Synthesis and Characterization of Novel C,N-Bisalkynylation Benzimidazoles as Heterocyclic Azaenediynes for the Bergman Cyclization: On the Way to Novel Antitumor Drugs

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presented by

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Zürich, 2005
Für meine Mutter,
die meine Ausbildung stets uneingeschränkt unterstützt hat.
Die Wissenschaft
braucht Zusammenarbeit.
in der sich das Wissen des einen
durch die Entdeckungen des anderen bereichert.

JOSÉ ORTEGA Y GASSET
Über die Liebe
Verleumdung
ist der schlechte Atem der Feigheit.
Die meisten denunzieren nicht aus Hass,
sondern aus Furcht, selbst denunziert zu werden.

FRANK THIESS
Publications

Parts of this thesis have already been published:

- P. Zimmermann, P. Chen
  "Synthesis of a Novel C,N-Bisalkynylated Benzimidazole as an Azaenediyne for the Bergman Cyclization"
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- P. Zimmermann, P. Chen
  "Synthesis of a Novel C,N-Bisalkynylated Benzimidazole as an Azaenediyne for the Bergman Cyclization"

- P. Zimmermann, P. Chen
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4. Abstract

In order to survive in their permanent struggle for life, several microorganisms have developed antibiotics in order to combat hostile competitors. Antibiotics are capable of effectively destroying adversary bacteria or of inhibiting their further growth. The family of the naturally occurring enediyne antibiotics is a masterpiece of Nature's ingenuity. Members of this subclass of antibiotics show exceedingly high cytotoxicity, and furthermore do feature a fascinating mode of action.

Enediyne antibiotics share a modular design — their three functional domains can be divided into a delivery system, a triggering device and a warhead. While the delivery system directs the antibiotic agent precisely to the construction plan of the cell (which is the DNA), the triggering device initiates the "explosion" of the warhead.

The warhead contains a highly reactive structural unit — an enediyne moiety. The unique mechanism of action lies in the Bergman cyclization of this key unit. This leads to a powerful weapon: A belligerent biradical intermediate, which can tear off hydrogen atoms from the DNA. The entire process can lead to strand breaks in the DNA helix — and the destruction of its essential genetic material ultimately leads to the death of the target cell.

The natural enediyne antibiotics are not only bioactive as highly bacteriotoxic compounds — they were also studied as candidates for potential antitumor drugs. The fight against the scourge cancer is a top priority issue for the pharmaceutical industry. In Switzerland, cancer is responsible for the second most frequent cause of death, while death cases due to cancer do range in the third position worldwide.

A great number of the naturally occurring enediyne antibiotics, as well as their synthetically designed derivatives were investigated as potential anticancer agents. But unfortunately, their clinical application was found to be hampered by severe and unacceptable toxic side effects — their cytotoxicity to ordinary tissue cells is too high.
How can the therapeutic range of enediyne antibiotics be increased?

A novel approach highlighting a modification of the warhead itself was elaborated previously in our group: In a computational study, the singlet–triplet gaps of three isoelectronic biradicals were compared — the para-benzyne biradical (5) (this is the reactive intermediate formed upon cyclization in the natural antibiotics), its nitrogen-analogue (the 2,5-didehydropyridine biradical (31)) and the protonated nitrogen-analogue (the 2,5-didehydropyridinium biradical (34)). The results suggested a clear trend in reactivity and thus, the ability to destroy DNA. While incorporation of a nitrogen atom (transforming the enediyne into an azaenediyne system) should decrease the reactivity, the protonation of that nitrogen should increase the reactivity dramatically.

Several tumor species show lower extracellular pH-values than normal tissue cells. What is more, the cytoplasm of some tumor cells can be selectively acidified. As a consequence, their intracellular pH could be used as a trigger for DNA-damage by the modified biradical. Using this microphysiological protonation handle, the chemist could tune the biradical reactivity — and create a drug being more selective for tumor cells, but leaving cells from healthy tissue unaffected.

The previously synthesized C,N-dialkynylimines, C,N-dialkynylimidates and C,N-dialkynylamides represented good model compounds for azaenediyne systems, which could serve as potential pH-selective anticancer drugs. However, in thermolysis experiments they turned out to be too sensitive to hydrolysis, heat or else they showed no convincing evidence of cyclization products.

Therefore, the aim of this thesis was to synthesize azaenediyne systems that are stable under the employed thermolysis conditions. The goal was achieved by developing a de novo-synthesis, which led to the first representatives of the new class of functionalized C,N-bisalkynylated benzimidazole-azaenediynes in good overall yield. This class features heterocyclic alkynylimines with a triple bond at each the N-1-nitrogen atom and the C-2-carbon atom. The N-3-nitrogen atom of the benzimidazole system can act as an acceptor for activators, triggering the Bergman rearrangement. Side products of the
synthetic pathway were subsequently characterized and mechanisms proposed for their formation.

First, the novel heterocyclic azaenediynes 198 and 199 (see Figure 4-1) were prepared, and fully characterized. They turned out to be astonishingly stable: They showed no reactivity at all in multitudinous cyclization experiments, under a variety of conditions in the liquid phase (in solution) as well as in the gas phase.

![Chemical structures of 198 and 199](image)

Figure 4-1: The novel heterocyclic, benzimidazole-based azaenediynes 198 (left column) and 199 (right column), displayed as valence-bond structures (top) and as scaled ball-and-stick models (bottom)

Protonation attempts of compounds 198 and 199 mainly led to decomposition and loss of starting material. Methylation, however, is an alternative solution, as it should result in the same electronic effect.

Therefore, the novel methyl-azaenediynes 206 and 208 (see Figure 4-2) were prepared, and fully characterized. Unfortunately, they were also relatively stable, similar to the parent azaenediynes 198 and 199. Only in a few cases a reactivity could be observed, which, however, gave no clear hints for cyclization products.
Figure 4-2: The novel heterocyclic, benzimidazole-based methyl-azaenediyynes 206 (left column) and 208 (right column), displayed as valence-bond structures (top) and as scaled ball-and-stick models (bottom).

The feasible reasons for the inactivity (regarding Bergman cyclization) of the azaenediyynes prepared in the course of this thesis were elucidated. Suggestions for further functional modifications of these challenging compounds were made — in order to enable future chemists the design of a powerful antitumor drug that is based on the concept of azaenediyynes.
5. Zusammenfassung

Um in dem permanenten Überlebenskampf bestehen zu können, haben zahlreiche Mikroorganismen Antibiotika für den Kampf gegen ihre Kontrahenten entwickelt. Antibiotika können konkurrierende Bakterien abtöten oder diese an ihrem Wachstum hindern.


Die in der Natur vorkommenden Endiin-Antibiotika sind nicht nur als extrem bakterien-toxische Substanzen bioaktiv — sie wurden auch als Kandidaten im Hinblick auf potenzielle Antitumorstoffe untersucht.

Der Kampf gegen die Geissel Krebs zählt zu den Projekten höchster Priorität für die pharmazeutische Industrie. Tumorerkrankungen sind die zweithäufigste Todesursache in der Schweiz; und weltweit nehmen durch Krebs bedingte Todesfälle den dritten Platz ein.

Wie kann die Therapie unter Verwendung von Endiin-Antibiotika optimiert werden?

Eine neuartige Strategie, die auf einer Modifizierung des eigentlichen Sprengkopfes beruht, wurde in unserer Arbeitsgruppe ausgeklügelt:

In computergestützten Berechnungen wurden die Singulett–Triplet-Lücken von drei iso-
elektronischen Biradikalen verglichen — dem para-Didehydrobenzol-Biradikal (5) (dieses ist das reaktive Intermediat, welches bei der Cyclisierung in den Naturstoff-Antibiotika gebildet wird), seinem Stickstoff-Analogon (dem 2,5-Didehydropyridin-Biradikal (31)) und dem protonierten Stickstoff-Analogon (dem 2,5-Didehydropyridinium-Biradikal (34)). Die Ergebnisse deuten auf einen klaren Reaktivitätstrend, und somit auf das Potenzial zur Zerstörung von DNS: Während der Einbau eines Stickstoffatoms (wodurch das Endiin-System in ein Aza-
endiin-System umgewandelt wird) die Reaktivität herabsetzen sollte, sollte die Protonierung dieses Stickstoffs zu einer drastischen Reaktivitätssteigerung führen.


Die bereits synthetisierten C,N-Dialkinylimine, die C,N-Dialkinylimidate und die C,N-Dialkinyl-

Das Ziel dieser Arbeit bestand somit in der Darstellung von Aza-endiin-Systemen, die unter den verwendeten Thermolyse-Bedingungen stabil bleiben.

Diese Zielvorgabe wurde erreicht durch die Ausarbeitung einer de novo-Synthese, welche in
guter Gesamtausbeute die ersten Vertreter der funktionalisierten C,N-bisalkinylierten Benz-
imidazol-azaendiine lieferte. Diese neue Substanzklasse enthält heterocyclische Alkinylimine.
mit jeweils einer Dreifachbindung an dem N-1-Stickstoffatom und dem C-2-Kohlenstoffatom. Das N-3-Stickstoffatom des Benzimidazol-Systems kann währenddessen als Akzeptor für Aktivierungsmittel fungieren, welche die Bergman-Cyclisierung auslösen. Im Rahmen der angewandten Synthesestrategie aufgefundene Nebenprodukte wurden charakterisiert, und es wurden Vorschläge für den Mechanismus ihrer Bildung gemacht.

Zunächst wurden die neuen heterocyclischen Aza-endiine 198 und 199 (siehe Figur 5-1 (vide infra)) dargestellt und vollständig charakterisiert. Sie erwiesen sich als erstaunlich stabile Verbindungen: Sie zeigten keinerlei Reaktivität in zahlreichen Cyclisierungs-Experimenten, wobei verschiedene Reaktionsbedingungen sowohl in der Flüssigphase (in Lösung), als auch in der Gasphase untersucht wurden.

![Chemische Strukturformeln für 198 und 199](image)

**Figur 5-1:** Die neuen heterocyclischen Benzimidazol-aza-endiine 198 (linke Spalte) und 199 (rechte Spalte), dargestellt als Valenzstrukturformeln (oben) sowie als skalierte Kugel-Stab-Modelle (unten)

Die durchgeführten Versuche zur Protonierung der Verbindungen 198 und 199 lieferten hauptsächlich Zersetzungsprodukte. Eine Methylierung stellt in diesem Fall eine interessante Alternative dar, da diese zu demselben elektronischen Effekt führen sollte. Daher wurden die neuen Methyl-aza-endiine 206 und 208 (siehe Figur 5-2 (vide infra)) synthetisiert und ebenfalls vollständig charakterisiert. Bedauerlicherweise stellten sich auch diese

6. Introduction

6.1. The Enediyne Antibiotics — Background

6.1.1. General and Introduction

According to a definition by Waksman in the year 1941, antibiotics (from Greek: anti = against and biotikos = concerning life) were defined as bacteriostatic or bacteriocidal metabolites from microorganisms. Antibiotics are capable of inhibiting growth of other bacteria or of killing them — already at relatively low concentrations. Nowadays also their half- and fully synthetic derivatives are called antibiotics, as well as compounds from algae, fungi, plants and animals.

No antibiotic agent is effective against all species of bacteria — each compound has its particular spectrum of activity and acts at a specific location in the target cell.

In the 1980s, the discovery of the majority of the naturally occurring enediyne antibiotics took place. They could be isolated from bacterial sources, and afterwards were also found in other organisms. The members of the family of the enediyne antibiotics share the same interesting key structural element: an enediyne moiety, or more precisely, a (Z)-hex-3-ene-1,5-diyne system. Three representatives of these challenging natural compounds — calicheamicin γ1 (1), esperamicin A1 (2) and dynemicin A (3) — are shown in Figure 6-1.
The excitement surrounding the above mentioned molecules lies in their molecular architecture, their biological activity, and their fascinating mode of action. Enediyne antibiotics are highly cytotoxic compounds, and are therefore also candidates for potent anticancer drugs.

6.1.2. Why are Enediyne Antibiotics Highly Cytotoxic?

Enediyne antibiotics show a modular design — they possess three functional domains: a delivery system, a triggering device and a warhead.

- The warhead is destined to "explode" upon suitable activation.
  It consists of an enediyne system or a system with similar reactivity. Upon activation, the warhead undergoes a Bergman cyclization reaction (see below) — the consequence is that...
the enediyne unit forms a biradical intermediate. The newly formed biradical is reactive and therefore a powerful weapon: it is capable of stripping hydrogen atoms from the sugar phosphate backbone of the DNA.

- **The delivery system** directs the **warhead** – the enediyne moiety – to its target. The target is a specific base sequence in the minor groove of the DNA. The reactive diradical formed upon cyclization is henceforth perfectly positioned in order to rip hydrogen atoms off the target cell’s DNA.

- **The triggering device** activates the **warhead**. The triggering device is a structural unit that initiates the cascade of reactions, which leads to the generation of the damaging biradical.

The entire process can lead to single strand breaks or to double strand breaks of the DNA in the target cell. While single strand breaks can be repaired by enzymes, scissions in the DNA double helix are difficult to repair — and the destruction of the genetic material of a cell ultimately leads to its death.

Hence it follows that the biological action of naturally occurring enediyne antibiotics lies in their ability to cleave DNA. The toxicity of these natural products is based on a unique mechanism of action: the cyclization of the enediyne moiety.

### 6.1.3. The Bergman Cyclization

The mechanism of the crucial cyclization was extensively studied by Bergman\(^7,8\) \textit{et al.} in the early 1970s. Prior to Bergman’s work, cyclization reactions involving the enediyne unit were also investigated by Masamune\(^9\) \textit{et al.} and Mayer and Sondheimer;\(^10\) and past these studies, but prior to the discovery of the naturally occurring enediynes, by Wong and Sondheimer.\(^11\) Earlier studies were already carried out in 1965 by Berry\(^12\) \textit{et al.} (compare\(^13\)), who investigated the photo-initiated decomposition of benzenediazonium-4-carboxylate. They suggested a biradical intermediate and the hex-3-ene-1,5-diyn system as relatively stable species formed upon the decomposition reaction.\(^12\)
Bergman\textsuperscript{7,8} demonstrated that heating of (Z)-hex-3-ene-1,5-diyne (4) to 200 °C in 2,6,10,14-tetramethylpentadecane as a solvent led to exclusive formation of benzene (6); and upon employment of tetrachloromethane as a solvent, they only found 1,4-dichlorobenzene (7) (Figure 6-2). This experiment, together with further investigations with deuterium labeled compounds, led to the following conclusions:

The cycloaromatization reaction of enediynes proceeds via the para-benzene biradical (5) (Figure 6-2). The biradical intermediate is highly reactive: It is capable of abstracting hydrogen atoms from solvents, and thus of undergoing a radical trapping reaction. Another exit channel from the 1,4-benzenoid diradical intermediate is the reverse reaction, leading to ring opening — as educt 4 and product 4 are identical, the Bergman cyclization is a degenerate rearrangement in this case. The Arrhenius activation energy for the cyclization was determined to be $E_A = 32 \text{ kcal-mol}^{-1}$.

The abstraction of hydrogen atoms is apparently also the key reaction used by Nature — upon cycloaromatization, the biradical intermediate abstracts hydrogen atoms from DNA, thus inflicting lethal damage on the target cell.
6.1.4. Different Cleavage Mechanisms of DNA by Hydrogen Atom Abstraction

If the enediyne unit finally is perfectly positioned at a specific site of the target cell’s DNA, how does the biradical formed upon cyclization rip off hydrogen atoms? According to the structure and reactivity of the particular enediyne antibiotic, hydrogen atoms can be abstracted at different locations from the sugar phosphate backbone of the DNA. The first abstraction leads to a DNA radical upon conversion of the para-benzyne biradical into a phenyl radical. The phenyl radical itself is even more reactive than its biradical precursor and is capable of abstracting hydrogen atoms at other sites of the DNA, thus inflicting even more damage.

Mechanisms for hydrogen abstraction at the positions C-5', C-4' and C-1' of the sugar moieties were identified.\(^4^,\,^5\)

C-5'-abstraction represents the major and the initial pathway in the course of DNA damage. In detail, an abstraction at position C-5' of deoxyribose 8 leads to radical 9 (Figure 6-3). The latter one then reacts with molecular oxygen to form a peroxyradical, which itself abstracts hydrogen to give peroxide 10. Subsequent reduction by glutathione transforms 10 into hemiacetal 11. The hemiacetal is unstable and eliminates the 5'-phosphate residue 13, yielding aldehyde 12. This elimination causes a single strand break in DNA.
Hydrogen abstraction can also start at position C-4' of deoxyribose 8 (Figure 6-4). The following addition of molecular oxygen to radical 14 and hydrogen abstraction give peroxide 15. The latter one can either fragment to give 3'-phosphate 16 and carboxylic acid 17 or be reduced to hemiacetal 18. Upon addition of water, hemiacetal 18 can lose the base to give 19, which itself eliminates the 3'-phosphate residue 16 yielding the enone 20.

Figure 6-3: Hydrogen atom abstraction at C-5' of deoxyribose as initiation of DNA strand cleavage
In several cases, first single strand breaks are caused by hydrogen abstraction at C-5' from the biradical intermediate. The subsequent second hydrogen abstraction is then caused by the resulting phenyl radical. This second abstraction rips off hydrogen atoms at position C-4' or C-1', respectively, of deoxyribose units of the complementary strand — and therefore leads to double strand scissions. Hence, the double strand cleavages due to C-4'- and C-1'-abstraction inflict the final lethal blow on the cell.

The C-1' pathway (Figure 6-5) follows the principles discussed above: Addition of oxygen to radical 21, hydrogen abstraction and reduction lead to hemiacetal 23. 23 then eliminates the base, and in a subsequent step also 3'-phosphate 16 is eliminated, causing a strand break.
Recent studies do not suggest the para-benzyne biradical being the ultimate warhead, but a quinone, which is formed upon the addition of oxygen.\textsuperscript{14,15} The quinone itself showed much higher toxicity than its enediyne precursor.\textsuperscript{14}

6.1.5. Naturally Occurring Enediyne Antibiotics — Properties and Mechanism of Action

6.1.5.1. Calicheamicin $\gamma_1^1$ (1)

The calicheamicins are a family of enediyne antibiotics isolated from *Micromonospora echinospora* ssp. *calichensis* and were discovered by Lee\textsuperscript{16,17} *et al.* in 1987. Calicheamicin $\gamma_1^1$ (1) (see Figure 6-1) is the most prominent member of this class of compounds.\textsuperscript{18,19} The iodine containing
calicheamicin family was found to be extremely active against a variety of bacteria (down to concentrations of 1 pg·mL$^{-1}$). Most importantly, they exhibited extraordinary potency against murine tumors$^{16,17,18,19}$ such as some leukemias and solid neoplasms with doses of 0.15 – 5 µg·kg$^{-1}$.

The calicheamicin $\gamma_1$-molecule (I) is a masterpiece of Nature's ingenuity. Its structure features the following three functional elements: the enediyne system embedded in a ten-membered ring as the warhead, the oligosaccharide fragment as the delivery system, and the trisulfide moiety as the triggering device. The following mechanism is thought to account for the damaging action on DNA:$^{16,17,20,21}$ Calicheamicin $\gamma_1$ (I) binds to the minor groove of double helical DNA. Binding occurs specifically at 5′-TCCT-3′ sites. The oligosaccharide-delivery system aids in the recognition and the orientation of the oligosaccharide tail towards the 3′-end of DNA.$^{22,23}$ A nucleophile (e.g. glutathione) then attacks the triggering device — the central sulfur atom of the trisulfide group$^{16,17,24}$ (Figure 6-6).

![Figure 6-6: DNA cleavage mechanism of calicheamicin $\gamma_1$ (I) (residues were omitted for clarity)](image)

This bioreduction process causes the formation of thiolate 26, which then attacks intramolecularly the $\alpha,\beta$-unsaturated ketone in the adjacent six-ring to give compound 27 (Figure 6-6). Upon conversion of the $sp^2$-carbon at the point of attack into an $sp^3$-carbon, the distance
between the terminal sp-carbon atoms of the enediyne unit is shortened significantly (from 3.35 Å in 1 to 3.16 Å in 27). The highly strained intermediate 27 – the warhead – is exceedingly susceptible to Bergman cyclization. The subsequently formed biradical 28 is already well positioned to abstract two hydrogen atoms (to give 29), one from the C-5' position of deoxy-cytidine and the other from a ribose C-4' position of the opposing strand. The DNA radicals so generated then proceed to react as described in Figure 6-3 and Figure 6-4 — the entire process leads to sequence specific double strand cuts.

6.1.5.2. Esperamicin A₁ (2)

The esperamicins were first isolated from cultures of Actinomadura verrucospora by Konishi et al. in 1985. They represent a subclass of enediyne antibiotics showing similarities to the calicheamicins regarding structure, biological activity and mode of action. The most prominent member is esperamicin A₁ (2) (see Figure 6-1).

Like the calicheamicins, the esperamicins feature an enediyne moiety within a ten-membered ring as a warhead, a polysulfide-triggering device as well as an α,β-unsaturated ketone and an oligosaccharide-delivery system. Their DNA cleavage mechanism is therefore identical, however, esperamicin A₁ (2) shows less sequence selectivity than calicheamicin γ₁ (1). Esperamicins are amongst the most potent anticancer agents, showing activity against various murine tumor models down to injected doses of 100 ng·kg⁻¹.

6.1.5.3. Dynemicin A (3)

The first member of the dynemicin family, dynemicin A (3) (see Figure 6-1), was discovered in 1989 in a culture of Micromonospora chersina. It exhibits very potent activity against a variety of cancer cell lines.

The dynemicins feature an embedded enediyne unit in a ten-membered ring as a warhead (like the calicheamicins and the esperamicins), and an anthraquinone chromophore as a delivery system. The epoxide serves as a triggering device: After bioreduction of the anthraquinone unit, a nucleophilic attack leads to epoxide opening, which causes the distance of the sp-carbons to shorten (as previously discussed) and hence facilitates Bergman cyclization.

Dynemicin A (3) cleaves double-stranded DNA, causing both single and double strand cuts, and preferably attacks the 3'-site of purine bases (adenine and guanine).
The DNA recognition takes place by both minor groove binding and intercalation of the planar anthraquinone unit.\textsuperscript{37} An impressive illustration of the perfect positioning of dynemicin A (3) in duplex DNA is shown in Figure 6-7.\textsuperscript{43}

![Figure 6-7: Computer generated models of free dynemicin A (3) (top) and DNA-bound dynemicin A (3) (bottom) (images taken from\textsuperscript{43})](image)

6.1.5.4. Further Enediyne Antibiotics Occurring in Nature

Several other naturally occurring enediyne antibiotics are known, which all show potent anti-tumor and antibacterial activity. Neocarzinostatin was already reported by Ishida\textsuperscript{44} et al. in 1965; it was isolated from \textit{Streptomyces carzinostaticus} Var. F-41. Neocarzinostatin occurs as a complex, consisting of a protein component (the apoprotein) and a chromophore (the enediyne compound neocarzinostatin itself).\textsuperscript{45,46,47} Its active structural unit is, strictly speaking, a cumulene (an enyne-allene system) and not an enediyne.

Amongst the more recently discovered enediyne antibiotics are kedarcidin (first reported in 1991 as the fermentation product of an actinomycete strain),\textsuperscript{48} C-1027 (first reported in 1988 and isolated from a culture of \textit{Streptomyces globisporus} C-1027),\textsuperscript{49} maduropeptin (isolated from \textit{Actinomadura madurae} H710-49 in 1990),\textsuperscript{50} namenamicin (first reported in 1996)\textsuperscript{51} and the shishijimicins A, B and C (structure and activity elucidation in 2003).\textsuperscript{52,53}
While the majority of the enediyne antibiotics discovered up to the present are of terrestrial origin, namenamicin was isolated from the ascidian (or the tunicate, respectively) *Polysyncracton lithostrotum* (from the coast of Namenalala Island, Fiji) — it is the first marine enediyne anti-tumor antibiotic.\(^{51,54,52}\) However, another suggestion features a symbiotically co-existing microorganism being responsible for the biosynthesis of namenamicin.\(^{54}\)

Recently, the shishijimicins A – C could be isolated from the thin encrusting orange ascidian *Didemnum proliferum*.\(^{53,52}\) They do represent further bioactive enediyne metabolites found in Japanese marine invertebrates.
6.2. The Scourge Cancer —

Applications of Enediyne Antibiotics in Cancer Treatment

In Switzerland, tumors caused more than 24% of the total death cases in 1980, while this number increased to nearly 26% in the year 2000. These numbers demonstrate cancer being responsible for the second most frequent cause of death in Switzerland, after cardiovascular diseases (1980: 48%, 2000: 40% of all death cases). Concerning the worldwide causes of death, cancers did range in position 3 with 12% of all death causes, after infectious and parasitic diseases (ca. 30%) and diseases of the circulatory system (ca. 30%) in the recent years. The long duration of the disease and the monumental suffering it causes the patients, their relatives and friends, has made it a high priority issue for scientists to continue with cancer research — in order to considerably improve prevention, early detection, diagnosis as well as the effective treatment of cancer.

Could enediyne antibiotics as broad spectrum antibiotics and highly potent DNA cleaving agents be employed in order to combat cancer?

Several of the naturally occurring enediyne antibiotics were investigated as potential anticancer agents by the pharmaceutical industry. However, in clinical trials their cytotoxicity for ordinary tissue cells turned out to be too high, or too many unacceptable side effects were observed. As an example, calicheamicin \( \gamma_1 \) (1) is too toxic for use as a drug — its mean effective dose is greater than the median lethal dose.

In order to either increase the toxicity against degenerated cells or to lower the toxicity against ordinary cells, groups like the ones of Nicolaou, Toshima, Hirama and Boger designed modified, novel enediyynes as antineoplastic agents. For example, the synthetic calicheamicin \( \theta_1 \) created by Nicolaou et al. is considerably more potent than any previously known natural and synthetic enediyne; and a targeted therapy approach using calicheamicin \( \theta_1 \) attached to a tumor-selective monoclonal antibody was reported. But unfortunately, despite a few promising results, there has been no real breakthrough in the fight against the scourge cancer up to the present.
6.3. Tuning the Reactivity of Enediyne Antibiotics

6.3.1. The Concept of the Singlet – Triplet Gap

As for a biradical in general, also for the intermediary \textit{para}-benzyne biradical (5) occurring in the Bergman cyclization, two different electronic spin states can be assigned: The spins of the two unpaired electrons can be parallel or antiparallel (see Figure 6-8). In case of antiparallel spins (for example due to coupling between the two electrons), the biradical is in a singlet state (ground state), and in case of parallel spins, it is in a triplet state (first excited state).\textsuperscript{65}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{singlet_triplet_gap.png}
\caption{Concept of the singlet – triplet gap}
\end{figure}

The energy difference between the two spin states is called singlet – triplet gap ($E_{ST}$) or singlet stabilization and defined as:\textsuperscript{66}

\[ E_{ST} = E_T - E_S, \]  
whereby $E_T$ = triplet energy and $E_S$ = singlet energy.
The stronger the interaction (or in other words, the coupling) between both electrons in the biradical, or the shorter the distance between the two radical sites in a molecule, respectively, the larger is the singlet – triplet gap.\textsuperscript{65}

### 6.3.2. A Comparison of Reactivity of Monoradicals, Triplet Biradicals and Singlet Biradicals

Logan and Chen\textsuperscript{67} compared the reactivity of the para-benzyne biradical (5) versus the phenyl radical using \textit{ab initio} computational methods. They found that the \( p \)-benzyne biradical (5) is less reactive (with regard to hydrogen abstraction) than the corresponding phenyl monoradical, and that the rate of hydrogen abstraction at rt should be about 14 times slower for \( p \)-benzyne 5.\textsuperscript{67} The singlet – triplet gap was computed to be \( E_{ST} \approx 2 \text{ kcal} \cdot \text{mol}^{-1} \). The triplet state was assigned to a hypothetical "non-interacting" triplet biradical, and the singlet to a state allowing interaction between the radical sites.

Wenthold, Squires and Lineberger\textsuperscript{68} determined an experimental value of \( 3.8 \text{ kcal} \cdot \text{mol}^{-1} \) for the singlet – triplet energy splitting of \( p \)-benzyne. This value was obtained from the photoelectron spectrum of the \textit{para}-benzyne radical anion in the gas phase by using UV-PES.

Schottelius and Chen\textsuperscript{69} employed the 9,10-dehydroanthracene biradical as a model for the \textit{para}-benzyne type biradicals implicated in DNA cleavage by enediyne antitumor antibiotics. They found that the biradical abstracted hydrogen about \( 100 – 200 \) times slower than the corresponding 9-anthryl radical or the phenyl radical.
6. INTRODUCTION

*Summa summarum*, Chen\(^6\) et al. elucidated the singlet – triplet gap being a measure of reactivity of diradicals relative to monoradicals: The phenyl monoradical was found to be more reactive than the \(p\)-benzyne biradical, and the \(p\)-benzyne biradical in triplet state is more reactive than the corresponding singlet biradical. For corresponding radical systems can be written (see Figure 6-9):

Reactivity (hydrogen abstraction ability) increase

Reactivity: singlet biradical \(<\) triplet biradical \(<<\) monoradical

Figure 6-9: Qualitative scheme comparing the reactivity of a \(para\)-benzyne singlet biradical with the triplet biradical and its corresponding phenyl monoradical

As energy can be correlated with reactivity (with respect to a specific reaction, *e.g.*, hydrogen abstraction), a smaller singlet – triplet gap should lead to an increased hydrogen atom abstraction rate. If the hydrogen abstraction by the biradical formed in the Bergman cyclization is relatively slow, then other competing processes are more likely to occur (for example, the retro-Bergman reaction, which is a ring-opening reaction).

6.3.3. Nature's Ingenuity of Using Biradical Intermediates instead of Monoradical Intermediates

What is the advantage of a biradical intermediate compared to a monoradical intermediate in the course of rearrangement of the naturally occurring enediyne antibiotics? Generally speaking, as a biradical shows lower reactivity than the corresponding monoradical, it does also show greater selectivity. The \(para\)-benzyne biradical (5) and the phenyl radical also show differential reactivity: While the first hydrogen abstraction by a \(p\)-benzyne-type biradical proceeds relatively slow (and therefore more selectively), it yields the phenyl radical, which is more reactive by two orders of magnitude.\(^7\) With this concept, Nature increases elegantly the probability for the second hydrogen abstraction to take place nearby, which, in the case of DNA cleavage, leads to a higher probability of double strand breaks.\(^7\)
6.3.4. Improving Nature's Ingenious Mechanism — Basic Thoughts

As mentioned above, several naturally occurring and synthetically designed enediyne antibiotics displayed high activity against a number of tumor cell lines, both in vitro and in vivo. But unfortunately, they also showed unacceptable toxic side effects in both animal and human trials.

How could the reactivity of biradicals like para-benzyne 5 be tuned in order to optimize their reactivity and selectivity?

The aim could be approached by a novel idea: In order to create a biradical intermediate that is a DNA-damaging agent with greater selectivity against tumor cells as compared to the parent p-benzyne biradical, the enediyne warhead itself could be modified. The longer a biradical "lives" before it is quenched, the more selectively it can act.

A redesign of the warhead part of the enediyne drugs could lead to a modified coupling between the radical sites. This, in turn, could then lead to a smaller singlet – triplet gap and therefore to a more reactive biradical. With this concept, the chemist could be able to tune the reactivity of biradical-based DNA-cleavage agents.

What handles does a synthetic chemist have to modify the enediyne unit in order to create novel drug candidates with a reactivity different from the naturally occurring products?

6.3.5. Novel Drug Candidates — Created by Reactivity Tuning of the Biradical Intermediate by Modifying the Singlet – Triplet Gap

As aforementioned, the magnitude of the singlet – triplet splitting in arene biradicals depends on the extent of through-bond coupling between the two radical sites. Hence it follows that by incorporating different substituents into the σ-framework of a biradical structure, the biradical should favor or disfavor through-bond coupling, respectively. By setting different magnitudes of through-bond coupling, the chemist is able to tune the rate of hydrogen abstraction of a biradical, and therefore could optimize the effective abstraction process.

Summa summarum, changing the singlet – triplet gap leads to a reactivity change of the biradical, which in turn allows a control of toxicity of enediyne anticancer drugs.
Chen et al. explored the brilliant idea of a formal substitution of one C-H-fragment in \textit{para}-benzyne biradical (5) by an isoelectronic nitrogen atom, thus obtaining the 2,5-didehydro- pyridine biradical (31). They calculated the singlet – triplet gaps of the \textit{para}-benzyne biradical (5), the 2,5-didehydropyridine biradical (31) and the 2,5-didehydropyridinium biradical (34) using CASSCF(6x6)/6-31G* and CASMP2(6x6)/6-31G* methods. In detail, the calculations gave the following values for the singlet – triplet gaps (the values were taken from \textit{ab initio} calculations at the CASSCF level for the adiabatic transitions): $E_{ST}$ (\textit{para}-benzyne biradical (5)) = 1.1 kcal·mol$^{-1}$, $E_{ST}$ (2,5-didehydropyridine biradical (31)) = 4.0 kcal·mol$^{-1}$ and $E_{ST}$ (2,5-didehydropyridinium biradical (34)) = 1.6 kcal·mol$^{-1}$ (see Figure 6-10; further calculations were performed later by Cramer\textsuperscript{74} in 1998, and afterwards by Kraka and Cremer\textsuperscript{75,76}).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figures/figure6-10.png}
\caption{Comparison of the singlet – triplet gaps of the \textit{para}-benzyne biradical (5), the 2,5-didehydropyridine biradical (31) and the 2,5-didehydropyridinium biradical (34)}
\end{figure}

In summary, they found a clear trend indicating that incorporation of a nitrogen atom into the ring increases the singlet – triplet splitting of the biradical by several kcal·mol$^{-1}$ relative to the \textit{p}-benzyne biradical (5).\textsuperscript{73} Moreover, protonation of this nitrogen was found to reduce the singlet – triplet splitting back to a value comparable to that in the hydrocarbon system 5.
Figure 6-11: Comparison of the Bergman rearrangements of enediyne 4, azaenediyne 30 and the protonated azaenediyne 33

A comparison of the Bergman cyclization of the computed biradicals 5, 31 and 34 is presented in Figure 6-11. As the unsubstituted azaenediyne 30 and the protonated azaenediyne 33 are elusive molecules, Chen et al. employed imine 36 as a more stable model compound. In trapping experiments, they heated 36 in diisopropyl ether as a solvent and a hydrogen donor, and searched for products deriving from biradical 37 (Figure 6-12). However, no hydrogen abstraction products were found, but mainly the ring opening product 38. Addition of 2.5 equivalents of an acid with a buffer mainly led to decomposition products, but also yielded 38 in small amount, and additionally traces of the trapping product 39.
How can the computational and experimental results be rationalized?
As mentioned above, an increased electron density in the σ-bonds connecting the two radical sites could increase the through-bond coupling, and hence increase the singlet – triplet splitting. Conversely, if the σ-framework is electronically poor, the through-bond coupling is weaker, which reduces the singlet – triplet gap.\(^7\)

Could the singlet – triplet gaps of the 2,5-didehydropyridine system 31 be farther tuned — by adding electron donating or electron withdrawing substituents?

The in-plane lone pair of the 2,5-didehydropyridine biradical (31) lies anti-periplanar to the scaffold of the σ-bonds, which couple to the orbitals bearing the two radical electrons, and therefore could donate electron density. However, when the nitrogen is protonated, the effect is reversed;\(^7\)

The singlet – triplet gap for 2,5-didehydropyridine biradical (31) was calculated to be much larger than for the para-benzylene biradical (5). The consequence is a much slower hydrogen abstraction rate of 31 compared to 5.

Protonation, on the other hand, both reduced the singlet – triplet splitting and showed a rate of hydrogen abstraction similar to the one of the parent \(p\)-benzylene 5. The calculations suggested hydrogen abstraction to occur 10 – 100 times faster for the protonated species 34 than for didehydropyridine 31.
6.3.6. The Concept of a pH-Selective Anticancer Drug

As shown above, the rate difference regarding hydrogen abstraction was found to be about two orders of magnitude, triggered by protonation. It was therefore predicted that biradicals, which are based on a 2,5-didehydropyridine core, do feature a pH-dependent abstraction ability. The handle for reactivity tuning is given by the nitrogen atom.

In 1927, Warburg et al. assumed that tumor cells, in order to satisfy their needs of energy, could undergo respiration (by "burning" glucose to carbon dioxide and water), as well as fermentation (by converting glucose into lactic acid). The first indications pointing to fermentation were found when they investigated cut pieces of tumors in vitro. The tumor tissue was found to be acidic in comparison to normal tissue. Cori et al. found that the concentration of lactic acid generally is higher than the one of glucose in tumor tissue.

A reason for the observed more acidic microenvironment in solid tumors than in normal tissues could be the poor delivery of oxygen (hypoxia) — a low oxygen concentration would prompt the cell to choose the anaerobic fermentation pathway and therefore to produce lactic acid.

Concluding, in several cases normal cells and solid tumor cells could be differentiated by their pH-values. More exactly, the extracellular pH in solid tumors was frequently found to be lower than the extracellular pH in normal tissues (due to the export of lactic acid), but the intracellular pH is regulated to physiological levels. While healthy tissue showed values of pH = 7.2 – 7.5, the extracellular pH of tumor cells was found to be in a range of pH = 5.8 – 7.6. How then, could the intracellular pH-value be dropped down?

According to Song et al., the major mechanisms regulating the intracellular pH in mammalian cells are the Na⁺/H⁺ exchange and the HCO₃⁻/Cl⁻ exchange through the plasma membrane via ion channels. Tannock et al. reported cell killing in an acidic environment in tissue culture by nigericin, which acidifies cells by transporting H⁺ from the extracellular space into the cytoplasm. Nigericin belongs to the class of cyclic polyethers and is capable of exchanging intracellular K⁺ for extracellular H⁺. In general, the application of drugs that inhibit the pH-regulatory mechanisms by blocking the particular ion channels was found to lower the intracellular pH, and therefore could increase the acidity of tumors in vivo.

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1 Hypoxia is a state of oxygen deficiency in cell tissue, and is caused by the reduction of partial pressure of oxygen, by inadequate oxygen transport, or by the inability of tissue to use oxygen.
Under certain physiological conditions, the pH in tumor cells could even be reduced by 1.7 units.\textsuperscript{86} The effect of hyperglycemia\textsuperscript{a} caused a further, significant acidification\textsuperscript{84} — from a pH of 7.2 down to an intracellular pH of 5.5.

Summa summarum, the fact that tumor cells can be selectively acidified offers a microphysiological handle for the selection of tumor over normal cells:

As the hydrogen abstraction rate was found to be pH-dependent — because the 2,5-didehydro-pyridine biradical (31) abstracts hydrogen atoms more readily at low pH-values — the intracellular pH could be used as a trigger for DNA-damage by the biradical. Therefore, biradical system 31 could serve as the prototype for a DNA-damaging agent, which is more selective for tumor cells. In turn, cells from healthy, non-hypoxic tissue would largely be left unaffected.

6.3.7. Further Considerations

If a singlet ground-state 1,4-arene biradical undergoes a radical reaction like the hydrogen abstraction reaction, it first has to overcome the singlet – triplet gap and go from the stabilized singlet ground state to the triplet state that is higher in energy.\textsuperscript{73} This is shown in Figure 6-13. In other words, in order to reach the triplet transition state (where the two unpaired electrons are uncoupled), the stabilization energy (given by through-bond coupling between the two unpaired electrons) of the singlet state has to be paid back.\textsuperscript{73}

\textsuperscript{a} Hyperglycemia is an increase in glucose level in the blood sugar. The consequence is an enhanced glycolysis rate of cancer cells, which causes a significant drop in the intracellular pH.
Figure 6-13: Qualitative energy profile of the Bergman cyclization of azaenediyne 33

Figure 6-11 shows, apart from the Bergman cyclization reaction of enediyne 4, azaenediyne 30 and the protonated azaenediyne 33, also a second exit channel: The particular biradicals 5, 31 and 34 can not only be trapped, but also undergo a ring opening reaction (a retro-Bergman cyclization). In case of enediyne 4, the rearrangement is degenerate and yields the same product 4 upon ring opening. However, retro-Bergman cyclization of 2,5-didehropyridine biradical (31) and 2,5-didehydropyridinium biradical (34) leads to the nitriles 32 and 35, respectively. Figure 6-13 shows that the nitriles are a thermodynamical sink, making the reverse reaction via the biradical irreversible.
6.4. The Impetus for This Thesis

The previously synthesized $C,N$-dialkynylimines, $C,N$-dialkynylimidates and $C,N$-dialkynylamides did represent good model compounds for azaenediyne systems, which could serve as potential pH-selective anticancer drugs. However, in thermolysis experiments they turned out to be too sensitive to hydrolysis, heat or else they showed no convincing evidence of cyclization products.\(^73,91\) What is more, the temperatures required for the trapping studies were in the majority of cases about 100 °C, which is much too high for an application under physiological conditions. Other previously realized syntheses failed,\(^92\) or they resulted in unstable compounds.\(^93\)

Therefore, the primary aim of this work was to synthesize and characterize novel azaenediyne systems that are stable under the employed thermolysis conditions. The proximate aim was to investigate the reactivity of the novel compounds regarding cyclization and to find out whether they could be employed as pH-selective antitumor agents. The ultimate goal would be the creation of an azaenediyne featuring high toxicity against acidified tumor cells and low toxicity to ordinary tissue cells.

The novel approach featured azaenediynes that are based on an imidazole core — it was supposed that functionalized imidazole or benzimidazole systems could provide the desired stability. Another advantage of employing imidazole-based azaenediynes was that these compounds cannot ring-open to the corresponding nitriles, and therefore are more likely to undergo a Bergman cyclization reaction with subsequent hydrogen abstraction.
7. Syntheses of Azaenediynes

7.1. Retrosynthetic Analysis

At the beginning of this work, azaenediynes based on an imidazole or a benzimidazole core were unknown. The following retrosynthetic analyses do summarize the approaches toward these systems. In the same order as displayed here, the approaches are discussed in detail in the following chapters. Most of the approaches shown were carried out.

The first scheme (Figure 7-1, see page 60) shows the retrosynthesis concerning the disconnection of an alkynyl moiety bound to position N-1 of an imidazole system.
First, Würthwein's method reacting a tosylated imidazole with an (1-alkynyl)-cuprate could be employed (Figure 7-1, (a)). Secondly, alkynyl cation equivalents could be used on an imidazole anion (b). The triple bond could also be built up with the aldehyde approach (c). Then, the retrosynthetic approach (d) suggests a coupling reaction. The base catalyzed isomerization reaction (e) and the dehydrohalogenation reaction (f) are further ways to design an N-1-alkynyl unit in an imidazole heterocycle. Finally, also 1-chloro-alkynes could be used to synthesize the desired system (g).
The second scheme (Figure 7-2) highlights the retrosynthetic analysis concerning the disconnection of an alkynyl moiety bound to position C-2 of a benzimidazole system.

Figure 7-2: Retrosynthetic approaches in order to build up an alkynyl moiety at position C-2 of a benzimidazole system.

Approach (h) in Figure 7-2 shows a coupling reaction. Another way to build up a benzimidazole-basedazaenediyne could be realized by the isocyanate route (i): An isocyanate could be attacked by an acetylide anion, and the resulting amide then could be deprotonated and reacted with an alkynyl cation equivalent. The nitro group of that product could be reduced and the resulting amine then condensed with the carbonyl function to give the benzimidazole.
The retrosynthesis shown in (j) displays an aldehyde approach. Also various condensation approaches could be employed for the design of an alkynyl moiety at position C-2: First, \( \alpha,\alpha' \)-diketones could be condensed with a propargyl aldehyde, if an additional ammonia donor is used (k). Secondly, condensation approach (l) shows the reaction of a 1,2-diamine with a propargyl aldehyde. And finally, a 1,2-diamine could also undergo a condensation reaction with an imidate salt (m).
7.2. Previous Works Carried out in our Group and Known Syntheses of Azaenediynes

7.2.1. Previous Works Conducted in our Group

Hoffner\textsuperscript{91} synthesized some azaenediynes, which represented good model compounds with regard to cyclization reactions. However, in thermolysis experiments they turned out to be too sensitive to hydrolysis, heat and / or they showed no evidence of cyclization products\textsuperscript{91,73} (Figure 7-3).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure7-3.png}
\caption{Some azaenediynes investigated by Hoffner\textsuperscript{91}}
\end{figure}

The imines 36 and 40 were easily destroyed upon hydrolysis, and heating gave barely evidence of cyclization products. Imidate 41 was more stable than 36 and 40; and the thermolyses results indicated the formation of traces of cyclized product. Amide 42 was a stable compound, however, heating did not lead to cyclization products at all.\textsuperscript{91}
Schön\textsuperscript{93} followed the procedure by Hoffner\textsuperscript{91} and also prepared amide \textsuperscript{42}, starting from phenylacetylene (\textsuperscript{43}) and phenylisocyanate (\textsuperscript{44}) (Figure 7-4). However, various deprotection attempts in order to cleave the trimethylsilyl group failed for amide \textsuperscript{42} and related systems.

An attempt in order to synthesize amidine \textsuperscript{48} starting from phenylacetylene (\textsuperscript{43}) and carboadiimide \textsuperscript{46} led to compound \textsuperscript{47}, which could not be converted into the desired product \textsuperscript{48} (Figure 7-4).
As amide-based azaenediynes were thought to be relatively stable and less acid sensitive compounds, Redmond\textsuperscript{92} tried to synthesize azaenediyne 52, which is based on a pyridone system (Figure 7-5).

![Chemical Diagram](image)

**Figure 7-5:** Attempts to build up a pyridone-based azaenediyne by Redmond\textsuperscript{92}

However, the synthesis of 52 failed: All attempts in order to $N$-alkynylate pyridone 49 (not only with alkynylidonium salt 69) gave the $O$-alkynylated 50 instead of the desired $N$-alkynylated 51.
7.2.2. Reaction of (1-Alkynyl)-cuprates with Oximes or Imines —
The Würthwein Method

7.2.2.1. Overview and Conclusion

Würthwein\textsuperscript{94, 95} et al. reported an interesting access to 1-alkylidene-amino-1-alkynes of type 55:
Upon reaction of 1 eq of (1-alkynyl)-cuprate\textsuperscript{iii} 54 with 2 eq of ketoxime derivative 53 (a Tos-protected imine), 2 eq of the N-alkynylated 55 were formed (Figure 7-6).

\begin{center}
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{NO} & \quad \text{Ph} \\
\text{Os} & \quad \text{Ph} \\
\text{Li}_2[(\text{Ph-}C\equiv C)_3\text{Cu}] \\
\rightarrow & \\
\text{2 LiOTos} & - \text{Ph-}C\equiv C\equiv C\equiv Cu
\end{align*}
\end{center}

Figure 7-6: Synthesis of an N-alkynylated imine by Würthwein\textsuperscript{94, 95}

Instead of tosylated ketoximes, also N-chlorinated imines were used.\textsuperscript{96}

\textsuperscript{iii} Dilithium-tris(phenylethynyl)-cuprate \text{Li}_2[(\text{Ph-}C\equiv C)_3\text{Cu}] (54) can be synthesized from 2 eq of phenylacetylene \text{Ph-}C\equiv C\equiv \text{H} (43), 2 eq of \text{BuLi} and 1 eq of phenylethynyl-copper(I) \text{Ph-}C\equiv C\equiv \text{Cu}, according to the equation:
2 \text{Ph-}C\equiv C\equiv \text{H} + 2 \text{BuLi} + \text{Ph-}C\equiv C\equiv \text{Cu} \rightarrow \text{Li}_2[(\text{Ph-}C\equiv C)_3\text{Cu}]. During the course of the reaction, 2 eq of butane (\text{BuH}) are lost.
Würthwein's method was also successfully applied by Kerwin\textsuperscript{97} \textit{et al.} for the preparation of the $C,N$-dialkynyl imine 59 (Figure 7-7).

![Synthesis of a non-cyclic azaenediyne by Kerwin\textsuperscript{97}](image)

Figure 7-7: Synthesis of a non-cyclic azaenediyne by Kerwin\textsuperscript{97}

However, the method of Würthwein was not used to build up $N$-alkynylated heterocycles so far.

### 7.2.3. Synthesis of an Azaenediyne with an Imidazole Core by Kerwin

In October 2002, Kerwin\textsuperscript{98} \textit{et al.} published the synthesis of azaenediyne 62 (Figure 7-8).

![Synthesis of an imidazole-based azaenediyne by Kerwin\textsuperscript{98}](image)

Figure 7-8: Synthesis of an imidazole-based azaenediyne by Kerwin\textsuperscript{98}

Kerwin\textsuperscript{98} claimed that no $N$-alkynyl benzimidazoles or imidazoles had been reported up to October 2002. However, a literature search proved that this statement is not correct (compare the literature cited in this thesis). What is more, compound 198, the first benzimidazole-based azaenediyne at all, was synthesized in the framework of this thesis already in June 2001.
7. Syntheses of Azaenediynes

7.3. Building up the Ethynyl Moiety at Position N-1 of Imidazole and Benzimidazole Systems

7.3.1. Ethynylation Reactions Employing Alkynyl Cation Equivalents

7.3.1.1. Access to Alkynyl Cation Equivalents by the Radioactive Decay of Tritium Compounds

7.3.1.1.1. Introduction, Overview and Syntheses

An unusual way to prepare an alkynyl cation was reported by Hanack and Speranza⁹⁹ et al.: They synthesized a tritiated terminal alkyne 63 (see Figure 7-9).

\[
\text{R-} \overset{\text{decay}}{= \text{C\equivC}} \overset{\beta}{=} \text{T} \quad \rightarrow \quad \text{R-} \overset{\text{3He}}{= \text{C\equivC}} \overset{\text{3He}}{=} \text{He} \quad \rightarrow \quad \text{R-} \overset{\text{3He}}{= \text{C\equivC}} \overset{\text{+ Nu}\text{\textsuperscript{-}}}{=} \quad \rightarrow \quad \text{R-} \overset{\text{Nu}}{= \text{C\equivC}} \overset{\text{Nu}}{=} \text{Nu}
\]

Figure 7-9: Synthesis of an alkynyl cation by nuclear decay of a tritium compound by Hanack and Speranza⁹⁹

The spontaneous nuclear decay of the tritium atom under emission of \( \beta \)-radiation led to the formation of cation 64, which released the \(^3\text{He}\)-isotope as a leaving group. The resulting alkynyl cation 65 (see also ¹⁰⁰, ¹⁰¹) could then react with nucleophiles (\( \text{Nu}^- \)) to yield acetylene 66.

The drawback of this reaction was not only the reaction time of six months at rt, but also the employment of radioactive material.
7.3.1.2. Alkynyliodonium Salts as Alkynyl Cation Equivalents — The Stang Approach

7.3.1.2.1. General Introduction and Overview

Groups like Stang\textsuperscript{102, 103} \textit{et al.} reported that alkynyliodonium salts can serve as alkynyl cation equivalents, or, more precisely, as electrophilic acetylene equivalents. An unsubstituted carbon-carbon triple bond is relatively electron-rich. Hence it follows that an attack of other electron-rich species like nucleophiles is not favored. Even haloalkynes (R–C≡C–Hal), which carry the halide as a potential leaving group, do not react following the typical SN1- or SN2-mechanism reaction.\textsuperscript{104} This is explained with the instability of alkynyl cations (R–C≡C\(^+\)) — the consequence is that nucleophilic substitution reactions at an acetylenic carbon do take place via an addition-elimination mechanism.\textsuperscript{105} The alkynyliodonium salts are known for several years;\textsuperscript{106, 107, 108, 109} the first example was reported in 1965.\textsuperscript{110} Non-nucleophilic counterions, such as tetrafluoroborate, do stabilize these salts. In case of the alkynyl(phenyl)iodonium salts (R–C≡C–I\(^+\)-Ph BF\(_4\)^−), the leaving group is neutral iodobenzene (Ph–I).\textsuperscript{111} The former ones belong to the polyvalent organic iodine species, where an alkynyl moiety and a phenyl group are bound to a positively charged iodine(III) atom.

7.3.1.2.2. Synthesis of Alkynyliodonium Tetrafluoroborates

General Introduction and Overview

The groups of Fujita\textsuperscript{112} \textit{et al.} and Ochiai\textsuperscript{113} \textit{et al.} reported syntheses toward trimethylsilyl-ethynyl(phenyl)-iodonium tetrafluoroborate (69), starting from iodosobenzene (67). The reaction of a complex of 67 and BF\(_3\)-Et\(_2\)O with alkynylsilanes like 68, followed by treatment with aqueous NaBF\(_4\) afforded alkynyliodonium salts 69 (Figure 7-10).

\[
\begin{align*}
\text{Ph–I} &= \text{O} \\
67 &\quad \xrightarrow{\text{1. BF}_3\cdot\text{Et}_2\text{O} / \text{CH}_2\text{Cl}_2} \\
\xrightarrow{\text{2. (CH}_3)_3\text{Si} – – – – – \text{Si(CH}_3)_2} &\quad \xrightarrow{\text{3. NaBF}_4(\text{aq})} (\text{CH}_3)_3\text{Si} – – – – – I^+\text{Ph BF}_4^- \\
\end{align*}
\]

Figure 7-10: Schematic synthesis of trimethylsilyl-ethynyl(phenyl)-iodonium tetrafluoroborate (69) by Fujita and Ochiai\textsuperscript{112, 113}
Iodosobenzene (67) ((Ph–IO)_n)

Introduction and Overview
A procedure for the synthesis of iodosobenzene (iodosylbenzene) (67) was described by Sharefkin et al. The formed iodosobenzene (67) is a polymer and better described by the formula (Ph–IO)_n.

Description of Synthesis
The reported synthesis started from purchasable diacetoxyiodobenzene (70). Addition of an excess of an aqueous solution of sodium hydroxide gave product 67 in good yield (Figure 7-11), beside sodium acetate and water.

\[
\text{Ph–I(OAc)}_2 + \text{NaOH} \xrightarrow{\text{aq}} \quad \text{Ph–I=O}
\]

Figure 7-11: Synthesis of iodosobenzene (67) by Sharefkin

Compound 67 was obtained as a pale yellow solid in a yield of 78 % (lit.: 85 – 93 %).

Conclusion and Product Analysis
Product 67 was only detected by its melting point, which was found to be 204 – 208 °C (decomposition took place, lit.: 210 °C).

Trimethylsilyl(phenyl)-iodonium tetrafluoroborate (69)

Introduction and Overview
Fujita et al. and Ochiai et al. reported the synthesis of trimethylsilyl(phenyl)-iodonium tetrafluoroborate (69) (compare also Figure 7-10): The first step requires the activation of iodosobenzene (67) with the aid of bortrifluorid-ethyletherat, BF_3·Et_2O, in dichloromethane (Figure 7-12). The formed complex 71 then attacks bis(trimethylsilyl)acetylene (68) in an electrophilic addition to give intermediate 72. The latter one eliminates BF_3 to form compound 73. Treatment with aqueous sodium tetrafluoroborate, NaBF_4, induces the elimination of NaOSi(CH_3)_3 and yields the alkynyliodonium salt 69.
Description of Synthesis

The synthesis was carried out according to the procedure given by the groups of Fujita\textsuperscript{112} and Ochiai\textsuperscript{113}. In an argon atmosphere, iodosobenzene (67) was suspended in dichloromethane and bortrifluorid-ethyletherat was added as an activator (see Figure 7-12). As the alkynylsilanc compound, 1,2-bis-trimethylsilyl-ethyne (68) was subsequently added and the reaction afterwards quenched by addition of a saturated solution of sodium tetrafluoroborate in water. After work-up, alkynyliodonium salt 69 was obtained as an ocher yellow solid in 44\% yield.

Conclusion and Product Analysis

An IR spectrum showed the stretching vibrations of the acetylenic bond at $\bar{\nu} = 2143$ cm$^{-1}$. The vibrations of the aromatic and the aliphatic C–H-bonds could be seen at $\bar{\nu} = 3063$ cm$^{-1}$, and $\bar{\nu} = 2959$ cm$^{-1}$ and 2900 cm$^{-1}$, respectively.

The ESI-MS showed the cation mass at $m/z = 301$ and the anion mass (of BF$_4^-$) at $m/z = 87$. However, the use of self-prepared 69 led to lower yield in alkynylation reactions compared to the employment of purchasable 69.
7.3.1.2.3. Mechanism of the Reaction of Alkynyliodonium Salts with Nucleophiles

The first step in the reaction of alkynyl(phenyl)iodonium tetrafluoroborates 69 with nucleophiles (Nu-) consists in a nucleophilic attack on the electron-deficient ß-carbon atom.\textsuperscript{115} (Figure 7-13). The formed ylide 74 is resonance-stabilized and undergoes loss of iodobenzene (Ph-I) to give carbene 75 as an intermediate.\textsuperscript{116, 117, 118} The carbene can rearrange to yield alkyne 76, if either of the two substituents on the ß-carbon is a group with a high migratory aptitude (which is the case for the trimethylsilyl group). The resulting alkyne 76 is a nucleophilic acetylenic substitution product, formed in an addition-elimination-rearrangement reaction.

Figure 7-13: Mechanism of the reaction of trimethylsilyl ethynyl(phenyl)-iodonium tetrafluoroborate (69) (anion omitted for clarity) with a nucleophile

7.3.2. Synthesis of N-1-Ethynylated Imidazoles and Benzimidazoles with Alkynyliodonium Salts

7.3.2.1. 1-Trimethylsilylethylnyl-1H-imidazole (78) — A NOVEL COMPOUND

7.3.2.1.1. Introduction and Overview

At the beginning of this thesis, only some simple ynamines synthesized with the aid of alkynyliodonium salts had been reported by Stang\textsuperscript{119} et al. However, imidazoles that were ethynyl-substituted at position N-1 were not known. A nucleotide containing an imidazole-1-ethynyl unit was described later by Kalman\textsuperscript{120} et al. in 2001; and in 2002, Kerwin\textsuperscript{98} et al. reported some 1,2-bis-ethynyl-1H-imidazoles.
The first aim was to synthesize the novel compound 1-trimethylsilylethynyl-1H-imidazole (78) — in order to see whether the ethynyl moiety could be attached to N-1 of 1H-imidazole (77) by the Stang approach at all (Figure 7-14).

