Development of Novel Methodology for the *in situ* Preparation of Halodiazo Compounds and Investigation of Reactivities of α-Onium Diazo Compounds

Dissertation for the Degree of Ph.D.

by

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Try not to become a man of success, but rather try to become a man of value.

Albert Einstein (1879-1955)

Acknowledgements

The work presented in this thesis has been carried out at the Department of Chemistry, University of Oslo, during the period January 2011-December 2013. It is unbelievable how fast these three years passed! Besides the scientific experience I gained during my PhD research here in Norway, the experience of spending years abroad in that beautiful country was a great personal enrichment to me.

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Christian Schnaars

Oslo, December 2013

Abstract

Diazo compounds have great synthetic potential as versatile reagents in organic synthesis. The formation of Rh(II) carbenoids from diazo compounds allows the selective formation of C-C and C-heteroatom bonds and the introduction of functionality into organic molecules. The thermal stability of diazo compounds, however, varies and depends strongly on the substituents and diazo compounds which are substituted by electron donating heteroatoms in α-position are known to decompose readily. They represent, however, a highly desirable class of diazo compounds as to allow the introduction of additional functional groups into organic molecules for further transformations. The development of new methodology for the α-functionalization of diazo compounds and introduction of new functionality into diazo compounds under mild conditions, that allows their application in catalytic carbenoid chemistry, is therefore highly desirable.

In Chapter 2, the development of a new methodology for the one-pot *in situ* electrophilic halogenation of diazophosphonates will be presented. The halodiazophosphonates could for the first time be applied in catalytic cyclopropanations with olefins. The methodology avoids the handling of potentially toxic α-metalated diazophosphonates and adds as a new convenient protocol to the preparation of diazo compounds. Parts of this chapter are published in **Paper I**.

A different and complementary approach to halodiazo compounds will be presented in Chapter 3. Based on α-aryliodonium diazo triflate salts, we developed three new alternative methods for the *in situ* nucleophilic halogenations of diazoesters, diazophosphonates and diazopiperidinylamides and the halodiazo compounds were successfully used in Rh(II) catalyzed cyclopropanations with styrene or thermal intramolecular C-H insertion. The work of this chapter is published in **Paper II**.

Chapter 4 deals with computational calculations of the transition states for the nucleophilic substitutions of the α-aryliodonium diazoester triflate salt with bromide, dimethylsulfide and triethylamine and gives an insight into the mechanism for the nucleophilic substitution reactions. The calculations were performed by Martin Hennum. Parts of this work are published in **Paper II**.

Experimental kinetic measurements of thermal decompositions and substitution rates in Chapter 5 give an insight into the stabilities and reactivities of the α-onium diazo triflate

salts and the effects of the substituents of the diazo compounds. Parts of this chapter are published in **Paper II**.

Synthetic applications of the unexplored α-aryliodonium, α-dimethylsulfonium and α-triethylammonium diazo triflate salts will then be presented and discussed in Chapter 6 and a variety of interesting and unexpected reactivities of these compounds were discovered. The results presented in this chapter are unpublished.

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Appendix: Papers I-II

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Paper I *Halodiazophosphonates, a New Class of Diazo Compounds for the Diastereoselective Intermolecular Rh(II) Catalyzed Cyclopropanation*

Christian Schnaars and Tore Hansen

Organic Letters **2012**, *14*, 2794-2797.

Paper II *Nucleophilic Halogenations of Diazo Compounds, a Complementary principle for the Synthesis of Halodiazo Compounds: Experimental and Theoretical Studies*

Christian Schnaars, Martin Hennum and Tore Bonge-Hansen

The Journal of Organic Chemistry **2013**, *78*, 7488-7497.

List of contributors

Martin Hennum (computational calculations, Chapter 4, **Paper II**)

Vitthal N. Yadav, Sigurd Øien (crystal structure measurements and refinements)

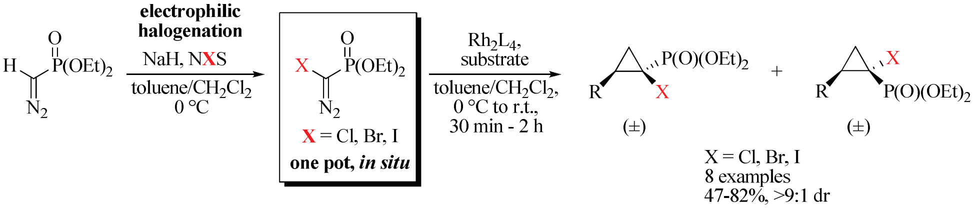
Abbreviations and units

aq.	aqueous
Ar	aryl
n-Bu	*n*-butyl
calcd.	calculated
cat.	catalyst
δ	delta, ppm (chemical shift)
Δ	reflux
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DFT	density functional theory
DOSP	*N*-(4-dodecylbenzenesulphonyl)prolinate
dr	diastereomeric ratio
d	doublet (NMR)
dd	doublet of doublets (NMR)
E	entgegen
EDA	ethyl diazoacetate
EDP	diethyl diazomethylphosphonate
EI	electron impact (MS)
eq.	eqivalent(s)
ESI	electrospray (MS)
esp	α,α,α',α'-tetramethyl-1,3-benzenepropionate
Et	ethyl
EWG	electron withdrawing group
h	hour(s)
^{1}H	proton (NMR)
HRMS	High Resolution Mass Spectroscopy
Hz	hertz
J	coupling constant (NMR)
kcal	kilocalories
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
μl	micro liter

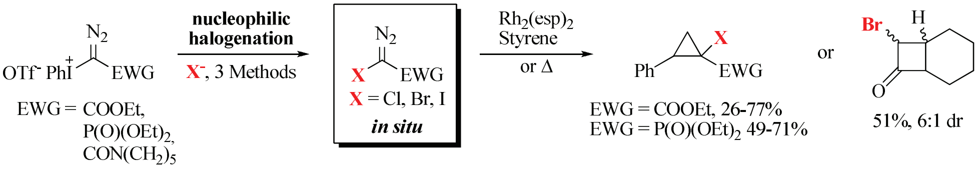
m	multiplet (NMR)
m/z	mass per charge (MS)
M^+	molecular ion (MS)
Me	methyl
MeCN	Acetonitrile
MEPY	methyl 2-oapyrrolidine-5-carboxylate
mg	milligram
Mhz	mega hertz
min	minute
mL	milliliter
mmol	millimole
MS	mass spectroscopy
n.d.	not determined
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NFSI	*N*-fluorobenzenesulfonamide
NIS	*N*-iodosuccinimide
n.r.	no reaction
NMR	nuclear magnetic resonance
OAc	acetate
oct	octanoate
PG	protecting group
Ph	phenyl
ppm	parts per million
PTTL	*N*-phthaloyl-*tert*-leucinate
r.t.	room temperature
t	triplet (NMR)
THF	tetrahydrofurane
TLC	thin layer chromatography
TBAB	tetrabutylammonium bromide
TBAC	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
Z	zusammen

Graphical abstract

Chapter 2 Development of a methodology for the electrophilic *in situ* preparation of halodiazophosphonates and their use in catalytic cyclopropanation

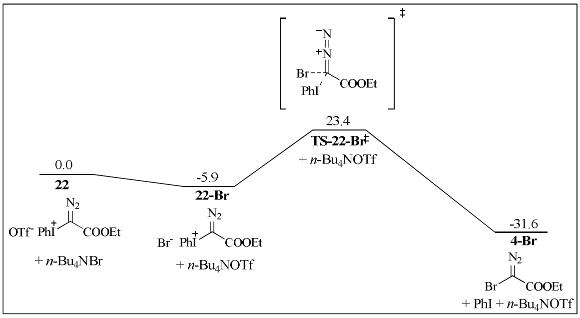


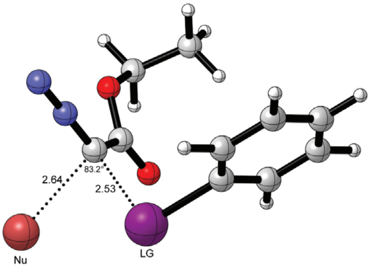
Chapter 3 Development of new methodologies for the *in situ* preparation of halodiazo compounds *via* nucleophilic halogenation



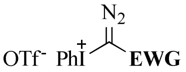
Method1: n-Bu_4NX, CH_2Cl_2; *Method 2*: KX, H_2O/CH_2Cl_2; *Method 3*: KX, 18-crown-6, CH_2Cl_2

Chapter 4 Computational studies of the mechanism and transition states for nucleophilic substitutions of α-aryliodonium diazoester triflate

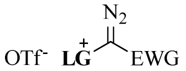




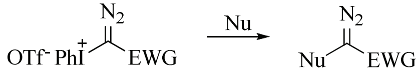
Chapter 5 Kinetic measurements of decompositions and nucleophilic substitutions of α-onium diazo triflate salts



Thermal stability increases in the order of
EWG: $CON(CH_2)_5 < P(O)(OEt)_2 < COOEt$



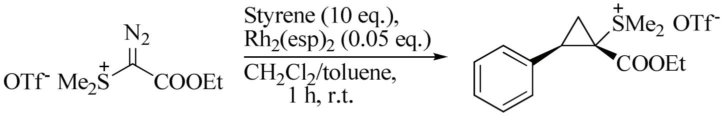
Thermal stability increases in the order of
LG = $PhI \ll SMe_2/NEt_3$

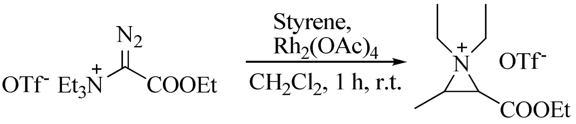


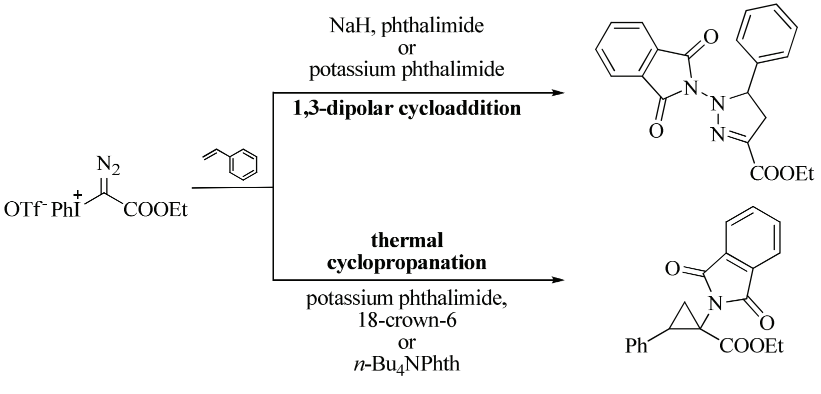
EWG = COOEt,
$P(O)(OEt)_2$,
$CON(CH_2)_5$

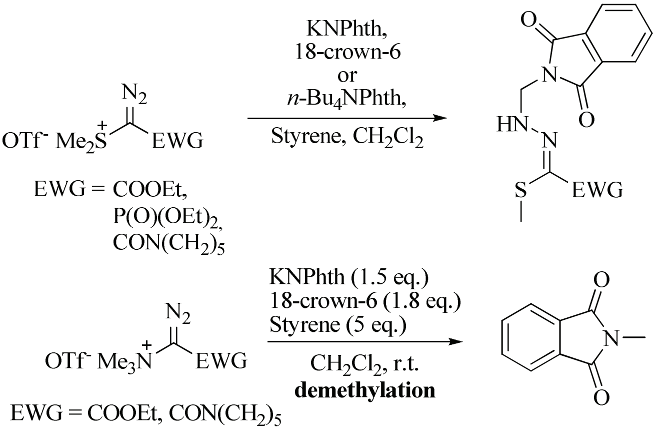
reaction rates: I > Br > Cl,
$NEt_3 > SMe_2$
$CON(CH_2)_5 > P(O)(OEt)_2 > COOEt$

Chapter 6 Reactivities of the α-onium diazo compounds and mechanistic investigations








KNPhth,
18-crown-6
or
n-Bu4NPhth,
Styrene, CH2Cl2
N2
OTf- Me2S+
EWG
EWG = COOEt,
P(O)(OEt)2,
CON(CH2)5
O
N
O
HN
N
S
EWG
KNPhth (1.5 eq.)
18-crown-6 (1.8 eq.)
Styrene (5 eq.)
CH2Cl2, r.t.
demethylation
N2
OTf- Me3N+
EWG
EWG = COOEt, CON(CH2)5
O
N
O

Chapter 1

Introduction

1.1 Diazo compounds: properties

Since the first diazo compound ethyl diazoacetate (EDA) was reported and synthesized by *Theodor Curtius* in 1883,[1] diazo compounds have emerged as an important class of reagents in organic synthesis. Their ability to generate transition-metal carbenoids made numerous important chemical transformations available, among which the selective formation of new C-C bonds and reaction with inert C-H bonds is of tremendous synthetic value, being an important area of current research.[2-4] The selective functionalization of C-H bonds formation of C-C bonds *via* transition-metal carbenoids generated from diazo compounds has found application in the synthesis of complex organic molecules such as natural products and pharmaceuticals.[5-8]

The geometry of the diazo group was unclear for a long time and in 1911 *Thiele*[9] proposed a linear structure for the diazo group in contrast to the cyclic diazirine structure (Figure 1.1). Experimental proof for the linearity of the diazo group was then, in 1957, presented by *Clusius* and *Lüthi*,[10] who performed an experiment by reduction and cleavage of a ^{15}N-labeled ethyl diazoacetate and afforded clean, ^{15}N-labeled ammonia and unlabeled glycine.

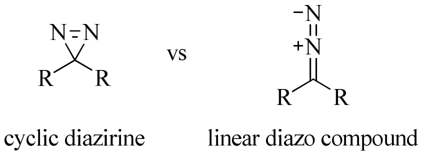


Figure 1.1 Cyclic diazirine structure and linear diazo structure.

One drawback associated with diazo compounds is their propensity and risk of detonation by extrusion of dinitrogen, generating free carbenes. The simplest diazo compound, diazomethane, first synthesized by *von Pechmann*[11] in 1894, is a gaseous compound at room temperature with a boiling point of -23 °C which has a tendency to explode unexpectedly.[12] Furthermore, diazo compounds and in particular diazomethane are known to be toxic, as reports about the carcinogenic action[13] and accidents upon exposure to diazomethane have revealed.[14] The introduction of electron withdrawing groups in the α-position to the diazo functionality is a general way to stabilize diazo compounds.[15] The previously mentioned ethyl diazoacetate, bearing one ester group, shows an increased resonance stabilization compared to diazomethane, which was determined by *Liebman* and *Hosmane* to be merely 4 kcal mol^{-1}.[16] EDA is, unlike diazomethane, a yellow liquid at room temperature with a boiling point of 140-141 °C and was shown to have a much lower tendency to explode when compared to diazomethane.[17-18] Thus, the small difference of 4 kcal mol^{-1} for the resonance stabilization of EDA results in a significant difference in its physical properties. "But, oh how grateful we are for this!", to say it with the words of *Liebman* and *Hosmane*[16]. Ethyl diazoacetate is nowadays a frequently employed diazo compound in chemical synthesis and can be handled with routine safety precautions.

The increase in stabilization of diazo compounds upon introduction of electron withdrawing groups is assumed to be due to a mesomeric effect.[16] The carbonyl group in α-position to the diazo carbon can participate in mesomeric delocalization of the electron pair at the diazo carbon atom resulting in mesomeric structure **C** (Figure 1.2). Resonance structure **B** has importance in explaining the ability of diazo compounds to react as nucleophiles at the diazo carbon atom, which is therefore also influenced by the α-substituents.[19]

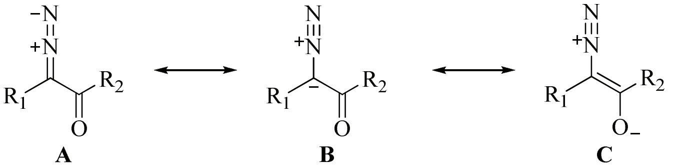


Figure 1.2 Resonance structures of an α-diazocarbonyl compound. In case of EDA (R_1 = H, R_2 = OEt) resonance structure **C** is assumed to be responsible for increased stability compared to diazomethane.

1.2 Reactivities and decomposition modes of diazo compounds: non-carbenoid-pathways

Diazo compounds show a large variety of reactivities and four general reaction modes can be distinguished: The reaction of diazo compounds without loss of the diazo group; reactions with loss of dinitrogen without carbene or carbenoid intermediates; reactions with loss of dinitrogen and generation of free carbenes; the (catalytic) generation of the corresponding transition-metal carbenoids and subsequent transformations. Selected examples of reactions with diazo compounds without carbene or carbenoid intermediates are shown in

Figure 1.3 in the left part. The 1,3-dipolar cycloaddition (a) (*Huisgen* Reaction) of diazo compounds with dipolarophiles is a common reaction with diazo compounds to prepare heterocycles such as pyrazoles or pyrazolines and demonstrates the ambiphilic character of diazo compounds.[20] The aza-*Darzens* reaction (b) is a method to prepare aziridines from nucleophilic addition of diazo compounds to imines under Lewis or Brønsted acid activation (*Brookhart*-*Templeton* aziridination).[21-23] The homologation of acyclic carbonyls (*Roskamp* reaction)[24-26] or ring expansion of cyclic ketones (*Tiffeneau-Demjanow*-type reaction)[27-29] (c) are common examples for rearrangements caused by nucleophilic addition of diazo compounds to carbonyls. An example of a reaction involving free carbenes is the *Arndt-Eistert* homologation of carboxylic acid derivatives[30-31] *via* a *Wolff* rearrangement (d),[32] shown in the right part of Figure 1.3.

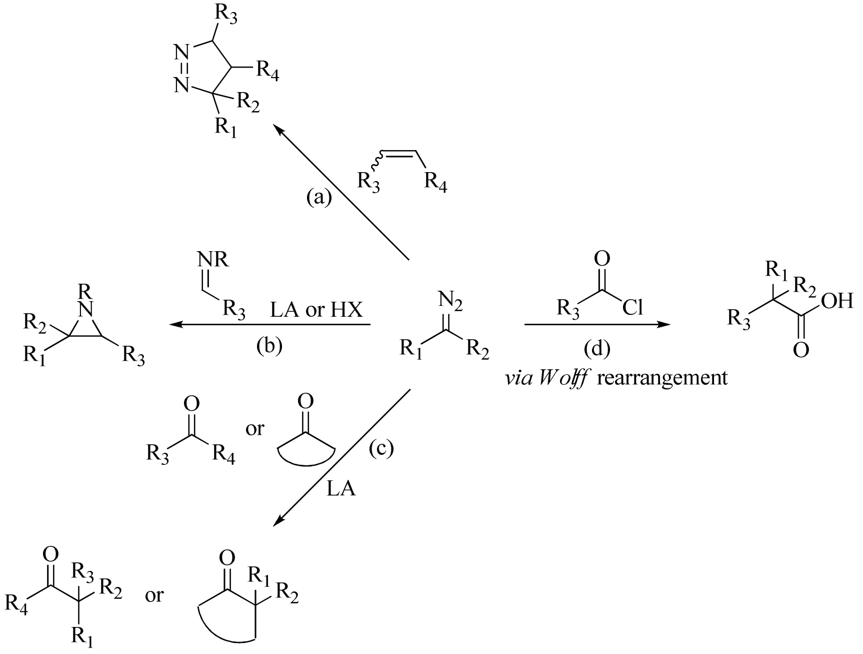
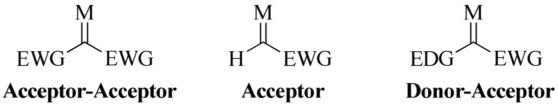


Figure 1.3 Selected examples of reactions of diazo compounds without carbenoid intermediates. LA = Lewis Acid.

The thermal or photochemical extrusion of dinitrogen from diazo compounds results in the generation of free carbenes, which are highly reactive species.[33] Carbenes are defined as divalent neutral carbon atoms with 6 electrons in its valence shell and can exist in the singlet or triplet state.[34] Studies about reactivities of differently substituted carbenes towards cyclopropanation with olefins by *Moss*[35] give an impression about the significant influence of the substituents on the carbene carbon and the subsequent reactivities of the carbenes as electrophiles or nucleophiles. The significant effect of the substituents on the stabilities and reactivities of carbenes is impressively shown by the discoveries of isolable, stable carbenes by *Arduengo*[36] and *Bertrand*.[37] The reactions presented in this thesis are mainly based on metal-carbenes or transition-metal carbenoids which will therefore be discussed in more detail in the next sections.

1.3 Transition-metal carbenoids

The decomposition of diazo compounds in the presence of appropriate transition-metal catalysts allows the generation of transition-metal carbenoids, also known as metal-carbenes. The first metal-carbene complex was proposed by *Yates*[38] in 1952 who described the decomposition of α-diazoketones in the presence of copper with the suggestion of a copper-carbene. Still being electrophilic species, the transition-metal carbenoids are less reactive than the free carbenes and allow therefore more selective reactions. The main parameters determining the electronic properties of the transition-metal carbenoid are the ligands of the metal catalyst[39-41] and the α-substituents of the carbenoid carbon atom.[42-44] Accordingly, transition-metal carbenoids can be categorized into three classes, namely acceptor-acceptor, acceptor and donor-acceptor carbenoids, defined by their substituents (Figure 1.4).[43]



EWG = CO_2R, COR, NO_2, $P(O)(OR)_2$, SO_2R, CN
EDG = vinyl, alkynyl, aryl, heteroaryl
M = Transition-metal

Figure 1.4 Three classes of transition-metal carbenoids by *Davies*.[43]

Acceptor groups attached to the carbenoid carbon atom increase the electrophilicity and thus the reactivity of the transient transition-metal carbenoid.[15] The generation of these carbenoids from the corresponding acceptor or acceptor-acceptor substituted diazo compounds require electrophilic catalysts due to higher stability of the corresponding diazo compounds.[15] Most of the C-H functionalization reactions with these acceptor-acceptor or acceptor carbenoids were performed intramolecularly,[45] with preference towards formation of 5-membered rings and to a lesser extent 4 and 6 membered rings.[46] Donor-acceptor carbenoids were introduced by *Davies et al.* in the 1980s and have since then found widespread application for efficient carbenoid transformations.[47] The donor substituent in donor-acceptor carbenoids has a stabilizing effect by lowering the electrophilicity of the carbenoid and modulates its reactivity. This type of carbenoids allows more selective carbenoid transformations as numerous examples for highly site selective intermolecular C-H insertions and cyclopropanations demonstrate.[5,48-49] The carbenoids which will be dealt with in this thesis consist of at least one electron withdrawing group.

1.3.1 Dirhodium(II) carbenoids

With the introduction and application of dirhodium tetraacetate $Rh_2(OAc)_4$ for O-H insertions with EDA by *Teyssié et al.* in 1973,[50] and later for the cyclopropanation of olefins,[51-53] and C-H insertions into paraffins,[54-55] a new era in carbenoid chemistry emerged. Since then, dirhodium(II) catalysts are by far the most frequently applied catalysts in carbenoid chemistry, displaying unique properties which sets them ahead of other catalysts for most of the catalytic transformations with carbenoids, as discussed below. Rh(II) carbenoids have been applied in numerous useful reactions affording high chemo-, regio- and stereoselectivities and yields.[48] Selected examples of common reactions involving Rh(II) carbenoids are presented in Figure 1.5.

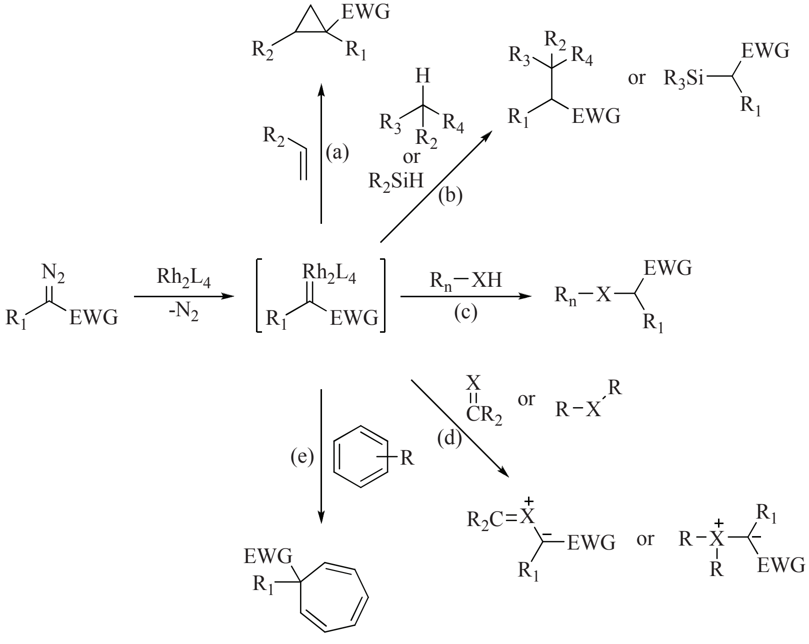


Figure 1.5 Selected reactions of Rh(II) carbenoids.

The cyclopropanation of olefins (a) is one of the most frequently studied reaction of transition-metal carbenoids.[56-57] It has emerged as a "benchmark reaction" for the comparison of the efficiency of carbenoid reactions (especially with styrene as substrate), and has high synthetic value since cyclopropanes are important structural entities for organic synthesis[58-59] and in natural products.[60] The analogous reaction of Rh(II) carbenoids with alkynes allows the preparation of cyclopropenes.[61-62] The cyclopropanation of alkenes or dienes with vinyl carbenoids can lead to subsequent *Cope Rearrangements* as shown in several examples by *Davies et al.*.[63] Mechanistic studies of the Rh(II) catalyzed cyclopropanations were performed by *Doyle*[64-65] and later *Singleton* and *Davies*[66] *via* kinetic isotope effects and DFT calculations suggesting an asynchronous concerted transition state. Another important reaction of Rh(II) carbenoids is the selective C-H insertion into either sp^2 or sp^3 C-H bonds[6,46,67] or Si-H insertion[68-70] (b). Two important examples for the enantioselective catalytic intramolecular C-H insertion are the synthesis of (*R*)-(-)-baclofen by *Doyle* and *Hu* employing dirhodium(II) carboxamidates[71] and (*R*)-(-)-rolipram by *Hashimoto et al*. employing dirhodium(II) phthaloyl derived carboxylates as catalysts.[72] Rh(II) carbenoids can also take part in insertion reactions into polarized heteroatom-hydrogen bonds (c) (X-H), even though copper catalysts can be efficient alternatives for these reactions.[73-76] The asymmetric intramolecular Rh(II) catalyzed N-H insertion allowed the efficient synthesis of the antibiotic (+)-thienamycin in 1980.[77] The reaction of transition-metal carbenoids with basic heteroatoms can lead to ylides (d),[78-80] which can undergo subsequent reactions such as cycloadditions[81-82] or rearrangements.[83-86] The cyclopropanation of aromatic compounds and subsequent ring expansion, also known as the *Buchner* reaction (e), dates back to 1908,[87] though recent examples by *Maguire et al.* with dirhodium(II) catalysts[88-89] and copper (bis)oxazolines[88,90] demonstrate its synthetic value.

Due to their transient character, the isolation and analytical characterization of electrophilic Rh(II) carbenoids is challenging. The first report of an isolated Rh(II) carbenoid was published by *Arduengo* and *Padwa et al.*[91] in 2001 based on a stabilized diaminocarbene (Figure 1.6a). The stabilization of the carbenoid carbon by π electron donation from the neighboring nitrogen atoms, however differs from the electron poor acceptor substituted Rh(II) carbenoids. Recently, *Davies* and *Berry et al.*[92] were able to characterize the first metastable Rh(II) donor-acceptor carbenoid with several methods and could for the first time get an insight into the spectroscopic properties of this reactive species. The carbenoid carbon in the carbenoid derived from $Rh_2(tpa)_4$ and methyl 2-diazo-2-(4-methoxyphenyl)acetate shows a highly deshielded ^{13}C signal at 242 ppm with a coupling constant of 27.3 Hz, demonstrating the high electrophilicity of that donor-acceptor carbenoid (Figure 1.6b).[92] Also, less covalent binding character of the Rh=C bond in the donor-acceptor carbenoid compared to the *Arduengo*[91] carbene complex was demonstrated by the smaller Rh=C coupling constant.[92] It was therefore strongly suggested, that electrophilic Rh(II) carbenoids are the key intermediates in the carbenoid transformations and an insight into the characteristics of these species was obtained.

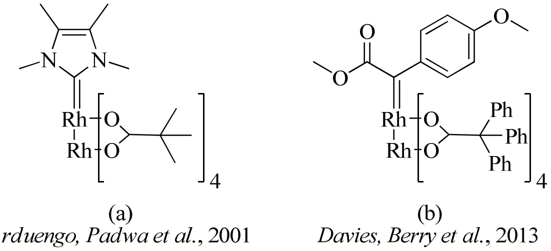


Figure 1.6 Characterized Rh(II) carbenoids by (a) *Arduengo* and *Padwa et al.*[91] and (b) *Davies* and *Berry et al.*[92]

1.3.2 The unique properties of Rh(II) catalysts

The Rh(II) catalysts are moisture- and heat-stable,[93] bimetallic, coordinatively unsaturated compounds, with a "paddlewheel" or "lantern"-like[93-94] geometry defined by the four bridging ligands around the Rh-Rh single bond (Figure 1.7).[95] The dirhodium(II) catalysts behave as Lewis acids and their electrophilicity and electron density is determined by the ligands.[40-41] Electron withdrawing ligands increase the electrophilicity of the catalysts and thus the reactivity towards decomposition of diazo compounds and carbenoid formation, while electron donating ligands decrease the reactivity and Lewis acidity. Consequently, the resulting reactivities of the Rh(II) carbenoids are influenced by the electronic properties of the ligands.[39,96-97]

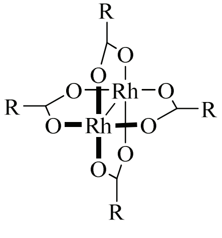
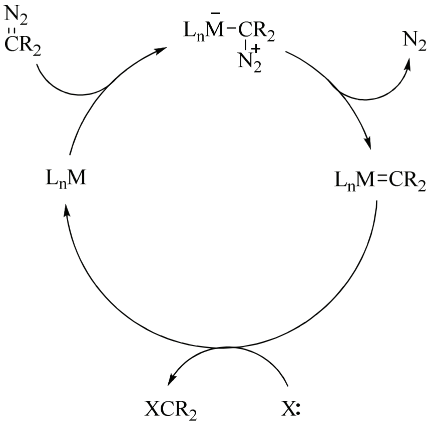


Figure 1.7 General structure of a Rh(II) carboxylate catalyst.

The formation of carbenoids is induced by nucleophilic attack and coordination of the basic carbon atom of the diazo compounds to one of the vacant axial positions of the rhodium atoms of the Lewis acidic catalyst.[15,98] Theoretical studies by *Nakamura et al.* towards the mechanism of intermolecular C-H insertions with rhodium carbenoids gave an insight into the unique properties of the dirhodium(II) catalysts.[99] After coordination of the diazo compound, irreversible extrusion of dinitrogen is the rate determining step[98-101] and results in formation of the carbenoid. The C-H insertion step is accomplished by an asynchronous, concerted hydride transfer followed by C-C bond formation.[99] The second rhodium atom can then act as an electron sink in the C-H activation/C-C bond formation step, increasing the electrophilicity of the carbene center, assisting the cleavage of the Rh-C bond and regeneration of the catalyst.[99] This unique behavior of the dirhodium(II) catalysts along with the ease of modification of the ligands (see below) makes them the catalysts of choice for the majority of selective carbenoid reactions. The general mechanism for transition-metal catalyzed decomposition of diazo compounds, carbenoid formation and reaction with a substrate is shown in Scheme 1.1.



Scheme 1.1 General mechanism for transition-metal catalyzed carbenoid reaction from diazo compounds. X = substrate.

Dirhodium(II) tetraacetate $Rh_2(OAc)_4$, the first Rh(II) catalyst that was employed in a catalytic carbenoid transformation with diazo compounds,[50] can be regarded as the prototype of this type of complexes and is applied in a vast amount of carbenoid reactions. $Rh_2(OAc)_4$ can be conveniently prepared from $RhCl_3 \cdot xH_2O$ in refluxing acetic acid[102] and serves as the precursor for other Rh(II) catalysts which can be synthesized *via* ligand exchange of the acetate ligands with other bridging ligands.[15,103-104] Numerous dirhodium(II) catalysts have subsequently been prepared and lead to efficient chiral dirhodium(II) catalysts for asymmetric reactions.[93] Selected examples are shown in Figure 1.8.

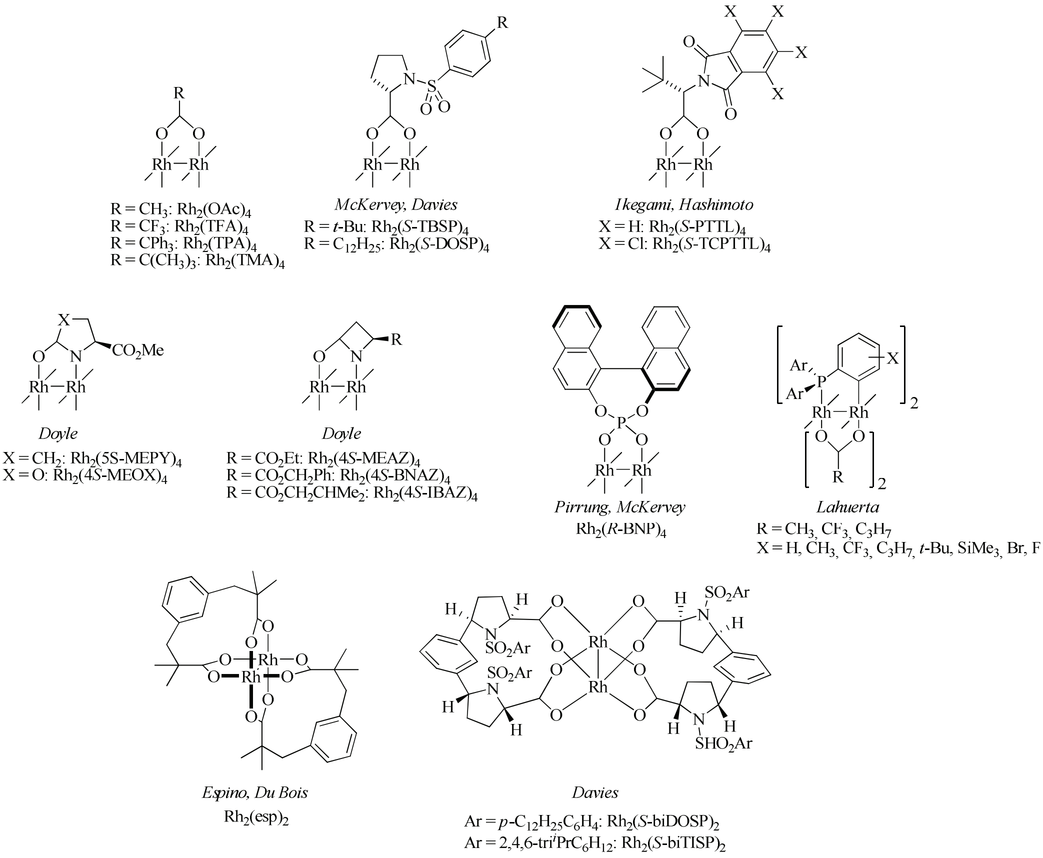


Figure 1.8 Selected examples of Rh(II) catalysts (simplified depiction of ligand types).

The most frequently employed classes of Rh(II) catalysts are the carboxylates and carboxamidates. Chiral carboxylate catalysts based on prolinates were developed by *McKervey et al.*[105] in 1990 and *Davies et al.*[106] in 1993 and were subsequently further developed.[107] At the same time *Ikegami* and *Hashimoto*[108] introduced chiral carboxylate ligands based on phthalimide protected amino acids which were then further developed by *Hashimoto et al.*[109] into benzene fused derivatives. *Doyle et al.*[110-112] developed chiral rhodium(II) catalysts based on carboxamidate ligands. These carboxamidate catalysts are less electrophilic and show increased selectivities in carbenoid reactions, but reduced reactivity towards diazo decomposition.[15] Homoleptic Rh(II) carboxylate catalysts with tethered, tetradentate ligands based on joined, dimeric arylsulfonyl prolinates have been developed by *Davies et al.*[113] and a catalyst based on tetramethylated *m*-benzenedipropionic acid by *Du Bois* and *Espino et al.*.[114] Other Rh(II) catalysts with ligands based on phosphonates were introduced by *Pirrung et al.*[115] and *Doyle* and *McKervey et al.*[116] and *ortho*-metalated arylphosphines introduced by *Lahuerta et al.*.[117-118] *Lacour et al.*[119] recently reported the first X-ray crystal structures of dirhodium(II) binaphthyl (Rh_2(*R*-BNP)$_4$) and octahydrobinaphtylphosphate (Rh_2(*R*-H_8-BNP)$_4$) complexes and evaluated the influence of halogen substituents in 3,3'-positions of the octahydrobinaphthylphosphate ligands in asymmetric cyclopropanations with styrene and Si-H insertions with aryldiazoacetates affording good yields and moderate enantioselectivities.

1.4 Synthesis of diazo compounds

Several different methods[15,120-121] for the synthesis of diazo compounds have been developed and they can be classified into two main categories; firstly the introduction or buildup of the diazo group into a parent prefunctionalized molecule, and secondly the functionalization or modification of a diazo compound under preservation of the already present diazo group.

1.4.1 Synthesis of diazo compounds *via* diazo group buildup or introduction

Selected, common examples for the buildup or introduction of the diazo group are shown in Figure 1.9.

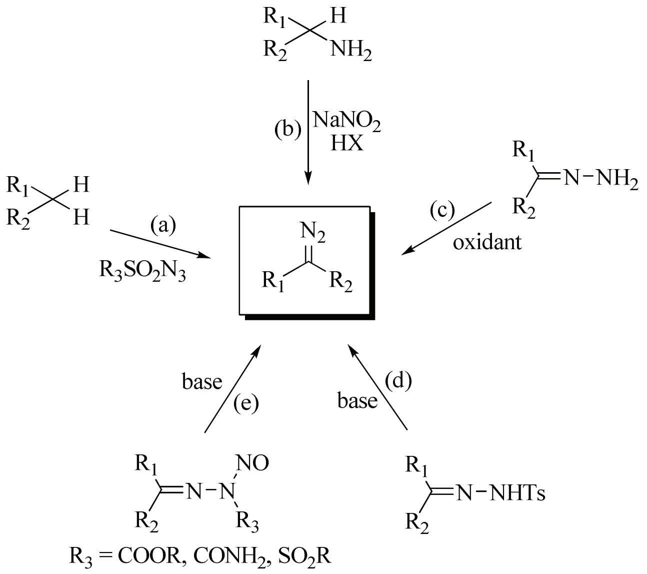


Figure 1.9 Selected common methods for the synthesis of diazo compounds *via* buildup or introduction of the diazo group.

