Alma Mater Studiorum – Università di Bologna

Dipartimento di Chimica Organica "A. Mangini"

Dottorato di Ricerca in Scienze Chimiche

XX Ciclo

CHIM/06

Synthetic and Mechanistic Investigation of New Radical Processes: Reaction of Organic Azides with Group-XIII Lewis Acids

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Esame finale anno 2008

IF YOU WISH TO UNDERSTAND THE FRAGRANCE OF THE ROSE,
OR THE TENACITY OF THE OAK;
IF YOU ARE NOT SATISFIED UNTIL YOU KNOW THE SECRET PATHS
BY WHICH THE SUNSHINE AND THE AIR ACHIEVE THESE WONDERS;
IF YOU WISH TO SEE THE PATTERN WHICH UNDERLIES ONE LARGE FIELD OF
HUMAN EXPERIENCE AND HUMAN MEASUREMENT, THEN TAKE UP CHEMISTRY.

C. A. COULSON, 1973.

THE PRESUMED CORRELATION BETWEEN HIGH REACTIVITY
AND LOW SELECTIVITY THAT PREVENTED ORGANIC CHEMISTS
FROM USING RADICALS IN SYNTHESIS HAS TURNED OUT TO BE WRONG.

BERND GIESE

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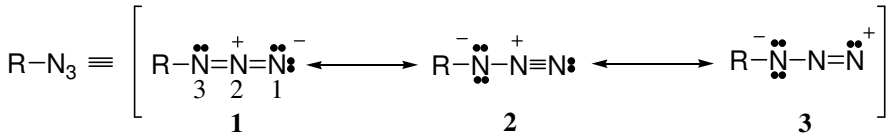
CHAPTER 1

Introduction

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, 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. Now 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

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.

The Huisgen reaction

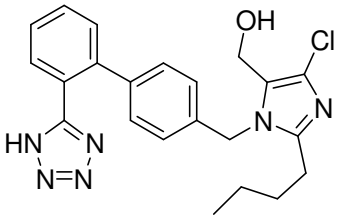
Many methods of synthesis of alkyl, aryl, and acyl azides have been reported[2c] but, for sake of brevity, in this introduction I will focus mainly on their reactivity, because this is the best way to understand the versatility and the importance of this functional group in organic chemistry.

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

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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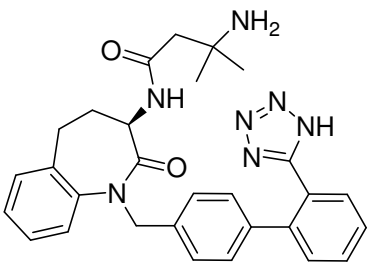

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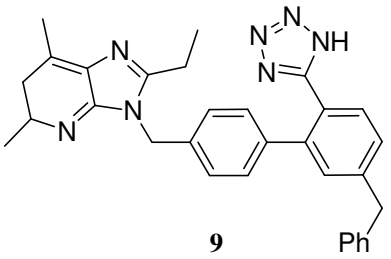

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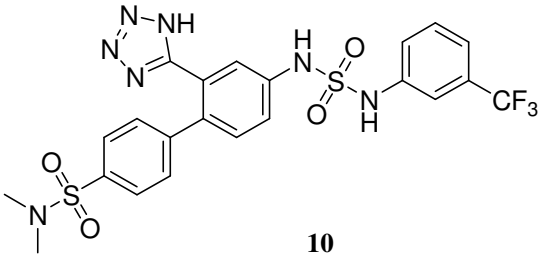

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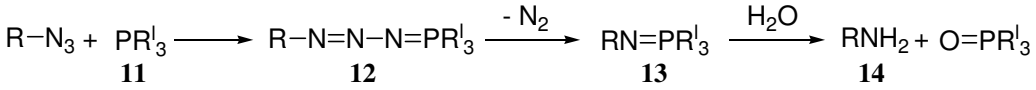
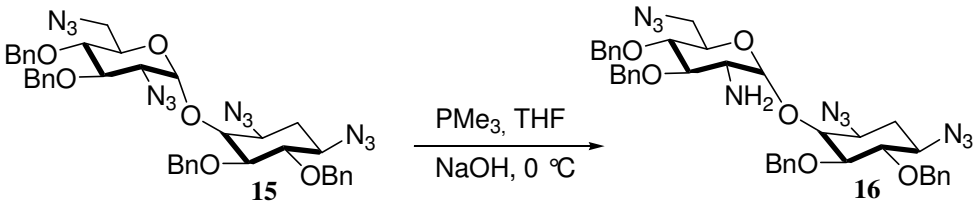
One of the most frequent applications of organoazides is the reaction with phosphorus nucleophiles. The Staudinger[14] reaction was developed as a procedure for the reduction of organoazides. This reaction involves the formation of a phosphazine intermediate (**12**) by nucleophilic attack of the phosphorous 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).



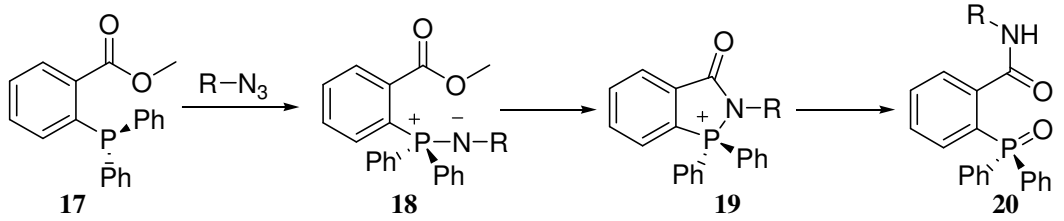
Scheme 3

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



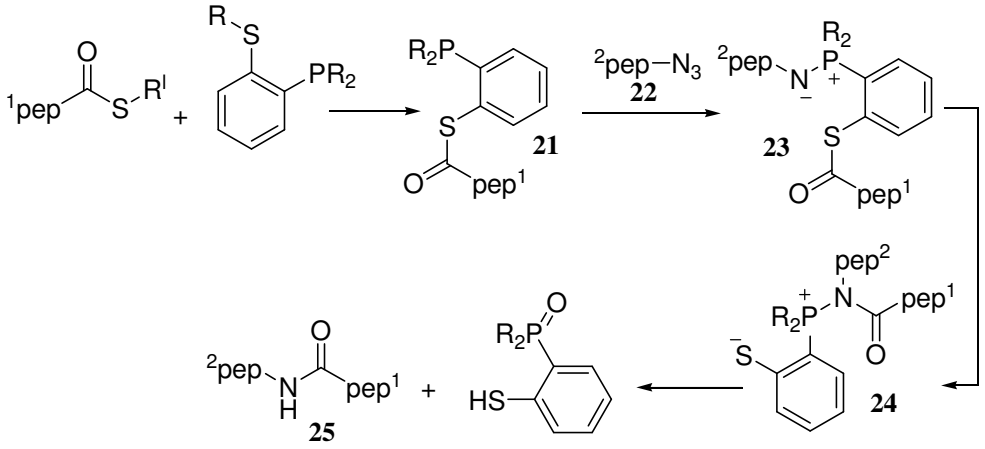
Scheme 4

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

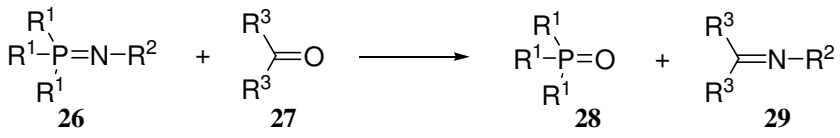
This reaction is compatible with a large number of functional groups and has hence found various uses in organic synthesis and biological chemistry. Staudinger ligation has been successfully used even on living organism such as a mouse.[24] This methodology was applied to peptide synthesis (**25**) by 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

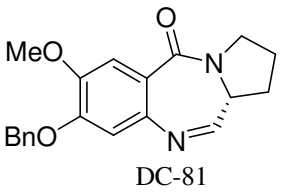
The intramolecular Staudinger ligation is a particularly efficient ring-closing reaction for the formation of medium-sized lactams that are difficult to prepare by other methods.[26]

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]



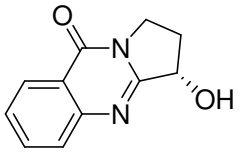
Scheme 7

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**).[26, 30]

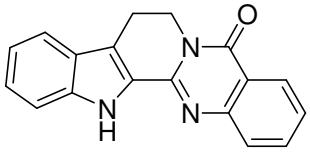


DC-81
30

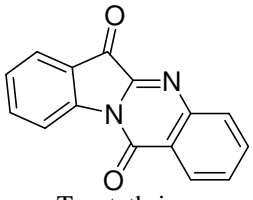
A series of natural products was synthesised by using a domino Staudinger-intramolecular Aza-Wittig reaction as the key step, (see, for example, vasicinon **31**,[31] rutecarpin **32**,[32] and tryptathrin **33**).[29]



Vasicinon
31



Rutecarpin
32

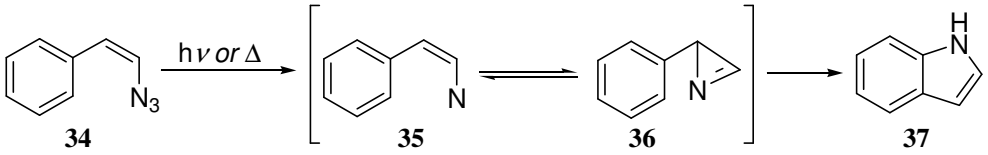


Tryptathrin
33

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.

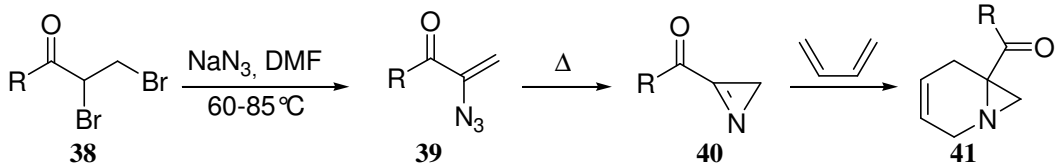
Cycloaddition, rearrangement, and insertion reactions are the main fields of nitrenes chemistry. The intermolecular cycloaddition of thermochemically or photolytically generated nitrenes to alkenes gives aziridines. This reaction is stereospecific and can be catalyzed by metal ions. In this context, 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).



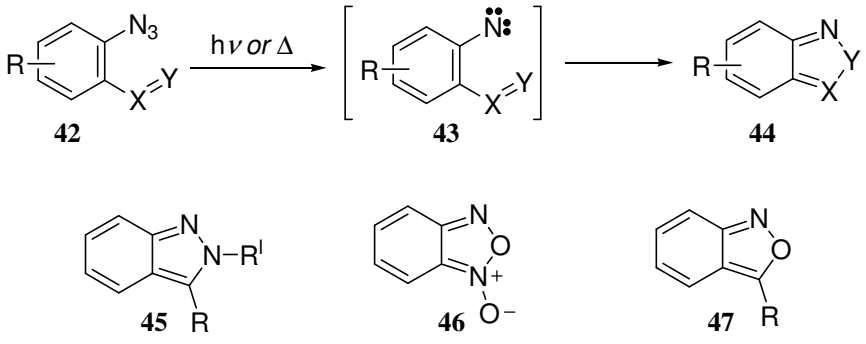
Scheme 8

Activated 2*H*-azirines 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

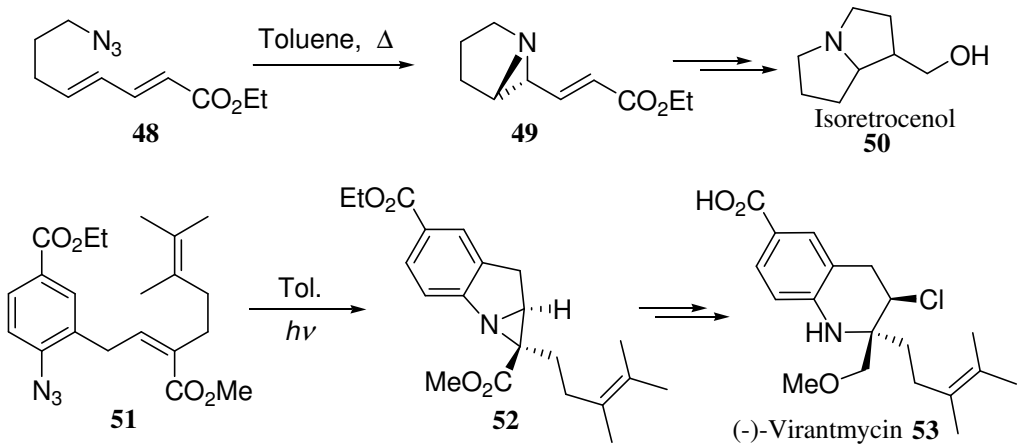
Aryl azides with a suitable double bond in the ortho position (**42**) decompose photochemically or thermally to form the corrisponding heterocycle by an electrocyclic mechanism.[37d, 38b] Indazoles,[38] benzofuroxanes,[39] benzisoxazoles,[40] interesting building blocks for other biologically active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



Scheme 10

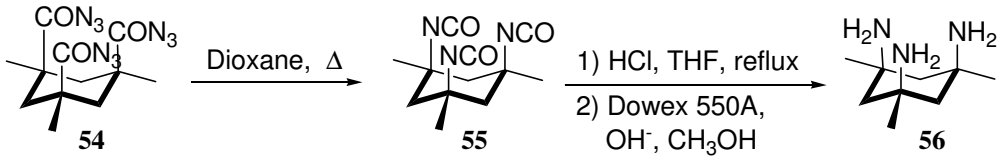
This method works very well also when the nitrene adds on simple carbon-carbon double bonds or alkene with electron-withdrawing groups, with formation of relatively strained bicyclic systems. In this cases, aziridines are key intermediates in the synthesis of two

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

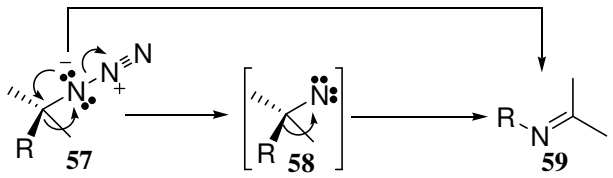
The rearrangement of acyl azides into isocyanates through the corresponding nitrenes is well known as the Curtius rearrangement.[44] This important reaction is the best way to converte acyl azides into amines and carbamates and it has been used to synthesize many complex natural products,[45] owing to 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

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]

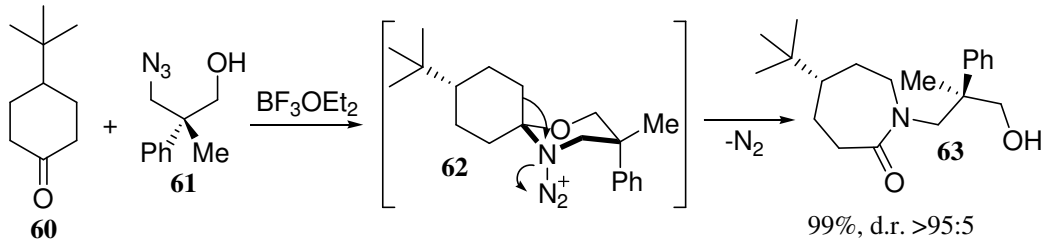
When alkyl azides are placed under pyrolysis or thermolysis conditions the reaction is called the Schmidt rearrangement.[48] It has not been established yet whether the reaction product (the imine) is obtained in a concerted fashion or through a two-step mechanism, i.e. nitrene formation followed by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



Scheme 13

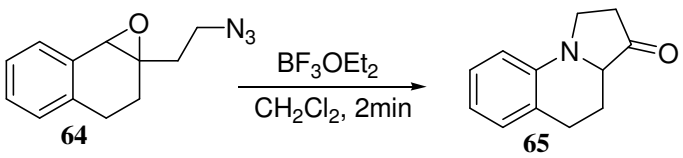
The Schmidt rearrangement has found interesting applications in the synthesis of natural products such as nicotine, starting from cyclobutyl azide,[49] in the rearrangement of azidocubanes,[50] in the synthesis of tetrazoles from fatty acids,[51] and in the total synthesis of stenine[52] and indolactam 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 are used with chiral azides, the reaction furnishes good yields in expanded lactams with high diastereoselectivity[55] (Scheme 14).



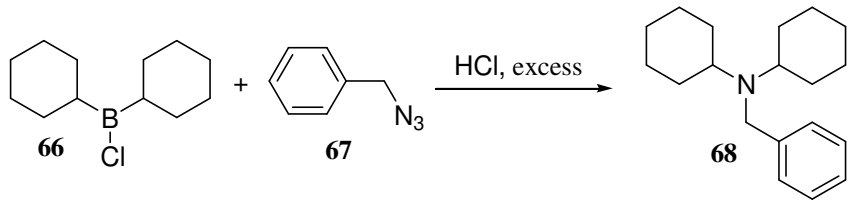
Scheme 14

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

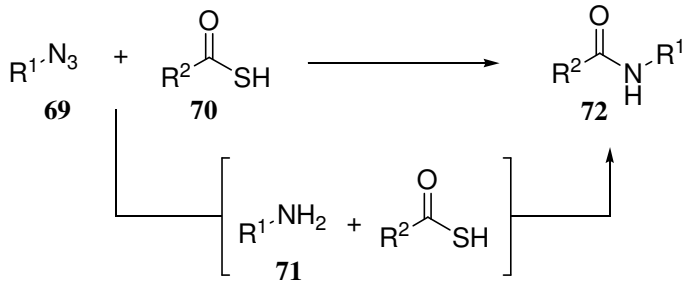
In the presence of strong acids, organic azides give aryl or alkyl nitrenium ions. These are extremely reactive species in intermolecular substitution and intramolecular cyclisation reactions involving aromatic groups.[57] Enantiomerically pure organoboron compounds can be usefully employed to easily obtain *alpha*-chiral amines.[58] The reaction between azides and halo-organoboron compounds 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 in high yields using strong acid conditions (Scheme 16)



Scheme 16

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]

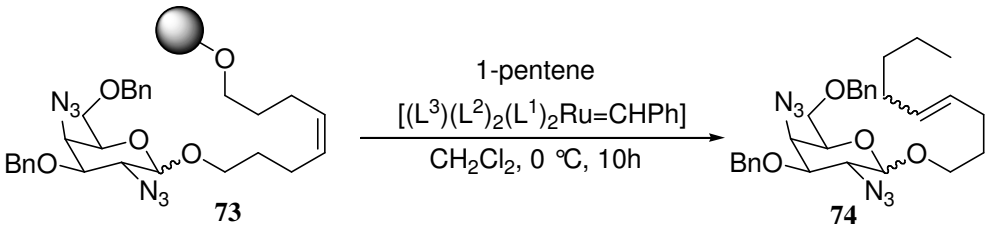
The direct conversion of organoazides into Boc-protected amines[67] and the mild transformation of thioacids (**69**) with azides which leads directly to amides[68] are attractive methods for peptides synthesis (**72**) (Scheme 17).



Scheme 17

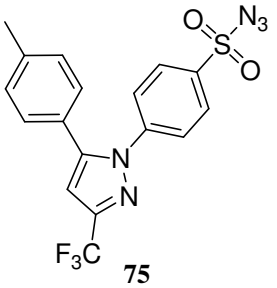
The azide function also provides a good possibility to protect coordinating primary amines, especially in sensitive substrates such as oligosaccharides, aminoglycoside antibiotics,[69] glycosoaminoglycans such as heparin,[70] and peptidonucleic acids.[71]

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



Scheme 18

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.[73]



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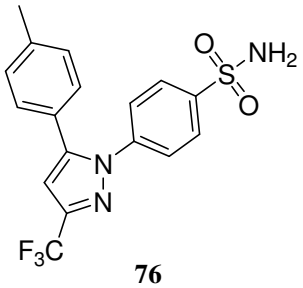

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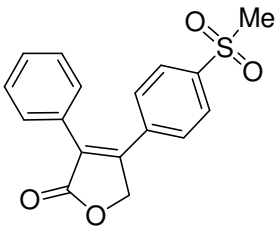

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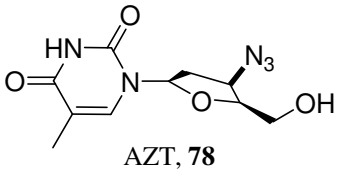
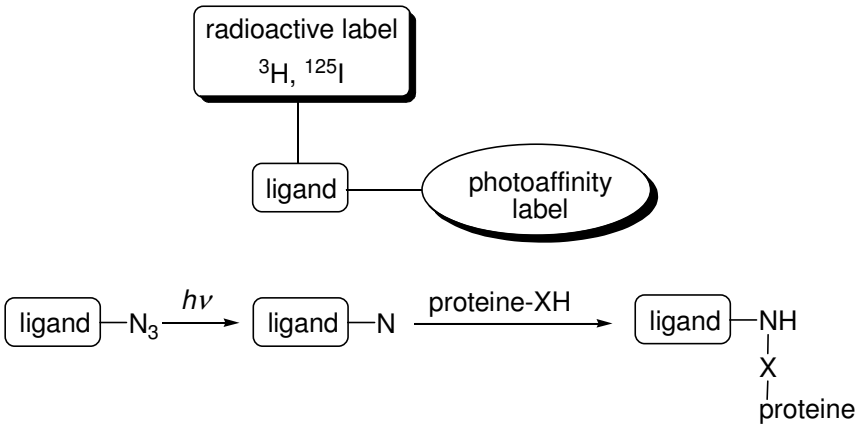
Comparison between a 1,1-dichloroethyl group (as in chloramphenicol) and the azidomethyl group has shown that they exhibit similar behaviour. A well known example of an important pharmacological application of the azido group is the anti-HIV medication AZT (**78**).[74]



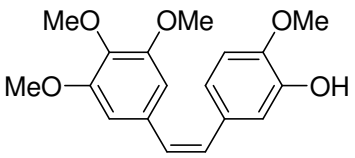
AZT, **78**

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).

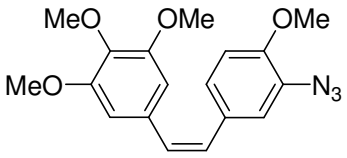


Scheme 19

This principle was used, for example, in the synthesis of combrestain analogues as molecular probes for tubulin polymerisation (Scheme 20).[76] It is worth noting that a growing number of applications in medicinal chemistry are continuosly appearing in the literature.[77]



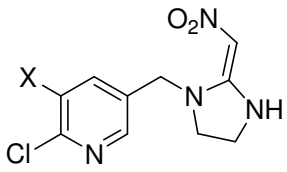
combrestatin A-4
79



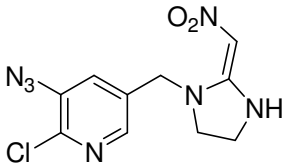
azide-analogous
combrestatin A-4
80

Scheme 20

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**).[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

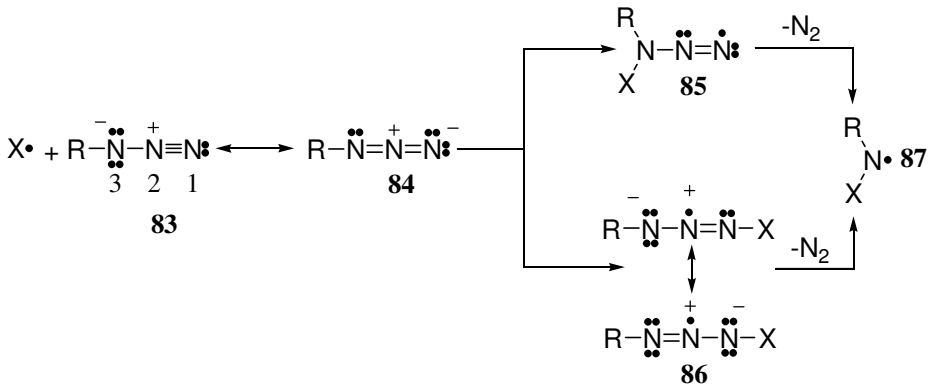


5-azidoimidacloprid
82

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]

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).



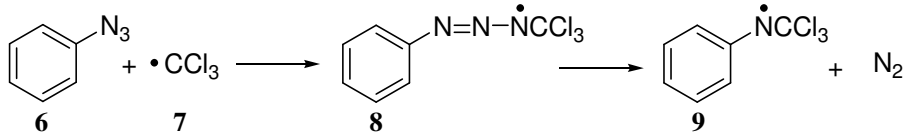
Scheme 21

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

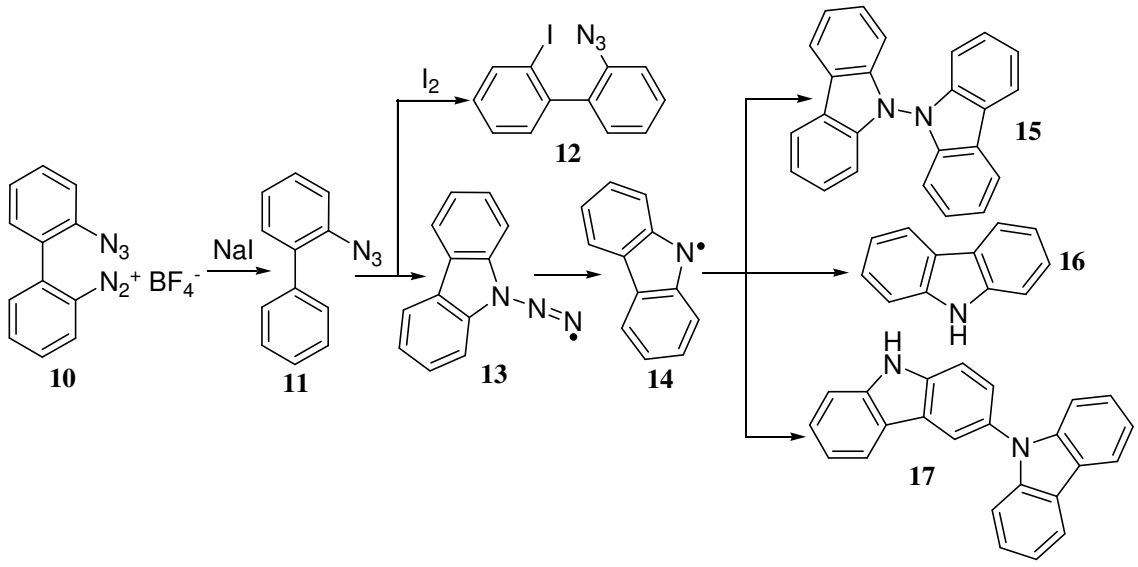
atom could settle as a bridge between N^3 and N^1 to form an intermediate containing a four-membered ring should also be taken into account.[91]

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 in carbon tetrachloride in the presence of benzoyl peroxide.[92] In this case, isolation of products derived from addition of the trichloromethyl radical (**89**) to the azido group was the incontrovertible evidence of radical decomposition of the azido group (Scheme 22).



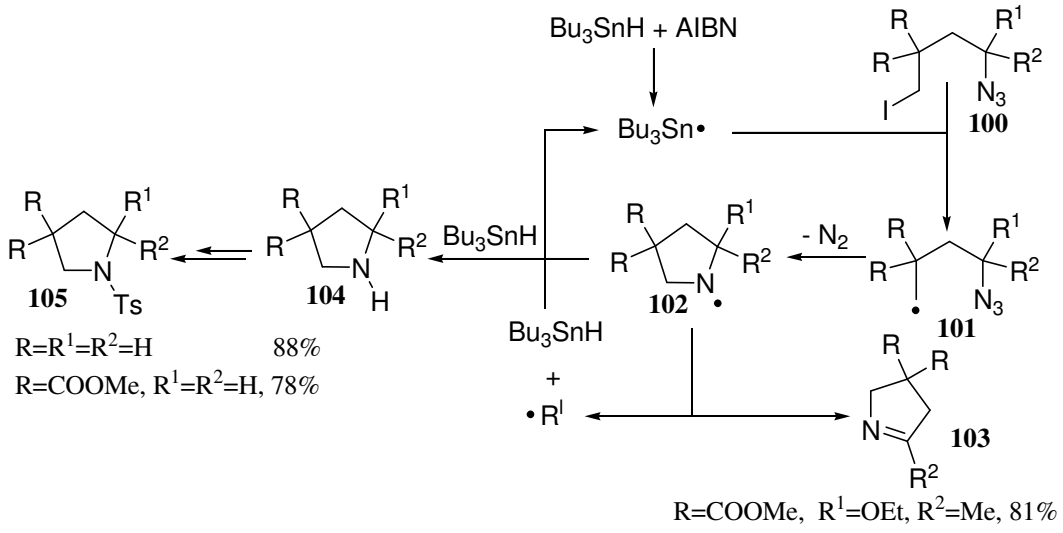
Scheme 22

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**) generated from 2-(2'-azido)biphenylyldiazonium tetrafluoroborate (**92**) by reaction with NaI in acetone, besides being partially trapped by iodine to give the corresponding iodide (**94**, 12%), added to the azido group to give *N,N*-dicarbazolyl (**97**, 23%), carbazole (**98**, 23%) and 3-(*N*-carbazolyl)carbazole (**99**, 17%) (Scheme 23). Compounds **97**, **98**, and **99** are clearly the results of generation of a cyclic aminyl radical (**96**), which can, respectively, dimerize, abstract a hydrogen atom, or be trapped by carbazole.



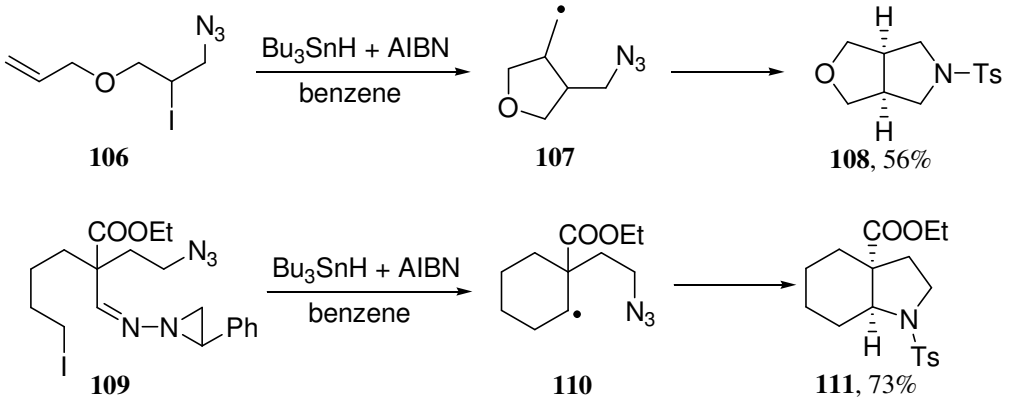
Scheme 23

It was not until the beginning of the nineties 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 pyrrolidines in high yields starting from easy available alkyl iodo azides. (Scheme 24)



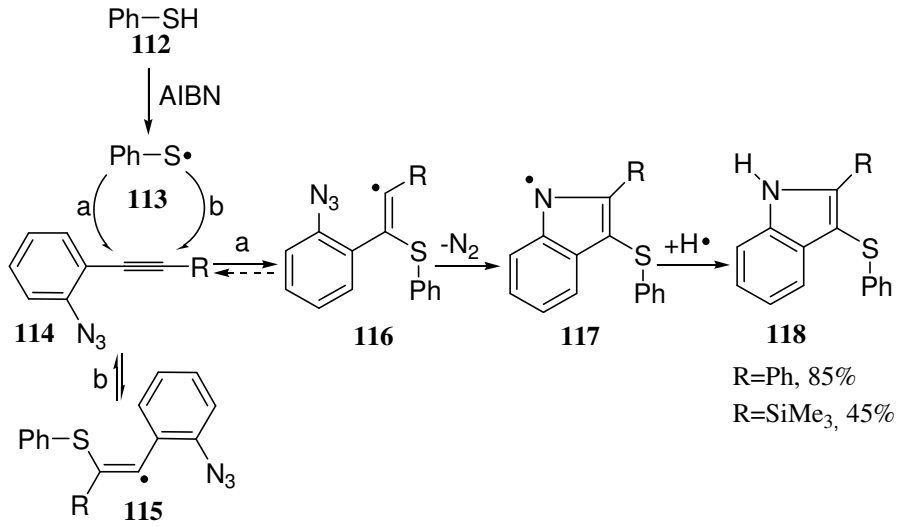
Scheme 24

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.



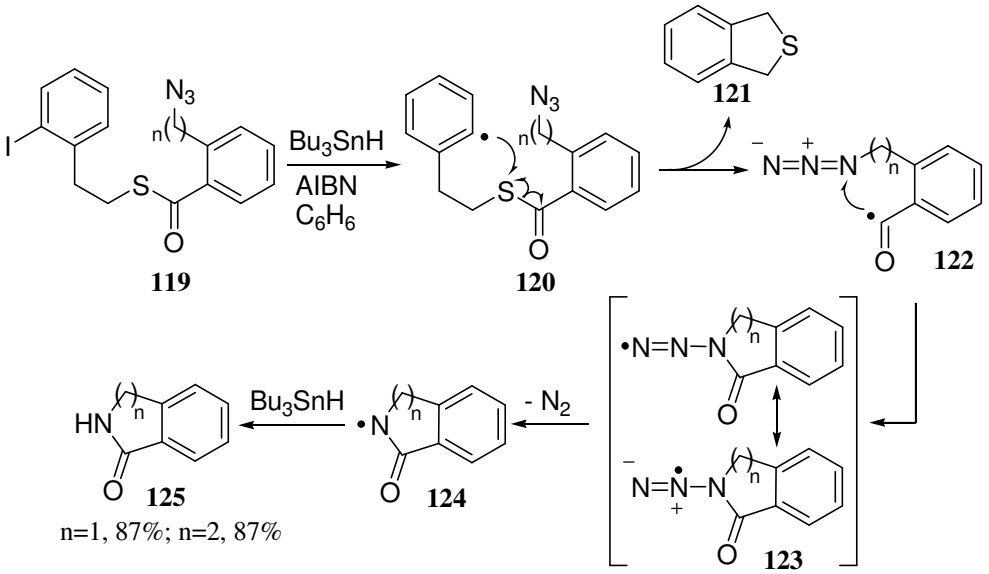
Scheme 25

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 to the alkyne moiety. Aromatic azidoacetylenes give the corresponding indole in high yield (Scheme 26).



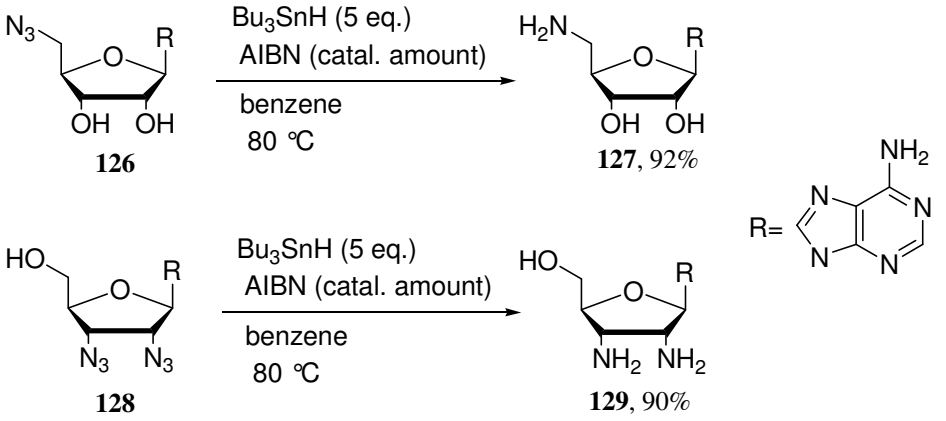
Scheme 26

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.



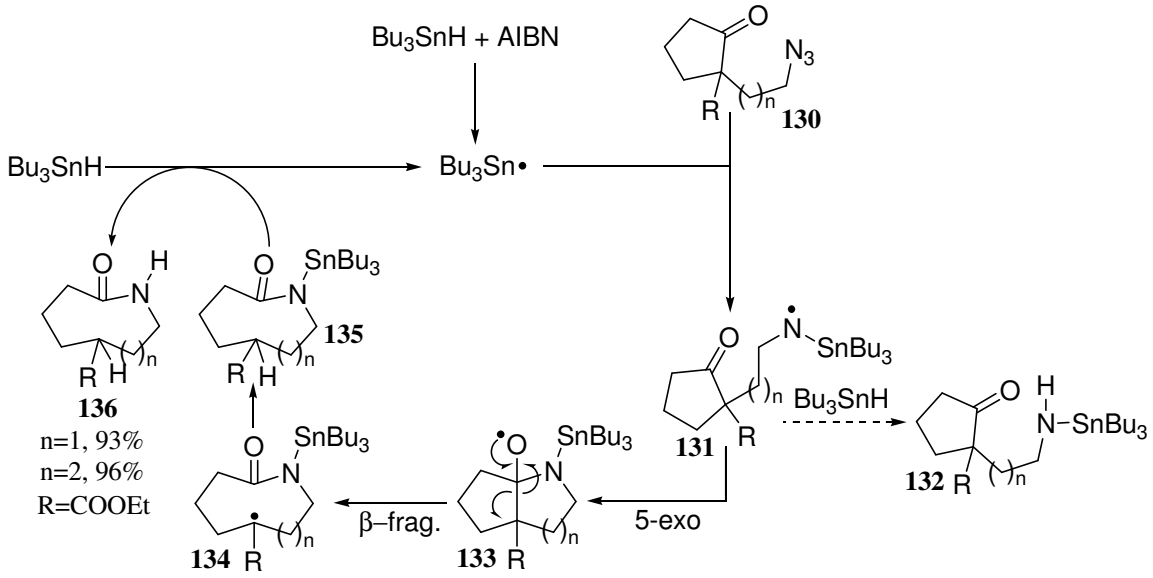
Scheme 27

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 furnished the corresponding amines 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 Raney nickel 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

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.

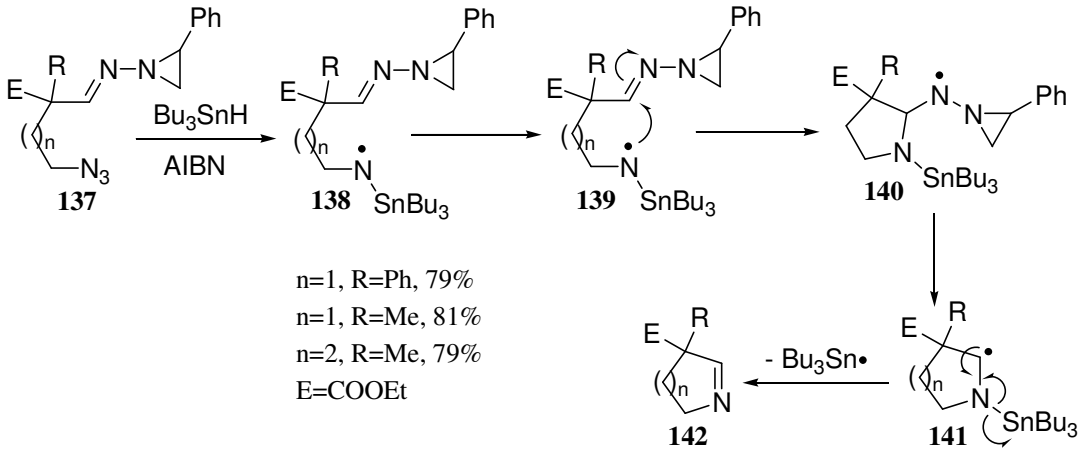


Scheme 29

The 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.

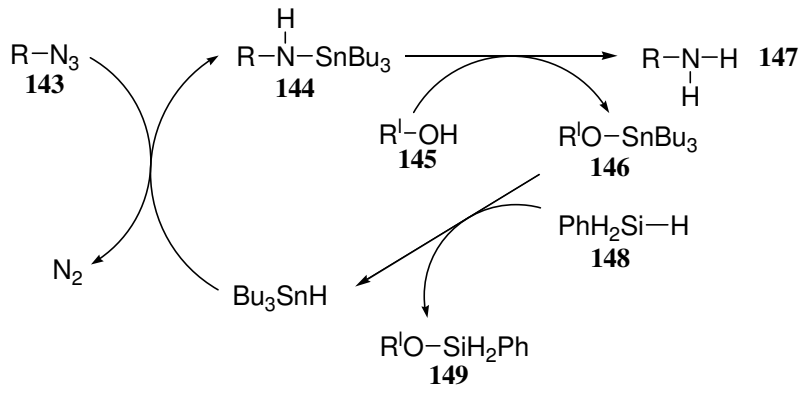
In another important paper, Kim described the radical cyclisation of stannylaminyl radicals onto the imino group.[83] The *N*-aziridinyl imino group was chosen as the radical

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.



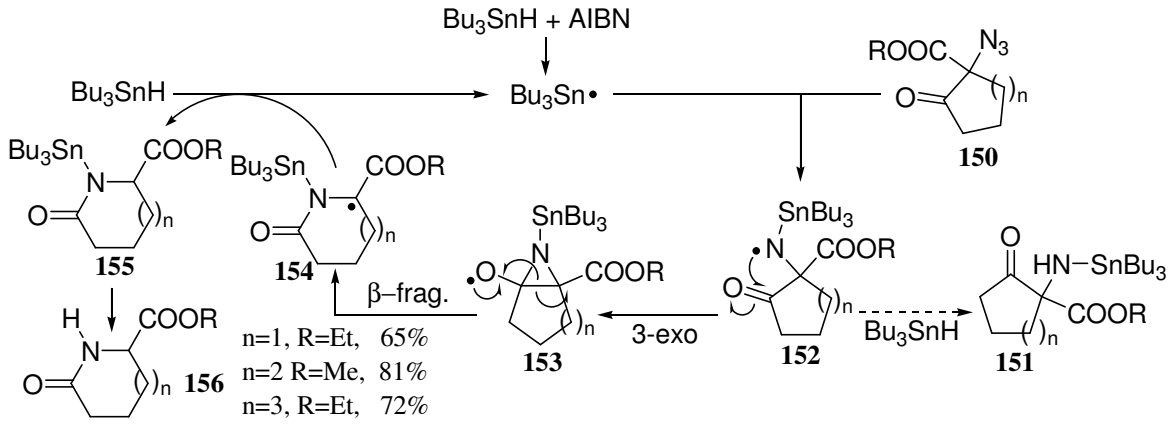
Scheme 30

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 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.



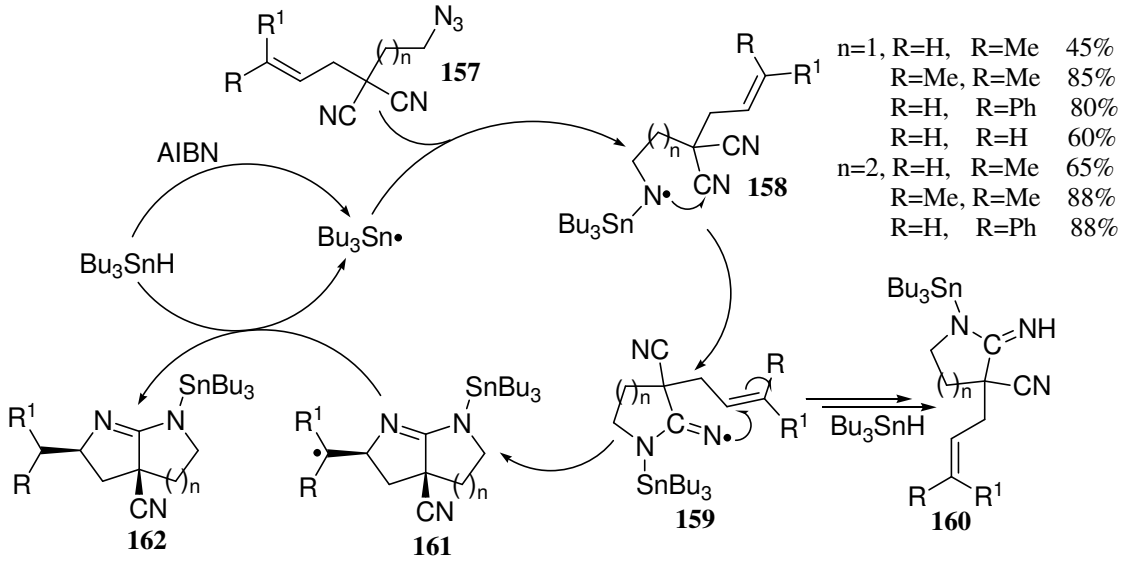
Scheme 31

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 (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

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 cyclisation 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

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.

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 bezenethiol 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.

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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 2

Introduction

I have shown so far how tin-free processes are related to the chemistry of group XIV elements of the periodic table, since, by the point of view of radical chemistry, there is a strong *chemical affinity* between tin and both silicon and germanium. Fortunately, this affinity does not involve all of their chemical properties, in that silicon and germanium are much less toxic than tin. However, the history of radical chemistry is not exclusive of group XIV elements: nitrogen-,[1] phosphorous-,[2] sulphur-,[3] and oxygen-[4] centred radicals have greatly shown their potentiality in free radical synthetic applications and many other different kinds of radicals can be exploited in useful processes.

As far as boron is concerned, in 1967 Davies and Roberts discovered that organoboranes can mediate and participate in free-radical processes.[5] Later on, in 1970, Brown[6] extended the radical properties of organoboron derivatives to organic reactions, establishing that the conjugate addition of trialkylborane to α,β-unsaturated carbonyl compounds is a radical reaction. The first examples of detection of boron centred radical by ESR spectroscopy were reported by Roberts[7] in 1983. The use of organoboranes as powerful radical mediators[8] has recently led to many novel, useful synthetic applications. On this basis, and following the spectacular development of radical chemistry in organic synthesis witnessed by the last decades, in the last 20 years the main group metals[9] have been investigated intensively in order to discover unknown radical reactivity.

Exploration inside the XIII group of the periodic system shows that examples of radical processes mediated by aluminium compounds are rare. The only noteworthy paper is the communication of Marek[10] who reported the successful iodine transfer cyclisation of iodo alkynylacetals mediated by DIBAL-H/THF via radical pathway. However, important limits to the applications of this reaction were also underlined by the author, for example the failure of six-membered alogen transfer cyclisations and the impossibility to use double instead of triple bonds.

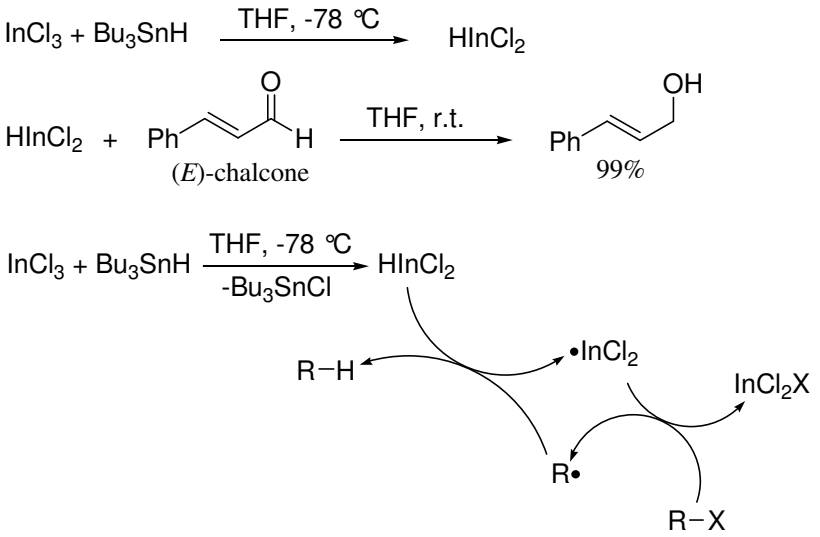
In order to find appealing, promising radical processes, attention must be paid to the chemistry of Indium(III) and Gallium(III) compounds.

Baba's discovery and applications

A new hydride on the radical way: $HInCl_2$.

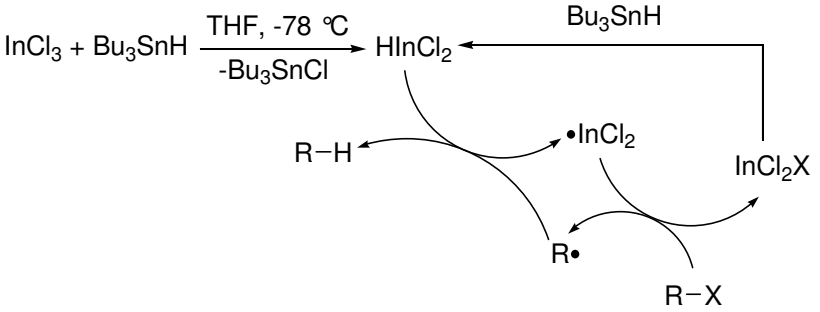
In 1998 Baba and co-workers synthesised for the first time a new and resourceful compound of indium(III). Following the well known transmetallation reactions of organotin reagents for the synthesis of reactive organometallic intermediates,[11] Baba reported the indium catalyzed allylation or alkynylation of carbonyl compounds via transmetallation between an indium trihalide and organotin compounds.[12] On this way he tried to prepare a new reagent suitable for practical and synthetical applications in organic chemistry and appropriate for reduction of carbonyl groups. Indeed, in 1998[13] he synthesised a novel monometallic hydride, dichloroindium hydride ($HInCl_2$) using a transmetallation reaction between indium trichloride ($InCl_3$) and tributyltin hydride (Bu_3SnH) at −78 °C in THF (eq. 1, Scheme 1). Low temperature was necessary to keep the hydride stable, but the most relevant role was played by THF, which was able to stabilize the hydride up to ambient temperature thanks to its coordinating properties toward to the metal centre. NMR and IR[14] characterisation confirmed a quite stability at room temperature of the novel hydride. The solvent was also fundamental to make the transmetallation complete: when the same reaction between Bu_3SnH and $InCl_3$ was performed in toluene it did not proceed at all.

The reactions resulted very efficient and, in some cases, interesting from a stereochemical point of view as well. This new reagent allowed for easy-to-make work-up procedures and efficient recover of the reaction products. In particular, Baba found that $HInCl_2$ was a mild, chemoselective reagent capable of predominantly reducing aromatic aldehydes to alcohols in the presence of other functional groups such as nitro, cyano, chlorine and esters. It was however noted that the chemistry of $HInCl_2$ was rather ambiguous because the it showed both ionic and radical characteristics. Indeed, while the reduction of alkyl and aryl aldehydes and ketones were well explained by an ionic mechanism, both the 1,4-regioselective reduction of (*E*)-chalcone[15] and the dehalogenation of alkyl bromide suggested a radical chain pathway mediated by the novel dichloroindyl radical (Scheme 1). The use of a radical scavenger like galvinoxyl, which affected in some cases the reactions, confirmed the hypothesis that dichloroindium hydride had apparently both radical and ionic characters.



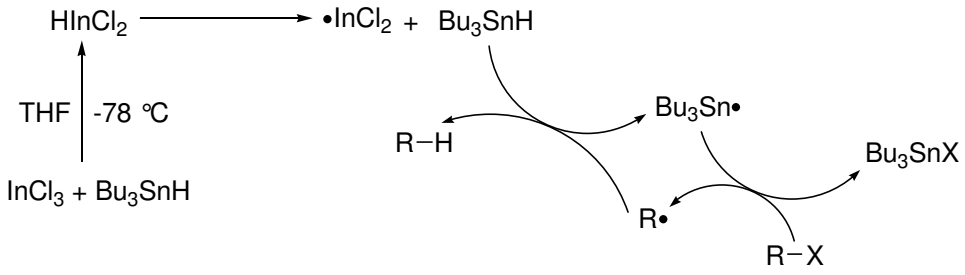
Scheme 1

Furthermore, no certain evidences could be obtained about the reaction mechanism, namely the intermediacy of dichloroindyl radicals, when the dehalogenation reaction was carried out under catalytic conditions. In this case only a small amount of $InCl_3$ (10% mol) was employed and stoichiometric Bu_3SnH was used as a source of indium hydride[16] (Scheme 2).



Scheme 2

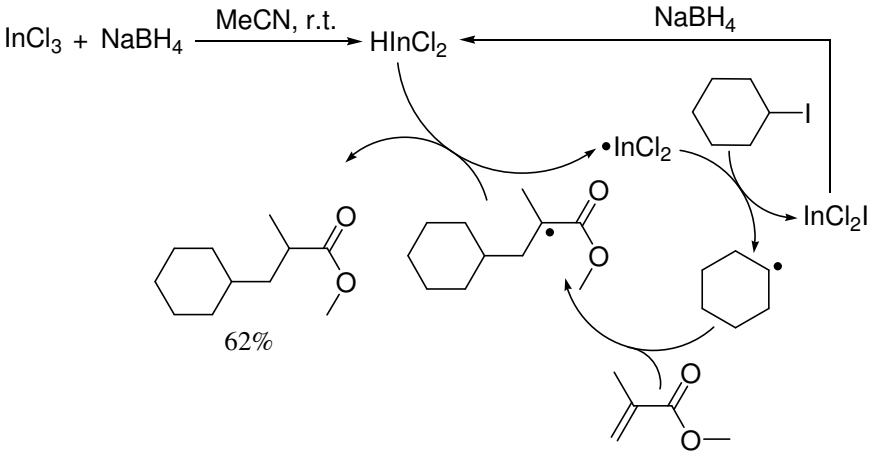
Although reductions gave successful results, the reaction mechanism could in fact entail direct halide reduction by Bu_3SnH, with $HInCl_2$ acting only as a radical initiator (Scheme 3).



Scheme 3

No tin, the right choice.

In order to avoid tin reagents, Baba developed a new process using sodium borohydride ($NaBH_4$) as a source of $HInCl_2$.[17] Sodium borohydride was the right choice also because it could not give radical reduction of alkyl/aryl halides, so that information about the real reaction mechanism were likely to be obtained. Indeed, the absence of $InCl_3$ completely suppressed the reaction, and so did the use of other different Lewis acids such as $AlCl_3$. Moreover, the employment of several plausible hydride sources such as CaH_2, LiH, and BH_3-THF in the presence of catalytic amount of $InCl_3$ gave no results. On the contrary, the system $NaBH_4/InCl_3$ proved to be the best alternative to Bu_3SnH. In particular, the catalytic performance of $InCl_3$ in the dehalogenation reaction was noteworthy. All the reactions were carried out at room temperature in MeCN by mixing $InCl_3$ and $NaBH_4$ and afforded reductive dehalogenation products as well as products from intramolecular 5-exo radical cyclisations and intermolecular couplings, all of them in good yields (Scheme 4).

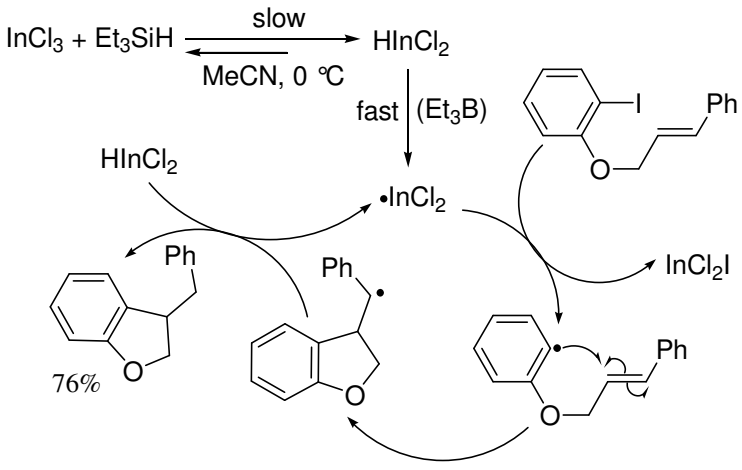


Scheme 4

From a mechanistic point of view, it is interesting to underline that the experimental value obtained for the rate constant for hydrogen abstraction from $HInCl_2$ by an aryl radical is quite similar to that reported for tributyltin hydride, indicating that the In-H bond dissociation energy is similar to that of the Sn-H bond of the tin hydride.[18, 13] It is also worth noting that, although the use of a radical scavenger confirmed the radical nature of this reagent, $HInCl_2$ is not like other classical radical reagents, since it did not need any classical radical initiator to generate dichloroindyl radicals: the latter are supposed to probably arise from spontaneous homolytic cleavage of the indium-hydrogen bond under the reaction conditions.[16]

The occurrence of side reactions was underlined by Baba when the $NaBH_4/InCl_3$ system was applied to the hydroindation of triple bonds to attain 5-exo cyclisation of the resulting vinyl radicals onto alkenes. The transmetallation process between $NaBH_4$ and $InCl_3$ generated BH_3, which gave undesired over-reduction of the triple bond, thus limiting the scope of the reaction. A new mild system was hence developed and Et_3SiH was employed as an alternative to $NaBH_4$.[19] Trialkylsilanes are stable liquids that are easy to handle[20] and have low toxicity. Furthermore, they possess low reactivity towards most functional groups.

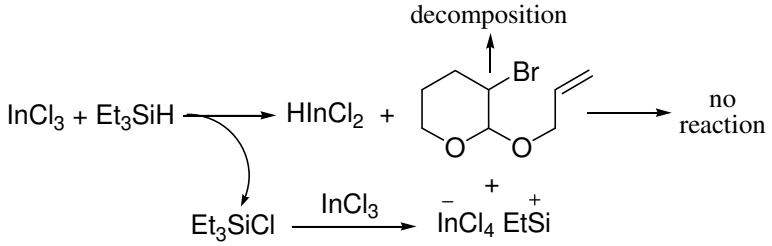
The efficacy of the transmetallation between Et_3SiH and $InCl_3$ in acetonitrile was proved by NMR experiments and the reaction efficiency was tested on radical dehalogenation reactions followed by 5-exo cyclisations of the resulting alkyl and aryl radicals, as well as hydroindation of alkynes and intermolecular radical addition reactions: all of these experiments gave successful results in or without the presence of triethylborane as a radical initiator. The $Et_3SiH/InCl_3$ system can however be used only under stochiometric conditions, due to the slow transmetallation reaction between Et_3SiH and $InCl_3$, which caused too a low concentration of dichloroindium hydride be present in the catalytic approach. The reactions were usually carried out with one equivalent of $InCl_3$ and excess Et_3SiH, mainly in the presence of Et_3B as a radical initiator: the last point is an important one, since acetonitrile has not a strong stabilizing effect on the hydride and the initiator speeds up the reaction at a sufficient rate as to avoid (or minimize) hydride decomposition (Scheme 5)



Scheme 5

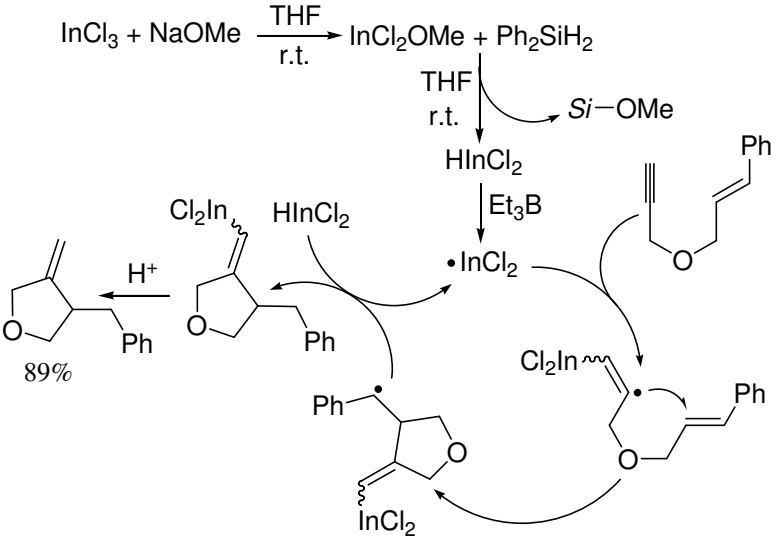
In the course of expanding the application to various substrates, some additional problems were encountered, especially when acid-sensitive compounds were tested. The co-product of the trasmetallation between $InCl_3$ and Et_3SiH is in fact Et_3SiCl. The side reaction between $InCl_3$ and Et_3SiCl, favoured by the slow transmetallation step, can result in the formation of a

strong Lewis acid[21] that may decompose substrates such as halo-acetals and alkynyl-ethers (Scheme 6).



Scheme 6

To overcome this serious problem Baba modified the hydride generation step, starting from an alkoxyindium compound generated in situ. The transmetallation reaction between Et_3SiH and this alkoxyindium would form an alkoxysilane as byproduct instead of Et_3SiCl, thus avoiding the strong acidic conditions involved with $InCl_3$. The reaction was carried out in THF and the first step consisted in the reaction between NaOMe and $InCl_3$ to prepare the indium alkoxyde. Then the silane and Et_3B were added. This new approach gave better results than the previous one with acid-sensitive substrates. In particular, some oxygen containing compounds furnished excellent yields in radical cyclisation products and the reactions could be also carried out in the presence of catalytic amounts of $InCl_3$. This low acid system was found to be applicable to many radical dehalogenation reactions already reported with the $Et_3SiH/InCl_3$ system, and very important results were also achieved in the radical intramolecular cyclisation of enynes, the first example of radical intramolecular addition of vinyl radicals onto alkenes (Scheme 7).



Scheme 7

Although yields are slightly lower in its absence, the presence of Et_3B is not fundamental anymore, because under these conditions the concentration of $HInCl_2$ is higher, due to a faster transmetallation step, and this allows for a good efficiency of the entire process.

Oshima's approach and applications

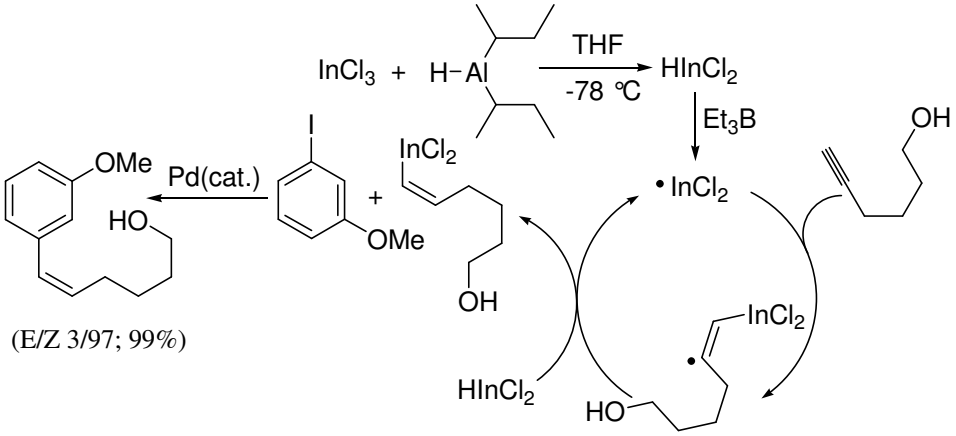
Radical synthesis of organoindium compounds.

If Baba disclosed the potentiality of dichloroindium hydride as a radical reagent, Oshima expanded the acquired knowledge to the useful synthesis of organoindium derivatives studying the radical hydroindation of alkynes.[22] The new alkenylindium species have been applied as valid cross-coupling reagents in the one-pot synthesis of (*Z*)-alkenes.

It is well known that the hydrometalation reaction usually furnishes (*E*)-alkenes. Hydroboration of alkynes always proceeds in a *syn* fashion to provide (*E*)-alkenylboranes. Preparation of a (*Z*)-alkenylborane reagent, starting from an alkyne, usually requires a multistep synthesis.[23] Moreover, protection of hydroxyl and carboxyl group is necessary in conducting hydroborations. Hydrostannylations[24] of alkynes is another efficient method to prepare vinylic metals. However, both Pd-catalyzed[25] and radical[26] hydrostannylations afford (*E*)-alkenylstannanes as a sole or major product, although the reactions are attractive in that the reagents are compatible with a variety of functional groups. Transition metal catalyzed hydrosilylation also yields mainly (*E*)-alkenylsilanes.[27] In conclusion, although during the last years hydrometalation reactions affording (*Z*)-alkenylmetals have been reported reported,[28] however operationally simple, mild procedures for tailored preparation of (*Z*)-alkenylmetal species from alkynes are still very limited.