### 7.3.2.1.2. Description of Synthesis

Introducing a trimethylsilyl-protected ethynyl moiety by the employment of trimethylsilyl-ethynyl(phenyl)-iodonium tetrafluoroborate (69) seemed to be the most convenient starting move: First, the TMS unit can be substituted later (substitution of TMS versus H\textsuperscript{121,122,123,124,125} or substitution of TMS versus Ph\textsuperscript{126,127,128}) and second, the SiMe\textsubscript{3}-group has a high migratory aptitude,\textsuperscript{115} which should facilitate the reaction.

![Figure 7-14: Synthesis of 1-trimethylsilylethynyl-1H-imidazole (78)](image_url)

The different conditions for the synthesis of 1-trimethylsilylethynyl-1H-imidazole (78) using trimethylsilylethynyl(phenyl)-iodonium tetrafluoroborate (69) are listed in Table 7-1. The reaction worked better at a certain dilution of the reaction mixture (concentration of educt c \approx 10^{-2} mol\text{-}1, entries 3, 4 and 5). Too high concentrations (c > 10^{-1} mol\text{-}1, entries 1 and 2) led to a decrease of yield.

At reaction times (stirring time at rt after the addition of 69) of \(\frac{1}{2}\) h, 1 h and 2 h no product could be detected, traces appeared after about 5 h. The highest yields were obtained after stirring for 24 h – 48 h. 1 eq (entry 5) or 2 eq (entry 7) of 69 worked best. Stronger cooling (below 0 °C, entry 8) prior to addition of 69 or subsequent heating (entry 9) after the addition of 69 both resulted in a decrease of yield.

Concerning the solvents, toluene and benzene (entry 10) worked best; n-hexane (entry 11) gave only traces and CH\textsubscript{3}CN (entry 12)\textsuperscript{iv,129} gave no yield at all. Et\textsubscript{2}O as a solvent with NaH as a base did not work (entries 13 and 14).

\[
\text{Acetonitrile as a solvent did not work at all as the } \alpha\text{-acidic proton of CH\textsubscript{3}CN is deprotonated by BuLi. That anion then attacks another CH\textsubscript{3}CN-molecule, leading finally to a dimerization product.}\]
Table 7-1: Various conditions for the synthesis of 1-trimethylsilyl-ethynyl-1H-imidazole (78). The best conditions are shaded in gray

<table>
<thead>
<tr>
<th>#</th>
<th>educt 77: conc.</th>
<th>solvent</th>
<th>base</th>
<th>69 / conditions</th>
<th>reaction time</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>c ≈ 10⁻¹ mol⁻¹</td>
<td>toluene</td>
<td>1 eq BuLi</td>
<td>1 eq</td>
<td>2 h</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>c ≈ 10⁻¹ mol⁻¹</td>
<td>toluene</td>
<td>1 eq BuLi</td>
<td>1 eq</td>
<td>24 h</td>
<td>traces</td>
</tr>
<tr>
<td>3</td>
<td>c ≈ 10⁻² mol⁻¹</td>
<td>toluene</td>
<td>1 eq BuLi</td>
<td>1 eq</td>
<td>1 h or 2 h</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>c ≈ 10⁻² mol⁻¹</td>
<td>toluene</td>
<td>1 eq BuLi</td>
<td>1 eq</td>
<td>5 h</td>
<td>traces</td>
</tr>
<tr>
<td>5</td>
<td>c ≈ 10⁻² mol⁻¹</td>
<td>toluene</td>
<td>1 eq BuLi</td>
<td>1 eq</td>
<td>24 h or 48 h</td>
<td>4%</td>
</tr>
<tr>
<td>6</td>
<td>c ≈ 10⁻² mol⁻¹</td>
<td>toluene</td>
<td>1 eq BuLi</td>
<td>0.5 eq</td>
<td>24 h</td>
<td>traces</td>
</tr>
<tr>
<td>7</td>
<td>c ≈ 10⁻² mol⁻¹</td>
<td>toluene</td>
<td>1 eq BuLi</td>
<td>2 eq</td>
<td>24 h – 48 h</td>
<td>4 – 5%</td>
</tr>
<tr>
<td>8</td>
<td>c ≈ 10⁻² mol⁻¹</td>
<td>toluene</td>
<td>1 eq BuLi</td>
<td>1 eq(\text{v})</td>
<td>24 h or 48 h</td>
<td>traces</td>
</tr>
<tr>
<td>9</td>
<td>c ≈ 10⁻² mol⁻¹</td>
<td>toluene</td>
<td>1 eq BuLi</td>
<td>1 eq(\text{vi})</td>
<td>24 h or 48 h</td>
<td>traces</td>
</tr>
<tr>
<td>10</td>
<td>c ≈ 10⁻² mol⁻¹</td>
<td>benzene</td>
<td>1 eq BuLi</td>
<td>1 eq</td>
<td>24 h or 48 h</td>
<td>3 %</td>
</tr>
<tr>
<td>11</td>
<td>c ≈ 10⁻² mol⁻¹</td>
<td>n-hexane</td>
<td>1 eq BuLi</td>
<td>1 eq</td>
<td>24 h</td>
<td>traces</td>
</tr>
<tr>
<td>12</td>
<td>c ≈ 10⁻² mol⁻¹</td>
<td>CH₃CN</td>
<td>1 eq BuLi</td>
<td>1 eq(\text{vii})</td>
<td>5 h</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>c ≈ 10⁻² mol⁻¹</td>
<td>Et₂O</td>
<td>1.05 eq NaH</td>
<td>1 eq</td>
<td>24 h</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>c ≈ 10⁻² mol⁻¹</td>
<td>Et₂O</td>
<td>1.05 eq NaH</td>
<td>1 eq(\text{viii})</td>
<td>24 h</td>
<td>-</td>
</tr>
</tbody>
</table>

7.3.2.1.3. Conclusion and Product Analysis

The synthesis worked best (see entry 5) using 1 eq of imidazole 77 in toluene and 1 eq of BuLi. At rt, addition of 1 – 2 eq of solid trimethylsilyl-ethynyl(phenyl)-iodonium tetrafluoroborate (69) and subsequent stirring for 24 – 48 h gave – after work-up and chromatography – the desired product as a yellow film in a yield of 4%.

1-Trimethylsilyl-ethynyl-1H-imidazole (78) was the first TMS-protected alkynylimine with a triple bond at a nitrogen atom that forms part of an imidazole system. Detection was mainly carried out by GC/MS-analysis: The GC showed a pure compound, and the molecular peak ion \(M^+\) was found at \(m/z = 164\). The loss of methyl (\(\Delta m/z = -15\)) is characteristic for compounds carrying a TMS-group,\(^{130}\) so also an intensive peak at \(m/z = 149\) could be found.

\(^{\text{v}}\) In each case, 1 eq of 77 was used.

\(^{\text{vi}}\) Further conditions: prior to addition cooling to -25 °C.

\(^{\text{vii}}\) Further conditions: after addition heating to +50 °C or +75 °C for 20 min or 2 h, resp.

\(^{\text{viii}}\) Further conditions: prior to addition cooling to -10 °C.

\(^{\text{ix}}\) Further conditions: after addition heating to 40 °C for 2 h.
A $^1$H-NMR spectrum in [D$_6$]-benzene showed the chemical shifts of the protons of the imidazole core and the TMS-group. In the $^{13}$C-NMR spectrum the imidazole carbons and the carbons of the TMS-group were found; however, due to their longer relaxation times the acetylenic $sp^{13}$C nuclei were not detected.

It was found out that compound 78 is unstable — it is sensitive to hydrolysis, acids and air. Hence it decomposed while standing at the air and in a CHCl$_3$-solution after 1 d. Compound 78 is also quite volatile, it coevaporated with toluene (even if toluene was blown off by a nitrogen stream and the solution kept at rt). However, it was much less volatile with EtOAc or n-hexane. Due to its sensitivity and volatility, the product was stored under argon and in the cold. Solvents after column chromatography were evaporated at low bath temperature (ca. 20 – 30 °C).

7.3.2.2. 1-Trimethylsilylethynyl-$^1$H-benzimidazole (80) — A NOVEL COMPOUND

7.3.2.2.1. Introduction and Overview

1-Trimethylsilylethynyl-$^1$H-imidazole (78) was a novel compound. However, its sensitivity and volatility and the obtained low yield made it unsuited for further investigations. The idea was that a benzimidazole core instead of an imidazole core could improve the stability.

7.3.2.2.2. Description of Synthesis

The synthetic conditions for the preparation of 1-trimethylsilylethynyl-$^1$H-benzimidazole (80) followed the ones that were improved for its imidazole derivative 78 (Figure 7-15).

![Figure 7-15: Synthesis of 1-trimethylsilylethynyl-$^1$H-benzimidazole (80)](image)

Under exclusion of moisture and air, $^1$H-benzimidazole (79) was suspended in toluene, the concentration not exceeding $c \approx 10^{-2}$ mol·l$^{-1}$. Then, the base was added slowly in the cold
LDA, DBU and BuLi were employed as different bases –, followed by the addition of trimethylsilylethynyl(phenyl)-iodonium tetrafluoroborate (69). The reaction time was 24 h at rt. After work-up and flash column chromatography, the desired product was obtained as a yellowish oil in a yield of 12%. Interestingly, also a side product could be isolated in amounts up to 10%, depending on the conditions (Figure 7-16).

![Figure 7-16: Product distribution upon the reaction of 1H-benzimidazole (79) with alkynyl-iodonium salt 69](image)

Table 7-2 shows the obtained yield of 80 after the use of LDA, DBU and BuLi as bases. BuLi (entry 1) and LDA (entry 2) gave 12% yield, whereas DBU (entry 3) gave 2%. LDA was freshly prepared and BuLi was titrated prior to use, whereas DBU was used without prior purification. Both LDA and DBU are sterically hindered bases, with a pK_a ≈ 36 for LDA\(^{131, x}\) and a pK_a ≈ 12 for DBU\(^{132, x}\). BuLi is even a stronger base (pK_a > 40) than LDA, but it can also act as a nucleophile leading to undesired side reactions.

The pK_a-value found for 1H-benzimidazole (79) is pK_a = 16.4\(^x\) and for 1H-imidazole (77) it is pK_a = 18.6,\(^{133, x}\) showing that 1H-benzimidazole (79) is more acidic.

In case of DBU (entry 3) the yield of side product 81 was 5%, showing a low overall yield. In contrast to that, BuLi (entry 1) gives a relatively high yield (10%) of the undesired side product. The highest product yield together with the lowest side product yield could only be achieved with LDA (entry 2).

---

\(^x\) The numbers given represent the pK_a(HA)-values for the following reactions: H–N(iPr)_2 → LDA, DBU\(^*\)–H → DBU, Bu–H → BuLi, 1H-benzimidazole (79) → benzimidazolate or 1H-imidazole (77) → imidazolate, resp.
Table 7-2: Various conditions for the synthesis of 1-trimethylsilyl-1H-benzimidazole (80) (and the side product 81). The best conditions are shaded in gray

<table>
<thead>
<tr>
<th>#</th>
<th>educt: eq</th>
<th>solvent</th>
<th>base</th>
<th>69</th>
<th>reaction time</th>
<th>yield 80</th>
<th>yield 81</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 eq 79</td>
<td>toluene</td>
<td>1 eq BuLi</td>
<td>1 eq</td>
<td>24 h</td>
<td>12 %</td>
<td>10 %</td>
</tr>
<tr>
<td>2</td>
<td>1 eq 79</td>
<td>toluene</td>
<td>1 eq LDA</td>
<td>1 eq</td>
<td>24 h</td>
<td>12 %</td>
<td>6 %</td>
</tr>
<tr>
<td>3</td>
<td>1 eq 79</td>
<td>toluene</td>
<td>1 eq DBU</td>
<td>1 eq</td>
<td>24 h</td>
<td>2 %</td>
<td>5 %</td>
</tr>
</tbody>
</table>

7.3.2.2.3. Conclusion and Product Analysis

Main Product: 1-Trimethylsilyl-1H-benzimidazole (80) — A NOVEL COMPOUND

The best reaction conditions were using 1 eq of 1H-benzimidazole (79) in toluene and 1 eq of LDA, with subsequent addition of 1 eq of solid trimethylsilyl-ethynyl(phenyl)-iodonium tetrafluoroborate (69) and stirring for 24 h (see entry 5). After a work-up procedure and chromatography, the product was obtained as a slightly yellowish oil with a sweetish smell. It turned out to be more stable and less volatile than its imidazole derivative 78, but it still had to be handled carefully in presence of water and air. Although the yield (12 %) was relatively low, it was much higher than for 78 (4 %).

Figure 7-17: 1-Trimethylsilyl-1H-benzimidazole (80)

The GC/MS-analysis of 80 (Figure 7-17) demonstrated a pure compound in the gas chromatogram, and in the mass spectrum the molecular peak $M^+$ was found at $m/z = 214$. The base peak (100 % intensity) at $m/z = 199$ shows the loss of methyl ($\Delta m/z = -15$), which is characteristic for compounds carrying a TMS-group.$^{130}$

In the $^1$H-NMR spectrum in $[D_6]$-acetone, the chemical shifts of the protons of the benzimidazole core and the TMS-group were found. The $^{13}$C-NMR spectrum showed – beside the benzimidazole carbons and the carbons of the TMS-group – clearly the acetylenic $sp^{13}$C nuclei at 89.5 ppm and at 76.6 ppm, which were detected as quaternary carbons in the DEPT-135
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spectrum. A clear distinction between both nuclei could be made as the \( ^1J \)-coupling between Si and the adjacent carbon atom could be seen; the coupling constant was found to be \( ^1J_{C-Si} = 41.3 \text{ Hz} \).

An NOE-experiment in order to see an interaction of a proton of the TMS-group with H-7, the nearest proton of the benzimidazole core, failed — the distance between the TMS-protons and H-7 is too large. A molecular stick model suggested a distance of \( > 3 \text{ Å} \) for these protons.

The IR spectrum showed the stretching vibrations of the aromatic C–H bonds at \( \tilde{v} = 3085 \text{ cm}^{-1} \), the aliphatic C–H bonds at \( \tilde{v} = 2960 \text{ cm}^{-1} \) and the C=C triple bond at \( \tilde{v} = 2192 \text{ cm}^{-1} \).

**Side Product: 1-Ethynyl-1H-benzimidazole (81) — A NOVEL COMPOUND**

The byproduct 81 (Figure 7-18) was presumably formed upon cleavage of the TMS-group by the base.

![Figure 7-18: 1-Ethynyl-1H-benzimidazole (81)](image)

The white solid was identified as a pure compound in the GC/MS. The molecular peak ion \( M^+ \) was found at \( m/z = 142 \) with an intensity of 100 %.

A \(^1H\)-NMR spectrum in [D₆]-acetone showed the chemical shifts of the protons of the benzimidazole core. The acetylenic proton was detected as a singlet at 4.11 ppm. This signal showed the \(^{13}C\)-satellites: The \( ^1J \)-coupling between the acetylenic proton and the terminal acetylenic carbon was found to be \( ^1J_{H-C} = 265.9 \text{ Hz} \), the \(^2J \)-coupling to the internal acetylenic carbon was \( ^2J_{H-C} = 57.6 \text{ Hz} \). Both values are in good agreement with the ones given in the literature. The \( ^1J_{H-C} \)-coupling is about 250 Hz, the \(^2J_{H-C} \)-coupling about 55 Hz for a proton of an acetylenic system.

In the \(^{13}C\)-NMR spectrum, the benzimidazole carbons were found. The quaternary acetylenic carbon appears at 70.8 ppm, the primary acetylenic carbon at 63.6 ppm.

Compound 81 was not stable; it decomposed upon standing within 1 – 2 d.
7.3.2.3. 5-Nitro-1-trimethylsilylethynyl-1H-benzimidazole (83) — A NOVEL COMPOUND

7.3.2.3.1. Introduction and Overview

1-Trimethylsilylethynyl-1H-benzimidazole (80) was already found to be more stable than 1-trimethylsilylethynyl-1H-imidazole (78). The reactive part of compounds 80 and 78 is the triple bond of the trimethylsilylethynyl moiety (Figure 7-19). In order to further increase the stability in air and water and toward acids, the triple bond should be made electronically poorer.

![Figure 7-19: Sensitivity of the electron rich triple bond in compounds 78 and 80 to oxygen and acids](image)

This could be achieved by lowering the electron density of the imidazole or benzimidazole core, respectively, by the attachment of electron withdrawing groups. For example, R = H in Figure 7-19 could be formally replaced by electron withdrawing substituents (R = F, CF₃, or NO₂, resp.). A first simple test reaction was carried out by using 5-nitro-1H-benzimidazole (82) as a starting material. The nitro group should also lead to a solid instead of an oil.

7.3.2.3.2. Description of Synthesis

For the synthesis of 5-nitro-1-trimethylsilylethynyl-1H-benzimidazole (83), the same reaction conditions were applied as for 1-trimethylsilylethynyl-1H-benzimidazole (80) (Figure 7-20): Excluding moisture and air, 5-nitro-1H-benzimidazole (82) was suspended in toluene; the concentration did not exceed c ≈ 10⁻² mol⋅l⁻¹. LDA as a base was added slowly in the cold, followed by the addition of trimethylsilylethynyl(phenyl)-iodonium tetrafluoroborate (69). The reaction time was 36 h at rt.
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Figure 7-20: Product distribution upon the reaction of 5-nitro-1H-benzimidazole (82) with alkynylidonium salt 69

After work-up and column chromatography, apart from the desired product 5-nitro-1-trimethylsilylethynyl-1H-benzimidazole (83), also its positional isomer 6-nitro-1-trimethylsilylethynyl-1H-benzimidazole (84) was isolated (Figure 7-20). The explanation can be found below.

7.3.2.3.3. Conclusion and Product Analysis

Upon deprotonation of a benzimidazole system like 79 at position N-1, a symmetrical, resonance-stabilized anion 85a / 85b is formed (Figure 7-21, R = H). The following attack of an electrophile EI⁺ leads to only one product, an N-1-substituted benzimidazole 87. However, if R = NO₂ (for 82) like in the reaction described above, the anion 86a / 86b is not symmetric anymore: An electrophile EI⁺ can attack at two positions that are energetically nearly equal (see Figure 7-21, R = NO₂). This leads to two products 88 and 89, which are positional isomers — the product distribution is about 50 : 50.
In the case of 5-nitro-1H-benzimidazole (82) as a starting material, the two positional isomers 83 (the 5-nitro-isomer) and 84 (the 6-nitro-isomer) were generated, one in 2% yield and the other one in 3% yield, giving a total yield of 5–6%. Both could be separated by flash column chromatography. The products were ocher, non-volatile solids that were stable in air.

Both positional isomers were characterized by GC/MS and NMR spectroscopy; however, it was not possible to unambiguously differentiate between either isomer. Other investigation methods like X-ray structure determination were not employed, because only the increased stability of the system due to the electron withdrawing nitro-group was investigated here.

An assignment could be made by means of NMR increments, though. In order to estimate the chemical shifts of benzene protons in the framework of nitro-benzene (90), the following increment system formula was used: \[ \delta[\text{ppm}] = 7.26 + I \]

For the NO2-substituent the ortho-increment is \( I_{\text{ortho}} = 0.95 \text{ ppm} \) and the meta-increment is \( I_{\text{meta}} = 0.26 \text{ ppm} \). From this follows that for a proton in ortho-position of a NO2-group the chemical shift is expected to be \( \delta = 8.21 \text{ ppm} \):
\[ \delta[\text{ppm}] = 7.26 + I_{\text{ortho}} = 7.26 + 0.95 = 8.21 \]

The chemical shift of a proton in meta-position of a NO\textsubscript{2}-group is then \( \delta = 7.52 \text{ ppm} \):

\[ \delta[\text{ppm}] = 7.26 + I_{\text{meta}} = 7.26 + 0.26 = 7.52 \]

Table 7-3 shows the presumed assignments based on the incremental calculations. The data suggest that the signals at 8.72 ppm, 8.35 ppm and 7.64 ppm correspond to H-4, H-6 and H-7 of the 5-nitro-isomer 83, respectively. These signals appear as multiplets. However, if treated as a simple first order NMR spectrum, H-4 gives a doublet (due to coupling to H-6), H-6 a doublet of doublets (coupling to H-4 and H-7) and H-7 a doublet (coupling to H-6).

In case of the 6-nitro-isomer 84, in a first order treatment H-7 appears as a doublet at 8.50 ppm and the other proton in ortho-position to the NO\textsubscript{2}-group, H-5, as a doublet of doublets at 8.28 ppm. H-4 appears as a doublet at a chemical shift of 7.90 ppm.

Table 7-3: Calculated (with NMR increments) and measured chemical shifts of the benzene protons in compounds 83 and 84 in ppm and the assumed assignments in parenthesis

<table>
<thead>
<tr>
<th>calculated shifts [ppm]: nitro-benzene system (90)</th>
<th>measured shifts [ppm]: 5-nitro-isomer 83</th>
<th>measured shifts [ppm]: 6-nitro-isomer 84</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.21 (ortho-H)</td>
<td>8.72 (H-4)</td>
<td>8.50 (H-7)</td>
</tr>
<tr>
<td>8.21 (ortho-H)</td>
<td>8.35 (H-6)</td>
<td>8.28 (H-5)</td>
</tr>
<tr>
<td>7.52 (meta-H)</td>
<td>7.64 (H-7)</td>
<td>7.90 (H-4)</td>
</tr>
</tbody>
</table>

For compound 83, the remaining NMR signals could be assigned clearly to the corresponding protons or carbons, respectively. In the \(^{13}\text{C}\)-NMR spectrum the acetylenic \( sp^{13}\text{C} \) nuclei were found at 86.9 ppm (C-8) and 78.6 ppm (C-9); both were proven to be quaternary carbons from the DEPT-135 spectrum.
According to the GC/MS spectrum, 5-nitro-1-trimethylsilylethynyl-1H-benzimidazole (83) was a pure compound with a retention time of \( R_t = 18.2 \) min. The mass spectrum showed the molecular peak \( M^+ \) at \( m/z = 259 \) and the base peak at \( m/z = 244 \) (typical loss of methyl, \( \Delta m/z = -15 \)).\(^{130}\) The GC/MS-analysis for 6-nitro-1-trimethylsilylethynyl-1H-benzimidazole (84) also demonstrated a pure compound in the gas chromatogram, the retention time was found to be \( R_t = 17.5 \) min. In the mass spectrum, the molecular peak \( M^+ \) was found at \( m/z = 259 \). The base peak (100 % intensity) at \( m/z = 244 \) showed the loss of methyl (\( \Delta m/z = -15 \)), which is characteristic for compounds carrying a TMS-group.\(^{130}\)

The remaining NMR signals for compound 84 could be assigned clearly. In the \(^{13}\)C-NMR spectrum, the \( sp^{3}\) nuclei of the triple bond were found at 86.7 ppm (C-8) and 78.9 ppm (C-9). Both were quaternary carbons according to the DEPT-135 spectrum.

### 7.3.3. Attempted Transformation of a Carbaldehyde at N-1 of Benzimidazole into an Acetylenic Group: The Aldehyde Approach

#### 7.3.3.1. Synthesis of a Perfluorinated, Electronically Poor Benzimidazole

#### 7.3.3.1.1. 4,5,6,7-Tetrafluoro-1H-benzimidazole (92)

**Introduction and Overview**

The synthesized nitro-substituted compounds 5-nitro-1-trimethylsilylethynyl-1H-benzimidazole (83) and 6-nitro-1-trimethylsilylethynyl-1H-benzimidazole (84) turned out to be stable compounds, more stable than the non-substituted benzimidazole 80 and the imidazole 78. It is assumed that this is because of the electronically deactivating NO₂-group, which lowers the reactivity of the triple bond. However, the overall yield of 5 – 6 % was quite low. What is more, the employed trimethylsilylethynyl(phenyl)-iodonium tetrafluoroborate (69) is a relatively expensive reagent.

Another synthetic procedure could build up the triple bond at N-1 by conversion of an aldehyde to an acetylenic bond. As a starting material, a perfluorinated benzimidazole could be used. This would not only act as an electronically extremely poor compound, but it would also be a symmetrical molecule with regard to substitution in position N-1 — which was not the case for 5-nitro-1H-benzimidazole (82) as an educt.
Description of Synthesis

Heaton et al. described the synthesis of perfluorinated 4,5,6,7-tetrafluoro-1H-benzimidazole (92) starting from 1,2-diaminotetrafluorobenzene (91) \(^{(136)}\) (Figure 7-22):

![Chemical structure](image)

Figure 7-22: Synthesis of 4,5,6,7-tetrafluoro-1H-benzimidazole (92) \(^{(136)}\)

According to this procedure, diamine 91 was refluxed in formic acid to give pale yellow crystals of benzimidazole 92 in a yield of 54% after work-up and recrystallization (lit. \(^{(136)}\): 71%).

Conclusion and Product Analysis

Product 92 was only detected by GC/MS-analysis: The GC showed a pure compound, and the molecular peak ion \(M^+\) (here identical with the base peak) was found at \(m/z = 190\). The fragment formed upon loss of hydrogen cyanide (HCN, \(\Delta m/z = -27\)) could be detected at \(m/z = 163\).

7.3.3.1.2. 1-Diethoxymethyl-4,5,6,7-tetrafluoro-1H-benzimidazole (94)

Introduction and Overview

A synthesis for compound 94 was not known, however, the protection of 1H-benzimidazole (79) to give the non-fluorinated 1-diethoxymethyl-1H-benzimidazole (93) was described by Suschitzky et al. \(^{(137)}\) (Figure 7-23), while others reported analytical data. \(^{(138)}\)

![Chemical structure](image)

Figure 7-23: Synthesis of 1-diethoxymethyl-1H-benzimidazole (93) by Suschitzky \(^{(137)}\)
Suschitzky\textsuperscript{137} also described the synthesis of \(1H\)-benzimidazole-2-carbaldehyde from 1-diethoxymethyl-\(1H\)-benzimidazole-2-carbaldehyde, however, the immediate object was to introduce the carbaldehyde in position \(N-1\).

The diethoxymethyl-protection of \(N-1\) of \(1H\)-imidazole (77) was carried out by several groups.\textsuperscript{139,140,141} It should be stressed, that Brown\textsuperscript{142} et al. obtained the product in 82\% yield, but they also admitted that protecting group to be readily hydrolyzed within minutes under neutral and acidic conditions. Chadwick\textsuperscript{143} et al. underlined the ease of removal of the diethoxy­methyl functionality, leading to decomposition to give the parent \(1H\)-imidazole (77). Ohta\textsuperscript{144} et al. did not isolate the protected compound, it was immediately used in a following reaction.

**Description of Synthesis**

Suschitzky\textsuperscript{137} et al. protected \(1H\)-benzimidazole (79) using triethyl orthoformate and \(p\)-toluenesulfonic acid as a Lewis acid catalyst (Figure 7-23). They reported a product yield of 77\%, however, they also emphasized the instability of compound 93 (see Figure 7-23) and they admitted the microanalysis to be unsatisfactory.

According to their procedure, 4,5,6,7-tetrafluoro-\(1H\)-benzimidazole (92) was used as a starting material (Figure 7-24).

![Figure 7-24: Attempted synthesis of 1-diethoxymethyl-4,5,6,7-tetrafluoro-\(1H\)-benzimidazole (94)](image)

In the course of the reaction, which was controlled by TLC, and after work-up mainly educt could be detected, though.

**Conclusion and Product Analysis**

The product, 1-diethoxymethyl-4,5,6,7-tetrafluoro-\(1H\)-benzimidazole (94), could not be detected or its tiny fraction decomposed during work-up. Another reaction in order to introduce an aldehyde functionality at position \(N-1\) had to be found.
7.3.3.1.3. 4,5,6,7-Tetrafluoro-1H-benzimidazole-1-carbaldehyde (95)

Introduction and Overview

The conversion of aldehydes (C-carbaldehydes) into terminal alkynes was already described in the literature (see, e.g., 145, 146, 147, 148). It does proceed via the chain elongation reaction by one carbon atom (Figure 7-25).

\[
\text{RCHO} \xrightarrow{\text{LiCl}, \text{BuLi}} \text{RC≡H}
\]

It should also be mentioned that apart from aldehydes, also methyl ketones (e.g., 149) could be converted into terminal acetylenes. Aryl ketones were converted into aryl alkynes (e.g., 150).

Could N-carbaldehydes be converted into N-alkynylimines?

Preparations of N-formyl compounds (N-carbaldehydes) like 1-formyl-1H-imidazole151, 152, 153 or 1-formyl-1H-benzimidazole (97) (benzimidazole-1-carbaldehyde)151 were described (see Figure 7-27). These compounds were used as effective formylating agents, especially for introducing the CHO-group at a nitrogen atom. 151, 154
A synthesis for the perfluorinated 95 (4,5,6,7-tetrafluoro-1H-benzimidazole-1-carbaldehyde) (Figure 7-26), however, was not known.

![Figure 7-26: 4,5,6,7-Tetrafluoro-1H-benzimidazole-1-carbaldehyde (95)](image)

**Description of Synthesis**

Staab\textsuperscript{151} \textit{et al.} reacted 1\textit{H},1\textit{H}-1,1'-carbonyl-bis-benzimidazole (\textit{N},\textit{N}'-carbonyl-bis-benzimidazole) (96) with formic acid in THF (Figure 7-27). Apart from the carbonylated product 97, also 1\textit{H}-benzimidazole (79) and CO\textsubscript{2} were formed:

![Figure 7-27: Synthesis of 1H-benzimidazole-1-carbaldehyde (97) by Staab\textsuperscript{151}](image)

**Conclusion**

The above-mentioned groups did stress that the \textit{N}-formylated imidazole derivatives were not isolated. They were found to be extremely hygroscopic and unstable (they converted into the non-substituted heterocycles under elimination of CO) — therefore they were used directly in a subsequent formylation reaction.

As a conclusion, the carbonylated imidazole derivatives may be employed as formylating agents, however, in order to convert the aldehydes into alkynes, a greater stability was required.

Synthetic attempts employing the conditions described by Staab\textsuperscript{151} \textit{et al.} in order to prepare 97, failed. No formylated product could be isolated or detected, respectively.
7.4. Building up the Ethynyl Moiety at Position C-2 and N-1 of Imidazole Systems Concurrently — Coupling Approaches

7.4.1. General Introduction and Overview

It was sought for a method to attach two acetylenic moieties to an imidazole or benzimidazole system simultaneously. Such a coupling reaction would lead to an azaenediyne in a few steps (Figure 7-28).

![Figure 7-28: Planned synthetic strategy for azaenediyne 99 via coupling reactions](image)

Coupling reactions between \(sp^2\)-carbon and \(sp\)-carbon centers are well explored by the Sonogashira coupling.\(^{155,156}\) However, the preparation of imidazole derivatives with an ethynyl moiety at \(N-1\) by transition metal couplings was not known at that time.

In 2001, Kalman\(^{120}\) et al. claimed to have synthesized a nucleotide carrying an \(N\)-ethynylated imidazole unit by a palladium(0)-catalyzed coupling reaction.

There was one example for the synthesis of an ynamide with the aid of (1-alkynyl)-cuprates, though: Balsamo\(^{157}\) et al. reported the Cu\(^1\)-catalyzed synthesis of ynamide 103 by reacting \(\beta\)-lactam 100 with propiolic acid ester 102 (Figure 7-29). The reaction proceeded via the copper(I)-acetylenide Cu\(^1\)-\(\equiv\)C–CO\(_2\)tBu 101.

![Figure 7-29: Synthesis of ynamide 103 by Balsamo\(^{157}\) et al.](image)
The case that the use of 1 eq of CuCl was essential and that the presence of molecular oxygen increased the yield, suggests a mechanism similar or equal to the Glaser-coupling\textsuperscript{158, 159} — the oxidative coupling of terminal alkynes (compare also\textsuperscript{160, 161}). It is noteworthy here that the alkynylated nitrogen is $sp^2$-hybridized and forms part of a cyclic system.

7.4.2. Activation of Position C-2 of Imidazole Derivatives

7.4.2.1. 2-Iodo-1-methyl-1H-imidazole (105)

7.4.2.1.1. Introduction and Overview

Shvartsberg\textsuperscript{162} et al. used the copper catalyzed replacement of halogen by acetylenic groups in order to synthesize acetylenic derivatives of imidazole. This reaction requires first an activation of position C-2, which they achieved by iodination.\textsuperscript{163}

7.4.2.1.2. Description of Synthesis

In this work, the iodination recipe from Knochel\textsuperscript{164} et al. was employed. They synthesized 2-iodo-1-methyl-1H-imidazole (105) from 1-methyl-1H-imidazole (104) by deprotonation with BuLi and subsequent iodination with molecular iodine (Figure 7-30):

\[
\begin{align*}
\text{N} & \quad \text{1. BuLi / THF} \\
\text{CH}_3 & \quad 2. \text{I}_2 / \text{THF} \\
\text{N} & \quad \text{104} \\
\text{CH}_3 & \quad \text{105}
\end{align*}
\]

Figure 7-30: Synthesis of 2-iodo-1-methyl-1H-imidazole (105) by Knochel\textsuperscript{164} et al.

Following these conditions, the product could be obtained in a yield of 56%.

7.4.2.1.3. Conclusion and Product Analysis

Compound 105 was identified by GC/MS and NMR analysis. However, a certain disadvantage here is that the protecting $N$-methyl group is difficult to cleave. And generally spoken, the attachment of protecting groups and their proximate cleavage requires additional synthesis steps.
7.4.2.2. 2-Bromo-1H-benzimidazole (107)

7.4.2.2.1. Introduction and Overview
The preparation of 2-bromo-1H-benzimidazole (107) was reported to start from 1H-benzimidazole (79)\textsuperscript{165} or from 1H-benzimidazole-2-thiol (106).\textsuperscript{166,167} The mentioned bromination reactions are interesting, because they do not require an N-protecting group.

7.4.2.2.2. Description of Synthesis
The procedure followed the one given by Ellingboe\textsuperscript{166} \textit{et al.}, which reacted 2-mercapto-1H-benzimidazole (106) in hydrobromic acid and acetic acid with bromine (Figure 7-31).

\begin{center}
\includegraphics[width=0.5\textwidth]{synthesis.png}
\end{center}

Figure 7-31: Synthesis of 2-bromo-1H-benzimidazole (107) by Ellingboe\textsuperscript{166} \textit{et al.}

The crude 2-bromo-1H-benzimidazole (107) could be isolated in 39 % yield (lit.\textsuperscript{166}: 70 %).

7.4.2.2.3. Conclusion and Product Analysis
Compound 107 was detected by GC/MS and NMR analysis. It served as an educt for the proximate coupling reactions.
7.4.3. Coupling Attempts with 2-Bromo-1H-benzimidazole (107):
1,2-Bis(phenylethynyl)-1H-benzimidazole (108) — Attempted Synthesis

7.4.3.1. Introduction and Overview

The Sonogashira coupling is a palladium- and copper-catalyzed cross-coupling reaction of organohalides with terminal alkynes (Figure 7-32).

\[
\text{Ar-X + H} \equiv \text{R} \xrightarrow{\text{(PPh}_3)_2\text{Pd}^{II}\text{Cl}_2, \text{Cu}^{+}} \text{Ar} \equiv \text{R}
\]

Figure 7-32: General scheme of the Sonogashira coupling

In the usual recipes (see, e.g.: 168, 169, 170, 171, 172), first a degassed solution of the organohalide in triethylamine or a solvent mixture like NEt\text{3} / THF or NEt\text{3} / DMF was prepared. Then, the Pd-catalyst (often bis(triphenylphosphine)palladium(II) dichloride, (PPh\text{3})_2\text{Pd}^{II}\text{Cl}_2, or tetrakis(triphenylphosphine)palladium(0), (PPh\text{3})_4\text{Pd}^0), the acetylenic compound and the Cu-catalyst (copper(I) iodide, Cu^{1I}) were added in an inert atmosphere. After heating for a certain time, the mixture was quenched with water, extracted and filtered to yield the crude product.

7.4.3.2. Description of Synthesis

Here was investigated whether the bis(alkynylated) 108 could be obtained directly from a Sonogashira coupling reaction (Figure 7-33).

Figure 7-33: Attempted synthesis of azaenediyn 108
The experimental procedure followed the ones described above. The reactions were carried out at rt, at 50 °C and at 80 °C with respective reaction times of 5 h and 20 h. The highest yields were obtained at 80 °C and after stirring for 20 h.

7.4.3.3. Conclusion and Product Analysis

Unfortunately, the only coupling product that could be detected was 109 in low yield (Figure 7-34). Also, apart from not converted educt, tiny amounts of the oxidative homo-coupling product 1,4-diphenylbutadiyne (110) from two molecules of phenylacetylene (43) could be found (formed during the generation of (PPh₃)₄Pd from (PPh₃)₂PdCl₂):

![Diagram of the coupling reaction of 2-bromo-1H-benzimidazole (107) to form products 109 and 110.](image)

Figure 7-34: Products upon the coupling reaction of 2-bromo-1H-benzimidazole (107)

It should be mentioned that Ito et al. carried out a coupling reaction of o-iodoaniline (111) with trimethylsilylacetylene (112) (Figure 7-35).

![Diagram of the coupling reaction of o-iodoaniline (111) to form product 113.](image)

Figure 7-35: Example for a coupling reaction in presence of an amino group — N-alkynylation does not take place

They reported a quantitative yield of coupling product 113 — but they did not observe any alkynylation product of the nitrogen of the amino group.
7.4.4. Coupling Attempts with 2-Bromo-1H-benzimidazole (107): 1-Aza-1,5,6,7,8-pentahydro-azecan\textsuperscript{xi}-3,9-diyne[1,2-a]1H-benzimidazole (115) — Attempted Synthesis

7.4.4.1. Introduction and Overview

Attaching two separate molecules of phenylacetylene did not work, but the reaction could proceed faster if both acetylenic moieties formed part of one molecule. As such a bis(acetylene) compound, octa-1,7-diyne (114) was employed (Figure 7-36).

7.4.4.2. Description of Synthesis

The synthesis procedure followed the one described above for the bis(alkynylated) 108 (Figure 7-36).

![Figure 7-36: Attempted synthesis of cyclic azaenediyne 115 via a coupling reaction](image)

The reactions were carried out at various temperatures (at rt, at 50 °C and at 80 °C) and reaction times (5 h, 20 h and 40 h).

7.4.4.3. Conclusion and Product Analysis

Unfortunately, under none of the studied conditions the desired product could be obtained. Only educt and decomposition products were found.

\textsuperscript{xi} Azecane is azacyclodecane, a 10-membered carbocyclic ring substituted with N–H.
Does the N-1-nitrogen of benzimidazole need further activation in order to react in coupling reactions?

7.4.5. Additional Activation of Position N-1 of Benzimidazole Derivatives

7.4.5.1. Potassium 2-Bromo-1H-benzimidazolate (116) — Attempted Synthesis

7.4.5.1.1. Introduction and Overview

Here was sought for a way to make the N-1-nitrogen of 2-bromo-1H-benzimidazole (107) more nucleophilic. The parent benzimidazole monopotassium salt was prepared from 1H-benzimidazole (79) with potassium amide\textsuperscript{174} or with potassium carbonate as a base.\textsuperscript{175,176} A synthesis starting from the brominated 107 was not known.

7.4.5.1.2. Description of Synthesis

In this work, the deprotonation recipe from Weidenhagen\textsuperscript{175} \textit{et al.} was employed (Figure 7-37). They synthesized potassium benzimidazolate with anhydrous K$_2$CO$_3$. However, they did not isolate the product, but submitted it to a successional reaction directly.

![Figure 7-37: Synthesis of potassium 2-bromo-1H-benzimidazolate (116)](image)

Following those conditions, the product could not be obtained as a pure compound.

7.4.5.1.3. Conclusion and Product Analysis

Compound 116 was only identified by ESI-MS analysis. In the anion mode, two peaks at $m/z = 195$ and at $m/z = 197$ were found, corresponding to the anion masses of benzimidazolate with the $^{79}$Br- and the $^{81}$Br-isotope, respectively. A GC/MS spectrum after extraction with dry acetone
still showed the educt 2-bromo-1H-benzimidazole (107), though. The product was not found to be pure.

7.4.5.2. 1,2-Dibromo-1H-benzimidazole (119) — Attempted Synthesis

7.4.5.2.1. Introduction and Overview

A bishalogenated compound could serve as a reactive precursor for coupling reactions. First, the synthesis of the di-brominated 119 (see Figure 7-39) was investigated. The preparation of 1,2-dibromo-1H-imidazole-4,5-dicarbonitrile (118) was described by Rasmussen et al. (Figure 7-38):

![Figure 7-38: Synthesis of 1,2-dibromo-1H-imidazole-4,5-dicarbonitrile (118) by Rasmussen et al.](image)

Another group assumed an N-1-brominated compound as a side product.

7.4.5.2.2. Description of Synthesis

Rasmussen et al. started from monopotassium 2-bromo-1H-imidazole-4,5-dicarbonitrile (117). Upon reaction with bromine, they obtained an unstable solid. Here, a slightly modified procedure starting from 2-bromo-1H-benzimidazole (107) was applied. However, an unstable mixture of products was obtained (Figure 7-39).
7.4.5.2.3. Conclusion and Product Analysis

A GC/MS analysis showed that the reaction did not stop at the di-brominated species (presumably 119), also a tri-brominated (presumably 120) and a tetra-brominated compound (presumably 121) had formed (see Figure 7-39).

An explanation is that the benzimidazole system 107 is reactive with regard to electrophilic aromatic substitution. In the literature recipe, this problem was circumvented by the use of a substituted system.

And, what is more, it could not be proven whether the bromine atom was connected to the N-1-nitrogen of the bromination products or to a carbon atom. It should be mentioned in this context, that also the N-Cl bond in 1,2,4,5,6,7-hexachloro-1H-benzimidazole was found to be very labile.\(^{179}\)

7.4.5.3. 2-Bromo-1-iodo-1H-benzimidazole (122) — Attempted Synthesis

7.4.5.3.1. Introduction and Overview

The parent system 2-bromo-1H-benzimidazole (107) was found to be too reactive with regard to bromination — a mixture of poly-brominated products was obtained. As it was undesirable to replace the educt by an electronically more deactivated compound, simply a less reactive electrophile could be employed. Such an electrophile would be the iodine cation, I\(^+\).
The preparations of an N-1-iodinated benzimidazole with the aid of iodine in an aqueous potassium iodide solution\(^{180, 181, 182}\) or with iodine chloride via an N-1-stannyl compound\(^{183}\) were mentioned in the literature. Best suited, however, seemed the procedure given by Rasmussen\(^{177}\) et al., who prepared 2-bromo-1-iodo-1H-imidazole-4,5-dicarbonitrile from 2-bromo-1H-imidazole-4,5-dicarbonitrile with iodine chloride (compare Figure 7-38).

### 7.4.5.3.2. Description of Synthesis

Following the procedure given by Rasmussen\(^{177}\) et al., who used a NaOH-solution of the educt and then added I–Cl, only educt could be isolated (Figure 7-40).

\[
\begin{align*}
\text{107} & \quad \text{1. H}_2\text{O} / \text{NaOH (1 eq)} \quad \cross \quad \text{2. I–Cl (1 eq)} \\
& \quad \text{122}
\end{align*}
\]

**Figure 7-40:** Attempted synthesis of 2-bromo-1-iodo-1H-benzimidazole (122)

### 7.4.5.3.3. Conclusion and Product Analysis

A GC/MS analysis showed only educt. Rasmussen\(^{177}\) et al. pointed out that the control of stoichiometry was essential, although this was carefully checked. Another possible reason could be that I–Cl had to be prepared freshly.
7.5. Other Approaches for Building up an Alkynyl Moiety at N-1 of Non-Cyclic and Cyclic Systems

Great general overviews concerning the preparation of mainly non-cyclic and some cyclic (but most of them non-aromatic) ynamines were published by Collard-Motte and Janousek and Himbert.

7.5.1. Base Catalyzed Isomerization Reactions

7.5.1.1. Introduction and Overview

A terminal acetylenic bond can migrate within a hydrocarbon chain to form an internal triple bond. More specifically, propargylic substrates (like 2-propynyl amines 123) may rearrange upon treatment with bases to give the corresponding heterosubstituted acetylenes (1-propynyl amines 125) via allene intermediates (allenyl amines 124, see Figure 7-41).

\[
\begin{align*}
\text{HC}=\text{C}=\text{C}-\text{NR}_2 & \quad \overset{\text{H}_2}{\Longleftrightarrow} \quad \text{H}_2\text{C}=\text{C}=\text{C}-\text{NR}_2 \quad \overset{\text{H}}{\Longleftrightarrow} \quad \text{H}_2\text{C}=\text{C}=\text{C}-\text{NR}_2
\end{align*}
\]

Figure 7-41: Base catalyzed rearrangement of 2-propynyl amines

However, the product distribution (depending on the position of equilibrium) of that base catalyzed rearrangement generally depends on the substituents of the parent system, the base and its strength and concentration, the solvent and other reaction conditions like reaction time and temperature.

7.5.1.2. Description of Syntheses

The alkynyl moiety attached to nitrogen that forms part of an aromatic system could therefore be built up by base catalyzed isomerization of a 2-propynyl-moiety: 10\(H\)-Phenothiazine (126) was converted into 10-(2-propynyl)-10\(H\)-phenothiazine (128) and than isomerized to 10-(1-propynyl)-10\(H\)-phenothiazine (129) by some groups (Figure 7-42).
In a similar way to that described above, also 10-(2-propynyl)-10H-acridine-9-one was prepared starting from 10H-acridine-9-one via 10-(1-propynyl)-10H-acridine-9-one by various groups.\textsuperscript{192, 193, 194}

Popov\textsuperscript{195} reacted benzimidazole derivative 130 with propargyl bromide (127) in acetone and with sodium hydroxide as a base. Amongst several other products, like acetylene 131 and allene 132, he claimed to have obtained a low yield of alkynyl imine 133 (Figure 7-43).

\textbf{7.5.1.3. Conclusion}

The base catalyzed isomerization of the 2-propynyl-moiet reveals several drawbacks for imidazoles and benzimidazoles as starting materials. Although compounds like 10H-phenothiazine...
7. SYNTHESSES OF AZAENEDIYNES

(126), 10H-phenoselenazine and 9H-carbazole could be converted into the corresponding N-(1-propynyl)-derivatives,\textsuperscript{190} this was not the case for the following heterocycles: Hubert \textit{et al.} reported that 1H-pyrole, 1H-pyrazole and 1H-imidazole only gave the corresponding 1-aminoallenes,\textsuperscript{196} and 1H-indole gave the desired acetylenic compound only in bad yield.

Another drawback of the base catalyzed isomerization of the 2-propynyl-moiety is that the 1-propynyl moiety of the product then carries a terminal methyl group. This group is difficult to substitute and hence impedes posterior functionalization.

All in all, in several cases rather the allenyl intermediate or the 2-propynyl educt than the 1-propynyl product was isolated — and the allenyl compound did polymerize in some cases.\textsuperscript{197} According to that, the conducted synthetic attempts failed.

7.5.2. Dehydrohalogenation Reactions

7.5.2.1. Introduction, Overview and Syntheses

7-Ethynyl-theophyllin (136) was prepared by converting the ethenyl-moiety (vinyl-moiety) at N-1 of the imidazole system of compound 134 into the 1,2-dibromo-adduct 135 (Figure 7-44). Subsequent twofold dehydrobromination with potassium tert-butyllate then gave the desired product 136.\textsuperscript{198} The ethynyl moiety is here connected to the N-1-nitrogen of an imidazole system.

\textbf{Figure 7-44: Synthesis of 7-ethynyl-theophyllin (136) by base induced dehydrobromination}\textsuperscript{198}

Paley\textsuperscript{199} \textit{et al.} prepared 1-ethynyl-1H-pyrole from the corresponding 1-(1,2-dichloro-vinyl)-precursor with methyl lithium as a base in 90 \% yield. Okamoto\textsuperscript{200} \textit{et al.} synthesized 9-ethynyl-9H-carbazole in a similar way. They used NaNH\textsubscript{2} in liquid ammonia as a base, obtaining 31 \% of crude product.
Zemlicka\textsuperscript{201} \textit{et al.} reported a synthesis of ynamines derived from nucleic acid bases (see Figure 7-45): Various nucleic bases \textsuperscript{137} were converted into the corresponding sodium salts \textsuperscript{138}, which then were ethylenated with tetrachloroethylene (\textsuperscript{139}) to give trichlorocynamines \textsuperscript{140}. The latter ones were finally converted into the ynamines \textsuperscript{141} with butyllithium. Also the enamines \textsuperscript{142} were formed.

\begin{equation}
\begin{array}{c}
R-H \\ 137
\end{array}
\xrightarrow{\text{NaH}}
\begin{array}{c}
R^- Na^+ \\ 138
\end{array}
\xrightarrow{\text{Cl}_2C=CCl_2}
\begin{array}{c}
\text{Cl} \quad 139 \\ \text{NaCl}
\end{array}
\xrightarrow{\text{BuLi}}
\begin{array}{c}
R-C≡C-H \\ 141
\end{array} +
\begin{array}{c}
R-C≡C-Cl \\ 142
\end{array}
\end{equation}

Figure 7-45: Principle of the synthesis of \textit{N}-1-ethynylated nucleic bases by base induced dehydrochlorination (R = \textit{N}-1-nucleo base)\textsuperscript{201}

In this manner, the purine base derivatives 1-ethyl-9\textit{H}-adenine and 2-amino-1-ethyl-9\textit{H}-adenine as well as the pyrimidine base derivatives 1-ethyl-1\textit{H}-thymine and 1-ethyl-1\textit{H}-cytosine could be obtained, at the best, in yields of about 50\%.

\subsection*{7.5.2.2. Conclusion}

A drawback of the dehydrohalogenation reactions is that an ethynyl moiety with a terminal proton is formed. These molecules tend to be reactive and unstable (like the prepared 1-ethyl-1\textit{H}-benzimidazole (\textsuperscript{81}), which is described above). Instead of a terminal proton, stabilizing groups like phenyl or trimethylsilyl would be preferred. And, what is more, various dehydrohalogenations carried out in this group were not successful.\textsuperscript{202}

\subsection*{7.5.3. Reaction of 1-Chloro-alkynes with Imines}

\subsection*{7.5.3.1. Overview and Conclusion}

Himbert\textsuperscript{203} \textit{et al.} used nucleophilic imines of the type H\textendash N\equiv CR\textsubscript{2} and reacted them with 1-chloro-alkynes, R\textendash C\equiv C\textendash Cl. The chlorine atom attached to the \textit{sp}-carbon was substituted in the course
of this reaction to give an $N$-alkynylated imine of the type $R-\mathrm{C}≡\mathrm{C}=\mathrm{N}=\mathrm{CR}_2$. They also used a TMS-protected imine of the type $\text{TMS-}\mathrm{N}=\mathrm{CR}_2$ to obtain the same product. However, the imidazoles and benzimidazoles used in this work were thought not to be nucleophilic enough compared to imines.

7.5.4. Flash Pyrolysis Reactions

7.5.4.1. Overview and Conclusion

1-Ethynyl-$1\text{H}$-pyrazole was prepared in a flash pyrolysis reaction from 1-pyrazole-1-yl-propyn-one. The product was obtained in low yield and as an impure mixture — making this reaction not of preparative significance.
7.6. Building up the Ethynyl Moiety at Position C-2 of Benzimidazole Systems — Condensation Approaches

7.6.1. General Introduction and Overview

It has been shown in a previous chapter that the more difficult synthetic problem – the attachment of an ethynyl moiety at position \( N-1 \) of imidazole and benzimidazole derivatives – could be solved.

However, the coupling approaches showed that the simultaneous attachment of alkynyl moieties at position C-2 and \( N-1 \) was not possible. Only little amounts (yield: 6 %) of 2-phenylethynyl-\( 1H \)-benzimidazole (109) could be obtained as a side product.

Hence it followed that the proximate challenge was to find a synthesis for benzimidazole systems bearing an ethynyl moiety at position C-2.

In general, imidazole and benzimidazole systems can be built up in manifold ways. \(^{206, 207}\)

7.6.2. Synthesis of Benzimidazole Derivatives from 2-Nitro-anilines

7.6.2.1. Overview and Conclusion

An interesting reaction is the preparation of C-2-substituted benzimidazole derivatives from \( N \)-alkyl-2-nitro-anilines. \(^{208, 209, 210, 211}\) Under basic conditions, these anilines undergo a condensation reaction to form \( 1H \)-benzimidazole-3-oxides, which are in a tautomeric equilibrium with their corresponding \( 1 \)-hydroxy-benzimidazoles (benzimidazol-1-oles).

Popov\(^ {208}\) et al. prepared 2-vinyl-\( 1H \)-benzimidazole-3-oxide (144) and 2-vinyl-benzimidazol-1-ol (145) (2-ethenyl-1-hydroxy-benzimidazole) from \( N \)-allyl-2-nitro-aniline (143) (allyl-(2-nitrophenyl)-amine) with the aid of sodium ethanolate in ethanol (Figure 7-46).
However, the involvement of a triple bond instead of a double bond (like in Figure 7-46) would lead to side reactions in the synthesis.

Other reactions require the reduction of the nitro group with the aid of hydrogen and a platinum or palladium catalyst (e.g.,\textsuperscript{212,213}). The drawback is here that a triple bond would also be reduced. Therefore, also a synthesis starting from 1-isocyanato-2-nitro-benzene (146) would not be appropriate (Figure 7-47). Isocyanate 146 could be reacted with a lithium acetylide 147 to give amide 148,\textsuperscript{214} which then – after reduction of the nitro group – could be converted into benzimidazole 149.

**Figure 7-47:** A possible strategy for the synthesis of a C-2-substituted benzimidazole starting from 1-isocyanato-2-nitro-benzene (146)

### 7.6.3. Synthesis of C-2-Ethynyl-Substituted Benzimidazole Derivatives

#### 7.6.3.1. Overview and Conclusion

Is it possible to build up a benzimidazole system carrying an alkynyl moiety at position C-2 in a few steps?

2-Phenylethynyl-1H-benzimidazole (109) was prepared in base catalyzed dehydrohalogenation reactions from 2-halogenostyryl-1H-benzimidazoles.\textsuperscript{215} Pfleiderer\textsuperscript{216} et al. synthesized 8-ethynyl-
theophylline (152) from 150 in a multi-step reaction via nitroso-uracil derivative 151 (Figure 7-48).

![Chemical structures](image)

Figure 7-48: Synthesis of 8-ethynyltheophylline (152) by Pfleiderer

The group of Popov et al. synthesized various C-2-alkynyl-substituted imidazoles and benzimidazoles and employed these in further reactions. parts of their work are patented.

One of their syntheses started from the 2-formyl-benzimidazole derivative 153 (Figure 7-49). With the aid of phosphorane 154, carbaldehyde 153 could be converted into acrylic acid ester 155 in a Wittig reaction. Base catalyzed dehydrohalogenation and ester cleavage led to propiolic acid derivative 156, which was decarboxylated to give the N-protected 2-ethynyl-benzimidazole 157.
However, there are several drawbacks concerning the above-described synthetic sequence: Popov\textsuperscript{217, 219} et al. reported carbaldehyde 153 to polymerize and found product mixtures or low yields upon decarboxylation. The numerous steps of their synthesis sequence and the requirement of a protecting group in position N-1 are also disadvantageous (the reported protecting groups, methyl and phenyl, are relatively difficult to cleave).

### 7.6.4. Synthesis of Imidazole and Benzimidazole Derivatives from $\alpha,\alpha'$-Diketones with Formamide

#### 7.6.4.1. General Introduction and Overview

Bredereck\textsuperscript{230} et al. synthesized various imidazoles (like 160) starting from $\alpha,\alpha'$-diketones ($\alpha$-diketones) like benzil (158) and an aldehyde (Figure 7-50).
They used reflux conditions and formamide (159) as a solvent. At a reaction temperature of 180 – 200 °C, amide 159 transforms into ammonia and carbon monoxide (Figure 7-51).

\[
\text{H} = \text{NH} \quad \text{159} \quad \xrightarrow{180 - 200 ^\circ C} \quad \text{NH}_3 + \text{CO}
\]

Figure 7-51: Formamide as an ammonia donor

The ammonia then delivers the nitrogen for the products.

### 7.6.4.2. 2-Phenylethynyl-1H-phenanthro[9,10-d]imidazole (163) — Attempted Synthesis

#### 7.6.4.2.1. Introduction and Overview

Here it was tested whether imidazole derivative 163 could be synthesized by the method of Bredereck et al. using formamide (159). A condensation reaction of this type involving phenylpropargyl aldehyde was not known.

#### 7.6.4.2.2. Description of Synthesis

Upon refluxing 9,10-phenanthrenequinone (161) with phenylpropargyl aldehyde (162) in formamide (159), only decomposition products and educt could be obtained (Figure 7-52).

Figure 7-52: Attempted synthesis of phenylethynyl-imidazole 163 with formamide as an ammonia donor
7.6.4.2.3. Conclusion and Product Analysis

Bredereck et al. reported difficulties when using phenanthrenequinone 161. They supposed that the dicarbonyl compound converted into an enediol, which does not continue with the conversion into the imidazole product.

7.6.4.3. 4,5-Diphenyl-2-phenylethynyl-1H-imidazole (164) — Attempted Synthesis

7.6.4.3.1. Introduction and Overview

As Bredereck et al. reported no problems when they used benzil (158) instead of phenanthrenequinone 161, the same conditions as described above were employed with 158 as dicarbonyl compound.

7.6.4.3.2. Description of Synthesis

Benzil (158) was refluxed with phenylpropargyl aldehyde (162) in formamide (159) (Figure 7-53). However, only decomposition products and educt could be obtained.

Figure 7-53: Attempted synthesis of phenylethynyl-imidazole 164 with formamide as an ammonia donor

7.6.4.3.3. Conclusion and Product Analysis

A possible reason could be that the conditions were too rough for the use of propargyl aldehyde 162. A reaction temperature of ca. 200 °C could have led to side reactions.
7.6.5. Synthesis of Imidazole and Benzimidazole Derivatives from \( \alpha,\alpha' \)-Diketones with Ammonium Acetate

7.6.5.1. General Introduction and Overview

Various simple imidazoles\(^\text{231, 232, 233} \) as well as phenanthroimidazoles\(^\text{234} \) and imidazoles derived from benzil\(^\text{235} \) were prepared from aldehydes with the aid of ammonium acetate, \( \text{NH}_4\text{OAc} \). When heated with acetic acid, \( \text{NH}_4\text{OAc} \) delivers \( \text{NH}_3 \) (Figure 7-54). The advantage of the ammonium salt over formamide is that lower temperatures (100 °C) are required in order to generate ammonia.