One frequently used method for the synthesis of diazo compounds is the *Regitz* diazo transfer (a).[122] The diazo group is introduced by transfer from a sulfonylazide to doubly C-H activated compounds such as 1,3-dicarbonyl compounds in the presence of a base. The deformylative diazo transfer[123] is a variation of that methodology that enables the diazo transfer to compounds with only one activating carbonyl group. The diazotization[124] (b) of primary aliphatic amines with an α-activating group is another common way to prepare α-acceptor diazo compounds and was used in the synthesis of the first reported diazo compound, ethyl diazoacetate.[1] Nitrosating agents, most commonly sodium nitrite, are used for this method under acidic conditions. Methods which build up the diazo group from functional groups that already contain two nitrogen atoms have also found wide applications. The oxidation of hydrazones with dehydrogenating agents (c) is a frequently used method and was first described in 1889 by *Curtius*.[125] The hydrazones are prepared from condensation of carbonyl groups with hydrazine, and several dehydrogenating agents based on heavy metals have found application for the oxidation of the hydrazones.[120] Recent versions of that methodology based on a *Swern* oxidation under mild metal-free conditions was reported by *Brewer* and *Javed*[126] and an *in situ* preparation of the diazo alkanes from silylhydrazones and difluoroiodobenezene by *Myers* and *Furrow*.[127] Another method to prepare diazo compounds from hydrazones is the *Bamford-Stevens* reaction (d).[128] Sulfonylhydrazones are prepared from condensation of carbonyl compounds with sulfonylhydrazines and decomposed by base *via* formal α-elimination to the corresponding diazo compounds. A continuous flow method of that reaction was recently presented by *Moody et al.* for the preparation of diazoesters and subsequent catalytic carbenoid N-H or O-H insertions[129] and later for S-H, P-H and sulfinate insertions.[130] Another base-mediated preparation of diazo compounds is the decomposition of nitrosamides (e), which first found application in the preparation of diazomethane by *von Pechmann* in 1891.[11] Different *N*-substituents have been employed such as carbamates, ureas and sulfonamides.[131] This methodology allows the preparation of diazo compounds which are not flanked by electron withdrawing groups. Other methods besides the selected ones in Figure 1.9 are the preparation of diazoacetates from bromoacetates and *N*,*N*'-ditosylhydrazine in the presence of DBU, recently published by *Fukuyama et al.*,[132] the *Forster* reaction[133-134] involving oximes and chloramine, the *House*-method[135] *via* sulfonylhydrazone acid chlorides by decomposition with alcohols and base and the conversion of azides into diazo compounds by phosphines, recently reported by *Raines* and *Myers*.[136]

1.4.2 Functionalization and modification of diazo compounds and *in situ* preparation

Despite the diversity of these methods and the huge amount of diazo compounds that have been synthesized, the preparation of unstable diazo compounds that are incompatible with the conditions of the above methods require alternative routes. The functionalization or modification of diazo compounds under mild conditions with preservation of the diazo group and the *in situ* generation of diazo compounds are possible alternatives. The modifications of diazo compounds can be sub-divided into modifications of the substituents that flank the diazo group (from now on, referred to as remote-modifications), and direct functionalizations of the diazo carbon atom with retention of the diazo group. Examples for remote-modifications are the vinylogous *Mukaiyama*-type addition of electrophiles to enol-diazo compounds[137-140] and the diazoacetylation of nucleophiles with succinimidyl diazoacetate[141-142] or diazoacetyl chloride.[143]

The *in situ* generation as a method to avoid the handling of unstable, hazardous and potentially explosive diazo compounds is of high interest and synthetic value. Studies of *in situ* generated diazo compounds from tosylhydrazones were recently reported by *Aggarwal et al.*[144] and later *Barluenga et al.*.[145] The *in situ* diazotizations of glycine ethyl ester hydrochloride to ethyl diazoacetate was demonstrated by *Charette* and *Wurz*[146] and *Carreira* and *Morandi et al.*.[147-150] The same authors have also developed a method for the *in situ* generation of diazomethane under safe conditions in a biphasic medium affording high yields in an iron catalyzed cyclopropanation with olefins.[151] Also, the previously mentioned continuous flow methods are alternatives for the *in situ* preparation of diazo compounds.[152] Several recent examples for the continuous flow preparation of diazomethane[153-155] have made the safe and scalable use of diazomethane available, even on an industrial scale.[156-157] These examples demonstrate the great synthetic potential of *in situ* generation of highly reactive diazo compounds as an alternative to overcome the safety issues associated with them.

Two orthogonal concepts for the direct functionalization of diazo compounds are the electrophilic and nucleophilic substitutions at the carbon atom that bears the diazo group, as sketched in Figure 1.10. While the electrophilic functionalization of diazo compounds has been known for a long time and applied in numerous examples,[158-159] the nucleophilic substitution, introduced by *Weiss et al.*[160] in 1994, has gained much less attention but has great synthetic potential with regard to the synthesis of diazo compounds. Both concepts will be discussed and explained in greater detail in the Chapters 2 and 3.

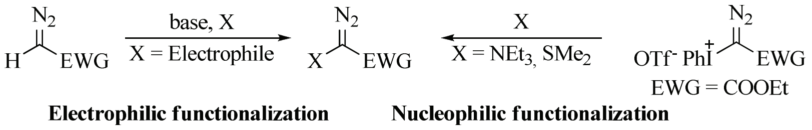


Figure 1.10 Simplified illustration of direct electrophilic and nucleophilic functionalization of diazo compounds.

We assumed that the combination of direct functionalization and *in situ* generation of diazo compounds could provide access to diazo compounds that were previously inaccessible or inapplicable to catalytic carbenoid chemistry. The next two chapters will therefore present and discuss our results towards the method development for the *in situ* generation of halodiazophosphonates *via* electrophilic halogenations and the *in situ* preparation of halodiazoesters, halodiazophosphonates and halodiazopiperidinylamides *via* nucleophilic halogenations and their applications in catalytic carbenoid chemistry. Particular focus is then directed towards the properties and synthetic applications of the α-onium diazo compounds prepared *via* nucleophilic substitutions (Chapters 4, 5 and 6). The *in situ* preparation of an α-phthalimido diazoester and discovery of unexpected reactivities will be presented and discussed in detail in Chapter 6.

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Chapter 2

Development of a methodology for the electrophilic *in situ* preparation of halodiazophosphonates and their use in catalytic cyclopropanations

2.1 Introduction

2.1.1 Biological and chemical relevances of phosphonates, halides and the cyclopropyl group

Halogens, phosphonates and cyclopropanes are important functional groups in biologically active organic molecules as well as for synthetic applications.[1-2] Several fluorinated drugs have therapeutic applications[3-4] and many naturally occurring biogenic organohalides contain chlorine and bromine and show important biological activity.[5-6] Phosphonates and phosphates,[7-8] in combination with the cyclopropyl group, are also known to show biological activities, for example as isosteres of aminocyclopropane carboxylic acids (ACC).[9] The phosphonate group is employed in several important organic reactions such as the *Horner-Wadsworth-Emmons*-Olefination,[10-12] the *Seyferth-Gilbert*-homologation[13] and the *Bestmann-Ohira* modifications.[14-16] Therefore, the development of methods which allow the direct introduction of these functional groups into organic molecules is of great interest. Halodiazophosphonates contain both the halide, as well as the phosphonate moiety in addition to the diazo group which allows the cyclopropanation of olefins (Figure 2.1). Thus, halodiazophosphonates have great synthetic value as small molecules with a high density of functional groups.

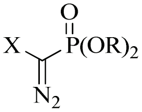
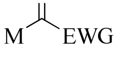


Figure 2.1 Halodiazophosphonate containing 3 functional groups: halide, phosphonate and diazo group (X = halide).

2.1.2 Diazophosphonates and electrophilic halogenations

The electrophilic substitution *via* deprotonation or metalation of the diazo carbon atom is a methodology to directly functionalize diazo compounds with retention of the diazo group.[17-19] This methodology has the advantage that, contrary to the other methods to prepare diazo compounds (see Chapter 1), the diazo group is already present in the parent molecule. Numerous examples of deprotonations of diazo compounds bearing an α-hydrogen are reported and different bases such as lithium diisopropylamide (LDA),[20] *n*-butyllithium (*n*-BuLi),[21-22] 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[23-25] triethylamine (NEt_3)[26] and NaH[27] have been applied. Reactions with imines in *Mannich*-analogue reactions,[28] carbonyls in aldol-analogue reactions[29-32] and esters or acid chlorides to generate *Claisen*-type products[33] are reported. The reaction of α-deprotonated diazo compounds with heteroatoms other than metals, however, is limited by means of available electrophilic reagents as well as resulting unstable α-heteroatom substituted diazo compounds. Nevertheless, the electrophilic substitution offers the possibility to prepare α-substituted diazo compounds which would otherwise be difficult to access, allowing mild reaction conditions.

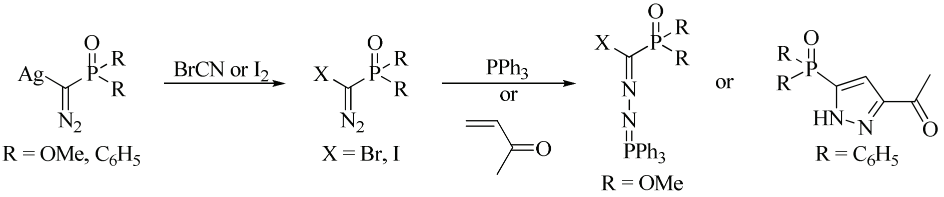
The first report of α-metalated diazo compounds dates back to the late 19th century, where *Buchner* described the preparation of diethyl mercury-bisdiazoacetate from ethyl diazoacetate (EDA) and mercury oxide.[34] Studies by *Schöllkopf et al.*[35-37] mainly for diazoesters and later *Regitz et al.*[18,38-40] for diazophosphonates and phosphinoxides showed their propensity for the synthesis of α-substituted diazo compounds among which electrophilic halogenations *via* halogen metal exchange[41-43] have been performed.



M = Hg, Li, Ag, Sn, Si, Ge, Pb, As, Mg, Zn
EWG = COOR, $P(O)(OR)_2$, $P(O)R_2$

Figure 2.2 Metalated diazo compounds as reactive nucleophiles.

Bromo and iododiazophosphonates were first reported and synthesized by *Regitz et al.*[39] in 1979 *via* electrophilic halogenation of the silverdiazophosphoantes by metal-halogen exchange with bromocyan or iodine (Scheme 2.1). Due to their thermal instability, the bromo and iododiazophosphonates were trapped with triphenylphosphine to the azine and methyl vinyl ketone in a [3+2] cycloaddition. No selective catalytic transformation *via* the corresponding carbenoid has been performed before the work presented in this thesis.



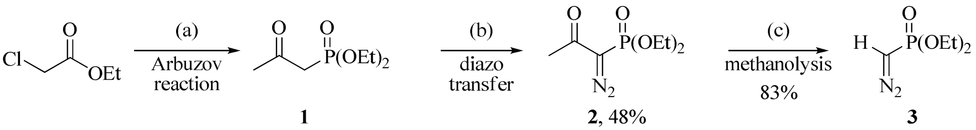
Scheme 2.1 First synthesis and trapping of bromo and iododiazophosphonates and -phosphinoxides by *Regitz et al.*.[39]

The ethyl silverdiazoacetate was reported by *Schöllkopf et al.* to be explosive.[36] Additionally, mercury and several other metals are known to be very toxic.[44-45] These factors, in addition to the synthetic and biological relevance mentioned before, demand the development of an applicable, convenient and safe method that also allows to use the halodiazophosphonates in catalytic carbenoid reactions and broadens the scope of available diazo compounds.

2.2 Results and discussion

2.2.1 Preparation of diethyl diazomethylphosphonate (EDP)

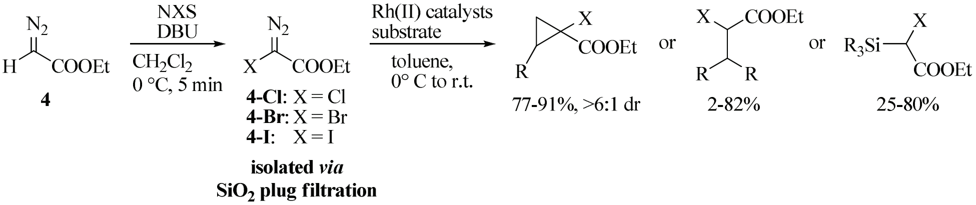
The *Seyferth-Gilbert* analogue[46] diethyl diazomethylphosphonate (EDP) **3** was chosen as the starting material for the electrophilic substitution. This compound was prepared in three steps according to reported literature procedures. Preparation of diethyl 2-oxopropylphosphonate **1** from chloroacetone and triethylphosphite *via* the *Arbuzov* reaction[47] was followed by diazo transfer with methanesulfonylazide[48] affording the *Bestmann-Ohira* reagent[16] diethyl 1-diazo-2-oxopropylphosphonate **2** in 48% yield after two steps. Deacylation of **2** *via* methanolysis with methanol and triethylamine[49] gave **3** in 83% isolated yield in the last step (Scheme 2.2).



Scheme 2.2 Reagents and conditions: (a) KI, $P(OEt)_3$, acetone/MeCN (1:1), r.t., 16 h;[47] (b) 1) NaH, toluene, $MeSO_2N_3$, THF, 0 °C then r.t., 16 h, 2) Celite filtration;[48] (c) NEt_3, MeOH, r.t., 16 h.[49]

2.2.2 Initial experiments towards the deprotonation and electrophilic halogenation of EDP based on a previously reported procedure for halodiazoesters

Initial experiments were performed in analogy to the previously reported procedure in our group for the preparation of halodiazoacetates **4-X** (X = Cl, Br, I) *via* electrophilic halogenation of ethyl diazoacetate (EDA) **4** with DBU and *N*-halosuccinimides (Scheme 2.3).[25,50-51] This protocol involved a two pot process by first generating and isolating the halodiazoacetates **4-X**, followed by Rh(II) catalyzed carbenoid transformation. The isolation of the halodiazoacetates was performed by washing the reaction mixture with a cooled, aqueous 20% $Na_2S_2O_3$ solution and drying over $MgSO_4$ at 0 °C, followed by silica plug filtration to remove the base and succinimide to avoid interference and side reactions in the catalytic step. A solvent exchange from CH_2Cl_2 to toluene at 0 °C was followed by addition of the substrate and a Rh(II) catalyst to perform the cyclopropanation,[25] C-H or Si-H insertion.[50]



Scheme 2.3 Reported procedure for the synthesis of halodiazoacetates and Rh(II) catalyzed cyclopropanation, C-H or Si-H insertion.

Following the above described protocol, the halogenation of EDP **3** was attempted. After addition of *N*-bromosuccinimide (NBS, 1.2 eq.) and DBU (1.4 eq.) to **3** in CH_2Cl_2 at 0 °C, a rapid color change of the bright yellow solution to orange was observed. TLC analysis of the reaction mixture showed an orange spot eluting faster than **3** ($R_f = 0.35$ vs. 0.13 for **3**, 2:1 *n*-hexanes/EtOAc). The mixture was stirred for 10 min at 0 °C, washed with 20% aq. $Na_2S_2O_3$ solution and dried over $MgSO_4$ at 0 °C. The following attempted silica plug filtration with -20 °C cooled CH_2Cl_2 was unsuccessful due to tailing and resulted in decomposition of the expected diethyl bromodiazophosphonate which could not be isolated *via* this method. At this point an alternative protocol had to be developed with conditions that avoided the SiO_2 plug filtration, were compatible with the thermal instability of the halodiazophosphonates and allowed subsequent catalytic transformation.

2.2.3 Development of a one pot method for the *in situ* generation of halodiazophosphonates and their catalytic cyclopropanations

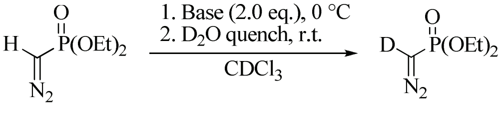
One way to overcome instabilities and avoid rapid decomposition of diazo compounds upon isolation was the *in situ* generation (Chapter 1, section 1.4.2). For an *in situ* generation of the halodiazophosphonates the reagents and conditions must be compatible to all reaction steps. Critical to this approach was the base, which had to be non-coordinating, and must not interfere with the catalyst or carbenoid transformation in the second step but had to be strong enough to perform a fast and efficient deprotonation. Additionally, if all components were present in one pot, side reactions from competitive catalytic decomposition of the non-halogenated EDP **3** had to be avoided. Hence, the halogenation had to be faster than the formation of the carbenoid with **3**.

As compatible, clean and easy to handle bases we thought of inorganic bases such as Cs_2CO_3, K_2CO_3 and NaH, in combination with crown ethers to improve their solubilities if necessary. Studies towards the α-deuteration of diazoacetates, diazoacetamides and diazoketones with potassium cabonate as base have recently been reported by *Bew et al.*[52] albeit in mixtures of an organic solvent with D_2O. We performed deprotonation experiments by adding the base (2.0 eq.) to **3** in $CDCl_3$ at 0°C. ^1H NMR analysis was performed after 5, 10 and 15 min, followed by quenching the reaction mixture with D_2O after 20 minutes to deuterated EDP **5** (Table 2.1). The formation of carbenes resulting from the reaction of NaH with chloroform *via* α-elimination was taken into consideration.[53] However, only the relevant α-H signal at $\delta = 3.76$ ppm (d, $J = 11.1$ Hz) of **3** was directly measured and followed, and was assumed to be independent from any side reactions.

Cs_2CO_3 showed no deprotonation in $CDCl_3$ after 15 minutes, however after quenching with D_2O approximately 80% deuterium exchange was detected, which probably resulted from increased solubility and reactivity of Cs_2CO_3 in D_2O. K_2CO_3 showed no deprotonation after 15 minutes in $CDCl_3$, and after adding 18-crown-6 to increase solubility, the degree of deprotonation could not be determined due to partial overlap of the proton signal of 18-crown-6 ($\delta = 3.62$ ppm) and the relevant proton of EDP **3**.

The most efficient base was sodium hydride, providing a fast, clean and irreversible deprotonation after 5 minutes and crown ethers could be avoided (Table 2.1, entry 4). The irreversible deprotonation with NaH, however, disables a catalytic process with regard to base. The use of base in catalytic amounts was shown previously by *Wang et al.* in a condensation of acyldiazomethanes to imines and aldehydes with DBU as base.[23]

Table 2.1 Deprotonation experiments of **3** with inorganic bases.

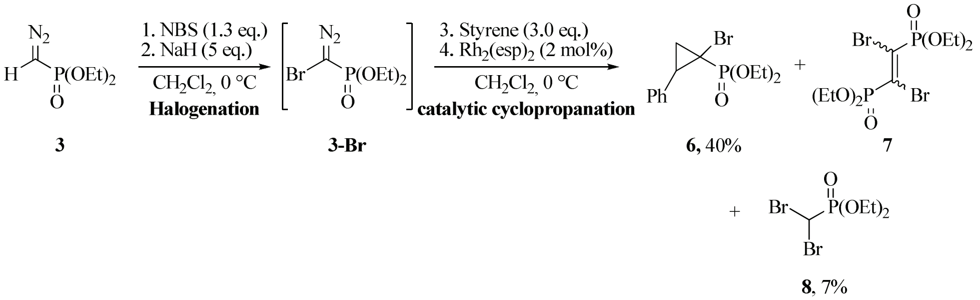


3 **5**

Entry	Base	Deprotonation after 5, 10, 15 min in $CDCl_3$[a]	Deprotonation after quenching with D_2O[a]
1	Cs_2CO_3	0%, 0%, 0%	80%
2	K_2CO_3	0%, 0%, 0%	76%
3	K_2CO_3, 18-crown-6	n.d.	n.d.
4	NaH	100%	n.d.

n.d. = not determined; [a]determined by ^{1}H NMR.

Having found NaH to be an efficient base, an initial test experiment was performed by adding NaH (5 eq.) to a mixture of EDP **3** and *N*-bromosuccinimide (1.3 eq.) in dry dichloromethane at 0 °C. A rapid color change to orange appeared and TLC analysis indicated full conversion of **3** within 5 minutes. Styrene (3.0 eq.) was chosen as the test substrate as it has been used in numerous cyclopropanation reactions, allowing an easy comparison of carbenoid cyclopropanations, and 2 mol% $Rh_2(esp)_2$ was chosen as a robust catalyst. Both have been efficient in the cyclopropanation of halodiazoacetates.[25] The addition of catalyst resulted in instant gas evolution as well as decolorization of the reaction mixture (slightly green from catalyst), which indicated the formation of a Rh(II) carbenoid by extrusion of N_2. Workup and purification of the reaction mixture afforded the bromocyclopropylphosphonate **6** in a promising isolated yield of 40% as a mixture of both diastereomers along with the dimer **7** and the dibrominated product **8** as byproducts (Scheme 2.4).



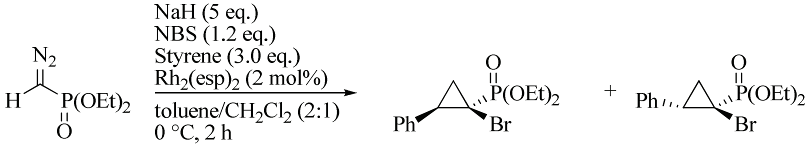
Scheme 2.4 Electrophilic bromination of **3** and Rh(II) catalyzed intermolecular cyclopropanation of bromo-EDP **3-Br** *via* bulk addition of reagents.

The obtained ethyl 1-bromo-2-phenylcyclopropanecarboxylate product **6** indicated the formation of diethyl bromodiazophosphonate **3-Br** (bromo-EDP) in the first step of the reaction. The dimerization product **7** supported this assumption, as dimers are common byproducts in carbenoid chemistry and dropwise addition of the diazo compound could reduce dimerizations. The dibrominated product **8** could result from reaction of **3** with bromine,[54-55] but only a minor amount (7%) of this byproduct was detected.

Having shown that the combination of reactants was compatible, and allowed catalytic cyclopropanation with bromo-EDP **3-Br** for the first time, we wanted to apply this methodology in a one pot procedure with dropwise addition of **3** to minimize the dimerization and thus increase yields of the desired cyclopropane. A fast *in situ* generation of bromo-EDP **3-Br** due to high excess of NaH and *N*-bromosuccinimide relative to the low concentration of EDP **3** would make an efficient catalytic cyclopropanation achievable.

Dropwise addition of a solution of **3** in dry dichloromethane over 2 hours to a mixture of 2 mol% $Rh_2(esp)_2$, NBS (1.2 eq.), NaH (5 eq.) and styrene (3.0 eq.) in dry toluene/CH_2Cl_2 (2:1) at 0 °C afforded, after removal of the CH_2Cl_2 at 0 °C, workup and purification, the bromocyclopropylphosphonate **6** in an isolated yield of 82% for both diastereomers with a diastereomeric ratio of 12:1 *trans:cis* (Scheme 2.5). Only traces of dimer **7** and the dibrominated product **8** could be detected, showing the advantage of dropwise addition. Toluene was chosen as a co-solvent to increase the efficiency of the catalytic cyclopropanation step, since it was beneficial in the cyclopropanation of the halodiazoesters.[25] Furthermore, the resulting sodium succinimide was insoluble in toluene and precipitated from the reaction mixture after removal of the dichloromethane, which made a convenient work up by celite filtration possible.

With the one pot *in situ* procedure in hand, we could double the yield for **6** from 40% in the batch addition procedure (Scheme 2.4) to 82% and only obtained very small amounts of byproducts (Scheme 2.5).



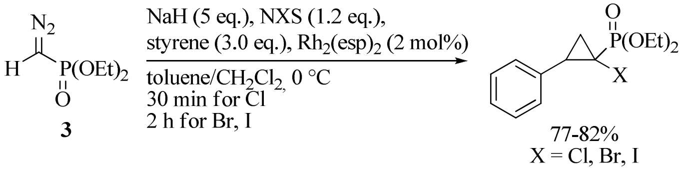
3 (±)-*trans*-**6** (±)-*cis*-**6**

82%, 12:1 *trans*:*cis*

Scheme 2.5 One pot synthesis of *trans*-**6** and *cis*-**6** *via in situ* generation of bromo-EDP **3-Br** (general procedure A).

The relative stereochemistry of the major isomer of **6** was determined by 2D-NOESY experiments to be the *trans* isomer with respect to the phosphonate group and aryl substituent. The analogous iodocyclopropylphosphonate **9** could be synthesized using *N*-Iodosuccinimide (NIS) and was obtained in 77% isolated yield in a 16:1 *trans*:*cis* diastereomeric ratio (Table 2.2, entry 2). For the chlorination, however, the analogous procedure with NCS did not afford the expected 1-chloro-2-phenylcyclopropanecarboxylate, but the cyclopropane product resulting from EDP **3**. The electrophilic chlorination step appeared to be slower than the electrophilic iodination and bromination, and the cyclopropanation with **3** preceded the chlorination. It could thus be hypothesized that for the chlorination the halogen transfer was the rate determining step, whereas for the iodination and bromination the Rh(II) catalyzed cyclopropanation with the halodiazophosphonates was rate determining. To solve this issue, the chlorination reaction was performed prior to addition of the catalyst and a stepwise addition of the reactants led to the chlorocyclopropylphosphonate **10** in 77% isolated yield and 12:1 dr (Table 2.2, entry 3). The electrophilic fluorination was also attempted using the electrophilic fluorination reagents Selectfluor©[56] and *N*-fluorobenzenesulfonimide (NFSI).[57] Unfortunately, no fluorinated diazophosphonate and resulting cyclopropane could be obtained.

Table 2.2 Preparation of **6** and **9** *via in situ* generation (general procedure A) and preparation of **10** *via* stepwise addition (general procedure B).



Entry	X	Product	Yield (%)[a]	dr (*trans*:*cis*)[b]
1	Br	**6**	82	12:1
2	I	**9**	77	16:1
3	Cl[c]	**10**	77	12:1
4	F[d]		0	

[a]Isolated yields of both diastereomers; [b]Estimated by ^{1}H NMR of the crude product mixture; [c]Sequential addition of NaH (5 eq.) to mixture of **3** and NCS (1.3 eq.) in dry CH_2Cl_2 at 0 °C, exchange of CH_2Cl_2 with toluene, followed by addition of styrene (3.0 eq.) and $Rh_2(esp)_2$ (2 mol%) (general procedure B); [d]Selectfluor© and NFSI as F-sources.

A reaction of **3** with NBS and styrene under inert atmosphere (Ar) and covered in alumina foil was performed to exclude side reactions from photochemical decomposition and moisture. Both parameters did not have an effect on the yields of the reaction, thus, dry and distilled solvents were used in the subsequent reactions under otherwise ambient conditions. The reaction in CH_2Cl_2 as single solvent without toluene gave a slightly lower yield and contained more succinimide in the crude mixture before purification.

Isolation of bromo-EDP was attempted by washing a solution of **3-Br**, NaH and sodium succinimide/NBS in $CDCl_3$ with cold H_2O and quick drying of the organic phase over $MgSO_4$ at 0°C before filtration. Unfortunately, no clean ^{1}H NMR spectrum of bromo-EDP **3-Br** could be obtained, due to decomposition.

2.2.4 Scope and limitations of the developed one pot procedure - catalysts

Having shown that the cyclopropanation of the halogenated phosphonates could be efficiently performed with $Rh_2(esp)_2$ as catalyst, we wanted to examine the scope and limitations of other transition metal catalysts. Catalysts based on rhodium, copper, ruthenium and silver were tested in the catalytic cyclopropanation reaction with styrene (Table 2.3).

Highest yields for the catalytic cyclopropanation with **3-Br** were obtained with $Rh_2(esp)_2$. The loading of $Rh_2(esp)_2$ could be lowered to 0.1 mol% without a significant drop in yield (74% by internal standard, Table 2.3, entry 1d) and the addition time of **3** was increased to compensate for lower catalyst loadings (5 h addition time for 0.1 mol% $Rh_2(esp)_2$). A reaction without catalyst only afforded the dimeric product **7**, no thermal cyclopropanation of bromo-EDP **3-Br** with styrene was obtained. $Rh_2(piv)_4$ and $Rh_2(oct)_4$ also gave high yields of 78% and 73%, respectively (Table 2.3, entries 2 and 3). These two catalysts were previously reported by *Charette et al.*[58] to be efficient in the catalytic cyclopropanation of EDP **3** with styrene, however showing low diastereomeric ratios. In our present system the halogen substituents seemed to significantly increase the *trans* selectivity compared to **3**[58] since all catalysts afforded diastereomeric ratios of >9:1, which was in a similar range to the diastereomeric ratios reported by *Charette et al*. for the diacceptor α-cyano diazophopshonates with several dirhodium catalysts and styrene.[59] $Rh_2(OAc)_4$ showed a reduced yield of 54%, $Rh_2(TPA)_4$ 43% and the electron poor $Rh_2(TFA)_4$ the lowest yield of 40%. The two chiral catalysts $Rh_2(S\text{-PTTL})_4$ and $Rh_2(S\text{-TBSP})_4$ gave moderate yields of 66% and 47% of **6** with *ee*s below 15% for the *trans* isomer in both cases. Further investigation of enantioselective reactions have not been performed. Surprisingly, none of the tested copper based catalysts afforded the cyclopropane product. $Cu(acac)_2$ gave 63% yield in a cyclopropanation reaction of 1-diazo-2,2,2-trifluoromethylphosphonate with styrene[60] but was inactive in our case.

Table 2.3 Catalyst screening for the synthesis of **6**.[a]

Entry	Catalyst	Loading (mol%)	Yield of 6[b] (%)	dr (*trans*:*cis*)[c]
1a	$Rh_2(esp)_2$	2	82, 78[d], 0[e,j]	
1b		1	88[f,g]	
1c		0.5	78[f,h]	12:1
1d		0.1	74[f,i]	
1e		0	0[f,j]	
2	$Rh_2(piv)_4$	2	78	12:1
3	$Rh_2(oct)_4$	2	73	14:1
4	$Rh_2(OAc)_4$	2	54	14:1
5	$Rh_2(TPA)_4$	2	43	9:1
6	$Rh_2(TFA)_4$	2	40	10:1
7	$Rh_2(S\text{-PTTL})_4$	2	66	14:1
8	$Rh_2(S\text{-TBSP})_4$	2	47	13:1
9	CuCl	2	0	-
10	$Cu(OTf)_2$	5	0	-
11	$Cu(acac)_2$	10	0	-
12	$RuCl_3$	10	0	-
13	Ag(OAc)	2	0	-

[a] Conditions: EDP **3** (0.7 mmol, 1.0 eq.) in 5 mL dry CH_2Cl_2, added dropwise to NaH (5 eq.), NBS (1.2 eq.), styrene (3.0 eq.), and catalyst in toluene/CH_2Cl_2 (10 mL/5 mL) at 0 °C; [b] Isolated yield of both diastereomers after column chromatography; [c] Measured by ^1H NMR of the crude product mixture; [d] 1.2 eq. NaH; [e] Reaction at room temperature; [f] Measured by internal standard from ^1H NMR of crude reaction mixture for both diastereomers; [g] 3 h addition time; [h] 4 h addition time; [i] 5 h addition time; [j] Only dimer **7** could be detected.

The efficiency of NaH was shown by reducing the amount to 1.2 eq., still affording 78% of **6**. A reaction at room temperature showed only formation of the dimeric product **7**, which means that the decomposition and dimerization of **3-Br** was faster than the catalytic cyclopropanation at room temperature. Lowering the temperature below 0 °C decreased the solubility of the *N*-bromosuccinimide and the yield of **6** dropped.

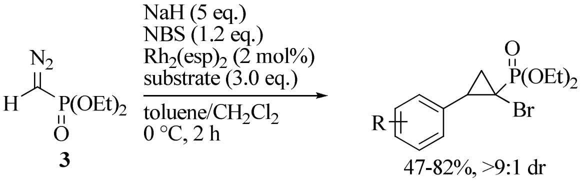
2.2.5 Scope and limitations of the developed one pot procedure - substrates

Several aromatic terminal alkenes with different electronic and steric properties as well as aliphatic 1-hexene were tested in the cyclopropanation reaction to investigate the substrate scope. Also, a C-H insertion with 1,4-cyclohexadiene was attempted (Table 2.4).

The relatively electron rich substrates styrene, 4-methylstyrene and 4-methoxystyrene afforded the highest yields of the corresponding bromocyclopropylphosphonates **6**, **11** and **12**. The more electron deficient substrates 4-chlorostyrene and 4-trifluoromethylstyrene afforded the bromocyclopropylphosphonates **13** and **14** in reduced yields of 67% and 62%. *N*-vinylphthalimide and 2-vinylnaphthalene both gave satisfactory 64% yield of the bromocyclopropylphosphonates **15** and **16**. To test a sterically more crowded 1,1-disubstituted double bond, 1,1-diphenylethylene was chosen as substrate and afforded a yield of 47% of product **17**. All substrates showed a high distereomeric preference for the *trans* isomer of the corresponding bromo cyclopropylphosphonates. An X-ray crystal structure of diethyl 1-bromo-2-(1,3-dioxoisoindolin-2-yl)cyclopropylphosphonate **16** was obtained and confirmed the *trans* diastereoselectivity for the major isomer (Figure 2.3). Cyclopropane **16** is a product of particular interest since it contains, besides the phosphonate and bromine, a protected amine which allows further functionalization and orthogonal reactivity of three functional groups.

No cyclopropanation with 1-hexene occurred, only the dimer **7** was obtained. To test an intermolecular C-H insertion, 1,4-cyclohexadiene was used as substrate, as it is known to be an activated and frequently used substrate for intermolecular C-H insertions with donor-acceptor carbenoids[61-64] and showed good yields in the Rh(II) catalyzed C-H insertion of bromo-EDA **4-Br**.[50] The bromo-EDP **3-Br**, however, did not afford the corresponding product from intermolecular C-H insertion, but formation of the dimer **7** occurred. To the best of our knowledge, no catalytic intermolecular C-H insertion with diazophopshonates has been reported to date and the halodiazophosphonates seemed to follow this trend. Intramolecular C-H insertions with diazophosphonates, however, have been frequently reported for the construction of α-phosphono-β-lactams,[65-68] α-(dialkoxyphosphoryl)lactones,[69] as well as carbocycles.[70-72] Further investigations towards intermolecular C-H insertions have not been conducted.

Table 2.4 Substrate scope of the Rh(II) catalyzed cyclopropanation of *in situ* generated bromo-EDA.[a]



Entry	Substrate	Product	Yield (%)[b]	dr (*trans*:*cis*)[c]
1	styrene	**6**	82	12:1
2	4-methylstyrene	**11**	79	15:1
3	4-methoxystyrene	**12**	81	17:1
4	4-chlorostyrene	**13**	67	13:1
5	4-trifluoromethylstyrene	**14**	62	13:1
6	2-vinylnaphthalene	**15**	64	9:1
7	*N*-vinylphthalimide	**16**	64	10:1
8	1,1-diphenylethylene	**17**	47	-
9	1-hexene		-	-
10	1,4-cyclohexadiene		-	-

[a]Conditions: EDP **3** (0.7 - 1.0 mmol, 1.0 eq.) in 5 mL dry CH_2Cl_2 added dropwise to NaH (5 eq.), NBS (1.2 eq.), substrate (3.0 eq.) and $Rh_2(esp)_2$ (2 mol%) in toluene/CH_2Cl_2 (10 mL/5 mL) at 0 °C; [b]Isolated yield of both diastereomers after column chromatography; [c]Measured by ^{1}H NMR of the crude product mixture.

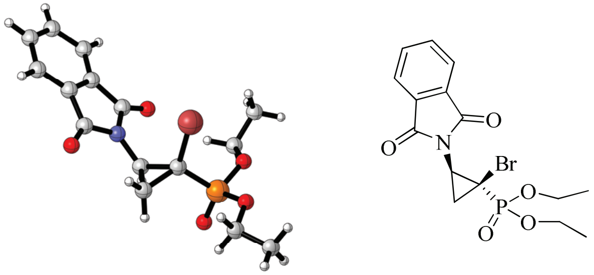


Figure 2.3 X-ray crystal structure of *trans*-diethyl 1-bromo-2-(1,3-dioxoisoindolin-2-yl)cyclopropylphosphonate **16** (CCDC 873532).[73]

2.2.6 Scope and limitations of the developed one pot procedure - electrophiles

As mentioned in section 2.2.3, electrophilic fluorinations with Selectfluor© and NFSI were attempted but no fluorinated product was obtained. This was also the case for the diazoesters.[25] Electrophilic aminations were also highly desirable since the resulting α-aminodiazophosphonates would be an entirely new class of diazo compounds and of great interest considering the biological and pharmacological activities of aminophosphonates.[74-75] Electrophilic amination reagents based on derivatives of *O*-(diphenylphosphonyl)-hydroxylamine[76-78] as well as *N*-(p-toluenesulfonyloxy)-phthalimide[79] and succinimide, which were tested for the electrophilic aminations, are shown in Figure 2.4. Unfortunately, none of the reagents was able to transfer the nitrogen moiety to the diazophosphonate in an electrophilic manner. However, as will be presented in Chapter 6, a nucleophilic amination of a diazoester with phthalimide was achieved.

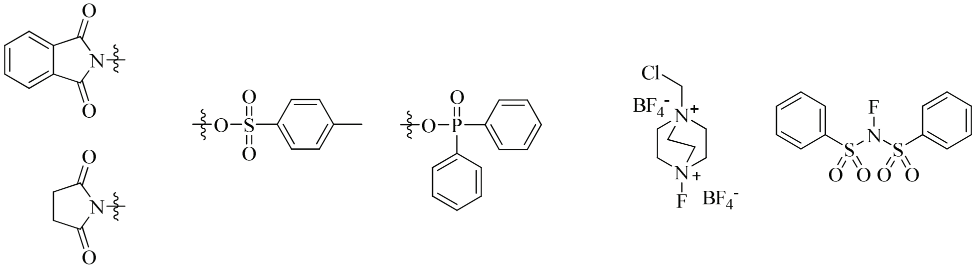
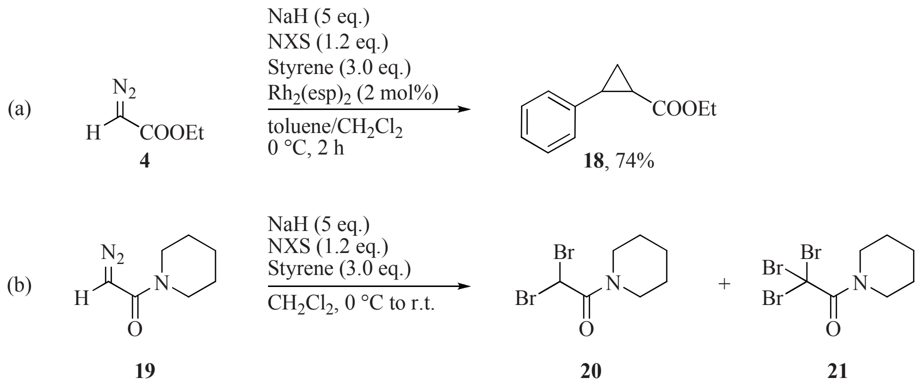


Figure 2.4 Reagents tried for the electrophilic amination and fluorination of diethyl diazomethylphosphonate **3**.

2.2.7 Scope and limitations of the developed one pot procedure - diazoesters and diazoamides

The developed one pot procedure for the *in situ* generation of bromo-EDP was applied to EDA **4** to test the generality of the method towards other classes of diazo compounds. Dropwise addition of EDA to the reaction mixture at 0 °C afforded 74% isolated yield of ethyl 2-phenylcyclopropanecarboxylate **18** resulting from cyclopropanation with non halogenated EDA (Scheme 2.6a). The deprotonation and halogenation of EDA appeared to be slower than the $Rh_2(esp)_2$ catalyzed cyclopropanation in contrast to the bromination and iodination with the phosphonates. A less active catalyst or lower temperatures could favor the electrophilic halogenation over cyclopropanation, though no further investigations were conducted since the reported procedure for the halodiazoacetates[25] has a very high efficiency.

As a representative for a diazoamide, the diazopiperidinylamide **19** was subjected to the one pot procedure. However, no product from thermal intramolecular C-H insertion, as expected from the corresponding bromodiazopiperidinylamide from previous studies[80-81] in our group, was obtained. Instead, only the di- and to a lesser extent tribrominated products **20** and **21** could be identified (Scheme 2.6b). The diazopiperidinylamide **19** seemed to have a higher tendency for over-halogenation compared to the esters and phosphonates under the applied conditions.



Scheme 2.6 Attempted one pot electrophilic bromonation/catalytic cyclopropanation with EDA **4** and attempted electrophilic bromination/thermal intramolecular C-H insertion with diazopiperidinylamide **19**.