The new approach proposed by Oshima focused around the stereoselective hydrometalation of alkynes achieved by addition of dichloroindyl radicals. To synthesize $HInCl_2$ Oshima started from $InCl_3$ and diisobutylaluminium hydride (DIBAL-H) as a novel hydride source. The transmetallation reaction was carried out in THF at −78 °C and furnished the same compound characterised by Baba.[29] Alkyne and Et_3B were then added to the indium hydride solution. A variety of alkynes were subjected to the hydroindation reaction, including those containing many interesting functionalities such as double bonds, hydroxyl, carbonyl, and carboxy groups, which did not interfere at all with the reaction outcome: the corresponding (*Z*)-alkenes were recovered quantitatively in all cases. The high selectivity for the *Z*-isomer was probably due to the low reactivity of dichloroindium radical toward the eventually formed (*Z*)-alkenylindium dichloride, thus preventing isomerisation of the (*Z*)-alkenylindium into its (*E*)-form via addition-elimination sequence.[30] The temperature played an important role to avoid isomerisation, and very different stereoselectivities were obtained when the same reaction was conducted at different temperatures.[31]

The alkenyl indium reagents were used in palladium/trifurylphosphine catalyzed coupling reactions: for instance, several iodoarenes were added to the THF solution of the indium alkenyl reagent, yielding, after 30 min at 66 °C, the corresponding (*Z*)-*β*-styrenes in high yields (Scheme 8).



Scheme 8

The radical mechanism of this reaction was confirmed by the addition of TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl), which completely inhibited the reaction. In any case, the absence of triethylborane did not inhibit the reaction at all and the reduction took place with only a slight lowering in yields. This confirmed Baba's assumption that the hydrogen-indium bond of $HInCl_2$ can undergo spontaneous homolytic scission to give indium-centred radicals.

Radical cyclisation of halo-acetals and haloaryl ethers.

Oshima applied the $InCl_3$/DIBAL-H system to radical cyclisation of halo-acetals and haloaryl ethers,[32] performing the reaction with stoichiometric amounts of $InCl_3$. The reactions proceeded smoothly at room temperature and afforded the desired products in only 30 minutes, outlining the high reactivity of $HInCl_2$. Et_3B was again not necessary to initiate the reaction, although it was strictly necessary to obtain complete conversion of the starting materials. It is worth noting that the yields obtained by Oshima are better than those of the analogous reactions outlined by Baba. The reason of this difference could be found in a different stabilisation of $HInCl_2$. Oshima in fact proposed the possibility of complexation between the indium hydride and the aluminium chloride derived from transmetallation: this new complex could be stable enough to make the indyl radical quite long-living to perform better in the cyclisation reactions. The $InCl_3$/Ph_2SiH_2 system used by Baba probably did not

bring any further stybilisation of the dichloroindium species by the transmetallation co-product. This could cause the indium radical to be not very stable, thus undergoing side reactions giving less performing reactions. The new method of Oshima did not give any problems of decomposition with both iodides and bromides and it proved to be extremely effective also for the reduction of bromoalky esters and ketones, showing the high chemoselectivity of the hydride toward sensitive, reducible functional groups.

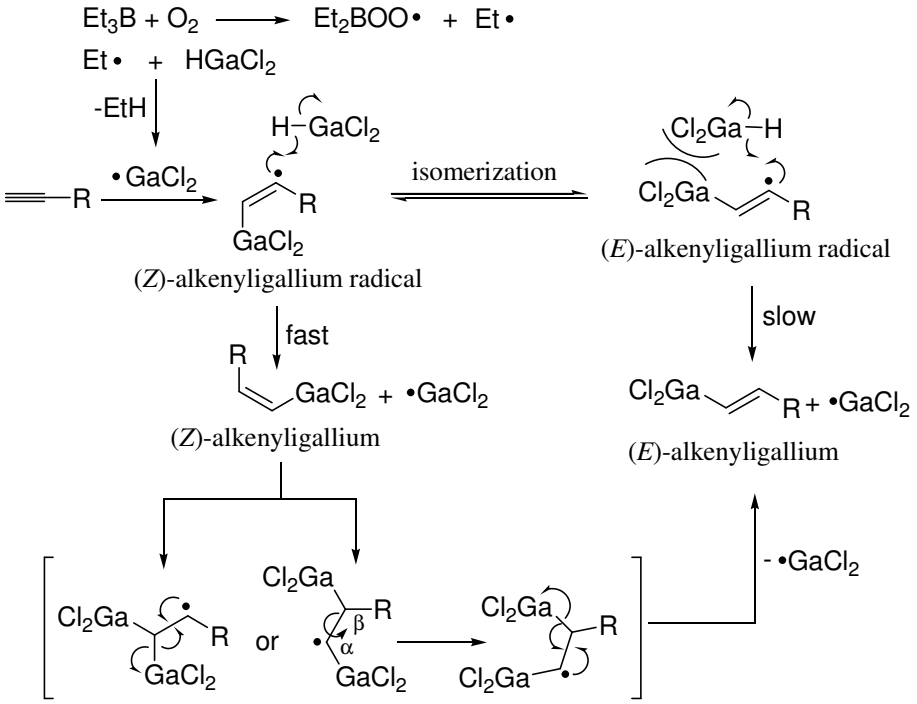
The method was also tested with catalytic amounts of $InCl_3$ in order to reduce costs. These reactions were carried out following two different strategies. The first one involved monochloro indane H_2InCl and indane H_3In, prepared by mixing $InCl_3$ with, resepctively, 2.0 and 3.0 equivalents of DIBAL-H: unfortunately, these hydrides could not endure the reaction conditions and decomposed immediately. The second strategy entailed dropwise addition of an hexane solution of DIBAL-H into a mixture of $InCl_3$, the substrate and Et_3B: in this case good results were obtained both with halo acetals and aryl halides, although yields were poorer than those of the reactions carried out with stoichiometric amounts.

Radical synthesis of organogallium compounds.

Analogously to what obtained with organoindium compounds, Oshima also developed a novel radical reaction of dichlorogallium hydride ($HGaCl_2$) for the synthesis of organogallium congeners.[33] In this case DIBAL-H and Red-Al (sodiumbis(2-methoxyethoxy)aluminium hydride) were employed to generate the hydride. The latter gave better selectivity (*E/Z* = 80/20) with respect to the former (*E/Z* = 77/23). In the absence of Et_3B the reaction did not proceed and the presence of TEMPO as a radical scavenger completely inhibited the process. These two evidences pointed out the radical nature of the reaction mechanism. Various alkynylethers and alkynylesters were employed by Oshima for the hydrogallation reactions: noteworthy, all of these functional groups did not interfere with the Et_3B induced reaction, whereas hydroaluminations often require the absence of such coordinating groups.

As pointed out before, the stereochemistry of the hydrogallation reaction is predominantly in favour of the (*E*)-isomer, but the selectivity is not as high as in the analogous reactions performed with $HInCl_2$. The stereochemical outcome strongly depended on the reaction time. Quenching the reaction of 1-dodecyne with $HGaCl_2$ after 2.5 hours provided a 55% yield as a mixture of *E*- and *Z*-isomers in a 28/72 ratio; after 3.0 hours the ratio changed to 56/44 (61% yield); the final ratio obtained after 4 hours was 80/20 (84% yield). The change of the ratio suggested that the reaction initially provided (*Z*)-alkenylgallium, which then isomerised to its

(*E*)-isomer. A plausible mechanism is described in Scheme 9. A dichlorogallium radical, generated by hydrogen abstraction from $HGaCl_2$, adds to the 1-alkyne to afford an alkenylgallium radical as an equilibrium mixture of (*Z*)- and (*E*)-isomers. Hydrogen donation to the (*Z*)-alkenylgallium is kinetically preferred with respect to that to the (*E*)-isomer because the (*Z*)-radical is more accessible for reduction by $HGaCl_2$: the (*Z*)-alkenylgallium intermediate is therefore the major product at the initial stage of the reaction. Isomerisation into the more thermodynamically stable (*E*)-alkenylgallium compound proceeds via gallium radical addition-elimination sequence involving rotation around the C_α-C_β bond of the two possible dimetallic radical species formed in the event.



Scheme 9

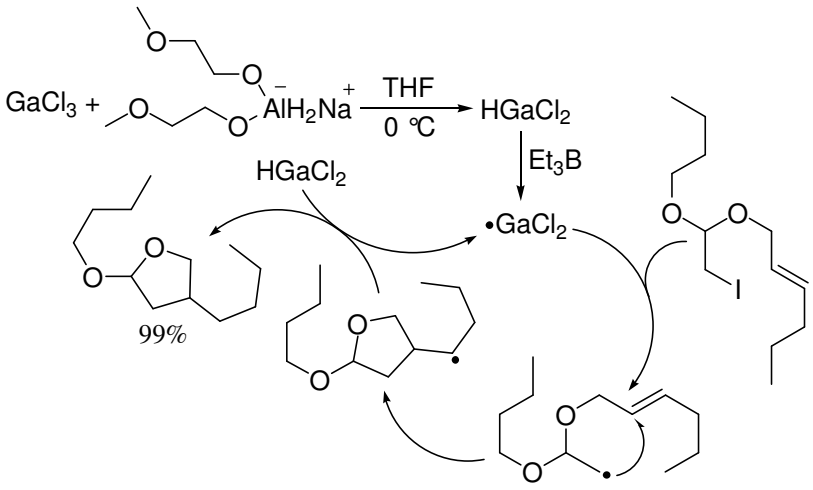
The new alkenylgalliums compounds have been utilised as key intermediates for cross-cupling reactions with aryl iodides. However, yields and selectivities are not as interesting as those observed with the indium congeners.

Interestingly, Oshima showed that dichlorogallium hydride could add easily to terminal alkenes furnishing the corresponding alkylgallium compounds: unfortunately, the use of a strong excess of methyllithium and the subsequent exposure to concentrated hydrochloridric acid made this application unsuitable for many functional groups, thus limiting its use.

A new valid alternative to tin alternative: radical cyclisation mediated by $HGaCl_2$.

Oshima furhter extended the application of dichlorogallium hydride to the generation of carbon centred radicals in 5-exo cyclisation reactions of halo acetals onto double bonds.[34] The reaction, carried out in tetrahydrofuran, was previously tested on simple reduction of halogen derivatives and gave successful results: alkyl iodides and bromides were reduced to the corresponding hydrocarbons in excellent yields, although the reactions sometimes needed a stoichiometric amount of Et_3B as an initiator. When the $HGaCl_2$ was used with halo-acetals, 5-exo reductive cyclisations proceeded smoothly with excellent yields (Scheme 10). Iodo acetals underwent radical cyclisation with 0.2 equivalents of Et_3B, while bromo acetals required a stoichiometric amount of initiator.

The reaction of $HGaCl_2$ with halo-acetals is particularly representative of the efficiency of this tin-free procedure: analogous reactions carried out under the same conditions but with Bu_3SnH furnished the desired products in moderate yields only.



Scheme 10

If a catalytic amount of $GaCl_3$ was used the yields were poorer, due to difficulties in keeping the reaction conditions under control: a too high concentration of Red-Al can in fact bring about over-reduction of gallium trichloride producing the unstable compound GaH_3, whose decomposition causes the reaction to stop before complete conversion of the starting material. On the other hand, if Red-Al addition is too slow, over reduction is avoided, but the concentration of dichlorogallium hydride cannot reach adequate values to allow the reaction

to go to completion. However, when the Red-Al addition is optimised excellent yields can be reached even under $GaCl_3$ catalytic conditions.

Allyl transfer reactions: allylgallium and allylindium reagents for radical C-C bond formation.

After the above described studies on the reactivity of gallium and indium hydrides, Oshima dedicated his attention to radical reactions mediated by organogallium and organoindium compounds,[35] focussing his interest mainly on radical allylation, vinylations, alkynylation and phenylation of α-halo carbonyl compounds.

Radical allylation reactions with allylstannanes represent an efficient method to introduce allyl groups into organic molecules.[36] However, like other tin-based radical processes, these are not suitable procedures for the synthesis of biologically and pharmaceutically interesting compounds, and allylating tin-free reagents should be very welcome in those applications. Indeed, allylsilanes[37] and allylsulfones[38] have been shown to be efficient alternatives to allyltin compounds, although the reaction conditions required by these reagents are usually not mild and nowadays more versatile methodologies are often required.

Oshima demonstrated that allylgallium and allylindium reagents are a powerful tool for radical allyl transfer reactions. The synthesis of the reagents was quantitatively accomplished by treatment of $GaCl_3$ and $InCl_3$ with an allylmagnesium chloride solution. Once the organometallic compound was formed, Et_3B and the halo esters were added; after extractive workup the reaction furnished the desired products in moderate yields. The radical mechanism was proved by usual experiments: the absence of triethylborane inhibited the reaction, as did the presence of a radical scavenger. The yields were improved when water was added to the reaction mixture. Although both organogallium and organoindium compounds are moisture sensitive, they showed a great stability in the presence of water.[39] The origin of this favourable solvent effect could be due to the highly polar nature of water,[40] which can cause aggregation of the hydrophobic organic molecules, thus entropically enhancing the radical addition step. Moreover, water molecules could activate the iodo ester and the corresponding radical through hydrogen-bonding with the carbonyl group. It is also probable that the structure of the allylgallium-allylindium species might change in the presence of water, giving rise to novel structures with greater reactivities. The effect of water is however very important, since it allowed the use of non-anhydrous solvents and reagents. Indium trichloride tetrahydrate can be utilised instead of anhydrous $InCl_3$ without any changes in reactivity,

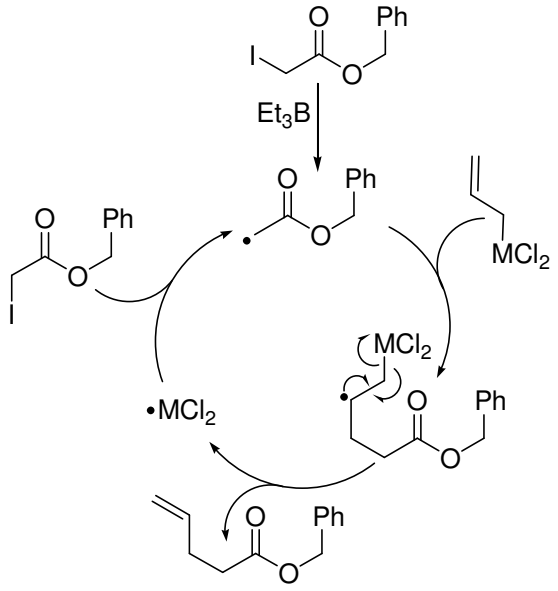
since the transmetallation step to prepare an allylindium reagent is faster than the reaction of the allyl Grignard reagent with the hydration water.

The mechanism proposed for the radical allylation is not clear yet. Two possible pathways could be envisaged:

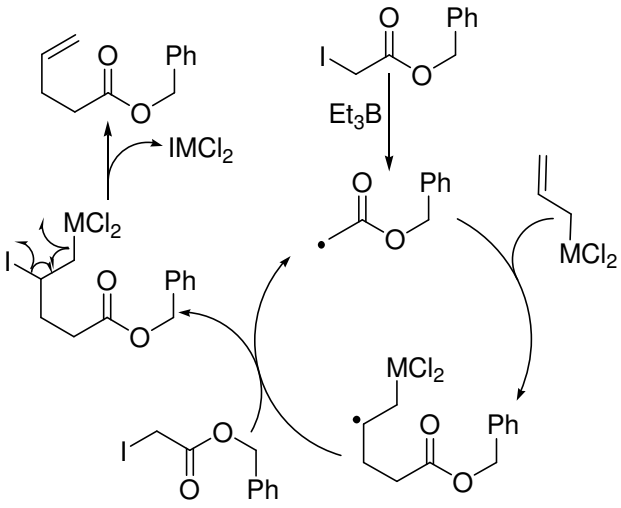
path A (Scheme 11) would involve elimination of a divalent metal radical from the β-dichlorometal-susbtituted alkyl radical intermediate;

path B (Scheme 12) would entail halogen atom abstraction from the starting α-halo carbonyl compound by the β-dichlorometal-susbtituted alkyl radical, followed by elimination of metal trihalide.

Both pathways would be compatible with a radical chain mechanism, but no evidences supporting either routes have been obtained so far.

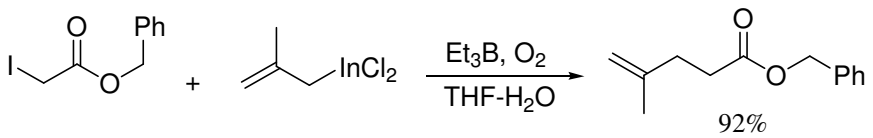


Scheme 11, path A



Scheme 12, path B

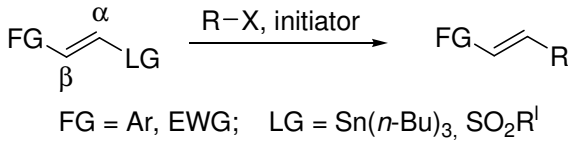
Various combinations of α-halo carbonyl compounds and allylic organometallic reagents were examined. Crotylindium and crotylgallium compounds gave particularly interesting yields, always with water as a co-solvent. Oddly, it is worth pointing out that methallylindium dichloride reacted efficiently with halo esters yielding the corresponding methallylated esters in quantitative yields (Scheme 13); on the contrary, the analogous methallylgallium compound was not able to furnish any methallylated products.



Scheme 13

Radical vinylation of halo carbonyl compound.

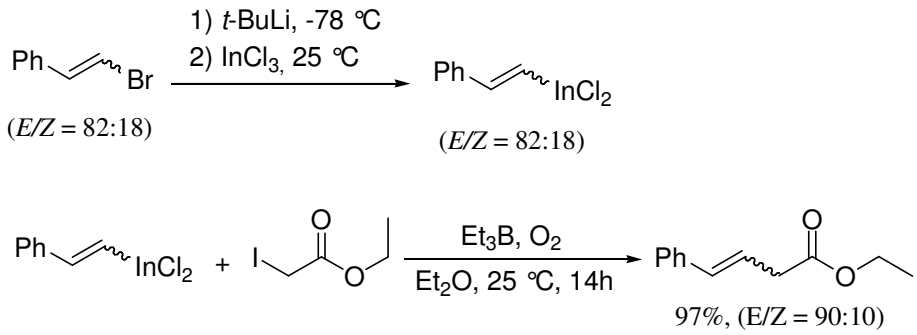
Radical vinylation of halo carbonyl compounds with vinylindium reagents represents now a valid alternative to previously reported methods,[41] which needed vigorous reaction conditions and required activation of the carbon-carbon double bond by means of electron-withdrawing moieties or aryl groups at the alkenyl β-carbon to provide successful results (Scheme 14).



FG = Ar, EWG; LG = Sn(*n*-Bu)$_3$, SO_2R^I

Scheme 14

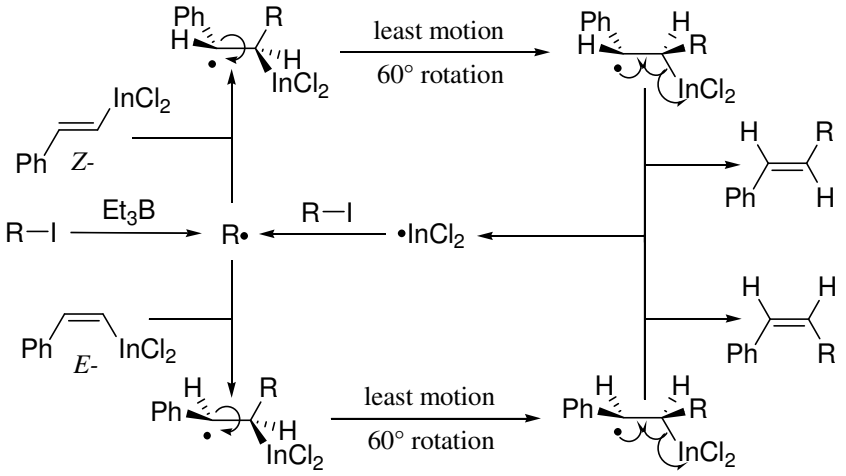
The (*E*)-vinylindium dichloride was prepared in situ by transmetallation of indium trichloride with (*E*)-enriched *β*-styryllithium (*E/Z* = 82:18) in diethyl ether. Treatment of several halo esters, ketones, and amides with an excess of vinylindium and Et_3B at room temperature afforded the alkenylation products in high yields with high (*E*)-selectivity. Triethylborane was necessary to activate the reaction. Different indium halides were tested but $InCl_3$ gave the best results (Scheme 15).



Scheme 15

When the reaction was carried out with (*Z*)-enriched styrylindium dichloride, the thermodynamically disfavoured (*Z*)-alkenylated product was mainly obtained. The same retention of configuration was observed during the reaction of unactivated alkenylindium compounds with ethyl iodoacetate: (*Z*)-alkenylindium, prepared from the corresponding iodide, afforded the alkenylated esters predominantly as the (*Z*)-isomer, whereas the reaction of (*E*)-alkenylindium dichloride afforded the (*E*)-alkenylated esters. The retention of

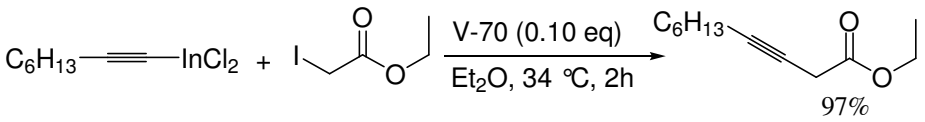
configuration could be explained quite well in terms of ease of the radical elimination step: the dichloroindium radical can be eliminated fast enough to proceed via a least motion process before any large rotations could take place (Scheme 16).



Scheme 16

Radical alkynylation and phenylation of α-iodo esters.

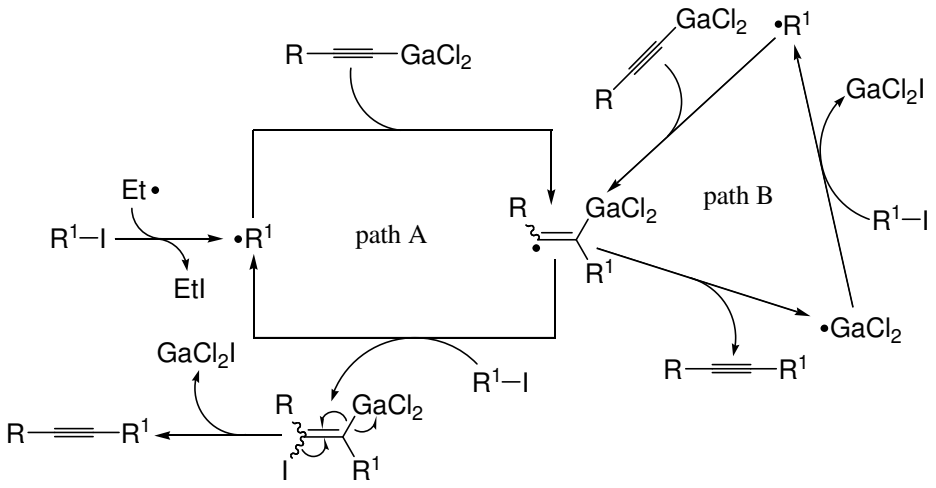
Further applications of organoindium- and organogallium-mediated radical reactions are well represented by alkynylation and phenylation of α-iodo esters. Alkynylindium[42] and alkynylgallium[43] dichloride were obtained by addition of an ethereal solution of a suitable lithium alkyl-(or aryl-)acetylide to a MCl_3 solution. Then a catalytic amount of radical initiator and the α-halo ester were sequentially added. The resulting mixture was stirred for 2 hours at reflux and then extractive workup gave the alkynylated ester in high yield (Scheme 17).



Scheme 17

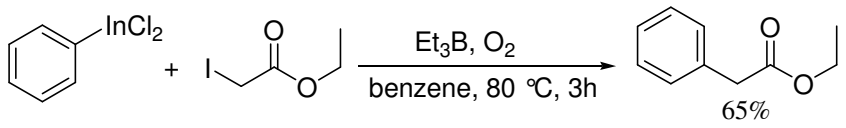
The mechanism of the radical alkynylation of α-halo esters could be explained again in terms of two possible pathways. As depicted in Scheme 18, after the iodine atom transfer process, the vinyl radical intermediate can follow two different routes: it could react with another iodo-ester molecule furnishing gallium trihalide, the desired product, and a new alkyl radical (path A), or, alternatively, it could afford the coupling product by direct elimination of

gallium dichloride radical, which in turn would act as an efficient chain carrier by abstracting a halogen atom from the substrate α-halo ester (path B).



Scheme 18

Phenylation via radical chain processes is quite a challenging task. Taking advantage from the high reactivity of organoindium reagents, an intermolecular radical phenylation reaction was successfully accomplished by treatment of ethyl iodoacetate with phenylindium dichloride in the presence of Et_3B in refluxing benzene (Scheme 19).



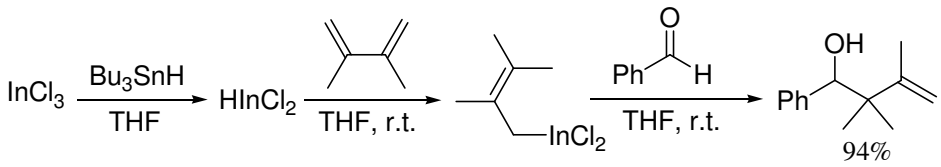
Scheme 19

Baba's challenge

Radical hydroindation and reaction with carbonyl compounds.

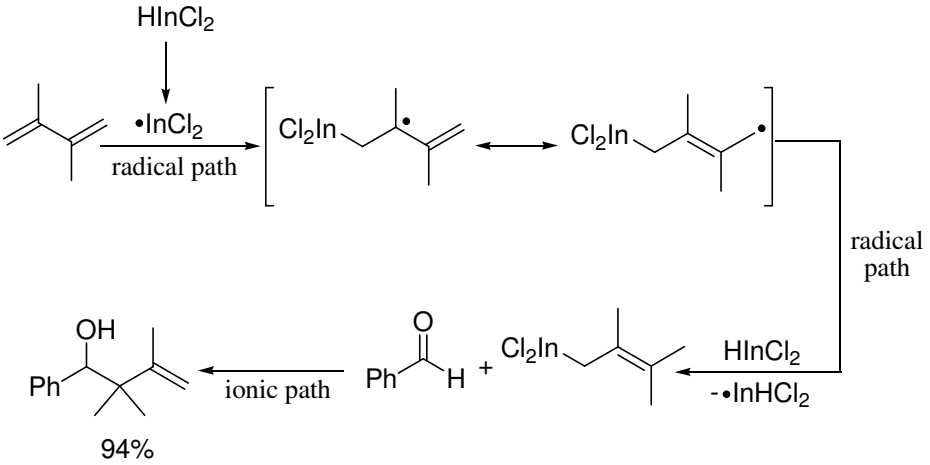
The generation of multisubstituted active allylic metals which can lead to tertiary or quaternary carbon centres by reactions with carbon electrophiles is an important tool in modern organic synthesis.[44] Quite recently, Baba directed his attention to this subject studying the radical generation of allylic indium(III) species and the subsequent one-pot allylation of aldehydes, ketones, and imines to produce tertiary and quaternary carbon centres.[45] Namely, he presented for the first time the synthesis of a novel multisubstituted allylindium dichloride reagent by an unusual hydroindation of 1,3-dienes. The whole process is divided into three

sequential steps: 1) transmetallation to generate $HInCl_2$; 2) 1,4-addition of dichloroindium hydride to the 1,3-diene; 3) allylation of the carbonyl compound (Scheme 20).



Scheme 20

When 2,3-dimethyl-1,3-butadiene was used to perform the allylation process, excellent yields were obtained with benzaldehyde derivatives bearing either electron-donating or electron-withdrawing substituents. Also aliphatic aldehydes gave good results. However, aryl and alkyl ketones and imines gave scarce results because of the low nucleophilicity of the sterically demanding γ-disubstitued allylindium species. In these cases, yields were improved by using 1,3-butadiene and isoprene, leading to a less substituted crotyl indium compound. A plausible reaction course is shown in Scheme 21. Dichloroindium radicals, generated by homolytic cleavage of the In-H bond, add to the terminal position of the 1,3-diene to give a resonance stabilised allylic radical, which is then quenched by $HInCl_2$. The carbonyl compound adds ionically to the γ-carbon of the resulting allylindium derivative furnishing the condensation product in high yields.



Scheme 21

Conclusions

The new emerging radical chemistry of indium and gallium hydrides can be considered a powerful tool for organic chemistry. Mild reaction conditions, easy purification procedures, and high chemoselectivities place these new reagents in *pole position* as one of the best protocols for tin- free radical applications. The good results obtained by Oshima with organogallium and organoindium derivatives are particularly noteworthy. The unusual characteristic of an organometallic compound to be allowed to be used in the presence of water differentiates these reagents from other tin alternatives and from tin reagents as well. Furthermore, these radical mediators could make radical applications more appealing from the point of view of green chemistry.

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CHAPTER 3

Introduction

As stated above, organic radicals have become a very powerful tool for organic chemistry. The new radical applications involving tin-free procedures and eco-friendly reagents are today very important and throw a bright light onto radical chemistry and the novel synthetic frontiers that can be opened. Although these new approaches are mainly focussed on the generation of carbon centered species, radicals centered on heteroatoms are becoming as well a fundamental target for developing new methodologies directed to the synthesis of heteroatom-containing compounds.

In order to investigate tin-free processes involving generation of aminyl radical as intermediates for construction of carbon-nitrogen bonds, part of my work has been devoted to study the azido group as a source of nitrogen-centered radicals. In particular, my study aimed at investigating the possibility to employ novel non toxic reagents that could generate radicals from the azido group in such a way as to bring about easy workup procedures and to avoid formation of toxic by-products. These new reagents should of course provide better or comparable results with respect to the use of Bu_3SnH, i.e. the main reagent previously employed for this purpose. The results reported in the previous chapters clearly suggested that a likely reagent for this aim could be dichloroindium hydride.

It will be reported below that the employment of $HInCl_2$ provides many advantages. All the reactions are generally carried out under mild conditions and, after easy aqueous work-up procedures, they furnish the desired compounds free from any indium by-products. The reactions can be carried out in non-carcinogenic solvents (e.g. benzene or other solvents usually employed in tin chemistry), even in the presence of water. Furthermore, in many cases, not only do the organoindium reagents mime efficiently radical tin chemistry, but they often give better results in terms of yields and stereochemistry.

Reaction of Organic Azides with $HInCl_2$

Background

In all of the above reactions between organic azides and tributyltin hydride,[1] a common, challenging aspect has always been purification of products from tin residues. If product crystallisation did not occur, chromatography and often further purification procedures were necessary.[2] In particular, since addition of tributylstannyl radicals to the azido group brings

about formation of a strong N-Sn bond, the usual destannylation procedure with aqueous KF is not sufficient and more severe conditions are generally required to cleave that bond in the reaction products. Treatment of the reaction mixture with DMAP and *p*-toluensolfonyl chloride in pyridine under reflux for some days is a suitable method but, under these conditions, huge problems can be encountered, especially when sensible functional groups are present in the target molecule. In addition, chromatography is necessary to further purify the desired products but organotin by-products often spread along the column, magically appearing in every fraction collected.

The decision to try for the first time dichloroindium hydride as a reagent to generate aminyl radicals from organic azides appeared therefore a reasonable idea that could open novel, bright perspectives for future applications. The choice of $InCl_3$ as a hydride source instead of $GaCl_3$ depended on some practical factors. First, the starting material stability, which helps in minimizing waste. Anhydrous $InCl_3$ can be purchased as a powder with a high grade of purity without the need of an inert-atmosphere packaging, since the reagent does not react violent with water or air. On the contrary, powdered gallium trichloride is more reactive and more moisture sensitive, and it could be easily destroyed if no argon atmosphere is provided during its storage and use. Second, although the reactivity of these new hydrides with nitrogen containing compounds and, in particular, organic azides was still unknown, it was reasonable to think it could be comparable to that displayed by other substrates. Dichloroindium hydride was shown to be more reactive if compared with dichlorogallium hydride in reductive dehalogenations, cyclisations of alkyl and alkenyl radicals, and hydrometallation reactions. Moreover, the In–H bond seems weaker than the Ga–H bond, as suggested by the fact that the In–H bond cleaves spontaneously without the need for a radical initiator: this aspect could be extremely important for triggering an efficient radical reaction. Third, the possibility of building some interesting organoindium derivatives suitable for further applications, both as initiators and radical reagents, appears easier with indium(III) chloride than with gallium(III) chloride. In particular, monoalkyl indium(III) derivatives results quite stable as to allow their use without any special precautions.[3] Since the C–In bond is in general weaker than the H–In bond, trialkyl indium compounds are extremely unstable and can be very difficult to prepare. However, this instability could be overcome if bulky or alkoxyl substituents are linked to the indium atom.[4] This might get access to interesting new alkyl or alkoxyl indium compounds that could be employed even in stereoselective radical reactions.

The DIBAL-H / $InCl_3$ system

It is finally well-known that also in radical reactions the electrophilicity and nucleophilicity of the reacting species, and polar factors in general, play a very important role for the reaction rate and for determining which reactive sites in a substrate are more likely to be attacked.[5] An electrophilic radical will more likely attack electron rich atoms or groups, whereas a nucleophilic radical will prefer electron-deficient sites. The azido group appears to be suitable for reactions with both electrophilic and nucleophilic radicals. This aspect is well displayed by the resonance mesomeric structures shown in Figure 1.

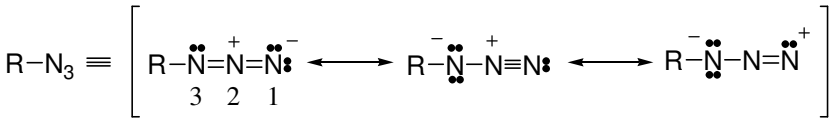


Figure 1

It is reasonable to think that when an electrophilic radical reacts with the azide, the attack position is N^3, which is the electron rich site; on the contrary, the electron-poorer N^1 would undergo preferential addition by a nucleophilic radical. Unfortunately, whatever the character of the radical, either positions of the azido moiety, N^1 and N^3, could actually work as radical acceptors and no clear evidences can be obtained supporting the hypothetical behaviour predicted on the basis of polar effects. For example, the addition of a silyl radical is probably directed to N^1 furnishing the 1,3-triazenyl radical in which the unpaired electron could be mainly associated with a σ orbital of the central nitrogen on the NNN plane,[6] as suggested by the ESR experiments of Roberts (Figure 2).

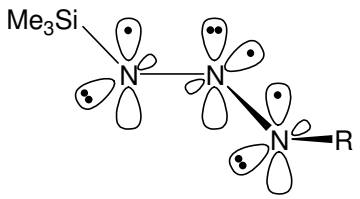


Figure 2

Unfortunately, no ESR evidences have ever been reported about the addition of stannyl radicals onto organic azides. Similarly to the case of (nucleophilic) silyl radicals, it could be assumed that the (nucleophilic as well) stannyl radicals coul behave in the same way, giving analogous 1,3-triazenyl radical adducts. However, the framework could be complicated by the

possibility that the initial 1,3-triazenyl adduct could undergo metallotropic interconversion, by migration of the stannyl moiety, to give the 3,3-adduct[7] or that the stannyl group could make a bridge between N^1 and N^3 to form a four-membered ring intermediate. Roberts investigated the mechanism of homolytic addition of several trisubstituted stannanes onto organic sulfonyl and acyl azides in order to throw some more light on this aspect. Unfortunately, in the case of sulfonyl azides, he found that both triphenylstannyl and tributylstannyl radicals attack N^1 and N^3 at quite similar rates. Using acyl azides, the addition of triphenylstannyl radicals is mainly directed to N^1, due to rearrangement of the N^3 adduct.

Although the site of attack is still debated, the azido group acts as a very good radical acceptor, furnishing aminyl radicals by eventual loss of molecular nitrogen. Since the behaviour of dichloroindium radicals resembles in many ways that of tributyltin analogs, it was reasonable to suppose that the azido group could be a good acceptor also for indium-centred radicals. Therefore, we decided to investigate the reactivity of organic azides with this new mild radical reagent under different conditions. We generally aimed at generating a new class of aminyl radicals, i.e. *N*-indium-substituted aminyl radicals, and studying their reactivity and possible synthetic applications.

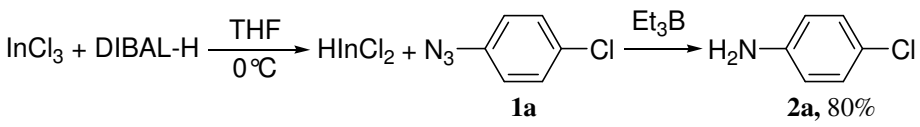
The first, simplest experiment we performed to test the feasibility of this new method, was the $HInCl_2$-mediated reduction of an aromatic azide. Since several methods were available for the synthesis of $HInCl_2$ (see previous chapters), it was obvious to eliminate those in contrast with the scope of the project or involving reagents not compatible with the azido group. Hence, we rejected the transmetallations carried out using both Bu_3SnH and $NaBH_4$, the former for the obvious reason that it employs a reagent (the stannane) we were searching for a substitute of, and the latter because $NaBH_4$ is a good reducing agent of organic azides.[8]

Therefore the first explorative reaction was carried out with the $HInCl_2$ generated from $InCl_3$ and DIBAL-H in THF, as reported by Oshima. Before any experiment were performed, the stability of each azide under the reaction conditions was verified by allowing all azides to stay in a THF solution in the presence of either $InCl_3$ or DIBAL-H: no reduction or other reactions took place after 6 hours. 1-Azido-4-chlorobenzene (**1a**) was chosen as a model aromatic compound to optimize the process, whereas 1-azidoundecane (**1b**) and 1-(3-azidopropyl)benzene (**1c**) were chosen as analogous models of aliphatic azides.

Dichloroindium hydride was first generated at −78°C[9] by slow addition of a hexane solution of DIBAL-H to a previously prepared solution of anhydrous $InCl_3$ in freshly distilled THF. All the reactions were carried out under an argon atmosphere to avoid any possible degradation of the reagents. After 30 min, triethylborane and 4-chlorophenyl azide were

added. The reaction was quenched after 3 hours with an aqueous 1 M solution of hydrochloric acid. The mixture was extracted with diethyl ether and the aqueous phase was basified with a 1 M solution of sodium hydroxide and then extracted again. The double aqueous work-up was performed in order to separate possible amounts of unreacted azide from the amine product without any need for column chromatograpy. The first test was however a failure, since no product could be isolated from the reaction mixture except for the starting azide.

After several attempts, the overall reactions conditions were optimised and, when both reaction steps (i.e. hydride generation and reaction with the azide) were carried out at 0 °C[10] and the work-up was performed simply with water, aniline **2a** was isolated by crystallisation in 80% yield (Scheme 1). No indium by-products contamination was noticed in the final 4-chloroaniline.[11]



1a **2a,** 80%

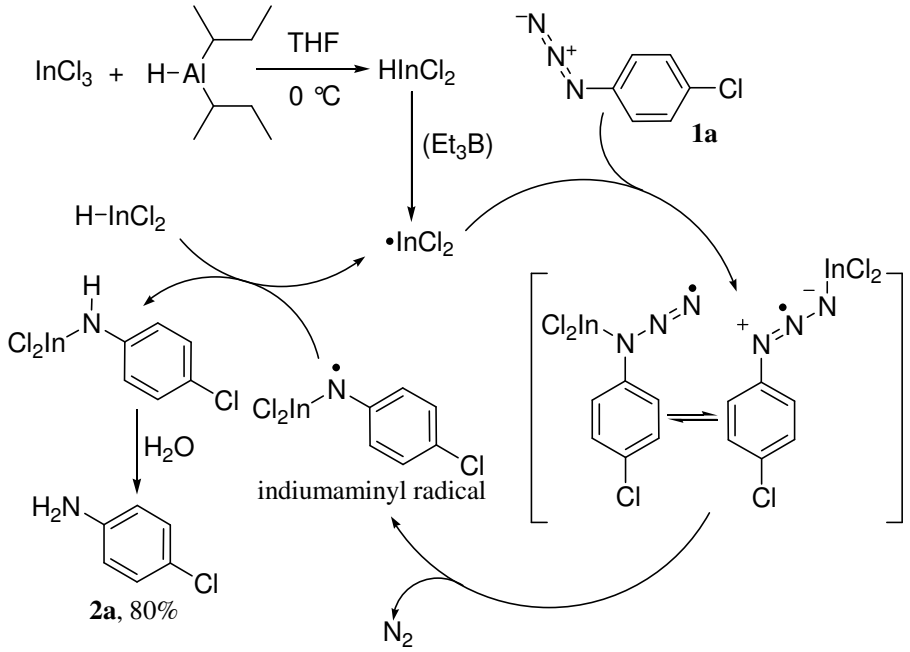
Scheme 1

The reaction yield could not be improved any further, neither by purification with chromatography over silica gel or alumina instead of crystallisation, nor by removal of the solvent (THF) before the extractive work-up. This fact probably points out to some limits of this reaction related to the purification stage. In fact, the starting aromatic azide was completely consumed and no other products were identified by GC-MS analysis except the aniline: the non-quantitative yield could therefore be explained by an incomplete recovery of the product, due to some plausible complexation between the basic aniline and Lewis acid derivatives of indium or aluminium present in the reaction mixture. The complexation could enhance water solubility of the organic substrate causing some loss of the desired product.

The reaction of 4-chlorophenyl azide was tested also in the absence of triethylborane, but no differences could be observed, in terms of neither yield nor reaction time. However, this results must not be surprising, since it is well-known that dichloroindium hydride spontaneously generates dichloroindyl radicals (•$InCl_2$), as already reported by Baba and Oshima[12] and, under our conditions, the radical chain seems to be efficient enough as to totally convert the starting material avoiding the use of the radical initiator.

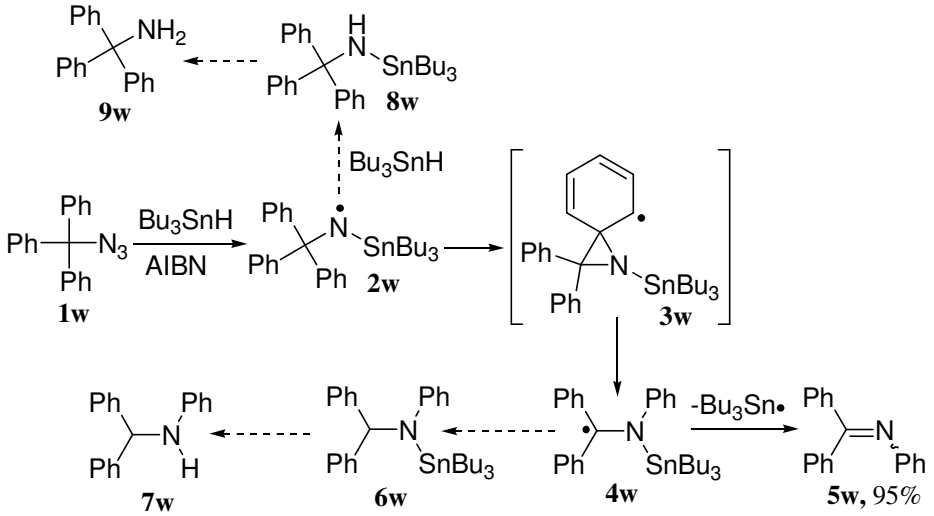
The mechanism of the reaction is shown in Scheme 2: the dichloroindyl radical, generated by triethylborane or spontaneously, adds to the azido group. Whatever the probable intermediate, i.e. either a 1,3- or a 3,3-triazenyl radical, this could lead to the formation of an

indiumaminyl radical. Hydrogen abstraction from another molecule of dichloroindium hydride furnishes the *N*-(dichloroindium)-substituted amine. Further hydrolysis of the latter gives amine **2a** in good yield.



Scheme 2

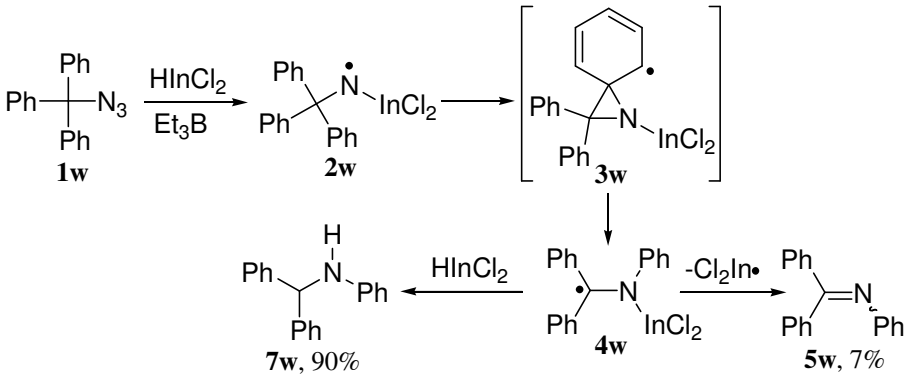
The system DIBAL-H/$InCl_3$, was examined also with triphenylmethyl azide **1w**, whose well-known reactivity under radical conditions[13] would confirm the above reaction mechanism. In fact, by reaction with tributyltin hydride and AIBN (i.e. in the presence of stannyl radicals), **1w** is known to furnish the product deriving from the 1,2-aryl radical rearrangement (**5w**) (Scheme 3).



Scheme 3

When $HInCl_2$ was used in a slight excess (1.2 eq) and a stochiometric amount of Et_3B was added, besides partial recovery of the starting azide (21%), *N*-phenylbenzophenonimine **5w** and amine **7w** were obtained in 20% and 64% yield, respectively. With a large excess of $HInCl_2$ (3 eq), the reaction furnished amine **7w** (90%) and imine **5w** (7%) (Scheme 4). It is worth noting that also amine **7w** is the result of a radical rearrangement pathway (Scheme 3).

These results are clearly compatible with the postulated radical chain mechanism and demonstrated that dichloroindyl radicals seem capable to add to the azido group giving a presumable *N*-(dichloroindium)aminyl radical (**2w**), whose evolution through 1,2-aryl radical rearrangement furnishes the observed products, although with a product distribution that is different from that observed with tin radicals. This can however be the result of the different reaction conditions and the different hydrogen-donor capability of our indium hydride. We can conclude that it is reasonable that $HInCl_2$ could react with aromatic azides in a radical fashion through generation of a novel radical intermediate, i.e. the indylaminyl radical.

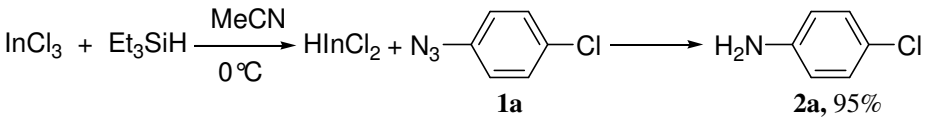


Scheme 4

The reactions of primary alkyl azides, i.e. 1-azidoundecane **1b** and 1-(3-azidopropyl)benzene **1c**, required 3 equiv of $HInCl_2$ to go to completion and, rather surprisingly, did not afford any trace of the corresponding amines. Even more surprisingly, no traces of other identifiable products could be observed in the final reaction mixtures. Nonetheless, the formation of the alkyl amines cannot be ruled out. As suggested for aromatic amines, a complexation between the amine, or some precursor of it, and a metal centre could occur, leaving the product into the aqueous phase. Since alkyl amines are more basic than aryl ones, and thence more capable to coordinate electrophilic sites, they could be easily complexated by some Indium- or Aluminium-containing Lewis acids present in the reaction mixture, thus lowering their recovery. Any attempt to modify the reaction workup to improve product isolation was unsuccessful.

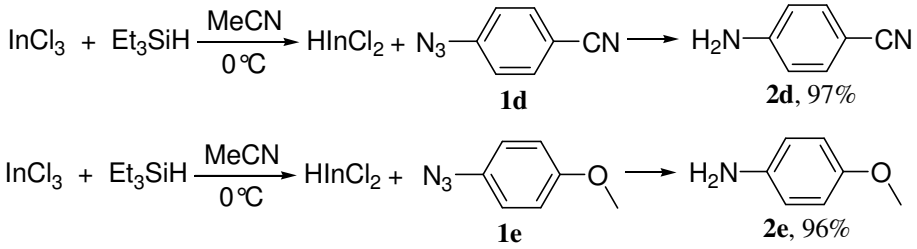
The Et_3SiH / $InCl_3$ system

Assuming that organoaluminium compounds could be the main cause of the inefficiency of the isolation/purification step of the above reaction, we decided to move on to Baba's system involving indium trichloride and triethylsilane.[14] As in the previous approach, 4-chlorophenyl azide was used as a model compound. All aromatic and alkyl azides were reacted with either triethylsilane or indium trichloride alone and were proved to be inert towards these single reagents. To carry out our radical reduction, triethylsilane was added to a solution of $InCl_3$ in acetonitrile at 0 °C. After 5 min 4-chlorophenyl azide was added and the solution was stirred until disappearance of the starting compound (15 minutes). A 1 M HCl aqueous solution was added to quench the reaction crude and diethyl ether was used to extract the silane residues. The aqueous phase was neutralised and extracted to furnish aniline **2a** in 95% yield (Scheme 5).



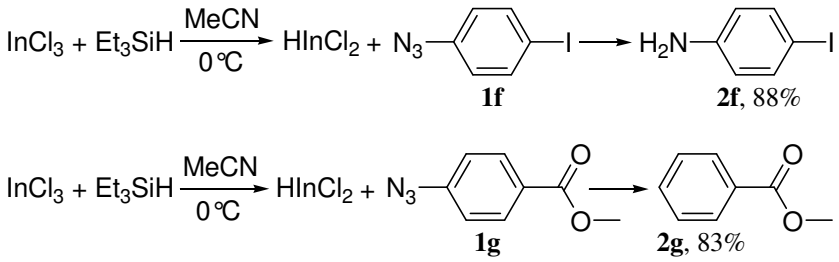
Scheme 5

This method[15] works better than the previous one, probably due to ease of isolation of the desired products. Many other aryl azides with various functionalities in the *para* position were reacted with $HInCl_2$ in acetonitrile giving the corresponding anilines as the sole product. Both electron withdrawing and electron releasing groups were compatible with the reaction conditions and gave comparable results: azides **1d** (4-azidobenzonitrile) and **1e** (1-azido-4-methoxybenzene) were both converted in 15 minutes to the corresponding anilines **2d** and **2e** in excellent yields, as shown in Scheme 6:



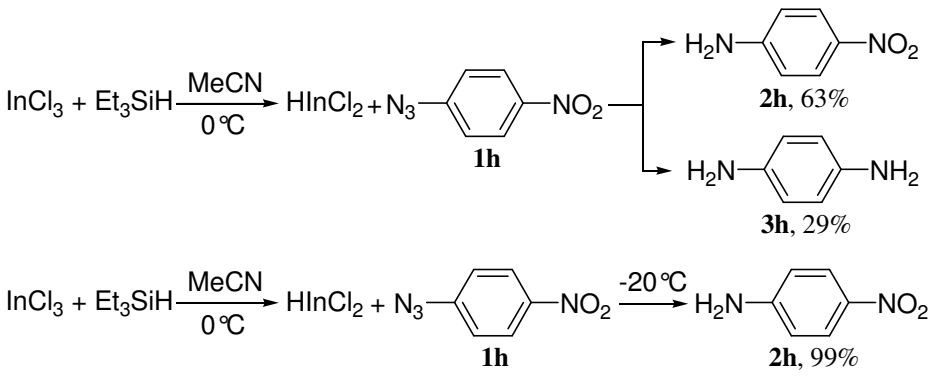
Scheme 6

1-Azido-4-iodobenzene **1f** and methyl 4-azidobenzoate **1g** were successfully reduced to anilines **2f** and **2g**, respectively: no traces of by-products deriving from competitive reductive reactions of their functional groups were identified (Scheme 7). The reaction of **1f** is extremely important because it shows that addition of $\bullet InCl_2$ radical to the azido group is faster than iodine abstraction, thus exhibiting a different behaviour from trialkyltin[16] and triethylsilyl[1d] radicals.



Scheme 7

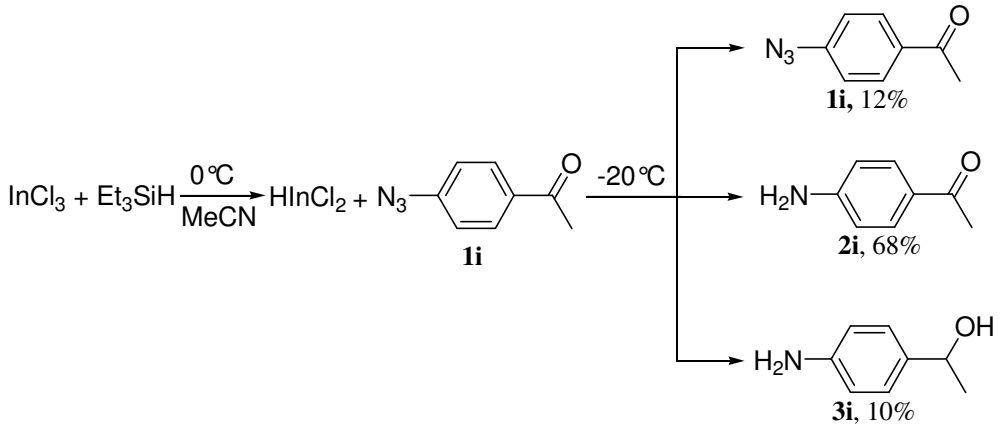
The high selectivity characteristics were further exploited in the reduction of 1-azido-4-nitrobenzene **1h**. The result obtained was extremely important because it is generally quite difficult to reduce preferentially an azido group in the presence of a nitro group. As showed in Scheme 8, conversion of azide **1h** to the corresponding 1-amino-4-nitroaniline **2h** was not completely selective when the reaction was carried on at 0 °C, although the absence of any traces of 1-azido-4-nitrobezene indicated that reduction of the azido group is faster than that of the nitro moiety. However, when the same reaction was carried out at −20 °C, aniline **2h** was quantitatively isolated.



Scheme 8

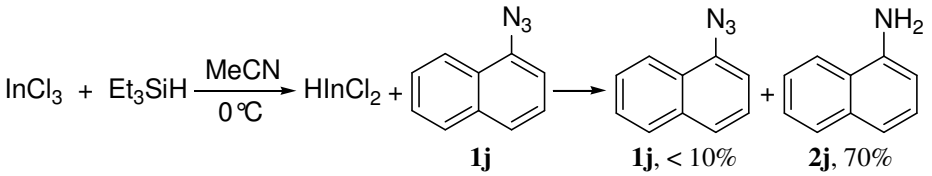
The reaction of 1-(4-azidophenyl)ethanone **1i** was first carried out at 0 °C. At this temperature **1i** gave a quite complicated mixture containing unreacted azide, 1-(4-

aminophenyl)ethanol **3i**, and some undefined by-products. In this case, reduction of the carbonyl group[17] clearly prevailed over the desired pathway. When the reaction mixture was kept overnight at −20 °C, much better results were obtained: besides starting azide (12%), the reaction afforded 1-(4-aminophenyl)ethanol **3i** (10%), identified by GC-MS analysis but not isolated, and 1-(4-aminophenyl)ethanone **2i** (68%), as result of chemoselective reduction of the azido group (Scheme 9).



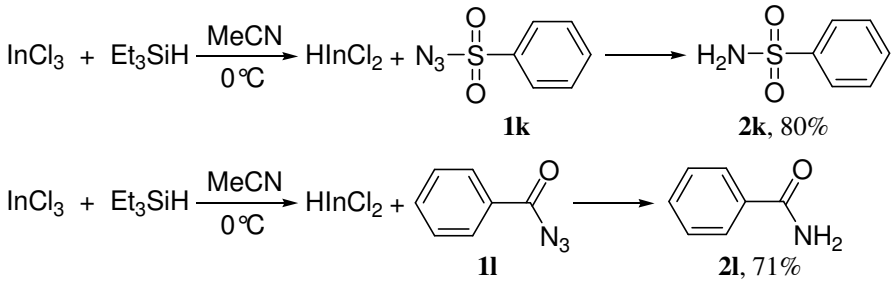
Scheme 9

Surprisingly, the reaction of 1-azidonaphtalene **1j** did not give complete conversion of the starting material. Even after 90 min 1-aminonaphtalene **2j** was isolated in 70% yield together with ca. 10% of the starting azide (Scheme 10).



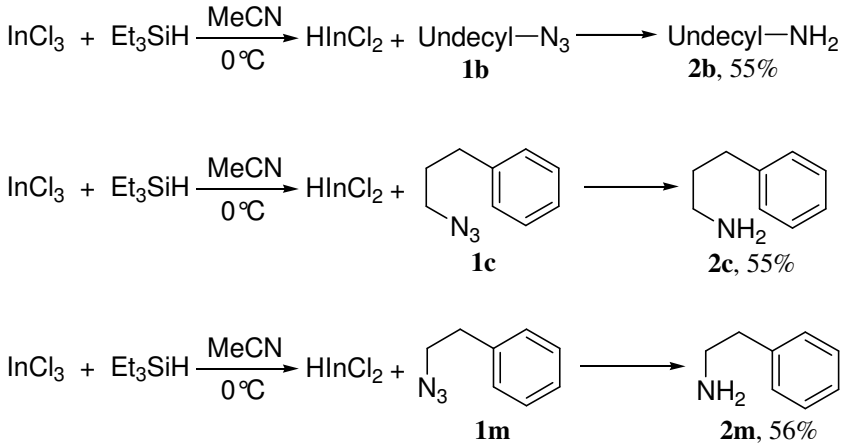
Scheme 10

Phenylsulfonyl azide **1k** gave the corresponding amide **2k** in good yield after 210 minutes. No products derived from radical deazidation processes were apparently detected. Analogously, benzoyl azide **1l** yielded benzamide **2l**. This outcome represents a novel, very mild entry to amidyl radicals[18] from acyl azides under conditions that avoid competitive Curtius rearrangements[7] (Scheme 11). This result, in our opinion, is worth of future developments, since synthetic applications of amidyl radicals are in principle very interesting but still rather rare, and available precursors of amidyl radicals are very limited.



Scheme 11

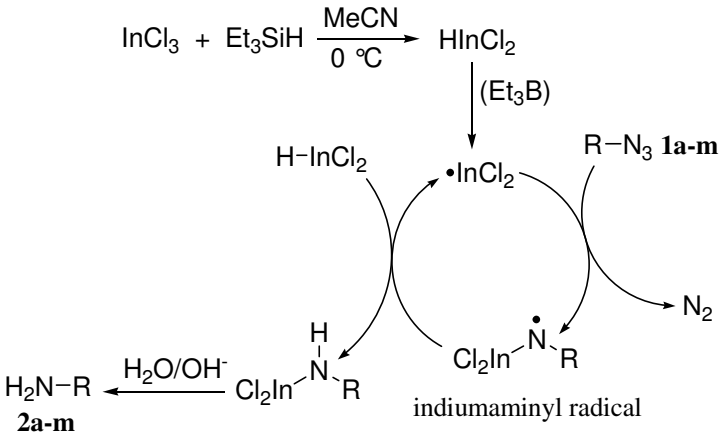
The reactions of alkyl azides gave worse results, compared to those of aryl azides. To be completely consumed, alkyl azides needed 2.2 equivalents of hydride and extractive work-up was extremely difficult. This common aspect with the reaction carried out with DIBAL-H reinforces the possibility that some complexation could occur, drastically affecting isolated yields. Results were however not as bad as with the DIBAL-H system. 1-Azidoundecane **1b** gave however the corresponding amine **2b** in 55% yield after 30 minutes and after basic aqueous work-up; identical yields were obtained with 1-(3-azidopropyl)benzene **1c** and 1-(2-azidoethyl)benzene **1m** (Scheme 12).



Scheme 12

The reaction outcome can again be well explained by the radical chain mechanism shown in Scheme 13. Since also in acetonitrile the hydride displayed spontaneous homolytic cleavage of the In–H bond, triethylborane was not necessary but was employed to substantiate the reaction mechanism, especially with those azides that required longer reaction times, i.e. aliphatic azides. Aromatic azides are more reactive and their conversion times are extremely short (15-30 min), so that the effect of Et_3B is not observable: in these cases, spontaneous production of $\bullet InCl_2$ radical is hence sufficient to sustain the radical chain reaction. On the

contrary, use of 0.2 equivalents of Et_3B with aliphatic azides **1j**, **1k**, and **1l** speeded up the reactions and conversion times were noticeably reduced (Table 1).



Scheme 13

azide	R	No Et_3B	yield	Et_3B	yield
1j	1-Naphthyl	90 min.	70(%)	60 min.	70(%)
1k	$PhSO_2$	210 min.	80(%)	90 min.	82(%)
1l	PhCO	180 min.	71(%)	60 min.	75(%)

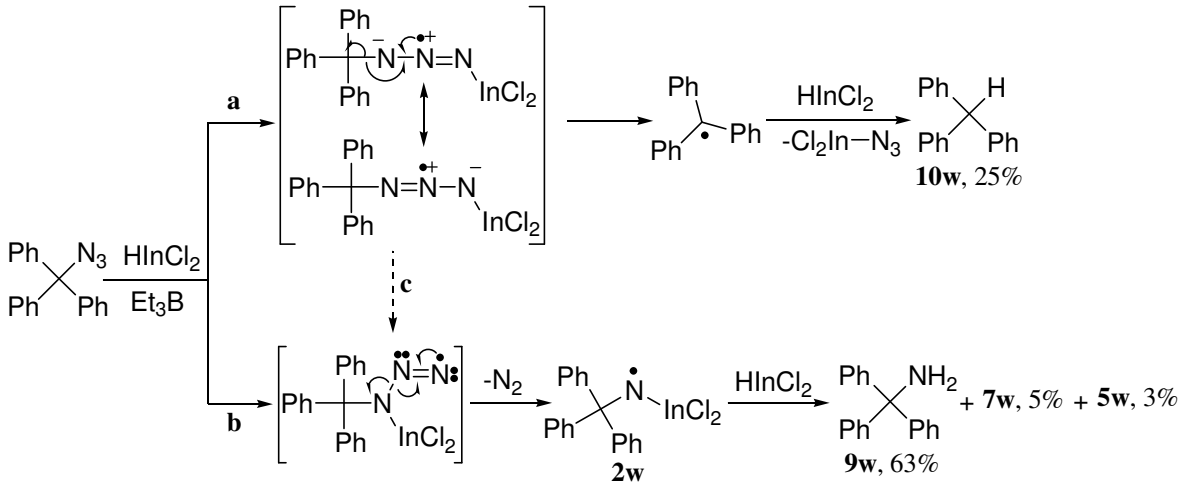
Table 1

We also analyzed again the reaction of triphenylmethyl azide **1w**, both with and without the radical initiator, and a different product distribution was observed. Two equivalents of $HInCl_2$ were not sufficient to consume **1w** (recovered in 25% yield) in the absence of Et_3B and, after purification, triphenylmethane **10w** (50%), triphenylamine **9w** (20%), and *N*-phenyl amine **7w** (< 1%) were isolated. On the contrary, the same excess of hydride in the presence of 0.1 eq. of Et_3B completely consumed the starting azide furnishing triphenylamine **9w** (63%) and triphenylmethane **10w** (25%), along with small amounts of **5w** (3%) and **7w** (5%) (Table 2).

