Alma Mater Studiorum – Università di Bologna

INNOVATIVE METHODS FOR THE GENERATION AND SYNTHETIC APPLICATIONS OF ORGANIC FREE-RADICALS

DOTTORATO DI RICERCA IN Scienze Chimiche *XXII ciclo*

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…Nature is beautiful, mysterious, complete.

Nature is perfect, but delicate.

Sometimes it fascinates, sometimes it intimidates.

It's powerful, but at the same time kind.

Nature is Chemistry...

... Chemistry is Nature... And more...

Contents

Preface

The work presented in this PhD thesis has been carried out at the Department of Organic Chemistry "A. Mangini", Alma Mater Studiorum- Università di Bologna, under the direction of Prof. Piero Spagnolo and the supervision of Prof. Daniele Nanni and Dott. Matteo Minozzi, PhD.

In the following pages, the main topic of my PhD research, will be presented. Starting from the historical background that saw the naissance of the radical chemistry, after overcoming the prejudices concerning its efficiency and poor selectivity, we will see the development and the useful synthetic transformations that it allows.

The thesis, after a brief introduction to the history and the basics of the radical chemistry, is divided in two sections that show its affirmation as powerful synthetic tool for organic chemists.

In particular, we will show new *tin-free methodologies* for the generation of *alkyl radicals* that employs more eco-friendly substrates (Chapter 3). The second part will be the exploration of *azido compounds* as new unprecedented source of *imynil radicals* and their application for the synthesis of biologically active compounds (Chapters 4, 5).

With this survey of the radical chemistry in the last years, we will try to open a new perspective on the usefulness of the radical chemistry, highlighting its synthetic power in different chemical transformations.

CHAPTER 1

INTRODUCTION TO THE RADICAL CHEMISTRY

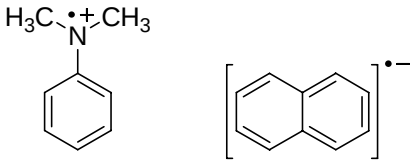
1.1 History of the radical chemistry

It is common to affirm that a good chemist is also a good cook. Both in a laboratory and in a kitchen "recipes" are performed, "ingredients" are weighed and mixed, the final result it is waited with anxiety to understand if the desired "product" has been obtained or not.
In this context, comparing organic chemistry to the culinary art, we can undoubtedly affirm that the radical chemistry is, in the field of organic synthesis, a recent "dish", not so known; a "plate" that to the eyes of a superficial and inexperienced "cook-chemist" is difficult to realize and with little profit for satisfying his own appetite. We will try to understand the raisons of such prejudices and to destroy them.

The term "radical" and "free-radicals" versus "caged-radicals". [1]

Originally, the term "radical" was used in organic chemistry to refer to some unchanging part, or "root" of a molecule while the other fragments of the molecule undergo chemical transformations. For example, in the sequence $C_2H_5Br \rightarrow C_2H_5CN \rightarrow C_2H_5CO_2H$, the ethyl "radical" remains unaltered. In 1850 the scientific community believed that C_2H_5, the ethyl radical, could be generated from its compounds as a gaseous chemical substance. Subsequently, it was understood that this gas was not a "free radical", but a mixture of ethane, ethene and butane. These results brought to the wrong conclusion that carbon was always tetravalent in all of its compounds.

Nowadays , a *radical* has been defined as *a molecular entity containing one or more unpaired electrons*. This definition also includes transition metal ions or atoms of the alkali metals (although they would rarely be referred to radicals), halogen atoms and species formed from organic molecules by losing or gaining a single electron, e.g. the amine radical cation **1** and naphthalene radical anion **2**.



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Additionally, a radical species can be defined "*free*" or "*caged*". In solution, when radicals can diffuse freely and independently through the solvent in which they have been generated, they

are defined “free” and they are sufficiently long-lived to engage in radical-molecule reactions. Contrarily, when two radicals are generated very close to each other so that they have no chance to diffuse away from the other one and they will probably interact, we can refer to them saying that they have not “escaped from the solvent cage” and they are so short-lived that they can not participate in radical reactions with other molecules present in the solvent, since this kind of reactions are too slow compared to the life of the radical species.

From Gomberg to today: a difficult beginning and an exponential growth

Historically, the naissance of the chemistry of radicals can be positioned to the beginning of the XX century, precisely in 1900, when Gomberg published his own studies on the triphenylmethyl, defining it a trivalent carbon[2] (Ph_3C) without gathering its real radical nature ($Ph_3C\cdot$).

The demonstration of the existence - even if very short- of the alkyl radicals has been given only thirty years later[3] thanks to Paneth’s work, while in 1937 Hey and Waters were able to determine the radical nature of a lot of common synthetic reactions.[4] Subsequently, mechanistic and synthetic studies on reactions of polymerization[5] contributed to broad the knowledge on different types of radical reactions; in addition, the studies of the organic physical chemists beginning from half of the 1970s allowed the scientific community to know structural characteristics and kinetics of reaction of a wide and various range of radicals.[6]

Despite this, the chemistry of radicals has been neglected in synthetic field for almost eighty years.

In the 1985 Cheves Walling, one of the pioneers of modern radical chemistry, came out to confess that “radical chemistry remained essentially mysterious to the synthetic community”.[7] Despite the fact that numerous methodologies of generation of radicals and their reactions were already known, - for instance the additions and cyclizations on multiple bonds- the prejudice that the radical reactions were poorly selective and could be hardly controllable was very strong, because of the high reactivity that distinguishes them.

Nevertheless, the huge amount of kinetic work carried out during the 1970s and the 1980s, mainly as a consequence of the development of electronic spin/paramagnetic resonance (ESR or EPR) and other spectroscopic techniques, has demonstrated that the reputed lack of selectivity so often attributed to radical reactions, was by no means universal and such prejudice failed. In this context, the synthetic chemistry governed by radicals, built upon solid grounds due to long and hard-

working experiments during the course of time, started growing, rushing, and expanding very quickly.

Indeed, Giese's reductive additions to carbon-carbon double bonds unequivocally showed that the addition of radicals to alkenes does not necessarily degenerate in polymerizations.[8] New methods to produce carbon- and heteroatom-centered radicals were proposed by Barton, [9] while Hart prepared some pyrrolizidines with methodologies that used a radical reaction as the key step.[10] Simultaneously, Keck recognized the importance of the radical allylation: his suggested strategy still remains of fundamental importance.[11] Radical species were employed by Stork as pivotal intermediates in some regio- and stereo-selective reactions in order to generate new carbon-carbon bonds.[12] Curran realized bright syntheses of natural products through tandem radical cyclisations, underlining the great peculiarity and selectivity of the radical reactions conducted in sequence.[13]

Thanks to a better understanding of radical science, nowadays the chemistry of radicals has become of fundamental importance. In everyday life, radical reactions are playing a vital role, being exploited in the production of many modern materials, plastics and other polymers, in the chemistry of paints and foodstuffs, in the oxidative degradation of lubricants, as well as in a broad spectrum of biochemical processes occurring in living organisms.

Over the time, the important and advantageous features of the radical chemistry- selectivity, generality, reactivity and predictability - have contributed to make it a widely recognized and essential synthetic tool, destined to be used more and more for the development of complex synthetic strategies.

1.2 Basics of the radical chemistry[14,15]

Heterolysis 'versus' homolysis

"Common" organic reactions are envisioned to occur by displacement of electron pairs: this dissociative process entails unsymmetrical cleavage of covalent bonds (**heterolysis**), in which both bonding electrons remain with one partner and there is consequent formation of charged species (*ions*).

The alternative possibility is a symmetrical bond breaking (**homolysis**), in which case each atom carries away one of the two original bonding electrons. In this way, neutral species bearing an unpaired electron (*radical intermediates*) are generated. Most radical reactions involve homolytic cleavage (*Figure 1*), but exceptions are usually encountered with electron-transfer processes.

Figure 1. *Heterolysis vs. Homolysis*

It is worth noting that, at least in gas phase, more familiar heterolysis is generally less feasible than homolysis. However, under more usual solution conditions, especially when (highly) polar solvents are employed, ionic solvatations become so important as to allow most reactions to proceed through heterolytic pathways. Since free radicals are often electrically neutral, solvent stabilization on those species are usually meaningless: consequently, only bonds with (particularly) low Bond Dissociation Energy (BDE) such as, for instance, Sn-H bonds (≈310 kJ mol^{-1} at 300 K in gas-phase), can be involved in alternative radical pathways. A main solvent effect is that "solvatated" ions have a low tendency to recombine and, therefore, can occur in somewhat high concentrations; on the other side, radical intermediates tend to recombine very quickly to non-radical products and so they usually occur in very low concentrations.

This is the main reason why radical intermediates are often not easily detectable even by spectroscopic methods and why free radical reactions have long been believed to be very poorly selective. Nevertheless, through a careful choice of the experimental conditions (solvent, temperature, reagent ratio and reagent concentration), radical reactions can allow highly useful synthetic transformations both in terms of product yield and by-product minimization.

Structure and stability of radicals

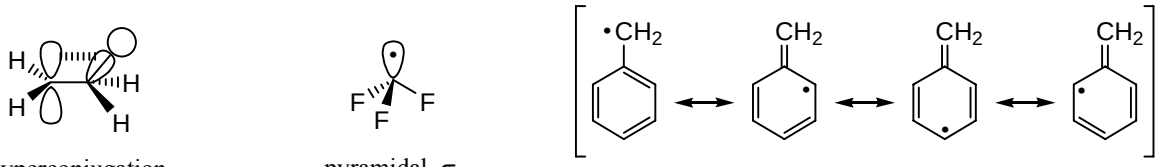
The structure and stability of free (carbon) radicals roughly resemble those of the corresponding (carbo)cations. In general, lowering of BDE values favour production of radical species which are therefore regarded as being more stable (*Table 1)*. Progressive substitution at the radical centre can usually enhance radical stability owing to inherent hyperconjugation and/or resonance effects (carbon radical stability follows the order: benzyl > tertiary > secondary > primary > methyl).

Table 1. *Approximate dissociation energies of selected bonds (kJ mol^{-1} at 300 K in gas-phase)*

CH_3-H	439	Cl_3C-H	402	$((CH_3)_3Si)_3Si$-H	331
CH_3CH_2-H	423	F-H	569	$(CH_3)_3Sn$-H	310
$(CH_3)_2CH$-H	410	Cl-H	431	C_2H_5-Cl	339
$(CH_3)_3C$-H	397	Br-H	366	C_2H_5-Br	289
CH_2=CH-H	431	I-H	297	C_2H_5-I	222
HC≡C-H	544	HO-H	498	RO-OR	155
C_6H_5-H	464	HOO-H	368	CH_3-CH_3	372
CH_2=$CHCH_2$-H	364	CH_3O-H	439	CH_3CH_2-CH_3	364
$C_6H_5CH_2$-H	372	C_6H_5O-H	360	$(CH_3)_2CH$-CH_3	360
RC(=O)-H	364	R_2NO-H	310	$(CH_3)_3C$-CH_3	351
$EtOCH(CH_3)$-H	385	CH_3S-H	385	Cl-Cl	243
N≡CCH_2-H	360	C_6H_5S-H	343	Br-Br	192
CH_3COCH_2-H	385	$(CH_3)_3Si$-H	377	I-I	151

The unpaired electron can occupy a *p* orbital or a hybrid orbital having some *s*-character: the corresponding radicals are referred to as π- and σ-radicals, respectively. Ethyl radical **1** as well as primary, secondary and tertiary alkyl radicals usually are "planar" π-radicals, but their geometry is affected by the presence of strongly electronegative substituents like fluorine or alkoxyl. In fact, trifluoromethyl **2** is a pyramidal σ-radical bearing its electron in a sp^3-orbital. Benzyl radical **3** also is a π-radical where the unpaired electron is delocalized onto the adjacent aromatic ring (Figure 2).

Similar to benzyl radical **3**, other π-radicals bearing an adjacent unsaturated substituent like the vinyl, cyano or carbonyl group are stabilized by conjugation with the adjacent π bond.



hyperconjugation in planar, π ethyl radical **1**

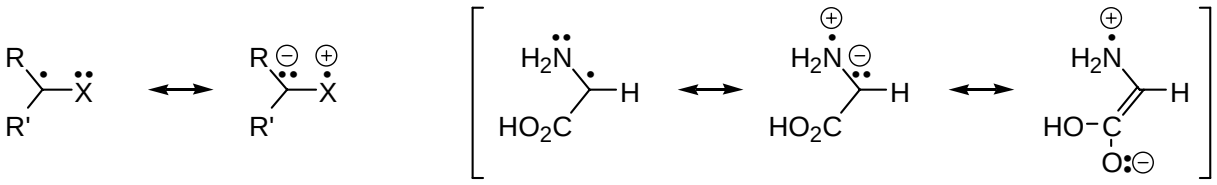
pyramidal, σ trifluoromethyl radical **2**

resonance in planar, π benzyl radical **3**

Figure 2. *Stucture and stabilisation effects in radicals*

Stabilization can additionally arise from overlapping of the orbital of the π-radical with the lone pair of a vicinal heteroatom including *inter alia* oxygen, nitrogen and, to a lesser extent, halogen atom; such interaction in fact leads to a resonance-stabilized 'three-electron bonding' where there is a separation of charge since an electron is donated from the heteroatom (*Figure 3)*. Consequently, the extent of such *lone pair* stabilization is expected to decrease with increasing the electronegativity of the heteroatom involved.

The concomitant presence of an electron-donating and electron-withdrawing group brings about a synergistic effect between the two groups and radical stabilization becomes greater than might be expected based on the sum of the effects of the two separate groups. The effect has been referred to as "*captodative"* stabilization, where the electron-withdrawing group is the "capto" group and the electron-donating group is the "dative" one. For instance, such effect is responsible for the very low BDE displayed by the α-C–H bond of glycine (318 kJ mol^{-1}, *Figure 3*).[16]



resonance with lone pairs

glycine radical

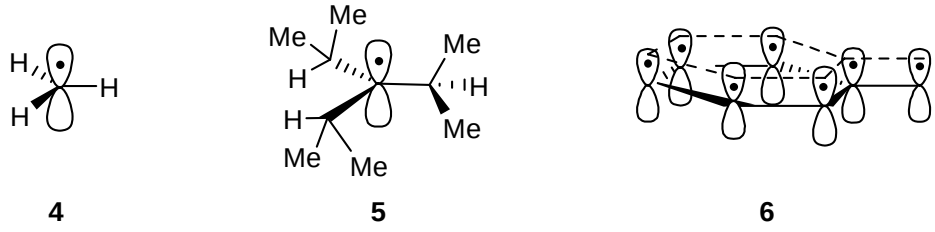
Figure 3. *Stabilization by lone pairs and captodative effect*

'Stability' versus 'persistence'

There is a further, important point concerning "radical stability" which is worth note: the difference between *thermodynamic stability* (or "**stability**") and *lifetime* (or "**persistence**") of a radical species.

Stability largely depends on electronic effects such as the mesomeric and inductive ones discussed above. On the other side, persistence is a general result of steric factors: the more congested is the radical centre the greater will be the radical lifetime. This is reflected in relatively high concentrations of radicals species occurring in solution and/or in self-reactions significantly less than the diffusion limit.

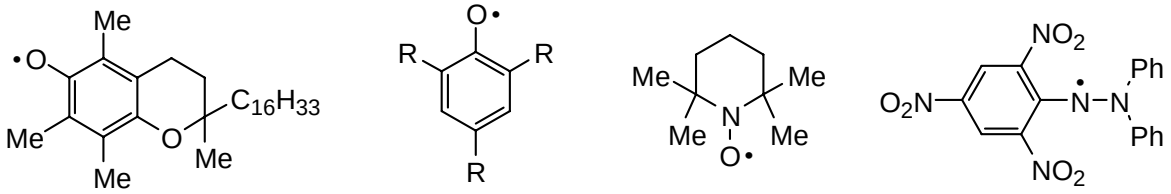
For example, methyl radical **4** has a half-life of 0.2×10^{-3} s at a 10^{-6} M concentration, whereas tri(*iso*-propyl)methyl radical **5** (a relatively 'persistent' radical), at the same concentration, has a half-life of 21 h! The longer the lifetime, the less reactive a radical intermediate will be, since its persistency will slow down the reaction rate with itself and other species. It is worth note that benzyl **6,** even though being 'stabilized' by resonance delocalization, undergoes diffusion-controlled self-reaction and hence is not at all a "persistent' radical (*Figure 4*).[17]



4 **5** **6**

Figure 4. *Stability vs. persistence: benzyl radical **6** is thermodynamically more 'stable' than **5**, but kinetically less persistent*

In certain cases of noteworthy persistency (due to both thermodynamic and kinetic factors), the lifetimes of radical species can be so long that they can survive for a very long time (like some biologically or industrially important phenoxyls) or even almost indefinitely as do some commercially available free-radicals such as TEMPO and DPPH) (*Figure 5*).



Vitamin E | 2,4,6-trisubstituted phenoxyls | TEMPO | DPPH

Figure 5. *Stable and persistent free-radicals*

The concept of persistency is hence strongly related to the mechanism of action of popular antioxidants which play a crucial role in the fields of food conservation and cell protection.

Moreover, the concept of radical persistency is also very important in organic synthesis as a radical generation method coupled with efficient trapping control: in fact, radical persistency is exploited in the achievement of living-radical polymerisations.[18]

'Philicity' of radicals and 'Hydrogen Abstraction'

The presence of electron-donating (EDG) and electron-withdrawing (EWG) substituents also affects the '*philicity*' of radicals species with important consequences for their chemical behaviour. Indeed, although radical reactions have long been considered to be independent of polar effects owing to the intervention of neutral intermediates, more recent studies have clearly established that those reactions can be largely governed by an appropriate choice of radical/molecule partners having opposite philicity.

This concept can be simply accounted for by considering that EDG groups can actually enhance the electron density on the radical centre, whereas EWG groups can behave in an opposite fashion. In fact, the oxidation/reduction potentials of radicals are largely affected by the electronic properties of their substituents: the presence of an EDG group will lower the oxidation potential of a radical centre, thus favouring possible occurrence of a corresponding (carbo)cation, while the presence of an EWG will lower the reduction potential, thus encouraging alternative occurrence of a corresponding (carb)anion. In the former cases '*electrophilic*' radicals will arise and in the latter '*nucleophilic*' ones (*Figure 6*).

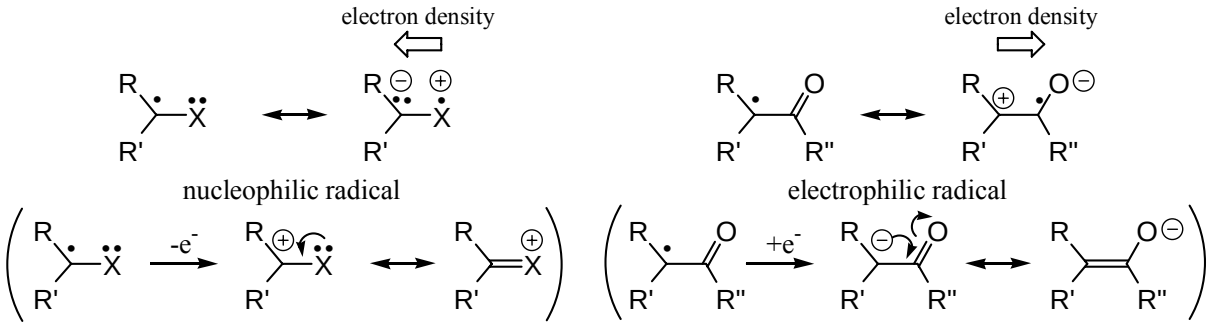


Figure 6. *Radical philicity*

The radical philicity can be explained more rigorously in terms of a frontier molecular orbital (FMO) approach.[19,20]

For a radical having a vicinal EDG substituent with a lone pair, interaction of the *p*-orbital containing the unpaired electron (SOMO) with the adjacent lone pair gives rise to two new molecular orbitals: two of the three electrons occupy the new lower energy orbital, while the third

electron occupies the new SOMO which is higher in energy than that of the original one (**Figure 7***a*). On the contrary, a radical bearing an unsaturated EWG substituent has a SOMO that is very close in energy to the antibonding π^*-orbital (LUMO) of the substituent: in this case, the interaction between the SOMO and the empty LUMO gives rise to a new SOMO that is lower in energy than the original one (***Figure* 7***b*). Accordingly, unlike ions, radicals are stabilized by both EDG and EWG substituents.

Furthermore, the FMO approach also explains the *high selectivity* of most radical reactions. Since in fast reactions small energy differences are required in SOMO-LUMO or SOMO-HOMO interactions, radicals with a high-energy SOMO have a tendency to interact with unfilled LUMO orbitals (such as those of electron-deficient olefins), and hence behave as electron-donating (nucleophilic) species. On the contrary, radicals with a low-energy SOMO tend to interact with SOMO filled orbitals (like those of electron-rich alkenes) and then behave as electrophilic species (*Figure 7c,d*).

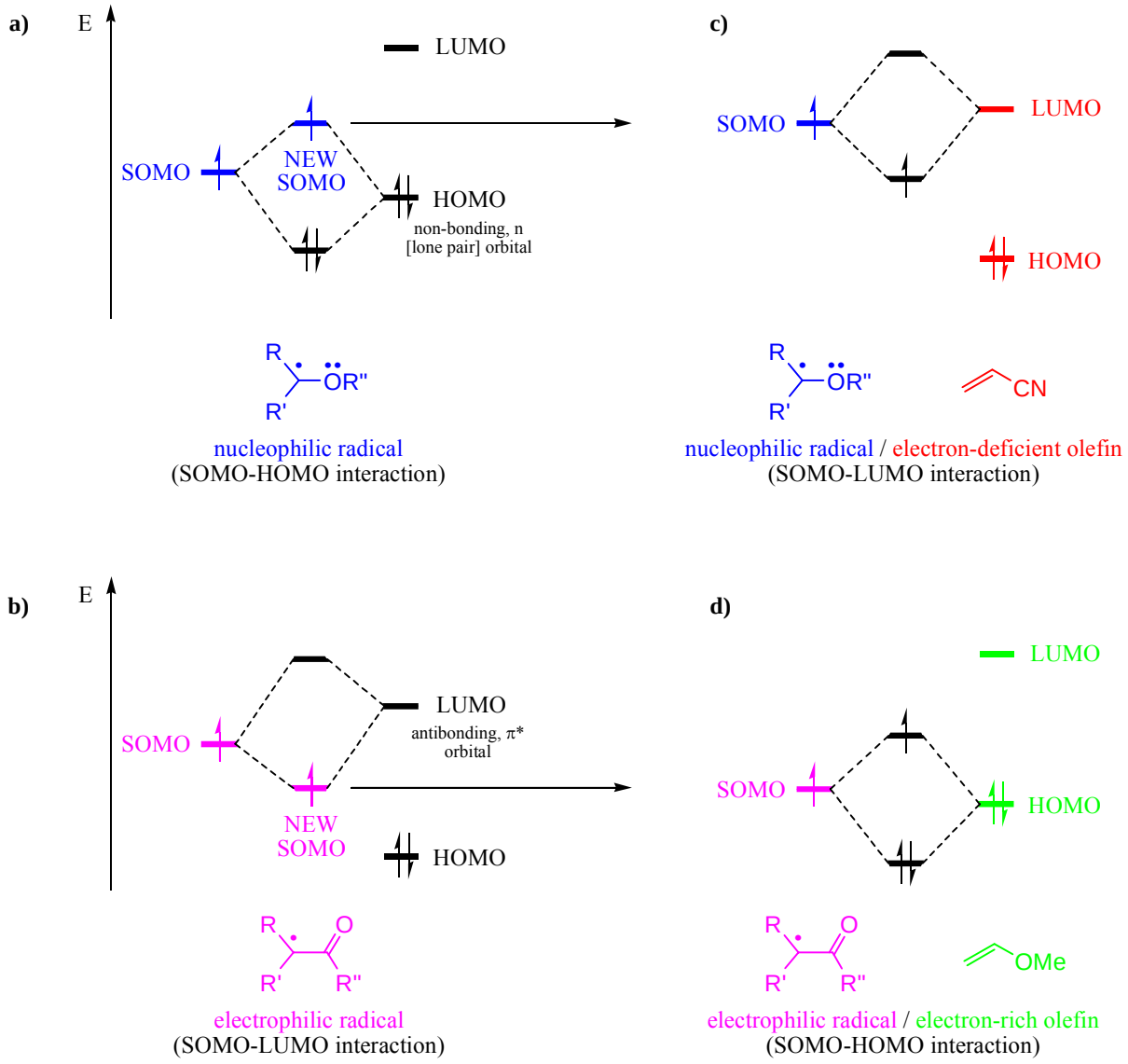


Figure 7. *Molecular orbitals and radical philicity*

An analogous explanation can account for the very high selectivity often observed in *hydrogen abstractions*. These reactions are known to be highly affected by polar factors and substituents capable to stabilize a partial charge separation in the transition state increase the reaction rate (*Figure 8*). For example, nucleophilic alkyl radicals abstract a hydrogen atom from a thiol with a kinetic constant of $\cong 10^7 - 10^8$ M^{-1} s^{-1}, whereas the same reaction with a silicon hydride has a kinetic constant of $\cong 10^3$ M^{-1} s^{-1} only. Since the sulfur–hydrogen bond (370 kJ mol^{-1}) has a similar strength to the silicon–hydrogen one (375 kJ mol^{-1}), the reaction is clearly not influenced by thermodynamic factors. Indeed, the reaction with thiols is fast because the nucleophilic alkyl radical rapidly abstracts the thiol hydrogen through a transition state with partial charge separation in which the carbon radical donates an electron to sulfur. With nucleophilic

silanes analogous charge separation in the transition state is evidently discouraged (*Figure 8a*). Of course, the opposite applies to for electrophilic radicals, which can rapidly abstract hydrogen from nucleophilic silanes but not from electrophilic thiols (*Figure 8b*).

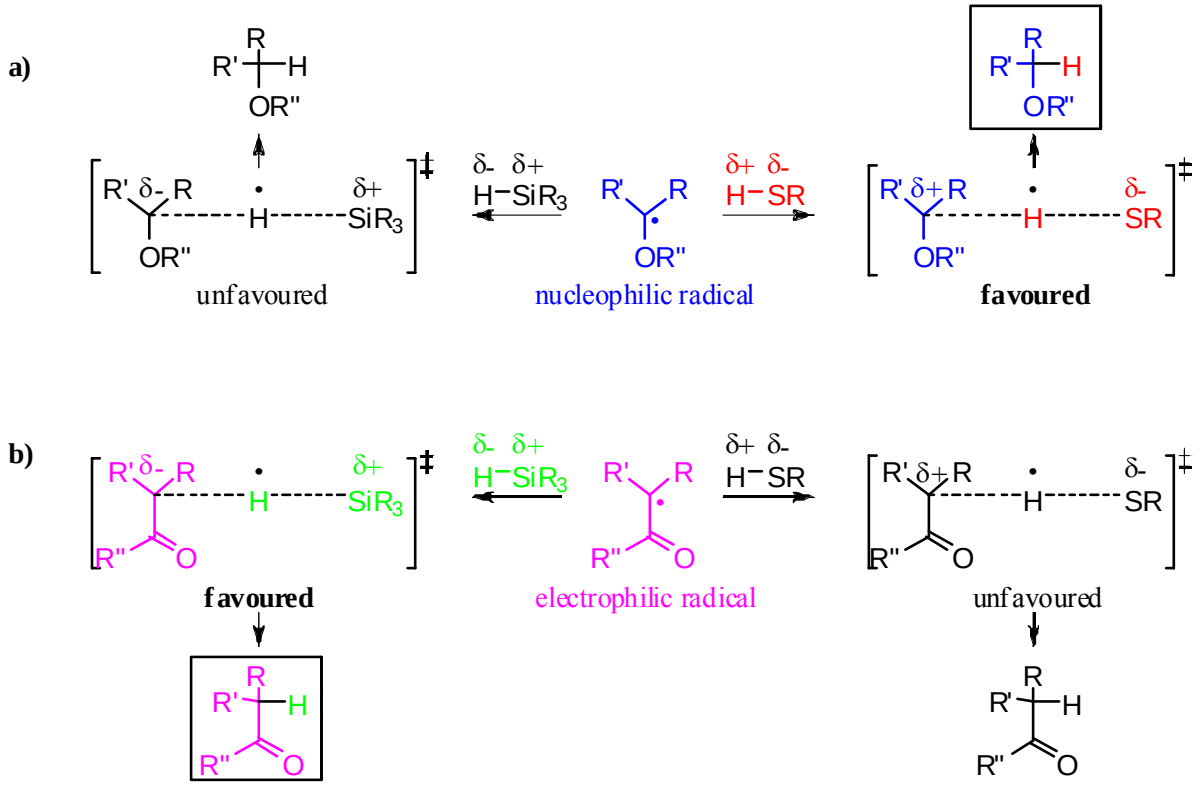


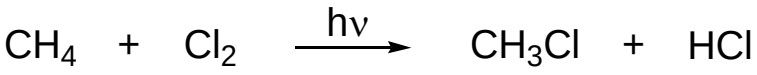
Figure 8. *Polar effects in hydrogen abstraction*

We can obtain the same rationale by the frontier molecular orbital approach. The hydrogen abstraction reaction is the result of the interaction between the SOMO of the radical and either the HOMO (σ) or the LUMO (σ*) of the C–H bond. Electron-withdrawing groups attached to the C–H bond will lower the HOMO and LUMO energies, whereas electron-donating groups will have the opposite effect. Therefore, electrophilic radicals will react faster with the electron-rich C–H bond of silanes through SOMO-HOMO interaction (see *Figure 7d*), whereas nucleophilic radicals will prefer to react with the electron-deficient C–H bond of thiols through SOMO-LUMO interaction (see *Figure 7c*).

Mechanism of radical transformations: "chain reactions" and unit steps

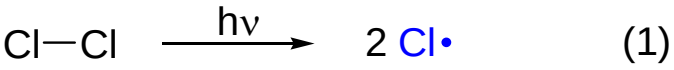
Many radical reactions are "chain reactions" and they are characterized by three fundamental steps: ***initiation***, ***propagation*** and ***termination*** of chain. For better understanding these concepts, we

shall examine the radical reaction of methane with molecular chlorine leading to formation of methyl chloride upon photochemical irradiation (*Reaction 1*).



Reaction 1. *Chlorination of methane*

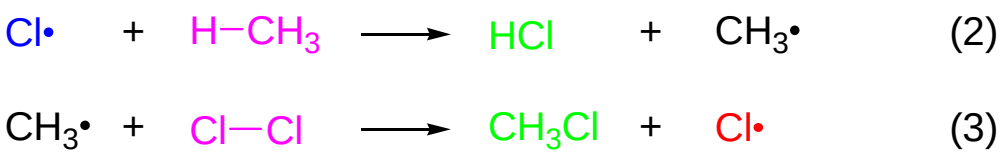
The first step of this reaction is the ***initiation*** of a radical chain: suitable irradiation causes initial fragmentation of molecular chlorine to chlorine atoms (*Equation 1*).



Equation 1. *Initiation step of radical chain*

Like in this case, an initiation step generally entails generation of some radical species from non-radical precursors (*initiators*).[21]

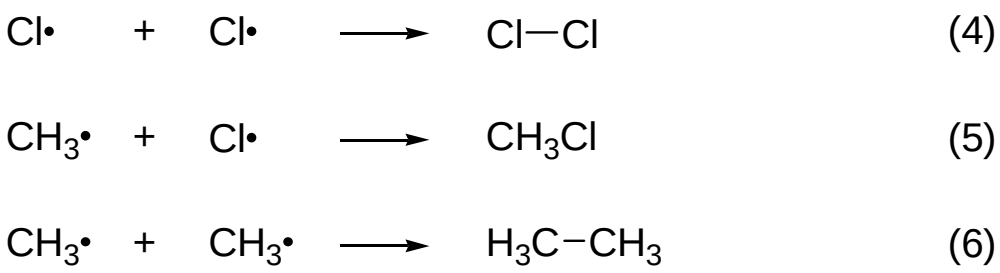
The second step involves ***propagation*** of a radical chain: an initially-formed chlorine abstracts a hydrogen atom from methane to form hydrochloric acid and a methyl radical (CH_3•) which then reacts with molecular chlorine to form chloromethane with regeneration of a chlorine atom (*Equation 2*).



Equation 2. *Propagation step of radical chain*

The repetitive character of *Equation 2* is referred to as propagation of a "radical chain": through radical chain propagation the starting reagents (molecular chlorine and methane) are consumed and chloromethane and hydrogen chloride products are formed.

The third and last step, occurring in competition with the propagation step, entails ***termination*** of a radical chain: pairs of radical species formed in *Equation 2* (Cl• and CH_3•) interact to form non-radical products[22] according to *Equation 3*.



Equation 3. *Termination step of radical chain*

We will now analyze more in details these three processes which are very important for successful applications of radical reactions in organic synthesis.

Radical Initiation

Radical reactions are commonly initiated by thermolysis or photolysis of suitable precursors, but radicals can also be produced by redox reactions (oxidations and reductions).[23] Also dioxygen can initiate radical processes, since the ground state of O_2 is a triplet with two unpaired electrons one of which is accommodated into two degenerate π^*-orbitals. Dioxygen is therefore a stable biradical and can, for instance, abstract hydrogen atoms from weak carbon–hydrogen bonds or act as a radical scavenger: these processes are of basic importance for example in lipid and polymer autoxidations.[24]

Radical generation by ***thermolysis*** can occur in solution at relatively low temperatures from molecules having suitably low BDEs (125-165 kJ mol^{-1}). Low BDEs are usually encountered with carbon–heteroatom, heteroatom–heteroatom, or metal–metal bonds, but carbon–carbon or carbon–hydrogen bonds are normally too strong to be thermally broken. Suitable molecules include diacyl and dialkyl peroxides, where O–O bonds are broken (125-150 kJ mol^{-1}), and azo-compounds, which undergo cleavage of two N–C bonds with concomitant formation of molecular nitrogen. Peroxides like di-*tert*-butyl, dilauroyl, or dibenzoyl peroxide and azobis-*iso*-butyronitrile (AIBN) are the most commonly used radical initiators, also employed in industrial applications (e.g. polymerisations) (*Figure 9a*). The decomposition temperature of a radical initiator largely depends

on structural features and electronic properties of substituents: its decomposition can range from room temperature (hyponitrites, peroxyoxalates, or V-70 [azobis(4-methoxy-2,4-dimethylvaleronitrile]) up to 140-150 °C.

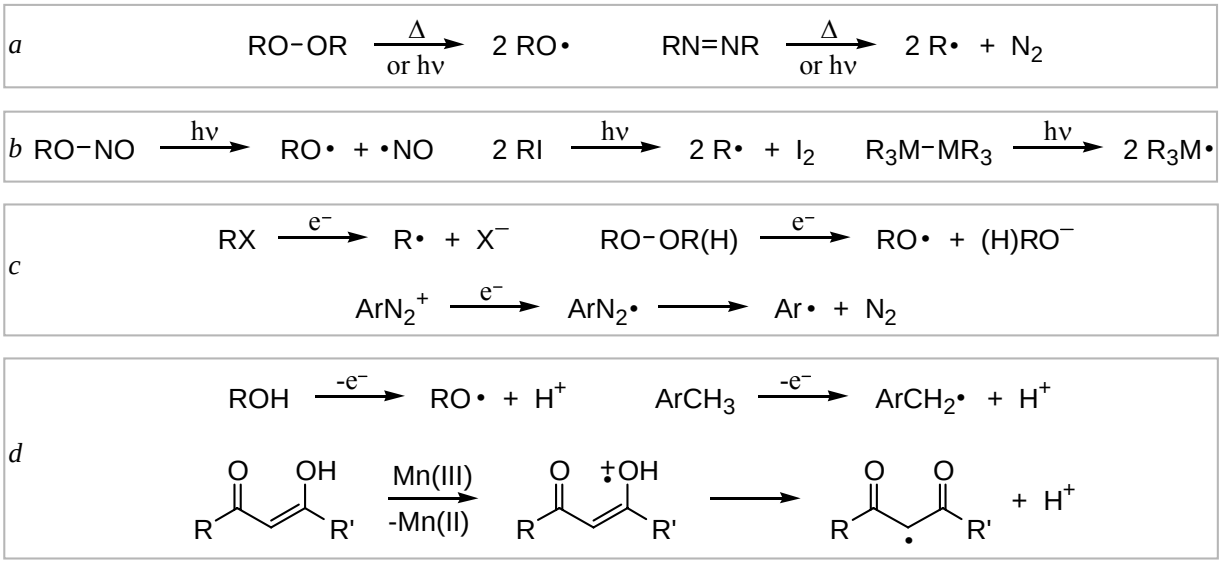


Figure 9. *Radical initiation methods*

Visible or UV light can promote low-energy or non-bonding electrons to antibonding orbitals, giving rise to excited states characterized by weaker bonds with respect to the ground states. Light can therefore be used to break bonds, providing that the molecule is able to absorb it. Under mild thermal conditions ***Photolysis*** can cleave even strong bonds, which would be otherwise broken at elevated temperatures, in a very selective way through selected choice of light of requisite energy. However, photolysis (especially UV irradiation) often requires special apparatus, reactors, and vessels, and is hence not as practical as other usual experimental procedures. Substrates that can be broken photolytically include peroxides, azo-compounds, halides (especially iodides), nitrites, and organometallics (to give metal-centred radicals) (*Figure 9a,b*). Carbonyl compounds absorb UV light (270-300 nm) yielding singlet excited states, through $n \rightarrow \pi^*$ transitions, that next form triplet states through intersystem crossing processes: the resulting di-radicals can participate in many radical reactions.

Neutral molecules can also be converted into radicals by ***electron-transfer*** routes: addition of an electron gives a radical anion that usually fragments to a radical and an anion, whereas extrusion loss of an electron generates a radical cation that commonly breaks into a radical and a cation.

Alternatively, radicals can be directly generated from anions or cations by removal or addition of an electron, respectively. These redox reactions are usually carried out by means of metal ions that change their oxidation state and thus behave like one-electron oxidizing or reducing agents. These processes normally occur under very mild conditions and are very selective. Single-electron transfer can also take place in electrolytic cells, where neutral molecules can be either reduced to radical anions at the cathode or oxidized to radical cations at the anode (in the same way, cations can add an electron at the cathode or anions can lose an electron at the anode). Radical generation by one-electron reduction can be easily accomplished with halides (which fragment to carbon radical and halide anion), peroxides or hydroperoxides (which break into alkoxyl radical and alkoxide or hydroxide anion) as well as with arenediazonium salts giving rise to diazenyl radicals that rapidly extrude dinitrogen (*Figure 9c*). Radical generation by one-electron oxidation can be achieved with carboxylic acids and alcohols (whose radical cations lose a proton to give acyloxyl or alkoxyl radicals, respectively), alkylarenes (which give rise to benzylic-type radicals by loss of a proton), and carbonyl compounds (mainly di-carbonyls, whose enolic form can be especially oxidized with Mn(III) salts), to give resonance-stabilized α–carbonyl or α,α-dicarbonyl radicals (*Figure 9d*).[25]

Radical propagation

Propagation reactions are processes in which a radical intermediate is converted into a new radical by means of either *unimolecular* (rearrangements and fragmentations) or *bimolecular* processes (intermolecular reactions with non-radical molecules); a number of these reactions can take place in sequence until a termination step pairs all of the electrons.[26]

Unimolecular propagation reactions encompass *rearrangements* and *fragmentations*. The former involve transformation of a precursor radical into a more stable (or more reactive!)[27] radical intermediate and usually occur through *migration of atoms* (e.g. 1,5-H shifts) *or groups* (e.g. 1,2-aryl shift), or by *intramolecular addition*[28] to C-C double and triple bonds and carbonyl moieties (*Figure 10*). Atom transfers are typically limited to 1,5 and 1,6 shifts, since lower-order migrations require strained transition states, whereas group translocations may occur also between vicinal atoms, like in the cases of neophyl rearrangement (1,2-aryl shift) and 1,2-acyloxy migration.

Fragmentations occur by *β– (or α–) elimination* of a radical species with concomitant formation of an unsaturated molecule. The driving force, besides the obvious increase in entropy, can be due to generation of a stable radical, formation of a strong π–system like a carbonyl group or an aromatic ring, or release of a very stable molecule (CO_2, CO, N_2). Alkyl radicals can suffer β–fragmentation

only in the presence of a weak σ–bond in the β–position, since the resulting alkene bond is not enough strong as to provide a suitable driving force (suitable β–substituents are halogen atoms, sulfanyl and stannyl groups). On the contrary, the fragmentation of alkoxyl or cyclohexadienyl radicals is strongly favoured by the formation of strong carbonyl groups or aromatic rings, respectively. Acyloxyl and diazenyl radicals have a high propensity to extrude carbon dioxide and nitrogen, respectively: with these radicals even aryl radicals can be generated in an efficient fashion.

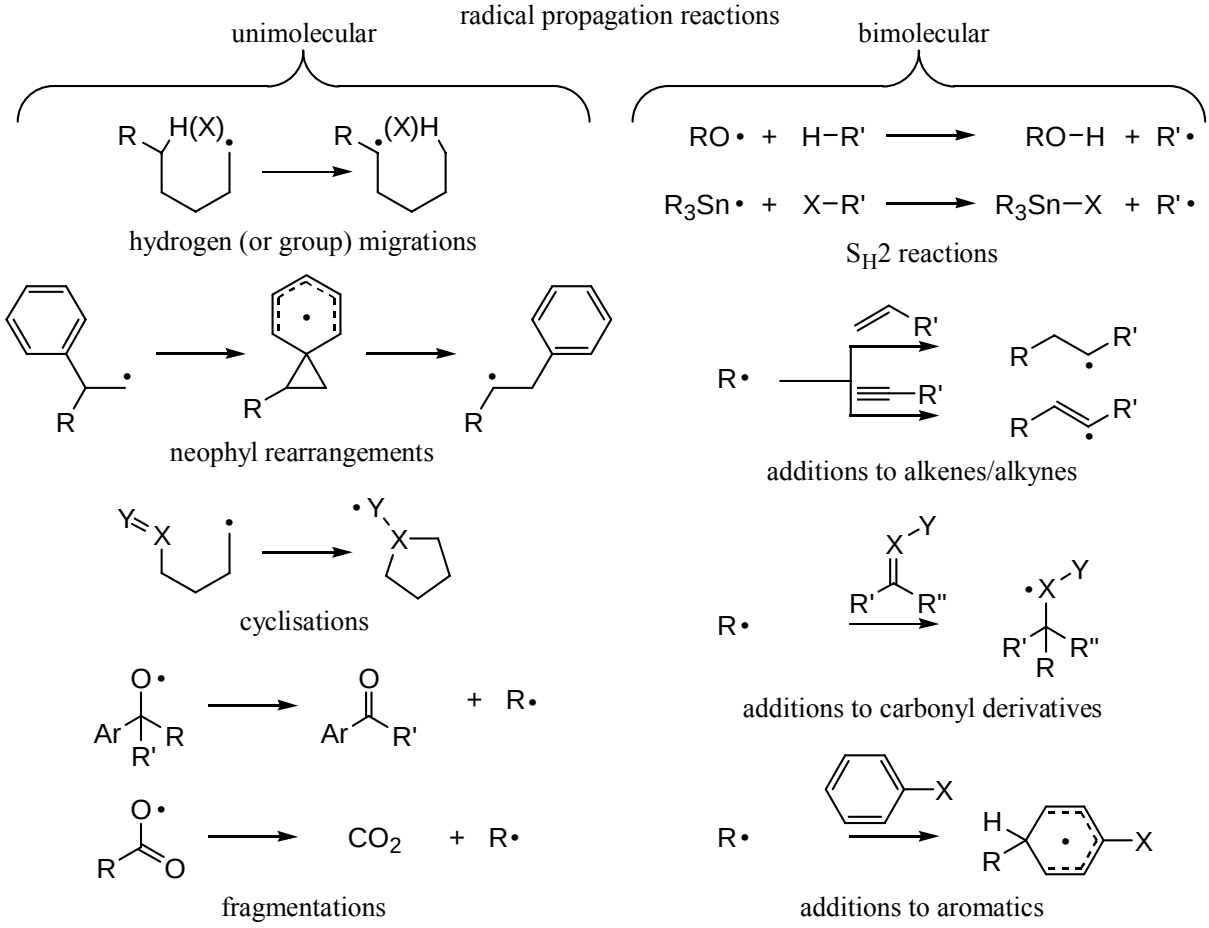


Figure 10. Intra- and intermolecular radical propagation reactions

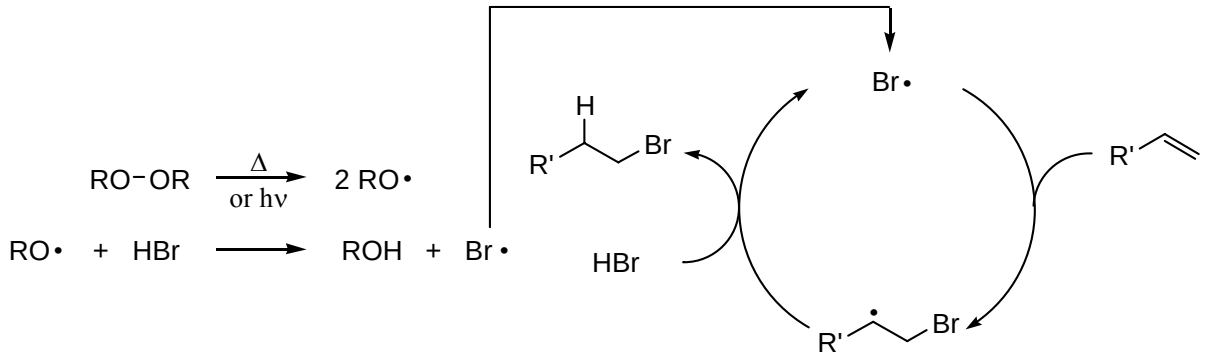
As far as ***bimolecular*** propagation reactions are concerned, they include atom abstractions (S_H2 reactions) and addition reactions to unsaturated moieties (alkenes, alkynes, carbonyls and their derivatives) and aromatic compounds (*Figure 10*).

Atom abstractions are analogous to the ionic S_N2 reactions: indeed, S_H2 stands for **S**ubstitution **H**omolytic Bimolecular (**2**) and the unimolecular analogue discussed above is often called S_Hi (**S**ubstitution **H**omolytic **i**ntramolecular). They are concerted displacement reactions where a hydrogen or halogen atom (but sometimes sulfanyl, stannyl, and other groups) is transferred from a molecule to a radical through the involvement of a linear transition state in which the radical orbital overlaps with the vacant σ^* orbital of the bond being broken. Hydrogen

abstractions are typically performed with alkoxyl radicals, which form alcohols having a strong O–H bond, whereas halogen abstractions are usually achieved with tin or silicon radicals in which cases the driving force arises from the formation of a strong metal-halogen bond at the expense of a weaker carbon-halogen bond.

Radical addition to unsaturated moieties is very common in the case of alkenes (e.g. in polymerisations), since the formation of a new C–C σ-bond (≅ 370 kJ mol^{-1}) at the expense of a weaker π–bond (≅ 235 kJ mol^{-1}) is usually a good driving force. With mono- or unsymmetrically-substituted alkenes, addition takes place preferentially at the less hindered position: such regiochemical outcome is probably a result of steric factors rather than stability of the ensuing radical adduct. The most popular reaction of this type is the *anti*-Markovnikov, peroxide-mediated addition of hydrobromic acid to alkenes (*Scheme 1*).

Unlike charged intermediates, radicals can add to both electron-rich and electron-poor multiple bonds, although the addition rate strongly depends on polar effects (see above) and bulkiness of the reactants. Alkenes and alkynes exhibit analogous regioselectivity, but alkyne reactions are usually slower due to ensuing generation of less stable vinyl radical adducts.



Scheme 1. *Anti-Markovnikov radical addition of HBr to olefins.*

Addition to carbonyl compounds is generally unfavourable, since the C=O π–bond is stronger than the alkene double bond by ca. 80 kJ mol^{-1}; therefore, most of the reported cases involve intramolecular examples. Carbon-centred radicals, especially the nucleophilic ones, show a certain propensity to attack electrophilic carbonyl carbons in a reversible fashion, whereas heteroatom-centred radicals like stannyls and silyls prefer to add to the carbonyl oxygen, due to alternative formation of a stronger metal–oxygen σ–bond. Very useful reactions, but largely confined to intramolecular examples, are those involving addition of nucleophilic radicals to the electrophilic carbon of nitriles, oximes, and hydrazones: these reactions are usually very fast and substantially

irreversible, since fairly stable radical adducts are formed and in such cases there is no efficient driving force for the reverse reaction to compete.

Radical addition to aromatic groups is rather slow, due to the great stability of the aromatic π–system. The resulting cyclohexadienyl radicals can either revert to the starting reactants or be oxidized, by formal loss of a hydrogen atom, to give substitution products in a process comparable to the electrophilic aromatic substitution. The addition rate strongly depends again on polar factors, hence nucleophilic and electrophilic radicals will react preferentially with electron-poor and electron-rich aromatics, respectively. The addition is often regioselective, since radicals prefer to attack the ring positions that give rise to cyclohexadienyls more stabilized by conjugative and/or inductive effects.

Radical Cyclisations as a powerful synthetic tool

Among the great number of useful radical transformations, ring closures reactions play undoubtedly a pivotal role in organic synthesis. Radical cyclisations can occur in sequence (tandem cyclisations) and can show high levels of regio- and even stereoselectivity, being probably the most popular, distinctive contribute of free-radical chemistry to the world of synthesis.

According to Baldwin's rule,[29] radical (and also non-radical) cyclisations can be classified into *exo* and *endo* modes, depending on whether ring closure occurs on either the inside or the outside of the unsaturated moiety, respectively. In other words, *exo*- or *endo*-cyclisations are those leading to new radicals that are *exo*cyclic or *endo*cyclic with respect to the newly-formed rings. The *exo* or *endo* term is usually preceded by a number indicating the ring size and followed by an additional term representative of the hybridisation of the (carbon) atom at the reaction site. Hence, cyclisations are called *tet*, *trig*, or *dig* when the reaction sites are *tet*rahedral sp^3, *trig*onal sp^2, or *dig*onal sp carbons, respectively (*Figure 11*). As an example, a "5-*exo*-*trig*" cyclisation (one of the most common radical ring-forming reactions) is a ring-closure reaction that gives rise to a 5-membered ring through attack of the starting radical to the inner carbon atom of an alkene moiety, with consequent formation of a new exocyclic radical.

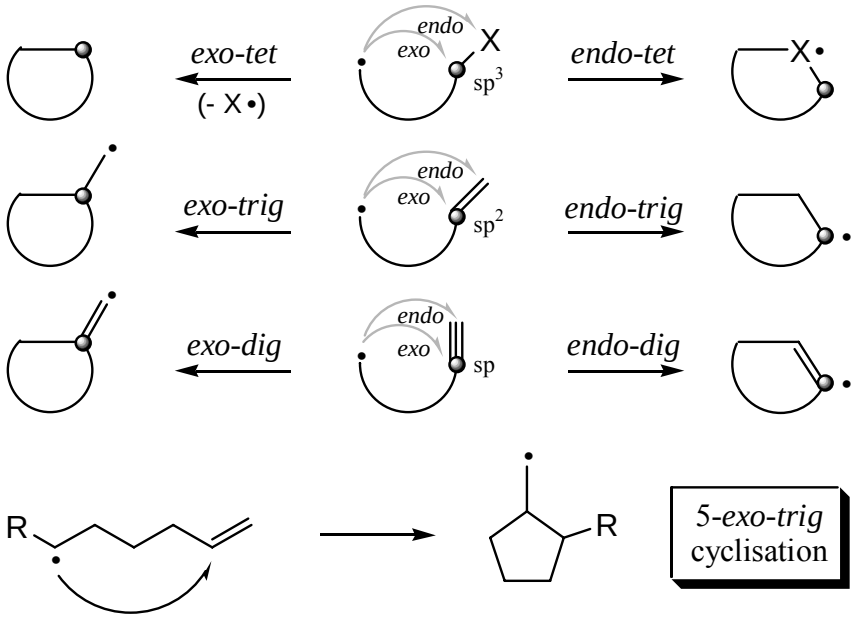


Figure 11. *Baldwin's rule for radical cyclisations.*

At this stage it is worth noting that most useful radical reactions are *exothermic* processes. According to Hammond Postulate, the *transition states* of exothermic reactions – and thence of the radical reactions – are generally *reagent-like* (*Figure 12*).

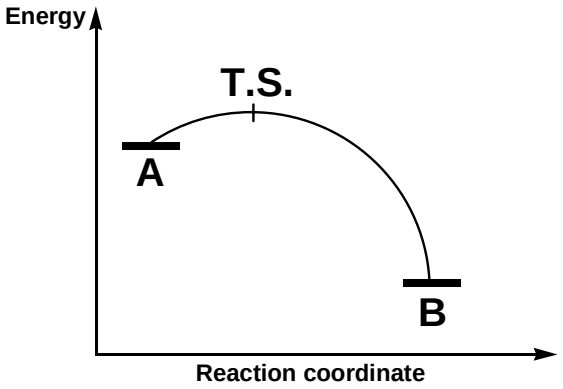


Figure 12**.** *Generalized reaction profile for an exothermic reaction: the transition state (T.S.) is closer to the reagent (A) than to the products (B) along both coordinate axes.*

In light of Hammond Postulate for two *similar exothermic processes* it is possible to envision a reaction profile like that shown in *Figure 13*. ***"Crossing" reaction profiles***, termed "*crossing*", where the process thermodynamically less favoured (A→B) has however a transition state of lower energy, and is therefore kinetically more favoured.