2.3 Summary and conclusions

In conclusion, a convenient, clean and safe *in situ* one pot procedure for the Rh(II) catalyzed intermolecular cyclopropanation of halodiazophosphonates with various styrene derivatives as substrates has been developed. The developed method is the first to allow halodiazophosphonates to react in a transition-metal catalyzed intermolecular cyclopropanation reaction and adds as a new protocol to the known electrophilic substitutions of diazo compounds. The halodiazophosphonates were generated *in situ* from diethyl diazomethylphosphonate (EDP) **3** *via* fast deprotonation with NaH and electrophilic halogenation with *N*-halosuccinimides, avoiding the risk of detonation and toxicological issues associated with their α-metalated analogues upon isolation.

For the bromination and iodination a one pot procedure by dropwise addition of EDP **3** to the reaction mixture was developed, whereas for the chlorination a stepwise addition sequence was successful. Several Rh(II) catalysts afforded moderate to high yields up to 82% of the bromocyclopropylphosphonates of different styrene analogues in >9:1 *trans*:*cis* diastereomeric ratio for all substrates. The catalyst loading of the most efficient $Rh_2(esp)_2$ could be reduced to 0.1 mol% without significant drop in product yields. The obtained yields and diastereomeric ratios for the bromocyclopropylphosphonates are in a good range compared to other published Rh(II) catalyzed intermolecular cyclopropanations with diazophosphonates[59,82] considering that the procedure is a two step process.

2.4 Experimental

Experimental procedures and product characterizations can be found in **Paper I**, Supporting Information (Appendix).

2.5 References and footnotes

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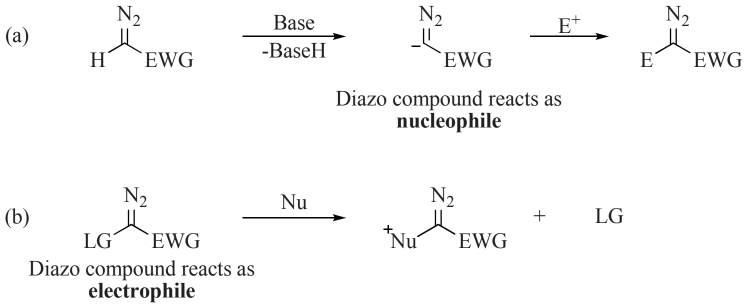
Chapter 3

Development of new methodologies for the *in situ* preparation of halodiazo compounds *via* nucleophilic halogenation

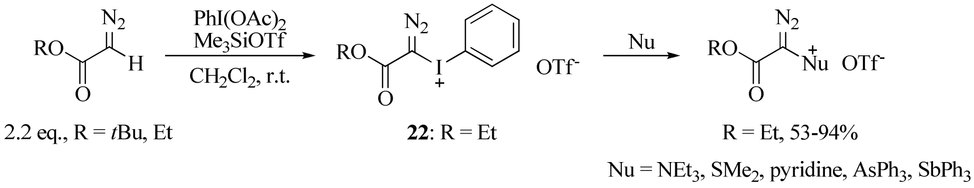
3.1 Introduction

As presented in Chapter 2, the reaction of diazo compounds with electrophiles is a well known methodology for the direct functionalization of diazo compounds.[1] A complementary approach was reported by *Weiss et al.*[2] in 1994, in which a nucleophilic substitution of a diazoester was presented for the first time. In this direct nucleophilic substitution the reactivity of the diazo compound is reversed, reacting as an electrophile, in contrast to the electrophilic substitution (Scheme 3.1).



Scheme 3.1 (a) Electrophilic substitution of diazo compounds *via* deprotonation, (b) nucleophilic substitution (LG = leaving group, Nu = nucleophile).

The report of *Weiss et al.* involved the preparation of the α-aryliodonium diazoester triflate salt **22** by reaction of 2.2 equivalents of *tert*-butyl diazoacetate or ethyl diazoacetate with diacetoxyiodobenzene ($PhI(OAc)_2$) and trimethylsilyl trifluoromethanesulfonate (TMSOTf). This α-aryliodonium diazo triflate salt **22**, bearing iodobenzene as leaving group, was then substituted with the neutral nucleophiles SMe_2, $AsPh_3$, $SbPh_3$, NEt_3 and pyridine to afford the corresponding substituted α-onium diazoester triflate salts *via* an "umpolung" of the diazo carbon (Scheme 3.2).[2]



22: R = Et

Scheme 3.2 Preparation and nucleophilic substitution of α-aryliodonium diazoester triflate **22** by *Weiss et al.*.[2]

Surprisingly, and to the best of our knowledge, this nucleophilic substitution has not been applied and established as a general pathway for the functionalization and synthesis of diazo compounds and thus seems to be largely unexplored though H. Heydt refers to this method in his review about methods for the preparation of diazo compounds, suggesting nucleophilic halogenations.[3] The synthetic potential of this methodology is huge given the amounts of nucleophiles which are available. Furthermore, the preparation of the stable α-onium diazoester triflate salts shown in Scheme 3.2 gives access to valuable diazo compounds flanked by heteroatoms such as S and N other than the known electron withdrawing NO_2,[4-7] SO_2,[8-12] and sulfoxide[13-16] groups. Also, by using negatively charged nucleophiles, neutral diazo compounds, which may otherwise be difficult or impossible to access, could be prepared in a mild and efficient way. Besides the actual scope of the nucleophilic substitution with different nucleophiles, the reactivity of the α-onium diazo triflate salts towards metal catalysis also opens up numerous interesting possibilities. Both reactivity trends and properties of these α-onium diazo compounds are unexplored, as well as the extension to other classes of diazo compounds such as phosphonates and amides. Furthermore, the mechanism and transition states would help to understand and thus optimize the methodology for future applications.

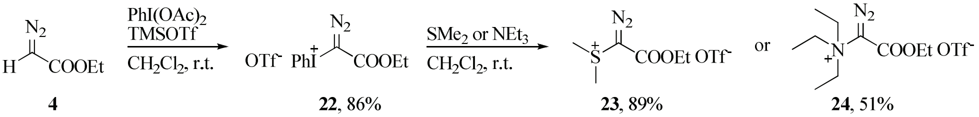
All these interesting aspects of that nucleophilic substitution methodology open up numerous possibilities for exciting research and the next chapters will deal with our results and investigations in that field. Our starting point was to investigate if we can use nucleophilic halogenations to prepare halodiazo compounds in a complementary way to our electrophilic halogenation procedures reported before. Thus, this chapter will focus on the development of nucleophilic halogenation methodology.

3.2 Results and discussion

3.2.1 Diazoesters

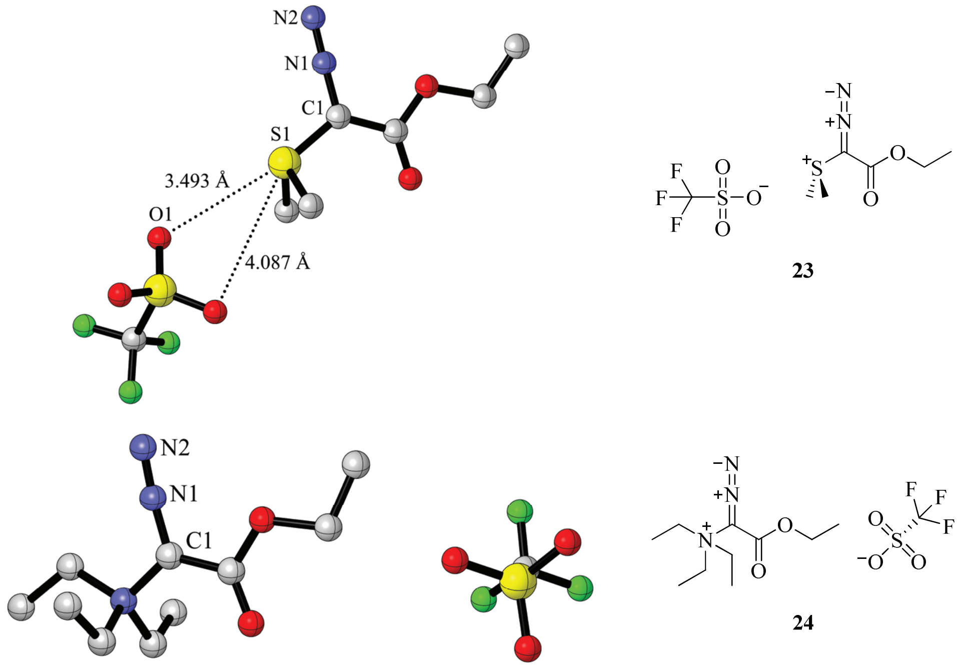
3.2.1.1 Preparation of α-aryliodonium, α-dimethylsulfonium and α-triethylammonium diazoester triflates 22, 23 and 24

α-Aryliodonium diazoester triflate **22** was prepared following the reported procedure by starting from EDA **4** (2.2 eq.).[2] Reaction with $PhI(OAc)_2$ and TMSOTf in dry CH_2Cl_2 and precipitation with Et_2O afforded **22** in an isolated yield of 86% as a yellow solid. No further purification was necessary, though recrystallization from EtOAc was possible to obtain yellow crystals of **22**. Reaction of **22** with dimethylsulfide in CH_2Cl_2 at room temperature afforded the α-dimethylsulfonium diazoester triflate **23** in 89% isolated yield as a colorless solid. The corresponding reaction with triethylamine gave α-triethylammonium diazoester triflate **24** as a light yellow solid in 51% yield (Scheme 3.3). All obtained yields were in accordance with the reported ones.[2] X-ray crystal structures of α-dimethylsulfonium and α-triethylammonium diazoester triflates **23** and **24** were obtained and add to the reported crystal structure of the tert-butylester analogue of **22** (Figure 3.1).[2]



Scheme 3.3 Preparation of **22**, **23** and **24** following the literature protocol.[2]

Both, **23** and **24**, crystallized as the *E*-rotamer with the diazo group and the carbonyl oxygen in a *trans*-relationship. The C1-N1-N2 bond angles in both crystals were, as expected, nearly linear with 178.7° for **23** and 174.6° for **24**. The C1-N1 bond length in **23** is 1.331 Å and the N1-N2 bond length 1.107 Å, the corresponding bond lengths in **24** 1.314 Å and 1.114 Å, respectively. In **23** the triflate anion is in proximity of the α-dimethylsulfonium moiety and the shortest S-O distance is 3.493 Å, albeit significantly larger than in the reported α-aryliodonium diazoester triflate with an I-O distance of 2.705 Å[2] which indicated weaker coordination in **23**. For further crystallographic detail see **Paper II**, Supporting Information.[17]



23

24

Figure 3.1 X-ray crystal structures of **23** (top, CCDC 914760) and **24** (bottom, CCDC 914758). Bond angles and distances were determined with Mercury V 3.1 from the refined CIF file.

The mechanism for the generation of **22** from PhI(OAc)$_2$ and TMSOTf was not fully described. The authors[2] suggested the formation of an α-silylated diazoester which acted as an auxiliary base in the first step with the result that one equivalent of the parent diazo compound (EDA in Scheme 3.3) was consumed. TMSOTf has been used frequently to silylate diazo compounds in combination with *Hünig's* base, (iPr)$_2$NEt.[18-21] We wanted to find a way to avoid using 2.2 equivalents of the parent diazo compound especially with regard to the later described diazophosphonates and diazoamides since they had to be prepared in 2-3 steps themselves.

^{1}H NMR experiments showed the formation of a byproduct upon addition of 2.2 equivalents of EDA to 1.0 equivalent TMSOTf at room temperature, presumably resulting from decomposition of the diazo compound as indicated by gas evolution. The decomposition was found to be much slower at -20 °C as no gas evolution was observed. This allowed us to perform the synthesis of **22** in a satisfactory 81% isolated yield by dropwise addition of only one equivalent EDA to PhI(OAc)$_2$ (1.0 eq.) and TMSOTf (1.0 eq.) at -20 °C. The precipitation process was performed with Et$_2$O at 0 °C. This modified procedure was a significant improvement to the original procedure with regard to cost efficiency and atom economy since only 1.0 equivalent of the parent diazo compound was employed. This procedure was also efficient for the corresponding diazophosphonate, giving 72% isolated yield of **34** (see 3.2.2.1) and the diazopiperidinylamide **38**, which was obtained in 65% albeit at -40 °C (see 3.2.3.1). The fact that only one equivalent of the diazo compound performed the reaction to **22** at -20 °C in same efficiency as the reported procedure at room temperature with 2.2 equivalents diazo compound indicated that no consumption of the diazo compound by means of α-silylation is involved. ^{1}H NMR monitoring of the dropwise addition of 1.0 eq. of EDA to TMSOTf (1.0 eq.) and $PhI(OAc)_2$ (1.0 eq.) in $CDCl_3$ at -20 °C did not show any byproduct formation resulting from decomposition of EDA, only clean formation of the α-aryliodonium diazoester triflate **22** was observed (Figure 3.2). We therefore postulate that a ligand exchange of the diacetoxyiodobenzene with triflate occurred to result in formation of trimethylsilylacetate and activated iodonium salt **25**.[22] The second step then involved the nucleophilic attack of the diazo compound on the PhI moiety and deprotonation with acetate to form acetic acid (Scheme 3.4).

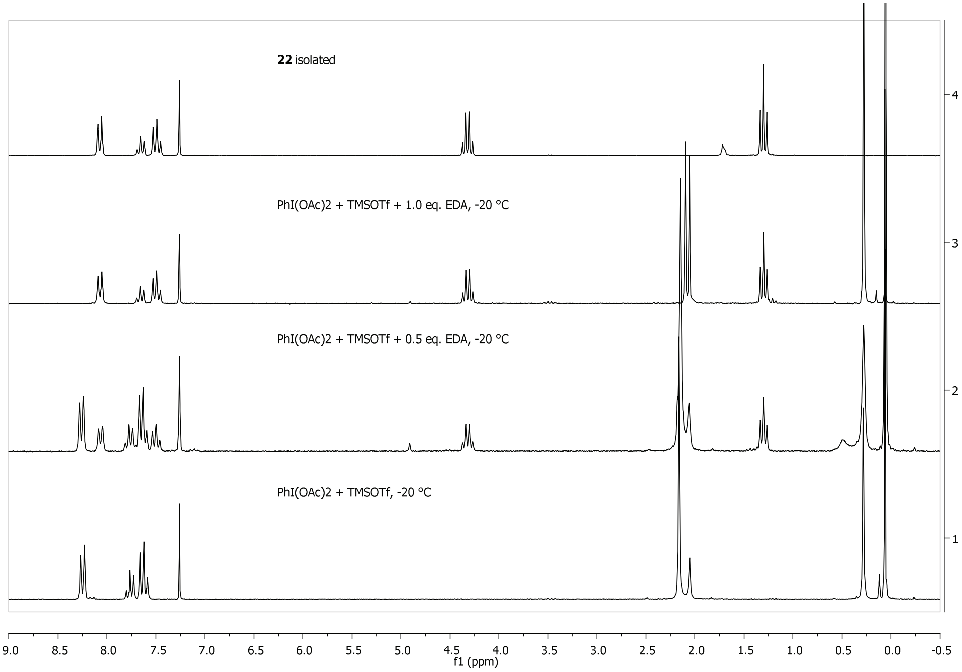
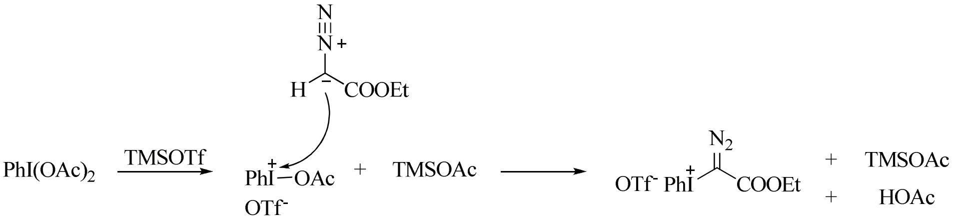


Figure 3.2 ^{1}H NMR monitoring of reaction of 1.0 eq. EDA with $PhI(OAc)_2$ (1.0 eq.) and TMSOTf (1.0 eq.) at -20 °C.

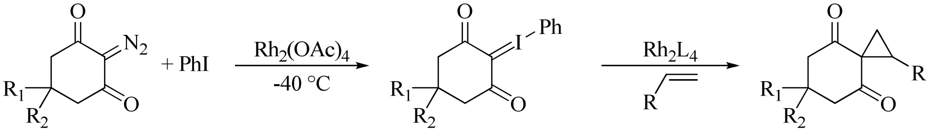


25 **22**

Scheme 3.4 Proposed mechanism for the formation of **22** *via* activated iodonium salt **25**.

3.2.1.2 Initial experiments toward the nucleophilic halogenations of 22

Having the three α-onium diazoester triflate salts **22**-**24** in hand, an initial nucleophilic halogenation experiment was performed. α-Aryliodonium diazoester triflate **22** was the choice of starting material, because iodobenzene was assumed to be the "most innocent" leaving group with regard to formation of byproducts in a one pot procedure without separation and isolation of the halodiazo compounds. The reaction of an intermediate Rh(II) carbenoid with PhI would give aryliodonium ylides.[23-24] Aryliodonium ylides, as the reported **27** from *Meldrum's* acid derived diazo compound **26** and PhI, are known to be carbenoid precursors themselves and can undergo Rh(II) catalyzed transformations (Scheme 3.5).[25-29] We thus expected compatibility of the iodobenzene as leaving group with the desired catalytic carbenoid reaction of the halodiazoester in the following step. The leaving groups dimethylsulfide and triethylamine in the cases of **23** and **24**, on the other hand, could interfere with the catalyst by axial coordination[30-32] or cause side reactions from ylide formations[33-34] or carbenoid C-H insertions into their α-activated C-H groups.[35-37] Also, iodobenzene was expected to be the best leaving group among the three, being least basic and nucleophilic and thus irreversible substitution was expected. However, as will be shown and discussed later, nucleophilic halogenations with **23** and **24** were tested but no substitution could be obtained.



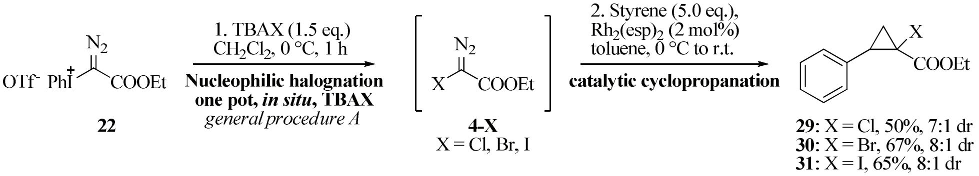
26 **27** **28**

Scheme 3.5 Formation of iodonium ylide **27** from reaction of *Meldrum's* acid derived diazo compound **26** and PhI by *Moriarty et al.*[24] and catalytic cyclopropanation of **27** with olefins to cyclopropanes **28** by *Müller et al.*[25]

As readily available, soluble and easy to handle organic halide sources for the nucleophilic halogenations tetrabutylammonium halides TBAX (X = I, Br, Cl, F) were the first choice. Addition of TBAB to **22** in dichloromethane at 0 °C gave rapid formation of the ethyl bromodiazoacetate **4-Br** as indicated by TLC analysis and ^{1}H NMR control of the reaction mixture. The nucleophilic substitution was monitored by ^{1}H NMR spectroscopy by following the amount of iodobenzene generated during the reaction (see Chapter 5 for kinetic measurements). Since compound **22** was thermally stable, following the amount of iodobenzene generated during the reaction allowed us to determine the degree of substitution. Tetrabutylammonium iodide (TBAI) and tetrabutylammonium chloride (TBAC) also showed conversion to the corresponding halodiazoesters **4-I** and **4-Cl**, though a slower reaction was observed for the chlorination. Nucleophilic fluorination with TBAF was attempted, but unsuccessful.

3.2.1.3 Catalytic cyclopropanation of *in situ* generated halodiazoesters *via* nucleophilic halogenation of 22 with tetrabutylammonium halides (general procedure A)

Having demonstrated that halides could replace iodobenzene in a nucleophilic substitution of **22** we wanted to apply this methodology in the catalytic cyclopropanation with the halodiazoesters to allow comparison to the electrophilic halogenations reported previously in our group.[38] Thus, choosing similar conditions to the electrophilic halogenations, **22** was dissolved in dry CH_2Cl_2 at 0 °C, TBAX (1.5 eq.) was added and the mixture stirred at 0 °C for 1 h to ensure full substitution. The CH_2Cl_2 was exchanged to toluene at 0 °C and styrene (5.0 eq.) and $Rh_2(esp)_2$ (2 mol%) were added and the mixture was allowed to stir at room temperature for 1 h. Purification of the reaction mixture on silica gel afforded the bromocyclopropylester **30** in 67% isolated yield in an 8:1 *trans*:*cis* diastereomeric ratio (general procedure A). A silica plug filtration before adding styrene and catalyst, in analogy to the electrophilic halogenation protocol with DBU,[38] was optional, showing no difference in yield for the obtained bromocyclopropylester **30**. The analogous iodination with TBAI gave a yield of 65% for the iodocyclopropylester **31** and diastereomeric ratio of 8:1 *trans*:*cis*. The chlorination, however, only afforded 50% isolated yield of the chlorocyclopropylester **29** with 7:1 dr *trans*:*cis* (Scheme 3.6).

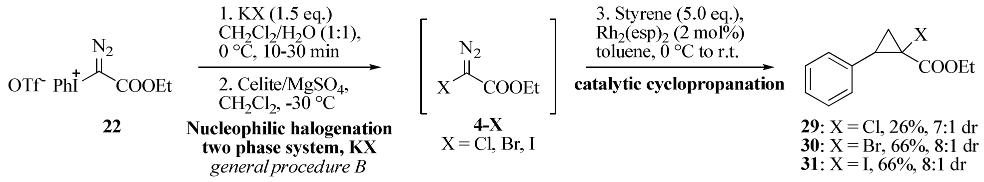


Scheme 3.6 Nucleophilic halogenation of **22** with tetrabutylammonium halides followed by catalytic cyclopropanation (general procedure A).

3.2.1.4 Catalytic cyclopropanation of halodiazoacetates *via* nucleophilic halogenation of 22 with potassium halides in a two phase system (general procedure B)

After the promising results with the tetrabutylammonium halides, we wanted to test alternative reagents and conditions for the nucleophilic substitution with a focus on the halide sources. Therefore, we thought of halide salts of Li, K and Na. Their poor solubility in organic solvents prompted us to test a biphasic reaction system, with an aqueous phase containing the halide salt and an organic phase containing the diazo compound. Test experiments revealed that **22** is stable and partially soluble in water when **22** was dissolved in D_2O, and no decomposition was detected after 2 days at room temperature. We proposed that a biphasic reaction medium should therefore be compatible with the nucleophilic halogenation process at 0 °C, since the stability of the halodiazoesters **4-X** towards H_2O was demonstrated in the electrophilic halogenations by washing the reaction mixture with 7% aq. $Na_2S_2O_3$ solution.[38]

The biphasic reaction was carried out by dissolving **22** (0.1-0.2 mmol) in 1 ml dichloromethane at 0 °C and adding a solution of potassium halide KX (1.5 eq.) in 1 ml H_2O cooled to 0 °C. The biphasic mixture was stirred vigorously for 10 min for X = I and Br and 30 min for X = Cl at 0 °C. The organic phase was then separated and passed through a celite/$MgSO_4$ plug with dichloromethane cooled to -20 °C to remove any residual water to eliminate the possibility of O-H insertions as side reactions in the next step. Selective catalytic carbenoid reactions in presence of water were, however, reported.[39-40] Solvent exchange with toluene, followed by addition of styrene (5.0 eq.) and $Rh_2(esp)_2$ (2 mol%) afforded after workup and purification 66% isolated yield of **30** and **31** in 8:1 dr *trans*:*cis* and a reduced yield of 26% for **29** (Scheme 3.7, general procedure B). While the yields for the iodo and bromocyclopropylesters were identical to the obtained yields with the tetrabutylammonium halides, the yield for the chlorinated product dropped by half. The lower nucleophilicity of the chloride anion compared to I^- and Br^-, due to the better solvation of Cl^- in H_2O, could be a reason for this drop in yield.[41] Longer reaction times for the nucleophilic substitutions did not increase the yields of the cyclopropane products.

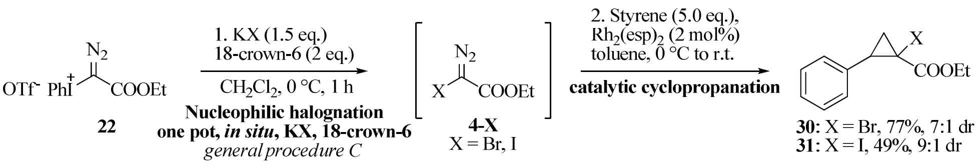


Scheme 3.7 Two phase procedure for the nucleophilic halogenations of **22** with potassium halides in CH_2Cl_2/H_2O (general procedure B).

The biphasic nucleophilic halogenation procedure gave a cleaner crude reaction mixture compared to the general procedure A and for the iodination and the bromination, this was a practical alternative to the reactions with the tetrabutylammonium salts though one more operational step was necessary to remove the water before the carbenoid reaction step. However, we have successfully shown that a nucleophilic halogenation of diazoesters can be achieved in a biphasic reaction medium under mild conditions. Other inorganic halide salts were then tested in the bromination process, however, LiBr and NaBr gave significantly lower yields of product **30**.

3.2.1.5 Catalytic cyclopropanation of halodiazoacetates generated *in situ via* nucleophilic halogenation of 22 employing potassium halides and 18-crown-6 (general procedure C)

A combination of the two presented procedures above into one procedure was then attempted and a one phase system with potassium halides in the presence of 18-crown-6 to solubilize and activate the halide salts was chosen. 18-crown-6 was shown by *Davies et al.* to be an unreactive substrate towards carbenoid C-H insertion with a donor-acceptor carbenoid[42] and crown ether derived diazo compounds have been used in photolytical intermolecular C-H insertions into methanol.[43] Crown ethers and analogous functionalized macrocycles were shown to be accessible *via* copper catalyzed dual O-H insertion of bis-diazo ketones into polyethylene glycols[44] by *McKervey et al.* and *via* Rh(II) catalyzed ylide formation-ring opening sequences as recently demonstrated by *Lacour et al.*.[45-48] We thus assumed 18-crown-6 to be compatible with the carbenoid reaction of the halodiazo compounds. Following general procedure A, but replacing the TBAX with the potassium halides and 18-crown-6 under otherwise identical conditions afforded, after workup and purification, a yield of 77% for the bromocyclopropylester **30**, which was the highest so far obtained yield for the nucleophilic halogenations and catalytic cyclopropanation protocol. The iodocyclopropylester **31**, however, was obtained in a reduced yield of 49%. In case of the chlorination, no product was obtained since KCl could not be dissolved in combination with 18-crown-6 (Scheme 3.8).

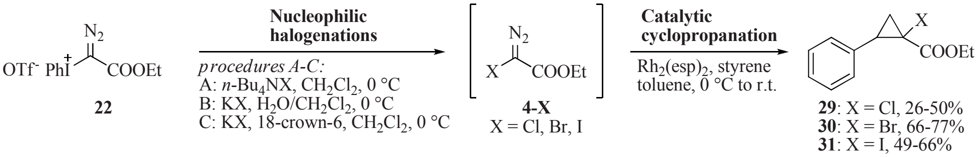


Scheme 3.8 One phase nucleophilic halogenation of **22** with potassium halides and 18-crown-6 (general procedure C).

A dropwise addition of the diazo compound **22** was attempted in a one pot reaction having all compounds present at the same time. Unfortunately, this gave a complex mixture of compounds which could not be characterized, and only traces of cyclopropane product were identified. The Rh(II) catalyzed decomposition of **22** as a competition reaction was assumed to take place which lead to side reactions.

Table 3.1 summarizes the results obtained with the three new developed nucleophilic halogenation protocols and compares the yields of the halocyclopropyl products with the electrophilic method.

Table 3.1 Nucleophilic halogenations of **22** with procedures A-C and subsequent catalytic cyclopropanation.



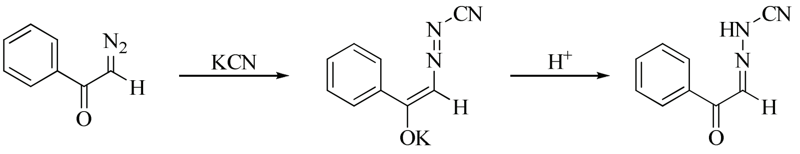
			Yield[a] (%) (dr (*trans*:*cis*))[b]			
Entry	**X**	**Product**	**Procedure A**[c]	**Procedure B**[d]	**Procedure C**[e]	**Electrophilic**[38]
1	Cl	**29**	50 (7:1)	26 (7:1)	-	87 (7:1)
2	Br	**30**	67 (8:1)	66 (8:1)	77 (7:1)	91 (9:1)
3	I	**31**	65 (8:1)	66 (8:1)	49 (9:1)	85 (7:1)

[a] Isolated yields of both diastereomers after column chromatography; [b] Estimated by ^{1}H NMR of the crude product mixture; [c] **22** (0.1-0.2 mmol) dissolved in dry CH_2Cl_2 (1-2 mL), 0 °C, TBAX (1.5 eq.) added, 1 h at 0 °C, SiO_2-plug optional, CH_2Cl_2 exchange with dry toluene (0 °C, 2 mL), styrene (5.0 eq.), 2 mol% $Rh_2(esp)_2$ in 1 mL dry toluene, 0 °C to r.t.; [d] **22** (0.1-0.2 mmol) dissolved in dry CH_2Cl_2 (1 mL), 0 °C, KX (1.5 eq.) in H_2O (1 mL) added, 0 °C for 10–30 min, $MgSO_4$/celite plug (CH_2Cl_2, -30 °C), CH_2Cl_2 exchange with dry toluene (0 °C, 2 mL), styrene (5.0 eq.), 2 mol% $Rh_2(esp)_2$ in 1 mL dry toluene, 0 °C to r.t.; [e] KX (1.5 eq.) and 18-crown-6 (2 eq.) dissolved in dry CH_2Cl_2 (1 mL), 0 °C, **22** (0.1-0.2 mmol) added, 0 °C for 1 h, CH_2Cl_2 exchange with dry toluene (2 mL), CH_2Cl_2 (0.5 mL) added, styrene (5.0 eq.), 2 mol% $Rh_2(esp)_2$ in 1 mL dry toluene, 0 °C to r.t..

Highest yields for the iodocyclopropylester **31** were achieved with procedures A and B *via* TBAI (65%) and the biphasic system (66%) and a diastereomeric ratio of 8:1 *trans*:*cis* in both cases. For the bromocyclopropylester **30** general procedure C, involving KBr and 18-crown-6, was most efficient and gave a good yield of 77% and a dr of 7:1 *trans*:*cis*. The chlorocyclopropylester **29**, however, was achieved in a moderate yield of 50% *via* procedure A, the two alternative methods based on potassium chloride were not efficient in this case. Increasing the equivalents of the halide sources did not lead to higher yields of the halocyclopropylesters for all three procedures A-C. Instead, more di- and trihalogenated esters were obtained as seen before for the halodiazophosphonates (Chapter 2, Scheme 2.4).

Although all three new methods gave lower yields than the previously reported electrophilic halogenation procedure, we have successfully demonstrated that the nucleophilic halogenation of α-aryliodinium diazoester triflate **22** was a synthetic alternative to generate halodiazoesters in a convenient way. Whereas the electrophilic substitution was based on a two step process involving deprotonation with base and addition of the electrophile, the nucleophilic substitution was a one step process under base free conditions. The byproducts from the nucleophilic substitution (KOTf or *n*-Bu_4NOTf and PhI) were easily removed by aqueous extraction, evaporation *in vacuo* and chromatography.

An explanation for the lower yields of the cyclopropanations *via* the nucleophilic halogenations could be the competitive nucleophilic attack of the halogen anion on the terminal nitrogen of the diazo group. It is known, that diazo compounds can react with nucleophiles under addition to the terminal nitrogen which results in formation of the corresponding azines.[49] The cyanide anion, being a pseudo halide, is reported to add to diazo ketone **32** to form the corresponding cyano hydrazones **33** (Scheme 3.9).[50-51] This general competitive reactivity of diazo compounds with nucleophiles must be taken into consideration for the discussed reactions. In Chapter 6, we will discuss and present results which correspond to that reactivity.



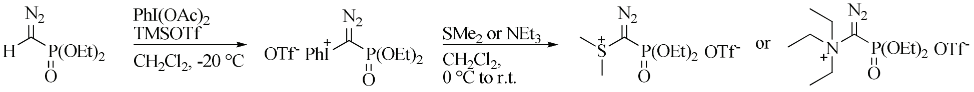
32 **33**

Scheme 3.9 Reaction of diazoacetophenone **32** with potassium cyanide to **33** by *Wolff*.[50-51]

3.2.2 Diazophosphonates

3.2.2.1 Preparation of α-aryliodonium, α-dimethylsulfonium and α-triethylammonium diazophosphonate triflates 34, 35 and 36

As seen and discussed in Chapter 2, halodiazophosphonates are valuable organic entities with high synthetic potential. Therefore, we aimed to extend the nucleophilic halogenations demonstrated for the diazoesters towards the diazophosphonates. The three new compounds **34**, **35** and **36** were prepared in analogy to the procedure used for the diazoesters starting from EDP **3** (Scheme 3.10). α-Aryliodonium diazophosphonate triflate **34** was obtained in 72% yield as a yellow solid, which was thermally less stable than the corresponding ester **22** and had to be handled and stored below 5 °C. The α-dimethylsulfonium diazophosphonate triflate **35**, on the other hand, was thermally stable and was obtained in almost quantitative yield from **34** as a colorless oil. The α-triethylammonium diazophosphonate triflate **36**, obtained as a bright yellow oil in 71% yield, was also stable under ambient conditions.



3 **34**, 72% **35**, 98% **36**, 71%

Scheme 3.10 Preparation of α-onium diazophosphonate triflates **34**, **35** and **36**.

The distinct differences in thermal stability of **34** compared to **35** and **36** as well as to the corresponding ester **22** prompted us to perform kinetic measurements on decompositions and nucleophilic substitution rates, which will be presented and discussed in Chapter 5.

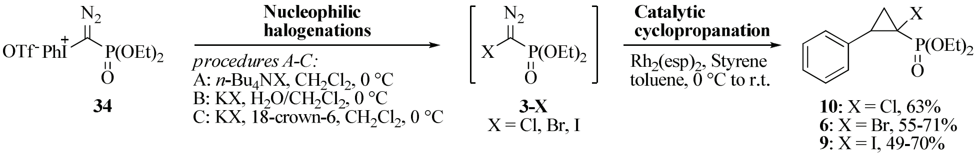
3.2.2.2 Catalytic cyclopropanation of halodiazophosphonates generated *in situ via* nucleophilic halogenation of 34 with general procedures A-C

The nucleophilic halogenation procedures A-C were applied to **34** and the yields of the isolated halocyclopropylphosphonates **6**, **9** and **10** were compared to the developed electrophilic halogenation method which was presented in Chapter 2 (Table 3.2).

The nucleophilic halogenation procedure A based on the tetrabutylammonium halides afforded the halocyclopropylphosphonates **6**, **9** and **10** in 63-71% yields and 12:1 dr *trans*:*cis*. The chlorocyclopropylphosphonate **10** was obtained in 63% yield which was higher than in case of the corresponding chlorocyclopropylester **29** with 50%, whereas the yields for the bromo and iodocyclopropylphosphonates were in a similar range to the esters. The biphasic procedure B lead to decreased yields for the chloro and bromocyclopropylphosphonates **10** and **6**, whereas the iodocyclopropylphosphonate **9** was obtained in a slightly increased yield of 70%. The low yield of **10** was in accordance with the observation for the diazoesters. Procedure C was again unsuccessful in case of the chlorination, but afforded 66% of the bromocyclopropylphosphonate **6** and 49% of the iodocyclopropylphosphonate **9**.

The most efficient method for the iodination appeared to be procedure B, which was also found for the diazoesters. Procedure C, on the other hand, gave the lowest yields of the iodocyclopropylacetates and phosphonates, whereas procedure A was most efficient for the bromination and chlorination of **34**.

Table 3.2 *In situ* nucleophilic halogenations of **34** with procedures A-C and subsequent catalytic cyclopropanation.



			Yield[a] (%) (dr (*trans*:*cis*))[b]			
Entry	**X**	**Product**	**Procedure A[c]**	**Procedure B[d]**	**Procedure C[e]**	**Electrophilic[52]**
1	Cl	**10**	63 (12:1)	<10		77 (12:1)
2	Br	**6**	71 (12:1)	55 (12:1)	66 (11:1)	82 (12:1)
3	I	**9**	66 (12:1)	70 (12:1)	49 (13:1)	77 (16:1)

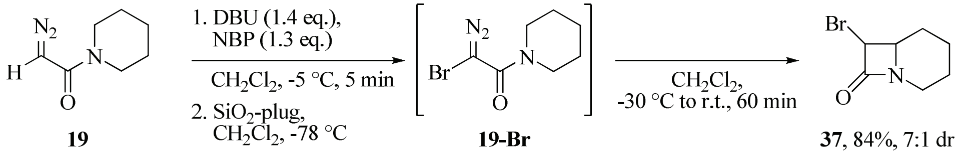
[a]Isolated yields of both diastereomers after column chromatography; [b]Measured by ^{1}H NMR of the crude product mixture; [c]**34** (0.1-0.2 mmol) dissolved in dry CH$_2$Cl$_2$ (2 mL) at 0 °C, TBAX (1.5 eq.) added, 1 h at 0 °C, CH$_2$Cl$_2$ exchange with dry toluene (0 °C, 2 mL), styrene (5.0 eq.), 2 mol% Rh$_2$(esp)$_2$ in 1 mL dry toluene, 0 °C to r.t.; [d]**34** (0.1-0.2 mmol) dissolved in dry CH$_2$Cl$_2$ (1 mL), 0 °C, KX (1.5 eq.) in H$_2$O (1 mL) added, 0 °C for 30-60 min, MgSO$_4$/celite plug (CH$_2$Cl$_2$, -30 °C), CH$_2$Cl$_2$ exchange with dry toluene (0 °C, 2 mL), styrene (5.0 eq.), 2 mol% Rh$_2$(esp)$_2$ in 1 mL dry toluene, 0 °C to r.t.; [e]KX (1.5 eq.) and 18-crown-6 (2 eq.) dissolved in dry CH$_2$Cl$_2$ (1 mL), 0 °C, **34** (0.1-0.2 mmol) added, 0 °C for 1 h, CH$_2$Cl$_2$ exchange with dry toluene (2 mL), CH$_2$Cl$_2$ (0.5 mL) added, styrene (5.0 eq.), 2 mol% Rh$_2$(esp)$_2$ in1 mL dry toluene, 0 °C to r.t..

Although the highest obtained yields for the halocyclopropylphosphonates *via* the nucleophilic substitutions were approximately 10% lower when compared to the corresponding electrophilic halogenations, we have successfully developed three new alternative methods for the *in situ* generation of halodiazophosphonates in addition to the electrophilic halogenation. When base sensitive substrates are to be used in the electrophilic one pot halogenation with NaH, the complementary nucleophilic halogenation offers a compatible alternative under base-free conditions.

3.2.3 Diazoamides

Diazoamides are an important and well described third class of diazo compounds. One of the most frequently applied reactions, among their known reactivities, are the intramolecular C-H insertions to lactams.[53-59]

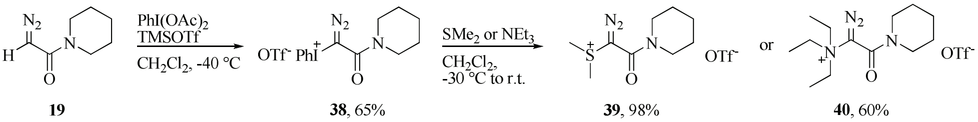
Our group recently reported the electrophilic brominations of different diazoacetamides employing DBU and *N*-bromophthalimide (NBP) to afford the corresponding α-bromodiazoamides which underwent thermal intramolecular C-H insertion to the corresponding α-bromo-β-lactam (Scheme 3.11).[60-61] The diazopiperidinylamide **19** was found to give high yields of the β-lactam **37** and we wondered if the alternative nucleophilic bromination was applicable to that substrate. α-Bromo-β-lactam **37** has previously been reported and synthesized by *Åkermark et al.* by thermal decomposition of (*N*-dibromoacetylpiperidine)phenylmercury and intramolecular C-H insertion of the resulting carbene.[62]



Scheme 3.11 Reported electrophilic bromination of diazopiperidinylamide **19** followed by thermal intramolecular C-H insertion to α-bromo-β-lactam **37**.[61]

3.2.3.1 Preparation of α-aryliodonium, α-dimethylsulfonium and α-triethylammonium diazopiperidinylamide triflates 38, 39 and 40

In analogy to the diazoesters and diazophosphonates, we prepared the three α-onium diazopiperidinylamides **38**, **39** and **40** from **19** (Scheme 3.12).



