce dernier problème, la solution fut d'utiliser des amides liés entre eux durant la réaction de diamination ce qui a permis d'aboutir à la diamination catalytique intramoléculaire.

En effet au cours de ces dernières années, le laboratoire de K. Muñiz a décrit plusieurs réactions de diamination catalytiques d'alcènes, basées sur l'utilisation de Palladium(II) comme catalyseur, combiné avec $\text{PhI}(\text{OAc})_2$ comme oxydant pour fournir des urées cycliques^{1,2} (Schéma 1, eq. 1) et des guanidines cycliques.³ Ce procédé sans précédent consiste en une réaction en 2 étapes: premièrement une aminopalladation⁴ suivie directement d'une formation de liaison $\text{Csp}^3\text{-N}$ par l'intermédiaire d'un complexe de Pd(IV). L'utilisation par la suite d'un catalyseur de Nickel(II) a permis de mettre en œuvre un protocole pour la diamination utilisant des sulfamides comme source d'azote, plus faciles à déprotéger afin d'obtenir les diamines libres (Schéma 1, eq. 2).⁵ Ces diamines obtenues ont également donné lieu à une application en synthèse de produit naturel.⁶

Schéma 1



1.2.) L'évolution de la version intramoléculaire durant ma thèse

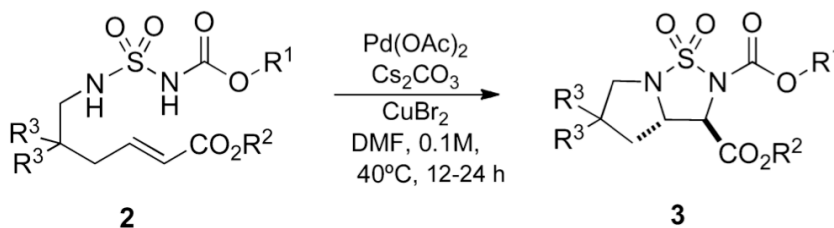
1.2.1.) Diamination catalytique des esters acryliques par des groupements sulfamides

La réaction de diamination d'esters acryliques avec les urées menant à des molécules tri-substituées, aux applications intéressantes⁶, et la déprotection aisée des sulfamides nous ont mené directement vers le prochain objectif : l'étude de la diamination d'esters acryliques en utilisant les sulfamides en tant que source d'azote.

Après avoir optimisé les conditions de cette réaction (Schéma 2),⁷ nous avons pu :

- mettre en valeur la portée de cette réaction grâce à de nombreux exemples (14)
- montrer l'utilité de ces molécules diaminées par une application en chimie des peptides
- proposer un mécanisme grâce à un intermédiaire réactionnel que nous avons isolé au cours de l'optimisation de la réaction.

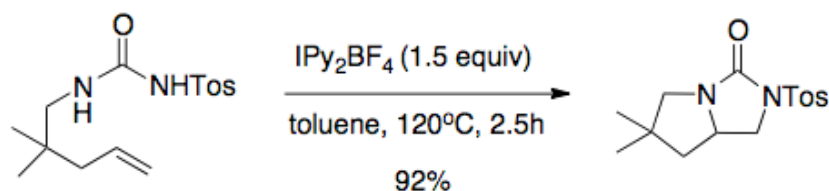
Schéma 2



1.2.2.) La diamination sans métal, catalysée par le bromure

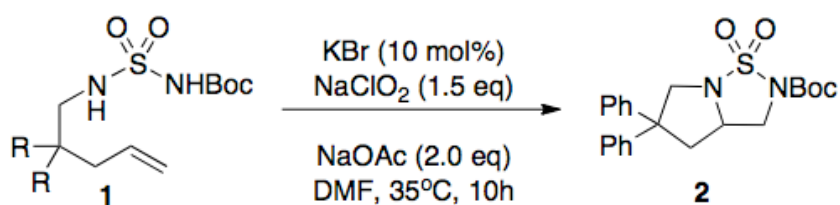
Le premier objectif ayant été atteint, nous nous sommes intéressés à la prochaine étape, la diamination catalytique sans métal. Pour ce faire nous sommes partis d'un résultat antérieur,⁸ une diamination d'urée par l'utilisation de IPy₂BF₄ (Schéma 3) en quantité stœchiométrique. De nombreuses publications ont mis en avant l'utilisation d'halogénures pour la difonctionnalisation d'alcènes de manière générale, et plus spécifiquement pour la diamination, mais très rarement de manière catalytique d'où notre engouement pour cette réaction.