Azide	$HInCl_2$	Et_3B	Azide	10w	9w	5w	7w
1w	2 eq.	-	27%	50%	20%	-	< 1%
1w	2 eq.	0.1 eq-	-	25%	63%	3%	5%

Table 2

A first effect of triethylborane is enhancing the steady concentration of •$InCl_2$ radical, thus allowing complete conversion of the azide. Even though no relevant amounts of rearrangement products were isolated, the formation of both triphenylamine and triphenylmethane can be explained in terms of a radical mechanism. The former as a product of early reduction of indiumaminyl radical **2w** by $HInCl_2$; the latter as a product of radical deazidation with loss of N_3InCl_2,[19] which however was not detected. Isolation of triphenylmethane is an important evidence of the radical addition mechanism of •$InCl_2$ onto the azido moiety, since **10w** can only be accounted for through homolytic scission of the N^3–C bond in the 1,3-triazenylindyl radical intermediate, followed by hydrogen abstraction of the resulting triphenylmethyl (trityl) radical from $HInCl_2$. This is a clear indication that addition of the dichloroindyl radical onto the azide occurs also onto N^1 (path **a**), as the corresponding addition of •$InCl_2$ onto N^3 would more likely result in nitrogen loss and formation of the aminyl radical. At this point, it is not possible to say whether the other products **9w**, **5w**, and **7w** derive directly from the 3,3-triazenylindyl radical adduct (path **b**), or they are instead the result of an indylaminyl radical **2w** arising from rearrangement of the 1,3-adduct (path **c**). Whatever mechanism would really operate, the reaction of azide **1w** definitely afforded some sound information about addition of indyl radicals onto the azido moiety[20] (Scheme 14).



Scheme 14

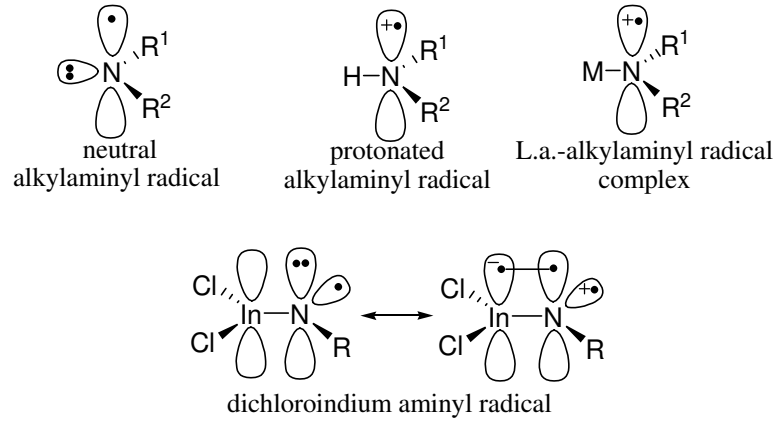
The possibility that alternative, competitive ionic mechanisms could operate cannot however be excluded by our present experimental data. Radical and non-radical pathways might simultaneosuly operate, prevailing over each others depending on the substrate and the reaction conditions.

To prove again the occurrence of a radical mechanism, the reaction of azide **1e** was carried out in the presence of 1 equivalent of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), a well-known radical trap. Under these conditions, more than 80% of unreacted azide was recovered after 3 hours and no traces of aniline were neither detected nor isolated. This clearly points to the exclusive presence of a radical mechanism, since a competitive ionic pathway affording the aniline had occurred occurred in the presence of TEMPO.

Because of the interesting results provided by our new reducing system, the following step should have been to verify its potentiality and versatility in more fascinating processes such as radical cyclisations.

Of course, since *N*-(dichloroindyl)aminyl radical is a novel intermediate, nothing has been reported yet about its reactivity and electronic structure. Generally, neutral mono-alkylaminyl and di-alkylaminyl radicals behave as electrophiles in hydrogen transfer reactions and as nuclephiles in additions to α-methylstyrene, but in both cases the reactions are sluggish, due to the low extent of 'philicity'. This low reactivity can be explained in terms of electronic repulsion. For example, the electronic repulsion between bonded electron pairs (N–C bond) and nitrogen lone pairs is greater than repulsion between bonded electron pairs (C–C or C–H) and other bonded electron pairs (C–C or C–H). Hence, although the N–C (69-75 kcal/mol)[21] and N–H (91 kcal/mol) bonds are quite strong, they are however weaker than the corresponding C–C (83-85 kcal/mol) and C–H (104 kcal/mol) bonds. As a result, cyclisations onto alkenes or hydrogen abstractions from quite good hydrogen donors like toluene are ineffective. The stannylaminyl radicals, due to the electropositive tin atom, display a nucleophilic character,[16, 22] thus being able to perform cyclisations onto carbonyl moieties. Their reactions with inactivated double bonds are however slow and inefficient.

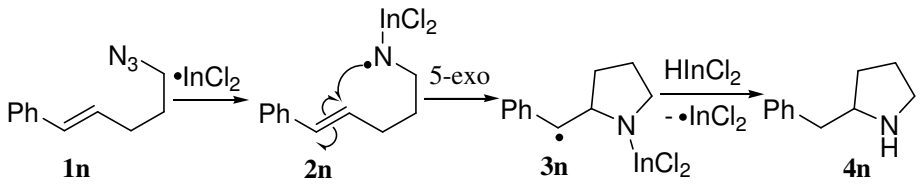
As far as the (dichloroindyl)aminyl radical is concerned, one could suppose that the electropositive character of indium, very similar to tin, could give rise to aminyl radicals with a philicity analogous to that of stannylaminyls; on the other hand, it would not be unreasonable to think that (dichloroindyl)aminyl radicals could display an electrophilic character, due to the presence of an empty *p* orbital on the indium metal atom directly bonded to the nitrogen. In the latter case, (dichloroindyl)aminyl radicals should be more similar to protonated or Lewis-acid-complexed *N*-centered radical, than to stannylaminyl radicals (Scheme 15), and their reactivity could be analogous to that of aminium cation radicals that easily cyclize and add intermolecularly to electron rich double bonds.[23]



Scheme 15

For this reason, to get more information about the reactivity of our novel aminyl radicals, we investigated the cyclisation reactions of both (*E*)-1-(5-azidopenten-1-enyl)benzene **1n** and *γ*-azidonitriles **1o-u**.

Indeed, the intermediate *N*-centered radical **2n** derived from alkyl azide **1n**, if electrophilic in nature, would have yielded the corresponding 2-benzylpyrrolidine **4n** by *5-exo* cyclisation onto the activated carbon-carbon double bond. This cyclisation would have been hence promoted by both kinetic (philicity) and thermodynamic (stabilisation of the intermediate benzyl radical **3n**) factors (Scheme 16). Unfortunately, we could not observe cyclisation of compound **1n** under any reaction conditions.

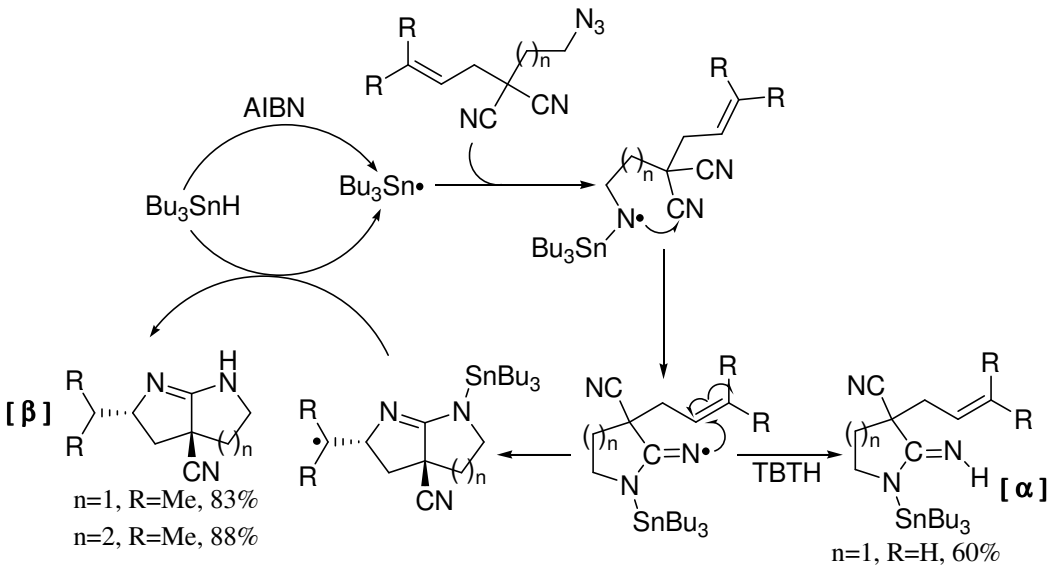


Scheme 16

On the contrary, the reactions of *γ*-azidonitriles **1o-u** were successful, giving the cyclised products in high yields through ring closure of intermediate indium-aminyl radicals onto the cyano group. These reactions thus furnished evidence supporting a nucleophilic rather than electrophilic character of our *N*-centered radical, hence similar to the tin congeners.

It is worth noting that the azidoalkyl nitriles employed in these experiments are the same already studied under tin chemistry conditions.[1a] When reacted with tributyltin hydride and AIBN in refluxing benzene, they exhibited highly efficient 5- and 6-exo cyclisation of the corresponding stannylaminyl radical intermediates onto the nitrile group to give aminoiminyl radicals, which in turn underwent 5-exo cyclisation onto the internal alkene moiety (Scheme

17). In this study we proved that the tandem cyclisation occurred undoubtedly through a radical pathway, and it was highly dependent both on the stability of the ensuing C-centered radical and on the electronic character of the alkene. In fact, when the alkenyl substituent was an allyl group, the 5-exo cyclised iminyl radical produced after the first cyclisation was trapped by Bu_3SnH, prior to a possible second cyclisation, to give the corresponding amidines (α).



Scheme 17

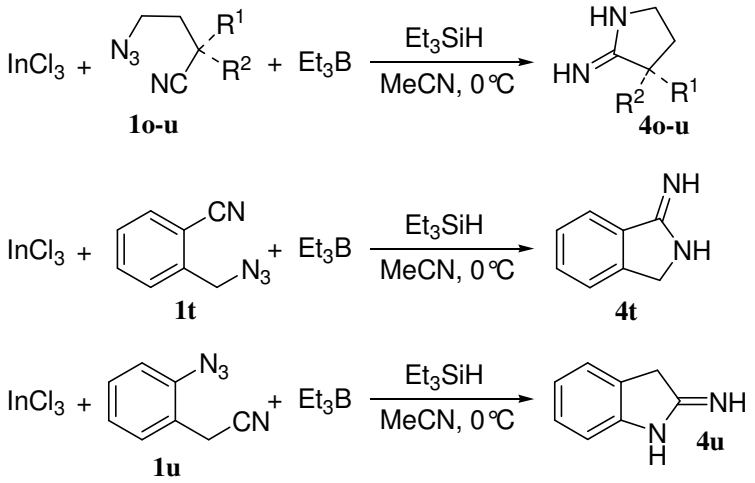
When reacted with dichloroindium hydride, the same azidonitriles furnished only the monocyclised amidines (α) in quantitative yields (Table 3).

Azide	**R^1**	**R^2**	**time**	**Et_3B**	**yield**
1o	CN	$C_6H_6CH_2$	30 min.	0.2 eq.	95(%)
1p	CN	$CH_2CH=C(CH_3)_2$	60 min.	0.2 eq.	98(%)
1q	CN	$CH_2CH=CHC_6H_6$	60 min.	0.2 eq.	97(%)
1r	$C_6H_6SO_2$	$CH_2CH=CHC_6H_6$	30 min.	0.2 eq.	92(%)
1s	C_6H_6	C_6H_6	10 min.	0.2 eq.	99(%)
1t	$-C_4H_4-$	–	60 min.	0.2 eq.	95(%)
1u	H	H	180 min.	0.2 eq.	85(%)

Table 3

The reactions were carried out by dissolving γ-azidonitriles **1o-u** into the acetonitrile solution of $InCl_3$ and Et_3B; then Et_3SiH was slowly added at 0 °C to perform transmetallation.

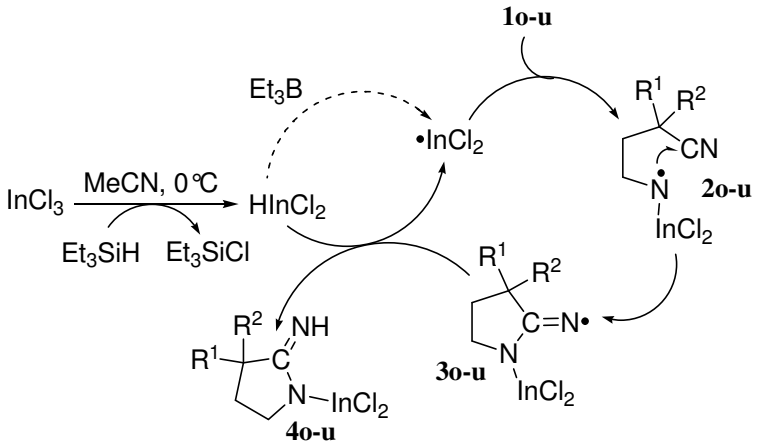
No reactions took place without triethylsilane after a few hours and comparable results were obtained by addition of the azides to a solution of freshly prepared $HInCl_2$. Interestingly, the result of these cyclisations was virtually independent of the aliphatic or aromatic nature of the azido and/or cyano moieties (Scheme 18) and all reactions worked with just one eq of indium hydride. The cyano group is evidently a very good trap for both aliphatic and aromatic indiumaminyl radicals, making cyclisation faster than competitive hydrogen abstraction from the hydride.



Scheme 18

These amidine products are not very common, but recent studies have disclosed that they can act as potent, selective, non-amino-acid-based inhibitors of human NOS (nitric oxide synthases) and they therefore represent the foundation for potential therapeutic agents.[24] The previously reported syntheses are rather complicated or involve cyclisations of aminonitriles at high temperatures.[25] To date, no reported procedure makes use of such a very mild environment and entails such a high product yield.

All the reactions were carried out under classical radical conditions in the presence of Et_3B (0.2 eq.); the plausible mechanism involving cyclisation of the indiumaminyl radical onto the cyano group followed by hydrogen transfer from $HInCl_2$ to the resulting aminoiminyl radical is displayed in Scheme 19:



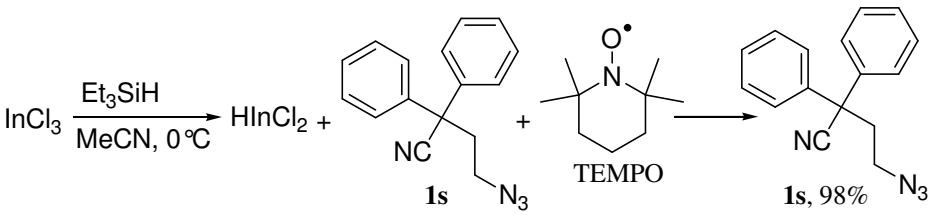
Scheme 19

Some reactions were examined to ascertain the effect of the radical initiator. In the absence of triethylborane compounds **1o** and **1s** were totally converted to 3-benzylpyrrolidin-2-imine **4o** and 3,3-diphenylpyrrolidin-2-imine **4s**, respectively, in 1 h at 0 °C, but the same reactions required only 10 min in the presence of the initiator. Additionally, the reaction of **1s** without initiator gave after 10 min a mixture of starting azide (56%) and pyrrolidin-2-imine (40%), whereas, in the presence of the initiator, **1s** was completely converted after the same time. The acceleration effect of triethylborane on the radical mechanism appears therefore evident (Table 4).

Azide	**Et_3B**	**amidine**	**No Et_3B**	**Azide**	**amidine**
1o	30 min.	95(%)	>60 min.		93(%)
1s	10 min.	99(%)	>60 min.		96(%)
1s			10 min.	56(%)	40(%)

Table 4

An additional prove in favour of a radical pathway was furnished by the use of TEMPO, which completely inhibited the reactions: azide **1s** was almost completely recovered (98%) after more than 1 hour under the usual reaction conditions (Scheme 20).



Scheme 20

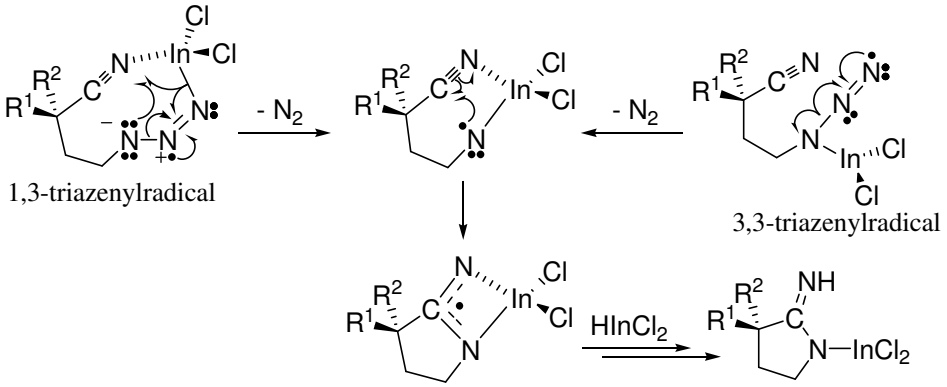
Furthermore, azides **1j**, **1l**, and **1s** were reacted with $HInCl_2$ using a UV lamp as a radical initiator. The 150 W medium-pressure Hg arc has indeed the same effect as Et_3B, providing efficient homolysis of the H-In bond and furnishing again the evidence that organic azides undergo reduction (**1j, l**) and provide efficient 5-exo cyclisation (**1s**) through a radical mechanism.

azide	No Et_3B	yield	UV	yield
1j	90 min.	70(%)	60 min.	70(%)
1l	180 min.	71(%)	60 min.	75(%)
1s	60 min.	93(%)	10 min.	98(%)

Table 5

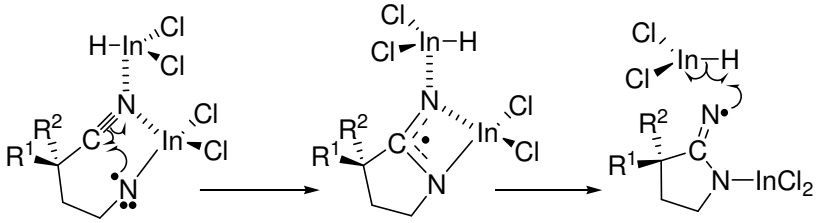
If a radical pathway is really involved, why the intermediate iminyl radicals do not cyclize? Why did not we obtain the same bicyclic products isolated under tin chemistry conditions?

An easy answer could be: “because an ionic mechanism prevail over the radical one”. Indeed, it cannot be excluded that, instead of cyclizing, the indium-aminyl radical could alternatively abstract a hydrogen atom from the hydride giving an indium-amine, which might then ionically cyclize onto che cyano group to give the amidine.[26] However, to our opinion, very efficient cyclisation of an amine to an amidine is highly unlikely to occur under our very mild experimental conditions (0 °C). Furthermore, all of our experimental data (the effects of radical trap and initiator) strongly support a radical mechanism. A possible explanation of the reaction outcome could be that the dichloroindium moiety, bonded to the indiumaminyl radical, could help the cyclisation process by means of its Lewis acid properties. Due to the possibility to coordinate more than 3 ligands, the dichloroindium moiety could chelate either the nitrogen of the cyano group through a μ-bond or the C-N triple bond through a π-interaction, thus expediting the cyclisation step. This complexation could arise mostly from the 1,3-triazenyl rather than the 3,3-triazenyl radical intermediate. This same complexation could however prevent the following step, since the resonance-stabilised aminoiminyl radical resulting from ring closure would not be able to properly approach the alkene to attain the subsequent cyclisation and would thence prefer to abstract hydrogen from the hydride to yield the monocyclic amidine (Scheme 21).



Scheme 21

The possibility that the cyano group could internally coordinate the dichloroindium moiety and also another molecule of $HInCl_2$, which would act purely as a Lewis acid, would explain the mono-cyclisation as well: this double coordination would in fact enhance the electrophilicity of the nitrile C-atom, making the ring closure of the indiumaminyl radical easier but favouring hydrogen abstraction by the iminyl radical because of the vicinity of the hydrogen source (Scheme 22).



Scheme 22

Conclusions

Dichloroindium hydride revealed to be a valid alternative to tributyltin hydride for radical reduction of organic (alkyl, aryl, acyl, solfonyl) azides. The new approach entails mild reaction conditions and provides high yields of the corresponding amines and amides, also showing high degrees of selectivity. Yields of alkyl amines were generally lower with respect to other derivatives, due to purification problems: it is however reasonable to think that they were formed quantitatively in the reaction crude. The good results obtained in five-membered ring closures of γ-azidonitriles to pyrrolidin-2-imines, which entails analogous alkyl intermediates, provided additional support to this hypothesis. The latter reaction is a very attractive approach to interesting amidine compounds in the absence of both toxic reagents and tedious purification procedures.

From a mechanistic point of view, we obtained good support to our idea that the system dichloroindium hydride / azides can be utilised as a new source of *aminyl radicals.* Compared to the already known tin-, silicon-, and germanium-hydride mediated reactions, the high reactivity showed by our novel system represents a easy, mild way for the generation of *N*-centered radicals from organic azides. For the specific case of γ-azidonitriles, the increased reaction efficiency is probably the results of more combined factors, the most important of which is perhaps the Lewis acid activity of $HInCl_2$.

The ambiguities still present in the reaction mechanism have however to be clarified to spread the synthetic applications of our methodology. We certainly hope that in the future a better knowledge of this reagent could make it a useful breakthrough as a tin alternative in *green* procedures.

Experimental Section

General Procedure for the Reaction of Azides with Dichloroindium Hydride

The starting azide (1 equiv.) was added at 0 °C to an acetonitrile solution of dichloroindium hydride (1.1 equiv.), generated in situ by stirring under argon anhydrous indium trichloride (1.1 equiv., previously dried by heating at 130 °C under argon for 1 h) and triethylsilane (1.1 equiv.) in acetonitrile (4 mL) for 5 min at 0 °C.[16] When used, triethylborane was added immediately after the azide. Or alternatively the reaction were carried out under photolysis with a 150 W medium pressure Hg arc UV-lamp. The resulting mixture was stirred at 0 °C until disappearance of the starting material. The final crude was quenched with an acid aqueous solution and extracted with diethyl ether to remove the silane residues. The aqueous phase was neutralised and extracted with diethyl ether to give the amine, which was in a few cases eventually purified by column chromatography.

Analogous results can be obtained by dissolving the azide into the solution of dry indium trichloride and then adding triethylsilane (and, when it is the case, triethylborane).

Preparation and Characterisation Data for Azides

Aromatic azides **1a, d-j** were prepared by standard diazotisation of the corresponding anilines followed by treatment with sodium azide, and were identified by comparison with literature data.

1a: R. N. Butler, S. Collier, A. F. M. Fleming, *J. Chem. Soc., Perkin Trans. 2* **1996**, 801.

1d: A. Nicolaides, T. Enyo, D. Miura, H. Tomioka, *J. Am. Chem. Soc.* **2001**, *123*, 2628.

1e: M. L. Huber, J. T. Pinhey, *J. Chem. Soc., Perkin Trans. 1* **1990**, 721.

1f: H. Tomioka, S. Sawai, *Org. Biomol. Chem.* **2003**, 4441.

4-Azidobenzoic acid methyl ester (**1g**) was previously reported (M. W. Logue, B. H. Han, *J. Org. Chem.* **1981**, *46*, 1638) but characterised as a mixture of products; IR (ν_{max}, $CHCl_3$) 2118 (N_3) and 1718 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.89 (3 H, s), 7.03 (2 H, A part of AA'BB', *J* = 8.9 Hz), 8.00 (2 H, B part of AA'BB', *J* = 8.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.6 (CH_3), 119.3 (CH), 127.3 (CH), 131.9 (CH), 145.2 (C), 166.7 (C).

1h: S. S. M. Hassan, F. S. Tadros, *Anal. Chem.* **1985**, *57*, 162.

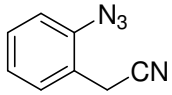
1i: Q. Liu, Y. Tor, *Org. Lett.* **2003**, *5*, 2571.

1j: S. P. Klump, H. Shechter, *Tetrahedron Lett.* **2002**, *43*, 8421.

Sulfonyl and acyl azides **1k, l** were synthesised by treatment of the corresponding acid chlorides with sodium azide in DMSO (M. Regitz, J. Hocker, A. Liedhegener, *Org. Synth.* Coll. Vol. V, **1973**, 179).

1k: H. -S. Dang, B. P. Roberts, *J. Chem. Soc., Perkin Trans. 1* **1996**, 1493.

1l: D. S. Bose, A. V. N. Reddy, *Tetrahedron Lett.* **2003**, *44*, 3543.



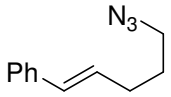
(2-Azidophenyl)acetonitrile (1u). (2-Aminophenyl)acetonitrile (commercially available) (5 mmol) was diazotised according to a standard procedure and treated dropwise in 45 min at 0-5 °C with an aqueous (10 mL) solution of sodium azide (10 mmol). The reaction crude was extracted with diethyl ether (3 × 25 mL), the organic phase was dried over magnesium sulfate, and the solvent evaporated to give azide **7** (3.1 mmol, 60%) as a solid, mp = 57.5-58.7 °C; IR (ν_{max}, $CHCl_3$) 2132 (N_3), and 2255 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.67 (2 H, s), 7.13-7.22 (2 H, m), 7.35-7.46 (2 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1 (CH_2), 117.1 (C), 117.9 (CH), 120.1 (C), 124.9 (CH), 129.3 (CH), 129.4 (CH), 137.7 (C); MS *m/z* (70 eV) 158 (M^+, 20%), 103 (100%).

Alkyl azides **1b, c, m-t** were prepared by treatment of the corresponding alkyl bromide or iodide with sodium azide in DMSO (G. L'abbé, I. Sannen, W. Dehaen, *J. Chem. Soc., Perkin Trans. 1* **1993**, 27).

1-Azidoundecane (1b) (B. C. Ranu, A. Sarkar, R. J. Chakraborty, *J. Org. Chem.* **1994**, **59**, 4114) : IR (ν_{max}, $CHCl_3$) 2096 (N_3) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83-0.95 (3H, m), 1.21-1.43 (16H, m), 1.52-1.66 (2H, m), 3.1-3.3 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8 (CH_3), 23.3 (CH_2), 27.4 (CH_2), 29.5 (CH_2), 29.8 (CH_2), 30.0 (CH_2), 30.1 (CH_2), 30.2 (CH_2), 30.3(CH_2), 32.6 (CH_2), 52.2 (CH_2).

3-Phenylpropyl azide (1c) (R. M. Moriarty, R. C. Reardon, *Tetrahedron* **1970**, *26*, 1379): IR (ν_{max}, $CHCl_3$) 2096 (N_3) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.91 (2 H, dt, J_d = 7.5, J_t = 6.7 Hz), 2.70 (2 H, t, J = 7.5 Hz), 3.27 (2 H, t, J = 6.7 Hz), 7.16-7.24 (3 H, m), 7.26-7.32 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4 (CH_2), 32.7 (CH_2), 50.6 (CH_2), 126.1 (CH), 128.4 (CH), 128.5 (CH), 140.8 (C).

2-Phenylethyl azide (1m) (A. R. Katritzky, G. Liso, E. Lunt, R. C. Patel, S. S. Thind, A. Zia, *J. Chem. Soc., Perkin Trans. 1* **1980**, 849): IR (ν_{max}, $CHCl_3$) 2097 (N_3) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.89 (2 H, t, J = 7.3 Hz), 3.49 (2 H, t, J = 7.3 Hz), 7.18-7.23 (2 H, m), 7.23-7.27 (1 H, m), 7.29-7.35 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.3 (CH_2), 52.4 (CH_2), 126.7 (CH), 128.6 (CH), 128.7 (CH), 138.0 (C).



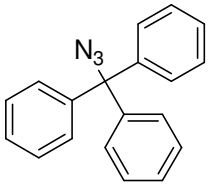
(*E*)-1-(5-azidopent-1-enyl)benzene (1n). $NiCl_2$ was dissolved in 2 ml of water, next a solution of PPh_3 in glacial acetic acid was added and the resulting mixture was stirred for 24 hours. The green suspension was filtered and washed with diethyl ether giving the resulting $(Ph_3P)_2NiCl_2$ in 80% yield. (Venanzi, *J. Chem Soc*. **1958**, 719).

5-Phenyl-(*E*)-4-penten-1-ol was prepared by adding a solution of phenylmagnesium bromide (10 mmol) to an etheral suspension of $(Ph_3P)_2NiCl_2$ (1 mmol) under argon. The solvent was then removed and benzene was added together with 10 mmol of dihydropyran.The final solution was refluxed for 20 hours. The cooled mixture was poured into a saturated ammonium chloride solution and extracted with diethyl ether. The mixture was then chromatographed over silica gel giving the desired alcohol in 70% yield. (Analytical data were comparable with those reported by E. Wenkert, *J. Org. Chem*. **1984**, *49*, 4894-4899.)

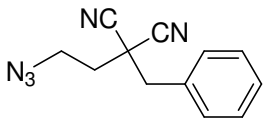
(*E*)-5-Phenylpent-4-enyl-4-methylbenzenesulfonate was prepared by adding 5-phenyl-(*E*)-4-penten-1-ol and tosyl chloride to a solution of triethylamine in dichloromethane. After 4 days under vigorous stirring the mixture was filtered and washed with water and then extracted with diethyl ether. The yield was quantitative. ^1H NMR (400 MHz, $CDCl_3$) δ 1.74-1.85 (2H, m), 2.35 (2H, dq, J_q = 7.4 Hz, J_d = 1.9 Hz), 2.43 (3H, s), 4.04 (2H, t, J_t = 6.4 Hz), 5.53 (1H, dt, J_d = 11.6 Hz, J_t = 7.2 Hz), 6.42 (1H, br dt, J_d = 11.6 Hz, J_t = 1.8 Hz), 7.17-7.35 (7H, m), 7.72-7.77 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9 (CH_3), 24.7 (CH_2), 29.3

(CH_2), 70.1 (CH_2), 127 (CH), 128.1 (CH) 128.4 (CH), 129.9 (CH), 130.4 (CH), 130.6 (CH), 133.3 (C), 137.4 (C), 144.9 (C).

The crude (*E*)-5-phenylpent-4-enyl-4-methylbenzenesulfonate was directly reacted without further purification with NaN_3 in an acetone/water mixture at 40 °C for 2 days giving **1n** in 75% yield. IR (ν_{max}, $CHCl_3$) 2098 (N_3) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.69-1.78 (2H, m), 2.41 (2H, dq, J_q = 7.3 Hz, J_d = 1.9 Hz), 3.28 (2H, t, J_t = 6.9 Hz), 5.62 (1H, dt, J_d = 11.6 Hz, J_t = 7.3 Hz), 6.47 (1H, br dt, J_d = 11.6 Hz, J_t = 1.9 Hz), 7.17-7.38 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7 (CH_2), 29.0 (CH_2), 50.9 (CH_2), 126.7 (CH), 128.2 (CH), 128.7 (CH), 130.0 (CH), 130.9 (CH), 137.3 (C).

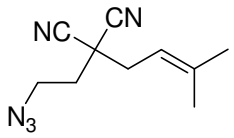


Azidotriphenylmethane (1w). Sodium azide (5 eq.) was added to a solution of triphenylmethyl bromide (5 mmol) in DMSO in the presence of molecular sieves under an argon atmosphere. The reaction was controlled several times by GC-MS until the concentration of bromide remained constant. Then the mixture was poured into water at 0 °C, extracted with diethyl ether, dried over $MgSO_4$ and filtered. By chromatography over silica gel, triphenylmethanol was isolated together with a 30% of **1w**. The triphenylmethyl alcohol (1 eq.) obtained was added to a cooled solution (−5 °C) of sodium azide (2 eq.) and trifluoroacetic acid (5 eq.) in $CHCl_3$. The resulting mixture was stirred for 4 hours at −5 °C and was then allowed to reach room temperature. The mixture was neutralised with a solution of ammonia (12%) and the organic layer separated, washed with water, dried and filtered to give 1w (95%) as a white solid. (IR and ^1H-NMR data were comparable with those reported by F. Franceschi, E. Solari, C. Floriani, M. Rosi, A. Chiesi-Villa, C. Rizzoli, *Chem. Eur. J.* **1999**, *5*, 707-721.); ^1H NMR (400 MHz, $CDCl_3$) δ 63.9 (C), 127.7 (CH), 128.2 (CH), 128.4 (CH), 143.1 (C).

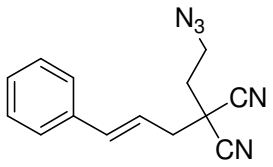


2-(2-Azidoethyl)-2-benzylmalononitrile (1o)[1a]: mp = 42-43 °C; IR (ν_{max}, $CHCl_3$) 2241 (CN) and 2098 (N_3) cm^{-1}; ^1H NMR (300 MHz) δ 2.17 (2 H, t, *J* = 7.0 Hz), 3.24 (2 H, s), 3.67 (2 H, t, *J* = 7.0 Hz), 7.32-7.43 (5 H, m); ^{13}C NMR (75 MHz) δ 36.59 (CH_2), 37.50 (C), 44.16

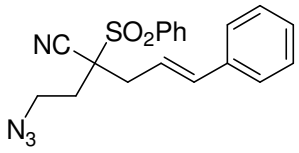
(CH_2), 47.89 (CH_2), 115.07 (CN), 129.68 (CH), 130.89 (CH), 131.99 (C); MS *m/z* (70 eV) (rel inten) 225 (M^+, <1), 197 (3), 118 (43), 91 (100).



2-(2-Azidoethyl)-2-(3-methyl-2-butenyl)malononitrile (1p)[1a]: oil; IR (ν_{max}, neat) 2249 (CN) and 2106 (N_3) cm^{-1}; ^1H NMR (300 MHz) δ 1.73 (3 H, br d, *J* = 1.1 Hz), 1.83 (3 H, br d, *J* = 0.8 Hz), 2.17 (2 H, t, *J* = 7.2 Hz), 2.73 (2 H, d, *J* = 7.7 Hz), 3.68 (2 H, t, *J* = 7.1 Hz), 5.28 (1 H, t quint, J_t = 7.7 Hz, J_q = 1.4 Hz); ^{13}C NMR (75 MHz) δ 18.31 (CH_3), 25.91 (CH), 35.46 (CH_2), 36.54 (CH_2), 47.22 (CH_2), 113.96 (CH), 114.73 (CN), 141.31 (C); MS (ESI) 226 (M + Na)$^+$.



2-(2-Azidoethyl)-2-[(*E*)-3-phenyl-2-propenyl]malononitrile (1q)[1a]: mp = 26-27 °C; IR (ν_{max}, $CHCl_3$) 2249 (CN) and 2094 (N_3) cm^{-1}; ^1H NMR (200 MHz) δ 2.14 (2 H, t, *J* = 7.2 Hz), 2.85 (2 H, br d, *J* = 8.0 Hz), 3.64 (2 H, t, *J* = 7.2 Hz), 6.19 (1 H, dt, J_d = 15.2 Hz, J_t = 8.0 Hz), 6.69 (1 H, br d, *J* = 15.2 Hz), 7.21-7.53 (5 H, m); ^{13}C NMR (50 MHz) δ 36.02 (CH_2), 41.72 (CH_2), 47.68 (CH_2), 115.04 (CN), 119.11 (CH), 127.24 (CH), 129.13 (CH), 129.26 (CH), 136.03 (C), 138.73 (CH); MS *m/z* (70 eV) (rel inten) 251 (M^+, 2), 223 (M^+ – 28, 18), 222 (61), 117 (100), 91 (30).

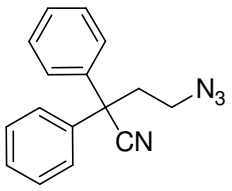


2-(2-Azidoethyl)-5-phenyl-2-(phenylsulfonyl)-4-pentenenitrile (1r).[16] 5-Phenyl-2-(phenylsulfonyl)-4-pentenenitrile was prepared in 70% yield from phenylsulfonylacetonitrile and cinnamyl bromide following a general method reported in the literature for the synthesis of 2-alkyl-2-aryl(phenylsulfonyl)acetonitriles (A. S. Abd-El-Aziz, C. R. de Denus, H. M. Hutton, *Can. J. Chem.* **1995**, *73*, 289); ^1H NMR (300 MHz, $CDCl_3$) δ 2.80 (1 H, dddd, J_1 = 14.1, J_2 = 10.4, J_3 = 7.4, J_4 = 1.4 Hz), 3.10 (1 H, dddd, J_1 = 14.1, J_2 = 7.4, J_3 = 4.5, J_4 = 1.4 Hz), 4.03 (1 H, dd, J_1 = 10.4, J_2 = 4.5 Hz), 6.08 (1 H, dt, J_d = 15.7, J_t = 7.4 Hz), 6.59 (1 H, dt,

J_d = 15.7, J_t = 1.1 Hz), 7.23-7.34 (5 H, m), 7.59-7.66 (2 H, m), 7.72-7.78 (1 H, m), 8.01-8.05 (2 H, m) (a ^{1}H NMR spectrum is reported in: X. Lu, X. Jiang, X. Tao, *J. Organomet. Chem.* **1988**, *344*, 109); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.8 (CH_2), 57.8 (CH), 114.1 (C), 121.0 (CH), 126.9 (CH), 128.6 (C), 129.0 (CH), 130.0 (CH), 130.1 (CH), 135.8 (CH), 135.9 (C), 136.3 (CH).

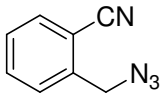
5-Phenyl-2-(phenylsulfonyl)-4-pentenenitrile was alkylated with 1,2-dibromoethane according to a reported general alkylation procedure (E. Diez-Barra, A. De La Hoz, A. Moreno, P. Sanchez-Verdù, *J. Chem. Soc., Perkin Trans. 1* **1991**, 2589) to give 2-(2-bromoethyl)-5-phenyl-2-(phenylsulfonyl)-4-pentenenitrile (92%); IR (ν_{max}, $CHCl_3$) 2237 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51-2.77 (2 H, m), 2.81 (2 H, dd, J_1 = 7.6, J_2 = 1.4 Hz), 3.53-3.69 (2 H, m), 6.06 (1 H, dt, J_d = 15.6, J_t = 7.5 Hz), 6.57 (1 H, dt, J_d = 15.6, J_t = 1.3 Hz), 7.24-7.38 (5 H, m), 7.62-7.72 (2 H, m), 7.75-7.84 (1 H, m), 8.00-8.09 (2 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5 (CH_2), 35.0 (CH_2), 37.1 (CH_2), 65.9 (C), 115.8 (C), 119.6 (CH), 126.9 (CH), 128.8 (CH), 129.1 (CH), 130.0 (CH), 131.2 (CH), 134.2 (C), 136.0 (CH), 136.1 (C), 137.7 (CH); MS *m/z* (70 eV) 405 (M^+ + 2, <1%), 403 (M^+, <1%), 263 (99%), 261 (100%).

Treatment of 2-(2-bromoethyl)-5-phenyl-2-(phenylsulfonyl)-4-pentenenitrile with sodium azide in DMSO gave azide **1r** (85%); IR (ν_{max}, $CHCl_3$) 1152 (SO_2Ph), 2102 (N_3), and 2254 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (1 H, ddd, J_1 = 14.7, J_2 = 8.5, J_3 = 6.5 Hz), 2.40 (1 H, ddd, J_1 = 14.7, J_2 = 8.5, J_3 = 6.5 Hz), 2.88 (2 H, dd, J_1 = 7.4, J_2 = 1.1 Hz), 3.57-3.77 (2 H, m), 6.07 (1 H, dt, J_d = 15.7, J_t = 7.4 Hz), 6.55 (1 H, dt, J_d = 15.7, J_t = 1.2 Hz), 7.21-7.39 (5 H, m), 7.60-7.71 (2 H, m), 7.73-7.83 (1 H, m), 8.00-8.10 (2 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.1 (CH_2), 37.4 (CH_2), 47.6 (CH_2), 64.4 (C), 116.2 (C), 119.8 (CH), 126.9 (CH), 128.7 (CH), 129.1 (CH), 130.0 (CH), 131.2 (CH), 134.2 (C), 135.9 (CH), 136.1 (C), 137.6 (CH); MS (ESI) 389 (M^+ + Na, 100%), 367 (M^+ + 1, 10%).



4-Azido-2,2-diphenylbutanenitrile (1s)[1a]: G. L'abbé, I. Sannen, Dehaen, W. *J. Chem. Soc., Perkin Trans. 1* **1993**, 27; mp = 46 °C; spectral data not reported. IR (ν_{max}, $CHCl_3$) 2103 (N_3) and 2238 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.62-2.72 (2 H, m), 3.32-3.43 (2 H, m), 7.27-7.42 (10 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.1 (CH_2), 47.8 (CH_2), 49.3 (C),

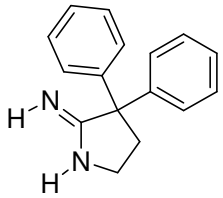
121.3 (C), 126.5 (CH), 128.2 (CH), 129.1 (CH), 139.0 (C); MS *m/z* (70 eV) 234 (M^+ – 28, 19%), 192 (36%), 105 (100%).



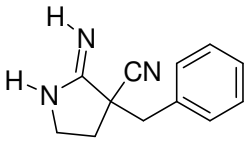
2-Azidomethylbenzonitrile (1t)[1a]: G. L'abbé, I. Sannen, Dehaen, W. *J. Chem. Soc., Perkin Trans. 1* **1993**, 27.

Characterisation Data for All the Reaction Products

All the amines obtained from azides **1a-m** are commercially available compounds and their identification was based on spectral comparison with authentic samples.

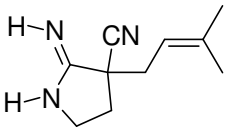


3,3-Diphenyl-2-pyrrolidinimine (4s). mp = 209.3-210 °C; IR (ν_{max}, $CHCl_3$) 3504 (NH), 3403 (NH), 1650 (C=N) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.85 (2 H, t, *J* = 6.4 Hz), 3.58 (2 H, t, *J* = 6.4 Hz), 9.12 (2 H, br s), 7.21-7.28 (5 H, m), 7.30-7.40 (5 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.8 (CH_2), 44.5 (CH_2), 61.1 (C), 127.8 (CH), 128.1 (CH), 128.9 (CH), 139.0 (C), 173.7 (C); MS (ESI) 237 (M^+ + 1). Anal. calcd for $C_{16}H_{16}N_2$: C, 81.33; H, 6.82; N, 11.85. Found: C, 81.46; H, 6.81; N, 11.73.

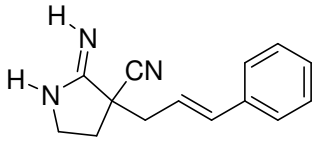


3-Benzyl-2-imino-3-pyrrolidinecarbonitrile (4o).[1a] mp = 160-161 °C; IR (ν_{max}, $CHCl_3$) 3400 (NH), 2234 (CN) and 1664 (C=N) cm^{-1} ;^1H NMR (300 MHz) δ 2.22-2.43 (2 H, m), 3.00 (1 H, A part of AB, *J* = 13.7 Hz), 3.13 (1 H, B part of AB, *J* = 13.7 Hz), 3.28-3.37 (1 H, m), 3.63 (1 H, ddd, J_1 = 11.4 Hz, J_2 = 8.3 Hz, J_3 = 3.0 Hz), 4.85 (2 H, br s, NH), 7.31-7.39 (5 H, m); ^{13}C NMR (75 MHz) δ 36.53 (CH_2), 41.82 (CH_2), 49.83 (C), 53.56 (CH_2), 121.35 (CN), 128.56 (CH), 129.34 (CH), 130.70 (CH), 135.00 (C), 162.89 (C=N); MS *m/z* (70 eV) (rel

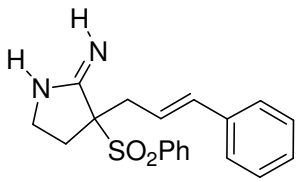
inten) 199 (M^+, 8), 91 (100). Anal. calcd for $C_{12}H_{13}N_3$: C, 72.33; H, 6.58; N, 21.09. Found: C, 72.28; H, 6.59; N, 21.13.



2-Imino-3-(3-methyl-2-butenyl)-3-pyrrolidinecarbonitrile (4p).[1a] mp = 110.9-112.6 °C; IR (ν_{max}, $CHCl_3$) 3405 (NH), 3501 (NH), 2238 (CN) and 1664 (C=N) cm^{-1}; ^1H NMR (300 MHz) δ 1.68 (3 H, d, J = 1.1 Hz), 1.78 (3 H, d, J = 0.8 Hz), 2.11-2.19 (1 H, ddd, J_1 = 13.0 Hz, J_2 = 7.2 Hz, J_3 = 3.9 Hz), 2.34-2.50 (2 H, dd, J_1 = 8.5 Hz, J_2 = 7.1 Hz), 2.58 (1 H, dd, J_1 = 14.6 Hz, J_2 = 7.7 Hz), 3.69 (1 H, ddd, J_1 = 13.6 Hz, J_2 = 8.5 Hz, J_3 = 3.9 Hz), 3.50-3.63 (1 H, m), 5.24 (1 H, t quint, J_t = 7.4 Hz, J_q = 1.4 Hz), 4.91 (2 H, br s, NH); ^{13}C NMR (75 MHz) δ 18.11 (CH_3), 25.91 (CH_3), 34.11 (CH_2), 35.82 (CH_2), 48.00 (C), 52.93 (CH_2), 116.8 (CH), 55.14 (CH_2), 120.71 (CN), 138.08 (C), 162.60 (C=N); MS (ESI) 178 $(M + 1)^+$. Anal. calcd for $C_{10}H_{15}N_3$: C, 67.76; H, 8.53; N, 23.71. Found: C, 67.87; H, 8.51; N, 23.62.

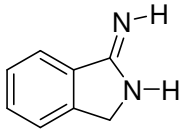


2-Imino-3-[(*E*)-3-phenyl-2-propenyl)-3-pyrrolidinecarbonitrile (4q).[1a] IR (ν_{max}, $CHCl_3$) 3404 (NH), 2238 (CN) and 1665 (C=N) cm^{-1}; ^1H NMR (300 MHz) δ 2.18-2.32 (1 H, m), 2.39-2.54 (1 H, m), 2.55-2.69 (1 H, m), 2.70-2.82 (1 H, m), 3.50-3.77 (2 H, m), 4.78 (2 H, br s, NH), 6.20 (1 H, m), 6.60 (1 H, br d, J = 16.0 Hz), 7.16-7.48 (5 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.8 (CH_2), 39.2 (CH_2), 47.9 (C), 53.1 (CH_2), 120.4 (CN), 121.8 (CH), 126.4 (CH), 128.0 (CH), 128.6 (CH), 135.9 (CH), 136.2 (C), 162.0 (C); MS *m/z* (70 eV) (rel inten) 225 (M^+, 12), 117 (100), 91 (51). Anal. calcd for $C_{14}H_{15}N_3$: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.59; H, 6.72; N, 18.69.



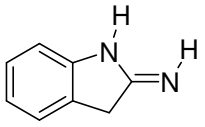
3-(3-Phenyl-2-propenyl)-3-(phenylsulfonyl)-2-pyrrolidinimine (4r).[1a] mp = 180.1-182.5 °C; IR (ν_{max}, $CHCl_3$) 3491 (NH), 3395 (NH), 1661 (C=N) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.17 (1 H, ddd, J_1 = 14.6, J_2 = 8.9, J_3 = 5.7 Hz), 2.39 (1 H, ddd, J_1 = 14.6, J_2 = 8.6,

J_3 = 4.4 Hz), 2.79 (1 H, ddd, J_1 = 14.1, J_2 = 8.7, J_3 = 5.7 Hz), 2.88 (1 H, ddd, J_1 = 13.9, J_2 = 9.0, J_3 = 0.8 Hz), 3.25 (1 H, ddd, J_1 = 13.9, J_2 = 5.7, J_3 = 1.7 Hz), 3.30 (1 H, ddd, J_1 = 13.9, J_2 = 9.0, J_3 = 4.4 Hz), 5.03 (2 H, br s), 6.05 (1 H, ddd, J_1 = 15.6, J_2 = 9.3, J_3 = 5.5 Hz), 6.56 (1 H, d, J = 15.7 Hz), 7.18-7.37 (5 H, m), 7.53-7.63 (2 H, m), 7.65-7.74 (1 H, m), 7.92-8.00 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.6 (CH_2), 34.2 (CH_2), 52.7 (CH_2), 77.2 (C), 121.7 (CH), 126.3 (CH), 127.7 (CH), 128.5 (CH), 129.1 (CH), 130.0 (CH), 134.3 (CH), 135.3 (C), 135.8 (CH), 136.5 (C), 159.9 (C); MS *m/z* (70 eV) 340 (M^+, 1%), 199 (100%); MS ESI 363 (M^+ + Na, 90%), 341 (M^+ + 1, 100%). Anal. calcd for $C_{19}H_{20}N_2O_2S$: C, 67.03; H, 5.29; N, 8.23. Found: C, 67.16; H, 5.28; N, 8.32.



1-Isoindolinimine (4t).[1a, 27] IR (ν_{max}, $CHCl_3$) 3417 (NH), 3326 (NH) and 1637 (C=N) cm^{-1}; ^{1}H NMR (300 MHz) δ 3.80 (2 H, br s), 4.70 (2 H, s), 7.38-8.00 (3 H, m), 8.15 (1 H, d, J = 8.5 Hz); MS *m/z* (70 eV) (rel inten) 132 (M^+, 88), 104 (100), 77 (54). Anal. calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.77; H, 6.12; N, 21.11.

The trifluoroacetate was also obtained and characterised, since it seems less susceptible to tautomerism with respect to the free base. ^{1}H NMR (300 MHz, DMSO-d_6/TFA) δ 4.83 (2 H, s), 7.60-7.70 (1 H, m), 7.75-7.85 (2 H, m), 8.30-8.37 (1 H, m), 9.45 (1 H, s, NH), 9.85 (1 H, s, NH), 10.59 (1 H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6/TFA) δ 51.4 (CH_2), 115.4 (CF_3), 124.0 (CH), 124.2 (CH), 128.4 (C), 128.6 (CH), 133.7 (CH), 144.5 (C), 158.9 (CO, TFA), 164.0 (C).



1,3-Dihydro-2*H*-indol-2-imine (4s). This compound is not stable and readily decomposed after the reaction mixture was quenched with water (a deep violet color developed after few minutes). Therefore, it was characterised as trifluoroacetate, as previously reported (P. Diana, P. Barraja, A. Lauria, A. M. Almerico, G. Dattolo, G. Cirrincione, *Tetrahedron* **2000**, *56*, 5177). The trifluoroacetate was obtained by quenching the reaction mixture directly with TFA, evaporating acetonitrile and excess TFA, and dissolving the residue in DMSO-d_6/TFA. ^{1}H NMR (400 MHz, DMSO-d_6/TFA) δ 4.12 (2 H, s), 7.18 (2 H, m), 7.33 (1 H, m), 7.39 (1 H, m), 9.39 (1 H, s, NH), 9.59 (1 H, s, NH), 11.95 (1 H, s, NH)

[above lit. ^{1}H NMR (200 MHz, DMSO-d_6/TFA) δ 4.17 (2 H, s), 7.12 (1 H, dt), 7.18 (1 H, dt), 7.27 (1 H, dd), 7.39 (1 H, dd), 9.86 (1 H, s), 10.02 (1 H, s), 12.41 (1 H, s)]; ^{13}C NMR (100 MHz, DMSO-d_6/TFA) δ 37.7 (CH_2), 113.9 (CH), 117.3 (CF_3), 126.4 (CH), 126.6 (CH), 128.1 (C), 130.4 (CH), 144.5 (C), 161.2 (CO, TFA), 173.9 (C).

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CHAPTER 4

Electron Spin Resonance

Spin and Magnetic Moment of Electron

Spin is an intrinsic, non classical, orbital angular momentum. The concept of spin was suggested by Uhlenbeck and Goudsmit in 1925[1] to account for the splitting of lines in the electronic spectra of alkali-metal atoms in a magnetic field. Such splitting, known as the *Zeeman effect*, could not arise from an orbital angular momentum, which is zero for electrons in the s orbitals of an alkali-metal atom. Spin functions were introduced theoretically in 1926 by Pauli, as a complement of spatial functions.[2] Later, Dirac[3] showed that spin emerges without additional postulates from a relativistic treatment of quantum mechanics. According with Pauli, a spin quantum number $S = ½$ is assigned to an electron. In the presence of a strong external magnetic field **B**, a second magnetic quantum number $M_S = +1/2$ or $-1/2$ becomes effective, and the functions associated with M_S are denoted α and β, respectively. The spin can be represented by a vector **S** precessing about **B** in the z direction (Figure 1).

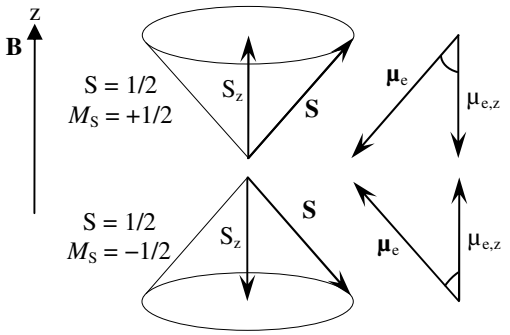


Figure 1

The length of this vector is $|\mathbf{S}| = \hbar\sqrt{S(S+1)} = \hbar\sqrt{3/2}$, where $\hbar = h/2\pi$ and $h = 6.6262\cdot10^{-34}$ J·s is Planck's constant. The component S_z in the z direction is $\hbar M_S = +\hbar/2$ or $-\hbar/2$, with the former being parallel and the latter antiparallel to the z direction. The spin with $M_S = +1/2$ is also called spin up (↑) and α, and its counterpart with $M_S = -1/2$ is named spin down (↓) and β. While precessing about **B**, the vector **S** traces a conic area with half-opening angle of $\arccos(1/\sqrt{3}) = 54.73°$. The components S_x and S_y, perpendicular to the z

direction of **B**, cannot be determined individually; however, the sum of their squares, $S_x^2 + S_y^2 = |\mathbf{S}|^2 - S_z^2 = \hbar\ [S(S+1) - M_S^2] = \hbar\ [3/4 - 1/4] = \hbar/2$ is an observable quantity.

Due to its spin an electron possesses a magnetic moment $\boldsymbol{\mu}_e$ which is proportional to **S** (Eq. 1).

$$\boldsymbol{\mu}_e = [g_e(-e)/(2m_e)]\mathbf{S} \qquad \text{Eq. 1}$$

with $|\boldsymbol{\mu}_e| = [g_e e/(2m_e)]\ \hbar\sqrt{S(S+1)}$ and $\mu_{e,z} = [g_e(-e)/(2m_e)]\ \hbar M_S$. Here, g_e is the (dimensionless) *g factor* of the electron, which is 2.0023 for a free electron (0.0023 is the relativistic correction), $e = 1.60022 \cdot 10^{-19}$ C is the elementary charge, and $m_e = 9.1096 \cdot 10^{-31}$ kg is the rest mass of the electron. Setting $\hbar e/(2m_e) = \mu_B = 9.2741 \cdot 10^{-24}$ A·m^2 or J·T^{-1}, where μ_B is the *Bohr magneton*, and T = Tesla = V·s·m^2 is the unit of magnetic field **B**, Eq. 1 becomes

$$\boldsymbol{\mu}_e = -[g_e \mu_B/\hbar]\mathbf{S} \qquad \text{Eq. 2}$$

with $|\boldsymbol{\mu}_e| = g_e \mu_B \sqrt{S(S+1)} = g_e \mu_B \sqrt{3}/2$ and $\mu_{e,z} = -g_e \mu_B M_S = -g_e \mu_B(\pm 1/2)$. As $g_e \approx 2$, $|\boldsymbol{\mu}_e| \approx \mu_B\sqrt{3}$ and $\mu_{e,z} \approx \pm \mu_B$. Due to the negative charge of the electron, the direction of $\boldsymbol{\mu}_e$ is opposite to that of **S** (Figure 1).

Zeeman Splitting and Resonance Condition

By virtue of its magnetic moment $\boldsymbol{\mu}_e$, the electron interacts with the external magnetic field **B**, the interaction energy E being equal to the negative value of the scalar product of $\boldsymbol{\mu}_e$ and **B**. Accordingly, this energy is

$$E = -\boldsymbol{\mu}_e \cdot \mathbf{B} = -\mu_{e,z} B = -(-g_e \mu_B M_S)B = +g_e \mu_B M_S B \qquad \text{Eq. 3}$$

where $|\mathbf{B}| = B$ the field strength, and $\mu_{e,z} = -g_e \mu_B M_S$. Therefore E is different for the two sorts of spin (Figure 2):

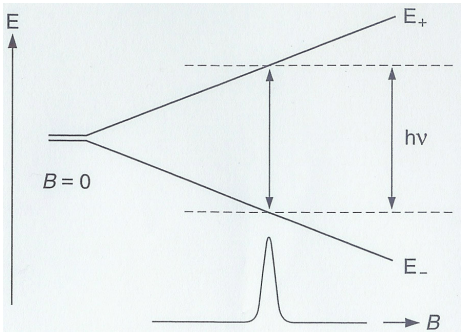


Figure 2

$E_+ = (+1/2) g_e \mu_B B$ for $M_S = +1/2$ (spin up; α)

$E_- = (-1/2) g_e \mu_B B$ for $M_S = -1/2$ (spin down; β) Eq. 4

The difference between E_+ and $E_- = g_e \mu_B B$ is the electron-Zeeman splitting, which is proportional to the strength, B, of the applied external magnetic field **B** (Figure 2). Transition $E_+ \rightarrow E_-$ and $E_- \rightarrow E_+$ between the two levels, comply with the selection rule $\Delta M_S = \pm 1$. These transitions can be induced by electromagnetic radiation hν, provided that

(1) the direction of the magnetic field associated with this radiation is perpendicular to that (z) of the external magnetic field **B**, it lies in the xy plane (Figure 2);

(2) the energy of the radiation is equal to that of the *Zeeman splitting*

$$h\nu = E_+ - E_- = g_e \mu_B B \qquad \text{Eq. 5}$$

a relation known as the resonance condition. This condition can be expressed as

$$\nu = g_e (\mu_B/h) B = \gamma_e B \quad \text{or} \quad \omega = g_e (\mu_B/\hbar) B = 2\pi\gamma_e B \qquad \text{Eq. 6}$$

where ν (in Hz = s^{-1}) is the frequency of the electromagnetic radiation, and $\omega = 2\pi\nu$ is the circular frequency, which is also the frequency of the spin **S** precessing about **B** (the *Larmor frequency*) at resonance. The conversion factor γ_e of the frequency into the field strength B, $\gamma_e = \nu/B = g_e\mu_B/h$, is called the *gyromagnetic* ratio of the electron. For g_e = 2.0023, $\gamma_e = 2.8024 \cdot 10^{10}$ Hz/T = 28.024 MHz/mT.

To satisfy the resonance condition, one can vary ν or B or both. For technical reasons, the frequency ν is kept constant and the field strength B is varied to bring it to the value at which

the resonance condition is fulfilled. One generally uses the microwave (MW) X band with a frequency v of ca. 9500 MHz, which requires a field strength of ca. 340 mT.

Spin-lattice Relaxation

Besides the resonance condition, other prerequisites must be met for a successful electron spin resonance experiment. To observe an ESR signal, a single electron is not sufficient, but many of them are needed. Also, the electrons should not be isolated but must be embedded in a suitable environment (*a lattice*), which is usually provided by atoms and molecules.

The number of electrons in the two Zeeman levels, E_+ and E_-, are their populations n_+ and n_-, respectively. According to the Boltzmann distribution law, the ratio of these population is

$$n_+/n_- = \exp[-(E_+ - E_-)/(kT)] = \exp[-(g_e \mu_B B)/(kT)] \quad \text{Eq. 7}$$

where $k = 1.3806 \cdot 10^{-23}$ J·K^{-1} is the Boltzmann constant, and T is the absolute temperature in K. In the absence of an external magnetic field, n+ is equal to n_-, but for $B > 0$, n_- is larger than n_+, i.e., there is an excess, $\Delta n = n_- - n_+$, of spins in the lower level E_- relative to the higher level E_+. To bring about this excess, some spins in E_+ (α, ↑) must be converted into spins E_- (β, ↓). Such a cooling process, leading to magnetization, requires energy transfer from the spin ensemble to the lattice and is effected by *spin-lattice relaxation* (SLR). The excess Δn_m, at full magnetization at B, is

$$\Delta n_m \approx (n/2)(g_e \mu_B B)/(kT) \quad \text{Eq. 8}$$

where $n = n_+ + n_-$ is the total number of spins in the ensemble. This excess is only slight: for $g_e = 2$, $B = 340$ mT, and $T = 298$ K, it amounts to merely 0.00077n. However, because the probability for an $E_+ \rightarrow E_-$ and an $E_- \rightarrow E_+$ transition is the same, it is due to an excess of this size that the radiation hv gives rise to net ESR absorption.

When the magnetic field is switched on, Δn should increase from 0 to Δn_m as a function of time t (Figure 3)

$$\Delta n = \Delta n_m(1 - \exp[-t/T_{1e}]) \quad \text{Eq. 9}$$

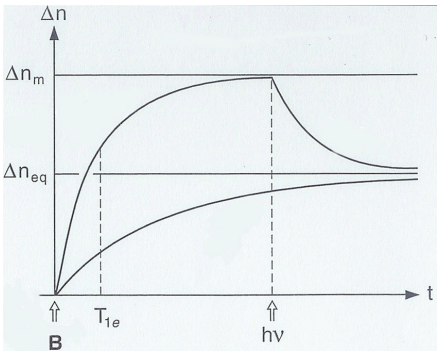


Figure 3

At t = 0 (switching on of *B*), Δn = 0, for t → ∞, Δn → Δn_m, and for t = T_{1e}, Δn = Δn_m(1 − exp[−1]) ≈ Δn_m (2/3). T_{1e} is called the *SLR time* of an electron, in which the number of hot spins drops to 1/e or to ca 1/3. A short or long T_{1e} means an efficient (or inefficient) SLR. This relaxation provides not only the means for magnetization in the field *B* but it also takes care that Δn does not vanish upon continuous radiation *hv*. When *hv* is applied, and if SLR was ineffective, the populations n_+ and n_- would equalize, with Δn decreasing from Δn_m to 0. This is because the number of transition $E_- \rightarrow E_+$ exceed that of $E_+ \rightarrow E_-$. The decrease of Δn known as *saturation*, follows the equation

$$\Delta n = \Delta n_m \exp(-2Pt) \qquad \text{Eq. 10}$$

Where P is the transition probability, common to $E_- \rightarrow E_+$ and $E_+ \rightarrow E_-$. At t = 0 (start of *hv* in **B**), Δn = Δn_m, and for t → ∞, Δn → 0. Fortunately, SLR counteract this effect and consequently, equilibrium is achieved at $0 < \Delta n_{eq} < \Delta n_m$:

$$\Delta n = \Delta n_m/(1 + 2PT_{1e}) \qquad \text{Eq. 11}$$

The dominator $1 + 2PT_{1e}$, referred to as the saturation term, is large when P is high and /or T_{1e} is long and small when P is low and/or T_{1e} is short. The most important mechanism of SLR is *spin-orbit coupling*, which is substantial for heavy atoms. For organic radicals lacking such atoms, SLR is not very efficient and T_{1e} is rather long. Therefore, to keep the saturation term PT_{1e} as small as possible, P must be relatively low, which is achieved by attenuating the intensity of *hv*. However because the ESR absorption is proportional to both P and Δn_{eq}, i.e. to $P/(1 + 2PT_{1e})$, the attenuation should be carried on until the P value is optimal for observing a strong signal. Such P value is not the same for different samples investigated: the shorter (or longer) T_{1e} is, the larger (or smaller) is the allowed intensity of *hv*. T_{1e} can be determined by

saturation experiments, in which the term PT_{1e} is measured as a function of the applied intensity of *hv*.