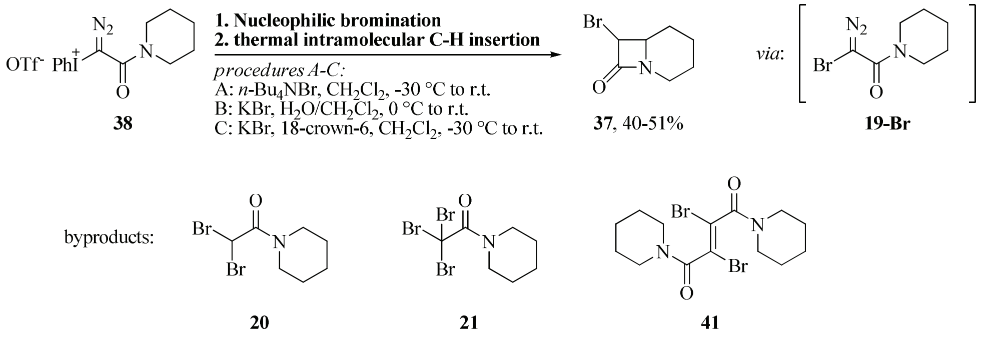
Scheme 3.12 Preparation of α-onium diazopiperidinylamide triflates **38**, **39** and **40**.

α-Aryliodonium diazopiperidinylamide **38** was found to decompose thermally at room temperature. Therefore the temperature for preparation of **38** had to be lowered to -40 °C and **19** had to be added dropwise in CH_2Cl_2. The precipitation of **38** was also more difficult compared to the esters and phosphonates, since addition of Et_2O at -40 °C lead to an emulsion which was reversed by raising the temperature to 0 °C followed by addition of Et_2O in portions until precipitation occurred. After 15 minutes at 0 °C, the mixture was cooled back to -40 °C and then quickly filtered and stored in the fridge at -20 °C. The adjusted procedure afforded 65% of **38** as a beautiful orange solid. The corresponding α-dimethylsulfonium diazopiperidinylamide triflate **39** was obtained in nearly quantitative yield as a yellow amorphous solid and the α-triethylammonium diazopiperidinylamide triflate **40** as a yellow semi-solid in 60% yield. As seen for the diazophosphonates, the α-dimethylsulfonium and α-triethylammonium diazopiperidinylamides **39** and **40** were thermally stable whereas the α-aryliodonium diazopiperidinylamide triflate **38** was significantly less stable and decomposed within 4 hours at room temperature (see Chapter 5).

3.2.3.2 Nucleophilic bromination of 38 and thermal intramolecular C-H insertion to 37

All three procedures A-C lead to nearly instant loss of iodobenezene from **38** when followed by ^{1}H NMR and TLC analysis. A rapid color change from yellow/orange to deep red indicated the formation of bromodiazopiperidinylamide **19-Br**. Upon warming to room temperature the thermal decomposition of **19-Br**, indicated by gas evolution and decolorization of the reaction mixture, afforded α-bromo-β-lactam **37**. The dibrominated **20** was formed as the main byproduct and **21** as well as dimer **41** as minor byproducts in different ratios and yields (Table 3.3). The highest obtained yield of **37** was achieved with procedure C, however, the reaction conditions had to be adjusted to compensate for byproduct formation and decomposition of **38**. Thus, a low concentration of **38** in dichloromethane and dropwise addition of the bromide source in slight excess (1.05-1.1 eq.) at -30 °C reduced the amount of over halogenated amides and formation of the dimer. However, the dibrominated product **20** was obtained in an average of 18%, whereas the electrophilic bromination gave only 3% of **20**.[61]

Table 3.3 Nucleophilic bromination of **38** with procedures A-C.



	yield[a] of **37** (*cis*+*trans*) [%], ratio *cis*-**37**:*trans*-**37**:**20**[b]	
	Nucleophilic	**Electrophilic**[61]
Procedure A[c]	45, 1:6:1.5	
Procedure B[d]	40, 1:5:1	84%, 1:6:0.2
Procedure C[e]	51, 1:6.3:1.3	

[a]Isolated yields of both diastereomers after column chromatography; [b]Determined by ^{1}H NMR of crude reaction mixture; [c]**38** (0.1-0.2 mmol) dissolved in dry CH$_2$Cl$_2$ (3-5 mL) at -30 °C, TBAB (1.05 eq.) in dry CH$_2$Cl$_2$ (3-5 mL) added dropwise over 15 min, -30 °C for 15 min, -30 °C to r.t.; [d]**38** (0.1-0.2 mmol) dissolved in dry CH$_2$Cl$_2$ (3-5 mL), 0 °C, KBr (1.0-1.1 eq.) in H$_2$O (1-2 mL) added, 0 °C for 15 min, 0 °C to r.t.; [e]KBr (1.0-1.1 eq.) and 18-crown-6 (1.5-2.0 eq.) dissolved in dry CH$_2$Cl$_2$ (5 mL) at r.t., added dropwise to solution of **38** (0.1-0.2 mmol) in dry CH$_2$Cl$_2$ (5 mL) at -30 °C, 15 min at -30 °C, -30 °C to r.t..

The low yield of **37** obtained with procedure B (40%) could be a result of the applied temperature of 0 °C though slightly lower temperatures could have been applied as well due to a lowered freezing point of the aqueous phase. At 0 °C some decomposition of **38** prior to the actual nucleophilic bromination could have occurred and lowered the yield. Also, a dropwise addition of a solution of KBr in H$_2$O was impractical due to the same reason. Since no catalyst was involved in the thermal intramolecular C-H insertion step, a phase separation to avoid any side reactions from catalytic O-H insertions was not necessary. Products from thermal O-H insertion of **19-Br** into H$_2$O were not detected, demonstrating the high preference of diazoamides for intramolecular C-H insertion. This was also shown recently by *Afonso et al.* in a photochemical[63] and catalytic asymmetric intramolecular C-H insertion of an α-diazoacetamide in water.[64-66]

Unfortunately, the iodination with TBAI and KI/18-crown-6 gave only 23% of the corresponding α-iodo-β-lactam. Significant amounts of iodine were detected during the reaction and the product released iodine upon standing at room temperature. It seemed that a redox reaction took place, causing the formation of I$_2$ during the reaction, which was observed to a much lesser extent for the esters and phosphonates. The α-iodo-β-lactam is, to the best of our knowledge, not reported, whereas the α-bromo and α-chloro-β-lactams are.[67-69] This may indicate an issue with the stability of the α-iodo-β-lactam.

The large difference in yield for the nucleophilic and electrophilic bromination is clearly a result of the formation of byproducts. In contrast to the diazoesters and diazophosphonates, which showed only traces of over halogenations, the diazopiperidinylamide seemed to have a higher affinity to react with more than 1 equivalent of NBS in the nucleophilic substitution. The lower thermal stability of **38** compared to **22** and **34** with regard to PhI extrusion indicated a higher reactivity of **38** towards nucleophilic substitution. Also, **19-Br** was assumed to be less stable and thus more reactive towards loss of N_2 compared to **4-Br** since the amide group is less electron withdrawing than the ester group. It is well known that the stability of diazo compounds towards extrusion of nitrogen increases with the electron withdrawing ability of the attached groups[70] and it could be hypothesized that the stabilities of the α-aryliodonium diazo triflates correlate with the reactivities of the halodiazo compounds. Kinetic measurements of thermal decompositions and nucleophilic substitution rates of the different classes of α-aryliodonium diazo triflates will be presented and discussed in Chapter 5.

3.3 Summary and conclusions

While being at the beginning of our research in the field of nucleophilic substitutions of the α-onium diazo compounds, we have successfully demonstrated that negatively charged halides can partake in nucleophilic substitutions of diazo compounds. We have developed three methods for the nucleophilic halogenation of diazoesters, diazophosphonates and diazopiperidinylamides which add as new synthetic alternatives to the electrophilic halogenation procedures. The α-aryliodonium diazo triflate salts **22**, **34** and **38** were prepared and used as the starting materials for the nucleophilic halogenations with tetrabutylammonium halides and potassium halides. The halodiazoesters and halodiazophosphonates gave moderate to good yields of the corresponding halocyclopropanes *via* Rh(II) catalyzed intermolecular cyclopropanation with styrene and the bromodiazopiperidinylamide reacted in a thermal intramolecular C-H insertion to afford the α-bromo-β-lactam in moderate yields. Although the obtained yields for the products were found to be lower than the ones for the electrophilic halogenations, the variability of reaction conditions of procedures A-C made this nucleophilic methodology an attractive and convenient alternative to the electrophilic halogenation. The results of this chapter are published in **Paper II**.[17]

The promising results obtained and presented in this chapter prompted us to intensify our research towards reactivities and properties of the α-onium diazo triflate salts. Computational calculations for nucleophilic substitutions of the α-onium diazoesters will be presented in the next chapter followed by kinetic measurements of decompositions and nucleophilic substitutions in Chapter 5.

3.4 Experimental

Experimental procedures and product characterizations can be found in **Paper II**.

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Chapter 4

Computational studies of the mechanism and transition states for nucleophilic substitutions of α-aryliodonium diazoester triflate

4.1 Introduction

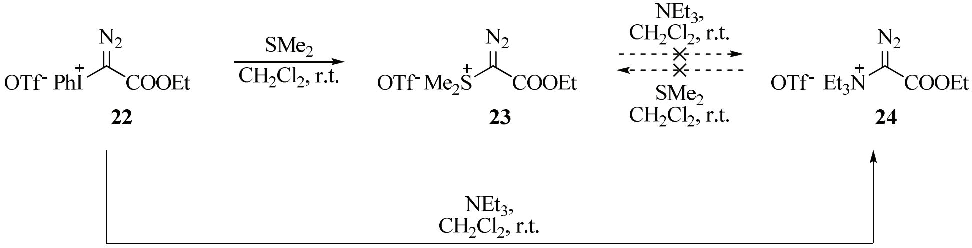
Our experimental results from the nucleophilic halogenations of the α-aryliodonium diazo compounds presented in the previous chapter prompted us to perform DFT calculations to get an insight into the mechanism and the transition states of the substitution reactions and to compare the experimental results and observations with theoretically obtained data. Since the α-aryliodonium diazoester triflate **22** is stable at room temperature and readily accessible from commercially available EDA, we focused our calculations on the diazoesters. The DFT calculations presented in the following sections were performed by Martin Hennum (see list of contributors). The results will be presented and discussed in this chapter as part of our research towards the reactivities of the α-onium diazo compounds.

4.2 Results and discussion

As seen in the previous chapter, nucleophilic halogenations of the α-aryliodonium diazo compounds **22**, **34** and **38** proceeded readily at room temperature. However, we asked ourselves, if nucleophilic halogenations were also possible with the corresponding α-dimethylsulfonium **23**, **35**, **39** and α-triethylammonium diazo compounds **24**, **36**, **40**. Furthermore, the preparation of the α-dimethylsulfonium and α-triethylammonium diazo triflate salts resulted in significantly thermally more stable diazo compounds compared to their parent α-aryliodonium diazo triflate salts and their preparation is based on the α-aryliodonium diazo triflates as starting materials. We wondered if we could prepare the α-triethylammonium diazoester triflate **24** from the α-dimethylsulfonium diazoester triflate **23** and *vice versa* and which energies and barriers for the transition states are involved.

4.2.1 Nucleophilic substitutions of 22, 23 and 24 with SMe_2 and NEt_3 (experimental)

To investigate the selectivities and reactivities of the nucleophilic substitutions with the neutral nucleophiles SMe_2 and NEt_3, we started our experiments by adding NEt_3 to a solution of **23** in CH_2Cl_2 at room temperature and followed the reaction by ^{1}H NMR. Interestingly, no product **24** could be detected, even after prolonged reaction times. We then attempted the analogous reversed reaction by starting from **24** and addition of SMe_2 at room temperature in CH_2Cl_2. Again, no substitution was observed, which indicated that the nucleophilic substitution of **22** with SMe_2 and NEt_3 was energetically favored, whereas the other two substitutions under these conditions were not (Scheme 4.1).



Scheme 4.1 Experimental results of nucleophilic substitutions of **22**, **23** and **24** with SMe_2 and NEt_3.

In addition to the nucleophilic substitution of **22** with NEt_3 and SMe_2 we also performed a reaction to test if the bromodiazoacetate **4-Br** can be substituted with NEt_3, and Br^- acting as leaving group. The preparation and isolation of **4-Br** was performed following the electrophilic halogenation procedure.[1] The addition of NEt_3 did not show any evidence of nucleophilic substitution at 0 °C, and lead to a mixture of several compounds which could not be identified upon warming to room temperature. To support the experimental results we calculated the energies for the transition states that were involved in the discussed reactions.

4.2.2 Transition states for the nucleophilic substitutions of 22 with SMe_2 and NEt_3

The calculated energies of the transition states for the nucleophilic substitutions of **22** with SMe_2 and NEt_3, as well as for **23** with NEt_3 are shown in Figure 4.1. The DFT calculations were performed on the Gaussian 09 program package[2] using B3LYP. Iodine was described by the LanL2DY basis set,[3-5] all other atoms by the 6-31+g(d,p) basis set[6-14] and the continuum solvation model CPCM was used for all calculations with dichloromethane as solvent. Further computational details can be found in **Paper II** and the Supporting Information.[15]

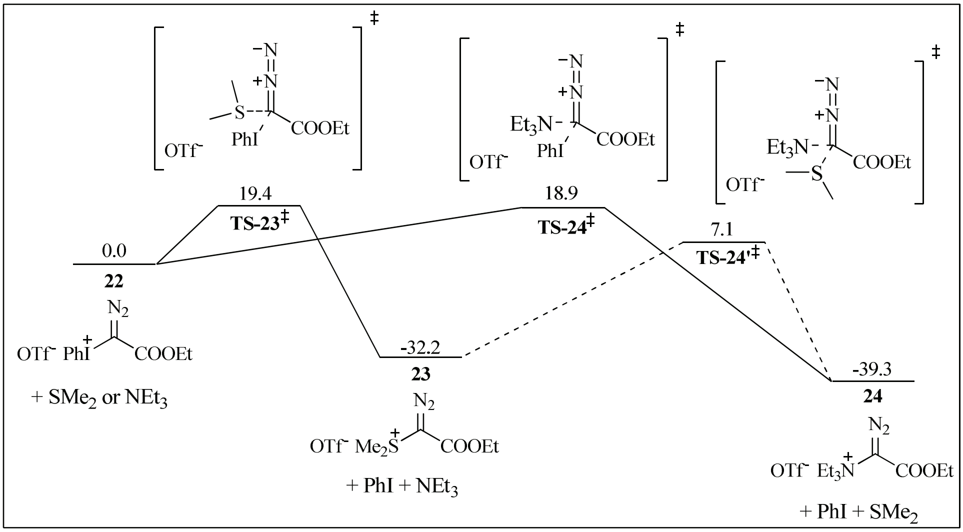


Figure 4.1 Calculated transition state energies for the nucleophilic substitutions of **22** with SMe_2 and NEt_3 and **23** with NEt_3. Energies are reported in kcal mol^{-1}.

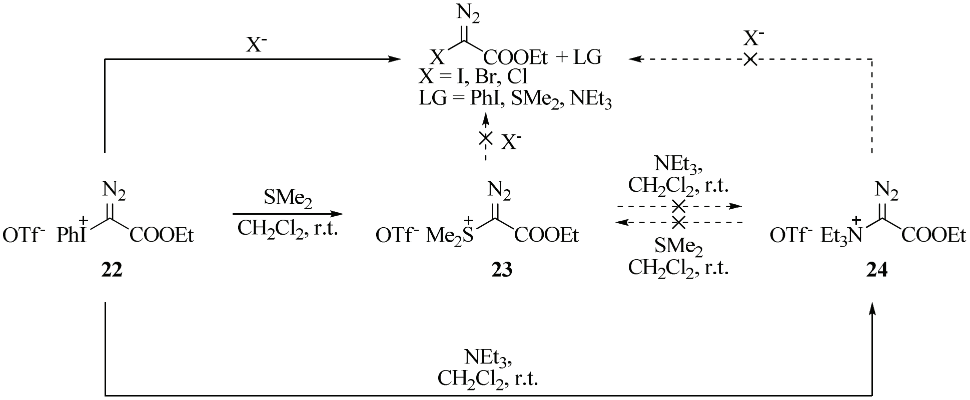
For the reaction of α-aryliodonium diazoester triflate **22** with SMe_2 a transition state energy of 19.4 kcal mol^{-1} for **TS-23**‡ resulted and an energy for the product **23** of -32.2 kcal mol^{-1} relative to **22**. For the reaction with NEt_3 the transition state **TS-24**‡ was with 18.9 kcal mol^{-1} only 0.5 kcal mol^{-1} lower in energy than for the reaction with SMe_2. However, the product **24** was 39.3 kcal mol^{-1} lower in energy than the starting material **22** and 7.1 kcal mol^{-1} relative to **23**. The energy that was gained when **22** reacted with either SMe_2 or NEt_3 indicated an increased thermal stability of the corresponding products **23** and **24** which was in accordance with the high driving force of the reaction. A thermal stability difference in case of the diazoesters **22**-**24** at room temperature was not observed experimentally since none of the α-onium diazoester triflate salts showed measurable decompositions at room temperature. For the phosphonates and piperidinylamides, however, the α-dimethylsulfonium and α-triethylammonium diazo triflates were significantly more stable than the α-aryliodonium diazo triflates with regard to measurable loss of leaving group and subsequent decomposition. The calculated transition state energy of **TS-24'**‡ for the reaction of **23** with NEt_3 was with 39.3 kcal mol^{-1} twice as high as for the reaction of **22** with NEt_3 which indicated a distinct leaving group dependence. The experimental result that no nucleophilic substitution was observed between **23** and NEt_3 was well as **24** and SMe_2 is therefore theoretically supported as to be kinetically disadvantageous under these conditions.

In general, the calculated results were in agreement with the experimental observations and showed that iodobenzene acted as a very potent leaving group compared to SMe_2 and

NEt_3. This allowed the conclusion that the nucleophilic substitutions are to be performed preferentially with **22** whereas the α-dimethylsulfonioum and α-triethylammonium triflate salts may, due to their higher stability, be the substrates of choice for catalytic carbenoid transformations in which elevated temperatures were necessary (see Chapter 6).

4.2.3 Experimental results towards the nucleophilic halogenations of 22, 23 and 24

In analogy to the neutral nucleophiles SMe_2 and NEt_3 (see above) we also tested the halides in nucleophilic substitution reactions with all three α-onium diazoesters. As seen in Chapter 3 and as will be presented in the next chapter, nucleophilic halogenations with α-aryliodonium diazoester **22** proceeded readily at room temperature in $CDCl_3$, with Cl^- showing the slowest rate (95% substitution after 35 min). However, none of the halides showed substitution with one of the two other α-onium diazoesters **23** and **24** which corresponded to the results obtained in the previous section for the reactions with NEt_3 and SMe_2 (Scheme 4.2).



Scheme 4.2 Experimental results of nucleophilic substitutions of **22**, **23** and **24** with SMe_2, NEt_3 and halides (X = Cl, Br, I; LG = PhI, SMe_2, NEt_3).

4.2.4 Transition states for the nucleophilic brominations of 22, 23 and 24

The calculated energy profile for the bromination of **22** is shown in Figure 4.2. TBAB was chosen as bromide source. In the first step of the nucleophilic bromination an ion exchange from triflate to bromide was assumed, which brings the Br^- in close proximity to the reaction center. This ion exchange resulted in an energy of -5.9 kcal mol^{-1} for **22-Br** relative to **22**. The transition state energy of **TS-22-Br**‡ for the nucleophilic bromination was calculated to be 29.3 kcal mol^{-1} relative to **22-Br** which was higher than for Me_2S and NEt_3, however significantly lower than the energy for the theoretical nucleophilic substitution of **22** with NEt_3 (39.3 kcal mol^{-1}). The α-bromodiazoacetate **4-Br** was 25.7 kcal mol^{-1} lower in energy than **22-Br**.

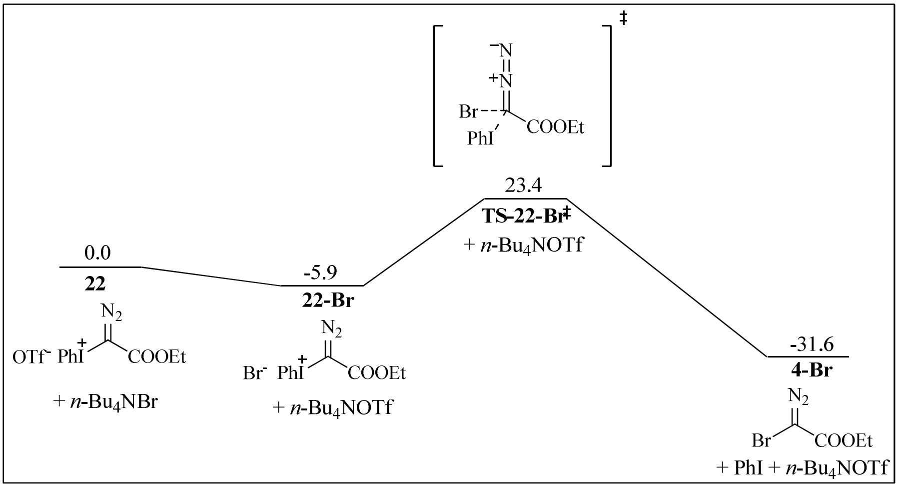


Figure 4.2 Calculated transition state energy for the nucleophilic bromination of **22**. Energies are reported in kcal mol^{-1}.

In case of the bromination the of α-dimethylsulfonium diazoester triflate **23** the transition state **TS-23-Br**‡ had a calculated energy of 35.7 kcal mol^{-1} relative to **23-Br**, and the product **4-Br** was 2.1 kcal mol^{-1} higher in energy than **23-Br** which made this reaction unfavorable compared to the nucleophilic bromination with **22** as seen in the experimental results (Figure 4.3).

For the nucleophilic bromination of the α-triethylammonium diazoester triflate **24** the calculated energy for the transition state **TS-24-Br**‡ was with 43.3 kcal mol^{-1} even higher than for **TS-23-Br**‡ and the α-bromodiazoacetate **4-Br** 8.6 kcal mol^{-1} higher in energy than **24-Br** which made this reaction the least favorable under these conditions (Figure 4.4).

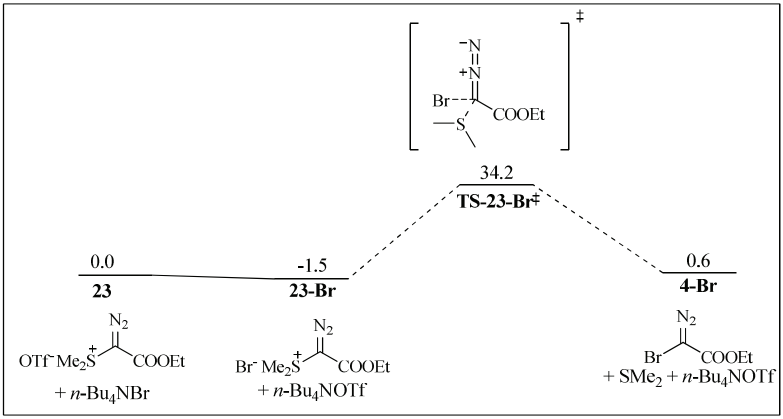


Figure 4.3 Calculated transition state energy for the nucleophilic bromination of **23** which is not observed experimentally. Energies are reported in kcal mol^{-1}.

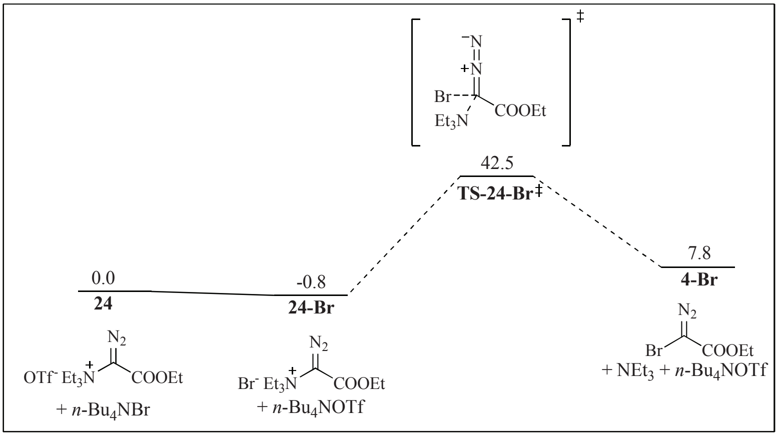


Figure 4.4 Calculated transition state energy for the nucleophilic bromination of **24** which is not observed experimentally. Energies are reported in kcal mol^{-1}.

The theoretical results for the nucleophilic bromination clearly showed the dependence of the reactivity on the leaving group which could then be ordered as PhI>>SMe_2>NEt_3. This trend also correlated inversely with their nucleophilicities for the nucleophilic substitutions shown in Figure 4.1 and Scheme 4.2. As will be seen in the next chapter, the kinetic measurements for the nucleophilic substitutions of **22** with SMe_2 and NEt_3, as well as different halides, clearly revealed a significant dependence on the nucleophile.

4.2.5 Geometries of the transition states and mechanistic results

Besides the energies of the transition states and compounds which were involved in the nucleophilic substitutions, the geometries of the transition states were of significant interest to get an insight into and understanding of the mechanism. For the nucleophilic substitution reaction of the α-aryliodonium diazoester **22** two different mechanisms could be possible. First, an out-of-plane addition-elimination with a tetrahedral transition state geometry and π* attack of the nucleophile. The second possibility was the S_N2-type mechanism with a linear transition state and in-plane σ* attack.

The geometries of the calculated energy-minimized transition states **TS-23**‡, **TS-24**‡, **TS-24'**‡ and **TS-22-Br**‡ are shown in Figure 4.5 and Figure 4.6. Relevant bond distances and angles of the transition states of the experimentally observed reactions are given in Table 4.1 (p. 67).

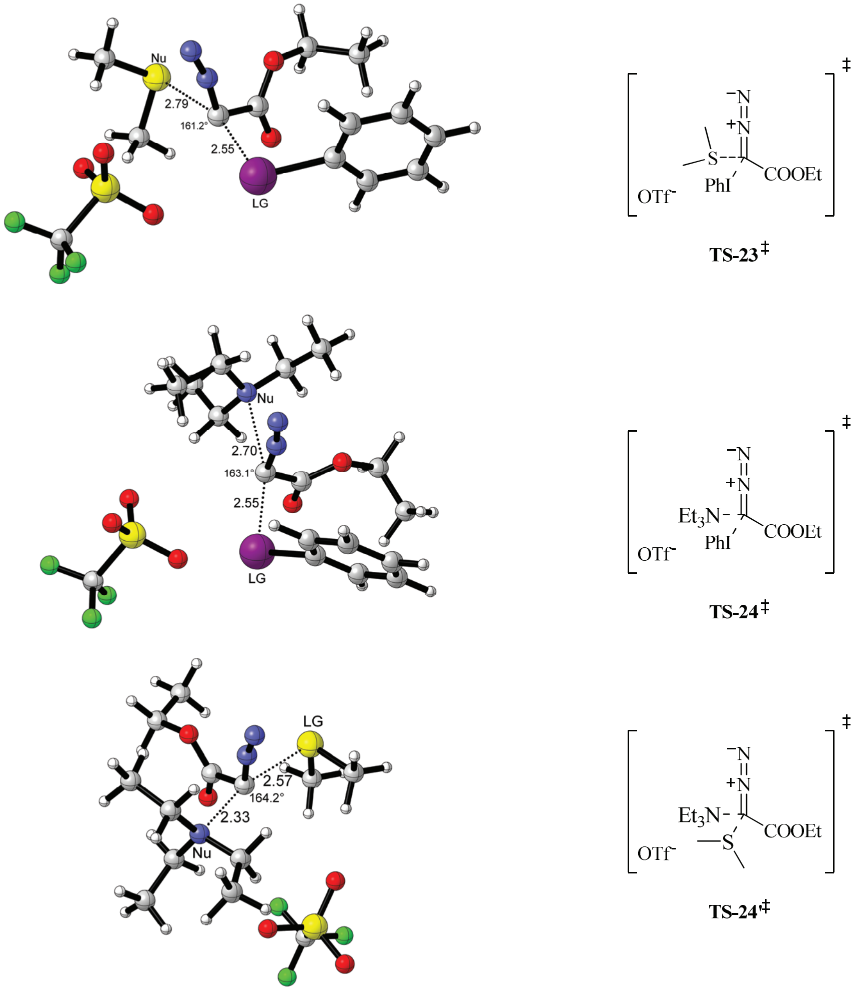
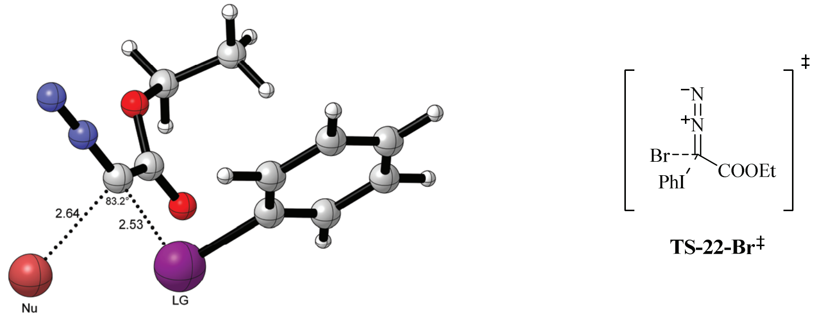


Figure 4.5 Geometries of energy-minimized calculated transition states **TS-23**‡ (top), **TS-24**‡ (middle) and **TS-24'**‡ (bottom). Relevant bond lengths [Å] and angles are shown. LG = leaving group, Nu = nucleophile.



TS-22-Br‡

Figure 4.6 Geometry of energy-minimized calculated transition state **TS-22-Br**‡. Relevant bond lengths [Å] and angle are shown. LG = leaving group (PhI), Nu = nucleophile (Br^{-}).

For the nucleophilic substitutions with the neutral nucleophiles SMe_2 (**TS-23**‡) and NEt_3 in (**TS-24**‡ and **TS-24'**‡) a nearly linear geometry for the Nu-C-LG angle was calculated. This geometry resembled an in-plane S_N2-type mechanism with back side attack on the σ* orbital of the C-I bond.

In contrast to the almost linear transition states obtained for the nucleophilic substitutions of **22** with SMe_2 and NEt_3, the transition state **TS-22-Br**‡ for the nucleophilic bromination was found to be non-linear. The Br-C-LG angle was with 83.2° roughly half as big as for **TS-23**‡ and **TS-24**‡ which could be due to *Coulomb* interactions between the positively charged I^{+} and the negatively charged Br^{-}. The geometry of **TS-22-Br**‡ resembled a tetrahedral-like transition state for addition-elimination mechanisms on carbonyls. The Br-C-N angle of 102°, close to the *Bürgi-Dunitz* angle of 105±5° resembled an addition of a nucleophile to carbonyl groups,[18-19] in contrast to 89° for **TS-23**‡ and 84° for **TS-24**‡ (Table 4.1). Another reason for the distinct difference in transition state geometry could be the presence of the triflate anion in **TS-23**‡ and **TS-24**‡ which was found to occupy the tetrahedral side of the reaction center and is absent in **TS-22-Br**‡.

Table 4.1 also shows the differences and changes in bond lengths in the transition states compared to the corresponding starting materials and products. The relevant bond lengths were the Nu-C bond related to the product and the LG-C related to the starting material. The differences could then give an indication if the transition state was reactant like or product like. As expected for a transition state, the developing nucleophile-carbon bond (Nu-C) and the breaking leaving group-carbon bond (LG-C) were significantly lengthened compared to the starting materials and products. In **TS-23**‡ the elongation of the nucleophile-carbon bond $\Delta(\text{Nu-C})_{\mathbf{23}}$ was 1.3Å (59%, Nu = SMe_2) and the leaving group-carbon bond difference

Δ(LG-C)$_{\mathbf{23}}$ = 0.45Å (21%, LG = PhI). In **TS-24**‡ the leaving group-carbon bond enlargement was with Δ(LG-C)$_{\mathbf{24}}$ = 0.44 Å (21%, LG = PhI) similar to **TS-23**‡, however, the nucleophile-carbon bond difference Δ(Nu-C)$_{\mathbf{24}}$ = 1.22 Å (82%, Nu = NEt_3) was significantly larger than in **TS-23**‡, indicating a less tight, more asynchronous and reactant like transition state. The relative large steric bulk of the NEt_3 group compared to the SMe_2 group could be one reason for the less tight transition state. For the bromination in **TS-22-Br**‡ the PhI-C bond difference Δ(LG-C)$_{\mathbf{4\text{-}Br}}$ = 0.36Å (17%) was slightly smaller than for the reactions with SMe_2 and NEt_3, and the developing Br-C bond had a difference of Δ(Nu-C)$_{\mathbf{4\text{-}Br}}$ = 0.75Å (40%) which was also smaller than in the two other transition states. As a consequence, **TS-22-Br**‡ was found to be a tighter, less asynchronous transition state, possibly due to the relatively small Br^- and the attraction of the charges (I^+/Br^-) in that transition state.

In general, in all transition states the Δ(Nu-C) bond differences were larger than the corresponding Δ(LG-C) bond differences, which was in agreement with the *Hammond* Postulate[20] for an asynchronous, reactant-like transition state of an exergonic reaction.

4.3 Summary and conclusions

In conclusion, the results of the DFT calculations for the trends of the energies of the nucleophilic substitutions were in agreement with the experimental results. We have found that nucleophilic substitutions with SMe_2 and NEt_3 or nucleophilic bromination only occured with α-aryliodonium diazoester triflate **22** and no nucleophilic substitution was observed with the other α-onium triflate salts. The corresponding transition state energies were calculated to be below 20 kcal mol^{-1} for the experimentally observed nucleophilic substitutions with SMe_2 and NEt_3, 29.3 kcal mol^{-1} for the bromination and above 30 kcal mol^{-1} for the experimentally not occurring substitutions with **23** and **24**. The experimental results showed clearly that a rapid nucleophilic substitution of **22** took place at room temperature with all nucleophiles. The α-dimethylsulfonium diazoester triflate **23** and the α-triethylammonium diazoester triflate **24** were calculated to have a lower inherent energy which was in agreement with the experimental observations for the trend of decompositions of the analogous diazophosphonates and diazopiperidinylamides (see next chapter). The transition states for the nucleophilic substitution with SMe_2 and NEt_3 showed a nearly linear geometry, indicating a S_N2-type mechanism. The transition state for the bromination on the other hand resembled an addition-elimination mechanism with a nearly *Bürgi-Dunitz* angle approach of 102° of the bromide. The changes of the bond lengths in the transition states compared to the starting materials or products indicated early asynchronous transition states which corresponded to exergonic reactions described in the *Hammond* Postulate.

The next chapter will focus on kinetic measurements and properties of the prepared α-onium diazo compounds.

4.4 References and footnotes

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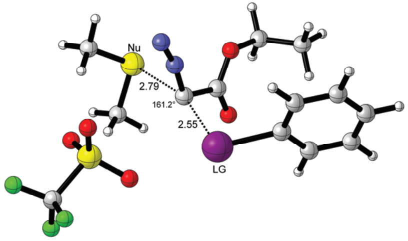
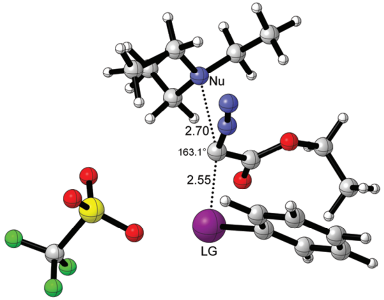
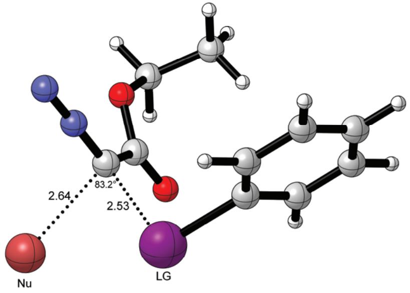
Table 4.1 Bond distances [Å] and bond angles of starting materials, transition states and products.







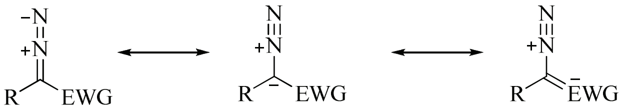
		22	**TS-23‡**	**23**	Δ [Å]	Δ [%]	**22**	**TS-24‡**	**24**	Δ [Å]	Δ [%]	**22-Br**	**TS-22-Br‡**	**4-Br**	Δ [Å]	Δ [%]
Distances [Å]	LG-C	2,104	2,552		0,45	21	2,104	2,547		0,44	21	2,17	2,533		0,36	17
	C-N	1,309	1,345	1,321			1,309	1,327	1,315			1,301	1,279	1,305		
	Nu-C		2,785	1,757	1,03	59		2,703	1,484	1,22	82		2,638	1,889	0,75	40
Angles [°]	LG-C-N	118,3	100,74				118,27	101,1				118,36	115,95			
	LG-C-C	120,8	103,37				120,79	103,25				120,41	113,56			
	Nu-C-LG		161,19					163,09					83,2			
	Nu-C-N		89,41	121				83,53	117				101,8	117,26		
	Nu-C-C		85,77	119				88,34	126,4				107	121,9		

Chapter 5

Kinetic measurements of decompositions and nucleophilic substitutions of α-onium diazo triflate salts

5.1 Introduction

One drawback associated with diazo compounds is their thermal, photochemical or acidic instability with regard to loss of dinitrogen in dependence of their substituents. While several studies are reported that deal with the acid mediated decomposition of diazo compounds,[1-4] reports about comparative experimental thermal stabilities of diazo compounds are, to the best of our knowledge, scarce. Early studies by *Staudinger et al.* from 1916, dealing with the acidic and thermal decomposition of diazo compounds revealed that the thermal and the acidic stability does not always correlate.[5] The availability of the electron pair on the carbon atom which bears the diazo group determines the basicity and stability of the diazo compound which is therefore dependent on the electron withdrawing group. In a series of studies conducted by *Jugelt et al.* in the late 1960s, the acid hydrolysis of diazocarbonyl compounds[6-9] and the analogous diazophosphonates[10] was investigated. The result was that the diazocarbonyls show a 2-6 times slower acidic hydrolysis than the diazophosphonates which was attributed to the increased mesomeric effect of the carbonyl group compared to the phosphonates.[10] The increased mesomeric delocalization of the electron pair of the diazo carbon in the diazoester was then responsible for the slower protonation.[10] Investigations of the thermolysis of diazophosphonates and phosphinoxides by the same authors revealed that electron withdrawing phosphonates and phosphinoxides, which decrease the electron density at the diazo carbon, disadvantage the elimination of dinitrogen compared to more electron rich phosphonates or phosphinoxides which promote the breaking of the C-N-bond.[11] In comparison to the esters on the other hand, the phosphonates showed higher thermal stabilities. This was explained with the increased double bond character of the C-N bond of the diazo group for the phosphonate resulting from higher presence of mesomeric structure **42a** for the phosphonate compared to **42c** for the ester (Figure 5.1).[10]



42a **42b** **42c**

EWG = P(O)(OR)$_2$:
higher basicity, higher thermal stability

EWG = COOR:
lower basicity, lower thernal stability

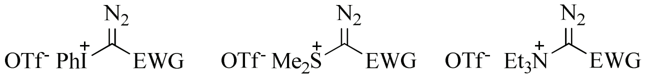
Figure 5.1 Mesomeric structures responsible for basicity and thermal stability of diazo compounds by *Jugelt et al.*.[10]

The α-onium diazo compounds described in Chapter 3 contain, formally, two leaving groups, the onium moiety and the dinitrogen group. The type of onium moiety (iodonium, dimethylsulfonium and triethylammonium) in combination with the second group that flanks the diazo carbon (ester, phosphonate or amide) was found to significantly influence the reactivity and stability of these diazo compounds (see Chapter 3 and 4). We asked ourselves if the analogy of basicity and electron density of the diazo carbon could be transferred to the α-onium diazo compounds and if the onium leaving groups are influenced by the electron withdrawing groups. Therefore, we investigated the thermal stabilities of the α-onium diazo compounds and measured the kinetics of the nucleophilic substitutions to get an insight into their reactivities and physical properties and obtain reactivity trends. All following measurements are based on monitoring the leaving group iodobenzene over time (unless otherwise noted) *via* ^{1}H NMR spectroscopy (200 Mhz). A relation between loss of iodobenzene and loss of N_2 was not determined. The decompositions were thus defined as to occur at the same rate as the loss of leaving group took place. The measured rates should give a qualitative comparison of trends of reactivities.