![Figure 7-54: Ammonium acetate as an ammonia donor](image)

7.6.5.2. 2-Phenylethynyl-1\(H\)-phenanthro[9,10-d]imidazole (163) — Attempted Synthesis

7.6.5.2.1. Introduction and Overview

The method for the preparation of imidazole derivative 163 followed the procedure used by Kesler\(^\text{234} \). A condensation reaction of this type involving phenylpropargyl aldehyde was not known.

7.6.5.2.2. Description of Synthesis

Upon refluxing a solution of 9,10-phenanthrenequinone (161) and phenylpropargyl aldehyde (162) in acetic acid with ammonium acetate, only decomposition products could be found (Figure 7-55).
7.6.5.2.3. Conclusion and Product Analysis

The approach was not the appropriate way to obtain the product, however, benzil (158) was also tried as an α-diketone.

7.6.5.3. 4,5-Diphenyl-2-phenylethynyl-1H-imidazole (164) — Attempted Synthesis

7.6.5.3.1. Introduction and Synthesis

For benzil (158) as an educt, the same reaction conditions were used as described above (Figure 7-56). No product, but only decomposition products were obtained.

7.6.5.3.2. Conclusion and Product Analysis

The reaction conditions used for the condensation reactions were relatively rough. Especially the temperature was presumably too high with respect to propargyl aldehyde 162.
7.6.6. Synthesis of 2-Phenylethynyl-Benzimidazole Derivatives from a 1,2-Diamine and an Aldehyde

7.6.6.1. General Introduction and Overview

In order to obtain benzimidazoles that are substituted in position C-2, aldehydes can be reacted with \( o \)-phenylenediamines.\(^{236} \) Depending on the conditions used, different products can be obtained (Figure 7-57).\(^{237} \)

\[
\begin{align*}
\text{(a)} & \quad \begin{array}{c}
\text{NH}_2 \\
\text{NH}_2 \\
\end{array} + 2 \text{R-CHO} \rightarrow \begin{array}{c}
\text{N} = \text{CHR} \\
\text{N} = \text{CHR} \\
\end{array} - 2 \text{H}_2\text{O} \rightarrow \begin{array}{c}
\text{N} = \text{CHR} \\
\text{CH}_2\text{R} \\
\end{array} \\
\text{(b)} & \quad \begin{array}{c}
\text{NH}_2 \\
\text{NH}_2 \\
\end{array} + 2 \text{R-CHO} \rightarrow \begin{array}{c}
\text{N} = \text{H} \\
\text{N} = \text{H} \\
\end{array} + \text{R-CHO} \rightarrow \begin{array}{c}
\text{N} = \text{H} \\
\text{R} \\
\end{array} + \text{R-CH}_2\text{OH}
\end{align*}
\]

Figure 7-57: Different products upon the reaction of \( o \)-phenylenediamine (165) with aldehydes.\(^{237} \)

First, upon loss of two equivalents of water, \( o \)-phenylenediamine (165) can react with two equivalents of an aldehyde (R-CHO, R = alkyl) to yield the Schiff's base 166 (Figure 7-57, path (a)). Upon migration of one hydrogen atom, diimine 166 then rearranges to the \( N \)-alkylated benzimidazole 167.

Secondly, also compound 168 can be formed, which is then oxidized to benzimidazole 169 in the course of the reaction (Figure 7-57, path (b)). The aldehyde is reduced to the corresponding alcohol.
7.6.6.2. 2-Phenylethynyl-1H-benzimidazole (109)

7.6.6.2.1. Introduction and Overview

Thiele et al. described a simple reaction following reaction path (a) in Figure 7-57. But which products would be obtained if phenylpropargyl aldehyde (162) would be used as an aldehyde? As a test reaction, a recipe given by Müller et al. was employed.

7.6.6.2.2. Description of Synthesis

Müller et al. obtained diyne 170 in a yield of 81% by refluxing o-phenylenediamine (165) and phenylpropargyl aldehyde (162) with formic acid in toluene (Figure 7-58, upper sequence).

Repeating this procedure, a mixture of products was obtained.

7.6.6.2.3. Conclusion and Product Analysis

After column chromatography, the mixture was analyzed by GC/MS spectrometry. It turned out that not only the diyne 170, but also the interesting 2-phenylethynyl-1H-benzimidazole (109) had been formed in small amount (Figure 7-58, below).

How could the yield of compound 109 be increased?
7.6.7. **Synthesis of 2-Phenylethynyl-Benzimidazole Derivatives**

**from a 1,2-Diamine and an Aldehyde with Copper(II) Acetate**

7.6.7.1. **2-Phenylethynyl-1H-benzimidazole (109)**

7.6.7.1.1. **Introduction and Overview**

A closer look at the stoichiometry of the reaction of diamine 165 with an aldehyde shows that not only one molecule of water is lost (condensation step), but that also an oxidation is involved. Hence, the addition of an oxidizing agent should lead to a higher yield of the C-2-substituted benzimidazole.

Weidenhagen\(^\text{237}\) oxidized cyclic \(\alpha\)-diamines with aldehydes in water or ethanol with the aid of copper(II) salts like \(\text{Cu}^{II}(\text{OAc})_2\) (Figure 7-59). Upon oxidation, formally two hydrogen atoms are abstracted, whereby copper(II) is reduced to copper(I) (see also\(^\text{240}\)).

\[
\text{R-CHO} + \text{Cu}^{II}(\text{OAc})_2 \\
\rightarrow \text{H}_2\text{O} - \text{2 HOAc} - [\text{Cu}^I]
\]

Figure 7-59: Synthesis of C-2-substituted benzimidazoles from aldehydes with a copper(II) salt\(^\text{237, 240}\)

7.6.7.1.2. **Description of Synthesis**

A synthesis involving phenylpropargyl aldehyde (162) was not known, so that modified recipes from Weidenhagen\(^\text{237, 241, 242}\) and others\(^\text{243, 244}\) were used.

In a typical procedure, \(\alpha\)-phenylenediamine (165) was dissolved in ethanol (or water), followed by addition of copper(II) acetate and phenylpropargyl aldehyde (162). After heating, the precipitated benzimidazole-copper(I) salt 171 was filtered and the product 109 then released with the aid of hydrogen sulfide, \(\text{H}_2\text{S}\) (Figure 7-60).
7.6.7.1.3. Conclusion and Product Analysis

The crude product was purified by column chromatography and analyzed by GC/MS spectrometry. Unfortunately, 109 was obtained in relatively low yield (4%). An explanation could be that phenylpropargyl aldehyde (162) is a relatively instable compound: Decomposition could be seen already on a silica TLC plate. Another drawback of this synthesis was also that it was quite uncomfortable to work with hydrogen sulfide.

7.7. Synthesis of 2-Phenylethynyl-Benzimidazole Derivatives — The Final Route

7.7.1. General Introduction and Overview

The previously described and conducted synthetic approaches displayed several downsides, such as numerous reaction steps, low yields or the demand for a protecting group in position N-1.

Unangst and Southwick reported a great way on the preparation of a 2-phenylethynyl-benzimidazole (Figure 7-61): They started from o-chloro-phenylpropionic acid (172) and converted it in two steps into the corresponding amide 173. The latter one was then transformed into imidate
salt 174. Upon a condensation reaction with o-phenylenediamine (165) and elimination of ethanol and ammonium tetrafluoroborate, benzimidazole 176 was formed. They supposed the reaction to proceed via intermediate 175.\textsuperscript{245}

In this work, in order to synthesize a C-2-alkynyl-substituted benzimidazole, the basic procedure given by Unangst\textsuperscript{245} et al. was employed. Apart from several modifications concerning the preparation itself, instead of the chlorinated 172, the parent compound phenylpropionic acid (177) was used. As diamines, o-phenylenediamine (165) as well as its perfluorinated analogue 91 were used (Figure 7-62).
The procedure displayed in Figure 7-62 does not only lack the disadvantages of the syntheses described above — a great advantage is also that the educts allow a manifold substitution pattern. Both the phenyl ring of the phenylpropiolic acid and the o-phenylenediamine can be modified in order to change the substitution pattern and the reactivity — both of the 2-phenylethynyl-benzimidazole and the subsequently prepared corresponding azaenediynes.

**7.7.2. Preparation of the Imidate Salt 180 — A NOVEL COMPOUND**

**7.7.2.1. Introduction and Overview**

The synthesis of imidate salt 180 followed in the main the procedure for the synthesis of the analogous chloro-imidate salt 174, which was described by Unangst\(^ {245} \) and Southwick. Good yields were obtained, and the novel compound 180 was characterized.

**7.7.2.2. Description of Synthesis**

Correspondingly, phenylpropiolic acid (177) was converted into phenylpropiolic acid chloride (178) by refluxing in benzene with thionyl chloride (Figure 7-63). Acid chloride 178 was then
transformed into phenylpropionic acid amide (179) by reaction with a concentrated aqueous solution of ammonia. The amide 179 could be obtained in a yield of 76 % after recrystallization (Unangst et al. reported a yield of 82 % for the analogous 173).

Carboxylic acid amide 179 was afterwards activated with the aid of Meerwein's reagent, Et₃O⁺BF₄⁻, by refluxing in dichloromethane (Figure 7-63). A yield of 82 % was obtained for 180 (Unangst et al. reported 77 % for the analogous 174).

![Figure 7-63: Synthesis of the novel imidate tetrafluoroborate 180](image)

**7.7.2.3. Conclusion and Product Analysis**

The novel imidate salt 180 could be synthesized in good yield. After recrystallization from dichloromethane, the colorless crystals of 180 were analyzed by UV/Vis and IR spectroscopy (the stretching vibration of the acetylenic bond was found at $\bar{v} = 2233 \text{ cm}^{-1}$). The elementary analysis and the HiRes-ESI-MS were in perfect agreement with the calculated values. The cation mass and a cluster cation (consisting of two cations and the tetrafluoroborate anion) could also be seen in the ESI-MS spectrum.
7.7.3. Preparation of the Perfluorinated Diamine 91

7.7.3.1. Introduction and Overview

An electronically highly deactivated, aromatic diamine is the perfluorinated \( o \)-phenylenediamine 91. It is also a symmetrical molecule and therefore a good precursor for a 2-phenylethynyl-benzimidazole. As a starting material for the synthesis of 91, the purchasable pentafluoro-nitrobenzene (184) was used. The latter one could be submitted to amination and subsequent reduction of the nitro group.

Seko\(^{246,247}\) et al. (see also\(^{248}\)) synthesized various \( o \)-nitro-aniline derivatives in nucleophilic aromatic substitution reactions. For example, \( o \)-nitro-aniline (182) was prepared from nitrobenzene (90) with \( O \)-methyl-hydroxylamine (181) (\( \text{H}_2\text{N}\text{-OMe} \)) as aminating agent and potassium tert-butylate as a base (Figure 7-64). Both \( o \)- (182) and \( p \)-nitro-aniline (183) were formed in a ratio of \( o:p = 65:35 \), in a total yield of 60%.

\[ \begin{align*}
\text{NO}_2 & \quad \text{H}_2\text{N-OMe} \quad 181 \\
\text{90} & \quad \text{tBuOK} \quad \text{DMF} \\
\text{NO}_2 & + \quad \text{NH}_2 \\
182 & \quad + \\
\text{NH}_2 & \quad 183
\end{align*} \]

Figure 7-64: Synthesis of \( o \)-nitro-aniline (182) by Seko\(^{246,247}\)

The preparation of perfluorinated \( o \)-phenylenediamine 91, however, was described by other groups: Selivanova\(^{249}\) et al. obtained a mixture of isomers by reacting pentafluoro-nitrobenzene (184) with liquid ammonia. This reaction gave the desired \( o \)-isomer only in low yield, though.

Brooke\(^{250}\) et al. treated pentafluoro-nitrobenzene (184) in diethyl ether with gaseous ammonia. They obtained an isomeric mixture, from which the desired \( o \)-isomer 185 could be isolated in a yield of 21% after recrystallization. Upon reduction with hydrogen over Raney nickel in ethanol, the perfluorinated diamine 91 was obtained in 66% yield.\(^{250,251}\)

Tanaka\(^{252}\) et al. reacted pentafluoro-nitrobenzene (184) with gaseous ammonia in benzene. The desired \( o \)-isomer 185 could be isolated in a yield of 48% from the isomeric mixture.

Heaton\(^{136}\) et al. used the most appropriate conditions in order to prepare compound 91: They aminated pentafluoro-nitrobenzene (184) with gaseous ammonia in diethyl ether, separated the mixture consisting of four isomers and obtained \( o \)-isomer 185 in a yield of 66%. Reduction of
the latter one with tin(II) chloride in acidic, protic medium resulted in tetrafluoro-diamine 91 in 64 % yield (Figure 7-65).

![Synthesis of perfluorinated diamine 91 by Heaton](image)

**Figure 7-65: Synthesis of perfluorinated diamine 91 by Heaton**

### 7.7.3.2. Description of Synthesis

The synthesis of diamine 91 followed basically the procedure reported by Heaton. Generally, good yields were obtained (in agreement with the literature).

The amination of pentafluoro-nitrobenzene (184) with the aid of ammonia gas was carried out in diethyl ether. The nucleophilic aromatic substitution reaction led to a mixture of four isomers (Figure 7-66), which could be separated by column chromatography. The first fraction contained the desired o-isomer 185, which was a low boiling, volatile solid. The p-isomer 186, a red solid, was found in the second fraction; and the third fraction contained both disubstituted isomers 187 and 188.
The perfluorinated o-nitro-aniline 185 was reduced with tin(II) chloride in concentrated hydrochloric acid and ethanol (Figure 7-66). Subsequent neutralization of the mixture yielded diamine 91.

7.7.3.3. Conclusion and Product Analysis

The overall yield of the reaction was good; precursor 185 could be obtained in 66 % yield and the desired perfluorinated diamine 91 in 67 % yield.
7.7.4. Synthesis of a Perfluorinated 2-Phenylethynyl-benzimidazole: 4,5,6,7-Tetrafluoro-2-phenylethynyl-1H-benzimidazole (191) — A NOVEL COMPOUND

7.7.4.1. Introduction and Overview

The preparation of the novel 2-alkynyl-benzimidazole 191 followed in the main the procedure described by Unangst\textsuperscript{245} and Southwick (see Figure 7-61) for an analogous system. They obtained a yield of 54% for the acetylenic benzimidazole 176.

7.7.4.2. Description of Synthesis

Two parallel synthetic pathways were combined at that point: The imidate tetrafluoroborate 180 was refluxed with the perfluorinated diamine 91 in dichloromethane (Figure 7-67). The desired product 191 was a novel compound and therefore fully characterized.

The reaction always led to a mixture of products; and after work-up and chromatography, the perfluorinated benzimidazole 191 was obtained in a relatively low yield of 21%. Several attempts in order to increase the yield were not successful. Therefore, a closer look at the reaction mechanism and the byproducts should be taken here (see mechanism in Figure 7-67):

An initial step should be the nucleophilic attack of a nitrogen of diamine 91 on the carbon of the imidate group of 180. The newly formed hemiaminal 189 now is capable of reacting in two ways:

First, the elimination of ammonia leads to the formation of imine 190. An analogous intermediate was also supposed by Unangst\textsuperscript{245} and Southwick (compare Figure 7-61). Compound 190 was isolated in 2% yield as a solid and only characterized by GC/MS analysis. Upon another attack of the remaining amino group of the diamine fragment on the carbon of the Schiff's base, elimination of ethanol takes place and benzimidazole 191 is formed. The yield of 21% of the slightly yellow solid suggests that another reaction channel competes with the formation of 191.

If ethanol is eliminated from hemiaminal 189, amidine 192 is formed. Protonation then leads to amidinium cation 193, and attack from the residual amino group of the diamine fragment on the electronically poor \textit{sp}-carbon leads — upon deprotonation — to enamine 194. The latter one can be transformed into its imine tautomer, the benzodiazepine 195. It is supposed that 195 is formed as a major byproduct in the course of the reaction. However, 195 was not isolated as it
transformed into compound 196 upon refluxing with methanol. The novel benzodiazepine 196 was isolated as a white solid in 16% yield.

Figure 7-67: Synthesis of the novel perfluorinated 2-alkynyl-benzimidazole 191 including the mechanism with intermediates and the novel benzodiazepine 196 as a byproduct.
7.4.3. Conclusion and Product Analysis

The novel 2-alkynyl-benzimidazole 191 was completely characterized. A GC/MS analysis showed the molecular ion peak $M^+$ at $m/z = 290$ (this was also the base peak) and a HiRes-MALDI analysis resulted in $m/z = 291$ for $M^+ + 1$ (H). In the IR spectrum, the stretching vibration of the acetylenic bond was found at $\tilde{\nu} = 2224$ cm$^{-1}$, and the acetylenic carbons appeared in the NMR spectrum as quaternary carbons at 92.5 ppm and 80.0 ppm. The elementary analysis was in perfect agreement with the calculated values, and the $pK_a$-value was determined to be $pK_a = 7.35$ by titration with aqueous sodium hydroxide solution. Protonation attempts in order to determine the basicity failed and led to decomposition.

![X-ray structure (ORTEP-3 diagram) of 191](image)

The X-ray analysis (Figure 7-68) showed a planar molecule. The angles at the C-2-carbon were ca. 120° ($<$ \text{N-1-C-2-C-8} = 120°, $<$ \text{N-3-C-2-C-8} = 126°). The bond length of the triple bond was found to be $d_{C-8-C-9} = 1.20$ Å.

Benzodiazepine 196 was also completely characterized as a novel compound. The GC/MS analysis showed the molecular peak $M^+$ at $m/z = 322$ (being also the base peak). A peak at $m/z = 291$ indicated the loss of the methoxy group and $m/z = 77$ indicated the phenyl cation. The HiRes-MALDI analysis resulted in $m/z = 323$ for $M^+ + 1$ (H).

The $^1$H-NMR spectrum showed a singlet for the methyl protons at 3.89 ppm and a non-resolved AB-system for the methylene group at 3.42 ppm. In the $^{13}$C-NMR spectrum, the quaternary carbons of the imine moiety appeared at 157.6 ppm and 156.9 ppm, while the methyl carbon was found at 56.0 ppm and the secondary methylene carbon at 36.6 ppm. IR analysis, elementary
analysis and X-ray analysis (Figure 7-69) gave further evidence for the structure of diazepine 196.

![X-ray structure (ORTEP-3 diagram) of 196](image)

The X-ray analysis (Figure 7-69) showed that the 7-membered ring of diazepine 196 was not planar: Both N-atoms were found to be localized below the plane of the benzene ring, as well as the phenyl ring and the methoxy group. The methylene group was localized above that plane.

7.7.5. Synthesis of 2-Phenylethynyl-1H-benzimidazole (109)

7.7.5.1. Introduction and Overview

After having explored a synthetic route for the perfluorinated benzimidazole 191, the non-fluorinated 2-alkynyl-benzimidazole 109 was prepared correspondingly (compare the work of Unangst and Southwick and Figure 7-62).

7.7.5.2. Description of Synthesis

Instead of tetrafluoro-\(\sigma\)-phenylenediamine 91, its non-fluorinated analogue 165 was reacted with imidate tetrafluoroborate 180 in refluxing dichloromethane (Figure 7-70).
7. Syntheses of Azaenediynes

The desired product 109 could be obtained in 37 % yield, while its perfluorinated analogue 191 was obtained in only 21 % yield. However, also the additional formation of a byproduct was observed: Compound 197 was isolated in a yield of 20 %. Its formation could be explained with the reaction mechanism shown in Figure 7-67 (see there for further details), which suggests that 197 is the analogous intermediate as 190 (although 190 was obtained in only 2 % yield).

7.7.5.3. Conclusion and Product Analysis

The preparation of benzimidazole 109 via o-phenylenediamine (165) and imidate salt 180 gave a higher yield (37 %) than the previously tried approaches for 109.

2-Alkynyl-benzimidazole 109 was characterized by GC/MS and NMR analysis. The molecular ion peak $M^+$ was found at $m/z = 218$, which was also the base peak. In the NMR spectrum, the acetylenic carbons appeared as quaternary carbons at 91.8 ppm and 80.9 ppm.

Compound 197 showed the molecular ion peak $M^+$ at $m/z = 264$ (being also the base peak); the phenyl cation was found at $m/z = 77$ with an intensity of 49 %.
7.8. Attaching Alkynyl Moieties at Position N-1: Building up Azaenediynes

7.8.1. Synthesis of a Perfluorinated Azaenediyne: 4,5,6,7-Tetrafluoro-2-phenylethynyl-1-trimethylsilylethynyl-1\textit{H}-benzimidazole (198) — A NOVEL COMPOUND

7.8.1.1. Introduction and Overview

As a precursor for azaenediyne 198, the electronically poor tetrafluoro-2-phenylethynyl-benzimidazole 191 was employed. The fluorine atoms were expected to make the target molecule stable in air and water. The conditions for the preparation of the novel perfluorinated azaenediyne 198 were already explored in the previous syntheses.

7.8.1.2. Description of Synthesis

Under exclusion of moisture and air, benzimidazole 191 was suspended in toluene, the concentration not exceeding $c \approx 10^{-2} \text{ mol l}^{-1}$. To achieve deprotonation, LDA was added slowly in the cold. Alkynylation was carried out by adding trimethylsilylethynyl(phenyl)-iodonium tetrafluoroborate (69) (Figure 7-71). The reaction was complete after stirring for 5 h at rt.

![Figure 7-71: Synthesis of perfluorinated azaenediyne 198 from tetrafluoro-benzimidazole 191](image)

After work-up and flash column chromatography, the desired product was obtained as a white solid in a yield of 53 %. Diffusion-controlled crystallization yielded fine, long, colorless and transparent needles. Azaenediyne 198 was a novel compound and therefore fully characterized.
7.8.1.3. Conclusion and Product Analysis

A GC/MS analysis showed the molecular ion peak $M^+$ at $m/z = 386$ (this was also the base peak). A peak at $m/z = 371$ (28\% intensity) indicated the loss of a methyl group ($\Delta m/z = -15$), which is characteristic for compounds carrying a TMS-group.\(^1\) The peaks corresponding to the phenyl cation and the TMS cation could be found at $m/z = 77$ and $m/z = 73$, respectively. The HiRes-MALDI analysis resulted in $m/z = 387$ for $M^+ + 1$ (H).

In the IR spectrum, the stretching vibrations of the acetylenic bonds were found at $\tilde{\nu} = 2232$ cm$^{-1}$ and $\tilde{\nu} = 2198$ cm$^{-1}$. The vibrations of the aromatic and the aliphatic C–H-bonds could also be seen.

In the $^{13}$C-NMR spectrum, several carbons appeared as multiplets due to the $^{13}$C–$^{19}$F couplings. The acetylenic carbons appeared as quaternary carbons: Concerning the phenylethynyl moiety, C-8 was found at 76.9 ppm and C-9 at 87.1 ppm (see Figure 7-72).

![Figure 7-72: 125 MHz-$^{13}$C-NMR spectrum of 198 in CD$_2$Cl$_2$, including an exploded view showing the resonance frequencies and the splitting of the acetylenic carbons](image)

Interestingly, the acetylenic carbons of the trimethylsilylethynyl moiety appeared as multiplets: C-16 (connected to nitrogen) appeared at 98.0 ppm as a doublet because of the coupling to fluorine; the coupling constant being $^4J_{C-1} = 0.7$ Hz. C-17 (adjacent to silicon) appeared at
80.4 ppm and clearly showed the presence of the Si-satellites ($^1J_{C-Si} = 40.0\ Hz$). A $^1$H- and a $^{19}$F-NMR spectrum gave further evidence of the structure.

The elementary analysis and the HiRes-MALDI analysis were in perfect agreement with the calculated values.

![Figure 7-73: X-ray structure (ORTEP-3 diagram) of 198](image)

The X-ray analysis (Figure 7-73) showed a planar molecule. The angles at the N-1-nitrogen and the C-2-carbon were larger than 120° ($<C_{7a}-N_{1}-C_{16} = 128\ ^\circ$, $<C_{2}-N_{1}-C_{16} = 125\ ^\circ$, $<N_{1}-C_{2}-C_{8} = 121\ ^\circ$, $<N_{3}-C_{2}-C_{8} = 126\ ^\circ$). The bond length of the triple bonds was found to be $d_{C_{8}-C_{9}} = 1.19\ \text{Å}$ and $d_{C_{16}-C_{17}} = 1.17\ \text{Å}$. The distances between the $sp$-carbons relevant for Bergman cyclization were $d_{C_{8}-C_{16}} = 2.92\ \text{Å}$ and $d_{C_{9}-C_{17}} = 4.15\ \text{Å}$, respectively.

Azaenediyne 198 was found to be unexpectedly stable. It could be stored on the air and was not hydrolyzed in water.
7.8.2. Synthesis of the Non-Fluorinated Azaenediyne 2-Phenylethynyl-1-trimethylsilylethynyl-1H-benzimidazole (199) — A NOVEL COMPOUND

7.8.2.1. Introduction and Overview

Azaenediyne 199 was prepared according to its perfluorinated analogue 198. As a precursor, 2-phenylethynyl-1H-benzimidazole (109) was employed. It was interesting to explore the properties of the non-fluorinated azaenediyne 199 and whether it showed a different reactivity compared to 198.

7.8.2.2. Description of Synthesis

Benzimidazole 109 was suspended in toluene under exclusion of moisture and air. After deprotonation with LDA, alkynylation was carried out by adding trimethylsilylethynyl(phenyl)-iodonium tetrafluoroborate (69) (Figure 7-74). The reaction was complete after stirring for 3 h at rt.

![Figure 7-74: Synthesis of the non-fluorinated azaenediyne 199 from benzimidazole 109](image)

After work-up and flash column chromatography, the desired product was obtained as a viscous yellow oil in a yield of 50%. The oil solidified in a vacuum to give a wax (melting point: 49 – 50 °C), but no crystals could be obtained. Azaenediyne 199 was a novel compound and therefore fully characterized.
7.8.2.3. Conclusion and Product Analysis

A GC/MS analysis showed the molecular ion peak $M^+$ at $m/z = 314$ (this was also the base peak). A peak at $m/z = 299$ (49 % intensity) indicated the loss of a methyl group ($\Delta m/z = -15$), which is characteristic for compounds carrying a TMS-group. The peaks corresponding to the phenyl cation and the TMS cation could be found at $m/z = 77$ and $m/z = 73$, respectively. The HiRes-MALDI analysis resulted in $m/z = 315$ for $M^+ + 1$ (H).

In the IR spectrum, the stretching vibrations of the acetylenic bonds were found at $\tilde{\nu} = 2228$ cm$^{-1}$ and $\tilde{\nu} = 2191$ cm$^{-1}$. The vibrations of the aromatic and the aliphatic C–H-bonds could also be seen.

The $^{13}$C-NMR spectrum showed the acetylenic carbons appearing as quaternary carbons: Concerning the phenylethynyl moiety, C-8 was found at 78.5 ppm and C-9 at 88.3 ppm (see Figure 7-75). The acetylenic carbons of the trimethylsilylethynyl moiety appeared at 96.1 ppm (C-16, adjacent to nitrogen) and at 79.6 ppm (C-17, adjacent to silicon). The latter one showed the presence of the Si-satellites.

![Figure 7-75: 100 MHz-$^{13}$C-NMR spectrum of 199 in CD$_2$Cl$_2$, including an exploded view showing the resonance frequencies and the splitting of the acetylenic carbons](image-url)
The elementary analysis and the HiRes-MALDI analysis were in perfect agreement with the calculated values.

The non-fluorinated azaenediyne 199 was found to be less stable than its perfluorinated analogue 198. It turned from light yellow to dark yellow while standing at the air.
7.9. *N*-Protonation of Azaenediyne — Attempts to Build up a More Reactive System for the Bergman Cyclization

7.9.1. The 4,5,6,7-Tetrafluoro-2-phenylethynyl-1-trimethylsilylthynyl-
1H-benzimidazol-3-iium Salts 200, 201 and 202 —
Attempted *N*-Protonations of Perfluorinated Azaenediyne 198

7.9.1.1. Introduction and Overview

In order to convert the perfluorinated azaenediyne 198 into a more reactive system concerning the Bergman cyclization, the *N*-3-nitrogen could be protonated. Various protonation reactions were carried out.

7.9.1.2. Description of Synthesis

Under exclusion of moisture and air, azaenediyne 198 was dissolved in diethyl ether or dichloromethane. As protonating agents, trifluoromethanesulfonic acid, trifluoroacetic acid and hydrochloric acid were employed (in the latter case, inert conditions were unnecessary) (Figure 7-76).

![Figure 7-76: Protonation attempts of perfluorinated azaenediyne 198 with trifluoromethanesulfonic acid, trifluoroacetic acid and hydrochloric acid](image)

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200, 201, 202: Referenced in the text.
The acids were added in equimolar amounts or in a tenfold excess. All reactions were also carried out with and without 2-fluoropyridine as a buffer, and conducted at rt or at 0 °C, respectively.

7.9.1.3. Conclusion and Product Analysis

The reactions were all monitored by ESI-MS. Although a product peak at $m/z = 387 [M^+ (cation)]$ could be detected, mainly decomposition products were found. The isolation of a protonated product failed.

It is assumed that azaenediynne 198 is protonated at the N-3-nitrogen first. However, the subsequent attack of a nucleophile on a triple bond would lead to successional species and finally to decomposition (compare Figure 8-4).
7.9.2. The 2-Phenylethynyl-1-trimethylsilylethynyl-1H-benzimidazol-3-i um Salts 203, 204 and 205 — Attempted N-Protonations of Non-Fluorinated Azaenediyne 199

7.9.2.1. Introduction and Overview

Correspondingly to its perfluorinated analogue 198, also the non-fluorinated azaenediyne 199 was employed in protonation reactions. Various conditions were tested in order to protonate the N-3-nitrogen.

7.9.2.2. Description of Synthesis

The synthesis conditions followed the ones described for azaenediyne 198. Compound 199 was dissolved in diethyl ether or dichloromethane and reacted with trifluoromethanesulfonic acid, trifluoroacetic acid and hydrochloric acid as protonating agents in equimolar amounts or in a tenfold excess (Figure 7-77).

![Figure 7-77: Protonation attempts of non-fluorinated azaenediyne 199 with trifluoromethanesulfonic acid, trifluoroacetic acid and hydrochloric acid](image)

All reactions were conducted at rt or at 0 °C and with or without 2-fluoropyridine as a buffer, respectively.
7.9.2.3. Conclusion and Product Analysis

All reactions were monitored by ESI-MS. Although a product peak at \( m/z = 315 \ [M^+ \text{ (cation)}] \) could be detected, mainly decomposition products were found. The isolation of a protonated product failed.

Azaenediyne 199 is supposed to be protonated at the N-3-nitrogen first — like its perfluorinated analogue 198. The subsequent attack of a nucleophile on a triple bond would lead to successional species, however, and finally to decomposition of the material (compare Figure 8-4).
7.10. *N*-Methylation of Azaenediynes — Ways of Building up a More Reactive System for the Bergman Cyclization

7.10.1. 4,5,6,7-Tetrafluoro-3-methyl-2-phenylethynyl-1-trimethylsilyl-ethynyl-1*H*-benzimidazol-3-ium Tetrafluoroborate (206) — A NOVEL COMPOUND

7.10.1.1. Introduction and Overview

Attempts in order to protonate perfluorinated azaenediyne 198 and the non-fluorinated azaenediyne 199 failed. Methylation, however, should result in the same effect in order to create a more reactive system for the Bergman cyclization. Furthermore, methylation was expected only to take place at the nitrogen, thus not affecting the triple bonds.

*N*-Methylation reactions can be conducted in several ways: Isbell and Seeman *et al.* investigated methylations of pyridine derivatives with methyl iodide and with trimethyloxonium tetrafluoroborate.\[^{253,254}\] Dimethylsulphate was also used in the methylation of benzimidazole derivatives (e.g.\[^{255}\]). Reichardt\[^{256}\] *et al.* successfully employed trimethyloxonium tetrafluoroborate and triethylxonium tetrafluoroborate in alkylation reactions of benzimidazoles.

7.10.1.2. Description of Synthesis

The reaction of azaenediyne 198 with dimethylsulphate only gave traces of product, which were detected in the ESI-MS. Another attempt employing methyl iodide in acetonitrile led to a bad yield of 2%. The use of Meerwein’s salt trimethylxonium tetrafluoroborate (Me$_3$O$^+$ BF$_4^-$), however, gave the desired product in a yield of 75% as a white solid. The reaction was carried out in refluxing dichloromethane under exclusion of moisture and air (Figure 7-78).
conditions:

a) 1. $\text{H}_3\text{C}-\text{O-S-O-CH}_3$, 2. NaBF$_4$ (aq) \( \gamma = \text{traces} \)

b) 1. CH$_3$I / CH$_3$CN, 2. NaBF$_4$ (aq) \( \gamma = 2\% \)

c) Me$_3$O$^+$ BF$_4^-$ / CH$_2$Cl$_2$, reflux \( \gamma = 75\% \)

Figure 7-78: Synthetic approaches toward the methylated, perfluorinated azaenediyne 206 with dimethylsulfate, methyl iodide and trimethyloxonium tetrafluoroborate as methylation reagents

After crystallization, the desired product was obtained as colorless, transparent crystals. The methyl-azaenediyne 206 was a novel compound and therefore fully characterized.

7.10.1.3. Conclusion and Product Analysis

The HiRes-ESI analysis resulted in \( m/z = 401 \) for \( M^+ \) (cation). In the ESI-MS, apart from the cation mass (\( m/z = 401 \)), also the addition of water (\( m/z = 419 \) [\( M^+ \) (cation) + 18 (H$_2$O)]) and the loss of a methyl group could be seen (\( m/z = 387 \) [\( M^+ \) (cation) + 1 (H) - 15 (Me)]).

In the IR spectrum, the stretching vibrations of the acetylenic bonds were found at \( \tilde{\nu} = 2217 \text{ cm}^{-1} \). The vibrations of the aromatic and the aliphatic C–H-bonds could also be seen.

The $^{13}$C-NMR spectrum of 206 was quite similar to the one of the non-methylated parent compound 198 (see there). The carbon of the newly introduced methyl group appeared at 36.3 ppm as tertiary carbon. The $^1$H-NMR spectrum showed the protons of this new methyl group at 4.24 ppm as a singlet.

The elementary analysis and the HiRes-ESI analysis were in perfect agreement with the calculated values.
The X-ray analysis (Figure 7-79) showed a planar molecule. The angles at the N-1-nitrogen and the C-2-carbon were larger than 120° ($< C_{7a} - N_{1} - C_{16} = 128^\circ$, $< C_{2} - N_{1} - C_{16} = 124^\circ$; $< N_{1} - C_{2} - C_{8} = 125^\circ$, $< N_{3} - C_{2} - C_{8} = 126^\circ$). The bond length of the triple bonds was found to be $d_{C_{8} - C_{9}} = 1.19\,\text{Å}$ and $d_{C_{16} - C_{17}} = 1.19\,\text{Å}$. The distances between the $sp$-carbons relevant for Bergman cyclization were $d_{C_{8} - C_{16}} = 2.92\,\text{Å}$ and $d_{C_{9} - C_{17}} = 4.15\,\text{Å}$, respectively.

The methylated, perfluorinated azaenediyne 206 was found to be unstable in air and sensitive towards hydrolysis. An interesting reaction occurred upon dissolving compound 206 in methanol (see below in Chapter 7.10.2).
7.10.2. Formation of (E)-1-Ethynyl-4,5,6,7-tetrafluoro-2-(2-methoxy-2-phenyl-vinyl)-3-methyl-1H-benzimidazol-3-ium Tetrafluoroborate (207) — A NOVEL COMPOUND

7.10.2.1. Introduction and Overview

Upon spraying a freshly prepared solution of the methylated, perfluorinated azaenediyne 206 in methanol in the ESI-MS, the peak at m/z = 401 for M⁺ (cation) disappeared and a new peak at m/z = 361 appeared. This reaction took place within minutes in a syringe, and already at slight warming (at a temperature of 25 – 30 °C).

7.10.2.2. Description of Synthesis

In order to investigate the product and to achieve complete conversion, the reaction was repeated by heating a solution of methyl-azaenediyne 206 in methanol to 35 – 40 °C for ½ h (Figure 7-80).

![Figure 7-80: Conversion of the methylated, perfluorinated azaenediyne 206 in methanol into the novel compound 207](image)

After crystallization, the desired product was obtained as pale yellow, transparent crystals in a yield of 77 %. 207 was a novel compound and therefore fully characterized.

7.10.2.3. Conclusion and Product Analysis

Methanol attacked as a nucleophile at the acetylenic carbon adjacent to the phenyl group. Due to the positive charge at the nitrogen atom carrying the methyl group, that carbon is relatively
electrophilic — the situation is similar to the one of a 1,4-nucleophilic addition to a Michael system. Interestingly, only the (E)-isomer was isolated in this addition of methanol. Furthermore, methanol also induced the cleavage of the trimethylsilyl group under formation of an ethynyl group.

A HiRes-MALDI analysis resulted in \( m/z = 361 \) for \( M^+ \) (cation). The ESI-MS showed the cation mass at \( m/z = 361 \) and the anion mass at \( m/z = 87 \) (tetrafluoroborate anion). A daughter spectrum of \( m/z = 361 \) indicated loss of methyl (\( m/z = 346 \)) from the cation.

In the IR spectrum, the stretching vibration of the acetylenic triple bond was found at \( \tilde{\nu} = 2175 \text{ cm}^{-1} \), and the vibration of the acetylenic C–H-bond at \( \tilde{\nu} = 3311 \text{ cm}^{-1} \). The aromatic and the aliphatic C–H-bonds could also be seen.

The \(^1\)H-NMR spectrum showed the olefinic proton (H-8) at 6.19 ppm as a non-resolved multiplet (see Figure 7-81). The methyl protons of the methoxy group (H-18, H-18', H-18") appeared at 4.06 ppm as a badly resolved doublet, the coupling constant being \( \tilde{J}_{H-18-H-8} = 1.5 \text{ Hz} \). The protons of the N-methyl group (H-19, H-19', H-19") were found at 4.28 ppm as a singlet, and the acetylenic H (H-17) appeared at 2.83 ppm as a singlet.

![Figure 7-81: 300 MHz-\(^1\)H-NMR spectrum of 207 in [D\(_6\)]-acetone](image-url)
In the $^{13}$C-NMR spectrum, the olefinic carbon carrying the methoxy group (C-9) appeared at 175.8 ppm as quaternary carbon, and the other olefinic carbon (C-8) at 81.1 ppm as primary carbon. The acetylenic carbon (C-16) adjacent to nitrogen appeared as a quaternary carbon at 71.0 ppm, and the primary acetylenic carbon (C-17) at 59.6 ppm. Concerning the carbons from the methyl groups, these tertiary carbons were found at 51.0 ppm (C-18, methoxy group) and at 37.0 ppm (C-19, N-methyl group).

The $^{19}$F-NMR spectrum showed the presence of the tetrafluoroborate anion and the four fluorine atoms of the benzimidazole moiety.

The elementary analysis and the HiRes-MALDI analysis were in perfect agreement with the calculated values.

![Figure 7-82: X-ray structure (ORTEP-3 diagram) of 207 (anion omitted for clarity)](image)

The X-ray analysis (Figure 7-82) presented a molecule with a planar benzimidazole moiety. The angles at the $N$-1-nitrogen were larger than 120° ($<C_{7a}-N_{-1}-C_{16} = 126°$, $<C_{2}-N_{-1}-C_{16} = 125°$). The bond length of the triple bond was found to be $d_{C_{16}-C_{17}} = 1.18$ Å.
7.10.3. 3-Methyl-2-phenylethynyl-1-trimethylsilylethynyl-1H-benzimidazol-3-ium Tetrafluoroborate (208) — A NOVEL COMPOUND

7.10.3.1. Introduction and Overview

After the successful methylation of the perfluorinated azaenediyne 198, the non-fluorinated azaenediyne 199 was supposed to react under the same reaction conditions.

7.10.3.2. Description of Synthesis

The reaction was carried out in refluxing dichloromethane under exclusion of moisture and air (Figure 7-83). As a methylating agent, the Meerwein's salt trimethyloxonium tetrafluoroborate (Me₃O⁺ BF₄⁻) was employed.

![Synthesis of the novel methylated, non-fluorinated azaenediyne 208](image)

The desired product was obtained in a yield of 98% as a white powder. Subsequent crystallization yielded colorless, transparent crystals. The methyl-azaenediyne 208 was a novel compound and therefore fully characterized.

7.10.3.3. Conclusion and Product Analysis

The HiRes-ESI-MS analysis resulted in \( m/z = 329 \) for \( M^+ \) (cation). In the ESI-MS, apart from the cation mass \( (m/z = 329) \), also the loss of a methyl group could be seen \( (m/z = 314 \ [M^+ \text{(cation)} - 15 \text{(Me)}]) \).

In the IR spectrum, the stretching vibrations of the acetylenic bonds were found at \( \tilde{\nu} = 2218 \text{ cm}^{-1} \). The vibrations of the aromatic and the aliphatic C–H-bonds could also be seen.
The $^{13}$C-NMR spectrum was quite similar to the one of the non-methylated parent compound 199 (see there). The carbon of the newly introduced methyl group appeared at 35.1 ppm as tertiary carbon. The $^1$H-NMR spectrum showed the protons of the newly introduced methyl group at 4.27 ppm as a singlet.

The elementary analysis and the HiRes-ESI analysis were in perfect agreement with the calculated values.

![Figure 7-84: X-ray structure (ORTEP-3 diagram) of 208 (anion omitted for clarity)](image)

The X-ray analysis (Figure 7-84) showed a planar molecule. The angles at the N-1-nitrogen and the C-2-carbon were larger than 120° ($<\text{C-7a-N-1-C-16} = 127°$, $<\text{C-2-N-1-C-16} = 124°$, $<\text{N-1-C-2-C-8} = 124°$, $<\text{N-3-C-2-C-8} = 128°$). The bond length of the triple bonds was found to be $d_{\text{C-8-C-9}} = 1.19\,\text{Å}$ and $d_{\text{C-16-C-17}} = 1.21\,\text{Å}$. The distances between the sp carbons relevant for Bergman cyclization were $d_{\text{C-8-C-16}} = 2.90\,\text{Å}$ and $d_{\text{C-9-C-17}} = 4.11\,\text{Å}$, respectively.

The methylated, non-fluorinated azaenediyne 208 was found to be more stable in air and less sensitive towards hydrolysis compared to its perfluorinated analogue 206.
7.11. *N*-Ethylation of Azaenediynes — Ways of Building up a More Reactive System for the Bergman Cyclization

7.11.1. **4,5,6,7-Tetrafluoro-3-ethyl-2-phenylethynyl-1-trimethylsilyl-ethynyl-1H-benzimidazol-3-ium Tetrafluoroborate (209) — Attempted Synthesis**

7.11.1.1. **Introduction and Overview**

Ethylation at the nitrogen *N*-3 of azaenediynes based on benzimidazoles should have a similar effect as the carried out methylation. Correspondingly, the analogous reaction conditions were used as for the methylation of azaenediynes 198 and 199, and furthermore the ones suggested by Reichardt\textsuperscript{256} et al..

7.11.1.2. **Description of Synthesis**

The employment of Meerwein's salt triethyloxonium tetrafluoroborate (Et\textsubscript{3}O\textsuperscript{+}BF\textsubscript{4}\textsuperscript{-}) as an ethylating agent, however, gave the desired product in bad yield and as an impure solid (Figure 7-85).

![Synthesis of the ethylated, perfluorinated azaenediyne 209 with triethyloxonium tetrafluoroborate as ethylation reagent](image)

Figure 7-85: Synthesis of the ethylated, perfluorinated azaenediyne 209 with triethyloxonium tetrafluoroborate as ethylation reagent

The reaction was carried out in refluxing dichloromethane under exclusion of moisture and air, but educt could still be detected after a reaction time of 20 h. Various crystallization attempts failed.
7.11.1.3. Conclusion and Product Analysis

In the ESI-MS, the cation mass ($m/z = 415$) of the product could be seen. A daughter spectrum of $m/z = 415$ showed the loss of the ethyl group ($m/z = 387 [M^+ + 1 (H) - 29 (Et)]$).

The bad yield of the reaction, however, suggested to discard further ethylation attempts.
8. Trapping and Collision Experiments

8.1. Thermolysis Experiments (Trapping Experiments) in the Liquid Phase (in Solution)

8.1.1. General Introduction and Overview

The principle of the thermolysis experiments was to heat the various synthesized azaenediynes in different solvents, at different temperatures and for different reaction times. In order to absolutely exclude moisture and oxygen, all employed solvents were dried and degassed, respectively; and for the removal of solvent impurities and stabilizers also distilled under argon. All reaction mixtures were prepared in closable pressure tubes and in a glove box.

A typical pressure tube contained 1 mg of azaenediyne in 1 ml of solvent, achieving a concentration of $c = 2.0 \cdot 10^{-3} - 2.6 \cdot 10^{-3}$ mol·l$^{-1}$. After heating in an oil bath for a given reaction time at a given reaction temperature, the thermolysis mixtures were cooled and analyzed by GC/MS (after a micro-filtration over celite), on TLC plates coated with silica or RP-18, and by ESI-MS analysis in order to detect trapping products.

8.1.2. Thermolyses in Hydrogen Donating Solvents

Upon Bergman cyclization of the prepared azaenediynes, biradicals were expected to be formed. These biradicals could abstract hydrogen from H-donor-solvents like isopropyl ether (diisopropyl ether),$^{202, 257}$ 1,4-dioxane$^{258}$ and 1,4-cyclohexadiene$^{97}$ (Figure 8-1).

![Figure 8-1: Solvents suited as hydrogen donors for radical trapping (abstractable hydrogen atoms are shown)]
8.1.3. **TEMPO (210) as a Radical Trap**

The reaction between two radicals is a termination step, leading to a neutral entity. Therefore, another interesting strategy could be the use of a stable radical in order to trap the biradical formed in the Bergman cyclization. Nitroxides belong to a class of persistent radicals, which react with a variety of carbon-centered radicals, even at room temperature.

A purchasable radical is the 2,2,6,6-tetramethyl-1-oxy-piperidinyl radical (TEMPO) (210), a free nitroxide radical. It is a red, stable and storable solid, can be purified by sublimation and is a paradigm of a "radical in a bottle" (Figure 8-2).

Grissom et al. heated several enediyne arenes of type 211 with an excess of the trapping agent TEMPO (210) in chlorobenzene as a solvent (Figure 8-3).

However, they did not isolate the primary radical trapping products 212, but the corresponding quinones 213.
8.1.4. Thermolyses of the Azaenediynes 198 and 199

8.1.4.1. Thermolysis of the Perfluorinated Azaenediyne 198 in Diisopropyl Ether

8.1.4.1.1. Results

Table 8-1: Thermolysis results of the perfluorinated azaenediyne 198 in diisopropyl ether

<table>
<thead>
<tr>
<th>#</th>
<th>temp. [°C]</th>
<th>time [h]</th>
<th>appearance of solution</th>
<th>TLC</th>
<th>GC/MS (main peaks)</th>
<th>ESI-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>½</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>1</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>2</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>24</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>48</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>½</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>1</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>8</td>
<td>70</td>
<td>2</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>9</td>
<td>70</td>
<td>24</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>10</td>
<td>70</td>
<td>48</td>
<td>clear, colorless</td>
<td>educt; start spot</td>
<td>educt</td>
<td>educt; 388</td>
</tr>
<tr>
<td>11</td>
<td>120</td>
<td>½</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>12</td>
<td>120</td>
<td>1</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>13</td>
<td>120</td>
<td>2</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>14</td>
<td>120</td>
<td>24</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>15</td>
<td>120</td>
<td>48</td>
<td>clear, slightly yellow</td>
<td>educt; start spot, other spots</td>
<td>educt</td>
<td>educt; 388</td>
</tr>
<tr>
<td>16</td>
<td>180</td>
<td>½</td>
<td>clear, slightly yellow</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>17</td>
<td>180</td>
<td>1</td>
<td>clear, slightly yellow</td>
<td>educt; start spot</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>18</td>
<td>180</td>
<td>2</td>
<td>clear, yellowish</td>
<td>educt; start spot</td>
<td>mainly educt</td>
<td>educt; 388</td>
</tr>
<tr>
<td>19</td>
<td>180</td>
<td>24</td>
<td>clear, yellowish</td>
<td>educt; start spot, other spots</td>
<td>mainly educt</td>
<td>educt; 388, 393</td>
</tr>
<tr>
<td>20</td>
<td>180</td>
<td>48</td>
<td>clear, yellowish</td>
<td>educt; start spot, other spots</td>
<td>mainly educt</td>
<td>educt; 388, 393</td>
</tr>
</tbody>
</table>

8.1.4.1.2. Conclusion

The thermolysis experiments in diisopropyl ether (Table 8-1) showed no changes at all at temperatures of 40 °C and 70 °C, and neither at 120 °C up to reaction times of 24 h (entries 1 –
14). Discoloration was observed at 120 °C for 48 h and at 180 °C (entries 15 – 20). The TLC plates showed the presence of educt 198 under all conditions, however, at longer reaction times (24 h at 70 °C and 120 °C, entries 10, 15) and at 180 °C (entries 17 – 20) also a tiny start spot could be detected. A GC/MS analysis always showed the presence of 198, however, at 180 °C and longer reaction times (entries 18 – 20) some small other peaks could be seen. The educt appeared in the ESI-MS as a peak at \( m/z = 387 \ [M^+ + 1 \text{ (H)}] \). At higher temperatures and longer reaction times (entries 10, 15, 18 – 20), additionally some small peaks at \( m/z = 388 \) and \( m/z = 393 \) were found.

Azaenediyne 198 turned out to be present under all conditions; it was not destroyed at higher temperatures and longer reaction times. The only observed changes consisted in weak start spots on the TLC plates, some additional peaks in the GC/MS and ESI-MS and slight color changes of the reaction mixture. The results did not point at cyclization products, but rather at decomposition products.

Evaporation of some samples, reweighing and TLC analysis showed that practically all starting material could be recovered. Non-identifiable decomposition products occurred in negligible amounts.
8.1.4.2. Thermolysis of the Perfluorinated Azaenediyne 198 in 1,4-Dioxane

8.1.4.2.1. Results

Table 8-2: Thermolyses results of the perfluorinated azaenediyne 198 in 1,4-dioxane

<table>
<thead>
<tr>
<th>#</th>
<th>temp. [°C]</th>
<th>time [h]</th>
<th>appearance of solution</th>
<th>TLC</th>
<th>GC/MS (main peaks)</th>
<th>ESI-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>½</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>1</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>2</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>24</td>
<td>clear, slightly yellow</td>
<td>educt; start spot, other spots</td>
<td>educt; other peaks</td>
<td>educt</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>48</td>
<td>clear, slightly yellow</td>
<td>educt; start spot, other spots</td>
<td>educt; other peaks</td>
<td>educt</td>
</tr>
<tr>
<td>6</td>
<td>160</td>
<td>½</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>7</td>
<td>160</td>
<td>1</td>
<td>clear, yellowish</td>
<td>educt; start spot</td>
<td>educt; other peaks</td>
<td>educt</td>
</tr>
<tr>
<td>8</td>
<td>160</td>
<td>2</td>
<td>clear, yellowish</td>
<td>educt; start spot</td>
<td>educt; other peaks</td>
<td>educt</td>
</tr>
<tr>
<td>9</td>
<td>160</td>
<td>24</td>
<td>clear, yellowish</td>
<td>educt; start spot, other spots</td>
<td>educt; other peaks</td>
<td>educt</td>
</tr>
<tr>
<td>10</td>
<td>160</td>
<td>48</td>
<td>clear, yellowish</td>
<td>educt; start spot, other spots</td>
<td>educt; other peaks</td>
<td>educt</td>
</tr>
<tr>
<td>11</td>
<td>210</td>
<td>½</td>
<td>clear, yellowish</td>
<td>educt, start spot</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>12</td>
<td>210</td>
<td>1</td>
<td>clear, yellow</td>
<td>educt; start spot</td>
<td>educt; other peaks</td>
<td>educt; 389</td>
</tr>
<tr>
<td>13</td>
<td>210</td>
<td>2</td>
<td>clear, yellow</td>
<td>educt; start spot</td>
<td>educt; other peaks</td>
<td>educt; 389</td>
</tr>
<tr>
<td>14</td>
<td>210</td>
<td>24</td>
<td>clear, dark yellow</td>
<td>educt; start spot, other spots</td>
<td>educt; other peaks</td>
<td>educt; 389</td>
</tr>
<tr>
<td>15</td>
<td>210</td>
<td>48</td>
<td>clear, dark yellow</td>
<td>educt; start spot, other spots</td>
<td>educt; other peaks</td>
<td>educt; 389</td>
</tr>
</tbody>
</table>

8.1.4.2.2. Conclusion

Thermolyses in 1,4-dioxane (Table 8-2) showed no changes at all at 100 °C for reaction times up to 2 h (entries 1 – 3). Longer heating and higher temperatures (entries 4 – 15) usually led to color changes and then to intensification of color, to an additional start spot on the TLC plates and further peaks in the GC/MS. The ESI-MS, however, showed only educt (m/z = 387 [M^+ + 1 (H)]) up to heating for ½ h at 210 °C (entries 1 – 11). Samples heated for longer time at 210 °C (entries 12 – 15) showed a tiny peak at m/z = 389 in the ESI-MS. A closer look at the isotopic
pattern and at the daughter spectra showed that the peak at \( m/z = 389 \) did not derive from a protonated 198 that added two hydrogen atoms, but is rather an artifact or belongs to the isotopic pattern of the protonated educt.

It was found that 1,4-dioxane was not suited as a hydrogen donor solvent at higher temperatures. A GC/MS analysis showed several decomposition peaks in samples of neat 1,4-dioxane that were heated for longer than 30 min at temperatures higher than 150 °C. Using 1,4-cyclohexadiene as a solvent presented similar problems: Temperatures over 120 °C led to several decomposition products of the solvent. Further attempts employing 1,4-dioxane and 1,4-cyclohexadiene were therefore discarded.

### 8.1.4.3. Thermolysis of the Perfluorinated Azaenediyne 198 in Neat Chlorobenzene

#### 8.1.4.3.1. Introduction

As a control experiment for the trapping with TEMPO (210), azaenediyne 198 was heated at 240 °C for different reaction times in neat chlorobenzene without other additives.

#### 8.1.4.3.2. Results

<table>
<thead>
<tr>
<th>#</th>
<th>temp. [°C]</th>
<th>time [h]</th>
<th>appearance of solution</th>
<th>TLC</th>
<th>GC/MS (main peaks)</th>
<th>ESI-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>240</td>
<td>1</td>
<td>clear, slightly yellow</td>
<td>educt; start spot, other spots</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>2</td>
<td>240</td>
<td>24</td>
<td>clear, slightly red</td>
<td>educt; start spot, other spots</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>3</td>
<td>240</td>
<td>48</td>
<td>clear, slightly brown</td>
<td>educt; start spot, other spots</td>
<td>educt</td>
<td>educt</td>
</tr>
</tbody>
</table>

#### 8.1.4.3.3. Conclusion

Apart from slight color changes and some additional spots on the TLC plate, only educt was found (Table 8-3). The color increase and the additional TLC-spots were thought to derive from burned material at the tube walls.
8. TRAPPING AND COLLISION EXPERIMENTS

8.1.4.4. Thermolysis of the Perfluorinated Azaenediyne 198 in Chlorobenzene with TEMPO (210)

8.1.4.4.1. Results

Table 8-4: Thermolysis results of the perfluorinated azaenediyne 198 in chlorobenzene with 1 eq or 3 eq of TEMPO (210)

<table>
<thead>
<tr>
<th>#</th>
<th>temp. [°C]</th>
<th>time [h]</th>
<th>appearance of solution</th>
<th>TLC</th>
<th>GC/MS (main peaks)</th>
<th>ESI-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>1</td>
<td>clear, salmon</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>24</td>
<td>clear, salmon</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>48</td>
<td>clear, slightly red</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
</tr>
<tr>
<td>4</td>
<td>150</td>
<td>1</td>
<td>clear, slightly brown</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
</tr>
<tr>
<td>5</td>
<td>150</td>
<td>24</td>
<td>clear, brown</td>
<td>educt; start spot, other spots</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
</tr>
<tr>
<td>6</td>
<td>150</td>
<td>48</td>
<td>clear, brown</td>
<td>educt; start spot, other spots</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
</tr>
<tr>
<td>7</td>
<td>240</td>
<td>1</td>
<td>clear, brownish</td>
<td>educt; start spot, other spots</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
</tr>
<tr>
<td>8</td>
<td>240</td>
<td>24</td>
<td>clear, brown</td>
<td>educt; start spot, other spots</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
</tr>
<tr>
<td>9</td>
<td>240</td>
<td>48</td>
<td>clear, brown</td>
<td>educt; start spot, other spots</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
</tr>
</tbody>
</table>

8.1.4.4.2. Conclusion

Freshly prepared solutions of azaenediyne 198 in chlorobenzene with 1 eq or 3 eq of TEMPO (210), respectively, showed a salmon color. The results for the thermolyses with 1 eq and 3 eq of TEMPO (210) were identical.

The trapping attempts for compound 198 with TEMPO (210) (Table 8-4) showed no cyclization products. At temperatures higher than 150 °C (entries 4 – 9), an increase of color of the solution could be seen, and also additional TLC spots. The GC/MS analyses, however, showed only educt and TEMPO\textsuperscript{xi} (210). In the ESI-MS, also only educt \((m/z = 387 [M^+ + 1 (H)])\) and TEMPO (210) \((m/z = 156 [M^+], 140 [M^+ - 16 (O)] \) or 142 \([M^+ - 16 (O) + 2 (2 H)]\) could be detected.

\textsuperscript{xii} TEMPO (210) was detected in the GC/MS as follows:
As a control, some samples were evaporated, reweighed and analyzed by TLC. The results showed that practically all starting material could be recovered. Non-identifiable decomposition products occurred in negligible amounts.

### 8.1.4.5. Testing the Sensitivity of the Perfluorinated Azaenediyne 198 to Hydrolysis and Heat

#### 8.1.4.5.1. Results

Table 8-5: Testing the sensitivity of the perfluorinated azaenediyne 198 to heat and hydrolysis in a mixture of water and diisopropyl ether

<table>
<thead>
<tr>
<th>#</th>
<th>temp. [°C]</th>
<th>time [h]</th>
<th>appearance of solution</th>
<th>TLC</th>
<th>GC/MS</th>
<th>ESI-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120</td>
<td>1</td>
<td>clear, colorless mixture (2 phases)</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>2</td>
<td>120</td>
<td>24</td>
<td>aqueous phase clear and colorless, organic phase clear and slightly yellow</td>
<td>educt, other spots</td>
<td>educt</td>
<td>educt</td>
</tr>
</tbody>
</table>

#### 8.1.4.5.2. Conclusion

A test whether azaenediyne 198 was stable in water was carried out by heating 0.5 ml of a solution of 1 mg of educt in 1 ml of diisopropyl ether with 1.5 ml of water. Only a slight color change was detected upon heating for 24 h at 120 °C (Table 8-5, entry 2). The TLC plates (the ether phase was spotted on silica plates, the aqueous phase on RP-18 plates) showed mainly educt. In the GC/MS and the ESI-MS only educt could be observed.