Line-width and Line-form

The Heisenberg uncertainty relation, $\Delta E \cdot \Delta t \approx \hbar$, can be expressed by an equivalent formula:

$$\Delta v \cdot \Delta t = \gamma_e \Delta B \cdot \Delta t \approx 1/(2\pi) \qquad \text{Eq. 12}$$

where Δv ($\gamma_e \Delta B$) (in Hz) or ΔB (in mT) stands for the width of the ESR signal, and Δt (in s) is the lifetime of a spin state. A long- (or short-) lived state thus gives thus rise to a narrow (or broad) ESR signal.

The lifetime, Δt, of the spin state α (↑) or β (↓) is determined by the relaxation time T_{1e} and T_{2e}:

$$1/\Delta t \approx (1/T_{1e}) + (1/T_{2e}) \qquad \text{Eq. 13}$$

where T_{1e} is the spin-lattice relaxation (SLR) time and T_{2e} is the spin-spin relaxation (SSR) time of electron. Whereas SLR governs energy exchange between the spin ensemble and the environment (lattice), SSR comprises interactions within the ensemble itself without such an exchange. For instance, two radicals, 1 and 2, may interchange the different states of their electron spin, so that their total energy is not changed, but, nevertheless, the lifetime of an individual spin is reduced:

$$\begin{matrix}\text{Radical} \\ \text{Spin}\end{matrix} \quad \begin{pmatrix}1 & 2 \\ \alpha & \beta\end{pmatrix} \rightarrow \begin{pmatrix}1 & 2 \\ \beta & \alpha\end{pmatrix}$$

Such a phenomenon, referred to as Heisenberg exchange, is particularly effective when the spin-bearing orbitals of the radicals overlap, which occurs with high radical concentration. As mentioned above, T_{1e} is long for organic radicals without heavy atoms (10^{-3} to 10^{-1} s). Because T_{2e} is much shorter (10^{-5} to 10^{-7} s), the relations $T_{1e} >> T_{2e}$ and $1/T_{1e} << 1/T_{2e}$ generally hold, leading to

$$1/\Delta t \approx 1/T_{2e} \qquad \text{Eq. 14}$$

Hence, according to the uncertainty principle, the line-width becomes

$$\Delta\nu = \gamma_e \Delta B \; \alpha \; 1/\Delta t \approx 1/T_{2e} \qquad \text{Eq. 15}$$

With $\Delta\nu \approx 10^5$ to 10^7 Hz and ΔB lies roughly in the range between 0.001 and o.1 mT. Thus T_{2e} can be determined from the measurements of the line-width ΔB.

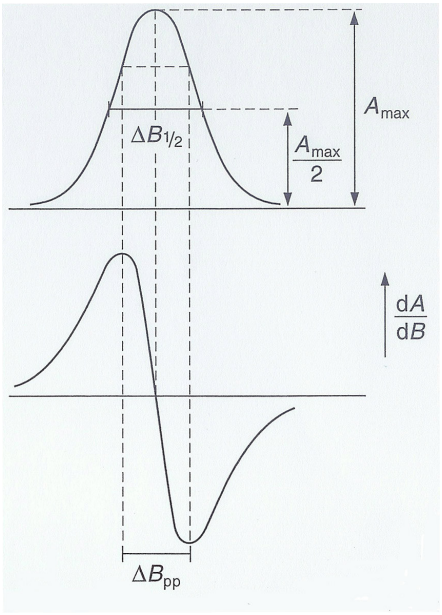


Figure 4

The ESR signal is usually recorded as the first derivative, dA/dB, of the absorption A with respect to B as a function of B (Figure 4). The form of A can be approximated by a *Gaussian* or a *Lorentzian* curve or by an appropriate mixture of both, in which T_{2e} is multiplied by a function of $(T_{1e})^2$, with $(T_{2e})^2$ either in the exponent (Gaussian) or in the denominator (Lorentzian). The characteristic values are A_{max}, the maximum of A, and $\Delta B_{1/2}$, the peak width at its half-height ($A_{max}/2$), and ΔB_{pp}, the peak to peak distance of the derivative curve dA/dB. For the Gaussian, $A_{max} = \gamma_e 2T_{2e}$, with $\Delta B_{1/2} \approx 0.47/(\gamma_e T_{2e})$ and $\Delta B_{pp} \approx 0.85\Delta B_{1/2} \approx 0.40/(\gamma_e T_{2e})$, and for the Lorentzian, $A_{max} = \gamma_e 2T_{2e}$, with $\Delta B_{1/2} \approx 0.32/(\gamma_e T_{2e})$ and $\Delta B_{pp} \approx 0.58\Delta B_{1/2} \approx 0.18/(\gamma_e T_{2e})$. The bell-like form of the Gaussian curve thus has a broader waist and shorter tails than its Lorentzian counterpart.

Spin Multiplicity

Radicals are a special class of paramagnetic molecules that are amenable to ESR spectroscopy. Although *diamagnetism* is a general property of matter, *paramagnetism* is diagnostic of molecules with an overall nonzero magnetic moment of their electrons. In such molecules the paramagnetism masks the diamagnetism, because the contribution of the former is two orders of magnitude larger than that of the latter. In atoms, magnetic moments are due to the electron spins as well as to nonzero orbital angular momenta characteristic of electrons in other than spherically shaped s orbitals. However, in molecules generally, and in organic molecules particularly, the orbital angular momenta are essentially ineffective, although they can slightly alter the g_e factor via spin orbit coupling. The paramagnetism of organic molecules thus arises almost entirely from the electron spins.

When speaking about magnetic resonance of such molecules, one is, therefore, justified in using the name *electron spin resonance* (ESR) instead of the more general expression *electron paramagnetic resonance* (EPR). Because organic molecules contain many electrons, the total spin function is derived from contributions by all electrons. These contributions cancel for most electrons (which occupy orbitals pairwise and have opposite spins). Thus, only electrons with unpaired spins in the singly occupied, usually uppermost, orbital are relevant to the total spin function. The spin-quantum numbers, ½, of the unpaired electrons and the spin multiplicity, $2S+1$, which is even (or odd) for an odd (or even) number of electrons, represent the multitude of the magnetic spin-quantum numbers, $M_S = S, S-1, \ldots\ldots -S$, associated with S. A single unpaired electron thus gives rise to a doublet, because $2S + 1 = 2$ for $S = ½$ and $M_S = +1/2$ or $-1/2$. Two unpaired electrons have either $S = (1/2) - (1/2) = 0$ or $S = (1/2) + (1/2) = 1$, i.e., they lead to a singlet with $2S + 1 = 1$ and $M_S = 0$ or a triplet with $2S + 1 = 3$ and $M_S = +1$, 0, or -1.

The pertinent singlet-spin function is

$$(1/\sqrt{2})(\alpha\beta - \beta\alpha) \quad \text{for } S = 0 \text{ and } M_S = 0 \qquad \text{Eq. 16}$$

and the analogous triplet functions are

$$\begin{aligned} &\alpha\alpha && \text{for } S = 1 \text{ and } M_S = +1 \\ &(1/\sqrt{2})(\alpha\beta - \beta\alpha) && \text{for } S = 1 \text{ and } M_S = 0 \\ &\beta\beta && \text{for } S = 1 \text{ and } M_S = -1 \end{aligned} \qquad \text{Eq. 17}$$

where the first and the second letters in $\alpha\alpha$, $\alpha\beta$, $\beta\alpha$, and $\beta\beta$ refer to the first and the second unpaired electron. The singlet function is *antisymmetric*, whereas the three components of the triplet are *symmetric* with respect to the exchange of the two electrons. Because the spin orbital, which is the product of the spin and the space (orbital) functions of electron, must be antisymmetric in this respect, the total function must be symmetric for the singlet and antisymmetric for the triplet.

Thus for a doublet with $S = 1/2$ and $M_S = +1/2$ or $-1/2$, the resulting values are essentially the same as those given in this chapter, and the illustration of **S** precessing about **B** (Figure 1) is also valid. For a singlet, with $S = M_S = 0$, the vectors **S** and $\boldsymbol{\mu}_e$ vanish, and so does the interactions of $\boldsymbol{\mu}_e$ with **B**. On the other hand, for a triplet, with $S = 1$ and $M_s = +1$, 0, or -1, one obtains

$$|\mathbf{S}| = \hbar\sqrt{2}\,, \quad S_z = +\hbar, 0, \text{ or } -\hbar; \quad |\boldsymbol{\mu}_e| = g_e \mu_B \sqrt{2}\,; \quad \text{and}$$

$$\mu_{e,z} = g_e \mu_B M_S = +g_e \mu_B, 0, \text{ or } -g_e \mu_B \qquad \text{Eq. 18}$$

As $g_e \approx 2$, $|\boldsymbol{\mu}_e| \approx 2\mu_B\sqrt{2}$ and $\mu_{e,z} \approx +2\mu_B$, 0, or $-2\mu_B$, the interaction of $\boldsymbol{\mu}_e$ with **B** is

$$E = \mu_{e,z} B = +g_e \mu_B M_S B = +g_e \mu_B B, 0, \text{ or } -g_e \mu_B B \qquad \text{Eq. 19}$$

for $M_S = +1$, 0, or -1, respectively.

According to the ESR-selection rules, $\Delta M_S = \pm 1$,transition should be allowed between the energy levels with $M_S = +1$ and 0, as well as between those with $M_s = 0$ and -1 when the resonance condition, $h\nu = g_e \mu_B B$, is fulfilled for both kinds of transition. In fact, the transition scheme is more complicated because of interaction between the spin vectors $\mathbf{S}_1$ and $\mathbf{S}_2$ of the unpaired electrons.

The spin multiplicities for any number of unpaired electrons in a molecule can be derived from a branching diagram: (Figure 5)

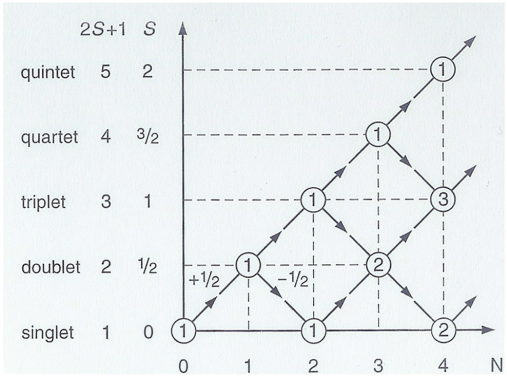


Figure 5

For example, three electrons yield one quartet and two doublets, and four electrons give rise to one quintet, three triplets, and one singlet. Clearly singlets with $|\boldsymbol{\mu}_e| = 0$ are diamagnetic, whereas molecules with higher spin multiplicities should exhibit paramagnetic properties.

The Hyperfine Splitting

In the context of ESR spectroscopy, the enormous importance of the nuclei consists in their magnetic interaction with unpaired electrons. This interaction give rise to the *hyperfine splitting* of ESR spectra, which provides the most important structural information for organic radicals.

The behaviour of a magnetic nucleus X in a field **B** upon irradiation *hv* is also described by formulas analogous to those for an electron. Thus the interaction energy is

$$E = -\boldsymbol{\mu}_n \cdot \mathbf{B} = -\mu_{n,z} B = -g_n \mu_N M_I B \qquad \text{Eq. 20}$$

where $\boldsymbol{\mu}_n$ and g_n are characteristic of X. The resonance condition for observing a signal in nuclear magnetic resonance spectra is

$$hv = g_n \mu_N B \qquad \text{Eq. 21}$$

in account of the selection rules $\Delta M_I = \pm 1$. Because the magneton μ_N is so much smaller than μ_B, the frequency v is substantially lower for NMR ($v = v_n$) than for ESR ($v = v_e$) spectroscopy, even with a higher field strength B; it is usually lies in the region of radio

waves. Analogous to the gyromagnetic ratio, γ_e, of the electron, its nuclear counterpart, γ_n, is defined by

$$\nu_n = \gamma_n B \qquad \text{Eq. 22}$$

For a paramagnetic organic molecule in a magnetic field **B**, the interaction due to the spins of unpaired electrons and magnetic nuclei is the sum of different components. An electron- and nuclear- Zeeman interactions (**S** · **B**) and (**I** · **B**) respectively, a nuclear-nuclear spin coupling (**I** · **I**) and the electron-nuclear interaction, the hyperfine-splitting (**S** · **I**). In a field strength *B* of 0.34 T, generally used in ESR spectroscopy

$$(\mathbf{S} \cdot \mathbf{B}) >> (\mathbf{I} \cdot \mathbf{B}) \approx (\mathbf{S} \cdot \mathbf{I}) >> (\mathbf{I} \cdot \mathbf{I}) \qquad \text{Eq. 23}$$

Because the magnetic electron-nuclear interaction (**S** · **I**) is usually much weaker than the electron Zeeman energy (**S** · **B**), the former can be treated as a perturbation of the latter. The perturbation by hyperfine interaction, which does not depend on B, splits every electron-Zeeman energy level E_+ and E_- into several sublevels.

This hyperfine interaction, E_{hf}, is the sum of the classical dipolar term, E_{dip}, and the "quantum mechanical" term called The Fermi-contact term E_{Fc}:

$$E_{hf} = E_{dip} + E_{Fc} \qquad \text{Eq. 24}$$

The anisotropic term E_{dip} depends on the relative position of the magnetic moments of the unpaired electron μ_e, and the nucleus μ_N. For example when an unpaired electron is in a $2p_z$ orbital of a C atom, the maximum and minimum of E_{dip} are found for the orbital axis in a parallel (z) and perpendicular (x, y) orientation respectively, relative to the direction of **B**. The anisotropic interaction is ineffective when the unpaired electron occupies a spherical orbital. This interaction is preferably studied in single crystals, but can also be observed in glasses and powders. Because electron-nuclear interaction is weaker than its electron-electron counterpart, E_{dip} is generally averaged out to zero by the Brownian motion of molecule in fluid solution, although in a viscous medium an incomplete averaging out merely broadens the ESR lines. Since most study are performed in fluid solution the value of E_{hf} exclusively depends on the isotropic Fermi-contact term E_{Fc}:

$$E_{Fc} = -(2/3)\mu_o(\boldsymbol{\mu}_e \cdot \boldsymbol{\mu}_n)\rho_S(0) = [(2/3)\mu_o g_e g_n \mu_B \mu_N \rho_S(0)]M_S M_I \qquad \text{Eq. 25}$$

in which $\rho_S(0)$ is the *spin density* $\rho_S(x, y, z)$ at the nucleus (x = y = z = 0), where it is contacted by the unpaired electron. Electron spin density ρ_S (x, y, z) is the number of electron per unit of volume at a given site in a molecule, defined by the space coordinates x, y, z. It can be considered as the algebraic sum due to electrons having spin up (↑, M_S = 1/2) and down (↓, M_S = −1/2):

$$\rho_S(x, y, z) = \rho^{\uparrow}(x, y, z) - \rho^{\downarrow}(x, y, z)$$

In diamagnetic molecules ρ_S (x, y, z) = 0, on the other hand, in paramagnetic molecules with at least one unpaired electron , the spin density, on the whole is nonzero. Because the spin up is assigned to the unpaired electron, $\rho^{\uparrow}$ (x, y, z) should be larger than or, at most, equal to $\rho^{\downarrow}$ (x, y, z), i.e., the spin density ρ_S (x, y, z) should generally be positive and rarely zero at some sites in the molecule.

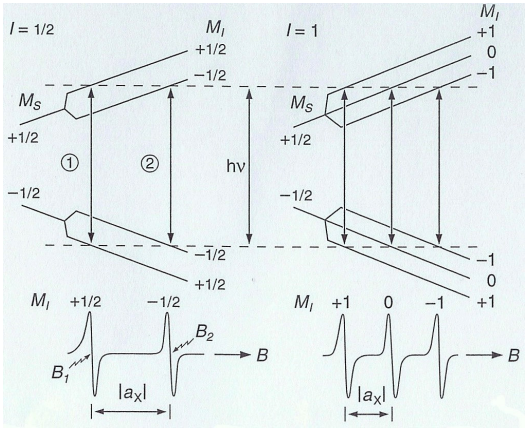


Figure 6

Figure 6 shows the hyperfine splitting by one nucleus X with I = 1/2 and I = 1 for a radical in a magnetic field **B** when both g_n of X and $\rho_S(0)$ are positive. According to the ESR selection rules $\Delta M_S = \pm 1$ and $\Delta M_I = 0$, two transition are allowed for I = 1/2 and three for I = 1. The hyperfine components (lines) have practically the same intensity, because the nuclear magnetization and the differences in populations of the nuclear-Zeeman levels are about three orders of magnitude smaller then their electron counterparts and can be neglected here. The distance between the lines is the absolute value of the hyperfine coupling constant a_X of the

nucleus X. Because $|a_X|$ is independent of field strength **B**, it is usually measured in the unit of this field.

The number of hyperfine lines grows multiplicatively with the number n of magnetic nuclei, because each additional nucleus X splits every line into equidistant $2I + 1$ lines of the same intensity; n non equivalent nuclei thus give rise to $(2I + 1)^n$ lines. However, when n nuclei X are equivalent, some of the lines coincide and their number reduced to $2nI + 1$. The hyperfine pattern then exhibits are characteristic distribution of intensities that is binomial for $I = 1/2$ and can be determined by the use of Pascal's triangle. Figure 7 shows the hyperfine splitting by two equivalent nuclei X with $I = 1/2$ and $I = 1$.

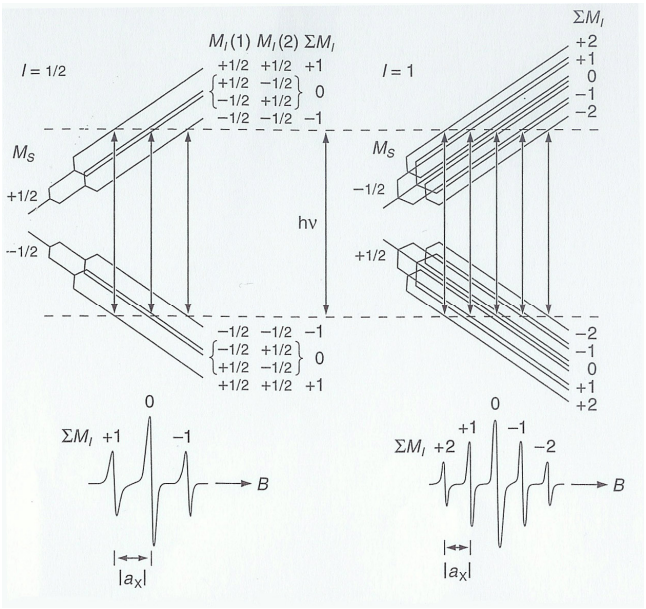


Figure 7

ESR Spectrometer

The main components of an ESR spectrometer are an **electromagnet** and a resonant **cavity** connected to a **klystron** and to a **crystal detector**. Between the cavity and the klystron are an **attenuator** and a **ferrite isolator**, and the **crystal detector** is connected to a recorder via an **amplifier**. The spectrometer also include a **field modulator**, which also operates on the cavity (Figure 8).

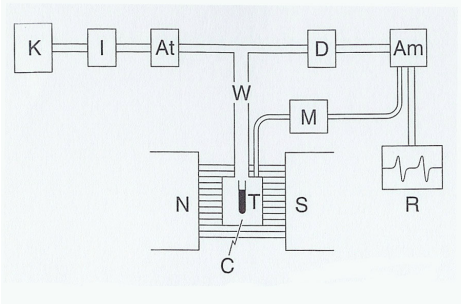


Figure 8

The field **B** of the most widely used **electromagnet** can generally scan up to 1 T and must be homogeneous in 1 part per $10^5 - 10^6$.

The **cavity**, which can be rectangular or cylindrical, is the heart of the spectrometer. Its quality is measured by its ability to store the *hv* of radiation supplied to it. Generally a rectangular cavity is slightly better.

The **klystron**, which represents the most common source of energy, is a vacuum tube producing microwave oscillations in a small range of frequencies. The emitted MW energy is directed to the sample through the **waveguide** and an adjustable hole in the cavity, the iris. A conventional X-band klystron is characterized by a frequency of 9500 MHz ($\lambda \approx 3$ cm).

The **attenuator** adjusts the level of microwave power incident on the sample, and the ferrite isolator protects the klystron from reflected radiation.

The **detector** is a silicon crystal diode in contact with a tungsten wire. The noise which appear even in the absence of ESR absorption, is the usual background of the signal.

The **amplifier** enhances the registered signal without, however, markedly changing the signal-to noise ratio. This ratio is greatly improved by the **field modulator**, which consist of a small Helmhotz coils placed on each side of the cavity along the direction of the field. Because of the modulation, the ESR-absorption curve has the familiar shape of its first derivative.

g_e factor

In a free radical the unpaired electron has an orbit kinetic moment due to its movement in space and a kinetic moment due to its rotation about itself. The *g* factor expresses the coupling between these two kinetic moments; this interaction, called spin orbit coupling, depends on the electronic environment.

The resonance condition, $h\nu = g_e \mu_B B$, implies that, for a constant MW frequency ν and a variable field strength B, the position of the ESR signal in the field **B** depends on the factor g_e of the electron. For organic radicals in fluid solution, this factor is isotropic, because the g_e anisotropy also is averaged out by molecular motion. In a multiline ESR spectrum, the g_e factor is measured at the centre of the spectrum. Departure from the centre results from second order hyperfine splitting, which occurs with large coupling constants. In this case, the observed value must be corrected for this splitting.

For paramagnetic species containing heavy atoms, the g_e factor provides important structural information, which is particularly valuable when hyperfine splittings are not observed. However, for organic radicals without heavy atoms, the g_e factor is much less informative than the hyperfine interaction. This is because the g_e factor of organic radicals is close to 2 or, more exactly, to the free-electron value of 2.0023.

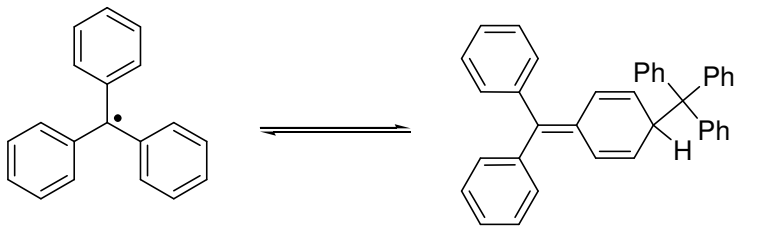
The g_e values can be determined indirectly by comparison with those of standard species, such as DPPH, or directly by measuring the field strength **B** with an NMR probe and the MW frequency ν with a wavemeter. According to the resonance condition, the g_e factor is then calculated as

$$g_e = (h/\mu_B)\, \nu/B = 7.144775 \cdot 10^{-2}\, \nu/B$$

where ν is in MHz and B is in mT.

Neutral Radicals

Radicals are paramagnetic molecules with one unpaired electron, like molecule in the doublet spin state. The existence of radicals was first proved in 1900 by Gomberg,[4] whose papers on triphenylmethyl marked the birth of organic radical chemistry. Gomberg identified the triphenylmethyl radical in equilibrium with its dimer (Scheme 1), which 60 years later was shown to be a derivative of cyclohexa-1,4-diene.[5]



triphenylmethyl radical cyclohexane-1,4-diene

Scheme 1

Radicals can be classified as π or σ according to the kind of orbital bearing the unpaired electron is of π or σ type. π Radicals, in particular those with an extended π system, are thermodynamically more stable than the σ ones, and so most radicals studied by ESR spectroscopy are of the π type. More relevant to the lifetime of radicals than their thermodynamic stability, however, is their kinetic stability (or persistence). Persistent radicals[6] are often sterically protected, so that dimerization and other reactions with paramagnetic or diamagnetic molecules are impeded.

The formation of neutral radicals involves homolytic cleavage of a covalent bond. To produce hydrocarbon radical, a C-H or a C-C bond must be broken, which requires a dissociation energy of 300 to 400 kJ · mol^{-1}. Clearly, such a large amount of energy is not readily provided by conventional reactions. Moreover, as the radicals thus formed are, in general, highly reactive and short-lived, they must be immobilized in inert matrices or produced so efficiently that a steady concentration is achieved. Transient alkyl radicals such as methyl, ethyl and allyl radicals, can be generated and characterized by ESR spectroscopy through a high energy (2.8 MeV) beam of electrons irradiating the liquid hydrocarbons,[7] but also less expensive procedures exist for generating hydrocarbon radicals. Alkyl radicals can be easily prepared in situ by photolysis of precursors such as compounds with a weaker C-halogen bond, preferably iodides,[8] diacylperoxides, or *tert*-butyl peresters. An efficient and relatively simple method makes use of a solution of di-*tert*-butyl peroxide in the hydrocarbon precursor[9], neat or diluited with cyclopropane. Photolysis of the peroxide at low temperature yields two *tert*-butoxyl radicals which abstract an H atom from the precursor to form a radical. A frequently used modification of this method involves radical formation from a halide by trialkylsilyl or trialkylstannyl radicals,[10] which can abstract a halogen from the halide.

Short-lived radicals, such as aminyl and oxyl radicals, can be generated from an appropriate precursor by X-irradiation in an adamantane matrix at room temperature.[11] This matrix functions as an isotropic medium, and the observed ESR spectra resemble those in fluid solution. In most persistent hydrocarbon radicals, the spin-bearing segment of the molecule is sterically protected by bulky substituents. Persistent neutral radicals with the unpaired electron largely located on heteroatoms are much more common than C-centred ones. This statement holds also, in particular, for radicals with N as heteroatom, for nitroxyls (TEMPO),[12] and for radicals such as aroxyls,[13] where the unpaired electron is largely located on an O atom protected by bulky substituents.

Radical Ions

The existence of organic radical ions was postulated as early as in 1920-1940. However, it was not until the advent of ESR spectroscopy that their structure could be established beyond any doubt.

Generation of ions requires a redox reaction, i.e., electron transfer from or to a neutral diamagnetic molecule. Electron abstraction from such a molecule, yielding a radical cation, is oxidation; whereas electron uptake, leading to a radical anion, is reduction. Thus, in the formation of its radical cation and anion, a molecule functions as an electron donor and acceptor, respectively. In the gas phase, the propensity of a molecule to release an electron is characterized by its ionization energy (IE), and its electron affinity (EA) is a measure of its readiness to admit an additional electron. Both quantities strongly depend on the molecular structure.[14] For organic molecules, IE is +5 to +15 eV (+500 to 1500 $kjmol^{-1}$), which is the amount of energy that has to be invested in ionization. The value of EA for organic molecules is +4 to -2 eV(+400 to -200 $kjmol^{-1}$). Actually, because EA is equal to IE of the resulting radical anion, positive values signify an energy decrease upon uptake of an electron and negative values signify an energy increase. Thus, from the energetic point of view, formation of radical anions should occur at less expense than formation of radical cations. The large amount of energy required for formation of radical cations and some radical anions in the gas phase, as indicated by the IE and EA values, seem discouraging at first sight. Fortunately, in solution, the energy balance between neutral molecules and their radical ions is often shifted in favour of the latter, because the radical ions benefit from interactions with the surrounding species, such as solvation by solvent molecules or the coulombic attraction of counterions. In principle, if appropriate conditions are found, every molecule can be oxidized to its radical cation and reduced to its radical anions. Thus, on the whole, generation of radical ions appears to be a more straightforward procedure than generation of neutral radical. Because of the charge, dimerization is less common for radical ions than for their neutral counterparts, and many of the former persist in solution when air and moisture are excluded. The methods for generation of radical ions are chemical (frequently combined with photolysis), electrolytic, and radiolytic.

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CHAPTER 5

The Scotland Experience: ESR Investigation of The Reaction of Organic Azides with Group-XIII Lewis Acids

Introduction

The generation of a new class of *N*-centred radicals was the main subject of the previous chapters. In particular, the reaction of dichloroindium hydride with organic aryl and alkyl azides emphasised the ability of that indium derivative to act as a radical reagent, bringing about processes interesting from both a synthetic and a mechanistic point of view.

Nevertheless, some points remained that needed to be clarified: the possible coexistence of radical and ionic pathways is still an open matter, especially when the reactions are carried out in the absence of radical initiator and thus the occurrence of a radical reaction mechanism must entail spontaneous homolytic cleavage of the indium-hydrogen bond. Unfortunately, it was difficult to design other chemical experiments that could throw some more light on this problem. The only possibility that we could envisage to get incontrovertible evidences about the generation of indiumaminyl radicals would seem to examine the reaction mixtures by ESR spectroscopy.

ESR spectroscopy is in fact the only powerful technique that allows identification and characterisation of paramagnetic species; furthermore, not only does it permit to get information about spin density, structure, and geometry of the radical intermediates, but it also allows to follow evolution of radical species directly inside the reaction mixture. Therefore, it would be the right choice to detect possible radical intermediates in the reactions of indium reagents with azides.

This chapter will hence deal with the ESR search for radical intermediates in the above described reactions and it is worth emphasizing that it will deal with the invention of new methods for the generation of dichloroindyl and the resulting aminyl radicals that could be suitable for ESR experiments, independently of their synthetic interest. The reactions were carried out only to get important mechanistic indications on radical generation and the obtained products were just taken (or not taken) as indicative of the existence of a radical mechanism: absolute and relative yields will not be discussed.

Change of Strategy: the use of Allyl dichloroindium

During my last PhD year, I spent a period of six months at the University of St. Andrews (UK) under the supervision of Prof. John C. Walton, one of the maximum experts in ESR spectroscopy, in order to perform some ESR experiments on my reactions, trying to generate efficiently both indyl and (dichloroindium)aminyl radicals and to study their structure and reactivity through ESR experiments. The main starting idea was to carry out a reaction directly into the ESR cavity by mixing the azide with a solution of indium trichloride in MeCN and then adding Et_3SiH and, if required, triethylborane. In case the reaction had followed a radical patway, it would in principle have been possible to detect and characterize one or some of the radical species involved. Unfortunately, it was immediately clear that the original conditions employed in our experiments were not suitable for ESR spectroscopy. In particular, three important aspects had to be modified: the solvent, the high (in some cases) reaction rate, and the presence of a strong hydrogen source.

The solvent required by our reactions is acetonitrile, which is characterised by a high value of the dielectric constant.[1] Highly polar solvents cause important absorptions of microwave energy during the ESR experiment, thus diminishing the absorption by the paramagnetic species that should be studied: this would generate very weak signals. This effect can be partially overcome either by freezing the solution, thus reducing the mobility of the solvent molecules, or by reducing the cross section of the sample cells.

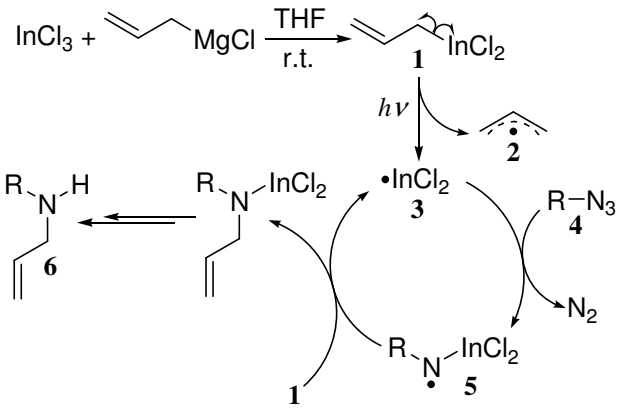
A high reaction rate is obviously not a problem, but rather a positive aspect, in synthetic laboratory experiments. However, as far as ESR spectroscopy is concerned, a too fast reaction could not allow to settle the proper experimental conditions and, more important, to reach a good steady concentration of radicals in solution. The latter problem prevents accumulation of intense, resolved signals.

The presence of dicloroindium hydride as a source of dichloroindyl radicals was underlined by Prof. Walton as the likely main problem. This powerful hydrogen source could act as a strong scavenger of possible aminyl radicals, thus avoiding any possibility to detect them. The likeliness of this idea is further supported by the reaction rate considerations reported above, since the high rate is probably (also) due to fast hydrogen transfer to any radical intermediate from the starting indium hydride. Some way had therefore to be invented to slow down the reactions by decreasing the rate of hydrogen donation, thus increasing the concentration of *N*-centred radicals in the ESR cavity and enhancing the possibilities to record their spectra.

This way, as suggested by Prof. Walton, could entail using different radical sources and initiators. In particular, the radical initiation is very important in ESR experiments, since a sufficiently high number of radical chains have to be sustained in the cavity to allow for a detectable concentration of radicals being reached. This is the reason why UV-lamp initiation is often used in the ESR cavity instead of a chemical initiator; UV-photolysis would in fact generate a constantly high number of photons, thus providing in every istant generation of many radical chains and attainment of a high steady concentration of radicals. Furthermore, by using UV-light it is also possible to stop the reaction at any time and manipulate the experimental conditions, for example the temperature.

Taking these suggestions into consideration, before my departure to St. Andrews, some attempts were made in order to change completely the approach to the generation of our indiumaminyl radicals. Since Oshima proved that organoindium compound such as allylindium dichloride gave excellent results in radical allylation of α-halogenocarbonyl compounds through the intermediacy of dichlorindyl radicals,[2] the behaviour of allylindium dichloride with organic azides was studied in order to ascertain whether this reaction could be consistent with the standards of rate and type of initiation required by Prof. Walton.

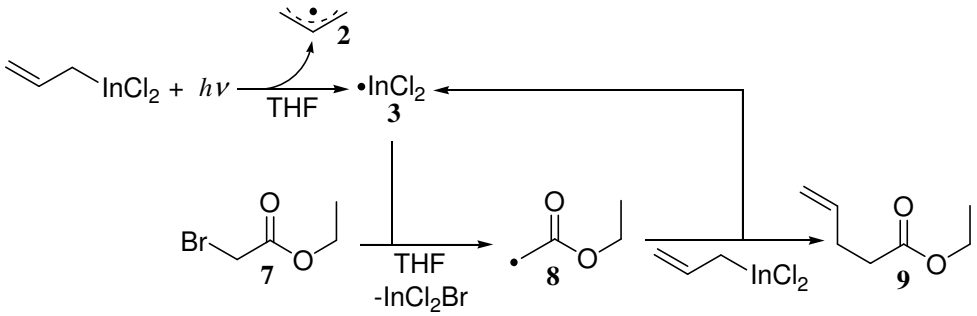
The synthesis of allylindium dichloride was performed by transmetallation between allylmagnesium chloride and $InCl_3$ at room temperature in THF: this is an additional positive aspect from a spectroscopic point of view, since the dielectric constant of THF is 5 times lower than that of MeCN: the corresponding ESR experiments, if possible, could therefore be carried out in a more convenient solvent. The reaction with the azide was performed under photolytic conditions to homolytically cleave the indium-allyl bond. The mechanism of reaction (Scheme 1) entails UV generation of dichloroindyl radicals **3**, their addition to azide **4** giving the (dichloroindyl)aminyl radical **5** with concomitant nitrogen evolution, then addition of the latter to another molecule of allylindium dichloride to give a new indium centred radical, the radical chain carrier, and allylamine **6** as the final product.



Scheme 1

Of course the mechanism efficiency depends on both the ease of homolytic fragmentation of the C-In bond in the allylindium compound and the rate of intermolecular addition of the aminyl radical to the allyl double bond.

Before carrying out the reaction reported in Scheme 1 directly into the ESR cavity, some experiments with product analysis were performed to prove its feasibility and scope. We initially repeated the Oshima reaction of $AllInCl_2$ with α-halogenoesters with a 150 W medium pressure Hg vapour lamp present in our laboratory and we observed formation of the desired allylation product (**9**) in excellent yield (Scheme 2). One should however keep in mind that the driving force of this reaction is probably the great polar affinity between the electrophilic radical intermediate **8** and the nucleophilic C-C double bond of the allyl dichloroindium compound: this effect could strongly speed up the addition step of **8** to allylindium dichloride, thus perfectly sustaining the radical chain. The successful result obtained with our lamp confirmed that it was possible to use allylindium dichloride as a radical reagent under photolytic initiation, with the UV light acting like triethylborane in chemical initiation. The result was not trivial, since no example had been reported yet of generation of indium centred radicals by photolysis.



Scheme 2

By replacing the haloester with several azides (Figure 1), different results were obtained.

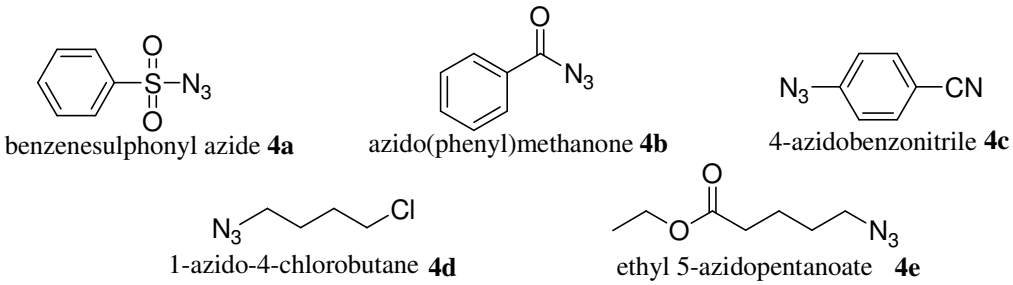
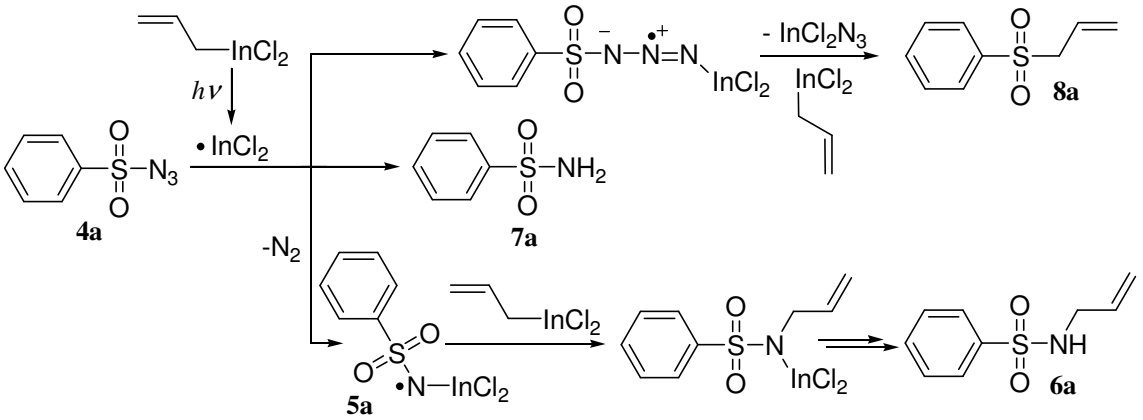


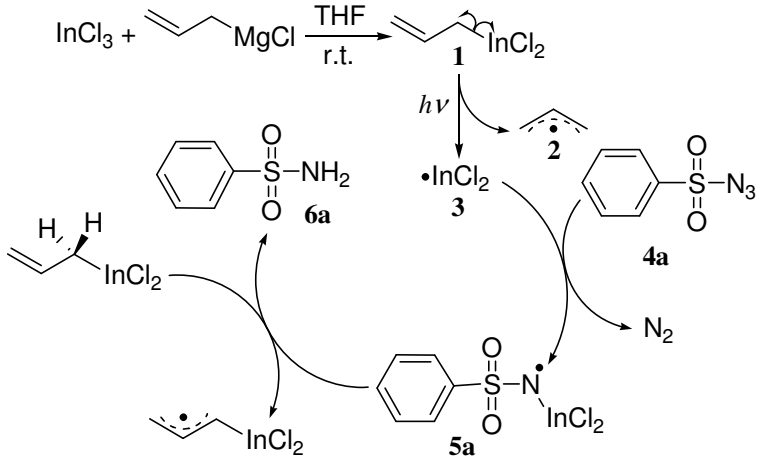
Figure 1

Azide **4a** is not new as a substrate for radical allylation, as reported by Roberts.[3] For this reason it was the first azide we tested to verify the efficiency of the allylindium reagent. The results obtained were encouraging because, after 3 h under photolysis, products were obtained in line with expectations (Scheme 3). Although the azide was not completely consumed, a GC-MS analysis clearly identified allylsulfonylbenzene **8a**, benzenesulfonylamide **7a**, and *N*-allyl phenylsulfonylamide **6a**. ^{1}H-NMR spectroscopic analysis identified **8a** and **7a** as the major products in a 1:1 ratio, while *N*-allyl phenylsulfonyl amide **6a** was a minor product (**6a/8a** ≈ 1:3).



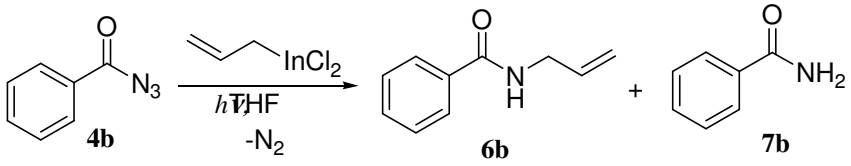
Scheme 3

These results are clearly consistent with a radical mechanism, thus proving that photolysis could be a proper alternative to chemical initiation fo generation of the desired radicals. Indeed, allylsulfonylbenzene **8a** can be easily accounted for through a radical deazidation pathway performed by •$InCl_2$ followed by allylation of the resulting sulfonyl radical by the starting allyl indiumdichloride; competing formation of indiumaminyl **5a** could explain formation of allylsulfonylamide **6a** by reaction with the starting allylindium reagent. The presence of **7a** in high yield was quite strange, although not completely unexpected: the only conceivable way to account for its formation is a hydrogen abstraction step by radical **5a** followed by hydrolysis. Since no $HInCl_2$ or other strong hydrogen donors were present in the reaction mixture, the hydrogen source could only be either the solvent (THF) or allylindium dichloride itself, through the hydrogen atoms of the allylic position. This latter hypothesis could also account for non complete conversion of the starting azide, since this pathway would consume allyl indiumdichloride in routes that would not furnish the desired •$InCl_2$ radicals required for the whole allylation process (Scheme 4).



Scheme 4

Analogous reasoning can be made for azide **4b** (Scheme 5). Also this compound furnished, as a major product, benzamide **7b** instead of *N*-allylbenzamide **6b** (**7b/6b** ≈ 3:1). Unfortunately, besides again some unreacted azide, this reaction also gave great amounts of unidentified byproducts.



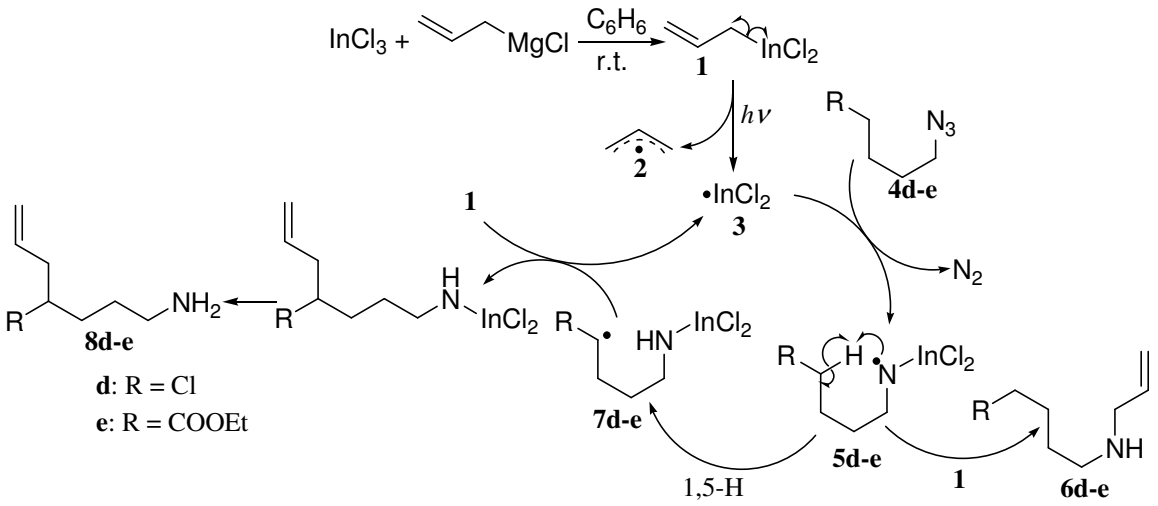
Scheme 5

Azides **4c**, **4d**, and **4e** did not give any interesting results, probably because the aminyl radicals initially formed, contrary to those generated from **4a** and **4b**, are not sufficiently electrophilic to add to the allyl moiety at a reasonable rate as to sustain the radical chain reaction.

Thinking that THF could somehow influence the efficiency of the reaction, for instance by donating hydrogen atoms or complexating the indium reagent, we tried to substitute THF with benzene.[1] In the following examples, THF was used only for generation of the organoindium compound; once this was formed, THF was evaporated under high vacuum and benzene was added together with the azide.

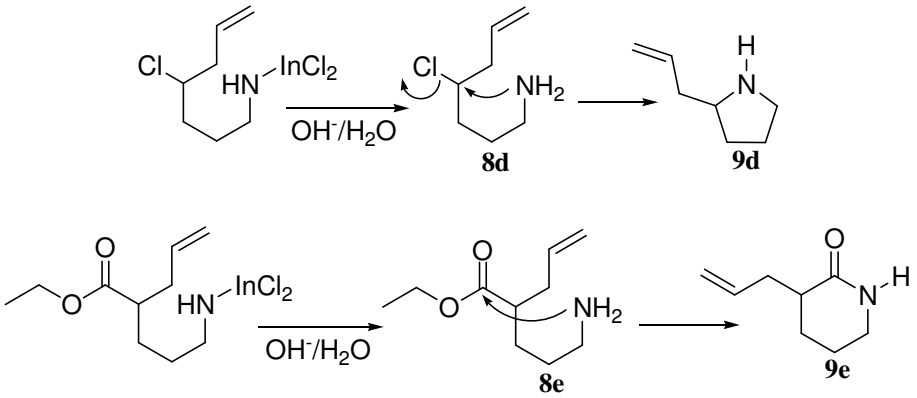
The reactions of azides **4a** and **4b** gave more or less the same results reported above, the only difference being complete disappearance of the starting azide in the case of benzoyl azide **4b**. Enormous differences were instead observed in the reactions of azides **4d** and **4e**. These compounds are quite interesting from a mechanistic point of view; indeed, they had

been chosen because they could generate indiumaminyl radicals (**5d-e**) capable of undergoing 1,5-hydrogen shift affording α-carbonyl- and α-halo-substituted radicals (**7d-e**) that, in turn, could be electrophilic enough as to be allylated by the indium reagent, thus sustaining the radical chain (Scheme 6).



Scheme 6

The analyses of the reaction mixtures confirmed complete conversion of azides **4d** and **4e** after 3 hours into the corresponding δ-C-allylated products **8d-e**. Furthermore, after the usual extractive work-up procedure and neutralisation with a sodium hydroxide solution, a GC-MS analysis showed that both **8d** and **8e** were partially transformed into their corresponding cyclised compounds **9d** and **9e**. A ^{1}H-NMR analysis performed on a sample stirred overnight under aqueous conditions confirmed the presence of 2-allylpyrrolidine **9d** and 3-allylpiperidi-2-one **9e** (Scheme 7).

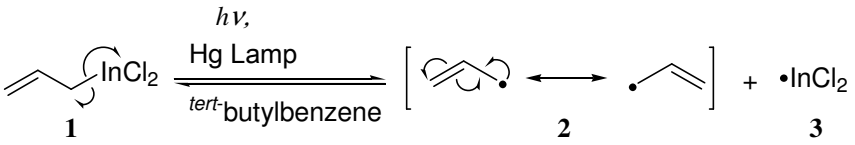


Scheme 7

It is worth pointing out that the *N*-centred radicals **5d-e** react selectively via intramolecular 1,5-H transfer and no products ascribable to their reactions with the allylindium reagent (**6d-e**) were observed. The radicals arising from **5d-e** by exclusive 1,5-H transfer could be interesting additional species detectable into the ESR cavity.

On these bases, the possibility to get some promising ESR spectra in reactions carried out with this new approach was tangible. Indeed, most of the problems pointed out by Prof. Walton seemed to be overcome: acetonitrile or THF were changed with a solvent (benzene) that is normally employed in ESR experiments and does not seem to interfere at all with the reaction outcome (in some cases the outcome seems even improved); allylindium dichloride proved to be a good photolytical source of $\bullet InCl_2$ radicals capable of adding to the azido group (the results obtained with azides **4a**, **4b** and, in particular, **4d** and **4e** can be exclusively explained through a radical mechanism). Two doubts still remained: the efficiency of the photolysis, in terms of the amount of radicals first produced, and the efficiency of the reaction, in terms of the rate of the main reaction steps.

Once arrived in St. Andrews, a preliminar experiment was performed to understand the efficiency of homolytic scission of the carbon-indium bond. A solution of allylindium dichloride in *tert*-butylbenzene[4] was prepared and, after being degassed, was inserted in a quartz tube, introduced into the resonant cavity, and photolyzed with a 500 W super pressure Hg arc. There was no possibility to detect a good resolved signal of $\bullet InCl_2$ radical because of the high quadrupolar moment typical of the Indium atom, hence all expectations were devoted to detection of the radical counterpart, i.e. the allyl radical (Scheme 8).



1 **2** **3**

Scheme 8

Several spectra were acquired at different temperatures until the best result was obtained when the sample was photolyzed at −13 °C. The resonance-stabilyzed allyl radical was detected and Figure 2 shows the result of 30 scans collected at this temperature. The hyperfine splitting constants measured allowed us to simulate the spectrum with a perfect correlation cofficient. The values reported in figure **2S** are virtually identical to those reported in the literature: a(1H) = 4.06, a(2H) = 13.9, a(2H) = 14.81, g = 2.00254.[5]

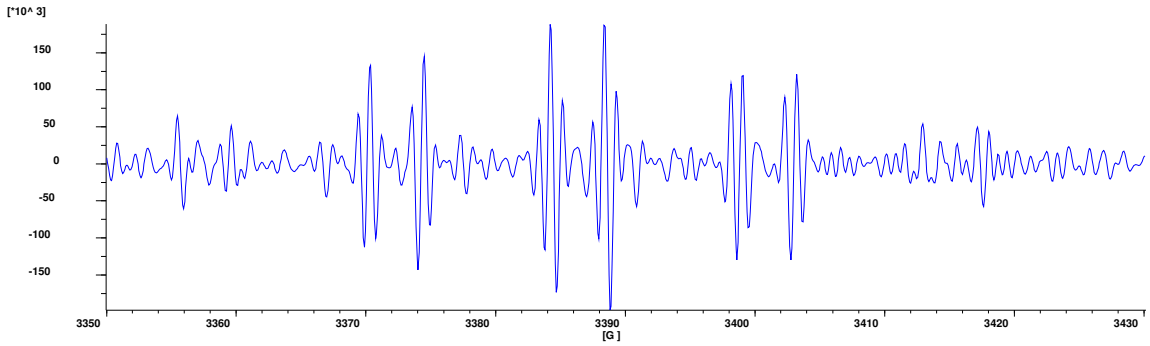


Figure 2: Allyl radical, 260 K, MW freq.: 9.5 GHz; M. A.: 0.6 Gpp; Power: 2mW; 1st der.; 30scans.

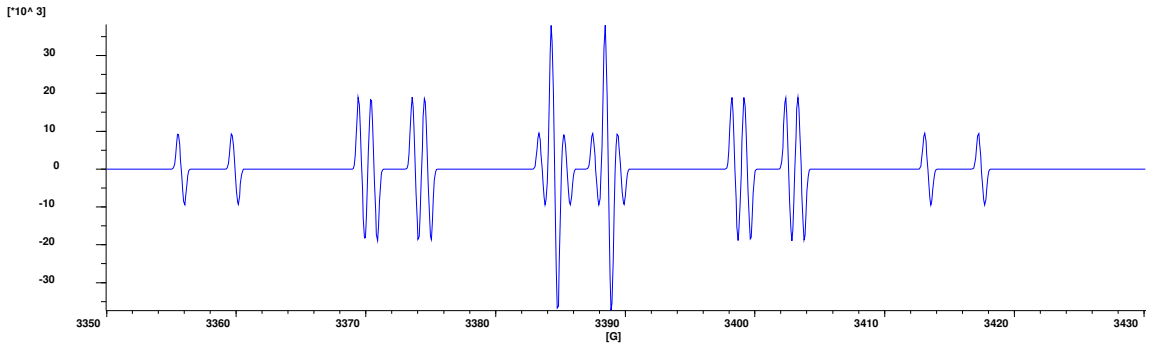


Figure 2S: Simulation of the Allyl radical; a(1H) = 4.0, a(2H) = 13.9, a(2H) = 14.8 G.

This was a very encouraging outcome because, although indirectly, it was the first experimental evidence of generation of the dichloroindium radical. This result strongly supports the suggestion that the experimental results obtained in the UV-induced reactions of allylindium dichloride with azides could be interpreted in terms of addition of dichloroindyl radicals to the azido moiety to generate indiumaminyl radicals.

Nevertheless, not all doubts were cancelled, because photolysis did not provided a very strong allyl signal (30 scans were needed in order to record a good quality spectrum). This could be due to a somewhat inefficient photolysis process or simply to the fact that photolysis of the allylindium compound is very likely to be a reversible process and, without any evolution of the dichloroindyl radicals, the concentration of free allyl radicals remains low, due to the recombination process. From the point of view of reaction efficiency, this could not be a problem if some process is present that could promptly subtract the indium-centred radicals thus shifting the reagent dissociation equilibrium towards •$InCl_2$. This possibility was studied by carrying out photolysis of allylindium dichloride in the presence of some azides.

Unfortunately, when azides **4a**, **4b**, **4d** and **4e** were allowed to react in ^{tert}-butylbenzene with allylindium dichloride, the allyl radical was again the only species identified. All the prepared samples were examined several times increasing the temperature up to 340 K. Once the quartz tube was removed from the resonant cavity, it was possible to see small gas bubbles

evolving inside the reaction mixture. TLC analysis performed on the reaction mixtures of azides **4a** and **4b** revealed that some azide was still present, along with compounds **6a/7a/8a** and **6b/7b**, respectively. This confirmed that the evolved gas was nitrogen ensuing from the decomposition of the azido moiety. The likely aminyl radical intermediates were not observed probably because this methodology is not very efficient and, although no strong hydrogen source is present to trap the aminyls (e.g. $HInCl_2$), the concentration of the latter radicals is too low as to allow any possibility of detection and characterisation. Furthermore, the detection of the allyl radical also under these conditions suggests that addition of the dichloroindium radical onto the azido group is slow and this could be the rate determining step of the reaction; meanwhile, the intermolecular addition of the aminyl radical onto the allylindium moiety, at least with these azides, could be fast enough to give the desired products, thus lowering concentration of the aminyl radicals beyond the detection limit and preventing their characterisation.

ESR study on the generation of indyl radicals from $HInCl_2$ and $InCl_3$

In chapter 3 it has been reported that also the reactions of $HInCl_2$, particularly those with longer reaction times, can be affected by using photolysis instead of chemical initiation. This suggested to attempt generation of indyl radicals from dichloroindium hydride under photolytical conditions inside the ESR cavity. The reaction procedure is similar to that reported before. Dichloroindium hydride was generated by transmetallation between $InCl_3$ and Et_3SiH at 0 °C in degassed MeCN; then the azide was added and the resulting solution was rapidly transferred into a capillary quartz tube and degassed again for a few minutes; the capillary tube was sealed, inserted into the resonant cavity, and then photolysed with a 500 W super pressure Hg arc lamp.

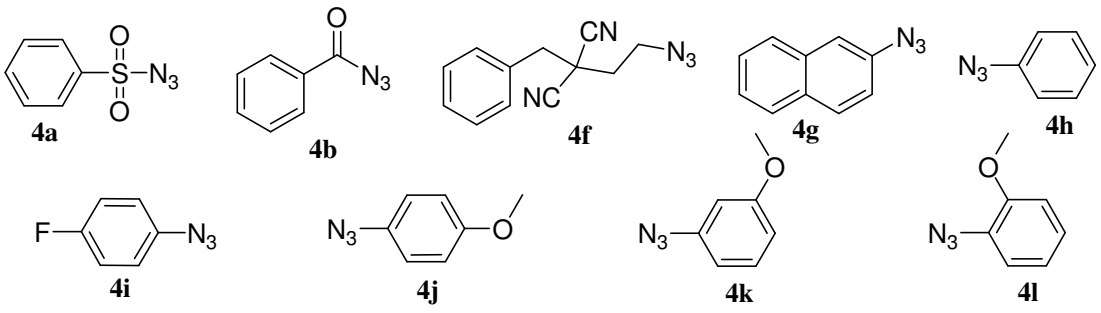
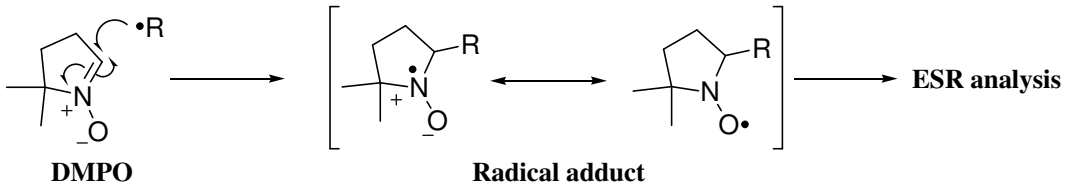


Figure 3

Unfortunately, no ESR signals were ever detected with all the examined azides (Figure 3). It is noteworthy that analysis of the crude mixtures of azides **4g**, **4i**, and **4k** revealed however the presence of the corresponding anilines **6g**, **6i**, and **6k** as the only reaction products. The unsuccessful result was probably related to the high reactivity, under the reaction conditions, of the generated radical species, which could evidently not reach such a concentration as to be detected.

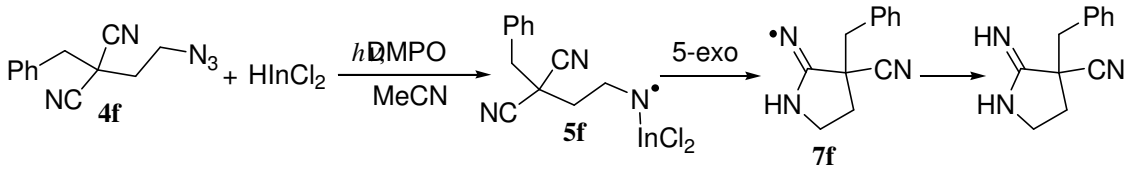
To prolong the life of radical species, we then decided to attempt some spin trap experiments, by using 5,5-dimethylpyrrolidin-*N*-oxide (DMPO) as a spin trap. Spin traps are molecules that easily undergo addition by radical species providing more stable and/or persistent radicals: since the radical adducts are more long living, their concentration in solution increases to such a value as to become detectable. Once the spectrum is recorded, it is possible to figure out the nature of the trapped radical by comparison of the hyperfine splitting constants and the *g* factor of the radical adduct with literature data (Scheme 9). But this analysis is not accurate at all because the only information one can obtain are on the atom directly bonded to the spin trap and not on its overall structure.



Scheme 9

Since some spin traps are known to decompose under photlytical conditions giving radical species that can interfere with the analysis, an ESR experiment on an acetonitrile solution of DMPO in the absence of other reagents was preliminary performed and no signals were recorded.

After 20 minutes under continuous photolysis, azide **4f** gave the complicated, not well-resolved spectrum displayed in Figure 4. The spectrum is consistent with an oxygen-centred radical derived from addition to DMPO, shows couplings with N, H_2, and H_3, and was simulated with the following values of hyperfine constants: a($1H_3$) = 1.0, a($1H_2$) = 11.2, a(1N) = 13.7 G (Figure 4S). By comparison with literature data, these values are in agreement with capture of a radical species centred on a nitrogen atom.



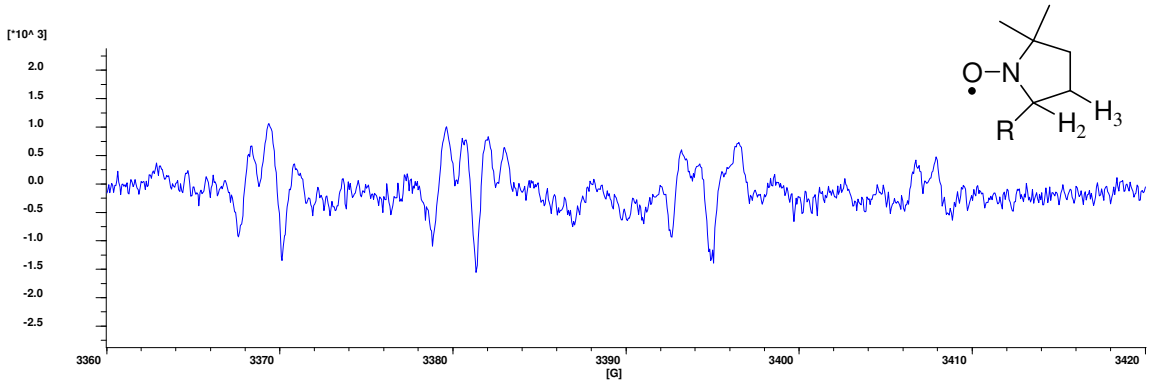


Figure 4: **4f** + DMPO, 298 K, MW freq.: 9.5 GHz; M. A.: 0.4 Gpp; Power: 2mW; 2nd der.

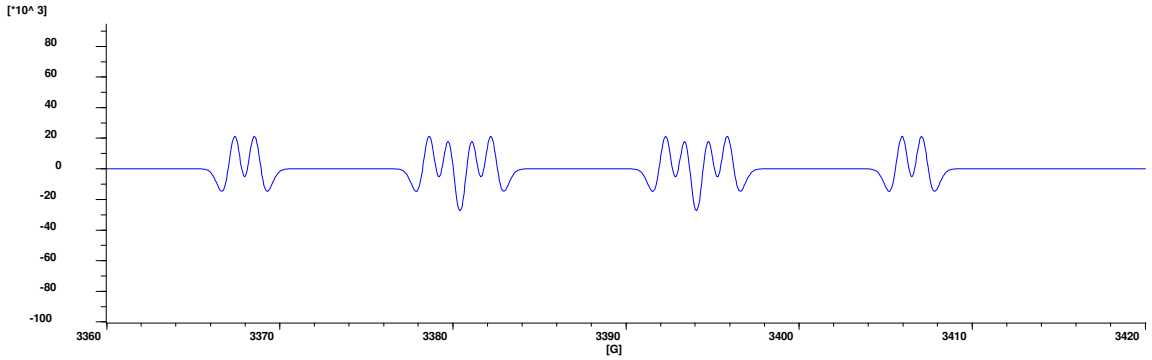
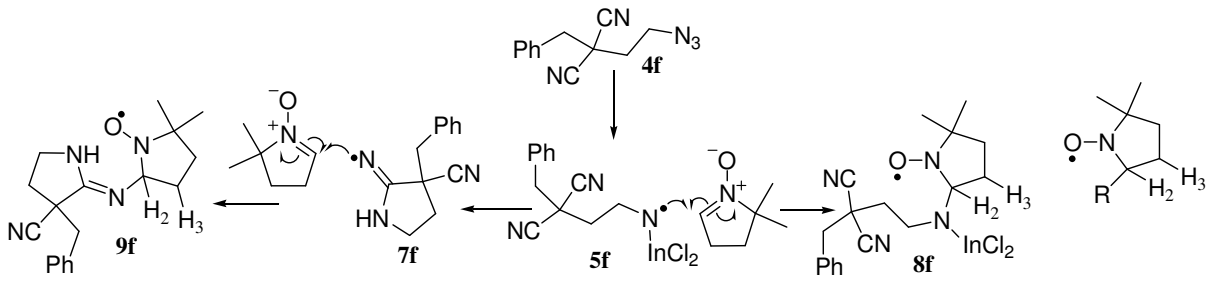


Figure 4S: simulation of **4f** + DMPO: a($1H_3$) = 1.0, a($1H_2$) = 11.2, a(1N) = 13.7 G.