Schéma 3



Nous avons donc débuté par la recherche de la source d'halogène la plus adéquate en utilisant PhI(OAc)₂ comme oxydant, en présence d'une base. Le bromure de potassium (KBr) s'est montré le meilleur candidat. Par la suite, le coût de PhI(OAc)₂ et la toxicité du sous produit formé (PhI) nous ont mené à tester d'autres oxydants ainsi que diverses bases pour finalement aboutir aux conditions optimales : NaClO₂ comme oxydant et NaOAc en tant que base (Schéma 4). Ce résultat étant très intéressant car le chlorite est un oxydant facile à utiliser, peu cher et ne formant aucun sous-produit organique.

Schéma 4⁹



Nous avons par la suite examiné la généralité de la réaction, et prouvé grâce aux nombreux exemples que celle-ci est applicable aux alcènes terminaux, substitués, internes, à différentes sources d'azote comme les esters acryliques, les sulfamides et les urées, et permet la

formation de cycles à 5 et également de cycles à 6 avec de bons ou excellents rendements de réaction.⁹

Des réactions supplémentaires ainsi que des études utilisant des composés deutérés nous ont également permis de proposer un mécanisme et un cycle catalytique.

Nous avons donc achevé notre étude de la diamination intramoléculaire par cette réaction au fort potentiel, peu onéreuse et très innovante par sa catalyse à base de bromure.

2.) Vers la diamination intermoléculaire :

L'étude de la version intramoléculaire étant quasiment achevée, nous nous sommes donc intéressés au prochain défi : la version catalytique intermoléculaire de la diamination des alcènes.

2.1.) Un premier pas vers l'intermoléculaire

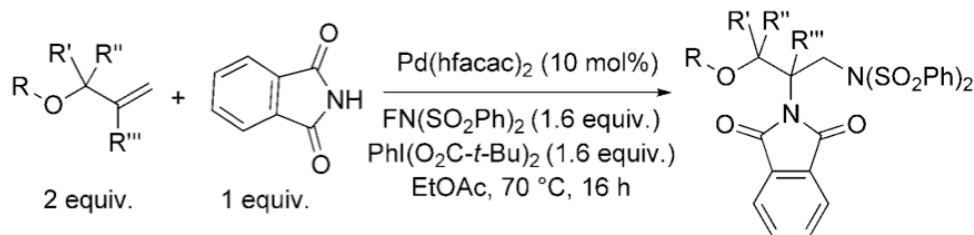
Notre but est la diamination en deux étapes : premièrement l'aminopalladation et deuxièmement la formation de la liaison Csp³-N par l'intermédiaire d'un Pd(IV). Nous nous sommes inspirés de travaux publiés antérieurement dans lesquels il est fait référence à chaque étape de manière indépendante.

La première étape, l'aminopalladation, a été observée par Stahl avec les éthers allyliques en utilisant le phthalimide comme source d'azote et le Palladium(II) comme catalyseur.¹⁰

La seconde étape a été mise en avant par Michael,¹¹ utilisant NFSI (N-Fluorobenzènesulfonimide) comme oxydant mais également comme source d'amide pour la seconde étape lors d'une catalyse au Palladium(II).

Nous nous sommes donc attelés à trouver les conditions idéales, permettant de combiner la première et la deuxième étape au sein d'une réaction unique afin d'obtenir la diamination intermoléculaire catalytique. Après avoir optimisé les conditions (solvant, température, concentration, source de Palladium et additifs), nous avons réussi à développer la première diamination catalytique intermoléculaire des éthers allyliques (Schéma 5).¹²

Schéma 5 :



Cette méthode est applicable à divers éthers allyliques (11 exemples) ainsi qu'au benzoate d'allyle. Les produits obtenus sont des molécules trisubstituées qui peuvent facilement être déprotégées et utilisées par la suite dans des réactions organiques, comme démontré dans la publication¹².