---

GC (50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min): Rₜ = 5.3 min; MS (EI, 70 eV): m/z (%): 156 (40 %) [M⁺], 141 (31 %) [M⁺ - 15 (Me)], 126 (18 %) [M⁺ - 30], 123 (14 %) [M⁺ - 33 (NH₂OH)], 83 (25 %) [M⁺ - 73], 81 (32 %) [M⁺ - 75], 74 (36 %) [M⁺ - 82], 73 (19 %) [M⁺ - 83], 70 (52 %) [M⁺ - 86], 69 (100 %) [M⁺ - 87], 67 (14 %) [M⁺ - 89], 57 (28 %) [M⁺ - 99], 56 (89 %) [M⁺ - 100], 55 (86 %) [M⁺ - 101], 53 (11 %) [M⁺ - 103].
8. TRAPPING AND COLLISION EXPERIMENTS

8.1.4.6. Thermolysis of the Non-Fluorinated Azaenediyne 199 in Diisopropyl Ether

8.1.4.6.1. Results

Table 8-6: Thermolysis results of the non-fluorinated azaenediyne 199 in diisopropyl ether

<table>
<thead>
<tr>
<th>#</th>
<th>temp. [°C]</th>
<th>time [h]</th>
<th>appearance of solution</th>
<th>TLC</th>
<th>GC/MS (main peaks)</th>
<th>ESI-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>2</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>24</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>1</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>24</td>
<td>clear, yellowish</td>
<td>educt; start spot, other spots</td>
<td>educt</td>
<td>educt, other peaks</td>
</tr>
<tr>
<td>5</td>
<td>180</td>
<td>1</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt, other peaks</td>
</tr>
<tr>
<td>6</td>
<td>180</td>
<td>24</td>
<td>clear, yellow</td>
<td>educt; start spot, other spots</td>
<td>mainly educt</td>
<td>educt, other peaks</td>
</tr>
</tbody>
</table>

8.1.4.6.2. Conclusion

The thermolysis experiments of 199 in diisopropyl ether (Table 8-6) showed no changes at all at temperatures of 70 °C, and neither at 100 °C at a reaction time of 1 h (entries 1 – 3). Color changes were observed at 100 °C for 24 h and at 180 °C for 24 h (entries 4 and 6). The TLC plates showed the presence of educt 199 under all conditions, however, at longer reaction times (24 h at 100 °C and 180 °C, entries 4 and 6) also other spots could be detected. A GC/MS analysis always showed the presence of 199. The educt appeared in the ESI-MS as a peak at \( m/z = 315 \) \( [M^+ + 1 \text{ (H)}] \). At higher temperatures and longer reaction times (entries 4 – 6), additionally other peaks were found. However, the results did not suggest the presence of cyclization products. Evaporation of some samples, reweighing and TLC analysis showed that practically all starting material could be recovered. Non-identifiable decomposition products occurred in negligible amounts.
8.1.4.7. Thermolysis of the Non-Fluorinated Azaenediyne 199 in Chlorobenzene with TEMPO (210)

8.1.4.7.1. Results

Table 8-7: Thermolysis results of the non-fluorinated azaenediyne 199 in chlorobenzene with 1 eq or 3 eq of TEMPO (210)

<table>
<thead>
<tr>
<th>#</th>
<th>temp. [°C]</th>
<th>time [h]</th>
<th>appearance of solution</th>
<th>TLC</th>
<th>GC/MS (main peaks)</th>
<th>ESI-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>1</td>
<td>clear, salmon</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>24</td>
<td>clear, salmon</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
</tr>
<tr>
<td>3</td>
<td>130</td>
<td>1</td>
<td>clear, salmon</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
</tr>
<tr>
<td>4</td>
<td>130</td>
<td>24</td>
<td>clear, salmon</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO</td>
</tr>
<tr>
<td>5</td>
<td>240</td>
<td>1</td>
<td>clear, yellow</td>
<td>educt, TEMPO; start</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO; start</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>spot, other spots</td>
<td></td>
<td>other spots</td>
</tr>
<tr>
<td>6</td>
<td>240</td>
<td>24</td>
<td>clear, brownish</td>
<td>educt, TEMPO; start</td>
<td>educt, TEMPO</td>
<td>educt, TEMPO; start</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>spot, other spots</td>
<td></td>
<td>other spots</td>
</tr>
</tbody>
</table>

8.1.4.7.2. Conclusion

Freshly prepared solutions of azaenediyne 199 in chlorobenzene with 1 eq or 3 eq of TEMPO (210), respectively, showed a salmon color. The results for the thermolyses with 1 eq and 3 eq of TEMPO (210) were identical.

The trapping attempts for compound 199 with TEMPO (210) (Table 8-7) showed no cyclization products. At temperatures of 240 °C (entries 5 – 6), an increase of color of the solution could be seen, and also additional TLC spots. The GC/MS analyses, however, showed mainly educt and TEMPO (210). In the ESI-MS, also educt (m/z = 315 [M+ + 1 (H)]) and TEMPO (210) (m/z = 156 [M+], 140 [M+ – 16 (O)] or 142 [M+ – 16 (O) + 2 (2 H)]) could be detected for all applied conditions. Only at 240 °C (entries 5 – 6) some additional tiny peaks could be seen, which derived from decomposition products.

As a control, some samples were evaporated, reweighed and analyzed by TLC. The results showed that practically all starting material could be recovered. Non-identifiable decomposition products occurred in negligible amounts.
8.1.5. Thermolyses of the *in situ*-Protonated Azaenediyne 198

8.1.5.1. Introduction

For the *in situ*-protonation of the perfluorinated azaenediyne 198 in different solvents and with different acids and subsequent thermolysis, the acid was added directly before heating the tube. The solvent should act as a hydrogen donor and the acid as protonating activator. Other attempts made by spraying an acidified solution of the parent azaenediyne 198 into the ESI-MS usually only showed protonated educt.
8.1.5.2. Thermolysis after *in situ*-Protonation of the Perfluorinated Azaenediyne 198 in Diisopropyl Ether with Triflic Acid

8.1.5.2.1. Results

Table 8-8: Thermolysis results after *in situ*-protonation of the perfluorinated azaenediyne 198 in diisopropyl ether with triflic acid

<table>
<thead>
<tr>
<th>#</th>
<th>temp. [°C]</th>
<th>time [h]</th>
<th>appearance of solution</th>
<th>TLC</th>
<th>GC/MS (main peaks)</th>
<th>ESI-MS (main peaks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1xiii</td>
<td>100</td>
<td>1</td>
<td>clear, colorless</td>
<td>educt; start spot</td>
<td>educt, other peaks</td>
<td>educt, other peaks</td>
</tr>
<tr>
<td>2xiii</td>
<td>100</td>
<td>24</td>
<td>clear, colorless</td>
<td>educt; start spot, other spots</td>
<td>educt, other peaks</td>
<td>educt, other peaks</td>
</tr>
<tr>
<td>3xiii</td>
<td>100</td>
<td>48</td>
<td>clear, slightly yellow</td>
<td>educt; start spot, other spots</td>
<td>educt, other peaks</td>
<td>educt, other peaks</td>
</tr>
<tr>
<td>4xiv</td>
<td>100</td>
<td>1</td>
<td>clear, slightly yellow</td>
<td>start spot, other spots</td>
<td>other peaks</td>
<td>educt, 391, other peaks</td>
</tr>
<tr>
<td>5xiv</td>
<td>100</td>
<td>24</td>
<td>clear, slightly yellow</td>
<td>start spot, other spots</td>
<td>other peaks</td>
<td>educt, 391, other peaks</td>
</tr>
<tr>
<td>6xiv</td>
<td>100</td>
<td>48</td>
<td>clear, slightly yellow</td>
<td>start spot, other spots</td>
<td>other peaks</td>
<td>educt, 391, other peaks</td>
</tr>
<tr>
<td>7xiii</td>
<td>150</td>
<td>1</td>
<td>clear, yellowish</td>
<td>educt; start spot, other spots</td>
<td>educt (weak), other peaks</td>
<td>educt, other peaks</td>
</tr>
<tr>
<td>8xiii</td>
<td>150</td>
<td>24</td>
<td>clear, yellowish</td>
<td>educt; start spot, other spots</td>
<td>other peaks</td>
<td>389, 391, other peaks</td>
</tr>
<tr>
<td>9xiii</td>
<td>150</td>
<td>48</td>
<td>clear, yellowish</td>
<td>educt; start spot, other spots</td>
<td>other peaks</td>
<td>389, 391, other peaks</td>
</tr>
<tr>
<td>10xiv</td>
<td>150</td>
<td>1</td>
<td>clear, yellowish</td>
<td>start spot</td>
<td>other peaks</td>
<td>educt; 391</td>
</tr>
<tr>
<td>11xiv</td>
<td>150</td>
<td>24</td>
<td>clear, yellowish</td>
<td>start spot</td>
<td>other peaks</td>
<td>393</td>
</tr>
<tr>
<td>12xiv</td>
<td>150</td>
<td>48</td>
<td>clear, yellowish</td>
<td>start spot</td>
<td>other peaks</td>
<td>393</td>
</tr>
</tbody>
</table>

xiii. These experiments were carried out with 1 eq of triflic acid, with and without buffer.
xiv. These experiments were carried out with 20 eq of triflic acid, with and without buffer.
8.1.5.2.2. Conclusion

The addition of 1 eq of acid to the sample led to partial decomposition, with and without the use of 2-fluoropyridine as a buffer (Table 8-8). However, the protonated species could be detected at $m/z = 387 [M^+ + 1 (H)]$ in the ESI-MS. When 20 eq of triflic acid were used (with and without buffer), educt 198 usually disappeared. Only non-identifiable decomposition products were detected, however, the ESI-MS-peaks at $m/z = 389$ and $m/z = 391$ suggested multiple protonation products. No evidence was found for a cyclization product that abstracted two hydrogen atoms (see also the last paragraph of Chapter 8.2.1, and Chapter 8.2.3).

At harsh conditions (entry 11 and 12), the analyzed tubes showed a relatively high pressure and the smell of propene. The formation of 1 eq of propene (together with 1 eq of iso-propanol) was explained by protonation and subsequent cleavage of 1 eq of diisopropyl ether upon heating with Brönsted acids.

8.1.5.3. Thermolysis after in situ-Protonation of the Perfluorinated Azaenediyne 198 in Diisopropyl Ether with Trifluoroacetic Acid

8.1.5.3.1. Results

Table 8-9: Thermolysis results after in situ-protonation of the perfluorinated azaenediyne 198 in diisopropyl ether with 1 eq of trifluoroacetic acid

<table>
<thead>
<tr>
<th>#</th>
<th>temp. [°C]</th>
<th>time [h]</th>
<th>appearance of solution</th>
<th>TLC</th>
<th>GC/MS (main peaks)</th>
<th>ESI-MS (main peaks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>1</td>
<td>clear, colorless</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>24</td>
<td>clear, colorless</td>
<td>educt; start spot, other spots</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>3</td>
<td>120</td>
<td>1</td>
<td>clear, slightly yellow</td>
<td>educt</td>
<td>educt</td>
<td>educt</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
<td>24</td>
<td>clear, slightly yellow</td>
<td>educt; start spot, other spots</td>
<td>educt, other peaks</td>
<td>other peaks</td>
</tr>
<tr>
<td>5</td>
<td>180</td>
<td>1</td>
<td>clear, brownish</td>
<td>educt; start spot, other spots</td>
<td>educt, other peaks</td>
<td>educt, other peaks</td>
</tr>
<tr>
<td>6</td>
<td>180</td>
<td>24</td>
<td>clear, brownish</td>
<td>educt; start spot, other spots</td>
<td>educt, other peaks</td>
<td>other peaks</td>
</tr>
</tbody>
</table>
8.1.5.3.2. Conclusion

When 1 eq of trifluoroacetic acid with diisopropyl ether as a solvent was used (Table 8-9), relatively short reaction times and moderate temperatures (entries 1 – 3) led to mainly educt. Harsher conditions (entries 4 – 6) gave mainly decomposition products.

8.1.5.4. Thermolysis after *in situ*-Protonation of the Perfluorinated Azaenediyne 198 in 1,4-Dioxane with Triflic Acid

8.1.5.4.1. Results

Table 8-10: Thermolysis results after *in situ*-protonation of the perfluorinated azaenediyne 198 in 1,4-dioxane with 1 eq of triflic acid

<table>
<thead>
<tr>
<th>#</th>
<th>temp. [°C]</th>
<th>time [h]</th>
<th>appearance of solution</th>
<th>TLC</th>
<th>GC/MS (main peaks)</th>
<th>ESI-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>160</td>
<td>1</td>
<td>clear, yellow</td>
<td>start spot, other spots</td>
<td>other peaks</td>
<td>educt, 389, other peaks</td>
</tr>
<tr>
<td>2</td>
<td>160</td>
<td>24</td>
<td>clear, yellow</td>
<td>start spot, other spots</td>
<td>other peaks</td>
<td>other peaks</td>
</tr>
<tr>
<td>3</td>
<td>210</td>
<td>1</td>
<td>clear, brown</td>
<td>start spot, other spots</td>
<td>other peaks</td>
<td>other peaks</td>
</tr>
<tr>
<td>4</td>
<td>210</td>
<td>24</td>
<td>clear, brown</td>
<td>start spot, other spots</td>
<td>other peaks</td>
<td>other peaks</td>
</tr>
</tbody>
</table>

8.1.5.4.2. Conclusion

Adding 1 eq of triflic acid to a sample in 1,4-dioxane (Table 8-10) and heating to 160 °C or 210 °C led to complete decomposition of the material.
8.1.5.5. Thermolysis after *in situ*-Protonation of the Perfluorinated Azaenediyne 198 in 1,4-Dioxane with Deutero-Hydrochloric Acid

8.1.5.5.1. Results

Table 8-11: Thermolysis results after *in situ*-protonation of the perfluorinated azaenediyne 198 in 1,4-dioxane with 1 eq of deutero-hydrochloric acid

<table>
<thead>
<tr>
<th>#</th>
<th>temp. [°C]</th>
<th>time [h]</th>
<th>appearance of solution</th>
<th>TLC</th>
<th>GC/MS (main peaks)</th>
<th>ESI-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>160</td>
<td>2</td>
<td>clear, colorless</td>
<td>start spot, other spots</td>
<td>other peaks</td>
<td>424, 426, other peaks</td>
</tr>
<tr>
<td>2</td>
<td>210</td>
<td>2</td>
<td>clear, colorless</td>
<td>start spot, other spots</td>
<td>other peaks</td>
<td>424, 426, other peaks</td>
</tr>
</tbody>
</table>

8.1.5.5.2. Conclusion

Adding 1 eq of deutero-hydrochloric acid to a sample in 1,4-dioxane (Table 8-11) and heating to 160 °C or 210 °C led to disappearance of azaenediyne 198 and decomposition products. No evidence was found for a cyclization product. The ESI-MS results suggested rather the addition of one molecule of DCl to the protonated product \( m/z = 424 \) from \([M^+ + 1 (H) + D^{-35}Cl]\) and \( m/z = 426 \) from \([M^+ + 1 (H) + D^{-37}Cl]\). The tiny product amounts made an isolation impossible.

It is assumed that azaenediyne 198 is deuterated at the N-3-nitrogen first (see Figure 8-4) to give imidazolium 214. The subsequent nucleophilic attack of chloride on the positively polarized terminal \( sp \)-carbon, which forms part of a Michael-type system, would lead to enamine 215. The latter one can undergo tautomerization to give imine 216. During the spray process in the ESI-MS, protonation can take place at the N-3-nitrogen of 216 — the resulting cation would have a mass of \( m/z = 424 \) or \( m/z = 426 \), respectively.
8.1.5.6. Thermolysis after in situ-Protonation of the Perfluorinated Azaenediyne 198 in Chlorobenzene with TFA and TEMPO (210)

8.1.5.6.1. Results

Table 8-12: Thermolysis results after in situ-protonation of the perfluorinated azaenediyne 198 in chlorobenzene with 1 eq of trifluoroacetic acid and 3 eq of TEMPO (210)

<table>
<thead>
<tr>
<th>#</th>
<th>temp. [°C]</th>
<th>time [h]</th>
<th>appearance of solution</th>
<th>TLC</th>
<th>GC/MS (main peaks)</th>
<th>ESI-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>1</td>
<td>clear, brown</td>
<td>educt, start spot, other spots</td>
<td>educt, TEMPO, other peaks</td>
<td>educt, TEMPO, other peaks</td>
</tr>
<tr>
<td>2</td>
<td>150</td>
<td>1</td>
<td>clear, brown</td>
<td>educt, start spot, other spots</td>
<td>educt, TEMPO, other peaks</td>
<td>educt, TEMPO, other peaks</td>
</tr>
<tr>
<td>3</td>
<td>240</td>
<td>1</td>
<td>black</td>
<td>start spot, other spots</td>
<td>TEMPO, other peaks</td>
<td>TEMPO, other peaks</td>
</tr>
</tbody>
</table>

Figure 8-4: Possible DCl-adducts formed in traces upon reaction of the perfluorinated azaenediyne 198 with deutero-hydrochloric acid
8.1.5.6.2. Conclusion

An experiment using 1 eq of trifluoroacetic acid on a solution of azaenediyne 198 in chlorobenzene with 3 eq of TEMPO (210) led to several decomposition products (Table 8-12).

8.1.6. Thermolyses of the Methylated Azaenediynes 206 and 208

8.1.6.1. Thermolysis of the Methylated, Perfluorinated Azaenediyne 206 in Diisopropyl Ether

8.1.6.1.1. Results

Table 8-13: Thermolysis results of the methylated, perfluorinated azaenediyne 206 in diisopropyl ether

<table>
<thead>
<tr>
<th>#</th>
<th>temp. [°C]</th>
<th>time [h]</th>
<th>appearance of solution</th>
<th>TLC</th>
<th>ESI-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>1</td>
<td>clear, colorless</td>
<td>start spot (educt)</td>
<td>educt</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>24</td>
<td>clear, colorless</td>
<td>start spot (educt)</td>
<td>educt</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>1</td>
<td>clear, colorless</td>
<td>start spot (educt)</td>
<td>educt</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>24</td>
<td>clear, slightly yellow</td>
<td>start spot (educt)</td>
<td>educt</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>1</td>
<td>clear, colorless</td>
<td>start spot (educt)</td>
<td>educt</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>24</td>
<td>clear, slightly yellow</td>
<td>start spot (educt)</td>
<td>educt; 461</td>
</tr>
<tr>
<td>7</td>
<td>180</td>
<td>1</td>
<td>clear, salmon</td>
<td>start spot</td>
<td>461, educt, 419</td>
</tr>
<tr>
<td>8</td>
<td>180</td>
<td>24</td>
<td>clear, brownish</td>
<td>start spot</td>
<td>461, educt, 419</td>
</tr>
</tbody>
</table>

8.1.6.1.2. Conclusion

The thermolysis experiments in diisopropyl ether (Table 8-13) showed no changes at all at temperatures of 40 °C and 70 °C (entries 1 – 4). At 100 °C, educt 206 was still the dominant peak in the ESI-MS spectrum (m/z = 401 [M⁺ (cation)]), but a tiny peak at m/z = 461 could also be seen (entry 6). Heating to 180 °C led to a color change. When heated for 1 h at 180 °C (entry 7), the peak at m/z = 401 became smaller, while the one at m/z = 461 got bigger. A heating time of 24 h showed m/z = 461 being the main peak, while m/z = 401 nearly disappeared (entry 8). How could the peak at m/z = 461 be explained?
8.1.6.1.3. Analyses

First, the reaction was repeated on a bigger scale. In order to separate the presumably ionic mixture, first TLC and HPLC attempts were conducted with various solvents, followed by preparative TLC on silica and on RP-18 plates in a glove box. However, mainly educt or non-identifiable decomposition products could be isolated.

The mass increase of $\Delta (m/z) = +60$ could be explained by addition of one molecule of iso-propanol. An analogous addition of methanol was already observed: The methyl-azaenediyne 206 was readily converted into its methanol-adduct 207, and iso-propanol should show a similar reactivity.

To test whether the employed diisopropyl ether remained stable under the thermolysis conditions or possibly transformed into a small amount of iso-propanol and propene, neat samples of diisopropyl ether were heated under analogous conditions as the reaction mixtures (for details, see Experimental Section, Chapter 11.3.6 and Subchapters). Various GC/MS analyses, however, showed no trace of iso-propanol. The heated sample also showed no color change, and no smell of propene could be detected.

8.1.6.2. Thermolysis of the Methylated, Perfluorinated Azaenediyne 206 in Chlorobenzene with TEMPO (210)

8.1.6.2.1. Results

Table 8-14: Thermolysis results of the methylated, perfluorinated azaenediyne 206 in chlorobenzene with 1 eq or 3 eq of TEMPO (210)

<table>
<thead>
<tr>
<th>#</th>
<th>temp. [°C]</th>
<th>time [h]</th>
<th>appearance of solution</th>
<th>TLC</th>
<th>ESI-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>1</td>
<td>clear, salmon</td>
<td>start spot, TEMPO</td>
<td>educt; 140, 558</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>24</td>
<td>clear, orange</td>
<td>start spot, TEMPO, other spots</td>
<td>558, 140; educt, 419</td>
</tr>
<tr>
<td>3</td>
<td>130</td>
<td>1</td>
<td>clear, salmon</td>
<td>start spot, TEMPO, other spots</td>
<td>419, 140, 142, other peaks</td>
</tr>
<tr>
<td>4</td>
<td>130</td>
<td>24</td>
<td>clear, brown</td>
<td>start spot, TEMPO, other spots</td>
<td>419, 142, other peaks</td>
</tr>
<tr>
<td>5</td>
<td>240</td>
<td>1</td>
<td>clear, light brown</td>
<td>start spot, TEMPO, other spots</td>
<td>142, other peaks</td>
</tr>
<tr>
<td>6</td>
<td>240</td>
<td>24</td>
<td>clear, dark brown</td>
<td>start spot, other spots, TEMPO (weak)</td>
<td>142, other peaks</td>
</tr>
</tbody>
</table>
8. TRAPPING AND COLLISION EXPERIMENTS

8.1.6.2.2. Conclusion

Freshly prepared solutions of azaenediyne 206 in chlorobenzene with 1 eq or 3 eq of TEMPO (210), respectively, showed a salmon color. Thermolyses with 1 eq and 3 eq of TEMPO (210) gave identical results.

When heated at 70 °C for 1 h (Table 8-14), mainly educt was detected, apart from tiny peaks at m/z = 140 and m/z = 558 (entry 1). When heated for 24 h (entry 2), however, the peaks at m/z = 558 and m/z = 140 became the main peaks in the spectrum, but also m/z = 401 (cation mass of the educt) and m/z = 419 could be seen.

At temperatures of 130 °C (entries 3 – 4), several peaks were found in the ESI-MS spectra. The peaks at m/z = 140 and at m/z = 142 were from TEMPO-fragments. The peak at m/z = 419 derived from educt and is a water adduct (m/z = 401 is from [M⁺ (cation)], and m/z = 419 from [M⁺ (cation) + 18 (H₂O)]).

Temperatures of 240 °C (entries 5 – 6) led to a color increase of the thermolysis mixtures. The ESI-MS analyses showed several peaks indicating decomposition, however, fragments from TEMPO (210) could be detected at m/z = 142.

8.1.6.2.3. Analyses

The thermolysis experiments carried out at 70 °C for 1 h, and especially for 24 h (entry 2, Table 8-14) showed an interesting peak at m/z = 558. This mass corresponds to the educt cation mass (m/z = 401) plus the mass of TEMPO (210) (m/z = 156) plus the mass of a proton. While Grissom²⁶² et al. reported the addition of two equivalents of TEMPO (210) to enediyne arenes under similar conditions, a peak corresponding to that respective mass was not found. However – due to possible steric reasons – also only one equivalent of TEMPO (210) could be added to azaenediyne 206 (Figure 8-5).

---

²⁶² TEMPO (210) and its respective decomposition products appeared in the ESI-MS spectrum as follows: m/z = 156 [M⁺], 140 [M⁺ – 16 (O)] or 142 [M⁺ – 16 (O) + 2 (H)].
As shown in Figure 8-5, addition of one moiety of TEMPO (210) and a hydrogen radical to 206 could lead to the isomers 217 and 218, respectively. These would show a mass of \( m/z = 558 \). The mono adducts 217 and 218 could then fragment (and add a hydrogen atom) to give a compound with the mass \( m/z = 419 \). Imaginable for this mass would be the isomeric carbonyl compounds 219 and 220, as well as the isomeric phenols 221 and 222.
On the other hand, a daughter MS spectrum of the mass at \( m/z = 558 \) gave no further hints. The intensity was relatively low, and daughter peaks at \( m/z = 401 \) and \( m/z = 156 \) could barely be seen.

This suggests the peak at \( m/z = 558 \) deriving from a gas phase adduct (educt cation mass plus TEMPO mass plus 1). A further indication for a gas phase adduct could be that \( m/z = 558 \) was also detected at more gentle conditions (heating at 70 °C for 1 h, see entry 1 in Table 8-14).

If azaenediyne 206 underwent Bergman rearrangement to form a compound like 217 or 218, respectively, it remains unclear from where the hydrogen in the product was abstracted (compare experiments in deuterated solvents below).

### 8.1.6.2.4. Scaling up some Thermolysis Experiments of the Methylated Azaenediyne 206 — The Search for Assumed Cyclization Products

In order to obtain more thermolyzed material, the reaction conditions described in entry 2 (see Table 8-14) were repeated for a 50 mg-scale of azaenediyne 206. The following results were obtained in further experiments:

**Changing the Amount of TEMPO (210)**

The thermolysis was conducted with 1 eq, 3 eq and 6 eq of TEMPO (210). Even the 6 eq-excess of TEMPO (210) did not lead to increased product-formation. In all cases, still tiny amounts of educt 206 could be detected.

**Exploring Deuterated Solvents**

The solvent chlorobenzene was replaced by its perdeuterated analogue [D₅]-chlorobenzene and the sample heated to 70 °C for 24 h. However, no uptake of deuterium could be seen in the ESI-MS. The reaction was also carried out with 1 eq, 3 eq and 6 eq of TEMPO (210).

In another attempt, chlorobenzene was replaced by deutero-dichloromethane. This experiment should not only aid in subsequent crystallization attempts, but also clarify whether a deuterium-uptake took place. The same ESI-MS spectrum was obtained, and no uptake of deuterium could be seen.

These experiments excluded the solvents as potential hydrogen donors: No deuterium uptake or other characteristic mass differences were observed.
Separation Attempts by Chromatography

Several attempts in order to isolate the compound with the peak at \( m/z = 558 \) or its possible degradation products were carried out. The difficulty that had to be faced here was the separation of an ionic mixture of compounds.

Preparative TLC separations were carried out on silica plates and on RP-18 plates with a huge variety of eluents. The separations using water-free eluent mixtures were also repeated in a glove box with absolute solvents and previously dried preparative TLC plates. Additionally, analytical TLC was done on CN plates and on alumina plates.

Other attempts were made using HPLC on silica and on RP-18 cartridges. Also column chromatography using Sephadex was done.

Only in case of the employment of acetonitrile (or even a mixture of acetonitrile and water) on a RP-18 phase, a partial separation could be achieved. However, no fraction was pure — in all cases numerous peaks were found in the ESI-MS analyses:

- A fraction containing a peak with the mass at \( m/z = 558 \) was not found.

- Degradation products of TEMPO (210) were found in all fractions. These appeared at \( m/z = 140 \) and \( m/z = 142 \) in the ESI-MS. A control experiment consisted in heating TEMPO (210) in neat chlorobenzene for 24 h, which gave the same result: The molecular ion peak at \( m/z = 156 \) \([M^+ (\text{TEMPO})]\) disappeared, and the following peaks were found: 142 \([M^+ - 16 (\text{O}) + 2 (2 \text{H})]\) and 140 \([M^+ - 16 (\text{O})]\).

  It is noteworthy that spraying a freshly prepared solution of TEMPO (210) gave a different fragmentation pattern: \( m/z = 156 \) \([M^+ (\text{TEMPO})]\), 157 \([M^+ + 1 (\text{H})]\), 123 \([M^+ - 33 (\text{NH}_2\text{OH})]\), which is consistent with literature data.\(^{263}\)

- A main peak with \( m/z = 419 \) was found to derive from unreacted educt \( (m/z = 401 \ [M^+ (\text{cation})], 419 \ [M^+ (\text{cation}) + 18 (\text{H}_2\text{O})]) \). Also when freshly prepared educt was sprayed, addition of water took place after a while.

  Therefore, the peak at \( m/z = 419 \) is unlikely derived from a supposed cyclization product (217 or 218, respectively) with the mass \( m/z = 558 \), which lost the 2,2,6,6-tetramethylpiperidinyl fragment by cleavage of the N–O-bond.
Crystallization Attempts and NMR Analyses

Various attempts were undertaken in order to obtain crystals directly from the thermolysis mixtures. Those included direct precipitation attempts from the reaction mixture and diffusion-controlled crystallizations with different combinations of solvents. Usually, oils showing mixtures were obtained (see Experimental Section, Chapter 11.3.7.3).

In a case employing dichloromethane and $n$-pentane as solvents, however, crystals were obtained. The X-ray analysis demonstrated that the substance was the salt 2,2,6,6-tetramethylpiperidinium tetrafluoroborate (223), in which the piperidinium moiety showed chair conformation (Figure 8-6).

![Figure 8-6: Formula of 2,2,6,6-tetramethyl-piperidinium tetrafluoroborate (223) and its X-ray structure (ORTEP-3 diagram)](image)

The X-ray data were in agreement with literature data for the chloride salt. \(^{264}\) compares \(^{265}\) Piperidinium salt 223 was formed upon degradation of TEMPO (210). In the ESI-MS, the corresponding cation mass was found to be $m/z = 142$.

NMR analyses usually failed because of remaining TEMPO (210). TEMPO (210), as a free radical, is paramagnetic and caused extreme line broadening in the NMR spectra due to increased relaxation times.
8.1.6.3.  Thermolysis of the Methylated, Non-Fluorinated Azaenediyne 208 in Diisopropyl Ether

8.1.6.3.1. Results

Table 8-15: Thermolysis results of the methylated, non-fluorinated azaenediyne 208 in diisopropyl ether

<table>
<thead>
<tr>
<th>#</th>
<th>temp. [°C]</th>
<th>time [h]</th>
<th>appearance of solution</th>
<th>TLC</th>
<th>ESI-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>1</td>
<td>clear, slightly yellow</td>
<td>start spot (educt)</td>
<td>educt</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>24</td>
<td>clear, slightly yellow</td>
<td>start spot (educt)</td>
<td>educt</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>1</td>
<td>clear, slightly yellow</td>
<td>start spot (educt)</td>
<td>educt</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>24</td>
<td>clear, slightly yellow</td>
<td>start spot (educt)</td>
<td>educt; 389, 374</td>
</tr>
<tr>
<td>5</td>
<td>180</td>
<td>1</td>
<td>clear, yellow</td>
<td>start spot (educt)</td>
<td>educt, 389</td>
</tr>
<tr>
<td>6</td>
<td>180</td>
<td>24</td>
<td>clear, yellow</td>
<td>start spot (educt)</td>
<td>educt, 389, 374</td>
</tr>
</tbody>
</table>

8.1.6.3.2. Conclusion

Heating to 70 °C for 1 h or 24 h in diisopropyl ether (Table 8-15) showed no changes at all, nor did heating to 100 °C for 1 h (entries 1 – 3). At 100 °C and 24 h (entry 4), additional small peaks at $m/z = 389$ and $m/z = 374$ could be seen. At a temperature of 180 °C, educt 208 was still the dominant peak in the ESI-MS spectrum ($m/z = 329$ [M$^+$ (cation)]), but also peaks at $m/z = 389$ and $m/z = 374$ could be seen. Heating to 180 °C also led to a color change. How could the peak at $m/z = 389$ be explained?

8.1.6.3.3. Analyses

Like for the thermolysis sample of its perfluorinated analogue 206, the reaction was also scaled-up. Preparative TLC on silica and on RP-18 plates as well as other separation attempts, however, yielded mainly educt or non-identifiable decomposition products. As in the diisopropyl ether-thermolysis of 206, the peak at $m/z = 389$ also showed a mass increase of $\Delta (m/z) = +60$ compared to the educt mass ($m/z = 329$). This could be explained by addition of one molecule of iso-propanol, although it was already found out that diisopropyl ether remained stable under the employed conditions and did not form iso-propanol and propene (for details, see Experimental Section, Chapter 11.3.6 and Subchapters).
8. TRAPPING AND COLLISION EXPERIMENTS

8.1.6.4. Thermolysis of the Methylated, Non-Fluorinated Azaenediyne 208 in Chlorobenzene with TEMPO (210)

8.1.6.4.1. Results

Table 8-16: Thermolysis results of the methylated, non-fluorinated azaenediyne 208 in chlorobenzene with 1 eq or 3 eq of TEMPO (210)

<table>
<thead>
<tr>
<th></th>
<th>temp. [°C]</th>
<th>time [h]</th>
<th>appearance of solution</th>
<th>TLC</th>
<th>ESI-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>1</td>
<td>clear, salmon</td>
<td>start spot, TEMPO</td>
<td>educt</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>24</td>
<td>clear, orange</td>
<td>start spot, TEMPO</td>
<td>educt; 486, 346, 140</td>
</tr>
<tr>
<td>3</td>
<td>130</td>
<td>1</td>
<td>clear, dark orange</td>
<td>start spot, TEMPO, other spots</td>
<td>educt; 486, 346, 140</td>
</tr>
<tr>
<td>4</td>
<td>130</td>
<td>24</td>
<td>clear, brown</td>
<td>start spot, TEMPO, other spots</td>
<td>142, other peaks</td>
</tr>
<tr>
<td>5</td>
<td>240</td>
<td>1</td>
<td>clear, brown</td>
<td>start spot, TEMPO, other spots</td>
<td>142, other peaks</td>
</tr>
<tr>
<td>6</td>
<td>240</td>
<td>24</td>
<td>clear, dark brown</td>
<td>start spot, other spots, TEMPO</td>
<td>142, other peaks</td>
</tr>
</tbody>
</table>

8.1.6.4.2. Conclusion

Thermolyses of azaenediyne 208 with 1 eq and 3 eq of TEMPO (210) gave identical results. When heated at 70 °C for 1 h (entry 1, Table 8-16), only educt was detected. Heating to 70 °C for 24 h and 130 °C for 1 h (entries 2 and 3) still showed educt as the main peak at m/z = 329. Additionally, small peaks at m/z = 486, m/z = 346 and m/z = 140 were found. Higher temperatures and longer reaction times (entries 4 – 6) led to several peaks due to decomposition products. A peak at m/z = 142 was supposed to derive from piperidinium salt 223 (see Figure 8-6), which was already detected in the thermolysis experiments of 206.

8.1.6.4.3. Analyses

An interesting peak was found at m/z = 486 (see entries 2 and 3, Table 8-16). This mass corresponds to the educt cation mass (m/z = 329) plus the mass of TEMPO (210) (m/z = 156) plus the mass of a proton (see the isomeric compounds 224 and 225 in Figure 8-5). In case of the perfluorinated azaenediyne 206, an analogous peak was found at m/z = 558.

A daughter MS spectrum of the mass at m/z = 486 showed peaks at m/z = 329 and m/z = 156, although the intensity was relatively low. Therefore, m/z = 486 could simply derive from a gas phase adduct (educt cation mass plus TEMPO mass plus 1). What is more, no hints for the
imaginable isomeric carbonyls 226 and 227 or the isomeric phenols 228 and 229 were found, as a peak with the corresponding mass (at \( m/z = 347 \)) could barely be detected (see Figure 8-5).

As for the thermolysis mixture of azaenediyne 206, the conditions given in entry 2 and 3 (Table 8-16) were repeated for a bigger scale of 208.

Upon separation attempts by chromatography (preparative and analytical TLC, HPLC and column chromatography, see Experimental Section, Chapter 11.3.7.2), apart from fragments of TEMPO (210), mainly unreacted educt 208 could be recovered from impure mixtures (\( m/z = 329 \) \([M^+ \text{ (cation)}]\)). A fraction containing a peak at \( m/z = 486 \) was not found. Crystallization attempts failed as well.

Changing the amount of TEMPO (210) (1 eq, 3 eq and 6 eq) did not lead to increased product-formation. Upon replacement of the solvent chlorobenzene with [D₆]-chlorobenzene or deuterodichloromethane, no uptake of deuterium could be seen in the ESI-MS.
8.2. Collision Experiments and Trapping Experiments in the Gas Phase

8.2.1. Introduction and Overview

Collision experiments were carried out on a modified Finnigan MAT TSQ 700 mass spectrometer, equipped with an ESI source. The principle was that products that were formed upon collision or reaction in the gas phase could be directly mass-analyzed. A $10^{-5}$ M solution of the respective azaenediyne in dichloromethane was sprayed into the ESI-MS. All analyses were carried out in the cation mode. The collision potential of the ions could be changed within a range of $-200$ V to $+200$ V (leading to different collision energies; the higher the acceleration of the ions, the more energy is delivered on impact).

After the spray process via a capillary, desolvation and focusing, the ions entered the 24-pole-region, where the first gas phase reactions could be carried out. The residence time in this region (collision cell) was about 10 ms, and pressures up to 10 mTorr were possible (the higher the pressure, the higher the probability of a collision). In the adjacent quadrupole, a mass scan or first mass selection could take place. The daughter ion mode permitted the selection of ions with a specific mass-to-charge ratio.

Afterwards, the ions entered the 8-pole, which served as a second reaction or collision chamber. The selected ions then could be collided with an inert gas leading to a collision induced dissociation (CID) or with a reactant gas. In the 8-pole-region, the duration of stay was with $<1$ ms (about $10-100$ µs) shorter than in the 24-pole-region. The maximum allowed pressures were also lower than in the 24-pole.

After passing through the 8-pole-region, the ions entered the second quadrupole and finally hit the detector.$^{266, 267}$

In some of the ESI-MS spectra of the investigated azaenediyynes, occasionally a peak corresponding to a mass at $m/z = M^* + 2$ was found. This mass could derive from the biradical, which picked up two hydrogen atoms. The intensities were very low, and it was unclear whether the peaks formed part of the isotopic pattern, so that collision experiments were conducted in order to clarify the origin of those peaks.
8. TRAPPING AND COLLISION EXPERIMENTS

8.2.2. Collisions with Argon and Xenon as Inert Gases

As inert collision gases, argon ($M_{Ar} = 40$) and xenon ($M_{Xe} = 131$) were employed.

Because of its higher molecular mass, xenon transmits more energy upon collision (due to the physical equations of conservation of momentum and center of mass) and therefore a reaction occurs more likely.\(^{266}\)

The collision experiments were carried out in the 8-pole-region.

Table 8-17: Results of the 8-pole-collision experiments of various azaenediynes employing various pressures of argon and xenon as inert gases

<table>
<thead>
<tr>
<th>#</th>
<th>Azaenediyne / Selected m/z</th>
<th>p (Ar) [mTorr]</th>
<th>m/z</th>
<th>p (Xe) [mTorr]</th>
<th>m/z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>198 / 387 $[M^+ 1 + (H)]$</td>
<td>0</td>
<td>387</td>
<td>0</td>
<td>387</td>
</tr>
<tr>
<td>2</td>
<td>198 / 387 $[M^+ 1 + (H)]$</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>387</td>
</tr>
<tr>
<td>3</td>
<td>198 / 387 $[M^+ 1 + (H)]$</td>
<td>10</td>
<td>387</td>
<td>10</td>
<td>387</td>
</tr>
<tr>
<td>4</td>
<td>199 / 315 $[M^+ 1 + (H)]$</td>
<td>0</td>
<td>315</td>
<td>0</td>
<td>315</td>
</tr>
<tr>
<td>5</td>
<td>199 / 315 $[M^+ 1 + (H)]$</td>
<td>10</td>
<td>315</td>
<td>10</td>
<td>315</td>
</tr>
<tr>
<td>6</td>
<td>206 / 401 $[M^+ \text{ (cation)}]$</td>
<td>0</td>
<td>401</td>
<td>0</td>
<td>401</td>
</tr>
<tr>
<td>7</td>
<td>206 / 401 $[M^+ \text{ (cation)}]$</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>401</td>
</tr>
<tr>
<td>8</td>
<td>206 / 401 $[M^+ \text{ (cation)}]$</td>
<td>10</td>
<td>401</td>
<td>10</td>
<td>401</td>
</tr>
<tr>
<td>9</td>
<td>208 / 329 $[M^+ \text{ (cation)}]$</td>
<td>0</td>
<td>329</td>
<td>0</td>
<td>329</td>
</tr>
<tr>
<td>10</td>
<td>208 / 329 $[M^+ \text{ (cation)}]$</td>
<td>10</td>
<td>329</td>
<td>10</td>
<td>329</td>
</tr>
</tbody>
</table>

Concerning the collisions with argon, at higher collision energies as well as at higher pressures, the selected mass usually disappeared, or the signal-to-noise ratio got worse. No hints for cyclization products could be seen (see Table 8-17). Analogous results were obtained upon the employment of xenon.

The highest collision energy used was 120 eV (offset = –123 V). The center of mass-energies in the collision experiments were calculated to be between 251.0 kcal·mol\(^{-1}\) and 311.8 kcal·mol\(^{-1}\) (depending on the particular azaenediyne) for the collisions with argon, and between 681.4 kcal·mol\(^{-1}\) and 812.8 kcal·mol\(^{-1}\) for the collisions with xenon (see Experimental Section, Chapter 11.4 and Table 11-1, for details). The center of mass-energy is the kinetic energy (released upon impact of the collision partners) that maximal can be converted into internal energy — and therefore is available for cyclization or fragmentation reactions.\(^{266}\)
8.2.3. Collisions with Chloroform and Deutero-Chloroform as Donors

Collision experiments were also carried out with chloroform as a hydrogen donor and deutero-chloroform as a deuterium donor. Upon collisions, these solvents could transmit hydrogen or deuterium to the presumably formed biradical. In the spectra was searched for peaks with a mass increase of $\Delta = +2$ or $\Delta = +4$, respectively.

Experiments in the 8-pole-region showed no other peaks than the respective cation mass, neither for higher collision energies. The duration of stay in the 8-pole-region was probably too short in order to observe a biradical formation with subsequent abstraction of hydrogen or deuterium. Hence, the experiments were repeated in the 24-pole as well.

Table 8-18: Results of the 24-pole-collision experiments of various azaenediyynes employing various pressures of CHCl$_3$ and CDCl$_3$ as donor gases

<table>
<thead>
<tr>
<th>#</th>
<th>Azaenediyne / m/z</th>
<th>p (CHCl$_3$) [mTorr]$^{\text{xvi}}$</th>
<th>m/z</th>
<th>p (CDCl$_3$) [mTorr]$^{\text{xvi}}$</th>
<th>m/z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>198 / 387 [M$^+$ + 1 (H)]</td>
<td>0</td>
<td>387</td>
<td>0</td>
<td>387</td>
</tr>
<tr>
<td>2</td>
<td>198 / 387 [M$^+$ + 1 (H)]</td>
<td>1000</td>
<td>387</td>
<td>840</td>
<td>387; 391 (weak)</td>
</tr>
<tr>
<td>3</td>
<td>198 / 387 [M$^+$ + 1 (H)]</td>
<td>--</td>
<td>--</td>
<td>1200</td>
<td>387; 391 (stronger)</td>
</tr>
<tr>
<td>4</td>
<td>199 / 315 [M$^+$ + 1 (H)]</td>
<td>--</td>
<td>--</td>
<td>0</td>
<td>315</td>
</tr>
<tr>
<td>5</td>
<td>199 / 315 [M$^+$ + 1 (H)]</td>
<td>--</td>
<td>--</td>
<td>1190</td>
<td>315; 317</td>
</tr>
<tr>
<td>6</td>
<td>206 / 401 [M$^+$ (cation)]</td>
<td>0</td>
<td>401</td>
<td>0</td>
<td>401</td>
</tr>
<tr>
<td>7</td>
<td>206 / 401 [M$^+$ (cation)]</td>
<td>1190</td>
<td>401</td>
<td>1170</td>
<td>401; 403</td>
</tr>
<tr>
<td>8</td>
<td>208 / 329 [M$^+$ (cation)]</td>
<td>--</td>
<td>--</td>
<td>0</td>
<td>329</td>
</tr>
<tr>
<td>9</td>
<td>208 / 329 [M$^+$ (cation)]</td>
<td>--</td>
<td>--</td>
<td>1170</td>
<td>329</td>
</tr>
</tbody>
</table>

Without using chloroform or deutero-chloroform as a collision gas, no increase of mass could be seen at all (Table 8-18, entries 1, 4, 6, 9). Upon rising the pressure, however, in some cases other small peaks could be detected. Entries 5 and 7 show for the collisions with CDCl$_3$ – apart from the educt mass – a tiny peak with a mass difference of $\Delta = +2$, which could not be explained. The only hint for an abstraction of deuterium gave entries 2 and 3: A small peak at m/z = 391 suggested the uptake of two deuterium atoms from a biradical deriving from 198 (m/z = 387).

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$x^{\text{vi}}$ Here, the source pressure is given. The pressure in the collision cell was lower.
8.2.4. Collisions with Nitrogen Monoxide as a Radical Trap

Nitrogen monoxide (•N=O) is a radical gas. Similar to the trapping experiments with TEMPO (210) in the liquid phase, nitrogen monoxide could act as a gaseous radical trap in the ESI-MS.

Roth\textsuperscript{268} and Hopf \textit{et al.} conducted a gas phase thermolysis of enediyne 4 at temperatures between 177 °C and 218 °C in a glass apparatus.\textsuperscript{269} They used nitrogen monoxide-partial pressures of 0.27 mbar – 4.94 mbar (202.52 mTorr – 3.71 Torr) in presence of 1000 mbar (750 Torr) of the inert gas sulfur hexafluoride (SF\textsubscript{6}). As a trapping product of biradical intermediate 5, they found compound 230 (Figure 8-7).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure8_7.png}
\caption{Employment of nitrogen monoxide as a gaseous radical trapping agent by Roth and Hopf\textsuperscript{268};\textsuperscript{269}}
\end{figure}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{#} & \textbf{Azaenediynne / m/z} & \textbf{p (NO) [mTorr]} & \textbf{m/z} \\
\hline
1 & 198 / 387 \([M^+ + 1 (H)]\) & 0 & 387 \\
2 & 198 / 387 \([M^+ + 1 (H)]\) & 1.8 (collision energy = 50 eV) & 387 \\
3 & 198 / 387 \([M^+ + 1 (H)]\) & 1.8 (collision energy = 100 eV) & 387 \\
4 & 206 / 401 \([M^+ (cation)]\) & 0 & 401 \\
5 & 206 / 401 \([M^+ (cation)]\) & 1.8 (collision energy = 50 eV) & 401 \\
6 & 206 / 401 \([M^+ (cation)]\) & 1.8 (collision energy = 100 eV) & 401 \\
\hline
\end{tabular}
\caption{Results of the 24-pole-collision experiments of various azaenediynnes employing various pressures of NO as a radical trap}
\end{table}

In the experiments carried out here, the collision cell did not allow pressures exceeding 10 mTorr. As can be seen in Table 8-19, no trapping products could be detected, neither at higher collision energies.
8.2.5. Collisions with Molecular Hydrogen in the LCQ

The collisions with hydrogen were performed on a Finnigan MAT LCQ mass spectrometer equipped with an ESI source. The LCQ is an ion trap device, and therefore allowed longer residence times (ca. 50 ms) of the ions in the analyzer region. The idea was to substitute helium – the standard gas used for daughter spectra after selecting a mass – with hydrogen in order to induce cyclization and to see an uptake of hydrogen. Dichloromethane was used as a spraying solvent. The gas pressure in the mass analyzer cavity was ca. 10 mTorr.

Table 8-20: Results of the collision experiments of various azacnediynes employing molecular hydrogen as a collision gas

<table>
<thead>
<tr>
<th>#</th>
<th>Azaenediyne / m/z</th>
<th>m/z (collision energy &lt; 80 %)</th>
<th>m/z (collision energy &gt; 80 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>198 / 387 [M⁺ + 1 (H)]</td>
<td>387</td>
<td>fragmentation products</td>
</tr>
<tr>
<td>2</td>
<td>199 / 315 [M⁺ + 1 (H)]</td>
<td>315</td>
<td>fragmentation products</td>
</tr>
<tr>
<td>3</td>
<td>206 / 401 [M⁺ (cation)]</td>
<td>401</td>
<td>fragmentation products</td>
</tr>
<tr>
<td>4</td>
<td>208 / 329 [M⁺ (cation)]</td>
<td>329</td>
<td>fragmentation products</td>
</tr>
</tbody>
</table>

As can be seen in Table 8-20, in no case an uptake of hydrogen could be observed. Collision energies higher than 80 % led to several fragmentation products, and below 80 % still the mass of the educt cation could be detected.
9. Discussion of Results: Achievements and Summarizing Overview

9.1. Syntheses of Azaenediynes — Conclusion

9.1.1. Conducted Approaches

In order to synthesize stable azaenediynes based on an imidazole or a benzimidazole core, several approaches were put into execution. Concerning the attachment of an alkynyl moiety to position N-1 of an imidazole system, the best method was the use of alkynyl cation equivalents on an imidazolate-type anion as a nucleophile. Attempts to build up the triple bond with the aldehyde approach, via a coupling reaction or via a base catalyzed isomerization reaction were not successful.

In order to build up a triple bond at position C-2 of a benzimidazole system, the conducted coupling reactions gave low yields. Various condensation approaches employing propargyl aldehyde with α,α'-diketones plus an ammonia donor or with a 1,2-diamine led to unsatisfying results. The condensation of a 1,2-diamine with an imidate salt, however, formed part of the final pathway.

9.1.2. The Final Synthetic Strategy

A generally applicable synthetic strategy leading to stable C,N-bisalkynylated benzimidazole-azaenediynes was developed. The universal applicability is due to the fact that the substitution pattern of the particular building blocks – the imidate salt and the 1,2-diamine – can be changed. This allows a further tuning of properties of the target molecules.
Figure 9-1: The ultimate synthetic strategy for the preparation of benzimidazole-based azaenediynes — Part I: Preparation of the phenylethynyl-benzimidazoles

The definitive synthetic pathway for the alkylnyl moiety at C-2 started from purchasable phenylpropiolic acid (177) (see Figure 9-1). Via its acid chloride 178, carboxylic acid 177 was converted into the acid amide 179. The latter one was obtained in a yield of 76%. Subsequent treatment of amide 179 with Meerwein's salt triethyloxonium tetrafluoroborate gave imidate
tetrafluoroborate $180$ in 82 % yield. It is noteworthy that instead of $177$, also other substituted propiolic acids could be used in order to employ an imidate with a different substitution pattern in posterior synthetic steps (compare also Figure 10-1 and Figure 10-2).

The synthesis of the benzimidazole core started from the aromatic 1,2-diamines $165$ or $91$, respectively (see Figure 9-1). However, in order to design a different substitution pattern at the benzimidazole system, also a differently substituted 1,2-diamine could be employed. For the preparation of phenylethynyl-benzimidazole $109$, simply purchasable $\alpha$-phenylene-diamine ($165$) could be used. Condensation with imidate $180$ gave $109$ in 37 % yield; intermediate $197$ was obtained in 20 % yield. The condensation reaction is the intersection point of two parallel syntheses.

For the perfluoro-pathway, first the perfluorinated 1,2-diamine $91$ had to be synthesized. This was carried out by transforming pentfluoro-nitrobenzene ($184$) into nitro-compound $185$ (66 % yield), which was then reduced to give the perfluorinated 1,2-diamine $91$ in 67 % yield. Condensation of $91$ with $180$ led to the perfluoro-phenylethynyl-benzimidazole $191$ in a yield of 21 %.

As a byproduct, the interesting perfluorinated benzodiazepine $196$ was isolated in 16 % yield. The low yields in the condensation steps could partially be explained with side reactions; the formation of byproducts could be elucidated mechanistically.

Heterocyclic azaenediyne were finally designed by using the alkynyliodonium salt $69$ as an alkyny cation equivalent on the particular phenylethynyl-benzimidazole ($191$ or $109$, respectively, see Figure 9-2). The perfluorinated azaenediyne $198$ was obtained in a yield of 53 %, and its non-fluorinated analogue $199$ in 50 % yield.

The conversion of the parent azaenediyne into their methylated derivatives was realized by employment of Meerwein's salt trimethyloxonium tetrafluoroborate. The perfluorinated, methylated azaenediyne $206$ could be produced in a yield of 75 %, and the non-fluorinated benzimidazolium tetrafluoroborate salt $208$ in 98 % yield (Figure 9-2).
Interestingly, methanolysis of methyl-azaenediyne 206 gave compound 207 in a yield of 77%. Methanol did not only attack as a nucleophile, but also induced cleavage of the trimethylsilyl group.
9.1.3. Novel Compounds

The aim of this work was to synthesize azaenediynes that were stable under thermolysis conditions. This objective was achieved with the synthesis of the novel compounds shown in Figure 9-3.

The perfluorinated azaenediyne 198 was the first representative of the novel class of benzimidazole-based, heterocyclic azaenediynes. This class features alkynylimines with a triple bond at a nitrogen atom, which forms part of a benzimidazole system. The second nitrogen atom acts as an acceptor for activators, triggering the Bergman rearrangement.

Methylation of 198 gave the perfluorinated methyl-azaenediyne 206, which showed an interesting chemistry. However, protonation and ethylation attempts in order to obtain a more reactive compound failed.

After the construction of the fluorinated systems, also the non-fluorinated azaenediyne 199 and its methyl derivative 208 were prepared.
The parent azaenediyne 198 and 199 (see Figure 9-3) turned out to be extremely stable in air and water, and especially under thermolysis conditions. The methylated analogues 206 and 208 were more sensitive to hydrolysis, but still showed sufficient stability in thermolysis experiments. All azaenediyne compounds were completely characterized and their reactivity and behavior in thermolyses investigated *in extenso*.

Several other compounds were prepared during the investigations concerning the best synthetic pathway or the exploration of reactivity. Novel and fully characterized compounds synthesized in the course of this thesis are presented in Figure 9-4.

![Figure 9-4: Miscellaneous novel and fully characterized compounds prepared in this thesis](image-url)
Partially characterized, but novel compounds prepared within the framework of this thesis are shown in Figure 9-5.

Figure 9-5: Miscellaneous novel and partially characterized compounds prepared in this thesis
9.2. Reactivity Considerations of the Synthesized Azaenediynes

The protonation attempts of azaenediynes 198 and 199 were undertaken in order to obtain more reactive compounds for the Bergman cyclization (see Introduction, Chapters 6.3.5 and 6.3.6). However, no protonated products could be isolated, and all *in situ*-protonations led to decomposition of material or did not show convincing results. Hoffner\textsuperscript{91} neither was able to satisfactorily show an activation caused by protonation.

A brilliant idea was then that a methyl group should have the same electronic effect as a proton. Therefore, methylation reactions were carried out, leading to the stable methyl-azaenediynes 206 and 208 (see Figure 9-6).

A comparison of the Bergman rearrangements of the non-methylated azaenediynes 198 and 199 with the methylated ones (206 and 208) is shown in Figure 9-6: Upon cyclization, in both cases – 233b / 234b and 231b / 232b – a resonance structure with an aromatic sextet in the newly formed ring can be drawn. However, structure 231b / 232b is unfavorable due to separated charges. In 233a / 234a and 231a / 232a those rings are not aromatic.
As a consequence, the methylated species 206 and 208 were expected to undergo Bergman cyclization more readily than 198 and 199. And because of their increased stability, the bi-radicals 233 / 234 were expected to show better hydrogen abstraction ability than 231 / 232.
9.3. Thermolysis Experiments in the Liquid Phase (in Solution) — Conclusion

9.3.1. Thermolyses of the Azaenediynes 198 and 199

The perfluorinated azaenediyne 198 turned out to be extremely stable under all tested thermolysis conditions. No hydrogen abstraction or addition of solvent fragments were observed upon heating in diisopropyl ether up to 180 °C and for 48 h. Heating in 1,4-dioxane (up to 210 °C, 48 h) and 1,4-cyclohexadiene showed the same results, however, these solvents were found to give decomposition products at higher temperatures and therefore were not used in further attempts.

Heating in neat chlorobenzene as well as in chlorobenzene with 1 eq or 3 eq of TEMPO (210) (both up to 240 °C and 48 h) neither showed any hints for cyclization. Only educt and TEMPO (210) were detected.

Even heating a sample of 198 in diisopropyl ether in an excess of water for 24 h at 120 °C did not destroy the compound. The starting material could be recovered.

Like its perfluorinated analogue 198, the non-fluorinated azaenediyne 199 turned out to be present under all conditions in diisopropyl ether. It was not destroyed at higher temperatures and longer reaction times. The only observed changes consisted in weak start spots on the TLC plates, some additional peaks in the GC/MS and ESI-MS and slight color changes of the reaction mixture when heated to 180 °C for 24 h. The results did not point at cyclization products, but rather at decomposition products derived from burned material at the tube walls.

When compound 199 was heated in chlorobenzene with 1 eq and 3 eq of TEMPO (210), even at temperatures up to 240 °C no cyclization products could be detected. Apart from unidentifiable decomposition products in negligible amounts, mainly educt 199 and TEMPO (210) were detected.
9.3.2. Thermolyses of the *in situ*-Protonated Azaenediyne 198

Various acids were added directly before heating the samples in pressure tubes. The thermolysis experiments of the *in situ*-protonated azaenediyne 198 showed, at gentle conditions (1 eq of acid, relatively low temperature, short reaction time), either educt on the TLC plates or in a GC/MS analysis, or protonated educt in the ESI-MS. At higher temperatures, longer reaction times or when an excess of acid was used, usually decomposition and loss of material took place. No evidence was found for a cyclization induced by protonation.