If the radical trapped by DMPO is really N-centred, this could be a valid support to our hypothesis that N-centred radicals are formed in the reaction of organic azides with $HInCl_2$. In the case of azide **4f**, no more details could be obtained from spectral analysis and it was therefore not possible to say whether the trapped radical was either the indiumaminyl **5f** or the cyclised iminyl radical **7f** (Scheme 10).



Scheme 10

To clarify this point, 2-naphthyl azide **4g** was used, since only one type of N-centred radical (the indiumaminyl) would arise from this compound.

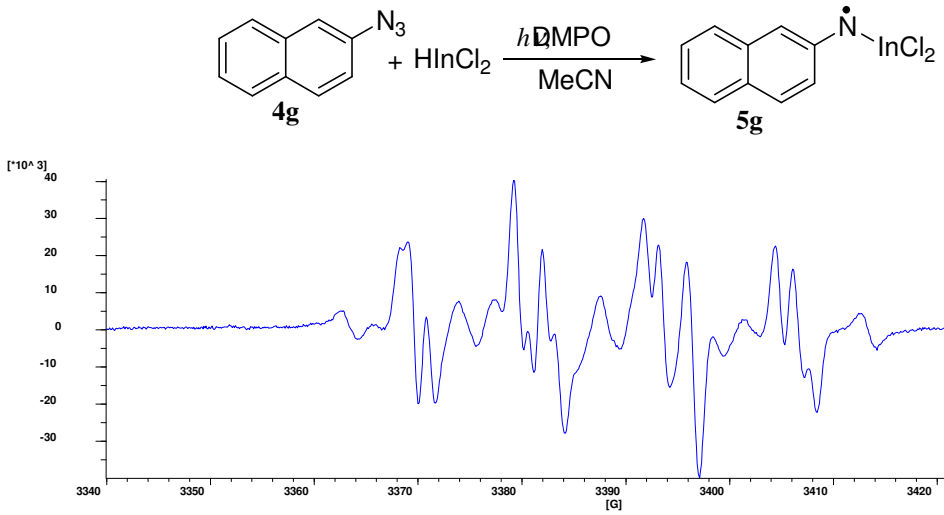


Figure 5: **4g** + DMPO, 310 K, MW freq.: 9.5 GHz; M. A.: 1.0 Gpp; Power: 4mW; 2nd der.

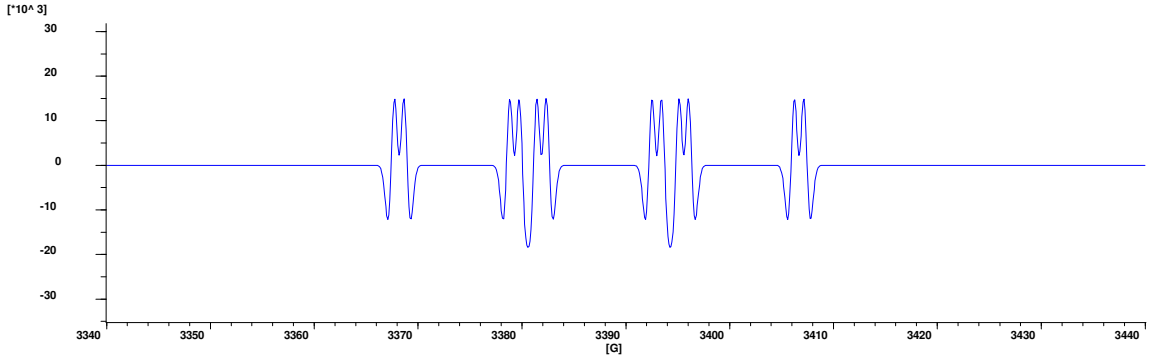
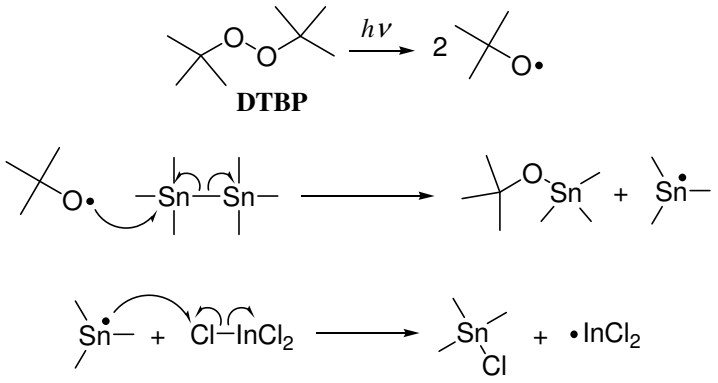


Figure 5S: simulation of **4g** + DMPO, a(1H_3) = 0.8, a(1H_2) = 11.1, a(1N) = 13.7 G.

In the presence of DMPO, azide **4g** gave the spectrum reported in Figure 5. Although the spectrum is not well resolved and other weak signals overlap, a pattern quite similar to the spectrum reported in Figure 4 can be observed. Also in this case, quite a good simulation was obtained employing more or less the same hyperfine constants used before: a(1H_3) = 0.8, a(1H_2) = 11.1, a(1N) = 13.7 G (Figure 5S). Since no other radical adducts with DMPO gave similar values of hyperfine splittings except nitrogen-centred radicals, and the radical trapped with azide **4g** seems the same as that obtained with azide **4f**, it is reasonable that the trapped radical species could be aminyl radicals arising from addition of •$InCl_2$ to the azido moiety.

These experiments clearly pointed out that our aminyl radicals, if formed, are highly reactive under all of the attempted conditions and their detection is possible only indirectly through the use of spin traps (DMPO). However, another experiment could be envisaged to prevent fast reaction of the aminyl with hydrogen donors or other efficient intra- or

intermolecular radical traps. In this experiment completely different conditions were used to generate indium-centred radicals, namely chlorine atom abstraction from indium trichloride by tin-centred radicals, in turn generated through di-*tert*-butyl peroxide (DTBP) induced homolyitc scission of hexamethylditin (Scheme 11).



Scheme 11

Under UV photolysis, di-*tert*-butyl peroxide generates *tert*-butoxyl radicals that are known to give homolytic substitution at the Sn-Sn bond of hexamethylditin to give trimethyltin radicals. Since tin-centred radicals are known to readily abstract halogen atoms from many substrates, trimethyltin radical could abstract chlorine from indium trichloride to give trimethyltin chloride and indium-centred radicals. These species, in the presence of an azide, might give rise to aminyl radicals that, under these conditions, can be rather long lived and can accumulate in solution as to be easily detected by ESR.

Under these novel conditions, 2-naphtylazide **4g** originated two different species. When the photolysis was carried out at 270 K in MeCN, the seven line spectrum displayed in Figure 6 appeared. When the lamp was switched off and the temperature increased up to 320 K, a six line spectrum was recorded as shown in Figure 6a. Switching again the lamp on, the same seven line spectrum of Figure 6 appeared again. A well correlated simulation of the seven line spectrum was obtained using the following hyperfine coupling constants: $a(1H_2) = a(1H_3) = a(1H_6) = a(1H_7) = 5.4$, $a(1N) = 4.7$ G (Figure 6S). The simulation results can be explained in terms of generation of an *N*-naphthylaminyl radical where the unpaired electron couples with four equivalent aromatic hydrogen atoms.

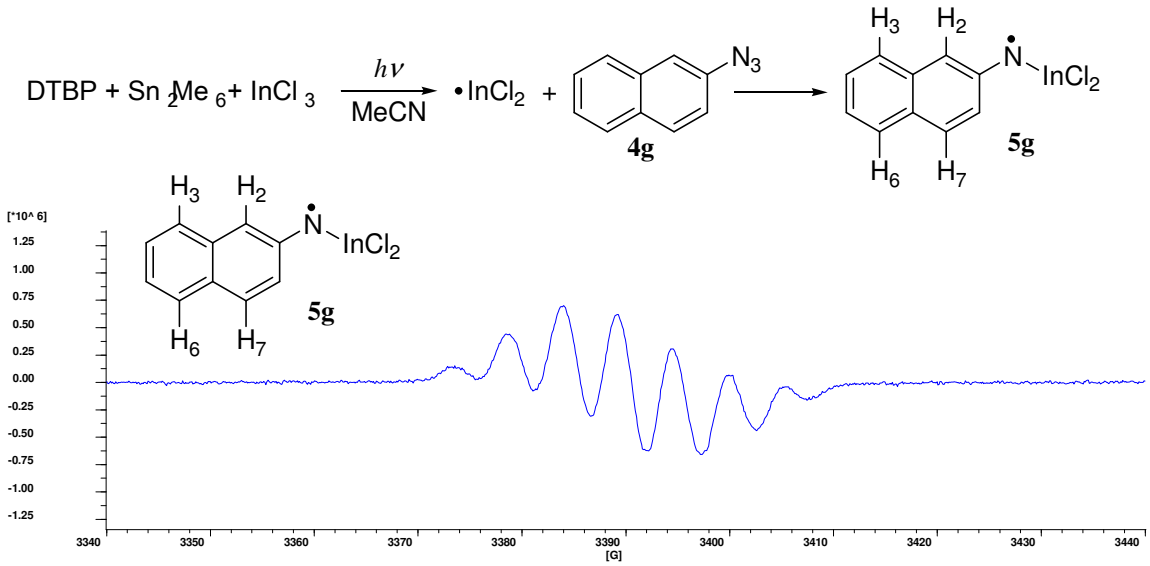


Figure 6: **4g+ $InCl_3$**, 270 K, MW freq.: 9.5 GHz; M. A.: 2.0 Gpp; Power: 2mW; 1st der.

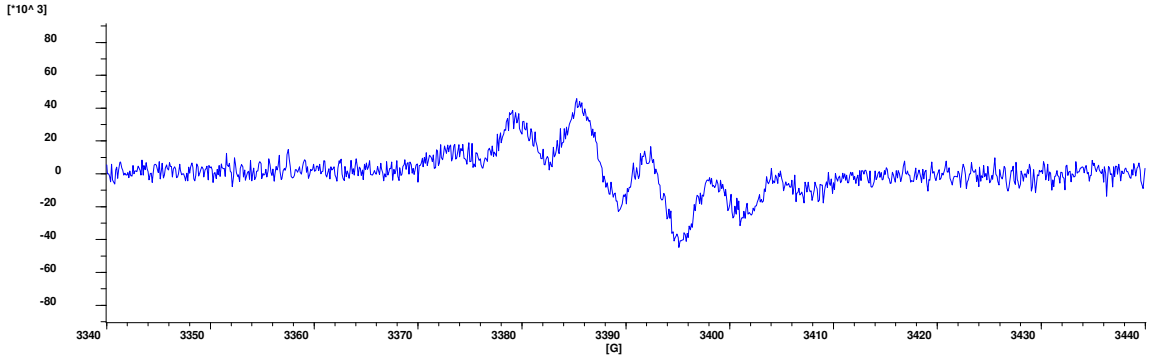


Figure 6a: **4g + $InCl_3$**, 320 K, MW freq.: 9.5 GHz; M. A.: 2.0 Gpp; Power: 2mW; 1st der, dark.

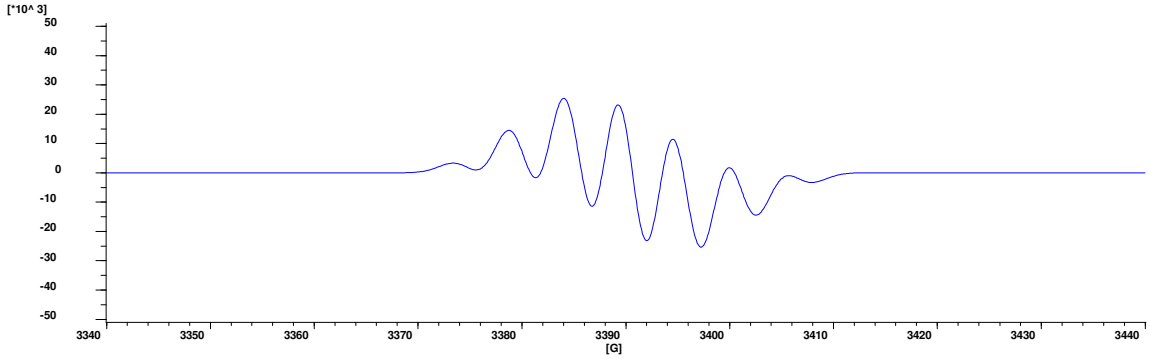


Figure 6S: simulation of **4g + $InCl_3$**, a($1H_2$) = a($1H_3$) = a($1H_6$) = a($1H_7$) = 5.4, a(1N) = 4.7 G.

We searched for different reaction conditions in order to improve spectral resolution and get a more detailed characterisation of the possible N-centred radical. In particular, we decided to change gradually the solvent moving from acetonitrile to dichloromethane, since it was known that dichloroindium-hydride-mediated radical dehalogenations and cyclisations

can be carried out also in dichloromethane,[6] and ESR experiments could take some advantage from the low dielectric constant value of this solvent.

When the reaction of azide **4g** was carried out at 298 K under UV-photolysis with the DTBP/Me_6Sn_2/$InCl_3$ system in a 1:1 (v/v) mixture of MeCN and CH_2Cl_2, the same six line spectrum reported in Figure **6a** was observed. This signal, which rapidly disappeared, could be the result of some change in the structure of **5g** that would cause a different number of couplings with the aromatic hydrogens to be observed. Nevertheless, this modification is not obvious at all and the additional observation that it could be a reversible process (see previous experiment) points to the more likely hypothesis of a conformation change in the structure of **5g**, which could account for the different observed conjugation with the aromatic ring. No data are however currently available to support either theories.

Analogous ESR experiments were performed with 4-methoxyphenyl azide **4j**, aiming at studying the solvent effect. Once the lamp was switched on, the reaction of azide **4j** in acetonitrile gave a strong, unresolved spectrum with eight signals that rapidly disappeared (Figure 7). The low resolution and the quick disappearance of the radical species did not allow any good simulation.

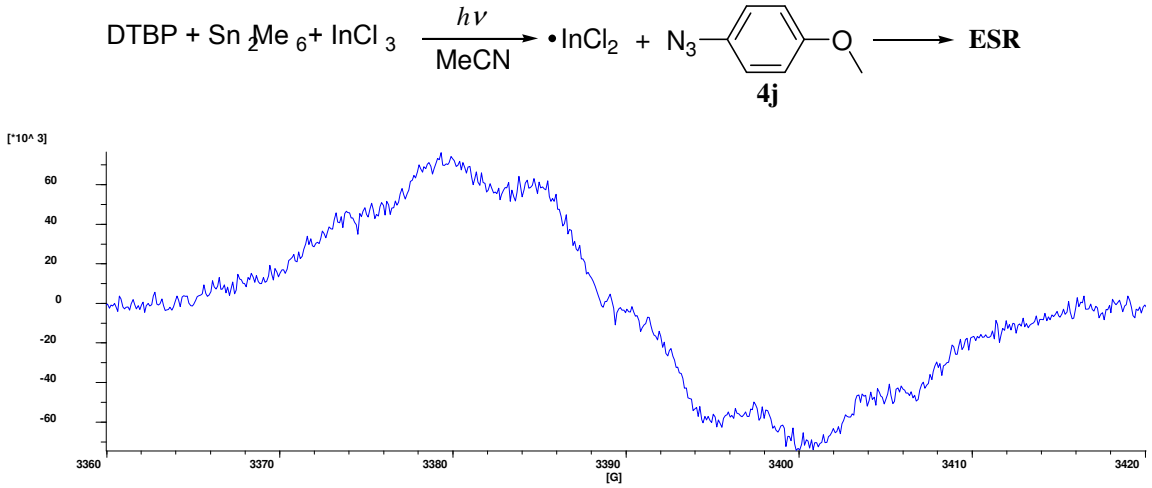


Figure 7: **4j+ $InCl_3$**, 270 K, MW freq.: 9.5 GHz; M. A.: 2.0 Gpp; Power: 2mW; 1st der.

When the same reaction was carried out in a 1:1 (v/v) mixture of acetonitrile and dichloromethane, under photolysis, the beautiful, strong signal reported in Figure 8 was obtained. The signal disappeared after 3 minutes although the lamp was still on: this common behaviour is probably related to the great instability, and hence reactivity, of the radical species, thus reinforcing the idea of the presence of a nitrogen centred radical. This signal, recorded using exactly the same parameters as the previous one, showed again eight groups of

lines, but also a fine structure that could indicate that the metal is directly bonded to the radical centre. If this were true, the fine structure showed in Figure 8a (3376 to 3387 G, line distance of 0.23 G) would be quite well explained by the nuclear spin number (I = 9/2) of indium metal, which would be split each line in (2I + 1) = 10 lines; further splitting could be additionally provided by chlorine atoms (I = 3/2).

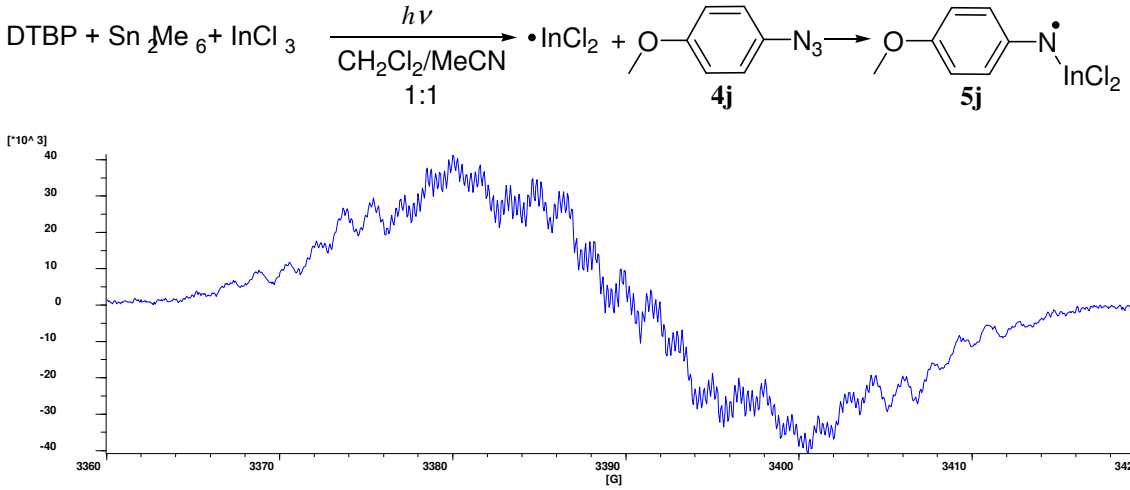


Figure 8: **4j+ $InCl_3$**, 270 K, MW freq.: 9.5 GHz; M. A.: 2.0 Gpp; Power: 2mW; 1st der.

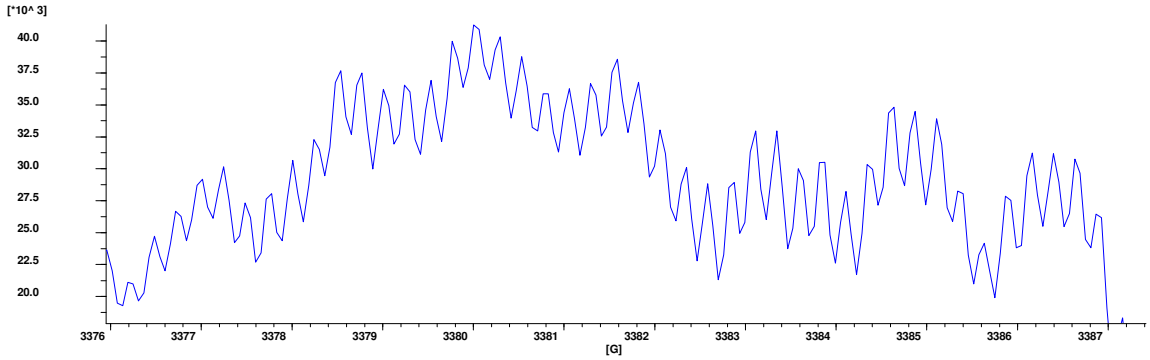


Figure 8a: **4j+ $InCl_3$**, 270 K, MW freq.: 9.5 GHz; M. A.: 2.0 Gpp; Power: 2mW; 1st der.

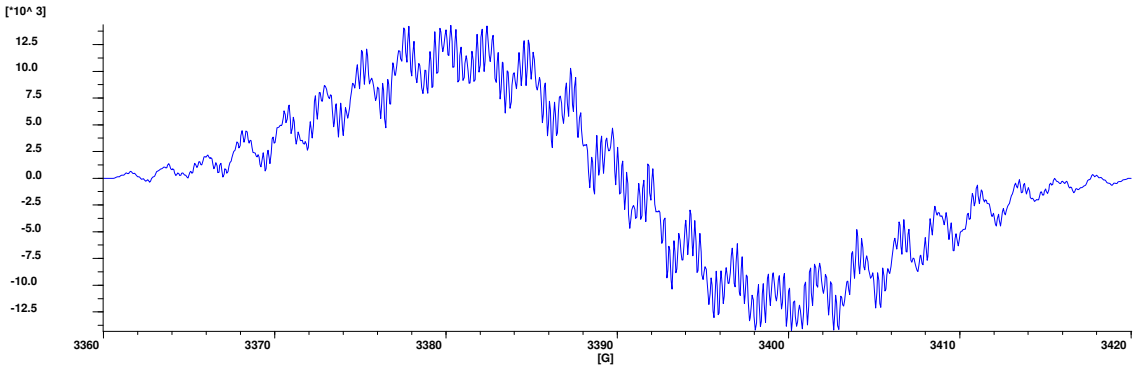


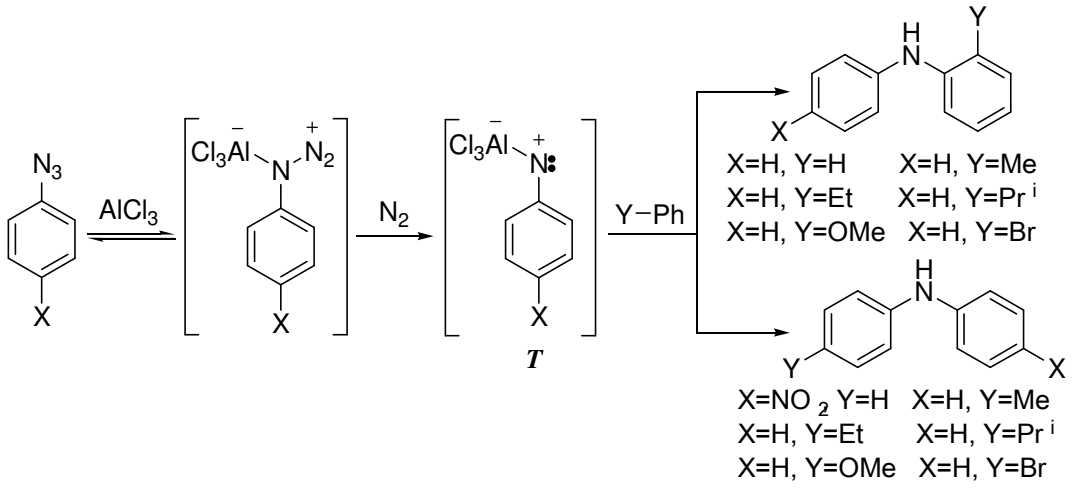
Figure 8S: simulation of **4j + $InCl_3$**, a(2Cl) = 0.26, a(1In) 1.53, a(2H) = 2.20, a(2H) = 4.27, a(2H) = 6.97, a(1N) = 3.05, a(1N) = 4.75 G. Line width 0.15.

Several attempts were made to simulate the spectrum and the best results were obtained with the parameters reported in Figure 8S. Although this simulation did not provide any certainty about identification of the radical species, and other experiments are clearly required to get some more information, it however furnished encouraging support to the intermediacy of indium-bounded aminyl radicals.

Since $InCl_3$ is first of all a Lewis acid, it could influence the structure of any N-centred radical by coordination to the nitrogen atom of the starting azido moiety. It could even actually react with the azido group, analogously to what has been reported for the reactions of other Lewis acids with azides. Thus, it cannot be excluded that the paramagnetic species detected so far could be the result of these competitive processes rather than the postulated pathway. In order to elucidate this point, we performed a product and ESR investigation on the reactions of $InCl_3$, $AlCl_3$, and $GaCl_3$ with some azides in various solvent, mainly dichloromethane or $MeCN/CH_2Cl_2$ mixtures. The results obtained were extremely interesting because, from one side, they showed that a novel kind of reaction takes place when these compounds are mixed together and, from the other, they demonstrated that the spectra recorded in our previous experiments did not derive from these possible side reactions. The following section will describe that the spectra obtained by reacting group-XIII Lewis acids with azides can be accounted for through formation of complex, stable radical species whose nature has still to be fully understand, but whose formation is symptomatic of a novel azide reactivity.

Reaction of Aromatic Azides with Group XIII Lewis Acids

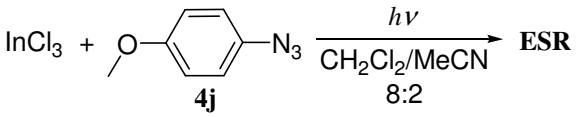
It has been reported by Takeuchi that when aromatic azides react with aromatic compounds in the presence of $AlCl_3$ a decomposition reaction occurs. The result of this decomposition is an extremely reactive *N*-containing species able to give *N*-aromatic substitution reactions.[7] To account for this reactivity, Takeuchi suggested that the aromatic electrophilic substitutions were performed by $AlCl_3$-complexed arylnitrenes ***T*** ensuing from aryl azide-$AlCl_3$ complexes (Scheme 12). Takeuchi also marginally observed that by mixing the aryl azide and $AlCl_3$ in CH_2Cl_2 at 243 K a strong blue colour developed; this colour faded completely, with concomitant nitrogen gas evolution, when the solution was warmed to 273 K. However, no product analysis of the resulting mixture was carried out and no other mechanistic or synthetic data were subsequently obtained about Lewis acid-catalysed decomposition of azides.



Scheme 12

We are going to show, by product analysis and ESR spectroscopy, that $AlCl_3$ and other group XIII Lewis acids react with aryl azides through generation of radical intermediates.

When 4-methoxyphenyl azide **4j** was mixed with $InCl_3$ in a 8:2 (v/v) CH_2Cl_2/MeCN mixture and the resulting solution was transferred in a quartz capillary tube and examined by ESR spectroscopy, a very persistent radical grew up at 260 K under UV photolysis conditions (Figure 9). The same sample was analyzed again after 12 days without UV light at 300 K and the signal was still present (Figure 9a).



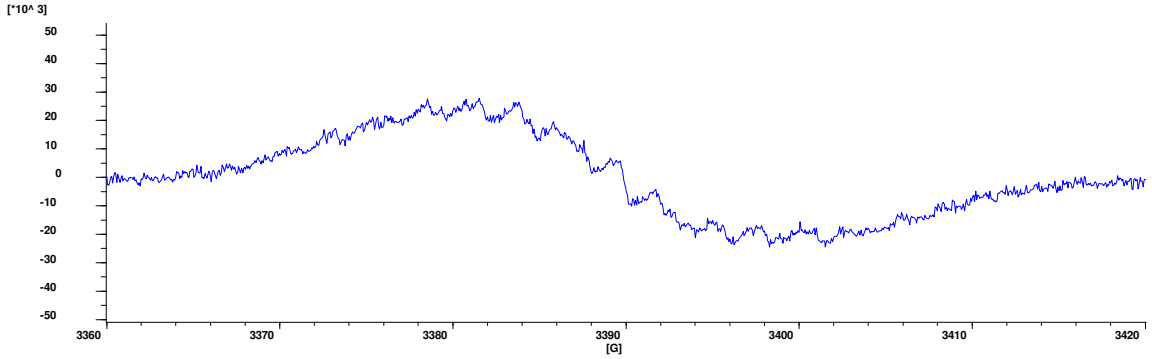


Figure 9: **4j + $InCl_3$**; 260 K; MW freq.: 9.5 GHz; M. A.: 0.6 Gpp; Power: 1 mW; 1st der.

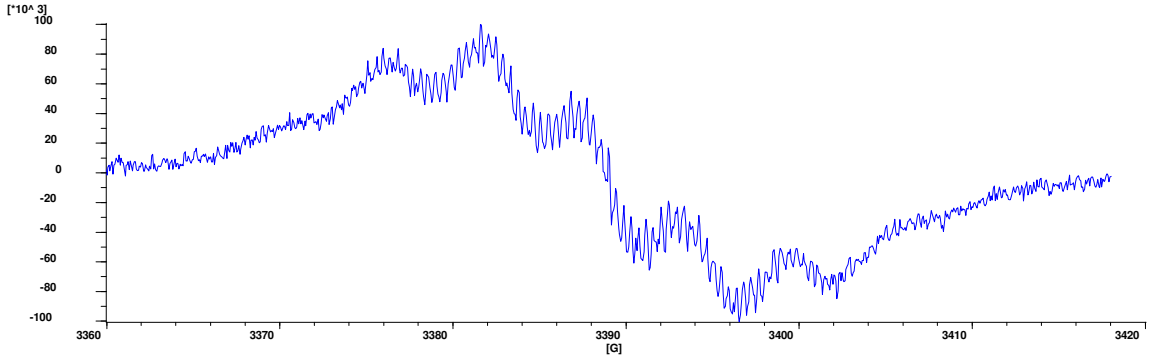


Figure 9a: **4j + $InCl_3$**; 300 K; MW freq.: 9.5 GHz; M. A.: 0.2 Gpp; Power: 1 mW; 1st der.

Although these spectra are similar to those recorded with the system DTBP/Me_6Sn_2/$InCl_3$ (Figures 7 and 8), it is very unlikely they are same species. They have in fact different line distances (0.42 G for Figure 9 and 0.23 G for Figure 8) and, above all, the samples showed a very different stability. It is therefore evident that different paramagnetic species are generated when aromatic azides reacts with $InCl_3$ alone.

The possibility that a nitrenium ion complex could be involved in the mechanism of decomposition of aromatic azides with $InCl_3$, analogously to what postulated by Takeuchi, was taken into account but promptly discarded. Nitrenium ions in the paramagnetic triplet state would have so short lifetimes as to make them undetectable by ESR spectroscopy. It is also unlikely that nitrenium ions could be the precursors of the observed paramagnetic species via oxidative or reductive electron transfers. Oxidation of a nitrenium ion is in fact improbable, if not impossible at all, and reduction, for example by the electron-rich azide, would afford aminyls with spectra analogous to those of Figure7 or 8 rather than that of Figure 9.

The reaction of 4-fluorophenyl azide **4i** with $InCl_3$ in dichloromethane was then investigated. A deep violet colour developed once the solution was heated at 323 K for 30 minutes. The colour persisted during the ESR acquisition and for several months afterwards. The spectrum recorded after 51 scans (Figure 10) was simulated but, unfortunately, no results with good correlation coefficients were obtained. The problems associated with spectral simulation (both in this case and with azide **4j**) are strictly related with both spectral complexity and the difficulties in product analysis of the reaction mixtures. In fact, isolation of some products from the ESR samples would give some hints about possible intermediates and would greatly help performing simulations. Unfortunately, these reactions generally furnished major amounts of the starting azide along with tars and trace amounts of other compounds difficult to characterize. It could be assumed that the strong signal observed might be due to a stable paramagnetic complex between the N_3 moiety and the metal, e.g. a triazenyl-like structure, but there are no similarities between our spectra and other ESR data of known triazenyl radical adducts, so that our hypothesis could not find any support.

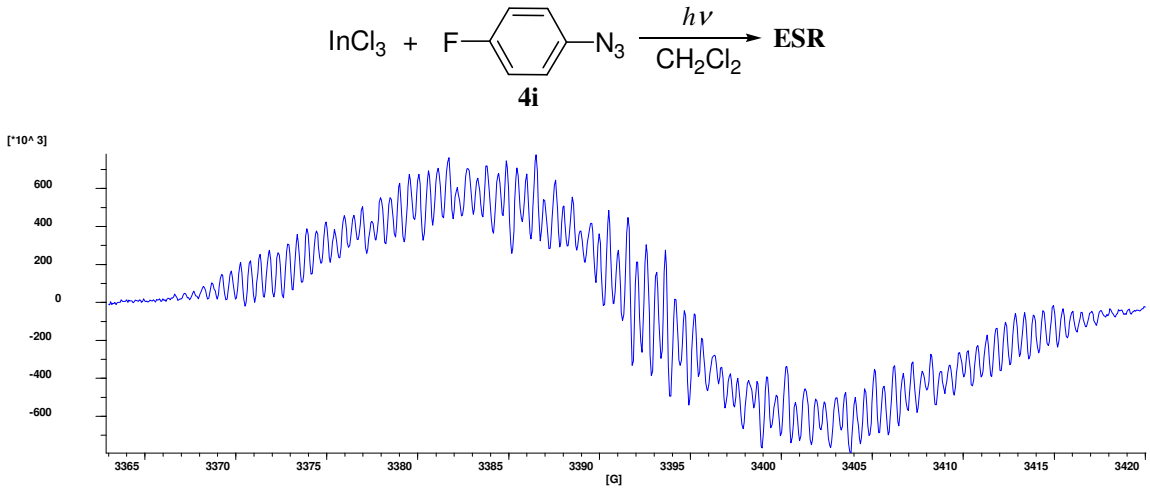
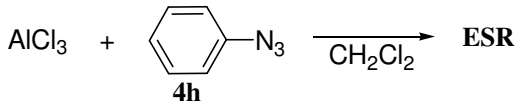


Figure 10: **4i + $InCl_3$**; 300 K; MW freq.: 9.5 GHz; M. A.: 0.2 Gpp; Power: 2 mW; 1st der; 51 scans.

The reactions between azides **4h**, **4k**, **4l** and indium trichloride were even worse, giving rise to poor signals and corresponding unreliable simulations, probably due to low reactivity of $InCl_3$. We therefore tried to force the conditions using a stronger Lewis acid such as aluminium trichloride.

Using the same procedure as described above, that is adding the azide (**4h** or **4j**) to a suspension of anhydrous $AlCl_3$ in CH_2Cl_2, a violent reaction occurred with strong gas evolution and persistent dark blue colour formation. ESR analysis of the reaction of **4h** at 305

K (Figure 10) showed a strong, broad signal whose resolution improved after several days (Figure 10a).



4h

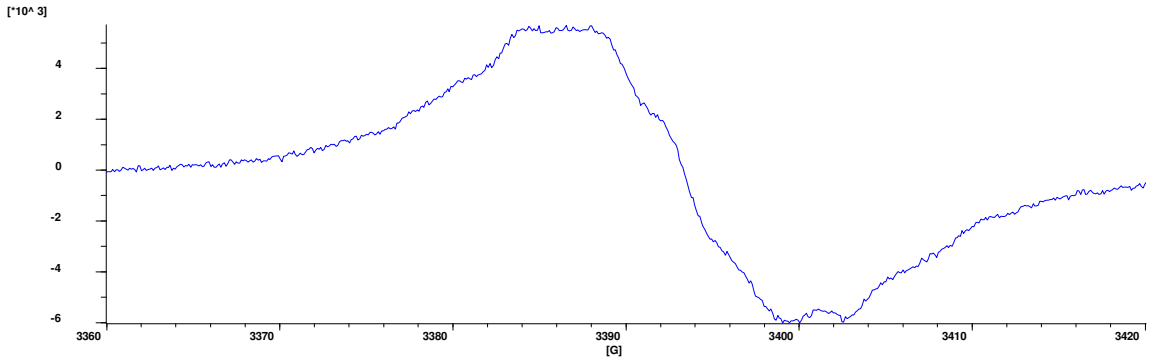


Figure 10: **4h + $AlCl_3$**; 305 K; MW freq.: 9.5 GHz; M. A.: 0.8 Gpp; Power: 2 mW; 1st der.

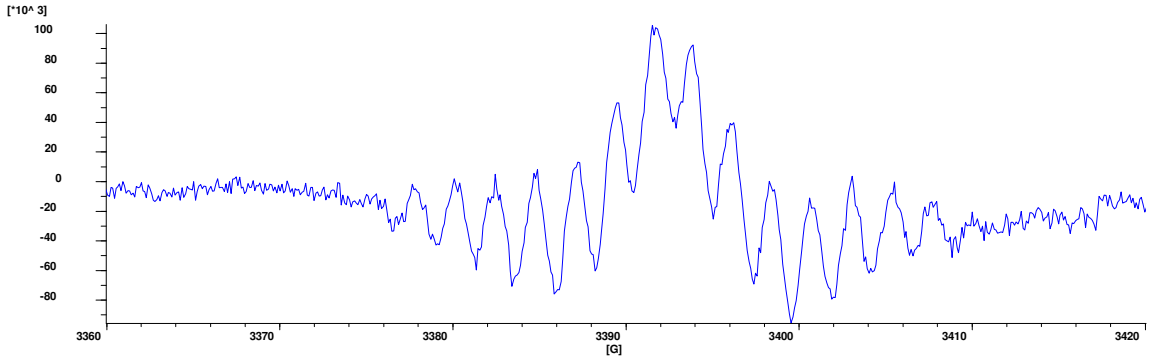


Figure 10a: **4h + $AlCl_3$**; 290 K; 3 days sample; M. A.: 1.2 Gpp; Power: 1.3 mW; 2nd der.

Azide **4j** reacted violently as well with aluminium trichloride in dichloromethane, giving a dark solution with generation of the radical species shown in Figure 11. Product analysis of both reaction mixtures gave no interesting results, showing only the starting azide along with unidentifiable tars, like in the case of $InCl_3$. The black, amorphous, tarry solid obtained after solvent evaporation was insoluble both in acids and in bases as well as in the most common polar and apolar organic solvents, thus preventing any spectroscopic (MS, IR, NMR) analysis.

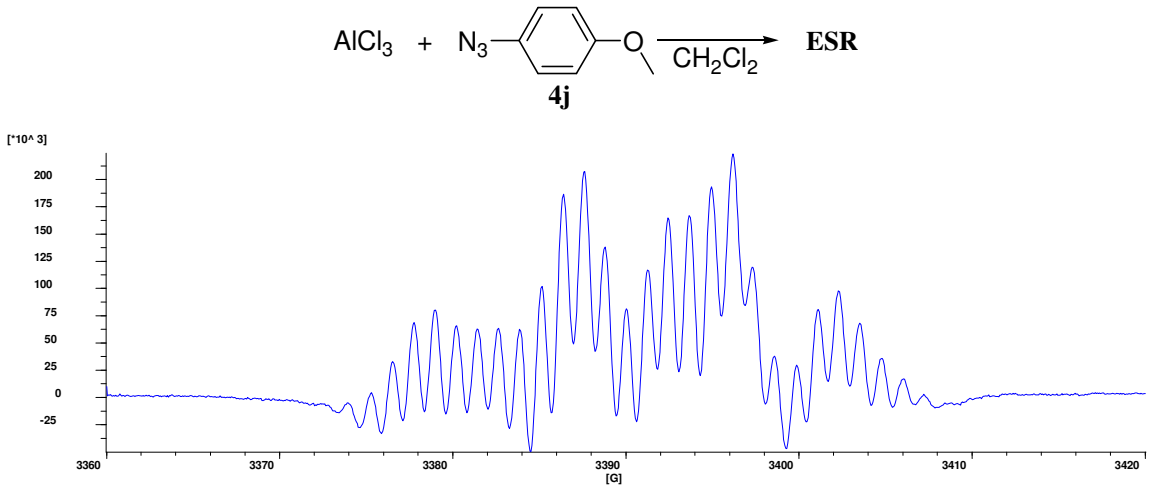


Figure 11: **4j + $AlCl_3$**; 220 K; MW freq.: 9.5 GHz; M. A.: 1.2 Gpp; Power: 2 mW; 2nd der.

More interesting results were obtained when gallium trichloride was employed. Gallium trichloride showed analogous reactivity with respect to $AlCl_3$, sometimes it was even more reactive, but the recorded spectra appeared at first analysis easier to simulate and to rationalise, due to the well-resolved fine structure. In particular, product and spectral analyses carried out on the reactions of phenyl azide and 4-methoxyphenyl azide gave greater information with respect to the analogous reactions with $InCl_3$ and $AlCl_3$.

The reaction were performed by adding a pentane solution of $GaCl_3$ to a CH_2Cl_2 solution of the azide. Once gas evolution stopped, a small amount of solution was transferred into a quartz capillary tube, was degassed with nitrogen, and then analyzed by ESR spectroscopy.

Mixing phenyl azide **4h** and $GaCl_3$ generated an impressive reaction with a beautiful, brilliant dark red colour developing as soon as the azide was added. The 1st derivative ESR spectrum is shown in Figure 12. The spectrum displayed a highly resolved line pattern that is a piece of news for this kind of reactions.

Also azide **4j** gave similar reactions, affording dark blue coloured solutions and faster gas evolution. The observed radical species was stable for several days and its ESR spectrum was quite similar in resolution to that obtained from **4h** (Figure 13)

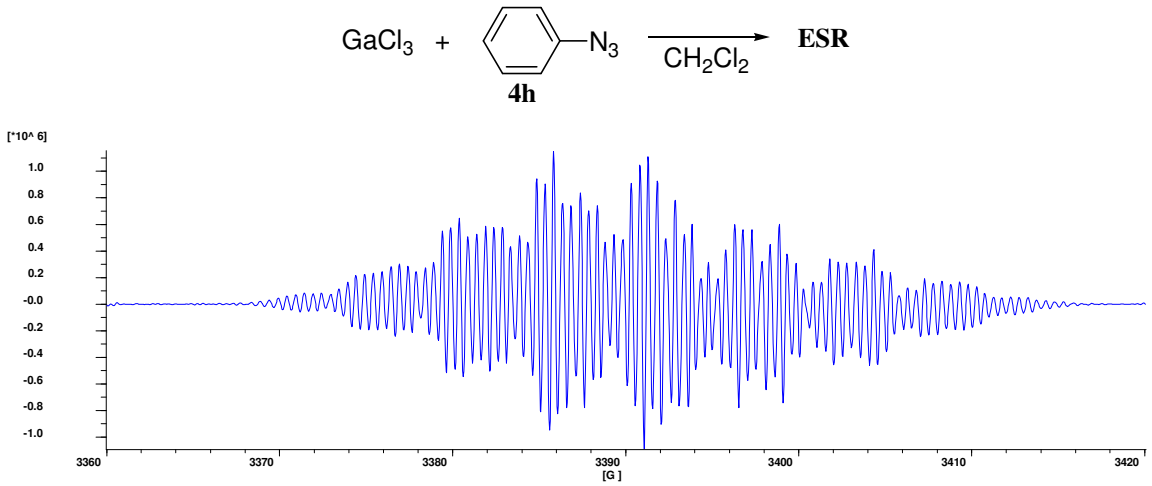


Figure 12: **4h + $GaCl_3$**; 300 K; MW freq.: 9.5 GHz; M. A.: 0.2 Gpp; Power: 0.8 mW; 1st der; 17 scans.

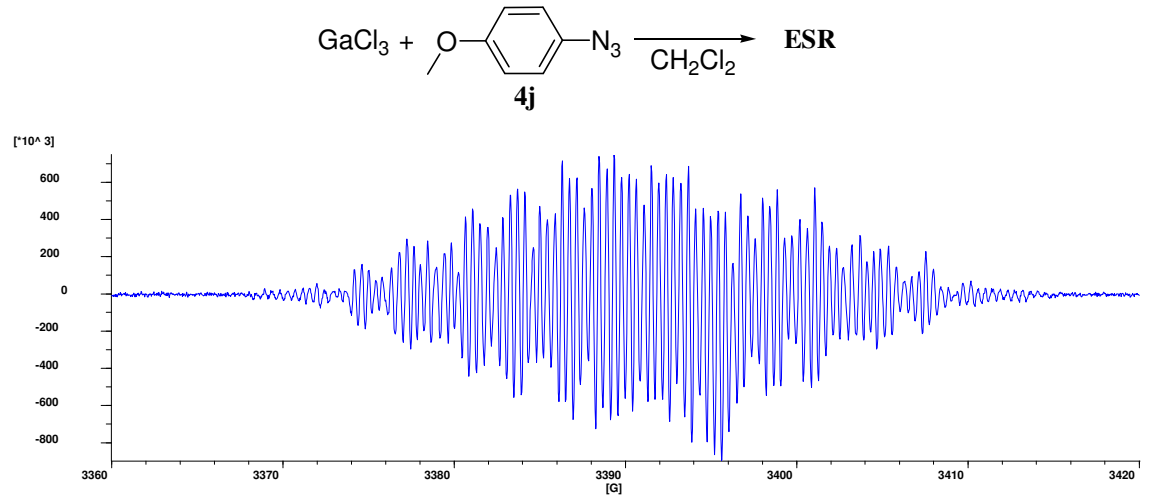


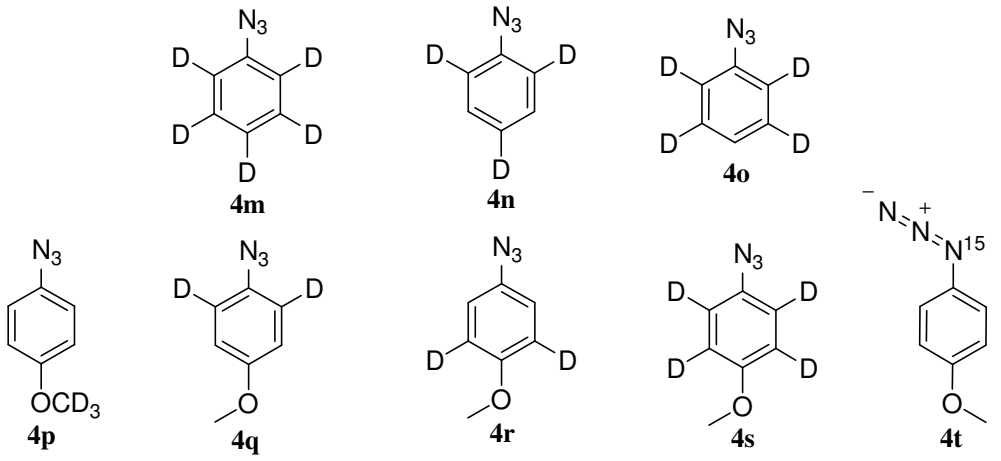
Figure 13: **4j + $GaCl_3$**; 298 K; MW freq.: 9.5 GHz; M. A.: 0.35 Gpp; Power: 1 mW; 2nd der; 43 scans.

These two spectra appeared however much more challenging than we might have thought at a first sight. They are in fact very large, approximately 48 G wide, and very different from the spectra of the postulated aminyls reported above; moreover, their width and complexity cannot be simulated by assuming the presence of the hydrogen atoms belonging to the starting azide and only one nitrogen atom (evolution of nitrogen during the reaction should however entail that, whatever intermediate is formed, it should contain just one nitrogen).

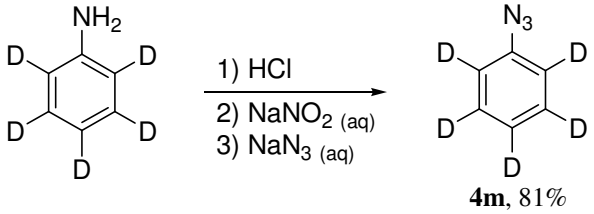
To overcome these difficulties, we decided to synthesize aromatic azides where some hydrogen atoms were replaced by deuterium. In fact, the isotopic replacement of several nuclei by their less abundant isotope in specific positions is one of the most reliable methods of assigning the observed coupling constants to specific nuclei. Such a replacement strongly changes the hyperfine pattern, because the two nuclei have different g_e factors and usually

also different spin quantum numbers ***I***. It is generally assumed that the electronic structure of the radical is not markedly affected by this replacement.

A number of deuteriated phenyl azides **4m-o** and 4-methoxyphenyl azides **4p-t** were prepared. In order to clarify the contribute of the nitrogen atom, the isotopic replacement involved this atom as well: the ^{15}N-labelled *p*-methoxyphenyl azide **4t**, in which the nitrogen isotope was directly bonded to the aromatic ring, was prepared. In the case of deuteriated azides, the isotopic replacement of the hydrogen atoms would increase the number of lines making the hyperfine pattern less simple [the spin quantum number of deuterium is $I = 1$, its spin multiplicity is $(2I + 1) = 3$]. Anyway, differences in the ESR spectra of these azides, compared with those already recorded, would have helped to simulate correctly the spectra of the unlabelled compounds and hence to define the structure of the paramagnetic species. Once determined a single structure, the other would be assigned by analogy.



Azide **4m** was sinthesised from the commercially available aniline *d*5 by standard diazotisation reaction. The sample was characterised via ^{1}H- and ^{13}C-NMR, and by EI mass spectrometry (Scheme 13).



Scheme 13

The pure phenyl azide-*d*5 was reacted with gallium trichloride in dichloromethane and the strongly dark violet coloured solution was analyzed by ESR. Looking at the spectrum of Figure 14, recorded at room temperature, it is possible to observe that the width of the whole signal is 38.2 G, thus closer to that of **4h**. This is consistent with the isotopic replacement of the hydrogen with its isotope.

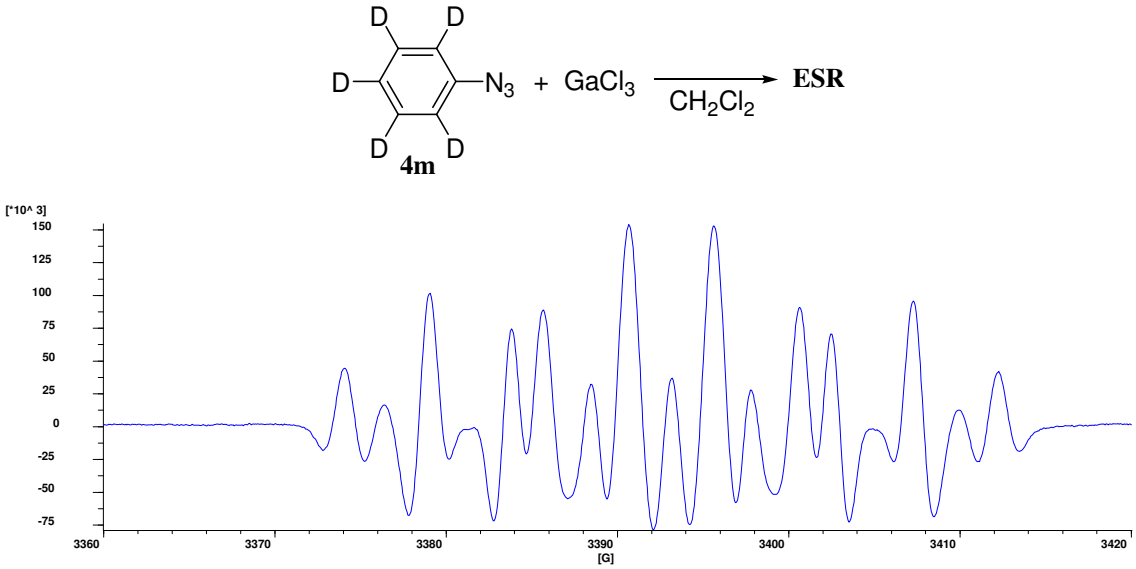
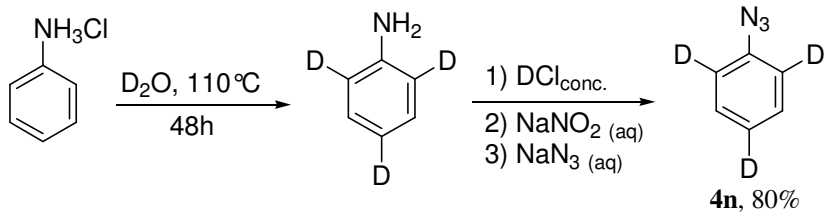


Figure 14: **4m + $GaCl_3$**; 298 K; MW freq.: 9.5 GHz; M. A.: 0.8 Gpp; Power: 1 mW; 2nd der; 5 scans.

The synthesis of azide **4n** was carried out by boiling aniline hydrochloride in D_2O for 24 hours in a sealed glass tube. The residual deuteriated water was then removed by distillation and replaced with fresh one. The mixture was boiled again for further 24 hours. Once D_2O was removed again the residual salt was dissolved in fresh DCl/D_2O 35% w/v solution, and was allowed to undergo the diazotisation reaction to furnish the desired azide **4n** after extractive work up (Scheme 14). EI mass analysis and ^{1}H-NMR and ^{13}C-NMR spectra were consistent for both the *d*3 aniline and the *d*3 azide.



Scheme 14

Also the reaction of **4n** with gallium trichloride showed an intense violet colour; the ESR spectrum has a width of 44.5 G (Figure 15).

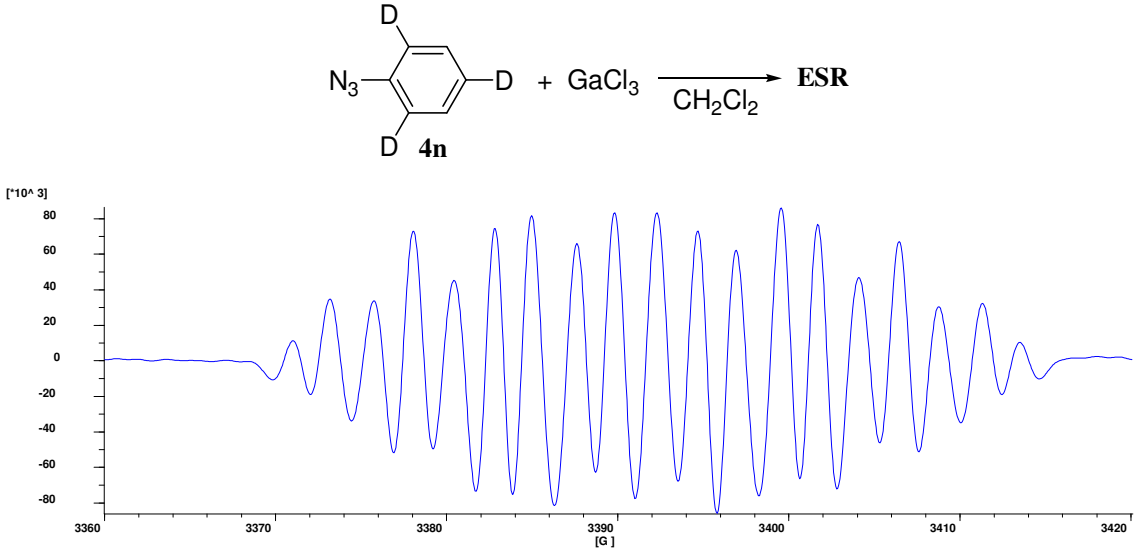
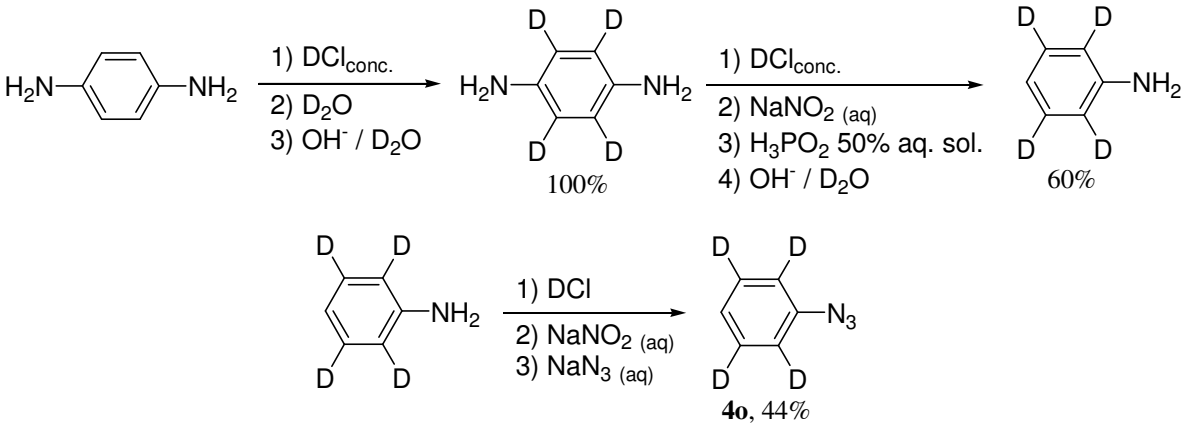


Figure 15: **4n + $GaCl_3$**; 300 K; MW freq.: 9.5 GHz; M. A.: 0.8 Gpp; Power: 1 mW; 2nd der; 20scans.

Azide **4o** was synthesised by the following synthetic approach. 1,4-p-Phenylenediamine dihydrochloride was deuteriated twice with boiling D_2O in a sealed glass tube for 72 hours. The resulting *4d*-1,4-p-phenylenediamine dihydrochloride was selectively diazotised and deaminated with H_3PO_2 furnishing the corresponding 2,3,5,6-tetradeuterioaniline in 60% yield after basic aqueous work up. Further diazotisation reaction with sodium azide gave 2,3,5,6-tetradeuteriophenyl azide **4o** in 44% yield (Scheme 15).



Scheme 15

The spectrum of the reaction of **4o** with $GaCl_3$ is showed in Figure 16. It looks quite similar to that of azide **4m** also as far as width is concerned (38.4 G). Since the spectrum of

4o should differ only by one proton from the spectrum of **4m**, this width value suggests that the spectral contribute of the hydrogen in the 4-position is not very important.

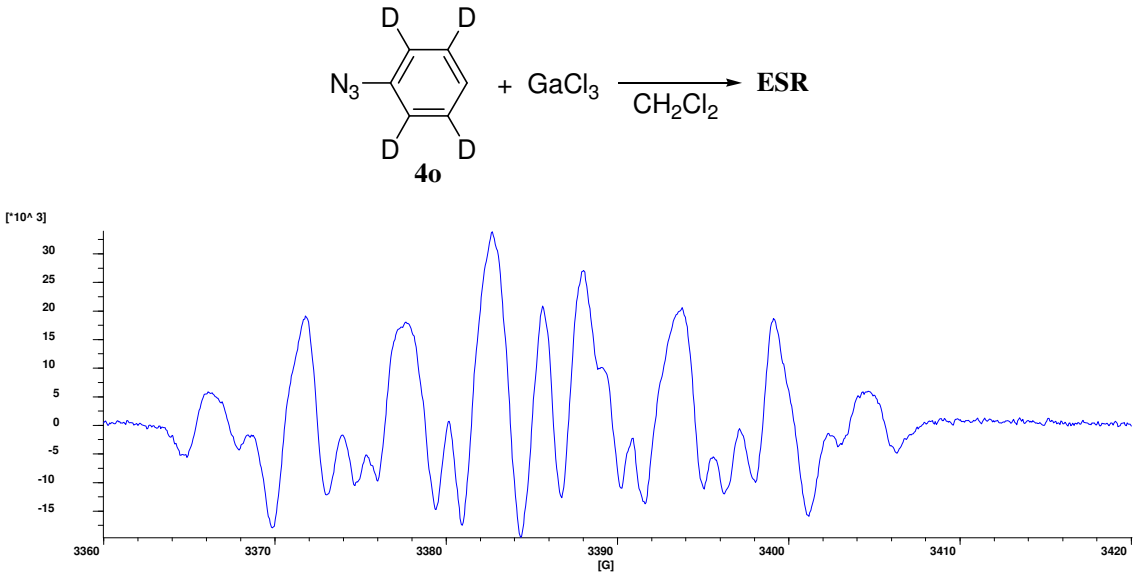
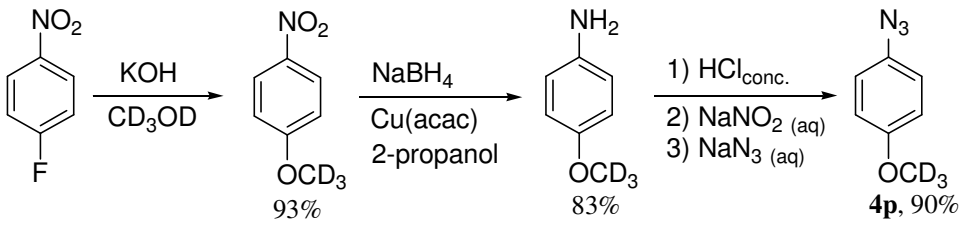


Figure 16: **4o + $GaCl_3$**; 300 K; MW freq.: 9.5 GHz; M. A.: 0.3 Gpp; Power: 1 mW; 2nd der; 70scans.

There was a good hope to obtain some relevant information from the 4-methoxyphenyl azide series as well, hence azides **4p, 4q**, **4r**, **4s**, and **4t** were prepared. The synthesis of azide **4p** was performed starting from 1-fluoro-4-nitrobenzene, which undergoes a rapid, efficient aromatic nucleophilc substitution of the fluorine atom by the methoxide anion, in turn obtained from commercially available methanol-*d*4 by treatment with KOH. The resulting 4-methoxy-*d*3-1-nitrobenzene was reduced with sodium borohydride and $Cu(acac)_2$ in 2-propanol to give the corresponding 4-methoxy-*d*3-aniline in 83% yield. The azide was synthesised by standard diazotisation reaction (Scheme 16).



Scheme 16

Azide **4p** reacted violently when treated with gallium trichloride in dichloromethane, generating a bright blue colour solution and a rapid evolution of nitrogen, analogously to **4j**. The ESR spectrum is reported in Figure 17. As expected, the width of this spectrum is

comparable to that of **4j** (≈ 48 G), indicating that the methoxy group does not interact very much with the unpaired electron. However a comparison between Figure 17 and Figure 13 (the spectrum of the hydrogenated analogue **4j**) shows that its contribute is small but evident.