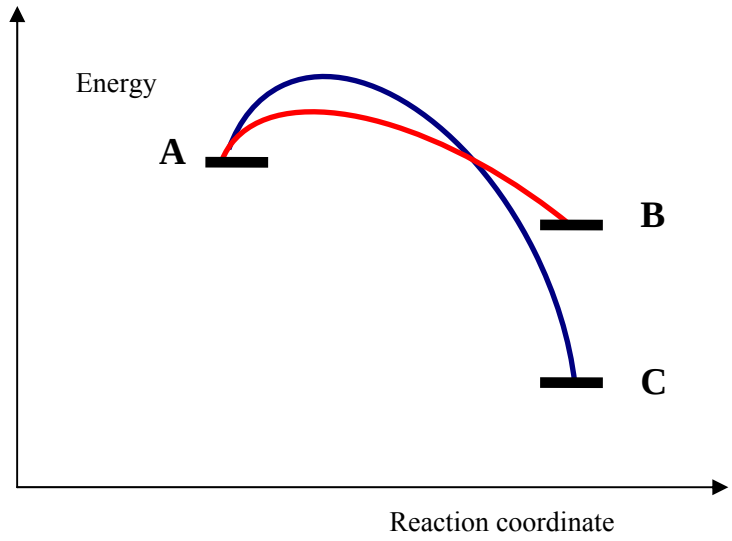


Figure 13. *"Crossing" reaction profiles*

The concepts just discussed can help to explain a very particular behaviour that occurs in the field of the radical cyclisations.

For radical reactions to be fast, the single occupied orbital (SOMO) of the reacting radical must overlap efficiently with a suitable orbital of the radicophilic partner. For intermolecular reactions this condition is easily fulfilled, since the reactants can rotate freely to ensure maximum overlap. On the other hand, intramolecular reactions, namely cyclisations, can be strongly affected by so-called "stereoelectronic effects", because not all the conformations are energetically favoured and the reaction could be kinetically controlled by the process triggered by the most favoured interaction. Cyclisation of the hex-5-en-1-yl radical is an emblematic example of this behaviour (*Figure 14*).

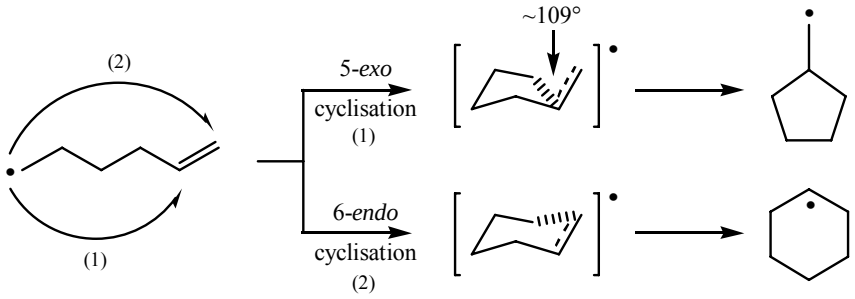
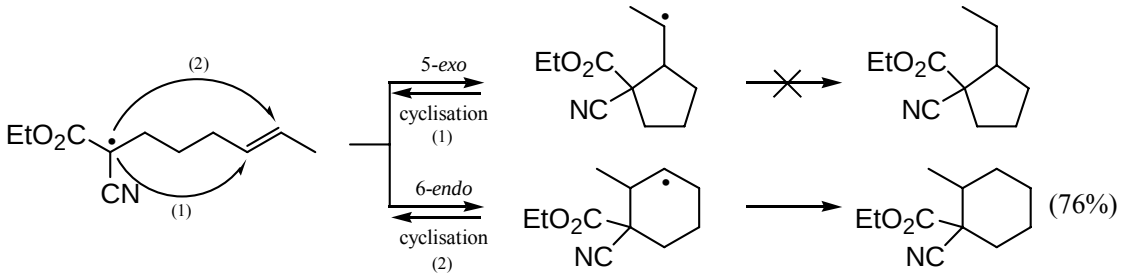


Figure 14. *Transition states for 5- and 6-membered hexenyl radical cyclisation (Beckwith models).*

For cyclisation of this radical, at 25 °C, the 5-*exo* mode ($k_{exo} = 2.3 \times 10^5\ s^{-1}$) is about 60 times faster than the 6-*endo* competitive ring closure ($k_{endo} = 4.1 \times 10^3\ s^{-1}$).[30] At first sight, this fact is unexpected at least for two well-founded reasons: *i)* the cyclopentane ring is more strained than the

cyclohexane ring, and *ii)* the radical arising from 5-membered cyclisation is a primary radical and should be therefore thermodynamically less stable than the secondary radical formed in the 6-membered ring closure. Nevertheless, at 25 °C, the 5-*exo* and 6-*endo* products are formed in a 98:2 ratio! Actually, stereo-electronic effects operate and the reaction is under kinetic rather then thermodynamic control. This is explained by the fact that the singly occupied orbital overlaps more favourably with the alkene π* orbital at the inner carbon atom, through a chair-like transition state (Beckwith model) that has been proved to be less strained and energetically favoured with respect to the 6-membered analogue: indeed, this overlap is characterised by an attack angle very close to 109 °C (i.e. the bond angle that is required in the product radical).

Since radicals are typically quite unstable, very reactive species, radical cyclisations are usually irreversible and kinetically controlled, and the product ratios (and even the stereochemistry!) strictly depend on stereo-electronic effects and can be often predicted on the basis of Beckwith models. However, if the cyclisation is reversible, due to the stability of the starting radical, the reaction can afford the thermodynamically favoured product, since ring opening of the less stable radical product can be faster than, for example, the hydrogen abstraction process involved in the reaction of *Scheme 2*.[31]



Scheme 2. *Thermodinamically controlled reaction due to reversible cyclisation*

Radical Termination

The termination reactions are processes in which radical intermediates are destroyed as a result of coupling (or *dimerisation*), *disproportionation*, or *one-electron exchanges*.

Coupling or **dimerisation** (heterocoupling or homocoupling) reactions[32] involve combination of two radical species to yield a non-radical molecule as a result of the formation of a covalent bond (*Figure 15*). These reactions are very fast and essentially diffusion controlled. Coupling products are though usually observed in very small amounts, since their formation requires fairly high radical concentrations, a condition rarely achieved due to the very short radical lifetimes.

Disproportionation entails transfer of a β–hydrogen between two carbon radicals with formation of a C=C π–bond and a C–H σ–bond. Also these reactions are very fast and the greater the number of β–hydrogens and the bulkier the radical centre, the more likely it is that a disproportionation will occur.

Electron transfer reactions convert radical species into anions and cations by one-electron reduction and oxidation processes, respectively. The 'redox reagent', as in the case of radical generation, can be a transition metal ion or an electrode. The reaction rate depends of course on the redox potential of the radicals: tertiary alkyl radicals are easily oxidized to carbocations, due to the stabilising +I inductive effect of the alkyl groups. Other less substituted carbon radicals can also be readily oxidized when bearing electron donating groups like OR and NR_2 which can play an important role in cation stabilisation. On the contrary, primary alkyls prefer reduction to carbanions, and the process is strongly favoured by electron-withdrawing groups (e.g. NO_2, COOR), which can stabilise the resulting negative charge by –M mesomeric effect (*Figure 15*).

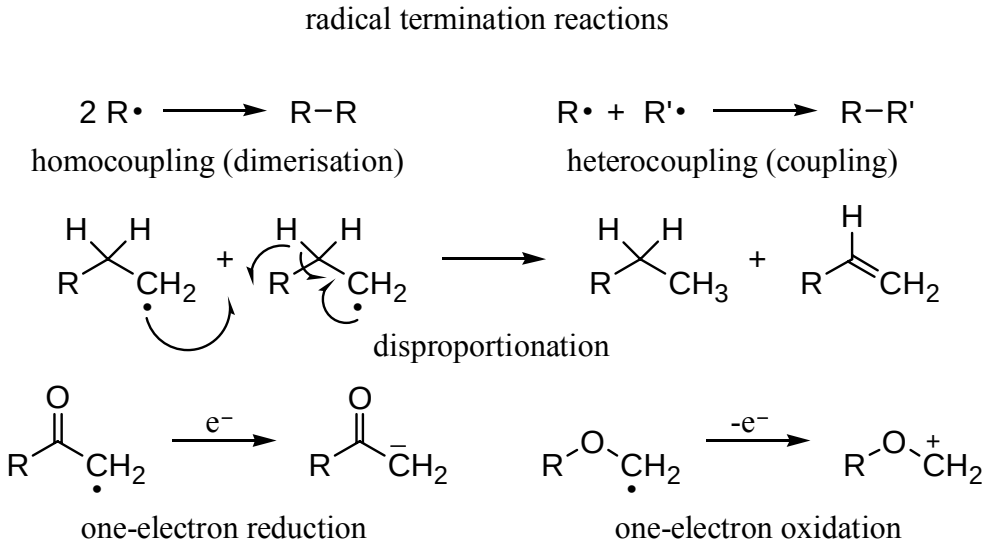


Figure 15. *Radical termination reactions*

Starting from these bases, we can now penetrate in the 'world' of the radicals and explore their use in synthetic organic chemistry.

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[16] The real importance of the captodative effect is however still debated. For a recent review, see: Stella, L.; Harvey, J. N. in *Radicals in Organic Synthesis*, Renaud, P. and Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001, Vol. 1, p. 360. See also: Viehe, H. –G.; Janousek, Z.; Merényi, R.; Stella, L. *Acc. Chem. Res.* **1985**, *18*, 148.

[17] It should also be underlined that the term "*unstable*" is inappropriate for many short-lived radicals. It is more usually used in the sense of *unimolecular instability*. In fact, in the vacuum methyl radical **4** would be long-lived!

[18] a) For a discussion on the persistent radical effect, see: Fischer, H. *J. Am. Chem. Soc.* **1986**, *108*, 3925 and Fischer, H. *Chem. Rev.* **2001**, *101*, 3581. For the use of nitroxides (such as TEMPO) in organic synthesis, see: b) Braslau, R.; Anderson, M. O. in *Radicals in Organic Synthesis*, Renaud, P. and Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001, Vol. 2, p. 127 and c) Studer, A. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 1108. d) For living-radical polymerisation, see Georges, M. *ibid.*, Vol. 1, p. 479.

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[20] Deepened discussions on this subject can be found on the books reported in: Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986, Chp. 2.

[21] In the brought example, the initiator is also a starting reagent (Cl_2), but it is always not this way.

[22] A chain can also finish through processes of *electron transfer* that oxidizes or reduces the radical to the corresponding ion.

[23] Additional, but not very used, radical sources include also radiolysis (with X– or γ–radiation) and sonolysis (with ultrasounds).

[24] Porter, N. A. *Acc. Chem. Res.* **1986**, *19*, 262.

[25] For excellent reviews on these subjects, see, for example: a) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519. b) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339.

[26] The reactions reported below in this section are the key processes that characterise the whole radical reactivity. Many famous radical reactions (e.g. the Sandmeyer reaction, the neophyl rearrangement, the Kolbe decarboxylation, the Barton-McCombie reaction, or even the Toray process for cyclohexanone oxime) can simply be regarded as sequences of these key steps.

[27] In reversible processes one can isolate products derived from a rearranged, less stable radical if this reacts very fast with a radical trap.

[28] Due to their importance in organic synthesis, radical cyclisations will be discussed more thoroughly in the subsequent section.

[29] Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

[30] Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. The whole Volume 41 of *Tetrahedron* is concerned with selectivity and synthetic applications of radical reactions.

[31] Julia, M. *Acc. Chem. Res.* **1971**, 386.

[32] "Dimerisation" (or homocoupling) usually refers to coupling between two identical radical species, whereas "coupling" (or heterocoupling) entails combination of two different radicals.

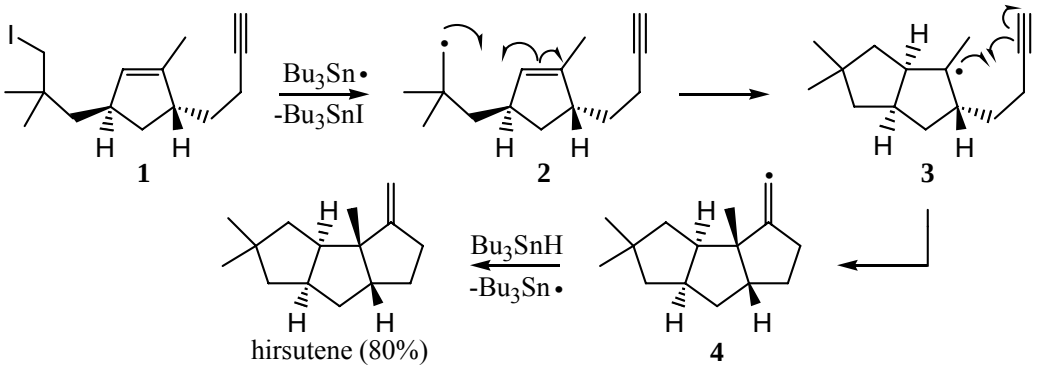
CHAPTER 2
TIN-FREE METHODOLOGIES

2.1 The "tyranny of tin" [1,2]

As we have seen in the previous chapter, for a reaction to proceed in solution by a radical pathway, it is fundamental that the energy of the bond to be homolytically broken is not too high. From this point of view, molecules that fully respect this requisite are ***organotin hydrides*** - in particular tributyltin hydride (Bu_3SnH, TBTH) - because their Sn-H Bond Dissociation Energy (BDE) is approximately 310 kJ mol^{-1}.

Radical reactions have already become an extremely useful tool in organic synthesis, particularly for the formation of carbon-carbon bonds in intra- and intermolecular processes.[3] The very rapid development of these reactions can be attributed to the emergence of highly efficient ways to conduct them. Among these methods, the organotin hydride mediated addition of radicals to activated alkenes has played a major role.[4] Ever since the original discovery of radical generation by organotin hydrides (R_3SnH),[5] an incredible number of applications have wound inexorably upward. At present, tin reagents dominate free radical chemistry, and their influence is reaching continually deeper into the synthetic science.[6] The domain of radical ring closures is strictly founded on tin-based methods and an overabundance of such annulations pervades the recent literature. The success of tin reagents has given them such prestige and notoriety that they practically monopolize the market place for homolytic synthetic and kinetic applications. This dominance has been referred to as the "*tyranny of tin*".

One of the first reported examples is the elegant synthesis of the tricyclic ring system of racemic hirsutene, carried out by Curran in the mid 80s (*Scheme 1*).[7] The starting material is iodide **1**, which, by classical treatment with tin radicals (generated by the system Bu_3SnH/AIBN; AIBN=azobis-*iso*-butyronitrile) gives alkyl radical **2** by iodine atom abstraction; tandem cyclisation of **2** onto the alkene double bond and of the resulting radical adduct **3** onto the alkyne triple bond yields vinyl radical **4**, which is in turn converted to hirsutene by hydrogen transfer from the tin hydride. The yield is about 80%. In each ring, the formation of the required *cis* fusion is controlled by ring strain, whereas the *trans*-disposition of the side chains in the starting iodide ensures the correct fusion of one ring with respect to the other one. This example gives a very good idea about how efficiently radical reactions can accomplish construction of hindered carbon–carbon bonds, including easy creation of quaternary centres.

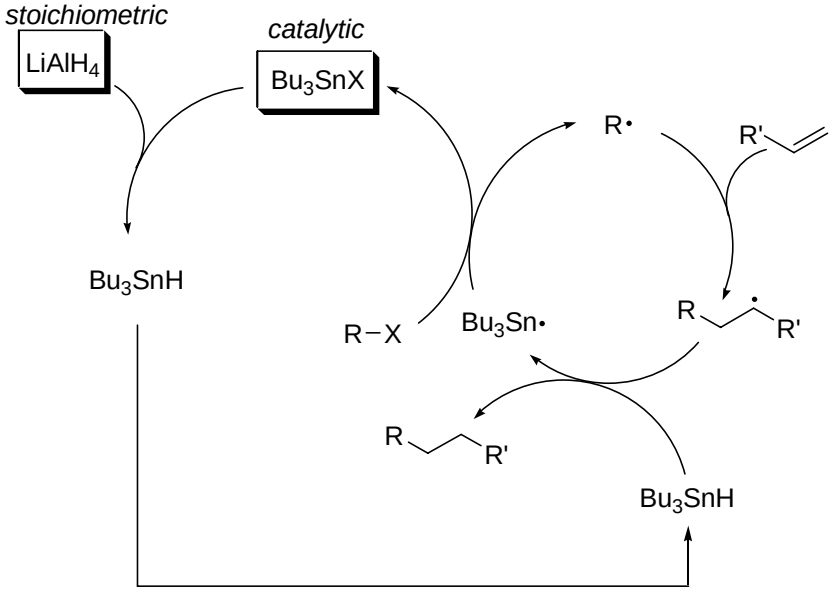


Scheme 1. *Synthesis of hirsutene.*

However, the application of this kind of reaction for the synthesis of pharmaceuticals is severely limited by the *toxicity of the tin reagents* and by the difficulty to completely remove from the final products the toxic tin by-products that are generated in stoichiometric amounts during the reaction.

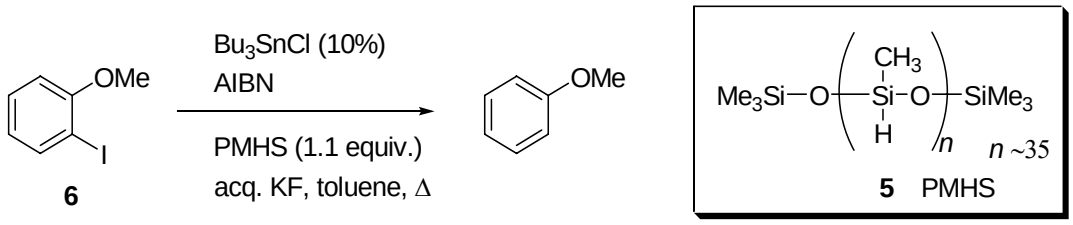
Therefore, alternative ways of running radical reactions are under intensive investigation and it is not surprising that many groups started research programs directed towards both efficient purification of organotin-containing mixtures and tin-catalysed or (better) ***tin-free radical chemistry***.[8]

The *tin-catalysed* processes are founded on the principle that the trialkyltin halide by-products can be efficiently reduced with lithium aluminium hydride ($LiAlH_4$) to the corresponding tin hydride. The reaction can be therefore carried out with catalytic amounts of organotin halide and stoichiometric amounts of $LiAlH_4$, which constantly regenerates the tin hydride from the corresponding halide (*Scheme 2*).



Scheme 2**.** *Example of a tin-catalysed process.*

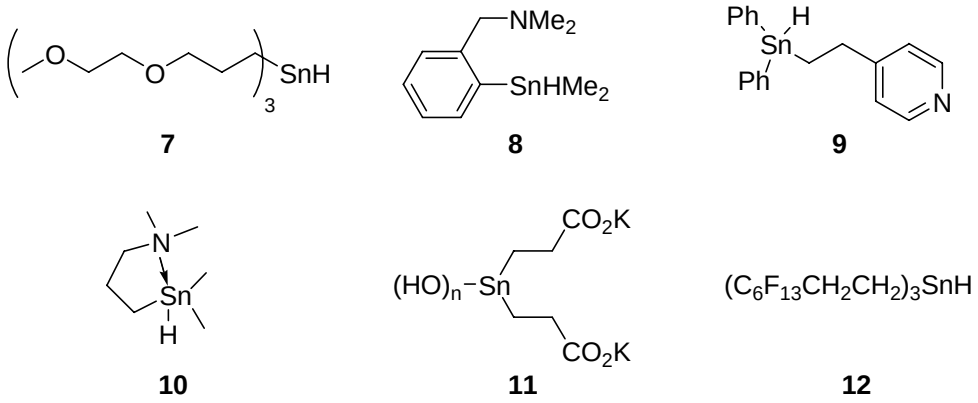
The first example of this methodology, i.e. the radical reduction of bromocyclohexane with catalytic amounts of tributyltin chloride using $LiAlH_4$ as the stoichiometric co-reducing reagent, was reported in 1963.[9] The same procedure has been further improved using sodium borohydride or sodium cyanoborohydride ($NaCNBH_3$).[10] Recently, Maleczka has shown that, upon addition of aqueous potassium fluoride, trialkyl tin hydrides can be regenerated from the corresponding tin halides using polymethylhydrosiloxane **5** (PMHS).[11] Efficient reduction of *o*-iodo-anisole **6** was achieved with 10% BuSnCl and PMHS as the stoichiometric reducing reagent in the presence of aqueous KF (*Scheme 3*).



Scheme 3**.** *The Maleczka reduction of o-iodo-anisole.*

In addition to these catalytic methods, *easily-removable tin-compounds* have been introduced so that a better, effective purification during the reaction work-up is possible. For example, trialkyltin chlorides, -bromides, and -iodides can be readily transformed into the corresponding high-melting, nonvolatile, insoluble polymeric tin fluorides, upon treatment with aqueous KF, which can be easily removed from the reaction crude.[12] Another possible approach is again the reduction of tin halides with $NaCNBH_3$ regenerating the tin hydrides, which are very unpolar compounds that can be separated rapidly by a silica gel chromatographic column with hydrocarbon eluants.[13]

Many compounds have been suitably created to facilitate the disposal of tin residual. For instance, tin hydrides **7**, **8**,[14] **9**,[15] and **10**,[16] and more importantly the corresponding tin derivatives generated during the reaction, can be separated by simple aqueous acidic workup. The water soluble dialkyl tin reagent **11** can be reduced in situ with $NaBH_4$ to a tin hydride that, after the reaction, gives a water soluble tin halide.[17] In addition, Curran developed fluorous tin hydrides such as **12** (*Figure 1*), whose by-products can be easily removed by partitioning with a fluorinated solvent.[18]



7 **8** **9**

10 **11** **12**

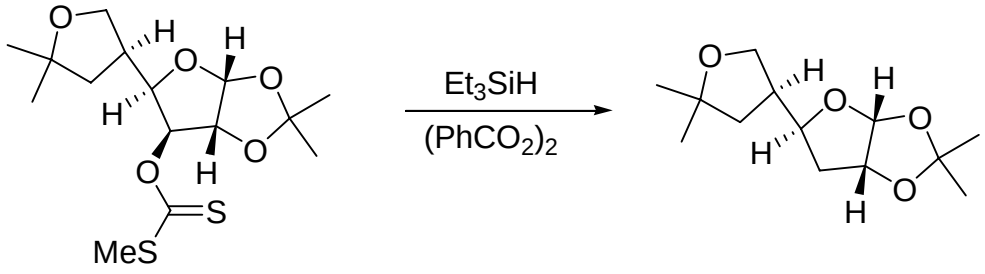
Figure 1. *'Easily-removable' tin stannanes.*

Finally, reductive radical chain reactions have been successfully carried out with polymer-bound tin hydrides,[19] which can also be used in catalytic quantities in the presence of stoichiometric amounts of a co-reducing reagent.[20] Although some benefits may accrue from the use of these novel tin reagents, the fundamental problem of tin toxicity remains a constant menace. This led to different approaches residing in the use of tin hydrides substitutes.

2.2 The 'silicon': a substitute of tin

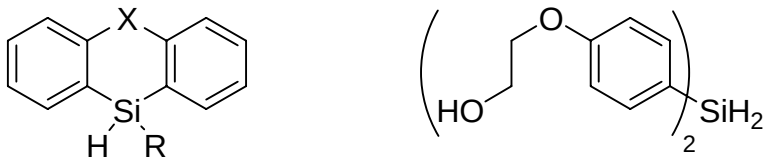
The silicon-hydrogen bond in simple ***triorganosilanes*** (R_3Si-H) is too strong for ready hydrogen transfer (i.e., $(CH_3)_3Si$-H has a BDE of 377 kJ mol^{-1}) and therefore chain processes are difficult to maintain. However, the replacement of the alkyl groups by other substituents allows the 'tuning' of the reactivity of the Si–H bond of the corresponding silane.[21] Even though triethylsilane (Et_3SiH) and diphenylsilane (Ph_2SiH_2) have been advocated as alternatives to organotin hydrides, the range of amenable substrates is limited and the reaction temperature is often undesirably high. Nevertheless, there are some applications that use these less reactive silanes. An interesting example is provided by the Barton-McCombie reaction of xanthate **13**, which is deoxygenated in 96% yield to afford tetrahydrofuran **14** using Et_3SiH as the reducing reagent (*Scheme 4*).[22] Similar reactions have been also carried out using Ph_3SiH and Ph_2SiH_2.[23]

The phenyl substituents at the silicon atom have only a small effect on the Si–H-reactivity in H-abstraction reactions. It has been found, however, that the siladihydroanthracene derivatives **15**, where the phenyl substituents at the silicon atom are conformationally locked, show enhanced H-donor abilities in radical reactions (*Figure 2*).[24] Interestingly, arylsilanes show enhanced reactivity if the chain reactions are conducted in water. Some water-soluble arylsilanes, similar to **16** in *Figure 2*, were used successfully in radical dehalogenations: the reductions were conducted in water at ambient temperature under aerobic conditions using Et_3B as initiator.[25]



13 **14**

Scheme 4. *Barton-McCombie deoxygenations using triethylsilane.*

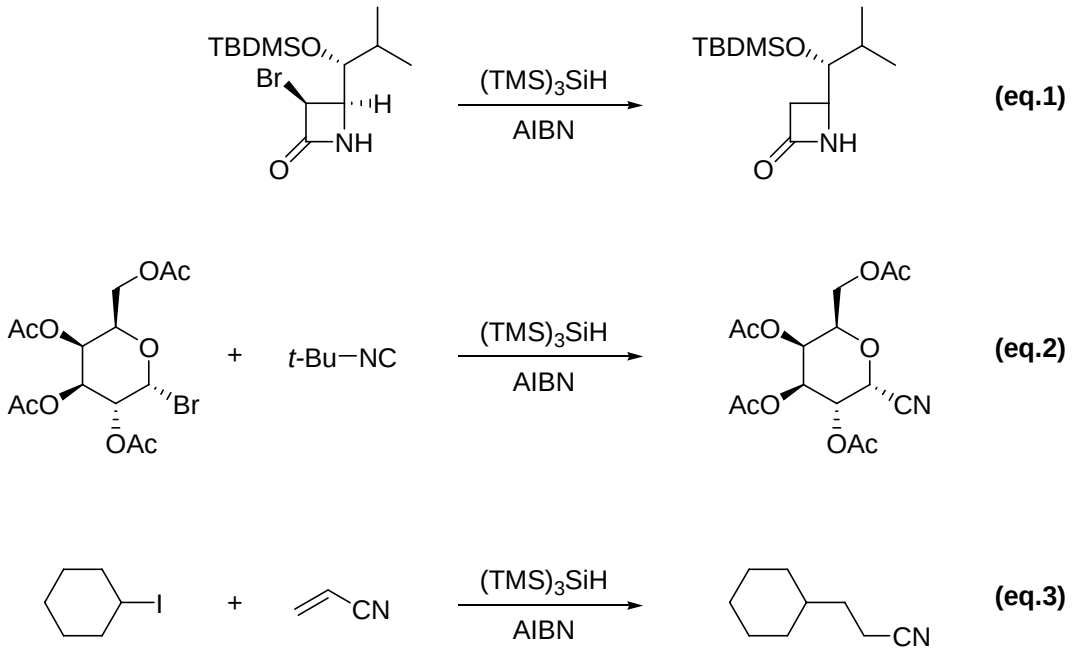


15 **16**

Figure 2. *Siladihydroanthracene and water-soluble arylsilanes.*

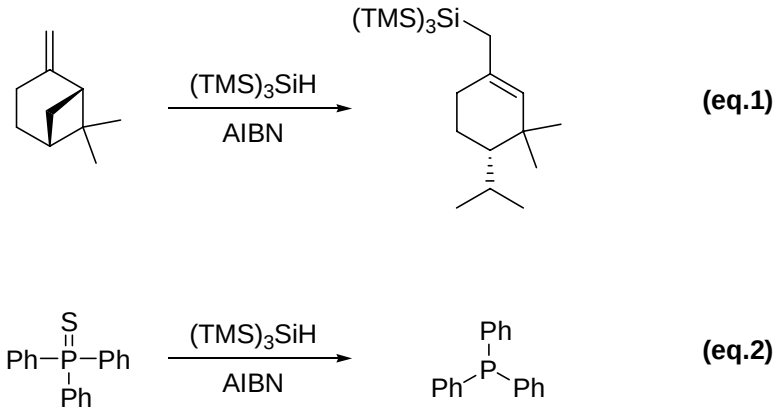
The most successful tin hydride substitute to date is *tris(trimethylsilyl)silane* [$(TMS)_3SiH$].[26] $(TMS)_3SiH$ (TTMSS) is slightly less reactive that TBTH in H-abstraction reactions with carbon-radicals (the Si-H BDE is 330 kJ mol^{-1}); this value is lower in comparison to a usual silane because of the presence of the three TMS (Me_3Si) groups. TTMSS is commercially available, and can perfectly replace tin hydrides in the most common radical reactions. Chatgilialoglu has recently summarised the use of TTMSS as the chief reagent in radical chain reactions using iodides, bromides, chlorides, selenides, isocyanides, acid chlorides, xanthates, and sulfides as radical precursors.[27] The reactions are generally conducted in analogy with the tin hydride mediated methodologies using a suitable radical initiator (depending on the reaction temperature, i.e. AIBN at 80 °C, Et_3B at r.t.) in an aromatic or hydrocarbon solvent.

An example of debromination is shown in eq. 1 (*Scheme 5*).[28] The introduction of a cyano group at the anomeric position of a sugar derivative (a radical cyanation) starting from the corresponding glycosyl bromide and *tert*-butyl isonitrile under radical conditions with TTMSS is depicted in eq. 2 (*Scheme 5*).[29] Moreover, Giese-type reductive addition reactions of alkyl halides onto activated olefins were successfully performed with TTMSS as depicted in eq. 3 (*Scheme 5*).[30]



Scheme 5. *$(TMS)_3SiH$ as tin hydride substitute in different radical reaction.*

In addition, TTMSS can be used in radical hydrosilylation reactions, as shown for the trasformation of *β*-pinene into the hydrosilylation/ring-opening product (eq. 1, *Scheme 6*), or to reduce phosphine sulfides and phosphine selenides to the corresponding phosphines (eq. 2, *Scheme* **6**).

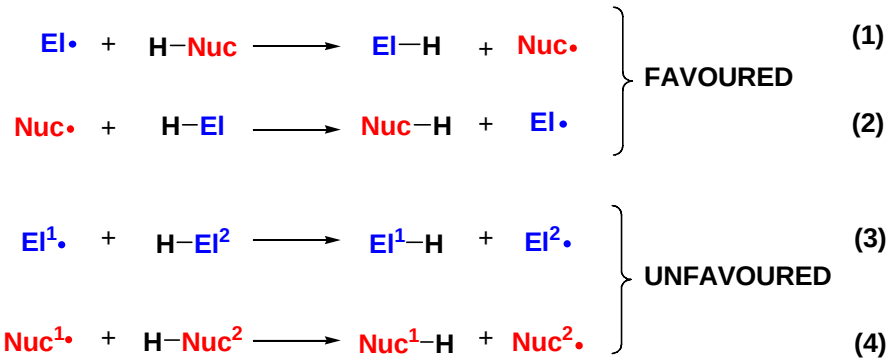


Scheme 6. *(TMS)$_3$SiH in reductive radical chain reactions.*

TTMSS is certainly a versatile reagent that can be used to accomplish a range of useful transformations. It has however a number of serious drawbacks, e.g. the propensity of the (TMS)$_3$Si• radical to add to multiple bonds, the quite high cost, and the need to handle under argon.

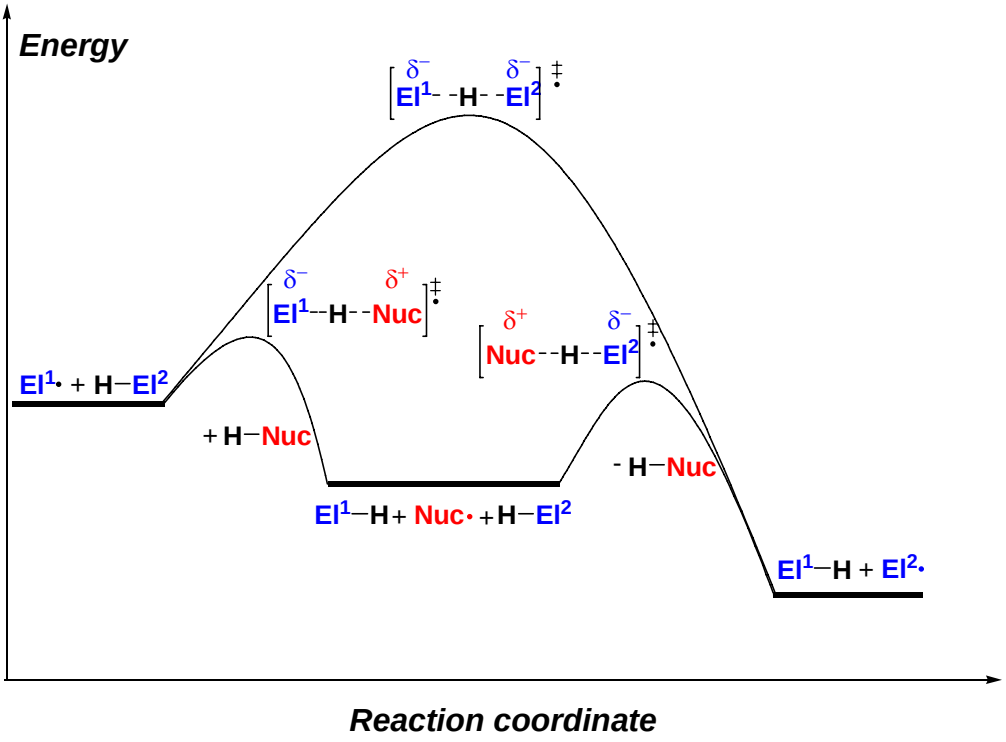
As far as the cost is concerned, it is worth noting that TTMSS, similar to organotin hydrides, can be used in catalytic amounts, employing sodium borohydride to regenerate the reagent from the silicon halides by-products. However, nothing in general can be done to prevent formation of by-products derived from side-reactions of (TMS)$_3$Si• radicals.

An alternative, effective way to generate silyl radicals from common silanes is based on the *polarity-reversal catalysis* (PRC) that as been intensively investigated by Roberts and co-workers using thiols as catalysts.[31] In this approach, it is possible to circumvent the problem of the high Si-H BDE in simple organosilanes (e.g., the very cheap, stable Et$_3$SiH) exploiting the 'philicity' of radical species (*see Chapter 1*). For a H-abstraction reaction, if El• and Nuc• represents an electrophilic and a nucleophilic radical, respectively, reactions (1) e (2) are favoured by polar effects, whereas reactions (3) and (4) are unfavoured (*Scheme 7*).



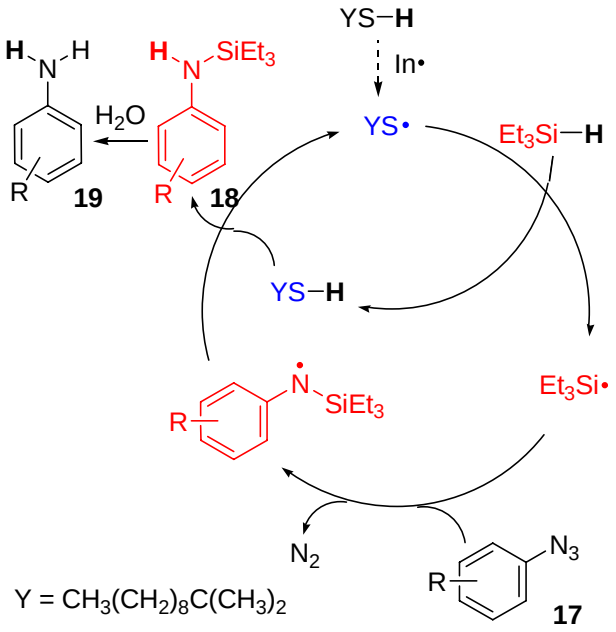
Scheme 7. *Polar effects in H-abstraction reactions.*

The PRC principle consists of replacing a direct H-abstraction reaction – that is slow because of unfavorable polar effects – by a two-step process, with an overall lower activation barrier, characterised by a sequence of two reactions each involving a radical/substrate couple with inverse polarity (*Scheme 8*).



Scheme 8. *The Polarity Reversal Catalysis principle.*

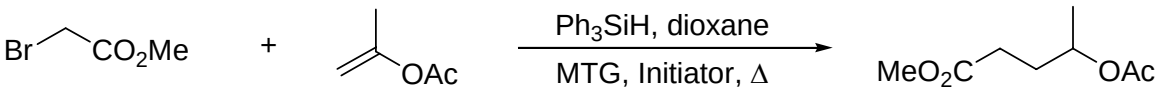
An example of PRC is the radical reduction of aromatic azides **17** to amines **19** carried out with Et_3SiH and *tert*-dodecanethiol as catalyst, realised by Spagnolo and co-workers[32] and shown in *Scheme 9*.



Scheme 9. *Reduction of aromatic azides with Et_3SiH using PRC.*

An important feature of this method is that it entails use of a 'normal' silane, e.g. a silane with a relatively strong Si-H bond, because the chain propagation is assured by the presence of the thiol (Y-SH) as a hydrogen donor (to the *N*-centered radical) and the thiyl radical (YS•) as a hydrogen abstractor (from the silane).

Another interesting example of a thiol/silane couple used as a tin hydride substitute is the reductive alkylations of electron-rich alkenes. Reaction of bromoacetate **20** with olefin **21** using triphenylsilane (Ph_3SiH) and a catalytic amount of methylthioglycolate (MTG) in dioxane under radical conditions provided the addition product **22** in 75% yield (*Scheme 10*).[33]

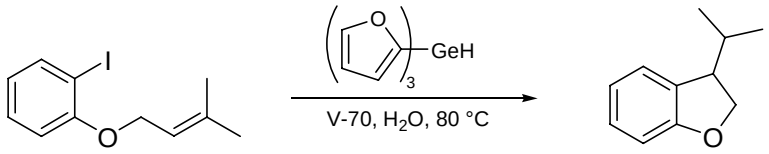


20 **21** **22**

Scheme 10**.** *Reductive alkylation of electron-rich alkenes using PRC.*

2.3 Other substitutes for stannanes: germanium-, indium-, and phosphorous hydrides, and isonitriles.

Besides silanes, many others classes of tin substitutes have been developed for radical processes, e.g. *germanium*-based reagents. In general, germanes are more reactive than silanes, but tributylgermanium hydride (Bu_3GeH) has a relatively strong Ge–H bond (≈ 340 kJ mol^{-1}), and therefore, on one hand, direct substrate reduction is usually not significant but, on the other hand, radical chains can be difficult to mantain. As in the Si-series, the H-donor ability of a germane depends on the other three substituents at the germanium atom. The most potent H-donor towards C-radicals to date is $(TMS)_3GeH$, whose rate constant for reduction of a primary C-radical is three times faster then TBTH.[34] Recently, Oshima used tri-(2-furyl)germane, besides its applications as a dehalogenating and a deoxygenating reagent, for radical cyclisation reactions. Good yields were achieved as well when the reaction was carried out with catalytic amounts of germanium and a stoichiometric co-reducing reagent. Moreover, water is tolerated as a solvent in reductive radical chain reactions with tri-(2-furyl)germane: V-70 [2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile] was used as a water soluble initiator in these reactions, as shown in *Scheme 11* for a typical radical 5-exo cyclisation.[35]



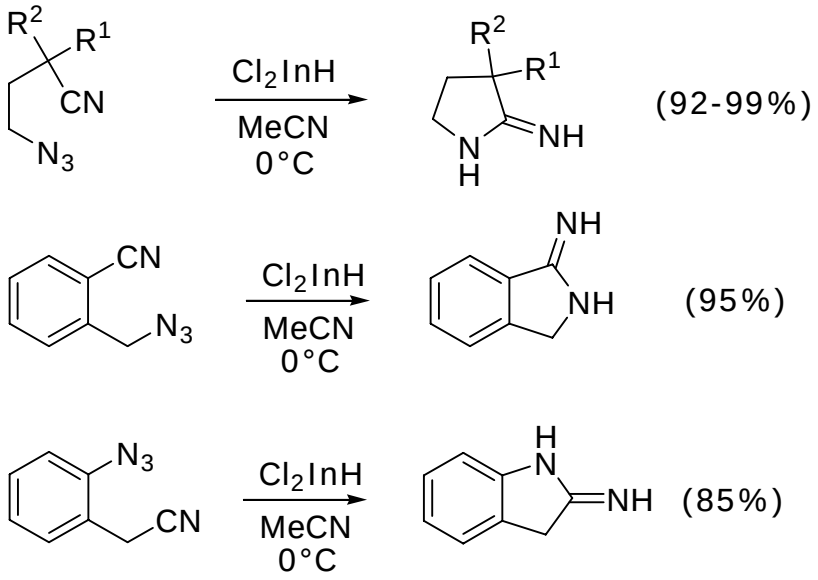
23 **24**

Scheme 11. *Reductive radical chain reaction using germanes.*

Also in this case, as shown above for silanes, it is possible to use the PRC system;[36] however, germanes are expensive and generally not very efficient, so that they are not used very often in preparative radical chemistry.

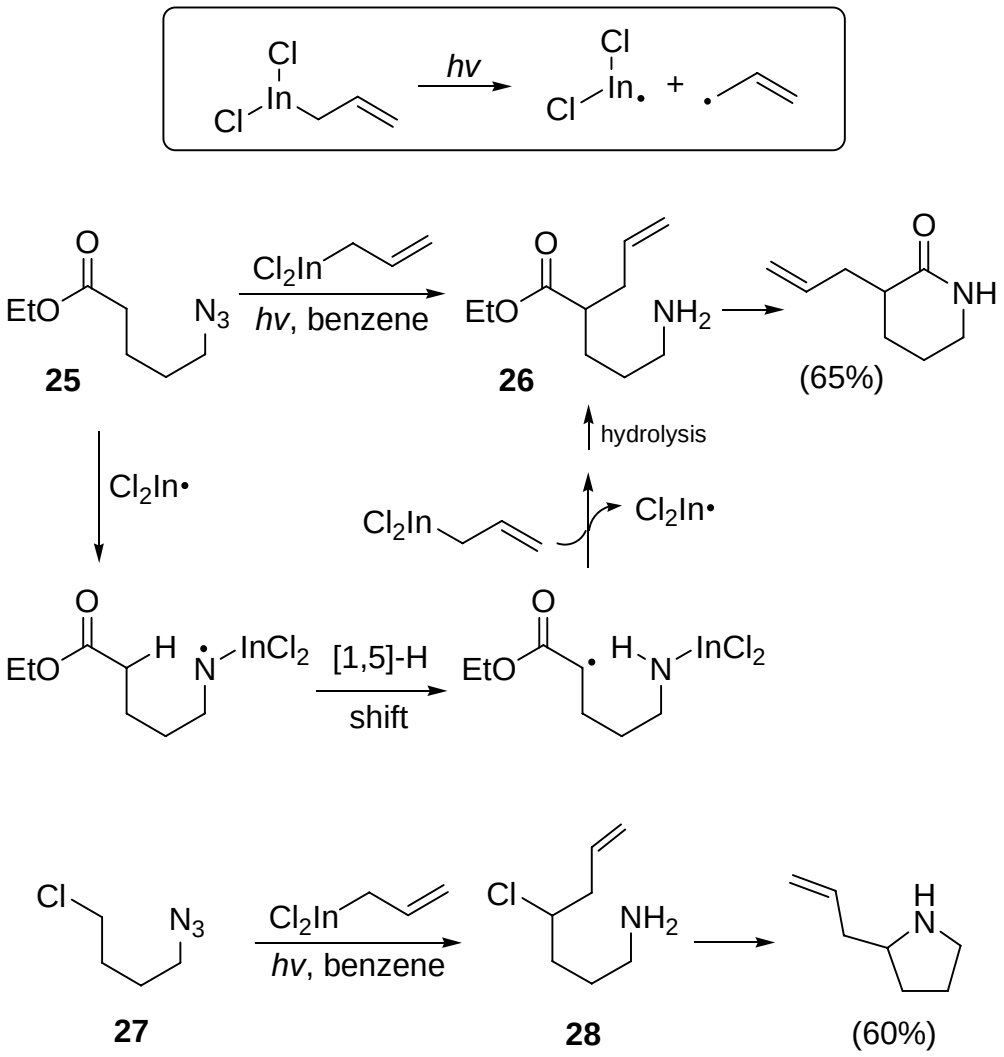
Highly rewarding results were instead provided by the use of *dichloroindium hydride* ($HInCl_2$), which, in recent years, has often replaced Bu_3SnH to promote 'green' radical chain reactions of various carbon compounds.[37,38] $HInCl_2$ is not commercially available, owing to its limited stability, but it is readily produced in situ from commercial indium trichloride ($InCl_3$) by several methods. Indium-hydride-mediated radical reactions can usually occur in the absence of any added radical initiator; however, it was found that the presence of triethylborane significantly enhanced the rates of the slower reactions. For example, the Spagnolo group has discovered that $HInCl_2$ can convert a variety of azidonitriles to cyclised pyrrolidin-2-imines in practically quantitative yields through

5-exo cyclization of presumable indium-aminyl radicals onto a cyano moiety (*Scheme 12*).[39] These amidine products are not very common, but recent studies have disclosed that they can act as potent, selective inhibitors of human NOS (nitric oxide synthases) and hence represent the foundation for potential therapeutic agents.[40] Their previous syntheses are rather complicated or involve cyclisations of aminonitriles at elevated temperatures and in modest yields.



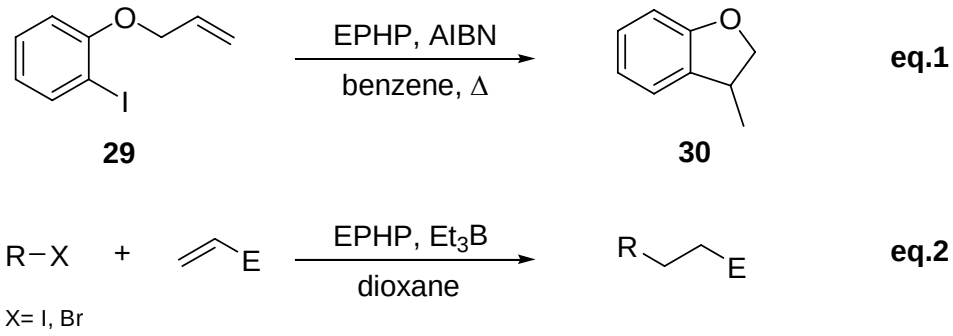
Scheme 12. *Radical synthesis of pyrrolidin-2-imines using dichloroindium hydride.*

Allylindium dichloride can be another tin-substitute reagent for radical reactions. Under photochemical conditions, allylindium dichloride undergoes fair homolytic fragmentation of the carbon-indium bond yielding allyl and dichloroindyl radicals that, in the presence, for example, of azido ester **25**, leads to efficient production of the allylated amine **26**, whose prompt condensation affords the corresponding allylated pyperidinone in good overall yield (*Scheme 13*). Similarly, chloroazide **27** is converted to the corresponding amine **28**, which eventually furnishes the allylated pyrrolidine to a comparable extent (*Scheme 13*).[41]



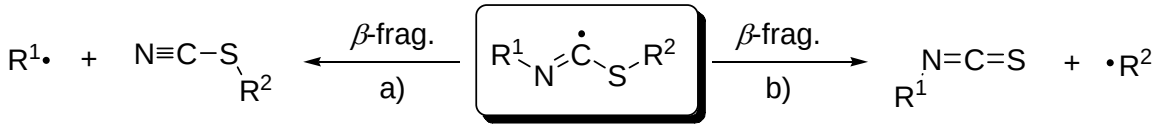
Scheme 13. *Radical allylation using allylindium dichloride.*

Hypophosphorous acid salts can be another alternative to stannanes. Murphy was the first to show that *N*-ethylpiperidine hypophosphite (EPHP) can be used as a reducing reagent in radical C─C bond forming reactions. For example, he reported the cyclisation of allyl ether **29** to benzofuran derivative **30** using EPHP, which is commercially available (*Scheme 14*, *eq.1*).[42] Recently, Jang studied intermolecular radical addition reactions using EPHP. Nucleophilic primary, secondary, and tertiary alkyl radicals, generated from the corresponding iodides, were allowed to react with various activated double bonds. Interestingly, only 1 equivalent of the olefin is necessary in order to achieve high yields. Alkyl bromides can also be used as radical precursors; however, higher temperatures are then necessary (*Scheme 14*, *eq.2*).[43]



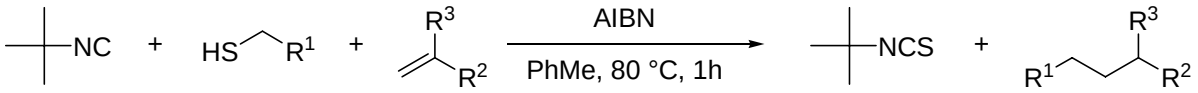
Scheme 14. *Radical cyclisation (eq.1) and intermolecular reductive addition (eq.2) with EPHP.*

Finally, also an isonitrile/thiol (R^1-NC/R^2-SH) couple can be used as a substitute for tin-based methodologies. Isonitriles are very efficient radical traps and, by addition of the sulfanyl radicals derived from thiols, are a source of *α*-thioimidoyl radicals; these intermediates can virtually suffer two competitive fragmentations: the former occurs through cleavage of the C-N bond, with formation of a thiocyanate (*pathway 'a', Scheme 15*), whereas the latter involves scission of the C-S bond and leads to an isothiocyanate (*pathway 'b', Scheme 15*).



Scheme 15. *The two possible β-fragmentation pathways of thioimidoyl radicals.*

Interestingly, Minozzi and co-workers[44] have shown that in *N,S*–dialkyl-substituted thioimidoyl radicals only fragmentation of the C–S bond, with formation of isothiocyanate and the alkyl radical (R^2•), is normally observed (*pathway 'b', Scheme 15*). This behaviour seems to be independent of the relative stability of the R^1• and R^2• radicals and even primary R^2• radicals can be smoothly released from variously *N*-substituted thioimidoyls (R^1 = Ar, *n*-Bu, *tert*-Bu), even at relatively low temperatures. This procedure is a good tin-free (and, in general, *metal-free*) methodology to conduct reductive radical chain (intra- and inter-molecular) reactions starting from isonitriles (as desulfuration reagents for generating the alkyl radicals) and thiols (as both the sources of the alkyl radicals and the reducing [H-donor] agents). When *tert*-butyl isonitrile is used, the by-product *tert*-butyl isothiocyanate can be easily removed from the reaction crude by distillation (rotating evaporator), thus providing a very straightforward workup procedure for purificating the reaction products.



Scheme 16. *Reductive radical chain reactions using thiols and isonitriles.*

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CHAPTER 3

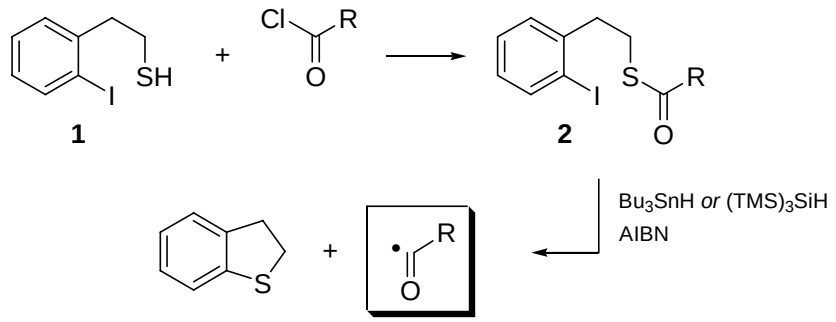
TIN-FREE GENERATION of ALKYL RADICALS from ALKYL 4-PENTYNYL-SULFIDES via HOMOLYTIC SUBSTITUTION at the SULFUR ATOM[1]

3.1 Intramolecular Homolytic Substitution at Sulfur

Radical reactions have become an important tool in synthetic organic chemistry.[2] Among many possible examples of applications of free-radical procedures to organic synthesis, inter- and intramolecular additions of nucleophilic acyl radicals [R-C(O)•] to multiple (mainly carbon-carbon) bonds represent a useful method for the production of cyclic and acyclic ketones.[3]

Up to the mid 80s, acyl aryl selenides were often the precursors of choice of acyl radicals owing to their ability to partecipate smoothly in chain sequences with tri-*n*-butylstannane and tris(trimethylsilyl)silane.[c,4,5] The replacement of acyl selenides by *thiol esters* would be attractive from a number of viewpoints, not least the enhanced stability and ease of preparation, but, unfortunately, thiol esters are normally very poor sources of acyl radicals, both photochemically and in conjuction with the standard stannanes and silanes[c,6]. This lack of reactivity may be however overcome by the inclusion of an additional propagation step in which an aryl radical brings about an *intramolecular homolytic substitution at sulfur*.

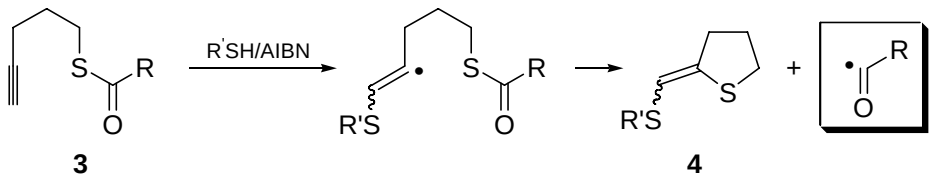
In fact, Crich has recently devised a brilliant strategy using iodothiol ester precursors of type **2**, available by reacting (2-iodophenyl)ethanethiol **1** with appropriate acyl chlorides. Compounds **2** smoothly release acyl radicals upon intramolecular attack at the sulfur by the aryl radicals that are initially formed by iodine atom abstraction by tributyltin or tris(trimethylsilyl)silyl radicals (*Scheme 1*).[7a]



Scheme 1. Generation of acyl radicals by intramolecular homolytic substitution at sulfur.