The conditions employed were diisopropyl ether with triflic acid (1 eq and 20 eq, with and without buffer), and diisopropyl ether with 1 eq of trifluoroacetic acid. At harsh conditions even diisopropyl ether was destroyed, forming propene. Also 1,4-dioxane with 1 eq of triflic acid or with 1 eq of deutero-hydrochloric acid was used. Harsh heating led to destruction of azaenediyne 198. Another experiment using 1 eq of trifluoroacetic acid on a solution of azaenediyne 198 in chlorobenzene with 3 eq of TEMPO (210) led to several decomposition products.

9.3.3. Thermolyses of the Methylated Azaenediynes 206 and 208

The methylated, perfluorinated azaenediyne 206 turned out to be relatively stable when heated in diisopropyl ether at moderate conditions. At rough conditions like at 180 °C for 24 h, however, apart from the educt at \( m/z = 401 \), additionally a peak with the mass of \( \Delta (m/z) = +60 \) was observed. Various separation attempts of up-scaled reactions did not lead to the isolation of a substance with \( m/z = 461 \).

A possible explanation would be the nucleophilic addition of one molecule of *iso*-propanol, as a similar methanol-addition was observed when compound 206 was reacted with methanol. On the other hand, no such product could be isolated, and various tests showed that the employed diisopropyl ether remained stable under the thermolysis conditions and did not transform into *iso*-propanol and propene.

The non-fluorinated methyl-azaenediyne 208 showed a similar behavior when heated in diisopropyl ether: It remained stable at relatively gentle conditions. At harsher conditions, apart from the cation mass of the educt \( m/z = 329 \), also a peak at \( m/z = 389 (\Delta (m/z) = +60) \) was observed. A molecule corresponding to the peak at \( m/z = 389 \) could not be isolated.
Thermolysis experiments employing TEMPO (210) as a radical trap gave the following results: When the methylated, perfluorinated azenidoiyne 206 was heated to 70 °C for 1 h or 24 h, apart from educt, also peaks at \( m/z = 558 \), \( m/z = 140 \) and occasionally at \( m/z = 419 \) were detected. Using TEMPO (210) even in large excess did not affect the product distribution. Chromatography and crystallization attempts in order to isolate a compound with the mass \( m/z = 558 \) or its possible degradation products were not successful. Presumably, that compound occurred in a low concentration, and what is more, it formed part of an ionic mixture.

The compound showing a peak at \( m/z = 558 \) could be a mono-trapping product, formed upon addition of a proton and one equivalent of TEMPO (210) to the biradical derived from 206. However, the source of hydrogen remained unclear. When the reaction was conducted in deuterated solvents, no deuterium uptake could be observed, which excluded the solvents as hydrogen donors.

Another possibility would be a nucleophilic attack of one equivalent of TEMPO (210) on the educt, which could lead to a similar product like 207. No such compound was found, though.

Finally, a third alternative suggested the peak at \( m/z = 558 \) being a gas phase adduct. A further indication for a gas phase adduct could be that \( m/z = 558 \) was also detected at more gentle conditions (heating at 70 °C for 1 h, see entry 1 in Table 8-14).

At temperatures of 130 °C and 240 °C, mainly decomposition occurred. A peak at \( m/z = 142 \) was found to originate from piperidinium salt 223. This TEMPO-fragmentation product could be crystallized and characterized by X-ray analysis.

A peak at \( m/z = 419 \) in the ESI-MS spectra was mainly caused by addition of water to the cation of educt 206.

For the methylated, non-fluorinated azenidoiyne 208, a peak at \( m/z = 486 \) suggested an adduct consisting of the educt cation (\( m/z = 329 \)) plus TEMPO (210) (\( m/z = 156 \)) plus a proton. This peak was found at moderate heating for 24 h at 70 °C and 1 h at 130 °C. An analogous peak was also found for the perfluorinated analogue 206 at \( m/z = 558 \).

However, as for 206, no compound with a peak at \( m/z = 486 \) could be isolated from the reaction mixture. Therefore, no evidence was found for a trapped product. The peak could also derive from a gas phase adduct with the same mass. A daughter MS spectrum of \( m/z = 486 \) neither gave further hints.
9.4. Collision Experiments and Trapping Experiments in the Gas Phase — Conclusion

In gas phase experiments in a TSQ ESI-MS device, the synthesized azaenediynes 198 and 199 and the methyl-azaenediynes 206 and 208 were collided with various reaction partners. The resulting mass spectrum was searched for products formed upon the collisions or trapping procedures.

Upon employment of argon and xenon as inert collision partners, even at high collision energies (leading to a huge delivery of energy on impact) and at the highest possible inert gas pressures (ensuring a high probability of collisions), no hints for cyclization products could be seen.

The collision experiments employing chloroform and deuterated chloroform as donors should clarify whether a delivery of hydrogen or deuterium, respectively, took place. Generally, no peaks showing such mass increase could be found, neither at higher collision energies nor at higher pressures. Only in case of a collision of azaenediyne 198 with deuterated chloroform, occasionally a mass peak of $\Delta (m/z) = +4$ could be observed.

The use of nitrogen monoxide as a gaseous radical trap showed no trapping products, but only the particular azaenediynes as educts.

The substitution of helium by molecular hydrogen in a LCQ ESI-MS device was done in order to reproduce an occasionally observed mass of $\Delta (m/z) = +2$ in some daughter spectra in case of compound 199. No uptake of hydrogen could be observed, though.
9.5. Why did the Synthesized Azaenediynes not Undergo Cyclization Reactions at all?

The non-methylated azaenediynes 198 and 199 gave no Bergman cyclization products at all, protonation mainly led to decomposition and the methylated azaenediynes 206 and 208 did not cyclize, showed decomposition products or only in some particular cases suggested a reactivity that might have derived from an assumed biradical as an intermediate, respectively. However, in none of the cases a clear evidence for a cyclization product was found. And unfortunately, the concept suggesting an increased reactivity of the azaenediynes upon protonation or methylation, respectively, could not be proven yet.

How could that inactivity concerning Bergman cyclization be explained?

First of all, the bulkiness of the trimethylsilyl group attached to one of the triple bonds in all investigated azaenediynes could be a reason: Upon cyclization, a steric hindrance with the phenyl group at the other triple bond could occur (Figure 9-7).

![Figure 9-7: Illustration of steric hindrance upon cyclization of the synthesized azaenediynes (anion omitted for clarity)](image)

The biradicals 231a / 232a and 233a / 234a could – if they are formed in the equilibrium at all – simply undergo the reverse reaction to form again the parent azaenediynes.
Secondly, Bergman cyclization was neither observed in similar systems: Kerwin\textsuperscript{98} \textit{et al.} reported the synthesis of the imidazole-based azaenediyne 62 (Figure 9-8). They started from the activated imidazole 60. Deprotonation and subsequent alkynylation with the alkynylidonium salt 235 led to compound 61 as organohalide. 61 was then converted into 62 in a coupling reaction using 43 as the acetylenic compound.

![Chemical Reaction Diagram](image)

Figure 9-8: Synthesis and cyclization attempts of an imidazole-based azaenediyne by Kerwin\textsuperscript{98}

When Kerwin\textsuperscript{98} \textit{et al.} heated a solution of 62 in chlorobenzene containing an excess of 1,4-cyclohexadiene for 2 d at 150 °C, they found no remaining azaenediyne 62. When they analyzed the reaction mixture by mass spectrometry, they found a peak proposing a compound that added two hydrogen atoms to 62. However, they were not capable of isolating that compound from the complex reaction mixture.

Kerwin\textsuperscript{98} \textit{et al.} also synthesized 237 (see Figure 9-9). They first followed the pathway already described in Figure 9-8. Then, a coupling reaction using organohalide 61 and acetylenic compound 236, gave – after cleavage of the protecting group – compound 237 (Figure 9-9). This heterocyclic azaenediyne shows no steric hindrance concerning Bergman cyclization. Upon heating a solution of 237 in neat 1,4-cyclohexadiene for 2 d at 100 °C, they obtained two major products: Cyclopentapyrazine 241 and cyclopropane-cyclopentapyrazine 242 (Figure 9-9). Their hypothetical explanation for these products was the following pathway: Azaenediyne 237 first formed biradical 238, which then underwent retro-Bergman cyclization (ring opening) to give the cyclic cumulene 239. Cumulene 239 subsequently rearranged to carbene 240, and reaction with 1,4-cyclohexadiene gave compounds 241 and 242.
Figure 9-9: Synthesis and cyclization hypotheses of an imidazole-based azaenediyne by Kerwin.98

However, heating of 237 in chlorobenzene containing an excess of 1,4-cyclohexadiene for 1 d at 100 °C led to imidazo[1,2-a]pyridine 244. Kerwin's hypothesis for the formation of 244 features the same pathway as described above (see Figure 9-9): Once cumulene 239 is formed, it could also rearrange to biradical 243, which then supposedly abstracted hydrogen from 1,4-cyclohexadiene and chlorine from chlorobenzene to yield 244.
Kerwin’s description\textsuperscript{98} of the abstraction of chlorine from chlorobenzene is surprising: and a ring opening (retro-Bergman cyclization) to the corresponding nitrile or the cyclic cumulene \textsuperscript{239} as well due to steric effects.

In neither of the thermolysis reactions, Kerwin\textsuperscript{98} \textit{et al.} were able to isolate direct trapping products corresponding to a putative biradical intermediate. Therefore, \textit{a second reason} could be that the azaenediyne systems \textsuperscript{198} and \textsuperscript{199} as well as \textsuperscript{206} and \textsuperscript{208} do not undergo Bergman cyclization at all — they simply do not react, decompose or react via other pathways.

\textit{A third reason} for the inactivity of the investigated azaenediynes concerning Bergman cyclization could be that the distance of the respective carbon atoms of the triple bonds is too large to undergo cyclization: From X-ray analyses, the distances \(d\) between the terminal \(sp\)-carbons were determined to be \(d = 4.15\ \text{Å} \) for \textsuperscript{198}, \(d = 4.18\ \text{Å} \) for \textsuperscript{206} and \(d = 4.11\ \text{Å} \) for \textsuperscript{208}.

Also Nicolaou\textsuperscript{270} proposed that the distance \(d\) between the terminal acetylenic carbon atoms is a major determinant of reactivity.\textsuperscript{271} While Nicolaou\textsuperscript{270} suggested values of \(d = 3.20\ \text{Å} \) to \(d = 3.31\ \text{Å} \) being necessary for biological relevant reactivity, calculations extended this range to \(d = 2.90\ \text{Å} - d = 3.40\ \text{Å}.\textsuperscript{272}

A comparison of these distances demonstrates that the azaenediynes prepared in the framework of this thesis are not prone to undergo cyclization.
9.6. **Perfluorinated versus Non-Fluorinated Azaenediynes — A Comparison of Reactivity**

A comparison of the perfluorinated system 198 with its non-fluorinated analogue 199 showed no change in reactivity — both compounds were practically inert under the thermolysis conditions. For the methylated azaenediynes, in the few cases suggesting a reactivity, the turnover for the perfluorinated 206 seemed to be higher than for the non-fluorinated 208. However, this was only found by ESI-MS data. A general difference in reactivity due to the fluorine substituents was not found.

An explanation could be that the distance between the fluorine atoms and the atoms directly involved in the Bergman cyclization was too large to result in an observable effect.

Effects were published for other systems, however: Jones and Warner reported enediyne systems that are halogenated at the double bond to cycloaromatize more slowly than their unsubstituted counterparts, and suggested a higher cyclization barrier for those cases.

On the other hand, they calculated the singlet – triplet gap to decrease as halogens were added to a para-benzylene-structure. Chen et al. elucidated the singlet – triplet gap being a measure of reactivity of diradicals relative to monoradicals: Non-interacting triplets show nearly radical reactivity, but the lower energy singlets show much lower reactivity. Concluding, a smaller singlet – triplet gap (caused by halogenation) should lead to an increased hydrogen atom abstraction rate.

A substituent in the acetylenic position was reported to show even a stronger effect than one in the vinyl position. The substitution with fluorine led to a strong activation of the enediyne (see).
10. Outlook

Several novel heterocyclic azaenediynes were synthesized and completely characterized in the course of this thesis. However, the azaenediynes 198 and 199 showed no reactivity concerning Bergman cyclization at all — they were extremely stable. Chen's creative suggestion to replace one carbon atom of the naturally occurring enediyne moiety with a nitrogen atom created a handle for reactivity tuning. However, protonation mainly led to decomposition, and the methylated azaenediynes 206 and 208 were too stable, or else indicated reactivity not pointing at Bergman cyclization, respectively — the influence of methylation on the aza-Bergman reactivity could not be proven yet.

With these results, how could the design of the synthesized azaenediynes be improved — in order to produce a biradical being able to abstract hydrogen atoms from DNA under physiological conditions?

Generally, the unexpected stability of the benzimidazole-based azaenediynes 198, 199, 206 and 208 does highlight a difference between the Bergman reaction of the parent enediynes and the chemistry of the N-analogous azaenediyne system. The novel compounds therefore represent a fertile area for further studies, which should encourage motivated researchers to continue exploring their reactivity.

It should not be forgotten that tumors are still amongst the main causes of death worldwide — with a tendency that increases yearly. The long duration of the illness and the monumental suffering it causes the patients, their relatives and friends, makes it an absolute duty for scientists to continue with cancer research — in order to considerably improve prevention, early detection, diagnosis, effective treatment and understanding of the biomolecular mechanisms of cancer.

In general, cyclization is much more likely to occur in case of a strained enediyne ring system. Nicolaou et al. compared the ring size, the distance between the acetylenic carbons that are relevant for cyclization and the respective stability concerning Bergman cyclization in strained cyclic systems with acyclic systems. They found that 10-ring systems are much more cyclization-prone than 11-ring and 12-ring systems bearing the enediyne moiety.
A cyclic azaenediyne system with a benzimidazole core could be built up by employing the generally applicable synthetic strategy developed within the framework of this thesis:
As was shown previously, the condensation of a 1,2-diamine 245 with an imidate salt 246 led to an azaenediyne 247 in a few steps (Figure 10-1).

![Reaction Scheme](image)

**Figure 10-1:** Feasible future approaches toward a heterocyclic 10-ring azaenediyne

It is noteworthy that the substitution pattern of the particular building blocks – the imidate 246 and the diamine 245 – can be changed. Although it was shown that perfluorination compared to a non-fluorinated azaenediyne 247 (if R¹ = F or R¹ = H) practically did not affect the cyclization reactivity, a different substitution pattern would allow a further tuning of properties. In order to create a water-soluble drug, e.g., the future chemist could tune the solubility by introducing hydrophilic groups for R¹ and R² (Figure 10-1).
The protecting TMS-group in compound 247 could be replaced by a phenyl group\textsuperscript{126,127,128} to give the heterocyclic azaenediyne 248. If \( R^2 = R^3 = 1 \) in compound 248, a ring closure (yielding 249) could be achieved by the Ullmann reaction.\textsuperscript{276,277} Ring formation could also be performed with the aid of a diazonium salt at one of the rings (\( R^2 = N_2^+ X^- \), \( R^3 = H \), or vice versa): The aryl portion of the diazonium moiety can couple with the other aromatic ring.\textsuperscript{278} The 10-ring azaenediyne 249 then could subsequently be methylated to give 250, using the methylation reactions carried out in this thesis.

Prior to ring closure, the triple bonds could be protected by complex formation with dicobalt octacarbonyl, \( \text{Co}_2(\text{CO})_8 \).\textsuperscript{279} Such protections result in an additional (\( \text{Co}(\text{CO})_3 \)) moiety (examples:\textsuperscript{280,281,282,283}), and were also carried out successfully on an alkynylimine by Hoffner.\textsuperscript{91} An interesting point is that upon protection, the usual angle of 180° at the triple bond is reduced to about 120°,\textsuperscript{281} which could further aid in a ring formation reaction as it could shorten the distance between the centers to be coupled.
Figure 10-2 shows a potential approach toward a heterocyclic 12-ring azaenediyne 251: If \( R^2 = R^3 = 1 \) in compound 248, a ring closure could be performed employing acetylene, H–C≡C–H, in a Sonogashira\textsuperscript{155,156} coupling reaction. Subsequent methylation could transform the 12-ring azaenediyne 251 into its methyl-analogue 252.

![Diagram](image-url)
11. Experimental Section

11.1. Materials and Methods

11.1.1. Solvents

All solvents used for reactions were purchased in puriss. p. a. quality. Solvents for column chromatography were distilled from technical grade solvents.

Solvents were dried as follows (refluxing or drying, respectively, with subsequent distilling carried out under a nitrogen atmosphere): 

- Acetonitrile, dichloromethane, iso-propanol and methanol were refluxed over calcium hydride.
- Diethyl ether and n-hexane were refluxed over a sodium/potassium-alloy.
- Diisopropylamine was refluxed for 5 min over sodium hydride.
- Triethylamine was refluxed for 2 h over calcium hydride.
- DMF was dried first over MgSO₄ and then overnight over activated 4 Å molecular sieve, and subsequently distilled in a high vacuum at a temperature below 40 °C.¹⁷⁺
- Ethanol was refluxed over sodium and ethyl phthalate.
- THF was refluxed over potassium.
- Toluene was refluxed over sodium.

11.1.2. Glassware

The glassware was dried at 150 °C for 2 d. Temperature sensitive glassware or plastic parts were dried in an exsiccator over phosphorus pentoxide and subsequently flushed with argon.

¹⁷⁺ At higher temperatures or upon standing at rt for several days, DMF decomposes to dimethylamine and carbon monoxide: H–(C=O)–N(CH₃)₂ → H–N(CH₃)₂ + C=O.
11.1.3. Reagents and Various

1,2-Phenylenediamine (o-phenylenediamine) (165) was purified by refluxing a dichloromethane solution, adding activated charcoal, continued refluxing for 5 min followed by hot filtration through two fluted filters and evaporation.\textsuperscript{284,285} The obtained solid was then recrystallized from hot dichloromethane, filtered and washed with dichloromethane. The latter procedure was repeated two times, and the obtained crystals were stored under argon and protected from light.

1,2-Diaminotetrafluorobenzene (91) was recrystallized from dichloromethane (with activated charcoal), filtered under argon and dried \textit{in vacuo}. The obtained crystals were stored under argon and protected from light. If quite brown, 91 was purified by flash column chromatography on silica with CH\textsubscript{2}Cl\textsubscript{2} as a solvent.

Molecular sieve 4 Å (type 4A-401 from CU, Chemie Uetikon AG, Switzerland) was activated by heating for 4 d to 250 °C in a Büchi GKR-51 Kugelrohr oven at 4·10\textsuperscript{-3} mbar.

Activated charcoal \textit{puriss.} (powder, Darco G60) was purchased from Fluka.

Some experiments were prepared inside a M-Braun labmaster100, a M-Braun labmaster130 or a M-Braun UNlab dry box in an argon atmosphere.

The progress of reactions was monitored by TLC and/or GC/MS-detection (the latter one after a micro-work-up).

11.1.4. Suppliers of Chemicals and Special Solvents

Special reagents (in alphabetical order) were purchased from the following suppliers:

- Ammonia gas (99.98 %) from Multigas.
- [D\textsubscript{5}] Chlorobenzene (99 %) from Cambridge Isotope Laboratories, Inc.
- 1,2-Phenylenediamine (99.5 %) from Aldrich.
- 2-Mercaptobenzimidazole (98 %) from Aldrich.
- 1,4-Dioxane \textit{puriss.} (absolute, over molecular sieve (H\textsubscript{2}O ≤ 0.01 %) from Fluka.
- 5-Nitrobenzimidazole (99 %) from Merck-Schuchardt.
- Benzimidazole \textit{purum} (98 %) from Fluka.
- Bis(trimethylsilyl)acetylene \textit{purum} (≥ 97 %) from Fluka.
- Butyllithium solution (≤ 1.6 M in hexanes) from Fluka.
11. Experimental Section

- Chlorobenzene puriss. (absolute, over molecular sieve (H₂O ≤ 0.005 %)) from Fluka.
- Cobalt carbonyl (dicobalt octacarbonyl) purum (90 – 95 % Co) from Fluka.
- Copper(I) iodide (99.999 %) from Aldrich.
- DBU (1,8-diazabicyclo-[5.4.0]-undec-7-ene) (98 %) from Aldrich.
- Diisopropylamine redistilled (99.5 %) from Aldrich.
- Hydrobromic acid puriss. p.a. (48 %) from Fluka.
- Imidazole puriss. p.a. (≥ 99.5 %) from Fluka.
- Iodine monochloride (99.998 %) from Aldrich.
- Isopropyl ether puriss. (dried over Na/Pb alloy (H₂O ≤ 0.01 %) from Fluka.
- Pentfluoronitrobenzene (98 %) from Aldrich.
- Phenylpropargyl aldehyde (phenylpropiolaldehyde) (≥ 95 %) from Fluka.
- Phenylpropionic acid purum (≥ 98 %) from Fluka.
- Sodium hydride purum (55 – 65 %) from Fluka.
- TEMPO free radical sublimed (99 %) from Aldrich.
- Tetrafluoroboric acid (54 weight-%-solution in diethyl ether) from Aldrich.
- Tetrakis(triphenylphosphine)palladium purum (≥ 97 %) from Fluka.
- Triethyloxonium tetrafluoroborate purum (≥ 97 %) from Fluka.
- Trifluoroacetic acid for UV-spectroscopy (≥ 99 %) from Fluka.
- Trimethylphosphonium tetrafluoroborate from Aldrich.
- Trimethylsilylethynyl(phenyl)-iodonium tetrafluoroborate from TCI (Tokyo Kasei Kogyo Co., Ltd.), Tokyo, Japan.

11.1.5. Chromatography

11.1.5.1. Column Chromatography and Filtrations

Silica for flash column chromatography at 0.1 – 0.5 bar nitrogen overpressure (silica gel 60, 0.040 – 0.063 mm, 230 – 400 mesh ASTM) was supplied by Fluka and for column chromatography (silica gel 60, 0.063 – 0.200 mm) by Merck.

Usually, the crude mixture was dissolved in dichloromethane or acetone and cautiously evaporated with coarse silica (silica gel 60, 60742, 0.2 – 0.5 mm, 35 – 70 mesh ASTM by Fluka). The resulting powder was then applied evenly on the silica used for separation. A 100-fold amount of silica (related to the crude mixture) was used; the dimension of the wet silica
in the column being normally diameter / height = 1:10 at a column filling rate of about 80 % of the total column volume.
The mixture of eluting solvents is mentioned with the particular ratio.

Filtrations were carried out over celite or silica (silica gel 60, 60742, 0.2 – 0.5 mm, 35 – 70 mesh ASTM) by Fluka.

11.1.5.2. TLC

Thin Layer Chromatography was performed on silica attached to aluminum foil (Alugram Sil G/UV254 sheets from Macherey-Nagel, 0.20 mm silica gel 60-layer\textsuperscript{xviii} with fluorescent indicator UV254), on RP-18 attached to aluminum foil (Alugram RP-18 W/UV254 sheets from Macherey-Nagel, 0.15 mm silica gel C 18-layer\textsuperscript{xix} with fluorescent indicator UV254) or on nitrile phase attached to glass plates (Nano SIL CN/UV254 plates from Macherey-Nagel, 0.20 mm silica gel CN-layer\textsuperscript{xx} with fluorescent indicator UV254). The spots were best detected by fluorescence quenching with a LAMAG-UV-lamp at a wavelength of 254 nm or 366 nm, respectively. Detection of acetylenes both with a solution of dicobalt octacarbonyl (Co\textsubscript{2}(CO)\textsubscript{8}) in petroleum ether\textsuperscript{286} or with a solution of 4-(4'-nitrobenzyl)pyridine in acetone,\textsuperscript{287} respectively, did not work well as no colorizing at all or only a weak color intensification could be detected.
The R\textsubscript{f}-value, the stationary phase and the mixture of eluting solvents is given with the particular ratio. The stationary phase is reported as follows: silica = silica gel 60, RP-18 = reversed phase (C 18, octadecyl-modification) on silica gel 60, CN = nitrile phase on silica gel 60.

11.1.5.3. P-TLC

Preparative TLC was performed on silica attached to glass plates (silica gel 60 on pre-coated PLC plates, 20 cm x 20 cm, with fluorescent indicator F\textsubscript{254}) from Merck or on alumina attached to glass plates (aluminum oxide 60 on pre-coated PLC plates, 20 cm x 20 cm, with fluorescent indicator F\textsubscript{254}) from Merck.

\textsuperscript{xviii} The base material was silica gel 60 (pore size 60 Å).
\textsuperscript{xix} The base material was silica gel 60 (pore size 60 Å), with a partial octadecyl-modification (C 18). The abbreviation RP means reversed phase and W means wettable (hydrophilic).
\textsuperscript{xx} The base material was silica gel 60 (pore size 60 Å), which was cyano-modified.
11.1.5.4. HPLC

For HPLC analyses a Merck Hitachi LaChrom (Interface Module D-7000) was used. The machine consisted of a L-7100 pump, a L-7450 UV-diode array detector, and a L-7490 refractive index detector. All solvents used were HPLC-grade. The mixture of eluting solvents and the flow rate are mentioned.

The analytical HPLC cartridges used were LiChroCART 125-4 (column length 12.5 cm, column diameter 4 mm; usual flow rate = 0.5 ml/min) with LiChrospher, Si 60, particle size 5 µm from Merck, or LiChroCART 125-4 (column length 12.5 cm, column diameter 4 mm; usual flow rate = 0.5 ml/min) with LiChrospher 100, RP-18, particle size 5 µm from Merck or LiChroCART 250-4 (column length 25.0 cm, column diameter 4 mm; usual flow rate = 1.0 ml/min) with LiChrospher 100, CN, particle size 5 µm from Merck.

11.1.6. Spectroscopy

11.1.6.1. IR-Spectroscopy

IR-spectra were taken neat or in KBr pellets using a Perkin Elmer Paragon 1000 FT-IR spectrometer. Peaks are given in cm\(^{-1}\) and intensities are reported as follows: vs = very strong, s = strong, m = medium, w = weak, vw = very weak, br = broad.

11.1.6.2. NMR Spectroscopy

1D-NMR spectra were taken either with a Bruker AMX 500 (\(^1\)H-NMR: 500 MHz, \(^{13}\)C-NMR: 125 MHz), a Bruker AMX 400 (\(^1\)H-NMR: 400 MHz, \(^{13}\)C-NMR: 100 MHz), a Varian Mercury 300 or Varian Gemini 300 (\(^1\)H-NMR: 300 MHz, \(^{13}\)C-NMR: 75 MHz) or a Varian Gemini 200 (\(^1\)H-NMR: 200 MHz, \(^{13}\)C-NMR: 50 MHz) spectrometer.

For several perfluorinated and alkynylated compounds, because of the long relaxation times of the acetylenic \(sp^{\text{13}}\)C nuclei and the electronically poor, de-shielded \(^{13}\)C nuclei connected to fluorine atoms, the following pulse sequence was used in the \(^{13}\)C-NMR (125 MHz or 100 MHz, respectively): Pulse — Acquisition time \(aq = 2\) sec — relaxation delay \(dl = 3\) sec — following pulse. The respective pulse sequence is mentioned in the NMR-assignments.
1H and 13C chemical shifts are reported in ppm relative to tetramethylsilane as external standard, with residual NMR-solvent proton resonances as internal standard. 19F chemical shifts are reported in ppm relative to CCl3F as external standard. 13C-NMR and 19F-NMR spectra were proton broad-band decoupled (13C-{1H}-BB-NMR or 19F-{1H}-BB-NMR, respectively). The deuterated NMR-solvents were purchased from Dr. Glaser AG, Basel, Switzerland.

The multiplicity of signals (in 1H-NMR and 19F-NMR spectra) is reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, tt = triplet of triplet, br = broad, qd = pseudo doublet, qr = pseudo triplet. If assignments were given in 13C-NMR spectra, they were according to DEPT-135 measurements: p = primary, s = secondary, t = tertiary and q = quaternary carbon atom. Coupling constants J are reported in Hz, integrals are reported in arbitrary units.

In some cases, 1H-NMR- and 13C-NMR-signals were assigned with the aid of the NMR-simulation program from ACD.288

11.1.6.3. UV/Vis Spectroscopy

UV/Vis spectra were taken with a Hitachi U-2010 spectrophotometer. Quartz cuvettes were used, the cuvette holders were temperature stabilized by a Haake F3 heat regulator. All solvents were purchased as UV grade.

Values are given for the respective solvent, the maxima of absorption \( \lambda_{\text{max}} \) in nm and the respective absorption coefficient \( \varepsilon \) in brackets.

In order to calculate the absorption coefficient \( \varepsilon \), the following formula was used:

\[
A = \varepsilon \cdot c \cdot d \iff \varepsilon = \frac{A}{c \cdot d},
\]

in which \( A \) is the absorption [without dimension], \( \varepsilon \) the absorption coefficient [l·mol\(^{-1}\)·cm\(^{-1}\)], \( c \) the concentration [mol·L\(^{-1}\)] and \( d \) the length of path (layer thickness) in [cm].

\[\text{xii} \, \text{DEPT-135: Distortionless Enhancement by Polarization Transfer, 135° pulse sequence.}\]
11.1.7. Spectrometry

11.1.7.1. GC/MS

GC/MS spectra were recorded with a *Fisons Instruments GC 8000 series* gas chromatograph, coupled to a *Fisons Instruments MD 800* mass spectrometer. In the gas chromatograph, a *DB-5 MS* capillary GC-column from *J&W Scientific* (12 m length, 0.25 mm internal diameter, 0.25 µm thickness of layer of the stationary phase consisting of 95 % dimethyl-5 % diphenyl-polysiloxane) was employed with helium as carrier gas (flow rate: 1.0 ml/min, helium pressure set to 30 kPa (300 mbar)).

The following temperature programs were used: 2 min at 50 °C, then heating at a rate of 10 °C min⁻¹ to 250 °C, followed by heating for 20 min at 250 °C (code: 50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min) or 5 min at 35 °C, then heating at a rate of 10 °C min⁻¹ to 250 °C, followed by heating for 20 min at 250 °C (code: 35 °C, 5 min, 10 °C min⁻¹, 250 °C, 20 min). The injector temperature was 200 °C.

The solvent delay was set to 3 min, and EI-ionization at 70 eV electron energy was employed in the mass spectrometer. The detector temperature was 250 °C.

Peaks are reported in \( m/z \), with an assignment relative to the molecular peak \( M^+ \) and the intensities (usually, if > 10 %) relative to the base peak.

For the GC/MS analyses of diisopropyl ether, a *Thermo Finnigan TraceGC/TraceMS* was used.

A *Zebron ZB-1* capillary GC-column from *Phenomenex* (60 m length, 0.25 mm internal diameter, 0.25 µm layer thickness of the stationary phase consisting of 100 % dimethyl-polysiloxane) was employed with helium as carrier gas (flow rate: 0.8 ml/min). The temperature program was 10 min at 40 °C, then heating at a rate of 50 °C min⁻¹ to 200 °C (duration: 4 min), followed by heating for 1 min at 200 °C (code: 40 °C, 10 min, 50 °C min⁻¹, 200 °C, 1 min). The solvent delay was set to 0 min.

11.1.7.2. MS

MS spectra were taken on a *VG Tribrid* (EI, 70 eV) by the *MS-Service of the Laboratorium für Organische Chemie der ETH Zürich*. Peaks are reported in \( m/z \), with an assignment relative to the molecular peak \( M^+ \) and the intensities (if > 10 %) relative to the base peak.
11. EXPERIMENTAL SECTION

11.1.7.3. HiRes-MS

HiRes-MS spectra were taken on a *VG Trigrid* (El, 70 eV), HiRes-ESI-MS spectra on an *Ultima* FT-ESI-MS (Fourier transform ESI mass spectrometer) from *IonSpec* and HiRes-MALDI spectra on an *Ultima* FT-MALDI-MS (Fourier transform MALDI mass spectrometer) from *IonSpec* by the MS-Service of the Laboratorium für Organische Chemie der ETH Zürich. The assignment of the examined mass is given, followed by the calculated mass in u, the measured mass in u and the deviation Δ in mDa and in ppm.

11.1.7.4. ESI-MS

ESI-MS spectra were performed on a *Finnigan MAT LCQ* mass spectrometer equipped with an ESI source. In most of the cases, dichloromethane was used as a spraying solvent, occasionally also methanol or acetonitrile. The standard conditions were as follows: Sheath gas flow rate: 40 (arbitrary units), aux gas flow rate: 0 (arbitrary units), spray voltage: 4.50 kV, spray current: 0.10 µA, capillary temperature: 170 °C, capillary voltage: 4.10 V, tube lens offset: +10.00 V (for more sensitive compounds: −10.00 V) and flow of syringe pump: 10 µl min⁻¹.

Collision experiments were performed on a modified *Finnigan MAT TSQ 700* mass spectrometer equipped with an ESI source.

11.1.8. Others

11.1.8.1. Melting Points

Melting points were measured in open glass capillaries in a *Dr. Tottoli*-melting point apparatus from *Büchi*, and are uncorrected.

11.1.8.2. Elementary Analyses

Elemental analyses were performed at the Microanalysis Lab of the Laboratorium für Organische Chemie der ETH Zürich.
11.1.8.3. X-Ray Crystallography

Crystals of 198 were measured on a Nonius CAD4 diffractometer with graphite monochromator from Bruker using Cu Kα radiation (λ = 1.54178 Å). Crystals of 191 and 206 were both measured on a Nonius Kappa-CCD diffractometer with graphite monochromator from Bruker; Mo Kα radiation (λ = 0.71070 Å) was used. The structures were solved by direct methods (SIR92) and refined by full-matrix least-squares analysis (SHELXL-97) including an isotropic extinction correction. All heavy atoms were refined anisotropically (H-atoms isotropically, whereby H-positions were based on stereochemical considerations).

Crystal data of 196, 207, 208 and 223 were collected on a Nonius Kappa-CCD diffractometer with graphite monochromator from Bruker employing Mo Kα radiation (λ = 0.71073 Å). All diagrams and calculations were performed using maXus. Concerning data and structure refinement, for cell refinement, HKL Scalepack and for data reduction, Denzo and Scalepack were used. The structures were solved with the program SIR97 and refined with the program SHELXL-97. For the structure analysis of 223, see also an additional reference.

The X-ray structures were presented in diagrams generated with the program ORTEP-3. Atoms were displayed in octant shaded style, and color codes were used as follows: C, H and bonds: black, N: cyan, O: red, F: green, Si: brown and B: magenta. The ellipsoid probability was set to 60 % for 208, to 50 % for 191, 196, 206 and 207, to 40 % for 198 and to 30 % for 223.
11.2. Syntheses

11.2.1. General

11.2.1.1. Synthesis of a Solution of Lithium Diisopropylamide (LDA)

11.2.1.1.1. Titration of Butyllithium (BuLi, \(n\)-C\(_4\)H\(_9\) Li)\(^{298}\), compare\(^{299}\)

Purchasable, \(\approx 1.6\) M butyllithium solutions in hexanes often did not match the concentration given on the bottle (due to limited shelf life, concentrations of \(0.7\) M – \(2.0\) M were found) and were therefore titrated before use as follows:

A previously dried three-necked flask, equipped with an argon inlet, a septum and an argon outlet connected to a bubbler, was charged with 2.000 ml of a purchasable 1.6 M solution of butyllithium in hexanes in an argon atmosphere. Then, a few small grains of dry 2,2'-bipyridinyl were added as an indicator in an argon counter stream. The resulting intensively red-brown solution was then titrated dropwise at rt via an exact syringe and a septum with a 1.600 M solution of dry tert-butanol, tBuOH, in dry THF. The end point was reached at the beginning of decolorization of the solution. The titration was repeated and both results were averaged. For 1 eq of BuLi, 1 eq of tBuOH is consumed in this reaction.

11.2.1.1.2. Preparation of Lithium Diisopropylamide (LDA, \(i\)Pr\(_2\)N Li)\(^{300}\)

Purchasable LDA solutions often did not match the concentration given on the bottle and contained other compounds leading to side products and bad yield upon employment as a base. Therefore, for the alkynylation reactions in order to synthesize azaenediynes, LDA was freshly prepared in the following way:

A previously dried three-necked flask, equipped with an argon inlet, a septum and an argon outlet connected to a bubbler, was charged with 20 ml of dry THF in an argon counter stream. In an argon atmosphere, 2.000 ml (1.440 g, 14.230 mmol, 1 eq) of freshly distilled, absolute
diisopropylamine, \textsuperscript{xii} \textit{iPr}_2\text{NH}, were then added via a syringe and a septum. The solution was cooled to 0 °C and stirred for 10 min. Via a syringe and a septum, slowly 8.894 ml (14.230 mmol, 1 eq) of a fresh, previously titrated 1.600 M BuLi solution in hexanes were then added dropwise. The addition of BuLi took place under vigorous stirring, and a dropping speed (≈ 1 drop in 2 sec) was chosen that allowed the resulting solution to remain nearly colorless. After the addition was complete, vigorous stirring of the solution was continued at 0 °C for ½ h under argon.

The prepared LDA solution in THF/hexanes had a concentration of \(c = 0.461 \text{ M}\) (with the total volume being 20 ml + 2 ml + 8.894 ml = 30.894 ml, the concentration of LDA is \(c = 14.230 \text{ mmol} / 30.894 \text{ ml} = 0.461 \text{ mol·l}^{-1}\)). The solution was employed immediately in a subsequent deprotonation reaction.

\textbf{11.2.1.2. Synthesis of the Stang Reagent 69}

\textbf{11.2.1.2.1. Iodosobenzene (67) ((Ph–IO)\textit{n})}

\[
\begin{array}{c}
\text{I} \\
\text{O} \\
67
\end{array}
\]

A two-necked flask, equipped with a mechanical precision stirrer and a septum, was charged with 10.000 g (31.046 mmol, 1 eq) of finely ground diacetoxyiodobenzene (70). Over a period of 5 min and under vigorous stirring, 46.570 ml (139.709 mmol, 4.5 eq) of a 3.0 M aqueous solution of NaOH were then added dropwise via a syringe. Upon continued stirring for ½ h at rt, the reaction mixture turned to a viscous, yellow slurry. Some lumps of solid that formed were macerated with a spatula. The reaction mixture was allowed to stand for 1 h at rt.

As a work-up procedure, 35 ml of water were added upon vigorous stirring. The crude product was then filtered over a Büchner funnel. The wet solid was returned to the flask, slurried in 70 ml of water and vacuum-filtered over a filter frit (pore size: 3), washed with 2 × 70 ml of water and sucked to dryness. Afterwards, the solid was transformed into a beaker, macerated in 25 ml of CHCl\textsubscript{3}, filtered over a Büchner funnel, again macerated in 25 ml of CHCl\textsubscript{3}, vacuum-

\textsuperscript{xii} Diisopropylamine (b.p. = 84 °C) was first refluxed for 5 min over sodium hydride in an argon atmosphere, and subsequently distilled into a dry Schlenk tube in an argon atmosphere. The flask was stored in a glove box in the dark.
filtered over a filter frit (pore size: 3) and washed with 25 ml of CHCl₃. The product was sucked to dryness and finally dried in a high vacuum.

**Yield**
5.308 g (78 %) (lit.¹¹⁴: 85 – 93 %) pale yellow solid.

**Melting Point**
204 – 208 °C (decomposition) (lit.¹¹⁴: 210 °C; caution was required as explosions were reported).

### 11.2.1.2.2. Trimethylsilylethynyl(phenyl)-iodonium tetrafluoroborate (69)²²ii

\[
\text{(CH}_3\text{)}_3\text{Si} \equiv \text{I} \equiv \text{Ph BF}_4^-
\]

A dried two-necked flask, equipped with an argon inlet, a septum and an argon outlet, was charged with 2.500 g (11.363 mmol, 1.6 eq) of dried iodosobenzene (67) in an argon atmosphere. Then, 30 ml of abs. CH₂Cl₂ were added and the pale yellow suspension was stirred for ½ h at rt. In an argon counter stream, 1.427 ml (1.613 g, 11.363 mmol, 1.6 eq) of borotrifluorid-ethyletherat, BF₃-Et₂O, were then added dropwise via a syringe and a septum. Upon addition, the suspension turned first deep yellow, then turned into a clear, yellowish solution and finally a deep yellow solid precipitated. Afterwards, 1.588 ml (1.210 g, 7.102 mmol, 1.0 eq) of 1,2-bis-trimethylsilyl-ethyne (68) were added dropwise via a syringe and a septum. The yellow solution turned turbid, still showing the precipitate. The reaction mixture was stirred for 5 h at rt under argon.

The reaction was quenched by addition of 70 ml of a saturated solution of sodium tetrafluoro­borate, NaBF₄, in water. After stirring for 15 min, the aqueous phase was extracted 4 times with CH₂Cl₂. The combined organic phases were dried over Na₂SO₄, filtered and the clear, yellow solution was evaporated at rt. The ocher solid was dried in a high vacuum and then refrigerated under argon.

²²ii The procedure was carried out also by changing the order of addition of 1,2-bis-trimethylsilyl-ethyne (68) and BF₃-Et₂O. In another attempt, iodosobenzene (67), 1,2-bis-trimethylsilyl-ethyne (68) and BF₃-Et₂O were employed each with 1 eq.
Yield
1.221 g (44%) ocher yellow solid.

IR
IR (film, a solution in CH₂Cl₂ was evaporated on a NaCl plate): \( \tilde{\nu} [\text{cm}^{-1}] = 3063 (\text{w}, \nu \text{C-H aromatic}), 2959 (\text{m}, \nu \text{C-H aliphatic}), 2900 (\text{w}, \nu \text{C-H aliphatic}), 2143 (\text{w}, \nu \text{C=C}), 1561 (\text{m}, \nu \text{C=C aromatic}), 1471 (\text{m}), 1443 (\text{m}), 1331 (\text{m}), 1307 (\text{m}), 1252 (\text{s}), 1070 (\text{s}), 848 (\text{s}), 761 (\text{m}), 741 (\text{s}), 699 (\text{m}), 653 (\text{w}), 551 (\text{s}).

ESI-MS
Cation mode: \( m/z = 301 [M^+ (\text{cation})] \) (main peak).
Anion mode: \( m/z = 87 [M^- (\text{anion}, \text{BF}_4^-)] \) (main peak).

11.2.2. Ethynylation Reactions of the N-1-Nitrogen of Imidazole and its Derivatives

11.2.2.1. Ethynylation Reactions of the N-1-Nitrogen of Imidazole

11.2.2.1.1. 1-Trimethylsilylethynyl-1H-imidazole (78) — A NOVEL COMPOUND

Successful Synthesis using BuLi as a Base
In an argon atmosphere, 172 mg (2.527 mmol, 1 eq) of 1H-imidazole (77) were suspended in 50 ml of dry toluene. The mixture was cooled to 0 °C. Via a syringe and a septum, slowly 1580 µl (2.527 mmol, 1 eq) of BuLi (1.6 M in hexanes) were added dropwise. The mixture was stirred for 15 min at 0 °C, then allowed to reach rt and stirred for another 15 min at rt.

\[^{xxiv}\] Dry benzene was also used instead of toluene.
980 mg (2.527 mmol, 1 eq) of trimethylsilylethynyl(phenyl)-iodonium tetrafluoroborate (69) were added as a solid in 4 portions. Upon adding, the mixture warmed up to 40 – 50 °C and turned brown after 1 – 2 h. The mixture was stirred for 24 h at rt.

As a work-up procedure, first ethyl acetate and then water were added. The mixture was extracted 5 times with ethyl acetate and the organic layer dried over Na₂SO₄ and evaporated. The product was purified by flash column chromatography with hexanes / EtOAc 15:1 or n-pentane / Et₂O 10:1, the latter one being easier to evaporate. The solvents were removed at rt and finally with a nitrogen stream; the product was kept under argon.

**Yield**

15 mg (4 %) volatile, yellow film;
soluble in EtOAc, CH₂Cl₂, Et₂O, toluene, benzene and n-hexane.

\[ R_f = 0.1 \text{ (silica, n-hexane / EtOAc 10:1), } R_f = 0.1 \text{ (silica, n-pentane / Et}_2\text{O 10:1).} \]

**GC/MS**

GC (35 °C, 5 min, 10 °C min⁻¹, 250 °C, 20 min): \( R_f = 7.2 \text{ min; } \) MS (EI, 70 eV): \( m/z \) (%): 164 (34 %) \([M^+], 163 (17 \%) [M^+ - 1 (H)], 150 (13 \%) [M^+ - 14], 149 (100 \%) [M^+ - 15 (Me)], 122 (19 \%) [M^+ - 42], 95 (15 \%) [M^+ - 69].

**NMR**

\(^1\)H-NMR (500 MHz, [D₆]-benzene, 300.0 K, TMS): \( \delta [ppm] = 7.32 \) (s, 1 H, H-1), 6.81 and 6.52 (2 × 1 m, 2 × 1 H, H-2, H-3), 0.12 (s, 9 H, TMS).

\(^1\)C-NMR (125 MHz, [D₆]-benzene, 298.0 K, TMS): \( \delta [ppm] = 140.2 \) (C-1), 121.4 (C-2 and C-3), –0.3 (TMS). The acetylenic carbons were not detected.

**Synthesis using NaH as a Base**

In an argon atmosphere, 172 mg (2.527 mmol, 1 eq) of 1H-imidazole (77) were suspended in 50 ml of dry diethyl ether. The mixture was cooled to 0 °C and 64 mg (2.653 mmol, 1.05 eq) of

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**Phenyl iodide was detected in the GC/MS as follows:**

GC: \( R_f = 4.9 \text{ min; } \) MS (EI, 70 eV): \( m/z \) (%): 204 (100 %) \([M^+], 127 (22 \%) [I^+], M^+ - 77 (Ph)], 77 (98 \%) [Ph^+, M^+ - 127 (1)].

---
sodium hydride were added. The mixture was stirred for 15 min at 0 °C, then allowed to reach rt and stirred for another 15 min at rt.

For the further synthesis, work-up procedure and the GC/MS analysis, see above.

A GC/MS analysis gave only traces of product, so that the attempts using NaH as a base were abandoned.

### 11.2.2.2. Ethynylation Reactions of the N-1-Nitrogen of Benzimidazole

#### 11.2.2.2.1. 1-Trimethylsilylethynyl-1H-benzimidazole (80) — A NOVEL COMPOUND

**Successful Synthesis using LDA as a Base**

In an argon atmosphere, 298 mg (2.527 mmol, 1 eq) of 1H-benzimidazole (79) were suspended in 50 ml of dry toluene. The mixture was cooled to 0 °C. Via a syringe and a septum, slowly 1.68 ml (2.527 mmol, 1 eq) of freshly prepared 1.5 M LDA solution in THF were added dropwise. The mixture was stirred for 15 min at 0 °C, then allowed to reach rt and stirred for another 15 min at rt.

980 mg (2.527 mmol, 1 eq) of trimethylsilylethynyl(phenyl)-iodonium tetrafluoroborate (69) were added as a solid in 4 portions. Upon adding, the mixture warmed up to 40 – 50 °C and turned brown after 1 – 2 h. The mixture was stirred for 24 h at rt.

As a work-up procedure, first ethyl acetate and then water were added. The mixture was extracted 5 times with ethyl acetate and the organic layer dried over Na2SO4 and evaporated.

The product was purified by flash column chromatography with hexanes / EtOAc 10:1. The solvents were removed at rt and finally some minutes in a high vacuum; the product was kept under argon.

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xxvi NaH is available as a suspension (ca. 60 %) in mineral oil, which could be washed out with n-hexane.
Flash column chromatography gave 2 products, the main product being 1-trimethylsilylethynyl-1\textit{H}-benzimidazole (80) and the side product 1-ethynyl-1\textit{H}-benzimidazole (81):

\textbf{11.2.2.2. Main Product: 1-Trimethylsilylethynyl-1\textit{H}-benzimidazole (80) — A NOVEL COMPOUND}

![Chemical Structure](image)

\textbf{Yield}

67 mg (12\%) slightly yellowish oil with a sweetish smell; soluble in acetone, MeOH, EtOAc, CH\textsubscript{2}Cl\textsubscript{2}, Et\textsubscript{2}O, \textit{n}-hexane and \textit{n}-pentane.

\textbf{R\textsubscript{f}}

\textbf{R\textsubscript{f}} = 0.2 (silica, \textit{n}-hexane / EtOAc 10:1).

\textbf{GC/MS}

GC (50 °C, 2 min, 10 °C min\textsuperscript{-1}, 250 °C, 20 min): R\textsubscript{f} = 13.4 min; MS (EI, 70 eV): \textit{m}/\textit{z} (%) : 215 (14\%) [\textit{M}\textsuperscript{+} + 1 (H)], 214 (75\%) [\textit{M}\textsuperscript{+}], 213 (66\%) [\textit{M}\textsuperscript{+} - 1 (H)], 200 (20\%) [\textit{M}\textsuperscript{+} - 14], 199 (100\%) [\textit{M}\textsuperscript{+} - 15 (Me)], 171 (22\%) [\textit{M}\textsuperscript{+} - 43], 159 (10\%) [\textit{M}\textsuperscript{+} - 55].

\textbf{NMR}

\textit{\textsuperscript{1}H}-NMR (500 MHz, [D\textsubscript{6}]-acetone, 300.0 K, TMS external): \(\delta [\text{ppm}] = 8.36 (s, 1 H, H-2), 7.75 \text{ and } 7.60 (2 \times 1 m, 2 \times 1 H, H-4, H-7), 7.45 \text{ and } 7.38 (2 \times 1 m, 2 \times 1 H, H-5, H-6), 0.32 (s, 9 H, TMS).

\textit{\textsuperscript{13}C}-NMR (125 MHz, [D\textsubscript{6}]-acetone, 298.0 K, TMS external, \textit{aq} = 2 sec, \textit{dl} = 3 sec): \(\delta [\text{ppm}] = 144.8 (C-2 (CH, p)), 142.9 \text{ and } 135.3 (C-3a \text{ and } C-7a \text{ (both C, q)}), 125.6 \text{ and } 124.7 (C-5 \text{ and } C-6 (\text{both CH, p)}), 121.4 \text{ and } 111.5 (C-4 \text{ and } C-7 (\text{both CH, p)}), 89.5 (C-8 \text{ (acetylenic C, q)}), 76.6 (C-9 \text{ (acetylenic C, q}, \textit{J_{C-Si}} = 41.3)), -0.05 (\text{TMS (CH\textsubscript{3}, \text{t}, \textit{J_{C-Si}} = 28.4))).

\textbf{NOE-experiment (H of TMS-group — H-7):}
Irradiation on H of TMS-group showed no NOE, because the distance between the proton of the TMS-group and H-7 is too large (> 3 Å).³⁰¹

**IR**

IR (neat): $\tilde{\nu}$ [cm$^{-1}$] = 3085 (w, $\nu$ C–H$_{aromatic}$), 2960 (m, $\nu$ C–H$_{aliphatic}$), 2192 (s, $\nu$ C=CH), 1613 (w, $\nu$ C=C$_{aromatic}$), 1498 (m), 1478 (w), 1455 (m), 1251 (m), 1091 (m), 844 (m), 741 (m).

**MS**

MS (El, 70 eV): m/z (%): 215.1331 (10.73%) [$M^+ + 1$ (H)], 214.1339 (53.54%) [$M^+$], 2131272 (28.68%) [$M^+ - 1$ (H)], 200.1104 (17.91%) [$M^+ - 14$], 199.1057 (100.00%) [$M^+ - 15$ (Me)].

**11.2.2.2.3. Side Product: 1-Ethynyl-1H-benzimidazole (81) — A NOVEL COMPOUND**

![Diagram of 1-Ethynyl-1H-benzimidazole (81)](image)

**Yield**

20 mg (6 %) white solid;
soluble in EtOAc, CH$_2$Cl$_2$, Et$_2$O, n-hexane and n-pentane;
decomposition upon standing within 1 – 2 d.

**R$_r$**

R$_r$ = 0.1 (silica, n-hexane / EtOAc 10:1).

**GC/MS**

GC (50 °C, 2 min, 10 °C min$^{-1}$, 250 °C, 20 min): R$_r$ = 9.2 min; MS (El, 70 eV): m/z (%): 143 (20 %) [$M^+ + 1$ (H)], 142 (100 %) [$M^+$], 115 (71 %) [$M^+ - 27$], 114 (26 %) [$M^+ - 28$], 102 (41 %) [$M^+ - 40$], 90 (11 %) [$M^+ - 52$], 88 (19 %) [$M^+ - 54$], 76 (16 %) [$M^+ - 66$], 75 (16 %) [$M^+ - 67$], 64 (11 %) [$M^+ - 78$], 63 (25 %) [$M^+ - 79$], 62 (15 %) [$M^+ - 80$].
NMR

$^1$H-NMR (500 MHz, [D$_6$]-acetone, 300.0 K, TMS external): $\delta$ [ppm] = 8.40 (s, 1 H, H-2), 7.75 and 7.63 (2 x 1 m, 2 x 1 H, H-4, H-7), 7.45 and 7.38 (2 x 1 m, 2 x 1 H, H-5, H-6), 4.11 (s, $^1$J$_{H-C:9}$ = 265.9, $^2$J$_{H-C:8}$ = 57.6, 1 H, acetylenic H).

$^{13}$C-NMR (125 MHz, [D$_6$]-acetone, 298.0 K, TMS external, $aq = 2$ sec, $dl = 3$ sec): $\delta$ [ppm] = 145.1 (C-2 (CH, p)), 142.9 and 135.3 (C-3a and C-7a (both C, q)), 125.6 and 124.7 (C-5 and C-6 (both CH, p)), 121.4 and 111.4 (C-4 and C-7 (both CH, p)), 70.8 (C-8 (acetylenic C, q)), 63.6 (C-9 (acetylenic CH, p)).

Synthesis using DBU as a Base

In an argon atmosphere, 298 mg (2.527 mmol, 1 eq) of 1H-benzimidazole (79) were suspended in 50 ml of dry toluene. The mixture was cooled to 0 °C. Via a syringe and a septum, slowly 0.38 ml (2.527 mmol, 1 eq) of DBU (1,8-diazabicyclo-[5.4.0]-undec-7-ene) were added dropwise. The mixture was stirred for 15 min at 0 °C, then allowed to reach rt and stirred for another 15 min at rt.

For the further synthesis, work-up procedure and the analyses, see above.

11.2.2.2.4. Main Product: 1-Trimethylsilylethynyl-1H-benzimidazole (80)

Yield

11 mg (2 %) slightly yellowish oil with a sweetish smell.

11.2.2.2.5. Side Product: 1-Ethynyl-1H-benzimidazole (81)

Yield

18 mg (5 %) white solid.

Synthesis using BuLi as a Base

In an argon atmosphere, 298 mg (2.527 mmol, 1 eq) of 1H-benzimidazole (79) were suspended in 50 ml of dry toluene. The mixture was cooled to 0 °C. Via a syringe and a septum, slowly 1580 µl (2.527 mmol, 1 eq) of BuLi (1.6 M in hexanes) were added dropwise. The mixture was stirred for 15 min at 0 °C, then allowed to reach rt and stirred for another 15 min at rt.

For the further synthesis, work-up procedure and the GC/MS analysis, see above.
11.2.2.2.6. Main Product: 1-Trimethylsilylethynyl-1H-benzimidazole (80)

Yield
66 mg (12 %) slightly yellowish oil with a sweetish smell.

11.2.2.2.7. Side Product: 1-Ethynyl-1H-benzimidazole (81)

Yield
36 mg (10 %) white solid.

11.2.2.3. Ethynylation Reactions of the N-1-Nitrogen of Nitro-Benzimidazole

11.2.2.3.1. 5-Nitro-1-trimethylsilylethynyl-1H-benzimidazole (83) and 6-Nitro-1-trimethylsilylethynyl-1H-benzimidazole (84) — NOVEL COMPOUNDS

In an argon atmosphere, 412 mg (2.526 mmol, 1 eq) of 5-nitro-1H-benzimidazole (82) were suspended in 50 ml of dry toluene. The mixture was cooled to 0 °C. Via a syringe and a septum, slowly 1.68 ml (2.526 mmol, 1 eq) of freshly prepared 1.5 M LDA solution in THF were added dropwise. The mixture was stirred for 15 min at 0 °C, then allowed to reach rt and stirred for another 15 min at rt.

980 mg (2.526 mmol, 1 eq) of trimethylsilylethynyl(phenyl)-iodonium tetrafluoroborate (69) were added as a solid in 4 portions. Upon adding, the mixture warmed up to 40 – 50 °C and turned brown after 1 – 2 h. The mixture was stirred for 36 h at rt.

As a work-up procedure, first ethyl acetate and then water were added. The mixture was extracted 5 times with ethyl acetate and the organic layer dried over Na2SO4 and evaporated.

The product was purified by flash column chromatography with hexanes / EtOAc 10:1. The solvents were removed in a high vacuum.

Flash column chromatography gave mainly two products, the positional isomers 5-nitro-1-trimethylsilylethynyl-1H-benzimidazole (83) and 6-nitro-1-trimethylsilylethynyl-1H-benzimidazole (84). The two isomers were separated and characterized by GC/MS and NMR spectroscopy; however, an exact discrimination between the two isomers was not possible.
11.2.2.3.2. Isomer I (presumably 5-Nitro-1-trimethylsilylethynyl-1H-benzimidazole (83)) — A NOVEL COMPOUND

Yield
16 mg (2 %) ocher solid; soluble in EtOAc and CH₂Cl₂.

Rᵣ
Rᵣ = 0.2 (silica, n-hexane / EtOAc 10:1).

GC/MS
GC (50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min): Rᵣ = 18.2 min; MS (EI, 70 eV): m/z (%): 259 (50 %) [M⁺], 258 (11 %) [M⁺ - 1 (H)], 245 (24 %) [M⁺ - 14], 244 (100 %) [M⁺ - 15 (Me)], 199 (14 %) [M⁺ - 60], 198 (55 %) [M⁺ - 61], 97 (14 %) [M⁺ - 162], 85 (10 %) [M⁺ - 174].

NMR
¹H-NMR (400 MHz, CDCl₃, 300.0 K, TMS external): δ [ppm] = 8.72 (m, 1 H, H-4), 8.35 (m, 1 H, H-6), 8.23 (s, 1 H, H-2), 7.64 (m, 1 H, H-7), 0.34 (s, 9 H, TMS).
¹³C-NMR (100 MHz, CDCl₃, 300.0 K, TMS external, aq = 2 sec, d1 = 3 sec): δ [ppm] = 146.6 (C-2 (CH, p)), 145.2 (C-5 (C=NO₂, q)), 141.4 and 138.4 (C-3a and C-7a (both C, q)), 120.4 (C-6 (CH, p)), 117.5 and 111.4 (C-4 and C-7 (both CH, p)), 86.9 (C-8 (acetylenic C, q)), 78.6 (C-9 (acetylenic C, q)), −0.19 (TMS (CH₃, t)).
11.2.2.3.3. Isomer II (presumably 6-Nitro-1-trimethylsilylethynyl-1H-benzimidazole (84)) — A NOVEL COMPOUND

![Chemical Structure](image)

**Yield**

18 mg (3%) ocher solid; soluble in EtOAc and CH₂Cl₂.