5.2 Results and discussion

5.2.1 Thermal decompositions in solution at room temperature

We started our investigations with measurements of rates of thermal decompositions of the α-onium diazo compounds in solution at room temperature. Only if the thermal decomposition was slower than the nucleophilic substitutions, were kinetic measurements of nucleophilic substitution rates possible and the dependencies on the nucleophiles could be determined (see 5.2.3 and 5.2.4). The set of investigated α-onium diazo compounds is shown in Figure 5.2.



EWG =	COOEt	**22**	**23**	**24**
	$P(O)(OEt)_2$	**34**	**35**	**36**
	$CON(CH_2)_5$	**38**	**39**	**40**

Figure 5.2 Investigated α-onium diazo compounds for thermal decomposition.

The first set of diazo compounds were the α-onium diazoesters **22-24**. The compounds were dissolved in $CDCl_3$ at room temperature in an approximate concentration of 0.02-0.05 M and ^1H NMR spectra were measured at different time intervals. All three α-onium diazoester triflates appeared to be stable at room temperature, no decomposition from extrusion of the α-onium group could be detected even after several days. The diazoesters **22-24** thus seemed to be a stable class of diazo compounds at room temperature. At 40 °C, however, **22** decomposed within 7 hours as an experiment in refluxing CH_2Cl_2 showed (see 5.2.2 and 6.2.1).

The α-onium diazophosphonates **34-36** were then investigated under similar conditions to allow a direct comparison of the influence of the electron withdrawing group (ester vs. phosphonate). The α-aryliodonium diazophosphonate **34** showed complete decolorization and decomposition by loss of iodobenzene within 4 days at room temperature in $CDCl_3$ and CH_2Cl_2. The decomposition was followed and monitored by direct integration of the relevant proton peaks of the starting material **34** ($\delta = 8.12$ ppm, d, 2H) and the generated iodobenzene ($\delta = 7.11$ ppm, m, 2H) (Figure 5.3). A half life of 28 h for **34** in $CDCl_3$ at room temperature was determined (Table 5.1). In contrast to the α-aryliodonium diazoester **22**, the phosphonate **34** showed significant decomposition at room temperature in $CDCl_3$. The electron withdrawing group had therefore a direct influence on the leaving group iodobenzene, with the phosphonate being less electron withdrawing than the ester moiety and increased leaving group activation for the diazophosphonate. The decomposition of **34** was found to be strongly solvent dependent. In the polar solvents MeOH and THF the decomposition of **34** was significantly slower, with a half life of 1 week. The non-polar solvents $CDCl_3$ and dichloromethane were assumed to accelerate the generation of the non-polar, neutral iodobenzene whereas the polar solvents could stabilize the charged, ionic starting materials assuming that the decomposition resembled a reversed nucleophilic addition.[12] The product from decomposition of **34** could, unfortunately, not be clearly identified. The ^1H NMR spectra showed an appearing doublet at $\delta = 4.63$ ppm, corresponding to one proton of a methine group, as well as a broad singlet at δ = 7.98 ppm, from a heteroatom bound proton.

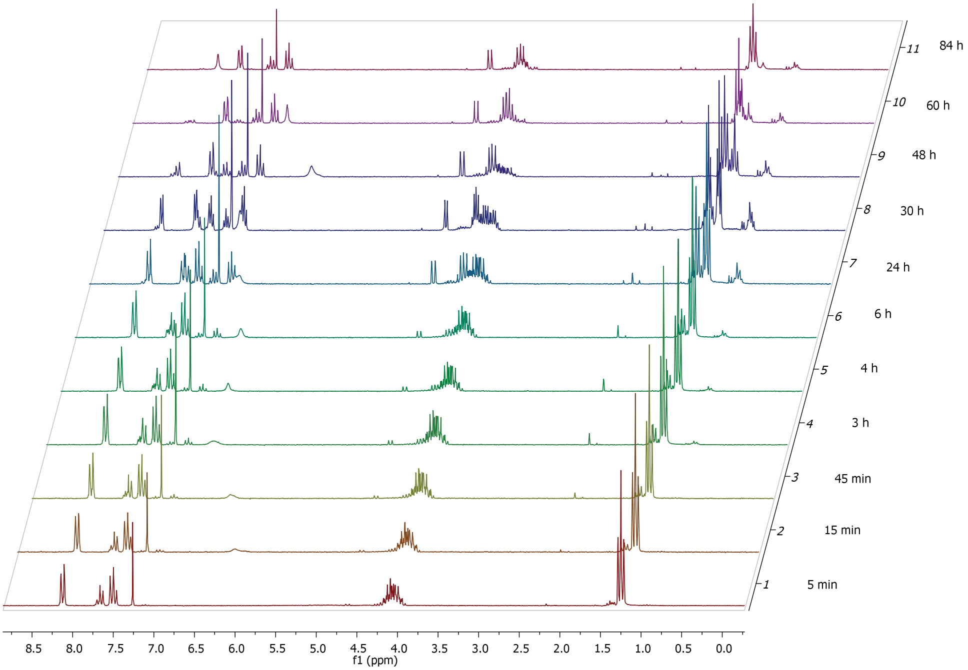
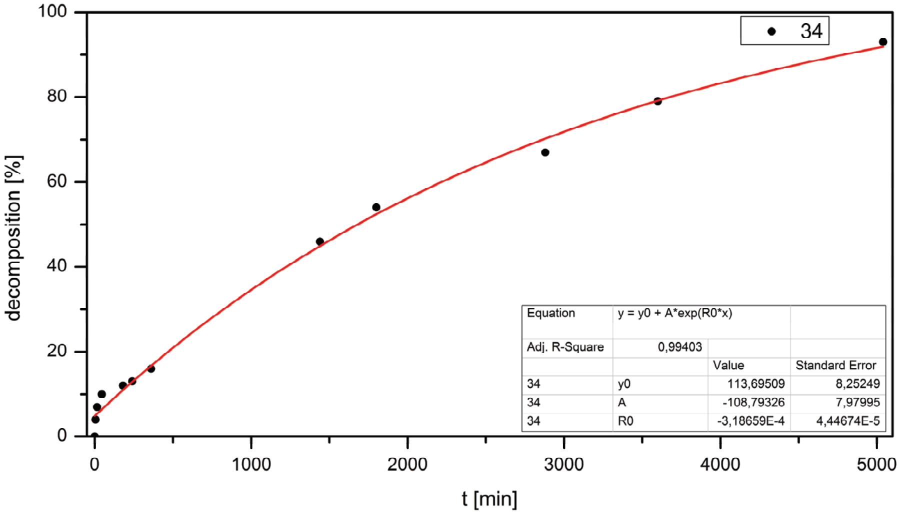


Figure 5.3 ^{1}H NMR of decomposition of **34** in $CDCl_3$ at room temperature.

Table 5.1 Decomposition of **34** in $CDCl_3$ at room temperature.

t [min]/[h]	Decomposition [%]
0 min	0
5 min	4
15 min	7
45 min	10
3 h	12
4 h	13
6 h	16
24 h	46
30 h	54
48 h	67
60 h	79
84 h	93



Equation	y = y0 + A*exp(R0*x)		
Adj. R-Square	0,99403		
		Value	Standard Error
34	y0	113,69509	8,25249
34	A	-108,79326	7,97995
34	R0	-3,18659E-4	4,44674E-5

Figure 5.4 Decomposition rate of **34** in $CDCl_3$ at room temperature.

The α-dimethylsulfonium diazophosphonate **35** and α-triethylammonium diazophosphonate **36** showed no decomposition at room temperature. This indicated a significant stabilization caused by the dimethylsulfonium and triethylammonium groups and their lower leaving group ability compared to iodobenzene. Even under reflux in toluene no decomposition of **36** occurred and the diazo functionality remained intact, while **35** decomposed within 1 h at that temperature (see Chapter 6, 6.2.1). This allowed the conclusion that the electron withdrawing ability of the dimethylsulfonium and triethylammonium group had a stabilizing effect on the diazo functionality.

In case of the α-aryliodonium diazopiperidinylamide **38** the decomposition rate was faster with a half life of approximately 20 min and complete loss of PhI and decomposition after 90 minutes (Figure 5.5, Table 5.2). It was therefore shown that the acceptor group had a significant influence on the stabilities of the α-aryliodonium diazo triflate salts with regard to leaving group activity, which should also have consequences for the nucleophilic substitution rates.

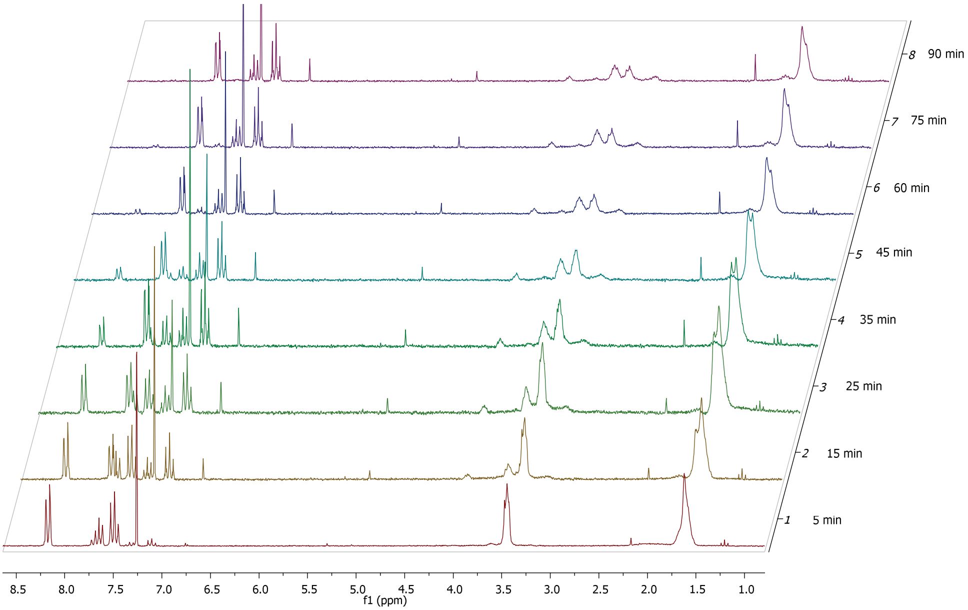


Figure 5.5 ^{1}H NMR of decomposition of **38** in $CDCl_3$ at room temperature.

Table 5.2 Decomposition of **38** in $CDCl_3$ at room temperature.

t [min]	Decomposition [%]
0	0
5	11
15	42
25	56
35	72
45	75
60	87
75	90
90	95

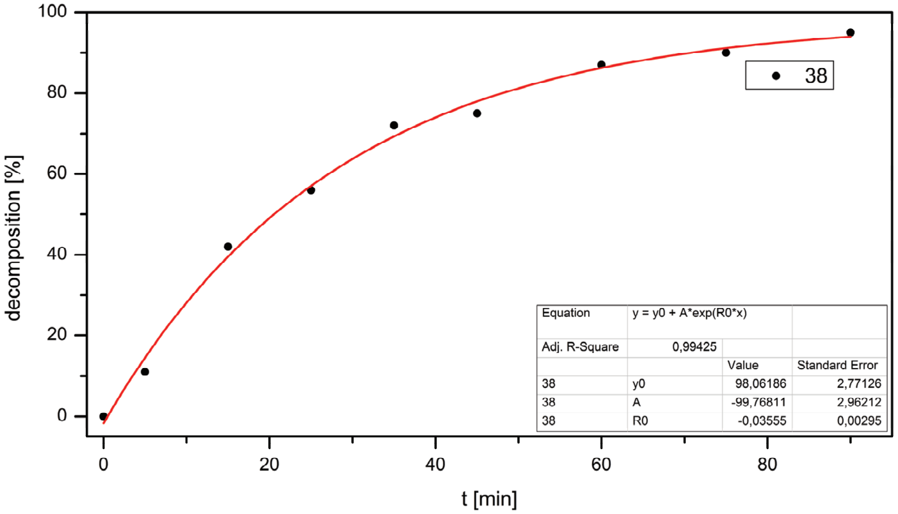
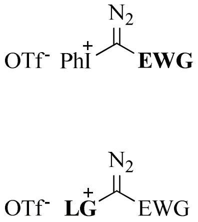


Figure 5.6 Decomposition rate of **38** in $CDCl_3$ at room temperature.

As for the esters and phosphonates, no decomposition of the α-dimethylsulfonium diazopiperidinylamide **39** and α-triethylammonium diazopiperidinylamide **40** was observed at room temperature.

The measured decomposition rates showed clearly the importance and influence of the acceptor group (EWG) on the activity of the leaving group iodobenzene with increasing activity and decomposition in the order of ester < phosphonate < amide (Figure 5.7a). Furthermore, dimethylsulfonium and triethylammonium as the second substituents significantly stabilized the diazo salts in comparison to iodobenzene (Figure 5.7b). Thus, both the leaving group, as well as the acceptor group were of importance for the thermal stabilities of the α-onium diazo compounds.



(a) Thermal stability increases in the order of
EWG: $CON(CH_2)_5 < P(O)(OEt)_2 < COOEt$

(b) Thermal stability increases in the order of
LG = PhI << SMe_2/NEt_3

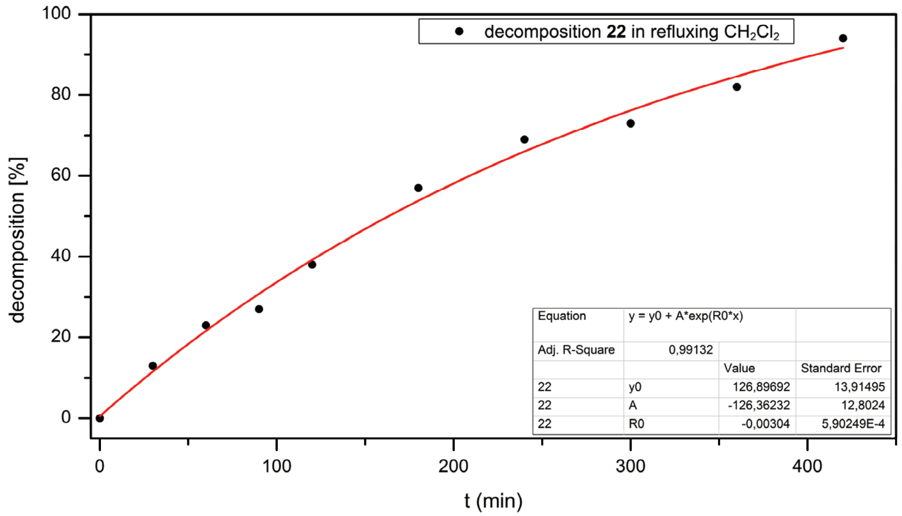
Figure 5.7 Influences of the acceptor group (EWG) and onium substituent (LG) on thermal stabilities.

5.2.2 Decomposition of α-aryliodonium diazoester triflate 22 at elevated temperature

While **22** was found to be stable at room temperature, it showed decomposition in refluxing dichloromethane (40 °C) within 8 hours (Table 5.3, Figure 5.8). The decomposition rates at elevated temperatures for the α-onium diazo triflates **23**, **24**, **35**, **36**, **39** and **40** will be discussed in the next chapter in context of their investigation towards thermal carbene chemistry.

Table 5.3 Decomposition of **22** in refluxing CH_2Cl_2.

t [min]	Decomposition [%]
0	0
30	13
60	23
90	27
120	38
180	57
240	69
300	73
360	82
420	94



Equation	y = y0 + A*exp(R0*x)		
Adj. R-Square	0,99132		
		Value	Standard Error
22	y0	126,89692	13,91495
22	A	-126,36232	12,8024
22	R0	-0,00304	5,90249E-4

Figure 5.8 Decomposition rate of **22** in refluxing CH_2Cl_2.

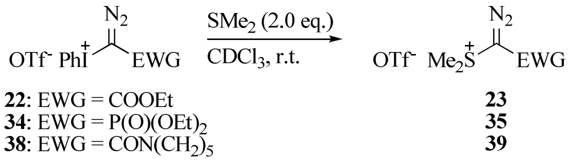
5.2.3 Kinetics of nucleophilic substitutions - influence of acceptor group

To verify the trends observed for the influence of the acceptor groups on the activation of the leaving group iodobenzene and the decomposition rates, we measured the rates of nucleophilic substitutions of **22**, **24** and **38** with 2.0 equivalents SMe_2 and NEt_3, respectively. The determination of the rates of decomposition and loss of leaving group PhI in the starting materials **22**, **34** and **38** was an important requirement since the nucleophilic substitutions had to occur at a higher rate to be measured reliably. The rates of nucleophilic substitution according to the decomposition rates would be expected to increase in the order **22** < **34** < **38**. The first set of nucleophilic substitutions was performed with SMe_2 as the nucleophile in $CDCl_3$ at room temperature.

The rates of nucleophilic substitutions with SMe_2 varied drastically depending on the class of α-aryliodonium diazo triflate salt (Table 5.4, Figure 5.9). As expected, the nucleophilic substitution of the diazoester **22** showed the slowest rate with nearly full substitution after 18 minutes. The α-aryliodonium diazophosphonate triflate **34** showed full conversion after 3 minutes, and the α-aryliodonium diazopiperidinylamide **38** reacted nearly instantly with complete substitution after one minute. All rates for the nucleophilic substitutions were significantly faster than the decomposition rates. Thus, the trend for the nucleophilic substitutions with SMe_2 was in agreement with the trend observed for the decompositions and the influence of the acceptor group was demonstrated.

The analogous reaction with 2.0 eq. NEt_3 resulted in nearly instant substitution even for the α-aryliodonium diazoester triflate **22**. The dependence on the nucleophile will be further discussed in the next sections.

Table 5.4 Rates of nucleophilic substitutions of **22**, **34** and **38** with 2.0 eq. SMe_2 in $CDCl_3$ at room temperature.



	Conversion [%]		
t [min]	**22**	**34**	**38**
0	0	0	0
1	28	92	100
2	45	97	
3	-	100	
4	65		
6	74		
8	80		
10	83		
12	85		
14	89		
16	94		
18	96		

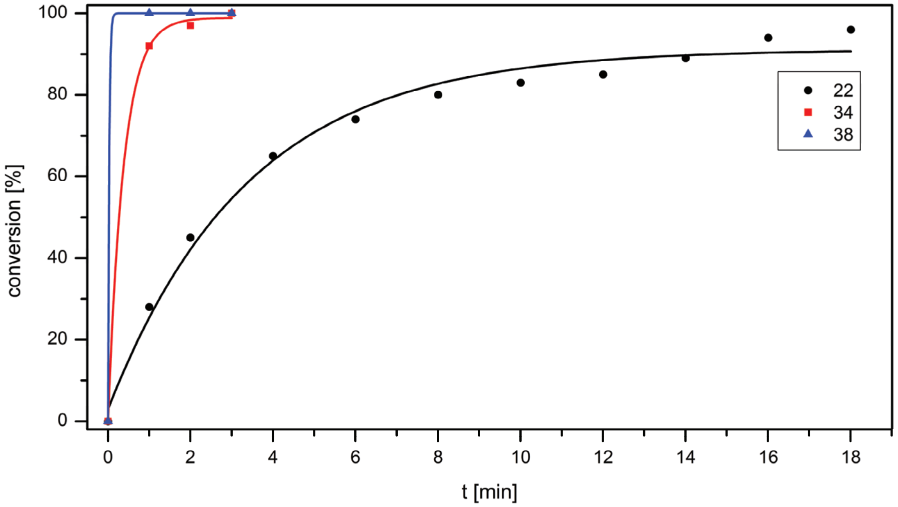
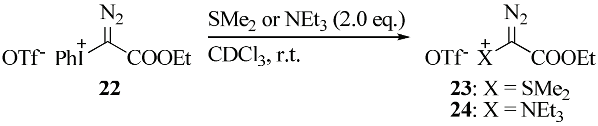


Figure 5.9 Rates of nucleophilic substitutions of **22**, **34** and **38** with 2.0 eq. SMe_2 at room temperature in $CDCl_3$.

5.2.4 Kinetics of nucleophilic substitutions - influence of the nucleophile

A comparison of the nucleophilic substitutions of **22** with 2.0 equivalents of the neutral nucleophiles SMe_2 and NEt_3 in $CDCl_3$ at room temperature should give insight into the influence of the nucleophile on the reaction rate. The nucleophilic substitution of **22** with SMe_2, as seen before, proceeded within 18 minutes to nearly completion. A drastic increase in reaction rate was observed for NEt_3, with full conversion after 1 minute (Table 5.5, Figure 5.10). NEt_3 is thus the more reactive nucleophile in this reaction compared to SMe_2.

Table 5.5 Rates of nucleophilic substitution of **22** with 2.0 eq. SMe_2 and NEt_3 in $CDCl_3$ at room temperature.



	Conversion [%]	
t [min]	**SMe_2**	**NEt_3**
0	0	0
1	28	100
2	45	
4	65	
6	74	
8	80	
10	83	
12	85	
14	89	
16	94	
18	96	

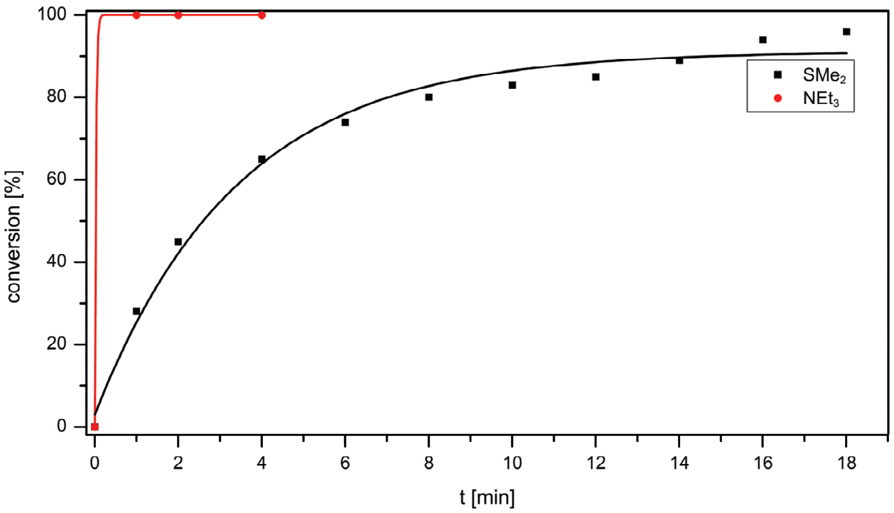


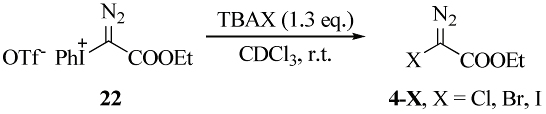
Figure 5.10 Rates of nucleophilic substitution of **22** with 2.0 eq. SMe_2 and NEt_3 in $CDCl_3$ at room temperature.

5.2.5 Kinetics of nucleophilic substitutions - halogenations

Having found a distinct nucleophile dependence for the substitutions with the neutral nucleophiles SMe_2 and NEt_3 we wanted to examine the rates for the nucleophilic halogenations of **22** with the negatively charged halides. The reactions were performed with 1.3 equivalents tetrabutylammonium halides in $CDCl_3$ at room temperature. The amount of iodobenzene developing over time was again the indicator for the reaction progress.

As seen in the previous section for SMe_2 and NEt_3, the nucleophilic substitution rate also depended on the nucleophilicity of the halides (Table 5.6, Figure 5.11). Chloride showed the slowest substitution rate with 95% conversion after 35 minutes. The bromination proceeded significantly faster with over 90% conversion after 8 minutes and the iodine reacted instantly albeit accompanied by partial release of elemental iodine.

Table 5.6 Rates of nucleophilic halogenations of **22** with 1.3 eq. TBAX in $CDCl_3$ at room temperature.



	Conversion [%] of 22		
t [min]	**X = Cl**	**X = Br**	**X = I**
0	0	0	0
1	13	43	100
2	15	51	
4	-	80	
5	26	-	
6	-	87	
8	-	90	
10	48	92	
12	-	93	
15	64		
20	76		
25	85		
30	93		
35	95		

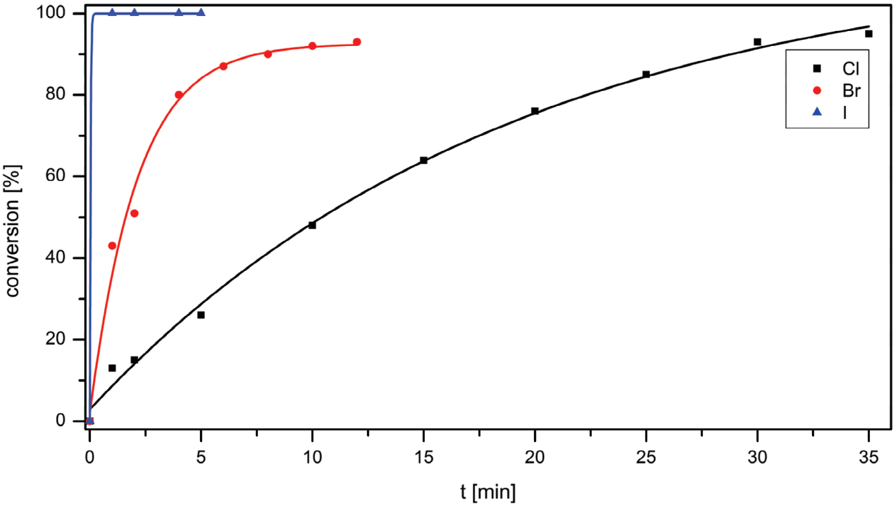


Figure 5.11 Nucleophilic halogenations of **22** with 1.3 eq. TBAX (X = Cl, Br, I) in $CDCl_3$ at room temperature.

5.3 Summary and conclusions

The results obtained from the kinetic measurements of the decompositions and nucleophilic substitutions showed that the electron withdrawing group and the α-onium substituent significantly influence the stability and reactivity of the α-onium diazo triflate salts. The thermal stabilities in solution towards loss of PhI from the α-aryliodonium diazo triflate salts **22**, **34** and **38** increased with the strength of the electron withdrawing group. The α-aryliodonium diazoester triflate **22** showed no loss of PhI at room temperature in $CDCl_3$, whereas the phosphonate decomposed within 4 days and the piperidinylamide in approximately 90 minutes. An analogous trend was observed for the rates of nucleophilic substitutions with SMe_2. The fastest rate of substitution was observed for the amide, a slower rate for the phosphonate and the ester showed the slowest rate for the nucleophilic substitution with SMe_2. The α-dimethylsulfonium and α-triethylammonium diazophosphonate triflates **35** and **36** and piperidinylamides **39** and **40** were significantly more stable than the corresponding α-aryliodonium triflates. Furthermore, a distinct dependence on the nucleophile for the substitutions was observed. Triethylamine reacted much faster with **22** than dimethylsulfide and the halides showed an increased reaction rate in the order of Cl < Br < I.

5.4 References and footnotes

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Chapter 6

Reactivities of the α-onium diazo compounds and mechanistic investigations

6.1 Introduction

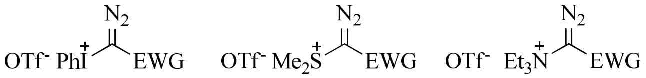
In the previous chapters we have shown that nucleophilic halogenations of the α-aryliodonium diazo triflate salts **22**, **34** and **38** could be applied successfully, leading to the corresponding halodiazo compounds which then underwent subsequent reactions. The chemistry of the α-onium diazo triflate salts, apart from the presented halogenations is unexplored. The investigation of the behavior of these compounds in carbene and transition-metal carbenoid chemistry and nucleophilic substitutions with alternative nucleophiles was therefore the focus of our reasearch. We wanted to investigate, if their reactivity corresponds to known and reported pathways of diazo compounds or if the α-onium moiety allows the introduction of new, interesting and unexpected reactivities and transformations. Optimizations and thorough exploration of reaction scopes and conditions were not performed, the current chapter should rather give an impression about general reactivity trends and mechanistic investigations.

Hence, the first part of this chapter presents results from reactions of the α-onium diazo triflate salts in catalytic carbenoid chemistry and catalyst free thermalizations. The second part of this chapter presents results from nucleophilic aminations and unexpected reactivities with phthalimide.

6.2 Results and discussion

6.2.1 Investigation of reactivities of α-onium diazo triflate salts *via* thermalization

The reactivities of the α-onium diazo compounds **22-24**, **34-36** and **38-41** (Figure 6.1) were investigated by first testing catalyst-free pathways to determine if any reactions resulted from free carbenes or decompositions at elevated temperatures and to set limitations for applicable reaction conditions.



EWG =	COOEt	**22**	**23**	**24**
	$P(O)(OEt)_2$	**34**	**35**	**36**
	$CON(CH_2)_5$	**38**	**39**	**40**

Figure 6.1 α-Onium diazo triflate salts investigated for reactivity towards thermal carbene chemistry and decomposition.

The α-aryliodonium diazo triflates **34** and **38** were previously shown to be unstable at room temperature (Chapter 5) and were thus decomposed at room temperature in $CDCl_3$ in the presence of styrene, to allow a free carbene (resulting from possible loss of N_2) to be trapped as the corresponding cyclopropane. Both diazo compounds did not show any traces of cyclopropanation after complete decomposition and the ^1H NMR spectra corresponded to the spectra obtained without styrene (see Chapter 5).

The remaining α-onium diazo triflate salts **22-24**, **35**, **36**, **39** and **41** were found to be stable at room temperature. To examine their behavior at elevated temperatures and to determine their temperature of decomposition in solution, the diazo compounds were heated to reflux in dichloromethane or to 90 °C in toluene if necessary (Table 6.1).

All decompositions were monitored by ^1H NMR. No distinct discrimination between decomposition by loss of dinitrogen or loss of leaving group could be made. The presented results should give a qualitative impression about the overall stability of the α-onium diazo compounds at elevated temperatures.

As seen in Chapter 5, section 5.2.2, the α-aryliodonium diazoester triflate **22** decomposed in refluxing CH_2Cl_2 within 7 h. The α-dimethylsulfonium diazoester triflate **23**, however, was stable under these conditions and decomposed at 90 °C in toluene within 4 h, while the α-triethylammonium diazoester triflate **24** showed the slowest decomposition rate for the diazoesters of approximately 10 hours at that temperature. The stability trends reported in Chapter 5 could therefore be confirmed as depending on the α-onium group with increasing stability in the order of PhI < SMe_2 < NEt_3. The α-dimethylsulfonium diazophosphonate **35** decomposed in less than 1 h at 90 °C, whereas the corresponding α-triethylammonium diazophosphonate triflate **36** showed an unexpected high stability and slow decomposition within 15 h at 90 °C. The α-onium diazopiperidinylamides decomposed significantly faster compared to their analogous diazoesters and diazophosphonates, with complete decomposition within 2 h at 40 °C for **39** and 5 h at 90 °C for **40** (Table 6.1).

Table 6.1 Decompositions of α-onium diazo triflate salts at elevated temperatures.

		Decomposition in solution		
Entry	**Compound**	**Room temperature**	**40 °C (refluxing CH_2Cl_2)**	**90 °C (toluene)**
1	**22**	stable	7 h[a]	
2	**23**	stable	stable	appr. 4 h[b]
3	**24**	stable	stable	appr. 10 h[c]
4	**34**	4 days[a]		
5	**35**	stable	stable	< 1h[d]
6	**36**	stable	stable	appr. 15 h[e]
7	**38**	90 min[a]		
8	**39**	stable	< 2 h[f]	
9	**40**	stable	stable	appr. 5 h[g]

[a]Decomposition followed by generation of PhI; [b]Followed by disappearance of singlet at δ = 3.34 ppm; [c]Followed by disappearance of quartet at δ = 3.86 ppm; [d]Complete absence of singlet at δ = 3.32 ppm; [e]Followed by disappearance of quartet at δ = 3.75 ppm; [f]Followed by disappearance of singlet at δ = 3.33 ppm; [g]Followed by relative integration of quartet at δ = 3.76 ppm and multiplet at 3.39 ppm.

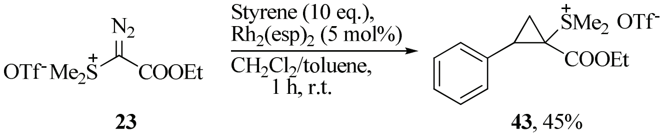
Having determined the decomposition temperatures, we thermalized the α-onium diazo compounds in the presence of large excess of styrene. None of the diazo compounds showed any cyclopropane product from thermal intermolecular cyclopropanation, the ^{1}H NMR spectra of the crude reaction mixtures corresponded to the obtained ones from the decompositions in the absence of styrene. This could either mean that no carbene intermediates were formed during the decomposition process or, if carbenes were generated, they reacted in other pathways. Other carbene trapping reagents were not tested. MeOH or amines for thermal O-H[1] or N-H[2] insertions or sulfides for ylide[3] formation could be an alternative.

6.2.2 Reactivities of the α-onium diazo triflate salts in catalytic carbenoid chemistry

The reactivities of the α-onium diazo triflate salts towards catalytic carbenoid cyclopropanation were then tested with Rh(II) catalysts. As the reaction system we chose dry dichloromethane as solvent and styrene as substrate with $Rh_2(OAc)_4$ or $Rh_2(esp)_2$ as catalysts. The initial experiment with **22** at -20 °C resulted in intense gas evolution upon addition of **22** to $Rh_2(OAc)_4$ and styrene in CH_2Cl_2. After warming to room temperature, the ^{1}H NMR spectrum of the crude reaction mixture showed the formation of iodobenzene and numerous additional signals which could not be assigned clearly. No product could be isolated or identified from the reaction mixture. Lowering the temperature even further to -40 °C and dropwise addition of **22** did not show any improvement. The gas evolution could be an indication that a carbenoid was formed, the iodobenzene, however, could result from decomposition of the carbenoid or a resulting product. The catalytic carbenoid reactions of **22** were not further investigated.

The α-dimethylsulfonium diazoester triflate **23** showed formation of the phenylcyclopropyl dimethylsulfonium triflate **43** upon catalysis with $Rh_2(esp)_2$ in the presence of styrene (10 eq.) in a mixture of CH_2Cl_2/toluene at room temperature (Scheme 6.1). A quantitative isolation of **43** could not be achieved though precipitation of **43** was possible with CH_2Cl_2/Et_2O as solvents. The reproducibility of the reaction was not satisfactory and the highest obtained isolated yield of **43** by precipitation was 45%. $Rh_2(OAc)_4$ appeared to be much less efficient and gave only very low amounts of product. The phenylcyclopropyl dimethylsulfonium triflate **43** is an unreported compound and offers the possibility for demethylation of the sulfonium moiety to obtain a neutral methylsulfide cyclopropane, but this reaction was not attempted in this project.

We were able to obtain an X-ray crystal structure of the main isomer of **43**, which showed a *cis* relationship between the ester group and the aryl substituent (Figure 6.2).



Scheme 6.1 Rh(II) catalyzed cyclopropanation of **23** with styrene to **43**.

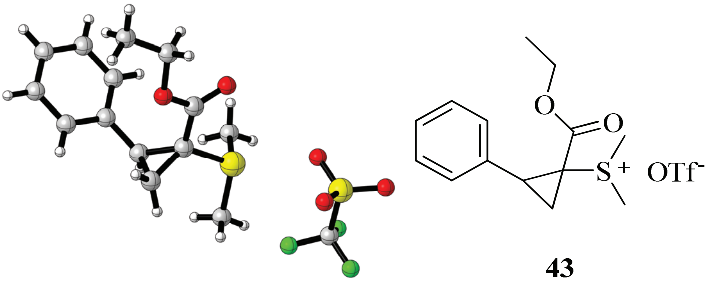
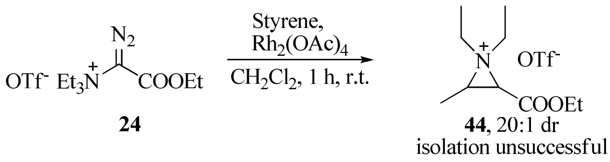


Figure 6.2 X-ray crystal structure of precipitated **43**.[4]

Studies by *Doyle*[5-6] and *Charette*[7-9] showed that the steric bulk and basicity of the electron withdrawing substituents in the diazo compound can determine and influence the stereochemistry in the cyclopropane product. The more basic group is able to donate electron density towards the electrophilic carbon of the approaching alkene in an out-of-plane conformation[7-8] in the transition state and directs its substituent (Ph in styrene) to a *trans* relation (*trans*-directing group). Under the assumption of **23** resembling a diacceptor diazo compound, we would assume the ester to be more basic which would then be the *trans*-directing group. The stereochemistry of the cyclopropane **43**, however, showed the opposite *cis* relation between the ester and the phenyl group.

Although the obtained yield for the catalytic cyclopropanation of **23** with styrene was moderate (45%), we have shown that the α-dimethylsulfonium diazoester triflate could partake in Rh(II) carbenoid cyclopropanation. Further investigations of scope and optimizations of the reaction have not been performed.

We then turned our attention to the α-triethylammonium diazoester triflate **24**, which is a particularly interesting compound since it formally contains an α-aminoacid moiety. Catalytic carbenoid transformations with this diazo compound therefore have high synthetic value. Our attempt to apply **24** in a catalytic cyclopropanation reaction with styrene, in analogy to **23**, however, did not give any cyclopropane product. Instead we assumed that we obtained the unexpected aziridinium triflate salt **44** as concluded from the analytical data discussed below (Scheme 6.2).

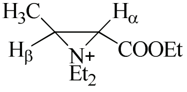
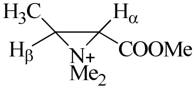
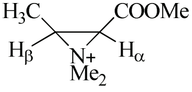


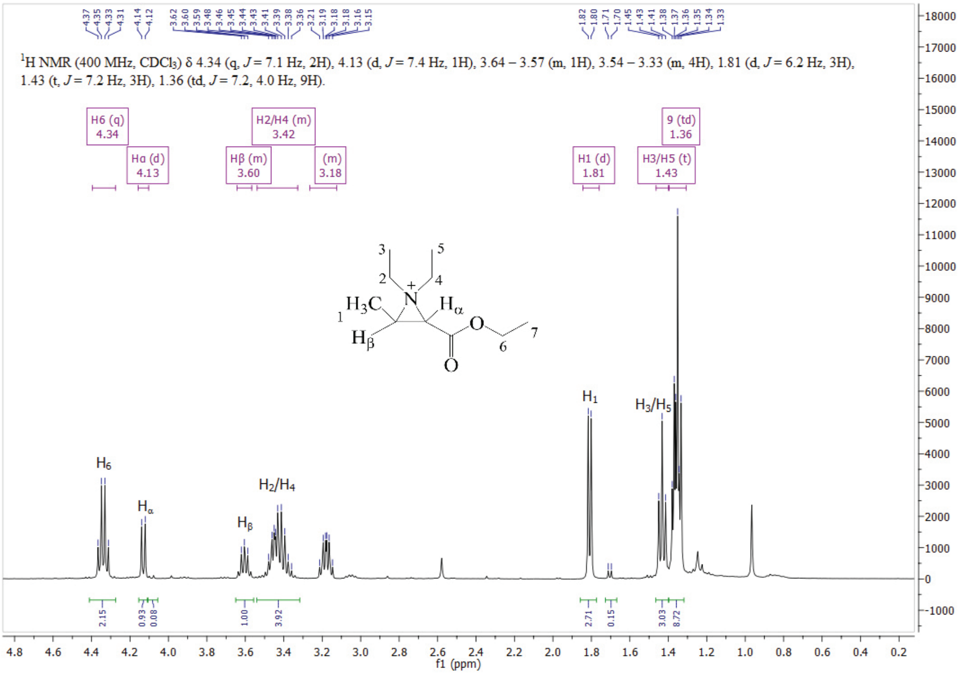
Scheme 6.2 Postulated catalytic intramolecular C-H insertion from **24** to aziridinium salt **44**.