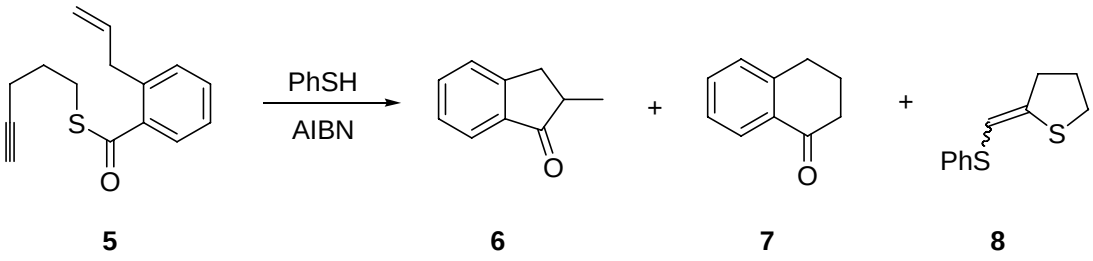
This strategy was subsequently extended to the use of arenediazonium salts as the alternative precursors to aryl radicals with the principal goal of avoiding the attendant problems of the undesirable use of toxic and/or expensive organotin or organosilane reagents.[7b]

During its own studies[8] on the intramolecular reactivity of acyl radicals towards the azido function, the Spagnolo group became interested in a search for other thiol ester compounds which might similarly act as valuable precursors to acyl radicals under reductive conditions but avoiding the need of stannanes or silanes. It thus occurred that, in principle, alkynylthiol esters of type **3** could represent attractive candidates in conjunction with standard thiols. Indeed, radical addition of a thiol to the terminal triple bond of **3** was expected to result in regioselective production of an intermediate sulfanylvinyl radical.[9] This intermediate, similarly to the aryl congener of Crich, was considered to be presumably capable of performing intramolecular substitution at sulfur to yield thiophene **4** with concomitant release of an acyl radical (*Scheme 2*).



Scheme 2. *Tin- (and silicon-) free protocol for the generation of acyl radicals using alkynylthiol esters.*

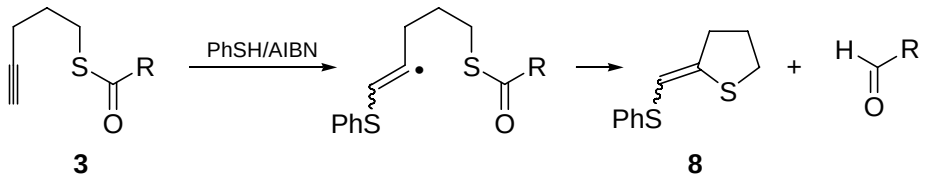
According to this protocol, it was possible to achieve acyl radical cyclisations onto suitably placed carbon-carbon double bonds: for example, thiol ester **5** led to isolate the cyclised indanone **6** and tetralone **7** in ca. 96:4 ratio and in 73% overall yield, along with comparable amounts of the anticipated dihydrothiophene **8** (as a mixture of *E*- and *Z*-isomers).[10]



Scheme 3. *Acyl radical cyclisations using alkynylthiol esters.*

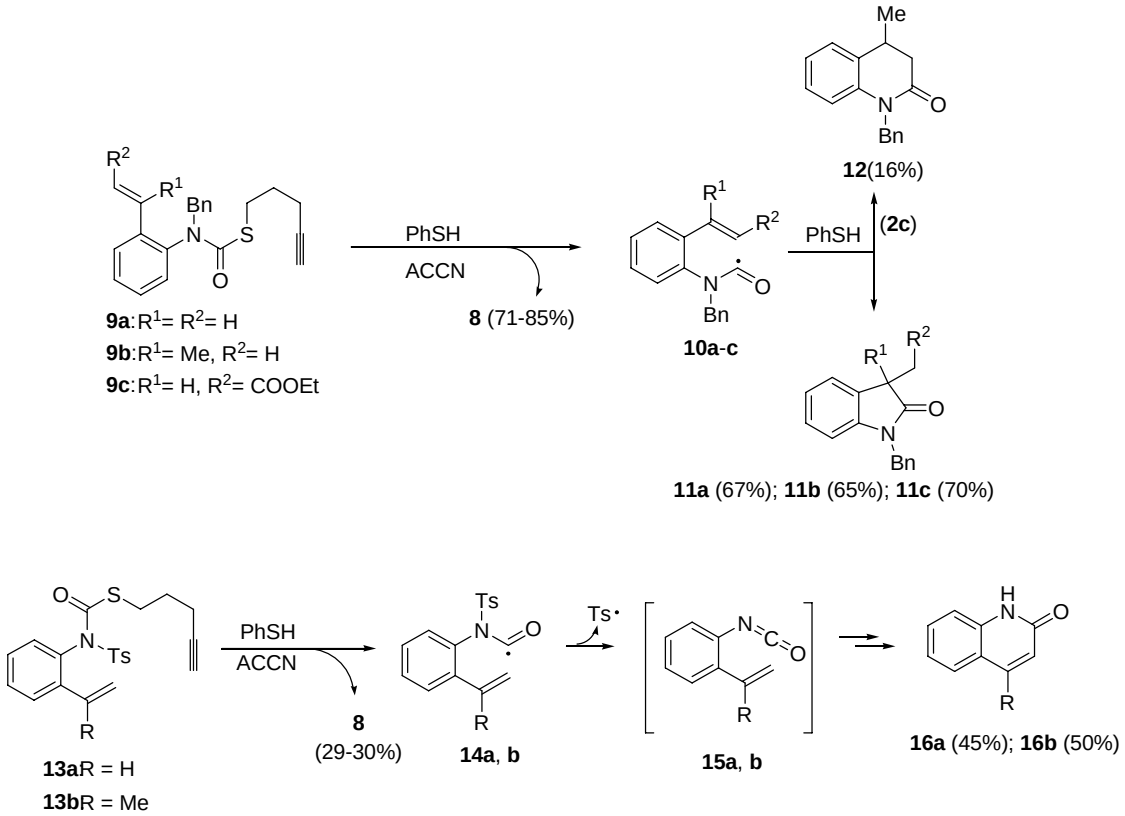
A subsequent study was undertaken with the aim of exploring the potential of this protocol as a novel radical entry for the reduction of carboxylic acids to aldehydes: the PhSH-mediated reaction of accessible pentynylthiol esters **3**, prepared by reacting the appropriate acyl chlorides with 4-pentyne-1-thiol, provides a valuable stannane/silane-free method for the production of aryl and primary alkyl aldehydes, also in the presence of substituents highly sensitive to reductive conditions. The method is of some utility also for vinylic and secondary aldehydes, but seems not

applicable to the tertiary ones because of preferential formation of the decarbonylated alkane; however, the tertiary bridgehead aldehydes can still be usefully produced (*Scheme 4*).[11]



Scheme 4. *Aldehydes generation by the alkynylthiol ester protocol.*

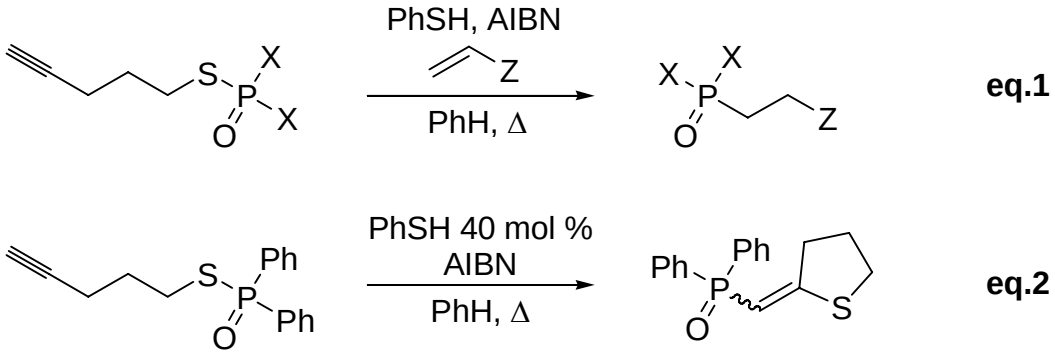
By adopting an analogous procedure with ACCN (1,1'-azo-bis-cyclohexane-1-carbonitrile) as initiator at 110 °C, *N*-benzyl- and *N*-tosyl-substituted pentynyl carbamothioates **9**,**13** were similarly found to release corresponding carbamoyl radicals in an efficient fashion.[12] For example, *N*-benzylcarbamoyl radicals **10** mostly gave indolones **11** through 5-*exo* cyclization onto internal alkenyl groups, whereas the *N*-tosylcarbamoyl counterparts **14** displayed a peculiar tendency to yield isocyanates **15** by *β*-elimination of tosyl radical (*Scheme 5*).



Scheme 5. *Carbamoyl radicals generation by the alkynylthiol ester protocol.*

Very recently, the same method has been suitably adopted by Malacria to achieve a novel, effective generation of *P*-centered radicals from *S*-pentynyl thiophosphonates.[13] Homolytic substitution of thiophosphine oxides, thiophosphonates, and thiodiaminophosphonates led to the corresponding radicals, which added smoothly onto olefins (*Scheme 6*, *eq. 1*). Moreover, the

efficient addition of *P*-centered radicals onto unsatured compounds led to uncover an unprecedented thiophosphinoylation reaction, in which both heteroatoms are introduced at both ends of the triple bond (*Scheme 6*, *eq. 2*).



Scheme 6. *Generation of P-centered radicals by the alkynylthiol esters protocol.*

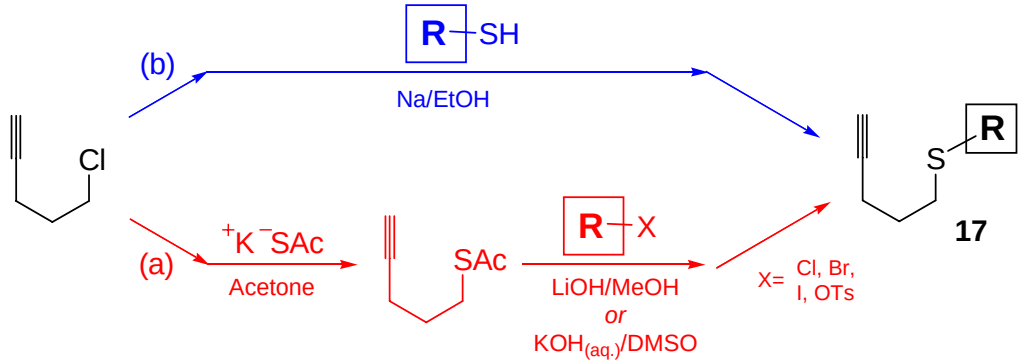
3.2 Results and discussion[1]

As seen in the earlier sections, although stannyl radicals are very attractive intermediates, their synthetic use is nevertheless discouraged by the known toxicity of organotin compounds and, additionally, the serious problems connected with full removal of toxic tin residues from the reaction mixtures. Therefore, alternative use of other 'green' radical methodologies is a crucial goal for synthetic applications of radical chemistry.

Therefore, with the aim of contributing to the growth of the 'no-tin' outlook, the present section will describe ***a novel methodology for generation of alkyl radicals*** and for development of reductive radical chain reactions starting from alkyl pentynyl sulfides and benzenethiol. This protocol is an extension of the previously described reactions of benzenethiol with *S*-4-pentynylthiol esters,[10] and I am going to show that not only are those reactions interesting for generation of stabilised acyl and P-centered radicals, but they can also be useful for the tin-free generation of unstabilised alkyl radicals via analogous homolytic substitution at the sulfur atom.

The intramolecular homolytic substitution of alkyl sulfides as a route to alkyl radicals is actually a long known process that has found considerable theoretical and synthetic attention. Recent studies have shown the precious utility of alkyl sulfides for generation of alkyl radicals, especially when other common radical precursors such as alkyl halides are inadequate. However, in the reported instances, not only were barely available alkyl haloaryl sulfides invariably employed, but, additionally, those radical precursors were often undesirably reacted with toxic or rather expensive stannane/silane reagents.[14,15] On the contrary, the procedure that will be described herein employs very easily accessible alkyl 4-pentynyl sulfides and thiophenol, which is rather inexpensive, definitely much less toxic than stannanes, and practically intert towards most functional groups.

The synthesis of the starting sulfides **17** can be indifferently accomplished in a very straightforward, convenient way by reacting either 4-pentyne-1-thiol acetate with alkyl chlorides, bromides, iodides, or tosylates (*pathway 'a', Scheme 7*) or 5-chloro-1-pentyne with aliphatic thiols (*pathway 'b', Scheme 7*).



Scheme 7. *Synthesis of the starting alkyl 4-pentynyl sulfides.*

5-Chloro-1-pentyne is a cheap, commercially available compound that is also a suitable starting material for the synthesis of 4-pentyne-1-thiol. This could indeed be obtained in just two steps by reaction of 5-chloro-1-pentyne with potassium thiolacetate in acetone, followed by treatment with sodium methoxide in methanol. This is an improved procedure with respect to that reported in the previous papers which started from 4-pentyn-1-ol.[16] However, there is no need to isolate the rather unstable thiol, since the aimed alkyl sulfides can be directly obtained in good to excellent yields by treating *S*-(4-pentynyl)thiolacetate with either lithium hydroxide in methanol or potassium hydroxide in aqueous DMSO in the presence of the alkylating reagent.[17] The former conditions are appropriate only for primary alkyl groups, whereas the latter can be used for both primary and secondary alkyls (both stabilised and unstabilised). Tertiary alkyl sulfides can be readily obtained from the corresponding thiols and 5-chloro-1-pentyne. The prepared sulfides **17** are reported in *Figure 1* together with their synthetic methods (*see Scheme 7, pathways 'a' and/or 'b';* yields for compounds **17e,g-i** are for the whole multistep synthesis – see the Experimental Section below).

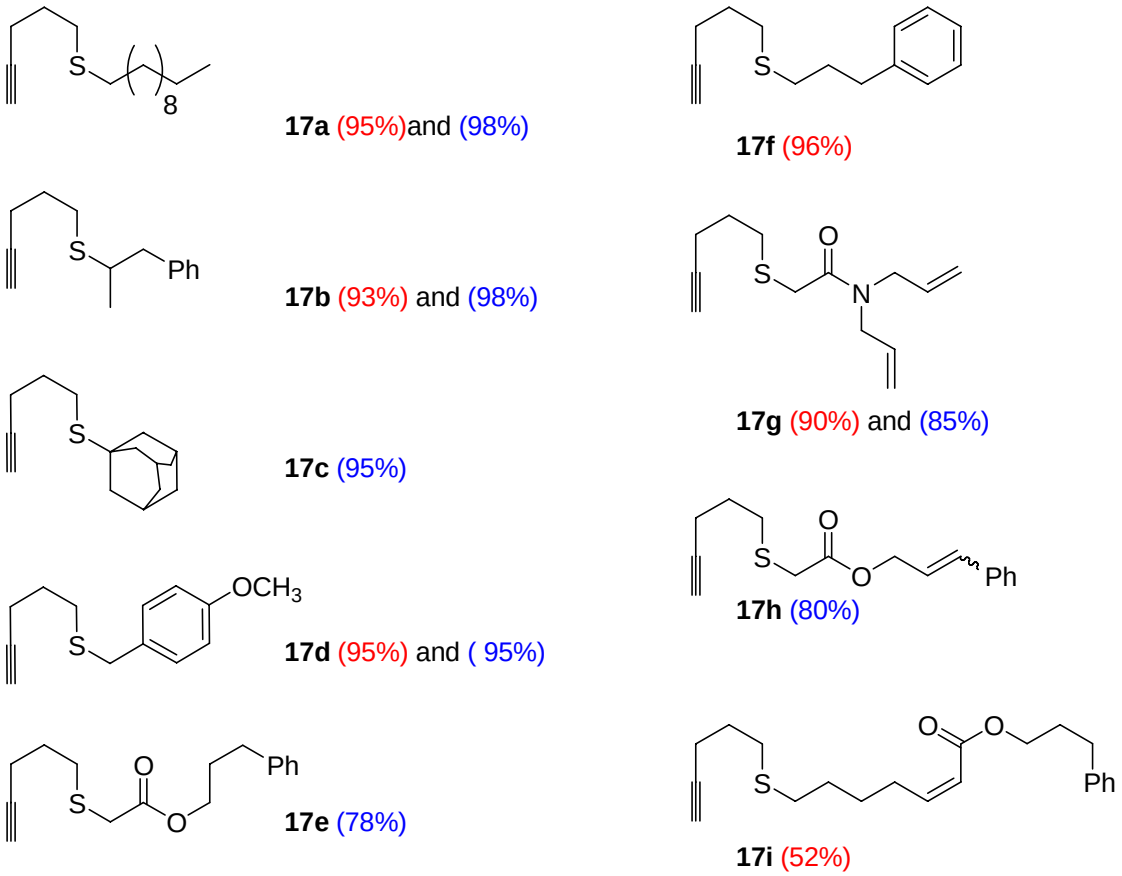


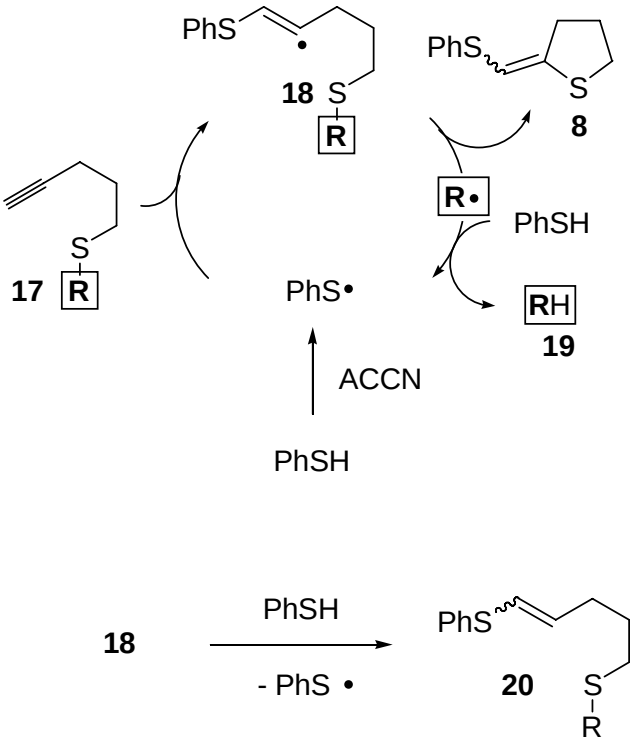
Figure 1. *Starting alkyl 4-pentynyl sulfides obtained from pathways 'a' and/or 'b'.*

The optmised reaction conditions for generation of alkyl radicals from sulfides **17** entail syringe pump addition (2-4 h) of a degassed toluene (13 mL) solution of PhSH (1.1 eq) and ACCN[18] (0.25 eq) to a boiling toluene (13 mL) solution of **17** (1 mmol) kept under a nitrogen atmosphere, followed by additional 1 h of reflux.

The reaction mechanism involves addition of benzenesulfanyl radical to the triple bond of sulfide **17** to give vinyl radical **18**, which gives rise to homolytic substitution at the sulfur atom to afford the aimed alkyl radical together with the thiophene derivative **8**[19] (*Scheme 8*). Hydrogen transfer from benzenethiol to the alkyl radical (or intermediates thereof, see below) yields alkane **19** and a new benzenesulfanyl radical that sustains the radical chain reaction. Under these optimized conditions by-products such as diphenyldisulfide and, above all, vinyl sulfide **20**, arising from competitive hydrogen transfer to vinyl radical **18**, were formed in trace amounts only (*Scheme 8*).

Very satisfactory results can be obtained also at 80 °C with AIBN as a radical initiatior, but only with stabilized radicals (*e.g.* **17e**). With other unstabilized ***R*** groups significant amounts of vinyl sulfides **20** were always obtained. Other solvents such as alcohols, acetonitrile, THF, or fluorobenzene gave much poorer results. Unsatisfactory outcomes were also achieved with other thiols that, on a theoretical basis, would possess more convenient hydrogen-donor properties: indeed, treatment of sulfide **17a** with *tert*-dodecanethiol or methyl thioglycolate ($HSCH_2COOMe$)

yielded, respectively, only unreacted starting material and a mixture of starting material and vinyl sulfide **20a**. The efficiency of the S_{Hi} mechanism at the sulfur atom is substantiated by the fact that *unstabilized alkyl radicals* can even be obtained by direct, *one-pot* treatment of the corresponding 4-pentynyl sulfides with benzenethiol, *i.e.* without syringe pump addition of the latter, although, under these conditions, significant amounts of vinyl sulfides **20** were also obtained.

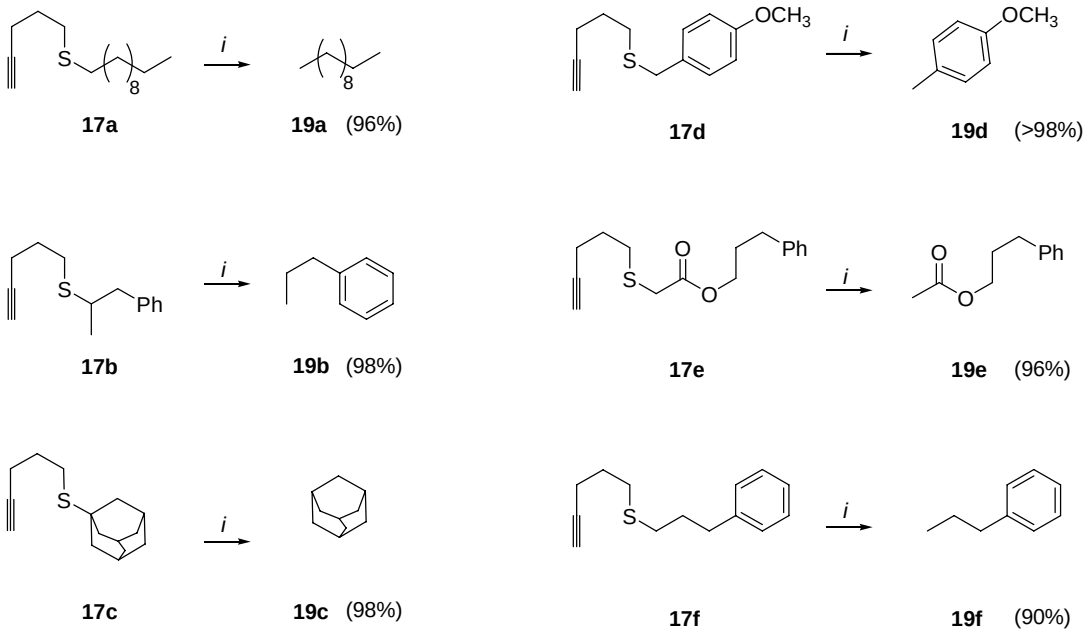


Scheme 8. *Mechanism of the radical chain for generating alkyl radicals from alkyl pentynyl sulfides.*

Sulfides **17a-f**, when treated under the standard conditions described above and after column chromatography, afforded practically quantitative yields of the corresponding alkanes **19a-f** (*Scheme 9*). As one can see, the reaction outcome is not influenced at all by the *nature* of the leaving R-group. Primary, unstabilised alkyl radicals are released with as the same efficiency as more substituted or stabilised radicals (such as benzyl **17d**), which, on the other hand, are capable of abstracting hydrogen from the thiol at a sufficient rate as to maintain the chain reaction. Furthermore, both electrophilic (**17e**) and nucleophilic (**17f**) radicals can be generated and reduced with comparable efficiencies.

Attempts were also made to generate α-oxy ($ROCH_2$-type) radicals (R = Ar, $^nC_8H_{17}$). The corresponding pentynyl sulfides can be easily synthesised but cannot be purified, due to their instability under all types of workup. Some reactions carried out on the crude sulfides yielded the expected reduction products accompanied by unreacted starting material and other unidentified side products.

Taking into account that sulfides **17** can be synthesised from both the corresponding halides, tosylates, or thiols (see *Scheme 7*), this procedure can be regarded as a very mild, efficient defunctionalization method of halogen-, hydroxyl-, and thiol-containing molecules. Radical dehalogenations and deoxygenations (Barton-McCombie reaction) are common techniques in organic synthesis; this is however a realm still strongly dominated by tin reagents and mild, and effective tin-free procedures to perform these transformations should always be welcome.[20] Furthermore, to date only one application of radical desulfuration of thiols has been reported.[21] The fact that benzenethiol is totally inert to those functional groups that are potentially sensitive to the stanane/silane reagents commonly used in radical reactions is certainly an additional important feature of the present protocol.



17a **19a** (96%) **17d** **19d** (>98%)

17b **19b** (98%) **17e** **19e** (96%)

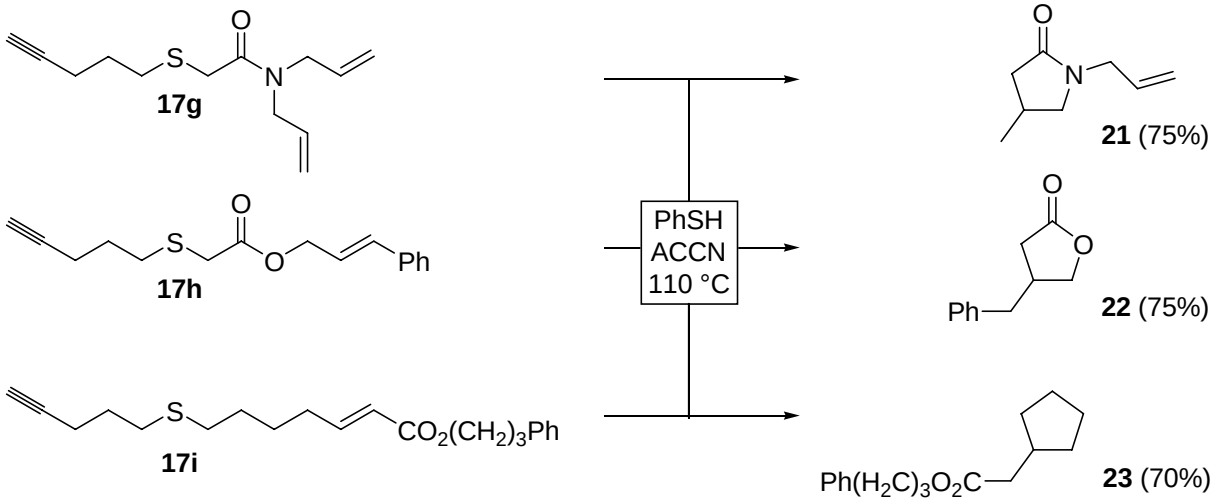
17c **19c** (98%) **17f** **19f** (90%)

i = PhSH / ACCN, 110 °C

Scheme 9. *Reduction of alkyl pentynyl sulfides to corresponding alkanes.*

Of course, one of the major breakthroughs of radical reactions in organic synthesis is the possibility to carry out C-C bond forming processes by trapping alkyl radicals prior to hydrogen abstraction, for instance by cyclization or intermolecular addition to olefins. Therefore, this methodology has been tested in 5-exo radical cyclizations and it has been found that it works very well, both with electrophilic and nucleophilic radicals.[22]

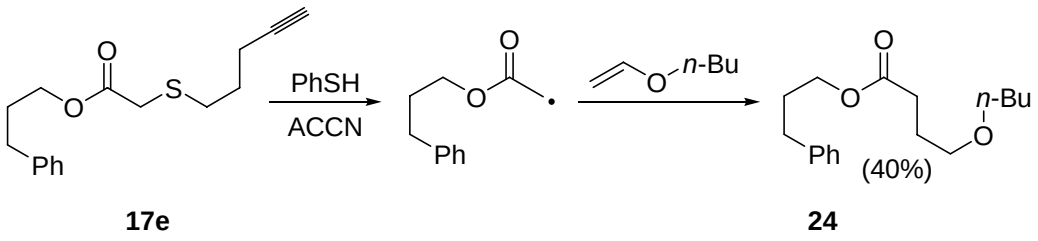
Indeed, the carbon radicals derived from sulfides **17g-h** gave smooth ring closure onto their electron-rich C-C double bonds to afford lactam **21** and lacton **22**, respectively, in good yields. Even more interestingly, the alkyl radical derived from **17i** gave rise to a very clean cyclisation onto the electron-poor acrylate moiety to give cyclopentane **23** in 70% yield (*Scheme 10*).



Scheme 10. *Cyclization products of alkyl radicals generated from alkyl pentynyl sulfides.*

The latter is a noteworthy result at least for two reasons. First, the alkyl radical arising from **17i** is nucleophilic in nature and should therefore be trapped very quickly by the thiol: however, under these conditions, this reaction is notably slower than cyclisation and no traces of the product of premature reduction of the alkyl radical (**19i**) were observed. Second, this kind of alkyl radical is not accessible by desulfurisation of the corresponding thiol, since the latter immediately cyclises (nucleophylically) onto the C-C double bond upon every attempt of synthesis: this means that this kind of cyclization is not available by our previous tin-free procedure,[21] and the present methodology therefore represents a suitable complement of that.

Attempts of intermolecular addition of alkyl radicals to olefins were also carried out. Sulfide **17e** was indeed reacted with *n*-butyl vinyl ether (1-10 eq) under the standard conditions. Although the resulting mixtures were always contaminated by some by-products formed in variable amounts, the reaction proved again to be synthetically useful, since, in the presence of 5 eq of alkene, it afforded the addition product **24** in 40% yield (*Scheme 11*).



Scheme 11. *Intermolecular addition of alkyl radicals to olefins.*

In conclusion, it has been shown that homolytic substitution at the sulfur atom of vinyl radicals **18**, obtained by benzenesulfanyl radical addition to alkyl 4-pentynyl sulfides **17**, is a very effective

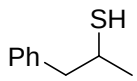
tool for the generation of all types of alkyl radicals. Owing to the accessibility of the starting materials, the low cost and the toxicity properties of benzenethiol, and its compatibility with most functional groups, this procedure can be an appealing substitute for many stannane/silane-mediated radical reactions and a valid complement to previous tin-free methodologies for generation of analogous radicals.

3.3 Experimental section

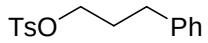
General Remarks.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions using tetramethylsilane as internal standard. Coupling constants are given in Hz. IR spectra were recorded in $CHCl_3$ solutions or as liquid films. Mass spectra were usually recorded using a ThermoFisher – Focus DSQ system. Column chromatography was performed on ICN silica gel (63–200, 60 Å) by gradual elution with *n*-hexane / diethyl ether. All the following chemicals were purchased from Aldrich and used without further purification: 1-bromododecane **26a**, 1-(2-bromopropyl)benzene **26b**, 1-(bromomethyl)-4-methoxybenzene **26d**, dodecane-1-thiol **27a**, 1-adamantanethiol **27c**, (4-methoxyphenyl)methanethiol **27d**, 1-(3-chloropropyl)benzene **33a**, 1-(3-bromopropyl)benzene **33b**, 1-(3-iodopropyl)benzene **33c**, 3-phenylpropan-1-ol, 2-bromoacetyl bromide **34**, 5-bromopentyl acetate, 5-chloropent-1-yne, thiophenol, 1,1'-azobis(cyclohexanecarbonitrile) (ACCN).

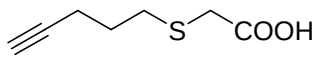
Precursors.



1-Phenylpropane-2-thiol (27b).[23] Thiol **27b** was prepared according to the previously reported procedure. MS: *m/z* (rel. inten.) 152 (23), 118 (4), 92 (100), 91 (89), 65 (19), 61 (75).

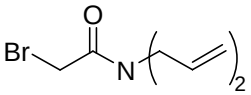


3-Phenylpropyl 4-methylbenzenesulfonate (33d).[24] The target compound was prepared starting from 3-phenylpropan-1-ol according to the previously reported procedure. MS: *m/z* (rel. inten.) 290 (1), 119 (12), 118 (96), 117 (100), 91 (46), 65 (20).



2-(Pent-4-ynylthio)acetic acid (28). Potassium hydroxide (2.2 mmol) was added at 0 °C to a solution of 2-mercaptoacetic acid (1 mmol) in degassed methanol (5 mL). After 20 min 5-chloropent-1-yne (1.1 mmol) was added. The resulting mixture was then heated under nitrogen between 40 °C and 50 °C for 2 h. The solution was subsequently evaporated under reduced pressure, the residue was dissolved in water, and the solution acidified with hydrochloric acid. The solution was extracted with dichloromethane and then dried over $MgSO_4$. The crude product was purified by column chromatography on silica gel using *n*-hexane / diethyl ether as eluant to give the target compound **13** in almost quantitative yield. Oil; IR (neat) ν_{max} (cm^{-1}) 3500, 3291, 2936, 1718, 1426; ^{1}H NMR (400 MHz) δ 1.84 (2 H, m) 1.98 (1 H, t J_t = 2.7), 2.34 (2 H, td, J_t = 7.0, J_d = 2.7), 2.8 (2 H, m), 3.27 (2 H, s), 8.41 (1 H, bs); ^{13}C

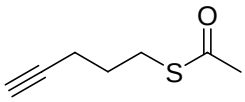
NMR (100 MHz) δ 17.3 (CH_2), 27.5, 31.5, 33.3, 69.2 (C), 83.1, 176.4 (C); MS: *m/z* (rel. inten.) 158 (24), 113 (45), 99 (100), 65 (95). HRMS calcd for $C_7H_{10}O_2S$: 158.0402; found: 158.0396.



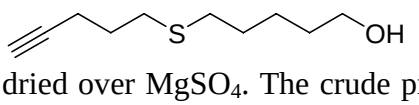
***N*,*N*-Diallyl-2-bromoacetamide (29)**.[25] Amide **29** was prepared according to the previously reported procedure. ^{1}H NMR (300 MHz) δ 3.87 (2 H, s), 4.68 (4 H, dt, J_d = 5.8, J_t = 1.3), 5.29 (2 H, dq, J_d = 10.4, J_q = 1.3), 5.38 (2 H, dq, J_d = 17.1, J_q = 1.3), 5.93 (2 H, ddt, J_{d1} = 17.1, J_{d2} = 10.4, J_q = 5.8).

***S*-Pent-4-ynyl ethanethioate (25)**.[26] Thioester **25** was prepared according to the previously reported procedure. ^{1}H NMR (400 MHz) δ 1.81 (2 H, quint, J_q = 7.1), 1.98 (1 H, t, J_t = 2.6), 2.28 (2 H, td, J_t = 7.0, J_d = 2.6), 2.34 (3 H, s), 2.98 (2 H, t, J_t = 7.0).

5-(Pent-4-ynylthio)pentan-1-ol (30). *S*-Pent-4-ynyl ethanethioate **10** (1.0 mmol) was added at 0 °C to a solution of potassium hydroxide (2.2 mmol) in degassed methanol (5 mL). After 10 min, 5-

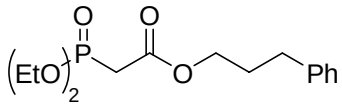


bromopentyl acetate (1.1 mmol) was added. The resulting solution was stirred overnight under nitrogen at room temperature and then additionally stirred for 2 h at 50 °C. The solution was then evaporated under reduced pressure, the residue was dissolved in water, and the solution acidified with hydrochloric acid. The solution was extracted with dichloromethane and then dried over $MgSO_4$. The crude product was purified by column chromatography on silica gel using *n*-hexane / diethyl ether as eluant to give the target compound **15** in 80% yield. Oil; IR ($CHCl_3$) ν_{max} (cm^{-1}) 3454, 3308, 2939, 2862; ^{1}H NMR (400 MHz) δ 1.36 (1 H, bs), 1.43-1.51 (2 H, m), 1.55-1.67 (4 H, m), 1.76-1.84 (2 H, m), 1.97 (1 H, t, J_t = 2.7), 2.33 (2 H, td, J_t = 7.0, J_d = 2.7), 2.53 (2 H, t, J_t = 7.5), 2.63 (2 H, t, J_t = 7.0), 3.65 (2 H, t, J_t = 6.5); ^{13}C NMR (100 MHz) δ 17.5 (CH_2), 25.0 (CH_2), 28.3 (CH_2), 29.4 (CH_2), 30.8 (CH_2), 32.0 (CH_2), 32.3 (CH_2), 62.7 (CH_2), 68.4, 83.5 (C); MS: *m/z* (rel. inten.) 113 (M^+ – 73, 6), 101 (11), 100 (100), 67 (18). Anal. calcd for $C_{10}H_{18}OS$: C, 64.46; H, 9.74. Found: C, 64.21; H, 9.70.



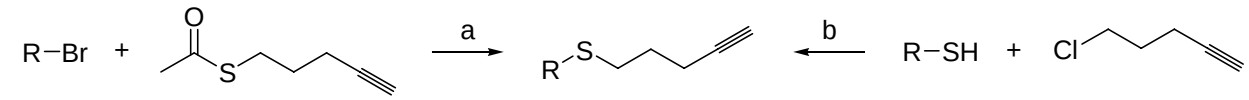
5-(Pent-4-ynylthio)pentanal (31). A dichloromethane (DCM, 2.5 mL) solution of DMSO (11.0 mmol) was added slowly at –78 °C to a DCM (10 mL) solution of oxalyl chloride (6.5 mmol). After stirring for 15 min, a DCM (5 mL) solution of 5-(pent-4-ynylthio)pentan-1-ol **15** (5 mmol) was added to the above solution. After stirring at –78 °C for 1 h, 11 mmol of TEA were added at –78 °C. The reaction mixture was slowly warmed to room temperature, quenched with saturated aqueous ammonium chloride, extracted with

DCM, dried over magnesium sulfate, and concentrated. Purification by column chromatography on silica gel (*n*-hexane / diethyl ether) afforded 4.2 mmol (82%) of the desired aldehyde **16** as a pale yellow oil. IR (neat) ν_{max} (cm^{-1}) 3290, 2938, 2862, 2725, 1722, 1432; ^{1}H NMR (400 MHz) δ 1.59-1.68 (2 H, m), 1.70-1.84 (4 H, m), 1.97 (1 H, t, J_t = 2.7), 2.33 (2 H, td, J_t = 7.0, J_d = 2.7), 2.47 (2 H, td, J_t = 7.2, J_d = 1.7), 2.54 (2 H, t, J_t = 7.2), 2.63 (2 H, t, J_t = 7.2), 9.78 (1 H, t, J_t = 1.7); ^{13}C NMR (100 MHz) δ 17.4 (CH_2), 21.1 (CH_2), 28.2 (CH_2), 28.9 (CH_2), 30.8 (CH_2), 31.6 (CH_2), 43.3 (CH_2), 68.9, 83.4 (C), 202.1; MS: *m/z* (rel. inten.) 155 (M^+ – 29, 3), 127 (4), 113 (9), 100 (100), 85 (9), 67 (15). Anal. calcd for $C_{10}H_{16}OS$: C, 65.17; H, 8.75. Found: C, 65.11; H, 8.72.



3-Phenyl-propyl (diethylphosphono)acetate (34). Diethylphosphono-acetic acid (2.2 mL of 1 M solution in DCM, 2.2 mmol) and DCC (2.2 mL of a 1 M solution in DCM, 2.2 mmol) were added to a solution of 3-phenylpropan-1-ol (2 mmol) in DCM (6 mL). The reaction mixture was stirred for 15 min, filtered through a sintered glass, and evaporated. The residue was purified by flash chromatography (50% to 70% ethyl acetate / petroleum ether) to give **19** as a colorless liquid (90%). IR (neat) ν_{max} (cm^{-1}) 2984, 2933, 1736, 1271, 1117, 1052, 1025, 971; ^{1}H NMR (400 MHz) δ 1.35 (6 H, td, J_t = 7.1, J_d = 0.5), 1.95-2.02 (2 H, m), 2.68-2.74 (2 H, m), 2.97 (2 H, d, $^{2}J_{P\text{-}H}$ = 21.3), 4.14-4.22 (6 H, m), 7.17-7.22 (3 H, m), 7.26-7.31 (2 H, m); ^{13}C NMR (100 MHz) δ 16.30 (d, $^{3}J_{P\text{-}C}$ = 5.6), 30.05 (CH_2), 31.93 (CH_2), 34.32 (CH_2, d, $^{1}J_{P\text{-}C}$ = 134), 62.62 (CH_2, d, $^{2}J_{P\text{-}C}$ = 6.5), 64.80 (CH_2), 126.01, 128.37, 128.42, 140.98 (C), 165.80 (C, d, $^{2}J_{P\text{-}C}$ = 5.9); MS: *m/z* (rel. inten.) 314 (2), 197 (8), 179 (14), 151 (11), 119 (12), 118 (100), 117 (77), 91 (22). Anal. calcd for $C_{15}H_{23}O_5P$: C, 57.32; H, 7.38. Found: C, 57.22; H, 7.36.

General procedure for the synthesis of sulfides 17a,b,c,d,f.



26 a,**b**,**d** **25** **17 a**,**b**,**c**,**d** **27 a**,**b**,**c**,**d**

Method A.

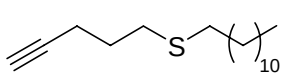
To a degassed solution of KOH (2.2 mmol) in MeOH (5 mL) was added *S*-pent-4-ynyl ethanethioate **25** (1.1 mmol) and the resulting mixture was stirred at 0 °C for 15 min under a nitrogen atmosphere. The proper bromide **26** was then added and the mixture was stirred for 2 h at 50 °C. The solution was then evaporated under reduced pressure, the residue was dissolved in water and the solution acidified with hydrochloric acid. The solution was extracted with dichloromethane and then dried over $MgSO_4$. Purification by column chromatography on silica gel (*n*-hexane / diethyl ether) afforded the desired sulfide **17** in good yield.

This method was applied to the preparation of sulfides **17a**,**b**,**d** starting from the corresponding bromides **26a**,**b**,**d**.

Method B.

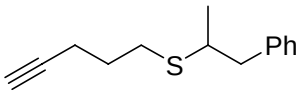
To a degassed solution of KOH (2.2 mmol) in MeOH (5 mL) was added the proper thiol **27** followed (after 15 min) by 5-chloropent-1-yne (1.1 mmol). The resulting mixture was stirred for 2 h at 50 °C. The solution was then evaporated under reduced pressure, the residue was dissolved in water and the solution acidified with hydrochloric acid. The solution was extracted with dichloromethane and then dried over $MgSO_4$. Purification by column chromatography on silica gel (*n*-hexane / diethyl ether) afforded the desired sulfide **17** in good yield.

This method was applied to the preparation of sulfides **17a-d** starting from the corresponding thiols **27a-d**.

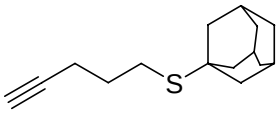


Dodecyl(pent-4-ynyl)sulfane (17a). Colorless liquid (Method A: 95% yield; Method B: 98% yield); IR (neat) ν_{max} (cm^{-1}) 3313, 2924, 2853, 1466; ^1H NMR (400 MHz) δ 0.88 (3 H, t, J = 7.1), 1.21-1.42 (18 H, m), 1.54-1.62 (2 H,m), 1.80 (2 H, m), 1.96 (1 H, t, J = 2.7), 2.32 (2 H, td, J_t = 7.0, J_d = 2.6), 2.51 (2 H, m), 2.62 (2 H, m); ^{13}C NMR (100 MHz) δ 14.1, 17.5 (CH_2), 22.7 (CH_2), 28.3 (CH_2), 28.9 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29,58 (CH_2), 29.61 (CH_2), 29.63 (CH_2), 29.67 (CH_2), 30.8 (CH_2), 31.9 (CH_2), 32.1 (CH_2),

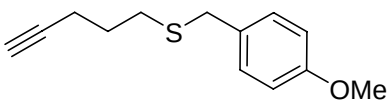
68.8, 83.6 (C); MS: *m/z* (rel. inten.) 155 (M^+ – 113, 4), 113 (8), 101 (10), 100 (100), 67 (6), 55 (10). Anal. calcd for $C_{17}H_{32}S$: C, 76.05; H, 12.01. Found: C, 75.94; H, 12.00.



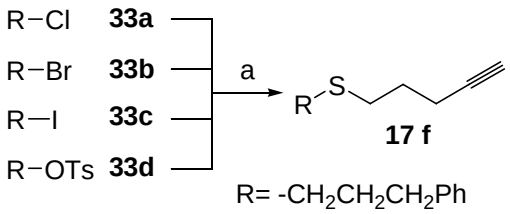
Pent-4-ynyl(1-phenylpropan-2-yl)sulfane (17b). Colorless oil (Method A: 93% yield; Method B: 98% yield); IR (neat) ν_{max} (cm^{-1}) 3296, 3027, 2958, 2924, 1453; ^1H NMR (400 MHz) δ 1.23 (3 H, d, J_d = 6.6), 1.75-1.82 (2 H, m), 1.97 (1 H, t, J_t = 2.7), 2.30 (2 H, td, J_t = 7.0, J_d = 2.7), 2.64 (3 H, t, J_t = 7.3), 2.96-3.02 (2 H, m), 7.16-7.24 (3 H, m), 7.27-7.32 (2 H, m); ^{13}C NMR (100 MHz) δ 17.6 (CH_2), 20.7, 28.5 (CH_2), 29.4 (CH_2), 41.4 (CH_2), 43.8, 68.9, 83.6 (C), 126.3, 128.3, 129.2, 139.5 (C); MS: *m/z* (rel. inten.) 218 (2), 217 (9), 176 (49), 127 (48), 100 (68), 93 (48), 91 (100), 77 (36), 65 (34). HRMS calcd for $C_{14}H_{18}S$: 218.1129; found: 218.1121.



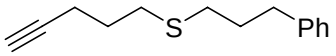
Pent-4-ynyl(1-adamantyl)sulfane (17c). Colorless oil (Method B: 95% yield); IR (neat) ν_{max} (cm^{-1}) 3308, 2904, 2849, 1449; ^1H NMR (400 MHz) δ 1.65-1.73 (6 H, m), 1.78 (2 H, m), 1.87 (6 H, bd, J_d = 2.6), 1.97 (1 H, t, J_t = 2.6), 2.04 (3 H, bs), 2.32 (2 H, td, J_t = 6.9, J_d = 2.6), 2.63 (2 H, t, J_t = 7.5); ^{13}C NMR (150 MHz) δ 17.8 (CH_2), 24.5 (CH_2), 29.1 (CH_2), 29.7, 36.3 (CH_2), 43.6 (CH_2), 44.3 (C), 68.8, 83.7(C); MS: *m/z* (rel. inten.) 234 (1), 206 (62), 135 (100). Anal. calcd for $C_{15}H_{22}S$: C, 76.86; H, 9.46. Found: C, 76.58; H, 9.44.



(4-Methoxyphenyl)(pent-4-ynyl)sulfane (17d). Colorless oil (Method A: 95% yield; Method B: 95% yield); IR (neat) ν_{max} (cm^{-1}) 3292, 2934, 2835, 1610, 1510, 1439, 1249; ^1H NMR (400 MHz) δ 1.76 (2 H, m), 1.94 (1 H, t, J_t = 2.6), 2.28 (2 H, td, J_t = 6.9, J_d = 2.7), 2.51 (2 H, t, J_t = 7.1), 3.66 (2 H, s), 3.79 (3 H, s), 6.84 (part of AA'BB' system, 2 H, J = 8.8), 7.22 (part of AA'BB' system, 2 H, J = 8.8); ^{13}C NMR (100 MHz) δ 17.5 (CH_2), 28.0 (CH_2), 30.0 (CH_2), 35.5 (CH_2), 55.2, 68.8, 83.5 (C), 113.8, 129.8, 130.3 (C), 158.6 (C); MS: *m/z* (rel. inten.) 220 (21), 173 (15), 121 (100). HRMS calcd for $C_{13}H_{16}OS$: 220.0922; found: 220.0912.

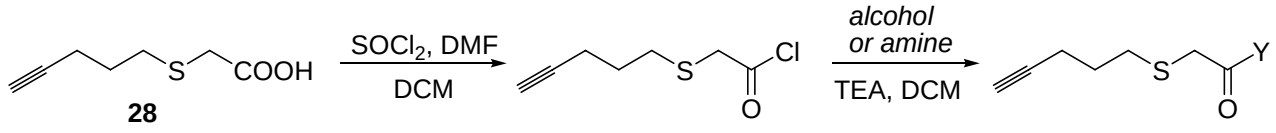


Sulfide **17f** was prepared (by Method A) starting from the corresponding chlorinated, brominated, iodinated, and tosilated alcane (**33a-d**) in order to test the versatility of the procedure. In all cases, the yield of the target sulfide after chromatographic purification (silica gel, *n*-hexane / ethyl ether 95:5 v/v) was almost quantitative.

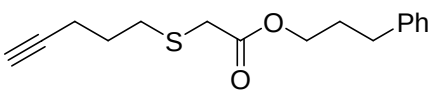


(Pent-4-ynyl)(3-phenylpropyl)sulfane (17f). Colorless oil (Method A: >96% yield); IR ($CDCl_3$) ν_{max} (cm^{-1}) 3308, 2939, 2858, 1496, 1453; ^{1}H NMR (400 MHz) δ 1.78 (2 H, m), 1.91 (2 H, m), 1.96 (1 H, t, J_t = 2.6), 2.32 (2 H, td, J_t = 7.0, J_d = 2.6), 2.53 (2 H, dd, J_{d1} = 7.2, J_{d2} = 7.4), 2.62 (2 H, dd, J_{d1} = 7.0, J_{d2} = 7.4), 2.72 (2 H, dd, J_{d1} = 7.2, J_{d2} = 7.7), 7.16-7.21 (3 H, m), 7.26-7.30 (2 H, m); ^{13}C NMR (100 MHz) δ 17.5 (CH_2), 28.3 (CH_2), 30.8 (CH_2), 31.1 (CH_2), 31.4 (CH_2), 34.8 (CH_2), 68.9, 83.5 (C), 125.9, 128.3, 128.4, 141.5 (C); MS: *m/z* (rel. inten.) 218 (3), 176 (6), 118 (43), 117 (84), 100 (100), 91 (37). HRMS calcd for $C_{14}H_{18}S$: 218.1129; found: 218.1121.

The preparation of sulfides **18e**,**g**,**h** was achieved by coupling the starting 2-(pent-4-ynylthio)acetic acid **28**, via the intermediate acyl chloride, with the corresponding alcohol or amine.

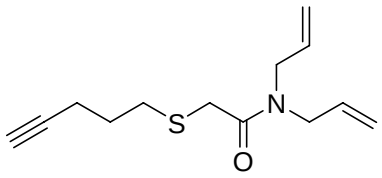


Y = -$OCH_2CH_2CH_2Ph$, -OCH_2CH=$CHPh$, -$N(CH_2CH$=$CH_2)_2$

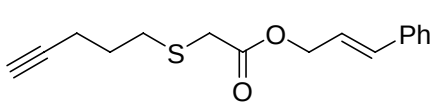


3-Phenylpropyl 2-(pent-4-ynylthio)acetate (17e). An anhydrous DCM (10 mL) solution of 2-(pent-4-ynylthio)acetic acid **28** (2 mmol), freshly distilled $SOCl_2$ (2.2 mmol), and two drops of dry DMF was stirred overnight at room temperature under a nitrogen atmosphere. The intermediate *S*-pent-4-ynyl chloromethanethioate was directly added – using a cannula – to a solution of 3-phenylpropan-1-ol (2.2 mmol) and TEA (2.4 mmol) in DCM (10 mL). The resulting solution was stirred for additional 2 h, then water was added and the mixture was extracted twice with DCM. The combined organic phases were dried over $MgSO_4$. Purification by column chromatography on silica gel (*n*-hexane / diethyl ether) afforded 1.55 mmol (78%) of the target sulfide **17e** as a colorless oil. IR (neat) ν_{max} (cm^{-1}) 3294, 2939, 1738, 1487; ^{1}H NMR (400 MHz) δ 1.84 (2 H, m), 1.95 (1 H, t, J_t = 2.7), 1.95-2.05 (2 H, m), 2.33 (2 H, td, J_t = 6.9, J_d = 2.7), 2.68-2.73 (2 H, m), 2.75-2.79 (2 H, m), 3.21 (2 H, s), 4.16 (2 H, t, J_t = 6.5), 7.16-7.22 (3 H, m), 7.26-7.31 (2 H, m); ^{13}C NMR (100 MHz) δ 17.4 (CH_2), 27.7 (CH_2), 30.1 (CH_2), 31.5 (CH_2), 32.1 (CH_2), 33.6 (CH_2), 64.6 (CH_2), 69.1 (C), 83.2, 126.0,

128.4, 128.5, 141.0 (C), 170.5 (C); MS: *m/z* (rel. inten.) 276 (2), 158 (3), 119 (13), 118 (100), 99 (9), 91 (84). HRMS calcd for $C_{16}H_{20}O_2S$: 276.1184; found: 276.1178.

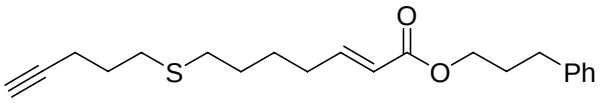


***N,N*-Diallyl-2-(pent-4-ynylthio)acetamide (17g)**. An anhydrous DCM solution (10 mL) of 2-(pent-4-ynylthio)acetic acid **28** (2 mmol), freshly distilled $SOCl_2$ (2.2 mmol), and two drops of dry DMF was stirred overnight at room temperature under nitrogen. The intermediate S-pent-4-ynyl chloromethanethioate was directly added – using a cannula – to a solution of diallylamine (2.2 mmol) and TEA (2.4 mmol) in DCM (10 mL). The resulting solution was stirred for additional 2 h, then water was added and the mixture was extracted twice with DCM. The combined organic phases were dried over $MgSO_4$. Purification by column chromatography on silica gel (*n*-hexane / diethyl ether) afforded 1.7 mmol (85%) of the target sulfide **1g** as a pale yellow oil. IR (neat) ν_{max} (cm^{-1}) 3299, 3082, 2931, 1638, 1444, 1442, 927; ^{1}H NMR (400 MHz) δ 1.86 (2 H, m), 1.96 (1 H, t, J_t = 2.6), 2.32 (2 H, td, J_t = 6.9, J_d = 2.6), 2.78 (2 H, t, J_t = 7.1), 3.27 (2 H, s), 3.96-4.01 (4 H, m), 5.13-5.24 (4 H, m), 5.71-5.86 (2 H, m); ^{13}C NMR (100 MHz) δ 17.3 (CH_2), 27.7 (CH_2), 30.9 (CH_2), 32.9 (CH_2), 47.8 (CH_2), 49.7 (CH_2), 68.9 (C), 83.3, 116.7 (CH_2), 117.1 (CH_2), 132.8, 132.9, 169.2 (C); MS: *m/z* (rel. inten.) 139 (M^+ – 98, 31), 138 (32), 124 (32), 56 (25), 41 (100). Anal. calcd for $C_{13}H_{19}NOS$: C, 65.78; H, 8.07. Found: C, 65.64; H, 8.05. Compound **17g** was also prepared in comparable yields by reacting bromoamide **29** with thiolester **25** according to Method A.