**Rf**

Rf = 0.1 (silica, n-hexane / EtOAc 10:1).

**GC/MS**

GC (50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min): Rₕ = 17.5 min; MS (EI, 70 eV): m/z (%): 259 (32%) [M⁺], 245 (19%) [M⁺ - 14], 244 (100%) [M⁺ - 15 (Me)], 198 (27%) [M⁺ - 61].

**NMR**

¹H-NMR (400 MHz, CDCl₃, 300.0 K, TMS external): δ [ppm] = 8.50 (m, 1 H, H-7), 8.29 (s, 1 H, H-2), 8.28 (m, 1 H, H-5), 7.90 (m, 1 H, H-4), 0.35 (s, 9 H, TMS).

¹³C-NMR (100 MHz, CDCl₃, 300.0 K, TMS external, aq = 2 sec, d1 = 3 sec): δ [ppm] = 147.9 (C-2 (CH, p)), 145.2 (C-6 (C-NO₂, q)), 145.9 and 134.0 (C-3a and C-7a (both C, q)), 121.2 (C-5 (CH, p)), 119.8 and 108.0 (C-4 and C-7 (both CH, p)), 86.7 (C-8 (acetylenic C, q)), 78.9 (C-9 (acetylenic C, q)), -0.18 (TMS (CH₃, t)).
11.2.3. The Aldehyde Approach

11.2.3.1. Synthesis of an Electronically Poor Benzimidazole

11.2.3.1.1. 4,5,6,7-Tetrafluoro-1H-benzimidazole (92)

1.600 g (8.884 mmol, 1 eq) of 3,4,5,6-tetrafluorobenzene-1,2-diamine (1,2-diaminotetrafluorobenzene) (91) and 57 ml of 98% formic acid (ca. 1510 mmol, ca. 167 eq) were heated for 3 h under reflux conditions. The obtained pale yellow solution was taken up in an excess of 10% aqueous sodium hydroxide solution (100 ml). The solution showing a pH = 11 was acidified with formic acid until pH = 5. The precipitated pale yellow solid was filtered and recrystallized from 5 ml of hot methanol to give nearly colorless crystals.

Yield
912 mg (54%) nearly colorless crystals; soluble in acetone.

Rf
Rf = 0.2 (silica, n-hexane / EtOAc 1:1).

GC/MS
GC (50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min): Rf = 10.9 min – 12.0 min; MS (El, 70 eV):
m/z (%): 190 (100%) [M⁺], 163 (33%) [M⁺ - 27 (HCN)], 136 (15%) [M⁺ - 54], 117 (13%) [M⁺ - 73], 113 (12%) [M⁺ - 77].

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xxxvii Boiling point of formic acid: b.p. (HCOOH) = 100 °C.

xxviii The product turned out to be soluble at pH = 5 – 10, and insoluble at pH = 0 – 4 and pH = 11 – 14.
11.2.3.1.2. 1-Diethoxymethyl-4,5,6,7-tetrafluoro-1H-benzimidazole (94) — Attempted Synthesis

In an argon atmosphere, 0.400 g (2.104 mmol, 1 eq) of 4,5,6,7-tetrafluoro-1H-benzimidazole (92) were heated with 1.400 ml (8.417 mmol, 4 eq) of triethyl orthoformate (triethoxymethane) and 0.010 g (0.053 mmol, 0.025 eq) of p-toluenesulfonic acid (ratio benzimidazole 92 : HC(OEt)$_3$ : p-TosOH = 40:160:1) to 125 – 130 °C for 22 h. The viscous, milky-white mixture turned into a clear solution after ½ h. Reaction control by TLC (after a micro-work-up by diluting a sample with EtOAc and neutralizing with Na$_2$CO$_3$) showed the same results after 1 h, 4 h and 22 h: Mainly educt was detected, apart from little amounts of another substance (R$_f$-values see below).

After 22 h, the mixture was allowed to cool to rt and the excess of triethyl orthoformate was removed in a rotavap previously flushed with argon. Then, 0.010 g (0.094 mmol, 0.045 eq) of solid Na$_2$CO$_3$ were added. Another TLC showed no evidence of product.

**R$_f$ (Mixture)**

$R_f = 0.3$ (silica, $n$-hexane / EtOAc 1:1); $R_f$ (educt) = 0.2;

$R_f = 0.4$ (CN, $n$-hexane / EtOAc 1:1); $R_f$ (educt) = 0.3.
11.2.4. Building up the Ethynyl Moiety at Position C-2 and N-1 of an Imidazole System Simultaneously — Coupling Approaches

11.2.4.1. Activation of Position C-2 of Imidazole Derivatives

11.2.4.1.1. 2-Iodo-1-methyl-1H-imidazole (105)

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\begin{align*}
\text{(105)}
\end{align*}
\]

In an argon atmosphere, 3.960 ml (4.10 g, 49.936 mmol, 1 eq) of 1-methyl-1H-imidazole (104) were dissolved in 50 ml of abs. THF in a three-necked flask. The solution in the flask, equipped with an argon inlet, a thermometer and a septum, was cooled to −90 °C with a cold bath (liquid N\(_2\) / n-pentane). Then, 31.210 ml (49.936 mmol, 1 eq) of a 1.6 M solution of n-BuLi in hexane were added dropwise via a syringe and afterwards the mixture was allowed to warm to 0 °C. The yellow solution was stirred for 10 min at 0 °C and then cooled to −60 °C (cold bath with liquid N\(_2\) / n-pentane). The septum was replaced by an addition funnel, and a solution of 13.960 g (55.002 mmol, 1.1 eq) of I\(_2\) in 10 ml of abs. THF was added slowly. The resulting mixture was then allowed to warm to 0 °C, stirred for \(\frac{1}{2}\) h and then quenched by adding 50 ml of a saturated Na\(_2\)S\(_2\)O\(_3\)-solution. After extraction with CHCl\(_3\) (4 times), the combined organic layers were dried over Na\(_2\)CO\(_3\) and the solvents were distilled off (350 mbar, 40 °C).

Vacuum distillation of the crude product gave a liquid as the main fraction, which distilled at 75 – 80 °C and 7 – 8 mbar (bath temperature: 100 – 120 °C).

**Yield**

5.780 g (56 %) light yellow oil;

b.p. 75 – 80 °C at 7 – 8 mbar (lit.\(^{164}\): 68 °C at 0.03 mm Hg);

soluble in CHCl\(_3\).

**GC/MS**

GC (50 °C, 2 min, 10 °C min\(^{-1}\), 250 °C, 20 min): \(R_t = 7.9\) min; MS (EI, 70 eV): \(m/z (%)\):

- 208 (100 %) [\(M^+\)],
- 127 (17 %) [\(M^+ - 81\)],
- 81 (4 %) [\(M^+ - 127 (I)\)],
- 54 (20 %) [\(M^+ - 154\)].
NMR

$^1$H-NMR (200 MHz, CDCl$_3$, 300.0 K, TMS): $\delta$ [ppm] = 7.03 and 7.00 (2 x 1 d, $^3J_{H-4-H-5} = 1.20, 2 \times 1$ H, H-4, H-5), 3.59 (s, 3 H, CH$_3$).

$^{13}$C-NMR (50 MHz, CDCl$_3$, 300.0 K, TMS): $\delta$ [ppm] = 132.0 and 123.7 (C-4 and C-5), 90.4 (C-2), 36.2 (C-6 (CH$_3$)).

11.2.4.1.2. 2-Bromo-$^1$H-benzimidazole (107)

In a three-necked flask, equipped with a thermometer, an addition funnel, a gas outlet (gas offtake pipe) and a mechanical precision stirrer, 100 ml of conc. acetic acid and 10 ml of a 48 % aqueous hydrobromic acid were cooled to about 10 °C. Under vigorous stirring, 10.000 g (0.067 mol, 1 eq) of 1H-benzimidazole-2-thiol (106) were added. Then, under continued vigorous stirring, 12 ml (0.234 mol, 3.5 eq) of Br$_2$ were added dropwise over a period of $\frac{1}{2}$ h. The mixture warmed slightly (to 20 – 30 °C) and turned highly viscous to nearly solid, so that additional acetic acid (100 ml) had to be added to aid the stirring. After the addition of bromine was complete, the mixture was stirred at rt for $4\frac{1}{2}$ h. To the ocher suspension, 200 ml of H$_2$O were added. The resulting light yellow solution was cooled in an ice bath and the pH was adjusted to pH ≈ 4 by addition of ≈ 45 g of solid NaOH. A fine white precipitate formed, which was collected by vacuum filtration. The product was washed with the mother liquid and recrystallized from acetone.

Yield

5.097 g (39 %) (lit. 166: 70 % crude product) pale yellow powder; soluble in DMF and DMSO.

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**xxix** The gas outlet led first to a bubbler, then to a gas-washing bottle filled with an aqueous solution of Cu(OAc)$_2$ (in order to remove excess hydrogen sulfide according to: $H_2S + Cu^{2+} \rightarrow CuS\downarrow$) and finally to a gas-washing bottle filled with an aqueous solution of sodium thiosulfate (in order to remove excess bromine according to: $Br_2 + 2 S_2O_3^{2-} \rightarrow 2 Br^- + S_4O_6^{2-}$ (tetrathionate)).

**xxx** Mechanical precision stirrer: "KPG" stirrer.
**GC/MS**

GC (50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min): R = 14.8 min; MS (EI, 70 eV): m/z (%): 198 (2%) \([M^+ \text{ (with } ^{81}\text{Br})]\), 196 (2%) \([M^+ \text{ (with } ^{79}\text{Br})]\), 117 (33%) \([M^{xxxi} - 80 \text{ (Br)}]\), 108 (33%) \([M^+ - 89]\), 107 (9%) \([M^+ - 90]\), 106 (37%) \([M^+ - 91]\), 105 (100%) \([M^+ - 92]\), 93 (64%) \([M^+ - 104]\), 91 (61%) \([M^+ - 106]\), 90 (93%) \([M^+ - 107]\), 88 (17%) \([M^+ - 109]\), 81 (52%) \([^{81}\text{Br}^+, M^+ \text{ (with } ^{81}\text{Br})- 117]\), 79 (49%) \([^{79}\text{Br}^+, M^+ \text{ (with } ^{79}\text{Br})- 117]\), 78 (23%) \([M^+ - 119]\), 77 (9%) \([M^+ - 120]\), 76 (15%) \([M^+ - 121]\), 75 (16%) \([M^+ - 122]\), 74 (17%) \([M^+ - 123]\), 65 (18%) \([M^+ - 132]\), 64 (64%) \([M^+ - 133]\), 63 (97%) \([M^+ - 134]\), 62 (51%) \([M^+ - 135]\), 61 (33%) \([M^+ - 136]\), 53 (10%) \([M^+ - 144]\), 52 (58%) \([M^+ - 145]\), 51 (43%) \([M^+ - 146]\), 50 (25%) \([M^+ - 147]\).

**NMR**

\(^1\text{H-NMR (400 MHz, [D}_7\text{-DMF, 300.0 K, TMS): }\delta [\text{ppm}] = 7.58 \text{ (m, 2} \times 1 \text{H, H-4, H-7), 7.24 (m, 2} \times 1 \text{H, H-5, H-6), 1.98 (s, 1 H, H-1 (N-H)).}$$

\(^{13}\text{C-NMR (100 MHz, [D}_7\text{-DMF, 300.0 K, TMS): }\delta [\text{ppm}] = 142.0 \text{ (C-3a and C-7a (both C, q)), 127.4 (C-2 (C, q)), 123.1 (C-5 and C-6 (both CH, p)), 115.3 (C-4 and C-7 (both CH, p)).}$$

### 11.2.4.2. Coupling Attempts

#### 11.2.4.2.1. 1,2-Bis(phenylethynyl)-1H-benzimidazole (108) — Attempted Synthesis

In an argon atmosphere, 600 mg (3.045 mmol, 1 eq) of 2-bromo-1H-benzimidazole (107) were suspended in 10 ml of dry and degassed triethylamine.\(^{xxxii}\) Then, 107 mg (0.152 mmol, 0.05 eq) of bis(triphenylphosphine)palladium(II) dichloride, \((\text{PPh}_3)_2\text{PdCl}_2\), and 87 mg (0.457 mmol, 0.15 eq) of copper(I) iodide, \(\text{Cu}^+\), were added. Phenylacetylene (43) was then added via a syringe and the mixture placed immediately into an oil bath of a temperature of 80 °C\(^{xxxiii}\) and stirred for 20 h.\(^{xxxiv}\)

As a work-up procedure, 30 ml of water were added and the mixture was extracted 4 times with CH\(_2\)Cl\(_2\). The turbid, dark yellow organic layer was filtered over celite, dried over MgSO\(_4\), filtered and evaporated to give a dark yellow solid.

\(^{xxxii}\) If not otherwise indicated (like "\(M^+ \text{ (with } ^{81}\text{Br})\)" or "\(M^+ \text{ (with } ^{79}\text{Br})\)"), the average mass of the product is specified as \(M^+ = 197\).

\(^{xxxii}\) The reaction was also carried out with a 1:1 mixture of dry DMF and dry NEt\(_3\).

\(^{xxxiii}\) The reaction temperatures that were tried were: 80 °C, 50 °C and rt (80 °C worked best).

\(^{xxxiv}\) The reaction times that were tried were: 20 h and 5 h (20 h worked best).
The mixture was purified by flash column chromatography with n-pentane / Et₂O 1:1 + 5 % NEt₃. From one fraction, upon slow evaporation at rt, a substance crystallized in colorless, fine needles.

**Yield**

2-Phenylethynyl-1H-benzimidazole (109):
41 mg (6 %) colorless, fine needles.

**Rᵣ**

1,4-Diphenylbutadiyne (110): Rᵣ = 0.7 (silica, n-pentane / Et₂O 1:3);
educt 2-bromo-1H-benzimidazole (107): Rᵣ = 0.4 (silica, n-pentane / Et₂O 1:3);
2-phenylethynyl-1H-benzimidazole (109): Rᵣ = 0.3 (silica, n-pentane / Et₂O 1:3).

**GC/MS**

2-Phenylethynyl-1H-benzimidazole (109):
GC (50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min): Rᵣ = 21.7 min; MS (EI, 70 eV): m/z (%): 219 (16%) [M⁺ + 1 (H)], 218 (100%) [M⁺], 217 (12%) [M⁺ - 1 (H)], 190 (13%) [M⁺ - 28], 109 (10%) [M⁺ - 109], 77 (7%) [Ph⁺, M⁺ - 141], 64 (10%) [M⁺ - 154], 63 (14%) [M⁺ - 155].
1,4-Diphenylbutadiyne (110):
GC (50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min): Rᵣ = 17.5 min; MS (EI, 70 eV): m/z (%): 205 (15%) [M⁺ + 3], 204 (88%) [M⁺ + 2], 203 (89%) [M⁺ + 1 (H)], 202 (100%) [M⁺], 201 (15%) [M⁺ - 1 (H)], 200 (14%) [M⁺ - 2], 192 (12%) [M⁺ - 100], 101 (27%) [M⁺ - 101], 89 (15%) [M⁺ - 113], 88 (11%) [M⁺ - 114], 77 (6%) [Ph⁺, M⁺ - 125], 76 (14%) [M⁺ - 126].

11.2.4.2. 1-Aza-1,5,6,7,8-pentahydro-azecan-3,9-diyne[1,2-a]1H-benzimidazole (115) — Attempted Synthesis

In an argon atmosphere, 500 mg (2.538 mmol, 1 eq) of 2-bromo-1H-benzimidazole (107) were dissolved in 15 ml of dry and degassed DMF. Then, 1.770 ml (12.689 mmol, 5 eq) of dry and degassed triethylamine and 0.510 ml (3.824 mmol, 1.5 eq) of octa-1,7-diyne (114) were added.
In an inert atmosphere, 293 mg (0.254 mmol, 0.1 eq) of powdered tetrakis(triphenylphosphine)palladium(0), (PPh$_3$)$_4$Pd, and 135 mg (0.709 mmol, 0.28 eq) of powdered copper(I) iodide, CuI, were mixed and afterwards added to the clear solution. The mixture was placed immediately into an oil bath of a temperature of 80 °C and stirred for 20 h.

As a work-up procedure, the solvents were evaporated completely. Then, 20 ml of EtOAc and 10 ml of an aqueous 10 % solution of nickel(II) sulfate were added, and the mixture was extracted 4 times with EtOAc. The dark yellow organic layer was filtered over celite, dried over MgSO$_4$, filtered and evaporated to give a brown solid.

The mixture could not be completely purified by flash column chromatography with n-pentane / Et$_2$O 1:1. HPLC separation attempts on a nitrile phase (with n-hexane / MtB-ether 2:3, or a gradient of 100 % n-hexane → n-hexane / MtB-ether 2:3 → 100 % MtB-ether, resp.) failed as well. Apart from educt, only decomposition products were found by TLC and GC/MS analysis.

11.2.4.3. Additional Activation of Position N-1 of Benzimidazole Derivatives

11.2.4.3.1. Potassium 2-Bromo-1H-benzimidazolate (116) — Attempted Synthesis

0.500 g (2.538 mmol, 1 eq) of 2-bromo-1H-benzimidazole (107) were suspended in 8 ml of water. Aqueous, diluted (≈ 10 %) HCl was added, so that the educt just dissolved. Then, 1.263 g (9.139 mmol, 3.6 eq) of anhydrous potassium carbonate, K$_2$CO$_3$, were added. Upon that, the product precipitated as a fine solid.

The mixture was stirred for $\frac{1}{2}$ h, filtered, washed with the mother liquid and dried over CaCl$_2$.

Yield

0.327 g (55 %) white solid.

GC/MS

Eeduct 2-bromo-1H-benzimidazole (107):

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xxxv The reaction temperatures that were tried were: 80 °C, 50 °C and rt.

xxxvi The reaction times that were tried were: 40 h, 20 h and 5 h.

xxxvii The Ni$^{II}$(SO$_4$)-solution was added in order to remove remaining DMF.
GC (50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min): Rᵣ = 14.8 min; MS (EI, 70 eV): m/z (%) : 198 (2 %) [M⁺ (with ⁸¹Br)], 196 (2 %) [M⁺ (with ⁷⁹Br)], 117 (33 %) [M⁺ₓₓₓₓ - 80 (Br)], 108 (33 %) [M⁺ - 89], 107 (9 %) [M⁺ - 90], 106 (37 %) [M⁺ - 91], 105 (100 %) [M⁺ - 92], 93 (64 %) [M⁺ - 104], 91 (61 %) [M⁺ - 106], 90 (93 %) [M⁺ - 107], 88 (17 %) [M⁺ - 109], 81 (52 %) [⁸¹Br⁺, M⁺ (with ⁸¹Br) - 117], 79 (49 %) [⁷⁹Br⁺, M⁺ (with ⁷⁹Br) - 117], 78 (23 %) [M⁺ - 119], 77 (9 %) [M⁺ - 120], 76 (15 %) [M⁺ - 121], 75 (16 %) [M⁺ - 122], 74 (17 %) [M⁺ - 123], 65 (18 %) [M⁺ - 132], 64 (64 %) [M⁺ - 133], 63 (97 %) [M⁺ - 134], 62 (51 %) [M⁺ - 135], 61 (33 %) [M⁺ - 136], 53 (10 %) [M⁺ - 144], 52 (58 %) [M⁺ - 145], 51 (43 %) [M⁺ - 146], 50 (25 %) [M⁺ - 147].

ESI-MS
Anion mode: m/z = 197 [M⁻ (anion, with ⁸¹Br)], m/z = 195 [M⁻ (anion, with ⁷⁹Br)].

11.2.4.4. 1,2-Dibromo-1H-benzimidazole (119) — Attempted Synthesis

500 mg (2.538 mmol, 1 eq) of 2-bromo-1H-benzimidazole (107) were dissolved in 15 ml of an aqueous solution of sodium hydroxide (containing 102 mg (2.538 mmol, 1 eq) of NaOH). Via a syringe, 0.300 ml (5.707 mmol, 2.25 eq) of bromine were added dropwise. The mixture thickened into an orange solution and a white precipitate formed. 15 ml of water were added and the mixture was stirred for 20 h. Then, the solid was filtered, washed with water and dried in a vacuum exsiccator over P₄O₁₀.

Yield

747 mg red-brown solid (crude).

GC/MS
Eeduct 2-bromo-1H-benzimidazole (107): not detectable.

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²²vii If not otherwise indicated (like "M⁺ (with ⁸¹Br)" or "M⁺ (with ⁷⁹Br)", resp.), the average mass of the product is specified as M⁺ = 197.
Di-brominated species (assumedly 119):
GC (50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min): Rᵣ = 18.4 min (relatively small peak); MS (EI, 70 eV): m/z (%): 278 (48 %) [M⁺ (with 2 × ⁸¹Br)], 276 (100 %) [M⁺ (with 1 × ⁸¹Br and 1 × ⁷⁹Br; this is also the average mass)], 274 (54 %) [M⁺ (with 2 × ⁷⁹Br)], 197 (18 %) [M⁺ (assumedly 79 Br)], 195 (19 %) [M⁺ - 81 (⁸¹Br)], 116 (64 %) [M⁺ - 2 Br], 89 (11 %) [M⁺ - 187], 88 (17 %) [M⁺ - 188], 81 (5 %) [M⁺ + 195], 79 (6 %) [⁷⁹Br⁺, M⁺ - 197], 64 (11 %) [M⁺ - 212], 63 (25 %) [M⁺ - 213], 62 (20 %) [M⁺ - 214], 61 (13 %) [M⁺ - 215].

Tri-brominated species (assumedly 120):
GC (50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min): Rᵣ = 21.2 min (relatively biggest peak); MS (EI, 70 eV): m/z (%): 358 (32 %) [M⁺ (with 3 × ⁸¹Br)], 356 (98 %) [M⁺ (with 2 × ⁸¹Br and 1 × ⁷⁹Br)], 354 (100 %) [M⁺ (with 1 × ⁸¹Br and 2 × ⁷⁹Br)], 352 (34 %) [M⁺ (with 3 × ⁷⁹Br)], 277 (9 %) [358 (M⁺ with 3 × ⁸¹Br) - 81 (⁸¹Br) or 356 (M⁺ with 2 × ⁸¹Br and 1 × ⁷⁹Br) - 79 (⁷⁹Br)], 275 (19 %) [356 (M⁺ with 2 × ⁸¹Br and 1 × ⁷⁹Br) - 81 (⁸¹Br) or 354 (M⁺ with 1 × ⁸¹Br and 2 × ⁷⁹Br) - 79 (⁷⁹Br), 273 (10 %) [354 (M⁺ with 1 × ⁸¹Br and 2 × ⁷⁹Br) - 81 (⁸¹Br) or 352 (M⁺ with 3 × ⁷⁹Br) - 79 (⁷⁹Br)], 196 (32 %) [M⁺ = 358 - 162 (2 × ⁸¹Br) or M⁺ = 356 - 160 (1 × ⁸¹Br and 1 × ⁷⁹Br) or M⁺ = 354 - 158 (2 × ⁷⁹Br)], 194 (34 %) [M⁺ = 356 - 162 (2 × ⁸¹Br) or M⁺ = 354 - 160 (1 × ⁸¹Br and 1 × ⁷⁹Br) or M⁺ = 352 - 158 (2 × ⁷⁹Br)], 115 (10 %) [M⁺ - 240 (3 × Br)], 88 (37 %) [M⁺ - 267], 87 (15 %) [M⁺ - 268], 81 (3 %) [⁸¹Br⁺, M⁺ - 274], 79 (3 %) [⁷⁹Br⁺, M⁺ - 276], 62 (22 %) [M⁺ - 293], 61 (20 %) [M⁺ - 294].

Tetra-brominated species (assumedly 121):
GC (50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min): Rᵣ = 22.6 min (relatively small peak); MS (EI, 70 eV): m/z (%): 438 (17 %) [M⁺ (with 4 × ⁸¹Br)], 436 (61 %) [M⁺ (with 3 × ⁸¹Br and 1 × ⁷⁹Br)], 434 (100 %) [M⁺ (with 2 × ⁸¹Br and 2 × ⁷⁹Br; this is also the average mass)], 432 (63 %) [M⁺ (with 1 × ⁸¹Br and 3 × ⁷⁹Br)], 430 (18 %) [M⁺ (with 4 × ⁷⁹Br)], 358 (16 %) [M⁺ - 80], 357 (6 %) [M⁺ - 77], 356 (47 %) [M⁺ - 78], 355 (12 %) [M⁺ - 79], 354 (51 %) [M⁺ - 80], 353 (9 %) [M⁺ - 81], 352 (18 %) [M⁺ - 82], 277 (6 %) [M⁺ - 157], 276 (18 %) [M⁺ - 158], 275 (14 %) [M⁺ - 159], 274 (36 %) [M⁺ - 160], 273 (9 %) [M⁺ - 161], 272 (18 %) [M⁺ - 162], 196 (19 %)

xviii If not otherwise indicated (like "M⁺ (with 2 × ⁸¹Br)", "M⁺ (with 1 × ⁷⁹Br and 1 × ⁸¹Br)" or "M⁺ (with 2 × ⁷⁹Br)", resp.), the average mass of the product is specified as M⁺ = 276.

xv If not otherwise indicated (like "M⁺ (with 2 × ⁸¹Br)", "M⁺ (with 1 × ⁷⁹Br and 1 × ⁸¹Br)" or "M⁺ (with 2 × ⁷⁹Br)", resp.), the average mass of the product is specified as M⁺ = 276.

xiv If not otherwise indicated (like "M⁺ (with 3 × ⁸¹Br)", "M⁺ (with 2 × ⁸¹Br and 1 × ⁷⁹Br)", "M⁺ (with 1 × ⁸¹Br and 2 × ⁷⁹Br)" or "M⁺ (with 3 × ⁷⁹Br)", resp.), the average mass of the product is specified as M⁺ = 355.

xviii If not otherwise indicated (please see above for the particular M⁺, which depends on the isotope distribution of 4 Br atoms in the molecule), the average mass of the product is specified as M⁺ = 434.
11. Experimental Section

\[ M^+ - 238], \ 195 \ (12 \%) \ [M^+ - 239], \ 194 \ (19 \%) \ [M^+ - 240], \ 193 \ (12 \%) \ [M^+ - 241], \ 168 \ (13 \%) \ [M^+ - 266], \ 166 \ (13 \%) \ [M^+ - 268], \ 88 \ (30 \%) \ [M^+ - 346], \ 87 \ (40 \%) \ [M^+ - 347], \ 86 \ (18 \%) \ [M^+ - 348], \ 81 \ (8 \%) \ \{^{81}\text{Br}^+, \ M^+ - 353\}, \ 79 \ (8 \%) \ \{^{79}\text{Br}^+, \ M^+ - 355\}, \ 62 \ (18 \%) \ [M^+ - 372], \ 61 \ (31 \%) \ [M^+ - 373].

Note:
In order to see possible substitution or cleavage products with regard to a supposed Br at N-1 (the N–Br-bond should be relatively weak), the product mixture was dissolved in CH\(_2\)Cl\(_2\) and stirred for 2 h with aqueous EtOH. A GC/MS analysis showed the same result as given above, even after addition of some KOH to the mixture.

11.2.4.5. 2-Bromo-1-iodo-1H-benzimidazole (122) — Attempted Synthesis

500 mg (2.538 mmol, 1 eq) of 2-bromo-1H-benzimidazole (107) were suspended in 20 ml of an aqueous solution of sodium hydroxide (containing 102 mg (2.538 mmol, 1 eq) of NaOH). After 1 h of stirring, the educt still was not dissolved. Then, 494 mg (3.043 mmol, 1.2 eq) of iodine chloride, I–Cl, were added, causing a yellow-brown precipitate. The slurry was stirred at rt for \(\frac{1}{2}\) h. The precipitated solid was filtered, washed with 100 ml of water and then with 500 ml of Et\(_2\)O and then dried in a high vacuum.

Yield

200 mg ocher powder (crude).

GC/MS

Only educt (2-bromo-1H-benzimidazole (107)) was detectable.
11.2.5. Building up the Ethynyl Moiety at Position C-2 of Benzimidazole Systems — Condensation Approaches

11.2.5.1. Synthesis of Imidazole and Benzimidazole Derivatives from \( \alpha,\alpha' \)-Diketones with Formamide

11.2.5.1.1. 2-Phenylethynyl-1H-phenanthro[9,10-d]imidazole (163) — Attempted Synthesis

1.500 g (7.204 mmol, 1 eq) of phenanthrene-9,10-dione (161) (9,10-phenanthrenequinone) were suspended in 35 ml of formamide (159). Then, 0.880 ml (0.938 g, 7.204 mmol, 1 eq) of phenylpropargyl aldehyde (162) were added to the reddish solution and the mixture heated to 210 °C within \( \frac{1}{2} \) h.\(^{xiii} \) The reaction mixture turned brown and was refluxed for 2½ h (ca. 200 °C). After cooling to rt, the mixture was poured into 50 ml of ice water. The brown precipitate was filtered and purified by flash column chromatography with hexanes / EtOAc 8:1 → hexanes / EtOAc 8:2.

**GC/MS**

Apart from several other peaks, which could not be assigned to the product 2-phenylethynyl-1H-phenanthro[9,10-d]imidazole (163), only educt (phenanthrene-9,10-dione (161)) was detected.

11.2.5.1.2. 4,5-Diphenyl-2-phenylethynyl-1H-imidazole (164) — Attempted Synthesis

1.515 g (7.206 mmol, 1 eq) of benzil (158) (1,2-diphenyl-ethane-1,2-dione) were suspended in 35 ml of formamide (159). Then, 0.880 ml (0.938 g, 7.204 mmol, 1 eq) of phenylpropargyl aldehyde (162) were added to the yellowish solution and the mixture heated to 210 °C within \( \frac{1}{2} \) h. The reaction mixture turned brown and was refluxed for 2½ h (ca. 200 °C). After cooling to rt, the mixture was poured into 100 ml of ice water. From the dark brown solution, an ocher, colloidal precipitate formed which could not be filtered.

\(^{xiii} \) Boiling point of formamide: b.p. \( \text{H}-(\text{C}=\text{O})-\text{NH}_2 = 210 \text{ °C} \).
An extraction sample from the precipitate showed several peaks that could not be assigned to the product 4,5-diphenyl-2-phenylethynyl-1H-imidazole (164). Only tiny amounts of the educt (benzil (158)) were detected.

11.2.5.2. Synthesis of Imidazole and Benzimidazole Derivatives from α,α'-Diketones with Ammonium Acetate

11.2.5.2.1. 2-Phenylethynyl-1H-phenanthro[9,10-d]imidazole (163) — Attempted Synthesis

In an argon atmosphere, 1.500 g (7.204 mmol, 1 eq) of phenanthrene-9,10-dione (161) (9,10-phenanthrenequinone) were suspended in 60 ml of glacial acetic acid and heated to 100 °C. Upon heating under reflux conditions, a reddish solution formed. To this solution, in a rapid manner were added first 1.178 g (144.081 mmol, 20 eq) of ammonium acetate, NH₄OAc (causing the release of a white vapor), and then 0.880 ml (0.938 g, 7.204 mmol, 1 eq) of phenylpropargyl aldehyde (162) (dissolved in 5 ml of glacial acetic acid). The mixture turned brown and was refluxed for 1 h at 115 °C. After cooling to rt, an ocher solid precipitated. The solid was filtered and washed with glacial acetic acid.

Solution attempts showed that the solid was insoluble in MeOH, EtOH, acetone, EtOAc, Et₂O, MrB-ether, CHCl₃ and CH₂Cl₂. It was slightly soluble in toluene and benzene.

11.2.5.2.2. 4,5-Diphenyl-2-phenylethynyl-1H-imidazole (164) — Attempted Synthesis

In an argon atmosphere, 1.515 g (7.206 mmol, 1 eq) of benzil (158) (1,2-diphenyl-ethane-1,2-dione) were suspended in 40 ml of glacial acetic acid and heated to 100 °C. Upon heating under reflux conditions, a yellowish solution formed. To this solution, in a rapid manner were added first 1.178 g (144.081 mmol, 20 eq) of ammonium acetate, NH₄OAc (causing the release of a white vapor), and then 0.880 ml (0.938 g, 7.204 mmol, 1 eq) of phenylpropargyl aldehyde (162) (dissolved in 5 ml of glacial acetic acid). The mixture turned dark brown and was refluxed.
11. Experimental Section

for 1 h at 115 °C. After cooling to rt, no precipitation of a solid occurred, neither after standing
in the refrigerator (4 °C) for 20 h.

GC/MS
A sample from the dark brown solution showed several peaks that could not be assigned to the
product 4,5-diphenyl-2-phenylethynyl-1H-imidazole (164).

11.2.5.3. Synthesis of 2-Phenylethynyl-Benzimidazole Derivatives from a
1,2-Diamine and an Aldehyde

11.2.5.3.1. 2-Phenylethynyl-1H-benzimidazole (109)
In a three-necked flask, equipped with a water separator connected to a reflux condenser, a
thermometer and a septum, 0.779 g (7.204 mmol, 1 eq) of o-phenylenediamine (165)
(1,2-phenylenediamine) were suspended in 40 ml of toluene. Then, 0.880 ml (0.938 g,
7.204 mmol, 1 eq) of phenylpropargyl aldehyde (162) and directly afterwards 0.260 ml (0.316 g,
cia. 7 mmol, 1 eq) of formic acid (96 %) were added. The mixture was refluxed\[^{xlv}\] at ca. 120 °C
for 2 h (until the formation of water stopped).\[^{xlv}\] After allowing to cool to rt, the brown mixture
was evaporated to dryness. The brown solid was purified by flash column chromatography with
hexanes / EtOAc 3:1.

Yield
2-Phenylethynyl-1-(3-phenyl-prop-2-ynyl)-1H-benzimidazole (170):
132 mg (6 %) (lit.\[^{239}\]: 81 %) slightly ocher solid.
2-Phenylethynyl-1H-benzimidazole (109):
71 mg (5 %) colorless solid.

R\[^{f}\]
2-Phenylethynyl-1-(3-phenyl-prop-2-ynyl)-1H-benzimidazole (170): R\[^{f}\] = 0.3 (silica, n-hexane /
EtOAc 3:1);
2-Phenylethynyl-1H-benzimidazole (109): R\[^{f}\] = 0.2 (silica, n-hexane / EtOAc 3:1).

\[^{xlv}\] B.p. (toluene) = 110 °C.
\[^{xlv}\] According to the stoichiometry of the reaction, at most 7.204 mmol (1 eq) of water are formed, corresponding to
0.130 g (= 0.130 ml) of H\(_2\)O.
11. EXPERIMENTAL SECTION

GC/MS

2-Phenylethynyl-1-(3-phenyl-prop-2-ynyl)-1H-benzimidazole (170):
GC (50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min): R<sub>t</sub> = 29.7 min; MS (EI, 70 eV): m/z (%): 333 (11 %) [M<sup>+</sup> + 1 (H)<sub>2</sub>], 332 (58 %) [M<sup>+</sup>], 331 (100 %) [M<sup>+</sup> – 1 (H)], 330 (17 %) [M<sup>+</sup> – 2], 329 (21 %) [M<sup>+</sup> – 3], 166 (18 %) [M<sup>+</sup> – 166], 165 (34 %) [M<sup>+</sup> – 167], 77 (7 %) [Ph<sup>+</sup>, M<sup>+</sup> – 255].

2-Phenylethynyl-1H-benzimidazole (109):
GC (50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min): R<sub>t</sub> = 21.0 min; MS (EI, 70 eV): m/z (%): 219 (16 %) [M<sup>+</sup> + 1 (H)<sub>2</sub>], 218 (100 %) [M<sup>+</sup>], 217 (12 %) [M<sup>+</sup> – 1 (H)], 190 (13 %) [M<sup>+</sup> – 28], 109 (10 %) [M<sup>+</sup> – 109], 77 (7 %) [Ph<sup>+</sup>, M<sup>+</sup> – 141], 64 (10 %) [M<sup>+</sup> – 154], 63 (14 %) [M<sup>+</sup> – 155].

11.2.5.4. Synthesis of 2-Phenylethynyl-Benzimidazole Derivatives from a 1,2-Diamine and an Aldehyde with Copper(II) Acetate

11.2.5.4.1. 2-Phenylethynyl-1H-benzimidazole (109)

In a three-necked flask, equipped with a reflux condenser, a gas inlet and a gas outlet, 0.884 g (8.175 mmol, 1 eq) of o-phenylenediamine (165) (1,2-phenylenediamine) were suspended in 30 ml of water. Then, 3.267 g (17.986 mmol, 2.2 eq) of copper(II) acetate, Cu<sup>II</sup>(OAc)<sub>2</sub>, were added. To the generated dark blue solution was then added a solution of 1.000 ml (1.064 g, 8.175 mmol, 1 eq) of phenylpropargyl aldehyde (162) in 15 ml of MeOH. The solution turned dark brown and was then heated to ca. 80 °C for 1 h. A dark precipitate formed, which was

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xlvii The solvents that were tried were: H<sub>2</sub>O, H<sub>2</sub>O / MeOH 1:1 and MeOH.
xlviii The solvents that were tried were: MeOH, H<sub>2</sub>O / MeOH 1:1 and H<sub>2</sub>O.
filtered and washed with water after cooling to rt. The yield of the crude benzimidazole-copper(I) salt was 4.030 g of a black solid.

The crude benzimidazole-copper(I) salt was suspended in 120 ml of water and heated to 80 °C. Hydrogen sulfide, H₂S, was then bubbled for 10 min through the hot suspension at 80 °C. Afterwards, in order to expel the excess of H₂S, nitrogen was bubbled through the suspension for 10 min. The mixture was filtered while still hot, giving a black filter cake (consisting of copper(I) sulfide, Cu₁₂S) and a light brown filtrate. Upon evaporating this filtrate to 50 ml, a light ocher solid precipitated. The solid was filtered, dried and analyzed by GC/MS. The sample was found not to be analytically pure.

**Yield**

2-Phenylethynyl-1H-benzimidazole (109):

113 mg (6 %) colorless solid.

**GC/MS**

2-Phenylethynyl-1H-benzimidazole (109):

GC (50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min): Rᵣ = 20.3 min; MS (EI, 70 eV): m/z (%): 219 (16 %) [M⁺ + 1 (H)], 218 (100 %) [M⁺], 217 (12 %) [M⁺ - 1 (H)], 190 (13 %) [M⁺ - 28], 109 (10 %) [M⁺ - 109], 77 (7 %) [Ph⁺, M⁺ - 141], 64 (10 %) [M⁺ - 154], 63 (14 %) [M⁺ - 155].

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xlviii The solvents that were tried were: H₂O and H₂O / EtOH 1:1.

xl The H₂S was generated in a three-necked flask charged with 10 g Fe⁺⁺ (or 10 g Na₂S). The flask was equipped with a dropping funnel filled with 50 ml of 50 % H₂SO₄, a gas inlet (for N₂) and a gas outlet (for H₂S). Before reaching the reaction flask, H₂S had to pass through 2 empty gas-washing bottles (for safety reasons). After leaving the reaction flask, H₂S was absorbed as Cu₁⁺ in a gas-washing bottle filled with an aqueous solution of Cu⁺⁺SO₄. This bottle was finally connected to a bubbler.
11.2.6. Synthesis of 2-Phenylethynyl-Benzimidazole Derivatives — The Final Route

11.2.6.1. Preparation of the Imidate Salt 180 — A NOVEL COMPOUND

11.2.6.1.1. Phenylpropionic Acid Chloride (178) (Phenylpropynoyl Chloride)

In a three-necked flask, equipped with a reflux condenser and a bubbler,\(^1\) a mechanical precision stirrer and a septum, 20.000 g (0.137 mol, 1 eq) of phenylpropionic acid (177) (phenylpropynoic acid) were suspended in 220 ml of dry benzene\(^{\text{II}}\) in an argon atmosphere. To the slightly yellow suspension,\(^{\text{i}}\) 19.915 ml (32.561 g, 0.274 mol, 2 eq) of freshly distilled thionyl chloride, SOCl\(_2\), were added via a syringe and a septum. The resulting mixture was stirred and refluxed (at ca. 85 °C) for 2 h under argon. Initially, a vigorous release of gas took place, which slowed down during the course of the reaction. The obtained yellow solution was allowed to cool to rt, and the solvent and excess SOCl\(_2\) were removed in a rotavap previously flushed with nitrogen (bath temp.: 40 °C, pressure: 100 mbar).

Phenylpropionic acid chloride (178) was obtained as a yellow oil. Due to the high sensitivity of acid chlorides to hydrolysis, no characterization was carried out — the product was submitted immediately to the following reaction.

\(^{\text{i}}\) The bubbler was connected to a gas-washing bottle filled with diluted aqueous NaOH-solution in order to remove hydrogen chloride and sulfur dioxide. These gases are formed according to the equation: R–COOH + SOCl\(_2\) → R–COCl + HCl + SO\(_2\).

\(^{\text{II}}\) Due to the toxicity of benzene, the reaction was also carried out in toluene. However, upon evaporation it is advantageous to use the former solvent: Benzene has a boiling point of b.p. (Ph–H) = 80 °C and thionyl chloride of b.p. (SOCl\(_2\)) = 76 °C, while for toluene it is b.p. (Ph–CH\(_3\)) = 110 °C. The acid chloride is heat-sensitive, and employment of toluene led to worse yield.

\(^{\text{i}}\) Phenylpropionic acid (177) dissolved partially.
11.2.6.1.2. Phenylpropiolic Acid Amide (179) (3-Phenylpropynoic Acid Amide)

A two-necked flask, equipped with a septum and a mechanical precision stirrer, was charged with 150 ml of a solution of concentrated (25 %) aqueous ammonia. The flask was chilled in an ice bath. Then, the in the previously described reaction obtained phenylpropiolic acid chloride (178) was added dropwise via a syringe, upon vigorous stirring of the mixture. An ocher solid precipitated; after addition the stirring was continued for 1 h and the mixture was then refrigerated (ca. 4 °C) for 12 h.

The crude product was filtered and then slurried in a chilled aqueous sodium carbonate solution, iii filtered again and washed 4 times with 200 ml of ice-cold water. After drying over P_4O_10, the product was purified by flash column chromatography with n-pentane / Et_2O 1:9 → Et_2O or by recrystallization from benzene and 5 drops of n-hexane added in the heat.

Yield
15.137 g (76 %) fine white crystals.

R_f
R_f = 0.3 (silica, n-pentane / Et_2O 1:9), R_f = 0.2 (silica, n-hexane / EtOAc 1:1).

Melting Point
104 °C (recrystallized from benzene + 5 drops of n-hexane).

GC/MS
Phenylpropiolic acid (177):
GC (50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min): R_f = 2.9 min; MS (EI, 70 eV): m/z (%): 146 (0 %) [M⁺ not detectable], 103 (10 %) [M⁺ - 43], 102 (100 %) [M⁺ - 44 (CO₂)], 76 (40 %)

iii The saturated Na₂CO₃-solution was used in order to remove remaining phenylpropiolic acid (177).
11.2.6.1.3. O-Ethyl-phenylpropiolic Imidate Tetrafluoroborate (180) — A NOVEL COMPOUND

[$M^+ - 70$], 75 (17 %) [$M^+ - 71$], 74 (26 %) [$M^+ - 72$], 63 (15 %) [$M^+ - 83$], 62 (10 %) [$M^+ - 84$], 61 (8 %) [$M^+ - 85$], 52 (10 %) [$M^+ - 94$], 51 (18 %) [$M^+ - 95$], 50 (18 %) [$M^+ - 96$].

Phenylpropiolic acid amide (179):

GC (50 °C, 2 min, 10 °C min$^{-1}$, 250 °C, 20 min): $R_t$ = 13.7 min; MS (EI, 70 eV): $m/z$ (%): 145 (37 %) [$M^+$], 129 (100 %) [$M^+ - 16$], 117 (16 %) [$M^+ - 28$], 101 (21 %) [$M^+ - 44$], 89 (13 %) [$M^+ - 56$], 77 (14 %) [Ph$^+$, $M^+ - 68$], 76 (13 %) [$M^+ - 69$], 75 (42 %) [$M^+ - 70$], 74 (30 %) [$M^+ - 71$], 63 (14 %) [$M^+ - 82$], 62 (12 %) [$M^+ - 83$], 61 (10 %) [$M^+ - 84$], 51 (20 %) [$M^+ - 94$], 50 (10 %) [$M^+ - 95$].

**Phenylpropiolic acid amide (179):**

In a three-necked flask, equipped with a reflux condenser with a bubbler, an argon inlet and a stopper, 8.000 g (55.112 mmol, 1 eq) of dried phenylpropiolic acid amide (179) were suspended in 100 ml of dry CH$_2$Cl$_2$ in an argon atmosphere. Then, 11.518 g (60.623 mmol, 1.1 eq, weighed out in a glove box) of triethyloxonium tetrafluoroborate, Et$_3$O$^+$ BF$_4^-$, were added and the mixture was heated (bath temp.: ca. 50 °C) under reflux for 1 h. The solids dissolved upon heating. After allowing to cool to rt, colorless crystals precipitated.

About half of the amount of CH$_2$Cl$_2$ was then blown off with a nitrogen stream, causing chilling and precipitation of further material. The flask was packed in an ice bath and another ca. 20 ml of CH$_2$Cl$_2$ were blown off (total time for removal of solvent: ca. 1 – 2 h). Afterwards, the product was quickly vacuum-filtered over a previously dried filter frit (pore size: 4), washed with 2 × 15 ml of dry CH$_2$Cl$_2$ and shortly sucked to dryness.

Due to its sensitivity to hydrolysis, imidate tetrafluoroborate 180 was submitted immediately to the following reaction. For analytic purposes, however, it was also recrystallized from CH$_2$Cl$_2$.

**Yield**

11.810 g (82 %) hygroscopic, colorless crystals; slightly soluble in CH$_2$Cl$_2$, insoluble in Et$_2$O.
Melting Point
121 °C (recrystallized from CH$_2$Cl$_2$).

IR
IR (KBr): $\tilde{\nu}$ [cm$^{-1}$] = 3302 (m, br, v N–H), 3153 (m, br, v N–H), 3005 (w, v C–H$_{aromatic}$), 2870 (w, v C–H$_{aliphatic}$), 2233 (s, v C≡C), 1688 (m), 1500 (m), 1445 (m), 1116 (m), 1038 (m), 995 (m).

UV/Vis
MeCN, $c = 3.969 \times 10^{-5}$ mol·l$^{-1}$, $d = 1$ cm: $\lambda_{	ext{max}} = 291$ (16805), 195 (25473).

ESI-MS
Cation mode: $m/z = 174$ [M$^+$ (cation)], $m/z = 435$ [2 × M$^+$ (cation) + M$^-$ (anion, BF$_4^-$)].

HiRes-MS
HiRes-ESI-MS: $m/z = 174$ [M$^+$ (cation)], calc. for C$_{11}$H$_{12}$ONBF$_4$: 174.0913, found: 174.0921 ($\Delta = -0.8$ mDa ≡ $-4.6$ ppm).

Elementary Analysis
Calc. [%] for C$_{11}$H$_{12}$ONBF$_4$: C 50.62, H 4.63, N 5.37, O 6.13, B 4.14, F 29.11. Found [%]: C 50.68, H 4.65, N 5.33.

11.2.6.2. Preparation of the Perfluorinated Diamine 91

11.2.6.2.1. 2,3,4,5-Tetrafluoro-6-nitro-phenylamine (185)

A three-necked flask, equipped with a gas inlet reaching into the solvent, a mechanical precision stirrer and a gas outlet, was charged with 300 ml of dry Et$_2$O. In an argon counter stream, 25.000 g (0.117 mol, 1 eq) of liquid pentafluoro-nitrobenzene (184) (1,2,3,4,5-pentafluoro-
6-nitro-benzene) were added. For 3 h, ammonia gas (99.98 %) was then bubbled through the solution at a speed of 10 bubbles in 5 sec. (experimental setup: see footnote\textsuperscript{lv}). The color of the solution turned from light yellow to dark yellow, and a colorless precipitate (NH\textsubscript{4}F) formed. After the disappearance of educt (complete after 2 – 3 h, monitored by TLC), the solution was filtered through a fluted filter. The filtrate was washed 1 × with 10 ml of a sat. solution of NaCl and then dried over MgSO\textsubscript{4}.

The crude orange mixture was purified by flash column chromatography with hexanes / toluene 1:1 or advantageously with petroleum ether (30 – 50 °C) / CH\textsubscript{2}Cl\textsubscript{2} 7:3 \textsuperscript{lv} and gave 3 main fractions (see \textit{Rf} below). The solvents were removed in a rotavap at 600 mbar and a bath temp. of 30 °C.

**Yield**

16.294 g (66 %) (lit.\textsuperscript{136}: 66 %) volatile, lemon yellow oil, which solidifies upon standing.

\textit{Rf}

Pentafluoro-nitrobenzene (184):

\[ \text{Rf} = 0.7 \text{ (silica, n-hexane / toluene 1:1)} \]; column forerun.

2,3,4,5-Tetrafluoro-6-nitro-phenylamine (185):

Yellow spot, \( \text{Rf} = 0.2 \) (silica, \textit{n}-hexane / toluene 1:1), \( \text{Rf} = 0.2 \) (silica, \textit{n}-hexane / CH\textsubscript{2}Cl\textsubscript{2} 2:1); fraction I.

2,3,5,6-Tetrafluoro-4-nitro-phenylamine (186):

Red spot, \( \text{Rf} = 0.1 \) (silica, \textit{n}-hexane / toluene 1:1), \( \text{Rf} = 0.1 \) (silica, \textit{n}-hexane / CH\textsubscript{2}Cl\textsubscript{2} 2:1); fraction II.

4,5,6-Trifluoro-2-nitro-benzene-1,3-diamine (188) and 2,4,5-trifluoro-6-nitro-benzene-1,3-diamine (187):

Red spot, \( \text{Rf} = 0.05 – 0.1 \) (silica, \textit{n}-hexane / toluene 1:1), \( \text{Rf} = 0.05 – 0.1 \) (silica, \textit{n}-hexane / CH\textsubscript{2}Cl\textsubscript{2} 2:1); fraction III (separates upon chromatography).

\textsuperscript{lv} Before reaching the reaction flask, NH\textsubscript{3} was passed from the steel gas-bottle through a bubbler and then through 2 empty gas-washing bottles (for safety reasons). After leaving the reaction flask, the excess NH\textsubscript{3} had to pass through an empty gas-washing bottle and was then absorbed in a 2 M solution of aqueous HCl.

\textsuperscript{lv} Compound 185 is volatile and partially coevaporates with toluene.
11. EXPERIMENTAL SECTION

Melting Point
41 – 42 °C (lit.\textsuperscript{136}: 41 – 43 °C).

GC/MS

2,3,4,5-Tetrafluoro-6-nitro-phenylamine (185):
GC (50 °C, 2 min, 10 °C min\textsuperscript{-1}, 250 °C, 20 min): \( R_t = 7.0 \) min; MS (El, 70 eV): \( m/z \) (%): 211 (8 %) \([M^+ + 1 (H)]\), 210 (97 %) \([M^+]\), 180 (24 %) \([M^+ - 30 (NO)]\), 164 (58 %) \([M^+ - 46 (NO_2)]\), 163 (15 %) \([M^+ - 47]\), 160 (21 %) \([M^+ - 50]\), 152 (13 %) \([M^+ - 58]\), 144 (50 %) \([M^+ - 66]\), 137 (100 %) \([M^+ - 73]\), 136 (17 %) \([M^+ - 74]\), 117 (21 %) \([M^+ - 93]\), 93 (14 %) \([M^+ - 117]\), 75 (13 %) \([M^+ - 135]\), 70 (11 %) \([M^+ - 140]\), 69 (28 %) \([M^+ - 141]\).

2,3,5,6-Tetrafluoro-4-nitro-phenylamine (186):
GC (50 °C, 2 min, 10 °C min\textsuperscript{-1}, 250 °C, 20 min): \( R_t = 8.7 \) min; MS (El, 70 eV): \( m/z \) (%): 210 (69 %) \([M^+]\), 180 (59 %) \([M^+ - 30 (NO)]\), 164 (55 %) \([M^+ - 46 (NO_2)]\), 152 (12 %) \([M^+ - 58]\), 144 (41 %) \([M^+ - 66]\), 137 (100 %) \([M^+ - 73]\), 117 (26 %) \([M^+ - 93]\), 93 (12 %) \([M^+ - 117]\), 82 (10 %) \([M^+ - 128]\), 75 (14 %) \([M^+ - 135]\), 70 (14 %) \([M^+ - 140]\), 69 (34 %) \([M^+ - 141]\), 51 (11 %) \([M^+ - 159]\).

4,5,6-Trimfluoro-2-nitro-benzene-1,3-diamine (188) and 2,4,5-trifluoro-6-nitro-benzene-1,3-diamine (187):
GC (50 °C, 2 min, 10 °C min\textsuperscript{-1}, 250 °C, 20 min): \( R_t = 10.3 \) min; MS (El, 70 eV): Some characteristic peaks of this mixture of isomers are: \( m/z \) (%): 207 (100 %) \([M^+]\), 177 (5 %) \([M^+ - 30 (NO)]\), 161 (28 %) \([M^+ - 46 (NO_2)]\).

NMR

\(^1\text{H}-\text{NMR} \quad \text{(300 MHz, CDCl}_3, 300.0 \text{ K, TMS)}: \delta \text{ [ppm]} = 5.80 \text{ (s, br, 2 H, NH}_2\text{).}

\(^19\text{F}-\text{NMR} \quad \text{(282 MHz, CDCl}_3, 300.0 \text{ K, CCl}_3\text{F external): } \delta \text{ [ppm]} = -144.60 \text{ (m, 1 F), -146.87 (m, 1 F), -160.07 (m, 1 F), -172.06 (m, 1 F).}
11. EXPERIMENTAL SECTION

11.2.6.2.2. 3,4,5,6-Tetrafluoro-benzene-1,2-diamine (91)

A four-necked flask, equipped with a mechanical precision stirrer, a reflux condenser, an addition funnel and a stopper, was charged with 407 ml (5.088 mol, ca. 66 eq) of a conc. (37 %) hydrochloric acid (c (HCl) ≈ 12.5 mol·L⁻¹). Then, 146.470 g (0.773 mol, 10 eq) of anhydrous tin(II) chloride, SnIICl2, and 78 ml (1.339 mol, ca. 17 eq) of dry EtOH were added. The solution was heated to reflux (ca. 120 °C), and slowly a solution of 16.230 g (0.077 mol, 1 eq) of 2,3,4,5-tetrafluoro-6-nitro-phenylamine (185) in 39 ml (0.670 mol, ca. 8.7 eq) of dry EtOH was added. The yellow solution turned to pale yellow during the course of the reaction. Refluxing was continued for another 40 min (total reflux time: ca. 1 h).

In the heat, 240 ml of water were added and the mixture was allowed to cool to rt. The solution was neutralized by careful addition of sodium hydrogencarbonate (sodium bicarbonate, NaHCO₃) and afterwards a sat. NaHCO₃-solution. The precipitated white solids were vacuum-filtered off with a filter frit (pore size: 4), and the filter cake was washed with CH₂Cl₂. The aqueous phase was extracted 4 × with 50 ml of CH₂Cl₂. The combined, colorless organic phase was dried over MgSO₄, filtered and evaporated to yield a pale yellow solid. Recrystallization from hot cyclohexane (after 1 d of crystallization at rt, the flask was refrigerated for 24 h at 4 °C) gave fine, pale yellow needles.

Purification procedure of 3,4,5,6-tetrafluoro-benzene-1,2-diamine (91):
1,2-Diaminotetrafluorobenzene (91) was recrystallized from dichloromethane (with activated charcoal), filtered under argon and dried in vacuo. The obtained crystals were stored under argon and protected from light. If quite brown, 91 was purified by flash column chromatography on silica with CH₂Cl₂ as a solvent.

Yield
9.350 g (67 %) (lit.¹³⁶: 64 %) thin pale yellow needles, which are sensitive to oxidation and should be stored in a glove box and in the dark.
Melting Point
128 – 130 °C (recrystallized from hot cyclohexane) (lit.\textsuperscript{136}: 130 °C).

GC/MS
GC (50 °C, 2 min, 10 °C min\(^{-1}\), 250 °C, 20 min): \(R_t = 6.6\) min; MS (EI, 70 eV): \(m/z\) (%): 181 (15 %) \([M^+ + 1 (H)]\), 180 (100 %) \([M^+]\), 179 (68 %) \([M^+ - 1 (H)]\), 159 (10 %) \([M^+ - 21]\), 153 (11 %) \([M^+ - 27]\), 152 (79 %) \([M^+ - 28]\), 134 (27 %) \([M^+ - 46]\), 133 (36 %) \([M^+ - 47]\), 132 (20 %) \([M^+ - 48]\), 124 (11 %) \([M^+ - 56]\), 106 (27 %) \([M^+ - 74]\), 90 (27 %) \([M^+ - 90]\), 82 (17 %) \([M^+ - 98]\), 75 (16 %) \([M^+ - 105]\), 70 (14 %) \([M^+ - 110]\).

NMR
\(^1\)H-NMR (300 MHz, [\(\text{D}_6\)]-acetone, 300.0 K, TMS): \(\delta\) [ppm] = 4.48 (s, br, 4 H, 2 \(\times\) NH\(_2\)).
\(^{19}\)F-NMR (282 MHz, [\(\text{D}_6\)]-acetone, 300.0 K, CCl\(_3\)F external): \(\delta\) [ppm] = \(-164.55\) (2 \(\times\) 1 m, 2 \(\times\) 1 F), \(-177.05\) (2 \(\times\) 1 m, 2 \(\times\) 1 F).