An intramolecular C-H insertion into one of the methylene groups of the α-triethylammonium substituent was assumed to take place and resulted in formation of the aziridinium triflate **44**. Unfortunately, we were not able to isolate **44**, precipitation attempts as well as reversed phase chromatography were not successful. The NMR and MS data, however, let us derive structure **44** (see below). Whereas **44** is an unreported compound, structurally analogous aziridinium salts are reported and described, and the associated spectroscopic data helped with the tentative structure elucidation of **44**.[10-11]

In the ^{1}H NMR spectrum, the two methine protons from the aziridinium ring could explicitly be identified (Figure 6.3). The doublet at $\delta = 4.13$ ppm (7.4 Hz) resulted from H_α, which coupled to H_β, the multiplet at $\delta = 3.6$ ppm. Both protons showed a correlation to methine carbons at $\delta = 53.7$ and 52.4 ppm in the HMQC spectrum. H_β also coupled to the methyl protons H_1, the doublet at $\delta = 1.81$ ppm (6.2 Hz). The CH_2-groups of the diethylammonium moiety (H_2/H_4) appeared as a multiplet at $\delta = 3.42$ ppm and coupled with their corresponding CH_3-groups at 1.43 ppm and 1.36 ppm, respectively. The coupling constant of $J = 7.4$ Hz for H_{α}-H_{β} corresponded to reported coupling constants for the structurally analogous *trans*-*N*,*N*-dimethylaziridinium salt *trans*-**45** (H_{α}-H_{β} = 7.3 Hz) (Table 6.2).[10] The H_{α}-H_{β} coupling constant of *cis*-**45** is reported to be significantly larger (8.9 Hz). The coupling constant for CH_3-H_{β} for the obtained **44**, however, was slightly closer to the reported coupling constant for the *cis*-**45** (6.2 Hz for **44**, 6.0 Hz for *cis*-**45**, 5.7 Hz for *trans*-**45**). The chemical shifts of the relevant protons H_{α} and H_{β} corresponded more to the reported values for *cis*-**45**. It was therefore not clear if the obtained compound **44** was the *trans* or *cis* isomer. The large difference of 1.5 Hz for the H_{α}-H_{β} coupling constant of **44** and *cis*-**45** may, as a compromise, slightly favor the *trans*-Isomer. The presence of a second diastereomer of **44** was indicated by the doublet at 1.71 ppm, which corresponded to a diastereomeric ratio of 20:1. The HRMS (ESI^+) peak of 186.1500 was in accordance with the proposed molecule **44** (see experimental section). The multiplet at $\delta = 3.18$ ppm, however, could not be assigned and may result from a byproduct. It represented a CH_2-group, that coupled with a CH_3-group that overlapped with the signal at $\delta = 1.36$ ppm. The same reaction of **24** with $Rh_2(esp)_2$ resulted in less aziridinium formation. Lowering or increasing the temperature with $Rh_2(OAc)_4$ gave lower product yield as estimated from the ^1H NMR spectrum of the crude product mixture.

Table 6.2 Comparison of ^1H NMR data of proposed **44** and reported *trans*-**45** and *cis*-**45**.

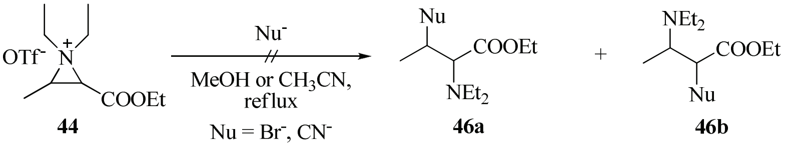
		 **44** **Obtained data**	 *trans*-**45** **Reported data**[10]	 *cis*-**45** **Reported data**[10]
δ (ppm)	H_{α}	4.13	3.70	3.90
	H_{β}	3.60	3.45	3.55
	CH_3	1.81	1.64	1.58
J (Hz)	H_{α}-H_{β}	7.4	7.3	8.9
	CH_3-H_{β}	6.2	5.7	6.0



^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (q, $J = 7.1$ Hz, 2H), 4.13 (d, $J = 7.4$ Hz, 1H), 3.64 – 3.57 (m, 1H), 3.54 – 3.33 (m, 4H), 1.81 (d, $J = 6.2$ Hz, 3H), 1.43 (t, $J = 7.2$ Hz, 3H), 1.36 (td, $J = 7.2$, 4.0 Hz, 9H).

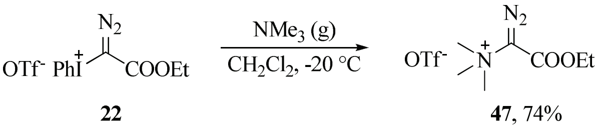
Figure 6.3 ^{1}H NMR (400 MHz) spectrum of crude product mixture. Proposed product **44**.

The synthesis of the aziridinium salt **44** formally corresponded to a catalytic intramolecular C-H insertion. The positive charge of the nitrogen atom, however, was expected to electronically deactivate the methylene groups for α-C-H insertion. Electrophilic carbenoids are known to show preference for C-H insertion into more electron rich "activated" C-H bonds[12-13] which is promoted by electron donating heteroatoms in α-position such as oxygen[14-17] or nitrogen[15,18-19] as efficient inter- and intramolecular C-H insertions into α-C-H bonds to these heteroatoms demonstrated.[20-26] A possible explanation for the unexpected behavior observed in the discussed reaction could be the close proximity of 6 protons from the CH_2-groups of the triethylammonium substituent to the intermediate carbenoid which thus lead to a kinetically promoted C-H insertion even though it was electronically disfavored. Diazo compounds have been applied to the synthesis of aziridines *via* carbenoid transfer to imines[27-28] or *via* Aza-*Darzens*-Type reactions of diazo compounds with imines (see Chapter 1, 1.2). The methodology to prepare aziridinium salts in our case is, to the best of our knowledge, unprecedented in the field of carbenoid chemistry. To indirectly prove our proposed structure **44**, we attempted a nucleophilic ring opening of the aziridinium salt in analogy to recently reported protocols,[29-30] and expected the two regioisomers **46a** and **46b** (Scheme 6.3). Unfortunately, no reaction was observed with either TBAB or potassium cyanide in refluxing methanol or acetonitrile and we did not further investigate this reaction at this point.



Scheme 6.3 Attempted nucleophilic ring opening of aziridinium salt **44** using KCN or TBAB.

We then assumed that we could achieve an intermolecular carbenoid reaction and avoid the intramolecular pathway by changing the α-triethylammonium group to an α-trimethylammonium substituent. Thus, we prepared the α-trimethylammonium diazoester triflate **47** in analogy to the procedure for **24**. Bubbling gaseous NMe_3 into the solution of **22** in CH_2Cl_2 at -20 °C afforded, after precipitation, **47** as a pale yellow solid in 74% isolated yield (Scheme 6.4).



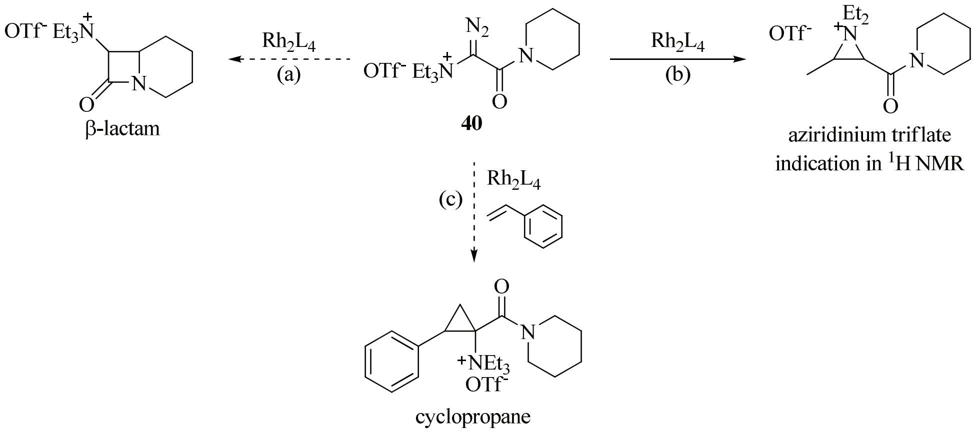
Scheme 6.4 Preparation of **47** from **22** and NMe_3.

Having compound **47** in hand, we attempted the analogous catalytic cyclopropanation as shown in Scheme 6.2. It appeared, however, that the solubility of **47** in dichloromethane was significantly lower than for the other α-onium diazo triflate salts, and a first attempt in CH_2Cl_2 as solvent resulted in an unidentifiable mixture of compounds and no NMR signals resulting from a cyclopropanation product could be identified. A solvent change to more polar solvents such as CH_3CN or mixtures of CH_2Cl_2 with CH_3CN improved the solubility of **47**, but resulted in a similar outcome as before. We then turned our attention towards the investigation of the α-onium diazophosphonates and diazopiperidinylamides.

The α-dimethylsulfonium diazophosphonate **35** showed no conversion at room temperature in a 1:1 mixture of CH_2Cl_2 and toluene with either $Rh_2(OAc)_4$ or $Rh_2(esp)_2$ and styrene. When refluxing in toluene, however, decomposition of **35** occurred but no product from catalytic cyclopropanation could be identified (see Table 6.1). α-Triethylammonium diazophosphonate triflate **36** did not show any conversion in presence of catalysts $Rh_2(OAc)_4$ or $Rh_2(esp)_2$ and styrene either, even at prolonged refluxing in toluene. The two quite sterically bulky groups attached to the diazo carbon of **36** could be a reason for hindered approach of the diazo carbon to the catalyst which could diminish carbenoid formation. Other catalysts and conditions were not tested and we continued with the investigations of the α-onium diazopiperidinylamides **39** and **40**.

The reaction of α-dimethylsulfonium diazopiperidinylamide triflate **39** with $Rh_2(esp)_2$ and styrene in CH_2Cl_2/toluene at room temperature resulted in an unidentifiable reaction mixture. The ^{1}H NMR spectrum of the crude reaction mixture showed a doublet at $\delta = 4.8$ ppm, which could result from a β-lactam from intramolecular C-H insertion. This could, however not be confirmed with the additional NMR and MS data.

The α-triethylammonium diazopiperidinylamide **40** offered the possibility for interesting competition experiments with regard to intramolecular C-H insertions. As postulated for the corresponding ester **24**, intramolecular C-H insertion into the α-position to the nitrogen in the triethylammonium moiety could be possible, as well as intramolecular C-H insertion into the piperidinyl group to afford the β-lactam. The first test reaction of **40** with $Rh_2(esp)_2$ in CH_2Cl_2/toluene at room temperature was performed in the presence of styrene to allow the possibility for intermolecular cyclopropanation in addition to the intramolecular C-H insertions (Scheme 6.5).



Scheme 6.5 Possible reaction pathways of **40** with Rh(II) catalysts and styrene: (a) intramolecular C-H insertion to β-lactam, (b) intramolecular C-H insertion to aziridinium salt, (c) intermolecular cyclopropanation. Pathway (b) was indicated in the ^{1}H NMR spectrum of the crude reaction mixture.

The ^{1}H NMR spectrum of the crude reaction mixture, however, indicated no conversion under these conditions. Upon heating the reaction mixture to 50 °C, the ^{1}H NMR spectrum showed peaks and a spin system that resembled the aziridinium salt **44** (Figure 6.4, Figure 6.5).

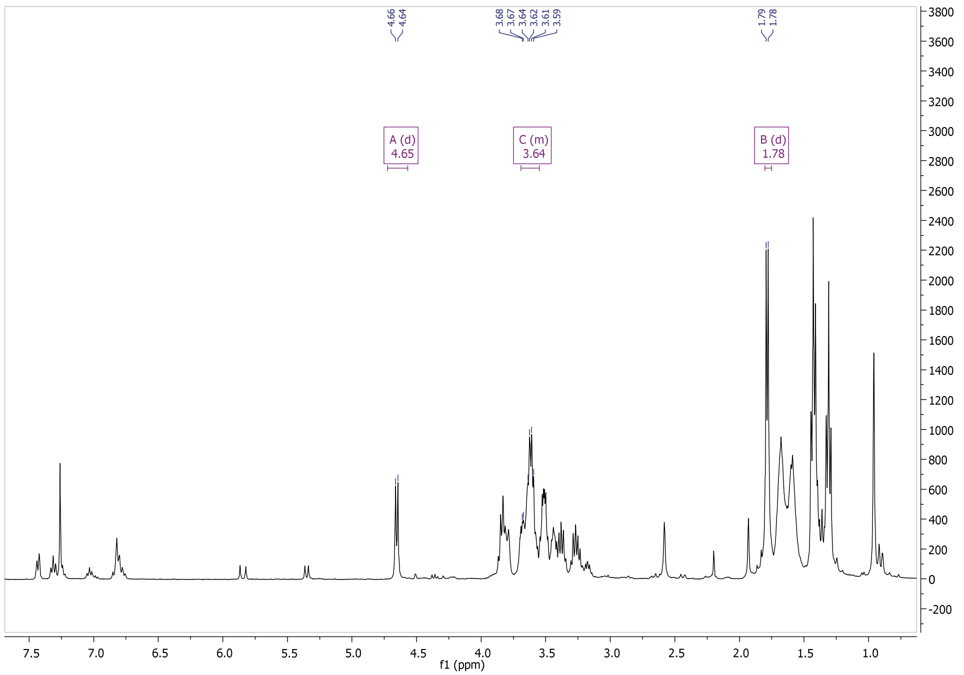


Figure 6.4 Obtained ^{1}H NMR spectrum of reaction of **40** with $Rh_2(esp)_2$ and styrene in 1:1 toluene/CH_2Cl_2 at 50 °C.

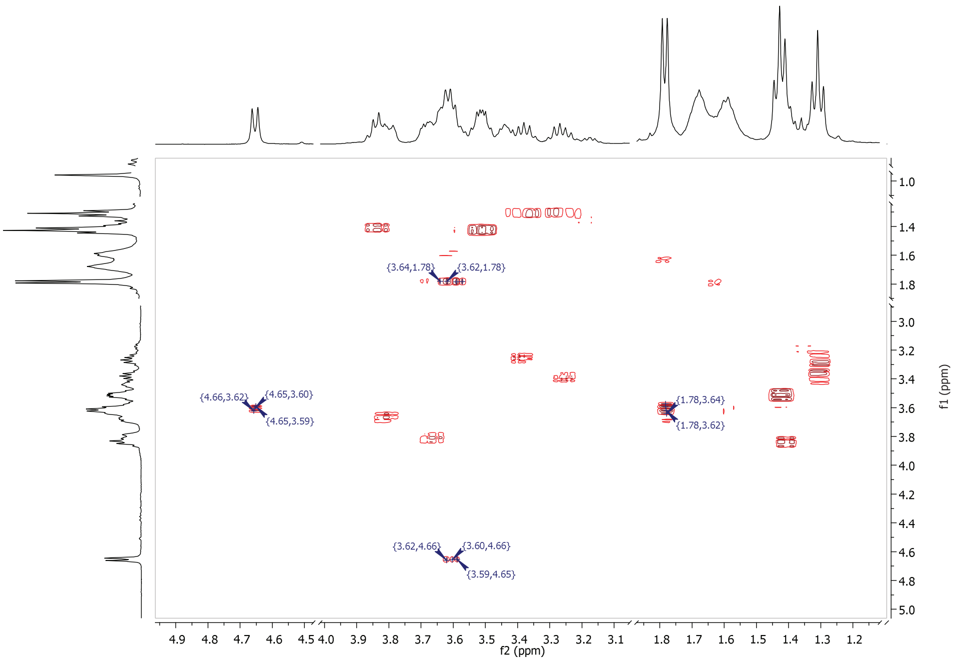


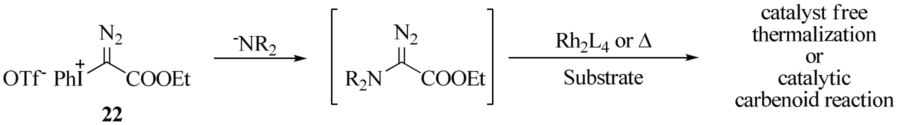
Figure 6.5 COSY spectrum of reaction of **40** with $Rh_2(esp)_2$ and styrene in 1:1 toluene/CH_2Cl_2 at 50 °C. The spin system resembling **44** is labeled.

In particular, a proton at δ = 4.65 ppm (d, 7.1 Hz) which coupled to a proton of a multiplet at δ = 3.62 ppm was observed. This proton at 3.62 ppm further coupled to an additional doublet at δ = 1.78 ppm (6.2 Hz). A molecular ion in the HRMS (ESI^+) of 225.1971 was measured which corresponds to the aziridinium salt or β-lactam expected from **40** (225.1961). Since we were not able to isolate a clean compound from the crude product mixture, it was not possible to clearly identify the products. From the obtained analytical data, however, it was indicated that the aziridinium salt was formed.

6.2.3 Nucleophilic substitutions: Aminations

6.2.3.1 Amination of 22 with potassium phthalimide and 18-crown-6

Besides their reactivities in catalytic carbenoid transformations, nucleophilic substitutions of the α-onium diazo triflate salts with nucleophiles other than halides were the focus of our research. The amount of potential nucleophiles was huge and we particularly focused on nucleophilic aminations since the corresponding α-amino diazo compounds are a valuable and highly desirable class of diazo compounds. They could serve as starting materials for the direct synthesis of cyclopropane α-amino acids which have shown biological activity.[31-33] The thermal instability associated with α-amino diazo compounds, other than the frequently reported α-nitro[34-36] and the in this study presented α-triethylammonium diazo compounds, however, require compatible and mild reaction conditions for their generation and an *in situ* preparation seemed logical. Nucleophilic aminations of the α-aryliodonium diazoester triflate **22** could allow us to prepare the corresponding α-amino diazoester and to subsequently perform carbene or carbenoid reactions as our previous attempts for the electrophilic aminations were unsuccessful (Chapter 2, 2.2.6). Two generally different approaches could be followed by either using neutral amine nucleophiles to generate α-ammonium diazo salts in analogy to **24** or negatively charged amines to generate neutral diazo compounds. We focused on negatively charged amine nucleophiles to avoid the difficulties in separation and purification of the resulting α-ammonium diazo salts as experienced previously (Scheme 6.6).



Scheme 6.6 Proposed nucleophilic amination of **22** with negatively charged amine nucleophile.

Davies et al.[37] have recently reported the efficient thermal cyclopropanation of olefins with α-*N*-phthalimido diazo compounds generated *in situ* from the corresponding 4-phthalimido-*N*-mesyl-1,2,3-triazoles based on a methodology to generate diazo compounds developed by *Fokin et al.*[38-40] Phthalimide seemed to be a suitable choice as a nucleophile in our case, since it could be easily handled, was readily available and allowed deprotection to the free amine. Thus, we attempted nucleophilic aminations with potassium phthalimide and **22** as an initial experiment. To confirm that phthalimide was an efficient nucleophile for the substitution we monitored the reaction by ^{1}H NMR in analogy to the previously performed kinetic measurements by following the amount of iodobenzene. The conversion of **22** with 2.0 eq. potassium phthalimide and 2.2 eq. 18-crown-6 at 0 °C showed nearly completion within 2 h. At room temperature, however, the same reaction showed nearly full conversion of **22** after approximately 15 minutes (90%) (Figure 6.6). This drastic temperature effect for the nucleophilic amination with potassium phthalimide was important to consider for the design and realization of the following reactions. At both temperatures, the ester signals of **22**, however, indicated the formation of byproducts as a multiplet in the ester region develops over time (Figure 6.6). Between 0 °C and room temperature, the nucleophilic amination of **22** and thermal decomposition of the potential α-phthalimido diazoester seemed to occur simultaneously and competitively which provided a challenge to the development of selective reactions with the α-phthalimido diazoester. Also, the nucleophilic attack on the terminal nitrogen could occur as a competitive pathway (see next section). Conditions, which avoided or minimized thermal decompositions of the α-amino diazo compound, but still allowed efficient nucleophilic substitutions, were thus highly desirable.

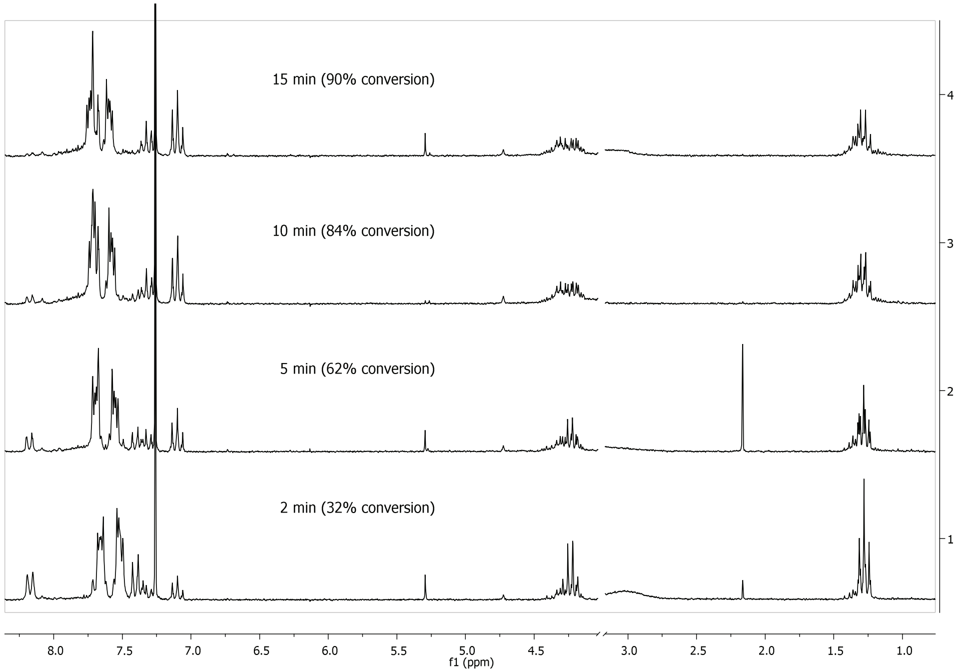
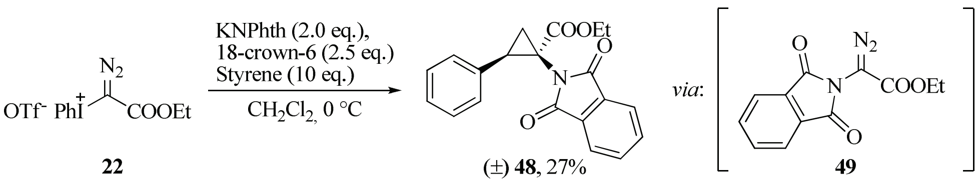


Figure 6.6 Nucleophilic amination of **22** with 2.0 eq. potassium phthalimide and 2.2 eq. 18-crown-6 at room temperature in $CDCl_3$. For clarity, the peak of 18-crown-6 is excluded (3.62 ppm). Conversion was measured by appearance of iodobenzene.

An initial cyclopropanation experiment was performed *via* bulk addition of **22** to a solution of potassium phthalimide (2.0 eq.), 18-crown-6 (2.5 eq.) and styrene (10 eq.) in CH_2Cl_2 at 0 °C. The mixture stirred for 2 h at 0 °C and upon warming to room temperature the ^{1}H NMR spectrum of the crude reaction mixture indicated formation of a cyclopropane product. After purification we obtained the protected cyclopropyl amino acid **48** as a colorless oil in an isolated yield of 27%, elucidated as the *trans* diastereomer (in accordance with reported data)[41] (Scheme 6.7). Byproducts from dimerization of **49** could not be isolated. The resulting cyclopropane product **48** allowed the assumption of formation of the α-phthalimido diazoacetate **49**, which performed the thermal, catalyst-free cyclopropanation reaction *via* the free carbene.

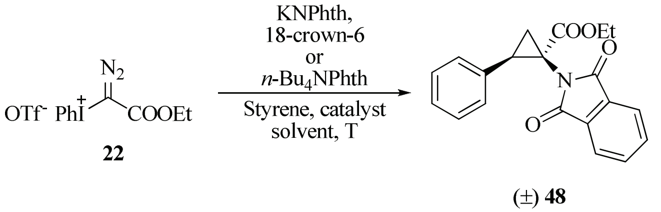


Scheme 6.7 Initial nucleophilic amination of **22** and thermal cyclopropanation with α-phthalimido diazoacetate **49** to **48**.

We then attempted to characterize the α-phthtalimido diazoacetate **49** and performed a reaction of **22** with 1.0 eq. of potassium phthalimide and 1.2 eq. of 18-crown-6 in a highly diluted mixture (0.02 M) in $CDCl_3$ at room temperature and followed the conversion by ^{1}H NMR. The reaction rate was slower than with 2.2 eq. potassium phthalimide, with 75% conversion after 90 minutes and full conversion and decolorization over night. Unfortunately, the ^{1}H NMR spectra taken at different time intervals did not show clean peaks of **49** and overlapping signals were obtained as previously (Figure 6.6). We were, unfortunately, not able to obtain a clean NMR spectrum of the α-phthalimido diazoester **49**.

As the isolation and distinct characterization of the α-phthalimido diazoacetate **49** was unsuccessful, we continued to focus on the reaction conditions for the *in situ* generation of **49**. Based on our initial experiment shown in Scheme 6.7, we performed the analogous reaction at room temperature and obtained 31% of **48** after isolation (Table 6.3, entry 2). The difference between 0 °C and room temperature thus seemed to have no significant effect on the thermal cyclopropanation reaction with styrene, though, as seen before, the rate for nucleophilic substitution changed and the reaction times were adjusted accordingly. We then increased the excess of styrene from 10 to 30 and 50 equivalents, which did not change the yields of **48** significantly (Table 6.3, entries 3 and 4). To minimize the possibility for dimerization, we changed the procedure to dropwise addition of a solution of **22** in CH_2Cl_2 to the mixture of potassium phthalimide, 18-crown-6 and styrene from thereon. A variation of the equivalents of potassium phthalimide resulted in a drop in yield of **48** to 21% when 1.0 equivalent of potassium phthalimide was used, whereas 5.0 equivalents of potassium phthalimide did not further increase the yields compared to 2.0 equivalents (Table 6.3, entries 5-7). As an alternative source of the phthalimide anion we prepared tetrabutylammonium phthalimide (TBAPhth) from tetrabutylammonium chloride (TBAC) and potassium phthalimide in acetone, which had the advantage of being soluble in organic solvents and the crown ether could be avoided. The nucleophilic amination with 2.0 equivalents TBAPhth, however, resulted in a reduced yield of 22% of the cyclopropane **48** (Table 6.3, entry 8). We then further examined the temperature effect of the reaction to confirm our findings for the reaction rates above and performed reactions in refluxing CH_2Cl_2 and at -30 °C. Both reactions showed a decrease in yields for **48** to 23% and 21%, respectively (Table 6.3, entries 9 and 10). This indicated and supported that the temperature range that afforded the highest yields of **48** was between 0 °C and room temperature for this reaction system.

Table 6.3 Nucleophilic amination of **22** and following thermal cyclopropanation to **48**.



Entry	Amine (eq.)	Styrene (eq.)	Catalyst (eq.)	Conditions	Yield of 48 [%][a]
1	KNPhth (2.0)	10	-	A[b]	27
2	KNPhth (2.0)	10	-	B[c]	31
3	KNPhth (2.0)	30	-	B[c]	28
4	KNPhth (2.0)	50	-	B[c]	27
5	KNPhth (1.0)	30	-	C[d]	21
6	KNPhth (2.0)	30	-	C[d]	32
7	KNPhth (5.0)	30	-	C[d]	29
8	*n*-Bu_4NPhth (2.0)	30	-	D[e]	22
9	KNPhth (2.0)	30	-	E[f]	23
10	KNPhth (2.0)	30	-	F[g]	21
11	KNPhth (2.0)	30	$Rh_2(OAc)_4$ (0.05)	G[h]	16
12	KNPhth (2.0)	30	$Rh_2(esp)_2$ (0.05)	G[h]	21
13	KNPhth (2.0)	30	-	H[i]	19
14	KNPhth (2.0)	30	-	I[j]	0

[a] Isolated yield of **48** after column chromatography; [b] Conditions A: CH_2Cl_2, 18-crown-6 (2.5 eq.), 0 °C, 2 h, bulk addition of **22** as solid; [c] Conditions B: CH_2Cl_2, 18-crown-6 (2.2 eq.), r.t., 1 h, bulk addition of **22** as solid; [d] Conditions C: CH_2Cl_2, 18-crown-6 (2-5 eq.), r.t., dropwise addition of **22** in CH_2Cl_2 over 2 h; [e] Conditions D: CH_2Cl_2, r.t., dropwise addition of **22** in CH_2Cl_2 over 2 h; [f] Conditions E: CH_2Cl_2, 18-crown-6 (2.2 eq.), 40 °C, dropwise addition of **22** in CH_2Cl_2 over 2 h; [g] Conditions F: CH_2Cl_2, 18-crown-6 (2.2 eq.), -30 °C, dropwise addition of **22** in CH_2Cl_2 over 2 h; [h] Conditions G: CH_2Cl_2, 18-crown-6 (2.2 eq.), r.t., catalyst (5 mol%), dropwise addition of **22** in CH_2Cl_2 over 2 h; [i] Conditions H: touene/CH_2Cl_2 (3:1), 18-crown-6 (2.2 eq.), r.t., dropwise addition of **22** in CH_2Cl_2 over 2 h; [j] Conditions I: THF, 18-crown-6 (2.2 eq.), r.t., dropwise addition of **22** in CH_2Cl_2 over 2 h.

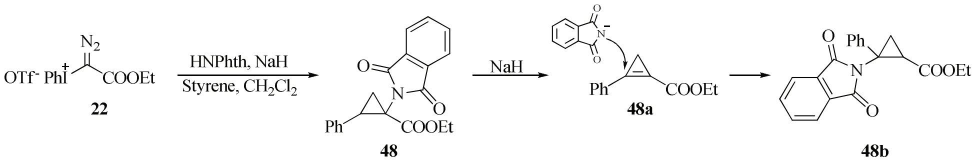
In the presence of the Rh(II) catalysts $Rh_2(OAc)_4$ or $Rh_2(esp)_2$, the yields for the cyclopropanation reaction dropped significantly (Table 6.3, entries 11 and 12). A possible explanation could be that different reaction pathways take place and selectivities change *via* an intermediate carbenoid in comparison to the thermally generated free carbene. Also, the phthalimide anion could, through coordination to the catalyst, inhibit its activity. It was, however, not possible to characterize and isolate any products other than the cyclopropane **48**. Performing the reaction in a mixture of dry toluene/CH_2Cl_2 (3:1) decreased the yield of **48** to 19% and no cyclopropanation was obtained in THF (Table 6.3, entries 13 and 14). A biphasic system in analogy to procedure B presented in Chapter 3 for the nucleophilic halogenations was not attempted.

Although the highest obtained yield of the cyclopropane **48** was a modest 32% after two steps, we have shown and demonstrated that the nucleophilic amination of the α-aryliodonium diazoester triflate **22** was possible and the assumed α-phthalimido diazoester **49**, which was formally a glycine derived diazo compound, could undergo thermal cyclopropanation with styrene. The temperature for the two step reaction consisting of nucleophilic amination and following thermal cyclopropanation of **49** to **48** appeared to be critical. It was found that the nucleophilic substitution rate was significantly higher at room temperature than at 0 °C, whereas the thermal decomposition of the intermediate α-phthalimido diazoester **49** seemed to proceed readily at both temperatures.

To the best of our knowledge, there is no report of the α-phthalimido diazoester **49** in the literature, which demonstrates the novelty of the presented reaction. The determination of the lifetime of **49** at different temperatures would be of high importance to optimize the reaction.

6.2.3.2 Reaction of 22 with phthalimide and NaH - the unexpected product 50

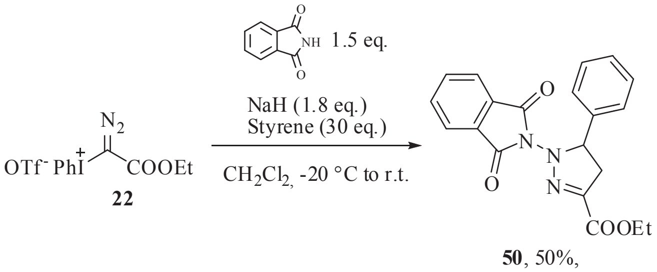
We wanted to examine, if phthalimide in combination with a base could give us an alternative access to the α-phthalimido diazoester **49** in absence of crown ether. The base, however, had to be chosen carefully, as it has to be non-nucleophilic to avoid competition with the phthalimide anion, but strong enough to efficiently deprotonate the phthalimide. We focused on inorganic bases and attempted a test reaction of **22** with 1.5 eq. phthalimide, 30 eq. styrene and 2.5 eq. Cs_2CO_3 in dichloromethane at 0 °C. No deprotonation or conversion were detected, even at room temperature, presumably due to the low solubility of Cs_2CO_3 in CH_2Cl_2. We then changed the base to sodium hydride and performed the reaction at -20 °C under otherwise same conditions. Besides the formation of cyclopropane product **48** we considered the possibility of deprotonation of **48** by the strong base NaH which could then have caused elimination of phthalimide to the cyclopropene **48a**. This could then undergo a Michael type addition of the phthalimide anion to form the isomeric, formally rearranged β-aminocyclopropanecarbocylic acid derivative **48b** (Scheme 6.8). Similar reactivity of bromocyclopropanes was reported recently.[42]



Scheme 6.8 Expected pathway for the reaction of **22** with phthalimide, styrene and sodium hydride.

We did not obtain either of the cyclopropanes **48** or **48b**. Instead, a product **50** with a molecular ion mass of 28 units above the expected 335 for **48** or **48b** was obtained as a white solid as the only product in 50% yield after workup and isolation *via* column chromatography. Furthermore, the ^{1}H NMR spectrum showed a spin system that indicated a CH_2/CH coupling, however with a significantly low field shifted CH proton at $\delta = 5.55$ ppm (dd), while the CH_2 protons were in a region expected for a cyclopropane (3.49 (dd, $J = 17.2, 10.3$ Hz, 1H) and 2.92 (dd, $J = 17.2, 14.4$ Hz, 1H)). We thus concluded that the dinitrogen unit of the diazo group is part of the product molecule and that no carbene intermediate was formed during the reaction (in contrast to the reaction with potassium phthalimide and 18-crown-6). The reaction of **22** with phthalimide and NaH to **50** was found to be slower than the direct nucleophilic substitution with KNPhth and 18-crown-6 to **48**, when the conversion of **22** was measured by ^{1}H NMR and full conversion of **22** was obtained after 2 h at room temperature. To elucidate the structure of product **50** we attempted the preparation of single crystals for X-ray crystallography and were successful by mixing 1 mg **50** with 1 mL 5:1 *n*-hexanes/EtOAc in a vial and adding a minimum amount of CH_2Cl_2 to dissolve the solid. The CH_2Cl_2 was then allowed to evaporate at room temperature and crystals for X-ray crystallography were grown. The obtained crystal structure is shown in Figure 6.7.

The crystal structure of **50** shows the formation of a pyrazoline ring, with the phthalimide bonded to the former terminal nitrogen of the diazo group and the phenyl group in 5-position. This result indicated that a 1,3-dipolar cycloaddition occurred, though in an unexpected pathway as discussed below (Scheme 6.9). The pyrazoline product **50** is, according to a Scifinder search (October 2013), not reported previously.



Scheme 6.9 Reaction of **22** with NaH, phthalimide and styrene to **50**.

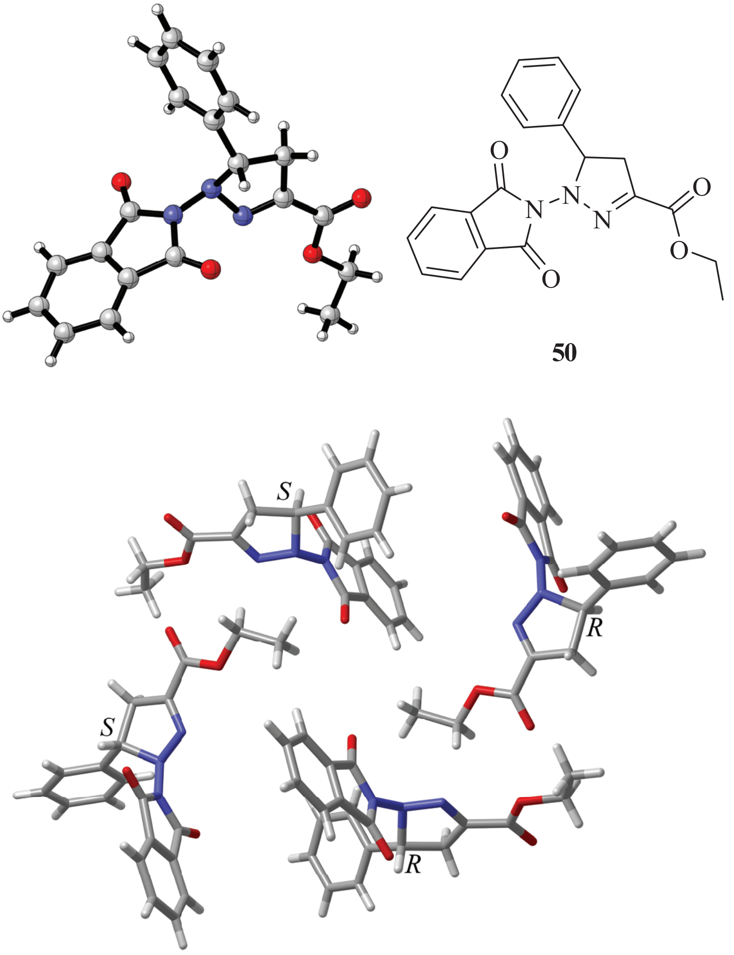
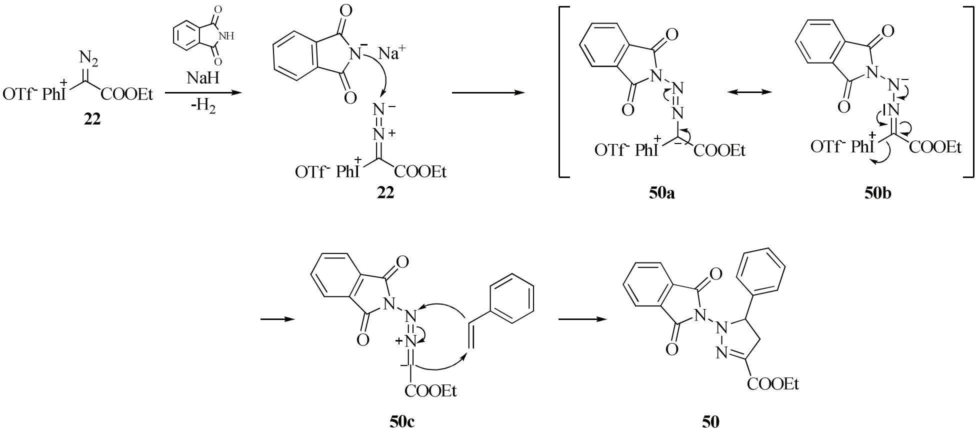


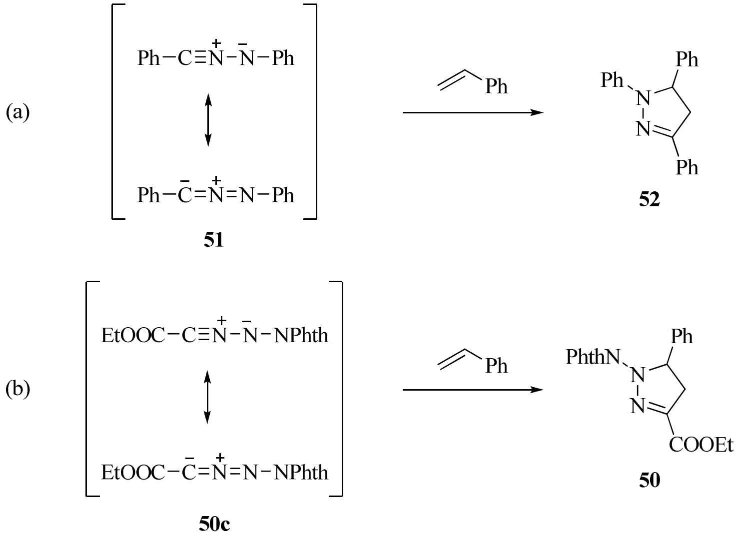
Figure 6.7 X-ray crystal structure of **50** as single molecule, *S*-enantiomer (top) and racemic unit cell, (bottom).