Cinnamyl 2-(pent-4-ynylthio)acetate (17h). An anhydrous DCM (10 mL) solution of 2-(pent-4-ynylthio)acetic acid **28** (2 mmol), freshly distilled $SOCl_2$ (2.2 mmol), and two drops of dry DMF was stirred overnight at room temperature under nitrogen. The intermediate S-pent-4-ynyl chloromethanethioate was directly added – using a cannula – to a solution of cinnamyl alcohol (2.2 mmol) and TEA (2.4 mmol) in DCM (10 mL). The resulting solution was stirred for additional 2 h, then water was added and the mixture was extracted twice with DCM. The combined organic phases were dried over $MgSO_4$. Purification by column chromatography on silica gel (*n*-hexane / diethyl ether) afforded 1.6 mmol (80%) of the target sulfide **17h** as a pale yellow oil. IR (neat) ν_{max} (cm^{-1}) 3293, 2937, 1734, 1270, 1125; ^{1}H NMR (400 MHz) δ 1.83 (2 H, m), 1.94 (1 H, t, J_t = 2.6), 2.32 (2 H, td, J_t = 7.0, J_d = 2.6), 2.77 (2 H, t, J_t = 7.4), 3.27 (2 H, s), 4.79 (2 H, dd, J_{d1} = 6.6, J_{d2} = 1.3), 6.29 (1 H, dt, J_d = 15.9, J_t = 6.6), 6.69 (1 H, bd, J_d = 15.9), 7.24-7.41 (5 H, m); ^{13}C NMR (100 MHz) δ 17.4 (CH_2), 27.6 (CH_2), 31.5 (CH_2), 33.6 (CH_2), 65.9 (CH_2), 69.1 (C), 83.2, 122.6, 126.6, 128.2, 128.6, 134.7, 136.0

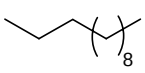
(C), 170.2 (C); MS: *m/z* (rel. inten.) 117 (M^+ – 157, 100), 115 (30), 91 (12). Anal. calcd for $C_{16}H_{18}O_2S$: C, 70.04; H, 6.61. Found: C, 70.00; H, 6.58.



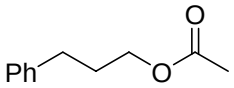
3-Phenylpropyl 7-(pent-4-ynylthio)hept-2-enoate (17i). 3-Phenylpropyl (diethylphosphono)acetate **34** (4.0 mmol) was added at room temperature under nitrogen to a dry THF (12 mL) suspension of sodium hydride (4.0 mmol), followed by addition of a THF (2 mL) solution of 5-(pent-4-ynylthio)pentanal **31** (4.0 mmol). The solution was stirred for 1.5 h. After being quenched into water, the aqueous layer was extracted with chloroform (3 × 5 mL). The combined organic phases were dried over $MgSO_4$. Purification by column chromatography on silica gel (*n*-hexane / diethyl ether) afforded 1.6 mmol (80%) of the target sulfide **17i** as a pale yellow oil. IR ($CDCl_3$) ν_{max} (cm^{-1}) 3293, 2935, 2858, 1718, 1654, 1454, 1266; ^{1}H NMR (400 MHz) δ 1.52-1.68 (4 H, m), 1.80 (2 H, quint, J_{quint} = 7.0), 1.95-2.03 (3 H, m), 2.23 (2 H, qd, J_q = 6.8, J_d = 1.5), 2.32 (2 H, td, J_t = 6.9, J_d = 2.5), 2.53 (2 H, t, J_t = 6.9), 2.62 (2 H, dd, J_{d1} = 7.4, J_{d2} = 6.9), 2.71 (2 H, dd, J_{d1} = 7.4, J_{d2} = 8.1), 4.15 (2 H, t, J_t = 6.5), 5.84 (1 H, dt, J_d = 15.7, J_t = 1.7), 6.94 (1 H, dt, J_d = 15.7, J_t = 6.9), 7.16-7.22 (3 H, m), 7.26-7.31 (2 H, m); ^{13}C NMR (100 MHz) δ 17.5 (CH_2), 28.1 (CH_2), 28.3 (CH_2), 29.0 (CH_2), 30.2 (CH_2), 30.8 (CH_2), 31.7 (CH_2), 31.7 (CH_2), 32.2 (CH_2), 63.5 (CH_2), 68.9 (C), 83.5, 121.5, 125.9, 128.4, 128.4, 141.2 (C), 148.8, 166.6 (C); MS: *m/z* (rel. inten.) 344 (2), 181 (6), 153 (5), 141 (5), 118 (29), 117 (39), 100 (100), 91 (62). HRMS calcd for $C_{21}H_{28}O_2S$: 344.1810; found: 344.1803.

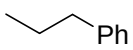
General Procedure for the Reactions of Sulfides 17a-f.

A degassed toluene solution (16.0 mL) of thiophenol (1.1 mmol) and ACCN (0.15 mmol) was added by siringe pump over 2 hours under a nitrogen atmosphere to a boiling, degassed toluene solution (10.0 mL) containing the appropriate sulfide **17a-f** (1.0 mmol). The resulting mixture was refluxed for additional 1 h, until virtual disappearance of the starting materials. The solution was then evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel, using *n*-hexane / diethyl ether as eluant, to give the desidered reduced product **19a-f**. Reaction products **19b** and **19f** are identical: for spectral data of **19f**, see data of **19b**.



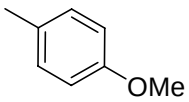
Dodecane (19a). Colorless liquid; ^{1}H NMR (600 MHz) δ 0.87 (6 H, t, J_t = 7.0), 1.21-1.27 (20 H, m); ^{13}C NMR (150 MHz) δ 14.1, 22.7 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 31.9 (CH_2); MS: *m/z* (rel. inten.) 170 (6), 127 (4), 113 (4), 85 (32), 71 (67), 57 (100), 43 (51).





1-Propylbenzene (19b). Colorless liquid; ^{1}H NMR (600 MHz) δ 0.94 (3 H, t, J_t = 7.3), 1.64 (2 H, tq, J_t = 7.9, J_q = 7.3, br sextet), 2.58 (2 H, t, J_t = 7.9), 7.15-7.19 (3 H, m), 7.25-7.29 (2 H, m); ^{13}C NMR (150 MHz) δ 13.8, 24.6 (CH_2), 38.1 (CH_2), 125.6, 128.2, 128.4, 142.7 (C).

Adamantane (19c). White solid; ^{1}H NMR (400 MHz) δ 1.73-1.77 (12 H, m), 1.87 (4 H, bs); ^{13}C NMR (100 MHz) δ 28.3, 37.8 (CH_2).

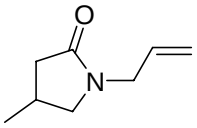


1-Methoxy-4-methylbenzene (19d). Liquid; ^{1}H NMR (400 MHz) δ 2.28 (3 H, s), 3.77 (3 H, s), 6.80 (2 H, part of AA'BB', J = 8.7), 7.08 (2 H, part of AA'BB', J = 8.7); ^{13}C NMR (100 MHz) δ 20.4, 55.2, 113.7, 129.8 (C), 129.9, 157.4 (C).

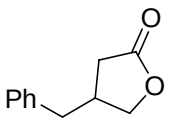
3-Phenylpropyl acetate (19e).[27] Oil; ^{1}H NMR (400 MHz) δ 1.92-2.00 (2 H, m), 2.05 (3 H, s), 2.69 (2 H, t, J_t = 7.4), 4.09 (2 H, t, J_t = 6.7), 7.17-7.22 (3 H, m), 7.26-7.31 (2 H, m); ^{13}C NMR (100 MHz) δ 20.9, 30.2 (CH_2), 32.2 (CH_2), 63.8 (CH_2), 126.0, 128.3, 128.4, 141.2 (C), 171.1 (C); MS: *m/z* (rel. inten.) 178 (1), 118 (75), 117 (100), 91 (38), 43 (37).

General Procedure for the Reactions of Sulfides 17g-i.

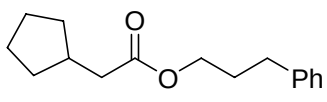
A degassed toluene solution (16.0 mL) of thiophenol (1.1 mmol) and ACCN (0.15 mmol) was added by siringe pump over 4 hours under a nitrogen atmosphere to a boiling, degassed toluene solution (10.0 mL) containing the appropriate sulfide **17g-i** (1.0 mmol). The resulting mixture was refluxed for additional 1 h, until virtual disappearance of the starting materials. The solution was then evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel, using *n*-hexane / diethyl ether as eluant, to give the desidered cyclized product **21-23**.



1-Allyl-4-methylpyrrolidin-2-one (21).[28] Elution with *n*-hexane / diethyl ether 70/30 v/v gave 0.75 mmol of the target compound as a pale yellow oil (75%); IR (neat) ν_{max} (cm^{-1}) 2961, 2872, 1690, 1440, 1419; ^{1}H NMR (400 MHz) δ 1.13 (3 H, d, J_d = 6.8), 2.05 (1 H, dd, J_{d1} = 16.5, J_{d2} = 6.8), 2.39-2.49 (1 H, m), 2.57 (1 H, dd, J_{d1} = 16.5, J_{d2} = 8.5), 2.92 (1 H, dd, J_{d1} = 9.7, J_{d2} = 6.0), 3.46 (1 H, bt, J_t = 7.8), 3.88 (2 H, d, J_d = 6.0), 5.15-5.21 (2 H, m), 5.67-5.78 (1 H, m); ^{13}C NMR (100 MHz) δ 19.8, 26.2, 39.3 (CH_2), 45.0 (CH_2), 54.0 (CH_2), 117.7 (CH_2), 132.4, 174.2 (C); MS: *m/z* (rel. inten.) 139 (45), 124 (13), 112 (7), 96 (12), 70 (100), 41 (41).

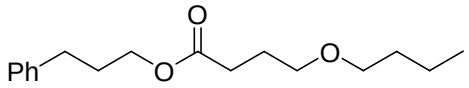


4-Benzyl-dihydrofuran-2(*3H*)-one (22).[29] Elution with *n*-hexane / diethyl ether 80/20 v/v gave 0.75 mmol of the target compound as a pale yellow oil (75%); IR (neat) ν_{max} (cm^{-1}) 2971, 2923, 1777; ^{1}H NMR (400 MHz) δ 2.29 (1 H, dd, J_{d1} = 17.6, J_{d2} = 6.9), 2.60 (1 H, dd, J_{d1} = 17.5, J_{d2} = 8.1), 2.76 (1 H, d, J_d = 3.8), 2.78 (1 H, d, J_d = 2.1), 2.80-2.91 (1 H, m), 4.03 (1 H, dd, J_{d1} = 9.2, J_{d2} = 6.0), 4.33 (1 H, dd, J_{d1} = 9.2, J_{d2} = 6.9), 7.13-7.17 (2 H, m), 7.22-7.27 (1 H, m), 7.29-7.35 (2 H, m); ^{13}C NMR (100 MHz) δ 34.2 (CH_2), 37.1, 38.9 (CH_2), 72.6 (CH_2), 126.8, 128.6, 128.8, 138.2 (C), 176.8 (C); MS: *m/z* (rel. inten.) 176 (24), 117 (12), 92 (59), 91 (100), 65 (13).



3-Phenylpropyl 2-cyclopentylacetate (23). Purification was performed on basic alumina using as eluant a solution of *n*-hexane / diethyl ether 80/20 v/v. The chromatography column gave 0.70 mmol of the target compound as a colorless oil (70%); IR ($CDCl_3$) ν_{max} (cm^{-1}) 2959, 1726; ^{1}H NMR (400 MHz) δ 1.38-1.78 (8 H, m), 1.95-2.04 (2 H, m), 2.18-2.29 (1 H, m), 2.66-2.74 (3 H, m), 4.10-4.27 (3 H, m), 7.16-7.23 (3 H, m), 7.27-7.32 (2 H, m); ^{13}C NMR (100 MHz) δ 25.6 (CH_2), 26.5 (CH_2),

28.7 (CH_2), 30.2 (CH_2), 32.1 (CH_2), 43.5, 64.8 (CH_2), 126.1, 128.4, 128.5, 140.9 (C), 175.2 (C); MS: *m/z* (rel. inten.) 118 (M^+ – 128, 100), 117 (44), 91 (32), 81 (34), 69 (7). Compound **23** partially decomposes upon chromatography on both silica gel and (to a minor extent) basic alumina: chromatographic separation must be therefore as fast as possible. Due to decomposition problems during purification and absence of molecular ion in the mass spectrum, for compound **23** we could obtain neither good elemental analysis nor accurate mass determination.



3-Phenylpropyl 4-butoxybutanoate (24). A degassed toluene solution (13.0 mL) of thiophenol (1.1 mmol) and ACCN (0.15 mmol) was added by siringe pump over 2 hours under a nitrogen atmosphere to a boiling degassed toluene solution (13.0 mL) containing 3-phenylpropyl 2-(pent-4-ynylthio)acetate **17e** (1.0 mmol) and 1-(vinyloxy)butane (5.0 mmol). The resulting mixture was refluxed for additional 1 h, until virtual disappearance of the starting materials. The solution was then evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel using increasing *n*-hexane / diethyl ether gradients to give 0.4 mmol of **24** as a yellow oil (40%). IR (neat) ν_{max} (cm^{-1}) 2978, 2931, 1742; ^{1}H NMR (400 MHz) δ 0.91 (3 H, t, J_t = 7.3), 1.31-1.43 (2 H, m), 1.50-1.58 (2 H, m), 1.86-2.00 (4 H, m), 2.40 (2 H, t, J_t = 7.4), 2.69 (2 H, t, J_t = 7.7), 3.40 (2 H, t, J_t = 6.7), 3.40 (2 H, t, J_t = 6.2), 4.09 (2 H, t, J_t = 6.7), 7.16-7.22 (3 H, m), 7.25-7.31 (2 H, m); ^{13}C NMR (100 MHz) δ 13.9, 19.3 (CH_2), 25.1 (CH_2), 30.2 (CH_2), 31.1 (CH_2), 31.8 (CH_2), 32.1 (CH_2), 63.6 (CH_2), 69.6 (CH_2), 70.7 (CH_2), 126.0, 128.4, 128.4, 141.2 (C), 173.6 (C); MS: *m/z* (rel. inten.) 278 (1), 119 (18), 118 (100), 117 (59), 91 (31), 57 (8). Anal. calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.19; H, 9.38.

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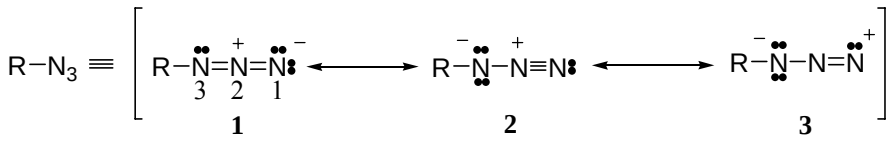
CHAPTER 4
THE CHEMISTRY OF THE AZIDO GROUP

4.1 The azido group

Few years ago, when someone talked about the chemistry of the azido group before its synthetic opportunities were expressed, the first thing coming to mind was the fear of an explosion.[1] Epic tales handed down from professors to students, the dangerous feeling surrounding this functional group, and sometimes ignorance made its chemistry unattractive for several researchers and for many years organic azides were used rarely.

Now, in spite of the often irrational fear of organic azides (referred to by K. B. Sharpless as *azidophobia*), organic azides are a stable starting point for many organic/inorganic chemical applications and industrial processes, and more than 1000 papers are published every year about organic azides. It seems that no more epic tales are handed down. So what happened? During the last decades many brave researchers have surely helped the azido group to conquer the right position in the elaborate world of organic chemistry. Many books, reviews, and papers have showed the versatility and the extraordinary synthetic ability of this functional group, pointing out its possible applicative features rather than explosion capabilities. Therefore, people do not believe in epic tales anymore.

To understand the chemical properties of this functional group, the best way is to look at its polar mesomeric structures[2] (*Scheme 1*).



Scheme 1. Polar mesomeric structures of azido group

The dipolar structures of type **2** and **3**[3] account for the facile decomposition into the corrisponding *nitrene* as well as the reactivity as a 1,3-dipole. The *regioselectivity* of their reactions with electrophiles and nucleophiles is explained on the basis of the mesomeric structure **3** (nucleophiles attack on N^1, whereas electrophiles attack on N^3).

The bond lengths in methyl azide were determined as d(R-N^3) = 1.472 Å, d(N^3-N^2) = 1.244 Å, and d(N^2-N^1) = 1.162 Å; slightly shorter N^2-N^1 bond lengths are observed in aromatic azides. The

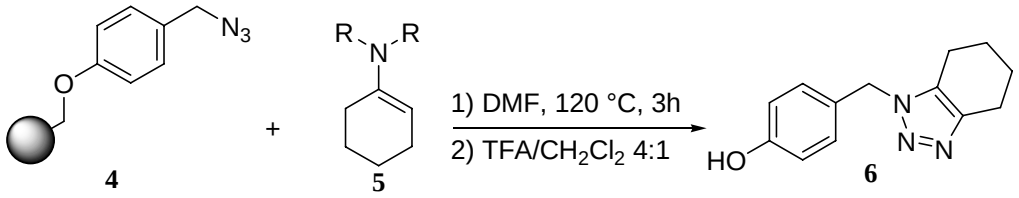
azide structure (N^3-N^2-N^1) is almost linear, with sp^2 hybridization at N^3 and a bond order of 2.5 between N^1 and N^2 and around 1.5 between N^2 and N^3.

The polar resonance structures **2,3** also account for the strong IR absorption at around 2114 cm^{-1} (for phenyl azide), the UV absorption (287 nm and 216 nm for alkyl azides), the weak dipole moment (1.44 D for phenyl azide), and the acidity of aliphatic azides.

4.2 ***The heterolytic reactivity of azides***

Many methods of synthesis of alkyl, aryl, and acyl azides have been reported[2c] but, for sake of brevity, this section will focus mainly on their reactivity, because this is the best way to understand the versatility and the importance of this functional group in organic chemistry.

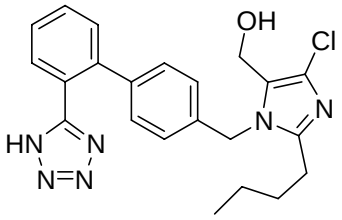
The *Huisgen reaction*[4] is an easy, biocompatible[5] way to obtain 1H-triazoles and Δ^2-1,2,3-triazolines[6] by reaction between alkyl or aryl azides, acting as dipoles, and different suitable dipolarophiles such as both electron-deficient and electron-rich alkenes (enol ethers[7] and enamines,[8] *Scheme 2*). A modern approach to this powerful reaction involves the use of microwaves,[9] especially in cases of dipolarophile unreactivity.



4 **5** **6**

Scheme 2. *The Huisgen reaction for triazoles synthesis*

Tetrazoles, interesting building blocks and target molecules in organic synthesis and pharmaceutical applications, can be obtained directly by a *[3 + 2] dipolar cycloaddition* between organoazides and nitriles. Tetrazoles are suitable for biological applications thanks to their lipofilicity and metabolic stability.[10] Certain classes of tetrazoles, i.e. biphenyltetrazoles, are potent and selective ligands for different proteins such as G proteine-coupled receptors, enzymes, and ion channels. Losartan (**7**),[6] a potent antihypertensive, and others biphenyltetrazoles useful to stimulate the release of growth hormones (**8**),[11] to inhibit metalloproteases (**9**),[12] and to be chloride-channel effectors (**10**)[13] are particularly interesting examples of industrial applications of these [3 + 2] cycloaddition reactions.



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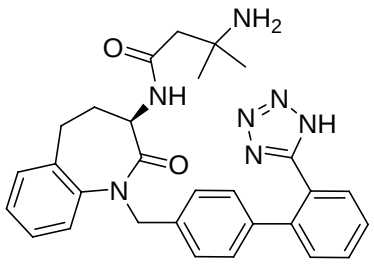

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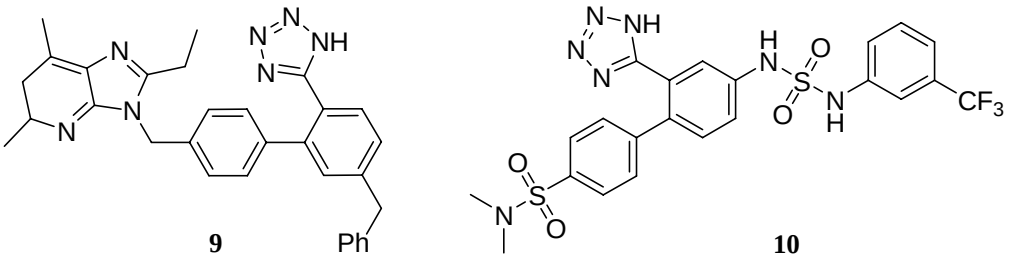
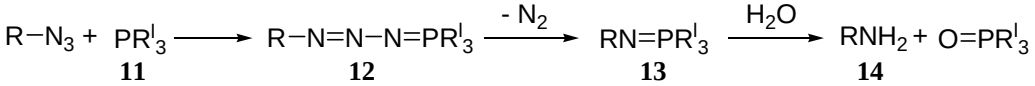


9 **10**

Figure 1. *Biological tetrazoles obtained by [3 + 2] cycloaddition reactions between azides and nitriles*

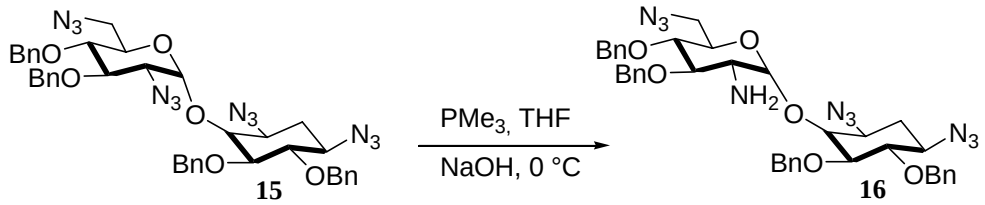
One of the most frequent applications of organoazides is the *reaction with phosphorus nucleophiles*. The Staudinger[14] reaction was developed as a procedure for the reduction of organoazides. This reaction involves the formation of a phosphazine intermediate (**12**) by nucleophilic attack of the phosphorous atom of a trialkyl or triaryl phosphine (**11**) onto the terminal nitrogen atom of the organoazide. The loss of dinitrogen forms an important and synthetically useful intermediate, i.e. iminophosphorane **13**,[15] which can be hydrolyzed, in the presence of water, to the corrisponding amine **14** (*Scheme 3*).



11 **12** **13** **14**

Scheme 3. *The Staudinger reduction of azides with phosphorus nucleophiles*

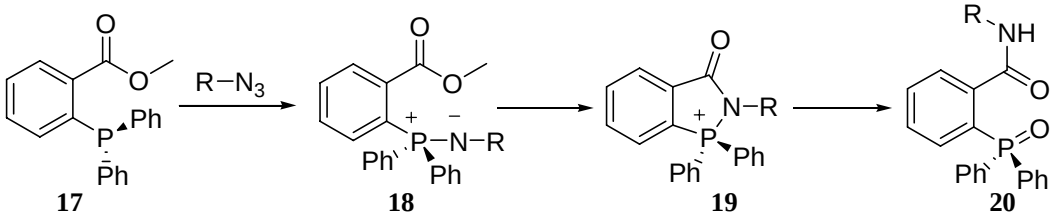
If the reduction is carried out at low temperatures, the azido function can be reduced chemoselectively (*Scheme 4*).[16]



15 **16**

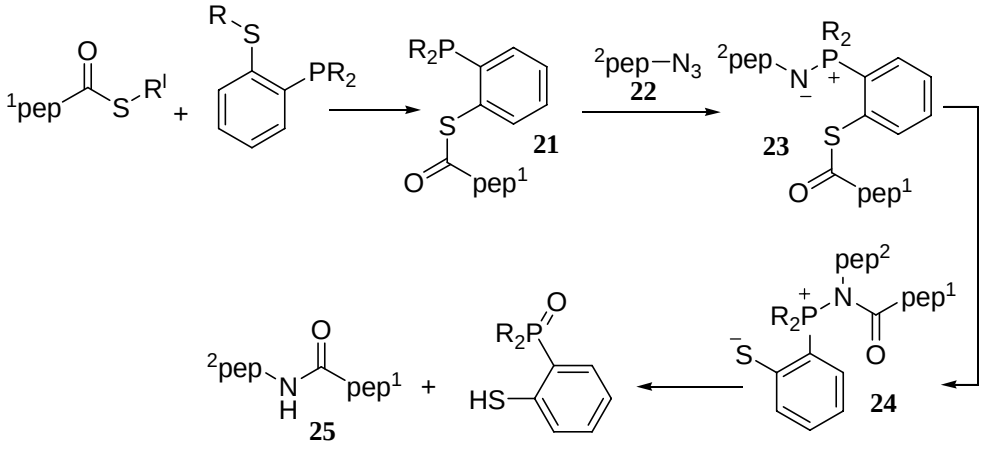
Scheme 4. *Chemoselectivity of Staudinger reduction*

The Staudinger reaction between phosphines and organoazides has been recently used in the synthesis of dendrimers,[17] long chain acylic phosphazenes,[18] amides,[19] glycosidated peptides,[20] and in the solid phase synthesis of 3,5-disubstituted oxazalidine-2-ones.[21] The high nucleophilicity of the nitrogen atom of the iminophosphorane intermediate can be exploited to attack an acyl donor in an inter- or intramolecular reaction for the synthesis of amides.[22] The intramolecular Staudinger ligation[23] is an example of generation of an amide bond (**20**) starting from organoazides and specifically functionalised phosphines (**17**) (*Scheme 5*).



Scheme 5.*The intramolecular Staudinger ligation*

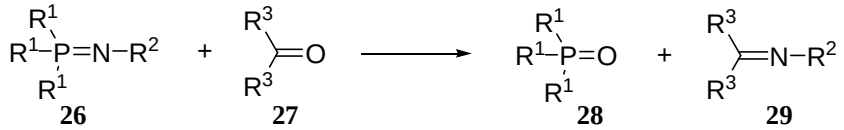
This reaction is compatible with a large number of functional groups and has hence found various uses in organic synthesis and biological chemistry. Staudinger ligation has been successfully used even on living organism such as a mouse.[24] This methodology was applied to *peptide synthesis* (**25**) by reaction between a peptide fragment with C-terminal phosphinylthioester (**21**) and a further peptide fragment with *N*-terminal azide functionality (**22**) (*Scheme 6*).[25]



Scheme 6. *Peptide synthesis by intramolecular Staudinger reaction*

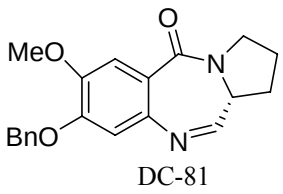
The intramolecular Staudinger ligation is a particularly efficient ring-closing reaction for the formation of medium-sized lactams that are difficult to prepare by other methods.[26]

Iminophosphoranes (**26**) obtainable by Staudinger reaction are used in reactions with carbonyl compounds (**27**) for the synthesis of imines (**29**) by the Aza-Wittig reaction (*Scheme 7*).[27]



Scheme 7. *Synthesis of imines by the Aza-Wittig reaction*

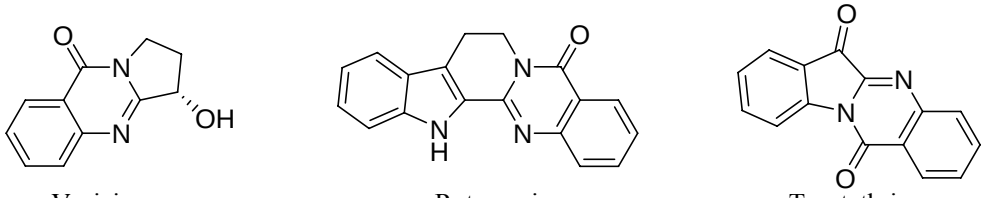
The intramolecular version of this reaction is one of the best methodologies for the preparation of nitrogen containing heterocycles,[28] e.g. isoxazolines,[29] and for the synthesis of five-, six-, and especially seven-membered nitrogen heterocycles such as the antitumor anthibiotic DC-81 **30** (*Figure 2*).[26, 30]



DC-81
30

Figure 2. *The antitumor anthibiotic DC-81*

A series of natural products was synthesised by using a domino Staudinger-intramolecular Aza-Wittig reaction as the key step: for example, vasicinon **31**,[31] rutecarpin **32**,[32] and tryptathrin **33** (*Figure 3*).[29]



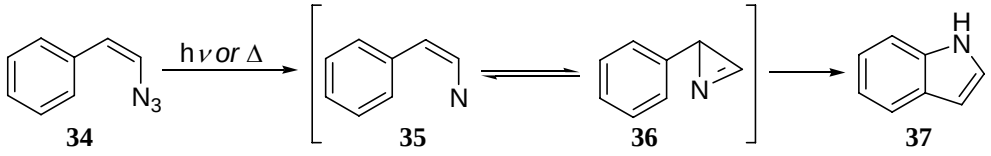
Vasicinon **31** | Rutecarpin **32** | Tryptathrin **33**

Figure 3. *Natural products synthesised by Aza-Wittig reaction*

Organic azides are a *source of nitrenes* by thermal or photochemical decomposition. Nitrenes are extremely reactive species and the complexity of their reaction products and diverse applications makes this compounds particularly interesting.

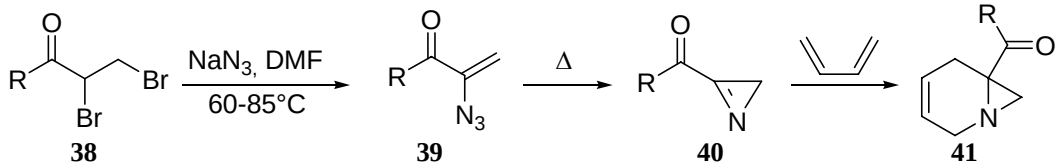
Cycloaddition, rearrangement, and insertion reactions are the main fields of nitrenes chemistry. The intermolecular cycloaddition of thermochemically or photolytically generated nitrenes to alkenes gives aziridines. This reaction is stereospecific and can be catalyzed by metal ions. In this context, enantioselective variants have been developed which use photolysis of aryl sulfonyl azides in the presence of copper ions.[33] Whereas acylnitrenes react in a secondary reaction to form isocyanates through a Curtius rearrangement,[34] ethyl azidoformate usually gives the corresponding aziridines in good yields.[35]

The thermal or photochemical decomposition of alkenyl azides **34** is a frequently used reaction for the synthesis of 2*H*-azirines **36**,[36] unstable compounds that can decompose, sometimes rapidly, with the formation of indoles **37** (*Scheme 8*).



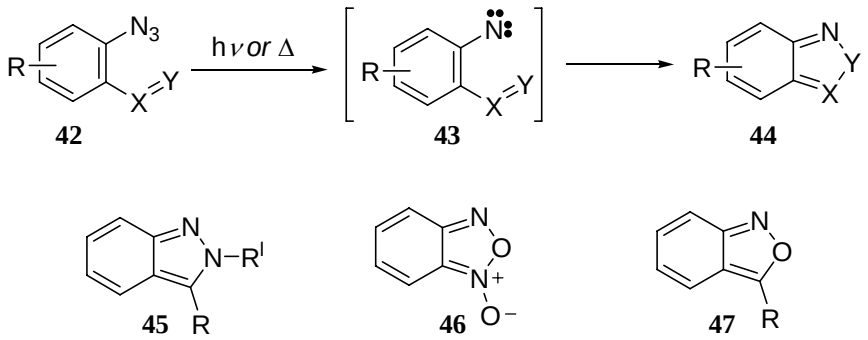
Scheme 8. *Indoles synthesis via nitrene from azides*

Activated 2*H*-azirines **40** with electron-withdrawing substituents have proved to be good dienophiles in endo-selective Diels-Alder reactions with electron rich dienes.[37] The use of chiral 2*H*-azirines, chiral dienophiles, or chiral Lewis acids allows the asymmetric synthesis of bridged aziridines (*Scheme 9*).



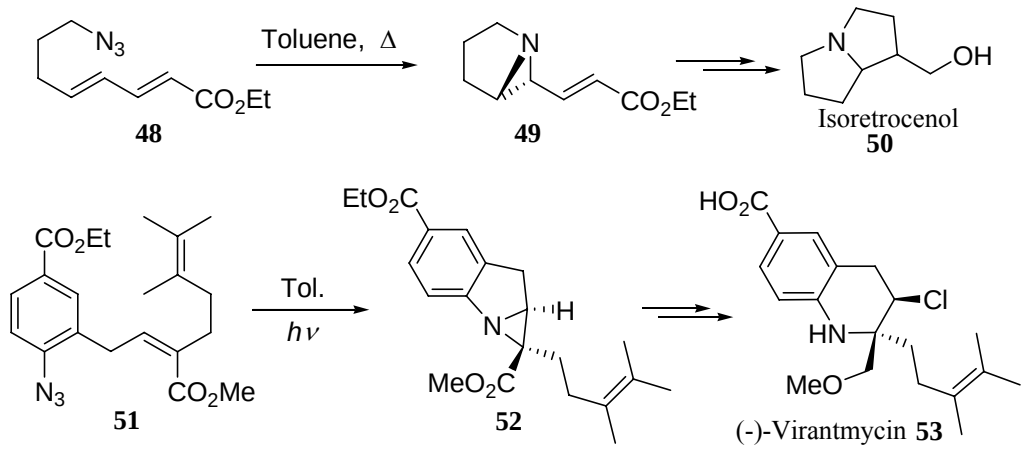
Scheme 9. *Diels-Alder reactions with 2H-azirines*

Aryl azides **42** with a suitable double bond in the ortho position decompose photochemically or thermally to form the corrisponding heterocycle by an electrocyclic mechanism.[37d, 38b] Indazoles,[38] benzofuroxanes,[39] benzisoxazoles,[40] interesting building blocks for other biologically active complex compounds,[41] are synthesised by the same methodology (*Scheme 10*).



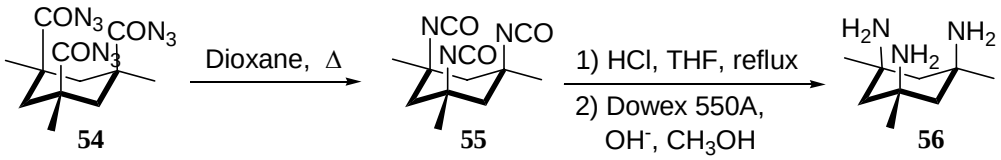
Scheme 10. *Synthesis of indazoles, benzofuroxanes and benzisoxazoles via nitrene*

This method works very well also when the nitrene adds on simple carbon-carbon double bonds or alkene with electron-withdrawing groups, with formation of relatively strained bicyclic systems. In this cases, aziridines are key intermediates in the synthesis of two important natural products such as isoretrocenol[42] **50** and (–)-virantmycin **53**, a powerfull antiviral against a series of different RNA and DNA viruses[43] (*Scheme 11*).



Scheme 11. *Isoretrocenol and (-)-virantmycin syntheses*

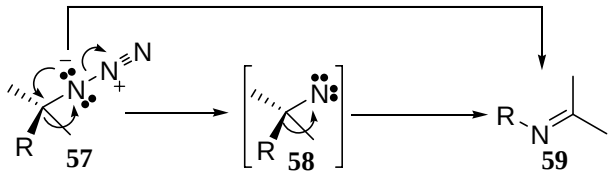
The rearrangement of acyl azides into isocyanates through the corresponding nitrenes is well known as the *Curtius rearrangement*.[44] This important reaction is the best way to converte acyl azides into amines and carbamates and it has been used to synthesize many complex natural products,[45] owing to the fact that it is a quantitative, stereospecific reaction with retention of configuration during the migration of the group bearing the chiral centre, as showed in *Scheme 12*.[46]



Scheme 12. *Curtius rearrangement in biological compounds*.

The Curtius rearrangement has been used for the solid-phase synthesis of amines starting from aromatic azides[47] and as a key step in the total synthesis of (+)-zamoanolide, a tumor-growth inihibitor.[42c]

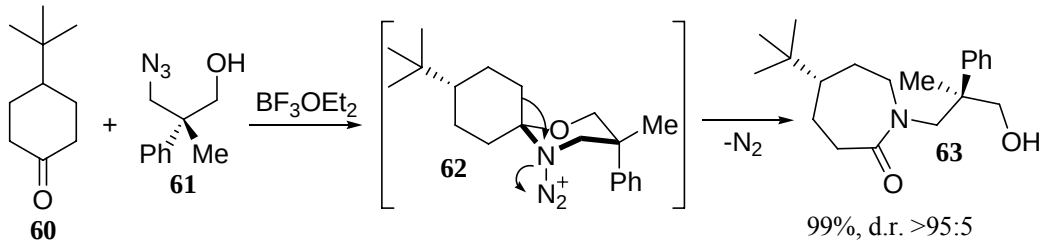
When alkyl azides are placed under pyrolysis or thermolysis conditions the reaction is called the *Schmidt rearrangement*.[48] It has not been established yet whether the reaction product (the imine) is obtained in a concerted fashion or through a two-step mechanism, i.e. nitrene formation followed by rearrangement (*Scheme 13*).



Scheme 13. *Schimdt rearrangement of alkyl azides*

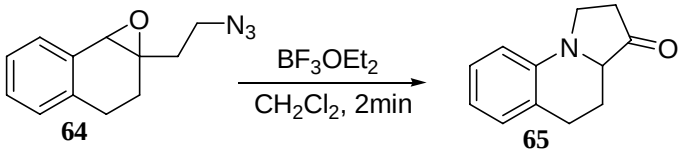
The Schmidt rearrangement has found interesting applications in the synthesis of natural products such as nicotine, starting from cyclobutyl azide,[49] in the rearrangement of azidocubanes,[50] in the synthesis of tetrazoles from fatty acids,[51] and in the total synthesis of stenine[52] and indolactam V.[53]

Suitable electrophiles (carbon electrophiles, protons, boranes) react with organoazides at N^3 to form initially an imine-substituted diazonium ion, which then loses nitrogen and rearranges or reacts with nucleophiles. Once the azide is attacked by the electrophile, the mechanism of this reaction is analogous to that of the Schmidt reaction and, generally, products with an expanded framework are obtained. This reaction is catalyzed by Lewis acids and it is a good methodology to obtain *N*-alkylated amides or lactams[54] starting from aliphatic ketones. If prochiral cycloalkanones **60** are used with chiral azides **61**, the reaction furnishes good yields in expanded lactams **63** with high diastereoselectivity[55] (*Scheme 14*).



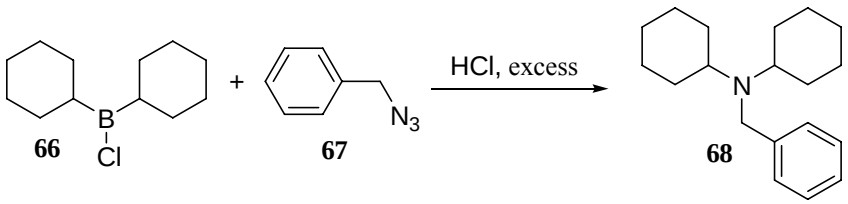
Scheme 14. *Diastereoselective synthesis of lactams*

Besides ketones, also epoxides **64** bearing the azido group on a lateral alkyl chain can be converted to amino-substituted aromatic systems **65** by elecrophilic cyclisation and subsequent Schmidt rearrangement (*Scheme 15*).[56]



Scheme 15. *Azidoepoxides reaction by Schimdt rearrangement*

In the presence of strong acids, organic azides give aryl or alkyl *nitrenium ions*. These are extremely reactive species in intermolecular substitution and intramolecular cyclisation reactions involving aromatic groups.[57] Enantiomerically pure organoboron compounds can be usefully employed to easily obtain *alpha*-chiral amines.[58] The reaction between azides **67** and halo-organoboron compounds **66** proceeds also with an intramolecular mechanism giving an easy access to chiral cyclic amines.[59] This class of electrophiles allows the synthesis of symmetrical and unsymmetrical alkyl amines **68** in high yields using strong acid conditions (*Scheme 16*).

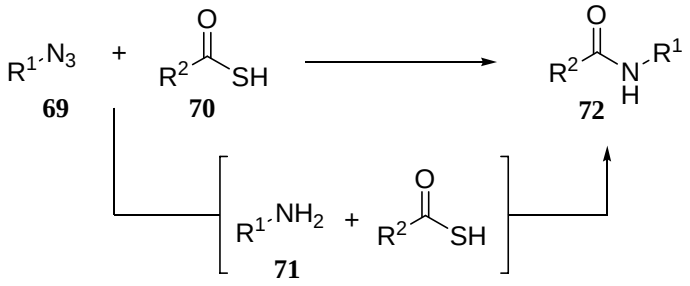


Scheme 16. *Synthesis of amines from azides via nitrenium ions*

Extremely versatile methods for the synthesis of amines entail direct reduction of the N_3 moiety of primary, secondary, and tertiary organic azides. Hundreds methods are available for this purpose,[60] and it is commonly possible to reduce selectively the azido function in the presence of almost any functional group. The use of H_2 in the presence of the Lindlar catalyst[61] is one of the most important and successful methods for the synthesis of amines. Such reagents as $LiAlH_4$, thiols,[62]

complex hydrides, boranes, borohydrides of Li, Na and Zn, are only a small example in the plethora of the available reducing agents.[63] The reduction takes place in good yields also with various metals in the presence of Lewis or Brønsted acids[64] (e.g. In/NH_4Cl). Good results are obtained in the synthesis of aryl, acyl and alkyl amines with SmI_2 as a mild reducing agent,[65] and high selectivities are achieved with tin reagents such as Bu_3SnH and $SnCl_2$ and tin complexes such as $NH_4^+Sn(SAr)_3^-$.[66]

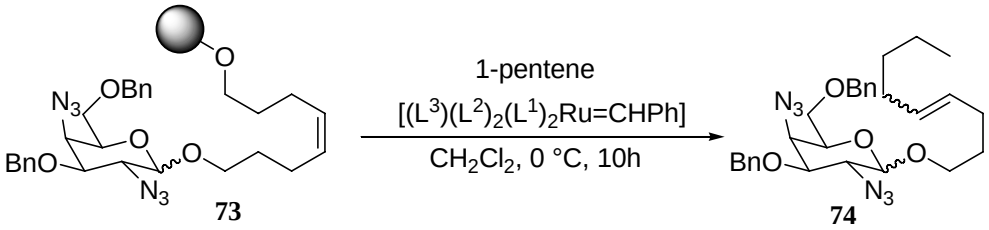
The direct conversion of organoazides into Boc-protected amines[67] and the mild transformation of azides **69** with thioacids **70** which leads directly to amides[68] **72** are attractive methods for peptides synthesis (*Scheme 17*).



Scheme 17. *Amides synthesis from organoazides*

The azide function also provides a good possibility to protect coordinating primary amines, especially in sensitive substrates such as oligosaccharides, aminoglycoside antibiotics,[69] glycosoaminoglycans such as heparin,[70] and peptidonucleic acids.[71]

Alkyl azides have been shown to be stable towards organometallic catalysts in cleaving alkene methatesis of saccharides[72] (*Scheme 18*).



Scheme 18. *Azides as protecting groups of amines*

To date there are many syntheses of natural products that make use of the azide functionality as a key intermediate, but surprisingly there are no natural products containing the N_3 group. This aspect is quite strange because the azido group sometimes demonstrated to possess a higher activity compared to other functional groups. For example, the fact that the azide functionality is smaller

than the aminosulfonyl and methylsulfonyl groups makes some particular products more *lipophilic*, giving them the capacity to better interact with arginine units with respect to other sulfonyl-function-containing analogs. Azide derivative **75** of the COX-2 inhibitors Colecoxib **76** and Refecoxib **77** is for instance more powerful than the parent derivatives (*Figure 4*).[73]

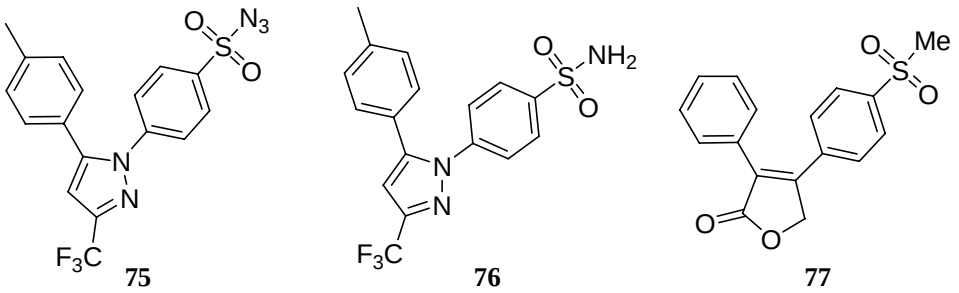
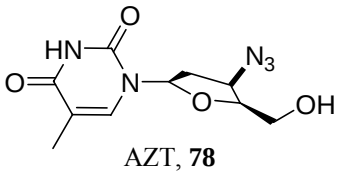


Figure 4. *Azide derivative **75** is more biologically active than the parent compounds **76** and **77***

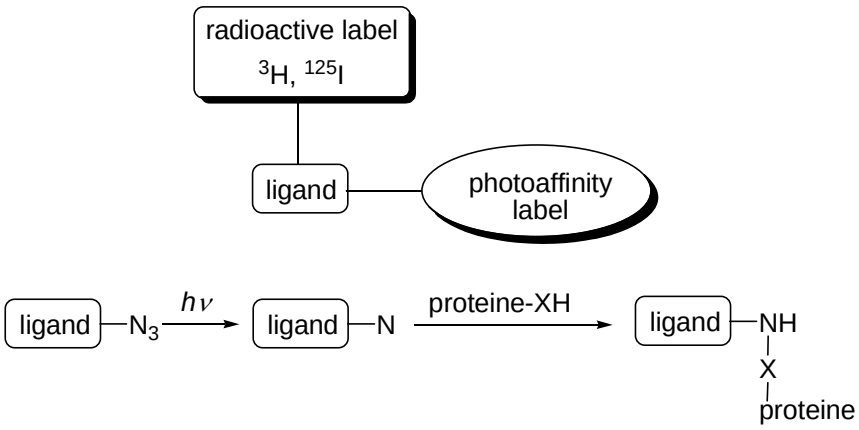
Comparison between a 1,1-dichloroethyl group (as in chloramphenicol) and the azidomethyl group has shown that they exhibit similar behaviour. A well known example of an important pharmacological application of the azido group is the anti-HIV medication AZT **78** (*Figure 5*).[74]



AZT, **78**

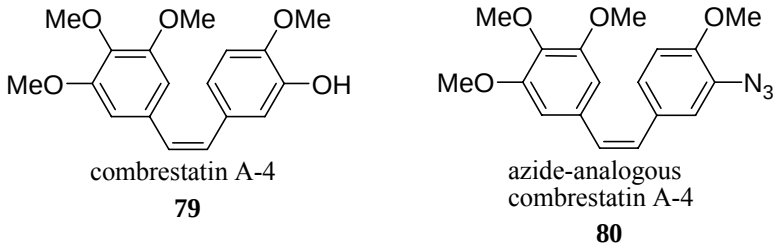
Figure 5. *Anti-HIV compound AZT*

Azides are suitable labels of receptor compounds in the field of the *photoaffinity labelling*, an important and extremely useful tool for tumor identification.[75] The ligand is equipped with this nitrene precursor at a position that does not distort its affinity for the receptor, but yet is close enough to its target protein. The azide group is particularly suitable for this labelling since, after photolysis with formation of nitrenes, the organoazide can be inserted into many carbon, nitrogen, oxygen, or sulfur compounds. An additional radioactive label can be used to identify the ligand-proteine complex (*Scheme 19*).



Scheme 19. *Azides in photoaffinity labelling*

This principle was used, for example, in the synthesis of combrestatin analogues as molecular probes for tubulin polymerisation (*Figure 6*).[76] It is worth noting that a growing number of applications in medicinal chemistry are continuosly appearing in the literature.[77]

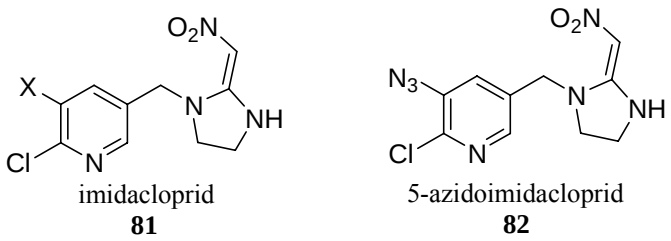


combrestatin A-4
79

azide-analogous combrestatin A-4
80

Figure 6. *Azide-analogous combrestatin A4 in photoaffinity labelling*

This process has also been used in modern plant protection research to analyze, for example, the interaction of proteins with insecticides, as for neonicotinoids such as imidacloprid **81**,**82** (*Figure 7*).[78] In this connection it was important that biological properties of the labelled compounds differed only to a small extent with respect to the starting compounds. The lipophilicity of organic azides brings great advantages in cases like that.



imidacloprid
81

5-azidoimidacloprid
82

Figure 7. *Insecticide compound and analogous azido labelled*

Not only can the interaction of small molecules with proteins[79] be investigated by photolabelling with organo azides, but also protein-protein and protein-nucleic acid interactions can be studied as

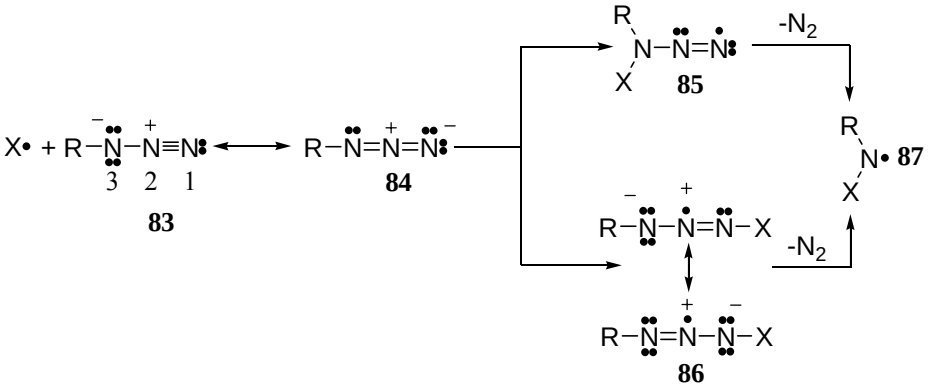
well.[80] The photoaffinity labelling can also be exploited in an intramolecular fashion, which leads to crosslinking. One current example is the covalent bonding of RNA duplex strand with an internally attached aryl azide by photolysis.[81]

4.3 The radical chemistry of the azido group: aminyl radicals

Another important feature concerning the chemistry of the azido group is the *radical chemistry*. Although the synthetic importance of radical chemistry has been recognised only in recent years, the number of papers reporting applications of radical chemistry in reactions involving the azido group is rather low. Organic azides are instead important, versatile compounds, since they can be used as a source of *N*-centred radicals, mainly aminyl radicals, by addition of carbon centred intermediates such as aryl,[82] alkyl,[83] vinyl,[84] and acyl[85] radicals, or even heteroatom-centred species such as stannyl,[86] silyl[87] and germyl[88] radicals.

What happens when a radical reacts with the azido group is still quite a debated matter. For sure, after the addition process to the N_3 group, elimination of nitrogen occurs and an aminyl radical is generated.

Nevertheless, the route to the aminyl has not been fully established yet, since it may involve concerted or stepwise mechanisms as well as different kinds of possible intermediates. Noteworthy researches in this field have been carried out by Roberts,[87a-c, 89] who performed some electron spin resonance studies on the radicals generated by addition of 1-hydroxy-1-methylethyl, triorganosilyl, and alkyl radicals to several organic azides and suggested that the real operating mechanism can be directly related to the nature of both the azide and the attacking radical. He found that homolytic addition to an azide can take place at either N^3 or N^1 to give a 3,3-triazenyl **85** or a 1,3-triazenyl radical **86**, respectively. Both routes bring eventually to the aminyl radical **87** by extrusion of molecular nitrogen by either intermediates (*Scheme 21*).

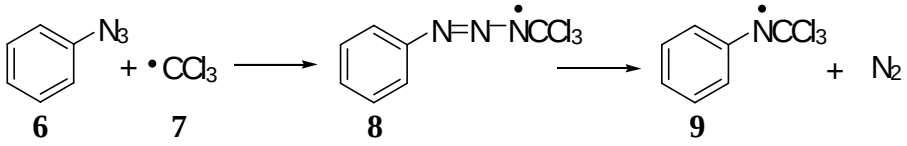


Scheme 21. *Homolytic addition to the azido group and aminyl radical generation*

Alkyl, acyl, aryl, and sulfonyl azides undergo decomposition when heated in 2-propanol at 34-80 °C in the presence of diethyl peroxydicarbonate and the key step is well described in terms of formation of a 3,3-triazenyl radical **85** instead of a 1,3-triazenyl intermediate.[90] However, when triorganosilyl radicals react with a variety of azides, the observed e.p.r. spectra are best interpreted in terms of the 1,3-triazenyl radical adduct **86**. Alkyl radicals react with alkyl and aryl sulfonyl azides at elevated temperature to displace the corresponding sulfonyl radical presumably via a 1,3-triazenyl radical intermediate **86**. When alkyl or aryl radicals react with the azido group in a intramolecular fashion, the 3,3-triazenyl radical **85** is the precursor of the final cyclic aminyl.