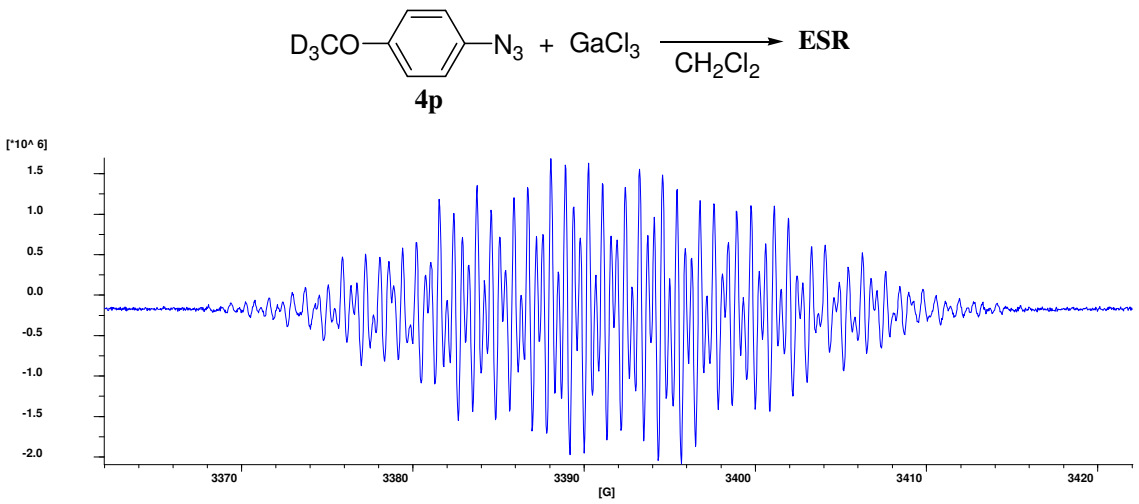


Figure 17: **4p + $GaCl_3$**; 300 K; MW freq.: 9.5 GHz; M. A.: 0.2 Gpp; Power: 0.8 mW; 2nd der; 100scans

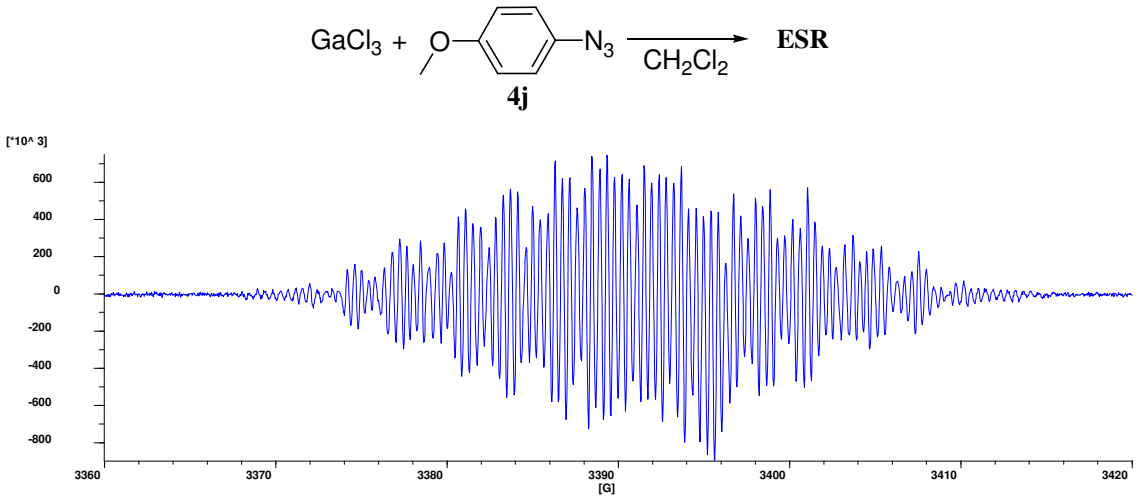
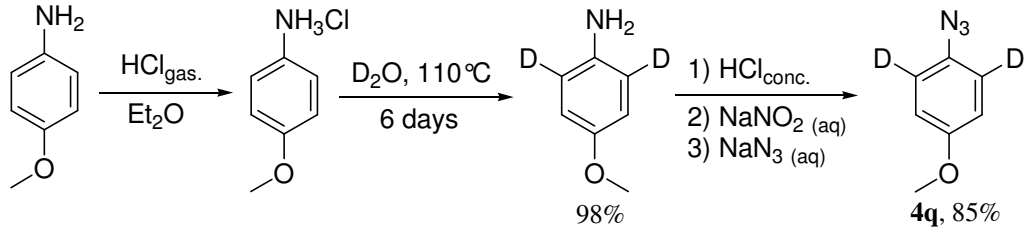


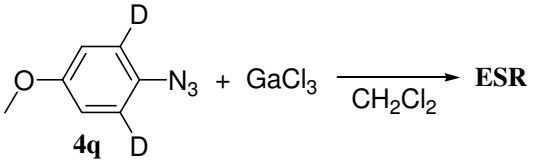
Figure 13 **4j + $GaCl_3$**; 298 K; MW freq.: 9.5 GHz; M. A.: 0.35 Gpp; Power: 1 mW; 2nd der; 43 scans.

2,6-Dideuterio-4-methoxyphenyl azide **4q** was prepared as showed in scheme 17. 4-Methoxyphenylaniline was reacted with gaseous hydrochloric acid in diethyl ether to give the corresponding salt, which was filtered, transferred in a glass tube, and dissolved with D_2O. Once the tube was sealed, the mixture was boiled for 6 days. Every 48 hours exhausted D_2O was distilled off and replaced with fresh one. The crude 2,6-dideuterio-4-methoxyaniline was diazotised to furnish **4q** in 85% yield (scheme 17)



Scheme 17

The reaction of **4q** with $GaCl_3$ followed the same trend pointed out by the 4-methoxy series. The ESR spectrum of the blue-violet solution showed again a complicated pattern of signals, but the spectrum width (42.4 G) is lower than that of **4j**, indicating that the deuterium replacement influences the radical structure (Figure 18). It is worth to emphasize the high persistence of the radical species, even in the presence of oxygen: the spectrum recorded after 20 days was identical to that recorded on the freshly prepared reaction mixture.



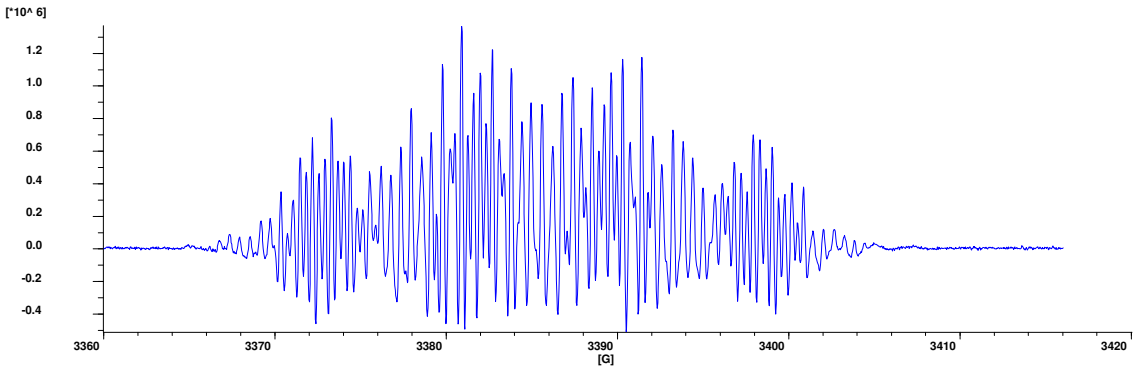
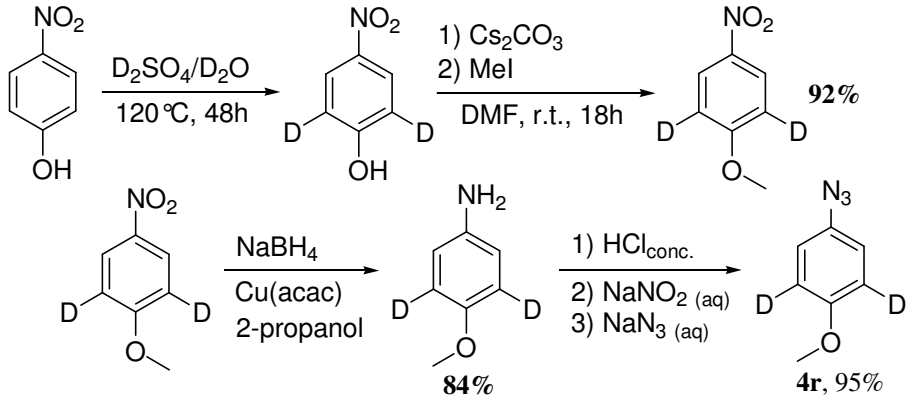


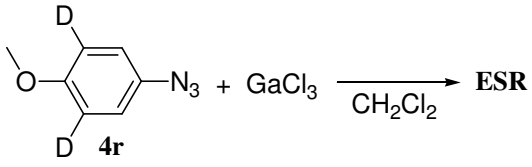
Figure 18: **4q + $GaCl_3$**; 300 K; MW freq.: 9.5 GHz; M. A.: 0.3 Gpp; Power: 2 mW; 2nd der; 35scans.

Azide **4r**, with the deuterium atoms in the meta positions, was prepared starting from 4-nitrophenol, which was deuteriated with a D_2SO_4/D_2O solution at 120 °C for 48 hours. The resulting 2,6-dideuterio-4-nitrophenol was methylated by reaction with Cs_2CO_3 and MeI, and the ensuing 2,6-dideuterio-1-methoxy-4-nitrobenzene was converted into the corresponding aniline by reduction with $NaBH_4$ and $Cu(acac)_2$ in isopropanol. Eventual diazotisation gave azide **4r** in 95% yield (Scheme 18).



Scheme 18

The ESR spectrum of **4r** was not well resolved because of some problems occurred to the instrument and was unfortunately the only spectrum we could record for this azide (Figure 19). It is however clear that this spectrum is comparable in width with that of azide **4q**.



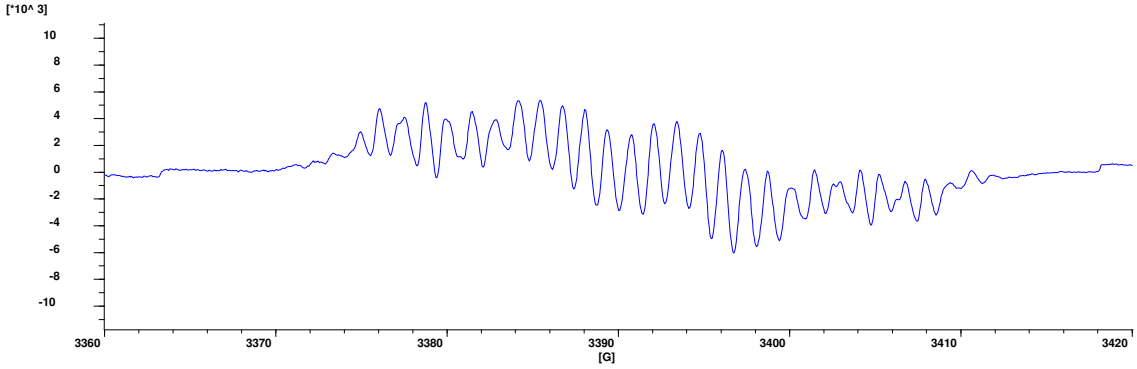
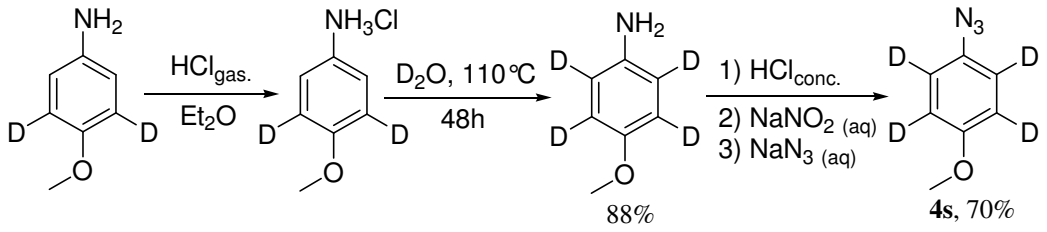


Figure 19: **4r + $GaCl_3$**; 300 K; MW freq.: 9.5 GHz; M. A.: 0.8 Gpp; Power: 2 mW; 1st der; 1scans.

2,3,5,6-Tetradeuterio-4-methoxyphenylazide **4s** was synthesised by diazotisation of 2,3,5,6-tetradeuterio-4-methoxyaniline, derived in turn from the reaction of 3,5-dideuterio-4-methoxyaniline hydrochloride with boiling D_2O for 4 days in a sealed tube (Scheme 19).



Scheme 19

The reaction of **4s** with gallium trichloride in dichloromethane gave the well known violet solution and the spectrum recorded showed a width of 38 G (Figure 20). Although the width was congruent with the isotopic replacement, the spectrum also showed additional quite small splittings: this is rather anomalous, because it would be expected to obtain broad, unresolved lines like in the case of the pentadeuteriated phenyl azide **4m**.

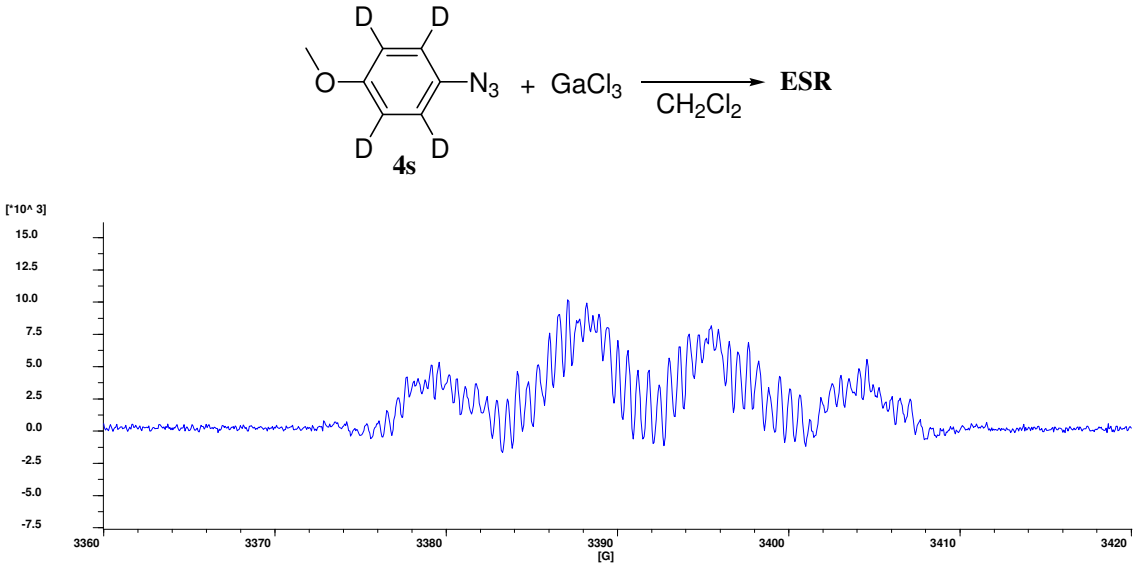
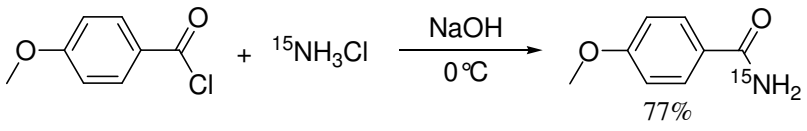


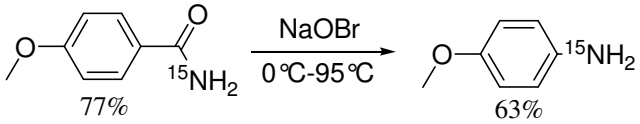
Figure 20: **4s + $GaCl_3$**; 300 K; MW freq.: 9.5 GHz; M. A.: 0.5 Gpp; Power: 1 mW; 2nd der.

The synthesis of azide **4t** was carried out by diazo transfer. This reaction required the synthesis of 4-methoxyaniline^{15}N and azido tris(diethylamino)phosphonium bromide.[8] First of all, 4-methoxybenzamide^{15}N was prepared by dissolving ammonium^{15}N chloride in a mixture of water and chloroform at 0 °C and then adding sodium hydroxide and 4-methoxybenzoyl chloride. After extractive work up and crystallisation, 4-methoxybenzamide^{15}N was obtained in 77% yield (Scheme 20).



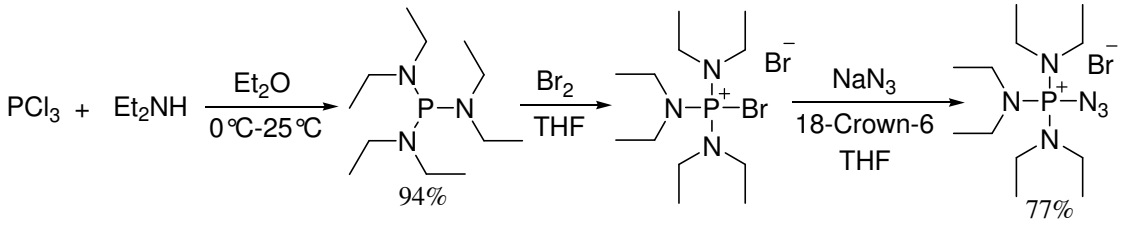
Scheme 20

Then, 4-methoxy benzamide^{15}N was added to a freshly prepared stirred aqueous solution of sodium hypobromide at 0 °C. The resulting mixture was heated at 95 °C for 4 days. The extractive work up furnished 4-methoxyaniline^{15}N (Scheme 21).



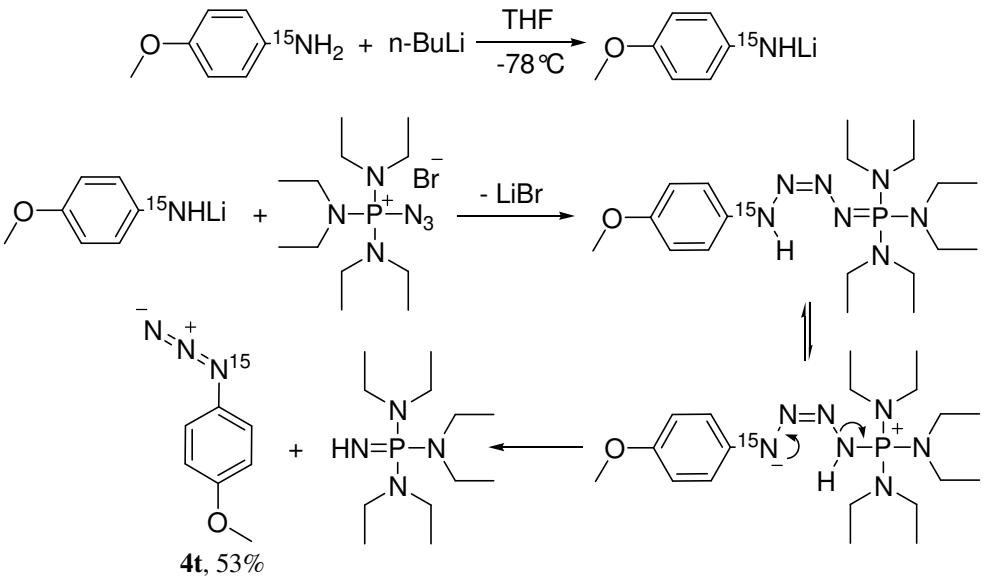
Scheme 21

The reaction of PCl_3 and diethylamine in diethyl ether gave the resulting tris(diethylamino)phosphine (94%), which was added to a THF solution of bromine. To the resulting mixture sodium azide was added and the reaction was stirred under nitrogen for two days. Crystallisation gave azido tris(diethylamino)phosphonium bromide in high yields (Scheme 22).



Scheme 22

4-Methoxyaniline^{15}N was deprotonated with n-BuLi in THF and the azidophosphonium bromide was added. The reaction mixture was neutralised with an ammonium chloride solution and extracted with dichloromethane to give 4-methoxyphenyl azide ^{15}N (**4t**) (Scheme 23).



Scheme 23

The ESR analysis of the reaction of azide **4t** with $GaCl_3$ in dichloromethane furnished the beautiful spectrum of Figure 21. Its width is 40.3 G, that is 8 G narrower than that of azide **4j**. This value agrees with the ^{15}N replacement of the ^{14}N atom. In fact, although the ratio of magnetogyric ratio of the two isotopes is 1.4027, so that the ^{15}N hyperfine splitting ($a^{15}N$) should be 1.4 times the ^{14}N hyperfine splitting ($a^{14}N$), the two isotopes differ by the nuclear spin quantum number (I = ½ for ^{15}N, whereas I = 1 for ^{14}N). Thus, according to the spin multiplicity ($2I + 1$), the number of lines generated by the ^{15}N splitting is 2, with a distance of $a^{15}N$, whereas for ^{14}N the splitting is 3, with a distance between each line of $|a(^{15}N)|/1.4$. This means that the contribute to the whole extension of the spectrum would be ($a^{15}N$) for ^{15}N, but $2|a(^{15}N)|/1.4$ for ^{14}N. This means that for the same radical species, i.e. when the contribute of the nitrogen is the same, like in our case, the spectrum with ^{14}N will be larger than that with ^{15}N.

Azide **4t** produced a spectrum (Figure 21) different from the ^{14}N sample (Figure 21a), and this is quite evident looking at the shape of the complicated line pattern. Preliminary, comparative simulations are in agreement with the idea that the nitrogen atom plays a fundamental role in the structure of our radical species.

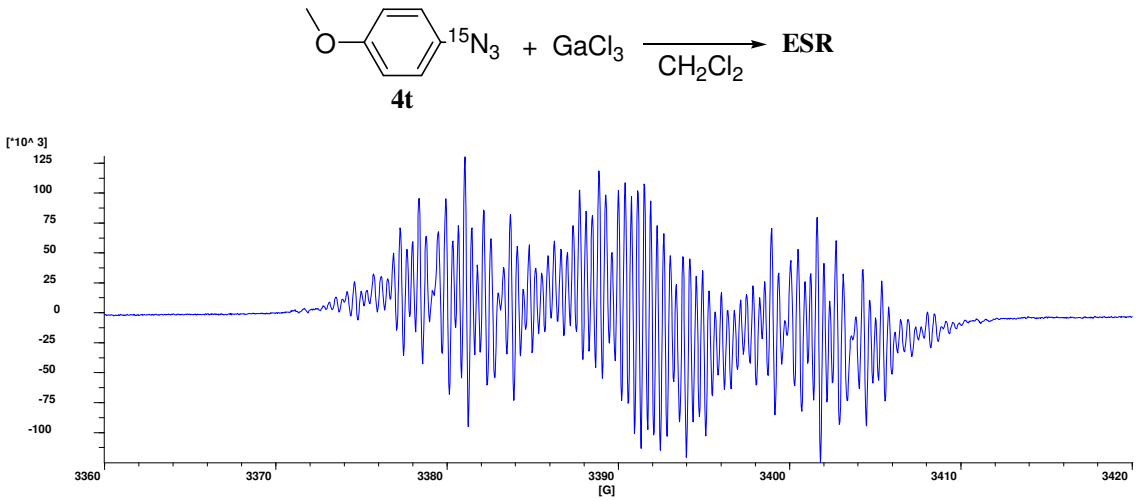


Figure 21: 4t + $GaCl_3$; 300 K; MW freq.: 9.5 GHz; M. A.: 0.2 Gpp; Power: 1 mW; 1st der; 8 scans.

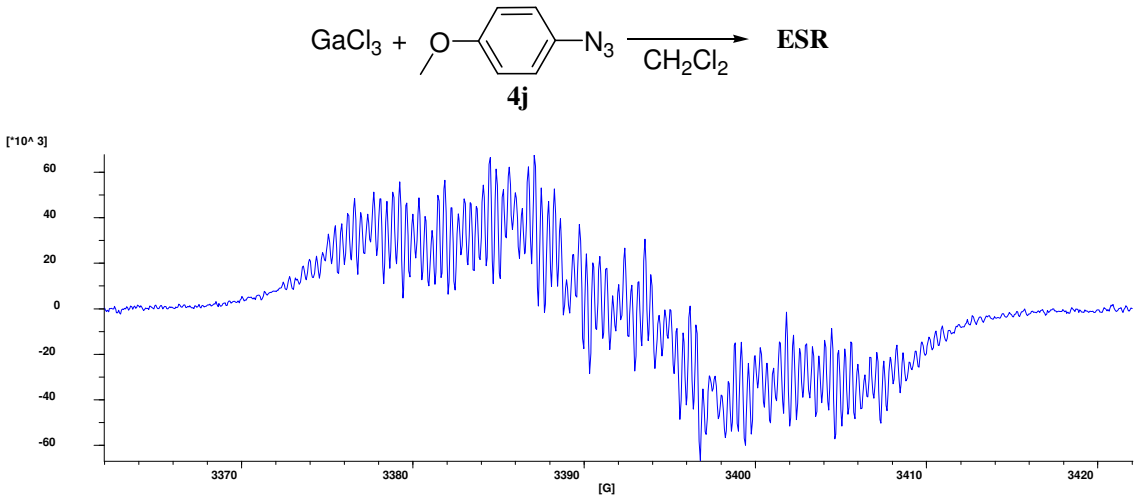


Figure 21a: 4j + $GaCl_3$; 300 K; MW freq.: 9.5 GHz; M. A.: 0.2 Gpp; Power: 2 mW; 1st der.

To rationalize the recorded spectra computer simulation is the most powerful tool. How does it work? Without giving any detailed explanation, it can be said that a software package allows to interact with the real recorded spectrum acquiring the instrumental parameters and measuring the real values of line distances. Each value must be associated to an atom of the paramagnetic intermediate that could interact with the unpaired electron. If there is a good overlay and a good correlation coefficient between the real spectrum and the simulated one, then the measured line distances correspond to the real hyperfine constants of the unpaired electron with the atom taken into consideration.

In order to achieve successful simulations, it is necessary to guess the structure of the paramagnetic species under study. For this reason, before the simulations of the phenylazide and the 4-methoxyphenyl azide series were carried out, product analyses of each reaction mixture were performed. Understanding of what kind of products were obtained would have

better clarified the nature of the radical species responsible for the interesting spectra recorded so far. Product analysis was however not so easy, since many reactions afforded very complicated mixtures where products were difficult to separate and identify. This was especially the case of the 4-methoxy series, where most of the time tarry, polymeric substances were isolated.

Analyses of the reaction mixtures were carried out principally via GC-MS. Once some products could be isolated by chromatographic separation, ^{1}H-NMR and ^{13}C-NMR spectroscopy were usefully employed for structure assignment. In some cases, direct analysis of the crude mixtures by ESI mass spectroscopy gave interesting details that helped in guessing probable reaction mechanisms.

The $C_6H_{5-n}D_nN_3$ Series

The reactions of phenyl azides **4i**, **4m-o** with gallium trichloride in dichloromethane gave reaction mixtures that were easily worked up with respect to the analogous reactions performed with aluminium trichloride. For this reason, product characterisation was mainly carried out on these samples.

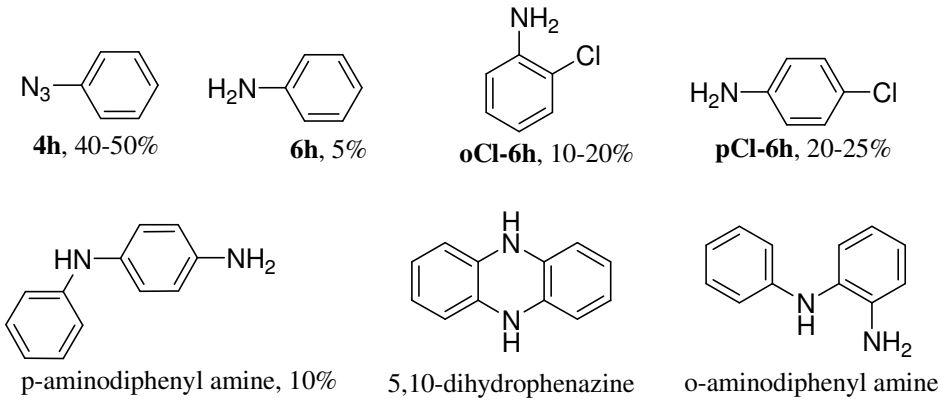
As it was said before, once the $GaCl_3$ pentane solution was added to the CH_2Cl_2 solution of the azide, the mixture colour immediately changed from pale yellow to dark green and violet. Gas evolution (probably nitrogen) was associated with the colour change.

Since the starting aryl azide was the only source of nitrogen gas, we thought that the azide was completely decomposed in the reaction mixture. Since the most probable product deriving from the azide decomposition associated with loss of nitrogen is the corresponding amine, we performed a basic aqueous work up followed by extraction with dichloromethane to isolate all of the possible basic reaction products. Phenyl azide **4h** will be used as a representative example of all the $C_6H_{5-n}D_nN_3$ series analysis.

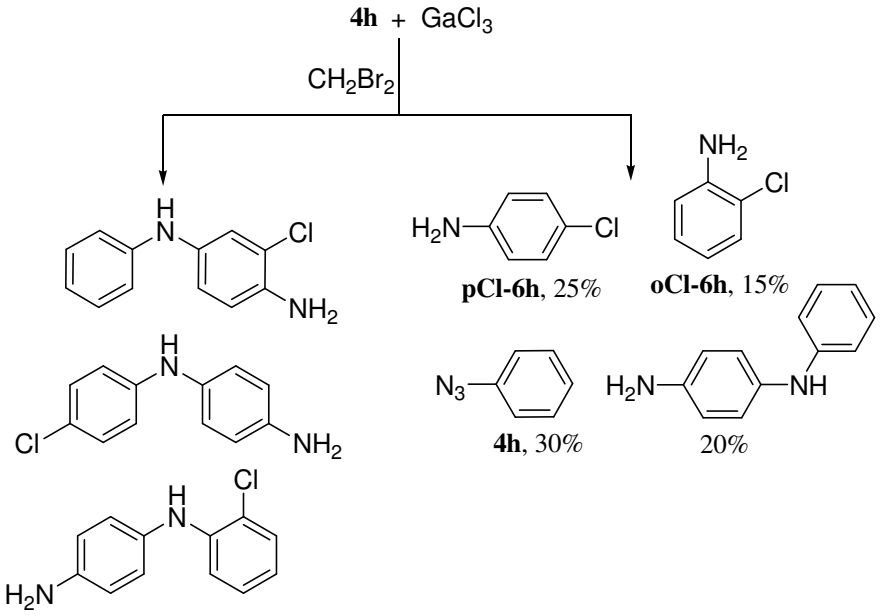
GC-MS analysis always showed complex mixtures composed by unreacted starting azide **4h**, aniline **6h**, ortho-chloroaniline **oCl-6h**, para-chloroaniline **pCl-6h,** and para-aminodiphenylamine, along with variable amounts, always traces, of 5,10-dihydrophenazine and ortho-aminodiphenyl amine (Scheme 24).

Analysis of Scheme 24 clearly shows that reaction product distribution is rather complicated and also, sometimes, irreproducible to some degree from one reaction to another. From one side, the complicated product mixtures could reasonably explain the complicated patterns in ESR experiments on this series of azides, also suggesting the presence of

overlapped signals from different intermediates; from the other, this possibility makes identification of the observed species an even more difficult task.



Scheme 24

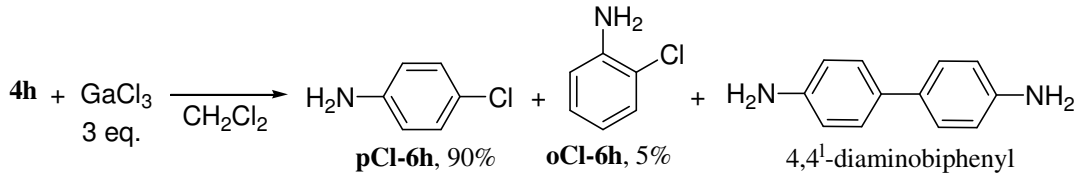


Scheme 25

To account for the formation of the main identified products, in particular the chloro-substituted anilines and p-aminodiphenylamine, some experiments were performed under different conditions. First of all, we decided to carry out a reaction in dibromomethane to understand if the solvent could be the source of the chlorine atoms. This reaction furnished again the chloroanilines, together with all the other products showed in Scheme 24; furthermore, trace amounts of the three isomers of ortho- and para-chlorinated p-aminodiphenylamine were detected by GC-MS, suggesting that the formed chloroanilines can react either with each other or with the starting azide. It is also worth noting that in this reaction the yield of p-aminodiphenylamine improved up to 20% (Scheme 25). These results

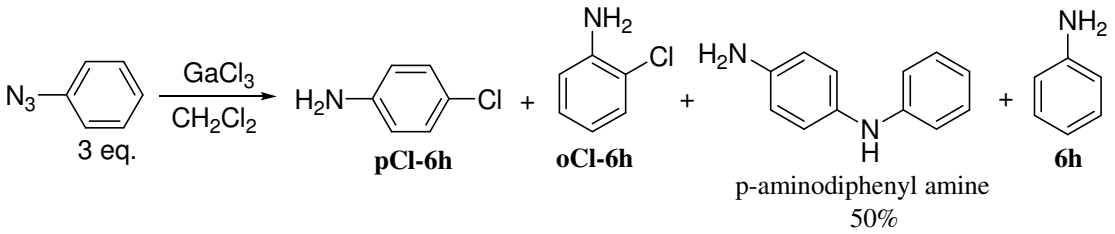
clearly point to the evidence that $GaCl_3$, rather than dichloromethane, must be the source of chlorine atoms, which are directly transferred from the metal to the aromatic ring somehow during the reaction.

When the reaction was carried out in dichloromethane with a 3-fold excess of gallium trichloride we observed total disappearance of the starting azide and formation of the **pCl-6h** as the almost exclusive product (90%), accompanied by small amounts of **oCl-6h** and traces of the 'dimer' 4,4'-diaminobiphenyl. This reaction clearly confirms the involvement of $GaCl_3$ in generation of the isolated chloroaniline (Scheme 26).



Scheme 26

On the other hand, when the reaction was performed using a 3-fold excess of azide only small amounts of anilines **6h**, **oCl-6h**, and **pCl-6h** were observed, and the main isolated product was the 'head-to-tail' dimeric product p-aminodiphenylamine in ca. 50% yield (Scheme 27). The great amount of dimer isolated in this reaction is the evidence that the starting azide plays a direct role in its formation. Although the exact reactive species is not known yet, it is reasonable to suppose that this intermediate could react with the azide, rather than with itself, to give the head-to-tail dimer. Furthermore, isolation of relevant amounts of that dimer could suggest that the main paramagnetic species responsible for our beautiful ESR spectra could be due to some intermediate structurally related to it rather than to the starting azide.



Scheme 27

Our reactions of aryl azides with gallium trichloride are carried out under oxidative acid conditions and it is well known that anilines, under similar condition, can be easily oxidised to

their corresponding resonance-stabilised radical cations, which can react further to give extremely persistent radical cation dimers by self coupling reaction.[9] The generation of these radical cations is strictly dependent on the reaction conditions, in particular the degree of protonation, which can make easier the electron transfer processes.[10] Furthermore, it has been reported that electrochemical oxidation of aromatic anilines can generate the same radical species, which are able to perform further polymerisation reaction to give oligomeric,[11] mainly polymeric, polyanilines.[11] ESR spectroscopy has been largely employed to study the structure of the aniline oligomeric radical cations, although most of the literature reports concern the simple dimeric structure, p-aminodiphenylamine radical cation, which is considered the most stable compound of the self-coupling reaction of aniline under oxidative conditions.[10,11,12]

Taking into account both the overall reported results and product analysis of our reaction mixtures, ESR simulation of the recorded spectra was approached by assuming that the radical cation of p-aminodiphenylamine could be one of the main paramagnetic reaction intermediates, giving rise to the strong, persistent signals recorded in our experiments.

The spectra from the $C_6H_{5-n}D_nN_3$ series were the best simulated and greatest confidence can be placed in these results. Although the R (correlation coefficient) values generally give a rough idea of the quality of the fit, R is affected by the quality and complexity of the experimental spectra as well as noise level, line width, baseline drift, and other such factors, and needs to be evaluated alongside visual inspection of the spectra. Small differences in R are probably not significant. The lower R value for the spectrum from **4o** is mainly due to the fact that the experimental spectrum was poor and rather unsymmetrical.

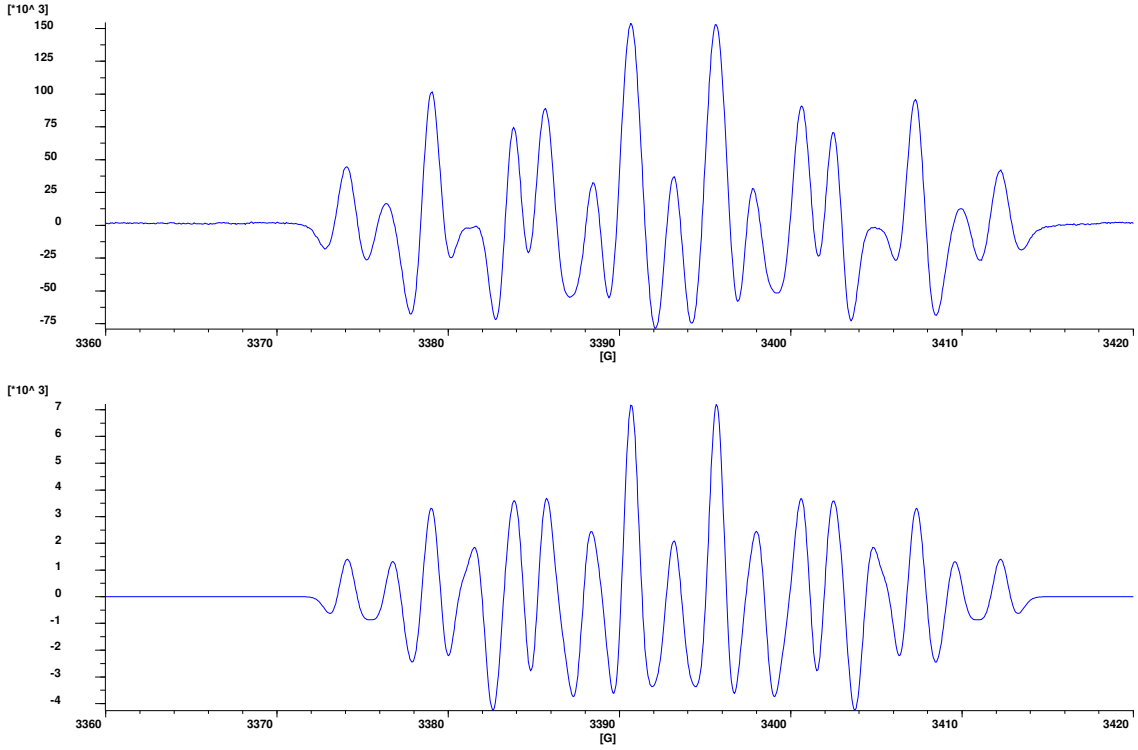
For this series the hyperfine splittings (hfs) form a reasonably consistent pattern. The spectra of the deuteriated species showed broader lines, just as would be expected for unresolved hfs from D-atoms. The spectra show comparatively large hfs from 4 or 5 H-atoms even when the precursor ring is fully deuteriated (**4m**): this suggests that protons were readily available in solution, presumably derived from the dichloromethane solvent. The spectrum of the species from **4h** shows hfs of 1.01 G from 2 ortho and 1 para H-atom of a phenyl ring together with hfs of 0.52 G from 2 meta H-atoms, i.e. a complete phenyl ring is present: this is confirmed by the spectrum from **4o**, which shows 1 para H-atom with hfs of 0.95 G, the two ortho D-atoms being unresolved. Similarly, the spectrum from the species derived from **4n** shows no hfs from the ortho and para D-atoms, as expected, and the small hfs from the two meta H-atoms was also unresolved in this case, due to the broader lines. In addition to this

phenyl ring, the species contains 2 non-equivalent N-atoms and hfs are observed for 4 or 5 additional H-atoms.

Azide								**R**
4m	6.53 [2H]	4.70 [2H]		5.13 [1N]	2.69 [1N]			0.939
40	6.20 [2H]	5.20 [2H]		5.40 [1N]	2.30 [1N]	0.95 [1H]		0.87
4n	7.10 [2H]	4.30 [2H]	4.30 [1H]	5.09 [1N]	2.30 [1N]			0.941
4h	6.56 [2H]	4.91 [2H]	4.91 [1H]	4.98 [1N]	2.46 [1N]	1.01 [3H]	0.52 [2H]	0.924

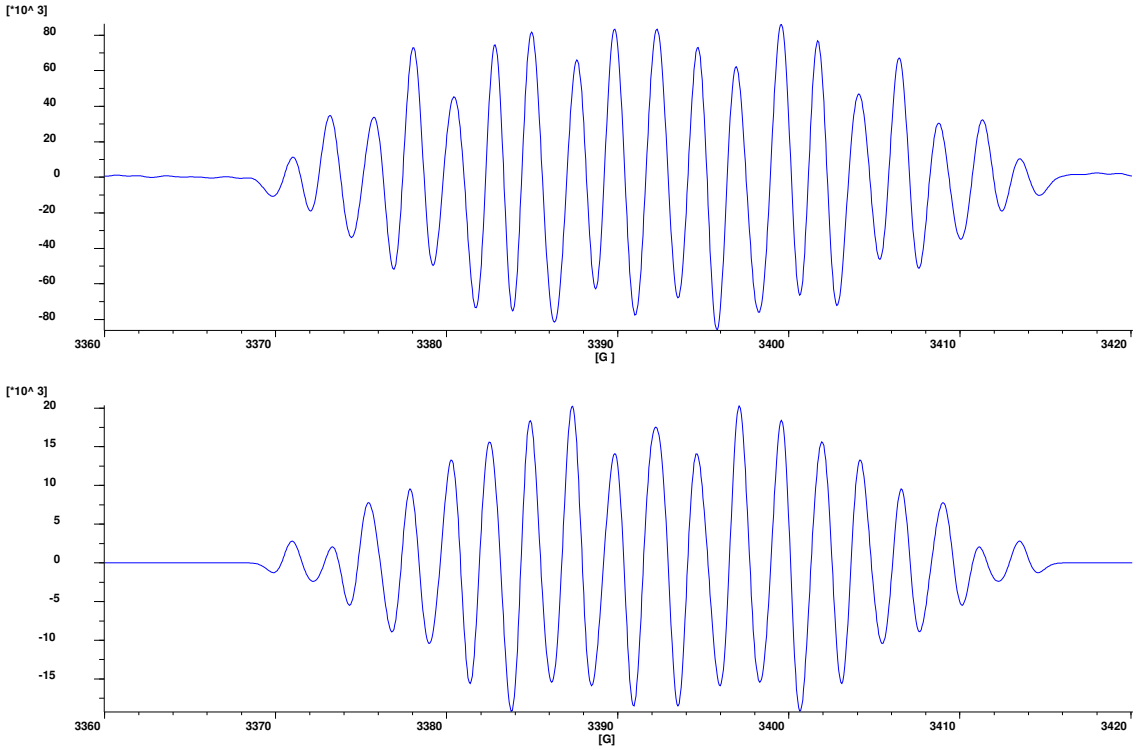
Table 1

Comparison between the real spectrum of **4m** + $GaCl_3$ in CH_2Cl_2 and its simulation:



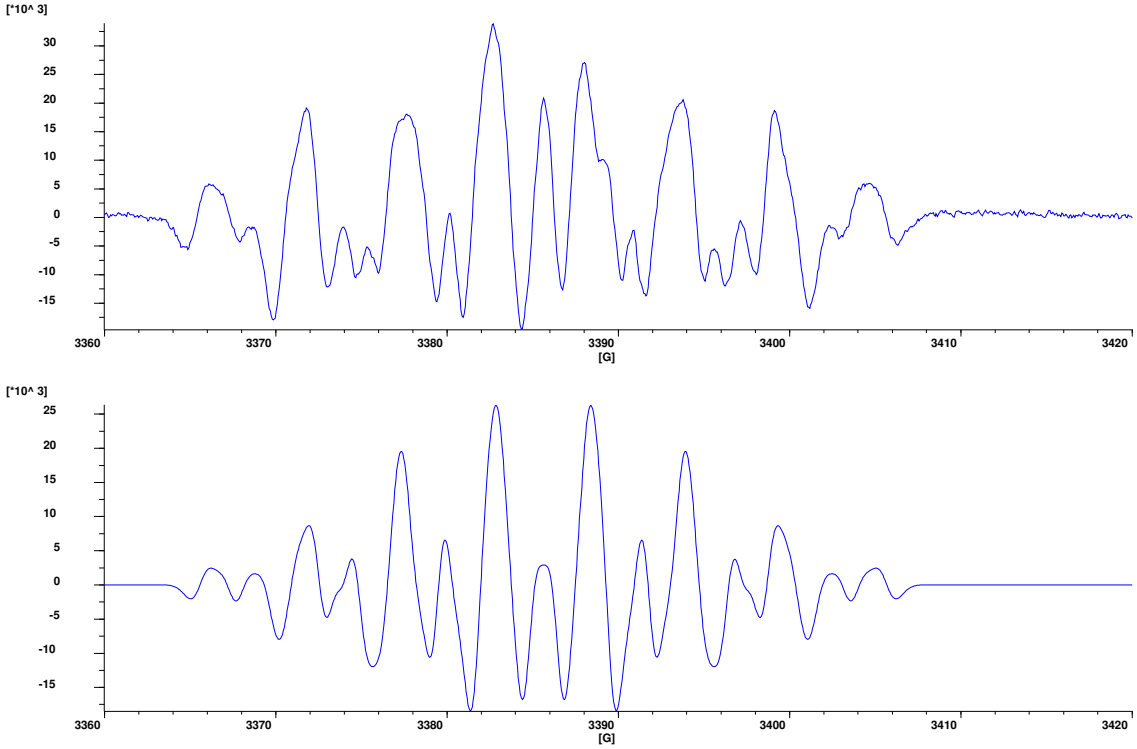
Simulation: a(2H) = 4.70, a(2H) = 6.53, a(1N) = 2.69, a(1N) = 5.15 G, Line width 1.95, R = 0.939

Comparison between the real spectrum of **4n** + $GaCl_3$ in CH_2Cl_2 and its simulation:



Simulation: a(2H) = 7.1, a(3H) = 4.3, a(1N) = 2.45, a(1N) = 5.25 G, Line width 2.10, R = 0.941

Comparison between the real spectrum of **4o** + $GaCl_3$ in CH_2Cl_2 and its simulation:

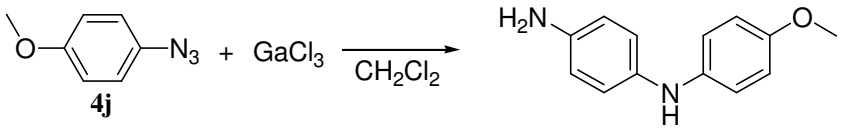


Simulation: a(1H) = 0.95, a(2H) = 5.2, a(2H) = 6.2, a(1N) = 2.3, a(1N) = 5.4 G, Line width 2.10, R = 0.941

The mechanism of formation of the observed products and the paramagnetic species will be discussed below.

The 4-MeOC$_6$H$_{4-n}$D$_n$N$_3$ Series

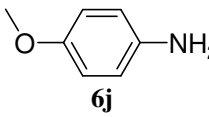
The reactions of 4-methoxyphenyl azides **4j**, **4p-t** generally did not furnish such complicated mixtures as it happened with the phenyl azide series, but the constant presence of considerable amounts of tars affected all of the reactions. Furthermore, these reactions appeared less sensitive to both reactants ratio and reaction conditions, and furnished, after work up procedures analogous to those employed for the phenyl azides, 4-amino-4'-methoxydiphenylamine, called *Variamine Blue*, as the main compound.[12] (Scheme 28).



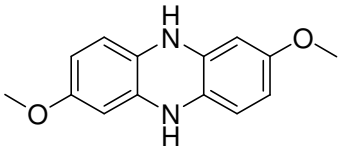
4j Variamine Blue

Scheme 28

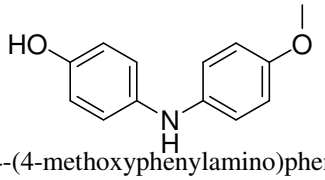
In same cases, the presence of 4-methoxyaniline **6j**, 2,7-dimethoxy-5,10-dihydrophenazine, and 4-(4-methoxyphenylamino)phenol, and its oxidised quinonic form as well, was observed (Scheme 29).



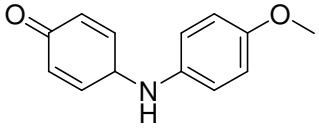
6j



2,7-dimethoxy-5,10-dihydrophenazine



4-(4-methoxyphenylamino)phenol

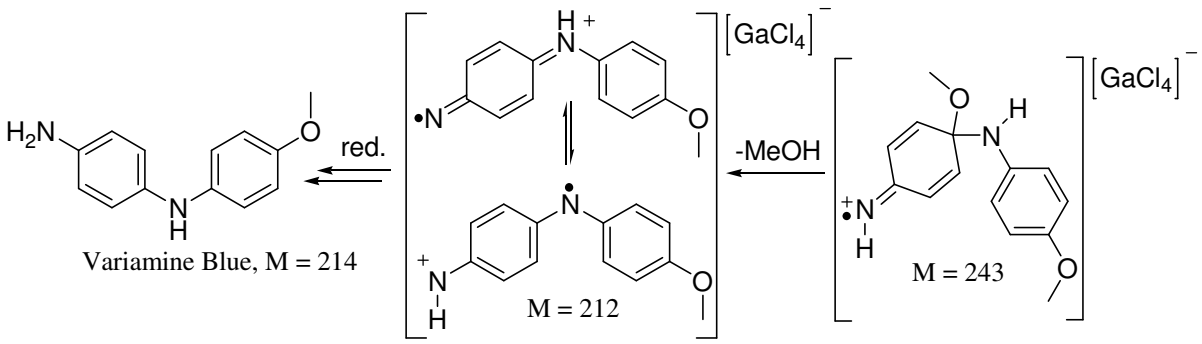


4-(4-methoxyphenylamino)cyclohexa-2,5-dienone

Scheme 29

From products analysis, it could be suggested that a precursor of amine **6j** must be responsible for all of the other compounds, in particular 4-amino-4'-methoxydiphenylamine, which can be explained by a mechanism involving some kind of aromatic substitution with replacement of the methoxy group by the nitrogen atom of a 4-methoxyaniline precursor. One of the most interesting data supporting the substitution mechanism is direct ESI-MS analysis of the reaction crude. In positive ions a compound was detected with a mass of 213 amu,

which corresponds to the protonated form of Variamine Blue quinonediimine form (which has a mass of 212 amu). Also a GC-MS analysis suggested that the latter could be the main reaction product, since the peak of Variamine Blue (214 amu) is accompanied by a broad baseline characterised by mass spectra containing mass 212 as the base peak (Scheme 30). Positive ions ESI-MS analysis also showed a compound with a mass of 243 amu, which would correspond to the protonated oxidised variamine precursor with the methoxy group still bonded to the aromatic ring (Scheme 30). Analysis of the same reaction crudes by negative ions ESI-MS always furnished a mass corresponding to $GaCl_4^-$, which could be the negative counterion of the observed cationic intermediates. This part of the analysis if however not conclusive, since also $GaCl_3$ give rise, under ESI conditions, to negative $GaCl_4^-$ ions.



Scheme 30

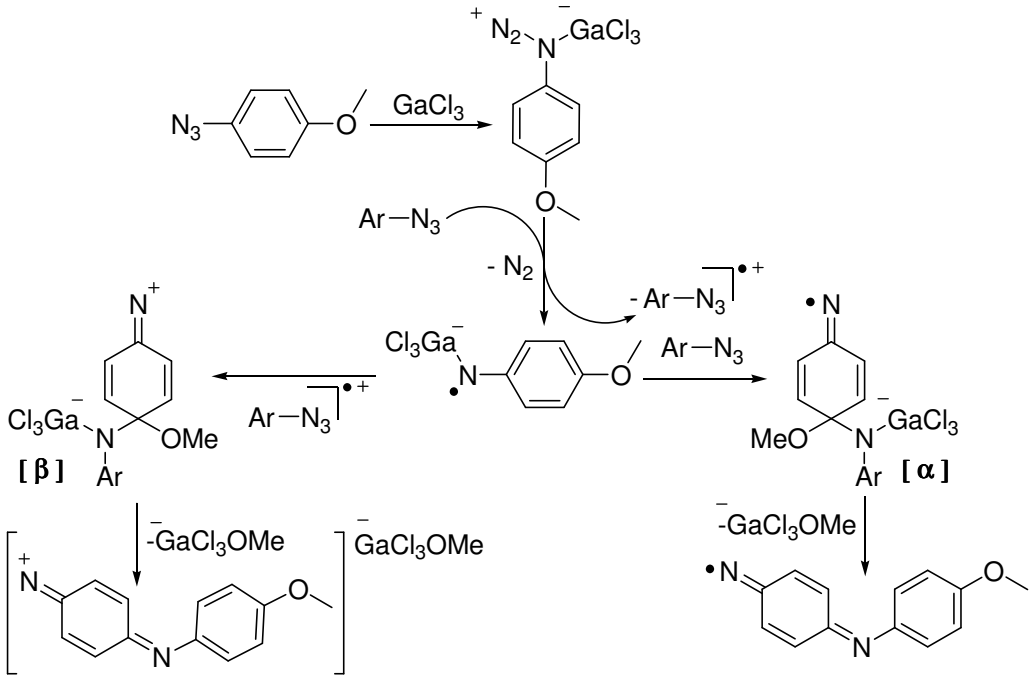
Unfortunately, in the case of the methoxy series simulations were less dependable. Several series members can in fact be each simulated with reasonable fits by using different numbers of hydrogen and also different hfs, and it is rather difficult to decide which is the most reliable one (Table 2).

Entry	Azide								R
1	**4j**	6.43 [1H]	3.01 [2H]	7.38 [1N]	2.83 [1N]	2.23 [4H]	0.87 [2H]	0.39 [2H]	0.902
2	**4t**	7.79 [1H]	2.67 [2H]	10.12 [^{15}N]	2.67 [^{15}N]	2.67 [2H]	1.54 [2H]	0.38 [2H]	0.910
3	**^{14}N eq**			7.2	1.9				
4	**4t**	8.30 [1H]	3.00 [2H]	10.90 [^{15}N]	3.85 [^{15}N]	2.31 [2H]	0.81 [4H]	0.34 [2H]	0.854
5	**^{14}N eq**			7.8	2.8				
6	**4p**	6.54 [1H]	3.48 [2H]	7.32 [1N]	2.53 [1N]	2.17 [4H]	1.46 [2H]	0.78 [2H]	0.873
7	**4p**	~7.5 [1H]	~5.1 [1H]	~6.3 [1N]	~2.8 [1N]	~2.7 [2H]			0.937
8	**4q**	~8.7 [1H]	~0.4 [2D]	~7.8 [1N]	~1.2 [1N]	~0.4 [2D]			0.989
9	**4s**	8.74 [1H]	~0.2 [2D]	7.97 [1N]	~1.2 [1N]	~0.2 [2D]			0.974

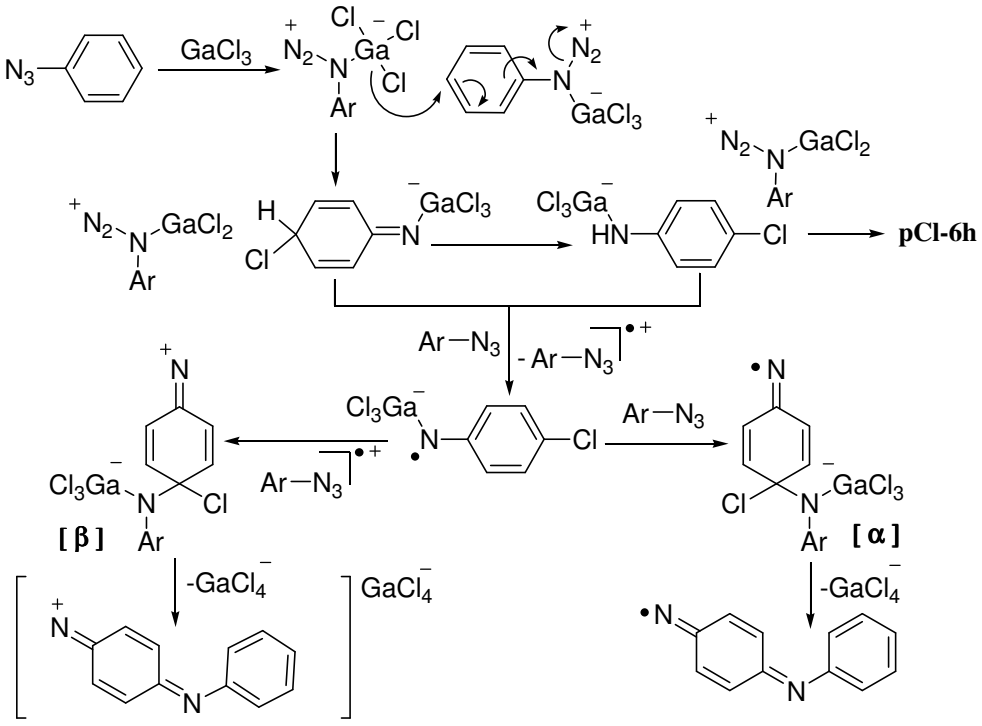
Table 2

Simulations for the spectra derived from 4-methoxyaniline^{15}N **4t** were visually quite good and the two possible fits are not very different. As a starting point, therefore, the ^{14}N hfs of the other members of this series should probably be ~10/1.4, i.e. something close to 7.8 or 7.2 G, for the first nitrogen, and 2.8 or 1.9 G for the second one. The spectra of the species obtained from $CD_3OC_6H_4N_3$ are not too far from this, but none of the spectra from the undeuteriated precursor agree well. The spectra from the other deuteriated precursors of this species were anomalous in that well-resolved spectra with narrow lines were observed in each case, whereas it was expected that the lines would become broad due to unresolved hfs from the D-atoms, as observed in the phenyl-series. The presence of hfs from H-atoms in every species indicates that protons must have been available in solution. The MeO-substituent would make the aromatic rings of these precursors highly susceptible to electrophilic aromatic substitution and one possibility is therefore that electrophilic substitution by protons has led to (partial) removal of the D-atoms from the rings. Hence the spectra may arise from mixtures of species with various numbers of H-atoms in their rings. The very first spectra recorded in each case presumably had least loss of D-atoms (and were indeed characterised by lower resolution). Simulations of these spectra and approximate best fit for major hfs for azide **4p** are reported in Table 2 (entries 6 and 7) These simulations for 4-$MeOC_6D_2N_3$ and 4-$MeOC_6D_4N_3$ seem, however, to show only one clearly resolved N-atom!

Scheme 31 reports a possible mechanism for the formation of the main reaction product of 4-methoxyphenyl azide, i.e. Variamine Blue. Coordination between the starting azide and GaCl3 gives rise to a Lewis base-acid adduct that can be reduced by the starting azide to give, after nitrogen loss, a gallium coordinated aminyl radical. This radical could react with either the starting azide or its radical cation to give species (α and β) closely related to Variamine blue, i.e. its quinonediimine precursors. Subsequent reduction of these species can eventually afford the isolated product. This hypothesis is supported by the above reported MS analyses of the reaction crudes, which clearly showed the presence of the quinonediimine as well as the methoxy containing precursor of the quinonediimine (α and/or β).



Scheme 31



Scheme 32

As far as the analogous mechanism of phenyl azide is concerned (Scheme 32), it is reasonable to suppose that formation of the head-to-tail dimer (p-aminodiphenylamine) would involve a 4-chloroaniline precursor rather than aniline or the starting azide. Indeed, as discussed above for **4j**, formation of the dimer requires the presence of a leaving group on the

aromatic ring, which, in this case, would be the chlorine atom. Therefore, formation of the dimer would entail a mechanism analogous to that reported in Scheme 31 for VB, whereas formation of the chloroanilines, p-chloroaniline in particular, not necessarily involves the intermediacy of paramagnetic species. As an additional support, the relative amounts of chloroanilines and dimer are strongly affected by the reaction conditions: in the presence of an excess of $GaCl_3$ chloroanilines predominate as the result of total complexation of the starting azide; when the azide is in excess dimer formation is preferred as a result of the reaction of the intermediate p-chloroaniline with the free, uncoordinated starting azide.

Of course, the mechanisms reported in Schemes 31 and 32 do not pretend to be exhaustive, since we did not get so far sufficient data to fully characterize all of the reaction intermediates (e.g. species α and β). However, whatever the real mechanism, the experimental results suggest the formation of paramagnetic species derived from dimeric products: although this is a behaviour commonly encountered in oxidation of aniline derivatives, it is a completely unreported outcome for organic azides.

Conclusions

The experimental work carried out in St. Andrews aimed at investigating the reactions of indium compounds with organic azides from a spectroscopic point of view. In particular, we tried to evidence and characterize possible nitrogen centred radicals that would be formed in those reactions.

Although the obtained data can not be considered conclusive, on the light of the overall results described in this chapter, the following conclusion can be drawn.

1) The reactions of azides with $HInCl_2$ did not afford any evidence of the presence of radical species of any kind. This could be due to the strong hydrogen donor capability of the indium hydride as well as to the high reactivity of the aminyl radicals that are supposed to be the main reaction intermediates. Spin trap experiments gave however some spectra compatible with trapping of nitrogen centred radical species, thus keeping open the possibility that indium aminyls could be really formed in our reactions.
2) When $HInCl_2$ was replaced by the system $InCl_3/Me_6Sn_2$/DTBP as a source of indium radicals, some spectra were obtained whose hyperfine structure seems compatible

with nitrogen centred radicals with the $InCl_2$ moiety linked to the nitrogen atom. This hypothesis has however to be confirmed by more thorough simulations.

3) Allylindium dichloride seems a good substitute for dichloroindium hydride for generation of indium centred radicals under photolytic conditions. Unfortunately, the ESR spectra recorded for the reactions of some azides with this indium reagent always showed the formation of the allyl radical: no other signals ascribable to nitrogen centred species were ever observed. From a synthetic point of view these reactions seem however interesting, since they allow allylation of electrophilic azides (e.g. phenylsulfonyl azide) and halogen or ester δ-substituted azides, the latter through a 1,5-H transfer rearrangement mechanism.

4) The reaction of azides with indium trichloride and other group XIII Lewis acids, in particular gallium trichloride, gives rise to strongly coloured, persistent paramagnetic species. Although we can not exclude that the observed ESR spectra could be the result of overlapping of different species, the data are consistent with the main presence of the radical cation of the head-to-tail dimer of the aniline corresponding to the starting azide. This hypothesis is supported by product analyses, which evidenced the formation of the dimer for 4-methoxyphenyl azide and mixtures of dimer and chloroanilines for phenyl azide. In the latter case, 4-chloroaniline is probably an intermediate in dimer formation.

Experimental Section

General Procedure

^{1}H and ^{13}C NMR spectra were recorded with Varian Gemini and Mercury spectrometer respectively at 300 and 400 MHz (75 or 100 MHz for ^{13}C) in deuteriochloroform, unless otherwise stated, using tetramethylsilane as the internal standard. Mass spectra were determined by the electron impact method (EI, 70 eV) or electron spray ionisation (ESI). IR spectra were recorded in chloroform. Column chromatography was carried out on ICN silica gel (70-230 or 230-400 mesh) by gradual elution with mixtures of light petroleum (bp 40-70 °C) and diethyl ether or dichloromethane or methanol and final elution with methanol. Previously reported reaction products were identified by spectral comparison. Photolysis was performed with a 150 W medium pressure Hg arc UV-lamp or with a 500 W super high pressure Hg arc UV-lamp. ESR spectra were obtained with a Bruker EMX 10/12 spectrometer operating at 9.5 GHz with 100 kHz modulation. Power 2.0 mW, Modulation amplitude usually 0.2 G_{pp}. Samples was contained in quartz capillary tubes (ca. 1 mm i.d.), deaerated by bubbling nitrogen for ca. 15 min and observed usually at RT. Spectra were long-lived – usually many hours and even days. Simulations were carried out with the Bruker Simfonia software package and these are the spectra shown. However, simulations were also carried out with the WinSim2002 Software package available from NIEHS. Hyperfines were optimised with this software and the reported Correlation Coefficients R were also derived from fits with this package.