The direct 1,3-dipolar cycloaddition of diazo compounds with alkenes,[43-48] alkynes[49-52] and other dipolarophiles[53-55] (*Huisgen* Reaction)[56-57] is well known and frequently described. In the discussed reaction, however, the parent diazo compound **22** was not directly transformed into the product pyrazoline **50** as the iodobenzene was cleaved off during the reaction and the phthalimide introduced at a different position. Furthermore, as no product from thermal cyclopropanation of the α-phthalimido diazoester **49** with styrene was obtained, we assumed a different mechanistic pathway had occurred in this reaction. Since **22** did not react in a 1,3-dipolar cycloaddition with styrene in absence of phthalimide and sodium hydride, we propose an activation of the α-aryliodonium diazoester triflate **22** by the phthalimide anion. *Chen et al.*[58] recently reported the formation of triazoles *via* an intramolecular cyclization of a proposed zwitterionic species resulting from nucleophilic attack of a *N*-PMP arylimine to the terminal nitrogen of EDA. The initial step of the reaction in our case was thus assumed to be the nucleophilic attack of the phthalimide anion on the terminal nitrogen, corresponding the reactivity with the anionic CN^-[59-60] as described in Chapter 3 section 3.1.2.5. This nucleophilic addition of the phthalimide anion could then lead to an intermediate with the resonance structures **50a** and **50b** (Scheme 6.10). After loss of iodobenzene, the resulting 1,3-dipole **50c** then reacted with styrene in the expected orientation to the corresponding pyrazoline product **50**. The reaction could thus be considered as a nucleophile induced 1,3-dipolar cycloaddition with *γ*-elimination of a neutral leaving group.



Scheme 6.10 Proposed mechanism for the formation of pyrazoline **50** *via* 1,3-dipolar cycloaddition.

The proposed 1,3-dipole **50c** resembles the diphenyl nitrilimine **51**, reported by *Huisgen*.[56-57] This diphenyl nitrilimine **51** was shown to react with styrene and other terminal olefines to the corresponding 5-substituted pyrazoline **52** in high yields (Scheme 6.11). This reactivity was also found in our reaction which could be considered as an analogous 1,3-dipolar cycloaddition and thus supporting our proposed mechanism.

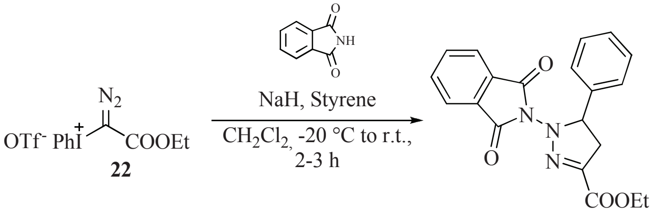


Scheme 6.11 (a) Reported 1,3-dipolar cycloaddition of diphenyl nitrilimine **51** with styrene to pyrazoline **52**[56-57] and (b) proposed 1,3-dipolar cycloaddition of **50c** with styrene to **50**.

We then tested the dependence of the reaction on the equivalents of phthalimide used (Table 6.4). The isolated yield of **50** increased with an increase in amount of phthalimide, with 62% as highest obtained yield for 2.5 equivalents phthalimide (Table 6.4, entry 3). We then tested if the order of addition of the components changed the outcome of the reaction. Thus, NaH was added to a mixture phthalimide and styrene prior to addition of **22** and we obtained a nearly unchanged yield of 55% of **50** (entry 4).

Reactions with electron rich or electron poor olefines could give further insight into the electronic properties of the 1,3-dipole (see Chapter 7, Future prospects).

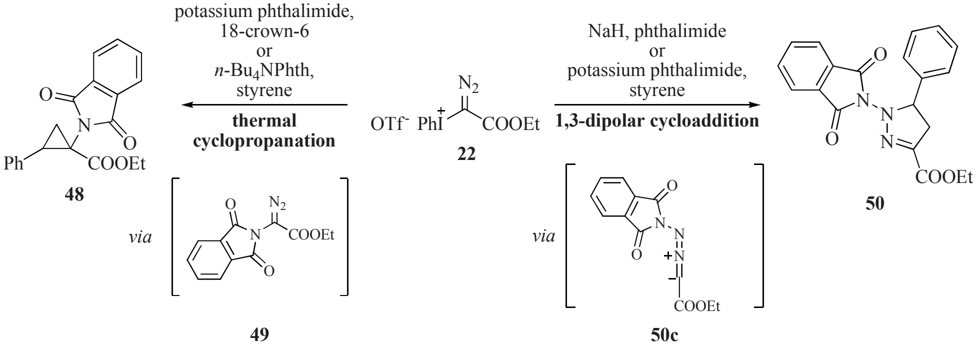
Table 6.4 Reaction of **22** with phthalimide and NaH to **50**.



Entry	Phthalimide (eq.)	NaH (eq.)	Styrene (eq.)	Yield[a] of 50 [%]
1	0.9	1.5	30	41
2	1.5	1.8	30	50
3	2.5	3.0	30	62
4	2.2	2.5	30	55

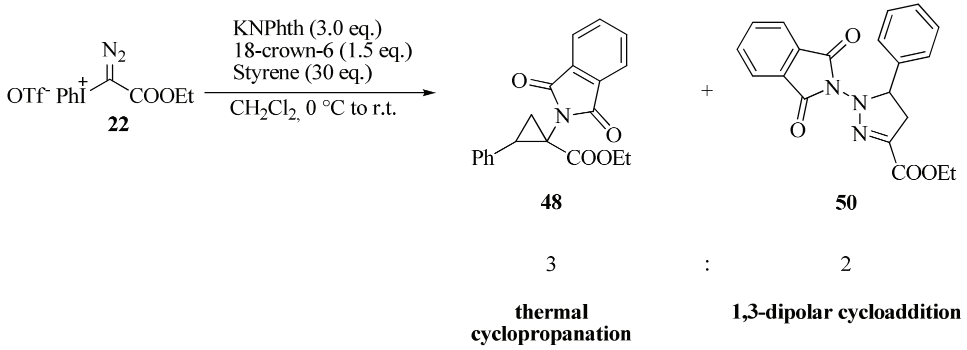
[a] Isolated yield after column chromatography

The difference for the pathways of the reaction of **22** with NaH and phthalimide in contrast to potassium phthalimide and 18-crown-6 (section 6.2.3.1) was unexpected. The change in reactivity of the phthalimide anion could be a result of the counter ion. In the reaction system with 18-crown-6 a nearly full separation of the phthalimide anion and the potassium cation was assumed, while in the reaction with NaH the *in situ* formation of sodium phthalimide could be expected. We therefore assumed that a reaction of **22** with sodium phthalimide would give the same pyrazoline product **50**. Since sodium phthalimide was not available we attempted a reaction with potassium phthalimide instead. We added potassium phthalimide (2.2 eq.) to a solution of **22** and styrene (30 eq.) in CH_2Cl_2 at 0 °C and stirred the reaction mixture at room temperature over night. The ^{1}H NMR spectrum of the crude reaction mixture showed formation of the pyrazoline product **50** which was obtained in 45% isolated yield. The counter ion of the phthalimide anion seemed to play a pivotal role in this reaction, clearly changing the reaction pathway and alters the selectivity of the reaction (Scheme 6.12). The presence or absence of 18-crown-6 in the reaction with potassium phthalimide allowed therefore the distinct alteration of the reaction pathway as to afford cyclopropanes or pyrazoles. While in the reaction with potassium phthalimide and 18-crown-6 the direct nucleophilic substitution of the iodobenzene in **22** to the α-phthalimido diazoester **49** occured, nucleophilic attack on the terminal nitrogen of the diazo group occured when potassium phthalimide or phthalimide and NaH are employed (Scheme 6.12).



Scheme 6.12 Reaction pathways for reaction of **22** with NaH/phthalimide and potassium phthalimide to **50** (right) and potassium phthalimide/18-crown-6 or n-Bu_4NPhth to **48** (left).

The aforementioned possibility of changing the reaction outcome by presence or absence of 18-crown-6 in the reaction of **22** with potassium phthalimide prompted us to attempt a competition experiment to proof our hypothesis. A reaction of **22** with 18-crown-6 and excess potassium phthalimide in the presence of styrene should allow the simultaneous formation of both products **48** and **50** in one pot. We thus mixed potassium phthalimide (3.0 eq.), 18-crown-6 (1.5 eq.) and styrene (30 eq.) in dry CH_2Cl_2 at 0 °C and added **22** as a solid to the mixture. The mixture was stirred at 0 °C for 15 min, then allowed to warm to room temperature and stirred for another 3 h at that temperature. We then separated the 18-crown6 and residual potassium phthalimide *via* column chromatography and obtained a mixture of the two compounds **48** and **50** in a ratio of 3:2, which demonstrated the two different, independent reaction pathways (Scheme 6.13). The ratio of 3:2 in favor of **48** could result from faster nucleophilic substitution of **22** to **49** compared to the 1,3-dipolar cycloaddition pathway as seen before.



Scheme 6.13 One pot experiment for the parallel preparation of cyclopropane **48** and pyrazole **50**, obtained in a 3:2 ratio.

The current methodology with NaH and phthalimide or potassium phthalimide gave an interesting insight into the reactivities of the α-aryliodonium diazoester triflate **22**. Thorough optimization and investigation of the scope of the reaction could give access to a large variety of differently substituted pyrazolines by employing different nucleophiles and dipolarophiles. An interesting methodology for the *in situ* generation of a 1,3-dipole was discovered, which will be further investigated in our group.

6.2.4 Reaction of 23 with potassium phthalimide and 18-crown-6

6.2.4.1 The unexpected product 53a - structure elucidation

After the interesting results obtained in the reactions of **22** with phthalimide we examined, how the α-dimethylsulfonium diazoester triflate **23** behaves in the reaction with phthalimide as a nucleophile. We considered the possibility of demethylation of the dimethylsulfonium moiety in addition to the nucleophilic attack on the terminal nitrogen of the diazo group as seen previously. Thus, we attempted a reaction in analogy to the α-aryliodonium diazoester triflate **22** by addition of **23** to a mixture of potassium phthalimide (2.0 eq.), 18-crown-6 (2.2 eq.) and styrene (30 eq.) in CH_2Cl_2 at -30 °C. The mixture changed to pale yellow upon addition of **23** and was allowed to warm to room temperature after 15 minutes. The ^1H NMR spectrum of the crude reaction mixture indicated the formation of products which did not result from cyclopropanation. Flash column chromatography afforded two solid pale yellow compounds which could in the first instance not be fully elucidated from the spectroscopic data (Figure 6.8a/b). The ^1H NMR spectra indicated that the dimethylsulfonium moiety was demethylated and a new CH_2-group developed. The CH_2-group at 5.36 ppm for the major product **53a** coupled to a proton at 7.65 ppm (Figure 6.8a). This proton at 7.65 ppm was found to be a heteroatom bound proton as confirmed by an exchange experiment with MeOD. As the ^1H NMR spectra of **53a** and **53b** resemble each other (except for the peaks at $\delta = 5.23$ and 9.95 ppm) and the molecular ion peak (321) in the mass spectrum were the same as for both compounds, it can be assumed that **53b** is an isomer of **53a**. Since **53b** could not be observed in the ^1H NMR spectrum of the crude product mixture, it could be assumed that it was formed during column chromatography. However, only trace amounts of **53b** were obtained and not further investigated.

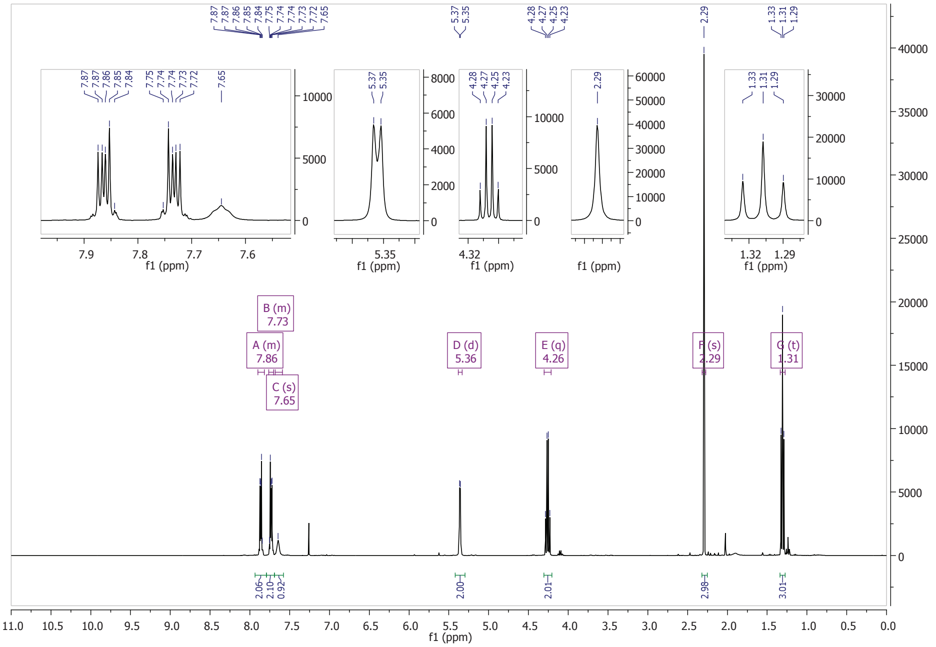


Figure 6.8a ^{1}H NMR spectrum of isolated major product **53a** from reaction of **23** with potassium phthalimide and 18-crown-6.

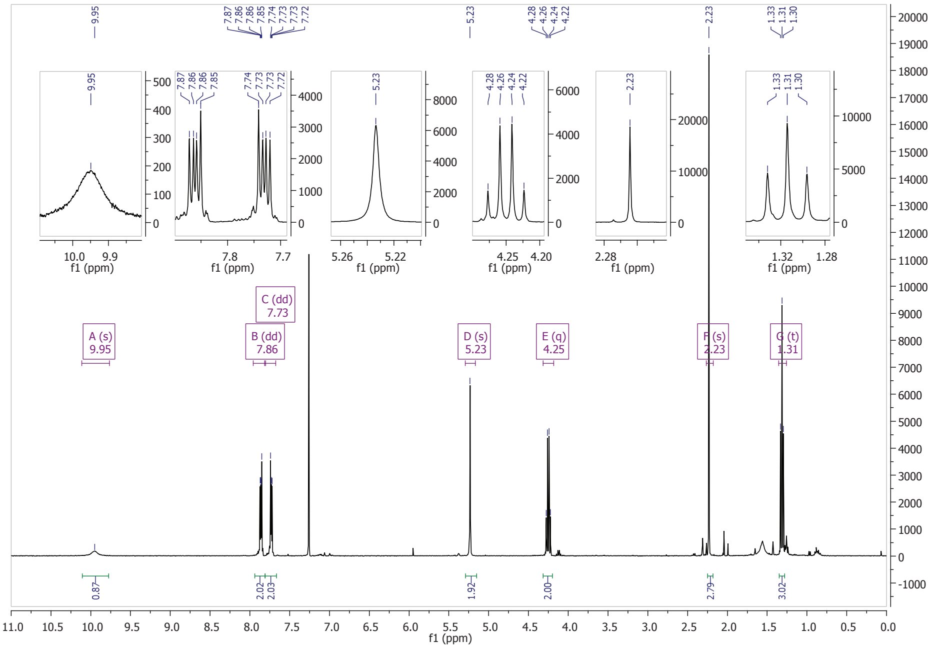


Figure 6.8b ^{1}H NMR spectrum of isolated minor product **53b** from reaction of **23** with potassium phthalimide and 18-crown-6.

The structural elucidation of the main isomer **53a** was achieved *via* X-ray crystallography (Figure 6.9), while the minor isomer could not be fully elucidated. Compound **53a** shows the demethylation of the sulfonium substituent as well as the introduction of a CH_2-group flanked by the terminal nitrogen of the former diazo group and the phthalimido group. This unexpected, interesting product prompted us to investigate the mechanism of that reaction.

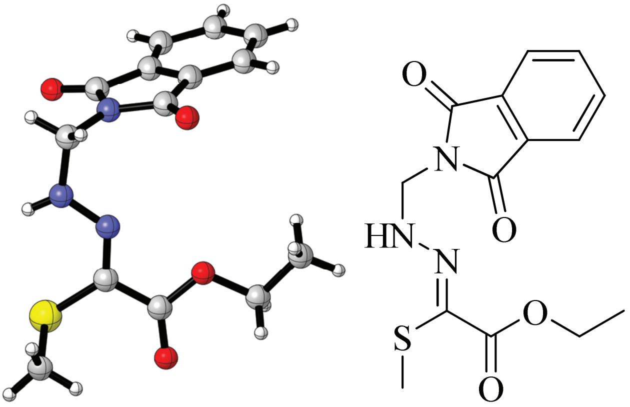
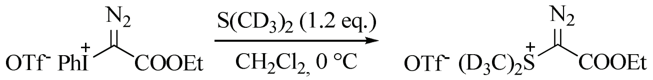


Figure 6.9 X-ray crystal structure of **53a**.

6.2.4.2 Investigation of the mechanism of formation of 53a - the dual role of the phthalimide anion

To get an insight into the mechanism we performed the analogous reaction with deuterated α-dimethylsulfonium diazoester triflate **D_6-23**, which was prepared in analogy to **23** from **22** with deuterated dimethylsulfide (Scheme 6.14).

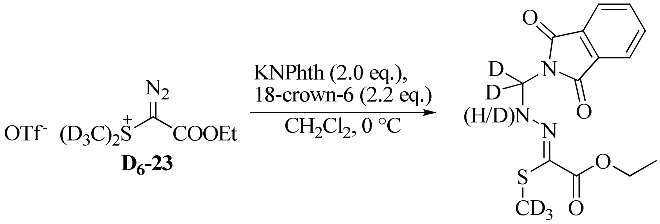


22

D_6-23, 88%

Scheme 6.14 Preparation of deuterated α-dimethylsulfonium diazoester triflate **D_6-23**.

If an internal transfer of one CH_3-group from the α-dimethylsulfonium group resulted in formation of the aminal methylene group, the two corresponding peaks (CH_3 and CH_2) were expected to disappear in the ^1H NMR spectrum of the deuterated product. Accordingly, the isolated major product **D_6-53a** from reaction of **D_6-23** with potassium phthalimide and 18-crown-6 resulted in an ^1H NMR spectrum that resembled the non-deuterated **23**, but with absence of the CH_2-group at 5.36 ppm and the methyl group at 2.29 ppm (Figure 6.10). The singlet at δ = 7.63 ppm presumably resulted from partial exchange of D with H on column chromatography over SiO_2. Whilst it could thus be concluded that a transfer of one CH_3-group occured, we wanted to get a closer insight and understanding of the mechanism of that transformation.



D_6-23

D_6-53a, 54%

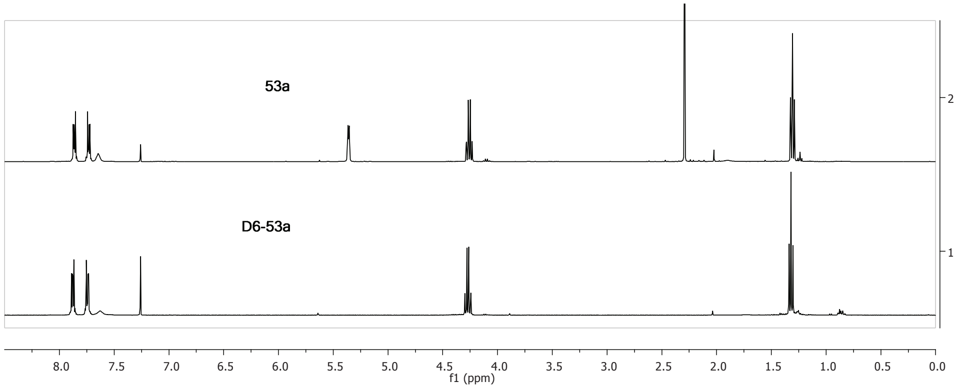


Figure 6.10 ^1H NMR spectrum of **D_6-53a** (bottom): absence of doublet at 5.36 ppm and singlet at 2.29 ppm compared to **Figure 6.8a**.

We then monitored the reaction of **23** with 1.5 eq. KNPhth and 18-crown-6 by ^1H NMR. After 2 minutes, the peak for the CH_3-groups of the dimethylsulfonium moiety of **23** at 3.34 ppm was absent and two new singlets at δ = 2.44 ppm and 2.29 ppm appeared (Figure 6.11). The singlet of the CH_3-group of the methylsulfide of the product **53a** at 2.29 ppm increased during the progress of the reaction, while the peak at 2.44 ppm decreased accordingly. Also, the characteristic doublet at 5.36 ppm growed in the same ratio as the methyl group. Two doublets in the aromatic region at δ = 7.26 and 7.05 ppm appeared in the beginning of the reaction with a coupling constant of 13.3 Hz. These signals disappeared upon formation of product **53a** which indicated the presence of an intermediate. We then concluded, that a rapidly occuring first step took place, which caused the formation of an intermediate that reacted to the product **53a**.

As a possibility we considered the demethylation of the dimethylsulfonium group by the phthalimide anion. That, however, would display the peak of the methyl group of the intermediate *N*-methylphthalimide in the ^{1}H NMR spectrum, which is reported to be at $\delta = 3.14\text{-}3.18$ ppm[61-62] in $CDCl_3$ and was absent in our obtained spectrum. Also, as expected from a demethylation, a diazo compound with an α-methylsulfide group would result which is assumed to be unstable and would probably decompose by loss of N_2.

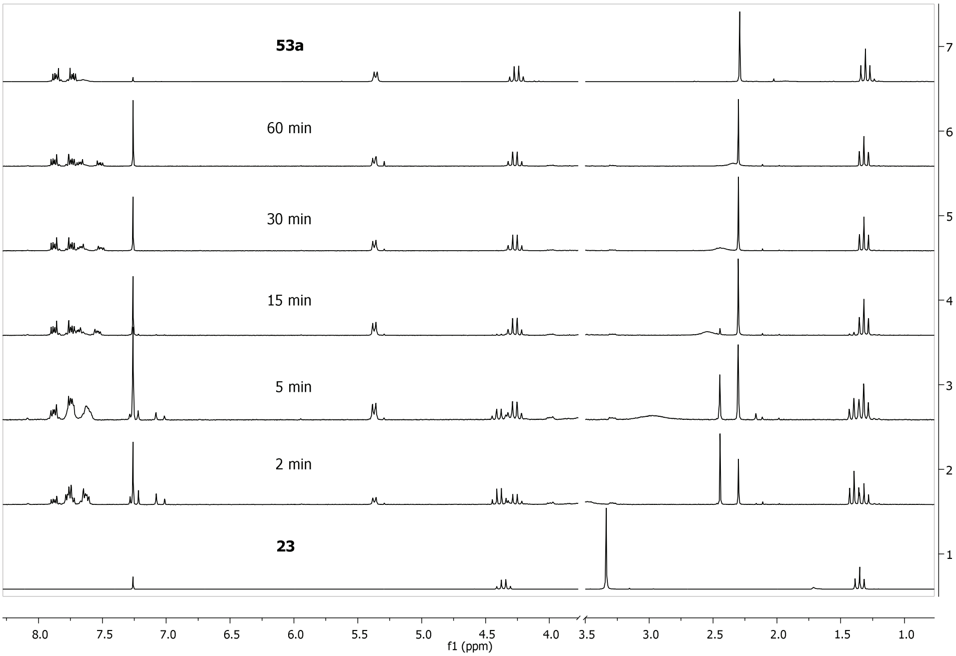


Figure 6.11 Monitoring of the reaction of **23** with 1.5 eq. KNPhth and 18-crown-6 to **53a**. For clarity, the peak of 18-crown-6 is excluded (3.62 ppm).

As an alternative mechanism, we considered a deprotonation of the dimethylsulfonium group in **23**. To investigate a base mediated reaction, we performed a reaction of **23** with 2.2 eq. potassium hexamethyldisilazide (KHMDS) in $CDCl_3$ at room temperature and followed the reaction by ^{1}H NMR. As seen for the reaction with potassium phthalimide and 18-crown-6, the singlet of the dimethylsulfonium group of **23** at 3.34 ppm was absent after 5 min (Figure 6.12). Furthermore, two new signals in the ^{1}H NMR spectrum of with KHMDS developed at 2.12 ppm and 2.45 ppm, of which the latter singlet at $\delta = 2.45$ ppm was identical to the one obtained with potassium phthalimide. Additionally, the doublets at $\delta = 7.26$ and 7.05 ppm, which were previously detected in the reaction of **23** with 18-crown-6 and potassium phthalimide, appear in the spectrum with KHMDS as well.

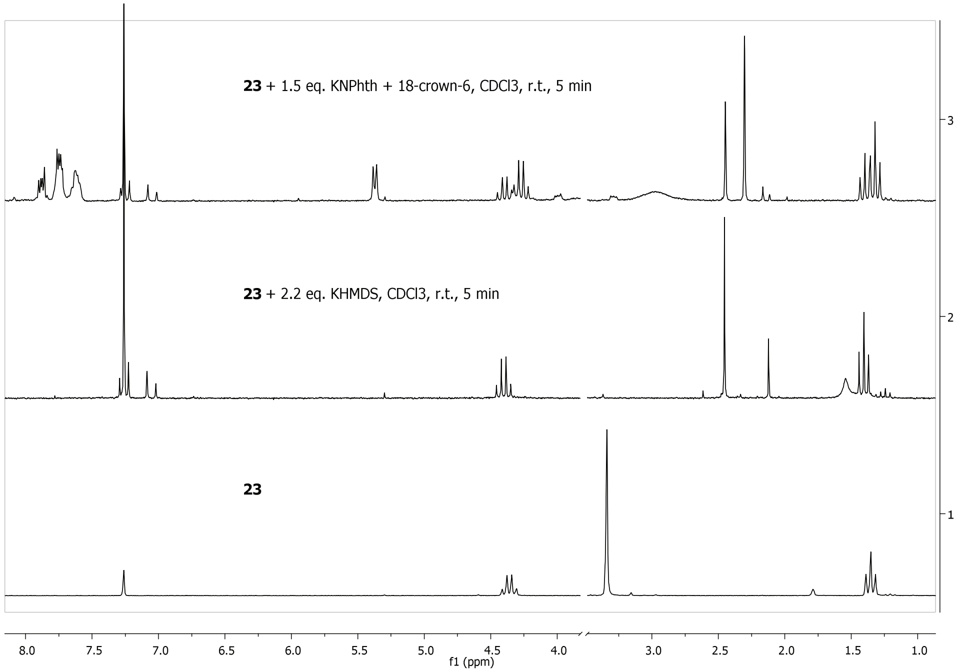
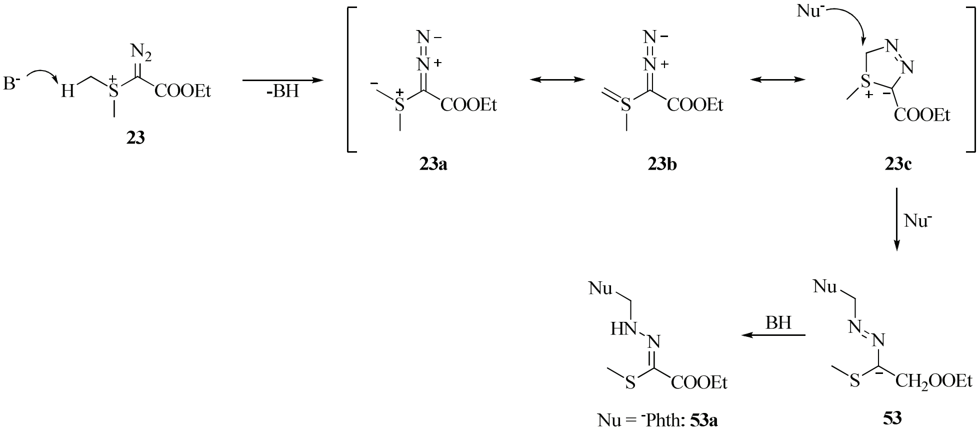


Figure 6.12 Reaction of **23** with 1.5 eq. KNPhth and 18-crown-6 (top) and 2.2 eq. KHMDS (middle) after 5 min at r.t. in $CDCl_3$. For clarity, the peak of 18-crown-6 is excluded (3.62 ppm).

We concluded that a common intermediate in both reactions is present and a proposed mechanism is shown in Scheme 6.15. Under the assumption of a fast deprotonation by the phthalimide anion in the first step of the reaction, the ylide **23a** with the resonance structures **23b** and **23c** would result. It is known, that the diazo group can participate in intramolecular cyclizations in vinyldiazoacetates to form pyrazoles,[63-65] which would resemble the formation of the cyclic ylide **23c** from **23b**. Furthermore, as mentioned in Chapter 3 and seen in the previous section, the terminal nitrogen of the diazo group could react with nucleophiles which would also support the intermediate **23c**. The deprotonation of the dimethylsulfonium group by the phthalimide anion seemed to be preferred over the nucleophilic attack of the phthalimide to the terminal nitrogen in **23**. Of the three resonance structures **23a**-**23c**, only thiadiazole analogue **23c** would, after nucleophilic attack of the phthalimide anion onto the bridging CH_2-group, lead to product **53a**. The singlet at $\delta = 2.45$ ppm in ^1H NMR spectrum in Figure 6.12 could then originate from one of the intermediates **23a**, **23b** or **23c** and its disappearance over time would be in agreement with the proposed mechanism. The two doublets in the aromatic region could originate from a geminal coupling of the protons of the

CH_2-group in **23c**. A 2D COSY, as well as a ^{13}C DEPT NMR could give confirmation for this assumption and is planned in our group for future investigations.



Scheme 6.15 Proposed mechanism for the formation of **53a** *via* deprotonation of **23** and following nucleophilic ring opening of **23c**. B^-, Nu^- = phthalimide anion

To further investigate our proposed mechanism, we attempted a stepwise addition of potassium phthalimide to **23**. Addition of 0.95 equivalents of potassium phthalimide to **23** in the presence of 18-crown-6 in $CDCl_3$ at room temperature should result in formation of the intermediate **23c** as expected for a stepwise mechanism with deprotonation as the first step. A second equivalent potassium phthalimide should then lead to product **53a** *via* nucleophilic ring opening. The phthalimide would then have a dual functionality as base and nucleophile in the same reaction.

The expected results were observed, as shown in Figure 6.13. After addition of 0.95 equivalents of potassium phthalimide to **23** and 18-crown-6, the intermediate was formed and the previously observed peaks at 2.45 ppm and in the aromatic region along with traces of unreacted **23** occurred (Figure 6.13, bottom). Upon addition of a second equivalent KNPhth, immediate color change to yellow and product formation took place indicated by appearance of the singlet at $\delta = 2.30$ ppm and the doublet at 5.36 ppm and completion of the reaction was obtained after 45 min. A stepwise mechanism appeared to be present and more than one equivalent of potassium phthalimide was neccessary to produce the final product. After deprotonation and ylide formation with the first equivalent of the phthalimide anion, nucleophile induced ring opening to **53** occurred, which was then protonated to form **53a** (Scheme 6.15). This protonation would then release another phthalimide anion which could act as a nucleophile again. The phthalimide was thus expected to act as a kind of proton shuttle. A minimum amount of excess of phthalimide anion should thus be enough to drive the reaction to completion and a test experiment with 1.1 eq. of potassium phthalimide and 18-crown-6 afforded full conversion of **23** after 3 h (followed by ^{1}H NMR, see Table 6.5, entry 6, section 6.2.4.3). The slower reaction rate with 1.1 equivalents compared to the reactions with 2.0 equivalents of KNPhth was in agreement with the assumption that the phthalimide anion was the initiator of the second reaction step which proceeded slower when the phthalimide anion was generated during the reaction. The base induced mechanism would allow to use different bases to generate the intermediate in the first step which could then react with different nucleophiles to give analogs of **53a**. The generation of analogs and the isolation of the intermediate by trapping after deprotonation were not attempted.

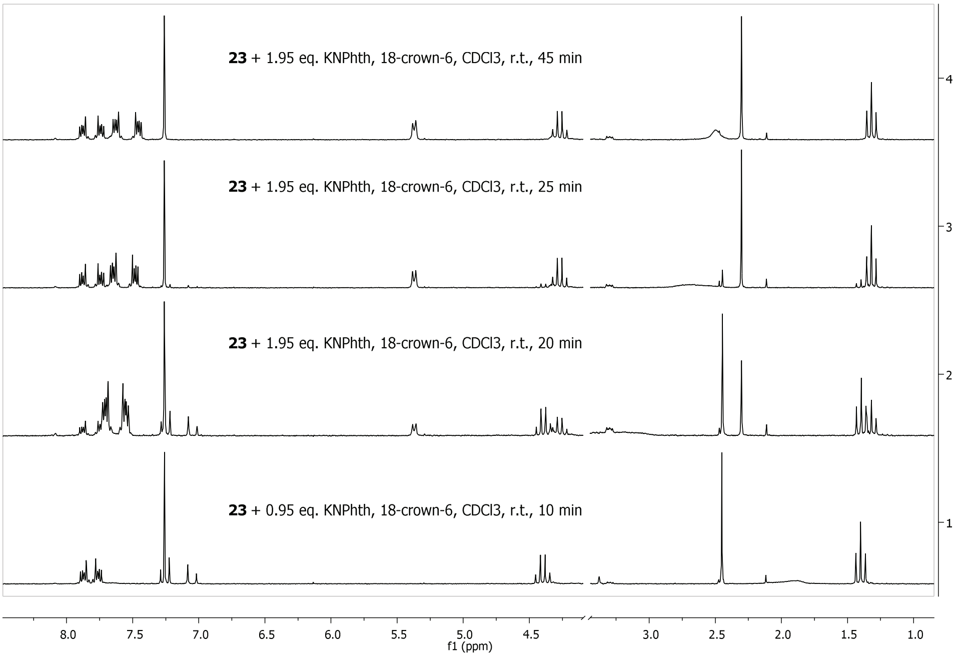
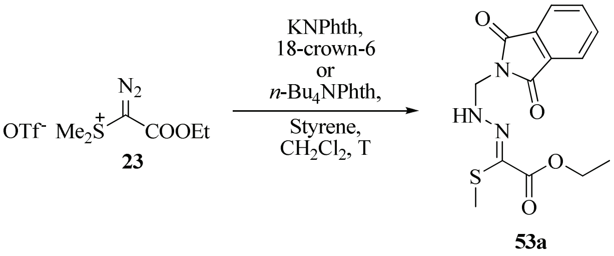


Figure 6.13 Stepwise addition of KNPhth to **23** and 18-crown-6 in $CDCl_3$ at room temperature. Formation of **53a** *via* two-step mechanism: 1. deprotonation, 2.nucleophilic substitution

6.2.4.3 Investigation of the reaction scope

As our initial experiment for the reaction of **23** with potassium phthalimide gave a promising isolated yield of 71% of **53a**, we investigated the versatility of that reaction under different conditions (Table 6.5). Since the minor product **53b** was obtained only in trace amounts in all reactions, yields will only be presented for **53a**. All reactions afforded moderate to high yields of **53a** with 83% as highest obtained yield (Table 6.5, entry 2). The presence of styrene did not have an influence on the reaction. The temperature for the reactions of **23** with potassium phthalimide and 18-crown-6 appeared to have no influence on product yield (Table 6.5, entries 1-3). Also, a dropwise addition of **23** over 2 h at room temperature did not show a significant change in yield (Table 6.5, entry 3). The reaction with tetrabutylammonium phthalimide, as seen before for the amination of **22**, gave a reduced yield of 58% of **53a** (Table 6.5, entry 4). In case of the deuterated product **D$_6$-53a** we were mainly interested in a qualitative isolation for mechanistic purposes and actual yields may be higher than the isolated 54%. As discussed in section 6.2.4.2, the reaction with 1.1 eq. potassium phthalimide was slower at room temperature than the reactions with 2.0 eq. though it went to completion after 3 h.

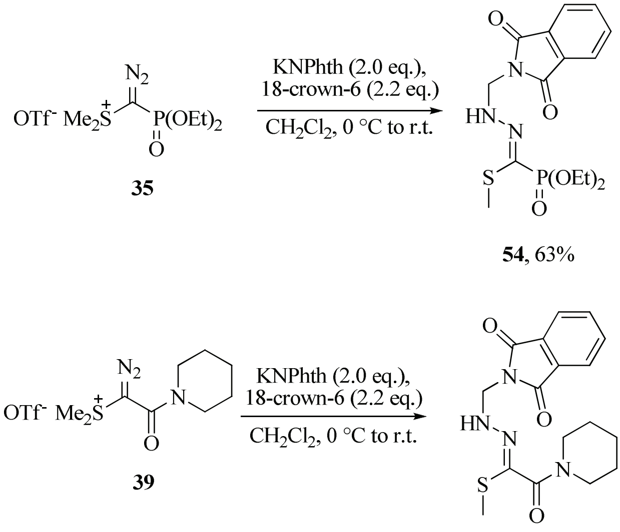
Table 6.5 Reaction of **23** with potassium phthalimide and 18-crown-6 to **53a**.



Entry	Amine (eq.)	T [°C]	t [h]	Conditions	Yield [%] of 53a[a]
1	KNPhth (2.0)	-30	1	A[b]	71
2	KNPhth (2.0)	0 to r.t.	1	B[c]	83
3	KNPhth (2.0)	r.t.	2	C[d]	75
4	TBANPhth (2.0)	0 to r.t.	1	D[e]	58
5	KNPhth (2.0)	0	1	E[f]	54[g]
6	KNPhth (1.1)	r.t.	3	F[h]	Full conversion

[a]Isolated yield after column chromatography; [b]18-crown-6 (2.2 eq.), styrene (30 eq.), CH$_2$Cl$_2$, bulk addition of **23** as solid (0.17 M); [c]18-crown-6 (2.2 eq.), CH$_2$Cl$_2$, bulk addition of **23** as solid (0.4 M); [d]18-crown-6 (2.2 eq.), CH$_2$Cl$_2$, dropwise addition of **23** over 2 h (0.21 M); [e]CH$_2$Cl$_2$, bulk addition of **23** as solid (0.12 M); [f]18-crown-6 (2.2 eq.) CH$_2$Cl$_2$, bulk addition of **D$_6$-23** as solid; [g]Yield of **D$_6$-53a**; [h]18-crown-6 (1.3 eq.), CDCl$_3$, bulk addition of **23** as solid, reaction monitoring *via* ^{1}H NMR, no product isolation.

The reaction could be extended to the analogous diazophosphonate **35**, affording 63% of the corresponding product **54** as a colorless oil, and the diazopiperidinylamide **39**, to afford 65% isolated yield of product **55** as a colorless solid (Scheme 6.16).