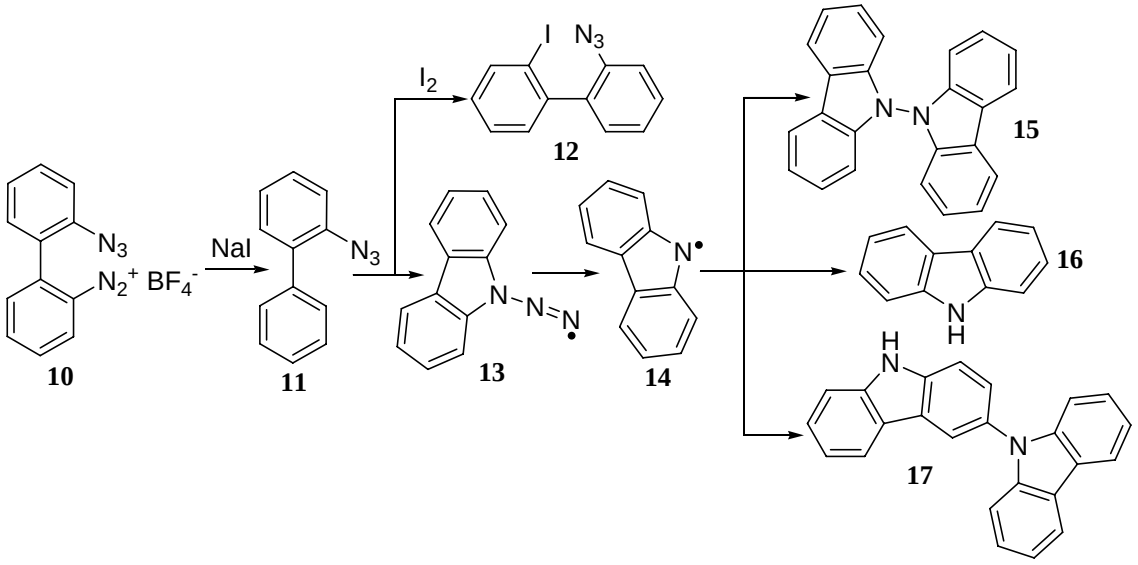
The intermolecular reaction of tributylstannyl radicals with alkyl and acyl azides entails addition to N^3, although addition to N^1 cannot be entirely ruled out, as metallotropic interconversion of 1,3- and 3,3-triazenyl adducts could be rapid. The possibility that the tin atom could settle as a bridge between N^3 and N^1 to form an intermediate containing a four-membered ring should also be taken into account.[91]

The first examples of radical reactions involving the azido group date back to the end of the sixties, when Gobson and Leffler studied the decomposition of phenyl azide (**6** in *Scheme 22*) in carbon tetrachloride in the presence of benzoyl peroxide.[92] In this case, isolation of products derived from addition of the trichloromethyl radical **89** (**7** in *Scheme 22*) to the azido group was the incontrovertible evidence of radical decomposition of the azido group (*Scheme 22*).



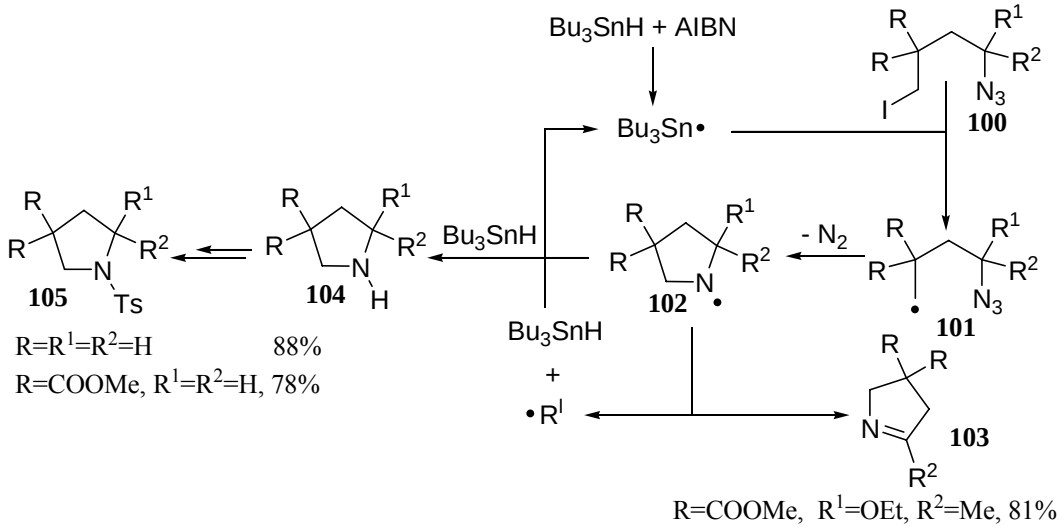
Scheme 22. *First examples of radical reaction of the azido group*

The first interesting, but not synthetically useful, application of a radical reaction involving the azido group, was probably the addition of an aryl radical to the azido moiety.[80] The aryl radical **93** (**11** in *Scheme 23*) generated from 2-(2'-azido)biphenylyldiazonium tetrafluoroborate **92** (**10** in *Scheme 23*) by reaction with NaI in acetone, besides being partially trapped by iodine to give the corresponding iodide **94** (12%, **12** in *Scheme 23*), added to the azido group to give *N,N*-dicarbazolyl **97** (23%, **15** in *Scheme 23*), carbazole **98** (23%, **16** in *Scheme 23*) and 3-(*N*-carbazolyl)carbazole **99** (17%, **17** in *Scheme 23*). Compounds **97**, **98**, and **99** are clearly the results of generation of a cyclic aminyl radical **96** (**14** in *Scheme 23*), which can, respectively, dimerize, abstract a hydrogen atom, or be trapped by carbazole.



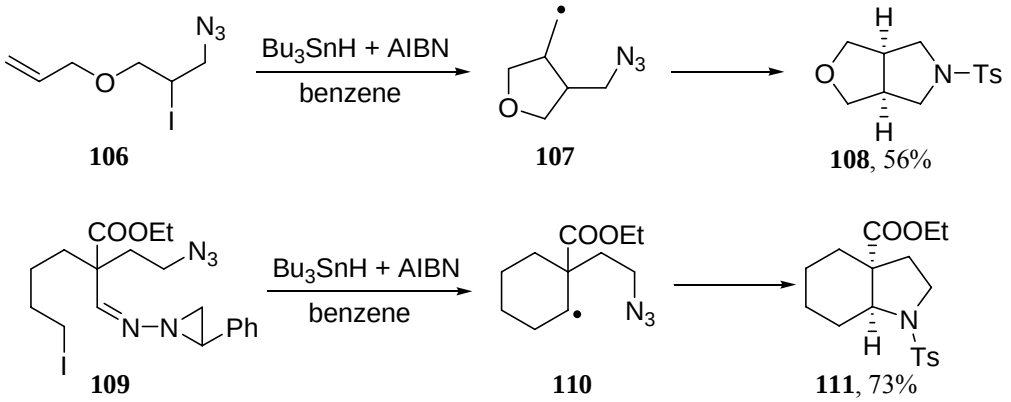
Scheme 23. *Addition of an aryl radical to the azido moiety*

It was not until the beginning of the 90s that some interesting synthetic applications concerning the radical reactions of the azido group started appearing in the literature. The first one was a 5-membered radical cyclisation involving direct carbon-nitrogen bond formation by intramolecular addition of alkyl radicals to the azido group, reported by Kim.[83] This methodology offered a new and powerful tool for the synthesis of *N*-heterocycles. The experimental evidence of the utility of this new approach has been shown by the synthesis of simple dihydropyrroles **103** or pyrrolidines **104** in high yields starting from easy available alkyl iodo azides **100**. (*Scheme 24*).



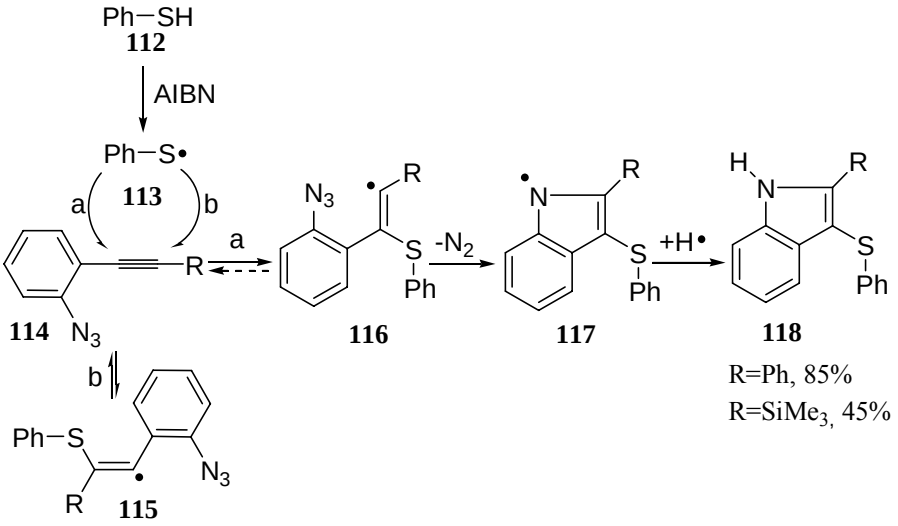
Scheme 24. *Intramolecular addition of alkyl radicals to the azido group*

The reaction, carried out with trybutiltin hydride in refluxing benzene, has been developed in more complicated and fascinating ways such as the tandem radical cyclisations to give fused *N*-heterocycles shown in *Scheme 25*.



Scheme 25. *Tandem radical cyclisation involving azides to the azido moiety*

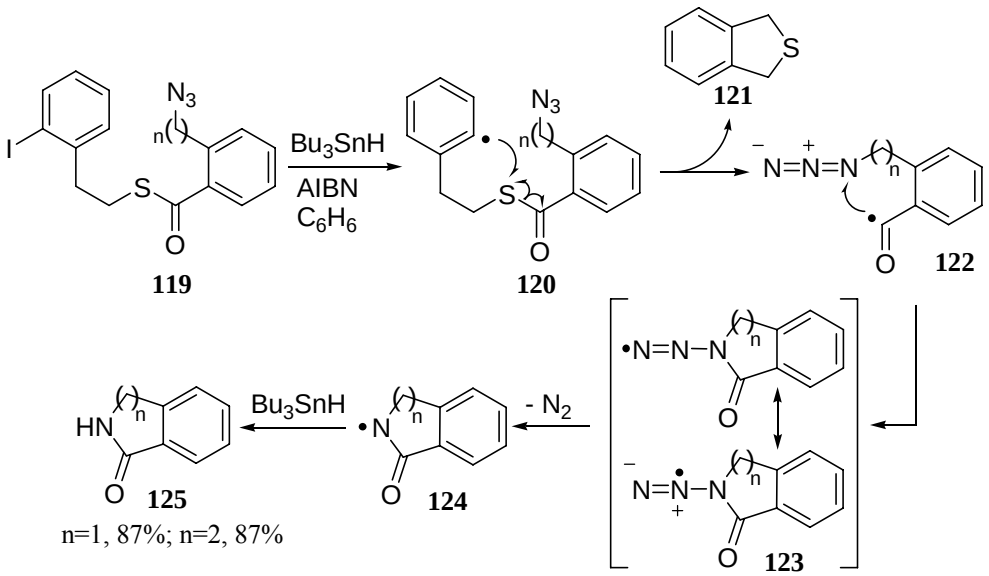
An interesting investigation of the reactivity of organic azides toward carbon centred radicals arises from the well studied cyclisation reaction of vinyl radicals onto the azido group carried out by Montevecchi.[82] In this case, aryl azidoacetylenes **114**, i.e. 2-azidodiphenylacetylene and (2-azidophenyl)trimethylsilylacetylene, are suitable acceptors for the vinyl radicals **116** generated from addition of benzenesulfanyl radicals **113** to the alkyne moiety. Aromatic azidoacetylenes give the corresponding indole **118** in high yield (*Scheme 26*).



Scheme 26. *Intamolecular addition of vinyl radicals to azides*

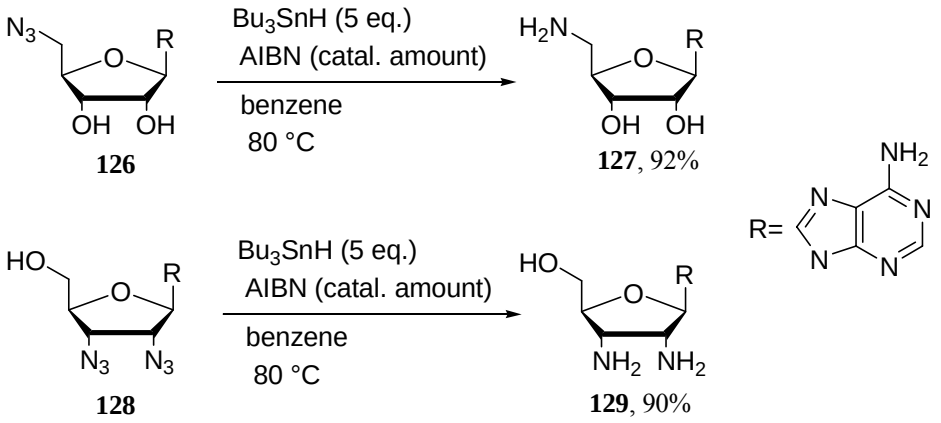
The synthesis of cyclised lactams from organic azides under radical conditions was developed for the first time by Benati and co-workers in 2002.[85] It was found that alkyl and aryl azidoacyl radicals

can cyclise onto the azido group to give cyclised lactams **125** after hydrogen abstraction of the resulting amidyl radical intermediates **124** (*Scheme 27*). Both five- and six-membered lactams can be obtained in high yields. The best results have been achieved from the reaction of aryl-derived azidoacyl radicals **122**, whereas decarbonylation of alkyl-derived acyl radicals occurred before acyl radical cyclisation onto the azido moiety,[93] leading to low yields of the corresponding alkyl-derived lactams.



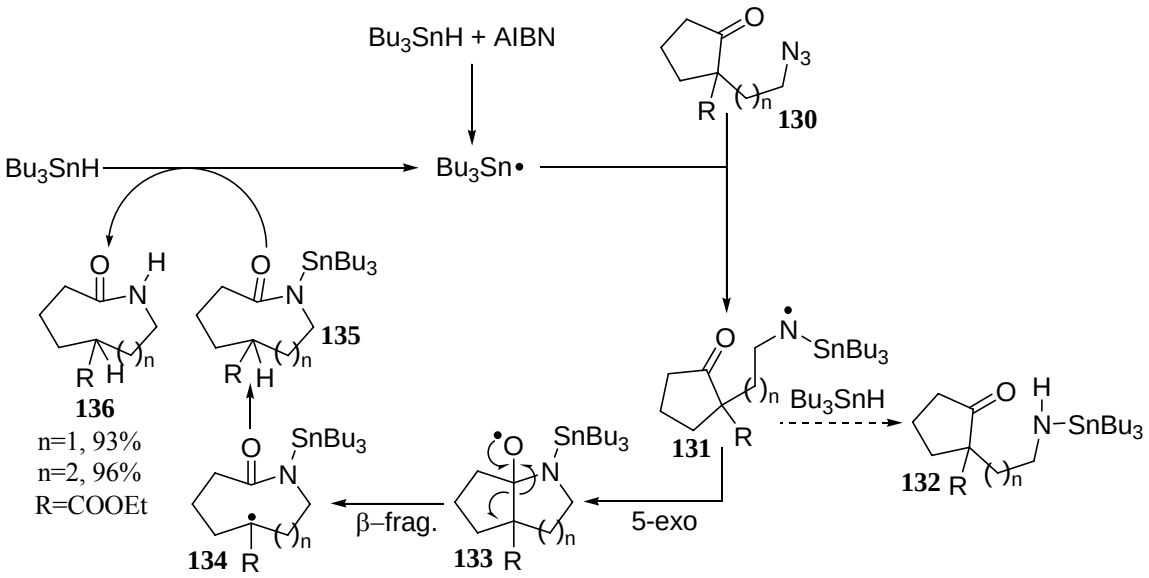
Scheme 27. *Benati radical synthesis of lactams from azides*

The first important application of radical addition to the azido group of a heteroatom centred radical was related to the synthesis of amines by azide reduction with the system tributyltin hydride / AIBN in boiling benzene. This example was particularly important because the conversion of unprotected azidonucleosides **126** furnished the corresponding amines **127** without any transient protection step. Another interesting example was the high yield achieved by this methodology in the conversion of the 2',3'-diazido-2',3'-dideoxyadenosine **128** to the corresponding amine **129** (*Scheme 28*). If compared with traditional reducing methods, which usually afforded yields less than 60%, (catalytic hydrogenolyses, reduction with nickel Raney with or without hydrazine, hydrogen sulphide/mercaptans, and the Staudinger phosphine/phosphate method),[94] this procedure appeared as a new, versatile radical process.



Scheme 28. *Amines synthesis by intermolecular addition to the azido group of stannyl-centred radicals*

A novel and useful application of this radical methodology was developed by Kim in the synthesis of formamides and lactams. He applied the Bu_3SnH/AIBN system to generate stannylaminyl radicals from organic azide and studied their addition reactions to differently functionalised aldehydes and ketones.[86, 95] The proposed radical chain mechanism was based on 5-exo stannylaminyl radical **131** cyclisation onto the carbonyl group to generate the unstable alkoxy radical **133**, which rapidly undergoes *β*-fragmentation[96] giving the resulting lactams **136** in high yields (*Scheme 29*). This was the first important example of an intramolecular radical cyclisation of an aminyl radical onto a carbonyl compound, showing the nucleophilic characteristics of this kind of radical intermediate.

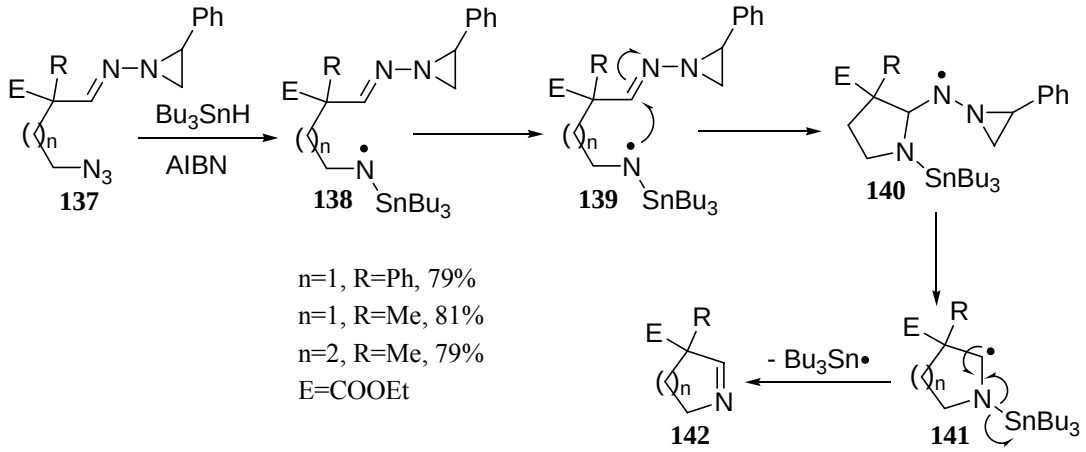


Scheme 29. *The radical Kim synthesis of lactams from ketoazides*

The results obtained by Kim opened new synthetic routes to employ nitrogen centred radical chemistry, overcoming the poor reactivity of usual aminyl radicals: neutral aminyl radicals (mono-

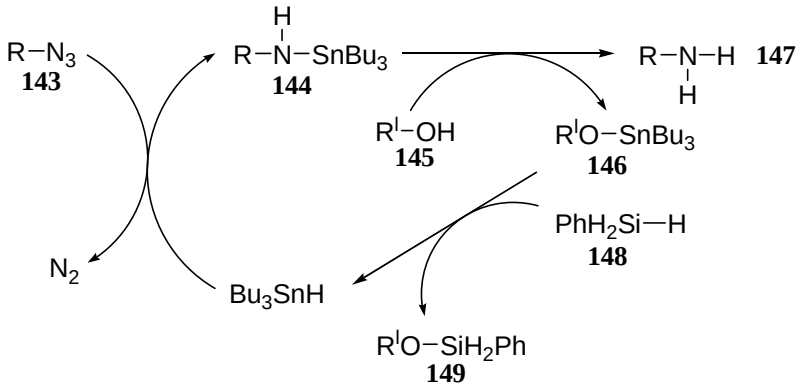
and di-alkyl-substituted aminyl radicals) possess in fact a scarce philicity (they are usually considered slightly electrophilic) that strongly limit their synthetic applications. Before Kim's work, the only way to make *N*-centred radicals more fascinating was to change completely their character upon protonation/complaxation with Lewis acids: the resulting aminium cation radicals have quite an electrophilic character and can be extremely useful in many organic transformations.[97] On the other hand, the seminal work of Kim showed that suitably substituted aminyl radicals can also be nucleophilic, hence extending their applications to a very wider set of reactions.

In another important paper, Kim described the radical cyclisation of stannylaminyl radicals onto the imino group.[83] The *N*-aziridinyl imino group was chosen as the radical acceptor because intramolecular addition of an aminyl radical to this moiety would be irreversible due to the fast *β*-fragmentation of the aziridine ring (*Scheme 30*).[98] This reaction is the first example of a catalytic employment of tributyltin hydride in a radical reaction involving the azido group.



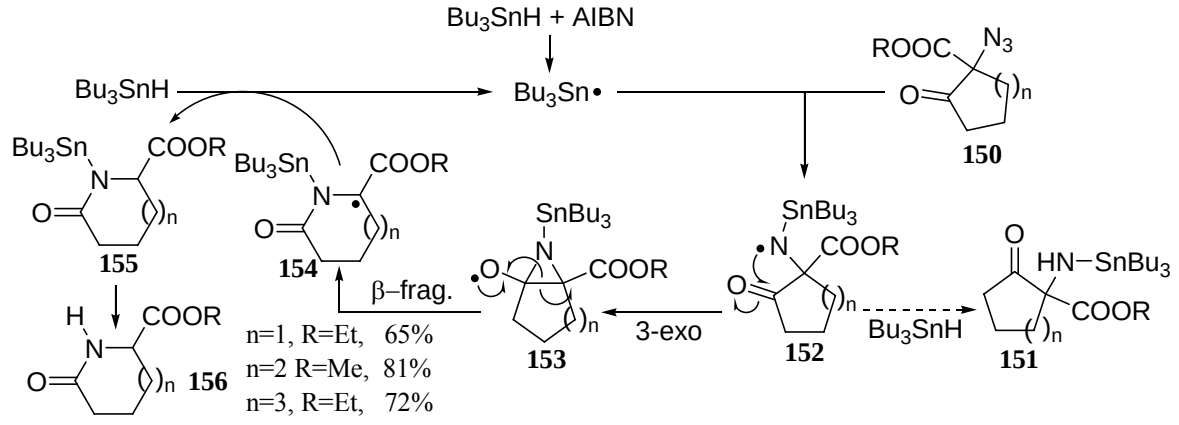
Scheme 30. *Kim cyclisation of stannylaminyl radicals onto the imino group with catalytic amount of Bu_3SnH*

Following this hint, Fu[99] and co-workers have used a strategy for carrying out Bu_3SnH catalyzed reactions that allow the reduction of aromatic and aliphatic azides to be accomplished with only 5 mol % Bu_3SnH. The reaction mechanism can be divided in two steps. In the first step the catalytic amount of tributyltin hydride reduces the organoazide **143** to an organostannyl amine **144**, then the latter reacts with *n*-propanol **145** to transfer the $SnBu_3$ group to the oxygen atom of the alcohol giving the final amine **147**. The formed tin alkoxyde **146** can then be reduced by $PhSiH_3$ **148** to regenerate the catalyst (*Scheme 31*). This Bu_3SnH-catalised reduction is very useful for practical purposes because it can be carried out in the presence of functional groups susceptible of reduction, e.g. alkynes, alkenes, aldehydes, ketones, nitro-groups and halo-compounds.



Scheme 31. *Bu_3SnH catalyzed reduction of aromatic and aliphatic azides*

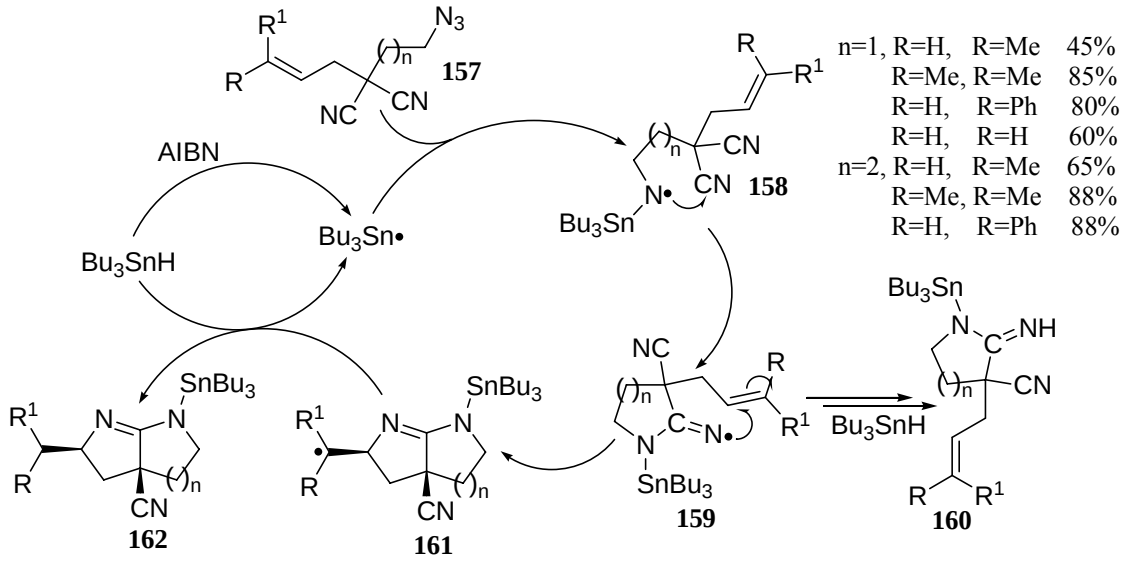
A further important application of intramolecular radical reactions of organic azides with carbonyl groups is the regiospecific nitrogen insertion reactions for the synthesis of amides and lactams developed by Benati and co-workers.[100] The reactions of α-azido-β-keto esters **150** were carried out with Bu_3SnH and AIBN in benzene and yielded the ring-expanded lactams **156** and amides as a result of a smooth 3-exo cyclisation of a transient (tributylstannyl)aminyl radical **152** onto the ketone group and subsequent *β*-scission of the derived alkoxy radical **153** (*Scheme 32*). The resonance stabilisation of the eventual amide group and the formation of the captodatively stabilised alkyl radical **154** are probably the driving forces for the process, although, in some cases, these effects are not strong enough to completely prevent early reduction of the stannylaminyl radical to the corresponding amine **151**. This methodology offers however a useful, versatile alternative to usual ionic methods, which often suffer from poor regioselectivity.[101]



Scheme 32. *Benati ring-expanded synthesis of lactams by radical nitrogen insertion*

Carbonyl compounds and imino derivatives are not the only examples that are liable of nuclephilic addition by stannylaminyl radicals. In 1997 Kim reported the first example of an intramolecular radical addition of stannylaminyl radicals onto a nitrile group,[102] but the first

application to the synthesis of appealing *N*-containing heterocycles was showed by Leardini and co-workers.[64e] Treatment of azidoalkylmalononitriles **157** with tributyltin hydride in the presence of AIBN furnishes stannylaminyl radicals **158** that are prone to give efficient 5- and 6-exo cyclisation onto the nitrile group. The derived resonance-stabilised aminoiminyl radical **159** can easily give 5-*exo* cyclisation onto a suitable internal alkene, thus offering a new valuable diastereoslective entry to pyrrolopyrroles and pyrrolopyridines **162** (*Scheme 33*).



Scheme 33. *Leardini synthesis of pyrroles via intramolecular addition of stannylaminyl radicals onto nitriles*

Although the system tributyltin hydride/AIBN is the most popular way to generate free radicals, in particular *N*-centred radicals derived from the azido group, this method suffers however from serious problems when used for preparative, pharmaceutical and biological applications, since tin hydrides and its derivatives are extremely toxic.[103] Furthermore, organotin traces are difficult to be removed completely from the reaction products *(see the precedent section of "tin-free methodologies")*.

To make tin hydride applications more environmentally friendly, one first possibility is to employ Bu_3SnH in catalytic amounts.[99, 104] Nevertheless, this approach does not represent the best solution, since small amounts of tin derivatives still remain in the final products.

In order to use less toxic compounds and, at the same time, to easily separate tin residues from the reaction mixture, one could consider the possibility to employ polymer-supported organotin reagents. To prepare the reagent, two different approaches have been developed: 1) functionalisation of a polystyrene with organotin moieties[105] and 2) copolymerisation with a monomer bearing organotin functionalities.[104, 106] Both these methods give reagents that are highly efficient in reduction of organic halides, isonitriles and thiocarbonates,[107] and allow to effectively

remove tin by-products from the target compounds. For example, using the first method, the residual amount of tin decreases from 98000 ppm to 26 ppm.[108] Moreover, both methods allow to recycle the organotin-supported polymer.

Highly fluorinated tin hydrides have been synthesised by Curran's group and studied as reagents for 'green' radical reactions.[109] These reactions are carried out in fluorinated solvents and the separation/recovery of organotin reagents is easily achieved by a simple liquid-liquid extraction with dichloromethane.

Even water soluble tin hydrides have been synthesised and applied as reducing agents for halides. In this case, in order to afford hydrophilicity, the alkyl chains of the triorganostannane were replaced by methoxyethoxypropyl substituents.[110]

The problem of contamination of radical reaction products by organotin residues can of course solved by substituting stannanes[111] with other non-tin-based radical reducing reagents such as silicon and germanium hydrides. As far as silanes are concerned, tris(trimethylsilyl)silane [$(TMS)_3SiH$],[112] although much more expensive than tributyltin hydride, has been proved to be a valid alternative to tin reagents[113] thanks to lack of toxicity and ease of purification of the reaction mixtures. Although these two reagents have sometime shown some relevant differences in reactivity, depending on the substrate, they can generally be used in radical reductive processes without any substantial change in the reaction outcome.[114] Usually, tris(trimethylsilyl)silane can be utilised with major success in radical reduction of chlorides and in reactions where good diasteroselectivity is required, probably due to the different steric hindrance compared to tributyltin hydride. Unfortunately, the high cost and, sometimes, also the not full stability of tris(trimethylsilyl)silane limit to some extent its use for preparative applications.

No examples have been reported of addition and useful synthetic applications of $(TMS)_3SiH$ with organic azides. Kim showed the $(TMS)_3SiH$ prefers to attack the carbonyl group instead of the azido group when both functionalities are present in the same molecule[83] and Minozzi[87d] demonstrated the tris(trimethylsilyl)silyl radical was unable to react completely with aromatic azides. On the contrary, in the same paper, good results have been obtained in the radical reduction of organic aryl azides with triethylsilane as the reducing agent and *tert*-dodecanethiol as the polarity-reversal catalyst.[115] The employment of triethylsilane and polarity-reversal catalysis (PRC) represents a new, fascinating challenge in the world of tin-free processes. Et_3SiH is safe, cheaper than both Bu_3SnH and $(TMS)_3SiH$, easily removable from the reaction mixtures, and as efficient as tributyltin hydride for the generation of carbon centred radicals by halogen abstraction.[113]

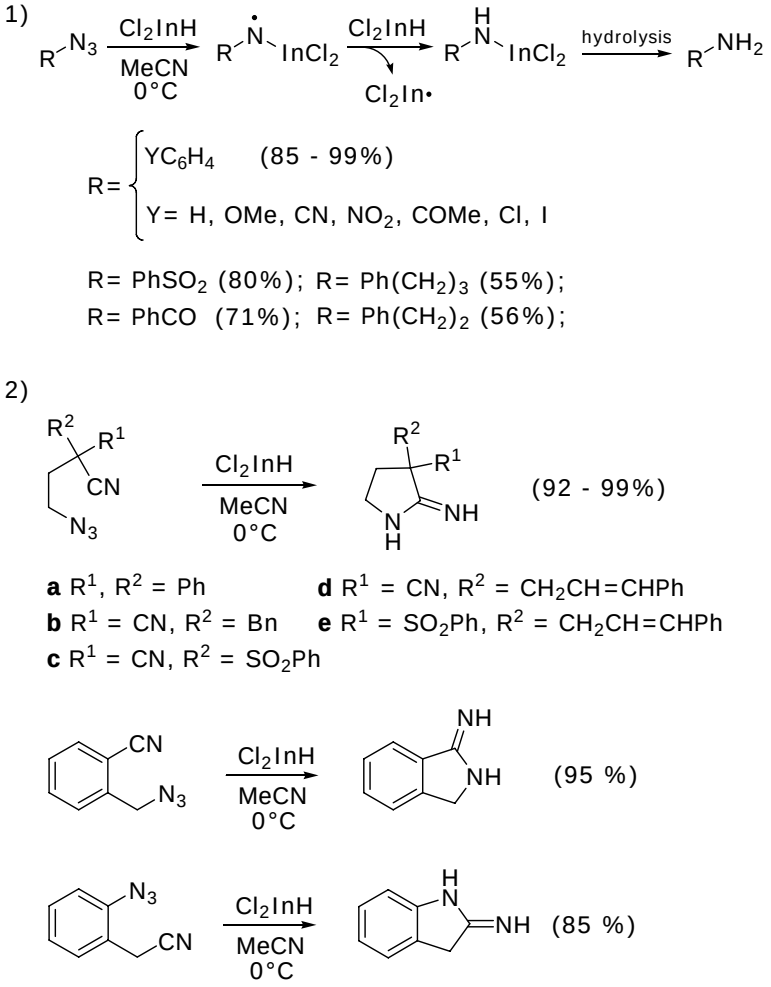
As far as germanium is concerned, applications of tributylgermanium hydride in tin-free reactions have been reported for the first time by Bowman.[116] Tributylgermanium hydride has several

practical advantages over tributyltin hydride, i.e. low toxicity, good stability, and greater ease of reaction work-up. It can be used to generate alkyl, vinyl, and aryl radicals from quite a large number of substrates and the slower rate of hydrogen abstraction from Bu_3GeH by carbon-centred radicals compared to Bu_3SnH can positively affect cyclisation reactions. When required, polarity reversal catalysis with benzenethiol can be successfully used. The latter approach has also been employed by Spagnolo and co-workers[88] in the first example of radical reduction of aryl azides with tributylgermanium hydride. Unfortunately, like $(TMS)_3SiH$, tributylgermanium hydride and other organogermanium derivatives are extremely expensive and this can strongly limit their application in organic synthesis.

Highly rewarding results were instead provided by the subsequent use of dichloroindium hydride, which, in recent years, has often replaced Bu_3SnH to promote 'green' radical chain reactions of various carbon compounds.[117]

Dichloroindium hydride is not commercially available, owing to its limited stability, but it is readily produced in situ from commercial indium trichloride by several methods. For the study with azides, it was found that the most convenient method was the known transmetallation reaction between $InCl_3$ and Et_3SiH in acetonitrile solution at 0 °C. Under these very mild conditions the produced indium hydride gave a very straightforward reaction with many phenyl azides bearing, inter alia, reducible groups such as cyano, nitro, methoxycarbonyl, and iodo, generally affording high to excellent yields of the corresponding anilines over a (relatively) brief time. Sulfonyl and acyl azides gave good yields as well of the corresponding amides, but over longer times. Contrary to the above reactions with triethylsilane and tributylgermane, also aliphatic azides afforded the respective amines in satisfactory, though a little less rewarding, yields [*Scheme 34, Eq. (1)*].[118]

Indium-hydride-mediated radical reactions can usually occur in the absence of any added radical initiator, and also the reactions with azides followed this rule; however, it was found that the presence of triethylborane significantly enhanced the rates of the slower reactions. Moreover, with certain azides the presence of TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) caused evident inhibition of the usual reduction. It was therefore suggested that the reduction of azides with dichloroindium hydride should likely involve a radical chain mechanism based on the key intermediacy of *N*-indium-substituted aminyl radicals [*Scheme 34, Eq. (1)*].



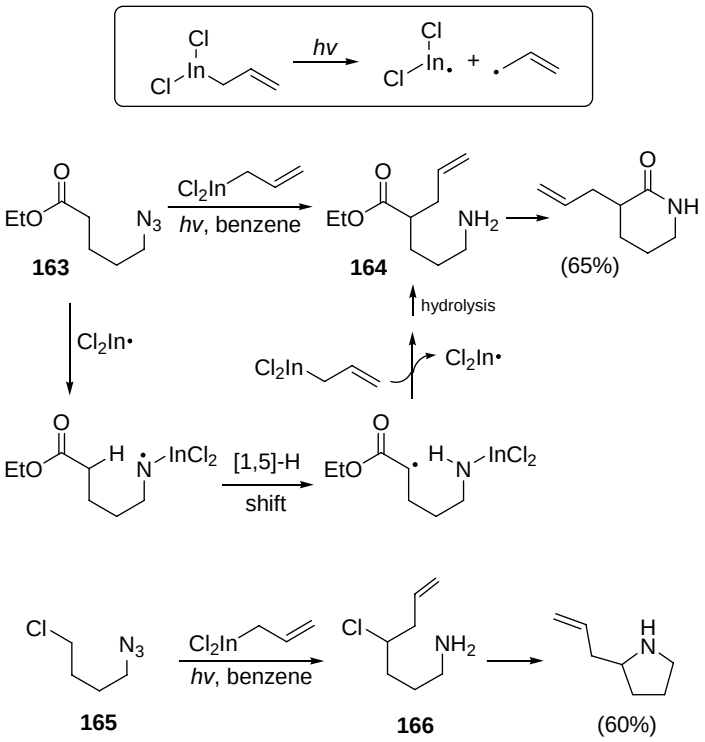
Scheme 34. *Radical reactions of azides with $InCl_2H$*

Novel indium-aminyl radicals were successfully exploited in an interesting transformation of aliphatic and aromatic azides bearing a cyano group in the side chain into pyrrolidine derivatives. Indeed, under the usual conditions reported above, dichloroindium hydride converted a variety of azidonitriles to cyclized pyrrolidin-2-imines in practically quantitative yields through 5-exo cyclization of presumable indium-aminyl radicals onto the cyano moiety. [*Scheme 34, Eq. (2)*].

Interesting information on the synthetic applications of dichloroindium-aminyl radicals were obtained by a recent study on the photochemical reaction of easily available allylindium dichloride with certain aliphatic azides bearing suitable substituents in the side chain. This study was solicited by ESR spectral evidence suggesting that, under photochemical conditions, allylindium dichloride would undergo fair homolytic fragmentation of the carbon-indium bond yielding allyl and dichloroindyl radicals.[119] Photolysis of allylindium dichloride in benzene solution in the presence of

azido ester **163** led to efficient production of the allylated amine **164**, whose prompt condensation afforded the corresponding allylated pyperidinone in good overall yield (*Scheme 35*).

Similarly, chloroazide **165** was converted to the corresponding amine **166**, which eventually furnished the allylated pyrrolidine to a comparable extent (*Scheme 35*). The allylated products **164,166** seemingly occurred through a tandem radical process entailing intramolecular 1,5-H transfer reaction of initial indium-aminyl radicals, followed by allylation of the (electrophilic) translocated carbon radical by the (nucleophilic) allylindium reagent. Similar 1,5-H transfer reactions are known to occur with stannylaminyl radicals, but under thermal conditions.[120] However, it was established that allyltributylstannane fails to react with alkyl azides such as **163,165** under analogous photochemical conditions.



Scheme 35. *Radical allylation using allylindium dichloride*

The overall results obtained with azides and indium-centered radicals show that indium reagents can likely provide a powerful tool for the synthetic application of aromatic and aliphatic azides under radical tin-free conditions.

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[1] For organic azides to be manipulable or non explosive, the rule is that the number of nitrogen atoms must not exceed that of carbons and that $(N_C + N_O)/N_N \geq 3$ (N = number of atoms).

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CHAPTER 5
THE NEW DISCOVERY:IMINYL RADICALS FROM AZIDES

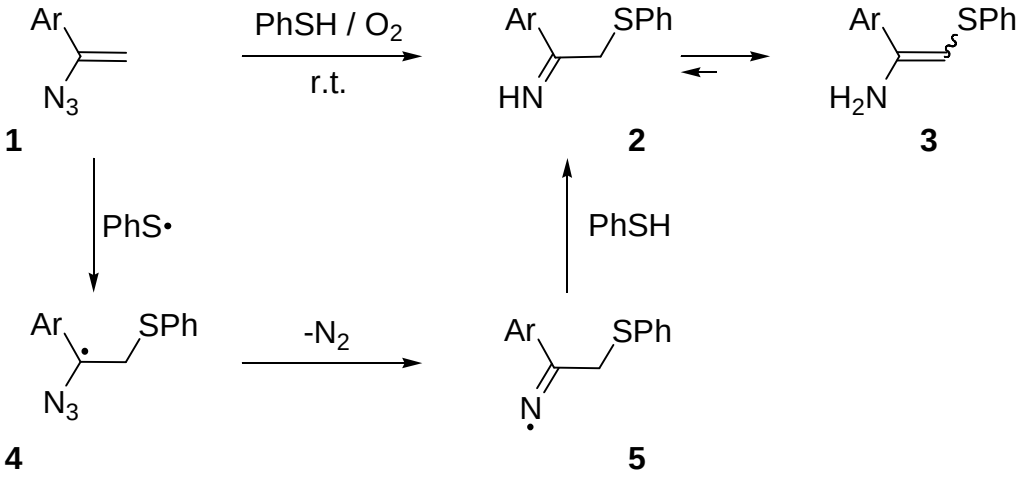
5.1 Introduction

As shown in precedent chapter, in recent years considerable attention has been devoted to the radical chemistry of alkyl and aryl azides, which have been shown to act, to a varying degree, as radical acceptors toward a range of carbon- and heteroatom-centered species yielding aminyl radicals after nitrogen loss from initial triazenyl adducts.[1]

The intramolecular additions of carbon radicals usefully afford cyclic aminyl radicals that are valuable intermediates for the synthesis of *N*-heterocycles.[2] The intermolecular additions of silyl,[3a] germyl,[3b] indyl,[3c] and, mainly, stannyl radicals[Errore. Il segnalibro non è definito.] efficiently lead to corresponding *N*-substituted aminyl radicals. In particular, *N*-stannylaminyl radicals[1] are the key intermediates in many azide cyclization / rearrangement processes mediated by tributyltin hydride (Bu_3SnH) and AIBN.[1,4]

Therefore, until last year the radical chemistry of aliphatic and aromatic azides has invariably been confined to the generation and synthetic applications of aminyl radicals, although a work appeared in 1997 seemingly suggesting that alkyl azides might additionally act as progenitors of iminyl radicals, provided that transient radicals be produced on the carbon atom linked to the azido function.[5]

The radical chain reaction of benzenethiol with α-azidostyrenes **1** was found to afford virtually quantitative yields of β-sulfanylated imines **2** and tautomeric enamines **3** clearly ascribable to the intervention of 2-sulfanyliminyl radicals **5**. These intermediates could result from sulfanyl radical attack at the azide β-carbon followed by β-elimination of molecular nitrogen from the ensuing α-azidobenzyl radical adduct **4** (*Scheme 1*).[5]



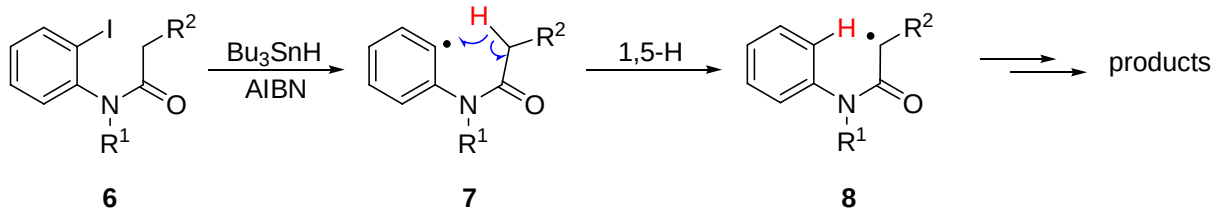
Scheme 1. *Alkyl azides as progenitors of iminyl radicals*

Surprisingly, despite that promising chemical information, the potential utility of alkyl azides in the production of iminyl radicals has remained totally ignored. Nevertheless iminyl radicals are of significant interest in synthetic radical chemistry due to their ability to perform cyclizations onto aromatic rings[6a,e,f] and double bonds,[7] and additional fragmentation reactions to give nitrile products.[5,7b,8]

Therefore, producing straightforwardly iminyl radicals from azides would have been very important.

5.2 Iminyl Radicals from α-Azido o-Iodoanilides via 1,5-H Transfer Reactions of Aryl Radicals: New Transformation of α-Azido Acids to Decarboxylated Nitriles[9]

In previous studies it has been shown that the radical reaction of Bu_3SnH/AIBN with *N*-substituted *o*-iodoanilides **6** results in smooth generation of the carbon radicals **8** adjacent to the carbonyl group via 1,5-hydrogen transfer reactions of the initially formed aryl radicals **7** .[10]

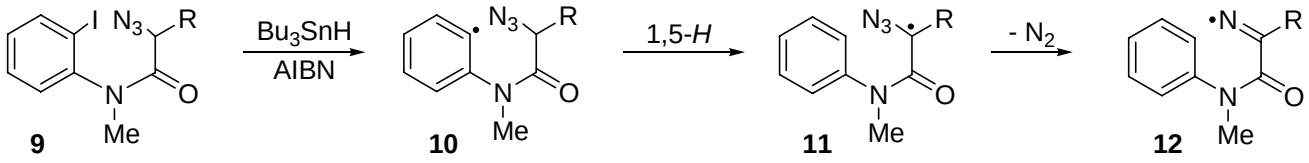


Scheme 2. *Generation of α-carbonyl C-radicals via 1,5-H transfer*

In light of these interesting findings, maybe it was possible that analogous *o*-iodoanilides bearing an azido function on the carbon attached to the carbonyl group should similarly provide an easy entry to corresponding α-azidoalkyl radicals, which might probably form iminyl radicals by subsequent elimination of molecular nitrogen.

Were therefore prepared several α-azido *o*-iodo-*N*-methylanilides (**9a-h**) in order to ascertain the possible synthetic potential of their radical reactions with Bu_3SnH for the generation of the corresponding iminyl radicals **12a-h** (*Scheme 3*). In view of previous evidence,[2c,f] it was expected that, in the presence of the azido moiety, stannyl radicals should perform selective iodine abstraction to give initial aryl radicals **10a-h**.

The hitherto unknown substrates **9a-h** were readily available using standard methodology. In particular, compounds **9a-d** were obtained by treatment of *o*-iodo-*N*-methylaniline with the appropriate α-bromoalkanoyl bromide/chloride followed by treatment of the resultant bromoanilide with sodium azide in DMSO. The azido compounds **9e-h** were similarly obtained, but in these cases the iodoaniline was reacted with preliminary α-azido acyl chlorides.

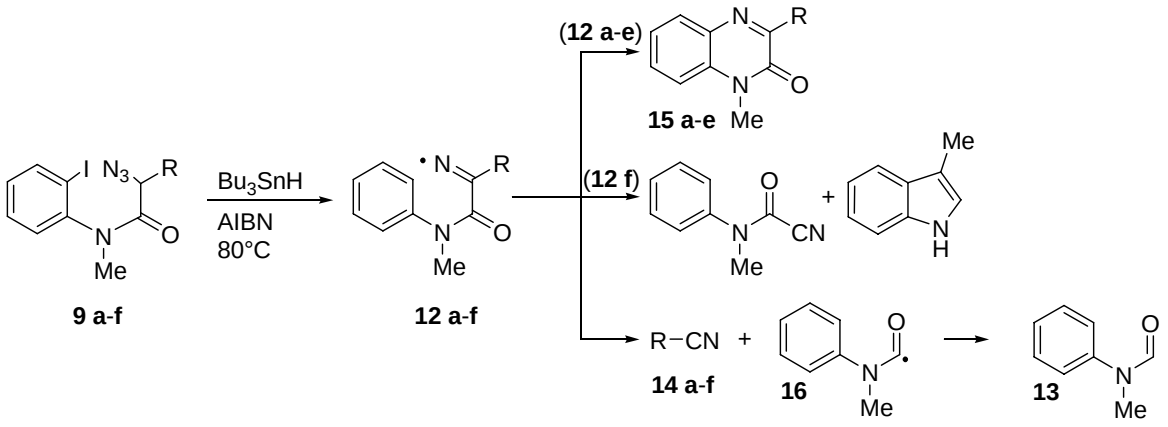


a: R = H; **b**: R = Me; **c**: R = *n*-$C_{11}H_{23}$; **h**: R = CH_2=$CHCH_2CH_2$
d: R = 1-adamantyl; **e**: R = $PhCH_2$;
f: R = (3-indolyl)CH_2; **g**: R = 4-MeO-C_6H_4;

Scheme 3. *Possible synthetic pathway for generation of iminyl radicals from aliphatic azides*

The reactions between azido iodoanilides **9** (0.5 mmol) and Bu_3SnH (0.65 mmol) were usually carried out in refluxing benzene (50 mL) and were initiated by thermal decomposition of AIBN (0.125 mmol). The reactions were prolonged until complete disappearance of the starting material (4-5 h) and the crude mixtures were then directly subjected to chromatographic separation.

Anilides **9c-e** invariably furnished high yields of the respective fragmentated nitrile, namely dodecanenitrile **14c**, 1-adamantanecarbonitrile **14d**, and phenylacetonitrile **14e**, along with a comparable amount of formanilide **13**. Compound **9c** additionally furnished a modest amount of 3-undecylquinoxalinone **15c**, while the congeners **9d,e** virtually failed to form the corresponding cyclized products **15d,e** (*Scheme 4* and *Table 1, entries 3-5*).



Scheme 4

Table 1. *Radical Reactions of Azidoanilides **9a-f** with Bu_3SnH/AIBN in Refluxing Benzene*.

entry	anilide	Products (%)[a] 13	14	15
1	**9a**	55	*b*	15
2	**9b**	60	*c*	18
3	**9c**	65	75	20
4	**9d**	84	86	<2
5	**9e**[d]	89	80	<2
6	**9f**[e]	45	50	-
7	**9c**[f]	80	85	13

[a]Yields isolated by column chromatography. [b]Hydrogen cyanide **14a** was not detected. [c]Acetonitrile **14b** was not detected. [d]Trace amounts of N-methyl-N-phenylcarbamoyl cyanide were also isolated. [e]3-Methylindole (18%) and N-methyl-N-phenylcarbamoyl cyanide (17%) were also isolated (see text). [f]Reaction carried out at 110 °C.

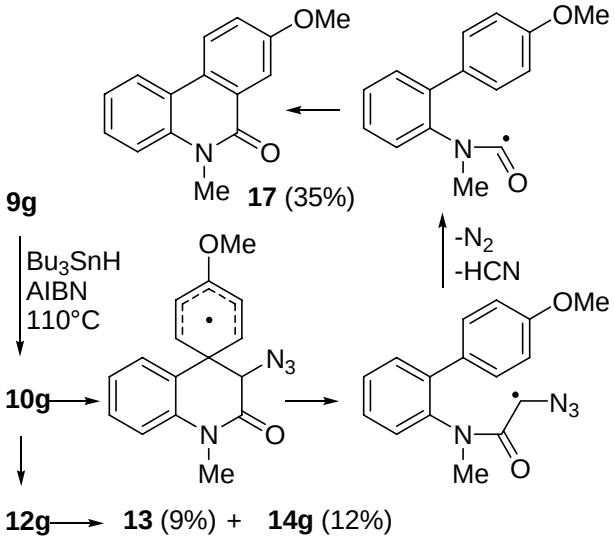
(3-Indolyl)propionamide **9f** similarly led to major production of (3-indolyl)acetonitrile **14f** and formamide **13**, but, in this case, minor production of *N*-methyl-*N*-phenylcarbamoyl cyanide and 3-methylindole additionally occurred (*Scheme 2* and *Table 1, entry 6*).

Further, an analogous behavior was encountered with acetanilide **9a** and propionanilide **9b**, since both compounds gave a fairly good yield of the usual formanilide **13** together with minor amounts of oxoquinoxalines **15a,b**. Under these circumstances, however, the presumable nitrilic products, i.e. hydrogen cyanide **14a** and acetonitrile **14b**, respectively, escaped detection (*Scheme 2* and *Table 1, entries 1 and 2*).

The encountered products evidently pointed to the actual intervention of the desired iminyl radicals **12a-f**. Despite our reductive conditions, these radicals **12** were essentially prone to undergo β-fragmentation to yield nitrile **14** and carbamoyl radical **16**,[11] and thence formanilide **13**, as well as, but to a (very) limited extent, competing aromatic cyclization to oxoquinoxaline **15**.[12] However, iminyl **12f** was also somewhat prone to afford *N*-methyl-*N*-phenylcarbamoyl cyanide and 3-methylindole by an alternative β-elimination of (3-indolyl)methyl radical.[13]

These observations prompted us to prove that under more forcing thermal conditions the production of nitrile **14** might conceivably be improved at the expense of quinoxaline **15**. Indeed, when the reaction of tridecanamide **9c** was repeated at 110 °C in a sealed tube, the outcoming yield of dodecanenitrile **14c** (and **13**) was usefully enhanced at the expense of **15c** (*Table 1*, entries 3 and

7). In light of this rewarding finding the behavior of the additional (4-methoxyphenyl)acetanilide **9g** was directly examined at 110 °C. Unexpectedly, compound **9g** failed to act as an efficient source of iminyl radical **12g**, since it actually led to a rather complex reaction mixture from which phenanthridone **17** was isolated in 35% yield along with only poor amounts of 4-methoxybenzonitrile **14g** and formanilide **13 (***Scheme 5***)**.



Scheme 5

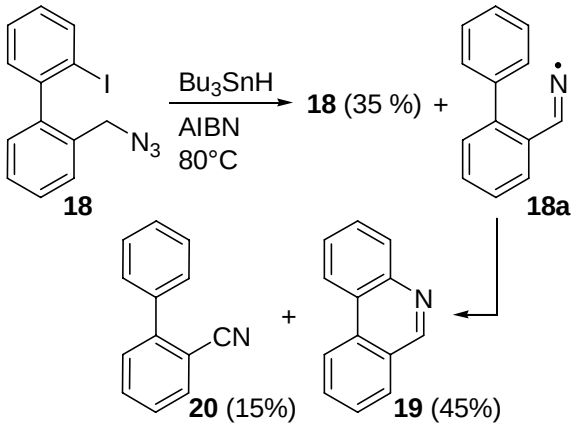
The observed phenanthridone **17** was presumably formed through the impressive cascade radical process outlined in *Scheme 5*. The derived aryl radical **10g** was seriously discouraged to undergo 1,5-H transfer in favor of six-membered ipso-cyclization onto the adjacent aromatic ring, despite the fact that in this case the H-transfer process might have been especially promoted by the generation of fairly stable azidobenzylic radical **11g**.

Our final attempt to study 2-azido-5-hexenanilide **9h** was unfortunately frustrated by the finding that this unsaturated azide, under our standard conditions, suffered fairly rapid decomposition, probably owing to intramolecular cycloaddition onto the alkene moiety.