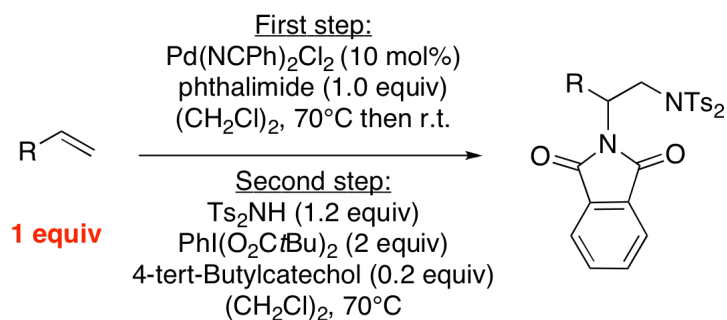
Cependant, deux problèmes principaux nous ont poussé à améliorer cette réaction: la nécessité d'utiliser deux équivalents d'alcène nécessaires et la limitation aux éthers allyliques.

2.2.) Amélioration de la version intermoléculaire de la diamination

Afin d'améliorer la version précédente, nous avons réitéré l'étape d'optimisation en modifiant l'ordre d'addition des réactifs, les divers additifs, mais aussi les étapes de purification pour qu'elles soient plus performantes.

Après des mois de recherche, nous avons finalement déterminé les conditions optimales¹³ (Schéma 6), consistant d'abord en la formation *in-situ* d'un précatalyseur, puis en l'ajout des réactifs en y additionnant le *tert*-butylcatechol, celui-ci diminuant la dégradation de l'alcène de départ durant la réaction.

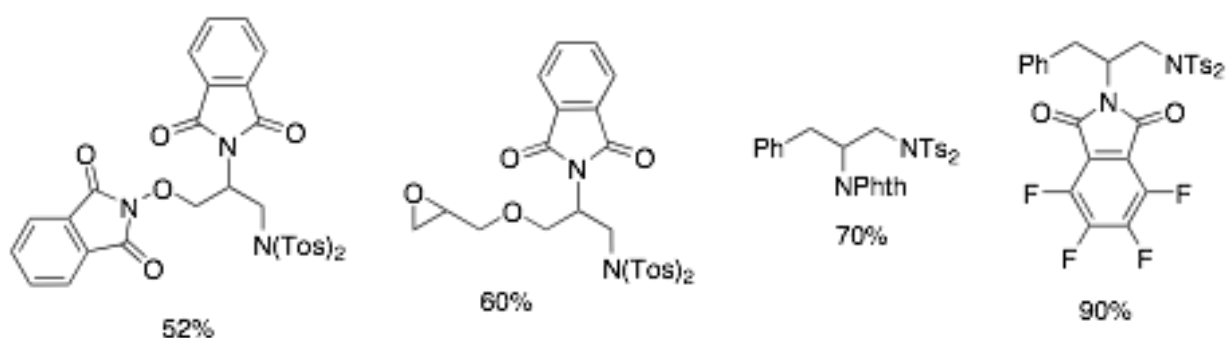
Schéma 6 :



Grâce à ces nouvelles conditions optimisées, nous avons pu diminuer la stoechiométrie de l'alcène à 1 équivalent en obtenant de bons rendements. De plus, ces nouvelles conditions de

réaction permettent la diamination des éthers allyliques précédents mais aussi des éthers allyliques plus sensibles contenant par exemple un deuxième groupement éther, un groupement époxyde et un alcène interne (Schéma 7). Nous avons également été agréablement surpris par la réactivité d'alcènes simples lors de l'utilisation de ces conditions, comme pour l'allylbenzene par exemple (Schéma 7). De plus nous pouvons maintenant varier la première source d'azote, en passant du phthalimide au tétrafluorophthalimide jusqu'à la saccharine, et il en est de même pour la deuxième source d'azote pour laquelle nous pouvons utiliser le bistosylamide mais aussi le bismésylamide, plus facile à déprotéger.

Schéma 7:



Nous avons donc atteint notre objectif grâce à ces conditions :

- utilisation d'un équivalent d'alcène de départ
- élargissement de la portée de cette diamination intermoléculaire

En parallèle, un autre objectif concernant la diamination intermoléculaire avait été fixé, celui de développer la première réaction générale de diamination-1,4 intermoléculaire des diènes conjugués.