35

54, 63%

39

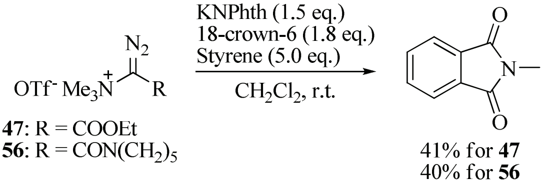
55, 65%

Scheme 6.16 Reactions of α-dimethylsulfonium diazophosphonate triflate **35** (top) and α-dimethylsulfonium diazopiperidinylamide triflate **39** (bottom) with potassium phthalimide and 18-crown-6 to the corresponding products **54** and **55**.

In contrast to the reactions of potassium phthalimide and 18-crown-6 with **22** (6.2.3.1) where the phthalimide anion reacted as a nucleophile to replace the iodobenzene, in the present system with the α-dimethylsulfonium diazo triflate salts **23**, **35** and **39** the phthalimide anion reacted as a base in the first step and as a nucleophile in the second step. Also, the previously obtained nucleophilic attack on the terminal nitrogen of the diazo group of **22** and following 1,3-diploar cycloaddition with styrene did not occur in case of the α-dimethylsufonium diazo triflate salts, presumably due to a higher preference for ylide formation. The functionality of the phthalimide thus depended, in addition to its counter ion, on the onium substituent of the diazo compound.

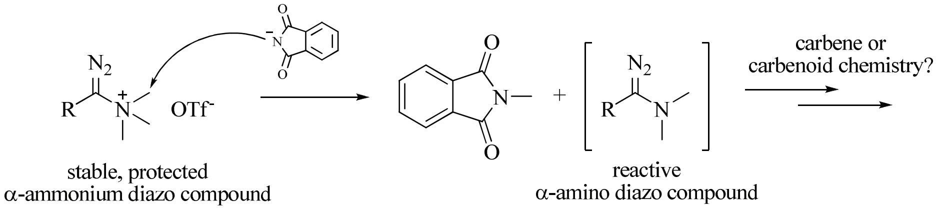
6.2.5 Demethylations of α-trimethylammonium diazoester triflate 47 and diazopiperidinylamide 56 with potassium phthalimide

After the results obtained in the previous sections, we considered the previously prepared α-trimethylammonium diazoester triflate **47** as an interesting substrate for reactions with the phthalimide anion. A low scale test reaction of 0.06 mmol of **47** with potassium phthalimide (1.5 eq.), 18-crown-6 (1.8 eq.) and styrene (5.0 eq.) in $CDCl_3$ at room temperature afforded, after column chromatography, 41% *N*-methylphthalimide (Scheme 6.17). The same reactivity was observed for the analogous α-trimethylammonium diazopiperidinylamide triflate **56**, which also afforded *N*-methylphthalimide in 40% yield after column chromatography.



Scheme 6.17 Formation of *N*-methylphthalimide from reactions of **47** and **56** with potassium phthalimide and 18-crown-6 *via* demethylation.

The formation of *N*-methylphthalimide was an important and particularly interesting result giving a proof of principle that demethylation of the α-trimethylammonium unit can be achieved. The intermediates resulting from the demethylation could not be identified as no products besides *N*-methylphthalimide could be isolated. The selective demethylation and release of a free α-dimethylamino diazo compound would, however, be a very powerful and elegant way to prepare previously inaccessible, unstable α-amino diazo compounds *in situ*. The α-trimethylammonium moiety can therefore be considered as a protecting group (Scheme 6.18). The methodology of demethylation of α-onium diazo compounds will be further discussed in the future prospects (Chapter 7).



Scheme 6.18 Proposed demethylation of α-trimethylammonium diazo triflate salts and *in situ* preparation of an α-amino diazo compound.

Besides the previously discussed reactions in which the phthalimide anion reacted as base or nucleophile, it displayed a third role in the reactions with the α-trimethylammonium diazo compounds as a demethylating agent. We have thus discovered and demonstrated a variety of reactivities of the employed α-onium diazo salts and generated several opportunities for following projects.

6.3 Summary and conclusions

In conclusion, the examined α-onium diazo triflate salts showed different types of unexpected reactivities in nucleophilic substitutions with different nucleophiles, as well as in Rh(II) catalyzed carbenoid chemistry, summarized in Table 6.6.

The α-dimethylsulfonium and α-triethylammonium diazo triflate salts were suitable substrates for Rh(II) carbenoid reactions. An aziridinium triflate salt was tentatively elucidated from Rh(II) catalyzed reaction of the α-triethylammonium diazoester triflate **24** *via* an assumed intramolecular C-H insertion. Isolation of the aziridinium salt, however, was not successful though yields were estimated to be moderate. The Rh(II) catalyzed reaction of α-dimethylsulfonium diazoester triflate **23** with styrene afforded the dimethylsulfonium cyclopropyl triflate salt **43** which showed *cis* stereochemistry with regard to the ester and phenyl substituent, as confirmed by X-ray crystal structure. The reaction showed, however, low reproducibility.

We have shown in Chapter 3 that nucleophilic halogenations of the α-aryliodonium diazo triflate salts gave access to the corresponding halodiazo compounds as a complementary pathway to the electrophilic halogenation presented in Chapter 2. The *in situ* prepared halodiazo compounds reacted in intermolecular Rh(II) catalyzed cyclopropanation reactions (esters and phosphonates) or thermal intramolecular C-H insertions (piperidinylamides) to the corresponding products in moderate to good, albeit lower yields than in the electrophilic pathway. The nucleophilic substitution methodology could be extended toward the *in situ* preparation of the α-phthalimido diazoester **49** from **22** with potassium phthalimide and 18-crown-6 or tetrabutylammonium phthalimide. α-Phthalimido diazoester **49** was found to react in a catalyst free thermal intermolecular cyclopropanation with styrene to the corresponding protected cyclopropylaminoacid **48** albeit in maximum yields of 32%.

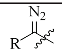
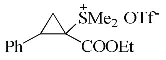
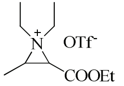
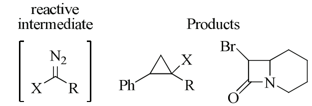
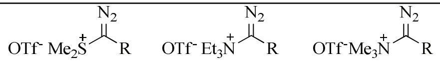
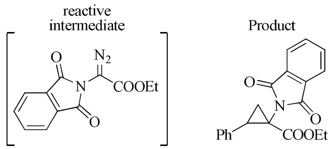
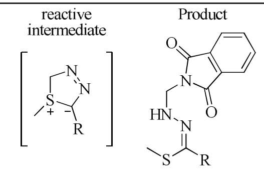
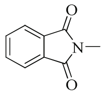
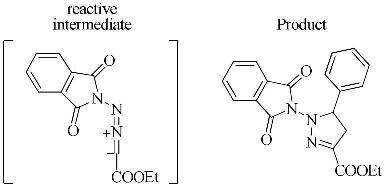
The alternative approach by using phthalimide and sodium hydride or potassium phthalimide lead to a different reaction pathway. We concluded that nucleophilic attack of the phthalimide anion on the terminal nitrogen of the diazo group of **22** occured and an intermediate resulted which reacted in a 1,3-dipolar cycloaddition with styrene to the pyrazoline product **50** in moderate yields.

Another different reaction mode was discovered when the α-dimethylsulfonium diazo triflates **23**, **35** and **39** were reacted with potassium phthalimide and 18-crown-6 or tetrabutylammonium phthalimide. The hydrazone **53a** was obtained as the major product in high yields up to 83% in the reaction with **23**. We postulated, after mechanistic investigations, that a two step mechanism was existent, the deprotonation of the α-dimethylsulfonium moiety occurring first, followed by nucleophilic ring opening of an intermediate resembling a thiadiazole. The phthalimide anion was assumed to act as a proton shuttle in a dual role as base and nucleophile in the same reaction.

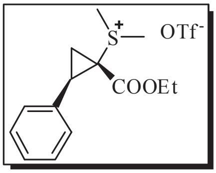
In the reactions of the α-trimethylammonium diazoester triflate **47** and diazopiperidinylamide **56** with potassium phthalimide, we isolated *N*-methylphthalimide and concluded that a demethylation reaction occurred which could be a possible method for the *in situ* generation of α-amino diazo compounds.

The results presented in this thesis reveal that reactions of α-onium diazo triflate salts with negatively charged nucleophiles, as well as in Rh(II) carbenoid transformations lead to interesting reaction modes, with dependence on the nucleophile and the α-onium diazo triflate salt employed.

Table 6.6 Overview of reactivities with α-onium diazo triflate salts obtained in our studies. Proposed reactive intermediates, final products and reaction types are displayed.

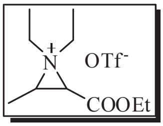
 R = COOEt, P(O)(OEt)$_2$, CO(CH$_2$)$_5$	**Onium substituent**			
Reagents	$\overset{+}{I}Ph$	$\overset{+}{S}Me_2$	$\overset{+}{N}Et_3$	$\overset{+}{N}Me_3$
Rh$_2$L$_4$, styrene	n.d.	 catalytic cyclopropanation	 catalytic intramolecular C-H insertion	no product obtained
Halides, Rh$_2$L$_4$, styrene KX, *n*-Bu$_4$NX X = Cl, Br, I,	 nucleophilic halogenation, catalytic intermolecular cyclopropanation / thermal intramolecular C-H insertion	no reaction	no reaction	not attempted
Neutral nucleophiles (SMe$_2$, NEt$_3$, NMe$_3$)	 nucleophilic substitution	no reaction	no reaction	not attempted
Phthalimide anion KNPhth/18-crown-6, *n*-Bu$_4$NPhth, styrene	 nucleophilic substitution, thermal intermolecular cyclopropanation	 deprotonation, nucleophilic ring opening	not attempted	 demethylation
Phthalimide anion + counter ion HNPhth/NaH, KNPhth, styrene	 addition of nucleophile on terminal N, loss of leaving group, 1,3-dipolar cycloaddition	not attempted	not attempted	

6.4 Experimental



(1-(ethoxycarbonyl)-2-phenylcyclopropyl)dimethylsulfonium trifluoromethanesulfonate (43)

$Rh_2(esp)_2$ (2.4 mg, 3.1 µmol, 2 mol%) was dissolved in 1 mL dry toluene at room temperature. To this solution styrene (0.181 mL, 1.58 mmol, 10 eq.) was added, followed by dropwise addition of a solution of **23** (51 mg, 158 µmol, 1.0 eq.) in 1 mL dry CH_2Cl_2 over 30 min *via* a syringe pump. The mixture stirred at room temperature for an additional 30 min and the solvents and residual styrene were removed *in vacuo* and the residue dried under reduced pressure. The crude mixture was then dissolved in CH_2Cl_2, and Et_2O was added until the solution became cloudy and was then stored in the fridge over night. Filtration of the precipitate afforded **43** (0.28 g, 71 µmol, 45%) as a colorless solid. Crystals for X-ray crystallography were obtained from vapor diffusion from CH_2Cl_2 and Et_2O/*n*-hexanes as anti-solvents. *cis*-Isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.21 (m, 5H, Ar-H), 3.95 – 3.74 (m, 2H, CH_2), 3.62 (t, *J* = 9.5 Hz, 1H, CH), 3.43 (s, 3H, CH_3), 3.28 (s, 3H, CH_3), 2.69 (t, *J* = 8.0 Hz, 1H, CH), 2.39 (dd, *J* = 9.5, 8.0 Hz, 1H, CH), 0.77 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7 (CO), 131.9 (C), 129.6 (CH), 129.1 (CH), 129.0 (CH), 121.1 (q, *J* = 320.0 Hz, CF_3), 63.7 (CH_2), 37.5 (C), 34.8 (CH), 25.8 (CH_3), 25.4 (CH_3), 20.8 (CH_2), 13.7 (CH_3); HRMS (ESI^+) $C_{14}H_{19}O_2S^+$ requires 251.1100, found 251.1103.

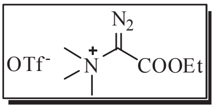


2-(ethoxycarbonyl)-1,1-diethyl-3-methylaziridinium trifluoromethanesulfonate (45)

Product **45** could not be isolated, spectroscopic data is reported from the crude reaction mixture.

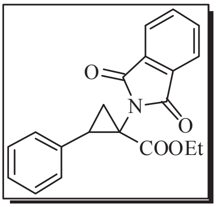
$Rh_2(esp)_2$ (4.0 mg, 5.2 µmol, 5 mol%) or $Rh_2(OAc)_4$ (2.3 mg, 5.2 µmol, 5 mol%) was dissolved in 1 mL dry toluene at room temperature under Ar. Styrene (109 µL, 0.95 mmol, 10 eq.) was added, followed by dropwise addition of a solution of **24** (34 mg, 95 µmol, 1.0 eq.) in 1 mL dry CH_2Cl_2 over 30 min *via* a syringe pump. The mixture was stirred at room temperature for 30 min and then concentrated *in vacuo*. ^1H NMR (400 MHz, $CDCl_3$) δ 4.34 (q, *J* = 7.1 Hz, 2H, CH_2), 4.13 (d, *J* = 7.4 Hz, 1H, CH), 3.64 – 3.57 (m, 1H, CH), 3.54 – 3.33 (m, 4H, 2xCH_2), 1.81 (d, *J* = 6.2 Hz, 3H, CH_3), 1.43 (t, *J* = 7.1 Hz, 3H, CH_3), 1.36 (td, *J* = 7.2, 4.0 Hz, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3 (CO), 120.7 (d, *J* = 320 Hz, CF_3), 64.3

(CH_2), 53.8 (CH), 52.5 (CH), 49.5 (CH_2), 48.1 (CH_2), 13.9 (CH_3), 10.7 (CH_3), 10.1 (CH_3), 8.9 (CH_3); HRMS (ESI$^+$) $C_{10}H_{20}NO_2^+$ requires 186.1487, found 186.1500.



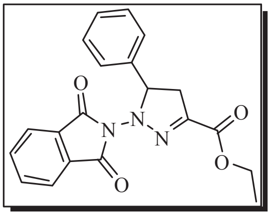
1-diazo-2-ethoxy-*N*,*N*,*N*-trimethyl-2-oxoethanaminium trifluoromethanesulfonate (47)

α-Aryliodonium diazoester triflate **22** (0.418 g, 0.898 mmol, 1.0 eq.) was dissolved in 10 mL dry CH_2Cl_2. The solution was cooled to -20 °C and gaseous trimethylamine was bubbled into the solution for 1 minute. The mixture became light yellow and cloudy after a few minutes, and was stirred at -20 °C for additional 30 minutes. Et_2O was added to the mixture until precipitation occurred. The solid was filtered off with suction and afforded **47** (0.213 g, 0.664 mmol, 74%) as a pale yellow solid. ^{1}H NMR (400 MHz, CD_3CN) δ 4.32 (q, *J* = 7.1 Hz, 2H, CH_2), 3.52 (s, 9H, 3xCH_3), 1.29 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CD_3CN) δ 161.0 (CO), 63.9 (CH_2), 57.5 (CH_3), 14.5 (CH_3); HRMS (ESI$^+$) $C_7H_{14}N_2O_3^+$ requires 172.1081, found 172.1091.



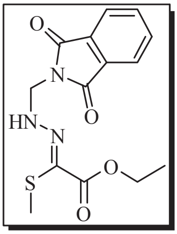
Ethyl 1-(1,3-dioxoisoindolin-2-yl)-2-phenylcyclopropanecarboxylate (48)

18-crown-6 (106 mg, 400 μmol, 2.2 eq.), potassium phthalimide (67 mg, 364 μmol, 2.0 eq.) and styrene (564 mg, 5.46 mmol, 30 eq.) were dissolved in 2.5 mL dry CH_2Cl_2 at room temperature. A solution of **22** (85 mg, 181 μmol, 1.0 eq.) in 2.5 mL dry CH_2Cl_2 was added dropwise over 2 h *via* a syringe pump. The mixture stirred at room temperature for an additional 1 h and was concentrated *in vacuo*. The crude product mixture was purified by flash column chromatography using gradient elution with *n*-hexanes/EtOAc (20:1 to 5:1) to afford 19.6 mg (59 μmol, 32%) of **48** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.52 (m, 4H, Ar-H), 7.18 – 7.02 (m, 5H, Ar-H), 4.28 – 4.08 (m, 2H, CH_2), 3.37 (dd, *J* = 9.8, 8.6 Hz, 1H, CH), 2.42 (dd, *J* = 8.6, 6.6 Hz, 1H, CH), 2.26 (dd, *J* = 9.8, 6.6 Hz, 1H, CH), 1.20 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0 (CO), 134.5 (C), 134.2 (CH), 128.1 (CH), 128.1 (CH), 127.3 (CH), 123.5 (CH), 62.2 (CH_2), 39.4 (C), 31.8 (CH), 19.3 (CH_2), 14.3 (CH_3); MS (EI) *m/z* (rel. int.) 335.1 (22, M$^+$), 289.1 (96), 261 (62), 245 (24), 132 (44), 115 (61), 104 (100), 76 (46); HRMS (EI) $C_{20}H_{17}NO_4$ requires 335.1158, found 335.1163.



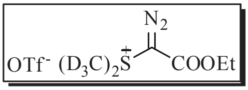
Ethyl 1-(1,3-dioxoisoindolin-2-yl)-5-phenyl-4,5-dihydro-1H-pyrazole-3-carboxylate (50)

a-Aryliodonium diazoester triflate **22** (82.6 mg, 177 µmol, 1.0 eq.) was dissolved in 10 mL dry CH_2Cl_2 at -20 °C. To this solution phthalimide (65 mg, 433 µmol, 2.5 eq.) was added, followed by styrene (552 mg, 607 µL, 30 eq.). The mixture stirred at -20 °C for 10 minutes, then NaH (23 mg, 531 µmol, 3 eq.) was added at that temperature until no more gas evolution was observed. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was then quenched by addition of ice water and the two phases separated. The aqueous phase was extracted twice with CH_2Cl_2, and the joined organic phases washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography using gradient elution with *n*-hexanes/EtOAc (100:0 to 5:1) to afford 39.5 mg (110µmmol, 62%) of **50** as a colorless solid. Single crystals for X-ray crystallography were obtained by addition of 1 mL of a mixture of *n*-hexanes/EtOAc (5:1) to 1 mg **50** in a vial, followed by a minimum amount of CH_2Cl_2 to dissolve the solid. The vial was then capped with a perforated lid and left at room temperature until crystal formation was observed and the solvents were removed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 5.5, 3.1 Hz, 2H, Ar-H), 7.61 (dd, *J* = 5.5, 3.1 Hz, 2H, Ar-H), 7.48 – 7.42 (m, 2H, Ar-H), 7.27 – 7.12 (m, 4H, Ar-H), 5.55 (dd, *J* = 14.4, 10.3 Hz, 1H, CH), 4.25 (m, 2H, CH_2), 3.49 (dd, *J* = 17.2, 10.3 Hz, 1H, CH), 2.92 (dd, *J* = 17.2, 14.4 Hz, 1H, CH), 1.24 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5 (CO), 145.7 (C), 136.9 (C), 134.8 (CH), 130.0 (C), 129.0 (CH), 128.8 (CH), 127.6 (CH), 72.3 (CH), 62.1 (CH_2), 41.7 (CH_2), 14.4 (CH_3); MS (EI) *m/z* (rel. int.) 363 (35, M^+), 290 (59), 216 (100), 171 (36), 115 (36), 104 (74), 76 (32); HRMS (EI) $C_{20}H_{17}N_3O_4$ requires 363.1219, found 363.1206.



Ethyl 2-(2-((1,3-dioxoisoindolin-2-yl)methyl)hydrazono)-2-(methylthio)acetate 53a and byproduct (53b)

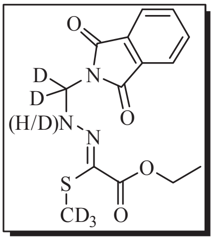
18-crown-6 (232 mg, 879 µmol, 2.2 eq.) and potassium phthalimide (148 mg, 799µmmol, 2.0 eq.) were dissolved in 5 mL dry CH_2Cl_2 at 0 °C. To this solution **23** (130 mg, 400 µmol, 1.0 eq.) was added as solid in one portion. The yellow solution was allowed to warm to room temperature and stirred for an additional 30 minutes at that temperature. The crude reaction mixture was concentrated *in vacuo* and purified by flash column chromatography using gradient elution with *n*-hexanes/EtOAc (10:1 to 5:1) to afford 107 mg (330 µmol, 83%) of **53a** as a pale yellow solid. Crystals for X-ray crystallography were obtained by vapor diffusion crystallization from EtOAc and Et_2O as colorless needles. ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.78 (m, 2H, Ar-H), 7.80 – 7.70 (m, 2H, Ar-H), 7.65 (s, br, 1H, NH), 5.36 (d, *J* = 4.6 Hz, 2H, CH_2), 4.26 (q, *J* = 7.1 Hz, 2H, CH_2), 2.29 (s, 3H, CH_3), 1.31 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9 (CO), 167.6 (CO), 162.3 (CO), 160.5 (CO), 134.4 (CH), 134.3 (CH), 132.1 (C), 132.0 (C), 130.2 (C), 128.4 (C), 123.8 (CH), 123.6 (CH), 61.9 (CH_2), 61.8 (CH_2), 53.2 (CH_2), 52.6 (CH_2), 15.4 (CH_3), 14.3 (CH_3), 14.1 (CH_3), 13.5 (CH_3); MS (EI) *m/z* (rel. int.) 321 (46, M^+), 174 (39), 160 (100), 147 (79), 104 (55), 76 (54), 50 (19), 29 (32); HRMS (EI) $C_{14}H_{15}N_3O_4S$ requires 321.0783, found 321.0774. Compound **53b** was obtained as a byproduct in the synthesis of **53a** and was not fully elucidated. ^1H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.86 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.1 Hz, 2H), 5.23 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.23 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0 (CO), 167.7 (CO), 160.6 (CO), 134.5 (CH), 134.3 (CH), 132.2 (C), 132.1 (C), 123.9 (CH), 123.7 (CH), 62.0 (CH_2), 61.9 (CH_2), 53.3 (CH_2), 52.7 (CH_2), 15.5 (CH_3), 14.4 (CH_3), 14.2 (CH_3), 13.5 (CH_3); MS (EI) *m/z* (rel. int.) 321 (41, M^+), 175 (24), 160 (100), 147 (17), 104 (18), 76 (18).



$\mathrm{OTf^-\ (D_3C)_2\overset{+}{S}{-}C({=}N_2){-}COOEt}$

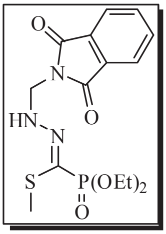
Deutero-(1-diazo-2-ethoxy-2-oxoethyl)dimethylsulfonium trifluoromethanesulfonate (D_6-23)

α-Aryliodonium diazoester triflate **22** (2.64 g, 5.67 mmol, 1.0 eq.) was dissolved in 10 mL dry CH_2Cl_2 at 0 °C. To this solution deuterated dimethylsulfide (0.5 mL, 6.8 mmol, 1.2 eq.) was added and the mixture stirred at 0 °C for 30 min. The solution decolorized and was allowed to warm to room temperature. Et_2O was added until the mixture became cloudy and precipitation occurred and stirring was continued for 30 minutes. The solid was filtered off with suction to afford 1.653 g (5.01 mmol, 88%) of **D_6-23** as a colorless solid. ^1H NMR (400 MHz, $CDCl_3$) δ 4.33 (q, *J* = 7.1 Hz, 2H, CH_2), 1.32 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4 (CO), 120.6 (q, *J* = 320 Hz, CF_3), 63.5 (CH_2), 55.1 (CN_2), 27.0 (CH_3), 14.2 (CH_3); HRMS (ESI^+) $C_6H_5D_6N_2O_2S^+$ requires 181.0912, found 181.0924.



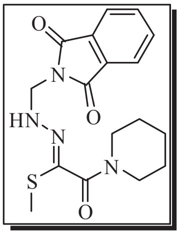
Deutero-ethyl 2-(2-((1,3-dioxoisoindolin-2-yl)methyl)hydrazono)-2-(methylthio)acetate (D_6-53a)

18-crown-6 (0.252 g, 0.954 mmol, 2.2 eq.) and potassium phthalimide (0.160 g, 0.868 mmol, 2.0 eq.) were dissolved in 5 mL dry CH_2Cl_2 at 0 °C. To this solution **D_6-23** (0.143 g, 0.434 mmol, 1.0 eq.) was added as solid in one portion. The yellow solution was allowed to warm to room temperature and stirred for an additional 30 minutes at that temperature. The crude reaction mixture was concentrated *in vacuo* and purified by flash column chromatography using gradient elution with *n*-hexanes/EtOAc (10:1 to 5:1) to afford 75.5 mg (0.23 mmol, 54%) of **D_6-53a** as a pale yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.81 (m, 2H, Ar-H), 7.81 – 7.70 (m, 2H, Ar-H), 7.63 (s, b, 1H, NH), 4.27 (q, J = 7.1 Hz, 2H, CH_2), 1.32 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9 (CO), 167.7 (CO), 162.4 (CO), 160.6 (CO), 134.5 (CH), 134.3 (CH), 132.2 (C), 132.1 (C), 123.8 (CH), 123.7 (CH), 62.0 (CH_2), 61.9 (CH_2), 31.6 (CH_2), 14.4 (CH_3), 14.2 (CH_3), 14.2 (CH_3); MS (EI) *m/z* (rel. int.) 326 (57, M^+), 179 (20), 162 (100), 147 (35), 106 (26), 76 (24), 50 (12); HRMS (EI) $C_{14}H_{10}D_5N_3O_4S$ requires 326.1097, found 326.1099; HRMS (EI) $C_{14}H_9D_6N_3O_4S$ requires 327.1160, found 327.1160.



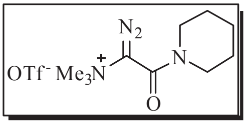
Diethyl 2-(2-((1,3-dioxoisoindolin-2-yl)methyl)hydrazono)-2-(methylthio)phosphonate (54)

18-crown-6 (120 mg, 455 μmol, 2.2 eq.) and potassium phthalimide (77 mg, 415 μmol, 2.0 eq.) were dissolved in 3 mL dry CH_2Cl_2 at 0 °C. To this solution **35** (81 mg, 207 μmol, 1.0 eq.) in 1 mL dry CH_2Cl_2 was added in one portion. The yellow solution was allowed to warm to room temperature and stirred for an additional 30 minutes at that temperature. The crude reaction mixture was concentrated *in vacuo* and purified by flash column chromatography using gradient elution with *n*-hexanes/EtOAc (5:1 to 1:1) to afford 55 mg (130 μmol, 63%) of **54** as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.79 (m, 2H, Ar-H), 7.79 – 7.64 (m, 2H, Ar-H), 7.35 (t, J = 5.7 Hz, 1H, NH), 5.28 (d, J = 5.7 Hz, 2H, CH_2), 4.21 – 4.00 (m, 4H, $2xCH_2$), 2.43 (s, 3H, CH_3), 1.30 (t, J = 7.1 Hz, 6H, $2xCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7 (CO), 134.5 (CH), 131.9 (C), 131.8 (C), 123.7 (CH), 63.7 (d, J = 6.5 Hz, CH_2), 52.6 (d, J = 1.2 Hz, CH_2), 16.3 (d, J = 6.6 Hz, CH_3), 14.9 (CH_3); MS (EI) *m/z* (rel. int.) 385 (57, M^+), 197 (49), 191 (45), 160 (100), 147 (89), 109 (67), 104 (59), 76 (59); HRMS (EI) $C_{15}H_{20}N_3O_5PS$ requires 385.0861, found 385.0866.



Methyl *N'*-(1,3-dioxoisoindolin-2-yl)methyl-2-oxo-2-(piperidin-1-yl)ethanehydrazonothioate (55)

18-crown-6 (21 mg, 83 µmol, 1.8 eq.) and potassium phthalimide (12.8 mg, 69.4 µmol, 1.5 eq.) were dissolved in dry CH_2Cl_2 (1 mL) at 0 °C. To this solution **39** (17 mg, 46 µmol, 1.0 eq.) was added in one portion at 0 °C. The reaction mixture stirred at 0 °C for 30 min, was then allowed to warm to room temperature and stirred for another 1 h at that temperature. The crude reaction mixture was concentrated *in vacuo* and purified by flash column chromatography using gradient elution with *n*-hexanes/EtOAc (10:1 to 5:1) to afford 10.8 mg (30 µmol, 65%) of **55** as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 – 7.79 (m, 2H, Ar-H), 7.79 – 7.63 (m, 2H, Ar-H), 6.13 (t, $J = 6.3$ Hz, 1H, NH), 5.15 (d, $J = 6.3$ Hz, 2H, CH_2), 3.60 – 3.51 (m, 2H, CH_2), 3.37 – 3.19 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 1.61 – 1.51 (m, 4H, 2xCH_2), 1.45 – 1.33 (m, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0 (CO), 161.1 (CO), 140.1 (C), 134.3 (CH), 132.1 (C), 123.7 (CH), 53.5 (CH_2), 48.0 (CH_2), 43.0 (CH_2), 26.4 (CH_2), 25.8 (CH_2), 24.6 (CH_2), 14.0 (CH_3); MS (EI) *m/z* (rel. int.) 360 (9, M^+), 185 (70), 147 (100), 112 (65), 104 (55), 84 (99), 69 (75); HRMS (EI) $C_{17}H_{20}N_4O_3S$ requires 360.1256, found 360.1260.



1-diazo-*N*,*N*,*N*-trimethyl-2-oxo-2-(piperidin-1-yl)ethanaminium trifluoromethanesulfonate (56)

α-Aryliodonium diazopiperidinylamide triflate **38** (67 mg, 132 µmol, 1.0 eq.) was dissolved in 5 mL dry CH_2Cl_2. The solution was cooled to -30 °C and gaseous trimethylamine was bubbled into the solution for 1 minute. The mixture became light yellow and cloudy after a few minutes, and was stirred at -30 °C for additional 15 minutes. The solvent was then removed *in vacuo* at 0 °C, and the residue dried on high vacuum to afford **56** as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 9H, 3xCH_3), 3.42 – 3.36 (m, 4H, 2xCH_2), 1.65 (d, $J = 4.7$ Hz, 2H, CH_2), 1.57 (d, $J = 4.1$ Hz, 4H, 2xCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 (CO), 120.7 (d, $J = 320$ Hz, CF_3), 66.0 (CN_2), 56.4 (CH_3), 46.7 (CH_2), 25.6 (CH_2), 24.3 (CH_2); HRMS (ESI^+) $C_{10}H_{19}N_4O^+$ requires 211.1553, found 211.1563.

6.5 References and footnotes

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Chapter 7

Future Prospects

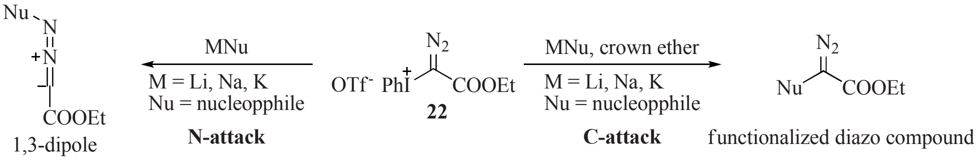
The reactions presented in the previous chapters offer numerous opportunities and deserve further investigation towards reaction scope, applications and mechanistic understanding. Especially the nucleophilic functionalizations and the discovered unexpected reactions deserve further investigation to gain a more thorough understanding of the reactivities. A few ideas will be presented in this chapter.

7.1 Nucleophiles for the nucleophilic substitutions of α-onium diazo triflate salts and applications

The nucleophiles that were applied for the nucleophilic substitutions of the α-aryliodonium diazo triflate salts in Chapters 3 and 6 were the neutral SMe_2, NEt_3, NMe_3 and the anionic Cl^-, Br^-, I^- and phthalimide. The amount of available nucleophiles is vast and a systematic study of different neutral and charged nucleophiles for the substitutions could lead to interesting new diazo compounds and reactions. As the α-onium diazoester triflates that were presented in this thesis showed a reasonably high thermal stability, the α-aryliodonium diazoester **22** would therefore be the substrate of choice for initial screening of nucleophiles.

7.1.1 Competition of C vs. N attack of the nucleophile

Of particular interest would be to investigate the competition of C vs. N attack of the nucleophiles as seen for the reaction of phthalimide with the α-aryliodonium diazoester triflate **22** resulting in a 1,3-dipole or a directly substituted diazo compound (Scheme 7.1). The general effect of the counter ion and the nucleophile are of interest as to modulate reactivity and it would be valuable to get an insight into general trends for reaction pathways. The nature of the nucleophile with regard to the HSAB concept could be a focus. Therefore, several nucleophiles with different counter ions in combination with or without crown ethers could be investigated to get an idea about general reactivity trends. The cations as counter ions have to be chosen carefully as to not act a Lewis acid for the decomposition of the diazo compounds.



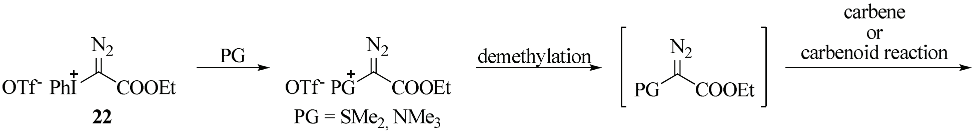
Anions: RO^-, RS^-, SCN^-, R_2N^-, Cl^-, Br^-, I^-, CN^-

Cations: Li^+, Na^+, K^+

Scheme 7.1 Proposal for competition experiments and investigation of reaction pathways in dependence of nucleophile and counter ion and proposed nucleophiles

7.1.2 α-Onium substituents as protecting groups

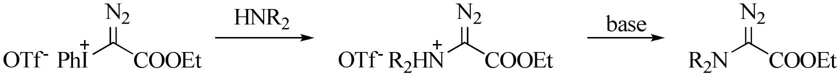
The neutral nucleophiles for the substitutions could offer the possibility to act as a protecting group or as a reactive site for intramolecular reactions with the carbenoid or carbene (as presented in the previous chapter). As seen in the previous chapter, one example for the protection of an α-amino diazoester was obtained with the α-trimethylammonium diazoester triflate **47**. This stable diazo salt could, after mild and selective demethylation, release a neutral α-dimethylamino diazoester for further transformations. Also, the α-dimethylsulfonium diazoester triflate **23** could offer the possibility for demethylation to release a neutral α-methylsulfide diazoester though propensity towards deprotonation and ylide formation has to be taken into consideration. The screening for demethylating agents and conditions would therefore be of interest. One demethylating agent that was found for the α-trimethylammonium diazoester triflate was the phthalimide anion, which, however showed different reactivity with the α-dimethylsulfonium diazoester triflate. Thus, different demethylating agents can be investigated (Scheme 7.2).



Scheme 7.2 General proposal for protection/deprotection of the α-aryliodonium diazoester triflate **22** *via* demethylation.

Possible demethylating agents could be phthalimide, thiocyanates,[1] triphenylphosphine[2] or thiolate anions.[3-4]

Another, similar approach to the deprotection method would be to use secondary amines as nucleophiles, which could, after deprotonation, release the neutral diazo compound (Scheme 7.3).



22

Scheme 7.3 General proposal for deprotection of an α-ammonium diazo triflate salt *via* deprotonation.

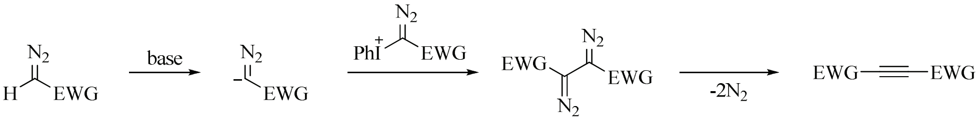
7.2 Cross couplings

7.2.1 Transition-metal catalyzed cross-couplings

Besides their use in catalytic carbenoid reactions, it would be interesting to investigate the abilities of the halodiazo compounds in cross-coupling reactions. Critical to this approach is the competition of diazo decomposition vs. oxidative addition by the transition metal catalyst. The palladium-catalyzed cross-couplings with diazo compounds *via* migratory insertion of a palladium-carbene species has found several recent applications.[5-6] This pathway, however, has to be prevented and the oxidative addition into the halogen-carbon bond of the halodiazo compound must be preferred under low temperatures to avoid the decomposition of the halodiazo compounds. A palladium-catalyzed cross-coupling under retention of the diazo group has been reported by *Wang et al.*[7] and an α-palladium diazoester was the reactive intermediate. If the halodiazo compounds are incompatible with the catalysts and conditions, the α-aryliodonium diazo triflate salts could be an alternative for the oxidative addition, since the I-C(N_2) bond in the α-aryliodonium diazo compounds seems to be quite labile. The higher thermal stability of **22** compared to the halodiazoesters could, however, be advantageous for the reaction conditions.

7.2.2 1,2-Bis diazo compounds and alkyne synthesis

The orthogonal reactivity of the diazo compounds presented in this thesis, precisely the electrophilic and nucleophilic reactivity, could allow a combination of both towards a coupling to 1,2-bis diazo compounds. 1,2-bis diazo compounds have been reported in the literature to eliminate 2 molecules dinitrogen to form the corresponding alkynes.[8] A reaction of a deprotonated diazo compound with the α-aryliodonium diazo triflate salt could therefore afford the substituted 1,2-bis diazo compounds and the corresponding substituted alkynes (Scheme 7.4). This methodology could then be expanded to remote functionalizations of enol-diazo compounds to form 1,4-bis diazo compounds.

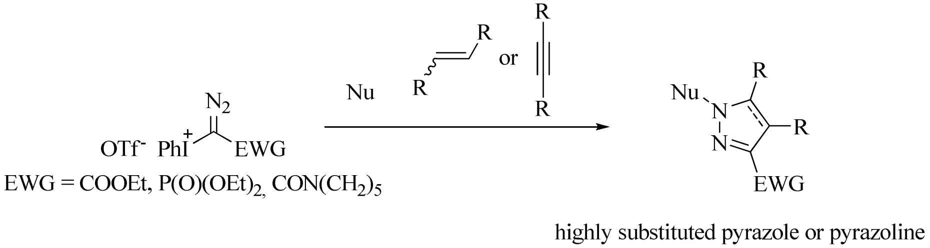


Scheme 7.4 Cross-coupling of diazo compounds to the 1,2-bis diazo compounds and resulting alkynes.

7.3 1,3-Dipolar cycloadditions and applications

The discovered 1,3-dipolar cycloaddition in Chapter 6, section 6.2.3.2 offers a convenient access to highly functionalized pyrazoles or pyrazolines. Pyrazolines and derivatives are valuable targets in synthetic organic chemistry and display biological activities.[9-11]

Investigations of the stability and the lifetime of the 1,3-dipole would be of interest for the optimization and further mechanistic insight. Experiments are planned for the characterization of the 1,3-dipole by NMR spectroscopy in solution at room temperature and under absence of a dipolarophile. A screening of nucleophiles which induce the formation of the 1,3-dipole, as well as the electronic properties of the 1,3-dipole with regard to cycloadditions with different dipolarophiles are of high interest for the optimization of the reaction. By choice of nucleophile, dipolarophile, and acceptor group of the α-aryliodonium diazo compound, three parameters could be varied conveniently. As the reaction was shown to give moderate to good yields for the α-aryliodonium diazoester triflate **22** and sodium or potassium phthalimide, the reactions with the corresponding phosphonates and piperidinylamides would be an obvious starting point (Scheme 7.5).



Scheme 7.5 Proposed preparation of highly substituted pyrazoles or pyrazolines by variation of nucleophile (Nu), electron withdrawing group (EWG) and dipolarophile.

7.4 References and footnotes

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Appendix

Paper I

Halodiazophosphonates, a New Class of Diazo Compounds for the Diastereoselective Intermolecular Rh(II) Catalyzed Cyclopropanation

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Paper II

Nucleophilic Halogenations of Diazo Compounds, a Complementary Principle for the Synthesis of Halodiazo Compounds: Experimental and Theoretical Studies

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