Thus, the general chemical evidence furnished by the above findings strictly suggests that anilides **9**, except when an aryl was present on the α-carbon, were able to cleanly afford the respective α-(aminocarbonyl)iminyl radicals **12**[14] via very fast 1,5-hydrogen transfer of primary aryl radicals **10** followed by rapid extrusion of dinitrogen from the resultant azidoalkyl radicals **11** (*Scheme 3*). This fact was further substantiated by our general failure to observe any deiodinated substrate, which might have resulted from tin hydride reduction of aryl radical **10** and/or translocated azidoalkyl radical **11**. The resulting iminyl radicals **12**, besides displaying a certain ability to give 6-membered aromatic cyclization onto the adjacent anilide ring, revealed a fair propensity to undergo selective β-elimination of carbamoyl radical **16** forming the corresponding nitrile **14**. Notably, the preferential

release of radical **16** was irrespective of the stability of the alkyl radical that might have been alternatively expelled.[15,16] Such peculiar behavior of iminyls **12** was rather unpredictable since it was still unknown that carbamoyl radical **16** would be more stable even than fairly stabilized alkyl radicals. Consequently, in view of the easy availability of α-azido acids by various established methods,[d,17] we were led to discover that the present anilides **9** can find interesting use in the unprecedented radical conversion of those azido acids into decarboxylated alkanenitriles.

In this work we also performed a brief investigation of the radical reactivity of another accessible alkyl azide, i.e. the iodo azide **18** shown in *Scheme 6*. Under our standard conditions, the progressive consumption of **18** was noticeably low, probably due to poorly efficient chain reaction with stannyl radicals.[18] Much unaltered material **18** (35%) was recovered even after prolonging the reaction time for 16 h and concomitantly using a double amount of AIBN. However, clean evidence was obtained that also under these circumstances tandem hydrogen translocation and dinitrogen extrusion offer an excellent entry to iminyl radical **18a**. In fact, phenanthridine **19** (45%) and nitrile **20** (15%)[19] were found to occur as the virtually exclusive reaction products (*Scheme 6*).



Scheme 6

In conclusion, *o*-iodo-*N*-methylanilides derived from α-azido acids can act as excellent precursors of novel α-(aminocarbonyl)iminyl radicals through very fast 1,5-hydrogen transfer reaction of the initial aryl radicals and subsequent extrusion of dinitrogen by the ensuing α-azidoalkyl radicals.

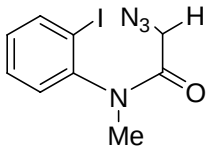
Those iminyl radicals have a peculiar tendency to form the corresponding nitrile by β-elimination of carbamoyl radical and therefore can be exploited for a new radical transformation of α-azido acids into decarboxylated nitriles. Regardless of the present mechanistic and synthetic implications, this work has clearly established that alkyl azides can be envisioned as powerful precursors not only of aminyl radicals but also of the iminyl congeners.

Experimental section

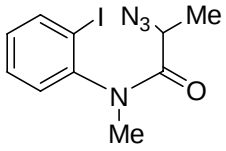
General Remarks.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions, using tetramethylsilane as internal standard. Coupling constants are given in Hz. IR spectra were recorded in $CHCl_3$ solutions or as liquid films. Mass spectra were recorded either by the electron spray ionization (ESI) method or with an electron impact (EI) GC-MS instrument. High resolution mass determinations (HRMS) were carried out by electron impact at 70 eV. Column chromatography was performed on ICN silica gel (63–200, 60 Å) by gradual elution with light petroleum (bp = 40–70 °C)/diethyl ether and final elution with dichloromethane or methanol. Tributyltin hydride was commercially available (Aldrich) and was used as received. Azobisisobutyronitrile (AIBN, Fluka) was recrystallized from $CHCl_3/CH_3OH$.

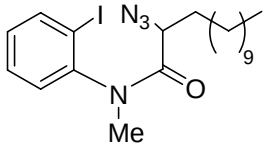
N-Methylformanilide **13**, 3-methyl-1*H*-indole, and nitrile products such as dodecanenitrile **14c**, 1-adamantanecarbonitrile **14d**, phenylacetonitrile **14e**, and 4-methoxybenzonitrile **14g** were identical to commercial (Aldrich) samples. (3-Indolyl)acetonitrile **14f** was identical to an authentic sample independently prepared.[20] Known products such as 1-methyl-2(1*H*)-quinoxalinone (**15a**),[21] 1,3-dimethyl-2(1*H*)-quinoxalinone (**15b**), and 8-methoxy-5-methyl-6(5*H*)-phenanthridone (**17**)[22] had spectral data consistent with those reported; owing to inadequate quantity, structural assignments to the already known 3-benzyl-1-methyl-2(1*H*)-quinoxalinone (**15e**)[23] and the hitherto unknown 3-(1-adamantyl)-1-methyl-2(1*H*)-quinoxalinone (**15d**) were based on MS spectral data, in addition to chemical expectation. The new 1-methyl-3-undecyl-2(1*H*)-quinoxalinone (**15c**) was characterized on the basis of spectral and analytical data. The ^{1}H and ^{13}C NMR spectra of azido anilides **9a-h** generally showed peaks due to the concomitant presence of syn and anti amido rotamers.



2-Azido-*N*-(2-iodophenyl)-*N*-methylacetamide (9a). Commercial 2-bromoacetyl bromide (Aldrich) (2 g, 10 mmol) in trichloromethane (5 mL) was added dropwise to a solution of 2-iodo-*N*-methylaniline (1.15 g, 5 mmol) and pyridine (0.6 g, 7.5 mmol) in trichloromethane (25 mL). The resultant mixture was stirred at room temperature for 2 h, then washed with water, dried over Na_2SO_4 and evaporated. The residue was passed through a short column of silica to give 1.5 g of crude 2-bromoanilide, which was directly used without further purification. The obtained compound was reacted with 0.75 g of sodium azide in DMSO (25 mL) for 8 h at room temperature. The resulting mixture was then poured into water (100 mL) and extracted with ether. Evaporation of the organic layer and eventual chromatography gave the title azide (1.3 g, 40% based on the starting acetyl bromide) as a solid, mp = 78-79 °C; IR ($CHCl_3$) ν_{max} (cm^{-1}) 3054, 2987, 2108, 1677; ^1H NMR (400 MHz) δ 3.23 (3 H, s), 3.52 (2 H, dd, J_{d1} = 15.9, J_{d2} = 22.7), 7.13 (1 H, td, J_t = 7.7, J_d = 1.5), 7.30 (1 H, dd, J_{d1} = 7.9, J_{d2} = 1.6), 7.46 (1 H, td, J_t = 7.7, J_d = 1.5), 7.95 (1 H, dd, J_{d1} = 7.9, J_{d2} = 1.5); ^{13}C NMR (100 MHz) δ 36.2, 51.1 (CH_2), 99.1 (C), 128.9, 130.3, 130.5, 140.5, 144.1 (C), 166.9 (C); MS (ESI) 339 $(M + Na)^+$.

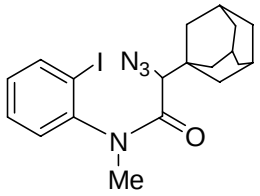


2-Azido-*N*-(2-iodophenyl)-*N*-methylpropanamide (9b). This compound was prepared in 45% overall yield from commercial 2-bromopropanoyl bromide (Aldrich) by using the same procedure as described above for the preparation of the analogue **9a**. The title azide was a solid, mp = 67-68 °C; IR ($CHCl_3$) ν_{max} (cm^{-1}) 2991, 2984, 2109, 1670, 1471, 1388, 1240; ^1H NMR (400 MHz) δ 1.34 (1.2 H rotamer A, d, J_d = 6.8), 1.47 (1.8 H rotamer B, d, J_d = 6.8), 3.21 (1.2 H rotamer A, s), 3.22 (1.8 H rotamer B, s), 3.35-3.47 (1 H, m), 7.10-7.14 (1 H, m), 7.26 (0.4 H rotamer A, dd, J_{d1} = 7.8, J_{d2} = 1.5), 7.35 (0.6 H rotamer B, dd, J_{d1} = 7.8, J_{d2} = 1.4), 7.43-7.49 (1 H, m), 7.94 (0.6 H rotamer B, dd, J_{d1} = 7.5, J_{d2} = 1.5), 7.97 (0.4 H rotamer B, dd, J_{d1} = 8.0, J_{d2} = 1.5); ^{13}C NMR (100 MHz) – mixture of the two rotamers – δ 16.2, 16.9, 36.4, 54.1, 54.8, 99.0 (C), 99.6 (C), 128.7, 129.4, 130.0, 130.2, 130.3, 130.4, 140.2, 140.6, 144.8 (C), 169.8 (C), 170.9 (C); MS (ESI) 353 $(M + Na)^+$.



2-Azido-*N*-(2-iodophenyl)-*N*-methyltridecanamide (9c).

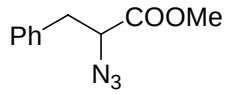
2-Bromotridecanoic acid was prepared by bromination of the commercial acid (Aldrich) according to a literature method.[24] The bromoacid (730 mg, 2.5 mmol) was dissolved in dry methylene chloride (6 mL) containing two drops of DMF and slowly treated with oxalyl chloride (2.5 mmol) at 0 °C under a stream of nitrogen. This mixture was stirred at room temperature under nitrogen for 3 h; then it was cooled to 0 °C and slowly treated with a solution of 2-iodo-*N*-methylaniline (5 mmol) in dry methylene chloride (15 mL). The resultant mixture was stirred at room temperature for 15 h, then cooled to 0 °C and treated with water (50 mL). After evaporation of the organic layer, the residue was passed through a silica-gel column to give 1.0 g of crude 2-bromoanilide, which was directly used without further purification. The obtained bromide was treated with 0.9 g of sodium azide in DMSO (20 mL) at room temperature for 10 h; the resulting mixture was poured into water (100 mL) and extracted with ether. Evaporation of the organic layer and eventual chromatographic purification gave the title azide (0.85 g, 72% based on the starting bromoacid) as a solid, mp = 37-38 °C; IR ($CHCl_3$) ν_{max} (cm^{-1}) 2925, 2854, 2103, 1673; ^{1}H NMR (400 MHz) δ 0.88 (3 H, td, J_t = 7.1, J_d = 1.3), 1.13-1.35 (18 H, m), 1.61-1.97 (2 H, m), 3.16-3.27 (1 H, m), 3.22 (3 H, bd, J_d = 0.9), 7.09-7.14 (1 H, m), 7.25 (0.5 H rotamer A, dd, J_{d1} = 7.9, J_{d2} = 1.5), 7.34 (0.5 H rotamer A, dd, J_{d1} = 7.9, J_{d2} = 1.6), 7.42-7.48 (1 H, m), 7.96 (1 H, td, J_t = 8.2, J_d = 1.5); ^{13}C NMR (100 MHz) – mixture of the two rotamers – δ 14.07, 22.64 (CH_2), 25.69 (CH_2), 25.96 (CH_2), 28.75 (CH_2), 29.05 (CH_2), 29.18 (CH_2), 29.22 (CH_2), 29.28 (CH_2), 29.40 (CH_2), 29.44 (CH_2), 29.51 (CH_2), 29.54 (CH_2), 30.41 (CH_2), 31.31 (CH_2), 31.86 (CH_2), 36.31, 36.37, 58.73, 59.14, 98.77 (C), 99.65 (C), 128.98, 129.54, 129.83, 130.03, 130.23, 130.27, 140.30, 140.56, 144.70 (C), 144.79 (C), 169.51 (C), 170.39 (C); MS (ESI) 393 $(M + Na)^+$.



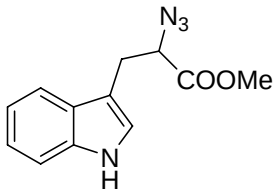
2-(1-Adamantyl)-2-azido-*N*-(2-iodophenyl)-*N*-methylacetamide (9d).

2-(1-Adamantyl)-2-bromoacetic acid was prepared by bromination of the commercial acid (Aldrich) according to a literature method.[25] This bromoacid was transformed into the title azide in 50% overall yield by using the same procedure as described above for the analogue **9c**, except that

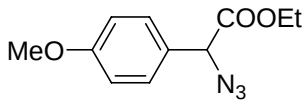
the eventual treatment with sodium azide in DMSO was performed at 90 °C for 72 h. The title azide was a solid, mp = 122-124 °C; IR ($CHCl_3$) ν_{max} (cm^{-1}) 2905, 2847, 2099, 1665; ^1H NMR (400 MHz) δ 1.46-1.97 (15 H, m), 2.91 (0.4 H rotamer A, s), 2.96 (0.6 H rotamer B, s), 3.22 (1.2 H rotamer A, s), 3.23 (1.8 H rotamer B, s), 7.07-7.12 (1 H, m), 7.24-7.28 (1 H, m), 7.42-7.48 (1 H, m), 7.96 (0.6 H rotamer B, dd, J_{d1} = 8.1, J_{d2} = 1.5), 7.97 (0.4 H rotamer A, dd, J_{d1} = 7.8, J_{d2} = 1.5); ^{13}C NMR (100 MHz) – mixture of the two rotamers – δ 28.17, 36.40, 36.62 (CH_2), 36.73 (CH_2), 38.76 (CH_2), 39.05 (CH_2), 39.48 (C), 67.61, 68.40, 98.19 (C), 99.29 (C), 129.52, 129.62, 129.78, 129.94, 129.96, 130.15, 140.54, 140.75, 145.26 (C), 145.42 (C), 167.23 (C), 167.86 (C); MS (ESI) 373 $(M + Na)^+$



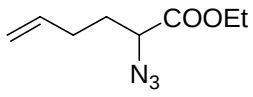
Methyl 2-azido-3-phenylpropanoate (21e). This azido ester was prepared from commercial phenylalanine methyl ester hydrochloride (Aldrich) in 85% yield by using the same diazotransfer procedure as recently reported;[26] IR ($CHCl_3$) ν_{max} (cm^{-1}) 3031, 2955, 2111, 1747, 1497, 1456, 1437.



Methyl 2-azido-3-(1*H*-indol-3-yl)propanoate (21f). This azido ester was prepared from commercial tryptophan methyl ester hydrochloride (Aldrich) by adopting a general diazotransfer procedure recently reported.[7b] To a solution of tryptophan methyl ester hydrochloride (1.2 g, 4.65 mmol) in water (5 mL) was added 0.95 g of NEt_3 (9.3 mmol) and 12 mg of $CuSO_4$; this mixture was cooled in an ice bath and treated dropwise with an acetonitrile solution of triflyl azide prepared from sodium azide (4.35 g, 6.7 mmol) and Tf_2O (1.57 g, 5.56 mmol) in acetonitrile (8 mL). The resultant mixture was stirred at room temperature for 15 h and then extracted with diethyl ether. Evaporation of the organic layer and chromatographic purification of the oily residue gave the title azide (1 g, 88%) as an oil; IR (neat) ν_{max} (cm^{-1}) 3112, 2110, 1736; ^1H NMR (400 MHz) δ 3.21 (1 H, dd, J_{d1} = 14.5, J_{d2} = 8.4), 3.36 (1 H, dd, J_{d1} = 14.5, J_{d2} = 8.4), 3.75 (3 H, s), 4.18 (1 H, bt, J_t = 6.8), 7.07 (1 H, bs), 7.17-7.23 (2 H, m), 7.33 (1 H, d, J_d = 8.0), 7.59 (1 H, d, J_d = 8.0), 8.14 (1 H, bs); ^{13}C NMR (100 MHz) δ 27.6 (CH_2), 52.6, 62.5, 109.9 (C), 111.3, 118.3, 119.6, 122.2, 123.2, 127.0 (C), 136.1 (C), 170.9 (C); MS (ESI) 267 $(M + Na)^+$.

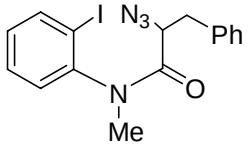


Ethyl 2-azido-2-(4-methoxyphenyl)acetate (21g). This azido ester was prepared from ethyl (4-methoxyphenyl)acetate by bromination with *N*-bromosuccinimide (NBS) followed by displacement of bromide with sodium azide according to a very recently reported procedure;[27] IR (neat) ν_{max} (cm^{-1}) 2102, 1740, 1610, 1513.

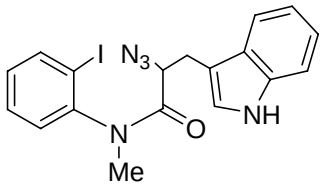


Ethyl 2-azido-5-hexenoate (21h). Ethyl 2-hydroxy-5-hexenoate was prepared in two steps from diethyl oxalate and 3-butenyl magnesium bromide by a literature method.[28] This hydroxy ester (2.5 g, 10.5 mmol) was reacted with methanesulfonyl chloride (1.45 g, 12.5 mmol) and pyridine (1.1 g, 13.8 mmol) in dry methylene chloride (25 mL) at room temperature for 5 days, after which TLC monitored the virtual absence of starting material. The resultant mixture was poured into water (100 mL) and the organic layer separated and evaporated. The residue was passed through a short column of silica to give 2.5 g of the crude mesylate, which was directly used without further purification. The obtained mesylate was treated with sodium azide (1.2 g) in DMSO **(**35 mL**)** at room temperature for 2 h; the resulting mixture was poured into water (150 mL) and extracted with ether. Evaporation of the organic layer and eventual chromatographic purification gave the title azide (1.75 g**,** 60 % based on the starting hydroxyester) as an oil; IR (neat) ν_{max} (cm^{-1}) 2982, 2106, 1742, 1262, 1188; ^{1}H NMR (400 MHz) δ 1.32 (3 H, t, J_t = 7.1), 1.79-1.98 (2 H, m), 2.12-2.28 (2 H, m), 3.84 (1 H, dd, J_{d1} = 8.7, J_{d2} = 5.2), 4.25 (2 H, q, J_q = 7.1), 5.03-5.12 (2 H, m), 5.73-5.84 (1 H, m); ^{13}C NMR (100 MHz) δ 14.1, 29.7 (CH_2), 30.5 (CH_2), 61.2 (CH_2), 61.7, 116.2 (CH_2), 136.3, 170.5 (C); MS (ESI) 206 $(M + Na)^+$.

Synthesis of the α-Azido 2-Iodoanilides 9e-h. General Procedure. A mixture of the appropriate azido ester **21e-h** (5 mmol) in 2 M NaOH (5 mL) and methanol (5 mL) was stirred at room temperature for ca 1 h. Water (25 mL) was added and the mixture extracted with diethyl ether. The aqueous phase was acidified with hydrochloric acid and then extracted with diethyl ether; the separated organic layer was washed with brine and dried over Na_2SO_4. Evaporation of excess ether gave the crude azido acid which was directly used without further purification. The obtained crude azido acid was dissolved in dry methylene chloride (10 mL) containing two drops of DMF and carefully treated with oxalyl chloride (4.8 mmol) at 0 °C under a stream of nitrogen. This mixture was stirred at room temperature under nitrogen for 3 h and then cooled to 0 °C and slowly treated with a solution of 2-iodo-*N*-methylaniline (9.6 mmol) in dry methylene chloride (25 mL). The resultant mixture was stirred at room temperature for 13-15 h, then cooled to 0 °C and washed with water (50 mL). Evaporation of the separated organic layer and eventual chromatographic purification of the residue gave the respective azido anilide **9e-h** in 65-75% yield, based on the starting azido ester.

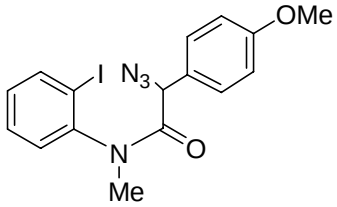


3-Phenyl-2-azido-*N*-(2-iodophenyl)-*N*-methylpropanamide (9e), solid, mp = 102-103 °C; IR ($CHCl_3$) ν_{max} (cm^{-1}) 3054, 2987, 2105, 1668; ^1H NMR (400 MHz) δ 2.91-3.42 (3 H, m), 3.14 (1.65 H rotamer A, s), 3.23 (1.35 H rotamer B, s), 6.98-7.46 (8 H, m), 7.89 (0.55 H rotamer A, dd, J_{d1} = 7.8, J_{d2} = 1.4), 7.94 (0.45 H rotamer B, dd, J_{d1} = 8.0, J_{d2} = 1.4); ^{13}C NMR (100 MHz) – mixture of the two rotamers – δ 36.18, 36.41, 36.94, 38.11, 59.93 (CH_2), 60.73 (CH_2), 98.82 (C), 99.24 (C), 126.91, 127.16, 128.61, 128.63, 128.99, 129.35, 129.40, 129.48, 129.65, 130.16, 130.38, 135.99 (C), 136.69 (C), 140.18, 140.27, 144.33 (C), 144.59 (C), 168.68 (C), 169.39 (C); MS (ESI) 429 $(M + Na)^+$.

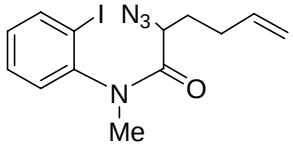


3-(1*H*-Indol-3-yl)-2-azido-*N*-(2-iodophenyl)-*N*-methylpropanamide (9f), solid, mp = 135-137 °C; IR ($CHCl_3$) ν_{max} (cm^{-1}) 3467, 3332, 3062, 2929, 2104, 1667, 1472; ^1H

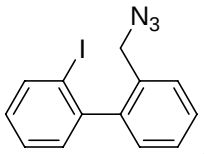
NMR (400 MHz) δ 3.12 (1.8 H rotamer A, s), 3.14-3.4 (2 H, m), 3.24 (1.2 H rotamer B, s), 3.55-3.64 (1 H, m), 6.77-7.44 (8 H, m), 7.83 (0.6 H rotamer A, dd, J_{d1} = 8.0, J_{d2} = 1.4), 7.91 (0.4 H rotamer B, dd, J_{d1} = 8.0, J_{d2} = 1.4), 8.16 (0.6 H rotamer A, bs), 8.28 (0.4 H rotamer B, bs); ^{13}C NMR (100 MHz) – mixture of the two rotamers – δ 26.96 (CH_2), 28.01 (CH_2), 36.27, 36.40, 58.69, 59.17, 98.86 (C), 99.04 (C), 109.98 (C), 110.41 (C), 111.24, 118.29, 118.31, 119.37, 119.54, 121.96, 122.20, 123.30, 123.54, 127.14 (C), 128.89, 129.44, 129.47, 129.87, 130.10, 130.31, 136.03 (C), 136.21 (C), 139.98, 140.32, 144.22 (C), 144.68 (C), 169.42 (C), 170.21 (C); MS (ESI) 468 (M + Na)$^+$.



2-(4-Methoxyphenyl)-2-azido-*N*-(2-iodophenyl)-*N*-methylacetamide (9g), solid, mp = 105-107 °C; IR ($CHCl_3$) ν_{max} (cm^{-1}) 2941, 2928, 2098, 1670, 1511, 1256; ^{1}H NMR (400 MHz) δ 3.19 (2.1 H rotamer A, s), 3.23 (0.9 H rotamer B, s), 3.80 (3 H, s), 4.32 (0.7 H rotamer A, s), 4.54 (0.3 H rotamer B, s), 6.54-7.50 (7 H, m), 7.82 (0.3 H rotamer B, d, J_d = 7.9), 7.96 (0.7 H rotamer A, d, J_d = 7.9); ^{13}C NMR (100 MHz) – mixture of the two rotamers – δ 36.4, 36.6, 55.2, 62.3, 63.7, 99.5 (C), 99.7 (C), 114.2, 125.3 (C), 125.9 (C), 129.3, 129.4, 129.5, 129.9, 130.0, 130.2, 140.0, 140.4, 144.0 (C), 144.5 (C), 160.1 (C), 160.3 (C), 168.5 (C), 168.7 (C); MS (ESI) 445 (M + Na)$^+$.



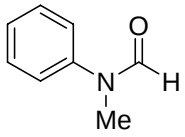
2-Azido-*N*-(2-iodophenyl)-*N*-methyl-5-hexenamide (9h), thick oil; IR ($CHCl_3$) ν_{max} (cm^{-1}) 2103, 1670, 1471; ^{1}H NMR (400 MHz) δ 1.66-2.21 (4 H, m), 3.22 (1.35 H rotamer A, s), 3.23 (1.65 H rotamer B, s), 3.24-3.35 (1 H, m), 4.82-4.98 (2 H, m), 5.41-5.70 (1 H, m), 7.12 (1 H, td, J_t = 7.8 J_d = 1.6), 7.25 (0.45 H rotamer A, dd, J_{d1} = 7.9, J_{d2} = 1.6), 7.34 (0.55 H rotamer B, dd, J_{d1} = 7.9, J_{d2} = 1.6), 7.43-7.50 (1 H, m), 7.96 (1 H, td, J_t = 7.9 J_d = 1.4); ^{13}C NMR (100 MHz) – mixture of the two rotamers – δ 29.6 (CH_2), 29.7 (CH_2), 29.9 (CH_2), 30.6 (CH_2), 36.3, 36.4, 58.1, 58.6, 98.8 (C), 99.6 (C), 115.7 (CH_2), 116.0 (CH_2), 128.9, 129.5, 129.9, 130.1, 130.3, 136.1, 136.6, 140.3, 140.6, 144.5 (C), 144.6 (C), 169.3 (C), 170.1 (C); MS (ESI) 393 (M + Na)$^+$.



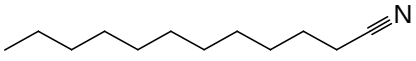
2-Iodo-2'-(azidomethyl)biphenyl (18). 2-Iodo-2'-methylbiphenyl was prepared from 2-bromoiodobenzene and 2-methylphenylmagnesium bromide following a very recent procedure.[29] A solution of this iodide (4.0 g, 13.6 mmol), *N*-bromosuccinimide (2.5 g, 13.9 mmol) and a few milligrams of benzoyl peroxide in 60 mL of carbon tetrachloride was refluxed for 3 h and then allowed to stand overnight to precipitate any dissolved succinimide. The mixture was then filtered and concentrated to give crude 2-iodo-2'-(bromomethyl)biphenyl[30] (4.75 g) as an orange oil. This bromide was directly treated with 1.6 g (25 mmol) of sodium azide in 40 mL of DMSO at room temperature for 4 h; the resulting mixture was then poured into water (100 mL) and extracted with ether. Evaporation of the organic layer and chromatographic purification of the crude gave 3.6 g of the title azide (78%, based on the original iodide) as a pale yellow oil; IR (neat) ν_{max} (cm^{-1}) 3054, 2930, 2097, 1462, 1258; ^{1}H NMR (300 MHz) δ 4.05 (1 H, d, J_d = 13.9), 4.19 (1 H, d, J_d = 13.9), 7.05-7.11 (1 H, m), 7.13-7.17 (1 H, m), 7.26 (1 H, dd, J_{d1} = 7.7, J_{d1} = 1.6), 7.37-7.48 (4 H, m), 7.94 (1 H, dd, J_{d1} = 8.0, J_{d1} = 1.1); ^{13}C NMR (100 MHz) δ 52.6 (CH_2), 99.9 (C), 128.1, 128.2, 128.5, 128.8, 129.3, 130.0, 130.1, 133.1 (C), 139.0, 144.0 (C), 144.8 (C); MS (ESI) 358 $(M + Na)^+$.

General Procedure for the Radical Reactions of Azido Anilides 9a-g with Tributyltin Hydride. A solution of azido anilide (0.5 mmol) and tributyltin hydride (0.75 mmol) in benzene (50 mL) containing AIBN (0.06 mmol) was refluxed for ca 1.5 h; after a further addition of AIBN (0.06 mmol), the resulting mixture was refluxed for additional 2-3 h (until TLC monitored the absence of any starting material). After cooling, the excess solvent was removed in vacuo and the residue chromatographed. The reactions of anilides **9c** and **9g** at 110 °C were performed in a similar fashion, but the respective benzene mixture was allowed to react in a sealed tube immersed in an oil bath kept at 110 °C. All yields of the isolated products are reported in *Table 1* and Scheme 5 included in the Text.

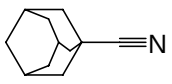
Physical and/or spectral data for the isolated compounds were as follows:



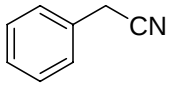
***N*-Methyl-*N*-phenylformamide (13)**. IR (neat) ν_{max} (cm^{-1}) 3057, 2918, 1676; ^1H NMR (400 MHz) δ 3.33 (3 H, s), 7.16-7.20 (2 H, m), 7.26-7.31 (1 H, m), 7.39-7.45 (2 H, m), 8.48 (1 H, s); ^{13}C NMR (100 MHz) δ 32.0, 122.4, 126.4, 129.1 (C), 129.6, 162.3; MS (EI) *m/z* (rel. inten.) 135 (88), 107 (12), 106 (100), 94 (20), 77 (27).



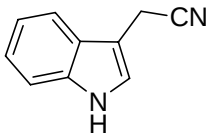
Dodecanenitrile (14c). ^1H NMR (400 MHz) δ 0.88 (3 H, t, J_t = 6.9), 1.22-1.34 (14 H, m), 1.49-1.49 (2 H, m), 1.62-1.70 (2 H, m), 2.33 (2 H, t, J_t = 7.2); ^{13}C NMR (100 MHz) δ 14.1, 17.1 (CH_2), 22.6 (CH_2), 25.4 (CH_2), 28.6 (CH_2), 28.7 (CH_2), 29.3 (2 CH_2 signals overlapped), 29.5 (CH_2), 29.6 (CH_2), 31.9 (CH_2), 119.8 (C).



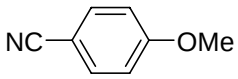
Adamantanecarbonitrile (14d). ^1H NMR (400 MHz) δ 1.73 (6 H, bs), 2.00-2.06 (9 H, m); ^{13}C NMR (100 MHz) δ 27.0, 30.1 (C), 35.6 (CH_2), 39.8 (CH_2), 125.1 (C).



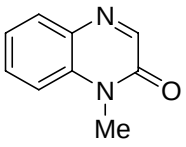
2-Phenylacetonitrile (14e). ^1H NMR (400 MHz) δ 3.75 (2 H, s), 7.30-7.40 (5 H, m); ^{13}C NMR (100 MHz) δ 23.5 (CH_2), 117.8 (C), 127.8, 127.9, 129.0, 129.8 (C).



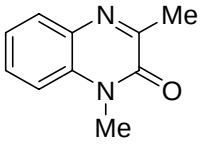
2-(1*H*-Indol-3-yl)acetonitrile (14f). ^{1}H NMR (600 MHz) δ 3.76 (2 H, s), 7.10 (1 H, s), 7.16 (1 H, t, J_t = 7.9), 7.23 (1 H, t, J_t = 7.9), 7.34 (1 H, d, J_d = 7.9), 7.56 (1 H, d, J_d = 7.9), 8.24 (1 H, bs); ^{13}C NMR (125 MHz) δ 14.2 (CH_2), 104.3 (C), 111.5, 117.9, 118.3 (C), 120.1, 122.7, 122.8, 125.9 (C), 136.2 (C).



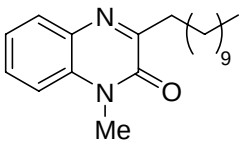
4-Methoxybenzonitrile (14g). ^{1}H NMR (400 MHz) δ 3.86 (3 H, s), 6.95 (2 H, part of AA'BB' system, $J_{AA'BB'}$ = 9.0), 7.59 (2 H, part of AA'BB' system, $J_{AA'BB'}$ = 9.0); ^{13}C NMR (100 MHz) δ 55.4, 103.8 (C), 114.7, 119.1 (C), 133.8, 162.7 (C).



1-Methyl-2(1*H*)-quinoxalinone (15a). ^{1}H NMR (400 MHz) δ 3.71 (3 H, s), 7.34-7.40 (2 H, m), 7.61 (1 H, ddd, J_{d1} = 8.4, J_{d2} = 7.4, J_{d3} = 1.5), 7.89 (1 H, dd, J_{d1} = 7.9, J_{d2} = 1.5), 8.32 (1 H, s); MS (EI) *m/z* (rel. inten.) 160 (100), 132 (58), 131 (79), 104 (27), 90 (10), 77 (20).

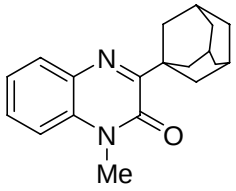


1,3-Dimethyl-2(1*H*)-quinoxalinone (15b). ^{1}H NMR (600 MHz) δ 2.61 (3 H, s), 3.71 (3 H, s), 7.31 (1 H, d, J_d = 8.2), 7.34 (1 H, td, J_t = 8.2, J_d = 1.5), 7.53 (1 H, t, J_t = 7.8), 7.81 (1 H, dd, J_{d1} = 7.8, J_{d2} = 1.5).

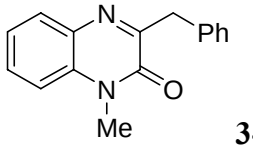


1-Methyl-3-undecyl-2(1*H*)-quinoxalinone (15c). Solid, mp = 62-63 °C; IR (neat) ν_{max} (cm^{-1}) 2924, 2853, 1735, 1656, 1601, 1466; ^{1}H NMR (400 MHz) δ 0.88 (3 H, t, J_t = 7.0), 1.22-1.48 (16 H, m), 1.78 (2 H, m), 2.91-2.97 (2 H, m), 3.70 (3 H, s), 7.28-7.36 (2 H, m), 7.52 (1 H, ddd, J_{d1} = 8.7, J_{d2} = 7.3, J_{d3} = 1.7), 7.83 (1 H, dd, J_{d1} = 7.9, J_{d2} = 1.5); ^{13}C NMR (100 MHz) δ 14.1,

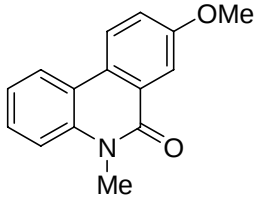
22.7 (CH_2), 26.9 (CH_2), 29.0, 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (2 CH_2 signals overlapped), 29.7 (CH_2), 31.9 (CH_2), 34.4 (CH_2), 113.5, 123.5, 129.5, 129.6, 132.8 (C), 133.1 (C), 154.9 (C), 161.4 (C); MS (EI) *m/z* (rel. inten.) 314 (9), 299 (7), 187 (14), 175 (13), 174 (100), 131 (10). Anal. Calcd for $C_{20}H_{30}N_2O$: C, 76.39; H, 9.62; N, 8.91. Found: C, 76.55; H, 9.61; N, 8.93.



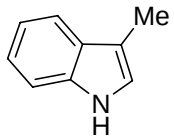
3-(1-Adamantyl)-1-methyl-2(1*H*)-quinoxalinone (15d). MS (EI) *m/z* (rel. inten.) 294 (100), 279 (25), 265 (4), 251 (4), 237 (7). HRMS calcd for $C_{19}H_{22}N_2O$ 294.1732; found, 294.1741



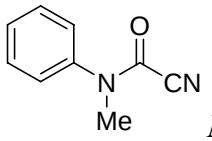
3-Benzyl-1-methyl-2(1*H*)-quinoxalinone (15e). MS (EI) *m/z* (rel. inten.) 250 (100), 249 (37), 235 (32), 221 (27), 131 (13), 91 (14). HRMS calcd for $C_{16}H_{14}N_2O$ 250.1106; found, 250.1096.



8-Methoxy-5-methyl-6(5*H*)-phenanthridinone (17). ^{1}H NMR (400 MHz) δ 3.78 (3 H, s), 3.94 (3 H, s), 7.24-7.32 (2 H, m), 7.35 (1 H, d, J_d = 8.5), 7.46 (1 H, ddd, J_{d1} = 8.5, J_{d2} = 7.2, J_{d3} = 1.5), 7.92 (1 H, d, J_d = 2.9), 8.10-8.14 (2 H, m); ^{13}C NMR (100 MHz) δ 30.0, 55.6, 109.1, 114.9, 119.3 (C), 122.1, 122.4, 122.5, 123.3, 126.7 (C), 127.0 (C), 128.3, 136.9 (C), 159.4 (C), 161.3 (C).

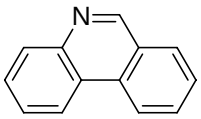


3-Methyl-1*H*-indole. ^{1}H NMR (600 MHz) δ 2.33 (3 H, s), 6.94 (1 H, bs), 7.12 (1 H, ddd, J_{d1} = 7.9, J_{d2} = 7.0, J_{d3} = 1.1), 7.18 (1 H, J_{d1} = 8.2, J_{d2} = 7.3, J_{d3} = 1.1), 7.32 (1 H, dt, J_d = 7.9, J_t = 0.9), 7.58 (1 H, d, J_d = 7.9), 7.81 (1 H, bs); ^{13}C NMR (125 MHz) δ 9.6, 110.9, 111.7 (C), 118.8, 119.1, 121.5, 121.8, 128.3 (C), 136.2 (C).

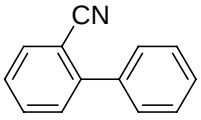


***N*-Methyl-*N*-phenylcyanoformamide**.[31] ^{1}H NMR (600 MHz) δ 3.37 (3 H, s), 7.29-7.34 (2 H, m), 7.46-7.56 (3 H, m); ^{13}C NMR (100 MHz) δ 36.7, 110.6 (C), 126.9, 129.7, 130.1, 139.7 (C), 144.5 (C).

Radical Reaction of 2-iodo-2'-(azidomethyl)biphenyl (18) with Tributyltin Hydride. A solution of azide **18** (335 mg, 1 mmol) and AIBN (0.25 mmol) in 100 mL of toluene was heated to 80 °C and then treated with a toluene (6 mL) solution of tributyltin hydride (1.5 mmol) and AIBN (0.25 mmol), which was slowly added over 6 h with a syringe pump. The resultant mixture was allowed to react at 80 °C for additional 12 h. Evaporation under reduced pressure followed by chromatography of the residue gave *(i)* unaltered starting material **18** (35%); *(ii)* phenanthridine (**19**, 45%), identical to a commercial (Aldrich) sample; and *(iii)* 2-phenylbenzonitrile (**20**, 15%), whose NMR spectral data were consistent with those reported.[32]



Phenanthridine (19). ^{1}H NMR (400 MHz) δ 7.66-7.78 (3 H, m), 7.86 (1 H, ddd, J_{d1} = 8.2, J_{d2} = 7.1, J_{d3} = 1.5), 8.05 (1 H, bd, J_{d} = 8.0), 8.2 (1 H, dd, J_{d1} = 8.2, J_{d2} = 1.4), 8.58 (1 H, dd, J_{d1} = 8.0, J_{d2} = 1.4), 8.61 (1 H, d, J_{d} = 8.2), 9.29 (1 H, s); ^{13}C NMR (100 MHz) δ 121.7, 122.1, 124.0 (C), 126.3 (C), 127.0, 127.3, 128.5, 128.6, 130.0, 130.8, 132.4 (C), 144.4 (C), 153.4.



2-Phenylbenzonitrile (20). ^{1}H NMR (400 MHz) δ 7.42-7.58 (7 H, m), 7.64 (1 H, td, J_{t} = 7.7, J_{d} = 1.5), 7.76 (1 H, ddd, J_{d1} = 7.7, J_{d2} = 1.4, J_{d3} = 0.5); ^{13}C NMR (100 MHz) δ 111.2 (C), 118.6 (C), 127.5, 128.6, 128.7, 129.0, 130.0, 132.7, 133.6, 138.0 (C), 145.4 (C).

5.3 Approach to Spirocyclohexadienimines and Corresponding Dienones through Radical ipso-Cyclization onto Aromatic Azides[33]

Introduction

Spirocyclohexadienones such as **22** and **24** are pivotal intermediates in the synthesis of important biologically active compounds (*Figure 1*). In particular, reduction and deprotection of **22** provides spirooxindole **23**, an intermediate previously reported in the synthesis of the vasopressin inhibitor SR121463A,[34,35,36,37] whereas spirodihydroquinolone **24** is a key intermediate in the preparation of *aza*-galanthamine[38a] and other indole alkaloids.[37b]

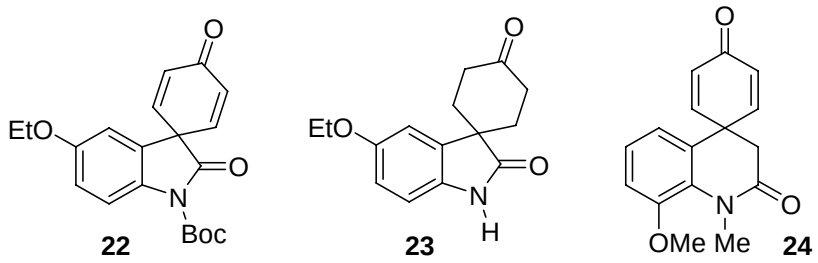
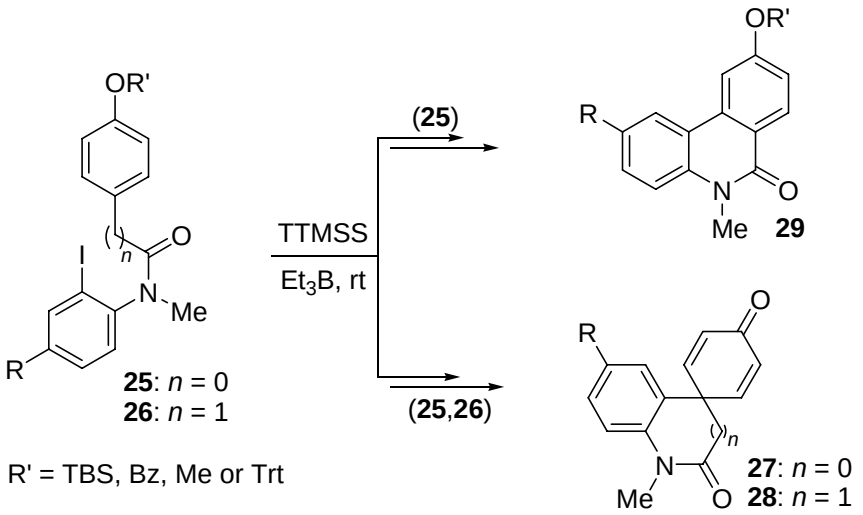


Figure 1. *Spirooxindoles (**22**, **23**) and spirohydroquinone (**24**) intermediates in the preparation of biologically active compounds*.

In a recent work, Curran has devised a skilful radical procedure for the synthesis of both spirooxindoles and spirodihydroquinolones entailing 5- and 6-membered *ipso*-cyclization of aryl radicals arising from deiodination of *p*-alkoxyl-substituted anilides **25**,**26**: the resulting spirocyclohexadienyl radicals afford dienones **27**,**28** upon β-cleavage of the O-R' bond with elimination of the alkyl/silyl R' radical (*Scheme 7*).[39] The effectiveness of this protocol is however somewhat limited by the efficiency of such β-elimination process, which was especially rewarding only when a highly stable species such as a triphenylmethyl (trityl) radical could be released. In addition, the construction of the trityloxy precursors **25**,**26** (R' = Trt) was not trivial at all since it entailed deprotection and tritylation of preliminary sililoxy anilides **25**,**26** (R' = TBS), which in turn required the rather tedious preparation of TBS-protected 4-hydroxybenzoyl and, especially, 2-(4-hydroxyphenyl)acetyl chloride (4 steps). Moreover, with benzanilides **25** the production of spirooxindole **27** was significantly limited by the concomitant occurrence of phenanthridinone **29**, arising from cyclization at the aromatic *ortho*-position.

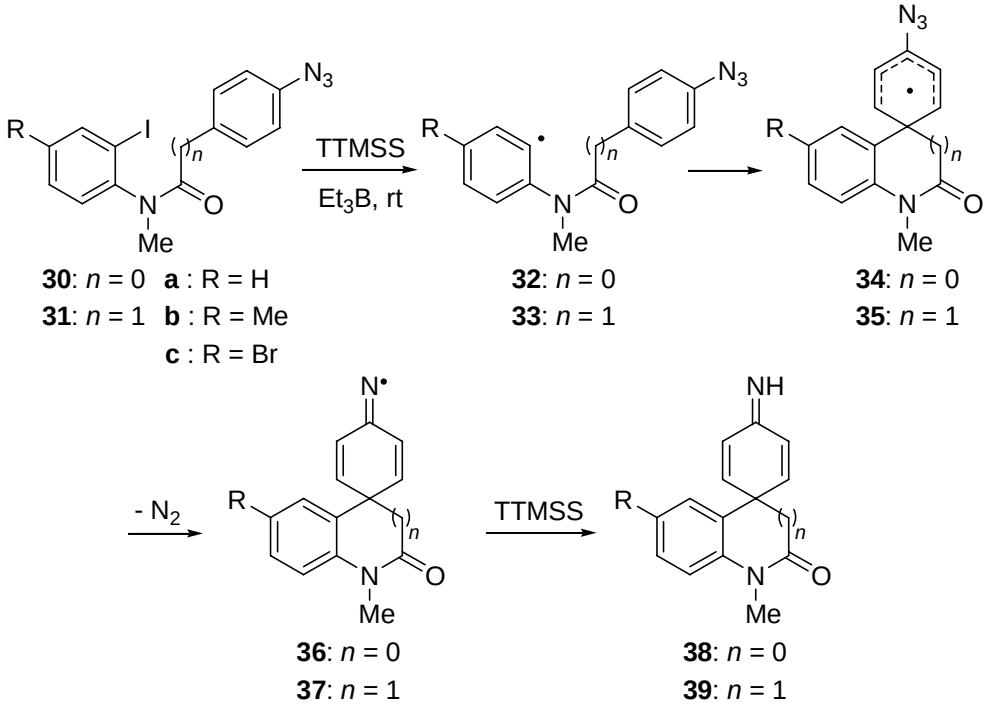


Scheme 7. *Curran synthesis of spirooxindoles and spirodihydroquinolones. TTMSS=tris-(trimethylsilyl)silane; TBS=tert-butyldimethylsilyl; Trt=triphenylmethyl.*

Results and discussion

In previous studies it was discovered that α-azidoalkyl radicals can form iminyl radicals by extrusion of dinitrogen (*see previous section*).[40]

In principle, suitable azidocyclohexadienyl radicals, which would arise from radical *ipso*-attack at the *para*-position of aromatic azides, might behave similarly to afford cyclohexadieniminyl radicals. It was therefore considered that spirocyclohexadienyl radicals analogous to those devised by Curran, but bearing a *p*-azido- rather than a *p*-alkoxyl-substituent, should be very attractive candidates for testing this assumption. Indeed, spirocyclic azidocyclohexadienyl radicals such as **34**,**35** (*Scheme 8*) might afford the corresponding iminyl radicals **36**,**37** which, under reductive conditions, would probably yield cyclohexadienimines **38**,**39** in an efficient fashion. Since those imines should undergo easy hydrolytic conversion into dienones, it was envisioned that this study might eventually lead to an alternative synthetic entry to spirocyclohexadienones **27**,**28** based on the primary radical reaction of *p*-azido-substituted 2-iodoanilides **30**,**31** with tris(trimethylsilyl)silane (TTMSS)/Et_3B.



Scheme 8. *Radical approach to cyclohexadienimines from azides*

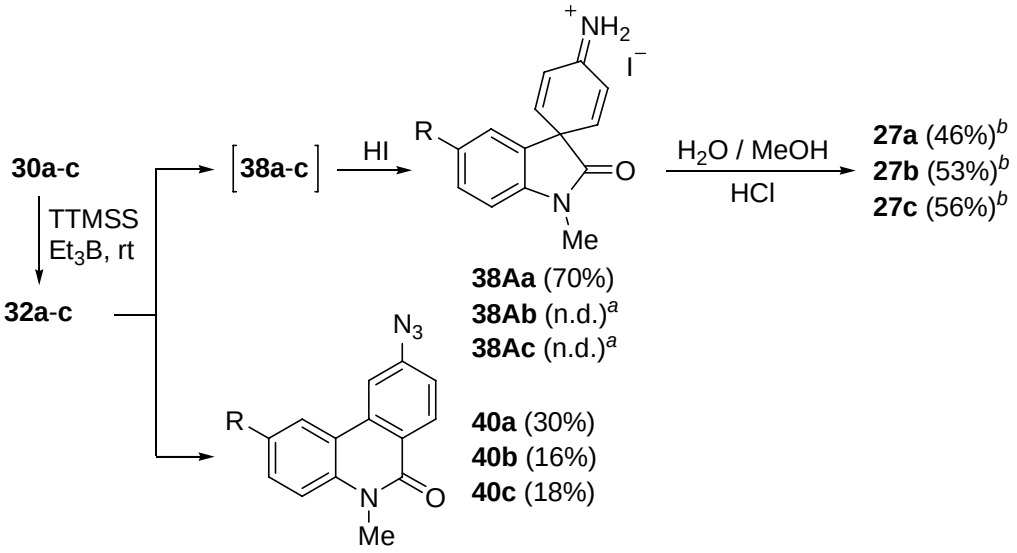
Aromatic azides are widely known to undergo smooth radical attack at the azido moiety giving aminyl radicals[41] but, before this study, their potential ability to act as alternative precursors of cyclohexadieniminyl radicals is totally unprecedented.

The use of azidoanilides **30**,**31** as radical cyclization precursors was also encouraged by expectation that those compounds should be more easily accessible than the oxygen-substituted counterparts **25**,**26**. Furthermore, previously reported data suggested that tris(trimethylsilyl)silyl radicals, rather than adding to the azido moiety, should be able to perform selective iodine abstraction from the azido iodides **30**,**31** to give aryl radicals **32**,**33**.[38a,39a,42] Finally, the azido functionality is known to be a strong radical stabilizing group compared to an alkoxyl one[43] and, in the case of **30**, this should enhance the 5- to 6-membered ring closure ratio of aryl radical **32**, hence disfavoring the competing formation of the phenanthridone.

Herein it was reported the highly rewarding results provided by preliminary study with azides **30a-c** and **31a-c** (*Scheme 8*) as well as with congener **42** (*Scheme 11*).

As anticipated, compounds **30a-c** and **31a-c** were prepared in good yields (65-85%) by coupling the appropriate *N*-methyl-substituted 2-iodoaniline with 4-azidobenzoyl or 2-(4-azidophenyl)acetyl chloride. These latter, known acyl chlorides were in turn readily prepared through conversion of the corresponding commercial amino acids into azides.

All azides were reacted by adopting experimental conditions strictly comparable with those previously employed with alkoxy-anilides **25**,**26**.[44] After 16 h, the reaction of benzamide **30a** gave rise to extensive precipitation of an orange solid which, after filtration, was found to be sparingly soluble in the common non-polar solvents, but fairly soluble in acetone, methanol, and, to a minor extent, even water. The whole spectral data were consistent with the structure of imine **38a** under the form of its hydroiodide salt **38Aa** (*Scheme 9*). This salt (70% yield) presumably arose from initially-formed **38a** through reaction with hydrogen iodide, possibly produced upon hydrolysis of tris(trimethylsilyl)iodosilane, and/or direct reaction with the iodosilane followed by fast hydrolysis of the ensuing *N*-silyl iminium iodide. Column chromatography of the solution remaining after filtration of **38Aa** isolated minor amounts (30%) of azidophenanthridinone **40a**, *i.e.* the expected product of competing 6-membered cyclization of aryl radical **32a**.

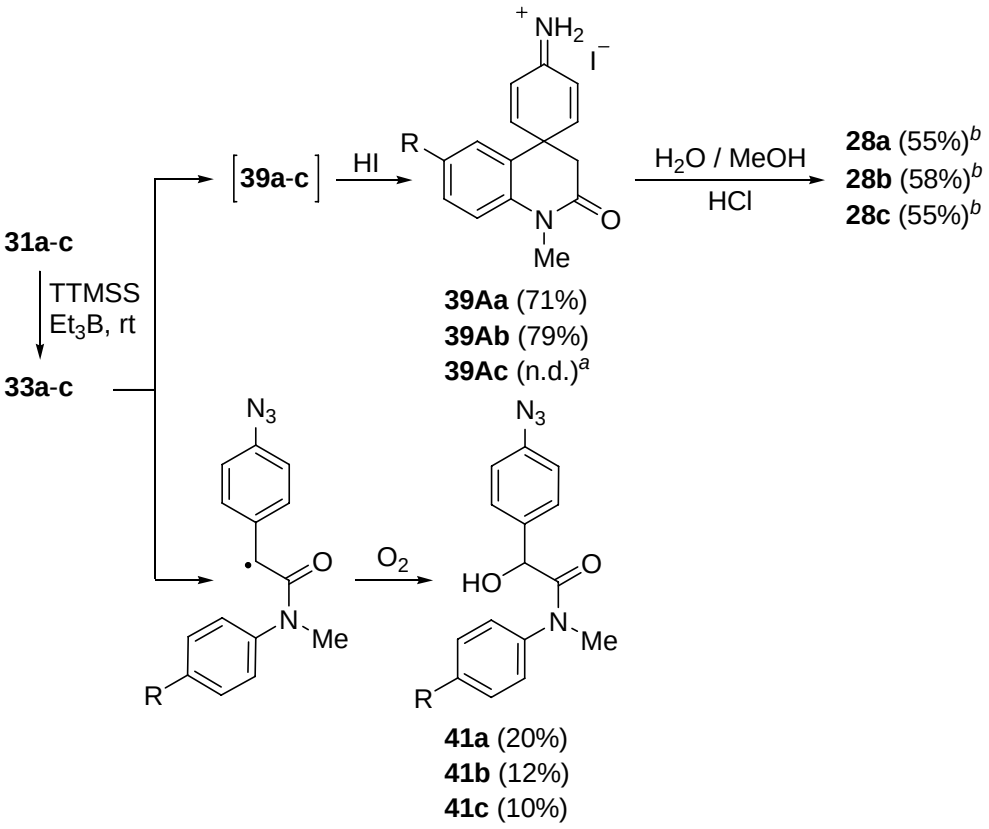


[a] Yield not determined owing to unsatisfactory purification.
[b] Yield based on the starting azides **30a-c**

Scheme 9. *Route to indolones by five-membered radical spirocyclization, and concurrent formation of phenathridinone by-products.*

In a similar fashion, by direct filtration of the reaction mixture, the radical reactions of benzanilides **30b**,**c** furnished comparable amounts of crude spirooxindole imine hydroiodides **38Ab**,**c**. Chromatographic separation of the residual solutions gave the respective phenanthridinone by-products **40b**,**c** (*Scheme 9*).