11.2.6.3. Synthesis of a Perfluorinated 2-Phenylethynyl-benzimidazole:
4,5,6,7-Tetrafluoro-2-phenylethynyl-1\(H\)-benzimidazole (191) — A NOVEL COMPOUND

![191]

A three-necked flask, equipped with a reflux condenser with a bubbler, an argon inlet, a septum and a strong stirrer, was charged with 10.100 g (38.694 mmol, 1 eq) of freshly prepared O-ethyl-phenylpropionic imidate tetrafluoroborate (180) in an argon atmosphere. Then, ca. 550 ml of dry CH\(_2\)Cl\(_2\) were added via a needle and the septum. The mixture was stirred at rt until nearly all of the imidate tetrafluoroborate 180 had dissolved. In an argon counter stream, 6.969 g (38.694 mmol, 1 eq) of freshly prepared or freshly purified\textsuperscript{\textsuperscript{\textsuperscript{bii}}} 3,4,5,6-tetrafluoro-benzene-

\(\textsuperscript{bii}\) For the purification procedure, see the synthesis of 3,4,5,6-tetrafluoro-benzene-1,2-diamine (91).
11. EXPERIMENTAL SECTION

11.2.6.3.1. Fraction III: 4,5,6,7-Tetrafluoro-2-phenylethynyl-1H-benzimidazole (191) — A NOVEL COMPOUND

Yield

2.360 g (21%) slightly yellow solid;

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\[ \text{1.2-diamine (91) were then added and the yellow mixture was heated for 1 h under reflux conditions (bath temp.: ca. 50 °C).} \]

Upon allowing to cool to rt, a white precipitate (partially ammonium tetrafluoroborate, \( \text{NH}_4\text{BF}_4 \)) and partially product\(^{\text{iii}}\) formed in the yellow solution. Various attempts (causing precipitation upon evaporating solvent or chilling, followed by filtration) in order to remove \( \text{NH}_4\text{BF}_4 \) failed as also product was found in the precipitate (analyzed by GC/MS after a micro-work-up). Hence, the crude mixture was evaporated and then recrystallized from hot MeOH (bath temp.: ca. 90 °C). After standing for 12 h at rt, the mixture was filtered and washed with MeOH, yielding 7.4 g of a white solid. The mother liquid was evaporated, recrystallized from hot MeOH, allowed to stand, filtered and washed as described above to yield 1.7 g of a slightly yellow solid. The solids were combined and purified by flash column chromatography with hexanes → hexanes / EtOAc 9:1 → hexanes / EtOAc 4:1 and gave — amongst others — 3 interesting fractions (see analyses below).

Note:
The 7.4 g solid from the first crystallization showed mainly 3 TLC-spots (fraction I (containing 190), fraction II (containing 196) and fraction III (containing 191)). The 1.7 g solid from the second crystallization showed mainly 4 TLC-spots (no 190, but 196 and 191 amongst 2 others).

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\(^{\text{i}}\) The anion \( \text{BF}_4^- \) of \( \text{NH}_4\text{BF}_4 \) was detected in an ESI-MS spectrum in the anion mode. What is more, \( \text{NH}_4\text{BF}_4 \) is soluble in \( \text{H}_2\text{O} \), but insoluble in acetone and MeOH.

\(^{\text{iii}}\) Product 191 was detected in a GC/MS spectrum.
fine transparent, nearly colorless crystals after dropping \( n \)-pentane into a concentrated solution in acetone;
soluble in acetone, insoluble in MeOH, EtOAc, CH\(_2\)Cl\(_2\), \( n \)-hexane, \( n \)-pentane.

\( \text{R}_f \)

\( \text{R}_f = 0.3 \) (silica, \( n \)-hexane / EtOAc 4:1).

**Melting Point**

261 °C (decomposition) (recrystallized from acetone / \( n \)-pentane).

**GC/MS**

GC (50 °C, 2 min, 10 °C min\(^{-1}\), 250 °C, 20 min): \( \text{R}_i = 19.7 \) min; MS (EI, 70 eV): \( m/z \) (%): 291 (17 %) \([M^+ + 1 \text{ (H)}] \), 290 (100 %) \([M^+] \), 289 (11 %) \([M^+ - 1 \text{ (H)}] \), 145 (15 %) \([M^+ - 145] \).

**NMR**

\( ^1 \text{H-NMR} \) (400 MHz, [D\(_7\)]-DMF, 300.0 K, TMS): \( \delta \) [ppm] = 7.72 (\( m \), 2 H, H-11, H-15), 7.56 (\( m \), 3 H, H-12, H-13, H-14), 4.42 (\( s \), br, 1 H, H-1).

\( ^{13} \text{C-NMR} \) (100 MHz, [D\(_7\)]-DMF, 300.0 K, TMS, \( aq \) = 2 sec, \( dI \) = 3 sec): \( \delta \) [ppm] = 139.5 (C-2 (C, \( q \))), 138.8 and 137.6 and 136.4 and 135.1 (C-4, C-5, C-6, C-7 (all C-F, \( q \), appearing as multiplets)), 132.7 and 129.7 (C-11, C-15 and C-12, C-14 (all CH, \( p \))), 131.0 (C-13 (CH, \( p \))), 125.8 (C-3a and C-7a (both C, \( q \), appearing as a multiplet)), 121.0 (C-10 (C, \( q \))), 92.5 (C-9 (acetylenic C (C-Ph), \( q \))), 80.0 (C-8 (acetylenic C, \( q \))).

**IR**

IR (KBr): \( \tilde{\nu} \) [cm\(^{-1}\)] = 2224 (m, v C=C), 1560 (s), 1533 (m), 1493 (s), 1422 (s), 1302 (s), 1024 (s), 1014 (s), 1003 (s), 810 (m), 754 (m), 687 (m).

**UV/Vis**

MeCN, \( c = 2.054 \cdot 10^{-5} \text{ mol-l}^{-1} \), \( d = 1 \text{ cm} \): \( \lambda_{\text{max}} = 320 (26,587), 308 (29,411), 252 (16,994), 197 (41,098) \).
11. EXPERIMENTAL SECTION

HiRes-MS
HiRes-MALDI: \( m/z = 291 \ [M^+ + 1 \ (H)] \), calc. for \( C_{15}H_6N_2F_4 + H \): 291.0540, found: 291.0544 (\( \Delta = +0.4 \text{ mDa} \equiv +1.37 \text{ ppm} \)).

Elementary Analysis
Calc. [%] for \( C_{15}H_6N_2F_4 \): C 62.08, H 2.08, N 9.65, F 26.18. Found [%]: C 61.83, H 2.29, N 9.73, F 26.33.
Acidity: \( pK_a = 7.35 \) (titration with 0.10 M NaOH at 25 °C in MCS / \( H_2O \) 4:1 as a solvent).
Basicity: No protonation could be observed upon titration with 0.10 M HCl at 25 °C in MCS / \( H_2O \) 4:1 as a solvent. The analysis indicated decomposition of the compound.

X-Ray
Fine, transparent crystals were obtained by dropping \( n \)-pentane into a concentrated solution in acetone and allowing to crystallize for 5 d at rt. For crystal data, structure refinement and X-ray structure see Appendix, Table 12-1 and Figure 12-1.

Note:
The spots corresponding to fractions I and II could not be separated cleanly by the chromatography procedure described above. Hence, the total 5.0 g of a white solid were separated by column chromatography on a plate column with hexanes / \( MIB \)-ether 30:1.

11.2.6.3.2. Fraction I: \( N\)-(2-Amino-3,4,5,6-tetrafluoro-phenyl)-3-phenyl-propynimidic Acid Ethyl Ester (190) — A NOVEL COMPOUND

![Chemical Structure](image)

Yield
0.235 g (2 %) white solid.
R<sub>f</sub>

R<sub>f</sub> = 0.6 (silica, n-hexane / EtOAc 4:1), R<sub>f</sub> = 0.4 (silica, n-hexane / MrB-ether 4:1).

**GC/MS**

GC (50 °C, 2 min, 10 °C min<sup>-1</sup>, 250 °C, 20 min): R<sub>t</sub> = 18.2 min; MS (El, 70 eV): m/z (%): 337 (8 %) [M<sup>+</sup> + 1 (H)], 336 (52 %) [M<sup>+</sup>], 308 (22 %) [M<sup>+</sup> - 28], 307 (22 %) [M<sup>+</sup> - 29], 293 (10 %) [M<sup>+</sup> - 43], 292 (9 %) [M<sup>+</sup> - 44], 291 (51 %) [M<sup>+</sup> - 45], 279 (36 %) [M<sup>+</sup> - 57], 267 (15 %) [M<sup>+</sup> - 69], 266 (100 %) [M<sup>+</sup> - 70], 265 (15 %) [M<sup>+</sup> - 71], 103 (20 %) [M<sup>+</sup> - 233], 91 (31 %) [M<sup>+</sup> - 245], 77 (29 %) [Ph<sup>+</sup>, M<sup>+</sup> - 259].

No further characterization was carried out.

11.2.6.3.3. Fraction II: 6,7,8,9-Tetrafluoro-2-methoxy-4-phenyl-3H-benzo[b][1,4]diazepine (196) — A NOVEL COMPOUND

![196](image)

**Yield**

2.055 g (16 %) white powder, colorless transparent crystals after recrystallization from n-hexane (3 d at ca. 4 °C), soluble in EtOAc, insoluble in n-hexane.

R<sub>f</sub>

R<sub>f</sub> = 0.5 (silica, n-hexane / EtOAc 4:1), R<sub>f</sub> = 0.3 (silica, n-hexane / MrB-ether 4:1).

**Melting Point**

122 – 124 °C (recrystallized from n-hexane).
11. EXPERIMENTAL SECTION

GC/MS
GC (50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min): R₁ = 17.8 min; MS (EI, 70 eV): m/z (%): 323 (16 %) [M⁺ + 1 (H)], 322 (100 %) [M⁺], 321 (88 %) [M⁺ – 1 (H)], 291 (18 %) [M⁺ – 31], 279 (27 %) [M⁺ – 43], 278 (14 %) [M⁺ – 44], 266 (32 %) [M⁺ – 56], 265 (12 %) [M⁺ – 57], 148 (12 %) [M⁺ – 174], 103 (33 %) [M⁺ – 219], 91 (16 %) [M⁺ – 231], 77 (27 %) [Ph⁺, M⁺ – 245], 57 (25 %) [M⁺ – 265], 51 (13 %) [M⁺ – 271].

NMR
¹H-NMR (500 MHz, CDCl₃, 300.0 K, TMS): δ [ppm] = 8.08 (m, 2 H, H-12, H-16), 7.51 (m, 3 H, H-13, H-14, H-15), 3.89 (s, 3 H, H-10 (CH₃)), 3.42 (m, 2 H, H-3 (CH₂, H-3α, H-3β)).
¹³C-NMR (125 MHz, CDCl₃, 298.0 K, TMS, aq = 2 sec, dI = 3 sec): δ [ppm] = 157.6 and 156.9 (C-2 and C-4 (both C, q)), 143.0 and 141.1 and 139.1 and 137.2 (C-6, C-7, C-8, C-9 (all C-F, q, appearing as multiplets)), 136.9 (C-11 (C, q)), 132.0 (C-14 (CH, p)), 129.2 and 128.8 (C-12, C-16 and C-13, C-15 (all CH, p)), 127.0 and 125.5 (C-5α and C-9α (both C, q, appearing as multiplets)), 56.0 (C-10 (CH₃, t)), 36.6 (C-3 (CH₂, s)).

IR
IR (KBr): ν [cm⁻¹] = 3004 (vw, ν C–H aromatic), 2962 (m, ν C–H aliphatic), 1730 (m, ν C=N), 1655 (s), 1634 (s), 1568 (m), 1508 (s), 1483 (s), 1443 (s), 1334 (s), 1313 (s), 1040 (s), 1024 (s), 1010 (m), 975 (s), 785 (m), 762 (m), 691 (m).

UV/Vis
MeCN, c = 2.048·10⁻⁵ mol·l⁻¹, d = 1 cm: λ_max = 320 (7,715), 254 (22,558), 200 (37,255).

HiRes-MS
HiRes-MALDI: m/z = 323 [M⁺ + 1 (H)], calc. for C₁₆H₁₀N₂OF₄ + H: 323.0802, found: 323.0804 (Δ = +0.2 mDa = +0.62 ppm).

Elementary Analysis
X-Ray
Colorless, transparent crystals were obtained by crystallization from n-hexane (3 d at ca. 4 °C). For crystal data, structure refinement and X-ray structure see Appendix, Table 12-2 and Figure 12-2.

Note:
Attempts in order to convert 196 into 191 failed. These experiments consisted in dissolving 196 in CH₂Cl₂, followed by addition of TFA or BF₃·Et₂O, respectively, in varying amounts. No formation of 191 could be detected in any case by monitoring the reaction with TLC.

11.2.6.4. 2-Phenylethynyl-1H-benzimidazole (109)

A three-necked flask, equipped with a reflux condenser with a bubbler, an argon inlet, a septum and a strong stirrer, was charged with 10.724 g (41.085 mmol, 1 eq) of freshly prepared O-ethylphenylpropioic imidate tetrafluoroborate (180) in an argon atmosphere. Then, ca. 550 ml of dry CH₂Cl₂ were added via a needle and the septum. The mixture was stirred at rt until nearly all of the imidate tetrafluoroborate 180 had dissolved. In an argon counter stream, 4.443 g (41.085 mmol, 1 eq) of freshly purified **ox-phenylenediamine** (165) (1,2-phenylenediamine) were then added and the yellow mixture was heated for 1 h under reflux conditions (bath temp.: ca. 50 °C).

Upon allowing to cool to rt for 1 h, a yellowish precipitate (partially ammonium tetrafluoroborate, NH₄BF₄,** and partially product**) formed in the orange-red solution.

The pale yellow precipitate (5.6 g crude material, mainly 1 spot on a TLC-plate, Rₜ = 0.1 (silica, n-hexane / EtOAc 4:1)) was filtered and purified by flash column chromatography with

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**lx** For the purification procedure, see below the synthesis of 2-phenylethynyl-1H-benzimidazole (109).

**lx** The anion BF₄⁻ of NH₄BF₄ was detected in an ESI-MS spectrum in the anion mode. What is more, NH₄BF₄ is soluble in H₂O, but insoluble in acetone and MeOH.

**lx** Product 109 was detected in a GC/MS spectrum.
hexanes / EtOAc 9:1 → hexanes / EtOAc 4:1 → hexanes / EtOAc 1:1 → EtOAc. Evaporation of the solvents gave 2.087 g of a yellowish solid.

The orange-red mother liquid was evaporated, yielding 8.0 g (crude material, mainly 3 spots on a TLC-plate, \( R_f = 0.1 \) and \( R_f = 0.2 \) and \( R_f = 0.5 \) (silica, n-hexane / EtOAc 4:1)) of an orange-red solid. Flash column chromatography with hexanes / EtOAc 9:1 → hexanes / EtOAc 4:1 → hexanes / EtOAc 1:1 → EtOAc followed by evaporation of the solvents yielded 1.200 g of a yellowish solid.

The fractions containing product from both columns were combined to give 3.287 g of a pale yellow solid.

Note:
The TLC-plates from the flash column chromatographies showed mainly 3 spots, which were assigned as follows: Fraction I (containing 197), fraction II (still several spots and low yield, so that fraction II was not further investigated) and fraction III (containing 109) (see analyses below).

Purification procedure of 1,2-phenylenediamine (165):
Purchasable o-phenylenediamine (165) was purified by refluxing a dichloromethane solution, adding activated charcoal, continued refluxing for 5 min followed by hot filtration through 2 fluted filters and evaporation.\(^{284, 285}\) The obtained solid was then recrystallized from hot dichloromethane, filtered and washed with dichloromethane. The latter procedure was repeated two times, and the obtained white crystals (m.p. = 99 – 100 °C from CH\(_2\)Cl\(_2\) (lit.\(^{302}\): 102 – 103 °C from CHCl\(_3\)) were dried in vacuo, stored under argon and protected from light.

11.2.6.4.1. Fraction III: 2-Phenylethynyl-1H-benzimidazole (109)

Yield
3.287 g (37 %) pale yellow solid;
pale yellow, nearly colorless needles after recrystallization from acetone;
soluble in acetone and hot MeOH, insoluble in CH\(_2\)Cl\(_2\) and n-hexane.
11. EXPERIMENTAL SECTION

**R<sub>r</sub>**

R<sub>r</sub> = 0.1 (silica, n-hexane / EtOAc 4:1), R<sub>r</sub> = 0.4 (silica, n-pentane / Et<sub>2</sub>O 1:9).

**Melting Point**

194 – 196 °C (recrystallized from acetone).

**GC/MS**

GC (50 °C, 2 min, 10 °C min<sup>-1</sup>, 250 °C, 20 min): R<sub>t</sub> = 20.6 min; MS (EI, 70 eV): m/z (%): 219 (16 %) [M<sup>+</sup> + 1 (H)], 218 (100 %) [M<sup>+</sup>], 217 (12 %) [M<sup>+</sup> – 1 (H)], 190 (13 %) [M<sup>+</sup> – 28], 109 (10 %) [M<sup>+</sup> – 109], 77 (7 %) [Ph<sup>+</sup>, M<sup>+</sup> – 141], 64 (10 %) [M<sup>+</sup> – 154], 63 (14 %) [M<sup>+</sup> – 155].

**NMR**

<sup>1</sup>H-NMR (400 MHz, [D<sub>7</sub>]-DMF, 300.0 K, TMS): δ [ppm] = 7.70 (m, 2 H, H-4, H-7), 7.68 (m, 2 H, H-11, H-15), 7.54 (m, 3 H, H-12, H-13, H-14), 7.30 (m, 2 H, H-5, H-6), 3.48 (s, br, 1 H, H-1).

<sup>13</sup>C-NMR (100 MHz, [D<sub>7</sub>]-DMF, 300.0 K, TMS, aq = 2 sec, d1 = 3 sec): δ [ppm] = 152.4 (C-2 (C, q)), 140.1 and 139.3 (C-3a and C-7a (both C, q)), 132.5 and 129.6 (C-11, C-15 and C-12, C-14 (all CH, p)), 130.6 (C-13 (CH, p)), 124.0 and 123.1 and 116.0 and 115.8 (C-4, C-5, C-6, C-7 (all C-H, p)), 121.5 (C-10 (C, q)), 91.8 (C-9 (acetylenic C (C-Ph), q)), 80.9 (C-8 (acetylenic C, q)).

**UV/Vis**

MeCN, c = 8.614·10<sup>-6</sup> mol·L<sup>-1</sup>, d = 1 cm: λ<sub>max</sub> = 327 (25,192), 307 (33,667), 254 (18,343), 203 (46,786).
11.2.6.4.2. Fraction 1: N-(2-Amino-phenyl)-3-phenyl-propynimidic Acid Ethyl Ester (197) — A NOVEL COMPOUND

Yield

2.183 g (20%) white solid.

Rf

Rf = 0.5 (silica, n-hexane / EtOAc 4:1), Rf = 0.7 (silica, n-pentane / Et2O 1:9).

GC/MS

GC (50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min): Rf = 18.4 min; MS (EI, 70 eV): m/z (%): 265 (18%), [M⁺ + 1 (H)], 264 (100%) [M⁺], 263 (18%) [M⁺ - 1 (H)], 249 (24%) [M⁺ - 15 (Me)], 236 (35%) [M⁺ - 28], 235 (56%) [M⁺ - 29 (Et)], 221 (14%) [M⁺ - 43], 220 (11%) [M⁺ - 44], 219 (53%) [M⁺ - 45], 218 (7%) [M⁺ - 46], 208 (11%) [M⁺ - 56], 207 (69%) [M⁺ - 57], 206 (16%) [M⁺ - 58], 195 (14%) [M⁺ - 69], 194 (84%) [M⁺ - 70], 193 (25%) [M⁺ - 71], 104 (14%) [M⁺ - 160], 103 (21%) [M⁺ - 161], 102 (15%) [M⁺ - 162], 91 (27%) [M⁺ - 173], 90 (30%) [M⁺ - 174], 89 (14%) [M⁺ - 175], 78 (8%) [M⁺ - 186], 77 (49%) [Ph⁺, M⁺ - 187], 76 (19%) [M⁺ - 188], 75 (8%) [M⁺ - 189], 65 (10%) [M⁺ - 199], 64 (10%) [M⁺ - 200], 63 (15%) [M⁺ - 201], 51 (18%) [M⁺ - 213].

NMR

¹H-NMR (400 MHz, CDCl₃, 300.0 K, TMS external): δ [ppm] = 8.07 and 7.50 and 7.44 and 7.31 and 7.22 (several m, altogether 9 H, H-11, H-12, H-13, H-14, H-15 and H-3, H-4, H-5, H-6), 4.28 (q, JH-16 - H-17 = 7.1, JH-15 - H-16 = 14.2, 2 H, H-16, H-16' (CH₂-group)), 3.30 (s, br, 2 H, H-2, H-2' (NH₂-group)), 1.29 (t, JH-17 - H-16 = 7.1, 3 H, H-17, H-17', H-17'' (CH₃-group)).

¹³C-NMR (100 MHz, CDCl₃, 300.0 K, TMS external, aq = 2 sec,dl = 3 sec): δ [ppm] = 154.4 (C-7 (C, q)), 140.1 and 138.5 and 138.0 (C-1 and C-2 and C-10 (all C, q)), 130.5 and 127.0 and
125.9 and 123.7 (C-3, C-4, C-5, C-6 (all CH, p)), 128.4 and 127.8 (C-11, C-15 and C-12, C-14 (all CH, p)), 128.2 (C-13 (CH, p)), 90.3 and 59.2 (C-8 and C-9 (both acetylenic C, q)), 63.4 (C-16 (CH₂), s), 14.2 (C-17 (CH₃), t).

No further characterization was carried out.

11.2.7. Attaching Alkynyl Moieties at N-1: Building up Azaenediynes

11.2.7.1. Building up a Perfluorinated Azaenediyne

11.2.7.1.1. 4,5,6,7-Tetrafluoro-2-phenylethynyl-1-trimethylsilylethynyl-1H-benzimidazole (198) — A NOVEL COMPOUND

A previously dried three-necked flask, equipped with an argon inlet, a septum and an argon outlet connected to a bubbler, was charged with 170 ml of dry toluene. In an argon atmosphere, 1.459 g (5.027 mmol, 1 eq) of dried 4,5,6,7-tetrafluoro-2-phenylethynyl-1H-benzimidazole (191) were then added (in an argon counter stream). The turbid suspension was stirred for 10 min at rt. Afterwards, the suspension was cooled to 0 °C in an ice bath and stirred for 10 min. Via a syringe and a septum, slowly 10.881 ml (5.027 mmol, 1 eq) of a freshly prepared 0.462 M LDA solution in THF were added dropwise. The mixture was stirred for 10 min at 0 °C (the solids dissolved nearly completely, resulting in a nearly clear, pale yellow solution), then allowed to reach rt and stirred for another 10 min at rt.

In an argon counter stream, 1.951 g (5.027 mmol, 1 eq) of trimethylsilylethynyl(phenyl)-iodonium tetrafluoroborate (69) were added as a solid in 4 portions. Upon adding, the mixture warmed up to 30 – 40 °C and turned dark yellow. Monitoring the reaction by TLC and GC/MS showed that still educt was left after ½ h, 1 h, 2 h and 3½ h. Therefore, after 1½ h another 1.000 g (2.577 mmol, 0.513 eq) of trimethylsilylethynyl(phenyl)-iodonium tetrafluoroborate (69) was added as a solid in 2 portions, leading to a reddish reaction mixture — the amounts of both
product 198 and phenyl iodide (C₆H₅–I) increased upon longer stirring and addition of 69. Addition of another 1.000 g (2.577 mmol, 0.513 eq) of 69 after 2½ h led to a brown color (in total, 1.000 eq + 1.025 eq = 2.025 eq of 69 were used). After a reaction time of 5 h, practically no educt could be detected.

As a work-up procedure, first ethyl acetate and then water were added. The mixture was extracted 6 times with ethyl acetate (until the organic layer remained colorless) and the combined organic layers dried over Na₂SO₄, filtered and evaporated. A two-dimensional TLC showed that no decomposition occurred on the silica TLC-plate.

The product was purified by flash column chromatography with hexanes / EtOAc 32.5:1. An analytical sample was additionally purified by HPLC on a Si 60 phase (with n-hexane / MIB-ether 30:1) or by flash column chromatography with n-hexane / MIB-ether 30:1, followed by diffusion-controlled crystallization (see below).

**Yield**
1.032 g (53 %) white solid;
fine, long, colorless and transparent needles after diffusion-controlled crystallization (for 2 d at 16 °C diffusion of n-pentane into a concentrated solution in CH₂Cl₂);
soluble in acetone, EtOAc, CH₂Cl₂, low solubility in Et₂O, CCl₄, n-hexane, n-pentane.

**Rₚ**
Rₚ = 0.3 (silica, n-hexane / EtOAc 32.5:1), Rₚ = 0.7 (silica, n-hexane / EtOAc 5:1), Rₚ = 0.7 (silica, n-hexane / MIB-ether 30:1).

**Melting Point**
171 – 172 °C (decomposition) (recrystallized from CH₂Cl₂ / n-pentane by diffusion-controlled crystallization for 2 d at 16 °C).

**GC/MS**

| GC (50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min): Rᵣ = 20.4 min; MS (EI, 70 eV): m/z (%): 387 (30 %) [M⁺ + 1 (H)], 386 (100 %) [M⁺], 385 (21 %) [M⁺ − 1 (H)], 371 (28 %) [M⁺ − 15 (Me)], 127 (98 %) [Ph⁺], 119 (98 %) [Ph⁺, M⁺ − 127 (Ph)]. |

| Phenyl iodide (C₆H₅–I) was detected in the GC/MS as follows: GC: Rᵣ = 4.0 min; MS (EI, 70 eV): m/z (%): 204 (100 %) [M⁺], 127 (22 %) [1⁺, M⁺ − 77 (Ph)], 77 (98 %) [Ph⁺, M⁺ − 127 (1)]. |
370 (14 %) [M⁺ – 16], 369 (19 %) [M⁺ – 17], 367 (14 %) [M⁺ – 19], 309 (10 %) [M⁺ – 77 (Ph)], 186 (13 %) [M⁺ – 200], 127 (13 %) [M⁺ – 259], 81 (14 %) [M⁺ – 305], 77 (16 %) [Ph⁺, M⁺ – 309], 73 (55 %) [Me₃Si⁺, M⁺ – 313].

**NMR**

1H-NMR (500 MHz, CD₂Cl₂, 300.0 K, TMS external): δ [ppm] = 7.66 (m, 2 H, H-11, H-15), 7.49 (m, 3 H, H-12, H-13, H-14), 0.32 (s, 9 H, TMS).

13C-NMR (125 MHz, CD₂Cl₂, 298.0 K, TMS external, aq = 2 sec, dl = 3 sec): δ [ppm] = 141.3 (C-2 (C, q, appearing as a multiplet)), 139.5 and 138.8 and 138.5 and 135.0 (C-4, C-5, C-6, C-7 (all C-F, q, appearing as multiplets)), 132.8 and 129.1 (C-11, C-15 and C-12, C-14 (all CH, p)), 131.1 (C-13 (CH, p)), 127.9 and 120.0 (C-3a and C-7a (both C, q, appearing as multiplets)), 120.4 (C-10 (C, q)), 98.0 (C-16 (acyclic C (C-N), q, appearing as a doublet, 4JC-F = 0.7)), 87.1 (C-9 (acyclic C (C-Ph, q)), 80.4 (C-17 (acyclic C (C-Si), q, 1JC-Si = 40.0 (Si-satellites))), 76.9 (C-8 (acyclic C, q)), −0.3 (TMS (3 × CH₃, r, 1JC-Si = 28.4 (Si-satellites))).

19F-NMR (282 MHz, CD₂Cl₂, 298.0 K, CCl₃F external): δ [ppm] = −154.05 and −160.99 and −161.26 and −163.56 (4 × 1 m, 4 × 1 F, F-4, F-5, F-6, F-7).

**IR**

IR (KBr): ν [cm⁻¹] = 3018 (vw, ν C–H aromatic), 2966 (w, ν C–H aliphatic), 2232 (m, ν C≡C), 2198 (m, ν C≡C), 1550 (s), 1532 (m), 1489 (s), 1474 (s), 1305 (s), 1250 (m), 1207 (m), 1032 (s), 1022 (m), 1004 (s), 869 (s), 849 (s), 759 (s), 686 (m).

**UV/Vis**

MeCN, c = 1.304·10⁻⁵ mol·l⁻¹, d = 1 cm; λmax = 307 (29,135), 219 (27,218), 196 (35,959).

**ESI-MS**

Cation mode: m/z = 387 [M⁺ + 1 (H)] (main peak).

**HiRes-MS**

HiRes-MALDI: m/z = 387 [M⁺ + 1 (H)], calc. for C₂₀H₁₄N₂F₄Si + H: 387.0935, found: 387.0932 (Δ = −0.3 mDa ≡ −0.78 ppm).
Elementary Analysis
Calc. [%] for C$_{20}$H$_{14}$N$_2$F$_4$Si: C 62.17, H 3.65, N 7.25, F 19.67, Si 7.27. Found [%]: C 62.32, H 3.77, N 7.16, F 19.74.

X-Ray
Fine, long, colorless and transparent needles were obtained by diffusion-controlled crystallization (for 2 d at 16 °C diffusion of n-pentane into a concentrated solution in CH$_2$Cl$_2$). For crystal data, structure refinement and X-ray structure see Appendix, Table 12-3 and Figure 12-3.

11.2.7.2. Building up a Non-Fluorinated Azaenediynne

11.2.7.2.1. 2-Phenylethynyl-1-trimethylsilylethynyl-1H-benzimidazole (199) — A NOVEL COMPOUND

A previously dried three-necked flask, equipped with an argon inlet, a septum and an argon outlet connected to a bubbler, was charged with ca. 200 ml of dry toluene. In an argon atmosphere, 2.015 g (9.232 mmol, 1 eq) of dried 2-phenylethynyl-1H-benzimidazole (109) were then added (in an argon counter stream). The turbid suspension was stirred for 10 min at rt. Afterwards, the suspension was cooled to 0 °C in an ice bath and stirred for 10 min. Via a syringe and a septum, slowly 19.983 ml (9.232 mmol, 1 eq) of a freshly prepared 0.462 M LDA solution in THF were added dropwise. The mixture was stirred for 10 min at 0 °C (the solids dissolved nearly completely, resulting in a nearly clear, pale yellow solution), then allowed to reach rt and stirred for another 10 min at rt.

In an argon counter stream, 3.582 g (9.232 mmol, 1 eq) of trimethylsilylethynyl(phenyl)-iodonium tetrafluoroborate (69) were added as a solid in 6 portions. Upon adding, the mixture warmed up to 30 - 40 °C and turned reddish brown. Monitoring the reaction by TLC and GC/MS showed that still educt was left after ½ h and 1 h. Therefore, after 1½ h another 1.700 g (4.381 mmol, 0.475 eq) of trimethylsilylethynyl(phenyl)-iodonium tetrafluoroborate (69) were
added as a solid in 2 portions, leading to a brown reaction mixture — the amounts of both product 199 and phenyl iodide (C₆H₅-I) increased upon longer stirring and addition of 69 (in total, 1.000 eq + 0.475 eq = 1.475 eq of 69 were used). After a reaction time of 3 h, practically no educt could be detected.

As a work-up procedure, the reaction mixture was vacuum-filtered over celite and washed until no product could be detected by TLC. The solvents were evaporated (bath temp. < 40 °C). A two-dimensional TLC showed that no decomposition occurred on the silica TLC-plate.

The product was purified by flash column chromatography with hexanes / EtOAc 10:1 → hexanes / EtOAc 7:1 → hexanes / EtOAc 5:1 (yield: 38 %). A mixed fraction was submitted again to flash column chromatography (hexanes / EtOAc 19:1 → hexanes / EtOAc 9:1, yield: 13 %).

**Yield**

1.463 g (50 %) viscous yellow oil, which solidifies in a vacuum (8·10⁻³ mbar) or upon cooling to give a yellow wax;

turned from light yellow to dark yellow while standing at the air;

several crystallization attempts failed (diffusion-controlled crystallization at rt by diffusing n-pentane into a concentrated solution in CH₂Cl₂, precipitation in a system of CH₂Cl₂ / H₂O, MeCN / H₂O, hexafluorobenzene (C₆F₆) / H₂O and EtOH / H₂O, freezing out of a solution of n-pentane at +4 °C, -20 °C or -78 °C, as well as sublimation at rt, 40 °C or 50 °C and 8·10⁻³ mbar only gave an oil or a pale yellow, non-crystalline solid, respectively);

purification for analytical purposes was carried out via Kugelrohr-distillation at ca. 150 °C and 10⁻² mbar, resulting in a light yellow oil;

soluble in acetone, EtOAc, MeCN, CH₂Cl₂, n-hexane, less soluble in n-pentane, insoluble in H₂O.

**R₁**

R₁ = 0.4 (silica, n-hexane / EtOAc 5:1).

**Melting Point**

49 – 50 °C (sublimed at 40 °C).

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[iii] Compound 199 is slightly volatile in a high vacuum (< 2·10⁻³ mbar) and could therefore be Kugelrohr-distilled.
11. EXPERIMENTAL SECTION

**GC/MS**

GC (50 °C, 2 min, 10 °C min⁻¹, 250 °C, 20 min): Rᵣ = 21.1 min; MS (EI, 70 eV): m/z (%) : 315 (24 %) [M⁺ + 1 (H)], 314 (100 %) [M⁺], 313 (29 %) [M⁺ - 1 (H)], 300 (10 %) [M⁺ - 14], 299 (49 %) [M⁺ - 15 (Me)], 297 (11 %) [M⁺ - 17], 255 (12 %) [M⁺ - 59], 142 (11 %) [M⁺ - 172], 127 (11 %) [M⁺ - 187], 77 (5 %) [Ph⁺, M⁺ - 237], 73 (14 %) [Me₅Si⁺, M⁺ - 241].

**NMR**

¹H-NMR (400 MHz, CD₂Cl₂, 300.0 K, TMS external): δ [ppm] = 7.73 - 7.32 (several m, altogether 9 H, H-4, H-5, H-6, H-7 and H-11, H-12, H-13, H-14, H-15), 0.32 (s, 9 H, TMS).

¹³C-NMR (100 MHz, CD₂Cl₂, 300.0 K, TMS external, aq = 2 sec, dI = 3 sec): δ [ppm] = 142.3 (C-2 (C, q)), 138.7 and 135.1 (C-3a and C-7a (both C, q)), 132.6 and 129.0 (C-11, C-15 and C-12, C-14 (all CH, p)), 130.5 (C-13 (CH, p)), 125.8 and 125.0 and 120.9 and 111.3 (C-4, C-5, C-6, C-7 (all C-H, p)), 121.2 (C-10 (C, q)), 96.1 (C-16 (acetylenic C (C-N), q)), 88.3 (C-9 (acetylenic C (C-Ph), q)), 79.6 (C-17 (acetylenic C (C-Si), q, Si-satellites visible)), 78.5 (C-8 (acetylenic C, q)), 0.1 (TMS (3 × CH₃, t, ¹³C-Si = 28.3 (Si-satellites))).

**IR**

IR (film): ̅ν [cm⁻¹] = 3065 (m, ν C-H aromatic), 2958 (s, ν C-H aliphatic), 2925 (s, ν C-H aliphatic), 2854 (m, ν C-H aliphatic), 2228 (s, ν C≡C), 2191 (s, ν C≡C), 1612 (m), 1598 (m), 1524 (s), 1480 (m), 1450 (s), 1383 (s), 1311 (s), 1276 (s), 1251 (s), 1190 (s), 1176 (m), 1142 (m), 883 (s), 856 (s), 757 (s), 741 (s), 688 (s), 655 (m), 641 (s) 617 (w), 602 (w).

**UV/Vis**

MeCN, c = 2.646·10⁻⁵ mol·L⁻¹, d = 1 cm: λ_max = 309 (29,178), 263 (12,662), 203 (33,223).

**ESI-MS**

Cation mode: m/z = 315 [M⁺ + 1 (H)] (main peak).

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¹xiv Phenyl iodide (C₆H₅-I) was detected in the GC/MS as follows:

GC: Rᵣ = 4.0 min; MS (EI, 70 eV): m/z (%) : 204 (100 %) [M⁺], 127 (22 %) [I⁺, M⁺ - 77 (Ph)], 77 (98 %) [Ph⁺, M⁺ - 127 (I)].
11. EXPERIMENTAL SECTION

HiRes-MS
HiRes-MALDI: m/z = 315 [M+ + 1 (H)], calc. for C₂₀H₁₈N₂Si + H: 315.1312, found: 315.1300 (Δ = −1.2 mDa ≡ −3.80 ppm).

Elementary Analysis
Calc. [%] for C₂₀H₁₈N₂Si: C 76.39, H 5.77, N 8.91, Si 8.93. Found [%]: C 76.18, H 6.01, N 8.91.

11.2.8. N-Functionalizations of Azaenediynes

11.2.8.1. N-Protonation of Azaenediynes

11.2.8.1.1. 4,5,6,7-Tetrafluoro-2-phenylethynyl-1-trimethylsilylethynyl-1H-benzimidazol-3-ium Salts 200, 201 and 202 — NOVEL COMPOUNDS —

Attempted Syntheses

Various protonation reactions were generally carried out as follows: The educt was dissolved in dry CH₂Cl₂ or dry Et₂O, with or without buffer and treated with 1 eq or 10 eq of an acid (triflic acid, TFA or HCl) at rt or at 0 °C, respectively.

A previously dried two-necked flask, equipped with an argon inlet, a septum and an argon outlet, was charged with ca. 10 ml of dry CH₂Cl₂. In an argon atmosphere, 40 mg (0.104 mmol, 1 eq) of dried 4,5,6,7-tetrafluoro-2-phenylethynyl-1-trimethylsilylethynyl-1H-benzimidazole (198) were then added (in an argon counter stream). Via a syringe and a septum, 9.032 µl (0.016 g,

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iv The reactions were also carried out with Et₂O as a solvent.

v The reactions were also carried out with 1 eq (8.894 µl, 0.010 g, 0.104 mmol) or 10 eq (88.941 µl, 0.101 g, 1.035 mmol) of 2-fluoropyridine as a buffer, respectively, depending on the amount of acid added.
11. EXPERIMENTAL SECTION

0.104 mmol, 1 eq\textsuperscript{lvii} of trifluoromethanesulfonic acid (triflic acid), CF$_3$SO$_2$H, were added dropwise to the resulting solution. The solution was stirred for 10 min at rt\textsuperscript{lviii} and afterwards directly analyzed by ESI-MS.

Correspondingly, also 7.921 µl (0.012 g, 0.104 mmol, 1 eq)\textsuperscript{lix} of trifluoroacetic acid (TFA), CF$_3$COOH and 8.281 µl (0.104 mmol, 1 eq)\textsuperscript{lxx} of hydrochloric acid (38 % HCl in H$_2$O, c = 12.5 mol-l$^{-1}$) were employed as acids under the mentioned conditions. In the latter case, absolute solvents and inert gas atmosphere were not necessary.

In the ESI-MS, not only the product peak of the cation could be detected, but mainly several peaks indicating decomposition products. The isolation of a protonated product was not possible.

ESI-MS

Cation mode: $m/z = 387$ [M$^+$ (cation)] (main peak).

11.2.8.1.2. 2-Phenylethynyl-1-trimethylsilylethynyl-1H-benzimidazol-3-ium Salts

\textbf{203, 204 and 205 — NOVEL COMPOUNDS — Attempted Syntheses}

\[
\begin{align*}
\text{H} &\quad X^- \\
\text{N}^+ &\quad \text{Si(CH$_3$)$_3$}
\end{align*}
\]

\[X^- = \text{F}_3\text{C-}SO_2^- \quad \text{203} \]
\[X^- = \text{F}_3\text{C-}COO^- \quad \text{204} \]
\[X^- = \text{Cl}^- \quad \text{205} \]

Various protonation reactions were generally carried out as follows: The educt was dissolved in dry CH$_2$Cl$_2$ or dry Et$_2$O, with or without buffer and treated with 1 eq or 10 eq of an acid (triflic acid, TFA or HCl) at rt or at 0 °C, respectively.

\textsuperscript{lvii} The reactions were also carried out with 10 eq of triflic acid (90.317 µl, 0.155 g, 1.035 mmol).
\textsuperscript{lviii} The reactions were also carried out at 0 °C.
\textsuperscript{lix} The reactions were also carried out with 10 eq of TFA (79.215 µl, 0.118 g, 1.035 mmol).
\textsuperscript{lxx} The reactions were also carried out with 10 eq of 38 % HCl (82.811 µl, 1.035 mmol).
A previously dried two-necked flask, equipped with an argon inlet, a septum and an argon outlet, was charged with ca. 10 ml of dry CH$_2$Cl$_2$. In an argon atmosphere, 40 mg (0.104 mmol, 1 eq) of dried 2-phenylethynyl-1-trimethylsilylethynyl-1H-benzimidazole (199) were then added (in an argon counter stream). Via a syringe and a septum, 9.032 µl (0.016 g, 0.104 mmol, 1 eq) of trifluoromethanesulfonic acid (triflic acid), CF$_3$SO$_3$H, were added dropwise to the resulting solution. The solution was stirred for 10 min at rt and afterwards directly analyzed by ESI-MS.

Correspondingly, also 7.921 µl (0.012 g, 0.104 mmol, 1 eq) of trifluoroacetic acid (TFA), CF$_3$COOH and 8.281 µl (0.104 mmol, 1 eq) of hydrochloric acid (38 % HCl in H$_2$O, c = 12.5 mol·L$^{-1}$) were employed as acids under the mentioned conditions. In the latter case, absolute solvents and inert gas atmosphere were not necessary.

In the ESI-MS, not only the product peak of the cation could be detected, but mainly several peaks indicating decomposition products. The isolation of a protonated product was not possible.

**ESI-MS**

Cation mode: $m/z = 315$ [$M^+$ (cation)] (main peak).

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**hxxi** The reactions were also carried out with Et$_2$O as a solvent.

**hxii** The reactions were also carried out with 1 eq (8.894 µl, 0.010 g, 0.104 mmol) or 10 eq (88.941 µl, 0.101 g, 1.035 mmol) of 2-fluoropyridine as a buffer, respectively, depending on the amount of acid added.

**hxiii** The reactions were also carried out with 10 eq of triflic acid (90.317 µl, 0.155 g, 1.035 mmol).

**hxiv** The reactions were also carried out at 0 °C.

**hxv** The reactions were also carried out with 10 eq of TFA (79.215 µl, 0.118 g, 1.035 mmol).

**hxvi** The reactions were also carried out with 10 eq of 38 % HCl (82.811 µl, 1.035 mmol).
11. EXPERIMENTAL SECTION

11.2.8.2. N-Methylation of Azaenediynes

11.2.8.2.1. 4,5,6,7-Tetrafluoro-3-methyl-2-phenylethynyl-1-trimethylsilylethynyl-1H-benzimidazol-3-ium Tetrafluoroborate (206) — A NOVEL COMPOUND

A previously dried three-necked flask, equipped with an argon inlet, a reflux condenser connected to a bubbler and a glass stopper, was charged with 0.360 g (0.932 mmol, 1 eq) of dried 4,5,6,7-tetrafluoro-2-phenylethynyl-1-trimethylsilylethynyl-1H-benzimidazole (198). In an argon atmosphere, ca. 80 ml of dry CH₂Cl₂ were then added. To the resulting clear solution, 0.152 g (1.025 mmol, 1.1 eq, weighed out in a glove box) of trimethyloxonium tetrafluoroborate, Me₃O⁺BF₄⁻, were added in an argon counter stream. The mixture was heated to reflux for 5½ h (bath temp. ca. 50 °C).

Monitoring the reaction by TLC and GC/MS showed that still educt was left after ½ h, 1 h, 2 h and 4 h. Therefore, after 2½ h another 0.138 g (0.932 mmol, 1.0 eq) of trimethyloxonium tetrafluoroborate, Me₃O⁺BF₄⁻ were added. After a reaction time of 5 h, practically no educt could be detected, but an intensive start spot had formed (TLC: hexanes / EtOAc 5:1).

The mixture was allowed to reach rt. After standing for 2 h at rt, a small amount of a colorless precipitate had formed in the pale yellow solution. The solvent was removed at rt by blowing argon over the reaction mixture. The residue was then dissolved again in a small amount of dry CH₂Cl₂, and afterwards crystallized by diffusion-controlled crystallization (diffusion of n-pentane, see below). The crystals were vacuum-filtered over a previously dried filter frit (pore size: 4), washed with the mother liquid, then with 1 × 10 ml of dry CH₂Cl₂ / n-pentane 1:1 and finally with 2 × 10 ml of dry n-pentane and quickly sucked to dryness. Residual solvents were removed in a high vacuum; the product was kept under argon.

Yield

0.341 g (75 %) white solid;
colorless, transparent crystals after diffusion-controlled crystallization (for 2 d at rt diffusion of 
\(n\)-pentane into a concentrated solution in \(\text{CH}_2\text{Cl}_2\));

unstable in air, sensitive to water;
soluble in acetone, DMF and DMSO, low solubility in \(\text{CH}_2\text{Cl}_2\) and \(\text{PhCl}\), insoluble in \(\text{EtOAc}\), 
\(i\text{Pr}_2\text{O}\), \(n\)-hexane, \(n\)-pentane.

**Melting Point**

165 – 168 °C (recrystallized from \(\text{CH}_2\text{Cl}_2 / n\)-pentane by diffusion-controlled crystallization for 
2 d at rt).

**NMR**

\(^1\text{H-NMR (400 MHz, CD}_2\text{Cl}_2, 300.0 \text{K, TMS external)}: \delta \text{[ppm] = 7.74 (m, 2 H, H-11, H-15),}

7.50 (m, 3 H, H-12, H-13, H-14), 4.24 (m, 3 H, H-19, H-19', H-19'' (CH\_3)), 0.28 (s, 9 H, TMS).

\(^1\text{C-NMR (100 MHz, CD}_2\text{Cl}_2, 300.0 \text{K, TMS external)}: \delta \text{[ppm] = 141.6 (C-2 (C, q, appearing as a multiplet)), 139.1 and 136.8 and 134.1 and 130.5 (C-4, C-5, C-6, C-7}

(all C-F, q, appearing as multiplets)), 132.9 and 128.5 (C-11, C-15 and C-12, C-14 (all CH, p)), 
132.6 (C-13 (CH, p)), 128.6 and 116.9 (C-3a and C-7a (both C, q, appearing as multiplets)), 
116.4 (C-10 (C, q)), 114.6 (C-16 (acetylenic C (C-N), q)), 85.6 (C-9 (acetylenic C (C-Ph), q)), 
82.4 (C-17 (acetylenic C (C-Si), q, appearing as a multiplet)), 69.7 (C-8 (acetylenic C, q)), 36.3 
(C-19 (CH\_3, t)), −1.9 (TMS (3 × CH\_3, t, \(J_{C-Si} = 28.7 \text{ (Si-satellites))})).

**IR**

IR (KBr): \(\tilde{\nu} \text{ [cm}^{-1}] = 3020 \text{ (vw, } \nu \text{ C–H}\text{aromatic)}, 2967 \text{ (w, } \nu \text{ C–H}\text{aliphatic)}, 2217 \text{ (s, } \nu \text{ C=)=C)}, 1568 \text{ (m), 1552 (m), 1496 (s), 1461 (m), 1445 (m), 1351 (m), 1252 (m), 1073 (s), 1022 (s), 928 (m)}, 
852 (s), 815 (m), 770 (m), 685 (w).

**UV/Vis**

MeCN, \(c = 4.219 \times 10^{-5} \text{ mol·l}^{-1}, d = 1 \text{ cm): } \lambda_{\text{max}} = 342 (23.915), 325 (21.142), 197 (33.965).

**ESI-MS**

Cation mode: \(m/z = 419 [M^+ \text{ (cation)} + 18 \text{ (H}_2\text{O)}], 401 [M^+ \text{ (cation)}] \text{ (main peak), 387 [M}^+ \text{ (cation)} + 1 \text{ (H)} - 15 \text{ (Me)}].}
Daughter spectrum of m/z = 401: m/z = 386 [M⁺ (cation) – 15 (Me)], 371 [M⁺ (cation) – 2 × 15 (2 × Me)].

**HiRes-MS**

HiRes-ESI: m/z = 401 [M⁺ (cation)], calc. for C₂₁H₁₇N₂F₄Si: 401.1092, found: 401.1095 (Δ = +0.3 mDa = +0.7 ppm).

**Elementary Analysis**


**X-Ray**

Colorless, transparent crystals were obtained by diffusion-controlled crystallization (for 2 d at rt diffusion of n-pentane into a concentrated solution in CH₂Cl₂). For crystal data, structure refinement and X-ray structure see Appendix, Table 12-4 and Figure 12-4.

Note:

4,5,6,7-Tetrafluoro-3-methyl-2-phenylethynyl-1-trimethylsilylethynyl-1H-benzimidazol-3-ium tetrafluoroborate (206) was converted into (E)-1-ethynyl-4,5,6,7-tetrafluoro-2-(2-methoxy-2-phenyl-vinyl)-3-methyl-1H-benzimidazol-3-ium tetrafluoroborate (207) by slightly warming in MeOH. The conversion took place already at 25 – 30 °C within 15 min in MeOH. Complete conversion (no educt detectable) occurred upon heating to 35 – 40 °C for ½ h in MeOH.

**11.2.8.2.2. (E)-1-Ethynyl-4,5,6,7-tetrafluoro-2-(2-methoxy-2-phenyl-vinyl)-3-methyl-1H-benzimidazol-3-ium Tetrafluoroborate (207) — A NOVEL COMPOUND**
A two-necked flask, equipped with a reflux condenser and a glass stopper, was charged with 0.200 g (0.410 mmol, 1 eq) of 4,5,6,7-tetrafluoro-3-methyl-2-phenylethynyl-1-trimethylsilyl-ethynyl-1H-benzimidazol-3-ium tetrafluoroborate (206). Then, ca. 20 ml of MeOH were added. The resulting pale yellow solution was stirred and heated to 35 – 40 °C for ½ h. Upon allowing to cool to rt, a pale yellow solid precipitated from the pale yellow solution. The solid was filtered and washed with ice cold MeOH. Evaporation of half of the volume of the mother liquid and chilling caused precipitation of further solid, which was filtered and washed with ice cold MeOH. The solids were combined, dissolved in acetone and crystallized by diffusion-controlled crystallization (diffusion of CH₂Cl₂, see below).

Note:
The conversion took place already at 25 – 30 °C within 15 min in a syringe filled with MeOH. Complete conversion (no educt detectable in an ESI-MS spectrum) occurred upon heating to 35 – 40 °C or higher for ½ h in MeOH.

Yield
0.142 g (77 %) pale yellow powder;
pale yellow, transparent crystals after diffusion-controlled crystallization (for 4 d at rt diffusion of CH₂Cl₂ into a concentrated solution in acetone);
soluble in acetone and hot MeOH, insoluble in CH₂Cl₂, n-hexane, n-pentane.

Melting Point
186 – 194 °C (decomposition) (recrystallized from acetone / CH₂Cl₂ by diffusion-controlled crystallization for 4 d at rt).

NMR
¹H-NMR (300 MHz, [D₆]-acetone, 300.0 K, TMS external): δ [ppm] = 7.60 (m, 2 H, H-11, H-15), 7.44 (m, 3 H, H-12, H-13, H-14), 6.19 (m, not resolved, 1 H, H-8 (olefinic H)), 4.28 (s, 3 H, H-19, H-19', H-19" (H of N-Me group)), 4.06 (d, badly resolved, 5 JH-18-H-8 = 1.5, 3 H, H-18, H-18', H-18" (H of O-Me group)), 2.83 (s, 1 H, H-17 (acetylenic H)).

³xxxiii The reaction was first carried out at a bath temperature of 90 – 100 °C for ½ h, giving the same result.
11. Experimental Section

^{13}\text{C}-\text{NMR} \hspace{1pt} (75 \text{ MHz, } [\text{D}_6]-\text{acetone}, 298.0 \text{ K, TMS external}): \delta \text{ [ppm]} = 175.8 \text{ (C-9 (olefinic C (C(Ph)-OMe), q))}, \hspace{1pt} 158.8 \text{ (C-2 (C, q))}, \hspace{1pt} 140.4^{\text{xvii}} \hspace{1pt} \text{ and } 139.0^{\text{xvii}} \hspace{1pt} \text{ and } 136.7^{\text{xvii}} \hspace{1pt} \text{ and } 133.7^{\text{xvii}} \hspace{1pt} \text{(C-4, C-5, C-6, C-7 (all C=\text{F, q, these shifts were calculated as they were not detected)}), 133.3 \hspace{1pt} \text{(C-10 (C, q))}, \hspace{1pt} 130.3 \hspace{1pt} \text{ and } 129.6 \hspace{1pt} \text{(C-11, C-15 and C-12, C-14 (all CH, p))}, \hspace{1pt} 130.1 \hspace{1pt} \text{(C-13 (CH, p))}, \hspace{1pt} 124.2^{\text{xvii}} \hspace{1pt} \text{ and } 116.5^{\text{xvii}} \hspace{1pt} \text{(C-3a and C-7a (both C, q, these shifts were calculated as they were not detected)}), 81.1 \hspace{1pt} \text{(C-8 (olefinic C (C(H)-benzimidazolium), p))}, \hspace{1pt} 71.0 \hspace{1pt} \text{(acetylenic C (C=\text{N), q))}, \hspace{1pt} 59.6 \hspace{1pt} \text{(C-17 (acetylenic C (C=H), p))}, \hspace{1pt} 51.0 \hspace{1pt} \text{(C-18 (O-\text{CH}_3), t)}, \hspace{1pt} 37.0 \hspace{1pt} \text{(C-19 (N-\text{CH}_3), t)}.

^{19}\text{F}-\text{NMR} \hspace{1pt} (282 \text{ MHz, } [\text{D}_6]-\text{acetone, 298.0 K, CCl}_3\text{F external}): \delta \text{ [ppm]} = -151.70 \text{ (m, 4 F, BF}_4^-), \hspace{1pt} -156.84 \hspace{1pt} \text{ and } -157.27 \hspace{1pt} \text{ and } -157.83 \hspace{1pt} \text{ and } -159.07 \hspace{1pt} (4 \times 1 \text{ m, } 4 \times 1 \text{ F, F}_4\text{-}, \hspace{1pt} -156.84 \hspace{1pt} \text{ and } -157.27 \hspace{1pt} \text{ and } -157.83 \hspace{1pt} \text{ and } -159.07 \hspace{1pt} (4 \times 1 \text{ m, } 4 \times 1 \text{ F, F}_4\text{-, F}_5\text{-, F}_6\text{-, F}_7\text{-}).

\text{IR} \\
\text{IR (KBr): } \tilde{\nu} \text{ [cm}^{-1}] = 3311 \hspace{1pt} (s, \nu \text{ C=H_acetylenic}), \hspace{1pt} 3052 \hspace{1pt} (m, \nu \text{ C=H_ aromatic}), \hspace{1pt} 2952 \hspace{1pt} (w, \nu \text{ C=H_aliphatic}), \hspace{1pt} 2851 \hspace{1pt} (w, \nu \text{ C=H_aliphatic}), \hspace{1pt} 2175 \hspace{1pt} (w, \nu \text{ C=C}), \hspace{1pt} 1610 \hspace{1pt} (s), \hspace{1pt} 1600 \hspace{1pt} (s), \hspace{1pt} 1576 \hspace{1pt} (s), \hspace{1pt} 1562 \hspace{1pt} (s), \hspace{1pt} 1535 \hspace{1pt} (s), \hspace{1pt} 1496 \hspace{1pt} (s), \hspace{1pt} 1443 \hspace{1pt} (m), \hspace{1pt} 1411 \hspace{1pt} (m), \hspace{1pt} 1374 \hspace{1pt} (s), \hspace{1pt} 1331 \hspace{1pt} (s), \hspace{1pt} 1251 \hspace{1pt} (s), \hspace{1pt} 1231 \hspace{1pt} (s), \hspace{1pt} 1137 \hspace{1pt} (m), \hspace{1pt} 1067 \hspace{1pt} (vs), \hspace{1pt} 999 \hspace{1pt} (m), \hspace{1pt} 978 \hspace{1pt} (m), \hspace{1pt} 776 \hspace{1pt} (s), \hspace{1pt} 684 \hspace{1pt} (m), \hspace{1pt} 596 \hspace{1pt} (m), \hspace{1pt} 521 \hspace{1pt} (s).

\text{UV/Vis} \\
\text{MeCN, } c = 1.384 \cdot 10^{-5} \text{ mol\cdot l}^{-1}, \hspace{1pt} d = 1 \hspace{1pt} \text{ cm: } \lambda_{\text{max}} = 333 \hspace{1pt} (17,419), \hspace{1pt} 325 \hspace{1pt} (17,491).

\text{ESI-MS} \\
\text{Cation mode: } m/z = 361 \hspace{1pt} [M^+ (\text{cation})] \hspace{1pt} (\text{main peak}); \hspace{1pt} \text{anion mode: } m/z = 87 \hspace{1pt} [M^- (\text{BF}_4^-)] \hspace{1pt} (\text{main peak}).

\text{Daughter spectrum of } m/z = 361: m/z = 346 \hspace{1pt} [M^+ (\text{cation}) - 15 (\text{Me})], \hspace{1pt} 335 \hspace{1pt} [M^+ (\text{cation}) - 26], \hspace{1pt} 318 \hspace{1pt} [M^+ (\text{cation}) - 43], \hspace{1pt} 303 \hspace{1pt} [M^+ (\text{cation}) - 58].

\text{HiRes-MS} \\
\text{HiRes-MALDI: } m/z = 361 \hspace{1pt} [M^+ (\text{cation})], \hspace{1pt} \text{calc. for } C_{19}H_{17}N_2\text{OF}_4: \hspace{1pt} 361.0959, \hspace{1pt} \text{found: 361.0955 (} \Delta = -0.4 \hspace{1pt} \text{ mDa } \equiv -1.11 \hspace{1pt} \text{ ppm}).

^{\text{xvii}} \hspace{1pt} \text{This shift was calculated.}
X-Ray
Pale yellow, transparent crystals were obtained by diffusion-controlled crystallization (for 4 d at rt diffusion of CH₂Cl₂ into a concentrated solution in acetone). For crystal data, structure refinement and X-ray structure see Appendix, Table 12-5 and Figure 12-5.

11.2.8.2.3. 3-Methyl-2-phenylethynyl-1-trimethylsilylethynyl-1H-benzimidazol-3-ium Tetrafluoroborate (208) — A NOVEL COMPOUND

A previously dried three-necked flask, equipped with an argon inlet, a reflux condenser connected to a bubbler and a glass stopper, was charged with 400 mg (1.272 mmol, 1 eq) of dried 2-phenylethynyl-1-trimethylsilylethynyl-1H-benzimidazole (199). In an argon atmosphere, ca. 40 ml of dry CH₂Cl₂ were then added. To the resulting clear solution, 226 mg (1.526 mmol, 1.2 eq, weighed out in a glove box) of trimethyloxonium tetrafluoroborate, Me₃O⁺BF₄⁻, were added in an argon counter stream. The mixture was heated to reflux for 3 h (bath temp. ca. 50 °C).