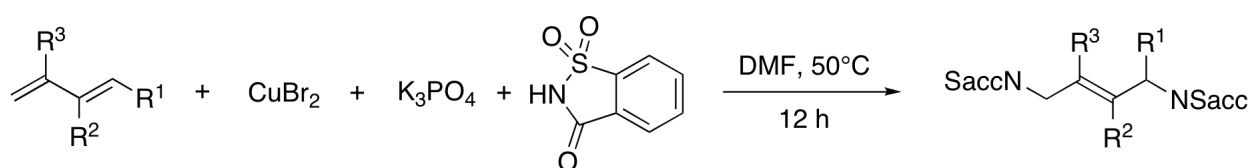
2.3.) La Diamination 1,4 des diènes

Le 1,4-diaminobutane (putrescine) ainsi que les polyamines qui en dérivent (spermidine, spermine) sont impliqués dans la synthèse in-vivo de protéines ainsi que dans la prolifération de cellule. Il a été démontré que les molécules comme le (*E*)-1,4-diaminobut-2-ène et ses dérivés possèdent des activités biologiques très intéressantes, comme par exemple des

propriétés antifongiques. Malgré cela, très peu de méthodes de synthèse impliquant la diamination 1,4 régio- et stéréosélective des diènes conjugués ont été développées, d'où notre intérêt pour cette réaction.

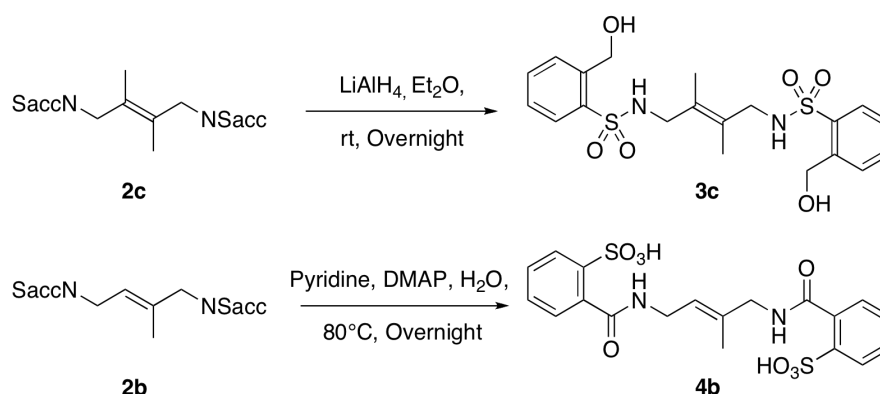
Nous avons donc développé un procédé à base de Cuivre(II) qui permet l'addition régiosélective en positions 1 et 4 sur les 1,3-diènes. Ce procédé¹⁴ met en jeu la saccharine comme source d'azote, en présence de Na_3PO_4 et de CuBr_2 . (Schéma 8)

Schéma 8 :



Cette méthode mène aux produits avec des rendements bons jusqu'à excellents, elle est générale car elle s'applique également au (*E*)-buta-1,3-dienylbenzene ainsi qu'à ses dérivés malgré la stabilisation du système styrénique qui favorise normalement l'addition 1,2. Durant l'optimisation de l'étape de déprotection de la saccharine, nous avons obtenu des résultats intéressants qui permettent d'ouvrir sélectivement la saccharine du côté du sulfamide ou bien du côté de l'amide (Schéma 9), les deux options nous menant à des produits pouvant avoir des activités biologiques des plus intéressantes.

Schéma 9 :



Nous avons donc par ce procédé réussi à atteindre l'objectif que nous nous étions fixé, c'est à dire l'addition-1,4 sélective d'amides sur des diènes conjugués afin d'obtenir des dérivés de

types 1,4-diaminobut-2-ene, sur lesquels nous pouvons modifier les substituants des alcènes en changeant le diène conjugué de départ.

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- (3). K. Muñiz, J. Streuff, C. H. Hövelmann, A. Nuñez, *Angew. Chem. Int. Ed.* **2007**, *46*, 7125.
- (4). A. Minatti, K. Muñiz, *Chem. Soc. Rev.* **2007**, *36*, 1142.
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- (7). P. Chávez, J. Kirsch, J. Streuff, K. Muñiz, *J. Org. Chemistry*, **2012**, *77*, 1922.
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