Highly satisfactory results were also obtained with acetanilides **31a-c**, since their radical reactions gave rise to analogous precipitation of large amounts of quinolone imine hydroiodides **39Aa-c**. In each case, column chromatography of the filtrate furnished rather modest amounts of the respective 2-hydroxy-substituted acetanilides **41a-c**, which conceivably arose from 1,5-H transfer reaction of aryl radicals **33a-c** followed by trapping of the translocated benzyl radicals by oxygen (*Scheme 10*).[a,45]



[a] Yield not determined owing to unsatisfactory purification.
[b] Yield based on starting azides **31a-c**

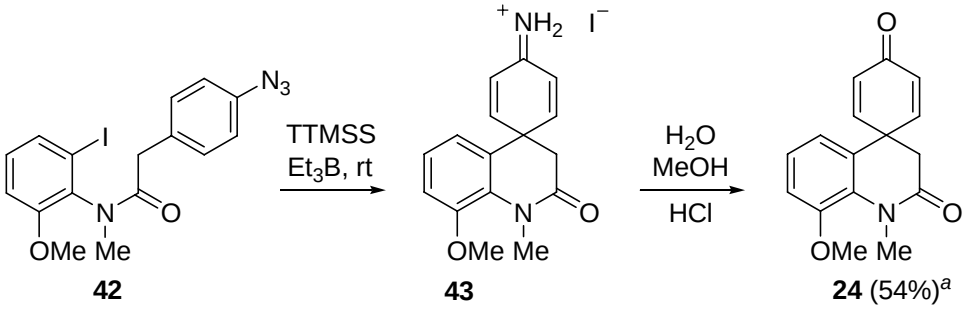
Scheme 10. *Route to quinolones by six-membered radical spirocyclization,and concurrent formation of 2-hydroxy-substituted acetanilide byproducts.*

The above overall results confirmed the original assumptions that aryl radicals **32**,**33** could give 5- and 6-membered spirocyclization onto the internal aromatic azide and the resulting intermediate spirocyclic azidocyclohexadienyl radicals **24**,**35** could extrude molecular nitrogen in a highly efficient fashion to afford cyclohexadieniminyl radicals **36**,**37** and thence the corresponding imines **38**,**39**. The yields of the latter compounds were significantly higher than those of cyclohexadienones **27**,**28** arising from silyloxy- and trityloxy-substituted amides **25**,**26** (R' = TBS or Trt): this fact validated the additional, crucial hypothesis that the azido substituent could promote aryl radical spirocyclization more effectively than an alkoxyl group.

These interesting observations might pave the way to future, important applications of aromatic azides for the construction of uncommon spirocyclic cyclohexadienimines.[46,47]

Gratifyingly, it was next found that, upon brief heating at 60 °C in methanol/water in the presence of a few drops of hydrochloric acid, **38A**,**39A** generally afforded the respective spirocyclohexadienones **27**,**28** in satisfactory yields based on the original azides **30**,**31** (*Schemes 9 and 10*).

It was finally decided to attempt the synthesis of the precious spiroquinolone **24**. Coupling of *N*-methyl-2-iodo-6-methoxyaniline with 2-(4-azidophenyl)acetyl chloride gave azido acetamide **42** in high yield (82%). Usual treatment of **42** with TTMSS/Et_3B led to isolation of pure imine hydroiodide **43** (80%), which was subjected to standard hydrolysis to give the target quinolone **24** in 54% overall yield (*Scheme 11*). Compound **24** had been originally prepared in moderate yield through a tedious, expensive multistep sequence based on intramolecular Heck cyclization of a protected 2-(4-oxocyclohexenyl)acetanilide[a] and, subsequently, in 40% yield, through direct radical reaction of the TBSO-analogue of azide **42**.



42 **43** **24** (54%)[a]

[a] Yield based on the starting azide **42**

Scheme 11. *Synthesis of spirodihydroquinolone **24***

Conclusions

In conclusion, it was shown that aromatic azides can provide an unprecedented straightforward synthetic entry to cyclohexadieniminyl radicals that can be suitably exploited in the valuable production of indolones and quinolones bearing spirocyclohexadienimine/spirocyclohexadienone rings

As far as the dienones are concerned, this new synthetic protocol is evidently superior to both Curran's radical procedure and other reported non-radical methods.[7] In fact, this protocol while giving rise to comparable or even better yields of those dienones, employs very easy to prepare azido precursors, entails very simple workup,[48] and results in highly minimized atom waste.

The present discovery could allow novel, highly appealing applications of radical chemistry in the synthesis of biologically active compounds.

Experimental section

General Remarks.

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury Plus 400 MHz (^{1}H: 400 MHz, ^{13}C: 100 MHz) using tetramethylsilane as an internal standard (with $CDCl_3$) or internal residual solvent signal (CD_3OD): ^{1}H-NMR spectra, δ 7.26 ppm for $CHCl_3$, δ 3.34 ppm for methanol; ^{13}C-NMR spectra, δ 77.0 for $CHCl_3$, δ 49.86 ppm for methanol. In reporting spectral data, the following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, bs = broad singlet.

IR spectra were recorded on a FT-IR Perkin Elmer Spectrum RXI instrument in $CHCl_3$, DCM solutions or as liquid films.

GC-MS spectra were usually recorded using a ThermoFisher − Focus DSQ system. Mass spectra were recorded either by the electron spray ionization (ESI) method or under electron impact (EI) conditions with Waters – Micromass ZQ4000 and Thermo – Finnigan MAT95 XP instruments, respectively. High resolution mass determinations (HRMS) were carried out by electron impact at 70 eV.

Melting Points were measured in a Stuart Scientific SMP3 Melting Point Apparatus and are uncorrected.

Column chromatography was performed on ICN silica gel (63−200, 60 Å) by gradual elution with hexane/diethyl ether.

Tris(trimethylsilyl)silane and Triethylborane (1.0 M solution in hexane) were commercially available and were used as received.

2-Iodo-*N*-methylbenzenamine,[49] 2-iodo-*N*,4-dimethylbenzenamine, 4-bromo-2-iodo-*N*-methyl-benzenamine, 2-iodo-6-methoxy-*N*-methylbenzenamine,[50] 4-azidobenzoic acid,[51] and 2-(4-azidophenyl)acetic acid[52] were prepared according to previous literature procedures.

The unknown azide compounds, like all azides, are usually suitable neither for elemental analysis nor for exact mass determination. In few cases (**30c**, **41a**,**b**), the presence of the molecular ion peak in the mass spectrum allowed HRMS analysis; in other cases (**30a-c**, **31a-c**, **40a,b**, **41c**, **42**), their purity was confirmed by NMR analysis.

General Procedure for Preparation of Benzamides 30.

To a stirred solution of 4-azidobenzoic acid (1.00 g, 6.10 mmol) and DMF (few drops) in anhydrous DCM (20 mL) at 0 °C was slowly added thionyl chloride (0.53 mL, 7.32 mmol). The reaction mixture was stirred for additional 2 hours at room temperature and the solvent was then evaporated. The resulting acyl chloride was obtained in almost quantitative yield and used for the next step without further purification.

To a stirred solution of 2-iodobenzenamine (5 mmol) in chloroform (20 mL) at r.t. was added TEA (0.84 mL, 6.00 mmol) and the previously prepared acyl chloride (6.1 mmol in 5 mL chloroform solution). The resulting reaction mixture was stirred for 3 hours and then diluted with chloroform (80 mL) and $NaHCO_3$ (40 mL, saturated aqueous solution). The separated organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue (on silica gel with increasing gradient elution: hexane/Et_2O) gave the pure amides in 75-80% yields.

General Procedure for Preparation of Acetamides 31 and 42.

To a stirred solution of 2-(4-azidophenyl)acetic acid (1.08 g, 6.10 mmol) and DMF (few drops) in anhydrous DCM (20 mL) at 0 °C was slowly added oxalyl chloride (0.62 mL, 7.32 mmol). The reaction mixture was stirred for additional 2 hours at room temperature; then the volume was reduced at about 5 mL. The resulting acyl chloride was obtained in almost quantitative yield (GC-MS analysis) and used for the next step without further purification.

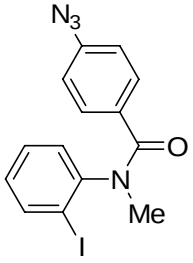
To a stirred solution of 2-iodobenzenamine (5 mmol) in DCM (20 mL) at r.t. was added TEA (0.84 mL, 6.00 mmol) and the previously prepared acyl chloride (6.1 mmol in 5 mL DCM solution). The resulting reaction mixture was stirred for 3 hours and then diluted with DCM (80 mL) and $NaHCO_3$ (40 mL, saturated aqueous solution). The separated organic layer war dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue (on silica gel with increasing gradient elution: hexane/Et_2O) gave the pure amides in 75-80% yields.

General Procedure for the Cyclization Reactions of Azides 30, 31, and 42.

To a stirred solution of the azide (0.5 mmol) in benzene or toluene (8 mL) was successively added Et_3B (1.2 equiv, 1.0 M solution in hexane) and TTMSS (1.2 equiv). The resulting mixture was stirred at r.t. under air until total consumption of the starting material (usually overnight). Filtration of the reaction mixtures afforded crude imine hydroiodides, whereas chromatography of the filtrates (on silica gel with increasing gradient elution: hexane/Et_2O) yielded the by-products (phenanthridones or hydroxyanilides).

General Procedure for the Hydrolysis of Imine Hydroiodide Salts 38, 39, and 43.

To a solution of the imine hydroiodide salt (0.25 mmol) in metanol (10 mL) and water (10 mL) were added 10 drops of concentrated hydrochloric acid. The resulting mixture was stirred at 60 °C for 30 minutes and methanol was then evaporated. The residual water solution was extracted several times with DCM and the separated organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue (on silica gel with increasing gradient elution: hexane/Et_2O) gave the corresponding ketone in 65-75% yields.



4-Azido-*N*-(2-iodophenyl)-*N*-methylbenzamide 30a:

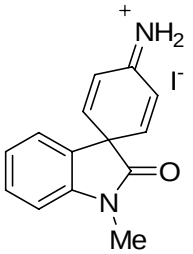
solid, mp = 104-106 °C;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 2129, 2095, 1645, 1604;

^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J_d = 7.7 Hz, 1 H), 7.36 (part of AA'BB' system, $J_{AA'BB'}$ = 8.3 Hz, 2 H), 7.24 (t, J_t = 7.7 Hz, 1 H), 7.10 (d, J_d = 7.7 Hz, 1 H), 6.92 (t, J_t = 7.7 Hz, 1 H), 6.79 (part of AA'BB' system, $J_{AA'BB'}$ = 8.3 Hz, 2 H), 3.36 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7 (C), 146.9 (C), 141.6 (C), 140.2, 132.1 (C), 130.3, 130.0, 129.5, 129.2, 118.2, 99.0 (C), 37.7;

MS (ESI) 401 $(M + Na)^+$.



1'-Methyl-2'-oxo-1',2'-dihydro-4*H*-spiro[cyclohexa-2,5-diene-1,3'-indol]-4-iminium iodide 38Aa:

solid;[53]

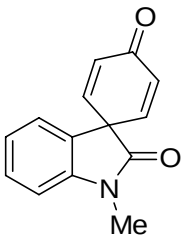
IR ($CHCl_3$) ν_{max} (cm^{-1}) 3300-2500 (v br), 2964, 1726, 1651, 1610;[54]

^1H NMR (400 MHz, CD_3OD) δ 7.53 (bt, J_t = 7.9 Hz, 1 H), 7.28 (part of AA'BB' system, $J_{AA'BB'}$ = 9.8 Hz, 2 H), 7.24 (bd, J_d = 7.5 Hz, 1 H), 7.19 (bt, J_t = 7.5 Hz, 1 H), 7.10-7.15 (m, 3 H), 3.37 (s, 3 H);[55]

^{13}C NMR (100 MHz, CD_3OD) δ 171.1 (C), 169.8 (C), 154.3, 146.5 (C), 132.8, 126.9, 126.0, 125.6 (C), 124.4, 112.2, 61.2 (C), 28.9;

MS $(ESI)^+$ 225 (M^+); MS $(ESI)^-$ 127 (Iodide);

HRMS calcd for $C_{14}H_{12}N_2O$[56] 224.0950; found 224.0957.



1'-Methyl-4*H*-spiro[cyclohexa-2,5-diene-1,3'-indol]-2',4(1'*H*)-dione 27a:

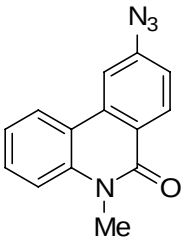
solid, mp= 168-170 °C (lit. 275-280 °C);[49,57]

IR ($CHCl_3$) ν_{max} (cm^{-1}) 3020, 1718, 1667, 1610, 1491, 1471, 1365, 1345;

^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (td, J_t = 7.6 Hz, J_d = 1.3 Hz, 1 H), 7.11 (td, J_t = 7.6 Hz, J_d = 0.9 Hz, 1 H), 7.04 (dd, J_{d1} =7.6 Hz, J_{d2} = 0.9 Hz, 1 H), 6.97 (bd, J = 7.6 Hz, 1 H), 6.60 (part of AA'BB' system, $J_{AA'BB'}$ = 10.4 Hz, 2 H), 6.55 (part of AA'BB' system, $J_{AA'BB'}$ = 10.4 Hz, 2 H), 3.32 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 185.2 (C), 171.4 (C), 143.8 (C), 143.5, 131.4, 130.0, 126.0 (C), 124.7, 123.7, 109.1, 55.9 (C), 27.3;

MS (EI) *m/z* (rel. inten.) 225 (100), 197 (79), 182 (40), 168 (33), 154 (21), 139 (17), 69 (17).



9-Azido-5-methylphenanthridin-6(5*H*)-one 40a:

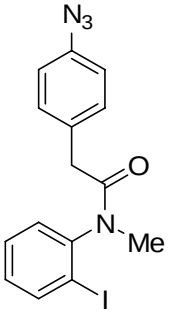
solid, mp = 178-180 °C;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 2111, 1643, 1610, 1446, 1345, 1263;

^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J_d = 8.6 Hz, 1 H), 8.15 (dd, J_{d1} = 1.1 Hz; J_{d2} = 8.2 Hz, 1 H), 7.75 (d, J_d = 2.1 Hz, 1 H), 7.56 (ddd, J_{d1} = 1.4 Hz, J_{d2} = 7.6 Hz, J_{d3} = 8.6 Hz, 1 H), 7.39 (bd, J_d = 8.6 Hz, 1 H), 7.31 (ddd, J_{d1} = 1.1 Hz, J_{d2} = 7.6 Hz, J_{d3} = 8.2 Hz, 1 H), 7.21 (dd, J_{d1} = 2.1 Hz, J_{d2} = 8.6 Hz, 1 H), 3.78 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9 (C), 144.3 (C), 138.5 (C), 135.2 (C), 131.1, 130.2, 123.3, 122.5 (C) and 122.5 (overlapped), 118.9, 118.4 (C), 115.1, 111.1, 29.9;

MS (ESI) 273 $(M + Na)^+$.



2-(4-Azidophenyl)-*N*-(2-iodophenyl)-*N*-methylacetamide 31a:

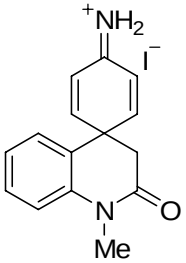
solid, mp = 60-61 °C;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 2112, 1664, 1506, 1471, 1376, 1285;

^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, J_{d1} = 1.5 Hz, J_{d2} = 7.9 Hz, 1 H), 7.40 (ddd, J_{d1} = 1.5 Hz, J_{d2} = 7.5 Hz, J_{d3} = 7.9 Hz, 1 H), 7.16 (dd, J_{d1} = 1.6 Hz, J_{d2} = 7.9 Hz, 1 H), 7.11 (ddd, J_{d1} = 1.6 Hz, J_{d2} = 7.5 Hz, J_{d3} = 7.9 Hz, 1 H), 7.05 (part of AA'BB' system, $J_{AA'BB'}$ = 8.6 Hz, 2 H), 6.90 (part of AA'BB' system, $J_{AA'BB'}$ = 8.6 Hz, 2 H), 3.37 (d, J_d = 14.9 Hz, 1 H), 3.25 (d, J_d = 14.9 Hz, 1 H), 3.19 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3 (C), 145.8 (C), 140.2 , 138.4 (C), 131.6 (C), 130.8, 130.0, 129.8, 129.4, 118.9, 99.9 (C), 40.7 (CH_2), 36.2;

MS (ESI) 415 $(M + Na)^+$.



1'-Methyl-2'-oxo-2',3'-dihydro-1'*H*,4*H*-spiro[cyclohexa-2,5-diene-1,4'-quinolin]-4-iminium iodide 39Aa:

solid;

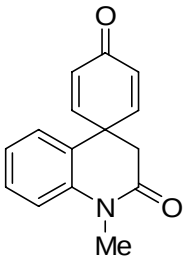
IR ($CHCl_3$) ν_{max} (cm^{-1}) 3300-2500 (v br), 2961, 1672, 1598, 1474, 1375;

^1H NMR (400 MHz, CD_3OD) δ 7.62 (part of AA'BB' system, $J_{AA'BB'}$ = 10.0 Hz, 2 H), 7.49 (ddd, J_{d1} = 1.7 Hz, J_{d2} = 7.3 Hz, J_{d3} = 8.2 Hz, 1 H), 7.36 (dd, J_{d1} = 1.0 Hz, J_{d2} = 8.2 Hz, 1 H), 7.15 (td, J_t = 7.5 Hz, J_d = 1.1 Hz, 1 H), 7.05 (dd, J_{d1} = 1.7 Hz, J_{d2} = 7.7 Hz, 1 H), 6.99 (part of AA'BB' system, $J_{AA'BB'}$ = 10.0 Hz, 2 H), 3.50 (s, 3 H), 2.94 (s, 2 H);

^{13}C NMR (100 MHz, CD_3OD) δ 169.1 (C), 168.9 (C), 160.1, 142.2 (C), 132.2, 128.5, 126.3, 123.8 (C), 122.5, 118.8, 47.7 (C), 40.8 (CH_2), 31.2;

MS $(ESI)^+$ 239 (M^+); MS $(ESI)^-$ 127 (Iodide);

HRMS calcd for $C_{15}H_{14}N_2O$ 238.1106; found 238.1113.



1'-Methyl-1'*H*,4*H*-spiro[cyclohexa-2,5-diene-1,4'-quinoline]-2',4(3'*H*)-dione 28a:

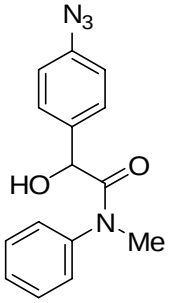
solid, mp = 170-175 °C (lit. 100-105 °C);[49,57]

IR ($CHCl_3$) ν_{max} (cm^{-1}) 1671, 1630, 1598, 1364;

^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (ddd, J_{d1} = 2.2 Hz, J_{d2} = 6.9 Hz, J_{d3} = 8.3 Hz, 1 H), 7.04-7.12 (m, 3 H), 6.95 (part of AA'BB' system, $J_{AA'BB'}$ = 10.2 Hz, 2 H), 6.39 (part of AA'BB' system, $J_{AA'BB'}$ = 10.2 Hz, 2 H), 3.46 (s, 3 H), 2.79 (s, 2 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 185.0 (C), 166.6 (C), 149.3, 139.8 (C), 129.6, 129.5, 126.5, 124.4 (C), 124.0, 115.8, 43.1 (C), 40.8 (CH_2), 29.7;

MS (EI) *m*/*z* (rel. inten.) 239 (M^+, 100), 210 (47), 182 (20), 168 (31), 115 (11).



2-(4-Azidophenyl)-2-hydroxy-*N*-methyl-*N*-phenylacetamide 41a:

solid, mp = 83-85 °C;

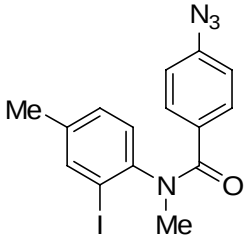
IR ($CHCl_3$) ν_{max} (cm^{-1}) 3420, 2124, 1651, 1596, 1505, 1498, 1367, 1294;

^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.26 (m, 3 H), 6.89-6.82 (m, 2 H), 6.80 (part of AA'BB' system, $J_{AA'BB'}$ = 8.5 Hz, 2 H), 6.76 (part of AA'BB' system, $J_{AA'BB'}$ = 8.5 Hz, 2 H), 4.99 (d, J_d = 6.7 Hz, 1 H), 4.51 (d, J_d = 6.7 Hz, 1 H), 3.30 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5 (C), 141.4 (C), 139.8 (C), 136.1 (C), 129.6, 128.8, 128.5, 127.9, 118.9, 70.9, 38.3;

MS (EI) *m*/*z* (rel. inten.) 282 (M^+, 6), 148 (76), 135 (82), 134 (100), 120 (85), 107 (70), 106 (64), 92 (20), 77 (56), 65 (24);

HRMS calcd for $C_{15}H_{14}N_4O_2$ 282.1117; found 282.1108.



4-Azido-*N*-(2-iodo-4-methylphenyl)-*N*-methylbenzamide 30b:

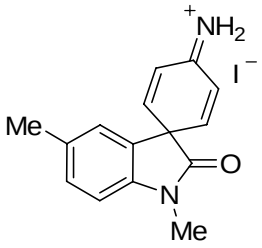
solid, mp = 78-80 °C;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 2125, 2092, 1644, 1604, 1489, 1422, 1365, 1284;

^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (bs, 1 H), 7.37 (part of AA'BB' system, $J_{AA'BB'}$ = 8.4 Hz, 2 H), 7.06-6.95 (m, 2 H), 6.81 (part of AA'BB' system, $J_{AA'BB'}$ = 8.4 Hz, 2 H), 3.34 (s, 3 H), 2.26 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8 (C), 144.2 (C), 141.4 (C), 140.5, 139.5 (C), 132.3 (C), 130.3 and 130.2 (overlapped), 129.3, 118.1, 98.7 (C), 37.7, 20.4;

MS (ESI) 393 $(M + H)^+$, 415 $(M + Na)^+$, 431 $(M + K)^+$.

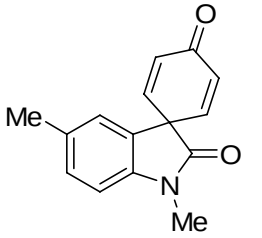


1',5'-Dimethyl-2'-oxo-1', 2'-dihydro-4*H*-spiro[cyclohexa-2, 5-diene-1, 3'-indol]-4-iminium iodide 38Ab:

solid;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 3300-2500 (v br), 1724, 1651, 1605, 1500, 1344;

MS $(ESI)^+$ 239 (M^+); MS $(ESI)^-$ 127 (Iodide).



1',5'-Dimethyl-4*H*-spiro[cyclohexa-2,5-diene-1,3'-indol]-2',4(1'*H*)-dione 27b:

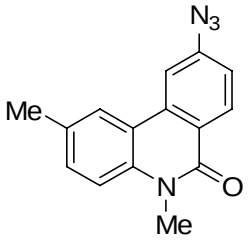
solid, mp = 183-186 °C (lit. 185-190°C);[49]

IR ($CHCl_3$) ν_{max} (cm^{-1}) 1719, 1668, 1500;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (ddd, J_{d1} = 0.7 Hz, J_{d2} = 1.6 Hz, J_{d3}= 7.9 Hz, 1 H), 6.87-6.84 (m, 2 H), 6.59 (part of AA'BB' system, $J_{AA'BB'}$ = 10.2 Hz, 2 H), 6.53 (part of AA'BB' system, $J_{AA'BB'}$ = 10.2 Hz, 2 H), 3.29 (s, 3 H), 2.32 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 185.2 (C), 171.2 (C), 143.7, 141.4 (C), 133.4 (C), 131.3, 130.1, 125.8 (C), 125.4, 108.8, 55.9 (C), 27.2, 20.9;

MS (ESI) 240 $(M + H)^+$, 262 $(M + Na)^+$, 278 $(M + K)^+$.



9-Azido-2,5-dimethylphenanthridin-6(5*H*)-one 40b:

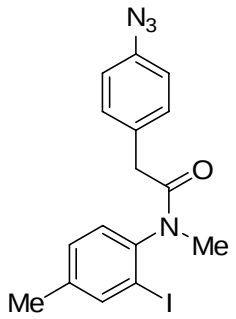
solid, mp = 142-144 °C;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 2112, 1645, 1610, 1346;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J_d = 8.6 Hz, 1 H), 7.91 (bs, 1 H), 7.72 (d, J_d = 2.2 Hz, 1 H), 7.36 (dd, J_{d1} = 1.9 Hz, J_{d2} = 8.6 Hz, 1 H), 7.27 (d, J_d = 8.4 Hz, 1 H), 7.20 (dd, J_{d1} = 2.2 Hz, J_{d2} = 8.6 Hz, 1 H), 3.75 (s, 3 H), 2.48 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8 (C), 144.2 (C), 136.3 (C), 135.1 (C), 132.0 (C), 131.2, 131.1, 123.3, 122.6 (C), 118.8, 118.2 (C), 115.0, 111.1, 29.8, 20.9;

MS (ESI) 287 $(M + Na)^+$.



2-(4-Azidophenyl)-*N*-(2-iodo-4-methylphenyl)-*N*-methylacetamide 31b:

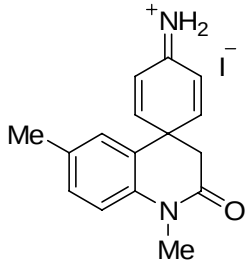
oil;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 2114, 1664, 1506, 1487, 1424, 1373, 1286;

^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, J_{d1} = 0.8 Hz, J_{d2} = 1.9 Hz, 1 H), 7.18 (ddd, J_{d1} = 0.8 Hz, J_{d2} = 1.9 Hz, J_{d3} = 8.0 Hz, 1 H), 7.07 (part of AA'BB' system, $J_{AA'BB'}$ = 8.6 Hz, 2 H), 7.03 (d, J_d = 8.0 Hz, 1 H), 6.90 (part of AA'BB' system, $J_{AA'BB'}$ = 8.6 Hz, 2 H), 3.35 (d, J_d = 15.1 Hz, 1 H), 3.25 (d, J_d = 15.1 Hz, 1 H), 3.16 (s, 3 H), 2.36 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (C), 143.2 (C), 140.5, 140.4 (C), 138.4 (C), 131.8 (C), 130.8, 130.5, 128.8, 118.8, 99.6 (C), 40.5 (CH_2), 36.2, 20.5;

MS (ESI) 407 $(M + H)^+$, 429 $(M + Na)^+$, 445 $(M + K)^+$.



1',6'-Dimethyl-2'oxo-2',3'-dihydro-1'*H*,4*H*-spiro[cyclohexa-2,5-diene-1,4'-quinolin]-4-iminium iodide 39Ab:

solid;

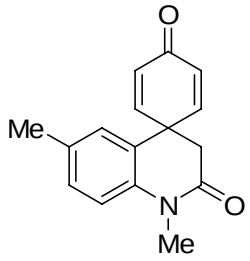
IR ($CHCl_3$) ν_{max} (cm^{-1}) 3300-2500 (v br), 1678, 1652, 1507, 1367;

^1H NMR (400 MHz, CD_3OD) δ 7.60 (part of AA'BB' system, $J_{AA'BB'}$ = 9.9 Hz, 2 H), 7.30 (dd, J_{d1} = 1.6 Hz, J_{d2} = 8.2 Hz, 1 H), 7.24 (d, J_d = 8.2 Hz, 1 H), 6.98 (part of AA'BB' system, $J_{AA'BB'}$ = 9.9 Hz, 2 H), 6.86 (bd, J_d = 1.6 Hz, 1 H), 3.45 (s, 3 H), 2.91 (s, 2 H), 2.30 (s, 3 H);

^{13}C NMR (100 MHz, CD_3OD) δ 168.9 (C), 160.2, 152.7 (C), 139.8 (C), 136.4 (C), 132.5, 129.0, 123.5 (C), 122.5, 118.7, 47.3 (C), 40.9 (CH_2), 31.2, 21.4;

MS $(ESI)^+$ 253 (M^+); MS $(ESI)^-$ 127 (Iodide);

HRMS calcd for $C_{16}H_{16}N_2O$ 252.1263; found 252.1271.



1',6'-Dimethyl-1'*H*,4*H*-spiro[cyclohexa-2,5-diene-1,4'-quinoline]-2',4(3'*H*)-dione 28b:

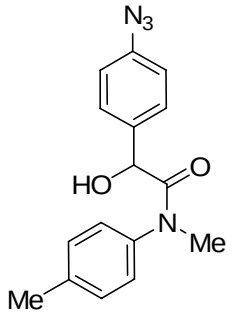
yellow oil;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 1670, 1506, 1414, 1364;

^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (ddd, J_{d1} = 0.8 Hz, J_{d2} = 2.0 Hz, J_{d3} = 8.2 Hz, 1 H), 6.99 (d, J_d = 8.2, 1 H), 6.94 (part of AA'BB' system, $J_{AA'BB'}$ = 10.1 Hz, 2 H), 6.87 (bd, J_d = 2.0 Hz, 1 H), 6.38 (part of AA'BB' system, $J_{AA'BB'}$ = 10.1 Hz, 2 H), 3.43 (s, 3 H), 2.76 (s, 2 H), 2.27 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 185.1 (C), 166.5 (C), 149.5, 137.4 (C), 133.7 (C), 129.8, 129.5, 127.0, 124.1 (C), 115.7, 43.1 (C), 40.8 (CH_2), 29.6, 20.5;

MS (EI) *m*/*z* (rel. inten.) 253 (M^+, 100), 238 (20), 225 (62), 224 (91), 211 (50), 210 (70), 196 (47), 182 (55), 168 (29), 167 (31), 115 (14).



2-(4-Azidophenyl)-2-hydroxy-*N*-methyl-*N*-*p*-tolylacetamide 41b:

solid, mp = 84-86 °C;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 3412, 2925, 2122, 1654, 1507, 1368, 1291;

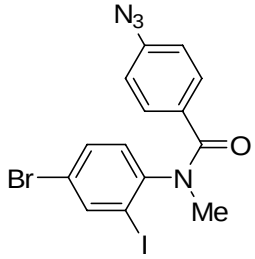
^1H NMR (400 MHz, $CDCl_3$) δ 7.09 (db, J_d = 8.1 Hz, 2 H), 6.81 (bs, 4 H), 6.72 (db, J_d = 8.1 Hz, 2 H), 4.99 (s, 1 H), 4.50 (bs, 1 H), 3.27 (s, 3 H), 2.37 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7 (C), 139.7 (C), 138.8 (C), 138.5 (C), 136.3 (C), 130.2, 128.8, 127.6, 118.8, 70.8, 38.4, 21.1;

MS (ESI) 297 $(M + H)^+$, 319 $(M + Na)^+$, 335 $(M + K)^+$;

MS (EI) *m*/*z* (rel. inten.) 296 (M^+, 10), 149 (70), 148 (82), 121 (70), 120 (100), 92 (33), 91 (52), 65 (51);

HRMS calcd for $C_{16}H_{16}N_4O_2$ 296.1273; found 296.1284.



4-Azido-*N*-(4-bromo-2-iodophenyl)-*N*-methylbenzamide 30c:

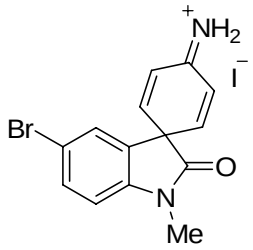
solid, mp = 96-98 °C;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 2127, 2092, 1648, 1603, 1467, 1355, 1300, 1284;

^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (bs, 1 H), 7.43-7.30 (m, 3 H), 6.96 (bd, J_d = 8.1 Hz, 1 H), 6.84 (bd, J_d = 7.7 Hz, 2 H), 3.33 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6 (C), 146.2 (C), 142.2, 141.9 (C), 132.7, 131.7 (C), 130.8, 130.2, 121.8 (C), 118.3, 99.7 (C), 37.6;

MS (ESI) 479 $(M + Na)^+$.

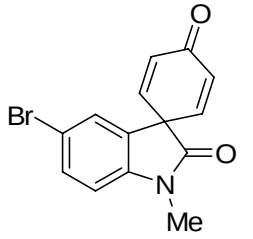


5'-Bromo-1'-methyl-2'-oxo-1',2'-dihydro-4*H*-spiro[cyclohexa-2,5-diene-1,3'-indol]-4-iminium iodide 38Ac:

solid;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 3300-2500 (v br), 1731, 1650, 1606, 1487, 1335;

MS $(ESI)^+$ 303 (M^+); MS $(ESI)^-$ 127 (Iodide).



5'-Bromo1'-methyl-4*H*-spiro[cyclohexa-2,5-diene-1,3'-indol]-2',4(1'*H*)-dione 27c:

solid, mp = 244-246 °C;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 1726, 1669, 1605, 1488;

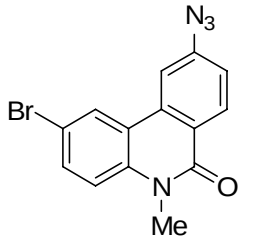
^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J_{d1} = 2.0, J_{d2} = 8.2 Hz, 1 H), 7.16 (d, J_d = 2.0 Hz, 1 H), 6.85 (d, J_d = 8.2 Hz, 1 H), 6.56 (s, 4 H), 3.97 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 184.8 (C), 170.8 (C), 142.8 (C), 142.5, 132.8, 131.8, 128.0 (C), 127.9, 116.2 (C), 110.5, 55.6 (C), 27.4;

MS (ESI) 304 $(M + H)^+$, 326 $(M + Na)^+$, 342 $(M + K)^+$;

MS (EI) *m*/*z* (rel. inten.) 303 (M^+, 74), 277 (100), 275 (81);

HRMS calcd for $C_{14}H_{10}BrNO_2$ 302.9895; found 302.9903.



9-Azido-2-bromo-5-methylphenanthridin-6(5*H*)-one 40c:

solid, mp = 184-186 °C;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 2113, 1649, 1611, 1336;

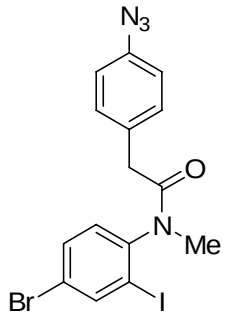
^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J_d = 8.6 Hz, 1 H), 8.27 (d, J_d = 2.2 Hz, 1 H), 7.71 (d, J_d = 2.2 Hz, 1 H), 7.65 (dd, J_{d1} = 2.2 Hz, J_{d2} = 9.0 Hz, 1 H), 7.30-7.27 (m, 2 H), 3.77 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7 (C), 144.8 (C), 137.5 (C), 134.0 (C), 132.9, 131.3, 126.1, 122.6 (C), 120.2 (C), 119.6, 116.9, 115.7 (C), 111.3, 30.0;

MS (ESI) 351 $(M + Na)^+$;

MS (EI) *m*/*z* (rel. inten.) 328 (46), 302 (100), 300 (83), 298 (34);

HRMS calcd for $C_{14}H_9BrN_4O$ 327.9960; found 327.9969.



2-(4-Azidophenyl)-*N*-(4-bromo-2-iodophenyl)-*N*-methylacetamide 31c:

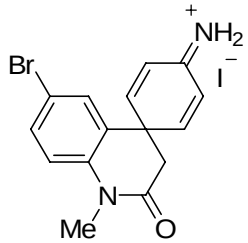
thick-oil;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 2112, 1667, 1503, 1465, 1367, 1285;

^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J_d = 2.2 Hz, 1 H), 7.52 (dd, J_{d1} = 2.2 Hz, J_{d2} = 8.2 Hz, 1 H), 7.05 (part of AA'BB' system, $J_{AA'BB'}$ = 8.6 Hz, 2 H), 7.00 (d, J_d = 8.2 Hz, 1 H), 6.91 (part of AA'BB' system, $J_{AA'BB'}$ = 8.6 Hz, 2 H), 3.36 (d, J_d = 15.2 Hz, 1 H), 3.24 (d, J_d = 15.2 Hz, 1 H), 3.15 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (C), 145.0 (C), 142.3, 138.6 (C), 133.0, 131.3 (C), 130.7, 130.4, 122.8 (C), 119.0, 100.8 (C), 40.7 (CH_2), 36.2;

MS (ESI) 471 $(M + H)^+$, 493 $(M + Na)^+$, 509 $(M + K)^+$.



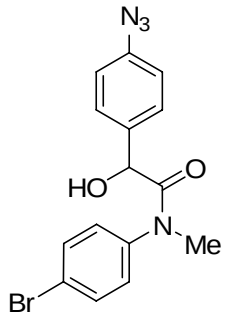
6'-Bromo-1'-methyl-2'-oxo-2',3'-dihydro-1'*H*,4*H*-spiro[cyclohexa-2,5-diene-1,4'-quinolin]-4-iminium iodide 39Ac:

solid;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 1683, 1655, 1606, 1489, 1409, 1361;

^1H NMR (400 MHz, CD_3OD) δ 7.63 (dd, J_{d1} = 2.3 Hz, J_{d2} = 8.8 Hz, 1 H), 7.59 (part of AA'BB' system, $J_{AA'BB'}$ = 10.1 Hz, 2 H), 7.29 (d, J_d = 8.8 Hz, 1 H), 7.16 (d, J_d = 2.3 Hz, 1 H), 7.00 (part of AA'BB' system, $J_{AA'BB'}$ = 10.1 Hz, 2 H), 3.48 (s, 3 H), 2.94 (s, 2 H);

MS $(ESI)^+$ 317 (M^+); MS $(ESI)^-$ 127 (Iodide).



2-(4-Azidophenyl)-*N*-(4-bromophenyl)-2-hydroxy-*N*-methylacetamide 41c:

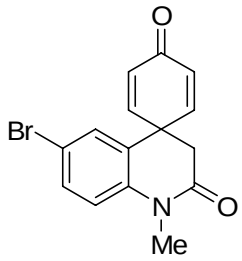
solid, mp = 107-110 °C;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 3423, 2122, 1649, 1487, 1290;

^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (bd, J_d = 8.5 Hz, 2 H), 6.87-6.79 (m, 4 H), 6.71 (bd, J_d = 7.8 Hz, 2 H), 4.95 (d, J_d = 6.7 Hz, 1 H), 4.44 (d, J_d = 6.7 Hz, 1 H), 3.27 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5 (C), 140.4 (C),135.8 (C), 132.9, 129.6, 128.8, 122.4 (C), 119.1, 118.9 (C), 71.1, 29.7;

MS (ESI) 383 $(M + Na)^+$, 399 $(M + K)^+$.



6'-Bromo-1'-methyl-1'*H*,4*H*-spiro[cyclohexa-2,5-diene-1,4'-quinoline]-2',4(3'*H*)-dione 28c:

solid, mp = 159-163 °C;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 1672, 1490, 1407, 1358;

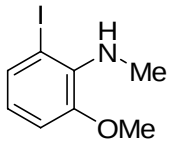
^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, J_{d1} = 2.2 Hz, J_{d2} = 8.6 Hz, 1 H), 7.19 (d, J_d = 2.2 Hz, 1 H), 6.98 (d, J_d = 8.6 Hz, 1 H), 6.91 (part of AA'BB' system, $J_{AA'BB'}$ = 10.1 Hz, 2 H), 6.42 (part of AA'BB' system, $J_{AA'BB'}$ = 10.1 Hz, 2 H), 3.44 (s, 3 H), 2.79 (s, 2 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 184.6 (C), 166.2 (C), 148.2, 139.0 (C), 132.3, 130.0, 129.4, 126.5 (C), 117.4, 116.7 (C), 42.8 (C), 40.6 (CH_2), 29.8;

MS (ESI) 340 $(M + Na)^+$;

MS (EI) *m*/*z* (rel. inten.) 317 (100), 288 (25), 210 (28);

HRMS (EI): calcd for $C_{15}H_{12}BrNO_2$: 317.0051; found: 317.0054.



2-Iodo-6-methoxy-*N*-methylbenzenamine:

dark-yellow oil;

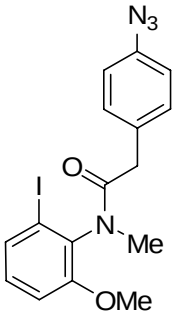
IR (neat) ν_{max} (cm^{-1}) 3367, 2958, 2831, 1572, 1471, 1420, 1231, 1029, 760;

^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J_{d1} = 1.3 Hz, J_{d2} = 8.0 Hz, 1 H), 6.81 (dd, J_{d1} = 1.3 Hz, J_{d2} = 8.2 Hz, 1 H), 6.62 (dd, J_{d1} = 8.0 Hz, J_{d2} = 8.2 Hz, 1 H), 3.83 (s, 3 H), 3.73 (bs, 1 H), 2.89 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3 (C), 140.8 (C), 131.3, 123.0, 111.6, 91.6 (C), 55.8, 35.1;

MS (EI) *m*/*z* (rel. inten.) 263 (100), 248 (66), 220 (25), 147 (40);

HRMS calcd for $C_8H_{10}INO$ 262.9807; found 262.9802.



2-(4-Azidophenyl)-*N*-(2-iodo-6-methoxyphenyl)-*N*-methylacetamide 42:

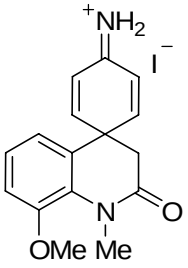
dark-yellow oil;

IR (neat) ν_{max} (cm^{-1}) 2939, 2113, 1666, 1506, 1470, 1433, 1373, 1283, 1115, 1028;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, J_{d1} = 1.3 Hz, J_{d2} = 8.0 Hz, 1 H), 7.07 (dd, J_{d1} = 8.0 Hz, J_{d2} = 8.2 Hz, 1 H), 7.03 (part of AA'BB' system, $J_{AA'BB'}$ = 8.6 Hz, 2 H), 6.91-6.86 (m, 3 H), 3.66 (s, 3 H), 3.33 (d, J_d = 15.1 Hz, 1 H), 3.23 (d, J_d = 15.1 Hz, 1 H), 3.09 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9 (C), 156.2 (C), 138.1 (C), 134.3 (C), 131.8 (C), 130.9, 130.8, 130.7, 118.6, 111.7, 101.5 (C), 55.6, 40.2 (CH_2), 34.4;

MS (ESI) 445 $(M + Na)^+$.



8'-Methoxy-1'-methyl-2'-oxo-2',3'-dihydro-1'*H*,4*H*-spiro[cyclohexa-2,5-diene-1,4'-quinolin]-4-iminium iodide 43:

solid;

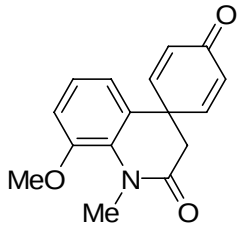
IR ($CHCl_3$) ν_{max} (cm^{-1}) 1669, 1489;

^{1}H NMR (400 MHz, CD_3OD) δ 7.53 (part of AA'BB' system, $J_{AA'BB'}$ = 9.9 Hz, 2 H), 7.21-7.15 (m, 2 H), 7.01 (part of AA'BB' system, $J_{AA'BB'}$ = 9.9 Hz, 2 H), 6.66 (dd, J_{d1} = 2.8 Hz, J_{d2} = 6.4 Hz, 1 H), 3.95 (s, 3 H), 3.50 (s, 3 H), 2.85 (s, 2 H);

^{13}C NMR (100 MHz, CD_3OD) δ 170.7 (C), 168.8 (C), 159.6, 153.1 (C), 132.3 (C), 128.6 (C), 128.3, 122.8, 120.4, 116.3, 57.6, 48.0 (C), 42.1 (CH_2), 36.5;

MS $(ESI)^+$ 269 (M^+); MS $(ESI)^-$ 127 (Iodide);

HRMS calcd for $C_{16}H_{16}N_2O_2$ 268.1212; found 268.1220.



8'-Methoxy-1'-methyl-1'*H*,4*H*-spiro[cyclohexa-2,5-diene-1,4'-quinoline]-2',4(3'*H*)-dione 24:

pale yellow oil;

IR ($CDCl_3$) ν_{max} (cm^{-1}) 1665, 1482, 1369, 1267;

^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (dd, J_{d1} = 7.7 Hz, J_{d2} = 8.4 Hz, 1 H), 6.97 (dd, J_{d1} = 1.2 Hz, J_{d2} = 8.4 Hz, 1 H), 6.89 (part of AA'BB' system, $J_{AA'BB'}$ = 10.3 Hz, 2 H), 6.69 (dd, J_{d1} = 1.4 Hz, J_{d2} = 7.7 Hz, 1 H), 6.39 (part of AA'BB' system, $J_{AA'BB'}$ = 10.3 Hz, 2 H), 3.90 (s, 3 H), 3.49 (s, 3 H), 2.72 (s, 2 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 184.9 (C), 168.1 (C), 150.3 (C), 149.0, 130.2 (C), 129.7, 129.2 (C), 125.5, 118.1, 113.2, 55.9, 43.4 (C), 41.7 (CH_2), 34.6;

MS $(ESI)^+$ 270 $(M + H)^+$, 292 $(M + Na)^+$, 308 $(M + K)^+$.

5.4 Improved Radical Approach to N-Unsubstituted Indol-2-one and Dihydro-2-quinolinone Compounds Bearing Spirocyclic Cyclohexanone/Cyclohexadienone Rings

Introduction

Spiroindolone **44** and spirodihydroquinolinones **46** are pivotal intermediates in the synthesis of important biologically active compounds. Indolone **44** is a key intermediate in the preparation of the potent, selective vasopressin inhibitor SR121463A **45**,[58] whereas the *N*-Boc dihydroquinolinones **46**, in the presence of primary amines, act as effective progenitors of peculiar tetracyclic ketones that are highly promising intermediates for the synthesis of indole alkaloids displaying a wide range of biological activities (*Figure 2*).[59,60]

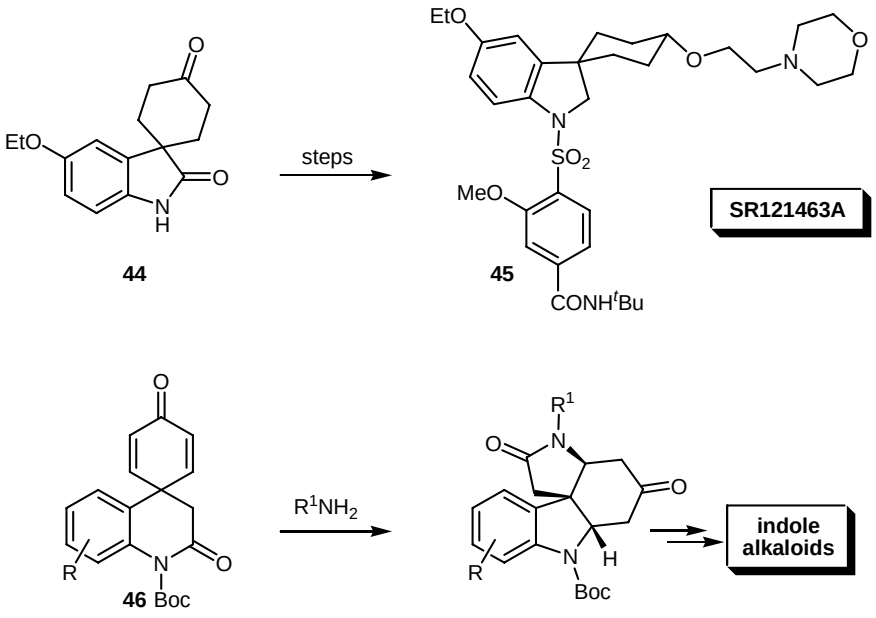
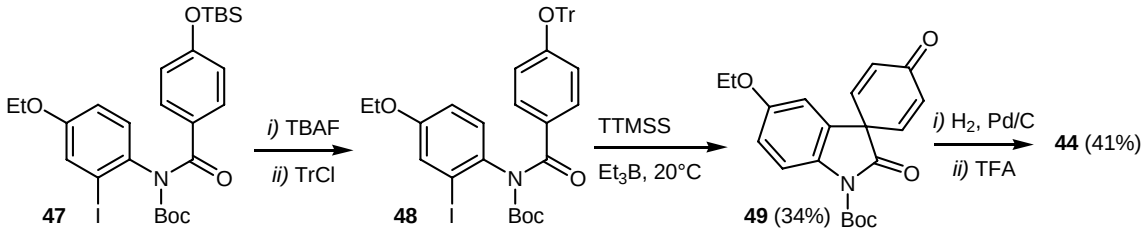


Figure 2**.** *Spiroketone derivatives as key intermediates in the syntheses of important biologically active compounds*.

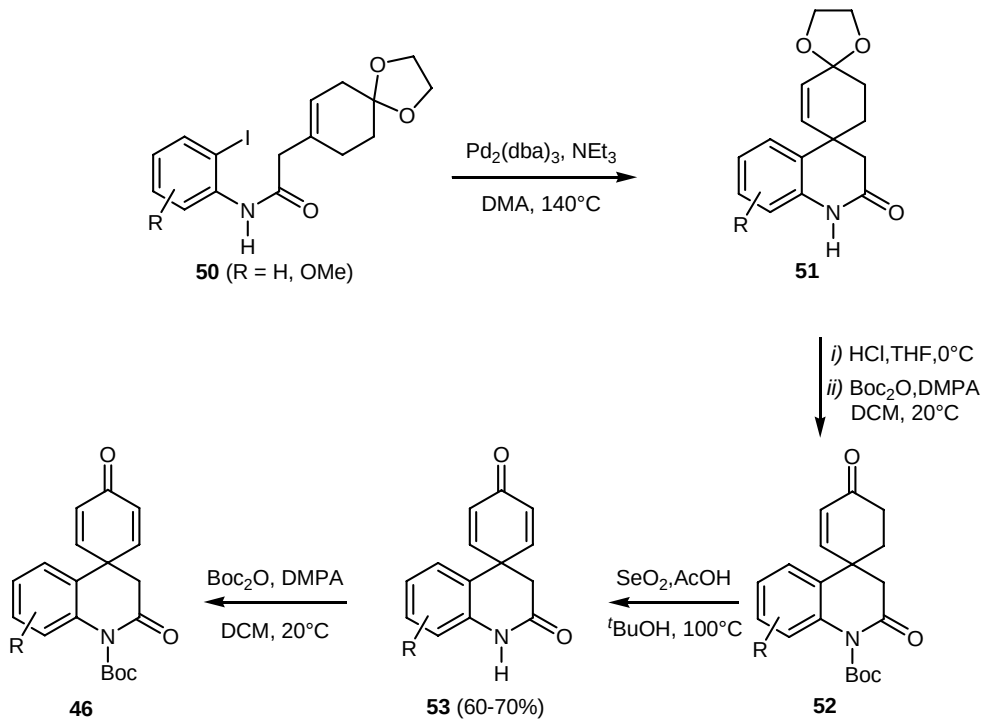
Structures such as compound **44** have been synthesized starting from 4-oxo-protected cyclohexyl derivatives,[61] oxindoles,[62] or substituted indolones.[63] More recently, compound **44** was prepared by Curran through reduction and deprotection of the indole spirocyclohexadienone **49** arising from radical spirocyclization of the *p*-trityloxy-substituted iodobenzanilide **48** mediated by tris(trimethylsilyl)-silane (TTMSS) and Et_3B initiator (*Scheme 12*).[64]



Scheme 12**.** *Curran synthesis of spiroindolone **44** (Tr = CPh_3).*

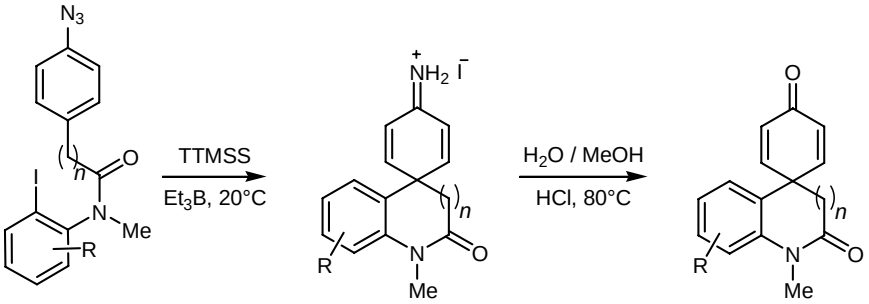
The effectiveness of this elegant method, however, is particularly spoiled by the fact that the crucial dienone **49** is formed only to a modest extent and, in addition, the construction of the requisite trityloxy precursor **48** is by no means trivial. Indeed, the synthesis of the latter entails deprotection and tritylation of preliminary *tert*-butyldimethylsililoxy (TBSO)-substituted anilide **47**, which, in turn, requires the rather tedious preparation of TBS-protected 4-hydroxybenzoyl chloride (*Scheme 12*).