General Procedure for the Reaction of Azides with Allylindium dichloride

A THF solution of allylmagnesium chloride (2 equiv.) was added dropwise to a stirring solution (2 ml) of anhydrous indium trichloride[2] (2 equiv., previously dried by heating at 130 °C under argon for 1 h) in dry THF at room temperature. After 20 minutes THF was replaced by benzene (2ml), the azide (1 equiv.) was added, and the solution was photolysed with a 150 W medium pressure Hg arc UV-lamp or with a 500 W super high pressure Hg arc UV-lamp. Once the reaction was finished generally 3 hours the final crude was quenched with water and when required NaOH was added to neutralize the solution. Extraction with diethyl ether furnished a crude mixture which was purified by column chromatography.

General Procedure for the Photolysis of Allylindium dichloride

A THF solution of allylmagnesium chloride (1 equiv.) was added dropwise to a stirring solution (2 ml) of anhydrous indium trichloride[2] (1 equiv., previously dried by heating at 130 °C under argon for 1 h) in dry THF at room temperature. Then THF was removed under reduced pressure and *tert*-butylbenzene was added and the new solution degassed with nitrogen. Then a small amount of the sample was transferred in a quartz glass tube, sealed, put into the ESR cavity, and photolyzed recording several spectra at different temperatures.

General Procedure for the ESR Analysis of the Reactions between Azides and Allylindium dichloride

A THF solution of allylmagnesium chloride (2 equiv.) was added dropwise to a stirring solution (2 ml) of anhydrous indium trichloride[2] (2 equiv., previously dried by heating at 130 °C under argon for 1 h) in dry THF at room temperature. After 20 minutes THF was replaced by *tert*-butylbenzene (2ml) and the azide (1 equiv.) was added. The new solution was transferred in a quartz glass tube, put into the ESR cavity, and photolyzed with a 500 W high pressure Hg arc UV-lamp recording several spectra at different temperatures.

General Procedure for the Reaction of Azides with Dichloroindium Hydride under Photolysis and ESR analysis

The starting azide (1 equiv.) was added at 0 °C to an acetonitrile solution of dichloroindium hydride (1.1 equiv.), generated in situ by stirring under argon anhydrous indium trichloride (1.1 equiv., previously dried by heating at 130 °C under argon for 1 h) and triethylsilane (1.1 equiv.) in acetonitrile (4 mL) for 5 min at 0 °C.[6] The resulting solution was rapidly transferred into a quartz capillary tube and nitrogen was bubbled inside for few minutes. Then the tube was sealed and put into the ESR cavity and analysed under photolysis with a 500 W super pressure Hg arc UV-lamp recording several spectra at different temperatures. Once the analysis was finished an aqueous work up with $NaHCO_3$ was performed followed by extraction with diethylether, and the reaction mixture characterised.

General Procedure for the Reaction of Azides with Dichloroindium Hydride and DMPO under Photolysis and ESR analysis

The starting azide (1 equiv.) was added at 0 °C to an acetonitrile solution of dichloroindium hydride (1.1 equiv.), generated in situ by stirring under argon anhydrous indium trichloride (1.1 equiv., previously dried by heating at 130 °C under argon for 1 h) and triethylsilane (1.1 equiv.) in acetonitrile (4 mL) for 5 min at 0 °C.[6] The resulting solution was rapidly transferred into a quartz glass capillary tube previously charged with DMPO at 0 °C. Then the tube was sealed and the reaction was analysed by ESR under photolysis with a 500 W super pressure Hg arc UV-lamp recording several spectra at different temperatures.

General Procedure for the Reaction of Azides with the system DTBP/Hexamethylditin/Indium trichloride under Photolysis and ESR analysis

Indium trichloride (1.1 equiv.) was dried under vacuum at 130 °C for 1 hour and then dissolved in acetonitrile. The solution was cooled to 0 °C and hexamethylditin (1.1 equiv.) and an acetonitrile solution of the azide (1 equiv. in 1 ml) were added. The mixture was transferred in a capillary quartz glass tube previously charged with DTBP (50 µl). The tube was sealed and put into the ESR cavity under photolysis with a 500 W super pressure Hg arc UV-lamp recording several spectra at different temperatures.

General Procedure for ESR analysis of the reaction of Aryl Azides with Indium Trichloride

Indium trichloride (1.1 equiv.) was dried under reduced pressure at 130 °C for 1 hour. Then it was dissolved in acetonitrile (3 ml) or dichloromethane (3 ml), or a mixture of them, and an acetonitrile or dichloromethane solution of the azide (1 equiv. in 1 ml) was added at room temperature. The resulting solution was then transferred in a capillary quartz glass tube and nitrogen was bubbled inside. Then the capillary was sealed and the sample was analysed by ESR under photolysis by a 500 W super pressure Hg arc UV-lamp acquiring several spectra at different temperatures. Products analysis was performed by quenching the reaction

with an aqueous solution of NaOH and extracting with dichloromethane. The obtained crude was analyzed by GC-MS and, when possible, by ^{1}H-NMR and ^{13}C-NMR spectroscopy. Products identification was performed by comparison with literature data.

General Procedure for ESR analysis of the reaction of Aryl Azides with Aluminium Trichloride

Aluminium trichloride (1.1 equiv.) was dried under reduced pressure at 25 °C for 1 hour. Then dichloromethane was added (3 ml) and a dichloromethane solution of the azide (1 equiv. in 1 ml) was added at room temperature. The resulting solution was then transferred in a capillary quartz glass tube and nitrogen was bubbled inside. Then the capillary was sealed and the sample was analysed by ESR acquiring several spectra at different temperatures. Products analysis was performed by quenching the reaction with an aqueous solution of NaOH and extracting with dichloromethane. The obtained crude was analyzed by GC-MS and, when possible, by ^{1}H-NMR and ^{13}C-NMR spectroscopy. Products identification was performed by comparison with literature data.

General Procedure for ESR analysis of the reaction of Aryl Azides with Gallium Trichloride

A 0.5 M pentane solution of gallium trichloride (1.1 equiv.) was added under nitrogen to a dichloromethane solution of the azide (1 equiv. in 4 ml) at room temperature. The resulting solution was then transferred in a capillary quartz glass tube and nitrogen was bubbled inside. Then the capillary was sealed and the sample was analysed by ESR acquiring several spectra at different temperatures. Products analysis was performed by quenching the reaction with an aqueous solution of NaOH and extracting with dichloromethane. The obtained crude was analyzed by GC-MS and, when possible, by ^{1}H-NMR and ^{13}C-NMR spectroscopy. Products identification was performed by comparison with literature data.

Preparation and Characterisation Data for Azides

Sulfonyl and acyl azides **4a, b** were synthesised by treatment of the corresponding acid chlorides with sodium azide in DMSO (M. Regitz, J. Hocker, A. Liedhegener, *Org. Synth.* Coll. Vol. V, **1973**, 179).

Alkyl azides **4e, f** were prepared by treatment of the corresponding alkyl bromide with sodium azide in DMSO (G. L'abbé, I. Sannen, W. Dehaen, *J. Chem. Soc., Perkin Trans. 1* **1993**, 27).

Ethyl 5-azidopentanoate (4e)[13]: IR (ν_{max}, $CHCl_3$), 1.718 (CO) and 2.092 (N_3) cm^{-1} ; ^1H NMR (400 MHz) δ 1.24 (3H, t, *J* = 7.2 Hz), 1.54-1.77 (4H, m), 2.32 (2H, t, *J* = 6.9 Hz), 3.28 (2H, t, *J* = 6.6 Hz), 4.13 (2H, q, *J* = 7.2 Hz).

2-(2-Azidoethyl)-2-benzylmalononitrile (4f)[14]: mp = 42-43 °C; IR (ν_{max}, $CHCl_3$) 2241 (CN) and 2098 (N_3) cm^{-1}; ^1H NMR (300 MHz) δ 2.17 (2 H, t, *J* = 7.0 Hz), 3.24 (2 H, s), 3.67 (2 H, t, *J* = 7.0 Hz), 7.32-7.43 (5 H, m); ^{13}C NMR (75 MHz) δ 36.59 (CH_2), 37.50 (C), 44.16 (CH_2), 47.89 (CH_2), 115.07 (CN), 129.68 (CH), 130.89 (CH), 131.99 (C); MS *m/z* (70 eV) (rel inten) 225 (M^+, <1), 197 (3), 118 (43), 91 (100).

1-Azido-4-chlorobutane (4d): In a flask charged with 4-chloro-1-butanol (15 mmol.) pyridine (5ml) and p-toluenesolphonyl chloride (1 equiv.) were added at 0 °C under magnetic stirring. The flask was kept at 0 °C for 3 hours then water was added and the resulting mixture was extracted with diethyl ether. The organic phase was washed with a solution 1M of HCl and the solvent was removed under reduced pressure. After purification by chromatography 4-chlorobutyl-4-methylbenzenesulfonate was obtained (12 mmol., 80%). ^1H-NMR (400 MHz) δ 1.78-1.85 (4H, m), 2.45 (3H, s), 3.47-3.53 (2H, m), 4.03-4.09 (2H, m), 7.36 (2H, A part of AA'BB', *J* = 8.6 Hz), 7.80 (2H, B part of AA'BB', *J* = 8.6 Hz); ^{13}C-NMR (100 MHz) δ 21.5 (CH_3), 26.1 (CH_2), 28.3 (CH_2), 44.9 (CH_2), 69.5 (CH_2), 127.8 (CH), 129.8 (CH), 132.8 (C), 132.8 (C).

An aqueous solution of NaN_3 (5 equiv.) and tetrabutylammonium bromide (0.2 equiv.) were added to a solution of 4-chlorobutyl-4-methylbenzenesulfonate in acetone (12 mmol.). The resulting mixture was heated at 45 °C until the complete disappearance of starting material. The solvent was evaporated and the residual oil was washed with 20 ml of water and

extracted with diethyl ether. After chromatography over silica gel, azide **4d** (8 mmol., 67%) identified by comparison with literature data.[15]

Aromatic azides **4c, 4g, 4h, 4i, 4j 4k and 4l** were prepared by standard diazotisation of the corresponding anilines followed by treatment with sodium azide, and were identified by comparison with literature data.

4c, 4d: A. Nicolaides, T. Enyo, D. Miura, H. Tomioka, *J. Am. Chem. Soc.* **2001**, *123*, 2628.
4g: M. O. Foster, H. E. Fierz, *J. Chem. Soc*. **1907**, 1942.
4h, 4i, 4j, 4l: M. L. Huber, J. T. Pinhey, *J. Chem. Soc., Perkin Trans. 1* **1990**, 721.
4k: L. D. Nunno, A. Scilimati, *Tetrahedron* **1986**, *42*, 3913.

2,3,4,5,6-Pentadeuteriophenyl azide 4m was prepared in 81% yield by standard diazotisation of the commercially available *d5*-aniline 98% atom d. (7.7 mmol.). IR (ν_{max}, neat) 2097 (N_3) cm^{-1} ; ^{13}C-NMR (100 MHz) δ 118,6 (CD, t, *J* = 24,2 Hz), 124.3 (CD, t, *J* = 24,2 Hz), 129.2 (CD, t, J = 24,2 Hz), 139.8 (C); TOF MS CI^+: 125.06 (M^+ + 1, 100%).

2,4,6-Trideuteriophenyl azide 4n. In a beaker containing aniline (20 mmol.), few ml of concentrated HCl were added and the resulting salt was washed with diethyl ether and dried over filter paper. Then it was dissolved in a glass tube containing D_2O (7 ml) and heated at 110 °C for 24 hours. Water was distilled off and the residual salt was dissolved with fresh D_2O (7 ml) and heated again for further 48 hours at 110 °C. The reaction mixture was then treated with a NaOH aqueous solution and extracted with diethyl ether to give 2,4,6-trideuterioaniline (18 mmol., 90%). ^{1}H-NMR (400 MHz) δ 3.67 (2H, brs, NH_2), 7.14 (2H, s); ^{13}C-NMR (100 MHz) δ 114,5 (CD, t, *J* = 23.7 Hz), 117.7 (CD, t, *J* = 23.7 Hz), 128.7 (CH), 146.6 (C), MS TOF EI^+: 96.07 (M^+, 100%), 80.06 (2%).

2,4,6-Trideuterioaniline (18 mmol.) was reacted with DCl/D_2O 35% to give the corresponding deuteriochloride salt which was diazotised in D_2O to give the azide **4n** (14.4 mmol., 80%). IR (ν_{max}, neat) 2098 (N_3) cm^{-1} ; ^{1}H-NMR (400 MHz) δ 7.35 (1H, s); ^{13}C-NMR (100 MHz) δ 118.6 (CD, t, *J* = 24.2 Hz), 124.5 (CD, t, *J* = 24.2 Hz), 129.5 (CH), 139.8 (C); TOF MS CI^+: 123.03 (M^+ + 1, 100%).

2,3,5,6-Tetradeuteriophenyl azide 4o. 1,4-p-Phenylendiamine dihydrochloride (12 mmol.) was deuteriated with boiling D_2O (7ml) in a sealed glass tube for 72 hours. Then

exhausted D_2O was removed by distillation and the salt was dissolved again with fresh D_2O (7ml) and boiled again. The reaction mixture was then treated with a NaOH aqueous solution and extracted with diethyl ether to give 2,3,5,6-tetradeuterio-p-phenylendiamine in 100% yield. ^{1}H-NMR (400 MHz) with toluene as internal standard δ 3.37 (4H, brs, $2NH_2$,); TOF MS EI$^+$: 112.04 (M^+, 100%).

2,3,5,6-Tetradeuterio-p-phenylendiamine (12 mmol.) was treated with DCl/D_2O 35% to give the corresponding deuteriochloride salt that was selectively diazotised with an excess of H_3PO_2 50% aqueous solution, furnishing the corresponding 2,3,5,6-tetradeuterioaniline (7.2 mmol., 60%) after basic aqueous work up. ^{1}H-NMR (400 MHz) δ 3.64 (2H, brs, NH_2), 6.77 (1H, s); ^{13}C-NMR (100 MHz) δ 114.72 (CD, t, *J* = 24.2 Hz), 118.3 (CH), 128.8 (CD, t, *J* = 24.2 Hz), 146.1 (C); TOF MS CI$^+$: 98.09 (M^+ + 1, 100%).

Standard diazotisation of 2,3,5,6-tetradeuterioaniline gave the corresponding azide **4o** (3.17 mmol., 44%). IR (ν_{max}, neat) 2102 (N_3) cm^{-1} ; ^{1}H-NMR (400 MHz) δ 7.15 (1H, s); ^{13}C-NMR (100 MHz) δ 118.6 (CD, t, *J* = 24.2 Hz), 126.6 (CH), 129.3 (CD, t, *J* = 24.2 Hz), 139.8 (C); TOF MS CI$^+$: 124.01 (M^+ + 1, 100%).

4-Methoxy-*d*3-phenyl azide 4p. To a cooled solution (0 °C) of KOH (1.5 equiv.) in *d4*-methanol (20 ml) 1-fluoro-4-nitrobenzene (13.28 mmol.) was slowly added under nitrogen. The mixture must be cooled if the temperature rapidly increase during the addition phase. The dark yellow mixture was reacted for 24 hours at room temperature. If the starting material was not completely converted the mixture was refluxed for 12 hours. The crude of reaction was poured into water and extracted with diethyl ether 3 times. The solvent was removed and the yellow oil crystallised by adding few drops of petroleum ether. 4-methoxy-*d*3-1-nitrobenzene was obtained as yellow crystals (12.35 mmol., 93%). ^{1}H-NMR (400 MHz) δ 6.95 (2 H, A part of AA'BB', *J* = 9.3 Hz), 8.19 (2 H, B part of AA'BB', *J* = 9.3 Hz); ^{13}C-NMR (100 MHz) δ 55.12 (CD_3, quint., *J* = 22 Hz), 114.0 (CH), 125.9 (CH), 141.5 (C), 164.6 (C); TOF MS EI$^+$: 156.06 (M^+, 100%).

To a suspension of $Cu(acac)_2$ (0.2 equiv.) in isopropanol (20 ml), an ethanol solution of $NaBH_4$ was added (1 equiv. in 10 ml). Then a solution of 4-methoxy-*d*3-1-nitrobenzene in isopropanol (12.35 mmol. in 20ml) was added after that a new ethanol solution of $NaBH_4$ (2 equiv. in 10 ml) was added dropwise in 1h. The solution was stirred at rom temperature for 18 hours. Then the solution was diluted with water and the solvent removed under reduced pressure. The aqueous phase was filtered from the black solid and extracted with dichloromethane. Organic phase was dried over $MgSO_4$ and the solvent removed under

reduced pressure. After purification by chromatography solid 4-methoxy-*d*3-aniline was obtained (10.23 mmol., 83%). ^{1}H-NMR (400 MHz) δ . 3.41 (2H, brs, NH_2), 6.65 (2 H, A part of AA'BB', *J* = 9.0 Hz), 6.75 (2 H, B part of AA'BB', *J* = 9.0 Hz); ^{13}C-NMR (100 MHz) δ 54.81 (CD_3, quint., *J* = 22 Hz), 114.7 (CH), 116.4 (CH), 139.8 (C), 152.7 (C); TOF MS EI^+: 126.08 (M^+, 55%), 108.04 ($M^+ - 18$, 100%)

Standard diazotisation of 4-methoxy-*d*3-aniline gave the corresponding azide **4p** (9.2 mmol., 90%). IR (ν_{max}, $CHCl_3$) 2097 (N_3) cm^{-1} ; ^{1}H-NMR (400 MHz) δ 6.88 (2 H, a part of AA'BB', *J* = 9.1 Hz), 6.96 (2 H, B part of AA'BB', *J* = 9.1 Hz); ^{13}C-NMR (100 MHz) 54.6 (CD_3, quint., *J* = 22 Hz), 115.0 (CH), 119.9 (CH), 132.2 (C), 156.9 (C); TOF MS CI^+: 153 ($M^+ + 1$, 48%), 135 (5%), 125 (100%).

2,6-Dideuterio-4-methoxyphenyl azide 4q. Gaseous HCl was bubbled in a solution of 4-methoxyaniline (10 mmol.) in diethyl ether to give the corresponding hydrochloridric salt which was filtered, transferred in a glass tube and dissolved with D_2O (6 ml). Once the glass was sealed the mixture was boiled for 3 days, then exhausted D_2O was removed by distillation and replaced with fresh D_2O (6 ml). The new mixture was boiled for 3 days again. The reaction was neutralised with a NaOH aqueous solution and extracted with dichloromethane to give the 2,6-dideuterio-4-methoxyaniline (9.8 mmol., 98%). ^{1}H-NMR (400 MHz) δ 3.42 (2H, brs, NH_2), 3.75 (3H, s), 6.75 (2H, s); ^{13}C-NMR (100 MHz) δ 55.7 (CH_3), 114.6 (CH), 116.1 (CD, t, *J* = 24.2 Hz), 139.7 (C), 152.7 (C); TOF MS EI^+: 125.08 (M^+, 50%), 110.05 (100%).

2,6-Dideuterio-4-methoxyaniline (9.8 mmol.) was diazotised following the classical methodology to give the corresponding azide **4q** (8.33 mmol., 85%). IR (ν_{max}, $CHCl_3$) 2098 (N_3) cm^{-1}; ^{1}H-NMR (400 MHz) δ 3.67 (3H, s), 6.72 (2H, s); ^{13}C-NMR (100 MHz) δ 55.5 (CH_3), 115.0 (CH), 119.7 (CD, t, J = 24.2 Hz), 132.2 (C), 157.0 (C); MS TOF CI^+: 152 ($M^+ + 1$, 23%), 124(100%).

3,5-Dideuterio-4-methoxyphenyl azide 4r. Commercially available 4-nitrophenol (20 mmol.) was added in a glass tube containing a solution of D_2SO_4 (4 ml) in D_2O (10 ml) at 0 °C. When 4-nitrophenol was dissolved the tube was sealed and the yellow solution was heated at 120°C for 48 hours. Then the mixture was cooled down and diluted with water and extracted 4 times with dichloromethane. The solvent was removed under reduced pressure and solid 2,6-dideuterio-4-nitrophenol was obtained without further purification procedures in quantitative yield. ^{1}H-NMR (400 MHz) δ 6.02 (1H, s, OH), 8.09 (2H, s); ^{13}C-NMR (100

MHz) δ 115.4 (CD, t, *J* = 25 Hz), 126.2 (CH), 141.4 (C), 161.3 (C); TOF MS ES^+: 164.02 (M^+ + Na, 100%).

2,6-Dideuterio-4-nitrophenol (20 mmol.) placed in a flask under nitrogen. DMF (50 ml), Cs_2CO_3 (2 equiv.) and MeI (2 equiv.) were added and the resulting mixture was stirred for 18 hours. Then the crude of reaction was poured into water and extracted 3 times with DCM. The organic phase was washed several times with water to remove DMF. The solvent was removed under reduced pressure and the brown oil was crystallised by adding water and petroleum ether. After 12 hour under reduced pressure, dried crystals of 2,6-dideuterio-1-methoxy-4-nitrobenzene were collected (18.4 mmol., 92%). ^{1}H-NMR (400 MHz) δ 3.90 (3H, s), 8.20 (2H, s); ^{13}C-NMR (100 MHz) δ 55.9 (CH3), 113.7 (CD, t, J = 24.9 Hz), 125.8 (CH), 141.5 (C), 164,5 (C); TOF MS EI^+: 155.05 (M^+, 100%), 125.05 (25%), 109.06 (3%).

To a suspension of $Cu(acac)_2$ (0.2 equiv.) in isopropanol (20 ml), an ethanol solution of $NaBH_4$ was added (1 equiv. in 20 ml). Then 2,6-dideuterio-1-methoxy-4-nitrobenzene (18.4 mmol) was added after that a new ethanol solution of $NaBH_4$ (2 equiv. in 30 ml) was added dropwise in 1h. The solution was stirred at room temperature for 18 hours. Then the solution was diluted with water and the solvent removed under reduced pressure. The aqueous phase was filtered from the black solid and extracted with dichloromethane. Organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. After purification by chromatography 3,5-dideuterio-4-methoxyaniline was obtained (15.46 mmol., 84%). ^{1}H-NMR (400 MHz) δ 3.47 (2H, brs, NH_2), 3.72 (3H, s), 6.61 (2H, s); ^{13}C-NMR (100 MHz) δ 55.2 (CH_3), 114.1 (CD, t, *J* = 24.2 Hz), 116.0 (CH), 139.7 (C), 152.2 (C); TOF MS EI^+: 125.08 (M^+, 50 %), 110.05 (100%).

Final diazotisation of 3,5-dideuterio-4-methoxyaniline gave the azide **4r** (14.68 mmol., 95%). IR (ν_{max}, neat) 2098 (N_3) cm^{-1}; ^{1}H-NMR (400 MHz) δ 3.79 (3H, s), 6.95 (2H, s); ^{13}C-NMR (100 MHz) δ 55.4 (CH_3), 114.8 (CD, t, *J* = 24.2 Hz), 119.9 (CH), 132.2 (C), 156.8 (C). TOF MS CI^+: 152.09 (M^+ + 1, 35%), 137.08 (15%), 124.08 (100%).

2,3,5,6-Tetradeuterio-4-methoxy-phenylazide 4s. Gaseous HCl was bubbled in a solution of 3,5-dideuterio-4-methoxyaniline (8.5 mmol.) in diethyl ether to give the corresponding hydrochloridric salt which was filtered, transferred in a glass tube and dissolved with D_2O (6 ml). Once the glass was sealed the mixture was boiled for 2 days, then exhausted D_2O was removed by distillation and replaced with fresh D_2O (6 ml). The new mixture was boiled for 2 days again. The reaction was neutralised with a NaOH aqueous solution and extracted with dichloromethane to give the 2,3,5,6-tetradeuterio-4-methoxy-

aniline (7.48 mmol., 88% yield). ^{1}H-NMR (400 MHz) δ 3.36 (2H, brs), 3.74 (3H, s); ^{13}C-NMR (100 MHz) δ 55.7 (CH_3), 114.4 (CD, t, *J* = 24.2 Hz), 116.0 (CD, t, *J* = 24.2 Hz), 139.7 (C), 152.7 (C). TOF MS EI^{+}: 127.07 (M^{+}, 62 %), 112.06 (100%).

2,3,5,6-tetradeuterio-4-methoxy-aniline was diazotised to give the corresponding azide **4s** (5.23 mmol., 70 % yield). IR (ν_{max}, neat) 2099 (N_3) cm^{-1}; ^{1}H-NMR (400 MHz) δ 3,79 (3H, s), ^{13}C-NMR (100 MHz) δ 55.5 (CH_3), 114.7 (CD, t, *J* = 24.2 Hz), 119.5 (CD, t, *J* = 24.9 Hz), 123.1 (C), 156.8 (C); TOF MS CI^{+}: 154.1 (M^{+} + 1, 25%), 139.09 (5%), 126.09 (100%).

4-Methoxyphenyl azide^{15}N 4t. Ammoniumchloride^{15}N (1 equiv.) was dissolved in a mixture of water (4 ml) and chloroform (30ml) and the solution was cooled down to 0 °C. Then anisoyl chloride (8.66 mmol.) and an aqueous solution of NaOH (2.2 equiv.) were added and the mixture was stirred all night at room temperature. A new solution of NaOH 1N in water was poured into the mixture and the chloroform layer was separated and washed 2 times with water. The solvent was distilled off and crystallisation of the white amorphous solid in water gave the 4-methoxy benzamide^{15}N (6.66 mmol., 77% yield).[16] ^{1}H-NMR (400 MHz) δ 3,85 (3H, s), 5.88 (2H, brs, NH2), 6.94 (2 H, A part of AA'BB', *J* = 9.0 Hz), 7.78 (2 H, B part of AA'BB', *J* = 9.0 Hz); ^{13}C-NMR (100 MHz) δ 55.4 (CH_3), 113.0 (CH), 129.3 (CH), 162.6 (C), 169.0 (C).

A solution of sodium hypobromide was prepared by dropwise addition of Br_2 (1 equiv.) to an ice cold stirring solution of NaOH (22 equiv.) in water (18 ml). After 5 minutes 4-methoxy benzamide^{15}N was added (6.35 mmol.) and the resulting suspension was stirred at room temperature for 20 minutes than it was slowly heated at 95 °C for 4 days. The reaction mixture was then cooled down and extracted with dichloromethane to give 4-methoxy aniline^{15}N (4 mmol., 63% yield).[16] ^{1}H-NMR (400 MHz) δ 3,27 (2H, brs, NH_2), 3.74 (3H, s), 6.65 (2 H, A part of AA'BB', *J* = 8.8 Hz), 6.75 (2 H, B part of AA'BB', *J* = 8.8 Hz); ^{13}C-NMR (100 MHz) δ 55.7 (CH_3), 114.8 (CH), 116.4 (CH), 153.9 (C), 152.8 (C); TOF MS EI^{+}: 124.06 (M^{+}, 55%), 109(100%).

A solution of PCl_3 (50 mmol.) in diethyl ether (20 ml) was added to a solution of diethylamine (6 equiv.) in diethyl ether (100 ml) at 0 °C under nitrogen. The resulting solution was stirred for 1 days at room temperature. The mixture was filtered to give the resulting tris(diethylamino)phosphine as a yellow oil (47 mmol., 94%). ^{1}H-NMR (400 MHz) δ 1.0 (18H, t, *J* = 7.0 Hz), 2.86-2.93 (12H, m); ^{31}P-NMR δ 116.6 (1P, s).

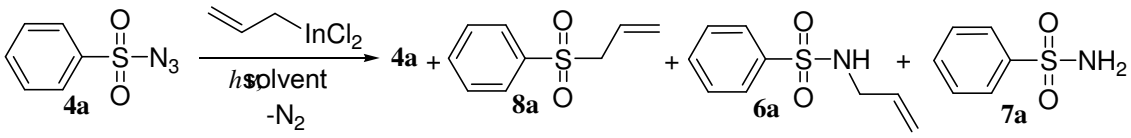
Tris(diethylamino)phosphine (47 mmol.) was added dropwise to a stirred solution of Br_2 (44.8 mmol) in 20 ml of THF at 0 °C. After the addition was complete, sodium azide (2

equiv.) and 18-crown-6 (0.2 equiv.) were added. The mixture was stirred under nitrogen for two days. Then the solvent was removed and the oil was crystallised from THF to give azidotris(diethylamino)phosphonium bromide (36.19 mmol., 77%). ^{1}H-NMR (400 MHz) δ 1.1 (18H, t, *J* = 7.1 Hz), 3.1-3.2 (12H, m); ^{31}P-NMR δ 36.97 (1P, s); TOF MS EI^{+}: 289.15 (M^{+} + 1, 95%), 175.08 (100%).

4-Methoxyaniline^{15}N (4 mmol.) was deprotonated with a 2.5 M hexane solution of n-BuLi (4.8 mmol.) in dry THF at -78 °C. Azidotris(diethylamino)phosphonium bromide (4.8 mmol.) was added as THF solution (31 ml). The reaction was stirred for 45 minutes at -78 °C. At ambient temperature, a 0.25 M aqueous solution of NH_4Cl was added and the mixture extracted with dichloromethane. Filtration over silica gel of the crude of reaction gave the azide **4t** (2.11 mmol., 53%). IR (ν_{max}, neat) 2097 (N_3) cm^{-1}; ^{1}H-NMR (400 MHz) δ 3,8 (3H, s), 6.88 (2 H, A part of AA'BB', *J* = 8.9 Hz), 6.95 (2 H, B part of AA'BB', *J* = 8.9 Hz) ^{13}C-NMR (100 MHz) δ 55.5 (CH_3), 115.1 (CH), 119.9 (CH), 132.3 (C), 157 (C); TOF MS CI^{+}: 150.06 (M^{+} + 1, 30%), 123.05 (100%), 107.03 (10%).

Reactions and ESR Analyses

Reaction of Phenysulfonyl azide with allylindium dichloride



Azide **4a** was reacted with allylindium dichloride according to the general procedure described above.

Phenysulphonyl azide	366 mg (2 mmol.)
$InCl_3$	884.72 mg (4 mmol)
Allylmagnesium chloride 2M in THF	2 ml (4 mmol)
THF	5 ml
Benzene	5 ml

After 3 hours the reaction was stopped and products were identified by GC-MS and by comparison with literature ^{1}H- and ^{13}C-NMR data.[17] Analogous results were obtained when this reaction was performed in THF or in benzene, both with 150 W medium pressure Hg arc and 500 W super pressure Hg arc UV lamp.

Yield from reaction performed in THF and in Benzene:

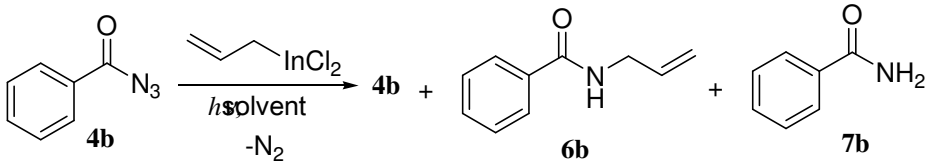
Phenylsulfonyl azide 4a: 10%

***N*-allylbenzenesulfonamide 6a**: 15%

Benzenesulfonamide 7a: 30%

1-(allylsulfonyl)benzene 8a: 33%

Reaction of Benzoyl azide with allylindium dichloride



Azide **4b** was reacted with allylindium dichloride according to the general procedure described above.

Benzoyl azide	147 mg (1 mmol.)
$InCl_3$	486.6 mg (2 mmol)
Allylmagnesium chloride 2M in THF	1 ml (2 mmol)
THF	3 ml
Benzene	3 ml

After 3 hours the reaction was stopped and products identification was based on spectral comparison with literature ^{1}H- and ^{13}C-NMR data,[18] with authentic samples and by GC-MS. Along with products 6b and 7b this reaction gave great amounts of unidentified byproducts.

Analogous products distribution was obtained when the same reaction was performed in THF and in benzene, even if in this last case azide 4b was completely disappeared. both with 150 W medium pressure Hg arc and 500 W super pressure Hg arc UV lamp.

Yield from reaction performed in THF:

Benzoyl azide 4b: 10%

***N*-allylbenzamide 6b**: R = 15%, ^{1}H-NMR (400 MHz) δ 4.07-4.1 (2H, m), 5.18 (1H, dd, J_1 = 10.4 Hz, J_2 = 1.2 Hz), 5.26 (1H, dd, J_1 = 17.1 Hz, J_2 = 1.2 Hz), 5.91-5.97 (1H, m), 6.33 (1H, brs, NH), 7.41-7.51 (3H, m), 7.77-7.79 (2H, m).

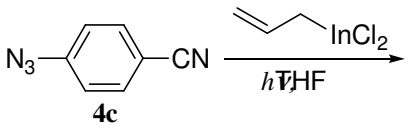
Benzamide 7b: 50 %

Yield from reaction performed in Benzene:

***N*-allylbenzamide 6b**: 19%

Benzamide 7b: 60%

Reaction of 4-Azidobenzonitrile with allylindium dichloride



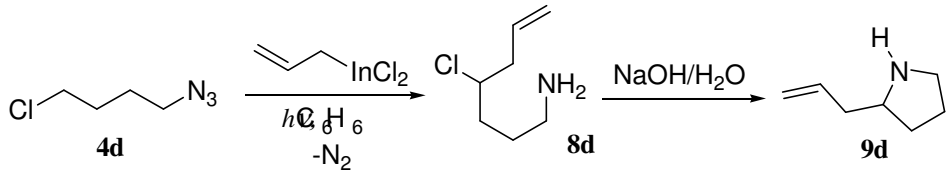
4c

Azide **4c** was reacted with allylindium dichloride according to the general procedure described above.

4-Azidobenzonitrile	144 mg (1 mmol.)
$InCl_3$	486.6 mg (2 mmol)
Allylmagnesium chloride 2M in THF	1 ml (2 mmol)
THF	4 ml

After 3 hours under continuous photolysis the starting azide was recovered completely unreacted.

Reaction of 1-Azido-4-chlorobutane with allylindium dichloride



Azide **4d** was reacted with allylindium dichloride according to the general procedure described above.

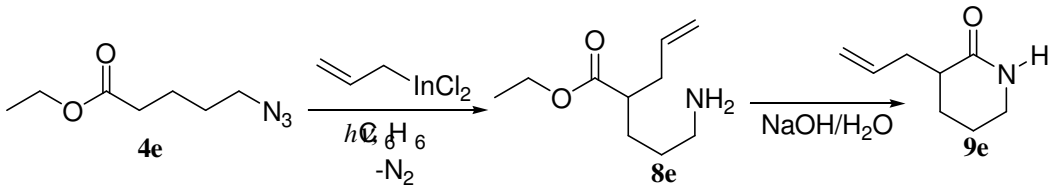
1-Azido-4-chlorobutane	133 mg (1 mmol.)
$InCl_3$	486.6 mg (2 mmol)
Allylmagnesium chloride 2M in THF	1 ml (2 mmol)
THF	3 ml
Benzene	3 ml

The analyses of the reaction mixtures confirmed complete conversion of azides **4d** after 3 hours into the corresponding δ-C-allylated products **8d**. Furthermore, after the usual extractive work-up procedure and neutralisation with a sodium hydroxide solution, a GC-MS analysis showed that **8d** was partially transformed into their corresponding cyclised compounds **9d**. A ^{1}H-NMR analysis performed on a sample stirred overnight under aqueous conditions extracted with diethyl ether and purified by chromatography, confirmed the presence of 2-allylpyrrolidine **9d** by comparison with literature data.[19]

8d: identify only by GC-MS *m/z* (70 eV): 146 ($M^+ - 1$, < 5%), 106 ($M^+ - 41$, 100%)

2-Allylpyrrolidine 9d: R = 60%; ^{1}H-NMR (400 MHz) δ 1.70-1.83 (1H, m), 2.02-2.19 (2H, m), 2.24-2.30 (1H, m), 2.46-2.53 (1H, m), 2.61-2.67 (1H, m), 3.33-3.45 (2H, m), 3.70-3.76(1H, m), 3.80-3.94 (1H, brs, NH), 5.26-5.37 (2H, m), 5.88-6.00 (1H, m); ^{13}C-NMR (100 MHz) δ 26.0 (CH_2), 32.4(CH_2), 39.2(CH_2), 48.3(CH_2), 63.2(CH), 122.1(CH_2), 138.5 (CH).

Reaction of Ethyl 5-azidopentanoate with allylindium dichloride



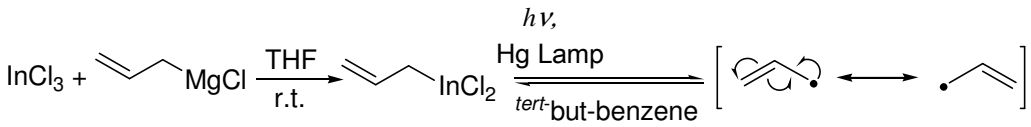
Azide **4e** was reacted with allylindium dichloride according to the general procedure described above.

Ethyl 5-azidopentanoate	171 mg (1 mmol.)
$InCl_3$	486.6 mg (2 mmol)
Allylmagnesium chloride 2M in THF	1 ml (2 mmol)
THF	3 ml
Benzene	3 ml

The analyses of the reaction mixtures confirmed complete conversion of azides and **4e** after 3 hours into the corresponding δ-C-allylated products **8e**. Furthermore, after the usual extractive work-up procedure and neutralisation with a sodium hydroxide solution, a GC-MS analysis showed that **8e** were partially transformed into their corresponding cyclised compounds **9e**. A ^{1}H-NMR analysis performed on a sample stirred overnight under aqueous conditions extracted with diethyl ether and purified by chromatography, confirmed the presence of 3-allylpiperidi-2-one **9e** by comparison with literature data[13]

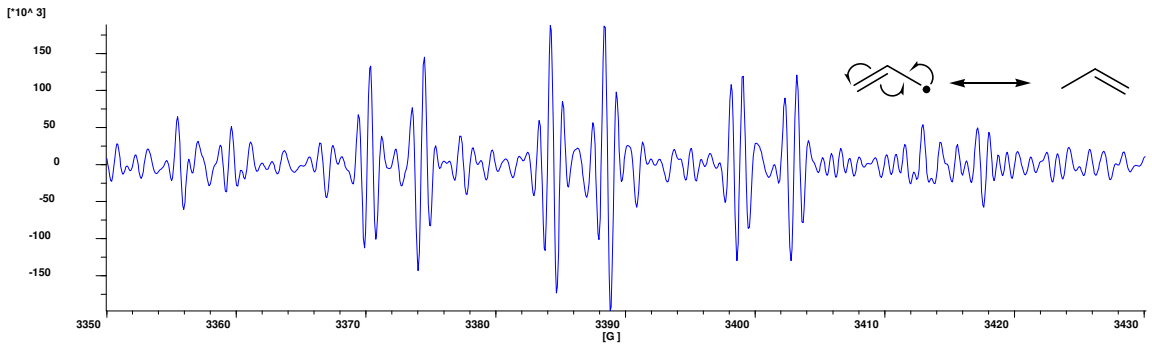
3-Allylpiperidi-2-one 9e: R = 65%, ^{1}H-NMR (400 MHz) δ 1.45-2.35 (7H, m), 3.21-3.51 (2H, m), 4.88-5.21 (2H, m), 5.52-6.15 (1H, m), 6.65 (1H, brs, NH).

ESR experiment of the Allylindium dichloride

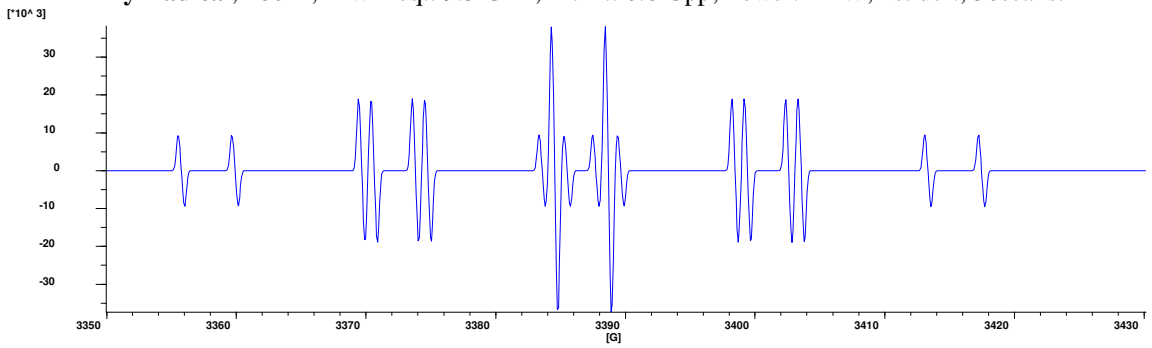


$InCl_3$	110.59 mg (0.5 mmol.)
Allylmagnesium chloride 2M in THF	0.250 ml (0.5 mmol)
THF	2 ml
tert-Butylbenzene	5 ml

Allylindium chloride was prepared and analyzed by ESR spectroscopy according to the general procedure described above. The spectrum of the allyl radical was recorded and simulated.

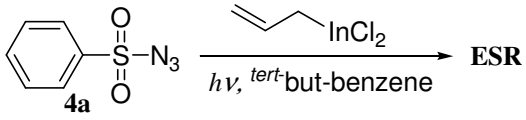


Allyl radical, 260 K, MW freq.: 9.5 GHz; M. A.: 0.6 Gpp; Power: 2mW; 1st der.; 30scans.



Simulation of the Allyl radical; a(1H) = 4.0, a(2H) = 13.9, a(2H) = 14.8 G.

ESR experiment of the reaction between Phenylsulfonyl azide and Allylindium dichloride

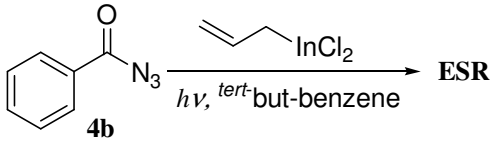


The reaction of azide **4a** with allylindium dichloride was analised by ESR spectroscopy according to the general procedure described above.

Phenysulfonyl azide	183 mg (1 mmol.)
$InCl_3$	486.6 mg (2 mmol)
Allylmagnesium chloride 2M in THF	1 ml (2 mmol)
THF	5 ml
tert-Butylbenzene	5 ml

After several experiments performed from 260 to 310 K only the allyl radical can be detected.

ESR experiment of the reaction between Benzoyl azide and Allylindium dichloride

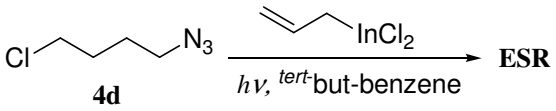


The reaction of azide **4b** with allylindium dichloride was analised by ESR spectroscopy according to the general procedure described above.

Benzoyl azide	147 mg (1 mmol.)
$InCl_3$	486.6 mg (2 mmol)
Allylmagnesium chloride 2M in THF	1 ml (2 mmol)
THF	5 ml
tert-Butylbenzene	5 ml

After several experiments performed from 260 to 330 K only the allyl radical can be detected.

ESR experiment of the reaction between 1-Azido-4-chlorobutane and Allylindium dichloride



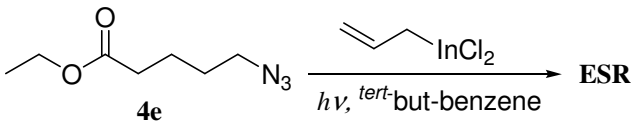
4d

The reaction of azide **4d** with allylindium dichloride was analised by ESR spectroscopy according to the general procedure described above.

1-Azido-4-chlorobutane	133 mg (1 mmol.)
$InCl_3$	486.6 mg (2 mmol)
Allylmagnesium chloride 2M in THF	1 ml (2 mmol)
THF	3 ml
tert-Butylbenzene	3 ml

After several experiments performed from 260 to 330 K only the allyl radical can be detected.

ESR experiment of the reaction between Ethyl 5-azidopentanoate and Allylindium dichloride

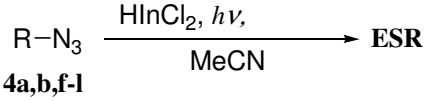


The reaction of azide **4e** with allylindium dichloride was analised by ESR spectroscopy according to the general procedure described above.

Ethyl-5-azidopentanoate	171 mg (1 mmol.)
$InCl_3$	486.6 mg (2 mmol)
Allylmagnesium chloride 2M in THF	1 ml (2 mmol)
THF	3 ml
tert-Butylbenzene	3 ml

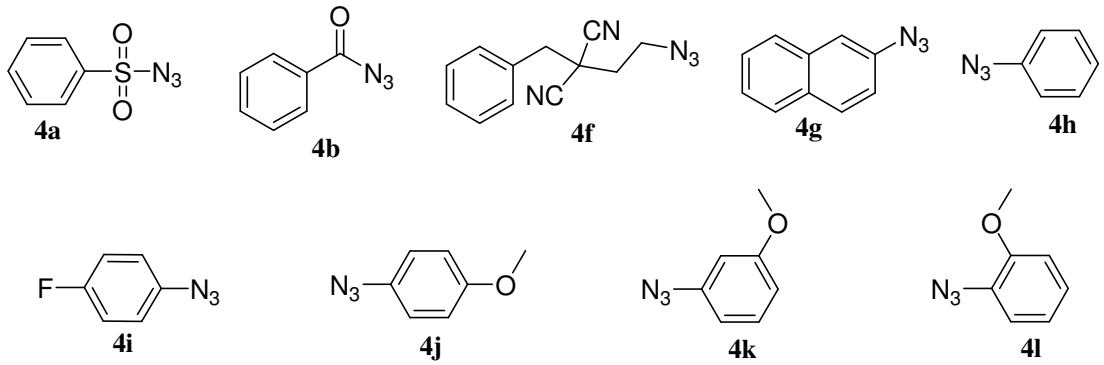
After several experiments performed from 260 to 330 K only the allyl radical can be detected.

ESR analysis of the reaction of Azides with Dichloroindium hydride under photolysis

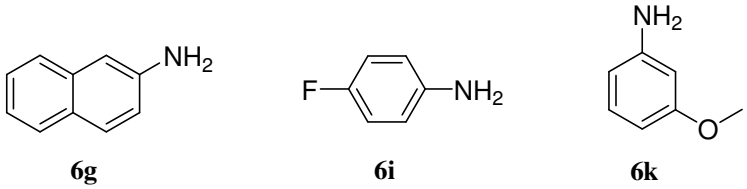


All azides reported below were reacted under photolysis with dichloroindium hydride and analyzed by ESR spectroscopy according to the general procedure described above.

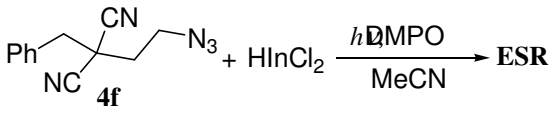
Azide	1 mmol.
$InCl_3$	243.3 mg (1.1 mmol.)
Et_3SiH	177 µl (1.1 mmol.)
MeCN	4 ml



Unfortunately no signals have never been recorded for each azide tested. In the case of azides **4g**, **4i** and **4k** the solution of reaction was removed from the quartz glass tube and quenched with a NaOH aqueous solution and extracted with diethyl ether or dichloromethane. The analysis on the organic phase revealed the presence of the corresponding aromatic amines **6g**,[20] **6i**[21] and **6k**[22] identified by comparison with literature data.

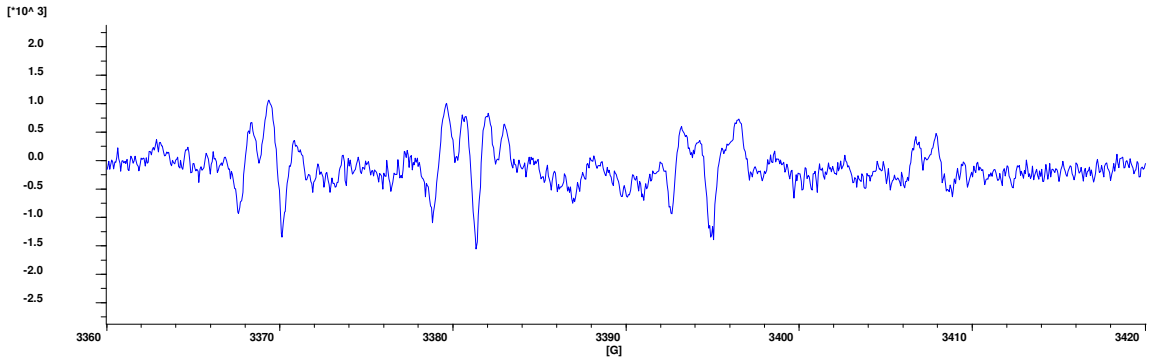


ESR analysis of the reaction of 2-(2-Azidoethyl)-2-benzylmalononitrile with Dichloroindium hydride and DMPO under photolysis

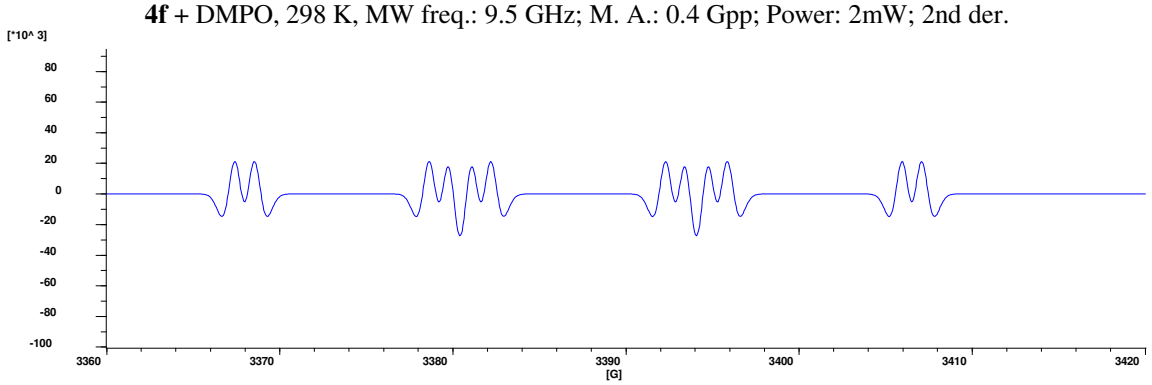


Azide **4f** was mixed with $HInCl_2$ and DMPO in acetonitrile; then 300 µl of the solution were transferred in a quartz glass tube and the reaction was analyzed by ESR spectroscopy under photolysis according to the general procedure described above. The spectrum recorded and its best simulation are reported below.

2-(2-Azidoethyl)-2-benzylmalononitrile	225 mg (1 mmol.)
$InCl_3$	243.3 mg (1.1 mmol.)
Et_3SiH	177 µl (1.1 mmol.)
DMPO	20 mg
MeCN	4 ml

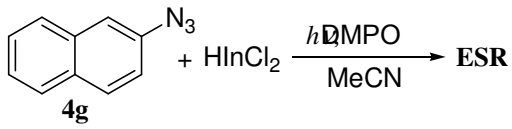


4f + DMPO, 298 K, MW freq.: 9.5 GHz; M. A.: 0.4 Gpp; Power: 2mW; 2nd der.



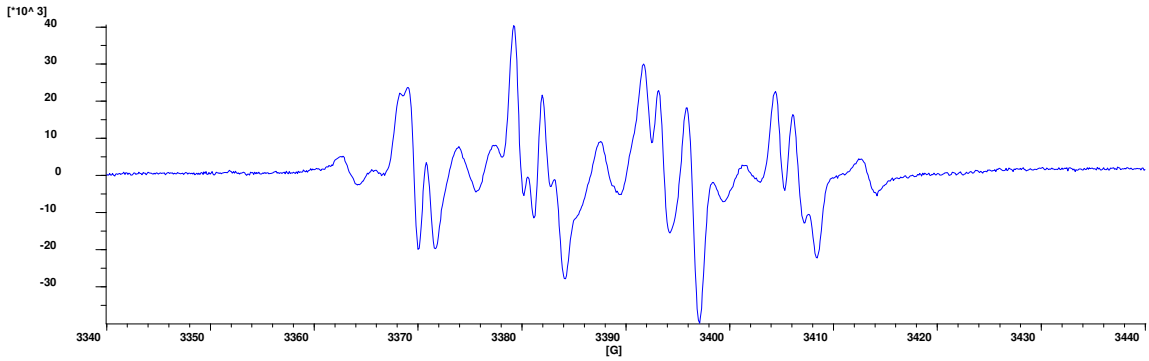
Simulation of 4f + DMPO: a($1H_3$) = 1.0, a($1H_2$) = 11.2, a(1N) = 13.7 G.

ESR analysis of the reaction of 2-Naphthyl azide with Dichloroindium hydride and DMPO under photolysis

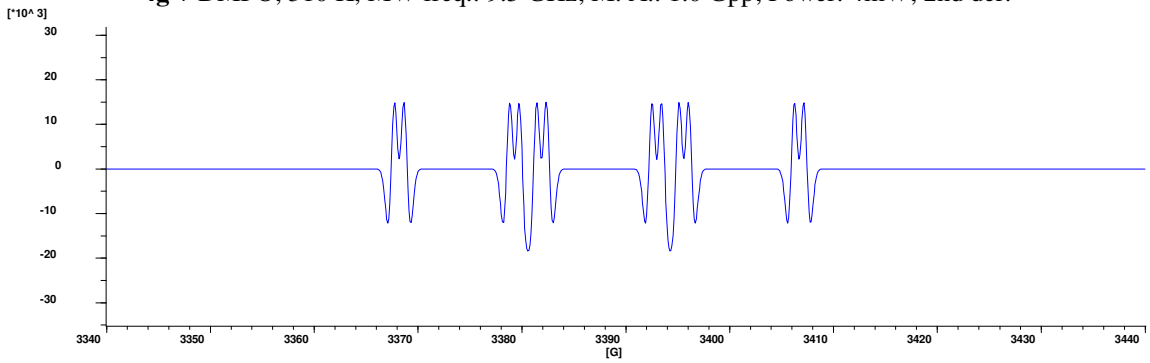


Azide **4g** was mixed with $HInCl_2$ and DMPO in acetonitrile; then 300 µl of the solution were transferred in a quartz glass tube and the reaction was analyzed by ESR spectroscopy under photolysis according to the general procedure described above. The spectrum recorded and its best simulation are reported below.

2-Naphthyl azide	169 mg (1 mmol.)
$InCl_3$	243.3 mg (1.1 mmol.)
Et_3SiH	177 µl (1.1 mmol.)
DMPO	20 mg
MeCN	4 ml

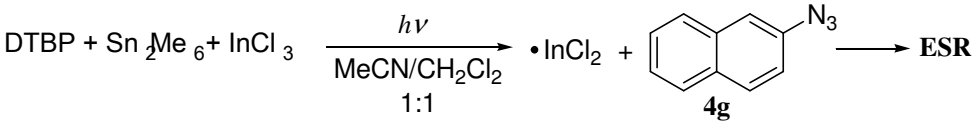


4g + DMPO, 310 K, MW freq.: 9.5 GHz; M. A.: 1.0 Gpp; Power: 4mW; 2nd der.



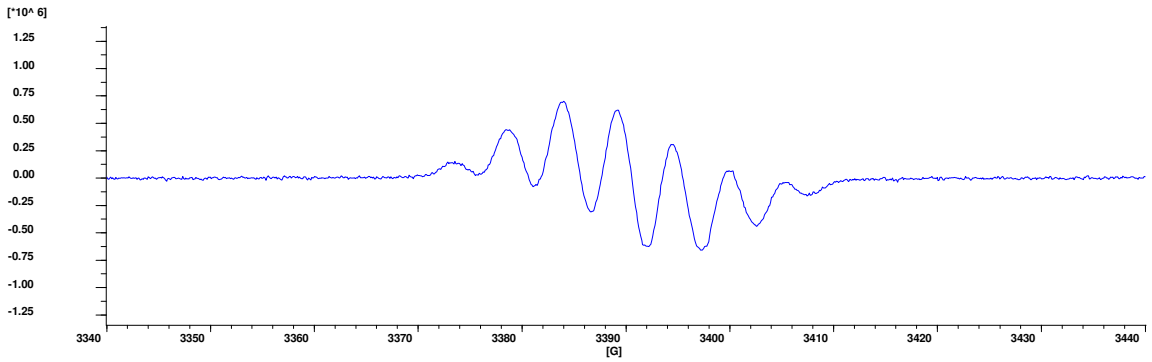
Simulation of 4g + DMPO, a($1H_3$) = 0.8, a($1H_2$) = 11.1, a(1N) = 13.7 G

ESR analysis of the reaction of 2-Naphthyl azide with the system DTBP/Sn_2Me_6/$InCl_3$ under photolysis in MeCN

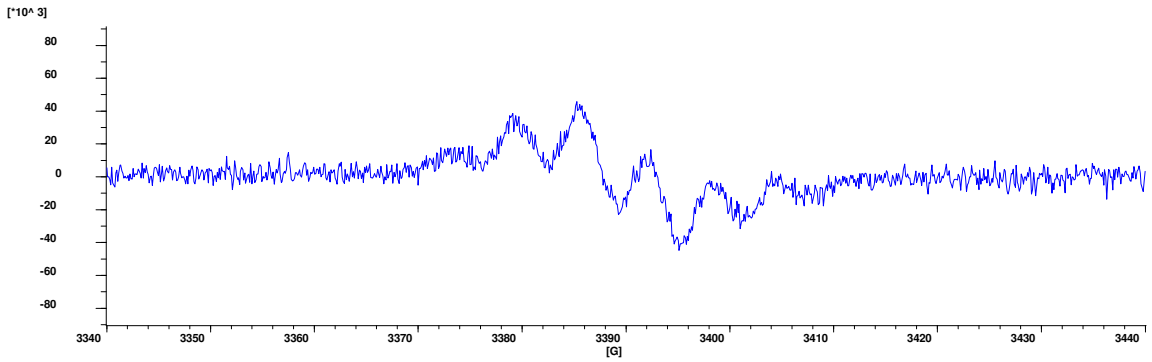


Azide **4g** was mixed with $InCl_3$, Sn_2Me_6 and DTBP in MeCN; then 300 µl of the solution were transferred in a quartz glass tube and the reaction was analyzed by ESR spectroscopy under photolysis according to the general procedure described above. The spectra recorded and their best simulation are reported below: the first spectrum (7 lines) was recorded under UV light, whereas the second one (6 lines) in the dark.

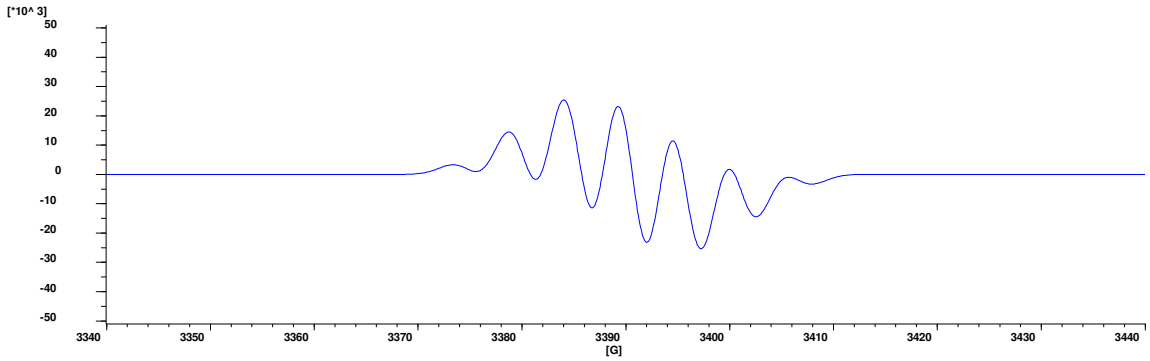
2-Naphthyl azide	42 mg (0.25 mmol.)
$InCl_3$	55 mg (0.275 mmol.)
Sn_2Me_6	82 mg (0.275 mmol.)
DTBP	80 µl
MeCN	4 ml



4g+ $InCl_3$, 270 K, MW freq.: 9.5 GHz; M. A.: 2.0 Gpp; Power: 2mW; 1st der.

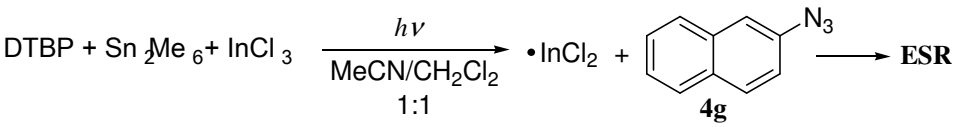


4g + $InCl_3$, 320 K, MW freq.: 9.5 GHz; M. A.: 2.0 Gpp; Power: 2mW; 1st der, dark.



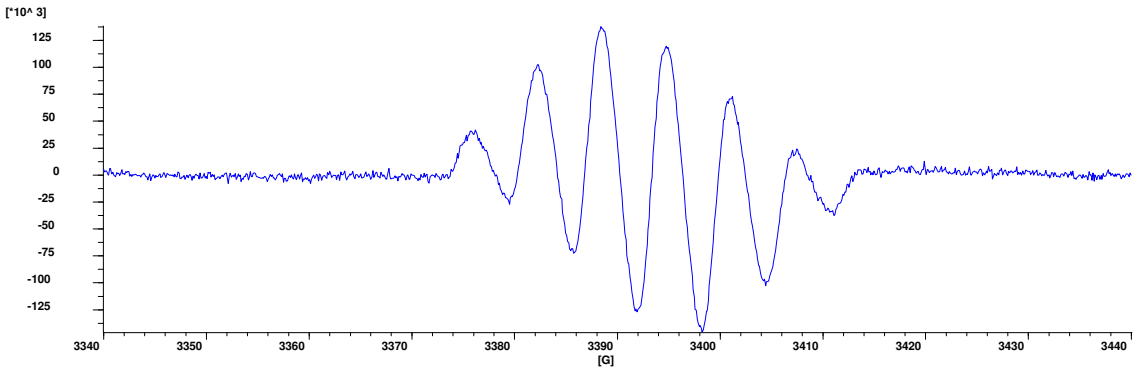
Simulation of 4g + $InCl_3$, $a(1H_2) = a(1H_3) = a(2H_4) = 5.4$, $a(1N) = 4.7$ G.

ESR analysis of the reaction of 2-Naphthyl azide with the system DTBP/Sn_2Me_6/$InCl_3$ under photolysis in 1:1 (v/v) mixture of MeCN and CH_2Cl_2



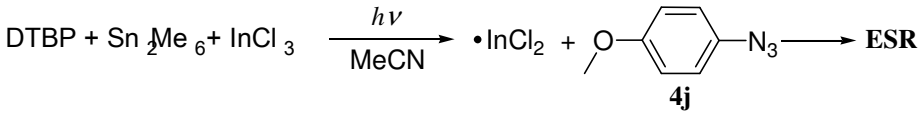
Azide **4g** was mixed with $InCl_3$, Sn_2Me_6 and DTBP in a mixture of MeCN and CH_2Cl_2; then 300 µl of the solution were transferred in a quartz glass tube and analyzed by ESR spectroscopy under UV according to the general procedure described above. The spectrum recorded is reported below: it is the same spectrum recorded for the previous reaction in the dark.