Monitoring the reaction by TLC and GC/MS showed that little amounts of educt were left after ½ h and 1½ h. After a reaction time of 3 h, practically no educt could be detected, but an intensive start spot had formed (TLC: hexanes / EtOAc 5:1).

The yellowish mixture was allowed to reach rt. About half of the volume of the solvent was removed at rt by blowing argon over the reaction mixture. Addition of dry n-pentane caused precipitation of a white solid, which was vacuum-filtered quickly over a previously dried filter frit (pore size: 4) and washed with 10 ml of dry Et₂O and 10 ml of dry n-pentane, yielding 91 % of product.

The mother liquid from the first precipitation was evaporated, the residue dissolved in dry CH₂Cl₂ and precipitated with dry n-pentane, filtered and washed as described above (yield: 7 %). The pale ocher solids from both precipitations were combined, dissolved in a small amount of dry CH₂Cl₂ and crystallized (see below) by dropping MeOAc into the solution. After vacuum-
filtration, washing with 2 × 5 ml of dry MeOAc and sucking to dryness, the residual solvents were removed in a high vacuum and the product was kept under argon.

**Yield**

520 mg (98 %) white powder after precipitation; colorless, transparent crystals after recrystallization (by dropping MeOAc into a concentrated solution in CH₂Cl₂); soluble in CH₂Cl₂, insoluble in EtOAc, MeOAc, Et₂O, n-hexane, n-pentane.

**Melting Point**

185 – 187 °C (decomposition) (recrystallized from CH₂Cl₂ / MeOAc).

**NMR**

¹H-NMR (400 MHz, CD₂Cl₂, 300.0 K, TMS external): δ [ppm] = 7.95 – 7.43 (several m, altogether 9 H, H-4, H-5, H-6, H-7 and H-11, H-12, H-13, H-14, H-15), 4.27 (s, 3 H, H-19, H-19', H-19'' (CH₃)), 0.37 (s, 9 H, TMS).

¹³C-NMR (100 MHz, CD₂Cl₂, 300.0 K, TMS external, aq = 2 sec, dI = 3 sec): δ [ppm] = 137.1 (C-2 (C, q)), 132.0 and 131.4 (C-3a and C-7a (both C, q)), 134.1 and 130.0 (C-11, C-15 and C-12, C-14 (all CH, p)), 133.9 (C-13 (CH, p)), 130.3 and 130.2 and 114.8 and 113.9 (C-4, C-5, C-6, C-7 (all C–H, p)), 118.2 (C-10 (C, q)), 114.5 (C-16 (acycetylenic C (C-N, q)). 87.1 (C-9 (acycetylenic C (C-Ph, q)), 83.9 (C-17 (acycetylenic C (C-Si, q)), 71.4 (C-8 (acycetylenic C, q)), 35.1 (C-19 (CH₃, t), –0.2 (TMS (3 × CH₃, t, ¹³JC–Si = 28.6 (Si-satellites)))).

**IR**

IR (KBr): ν [cm⁻¹] = 3092 (vw, v C–H aromatic), 3030 (vw, v C–H aromatic), 2968 (w, v C–H aliphatic), 2903 (w, v C–H aliphatic), 2218 (s, v C≡C), 1615 (w), 1558 (m), 1465 (m), 1453 (m), 1444 (m), 1254 (m), 1061 (vs), 864 (s), 838 (m), 766 (s), 756 (s), 703 (m), 690 (m), 536 (w), 521 (w).

**UV/Vis**

MeCN, c = 9.032·10⁻⁶ mol·l⁻¹, d = 1 cm: λmax = 338 (26,683), 325 (24,690), 202 (26,351).

CH₂Cl₂, c = 9.224·10⁻⁶ mol·l⁻¹, d = 1 cm: λmax = 346 (37,619), 325 (30,572), 225 (22,550).
EXPERIMENTAL SECTION

ESI-MS
Cation mode: \( m/z = 329 \ [M^+ \text{ (cation)}] \) (main peak), 314 \([M^+ \text{ (cation)} - 15 \text{ (Me)}] \).

HiRes-MS
HiRes-ESI: \( m/z = 329 \ [M^+ \text{ (cation)}] \), calc. for \( C_{21}H_{21}N_2Si: 329.1469, \) found: 329.1470 (\( \Delta = +0.1 \text{ mDa} \equiv +0.30 \text{ ppm} \)).

Elementary Analysis
Calc. [%] for \( C_{21}H_{21}N_2Si BF_4: C \ 60.59, \ H \ 5.08, \ N \ 6.73, \ F \ 18.25, \ Si \ 6.75, \ B \ 2.60. \) Found [%]: \( C \ 60.35, \ H \ 5.26, \ N \ 6.79. \)

X-Ray
Colorless, transparent crystals were obtained by recrystallization (by dropping MeOAc into a concentrated solution in CH₂Cl₂). For crystal data, structure refinement and X-ray structure see Appendix, Table 12-6 and Figure 12-6.

11.2.8.3. N-Ethylation of Azaenediyynes

11.2.8.3.1. 4,5,6,7-Tetrafluoro-3-ethyl-2-phenylethynyl-1-trimethylsilylethynyl-1H-benzimidazol-3-ium Tetrafluoroborate (209) —
A NOVEL COMPOUND

A previously dried three-necked flask, equipped with an argon inlet, a reflux condenser connected to a bubbler and a glass stopper, was charged with 60 mg (0.155 mmol, 1 eq) of dried 4,5,6,7-tetrafluoro-2-phenylethynyl-1-trimethylsilylethynyl-1H-benzimidazole (198). In an argon atmosphere, ca. 20 ml of dry CH₂Cl₂ were then added. To the resulting clear solution, 32 mg
(0.171 mmol, 1.1 eq, weighed out in a glove box) of triethyloxonium tetrafluoroborate, Et₃O⁺ BF₄⁻, were added in an argon counter stream. The mixture was heated to reflux for 21 h (bath temp. ca. 50 °C).

Monitoring the reaction by TLC and GC/MS showed that still educt was left after 1 h, 2 h, 4 h and traces after 20 h. Therefore, both after 2½ h and 4½ h another 29 mg (0.155 mmol, 1.0 eq) of triethyloxonium tetrafluoroborate, Et₃O⁺ BF₄⁻, were added (in total, 1.1 eq + 1.0 eq + 1.0 eq = 3.1 eq of Et₃O⁺ BF₄⁻ were used). After a reaction time of 20 h, still some educt could be detected, but also a start spot had formed (TLC: hexanes / EtOAc 30:1).

The mixture was allowed to reach rt. Neither after standing for 2 h at rt nor after refrigerating at +4 °C for 2 d crystals formed. Various crystallization attempts failed (diffusion-controlled crystallizations like diffusion of n-pentane into a concentrated solution in CH₂Cl₂ or CH₂Cl₂ / EtOAc 1:1 or acetone, respectively, for 2 d at rt as well as crystallization from a concentrated solution in CH₂Cl₂ or in CH₂Cl₂ / acetone 1:1 for 4 d at +4 °C). The crystallization attempts yielded no crystals or small amounts of an impure solid, which was only analyzed by ESI-MS.

**ESI-MS**

Cation mode: m/z = 415 [M⁺ (cation)] (main peak); daughter spectrum of m/z = 415 shows m/z = 387 [M⁺ + 1 (H) − 29 (Et)].
11.3. Thermolysis Experiments (Trapping Experiments) in the Liquid Phase (in Solution)

11.3.1. Treatment of Solvents

In order to absolutely exclude moisture, oxygen\textsuperscript{ixix} and solvent impurities as well as stabilizers, all employed solvents were dried, degassed and distilled under argon, respectively, and hence treated as follows:

Chlorobenzene, \([D_3]-\text{chlorobenzene}\) and 1,4-dioxane were dried for 4 d over activated 4 Å molecular sieve, then distilled and subsequently freeze-pumped\textsuperscript{ixxx} (4 times) under an argon atmosphere.

1,4-Cyclohexadiene was dried over CaCl\(_2\), distilled and freeze-pumped\textsuperscript{ixxx} (4 times) under an argon atmosphere.

Isopropyl ether (diisopropyl ether) was refluxed over calcium hydride, distilled and freeze-pumped\textsuperscript{ixxx} (4 times) under an argon atmosphere and subsequently stored in the dark.

11.3.2. Preparation of the Thermolysis Mixtures

All samples were prepared in a glove box, or in an argon atmosphere. First, a standard solution in the particular solvent (diisopropyl ether, 1,4-dioxane, 1,4-cyclohexadiene, chlorobenzene; \([D_3]-\text{chlorobenzene}\) or CD\(_2\)Cl\(_2\), respectively) was prepared, which contained 1 mg (2.0·10\(^{-6}\) – 2.6·10\(^{-6}\) mol) of the respective azahenediyne (198, 199, 206 or 208). Then, 1 ml of the solution was pipetted into the pressure tube.

For the \textit{in situ}-protonation experiments, to each solution of the azahenediynes 198 and 199, a solution of 1 eq or 20 eq of trifluoromethanesulfonic acid (triflic acid), CF\(_3\)SO\(_2\)H, 1 eq of trifluoroacetic acid (TFA), CF\(_3\)COOH, or 1 eq of deuterio-hydrochloric acid (38 % DCI in D\(_2\)O,

\textsuperscript{ixix} Note that oxygen in its ground state (triplet oxygen, \(^3\)O\(_2\)), is also a biradical.

\textsuperscript{ixxx} Freeze-pumping in order to remove gaseous compounds:

Under argon, the distilled solvent was filled into a dry Schlenk tube, closed with a glass stopper and attached to a vacuum pump. After that, the following procedure was repeated four times:

With the stopcock closed, the liquid was frozen in liquid nitrogen; then the stopcock was opened in order to evacuate the Schlenk tube. The stopcock was closed again, and the liquid was allowed to thaw.
c = 12.5 mol·l⁻¹), respectively, was added. All experiments were carried out with and without 1 eq of 2-fluoropyridine as a buffer.

For the trapping experiments with 2,2,6,6-tetramethyl-1-oxy-piperidinyl radical (210) (TEMPO), the azaenediynes (198, 199, 206 or 208, respectively) were dissolved in chlorobenzene or in [D₅]-chlorobenzene, and a solution of 1 eq or 3 eq of 2,2,6,6-tetramethyl-1-oxy-piperidinyl radical (210) (TEMPO) in the respective solvent was added.

The final mixture in the pressure tubes contained 1 mg of azaenediyne in 1 ml of solvent (c = 2.0·10⁻³ – 2.6·10⁻³ mol·l⁻¹). Each tube was filled with a total volume of 2 ml of reaction mixture in a glove box and subsequently thermolyzed.

11.3.3. Experimental Conditions — Temperatures and Reaction Times

As pressure tubes, lockable glass tubes from Ace Glass Incorporates, total height 19.6 cm, external diameter 2.5 cm, internal diameter 1.9 cm) were employed. They could be closed with a Teflon screw cap and a seal. According to an unofficial information from Aldrich, the employed pressure tubes do withstand a maximum pressure of 14 bar.

As the pressure of a heated liquid in a closed system increases with rising temperature, the maximum allowed temperature was calculated with the aid of the Clausius-Clapeyron equation. Various temperatures were tested, the highest being the particular value causing a solvent pressure of ca. 12 bar.

The pressure tubes were heated in an oil bath with a contact thermometer in order to maintain a constant temperature. For higher temperatures (> 180 °C) and longer reaction times (24 h and longer), a graphite bath with a contact thermometer was used. Typical reaction times were ½ h, 1 h, 2 h, 24 h and 48 h.

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The Clausius-Clapeyron equation describes the pressure in dependence on the temperature:

\[ p_1 = p_0 \cdot \exp \left[ -(\Delta H_{\text{evaporation}} / R) \cdot (1/T_1 - 1/T_0) \right], \]

in which \( p_0 = 1 \) bar, \( T_0 = \) b.p., \( \Delta H_{\text{evaporation}} = \) molar enthalpy of evaporation; \( p_1 \) and \( T_1 \) are variables.

Boiling points of the employed solvents: b.p. (diisopropyl ether) = 69 °C, b.p. (1,4-dioxane) = 102 °C, b.p. (1,4-cyclohexadiene) = 88 – 90 °C, b.p. (chlorobenzene) = 132 °C.
11.3.4. Work-up and Analyses

After the reaction time had elapsed, the pressure tubes were cooled as fast as possible (first at the air, then in water).

For GC/MS analyses, a fraction of the sample was first submitted to micro-filtration over celite, and then washed with the solvent used in the reaction and injected into the GC/MS.

For TLC analyses (on silica and RP-18, each using n-hexane / EtOAc 30:1), the mixture was spotted directly onto the TLC-plates.

For ESI-MS analyses, a fraction of the mixture was diluted in dry CH$_2$Cl$_2$ to achieve a $10^{-5}$ M-solution and sprayed.

With other fractions of the sample, crystallization attempts and further separation attempts were started (see below).

11.3.5. Scaling up some Thermolysis Experiments of the Methylated Azaenediynes 206 and 208 — The Search for Assumed Cyclization Products

In a glove box, a previously dried three-necked flask was charged with 0.050 g (0.102 mmol, 1 eq) of 4,5,6,7-tetrafluoro-3-methyl-2-phenylethynyl-1-trimethylsilylethynyl-1H-benzimidazol-3-ium tetrafluoroborate (206). Then, 50 ml of dried and degassed PhCl were added. The suspension was stirred for 10 min, until all of the solid had dissolved. A solution of 0.048 g (0.307 mmol, 3 eq) of 2,2,6,6-tetramethyl-1-oxy-piperidinyl radical (210) (TEMPO) in 30 ml of dried and degassed PhCl was added. The flask with the salmon colored solution was brought out of the glove box, equipped with a reflux condenser, an argon inlet and an argon outlet and heated to 70 °C for 24 h in an argon atmosphere.

The reaction was repeated with 0.043 g (0.102 mmol, 1 eq) of 3-methyl-2-phenylethynyl-1-trimethylsilylethynyl-1H-benzimidazol-3-ium tetrafluoroborate (208) as an educt.

Both reactions were conducted with 3 eq of TEMPO (210) as described above and 1 eq (0.016 g, 0.102 mmol) of TEMPO (210).

A large excess of TEMPO (210) (up to 6 eq) did not lead to increased product-formation. In all cases, still educt 206 or 208, respectively, could be detected.
In another attempt, the solvent PhCl was replaced with CD\textsubscript{2}Cl\textsubscript{2} and the sample heated to 70 °C for 24 h. This experiment should not only aid a subsequent diffusion-controlled crystallization with \textit{n}-pentane, but also clarify whether a deuterium-uptake took place. In the ESI-MS, no uptake of deuterium could be seen; and no crystals were obtained. The solvent PhCl was also replaced with [D\textsubscript{x}]-chlorobenzene ([D\textsubscript{x}]-PhCl) and the sample heated to 70 °C for 24 h. No uptake of deuterium could be seen in the ESI-MS. The reaction was conducted with 1 eq, 3 eq and 6 eq of TEMPO (210).

11.3.6. Testing the Stability of Diisopropyl Ether under Thermolysis Conditions

In the following experiments it was tested whether diisopropyl ether remained stable even under extreme reaction conditions, or transformed into \textit{iso}-propanol and propene upon heating. The analyses were carried out by GC/MS\textsuperscript{ixxxxii} on a Zebron ZB-I capillary GC-column with a length of 60 m. A syringe was filled with 1 µl of the gas phase over the liquid of each sample, and injected directly into the GC/MS. The employed solvents – diisopropyl ether (iPr\textsubscript{2}O) and \textit{iso}-propanol (iPrOH) – were previously dried, distilled and degassed, and treated like under the employed thermolysis conditions.\textsuperscript{ixxxxiii}

\textit{First}, in a control experiment the following samples were injected: Neat diisopropyl ether, neat \textit{iso}-propanol, a mixture of iPr\textsubscript{2}O / iPrOH 1:1 and a mixture of iPr\textsubscript{2}O / iPrOH 100:1:

11.3.6.1. GC/MS of the Gas Phase (at rt) of \textit{iso}-Propanol (iPrOH)

iPrOH (main peak):

\textbf{GC (40 °C, 10 min, 50 °C min\textsuperscript{-1}, 200 °C, 1 min): } R\textsubscript{t} = 5.5 min; MS (EI, 70 eV): m/z (%): 60 (2 %) [M\textsuperscript{+}], 59 (17 %) [M\textsuperscript{+} – 1 (H)], 45 (100 %) [M\textsuperscript{+} – 15 (Me)], 43 (74 %) [iPr\textsuperscript{+}, M\textsuperscript{+} – 17 (OH)], 41 (33 %) [M\textsuperscript{+} – 19], 39 (22 %) [M\textsuperscript{+} – 21], 31 (17 %) [M\textsuperscript{+} – 29], 29 (28 %) [M\textsuperscript{+} – 31], 27 (36 %) [M\textsuperscript{+} – 33].

\textsuperscript{ixxxxiii} Note: ESI-MS experiments were also carried out (1 drop of the respective solvent or mixture was dissolved in ca. 5 ml of CH\textsubscript{2}Cl\textsubscript{2}), but they were found not to be suited as iPr\textsubscript{2}O and iPrOH only showed very low intensity when sprayed.

\textsuperscript{ixxxxiii} Boiling points of the solvents diisopropyl ether and \textit{iso}-propanol: b.p. (iPr\textsubscript{2}O) = 69 °C, b.p. (iPrOH) = 82 °C.
Water (H₂O):
GC (40 °C, 10 min, 50 °C min⁻¹, 200 °C, 1 min): R₁ = 4.7 min; MS (EI, 70 eV): m/z (%): 18 (100%) [M⁺], 17 (22%) [OH⁺, M⁺ – 1 (H)].

Air (N₂, O₂, Ar):
GC (40 °C, 10 min, 50 °C min⁻¹, 200 °C, 1 min): R₁ = 4.5 min; MS (EI, 70 eV): m/z (%): 40 (3%) [Ar, M⁺]; 32 (31%) [O₂, M⁺]; 28 (100%) [N₂, M⁺]; 18 (3%) [H₂O, M⁺].

11.3.6.2. GC/MS of the Gas Phase (at rt) of Diisopropyl Ether (iPr₂O)

iPr₂O (main peak):
GC (40 °C, 10 min, 50 °C min⁻¹, 200 °C, 1 min): R₁ = 7.2 min; MS (EI, 70 eV): m/z (%): 102 (7%) [M⁺], 87 (68%) [M⁺ – 15 (Me)], 69 (21%) [M⁺ – 33], 59 (46%) [M⁺ – 43 (iPr)], 45 (100%) [M⁺ – 57], 43 (86%) [iPr⁺, M⁺ – 59], 41 (58%) [M⁺ – 61], 39 (26%) [M⁺ – 63], 28 (19%) [M⁺ – 74], 27 (27%) [M⁺ – 75].

Water (H₂O):
GC (40 °C, 10 min, 50 °C min⁻¹, 200 °C, 1 min): R₁ = 4.7 min; MS (EI, 70 eV): m/z (%): 18 (100%) [M⁺], 17 (22%) [OH⁺, M⁺ – 1 (H)].

Air (N₂, O₂, Ar):
GC (40 °C, 10 min, 50 °C min⁻¹, 200 °C, 1 min): R₁ = 4.5 min; MS (EI, 70 eV): m/z (%): 40 (3%) [Ar, M⁺]; 32 (31%) [O₂, M⁺]; 28 (100%) [N₂, M⁺]; 18 (3%) [H₂O, M⁺].

11.3.6.3. GC/MS of the Gas Phase (at rt) of a Mixture of iPr₂O / iPrOH 1:1

The peaks of both iPr₂O and iPrOH were well separated according to the respective retention time (see above). The fragmentation pattern could be assigned clearly to the respective parent compounds.

11.3.6.4. GC/MS of the Gas Phase (at rt) of a Mixture of iPr₂O / iPrOH 100:1

As above, the peaks of both iPr₂O and iPrOH were separated according to the respective retention time (see above). The fragmentation pattern could be assigned to the respective parent compounds.
Then, a sample treated under thermolysis conditions was injected. This sample showed no color change, and no smell of propene was detected.

11.3.6.5. GC/MS of the Gas Phase of Diisopropyl Ether (iPr₂O) after Heating to 180 °C for 24 h

The GC/MS spectrum of heated iPr₂O showed exactly the same result as for iPr₂O at rt (see above): Only the respective peaks for iPr₂O, water and air were found. No trace of iPrOH could be detected.

11.3.7. Separation and Characterization Attempts of the Thermolysis Mixtures of the Methylated Azaenediynes 206 and 208

11.3.7.1. Separations by Chromatography of the Thermolysis Mixtures in Diisopropyl Ether

In order to isolate assumed cyclization products, the thermolysis samples of the azaenediynes 206 and 208 in diisopropyl ether were treated as follows:

P-TLC was carried out on silica plates with acetone or CH₂Cl₂, on RP-18 plates with MeCN or MeOH, and analytical TLC on CN plates with acetone or CH₂Cl₂ as eluents. The separations were repeated with absolute solvents and previously dried P-TLC plates (50 °C, 24 h) in a glove box.

HPLC separation was carried out on silica with 1,2-dichloroethane or on RP-18 with MeCN as an eluent.

Mainly educt or non-identifiable decomposition products could be isolated.

11.3.7.2. Separations by Chromatography of the Thermolysis Mixtures in Chlorobenzene with TEMPO (210)

The thermolysis samples of the azaenediynes 206 and 208 in chlorobenzene with 1 eq or 3 eq of TEMPO (210) were treated as follows:

P-TLC was carried out on silica plates with acetone, MeCN, nitromethane (CH₃NO₂), CH₂Cl₂, CH₂Cl₂ / MeOH 98:2 and n-hexane / EtOAc 3:1 and on RP-18 plates with MeOH, H₂O / MeOH
11. EXPERIMENTAL SECTION

1:1, EtOH, iPrOH, acetone, nitromethane (CH$_3$NO$_2$), THF, MeCN, MeCN / H$_2$O 40:1 and 20:1 and 5:1, CH$_2$Cl$_2$ and n-hexane / EtOAc 1:1. Separations using water-free eluents could be repeated in a glove box with absolute solvents and previously dried P-TLC plates (50 °C, 24 h). Analytical TLC was done on CN plates or on alumina plates with acetone, nitromethane (CH$_3$NO$_2$), MeCN, CH$_2$Cl$_2$, n-hexane / EtOAc 1:1 and 4:1. HPLC was carried out on silica with 1,2-dichloroethane or 1,2-dichloroethane / MeOH 98:2) as an eluent, and on RP-18 using MeCN or MeCN / H$_2$O 20:1. Column chromatography under argon was carried out using Sephadex LH-20 as a stationary phase and MeCN as an eluent (flow rate: 0.05 ml/min, or 5 cm/h).

Only in case of the employment of MeCN or MeCN / H$_2$O 20:1 on a RP-18 phase a partial separation could be achieved. No fraction was pure — in all cases numerous peaks were found in the ESI-MS analyses:

Degradation products of TEMPO (210) were found in all fractions at $m/z = 140$ and $m/z = 142$. As a control experiment, TEMPO (210) was heated in PhCl for 24 h. The molecular ion peak disappeared, and the following peaks were found: $m/z = 156$ (traces) [$M^+$ (TEMPO)], 142 [$M^+ - 16$ (O) + 2 (2 H)], 140 [$M^+ - 16$ (O)].

Note that spraying a freshly prepared solution of TEMPO (210) showed the following result: $m/z = 156$ [$M^+$ (TEMPO)], 157 [$M^+ + 1$ (H)], 123 [$M^+ - 33$ (NH$_2$OH)].

11.3.7.2.1. Analysis for 206

A main peak with $m/z = 419$ was found to derive from unreacted educt ($m/z = 401$ [$M^+$ (cation)], 419 [$M^+$ (cation) + 18 (H$_2$O)]). Also when freshly prepared educt was sprayed, addition of water took place after a while. The peak at $m/z = 558$ could not be found in the fractions.

11.3.7.2.2. Analysis for 208

Analogous results were obtained for 208: Here, mainly unreacted educt could be recovered from impure mixtures ($m/z = 329$ [$M^+$ (cation)]). The peak at $m/z = 486$ was not found in the fractions.

---

Sephadex LH-20 from Pharmacia Biotech is prepared by hydroxypropylation of Sephadex G-25, a bead-formed dextran gel. The dextran chains are cross-linked to give a three-dimensional polysaccharide network. Sephadex LH-20 is used for gel filtration in organic solvents; the molecules are eluted from Sephadex-columns in order of decreasing molecular weight (or molecular size, respectively).
11.3.7.3. Crystallization Attempts and Crystal Analyses

After the reaction was complete, a 5 ml aliquot of the reaction mixture was evaporated in a rotavap (bath temp. < 50 °C). An attempted diffusion-controlled crystallization with CH₂Cl₂ and n-pentane only led to an oil, as well as refrigerating (4 °C) various mixtures containing acetone / n-hexane, CH₂Cl₂ / n-hexane, CH₂Cl₂ / n-pentane or CH₂Cl₂ / acetone. Direct precipitation attempts from the reaction mixture by adding n-hexane or n-pentane failed as well. In a case employing dichloromethane and n-pentane as solvents, however, crystals of piperidinium salt 223 were obtained:

11.3.7.3.1. Analysis of 2,2,6,6-Tetramethyl-piperidinium Tetrafluoroborate (223)

\[
\text{NMR}
\]

NMR analyses usually failed because of remaining TEMPO (210). TEMPO (210), as a free radical, is paramagnetic and caused extreme line broadening in the NMR spectra due to increased relaxation times.

\[
\text{ESI-MS}
\]

Cation mode: \( m/z = 142 [M^+ \text{ (cation)}] \) (main peak).

\[
\text{X-Ray}
\]

Nearly colorless, transparent crystals were obtained by diffusion-controlled crystallization (for 4 d at 20 °C diffusion of n-pentane into a concentrated solution in CH₂Cl₂). For crystal data, structure refinement and X-ray structure see Appendix, Table 12-7 and Figure 12-7.
11.4. Collision Experiments and Trapping Experiments in the Gas Phase

Collision experiments were carried out on a modified Finnigan MAT TSQ 700 mass spectrometer by spraying a $10^{-5}$ M solution in CH$_2$Cl$_2$ of the respective azaenediynes.

The collisions with the noble gases Ar and Xe were carried out in the 8-pole-region. Ar (purity 4.8 (≥ 99.998 %)) and Xe (purity 4.8 (≥ 99.998 %)) were purchased from PanGas, Luzern, Switzerland.

Collision experiments with CHCl$_3$ and CDC$_1_3$ were done in the 8-pole-region and in the 24-pole-region. The solvents were previously dried, distilled and freeze-pumped.

Experiments with NO (purity 2.5 (≥ 99.5 %), purchased from PanGas, Luzern, Switzerland) were done in the 24-pole-region.

For the collision experiments using H$_2$ in the Finnigan MAT LCQ mass spectrometer, the device was purged for 2 d with molecular hydrogen instead of helium. H$_2$ (purity 4.0 (≥ 99.990 %)) and He (purity 5.0 (≥ 99.9990 %)) were purchased from PanGas, Luzern, Switzerland. The azaenediynes were sprayed in dichloromethane using the previously described standard conditions.

Upon collision of the accelerated ions (generated out of the azaenediynes) with the noble gases, the kinetic energy of the mass center of the collision partners is conserved (according to the law of conservation of total momentum). Hence, for the conversion into internal energy – and thus for fragmentation reactions – the entire kinetic energy of the collision partners in the center of mass-system is available.$^{266}$

The kinetic energy is defined as

$$E_{\text{kin}} = \frac{1}{2} m \cdot v^2,$$

in which $E_{\text{kin}}$ is the kinetic energy, $m$ the mass and $v$ the velocity of the accelerated ion.

The following formula represents the center of mass-energy (the kinetic energy that maximum can be converted into internal energy):

$$E_{\text{center of mass}} = \frac{1}{2} \frac{m_1 \cdot m_2}{m_1 + m_2} \cdot v^2,$$
in which \( m_1 \) and \( m_2 \) represent the molecular masses of the collision partners and \( v \) the velocity of the accelerated ion.

If the formula for the kinetic energy is solved for \( v^2 \), the highest collision energy that was used (\( E = 120 \) eV) inserted for \( E_{\text{kin}} \) and the mass of the particular azaenediyne-ion (\( M^* + 1 \) (H) = 387 g·mol\(^{-1}\), \( M^* + 1 \) (H) = 315 g·mol\(^{-1}\), \( M^* = 401 \) g·mol\(^{-1}\) or \( M^* = 329 \) g·mol\(^{-1}\), respectively) inserted for \( m \), the following term results:

\[
v^2 = \frac{2 \cdot E_{\text{kin}}}{m_{\text{azaenediyne-ion}}} \Rightarrow v^2 = \frac{2 \cdot 120 \text{ eV}}{m_{\text{azaenediyne-ion}}}.
\]

Insertion of \( v^2 \) into the equation for the center of mass-energy gives then, after reducing the fractions:

\[
E_{\text{center of mass}} = \frac{1}{2} \cdot \frac{m_{\text{azaenediyne-ion}} \cdot m_{\text{noble gas}} \cdot v^2}{m_{\text{azaenediyne-ion}} + m_{\text{noble gas}}} = \frac{m_{\text{noble gas}}}{m_{\text{azaenediyne-ion}} + m_{\text{noble gas}}} \cdot 120 \text{ eV}.
\]

The respective center of mass-energies were calculated, and are displayed in Table 11-1.

Table 11-1: Center of mass-energies in collision experiments of various azaenediynes with argon and xenon as inert gases

<table>
<thead>
<tr>
<th>#</th>
<th>Azaenediyne</th>
<th>( m_{\text{azaenediyne-ion}} ) [g·mol(^{-1})]</th>
<th>( m_{\text{noble gas}} ) [g·mol(^{-1})]</th>
<th>( E_{\text{center of mass}} ) [eV]</th>
<th>( E_{\text{center of mass}} ) [kcal·mol(^{-1})]\textsuperscript{bxxv}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>198</td>
<td>387 [( M^* + 1 ) (H)]</td>
<td>( m_{M^*} = 40 )</td>
<td>11.2</td>
<td>259.2</td>
</tr>
<tr>
<td>2</td>
<td>199</td>
<td>315 [( M^* + 1 ) (H)]</td>
<td>( m_{M^*} = 40 )</td>
<td>13.5</td>
<td>311.8</td>
</tr>
<tr>
<td>3</td>
<td>206</td>
<td>401 [( M^* ) (cation)]</td>
<td>( m_{M^*} = 40 )</td>
<td>10.9</td>
<td>251.0</td>
</tr>
<tr>
<td>4</td>
<td>208</td>
<td>329 [( M^* ) (cation)]</td>
<td>( m_{M^*} = 40 )</td>
<td>13.0</td>
<td>300.0</td>
</tr>
<tr>
<td>5</td>
<td>198</td>
<td>387 [( M^* + 1 ) (H)]</td>
<td>( m_{Xe} = 131 )</td>
<td>30.3</td>
<td>699.8</td>
</tr>
<tr>
<td>6</td>
<td>199</td>
<td>315 [( M^* + 1 ) (H)]</td>
<td>( m_{Xe} = 131 )</td>
<td>35.2</td>
<td>812.8</td>
</tr>
<tr>
<td>7</td>
<td>206</td>
<td>401 [( M^* ) (cation)]</td>
<td>( m_{Xe} = 131 )</td>
<td>29.5</td>
<td>681.4</td>
</tr>
<tr>
<td>8</td>
<td>208</td>
<td>329 [( M^* ) (cation)]</td>
<td>( m_{Xe} = 131 )</td>
<td>34.2</td>
<td>788.1</td>
</tr>
</tbody>
</table>

\textsuperscript{bxxv} 1 eV = 96.485 kJ·mol\(^{-1}\); 1 kcal = 4.184 kJ.
# 12. Appendix: X-Ray Data

Table 12-1: Crystal data and structure refinement for 191

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Data for 191</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C&lt;sub&gt;12&lt;/sub&gt;H&lt;sub&gt;26&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;F&lt;sub&gt;6&lt;/sub&gt;</td>
</tr>
<tr>
<td>Formula weight</td>
<td>290.22</td>
</tr>
<tr>
<td>Temperature</td>
<td>223(2) K</td>
</tr>
<tr>
<td>Radiation</td>
<td>Mo Kα</td>
</tr>
<tr>
<td>Wavelength λ,</td>
<td>0.71070 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Monoclinic, P2(1)/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>2525.34(8) Å&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Z, Calculated density</td>
<td>8.1527 Mg/m&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.134 mm&lt;sup&gt;-1&lt;/sup&gt;</td>
</tr>
<tr>
<td>F(000)</td>
<td>1168</td>
</tr>
<tr>
<td>Approximate crystal size</td>
<td>0.35 x 0.30 x 0.25 mm</td>
</tr>
<tr>
<td>Diffractometer</td>
<td>Bruker-Nonius Kappa-CCD diffractometer with graphite monochromator</td>
</tr>
<tr>
<td>θ range for data collection</td>
<td>3.08 - 27.48°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-9 ≤ h ≤ 9, -23 ≤ k ≤ 23, -24 ≤ l ≤ 24</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>11288 / 5761 [R(int) = 0.0279]</td>
</tr>
<tr>
<td>Completeness to 2θ = 27.48</td>
<td>96.3 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>no correction</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.9674 and 0.9548</td>
</tr>
<tr>
<td>Structure solution</td>
<td>SIR92</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>5761 / 0 / 392</td>
</tr>
<tr>
<td>Goodness-of-fit on F&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.952</td>
</tr>
<tr>
<td>Final R indices [1 &gt; 2σ(1)]</td>
<td>R1 = 0.0412, wR2 = 0.1033</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>0.0143(19)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.178 and -0.168 e·Å&lt;sup&gt;-3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Figure 12-1: X-ray structure (ORTEP-3 diagram) of 191
Table 12-2: Crystal data and structure refinement for 196

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Data for 196</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C₈₆H₉₀ON₂F₄</td>
</tr>
<tr>
<td>Formula weight</td>
<td>322.26</td>
</tr>
<tr>
<td>Temperature</td>
<td>298 K</td>
</tr>
<tr>
<td>Radiation</td>
<td>Mo Kα</td>
</tr>
<tr>
<td>Wavelength λ</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Triclinic, P1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 7.6765(2) Å; α = 64.3415(13) °</td>
</tr>
<tr>
<td></td>
<td>b = 10.1865(3) Å; β = 84.4989(13) °</td>
</tr>
<tr>
<td></td>
<td>c = 10.4421(3) Å; γ = 74.2614(14) °</td>
</tr>
<tr>
<td>Volume</td>
<td>708.21(3) Å³</td>
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<tr>
<td>Z. Calculated density</td>
<td>2.1511 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.132 mm⁻¹</td>
</tr>
<tr>
<td>Approximate crystal size</td>
<td>0.4 x 0.2 x 0.06 mm</td>
</tr>
<tr>
<td>Diffractometer</td>
<td>Bruker-Nonius Kappa-CCD diffractometer with graphite monochromator</td>
</tr>
<tr>
<td>0 range for data collection</td>
<td>0.998 - 28.700 °</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-9 ≤ h ≤ 10, -13 ≤ k ≤ 13, -14 ≤ l ≤ 14</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>6304 / 3613 [R(int) = 0.035]</td>
</tr>
<tr>
<td>Completeness to 2θ = 57.28</td>
<td>98.90 %</td>
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<tr>
<td>Absorption correction</td>
<td>no correction</td>
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<td>Structure solution</td>
<td>SIR97</td>
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<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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<td>Data / restraints / parameters</td>
<td>3613 / 0 / 248</td>
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<tr>
<td>Goodness-of-fit on F²</td>
<td>1.040</td>
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<tr>
<td>Final R indices [I &gt; 2σ (I)]</td>
<td>R1 = 0.0526, wR2 = 0.1436</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>none</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.192 and -0.188 e Å⁻³</td>
</tr>
</tbody>
</table>

Figure 12-2: X-ray structure (ORTEP-3 diagram) of 196
Table 12-3: Crystal data and structure refinement for 198

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Data for 198</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{38}H_{54}N_{2}F_{5}Si</td>
</tr>
<tr>
<td>Formula weight</td>
<td>386.42</td>
</tr>
<tr>
<td>Temperature</td>
<td>243(2) K</td>
</tr>
<tr>
<td>Radiation</td>
<td>Cu Kα</td>
</tr>
<tr>
<td>Wavelength λ</td>
<td>1.54178 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Orthorhombic, Pna2(1)</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 15.796(3) Å; α = 90°</td>
</tr>
<tr>
<td></td>
<td>b = 18.413(4) Å; β = 90°</td>
</tr>
<tr>
<td></td>
<td>c = 6.858(1) Å; γ = 90°</td>
</tr>
<tr>
<td>Volume</td>
<td>1994.7(6) Å</td>
</tr>
<tr>
<td>Z, Calculated density</td>
<td>4.1.287 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>1.427 mm⁻¹</td>
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<tr>
<td>F(000)</td>
<td>792</td>
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<tr>
<td>Approximate crystal size</td>
<td>0.35 × 0.35 × 0.32 mm</td>
</tr>
<tr>
<td>Diffractometer</td>
<td>Bruker-Nonius CAD4 diffractometer with graphite monochromator</td>
</tr>
<tr>
<td>θ range for data collection</td>
<td>3.69 - 64.89°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>0 ≤ h ≤ 18, 0 ≤ k ≤ 21, 0 ≤ l ≤ 7</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>1890 / 1864 [R(int) = 0.040]</td>
</tr>
<tr>
<td>Completeness to 2θ = 64.89°</td>
<td>95.2%</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>no correction</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.6581 and 0.6351</td>
</tr>
<tr>
<td>Structure solution</td>
<td>SIR92</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>1760 / 1 / 245</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.189</td>
</tr>
<tr>
<td>Final R indices [I &gt; 2σ (I)]</td>
<td>R1 = 0.0593, wR2 = 0.1892</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>0.10(12)</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>0.0005(3)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.294 and -0.476 e Å⁻³</td>
</tr>
</tbody>
</table>

Figure 12-3: X-ray structure (ORTEP-3 diagram) of 198
### Table 12-4: Crystal data and structure refinement for 206

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Data for 206</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C$_2$H$_7$N$_2$F$_5$BSi</td>
</tr>
<tr>
<td>Formula weight</td>
<td>488.27</td>
</tr>
<tr>
<td>Temperature</td>
<td>223(2) K</td>
</tr>
<tr>
<td>Radiation</td>
<td>Mo K$_{\alpha}$</td>
</tr>
<tr>
<td>Wavelength $\lambda$</td>
<td>0.71070 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Triclinic, P-1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>$a = 11.6671(3)$ Å; $\alpha = 100.85(1)$ $^\circ$</td>
</tr>
<tr>
<td></td>
<td>$b = 14.3450(4)$ Å; $\beta = 104.52(1)$ $^\circ$</td>
</tr>
<tr>
<td></td>
<td>$c = 15.0171(4)$ Å; $\gamma = 100.19(1)$ $^\circ$</td>
</tr>
<tr>
<td>Volume</td>
<td>2322.23(11) Å$^3$</td>
</tr>
<tr>
<td>Z, Calculated density</td>
<td>4.1.397 Mg/m$^3$</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.176 mm$^{-1}$</td>
</tr>
<tr>
<td>F(000)</td>
<td>992</td>
</tr>
<tr>
<td>Approximate crystal size</td>
<td>0.30 $\times$ 0.20 $\times$ 0.20 mm</td>
</tr>
<tr>
<td>Diffractometer</td>
<td>Bruker-Nonius Kappa-CCD diffractometer with graphite monochromator</td>
</tr>
<tr>
<td>$\theta$ range for data collection</td>
<td>1.80 $^\circ$ - 25.09 $^\circ$</td>
</tr>
<tr>
<td>Index ranges</td>
<td>$-13 \leq h \leq 13, -17 \leq k \leq 17, -17 \leq l \leq 17$</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>14646 / 7982 [R(int) = 0.0314]</td>
</tr>
<tr>
<td>Completeness to $2\theta = 25.09$</td>
<td>96.8 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>no correction</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.9657 and 0.9492</td>
</tr>
<tr>
<td>Structure solution</td>
<td>SIR92</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F$^2$</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>7982 / 0 / 621</td>
</tr>
<tr>
<td>Goodness-of-fit on F$^2$</td>
<td>1.068</td>
</tr>
<tr>
<td>Final R indices [1 &gt; 2x (B)]</td>
<td>R1 = 0.0893, wR2 = 0.2232</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>0.011(6)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.871 and $-0.651$ e Å$^{-3}$</td>
</tr>
</tbody>
</table>

![Figure 12-4: X-ray structure (ORTEP-3 diagram) of 206](image-url)
Table 12-5: Crystal data and structure refinement for 207

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Data for 207</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{10}H_{10}ON_{2}F_{8}B</td>
</tr>
<tr>
<td>Formula weight</td>
<td>454.17</td>
</tr>
<tr>
<td>Temperature</td>
<td>100 K</td>
</tr>
<tr>
<td>Radiation</td>
<td>Mo Kα</td>
</tr>
<tr>
<td>Wavelength λ</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Monoclinic, P2(1)/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>10.6481(2) Å; α = 90°</td>
</tr>
<tr>
<td>b</td>
<td>14.0290(3) Å; β = 105.6516(14)°</td>
</tr>
<tr>
<td>c</td>
<td>13.0237(3) Å; γ = 90°</td>
</tr>
<tr>
<td>Volume</td>
<td>1873.37(7) Å³</td>
</tr>
<tr>
<td>Z. Calculated density</td>
<td>4.1610 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.154 mm⁻¹</td>
</tr>
<tr>
<td>Approximate crystal size</td>
<td>not determined</td>
</tr>
<tr>
<td>Diffractometer</td>
<td>Bruker-Nonius Kappa-CCD diffractometer with graphite monochromator</td>
</tr>
<tr>
<td>θ range for data collection</td>
<td>0.998 – 31.507°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-15 ≤ h ≤ 15, -20 ≤ k ≤ 19, -19 ≤ l ≤ 19</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>11951 / 6215 [R(int) = 0.028]</td>
</tr>
<tr>
<td>Completeness to 2θ = 63.00</td>
<td>99.70 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>no correction</td>
</tr>
<tr>
<td>Structure solution</td>
<td>SIR97</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>6215 / 0 / 332</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.431</td>
</tr>
<tr>
<td>Final R indices [I &gt; 2σ (I)]</td>
<td>R1 = 0.0702, wR2 = 0.2023</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>none</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.479 and -1.383 e·Å⁻³</td>
</tr>
</tbody>
</table>

Figure 12-5: X-ray structure (ORTEP-3 diagram) of 207 (anion omitted for clarity)
Table 12-6: Crystal data and structure refinement for 208

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Data for 208</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C₂₁H₂₃N₂F₄BSi</td>
</tr>
<tr>
<td>Formula weight</td>
<td>416.30</td>
</tr>
<tr>
<td>Temperature</td>
<td>172 K</td>
</tr>
<tr>
<td>Radiation</td>
<td>Mo Kα</td>
</tr>
<tr>
<td>Wavelength λ</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Orthorhombic, Pmcn</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 6.9688(2) Å; α = 90°</td>
</tr>
<tr>
<td></td>
<td>b = 15.5439(5) Å; β = 90°</td>
</tr>
<tr>
<td></td>
<td>c = 19.7436(6) Å; γ = 90°</td>
</tr>
<tr>
<td>Volume</td>
<td>2138.67(11) Å³</td>
</tr>
<tr>
<td>Z, Calculated density</td>
<td>4.1293 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.153 mm⁻¹</td>
</tr>
<tr>
<td>Approximate crystal size</td>
<td>0.30 x 0.06 x 0.06 mm</td>
</tr>
<tr>
<td>Diffractometer</td>
<td>Bruker-Nonius Kappa-CCD diffractometer with graphite monochromator</td>
</tr>
<tr>
<td>θ range for data collection</td>
<td>0.998 - 27.485°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-9 ≤ h ≤ 9, -20 ≤ k ≤ 20, -25 ≤ l ≤ 25</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>4819 / 2640 [R(int) = 0.033]</td>
</tr>
<tr>
<td>Completeness to 20 = 54.98</td>
<td>99.70 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>no correction</td>
</tr>
<tr>
<td>Structure solution</td>
<td>SIR97</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>2640 / 0 / 160</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.905</td>
</tr>
<tr>
<td>Final R indices [1 &gt; 2σ (I)]</td>
<td>R1 = 0.0946, wR2 = 0.2658</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>none</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>1.726 and -1.141 e·Å⁻³</td>
</tr>
</tbody>
</table>

Figure 12-6: X-ray structure (ORTEP-3 diagram) of 208 (anion omitted for clarity)
Table 12-7: Crystal data and structure refinement for 223

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Data for 223</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{6}H_{12}NBF_{4}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>229.07</td>
</tr>
<tr>
<td>Temperature</td>
<td>172 K</td>
</tr>
<tr>
<td>Radiation</td>
<td>Mo Kα</td>
</tr>
<tr>
<td>Wavelength λ</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Orthorhombic. P2(1)/b</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td></td>
</tr>
<tr>
<td>a = 9.6890(14) Å; α = 90°</td>
<td></td>
</tr>
<tr>
<td>b = 15.496(2) Å; β = 90°</td>
<td></td>
</tr>
<tr>
<td>c = 16.016(2) Å; γ = 90°</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>2404.7(6) Å³</td>
</tr>
<tr>
<td>Z. Calculated density</td>
<td>8,1265 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.116 mm⁻¹</td>
</tr>
<tr>
<td>Approximate crystal size</td>
<td>0.46 x 0.28 x 0.14 mm</td>
</tr>
<tr>
<td>Diffractometer</td>
<td>Bruker-Nonius Kappa-CCD diffractometer with graphite monochromator</td>
</tr>
<tr>
<td>θ range for data collection</td>
<td>0.998 – 23.817°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-11 ≤ h ≤ 10, -17 ≤ k ≤ 17, -16 ≤ l ≤ 18</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>3984 / 2673 [R(int) = 0.055]</td>
</tr>
<tr>
<td>Completeness to 2θ = 47.62</td>
<td>90.30 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>no correction</td>
</tr>
<tr>
<td>Structure solution</td>
<td>SIR97</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>2673 / 1 / 270</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>2.052</td>
</tr>
<tr>
<td>Final R indices [I &gt; 2σ(I)]</td>
<td>R1 = 0.1187, wR2 = 0.3029</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>none</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.431 and -0.321 eÅ⁻³</td>
</tr>
</tbody>
</table>

Figure 12-7: X-ray structure (ORTEP-3 diagram) of 223
13. Acknowledgements


Prof. Dr. Erick M. Carreira übernahm freundlicherweise das Korreferat.

Die vorliegende Dissertation hätte ohne die offene und positive Atmosphäre an der ETH Zürich sowie dem wissenschaftlichen und sozialen Umfeld nicht gelingen können. Somit sollen im Folgenden auch die Kollegen, Angehörigen und Freunde gebührende Erwähnung finden, die mich auf diesem Wege — per aspera ad astra — begleitet haben.

Den aktuellen und den Ex-Mitgliedern der Chen-Group möchte ich für den great team spirit danken:

- André Müller danke ich für das tolle Arbeitsklima im Labor, sowie für das Schwizertöütsch-Training. André brachte mir nicht nur chemische Klassiker bei (unvergessen: s’ineschläufe des Öls 199 unter Argon in ein Röhrchen für die Mikroelementaranalyse), sondern kaum auch bei der Vergrößerung verschiedener Ansätze und lehrte mich alle letzten Geheimnisse rund um die Chromatographie.


- Marc Bornand war immer mit einem aufmunternden Rat zur Stelle, wenn die Frustration-Kompensationsfähigkeiten allzu sehr strapaziert wurden. Ansonsten sorgte "da Mac" für jede Menge "Spass" auf der Konferenz in Ascona ...

- Rolf Dietiker möchte ich vor allem für seine aufopferungsvolle Tätigkeit als Systemadministrator danken. Ohne Rolf hätte sich keiner CPU-Lüfter gedreht und wäre kein Windows Metafile eingefügt worden — und längst hätten trojanische Pferde die totale Kontrolle übernommen!

- Martin Jufer danke ich herzlich für das offene Ohr, die Diskussionen bei gemeinsamen Bierabenden nach den KIESER-Trainings und für das team work in gefährlichen Situationen, wie sie in den dungeons und bei den cows vorherrschen.

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Auch Dr. Christian Adlhart, Dr. Andreas Bach, Heinz Benz, Luca Castiglioni, Luca Cereghetti, Xueyi Chen (my lab colleague — thanks for bringing me closer to Chinese culture, habits and food), Dr. Jim Clarke, Martin Dietschi, Fabio Di Lena (*grazie per il Limoncello*), René Dreier (für seine unschlagbaren Konstruktionen aus der mechanischen Werkstatt), Dr. Derek Feichtinger, Prof. Dr. Ingo Fischer, Dr. Gerd Gerdes, Dr. Thomas Gilbert, Dr. Loubna Hammad (thanks for providing a deeper insight into biradical chemistry and into the American Way of Life), Dr. Ruedi Hartmann, Dr. Christian Hinderling, Dr. Johannes Hoffner (ihm gebührt Dank für die Diskussionen über Aza-endiin-Synthesen sowie dafür, dass er – *nolens volens* – mich hat seine Dissertation als Inspirations-Quelle verwenden lassen), Jonas Hostettler, Dr. Xiaohong Li, Dr. Changkun Liu, Dr. Hongping Liu, Christian von Merkatz, Sanja Narančić, Robert J. Pfab, Alessandro Pistillo, Dr. Kate Redmond (thx for teaching me the Alphabet of Chemistry), Dr. Eva Schön, Dr. Joëlle Viallon und Dr. Xiangyang Zhang möchte ich für ihre Beiträge zu dem *unique spirit* der Chen-Group danken. Cheers!

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Prof. Dr. Bernhard Jaun schulde ich herzlichen Dank für die ausführlichen, inspirierenden Diskussionen und für seine wertvollen Anregungen. Ferner möchte ich mich für die Ausarbeitung einer speziellen Pulssequenz und das zeitintensive "Hirnen" über den komplexen NMR-Spektren bedanken.

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- María Inmaculada Galdón Sañudo — *tienes un don y una picardía para disfrutar de la vida que es inigualable. Un millón de gracias por entenderme y por darme ánimo y fuerza, especialmente al principio de mi tesis. Andalucía — ¡sólo hay una!*
- Mako Yamazaki understood me with all her heart — and introduced me to a myriad of nice places in Zürich and to the beauty of Japanese culture. *Mako-san, watashi wa, anata no koto wa kesshite wasuremasen.*
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• In memoriam Markus Knechtel.
  
  Lo único importante en la vida sean las huellas del amor que dejemos cuando nos vayamos.

• Dr. Stefano Piana — special thanks go to Stefano for the arduous badminton training sessions, for being my trusted doubles partner in tournaments and for introducing me to Italy's fine culinary traditions.


• Zu guter Letzt: Wenn absolut alternative Ratschläge gefragt waren, dann war sonntags Privatdetektiv Philip Maloney\textsuperscript{xxxvi} mit seinen prägenden Ansichten und seiner unkonventionellen Lebensphilosophie zur Stelle. So geht das.

\textsuperscript{xxxvi} Nota bene, die haarsträubenden Fälle des Philip Maloney stehen der akribisch exakten und geistig anspruchsvollen Welt der Wissenschaft diametral gegenüber. Schauspieler Michael Schacht, alias Philip Maloney, ist jeweils sonntags zwischen 11:00 und 12:00 Uhr auf Radio DRS 3 (103.80 MHz) zu hören.
Es justamente la posibilidad de realizar un sueño
lo que hace que la vida sea interesante.

PAULO COELHO
El Alquimista
### 14. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A$</td>
<td>absorption (UV)</td>
</tr>
<tr>
<td>$A$</td>
<td>adenine</td>
</tr>
<tr>
<td>Å</td>
<td>Ångström ($1,\text{Å} = 10^{-10},\text{m}$)</td>
</tr>
<tr>
<td>abs.</td>
<td>absolute</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>anhydr.</td>
<td>anhydrous</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
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<tr>
<td>Ar</td>
<td>aryl; argon</td>
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<td>b.p.</td>
<td>boiling point</td>
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<td>Bn</td>
<td>benzyl</td>
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<tr>
<td>br</td>
<td>broad (IR)</td>
</tr>
<tr>
<td>$br$</td>
<td>broad (NMR)</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
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<tr>
<td>BuLi</td>
<td>butyllithium</td>
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<tr>
<td>C</td>
<td>cytosine</td>
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<td>concentration</td>
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<td>calc.</td>
<td>calculated</td>
</tr>
<tr>
<td>CASMP2</td>
<td>Complete Active Space Møller-Plesset theory, 2\textsuperscript{nd} order</td>
</tr>
<tr>
<td>CASSCF</td>
<td>Complete Active Space Self-Consistent Field</td>
</tr>
<tr>
<td>CID</td>
<td>collision induced dissociation</td>
</tr>
<tr>
<td>conc.</td>
<td>concentrated; concentration</td>
</tr>
<tr>
<td>d</td>
<td>day(s)</td>
</tr>
<tr>
<td>$d$</td>
<td>doublet (NMR); length of path or layer thickness (UV); distance (X-ray)</td>
</tr>
<tr>
<td>Da</td>
<td>Dalton</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo-[5.4.0]-undec-7-ene</td>
</tr>
<tr>
<td>$dd$</td>
<td>doublet of doublet (NMR)</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless Enhancement by Polarization Transfer</td>
</tr>
<tr>
<td>dist.</td>
<td>distilled</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N$-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>DNS</td>
<td>Desoxyribonucleinsäure</td>
</tr>
<tr>
<td>dt</td>
<td>doublet of triplet (NMR)</td>
</tr>
<tr>
<td>$E$</td>
<td>energy</td>
</tr>
<tr>
<td><em>e.g.</em></td>
<td><em>exempli gratia</em> (for example)</td>
</tr>
<tr>
<td>$E_A$</td>
<td>Arrhenius activation energy</td>
</tr>
<tr>
<td>$E_{\text{center of mass}}$</td>
<td>kinetic energy of the center of mass</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>$E_{\text{kin}}$</td>
<td>kinetic energy</td>
</tr>
<tr>
<td>El</td>
<td>electrophile</td>
</tr>
<tr>
<td>eq</td>
<td>equivalent</td>
</tr>
<tr>
<td>$E_S$</td>
<td>singlet energy</td>
</tr>
<tr>
<td>ESI-MS</td>
<td>electrospray ionization mass spectrometry</td>
</tr>
<tr>
<td>$E_{\text{ST}}$</td>
<td>singlet – triplet gap</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>$E_T$</td>
<td>triplet energy</td>
</tr>
<tr>
<td>et al.</td>
<td><em>et alii</em> (and others)</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>eV</td>
<td>electron volt</td>
</tr>
<tr>
<td>FT</td>
<td>Fourier transform</td>
</tr>
<tr>
<td>FT-IR</td>
<td>Fourier transform infrared</td>
</tr>
<tr>
<td>G</td>
<td>guanine</td>
</tr>
<tr>
<td>GC/MS</td>
<td>gas chromatography / mass spectrometry</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>Hal</td>
<td>halogen</td>
</tr>
<tr>
<td>HiRes-MS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>HMPTA</td>
<td>hexamethylphosphoric triamide (hexamethylphosphoric(V) acid triamide)</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance (pressure) liquid chromatography</td>
</tr>
<tr>
<td>HV</td>
<td>high vacuum</td>
</tr>
<tr>
<td>i</td>
<td>iso</td>
</tr>
<tr>
<td><em>i.e.</em></td>
<td><em>id est</em> (that is to say)</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>$J$</td>
<td>coupling constant (NMR)</td>
</tr>
<tr>
<td>k</td>
<td>kilo</td>
</tr>
</tbody>
</table>
14. ABBREVIATIONS

LASE R  light amplification by stimulated emission of radiation
LDA  lithium diisopropylamide
lit.  literature
m  medium (IR); milli
m  multiplet (NMR); meta; mass
M  molar (concentration in mol·l\(^{-1}\))
M  molecular mass in g·mol\(^{-1}\)
m.p.  melting point
m/z  mass over charge (MS)
\( M^+ \)  molecular peak, molecular ion peak (MS)
MALDI  matrix assisted laser desorption / ionization
MCS  2-methoxyethanol
Me  methyl
mg  milligram
min  minute(s)
mmol  millimole
MS  mass spectrometry
MrB-ether  tert-butyl methyl ether
n  nano (10\(^{-9}\))
n  normal
nm  nanometer
NMR  nuclear magnetic resonance
NOE  Nuclear Overhauser Effect
Nu  nucleophile
\( o \)  ortho
p  pico (10\(^{-12}\))
\( p \)  primary (NMR); para
p.  page
PG  protecting group
Ph  phenyl
pp.  pages
ppm  parts per million
Pr  propyl
P-TLC  preparative thin layer chromatography
14. ABBREVIATIONS

Py  pyridine
q   quaternary (NMR); quartet (NMR)
rc  reaction
resp. respectively
Rf  retention factor (ratio of front)
rotavap  rotary (film) evaporator
rt  room temperature
Rt  retention time
s   secondary (NMR); singlet (NMR)
s   strong (IR)
sat. saturated
sec second(s)
ssp. subspecies
t   tertiary (NMR); triplet (NMR)
T   thymine
tBu tert-butyl, tertiary butyl
temp. temperature
TEMPO 2,2,6,6-tetramethyl-1-oxo-piperidinyl radical
 tert  tertiary
TFA  trifluoroacetic acid
THF  tetrahydrofuran
TLC  thin layer chromatography
TMS  trimethylsilyl
Tos toluenesulfonyl-, tosyl-
tt  triplet of triplet (NMR)
u   atomic mass unit (1 u = 1.6605655 \times 10^{-27} \text{ kg})^{304}
UV  ultraviolet
UV-PES ultraviolet photoelectron spectroscopy
v   velocity
V   volt
Vis  visible
vs  very strong (IR)
w  weak (IR)
WHO World Health Organization
14. Abbreviations

- y. yield
- δ chemical shift in ppm (NMR)
- Δ delta (a difference)
- ε absorption coefficient (UV)
- λ max maximum (maxima) of absorption (UV)
- μ micro (10^-6)
- μl microliter
- μm micrometer
- ν stretching vibration (IR)
- ᴣ wavenumber in cm⁻¹ (IR)
- ηd pseudo doublet (NMR)
- ηt pseudo triplet (NMR)
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