As far as the dihydroquinolinones **46** are concerned**,** these are achieved by standard reaction of the respective *N*-unsubstituted quinolinones **53** with Boc_2O (*Scheme 13*). Unfortunately, the preparation of compounds **53** is to date restricted to an expensive, long-winded, multistep protocol entailing primary Heck cyclization of oxo-protected 2-(4-oxo-1-cyclohexenyl)acetanilides **50** to dihydroquinolinones **51** under harsh conditions. After hydrolysis of the dioxolane group of **51** and protection of the amide function with Boc_2O, a very prolonged oxidation (72 h) of the cyclohexenone moiety of the resulting product **52** with an excess of (very toxic) selenium dioxide at 100 °C eventually affords the requisite compounds **53** (*Scheme 13*). [b]



Scheme 13. *Reported synthesis of dihydroquinolinones* ***46*** *[$Pd_2(dba)_3$ = tris(dibenzylideneacetone)dipalladium(0)].*

In a latest work on the radical reactivity of organic azides[65b] (*see previous section*) it was discovered that easily accessible *N*-methyl-substituted *p*-azidobenzanilides **54**, as well as the corresponding 2-(*p*-azidophenyl)acetanilides **55**, undergo smooth radical reaction with TTMSS/Et_3B at ambient temperature giving rise to precipitation of extensive amounts of indolone/quinolinone imine hydroiodides **56**/**57**, isolable by direct filtration of the reaction mixtures (*Scheme 14*). Under those circumstances, 5- or 6-membered spirocyclizations of derived aryl radicals onto the respective azido-substituted aromatic rings result in highly efficient production of transient cyclohexadieniminyl radicals, from which hydroiodide salts **56,57** eventually arise.[66] The isolated imine compounds **56,57** undergo fair hydrolytical conversion into the corresponding dienones **58,59**, thus allowing a straightforward access to *N*-methyl indol-2-ones and 3,4-dihydro-2-quinolinones bearing spirocyclo-hexadienone rings (*Scheme 14*).[65b]



54, *n* = 0
55, *n* = 1
R = H, Me, Br, OMe

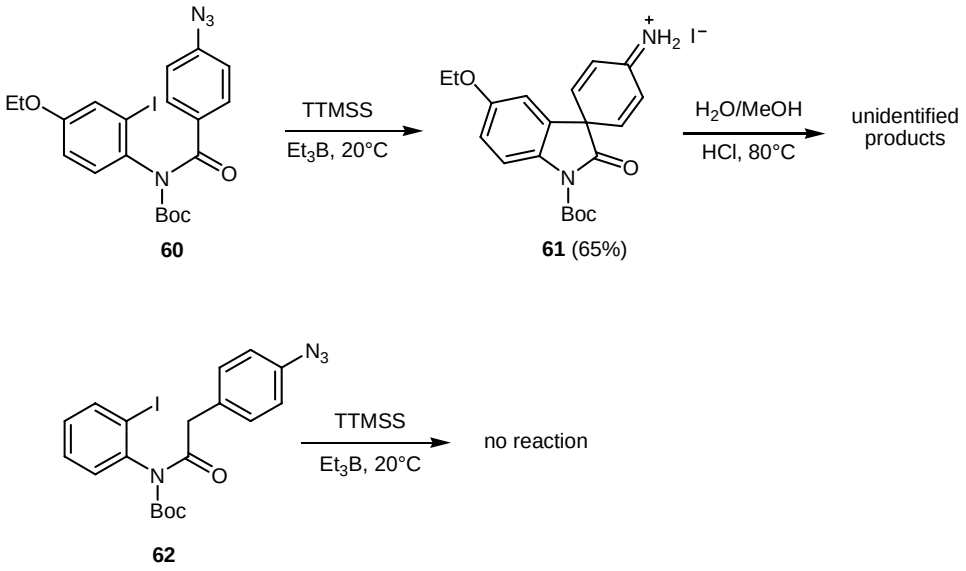
56, *n* = 0
57, *n* = 1

58, *n* = 0
59, *n* = 1

Scheme 14. *Approach to spiranic indol-2-ones and 3,4-dihydro-2-quinolinones through spirocyclization of aryl radicals onto aromatic azides.*

Results and Discussion

In light of those successful findings**,** it was envisioned that a similar method could enable a rewarding synthetic entry to *N*-Boc-substituted spirocyclic analogues, such as the spirooxindole **49** and spirodihydroquinolinones **46**, and/or their ultimate deprotected counterparts. Therefore, we were initially prompted to prepare the *N*-Boc-protected azidobenzamide **60** and azidoacetamide **62** (*Scheme 15*) in order to prove their potential utility in the respective construction of indolone **49** and dihydroquinolinone **46** (R = H). Following a procedure analogous to that previously employed for the preparation of anilides **54,55**,[b] the *N*-Boc congeners **60**,**62** were readily obtained through coupling of the appropriate *N*-Boc-2-iodoaniline with *p*-azidobenzoyl or 2-(*p*-azidophenyl)acetyl chloride.[67]



Scheme 15. *Attempted spirocyclization reactions of azidobenzamide **60** and azidoacetamide **62**.*

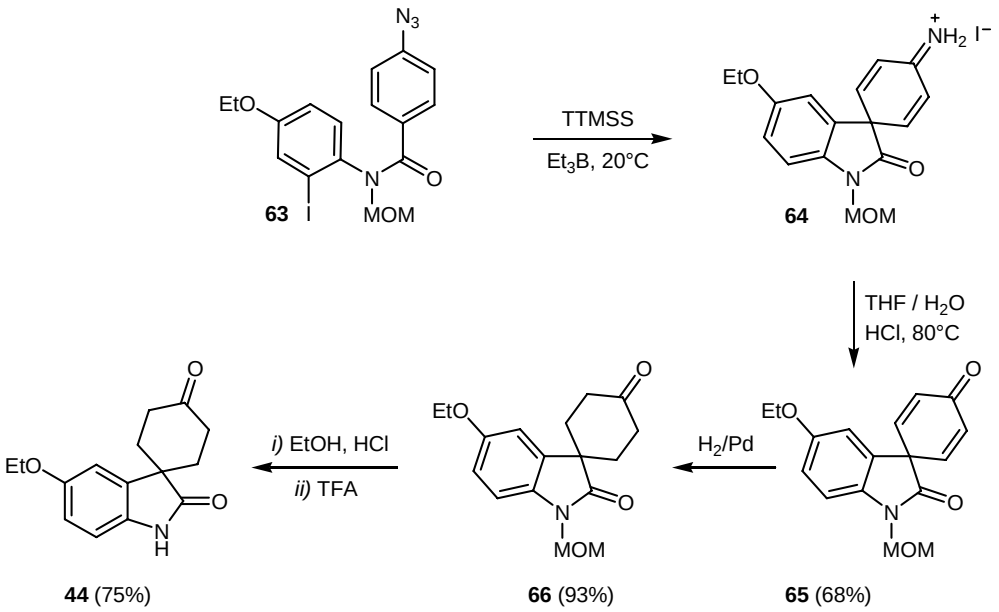
Under experimental conditions strictly comparable with those adopted with compounds **54/55**,[b] the new azidobenzamide **60** was actually able to undergo radical spirocyclization in benzene solution in the presence of TTMSS (1.2 equiv) and Et_3B (1.2 equiv) affording the indolone imine hydroiodide **61** in good isolated yield (*Scheme 15*). However, subsequent efforts to achieve the protected (or deprotected) cyclohexadienone **49** upon conventional acid hydrolysis of **61**[b,68] unfortunately failed, probably owing to a high propensity of **61** and/or **49** to suffer ring-cleavage of the pyrrolinone moiety upon nucleophilic attack at the lactam carbonyl carbon. Total failure to achieve **49** was also encountered even when hydrolysis was attempted by slow passage of **61** down a neutral alumina column (Brockmann activity II).[69]

The aim of exploiting the iodoazidoacetanilide **62** as synthetic precursor of dihydroquinolinone **46** (R = H) was still more frustrated by the surprising finding that **62** remained virtually unchanged in the presence of up to a threefold excess of TTMSS and/or Et_3B (*Scheme 15*). The actual reasons for the striking reluctance of iodide **62** to form usual aryl radicals with TTMSS/Et_3B remain obscure at this stage. It is hoped that future studies will shed light on this very intriguing point.

After ascertaining that the *N*-Boc anilides **60,62** were of no utility for the desired production of the corresponding spirocyclohexadienones, it was decided to examine the alternative use of *N*-MOM-substituted precursors. MOM (methoxymethyl) was envisioned as an especially promising protecting group owing to its fairly close affinity with the original *N*-methyl substituent as well as predictably fair removal under acid conditions.

The *N*-MOM-substituted azidobenzanilide **63** (*Scheme 16*) and the corresponding (azidophenyl)-acetanilides **67a-c** (*Scheme 17*) were thus easily synthesized by coupling of the suitable 2-iodoaniline with the respective azidoacyl chloride followed by treatment of the lithium salt of the ensuing benzamide or acetamide with chloromethyl methyl ether.

The usual radical reaction of **63** with TTMSS/Et_3B gave rise to precipitation of a large amount of imine hydroiodide **64**, which was simply recovered by filtration of the reaction mixture and then subjected to hydrolysis without any further purification: brief treatment in THF/water at 70 °C in the presence of some hydrochloric acid led to isolation of the *N*-MOM-substituted spiroindolone **65** in 68% overall yield (*Scheme 16*).

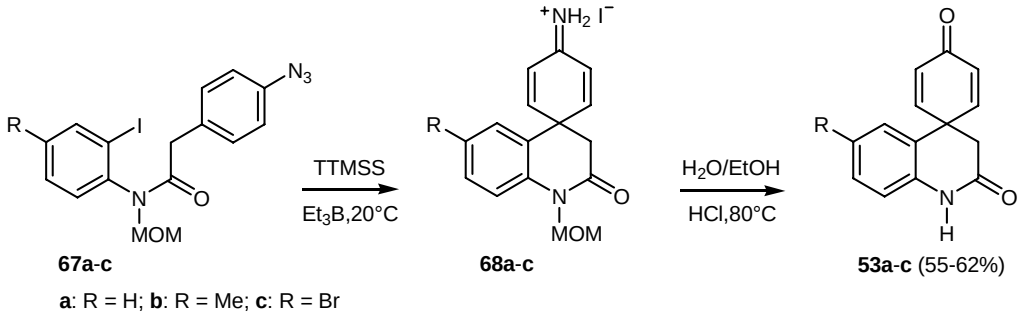


Scheme 16. *Improved synthesis of spiroindolone **44** through key radical cyclization of azidobenzamide **63**.*

Additionally, indolinone **65** was even superior to the Boc-substituted analogue **49** as precursor of spirocyclohexanone **44**. Indeed, Pd-mediated hydrogenation of **65** afforded the reduced cyclohexanone **66** in 93% yield; heating of **66** at 100 °C in ethanol/water containing catalytic amounts of hydrochloric acid and treatment of the ensuing *N*-ethoxymethyl derivative with TFA gave the eventual compound **44** in 75% yield.[70] Spiroindolone **44** could hence be attained from **65** in an overall yield largely superior to that originally obtained from **49** (*Schemes 16 and 12*).

As a result, the spirocyclic compound **44** became available through a novel protocol, based on latest radical chemistry of aromatic azides, which is far better than the recent radical method devised by Curran (*Scheme 12*). The present procedure, besides providing a deeply enhanced yield of **44**, employs a much more convenient azido precursor and also results in highly minimized atom waste; furthermore, it compares very favorably even with other reported non-radical methods.[b-c,-]

Highly gratifying results were also obtained with the azido substrates **67a-c**. As a matter of fact, standard reaction of **67a-c** with TTMSS/Et_3B similarly led to extensive precipitation of quinolone imine hydroiodides **68a-c**, which were again separated by simple filtration. Upon suitably prolonged heating at 80 °C in ethanol/water in the presence of hydrochloric acid, crude iminium salts **68a-c** underwent expected hydrolysis along with concomitant removal of the MOM-substituent, hence allowing direct isolation of the deprotected dienones **53a-c** in 55-62% yields based on the starting azides **67a-c** (*Scheme 17*).[71]



67a-c

a: R = H; **b**: R = Me; **c**: R = Br

68a-c

53a-c (55-62%)

Scheme 17. *Improved synthesis of spirodihydro-quinolinones **53** through key radical cyclization of azidoacetamides **67**.*

It was therefore discovered a very useful, novel synthetic route to *N*-unsubstituted spirodihydro-quinolinones **53.** Although the outcoming yields are a little lesser, compared to those previously reported, our new approach to compounds **53** is evidently superior to the one involving Heck cyclization of oxo-protected cyclohexenone anilides **7** (*Scheme 13*).[b] In particular, it is remarkably easier and quicker, entails far milder reaction conditions, and, furthermore, avoids unattractive use

of precursors such as **7** that require troublesome preparation of protected 2-(4-oxo-1-cyclohexenyl)acetic acid.[72]

Conclusions

In conclusion, it was shown that radical spirocyclization of easily accessible *N*-MOM-protected 2-iodoanilides derived from 2-(4-azidophenyl)acetic acid allows a significantly improved approach to *N*-unsubstituted 3,4-dihydro-2-quinolinones bearing spirocyclohexadienone rings, compounds that have been very recently reported as pivotal precursors of biologically important indole alkaloids. Application of an analogous radical methodology to a suitable *N*-MOM-substituted 4-azidobenzanilide enables a superior synthetic entry to the oxindole spirocyclohexanone **44**, a key intermediate involved in the synthesis of the vasopressin inhibitor SR121463A.

With respect to the previously reported methods, these novel radical processes entail more easily accessible precursors, avoid the use of troublesome procedures and/or toxic reagents, and are characterized by a superior atom economy quality. These features, additionally associated with ease of workup in the key step (the imine hydroiodides can be effectively recovered in high purity by straightforward filtration of the reaction mixtures) make these reactions enter the realm of sustainable and 'green' chemistry, a domain that is particular worthy when applied to the synthesis of biologically significant targets.

Experimental section

General Remarks

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury Plus 400 MHz (^{1}H: 400 or 300 MHz, ^{13}C: 100 or 75 MHz) in $CDCl_3$ solutions, unless otherwise stated, using tetramethylsilane as internal standard: ^{1}H NMR spectra, δ 7.26 ppm; ^{13}C NMR spectra δ 77.0 ppm. In reporting spectral data, the following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, td = triplet of doublets, bs = broad singlet, bd = broad doublet. Coupling constants are given in Hz.

IR spectra were recorded on a FT-IR Perkin Elmer Spectrum RXI instrument in $CHCl_3$ solutions or as liquid films.

GC-MS spectra were recorded using a ThermoFisher – Focus DSQ system. Mass spectra were recorded either by the electron spray ionization (ESI) method or under electron impact (EI) conditions with Waters – Micromass ZQ4000 and Thermo – Finnigan MAT95 XP instruments, respectively. High resolution mass determinations (HRMS) were carried out by electron impact at 70 eV.

Reactions were monitored by TLC and GC-MS. Column chromatography was performed on ICN silica gel (63-200, 60 Å) by gradual elution with *n*-hexane/diethyl ether and final elution with dichloromethane or methanol.

4-Aminobenzoic acid, (4-aminophenyl)acetic acid, 2-iodophenylamine, *p*-tolylamine, 4-bromophenylamine, 4-ethoxyphenylamine, thionyl chloride, chloromethyl methyl ether (MOM-Cl), tris(trimethylsilyl)silane (TTMSS), and triethylborane (1.0 M solution in hexanes) were commercially available (Aldrich) and were used as received. THF and Et_2O were distilled from sodium/benzophenone ketyl before use; CH_2Cl_2 (DCM) was purified by elution on an aluminum oxide (Brockman Activity I) column.

4-Azidobenzoic acid,[73] (4-azidophenyl)acetic acid,[74] 2-iodo-4-methylphenylamine,[75] 4-bromo-2-iodophenylamine,[75] (4-ethoxyphenyl)carbamic acid *tert*-butyl ester,[76] (4-ethoxy-2-iodophenyl)carbamic acid *tert*-butyl ester,[77] and 4-ethoxy-2-iodophenylamine[78] were prepared according to previous literature procedures.

The unkown azide compounds, like all azides, are usually suitable neither for elemental analysis nor for exact mass determination; in the case of 2-(4-azidophenyl)-*N*-(2-iodophenyl)acetamide the presence of a significant molecular ion allowed exact mass determination. In all cases the purity of the new azides was confirmed by NMR analysis.

Azido-*N*-(4-ethoxy-2-iodophenyl)benzamide

To a stirred solution of 4-azidobenzoic acid[73] (1.00 g, 6.10 mmol) and DMF (few drops) in anhydrous DCM (17 mL) at 0 °C thionyl chloride (0.53 mL, 7.32 mmol) was slowly added. The reaction mixture was stirred overnight at r.t.. The resulting acyl chloride was obtained in apparent quantitative yield (GC-MS analysis) and was used for the next step without further purification.

To a stirred solution of 4-ethoxy-2-iodophenylamine (5.0 mmol) in anhydrous DCM (58 mL) at r.t. were added pyridine (0.8 mL, 10.0 mmol), dimethylaminopyridine (DMAP, 0.060 g, 0.50 mmol), and a DCM solution (17 mL) of the previously prepared acyl chloride (6.1 mmol). The resulting mixture was stirred for 7 hours and then diluted with DCM (80 mL) and saturated aqueous $NaHCO_3$ solution (40 mL). The separated organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue gave the pure amide in 70% yield.

General Procedure for the Preparation of Azidoacetanilides

To a stirred solution of 2-(4-azidophenyl)acetic acid[74] (1.08 g, 6.10 mmol) and DMF (few drops) in anhydrous DCM (17 mL) at 0 °C thionyl chloride (0.53 mL, 7.32 mmol) was slowly added. The reaction mixture was stirred overnight at r.t.. The resulting acyl chloride was obtained in apparent quantitative yield (GC-MS analysis) and was used for the next step without further purification after reducing the solution volume to about 5 mL.

To a stirred solution of 2-iodoarylamine (5.0 mmol) in anhydrous DCM (58 mL) at r.t. were added pyridine (0.8 mL, 10.0 mmol), DMAP (0.060 g, 0.50 mmol), and the previously prepared acyl chloride DCM solution (6.1 mmol). The resulting mixture was stirred overnight and then diluted with DCM (80 mL) and saturated aqueous $NaHCO_3$ solution (40 mL). The separated organic layer war dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue gave the pure amides in 75-80% yields.

General Procedure for the Preparation of *N*-(MOM)-protected Azidobenzamide (63) and Azidoacetamides (67a-c)

To a stirred solution of di-*iso*-propylamine (0.147 mL, 1.05 mmol) in anhydrous THF (5 mL) at 0 °C under a nitrogen atmosphere *n*-BuLi (1.6 M in hexane, 0.650 mL, 1.05 mmol) was added dropwise *via* syringe. The reaction mixture was then stirred for 20 minutes at 0 °C and the resulting LDA solution was added dropwise to a stirred solution of azidoamide (1.00 mmol) in anhydrous THF (5 mL) at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 2 hours at r.t. and then MOM-Cl (0.151 mL, 2.00 mmol) was slowly added. The final reaction mixture was stirred overnight at r.t., was quenched with water, and the solvent was evaporated. The residual

aqueous solution was extracted several times with Et_2O and the organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue gave the corresponding azido *N*-MOM-protected amide in 70-80% yields.

General Procedure for the Cyclization Reactions of Azides (63, 67a-c) and Hydrolysis of Imine Hydroiodide Salts (64, 68a-c)

To a stirred solution of the azide (0.5 mmol) in benzene or toluene (8 mL) were successively added Et_3B (620 μL, 1.2 equiv) and TTMSS (190 μL, 1.2 equiv). The resulting mixture was stirred at r.t. under air until total consumption of the starting material (usually overnight). Filtration of the reaction mixture afforded the imine hydroiodide salt, which was used for the next step without further purification. For sake of thoroughness, compound **68a** (64% yield) was however isolated and fully characterized.

Two different methods were developed for hydrolysis of the iminium salts.

1) To a solution of the imine hydroiodide salt (0.25 mmol) in THF or methanol (12 mL) and water (6 mL) were added 20 drops of concentrated hydrochloric acid. The resulting mixture was stirred at 80 °C for 1.5-4 hours and the solvent was then evaporated. The residual aqueous solution was extracted several times with Et_2O and the organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The corresponding *N*-MOM-protected ketone was obtained in 68-98% yields. This procedure was applied to salts **64**, **68a-c** to obtain spirocycles **65** and the *N*-MOM-protected derivatives of **53a-c**.

2) To a solution of the imine hydroiodide salt (0.25 mmol) in EtOH (12.5 mL) and water (12.5 mL) were added 50 drops of concentrated hydrochloric acid. The resulting mixture was stirred at 80 °C for 24 hours and the solvent was then evaporated. The residual aqueous solution was extracted several times with Et_2O and the organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue gave the corresponding ketone in 55-62% yields. This procedure was applied to salts **68a-c** to obtain compounds **53a-c**. It is worth noting that this hydrolysis method, when applied to salt **64**, gave a very complicated mixture without any trace of the desired *N*-MOM-deprotected derivative of **65**.

5'-Ethoxy-1'-MOM-spiro[cyclohexane-1,3'-(3'*H*)-indole]-2',4-(1'*H*)-dione (66)

To a stirred solution of **65** (0.305 g, 1.02 mmol) in ethyl acetate (18 mL) 10% Pd/C (536 mg, 0.51 mmol of Pd) was added; the reaction vessel was purged with hydrogen and then kept under stirring under a hydrogen atmosphere (2 bar) for 2 hours. The crude reaction mixture was filtered over silica

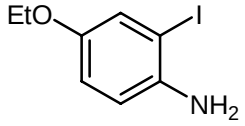
gel eluting with Et_2O. The solvent was concentrated in vacuo and pure ketone **66** was obtained in 93% yield as a white solid without any need for further purification.

5'-Ethoxyspiro[cyclohexane-1,3'-(3'*H*)-indole]-2',4-(1'*H*)-dione (44)

To a stirred solution of **66** (0.152 g, 0.500 mmol) in EtOH (25 mL) and water (5 mL) 75 drops of concentrated hydrochloric acid were added. The resulting mixture was stirred at 100 °C overnight and the solvent was then evaporated. The residual aqueous solution was extracted several times with DCM and the organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting *N*-ethoxymethyl-derivative was obtained in almost quantitative yield [GC-MS analysis: *m/z* (rel. inten.) 317 (M^+, 100), 272 (22), 259 (23), 244 (11), 202 (19), 189 (49), 188 (11), 161 (29), 160 (19), and 59 (31); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, t, J_t = 7.01 Hz), 1.42 (3H, t, J_t = 7.00 Hz), 2.12-2.23 (4H, m), 2.50 (2H, dt, J_d = 15.3 Hz, J_t = 5.60 Hz), 3.08-3.23 (2H, m), 3.73 (2H, q, J_q = 7.01 Hz), 4.01 (2H, q, J_q = 7.00 Hz), 5.18 (2H, s), 6.80-6.88 (2H, m), 7.01 (1H, d, J_d = 8.30 Hz)] and was used for the next step without further purification.

To a stirred solution of the previously prepared *N*-ethoxymethyl derivative in DCM (3 mL) neat TFA (3.0 mL, 40.0 mmol) was added. The resulting mixture was stirred at 40 °C for 4 hours and then at r.t overnight. Finally, it was diluted with DCM and saturated aqueous $NaHCO_3$ solution; the organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography of the residue (DCM/Et_2O: 70/30) gave pure amide **44** in 75% yield.

4-Ethoxy-2-iodophenylamine



dark-brown oil;

IR (neat) ν_{max} (cm^{-1}) 3437, 3352, 3204, 2977, 2927, 1597, 1493, 1393, 1271, 1229, 1047;

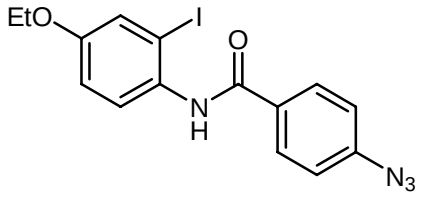
MS (EI) *m/z* (rel. inten.) 263 (M^+, 81), 235 (100), 234 (87), 206 (30), 108 (87), 107 (62), 79 (46), 52 (62);

HRMS calcd for $C_8H_{10}NOI$ 262.9807; found 262.9805;

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, t, J_t = 7.0 Hz), 3.69 (2H, bs), 3.92 (2H, q, J_q = 7.0 Hz), 6.68 (1H, d, J_d = 8.7 Hz), 6.76 (1H, dd, J_{d1} = 8.7 Hz, J_{d2} = 2.7 Hz), 7.21 (1H, J_d = 2.7 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 64.3 (CH_2), 84.3 (C), 115.3, 116.8, 124.4, 140.7 (C), 152.0 (C).

4-Azido-*N*-(4-ethoxy-2-iodophenyl)benzamide



pale-yellow solid;

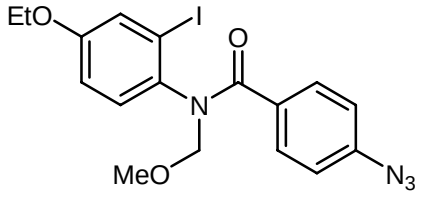
IR ($CHCl_3$) ν_{max} (cm^{-1}) 3402, 3154, 2983, 2897, 2129, 1674, 1604, 1521, 1505, 1475, 1393, 1291, 1261, 1211, 1098, 1047;

MS (ESI)$^+$ 431 $(M + Na)^+$, 403 $([M - 28] + Na)^+$;

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (3H, t, J_t = 7.0 Hz), 4.02 (2H, q, J_q = 7.0 Hz), 6.95 (1H, dd, J_{d1} = 9.1 Hz, J_{d2} = 2.8 Hz), 7.15 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 8.7 Hz), 7.36 (1H, d, J_d = 2.8 Hz), 7.95 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 8.7 Hz), 7.99 (1H, bs), 8.18 (1H, d, J_d = 9.1 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 64.1 (CH_2), 91.3 (C), 115.3, 119.3, 123.0, 124.5, 128.9, 131.0 (C), 131.4 (C), 143.9 (C), 156.2 (C), 164.2 (C).

4-Azido-*N*-(4-ethoxy-2-iodophenyl)-*N*-MOM-benzamide (63)



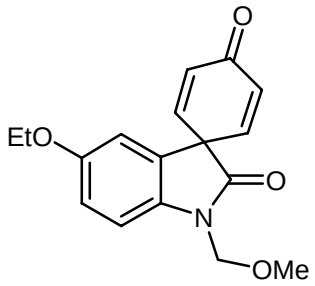
yellow oil;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 2986, 2895, 2125, 1680, 1605, 1450, 1395,1286, 1210, 1050;

MS (ESI)$^{+}$ 491 $(M + K)^{+}$, 475 $(M + Na)^{+}$, 447 $([M - 28] + Na)^{+}$;

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (3H, t, J_t = 7.0 Hz), 3.50 (3H, s), 3.94 (2H, q, J_q = 7.0 Hz), 4.58 (1H, d, J_d = 9.9 Hz), 5.72 (1H, d, J_d = 9.9 Hz), 6.74-6.87 (3H, m), 7.1 (1H, bd, J_d = 8.3 Hz), 7.28 (1H, bs), 7.39 (2H, bd, J_d = 7.4 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 57.2, 63.9 (CH_2), 79.5 (CH_2), 100.0 (C), 115.2, 118.0, 125.1, 130.2, 131.4, 131.8 (C), 136.6 (C), 141.6 (C), 158.4 (C), 170.3 (C).



5'-Ethoxy-1'-MOM-spiro[cyclohexa-2,5-diene-1,3'-(3'*H*)-indole]-2',4-(1'*H*)-dione (65)

white solid;

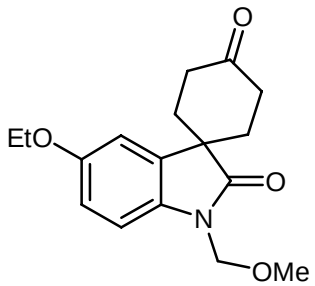
IR ($CHCl_3$) ν_{max} (cm^{-1}) 2984, 2936, 1724, 1687, 1627, 1602, 1497, 1450, 1399, 1325, 1282, 1224, 1190, 1097, 1043;

MS (EI) *m/z* (rel. inten.) 299 (M^{+}, 55), 269 (15), 241 (9), 220 (9), 205 (47), 84 (10), 71 (12), 57 (27), 45 (100);
MS (ESI)$^{+}$ 322 $(M + Na)^{+}$;

HRMS calcd for $C_{17}H_{17}NO_4$ 299.1157; found 299.1158;

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, t, J_t = 7.0 Hz), 3.37 (3H, s), 3.97 (2H, q, J_q = 7.0 Hz), 5.16 (2H, s), 6.54 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 10.2 Hz), 6.61-6.66 (3H, m), 6.91 (1H, dd, J_{d1} = 8.6 Hz, J_{d2} = 2.6 Hz), 7.05 (1H, d, J_d = 8.6 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 56.4, 56.5 (C), 64.1 (CH_2), 72.2 (CH_2), 111.2, 111.8, 115.5, 126.8 (C), 131.4, 135.1 (C), 143.3, 156.3 (C), 171.6 (C), 185.0 (C).



5'-Ethoxy-1'-MOM-spiro[cyclohexane-1,3'-(3'*H*)-indole]-2',4-(1'*H*)-dione (66)

white solid;

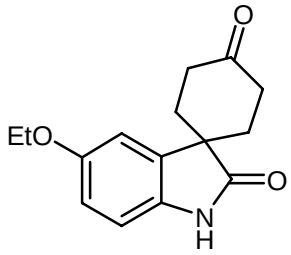
IR ($CHCl_3$) ν_{max} (cm^{-1}) 3020, 2932, 1711, 1600, 1497, 1450, 1342, 1284, 1225, 1093, 1044;

MS (EI) *m/z* (rel. inten.) 303 (M^+, 100), 272 (21), 244 (23), 233 (24), 202 (26), 174 (15), 160 (7), 146 (7), 55 (7);

HRMS calcd for $C_{17}H_{21}NO_4$ 303.1471; found 303.1474;

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (3H, t, J_t = 7.0 Hz), 2.13-2.22 (4H, m), 2.50 (2H, dt, J_d = 15.2 Hz, J_t = 5.6 Hz), 3.09-3.23 (2H, m), 3.35 (3H, s), 4.01 (2H, q, J_q = 7.0 Hz), 5.14 (2H, s), 6.80-6.88 (2H, m), 6.99 (1H, d, J_d = 8.5 Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 33.9 (CH_2), 36.8 (CH2), 46.1 (C), 56.2, 64.1 (CH_2), 71.2 (CH_2), 110.0, 110.9, 112.9, 133.8 (C), 134.1 (C), 155.5 (C), 179.4 (C), 210.1 (C).



5'-Ethoxyspiro[cyclohexane-1,3'-(3'*H*)-indole]-2',4-(1'*H*)-dione (44)

white solid, mp = 176-180 °C;

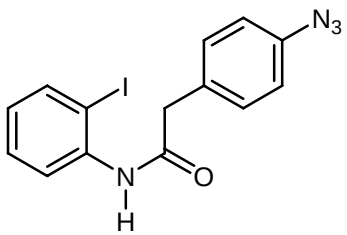
IR ($CHCl_3$) ν_{max} (cm^{-1}) 3426, 1708, 1498;

MS (EI) *m/z* (rel. inten.) 259 (M^+, 100), 230 (14), 190 (12), 189 (91), 161 (78), 160 (25), 133 (9);

HRMS calcd for $C_{15}H_{17}NO_3$ 259.1208; found 259.1210;

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (3H, t, J_t = 6.9 Hz), 2.12-2.24 (4H, m), 2.50 (2H, dt, J_d = 15.2 Hz, J_t = 5.6 Hz), 3.09-3.22 (2H, m), 4.00 (2H, q, J_q = 6.9 Hz), 6.70-6.90 (3H, m), 8.6 (1H, bs);

^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 33.6 (CH_2), 36.8 (CH_2), 46.4 (C), 64.1 (CH_2), 110.3, 111.1, 112.9, 133.0 (C), 134.9 (C), 155.1 (C), 181.5 (C), 210.4 (C);



2-(4-Azidophenyl)-*N*-(2-iodophenyl)acetamide

white solid;

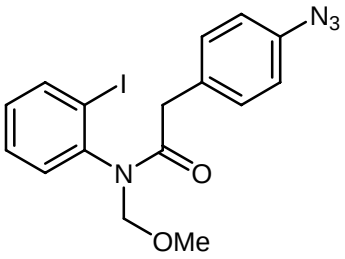
IR ($CHCl_3$) ν_{max} (cm^{-1}) 3350, 2412, 2116, 1692, 1585, 1508, 1433, 1290;

MS (EI) *m/z* (rel. inten.) 378 (M^+, 13), 246 (25), 245 (19), 132 (25), 119 (36), 106 (40), 105 (100), 78 (18), 77 (16), 71 (18), 57 (19);

HRMS calcd for $C_{14}H_{11}IN_4O$ 377.9978; found 377.9971;

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (2H, s), 6.81 (1H, td, J_t = 7.8 Hz, J_d = 1.4 Hz), 7.08 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 8.4 Hz), 7.29-7.34 (1H, m), 7.37 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 8.4 Hz), 7.43 (1H, bs), 7.70 (1H, dd, J_{d1} = 7.9 Hz, J_{d2} = 1.2 Hz), 8.23 (1H, d, J_d = 8.2 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 44.4 (CH_2), 89.4 (C), 119.8, 121.5, 126.0, 129.2, 130.5 (C), 131.4, 137.8 (C), 138.7, 139.7 (C), 168.9 (C).



2-(4-Azidophenyl)-*N*-(2-iodophenyl)-*N*-(MOM)acetamide (67a)

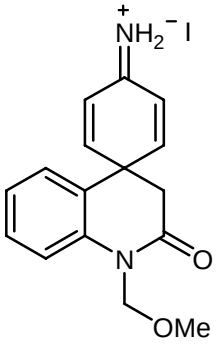
yellow oil;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 2937, 2413, 2115, 1670, 1610, 1579, 1507, 1470, 1377, 1286, 1248, 1184, 1110, 1077, 1019;

MS (ESI)$^+$ 461 $(M + K)^+$, 445 $(M + Na)^+$, 417 $([M – 28] + Na)^+$;

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.28 (1H, d, J_d = 15.4 Hz), 3.39 (1H, d, J_d = 15.4 Hz), 3.42 (3H, s), 4.37 (1H, d, J_d = 10.3 Hz), 5.61 (1H, d, J_d = 10.3 Hz), 6.91 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 8.6 Hz), 7.06 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 8.6 Hz), 7.10-7.15 (1H, m), 7.17 (1H, dd, J_{d1} = 7.8 Hz, J_{d2} = 1.6 Hz), 7.37-7.42 (1H, m), 7.98 (1H, dd, J_{d1} = 7.9 Hz, J_{d2} = 1.5 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 41.1 (CH_2), 57.0, 78.4 (CH_2), 100.7 (C), 118.9, 129.5, 130.3, 130.8, 131.1 (C), 131.4, 138.6 (C), 140.1, 143.1 (C), 171.5 (C).



1'-MOM-spiro[cyclohexa-2,5-diene-1,4'-(3'*H*)-quinoline]-2'-(1'*H*)-oxo-4-iminium iodide (68a)

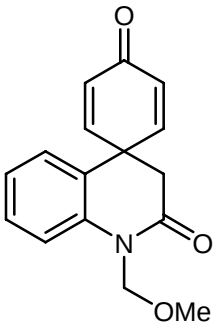
dark-brown solid;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 3676, 3550-2500 (v br), 1682,1599, 1495, 1457, 1380, 1212, 1078;[79]

MS (ESI)$^+$ 269 (M^+); **MS (ESI)$^-$** 127 (Iodide);

^{1}H NMR (400 MHz, CD_3OD) δ 2.97 (2H, s), 3.44 (3H, s), 5.40 (2H, s), 6.95 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 9.9 Hz), 7.02 (1H, dd, J_{d1} = 7.7 Hz, J_{d2} = 1.3 Hz), 7.13 (1H, td, J_t = 7.5 Hz, J_d = 1.3 Hz), 7.39-7.44 (1H, m), 7.50 (1H, dd, J_{d1} = 8.3 Hz, J_{d2} = 1.1 Hz), 7.58 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 9.9 Hz);

^{13}C NMR (100 MHz, CD_3OD) δ 40.9 (CH_2), 47.8, 57.8 (C), 76.3 (CH_2), 119.6, 122.6, 123.7 (C), 126.8, 130.2, 132.2, 141.4 (C), 159.8, 168.9 (C), 169.9 (C).



1'-MOM-spiro[cyclohexa-2,5-diene-1,4'-(3'*H*)-quinoline]-2',4-(1'*H*)-dione

yellow solid;

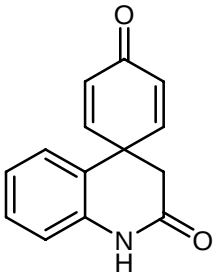
IR ($CHCl_3$) ν_{max} (cm^{-1}) 2957, 2928, 2856, 1686, 1670, 1628, 1599, 1456, 1380, 1306, 1123, 1076;

MS (EI) *m/z* (rel. inten.) 269 (M^+, 77), 254 (22), 238 (17), 211 (45), 205 (13), 196 (16), 167 (18), 149 (24), 45 (100);
MS (ESI)$^+$ 292 $(M + Na)^+$;

HRMS calcd for $C_{16}H_{15}NO_3$ 269.1052; found 269.1050;

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (2H, s), 3.46 (3H, s), 5.41 (2H, s), 6.40 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 10.3 Hz), 6.94 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 10.3 Hz), 7.07-7.11 (2H, m), 7.33-7.39 (1H, m), 7.41-7.45 (1H, m);

^{13}C NMR (100 MHz, $CDCl_3$) δ 40.8 (CH_2), 43.2 (C), 56.7, 74.0 (CH_2), 117.0, 124.3 (C), 124.6, 126.4, 129.6, 129.7, 138.9 (C), 149.0, 167.6 (C), 184.6 (C).



Spiro[cyclohexa-2,5-diene-1,4'-(3'*H*)-quinoline]-2',4-(1'*H*)-dione (53a)

yellow solid;

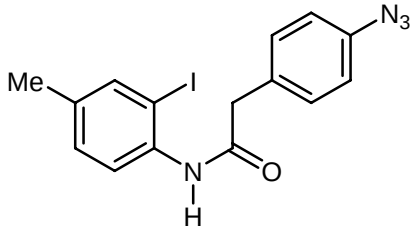
IR ($CHCl_3$) ν_{max} (cm^{-1}) 3402, 3201, 3155, 3076, 2981, 2903, 1686, 1670, 1629, 1595, 1488, 1477, 1379, 1249, 1176, 1095;

MS (EI) *m/z* (rel. inten.) 225 (M^+, 100), 197 (44), 196 (78), 183 (24), 168 (42), 154 (38), 77 (9);

HRMS calcd for $C_{14}H_{11}NO_2$ 225.0790; found 225.0788;

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (2H, s), 6.41 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 10.3 Hz), 6.96-6.99 (1H, m), 7.01 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 10.3 Hz), 7.04-7.10 (2H, m), 7.30 (1H, ddd, J_{d1} = 7.8 Hz, J_{d2} = 6.9 Hz, J_{d3} = 1.8 Hz), 9.41 (1H, bs);

^{13}C NMR (100 MHz, $CDCl_3$) δ 40.0 (CH_2), 43.6 (C), 116.7, 122.0 (C), 124.4, 126.6, 129.4, 129.6, 136.6 (C), 149.2, 168.5 (C), 184.9 (C).



2-(4-Azidophenyl)-*N*-(2-iodo-4-methylphenyl)acetamide

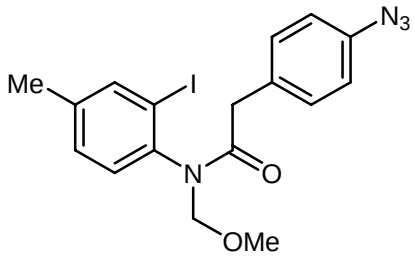
pale-yellow solid; mp = 73-75 °C;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 3352, 2924, 2117, 1687, 1603, 1573, 1508, 1466, 1386, 1288, 1129, 1037;

MS (ESI)$^+$ 431 $(M + K)^+$, 415 $(M + Na)^+$, 387 $([M - 28] + Na)^+$;

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (3H, s), 3.74 (2H, s), 7.08 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 8.5 Hz), 7.12 (1H, dd, J_{d1} = 8.4 Hz, J_{d2} = 1.8 Hz), 7.33 (1H, bs), 7.37 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 8.5 Hz), 7.53 (1H, bs), 8.06 (1H, d, J_d = 8.4 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 44.3 (CH_2), 89.6 (C), 119.8, 121.4, 129.8, 130.6 (C), 131.4, 135.4 (C), 136.1 (C), 138.9, 139.7 (C), 168.8 (C).



2-(4-Azidophenyl)-*N*-(2-iodo-4-methylphenyl)-*N*-MOM-acetamide (67b)

yellow oil;

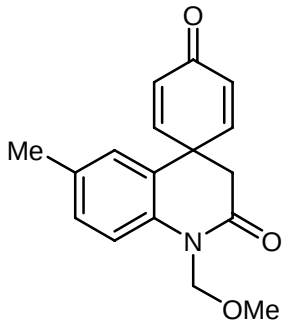
IR ($CHCl_3$) ν_{max} (cm^{-1}) 2937, 2413, 2116, 1670, 1608, 1507, 1486, 1376, 1286, 1196, 1113, 1078, 1043;

MS (ESI)$^+$ 459 $(M + Na)^+$, 431 $([M - 28] + Na)^+$;

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (3H, s), 3.28 (1H, d, J_d = 15.4 Hz), 3.38 (1H, d, J_d = 15.4 Hz), 3.41 (3H, s), 4.34 (1H, d, J_d = 10.1 Hz), 5.59 (1H, d, J_d = 10.1 Hz), 6.92 (2H, part of AA′BB′

system, $J_{AA'BB'}$ = 8.5 Hz), 7.04 (1H, d, J_d = 8.0 Hz), 7.08 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 8.5 Hz), 7.19 (1H, dd, J_{d1} = 8.0 Hz, J_{d2} = 1.5 Hz), 7.80 (1H, d, J_d = 1.5 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 40.9 (CH_2), 57.0, 78.4 (CH_2), 100.4 (C), 118.9, 130.2, 130.7, 130.9, 131.3 (C), 138.6 (C), 140.4, 140.5 (C), 140.7 (C), 171.7 (C).



6'-Methyl-1'-MOM-spiro[cyclohexa-2,5-diene-1,4'-(3'*H*)-quinoline]-2',4-(1'*H*)-dione

yellow solid;

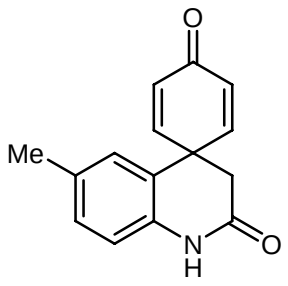
IR ($CHCl_3$) ν_{max} (cm^{-1}) 2938, 1669, 1629, 1504, 1458, 1415, 1377, 1305, 1245, 1195, 1124, 1076;

MS (EI) *m/z* (rel. inten.) 283 (M^+, 86), 268 (14), 252 (17), 225 (30), 210 (17), 88 (58), 49 (42), 47 (100), 45 (75);
MS (ESI)$^+$ 306 $(M + Na)^+$;

HRMS calcd for $C_{17}H_{17}NO_3$ 283.1208; found 283.1208;

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (3H, s), 2.82 (2H, s), 3.45 (3H, s), 5.39 (2H, s), 6.39 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 10.2 Hz), 6.87 (1H, d, J_d = 1.8 Hz), 6.93 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 10.2 Hz), 7.15 (1H, ddd, J_{d1} = 8.4 Hz, J_{d2} = 2.0 Hz, J_{d3} = 0.7 Hz), 7.31 (1H, d, J_d = 8.4 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (CH_2), 40.8, 43.1 (C), 56.5, 73.9 (CH_2), 116.9, 124.0 (C), 126.9, 129.5, 130.0, 134.3 (C), 136.4 (C), 149.2, 167.5 (C), 184.9 (C).



6'-Methylspiro[cyclohexa-2,5-diene-1,4'-(3'*H*)-quinoline]-2',4-(1'*H*)-dione (53b)

yellow solid;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 3403, 3155, 3050, 2928, 1684, 1670, 1629, 1506, 1466, 1379, 1357, 1250, 1174, 1096;

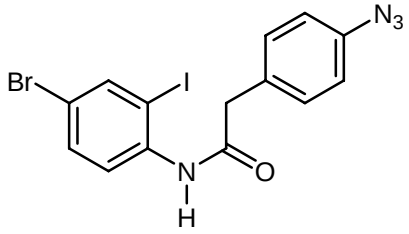
MS (EI) *m/z* (rel. inten.) 239 (M^+, 6), 223 (6), 205 (17), 149 (100), 69 (7), 57 (17), 41 (9);
MS (ESI)$^+$ 262 $(M + Na)^+$;

HRMS calcd for $C_{15}H_{13}NO_2$ 239.0946; found 239.0948;

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (3H, s), 2.75 (2H, s), 6.40 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 10.2 Hz), 6.83-6.87 (2H, m), 6.99 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 10.2 Hz), 7.09 (1H, bd, J_d = 8.0 Hz), 9.12 (1H, bs);

^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 40.0 (CH_2), 43.6 (C), 116.5, 121.8 (C), 127.0, 129.3, 130.1, 134.1 (C), 134.2 (C), 149.4, 168.2 (C), 185.0 (C).

2-(4-Azidophenyl)-*N*-(4-bromo-2-iodophenyl)acetamide



yellow solid;

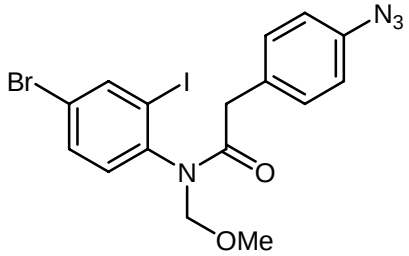
IR ($CHCl_3$) ν_{max} (cm^{-1}) 3340, 2113, 1685, 1590, 1510, 1459, 1286;

MS (ESI)$^+$ 479 $(M + Na)^+$, 451 $([M - 28] + Na)^+$;

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (2H, s), 7.09 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 8.5 Hz), 7.37 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 8.5 Hz), 7.40 (1H, bs), 7.44 (1H, dd, J_{d1} = 8.8 Hz, J_{d2} = 2.2 Hz), 7.83 (1H, d, J_d = 2.2 Hz), 8.17 (1H, d, J_d = 8.8 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 44.4 (CH_2), 89.5 (C), 117.4 (C), 120.0, 122.1, 130.2 (C), 131.4, 132.2, 137.1 (C), 139.9 (C), 140.4, 168.9 (C).

2-(4-Azidophenyl)-*N*-(4-bromo-2-iodophenyl)-*N*-MOM-acetamide (67c)



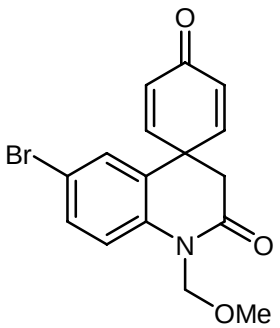
yellow oil;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 2945, 2114, 1673, 1506, 1465, 1382, 1368, 1284, 1194, 1112, 1079, 1039;

MS (ESI)$^+$ 525, 523 $(M + Na)^+$, 497, 495 $([M - 28] + Na)^+$, 355, 353;

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.29 (1H, d, J_d = 15.5 Hz), 3.39 (1H, d, J_d = 15.5 Hz), 3.40 (3H, s), 4.31 (1H, d, J_d = 10.3 Hz), 5.58 (1H, d, J_d = 10.3 Hz), 6.93 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 8.6 Hz), 7.01 (1H, d, J_d = 8.2 Hz), 7.06 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 8.6 Hz), 7.52 (1H, dd, J_{d1} = 8.4 Hz, J_{d2} = 2.2 Hz), 8.12 (1H, d, J_d = 2.2 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 41.1 (CH_2), 57.0, 78.2 (CH_2), 101.6 (C), 119.0, 123.2 (C), 130.7, 130.8 (C), 132.2, 132.6, 138.8 (C), 142.1, 142.2 (C), 171.2 (C).



6'-Bromo-1'-MOM-spiro[cyclohexa-2,5-diene-1,4'-(3'*H*)-quinoline]-2',4-(1'*H*)-dione

yellow solid;

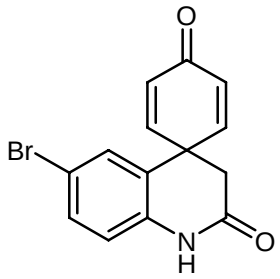
IR ($CHCl_3$) ν_{max} (cm^{-1}) 2939, 1692, 1671, 1488, 1411, 1368, 1302, 1196, 1124, 1076;

MS (EI) *m/z* (rel. inten.) 349 (21), 347 (M^+, 21), 291 (11), 289 (12), 84 (34), 69 (24), 45 (100);

HRMS calcd for $C_{16}H_{14}NO_3Br$ 347.0157; found 347.0157;

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.84 (2H, s), 3.45 (3H, s), 5.38 (2H, s), 6.42 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 10.1 Hz), 6.90 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 10.1 Hz), 7.19 (1H, d, J_d = 2.3 Hz), 7.31 (1H, d, J_d = 8.8 Hz), 7.46 (1H, dd, J_{d1} = 2.3 Hz, J_{d2} = 8.8 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 40.6 (CH_2), 42.9 (C), 56.7, 74.0 (CH_2), 117.4 (C), 118.7, 126.4 (C), 129.3, 130.0, 132.5, 138.0 (C), 148.0, 167.1 (C), 184.4 (C).



6'-Bromospiro[cyclohexa-2,5-diene-1,4'-(3'*H*)-quinoline]-2',4-(1'*H*)-dione (53c)

yellow solid;

IR ($CHCl_3$) ν_{max} (cm^{-1}) 3401, 3156, 2928, 1689, 1671, 1630, 1488, 1378, 1266, 1086;

MS (EI) *m/z* (rel. inten.) 305 (30), 303 (M^+, 28), 276 (16), 274 (15), 196 (16), 149 (100), 69 (35), 57 (33);
MS (ESI)$^+$ 328, 326 $(M + Na)^+$; **MS (ESI)$^-$** 304, 302 $(M - H)^-$;

HRMS calcd for $C_{14}H_{10}NO_2Br$ 302.9895; found 302.9892;

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (2H, s), 6.43 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 10.1 Hz), 6.84 (1H, d, J_d = 8.4 Hz), 6.96 (2H, part of AA′BB′ system, $J_{AA'BB'}$ = 10.1 Hz), 7.19 (1H, d, J_d = 2.1 Hz), 7.41 (1H, dd, J_{d1} = 2.1 Hz, J_{d2} = 8.4 Hz), 9.03 (1H, bs);

^{13}C NMR (100 MHz, $CDCl_3$) δ 39.8 (CH_2), 43.4 (C), 116.8 (C), 118.1, 124.2 (C), 129.6, 129.9, 132.5, 135.7 (C), 148.1, 167.8 (C), 184.5 (C).

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[14] To the best of our knowledge no previous instances of α-(aminocarbonyl)iminyl radicals are available in the literature. The chemistry of other α-carbonyl-substituted analogues is virtually unknown, but recent chemical and/or spectral evidence would indicate that α-benzoyliminyl radical undergoes rapid fragmentation into benzoyl radical and a nitrile at temperatures exceeding −60 °C, whereas the α-fluoroformyl counterpart is relatively stable, see: (a) Groenenboom, C. J.; Hageman, H. J.; Oosterhoff, P.; Overeem, T.; Verbeck, J. *J. Photochem. Photobiol. A* **1997**, *107*, 261. (b) Bucher, G.; Kolano, C.; Schade, O.; Sander, W. *J. Org. Chem.* **2006**, *71*, 2135.

[15] In the case of iminyl **12f**, alternative fragmentation at the alkyl side could be somewhat promoted by the notable stability of the released (3-indolyl)methyl radical.

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[55] The NH_2 group is not detectable under these conditions.

[56] All imine hydroiodides show loss of hydrogen iodide in the mass spectrometer source, giving the molecular ion peak of the free base.

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[67] *p*-Azidobenzoyl and 2-(*p*-azidophenyl)acetyl chloride are prepared by conversion of the commercially available amino acids into azides via conventional treatment of the diazonium salts with sodium azide.

[68] Heating of the iminium hydroiodide **61** in methanol/water or THF/water in the presence of hydrochloric acid gave rise to unclear product mixtures from which we gained no diagnostic ^{1}H NMR data in favor of protected (or deprotected) indolone **49**

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[70] It has happened to observe that deprotection of the oxindole cyclohexanone **66** could be significantly improved through preliminary conversion of *methoxy*methyl to *ethoxy*methyl group.

[71] Parallel experiments suggested that the imine hydroiodides **68**, when similarly reacted in THF/water or methanol/water, undergo usual hydrolysis exclusive of deprotection of the MOM-group (see following Experimental Section).

[72] Iodoacetanilides **7** are obtained by heating the corresponding 2-iodoanilines with oxo-protected 2-(4-oxo-1-cyclohexenyl)acetic acid in the presence of 2-chloro-1-methylpyridinium iodide and NEt_3: see ref. 2b. The requisite acid is achieved by troublesome Birch reduction of 2-(*p*-

methoxyphenyl)acetic acid with fivefold excess of lithium wire in dried ammonia at −78 °C, followed by protection with ethylene glycol/BF_3·OEt_2, see: M. Varin, E. Barrè, B. Iorga, C. Guillou, *Chem. Eur. J*. **2008**, *14*, 6606.

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CHAPTER 6

SUMMARY AND OUTLOOK

As shown in this brief “journey” of radical chemistry, it is undoubted that its initial slow development has been caused by several prejudices concerning its poor selectivity and the difficulty of controlling reactive substrates as radical species. Despite this, fortunately, chemists’ curiosity led to an initial yet slow exploration of their synthetic utility that, after time, was able to destroy the bad reputation of the radical chemistry.

In this context, we have shown the historical background and the basics of the radical chemistry, trying to provide an easy approach to lectors.

In particular, we have reported new *tin-free methodologies* for the generation of *alkyl radicals* at the aim of forming new carbon-carbon bonds, employing more eco-friendly substrates like sulfides- and thiols-based reagents.

Additionally, we have demonstrated, through the exploration of *azido compounds* as new unprecedented source of *imynil radicals*, the wide applicability of radical chemistry to the synthesis of biologically active compounds, providing an efficient protocol for achieving highly important intermediates like spirocyclic molecules.

With this survey of the radical chemistry in the last years, we have tried to open a new perspective on the usefulness of the radical chemistry, highlighting its synthetic power in different chemical transformations.

Lanza Tommaso

Papers

1) Bencivenni G., Lanza T., Leardini R., Minozzi M., Nanni D., Spagnolo P., Zanardi G., **"Tin-free Generation of Alkyl Radicals from Alkyl 4-Pentynyl Sulfides via Homolytic Substitution at the Sulfur Atom"** *Organic Letters.*, **2008**, *10*, 1127-1130.

2) Bencivenni G., Lanza T., Leardini R., Minozzi M., Nanni D., Spagnolo P., Zanardi G., **"Iminyl Radicals from alpha-Azido *o*-Iodoanilides via 1,5-H Transfer Reactions of Aryl Radicals. New Transformation of alpha-Azido Acids to Decarboxylated Nitriles"** *The Journal of Organic Chemistry*, **2008**, *73*, 4721-4724.

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4) Lanza T., Minozzi M., Monesi A., Nanni D., Spagnolo P. and Chiappe C., **" Radical Additions of Thiols to Alkenes and Alkynes in Ionic Liquids"** *Current Organic Chemistry*, **2009**, *13*, 1726-1732.

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6) Lanza T., Leardini R., Minozzi M., Nanni D., Spagnolo P., Zanardi G., "**Improved Radical Approach to *N*-Unsubstituted Indol-2-one and Dihydro-2-quinolinone Compounds Bearing Spirocyclic Cyclohexanone/Cyclohexadienone Rings"** *Advanced Synthesis and Catalysis*, **2010**, Submitted.