2-Naphthyl azide	42 mg (0.25 mmol.)
$InCl_3$	55 mg (0.275 mmol.)
Sn_2Me_6	82 mg (0.275 mmol.)
DTBP	50 µl
MeCN/CH_2Cl_2	2 ml/2 ml



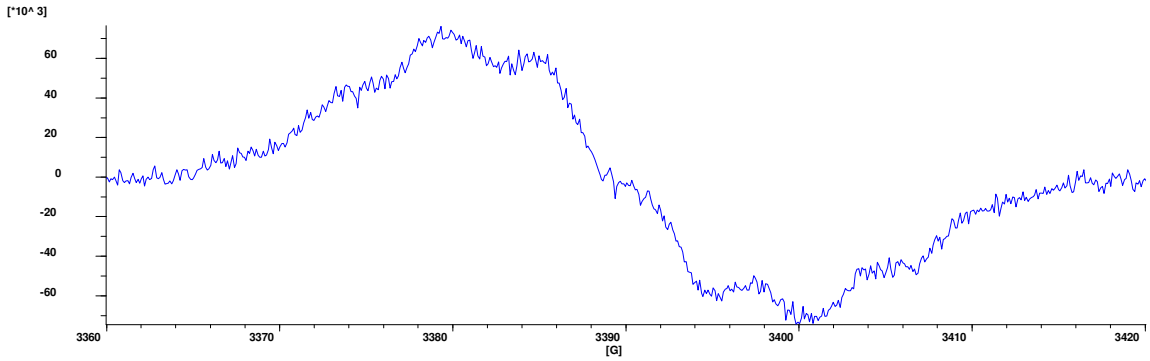
4g + $InCl_3$, 320 K, MW freq.: 9.5 GHz; M. A.: 1.0 Gpp; Power: 2mW; 1st der.

ESR analysis of the reaction of 4-Methoxyphenyl azide with the system DTBP/Sn_2Me_6/$InCl_3$ under photolysis in MeCN



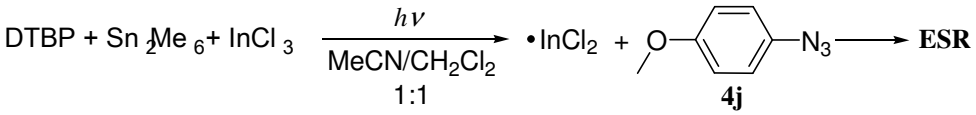
Azide **4j** was mixed with $InCl_3$, Sn_2Me_6 and DTBP in acetonitrile; then 300 µl of the solution were transferred in a quartz glass tube and the reaction was analyzed by ESR spectroscopy under photolysis according to the general procedure described above. The spectrum recorded is reported below.

4-Methoxyphenyl azide	37.2 mg (0.25 mmol.)
$InCl_3$	55 mg (0.275 mmol.)
Sn_2Me_6	82 mg (0.275 mmol.)
DTBP	50 µl
MeCN	4 ml



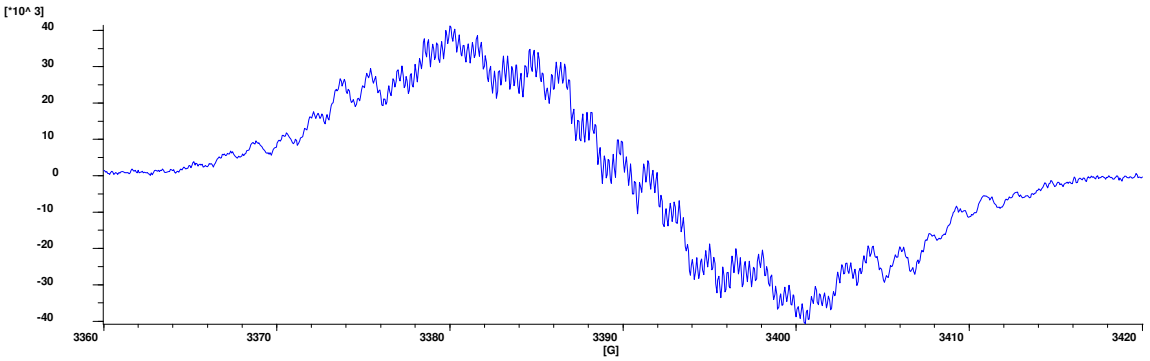
4j+ $InCl_3$, 270 K, MW freq.: 9.5 GHz; M. A.: 2.0 Gpp; Power: 2mW; 1st der.

ESR analysis of the reaction of 4-Methoxyphenyl azide with the system DTBP/Sn_2Me_6/$InCl_3$ under photolysis in 1:1 (v/v) mixture of MeCN and CH_2Cl_2

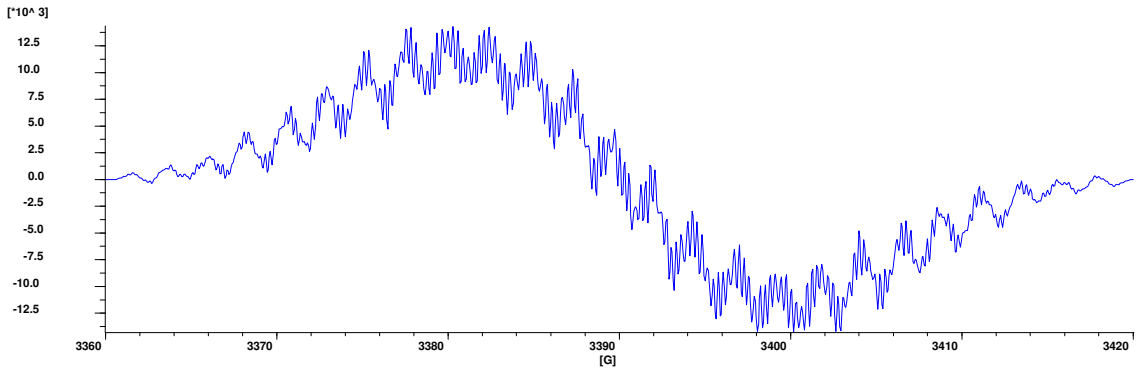


Azide **4j** was mixed with $InCl_3$, Sn_2Me_6 and DTBP in mixture of MeCN and CH_2Cl_2; then 300 µl of the solution were transferred in a quartz glass tube and analyzed by ESR spectroscopy under photolysis according to the general procedure described above. The spectrum recorded and its best simulation are reported below.

4-Methoxyphenyl azide	37.2 mg (0.25 mmol.)
$InCl_3$	55 mg (0.275 mmol.)
Sn_2Me_6	82 mg (0.275 mmol.)
DTBP	50 µl
MeCN/CH_2Cl_2	2 ml/2 ml

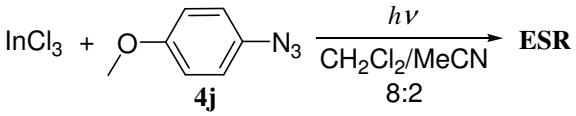


4j+ $InCl_3$, 270 K, MW freq.: 9.5 GHz; M. A.: 2.0 Gpp; Power: 2mW; 1st der.



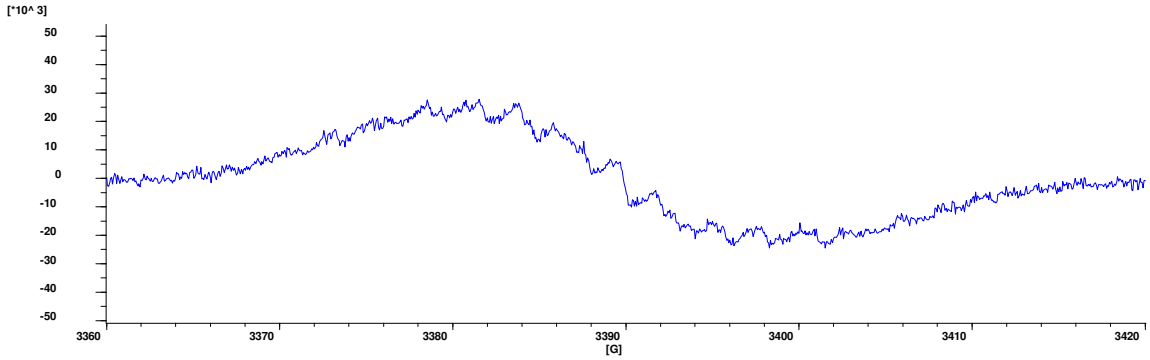
Simulation of 4j + $InCl_3$, a(2Cl) = 0.26, a(1In) 1.53, a(2H) = 2.20, a(2H) = 4.27, a(2H) = 6.97, a(1N) = 3.05, a(1N) = 4.75 G. Line width 0.15.

Reaction of 4-Methoxyphenyl azide with Indium Trichloride and ESR analysis

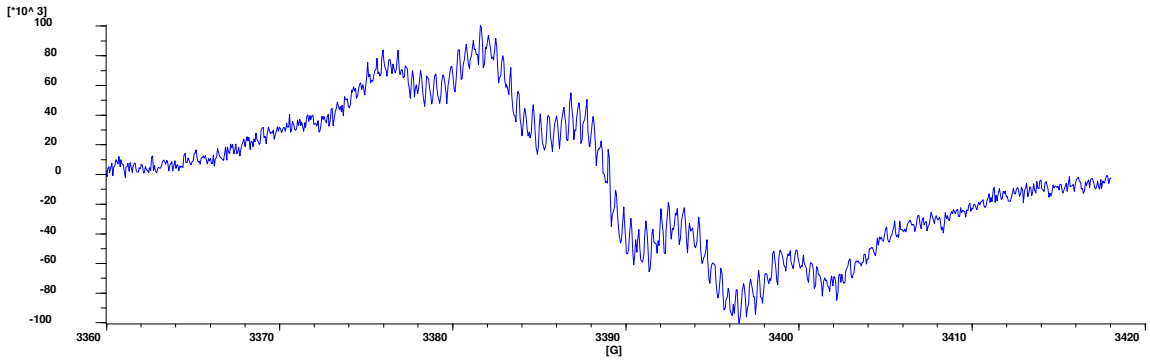


Azide **4j** was mixed with $InCl_3$ in a 8:2 (v/v) mixture of CH_2Cl_2 and MeCN, then 300 µl of the solution were transferred in a quartz glass tube and the reaction was analyzed by ESR spectroscopy under photolysis according to the general procedure described above. The spectra recorded after a few minutes and after 12 days, respectively, are reported below.

4-methoxyphenyl azide	37.25 mg (0.25 mmol.)
$InCl_3$	55 mg (0.275 mmol.)
MeCN	1.6 ml
CH_2Cl_2	6.4 ml

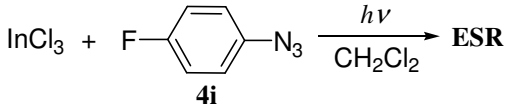


4j + $InCl_3$; 260 K; MW freq.: 9.5 GHz; M. A.: 0.6 Gpp; Power: 1 mW; 1st der.



4j + $InCl_3$; 300 K; MW freq.: 9.5 GHz; M. A.: 0.2 Gpp; Power: 1 mW; 1st der, 12 days sample.

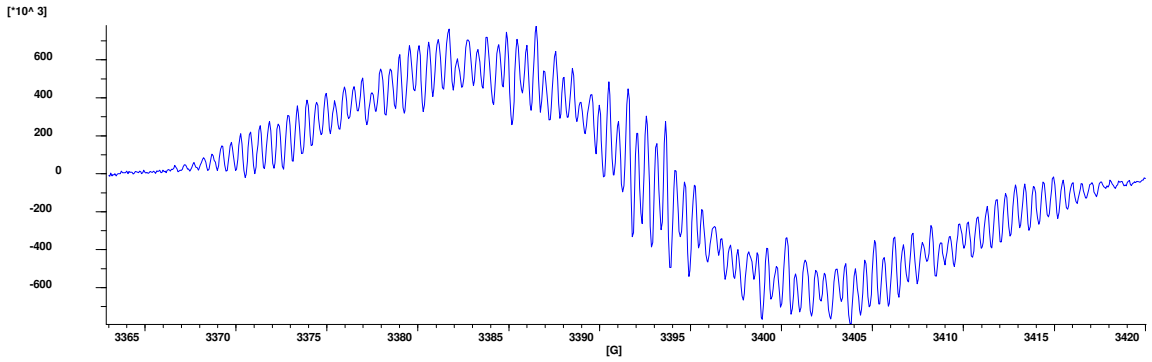
Reaction of 4-Fluorophenyl azide with Indium trichloride and ESR analysis



4i

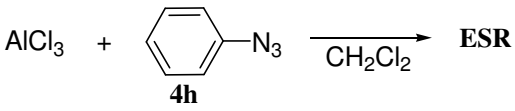
Azide **4i** was mixed with $InCl_3$ in dichloromethane, then 300 µl of the solution were transferred in a quartz glass tube and the reaction was analyzed by ESR spectroscopy under photolysis according to the general procedure described above. A deep violet colour developed once the solution was heated in the ESR cavity at 323 K for 30 minutes. The colour persisted during the ESR acquisition and for several months afterwards. The spectrum recorded is reported below.

4-Fluorophenyl azide	34.2 mg (0.25 mmol.)
$InCl_3$	55 mg (0.275 mmol.)
CH_2Cl_2	4 ml



4i + $InCl_3$; 300 K; MW freq.: 9.5 GHz; M. A.: 0.2 Gpp; Power: 2 mW; 1st der; 51 scans, after UV.

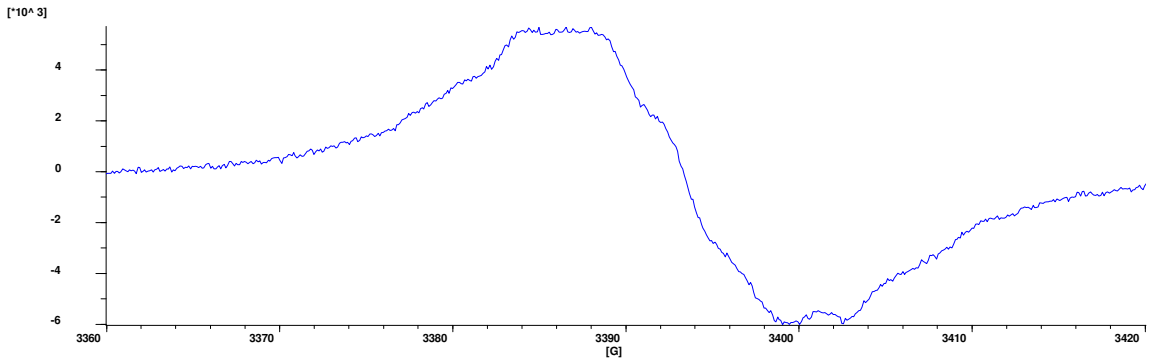
Reaction of Phenyl azide with Aluminium trichloride and ESR analysis



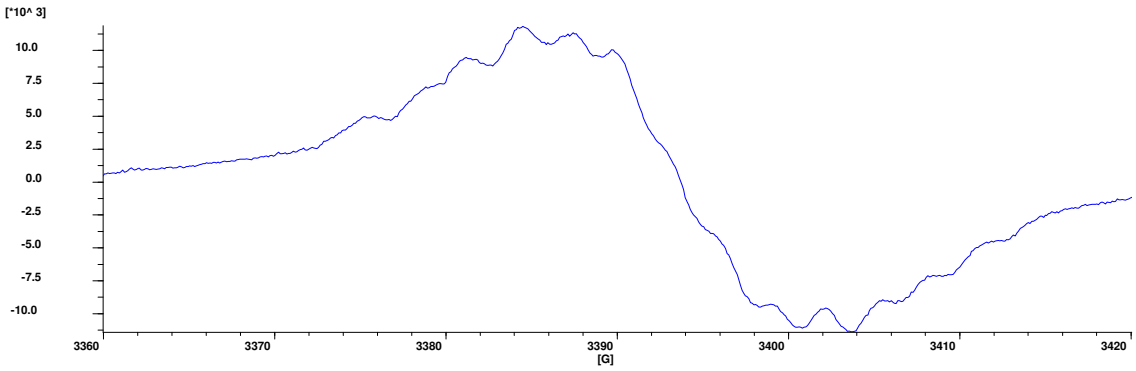
4h

Azide **4h** was mixed with $AlCl_3$ in dichloromethane, then 300 µl of the solution were transferred in a quartz glass tube and the reaction was analyzed by ESR spectroscopy according to the general procedure described above. When **4h** was added a violent reaction occurred with gas evolution and a persistent dark blue colour developed. The spectra recorded are reported below.

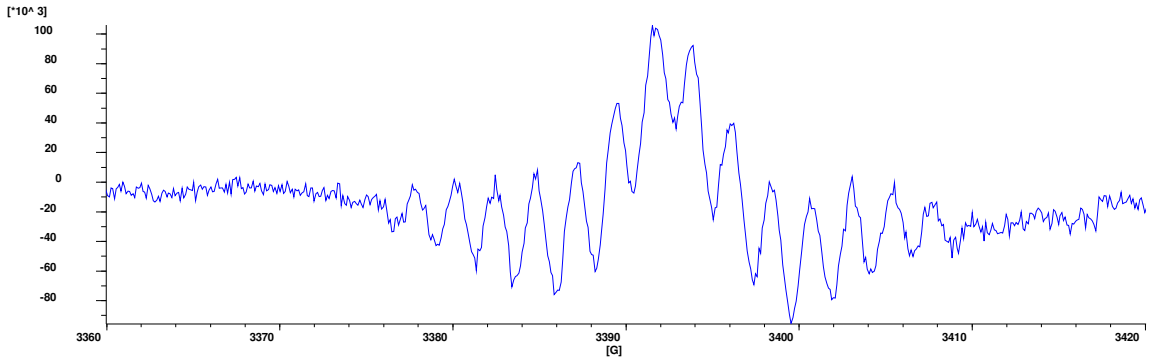
Phenyl azide	29.7 mg (0.25 mmol.)
$AlCl_3$	36.7 mg (0.275 mmol.)
CH_2Cl_2	4 ml



4h + $AlCl_3$; 305 K; MW freq.: 9.5 GHz; M. A.: 0.8 Gpp; Power: 2 mW; 1st der.

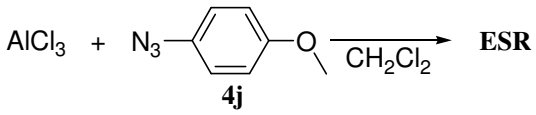


4h + $AlCl_3$; 280 K; MW freq.: 9.5 GHz; M. A.: 1 Gpp; Power: 2 mW; 1st der.; 3 days sample.



4h + $AlCl_3$; 290 K; 3 days sample; M. A.: 1.2 Gpp; Power: 1.3 mW; 2nd der, 3 days sample.

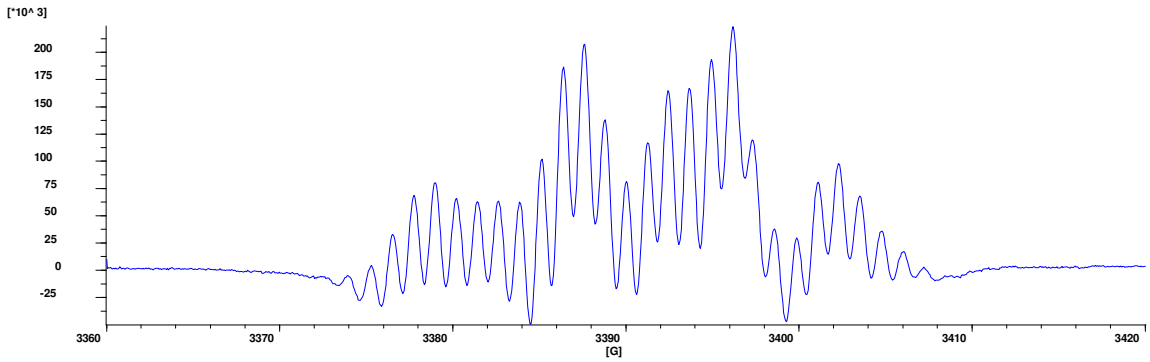
Reaction of 4-Methoxyphenyl azide with Aluminium trichloride and ESR analysis



4j

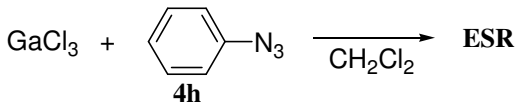
Azide **4j** was mixed with $AlCl_3$ in CH_2Cl_2; then 300 µl of the solution were transferred in a quartz glass tube and the reaction was analyzed by ESR spectroscopy according to the general procedure described above. When **4j** was added a violent reaction occurred with gas evolution and a persistent dark violet colour developed. Product analysis of the reaction mixture gave no interesting results, showing only the starting azide along with unidentifiable tars. The spectra recorded are reported below.

4-Methoxyphenyl azide	37.25 mg (0.25 mmol.)
$AlCl_3$	55 mg (0.275 mmol.)
CH_2Cl_2	6.4 ml



4j + $AlCl_3$; 220 K; MW freq.: 9.5 GHz; M. A.: 1.2 Gpp; Power: 2 mW; 2nd der.

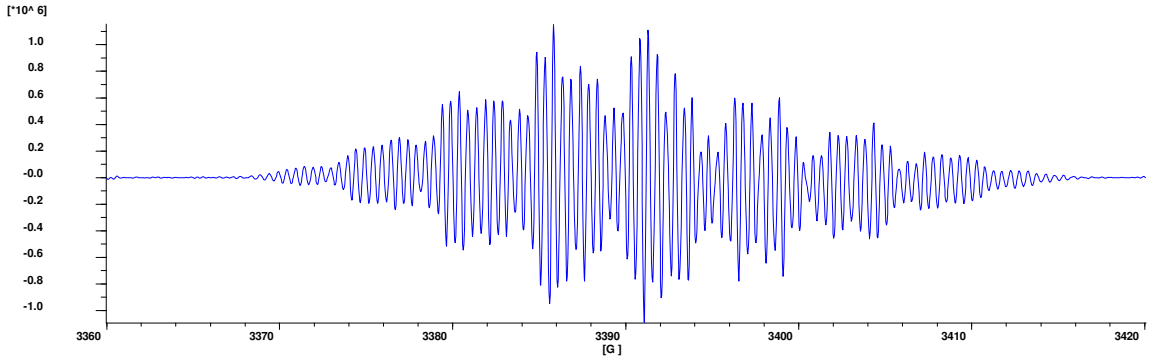
Reaction of Phenyl azide with Gallium trichloride and ESR analysis



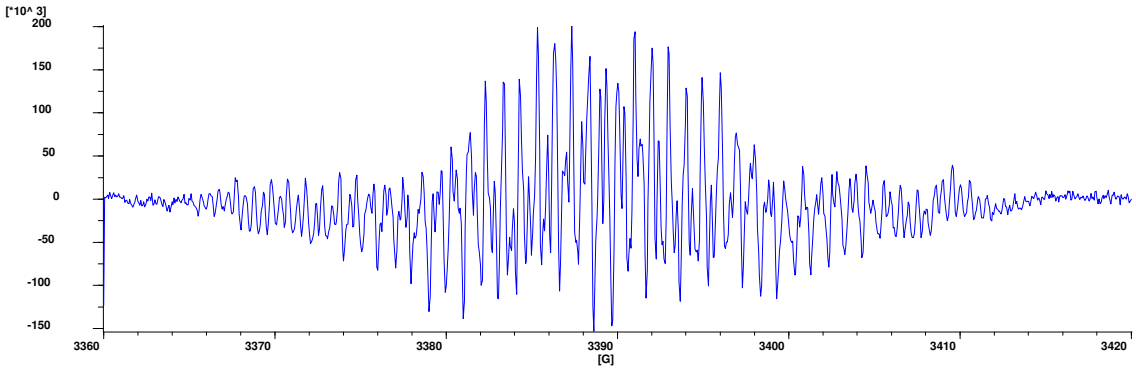
4h

Azide **4h** was mixed with $GaCl_3$ in CH_2Cl_2; then 300 µl of the solution were transferred in a quartz glass tube and the reaction was analyzed by ESR spectroscopy according to the general procedure described above. When $GaCl_3$ was added a violent reaction occurred affording dark red coloured solutions and fast gas evolution. The spectra recorded are reported below: the first spectrum was recorded as 1 st derivative and the second was recorded as 2nd derivative.

Phenyl azide	29.7 mg (0.25 mmol.)
$GaCl_3$ 0.5 M in pentane	0.55 ml (0.275 mmol.)
CH_2Cl_2	4 ml

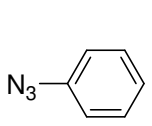


4h + $GaCl_3$; 300 K; MW freq.: 9.5 GHz; M. A.: 0.2 Gpp; Power: 0.8 mW; 1st der; 17 scans.

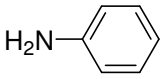


4h + $GaCl_3$; 295 K; MW freq.: 9.5 GHz; M. A.: 0.2 Gpp; Power: 2 mW; 2nd der.

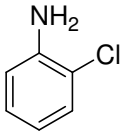
GC-MS analysis always showed complex mixtures of products, identified by comparison with commercial samples, composed by unreacted starting azide **4h**, aniline **6h**, ortho-chloroaniline **oCl-6h**, para-chloroaniline **pCl-6h,** and para-aminodiphenylamine, along with variable amounts, always traces, of 5,10-dihydrophenazine and ortho-aminodiphenyl amine.



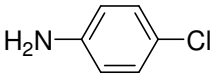
4h, 40-50%



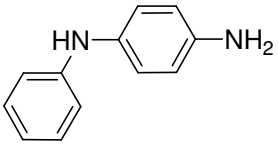
6h, 5%



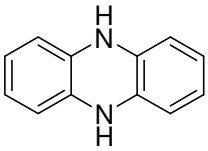
oCl-6h, 10-20%



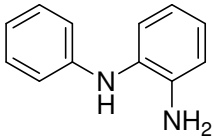
pCl-6h, 20-25%



p-aminodiphenyl amine, 10%

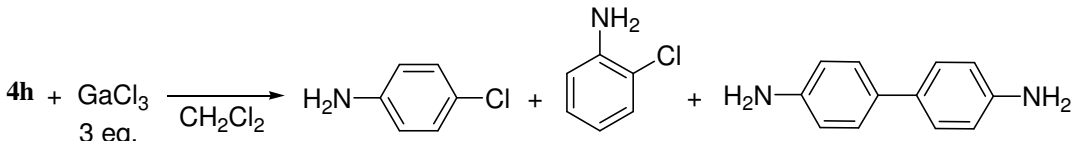


5,10-dihydrophenazine



o-aminodiphenyl amine

Reaction of Phenyl azide with Gallium trichloride 1:3



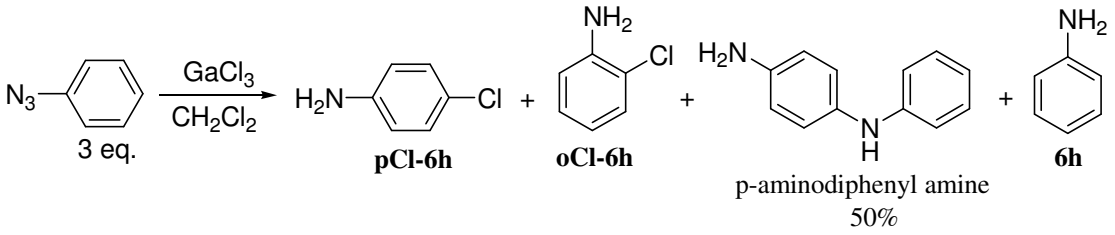
pCl-6h, 90% **oCl-6h**, 5% 4,4[1]-diaminobiphenyl

Azide **4h** was reacted with $GaCl_3$ in CH_2Cl_2; according to the general procedure described above.

Phenyl azide	119 mg (1 mmol.)
$GaCl_3$ 0.5 M in pentane	6.6 ml (3.3 mmol.)
CH_2Cl_2	4 ml

When the pentane solution of $GaCl_3$ was added to the azide solution, the well known dark brown-red colour developed and a huge amount of gas evolved. After 30 minutes an aqueous solution of NaOH was added and extraction with dichloromethane was performed to give the products showed in the reaction scheme.

Reaction of Phenyl azide with Gallium trichloride 3:1

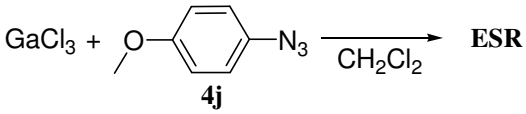


Azide **4h** was reacted with $GaCl_3$ in CH_2Cl_2; according to the general procedure described above.

Phenyl azide	178.5 mg (1.5 mmol.)
$GaCl_3$ 0.5 M in pentane	1.1 ml (0.5 mmol.)
CH_2Cl_2	4 ml

When the pentane solution of $GaCl_3$ was added to the azide solution, the solution became dark green, then rapidly changed to violet and finally became dark red. Also this reaction was characterised by evolution of nitrogen from the solution. After 30 minutes an aqueous solution of NaOH was added and extraction with dichloromethane was performed to give the products showed in the reaction scheme.

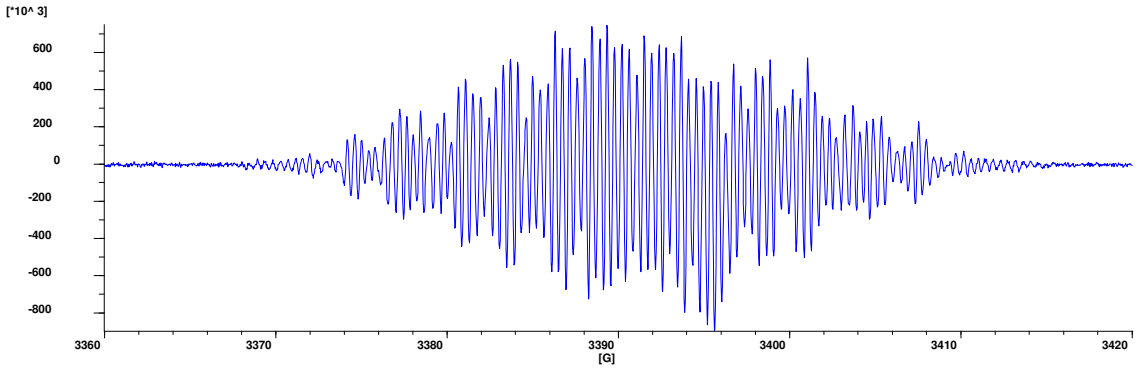
Reaction of 4-Methoxyphenyl azide with $GaCl_3$ and ESR analysis



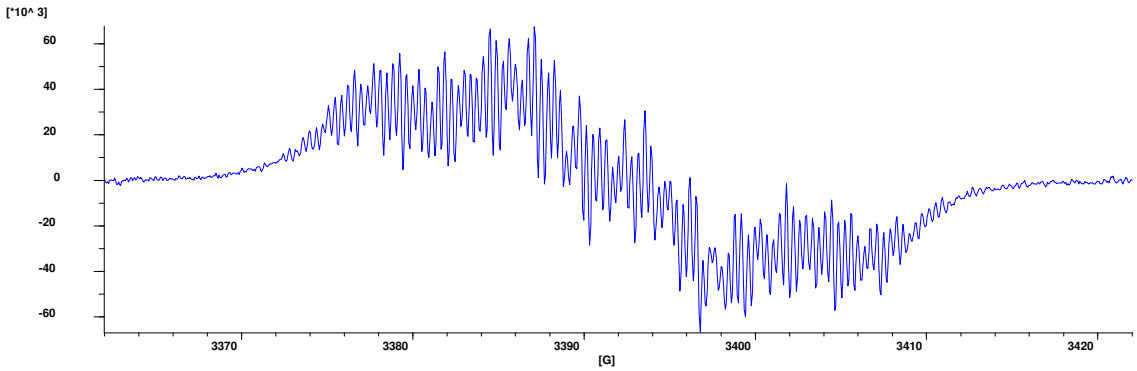
4j

Azide **4j** was mixed with $GaCl_3$ in CH_2Cl_2; then 300 µl of the solution were transferred in a quartz glass tube and the reaction was analyzed by ESR spectroscopy according to the general procedure described above. When $GaCl_3$ was added a violent reaction occurred affording dark blue coloured solutions and fast gas evolution. The observed radical species was stable for several days and its ESR spectrum was quite similar in resolution to that obtained from phenyl azide The spectra recorded are reported below: the first spectrum was recorded as 2nd derivative and the second was recorded as 1 st derivative.

4-Methoxyphenyl azide	37.25 mg (0.25 mmol.)
$GaCl_3$ 0.5 M in pentane	0.55 ml (0.275 mmol.)
CH_2Cl_2	4 ml

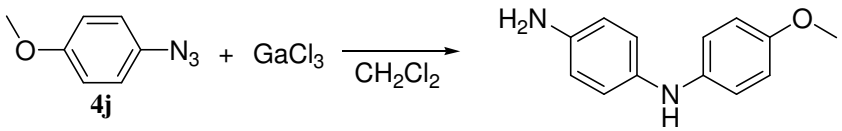


4j + $GaCl_3$; 298 K; MW freq.: 9.5 GHz; M. A.: 0.35 Gpp; Power: 1 mW; 2nd der; 43 scans.



4j + $GaCl_3$; 298 K; MW freq.: 9.5 GHz; M. A.: 0.2 Gpp; Power: 2 mW; 1st der.

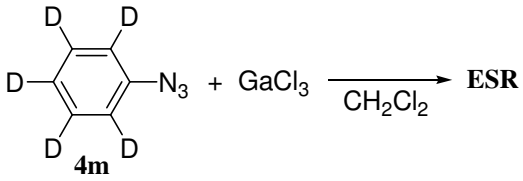
After work up procedures, along with the constant presence of considerable amounts of tars, 4-amino-4'-methoxydiphenylamine, called *Variamine Blue*, was isolated as the main compound and characterised by comparison with a commercial sample.



4j

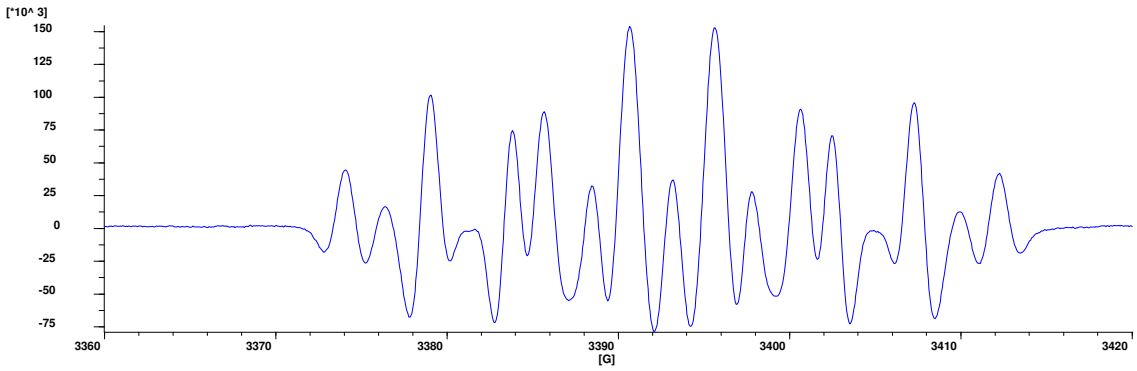
Variamine Blue

Reaction of Phenyl azide *d5* with Gallium trichloride

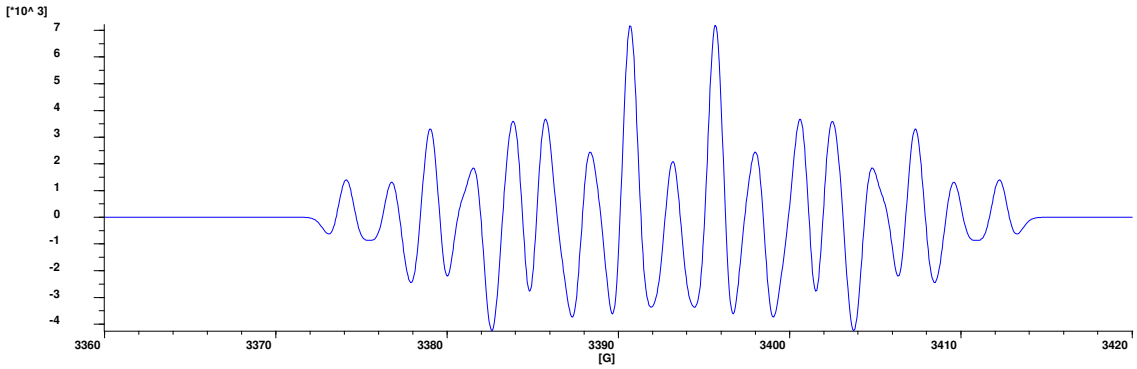


Azide **4m** was mixed with $GaCl_3$ in CH_2Cl_2; then 300 µl of the solution were transferred in a quartz glass tube and the reaction was analyzed by ESR spectroscopy according to the general procedure described above. When $GaCl_3$ was added a violent reaction occurred affording dark violet coloured solutions and fast gas evolution. The spectra recorded and its best simulation are reported below.

Phenyl azide *d5*	124 mg (1.0 mmol.)
$GaCl_3$ 0.5 M in pentane	2.2 ml (1.1 mmol.)
CH_2Cl_2	4 ml

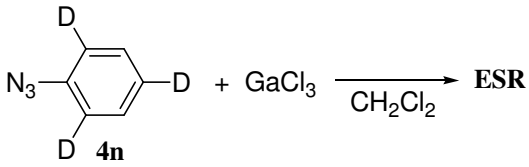


4m + $GaCl_3$; 298 K; MW freq.: 9.5 GHz; M. A.: 0.8 Gpp; Power: 1 mW; 2nd der; 5 scans.



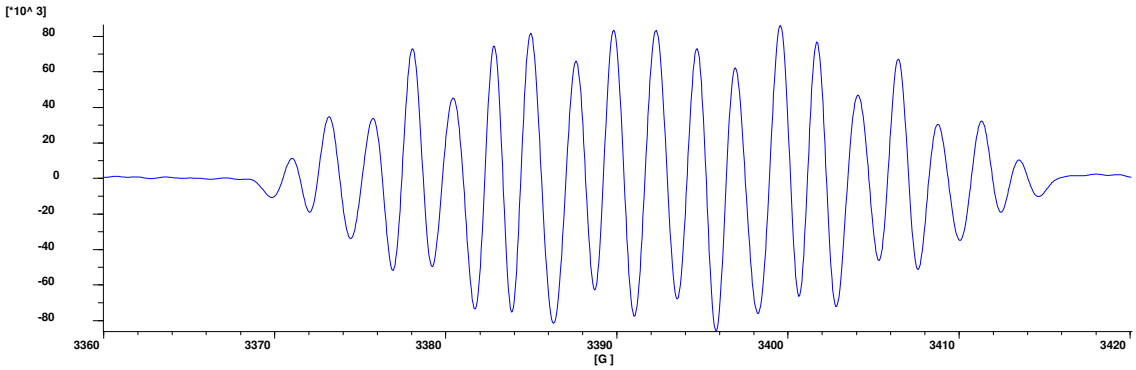
Simulation of 4m: a(2H) = 4.70, a(2H) = 6.53, a(1N) = 2.69, a(1N) = 5.15 G, Line width 1.95, R = 0.939

Reaction of 2,4,6-Trideuteriophenyl azide with Gallium trichloride

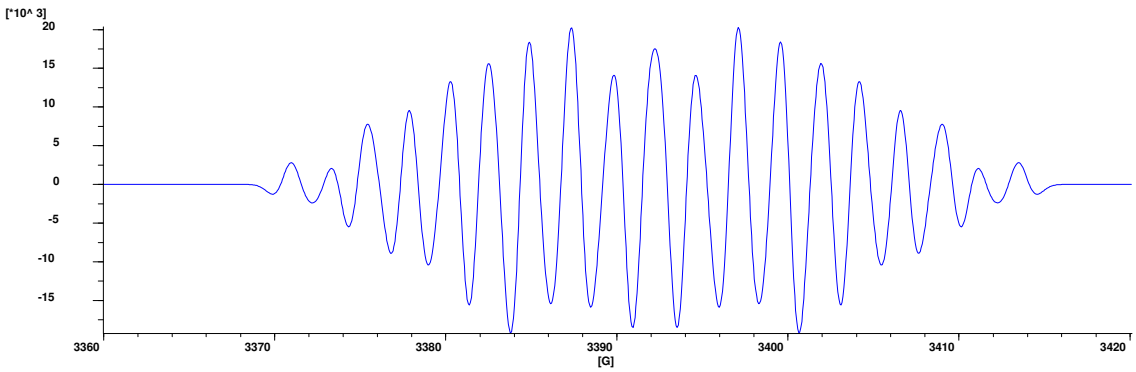


Azide **4n** was mixed with $GaCl_3$ in CH_2Cl_2; then 300 µl of the solution were transferred in a quartz glass tube and the reaction was analyzed by ESR spectroscopy according to the general procedure described above. When $GaCl_3$ was added a violent reaction occurred affording an intense violet coloured solutions and fast gas evolution. The spectra recorded and its best simulation are reported below.

2,4,6-Trideuteriophenyl azide	61 mg (0.5 mmol.)
$GaCl_3$ 0.5 M in pentane	1.1 ml (0.55 mmol.)
CH_2Cl_2	4 ml

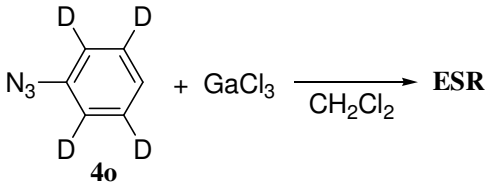


4n + $GaCl_3$; 300 K; MW freq.: 9.5 GHz; M. A.: 0.8 Gpp; Power: 1 mW; 2nd der; 20scans.



Simulation: a(2H) = 7.1, a(3H) = 4.3, a(1N) = 2.45, a(1N) = 5.25 G, Line width 2.10, R = 0.941

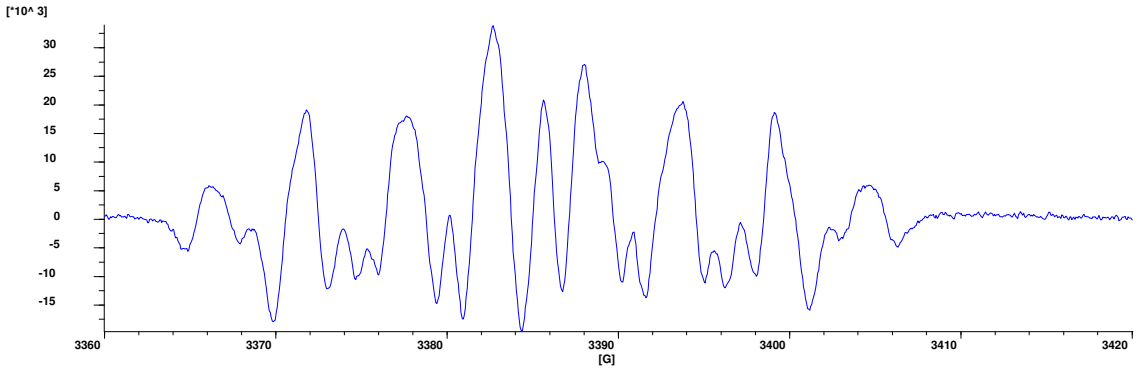
Reaction of 2,3,5,6-Tetradeuteriophenyl azide with Gallium trichloride



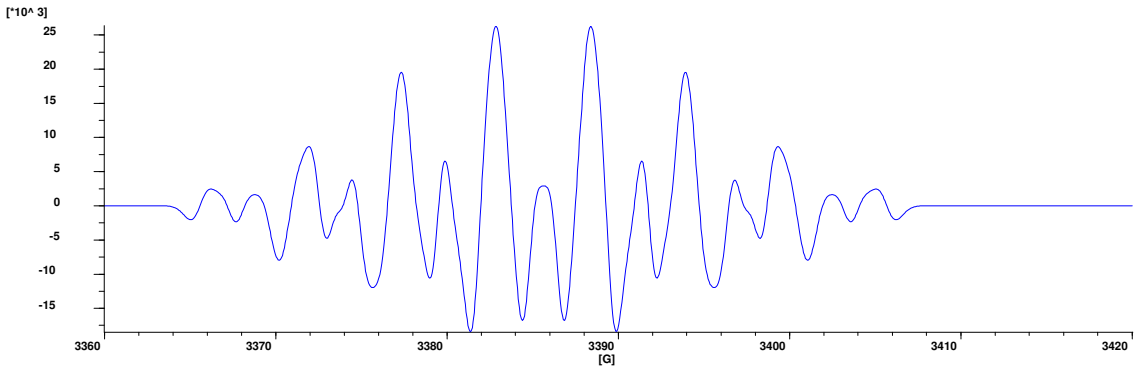
4o

Azide **4o** was mixed with $GaCl_3$ in CH_2Cl_2; then 300 µl of the solution were transferred in a quartz glass tube and the reaction was analyzed by ESR spectroscopy according to the general procedure described above. When $GaCl_3$ was added a violent reaction occurred affording an intense violet coloured solutions and fast gas evolution. The spectra recorded and its best simulation are reported below.

2,3,5,6-Tetradeuteriophenyl azide	61.5 mg (0.5 mmol.)
$GaCl_3$ 0.5 M in pentane	1.1 ml (0.55 mmol.)
CH_2Cl_2	4 ml

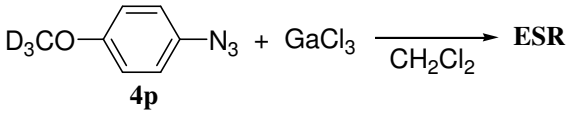


4o + $GaCl_3$; 300 K; MW freq.: 9.5 GHz; M. A.: 0.3 Gpp; Power: 1 mW; 2nd der; 70scans.



Simulation: a(1H) = 0.95, a(2H) = 5.2, a(2H) = 6.2, a(1N) = 2.3, a(1N) = 5.4 G, Line width 2.10, R = 0.941

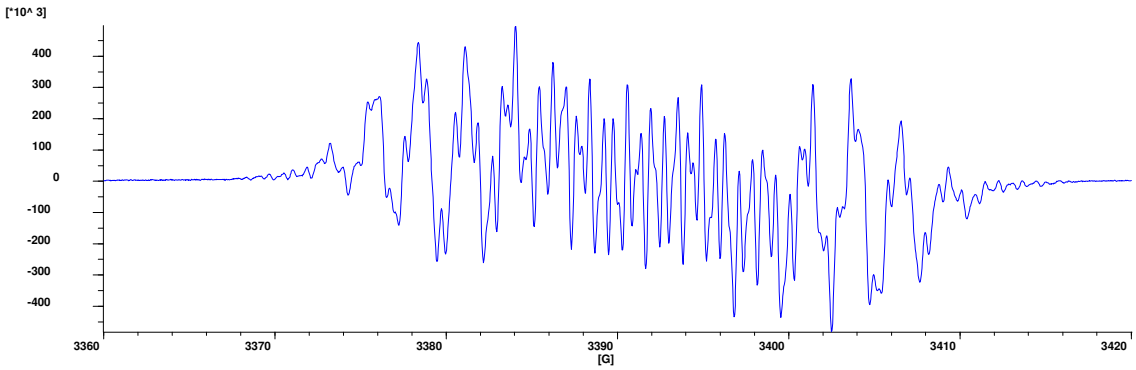
Reaction of 4-Methoxy-*d*3- phenyl azide with Gallium trichloride



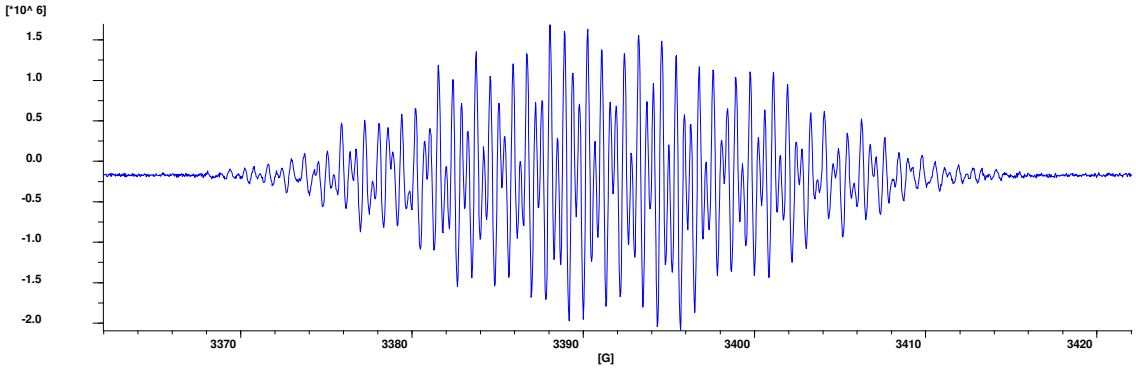
4p

Azide **4p** was mixed with $GaCl_3$ in CH_2Cl_2; then 300 µl of the solution were transferred in a quartz glass tube and the reaction was analyzed by ESR spectroscopy according to the general procedure described above. When $GaCl_3$ was added a violent reaction occurred affording an intense blue-violet coloured solutions and fast gas evolution. The spectra recorded are reported below: the first spectrum was recorded as 1st derivative and the second was recorded as 2nd derivative.

4-Methozy-*d3*-phenyl azide	76 mg (0.5 mmol.)
$GaCl_3$ 0.5 M in pentane	1.1 ml (0.55 mmol.)
CH_2Cl_2	4 ml

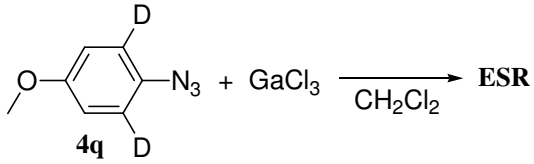


4p + $GaCl_3$; 300 K; MW freq.: 9.5 GHz; M. A.: 0.2 Gpp; Power: 1 mW; 1st der; 29scans



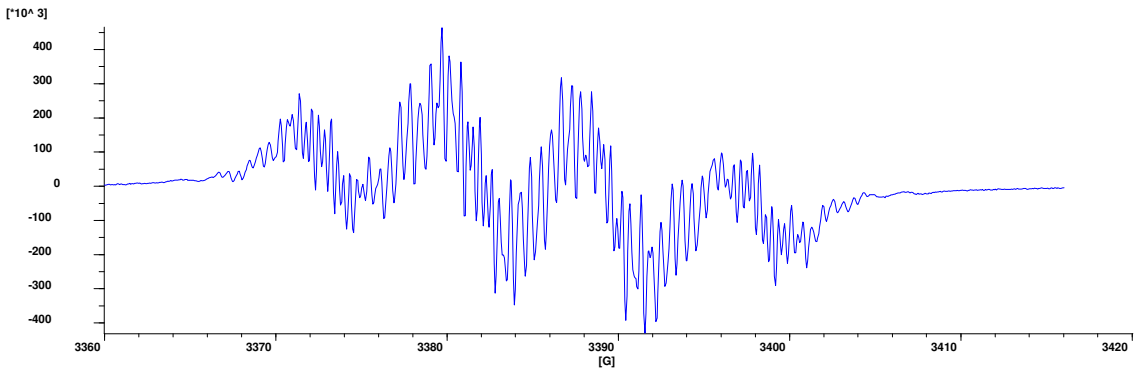
4p + $GaCl_3$; 300 K; MW freq.: 9.5 GHz; M. A.: 0.2 Gpp; Power: 0.8 mW; 2nd der; 100scans

Reaction of 2,6-Dideuterio-4-methoxyphenyl azide with Gallium trichloride

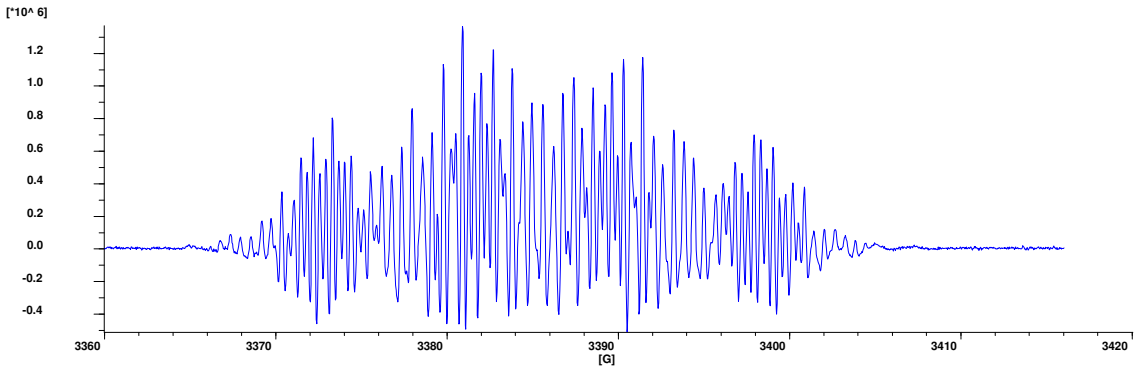


Azide **4q** was mixed with $GaCl_3$ in CH_2Cl_2; then 300 µl of the solution were transferred in a quartz glass tube and the reaction was analyzed by ESR spectroscopy according to the general procedure described above. When $GaCl_3$ was added a violent reaction occurred affording an intense violet coloured solutions and fast gas evolution. The spectra recorded are reported below: the first spectrum was recorded as 1st derivative and the second was recorded as 2nd derivative.

2,6-Dideuterio-4-methoxyphenyl azide	75.5 mg (0.5 mmol.)
$GaCl_3$ 0.5 M in pentane	1.1 ml (0.55 mmol.)
CH_2Cl_2	4 ml

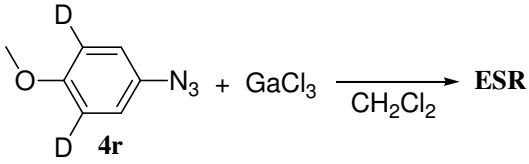


4q + $GaCl_3$; 300 K; MW freq.: 9.5 GHz; M. A.: 0.2 Gpp; Power: 2 mW; 1st der; 20scans.



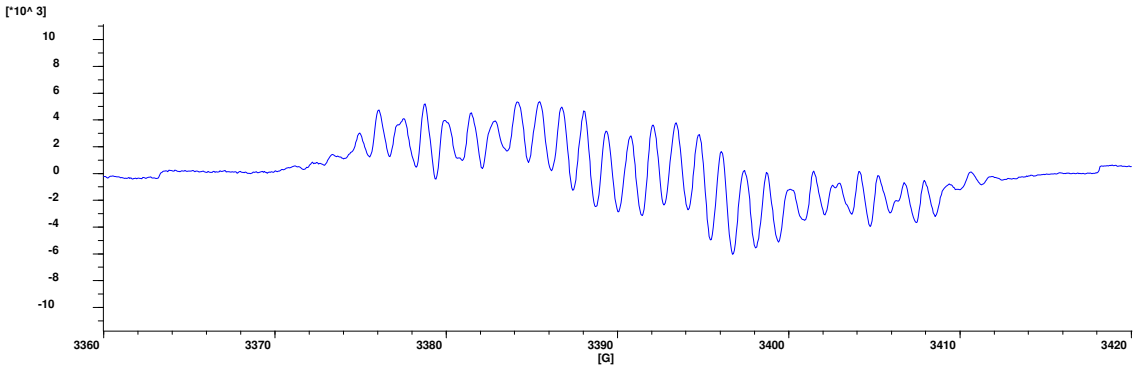
4q + $GaCl_3$; 300 K; MW freq.: 9.5 GHz; M. A.: 0.3 Gpp; Power: 2 mW; 2nd der; 35scans.

Reaction of 3,5-Dideuterio-4-methoxyphenyl azide with Gallium trichloride



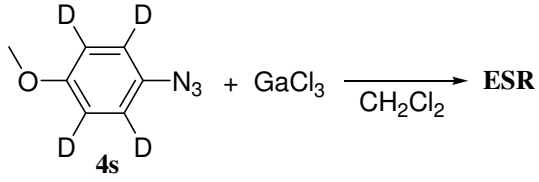
Azide **4r** was mixed with $GaCl_3$ in CH_2Cl_2; then 300 µl of the solution were transferred in a quartz glass tube and the reaction was analyzed by ESR spectroscopy according to the general procedure described above. When $GaCl_3$ was added a violent reaction occurred affording an intense blue coloured solutions and fast gas evolution. The only spectrum recorded is reported below. Although the spectrum is not well resolved, it is however clear that it is comparable in width with that of azide **4q**

3,5-Dideuterio-4-methoxyphenyl azide	75.5 mg (0.5 mmol.)
$GaCl_3$ 0.5 M in pentane	1.1 ml (0.55 mmol.)
CH_2Cl_2	4 ml



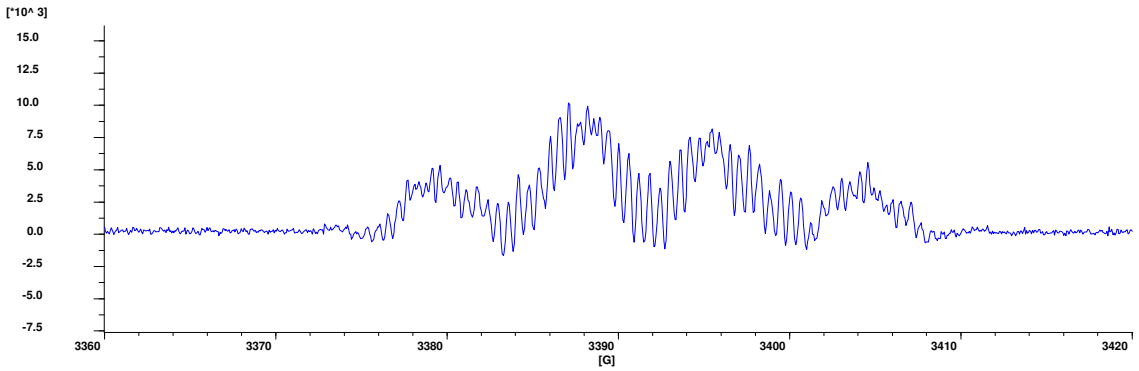
4r + $GaCl_3$; 300 K; MW freq.: 9.5 GHz; M. A.: 0.8 Gpp; Power: 2 mW; 1st der; 1scans.

Reaction of 2,3,5,6-Tetradeuterio-4-methoxyphenyl azide with Gallium trichloride



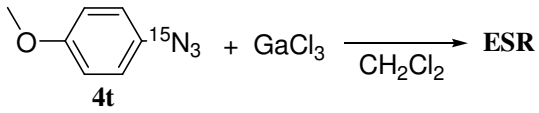
Azide **4s** was mixed with $GaCl_3$ in CH_2Cl_2; then 300 µl of the solution were transferred in a quartz glass tube and the reaction was analyzed by ESR spectroscopy according to the general procedure described above. When $GaCl_3$ was added a violent reaction occurred affording an intense violet coloured solutions and fast gas evolution. The spectrum recorded is reported below. Although the width is congruent with the isotopic replacement (38 G), the spectrum also showed additional quite small splittings: this is rather anomalous, because it would be expected to obtain broad, unresolved lines like in the case of the pentadeuteriated phenyl azide **4m**.

2,3,5,4-Tetradeuterio-4-methoxyphenyl azide	77.5 mg (0.5 mmol.)
$GaCl_3$ 0.5 M in pentane	1.1 ml (0.55 mmol.)
CH_2Cl_2	4 ml



4s + $GaCl_3$; 300 K; MW freq.: 9.5 GHz; M. A.: 0.5 Gpp; Power: 1 mW; 2nd der.

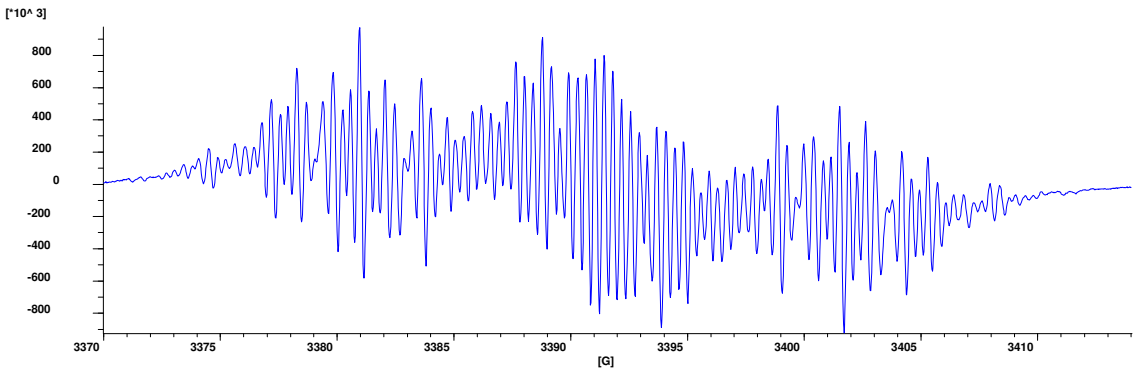
Reaction of 4-Methoxyphenyl azide^{15}N with Gallium trichloride



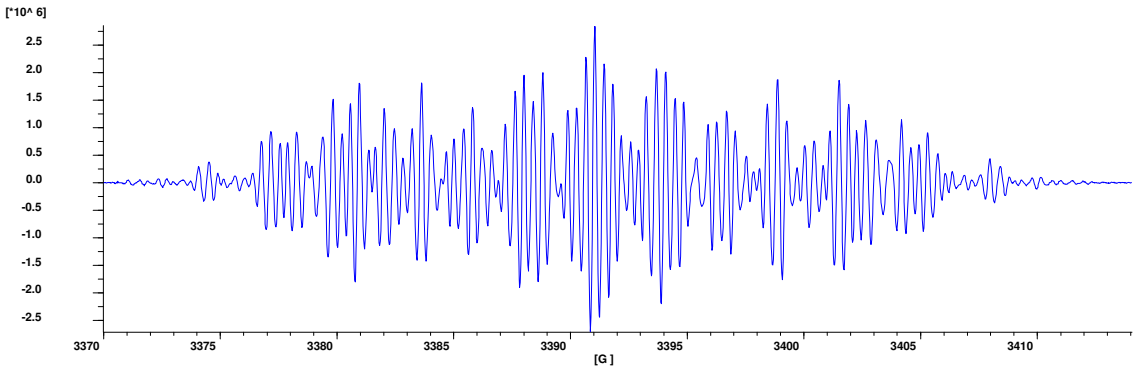
4t

Azide **4t** was mixed with $GaCl_3$ in CH_2Cl_2; then 300 µl of the solution were transferred in a quartz glass tube and the reaction was analyzed by ESR spectroscopy according to the general procedure described above. When $GaCl_3$ was added a violent reaction occurred affording an intense violet coloured solutions and fast gas evolution. The spectra recorded are reported below: the first spectrum was recorded as 1st derivative and the second was recorded as 2nd derivative. The width is congruent with the isotopic replacement (40.3 G): the spectra showed a different shape and line pattern in comparison with the ^{14}N sample **4j**.

4-Methoxyphenyl azide^{15}N	37.5 mg (0.25 mmol.)
$GaCl_3$ 0.5 M in pentane	0.55 ml (0.275 mmol.)
CH_2Cl_2	4 ml



4t + $GaCl_3$; 300 K; MW freq.: 9.5 GHz; M. A.: 0.2 Gpp; Power: 1 mW; 1st der; 8 scans.



4t + $GaCl_3$; 300 K; MW freq.: 9.5 GHz; M. A.: 0.25 Gpp; Power: 1 mW; 2nd der; 105 scans.

References and Notes

[1] For acetonitrile (MeCN) ε_r = 37.5; for tetrahydrofuran (THF) ε_r = 7.6; for dichloromethane (DCM) ε_r = 8.9; for benzene ε_r = 2.3.

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